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ORIGINAL ARTICLE

Correlation between combining ^{18}F–FDG PET/CT metabolic parameters and other clinical features and ALK or ROS1 fusion in patients with non-small-cell lung cancer

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Abstract

Purpose Our study intended to explore the association between combining ^{18}F–FDG PET/CT metabolic parameters and other clinical features and anaplastic lymphoma kinase (ALK) or c-ros oncogene 1 (ROS1) fusion in non-small-cell lung cancer (NSCLC).

Methods Eight hundred and six patients with wild-type epidermal growth factor receptor (EGFR) mutation were screened for ALK or ROS1 fusion and subjected to ^{18}F–FDG PET/CT prior to treatment at our hospital. The associations between ALK or ROS1 fusion and clinical characteristics and the PET/CT parameters were analyzed. Multivariate logistic regression analysis was performed to explore independent deterministic factors associated with ALK and ROS1 fusion.

Results Eighty-two patients (11.7%) with ALK fusion were found. Multivariate analysis demonstrated that high pSUVmax ≥ 10.6, low primary tumor lesion glycolysis (pTLG) < 101.8, young age, nonsmoker status, and high carcinoembryonic antigen (CEA) level correlated with ALK fusion in NSCLC. The receiver operating characteristic (ROC) curve yielded the area under curve (AUC) values of 0.603 and 0.873 for high pSUVmax alone and the combination of the five factors, respectively. Twenty-six patients (5.6%) with ROS1 fusion were found. Multivariate analysis revealed that high pSUVmax ≥ 8.8, young age, and nonsmoker status correlated with ROS1 fusion in NSCLC. The ROC curve yielded AUC values of 0.662 and 0.813 for high pSUVmax alone and the combination of the three factors, respectively.

Conclusion The study indicated that combining ^{18}F–FDG PET/CT metabolic parameters and other clinical parameters were correlated with ALK and ROS1 mutation in NSCLC patients and may help to refine the process of optimal patient selection to gene test for targeted therapy.

Keywords Anaplastic lymphoma kinase · C-ros oncogene 1 · Non-small cell lung cancer · Standard uptake value · Total lesion glycolysis

Introduction

Non-small-cell lung cancer (NSCLC) leads to one of the major causes of cancer mortality in the world, which accounts for a proportion of lung cancer [1]. Several genetic alterations have been founded in lung carcinoma, which may be specific targets for personalized treatment [2]. Recently, anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) have been found as driver genes in NSCLC patients [3]. The fusion rate of echinoderm microtubule-associated protein-like 4 (EML4) gene and ALK gene is 2–7% in NSCLC patients [4]. Several clinical studies have revealed that NSCLC patients with ALK fusion have remarkable and rapid response to crizotinib therapy [5, 6]. These studies recommend molecular identification as the standard treatment procedure for

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advanced NSCLC patients [7]. Additionally, *ROS1* shares a significant amino acid homology to the kinase domain of ALK as a receptor tyrosine kinase of the insulin receptor family [8], and ROS1 rearrangement is occurring in 1–2% of lung cancer patients [9]. In the East Asian population, the incidence is slightly higher with a frequency of 2% to 3% [10]. Several clinical researches have revealed that crizotinib has a response rate of 72–80% with NSCLC patients harboring ROS1 fusion [11, 12]. Based on these inspirational results, the American, Japanese, and Chinese authorities have approved crizotinib for NSCLC patients with ROS1 fusion treatment.

Due to promising studies of crizotinib therapy for NSCLC patients with ALK or ROS1 fusion, attention should be paid to the accurate and economical identification of ALK or ROS1 fusion patients. To effectively screen and differentiate NSCLC patients with ALK or ROS1 fusion, the specific features of ALK or ROS1 fusion tumor need to be adequately defined. However, multiple hurdles such as costs, feasibility of tissue examination, and limited sensitivity of serum molecular testing hinder the widespread identification of NSCLC patients with ALK or ROS1 fusion [13].

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scan is currently one of important imaging modalities in lung cancers diagnosis and staging which is based on different ^{18}F–FDG PET metabolic levels. Many researches have revealed correlation between maximal standardized uptake value (SUVmax) and cancer biologic characteristics including proliferation, histologic type, tumor differentiation, and hypoxia [14]. SUVmax is also correlated with genetic mutations, and it is revealed that lung cancers with epidermal growth factor receptor (EGFR) mutation have specific SUVmax pattern [15, 16]. Previous studies concerning the correlation between SUVmax and ALK fusion are conflicting and unconvincing with small samples [13, 17–19], and little is known about the association between SUVmax and ROS1 fusion. However, the usefulness of SUVmax may be limited because it only represents a value of single voxel and not adequately reflects the entire tumor burden. Therefore, experts are interested in volume-based PET measurements of metabolic tumor volume (MTV) and tumor lesion glycolysis (TLG) because they can measure the burden of metabolic tumors by combining metabolic activity and volume data [20]. In addition, MTV and TLG have been considered as prognostic factors in patients with NSCLC [21]. And rare reports reveal the associations between volumetric parameters of MTV and TLG and ALK or ROS1 fusion before.

Tumor markers widely apply to diagnose and monitor treatment response and recurrence in NSCLC [16, 22]. However, few reports had studied the association between combining ^{18}F–FDG PET/CT metabolic parameters and other clinical features and ALK or ROS1 fusion in NSCLC. Thus, we try to conduct this retrospective study to explore these parameters and evaluate the association with ALK and ROS1 fusion in NSCLC.

Materials and methods

Study population and inclusion criteria

We retrospectively reviewed all 9741 patients with NSCLC who underwent PET/CT examination at Shanghai Chest Hospital from August 2016 to August 2018 to select patients with ALK or ROS1 status. Eight thousand nine hundred and thirty-five patients' exclusion reasons are as follows: history of other malignant tumor (unless more than 5 years of disease-free state); preoperative anticancer therapy, such as radiotherapy and chemotherapy; no ALK or ROS1 detection after operation; patients with primary tumor lesion less than 1 cm in diameter, which may lead to errors in PET/CT imaging due to a partial volume effect. And we analyzed the metabolic feature of metastatic lymph nodes with enlarged lymph nodes (short diameter more than 1 cm) to reduce partial volume effect. Besides, patients with ALK or ROS1 status were chosen and routinely recommended for NSCLC patients with EGFR wild-type. Ultimately, a total of 806 patients were selected in this study. Patient clinical features including age, sex, smoking history, histopathology, tumor size, SUVmax, MTV, TLG of primary tumor, nodal and metastases lesions, tumor involvement, nodal involvement, distant metastasis, tumor stage, and tumor markers were analyzed. Patients who never smoked or smoked less than 100 cigarettes totally were considered as nonsmokers. The rest were defined as ever smokers. Tumor node metastasis (TNM) staging was on the basis of the IASLC 8th TNM Lung Cancer Staging System. PET/CT or other imaging studies detection of lymph nodes and metastases confirmed by pathology was used to determine cancer stage. When pathologic diagnosis was unavailable for suspicious lesions, the lesions were follow-up for over 6 months; metastasis was decided when a lesion had progression or remission on follow-up examinations which were consistent with the primary lung lesion response.

