Abstract

Objective To evaluate the relevance of high-resolution computed tomography (HRCT) findings and fluorine-18-fluorodeoxyglucose (^{18}F-FDG) uptake for risk stratification of visceral pleural invasion by lung adenocarcinoma.

Methods The HRCT findings and ^{18}F-FDG uptake for lung adenocarcinomas with pleural contact on CT were retrospectively analyzed in 208 consecutive patients (94 females and 114 males; median age, 69.0 years) between January 2009 and December 2013, with institutional review board approval. The HRCT findings and maximum standardized uptake value (SUVmax) were recorded for each patient. Multivariate logistic regression was used for statistical analysis, and subgroup analysis stratified for whole tumor size ≤ 3 cm was also performed.

Results Multivariate analysis showed that SUVmax (odds ratio [OR]: 1.09, 95% confidence interval [CI]: 1.02-1.16, P = 0.014) and obtuse angle (OR: 4.14, 95% CI: 1.97-8.74, P < 0.001) were significant independent predictors for visceral pleural invasion. Receiver operating characteristic (ROC) analysis showed that, compared with the multivariate models (area under the curve [Az]: 0.819-0.829), SUVmax alone (Az: 0.815) was useful in predicting visceral pleural invasion. In the subgroup analysis, multivariate analysis showed that SUVmax (OR: 1.29, 95% CI: 1.12-1.50, P = 0.001)

and contact length with the pleura (OR: 1.13, 95% CI: 1.05-1.22, P = 0.001) were significant independent predictors for visceral pleural invasion. ROC analysis showed that SUVmax alone (Az: 0.844) showed similar diagnostic performance to the multivariate models (Az: 0.845-0.857).

Conclusions SUVmax alone and multivariate models including SUVmax are useful for the prediction of visceral pleural invasion by lung adenocarcinoma.

Keywords Lung adenocarcinoma, Visceral pleural invasion, ^{18}F-FDG, PET/CT, HRCT

Introduction

The clinical staging of non-small-cell lung carcinoma (NSCLC) is an important factor for establishing a therapeutic plan. The diagnostic accuracy of preoperative clinical staging of lung carcinoma has been improved by advances of various imaging modalities such as ultrasonography, computed tomography (CT), magnetic resonance imaging, and fluorine-18-fluorodeoxyglucose-positron emission tomography (^{18}F-FDG PET). Independent predictors of chest wall invasion by lung carcinoma include chest pain and obvious chest wall invasion to the soft tissue or ribs on preoperative chest CT [1]. Furthermore, the diagnostic accuracy of chest wall invasion has been improved by using ultrasonography [2], CT [3, 4] and magnetic resonance imaging [5], including respiratory dynamic studies. However, no sufficiently reliable method for the preoperative diagnosis of visceral pleural invasion has been established, and its determination represents a dilemma in terms of the appropriate diagnostic gold standard.

In previous reports, tumor invasiveness, such as pleural invasion and angiolymphatic invasion, has been shown to be an independent adverse prognostic factor for NSCLC [6-8]. Visceral pleural invasion by lung carcinoma is one of the

factors increasing the T stage of tumors ≤ 3 cm in diameter according to the seventh edition of the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) classification [9].

^{18}F-FDG PET permits characterization of tumor glucose metabolism and plays an important role in the staging of various malignant tumors, including NSCLC. Higashi et al. [10], and references therein, showed that ^{18}F-FDG uptake in NSCLC correlates with tumor invasiveness and prognosis, and that the ^{18}F-FDG uptake in adenocarcinoma significantly differed from that in other NSCLC subtypes. Adenocarcinoma is the most common subtype of lung cancer and typically peripherally located. We hypothesized that visceral pleural invasion by lung adenocarcinoma would also correlate with ^{18}F-FDG uptake and that the semi-quantitative analysis of ^{18}F-FDG uptake would change the preoperative T stage regardless of the tumor size.

The aim of this study was to evaluate the relevance of high-resolution CT (HRCT) findings and ^{18}F-FDG uptake for risk stratification of visceral pleural invasion by lung adenocarcinoma with pleural contact. To our knowledge, this is the first report precisely evaluating the diagnostic performance of both HRCT and ^{18}F-FDG PET for the prediction of visceral pleural invasion by lung adenocarcinoma.

