Relationships between dynamic contrast-enhanced MRI findings and pattern of invasion for tongue carcinoma

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Abstract. The purpose of this study was to evaluate the effectiveness of dynamic contrast-enhanced MRI (DC-MRI) for assessing the pattern of invasion of tongue carcinomas. We studied 20 cases of squamous cell carcinoma of the tongue that showed peripheral enhancement patterns on DC-MRI. The diameter of each tumor was >2.0 cm and no apparent artifacts were seen. The signal enhancement to noise ratio (SE/N) of the regions of interest, which were located in the central and peripheral regions of the tumor, were measured using DC-MRI, while maximum SE/N, %-wash out, and the ascending rate of SE/N were also calculated. The histopathological pattern of invasion was assessed in each case and used to classify them into clear (13 cases) and diffuse (7 cases) groups, after which the 4 parameters were compared between the 2 groups. The ascending rate of SE/N in the peripheral region was significantly lower in the diffuse group (p=0.047). There were no other significant differences between the 2 groups for any parameter in either tumor region. These results suggest that DC-MRI is able to show the histopathological pattern of invasion into surrounding structures.

Introduction

Dynamic contrast-enhanced MRI (DC-MRI) is widely used in the field of oral and maxillofacial surgery, and we utilized it to assess the extension of tumors, including tongue carcinomas (1). We consider that DC-MRI findings may have a correlation to clinico-pathological features, while they are also useful for planning treatment and predicting prognosis for each patient, as well as determining the mode of invasion, including factors related to the tumor-host relationship, which is one of the most reliable histopathological indicators (2). Clinically, we perform DC-MRI before treatment, and analyze the relationships between each histopathological parameter and treatment outcome, as well as prognosis.

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In this study, we determined whether a relationship existed between the features of DC-MRI findings and the histopathological pattern of invasion of tongue carcinomas.

Patients and methods

Patients. Twenty patients with squamous cell carcinoma (Sq.C.C.) of the oral tongue were enrolled into this study (Table I). The patients underwent DC-MRI examinations before any other examinations or treatments, which included incisional biopsy, surgery, chemotherapy, and radiotherapy. The diameter of each carcinoma was >2.0 cm and no apparent artifacts were seen, including those associated with motion and susceptibility.

Analysis of histopathological features. All patients underwent an incisional or excisional biopsy after undergoing the DC-MRI examination. These specimens were fixed with paraffin, and stained with hematoxylin and eosin. According to the mode of invasion, which is one of the best indicators of tumor aggressiveness (2), the patients were divided into the clear group (grade 1, 2, and 3 mode of invasion) and diffuse group (grade 4 mode of invasion).

DC-MRI system and imaging protocol. The DC-MRI examinations were performed using a Signa (General Electric Medical Systems, Milwaukee, WI) scanner operating at 1.5 tesla, with a head coil diameter of 28 cm. All sequences were performed with a slice thickness of 5.0 mm and an intersection gap of 0-1.0 m, a 256x256 imaging matrix, and a field of view of 26 cm. T1 weighted spin echo images (SE-T1WI, TR/TE = 400-500/20), T2 weighted spin echo images (SE-T2WI, TR/TE = 2000/70), or fast SE-T2WI (TR/TE/ET = 4000/102/106-18) were obtained prior to performing DC-MRI. Thus, sagittal and axial T1WI, coronal and/or axial T2WI, and coronal DC-MR images followed by enhanced axial T1WI were obtained.

Imaging protocol and data analysis. Before performing DC-MRI (T1WI, TR/TE2 = 200/20), the location of the tumor was detected using axial and/or coronal T1WI and/or T2WI, and 4 coronal slices were taken, of which one of the slices included the largest dimension of the tumor. A paramagnetic contrast material, Gd-DTPA (Magnevist, Japan-Scheling, Osaka, Japan), was used at a total dose of 0.1 mmol/kg of body weight. After placement of a needle into an antecubital vein, the first image was taken as a precontrast image. Then

