Eur J Nucl Med Mol Imaging (2010) 37:691–698
DOI 10.1007/s00259-009-1291-x

ORIGINAL ARTICLE

Revisiting the prognostic value of preoperative ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) positron emission tomography (PET) in early-stage (I & II) non-small cell lung cancers (NSCLC)

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Received: 21 May 2009 / Accepted: 25 September 2009 / Published online: 14 November 2009

Abstract
Purpose The aims were to determine if the maximum standardized uptake value (SUV_{max}) of the primary tumor as determined by preoperative ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) positron emission tomography (PET) is an independent predictor of overall survival and to assess its prognostic value after stratification according to pathological staging.
Methods A retrospective clinicopathologic review of 363 patients who had a preoperative ^{18}F-FDG PET done before undergoing attempted curative resection for early-stage (I & II) non-small cell lung cancer (NSCLC) was performed. Patients who had received any adjuvant or neoadjuvant chemotherapy or radiation therapy were excluded. The primary outcome measure was duration of overall survival. Receiver-operating characteristic (ROC) curves were plotted to find out the optimal cutoff values of SUV_{max} yielding the maximal sensitivity plus specificity for predicting the overall survival. Survival curves stratified by median SUV_{max} and optimal cutoff SUV_{max} were estimated by the Kaplan-Meier method and statistical differences were assessed using the log-rank test. Multivariate proportional hazards (Cox) regression analyses were applied to test the SUV_{max}'s independency of other prognostic factors for the prediction of overall survival.
Results The median duration of follow-up was 981 days (2.7 years). The median SUV_{max} was 5.9 for all subjects, 4.5 for stage IA, 8.4 for stage IB, and 10.9 for stage IIB. The optimal cutoff SUV_{max} was 8.2 for all subjects. No optimal cutoff could be established for specific stages. In univariate analyses, each doubling of SUV_{max} [i.e., each log (base 2) unit increase in SUV_{max}] was associated with a 1.28-fold [95% confidence interval (CI): 1.03–1.59, p=0.029] increase in hazard of death. Univariate analyses did not show any significant difference in survival by SUV_{max} when data were stratified according to pathological stage (p=0.119, p=0.818, and p=0.882 for stages IA, IB, and IIB, respectively). Multivariate analyses demonstrated that SUV_{max} was not an independent predictor of overall survival (p>0.05).
Conclusion Each doubling of SUV_{max} as determined by preoperative PET is associated with a 1.28-fold increase in hazard of death in early-stage (I & II) NSCLC. Preoperative SUV_{max} is not an independent predictor of overall survival.

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Keywords ^{18}F-FDG PET · Non-small cell lung cancer · Prognosis · Survival · SUV

Abbreviations

^{18}F-FDG	^{18}F-Fluoro-2-deoxyglucose
NSCLC	Non-small cell lung cancer
PET	Positron emission tomography
SUV_{max}	Maximum standardized uptake value

Introduction

^{18}F-Fluoro-2-deoxyglucose (^{18}F-FDG) positron emission tomography (PET) has been demonstrated to be very useful in the diagnosis and staging of non-small cell lung cancers (NSCLC) [1, 2]. As a result there has been increasing interest in the prognostic utility of the preoperative standardized uptake value (SUV) of the primary tumor. Many prior studies have investigated this issue [3–16]. Several prior studies have reported an association between higher maximum SUV (SUV_{max}) and poor prognosis, but some recent studies have failed to find any independent correlation between them. To elucidate the prognostic significance of preoperative SUV_{max} of the primary tumor in early-stage (I & II) NSCLC, a retrospective review of 363 consecutive patients who had a preoperative ^{18}F-FDG PET done before undergoing attempted curative resection for early-stage (I & II) NSCLC was performed.

Materials and methods

Approval of human data exemption was obtained from the Institutional Review Board for this Health Insurance Portability and Accountability Act (HIPAA) compliant study.

Objectives

The aims were to determine if SUV_{max} as measured by preoperative ^{18}F-FDG PET is an independent predictor of survival and to determine if SUV_{max} as measured by preoperative ^{18}F-FDG PET is of prognostic value after stratification according to pTNM staging.

