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Prognostic value of nodal SUV_{max} of ^{18}F-FDG PET/CT in nasopharyngeal carcinoma treated with intensity-modulated radiotherapy

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Purpose: To investigate the predictive role of maximum standardized uptake value (SUV_{max}) of 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) in nasopharyngeal cancer patients treated with intensity-modulated radiotherapy (IMRT).

Materials and Methods: Between October 2006 and April 2016, 53 patients were treated with IMRT in two institutions and their PET/CT at the time of diagnosis was reviewed. The SUV_{max} of their nasopharyngeal lesions and metastatic lymph nodes (LN) was recorded. IMRT was delivered using helical tomotherapy. All patients except for one were treated with concurrent chemoradiation therapy (CCRT). Correlations between SUV_{max} and patients' survival and recurrence were analyzed.

Results: At a median follow-up time of 31.5 months (range, 3.4 to 98.7 months), the 3-year overall survival (OS) and disease-free survival (DFS) rates were 83.2% and 77.5%, respectively. In univariate analysis, patients with a higher nodal pre-treatment SUV_{max} (≥ 13.4) demonstrated significantly lower 3-year OS (93.1% vs. 55.5%; p = 0.003), DFS (92.7% vs. 38.5%; p < 0.001), locoregional recurrence-free survival (100% vs. 50.5%; p < 0.001), and distant metastasis-free survival (100% vs. 69.2%; p = 0.004), respectively. In multivariate analysis, high pre-treatment nodal SUV_{max} (≥ 13.4) was a negative prognostic factor for OS (hazard ratio [HR], 7.799; 95% confidence interval [CI], 1.506–40.397; p = 0.014) and DFS (HR, 9.392; 95% CI, 1.989–44.339; p = 0.005).

Conclusions: High pre-treatment nodal SUV_{max} was an independent prognosticator of survival and disease progression in nasopharyngeal carcinoma patients treated with IMRT in our cohort. Therefore, nodal SUV_{max} may provide important information for identifying patients who require more aggressive treatment.

Keywords: Nasopharyngeal carcinoma, SUV_{max}, Prognostic factor

Introduction

Overall, survival and local control of nasopharyngeal cancer patients have both significantly improved due to advances in diagnostic imaging and the introduction of systemic chemotherapy and intensity-modulated radiotherapy (IMRT), but distant metastasis is still a major cause of treatment failure [1-3]. Therefore, early identification of patients with

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a high risk of disease progression before treatment is very important because administration of individualized therapy to these patients may improve their clinical outcome. As current prognostic factors are limited when identifying high-risk patients who require more aggressive treatment [4-6], newer prognostic factors for clarifying the risk stratification of patients are needed.

Maximum standardized uptake value (SUV_{max}) of 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is an index that reflects tumor metabolism. The clinical significance of a high SUV_{max} has already been identified for many carcinomas such as breast and lung cancer [7,8]. In addition, the findings of several studies have suggested poorer prognosis in nasopharyngeal cancer patients with a higher SUV_{max} [9-15]. Accordingly, we conducted a study to clarify the prognostic significance of high pre-treatment SUV_{max} and evaluated the significance of the SUV_{max} in both primary site and metastatic nodes.

Materials and Methods

1. Study patients

Between October 2006 and April 2016, 67 nasopharyngeal patients were initially treated with IMRT in two institutions. We retrospectively analyzed these patients' medical records and excluded patients with distant metastasis at the time of diagnosis or who had another malignancy. In addition, patients who had previously received radiotherapy at another hospital and did not complete the planned radiation therapy were excluded. Finally, 53 patients were included in this study that met the following criteria: (1) biopsy-proven nasopharyngeal carcinoma; (2) stage I to IVB according to the American Joint Committee on Cancer (AJCC) staging, 7th edition; and (3) underwent treatment with IMRT using helical tomotherapy (Accuray Inc., Sunnyvale, CA, USA).

All patients underwent a complete medical history taking and physical examination at the time of diagnosis. Fiber-optic nasopharyngoscopy, complete blood count (CBC), and baseline blood chemistry were also performed. Neck CT and/or neck magnetic resonance imaging (MRI), chest radiography with chest CT, abdominal CT, a bone scan, and PET/CT were performed for staging evaluation.

We reviewed the medical records and diagnostic images of all patients, and investigated prognostic factors including SUV_{max}. All patients were re-staged according to the 7th edition of the AJCC. We reviewed neck MRI or neck CT (if neck MRI was not performed) for evaluating the node size of patients with LN metastasis, and evaluated the longest diameter of the coronal (long axis) and axial scan (short axis) for the largest metastatic nodes. Nodal size was evaluated in 40 patients, excluding 6 patients whose initial imaging was insufficient. We retrospectively reviewed the initial PET/CT of all patients and the pre-treatment SUV_{max} of the primary nasopharyngeal lesion and metastatic nodes. The pre-treatment SUV_{max} of the primary site was identified for all 53 patients. Because 7 patients did not have any metastatic lymph nodes (N0) or did not have a numerical value of the SUV_{max} of metastatic LNs recorded, pre-treatment nodal SUV_{max} was identified for 46 patients. For patients with multiple metastatic nodes, the highest SUV_{max} value among several nodal lesions was selected as the nodal SUV_{max}. We also reviewed PET/CT performed within 3 months after completion of RT, and we examined the post-RT metabolic response in 26 patients.

