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Original article

Prognostic Value of Fluoro-D-glucose Uptake of Primary Tumor and Metastatic Lesions in Advanced Nonsmall Cell Lung Cancer

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Abstract

To assess the prognostic value of maximum standardized uptake value (maxSUV) of the primary tumor ($maxSUV_{pt}$), maxSUV of whole-body tumors ($maxSUV_{wb}$) and sum of maximum standardized uptake value (sumaxSUV) measured by the sum of maxSUVs of the primary tumor, metastatic lymph nodes, and metastatic lesions per each organ on fluoro-D-glucose-positron emission tomography/computed tomography in advanced non-small cell lung cancer (NSCLC). Eighty-three patients (49 male, 34 female) with advanced NSCLC were enrolled. Seventeen patients had Stage IIIA, 21 Stage IIIB, and 45 Stage IV. $maxSUV_{pt}$, $maxSUV_{wb}$, sumaxSUV, age, gender, tumor-cell type, T stage, N stage, overall stage, primary tumor size, and specific treatment were analyzed for correlation with overall survival. Median follow-up duration was 13 months. Fifty patients were dead during a median follow-up time of 11 months and 33 patients were alive with a median time of 15 months. Univariate analysis revealed that overall survival was significantly correlated with sumaxSUV ($\geq$35 vs. <35, $P = 0.004$), T stage (T4 vs. T1-T3, $P = 0.025$), overall stage (IV vs. III, $P = 0.002$), gender (male vs. female, $P = 0.029$) and specific treatment (no vs. yes, $P = 0.011$). $maxSUV_{pt}$ and $maxSUV_{wb}$ were not correlated with overall survival with P value of 0.139 and 0.168, respectively. Multivariate analysis identified sumaxSUV, T stage, gender, and specific treatment as independent prognostic indicators. Patients with a sumaxSUV of $\geq$35 were 1.921 times more likely to die than those with a sumaxSUV of < 35 ($P = 0.047$). Median survival time was 14 months for patients with sumaxSUV $\geq$ 35 compared with 20 months for those with sumaxSUV < 35. In patients with metastatic NSCLC, sumaxSUV with cut-off of 35 was much more significant for survival prognosis ($P = 0.021$). sumaxSUV is a new prognostic measure, independent of tumor stage, gender, and specific treatment in advanced NSCLC. sumaxSUV may be better than $maxSUV_{pt}$ and $maxSUV_{wb}$ in prediction of survival. A large prospective cohort study is necessary to validate these results.

Keywords: 2-deoxy-2-[^{18}F]-fluoro-D-glucose, nonsmall cell lung cancer, sum of maximum standardized uptake value, tumor burden

Introduction

Lung cancer is one of the leading causes of cancer deaths throughout the world. The disease accounted for 1.3 million deaths in 2004 following the report of WHO.[1] In Vietnam, lung cancer was the most common in males and the six most common in females after breast cancer, cervical cancer, stomach cancer, liver cancer, and colorectal cancer. The age standardized rate of lung cancer was 24.6 in males and 6.8 in females in Ho Chi Minh city and 38.8 in males and 5.6 in females in Hanoi city.[2]

At present, prognosis in nonsmall cell lung cancer (NSCLC) primarily depends on tumor-node-metastasis stage.[3,4] However, the staging system is not entirely satisfactory in terms of explaining relative risk of recurrence, and death. Certain other prognostic factors are predictive of

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survival in patients with NSCLC, such as performance status, weight loss, and gender.[5]

Nonsmall cell lung cancer features the characteristics of derangements of glucose metabolism. Increased glucose consumption, and glycolytic activity have been reported in NSCLC,[6] and the altered glucose metabolism can be assessed *in vivo* by positron emission tomography (PET) using 2-deoxy-2-[^{18}F]-fluoro-D-glucose (FDG).[7] The level of FDG uptake of the tumor can be quantified by the SUV on PET or PET/computed tomography (CT), and maximum standardized uptake value (maxSUV) is a representative parameter for the maximal glucose metabolism of the tumor.