Study population

Subjects were identified through the institutional tumor registry.

Patients were included in the study if they had a preoperative ^{18}F-FDG PET done from 5 February 1999 through 21 March 2007 before undergoing attempted curative resection for pathologically documented stage I and II NSCLC and histological diagnosis was available.

Patients were excluded from the study if they had received any adjuvant or neoadjuvant chemotherapy or radiation therapy, had any prior history of lung cancer, or if SUV_{max} was not available due to the non-availability of SUV_{max} from the reports and the non-availability of PET images.

PET

Scans performed since July 2004 were obtained by a dedicated 16-slice whole-body PET/CT scanner (GE Discovery DST, GE Medical Systems, Milwaukee, WI, USA). All patients with 4-h fasting before the examination received an average of 560 MBq ^{18}F-FDG intravenous injections. PET images were obtained 1 h after injection. The PET images were obtained at each bed position for 3 min with six to eight bed positions to cover the entire body. The PET images were obtained using a two-dimensional high-sensitivity mode with an axial field of view of 15 cm in a 256×256 matrix. A 3-slice overlap was utilized between the bed positions. The PET images were reconstructed iteratively on a 128×128 matrix using an ordered subsets expectation maximization algorithm for 30 subsets and two iterations, with a 7.0-mm post-reconstruction filter. In-plane resolution of 6.2 mm and axial resolution of 5.0 mm was obtained. Concomitant CT data were used for attenuation correction of all PET images in the quantitative analysis of SUV. The CT component of image acquisition used the following imaging parameters: 140 kVp, 120–200 mA, 0.8 s per CT rotation, pitch 1.75:1, detector configuration of 16×1.25 mm, and 3-mm slice thickness with oral contrast only.

PET and CT images were merged (fusion analysis) for functional and anatomic correlation. CT/PET images were displayed on AW/Xeleris and Medview workstations (General Electric Medical Systems, Milwaukee, WI, USA and Medimage, Ann Arbor, MI, USA). Scans performed before July 2004 were obtained on a dedicated whole-body PET only scanner (Advance, General Electric Medical Systems, Milwaukee, WI, USA) 1 h after injection of ^{18}F-FDG (370 MBq, on average) and after the patients had fasted about 4 h. PET images were reconstructed using an iterative reconstruction algorithm with segmented attenuation correction. All PET data were visually examined and compared to the patient's recent CT. The decision was finally made by correlating PET with CT to make sure the non-tumor regions were excluded from analysis. The SUV from both cameras were validated and correlated with phantom studies.

SUV was calculated using the following formula:

$$\mathrm{SUV} = \text{lung cancer activity} / (\text{dose}/\text{body mass})$$

The SUV_{max} was obtained by selecting volumetric regions of interest (VOIs) within the primary cancer site to include

all tumor tissue but not any non-tumor tissue with potentially higher SUV than that of the tumor. The glucose concentration was also recorded for each patient before the injection of the ^{18}F-FDG radiotracer in each PET scan.

Data collection

In 325 subjects SUV_{max} of the primary tumor was obtained from the initial PET reports. PET study interpretation had been independently performed by five experienced nuclear medicine physicians. In 38 subjects SUV_{max} was calculated from the PET images as it was not reported in the initial PET reports.

Baseline demographic, clinical, and tumor characteristics, treatment, follow-up, and survival data were obtained from the electronic medical record system and institutional tumor registry records.

The histological type was categorized according to the WHO classification system [17].

End-point assessment

The primary outcome measure was the duration of overall survival. It was measured from the date of surgery to the date of death from any cause with surviving patients censored at the time of last contact.

Statistical methods

Variables studied included age, race, gender, preoperative SUV_{max}, pathological stage, tumor size, tumor laterality, type of surgery, histology subtype, and cytologic grade.

The continuous variables SUV_{max}, tumor size, and age were examined for normality and skewness. SUV and tumor size needed log transformations (with base 2).

