Apparent diffusion coefficients of benign and malignant salivary gland tumors. Comparison to histopathological findings

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KEYWORDS
Salivary gland; Tumor; Magnetic resonance imaging; Diffusion imaging; Apparent diffusion coefficient

Abstract
Objective. — To evaluate the apparent diffusion coefficient (ADC) of benign and malignant salivary gland tumors in comparison to histopathological findings.

Materials and methods. — This study included 32 patients with a wide spectrum of major salivary gland tumors (17 benign, 15 malignant). Diffusion-weighted imaging (DWI) and ADC measurements were performed in all patients. The degrees of extracellular components (myxoid and chondroid matrices, microcysts and hyalinization), were histopathologically classified as mild, moderate and conspicuous. Comparisons were made of mean ADC values between benign and malignant tumors, and among tumors showing different degrees of extracellular components.

Results. — Mean ADC values were 1.09 ± 0.34 × 10⁻³ mm²/s in malignant salivary gland tumors and 1.40 ± 0.43 × 10⁻³ mm²/s in benign salivary gland tumors. No significant difference in mean ADC values was found between benign and malignant tumors (P > 0.05). However, mean ADC values increased with the degree of extracellular components. Mean ADC values were significantly different between mild and moderate degrees (P < 0.05) of extracellular components, and between mild and conspicuous degrees (P < 0.05), in both benign and malignant tumor groups.

Conclusion. — In this study, ADC values alone did not allow differentiation between benign and malignant salivary gland tumors. Comparison with histopathological findings suggests a correlation between the amount of extracellular components and mean ADC values in salivary gland tumors.

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MOTS CLÉS
Glande salivaire;

Résumé
Objectif. — Évaluer le coefficient de diffusion apparent (ADC) des tumeurs bénignes et malignes des glandes salivaires et comparer les résultats aux données histopathologiques.
Introduction

Diffusion-weighted imaging (DWI) is a technique for evaluating the rate of microscopic water diffusion within tissues. It has been used to evaluate tumors of the central nervous system [3,14]. Results of studies comparing the apparent diffusion coefficient (ADC) values and histopathological findings strongly suggest that greater cellularity is associated with more restricted diffusion [3,14]. More recently, it has been reported that DWI might be useful for characterizing of head and neck tumors, suggesting that malignant tumors have lower ADC values than benign tumors [10, 16,17]. Although results of these initial studies are promising, it remains uncertain if ADC values are useful to distinguish malignant from benign salivary gland tumors across a wide range of cases.

The histopathology of interstitial spaces in salivary gland tumors is somewhat peculiar compared with that of brain tumors. For example, myxoid and chondroid matrices are frequently found in some salivary gland tumors such as pleomorphic adenomas [15]. The stroma within adenoid cystic carcinomas is generally hyalinized and may present with mucinous or myxoid features [1]. These particular extracellular findings are rarely seen in brain tumors such as gliomas. We surmised that several histopathological conditions in extracellular spaces might influence the ADC values in salivary gland tumors. This study was intended to evaluate the ADC values of benign and malignant salivary gland tumors in comparison to histological findings.

Materials and methods

Subjects

Over a 56-month period, 413 consecutive patients with a head and neck tumor underwent magnetic resonance imaging (MRI) at our university hospital. This study used the following criteria for inclusion: 1) tumors were located in a major salivary gland (parotid, submandibular, sublingual); 2) tumor pathology was confirmed by biopsy or surgery; 3) MRI studies, including DWI, were performed before initiation of radiation or chemotherapy; 4) image quality was not degraded by the patient’s movements. Consequently, 32 patients representing a wide range of types of major salivary gland tumors (17 benign and 15 malignant) were included in this study. The patients with benign tumors included 10 women and seven men (32-79 years; mean age, 56 years); the patients with malignant tumors included six women and nine men (54-84 years; mean age, 68 years). The details of tumor classifications are shown in Table 1. Benign salivary gland tumors included 16 parotid gland tumors and one submandibular gland tumor; malignant salivary gland tumors included 9 parotid gland tumors, 5 submandibular gland tumors, and 1 sublingual tumor. The mean maximum diameters of the tumors on MRI were 31 ± 7.8 mm (22-50 mm) for benign salivary gland tumors and 39 ± 14 mm (20-68 mm) for malignant tumors.

MRI methods

For this study, MRI was performed using a 1.5-T MRI system. All patients underwent conventional MRI. An axial T1-weighted spin-echo sequence [516/9 (repetition time in ms/echo time in ms)] and an axial T2-weighted fast spin-echo sequence (3200/84, echo train length 8), with and without fat suppression, were used with a matrix of 256 × 224, a field of view of 20 × 20 to 22 × 22 cm, a section thickness of 5 mm with a between-section gap of 1 mm and three signal acquisitions.

