Original Article

A study about different findings of PET-CT between neoadjuvant and non-neoadjuvant therapy: SUV_{max} is not a reliable predictor of lymphatic involvement after neoadjuvant therapy for esophageal cancer

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Background: No definitive findings or established guidelines have been published for the evaluation of esophageal tumors (tumor) and regional lymph nodes (LN) using positron emission tomography computed tomography (PET-CT) in patients with esophageal cancer. In addition, it remains unclear whether PET-CT findings vary between neoadjuvant (NT) and non-neoadjuvant (non-NT) therapy cases. Therefore, preoperative evaluation using PET-CT might provide unreliable information and influence the management plan for esophageal cancer. The purpose of the present study is to clarify the different findings of PET-CT between NT and non-NT in surgical esophageal cancer cases and to predict LN metastasis.

Methods: We retrospectively reviewed the medical records of 192 consecutive cases that met this study's inclusion criteria from January 2009 to December 2014. All patients underwent curative and complete esophagectomy for intra-thoracic esophageal cancer at the department of thoracic and cardiovascular surgery in a single tertiary Korean hospital. We compiled and analyzed maximum standard uptake values (SUV_{max}) of tumor and LNs with other clinical information (chronic lung disease, history of previous other primary cancer, sex, pathological findings, NT, and other clinical data).

Results: (I) In NT, a positive correlation between T stage and SUV_{max} was found (tumor SUV_{max} P<0.001, LN SUV_{max} P=0.010); however, no relationship between N stage and SUV_{max} was found. In non-NT, a positive correlation between pathological stage (T and N stage) and SUV_{max} was found (T stage, tumor SUV_{max} P<0.001, LN SUV_{max} P=0.001; N stage, tumor SUV_{max} P=0.003, LN SUV_{max} P=0.021); (II) In NT, the low SUV_{max} group had higher disease-free survival (DFS) and overall survival (OS) than the high SUV_{max} group (DFS, tumor SUV_{max} P<0.001, LN SUV_{max} P=0.142; OS, tumor SUV_{max} P<0.001, LN SUV_{max} P=0.002). In non-NT, the low SUV_{max} group also had higher DFS and OS than the high SUV_{max} group (DFS, tumor SUV_{max} P<0.001, LN SUV_{max} P=0.008; OS, tumor SUV_{max} P=0.029, LN SUV_{max} P=0.016). SUV_{max} values being equal, non-NT had significantly higher DFS and OS than NT (P=0.011, P=0.009, respectively), despite the absence of significant differences in pathological stage; (III) Tumor SUV_{max} had a positive correlation with LN SUV_{max} in both NT and non-NT (P=0.006, P<0.001, respectively); (IV) In NT, there were no diagnostic findings of LN metastases using SUV_{max}. However, in non-NT, significant cutoff values for diagnosis of LN metastases using both tumor and LN SUV_{max} were found (tumor SUV_{max} cutoff value 4.9, P=0.008; LN SUV_{max} cutoff value 2.5, P=0.045); (V) In NT, there was no significant difference in LN SUV_{max} between pathologically negative and positive LNs. However, in non-NT, the LN SUV_{max} of pathologically positive LNs was significantly higher than that of pathologically negative LNs (P=0.042); (VI) There were no significant differences in tumor and LN SUV_{max} according to various factors, including chronic lung disease

(COPD, bronchiectasis), age, previous cancers, and sex, regardless of NT.

Conclusions: This study showed that there were some different findings of PET-CT using SUV_{max} between NT and non-NT. These findings should be clarified for further evaluation and management, especially of surgery, which should not be withheld out of ignorance of these different PET-CT findings and should be considered carefully in conjunction with other conditions. In addition, further studies about the effects of NT on PET-CT findings are required to improve the utility of PET-CT to evaluate the LNs in esophageal cancer.

Keywords: Positron emission tomography computed tomography (PET-CT); esophageal cancer; neoadjuvant therapy (NT)

Submitted Jan 18, 2016. Accepted for publication Feb 13, 2016.
doi: 10.21037/jtd.2016.03.20
View this article at: http://dx.doi.org/10.21037/jtd.2016.03.20

Introduction

Oncologists should evaluate a patient's exact cancer status when managing esophageal cancer, especially when planning surgery (1). Positron emission tomography computed tomography (PET-CT) has been essential to the evaluation of exact cancer status, especially distant or lymph node (LN) metastases, in esophageal cancer (1-3). Because ^{18}Fludeoxyglucose (^{18}FDG, a radiopharmaceutical for PET-CT) uptake in tissues is a marker for the tissue uptake of glucose, which is in turn closely associated with tissue metabolism, correlations between the maximum standard uptake value (SUV_{max}) in the lesions and cancer progression are well known (1,3,4). Neoadjuvant therapy (NT) is usually recommended in esophageal cancer when the preoperative clinical stage is T3N1 or greater (5-7). A lesion is usually considered to be positive for malignancy when the SUV_{max} via PET-CT is more than 2.5 and the lesion is larger than 1 cm in diameter (8,9). However, discrepancies between PET-CT and pathologic findings are common, especially in regional LN status. Thus, preoperative evaluation using PET-CT might provide unreliable information and influence the management plan for esophageal cancer (4,5,10). No definitive findings or established guidelines have been published for the evaluation of esophageal tumors (tumor) and regional LN using PET-CT in patients with esophageal cancer (2,7,8,10). In addition, it remains unclear whether PET-CT findings vary between patients treated with and without NT (2,11). The purpose of the present study is to clarify any variation in PET-CT findings between esophageal cancer patients treated with and without NT and to predict LN metastases for better prognosis.

