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MRI in differentiation of benign and malignant tongue tumors

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1. ABSTRACT

The differential diagnosis of benign and malignant tongue tumors is crucial to treatment and prognosis. Magnetic resonance imaging (MRI) is the preferred modality for the evaluation of tongue carcinomas. Dynamic contrast-enhanced (DCE)-MRI can reflect the density, integrity, and leakiness of tumor vasculature, and the time-intensity curve (TIC) patterns derived from DCE-MRI results can differentiate benign from malignant tumors based on differences in vascular structure. Diffusion-weighted (DW)-MRI is based on the random thermal motion of water molecules and can provide information on the cellular and tissue microstructure of the tumor. A low apparent diffusion coefficient (ADC) derived from DW-MRIs may indicate a malignant tumor. Thus, ADC values and TIC parameters yield complementary information on tumors that may improve diagnostic accuracy. Indeed, the combination of DCE-MRI and DW-MRI is a comprehensive reflection of the pathological status of the tongue tumor, so utilization of these MRI modalities may facilitate the diagnostic differentiation of benign from malignant tumors of the tongue.

2. INTRODUCTION

Tongue cancer is the most common intra-oral malignancy. It accounts for nearly 30% of all oral cancers and is usually seen in men aged 50–60 years old (1-3). The vast majority of tongue malignancies (>95%) are squamous cell carcinomas (SCC) (4,5). There has been an increase in the incidence of tongue SCC and associated mortality over recent decades in both Europe and the United States (5-7). In spite of advances in cancer therapy, the 5-year survival rate of tongue SCC patients has remained relatively constant at approximately 50% in developed countries since the early 1970s (4,5). The tumor-node-metastasis (TNM) stage at which the disease is diagnosed is the single most important predictor of survival (4). Thus, early diagnosis of tongue tumors, especially differential diagnosis of malignant from benign tumors, is crucial for treatment and prognosis.

Pathological biopsy is a minimally invasive procedure used for preoperative diagnosis of tongue tumors. However, poor biopsy specimens are sometimes obtained and the pathology results are not always conclusive (8). Therefore, preoperative imaging plays an important role in treatment selection and surgical planning. Static magnetic resonance imaging (MRI) has been used extensively for the diagnosis of tumors of the oral and maxillofacial region, and is the preferred method to examine tongue tumors because the abnormal signals on MRI are well correlated with pathological findings (9). In addition, sagittal MR images can show manifestations of tongue base involvement and pharyngeal infiltration range that cannot be seen on CT.

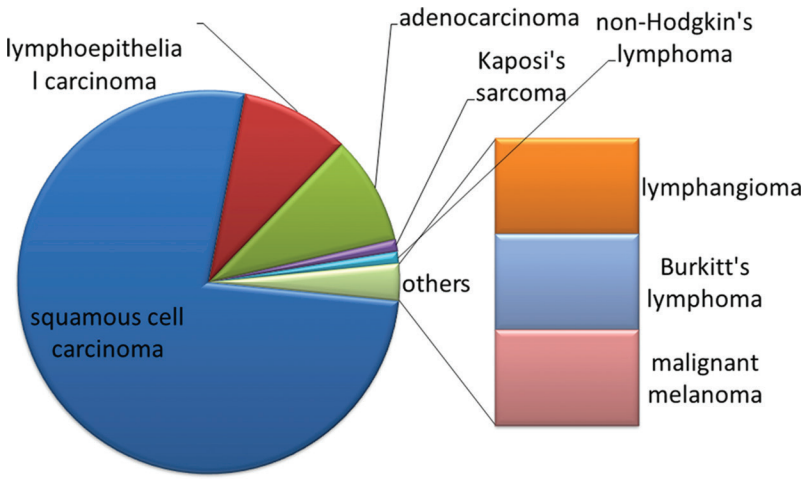

Figure 1. The histopathological types of malignant tongue tumors. The most common type of malignant tongue tumor is squamous cell carcinoma, less types are lymphoepithelial carcinoma and adenocarcinoma. Kaposi's sarcoma, non-Hodgkin's lymphoma, lymphangioma, Burkitt's lymphoma, and malignant melanoma also account for tongue tumors, while they are all statistically uncommon.

