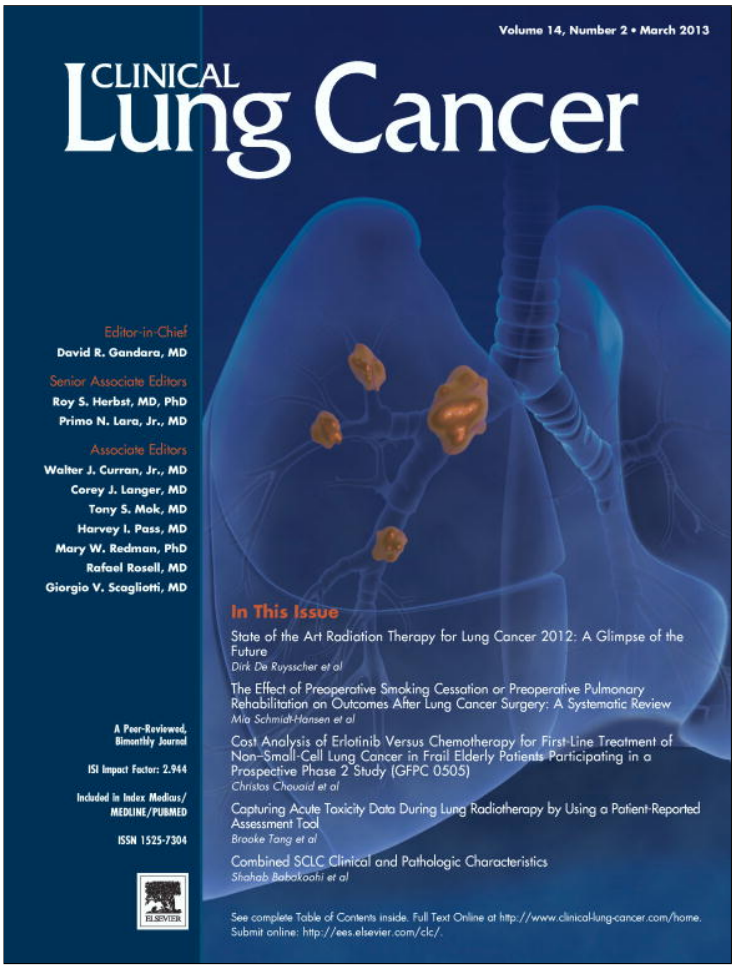

Original Study

The Prognostic Significance of Maximum Standardized Uptake Value of Primary Tumor in Surgically Treated Non–Small-Cell Lung Cancer Patients: Analysis of 413 Cases

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Abstract

We assessed the prognostic significance of tumor maximum standardized uptake value (SUV_{max}) at positron emission tomography and computed tomography (PET/CT) in surgically resected lung cancer patients and whether a novel standardized SUV ratio of tumor SUV_{max} to liver or blood pool SUV_{max} was additionally prognostically significant in 413 patients. Tumor SUV_{max} was an independent prognostic factor but both ratios were not. Our results could help plan adjuvant treatment.

Background: Integrated PET/CT is widely used in the preoperative staging and prognostic assessment of non–small-cell lung cancer (NSCLC) patients. The aims of this study were to evaluate the prognostic significance of SUV_{max} of primary tumor in patients undergoing surgical treatment and, in order to minimize technical interferences, to verify whether SUV_{max} standardized by SUV_{max} liver or SUV_{max} blood pool provided additional prognostic information. **Patients and Methods:** A retrospective study of 413 consecutive NSCLC patients undergoing potentially curative surgical resection after PET/CT obtained in the same PET center over a 6-year period. The SUV_{max} was calculated drawing region of interest around the primitive tumor, the liver, and the aortic arch in PET images. The same procedure was performed for 2 adjacent planes and the average of these measures was considered. **Results:** Nine patients were considered 30-day postoperative deaths and were excluded from the analysis. At the end of the study, 312 (77.2%) of the 404 patients were alive (median follow-up, 26 months) and 92 had died (median survival, 17 months). At multivariate analysis tumor-node-metastasis stage, primary tumor grading and primary tumor SUV_{max} (T-SUV_{max}) were found to be independent prognostic factors, while T-SUV_{max}/SUV_{max} blood pool ratio, and T-SUV_{max}/SUV_{max} liver ratio were not. **Conclusions:** T-SUV_{max} is an independent predictor for survival in NSCLC patients undergoing surgery and might be helpful in guiding adjuvant treatment strategies. SUV_{max} of primary tumor normalized by SUV blood pool or SUV liver does not provide additional prognostic information.

Clinical Lung Cancer, Vol. 14, No. 2, 149-56
Keywords: PET/CT, Prognosis, SUV_{max}

Introduction

Lung cancer remains the biggest cause of cancer deaths worldwide.[1] Pulmonary resection provides the only potentially curative option for patients with localized non–small-cell lung cancer (NSCLC).[2] Accurate preoperative staging determines the treatment modality that will be appropriate for the patient.[3] Positron emission tomography (PET) with radiolabeled [^{18}F] fluorodeoxy-D-glucose (FDG), which targets the increased metabolism present in most tho-

Presented in part at the IASLC meeting in Amsterdam, July 2011.

