Original Article

Modified method to improve the diagnostic efficiency of ^{18}F-FDG PET/CT in regional lymph node metastasis of esophageal squamous cell carcinoma

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Background: Regional lymph node (LN) metastasis is a significant factor influencing the treatment choice of esophageal squamous cell carcinoma (ESCC). The performance PET/CT as an imaging evaluation method for regional LNs in ESCC, is unsatisfactory due to the lack of logical criterion. We explored how a modified criterion improved the diagnostic value of ^{18}F-FDG PET/CT in regional LN metastasis.

Methods: The data from 111 patients with ESCC were analyzed retrospectively. All patients underwent preoperative PET/CT examination, resection of the cancer, and regional LN dissection. The PET/CT images were interpreted by two experienced diagnosticians. LNs were allocated to five subregions. Each LN was diagnosed by two diagnostic criteria of PET/CT (traditional criterion and the modified criterion) one by one across the same field, and the accuracy of PET/CT was determined using the histopathologic results as the reference standard.

Results: A total of 4,847 LNs were dissected, of which 147 were confirmed as metastases by postoperative pathology. A total of 656 LNs were screened by ^{18}F-FDG PET/CT imaging. The determination of all 656 LNs by PET/CT was compared with the pathological results. The diagnostic accuracy of the modified and traditional criteria for the five subregions (paraesophageal, neck, upper mediastinal, middle-lower mediastinal and ventral subregions) was: 74.60% *vs.* 61.90%, 86.44% *vs.* 81.36%, 90.26% *vs.* 70.78%, 96.19% *vs.* 75.09%, and 87.91% *vs.* 85.71%, respectively.

Conclusions: The modified diagnostic criterion had better diagnostic efficiency because it combined PET and CT imaging data.

Keywords: ^{18}F-FDG PET/CT; diagnostic criteria; esophageal cancer; regional lymph node metastasis

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Introduction

Esophageal cancer is a common gastrointestinal neoplasm with high invasiveness and poor prognosis. It ranks seventh in morbidity and sixth in mortality globally (1). In China, even with its declining morbidity and mortality, it is still one of the top four common cancers, ranking below lung cancer, gastric cancer, and liver cancer.

There are two main histological subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). The most common type in China is ESCC, accounting for more than 90% of cases of esophageal cancer, while in Western countries EAC is more common (2).

Lymph node (LN) metastasis is one of the main routes of spread in esophageal cancer. The incidence of LN metastasis is high, even with superficial esophageal cancer, about 50% in submucosal SCC totally (3). According to the eighth edition of the tumor-node-metastasis (TNM) staging guidelines for esophageal cancer released jointly by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) (4), N staging of esophageal cancer is related to the number of metastatic LNs and closely related to the survival rate of esophageal cancer. Therefore, analysis of even a single LN is significant for accurately determining the N stage. The 5-year survival rate of patients with and without positive LNs is reportedly <15% or >40% (5-8). Yamashita *et al.* concluded that about 59.7% of all recurrent cases were mainly due to LN involvement after radical resection (9). N staging is an important independent prognostic factor, and accurate N staging is essential for successful treatment (8).

At present, the methods for N staging of esophageal cancer can be divided into invasive and noninvasive detection. Invasive detection is mainly based on regional LN biopsy by endoscopy and mediastinoscopy. Invasive LN biopsy has high sensitivity and specificity. Both thoracoscopic and laparoscopic detection methods perform well in the diagnosis of regional LN and distal metastasis (10), but they are invasive and traumatic to patients.

Noninvasive detection methods are mainly based on imaging evaluation, including computed tomography (CT), endoscopic ultrasound (EUS), and positron emission tomography (PET)/CT, each with its own advantages in the diagnosis of esophageal cancer.

EUS is considered to be the most accurate imaging method for evaluating the depth of invasion of primary esophageal cancer, with an accuracy of 89% (11). However, its accuracy in N staging is not satisfactory at 73% (12). Furthermore, its effectiveness is usually affected by factors such as instrument performance, operation technology, and diagnostic criteria. It is difficult to assess LNs below the primary lesion in cases of severe esophageal stenosis. CT is widely used in the staging of esophageal cancer, but can only provide anatomic information on the LNs, mainly relying on their size. In fact, some obviously enlarged LNs may be the result of benign hyperplasia, and small LNs may also be malignant (13). Therefore, the diagnostic effectiveness of CT for regional LNs in esophageal cancer is not ideal. Li *et al.* reported that the shortest diameter for the diagnostic criterion of LNs in esophageal cancer could be <10 mm on CT (14). As for radiotherapy, a CT-based study suggested that regional LN groups should be electively included in the clinical target volume for precise radiation administration (15).

PET/CT is becoming more and more widely used for preoperative evaluation of esophageal cancer because of its unique value in diagnosis, staging, and prognostic and treatment evaluation (16). However, according to the literature, the accuracy of PET/CT in the diagnosis of regional LN metastasis of esophageal cancer is limited, mainly because the diagnostic criteria simply depend on SUV alone, or singly combine with the data such as the density or length of LNs from CT images. For example, in research by Kim *et al.* (17), the sensitivity, specificity and accuracy of PET/CT were 58.8%, 74.5% and 70.8%, respectively, using the diagnostic criterion "structurally identifiable nodes with FDG uptake focally prominent compared with background mediastinal activity was considered as positive for malignancy by PET/CT"; however, the specificity and accuracy improved to 90.9% and 80.3% respectively when LNs >71 Hu were excluded from the PET/CT diagnosis of metastases, the study confirmed that the more logical the diagnostic criteria, the better the diagnostic capacity. Ela Bella *et al.* (18) concluded that diagnostic accuracy differed obviously according to the variable SUVmax cutoff value, and best ability to distinguish benign from malignant occurred at an SUVmax cutoff value of 4.1, with sensitivity, specificity, and accuracy of 80%, 92%, and 90%, respectively. Furthermore, the higher the cutoff value in the range of 1.1–17.8, the lower the diagnostic sensitivity and the higher the specificity. A meta-analysis published by Jiang *et al.* showed that PET/CT diagnostic results varied significantly according to the different criteria used (19).