Materials and Methods

Patients

The study subjects were 208 consecutive patients with lung adenocarcinoma who were examined by both HRCT and ^{18}F-FDG PET and subsequently underwent anatomic surgical resection at our institution between January 1 2009 and December 31 2013, and who met the following criteria: (a) pathologically confirmed primary lung adenocarcinoma, (b) preoperative ^{18}F-FDG PET/CT scan at an adjacent PET center, and (c) the presence of pleural contact by the lung tumor on preoperative CT, including pleural indentation. Patients who underwent neoadjuvant chemotherapy or radiation therapy were excluded, as were patients with a history of poorly controlled diabetes or granulomatous lung diseases. The institutional review board approved this retrospective study, with waiver of the patient informed consent requirement. The clinicopathological parameters, including age, sex, histological grade (well-, moderately-, or poorly-differentiated), pleural invasion (PL0, no pleural invasion; PL1, invasion beyond the elastic layer of the visceral pleura; PL2, invasion to the visceral pleural surface; or PL3, invasion to the parietal pleura), lymphatic invasion, vascular

invasion, and lymph node metastasis, were analyzed. The histological type was determined according to the World Health Organization classification [11]. The seventh edition of the UICC TNM classification [9] was used for the staging of all tumors.

Chest CT

Chest CT was performed with one of six helical scanners: Aquilion ONE ViSION Edition (Toshiba Medical Systems, Otawara, Japan, n = 34), Aquilion 64 (Toshiba Medical Systems, n = 14), Aquilion 16 (Toshiba Medical Systems, n = 79), Aquilion 4 (Toshiba Medical Systems, n = 6), SOMATOM Definition Flash (Siemens AG, Forchheim, Germany, n = 35), and Discovery CT750 HD (GE Healthcare, Milwaukee WI, n = 40). In 178 patients, an intravenous contrast-enhancement was performed for the preoperative evaluation of the entire lung. For HRCT images of the tumors, the following parameters were used: 120 kVp, 300 mA or auto mA mode, 1-2-mm axial sections, and 2-3-mm coronal and sagittal sections, which were reconstructed by a high-spatial resolution reconstruction algorithm. All images were displayed at the lung (level, -600 HU; width, 1500 HU) and mediastinal (level, 30 HU;

width, 350 HU) window settings for the tumor evaluation. For recording of each tumor size and contact length with the pleura, the largest of the three diameters (mm) was used.

The chest CT scans were reviewed by two radiologists with 8 and 15 years experience, blinded to the clinical information. Differences in their findings were resolved by discussion and through reaching a consensus.

In reference to previous reports on chest wall invasion by lung carcinoma [12-14], the HRCT findings recorded for each patient were whole tumor size (mm), solid component size (mm), solid component ratio, contact length with the pleura (mm), pleural thickening, local pleural effusion, extrapleural fat abnormality, angle between the tumor and pleura (sharp or obtuse), rib destruction, obvious chest wall invasion, position of pleural contact (chest wall, mediastinum, or interlobar), and HRCT features (pure ground-glass opacity [GGO], mixed GGO, or solid). When the angle of the tumor with the pleura was acute and obtuse in different areas, it was classified as obtuse. Pure GGO was defined as hazy, increased opacity that did not obscure underlying vascular or bronchial structures at the lung window setting; mixed GGO was defined as GGO with a solid component; and solid was defined as a homogenous increase in pulmonary parenchymal attenuation that obscured the margins of the underlying structures. The

solid component ratio was calculated by the solid component size/whole tumor size.

^{18}F-FDG PET/CT

All ^{18}F-FDG PET/CT examinations were performed using an integrated PET/CT scanner (Biograph LS/Sensation16, Siemens, München, Germany) at an adjacent PET center. PET image acquisition started 90 min after injection of ^{18}F-FDG, with the patient in a relaxed supine position. After fasting for at least 5 h, the patients received an intravenous injection of 3.7 MBq/kg ^{18}F-FDG. The serum glucose level prior to the radiotracer injection was less than 140 mg/dl in all patients. First, a total-body low-dose CT scan for calculation of attenuation correction was performed, using a standardized protocol involving 140 kV, 12-14 mAs, a rotation time of 0.5 s, a pitch of 0.8, a section thickness of 3 mm, and a scan field from the head to the mid-thigh level. Subsequently, PET imaging consisting of 7-8 bed positions with 2.4 min per table position over the same region was immediately performed. The PET images were reconstructed with an ordered-subset expectation maximization iterative reconstruction algorithm. Integrated, co-registered PET/CT images were obtained using a workstation (PET Viewer, AZE Technology Inc., Cambridge, MA), enabling image

fusion and analysis.