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Submitted: Feb 8, 2012; Revised: Apr 21, 2012; Accepted: Apr 23, 2012; Epub: Jun 7, 2012

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1525-7304/$ - see frontmatter
http://dx.doi.org/10.1016/j.cllc.2012.04.007

racic cancers, is now routinely used for preoperative staging and screening for distant metastases. When combined with computed tomography (CT), the anatomical resolution of the latter adds to the accuracy of staging of PET scanners. Thus, PET/CT is now recommended for preoperative staging of patients with lung cancer.[4] The increased uptake of FDG of lung cancer cells, measured by the maximum standardized uptake value (SUV_{max}), has been reported to have prognostic significance and predict biological aggressiveness in both early and advanced NSCLC.[5-13] Although SUV_{max} accurately measures the metabolic activity of tumors, it has been reported to vary between different PET scanners.[11] To provide a better and more homogeneous prognostic value, a ratio of tumor SUV_{max} to liver SUV_{max} (the SUV index), as well as tumor SUV_{max} to blood pool SUV_{max} have been shown to significantly predict disease recurrence and to be reproducible between scanners.[14,15] The purpose of our study was to test for the prognostic significance of tumor SUV_{max} and to assess whether SUV_{max} corrected for liver or blood pool provided any additional prognostic information in a cohort of patients undergoing surgical resection for proven NSCLC.

Patients and Methods

Patient Population

This is a retrospective review of 413 consecutive patients who underwent surgery (mediastinoscopy, anterior mediastinotomy, and/or thoracotomy) for suspected or pathologically proven localized, clinically resectable NSCLC over a 6-year period between August 2004 and January 2010.

Patients who had PET/CT performed elsewhere, who received induction chemotherapy and/or radiation therapy were excluded. All 413 patients had an integrated PET/CT scan performed at the same PET center with the same integrated scanner to complete the disease staging, and were enrolled in this study. In addition to integrated PET/CT, all enrolled patients had conventional diagnostic workup, including a thorough history and physical examination, laboratory tests, spirometry, chest x-ray, contrast-enhanced brain, chest, and upper abdomen CT, and bronchoscopy. Integrated PET/CT was performed no more than 3 weeks before surgery, and all patients provided informed written consent. Patient data were retrospectively collected and analyzed from a prospectively compiled electronic database.

Integrated PET/CT

Patients were asked to fast for at least 6 hours before examination and a serum glucose level below 160 mg/dL was ensured. Image acquisition using integrated PET/CT scanner (Discovery ST; GE Medical Systems) was performed 60 minutes after intravenous administration of FDG (3.5-4.5 MBq/kg). After determining the imaging field (CT scout view), a CT scan (140 kV, tube current 60 mA/s) was performed and it was used for both anatomical localization and for calculation of attenuation correction. Then, the PET data were acquired in 3-dimensional mode from the pelvic floor to the skull bases in 6 to 8 bed positions. The acquisition time for PET was 3 minutes per bed position. Coronal, sagittal, and transverse data sets were reconstructed. Coregistered scans were displayed by using dedicated software (Advantage 4.2; GE Healthcare) and integrated PET/CT data sets were prospectively evaluated in consensus by 2 nuclear medicine physicians (E.P. and V.A.) who were aware of clinical and stand-alone contrast-enhanced CT results, but blinded to the histologic findings. The SUV_{max} of the primary tumor was measured with a region of interest technique and calculated by the software according to standard formulas. The SUV_{max} of the liver and vascular pool were both measured. The SUV_{max} was calculated drawing region of interest around the primitive tumor, the liver, and the aortic arch in PET images. The same procedure was performed for 2 adjacent planes and the average of these measures was considered.

Pulmonary and mediastinal lymph node stations, localized according to the classification scheme of the seventh edition tumor-node-metastases (TNM),[16] were deemed positive for metastatic spread if they exhibited focally increased FDG uptake higher than the normal background activity, as determined by qualitative analysis.

