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Research Paper

Role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in predicting pathological response to preoperative super-selective intra-arterial chemoradiotherapy for advanced squamous cell carcinoma of the mandible

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ABSTRACT

Introduction: Although chemoradiotherapy (CRT) for oral squamous cell carcinoma (SCC) has been shown to preserve organ function and improve cosmetic results, site-specific data, especially mandible, are limited. The aim of this study was to evaluate the predictability of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) on response to super-selective intra-arterial CRT for advanced SCC of the mandible.

Methods: Fifteen patients with advanced SCC of the mandible underwent super-selective intra-arterial CRT followed by radical resection. Maximum standardized uptake value (SUVmax) of the mandibular lesion was evaluated with FDG-PET/CT before and after CRT. The SUVmax before and after CRT was defined as pre-SUVmax and post-SUVmax, respectively. The difference between pre- and post-SUVmax was calculated as SUVmax reduction rate to evaluate treatment response of the mandibular lesion. Each SUVmax reduction rate and surgical specimen of the corresponding lesion was analyzed to evaluate an accuracy of the modality for predicting pathological response.

Results: The median of pre-SUVmax was significantly lower than that of post-SUVmax ($p = 0.001$). Of the 15 patients, 6 had a pathological complete response (pCR) and 9 had a non-pCR. Neither pCR patients nor non-pCR patients showed significant difference of the median of SUVmax between pre- and post-CRT (pre-CRT $p = 0.099$ post-CRT $p = 0.074$). The SUVmax reduction rate in patients with pCR was significantly higher than that with non-pCR ($p = 0.002$). Receiver operating characteristic analysis revealed that the optimal cut-off point of the reduction rate was 64.7%, with 83% sensitivity and 100% specificity.

Conclusions: These results concluded that SUVmax reduction rate can predict pathological complete response of preoperative super-selective intra-arterial CRT for advanced SCC of the mandible.

1. Introduction

In oral cancer treatment, surgery is the most established mode of initial definitive treatment [1,2]. Advanced oral squamous cell carcinoma (SCC) is commonly treated with surgery, radiotherapy (RT) and/or chemotherapy [3–7]. However, postoperative dysfunction such as disturbances of speech, swallowing, mastication and esthetics can affect quality of life in advanced cases [2,8]. Studies employing adjuvant RT or chemoradiotherapy (CRT) after surgery outnumber studies of preoperative concepts, although preoperative therapy concepts have achieved good loco-regional control and a good survival rate as the standard approach in some institutions and have been rated positively in analytical reports [5–7,9,10]. Therefore, in recent decades, concurrent CRT for advanced oral SCC has been used to enable minimally invasive surgery or organ preservation [3,4,8,9,11]. However, accurate assessment of the treatment response is required to improve the quality of life of patients with advanced oral cancer.

18F-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), which is a functional imaging modality assessing the metabolism of glucose within tumor cells, has become

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increasingly important in the diagnosis and staging of head and neck cancer in recent years [4,12,13]. It is also used to assess the treatment response of chemotherapy and/or RT as well as detect unknown primary cancer, secondary cancer, recurrence and distant metastasis [4,12,13]. However, the utility of FDG-PET/CT for determining the pathological response of patients with advanced oral SCC to CRT has rarely been investigated [4].

Gingival SCC is relatively rare and represents < 10% of all oral cancers in the United States [14], while gingival SCC is the second-most common oral cancer in Japan [15]. Surgical resection (marginal or segmental mandibulectomy) for SCC of the mandible is usually the preferred primary treatment because systemic chemotherapy is regarded as inadequate against a tumor with extensive bone destruction [16]. Despite clinical trials of various treatment strategies, prognosis and locoregional control remain poor in advanced cases of SCC in the mandible because involvement of the retromandibular trigone is more likely to be associated with multidirectional invasion [16]. Although CRT including superselective intra-arterial infusion has been shown to preserve organ function and improve cosmetic results [8], only a small number of patients with SCC of the mandible have been included in several studies and site-specific data are limited [16]. The purpose of this study was to evaluate the usefulness of FDG-PET/CT in predicting pathological response after preoperative super-selective intra-arterial CRT for advanced SCC of the mandible.

