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FULL PAPER

The role of changes in maximum standardized uptake value of FDG PET-CT for post-treatment surveillance in patients with head and neck squamous cell carcinoma treated with chemoradiotherapy: preliminary findings

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The authors MM, HT, YS, TK, KO and HT took part in the design of the study, contributed to the data collection and participated in writing the article.

Objective: No clear consensus exists regarding the optimal interval and frequency of follow-up positron emission tomography (PET)-CT in patients with head and neck squamous cell carcinoma (HNSCC) treated with chemoradiotherapy (CRT). Here, we sought to clarify whether the changes in the maximum standardized uptake value ($\Delta\text{SUV}_{\text{max}}$) may be a valid parameter to help decision-making for surveillance management after CRT.

Methods: 40 patients underwent PET-CT at pre-treatment and 3 months after CRT. Patients were followed by sequential PET-CT for 2 years after CRT. The $\Delta\text{SUV}_{\text{max}}$ of the primary tumour and the metastatic nodes were calculated between pre-treatment and 3 months after the CRT, and we evaluated the associations between $\Delta\text{SUV}_{\text{max}}$ and the manifestation of recurrence, time to recurrence and the patient survival.

Results: The $\Delta\text{SUV}_{\text{max}}$ of the primary tumour was significantly lower for the lesions with recurrence than that for

those with non-recurrence for both the primary site and the nodal site ($p = 0.007$, 0.02). A significant correlation was found between the time to recurrence and the $\Delta\text{SUV}_{\text{max}}$ of the primary tumour ($r = 0.63$, $p < 0.05$). The threshold $\Delta\text{SUV}_{\text{max}}$ of the primary tumour of 1.04 revealed 76.9% sensitivity and 86.4% specificity for distinguishing recurrence from non-recurrence. The progression-free survival and overall survival of the two patient groups divided by the $\Delta\text{SUV}_{\text{max}}$ of the primary tumour at 1.04 showed a significant difference ($p = 0.003$, 0.02). The $\Delta\text{SUV}_{\text{max}}$ of the metastatic nodes did not show a significant association with recurrence or patient survival.

Conclusion: The $\Delta\text{SUV}_{\text{max}}$ of the primary tumour showed a significant association with recurrence and patient survival.

Advances in knowledge: The $\Delta\text{SUV}_{\text{max}}$ of the primary tumour may be a valid clinical parameter to help decision-making for the surveillance management of patients with HNSCC after CRT.

INTRODUCTION

Surgery with or without adjuvant chemotherapy or radiotherapy remains the mainstay of treatment for locally advanced head and neck squamous cell carcinoma (HNSCC). However, during the past two decades, organ preservation strategies using chemoradiotherapy (CRT) have become an important treatment approach for locally advanced HNSCC, and these non-surgical approaches have been shown to produce an excellent response at the primary tumour site and at cervical lymph nodes, resulting in

high rates of locoregional control.¹ However, CRT does not always provide satisfactory treatment responses and clinical outcomes, even though the clinical staging and treatment method are the same as in the study of Furusaka et al.² Moreover, residual recurrent tumour occurs in as many as 30–40% of cases,³ and approximately 80% of tumour recurrences occur during the first 2 years after treatment.⁴

The guidelines of the National Comprehensive Cancer Network recommend clinical surveillance with history and

physical examinations every 1–3 months during the first year after the treatment of patients with HNSCC, tapering to every 6–12 months after 5 years. The optimal timing of the follow-up imaging after CRT treatment has not been established. In addition, the early detection of recurrent disease could provide a chance of cure by early salvage treatment, and potentially a survival benefit.⁵ However, the early detection of recurrence by anatomical imaging modalities such as CT and MRI may be limited owing to post-treatment changes in the normal tissue.⁶

