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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