Each variable was analyzed using univariate proportional hazards (Cox) regression analysis. Multivariate proportional hazards (Cox) regression analyses were applied to test the SUV_{max}'s independency of other prognostic factors for the prediction of overall survival.

In the initial multivariate Cox regression model, all variables that on univariate analysis were found to have a p value of less than 0.10 were included as covariates. SUV_{max}, tumor size, and age were treated as continuous variables. Variables were retained in the subsequent Cox regression modeling if they met the p value of less than 0.05 in the model. Nonsignificant variables were removed by stepwise backward elimination. Pathological staging was excluded from multivariate analysis due to potential interaction with tumor size.

The continuous variables SUV_{max}, tumor size, and age were then dichotomized by a median split. Survival curves stratified by median SUV_{max} were estimated by the Kaplan-Meier method and statistical differences were assessed using the log-rank test. Multivariate analyses were repeated after replacing continuous variables with median SUV_{max}, median tumor size, and median age.

Receiver-operating characteristic (ROC) curves were plotted to find out the optimal cutoff values of SUV_{max} yielding the maximal sensitivity plus specificity for predicting the overall survival. Survival curves stratified by optimal cutoff SUV_{max} were estimated by the Kaplan-Meier method, and statistical differences were assessed using the log-rank test. Multivariate analyses were performed again after replacing median SUV_{max} with optimal cutoff SUV_{max}.

The data were then stratified according to the pathological stage. The median SUV_{max} for each specific stage was calculated. For specific stages, survival curves stratified by median SUV_{max} were estimated by the Kaplan-Meier method, and statistical differences were assessed using the log-rank test. By plotting the ROC curves, we attempted to find out the optimal cutoff values of SUV_{max} for specific stages yielding the maximal sensitivity plus specificity for predicting the overall survival, but none could be established. No stage-specific analysis was performed for stage IIA due to the small number of subjects.

Statistical analyses were performed using SPSS® version 13.0 (SPSS Inc., Chicago, IL, USA).

In order to address the effects of the partial volume effects, the recovery coefficient (RC) was determined, and the SUV_{max} was corrected using the diameters of the tumor as the following:

$$SUV_{measured} = \frac{Counts.CF(kBq/ml/kg)}{ID(kBq/ml)/Mass(kg)}$$

where CF = calibration factor and ID = injected dose.

The partial volume corrected SUV (SUVpvc) was given by:

$$SUV_{pvc} = SUV_{bkg} + \left(SUV_{measured} - SUV_{bkg}\right)/RC$$

where SUVbkg = background SUV.

Results

A total of 363 subjects met the inclusion and exclusion criteria. The median duration between preoperative ^{18}F-FDG PET and attempted curative resection was 38 days. The median duration of follow-up was 981 days (2.7 years). The clinicopathologic characteristics are summarized in Table 1 along with the mortality information.

The median SUV_{max} was 5.9 for all subjects, 4.5 for stage IA, 8.4 for stage IB, and 10.9 for stage IIB (Fig. 1). The optimal cutoff value of SUV_{max} was 8.2 for all subjects. No optimal cutoff value of SUV_{max} could be established for specific stages with acceptable sensitivity and specificity for predicting the overall survival. No stage-

Table 1 Patient characteristics

Variable	Total (*n*)	Died (*n*)	Died (%)	Censored (*n*)
Pathological TNM stage				
Stage IA	223	34	15.20	189
Stage IB	112	25	22.30	87
Stage IIA	8	1	12.50	7
Stage IIB	20	6	30.00	14
Laterality				
Right	224	40	17.90	184
Left	139	26	18.70	113
Type of surgery				
Lobectomy	293	53	18.10	240
More extensive resection (bilobectomy or pneumonectomy)	18	6	33.30	12
Limited resection (wedge/segment/lingular resection)	52	7	13.50	45
Tumor grade				
Low grade	73	11	15.10	62
Intermediate grade	153	28	18.30	125
High grade	131	27	20.60	104
Histology type				
Squamous cell carcinoma	90	19	21.10	71
Adenocarcinoma	227	41	18.10	186
Others	46	6	13.00	40
Age group				
<50 years	17	0	0.00	17
50–59 years	49	3	6.10	46
60–69 years	112	16	14.30	96
70–79 years	139	38	27.30	101
>79 years	46	9	19.60	37
Race				
White	344	63	18.30	281
Others	19	3	15.80	16
Sex				
Male	175	39	22.30	136
Female	188	27	14.40	161
Overall	**363**	**66**	**18.20**	**297**

specific analysis was performed for stage IIA due to the small number of subjects.