The use of molecular imaging by positron emission tomography (PET) offers the potential to overcome this challenge in image interpretation by identifying residual disease based on metabolic activity rather than the presence or absence of anatomical abnormalities.⁷ The most widely available PET tracer is fludeoxyglucose (FDG), a glucose analogue. It has been revealed that in several malignancies including HNSCC, PET or PET-CT is capable of distinguishing post-treatment tissue changes from a recurrence that is undetectable by routine clinical follow-up by physical examination, CT or MRI.⁸ In addition, approaches for objectively assessing metabolic activity using the tumour uptake of FDG have become the standard for the assessment of treatment response.⁹

Compared with CT and MRI, PET-CT is an effective technique for the detection of recurrent HNSCC tumour and distant metastases after treatment.^{10,11} Several studies have applied PET-CT to the prediction of tumour recurrence after the completion of radiotherapy or CRT, revealing that the most important value of post-treatment PET is a high negative-predictive value (NPV).^{12,13} The most common quantitative PET index is the maximum standardized uptake value (SUV_{max}) as a semi-quantitative measurement of tumour uptake. SUV_{max} may be a significant prognostic marker for locoregional control or patient survival after treatment.^{14–16} Thus, although PET-CT is costly and administers a high dose of radiation, this technique is widely used for the post-treatment surveillance of patients with HNSCC. However, no clear consensus exists regarding the optimal interval and frequency of follow-up PET-CT in these patients. A useful parameter for post-treatment surveillance management has also not been established.

The purpose of this study was to clarify the relationships between the changes in the maximum standardized uptake value (ΔSUV_{max}) of FDG PET-CT results at the completion of CRT and the manifestation of recurrence, the time to recurrence and the patient survival in HNSCC. Our findings indicate that the ΔSUV_{max} may be a valid parameter to help decision-making for the surveillance management of patients with HNSCC after CRT.

METHODS AND MATERIALS

Study design

This prospective study was approved by the Committee on Clinical Study at our institution, and written informed consent to participate was obtained from all patients.

The study population consisted of patients with histologically confirmed primary HNSCC who were treated with CRT

between January 2008 and July 2011 at our institution. The selection of CRT for definitive therapy was determined by the following criteria: the patient tumour was stage T1 or T2; the tumour was not resectable by a transoral approach; the patient was inoperable because of medical complication(s); or the patient declined surgical treatment.

The patient selection was performed according to the following criteria: no previous treatment history (primary tumour); no history of radiotherapy in the head/neck region; a performance status of 0–1 on the Eastern Cooperative Oncology Group (ECOG) scale; age less than or equal to 80 years; and adequate bone marrow, liver and kidney functions. Patients were also excluded if they had any of the following: active concomitant malignancies, distant metastases at initial presentation or serious complications; active infectious disease, interstitial pneumonia, cardiac failure, renal failure or liver dysfunction.

40 patients (36 males, mean age 69.8 years; 4 females, mean age 65.5 years) met the above criteria and were enrolled in this study. At study entry, information on lifestyle factors including smoking history and alcohol consumption were collected. 28 patients were “current smokers”, whose mean cumulative tobacco smoking was 3.5 packs of cigarettes per month. Regarding alcohol consumption, 20 patients reported that they regularly consumed 2–4 alcoholic beverages per week and 5 patients reported that they regularly consumed 5–7 alcoholic beverages per week.

All patients underwent PET-CT for tumour staging according to the Tumor-node-metastasis classification within 4 weeks before treatment (mean 20.6 days). This pre-treatment PET-CT was used as the baseline (PET1), and the post-treatment PET-CT (PET2) to assess the patient therapeutic response was conducted at 3 months after the completion of CRT in each patient. The timing of PET imaging after the completion of CRT for HNSCC correlates with the imaging diagnostic accuracy, but the optimal timing for the analysis of FDG uptake to accurately evaluate the treatment response remains uncertain. However, there is a general consensus that the optimum time for post-radiotherapy assessment should be later than 3 months, because radiation-induced inflammation is likely to have declined by that time.¹⁰

The present patients who had no evidence of a residual lesion shown by a clinical examination (CE) including panendoscopy underwent routine follow-up PET-CT examinations at 3–6 months, 6–12 months and 12–18 months after PET2. These patients were also followed by CE every 1–2 months during the first year, and every 2–4 months during the second year after the CRT. The patients whose CE or follow-up PET-CT results suggested that a recurrence may have developed underwent a biopsy for confirming or excluding recurrence.