Fluoro-D-glucose uptake of the primary tumor has been identified as an independent prognostic indicator for survival in early stage NSCLC at diagnosis.[8-14] However, its prognostic value has been found disappointing in advanced NSCLC.[15-18] Recent studies reported that initial prognosis in NSCLC was related with tumor burden measurement. Whole-body metabolic tumor volume (MTV), total lesion glycolysis (TLG), and the total number of tumors (TTn) have been found to be correlated with survival in patients with Stage I-IV,[19-23] and also in separate Stage IV NSCLC.[24] It seems that FDG uptake of the primary tumor on FDG-PET or PET/CT may be valuable in initial prognosis for early stage NSCLC, and whole-body tumor burden may be responsible for prognosis in advanced NSCLC.

It is unknown whether there is a correlation between survival and metabolic tumor burden, represented by so-called sum of maximum standardized uptake value (sumaxSUV), which is calculated by the sum of maxSUVs of the primary tumor, maxSUV of metastatic lymph nodes, and maxSUV of metastatic lesions per each organ in patients with advanced NSCLC.

The aim of this study was to investigate prognostic value of maxSUV of the primary tumor ($maxSUV_{pt}$), maxSUV of whole-body tumors ($maxSUV_{wb}$), metabolic tumor burden measured by sumaxSUV, and other conventional factors on overall survival in patients with advanced NSCLC.

Materials and Methods

Patient population

A total of 83 consecutive patients with advanced Stage III-IV NSCLC who did not received any specific treatment before undergoing FDG-PET/CT study at Cho Ray hospital, Vietnam from March 2009 to May 2012 were enrolled in the study. This study was approved by the Research Ethical Board of Hospital. The clinical and histopathologic data were collected from medical records and the treatments were following the guideline of the referral hospitals. Written informed consent was obtained from all patients for the FDG PET/CT study. Patients or relatives agreed to be contacted to provide information of current health status for every 3-6 months after PET/CT study. Patients with estimated life expectancy or follow-up time of <3 months were excluded from the study.

Fluoro-D-glucose-positron emission tomography/computed tomography imaging

All patients are fasted for at least 4 h before FDG-PET/CT study. The finger blood glucose level was measured 102.9 ± 17.0 mg/dl (ranged from 78 to 178 mg/dl) before administration of FDG. The patients were injected the dose of 5.18 MBq/kg (0.14 mCi/kg) of FDG. The patients had no renal failure and history of prior allergy-like reaction to contrast media. Whole-body scanning was performed at 60 min after FDG injection from skull vertex to upper thigh in a PET/CT scanner (biograph true D w/true V, Siemens Medical System). Firstly, a contrast-enhanced CT scan was performed for the attenuation correction and diagnosis under the supervision of radiologist and nuclear medicine physician. Contrast media of iopromide (Ultravist) or iopamidol (iopamiro) 300 mg I/ml was used as dose of 1.2 ml/kg body weight of the patient and infused at a rate of 2 ml/s for two-third of volume, then 1 ml/s for the remain one-third of volume. The CT scan was started around 60 s after initiation of intravenous contrast material infusion. Then PET scan was acquired in three-dimensional mode with an axial field of view 21.6 cm, slices of thickness of 5 mm and an axial and transaxial resolution with full width at half maximum (FWHM) at 1 cm of 4.7 and 4.2 mm, respectively. Multimodality workstation with Syngo TrueD software (Siemens) was used to display the images. A nuclear medicine and a radiologist worked together in assessment and interpretation of FDG-PET/CT images.