2. Protocol of PET/CT and imaging analysis

All patients underwent PET/CT before treatment. Both institutions used the same PET/CT protocol (fasting duration, pre-injected blood glucose level, amount of injected ^{18}F-FDG, post-injection interval), but the PET/CT scanner used was different—one institution used Biograph Duo (Siemens Medical Solutions, Knoxville, TN, USA) and the other institution used Discovery STE (GE Healthcare Inc., Milwaukee, WI, USA). Subjects fasted for at least 6 hours before PET/CT scans, and their blood glucose levels were measured before injection of ^{18}F-FDG. None of the patients had blood glucose levels greater than 130 mg/dL before injection. A dose of 5.5–7.4 MBq/kg of FDG was administered intravenously and scanning began 60 minutes after injection. The CT scan began at the orbitomeatal line and progressed to the proximal thigh (Biograph Duo: 130 kVp, 80 mA, and 5 mm slice thickness; Discovery STE: 140 kVp, auto mA, and 3.75 mm slice thickness). The PET scan followed immediately over the same body region. The CT data were used for attenuation correction, and images were reconstructed using a standard ordered-subset expectation maximization (OSEM) algorithm (2 iterations, 8 subsets). The axial resolution was 6.5 or 4.5 mm at the center of the field of view.

All PET/CT images were analyzed by experienced nuclear medicine physicians. The metabolic activity of any lesion with a visually abnormal FDG uptake was analyzed using the standardized uptake value (SUV). SUV was calculated by the following formula:

$$SUV = \frac{\text{Radioactivity concentration in tissue (MBq/kg)}}{\text{Injected radioactivity (MBq)/Patient's weight (kg)}}$$

SUV_{max} of ^{18}F-FDG was measured by visually placing the region of interest (ROI) around the site of increased FDG uptake.

3. Radiotherapy

For simulation and treatment, patients were placed in the supine position and immobilized from head to neck with a thermoplastic mask (CIVCO Radiotherapy Inc., Coralville, IA, USA). A CT simulation was performed with a slice thickness of 2.5 mm extending from the vertex to the upper chest using a LightSpeed RT 16 CT scanner (GE Healthcare Inc.). All patients were treated with IMRT with a radical aim with a 6-MV photon beam using helical tomotherapy, 5 days per week. Gross tumor volume (GTV) was delineated based on enhanced neck CT, neck MRI, and PET/CT. IMRT was performed by using a simultaneous integrated boost technique for each GTV of the nasopharynx and metastatic nodes, and clinical target volume (CTV) 1, 2, and 3. CTV1 was defined as the GTV of the nasopharynx plus a 5-mm to 1-cm margin to cover the risky sites of microscopic tumor cell infiltration around the GTV and anatomic extension of the nasopharynx. CTV2 was defined as the high-risk region of lymph node metastasis (both II, III, and Va), and CTV3 was defined as the low-risk region of lymph node metastasis (both IV and Vb). The planning target volume (PTV) was defined as the 3–5 mm margin of each CTV. The prescription dosage was 68–76 Gy/32–36 fractions (fraction size, 2.12–2.3 Gy) to the GTV of the primary site and metastatic nodes, respectively, 60–66 Gy/32–36 fractions (fraction size, 1.8–2 Gy) to CTV1, 57–61 Gy/32–36 fractions (fraction size, 1.7–1.9 Gy) to CTV2, and 50–56 Gy/24–36 fractions (fraction size, 1.6–2.12 Gy) to CTV3. For CTV3, some patients were scheduled for 50.8 Gy/24 fractions (fraction size, 2.12 Gy) or 50 Gy/25 fractions (fraction size, 2.0 Gy) and were excluded from the target volume in a cone down plan. The prescription dose of PTV was 80%–100% of the dose to each CTV. The prescribed dose encompassed at least 95% of the target volume. Critical adjacent structures such as the brainstem, optic nerve, optic chiasm, parotid gland, submandibular gland, and mandible were spared as much as possible so as not to exceed the tolerance dose.