Methods

Study subjects and methods

We retrospectively compiled and analyzed data from 192 consecutive patients who had undergone curative and complete surgery for intra-thoracic esophageal cancers at a single tertiary Korean hospital from January 2009 to December 2014. Inclusion criteria were complete and curative surgery cases, intra-thoracic esophageal cancer, PET-CT acquisition for initial evaluation and re-evaluation after NT, and preoperatively proven histology of squamous cell carcinoma. Exclusion criteria were palliation or salvage cases, other uncured previous or current primary cancers, and concurrent active inflammation cases. The preoperative assessments included esophagogastroduodenoscopy, esophagography, chest CT, abdominal CT, PET-CT, endoscopic ultrasound, and bone scan. NT and adjuvant therapies were performed following the National Comprehensive Cancer Network (NCCN) guidelines; the recommendations of a multidisciplinary team who assessed cancer status, resectability, or operability; and each patient's condition (5). NT usually consisted of two cycles of cisplatin and 5-fluorouracil, plus 25 fractions of radiation therapy (over 5 weeks) to a total of 41–45 Gray. Re-evaluation by PET-CT was performed 4 weeks after completion of NT, and further management was determined. The surgery was performed 5 or 6 weeks after completion of NT. In the present study, preoperative stage in neoadjuvant cases was defined as clinical stage by PET-CT reevaluation after NT and before surgery. Surgeries were performed by two surgeons using the Ivor Lewis or the McKeown procedures, depending on cancer status and patient condition.

Two-field LN dissections were performed. We retrospectively compiled PET-CT SUV_{max} data on tumors and LNs. To clarify the different findings between NT and non-neoadjuvant therapy (non-NT) group and to predict LN metastases, we assessed the relationship between SUV_{max} values and pathologic stage, compared disease-free survival (DFS) and overall survival (OS), investigated the relationship between tumor and LN SUV_{max} values, evaluated and predicted LN metastases using SUV_{max} values, compared pathologically negative and positive LNs using SUV_{max} values, and examined the effects of NT on SUV_{max}. Those findings were analyzed in the context of the pathologic findings. We analyzed the histopathological findings of specimens using the multiple serial sectional and immunohistochemistry methods and determined cancer stage according to the seventh American Joint Committee on Cancer (AJCC) staging system.

Protocol for PET-CT measurements and evaluations

All subjects gave written informed consent before PET-CT measurement for the possible future use of their clinical evaluations in research. Subjects fasted for at least 6 h before their PET-CT scans, and their blood glucose levels were measured before injection of ^{18}FDG, a radiopharmaceutical. If blood glucose level was greater than 160 mg/dL, the scan was postponed. An hour after the injection of ^{18}FDG (dosage 0.2 mCi/kg), positron emission images were acquired from the orbitomeatal plane to the proximal thigh. A CT scan was acquired concurrently with positron emission scans for exact anatomic localization of any ^{18}FDG-avid lesion. SUV_{max} calculated by identifying the region of interest on an axial slice with the highest uptake of ^{18}FDG within a lesion, was used to present the uptake of ^{18}FDG within a lesion. Two nuclear medicine physicians independently evaluated the SUV_{max} values for each scan. Medical records were also reviewed to discriminate malignancy or metastasis from a nonspecific ^{18}FDG-avid lesion. We compiled the SUV_{max} values as the highest uptake of ^{18}FDG within a tumor and individual LN later pathologically dissected and confirmed. We defined LN SUV_{max} as the highest SUV_{max} value among all pathologically dissected and confirmed LNs. Tumors and LNs were regarded as positive for malignancy or metastasis when the SUV_{max} value was >2.5 on a PET scan and the size was >1 cm on a CT scan, following previous studies and our hospital policy (8).

Statistical considerations and study approval

Due to non-normal distribution of data, we used non-parametric statistical hypothesis tests. The comparisons among subgroups were evaluated using the Mann-Whitney U or the Jonckheere-Terpstra test after propensity score matching methods, if needed. We used the Wilcoxon signed rank test when comparing two matched data and evaluated comparisons for categorical variables with the χ^2 test or Fisher's exact test, as appropriate. Association studies were evaluated using the Spearman' rho test, and survival analyses were performed using Kaplan-Meier survival estimation, with the log-rank test used to search for differences in survival across these strata. We performed receiver operating characteristic (ROC) analysis for diagnostic evaluation. We used the Statistical Package of Social Sciences version 22.0 (SPSS, Chicago, IL, USA) for all analyses. A P value <0.05 was considered statistically significant. The present study was approved by the Institutional Review Board of Seoul St Mary's Hospital (Approval number: KC15RISI0763).

Results

Study subjects

We included 192 patients (male 178, female 14; mean age 63.9 years) who had undergone curative and complete surgery for esophageal cancers from January 2009 to December 2014 in this study. Seventy patients received NT (initial clinical stage: IIa 4, IIb 6, IIIa 20, IIIb 20, and IIIc 20 cases). All cancer histologies were squamous cell carcinomas. Tumors were located in the upper thoracic esophagus (32 cases), middle thoracic esophagus (76 cases), and lower thoracic esophagus (84 cases). Mean tumor length and size were 3.2±2.0 cm and 9.3±11.2 cm^2, respectively. Mean tumor and regional LN SUV_{max} were 6.71±5.12 and 2.98±2.33, respectively. The mean number of regional LNs dissected was 25.2±13.8. The mean observation period was 24.7±18.6 months. The overall clinic-pathologic characteristics for the study subjects are summarized in *Table 1*.

