

# Prognostic Value of Preoperative Metabolic Tumor Volumes on PET-CT in Predicting Disease-free Survival of Patients with Stage I Non-small Cell Lung Cancer

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**Abstract.** *Background:* This study aimed to determine the relationship between the pre-operative metabolic tumor volume (MTV) and the disease-free survival (DFS) of patients with stage I non-small cell lung cancer (NSCLC) using F-18 2-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography-computed tomography (PET-CT) scanning. *Materials and Methods:* Data from sixty patients with stage I NSCLC who had undergone preoperative F-18 FDG PET-CT scanning were retrospectively analyzed. The early and late maximum standardized uptake values (eSUVm and lSUVm, respectively) were measured from attenuation-corrected F-18 FDG PET-CT images. Three MTV segmentation methods were applied as an isocontour at an early SUV of 2.5 (MTV2.5) or using fixed thresholds of either 40% (MTV40%) or 50% (MTV50%) of the maximum intratumoral F-18 FDG activity. DFS was compared by employing the Kaplan-Meier method, using the median values as cutoffs for each parameter. The log-rank test and

Cox regression were performed to explore the effect of the different MTV variables on DFS. Time-dependent receiver operating characteristic (ROC) curves were created to evaluate the predictive performance. *Results:* During a median follow-up duration of 24 months, two patients died of disease progression, and 11 experienced recurrent tumors (eight intrathoracic tumors, two distant metastasis, and one both types of recurrences). The univariate analyses showed that pathological stage 1B, histological type of squamous cell carcinoma, male sex, maximum tumor size over 2 cm, eSUVm, lSUVm, and MTV2.5 were associated with reduced DFS. Patients who had tumors with large eSUVm or large lSUVm had a significantly lower 2-year DFS, compared with patients who had smaller tumors (65% vs. 96%,  $p=0.002$ ; 63% vs. 96%,  $p=0.000$ ). Patients with an MTV2.5 greater than 9.8 ml had a lower 2-year DFS than those with an MTV of 9.8 ml or greater (59 vs. 85%,  $p=0.02$ ). However, multivariate analysis showed that lSUVm over 3.4 was the only parameter that exhibited an impact on DFS ( $p=0.05$ , hazard ratio=10.7), and the observed influence was marginal. *Conclusion:* For patients with stage I NSCLC treated with surgery, preoperative MTV parameters have a limited prognostic value for predicting DFS.

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Stage I non-small cell lung cancer (NSCLC), including T1N0M0 and T2aN0M0 (1), is a common form of cancer. Currently, surgical resection is the first treatment option for NSCLC. Adjuvant chemotherapy is usually recommended for some patients harboring high-risk pathological features (2). Previous studies have suggested that several factors are associated with recurrence or reduced survival, such as carcinoembryonic antigen, epithelial growth factor receptor,

and cytokeratin-19 fragment (3, 4). However, these factors have not been shown to be independent prognosticators (5). Recently, two investigators suggested that certain parameters measured using F-18 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography and computed-tomography (PET-CT), such as the maximal standard uptake value (SUVmax), the metabolic tumor volume (MTV), and the total lesion glycolysis, were associated with clinical outcome of patients with advanced NSCLC (6, 7). However, which of these quantitative PET-related measurements is the best predictor of clinical outcome is unclear.

Out of these methods, the approach based on SUVmax has been the most frequently examined. Some studies indicated that a higher SUVmax of primary tumors is associated with poorer prognosis in NSCLC (7). However, the optimal threshold of SUVmax in predicting outcome remains undetermined for patients with stage I NSCLC (8). Perhaps overlapping of the SUVmax values between tumors and non-tumorous lesions might reduce its prognostic value in assessing treatment options (9). In contrast, the MTV, which can be calculated from attenuation-corrected F-18 FDG PET images as the volume of tumor with increased glycolytic activity, provides both anatomical and functional information. Several studies have suggested that the MTV may represent an independent prognostic factor in advanced NSCLC (10-13). However, investigations on the role of pre-operative MTV in early-stage NSCLC are scant. We hypothesized that the pre-treatment MTV, as measured using F-18 FDG PET-CT, is associated with survival of patients with NSCLC. Thus, we conducted our retrospective study to compare the predictive values of pre-operative SUVmax and various MTV parameters