4. Chemotherapy

All patients except for one (who was treated with definitive radiotherapy alone) were treated with concurrent chemoradiation therapy (CCRT). Among these, 14 patients were treated with CCRT alone, 4 patients underwent neoadjuvant chemotherapy, 32 patients underwent adjuvant chemotherapy, and 2 patients underwent both neoadjuvant and adjuvant chemotherapy. Forty-eight out of 52 patients were treated with a cisplatin-based regimen (cisplatin 30 mg/m^2 on day 1 and every week for 6 or 7 cycles or cisplatin 100 mg/m^2 on day 1 and then every 3 weeks for 3 or 4 cycles during radiotherapy). The other four patients were administered either cisplatin (100 mg/m^2)/5-fluorouracil (5-FU; 1,000 mg/m^2), carboplatin (30 mg/m^2), etoposide (120 mg/m^2)/cisplatin (60 mg/m^2), or cetuximab, respectively. Cisplatin (100 mg/m^2 on day 1)/5-FU (1,000 mg/m^2 on days 1–5) was administered every month for 3 or 4 cycles, and docetaxel (70 mg/m^2 on day 1)/cisplatin (70 mg/m^2 on day 1)/5-FU (700 mg/m^2 on days 1–4) were administered every 3 weeks for 2 or 3 cycles, as induction or adjuvant chemotherapy.

5. Patient assessments and follow-up

All patients were evaluated weekly during RT, and then they underwent follow-up every 2–3 months after completion of RT for the first 2 years and every 4–6 months after that. Fiber-optic nasopharyngoscopy, CBC, blood chemistry, and physical examination including neck node palpation were performed at each follow-up. Neck CT or neck MRI was performed one month after the end of RT and PET/CT was performed three months for initial therapeutic response evaluation. Initial therapeutic response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1.

6. Study endpoints and statistical analysis

The primary endpoint of this study was the prognostic value of the SUV_{max} of PET/CT for treatment outcomes. Secondary end points were overall survival (OS), disease-free survival (DFS), locoregional recurrence-free survival (LRRFS), and distant metastasis-free survival (DMFS). We analyzed survival, recurrence, and prognostic factors including SUV_{max} of PET/CT. All statistical analysis was performed using SPSS ver. 18 for Windows, (SPSS Inc., Chicago, IL, USA). Actuarial 3-year OS, DFS, LRRFS, and DMFS were analyzed by the Kaplan-Meier method and the correlation of the survival rates with prognostic factors was analyzed by the log-lank test. Multivariate Cox proportional hazard models for OS and DFS were built with prognostic factors with a p-value of <0.1 in univariate analysis. A p-value less than 0.05 was defined as statistically significant. Chi-square tests and independent-sample t-tests were used to compare characteristics between the two groups classified by the cut-off of 13.4 for SUV_{max}-n. The correlation between primary site SUV_{max} and nodal SUV_{max},

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and the correlation between nodal size and nodal SUV_{max} were analyzed by linear regression. OS, DFS, LRRFS, and DMFS were calculated from the first date of treatment to the date of an event or the last follow-up visit. The endpoint of OS was defined as the occurrence of any death or last follow-up visit and the endpoint of DFS was defined as the occurrence of disease-related death or the diagnosis of a recurrence.

Results

1. Patient characteristics and clinical outcomes

A total of 53 patients who underwent IMRT between October 2006 and April 2016 were analyzed. The median age of this group was 49 years (range, 14 to 75 years) and the majority was men (79.2%). Thirty-nine patients (73.6%) out of 53 patients were positive for Epstein-Barr virus (EBV). Their pathologic classification was based on the 2005 World Health Organization classification. However, when the tissue type was described only as poorly differentiated nasopharyngeal carcinoma, it was categorized as 'poorly differentiated carcinoma', and when the tissue type was described only as a nasopharyngeal carcinoma; it was categorized as 'unclassified'. The most common pathologic type was non-keratinizing carcinoma (42 patients, 79.2%). Most of the patients (79.2%) had an advanced stage (stage III–IVB) and all patients had a performance status below Eastern Cooperative Oncology Group performance status 2. The patient characteristics are summarized in Table 1. Comparative assessment of the patients' characteristics between the two groups based on the nodal SUV_{max} cut-off value of 13.4 did not demonstrate any significant differences (Table 2). The median nodal size of the largest metastatic LN for the long axis was 31 mm (range, 12 to 59.04 mm) and 26 mm (range, 14 to 48.7 mm) for the short axis in the total cohort.

The median follow-up duration was 31.5 months (range, 3.4 to 98.7 months). Eight patients died and 8 patients experienced a recurrence during the follow-up period. Among the patients who experienced a recurrence, there was 1 patient with an isolated local recurrence, 2 patients with a distant recurrence without locoregional recurrence, 3 patients with local and regional recurrences, 1 patient with regional and distant recurrence, and 1 patient with local, regional, and distant recurrences. Recurrence or progression in the lymph node was categorized as a regional recurrence regardless of the presence of lymph node metastasis at initial diagnosis.