Imaging and interpretation

Patients were injected intravenously 5 MBq per kg ± 10% of ^{18}F-FDG after fasting for at least 6 h with blood glucose level < 180 mg/dl. They were all scanned on the only one scanner of a combined PET/CT scanner (Siemens Biograph 64). Same scanner model, protocol for acquisition and reconstruction software, was used for all patients. All scans were started 60 ± 10 min after injection. During image examination, attenuation correction was conducted by a CT scan first, and an emission scan was consecutively inspected from the skull base to the proximal thigh. PET/CT was analyzed for ^{18}F-FDG uptake of lesions by semiquantitative method by 2 attending nuclear medicine physicians who were blinded to the ALK or ROS1 status. Discrepant results were resolved by consensus review. For the semiquantitative analysis, functional images of the

standardized uptake value (SUV) were obtained using attenuation-corrected transaxial images, the injected doses of ^{18}F-FDG, the patient's body weight, and the cross-calibration factor between PET and the dose calibrator. SUV was defined as follows: SUV = tissue concentration (MBq/g)/ [injected dose (MBq)/body weight(g)]. We used Siemens syngo.via software to automatically calculate the MTV and TLG (defined as MTV multiplied by SUV_{mean}) of each lesion by using SUV thresholds of 2.5, which has been widely approved for NSCLC [23]. According to the PERCIST recommendations [24, 25], the measurement of total lesion glycolysis measured using a systemic approach (TLG-S) was based on the delineation of target lesions (two or fewer lesions per organ, with a maximum of five lesions), and the sum of metabolic tumor volume (MTV-S) was defined as the sum of target lesions MTV. Considering the discrepancies in genetic alterations and the SUV differences between primary and metastatic tumors [26–28], all SUVmax and volume-based PET/CT parameter MTV and TLG of primary lesion, nodal metastasis, and distant metastasis were measured separately to explore the associated factors with ALK or ROS1 fusion gene, in addition to whole-body metrics.

Mutational analysis and tumor marker analysis

Tumor samples acquired by either surgical or diagnostic approaches were used for detection of ALK or ROS1 status. ROS1 fusion was tested by quantitative real-time (qRT)-PCR, and immunohistochemistry (IHC) analysis was conducted to test ALK fusion using a monoclonal D5F3 antibody (Ventana Medical Systems, Tucson, AZ, USA). Fluorescence in situ hybridization (FISH) was conducted to confirm the results when the results of (qRT)-PCR or IHC detection were uncertain. Blood samples were collected before surgery, and tumor markers of cancer antigen 199(CA199), carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCCA), neuron specific enolase (NSE), and cancer antigen 125(CA125) were tested in the clinical laboratory of our hospital.

Statistical analysis

^{18}F–FDG PET/CT metabolic parameters and other clinical features of the ALK or ROS1 status were compared using the chi-square test, student's t test, and non-parametric Wilcoxon rank sum test. A two-sided p value < 0.05 was considered as statistically significant. Receiver operating characteristics (ROC) curves were conducted to acquire the cutoff value of the primary tumor SUVmax (pSUVmax), primary tumor TLG (pTLG), and TLG-S for exploring the association with the ALK or ROS1 fusion. The value best discriminating the maximum sensitivity and specificity between the 2 groups was defined as the optimum cutoff point. Independent deterministic factors of the ALK or ROS1 status were analyzed by logistic regression analysis. Clinical parameters association with ALK or ROS1 status with the value of $p < 0.2$ in the univariate analysis were further analyzed by multivariate regression analysis. Independent deterministic factors were regarded as variates with $p < 0.05$ in the multivariate analysis. The combined independent deterministic factors association with ALK or ROS1 fusion were analyzed by ROC curves. All results were conducted using the SPSS software (version 16.0; SPSS, Chicago, IL, USA).

Results

Among the 806 NSCLC patients with wild-type EGFR were tested for ALK and ROS1 status in our hospital between August 2016 and August 2018. Six hundred and ninety-nine patients were tested for ALK, 462 patients were tested for ROS1, and 355 patients were tested for both ALK and ROS1. The clinical characteristics are summarized in Tables 1 and 2 according to whether the patients were tested for ALK or ROS1.

Association between ^{18}F–FDG PET/CT metabolic parameters and other clinical features and ALK status

Eighty-two (11.7%) were positive for ALK in the 699 patients tested for ALK. The ALK fusion NSCLC patients were found more frequently in younger age (53.37 ± 11.92 vs. 63.94 ± 9.11; $p = 0.001$). Positive ALK expression was found only in the ADC patients (82/82 vs. 371/617; $p = 0.001$) (Table 1). ALK fusion and ALK wild-type groups had significantly difference in sex and smoking history with female predilection (51.2% vs. 48.8%) and nonsmokers (73.2% vs. 28.8%). Moreover, positive ALK expression was found in TTF-1(97.6%), and CK (100%) positive NSCLC patients, while positive expression of ALK was only observed in P40 (6.1%) and CD56 (2.4%) positive NSCLC patients. The pSUVmax (12.56 ± 7.06 vs. 10.46 ± 7.51; $p = 0.017$) was significantly higher in the ALK fusion group than in the ALK wild-type group. And, primary tumor MTV (pMTV) (26.7 ± 36.13 vs. 74.82 ± 119.47; $p < 0.001$), pTLG (171.74 ± 243.56 vs. 555.42 ± 936.35; $p < 0.001$), the MTV-S (48.65 ± 56.38 vs. 94.37 ± 134.16; $p = 0.03$), and TLG-S (301.82 ± 348.73 vs. 688.24 ± 1051.21; $p = 0.01$) were significantly lower in the ALK fusion group than in the ALK wild-type group, respectively. Besides, the distant metastases SUVmax (mSUVmax) (13.45 ± 6.72 vs. 11.88 ± 7.40; $p = 0.056$) was marginally higher in the ALK fusion group than in the ALK wild-type group, while the tumor size, nodal metastases SUVmax (nSUVmax), nodal metastases MTV (nMTV), nodal metastases TLG (nTLG), distant metastases MTV (mMTV), and distant metastases TLG (mTLG) between the two groups were not significantly different. Additionally, the

tumor, nodal, metastasis, and stage distribution between the two groups were not significantly different. The value of cancer antigen 199 (CA199) (5.64 ± 21.56 vs. 10.15 ± 22.46; p = 0.001) was significantly lower in the ALK fusion patients than in the ALK wild-type patients. While the value of carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCCA), neuron specific enolase (NSE), and cancer antigen 125(CA125) between the two groups were not significantly different.

