**UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II**

THESIS

# PROGNOSTIC VALUE OF FDG UPTAKE OF PRIMARY TUMOR AND METASTATIC LESIONS IN ADVANCED NON-SMALL CELL LUNG CANCER

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# 1. ABBREVITATIONS

| | |
|---|---|
| $^{18}$F-FDG | 2-deoxy-2-[$^{18}$F]-fluoro-D-glucose |
| ASR | Age Standardized Rate |
| FDG | 2-deoxy-2-[$^{18}$F]-fluoro-D-glucose |
| FDG-PET | Positron emission tomography with 2-deoxy-2-[$^{18}$F]-fluoro-D-glucose |
| FDG-PET/CT | 2-deoxy-2-[$^{18}$F]-fluoro-D-glucose Positron emission tomography / computed tomography |
| NSCLC | Non-small cell lung cancer |
| maxSUV | Maximum standardized uptake value |
| $maxSUV_{pt}$ | maxSUV of primary tumor |
| $maxSUV_{wb}$ | maxSUV of whole body tumors |
| meanSUV | Mean standardized uptake value |
| MTV | Metabolic tumor volume |
| Nn | Number of nodal metastases |
| non-sqc | Non-squamous cell carcinoma |
| PET | Positron emission tomography |
| PET/CT | Positron emission tomography / computed tomography |
| SCLC | Small cell lung cancer |
| sumaxSUV | Sum of maxSUVs of primary tumor, lymph nodes, and metastatic lesions per each organ in whole body. |
| SUV | Standardized uptake value |
| sqc | Squamous cell carcinoma |

| | |
|---|---|
| TLG | Total lesion glycolysis |
| TNM | Tumor - node - metastasis |
| TTn | Total number of tumors |

# 2. ABSTRACT

***Purpose:*** To assess the prognostic value of metabolic tumor burden as sumaxSUV measured by sum of the maxSUVs of primary tumor, metastatic lymph nodes and metastatic lesions per each organ on FDG-PET/CT in patients with advanced NSCLC.

***Materials and methods:*** Eighty three patients with advanced NSCLC were enrolled. Seventeen patients had stage IIIA, 21 had stage IIIB and 45 had stage IV. SumaxSUV, maxSUV of primary tumor ($maxSUV_{pt}$), maxSUV of whole body tumors ($maxSUV_{wb}$), age, gender, tumor-cell type, T stage, N stage, overall stage, primary tumor size, specific treatment were analyzed for correlation with overall survival. Median follow-up duration was 13 months.

***Results:*** Fifty (60.2%) of the 83 patients were dead during a median follow-up time of 11 months and 33 patients (39.8%) were alive with a median follow-up time of 15 months. Univariate analysis revealed that overall survival was significantly correlated with sumaxSUV (≥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, $p = 0.011$). Multivariate analysis identified sumaxSUV, T stage, gender and specific treatment as independent prognostic indicators in advanced NSCLC. 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 with sumaxSUV ≥35 compared to 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 ($p = 0.021$).

***Conclusion:*** 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 in advanced NSCLC. A large prospective cohort study is necessary to validate these results.

# 3. 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 (ASR) of lung cancer was 24.6 in males and 6.8 in females in Hochiminh city and 38.8 in males and 5.6 in females in Hanoi city [2].

At present, prognosis in non-small cell lung cancer (NSCLC) primarily depends on tumor-node-metastasis (TNM) stage [3, 4], and the oncologists commonly use TNM staging system for deciding the best treatment methods for the patients.

However, the staging system is not entirely satisfactory in terms of explaining relative risk of recurrence, and death. It is likely due to the heterogeneous nature of disease stage. Besides of early stage disease at diagnosis, certain other prognostic factors are predictive of survival in patients with NSCLC such as performance status, weight loss, and gender [5].

NSCLC 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

standardized uptake value (SUV) on PET, and the maxSUV is representative parameter for the maximal glucose metabolism of the tumor.

FDG uptake of 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 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 primary tumor on FDG-PET may be an independent prognostic factor for early stage NSCLC, which may be treated by surgical resection and whole body tumor burden may be responsible for prognosis in advanced NSCLC.

On the other hand, level of FDG uptake in primary tumor significantly correlated with the incidence of regional lymph node metastasis [25, 26], and distant metastases in NSCLC [15, 27]. The aggression of primary tumor and metastatic lesions, which can contribute to the actual causes of death in advanced NSCLC may be reflected by evaluation of glucose metabolic activity by FDG uptake on PET or PET/CT.

It is unknown whether there is correlation between survival, and metabolic tumor burden measured by sum of highest glucose metabolism levels of primary tumor, metastatic lymph nodes and metastatic lesions per each organ,

represented by so-called sumaxSUV, which is calculated by sum of maxSUV of primary tumor, maxSUV of metastatic lymph nodes, and maxSUV of metastatic lesions per each organ in patients with advanced NSCLC.

This prospective study was to test our hypothesis on prognostic value of sumaxSUV measurement, and other conventional factors on overall survival in patients with advanced NSCLC.

# 4. BACKGROUND

## 4.1. Introduction of PET and PET/CT

Positron emission tomography (PET) is a powerful, non-invasive nuclear medical imaging that provides metabolic information within the human body. PET can detect and follow-up variety of diseases with changes in metabolism which often precedes changes in structure or anatomy. PET has been extensively using in fields of oncology, neurology and cardiology.

From year of 2000, PET/CT with integration of PET and computed tomography (CT) scanners in one combined scanning system that can provide metabolic and anatomic information in the human body in a single scan. The CT in PET/CT is used for attenuation correction, better localization of lesions in the body and anatomic diagnosis with using contrast media.

2-deoxy-2-[$^{18}$F]-fluoro-D-glucose ($^{18}$F-FDG or FDG), a positron emitting radiopharmaceutical is commonly used in PET imaging (FDG-PET). Fluorine $^{18}$F in FDG is radioactive isotope, which decays by positron ($\beta^{+}$) emission and has a half-life of 109.7 minutes.

FDG is administered by intravenous injection. FDG, a glucose analog, concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathophysiological conditions. FDG is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to FDG-6-phosphate by the enzyme hexokinase. Once phosphorylated, it cannot exit until it is dephosphorylated by glucose-6-phosphatase. Therefore, within a given tissue or

pathophysiological process, the retention and clearance of FDG reflect a balance involving glucose transporter, hexokinase and glucose-6-phosphatase activities [28].

FDG-PET reflects glucose metabolism and has been used for diagnosis and follow-up of cancers. The advantage of PET technique is the ability to quantity the tracer uptake. Standardized uptake value (SUV), a semi-quantitative parameter is measured on PET. SUV is calculated by (activity concentration in tissue) / (injected activity / body size). The body size can be measured for body weight, lean body mass or body surface area. Body weight is more frequently used in SUV calculation.

To measure SUV, a region of interest (ROI) or a volume of interest (VOI) is drawn in the target tissue using interactive workstation. The software will generate the value of SUV by the programming formula calculation. Mean SUV and maximum SUV (maxSUV) can be used in clinical application. MaxSUV is the most frequently used and represents the highest FDG uptake in PET or PET/CT. MaxSUV value reflects the highest level of glucose metabolic activity in target tissue.

In the field of oncology, FDG-PET and PET/CT are put into clinical application for diagnosis, follow-up and prognosis of cancerous diseases.

### 4.2. FDG-PET in diagnosis of a solitary pulmonary nodule

The initial application of FDG-PET in lung cancer is to differentiate benign from malignant solitary pulmonary nodule (SPN). SPN is one of the most common radiological abnormalities that require further clinical work-up to confirm a benign or malignant lesion or periodic follow-up.

Assessment of morphologic characteristics, including size, contour, margins and internal characteristics was not completely reliable with conventional imaging to differentiate benign or malignant SPNs [29].

Diagnosis of malignant SPN is improved by using contrast-enhance CT and PET. Malignant nodules were significantly enhanced on contrast CT more than granulomas and benign neoplasms. With 20 HU as the threshold for a positive test result, the sensitivity was 98%, specificity was 73%, and accuracy was 85%. Enhancement appeared to be an indicator of malignancy and vascularity [30].

FDG-PET is a noninvasive method to assess indeterminate SPNs and helps reduce the need for invasive biopsy. In general, the malignant lesions demonstrate glucose hypermetabolism and high level of FDG uptake in FDG-PET. In a meta-analysis of study on accuracy of PET for diagnosis of pulmonary nodules and mass lesions, Gould, M.K., et al. found that FDG-PET was very sensitive (96.8%) though not very specific (77.8) in accuracy to differentiate malignant and benign lesions [31].

The majority of false negative cases on FDG-PET was due to subcentimeter nodules [32-34], and certain histological types with low metabolic activity (such

as bronchioalveolar carcinoma and typical carcinoid) [34]. Common causes of false positive cases were granulomatous and infectious processes. FDG-PET has a high false positive rate in areas with a high incidence of tuberculosis and combined PET and CT (PET/CT) can improve the diagnostic accuracy in the differentiation of an SPN [35]. In a region with a high prevalence of pulmonary fungal infection, FDG-PET was sensitive but lower specific in detecting malignant SPNs [36].

### 4.3. FDG-PET in staging lung cancer

FDG-PET has been found to be superior to conventional imaging in staging lung cancer. FDG-PET has the advantage of being able to detect distant metastases on a single whole body survey and is a reliable method for preoperative staging of patients with lung cancer and would help to optimize management.

FDG-PET is more accurate than computed tomography in detecting mediastinal lymph node metastases. PET gave a sensitivity of 83% and specificity of 92% and CT gave sensitivity and specificity of 59 and 78%, respectively [37]. FDG-PET correctly changed the N stage in 21-35% cases [38, 39]. In case of a negative FDG-PET for mediastinal lymph nodes, mediastinoscopy can be omitted and the patient may proceed directly to surgery. Differentiation between N2 and N3 lymph node metastasis is important to classify patients into stage IIIA or IIIB, which will be decided to do an operation or move to induction treatment. PET was superior to CT for correct identification between N2 and N3 lymph node disease in lung cancer [40, 41].

NSCLC commonly metastasizes to lymph nodes, bones, brain, liver and other regions of the body. PET and PET/CT was superior to conventional imaging in detection of distal metastasis. PET/CT revealed metastases in 20% of the patients without metastases found by conventional imaging and modified the stage of the disease in 28% of the cases [42].

For diagnosis of adrenal metastasis, FDG-PET was an accurate, noninvasive way and better than conventional imaging in differentiate benign from metastatic adrenal lesion. The sensitivity of FDG-PET for detecting adrenal metastatic disease was 97-100%, and the specificity was 80-94% in patients with lung cancer [43, 44].

However, FDG-PET was found poor efficacy in detecting cerebral metastases, partially due to high background caused by physiologic cerebral FDG uptake. FDG uptake in metastatic brain lesions was variable. One third of brain metastasis from lung cancer showed glucose hypometabolism. NSCLC was more frequently associated with hypermetabolic metastatic brain lesions than small cell lung cancer (SCLC). The PET findings of brain lesions were affected not only by the size of lesion but also by its biological characteristics [45]. The sensitivity of FDG-PET/CT in revealing cerebral metastases in patients with lung adenocarcinoma has been reported at 24% in compared with 88% by brain MRI. Thus, adding dedicated brain MRI to PET/CT was necessary for enhancing detection of brain metastasis [46].