Three-year OS, DFS, LRRFS, and DMFS rates were 83.2%, 77.5%, 85.4%, and 90.9%, respectively. There were 28 patients (52.8%) with a complete response, 21 (39.6%) with a partial response, 2 with stable disease, and no patients with progressive disease at initial therapeutic response evaluation. The post-RT metabolic response was evaluated in 26 patients who underwent PET/CT within 3 months after completion of RT. Twelve patients had a metabolic complete response (SUV_{max}

Table 1. Clinical characteristics of patients (n = 53)

characteristic	No. of patients (%)
Sex	
Male	42 (79.2)
Female	11 (20.8)
Age (yr)	
<49	26 (49.1)
≥49	27 (50.9)
EBV status	
(–)	4 (7.5)
(+)	39 (73.6)
Unknown	10 (18.9)
ECOG performance status	
0	31 (58.5)
1	21 (39.6)
2	1 (1.9)
Pathology	
Keratinizing	5 (9.4)
Non-keratinizing	42 (79.2)
Poorly differentiated	4 (7.6)
Unclassified	2 (3.8)
T stage	
T1–T2	29 (54.7)
T3–T4	24 (45.3)
N stage	
N0	7 (13.2)
N1–N2	40 (75.5)
N3	6 (11.3)
AJCC stage	
I–II	11 (20.8)
III–IVB	42 (79.2)
Treatment	
CCRT alone	14 (26.4)
NCT + CCRT	4 (7.5)
CCRT + ACT	32 (60.4)
NCT + CCRT + ACT	2 (3.8)
RT alone	1 (1.9)

EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; Keratinizing, keratinizing squamous cell nasopharyngeal carcinoma; Non-keratinizing, non keratinizing nasopharyngeal carcinoma; Poorly differentiated, poorly differentiated nasopharyngeal carcinoma; AJCC, American Joint Committee on Cancer; CCRT, concurrent chemoradiation therapy; NCT, neoadjuvant chemotherapy; ACT, adjuvant chemotherapy; RT, radiotherapy.

Table 2. Patients' characteristics according to SUV_{max}-n group (n = 46)

	SUV_{max}-n < 13.4 (n = 33)	SUV_{max}-n ≥ 13.4 (n = 13)	p-value
Sex			
Male	26 (78.8)	11 (84.6)	0.409
Female	7 (21.2)	2 (15.4)	
Age (yr)			
<49	21 (63.6)	8 (61.5)	1
≥49	12 (36.4)	5 (38.5)	
EBV status			
(–)	3 (9.1)	0 (0)	0.562
(+)	25 (75.8)	9 (69.2)	
ECOG performance status			
0	18 (54.5)	9 (69.2)	0.154
1	15 (45.5)	3 (23.1)	
2	0 (0)	1 (7.7)	
Pathology			
Keratinizing	1 (3)	3 (23)	0.138
Non-keratinizing	27 (81.8)	9 (69.2)	
Poorly differentiated	3 (9.1)	1 (7.7)	
T stage			
T1–T2	17 (51.5)	10 (76.9)	0.115
T3–T4	16 (48.5)	3 (23.1)	
N stage			
N0–N1	11 (33.3)	4 (30.8)	1
N2–N3	22 (66.7)	9 (69.2)	
AJCC stage			
I–II	6 (18.2)	3 (23.1)	0.698
III–IVB	27 (81.8)	10 (76.9)	
Treatment			
CCRT	10 (30.3)	2 (15.4)	0.684
NCT + CCRT	3 (9.1)	1 (7.7)	
CCRT + ACT	19 (57.6)	9 (69.2)	
NCT + CCRT + ACT	1 (3.0)	1 (7.7)	
Node size (mm)			
Long axis	30.889	35.012	0.231
Short axis	26.333	28.069	0.528

Values are presented as number (%).
EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; Keratinizing, keratinizing squamous cell nasopharyngeal carcinoma; Non-keratinizing, non keratinizing nasopharyngeal carcinoma; Poorly differentiated, poorly differentiated nasopharyngeal carcinoma; AJCC, American Joint Committee on Cancer; CCRT, concurrent chemoradiation therapy; NCT, neoadjuvant chemotherapy; ACT, adjuvant chemotherapy.

≤ 2.5), and 14 patients had a metabolic partial response (SUV_{max} > 2.5); no patients had metabolic stable disease or progressive disease.

2. SUV_{max} value of primary site and metastatic node and interaction

The pre-treatment SUV_{max} of the primary site and metastatic lymph node were investigated and were named 'SUV_{max}-p' and 'SUV_{max}-n', respectively. The median SUV_{max}-p was 11.4 (range, 4.1 to 23.4) and the median SUV_{max}-n was 9.8 (range, 2.3 to 24.5) in our cohort. The best cut-off value of the SUV_{max}-p and SUV_{max}-n was 13.2 (area under the curve [AUC], 0.812; p = 0.010) and 13.4 (AUC, 0.976; p < 0.001) by receiver operating characteristic (ROC) curve analysis for recurrence (Fig. 1). When we analyzed the association between SUV_{max}-p and SUV_{max}-n by linear regression, a weak correlation was found between