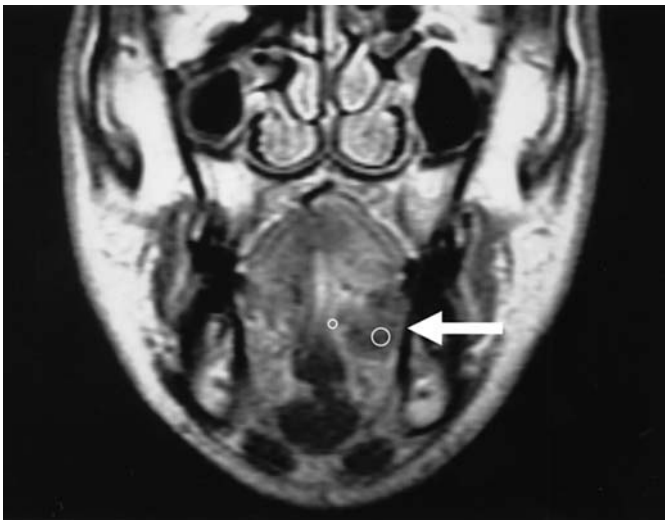


Figure 1. Region of interest (ROI). Arrow, tumor; large circle, superficial central area; small circle, deep peripheral area.

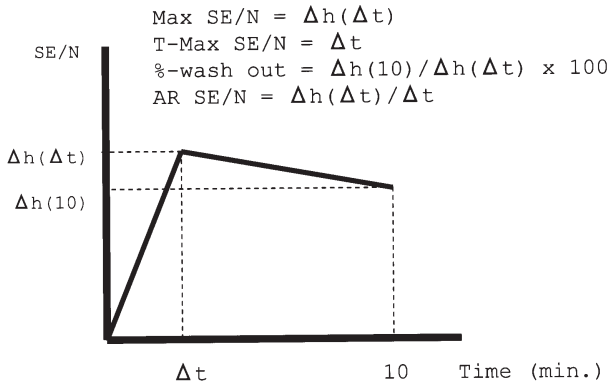
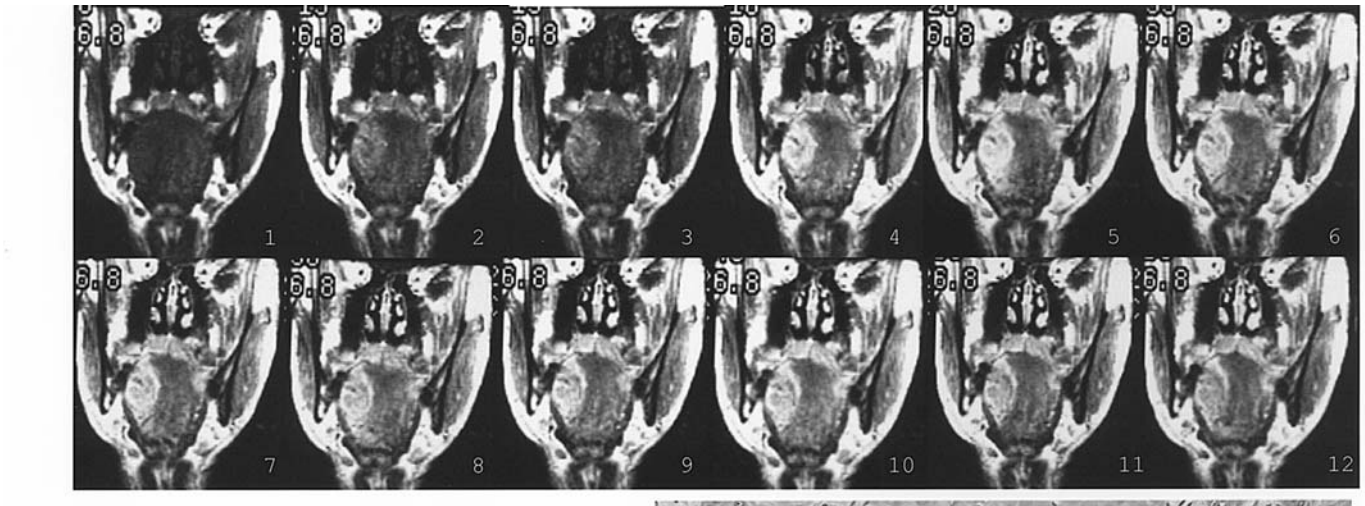
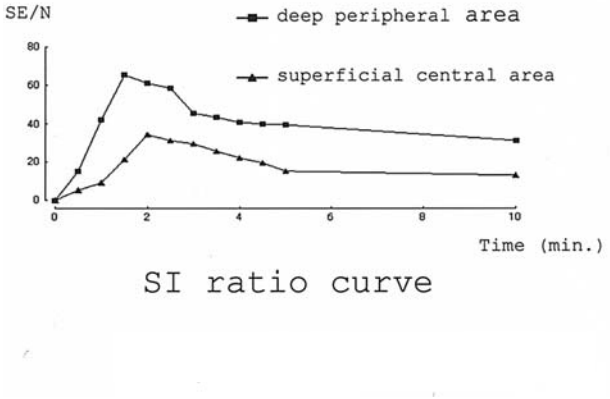


