# Prognostic Value of Metabolic Tumor Burden from $^{18}$F-FDG PET in Surgical Patients with Non–small-cell Lung Cancer

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**Objective:** To assess the prognostic value of metabolic tumor burden as measured with metabolic tumor volume (MTV) and total lesion glycolysis (TLG) on 2-deoxy-2-($^{18}$F)fluoro-D-glucose ($^{18}$F-FDG) positron emission tomography (PET)/computed tomography (CT), independent of current Union Internacional Contra la Cancrum/American Joint Committee on Cancer tumor, node, and metastasis (TNM) stage; in comparison with that of standardized uptake value (SUV) in surgical patients with non–small-cell lung cancer (NSCLC).

**Material and Methods:** This study retrospectively reviewed 104 consecutive surgical patients (47 males, 57 females, median age at PET/CT scan of 67.92 years) with diagnosed stage I to IV NSCLC who had baseline $^{18}$F-FDG PET/CT scans. The $^{18}$F-FDG PET/CT scans were performed in accordance with National Cancer Institute guidelines. The MTV of tumors in the whole body ($MTV_{WB}$), TLG of tumors in the whole body ($TLG_{WB}$), the maximum standardized uptake value of tumors in the whole body ($SUV_{maxWB}$) as well as the mean standardized uptake value of tumor in the whole body ($SUV_{meanWB}$) were measured. The median follow-up among 67 survivors was 42.07 months from the PET/CT (range 2.82–80.95 months). Statistical methods included Kaplan-Meier curves, Cox regression, and C-statistics. The interobserver variability of $SUV_{maxWB}$, $SUV_{meanWB}$, $MTV_{WB}$, and $TLG_{WB}$ between two observers was analyzed using concordance correlation coefficients (CCCs).

**Results:** The interobserver variability of $SUV_{maxWB}$, $SUV_{meanWB}$, $MTV_{WB}$ and $TLG_{WB}$ was very low with CCCs greater than 0.882. There was a statistically significant association of stage with overall survival (OS). The hazard ratio (HR) of stage III and stage IV as compared with stage I was 3.60 ($P$ = .001) and 4.00 ($P$ = .013), respectively. The $MTV_{WB}$ was significantly associated with OS with a HR for 1-unit increase of $\ln(MTV_{WB})$ of 1.40/1.32 ($P$ = .004/.039), before/after adjusting for stage and other prognostic factors including chemoradiation therapy, and surgical procedure, respectively. $TLG_{WB}$ had a statistically significant association with OS before and after adjusting for stage and the other prognostic factors. The HR for 1-unit increase in $\ln(TLG_{WB})$ was 1.26 ($P$ = .011) and 1.25 ($P$ = .031), before and after the adjustment, respectively. Subjects with conditions that led to pneumonectomy (HR = 2.82, $P$ = .035) or segmental resection (HR = 3.44, $P$ = .044) had significantly worse survival than those needing lobectomy. There was no statistically significant association between OS and age, gender, tumor histology, $\ln(SUV_{maxWB})$, and $\ln(SUV_{meanWB})$ (all $P > .05$). There were 37 deaths during follow-up.

**Conclusion:** Baseline whole-body metabolic tumor burden as measured with $MTV_{WB}$ and $TLG_{WB}$ on FDG PET is a prognostic measure independent of clinical stage and other prognostic factors including chemoradiation therapy and surgical procedure with low interobserver variability and may be used to further risk stratify surgical patients with NSCLC. This study also suggests that MTV and TLG are better prognostic measures than $SUV_{max}$ and $SUV_{mean}$. These results will need to be validated in larger cohorts in a prospective study.

**Key Words:** 18F-FDG; non–small-cell lung cancer; tumor burden; metabolic tumor volume; total lesion glycolysis.



Lung cancer is the most common cause of cancer death in the world (1), the second most common cancer in both men and women, and the number one cause of cancer-related deaths in the United States. Non–small-cell lung cancer (NSCLC) comprises 80%–85% of all lung cancer cases (2). The treatment and prognosis of NSCLC depend mainly on disease stage as defined by the Union Internacional Contra la Cancrum (UICC)/American Joint Committee on Cancer (AJCC) (3–5). The stage based on the evaluation of the T, N, and M components and the assignment to a stage grouping (I to IV) (3) is the single most prognostic factor in predicting the outcomes of both surgical and nonsurgical patients with NSCLC (3,6–9). A retrospective study from the Netherlands that examined outcomes of 2361 patients who underwent surgery for resectable NSCLC from 1970 to 1992 found that the 5-year survival rate ranges from 19%

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in stage IIIA to 63% in stage IA (8). In a multicenter North American clinical trial (9), involving 458 patients with unresectable NSCLC cancers, but without metastases or significant weight loss, the patients were randomized to three groups: standard once-daily radiation therapy alone; chemotherapy, followed by standard radiation; and hyperfractionated radiation. Five-year survival rates were only 5%, 8%, and 6% in these three groups, respectively. These two studies highlight the dramatic difference in survival between surgical and nonsurgical patients with NSCLC.

