Additional Value of PET/CT over PET in Assessment of Locoregional Lymph Nodes in Thoracic Esophageal Squamous Cell Cancer

Shuanghu Yuan[1], Yonghua Yu[1], K.S. Clifford Chao[2], Zheng Fu[3], Yong Yin[1], Tonghai Liu[1], Shaoqing Chen[1], Xinhua Yang[1], Guoren Yang[3], Hongbo Guo[4], and Jinming Yu[1]

[1]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Jinan, China; [2]Department of Radiation Oncology, M.D. Anderson Cancer Center, University of Texas, Houston, Texas; [3]Department of Nuclear Medicine, Shandong Cancer Hospital and Institute, Jinan, China; and [4]Department of Thoracic Surgery, Shandong Cancer Hospital and Institute, Jinan, China

The aim of this study was to compare the value of reviewing combined ^{18}F-FDG PET/CT images with that of reviewing side-by-side PET and CT images in the diagnosis of locoregional lymph node metastases in patients with esophageal squamous cell cancer. **Methods:** From November 2003 to December 2005, 45 patients with thoracic esophageal squamous cell cancer underwent ^{18}F-FDG PET/CT before surgery. The results of reviewing combined PET/CT images and side-by-side PET and CT images for the diagnosis of locoregional lymph node metastases were compared prospectively in relation to pathologic findings. **Results:** All patients underwent successful surgery, and pathologic examination confirmed nodes positive for metastasis in 32 patients and 82 of 397 excised nodal groups. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET/CT were 93.90% (77/82 nodal groups), 92.06% (290/315), 92.44% (367/397), 75.49% (77/102), and 98.31% (290/295), respectively, whereas those of PET were 81.71% (67/82), 87.30% (275/315), 86.15% (342/397), 62.62% (67/107), and 94.83% (275/290), respectively. *P* values were 0.032, 0.067, 0.006, 0.063, and 0.037, respectively. The differences in sensitivity, accuracy, and negative predictive value between PET and PET/CT were statistically significant. **Conclusion:** PET/CT improves the sensitivity, accuracy, and negative predictive value of ^{18}F-FDG imaging in the assessment of locoregional lymph nodes in thoracic esophageal squamous cell cancer and provides data of diagnostic significance.

Key Words: gastroenterology; oncology; PET/CT; computed tomography; esophageal cancer; lymph node

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Nodal involvement is an important prognostic factor for patients with esophageal cancer, in that the cure rate in patients with affected nodes is dramatically lower than in patients without (*1*). The accurate assessment of locoregional lymph nodes in esophageal cancer is essential to the selection of appropriate treatments and to the anticipation of disease progression.

Because of their dependence on tumor-associated structural changes, conventional imaging modalities are inaccurate in lymph node metastases in esophageal cancer. One of these modalities, CT, has been used widely for preoperative evaluation but is known to be insensitive for the detection of metastases to lymph nodes in esophageal cancer (*2–4*).

PET is a fundamentally different imaging technology that identifies, with high specificity, focal areas of increased metabolism associated with malignancies. ^{18}F-FDG PET may be more sensitive than CT because the alterations in tissue metabolism measured by PET generally precede anatomic changes (*5*). However, PET lacks precise localization landmarks, making it difficult to definitively characterize foci of increased ^{18}F-FDG uptake (*6*). The role of PET in the detection of nodal metastases is still controversial and its efficacy far from perfect (*7–12*).

Coregistration of PET and CT by using a combined PET/CT system has shown additional value for the interpretation of images by both modalities, providing complementary information for both (*13*). Data on the use of PET/CT in esophageal cancer are limited (*14*). To the best of our knowledge, no published study has concentrated on the value of PET/CT in the diagnosis of locoregional lymph node metastases in patients with esophageal cancer. The purpose of the present study was to assess the contribution of simultaneous functional/anatomic imaging using hybrid ^{18}F-FDG PET/CT, in relation to that of side-by-side review of PET and CT, for the assessment of locoregional lymph node metastases in patients with thoracic esophageal squamous cell cancer.