### 4.4. Prognostic value of FDG-PET in NSCLC

Until now, TNM stage is the most important determinant of survival and a vital guide for treatment choices in NSCLC. The other prognostic factors include performance status, weight loss, and gender [5].

Recent advance in molecular biology and immunohistochemistry helps to understand about biomarkers and its influence on survival of patients with NSCLC. NSCLC presents derangements of glucose metabolism and cell proliferative activity. Glucose transporter type I (Glut-1) is a chief glucose transporter responsible for glucose uptake into the viable cell of NSCLC [47]. Overexpression of Glut-1 has been associated with poor prognosis of NSCLC [48, 49]. In addition, Ki-67 antigen is a molecular marker of tumor proliferation, and its over-expression has been linked to a poorer prognosis in NSCLC [50, 51].

FDG uptake of primary tumor may reflect activities of glucose metabolism and cell proliferation in NSCLC. Significant correlations have been found between FDG uptake on PET and the biomarkers of glucose transport by Glut-1 expression [52-55], and proliferative activity by Ki-67 expression in NSCLC [54-57]. In addition, FDG uptake of primary tumor in NSCLC was presented to be correlated significantly with number of viable tumor cells [58], characteristics of tumor vitality (such as high tumor cell density, high cell proliferation, and extracellular acidosis) [12], and angiogenesis proteins (vascular endothelial growth factor: VEGF) [55, 56, 59]. These findings indicated that the FDG uptake of primary tumors might reflect the biological malignant potential in NSCLC and the relationship between FDG uptake and

these biomarkers may lead to a more rational use of FDG-PET scan in NSCLC, particularly, in prognosis at diagnosis.

### 4.4.1. Prognostic value of FDG uptake of primary tumor in stage I and II NSCLC

Stage I and II NSCLC is considered as early stage and can be treated by surgical resection as “standard of care” with or without chemotherapy or radiation therapy.

We reviewed 7 studies from Pubmed to focus on prognostic value of FDG uptake of primary tumor, measured on PET or PET/CT in patients with stage I-II NSCLC at diagnosis. All patients were underwent surgical resection after PET or PET/CT study. Characteristics of these studies were showed in *table 1*.

All these studies used FDG uptake of primary tumor as one of potential variables in the survival analysis. FDG on PET or PET/CT was represented by maxSUV in 4 studies, by maxSUV and PVC-maxSUV (maxSUV partial volume corrected for lesion size) in 2 studies, by both maxSUV and doubling of maxSUV in 1 study.

All these studies showed that FDG uptake of primary tumor was significantly correlated with disease free survival or overall survival in early stage NSCLC, although the parameters to assess FDG uptake were various. FDG uptake represented by maxSUV was identified as independent prognostic indicator in 4 studies, by maxSUV and PVC-maxSUV in 1 study, by PVC-maxSUV in 1 study and by doubling of maxSUV in 1 study.

*Table 1:* Characteristics of the 7 studies focused on the prognostic value of FDG uptake in primary tumor for survival in stage I-II NSCLC

| *Study* | *Year* | *N of patients* | *Stage* | *Type of SUV* | *Best cut-off* | *High FDG uptake as prognosis for survival* |
|---|---|---|---|---|---|---|
| Goodgame B et al. [8] | 2008 | 136 | I | maxSUV | 5.5 | Unfavorable |
| Hanin FX et al. [9] | 2008 | 96 | I-II | maxSUV | 7.8 | Unfavorable |
| Kim HR et al. [10] | 2009 | 107 | I | maxSUV | 4 | Unfavorable |
| Um SW et al. [11] | 2009 | 145 | I | maxSUV | 5.2 and 13.8* | Unfavorable |
| | | | | PVC-maxSUV | | Unfavorable |
| Dooms C et al.[(a)] [12] | 2009 | 91 | I-II | maxSUV | ≥median | Undetermined |
| | | | | PVC-maxSUV | ≥median | Unfavorable |
| Nair VS et al. [13] | 2010 | 75 | IA | maxSUV | 5 | Unfavorable |
| Agarwal M et al. [14] | 2010 | 363 | I-II | maxSUV | 8.2 | Undetermined |
| | | | | doubling of maxSUV | | Unfavorable |

** 5.2 for Adenocarcinoma and 13.8 for other histology of NSCLC. [(a)]Prospective study*

In a retrospective study to evaluate the prognostic value of the FDG uptake in 145 patients with resected pathologic stage I NSCLC according to histologic types of the tumors, Um SW et al. found that both maxSUV and PVC-maxSUV were significantly associated with DFS and there was a difference on the optimal cutoff values of maxSUV to predict cancer recurrences according to tumor histologies (adenocarcinoma or others) [11]. A prospective study of Doom C et al. assessed the FDG uptake, measured as maxSUV in stages I and II

NSCLC for its prognostic value and association with in vitro quantitative morphology of tumor vitality. The authors showed that PVC-maxSUV ≥ median had a prognostic value in completely resected stages I and II NSCLC. A high-quantitative FDG uptake was associated with characteristics of tumor vitality such as high tumor cell density, high cell proliferation, and extracellular acidosis. Meanwhile, SUVmax ≥ median was associated with an increased risk of death in univariable analysis, but lost prognostic significance after correcting for stage, tumor size and age in multivariable analysis [12]. In a retrospective study to determine the prognostic value of maxSUV of the primary tumor in curative resection for early-stage (I & II) NSCLC, Agarwal M et al. found that maxSUV was not an independent predictor of overall survival. However, the result demonstrated that each doubling of maxSUV as [i.e., each log (base 2) unit increase in maxSUV] determined by preoperative PET was associated with a 1.28-fold increase in hazard of death in early-stage (I & II) NSCLC.[14, 60] Accompany with FDG uptake, the other factors, such as T-classification, age, and histology has been identified as the independent predictors for recurrence and mortality in NSCLC [8]. The best cut-off of maxSUV to determine prognostic significance ranged from 4 to 13.8 in those studies. This may be explained by some different characteristics of patients such as tumor-cell type, calculation of SUV based on body weight or lean body mass.

There are some reasons to explain FDG uptake in primary tumor as an important prognostic indicator for patients with stage I-II NSCLC. The FDG uptake in primary tumor is influenced by multiple biological factors. Glut-1, a mediator of glucose uptake and Ki-67, a molecular marker of tumor proliferation were commonly overexpressed and correlated with FDG uptake of

primary tumor in NSCLC [52-57]. FDG uptake has been also known to be related to hexokinase and glucose-6-phosphatase activities in cancer cells [61-63], tumor blood flow, intratumoral microvessel densities [64], and number of viable tumor cells [12, 58]. FDG uptake may reflect aggressiveness at the whole tumor level. The more aggressive the tumor behavior, the more aggressive the biological factors represented by FDG uptake. Therefore, the greater FDG uptake in the primary tumor may appear the more aggressive disease and the higher risk for recurrence or death in stage I-II NSCLC.

Thus, FDG uptake should be added to other well-known factors in prognosis of stage I-II NSCLC. And it is essential to use FDG uptake as in vivo biomarker for stratifying patients at increased risk of recurrence or death for closer surveillance or adjuvant chemotherapy after surgery.

### 4.4.2. Prognostic value of FDG uptake of primary tumor in stage III-IV NSCLC

Stage III and IV NSCLC has been considered as advanced stage. Locally advanced NSCLC may be divided into stage IIIA and stage IIIB. Stage IIIA NSCLC represents a heterogeneous group (T3 N1, T1–3 N2), from apparently resectable tumors with occult nodal microscopic metastasis to unresectable, bulky multistation nodal disease [65]. Majority of patients with stage IIIB and IV cannot be treated by surgery. Chemotherapy or radio-chemotherapy is recommended for these patients. Radiation alone is usually used for symptom control.

We reviewed 4 studies from Pubmed to focus on prognostic value of FDG uptake of primary tumor, measured on PET or PET/CT in patients with stage III-IV NSCLC at diagnosis. Characteristics of these studies were showed in *table 2.*

Three of 4 studies have not identified FDG uptake as prognostic factor for survival in patients with stage III and IV NSCLC. Stage of disease, performance status, serum albumin levels, bone metastases and metabolic tumor volume (MTV) - a volumetric parameter of FDG-PET were better independent predictors of survival than maxSUV of the primary tumor in patients with stage III and IV NSCLC [16-18].

In a study to evaluate the influence of FDG uptake of primary tumor on prognosis and occurrence of distant metastases in 159 patients with stage IIIA or IIIB NSCLC, Eschmann SM et al found that the incidence of distant metastases significantly correlated with meanSUV. Overall survival tended to decrease with increasing meanSUV, however, significance was only reached when a cut-off of 12.0 was applied ($p=0.05$). FDG uptake is an independent prognostic factor in patients with UICC stage III NSCLC, although less distinctively so than has been reported for stage I/II tumors [15].

It seems that role of FDG uptake of primary tumor in initial prognosis of survival was disappointed in advanced NSCLC. FDG uptake of primary tumor could not reflect a picture of whole advanced disease, which may be presenting potential wide-spread of occult or cleared metastasis.

*Table 2:* Characteristics of the 4 studies focused on the prognostic value of FDG uptake in primary tumor for survival in stage III-IV NSCLC.

| *Study* | *Year* | *N of Patients* | *Stage* | *Impression* |
|---|---|---|---|---|
| Eschmann SM et al. [15] | 2006 | 159 | III | FDG uptake (meanSUV) was an independent prognostic factor in patients with stage III NSCLC, although less distinctively so than has been reported for stage I/II tumors. Overall survival tended to decrease with increasing meanSUV. However, significance was only reached when a cut-off of 12.0 was applied (p=0.05). |
| Hoang JK et al. [16] | 2008 | 214 | III-IV | Stage of NSCLC even in the advanced stage was still the best predictor of survival. FDG uptake (maxSUV) of the primary tumor did not have a significant relationship with survival and decisions regarding management options should not be made based on level of metabolic activity of the primary tumor on FDG PET for patients with a new diagnosis of advanced-stage NSCLC. |
| Yan H et al. [17] | 2011 | 120 | III-IV | Metabolic tumor volume (MTV), a volumetric parameter of FDG-PET, was an important independent prognostic factor for survival and a better predictor of survival than maxSUV for the primary tumor in patients with advanced NSCLC. |
| Inal A et al. [18] | 2012 | 120 | III-IV | FDG uptake (maxSUV) of the primary lesion was not associated with prognosis, while performance status, serum albumin levels and bone metastases were independent prognostic factors for overall survival in locally advanced or metastatic NSCLC. |

### 4.4.3. Prognostic value of FDG uptake of primary tumor in all stage of NSCLC

We extracted 14 studies from Pubmed to focus on prognostic value of FDG uptake of primary tumor, measured on PET or PET/CT in patients with stage I to III-IV NSCLC at diagnosis. Patients received diversity of therapies due to various stages. Eight of 14 studies included all patients underwent surgical resection as one of optional treatments after PET study. Twelve studies analyzed the influence of maxSUV or meanSUV of primary tumor and other conventional parameters on survival. One study used maxSUV and PCV-maxSUV and one other study used the percentage change in maxSUV (△maxSUV) between the early and the delayed imaging for survival analysis. Characteristics of these studies were showed in *table 3.*

Eleven studies identified a high FDG uptake represented by maxSUV or meanSUV of the primary tumor as a poor prognostic factor for survival [54, 66-75]. However, one study demonstrated that maxSUV independently predicted overall survival for men but not for women with surgically treated early NSCLC [74]. The best threshold of SUV allowing to distinguish between long and short survival patients ranged from 5 to 15 regarding to each study.