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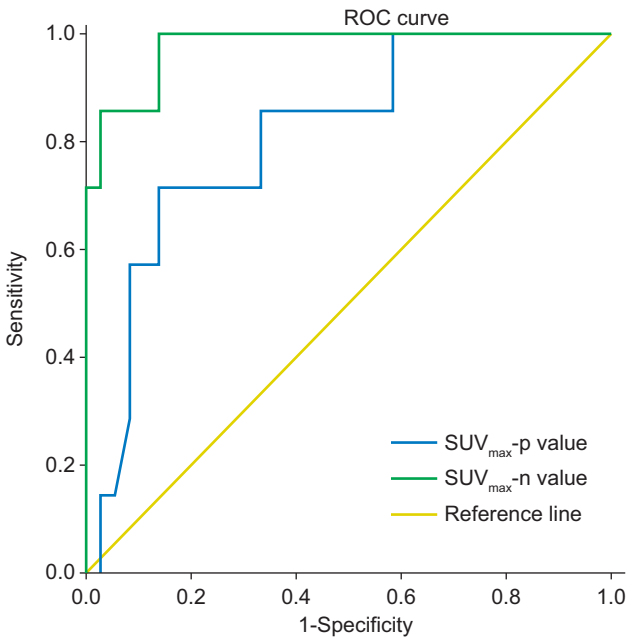

Fig. 1. Receiver operating characterstic (ROC) curve of SUV_{max} of the primary site and metastatic node for predicting recurrence. The best cut-off values for SUV_{max}-p and SUV_{max}-n depicted by the ROC curve were 13.2 and 13.4 for recurrence. SUV_{max}, maximum standardized uptake value; SUV_{max}-p, pretreatment SUV_{max} of primary site; SUV_{max}-n, pretreatment SUV_{max} of metastatic nodes.

them (R^2 = 0.144, p = 0.010, data not shown). In addition, the node size of the short axis and SUV_{max}-n showed no significant correlation (R^2 = 0.118, p = 0.103), while the node size of the long axis and SUV_{max}-n showed a weak correlation (R^2 = 0.106, p = 0.043).

3. Prognostic significance of SUV_{max} on survival and recurrence

In univariate analysis, pathology, high SUV_{max}-p (≥13.2), and high SUV_{max}-n (≥13.4) were significant prognostic factors (Table 3). The non-keratinizing (differentiated and undifferentiated) nasopharyngeal carcinoma pathology group had a significantly higher OS (p = 0.006), DFS (p = 0.017), and LRRFS (p < 0.001) at 3 years than the keratinizing squamous cell carcinoma pathology group. The higher SUV_{max}-p (≥13.2) group had a significantly lower DFS (p = 0.023) than the lower SUV_{max}-p group (<13.2). A higher SUV_{max}-n (≥13.4) was a negative prognostic factor for 3-year OS (93.1% vs. 55.5%; p = 0.003) as well as for DFS (92.7% vs. 38.5%; p < 0.001), LRRFS (100% vs. 50.5%; p < 0.001), and DMFS (100% vs. 69.2%; p = 0.004) (Fig. 2). There was no statistically significant difference between the two groups when classified by median value of largest nodal size. Additionally, a metabolic complete response response did not demonstrate significant results for survival and recurrence in univariate analysis. In multivariate analysis, only a high SUV_{max}-n (≥13.4) was statistically significant. A high SUV_{max}-n (≥13.4) was a negative and independent prognostic factor for OS (hazard ratio [HR], 7.799; 95% confidence interval [CI], 1.506–40.397; p = 0.014) as well as for DFS (HR, 9.392; 95% CI, 1.989–44.339; p = 0.005) (Table 4).

Discussion and Conclusion

Identifying prognostic factors for individualized therapy in patients with nasopharyngeal carcinoma is currently a major issue, and several studies have been conducted on risk stratification of patients using EBV DNA level and PET/CT parameters [16-20]. Several previous studies have suggested pre treatment SUV_{max} has prognostic value for nasopharyngeal cancer, as shown in Table 5 [9-15], but for most of these studies, only the SUV_{max} of the primary site was analyzed. This study focused on the importance of both the nodal and primary site SUV_{max}, and we found that nodal SUV_{max} is an independent prognostic factor for OS and DFS. This is consistent with a previous study by Chan et al. [13], in which a higher nodal SUV_{max} (≥6.5) was a negative prognostic factor for DFS (HR, 4.1; 95% CI, 1.045–16.084; p=0.043) in nasopharyngeal cancer patients. In addition, in a study of 178 patients with head and neck squamous cell carcinoma, that included 28 patients with nasopharyngeal carcinoma, the higher nodal SUV_{max} (≥6) group had a significantly lower DFS rate (HR, 1.81; 95% CI, 1.02–3.23; p = 0.04) and a DMFS rate (HR, 3.34; 95% CI, 1.25–8.92; p = 0.016). In addition, nodal SUV_{max} was found to be a stronger prognostic factor than SUV_{max} of the primary site [21].

