Comparison of the value of different measuring parameters in the diagnosis of mediastinal lymph node metastases in patients withlung adenocarcinoma on ^{18}F-FDG PET/CT

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Abstract

Background

^{18}F-FDG PET/CT has been used worldwide for the staging of lung cancer, but the criteria used for classifying mediastinal lymph nodes as malignant are underdispute. The aim of this study was to evaluate the diagnostic ability of using different standardized uptake value (SUV) parameters in the detection of mediastinal lymph node metastases of lung adenocarcinoma.

Method

A retrospective review of 61 patients with lung adenocarcinoma who underwent^{18}F-FDG PET/CT from 2015 to 2018 in the nuclear medicine department of our hospital was performed. Patients with mediastinal lymph nodes shown on PET/CT and who underwent apathological examination were enrolled in our study. Different SUV parameters (e.g.,mediastinal lymph node SUVmax, node/liver SUVmax ratio, and node/mediastinum SUVmax ratio) were evaluated.Histology was used as the gold standard to evaluate the diagnosis of mediastinal lymph node metastasis. Receiver operating characteristic(ROC) curves were used to evaluate the accuracy of the three methods mentioned above. A *P*value <0.05 was considered statistically significant.

Results

The pathological examination confirmed lymph node metastasis in 42 of 104 lymph node sections from 50 patients.The lymph node SUVmax, node/liver SUVmaxratio, and node/mediastinum SUVmax ratio of metastatic lymph nodes were higher than those of benign lymph nodes (P<0.05). The areas under the ROC curves of themediastinallymph node SUVmax, node/liver SUVmax ratio, and node/mediastinum SUVmax ratio were 0.81, 0.88, and 0.83, respectively, with cut-off values of 3.15,1.65, and 1.73, respectively.

Conclusion

The mediastinal lymph node SUVmax, node/liver SUVmax ratio, and node/mediastinum SUVmax ratio each have quite high accuracy in the detection of mediastinal lymph node metastases of lung adenocarcinoma, and a node/liver SUVmax ratio≥1.65 has higher accuracy than the other two parameters.

1. Background

Lung cancer is one of the mainly diagnosed cancer with 11.6% of the total cases,and lung cancer is confirmed as the common cause of the death induced cancer with 18.4% of the cancer deaths worldwide, especially in males (with 14.5% of incidence and 22.0% of mortality)[1]. From 1991 to 2013, the lung cancer mortality rate in China increased by an average of 7.7% each year[2]. Although great progress has been made in the diagnosis and treatment technology of lung cancer in recent years, the 5-year survival rate is only 17.4%[3],which is mainly related to the staging of lung cancer. Studies have shown that the 5-year survival rate of patients with lung cancer without distant metastasis is 54.8%[3], while that of patients with stage N1 disease is 40-50%, and that of patients with stage N2 disease is 15%[4]. PET/CT combines glucose metabolism information obtained from PET and anatomical information obtained from CT, and is a non-invasive examination that plays an important role in the differential diagnosis of inflammation and malignant lesions. Therefore, ^{18}F-FDG PET/CT has been widely accepted for staging lung cancer [5–6].

Although ^{18}F-FDG PET/CT has been widely used for staging lung cancer, the criteria used for differentiating benign from malignant thoracic lymph nodes are still controversial. At present, ^{18}F-FDG PET/CT has many criteria for differentiating benign and malignant lymph nodes. For example, Wang et al. [7] found that the maximum standardized uptake value (SUVmax) of metastatic lymph nodes was significantly higher than that of benign lymph nodes. However, it is not accurate to use the SUVmax as a parameter to identify benign and malignant lymph nodes associated with lung cancer, especially thoracic lymph nodes exposed to environmental pathogens and toxins for a long time. M. Sollini et al. [8] found that themetastatic lymph node SUVmax/mediastinalSUVmax was higher than the benign lymph node SUVmax/liver SUVmaxafter comparison. Scholars such as D. Divis[9] believe that the metastatic lymph node SUVmax/mediastinalSUVmax and thebenign lymph node SUVmax/mediastinalSUVmax are important and have statistical significance. By comparing the accuracy of the above three methods, we provide accurate information for the clinical diagnosis and treatment of lung cancer patients,that may improve their quality of life.