The relationship between SUV_{max} and pathologic stage, and other various factors

In NT, we found a positive correlation between pathological T stage and SUV_{max} (tumor SUV_{max} P<0.001, LN SUV_{max} P=0.010); however, we found no relationship between pathological N stage and SUV_{max}. In non-NT, we found a positive correlation between pathological stage and SUV_{max}

Table 1 The overall clinic-pathologic characteristics for the study subjects

Characteristics	No. of patients (N=192)
Age (year) (mean ± SD)	63.9±9.36
Sex	
Male	178
Female	14
Previous other primary cancers	
No	173
Yes	19
Current smoking	
No	98
Yes	73
Unknown	21
Preoperative stage	
Ia	5
Ib	45
IIa	20
IIb	88
IIIa	31
IIIb	3
Pathologic stage after surgery	
Complete remission	10
Ia	9
Ib	58
IIa	14
IIb	58
IIIa	21
IIIb	10
IIIc	12
Location of cancer	
Upper thoracic	32
Middle thoracic	76
Lower thoracic	84
Method of surgery	
Ivor Lewis	154
McKeown	38
Pre-operative SUV_{max} (mean ± SD)	
Esophageal tumor	6.71±5.12
Regional lymph node	2.98±2.33
Differentiation	
Well	23
Moderate	146
Poor	23
Neoadjuvant therapy	
No	122
Yes	70

(T stage, tumor SUV_{max} P<0.001, LN SUV_{max} P=0.001; N stage, tumor SUV_{max} P=0.003, LN SUV_{max} P=0.021) (*Figure 1*). Tumor SUV_{max} values in the subgroup with tumor lymphatic invasion were higher than in the subgroup without lymphatic invasion, regardless of NT (NT P<0.001, non-NT P=0.001). We found no significant difference in tumor or LN SUV max with various other factors, chronic lung disease (COPD and bronchiectasis), age, history of previous other primary cancer, and sex, regardless of NT. Preoperative N staging using PET-CT had a tendency of overestimation regardless of NT. However, despite the inaccurate evaluation of individual LN status via PET-CT, we found no significant difference between preoperative and pathologic N stage.

Disease-free survival (DFS) and overall survival (OS) analyses according to SUV_{max} values

We divided patients into two groups by the mean preoperative SUV_{max} (NT, tumor SUV_{max} 6.0, LN SUV_{max} 3.1; non-NT, tumor SUV_{max} 7.1, LN SUV_{max} 2.9). In NT, the low SUV_{max} group had higher DFS and OS than the high SUV_{max} group (DFS, tumor SUV_{max} P<0.001, LN SUV_{max} P=0.142; OS, tumor SUV_{max} P<0.001, LN SUV_{max} P=0.002). In non-NT, the low SUV_{max} group also had higher DFS and OS than the high SUV_{max} group (DFS, tumor SUV_{max} P<0.001, LN SUV_{max} P=0.008; OS, tumor SUV_{max} P=0.029, LN SUV_{max} P=0.016) (*Figure 2*).

The relationship between tumor and lymph nodes (LN) SUV_{max}

Tumor SUV_{max} had a positive correlation with LN SUV_{max} in both NT and non-NT (P=0.006, P<0.001, respectively). In addition, tumor SUV_{max} also had a positive correlation with LN SUV_{max} in both pathologically positive and negative LN (P=0.002, P<0.001, respectively) (*Figure 3*).

Receiver operating characteristic (ROC) analysis for evaluation of lymph nodes (LN) metastasis using SUV_{max}

Twenty-eight of the 98 patients with LN SUV_{max} ≤2.5 had a pathologic N stage of one or greater (pN1–3), and 53 of 94 patients with LN SUV_{max} >2.5 had a pathologic N stage of zero (pN0). In non-NT, when the ratio of LN SUV_{max} to tumor SUV_{max} was >1.0 (when LN SUV_{max} was larger than tumor SUV_{max}), the LNs were statistically benign regardless of LN SUV_{max} (P=0.009). ROC analysis also revealed