When the ADC group was separately analyzed (Table 2), the value of mSUVmax was significantly related with positive ALK group, while the expression of P40 was not significantly related with positive ALK group (Table 2). The other results were similar with those of the NSCLC groups.

Association between ^{18}F–FDG PET/CT metabolic parameters and other clinical features and ROS1 status

The clinical characteristics of the NSCLC patients are summarized in Table 1 on the basis of the ROS1 status. Of the 462 patients tested for ROS1, 26 (5.6%) were positive for ROS1. ROS1 fusion were found more frequently in younger age (55.62 ± 12.21 vs. 64.17 ± 9.23; p = 0.002), female predilection (57.7% vs. 42.3%; p = 0.001), nonsmokers (65.4% vs. 27.8%; p = 0.001), and ADCs (100.0% vs. 56.9%; p = 0.001). Positive expression of TTF-1 (100.0% vs. 56.7%; p = 0.001) and negative expression of IHC marker P40 (0.0% vs. 35.8%; p = 0.001) were significantly associated with ROS1 fusion, while the expression of CK and CD56 between the two groups were not significantly different. The PET parameter of pSUVmax (12.91 ± 4.93 vs. 10.43 ± 7.75; p = 0.005) was significantly higher in the ROS1 fusion NSCLCs than in the ROS1 wild-type NSCLCs, while the other clinical features between the two groups were not significantly different.

When the ADC group was separately analyzed (Table 2), high $nSUV_{max}$ (11.14 ± 7.98 vs. 8.17 ± 7.55; p = 0.049) and low CEA value (5.41 ± 6.70 vs. 35.56 ± 81.01; p = 0.004) were significantly related with positive ROS1 expression (Table 2). The expression of IHC marker P40 was not significantly associated with ROS1 fusion. The other results were similar with those of the NSCLC groups.

Comparison ^{18}F–FDG PET/CT metabolic parameters and other clinical features between ALK fusion and ROS1 fusion

None patient harbored coexisting ALK/ROS1 fusion in the present study. When positive ALK and ROS1 group were separately analyzed to compare their clinical characteristics (Table 1), the CEA value were significantly higher in the ALK fusion group (36.30 ± 94.01 vs. 5.41 ± 6.70; p = 0.004) than in the ROS1 fusion group, while the pMTV value were significant lower in the ALK fusion group (26.7 ± 36.13 vs. 65.26 ± 124.03; p = 0.035) than in the ROS1 fusion group. And the pTLG was lower in the ALK fusion group than in the ROS1 fusion group (171.74 ± 243.56 vs. 376.16 ± 678.33), with a marginal p value with 0.051. Besides, the nSUVmax was lower in the ALK fusion group than in the ROS1 fusion group (7.92 ± 7.29 vs. 11.14 ± 7.98), with a marginal p value with 0.058. The other results were not statistically significant between two groups.

Exploring independent deterministic factors of ALK mutation

Univariate regression showed that age, sex, smoking status, pSUVmax, pTLG and TLG-S were statistically significant variates that were correlated with positive ALK expression in the NSCLC group (Table 3). In the multivariate analysis, young age (OR, 0.924; p = 0.001), never smoker (OR, 6.040; p = 0.001), high pSUVmax level (OR, 7.395; p = 0.001), low pTLG (OR, 3.974; p = 0.001), and high CEA value (OR, 1.003; p = 0.024) were the independent deterministic factors of ALK fusion, while the sex status, TLG-S, and CA199 level were not correlated with ALK status. Additionally, a ROC curve analysis was used to analyze the value of these factors (Fig. 1). ROC curve analysis revealed cutoff points for pSUVmax, pTLG, and TLG-S of 10.6, 101.8, and 848.5, with AUCs of 0.603, 0.657, and 0.61 with p value of 0.031, 0.001, and 0.001, respectively. When the five factors (age, smoking status, pSUVmax, pTLG, and CEA) were used together, the AUC was 0.873 with p value of 0.02.

When 453 ADC patients were separately analyzed, the univariate regression showed that age, sex, smoking status, pSUVmax, pTLG, and TLG-S were statistically different between ALK fusion group and wild type ALK group (Table 4). In the multivariate analysis, young age (OR, 0.932;p = 0.001), never smoker (OR, 3.645;p = 0.001), high pSUVmax value (OR,10.505; p = 0.001), and low pTLG (OR, 3.326; p = 0.01) were still the independent deterministic factor of ALK fusion, while sex and TLG-S were not statistically significant variate with ALK fusion.

Exploring independent deterministic factors of ROS1 mutation

The univariate logistic regression analysis showed that age, sex, smoking status, and $pSUV_{max}$ were significantly correlated with ROS1 fusion in the NSCLC group (Table 5). The multivariate regression analysis showed that young age (OR, 0.936; p = 0.002), nonsmoker status (OR, 6.354; p = 0.001), and high $pSUV_{max}$ (OR, 10.044; p = 0.001) were significant

Table 1 Association between clinical and ^{18}F-FDG PET characteristics and the ALK or ROS1 status in NSCLC