Overall, improved diagnostic ability of PET/CT depends on efficient criteria. However, most of the traditional

diagnostic criteria in the literature rely on SUVmax alone, and a minority combine data such as the density or length of LNs from CT images only. Furthermore, the definition of lymph node was region by region, not one by one in former literature. We have used a traditional criterion to evaluate regional LNs of ESCC in our clinic work but with unsatisfactory results. So in our study, we not only set a modified criterion that used a significant combination of PET and CT images, but also determine nature of lymph nodes one by one. The modified criterion excluded LNs with relatively defined benign CT signs from malignant regardless of FDG uptake. The modified criterion performed better in our clinic work, so we designed the present study to explore how our modified criterion improved the diagnostic efficiency of PET/CT.

We present the following article in accordance with the STARD reporting checklist (available at https://dx.doi.org/10.21037/atm-21-4926).

Methods

Patient selection

This study retrospectively collected the data for all patients with esophageal cancer treated in hospital between June 2016 and December 2018 with thoracic surgery and who were evaluated preoperatively with ^{18}F-FDG PET/CT. A total of 111 patients were selected based on the following inclusion criteria: (I) diagnosed as ESCC by preoperative gastrointestinal biopsy with related auxiliary examination tools indicating surgical treatment; (II) non-esophageal and gastric junction area tumors; (III) no history of malignant tumors of other organs or previous malignant tumors during the same time period; (IV) no preoperative antitumor treatment or endoscopic tumor resection; (V) PET/CT examination performed in-hospital and completed within 2 weeks of surgery; and (VI) able to tolerate surgery and radical tumor resection and having complete postoperative pathological data. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Fujian Medical University Union Hospital (No. 2015KY021). Individual consent for this retrospective analysis was waived.

Surgery and pathology

Radical surgery was performed with a full-cavity neck–thoracoabdominal incision (McKeown) surgical approach. The specific operative protocol is described below.

After the patient was anesthetized, single-lumen tracheal intubation was performed. With the patient in the left lateral prone position and accompanied by CO_2 artificial pneumothorax, freeing of the thoracic esophagus under thoracoscopy and dissection of the mediastinal LNs were performed. After thoracic surgery was completed, the patient was placed in the supine position for laparoscopic freeing of the stomach and perigastric LNs, while at the same time in the left neck the esophagus was removed. Next, a 10-cm incision was made in the midline of the upper abdomen for removal of the esophagus and stomach. The stomach was formed into a tube and anastomosed to the left neck. Samples of the LNs dissected with the esophagus and some stomach specimens were sent for routine pathologic examination. Evaluation of the anterior cervical LNs and the pathologic findings of frozen LNs adjacent to the right recurrent laryngeal nerve were the basis for selective removal of cervical LNs. Finally, a conventional indwelling gastrointestinal decompression tube and jejunostomy tube were placed. After surgery, all LNs were isolated from the resected esophageal specimens and tissues around the esophagus, and the LN groups of each anatomic site were numbered according to the number of corresponding LN groups in the eighth edition of the AJCC/UICC esophageal cancer TNM staging. The isolated specimens were fixed in 10% formalin buffer and embedded in paraffin. Each LN was cut into 3-μm thick slices along the longest axis, stained with hematoxylin and eosin, and then examined microscopically by two senior pathologists. Metastatic LNs were positive, and the benign ones were negative.

Equipment

The PET/CT equipment was a hybrid system (GE Discovery LS). The imaging agent was ^{18}F-FDG (Nanjing Jiangyuan Andy Electronics Research and Development Co. Ltd. Fuzhou Branch). All patients fasted for 6–8 h before the examination, ensuring that their fasting blood glucose values were within the acceptable range. Each patient received an intravenous injection of 4.44–5.55 MBq/kg ^{18}F-FDG, before resting quietly supine for 45–60 min in a darkened room. Image acquisition ranged from the cranial crest to the middle femur. The CT scanning parameters were 120 KV, 150 mA, and a scanning layer thickness of 4.25 mm. PET scan parameters were 2.5 min/bed for a total of 6–8 beds, three-dimensional acquisition, and an

acquisition time of approximately 18–20 min. After imaging was completed, the CT data were used for attenuation correction, and the data were reconstructed by the iterative method for image fusion to obtain PET, CT, and PET/CT fusion images in cross-section, the sagittal plane, and the coronal plane, respectively.

Image analysis and comparison of examinations

Both the PET and CT images were separately reviewed by two experienced PET/CT physicians. PET image analysis mainly used visual and semiquantitative analytical methods. Visual analysis determined if the radioactive uptake of the lesion on the PET image was higher than that of the surrounding background; in the semiquantitative analysis a region of interest was drawn on the PET image, and the SUVmax was automatically calculated by the computer. CT was used mainly to obtain information such as the location, number, size, density, and shape of LNs in the esophagus. These image observation results were analyzed and recorded by the same PET/CT physician using the two diagnostic criteria separately, one is traditional like in the former study, the other one is modified based on the traditional. Pathologic examination was selected as the gold standard for determining the nature of the LNs. Each LN was diagnosed and compared with the postoperative pathologic examination one by one across the same field to evaluate the diagnostic value of PET/CT (with the two diagnostic criteria).