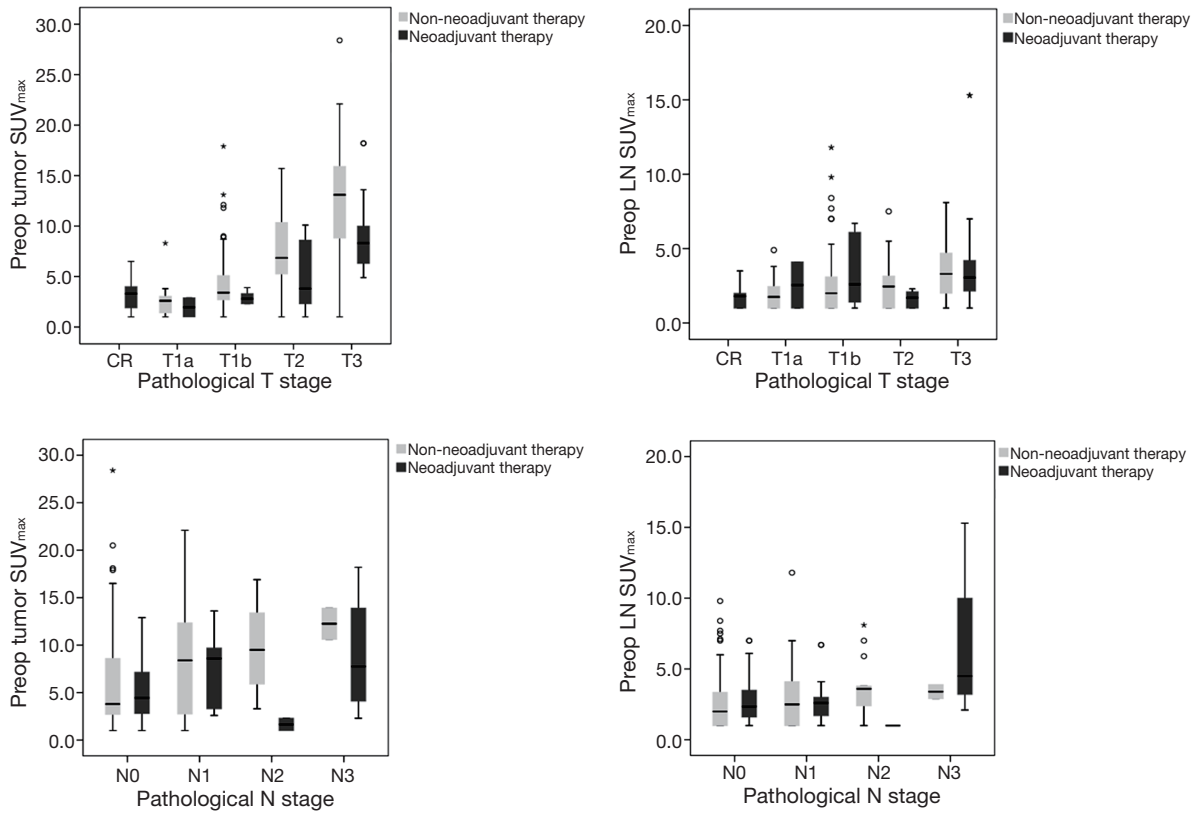

Figure 1 The relationship between pathological stage and SUV_{max} differs in neoadjuvant and non-neoadjuvant therapy cases. Positive correlations between stage and SUV_{max} occur only in non-neoadjuvant therapy cases (T stage, tumor SUV_{max} P<0.001, LN SUV_{max} P=0.001; N stage, tumor SUV_{max} P=0.003, LN SUV_{max} P=0.021). In neoadjuvant therapy cases, a positive correlation occurred between pathological T stage and SUV_{max} (tumor SUV_{max} P<0.001, LN SUV_{max} P=0.010); however, no relationship appeared between pathological N stage and SUV_{max}. SUV_{max}, maximum standard uptake values; LN, lymph nodes.

significant cutoff values for diagnosis of LN metastases using both tumor and LN SUV_{max} (tumor SUV_{max}, cutoff value 4.9, sensitivity 71.8%, specificity 56.6%, area =0.650, P=0.008; LN SUV_{max}, cutoff value 2.5, sensitivity 64.1%, specificity 57.8%, area =0.613, P=0.045). However, in NT, the ratio of LN SUV_{max} to tumor SUV_{max} was not related with diagnosis of LN metastases, and ROC analysis showed no significant findings of LN metastases using SUV_{max} values. ROC analysis for using SUV_{max} to diagnose LNs metastasis is shown in *Figure 4*.

Therefore, we investigated the possibility of predicting LN metastases based on tumor SUV_{max} in NT. When tumor SUV_{max} value was >2.5 and larger than LN SUV_{max} value, ROC analysis revealed the presence of a significant cutoff value for diagnosis of LN metastases using tumor SUV_{max}: cutoff value 8.2, sensitivity 70.0%, specificity 80.0%, area =0.697, P=0.019. However, if tumor SUV_{max} was ≤2.5, the value of tumor SUV_{max} did not provide an appropriate diagnostic value for LN metastasis.

Comparison between neoadjuvant (NT) and non-neoadjuvant (non-NT) therapy cases

Due to heterogeneity of the data between NT and non-NT, we used the propensity score matching method to compare NT and non-NT cases to overcome this bias (*Table 2*). SUV_{max} being equal, we found no significant differences in pathological T and N stage between NT and non-NT. In addition, non-NT had significantly higher DFS and OS than NT (P=0.011, P=0.009, respectively), despite the absence of significant differences in pathological stage between NT and non-NT (*Figure 5*).