Measurement of fluoro-D-glucose uptake on positron emission tomography/computed tomography

The measurement and record of FDG uptake on PET/CT were performed by a nuclear medicine physician. Volume-of-interest (VOI) was drawn over primary tumor and metastatic lesions. Standardized uptake value (SUV) was a semi-quantitative measure, representative for FDG uptake. SUV was calculated as radioactivity in VOI (Bq/ml) × body weight (kg)/injected radioactivity (Bq). maxSUV was highest SUV representing the maximum glucose metabolic activity in tissue. sumaxSUV was defined as a sum of maximum standardized uptake value of the primary tumor, the maxSUV of local-regional lymph

node metastasis (N1-N3) and sum of all maxSUVs of metastatic lesions per each organ in the whole-body. sumaxSUV was calculated based on Microsoft Excel 2010 for windows 7. Distal lymph node was considered as an organ. Other metastatic lobe of the lung was considered as one more metastatic organ. The maxSUV of brain metastasis detected by contrast-enhanced CT or magnetic resonance imaging with or without avid-FDG uptake was measured and added in sumaxSUV.

Data analysis

Statistical analysis was performed using software of SPSS statistics 17.0 (SPSS Inc).

Overall survival time of the patient was defined as the time between the PET/CT study and death or last follow-up date of patients. For analysis of overall survival, $maxSUV_{pt}$, $maxSUV_{wb}$ and sumaxSUV were dichotomized into two groups around median values to identify the best discriminatory cut-off value for survival prediction. The univariate analysis was conducted using the Kaplan–Meyer log-rank test. Other prognostic factors, such as age, gender, tumor-cell type, stage of the primary tumor, stage of lymph node metastasis, overall stage, size of the primary tumor, and specific treatment were also assessed in survival analysis. In addition, $maxSUV_{pt}$, $maxSUV_{wb}$, sumaxSUV, and size of the primary tumor were separately entered as continuous values in a Cox proportional hazard model to assess their association with overall survival. Interactions among variables with significant effect on the overall survival were evaluated by multivariate analysis using the Cox proportional hazard model. $P < 0.05$ were considered as significant [Figure 1].

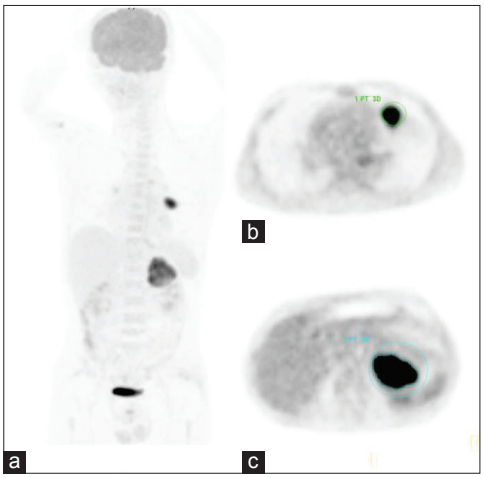

Figure 1: Fluoro-D-glucose-positron emission tomography (FDG-PET) images of non-small cell lung cancer with left adrenal metastasis. (a) Maximum intensity projection FDG-PET image. (b) maximum standardized uptake value (maxSUV) of lung primary tumor was 19.5. (c) maxSUV of adrenal metastasis was 17.3. Sum of maxSUV of 36.8 was calculated as sum of maxSUVs of lung primary tumor and left adrenal metastasis

Results

Patient characteristics

The study included a total of 83 consecutive patients with NSCLC (49 male and 34 female). Mean age of patients was 58.9 ± 11.0 years old. Mean age was 58.0 ± 10.1 for male and 60.3 ± 12.2 years old for female patients. The histopathologic subtype was squamous cell carcinoma (Sqc) in 15 patients, adenocarcinoma in 66 patients, adenosquamous cell carcinoma in 1 patient and large cell carcinoma in 1 patient. Twelve (24.5%) of 49 male and 3 (8.8%) of 34 female patients had Sqc. There were 17 patients with Stage IIIA, 21 with Stage IIIB and 45 with Stage IV classified according to stage definition by AJCC 6th edition.[3] The characteristics of the patients were summarized in Table 1.