MATERIALS AND METHODS

Patients

All patients with a first diagnosis of biopsy-proven squamous cell cancer of the thoracic esophagus seen in our hospital from

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For correspondence or reprints contact: Jinming Yu, PhD, MD, Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Jiyan Rd. 440, Jinan 250117, Shandong Province, P.R. China.

E-mail: fishtigers@yahoo.com.cn

November 2003 to December 2005 were candidates for this study. They underwent the standard preoperative staging procedures, including physical examination, laboratory testing, ultrasound of the neck and abdomen, chest radiography, and esophagography, and their clinical history was recorded. Patients who had received prior anticancer treatment were excluded, as were patients with diabetes mellitus or inflammatory lung disease and those ineligible for surgery for medical reasons. At our institution, all patients without metastasis to distant organs or definite direct tumor invasion of adjacent organs on imaging are routinely scheduled for esophageal resection and extensive regional lymph node dissection. We did not consider stage M1a cancer (i.e., metastasis to cervical lymph nodes in patients with upper esophageal cancer or to celiac lymph nodes in patients with lower esophageal cancer) to be a contraindication to surgery. Patients with operable disease who refused surgery were ineligible for the study, as were patients who refused to pay at least 30% of the charge for PET/CT. Whole-body ^{18}F-FDG PET/CT examinations were, therefore, performed prospectively in 45 consecutive eligible patients before curative surgery (32 men and 13 women; age range, 40–73 y; mean, 57.5 y). This study protocol received approval from the institutional review board of our hospital. Informed consent was obtained from each patient.

^{18}F-FDG PET/CT

^{18}F-FDG PET/CT scans were obtained with an advanced PET/CT scanner (Discovery LS; GE Healthcare). All patients fasted for at least 6 h before the PET examination, and each patient's blood glucose level was measured before injection of the tracer. Patients did not undergo urinary bladder catheterization and received no oral muscle relaxants; no CT contrast agents were administered. Sixty minutes after intravenous injection of 370 MBq (10 mCi) of ^{18}F-FDG, emission scans were obtained from head to thigh for 5 min per field of view, each covering 14.5 cm, at an axial sampling thickness of 4.25 mm/slice. The PET/CT system was used for 4-slice helical CT acquisition, followed by a full-ring dedicated PET scan of the same axial range. The CT component was operated with an x-ray tube voltage peak of 120 keV, 90 mA, a 6:1 pitch, a slice thickness of 4.25 mm, and a rotational speed of 0.8 s/rotation. Both the PET scans and the CT scans were obtained during normal tidal breathing. PET images were reconstructed with CT-derived attenuation correction using ordered-subset expectation maximization software.

The attenuation-corrected PET images, CT images, and fused PET/CT images were available for review in axial, coronal, and sagittal planes, as was a cine display of maximum intensity projections of the PET data, using the manufacturer's review station (Xeleris; GE Healthcare).

First, a team of experienced nuclear medicine physicians, unaware of the patient's clinical history and the results of previously performed conventional imaging tests, interpreted the ^{18}F-FDG PET images with side-by-side review of the CT images. Then, fused PET/CT images were reviewed by a combined team of nuclear medicine physicians and radiologists.

When an area of presumed lymph node showed ^{18}F-FDG uptake that was focally prominent compared with surrounding tissues and not related to normal physiologic uptake, the area was considered to be positive for malignancy. A site of increased ^{18}F-FDG uptake was defined as negative when it was related to a known nonmalignant process or to the physiologic biodistribution of ^{18}F-FDG. Disagreements concerning final interpretation were resolved by a majority opinion. The physicians recorded the presence, number, size, standardized uptake value (SUV), character, and precise location of presumed lymph nodes with metastases.