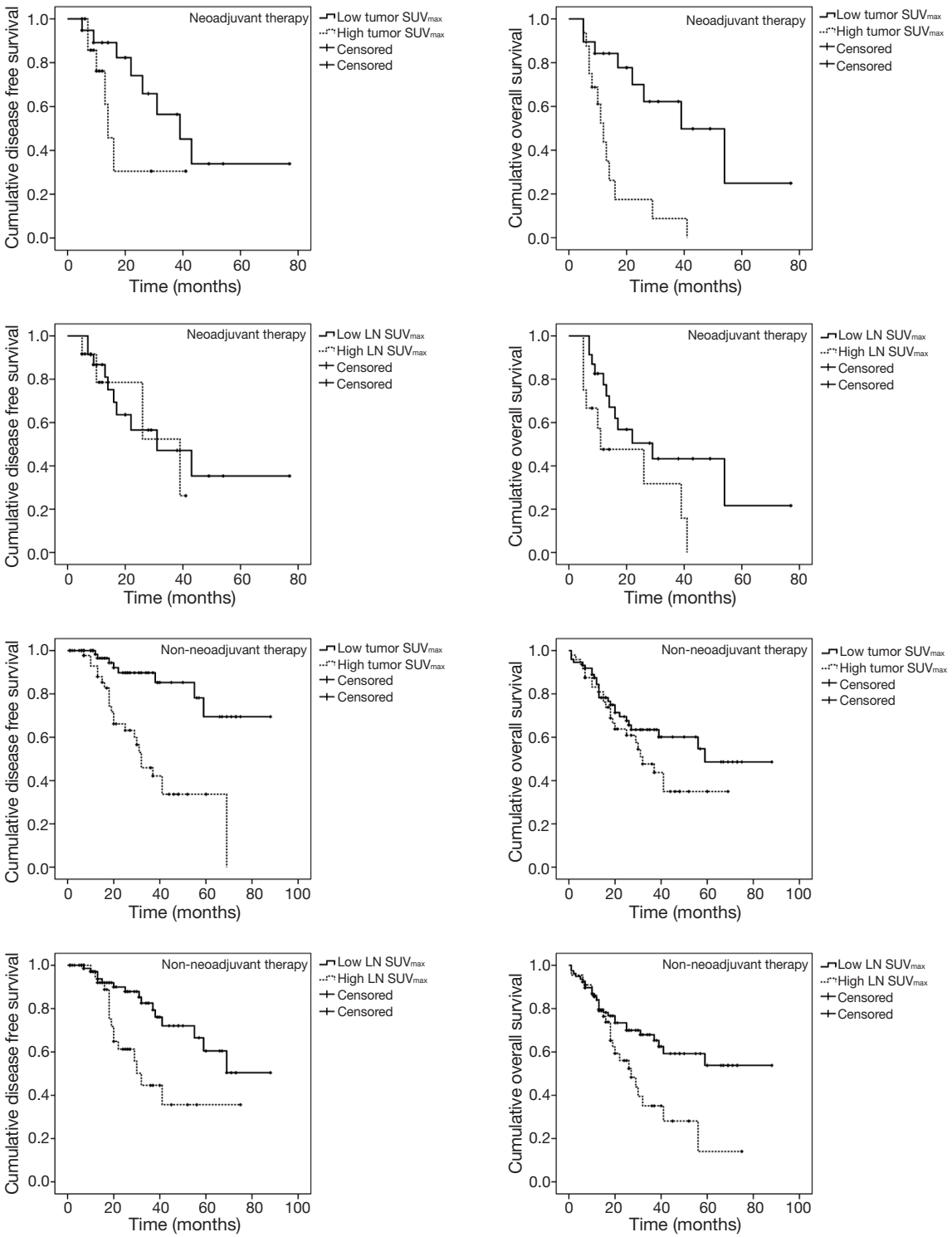

Figure 2 Disease survival analyses according to SUV_{max} value shows that the low SUV_{max} group had higher DFS and OS than the high SUV_{max} group in both NT (DFS, tumor SUV_{max} P<0.001, LN SUV_{max} P=0.142; OS, tumor SUV_{max} P<0.001, LN SUV_{max} P=0.002) and non-NT (DFS, tumor SUV_{max} P<0.001, LN SUV_{max} P=0.008; OS, tumor SUV_{max} P=0.029 LN SUV_{max} P=0.016). SUV_{max}, maximum standard uptake values; DFS, disease-free survival; OS, overall survival; NT, neoadjuvant therapy; LN, lymph nodes.