Among 45 patients with Stage IV, there were 23 patients with metastasis in a single organ, 16 patients with 2-organ metastasis and every 2 patients with either 3 or 4, or 5-organ metastasis. 28 patients had bone metastasis, 16 had lung metastasis in other lobes, 12 had adrenal metastasis, 8 had brain metastasis, 6 had liver metastasis, 6 had distal lymph node metastasis and 1 had pancreatic metastasis, 1 had spleen metastasis and 1 had soft tissue metastasis.

Seventy-seven patients received specific treatments and 6 patients had supportive treatments. Of 77 patients with specific treatments, 9 patients were treated with surgery, chemotherapy and radiotherapy, 10 with surgery and chemotherapy, 18 with chemotherapy and radiotherapy or concurrent chemo-radiotherapy, 2 with surgery, 35 with chemotherapy and 3 with radiotherapy

Table 1: Patient characteristics (n=83)

Characteristics	No. of patients	Percentage
Sex		
Male	49	59.0
Female	34	41.0
Tumor-cell type		
Squamous cell carcinoma	15	18.1
Adenocarcinoma	66	79.5
Adenosquamous cell carcinoma	1	1.2
Large cell carcinoma	1	1.2
Tumor stage		
T1	8	9.6
T2	18	21.7
T3	17	20.5
T4	40	48.2
Lymph node metastasis		
No	9	10.8
N1	5	6.0
N2	43	51.8
N3	26	31.3
Stage		
IIIA	17	20.5
IIIB	21	25.3
IV	45	54.2

only. Median follow-up time was 13.0 months (range, 4–31 months, mean = 14.2 ± 6.8 months).

Univariate analysis of overall survival

Fifty (60.2%) of the 83 patients were dead during a median follow-up time of 11 months (range, 4-27 months). Thirty-three patients (39.8%) were alive with a median follow-up time of 15 months (range, 8-31 months).

In this study population of 83 patients, sumaxSUV ranged between 4 and 116.4 with a median of 26.5. sumaxSUV was dichotomized into two groups with 5-unit change around the median value. Univariate analysis based on dichotomizing sumaxSUV revealed that sumaxSUV was significantly correlated with overall survival by the log-rank test, and a cut-off value of 35 was identified as the best discriminatory value for overall survival with $P = 0.004$ [Figure 2].

$maxSUV_{pt}$ ranged from 2.8 to 27.6 with a median of 12.8, and $maxSUV_{wb}$ ranged from 2.8 to 47.5 with a median of 13. The dichotomization of $maxSUV_{pt}$ and $maxSUV_{wb}$ was performed with 1-unit change around its median value into two groups with cut-off change from 7 to 22. The analysis did not find any discriminatory cut-off value of $maxSUV_{pt}$ and of $maxSUV_{wb}$ to be significantly correlated with overall survival. Log-rank P value changed from 0.139 to 0.962 for $maxSUV_{pt}$ and from 0.168 to 0.851 for $maxSUV_{wb}$. The best discriminatory value was 20 for $maxSUV_{pt}$ ($P = 0.139$), and 15 for $maxSUV_{wb}$ ($P = 0.168$) in correlation with overall survival.

Univariate analysis was also performed for other potential factors. Overall survival was significantly correlated with primary tumor stage (T4 vs. T1–T3), overall stage (IV vs. III), gender, and specific treatment. Overall survival was not significantly related to age (≤60 vs. >60 years old), size of the primary tumor (≤3 cm vs. >3 cm), tumor-cell type (squamous vs. non-squamous cell carcinoma), lymph node metastasis (N3 vs. N1–N2). The summary of univariate analysis of overall survival for all factors was demonstrated in Table 2.