For semi-quantitative analyses of ^{18}F-FDG uptake, the images were evaluated by an experienced nuclear medicine physician, blinded to the clinical and conventional evaluation results. A region of interest was drawn manually over the primary tumor on multiple axial slices. When necessary, CT was used to help localize the tumor. The maximum standardized uptake value (SUVmax) was recorded for each patient, as previous reports have shown that the differences of SUVmax between observers were lower than those for mean SUV[15]. The maximum SUVmax was obtained from the image, which have had the highest SUVmax within the primary tumor volume. The median time interval between HRCT and ^{18}F-FDG PET/CT was 13 days (0-29 days).

Statistical Analyses

A Spearman correlation coefficient was used to compare the relationship between the degree of pleural invasion and SUVmax. To determine the predictive factors for visceral pleural invasion by lung adenocarcinoma, it was analyzed using univariate analysis in relation to age, sex, SUVmax, whole tumor size, solid component size, solid component ratio, contact length with the pleura, pleural thickening, local

pleural effusion, extrapleural fat abnormality, angle, rib destruction, and obvious chest wall invasion. All covariates with a P-value < 0.10 in the univariate analyses were included in the multivariate models of HRCT findings and ^{18}F-FDG PET. Multivariate logistic regression analysis was used to estimate the P-values, adjusted odds ratios (ORs), and 95% confidence intervals (CIs) of visceral pleural invasion. Backward stepwise selection was used to obtain multivariate Model 1. The removal variables were based on likelihood ratio statistics, with a P-value < 0.10. We adjusted for age and sex (Model 2), and, finally, solid tumor size, solid component ratio, and contact length with pleura (Model 3). Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive performance of the models by assessing its discrimination (ability to correctly classify). Discrimination ability was measured by the area under the curve (Az). We evaluated the optimal cut-off and Az values of continuous variables that were significant in the multivariate regression models. Optimal cut-off values were determined to maximize the sensitivity and specificity. Additionally, we performed subgroup analysis stratified for whole tumor size ≤ 3 cm (n = 131). All analyses were performed using IBM SPSS Statistics (version 22; IBM Corp., Armonk, NY, USA), with P-values < 0.05 considered statistically significant.

Results

The clinical and pathological characteristics of all 208 patients (94 females and 114 males; median age, 69.0 years; range, 32-88 years) are provided in Table 1. All patients were diagnosed as adenocarcinoma and underwent surgical resection. Of all 208 tumors, 47 (22.6%) showed pathological pleural invasion. The median SUVmax, whole tumor size, solid component size, and contact length with the pleura were 2.87 (range, 0.5-35.3), 26.5 mm (7-112 mm), 20.0 mm (0-112 mm), and 8.0 mm (1-112 mm), respectively. No case with SUVmax ≤ 1.3 showed pleural invasion. Pleural invasion and SUVmax showed a moderate, significant correlation ($r = 0.456$, $P < 0.001$). Univariate analyses revealed significant differences in sex ($P = 0.018$), whole tumor size ($P = 0.004$), solid tumor size ($P < 0.001$), solid component ratio ($P = 0.002$), contact length with the pleura ($P < 0.001$), extrapleural fat abnormality ($P = 0.001$), angle ($P < 0.001$), and SUVmax ($P < 0.001$) between patients with and without visceral pleural invasion (Table 2). Multivariate analyses indicated both obtuse angle and SUVmax as significant independent predictors for visceral pleural invasion by lung adenocarcinoma (Table 3). ROC analyses showed that the Az values were 0.829 (95% CI: 0.759-0.899), 0.820 (95% CI: 0.749-0.891), and 0.819 (95% CI: 0.748-0.890) for Models 1-3,

respectively ($P < 0.001$ for all).

