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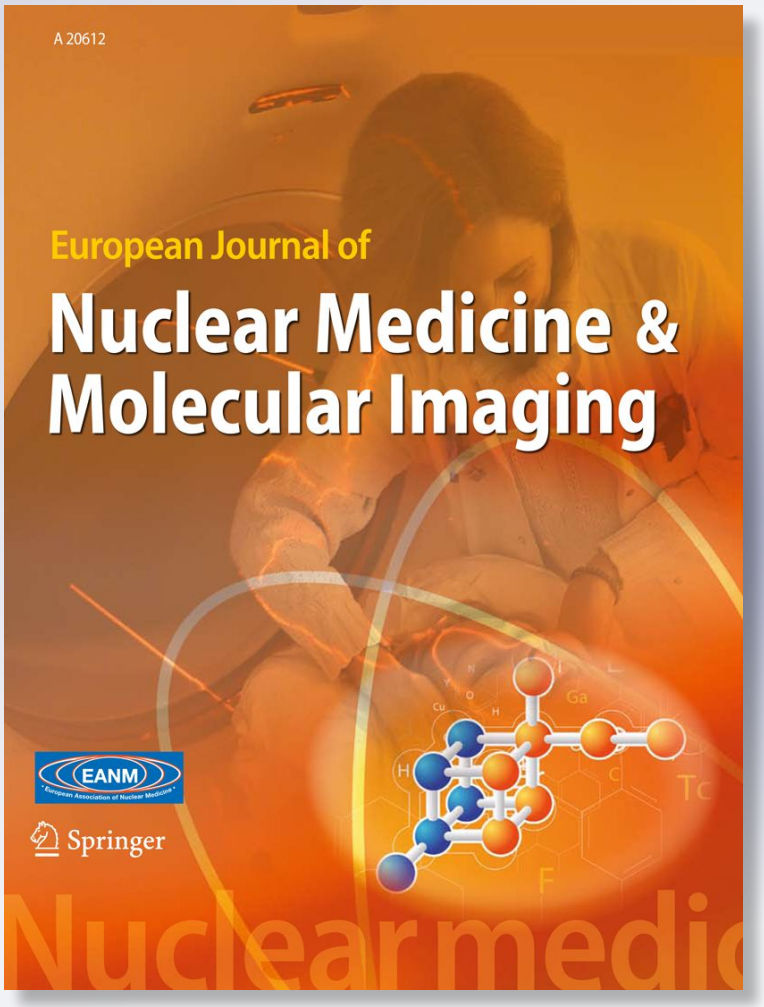

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ORIGINAL ARTICLE

Prognostic value of metabolic tumor burden on ^{18}F-FDG PET in nonsurgical patients with non-small cell lung cancer

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Abstract
Purpose The objective of this study was to assess the prognostic value of metabolic tumor burden on 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) positron emission tomography (PET)/CT measured with metabolic tumor volume (MTV) and total lesion glycolysis (TLG), independent of Union Internationale Contra la Cancrum (UICC)/American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) stage, in comparison with that of standardized uptake value (SUV) in nonsurgical patients with non-small cell lung cancer (NSCLC).
Methods This study retrospectively reviewed 169 consecutive nonsurgical patients (78 men, 91 women, median age of 68 years) with newly diagnosed NSCLC who had pretreatment ^{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 whole-body tumor (MTV_{WB}), of primary tumor (MTV_T), of nodal metastases (MTV_N), and of distant metastases (MTV_M); the TLG of whole-body tumor (TLG_{WB}), of primary tumor (TLG_T), of nodal metastases (TLG_N), and of distant metastases (TLG_M); the SUV_{max} of whole-body tumor (SUV_{maxWB}), of primary tumor (SUV_{maxT}), of nodal metastases (SUV_{maxN}), and of distant metastases (SUV_{maxM}) as well as the SUV_{mean} of whole-body tumor (SUV_{meanWB}), of primary tumor (SUV_{meanT}), of nodal metastases (SUV_{meanN}), and of distant metastases (SUV_{meanM}) were measured with the PETedge tool on a MIMvista workstation with manual adjustment. The median follow-up among survivors was 35 months from the PET/CT (range 2–82 months). Statistical methods included Kaplan-Meier curves, Cox regression, and C-statistics.
Results There were a total of 139 deaths during follow-up. Median overall survival (OS) was 10.9 months [95% confidence interval (CI) 9.0–13.2 months]. The MTV was statistically associated with OS. The hazard ratios (HR) for 1 unit increase of $\ln(MTV_{WB})$, $\sqrt{(MTV_T)}$, $\sqrt{(MTV_N)}$, and $\sqrt{(MTV_M)}$ before/after adjusting for stage were: 1.47/1.43 ($p<0.001/<0.001$), 1.06/1.05 ($p<0.001/<0.001$), 1.11/1.10 ($p<0.001/<0.001$), and 1.04/1.03 ($p=0.007/0.043$), respec-

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tively. TLG had statistically significant associations with OS with the HRs for 1 unit increase in ln(TLG_{WB}), √(TLG_T), √(TLG_N), and √(TLG_M) before/after adjusting for stage being 1.36/1.33 ($p<0.001/<0.001$), 1.02/1.02 ($p=0.001/0.002$), 1.05/1.04 ($p<0.001/<0.001$), and 1.02/1.02 ($p=0.003/0.024$), respectively. The ln(SUV_{maxWB}) and √(SUV_{maxN}) were statistically associated with OS with the corresponding HRs for a 1 unit increase before/after adjusting for stage being 1.46/1.43 ($p=0.013/0.024$) and 1.22/1.16 ($p=0.002/0.040$). The √(SUV_{meanN}) was statistically associated with OS before and after adjusting for stage with HRs for a 1 unit increase of 1.32 ($p<0.001$) and 1.24 ($p=0.015$), respectively. The √(SUV_{meanM}) and √(SUV_{maxM}) were statistically associated with OS before adjusting for stage with HRs for a 1 unit increase of 1.26 ($p=0.017$) and 1.18 ($p=0.007$), respectively, but not after adjusting for stage ($p=0.127$ and 0.056). There was no statistically significant association between OS and √(SUV_{maxT}), ln(SUV_{meanWB}), or √(SUV_{meanT}). There was low interobserver variability among three radiologists with intraclass correlation coefficients (ICC) greater than 0.94 for SUV_{maxWB}, ln(MTV_{WB}), and ln(TLG_{WB}). Interobserver variability was higher for SUV_{meanWB} with an ICC of 0.806.

Conclusion Baseline metabolic tumor burdens at the level of whole-body tumor, primary tumor, nodal metastasis, and distant metastasis as measured with MTV and TLG on FDG PET are prognostic measures independent of clinical stage with low inter-observer variability and may be used to further stratify nonsurgical patients with NSCLC. This study also suggests 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.

Keywords ^{18}F-FDG · Non-small cell lung cancer · Tumor burden · Metabolic tumor volume · Total lesion glycolysis

Introduction

Lung cancer is the most common cause of cancer death in the world [1]. Lung cancer is the second most common cancer in both men and women and number one cause of cancer-related deaths in the USA. In the USA in 2010, 157,300 people were projected to die from lung cancer, which is more than the number of deaths from colon and rectal, breast, and prostate cancer combined [2]. Non-small cell lung cancer (NSCLC) comprises 80–85% of all lung cancer cases [3]. The treatment and prognosis of NSCLC depend mainly upon the stage defined according to the Union Internationale Contra la Cancrum (UICC)/American Joint Committee on Cancer (AJCC) staging system [4, 5]. The stage based on the evaluation of the T, N, and M components and the assignment of a stage grouping (I–IV) [4] is the single most prognostic factor in predicting the outcomes of patients with lung cancer [4, 6–8].