Surgery and Histopathology

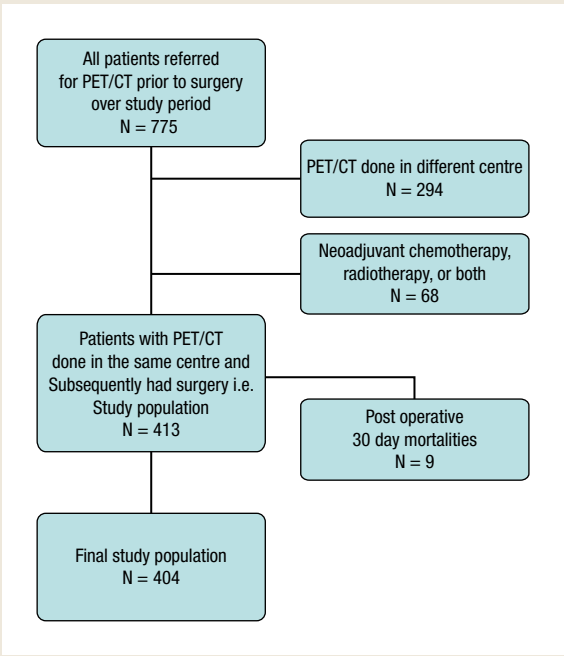
All 413 patients underwent surgical staging. Invasive mediastinal staging procedures were performed in patients considered N2/N3 lymph node positive by PET/CT. Cervical mediastinoscopy was used to sample stations 2R, 4R, 2L, 4L, and 7, and anterior mediastinotomy was used to sample stations 5 and 6. Patients were excluded from subsequent surgery if cervical mediastinoscopy revealed multistation N2 or N3 disease. These patients were, however, not excluded from our study. Patients found to have no mediastinal nodal metastases or only single-station intranodal metastatic deposits went on to have a lung resection and systematic nodal dissection. Patients with no evidence of mediastinal metastases at PET/CT proceeded to have surgical resection without invasive mediastinal nodal staging. Anatomic lung resections (pneumonectomy, bilobectomy, lobectomy, or segentectomy) were performed according to standard clinical indications and patient fitness. At thoracotomy, complete thoracic lymphadenectomy was routinely performed, which consisted of en bloc resection of all lymph nodes that were accessible in the mediastinum and hilum. Intrapulmonary lymph nodes (stations 11 and 12) were removed in the resected lung specimen. At the subcarinal level, the contralateral mediastinal lymph nodes, lying on the opposite main stem bronchus, were removed if found.

Pathologic review (primary tumor characteristics and lymph node status) was performed by standard techniques and immunohistochemistry was used when appropriate. Pathologic TNM staging, according to the seventh edition, was performed and disease was classified accordingly from stage IA to IV.

Data Analysis

Continuous data are reported with medians and ranges, and categorical data are reported with counts and percentages. Survival was measured from the date of PET/CT scanning. Survival and prognostic factors were analyzed by the Kaplan–Meier method. Univariate analysis of data was performed using χ^2 test, log-rank test, Fischer's exact test, unpaired t test, and anaysis of variance, where appropriate. Factors that significantly affected survival in univariate analysis (at $P < .10$) were tested for their independent role in multivariate analysis using the Cox proportional hazards model. The stepwise backward procedure based on the likelihood ratio was used to assess the significance of covariates included in the model. Hazard ratios and 95% confidence intervals were calculated. A P value $<.05$ was con-

Figure 1 Flow Chart Showing All Patients Reviewed During Study Period and Those Excluded



sidered statistically significant. All analyses were conducted using the SPSS (version 18, SPSS Inc) software package.

Results

Between August 2004 and January 2010, 413 patients had an integrated PET/CT scan for staging of proven or suspected localized NSCLC before surgery. Patient accrual for the study is summarized in Figure 1. Four hundred and eight patients (99%) underwent complete resection. The demographic, clinical, and pathologic characteristics of the study population are summarized in Table 1. Nine patients (myocardial infarction, n = 2; respiratory failure, n = 6; sepsis and multiorgan failure, n = 1) died within 30 days of surgery and these were excluded from the study.

At the time of the study, the remaining patients (n = 404) had a median follow-up of 26 months (range, 2-72.8 months).

The mortality rate at follow-up was 22.8% (92 patients) with a median survival of 16.8 months. Median follow-up of the 312 living patients was 26 months. The survival at 2 years was 79.5% and at 5 years 61.4%.

In the study population the median tumor SUVmax was 8.6 (range, 3.1-54), the median SUV_{max} vascular pool was 5 (range, 0.6-30), and the median SUV_{max} of the liver was 3.7 (range, 0.5-16.9). The median primary tumor SUV_{max} (T-SUV_{max}), ratio T-SUV_{max}/liver SUV_{max}, and ratio T-SUV_{max}/blood pool SUV_{max} were 8.6, 3.7, and 5.0, respectively.

No differences were observed in the SUV_{max} in patients with right or left side lesions. Centrally located tumors (n = 131) had a higher SUV_{max} than peripheral tumors (11.8 vs. 8.7, $P = .000003$). Larger tumors (≥30 mm; n = 195) had a higher SUV_{max} than smaller (12.7 vs. 6.0; $P < .000001$). Adenocarcinoma subtype (n = 238) had a lower SUV_{max} than squamous cell carcinoma (n = 103) (8.3 vs. 12.5; $P < .00001$).

