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# Nodal Staging of Esophageal Cancer using $^{18}$F-FDG PET: Comparisons with CT and Endoscopic Ultrasonography

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## Abstract

We prospectively investigated the accuracy of $^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in the preoperative nodal staging of esophageal cancer in comparison with CT and endoscopic sonography (EUS). Sixty-one consecutive patients with histologically proven primary esophageal cancer were studied prospectively with $^{18}$F-FDG PET. All patients underwent CT and EUS. Thirteen patients treated non-surgically were excluded from data analysis. The remaining 48 patients underwent esophagectomy and lymph node dissection. The accuracy of $^{18}$F-FDG PET, CT, and EUS were compared with histological findings. After operation, a total of 382 lymph nodes were dissected in 48 patients, of which 100 nodes in 32 patients were malignant on histological examination. EUS could not be performed in 3 patients due to the patient's refusal, and complete examination was not possible in another 12 patients due to esophageal stenosis. For nodal metastasis, $^{18}$F-FDG PET showed 57% sensitivity, 97% specificity and 86% accuracy. However, CT showed lower sensitivity (18%, $p < 0.0001$), higher specificity (99%, $p = 0.033$) and lower accuracy (78%, $p = 0.003$) than $^{18}$F-FDG PET did. For N staging, $^{18}$F-FDG PET was correct in 83% of patients (40/48), whereas CT and EUS were correct in 60% (29/48, $p = 0.006$) and 58% (26/45, $p = 0.003$), respectively. In conclusion, $^{18}$F-FDG PET is more accurate than CT and EUS for evaluating lymph node metastasis and may be helpful in determining the therapeutic plan in patients with esophageal cancer.

## I. Introduction

Esophageal cancer has one of the most unfavorable prognosis in gastrointestinal malignancies because most patients present with advanced disease at the time of diagnosis. The accurate determination of the extent of local tumor invasion, tumor size, lymph node involvement and the presence of distant metastasis at the time of diagnosis provides valuable prognostic information and is helpful in selecting appropriate treatment.

Lymph node stage in esophageal cancer is important as an independent prognostic indicator. Both the number and location of metastatic lymph nodes are significant factors for predicting the survival of patients undergoing resection of esophageal cancer.[1-6] Current modalities for preoperative staging of esophageal cancer include computed tomography (CT) and endoscopic ultrasonography (EUS). These modalities depend on morphological change of lymph node for nodal staging. However, CT shows poor sensitivity for assessing lymph node involvement because small to normal-sized nodes containing tumor cells are disregarded on CT[7,8] Endoscopic ultrasonography is more accurate than CT in differentiating benign from malignant lymph nodes in esophageal cancer.[9,10] However, complete assessment of tumor staging is not possible in approximately one third of patients because of failure to pass through the stenotic lesion.[9,10] Thus, a more accurate diagnostic modality is necessary for the preoperative nodal staging of esophageal cancer.

Recently, there have been several reports on diagnostic accuracy of positron emission tomography (PET) using $^{18}$F-fluorodeoxyglucose (FDG). $^{18}$F-FDG PET is more accurate than CT in detecting lymph node and distant metastasis in esophageal cancer.[11-13] However, most of these studies are concerned with the accuracy for detecting lymph node metastasis on a person to nodal basis because of the limited and variable range of lymph node dissection. So, the true accuracy of $^{18}$F-FDG PET for determining the presence of malignancy in individual nodal group has not been clearly demonstrated. In addition, we are not aware of any previous reports comparing the accuracy of $^{18}$F-FDG PET with that of EUS in evaluating esophageal cancer.

We thus prospectively investigated the accuracy of $^{18}$F-FDG PET in detecting lymph node metastasis compared with CT and EUS in patients with esophageal cancer before undergoing 2 (thoracoabdominal) or 3 field (thoracoabdominal and cervical) lymph node dissection.