Figure 2. Signal enhancement to noise ratio (SI ratio) curve and definition of parameters.

the bolus injection of contrast material was started and at the same time serial images were taken 6-11 times. In addition, 10 min after injection of the contrast materials, the final image was obtained as a delayed image. Contrast material was administered as an intravenous injection within 15 sec. For a quantitative evaluation of DC-MRI, signal intensities were measured in the operator-defined region of interest (ROI) in the deep peripheral and superficial central area of the tumor, and in the image background (Fig. 1). The signal enhancement to noise ratio (SE/N) was calculated using the following





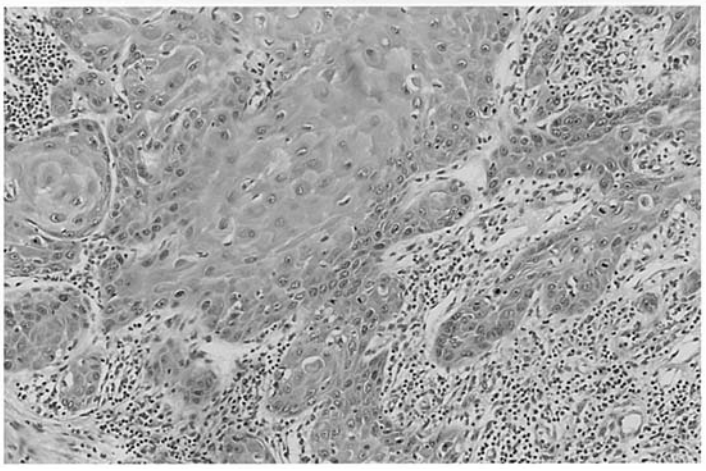


Figure 3. DC-MRI and histopathological features of the squamous cell carcinoma of the right lateral border of the tongue. Top: DC-MRI. 1, Precontrast image; 2-11, serial images (0.5-5.0 min); 12, delayed image (10 min). Bottom left: SI ratio curve. Max SE/N, deep peripheral area - 65.3 and superficial central area - 34.1; T-Max SE/N, deep peripheral area - 1.5 and superficial central area - 2.5; %-wash out, deep peripheral area - 47.8 and superficial central area - 36.4; AR SE/N, deep peripheral area - 43.5 and superficial central area - 17.1. Bottom right: histopathological examination of the patients showed grade 3 mode of invasion (hematoxylin and eosin stain x33).

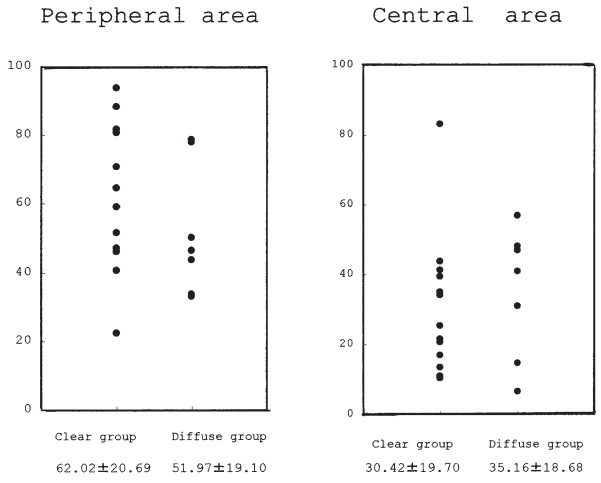


Figure 4. Maximum SE/N.

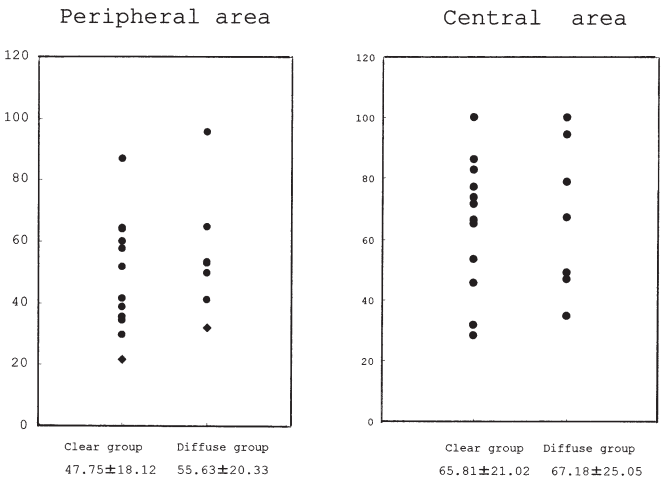


Figure 6. %-wash out.

