FULL PAPER

Lymph node standardized uptake values at pre-treatment 18F-fluorodeoxyglucose positron emission tomography as a valuable prognostic factor for distant metastasis in nasopharyngeal carcinoma

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Objective: The aim of the present study was to evaluate prognostic values of pre-treatment fluorine-18 fludeoxyglucose (^{18}F-FDG) positron emission tomography (PET) parameters for predicting the distant metastasis (DM) of nasopharyngeal cancer.

Methods: 73 patients diagnosed with nasopharyngeal cancer with regional lymph node (LN) involvement, who underwent pre-treatment ^{18}F-FDG PET evaluation between January 2005 and December 2012, were retrospectively reviewed. We assessed the ^{18}F-FDG PET parameters of the primary tumours (T–) and regional LNs (N–). For patients with bilateral retropharyngeal, bilateral neck and/or supraclavicular LN involvement, we also assessed the ^{18}F-FDG PET parameters of the farthest LN station [N(f)–]. The following ^{18}F-FDG PET parameters were evaluated: maximum standardized uptake value (SUV_{max}), mean standardized uptake value (SUV_{mean}), peak standardized uptake value (SUV_{peak}), metabolic tumour volumes (MTVs) (MTV_{30}–MTV_{70}, which were calculated as the tumour volume with 30%, 40%, 50%, 60% and 70% of the SUV_{max} as the threshold, respectively) and total lesion glycolysis (TLG) (TLG_{30}–TLG_{70}, which were determined by the product of each MTV and the corresponding SUV_{mean} within that MTV). Distant metastasis-free survival (DMFS) rates were estimated from the date of the start of radiotherapy to the date of DM or last follow-up by the Kaplan–Meier method.

Univariate and multivariate analyses were performed to identify prognostic factors for DMFS. The median follow-up period was 53 months (range 12–110 months).

Results: Most patients (95%) received concurrent chemoradiotherapy. The major failure pattern was DM (15 of all patients, 21%) and the 5-year DMFS was 79%. In univariate analysis, the T–SUV_{max}, T–SUV_{mean}, T–SUV_{peak}, N–SUV_{max}, N–SUV_{peak}, $N(f)$–SUV_{max} and $N(f)$–SUV_{peak} were significant prognostic factors for DMFS. In multivariate analysis, the T–SUV_{max}, T–SUV_{peak}, $N(f)$–SUV_{max} and $N(f)$–SUV_{peak} were significant prognostic factors for DMFS. Of these parameters, the $N(f)$–SUV_{max} (hazard ratio = 6.524; $p = 0.001$) and $N(f)$–SUV_{peak} (hazard ratio = 5.399; $p = 0.001$) were the strongest prognostic factors for DMFS.

Conclusion: In patients with nasopharyngeal cancer with LN involvement, the standardized uptake value parameter of the farthest LN station seems to be an important ^{18}F-FDG PET parameter for predicting DM. Further studies are needed to validate its clinical significance.

Advances in knowledge: We found that pre-treatment ^{18}F-FDG PET parameters of primary tumours and regional LNs (the SUV_{max} and SUV_{peak} of the primary tumour and the farthest LN station) were significant prognostic factors for DMFS in patients with nasopharyngeal carcinoma with LN involvement.

INTRODUCTION

Nasopharyngeal carcinoma is an uncommon cancer with an annual worldwide incidence of 80,000 and a distinct geographic distribution.[1,2] The standard treatment for nasopharyngeal carcinoma is radiotherapy or concurrent chemoradiotherapy and the locoregional control rates are reported to be >90% with intensity-modulated radiation therapy (IMRT), a recently developed advanced

radiotherapy technique.[3–12] In contrast to these excellent locoregional control rates, distant metastasis (DM) remains a major pattern of failure and was reported as 10–15% at 2 years, 14–22% at 3 years and 34% at 4 years.[3,5–9,11,12] To improve outcomes, the role of adding chemotherapy to concurrent chemoradiotherapy has been investigated, but a definite benefit has not been proved yet.[13] The role of induction chemotherapy is being investigated in several ongoing trials based on the result of Hui et al,[14] which showed a survival benefit from induction chemotherapy.[13] However, to date, no randomized trial has demonstrated a survival benefit from adjuvant chemotherapy.[13] Therefore, it has been an important issue to identify patients at high risk of DM, who may benefit from more aggressive treatments. Traditionally, the stage classifications of the American Joint Committee on Cancer and Ho have been considered the most important prognostic factors for DM and have been widely used. However, these stage classifications are based on anatomic imaging, which assesses the extent of the primary tumour and the size, laterality and level of involved lymph nodes (LNs), and which has limitations in evaluating biologic aggressiveness in each patient.

Fluorine-18 fludeoxyglucose (^{18}F-FDG) positron emission tomography (PET) has recently been frequently used in pre-treatment diagnostic evaluation to determine the DM status and for post-treatment monitoring of various cancers. ^{18}F-FDG PET is based on the metabolic activity of the tumour and several studies have evaluated whether ^{18}F-FDG PET parameters have an additional prognostic impact on the traditional stage classification, based on the hypothesis that ^{18}F-FDG PET parameters can reflect the biologic aggressiveness of tumours. However, most previous studies focused on the maximum standardized uptake values (SUV_{max}), especially those of the primary tumour.[15–26] There have been limited published data on the prognostic values of ^{18}F-FDG PET parameters other than SUV_{max}, such as volumetric parameters,[15,17–19,26] especially those of regional LNs,[15–19] and these remain to be extensively studied.