Three studies found no significant correlation between maxSUV and survival [76-78]. Vesselle H et al. reported that neither maxSUV nor PVC-maxSUV provided significantly additional prognostic information over stage, tumor size, and age [76].

*Table 3:* Characteristics of the 14 studies focused on the prognostic value of FDG uptake in primary tumor for survival in all stage I-III/IV NSCLC.

| *Study* | *Year* | *N of Patients* | *Stage* | *Type of SUV* | *cut-off* | *High FDG uptake as prognostic factor for survival* |
|---|---|---|---|---|---|---|
| Vansteenkiste et al. [66] | 1999 | 125[(a)] | I-IIIB | maxSUV | 7 | Unfavorable |
| Higashi et al. [67] | 2002 | 57[(a)] | I-III | meanSUV* | 5 | Unfavorable |
| Jeong et al. [68] | 2002 | 73 | I-IV | maxSUV | 7 | Unfavorable |
| Downey RJ et al. [69] | 2004 | 100[(a)] | I-IIIB | maxSUV | 9 | Unfavorable |
| Sasaki et al. [70] | 2005 | 162 | I-III | maxSUV | 5 | Unfavorable |
| Borst et al. [71] | 2005 | 51 | I-III | maxSUV | 15 | Unfavorable |
| Zhang ZJ et al. [72] | 2007 | 82[(a)] | I-III | maxSUV | 11 | Unfavorable |
| Nguyen XC et al. [54] | 2007 | 53[(a)] | I-III | maxSUV* | 7 | Unfavorable |
| Vesselle H et al. [76] | 2007 | 208[(a)] | I-IV | maxSUV*<br>PVC-maxSUV* | 7<br>7 | Undetermined<br>Undetermined |
| Chen X et al. [75] | 2008 | 144 | I-IV | maxSUV | 8 | Unfavorable |
| Al-Sarraf N et al. [73] | 2008 | 176[(a)] | I-IV | maxSUV | 15 | Unfavorable |
| Houseni M et al. [77] | 2010 | 100 | I-IV | maxSUV<br>△maxSUV | 10<br>25% | Undetermined<br>Unfavorable |
| Wainer Z et al. [74] | 2012 | 189[(a)] | I-IV | maxSUV* | 8 | Unfavorable for men. Undetermined for women. |
| Erdem V et al. [78] | 2012 | 101 | I-IV | maxSUV | 12 | Undetermined |

** corrected by lean body mass. [(a)] patients underwent surgery treatment after PET study.*

Houseni M et al. found that dual-phase FDG-PET reflected the dynamics of glucose metabolism. Percentage of maxSUV change over time, platelet count, staging and metastatic status were strong prognostic factors in patients with lung adenocarcinoma [77].

Patients in these studies were classified in various stages, so it was hard to evaluate role of FDG uptake in stratification of early or advanced stages from each study. However, these studies found the significant prognosis of preoperative FDG uptake in patients with curative intent surgical treatment. FDG uptake in primary tumor seemed to be much more related with survival in patients in early stage in compare with late stage NSCLC.

### 4.4.4. Beyond of FDG uptake of primary tumor

Recent studies were more interested in role of tumor burden measurement on survival of patients with NSCLC. Tumor burden measurement includes metabolic tumor volume (MTV), number of tumors (TTn) and total lesion glycolysis (TLG).

Whole body MTV and whole body TLG on FDG PET/CT have been used in some studies. MTV was defined as the total volume of all tumors in the body in milliliters. It provides volumetric information based on FDG-PET/CT and does not assess metabolic activity of malignant lesions. TLG provides combination of volumetric and metabolic information of FDG PET. Measure of MTV and TLG were performed several times and intra- and inter-observer variability of MTV and TLG should be assessed. Impression of studies was demonstrated in *table 4.*

*Table 4:* The impression of the 5 studies to investigate tumor burden measurements on survival in NSCLC.

| *Study* | *Year* | *N of Patients* | *Stage* | *Impression* |
|---|---|---|---|---|
| Lee P et al. [19] | 2007 | 19 | I-IV | High tumor burden assessed by PET MTV (metabolic tumor volume) in whole body was an independent poor prognostic feature in lung cancer, promising for stratifying patients in randomized trials and ultimately for selecting risk-adapted therapies. |
| Chen HH et al. [20] | 2012 | 105 | I-IV | Whole body TLG (total lesion glycolysis) was of prognostic value for NSCLC. It may be a promising tool for stratifying patients with NSCLC for risk-adapted therapies. |
| Liao S et al. [21] | 2012 | 169 | I-IV | Whole body MTV and whole body TLG on FDG PET were prognostic measures independent of clinical stage for survival with low inter-observer variability and may be used to further stratify nonsurgical patients with NSCLC. Pretreatment MTV and TLG were better prognostic measures than maxSUV and meanSUV of all lesions. |
| Liao S et al. [24] | 2012 | 92 | IV | Whole body MTV and whole body TLG on FDG-PET were independent prognostic measures for survival in patients within Stage IV NSCLC with low inter-observer variability.<br>Pretreatment MTV and TLG measurements may be used to further stratify patients with Stage IV NSCLC and was better prognostic measures than maxSUV and meanSUV measurements of all lesions. |

*Table 4: (continued)*

| *Study* | *Year* | *N of Patients* | *Stage* | *Impression* |
|---|---|---|---|---|
| Zhang H et. [22] | 2012 | 140 | I-IV | The total number of tumors in whole body and number of nodal metastases, as metabolic tumor burden measurements in FDG-PET/CT, were prognostic markers independent of clinical stage, age, gender, and SUV measurement in non-surgical patients with NSCLC. |
| Zhang H et. [23] | 2013 | 104 | I-IV | Whole body MTV and TLG on FDG-PET were prognostic measures independent of clinical stage and other prognostic factors including chemoradiation therapy and surgical procedure with low inter-observer variability and may be used to further risk stratify surgical patients with NSCLC. MTV and TLG were better prognostic measures than maxSUV and meanSUV. |

In a pilot study, Lee P et al. reported that high tumor burden measured by whole body metabolic tumor volume (MTV) on FDG-PET/CT was an independent poor prognostic feature in lung cancer. An increase in MTV of 25 ml was significantly associated with increased hazard of 5.4 fold for progression and 7.6 fold for death [19].

Studies of Liao S et al. [21, 24] and Zhang H et al. [23] reported that whole body MTV and whole body TLG on FDG PET were independent prognostic measures for survival. Pretreatment MTV and TLG measurements were better prognostic measures than SUVmax and SUVmean measurements and may be used to further stratify patients with NSCLC.

Meanwhile, study of Chen HH et al. [20] found that whole body TLG, whole body MTV, lung TLG, lung MTV, maximum SUV, performance status, T stage, N stage, clinical stage, and treatment method were significant prognostic factors

for PFS in univariate analysis and only whole body TLG and treatment method were the two independent prognostic factors for survival in multivariate analysis. The 1-year overall survival was 58.8% for patients with whole body TLG >655 and 84.1% for those with whole body TLG ≤655. While whole-body MTV lost it role in prognosis in multivariate analysis [20].

Another study to determine whether the number of tumors seen in FDG-PET/CT scans could be a prognostic factor in non-surgical patients with stage I-IV NSCLC, Zhang H et al. reported that the total number of tumors in whole body and number of nodal metastases, as metabolic tumor burden measurements in FDG-PET/CT were prognostic markers of overall survival independent of clinical stage, age, gender, and SUV of the tumors [22].

In this review of the role of FDG-PET and PET/CT in prognosis for patients with NSCLC, we recognize that glucose metabolic activity of primary tumor based on FDG uptake on FDG-PET and PET/CT should be considered as independent prognostic indicator for patients with NSCLC in early stage or intent to be treated by surgery as the first choice. FDG uptake of primary tumor should be added in the well-known prognostic factors and used to stratify patients necessary for further post-operative adjuvant therapy. Tumor burden measurement may provide additive prognostic information for patients with advanced NSCLC and be evaluated in large prospective cohort studies.

# 5. AIM OF STUDY

The aim of the prospective study was to test the hypothesis on the additive prognostic value of sumaxSUV which is calculated sum of maxSUVs on FDG-PET/CT of primary tumor, metastatic lymph nodes and metastatic lesions per each organ for overall survival in patients with advanced NSCLC.

# 6. MATERIALS AND METHODS

## 6.1. Patient population

We designed the prospective study on patients with advanced stage III-IV NSCLC who did not received any specific treatment before undergoing FDG-PET/CT study at Choray hospital, Vietnam from March 2009 to May 2012. This study was approved by the research ethical board of hospital. Eighty three patients were enrolled in the study. Patients were indicated to PET/CT study from various hospitals in South Vietnam. After PET/CT study and clinical and histopathologic diagnoses, the patients were treated following the guideline of the referral hospitals. We collected the study data from hospital records and clinicians. We contacted the patients or their relatives every 3-6 months to get information involving the status of patients. Patients with life expectancy or follow-up time of less than 3 months were excluded from the study.

## 6.2. FDG-PET/CT Imaging

All patients are fasted for at least 4 hours before FDG-PET/CT study at the center of PET/CT and Cyclotron of Choray hospital, Vietnam. The patients with diabetes mellitus were recommended to discontinue metformin 2 days prior to PET/CT.

The patients were examined and explained thoroughly on the FDG-PET/CT procedure. No one had renal failure and a history of prior allergy-like reaction to contrast media. The finger blood glucose level was measured before

administration of $^{18}$F-FDG (FDG). The mean glucose level of all patients was 102.9±17.0 mg/dl (ranged from 78 to 178 mg/dl).

The patients were injected the dose of 5.18 MBq/kg (0.14 mCi/kg) of $^{18}$F-FDG which was produced on-site following standard operating procedures. Whole-body scanning was performed at 60 minutes after $^{18}$F-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, following the guideline of hospital and under the supervision of radiologist and nuclear medicine physician. The dose of contrast media of Iopromide (Ultravist) or Iopamidol (Iopamiro) 300mg I/ml was 1.2 ml/kg body weight of patient and it was infused at a rate of 2 ml per second for two-third of volume, then 1 ml per second for the remain one-third of volume. The CT scan was started 60 seconds after initiation of intravenous contrast material infusion**.** Then PET scan was acquired in three-dimensional (3D) mode with an axial field of view 21.6 cm, slices of thickness of 5 mm and an axial and transaxial resolution (FWHM @ 1cm) of 4.7 and 4.2 mm, respectively. The PET acquisition time was 3 minutes per bed with slice overlap at the borders of the field of view to avoid artifacts. Siemens Multimodality workstation with syngo TrueD software were used to display the images of attenuation-corrected PET, CT, and fused PET/CT in the transverse, coronal, and sagittal planes. A rotating maximum intensity projection image was displayed from the software. A nuclear medicine and a radiologist worked together in assessment and interpretation of FDG-PET/CT images.

### 6.3. Measurement of FDG uptake on PET/CT

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: SUV = radioactivity in VOI (Bq/ml) × body weight (kg) / injected radioactivity (Bq). Maximum SUV (maxSUV) was highest SUV representing the maximum glucose metabolic activity in tissue.