The patients with non-recurrence were followed for at least 2 years after their CRT. Tumour recurrence was defined as a local recurrence, a regional lymph node extension or distant metastasis during the follow-up period based on either histopathological proof or clinically suspected recurrence, resulting in a clinical assessment and an increase of lesion size on a serial

contrast-enhanced CT examination using a multidetector scanner (Sensation16; Siemens, Erlangen, Germany). Figure 1 provides a timeline that summarizes the consecutive different methodological steps in this patient series.

Radiotherapy and chemotherapy

All 40 patients underwent concurrent CRT; CT-based three-dimensional conformal radiotherapy was routinely performed. Radiotherapy was delivered 5 days/week using a once-daily fractionation of 2.0 Gy with 4-MV X-ray. The total radiation dose administered to the gross tumour volume and the bulky lymph nodes was 60–70 Gy (median 68.4 Gy). All patients received prophylactic lymph node irradiation. A prophylactic nodal area was irradiated up to 40–50 Gy (median 44.6 Gy). All patients underwent concurrent chemotherapy in addition to radiotherapy. This concurrent chemotherapy consisted of weekly cisplatin at the dose of 30 mg m^{-2} for 3 weeks followed by 1 week of rest ($n = 31$), or cisplatin 100 mg m^{-2} at Weeks 1 and 4 ($n = 9$).

Fludeoxyglucose positron emission tomography-CT examination

All PET-CT studies were performed using a Biograph Sensation 16 scanner (Siemens Medical Systems). All patients fasted at least 6 h before the PET-CT examination. The plasma glucose level was checked before the injection of FDG and was confirmed to be $<180 \text{ mg dl}^{-1}$ in all patients. PET-CT imaging was initiated 60 min after an i.v. injection of FDG (250–300 MBq). The CT data were collected in the helical acquisition mode. Each patient's CT images were matched to the pixel size of his or her PET data in order to match the in-slice resolution of the PET images. Without changing the patient position, whole-body PET images covering the same field of view were acquired in two-dimension mode at 3 min/bed position. The PET data were reconstructed with an ordered-subset expectation algorithm using the CT images for attenuation correction. The PET-CT images were analyzed on a dedicated workstation.

Imaging analysis

At PET1, the primary tumour and metastatic node were identified as the target lesions. Regarding metastatic node, the metastatic lymph node with the highest FDG-avid lesion was chosen. The same target lesions were identified at PET2, and we

performed a semi-quantitative analysis of target lesions identified at PET1 and PET2 using the parameter SUV_{max} , which was measured as the maximum value of the standardized uptake value in each voxel within the volume of interest (VOI) drawn on the lesions. The VOI was placed over each targeted lesion so as to encompass the entire FDG-avid lesion of interest with boundaries guided by CT delineation. The SUV_{max} values of the target lesions were measured by two radiologists with 6 and 7 years' experience in PET-CT imaging, in the same setting for each patient but independently to avoid bias of the VOI placement for the measurement of SUV_{max} ; a consensus was reached when varying interpretations were made.