LN grouping needs to be simplified to facilitate data analysis, according to the research of Yamada *et al.* (20). Our diagnosis by PET/CT and the pathologic examination were divided into five subregions: (I) paraesophageal group (mediastinal 8 U/M/L group); (II) neck area (mediastinal 1 R/L group); (III) upper mediastinum (mediastinal 2 R/L group); (IV) middle-lower mediastinum (mediastinal 4, 7, 9 R/L group); and (V) abdominal area (groups 15–20), based on the eighth edition of the UICC/AJCC TNM staging guidelines for LN grouping. When the grouping of LNs was controversial, the results were decided by consensus of the surgeon and PET/CT physicians.

Diagnostic criteria

We used two diagnostic criteria in the analysis of the PET/CT images, which we named Criterion 1 (the traditional one) and Criterion 2 (the modified one).

Criterion 1 was based on traditional diagnostic criteria derived from the literature (17,18,21-24), and summarize their experience in improving diagnostic capacity. For example, Yamada *et al.* (20) considered that the SUVmax threshold for malignant LNs in the tracheal bifurcation and pulmonary hilum should be higher than for other sites. So in our Criterion 1, the LN was diagnosed positive if the FDG uptake was higher than that of the liver in the middle-lower mediastinum and focally prominent compared with background mediastinal activity in the remaining areas with structurally identifiable nodes.

Criterion 2 was modified fully formulated with the CT images. It excluded LNs with relatively defined benign CT signs from malignant, regardless of FDG uptake based on Criterion 1. The defined benign CT signs were derived from previous literature (17,25). In our Criterion 2, LN status was positive when the following conditions were met: FDG uptake higher than the liver in the middle-lower mediastinum and focally prominent compared with background mediastinal activity in the remaining areas with structurally identifiable nodes. At the same time, if any one of clear CT benign signs existed, including holistic high density (CT value >71 HU), mature calcification, identifiable hilum of the lymph gland and fat density, malignancy was excluded regardless of FDG uptake.

Statistical analysis

Statistical analysis was performed by IBM SPSS Statistics version 23 software (SPSS Inc., Chicago, IL, USA). Taking the pathologic reports of surgically removed specimens as the standard, the diagnostic efficiency of the two diagnostic criteria was analyzed. The diagnostic performance of the two criteria was compared by Chi-square test with exact method. The sensitivity, specificity, accuracy, false-positive rate, false-negative rate, negative predictive value (NPV) and positive predictive value (PPV) were calculated. Differences were considered statistically significant when $P<0.05$.

Results

LN status

The 111 cases included were all ESCC. A total of 4,847 LNs were surgically removed, of which 147 were pathologically confirmed as metastases with the following regional distribution: 38 paraesophageal sulcus, 14 cervical area, 34 upper mediastinum, 17 middle-lower mediastinum,

Table 1 Patient characteristics

Characteristics	Number of patients (n=111)
Age (years), median [range]	60.2 [40–88]
Gender, n (%)	
Male	84 (75.7)
Female	27 (24.3)
Location of cancer, n (%)	
Upper thoracic	12 (10.8)
Middle thoracic	65 (58.6)
Lower thoracic	34 (30.6)
Pathological T stage[a], n (%)	
T1	24 (21.6)
T2	16 (14.4)
T3	69 (62.2)
T4	2 (1.8)
Pathological N stage[a], n (%)	
N0	61 (55.0)
N1	27 (24.3)
N2	19 (17.1)
N3	4 (3.6)
Pathological M stage[a], n (%)	
M0	111 (100.0)
M1	0 (0.0)
P stage[a], n (%)	
IA	1 (0.9)
IB	25 (22.5)
IIA	20 (18.0)
IIB	19 (17.1)
IIIA	2 (1.8)
IIIB	40 (36.0)
IV	4 (3.6)

[a], TNM Classification of Malignant Tumors (8th edition).

and 44 abdominal area. A total of 652 LNs were screened [diameter >0.4 cm, with a soft tissue component (26)] on a dedicated imaging workstation, while a total of 656 LNs were analyzed (4 missed small LNs in the esophageal group were artificially added in because of their pathologically positive nature in order to facilitate data analysis and PET/CT diagnosis, which was assumed to be false negative). Of the 656 LNs, the respective positive rate of LNs in the five subregions (the number of pathologically positive LNs/number of LNs selected by the image in the corresponding area) were as follows: 60.32% (38/63) in the paraesophageal group, 23.72% (14/59) in the neck area, 22.07% (34/154) in the upper mediastinal area, 5.88% (17/289) in the middle-lower mediastinum, and 48.35% (44/91) in the abdominal area. The patients' characteristics are summarized in *Table 1*.

Table 2 Comparison of Criterion 1 PET/CT with pathological diagnosis

PET/CT	Postoperative pathology		Total
	+	–	
Criterion 1			
+	106	124	230
–	41	385	426
Total	147	509	656

Criterion 1 diagnostic results

For all 656 LNs, the overall results for Criterion 1 are summarized in *Table 2*. Of them, 230 were judged to be positive (including 124 false positives), and the remaining 426 were judged to be negative (including 41 false negatives). The 124 false positives were distributed as follows: 13, 8, 33, 64, 6 respectively in the paraesophageal area, cervical area, upper mediastinum, medial-inferior mediastinum, and abdominal region. The 41 false negatives were distributed as follows: 11, 3, 12, 8, 7 respectively in the paraesophageal group, neck area, upper mediastinum, mid-inferior mediastinum and 7 in the abdominal area.