Characteristics	ALK Positive	ALK Negative	Total	p value	ROS Positive	ROS Negative	Total	*p* value	ALK positive VS. ROS1 positive *p* value
Number of patients	82	617	699		26	436	462		
Age (years), Mean ± SD (range)	53.37 ± 11.92	63.94 ± 9.11	62.7 ± 10.07	0.001	55.62 ± 12.21	64.17 ± 9.23	63.68 ± 9.61	0.002	0.406
Sex				0.001				0.001	0.565
Male	40 (48.8%)	476 (77.1%)	516 (73.8%)		11 (42.3%)	345 (79.1%)	356 (77.1%)		
Female	42 (51.2%)	141 (22.9%)	183 (26.2%)		15 (57.7%)	91 (20.9%)	106 (22.9%)		
Smoking Status				0.001				0.001	0.444
Never smoker	60 (73.2%)	178 (28.8%)	238 (34%)		17 (65.4%)	121 (27.8%)	138 (29.9%)		
Ever smoker	22 (26.8%)	439 (71.2%)	461 (66%)		9 (34.6%)	315 (72.2%)	324 (70.1%)		
Tumor size, Mean ± SD	4.29 ± 2.03	4.51 ± 2.77		0.395	4.37 ± 2.61	4.83 ± 3.0		0.448	0.876
pSUVmax, Mean ± SD	12.56 ± 7.06	10.46 ± 7.51		0.017	12.91 ± 4.93	10.43 ± 7.75		0.005	0.816
nSUVmax, Mean ± SD	7.92 ± 7.29	7.56 ± 7.92		0.498	11.14 ± 7.98	8.59 ± 8.05		0.074	0.058
mSUVmax, Mean ± SD	13.45 ± 6.72	11.88 ± 7.40		0.056	12.01 ± 1.66	12.32 ± 7.80		0.936	0.39
pMTV, Mean ± SD	26.7 ± 36.13	74.82 ± 119.47		< 0.001	65.26 ± 124.03	83.25 ± 127.97		0.168	0.035
nMTV, Mean ± SD	21.81 ± 24.73	17.76 ± 23.09		0.147	18.13 ± 18.13	18.04 ± 22.57		0.73	0.696
mMTV, Mean ± SD	24.67 ± 25.43	26.11 ± 47.71		0.251	11.23 ± 11.37	30.38 ± 53.98		0.527	0.393
pTLG, Mean ± SD	171.74 ± 243.56	555.42 ± 936.35		< 0.001	376.16 ± 678.33	627.75 ± 1026.47		0.093	0.051
nTLG, Mean ± SD	136.72 ± 167.64	123.3 ± 247.25		0.146	128.49 ± 161.31	128.91 ± 260.77		0.623	0.695
mTLG, Mean ± SD	131.75 ± 139.33	171.73 ± 349.47		0.382	76.17 ± 88.74	200.67 ± 387.81		0.684	0.542
MTV-S, Mean ± SD	48.65 ± 56.38	94.37 ± 134.16		0.03	82.32 ± 126.89	107.33 ± 142.95		0.145	0.168
TLG-S, Mean ± SD	301.82 ± 348.73	688.24 ± 1051.21		0.01	496.6 ± 706.90	793.94 ± 1148.97		0.126	0.133
Tumor involvement				0.832				0.64	0.167
I	38 (46.3%)	281 (45.5%)	319 (45.6%)		6 (23.1%)	101 (23.2%)	107 (23.2%)		
II	24 (29.3%)	200 (32.4%)	224 (32%)		12 (46.2%)	149 (34.2%)	161 (34.8%)		
III	8 (9.8%)	65 (10.5%)	73 (10.4%)		4 (15.4%)	102 (23.4%)	106 (22.9%)		
IV	12 (14.6%)	71 (11.5%)	83 (11.9%)		4 (15.4%)	84 (19.3%)	88 (19.0%)		
Nodal involvement				0.345				0.147	0.202
0	28 (34.1%)	216 (35%)	244 (34.9%)		4 (15.4%)	117 (26.8%)	121 (26.2%)		
I	3 (3.7%)	41 (6.6%)	44 (6.3%)		0 (0%)	38 (8.7%)	38 (8.2%)		
II	25 (30.5%)	214 (34.7%)	239 (34.2%)		11 (42.3%)	159 (36.5%)	170 (36.8%)		
III	26 (31.7%)	146 (23.7%)	172 (24.6%)		11 (42.3%)	122 (28.0%)	133 (28.8%)		
Metastasis				0.538				0.297	0.27
0	51 (62.2%)	405 (65.6%)	456 (65.2%)		13 (50.0%)	263 (60.3%)	276 (59.7%)		
I	31 (37.8%)	212 (34.4%)	243 (34.8%)		13 (50.0%)	173 (39.7%)	186 (40.3%)		
Stage				0.856				0.689	0.375

Table 1 (continued)

Characteristics	ALK Positive	ALK Negative	Total	p value	ROS Positive	ROS Negative	Total	*p* value	ALK positive VS. ROS1 positive *p* value
I	18 (22.0%)	127 (20.6%)	145 (20.7%)		3 (11.5%)	56 (12.8%)	59 (12.8%)		
II	8 (9.8%)	54 (8.8%)	62 (8.9%)		1 (3.8%)	46 (10.6%)	47 (10.2%)		
III	26 (31.7%)	226 (36.6%)	252 (36.1%)		9 (34.6%)	162 (37.2%)	171 (37.0%)		
IV	30 (36.6%)	210 (34.0%)	240 (34.3%)		13 (50.0%)	172 (39.4%)	185 (40.0%)		
Histology				0.001				0.001	NA
Adenocarcinoma	82 (100.0%)	371 (60.1%)	453 (64.8%)		26 (100.0%)	248 (56.9%)	274 (59.3%)		
Squamous cell carcinoma	0 (0.0%)	220 (35.7%)	220 (31.5%)		0 (0.0%)	166 (38.1%)	166 (35.9%)		
Large cell carcinoma	0 (0.0%)	12 (1.9%)	12 (1.7%)		0 (0.0%)	15 (3.4%)	15 (3.2%)		
Undefined NSCLC	0 (0.0%)	14 (2.3%)	14 (2.0%)		0 (0.0%)	7 (1.6%)	7 (1.5%)		
CK				1				1	NA
Negative	0 (0.0%)	5 (0.8%)	5 (0.7%)		0 (0.0%)	5 (1.1%)	5 (1.1%)		
Positive	82 (100.0%)	612 (99.2%)	694 (99.3%)		26 (100.0%)	431 (98.9%)	457 (98.9%)		
TTF-1				0.001				0.001	1
Negative	2 (2.4%)	250 (40.5%)	252 (36.1%)		0 (0.0%)	189 (43.3%)	189 (40.9%)		
Positive	80 (97.6%)	367 (59.5%)	447 (63.9%)		26 (100.0%)	247 (56.7%)	273 (59.1%)		
P40				0.001				0.001	0.451
Negative	77 (93.9%)	409 (66.3%)	486 (69.5%)		26 (100.0%)	280 (64.2%)	306 (66.2%)		
Positive	5 (6.1%)	208 (33.7%)	213 (30.5%)		0 (0.0%)	156 (35.8%)	156 (33.8%)		
CD56				0.31				0.156	1
Negative	80 (97.6%)	581 (94.2%)	661 (94.6%)		26 (100.0%)	393 (90.1%)	419 (90.7%)		
Positive	2 (2.4%)	36 (5.8%)	38 (5.4%)		0 (0.0%)	43 (9.9%)	43 (9.3%)		
CEA	36.30 ± 94.01	22.22 ± 64.85		0.274	5.41 ± 6.70	22.80 ± 63.09		0.072	0.004
CA199	5.64 ± 21.56	10.15 ± 22.46		0.001	10.31 ± 26.06	11.23 ± 23.32		0.698	0.363
SCCA	1.09 ± 1.38	1.49 ± 3.81		0.067	2.41 ± 3.65	2.76 ± 6.94		0.386	0.083
NSE	24.05 ± 26.38	23.42 ± 18.84		0.577	24.06 ± 14.74	23.30 ± 13.83		0.881	0.998
CA125	91.53 ± 178.10	62.18 ± 136.68		0.067	106.54 ± 208.71	63.61 ± 129.68		0.452	0.72

Abbreviations: NSCLC, non-small-cell lung cancer; ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1; SD, standard deviation; SUVmax, maximal standard uptake value; pSUVmax, primary tumor SUVmax; nSUVmax, nodal metastasis SUVmax; mSUVmax, distant metastasis SUVmax; pMTV, primary tumor MTV; nMTV, nodal metastases MTV; mMTV, distant metastases MTV; pTLG, primary tumor TLG; nTLG, nodal metastases TLG; mTLG, distant metastases TLG; MTV-S, the sum of metabolic tumor volume; TLG-S, total lesion glycolysis measured using a systemic approach; NA, not able to statistics; CA199, cancer antigen 199; CEA, carcinoembryonic antigen; SCCA, squamous cell carcinoma antigen, NSE, neuron specific enolase and CA125, cancer antigen 125

