

Clinical Paper
Head and Neck Oncology

Hypoxic volume evaluated by ^{18}F -fluoromisonidazole positron emission tomography (FMISO-PET) may be a prognostic factor in patients with oral squamous cell carcinoma: preliminary analyses

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Abstract. Tumour hypoxia can be detected by ^{18}F -fluoromisonidazole positron emission tomography (FMISO-PET). Few studies have assessed the relationships of new PET parameters, including hypoxic volume (HV), metabolic tumour volume (MTV), and total lesion glycolysis (TLG), with 5-year survival of patients treated surgically for oral squamous cell carcinoma (OSCC). This study evaluated the relationships between these PET parameters and 5-year survival in OSCC patients. Twenty-three patients (age 42–84 years; 15 male, eight female) with OSCC underwent FMISO- and ^{18}F -fluoro-2-deoxyglucose (FDG)-PET computed tomography before surgery. All of them underwent radical surgery and were followed up for more than 5 years. The FDG-PET maximum standardized uptake value (SUV_{max}), HV, MTV, and TLG were measured. The ability of PET parameters to predict disease-free survival (DFS) and loco-regional recurrence (LR) was evaluated using receiver operating characteristic curve analysis. During the follow-up period, five of the 23 patients (22%) died and six (26%) experienced LR.

Although FDG-PET SUV_{max} was not significantly associated with DFS or LR, HV correlated significantly with both DFS and LR. TLG, but not MTV, was significantly associated with DFS; however neither MTV nor TLG was related significantly to LR. In conclusion, tumour HV may predict outcomes in patients with OSCC.

Key words: hypoxia; FMISO-PET; hypoxic volume HV; FDG-PET; metabolic tumour volume MTV; total lesion glycolysis TLG; oral squamous cell carcinoma; prognosis.

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Approximately 30% of head and neck cancers arise in the oral cavity, with the major pathology being squamous cell carcinoma (SCC)¹. Oral cancer is now recognized as one of the most common malignancies². Although modalities for the diagnosis and treatment of patients with oral cancer are improving, no significant improvement in survival rate has been observed over the last 40 years, especially in patients with advanced oral SCC (OSCC)^{3–5}. Strategies that use novel prognostic factors are required to improve outcomes in patients with OSCC.

Intratumoural hypoxia is a common feature and prognostic factor in many types of cancer^{6–8}. Low oxygenation levels in tumours are associated with a poor patient prognosis, largely due to the effects of hypoxia on resistance to treatment and the malignant progression of tumours^{7,8}. Hypoxia, independent of standard prognostic factors such as tumour size, nodal status, levels of tumour differentiation, and mode of invasion, has been implicated as an adverse prognostic factor².

¹⁸F-fluoromisonidazole positron emission tomography (FMISO-PET) is the imaging method used most frequently to evaluate the hypoxic condition in tumours^{8–10}. FMISO-PET is sensitive to the presence of hypoxia in viable cells, as well as covering the entire region of interest^{11,12}. Previous studies by the present authors found that non-invasive FMISO-PET evaluations of tumour hypoxia yielded highly reproducible results for head and neck cancers^{8,13,14}. The retention of FMISO has been associated with a higher risk of loco-regional failure and shorter progression-free survival in head and neck carcinoma¹⁵. With regard to the relationship between FMISO-PET and hypoxia in OSCC⁴, significant relationships between FMISO-PET uptake and the expression of hypoxia-inducible factor 1 α (HIF-1 α), which is a transcription factor that plays a key role in initial molecular responses to hypoxia, have been observed in OSCC⁸. The hypoxic volume (HV) of the tumour is a new PET parameter that has been evaluated using FMISO-

PET computed tomography (CT)^{16,17}. It is thought that this new PET parameter may have potential use in the discovery of new tumour biology and characteristics, as well as for the assessment of the usual clinical and pathological parameters in OSCC. Only a small number of clinical studies on hypoxia in OSCC have been performed.

¹⁸F-fluoro-2-deoxyglucose (FDG)-PET is used to diagnose tumours and to evaluate treatment outcomes⁶. In OSCC, the maximum standardized uptake value (SUV_{max}) of FDG-PET has been associated with proliferative activity and cellularity^{18,19}. Diagnostic imaging using FDG-PET has been used widely to detect primary tumours and lymph node and distant metastases, and more recently to determine therapeutic efficacy²⁰. The results of FDG-PET CT have a direct impact on the decision regarding therapy and on the outcome. SUV_{max} is the most widely used parameter to measure metabolic tumour activity in oncological FDG-PET CT imaging²¹. Other semi-quantitative parameters based on FDG-PET, such as the metabolic tumour volume (MTV) and total lesion glycolysis (TLG), may also correlate with clinical outcomes in patients with head and neck cancer^{3,22}. However, it appears that few studies to date have investigated the clinical and prognostic significance of MTV and TLG in patients with OSCC²², or have evaluated the relationships between 5-year survival of surgically treated OSCC patients and new PET parameters such as HV, MTV, and TLG. This study was therefore performed to evaluate the relationships between new PET parameters, in particular HV, and 5-year survival of patients with OSCC.

Materials and methods

Patients

Twenty-three consecutive patients with untreated primary OSCC undergoing medical examination and radical surgery at Hokkaido University Hospital, between October 2009 and October 2011, were

enrolled in this study; 15 were male and eight were female, and their median age was 67 years (range 42–84 years) (Table 1)⁸. None received palliative treatment. The primary tumour sites were the tongue ($n = 5$), upper gingiva ($n = 6$), lower gingiva ($n = 9$), buccal mucosa ($n = 1$), and oral floor ($n = 2$). Two tumours (9%) were classified as pathological (p) T1, nine (39%) as pT2, three (13%) as pT3, and nine (39%) as pT4a. The N classification was preoperative clinical (c) N0 in 13 patients (56%), cN1 in five (22%), and cN2 in five (22%)⁸. Eighteen patients (78%) underwent neck dissection, with eight patients having a pathological (p) N classification of pN0, five classified as pN1, and five as pN2.

All of the patients enrolled in this study were followed up for over 5 years postoperative. Five (22%) patients died during the follow-up period (patients 3, 6, 8, 9, and 12), including one of secondary lung cancer (patient 12) and one of distant metastasis to the lung (patient 8). Six patients (26%) experienced loco-regional recurrence (patients 3, 6, 9, 13, 18, and 20), of whom three experienced only primary recurrences (patients 6, 9, and 18). Three patients remained alive without cancer after a salvage operation (patients 13, 18, and 20).

Operative strategy

The basic treatment strategy used at the study institution for patients with resectable OSCC is first to perform surgery. A short period of oral chemotherapy is sometimes included while awaiting surgery.

The primary tumours of the study patients were surgically resected with ample safety margins of >10 mm where possible. Examination of frozen sections showed pathological cancer-free margins for all of the primary tumours resected. Patients who were clinically node-positive also underwent radical neck dissection. No patient with an N0 tumour underwent elective neck dissection.

Seventeen patients (74%) received preoperative chemotherapy with oral anticancer agents, among whom two received oral

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