Criterion 2 diagnostic results

The overall diagnostic results of Criterion 2 are shown in *Table 3*. Of all 656 LNs, 124 were diagnosed as positive and the remaining 532 as negative, including 19 false positives and 42 false negatives. The distribution of all the false positives was as follows: 5, 5, 3, 2, 4 respectively in the paraesophageal group, cervical area, upper mediastinum, mid-inferior mediastinum and abdominal region. The distribution of the 42 false negatives was: 11, 3, 12, 9, 7 respectively in the paraesophageal group, cervical region, upper mediastinal, mid-inferior mediastinum and

Table 3 Comparison of Criterion 2 PET/CT with pathological diagnosis

PET/CT	Postoperative pathology		Total
	+	–	
Criterion 2			
+	105	19	124
–	42	490	532
Total	147	509	656

abdominal area.

Comparison of the diagnostic efficacy of the two criteria for LN metastases

The overall accuracy, sensitivity, specificity, false-positive rate, false-negative rate, PPV, and NPV of Criterion 1 versus Criterion 2 were as follows: 74.85% *vs.* 90.70%, 72.11% *vs.* 71.43%, 75.64% *vs.* 96.27%, 24.36% *vs.* 3.73%, 27.89% *vs.* 28.57%, 46.09% *vs.* 84.68%, and 90.38% *vs.* 92.11%. The diagnostic efficiency of Criterion 2 for both the overall LNs and for the five subregions was significantly higher than that of Criterion 1 (P<0.001). For malignant lymph nodes up to PET resolution in diameter, diagnostic accuracy of both criteria is satisfactory (*Figure 1*). But for small nodes beyond PET resolution and hard to observe CT sign, missed diagnosis is common in both criteria (*Figure 2*). Compared with Criterion 1, Criterion 2 was obviously better, with a significant reduction in the false-positive rate (*Figures 3,4*). The diagnostic efficacy of the two criteria is showed in *Tables 4,5*.

Discussion

Metastasis to the LNs is a highly significant prognostic factor in esophageal cancer, with the LN stage also being influential on outcome. Therefore, accurate evaluation of the LNs before operation is critical in clinical practice. The most frequently used noninvasive detection methods includes EUS, CT, and PET/CT. For EUS, it is difficult to assess LNs below the primary lesion in cases of severe esophageal stenosis. CT is widely used although, but it can only provide anatomic information on the LNs, such as their size, morphology and density, which leads to unsatisfactory diagnostic effectiveness. PET/CT, combines CT with PET, and lymph node images are made by morphological characteristics as well as biological metabolism. In diagnosing, ^{18}F-FDG PET/CT would also take lymph node grouping metabolism into account, using SUVmax and CT sign for analysis. Diagnosis of lymph node metastasis by this method may be more acutely and objectively. However, the relevant literature reports that the diagnostic ability for regional LN metastasis of esophageal cancer is limited, so improvement in diagnostic ability for LN metastases has clinical significance. Kim *et al.* (17) concluded that compared with CT, PET/CT performed worse for diagnostic accuracy, specificity, and similar sensitivity for regional LNs, at 70.8%, 74.5%, and 58.8% respectively. We believe those researchers did not take full advantage of the combination of PET and CT imaging, because their diagnostic criteria adopted relied solely on the SUVmax threshold or combination with only the CT value/LN diameter. Thus, the diagnostic efficiency remained unsatisfactory. Research by Ela Bella *et al.* (18) and Jiang *et al.* (19) confirmed that the criterion of SUVmax threshold combined with the CT value or SUVmax threshold stratification could improve diagnostic efficiency. However, PET/CT imaging determined LNs "group by group" or "person by person", in their research, not by individual nodes, so their results did not truly reflect the diagnostic capability of PET/CT. We believe that different PET/CT equipment, different scanning parameters, and different physiologic states of the patients all lead to different optimal diagnostic SUVmax thresholds, so diagnostic methods that solely rely on SUVmax thresholds will have poor repeatability and universality. In addition, each of the LNs screened by PET/CT imaging in our study was compared one by one with the pathologic results, and also divided into five subregions for discussion. As the representative of traditional diagnostic methods, Criterion 1 in our study integrated the criteria in the previous literature to maximize their strengths and avoid weaknesses. For example, SUVmax threshold stratification was adopted, and a positive SUVmax threshold for the middle-lower mediastinum was determined as being higher than the liver background and higher than the surrounding background for the remaining areas. Our modified diagnostic method, represented as Criterion 2, combined the data provided by CT images on the basis of Criterion 1, and fully utilized the advantages of combined anatomic and functional imaging by PET/CT.