Surgery

The surgical approach was determined by the locations of the proximal pole of the tumor and of the positive lymph nodes, indicated by the preoperative imaging examinations. Nineteen patients, 4 with upper thoracic esophageal cancer and 15 with middle thoracic esophageal cancer, underwent transthoracic esophagectomy (involving laparotomy, right thoracotomy, and cervical anastomosis) with lymph node dissection in 3 fields (thoracic, abdominal, and cervical). Seventeen patients (13 with middle thoracic esophageal cancer and 4 with lower thoracic esophageal cancer) underwent left thoracotomy and cervical anastomosis with lymph node dissection in 2 fields (thoracic and abdominal). Nine patients with lower thoracic esophageal cancer underwent extended left thoracophrenotomy through the sixth intercostal space with lymph node dissection in 2 fields (thoracic and abdominal). During surgery, 2 thoracic surgeons with more than 18 y of experience dissected all visible and palpable lymph nodes in the surgical field, taking into consideration all results from the preoperative imaging examinations. Thereafter, lymph nodes were sought, and the number, size, character, and precise location of the nodes were recorded. Sections were obtained for histopathologic evaluation of the tumor, the nonneoplastic mucosa, the proximal and distal lines of resection, and the lymph nodes. The specimens were stained by a standard hematoxylin–eosin technique and examined with light microscopy. Then, the presumed lymph nodes on preoperative imaging were correlated with surgical and pathologic data for each nodal group.

Data Analysis

The results of the imaging modalities were compared with a reference standard provided by pathologic examination of each nodal group. PET- and PET/CT-positive results were defined as true positive (TP) when confirmed by histopathologic examination as lymph node metastases and as false positive (FP) when histopathologic examination of the resected nodal group revealed no evidence of metastasis. A site characterized as a negative area was defined as true negative (TN) when histopathologic examination of the resected nodal group revealed no metastatic disease and as false negative (FN) when there was subsequent histopathologic proof of lymph node metastasis. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET and PET/CT for the detection of locoregional lymph node metastases were calculated and compared. Statistical software (SPSS, version 12.0; SPSS Inc.) was used for the analysis. The significance of each difference was calculated using the McNemar test. P values of less than 0.05 were considered statistically significant.

RESULTS

Extent of Lymph Node Sampling

All 45 patients underwent esophagectomy and lymphadenectomy. Four patients had upper thoracic esophageal cancer, 28 had middle thoracic esophageal cancer, and 13 had lower thoracic disease. A total of 397 nodal groups (25 cervical, 44 hilar, 106 abdominal, and 222 mediastinal,

including 87 paraesophageal) were dissected in the 45 patients, and 82 of these (6 cervical, 1 hilar, 22 abdominal, and 53 mediastinal, including 28 paraesophageal) in 32 patients were proven to be positive for malignancy on pathologic examination. Table 1 compares the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of hybrid PET/CT with those of PET reviewed side-by-side with CT in relation to the reference standard for the detection of locoregional lymph node metastases.

Sensitivity

The sensitivity of PET/CT was significantly higher than that of PET for lymph node evaluation (93.90% vs. 81.71%, $P = 0.032$). Findings on PET were later shown to be FN in 15 nodal groups; 10 of these were correctly shown by PET/CT to contain metastasis, including 2 groups of supraclavicular lymph nodes with diameters of 0.5–1 cm and SUVs of 2.8–4.0, 4 groups of paraesophageal nodes with diameters of 0.5–1.2 cm and SUVs of 3.0–4.6 (Fig. 1), 1 left gastric arterial lymph node with a diameter of 0.8 cm and an SUV of 3.8, 1 lymph node at cardia ventriculi with a diameter of 0.6 cm and an SUV of 2.8, and 2 groups of lymph nodes at the lesser curvature of the stomach with diameters of 0.6–0.8 cm and SUVs of 3.0–3.5.