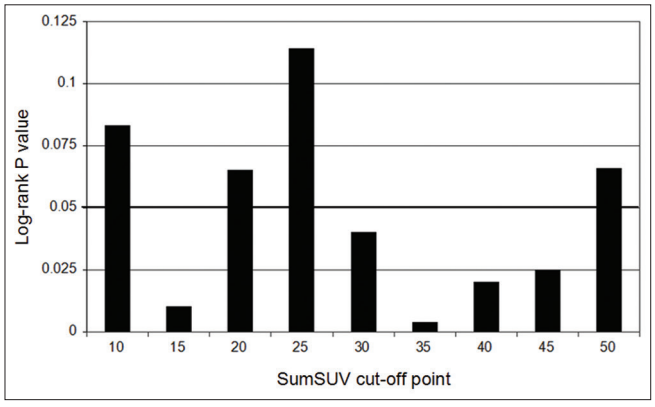

Figure 2: Relationship between various sum of maximum standardized uptake value cut-off values and their discriminative significance for overall survival, as assessed by the log-rank test

For the further analysis of continuous variables, $maxSUV_{pt}$, $maxSUV_{wb}$, and tumor size were not significantly correlated with overall survival ($P = 0.314$, 0.112, and 0.643, respectively). sumaxSUV was found as the only continuous variable associated significantly with overall survival ($P = 0.004$). A 1-unit increase in sumaxSUV corresponded to an increase in the hazard ratio for death by a factor 1.018 (with a 95% confidence interval; 1.006-1.031).

Multivariate analysis with respect to overall survival

Combinatorial effects and interactions among potential variables correlated with overall survival in univariate analysis were examined in Cox proportional hazard models. The five variables subjected to this analysis were sumaxSUV, T stage, overall stage, gender, and specific treatment. Multivariate Cox analysis identified T stage (T4 vs. T1-T3), gender (male vs. female), specific treatment (no vs. yes) and sumaxSUV (≥35 vs. <35) remained as significant independent predictors of overall survival [Table 3].

Patients with a sumaxSUV of ≥ 35 were 1.921 times more likely to die from NSCLC than those with a sumaxSUV of < 35 ($P = 0.047$). The median survival time was 14 months for patients ($n = 25$) with sumaxSUV ≥ 35 and 20 months for those with sumaxSUV < 35 ($n = 58$). The relative risk and median survival time based on T stage, gender, specific treatment, and sumaxSUV were also demonstrated in Table 3 and Figures 3-6.

Survival analysis in patients with Stage IV nonsmall cell lung cancer

In 45 patients with metastatic NSCLC, 34 patients (75.6%) were dead during a median follow-up time of

Table 2: Univariate analysis of overall survival

Variables	Log-rank *P*
Gender (male vs. female)	0.029
Age (>60 vs ≤60 year old)	0.311
Tumor-cell type (Sqc vs. non-sqc)*	0.053
Lymph node metastasis (N3 vs. N1-N2)	0.056
T stage (T4 vs. T1-T3)	0.025
Overall stage (IV vs. III)	0.002
Tumor size (>3 cm vs. ≤3 cm)	0.724
sumaxSUV (≥35 vs. <35)	0.004
$maxSUV_{pt}$ (≥20 vs. <20)	0.139
$maxSUV_{wb}$ (≥15 vs. <15)	0.168
Specific treatment (no vs. yes)	0.011

Sqc: Squamous cell carcinoma; Nonsqc: Nonsquamous cell carcinoma; sumaxSUV: Sum of maximum standardized uptake value; $maxSUV_{pt}$: Maximum standardized uptake value of primary tumor; $maxSUV_{wb}$: Maximum standardized uptake value of whole-body tumor

11 months (range, 4–26 months) and 11 patients (24.4%) were alive with a median follow-up time of 14 months (range, 8–28 months).

A univariate analysis demonstrated that sumaxSUV with cut-off of 35 and specific treatment were correlated with overall survival with a log-rank *P* value of 0.033 and 0.023, respectively. No significant correlation was found between overall survival and other factors, such as gender, T stage, N stage, $maxSUV_{pt}$, $maxSUV_{wb}$, size of the primary tumor, tumor-cell type, age, and number of metastatic organs.