Next, as the semi-quantitative index of PET-CT for our evaluation of its relationship with recurrence during the follow-up period, we calculated the changes in the maximum standardized uptake value of the primary tumour ($\Delta\text{T-SUV}_{\text{max}}$) and changes in the maximum standardized uptake value of a metastatic node ($\Delta\text{N-SUV}_{\text{max}}$) based on the SUV_{max} at PET1 and PET2 using the following formula: $(\text{SUV}_{\text{max}} \text{ at PET1} - \text{SUV}_{\text{max}} \text{ at PET2}) / (\text{SUV}_{\text{max}} \text{ at PET1} - 1)$, in which the value of the background standardized uptake value is considered 1.¹⁷

We used a routine clinical qualitative analysis to interpret each follow-up PET-CT result; a lesion with an FDG uptake that was equal to or less than the background uptake was considered to show no evidence of tumour recurrence (*i.e.* it was negative for recurrence), and focal and/or distant areas with FDG uptake that exceeded the activity observed in the adjacent background outside the borders of lesion were suspected to have tumour recurrence (*i.e.* these areas were positive for recurrence). FDG uptake that was definitively physiologic, such as that observed in the muscle or brown fat, was considered a negative finding. A quantitative analysis of FDG uptake was not applied at each follow-up PET-CT.

Statistical analysis

We used the χ^2 test to determine the sensitivity, specificity, positive-predictive value (PPV), NPV and accuracy of the follow-up PET-CT and CE examinations for the diagnosis of recurrence. The $\Delta\text{T-SUV}_{\text{max}}$ and $\Delta\text{N-SUV}_{\text{max}}$ values indicating recurrence *vs* non-recurrence were compared with the Mann-Whitney *U*-test. To assess the relationship between the time to recurrence and the $\Delta\text{T-SUV}_{\text{max}}$ or the $\Delta\text{N-SUV}_{\text{max}}$, respectively, we used the Spearman rank test.

We conducted a receiver-operating characteristic analysis with the area under the curve to determine the discriminatory capability of variables as indicators distinguishing recurrence from non-recurrence. To identify the significant predictive value of variables for recurrence, we defined the optimal threshold as the value corresponding to the highest average of the sensitivity and the specificity. When the threshold value was adopted, we determined the sensitivity, specificity, PPV and NPV for the distinguishing the capability of each index by using the χ^2 test.

To evaluate the usefulness of variables for the patient outcome after CRT, we compared the progression-free survival (PFS) and the overall survival (OS) for the two groups of patients divided

Figure 1. Timeline detailing the protocol of study. $\Delta\text{N-SUV}_{\text{max}}$, changes in the maximum standardized uptake value of a metastatic node; $\Delta\text{T-SUV}_{\text{max}}$, changes in the maximum standardized uptake value of the primary tumour; CRT, chemoradiotherapy; PET, positron emission tomography.

by the optimal threshold value, using the Kaplan–Meier method followed by the log-rank test.

Statistical analyses were performed with SPSS® v. 15.0 statistical software (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL), and p -values <0.05 were considered significant.

RESULTS

Treatment outcomes and accuracy of lesion detection

Of the 40 patients, 2 patients had residual primary tumour at the completion of CRT, 2 patients did not complete the treatment because of toxicities associated with CRT and 1 patient refused the CRT during the course of treatment. The remaining 35 patients were considered to have no evidence of residual tumour at the end of their CRT (Table 1). 22 of these 35 patients still had non-recurrence at the end of the 2-year post-CRT follow-up period. The other 13 patients were found to have recurrence within 2 years after CRT; 5 patients developed an isolated local recurrence; 2 patients developed a regional lymph node extension without primary tumour recurrence; 3 patients developed a simultaneous locoregional tumour recurrence; 1 patient developed a simultaneous locoregional tumour recurrence and distant metastasis (lung metastasis); and 2 patients

developed a distant metastasis alone (lung metastasis). The patients with locoregional recurrence were treated with salvage surgery and/or neck dissection with or without adjuvant chemotherapy. For the patients who were inoperable, only chemotherapy was performed.