Recently several studies demonstrated that metabolic tumor burden as measured with metabolic tumor volume (MTV) or total lesion glycolysis (TLG) is a prognostic marker in nonsurgical patients with NSCLC independent of TNM tumor stage (10–12). However, none of the studies specifically studied its prognostic value in the surgical patients. Lee et al was the first who found that the baseline whole body MTV ($MTV_{WB}$) measured semiautomatically is a statistically significant prognostic index and better than $SUV_{max}$ and $SUV_{mean}$ in the prediction of patient outcome in 19 lung cancer patients treated with different modalities (13). In their recent study, they expanded to a cohort of 61 patients with NSCLC treated with different modalities and confirmed the significant association of high $MTV_{WB}$ with decreased overall and progression-free survival in patients who received definitive therapy (14). In another recent study in 120 patients treated nonsurgically with advanced NSCLC by Yan et al, MTV of the primary tumor was found to be an important independent prognostic factor of survival and better than the $SUV_{max}$ (12) in this regard. More recent studies showed that baseline whole-body metabolic tumor burden as measured with MTV and TLG on positron emission tomography (PET) is a prognostic measure independent of clinical stage in nonsurgical patients (10) and in homogeneous stage IV NSCLC (11). However, based on our extensive literature search, there was no report in the literature about the prognostic value of the MTV and TLG in surgical patients with NSCLC independent of the clinical TNM stage.

Because prognosis of surgical patients with NSCLC is much better than nonsurgical patients (8,9), the prognostic value of the metabolic tumor burden in the surgical and nonsurgical patients need to be studied separately. Here we measured the $MTV_{WB}$ and $TLG_{WB}$ semiautomatically with commercially available PET/CT software to determine the additive prognostic value of MTV and TLG independent of tumor stage in 104 surgical patients with stage I to IV NSCLC. The prognostic value of the MTV and TLG independent of the clinical TNM stage of the tumor was compared with that of SUV measurements.

## MATERIALS AND METHODS

### *Patient Recruitment*

This study was approved by our hospital's Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act. We conducted a retrospective review of the medical records of patients with NSCLC. There were a total of 1023 cases with NSCLC who were diagnosed and treated in the authors' institution between January 1, 2004, and December 22, 2007. We identified the 104 consecutive surgical patients with NSCLC for this study from this retrospective database based on the following inclusion criteria: 1) all patients had a pretherapy baseline PET/CT scan, 2) they had definitive surgery, 3) they had stage I to IV NSCLC, and 4) they had no history or concurrent diagnosis of another type of cancer. The purpose of the PET/CT scan for this group of patients was to stage the disease or for the diagnosis of lung lesions. They had been followed with chest x-rays and CT of the chest and abdomen at our hospital at irregular intervals. These patients had been also followed by our Cancer Registry semiannually. Their survival status was determined through clinical follow-up and the Social Security Death Index. Clinical follow-up and the Illinois State Death Inquiry System were used to determine the causes of death whenever possible.

The UICC/AJCC staging system for NSCLC (3–5) was used to stage patients. The pathological stage of each case was assigned according to the sixth edition and clinical stage of each case was assigned according to both the sixth and seventh editions of the staging system. The clinical stage of the disease was based on patients' infused CT and PET/CT. The pathological stage of the disease was based on the pathology reports from the definitive surgery in all cases. Mediastinoscopic findings were also used for staging in 23 of the 104 patients who had mediastinoscopy/bronchoscopy before the definitive surgical treatment. The other 81 of the 104 had needle or bronchoscopic biopsy before definitive surgery.

### *Imaging Protocols*

***PET/CT imaging.*** The baseline pretreatment 2-deoxy-2-($^{18}$F)fluoro-D-glucose ($^{18}$F-FDG) PET/CT scans were performed in accordance with National Cancer Institute guidelines (15) in all 104 patients. The $^{18}$F-FDG PET images were obtained using a PET/CT scanner (Reveal HD, CTI, Knoxville, TN) equipped with high-resolution bismuth germanate detectors and a dual-slice CT scanner. The patients fasted for at least 4 hours before intravenous administration of 370–555 MBq of $^{18}$F-FDG. In addition, the serum glucose levels were tested via finger stick sampling before injection and found to be less than 200 mg/dL. A whole-body unenhanced CT scan with no intravenous contrast administration was performed first for PET attenuation correction. We used a standard protocol for the CT with 130 kvp, 70–80 mAs, a transaxial field of view 50 cm in diameter, a tube rotation time of 0.8 seconds per rotation, and a pitch of 3.0. About 90 minutes ± 30 minutes after injection of the $^{18}$F-FDG, a whole-body static PET scan was acquired for about 30–35 minutes, starting at the thighs and proceeding to the head. PET scans were obtained with an acquisition time of 3–5 minutes per cradle position, with slice overlap at the borders of the field of view to avoid artifacts. The PET camera has a