2. Materials and methods

2.1. Patients

We retrospectively investigated 1159 with oral cancer patients visited to our department between April 2006 and October 2016. There were 177 patients with lower gingival cancer, and 95 patients of them had T4 lower gingival cancer. Of 95 patients, 34 underwent surgery alone and 21 patients underwent surgery after preoperative super-selective intra-arterial CRT. The remains had palliative care, or underwent other treatment such as chemotherapy alone, radiotherapy alone, or CRT alone. T4 mandibular SCC patients who underwent with PET/CT, CT, and magnetic resonance imaging (MRI) preoperative and 4 weeks after preoperative superselective intra-arterial CRT were included in this study. Patients who had recurrent primary lesion after surgery or distant metastatic disease, or underwent other preoperative treatment were excluded. Only 15 patients with newly diagnosed as advanced SCC of the mandible (10 men and 5 women; mean age, 65 years; age range, 53–80 years) who had not been treated previously and had no distant metastasis served as subjects in this study. Contrast-enhanced CT and FDG-PET/CT were used for diagnosis of neck and distant metastasis. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1, a white blood cell count of at least 3500 cells/mm^3, a platelet count of at least 100,000/mm^3, and a hemoglobin level of at least 9 g/dL. Patients with contrast medium allergy, cerebral infarction and severe liver, kidney, heart, or lung dysfunction were also excluded. Based on the 2009 Union for International Cancer Control TNM classification (7th edition), all patients were classified as T4. Patient characteristics are summarized in Table 1. The study protocol was approved by the institutional ethics committee.

2.2. Treatment

All patients underwent retrograde super-selective intra-arterial CRT as the preoperative treatment. Before treatment, three-dimensional computed tomography angiography of the carotid artery was performed to identify the main tumor-feeding arteries and determine the morphology of the tumor-feeding artery originating from the external carotid artery. Catheterization from the superficial temporal artery and occipital artery was performed [8], and the catheters were inserted into tumor-feeding arteries such as the maxillary artery and facial artery (Fig. 1). Docetaxel and cisplatin were injected in a bolus through the intra-arterial catheter when radiotherapy was performed. The dose of docetaxel was 10 mg/m^2/week (total 40–50 mg/m^2) and that of cisplatin was 5 mg/m^2/day (total 80–100 mg/m^2). Conventional radiotherapy was performed at 1.8 or 2 Gy/fraction/day, and the total dose was delivered in 39.6–50 Gy/20–25 fractions. All patients underwent radical surgery 4–6 weeks after completion of preoperative CRT, and pathological analysis of the resected tumor tissue was performed.

2.3. FDG-PET/CT imaging

All patients underwent FDG-PET/CT before and 4 weeks after preoperative intra-arterial CRT. PET/CT images were acquired (Eminence SOPHIA; Shimadzu Corporation, Kyoto, Japan). Patients fasted for 5 h before FDG administration and the dosage range was 150–250 MBq (5.0 MBq/kg). Whole blood glucose concentration was measured before FDG administration and was below 150 mg/dl in each patient. Data acquisition started 60 min after injection of FDG and the PET scan was acquired with an acquisition time of 100 s per bed position. The sequential PET scanning was performed at the same institution.

2.4. Conventional imaging

All patients underwent contrast-enhanced CT and magnetic resonance imaging (MRI) before and 4 weeks after preoperative intra-arterial CRT. CT scans were obtained using a 64-slice CT scanner (Aquilion 64; Toshiba Medical Systems, Tokyo, Japan). MRI was performed using a 1.5T scanner (Philips Medical Systems, Best, the Netherlands).