Fig. 1a shows the ROC curves of Model 1 and SUVmax alone. The optimal cut-off value of SUVmax to predict visceral pleural invasion was 4.3. Using this cut-off, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were 85.1%, 71.4%, 46.5%, 94.3%, and 74.5%, respectively. The Az value of the SUVmax was 0.815 (95% CI: 0.755-0.875; $P < 0.001$). The obtuse angle had low diagnostic performance compared with SUVmax: sensitivity, 59.6%; specificity, 80.7%; PPV, 47.5%; NPV, 87.2%; and accuracy, 76.0%.

In patients with whole tumor size ≤ 3 cm (67 females and 64 males; median age, 69.0 years; range, 32-88 years), pleural invasion was observed in 22 patients (16.8%). The median SUVmax, whole tumor size, solid component size, and contact length were 2.07 (range, 0.54-14.8), 21.0 mm (7-30 mm), 16.0 mm (0-30 mm), and 5.0 mm (1-30 mm), respectively. Univariate analyses showed that there were significant differences in whole tumor size ($P = 0.048$), solid component size ($P = 0.001$), solid component ratio ($P = 0.036$), contact length with pleura ($P < 0.001$), local pleural effusion ($P = 0.037$), extrapleural fat abnormality ($P = 0.024$), angle ($P < 0.001$), and SUVmax ($P < 0.001$) between patients with and without visceral pleural invasion (Table 4). Multivariate analyses showed that both contact length with the pleura and SUVmax

were significant independent predictors for visceral pleural invasion (Table 5). ROC analyses showed that the Az values of Models 1-3 were 0.857 (95% CI: 0.772-0.943), 0.845 (95% CI: 0.741-0.949), and 0.857 (95% CI: 0.763-0.951), respectively ($P < 0.001$ for all).

Fig. 1b shows the ROC curves of Model 1, contact length with the pleura, and SUVmax. The optimal cut-off values of contact length with the pleura and SUVmax to predict visceral pleural invasion were 12 mm and 4.3, respectively. The sensitivity, specificity, PPV, NPV, and accuracy for contact length with the pleura and SUVmax were 63.6%, 88.1%, 51.9%, 92.3%, and 84.0%; and 81.8%, 78.0%, 42.9%, 95.5%, and 78.6%, respectively. The Az values were 0.789 (95% CI: 0.675-0.903, $P < 0.001$) and 0.844 (95% CI: 0.767-0.921, $P < 0.001$), respectively.

Discussion

The results of the present study indicate that multivariate models including HRCT findings and SUVmax are useful in predicting visceral pleural invasion by lung adenocarcinoma, and that ^{18}F-FDG PET was also useful and robust in predicting visceral pleural invasion.

SUVmax has been reported to correlate with visceral pleural invasion in NSCLC [16-19]; the greater the ^{18}F-FDG uptake, the higher the proliferation and invasiveness of the tumor. Accordingly, the present study also revealed a significant correlation between pleural invasion and SUVmax. Further, other reports have shown that an extremely low SUVmax can reflect pathological non-invasiveness [20] and that no case with SUVmax $\leq$ 1.0 showed pleural invasion in clinical stage IA lung adenocarcinoma [18]. Similarly, our results also showed that pleural invasion was not seen in patients with an SUVmax $\leq$ 1.3, regardless of the tumor size. These results suggest that lung adenocarcinoma with an SUVmax of no more than approximately 1.0 is not at risk of visceral pleural invasion, with high specificity. Moreover, the optimal cut-off value of SUVmax was determined as 4.3, with acceptable accuracy. No previous reports have evaluated the optimal cut-off value of SUVmax for visceral pleural invasion by using ROC analysis. Moreover, we showed significant differences between the SUVmax of patients with and without visceral pleural invasion in both the univariate and multivariate analyses. Hence, we considered that such a cut-off has the potential to predict pathological pleural invasion preoperatively. However, SUVmax is influenced by the spatial resolution of PET scanner, and differences in the PET protocol and equipment between facilities [17]. Standardized SUVmax will therefore need to be

established before the optimal cut-off values of SUVmax can be used as a diagnostic tool.