Patients with no vascular invasion in the primary lung cancer lesion (n = 296) had a lower SUV_{max} compared with patients with vascular invasion (9.1 vs. 11.1; $P = .005$). Patients with no intralesion necrosis (n = 152) had a lower SUV_{max}, compared with patients with focal (n = 132) or extensive necrosis (n = 119) (6.6 vs. 10.6 vs. 12.6; $P < .000001$). Tumor with grading 1 (n = 54) had a lower

Table 1 Baseline Characteristics of the Study Population (n = 404)

Characteristic	Number	Percentage
Sex (Male)	288	71.3
Median Age, Years (Range)	67 (37-86)	
Site of Disease		
Right	234	57.9
Left	170	42.1
Location of Disease		
Central	131	32.4
Peripheral	273	67.6
Histology		
Adenocarcinoma	238	58.9
Squamous cell	103	25.5
Other NSCLC cell types	63	15.6
Stage		
I	222	54.9
II	95	23.5
IIIA	79	19.6
IIIB and IV	8	2.0
Primary Tumor SUV_{max} Median (Range)	8.6 (1.1-54)	
<8.6	209	51.8
≥8.6	195	48.2
SUV_{max} Corrected by SUV_{max} Liver Median (Range)[a]	3.7 (0.5-16.9)	
<3.7	193	50.4
≥3.7	189	49.6
SUV_{max} Corrected by SUV_{max} Blood Pool Ratio Median (Range)[a]	5.0 (0.6-30)	
<5	198	50.6
≥5	193	49.4
Surgery		
Invasive Staging Procedures Alone	5	1.2
Invasive Staging Procedures Followed by Thoracotomy	28	6.9
Thoracotomy Alone	371	91.9

Abbreviations: NSCLC = non–small-cell lung cancer; SUV_{max} = maximum standardized uptake value.
[a] Some of these data are missing.

SUV_{max} compared with tumors with grading 2 (n = 168) and grading 3 (n = 173) (5.3 vs. 9.2 vs. 11.7; $P < .000001$).

SUV_{max} did not vary significantly according to the T stage. Primary NSCLC with positive lymph nodes (n = 122) had a higher SUV_{max} than lesions with lymph nodes negative (11.3 vs. 9.0; $P = .0006$).

At multivariate analysis the following factors were independent prognostic factors for higher SUVmax: increasing tumor diameter ($P = .0001$; hazard ratio [HR], 1.06; 95% confidence interval [CI], 1.04-1.08), presence of necrosis in tumor ($P = .006$; HR, 2.14 95% CI, 1.52-3.01), higher tumor grade (G3) ($P = .0001$; HR. 1.7; 95% CI, 1.17-2.58).

We then analyzed for prognostic factors for survival in the study population. At univariate analysis, T-SUV_{max} ($P = .00016$), T-SUV_{max}/SUV_{max} blood pool ($P = .0005$), and T-SUV_{max}/SUV_{max} liver ($P = .00017$); as well as sex ($P = .03$), T stage ($P = .00004$), N stage ($P < .000001$), TNM stage ($P < .000001$), primary tumor characteristics including presence of necrosis ($P = .004$), presence of vascular invasion ($P = .0012$), and grading ($P = .001$), were significantly associated with survival. These are summarized in Table 2. Median survival and 2- and 5-year survival of patients with a SUV_{max} <8.6 (n = 209) was 26.4%, 88.4%, and 72.1%, respectively. Median survival and 2- and 5-year survival of patients with an SUV_{max} ≥8.6 (n = 195) was 19.6%, 71%, and 47.8%, respectively (Figure 2).

Median survival and 2- and 5-year survival of patients with a T-SUV_{max}/SUV_{max} liver <3.7 (n = 192) was 24.3%, 85.8%, and 65.1%, respectively. Median survival and 2- and 5-year survival of patients with a T-SUV_{max}/SUV_{max} liver ≥3.7 (n = 190) was 19.2%, 73.5%, and 53.9%, respectively.

Median survival and 2- and 5-year survival of patients with a T-SUV_{max}/SUV_{max} blood pool <5 (n = 193) was 25.1%, 86.3%, and 68.8%, respectively. Median survival and 2- and 5-year survival of patients with a T-SUV_{max}/SUV_{max} blood pool ≥5 (n = 189) was 19.9%, 72.9%, and 50.3%, respectively.

Median and 5-year survival of patients in stage I, II, and IIIA/IIIB/IV were, respectively 24.8, 22.8, 17.4, and 14.9 months, and 76%, 65.5%, 31.3%, and 23.3%, respectively (Figure 3).

Median survival for well, moderately, and poorly differentiated tumors were 25.6, 25.6, and 19.7 months and respectively; 2- and 5-year survival for well differentiated cancer was 98% and 88%, for moderately differentiated cancer was 79% and 56.8%, and for poorly differentiated cancer was 74% and 51% (Figure 4). Moreover, the median survival and 5-year survival for tumor with focal and extensive necrosis or without necrosis were and 26.2, 18.1, and 24.7 months and 58.6%, 54.5% and 70.3%; for tumor with or without vascular invasion were 22.3 and 24.7 months and 32.7% and 71.2%, respectively.