In the present study, we evaluated the prognostic values of various pre-treatment ^{18}F-FDG PET parameters [SUV_{max}, mean standardized uptake value (SUV_{mean}) and peak standardized uptake value (SUV_{peak}); metabolic tumour volume (MTV); total lesion glycolysis (TLG)] of both primary tumours and LNs for predicting DM in nasopharyngeal carcinoma.

METHODS AND MATERIALS
Patients
We retrospectively reviewed the records of 145 patients with pathologically proven nasopharyngeal cancer who received definitive radiotherapy with or without chemotherapy at Asan Medical Center between January 2005 and December 2012. Of the 145 patients, 36 patients were excluded for the following reasons: (1) DM at initial diagnosis ($n = 5$), (2) no pre-treatment ^{18}F-FDG PET evaluation ($n = 2$), (3) pre-treatment ^{18}F-FDG PET evaluation in another hospital ($n = 24$) or (4) a short follow-up period of less than 12 months ($n = 5$). In addition, we also excluded 21 patients who had pre-treatment ^{18}F-FDG PET evaluation by a scanner other than a Biograph

Sensation 16 (Siemens Medical Systems) or TruePoint 40 (Siemens Medical Systems) to minimize differences between scanner types. Of the remaining 88 patients, 73 patients had regional LN involvement at diagnosis. We eventually included these 73 patients in the present study to evaluate the prognostic value of the ^{18}F-FDG PET parameters of both primary tumours (T–) and regional LNs (N–).

Pre-treatment evaluations were performed *via* medical history, physical examination, laboratory tests (including complete blood count and chemistry), fibreoptic nasopharyngoscopy with biopsy, CT or MRI of the head and neck, chest radiography and ^{18}F-FDG PET. The clinical stage of the cancer was assessed according to the American Joint Committee on Cancer (7th edition) TNM stage classification. The definition of positive LNs included (1) the presence of central necrosis or a contrast-enhanced rim; (2) the presence of extracapsular spread; (3) a shortest axial diameter of ≥5 mm for retropharyngeal LN, ≥11 mm for the jugulodigastric LN or ≥10 mm for any other neck LN; (4) the presence of a cluster of three or more LNs, each with a borderline size.[27] This study was approved by the Institutional Review Board of Asan Medical Center.

Treatment
All patients underwent IMRT using 6-MV or 15-MV photon beams from a linear accelerator (Varian, Palo Alto, CA). Each patient was placed in a head-extended, supine position and immobilized with a custom-made thermoplastic mask encompassing the entire head and neck. All patients underwent simulation with a CT scanner (LightSpeed RT 16; GE Healthcare, Waukesha, WI) from the vertex to the carina at an interval of 2.5 mm or 5 mm and target volumes were delineated on each slice of the CT images. The gross tumour volume (GTV) was defined as the primary nasopharyngeal lesion and the involved LN according to physical examination, fibreoptic nasopharyngoscopy and radiologic examinations such as CT or MRI of the head and neck and ^{18}F-FDG PET. The total radiation dose was typically 70–72 Gy for the GTV, 60 Gy for a high-risk clinical target volume (CTV) and 46 Gy for a low-risk CTV in 2–2.4 Gy fractions for GTV and 1.9–2 Gy fractions for CTV. The concurrent chemotherapy was delivered in 3 cycles of high-dose cisplatin (80 mg m^{-2} or 100 mg m^{-2}, i.v. on Days 1, 22 and 43) or in 6–7 cycles of weekly cisplatin (40 mg m^{-2}, i.v. on Days 1, 8, 15, 22, 29, 36 and 43) during radiotherapy. In patients treated before 2006, three cycles of induction chemotherapy with various combination regimens that included cisplatin were performed before the concurrent chemoradiotherapy. The patients were interviewed weekly during the treatment, in conjunction with an evaluation of their complete blood count and body weight and a physical examination. 1 month after the completion of treatment, response evaluation was performed by physical examination and fibreoptic nasopharyngoscopy. Post-treatment ^{18}F-FDG PET evaluations were performed 1–3 months after treatment completion. The patients were followed up periodically with 3-month intervals for the first 3 years and every 6 months or 1 year thereafter with physical examination and fibreoptic nasopharyngoscopy with or without CT, MRI or ^{18}F-FDG PET.

Fluorine-18 fludeoxyglucose positron emission tomography imaging

All patients underwent ^{18}F-FDG PET/CT scans with a Biograph Sensation 16 system ($n = 42$) or TruePoint 40 system ($n = 31$) that was equipped with a 16-slice or 40-slice CT scanner. The patients were instructed to fast for at least 6 h before the ^{18}F-FDG PET scanning and all patients had serum glucose concentrations of <150 mg dl^{-1} before the i.v. administration of ^{18}F-FDG (7.4 MBq per kilogram of body weight, with a minimum of 370 MBq). The whole-body images were obtained 50–70 min after the administration of ^{18}F-FDG and the CT scanning was performed from the skull base to the proximal thigh in spiral mode at 120 kV and auto milliampere with a section width of 5 mm and collimation of 0.75 mm. No contrast medium was used for CT acquisition. The emission scans were obtained from the skull base to the proximal thigh in the craniocaudal direction and the acquisition time was 2 min or 3 min per bed position using 7–8 bed positions. The ^{18}F-FDG PET images were reconstructed with CT attenuation correction using an ordered subsets expectation-maximization algorithm (2 iterations, 16 subsets) resulting in a 128×128 matrix, and post-reconstruction smoothing with a Gaussian filter (full width at half maximum, 6 mm) was applied.