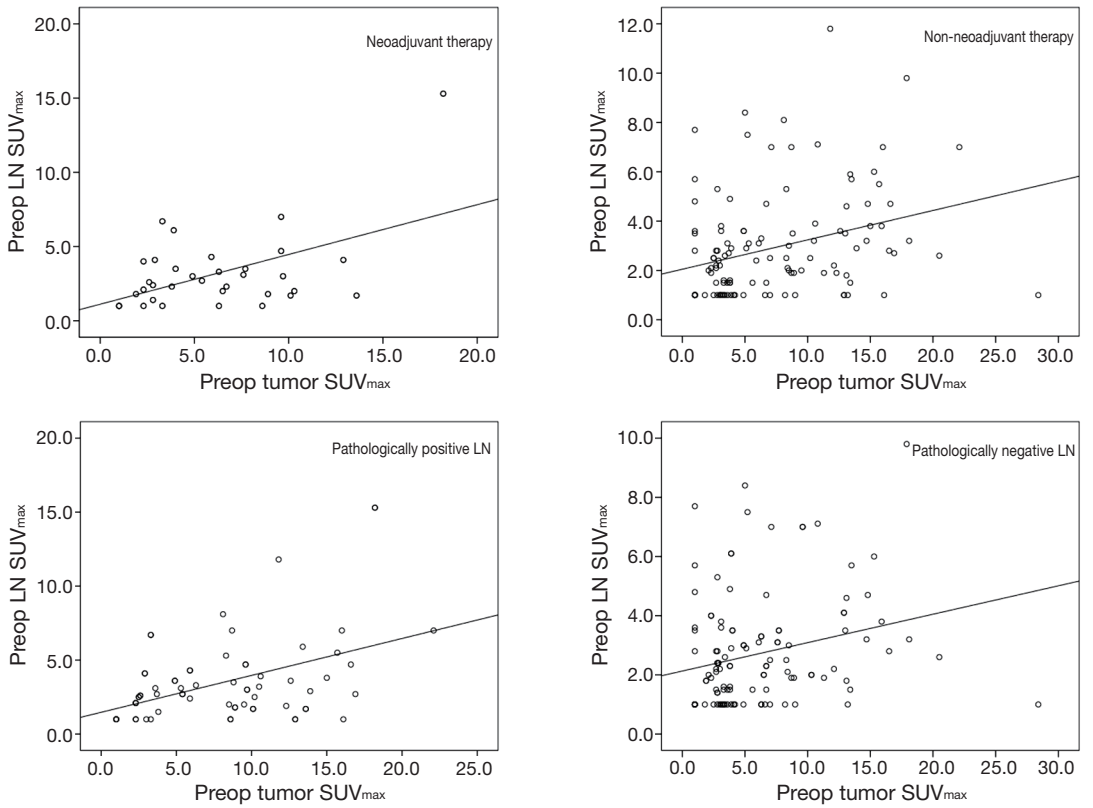

Figure 3 The scatter plot shows positive correlations between tumor and LN SUV_{max} in both NT and non-NT (P=0.006, P<0.001, respectively). In addition, tumor SUV_{max} had a positive correlation with LN SUV_{max} in both pathologically positive and negative LNs (P=0.002, P<0.001, respectively) (line: a linear regression line). LN, lymph nodes; SUV_{max}, maximum standard uptake values; NT, neoadjuvant therapy.

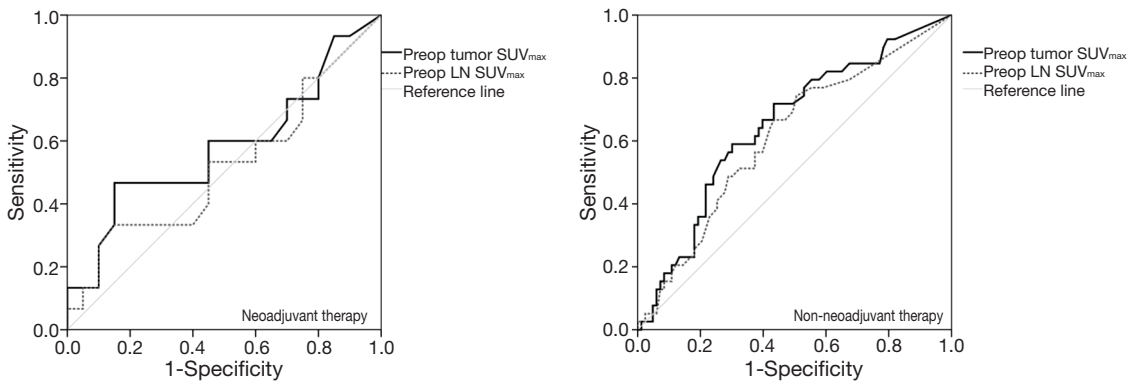

Figure 4 Receiver operating characteristic curve shows the presence of cutoff values for diagnosing LN metastasis using both tumor and LN SUV_{max} in non-NT (tumor SUV_{max}, cutoff value 4.9, sensitivity 71.8%, specificity 56.6%, area =0.650, P=0.008; LN SUV_{max}, cutoff value 2.5, sensitivity 64.1%, specificity 57.8%, area =0.613, P=0.045). However, SUV_{max} value cannot provide an appropriate diagnostic value for LN metastasis in NT. LN, lymph nodes; SUV_{max}, maximum standard uptake values; NT, neoadjuvant therapy.

Table 2 Propensity score matching data description

Parameters	Total population				Propensity-matched population			
	Non-NT (n=122)	NT (n=70)	P value	Standardized difference	Non-NT (n=70)	NT (n=70)	P value	Standardized difference
Age	63.9±9.1	63.9±9.9	0.991	−0.002	64.0±8.5	63.9±9.9	0.934	−0.013
Male	110 (90.2%)	68 (97.1%)	0.088	−0.416	68 (97.1%)	68 (97.1%)	1.000	0.000
Tumor SUV_{max}	7.1±5.6	6.0±4.0	0.115	−0.277	6.2±5.0	6.0±4.0	0.820	−0.044
LN SUV_{max}	2.9±2.1	3.1±2.6	0.508	0.088	3.2±2.2	3.1±2.6	0.911	−0.017

NT, neoadjuvant therapy; SUV_{max}, maximum standard uptake values; LN, lymph nodes.