2. Data And Methods

2.1. Clinical data

A retrospective analysis of 61 patients with lung adenocarcinoma who underwent ^{18}F-FDG PET/CT in the nuclear medicine department of our hospital from 2015 to 2018 was performed. ^{18}F-FDG PET/CT results revealed the mediastinal lymph nodes of the patients, and the lymph nodes were examined pathologically. According to the pathological results, the lymph nodes of patients who met the criteria were divided into a metastatic group and a non-metastatic group.

2.2. PET/CT

The image acquisition protocol was as follows: Patients fasted for at least 4 h, and blood sugarlevels were assessed to ensure levels <10 mmol/L.Next,3.7 MBq/kg ^{18}F-FDG wasinjected intravenously, and scans were acquired after approximately60 min of uptake. Patients were scanned from the top of the skull to the middle of the thigh with their arms up on a Siemens PET/mCT scanner. Emission images wereacquiredover 10–13 bed positions, with 2 min for each bed position.CT scans were performed during tidal breathing without using contrast agent. CT scanning parameters were as follows: 140 KeV, 200 mA, and 5 mm thickness.

The FDG PET image was analysed as follows:SUVmax = specific activity of the lesion (MBq/g)/injection dose of the imaging agent (MBq)/body weight (g). A round region of interest (ROI) was placed on the lymph nodes, and the maximum value was taken as the SUVmax at the axial level. The liver SUVmaxwas obtained by placing ROI on the right lobe of the liver. Because weight is easy to obtain, the SUV parameters were corrected by total weight rather than fat-free weight.

The lymph nodes were divided into groups 2, 4, 5, 6, 7, 8 and 10 according to the criteria of the International Association for Lung Cancer Research.

2.3. Data analysis

The lymph node SUVmax, lymph node SUVmax/liver SUVmax (N/L) and lymph node SUVmax/mediastinalSUVmax (N/M) were obtained separately. The difference between metastatic and non-metastatic lymph nodes was assessed by Student's t-test. Cut-off values were obtained from receiver operating characteristic (ROC) curves. The area under the curve (AUC) was compared according the method of Hanley and McNeil [7] to determine the accuracy of the three methods. The AUC is more accurate than specificity and sensitivity due to the removal of the threshold effect. IBM SPSS STATISTICS 19.0was used to process data and draw ROC curves. A P value<0.05 was considered statistically significant.

3. Results

A total of 50 eligible patients (27 males and 23 females, with an average age of 53 ±12 years) were enrolled. There were 104 lymph nodes in 50 patients with primary lesions. Pathological results showed 42 metastatic lymph nodes and 62 benign lymph nodes among 104 lymph nodes. The comparison of lymph nodes between themetastatic and non-metastatic groups is shown in Table 1.

Table 1
Comparison of lymph nodes in the metastatic and non-metastatic groups

	Metastaticgroup(n=42)	Non-metastatic group(n=62)	*P*value
Lymph node SUVmax	5.38±3.23	2.99±1.39	0.00
N/L	2.30±1.09	1.16±0.58	0.00
N/M	2.79±1.61	1.59±0.70	0.00

Table 1 shows that the lymph node SUVmax, lymph node SUVmax/liverSUVmax and lymph node SUVmax/mediastinalSUVmaxweresignificantly higher in the metastaticgroup than in the non-metastatic group ($P < 0.05$).

Figure 2a. shows the ROC curve according to the lymph node SUVmax; Fig. 2b.shows the ROC curve according tothe lymph node SUVmax/SUVmax; and Fig. 2c.shows the ROC curve according tothe lymph node SUVmax/mediastinalSUVmax.