At multivariate analysis factors independently associated with survival were grade of differentiation of the tumor, TNM staging and SUV_{max} of the tumor (Table 3). The greatest HRs for death were observed for poorly differentiated NSCLC (4.5 times more compared with patients with well differentiated lung cancer), for advanced TNM staging, stage IIIB and IV (5.46 times more compared with patients with stage IA) and for tumors with a higher SUV_{max}.

Table 2 Univariate Analysis (n = 404)

Variable	HR	95% CI	P
Sex (Female vs. Male)	1.7	1.03-2.79	.034
Tumor Diameter	1.02	1.01-1.03	.0001
T Stage			
T1	1		
T2	2.33	1.37-3.96	.002
T3	3.46	1.88-6.35	.0001
T4	3.77	1.51-9.39	.004
N Stage			
N0	1		
N1	1.86	1.02-3.38	.042
N2/N3	3.44	2.19-5.41	.0001
TNM Stage			
Stage I	1		
Stage II	1.53	0.86-2.72	.14
Stage IIIa	4.17	2.59-6.72	.0001
Stage IIIB and IV	6.59	2.31-18.85	.0001
Grade of Differentiation			
Good	1		
Moderate	5.34	1.65-17.24	.005
Poor	7.1	2.21-22.82	.001
Vascular Invasion (No vs. Yes)	1.99	1.31-3.04	.001
Necrosis			
Absent	1		
Focal	1.27	0.75-2.15	.37
Extended	2.24	1.33-3.70	.002
Tumor SUV_{max}	1.05	1.03-1.08	.0001
Tumor SUV_{max}/SUV_{max} Blood Pool	1.09	1.04-1.13	.0001
Tumor SUV_{max}/SUV_{max} Liver	1.14	1.07-1.22	.0001

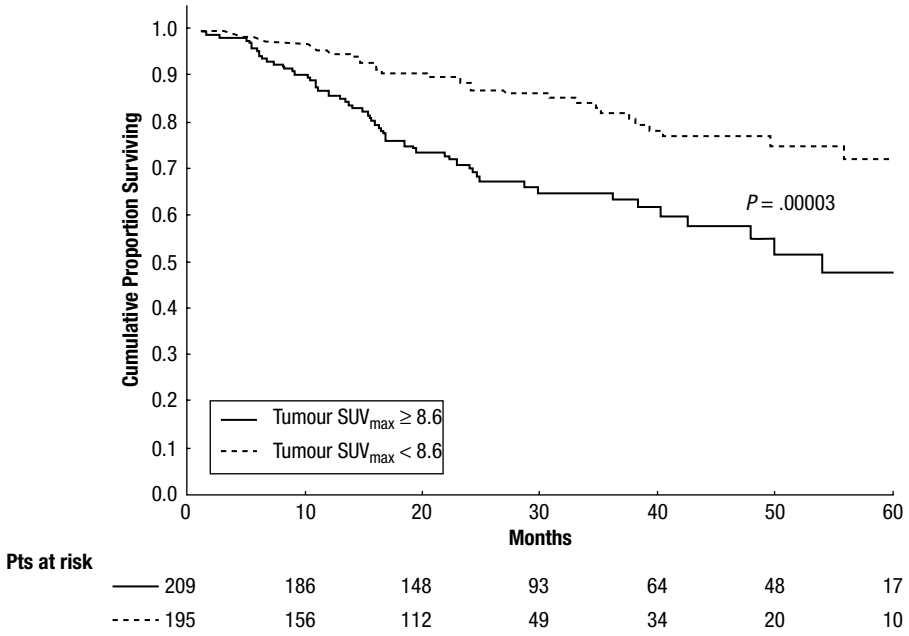
Abbreviations: HR = hazard ratio; SUV_{max} = maximum standardized uptake value; TNM = tumor-node-metastases.

At multivariate analysis stratifying the study population for histology (adenocarcinoma vs. squamous cell carcinoma) T-SUV_{max}/SUV_{max} blood pool and T-SUV_{max}/SUV_{max} liver ($P = .00017$) were not independent prognostic factors, only TNM stage and SUV_{max} were independently associated with survival ($P < .000001$).

We ran a receiver operating characteristic (ROC) curve subgroup analysis in stage I patients. The cutoff value of the SUV_{max} was 7.8 (area 0.592, $P = .1$; 95% CI, 0.5-0.68). In stage I patients at univariate analysis SUV_{max}, SUV ratio vascular pool and liver did not correlate with survival, only male sex ($P = .0047$), patients with advanced age >70 years ($P = .004$), and presence of necrosis in the tumor ($P = .01$) were significant prognostic factors. However, only advanced age and presence of necrosis were independent risk factors for worse survival. All the SUV parameters were not significant.