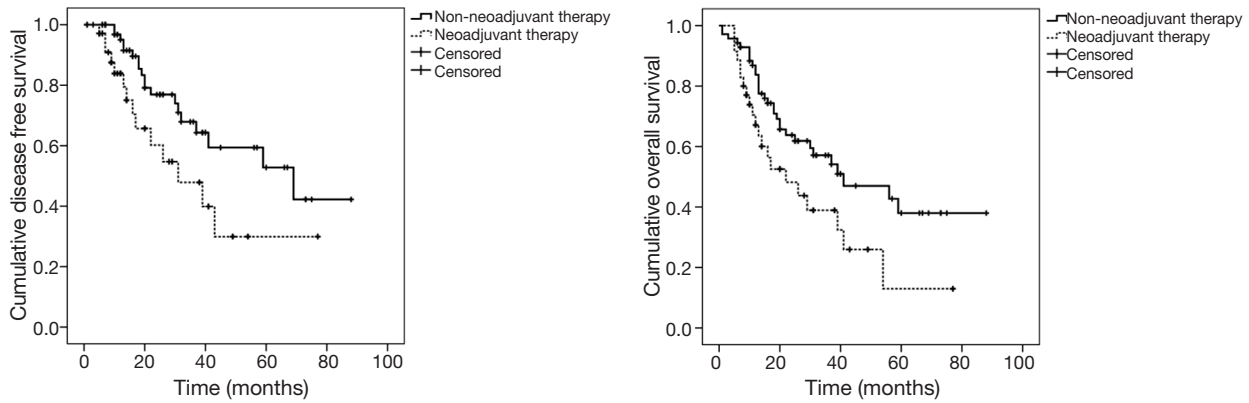

Figure 5 Disease survival analyses according to SUV_{max} values show that non-NT had significantly higher disease-free and overall survival than NT (P=0.011, P=0.009, respectively), despite the absence of significant differences in pathological stage between NT and non-NT. SUV_{max}, maximum standard uptake values; NT, neoadjuvant therapy.

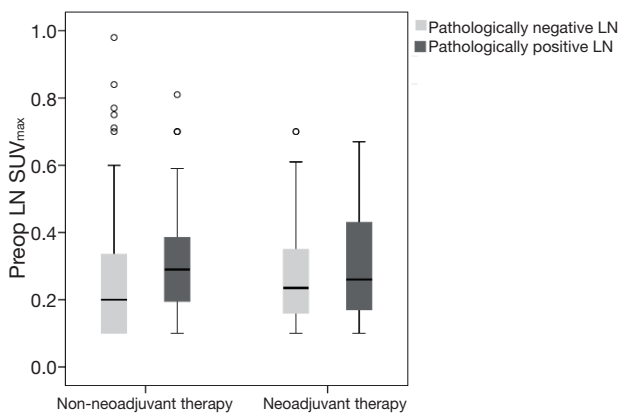

Figure 6 No significant difference in SUV_{max} value between pathologically negative and positive LNs is shown in NT. However, SUV_{max} values of pathologically positive LNs are significantly higher than those of pathologically negative LNs in non-NT (P=0.042). SUV_{max}, maximum standard uptake values; LN, lymph nodes; NT, neoadjuvant therapy.

Neoadjuvant therapy (NT) effects on SUV_{max}

Seventy patients received NT (initial clinical stage: IIa 4, IIb 6, IIIa 20 IIIb 20, and IIIc 20 cases). After NT, clinical stage as determined via PET-CT changed [down staging (56/70, 80%) and no change (14/70, 20%)], with significant decreases in both tumor and LN SUV_{max} (both, P<0.001). Interestingly, we also found significant decreases of SUV_{max} in both pathologically positive and negative LN after NT (both, P<0.001). In NT, we found no significant difference of LN SUV_{max} between pathologically negative and positive LN. However, in non-NT, LN SUV_{max} of pathologically positive LN was significantly higher than that of pathologically negative LN (P=0.042) (*Figure 6*). In addition, after NT, we found significant decreases in tumor and LN SUV_{max} in both complete and non-complete remission cases (both, P<0.001).

Discussion

PET-CT has become an essential tool to assess exact cancer

status, especially distant or LNs metastases in esophageal cancer (1). Most thoracic surgeons will consider NT instead of prompt surgery as initial management for esophageal cancer if a preoperative evaluation using PET-CT reveals possible LN metastasis (5). PET-CT thus promotes appropriate decisions in managing esophageal cancer by providing qualitative and quantitative information about a lesion by measuring its metabolic activity (4,5). However, discordance commonly occurs between PET-CT and pathologic findings, especially in LN status (1,3,8). In addition, the assessment of LN status using PET-CT in patients with esophageal cancer varies by institute because no established findings or qualitative features of PET-CT have been published (2,7,8). To clarify PET-CT findings in esophageal cancer, we investigated the different findings of PET-CT between NT and non-NT, especially in assessment of LNs for surgery, from the viewpoint of a thoracic surgeon. For the purposes of this study, we considered a lesion to be malignant or metastatic when its SUV_{max} was >2.5 and its size on CT scan was >1 cm (8).

Like many previous studies, the present study showed that tumor SUV_{max} correlated with the progression of esophageal cancer (i.e., pathologic stage and lymphatic invasion) and survival (DFS and OS) regardless of NT (1-4,8,9,12). However, N stage had no correlation with SUV_{max} following NT (3,13). Preoperative N staging using PET-CT tended toward overestimation regardless of NT (5,13). However, despite inaccurate evaluation of individual LN status using PET-CT, we found no significant difference between preoperative and pathologic N stage. Interestingly, we found a significant decrease in SUV_{max} in both pathologically positive and negative LNs after NT along with tumor and LN SUV_{max} decreases in both complete remission and non-complete remission cases. We also found no difference in SUV_{max} between pathologically positive and negative LNs in NT. However, in non-NT, LN SUV_{max} of pathologically positive LN was significantly higher than that of pathologically negative LN. Those results indicate the impossibility of distinguishing pathologically positive and negative LNs using only SUV_{max} levels in NT. SUV_{max} value is thus not an appropriate diagnosis value for LN metastasis in NT, as shown in the ROC analysis, which indicates the importance of considering other conditions to assess LNs exactly (1,3,8,9,14). We also propose that the impossibility of discriminating complete remission from non-complete remission cases by SUV_{max} level is caused by the fact that a significant portion of pathologically positive LNs convert to negative ones after NT, and fewer effects of NT develop in pathologically positive LNs than in pathologically negative ones (4,14).