Sum of maxSUVs of primary tumor, lymph node and distal metastases per each organ in the whole body (sumaxSUV) was defined as sum of the maxSUV of 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 *(figure. 1)*. The data of maxSUVs was updated and sumaxSUV was calculated based on Exel software. Distal lymph node was considered as an organ. Metastatic lung to other lobes was considered as one more metastatic organ. The maxSUV of brain metastasis with or without avid-FDG uptake was all used in sumaxSUV. Brain metastatic lesions without avid-FDG uptake detected by contrast-enhanced CT or MRI were also measured maxSUV.

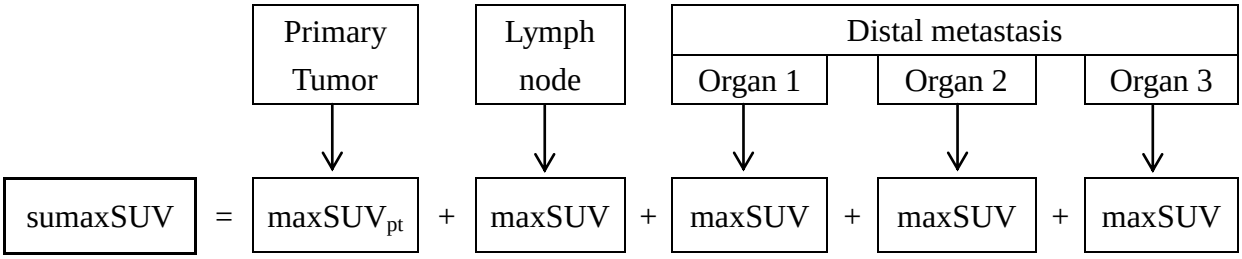


*Figure 1:* Diagram illustrates how to calculate sumaxSUV

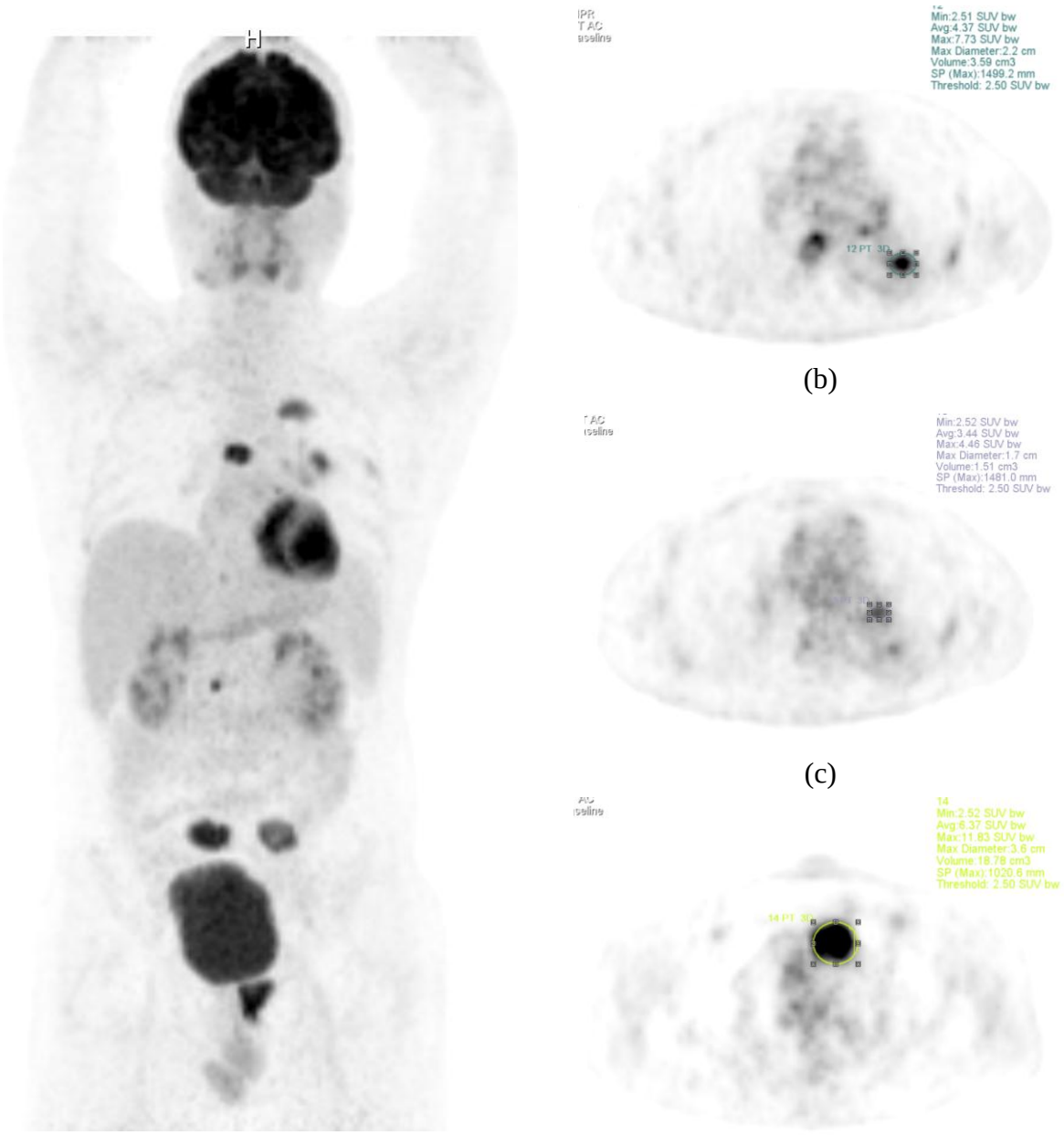


*Figure 2:* FDG-PET/CT images of NSCLC with lymph node and bone metastases. (a) Maximum intensity projection FDG-PET image. (b) maxSUV of lung primary tumor was 7.7, (c) maxSUV of lymph node was 4.5, and (d) maxSUV of bone metastasis was 11.8 (left pubic). SumaxSUV of 24 was calculated on exel software as sum of maxSUVs of lung primary tumor, lymph node and bone metastasis.

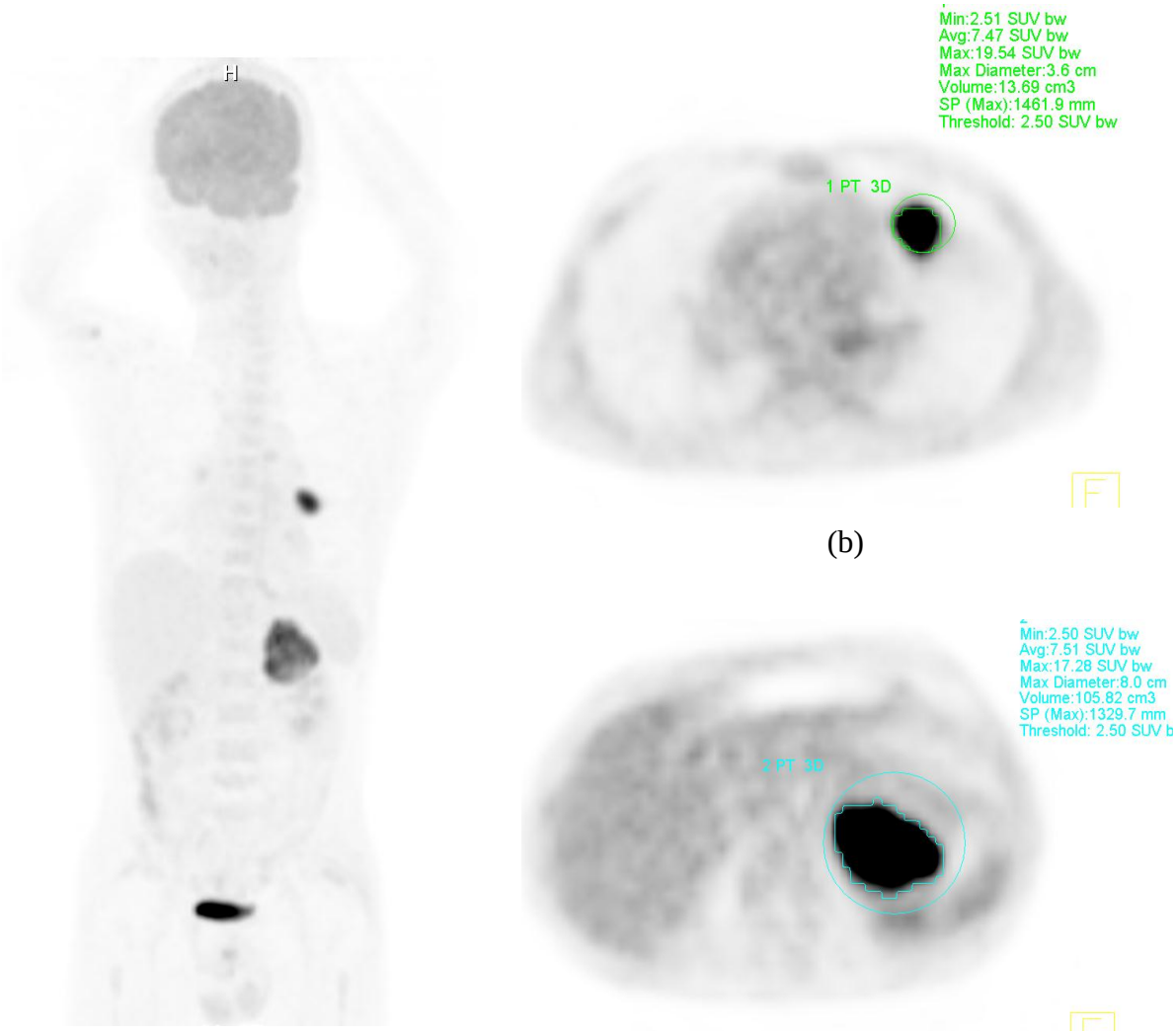


*Figure 3:* FDG-PET/CT images of NSCLC with left adrenal metastasis. (a) Maximum intensity projection FDG-PET image. (b) maxSUV of lung primary tumor was 19.5. (c) maxSUV of adrenal metastasis was 17.3. SumaxSUV of 36.8 was calculated on exel software as sum of maxSUVs of lung primary tumor and left adrenal metastasis.

### 6.4. Data analysis

Statistical analysis was performed using SPSS software (version 17.0).

Overall survival of 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, sumaxSUV (of primary tumor, lymph node metastases and distal metastases per each organ), maxSUV of primary tumor ($maxSUV_{pt}$) and maxSUV of whole body tumors ($maxSUV_{wb}$) were dichotomized into two groups around median values to identify the best discriminatory cutoff value for survival prediction. The analysis was conducted using the Kaplan–Meyer log-rank test.

Other prognostic factors, such as, age, gender, tumor-cell type, stage of primary tumor, stage of lymph node metastasis, overall stage, size of primary tumor, specific treatment were also assessed in survival analysis.

In addition, sumaxSUV, $maxSUV_{pt}$, $maxSUV_{wb}$ and size of primary tumor were separately entered as continuous values in a Cox proportional hazard model to assess their associations with survival.

Interactions between variables found significant effect on the survival were evaluated by multivariate analysis using the Cox proportional hazard model. P values of less than 0.05 were considered significant.