In univariate proportional hazards (Cox) regression analysis, each doubling of SUV_{max} [i.e., each log (base 2) unit increase in SUV_{max}] was associated with a 1.28-fold [95% confidence interval (CI): 1.0–1.6, $p=0.029$] increase in hazard of death (Table 2). Kaplan-Meier survival analyses showed significant difference in overall survival when stratified by median SUV_{max} (Fig. 2) and optimal cutoff SUV_{max} (Fig. 3) in the whole group of cases (log-rank test, $p=0.018$ and $p=0.004$, respectively). The mean survival times of patients with SUV_{max} of primary tumor equal to or more than median value 5.9 and optimal cutoff value of 8.2 were 66.6 months and 58.9 months, respectively, compared with overall mean survival time of 73.5 months.

Primary analysis with the multivariate Cox proportional hazards model showed that SUV_{max} was not an independent predictor of overall survival ($p>0.05$). Repeat analyses after replacing the continuous variables tumor size, age, and SUV_{max} with the dichotomous variables median tumor size, median age, and median SUV_{max} or optimal cutoff SUV_{max} again failed to show the SUV_{max}'s independency of other prognostic factors for the prediction of overall survival ($p>0.05$ in all multivariate models).

There was high correlation between SUVpvc and the uncorrected SUV_{max} (Fig. 4). Thus, the statistical analysis on the original data is still valid.