Table 3: Results of multivariate analysis of overall survival (Cox proportional hazard model)

Variable	*P* value	RR	95% CI[a]
T stage (T4 vs. T1-T3)	0.011	2.115	1.185-3.775
Gender (male vs. female)	0.019	2.108	1.131-3.930
Specific treatment (no vs. yes)	0.020	3.215	1.205-8.573
SumaxSUV (≥35 vs. <35)	0.047	1.921	1.008-3.660
Overall stage (IV vs. III)	0.056		

[a]95% CI for RR. RR: Relative risk; CI: Confidence interval; sumaxSUV: Sum of maximum standardized uptake value

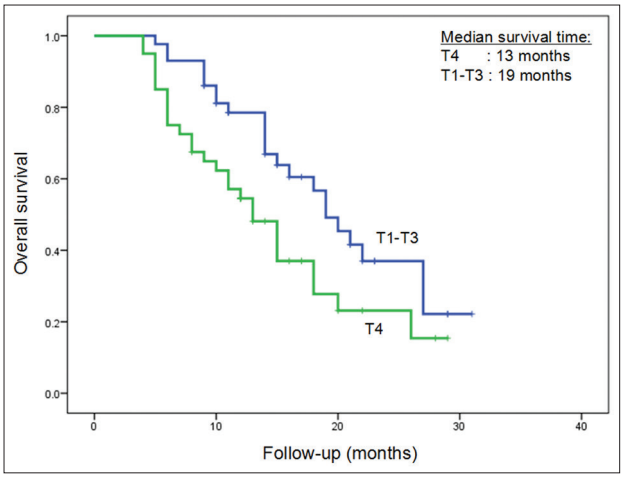

Figure 3: Overall survival curves based on T stage

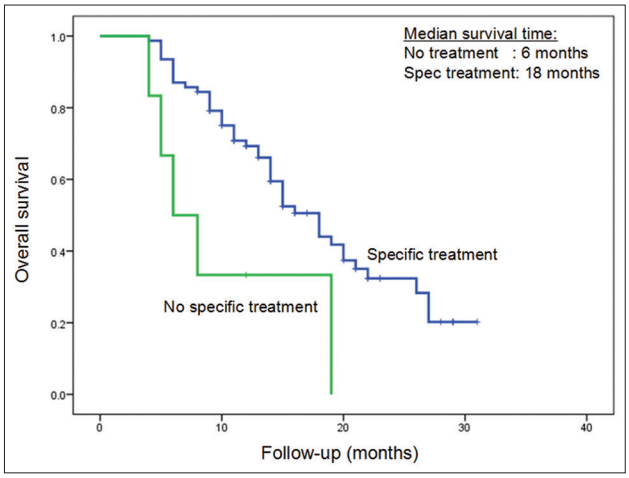

Figure 5: Overall survival curves based on treatment

sumaxSUV and specific treatment both remained significant on multivariate analysis in Cox Proportional Hazard Model with $P = 0.021$ for sumaxSUV and 0.013 for specific treatment. Patients with metastatic NSCLC, who had sumaxSUV of ≥ 35 were 2.371 times more likely to die from disease than those with sumaxSUV of < 35. The median survival time was 11 months for patients with sumaxSUV ≥ 35 compared with 19 months for those with sumaxSUV < 35. Patients with metastatic NSCLC, who did not receive any specific treatment were 3.568 times more likely to die from disease than those with specific treatment. The median survival time was 6 months for patients without specific treatment compared with 15 months for those with specific treatment.

