ORIGINAL ARTICLE

One-by-One Comparison of Lymph Nodes Between ^{18}F-FDG Uptake and Pathological Diagnosis in Esophageal Cancer

Shuntaro Yoshimura, MD, PhD,* Miwako Takahashi, MD, PhD,† Susumu Aikou, MD, PhD,*
Yasuhiro Okumura, MD, PhD,* Keiichi Jinbo, MD, PhD,* Haruna Onoyama, MD, PhD,*
Masayuki Urabe, MD, PhD,* Koichiro Kawasaki, MD,* Koichi Yagi, MD, PhD,*
Masato Nishida, MD, PhD,* Kazuhiko Mori, MD, PhD,‡ Hiroharu Yamashita, MD, PhD,*
Sachiyo Nomura, MD, PhD,* Keitaro Koyama, MD, PhD,† Toshimitsu Momose, MD, PhD,†
Hiroyuki Abe, MD, PhD,§ Tetsuo Ushiku, MD, PhD,§
Masashi Fukayama, MD, PhD,§ and Yasuyuki Seto, MD, PhD*

Purpose: Esophagectomy with extended lymph node (LN) dissection is a standard treatment for resectable esophageal cancer to prevent recurrence, but severe, potentially life-threatening postoperative complications are still important issues. Accurate diagnosis of LN metastases would enable the decision to dissect or leave the LNs in regions with high risk of complications. Advancements in intraoperative gamma probe and radioactivity detectors have made intraoperative navigation surgery possible using a radiotracer as a marker. ^{18}F-FDG is one such candidate markers, and the diagnostic power of FDG through counting the radioactivity close to each LN should be elucidated.

Materials and Methods: In 20 patients, 1073 LNs including 38 metastatic LNs were prospectively investigated. Preoperative FDG PET was performed on the same day before esophagectomy and visually surveyed in each LN station to identify abnormal uptake. The FDG radioactivity of each individual dissected LN was measured by a well-type counter, and the pathological diagnosis was compared with LN radioactivity on a one-by-one basis and with the preoperative FDG PET findings for each LN station.

Results: Lymph node station-based analysis showed a sensitivity and specificity of 28.6% and 96.7%, respectively. One-by-one LN-based analysis using a cutoff value obtained from the receiver operating characteristic curve showed a sensitivity and specificity of 94.7% and 78.7%, respectively, demonstrating higher accuracy compared with the use of LN weight or the shortest diameter.

Conclusions: The FDG uptake by each LN is a potentially useful marker for navigation surgery in esophageal cancer and has higher accuracy than LN weight or diameter.

Key Words: ^{18}F-FDG, esophageal cancer, lymph node metastasis, PET, navigation surgery

(*Clin Nucl Med* 2020;45: 741–746)

Esophageal cancer is one of the most aggressive diseases, characterized by poor prognosis. The overall 5-year survival of patients with esophageal cancer is approximately 40%.[1,2] One of the most important prognostic factors is the presence of lymph node (LN) metastases,[1,2] which, however, is difficult to determine because the location of metastatic LNs is often independent of that of the primary tumor and potentially extends from the cervical to the abdominal LN field. Tsurumaru et al[3] reported that patients with lower thoracic esophagus cancer developed LN metastases mostly in the abdomen, but approximately 30% of the patients developed LN metastases in the cervical or upper mediastinum areas. Therefore, prophylactic LN dissection has been regarded as a standard and necessary procedure for curative purposes. A prospective randomized trial has revealed that esophagectomy with 3-field extended lymphadenectomy could prevent recurrence and prolong survival after surgery; however, patients who underwent extended lymphadenectomy had significantly more postoperative complications, such as phrenic nerve palsy, tracheostomies, and recurrent nerve palsy in almost 60% of the patients,[4] and the hospital death rate was as high as 7.9%.[1]

Accurate diagnosis of LN metastases would allow avoiding extensive lymphadenectomy, thus decreasing the prevalence of postoperative complications. CT and ^{18}F-FDG PET have been used to assess LN metastases. A meta-analysis determined the pooled sensitivity and specificity of CT and FDG PET for the detection of regional LN metastases. The sensitivity and specificity of CT were 50% and 83%, respectively, and those of FDG PET were 57% and 85%, respectively,[5] which are not enough to accurately detect all metastatic LNs. In addition, even if metastatic LNs are identified on preoperative images, it is difficult to localize the same LNs in the intraoperative field because the patient position is changed and the organs are shifted after the operative procedures.