## Materials and Methods

**Patient population.** Between January 2009 and February 2011, 60 patients newly-diagnosed with stage I NSCLC who underwent curative surgical resection at China Medical University Hospital were enrolled in our retrospective study (Institutional Review Board certificate DMR99-IRB-010-1). They had all undergone an F-18 FDG PET-CT scan before resection surgery. The interval between the acquisition of images and the commencement of radiotherapy was less than four weeks. Each patient had an unremarkable serum glucose level before the PET-CT was performed. The pathological stage was evaluated using the tumor-node-metastasis (TNM) method (1). The cohort data are listed in Table I.

**PET-CT imaging protocol.** Our PET-CT procedure has been previously described (14). All patients were instructed to fast for at least 4 h before the PET-CT scan. Patients were injected intravenously with 370 MBq of F-18 FDG, and rested in a supine position in a quiet, dimly lit room. PET-CT scanning was initiated at approximately 45 min after the F-18 FDG injection using a Discovery STE instrument (GE Healthcare, Milwaukee, WI, USA). Delayed PET-CT images were obtained at approximately 70 min

after the F-18 FDG injection. PET emission images were obtained from CT scans at 2 min per field of view in the 3-D acquisition modes. The initial CT images were reconstructed onto a 512×512 matrix with a section thickness of 3.75 mm, reconstructed onto a 128×128 matrix, and converted into 511-keV-equivalent attenuation factors for correction of the corresponding PET emission images. CT images were acquired twice for every patient. The SUV was defined as tracer activity in the target region per unit mass divided by the amount of injected radioactivity per unit body mass. The SUVmax of the primary tumor in both early and delayed F-18 FDG PET-CT images was obtained, and were abbreviated as eSUVm and ISUVm, respectively.

**MTV definition and measurement.** MTV values were measured from attenuation-corrected F-18 FDG-PET-CT images using an SUV-based automated contouring program (Advantage Workstation Volume Share version 2, GE Healthcare). Initially, the F-18 FDG-PET data were introduced into the workstation in a DICOM format, and these images were reviewed to localize the target lesions that had been confirmed by two nuclear medicine physicians. MTV was defined as the sum of the metabolic volumes of the primary tumors. To define the contouring margins around the tumor, we used an eSUVmax of 2.5 (MTV2.5), 40% of the eSUVmax (MTV40%), and 50% of the eSUVmax (MTV50%). The MTV40% and MTV50% were defined as the volume greater than a fixed threshold of 40% and 50% of the maximum intratumoral activity, respectively. The volume boundaries were automatically drawn to incorporate each target lesion in the axial, coronal, and sagittal PET-CT.

**Treatment and follow-up.** Following curative surgery, 16 of the 22 patients with stage IB disease were treated with adjuvant chemotherapy. The regimens used for these 16 patients were carboplatin plus gemcitabine (n=7), cisplatin plus gemcitabine (n=3), docetaxel (n=3), and oral Tegafur-Uracil (n=3). The follow-up examinations were performed every 1-2 months over the first 2 years and every 3-4 months thereafter. The definitions of local recurrence and distant recurrence were based on chest CT scanning, F-18 FDG PET-CT analysis, or pathological findings.