We analyzed patients in stage II, III, and IV who received adjuvant chemotherapy. In this group, the patients with an SUV_{max} <8.7 had

Figure 2 Kaplan–Meier Survival Curve According to the Primary Tumor Maximum Standardized Uptake Value (SUV_{max})



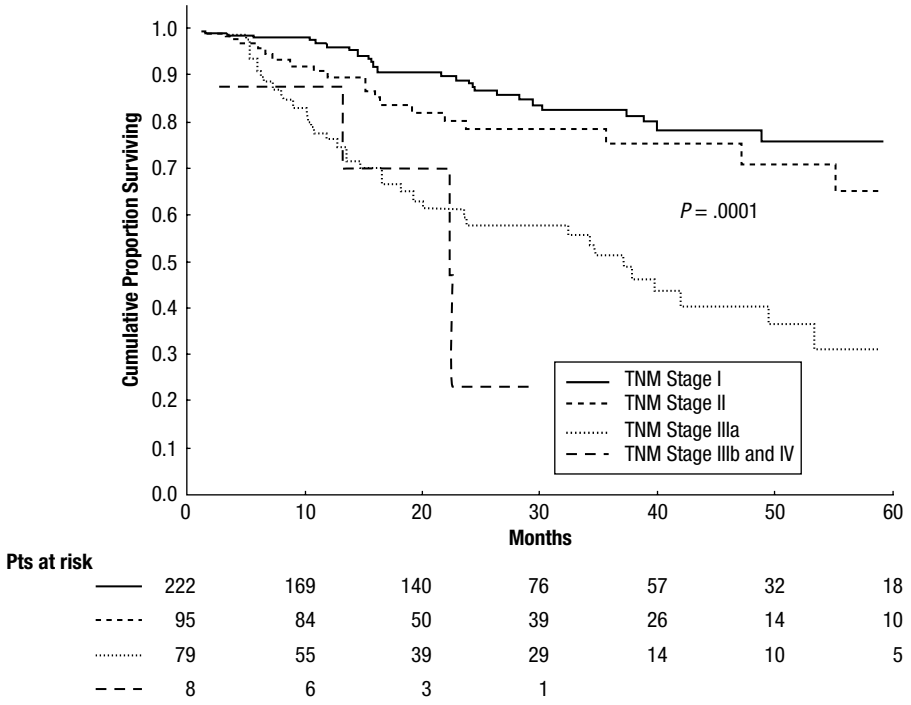
a better survival than patients with a SUV_{max} ≥8.7(P = 0.00021), with a 2- and 5-year survival of 81% and 65%, and 55.1% and 15% in the 2 groups, respectively. This is confirmed also in the subanalysis per group; in stage II and III/IV patients with SUV_{max} < 8.7 had a better prognosis (P = .008 and P = .004, respectively). In patients in stage II with SUV_{max} <8.7 who received chemotherapy, all are alive at 2 years; no death (n = 14). In stage II with SUV_{max} >8.7 survival was 75.5% and 66% at 2 and 5 years, respectively. In stage III and IV, 2- and 5-year survival are 76.2% and 54.5% in SUV_{max} <8.7 and 48.2% and 15.6% in patients with SUV_{max} >8.7.

Discussion

PET using FDG has firmly moved into the mainstream of management of NSCLC over the last decade. The main application of PET/CT is 2-fold. First it is used in screening for regional and distant metastases as part of staging. Second, it is useful in monitoring response to treatment for patients having chemotherapy and/or radiation therapy.[17] In addition, various studies have now reported the prognostic significance of SUV_{max} in both early and advanced NSCLC.[5-13] A systematic review and meta-analysis of the various studies confirms the prognostic value of PET SUV_{max} in patients treated with surgery or other modalities.[8] All patients in our study had an integrated PET/CT for staging before surgery. We divided our patients into 2 groups by median value of SUV_{max}. The median SUV_{max} was 8.6. Multivariate analysis in our study showed tumor SUV_{max} to independently predict survival. Tumor differentiation likewise, was an independent prognostic factor for survival with patients with poorly differentiated tumors having a lower median survival compared with those with well differentiated tumors. Because SUV_{max} is a measure of uptake of radiolabeled glucose of tumor cells, it probably follows that it measures biological aggressiveness of NSCLC and correlates with other known markers of poor prognosis such as tumor differentiation.[18] This may relate to overexpression of glucose transporters which has been noted in cancer cells, and especially lung cancer.[19,20] Tumor SUV_{max} has been reported to correlate, not only with grade, but also clinical stage and pathologic type.[21] In keeping with published data, we found tumor necrosis, larger, and more centrally located tumors to be independent predictive factors for higher tumor SUV_{max}.[18,21] We also noted a higher SUV_{max} for squamous cell carcinomas.