For this study, DWI was performed using line-scan DWI (LSDWI). These LSDWI studies were conducted within the guidelines of the research committee of our institution. Informed consent was obtained from patients or their authorized representatives. The LSDWI method has been described elsewhere [6-8,11]. Neither cardiac gating nor respiratory triggering was employed in LSDWI, and no anti-susceptibility devices on the neck were used to reduce susceptibility artifacts. The LSDWI images were acquired using
the following scan parameters: TR = 2376-3124 ms, TE = 57.1-70.7 ms, one excitation, field of view of 20 × 20 to 22 × 22 cm and a matrix of 128 × 128. The effective section thickness was set to 5 mm with a between-section gap of 1 mm. The LSDWI images were obtained with two different b values, with the maximum b value applied along three orthogonal directions: one with a low diffusion weighting (b factor) of 5 s/mm² and the other with a high (maximum) b factor of 1000 s/mm². The scan time per slice was 30-45 s, and three to five slices were obtained in the axial plane according to the lesion size. Subsequently, spin-echo T1-weighted images (516/9) and/or gradient-echo T1-weighted fat-suppression images (130/3, flip angle 80) were obtained, following the intravenous injection of contrast media.

Data analysis

Isotropic diffusion images with a b factor of 1000 s/mm² were generated from the three diffusion directions assessed. Trace ADC maps were generated using the equation described by Stejskal and Tanner [13], \( S = S_0 e^{-bADC} \), where b is the diffusion weighting factor, S is the signal intensity of the diffusion trace for b = maximum, and \( S_0 \) is the signal intensity for \( b = 5 \) s/mm². The ADC value measurements were obtained from the trace ADC maps, and a region of interest (ROI) was placed over each tumor. An area that was 80 mm² or greater from each ROI was included in the computation. For ROI measurement of tumors, special care was taken to include the solid-looking areas of the tumors and to exclude obviously necrotic or cystic regions, as detected in the corresponding T2-weighted and contrast-enhanced MRIs. The ADC values are expressed in this report as mean ± S.D.

Histopathological evaluation was performed using biopsy or surgical specimens. An experienced histopathologist was asked to assess the tumor samples in terms of extracellular components, including myxoid and chondroid matrices, microcysts and hyalinization. The amounts of these extracellular components were classified as mild, moderate or conspicuous, with mild corresponding to a ratio of extracellular component to tumor areas of less than 0.2, moderate corresponding to a ratio of 0.2-0.6 and conspicuous corresponding to a ratio of more than 0.6.

The Mann-Whitney U-test was used to detect significant differences in mean ADC values in benign and malignant salivary gland tumors, and among the different classifications of extracellular component degrees. A P value less than 0.05 was considered to indicate a statistically significant finding.

### Results

#### ADC values of salivary gland tumors

The use of LSDWI yielded excellent diagnostic images and permitted ADC values to be measured without susceptibility artifacts (Figs. 1-4). Details of mean ADC values of each salivary gland tumor are summarized in Table 1. Overall, the mean ADC values were 1.09 ± 0.34 × 10⁻³ mm²/s for malignant salivary gland tumors, and 1.40 ± 0.43 × 10⁻³ mm²/s for benign salivary gland tumors. Considerable overlap in ADC values was seen between benign and malignant salivary gland tumors (Fig. 5), with no significant difference between the two types of tumors (P > 0.05).

Of the benign salivary gland tumors, the mean ADC values for pleomorphic adenoma (n = 12) and for neurofibroma (n = 1) were greater than 1.5 × 10⁻³ mm²/s, whereas the mean ADC value for Warthin’s tumors (n = 4) was 0.89 ± 0.18 × 10⁻³ mm²/s. The mean ADC value was significantly lower for Warthin’s tumor than for either pleomorphic adenoma or neurofibroma (P < 0.05).

The ADC values among malignant salivary gland tumors ranged from 0.68 × 10⁻³ to 1.87 × 10⁻³ mm²/s. The mean ADC values for adenoid cystic carcinoma (n = 4) and for myxoid liposarcoma (n = 1) were greater than 1.4 × 10⁻³ mm²/s and, for the remaining malignant tumors, no more than 1.00 × 10⁻³ mm²/s. The respective mean ADC values for the former malignant tumors and the latter group were significantly different (P < 0.01).

The mean ADC value for Warthin’s tumors was particularly low (mean 0.89 × 10⁻³ mm²/s) among those of benign tumors, but no significant difference was found between mean ADC values for Warthin’s tumors and malignant tumors (P = 0.25).