Williford et al. reported that an obtuse angle of the tumor with the pleura was the most helpful sign for predicting pleural involvement on 10-mm thickness CT images, although the study subjects in their report included various lung and pleural diseases [21]. Herein, obtuse angle of the tumor with pleura was an independent predictor of visceral pleural invasion by lung adenocarcinoma in all study subjects; however, the diagnostic performance was relatively poor, and this factor was not an independent predictor in the subgroup analysis of lesions ≤ 3 cm. This result indicates that the presence of an obtuse angle of the tumors with pleura may not contribute to the preoperative T stage of lung adenocarcinoma. Additionally, multivariate analyses showed that the contact length with pleura in lesions ≤ 3 cm was also an independent predictor of visceral pleural invasion by lung adenocarcinoma. This factor showed better diagnostic performance than the obtuse angle of the tumors with pleura, and was considered reliable for the prediction of visceral pleural invasion compared with our other HRCT findings. However, ROC analysis in the lesions ≤ 3 cm showed that the differences in the Az values between multivariate Model 1 and SUVmax were minimal, suggesting that SUVmax contributed to multivariate Model 1 more than the contact

length with pleura.

For the evaluation of chest wall invasion by lung cancer, Glazer et al. reported that contact length with pleura > 3 cm and pleural thickening were very sensitive, but not specific, CT signs of chest wall invasion [12]. However, pleural thickening was not an independent predictive factor in our multivariate analyses and was not a sensitive HRCT sign of visceral pleural invasion. However, it should be noted that the previous reports evaluated these factors using 10-mm thickness CT images [12], and were unable to rigorously differentiate pleural thickening from other HRCT findings such as extrapleural fat abnormality and local pleural effusion due to the spatial resolution. Conversely, we evaluated all tumors on 1-3-mm thickness HRCT images, which yielded a more precise analysis of the pleural and lung structures. These slice thickness differences were thought to be one of the reasons for the discrepancies in the results. Further, other reports have shown that the degree of solid component on chest CT was more highly relevant to the pathological invasiveness and prognosis than the total tumor size [22-24], whereas our results showed that SUVmax was a more reliable predictive factor of visceral pleural invasion than the solid component size and ratio on HRCT. In fact, SUVmax contributed the most to the multivariate models, and the present study demonstrated that the diagnostic performance for visceral pleural invasion could be

improved by using SUVmax values as a reference in addition to HRCT findings such as the contact length with the pleura and degree of solid component.

Nonetheless, the present study has certain limitations. First, this was a retrospective, single-center study. Second, the number of lesions with pleural invasion might be underestimated because tumors treated with preoperative therapy, which might have invaded the visceral pleura, were excluded. Finally, even though the slice thickness was quite thin, the chest CT images were obtained by various helical scanners. Therefore, further multi-institutional prospective studies including advanced-stage lung carcinoma patients are necessary to confirm the diagnostic capacity of HRCT and ^{18}F-FDG PET. Despite these limitations, we demonstrated that SUVmax might have the potential to differentiate between patients with or without visceral pleural invasion by lung adenocarcinoma.

In conclusion, SUVmax was found to be an independent predictor of visceral pleural invasion by lung adenocarcinoma, and we estimated the optimal cut-off value of SUVmax with acceptable accuracy. SUVmax alone and multivariate models including SUVmax are useful for the prediction of visceral pleural invasion by lung adenocarcinoma. Furthermore, contact length with the pleura was also an independent predictor of visceral pleural invasion by lung adenocarcinoma in lesions $\leq$ 3 cm.

SUVmax and contact length with pleura may have an influence on the preoperative T staging of lung adenocarcinoma.

Conflict of interest No potential conflicts of interest were disclosed

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Figure Legends

Fig. 1 Graphs showing receiver operating characteristics curves and the corresponding area under the curve (Az) values for multivariate logistic Model 1 and the maximum standardized uptake value (SUVmax) in all tumors (a), and for multivariate logistic Model 1, the SUVmax, and the contact length with the pleura in tumors ≤ 3 cm (b) for the prediction of visceral pleural invasion by lung adenocarcinoma.