Cerfolio and Bryant have reported the use of PET SUV_{max} in predicting lymph node metastases in patients with detected N2 disease using a ratio to correct for potential variability between different PET centers.[22] Similar results have since been reported in a series of 335 patients.[23] However, a consistently reported pitfall of SUV_{max} is its variability between centers due to lack of standardization in acquisition and processing protocols.[8,14,23] This presents a problem as it makes it difficult to compare results from different PET scanners and centers. Different methods have been proposed to correct for variability in recording SUV_{max} with the authors reporting apparent reproducibility of the results between scanners.[15,23-25] They all involve using a ratio of tumor SUV_{max} with either liver, or blood SUV_{max}. By using a ratio as opposed to an absolute value for SUV_{max}, the authors hoped to overcome 2 pitfalls of SUV_{max}. First, there is controversy as to what cutoff value of tumor SUV_{max} accords the most significant diagnostic and prognostic information. To ascertain the optimal SUV_{max} that accords the maximal specificity and sensi-

Figure 3 Kaplan–Meier Survival Curve According to the Tumor-Node-Metastases (TNM) Stage



tivity to predict survival, ROC curves are plotted. This value of SUV_{max} is used to divide patient groups for comparison of survival. However, the optimal value of SUV_{max} is very variable and has been reported variously as ranging between 2.5 and 15.[8] Second, the ratio provides a value obtained by using the same method of SUV acquisition for 2 different areas (either liver or blood pool, and tumor) in the same patient using the same information acquired from the same scanner. This ratio can therefore eliminate the bias that may be introduced by nonstandardized protocols for data acquisition and processing from different PET centers. The ratio (or index) of tumor SUV_{max} to liver or blood SUV_{mean} has been reported to significantly predict the risk of disease recurrence in patients with lung cancer.[15] We applied the same method for computing the SUV ratio. The median values for tumor SUV_{max}/liver SUV_{max}, and tumor SUV_{max}/blood pool SUV_{max} were 3.7 and 5.0, respectively. Although both these ratios significantly predicted survival in the univariate analysis, they both failed to achieve statistical significance at multivariate analysis. In addition to technical variations between PET centers relating to image acquisition, reconstruction, analysis, as well as PET and CT scan attenuation correction, a number of physiological factors can affect SUV. These include blood glucose level, patient respiratory movement during image acquisition, duration between administration of FDG and image acquisition, inflammation around tumor, serum levels of insulin, and renal clearance of FDG.[25,26] The effects these variables have on plasma concentration of FDG as well as affecting the tumor-to-background contrast in SUV are bound to affect the readings of SUV and CT image superimposition.[26] Whereas the technical differences can be eliminated by use of a ratio, some physiological factors will still affect tumor SUV_{max} and not liver or blood $SUV_{max,}$ and vice versa. This, coupled with a relatively short follow-up could have influenced the results of the multivariate analysis for tumor SUV_{max}/liver SUV_{max} and tumor SUV_{max}/blood pool SUV_{max}. These physiological factors could influence the accuracy of the ratios and therefore their role as independent prognostic factors in the multivariate analysis.

It must be noted that normalization of SUV for parameters such as plasma glucose, lean body mass, body mass index, injected dose of FDG, and body surface area, have not been shown to improve correlation of SUV readings done at different times or improve retest variability in both cancer-free volunteers and patients with NSCLC.[27-29] The authors of these reports have recommended that SUV readings should therefore not be adjusted for these parameters. Although these represent completely different methods for correction of SUV to potentially eliminate bias caused by lack of uniformity in PET methodology, it may be that the ratios we report here do not improve prognostic accuracy of PET in lung cancer in a likewise manner. This will require further prospective multicenter studies to clarify.

Of course, one of the applications of our results could be to plan adjuvant treatment strategies for patients. We therefore ran subgroup analysis in 2 groups of patients. First, in stage I patients in whom international guidelines do not recommend adjuvant treatment, we aimed to assess for factors that may be predictors of survival that could be targets for adjuvant treatment. To more accurately stratify