## II. Materials and Methods

### Subjects

Between February 1997 and December 1998, a total of 61 consecutive patients with biopsy-proven esophageal cancer were prospectively included in the study. All patients underwent preoperative $^{18}$F-FDG PET. The patients underwent bone scintigraphy, esophagogastroduodenoscopy, EUS, abdominal ultrasonography and CT of the chest and upper abdomen as routine examination. Additional studies such as bronchoscopy, neck CT, abdominal CT or magnetic resonance imaging were obtained when they were indicated clinically. In our institute, esophageal resection with extensive regional lymph node dissection is routinely performed if the clinical condition permits and there is no evidence of extensive direct invasion to adjacent organs or distant metastases. The presence of extensive lymph node metastasis at a clinical staging is not a contraindication to surgical resection if they are included in the primary resection field.

Esophagectomy was not performed in 13 patients. Five of these had surgically resectable disease but they were excluded from the study because the patients refused to undergo surgery. The remaining 8 patients were inoperable; four patients demonstrated distant metastatic lesions on $^{18}$F-FDG PET, three turned out to have disease with direct invasion to adjacent organs (main bronchus, thyroid gland, epiglottis, respectively) seen by bronchoscopy, imaging study or biopsy, one had a disease with omental seeding found at laparotomy. Finally, a total of 48 patients (45 men and 3 women; 46-77 years old) underwent esophagectomy with lymph node dissection.

### CT Imaging

Helical CT scans with 7-mm collimation were obtained from the level of thoracic inlet to the bottom of the level of mid-pole kidneys after intravenous injection of contrast media (100 ml of Iopamidil; Iopaminin 300; Bracco, Milan, Italy). GE Hispeed Advantage scanner (General Electric, Milwaukee, WI, USA.) was used. If the primary tumor located in the cervical or upper thoracic esophagus, CT scans of the neck were also added. Images of both mediastinal and lung windows were printed. The images were interpreted by one radiologist who blinded to the results of PET, prior to surgery. Regional lymph nodes with a short axis greater than 10 mm were considered positive for malignancy by CT.

**Endoscopic Ultrasonography**

EUS was performed in all patients except 3 who could not endure the endoscopic procedure. A 7.5/12 MHz ultrasonic endoscope (GF-UM 20, Olympus Optical Co,. LTD. Tokyo, Japan). was used. Lymph nodes were considered positive for malignancy if they fulfilled one or more of the following criteria: distinct borders, rounded appearance, hypoechogenicity, and size larger than 10 mm. Endoscopic evaluation with EUS could not be completed in 26.7% of patients (12/45) by EUS due to esophageal stenosis.

**PET Imaging**

All patients were fasted for at least 6 h prior to the PET study. PET scans were performed using a GE Advance PET scanner (General Electric, Milwaukee, WI, USA.) of which in-plane and axial resolution was 4.9 and 3.9 mm full-width at half maximum (FWHM), respectively. Emission scans were performed from head to thighs for 5 min per frame, 45 min after the intravenous injection of 370 MBq $^{18}$F-FDG. Tomographic images were reconstructed without attenuation correction using a Hanning filter (cut-off frequency = 8.0 mm) and displayed in 128 × 128 matrix (pixel size = 4.29 × 4.29 mm with a slice thickness of 4.25 mm). In addition, attenuation corrected images were acquired in the thorax and/or upper abdomen level by reconstruction using ten-minute post-emission transmission and/or preinjection transmission images with $^{68}$Ge rods.

Tomographic images were displayed as coronal, sagittal and transaxial slices. These were viewed on a Hewlett Packard workstation and interpreted by consensus of two nuclear physicians, blinded to the CT and surgical results. Regional lymph nodes were considered positive for malignancy if focal prominent $^{18}$F-FDG uptake, compared to the normal lung parenchyma, was found in more than 2 consecutive transaxial slices. The exact name of positive lymph node by PET was determined with an aid of a thoracic surgeon who operated the patients according to the modified lymph node mapping system for esophageal cancer (Table 1).[5]

**Surgical Resection**

All patients underwent transthoracic esophagectomy except 3 patients with carcinoma in-situ (transhiatal esophagectomy) with two-field (thoracoabdominal; n = 35) or three-field (thoracoabdominal and cervical; n = 13) lymph node dissection. A thoracic surgeon dissected all visible or palpable lymph nodes within the surgical field with knowledge of all the results from preoperative staging work-up including $^{18}$F-FDG PET results. Each dissected lymph node was

named according to the modified lymph node mapping system for esophageal cancer (5) and was histologically examined for malignancy (Table 1).