Table2. Differentiation of metastatic and non-metastatic lymph nodes in lung adenocarcinoma based on PET/CT diagnostic criteria

Parameter	Cut-off	Susceptibility	Specificity	AUC
Lymph node SUVmax	3.15	0.79	0.74	0.81
N/L	1.65	0.83	0.89	0.88
N/M	1.73	0.81	0.76	0.83

Figure 2 and Table 2show that when the lymph node SUVmaxwas ≥ 3.15, the lymph node SUVmax/liver SUVmaxwas ≥1.65, and the lymph node SUVmax/liver SUVmaxwas ≥ 1.73, their sensitivities were 0.79, 0.83, and 0.81, respectively, and their specificities were 0.74, 0.89 and 0.76, respectively. Therefore, the accuracy of the lymph node SUVmax/liver was the highest. The sensitivity and specificity of anSUVmax ≥ 1.65 in differentiating metastatic and benign lymph nodes of lung cancer were greater than those of the other two parameters.

4. Discussion

Lung adenocarcinoma staging was based on the TNM staging system of the International Association for the Study of Lung Cancer (IASLC). Generally, early stage refers to stage II/III disease with no lymph node metastasis ($T_{1-2}N_0$), locally advanced refers to stage II/III disease with lymph node metastasis (N+), and late stage refers to stage IV disease with distant metastasis. At present, the treatment principle of early-stage lung adenocarcinoma is surgery, and the treatment of patients with resectable stage II/III lung adenocarcinoma is complete surgical resection supplemented with postoperative chemotherapy and radiotherapy.For patients with inoperable lung adenocarcinoma(mostly stagesIIIb,IIIc and IV lung adenocarcinoma), radiotherapy combined with chemotherapy is the standard treatment[10].Therefore,

mediastinal lymph node metastasis plays a decisive role in the treatment of early-stage and locally advanced lung cancerpatients.

Cha J[11]proved that ^{18}F-FDG PET/CT is superior to CT in differentiating benign and malignant thoracic lymph nodes. The specificity of ^{18}F-FDG PET/CT is 94.5%, and its negative predictive value is very high [12]. From the results presented above, we also confirmed that three parameters, lymph node SUVmax, lymph node SUVmax/liver SUVmax, and lymph node SUVmax/mediastinalSUVmax, have high accuracy in differentiating metastatic and non-metastatic lymph nodes of lung cancer. This study provides a good basis for the clinical evaluation of lymph node metastasis in lung cancer [13]. However, the cut-off value used in this study was larger than that used in previous studies [14–16]. This is mainly due to the large number of inflammatory lymph nodes in our study, and inflammatory lymph nodes can lead to an increase inthe SUV [17–18]. This further suggests that population differences should be taken into account if the above methods are to be more widely used in the differential diagnosis of lung cancer lymph nodes.

Li's[19]meta-analysis of PET/CT in the diagnosis and staging of mediastinal lymph nodes of lung cancershowed that if the analysis was based on patients,the total sensitivity and specificity were 78% and 87%, respectively; however, if the analysis was based onlymph nodes, the sensitivity and specificity were 66% and 94%, respectively. However,in the clinic,the N stage of lymph node metastasis and the TNM stage of lung cancer are determined by lymph node grouping. Therefore, this study usedthe lymph node group as the research object to analyse PET/CT in the differential diagnosis of mediastinal lymph nodes.

Our study showed that although the lymph node SUVmax, lymph node SUVmax/liver SUVmax and lymph node SUVmax/mediastinalSUVmax have high accuracy in differentiating metastatic and non-metastatic lymph nodes of lung cancer, the accuracy of a lymph node SUVmax/liver SUVmax≥1.65 is better than that of the other two parameters.

Although the accuracy of PET/CT in the diagnosis of lymph node metastasis is very high, there are still many false negatives and false positives. Falsenegatives are more common in microlymph node metastasis, which is mainly related to the low resolution of PET/CT. Falsepositives, such as fibrotic lymph nodes and inflammatory proliferative lymph nodes, also increase FDG metabolism in these lymph nodes, especially in patients with tuberculosis and silicosis [20]. PET-CT should be combined with medical history and other objective examinations for a comprehensive diagnosis to reduce the occurrence of false negatives and false positives.

