RESEARCH

Role of diffusion-weighted MRI in differentiation of masticator space malignancy from infection

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Objective: The aim of this study was to assess the role of the apparent diffusion coefficient (ADC) value in differentiation of masticator space malignancy from infection.

Methods: A retrospective study of 49 patients (31 male and 18 female; age range 5–66 years) with masticator space lesion was conducted. They underwent spin-echo-type echo planar diffusion-weighted MRI of the head and neck with *b*-values of 0 mm² s⁻¹, 500 mm² s⁻¹ and 1000 mm² s⁻¹. The ADC maps were reconstructed and the ADC value of the masticator space lesion was calculated.

Results: The mean ($\pm$ standard deviation) ADC value of masticator space malignancy ($0.91 \pm 0.21 \times 10^{-3}$ mm² s⁻¹) was significantly lower ($p = 0.001$) than that of masticator space infection ($1.59 \pm 0.32 \times 10^{-3}$ mm² s⁻¹). When an ADC value of 1.20×10^{-3} mm² s⁻¹ was used as a threshold value for differentiating masticator space malignancy from infection, the best result was obtained with an accuracy of 88%, sensitivity of 88%, specificity of 87%, negative predictive value of 94%, positive predictive value of 86% and area under the curve of 0.92. There was a significant difference in the ADC value between squamous cell carcinoma and soft tissue sarcoma ($p = 0.001$), as well as between bacterial and fungal infection of the masticator space ($p = 0.001$).

Conclusion: We concluded that ADC value is a non-invasive promising imaging parameter that can be used for differentiation of masticator space malignancy from infection.

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Introduction

An early and correct differentiation of malignant tumours of masticator space from infections is pivotal for treatment planning and prognosis of the patient. Some chronic infections or inflammatory lesions in the masticator space may simulate malignant tumour clinically. The masticator space is difficult to explore by means of clinical examination alone.^{1–3} Differentiation of chronic infections from malignant tumours in the masticator space with CT and MRI is often difficult.^{4–5} MR spectroscopy has been used for differentiation, but

it is of limited value and needs special software.⁶ Biopsy has been used, but it is an invasive procedure and may be associated with complications.⁷

Diffusion-weighted MRI has been used for differentiation of malignant tumours of head and neck from benign tumours.^{8–12} However, a few limited studies discussed the role of diffusion MRI in differentiation of malignancy from inflammatory lesions of the orbit, skull base and paranasal sinuses.^{13–15} Also, diffusion-weighted MRI has been used for evaluation of solid lesions of masticator space.¹⁶

The aim of this work was to assess the role of the apparent diffusion coefficient (ADC) value in differentiation of masticator space malignancy from infection.

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Materials and methods

Retrospective analysis was performed upon 52 patients with masticator space lesions over a period of 7 years. The inclusion criteria were untreated patients with solid masticator space lesion who underwent routine MRI with diffusion MRI series, searched for from the database of the hospital. Three patients were excluded from the study owing to bad image quality with motion and susceptibility artefacts. The final patients included in this study were 49 patients (31 males and 18 females; age range 5–66 years, mean 39 years). They presented with trismus ($n = 33$), facial swelling ($n = 28$), facial pain ($n = 26$), otalgia ($n = 7$) and proptosis ($n = 5$). The final diagnosis of masticator space lesions was confirmed at pathological examination by surgical excision ($n = 24$) and biopsy ($n = 17$) and follow-up after medical treatment of inflammatory lesions ($n = 8$). Ethical committee approval of this study was obtained, and informed consent was waived because this is a retrospective study.

MRI of the head and neck was performed on a 1.5 T MR machine (Symphony; Siemens AG Medical Systems, Forchheim, Germany) using a head circular polarization surface coil. All patients underwent T_1 weighted images [repetition time (TR) of 800 ms; echo time (TE) of 15 ms] and T_2 weighted fast spin-echo images (TR/TE of 4500/80 ms) with a section thickness of 5 mm, an interslice gap of 1–2 mm, a field of view (FOV) of 25×20 cm and an acquisition matrix of 256×256 . The images were obtained in the transverse plane.