Table 2 shows the results of the CE and follow-up PET-CT examinations in the patients with recurrence. Of the 13 patients found to have recurrence after CRT, 9 patients were identified by CE and PET-CT, and 4 patients had recurrence detected by PET-CT only. Regarding false-positive findings of recurrence among the 22 patients with non-recurrence during the follow-up period, recurrence was suspected in 1 patient by both CE and PET-CT, in 2 patients by PET-CT only and in 2 patients by CE only. The following values were thus obtained for PET-CT: 100% sensitivity, 86.4% specificity, 81.3% PPV, 100% NPV and 91.4% accuracy for the detection of recurrence. For CE, the following values were obtained: 69.2% sensitivity, 86.4% specificity, 75.0% PPV, 82.6% NPV and 80.0% accuracy for the detection of recurrence. A significant difference in the performance of PET-CT vs that of CE was demonstrated ($p = 0.02$).

Associations between changes in the maximum standardized uptake value and recurrence

Regarding the primary tumour site, the $\Delta T-SUV_{max}$ values were significantly lower for the lesions with recurrence than that for those with non-recurrence, whereas there was no significant difference in $\Delta N-SUV_{max}$ values between the lesions with recurrence and those with non-recurrence (Table 3). Likewise, regarding the nodal sites, the $\Delta T-SUV_{max}$ values were significantly lower for the lesions with recurrence than that for those with non-recurrence, whereas there was no significant difference in $\Delta N-SUV_{max}$ values between the lesions with recurrence and those with non-recurrence (Table 4).

Regarding the correlations between the time to recurrence and $\Delta T-SUV_{max}$ and $\Delta N-SUV_{max}$, a significant correlation was found between the time to recurrence and $\Delta T-SUV_{max}$ ($r_s = 0.63$, $p < 0.05$) (Figure 2), but not between the time to recurrence and $\Delta N-SUV_{max}$.

The results of the receiver-operating characteristic analysis for the discriminating capabilities of $\Delta T-SUV_{max}$ and $\Delta N-SUV_{max}$ as indicators for distinguishing recurrence from non-recurrence showed that the area under the curve values of $\Delta T-SUV_{max}$ and $\Delta N-SUV_{max}$ were 0.84 and 0.69, respectively (Figure 3); these values are significantly different ($p = 0.04$). The feasible threshold values for distinguishing recurrence from non-recurrence using the $\Delta T-SUV_{max}$ and $\Delta N-SUV_{max}$ were 1.04 and 1.13, respectively. The sensitivity, specificity, PPV, NPV and accuracy values of the $\Delta T-SUV_{max}$ and $\Delta N-SUV_{max}$ obtained when these threshold values are used are shown in Table 5.

Progression-free survival and overall survival

The difference in PFS between the two groups of patients divided by the threshold values of $\Delta T-SUV_{max}$ was significant (Figure 4) ($p = 0.003$), whereas there was no significant difference in PFS between the two groups divided by the threshold value of $\Delta N-SUV_{max}$.

Table 1. Patient characteristics

Characteristics	Number of patients ($n = 35$)
Age (years)	
Median	67.6
Range	50–80
Sex, male/female	32/3
Tumour location	
Oropharynx	9
Hypopharynx	12
Larynx	11
Oral cavity	3
T stage (UICC)	
T2	13
T3	16
T4	6
N stage (UICC)	
N0	13
N1	4
N2	16
N3	2
Stage (UICC)	
II	4
III	10
IV	21

UICC, Union Internationale Contre le Cancer.

Table 2. Data of patients with tumour recurrence

Patient	Sex	Age (years)	Site	Clinical stage	CE	PET-CT Time of TR (months)	Site of TR
1	M	67	Hypopharynx	T1N2M0	Positive	3–6	L/R
2	F	74	Hypopharynx	T2N2M0	Positive	6–12	L
3	M	63	Hypopharynx	T4N2M0	Positive	6–12	R
4	M	70	Hypopharynx	T2N2M0	Negative	3–6	L/R/D
5	M	66	Hypopharynx	T3N2M0	Negative	6–12	D
6	M	62	Oropharynx	T4N2M0	Positive	3–6	L
7	M	77	Oropharynx	T2N2M0	Positive	6–12	R
8	M	61	Oropharynx	T4N2M0	Negative	3–6	L/R
9	M	61	Larynx	T2N1M0	Positive	12–18	L
10	M	69	Larynx	T3N3M0	Negative	3–6	D
11	M	53	Oral cavity	T2N0M0	Positive	3–6	L/R
12	F	74	Oral cavity	T2N0M0	Positive	3–6	L
13	M	78	Oral cavity	T2N0M0	Positive	6–12	L

CE, clinical examination; D, distant metastasis; F, female; L, local recurrence; M, male; PET, positron emission tomography; R, regional lymph node extension; TR, tumour recurrence.