2.5. Data analysis

Standardized uptake value (SUV) was semi-quantitatively measured by FDG uptake within the regions of interest (ROI) over the primary lesion. The ROI (round, 5 mm in diameter) was placed manually over the area of most interest in the primary lesion on the SUV image. SUV was calculated using the formula: SUV = tissue radioactivity concentration (Bq/g)/[injected FDG dose (Bq)/body weight (g)]. The maximum SUV (SUVmax) of the ROIs was used to represent tumor FDG uptake. The SUVmax obtained before and after preoperative CRT was defined as the pre-SUVmax and post-SUVmax, respectively. The reduction rate of SUVmax was calculated as: SUVmax reduction rate = [(pre-SUVmax − post-SUVmax)/pre-SUVmax] ×100 (%).

Furthermore, treatment response of the primary lesions was assessed by contrast-enhanced CT and MRI using Response Evaluation Criteria in Solid Tumors (RECIST). Complete response (CR) was defined as no clinical evidence of disease, whereas non-CR implied residual abnormalities. CR using RECIST was defined as disappearance of all target lesions. Non-CR encompassed partial response (PR), progressive disease (PD), and stable disease (SD). PR was defined as at least a 30% decrease in the sum of the longest diameter of target lesions using as reference the baseline sum longest diameter. However, there was no requirement for confirmation of response. PD was defined as at least a 20% increase in the sum of the longest diameter of target lesions or the appearance of new lesions. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increased measurement to qualify for PD using the smallest sum longest diameter from pretreatment imaging.

2.6. Pathological evaluation

A pathological CR (pCR) was defined as no residual tumor cells and a non-pCR was defined as persistence of any residual tumor cells by histopathological examination of surgical specimens. The pathological response and remained site of the primary tumor after preoperative

Table 1
Patient and primary lesion characteristics.

Case No.	Age (years)	Sex	TNM classification	Stage	Total irradiation dose (Gy)	Pre- SUVmax	Post-SUVmax	SUVmax reduction rate (%)	Pathological response
1	66	M	T4aN2bM0	IVA	39.6	10.2	3.8	62.7	pCR
2	62	M	T4bN1M0	IVB	39.6	11.6	3.8	67.2	pCR
3	63	M	T4aN2bM0	IVA	40	11.2	4.7	58.0	Non-pCR
4	58	F	T4aN2cM0	IVA	46	8.5	3.8	55.3	Non-pCR
5	60	M	T4bN2bM0	IVB	40	12.3	3.0	75.6	pCR
6	75	F	T4aN1M0	IVA	50	5.5	3.6	34.5	Non-pCR
7	67	M	T4aN2bM0	IVA	40	10.5	2.9	72.4	pCR
8	55	M	T4aN0M0	IVA	50	4.7	2.9	38.3	Non-pCR
9	61	M	T4aN2cM0	IVA	40	10.7	3.6	66.4	pCR
10	61	M	T4aN2cM0	IVA	40	7.7	4.5	41.6	Non-pCR
11	80	F	T4aN1M0	IVA	40	13.5	5.0	63.0	Non-pCR
12	53	M	T4aN2bM0	IVA	40	9.2	3.4	63.0	Non-pCR
13	75	F	T4aN1M0	IVA	40	9.1	3.8	58.2	Non-pCR
14	72	F	T4aN1M0	IVA	40	18.6	9.7	47.8	Non-pCR
15	73	M	T4aN1M0	IVA	40	30.6	2.0	93.5	pCR

Pre-SUVmax, maximum standardized uptake value before treatment; post-SUVmax, maximum standardized uptake value after treatment; CR, complete response; PR, partial response; SD, stable disease.