Diffusion-weighted MR images were obtained using a multislice spin-echo planar imaging sequence. The imaging parameters were TR/TE of 1000/108 ms, FOV of 25×20 cm, an acquisition matrix of 256×128 and section thickness of 5 mm, with an interslice gap of 1–2 mm. Diffusion-probing gradients were applied in the three orthogonal directions (x , y and z) with the same strength. Diffusion-weighted MR images were acquired with diffusion-weighted factor b -values of $0 \text{ mm}^2 \text{ s}^{-1}$, $500 \text{ mm}^2 \text{ s}^{-1}$ and $1000 \text{ mm}^2 \text{ s}^{-1}$. After application of the diffusion-weighted sequence, we obtained a set of images corresponding to each b -value applied. The ADC map was automatically calculated by commercially available software (Leonardo, v. 2.0; Siemens AG Medical systems, Forchheim, Germany). The data acquisition time for the diffusion-weighted MR images was 1 min. Finally, enhanced fat-suppressed T_1 weighted images (TR/TE of 800/15 ms) were obtained after an intravenous bolus injection of 0.1 ml kg^{-1} of body weight of gadopentate dimeglumine (Magnevist; Bayer HealthCare Pharmaceuticals, Wayne, NJ) in all patients.

Image analysis was performed by one radiologist (AAR) with 20 years of experience in head and neck imaging. A region of interest (ROI) was drawn on the ADC map using the electronic cursor around the margin of the solid part in the lesion, avoiding the cystic parts as far as possible because it could give falsely elevated ADC values. The ADC value of the lesion was automatically calculated in $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$.

The description of data was done in the form of mean and standard deviation. The Kolmogorov–Smirnov test was done for diagnosis normality of data distribution. All data were revealed to be parametric with normal distribution. The analysis of data was done to test statistically significant differences between malignant tumours and infection of the masticator space. To compare between the two groups, Student's t -test was used. To compare between more than two groups, one-way analysis of variance test was used. Receiver operating characteristic (ROC) curve was used to determine the cut-off point with highest accuracy that was used to differentiate masticator space malignancy from infection. The $p \leq 0.05$ was considered significant at 95% confidence interval. The statistical analysis of data was done using SPSS® v. 10 (SPSS Inc., Chicago, IL).

Results

The final diagnosis of masticator space lesions were as follows: malignant tumours, $n = 34$; infections, $n = 15$. The mean ADC value of malignant tumours (Figure 1) was $0.91 \pm 0.21 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ and of infection (Figure 2) was $1.59 \pm 0.32 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$. There was a statistically significant difference in the ADC values between the malignant tumours and infections ($p = 0.001$). Table 1 and Figure 3 show the mean and standard deviations of ADC value of malignant tumours and infection of the masticator space. Figure 4 shows the ADC values of each lesion of malignant tumours and infection of the masticator space. When an ADC value of $1.2 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ was used as a threshold value for differentiating malignant tumours from masticator space infection, the best result was obtained with an accuracy of 88%, sensitivity of 88%, specificity of 87%, negative predictive value of 94%, positive predictive value of 86% and area under the curve of 0.92 (Figure 5).

The malignant tumours of masticator space were rhabdomyosarcoma ($n = 9$), non-Hodgkin lymphoma ($n = 4$), Ewing sarcoma ($n = 2$), synovial sarcoma ($n = 2$), fibrosarcoma ($n = 2$), undifferentiated sarcoma ($n = 1$), granulocytic sarcoma ($n = 1$), malignant fibrous histiocytoma ($n = 1$), haemangiopericytoma ($n = 1$), squamous cell carcinoma ($n = 8$) and nasopharyngeal carcinoma ($n = 3$). The mean ADC value of malignant tumours was $0.91 \pm 0.21 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$. The lowest ADC value ($0.55 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) of malignancy was detected in patients with non-Hodgkin lymphomas. Squamous cell carcinoma of the oral cavity ($n = 5$) and retromolar region ($n = 3$), and nasopharyngeal carcinoma ($n = 3$), were extended into the masticator space. There was significant difference ($p = 0.001$) in the ADC value between squamous cell carcinoma ($1.14 \pm 11 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) and non-Hodgkin lymphoma ($0.59 \pm 0.04 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$). There was significant difference ($p = 0.001$) in the ADC value between squamous cell carcinoma and soft tissue sarcomas. Also, there was significant difference in the ADC value of nasopharyngeal

Figure 1 Rhabdomyosarcoma of the masticator space. (a) Axial contrast T_1 weighted image shows large ill-defined infiltrative and intense enhancing mass involving the left masticator space. (b) Apparent diffusion coefficient (ADC) map shows restricted diffusion of the masticator mass with low ADC value ($0.83 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)

carcinoma and soft tissue sarcomas ($p = 0.001$). There was no significant difference in the ADC value within different types of sarcomas ($p = 0.08$).