The overall and regional diagnostic efficiency of Criterion 2 was significantly higher than that of Criterion 1. The major shortcoming of Criterion 1 was its high false-positive rate, which was mainly distributed in

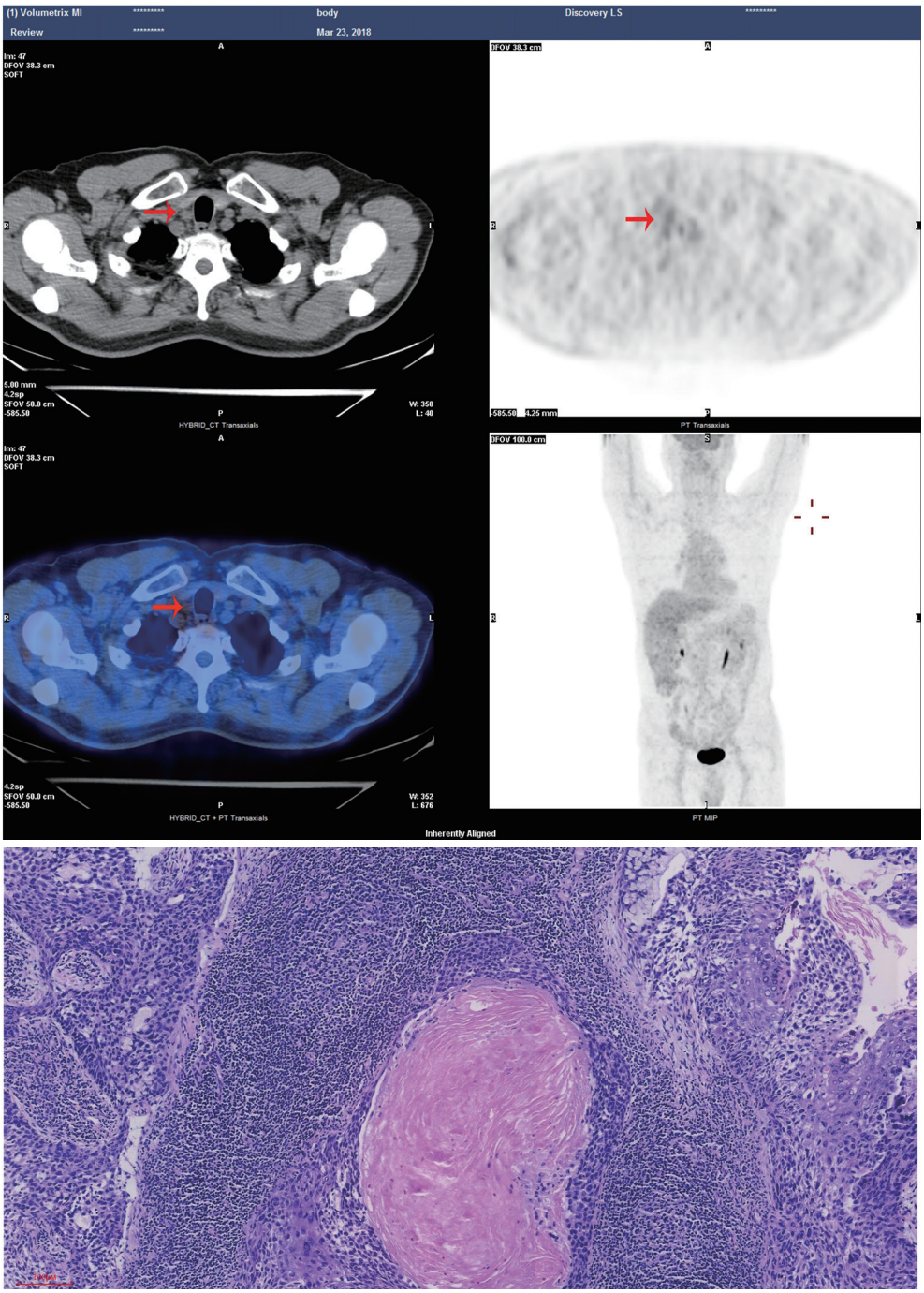

Figure 1 A malignant lymph node of Oesophageal squamous cell carcinoma. Images obtained with PET/CT showed a lymphatic node with FDG uptake higher than background in Group 2R (arrow), without clear CT benign signs. Both criteria diagnosed as malignant; histological section showed a metastatic squamous cell carcinoma (haematoxylin-eosin stain; original magnification, ×100).