Fluorine-18 fludeoxyglucose positron emission tomography interpretation

The ^{18}F-FDG PET images were imported into the workstation in digital imaging and communications in medicine format and evaluated using a commercial software package (INFINITT PACS; INFINITT Healthcare Co. Ltd, Seoul, Republic of Korea). The ^{18}F-FDG PET parameters evaluated were as follows: SUV$_{max}$, SUV$_{mean}$, SUV$_{peak}$, MTVs (MTV$_{30}$–MTV$_{70}$) and TLGs (TLG$_{30}$–TLG$_{70}$). The standardized uptake value (SUV) was determined as the ratio of the decay-corrected activity in the tissue (in millicurie per millilitre) and the injected dose of ^{18}F-FDG (in millicurie) divided by the patient body weight (in grams). The SUV$_{max}$, SUV$_{mean}$ and SUV$_{peak}$ were defined as the value of the most intense voxel within the volume of interest (VOI), the average value within the VOI and the average value within a 1 cm^3 spherical volume surrounding the hottest voxels within the VOI, respectively. These values were calculated automatically by the software. The volumetric parameter MTV$_{30}$–MTV$_{70}$ was automatically calculated as the tumour volume with 30%, 40%, 50%, 60% and 70% of the SUV$_{max}$ as the threshold, respectively, and TLG$_{30}$–TLG$_{70}$ were determined by the product of each MTV and the corresponding SUV$_{mean}$ within that MTV. The spherical or ellipsoidal VOIs were drawn to encompass entire tumour lesions or metastatic LNs that showed hypermetabolism on PET and were checked in three dimensions (axial, sagittal and coronal planes) to exclude adjacent FDG-avid structures such as the brain. For primary tumours (T–), the SUV$_{max}$, SUV$_{mean}$, SUV$_{peak}$, MTV$_{30}$–MTV$_{70}$ and TLG$_{30}$–TLG$_{70}$ were assessed. For regional LNs, the SUV$_{max}$ and SUV$_{peak}$ were assessed because other parameters might be highly dependent on the differences in VOIs among physicians. When multiple VOIs for regional LNs were inevitably necessary because of bilateral retropharyngeal, bilateral neck and/or supraclavicular LN involvement, the ^{18}F-FDG PET parameters of the regional LNs were separately assessed for the farthest LN station [N(f)–] and

for the LN station with the highest SUV$_{max}$ value (N–). The order of the farthest LN was as follows: ipsilateral retropharyngeal; contralateral retropharyngeal; ipsilateral neck; contralateral neck; ipsilateral supraclavicular; contralateral supraclavicular LN. The laterality was determined according to the epicentre of the primary tumour. In patients who needed only one VOI for regional LN, ^{18}F-FDG PET parameter for the farthest LN station [N(f)–] and that for LN station that had the highest SUV$_{max}$ value (N–) were used as the same values for the analysis. The ^{18}F-FDG PET parameters were interpreted by a board-certified radiation oncologist (YJ). YJ drew and checked VOIs, and read automatically calculated values of SUV and volumetric parameters. The interpretation was performed twice by random sampling.

Statistics

Distant metastasis-free survival (DMFS) and overall survival (OS) rates were estimated from the date of the start of radiotherapy to the date of DM or last follow-up and to death from any cause or last follow-up, respectively, by the Kaplan–Meier method. Univariate and multivariate analyses by Cox proportional hazards models were performed to evaluate the prognostic impact of ^{18}F-FDG PET parameters and other clinical variables on DMFS. The ^{18}F-FDG PET parameters included in the univariate analysis were the SUV$_{max}$, SUV$_{mean}$, SUV$_{peak}$, MTV$_{30}$–MTV$_{70}$ and TLG$_{30}$–TLG$_{70}$. Of these, the MTV$_{30}$–MTV$_{70}$ and TLG$_{30}$–TLG$_{70}$ showed a skewed distribution and thus, their natural log-transformed variables were used in the analysis. For the SUV$_{max}$, SUV$_{mean}$ and SUV$_{peak}$, both continuous variables and binary variables were used for the univariate analysis. The optimal cut-off point of the continuous variable was determined by the R software package "maxstat", and the value with the smallest p-value for DMFS in the log rank statistics was chosen for the analysis. The clinical variables other than ^{18}F-FDG PET parameters included in the univariate analysis were age, sex, T stage, N stage, overall stage, radiotherapy dose and induction chemotherapy. Multivariate Cox proportional hazard models for DMFS were built with clinical variables with a p-value of <0.1 and each ^{18}F-FDG PET parameter with a p-value of <0.1. All statistical tests were two-sided and performed at the 5% level of significance using SPSS® v. 21.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) and R software version v. 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org).