The difference in OS between the two groups divided by the threshold value of $\Delta T-SUV_{max}$ was significant (Figure 5) ($p = 0.02$). The OS was not significantly different between the two groups divided by the threshold value of $\Delta N-SUV_{max}$.

DISCUSSION

Many studies have been conducted to determine the accuracy of PET and PET-CT for the detection of locoregional recurrence and distant metastasis in the post-treatment follow-up setting for patients with HNSCC. In a meta-analysis of 17 studies, Gupta et al¹⁰ reported that PET or PET-CT had a sensitivity of 87.7%, specificity of 87.8%, PPV of 75.7% and NPV of 94.3% for the detection of locoregional recurrence or distant metastasis of HNSCC. Abgral et al¹⁸ reported that the sensitivity, specificity, PPV, NPV and accuracy of PET-CT for the detection of recurrence in patients with HNSCC without clinical suspicion of recurrence during the 12 months after the treatment were 100%, 85%, 77%, 100% and 90%, respectively. In addition, Paidpally et al¹⁹ reported the added value of follow-up PET-CT for the clinical assessment of HNSCC recurrence between 4 and 24 months after the treatment. According to their report, PET-CT identified recurrence in 5% of the scans obtained without prior clinical suspicion and

excluded recurrence in 50% of the scans obtained with clinical suspicion of recurrence.

Liu et al²⁰ reported the usefulness of PET for the detection of recurrence in patients with HNSCC in comparison with other imaging modalities. The sensitivity and specificity in detecting asymptomatic recurrence for PET (95% and 90%, respectively) were significantly higher than those for both CT (76% and 59%, respectively) and MRI (78% and 76%, respectively). Our present findings regarding the detection of recurrence in patients with HNSCC treated by CRT were comparable with those of previous studies, and we observed that the accuracy of follow-up PET-CT was significantly higher than that of conventional CEs. Moreover, of the 13 patients with recurrence, the recurrence in 4 (30.8%) patients was detected by PET-CT only. Therefore, the use of PET-CT for the post-treatment surveillance of patients with HNSCC might add value to the detection of recurrence in patients who are asymptomatic, and PET-CT might be more accurate than other imaging modalities such as CT or MRI in detecting asymptomatic recurrence. However, the optimal duration and frequency of post-treatment follow-up PET-CT examinations for the early detection of recurrence remains an area of ongoing research.

Table 3. Comparison of changes in the maximum standardized uptake value between non-recurrence and recurrence in the primary site

Changes in SUV_{max}	Non-recurrence ($n = 22$)	Recurrence ($n = 9$)	p -value
$\Delta T-SUV_{max}$	1.04 ± 0.25	0.69 ± 0.32	0.007
$\Delta N-SUV_{max}$	1.21 ± 0.13	0.92 ± 0.39	NS

$\Delta N-SUV_{max}$, changes in the maximum standardized uptake value of a metastatic node; $\Delta T-SUV_{max}$, changes in the maximum standardized uptake value of the primary tumour.

Data are expressed as mean $\pm$ standard deviation, NS, no significance = p -value ≥ 0.05 .