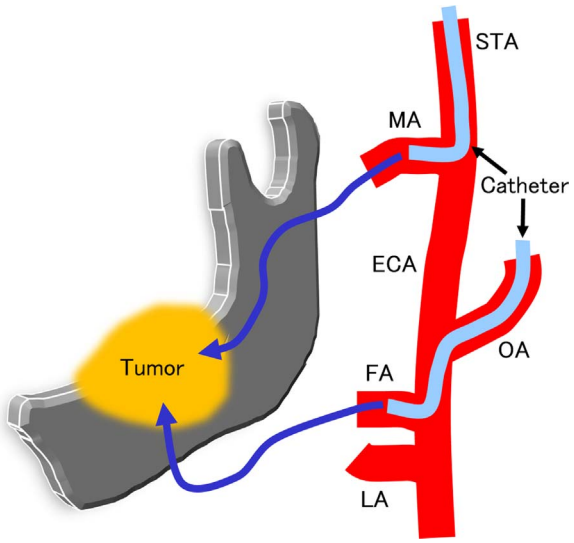

Fig. 1. Schema of super-selective intra-arterial catheterization via the superficial temporal artery and occipital artery for lower gingival carcinoma. ECA, external carotid artery; FA, facial artery; LA, lingual artery; MA, maxillary artery; OA, occipital artery; STA, superficial temporal artery.

intra-arterial CRT was evaluated.

2.7. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 20. The correlation between pre-SUVmax and post-SUVmax was determined using Wilcoxon signed-rank test. The correlation between pCR and non-pCR for each pre-SUVmax and post-SUVmax was determined using Mann-Whitney's *U* test. The difference in mean SUVmax reduction rates for each pCR or non-pCR was evaluated using *t*-test. The diagnostic accuracy of FDG-PET/CT in the assessment of pathological response to preoperative CRT was compared by calculating the area under the receiver operation characteristic (ROC) curves. The area under the curve (AUC), sensitivity, specificity, and positive and negative predictive values were calculated.

3. Results

PET/CT findings and the pathological response for each patient are summarized in Table 1. Median pre-SUVmax and post-SUVmax were 10.5 (range, 4.7–30.6) and 3.8 (2.9–9.7), respectively (Table 1). The mean SUVmax reduction rate was 59.8 ± 15.3%. There were 6 patients with pCR and 9 patients with non-pCR, for a pCR rate of 40% (Table 1). In non-CR group, 7 patients had residual tumor in the mandibular bone, 2 had in the soft tissue, and 1 had both sites. Not significant difference was seen between the pCR and non-pCR groups in pre-SUVmax (median (range): 11.15 (10.2–30.6) vs. 9.1 (4.7–18.6), p = 0.099) or post-SUVmax (3.30 (2.0–3.8) vs. 3.80 (2.9–9.7), p = 0.074). However, the mean SUVmax reduction rate was significantly different between the two groups (mean ± SD: 73.0 ± 11.1% vs. 51.1 ± 10.8%, p =0.002). One patient (Case 11) had local recurrence after radical surgery following preoperative CRT.

ROC analysis revealed that the SUVmax reduction rate could predict pathological response (AUC: 0.963, p = 0.003, Fig. 2), and the optimal cut-off point of the SUVmax reduction rate was 64.7%. When the reduction rate was ≥ 64.7%, pCR could be predicted with a sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio of 0.83, 1, 1, 0.9, infinity and 0.17, respectively.

Both contrast-enhanced CT and MRI taken 4 weeks after preoperative superselective intra-arterial CRT showed that treatment response of the primary lesions was non-CR in all patients.