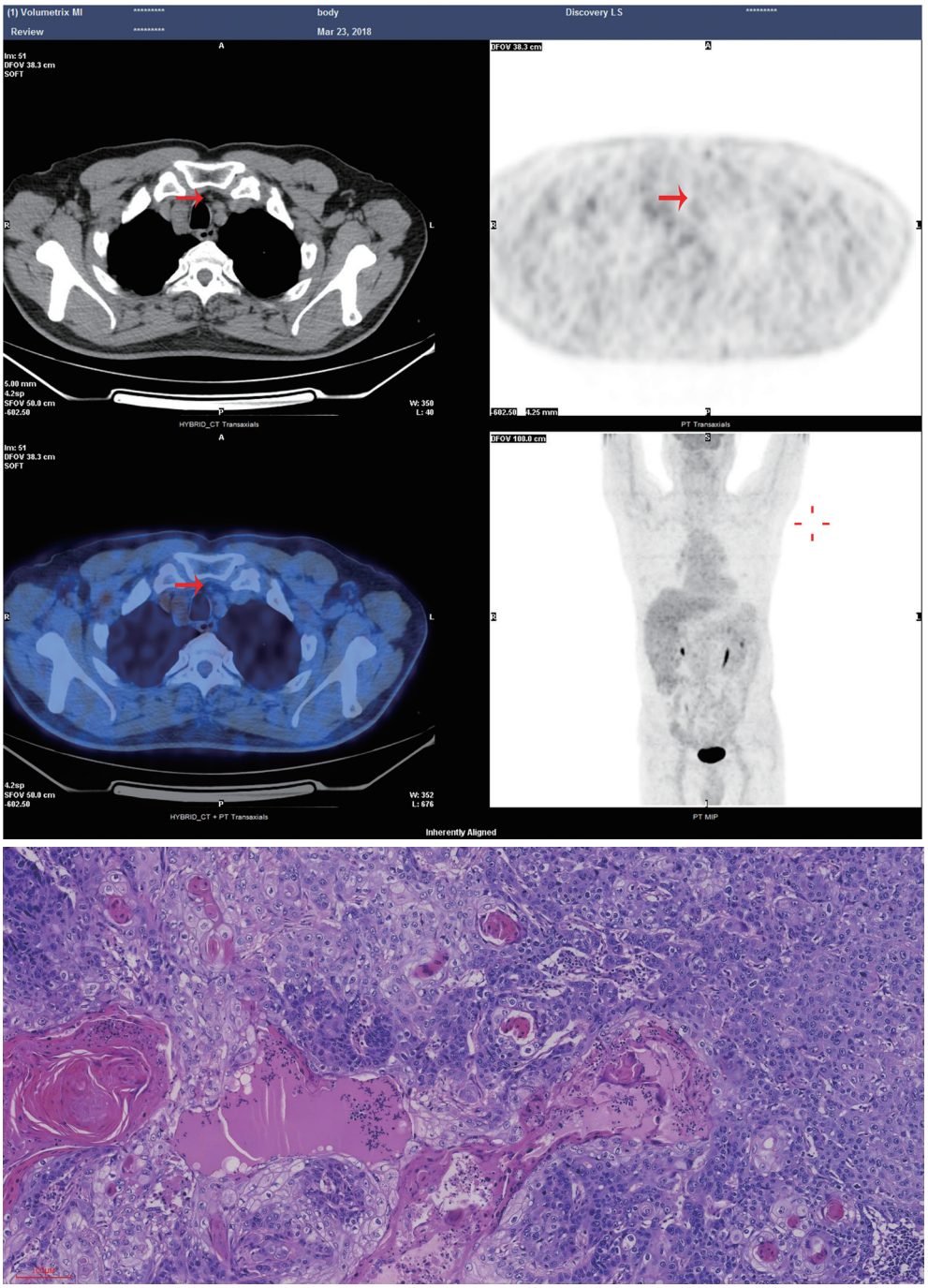

Figure 2 A malignant lymph node of Oesophageal squamous cell carcinoma. Images obtained with PET/CT showed a small lymph node in Group 2L (arrow), 0.3 cm in diameter, too small to reach the revolution of PET and hard to observe CT sign, no increased FDG uptake, both criteria missed diagnosis. Histological section showed a metastatic squamous cell carcinoma (haematoxylin-eosin stain; original magnification, ×100).