RESULTS

Patient characteristics are summarized in Table 1. The median age was 49 years and the male/female ratio was 2.8. The overall stages were II, III and IV in 18%, 44% and 38% of patients, respectively. Most patients (95%) received concurrent chemoradiotherapy and induction chemotherapy was performed in 27% patients. The total radiotherapy dose was a median of 68 Gy (range, 54–70 Gy). The median interval between the pretreatment ^{18}F-FDG PET and start of radiotherapy was 0.7 months (range, 0.1–4.1 months). The ^{18}F-FDG PET parameters of the primary tumour (T–), LN (N–) and the farthest LN station [N(f)–] are summarized in Table 2. For primary tumour, the median SUV$_{max}$, SUV$_{mean}$ and SUV$_{peak}$ were 8.2,

3.3 and 6.7, respectively. For regional LNs, the median SUV_{max} and SUV_{peak} of LNs were 8.0 and 5.8, respectively. The median SUV_{max} and SUV_{peak} of the farthest LN station were 6.3 and 4.7, respectively. When assessing ^{18}F-FDG PET parameters of regional LNs, 51 patients had bilateral retropharyngeal, bilateral neck and/or supraclavicular LN involvement, and VOIs were separately drawn for ipsilateral retropharyngeal, contralateral retropharyngeal, ipsilateral neck, contralateral neck, ipsilateral supraclavicular and/or contralateral supraclavicular LN, respectively. In these 51 patients, the number of assessed VOIs for regional LNs were 2, 3 and 4 in 27 (37%) patients, 15 (21%) patients and 9 (12%) patients, respectively. In all patients, the locations of the farthest LN station were ipsilateral retropharyngeal, contralateral retropharyngeal, ipsilateral neck, contralateral neck, ipsilateral supraclavicular and contralateral supraclavicular LN in 3 (4%) patients, 1 (1%) patient, 22 (30%) patients, 38 (52%) patients, 5 (7%) patients and 4 (5%) patients, respectively. In 13 patients with N3b stage, the location of supraclavicular LNs were ipsilateral and contralateral in 9 patients and 4 patients, respectively. Among nine patients with ipsilateral supraclavicular LN involvement, four patients also had contralateral neck LN involvement, but ipsilateral supraclavicular LN was closely connected to ipsilateral neck LN and could not be evaluated separately from the ipsilateral neck LN. So, in these four patients, contralateral neck LN instead of ipsilateral supraclavicular LN was defined as the farthest LN station. The ^{18}F-FDG PET parameters of N– and N(f)– were the same in 22 patients with a single VOI and in 19 of 51 patients with multiple VOIs who had the highest SUV_{max} in the farthest LN station.

The median follow-up period was 53 months (range, 12–110 months). The pattern of failure was DM, locoregional recurrence and both DM and locoregional recurrence in 13 (18%) patients, 4 (6%) patients and 2 (3%) patients, respectively. The 3-year and 5-year OS rates were 88% and 83%, respectively (Figure 1a). The 3-year and 5-year DMFS rates were 83% and 79%, respectively (Figure 1b). In univariate analysis, the T–SUV_{max} (≤ 8.0 vs >8.0; $p = 0.023$), T–SUV_{mean} (≤ 3.2 vs >3.2; $p = 0.035$), T–SUV_{peak} (≤ 10.2 vs >10.2; $p = 0.007$), N–SUV_{max} (≤ 10.6 vs >10.6; $p = 0.008$), N–SUV_{peak} (≤ 7.7 vs >7.7; $p = 0.032$), N(f)–SUV_{max} (≤ 10.6 vs >10.6, $p < 0.001$; continuous variable, $p = 0.001$) and N(f)–SUV_{peak} (≤ 8.5 vs >8.5, $p < 0.001$; continuous variable, $p = 0.003$) were significant prognostic factors for DMFS (Tables 3 and 4). Among the clinical variables, N stage was the only variable with a p-value of <0.1 in the univariate analysis.

Table 1. Patient characteristics

Characteristics	Number (%)
Age (years)	
Median (range)	49 (13–72)
Gender	
Male/female	54 (74)/19 (26)
T stage (AJCC 7th edition)	
T1/T2/T3/T4	19 (26)/17 (23)/18 (25)/19 (26)
N stage (AJCC 7th edition)	
N1/N2/N3b	28 (38)/32 (44)/13 (18)
Overall stage (AJCC 7th edition)	
II/III/IV	13 (18)/32 (44)/28 (38)
Pathologic classification	
Keratinizing squamous cell carcinoma	3 (4)
Non-keratinizing carcinoma[a]	62 (85)
Unspecified	8 (11)
Radiotherapy dose (Gy)	
Median (range)	68 (54–70)
Induction chemotherapy	
Yes/no	20 (27)/53 (73)
Concurrent chemoradiotherapy	
Yes/no	69 (95)/4 (6)

AJCC, American Joint Committee on Cancer.
[a]Among 62 patients with non-keratinizing carcinoma, differentiation status was evaluated in 28 patients. The 8 patients had differentiated carcinoma and 20 patients had undifferentiated carcinoma.

