RESEARCH ARTICLE

Differential diagnostic value of diffusion-weighted and dynamic contrast-enhanced MR imaging in non-cystic lesions in floor of the mouth

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Objectives: To evaluate the potential use of diffusion-weighted imaging and dynamic contrast-enhanced MRI in the differential diagnosis of non-cystic lesions in the floor of the mouth (FOM).

Methods: A total of 82 patients were included in this study. The apparent diffusion coefficient (ADC) values and time-signal intensity curves (TICs) were measured. Clinical characteristics, ADC value, and TIC pattern were compared between benign and malignant FOM lesions. Receiver operating characteristic curve and logistic regression analyses were performed to evaluate respective and combined value of ADC value and TIC pattern for differential diagnosis. The retrospective study was approved by our institutional review board, and the need for informed consent was waived.

Results: The area under the curve ADC value and TIC pattern were 0.71 and 0.73, respectively. The combined use of ADC value and TIC pattern increased the area under the curve value to 0.81 [95% confidence interval (CI), (0.66–0.97)]. $ADC < 1.23 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ (odds ratio, 45.8; 95% CI, 2.8–737.9) and both the plateau and washout TIC patterns (OR, 6.8; 95% CI, 1.8–24.8) were significantly associated with malignancy of FOM lesions.

Conclusions: Our results suggest that both diffusion-weighted imaging and DCE-MRI could contribute to the differential diagnosis of non-cystic FOM lesions, especially when used in combination.

Dentomaxillofacial Radiology (2019) 48, 20180240. doi: [10.1259/dmfr.20180240](https://doi.org/10.1259/dmfr.20180240)

Cite this article as: Yuan Y, Jiang M, Wu L, Tao X. Differential diagnostic value of diffusion-weighted and dynamic contrast-enhanced MR imaging in non-cystic lesions in floor of the mouth. *Dentomaxillofac Radiol* 2019; 48: 20180240.

Keywords: diffusion magnetic resonance imaging; magnetic resonance imaging; mouth floor; neoplasms

Introduction

According to data collected by the National Central Cancer Registry, oral cancer is the 20th most common cancer in China. The overall crude incidence and mortality rates are 2.93/100,000 and 1.26/100,000, respectively.¹ The floor of the mouth (FOM) is an U-shaped space located under the tongue, between the mucosal surface and mylohyoid muscle.² The most important

components of the FOM are the salivary glands and the lingual nerve, artery, and vein. Correspondingly, FOM lesions represent a histopathologically diverse group of both malignant and benign growths. The pre-treatment diagnosis of malignancy and accurate survival prediction are helpful to direct personalized treatment.

MRI is a reliable tool to evaluate FOM lesions, given its superior soft-tissue contrast and multiplanar demonstration. Imaging is essential particularly for masses that extend deep and are beyond the reach of physical examination. Conventional MRI is based on anatomy and hence may not be adequate to accurately visualize and

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Received 25 June 2018; revised 23 October 2018; accepted 07 November 2018
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evaluate the lesion. Diffusion-weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI) are clinically available, advanced MRI techniques that aim to record the Brownian motion of water protons and assess the microvascular parameters of tissue perfusion, respectively. Previous studies have approved the potential use of DWI and DCE-MRI in head and neck tumors,^{3,4} specifically in the differentiation and characterization of primary tumors,^{5,6} correlation with clinical stage,⁷ evaluation and prediction of treatment response,^{8,9} and presenting information regarding the possible prognosis.^{10,11} However, to the best of our knowledge, no previous studies have discussed the potential use of DWI and DCE-MRI in differential diagnosis of FOM lesions.

Therefore, in this current study, we reviewed patients from a retrospective database at our institution (Shanghai Ninth People's Hospital) to evaluate the potential ability of the apparent diffusion coefficient (ADC) value and time-intensity curve (TIC) pattern to differentiate benign from malignant FOM lesions.