Tables

Table 1: Characteristics of 208 study subjects

	N	(%)
Age, years, mean, (SD)	68.0	(10.7)
Sex		
Female	94	(45.2)
Male	114	(54.8)
Tumor location		
Chest wall	163	(78.4)
Mediastinum	16	(7.7)
Interlobar	29	(13.9)
CT feature		
pure GGO	27	(13.0)
mixed GGO	85	(40.9)
solid	96	(46.1)
Histological grade		
Well-differentiated	132	(63.5)
Moderately-differentiated	51	(24.5)
poorly-differentiated	25	(12.0)
Pleural invasion		
PL0	161	(77.4)
PL1	31	(14.9)
PL2	5	(2.4)
PL3	11	(5.3)
Lymphatic invasion		
Negative	175	(84.1)
Positive	33	(15.9)
Vascular invasion		
Negative	177	(85.1)
Positive	31	(14.9)
Lymph node metastasis		
Negative	188	(90.4)
Positive	20	(9.6)

SD standard deviation, *GGO* ground-glass opacity, *PL* pleural invasion

Table 2: ^{18}F-FDG and CT findings with risk of pleural invasion by lung adenocarcinoma, all 208 subjects

Variables	No Pleural Invasion (n =161)		Pleural Invasion (n =47)		OR	(95% CI)	*P*-value
	N	(%)	N	(%)			
Age (years), mean, (SD)	67.9	(10.6)	68.4	(11.0)	1.00	(0.97-1.04)	0.781
Sex							
Female	80	(49.7)	14	(29.8)	1.00	—	—
Male	81	(50.3)	33	(70.2)	2.33	(1.16-4.68)	0.018*
SUVmax	2.08	(0.5-35.3)	7.64	(1.4-30.5)	1.14	(1.08-1.22)	<0.001*
Whole tumor size (mm)	25.0	(7-112)	34.0	(13-80)	1.03	(1.01-1.05)	0.004*
Solid component size (mm)	18.0	(0-112)	30.0	(6-80)	1.04	(1.02-1.06)	<0.001*
Solid component ratio	1.00	(0-1.00)	1.00	(0.27-1.00)	38.36	(3.67-400.58)	0.002*
Contact length with pleura (mm)	5.0	(1-112)	19.0	(1-80)	1.04	(1.02-1.06)	<0.001*
Pleural thickening							
Negative	157	(97.5)	43	(91.5)	1.00	—	—
Positive	4	(2.5)	4	(8.5)	3.57	(0.99-12.92)	0.053
Local pleural effusion							
Negative	145	(90.1)	40	(85.1)	1.00	—	—
Positive	16	(9.9)	7	(14.9)	1.59	(0.61-4.12)	0.344
Extrapleural fat abnormality							
Negative	157	(97.5)	39	(83.0)	1.00	—	—
Positive	4	(2.5)	8	(17.0)	8.05	(2.31-28.11)	0.001*
Angle							
Sharp	130	(80.7)	19	(40.4)	1.00	—	—
Obtuse	31	(19.3)	28	(59.6)	6.18	(3.06-12.47)	<0.001*
Rib destruction							
Negative	161	(100.0)	45	(95.7)	1.00	—	—
Positive	0	(0.0)	2	(4.3)			
Obvious chest wall invasion							
Negative	161	(100.0)	45	(95.7)	1.00	—	—
Positive	0	(0.0)	2	(4.3)			

Mean and SD for age, median and range for other continuous variables, number and percentage for dichotomous variables

SD standard deviation, *SUVmax* maximal standardized uptake value, *OR* odds ratio, *CI* confidence interval, * $P < 0.05$

Table 3: Significant Predictors of pleural invasion by lung adenocarcinoma, all 208 subjects

Variable	Model 1[a]			Model 2[b]			Model 3[c]		
	OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value
SUVmax	1.09	(1.02-1.16)	0.014*	1.09	(1.02-1.16)	0.016*	1.09	(1.01-1.17)	0.031*
Angle (Obtuse=1)	4.14	(1.97-8.74)	<0.001*	4.15	(1.89-9.08)	<0.001*	4.45	(1.59-12.44)	0.004*
Solid component ratio	9.32	(0.92-94.40)	0.059	9.06	(0.89-92.39)	0.063	8.90	(0.78-102.17)	0.079
Age				0.99	(0.96-1.02)	0.524	0.99	(0.96-1.02)	0.521
Sex (Male=1)				1.16	(0.51-2.64)	0.719	1.18	(0.51-2.72)	0.695
Solid component size							1.00	(0.96-1.05)	0.928
Contact length with pleura (mm)							1.00	(0.96-1.04)	0.854

SUVmax maximal standardized uptake value, *OR* odds ratio, *CI* confidence interval, * $P < 0.05$

[a] *Model 1* backward stepwise selection, variables excluded by the stepwise procedure for model 1 were sex, whole tumor size, solid component size, contact length with pleura, pleural thickening and extrapleural fat abnormality.