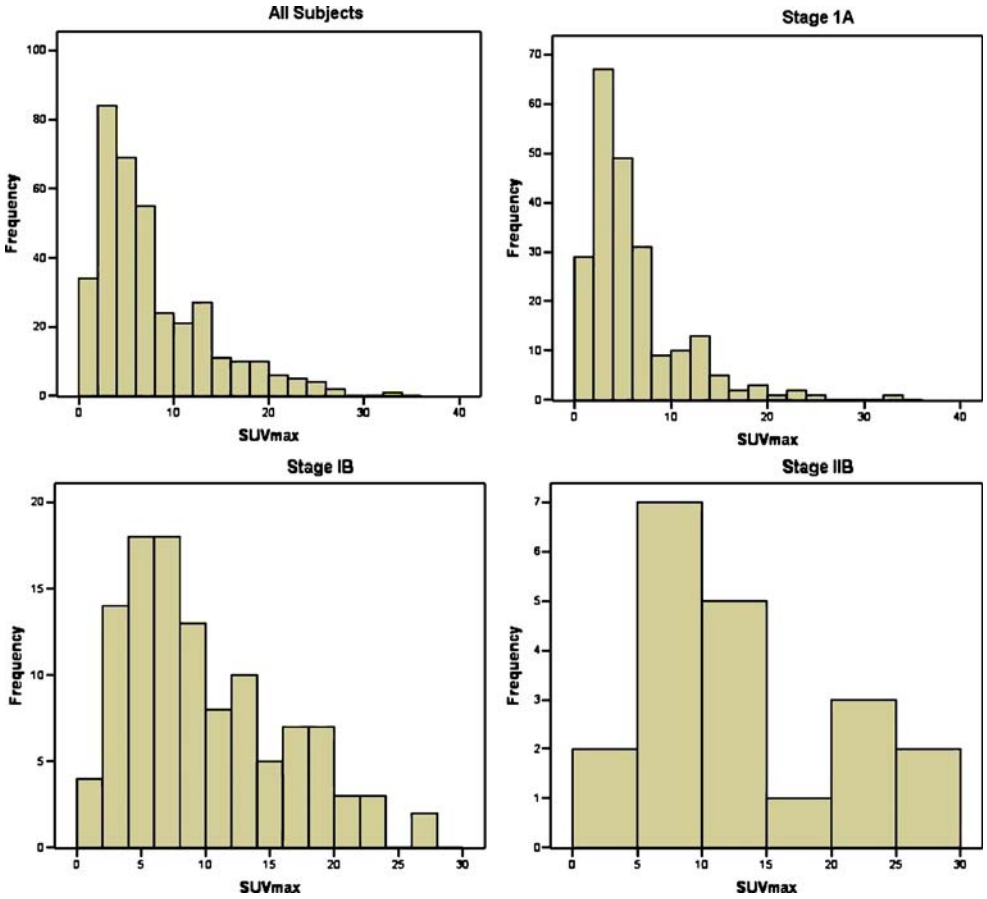

Fig. 1 Frequency distribution of SUV_{max}

The average size of all tumors was 2.6±1.8 cm (SD). The resolution reported in the method section was at 1 cm. In a realistic clinical setting, the resolution at 10 cm will be a better representation. The full-width half-maximum (FWHM) tangential resolution of PET alone camera was 4.9 mm and the radial resolution was 4.4 mm compared to that of respective resolutions of PET/CT at 5.8 and 6.6 mm. Thus, our average tumor size exceeded twice that of FWHM in both PET cameras.

Subgroup analyses

Univariate proportional hazards (Cox) regression analyses did not show any significant difference in survival by SUV_{max} when data were stratified according to the pathological stage (p=0.119, p=0.818, and p=0.882 for pTNM stages IA, IB, and IIB, respectively, Table 2).

Kaplan-Meier survival analyses also did not detect any significant survival differences in any of the pathological stage subgroups considered when patients were stratified according to the stage-specific median SUV_{max} (log-rank test, p=0.071, p=0.682, and p=0.928 for pTNM stages IA, IB, and IIB, respectively, Figs. 5, 6, and 7).

Discussion

Several studies in the past have reported that preoperative SUV is of prognostic value in early-stage (I & II) NSCLC [3–11, 14, 15]. But some recently published data have cast

Table 2 Univariate proportional hazards (Cox) regression analyses

Univariate proportional hazards (Cox) regression analyses			
	Hazard ratio (per factor of 2 increase in SUV_{max})	95.0% CI for HR	p
Stage IA	1.296	0.935–1.796	0.119
Stage IB	1.047	0.709–1.546	0.818
Stage IIB	1.054	0.528–2.105	0.882
All stages	**1.276**	**1.025–1.590**	**0.029**

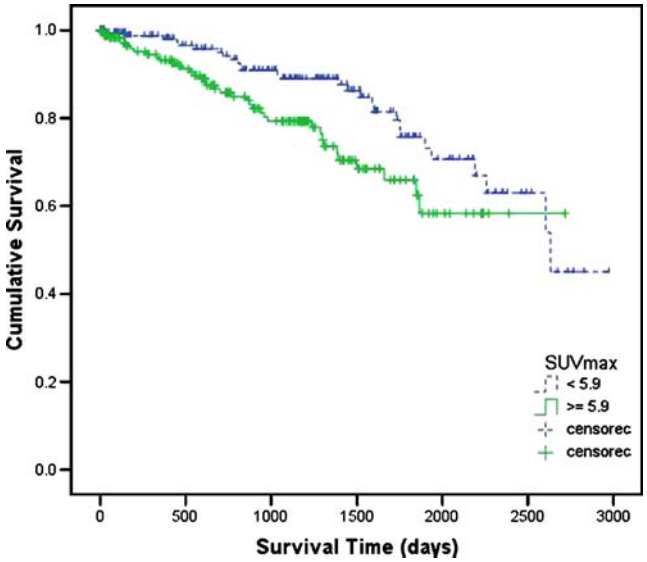

Fig. 2 Kaplan-Meier survival curves by median SUV_{max} (5.9) in all subjects (log-rank p=0.018)