Methods and materials

Patient selection

We retrospectively reviewed the clinical records and MR images of patients with primary FOM lesions between January 2013 and December 2015. All lesions were histopathologically verified after biopsy or surgery. The cystic lesions without soft tissue components were excluded, which did not rely on DWI and DCE-MRI for diagnosis. The following patients were excluded: (1) those with imaging artifacts that interfered with interpretation; (2) those that previously underwent surgery or radiation in the head and neck region; or (3) those that received treatment for the FOM lesion before undergoing the MRI. Lesions <10 mm were also excluded to avoid partial volume effects. Subjects who had smoked over 100 cigarettes during their lifetimes were classified as ever-smokers, and all others as never-smokers. Those who had consumed alcoholic beverages at least once a week for 1 year were categorized as ever-drinkers, and all others as never-drinkers. This retrospective study was approved by our institutional review board, and the need for informed consent was waived.

MRI acquisition: All patients underwent MRI on a 1.5 T system (Signa Excite; GE Medical Systems, Milwaukee, WI) in the 2 weeks before undergoing surgery or biopsy. DWI was performed with single-shot spin-echo echo-planar imaging sequence [repetition time/echo time, 2200/70; matrix, 128 × 128 mm; field of view, 240 × 240 mm; thickness/gap, 5.0/0.5 mm; *b*, 0 and 1000 smm⁻²; *x*-, *y*-, and *z*-gradient directions]. DCE-MRI (repetition time/echo time, 4.8/2.2 ms; field of view, 240 × 240 mm; matrix, 256 × 192 mm; thickness/gap, 5.0/0.5 mm) was obtained after intravenous injection of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) at a dosage of 0.1 mmol/kg⁻¹ of body weight using a power

injector with a flow rate of 3 ml s⁻¹, followed by a 20 ml saline flush. According to our routine MRI protocol for the head and neck region,¹² the conventional pre- and post-contrast enhanced MRI sequences were also obtained in the axial and coronal planes, which helped define the regions of interest (ROIs) during post-processing of DWI and DCE-MRI in the current study.

Calculation of parameters on the images

The DWI and DCE-MRI were post-processed with the Functool software (GE Healthcare, Milwaukee, WI) by three radiologists with more than 8 years of experience in interpreting head and neck MRIs. The assessors were blinded to the histopathologic results. To generate the ADC value, freehand ROI was drawn on the image, taking care to exclude obvious hemorrhage, necrotic, or other non-perfused areas, and to avoid the most peripheral portions to exclude partial volume effects from adjacent normal tissue. ADC values were manually measured three times, and the average value was obtained as a representative ADC value for each lesion. For postprocessing of DCE-MRI, we placed ROIs (~25–50 mm²) over the lesion. The TIC with the most prominent enhancement was selected by consensus as the representative curve for each lesion. We categorized the TICs into four groups according to previous studies^{13,14}: (1) flat pattern: without obvious enhancement; (2) persistent pattern: $T_{peak} > 120$ s; (3) plateau pattern: $T_{peak} \leq 120$ s, washout ratio $\leq 30\%$; (4) washout pattern: $T_{peak} \leq 120$ s, WR $> 30\%$. The detailed method has been described in our previous studies.^{12,15}

Statistical analysis: Clinical characteristics, ADC value, and TIC pattern were compared between benign and malignant FOM lesions by using X² testing (Fisher exact test when necessary) for categorical variables and unpaired *t*-test for noncategorical data. To determine the association of ADC value and TIC pattern with malignancy, we adopted logistic regression analyses to compute odds ratios (ORs) and 95% confidence intervals (CIs), adjusted to variables of age, sex, and smoking and drinking status. To evaluate the diagnostic ability of ADC value and TIC pattern, we conducted receiver operator characteristics (ROC) analysis, and assessed the area under the ROC curve (AUC). The optimal cut-off value was defined as the point which maximized the correct classification rate. ROC analysis was also performed to evaluate the combined application of ADC value and TIC pattern in differential diagnosis. Statistical analyses were carried out with STATA v. 14.0 (College Station, TX). *p* < 0.05 was considered statistically significant.