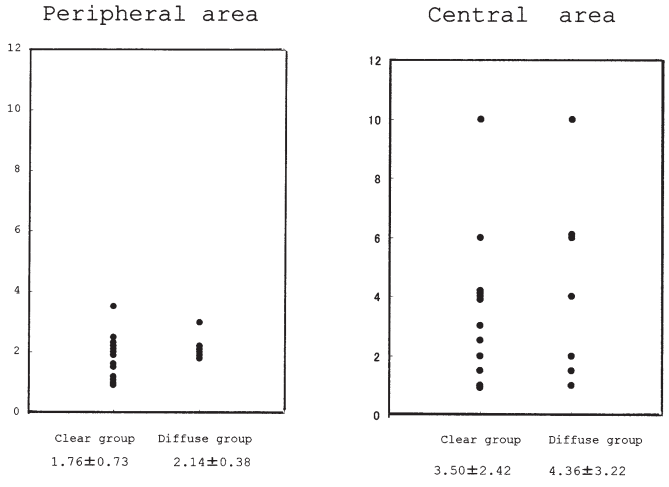


Figure 5. Time of maximum SE/N.

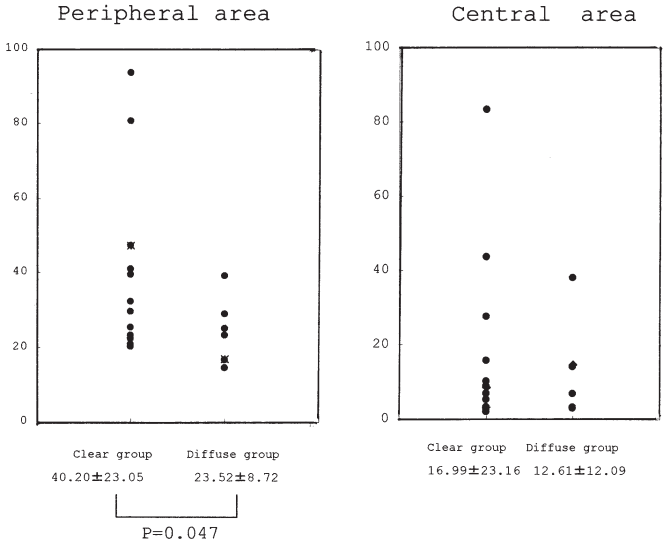


Figure 7. Ascending rate of SE/N.

formula: SE/N = (S^{post}-S^{pre})/N^{sd}, where S^{post} and S^{pre} are the signal intensities of the ROIs before and after contrast application, and N^{sd} is the standard deviation of background noise (3). Time versus SE/N was plotted (SI-ratio curve), and maximum SE/N (Max SE/N), time of maximum SE/N (T-Max SE/N), the ascending rate of SE/N (AR SE/N), and %-wash out were also calculated as parameters of DC-MRI. These imaging parameters were designated as follows: Max SE/N = the value in which SE/N showed the highest degree, T-Max SE/N = the time that showed Max SE/N, AR SE/N = Max SE/N/T-Max SE/N, and %-wash out = SE/N of delayed image/Max SE/N x100 (Fig. 2). These 4 parameters were determined for each peripheral and central region, and the results were compared between the 2 groups.

Statistical analysis. For statistical analysis, the parameters determined in the peripheral and central regions were compared using the Mann-Whitney U test. Statistical analyses was performed with PC software (JMP version 5.1.2, SAS Institute Inc.) and the level of significance was set at $p<0.05$.

Results

Histopathologically, 13 of 20 cases were classified into the clear group and the remaining 7 were classified into the diffuse group. Deep peripheral area of the tumor mass was apparently ehanced compare to that of superficial central area (Fig. 3).

Maximum SE/N. There were no significant differences in the peripheral area, though the clear group showed a slightly higher value as compared to that of the diffuse group. In the central area, no apparent tendency was seen (Fig. 4).

Time of maximum SE/N. There was no apparent tendency concerning T-Max SE/N in a comparison of the peripheral and central areas (Fig. 5).

%-wash out. In the peripheral area, %-wash out in the clear group tended to show a lower value. In the central area, the average value of each group was nearly equal (Fig. 6).

Ascending rate of SE/N. In the peripheral area, the clear group showed a significantly higher value for AR SE/N as

Table I. Clinical characteristics.