Herein, we review recent findings on malignant and benign tumors of the tongue and recent developments in MRI imaging that may allow for the differential diagnosis of benign and malignant tongue tumors.

3. BENIGN TONGUE TUMOR

A benign tongue tumor is an abnormal new growth on the tongue that is unlikely to spread to other parts of the body. It usually occurs singly and grows slowly over 2–6 years. Benign lesions generally include vascular malformation, inflammatory mass, cyst, and pleomorphic adenoma. Vascular malformations are treated with sclerotherapy, laser, catheter embolization, or direct puncture (10-12). Local excision of the cyst mass or adenoma with safety margins is performed to treat these benign tumors (13,14).

4. MALIGNANT TONGUE TUMOR

The tongue is divided into two separate anatomical areas, the oral tongue and the base of the tongue. Oral tongue tumors tend to remain in the tongue, while tongue base tumors tend to spread with deep infiltration. The most common type of malignant tongue tumor is squamous cell carcinoma. Other histopathological types include lymphoepithelial carcinoma, adenocarcinoma in the minor salivary glands, Kaposi's sarcoma, non-Hodgkin's lymphoma, lymphangioma, Burkitt's lymphoma, and malignant melanoma, but these are all statistically uncommon (Figure 1).

Treatment of malignant tongue carcinoma generally involves surgery in combination with radiotherapy. Surgical treatment of tongue carcinoma requires extensive resection of the oropharynx that often lead to significant functional deficits (15, 16).

5. USE OF MRI FOR THE DIFFERENTIAL DIAGNOSIS OF BENIGN AND MALIGNANT TONGUE TUMORS

5.1. MRI in tumor diagnosis

Malignant tumors rely not only on passive diffusion of oxygen and nutrients from host blood vessels, but also on newly developed vasculature (angiogenesis) in order to survive or sustain high rates of proliferation. Vessels produced by angiogenesis associated with malignancies are leaky, fragile, and incompletely formed. In static MR images, malignant tumors are characterized by an irregular tumor margin, heterogenous signal intensity, infiltration into surrounding tissue, and low signal intensity on T2-weighted images. There are different views on the value of static MR imaging for the differentiation of benign from malignant tumors. Som and Biller (17) reported that malignant parotid tumors were commonly associated with poorly defined margins and low signal intensity on both T1- and T2-weighted images. Conversely, Freling concluded that tumor margin, homogeneity, and signal intensity are not discriminative factors that can accurately distinguish benign from malignant disease (18). Similarly, Teresi found that tumor