The mean ADC value of infection of masticator space was $1.59 \pm 0.32 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$. The inflammatory lesions of the masticator space were extending from odontogenic infection ($n = 8$), necrotizing otitis externa ($n = 5$) and invasive fungal infection with skull base osteomyelitis ($n = 2$). The odontogenic infection and necrotizing otitis externa were due to bacterial infection. There was no significant difference in the ADC value between masticator infection due to odontogenic infection and that due to necrotizing otitis externa

($p = 0.09$). The lowest ADC value of masticator space infection was seen in two patients with invasive fungal infection that showed restricted diffusion with a low ADC value ($0.57 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) on the ADC map. Patients with invasive fungal infection were misdiagnosed as malignant tumour. There was significant difference in the ADC value between bacterial and fungal infections of the masticator space ($p = 0.001$).

Discussion

The most common masticator space lesions are odontogenic infection, whereas masticator space tumours are

Figure 2 Necrotizing otitis externa with extension of infection into masticator space. (a) Axial contrast T_1 weighted image shows an ill-defined infiltrative lesion involving the right masticator space. (b) Apparent diffusion coefficient (ADC) map shows unrestricted diffusion of the lesion in the masticator space with high ADC value ($1.74 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)

Table 1 Mean and standard deviation (range) of the ADC value ($10^{-3} \text{ mm}^2 \text{ s}^{-1}$) of malignant tumours and infection of masticator space

Pathology	ADC value
Malignant tumours ($n = 34$) ^a	0.91 ± 0.21 (0.55–1.25)
Rhabdomyosarcoma ($n = 9$)	0.77 ± 0.10 (0.66–0.91)
Non-Hodgkin lymphoma ($n = 4$)	0.59 ± 0.04 (0.55–0.65)
Ewing sarcoma ($n = 2$)	0.78 ± 0.08 (0.72–0.84)
Synovial sarcoma ($n = 2$)	0.94 ± 0.07 (0.94–0.95)
Fibrosarcoma ($n = 2$)	0.89 ± 0.07 (0.84–0.95)
Undifferentiated sarcoma ($n = 1$)	0.83
Granulocytic sarcoma ($n = 1$)	0.97
Malignant fibrous histiocytoma ($n = 1$)	0.99
Haemangiopericytoma ($n = 1$)	0.93
Squamous cell carcinoma ($n = 8$)	1.14 ± 0.11 (0.97–1.25)
Nasopharyngeal carcinoma ($n = 3$)	1.16 ± 0.07 (1.07–1.21)
Infection ($n = 15$) ^b	1.59 ± 0.32 (0.75–1.87)
Odontogenic infection ($n = 8$)	1.67 ± 0.14 (1.44–1.87)
Necrotizing otitis externa ($n = 5$)	1.76 ± 0.08 (1.65–1.85)
Invasive fungal infection ($n = 2$)	0.87 ± 0.16 (0.75–0.98)

ADC, apparent diffusion coefficient.

^aSignificant difference ($p = 0.001$) in ADC value between malignancy and infection. Significant difference ($p = 0.001$) in ADC value between squamous cell carcinoma and soft tissue sarcomas.^bSignificant difference ($p = 0.001$) in ADC value between bacterial and fungal infections.

rare. Patients with masticator space lesions complain of pain, swelling and trismus. They may not be able to open their mouths and the physical examination is, therefore, rather limited. Both CT and MRI are accurate to detect extent of lesion, but they may not be able to differentiate malignant tumours from infection in some cases.^{1–5} Only one study discusses the role of diffusion-weighted MRI of masticator space.¹⁶ The authors of that study reported that the ADC value of

benign lesions was significantly higher than that of malignancy, but they were unable to detect significant difference in the ADC value between inflammatory lesions and malignancy.¹⁶ They added that a high ADC value potentially indicates benign lesions, and a low ADC value indicates malignancy.¹⁶

A few limited studies have been done to differentiate head and neck malignancy from infection with ADC.^{13–15} Diffusion-weighted MRI has been used in differentiation of inflammatory pseudotumour of the orbit from orbital lymphoma and abscess.¹³ Ozgen *et al*¹⁴ reported that the ADC value could differentiate skull base osteomyelitis from nasopharyngeal carcinoma and lymphoma. Sasaki *et al*¹⁵ added that diffusion-weighted MRI could differentiate inflammatory from neoplastic lesions of the paranasal sinuses. The diffusion characteristics of the tissue depend on its microstructure (its cellularity, nucleus:cytoplasm ratio, nature of the extracellular matrix, and so forth).^{10–18}

In this study, the ADC value of masticator space inflammatory lesions was significantly higher than that of malignancy. This was attributed to the fact that malignant tumours show hypercellularity, with a high ratio of intracellular water to extracellular water and restricted diffusion, while inflammatory lesions are usually associated with a low ratio of intracellular water to extracellular water and unrestricted diffusion.^{8–11,15} This is different from the study of Wang *et al*¹⁶, who reported that there is no significant difference in the ADC value between inflammatory and malignant masticator space lesions. The difference in both series may be due to different pathology of patient groups as