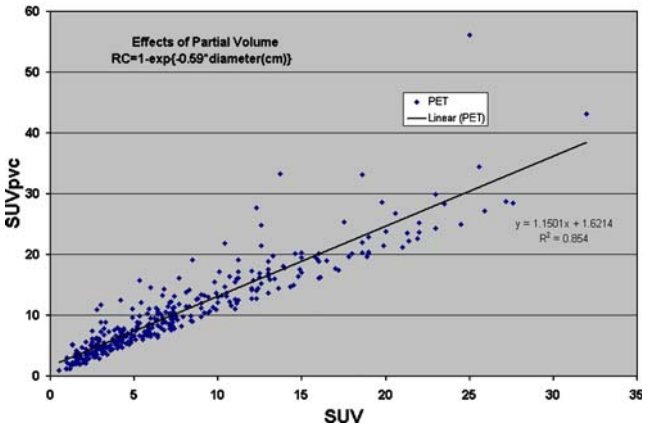

Fig. 4 Effects of partial volume

doubt on this conclusion [12, 13]. Hoang et al. [16] also reported similarly disappointing results in advanced-stage (III & IV) NSCLC. The results of the current study are consistent with these recent studies. They confirmed the observation that in early-stage (I & II) NSCLC patients with higher SUV had significantly higher risks of dying; but they also demonstrated that preoperative SUV was not an independent predictor of survival. Some studies have dichotomized age [9, 14]. This can result in significant loss of statistical power [18], which may cause underestimation of the prognostic importance of age and thus can lead to overestimation of the prognostic importance of other variables in the multivariate models. Other studies did not include age in the multivariate models [3, 4]. Tumor size was also not included in the multivariate models in many prior studies [9, 14], which has been an important prognostic factor. In addition, many of them did not control for other potential confounding factors or were limited by small sample size [5–7, 9, 15]. Some studies did not report multivariate analysis results [5, 11, 15]. It is believed that all these factors can at least partly explain the different conclusions reached.

Several studies have tried to establish optimal SUV cutoff values that differentiate between good and poor prognosis groups in NSCLC. Numerous cutoffs have been suggested. These cutoffs have ranged from 4.3 to 10 [3, 4, 6, 7, 9, 10, 12, 13]. But this approach has the risk of artificial reduction in p values and overestimation of prognostic significance [19]. These cutoff points may be data specific and can also introduce a statistical artifact known as the Will Rogers phenomenon [20]. This has made comparison between different studies difficult. Prior studies have tried dichotomi-

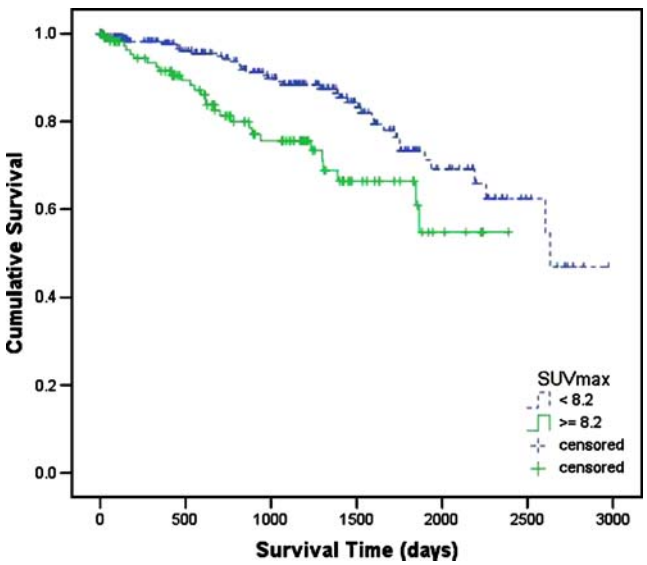

Fig. 3 Kaplan-Meier survival curves by optimal cutoff SUV_{max} (8.2) in all subjects (log-rank p=0.004)