Table 2. Positron emission tomography parameters for primary tumour (T−), lymph node (LN) (N−) and the farthest LN [N(f)−]

Parameter	Median (range)	Parameter	Median (range)
$T–SUV_{max}$	8.2 (2.2–25.8)	$\ln(T−MTV_{30})$	2.6 (0.6–4.8)
$T−SUV_{mean}$	3.3 (1.1–11.9)	$\ln(T−MTV_{40})$	2.2 (−0.2–4.6)
$T−SUV_{peak}$	6.7 (1.6–19.6)	$\ln(T−MTV_{50})$	1.7 (−0.6–4.5)
$N−SUV_{max}$	8.0 (1.6–21.7)	$\ln(T−MTV_{60})$	1.2 (−1.6–4.1)
$N−SUV_{peak}$	5.8 (1.2–18.4)	$\ln(T−MTV_{70})$	0.7 (−2.7–3.2)
$N(f)−SUV_{max}$	6.3 (1.6–20.1)	$\ln(T−TLG_{30})$	4.0 (1.8–6.6)
$N(f)−SUV_{peak}$	4.7 (1.2–14.4)	$\ln(T−TLG_{40})$	3.8 (1.3–6.5)
		$\ln(T−TLG_{50})$	3.4 (1.0–6.4)
		$\ln(T−TLG_{60})$	3.1 (0.2–6.1)
		$\ln(T−TLG_{70})$	2.6 (−0.1–5.3)

ln, natural log; MTV, metabolic tumour volume; MTV_{30}–MTV_{70}, tumour volume with 30%, 40%, 50%, 60% and 70% of the maximum standardized uptake value as the threshold; SUV_{max}, maximum standardized uptake value; SUV_{mean}, mean standardized uptake value; SUV_{peak}, peak standardized uptake value; TLG, total lesion glycolysis; TLG_{30}–TLG_{70}, product of each MTV and the corresponding mean standardized uptake value within that MTV.

The seven PET parameters ($T–SUV_{max}$, $T–SUV_{mean}$, $T–SUV_{peak}$, $N–SUV_{max}$, $N–SUV_{peak}$, $N(f)–SUV_{max}$ and $N(f)–SUV_{peak}$) with p-values of <0.1 in the univariate analysis were incorporated into seven separate multivariate Cox proportional hazard models for DMFS after adjusting for the N stage (Table 5). The SUV_{max} (hazard ratio = 4.169; $p = 0.033$) and SUV_{peak} (hazard ratio = 3.973; $p = 0.022$) of the primary tumour and the SUV_{max} (hazard ratio = 6.524; $p = 0.001$) and SUV_{peak} (hazard ratio = 5.399; $p = 0.001$) of the farthest LN station were significant prognostic factors for DMFS in multivariate analysis. The C statistic indexes for all models were >0.7. The 5-year DMFS rates were significantly higher in patients with a lower SUV_{max} (≤10.6 vs >10.6, 88% vs 43%; $p < 0.001$) and SUV_{peak} (≤8.5 vs > 8.5, 86% vs 47%; $p < 0.001$) of the farthest LN station (Figure 2a,b).

DISCUSSION

In our present study, various pre-treatment ^{18}F-FDG PET parameters of primary tumours and regional LNs (the SUV_{max} and SUV_{peak} of the primary tumour and the farthest LN station) were found to be significant prognostic factors for DMFS in patients with nasopharyngeal carcinoma with LN involvement.

In particular, the SUV parameters of the farthest LN station [$N(f)–SUV_{max}$ and $N(f)–SUV_{peak}$] were the strongest prognostic factors.

To our knowledge, our present study is the first to evaluate and determine the prognostic value of the ^{18}F-FDG PET parameters of the farthest LN station. Because patients with nasopharyngeal carcinoma often have multiple LN involvement, such as bilateral retropharyngeal, bilateral neck and/or supraclavicular LNs, the definition of multiple VOIs of separate LN stations may be required, and ^{18}F-FDG PET parameters have to be measured separately at each VOI. However, it is difficult to select the ^{18}F-FDG PET parameters of one of the multiple VOIs or to completely integrate the metabolic information of multiple VOIs. Moreover, ^{18}F-FDG PET parameters of regional LNs might be highly dependent on the differences in VOIs among physicians. For these reasons, few studies evaluated the prognostic value of ^{18}F-FDG PET parameters of regional LNs for predicting DMFS, and the SUV_{max} of regional LNs has been the most widely used parameter because of its convenience and reproducibility.[15–19] The SUV_{max} of LNs ($N–SUV_{max}$) was reported as a significant prognostic factor for DMFS as itself or

Figure 1. Kaplan–Meier survival curves for overall survival rates (a) and distant metastasis-free survival rates (b).
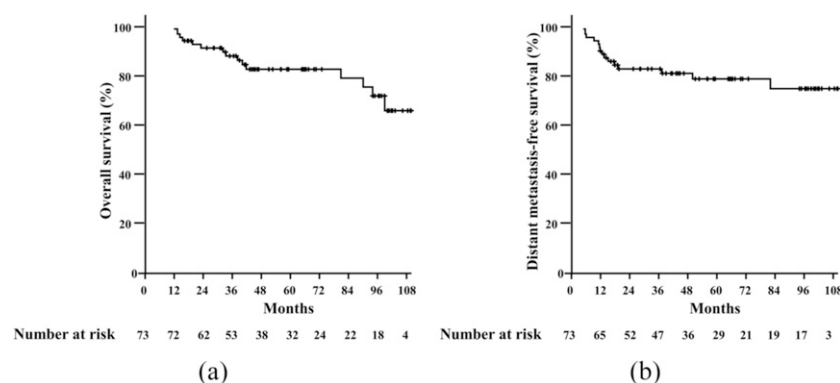
Table 3. Univariate Cox proportional hazard model for distant metastasis-free survival rates