# 7. RESULTS

## 7.1. Patient characteristics

A total of 83 patients with NSCLC (49 male and 34 female) were enrolled in the present study. Mean age of patients was 58.9 ± 11.0 year old. Mean age was 58.0 ± 10.1 for male and 60.3 ± 12.2 year old for female patients. The histologic subtype was squamous cell carcinoma 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 squamous cell carcinoma.

The clinical stage of patients was classified according to stage definition by AJCC 6$^{th}$ edition, 2002 [3]. There were 17 patients with stage IIIA, 21 with stage IIIB and 45 with stage IV. Among patients with stage IV, there were 23 patients who had single organ metastasis, 16 patients had 2-organ metastasis and 2 patients had either 3, or 4, or 5 organ metastasis. The characteristics of the patients are summarized in *Table 5.*

There were 28 (33.7%) of 83 patients who had bone metastasis, 16 (19.3%) had lung metastasis in other lobes, 12 (14.5%) had renal metastasis, 8 (9.6%) had brain metastasis, 6 (7.2%) had liver metastasis, 6 (7.2%) had distal lymph node metastasis and 1 (1.2%) had pancreas metastasis 1 (1.2%) had spleen metastasis and 1 (1.2%) had soft tissue metastasis.

After the performance of PET/CT study and a confirmation of diagnosis, seventy seven patients received specific treatments and 6 patients had supportive treatments.

*Table 5.* Patient characteristics (n=83)

| *Characteristics* | *N. of patients* | *%* |
|---|---|---|
| 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 | | |
| Stage IIIA | 17 | 20.5 |
| Stage IIIB | 21 | 25.3 |
| Stage IV | 45 | 54.2 |

Among patients with specific treatments, nine 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 only. Types of treatment was summarized in *table 6.*

*Table 6.* Types of treatment

| *Types of treatment* | *N of patients* | *%* |
|---|---|---|
| Surgery, chemotherapy, radiotherapy | 9 | 10.8 |
| Surgery, chemotherapy | 10 | 12.0 |
| Chemotherapy, radiotherapy | 18 | 21.7 |
| Surgery | 2 | 2.4 |
| Chemotherapy | 35 | 42.2 |
| Radiotherapy | 3 | 3.6 |
| Supportive treatment | 6 | 7.2 |

Thirteen (76.5%) of 17 patients with stage IIIA and 8 (12.1%) of 66 patients with stage IIIB/IV were treated with surgery. Of 72 patients receiving chemotherapy, 66 patients were treated intravenous chemotherapy and 6 patients were treated orally by erlotinib or gefitinib as the firstline monotherapy. The combination of Carboplatin-paclitaxel with or without bevacizumab was commonly used for most of the intravenous chemotherapy.

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

## 7.2. 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, mean±s.d. = 12.3±6.2 months). Thirty-three patients (39.8%) were alive with a median follow-up time of 15 months (range, 8-31 months, mean±s.d. = 17.0±6.8 months).

In the study population of 83 patients, the sumaxSUV ranged between 4 and 116.4 with median of 26.5 and mean±s.d. of 30.1±19.8. The sumaxSUV was continuous variable, so we dichotomized it into 2 groups with 5-unit increase or decrease around the median value, relatively. Univariate survival 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. *(table 7 and figure 4).*

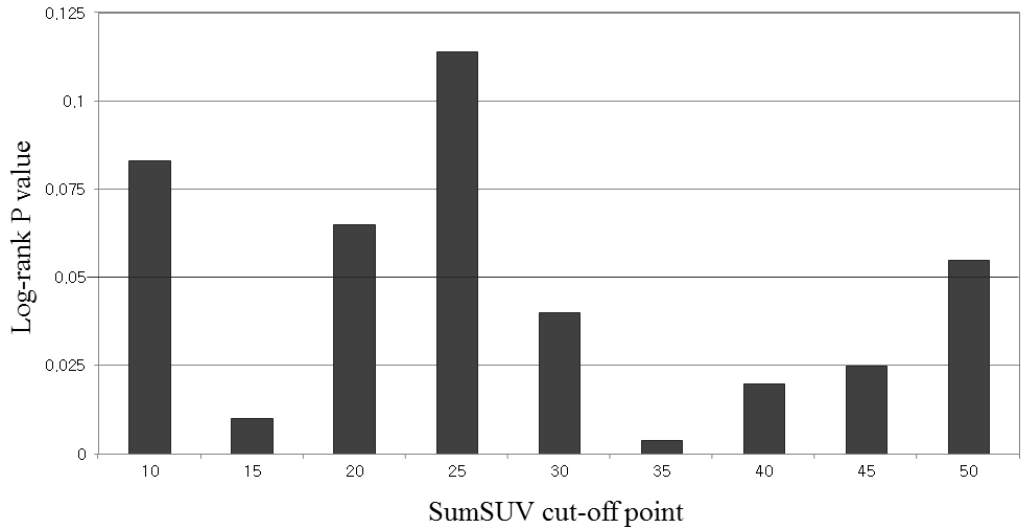


*Figure 4.* Relationship between various sumaxSUV cut-off values and their discriminative significance for overall survival, as assessed by the Log-rank test.

*Table 7.* Relation between cut-off values of sumaxSUV and overall survival as determined by the log-rank test.

| *Cut-off value (sumaxSUV)* | *N of patients* | *Log-rank P* |
|---|---|---|
| <10 | 5 | 0.083 |
| ≥10 | 78 | |
| <15 | 16 | 0.010 |
| ≥15 | 67 | |
| <20 | 27 | 0.065 |
| ≥20 | 56 | |
| <25 | 41 | 0.114 |
| ≥25 | 42 | |

| *Cut-off value (sumaxSUV)* | *N of patients* | *Log-rank P* |
|---|---|---|
| <30 | 50 | 0.040 |
| ≥30 | 33 | |
| <35 | 58 | 0.004 |
| ≥35 | 25 | |
| <40 | 66 | 0.020 |
| ≥40 | 17 | |
| <45 | 74 | 0.025 |
| ≥45 | 9 | |
| <50 | 76 | 0.066 |
| ≥50 | 7 | |

For maxSUV of primary tumor ($maxSUV_{pt}$, ranged from 2.8 to 27.6 with median of 12.8 and mean±s.d. of 13.5±5.4), and maxSUV of whole body tumors ($maxSUV_{wb}$, ranged from 2.8 to 47.5 with median of 13 and mean±s.d. of 14.5±6.6). A 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 $maxSUV_{pt}$ and $maxSUV_{wb}$ to be significantly correlated with survival. Log-rank *p* value was from 0.139 to 0.962 for $maxSUV_{pt}$ and from 0.168 to 0.851 for $maxSUV_{wb}$. The best discriminatory value for overall survival was 20 for $maxSUV_{pt}$ ($p = 0.139$), and 15 for $maxSUV_{wb}$ ($p = 0.168$). *(table 8 and table 9)*

*Table 8.* Relation between cut-off values of maxSUV of primary tumor and overall survival as determined by the log-rank test.

| *Cut-off value ($maxSUV_{pt}$)* | *N of patients* | *Log-rank P* |
|---|---|---|
| <7 | 10 | 0.962 |
| ≥7 | 70 | |
| <8 | 12 | 0.792 |
| ≥8 | 71 | |
| <9 | 17 | 0.775 |
| ≥9 | 66 | |
| <10 | 23 | 0.389 |
| ≥10 | 60 | |
| <11 | 30 | 0.538 |
| ≥11 | 53 | |
| <12 | 35 | 0.691 |
| ≥12 | 48 | |
| <13 | 42 | 0.907 |
| ≥13 | 41 | |
| <14 | 49 | 0.466 |
| ≥14 | 34 | |

| *Cut-off value ($maxSUV_{pt}$)* | *N of patients* | *Log-rank P* |
|---|---|---|
| <15 | 54 | 0.749 |
| ≥15 | 29 | |
| <16 | 59 | 0.664 |
| ≥16 | 24 | |
| <17 | 62 | 0.398 |
| ≥17 | 21 | |
| <18 | 64 | 0.317 |
| ≥18 | 19 | |
| <19 | 66 | 0.372 |
| ≥19 | 17 | |
| <20 | 71 | 0.139 |
| ≥20 | 12 | |
| <21 | 73 | 0.418 |
| ≥21 | 10 | |
| <22 | 74 | 0.563 |
| ≥22 | 9 | |

*Table 9.* Relation between cut-off values of maxSUV of whole body tumors and overall survival as determined by the log-rank test.

| *Cut-off value ($maxSUV_{wb}$)* | *N of patients* | *Log-rank P* | *Cut-off value ($maxSUV_{wb}$)* | *N of patients* | *Log-rank P* |
|---|---|---|---|---|---|
| <7 | 7 | 0.553 | <15 | 48 | 0.168 |
| ≥7 | 76 | | ≥15 | 35 | |
| <8 | 9 | 0.842 | <16 | 55 | 0.310 |
| ≥8 | 74 | | ≥16 | 28 | |
| <9 | 13 | 0.464 | <17 | 32 | 0.358 |
| ≥9 | 70 | | ≥17 | 18 | |
| <10 | 20 | 0.328 | <18 | 59 | 0.365 |
| ≥10 | 63 | | ≥18 | 24 | |
| <11 | 26 | 0.319 | <19 | 62 | 0.236 |
| ≥11 | 57 | | ≥19 | 21 | |
| <12 | 32 | 0.580 | <20 | 68 | 0.169 |
| ≥12 | 51 | | ≥20 | 15 | |
| <13 | 40 | 0.673 | <21 | 70 | 0.443 |
| ≥13 | 43 | | ≥21 | 13 | |
| <14 | 46 | 0.245 | <22 | 72 | 0.851 |
| ≥14 | 37 | | ≥22 | 11 | |

Suvival 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 found to significantly relate to age (≤60 vs. >60 years old), size of 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 10.*

*Table 10.* 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 |
| Stage (IV vs. III) | 0.002 |
| Tumor size (>3 cm vs. ≤3 cm) | 0.724 |
| SumaxSUV (≥35 vs. <35) | 0.004 |
| MaxSUV of primary tumor (> 20 vs. ≤ 20) | 0.139 |
| MaxSUV of whole body tumors (> 15 vs. ≤ 15) | 0.168 |
| Specific treatment (no vs. yes) | 0.011 |

** Sqc: squamous cell carcinoma, non-sqc: non squamous cell carcinoma.*

For the further analysis of continuous variables, $maxSUV_{pt}$, $maxSUV_{wb}$, and tumor size were not significantly related 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 one-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).

### 7.3. 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, primary tumor stage, clinical 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 significant independent predictors of overall survival. *(table 11)*

*Table 11*. Results of multivariate analysis of overall survival (Cox proportional hazard model).

| *Variable* | *P value* | *Relative risk* | *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 |
| Stage (IV vs. III) | 0.056 | | |

[a] *95% confidence interval for relative risk.*

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 with sumaxSUV ≥35 and 20 months for those with sumaxSUV <35. Relative risk and median survival time of patient groups based on T stage, gender and specific treatment were also demonstrated in *table 11 and table 12*.