Other patient-specific factors such as age, pulmonary function, and comorbidity may also alter the selection of the treatment options. In early-stage NSCLC, surgical resection remains the standard of care in fit patients. In patients with unresectable, locally advanced, stage III NSCLC, chemotherapy in combination with thoracic radiation therapy is the standard of care. Systemic chemotherapy is the standard care for stage IV NSCLC [9].

Modern positron emission tomography (PET)/CT scanners provide three-dimensional (3-D) metabolic volumetric images. The metabolic tumor burden measurements including metabolic tumor volume (MTV) [10, 11] and total lesion glycolysis (TLG) of tumors [12] have been developed because they incorporate both metabolic activity and tumor volume. The MTV is the tumor volume on PET measured with a segmentation technique [10, 11, 13, 14], while TLG can be calculated by multiplying the mean standardized uptake value (SUV_{mean}) by the MTV [12]. Lee et al. found that the baseline total body MTV 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 [10]. In their recent study, they expanded the cohort to 61 patients with NSCLC and confirmed the significant association of high MTV with decreased overall survival in the subgroup of patients who were treated definitively [15].

Additionally, in multiple studies in other types of cancer, the manual or semiautomatic measurement of the baseline MTV has been shown to be better than the SUV in predicting patients' prognosis in small cell lung cancer [16], head and neck cancer [17–19], esophageal cancer [20], and thyroid cancer [21] in locally advanced stages with or without metastasis. It has also been demonstrated that baseline gross tumor volume, determined by manual contouring on X-ray computed tomography (CT) images as part of 3-D conformal radiation treatment planning, predicts overall and cause-specific survival, as well as local tumor control in NSCLC [22].

However, until now, NSCLC staging has been based primarily on surgical resectability of the tumor; no metabolic tumor burden or volumetric information has been used from PET/CT in the AJCC TNM staging system for NSCLC [4]. Only a one-dimensional measurement on CT or magnetic resonance (MR) scans is required for the primary tumor TNM staging and an existence decision, defining whether any lymph node or metastasis is 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) positive, is required for lymph nodes or distant metastases in this staging system. This may be partly because the measurement of the MTV manually or semiautomatically is time consuming and therefore it is not clinically practical. It may be also

because the usefulness of this time-consuming measurement has not been fully determined.

With the development of computer-aided diagnosis (CAD), it should be possible to create software to semiautomatically detect and quantify all tumors in the whole body and therefore measure whole-body metabolic tumor burden efficiently [23]. However, since the development of such a sophisticated CAD tool is a major undertaking, it is necessary to further determine the prognostic value of the metabolic tumor burden independent of simple TNM stage in a large patient population with NSCLC. Here we measured the MTV of whole-body tumor (MTV_{WB}), primary tumor (MTV_T), nodal metastases (MTV_N), distant metastases (MTV_M); TLG of whole-body tumor (TLG_{WB}), primary tumor (TLG_T), nodal metastases (TLG_N), and distant metastases (TLG_M) semiautomatically with commercially available PET/CT software to further determine the additive prognostic value of MTV and TLG independent of tumor stage in 169 nonsurgical patients with 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 816 cases with NSCLC who were diagnosed and treated in the University of Chicago Medical Center from 1 January 2004 to 31 December 2007. We identified the 169 consecutive nonsurgical patients with NSCLC for this study from this retrospective database by inclusion criteria. The inclusion criteria were as follows: (1) all patients had a pre-therapy baseline PET/CT scan, (2) they had no surgery, (3) they had no known brain metastasis (since our whole-body PET/CT did not cover the whole brain), 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. There were 78 male and 91 female patients with a median age of 68. There were 16 cases with stage I, 5 with stage II, 56 with stage III, and 92 with stage IV NSCLC. The reasons for not having surgery were: (1) contraindication for surgery (6 patients with stage I, 2 patients with stage II, 5 patients with stage IIIA), (2) patient's refusal to have surgery (5 in stage I, 2 patients with stage IIIA), (3) not the first course of treatment (5 in stage I, 3 patients with stage II, 21 patients with stage IIIA), and (4) advanced disease (27 with stage IIIB and 92 with stage IV NSCLC). In one patient with stage IIIA, the surgery was recommended but was not performed. One hundred forty patients had chemotherapy and/or radiation therapy. The mean time between the PET/CT scan and start of therapy was 4.9 weeks with a standard deviation of 5.7 weeks. In the remaining 29 patients, neither chemotherapy nor radiation therapy was performed. There were 35 patients with adenocarcinoma, 1 patient with bronchioloalveolar carcinoma, 11 patients with large cell carcinoma, 39 patients with squamous cell carcinoma, 1 patient with large cell neuroendocrine carcinoma, and 82 patients with NSCLC of a type that was not further specified. They had been followed with CT of the chest and abdomen at the University of Chicago at irregular intervals of 1–6 months. 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 when possible.

Imaging protocols

PET/CT imaging

The baseline pretreatment ^{18}F-FDG PET/CT scans were performed in accordance with National Cancer Institute guidelines [24] in all 169 patients. The ^{18}F-FDG PET images were obtained using a PET/CT scanner (Reveal HD, CTI, Knoxville, TN, USA) equipped with high-resolution bismuth germanate (BGO) detectors and a dual-slice CT scanner. The patients fasted for at least 4 h 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 IV 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 s per rotation, and a pitch of 3.0. Sixty minutes following injection of the ^{18}F-FDG, a whole-body static PET scan was acquired for about 30–35 min, starting at the thighs and proceeding to the head. PET scans were obtained with an acquisition time of 3–5 min per cradle position, with slice overlap at the borders of the field of view to avoid artifacts. The PET camera has a bed position length of 14.6 cm and a transaxial field of view 66.6 cm in diameter. PET images were reconstructed using the ordered subsets expectation maximization (OSEM) iterative algorithm with 8 subsets, 2 iterations, and 128 × 128 pixels. The slice thickness was 2.4 mm, with 5 mm full-width at half-maximum (FWHM) 3-D Gaussian smoothing after reconstruction. We used the 3-D imaging mode with Fourier rebinning and model-based scatter correction. Monthly concentration calibrations were conducted using a ^{68}Ge tub phantom.

Measurement of tumor volume on PET/CT

The MTV and TLG, as well as the SUV_{max} and SUV_{mean}, of whole-body tumors were measured with the PETedge tool of the MIMvista software (MIMvista Corp, Cleveland, OH, USA) with manual adjustment (Fig. 1). The software used a gradient-based tumor segmentation method [25]. In comparison with manual and constant threshold methods in a phantom study, the software was the most accurate and consistent technique for the segmentation of tumors, with less interobserver variation, and was the most robust for varying imaging conditions [25].