Factors	Hazard ratio	95% CI	*p*-value
Age	0.997	0.961–1.034	0.869
Gender (male)	0.369	0.083–1.641	0.191
T stage (T1–2)	1.675	0.595–4.717	0.329
N stage			0.087
N2 (N1)	5.513	1.203–25.275	0.028[a]
N3b (N1)	3.562	0.594–21.353	0.164
Overall stage			
IV (II–III)	1.465	0.531–4.043	0.461
Radiotherapy dose	1.001	1.000–1.002	0.210
Induction CTx (yes)	0.727	0.227–2.323	0.590
$T–SUV_{max}$	1.079	0.990–1.176	0.085
$T–SUV_{mean}$	1.168	0.966–1.411	0.109
$T–SUV_{peak}$	1.120	0.993–1.263	0.065
$N–SUV_{max}$	1.088	0.988–1.198	0.088
$N–SUV_{peak}$	1.077	0.939–1.235	0.292
$N(f)–SUV_{max}$	1.213	1.081–1.360	0.001[a]
$N(f)–SUV_{peak}$	1.298	1.092–1.543	0.003[a]
ln $(T–MTV_{30})$	0.986	0.542–1.796	0.964
ln $(T–MTV_{40})$	1.055	0.609–1.828	0.849
ln $(T–MTV_{50})$	1.116	0.667–1.867	0.675
ln $(T–MTV_{60})$	1.166	0.713–1.905	0.541
ln $(T–MTV_{70})$	1.141	0.709–1.838	0.587
ln $(T–TLG_{30})$	1.342	0.800–2.250	0.265
ln $(T–TLG_{40})$	1.349	0.829–2.196	0.229
ln $(T–TLG_{50})$	1.365	0.859–2.169	0.187
ln $(T–TLG_{60})$	1.391	0.885–2.185	0.152
ln $(T−TLG_{70})$	1.384	0.873–2.195	0.167

CI, confidence interval; CTx, chemotherapy; ln, natural log; MTV, metabolic tumour volume; MTV_{30}–MTV_{70}, tumour volume with 30%, 40%, 50%, 60% and 70% of the maximum standardized uptake value as the threshold; SUV_{max}, maximum standardized uptake value; SUV_{mean}, mean standardized uptake value; SUV_{peak}, peak standardized uptake value; TLG, total lesion glycolysis; TLG_{30}–TLG_{70}, product of each MTV and the corresponding mean standardized uptake value within that MTV.
[a]*p*-value <0.05.

in combination with the SUV_{max} of the primary tumour ($T–SUV_{max}$).[15–17,19] In the two recent studies, prognostic values of volumetric parameters of regional LN were also evaluated, but the results were not consistent.[18,19] In the study of Chang et al,[18] which evaluated TLG of the primary tumour (T–), LN (N–) and their combination (Total–), neither N–TLG nor Total–TLG was a significant prognostic factor for DMFS. In the study of Lin et al,[19] both MTV and TLG of LN were significant prognostic factors for DMFS as itself or in the combination with those of the primary tumour. However, those prognostic values were not consistent in the multivariate analysis.

In the present study, we hypothesized that the metabolic activity of the farthest LN station would have a prognostic impact on DMFS, even though that LN station did not show higher metabolic activity than other LN stations, and measured the ^{18}F-FDG PET parameters of the farthest LN station [N(f)–] as well as the ^{18}F-FDG PET parameters of the LN station that had the highest SUV_{max} value (N–). Surprisingly, the SUV parameters of the farthest LN station [$N(f)–SUV_{max}$ and $N(f)–SUV_{peak}$] were the strongest prognostic factors for predicting DMFS. There were huge differences in 5-year DMFS depending on the obtained, optimal cut-off values of $N(f)–SUV_{max}$ and $N(f)–SUV_{peak}$ (88% *vs* 43%, $p < 0.001$; 86% *vs* 47%, $p < 0.001$). Further studies with larger number of patients seem to be needed to confirm the prognostic value of $N(f)–SUV_{max}$ and $N(f)–SUV_{peak}$. In contrast, the SUV parameters of the LN station with the highest SUV_{max} ($N–SUV_{max}$ and $N–SUV_{peak}$) were

Table 4. Optimal cut-off and its corresponding 5-year distant metastasis-free survival (DMFS) rates

Factors	Cut-off	5-year DMFS (%)	p-value
T–SUV$_{max}$	≤8.0 ($n = 35$)	89	0.023[a]
	>8.0 ($n = 38$)	69	
T–SUV$_{mean}$	≤3.2 ($n = 30$)	91	0.035[a]
	>3.2 ($n = 43$)	71	
T–SUV$_{peak}$	≤10.2 ($n = 52$)	87	0.007[a]
	>10.2 ($n = 18$)	60	
N–SUV$_{max}$	≤10.6 ($n = 52$)	87	0.008[a]
	>10.6 ($n = 21$)	60	
N–SUV$_{peak}$	≤7.7 ($n = 44$)	87	0.032[a]
	>7.7 ($n = 20$)	63	
N(f)–SUV$_{max}$	≤10.6 ($n = 59$)	88	<0.001[a]
	>10.6 ($n = 14$)	43	
N(f)–SUV$_{peak}$	≤8.5 ($n = 50$)	86	<0.001[a]
	>8.5 ($n = 15$)	47	

SUV$_{max}$, maximum standardized uptake value; SUV$_{mean}$, mean standardized uptake value; SUV$_{peak}$, peak standardized uptake value.
[a]p-value <0.05.

significant prognostic factors in the univariate analysis but not in the multivariate analysis that was adjusted for the N stage. When we consider that the conventional nodal stage was assessed according to the size, laterality and level of the involved LNs, the metabolic activity of the farthest LN station may provide additional values for predicting DMFS. However, in patients without LN involvement, the ^{18}F-FDG PET parameters of LNs cannot be evaluated, which may be the reason for the small number of studies examining the ^{18}F-FDG PET parameters of LNs.