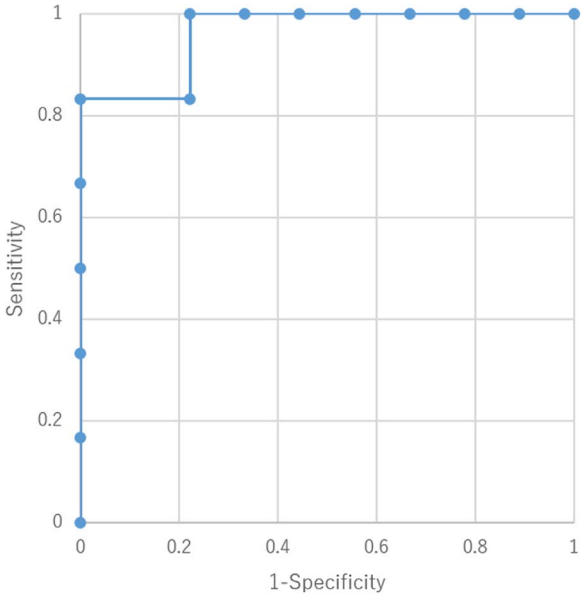

Fig. 2. ROC curve for predicting a pathological complete response by FDG-PET/CT.

4. Discussion

Advanced oral SCC is treated with a combination of surgery, RT and/or chemotherapy, whereas early-stage oral SCC is commonly treated with surgery [7]. Preoperative CRT with radical surgery is highly effective for advanced oral SCC and has the potential to become the standard multimodal treatment offering excellent local control and improved survival rates [3,6,7,10]. Kirita et al. [7] performed preoperative CRT (40 Gy irradiation and concurrent cisplatin-based systemic chemotherapy) for oral SCC at stages II-IV, and the CR rate and pCR rate for the primary tumor were 60.1% and 71.2%, respectively. In their study, pCR in the primary tumor was seen in 89.1% of patients with CR. They reported that it might be possible to perform minimally invasive surgery when the extent of the resection needed was reduced because of a good response to preoperative CRT. However, few studies have focused on CRT for advanced SCC of the mandible.

Nakasato et al. [16] reported the outcome of combined intra-arterial infusion and systemic CRT (range 30–60 Gy; median total dose, 60 Gy) for stage IV SCC of the mandibular gingiva. The CR rate and local control rate were 81.8% and 72.7%, respectively. Mukai et al. [11] published the outcome of radiation therapy with concurrent retrograde super-selective intra-arterial chemotherapy (median total dose, 60 Gy) for gingival SCC. Of 34 patients, 29 (85%) achieved CR and 5 had residual tumor. Two (6.9%) of the 29 patients with CR had local recurrences at 5 and 15 months after CRT, and the local control rate was 79.4%. In contrast, the present study showed a pathological CR rate of 40% after preoperative super-selective intra-arterial CRT (total dose, 40–50 Gy). Of the 15 patients who underwent radical surgery, 1 (6.7%) had local recurrence during follow-up. The lower CR rate in our study may be related to the duration of CRT (lower dose, 10–20 Gy). In the study by Nakasato et al. [16], there was possibility of lower CR rate in only T4 patients because their stage IV SCC included three T2 patients (13.6%). Furthermore, differences in anticancer agents and in the administration method (Seldinger method) may also affect the CR rate. In a study reported by Mukai et al. [11], the difference in CR rate also resulted from the inclusion of 19 patients with maxillary gingival SCC (55.8%) and 10 patients with early-stage gingival SCC (29.4%).

Even if a patient with advanced SCC of the mandible with extensive bone invasion was to achieve CR after CRT, a pathological fracture would require mandibular reconstruction [16]. In cases where there is a possibility of pathological fracture, we perform preoperative CRT with super-selective intra-arterial infusion and mandibular reconstruction to improve local control. If the risk is absent, we select the organ preservation protocol (super-selective intra-arterial CRT) [8]. Even when biopsy or noninvasive diagnostic imaging such as CT and MRI after CRT were performed, the findings were not always accurate for fibrous change of tumors. In this study, both contrast-enhanced CT and MRI 4 weeks after preoperative super-selective intra-arterial CRT showed that treatment response of the primary lesions was non-CR in all patients, and the accurate diagnosis after the preoperative CRT could be performed. Therefore, for minimally invasive surgery or nonsurgical organ preservation, further investigations must focus on better detection of patients who are likely to achieve CR after CRT [6].