This was done by two board certified radiologists with PET/CT imaging experience, as well as familiarity with the MIMvista software and our PACS system (iSite, Philips, Cleveland, OH, USA). With the MIMvista PET software and our PACS system, the first radiologist reviewed the cases using the original PET/CT reports to determine the location and extent of the tumor. She then used the PET edge tool to draw the tumor contours. She indicated the approximate center of the tumor. The volumes of interest (VOIs) were drawn automatically using spatial derivatives to locate tumor boundaries after the radiologist had identified the major and minor axes of the tumor in one plane. Manual adjustment of the estimated tumor surface was often needed to include the entire tumor within the margins of the VOIs. This was done visually by the reader using a 2-D "ball" tool in the MIMvista contouring software. She then saved the tumor contours she had drawn on all the detected tumors as radiation therapy structure (RT_{struct}) images and exported her PET measurement results. The second radiologist reviewed the cases again with the workstation running MIMvista software and our PACS system. He then opened the RT_{struct} images saved by the first radiologist to determine if he agreed with the first radiologist's reading. He made notes on the cases having different tumor contours and/or locations or in cases he thought there were additional tumors, or he thought some of the lesions detected by the first reader were not tumor. The disagreements in the tumor detection and contours were reconciled by both radiologists looking at the cases together. Through discussion, the final consensus readings were decided. Therefore the final tumor contours were determined based on reader consensus and they were determined using visual analysis. The resultant SUV and volume values of all tumors in the body were exported to an Excel spreadsheet. In this study, the SUV_{max} was defined as SUV_{max} = maximum activity concentration in the tumor/(injected dose/body weight). The SUV_{mean} was defined as the mean concentration of FDG in the tumor/(injected dose/body weight). The output results included SUV_{max}, SUV_{mean}, MTV, and TLG of individual tumors. The tumor location and whether the tumor was primary, nodal, or a distant metastasis were determined by the readers. The whole-body SUV_{max} (SUV_{maxWB}) was the maximum SUV_{max} of all the tumors in the whole body. The SUV_{max} of primary tumor (SUV_{maxT}) was the SUV_{max} of all primary tumors. The SUV_{maxN} was the SUV_{max} of all mediastinal, hilar, and supraclavicular nodal metastases. The SUV_{maxM} was the SUV_{max} of distant metastases (M_1 lesions). The whole-body SUV_{mean} (SUV_{meanWB}) was the mean SUV_{mean} of all the tumors in the whole body. It was calculated as $SUV_{meanWB} = (TLG_{WB}/MTV_{WB})$. The SUV_{mean} of primary tumor (SUV_{meanT}) is the SUV_{mean} of all primary tumors. The SUV_{meanN} is the SUV_{mean} of all mediastinal, hilar, and supraclavicular nodal metastases. The SUV_{meanM} is the SUV_{mean} of distant metastases (M_1 lesions). By summing the corresponding values for all lesions, the whole-body MTV (MTV_{WB}) and whole-body TLG (TLG_{WB}) were computed. The MTV of the primary tumor (MTV_T), mediastinal, hilar, and supraclavicular nodal metastases (MTV_N), and distant metastases (MTV_M); and the TLG of the primary tumor (TLG_T), mediastinal, hilar, and supraclavicular nodal metastases (TLG_N), and distant metastases (TLG_M) were also computed. These values of the above consensus PET measurements were used in the survival analyses described herein. For the evaluation of the interobserver variability of the SUV_{maxWB}, SUV_{meanWB}, MTV_{WB},

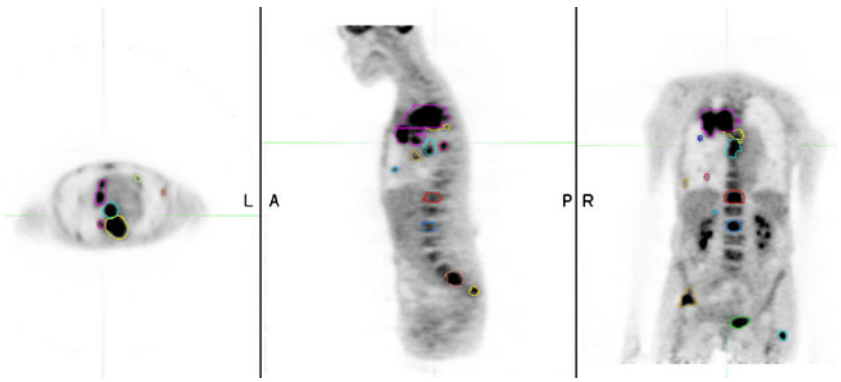

Fig. 1 Axial, sagittal, and coronal images from a PET scan of a 68-year-old woman with a new diagnosis of NSCLC, showing the measurements of maximum and mean SUVs, MTV, and TLG of tumors with the MIMvista PETedge tool

and TLG_{WB}, an additional two board certified radiologists independently performed the above PET measurements in a subgroup of 77 patients with stage I–III NSCLC with reference of original PET/CT reports. Their data and the first radiologist's data from this subgroup of patients were used for interobserver variability analysis. In order to determine the amount of time needed to measure the MTV and TLG in the whole body, we measured the time taken by one observer to complete the PET tumor measurements in the 193 lesions of the 77 patients with stage I–III NSCLC.

The UICC/AJCC staging system for NSCLC (6th edition) [5] was used to stage patients. The clinical stage of the disease was based on patient's history, physical examinations, chest X-ray, infused CT, and PET/CT taken from his/her electronic medical charts. Brain MRI was done if clinical symptoms suggested brain metastasis. If the patients had mediastinoscopy, those findings superseded the imaging findings in mediastinal nodal staging.

Statistical analysis

The distributions of MTV, TLG, SUV_{mean}, and SUV_{max} were skewed, so a natural logarithm or square root transformation was applied and the transformed variables were used in the analysis (some variables had legitimate values of zero, so the square root transformation was applied to them). Univariate and multivariate analyses using Cox proportional hazards regression [26] were performed for assessment of the relationship between initial PET/CT measurements and overall survival (OS). The multivariate models adjusted for stage (stage I + II vs III vs IV). Models that adjusted for stage, age, and gender (factors that might influence OS) were also fit, but conclusions were similar in most cases so they are not shown since whether the PET/CT measurements had additional prognostic value compared to traditional staging was of primary interest. The C-statistic [27] (higher values indicating better discriminatory power) from the model only including stage versus the models with stage + MTV (or TLG etc.) was used to assess whether these new measures provide additional information about survival over and above what the long-established risk factor of disease stage provides. OS was calculated from the date of the initial PET/CT to death. The proportional hazards assumption was tested using Schoenfeld residuals [28]. Kaplan-Meier curves [29] were constructed after creating three roughly equal sized groups using tertiles of each PET/CT measurement. Tertiles were used to define the three groups for illustrative purposes only; this may not be the optimum value for discrimination. The intraclass correlation coefficients (ICCs) were calculated based on random-effects models treating both patient and observer as random for the evaluation of interobserver variability [30].

A p value <0.05 was considered statistically significant. Analyses were performed using Stata Version 11 (Stata Corp, College Station, TX, USA).

Results

Median OS was 10.9 months [95% confidence interval (CI) 9.0–13.2 months]. Of the 169 patients, 97 died of the NSCLC, 41 died of unknown causes, and 1 died of an unrelated cause. The median follow-up was 35 months (range 2–82 months) among the 30 survivors.

A summary of PET measurements, median OS, and OS probabilities is shown in Table 1. Kaplan-Meier curves of OS are provided for descriptive purposes in Figs. 2, 3, 4, 5, and 6. There was evidence of trends of worse survival with higher values of MTV and TLG at the whole-body tumor burden, primary tumor, nodal metastasis, and distant metastasis level (weakest for MTV_M). Such a trend was also seen for SUV_{maxN}, SUV_{maxM}, SUV_{meanN}, and SUV_{meanM} and to a lesser extent with SUV_{maxWB}. No such trend was seen for the SUV_{maxT}, SUV_{meanWB}, and SUV_{meanT} (Table 1). In univariate analyses (Table 2), there was a statistically significant association of OS with clinical stage with a hazard ratio (HR) of 1.91 for stage III cancer and HR of 2.15 for stage IV cancer (p=0.034 and 0.009, respectively) as compared with stage I+II cancer. Median OS was 18.6, 10.2, and 9.7 months for stage I+II, stage III, and stage IV patients, respectively. There was a statistically significant association of OS with gender (p=0.030). There was no statistically significant association between age and OS (p=0.812). In addition, there was a statistically significant association between OS and MTV. The HRs for 1 unit increase of $\ln(MTV_{WB})$, $\sqrt{(MTV_T)}$, $\sqrt{(MTV_N)}$, and $\sqrt{(MTV_M)}$ were 1.47 (p<0.001), 1.06 (p<0.001), 1.11 (p<0.001), and 1.04 (p=0.007), respectively. There was a statistically significant association between OS and TLG. The HRs for 1 unit increase of $\ln(TLG_{WB})$, $\sqrt{(TLG_T)}$, $\sqrt{(TLG_N)}$, and $\sqrt{(TLG_M)}$ were 1.36 (p<0.001), 1.02 (p=0.001), 1.05 (p<0.001), and 1.02 (p=0.003), respectively. There was a statistically significant association between OS and SUV_{max}. The HRs for 1 unit increase of $\ln(SUV_{maxWB})$, $\sqrt{(SUV_{maxN})}$, and $\sqrt{(SUV_{maxM})}$ were 1.46 (p=0.013), 1.22 (p=0.002), and 1.18 (p=0.007), respectively. The $\sqrt{(SUV_{meanN})}$ and $\sqrt{(SUV_{meanM})}$ were significantly associated with OS, with HRs for a 1 unit increase of 1.32 (p<0.001) and 1.26 (p=0.017), respectively. There was no statistically significant association between OS and the $\sqrt{(SUV_{maxT})}$, $\ln(SUV_{meanWB})$, or $\sqrt{(SUV_{meanT})}$.