The other 5 FN nodal groups on PET were also missed on PET/CT. These included 1 left cervical lymph node with a diameter of 0.5 cm, 2 groups of paraesophageal nodes with diameters of 0.4–0.6 cm, 1 paratracheal node with a diameter of 0.3 cm, and 1 group of left gastric arterial nodes with diameters of 0.4–0.8 cm. In all 5 of these cases, the histology reports mentioned that the lymph nodes had only limited microscopic invasion and were not macroscopically enlarged.

Of the 87 excised nodal groups that were nearest the tumor, 28 were positive for metastases on pathologic examination, 22 were TP on both PET and PET/CT, 4 were FN on PET but positive on PET/CT, and 2 were FN on both PET and PET/CT. The average diameter of the nodes that were FN on PET but positive on PET/CT was 0.73 cm, whereas that of the nodes that were TP on PET was 1.14 cm ($P = 0.039$); the average SUV for nodes that were FN on PET but positive on PET/CT was 3.4, whereas that of the nodes that were TP on PET was 5.3 ($P = 0.044$).

Specificity

For diagnosis of lymph node metastases, the specificities of ^{18}F-FDG PET/CT and PET were 92.06% and 87.30%, respectively ($P = 0.067$). Forty nodal groups had FP interpretations on PET. Fifteen of these were correctly shown to have no metastasis by PET/CT, including 11 that were interpreted as FP because of physiologic tracer uptake (3 in the cervical region and 8 in the gastrointestinal tract) and 4 foci of heterogeneous tracer uptake in the primary tumor that were incorrectly interpreted as local nodal involvement. The 25 nodal groups that had FP interpretations on both PET/CT and PET included 2 supraclavicular groups with SUVs of 4.5 and 3.8 for reactive hyperplasia; 2 paraesophageal groups with SUVs of 2.8 and 3.6, which were shown on histologic examination to be enlarged and inflamed; 3 subcarinal groups, 1 being lymphoid tuberculosis with an SUV of 3.2 and the others granulomatous inflammation with SUVs of 3.5–4.0; 17 hilar groups, all consisting of hyperplasia reactive for inflammation, with diameters of less than 1 cm and a mean SUV of 2.8; and 1 lesion above the diaphragm, with an SUV of 2.7 and no pathologic lesion.

Accuracy and Predictive Value

The accuracy of PET/CT was higher than that of PET in the diagnosis of lymph node metastases (92.44% vs. 86.15%, $P = 0.006$). In the 397 dissected nodal groups, the numbers of TN and TP interpretations were 367 on PET/CT and 342 on PET. Altogether, 10 FN interpretations and 15 FP interpretations on PET were corrected by PET/CT. These resulted in negative predictive values of 98.31% for PET/CT and 94.83% for PET ($P = 0.037$) and positive predictive values of 75.49% for PET/CT and 62.62% for PET ($P = 0.063$).

DISCUSSION

^{18}F-FDG PET tends to underestimate regional lymph node involvement in esophageal cancer because of the presence of microscopic spread, high ^{18}F-FDG uptake in the adjacent primary tumor, or tracer uptake in physiologic structures at the thoracoabdominal interface (*7–12*). The performance of CT in this application is limited, primarily by the size criteria for the definition of pathologic findings

TABLE 1
Comparative Performance of ^{18}F-FDG PET/CT and PET for Detection of Lymph Node Metastases in Thoracic Esophageal Squamous Cell Cancer

Parameter	TP	TN	FP	FN	Sensitivity	Specificity	Accuracy	NPV	PPV
PET/CT	77	290	25	5	93.90%	92.06%	92.44%	98.31%	75.49%
PET	67	275	40	15	81.71%	87.30%	86.15%	94.83%	62.62%
χ^2					4.613	3.362	7.589	4.354	3.460
P					0.032	0.067	0.006	0.037	0.063

NPV = negative predictive value; PPV = positive predictive value.