Table 4. Comparison of changes in the maximum standardized uptake value between non-recurrence and recurrence in the nodal site

Changes in SUV _{max}	Non-recurrence (<i>n</i> = 17)	Recurrence (<i>n</i> = 5)	<i>p</i> -value
ΔT-SUV _{max}	1.01 ± 0.23	0.75 ± 0.50	0.02
ΔN-SUV _{max}	1.21 ± 0.13	1.19 ± 0.10	NS

ΔN-SUV_{max}, changes in the maximum standardized uptake value of a metastatic node; ΔT-SUV_{max}, changes in the maximum standardized uptake value of the primary tumour.

Data are expressed as mean ± standard deviation, NS, no significance = *p*-value ≥ 0.05.

There have been a few studies with respect to the interval and frequency of surveillance PET-CT in treated patients with HNSCC. Beswick et al²¹ reported that the use of PET-CT beyond 24 months after therapy may be wasteful. Kim et al²² reported that systematic PET-CT at 3–6 months and at 12 months after treatment was beneficial for the early detection of recurrence. Several studies also pointed out that FDG-PET and PET-CT after CRT have a high NPV and specificity for excluding residual or recurrent locoregional disease,^{12,13} and McDermott et al²³ reported that two consecutive PET-CT examinations with negative findings at 6 months after treatment resulted in an NPV of 98%. In the present study, ΔT-SUV_{max} at 3 months after the completion of CRT showed a significant association with recurrence, and the optimal threshold value of ΔT-SUV_{max} for distinguishing recurrence from non-recurrence was 1.04. Moreover, ΔT-SUV_{max} showed a significantly positive correlation with the time to recurrence. Our findings thus suggest that ΔT-SUV_{max} might be a useful parameter in decision-making in the PET-CT surveillance for the early detection of recurrence in patients with HNSCC treated with CRT; in addition, for a subset of patients with a ΔT-SUV_{max} < 1.04,

who are likely to have recurrence, more aggressive monitoring is justified.

There are several studies in which the SUV_{max} either before or after radiotherapy/chemotherapy offered additional prognostic information.^{14–16} In contrast, some studies showed that a significant association was not found between SUV_{max} and prognosis.²⁴ A single measurement of SUV_{max} either before or after treatment may not be sufficient to predict the degree of treatment-induced metabolic damage, and the changes in the SUV_{max} on sequential PET-CT may be important to predict the patient outcome after the treatment. Actually, several studies demonstrated that a reduction in tumoral metabolic activity on serial PET-CT was predictive of both tumour chemosensitivity and survival. In a study by Kikuchi et al²⁵ of induction chemotherapy for HNSCC, a reduction of >55% in the SUV_{max} in HNSCC was predictive of a good response to chemotherapy and survival. In addition, Hentschel et al²⁶ reported that a decrease in the SUV_{max} from pre-treatment to Weeks 1 and 2 of CRT might be a potential prognostic marker for patients with HNSCC.

Figure 2. The correlation between the time to recurrence and changes in the maximum standardized uptake value of the primary tumour (ΔT-SUV_{max}).

Figure 3. Receiver-operating characteristic curves showing the capability of changes in the maximum standardized uptake value of the primary tumour (ΔT-SUV_{max}) and changes in the maximum standardized uptake value of a metastatic node (ΔN-SUV_{max}) for distinguishing recurrence from non-recurrence.

Table 5. Distinguishing the capability of feasible threshold of changes in the maximum standardized uptake value of the primary tumour and changes in the maximum standardized uptake value of a metastatic node

Changes in SUV_{max}	Feasible threshold value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
$\Delta T-SUV_{max}$	1.04	76.9 (10/13)	86.4 (19/22)	76.9 (10/13)	86.4 (19/22)	82.9 (29/35)
$\Delta N-SUV_{max}$	1.13	60.0 (6/10)	66.7 (8/12)	60.0 (6/10)	66.7 (8/12)	63.6 (14/22)

NPV, negative-predictive value; PPV, positive-predictive value.

Data in parentheses are number/total of patients.