In multivariate analysis (Table 2), statistically significant associations of OS with MTV remained after adjusting for clinical stage of disease. The HRs for 1 unit increase of $\ln(MTV_{WB})$, $\sqrt{(MTV_T)}$, $\sqrt{(MTV_N)}$, and $\sqrt{(MTV_M)}$ were 1.43 (p<0.001), 1.05 (p<0.001), 1.10 (p<0.001), and 1.03

Table 1 OS based on stage, gender, age, and PET/CT measurements in 169 nonsurgical cases with NSCLC

	PET measurement Mean (SD)	Survival		
		Median (months)	2-year (proportion)	3-year (proportion)
Total group		10.9	0.24	0.15
Stage				
I + II, *n*=21		18.6	0.48	0.31
III, *n*=56		10.2	0.16	0.16
IV, *n*=92		9.7	0.24	0.11
Gender				
Female, *n*=91		12.9	0.28	0.20
Male, *n*=78		9.5	0.20	0.09
Age at PET	66.6 (11.0)			
1st T, *n*=60	54.7 (6.4)	11.7	0.22	0.18
2nd T, *n*=55	67.8 (2.8)	8.6	0.20	0.14
3rd T, *n*=54	78.6 (4.4)	12.9	0.32	0.12
SUV_{max}				
SUV_{maxWB}	10.8 (5.7)			
1st T, *n*=57	5.8 (1.8)	13.9	0.31	0.22
2nd T, *n*=56	9.7 (1.0)	9.5	0.22	0.11
3rd T, *n*=56	16.9 (5.4)	9.9	0.19	0.12
SUV_{maxT}	9.5 (4.9)			
1st T, *n*=57	4.6 (1.8)	13.6	0.29	0.22
2nd T, *n*=56	9.0 (0.9)	8.2	0.20	0.11
3rd T, *n*=56	15.1 (3.5)	10.2	0.24	0.12
SUV_{maxN}	5.0 (5.3)			
1st T, *n*=57	0.2 (0.6)	15.9	0.37	0.22
2nd T, *n*=56	4.5 (1.1)	9.5	0.23	0.12
3rd T, *n*=56	10.4 (5.4)	8.1	0.14	0.11
SUV_{maxM}	3.5 (5.2)			
1st T, *n*=84	0 (0)	13.9	0.29	0.17
2nd T, *n*=29	3.1 (1.0)	10.9	0.27	0.19
3rd T, *n*=56	9.0 (5.8)	6.9	0.16	0.10
SUV_{mean}				
SUV_{meanWB}	3.7 (1.4)			
1st T, *n*=57	2.5 (0.5)	13.7	0.27	0.21
2nd T, *n*=56	3.5 (0.3)	6.6	0.17	0.09
3rd T, *n*=56	5.1 (1.4)	13.2	0.29	0.14
SUV_{meanT}	3.6 (1.3)			
1st T, *n*=57	2.3 (0.7)	12.7	0.28	0.21
2nd T, *n*=56	3.5 (0.3)	7.3	0.12	0.08
3rd T, *n*=56	5.1 (0.8)	14.0	0.33	0.16
SUV_{meanN}	2.6 (4.6)			
1st T, *n*=57	0.1 (0.4)	15.9	0.37	0.22
2nd T, *n*=56	2.5 (0.3)	10.9	0.19	0.14
3rd T, *n*=56	5.2 (7.2)	7.3	0.17	0.09
SUV_{meanM}	1.5 (1.8)			
1st T, *n*=84	0 (0)	13.9	0.29	0.17
2nd T, *n*=29	1.9 (0.6)	10.9	0.24	0.17
3rd T, *n*=56	3.7 (1.4)	6.9	0.17	0.11
MTV				
MTV_{WB}	212.7 (247.9)			
1st T, *n*=57	33.5 (21.0)	19.9	0.47	0.25
2nd T, *n*=56	134.9 (38.7)	10.0	0.16	0.14
3rd T, *n*=56	473.0 (278.2)	6.6	0.08	0.05
MTV_T	129.0 (177.8)			
1st T, *n*=57	12.7 (7.9)	12.9	0.35	0.17
2nd T, *n*=56	64.9 (27.0)	13.6	0.27	0.16
3rd T, *n*=56	311.4 (209.0)	7.3	0.11	0.11
MTV_N	34.6 (56.6)			
1st T, *n*=57	0.1 (0.4)	16.3	0.37	0.23
2nd T, *n*=56	11.5 (7.5)	10.2	0.23	0.11
3rd T, *n*=56	92.7 (67.2)	6.6	0.13	0.10
MTV_M	47.8 (159.7)			
1st T, *n*=84	0 (0)	13.9	0.29	0.17
2nd T, *n*=29	4.4 (2.8)	7.3	0.23	0.14
3rd T, *n*=56	142.1 (253.6)	9.7	0.18	0.14
TLG				
TLG_{WB}	832.2 (994.8)			
1st T, *n*=57	107.3 (74.5)	17.4	0.44	0.20
2nd T, *n*=56	504.0 (140.1)	9.0	0.19	0.19
3rd T, *n*=56	1898.1 (1089.2)	8.1	0.09	0.06
TLG_T	529.5 (755.8)			
1st T, *n*=57	40.3 (31.5)	13.9	0.37	0.19
2nd T, *n*=56	248.1 (121.4)	10.2	0.23	0.15
3rd T, *n*=56	1308.7 (884.5)	8.2	0.13	0.10
TLG_N	128.8 (243.8)			
1st T, *n*=57	0.3 (1.0)	15.5	0.37	0.23
2nd T, *n*=56	32.6 (22.8)	10.9	0.25	0.11
3rd T, *n*=56	355.7 (319.5)	6.8	0.11	0.11
TLG_M	169.4 (571.9)			
1st T, *n*=84	0 (0)	13.9	0.29	0.17
2nd T, *n*=29	10.3 (7.8)	9.0	0.26	0.17
3rd T, *n*=56	505.7 (909.3)	9.0	0.16	0.12

T tertile, *MTV* metabolic tumor volume, MTV_{WB} MTV of whole-body tumor, MTV_T MTV of primary tumor, MTV_N MTV of nodal metastasis, MTV_M MTV of distant metastasis, *SD* standard deviation, SUV_{max} maximum standardized uptake value, SUV_{maxWB} SUV_{max} of whole-body tumor, SUV_{maxT} SUV_{max} of primary tumor, SUV_{maxN} SUV_{max} of nodal metastasis, SUV_{maxM} SUV_{max} of distant metastasis, SUV_{mean} mean standardized uptake value, SUV_{meanWB} SUV_{mean} of whole-body tumor, SUV_{meanT} SUV_{mean} of primary tumor, SUV_{meanN} SUV_{mean} of nodal metastasis, SUV_{meanM} SUV_{mean} of distant metastasis, *TLG* total lesion glycolysis, TLG_{WB} TLG of whole-body tumor, TLG_T TLG of primary tumor, TLG_N TLG of nodal metastasis, TLG_M TLG of distant metastasis