**Statistical analysis.** In this study, the median values for the MTV2.5, MTV40%, MTV50%, eSUVm, and ISUVm were used as cutoff points for dichotomization of the patient cohort. Correlations between MTV and SUVmax were examined using Pearson's correlation, with the level set at 0.01. Because we sought to identify the impact of pre-treatment PET-CT parameters on cancer recurrence only, the study end-point was disease-free survival (DFS). DFS was measured from the date of diagnosis to the date of recurrence or last clinical follow-up. We analyzed MTV2.5, MTV40%, MTV50%, eSUVmax, ISUVmax, and pathological stage as categorical variables. Accordingly, the DFS curves were determined using the Kaplan-Meier method. The log-rank test and Cox regression were performed to explore the relationships between the categorical variables and DFS. The optimal predictive values of these parameters for disease recurrence were calculated by ROC curve analysis. *p*-Values less than 0.05 were considered statistically significant.

## Results

**SUVmax and MTV measurement.** The mean eSUVm±SD was 3.2±2.3 (median=2.5; range=0.6-10.8), whereas the mean

Table I. Patients' characteristics.

Parameter	No. of patients (n=60)
Gender	
Male	26
Female	34
Age	
Median (years)	63
Range from (years)	38-85
AJCC stage (7th edition)	
Pathological stage IA	38
Pathological stage IB	22
Histopathological findings	
Squamous cell carcinoma	5
Adenocarcinoma	55

ISUVm±SD was 3.8±2.8 (median=3.2; range=0.6-13.4). The MTV2.5 ranged from 1.08 to 78.2 ml (median=9.8 ml, mean=11.4±12.9 ml). The mean MTV40% was 7.3±5.9 (median=5.8; range=1.7-39.0), and the mean MTV50% was 5.6±4.3 (median=4.4; range=1.2-28.0). Our data did not reveal significant correlations between the eSUVm and MTV parameters ( $r=0.1$  for MTV2.5,  $p=0.46$ ;  $r=0.31$  for MTV40%,  $p=0.02$ ;  $r=0.32$  for MTV50%,  $p=0.01$ ).

**Treatment outcome.** The median follow-up duration was 24 months (range 8-36 months). Two patients died of disease progression, and 11 experienced recurrent tumors, including eight with intrathoracic tumors, two with distant metastasis, and one with both types of recurrence. Overall, the 2-year DFS was 81%.

**Prognostic value of PET-related parameters.** Table II shows a summary of the effect of the tumor and the treatment-related parameters on DFS by univariate and multivariate analyses. In the univariate analysis, pT1b, squamous cell carcinoma, male sex, maximum tumor size greater than 2 cm, eSUVm, ISUVm, and MTV2.5 were associated with reduced DFS.

As shown in Figures 1A and B, patients who had tumors with large eSUVm or large ISUVm had significantly lower 2-year DFS compared with patients who had smaller tumors (65% vs. 96%,  $p=0.002$ ; 63% vs. 96%,  $p=0.000$ ). Figure 2 shows that patients with an MTV2.5 greater than 9.8 ml had an inferior 2-year DFS than those with smaller MTV2.5 volumes (59% vs. 85%,  $p=0.02$ ). However, multivariate analysis showed that ISUVm over 3.4 was the only parameter that exhibited an impact on DFS ( $p=0.05$ , hazard ratio=10.7), and the observed influence was marginal. Overall, ISUVm yielded the best prediction for tumor recurrence. When using an ISUVm greater than 3.4 to predict disease recurrence, the

Table II. Result of univariate, multivariate analysis for disease-free survival.

Variable	Univariate p-value	Multivariate p-value
Age (years)		
≤63 vs. >63	0.32	0.69
Smoking		
Yes vs. no	0.12	0.26
Gender		
Male vs. female	0.01	0.98
eSUVm		
≤2.5 vs. >2.5	0.002*	0.11
ISUVm		
≤3.4 vs. >3.4	0.000*	0.05
MTV2.5 (ml)		
≤9.8 vs. >9.8	0.02*	0.49
MTV40% (ml)		
≤5.8 vs. >5.8	0.08	0.97
MTV50% (ml)		
≤4.4 vs. >4.4	0.34	0.24
Pathological stage		
IA vs. IB	0.000*	0.56
Histological type		
Squamous cell vs. adenocarcinoma	0.04	0.3
Maximum tumor diameter (cm)		
≤2.0 vs. >2.0	0.02*	0.63

eSUVm, Early maximum SUV; ISUVm, late maximum SUV; MTV2.5 and MTV20%, applying an isocontour at a SUV of 2.5; MTV40% and MTV50%, using fixed thresholds of 40% and 50% of the eSUVm; \*statistically significant.