5. Conclusion

This study found that a lymph node SUVmax ≥ 3.15, a lymph node SUVmax/liver SUVmax ≥ 1.65, and a lymph node SUVmax/mediastinalSUVmax ≥ 1.73 can differentiate benign and malignant lymph nodes in the primary lesions of lung adenocarcinoma patients, and the accuracy of a lymph node SUVmax/liver SUVmax ≥ 1.65 is better than that of the other two parameters. Providing an objective and accurate diagnostic basis is helpful for the formulation of clinical treatment plans, as it reduces unnecessary or

excessive treatment and thus reduces the proportion of patients who receive improper treatment. However, this study was limited by the small number of patients enrolled and the number of metastatic lymph nodes assessed.

Abbreviations

Abbreviations	The name in full
SUV	standardized uptake value
ROC	Receiver operating characteristic
SUVmax	the maximum standardized uptake value
ROI	region of interest
AUC	The area under the curve
N/L	lymph node SUVmax/liver SUVmax
N/M	lymph node SUVmax/mediastinalSUVmax

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

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Availability of data and materials

Data necessary to support the conclusions of this article are presented in “Results” section. Additional data is available on reasonable request to the corresponding author.

Author contributions

Yongan Hu was responsible for PET/CT image acquisition; Sisi Wang collected the clinical data; Qifeng Huang finished the draft manuscript; Guanghua Wen revised the paper; all authors approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figures