**Data Analysis and Statistics**

The results of nodal staging using $^{18}$F-FDG PET, CT and EUS were each compared to histological results. The comparison for nodal staging between $^{18}$F-FDG PET and CT was done twice; once for the accuracy of N staging (node to person) in each patient and second for the accuracy in all dissected lymph nodes (node to node). The nodal staging result of EUS was compared with that of $^{18}$F-FDG PET or CT in only the accuracy of N staging in each patient because direct anatomic correlation between nodal status by EUS and histological nodal status was not practical.

Fisher' s exact test was used for the comparisons of accuracy for nodal status between CT, EUS, and $^{18}$F-FDG PET. A p value lower than 0.05 was considered statistically significant.

## III. Results

Histological type of the primary mass consisted of 41 squamous cell carcinomas, 4 sarcomatoid carcinomas and 3 carcinomas in situ. After operation, a total of 382 lymph nodal groups consisting of 24 cervical, 243 thoracic and 115 abdominal nodal groups were dissected in 48 patients, of which 100 nodes in 32 patients were malignant on histological examination.

**Accuracy of $^{18}$F-FDG PET for detecting metastasis in individual nodal group**

For detecting nodal metastasis, $^{18}$F-FDG PET showed a moderate sensitivity of 57% (57/100), high specificity of 97% (273/282) and accuracy of 86% (330/382). However, CT found only 18% (18/100) of the metastatic lymph nodes ($p < 0.0001$) and showed a poorer accuracy of 78% (298/382) compared to that of $^{18}$F-FDG PET ($p = 0.003$). Figure 1 demonstrates superior sensitivity of $^{18}$F-FDG PET to CT for detecting nodal metastasis.

Nine of 43 false negative nodes (20.9%) in PET were located adjacent to the primary mass. Six of 8 patients with false positive nodes by PET had active inflammatory pulmonary disease which consisted of pulmonary tuberculosis in 5 and bronchopneumonia in 1 (Figure 2).

Then, we evaluated whether the accuracy of $^{18}$F-FDG PET was different according to the location

of lymph node (cervical, thoracic and abdominal). The sensitivity was higher in thoracic nodes (66.1%; 41/62) than in abdominal (46.7%; 14/30, p = 0.074) or cervical nodes (37.5%; 3/8, p = 0.115). The specificity was 95.0% (172/181) in thoracic nodes, and 100% in cervical (16/16) and abdominal nodes (85/85). In other words, PET found no false positive nodes in cervical and abdominal areas.

**Accuracy of $^{18}$F-FDG PET for N staging**

For evaluating N staging, PET (81%, 26/32) was more sensitive than CT (41%, 13/32, p = 0.0009) and EUS (50%, 15/30, p = 0.009) without significance difference in specificity. Thus, N staging by $^{18}$F-FDG PET was correct in 83% of patients (40/48). However, both CT (60%, 29/48, p = 0.006) and EUS (58%, 26/45, p = 0.003) were less accurate than $^{18}$F-FDG PET for N staging. It is noteworthy that no understaged patients were found in N staging by CT, and that overstaging of the N stage was most frequent with EUS (8.9%, 4/45).

## IV. Discussion

Lymph node stage in esophageal cancer is important as a prognostic indicator. As both the number and location of metastatic lymph nodes influenced the survival of patients with esophageal cancer,[1-6] accurate non-invasive evaluation for nodal metastasis is essential to determine the therapeutic plan in such patients. Recently, several studies have reported that $^{18}$F-FDG PET was more accurate than CT in detecting lymph node and distant metastasis in esophageal cancer.[11-13] In addition, it has been reported that a high tumor SUV of $^{18}$F-FDG PET suggests poor prognosis in patients with esophageal cancer.[14] The results of this study showed that $^{18}$F-FDG PET was more accurate than conventional imaging methods including CT and EUS for the evaluation of nodal staging in esophageal cancer. In particular, $^{18}$F-FDG PET showed a high accuracy of 86% in the evaluation of individual lymph node status in comparison with histological results.