*Table 12.* The median overall survival time based on independent prognostic factors.

| *Patient with characteristics:* | | *Median survival time (month)* | | |
|---|---|---|---|---|
| | | Estimate | 95% Confidence Interval | |
| | | | Lower Bound | Upper Bound |
| T Stage | T4 | 13 | 9.8 | 16.2 |
| | T1-T3 | 19 | 15.6 | 22.5 |
| Gender | male | 15 | 13.3 | 16.7 |
| | female | 20 | 13.0 | 27 |
| Specific treatment | no | 6 | 2.4 | 9.6 |
| | yes | 18 | 14.7 | 21.3 |
| SumaxSUV | ≥ 35 | 14 | 9.7 | 18.3 |
| | < 35 | 20 | 17.1 | 23.0 |

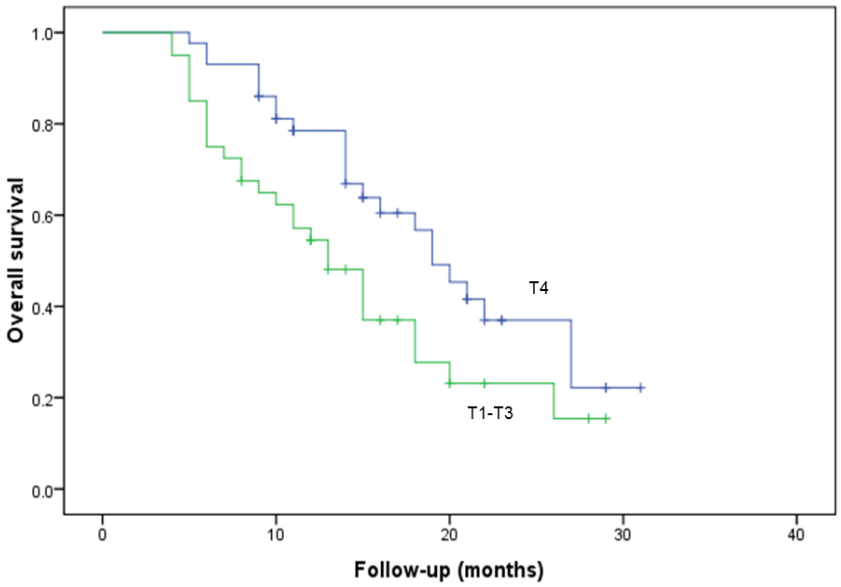


*Figure 5.* Overall survival curves based on T stage.

The patients with T4 stage (n=40) had median survival time of 13 months, that was lower than those with T1-T3 stage (n=43, 19 months).

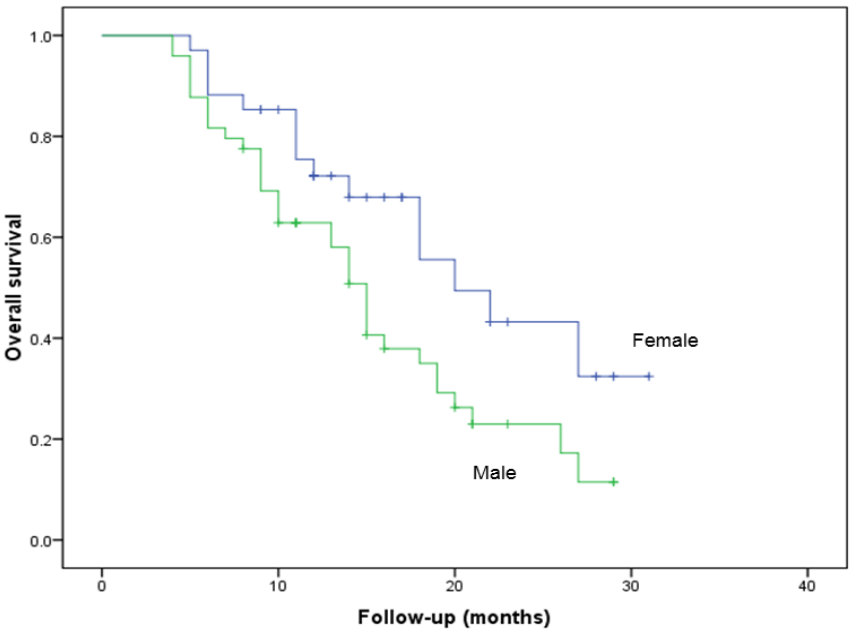


*Figure 6.* Overall survival curves based on gender.

Male patients (n=49) had median survival time of 15 months, that was lower than female patients (n=34, 20 months).

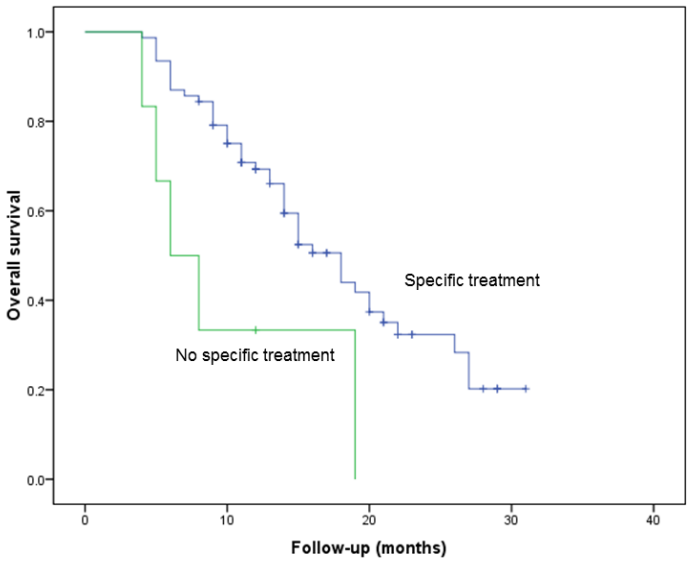


*Figure 7.* Overall survival curves based on treatment.

The median survival time was 18 months for patients with specific treatment (n=77), compared to only 6 months for those without specific treatment (n=6).

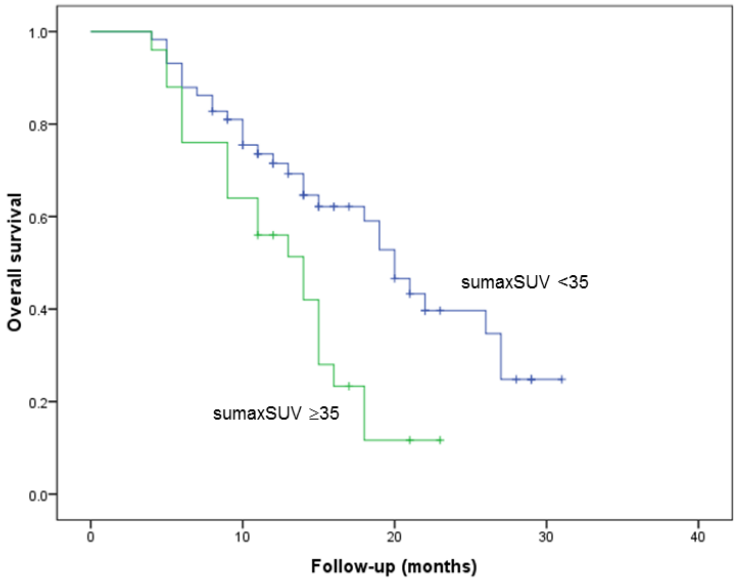


*Figure 8.* Overall survival curves based on sumaxSUV cut-off.

The patients with sumaxSUV ≥35 (n=25) had median survival time of 14 months, that was lower than those with sumaxSUV <35 (n=58, 20 months).

### 7.4. Survival analysis in patients with stage IV NSCLC

In 45 patients with metastatic NSCLC, thirty four patients (75.6%) were dead during follow-up at a median 11 months (range, 4-26 months, mean±s.d. = 11.8±5.9 months) and 11 patients (24.4%) were alive with a median follow-up time of 14 months (range, 8-28 months, mean±s.d. = 15.7±6.1 months).

A univariate analysis demonstrated sumaxSUV with cut-off of 35 and specific treatment were correlated with overall survival with a log-rank *p* value of 0.33 and 0.23, respectively. No significant correlation was found between overall survival and one of other factors, such as gender, T stage, N stage, $maxSUV_{pt}$, $maxSUV_{wb}$, size of primary tumor, tumor-cell type, age, and number of metastatic organs in univariate analysis.

SumaxSUV and specific treatment both remained significant on multivariate analysis in Cox Proportional Hazard Model with *p* value of 0.021 for sumaxSUV and 0.013 for specific treatment. Patients with metastatic NSCLC who had a sumaxSUV of ≥ 35 were 2.371 times more likely to die from disease than those with a sumaxSUV of ≤35. The median survival time was 11 months for patients with sumaxSUV ≥35 compared to 19 months for those with sumaxSUV <35.

Patients with metastatic NSCLC who did not received any specific treatment, were 3.568 times more likely to die. The median survival time was 6 months for patients without specific treatment compared to 15 months for those with specific treatment.

# 8. DISCUSSION

The main findings of this study is that sum of maximum glucose metabolism of primary tumor, local-regional lymph node metastasis and distal metastasis per each organ in the whole body determined by sumaxSUV measurement and other factors such as gender, tumor stage and specific treatment are the independent prognostic factors for overall survival. SumaxSUV was presented more significant in survival prognosis for subgroup of metastatic NSCLC. The maxSUV of primary tumor and maxSUV of whole body tumors did not provide prognostic information in patients with advanced NSCLC.

A sumaxSUV cut-off of 35 was the best discriminative value for overall survival. Moreover, sumaxSUV was also a continuous variable which showed significant correlation with overall survival in present study.

The maximum glucose metabolism of primary tumor represented by maxSUV of FDG uptake on PET or PET/CT has been reported as initial prognostic factor for early stage NSCLC in some previous studies [8-14]. In the early stage NSCLC, the disease is localized and able to be treated by curative intent surgery. The risk of disease recurrence after surgery may be partially determined by the aggressive biologic behavior of primary NSCLC. High FDG uptake of primary tumor reflects the variety of aggressively biological processes in the whole tumor which can consist of the glucose metabolic activity represented by Glut-1 over expression [52-55], proliferative activity by Ki-67 expression [54-57], hexokinase and glucose-6-phosphatase activities [61-63], number of viable tumor cells [12, 58], angiogenesis [55, 56, 59], tumor blood flow, and intratumoral microvessel densities [64]. Thus, high FDG uptake of

primary tumor, presented by maxSUV on PET or PET/CT was significantly associated with poor prognosis of early stage NSCLC [8-14].

The present study did not identified maxSUV of primary tumor ($maxSUV_{pt}$) and maxSUV of whole body tumors ($maxSUV_{wb}$) as predictors of survival in advanced NSCLC. This findings are 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. Treatment options should not be made based on level of metabolic activity of the primary tumor as well as the metastatic lesion only in advanced NSCLC.

In advanced NSCLC, the aggressive behavior of the primary tumor only may not reflect the whole disease status when the high risk of occult widespread dissemination of the tumor cells or actually metastasis to other organs through lymphatic or blood vessels. Moreover, the aggression of lesions in different organs commonly presents various glucose metabolic activities and $maxSUV_{wb}$ reflects the aggression of only one in variety of impaired organs of disease. Risk of death can be original from organ's malignant lesions with maxSUV that can be less than $maxSUV_{wb}$. Thus, glucose metabolism of the primary tumor or metastatic lesions of single organ only could be not enough to provide additive prognostic information in advanced NSCLC.