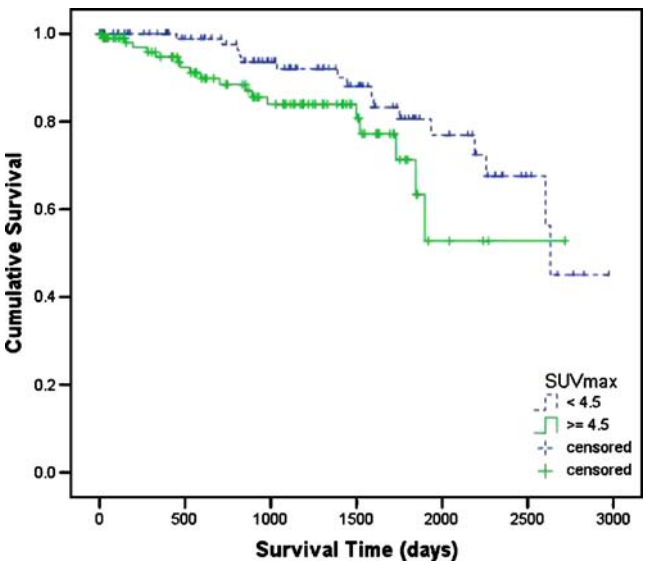

Fig. 5 Kaplan-Meier survival curves by median SUV_{max} (4.5) in stage IA patients (log-rank p=0.071)

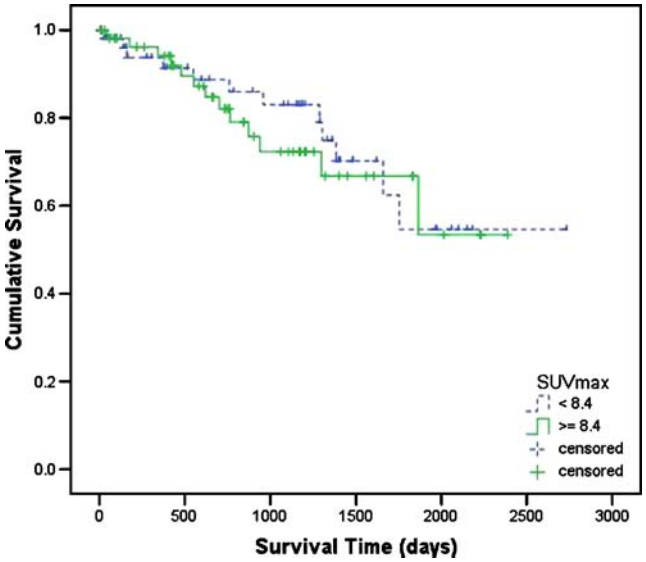

Fig. 6 Kaplan-Meier survival curves by median SUV_{max} (8.4) in stage IB patients (log-rank $p=0.682$)

zation by median split [8, 14, 15], which can result in significant loss of statistical power and therefore might not be suitable for estimation of prognosis [18]. A few authors have tried grouping subjects into more than two groups [5, 11]. The present study analyzed SUV_{max} as a continuous variable in early-stage (I & II) NSCLC. This prevented the introduction of all the biases associated with dichotomization and results in maximal statistical power. Another strength of the current study was the exclusion of patients who had received any adjuvant or neoadjuvant chemotherapy or radiation therapy. This avoided the profound confounding effect of multiple treatment protocols. Also the current study population was one of the largest reported to date allowing statistical analyses for adjustment for potential confounders. Moreover, to facilitate comparison with prior studies, additional analyses after dichotomization of SUV_{max} at both optimal cutoff value and median SUV_{max} were performed. All three methods produced similar results. Therefore, we believe that our results are valid and generalizable. Although no sharp natural binary cutoff likely exists, the higher the preoperative SUV_{max}, the higher the probability of death.