CT has been used for the preoperative staging of esophageal cancer. However, in this study, CT showed a poor sensitivity of 18% in detecting metastatic lymph nodes compared with a sensitivity of 57% for $^{18}$F-FDG PET. This resulted in understaging of the nodal status in 60% of patients with N1 disease. This result is comparable to the poor sensitivity of 28% described by Flanagen and colleagues.[11] Because CT detection of lymph node metastasis is based on the size of the nodes,

limited microscopic metastasis in small to normal-sized nodes or either reactive hyperplasia or granulomatous inflammation in enlarged nodes can lead to false interpretation.

Recently, there have been reports that EUS was more accurate than CT in differentiating benign from malignant lymph nodes in esophageal cancer.[9,10] However, in our study EUS showed a lower accuracy of 58% than that of 83% by $^{18}$F-FDG PET for the evaluation of N stage, while there was no significant difference in accuracy between EUS and CT. This may be partly explained by including in the analysis, 12 patients with incomplete EUS examination due to esophageal stenosis in our study. Also, overstaging in N stage was most frequent with EUS. Thus, EUS may have few advantages over either $^{18}$F-FDG PET or CT for evaluating nodal status in esophageal cancer due to its poor accuracy and limited applicability in patients with severely stenotic esophagus.

With a high accuracy of 86% for detecting individual metastatic nodes in this study, $^{18}$F-FDG PET may provide useful prognostic information and be helpful to determine the therapeutic plan in patients with esophageal cancer. However, though more accurate than CT and EUS, the 57% sensitivity for detection metastatic nodes obtained by $^{18}$F-FDG PET is still not satisfactory. This suggests that $^{18}$F-FDG PET may not be able to detect microscopic nodal metastasis due to its limitation in spatial resolution. Also, the limited spatial resolution of PET scanner and scatter effects may explain the presence of 21% false negative nodes located adjacent to the primary mass. $^{18}$F-FDG PET showed relatively poorer sensitivity in evaluating cervical and abdominal lymph nodes than in thoracic nodes. Attenuation correction was not performed routinely for cervical and abdominal area and peristalsis of the esophagus and stomach may induce motion artifacts in PET images. These may decrease the sensitivity of $^{18}$F-FDG PET for detecting nodal metastasis. Because $^{18}$F-FDG PET depends on regional changes in glucose metabolism, it is not completely specific for tumors. In this study, there were no false positive nodes in cervical and abdominal area by $^{18}$F-FDG PET. The 6 of 8 patients with false positive nodes by $^{18}$F-FDG PET had active inflammatory pulmonary disease which was proven clinically. Flanagan et al.[11] also reported similar results. Thus, one should be cautious of the fact that increased accumulation of FDG in lymph nodes with reactive hyperplasia or active inflammation may contribute to false positive interpretation of thoracic lymph nodes in patients with active inflammatory pulmonary disease.

Only a few reports of the preoperative nodal staging in patients with esophageal carcinoma by $^{18}$F-FDG PET have been published to date.[11-13] Because they were not prospective in design, many of subjects underwent transhiatal esophagectomy instead of transthoracic esophgectomy. A transthoracic approach allows direct visualization and sampling of nodes; as, in the transhiatal

esophagectomy, the same nodes, although not directly visualized, are removed en bloc with esophagectomy specimen, it is difficult to correlate directly histological review with imaging results and to perform adequate regional lymph node dissection. Thus, in this study, transthoracic esophagectomy was prospectively performed in all subjects except for 3 patients with carcinoma in-situ where the likelihood of nodal metastasis was low. In addition, the number of subjects to evaluate the accuracy of $^{18}$F-FDG PET for nodal metastasis was relatively smaller in those than in this study. Our accuracy and sensitivity of 83% and 81% for nodal staging is slightly better than those of 76% and 72%,[11] 48% and 45%,[12] and 56% and 45%[13] in other reports. One plausible explanation for this discrepancy is the difference in spatial resolution between the PET scanners. The spatial resolutions of PET scanners were 10 mm FWHM in 2 reports[11,13] and 6 mm FWHM in the other[12] whereas our system had a FWHM of 4.9 mm. As lymph nodes are small in size and vulnerable to partial volume effect, the spatial resolution of PET scanner may have a significant influence on the accuracy of $^{18}$F-FDG PET for detecting metastatic lymph nodes. Another difference is the method of attenuation correction. Attenuation correction was not performed in one report.[12] While others[11,13] used a segmentation method with 2 min transmission scans. In this study, we measured attenuation correction by 10 min transmission scan. As the regional lymph nodes of esophageal carcinoma are usually located in the innermost highly attenuated part of body and are usually less than 2 cm in short axis diameter, the accurate attenuation correction may play a important role in evaluating the lymph nodes accurately with $^{18}$F-FDG PET.