Discussion

The principal findings of this study were that sum of maximum glucose metabolism of the primary tumor, local-regional lymph node metastasis and distal metastasis per each organ in the whole-body determined

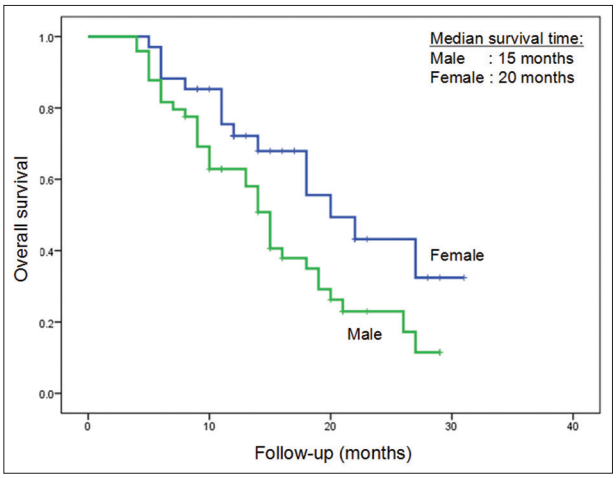

Figure 4: Overall survival curves based on gender

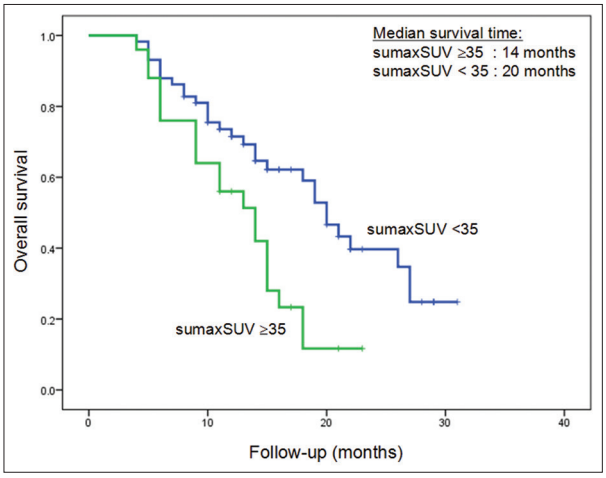

Figure 6: Overall survival curves based on sum of maximum standardized uptake value

by sumaxSUV measurement and other factors, such as gender, tumor stage, and specific treatment were the independent prognostic indicators for overall survival. $maxSUV_{pt}$ and $maxSUV_{wb}$ did not provide prognostic information in patients with advanced NSCLC. sumaxSUV presented more significant in survival prognosis in the subgroup of metastatic NSCLC. A sumaxSUV cut-off of 35 was identified as the best discriminative value and sumaxSUV was a continuous variable insignificant correlation with overall survival.

Although the maximum glucose metabolism of the primary tumor represented by maxSUV of FDG uptake on PET or PET/CT has been reported as initial prognostic factor for early stage NSCLC,[8-14] but it lost prognostic significance in advanced NSCLC.[16-18] It is likely that the disease status was still localized and able to be treated by curative intent surgery in the early stage NSCLC. Hence, the risk of disease recurrence or death may be determined by the aggressive biologic behavior of the primary tumor reflected by high FDG uptake. In advanced NSCLC, the survival prognosis may not be relied on FDG uptake of the primary tumor. This study did not find $maxSUV_{pt}$ and $maxSUV_{wb}$ as predictors of survival in advanced NSCLC. These findings were consistent with some previous studies, which reported that $maxSUV_{pt}$[16-18] and $maxSUV_{wb}$[20,21,23,24] were not significantly associated with survival. The aggressive behavior of the primary tumor seemed not to reflect the whole disease status in advanced NSCLC, where the high risk of occult widespread dissemination of the tumor cells or actually metastasis to other organs through lymphatic or blood vessels.

Fluoro-D-glucose uptake of the primary tumor significantly related with the incidence of regional lymph node metastasis,[25,26] and distant metastases in NSCLC,[15,27] and it was unknown whether FDG uptake of the primary tumor has affected in the aggression of metastatic organs. Moreover, metastatic lesions in different organs commonly appear various glucose metabolic activities and maximum FDG uptake of whole-body tumors reflects the aggression of only one in variety of impaired organs of disease. Risk of death can come from the impact of the primary tumor or organ's malignant lesions, which shows a maximum FDG uptake less than that of whole-body tumors. Thus, maximum glucose metabolism of the primary tumor or metastatic lesions of a single organ only may not be enough to provide additive prognostic information in advanced NSCLC.