	No.
Sex	
Male	13
Female	7
Age (years)	
Mean	56.1
Range	26-73
Growth pattern	
Exophitic	11
Endophytic	9
T stage	
T2	8
T3	6
T4	6
Mode of invasion	
1	1
2	3
3	9
4	7

compared to the diffuse group (p=0.047). However, in the central area, no apparent difference was seen between the 2 groups (Fig. 7).

Discussion

To determine histopathological grading of an oral Sq.C.C., mode of invasion, which is a marker of the tumor aggressiveness, is well accepted as useful parameter for the assessment of tumor nature and prognosis (2,4). Moriyama *et al* (5) reported that vessel density in the diffuse type of mode of invasion was significantly lower as compared to that of the clear type. According to the results of these investigations, a modality that can show tumor vessel density might also have the potential to demonstrate tumor grading parameters, particularly the mode of invasion.

DC-MRI procedures are used for lesion detection, as well as determination of tumor angiogenesis and patient survival (6,7). Konouchi *et al* (8) reported that assessment of DC-MRI parameters may provide valuable information for tumor cell proliferation in patients with oral cancer. Dynamic contrast enhancement patterns can be affected by a wide range of physiological factors, including vessel density, blood flow, endothelial permeability, and the size of the extravascular extracellular space in which the contrast material is distributed (9). We considered it necessary to clarify the potential of DC-MRI, to determine whether it could be used to show the histopathological nature of an oral tumor.

Gleich *et al* (10) reported that an understanding of angiogenesis in the area of a tumor, which shows the highest microvessel density immediately adjacent to infiltrating neoplastic cells, failed to predict the aggressiveness of T1 oral cavity carcinomas. In contrast, William *et al* (11) reported that angiogenesis had a strong correlation with regional recurrence and could be used as an independent prognostic indicator for an oral cavity Sq.C.C. In addition, Shieh *et al* recently reported that microvessel densities in the peritumoral and intratumoral areas were correlated with histologic differentiation and tumor progression (12). In the present study, because the signal enhancement patterns were different, we divided each tumor into 2 areas on the MR images, the superficial central area and deep peripheral area, and found that enhancement of the superficial central area was weaker. This finding suggests that a larger amount of contrast material had reached the deep peripheral area as compared to the central superficial area.

Fujimoto *et al* (6) reported that the maximum enhancement ratio (not used in the present study) and slope value, which is nearly the same as the present parameter AR SE/N, were positively correlated, while T-Max, nearly the same as the present T-Max SE/N, was negatively correlated with microvessel count. In the present study, none of the parameters in the superficial central areas on the DC-MR images showed significant differences between the 2 groups. On the other hand, in the peripheral deep area, AR SE/N of the diffuse group showed a significantly lower value than that of the clear group. The average value of Max SE/N of tumors that showed a clear type mode of invasion tended to show a high value, whereas that of T-Max SE/N tended to show a low value in these tumors. The other parameters did not show a significant difference between the groups. Based on our results, we speculated that a tumor with a clear type of mode of invasion might have a higher vessel density as compared to the diffuse type in the deep peripheral area. Our results also correlated well to the histopathological features reported by Moriyama *et al* (5). However, the uptake of contrast media by tissues is influenced by a complex set of physiological factors and the interstitial space (extracellular-extravascular space) of a malignant tumor may be several times larger than normal or even edematous tissue (13). Thus, additional study is required to further elucidate these findings.

In a Sq.C.C. of the oral cavity, teeth, as well as prosthodontics and other kinds of materials may irritate the tumor, resulting in a secondary infection and/or edema of the tumor and surrounding structures. Such conditions could influence signal intensity and enhancement patterns seen with MRI. Moon *et al* (14) compared DC-MR images of abscess walls and VX2 carcinomas in rabbit thighs, and reported an early enhancement peak and rapid decay, especially in VX2 carcinomas with gadopentetate dimeglumine, while the enhancement ratios obtained with blood-pool contrast agents correlated well with the microvessel densities of the bacterial abscesses and VX2 carcinomas. For further understanding of the relationship between microvessel density and DC-MRI findings, a study using blood-pool contrast agents is required.

We recently investigated the relationships among DC-MRI features, chemosensitivity test results, and tumor response to chemotherapy, in addition to patient outcomes in patients with oral squamous cell carcinoma (15). The results of the present study suggest that DC-MRI is useful to show the histopathological mode of invasion into surrounding structures indirectly, though additional investigation is needed.

In summary, DC-MRI features were independent for each carcinoma and demonstrated a potential to show tumor histopathological features.

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