sensitivity, specificity, positive predictive value, the negative predictive value, and the accuracy were 100%, 63.2%, 37.9%, 100%, and 70%, respectively.

To minimize the limitation of the MTV definition in some tumors with a lower eSUVmax, an additional ROC analysis was performed for 41 of the participants who had an eSUVm greater than 2.0. The results in this subgroup also indicated that the MTV methods did not exhibit a higher predictive value than the SUVmax approach.

## Discussion

Beyond the use of TNM staging, there is a need for additional prognostic markers to identify patients who are more appropriate for adjuvant therapy of early-stage NSCLC. Currently, SUVmax and MTV have been examined as prognosticators across the PET-related parameters (10-14). This study is a preliminary investigation comparing the predictive value of each in early and delayed SUVmax, as well as various MTV parameters. Theoretically, SUVmax represents the highest activity of a single pixel within the tumor, whereas the MTV represents the area where the

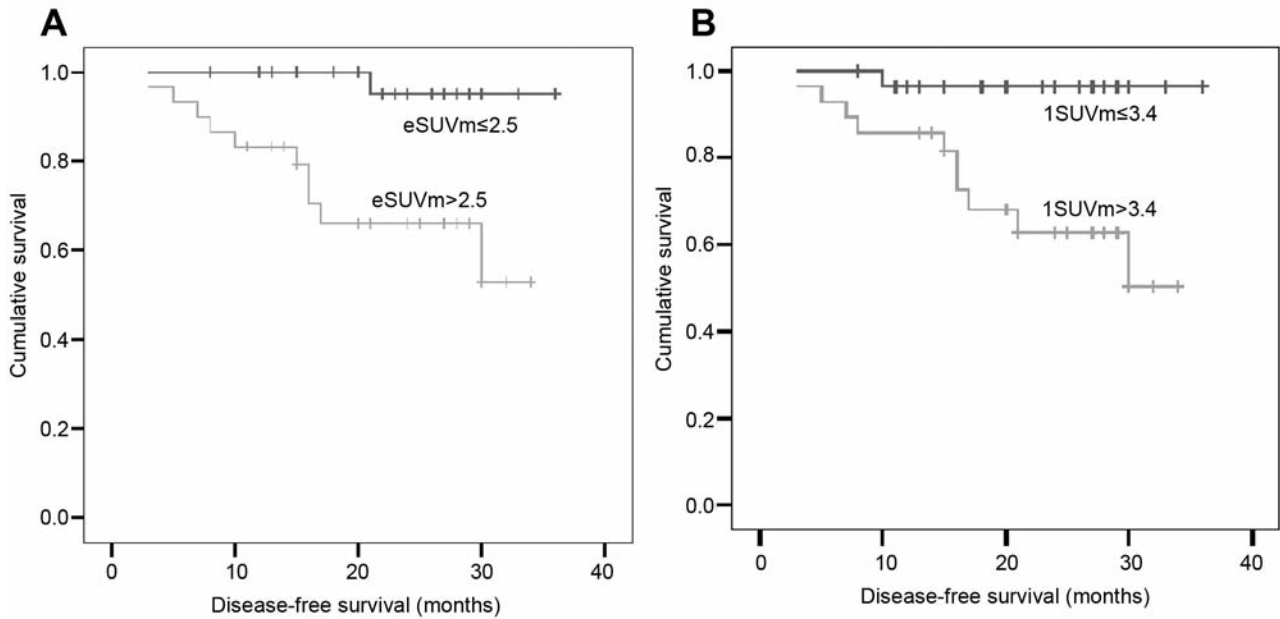


Figure 1. A: Disease-free survival curves according to early standardized uptake values (eSUVm). Data represent eSUVm >2.5 and eSUVm ≤2.5. B: Disease-free survival curves according to delayed SUVmax (1SUVm). Data represent 1SUVm >3.4 and 1SUVm ≤3.4.