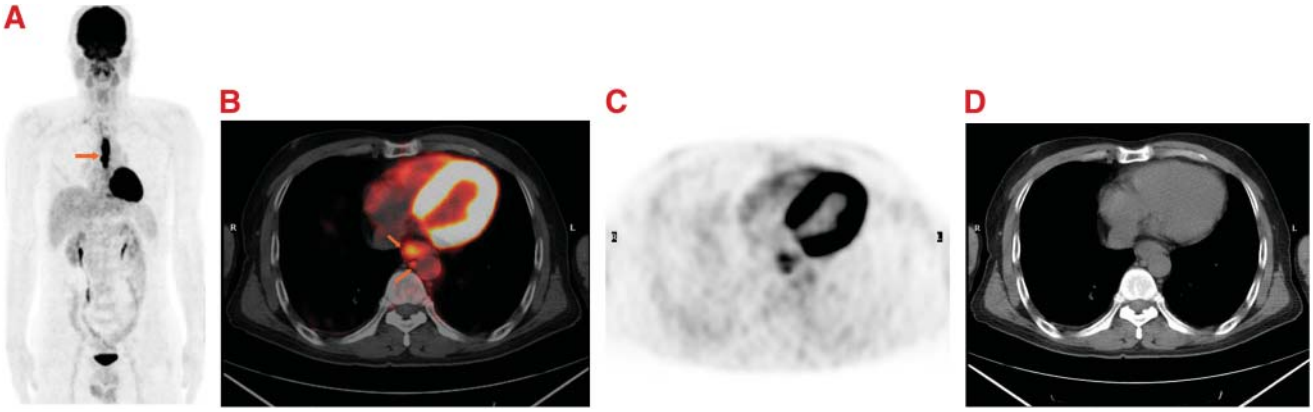

FIGURE 1. 50-y-old man with well-differentiated squamous cell cancer of middle thoracic esophagus was referred for preoperative disease staging. (A) Maximum-intensity-projection ^{18}F-FDG PET image shows focus of intense, inhomogeneous pathologic uptake at site of primary esophageal tumor (arrow). (B) Transaxial PET/CT image shows that intense focus of ^{18}F-FDG uptake (SUV, 6.5) is near primary tumor (upper arrow) and defines additional focus of abnormal ^{18}F-FDG uptake (diameter, 0.8 cm; SUV, 3.5) in paraesophageal lymph node (lower arrow), which was confirmed as lymph node metastasis of well-differentiated squamous cell cancer on pathologic examination. This focus, in close proximity to intense uptake in primary esophageal lesion, could not be identified on PET image (C) reviewed side-by-side with CT image (D). Findings on PET/CT were defined as TP, and findings on side-by-side review of PET and CT were defined as FN.

(*2–4*), but CT provides a high-resolution structural map in anatomically crowded regions.

As a hybrid of traditional anatomic imaging and functional imaging, PET/CT can overcome some of these limitations by improving the characterization of ^{18}F-FDG activity near a highly tracer-avid primary tumor or near organs with high physiologic uptake.

In the current study, FN interpretations of paraesophageal lymph node groups on PET could be explained in terms of the difficulty of discriminating peritumoral lymph node metastases from primary tumor. This difficulty was primarily attributable to intense tracer accumulation by the primary tumor, limited resolution, and ill-defined anatomic boundaries because of esophageal motion or limited microscopic invasion of the lymph nodes. FN lesions around the stomach might have related to gastrointestinal motion and physiologic uptake. Cervical FN lesions could be explained by the complexity of cervical anatomy and by physiologic uptake in the muscles of that region. As a hybrid of traditional anatomic imaging and functional imaging, PET/CT corrected 66.7% (10/15) of the interpretations that were FN on PET and resulted in a high sensitivity by providing a high-resolution structural map of anatomically crowded regions, allowing exclusion of the effects of adjacent tumor, physical motion, or uptake by adjacent organs.