Figure 3 Scatter plot of apparent diffusion coefficient (ADC) value of masticator space malignancy and infection. The mean ADC value of masticator space malignancy ($0.91 \pm 0.21 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) was significantly lower ($p = 0.001$) than that of infection ($1.59 \pm 0.32 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)

Figure 4 Scatter plot of the apparent diffusion coefficient (ADC) value of each lesion of masticator space malignancy and infection. Lesions: 1, rhabdomyosarcoma; 2, non-Hodgkin lymphoma; 3, Ewing sarcoma; 4, synovial sarcoma; 5, fibrosarcoma; 6, other malignant; 7, squamous cell carcinoma; 8, nasopharyngeal carcinoma; 9, odontogenic infection; 10, necrotizing otitis externa; 11, invasive fungal infection

well as different data acquisitions. In this work, we applied three b -values to calculate the ADC value, while Wang *et al*¹⁶ used only two b -values.

Figure 5 Receiver operating characteristic (ROC) curve. The cut-off value of the apparent diffusion coefficient (ADC) value used for differentiation of masticator space malignancy from infection is $1.20 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ with an accuracy of 88%, sensitivity of 88%, specificity of 87%, negative predictive value of 94%, positive predictive value of 86% and area under the curve of 0.92

Differentiation between tumours arising *de novo* and those extending into the masticator space is important for prognosis and treatment planning.^{16–19} Primary *de novo* malignant tumours of the masticator space are most frequently sarcomas, as the main constituent of the space is muscle, while tumours extending from the surrounding structures are mostly squamous cell carcinomas of the oral cavity and nasopharyngeal carcinoma.^{17–19} Diffusion MRI may further demonstrate specific diffusion parameters related to the histopathological characteristics of the lesions. It has been shown that the ADC value is significantly lower in lymphoma than in nasopharyngeal carcinoma.^{8–10} In this study, the ADC values of nasopharyngeal carcinoma and oral squamous cell carcinoma that extend into masticator space were significantly higher than those of non-Hodgkin lymphoma and other soft tissue sarcomas arising *de novo* from the masticator space. This was attributed to soft tissue sarcoma and non-Hodgkin lymphoma being more cellular and with more compact cells than squamous cell carcinoma.^{8,10,15}

Masticator space infections may be due to odontogenic infection. Also, they arise from the spread of an ear infection called necrotizing otitis externa. The causative organism is the *Pseudomonas* bacterium in diabetic or immunocompromized patients.^{20–23} In this study, bacterial infection of masticator space in patients with necrotizing otitis externa and odontogenic infection showed unrestricted diffusion with a high ADC value. Normally, inflammation causes an increase in the extracellular water, resulting in an increase in the ADC values. The ADC value of inflammatory lesions varies

across different studies. The mean ADC value of inflammation was $1.47 \pm 0.18 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ in patients with skull base osteomyelitis,¹⁴ and it was $2.76 \pm 0.32 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ in patients with inflammation of the head and neck.²⁴ This difference may be related to the characteristics of the magnet and the stage of inflammation (either acute or chronic), and skull base inflammatory lesions do not contain fluids similar to those found in soft tissue inflammation.

In this work, two patients with fungal infection of the skull base with extension into the masticator space were misdiagnosed as malignancy. This is attributed to the fact that fungal infections had significantly smaller overall ADC values and greater percentages of total tumour areas with extremely low or low ADCs among the inflammatory and benign lesions.¹⁵ Diffusion-weighted MRI has some limitations in differentiation of malignant from benign tumours of the head and neck.^{8–11} The final distinction between benign and

malignant parotid gland tumours based on ADCs was not possible, owing to an overlap between values for Warthin's tumour and malignancy.²⁵

There are few limitations of this study. First, this study was limited by the heterogeneity of pathological types of masticator space in adult and children. Further studies are recommended to be done at a large scale on certain pathological lesions in adults or children. Second, we excluded three patients owing to motion and susceptibility artefacts, and we expect that future studies with application of parallel imaging will increase image contrast and decrease susceptibility artefacts. Third, there was potential bias related to ROI selection, as well as the presence of associated tumour necrosis. Application of new post-processing methods such as non-Gaussian (diffusion kurtosis) modelling or *k*-means clustering algorithms may provide a better characterization of different components of the tumour compared with the whole-lesion mean ADC value.^{9,26,27}

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