activity of the voxels is above a selected value. The application of MTV seems more promising because MTV may combine information on tumor burden and cancer aggressiveness. Although some investigators have suggested that MTV is a useful prognostic for survival in NSCLC patients (10-14), our study failed to identify an independent predictor for DFS in patients with operable stage I NSCLC.

A recent study (14) that enrolled patients with stage I to IIIA NSCLC, undergoing surgery indicated that MTV<sub>2.5</sub> was a significant prognostic factor for DFS, and 42% of patients were categorized as stage II to IIIA disease. Consequently, the measured values of SUVmax or MTV would have been greater than ours. Because small tumor volume is usually associated with relatively smaller MTV, the predictive effect of MTV may be diminished because of the limitation of spatial resolution. Nonetheless, an interesting question emerges as to which threshold values for real tumor volume or SUVmax may increase the sensitivity of the predictive power of MTV using current PET-CT technologies. Future work should focus on the determination of an optimal threshold value.

There were several limitations to our study. Firstly, the median follow-up duration may not have been long enough, and further subsequent recurrences may not have been identified, resulting in the lack of affirmative findings based on the multivariate analysis. Secondly, some patients had a low SUVmax value or a small tumor volume. Thus, some

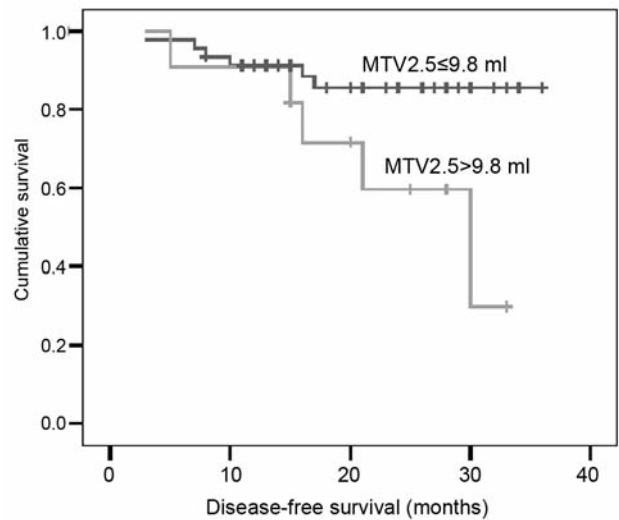


Figure 2. Disease-free survival curves based on metabolic tumor volume<sub>2.5</sub> >9.8 ml and MTV<sub>2.5</sub> ≤9.8 ml.

technical constraints existed after measuring the MTV parameters. Regardless, the subgroup analysis did not show a contradictory result after excluding those with eSUVm less than 2.0. Nevertheless, our study represents a clinical circumstance in which the MTV approaches were restrained.

## Conclusion

For patients with stage I NSCLC treated with surgery, pre-operative MTV parameters have a limited prognostic value for DFS. Further studies are needed to clarify the threshold values for tumor volume or SUVmax to increase the sensitivity of the predictive power of MTV measurements.

## Conflicts of Interest

All Authors declare they encountered no actual or potential conflicts of interest in conducting this study.