FDG-PET has been recently used to evaluate therapeutic response after RT, chemotherapy or CRT in various cancers [12,17–20], and meta-analyses or systematic reviews revealed that FDG-PET could predict the pathological response to preoperative therapy [18–20]. In head and neck SCC, including oral SCC, biological information from FDG-PET/CT is similarly important and is often more predictive of pathological outcomes than that from other anatomical imaging modalities such as CT or MRI with intravenous contrast [4,12,13,21].

Various studies show that the optimal PET/CT timing for assessment of radiotherapy or CRT effects is 8–12 weeks after radical treatment (organ preservation). PET/CT timing of 4 weeks after preoperative CRT is early and has false positive by inflammation including mucositis. But, this study focused treatment response of preoperative intra-arterial CRT using PET/CT. For preoperative intra-arterial CRT, there is possibility of residual tumor (Residual rate was 60% in this study). Several authors [3,4,7] suggest that radical surgery should be performed within 4–6 weeks after preoperative CRT. Kikuchi et al. [13] has reported early PET/CT timing (mean 20.5 days, range from 14 to 32 days), as early evaluation of neoadjuvant chemotherapy response using FDG-PET/CT for patients with head and neck SCC. Therefore, we also performed PET/CT imaging 4 weeks after preoperative intra-arterial CRT and assessed SUV uptake including effect of inflammation.

SUVmax is commonly used to predict the therapeutic response [22], although recent studies have revealed that the SUVmax reduction rate is better for prediction [4,12,13]. Shimomura et al. [4] evaluated the usefulness of FDG-PET in assessing the histopathological response to preoperative concurrent CRT in patients with advanced oral SCC. Pre-SUV and post-SUV were significantly lower in patients with pCR than in those with non-pCR. However, pCR patients could not be distinguished from non-pCR patients based solely on SUVmax values after CRT. Although the SUVmax reduction rate was higher in patients with pCR than in those with non-pCR in their study, they did not carry out ROC analysis and so could not give a cut-off point for the SUVmax reduction rate. Kikuchi et al. [13] performed ROC analysis and showed that post-SUVmax (cut-off point of 3.5) and the SUVmax reduction rate (cut-off point of 55.5%) in FDG-PET/CT could predict the pathological response after neoadjuvant chemotherapy for head and neck SCC with a sensitivity of 71% and 86%, specificity of 89% and 95%, positive predictive value of 71% and 86%, and negative predictive value 89% and 95%, respectively. Thus, a decrease in SUVmax was a better predictor of pathological response. Although our study showed that pre-SUVmax and post-SUVmax did not show a significant difference between patients with pCR and those with non-pCR, the SUVmax reduction rate showed a significant difference between the two groups. According to our ROC analysis of the SUVmax reduction rate, the cut-off point of 64.7% had the highest diagnostic accuracy with a sensitivity, specificity, positive predictive value and negative predictive value of 83%, 100%, 100% and 90%, respectively. Therefore, the SUVmax reduction rate rather than SUVmax can be a reliable predictor in evaluating pathological response to preoperative intra-arterial CRT.

There were several limitations in this study, such as retrospective design and the small number of included patients. Nevertheless, we found that SUVmax reduction rate of FDG-PET/CT can predict pathological response to preoperative super-selective intra-arterial CRT for advanced SCC of the mandible. However, further prospective study is required to assess possibility of organ preservation by super-selective intra-arterial CRT for 6 weeks (60 Gy radiation).

5. Conclusions

SUVmax reduction rate can predict a good pathological response to preoperative super-selective intra-arterial CRT for advanced SCC of the mandible. When the SUVmax reduction rate was $\geq$ 64.7%, surgeons can perform minimally invasive surgery including tumor ablation with less soft tissue margin (avoidance of skin resection or preservation of the nerve such as the lingual, sublingual and facial nerve).

Conflict of interest statement

The authors declare that they have no conflict of interest.

Ethical approval

This study was reviewed and approved by the Institutional Review Board of Yokohama City University. Informed consent was obtained from all individual participants in the study.

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