In our univariate analysis, SUV_{max}-n was found to be a significant factor for LRRFS (100% vs. 50.5%; p < 0.001) and DMFS (100% vs. 69.2%; p = 0.004). However, multivariate analysis for SUV_{max}-n was not performed for LRRFS and DMFS because both locoregional recurrence and distant metastasis only occurred in the higher SUV_{max}-n group. Therefore, further information about the relationships between SUV_{max}-n and locoregional recurrence and distant metastasis can be achieved through further study.

Additionally in the univariate analysis, we found the early AJCC stage group (I–II) had a lower DMFS than the advanced stage group (III–IVB). Because early AJCC stage was only observed in one out of 4 patients with distant metastasis, we thought this likely to be a bias caused by the small sample size.

Table 3. Univariate analysis of prognostic factors

	No. of patients	3-yr OS		3-yr DFS		3-yr LRRFS		3-yr DMFS	
		%	p-value	%	p-value	%	p-value	%	p-value
Sex									
Male	42	78.8	0.123	74.1	0.353	81.3	0.177	90.9	0.897
Female	11	100		90.0		100		90.0	
Age (yr)									
<49	26	90.2	0.377	80.8	0.587	85.0	0.989	91.3	0.913
≥49	27	76.2		74.5		85.7		90.7	
T stage									
T1–T2	29	82.6	0.847	80.0	0.824	88.1	0.817	83.7	0.067
T3–T4	24	84.1		74.6		81.9		100	
N stage									
N0–N1	21	93.8	0.098	88.8	0.195	88.8	0.728	93.8	0.527
N2–N3	32	76.0		70.2		82.5		89.1	
AJCC stage									
I–II	11	87.5	0.510	90.0	0.402	90.0	0.807	87.5	0.870
III–IVB	42	81.5		74.3		84.1		91.5	
EBV									
(–)	4	100	0.872	75.0	0.887	75.0	0.486	100	0.525
(+)	39	85.3		81.2		89.8		90.2	
Pathology									
Keratinizing	5	50.0	0.006*	25.0	0.017*	25.0	<0.001*	75.0	0.243
Non-keratinizing	42	84.6		80.5		90.8		91.2	
Treatment									
CCRT	14	61.1	0.124	57.7	0.158	85.7	0.659	85.7	0.822
NCT + CCRT	4	66.7		66.7		66.7		100	
CCRT + ACT	32	89.3		83.7		86.7		90.3	
SUV_{max}-p									
<13.2	32	89.4	0.104	89.4	0.023*	92.6	0.101	96.4	0.140
≥13.2	21	71.5		56.1		69.8		82.1	
SUV_{max}-n									
<13.4	33	93.1	0.003*	92.7	<0.001*	100	<0.001*	100	0.004*
≥13.4	13	55.5		38.5		50.5		69.2	
Node size (mm)									
Long axis									
<31	20	89.1	0.360	89.1	0.185	95.0	0.495	89.7	0.645
≥31	20	74.3		71.7		86.2		94.4	
Short axis									
<26.5		84.5	0.816	81.3	0.948	90.9	0.966	80.5	0.046
≥26.5		79.8		80.4		88.9		100	

OS, overall survival; DFS, disease-free survival; LRRFS, locoregional recurrence-free survival; RRFS, regional recurrence-free survival; DMFS, distant metastasis-free survival; AJCC, American Joint Committee on Cancer; EBV, Epstein-Barr virus; Keratinizing, keratinizing squamous nasopharyngeal carcinoma; Non-keratinizing, non-keratinizing nasopharyngeal carcinoma; CCRT, concurrent chemoradiation therapy; NCT, neoadjuvant chemotherapy; ACT, adjuvant chemotherapy; SUV_{max}-p, pretreatment SUV_{max} of primary site; SUV_{max}-n, pretreatment SUV_{max} of metastatic nodes.
*$p < 0.05$.

In this study, we did not find any significance of post-RT metabolic response on patients' survival and recurrence. However, there is a previous study in which a post-treatment metabolic complete response state was found to be a favorable factor for overall survival and DFS [11]. And, because of the limited number of patients, further studies with more patients