One potential limitation of this study is that not all subjects had neck dissection. Cervical and supraclavicular node dissection was done in only 27% of the subjects most of whom primary tumor was located in cervical or upper esophagus. There was no definite evidence of cervical nodal metastasis by clinical and imaging studies in the remaining patients at the time of surgery. However, as lymphatic spread of esophageal cancer is usually extensive along the whole esophagus irrespective of the site of primary tumor, there is a possibility of microscopic metastasis in these areas not found by the imaging studies including PET.

In conclusion, preoperative FDG-PET is more accurate than CT and EUS for evaluating lymph node status in patients with esophageal cancer and may be helpful to determine the therapeutic plan in these patients.

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**Table 1.** Lymph Node Mapping System for Esophageal Cancer to Compare Imaging Findings with Histological Results (Modified from Reference 5).

| Station | Description | Location |
|---|---|---|
| RJ/LJ | Right/left jugular nodes | Along the course of the internal jugular vein |
| 2R | Right upper paratracheal nodes | Between intersection of caudal margin of innominate artery with trachea and the apex of the lung |
| 2L | Left upper paratracheal nodes | Between top of aortic arch and apex of the lung |
| 4R | Right lower paratracheal nodes | Between intersection of caudal margin of innominate artery with trachea and cephalic border of azygos vein |
| 4L | Left lower paratracheal nodes | Between top of aortic arch and carina |
| 5 | Aortopulmonary nodes | Subaortic and para-aortic nodes lateral to the ligamentum arteriosum |
| 7 | Subcarinal nodes | Caudal to the carina of the trachea |
| 8M | Middle paraesophageal nodes | From the tracheal bifurcation to the caudal margin of the inferior pulmonary vein |
| 8L | Lower paraesophageal nodes | From the caudal margin of the inferior pulmonary vein to the esophagogastric junction |
| 9 | Pulmonary ligament nodes | Within the inferior pulmonary ligament |
| 10R | Right tracheobronchial nodes | From cephalic border of azygos vein to origin of RUL bronchus |
| 10L | Left tracheobronchial nodes | Between carina and LUL bronchus |
| 15 | Diaphragmatic nodes | Lying on the dome of the diaphragm, and adjacent to or behind its crura |
| 17 | Left gastric nodes | Along the course of the left gastric artery |
| 18 | Common hepatic nodes | Along the course of the common hepatic artery |
| 20 | Celiac nodes | At the base of the celiac artery |
| PA | Para-aortic nodes | Along the course of abdominal aorta distal to the celiac trunk |

**Figure. 1.** Transaxial images of $^{18}$F-FDG PET (A, C, E, G) and concomitant CT images (B, D, F, H) of a patient. $^{18}$F-FDG PET demonstrated abnormal increased uptake in the right upper paratracheal lymph node (A), subcarinal lymph node (C), left gastric lymph node (E), common hepatic lymph node, and celiac node (G), which were positive for malignancy. However, only enlarged left gastric lymph node (F, black arrow) was found in contrast enhanced CT.

(A) (B)

(C) (D)

(E) (F)

(G) (H)

**Figure 2.** Transaxial images of $^{18}$F-FDG PET (A, C) and concomitant CT images (B, D) of a patient. Increased $^{18}$F-FDG uptake and multiple cavitary or centrilobular nodules by CT in both upper lobes suggested active pulmonary tuberculosis (A, B). Increased $^{18}$F-FDG uptake was found in left lower paratracheal lymph node (C) and CT also shows enlarged left lower paratracheal node (D, white arrow). However, there were no malignant cells on histological examination and the patient's AFB staining from sputum was positive.

(A) (B)

(C) (D)