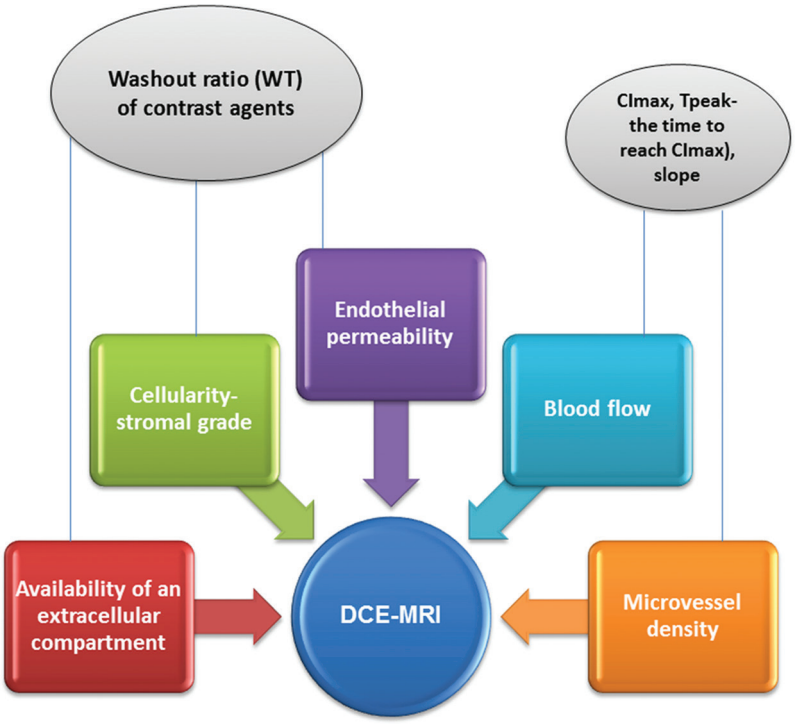

Figure 2. Parameters affect image patterns on DCE-MRI (dynamic contrast-enhanced magnetic resonance imaging). Image patterns on DCE-MRI are influenced by a large number of pathophysiologic variables, including microvessel density, blood flow, endothelial permeability, cellularity-stromal grade, and the availability of an extracellular compartment. Microvessel density and blood flow are closely related to the contrast index at maximum enhancement (CImax), the time to CImax (Tpeak-the time to reach CImax) and the slope. The endothelial permeability, cellularity-stromal grade, and availability of an extracellular compartment correlate with the washout ratio (WT) of contrast agents.

homogeneity is not a useful criterion to distinguish between benign and malignant tumors (19). Static MRI cannot distinguish between inflammatory disease and malignancy in some cases (18, 20).

5.2. Dynamic contrast-enhanced (DCE)-MRI for the differential diagnosis of tongue tumors

Dynamic contrast-enhanced (DCE)-MRI is an imaging modality that uses paramagnetic contrast enhancing agents to reveal the density, integrity, and leakiness of tumor vasculature. The parameters calculated from DCE-MRI are also used to assess the histological properties of the tumor (21). Many investigators have therefore attempted to identify the difference between benign and malignant tumors by vascular imaging in addition to grading the malignancy of tumors using DCE-MRI (22-26).

Image patterns on DCE-MRI are influenced by a large number of pathophysiologic variables, including microvessel density, blood flow, endothelial permeability, cellularity-stromal grade, and the availability of an extracellular compartment (21). Microvessel density and blood flow are closely related to the contrast index at maximum enhancement (CI_{max}), the time to CI_{max} (T_{peak}-the time to reach CImax) and the slope (24). The endothelial permeability, cellularity-stromal grade, and availability of an extracellular compartment correlate with the washout ratio (WT) of contrast agents (figure2). An extracellular compartment with fibrous stromata retains contrast agents for a longer time period (24, 27). Malignant tumors are generally associated with increased microvessel density, high vascularity, and cellularity. Therefore, rapid wash-in of contrast agents (as reflected by the slope and T_{peak}) with substantial peak contrast enhancement (CI_{max}) and persistent plateau on DCE-MRI may be more indicative of malignancy.

Time-intensity curve (TIC) parameters and vascular patterns derived from DCE-MRI results are crucial for the diagnosis of oral tumors. Asaumi *et al.* (22) found that the CI_{max}, time to

reach the CI_{max}, and TIC patterns were useful for the differentiation of malignant lymphomas from SCCs. Hisatomi *et al.* (23) and Yabuuchi *et al.* (24) reported that DEC-MRI parameters and TIC patterns aided in the differential diagnosis of salivary gland tumors based on the combined assessment of T_{peak}, CI_{max}, and WR. A WR of 30% enabled differentiation between malignancy and Warthin's tumor (23, 24). In tongue tumor, TIC parameters and patterns may allow for differential diagnosis of benign and malignant lesions, but this needs to be confirmed.

5.3. Diffusion-weighted (DW) MRI in differential diagnosis of tongue tumors

Diffusion-weighted (DW)-MRI is based on the random thermal motion of water molecules, termed Brownian motion. Differences in the translational diffusion of water molecules are quantified using apparent diffusion coefficients (ADCs) (28). These ADCs vary according to tissue microstructure, which is related to pathophysiological state, and are inversely correlated with tissue cellularity (28). Malignant tumors are associated with alterations in cellularity, cellular and nuclear contours, and with changes in the size and composition of the extracellular space. The use of DW-MRI to distinguish benign from malignant tumors or to grade malignancies has been reported (29-36).