Many studies have investigated the effects of NT in terms of predicting LN metastases based on the SUV_{max} of the primary lesions and have shown success in conditions such as hepatocellular carcinoma, breast cancer, and lung cancer (10). We showed that when LN SUV_{max} was higher than tumor SUV_{max}, the LN was considered to be benign regardless of SUV_{max} in non-NT and that predicting LN metastases based on the SUV_{max} of primary lesions was possible only in non-NT. Using SUV_{max} values of primary lesions to predict LN metastases was difficult in NT (3,4), probably because of the various effects of NT on tumor and LN (9). Therefore, to predict LN metastases for better diagnostic accuracy and prognosis, we attempted to find new findings for NT cases using esophageal tumor SUV_{max}. We found that if the tumor SUV_{max} was higher than the LN SUV_{max} and was higher than the value of 2.5, it was possible to diagnose LNs using the value of the tumor SUV_{max}. However, if the tumor SUV_{max} was ≤2.5, it could not provide an appropriate diagnosis value for LN metastases. We attribute this result to the assumption that FDG uptake in more advanced esophageal cancers provides better diagnostic accuracy because FDG uptake of the primary lesion is positively correlated with that of LN (10,13).

Recent studies have shown a survival benefit from initial NT followed by surgery over the prompt surgery in advanced esophageal cancer and have demonstrated that the improved survival rates result from the NT, not more radical surgery (1,4,14). However, we showed that SUVmax values being equal, non-NT had significantly higher DFS and OS than NT, despite the absence of differences in pathological stage between NT and non-NT. These findings could reflect that NT was in more advanced status. Also, the survival superiority of NT followed by surgery over prompt surgery could result from occult metastases undetected by PET-CT (11,15). We also attribute this finding to the survival superiority of NT followed by surgery over prompt surgery.

In summary, the present study showed similar and different PET-CT findings between NT and non-NT in esophageal cancer. The similar findings pertain to the relationship between T stage and SUV_{max}, DFS and OS, the relationship between tumor and LN SUV_{max}, and the relationship with various factors (chronic lung disease, age, history of previous other primary cancer, and sex). The different findings pertain to the relationship between N stage and SUV_{max}, assessment of LN metastases, and any

difference in SUV_{max} between pathologically positive and negative LN. Some studies reported that preoperative staging using PET-CT shows no survival benefit and no improvement in early recurrence following surgery (15-18). We suggest with caution that surgery should not be withheld only due to preoperative N stage using PET-CT after NT because there is no clear method for evaluation LN status after NT, and PET-CT findings differ between NT and non-NT (4). Further large-scale studies about PET-CT findings in NT are needed to draw definitive conclusions or establish guidelines for the use of PET-CT to diagnose patients with esophageal cancer.

The present study has several limitations, including its retrospective and single center design, small sample size and selection bias, and the shine-through phenomenon. Because the present study included only surgical cases, it mostly consisted of early-stage esophageal cancer, thereby reducing the incidence of LN metastases, which might affect the preoperative assessment (13). The small number of NT cases and the heterogeneity of the data could have affected the study findings. To overcome that bias, we used the propensity score matching method to compare NT and non-NT. Because the measurement of the metabolic activity in a lesion by PET-CT involves considerable variability in conditions, various factors can influence the SUV_{max} level, especially in early-stage esophageal cancer (13,18). In addition, interpreting SUV_{max} data using only empirical and quantitative standardization can influence the preoperative assessment, especially in the early stages (8,13,18). The findings from the present study should be confirmed with prospective, randomized studies to provide definitive findings or establish guidelines for the use of PET-CT for the preoperative evaluation of the patients with esophageal cancer. Presently, because we regard evaluation of LNs by SUV_{max} to not be fully reliable, we chose prompt surgery instead of initial NT in a significant number of cases with preoperative high N stage according to PET-CT findings. To the best of our knowledge, the present study is the first and systematic comparison of PET-CT findings between NT and non-NT.

Conclusions

This study showed different PET-CT findings between NT and non-NT cases, which should be clarified for preoperative evaluation and disease management, especially for surgery. Surgery should not be withheld based on ignorance of the different PET-CT findings, which must be carefully considered in conjunction with other conditions. In addition, further studies on the effects of NT on PET-CT findings are required to improve the evaluation of LNs using PET-CT in esophageal cancer.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Park JK, Kim JJ, Moon SW. A study about different findings of PET-CT between neoadjuvant and non-neoadjuvant therapy: SUV_{max} is not a reliable predictor of lymphatic involvement after neoadjuvant therapy for esophageal cancer. J Thorac Dis 2016;8(5):784-794. doi: 10.21037/jtd.2016.03.20