In this study, sumaxSUV was identified as an important predictor for advanced NSCLC, independent of tumor stage, gender, and specific treatment after analyzing for combinatorial effects and interactions. sumaxSUV has been not investigated so far. sumaxSUV is a combined measurement of all maximum glucose metabolic activities from the primary tumor, loco-regional lymph nodes and metastatic lesions per each organ. It may reflect the aggressive level of whole-body in general with all active malignant lesions in regarding to aspect of metabolic activity.

Recently, the impact of metabolic tumor burden on survival prognosis for patients with NSCLC has been reported in several studies.[19-24] High tumor burden measured by whole-body MTV and whole-body TLG on FDG-PET/CT has been found as independent poor prognostic feature in NSCLC.[19-21,23,24] MTV provides volumetric information based on FDG-PET/CT and does not assess metabolic activity of malignant lesions. TLG provides metabolic and volumetric combined information. MTV and TLG have been recommended to be used to stratify patients with NSCLC.[19-21,23,24] The disadvantages of MTV and TLG measurement were low inter-observer variability and necessary to have available software. This study demonstrated a new measurement of metabolic tumor burden, so-called sumaxSUV, which has provided prognostic value in advanced NSCLC, and particularly in metastatic stage. Lesions with highest FDG uptake were easily selected in FDG-PET/CT images and the calculation of sumaxSUV was simple and reproducible.

This study showed that T4 stage was significantly associated with poor prognosis. Overall stage (IV vs. III) was only correlated with survival in univariate analysis ($P = 0.002$) and lost significant statistically in multivariate analysis ($P = 0.056$). This can be explained that clinical stages of patients in the study were classified based on staging system of AJCC 6th edition. Malignant pleural effusion belongs to T4 stage following AJCC 6th edition, instead of M1a stage by AJCC 7th edition.[4]

There was a significant difference in overall survival between male and female patients. Male had shorter survival time than female patients did. No significant differences in age or tumor-cell type were seen between male and female patients ($P > 0.05$, not presented in the result) and smoking status was not surveyed from this study. While some previous studies showed that women with lung cancer had better survival than men with lung cancer, because women were smoked less intensively, disease-diagnosed at an earlier age and had histopathology of adenocarcinoma.[28-30]

This study had certain limitations. Patients were enrolled with Stages IIIA to IV NSCLC and received various treatments. The survival was analyzed for only one factor as specific treatment, which consisted of surgery, chemotherapy and radiation or combination of these

treatments. The impact of each therapeutic method on the result of survival was not assessed. On the other hand, one of important factors for survival prognosis was performance status, not assessed in this study. However, we found that most of patients in poor performance status could not suffer a specific therapy and had shorter survival time.

A contrast media used during the FDG PET/CT helped attenuation correction, better localization and anatomic diagnosis. Contrast-enhanced CT could influence on measurement of SUV in this study. The other study showed that maxSUV was increased in all anatomic sites on the contrast-enhanced PET/CT and the differences in mean maxSUV between enhanced and nonenhanced PET/CT were 5.9% ± 3.9% for lung lesions, 6.3% ± 3.8% for lymph nodes and 3.6% ± 3.4% for metastatic lesions, respectively.[31] Contrast-enhanced CT has been reported suitable for attenuation correction in combined PET/CT and not to produce any clinically significant artifact in patients with lung cancer.[31,32]

Conclusion

Sum of maximum standardized uptake value of the primary tumor, loco-regional lymph node and distal metastases per each organ on FDG-PET/CT is a new prognostic measure, independent of tumor stage, gender and specific treatment in advanced NSCLC. sumaxSUV may be better than maxSUV of the primary tumor and maxSUV of whole-body tumors in prediction of overall survival in advanced NSCLC. A large prospective cohort study is necessary to validate these results.

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