Table 2 Association between clinical and ^{18}F-FDG PET characteristics and the ALK or ROS1 status in adenocarcinoma

Characteristics	ALK positive	ALK negative	Total	p value	ROS positive	ROS negative	Total	*p* value
number of patients	82	371	453		26	248	274	
Age (years), Mean ± SD (range)	53.37 ± 11.92	62.73 ± 9.71		0.001	55.62 ± 12.21	62.74 ± 9.99		0.001
Sex				0.001				0.003
Male	40 (48.8%)	253 (68.2%)	293 (64.7%)		11 (42.3%)	175 (70.6%)	186 (67.9%)	
Female	42 (51.2%)	118 (31.8%)	160 (35.3%)		15 (57.7%)	73 (29.4%)	88 (32.1%)	
Smoking status				0.001				0.011
Never smoker	60 (73.2%)	149 (40.2%)	209 (46.1%)		17 (65.4%)	98 (39.5%)	115 (42.0%)	
Ever smoker	22 (26.8%)	222 (59.8%)	244 (53.9%)		9 (34.6%)	150 (60.5%)	15 9 (58.0%)	
Tumor size, Mean ± SD	4.29 ± 2.03	4.16 ± 2.91		0.618	4.37 ± 2.61	4.65 ± 3.42		0.946
pSUVmax, Mean ± SD	12.56 ± 7.06	7.54 ± 5.49		0.001	12.91 ± 4.93	9.33 ± 5.78		0.003
nSUVmax, Mean ± SD	7.92 ± 7.29	7.02 ± 7.55		0.244	11.14 ± 7.98	8.17 ± 7.55		0.049
mSUVmax, Mean ± SD	13.45 ± 6.72	10.16 ± 6.40		0.005	12.01 ± 1.66	11.03 ± 6.76		0.774
pMTV, Mean ± SD	26.7 ± 36.13	61.65 ± 123.01		0.027	65.26 ± 124.03	75.85 ± 142.04		0.801
nMTV, Mean ± SD	21.8 ± 24.73	15.85 ± 18.52		0.101	18.13 ± 18.13	16.14 ± 19.11		0.684
mMTV, Mean ± SD	24.67 ± 25.43	22.87 ± 36.26		0.169	11.23 ± 11.37	24.68 ± 42.43		0.774
pTLG, Mean ± SD	171.74 ± 243.56	433.2 ± 895.06		0.028	376.16 ± 678.33	533.48 ± 1032.48		0.658
nTLG, Mean ± SD	136.72 ± 167.64	100.61 ± 183.28		0.087	128.49 ± 161.31	104.18 ± 202.11		0.555
mTLG, Mean ± SD	131.75 ± 139.33	144.2 ± 272.20		0.247	76.17 ± 88.74	153.68 ± 305.23		0.936
MTV-S, Mean ± SD	48.65 ± 56.38	79.44 ± 133.68		0.001	82.32 ± 126.89	97.7 ± 152.57		0.629
TLG-S, Mean ± SD	301.82 ± 348.73	544.94 ± 965.90		0.001	496.6 ± 706.90	672.16 ± 1102.43		0.675
Tumor involvement				0.261				0.672
I	38 (46.3%)	134 (36.1%)	172 (38.0%)		6 (23.1%)	71 (28.6%)	77 (28.1%)	
II	24 (29.3%)	116 (31.3%)	140 (30.9%)		12 (46.2%)	82 (33.1%)	94 (34.3%)	
III	8 (9.8%)	61 (16.4%)	69 (15.2%)		4 (15.4%)	52 (21.0%)	56 (20.4%)	
IV	12 (14.6%)	60 (16.2%)	72 (15.9%)		4 (15.4%)	43 (17.3%)	47 (17.2%)	
Nodal involvement				0.581				0.277
0	28 (34.1%)	141 (38.0%)	169 (37.3%)		4 (15.4%)	70 (28.2%)	74 (27.0)	
I	3 (3.7%)	14 (3.8%)	17 (3.8%)		0 (0.0%)	14 (5.6%)	14 (5.1%)	
II	25 (30.5%)	126 (34.0%)	151 (33.3%)		11 (42.3%)	89 (35.9%)	100 (36.5%)	
III	26 (31.7%)	90 (24.3%)	116 (25.6%)		11 (42.3%)	75 (30.2%)	86 (31.4%)	
Metastasis				0.937				0.724
0	51 (62.2%)	229 (61.7%)	280 (61.8%)		13 (50.0%)	133 (53.6%)	146 (53.3%)	
I	31 (37.8%)	142 (38.3%)	173 (38.2%)		13 (50.0%)	115 (46.4%)	128 (46.7%)	
Stage				0.69				0.931
I	18 (22.0%)	91 (24.5%)	109 (24.1%)		3 (11.5%)	34 (13.7%)	37(13.5%)	

Table 2 (continued)

Characteristics	ALK positive	ALK negative	Total	p value	ROS positive	ROS negative	Total	*p* value
II	8 (9.8%)	23 (6.2%)	31 (6.8%)		1 (3.8%)	22 (8.9%)	23(8.4%)	
III	26 (31.7%)	116 (31.3%)	142 (31.3%)		9 (34.6%)	77 (31.0%)	86 (31.4%)	
IV	30 (36.6%)	141 (38.0%)	171 (37.7%)		13 (50.0%)	115 (46.4%)	128 (46.7%)	
CK				1				1
Negative	0 (0.0%)	4 (1.1%)	4 (0.9%)		0 (0.0%)	4 (1.6%)	4 (1.5%)	
Positive	82 (100.0%)	367 (98.9%)	449 (99.1%)		26 (100.0%)	244 (98.4%)	270 (98.5%)	
TTF-1				0.028				0.033
Negative	2 (2.4%)	37 (10.0%)	39 (8.6%)		0 (0.0%)	46 (18.5%)	46 (16.8%)	
Positive	80 (97.6%)	334 (90.0%)	414 (91.4%)		26 (100.0%)	202 (81.5%)	228 (83.2%)	
P40				0.183				1
Negative	77 (93.9%)	360 (97.0%)	437 (96.5%)		26 (100.0%)	239 (96.4%)	265 (96.7%)	
Positive	5 (6.1%)	11 (3.0%)	16 (3.5%)		0 (0.0%)	9 (3.6%)	9 (3.3%)	
CD56				0.615				1
Negative	80 (97.6%)	366 (98.7%)	446 (98.5%)		26 (100.0%)	241 (97.2%)	267 (97.4%)	
Positive	2 (2.4%)	5 (1.3%)	7 (1.5%)		0 (0.0%)	7 (2.8%)	7 (2.6%)	
CEA	36.30 ± 94.01	32.88 ± 81.50		0.686	5.41 ± 6.70	35.56 ± 81.01		0.004
CA199	5.64 ± 21.56	7.77 ± 19.73		0.001	10.31 ± 26.06	7.73 ± 16.48		0.424
SCCA	1.09 ± 1.38	1.41 ± 4.01		0.181	2.41 ± 3.65	1.24 ± 1.99		0.562
NSE	24.05 ± 26.38	23.70 ± 22.13		0.742	24.06 ± 14.74	23.75 ± 15.22		0.979
CA125	91.53 ± 178.10	80.57 ± 165.16		0.304	106.54 ± 208.71	83.01 ± 155.81		0.954