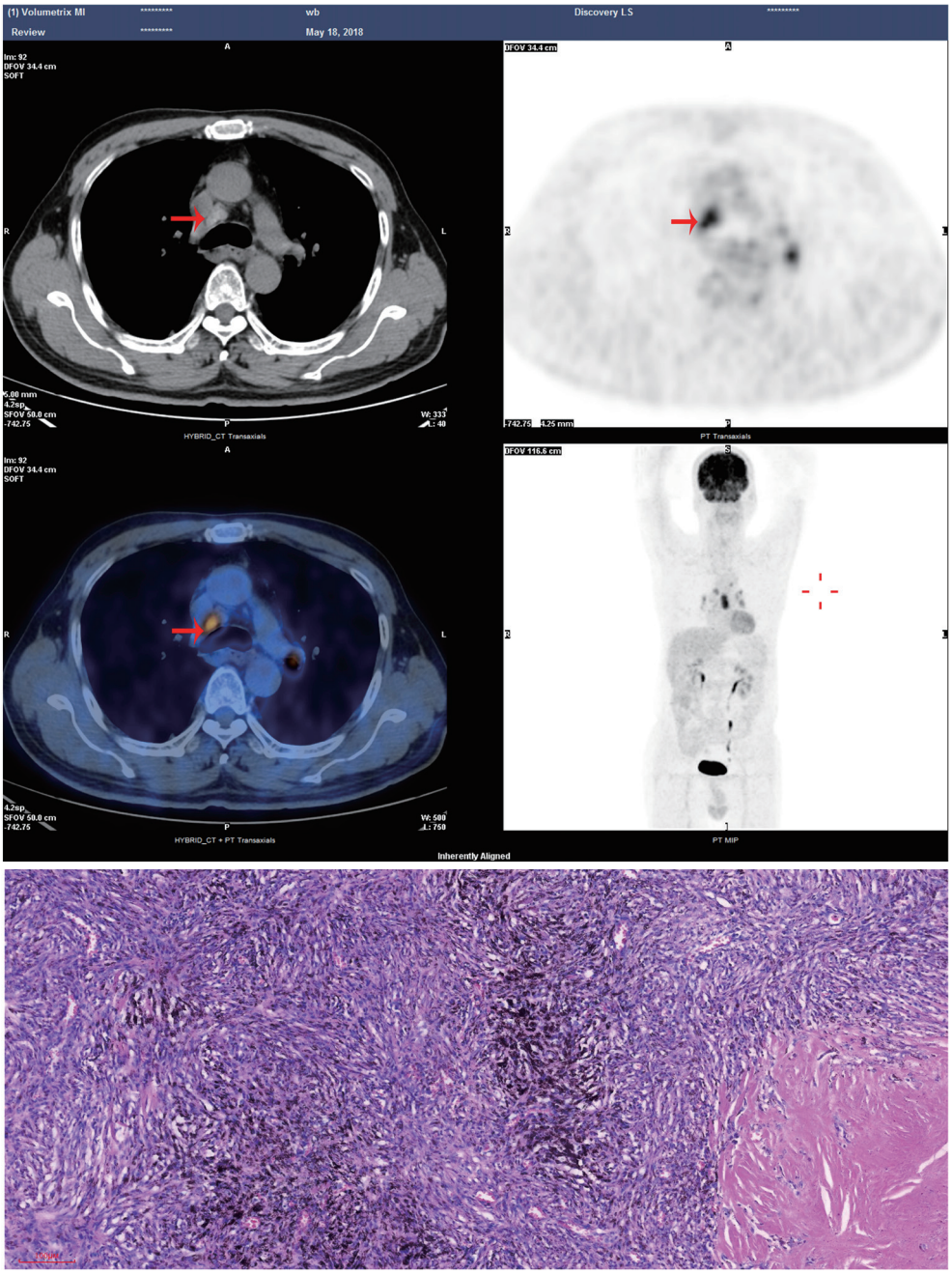

Figure 3 A benign lymph node in Group 4R. PET/CT image showed a node with FDG uptake higher than background with holistic high density (arrow). Criterion 1 diagnosed as malignant while Criterion 2 as benign. Histological section showed extensive collagenous fibrous tissue deposition surrounded by proliferating fibroblasts (haematoxylin-eosin stain; original magnification, ×100).

para-esophageal sulcus region and mediastinum, often complicated with chronic pneumonia, pulmonary tuberculosis, or pneumoconiosis. We believe it is because Criterion 1 relies too heavily on SUVmax thresholds. It is difficult to differentiate LNs only by the degree of glucose metabolism, because both metastatic LNs and inflammatory LNs can be hypermetabolic in FDG uptake, and their SUVmax will have a wide cross-sectional area. Furthermore,

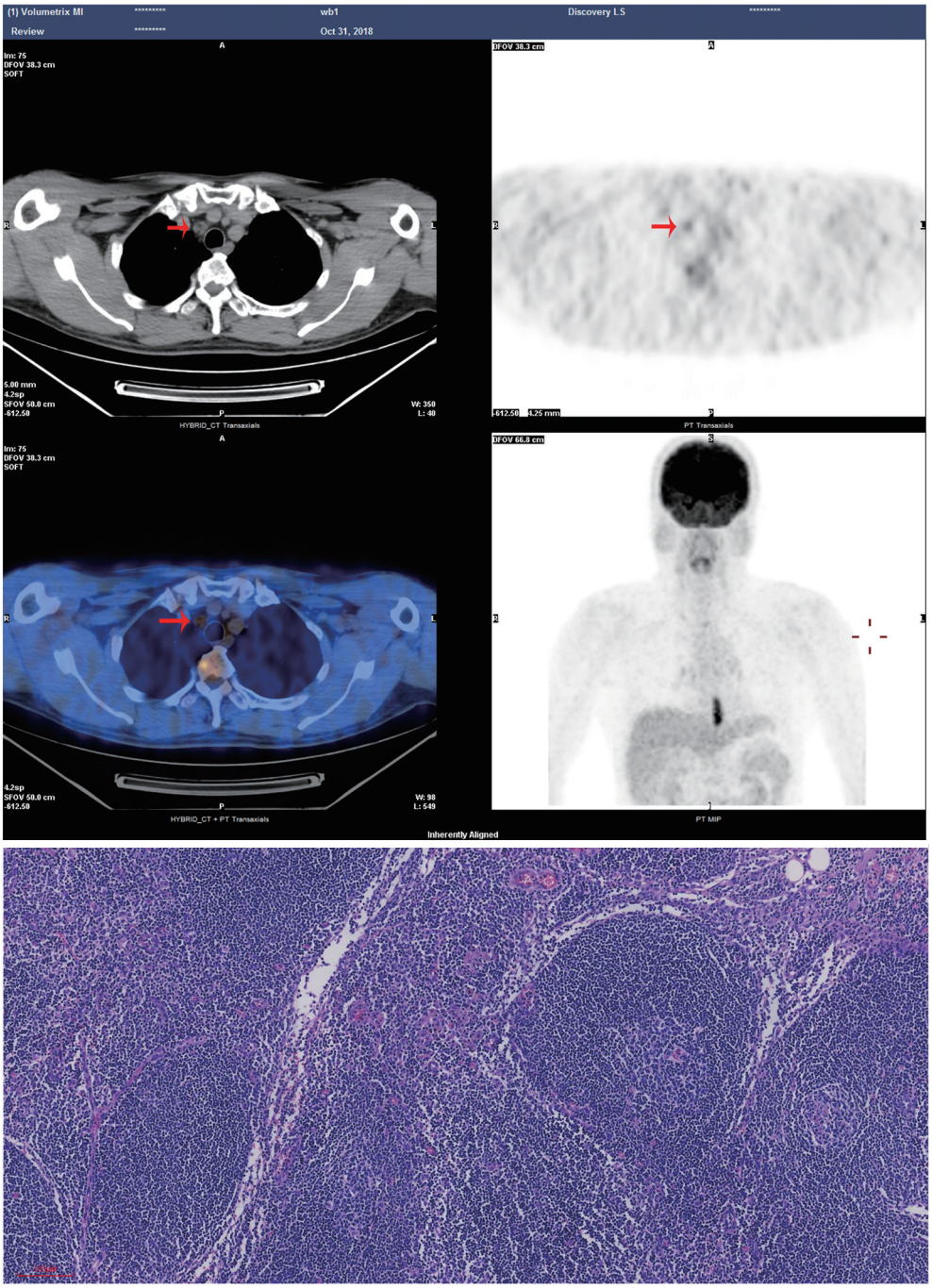

Figure 4 A benign lymph node in Group 2R. Images obtained with PET/CT showed a lymph node higher than liver in FDG uptake with identifiable lymphatic hilum structure (arrow). Criterion 1 diagnosed as malignant while Criterion 2 as benign. Histological section showed no malignant cell (haematoxylin-eosin stain; original magnification, ×100).