(p=0.043), respectively. There were also statistically significant associations of OS with TLG. After adjusting for

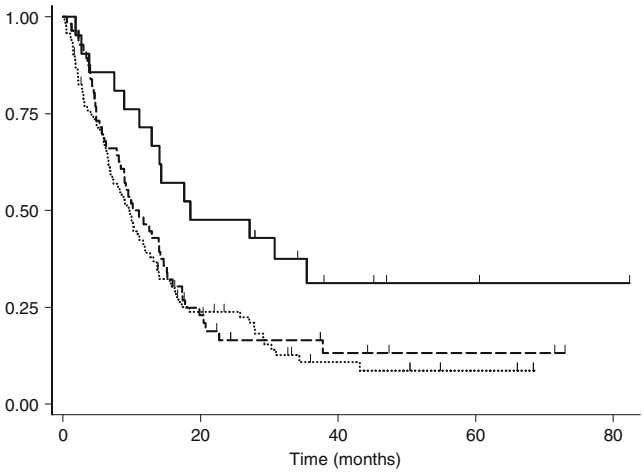

Fig. 2 Kaplan-Meier curves of OS after baseline PET/CT grouped according to the clinical stages in 169 nonsurgical patients with stage I–IV NSCLC. The *solid line* indicates the survival curve of the group with stage I and II NSCLC. The *dashed line* indicates the survival curve of the group with stage III NSCLC. The *dotted line* indicates the survival curve of the group with stage IV NSCLC

stage, the HRs for 1 unit increase of $\ln(TLG_{WB})$, $\sqrt{(TLG_T)}$, $\sqrt{(TLG_N)}$, and $\sqrt{(TLG_M)}$ were 1.33 ($p<0.001$), 1.02 ($p=0.002$), 1.04 ($p<0.001$), and 1.02 ($p=0.024$), respectively. The $\ln(SUV_{maxWB})$, $\sqrt{(SUV_{maxN})}$, and $\sqrt{(SUV_{meanN})}$ were significantly associated with OS with HRs for a 1 unit increase, after adjusting for stage, of 1.43 ($p=0.024$), 1.16 ($p=0.040$), and 1.24 ($p=0.015$), respectively. The multivariate models that adjusted for stage, age, and gender resulted in similar conclusions (data not shown). As further evidence of the prognostic value of the MTV and TLG variables, the C-statistics (a measure of discriminatory power) from the multivariate models including these measures in addition to clinical stage were all larger than the C-statistic of 0.55 for the model including stage only. The C-statistics for the corresponding models which included the MTV or TLG variables were also larger than those that included the SUV_{mean} or SUV_{max} variables, except for MTV_M and TLG_M. A sensitivity analysis was performed by only including the 140 patients who received chemotherapy and/or radiation; results provided further evidence for the prognostic value of MTV and TLG (Table 3).

The ICC for SUV_{maxWB} was 0.992 with 95% CI of 0.988–0.995. The ICC for SUV_{meanWB} was 0.806 with 95% CI of 0.662–0.885. The ICC for $\ln(MTV_{WB})$ was 0.949 with 95% CI of 0.861–0.976. The ICC for $\ln(TLG_{WB})$ was 0.975 with 95% CI of 0.953–0.985. It took 7 h and 10 min for one observer to complete the measurement of the 193 tumor lesions in the whole body in the 77 patients with stage I–III NSCLC. On average, it took him 2.3 min to complete the PET measurement on one lesion.

Discussion

In the present study, the MTV and TLG were prognostic indices independent of the UICC/AJCC TNM stage at three different levels (i.e., whole-body tumor burden, the primary tumor, and nodal/distant metastasis) and, in most cases, had more prognostic value than the corresponding SUV_{max} or

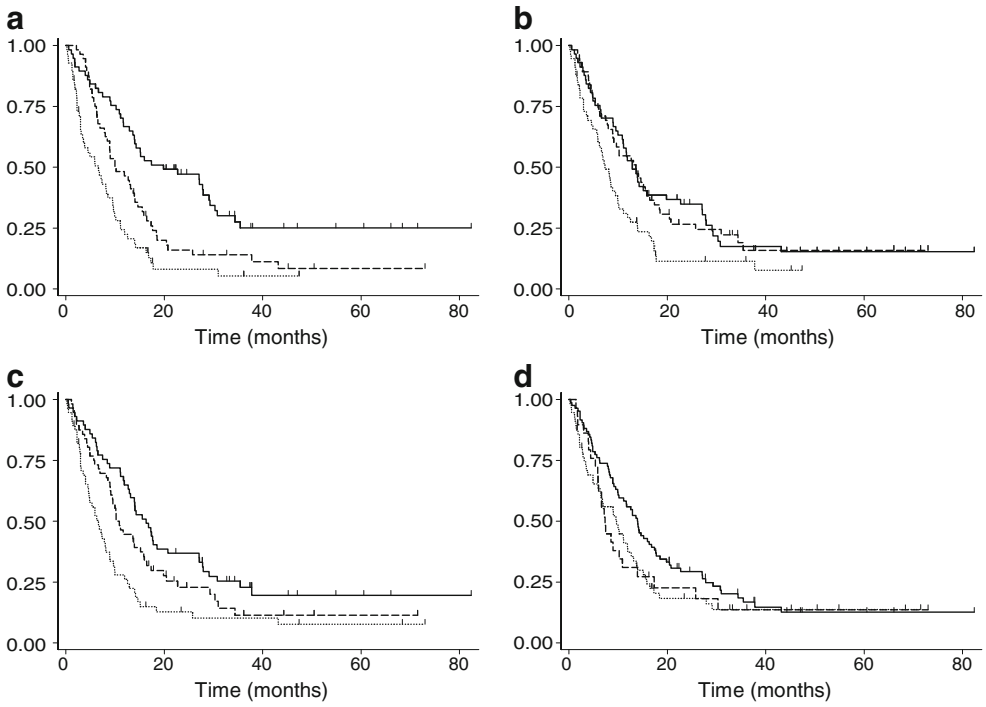

Fig. 3 Kaplan-Meier curves of OS after baseline PET/CT grouped according to MTV measurements in 169 nonsurgical patients with stage I–IV NSCLC. The *solid line* indicates the group with the values of MTV in the bottom tertile. The *dashed line* is the group with the values in the middle tertile. The *dotted line* indicates the group with the values in the top tertile. **a** Whole-body MTV. **b** MTV of primary tumor. **c** MTV of nodal metastases. **d** MTV of distant metastases