Abbreviations: ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1; SD, standard deviation; SUVmax, maximal standard uptake value; pSUVmax, primary tumor SUVmax; nSUVmax, nodal metastasis SUVmax; mSUVmax, distant metastasis SUVmax; pMTV, primary tumor MTV; nMTV, nodal metastases MTV; mMTV, distant metastases MTV; pTLG, primary tumor TLG; nTLG, nodal metastases TLG; mTLG, distant metastases TLG; MTV-S, the sum of metabolic tumor volume; TLG-S, total lesion glycolysis measured using a systemic approach; CA199, cancer antigen 199; CEA, carcinoembryonic antigen; SCCA, squamous cell carcinoma antigen, NSE, neuron specific enolase and CA125, cancer antigen 125

independent deterministic factors of ROS1 fusion, while the sex and CEA level were not statistically significant. The ROC curve analysis showed that the cutoff point for the pSUVmax was 8.8 with the area under curve (AUC) of 0.662 with p value of 0.042 (Fig. 2). When the three factors (age, smoking status, pSUVmax) were analyzed together, the AUC was 0.813, with $p < 0.001$.

When ADC patients were separately analyzed (Table 6), the univariate logistic regression analysis revealed that age, sex, smoking status, pSUVmax, and CEA were correlated with ROS1 fusion. In the multivariate logistic regression analysis, young age (OR, 0.947; $p = 0.011$), female predilection (OR, 3.896; $p = 0.003$), and high $pSUV_{max}$ (OR, 7.441; $p = 0.001$) were still independent deterministic factors of ROS1 fusion in ADC patients, while smoking status and CEA were not statistically significant.

Discussion

^{18}F-FDG uptake of cancer cells is a significant biomarker for metabolic features, as it has associations with important biologic characteristics including proliferation, histologic type, tumor differentiation, and hypoxia [14, 29]. Our paper studied the SUVmax and volumetric PET/CT parameters of ALK and ROS1 fusion in NSCLC. Previous studies concerning the correlation between SUVmax and ALK fusion are conflicting and unconvincing with small samples. For ALK fusion patients, our study revealed that ALK fusion lung cancers were correlated with high pSUVmax on ^{18}F-FDG PET-CT which suggests that ALK fusion lung cancer may be associated with more malignant features with higher SUVmax uptake [13, 17, 19]. As to genetic mutations, ALK fusion gene activates several other oncogenes such as AKT that is associated with

Table 3 Univariate and multivariate analysis of various factors association with the ALK status in NSCLC

Characteristics	Univariate analysis OR (95% CI)	p value	Multivariate analysis OR (95% CI)	p value
Age	0.907 (0.886–0.929)	0.001	0.924 (0.899–0.949)	0.001
Sex		0.001		0.187
Male	Reference			
Female	3.545 (2.211–5.683)			
Smoking status		0.001		0.001
Never smoker	6.726 (4.004–11.298)		6.040 (3.273–11.146)	
Ever smoker	Reference		Reference	
Histology		0.994		
Adenocarcinoma	Reference			
Non-adenocarcinoma	0			
Tumor size	0.969 (0.884–1.064)	0.499		
pSUVmax		0.002		0.001
< 10.6	Reference		Reference	
≥ 10.6	2.122 (1.327–3.394)		7.395 (3.734–14.648)	
pTLG		0.001		0.001
< 101.8	2.798 (1.735–4.512)		3.974 (2.069–7.635)	
≥ 101.8	Reference		Reference	
TLG-S		0.01		0.103
< 848.5	4.36 (1.863–10.207)			
≥ 848.5	Reference			
Stage		0.857		
I	Reference			
II	1.045 (0.429–2.549)	0.922		
III	0.812 (0.428–1.538)	0.522		
IV	1.008 (0.540–1.882)	0.98		
CEA	1.002 (1.000–1.005)	0.092	1.003 (1.000–1.006)	0.024
CA199	0.978 (0.952–1.005)	0.108		0.142

Abbreviations: NSCLC, non-small-cell lung cancer; ALK, anaplastic lymphoma kinase; SUVmax, maximal standard uptake value; pSUVmax, primary tumor SUVmax; pTLG, primary tumor TLG; TLG-S, total lesion glycolysis measured using a systemic approach; CA199, cancer antigen 199; CEA, carcinoembryonic antigen; OR, odds ratio; CI, confidence interval

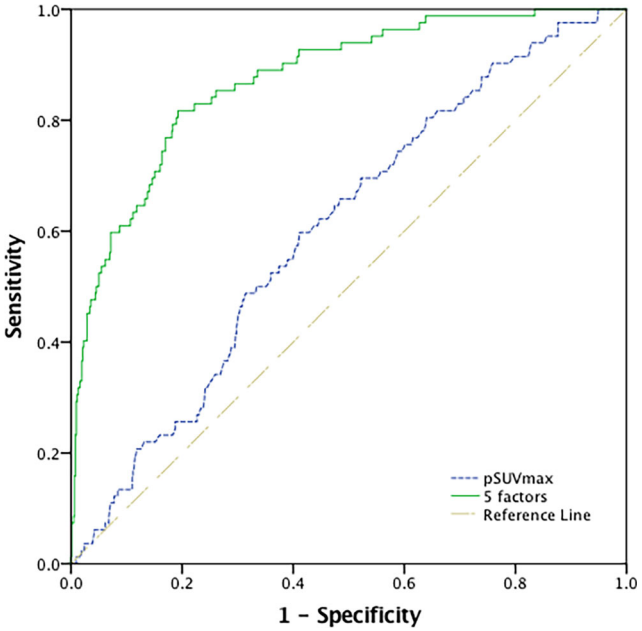

Fig. 1 Receiver operating characteristic curves yielded the area under curve (AUC) values of 0.603 and 0.873 for primary tumor SUVmax and combination of five factors (pSUVmax, pTLG, age, smoking history, and CEA level) were associated with ALK fusion, respectively