Figure 4 Kaplan–Meier Survival Curve According to the Tumor Differentiation

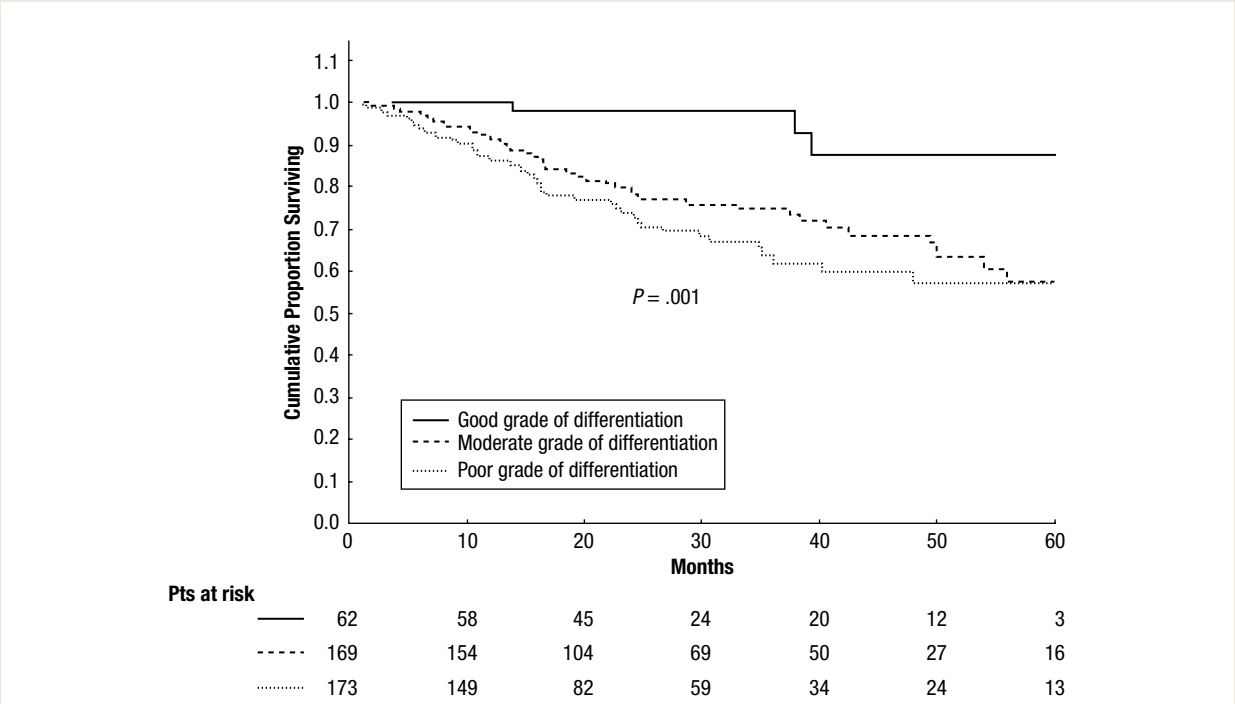


Table 3 Multivariate Analysis (n = 382)

Characteristic	HR	95% CI	*P*
Grade of Differentiation			.04
Good	1		
Moderate	3.7	1.13-12.13	.03
Poor	4.5	1.38-14.86	.01
TNM Stage			.0001
Stage I	1		
Stage II	1.12	0.59-2.13	.73
Stage IIIA	3.70	2.25-6.09	.0001
Stage IIIB and IV	5.46	1.89-15.75	.002
Tumor SUV_{max}	1.04	1.01-1.07	.006

Abbreviations: HR = hazard ratio; SUV_{max} = maximum standardized uptake value; TNM = tumor-node-metastases.

these patients by SUV_{max}, we ran a ROC curve and obtained a cutoff value. We, however, found that the SUV values (tumor SUV_{max} and ratio) did not independently predict survival in this group of patients. The factors that achieved statistical significance at multivariate analysis in stage I patients were advanced age and tumor necrosis, both of which are nonmodifiable. It is worth noting that patients in stage I generally have smaller primary tumors and these may be below the accurate resolution of PET/CT.[30]

Second, we subanalyzed patients who had received adjuvant chemotherapy because they had stage II, and III or IV disease. In these patients, a lower SUV_{max} below our median value was associated with a better survival. This was statistically significant and was the case both in all patients with stage II, and III and IV disease, and also in their individual stages (stage II alone, III alone, and IV alone). It is perhaps patients with higher tumor SUV_{max} above 8.7 who would benefit most with targeted adjuvant treatments.

Conclusion

Being a retrospective study, it may be difficult to generalize the findings of our report. Although this is a preliminary report we think that it gives important insights into the significance of tumor SUV_{max} in predicting survival in a large cohort of surgical patients. The problem of lack of standardization of tumor SUV_{max} in lung cancer continues to blight an otherwise excellent tool in management of lung cancer patients. One way of addressing this is to implement very elaborate and rather cumbersome criteria as laid out in detailed protocols such as that proposed by Boellaard et al.[26] Alternatively, more studies evaluating the SUV ratio that we report here may provide a less laborious, yet effective, tool in prognostication of NSCLC patients undergoing surgery.

Clinical Practice Points

- Integrated PET/CT is an important tool for clinical staging of lung cancer and is recommended for all surgical patients as part of preoperative workup.
- Tumor SUV_{max} at PET/CT has been reported to correlate with prognosis in both early and advanced lung cancer with patients

having a high SUV_{max} generally having a poorer prognosis than those with lower SUV_{max}.

- Tumor SUV_{max}, however, varies between different PET centers because of lack of standardization in acquisition and processing protocols.
- Our study aimed to assess prognostic significance of tumor SUV_{max} in a large homogeneous cohort of patients.
- The unique features of our study are 4-fold; first, it is a large cohort of 413 patients. Second, all patients had a PET/CT scan done in the same center and reported by the same radiologists. Third, all our patients were clinically staged as early lung cancer (stage I, II, and single station IIIA) and had surgery. Fourth, we assessed a new tool to standardize tumor SUV_{max} as a ratio of tumor SUV_{max} to SUV_{max} of the liver or blood pool.
- Our results show that tumor SUV_{max} and tumor grade are independent prognostic factors. The SUV ratio was, however, not an independent prognostic factor.
- Patients with high tumor SUV_{max} could be a target for neoadjuvant and adjuvant treatment strategies to improve prognosis.

Disclosure

All authors have no conflicts of interest.

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