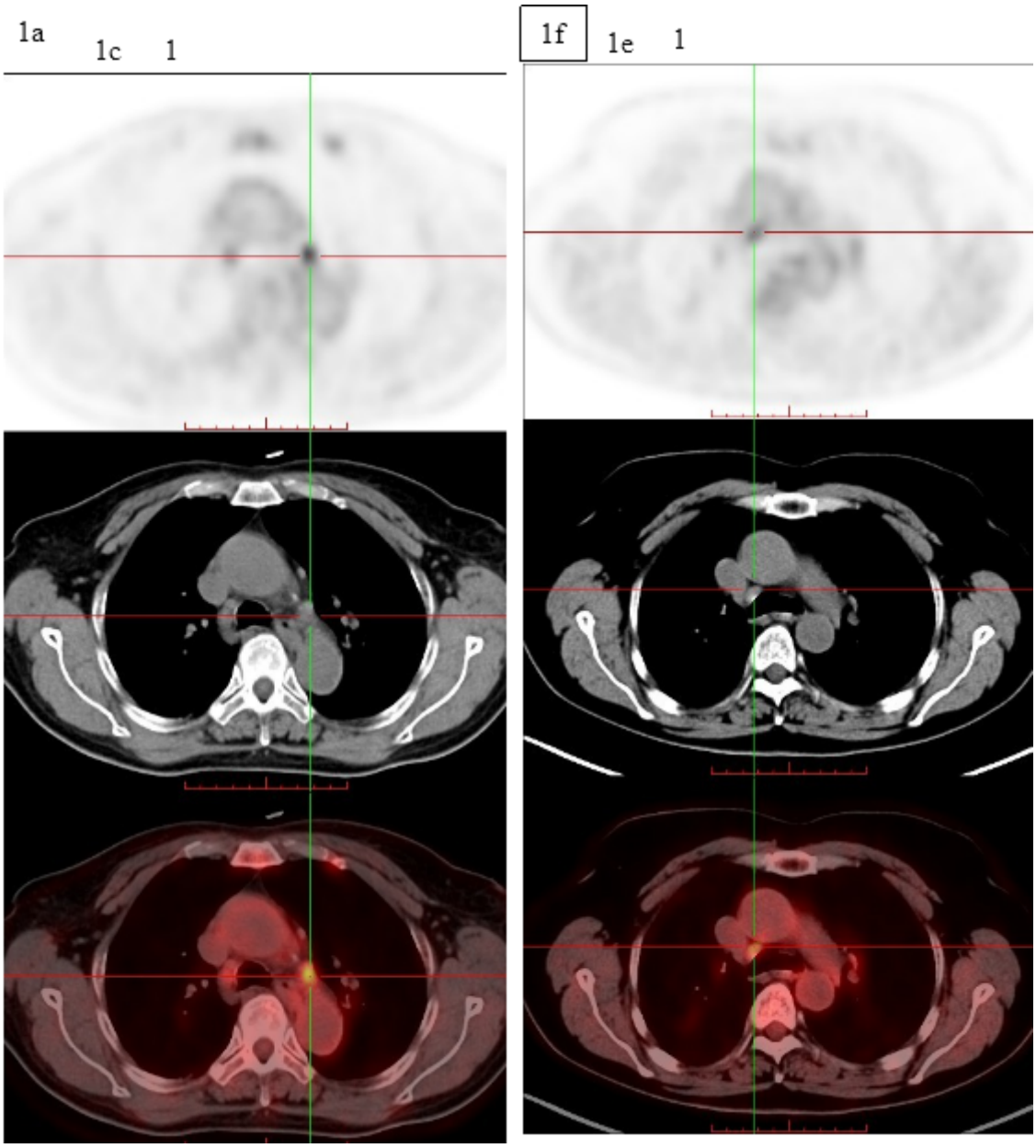

Figure 1

1a, 1b, and 1cshow a 70-year-old female patient with lung adenocarcinoma whose No.5 lymph node was enlarged, lymph node SUVmaxwas 5.1, lymph node SUVmax/liver SUVmaxwas 1.72, and lymph node SUVmax/liver SUVmaxwas 2.17. Postoperative pathology confirmed metastatic lymph nodes. Fig. 1d, 1e, and 1fshow a62-year-old female patientwith lung adenocarcinoma whose fourth lymph node was enlarged, lymph node SUVmaxwas 3.4,lymph node SUVmax/liver SUVmax was 1.06, and lymph node SUVmax/liver SUVmax was 1.33. Postoperative pathology confirmed chronic inflammation.