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## References

- Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti III A (eds.): *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer, pp. 253-270, 2010.
- Heon S and Johnson E: Adjuvant chemotherapy for surgically resected non-small cell lung cancer. *J Thorac Cardiovasc Surg* 144: S39-42, 2012.
- Ou SH, Zell JA, Ziogas A and Anton-Culver H: Prognostic factors for survival of stage I non-small cell lung cancer patients. A population-based analysis of 19,702 stage I patients in the California cancer registry from 1989 to 2003. *Cancer* 110: 1532-1541, 2007.
- Ost D, Goldberg J, Rolnitzky L and Rom WN: Survival after surgery in stage IA and IB non-small cell lung cancer. *Am J Respir Crit Care Med* 177: 516-523, 2008.
- Mumbarkar PP, Raste AS and Ghadge MS: Significance of tumor markers in lung cancer. *Ind J Clin Biochem* 21: 173-176, 2006
- Huang W, Zhou T, Ma L, Sun H, Gong H, Wang J, Yu J and Li B: Standard uptake value and metabolic tumor volume of 18F-FDG PET/CT predict short-term outcome early in the course of chemoradiotherapy in advanced non-small cell lung cancer. *Eur J Nucl Med Mol Imaging* 38: 1628-1635, 2011.
- Paesmans M, Berghmans T, Dusart M, Garcia C, Hossein-Foucher C, Lafitte JJ, Mascaux C, Meert AP, Roelandts M, Scherpereel A, Terrones Munoz V, Sculier JP; European Lung Cancer Working Party, and on behalf of the IASLC Lung Cancer Staging Project: Primary tumor standardized uptake value measured on fluoridese positron-emission tomography is of prognostic value for survival in non-small cell lung cancer: Update of a systematic review and meta-analysis by the European lung cancer working party for the international association for the study of lung cancer staging project. *J Thorac Oncol* 5: 612-619, 2010.
- Nair VS, Krupitskaya Y, and Gould MK: Positron-emission tomography <sup>18</sup>F-fluorodeoxyglucose uptake and prognosis in patients with surgically treated, stage I non-small cell lung cancer: A systematic review. *J Thorac Oncol* 4: 1473-1479, 2009.
- Nawara C, Rendl G, Wurstbauer K, Lackner B, Rettenbacher L, Datz L, Studnicka M, Sedlmayer F and Pirich C: The impact of PET and PET/CT on treatment planning and prognosis of patients with NSCLC treated with radioation therapy. *Q J Nucl Med Mol Imaging* 56: 191-201, 2012.
- Yan H, Wang R, Zhao F, Zhu K, Jiang S, Zhao W, and Feng R: Measurement of tumor volume by PET to evaluate prognosis in patients with advanced non-small cell lung cancer treated by non-surgical therapy. *Acta Radiol* 52: 646-650, 2011.
- Liao S, Penney BC, Zhang H, Suzuki K and Pu Y: Prognostic value of the quantitative metabolic volumetric measurement on 18F-FDG PET/CT in stage IV nonsurgical small-cell lung cancer. *Acad Radiol* 19: 69-77, 2012.
- Liao S, Penney BC, Wroblewski K, Zhang H, Simon CA, Kampalath R, Shih MC, Shimada N, Chen S, Salgia R, Appelbaum DE, Suzuki K, Chen CT and Pu Y: Prognostic value of metabolic tumor burden on <sup>18</sup>F-FDG PET in nonsurgical patients with non-small cell lung cancer. *Eur J Nucl Med Mol Imaging* 39: 27-38, 2012.
- Lee P, Bazan JG, Lavori PW, Weerasuriya DK, Quon A, Le QT, Wakelee HA, Graves EE and Loo BW: Metabolic tumor volume is an independent prognostic factor in patients treated definitively for non-small-cell lung cancer. *Clin Lung Cancer* 13: 52-58, 2012.
- Kim KY, Kim SJ, Kim IJ, Kim YS, Pak KG and Kim HY: Prognostic value of volumetric parameters measured by F-18 FDG PET/CT in surgically resected non-small-cell lung cancer. *Nucl Med Commun* 33: 613-620, 2012.

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