In the present 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. The sumaxSUV measure has been not investigated so far. The sumaxSUV, presenting all maximum glucose metabolic activities from primary tumor, loco-regional

lymph nodes and metastatic lesions per each organ may reflect the aggressive levels of all organs with active malignant lesions in the whole body with regarding to aspect of metabolic activity.

FDG uptake in primary tumor significantly correlated with the incidence of regional lymph node metastasis [25, 26], and distant metastases in NSCLC [15, 27]. However, FDG uptake in primary tumor has not been reported to be correlated with the aggression of metastatic organs. While the risk of death in patients with advanced NSCLC can come from metastatic lesions in various organs. This study showed that the sumaxSUV seemed to be suitable parameter presenting biologic behavior and aggressiveness of whole body disease. Thus, it should be considered to add sumaxSUV into known prognostic factors in advanced NSCLC.

Recently, the impact of metabolic tumor burden on survival prognosis for patients with NSCLC has been assessed in several studies [19-24]. High tumor burden measured by whole body metabolic tumor volume (MTV) and whole body total lesion glycolysis (TLG) on FDG-PET/CT has been reported 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 information based on FDG-PET/CT derived from the whole body. MTV and TLG have been recommended to be used to stratify patients with NSCLC [19-21, 23, 24]. However, those studies did not include patients with brain metastasis, because whole body PET/CT did not cover the whole brain and the measurement of MTV and TLG gave a result of low inter-observer variability.

Another measure of metabolic tumor burden on FDG-PET/CT is to count the total number of tumors in whole body (TTn) and number of nodal metastases (Nn). TTn and Nn have been found to be prognostic markers of overall survival, independent of clinical stage, age, gender, and SUV of the tumors in non-surgical patients with stage I-IV NSCLC [22].

This present study demonstrated a new measurement of metabolic tumor burden, so-called sumaxSUV, which has proved prognostic value in advanced NSCLC, particularly in metastatic stage. Lesions with highest FDG uptake per each organ are easily selected in FDG-PET/CT and the calculation of sumaxSUV is simple and reproducible.

Another principal finding of this study is 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 were classified based on staging system of AJCC 6$^{th}$ edition. Malignant pleural effusion belongs to T4 stage following AJCC 6$^{th}$ edition, instead of M1a stage by AJCC 7$^{th}$ edition [79]. Eight (38.1%) of 21 patients with stage IIIB and 14 (31.1%) of 45 patients with stage IV had malignant pleural effusion or epicardial invasion (1 case) in this study.

There was a significant difference in survival between male and female patients. Male had shorter survival time than female patients did. No significant difference in age and tumor-cell type was seen between male and female patients ($p>0.05$, not presented in result) and smoking status was not surveyed from this study. While some previous studies showed that women with lung

cancer have better survival than men with lung cancer. It was likely that women were smoked less intensively, disease-diagnosed at an earlier age and had histology of adenocarcinoma [80-82].

This study had certain limitations. Patients were enrolled with different stages IIIA to IV NSCLC and received various treatments. Thirteen of 17 patients (76.5%) with stage IIIA and 8 of 66 patients (12.1%) with stage IIIB/IV were treated with surgery. We analyzed survival involving only one factor of specific treatment which represented for surgery, chemotherapy and radiation or combination treatment. The impact of each therapeutic method on result of survival was not analyzed.

One of important factors for survival prognosis is performance status of patients which 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 of PET images, better localization and anatomic diagnosis. Contrast-enhanced CT can influence on measurement of SUV. MaxSUV has been demonstrated to be increased in the contrast-enhanced PET/CT at all anatomic sites. The mean differences of maxSUV between enhanced and non-enhanced 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 [83]. Contrast-enhanced CT is suitable for attenuation correction in combined PET/CT and did not produce any clinically significant artifact in patients with lung cancer [83, 84].

# 9. CONCLUSION

Sum of the maxSUVs of primary tumor, loco-regional lymph node and distal metastases per each organ on FDG-PET/CT is 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 in advanced NSCLC. A large prospective cohort study is necessary to validate these results.

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# 11. APPENDIX

## LIST OF PATIENTS ENROLLED IN THE STUDY

| *Pts* | *Age* | *M/F* | *H* | *Staging* | | | | *Specific treatment* | | | *Status* | *Duration* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *T* | *N* | *M* | *TNM* | *S* | *C* | *R* | | *(months)* |
| 1 | 67 | F | A | 4 | 3 | 1 | 4 | N | N | N | D | 8 |
| 2 | 55 | M | S | 2 | 3 | 1 | 4 | N | N | Y | D | 16 |
| 3 | 51 | F | A | 4 | 3 | 1 | 4 | N | Y | N | D | 18 |
| 4 | 67 | F | A | 4 | 3 | 0 | 3B | N | Y | N | D | 6 |
| 5 | 53 | M | A | 4 | 2 | 1 | 4 | N | Y | Y | D | 13 |
| 6 | 51 | M | A | 4 | 3 | 1 | 4 | N | Y | Y | D | 26 |
| 7 | 82 | M | A | 1 | 1 | 1 | 4 | N | N | N | D | 19 |
| 8 | 68 | F | S | 4 | 3 | 1 | 4 | N | Y | Y | D | 11 |
| 9 | 42 | M | A | 2 | 2 | 1 | 4 | N | Y | N | D | 21 |
| 10 | 42 | M | A | 4 | 3 | 1 | 4 | N | Y | N | D | 15 |
| 11 | 39 | M | S | 4 | 3 | 0 | 3B | N | Y | N | D | 13 |
| 12 | 68 | F | A | 4 | 2 | 1 | 4 | N | Y | N | D | 6 |
| 13 | 60 | F | S | 2 | 2 | 0 | 3A | N | Y | N | D | 11 |
| 14 | 52 | M | S | 1 | 2 | 0 | 3A | Y | Y | N | D | 27 |
| 15 | 56 | F | A | 1 | 2 | 1 | 4 | N | Y | N | A | 23 |
| 16 | 33 | F | A | 1 | 0 | 1 | 4 | N | Y | Y | D | 14 |
| 17 | 60 | M | A | 2 | 3 | 1 | 4 | N | Y | N | D | 18 |
| 18 | 53 | F | A | 1 | 2 | 0 | 3A | Y | Y | Y | A | 31 |
| 19 | 72 | F | A | 1 | 2 | 1 | 4 | N | N | N | D | 6 |
| 20 | 73 | M | A | 4 | 2 | 0 | 3B | N | Y | Y | D | 4 |
| 21 | 42 | M | A | 4 | 3 | 1 | 4 | N | Y | N | D | 7 |
| 22 | 55 | F | A | 4 | 2 | 1 | 4 | N | Y | Y | D | 20 |
| 23 | 52 | F | A | 2 | 2 | 0 | 3A | Y | Y | N | D | 27 |
| 24 | 65 | M | L | 2 | 2 | 0 | 3A | Y | N | N | D | 14 |
| 25 | 70 | M | AS | 4 | 3 | 0 | 3B | N | Y | N | A | 29 |
| 26 | 61 | M | A | 3 | 2 | 1 | 4 | Y | Y | N | D | 9 |
| 27 | 52 | F | A | 3 | 2 | 1 | 4 | N | Y | Y | A | 15 |
| 28 | 50 | M | S | 1 | 2 | 0 | 3A | Y | Y | N | A | 29 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 29 | 60 | F | A | 3 | 3 | 0 | 3B | N | Y | Y | A | 29 |
| 30 | 58 | F | A | 4 | 2 | 1 | 4 | N | Y | N | A | 28 |
| 31 | 82 | F | A | 4 | 1 | 1 | 4 | N | Y | N | D | 5 |
| 32 | 76 | F | A | 2 | 3 | 0 | 3B | N | Y | Y | D | 22 |
| 33 | 64 | M | A | 4 | 0 | 1 | 4 | N | Y | N | D | 15 |
| 34 | 63 | M | A | 1 | 2 | 1 | 4 | N | Y | N | D | 19 |
| 35 | 52 | M | A | 2 | 0 | 1 | 4 | N | Y | Y | D | 10 |
| 36 | 63 | M | A | 2 | 2 | 0 | 3A | Y | Y | Y | D | 9 |
| 37 | 54 | M | A | 2 | 2 | 0 | 3A | Y | Y | N | A | 23 |
| 38 | 81 | M | A | 3 | 2 | 1 | 4 | N | Y | N | A | 11 |
| 39 | 46 | M | A | 3 | 0 | 1 | 4 | N | Y | N | D | 15 |
| 40 | 55 | M | S | 2 | 2 | 1 | 4 | N | Y | N | D | 6 |
| 41 | 56 | M | S | 3 | 3 | 1 | 4 | N | Y | N | D | 5 |
| 42 | 67 | F | A | 4 | 2 | 0 | 3B | N | Y | N | A | 22 |
| 43 | 54 | F | A | 4 | 2 | 1 | 4 | N | Y | Y | D | 12 |
| 44 | 55 | F | A | 4 | 3 | 0 | 3B | Y | Y | N | D | 18 |
| 45 | 84 | F | A | 2 | 2 | 1 | 4 | N | Y | N | A | 22 |
| 46 | 61 | M | A | 2 | 2 | 0 | 3A | N | Y | Y | A | 21 |
| 47 | 58 | M | A | 2 | 2 | 0 | 3A | Y | Y | Y | A | 21 |
| 48 | 74 | M | S | 4 | 2 | 0 | 3B | N | N | Y | D | 10 |
| 49 | 54 | M | A | 2 | 0 | 1 | 4 | N | Y | N | D | 9 |
| 50 | 40 | M | A | 4 | 0 | 0 | 3B | N | Y | N | A | 20 |
| 51 | 74 | M | A | 4 | 2 | 1 | 4 | Y | Y | N | D | 5 |
| 52 | 56 | M | A | 3 | 2 | 1 | 4 | N | Y | Y | D | 20 |
| 53 | 59 | M | S | 2 | 2 | 0 | 3A | Y | Y | Y | D | 14 |
| 54 | 51 | M | S | 4 | 3 | 1 | 4 | N | N | N | D | 5 |
| 55 | 66 | M | S | 4 | 2 | 0 | 3B | Y | Y | N | D | 15 |
| 56 | 47 | M | A | 4 | 3 | 1 | 4 | N | Y | N | D | 9 |
| 57 | 48 | F | A | 4 | 2 | 0 | 3B | N | Y | N | A | 17 |
| 58 | 58 | M | A | 2 | 2 | 0 | 3A | Y | Y | N | A | 16 |
| 59 | 71 | M | S | 2 | 3 | 1 | 4 | N | Y | N | D | 14 |
| 60 | 49 | M | S | 4 | 2 | 0 | 3B | Y | Y | Y | D | 8 |
| 61 | 51 | F | A | 4 | 3 | 1 | 4 | N | Y | N | D | 11 |
| 62 | 53 | F | A | 3 | 2 | 0 | 3A | Y | Y | Y | A | 17 |
| 63 | 61 | M | A | 4 | 3 | 1 | 4 | N | Y | N | D | 6 |
| 64 | 47 | M | A | 4 | 2 | 1 | 4 | N | Y | N | D | 6 |
| 65 | 56 | M | A | 3 | 3 | 0 | 3B | N | Y | N | A | 15 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 66 | 49 | F | A | 4 | 0 | 1 | 4 | N | Y | Y | A | 16 |
| 67 | 58 | M | A | 4 | 1 | 0 | 3B | Y | Y | Y | D | 5 |
| 68 | 58 | M | A | 4 | 2 | 0 | 3B | Y | Y | N | A | 14 |
| 69 | 79 | F | S | 3 | 2 | 1 | 4 | N | Y | N | A | 14 |
| 70 | 40 | F | A | 4 | 3 | 1 | 4 | N | Y | N | A | 13 |
| 71 | 60 | M | A | 3 | 3 | 0 | 3B | N | Y | Y | D | 10 |
| 72 | 44 | F | A | 4 | 0 | 0 | 3B | N | N | N | A | 12 |
| 73 | 66 | F | A | 4 | 2 | 0 | 3B | N | Y | Y | A | 12 |
| 74 | 67 | F | A | 3 | 3 | 0 | 3B | N | Y | Y | A | 9 |
| 75 | 60 | F | A | 4 | 2 | 1 | 4 | N | Y | N | A | 12 |
| 76 | 56 | F | A | 4 | 2 | 0 | 3B | Y | Y | Y | A | 12 |
| 77 | 70 | M | A | 3 | 0 | 1 | 4 | N | Y | N | A | 11 |
| 78 | 61 | M | A | 3 | 2 | 0 | 3A | N | Y | Y | A | 11 |
| 79 | 83 | F | A | 3 | 1 | 0 | 3A | Y | N | N | A | 10 |
| 80 | 63 | F | A | 3 | 1 | 0 | 3A | N | N | Y | A | 9 |
| 81 | 66 | M | A | 3 | 2 | 0 | 3A | Y | Y | Y | A | 10 |
| 82 | 56 | M | A | 4 | 3 | 1 | 4 | N | Y | N | A | 8 |
| 83 | 58 | M | A | 4 | 3 | 1 | 4 | N | N | N | D | 4 |