In previous studies, clinical factors such as sex,[15,16,20] T stage,[20,28] N stage[21,28–30] and overall stage[15,16,21] were reported as prognostic factors for DMFS in nasopharyngeal carcinoma. Among the ^{18}F-FDG PET parameters, the SUV$_{max}$ of the primary tumour was the most frequently reported prognostic factor for DMFS[20,21] or disease free survival rate.[22–25] The SUV$_{max}$ is the most simple and reproducible ^{18}F-FDG PET parameter because it is less affected by physician-dependent differences in the VOI setting. Moreover, it can be widely used regardless of LN involvement. However, the SUV$_{max}$ is highly sensitive to noise and is not representative of the metabolic activity of the whole tumour, even though it reflects the part with the highest metabolic activity.[31] The SUV$_{mean}$ of the primary tumour may provide more information for whole-tumour metabolism and is less susceptible to noise. However, its prognostic value has not been commonly evaluated, possibly because the SUV$_{mean}$ is sensitive to physician-dependent differences in the VOI setting. To our knowledge, only one study has evaluated the prognostic value of the SUV$_{mean}$ of the primary tumour in nasopharyngeal carcinoma, but this parameter was not a significant prognostic factor for DMFS.[17] The SUV$_{peak}$ of the primary tumour is less sensitive to noise than the SUV$_{max}$ and less affected by the physician-dependent VOI definition than the SUV$_{mean}$; but, no study has evaluated this parameter. In the

present study, we evaluated the T–SUV$_{mean}$ and T–SUV$_{peak}$ as well as the T–SUV$_{max}$, finding that the T–SUV$_{max}$ and T–SUV$_{peak}$ were significant prognostic factors for DMFS.

Recently, the GTV of primary tumour has been evaluated as a prognostic factor for DMFS owing to the hypothesis that GTV may provide more information on overall tumour burden than T stage, which is determined by the anatomic location and extent of the tumour. In the study of Guo et al,[32] the GTV of primary tumour was an independent prognostic factor for DMFS and improved the prognostic validity of T stage classification. On the hypothesis that volumetric ^{18}F-FDG PET parameters may also predict DMFS, we evaluated the prognostic values of the MTV and TLG. When defining the MTV, the optimal threshold to determine VOI of MTV has not been established yet, even though an SUV value of 2.5 or 3.0 has been the most widely used threshold.[33] So, we examined various percentages (30%, 40%, 50%, 60% and 70%) of SUV$_{max}$ as the thresholds for VOIs of MTV. Although the ln (T−MTV$_{60}$) and ln (T−TLG$_{60}$), which used 60% of SUV$_{max}$ as the threshold, showed the lowest p-values, neither MTVs nor TLGs were significant prognostic factors for DMFS in the univariate analysis. In other studies, the MTV and TLG were reported as significant prognostic factors for disease free survival rate and OS,[14,17,18,31] but prognostic values of the MTV and TLG for predicting DMFS were not consistent in the multivariate analysis.[14,16–18] The negative findings of volumetric parameters for predicting DMFS might have due to three possible reasons. First, the number of patients might be too small to show the prognostic value of volumetric parameters. Second, in the development of DM, the highest metabolic activity of the primary tumour, regional LN and farthest LN station might be more important than the overall tumour burden, especially in nasopharyngeal carcinoma, which is more radiosensitive than other head and neck cancers.

Table 5. Association between PET parameter and distant metastasis-free survival rates adjusted for N stage by multivariate Cox proportional hazard model

| Factors	Hazard ratio	95% CI	*p*-value	C index
Model 1: T–SUV_{max}				
N stage				
N1 *vs* N2	4.156	0.893–19.352	0.069	
N1 *vs* N3b	2.894	0.479–17.474	0.247	
T−SUV_{max} (≤8.0 *vs* >)	4.169	1.123–15.476	0.033[a]	0.763
Model 2: T–SUV_{mean}				
N stage				
N1 *vs* N2	4.215	0.908–19.576	0.066	
N1 *vs* N3b	2.844	0.471–17.164	0.255	
T–SUV_{mean} (≤3.2 *vs* >)	4.385	0.969–19.849	0.055	0.746
Model 3: T–SUV_{peak}				
N stage				
N1 *vs* N2	4.559	0.986–21.083	0.052	
N1 *vs* N3b	3.558	0.473–26.771	0.218	
T–SUV_{peak} (≤10.2 *vs* >)	3.973	1.215–12.991	0.022[a]	0.769
Model 4: N–SUV_{max}				
N stage				
N1 *vs* N2	4.323	0.916–20.389	0.064	
N1 *vs* N3b	2.697	0.437–16.640	0.285	
N–SUV_{max} (≤10.6 *vs* >)	2.860	0.994–8.228	0.051	0.725
Model 5: N–SUV_{peak}				
N stage				
N1 *vs* N2	4.415	0.903–21.573	0.067	
N1 *vs* N3b	2.008	0.273–14.786	0.493	
N–SUV_{peak} (≤7.7 *vs* >)	2.222	0.714–6.914	0.168	0.715
Model 6: N(f)–SUV_{max}				
N stage				
N1 *vs* N2	4.490	0.965–20.896	0.056	
N1 *vs* N3b	1.742	0.274–11.084	0.557	
N(f)–SUV_{max} (≤10.6 *vs* >)	6.524	2.228–19.108	0.001[a]	0.756
Model 7: N(f)–SUV_{peak}				
N stage				
N1 *vs* N2	4.662	1.013–21.466	0.048[a]	
N1 *vs* N3b	2.206	0.364–13.371	0.389	
N(f)–SUV_{peak} (≤8.5 *vs* >)	5.399	1.935–15.068	0.001[a]	0.745