alterations of tumor proliferation, growth, and metabolism [30]. This genetic interaction would be related to high SUVmax and aggressive characteristics of ALK fusion in NSCLC. However, compared with ALK wild-type lung cancers, ALK fusion lung cancers were correlated with low pMTV, pTLG, MTV-S, and TLG-S. A possible explanation for these observations is that simple SUVmax might fail to reflect the spatial features and behaviors of a primary lesion in imaging [31], while volume-based PET/CT parameter TLG provides complementary information about tumor heterogeneity, total disease burden, which may be prognostic for outcomes and tumor metabolic activity [32, 33]. And a meta-analysis proposed that metabolic parameters such as TLG and MTV were better predictors of treatment outcomes than SUVmax in lung cancer [34]. Besides, previous studies revealed that the overall survival of NSCLC patients with ALK fusion was much shorter than that of NSCLC patients with EGFR-mutated or wild-type [35, 36]. However, other reports revealed that the overall survival was longer in ALK fusion lung cancer patients than in ALK wild-type patients on contrary [37–39]. So, the prognostic significance of ALK fusion remains inconclusive. However, we could not analyze patients' survival in our study due to heterogeneity of therapy modality and insufficient follow-up time. Therefore, prospective clinical trials are necessary to further study this finding. For ROS1 fusion, our study reveals that ROS1 fusion lung cancers were also associated with high pSUVmax on ^{18}F-FDG PET-CT, while volume-based PET/CT parameter of MTV and TLG not. Among the ADC patients, the nSUVmax was higher in the ROS1 fusion group than in the ROS1 wild-type group. However, there was no difference in the mSUVmax between the two groups. Jin et al. revealed that ROS1 fusion status was highly related with micropapillary component and aerogenous spread, which has been reported as a marker of aggressive tumor biology which may support the high pSUVmax in ROS1 fusion lung cancers [40]. Due to limited patient samples, larger patient scales and more studies are needed to further study the glucose metabolism of ROS1 fusion in NSCLC.

Our study revealed other clinical characteristics of patients with ALK and ROS1 fusion lung cancer. Several studies have revealed that NSCLC patients with ROS1 fusion have many similar clinicopathological characteristics with ALK fusion patients [41, 42]. Our study shows a similar trend; both ALK fusion and ROS1 fusion lung cancer are tended to be younger on average, female predilection, no history of smoking consistent with previous studies [41, 43]. In addition, they both have strong positive relationship with TTF-1 expression [17, 44]. And lung cancers with the ALK or ROS1 fusion were mostly lung adenocarcinomas with a few exceptions [43, 44]. Our study shows no difference in the tumor, nodal, metastasis involvement, and tumor stage between the two groups in ALK and ROS1 fusion lung cancers, while some study showed that ALK or ROS1 fusion lung cancers had tendency of more lymph node metastases and higher stage of disease at diagnosis [43, 45, 46]. The gene test of EGFR, ALK, and ROS1 mutation have been routinely recommended in clinic. And EGFR is preferred when tumor tissue is limited. When EGFR wild-type is detected, both test of ALK and ROS1 genes are routinely recommended. The frequencies of ALK and ROS1 with wild-type EGFR spiked to 11.7% and 5.6% in our study, respectively. When comparing ALK with ROS1 fusion group, the CEA and pMTV value was the only two factors that were significantly different between two groups.

CEA, CA125, CA199, NSE, and SCCA biomarkers are related to lung cancer [47]. The detection of these markers has been automated [48] and is convenient for screening lung cancer on a larger scale. Consequently, serum tumor markers before surgery were chosen for the present study. The present study revealed that the value of CA199 is significantly lower in ALK fusion group than in ALK wild-type group, while it is not significantly different in the multivariate analysis. CA199, a glycoprotein, is a ganglioside on cancer cells in the diagnosis of lung cancer. CA199 is mainly used for the detection of pancreas cancer and gastrointestinal cancer [49, 50]. Detection of serum CEA is a sensitive method for the potential molecular diagnosis of NSCLC [51, 52]. Wang et al. revealed that preoperative high serum CEA levels were correlation with the pathological type with more aggressive biologic features

[53]. Furthermore, the CEA level in serum fluctuates with disease progression and treatment in patients with NSCLC [54]. Previous study reported that an elevated serum CEA level generally indicated poor prognosis in patients with NSCLC [55]. However, the associations of CEA with ALK fusion remain controversial. Several studies have reported that high serum CEA levels before surgery (CEA > 20 ng/mL) were independently related to ALK fusion protein expression [56]; however, the sample size was relatively small and needs to be verified by a larger sample studies, while other researchers have found lung cancer patients with ALK fusion were more likely to have lower or normal serum CEA level [53, 57, 58]. Our study found that in the multivariate analysis, high CEA value (OR, 1.003; $p = 0.024$) were the independent deterministic factor of ALK positivity in NSCLC. And the CEA value were significant higher in the ALK fusion patients (36.30 ± 94.01 vs. 5.41 ± 6.70; $p = 0.004$) than in the ROS1 fusion patients. So, our study indicated that preoperative serum CEA level was significantly higher with ALK than ROS1 fusion.

Detection of the ALK or ROS1 fusion is often challenging in advanced NSCLC patients because of financial and technical problems [17, 59]. In many lung cancer patients with inoperable and/or unresectable condition, the limitation amount of the biopsy material raised the question of which molecular test should be given priority for the appropriate targeted therapy [17]. A prescreen process could dramatically reduce the number of NSCLC patients entering ALK or ROS1 fusion test and therefore reduce the whole health cost. Evaluation of the clinical pathologic features and glucose metabolism of NSCLC patients was the first step of prescreening. Our study indicated that for ALK fusion, pSUVmax ≥ 10.6 was related with ALK fusion in NSCLC, and the AUC of the ROC curve analysis of five factors, including high pSUVmax ≥ 10.6, low pTLG < 101.8, young age, nonsmoker status, and high CEA level

Table 4 Univariate and multivariate analysis of various factors association with the ALK status in adenocarcinoma

Characteristics	Univariate analysis OR (95% CI)	*p* value	Multivariate analysis OR (95% CI)	*p* value
Age	0.923 (0.901–0.945)	0.001	0.932 (0.907–0.958)	0.001
Sex		0.001		0.152
Male	Reference			
Female	2.251 (1.386–3.657)			
Smoking status		0.001		0.001
Never smoker	4.063 (2.390–6.909)		3.645 (1.944–6.834)	
Ever smoker	Reference		Reference	
Tumor size	1.017 (0.936–1.105)	0.69		
pSUVmax		0.001		0.001
< 10.6	Reference		Reference	
≥ 10.6	4.253 (2.583–7.004)		10.505 (25.206–21.196)	
pTLG		0.02		0.01
< 101.8	1.800 (1.099–2.948)		3.326 (1.664–6.645)	
≥ 101.8	Reference		Reference	
TLG-S		0.012		0.221
<848.5	3.050 (1.278–7.281)			
≥ 848.5	Reference			
Stage		0.695		
I	Reference			
II	1.758 (0.680–4.548)	0.244		
III	1.133 (0.585–2.194)	0.711		
IV	1.076 (0.567–2.042)	0.824		
CEA	1.000 (0.998–1.003)	0.738		
CA199	1.000 (0.988–1.012)	1		