Results

A total of 82 patients were included in this study (mean age: 53.4 ± 11.0 years; 68 male, 14 female). Malignant tumors were diagnosed in 71 patients that included squamous cell carcinoma (*n* = 54), adenoid cystic

Figure 1 The plot of ROC curves of DWI alone (A), DCE-MRI alone (B), and combined use of DWI and DCE-MRI (C) in differentiating benign from malignant MOF lesions. The ROC curves depict a true positive rate (sensitivity) vs a false-positive rate (1–specificity). ADC, apparent diffusion coefficient; DCE-MRI, dynamic contrast-enhanced MRI; DWI, diffusion-weighted imaging; MOF, mouth of the floor; ROC, receiver operating characteristic; TIC, time-signal intensity curve.

carcinoma ($n = 8$), mucoepidermoid carcinoma ($n = 3$), lymphoma ($n = 2$), malignant pleomorphic adenoma ($n = 2$), alveolar soft part sarcoma ($n = 1$), and malignant fibrous histiocytoma ($n = 1$). The remaining 11 patients with benign FOM lesions were diagnosed as having chronic inflammation ($n = 6$), schwannoma ($n = 2$), venous malformation ($n = 1$), and benign hyperplasia ($n = 2$). Demographics and clinical characteristics of patients are summarized in Table 1. Statistically significant differences were only found with respect to alcohol consumption status ($p = 0.01$) between patients with benign and malignant lesions.

All included patients underwent DWI and DCE-MRI. The ADC value ($p = 0.02$) and TIC pattern ($p = 0.001$) showed significant differences between benign and malignant FOM lesions (Table 1). The ROC curves were generated for ADC value and TIC pattern, respectively (Figure 1A,B). The AUCs for ADC value

and TIC pattern were 0.71 (95% CI: 0.50–0.91) and 0.73 (95% CI: 0.57–0.89), respectively. The ADC cut-off value of $1.23 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ offered the best diagnostic performance, with a sensitivity of 95.8% and specificity of 54.6%. The lesions with $\text{ADC} < 1.23 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ were nearly 46-times more likely to be malignant than those with $\text{ADC} \geq 1.23 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ (OR, 45.8; 95% CI, 2.8–737.9). When adopting the plateau or washout TIC pattern as malignant criteria, the differential sensitivity and specificity were 67.6 and 72.7%, respectively. The lesions with plateau or washout TIC pattern were almost seven times more likely to be malignant than those with flat or persistent pattern (OR, 6.8; 95% CI, 1.8–24.8). Figures 2 and 3 show representative cases of benign and malignant lesions with images of conventional MRI, DWI, and DCE-MRI.

By combining the ADC value and TIC pattern, we found that FOM lesions with both $\text{ADC} \geq 1.23 \times 10^{-3}$

Table 1 Demographics, clinical and imaging characteristics of patients with MOF lesions

Variables	All ($n = 82$) n (%)	Malignant ($n = 71$) n (%)	Benign ($n = 11$) n (%)	p -value ^a
Age (year) ^b	53.4 $\pm$ 11.0	54.0 $\pm$ 9.7	49.5 $\pm$ 17.7	0.61
Sex				
Male	68 (82.9)	60 (84.5)	8 (72.7)	0.39
Female	14 (17.1)	11 (15.5)	3 (27.3)	
Smoking				
Ever	34 (41.5)	32 (45.1)	2 (18.2)	0.11
Never	48 (58.5)	39 (54.9)	9 (81.8)	
Alcohol drinking				
Ever	27 (32.9)	27 (38.0)	0 (0)	0.01
Never	55 (67.1)	44 (62.0)	11 (100.0)	
Lesion size(mm) ^b	33.8 $\pm$ 15.2	33.5 $\pm$ 16.0	35.7 $\pm$ 8.5	0.28
ADC value ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	0.97 $\pm$ 0.28	0.93 $\pm$ 0.25	1.21 $\pm$ 0.35	
≥ 1.23	10 (12.2)	4 (5.6)	6 (54.5)	
< 1.23	72 (87.8)	67 (94.4)	5 (45.5)	0.001
TIC pattern				
Flat	2 (2.4)	0	2 (18.2)	
Persistent	29 (35.4)	23 (32.4)	6 (54.5)	
Plateau	50 (61.0)	47 (66.2)	3 (27.3)	
Washout	1 (1.2)	1 (1.4)	0	

ADC, apparent diffusion coefficient; MOF, mouth of the floor; TIC, time intensity curve.