CI, confidence interval; SUV_{max}, maximum standardized uptake value; SUV_{mean}, mean standardized uptake value; SUV_{peak}, peak standardized uptake value.
[a]*p*-value <0.05.

Third, the thresholds which were used for determining volumetric parameters in the previous studies might be inappropriate to predict DMFS. In the present study, we defined MTV and TLG with the thresholds of the various percentages (30%, 40%, 50%, 60% and 70%) of SUV_{max}, but neither MTVs nor TLGs predicted DMFS. Even in the studies which defined volumetric parameters with the most commonly used threshold, the absolute SUV value of 2.5, volumetric parameters were significant prognostic factors for

Figure 2. Kaplan–Meier survival curves for distant metastasis-free survival rates depending on the maximum standardized uptake value of the farthest lymph node (LN) [N(f)–SUV$_{max}$] (a) and the peak standardized uptake value of the farthest LN [N(f)–SUV$_{peak}$] (b).

(a)   (b)
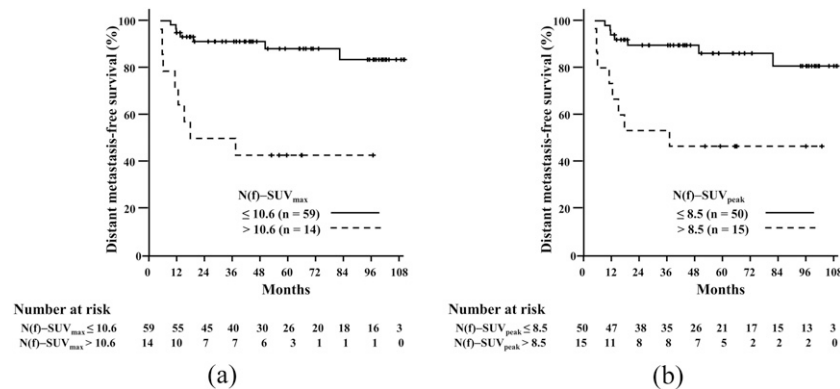
DMFS in the univariate analysis, but not in the multivariate analysis.[15,17–19] Therefore, to conclude the prognostic value of volumetric parameters, further studies which include larger number of patients and evaluate volumetric parameters with more various thresholds seem to be needed.

There were several limitations to the present study. First, because of the relatively small number of patients compared with the number of variables and the possible correlation within the ^{18}F-FDG PET parameters, it was difficult to enter all variables with a p-value of <0.1 in the univariate analysis into the multivariate analysis. As an alternative, we built seven multivariate Cox proportional hazard models with clinical variables with p-values of <0.1 and each ^{18}F-FDG PET parameter with a p-value of <0.1, and all models showed a C statistic index of >0.7. Second, because of the retrospective nature of this study, treatment characteristics, especially those of the chemotherapy regimen, were heterogeneous, which might have influenced the outcomes. Third, although ^{18}F-FDG PET scanning was performed with an in-house standardized protocol and we excluded patients who had pre-treatment ^{18}F-FDG PET evaluation at another hospital or by a scanner other than a Biograph Sensation 16 (Siemens Medical Systems) or TruePoint 40 (Siemens Medical Systems) to minimize possible interscanner variability, biological and technological variabilities would still have existed. Fourth, the optimal cut-off value of ^{18}F-FDG PET parameters in the present study may not consistently be the best discrimination value in other studies. Fifth, although we examined various percentages (30%, 40%, 50%, 60% and 70%) of SUV$_{max}$ as the thresholds for VOIs of MTV, the most commonly used threshold, the SUV of 2.5, was not examined. Sixth, all of the ^{18}F-FDG PET parameters in the present study were characterized by calculating the SUV. Although the SUV has been used as the major parameter for the ^{18}F-FDG PET interpretation, it does not differentiate metabolized and unmetabolized ^{18}F-FDG and so, its robustness is strongly discussed now.[34] Nevertheless, to our knowledge, our present study is the only one to evaluate the prognostic value of various pre-treatment ^{18}F-FDG PET parameters of both primary tumours and LNs in predicting DMFS in the IMRT era and show a strong prognostic impact of the ^{18}F-FDG PET parameters of the farthest LN station.

CONCLUSION
In patients with nasopharyngeal cancer with LN involvement, the SUV parameter of the farthest LN station seems to be an important ^{18}F-FDG PET parameter for predicting DM. Further studies are needed to validate its clinical significance.

FUNDING

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