*Abbreviations:*

Pts: patients, M/F: Male/Female.

H: Histology (A: Adenocarcinoma, S: Squamous cell carcinoma, AS: Adenosquamous cell carcinoma and L: Large cell carcinoma)

T: Tumor, N: Lymph node, M: Metastasis, TNM: Tumor - Node - Metastasis.

Specific treatment (S: Surgery, C: Chemotherapy, R: Radiation, Y: yes, N: no)

Status ( A: Alive and D: deceased)

## LIST OF PATIENTS ENROLLED IN THE STUDY (continued)

| *Pts* | *T* | *maxSUV* | | | | | | | | | | | *Sumax-* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *size* | *T* | *LN* | *Lu* | *Bo* | *Li* | *Br* | *Ad* | *Sp* | *Pa* | *So* | *d-LN* | *SUV* |
| 1 | 2.6 | 11.7 | 10.8 | 2.4 | 9 | | | | | | | | 33.9 |
| 2 | 9.5 | 22.1 | 13.4 | 14.5 | | | | | | | | | 50 |
| 3 | 7 | 23.2 | 2.7 | 15 | | | | | | | | | 40.9 |
| 4 | 3 | 14.2 | 2.3 | | | | | | | | | | 16.5 |
| 5 | 6.2 | 12.4 | 6.7 | 5.8 | | | | | | | | | 24.9 |
| 6 | 7.2 | 11.6 | 4.6 | | 6.1 | 7.3 | | | | | | | 29.6 |
| 7 | 2.4 | 17.8 | 6.2 | | 7.2 | | | | | | | | 31.2 |
| 8 | 5.7 | 20.3 | 34.6 | | 20.8 | 14.1 | 10.1 | 11 | | | | | 110.9 |
| 9 | 3.7 | 7.7 | 4.5 | | 11.8 | | | | | | | | 24 |
| 10 | 4.6 | 13 | 8 | 1 | 12.3 | | | 4.6 | | | | | 38.9 |
| 11 | 6 | 21.7 | 14.1 | | | | | | | | | | 35.8 |
| 12 | 3 | 6.7 | 7.1 | | 3 | | | 2.8 | | | | | 19.6 |
| 13 | 7.4 | 15 | 7.1 | | | | | | | | | | 22.1 |
| 14 | 3 | 13.6 | 9.8 | | | | | | | | | | 23.4 |
| 15 | 2 | 11.9 | 8 | | 23.9 | | | | | | | | 43.8 |
| 16 | 2.5 | 13.2 | | | | | 16.6 | | | | | | 29.8 |
| 17 | 3.5 | 19.4 | 8.9 | | 11.8 | | | 6 | | | | | 46.1 |
| 18 | 2.3 | 2.8 | 2.4 | | | | | | | | | | 5.2 |
| 19 | 2.5 | 8.5 | 8.3 | | 15.2 | | | 11.4 | | | | | 43.4 |
| 20 | 5.2 | 12.1 | 9.5 | | | | | | | | | | 21.6 |
| 21 | 2.7 | 7.9 | 4.5 | | 9.2 | | | | | | | | 21.6 |
| 22 | 5.8 | 9.9 | 3 | | 2.1 | | | 9.8 | | | | | 24.8 |
| 23 | 4.5 | 22.4 | 4.4 | | | | | | | | | | 26.8 |
| 24 | 5.3 | 11.3 | 2.2 | | | | | | | | | | 13.5 |
| 25 | 5.8 | 15.8 | 11.7 | | | | | | | | | | 27.5 |
| 26 | 7.5 | 24.3 | 2.8 | | | | | 16.2 | | | | | 43.3 |
| 27 | 2.4 | 19.2 | 4 | | | | 8.9 | | | | | | 32.1 |
| 28 | 2.2 | 10.9 | 3.7 | | | | | | | | | | 14.6 |
| 29 | 9.4 | 19.6 | 15.2 | | | | | | | | | | 34.8 |
| 30 | 2.8 | 13 | 2.8 | 0.5 | 7.4 | | | | | | | | 23.7 |
| 31 | 2 | 6 | 4.9 | | 5.1 | 5.3 | | | | | | 5.2 | 26.5 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 32 | 4.5 | 6.7 | 2.9 | | | | | | | | | 9.6 |
| 33 | 2.3 | 14.6 | | | 23.3 | | | | | | | 37.9 |
| 34 | 2.5 | 6.6 | 6.3 | 0.9 | | | | | | | | 13.8 |
| 35 | 7 | 6.3 | | 3.7 | | | 6.6 | | | | | 16.6 |
| 36 | 3.2 | 10.3 | 6.2 | | | | | | | | | 16.5 |
| 37 | 3.7 | 14.4 | 6.7 | | | | | | | | | 21.1 |
| 38 | 4.2 | 22.8 | 11.2 | | 17.8 | 9.5 | | 9.1 | | 27.2 | | 97.6 |
| 39 | 5.6 | 24 | | | | | 17.1 | | | | | 41.1 |
| 40 | 7 | 27.6 | 21.9 | | 47.5 | | | 19.4 | | | | 116.4 |
| 41 | 4 | 10.9 | 14.6 | 8 | 2.1 | | | | | | 21.5 | 57.1 |
| 42 | 3.8 | 12.1 | 8.3 | | | | | | | | | 20.4 |
| 43 | 5.2 | 16 | 5.1 | | 6.8 | | | | | | | 27.9 |
| 44 | 4.5 | 9.2 | 5.4 | | | | | | | | | 14.6 |
| 45 | 5 | 13 | 10.9 | 10.6 | | | | | | | | 34.5 |
| 46 | 3.9 | 8.9 | 7.7 | | | | | | | | | 16.6 |
| 47 | 6.4 | 16.7 | 18.5 | | | | | | | | | 35.2 |
| 48 | 5.2 | 18.7 | 5.8 | | | | | | | | | 24.5 |
| 49 | 3.2 | 19.5 | | | 3.2 | | | 14.1 | | | | 36.8 |
| 50 | 3.2 | 4 | | | | | | | | | | 4 |
| 51 | 6.7 | 15.2 | 10.5 | | | | | | | | 4.9 | 30.6 |
| 52 | 4.8 | 15.5 | 11.2 | 3.1 | | | | | | | | 29.8 |
| 53 | 5.5 | 22.1 | 13.7 | | | | | | | | | 35.8 |
| 54 | 7 | 14.5 | 19.5 | 8.8 | | | 5.8 | | | | | 48.6 |
| 55 | 4 | 19.7 | 12.4 | | | | | | | | | 32.1 |
| 56 | 9 | 12.1 | 9.1 | | 3.4 | 8.5 | 13.1 | 9 | | | 8.4 | 63.6 |
| 57 | 3.1 | 16.3 | 3.5 | | | | | | | | | 19.8 |
| 58 | 4.2 | 9 | 2.5 | | | | | | | | | 11.5 |
| 59 | 3.8 | 14.7 | 12.2 | | 12.4 | | | | | | | 39.3 |
| 60 | 4 | 13.6 | 8.7 | | | | | | | | | 22.3 |
| 61 | 2.3 | 12.8 | 10.4 | | 9 | | | | | | 8.3 | 40.5 |
| 62 | 5.6 | 22.2 | 19 | | | | | | | | | 41.2 |
| 63 | 3.8 | 11.4 | 13 | 5.1 | | | | | 10.2 | | | 39.7 |
| 64 | 4.3 | 4.9 | 7.5 | 2.2 | 5.8 | | | | | | | 20.4 |
| 65 | 3.7 | 9.4 | 3.3 | | | | | | | | | 12.7 |
| 66 | 3.5 | 10.9 | | | | | 8.2 | | | | | 19.1 |
| 67 | 5.8 | 10.9 | 7.9 | | | | | | | | | 18.8 |
| 68 | 4.5 | 6.5 | 4.3 | | | | | | | | | 10.8 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 69 | 5 | 12.5 | 5.7 | | 11.5 | | | | | | 29.7 |
| 70 | 4.7 | 17.2 | 12.4 | 4.1 | | | | | | | 33.7 |
| 71 | 7 | 10.7 | 5.2 | | | | | | | | 15.9 |
| 72 | 2 | 8.9 | | | | | | | | | 8.9 |
| 73 | 7.5 | 8.5 | 3.5 | | | | | | | | 12 |
| 74 | 4.2 | 15.9 | 11.4 | | | | | | | | 27.3 |
| 75 | 5 | 13 | 10.4 | | 12 | 6.5 | | 5 | 5.7 | 5.7 | 58.3 |
| 76 | 8.7 | 8.3 | 5.5 | | | | | | | | 13.8 |
| 77 | 7.5 | 10.7 | | | 8.9 | | | | | | 19.6 |
| 78 | 14.3 | 9.5 | 3.4 | | | | | | | | 12.9 |
| 79 | 7 | 9.55 | 3.7 | | | | | | | | 13.25 |
| 80 | 2.8 | 12.4 | 5.3 | | | | | | | | 17.7 |
| 81 | 6.4 | 18.3 | 6.4 | | | | | | | | 24.7 |
| 82 | 9 | 4.5 | 2.6 | 2.8 | | | | | | | 9.9 |
| 83 | 4.5 | 20.1 | 15.1 | | 7.1 | | | | | | 42.3 |

*Abbreviations:*

T: tumor, LN: lymph node, Lu: lung, Bo: bone, Li: liver, Ad: adrenal, Sp: spleen, Pa: pancreas, So: soft tissue, d-LN: distal lymph node metastasis.