^a p -values for comparison of demographics and characteristics between malignant and benign lesions

^bPresented as mean $\pm$ standard deviation (SD)

mm^2s^{-1} and flat or persistent TIC pattern showed the lowest possibility of detecting a malignant lesion. The joint differential value of ADC value and TIC pattern is presented in Table 2. By considering the lesions with $\text{ADC} \geq 1.23 \times 10^{-3} \text{ mm}^2\text{s}^{-1}$ and flat or persistent TIC pattern as the reference group, the risk of malignancy progressively increased among lesions with $\text{ADC} \geq 1.23 \times 10^{-3} \text{ mm}^2\text{s}^{-1}$ and plateau or washout TIC pattern (OR, 5.0); $\text{ADC} < 1.23 \times 10^{-3} \text{ mm}^2\text{s}^{-1}$ and flat or persistent TIC pattern (OR, 17.5); and $\text{ADC} < 1.23 \times 10^{-3} \text{ mm}^2\text{s}^{-1}$ and plateau or washout TIC pattern (OR, 57.5) (Table 2). The ROC curve for the combined use of ADC value and TIC pattern was also generated, with an AUC of 0.81 [95% CI (0.66–0.97)] (Figure 1C). The best differential sensitivity 98.3% was achieved by taking the malignant criteria of $\text{ADC} < 1.23 \times 10^{-3} \text{ mm}^2\text{s}^{-1}$ and/or plateau or washout TIC pattern, while adopting a malignant criteria of both $\text{ADC} < 1.23 \times 10^{-3} \text{ mm}^2\text{s}^{-1}$ and plateau or washout TIC pattern could increase the specificity to 88.9%.

Discussion

The FOM lesions represent a diverse group of histopathological entities, and modern imaging techniques are helpful in pre-operative assessment. In this preliminary

study, we investigated the individual and combined performance of DWI and DCE-MRI in the differential diagnosis of FOM lesions. We found lower ADC value and plateau or washout TIC pattern were associated with malignant diagnosis. The joint application of ADC and TIC pattern further increased the differential ability, with the best sensitivity of 98.3% under the malignant criteria of $\text{ADC} < 1.23 \times 10^{-3} \text{ mm}^2\text{s}^{-1}$ and/or plateau or washout TIC, and a specificity of 88.9% by adopting a malignant criterion of both $\text{ADC} < 1.23 \times 10^{-3} \text{ mm}^2\text{s}^{-1}$ and plateau or washout TIC pattern.

Advanced MRI techniques such as DWI and DCE-MRI allow for quantifying or semi-quantifying tumor characteristics of cellularity and vascularity. In addition to structural imaging, these MRI techniques have shown their capability in differential diagnosis of head and neck tumors.^{4,5,16–19} In our previous studies, we have also detected the ability of ADC value and TIC pattern in differentiating orbital,²⁰ thyroid,^{21,22} palatal,¹² and parotid gland lesions,¹⁵ either used alone or in combination with conventional MRI.

Diffusivity is affected by cell size, density, and integrity. In malignant lesions, increased cell number, cell volume, and microstructural density restrict diffusion and therefore decrease ADC values. Although exceptions and overlap in ADC results exist because of the

Figure 2 A 34-year-old male with nerve sheath tumor at the mouth of the floor. Axial T_1 weighted imaging (a), T_2 weighted imaging (b) and contrast-enhanced T_1 weighted imaging (c) show a well-circumscribed, homogeneously enhancing mass in the front of MOF (arrows). The round cursors stand for the regions of interest selected for measuring the ADC value (d) and TIC pattern (e). The ADC value of $1.24 \times 10^{-3} \text{ mm}^2\text{s}^{-1}$ (d) and persistent TIC pattern (f) indicate a benign diagnosis which is consistent with pathologic results. ADC, apparent diffusion coefficient; TIC, time-signal intensity curve.