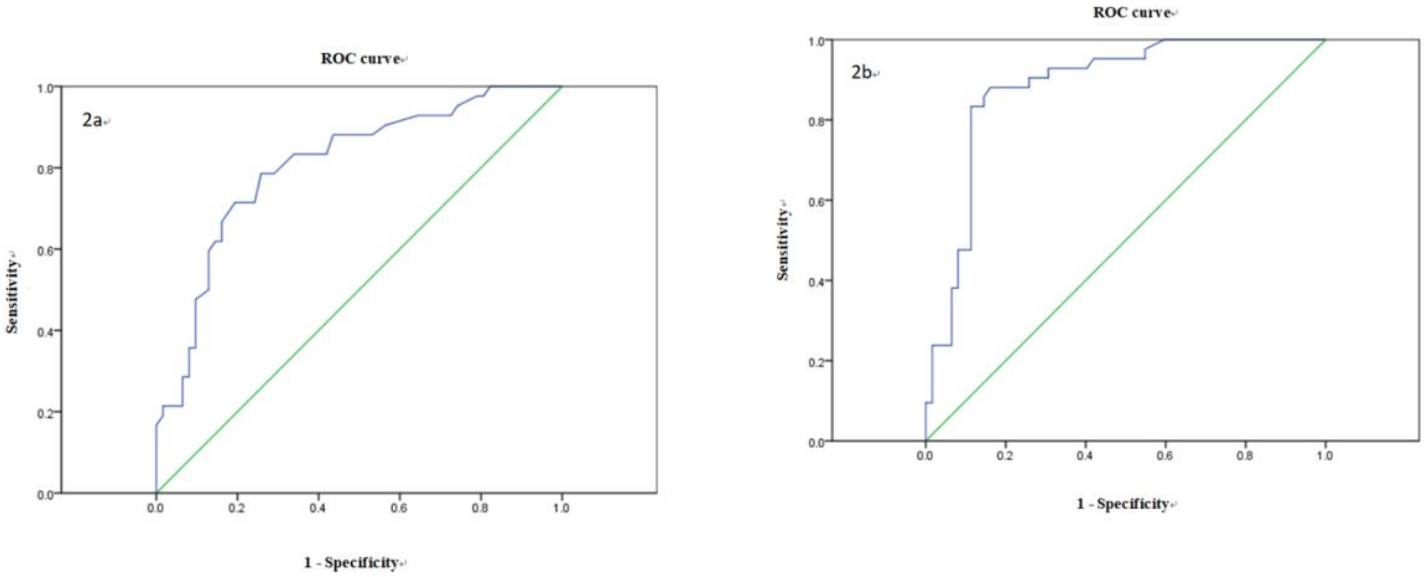

Figure 2

ROC curve of metastatic and non-metastatic lymph nodes in lungadenocarcinoma

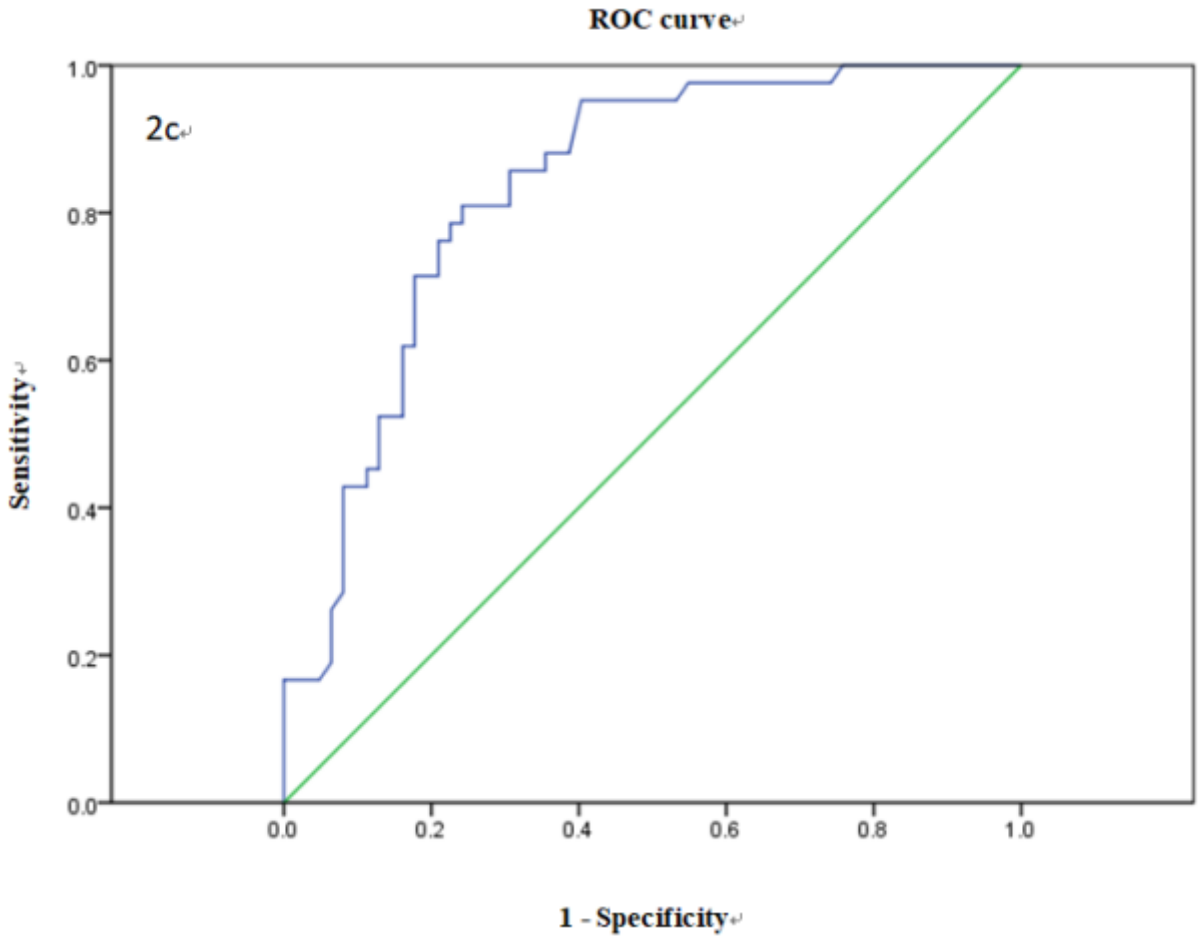

Figure 3

a. shows the ROC curve according to the lymph node SUVmax; Fig.2b.shows the ROC curve according tothe lymph node SUVmax/SUVmax; and Fig.2c.shows the ROC curve according tothe lymph node SUVmax/mediastinalSUVmax.