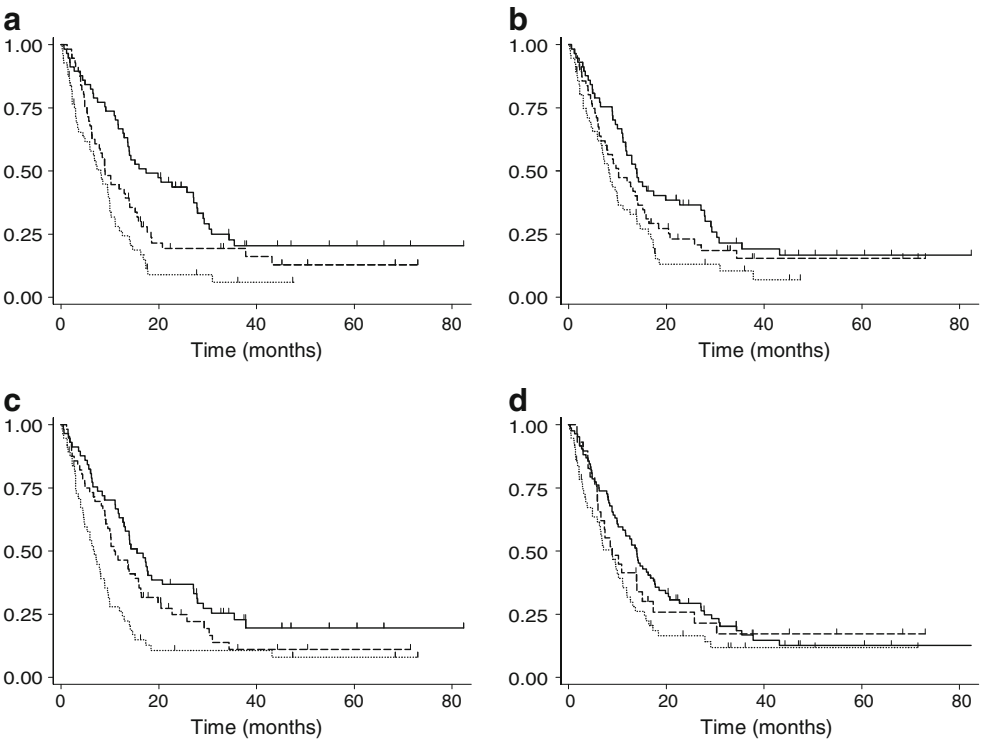

Fig. 4 Kaplan-Meier curves of OS after baseline PET/CT grouped according to TLG measurements in 169 nonsurgical patients with stage I–IV NSCLC. The *solid line* indicates the group with values of TLG in the bottom tertile. The *dashed line* is the group with the values in the middle tertile. The *dotted line* indicates the group with the values in the top tertile. **a** Whole-body TLG. **b** TLG of primary tumor. **c** TLG of nodal metastases. **d** TLG of distant metastases

SUV_{mean} of the tumor. We did not find a statistically significant association between OS and SUV_{maxT}, SUV_{maxM}, SUV_{meanWB}, SUV_{meanT}, or SUV_{meanM} after adjusting for the patient's clinical stage. These findings are consistent with a prior study by Lee et al. [10] that found a statistically significant association between MTV and OS and progression-free survival. However, the current study used commercially available software in a larger patient population with NSCLC. In Lee et al.'s first study, they used custom software for the segmentation of the metabolically active

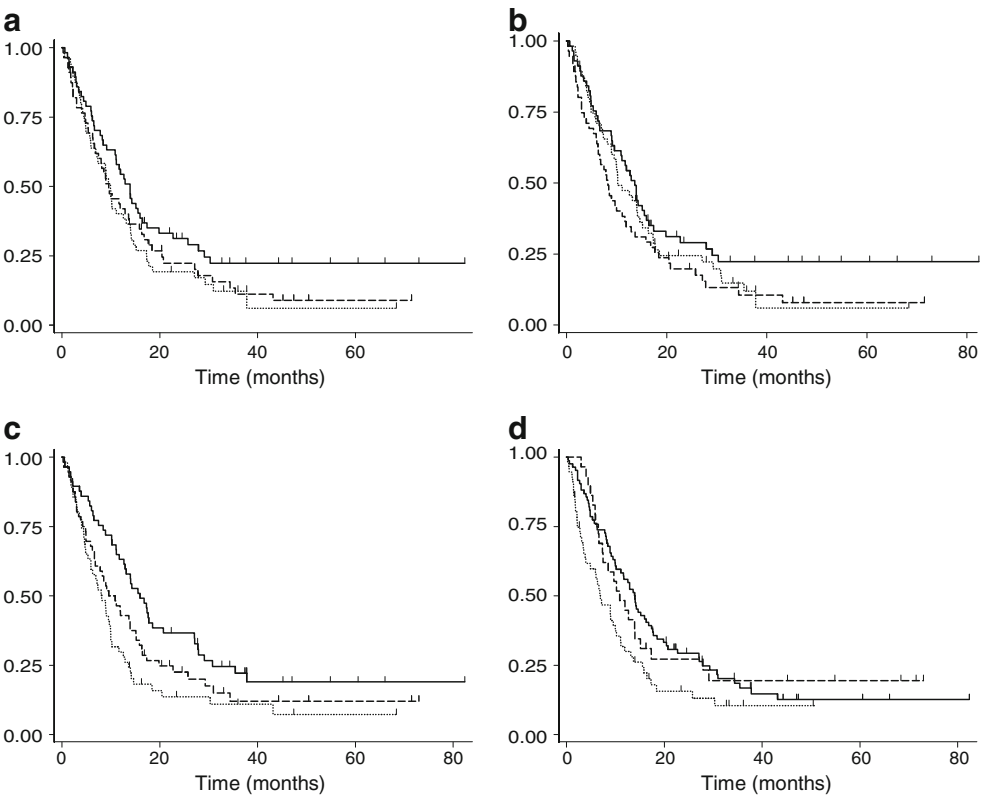

Fig. 5 Kaplan-Meier curves of OS after baseline PET/CT grouped according to SUV_{max} measurements in 169 nonsurgical patients with stage I–IV NSCLC. The *solid line* indicates the group with values of SUV_{max} in the bottom tertile. The *dashed line* is the group with the values in the middle tertile. The *dotted line* indicates the group with the values in the top tertile. **a** Whole-body SUV_{max}. **b** SUV_{max} of primary tumor. **c** SUV_{max} of nodal metastases. **d** SUV_{max} of distant metastases

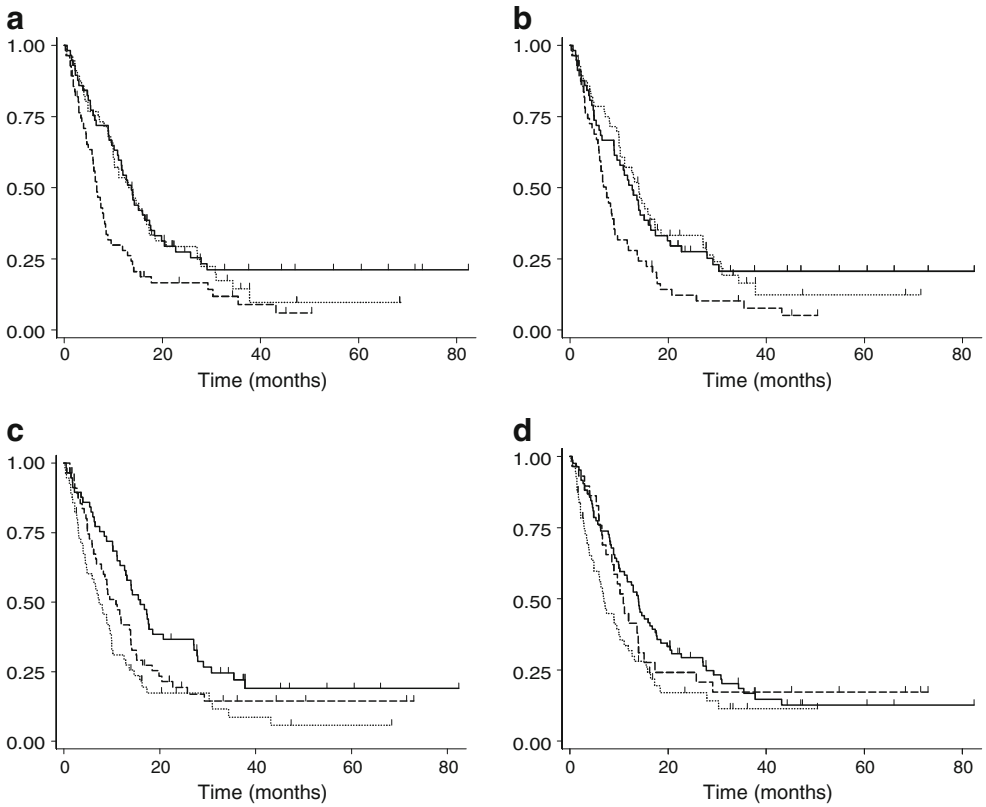

Fig. 6 Kaplan-Meier curves of OS after baseline PET/CT grouped according to SUV_{mean} measurements in 169 nonsurgical patients with stage I–IV NSCLC. The *solid line* indicates the group with values of SUV_{mean} in the bottom tertile. The *dashed line* is the group with the values in the middle tertile. The *dotted line* indicates the group with the values in the top tertile. **a** Whole-body SUV_{mean}. **b** SUV_{mean} of primary tumor. **c** SUV_{mean} of nodal metastases. **d** SUV_{mean} of distant metastases