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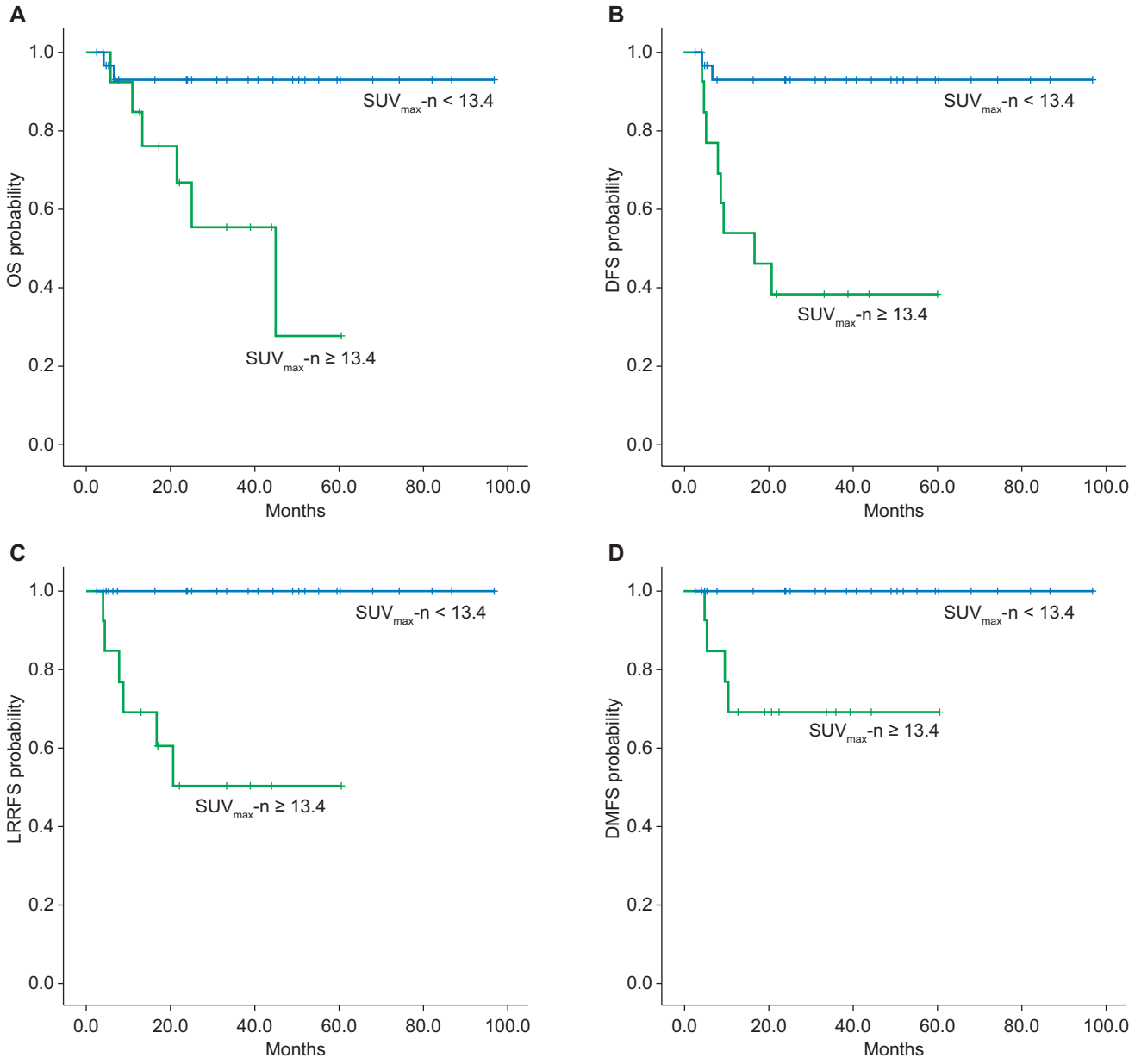

Fig. 2. Kaplan-Meier estimates of survival curves for the SUV_{max}-n < 13.4 and SUV_{max}-n ≥ 13.4 groups. (A) Overall survival (OS) of two groups (93.1% vs. 55.5%; p = 0.003). (B) Disease-free survival (DFS) of two groups (92.7% vs. 38.5%; p < 0.001). (C) Locoregional recurrence-free survival (LRRFS) of two groups (100% vs. 50.5%; p < 0.001). (D) Distant metastasis-free survival (DMFS) of two groups (100% vs. 69.2%; p = 0.004).

will be needed.

We did not find an independent association of primary SUV_{max} with survival and disease progression. When we analyzed the correlation between primary SUV_{max} and nodal SUV_{max}, only a weak correlation (R^2 = 0.144, p = 0.010) was found. Therefore, nodal SUV_{max} is a prognostic factor that provides more significant information about the patient's clinical outcome than the primary SUV_{max}. In addition, only the long axis nodal size showed a weak correlation with SUV_{max}-n (R^2 = 0.106, p = 0.043), unlike the short axis node size. This suggests that nodal SUV_{max} is a factor that reflects biologic aggressiveness of nodal metastasis and can predict the prognosis of patients independently of node size.

In this study, we used a relatively high cut-off value (SUV_{max}-p, 13.2; SUV_{max}-n, 13.4) compared with previous studies on SUV_{max} in nasopharyngeal carcinoma. Compared

Table 4. Multivariate analysis of prognostic factors

	HR (95% CI)	p-value
3-yr OS		
Pathology (keratinizing vs. non-keratinizing)	0.370 (0.070–1.943)	0.240
SUV_{max}-n (<13.4 vs. ≥13.4)	7.799 (1.506–40.397)	0.014
3-yr DFS		
Pathology (keratinizing vs. non-keratinizing)	0.439 (0.106–1.827)	0.258
SUV_{max}-p (<13.2 vs. ≥13.2)	1.981 (0.467–8.399)	0.354
SUV_{max}-n (<13.4 vs. ≥13.4)	9.392 (1.989–44.339)	0.005

HR, hazard ratio; CI, confidence interval; OS, overall survival; DFS, disease-free survival; Keratinizing, keratinizing squamous nasopharyngeal carcinoma; Non-keratinizing, non-keratinizing nasopharyngeal carcinoma; SUV_{max}-p, pretreatment SUV_{max} of primary site; SUV_{max}-n, pretreatment SUV_{max} of metastatic nodes.