DW-MRI and ADC measurement are a promising method for the differentiation of benign from malignant tongue tumors. Shrinivasan *et al.* (30) found that malignant lesions exhibited a significantly lower average ADC compared to benign lesions, and a threshold ADC value of $1.3.\times10^{-3}$ mm^2/s was used to distinguish benign from malignant head and neck lesions. Wang *et al.* (31) demonstrated that the mean ADCs of malignant lymphomas and carcinoma were significantly lower than that of benign tumors. In this case, an ADC value less than $1.2.2\times10^{-3}$ mm^2/s was used to predict malignancy. Diffusion-weighted MRI has also been utilized to assess metastatic lymph nodes and for the grading of malignancies. For example, the ADC of high-grade malignant lymphoma was significantly lower than that of SCCs (32, 33). Vandecaveye *et al.* (34) suggested that the ADC of malignant lymph nodes was significantly lower than that of benign lymph nodes, and used a threshold value of less than $0.8.5\times10^{-3}$ mm^2/s to distinguish the malignant from benign status of each lymph node. In contrast, Sumi *et al.* (35, 36) found that the ADC was significantly larger in metastatic lymph nodes than in benign lymphadenopathy. Thus, a low value of ADC could be used to differentiate malignant tongue tumors from benign lesions, but this requires experimental support as exceptions have been found.

The ADC values are ultimately dependent on changes in the diffusion of proton H in water. The diffusion of protons into and through tissues reflects diffusion of extracellular water, influx of extracellular water into cells across the cell membrane, the diffusion of intracellular water, and water efflux. Because water protons in each compartment contribute differently to the average diffusion of protons in tissue, ADC is highly dependent on the cytoarchitecture of the tissue, and malignant tumors have a distinct tissue microstructure compared to many benign growths. Thus, the signal intensity in DW-MRIs and derived ADCs vary with the pathophysiological status of the tissue. Malignant tumors are characterized by hypercellularity and enlarged nuclei, both of which act to reduce ADCs. Hypercellularity also reduces the extracellular matrix and diffusion space of the extracellular compartment (37, 38). Moreover, the larger and more angular nuclei in malignant tumors decrease the cytosolic dimensions, resulting in further reductions in ADC. Thus, the mean ADC values of malignant tumors are usually significantly lower than those of benign tumors. There are exceptions, however; exceptions that could lead to an improper diagnosis are ADC values from mucoepidermoid carcinoma and pleomorphic adenoma where the mobility of water protons is anomalous.

6. SUMMARY AND CONCLUSION

Dynamic contrast-enhanced MRI and DW-MRI each yield unique but complementary information on tumor microstructure and vascularity that may greatly facilitate the differential diagnosis of malignant and benign tumors of the tongue. Apparent diffusion coefficients from DW-MRI are particularly useful when differentiating benign tumors in which the DCE-MRI data exhibits a higher slope value more indicative of malignancy. In general, the analysis of TIC parameters derived from DCE-MRI results are extremely valuable for distinguishing a benign tumor with a low ADC value from a malignant tumor with a high ADC value. Therefore, the combination of DCE-MRI and DW-MRI hold the potential for improved diagnostic specificity and accuracy in the characterization of tongue tumors.

Furthermore, DCE-MRI provides hemodynamic information not provided by conventional MRI that could be applied to differentiate benign from malignant tumors. However, DCE-MRI provides no information on cellularity, mitosis, or atypia specific to tumor cells, important determinants for tumor categorization. In contrast, DW-MRI reveals tumor cellularity, mitosis, and nuclear contour differences by the molecular translational motion of water. Therefore, the combination of DCE- and DW-MRI provide complementary information to reveal both the vascular and cellular properties of tumors, and both provide important information complementary to the findings obtained through conventional spin echo MRI.

In conclusion, DCE- or DW-MRI may be useful MRI modalities for differentiating benign from malignant tumors of the tongue. The combination of DCE-MRI and DW-MRI provides a more comprehensive reflection of the pathological status of the tongue tumor, and so utilization of it may facilitate the diagnostic differentiation of benign from malignant tumors of the tongue.

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Abbreviations: MRI, Magnetic resonance imaging; CT, computed tomography; SCC, Squamous cell carcinoma; MDCT, All Multi detector

Key Words: Diffusion; Dynamic; enhancement; MRI, Tongue, Tumor, Review

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