[b] *Model 2* Model 1 adjusted for sex and age.

[c] *Model 3* Model 2 adjusted for solid component size and contact length with pleura.

Table 4: ^{18}F-FDG and CT findings with risk of pleural invasion by lung adenocarcinoma, 131 subjects with whole tumor size ≤ 3 cm

Variables	No Pleural Invasion (n =109)		Pleural Invasion (n =22)		OR	(95% CI)	*P*-value
	N	(%)	N	(%)			
Age (years), mean, (SD)	67.7	(10.5)	67.5	(12.2)	0.998	(0.96-1.04)	0.923
Sex							
Female	57	(52.3)	10	(45.5)	1.00	—	—
Male	52	(47.7)	12	(54.5)	1.32	(0.52-3.30)	0.559
SUVmax	1.57	(0.5-13.5)	5.72	(1.4-14.8)	1.37	(1.20-1.58)	<0.001*
Whole tumor size (mm)	20.0	(7-30)	23.5	(13-30)	1.09	(1.00-1.18)	0.048*
Solid component size (mm)	15.0	(0-29)	23.5	(6-30)	1.15	(1.06-1.24)	0.001*
Solid component ratio	1.00	(0-1.00)	1.00	(0.27-1.00)	39.86	(1.28-1242.77)	0.036*
Contact length with pleura (mm)	1.0	(1-25)	15.5	(1-30)	1.17	(1.10-1.26)	<0.001*
Pleural thickening							
Negative	109	(100.0)	21	(95.5)	1.00	—	—
Positive	0	(0.0)	1	(4.5)			
Local pleural effusion							
Negative	101	(92.7)	17	(77.3)	1.00	—	—
Positive	8	(7.3)	5	(22.7)	3.71	(1.09-12.70)	0.037*
Extrapleural fat abnormality							
Negative	107	(98.2)	19	(86.4)	1.00	—	—
Positive	2	(1.8)	3	(13.6)	8.45	(1.32-53.97)	0.024*
Angle							
Sharp	93	(85.3)	10	(45.5)	1.00	—	—
Obtuse	16	(14.7)	12	(54.5)	6.98	(2.58-18.82)	<0.001*
Rib destruction							
Negative	109	(100.0)	22	(100.0)	1.00	—	—
Positive	0	(0.0)	0	(0.0)			
Obvious chest wall invasion							
Negative	109	(100.0)	22	(100.0)	1.00	—	—
Positive	0	(0.0)	0	(0.0)			

Mean and SD for age, median and range for other continuous variables, number and percentage for dichotomous variables

SD standard deviation, *SUVmax* maximal standardized uptake value, *OR* odds ratio, *CI* confidence interval, * $P < 0.05$

Table 5: Significant Predictors of pleural invasion by lung adenocarcinoma, 131 subjects with whole tumor size ≤ 3 cm

Variable	Model 1[a]			Model 2[b]			Model 3[c]		
	OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value
SUVmax	1.29	(1.12-1.50)	0.001*	1.32	(1.13-1.53)	0.001*	1.34	(1.09-1.64)	0.005*
Contact length with pleura (mm)	1.13	(1.05-1.22)	0.001*	1.14	(1.06-1.24)	0.001*	1.16	(1.06-1.26)	0.001*
Age				0.99	(0.93-1.04)	0.602	0.99	(0.94-1.04)	0.608
Sex (Male=1)				0.52	(0.15-1.80)	0.302	0.42	(0.11-1.60)	0.203
Solid component size							0.94	(0.82-1.09)	0.415
Solid component ratio							10.18	(0.22-476.28)	0.237

SUVmax maximal standardized uptake value, *OR* odds ratio, *CI* confidence interval, * $P < 0.05$

a *Model 1* backward stepwise selection, variables excluded by the stepwise procedure for model 1 were whole tumor size, solid component size, solid component ratio, local pleural effusion, extrapleural fat abnormality and angle.

[b] *Model 2* Model 1 adjusted for sex and age.

[c] *Model 3* Model 2 adjusted for solid component size and solid component ratio.