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**Table 1** Benign and malignant salivary gland tumors and ADC values

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>ADC (×10⁻³ mm²/s)</th>
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</thead>
<tbody>
<tr>
<td><strong>Benign (n = 17)</strong></td>
<td></td>
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<tr>
<td>Pleomorphic adenoma (n = 12)</td>
<td>1.54 ± 0.35</td>
</tr>
<tr>
<td>Warthin’s tumor (n = 4)</td>
<td>0.89 ± 0.18</td>
</tr>
<tr>
<td>Neurofibroma (n = 1)</td>
<td>1.91</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma (n = 4)</td>
<td>1.41 ± 0.13</td>
</tr>
<tr>
<td>Malignant lymphoma (n = 2)</td>
<td>0.72 ± 0.05</td>
</tr>
<tr>
<td>Carcinoma ex pleomorphic adenoma (n = 2)</td>
<td>0.93 ± 0.19</td>
</tr>
<tr>
<td>Myoepithelial carcinoma (n = 1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma (n = 1)</td>
<td>0.91</td>
</tr>
<tr>
<td>Squamous cell carcinoma (n = 1)</td>
<td>0.99</td>
</tr>
<tr>
<td>Undifferentiated carcinoma (n = 1)</td>
<td>0.80</td>
</tr>
<tr>
<td>Salivary duct carcinoma (n = 1)</td>
<td>0.88</td>
</tr>
<tr>
<td>Malignant melanoma (n = 1)</td>
<td>0.99</td>
</tr>
<tr>
<td>Myxoid liposarcoma (n = 1)</td>
<td>1.87</td>
</tr>
</tbody>
</table>

**Malignant (n = 15)**

<table>
<thead>
<tr>
<th>Histopathology</th>
<th>ADC (×10⁻³ mm²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myxoid liposarcoma</td>
<td>1.54 ± 0.35</td>
</tr>
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<td>Myxoid liposarcoma</td>
<td>1.87</td>
</tr>
</tbody>
</table>

Note: Data are mean ± S.D.
Details of the amounts of myxoid and chondroid matrices, microcysts and hyalinization, and their corresponding ADC values, are presented in Table 2. For both benign and malignant salivary gland tumors, mean ADC values were higher, the greater the degree of severity of extracellular components. Mean ADC values were significantly different between the mild and moderate classifications ($P < 0.05$), and between the mild and conspicuous classifications ($P < 0.05$), in both benign and malignant tumors, whereas no significant difference was found between mean ADC values for moderate and conspicuous classifications (benign, $P = 0.30$; malignant, $P = 0.17$).

Discussion

It is important to determine whether a salivary gland tumor is benign or malignant. To this end, MRI screening is a powerful tool for determining the morphology and extent of head and neck tumors as well as their relationship to adjacent normal structures, prior to surgery. However, conventional MRI cannot yield a clear distinction between benign and malignant salivary gland tumors [2,5,12,15]. Nevertheless, salivary gland tumors can be diagnosed by fine-needle aspiration cytology. This minimally invasive method can be used to diagnose a tumor, but it entails the risk of tumor spillage and possibly inconclusive results because of an insufficient sample for histopathological ana-
lyses. For that reason, preoperative imaging methods have an important role in the evaluation of tumor characteristics.

The DWI studies and ADC measurements provide useful information regarding tumor cellularity: an inverse correlation between tumor cellularity and ADC values has been reported for brain tumors [3,14]. Sugahara et al. [14] reported that the minimum ADC values showed an inverse relationship with histological cellularity in gliomas. Guo et al. [3] also reported a clear inverse relationship between ADC values and cellularity of brain tumors such as lymphomas and high-grade astrocytomas. Their findings suggest that greater cellularity is associated with more restricted diffusion. However, ADC values could be affected not only by cellularity, but also by the characteristics of the extracellular components.

Several salivary gland tumors are histopathologically unique in terms of extracellular substances compared with brain tumors such as gliomas. For example, pleomorphic adenomas frequently exhibit myxoid and/or chondroid matrices [15], which is rarely seen in brain tumors. The findings for neurofibroma and chondrosarcoma in the present study are consistent with that. These salivary gland tumors contain abundant free water in myxoid and/or chondroid matrices. For that reason, this particular pathological finding in salivary gland tumors appears to be related to ADC values.

In our present results, tumors with myxoid and/or chondroid matrices included pleomorphic adenoma, neurofibroma and myxoid liposarcoma, all of which showed higher ADC values. Mean ADC values for these cases were greater than $1.5 \times 10^{-3}$ mm$^2$/s. Motoori et al. [10] reported that higher ADC values in pleomorphic adenoma are probably attributable to an abundance of myxoid and/or chondroid matrices. Our results for ADC values and histopathological analyses are consistent with their results. Adenoid cystic
There is a considerable overlap in ADC values between the two groups. No significant difference is evident between the two ($P > 0.05$).

Figure 5: Scatter plot of ADC values for benign ($n = 17$) and malignant ($n = 15$) salivary gland tumors.