Figure 3 A 60-year-old male with squamous cell carcinoma at the mouth of the floor. Axial T_1 weighted imaging (a), T_2 weighted imaging (b) and contrast-enhanced T_1 weighted imaging (c) show an ill-defined, heterogeneously enhancing mass in the front of MOF (arrows). The round cursors stand for the regions of interest selected for measuring the ADC value (d) and TIC pattern (e). The ADC value of $0.86 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ (d) and plateau TIC pattern (f) indicate a malignant possibility which is consistent with final diagnosis. ADC, apparent diffusion coefficient; MOF, mouth of the floor; TIC, time-signal intensity curve.

heterogeneous group of benign and malignant lesions, lower ADC values have been reported for most malignant head and neck tumors.²³ In the current study, the mean ADC value for malignant lesions ($0.92 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) was significantly lower than that of benign lesions ($1.25 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$). When adopting the optimal cut-off value of $1.23 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, we found that lesions with $\text{ADC} < 1.23 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ were 46 times more likely to be malignant than those with $\text{ADC} \geq 1.23 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$. However, the specificity (55.6%) was still far from satisfactory.

Intravenous contrast is commonly used in MRI and can evaluate blood vessels and better characterize soft-tissue lesions. The incidence of adverse events after administration of Gd contrast is low. In a previous study, in the absence of known renal failure, neonates receiving standard inpatient care do not appear to be at increased risk for developing renal toxicity due to administration

of intravenous gadolinium-based contrast material.²⁴ In the current study, adverse events to gadolinium-based contrast agents including allergic-like reactions, nephrotoxicity, extravasation and nephrogenic systemic fibrosis were not reported. However, to evaluate the cost-effective of gain in accuracy is greater than the risks of an intravenous contrast MRI, further analysis could be conducted. Moreover, although the incidence of adverse events after administration of contrast is low, it is important that clinicians and radiologists minimize risks and respond quickly and effectively when reactions occur.

The present study has several potential limitations. First, although we sought to define thresholds for differential diagnosis, the ADC cut-off value defined in this study may likely not be extrapolated to other hospitals, given the differences in scanner and imaging protocols.^{23,25,26} Site-specific ADC cut-off values are, therefore,

Table 2 Joint differential value of ADC and TIC pattern in MOF lesions

ADC value ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	TIC pattern	Malignant ($n = 71$) n (%)	Benign ($n = 11$) n (%)	OR (95% CI)
≥ 1.23	Flat/persistent	2 (2.8)	5 (45.5)	1.0
≥ 1.23	Plateau/washout	2 (2.8)	1 (9.1)	5.0 (0.3–91.5)
< 1.23	Flat/persistent	21 (29.6)	3 (27.3)	17.5 (2.3–134.3)
< 1.23	Plateau/washout	46 (64.8)	2 (18.2)	57.5 (6.6–501.8)

ADC, apparent diffusion coefficient; CI, confidence interval; MOF, mouth of the floor; OR, odds ratio; TIC, time-signal intensity curve.

recommended for routine clinical application, and further research is needed before DWI can be routinely and reliably used in all head and neck cancer centers. Second, the freehand ROI analysis we adopted in the current study is inherently user-dependent and hence prone to sampling bias, although we elaborately evaluated the representative ADC by repeated measurement, and defined representative TIC as that with the most prominent enhancement with consensus. A histogram analysis was conducted in a recently published study,²⁷ based on all slices encompassing the entire tumor to obtain a better understanding of the heterogeneity of the metrics within tumors, which may generate more objective and reliable results and be worthy of comparison with traditional measurements. Third, our sample size was small, and not every examined tumor entity

could be represented by a satisfactory number of cases. For example, no benign salivary tumor was included. Furthermore, the demographic, clinical, and radiological data for the cohort were collected retrospectively, and the included patients were all hospital based. Therefore, prospective larger studies are warranted to validate our findings.

Conclusion

In this preliminary study, DWI and DCE-MRI proved beneficial to differential diagnosis of non-cystic FOM lesions, especially when used in combination. Prospective and multicenter studies are warranted to further strengthen the results of our study.

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