Navigation surgery using a handheld gamma probe after FDG administration before surgery has been applied in various malignancies including colorectal, lung, ovarian, and breast cancer. Its feasibility and efficacy in evaluating disease distribution and confirming complete cytoreduction have been reported.[6–10] In particular, disseminated disease undetected by preoperative images or initial surgical exploration was instead revealed intraoperatively by a handheld gamma probe. The intraoperative use of such gamma probes is expected to improve diagnostic accuracy even for small lesions.

Moreover, the marked increase of FDG uptake in esophageal cancer is well known. The degree of FDG uptake is correlated with the LN metastatic stage.[11,12] Intraoperative handheld gamma probes or similar devices can closely approach each LN, leading

TABLE 1. Clinicopathological Characteristics of 20 Patients

Age, mean (range), y	65 (51–82)
Sex, male/female	14/6
Tumor location	
Upper	2
Middle	11
Lower	6
Abdominal	1
Histological type	
Squamous cell carcinoma	19
Adenocarcinoma	1
Surgical procedure	
Ivor Lewis	4
McKeown	16
T status	
pT0/pT1/pT2/pT3/pT4	3/7/2/7/1
N status	
pN0/pN1/pN2/pN3	9/7/3/1
P stage	
0/IA/IB/IIA/IIB/IIIA/IIIB/IIIC	2/4/2/1/5/2/3/1
Neoadjuvant therapy, n (%)	
Chemotherapy	9 (45%)
Radiotherapy	2 (10%)

to higher detector sensitivity compared with preoperative FDG PET. Therefore, FDG combined with intraoperative radioactivity measurements can potentially be used as a marker for intraoperative navigation surgery in esophageal cancer.

The aim of this study was to clarify the diagnostic power of FDG as a marker of navigation surgery for esophageal cancer.

MATERIALS AND METHODS

Patients

Between September 2014 and April 2016, candidate subjects were recruited at the Department of Gastrointestinal Surgery in our hospital. Inclusion criteria for this study were (1) esophageal cancer diagnosed by pathological review of endoscopic biopsy specimens, (2) esophagectomy performed with curative intent, (3) age 85 years or younger, (4) normal renal function, and (5) Eastern Cooperative Oncology Group performance status (ECOG-PS) ≤1. Exclusion criteria were the evidence of (1) diabetes, (2) history of malignant diseases, and (3) synchronous malignancies other than esophageal cancer. All patients underwent either Ivor Lewis or Mckeown esophagectomy with 2- or 3-field lymphadenectomy and gastric conduit reconstruction via the posterior mediastinal route.

This prospective study was approved by the institutional review board of our hospital. All study participants provided informed consent.