Table 2: ADC values of tumors versus degree of extracellular components

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Mild</th>
<th>Moderate</th>
<th>Conspicuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>$0.95 \pm 0.21^a$</td>
<td>$1.51 \pm 0.42$</td>
<td>$1.67 \pm 0.27$</td>
</tr>
<tr>
<td>Malignant</td>
<td>$0.86 \pm 0.11^a$</td>
<td>$1.25 \pm 0.20$</td>
<td>$1.61 \pm 0.22$</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± S.D.

* ADC values significantly differ between mild and moderate, and mild and conspicuous ($P < 0.05$).

Adenoid cystic carcinoma showed higher ADC values than other malignant tumors, except for myxoid liposarcoma. Adenoid cystic carcinoma also showed an abundance of extracellular matrix composed of mucinous, myxoid or hyalinized material (Fig. 3). These extracellular components also appear to be rich in free water, resulting in a higher ADC value. On the basis of the ADC values for salivary gland tumors versus degrees of extracellular substances, the moderate and conspicuous classifications showed significantly higher ADC values than the mild classification. For this reason, we infer that extracellular components significantly influence diffusion in salivary gland tumors.

Warthin’s tumor has generally been regarded as the second most common benign tumor of the parotid gland, after pleomorphic adenoma. MRI features of Warthin’s tumor are described as mimicking a malignant neoplasm [9]. Ikeda et al. [4] reported that the mean ADC value of 19 Warthin’s tumors ($0.96 \pm 0.13 \times 10^{-3} \text{ mm}^2/\text{s}$) was significantly lower than that of 17 malignant parotid tumors ($1.19 \pm 0.19 \times 10^{-3} \text{ mm}^2/\text{s}$) on echo-planar DWI. The mean ADC values in the present study, including four Warthin’s tumors ($0.89 \pm 0.18 \times 10^{-3} \text{ mm}^2/\text{s}$) and 15 malignant salivary gland tumors ($1.09 \pm 0.34 \times 10^{-3} \text{ mm}^2/\text{s}$), were similar to those obtained by Ikeda et al. However, no significant difference was evident between these two groups in our results ($P = 0.25$), probably because of the small number of Warthin’s tumors in our study.

It is interesting that Warthin’s tumors show low ADC values that can overlap with those of malignant tumors. We speculate that a hypercellular stroma or matrix composed of dense lymphoid tissue contributes to the low ADC value for Warthin’s tumors because this would reduce the extracellular spaces (Fig. 2d). Therefore, different types of extracellular stroma or matrix can decrease ADC values in these tumors, but not a myxoid matrix, microcysts or hyalinization.

Previous studies have suggested that the mean ADC values of benign solid lesions are significantly higher than those of malignant tumors of the head and neck [16,17]. Those studies concluded that ADC values might provide useful in the differential diagnosis of benign and malignant head and neck lesions. However, those studies included lesions from a diversity of anatomical locations as well as a variety of histopathologies, including benign lesions such as mucoceles and polyps [16,17]. In general, it is easy to diagnose such benign lesions correctly without the aid of ADC measurements.

In contrast to the results of those earlier reports, ours suggest that ADC values alone might not be sufficient to allow differentiation between malignant and benign tumors. In our study, the considerable overlap between the two groups is, for the most part, attributable to the lower ADC values for Warthin’s tumor compared with other benign tumors, and higher ADC values for adenoid cystic carcinoma compared with other malignant tumors. These results suggest that special care needs to be taken when characterizing these two particular salivary gland tumors using ADC values.

We used LSDWI to investigate the ADC values of salivary gland tumors. The use of LSDWI has the advantage of providing excellent DWI images and, thus, exact data for ADC values in the head and neck. Unlike single-shot echo-planar DWI, with LSDWI, susceptibility-related image distortions, and signal loss caused by proximate dental work and circumjacent air and bone are minimal [6-8,11]. Therefore, we believe that LSDWI is a more suitable method for evaluation of ADC in head and neck lesions.

This study has several limitations, one of which is the small number of participating patients and, therefore, only a small number of different types of benign and malignant tumors. For this reason, the study is only preliminary. Further studies of a larger scale need to be carried out, with a wider range of types of tumor to verify the results of this preliminary study. Another drawback is that our histopathological analyses were performed on small specimens, which means that the amount of extracellular components may not necessarily be an accurate representation of the ADC values determined by the ROI measurements taken of the entire solid mass. Nevertheless, and despite these limitations, our results suggest that the degree of extracellular components has an influence upon ADC values.

In conclusion, a considerable overlap of ADC values was found in our study between benign and malignant salivary...
gland tumors. ADC values alone may not contribute to a differential diagnosis between the two types of tumors. Comparison with histopathological findings suggests a correlation between the degree of extracellular components and ADC values in salivary gland tumors.

References