Subgroup analyses

Recently Hannin et al. [15] reported that in stage I high SUV_{max} was associated with significantly decreased overall survival. In this study stage I was not subclassified into stages IA and IB. The current study demonstrated that SUV_{max} would lose its prognostic value after stratification according to pathological staging into IA, IB, and IIB. The current results are consistent with those reported by Downey et al. [13]. In their study prediction of survival by SUV_{max} was not found to be independent of pathological staging in early-stage NSCLC. In fact, in our study when pTNM stage subgroups IA and IB were combined, univariate proportional hazards (Cox) regression analysis and Kaplan-Meier survival analysis did detect significant survival differences. Thus, the findings of Hannin et al. may be due to the combining of stages IA and IB cancers. Cerfolio et al. [10] also reported a very significant ($p<0.001$) difference in overall survival when all patients were stratified by a SUV_{max} of 10. But this p value rose dramatically in stage-specific analysis when patients were stratified by stage-specific median SUV_{max} values (p not significant, $p=0.048$, and $p=0.028$ for stages IA, IB, and II, respectively; no separate p values for stages IIA and IIB were reported). Many previous studies have used the median or optimal cutoff SUV of the combined sample for the stage-specific analysis [6, 13]. As higher stage NSCLC tumors have higher SUV [10], pathological stage distribution of the study population significantly affects the calculated median and optimal cutoff SUV of the combined sample. This has made comparison between different studies difficult. Also one SUV cutoff might not be suitable for all stages. This issue was addressed by using stage-specific median SUV_{max} for stage-specific analysis. This yielded more generalizable results. The study also showed that there was no stage-specific optimal cutoff value for pTNM stages IA, IB, or IIB with acceptable sensitivity and specificity for predicting the overall survival. This strengthens the conclusion that SUV_{max} loses its prognostic value after stratification according to pathological staging.

Limitations

One limitation of the study was the retrospective nature of the data. Also the relatively small number of stage II

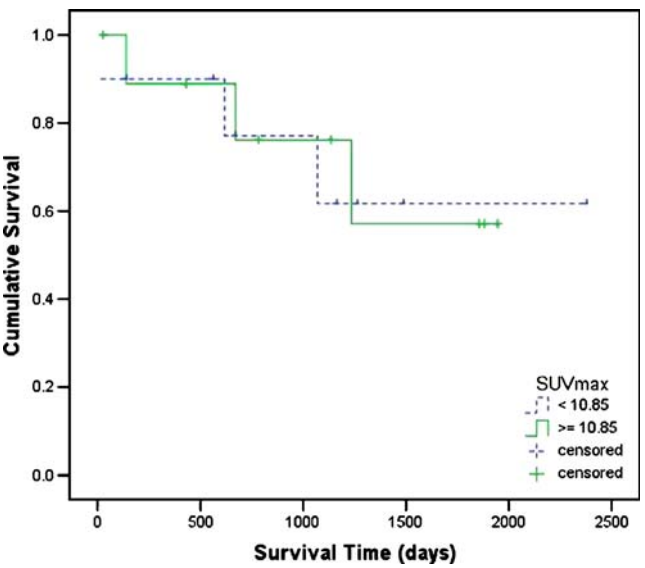

Fig. 7 Kaplan-Meier survival curves by median SUV_{max} (10.85) in stage IIB patients (log-rank $p=0.928$)

patients somewhat limited the types of statistical analyses possible. This has been a recurrent problem for studies which assessed the outcome of surgically treated early lung cancer patients [6, 9, 13]. Despite these limitations, the current study provides important insights into the prognostic importance of preoperative SUV_{max}. However, the results were complementary to a previous publication, which was one of the first investigations to declare the absence of relation between SUV and prognosis in 178 patients [21]. Until more data are available to determine this conclusively, it is prudent to avoid making any treatment decisions solely on the basis of preoperative SUV_{max} without considering other tumor and patient characteristics. Ultimately, a prospective study with even a larger sample size than the current study is needed to conduct stage-specific analyses.

Conclusion

The results demonstrate that each doubling of SUV_{max} as determined by preoperative PET is associated with a 1.28-fold increase in hazard of death in early-stage (I & II) NSCLC. Preoperative SUV_{max} is not an independent predictor of overall survival in that it loses its prognostic value in multivariate analyses and also after stratification according to pathological staging.

Funding information: The authors received no funding for this study.

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