In the present study, the PFS and OS rates of the two patient groups divided by the threshold value of $\Delta T-SUV_{max}$ for distinguishing recurrence from non-recurrence were significantly different, and the patients with higher $\Delta T-SUV_{max}$ values over the threshold value showed significantly better PSF and OS than those with lower $\Delta T-SUV_{max}$ values. Our results suggest that the $\Delta T-SUV_{max}$ in patients with HNSCC treated with CRT may have the ability to offer additional prognostic information. Caution should thus be exercised in a post-treatment follow-up for a subset of patients with lower $\Delta T-SUV_{max}$ so as not to lose the chance of cure by early salvage treatment.

We also observed that the $\Delta N-SUV_{max}$ did not show significant association with recurrence or patient survival. The response rates at the primary tumour site are generally high with CRT, and there have been several studies in which the utility of PET-CT for the detection of residual metastatic nodes after CRT is the main focus. Ong et al²⁷ reported that FDG PET-CT at least 8 weeks after the completion of CRT detected residual nodal

disease with 71% sensitivity, 89% specificity, a PPV of 38% and an NPV of 97%. They also noted that necrotic cells or non-viable tumour cells but abundant inflammation was present in PET false-positive lymph nodes. In addition, the median time between the end of CRT and PET-CT was 9 weeks in the PET false-positive cases and 14 weeks in PET true-positive cases.

In the present study, we assessed the $\Delta N-SUV_{max}$ at 3 months after the completion of CRT because it was reported that radiation-induced inflammation has declined by that time.¹⁰ However, it was speculated that inflammation or granulomatous change in lymph nodes after CRT mainly influenced the evaluation of the $\Delta N-SUV_{max}$ in association with recurrence and patient survival.

Our study has some limitations. First, the patient population was relatively small and heterogeneous, including tumours from various head and neck sites. In addition, patients with an oral cavity carcinoma (which is usually treated with surgery as the

Figure 4. Progression-free survival (PFS) of patients with head and neck squamous cell carcinoma assessed by changes in the maximum standardized uptake value of the primary tumour ($\Delta T-SUV_{max}$): the graph shows the PFS period of patients with $\Delta T-SUV_{max} \geq 1.04$ was significantly better than that of patients with $\Delta T-SUV_{max} < 1.04$ ($p = 0.003$).

Figure 5. Overall survival (OS) of patients with head and neck squamous cell carcinoma assessed by changes in the maximum standardized uptake value of the primary tumour ($\Delta T-SUV_{max}$): the graph shows the OS of patients with $\Delta T-SUV_{max} \geq 1.04$ was significantly better than that of patients with $\Delta T-SUV_{max} < 1.04$ ($p = 0.02$).

preferred treatment option) were enrolled, because their disease was considered inoperable based on the tumour extent and/or medical reasons. Further studies are needed with larger number of patients without potential selection bias. Second, it was reported that approximately 80% of locoregional recurrences occur within the first 2 years after treatment.⁴ In the present patient series, the routine follow-up PET-CT was performed only during the 18 months after CRT. However, considering the high cost and radiation burden of PET-CT, it may not be reasonable to perform routine follow-up PET-CT examinations during the 2 years after treatment.

Third, biological differences in HNSCCs associated with tobacco and alcohol use, epidermal growth factor receptor overexpression and human papillomavirus infection have been suggested as

prognostic factors. Patients with human papillomavirus-positive oropharyngeal carcinoma, in particular, have an improved OS rate compared with patients with human papillomavirus-negative oropharyngeal carcinomas.²⁸ Many of the present study patients had a history of chronic smoking and/or chronic alcohol ingestion, but they were not tested for human papillomavirus infection.

In conclusion, the results of our preliminary study demonstrate that the $\Delta T-SUV_{max}$ at 3 months after CRT showed significant associations with the manifestation of recurrence, the time to recurrence and patient survival. Our findings suggested that patients with $\Delta T-SUV_{max} < 1.04$ should be considered for more aggressive monitoring after CRT. However, a larger scale study is needed to determine a more reliable cut-off threshold of $\Delta T-SUV_{max}$.

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