tumor regions in 18 patients with NSCLC and 1 patient with small cell lung cancer and found that the baseline total body MTV measured semiautomatically was a statistically significant prognostic index and better than SUV_{max} and SUV_{mean} in the prediction of patient outcome [10]. Their recent study with 61 patients with NSCLC confirmed the significant association of high MTV with decreased overall survival in the subgroup of patients who were treated definitively [15]. The clinical implication of these results are that PET may give the ability to further stratify patients with the same stage of NSCLC since many of the quantitative PET measures have prognostic value independent of clinical stage.

The prognostic value of SUV_{max} independent of clinical stage demonstrated in the current study is consistent with prior studies [31–34]. The cumulative (Kaplan-Meier) survival differences in patients at 2 and 3 years in the top and bottom tertiles of SUV_{maxWB} were 12 and 10%, respectively. The survival differences in patients at 2 and 3 years in the top and bottom tertiles of SUV_{maxN} were 23 and 11%, respectively (Table 1). The SUV_{mean} of nodal metastasis was also a prognostic index independent of clinical stage. The survival differences in patients at 2 and 3 years in the top and bottom tertiles of SUV_{meanN} were 20 and 13%, respectively. In a prior study with a large patient population (498 patients) reported by Davies et al. [32], the cumulative (Kaplan-Meier) survival differences at 12, 18, and 24 months between patients in the top and bottom quintiles of SUV_{max} were 18, 33, and 24%, respectively.

There are several limitations of this study. Firstly, the measurement of all tumors in the body is time consuming. Hopefully this problem will be solved with computer-aided programs. In fact, the recent publication by Lee et al. [15] used open source software developed in their institution. With their software, they semiautomatically quantified the whole-body MTV efficiently and reduced interobserver variability. With their software the user interaction was limited to visually identifying the hypermetabolic foci on PET maximum intensity projection images, leaving the tedious segmentation step to their automatic program. Secondly, we could not perform disease-specific survival analysis because 29.5% (41/139) of the deaths of patients in the study group had unknown causes of death. However, NSCLC is a deadly cancer, especially for nonsurgical patients. The 5-year OS rate of patients with stage IV NSCLC is only about 1–8% dependent on whether the metastasis is distant or intrathoracic, respectively [35]. The vast majority of the nonsurgical NSCLC patients should have died of the cancer. Therefore, OS would be expected to be quite close to the disease-specific survival.

Conclusion

Baseline metabolic tumor burdens at the levels: (1) whole-body tumor, (2) primary tumor, (3) nodal metastasis, and (4) distant metastasis as measured with MTV and TLG on ^{18}F-FDG PET/CT are prognostic measures independent of

Table 2 Association of OS with stage, gender, age, and PET/CT measurements in 169 nonsurgical patients with NSCLC

	Univariate analysis		Multivariate analysis[a]		
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	C-statistic
Stage (C-statistic =0.55)					
I+II	Reference				
III	1.91 (1.05–3.49)	0.034			
IV	2.15 (1.21–3.80)	0.009			
Gender					
Female	Reference				
Male	1.45 (1.04–2.03)	0.030			
Age at PET (years)	1.00 (0.98–1.01)	0.812			
SUV_{max}					
$\ln(SUV_{maxWB})$	1.46 (1.08–1.98)	0.013	1.43 (1.05–1.96)	0.024	0.58
$\sqrt{}(SUV_{maxT})$	1.18 (0.98–1.41)	0.083	1.19 (0.99–1.44)	0.069	0.57
$\sqrt{}(SUV_{maxN})$	1.22 (1.08–1.38)	0.002	1.16 (1.01–1.33)	0.040	0.58
$\sqrt{}(SUV_{maxM})$	1.18 (1.05–1.34)	0.007	1.16 (1.00–1.35)	0.056	0.58
SUV_{mean}					
$\ln(SUV_{meanWB})$	1.48 (0.96–2.29)	0.079	1.39 (0.88–2.20)	0.158	0.56
$\sqrt{}(SUV_{meanT})$	1.27 (0.85–1.90)	0.248	1.22 (0.81–1.83)	0.343	0.56
$\sqrt{}(SUV_{meanN})$	1.32 (1.13–1.54)	<0.001	1.24 (1.04–1.48)	0.015	0.58
$\sqrt{}(SUV_{meanM})$	1.26 (1.04–1.53)	0.017	1.20 (0.95–1.53)	0.127	0.57
MTV					
$\ln(MTV_{WB})$	1.47 (1.27–1.71)	<0.001	1.43 (1.23–1.68)	<0.001	0.63
$\sqrt{}(MTV_{T})$	1.06 (1.03–1.09)	<0.001	1.05 (1.03–1.08)	<0.001	0.61
$\sqrt{}(MTV_{N})$	1.11 (1.07–1.16)	<0.001	1.10 (1.05–1.15)	<0.001	0.62
$\sqrt{}(MTV_{M})$	1.04 (1.01–1.07)	0.007	1.03 (1.00–1.06)	0.043	0.57
TLG					
$\ln(TLG_{WB})$	1.36 (1.20–1.55)	<0.001	1.33 (1.16–1.52)	<0.001	0.62
$\sqrt{}(TLG_{T})$	1.02 (1.01–1.03)	0.001	1.02 (1.01–1.03)	0.002	0.59
$\sqrt{}(TLG_{N})$	1.05 (1.03–1.07)	<0.001	1.04 (1.02–1.06)	<0.001	0.61
$\sqrt{}(TLG_{M})$	1.02 (1.01–1.04)	0.003	1.02 (1.00–1.04)	0.024	0.57

CI confidence interval, *HR* hazard ratio, *C-statistic* Gönen and Heller's K concordance measure, *ln* natural log, √ square root; other abbreviations are as in Table 1

[a]Adjusted for stage

Table 3 Associations with OS in 140 nonsurgical patients with NSCLC who received chemotherapy and/or radiation

	Univariate analysis		Multivariate analysis[a]		
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	C-statistic
Stage (C-statistic=0.53)					
I+II	Reference				
III	1.80 (0.92–3.52)	0.087			
IV	1.83 (0.97–3.48)	0.064			
SUV_{max}					
$\ln(SUV_{maxWB})$	1.32 (0.93–1.88)	0.125	1.34 (0.94–1.91)	0.112	0.56
SUV_{mean}					
$\ln(SUV_{meanWB})$	1.23 (0.73–2.07)	0.434	1.24 (0.73–2.10)	0.433	0.54
MTV					
$\ln(MTV_{WB})$	1.44 (1.21–1.72)	<0.001	1.41 (1.17–1.70)	<0.001	0.61
TLG					
$\ln(TLG_{WB})$	1.33 (1.14–1.55)	<0.001	1.30 (1.11–1.52)	0.001	0.60

The abbreviations are as in Tables 1 and 2

[a]Adjusted for stage

clinical stage in nonsurgical patients with NSCLC with low inter-observer variability. The metabolic tumor burden may be used to further stratify nonsurgical patients with NSCLC. This study also suggests 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.