Abbreviations: ALK, anaplastic lymphoma kinase; SUVmax, maximal standard uptake value; pSUVmax, primary tumor SUVmax; pTLG, primary tumor TLG; TLG-S, total lesion glycolysis measured using a systemic approach; CA199, cancer antigen 199; CEA, carcinoembryonic antigen; OR, odds ratio; CI, confidence interval

Table 5 Univariate and multivariate analysis of various factors association with the ROS1 status in NSCLC

Characteristics	Univariate analysis OR (95% CI)	*p* value	Multivariate analysis OR (95% CI)	*p* value
Age	0.922 (0.888–0.958)	0.001	0.936 (0.898–0.976)	0.002
Sex		0.001		0.356
Male	Reference			
Female	5.170 (2.296–11.640)			
Smoking status		0.001		0.001
Never smoker	4.917 (2.134–11.330)		6.354 (2.519–16.024)	
Ever smoker	Reference		Reference	
Histology		0.995		
Adenocarcinoma	Reference			
Non-adenocarcinoma	0			
Tumor size	0.940 (0.801–1.102)	0.445		
pSUVmax		0.002		0.001
< 8.8	Reference		Reference	
≥ 8.8	5.450 (1.847–16.076)		10.044 (3.158–31.947)	
pTLG	1.000 (0.999–1.000)	0.227		
TLG-S	1.000 (0.999–1.000)	0.202		
Stage		0.634		
I	Reference			
II	0.406 (0.041–4.033)	0.441		
III	1.037 (0.271–3.966)	0.958		
IV	1.411 (0.388–5.131)	0.601		
CEA	0.963 (0.918–1.012)	0.135		0.123
CA199	0.998 (0.980–1.017)	0.847		

Abbreviations: NSCLC, non-small-cell lung cancer; ROS1, c-ros oncogene 1; SUVmax, maximal standard uptake value; pSUVmax, primary tumor SUVmax; pTLG, primary tumor TLG; TLG-S, total lesion glycolysis measured using a systemic approach; CA199, cancer antigen 199; CEA, carcinoembryonic antigen; OR, odds ratio; CI, confidence interval

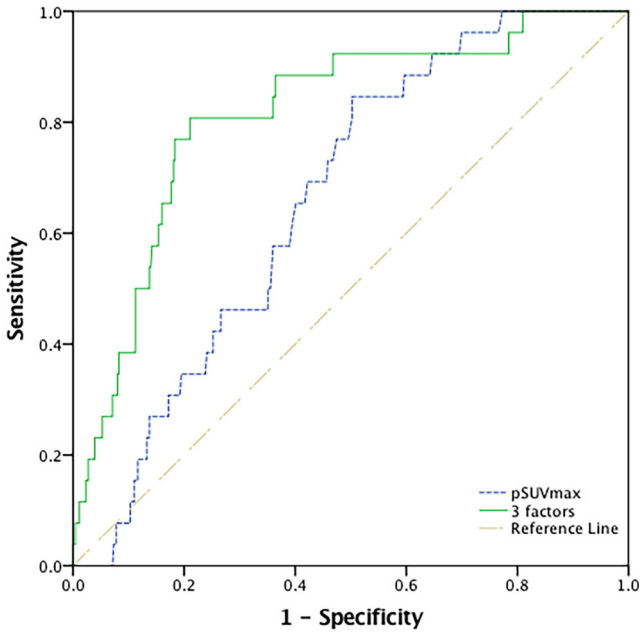

Fig. 2 Receiver operating characteristic curves yielded the area under curve (AUC) values of 0.662 and 0.813 for primary tumor SUVmax and combination of three factors (pSUVmax, age, and smoking history) were associated with ROS1 fusion, respectively

together was 0.873; for ROS1 fusion, pSUVmax ≥ 8.8 was related with ROS1 mutation in NSCLC, and the AUC of the ROC curve analysis of three factors, including high pSUVmax ≥ 8.8, young age, and nonsmoker status together was 0.813. Our findings may contribute to patient selection for targeted therapy with ALK or ROS1 inhibitors.

In conclusion, the results of our study suggest that ^{18}F-FDG PET/CT metabolic parameters and other clinical features are correlated with ALK and ROS1 mutation with NSCLC. The association of these combination factors with ALK and ROS1 mutation may help to improve stratification of this patient cohort, but not replace molecular testing, especially for patients with inadequate sampling or when genetic testing is not available, and it may or could refine the process of optimal patient selection. However, gene analysis is still mandatory when selecting appropriate target therapy.

There are several limitations to this study. Firstly, select ALK or ROS1 status patients chosen only for NSCLC patients with wild-type EGFR were analyzed in this study so that it

Table 6 Univariate and multivariate analysis of various factors association with ROS1 status in adenocarcinoma

Characteristics	Univariate analysis OR (95% CI)	*p* value	Multivariate analysis OR (95% CI)	*p* value
Age	0.940 (0.905–0.976)	0.001	0.947 (0.908–0.987)	0.011
Sex		0.005		0.003
Male	Reference		Reference	
Female	3.269 (1.433–7.456)		3.896 (1.592–9.536)	
Smoking status		0.014		0.199
Never smoker	2.891 (1.239–6.745)			
Ever smoker	Reference			
Tumor size	0.972 (0.849–1.113)	0.681		
pSUVmax		0.001		0.001
< 8.8	Reference		Reference	
≥ 8.8	6.059 (2.029–18.096)		7.441 (2.372–23.344)	
pTLG	1.000 (0.999–1.000)	0.455		
TLG-S	1.000 (0.999–1.000)	0.433		
Stage		0.825		
I	Reference			
II	0.515 (0.050–5.273)	0.576		
III	1.325 (0.337–5.200)	0.687		
IV	1.281 (0.345–4.760)	0.711		
CEA	0.946 (0.894–1.000)	0.049		0.079
CA199	1.006 (0.989–1.024)	0.487		

Abbreviations: ROS1, c-ros oncogene 1; SUVmax, maximal standard uptake value; pSUVmax, primary tumor SUVmax; pTLG, primary tumor TLG; TLG-S, total lesion glycolysis measured using a systemic approach; CA199, cancer antigen 199; CEA, carcinoembryonic antigen; OR, odds ratio; CI, confidence interval

may had a selection bias. Secondly, the retrospective design may have introduced bias. Thirdly, even though it was a single-center study with relatively large sample size, the patient population was not so big enough, particularly in ROS1 fusion group due to the small rate of ALK or ROS1 fusion in lung cancer. A larger prospective multicenter study is warranted for validation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were approved by the Institutional Review Board of Shanghai Jiao Tong University-affiliated Shanghai Chest Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. This article does not contain any animal experiments.

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