At same time, 37.5% (15/40) of the interpretations that were FP on PET were corrected by PET/CT. These included 4 with asymmetric tracer accumulation by the primary tumor and 11 in which physiologic uptake in the anatomically crowded cervical region or gastrointestinal tract was interpreted as metastasis. Corrections of FP interpretations also may have been related to the value of the accurate fusion and subsequent precise localization provided by PET/CT.

By virtue of its high sensitivity, accuracy, and negative predictive value, PET/CT has a significant impact on the definition and localization of specific sites of abnormal ^{18}F-FDG uptake, and this impact may have important diagnostic and therapeutic implications, including determination of the surgical approach and the field of radiotherapy.

Despite the overall superiority of PET/CT, however, there were still 25 FP interpretations on PET/CT, including nodes in the supraclavicular, hilar, subcarinal, and paraesophageal regions. More than half the FP interpretations were of uptake localized in the hilum of the lung in patients with chronic inflammation or a long history of smoking. Confirmation by histopathologic examination is therefore mandatory, especially when positive PET/CT findings would deny a patient a chance for potentially curative treatment.

There were also 5 FN interpretations on PET/CT in the current study. These nodes were macroscopically unenlarged and had limited microscopic invasion. These FN interpretations may have been related to a minimal tumor load that created difficulties with resolving increased ^{18}F-FDG uptake, or they may have represented foci that were too small to be detected by the PET/CT system or disease that was well differentiated.

Most previous reports evaluating PET in esophageal cancer were confined to PET alone, without side-by-side review of CT. Compared with those, the current study defined relatively high sensitivities and accuracies for ^{18}F-FDG PET/CT and PET reviewed side by side with CT in the detection of lymph node metastases (*7–12*); these higher sensitivities and accuracies are related mainly to the additional help of the structural map provided by CT.

To the best of our knowledge, only 1 prior study specifically evaluated the contribution of PET/CT technology in the assessment of esophageal cancer (*14*). Bar-Shalom et al. reported that hybrid PET/CT accurately assessed locoregional

involvement by separating nodal uptake from uptake in adjacent tumor at 64% of these sites. Although only a few regional sites were assessed, the results indicate a potential role for PET/CT in optimized evaluation of locoregional nodal involvement, a potential that has been borne out by the findings of the current study. In that study, the special value of image fusion for interpretation of cervical and abdominopelvic sites was more pronounced than in the current study. One reason may be related to the inclusion criteria we used. This study included only patients who underwent esophagectomy with lymph node dissection. Therefore, more cases of early-stage disease and fewer patients with cervical or abdominopelvic lymph node metastases were included. The exclusion of cervical esophageal cancer further lowered the proportion of cervical lymph node metastases.

The main bias in the current study population was the selection of patients who were surgical candidates. Another source of potential bias in the present study was the exclusion of patients with advanced disease, lowering the prevalence of metastatic lesions and increasing the FP rate.

In any case, review of combined PET/CT images has additional value over review of side-by-side PET and CT images in the assessment of lymph node metastases in patients with squamous cell cancer of the thoracic esophagus. This study indicates that, for patients with thoracic esophageal cancer, the clinical impact of PET/CT is related mainly to its ability to determine the precise location of pathologic ^{18}F-FDG uptake near the primary tumor and to exclude malignancy at sites of physiologic or benign tracer uptake. These arguments justify the routine use of ^{18}F-FDG PET/CT in the clinical lymph node staging of thoracic esophageal cancer. When positive ^{18}F-FDG PET/CT findings would deny a patient a chance for potentially curative treatment, however, confirmation by histopathologic examination is mandatory.

CONCLUSION

Review of combined ^{18}F-FDG PET/CT images has additional value over review of side-by-side ^{18}F-FDG PET and CT images in the assessment of locoregional lymph nodes for patients with thoracic esophageal squamous cancer. This additional value is related mainly to its ability to determine the precise location of pathologic ^{18}F-FDG uptake in the vicinity of the primary tumor and anatomically crowded regions while excluding malignancy at sites of physiologic or benign tracer uptake.

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