Conflicts of interest None.

References

1. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. Eur J Cancer 2001;37 Suppl 8:S4–S66.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60(5):277–300.
3. Traynor AM, Schiller JH. Systemic treatment of advanced non-small cell lung cancer. Drugs Today (Barc) 2004;40(8):697–710.
4. UyBico SJ, Wu CC, Suh RD, Le NH, Brown K, Krishnam MS. Lung cancer staging essentials: the new TNM staging system and potential imaging pitfalls. Radiographics 2010;30(5):1163–81.
5. American Joint Committee on Cancer. AJCC cancer staging manual. 6th ed. New York: Springer; 2002.
6. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710–7.
7. Adebonojo SA, Bowser AN, Moritz DM, Corcoran PC. Impact of revised stage classification of lung cancer on survival: a military experience. Chest 1999;115:1507–13.
8. van Rens MT, de la Rivière AB, Elbers HR, van Den Bosch JM. Prognostic assessment of 2,361 patients who underwent pulmonary resection for non-small cell lung cancer, stage I, II, and IIIA. Chest 2000;117:374–9.
9. Socinski MA, Morris DE, Masters GA, Lilenbaum R, American College of Chest Physicians. Chemotherapeutic management of stage IV non-small cell lung cancer. Chest 2003;123:226S–43S.
10. Lee P, Weerasuriya DK, Lavori PW, Quon A, Hara W, Maxim PG, et al. Metabolic tumor burden predicts for disease progression and death in lung cancer. Int J Radiat Oncol Biol Phys 2007;69:328–33.
11. La TH, Filion EJ, Turnbull BB, Chu JN, Lee P, Nguyen K, et al. Metabolic tumor volume predicts for recurrence and death in head-and-neck cancer. Int J Radiat Oncol Biol Phys 2009;74:1335–41.
12. Larson SM, Erdi Y, Akhurst T, Mazumdar M, Macapinlac HA, Finn RD, et al. Tumor treatment response based on visual and quantitative changes in global tumor glycolysis using PET-FDG imaging. The visual response score and the change in total lesion glycolysis. Clin Positron Imaging 1999;2:159–71.
13. Berkowitz A, Basua S, Srinivasa S, Sankarana S, Schuster S, Alavi A. Determination of whole-body metabolic burden as a quantitative measure of disease activity in lymphoma: a novel approach with fluorodeoxyglucose-PET. Nucl Med Commun 2008;29:521–6.
14. Roedl JB, Colen RR, Holalkere NS, Fischman AJ, Choi NC, Blake MA. Adenocarcinomas of the esophagus: response to chemoradiotherapy is associated with decrease of metabolic tumor volume as measured on PET-CT. Comparison to histopathologic and clinical response evaluation. Radiother Oncol 2008;89:278–86.
15. Lee P, Bazan JG, Lavori PW, Weerasuriya DK, Quon A, Le QT, Wakelee HA, Graves EE, Loo BW Jr. Metabolic tumor volume is an independent prognostic factor in patients treated definitively for non-small-cell lung cancer. Clin Lung Cancer 2011 Jun 22. [Epub ahead of print].
16. Zhu D, Ma T, Niu Z, Zheng J, Han A, Zhao S, et al. Prognostic significance of metabolic parameters measured by (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with small cell lung cancer. Lung Cancer 2011;73:332–7.
17. Seol YM, Kwon BR, Song MK, Choi YJ, Shin HJ, Chung JS, et al. Measurement of tumor volume by PET to evaluate prognosis in patients with head and neck cancer treated by chemo-radiation therapy. Acta Oncol 2010;49:201–8.
18. Xie P, Yue JB, Zhao HX, Sun XD, Kong L, Fu Z, et al. Prognostic value of 18F-FDG PET-CT metabolic index for nasopharyngeal carcinoma. J Cancer Res Clin Oncol 2010;136(6):883–9.
19. Chung MK, Jeong H-S, Park SG, Jang JY, Son Y-I, Choi JY, et al. Metabolic tumor volume of [18F]-fluorodeoxyglucose positron emission tomography/computed tomography predicts short-term outcome to radiotherapy with or without chemotherapy in pharyngeal cancer. Clin Cancer Res 2009;15:5861–8.
20. Hyun SH, Choi JY, Shim YM, Kim K, Lee SJ, Cho YS, et al. Prognostic value of metabolic tumor volume measured by 18F-fluorodeoxyglucose positron emission tomography in patients with esophageal carcinoma. Ann Surg Oncol 2010;17:115–22.
21. Wang W, Larson SM, Fazzari M, Tickoo SK, Kolbert K, Sgouros G, et al. Prognostic value of [18F]fluorodeoxyglucose positron emission tomographic scanning in patients with thyroid cancer. J Clin Endocrinol Metab 2000;85:1107–13.
22. Bradley JD, Ieumwananonthachai N, Purdy JA, Wasserman TH, Lockett MA, Graham MV, et al. Gross tumor volume, critical prognostic factor in patients treated with three-dimensional conformal radiation therapy for non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys 2002;52:49–57.
23. Doi K. Computer-aided diagnosis in medical imaging: historical review, current status and future potential. Comput Med Imaging Graph 2007;31:198–211.
24. Shankar LK, Hoffman JM, Bacharach S, Graham MM, Karp J, Lammertsma AAA, et al. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. J Nucl Med 2006;47:1059–66.
25. Werner-Wasik M, Nelson AD, Choi W, Arai Y, Faulhaber PF, Kang P, Almeida FD, Xiao Y, Ohri N, Brockway KD, Piper JW, Nelson AS. What is the best way to contour lung tumors on PET scans? Multiobserver validation of a gradient-based method using a NSCLC digital PET phantom. Int J Radiat Oncol Biol Phys. 2011 Apr 28. [Epub ahead of print].
26. Cox DR. Regression models and life-tables (with discussion). J R Stat Soc Series B Stat Methodol 1972;34:187–220.
27. Gönen M, Heller G. Concordance probability and discriminatory power in proportional hazards regression. Biometrika 2005;92:965–70.
28. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515–26.
29. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
30. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86(2):420–8.
31. Borst GR, Belderbos JS, Boellaard R, Comans EF, De Jaeger K, Lammertsma AA, et al. Standardised FDG uptake: a prognostic factor for inoperable non-small cell lung cancer. Eur J Cancer 2005;41:1533–41.

32. Davies A, Tan C, Paschalides C, Barrington SF, O'Doherty M, Utley M, et al. FDG-PET maximum standardised uptake value is associated with variation in survival: analysis of 498 lung cancer patients. Lung Cancer 2007;55:75–8.
33. van Baardwijk A, Dooms C, van Suylen RJ, Verbeken E, Hochstenbag M, Dehing-Oberije C, et al. The maximum uptake of (18)F-deoxyglucose on positron emission tomography scan correlates with survival, hypoxia inducible factor-1alpha and GLUT-1 in non-small cell lung cancer. Eur J Cancer 2007;43:1392–8.
34. de Geus-Oei LF, Oyen WJG. Predictive and prognostic value of FDG-PET. Cancer Imaging 2008;8:70–80.
35. William Jr WN, Lin HY, Lee JJ, Lippman SM, Roth JA, Kim ES. Revisiting stage IIIB and IV non-small cell lung cancer: analysis of the surveillance, epidemiology, and end results data. Chest 2009;136:701–9.