Table 5. Other studies of SUV_{max} in nasopharyngeal cancer

Study	Stage	SUV_{max}		SUV_{max} cut-off			p-value					
							3-yr OS		3-yr DFS		3-yr DMFS	
		P	N	P	N	N(f)	P	N	P	N	P	N
Lee et al. [9]	I–IVB	6.48 (2.3–26.0)	-	8	-		NA	-	0.043	-	NA	-
Chan et al. [10]	I–IVB	-	-	12	-	-	NS	-	NS	-	0.012	-
Xie et al. [11]	III–IVB	8.55 (2.8–24.6)	-	8	-	-	0.019*	-	0.0163*	-	NA	-
Liu et al. [12]	I–IVB	4.9 (2.7–15.5)	-	5	-	-	0.065	-	<0.001	-	NA	-
Chan et al. [13]	I–IV	7.8 (2.6–21.3)	6.9 (1.5–20.9)	7.5	6.5	-	NA	NA	0.025	0.043	NA	NA
Xiao et al. [14]	I–IVB	10.23 (2.7–33.10)	-	10.2	-	-	0.004	-	NA	-	0.002	-
Jeong et al. [15]	II–IVB	8.2 (2.2–25.8)	8.0 (1.6–19.6)	8	-	10.6	NA	NA	NA	NA	0.033	0.001
This study	I–IVB	11.4 (4.1–23.4)	9.8 (2.3–24.5)	13.2	13.4	-	NS	0.014	0.023*	0.005	NS	0.004*

Values are presented as median (range) or number.
SUV_{max}, maximum standardized uptake value; OS, overall survival; DFS, disease free-survival; DMFS, distant metastasis-free survival; P, primary site; N, metastatic node; N(f), farthest metastatic lymph node; NA, no analysis; NS, no significance.
*p-value was significant only in univariate analysis.

with other studies, the median SUV_{max} itself was relatively higher, as shown in Table 5 [9-15]. This may be because of the measuring protocol and device used, and may be a reflection of the tumor burden, because 80% of the study objects were in an advanced stage.

This study has several limitations. First, as a retrospective study, there could be a selection bias for treatment strategy and chemotherapy that was performed heterogeneously among patients. Second, it includes a relatively low number of patients and few events. Third, there may have been few inconsistencies in the SUV_{max} because two different PET scanners were used, although they used the same protocol. In general, SUV measurements may vary from institution to institution depending on the differences in PET/CT protocols, PET/CT scanners, and imaging analysis methods. This imposes limitations on reproducibility. Because of these limitations, the optimal cut-off value of this study may not consistently be the best discrimination value in other patient groups. In addition, SUV_{max} has a limitation in that it does not reflect the heterogeneity of the total tumor lesion and volume.

To overcome these limitations, studies using prognostic factors such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) of PET/CT have recently been proposed. Yoon et al. [22] reported high MTV (≥31.45 cm^3 if set to cut-off 2.5; ≥23.01 cm^3 if set to cut-off 3.0) was a negative prognostic factor for OS (HR, 3.7019; 95% CI, 0.4746–9.3602; p = 0.0453 and HR, 5.1274; 95% CI, 1.1594–15.6541; p = 0.0198) in nasopharyngeal cancer patients. The TLG is the value obtained by multiplying the SUV_{mean} by MTV; it reflects the volumetric factor as well as biologic activity of the whole tumor. In a study

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by Chan et al. [19] high TLG (>330) was found to be a negative prognostic factor for OS (HR, 1.0013; 95% CI, 1.0005–1.0021; p = 0.0014) and DFS (HR, 3.0263; 95% CI, 1.6307–5.6164; p = 0.0005). Theoretically, TLG reflects the disease activity of the entire tumor lesion and its volume factor may be superior to SUV_{max} or MTV in prognostication, but this has not yet been proven [20,23,24]. In a recent meta-analysis of ^{18}F-FDG-PET/CT in nasopharyngeal carcinoma by Lin et al. [25] SUV, MTV, and TLG were found to be significant prognostic factors for OS and event-free survival, respectively. Although MTV and TLG were not analyzed in this study, the prognostic significance of SUV_{max} has been demonstrated several times in previous studies [9-15]. The results of this study were meaningful in suggesting the importance of nodal SUV_{max}, unlike previous studies focusing on primary tumors.

In conclusion, high pre-treatment nodal SUV_{max} was an independent prognosticator of survival and disease progression in nasopharyngeal carcinoma patients treated with IMRT in our cohort. Therefore, it may provide important information for identifying patients who require more aggressive treatment.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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