the mediastinum has many more inflammatory LNs because it is a common drainage area, especially in patients with chronic chest inflammation. Criterion 2 was able to reduce the false-positive rate for the para-esophageal region and mediastinum, mainly because it fully combined benign CT signs, such as mature calcification, higher

Table 4 Comparison of the diagnostic efficiency of the two criteria

Lymph node location	Criterion	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	P value
Cervical region	Criterion 1	57.89	92.50	78.57	82.22	81.36	<0.001
	Criterion 2	68.75	93.02	78.57	88.89	86.44	
Upper mediastinum region	Criterion 1	40.00	87.88	64.71	72.50	70.78	<0.001
	Criterion 2	88.00	90.70	64.71	97.50	90.26	
Middle-lower mediastinum region	Criterion 1	12.33	96.30	52.94	76.47	75.09	<0.001
	Criterion 2	80.00	96.77	47.06	99.26	96.19	
Para-esophageal sulcus region	Criterion 1	67.50	52.17	71.05	48.00	61.90	<0.001
	Criterion 2	84.38	64.52	71.05	80.00	74.60	
Abdominal region	Criterion 1	86.05	85.42	84.09	87.23	85.71	<0.001
	Criterion 2	90.24	86.00	84.09	91.49	87.91	
Overall	Criterion 1	46.09	90.38	72.11	75.64	74.85	<0.001
	Criterion 2	84.68	92.11	71.43	96.27	90.70	

Table 5 The false positive rate and false negative rate of two diagnostic criteria

Lymph node location	False positive rate (%)		False negative rate (%)	
	Criterion 1	Criterion 2	Criterion 1	Criterion 2
Cervical region	17.78	11.11	21.43	21.43
Upper mediastinum region	27.50	2.50	35.30	35.30
Middle-lower mediastinum region	23.53	0.74	47.10	52.90
Para-esophageal sulcus region	52.00	20.0	28.95	28.95
Abdominal region	12.77	8.51	15.91	15.91
Overall	24.36	3.73	27.89	28.57

PPV, positive predictive value; NPV, negative predictive value; P stage, pathological stage.

density or clear lymphoid hilum structure. So Criterion 2 avoided misdiagnosis of hypermetabolic mediastinal LNs, which makes it highly suitable for patients with chronic thoracic inflammation. Although the false-positive rate was greatly reduced in the mediastinum, it was still relatively high in the para-esophageal region and cervical region. The scalenus and sternocleidomastoid muscles are usually visually hypermetabolic, because of their complex structure and active motor function, which may visually obscure the metabolism of adjacent small LNs; therefore visual assessment may be misled while benign CT signs are detected difficultly.

The false-negative rate of Criterion 2 was similar to (slightly higher than) that of Criterion 1.We believe that the reasons for missed diagnosis are as follows: (I) the volume of the LNs was too small (mostly diameter <0.5 cm), beyond the resolution of PET; (II) the narrow sulcus between the LNs and esophageal wall, and the rich vessels in the abdominal region with complex geometry lead to missed diagnosis on CT images; (III) visual coverage of hypermetabolism of the adjacent primary lesion, vessels and peripheral inflammatory LNs will result in difficulty in observing the metabolic status of metastatic LNs.

In summary, Criterion 2 can especially improve the diagnostic value of PET/CT in ESCC patients with chronic pulmonary inflammation. Misdiagnosis or overlooking of LNs when using Criterion 2 usually occurs in the following situations: (I) presence of small LNs beyond

PET resolution; and (II) LNs visually covered by positron ray scattering (from adjacent blood vessels, muscles or the primary esophageal cancer). Therefore, the diagnostic efficacy of the modified criterion still needs to be improved for small LNs close to blood vessels, muscles, or the primary focus, such as those in the cervical region. In addition, we found that among all 656 LNs screened by PET/CT, the pathologic positive rate in the paraesophageal area was the highest (as high as 60.32%), but the diagnostic value was lower than that in this subregion, mainly because of the high false-negative rate, suggesting that LNs in the paraesophageal groove are easily missed. So, for small-volume LNs in the cervical region and paraesophageal area, the diagnostic ability of our modified criterion is still unsatisfactory.

For misdiagnosis or overlooking mentioned above, a few measures are suggested: (I) LNs diagnosis in the paraesophageal groove needs to be aggressive; (II) for small LNs beyond PET resolution, enhanced CT would be helpful; (III) improved PET resolution is important.

Conclusions

Optimizing the diagnostic criteria is very important for improving the diagnostic efficiency of PET/CT for regional LN metastasis in esophageal cancer. Our new diagnostic criterion had good diagnostic value because for the first time it fully combined the data provided by PET and CT, and analyzed LNs one by one, truly reflecting the diagnostic ability of PET/CT.

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