LN Station-Based Analysis by Preoperative ^{18}F-FDG PET/CT

Comparison between preoperative FDG PET images and pathological LN status was based on the LN station because the precise identification of individual LNs between FDG PET images and dissected LNs is difficult. The patients who met the inclusion criteria underwent preoperative FDG PET according to the standard clinical protocol on the same day of surgery. Patients fasted for at least 5 hours before FDG PET, and a blood glucose level of less than 150 mg/dL was required at the time of FDG injection. Each patient was administered 4.5 MBq/kg (0.12 mCi/kg) FDG approximately 3 hours before the scheduled time of surgery. FDG PET/CT scan was started 50 minutes after the injection using a PET/CT scanner (Aquiduo; Toshiba Medical System, Otawara, Japan). The spatial resolution was 4.3-mm full-width at half-maximum at the center of the field of view. Low-dose CT was performed for photon attenuation correction, and a 2.5-minute emission scan per position was
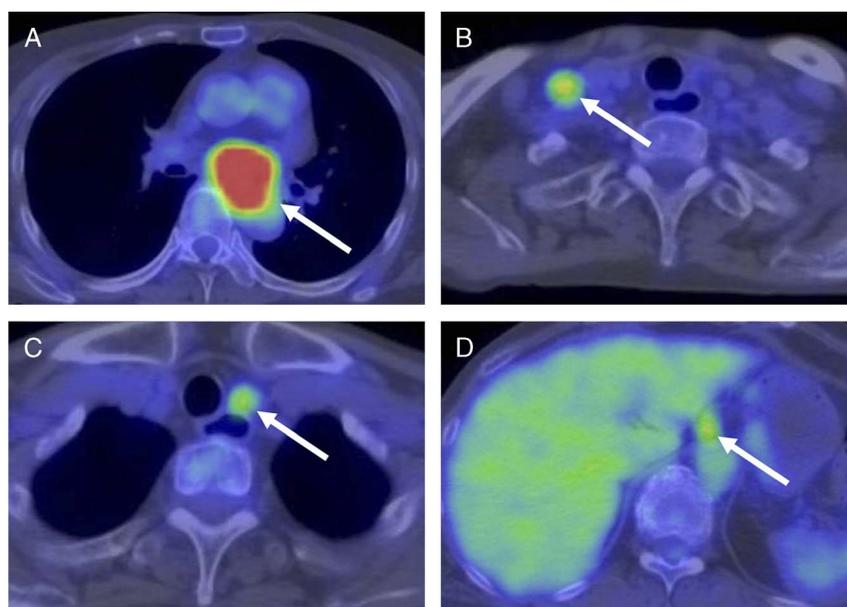
FIGURE 1. Representative true-positive FDG PET/CT findings for patient 11. The primary esophageal lesion with the SUV$_{max}$ of 16.5 (**A**), PET-positive finding in the right supraclavicular LN station with SUV$_{max}$ of 4.2 (**B**), in the left recurrent nerve LN station with SUV$_{max}$ of 3.5 (**C**), and in the gastric cardiac LN station with SUV$_{max}$ of 3.6 (**D**), which are visually identified; the LN stations are pathologically confirmed to include metastatic LN.
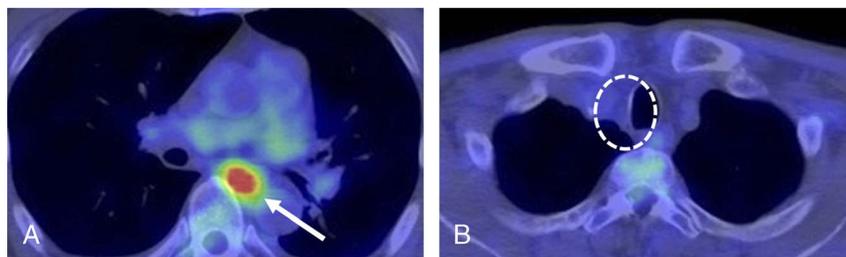
FIGURE 2. Representative false-negative FDG PET/CT finding for patient 7. **A,** The primary esophageal lesion has the SUV$_{max}$ of 9.1. **B,** The right cervical paraesophageal LN station (white circle) is pathologically confirmed to include metastatic LN, but the PET finding is negative.

used. PET images were reconstructed in a $128 \times 128 \times 41$ matrix with a voxel size of $2.0 \times 2.0 \times 4.0$ mm.

FDG PET images were visually investigated by 2 nuclear medicine experts among the authors. Immediately after FDG PET, the surgeons received a report about abnormal FDG PET findings from the nuclear medicine department and checked whether the findings were contraindicative for the scheduled surgery; after this, surgery was performed.

The FDG uptake of the primary esophageal lesion was calculated as the SUV$_{max}$ by placing a region of interest at the FDG-avid lesion on the FDG PET image. In addition to a routine clinical survey of FDG PET, visual inspection of each LN station was performed. The LN stations with a higher uptake area than their background were classified as "PET positive," and their SUV$_{max}$ was calculated. If the LN station included LNs harboring pathologically diagnosed metastases, the area was classified as a metastatic LN station. All SUV measurements were normalized for patients' body weight and for the time elapsed from injection until data acquisition.

One-by-One LN-Based Analysis by Measurement of Dissected LNs

After esophagectomy with 2- or 3-field lymphadenectomy, all LNs were harvested from the resected specimen, and their radioactivity was individually measured for 60 seconds using the CAPRAC-t well-type counter (Capintec, Inc, Pittsburgh, PA), with the energy window set at 464.7 to 557.3 keV before formalin fixation. To assess the FDG uptake of each LN, we used counts per second (cps), directly calculated by the well-type counter and corrected for the elapsed time from FDG injection (decay-corrected cps).

Pathological Diagnosis

Surgical specimens including the excised esophagus and LNs were examined by 2 experienced pathologists among the authors with no knowledge of either FDG PET/CT findings or LN

radioactivity. Tumor staging was conducted according to the seventh edition of the American Joint Committee on Cancer (AJCC) TNM cancer staging manual for the esophagus.[13] Each LN was examined using 2-mm–spaced slices using hematoxylin-eosin–stained sections to avoid missing small focal metastases.

Statistical Analysis

Measurements such as SUV$_{max}$ obtained from the preoperative FDG PET, and weight, shortest LN diameter, cps, decay-corrected cps, and elapsed time obtained through the one-by-one LN comparison study were compared between metastatic and nonmetastatic LNs using the Mann-Whitney U test; P values less than 0.05 were considered statistically significant. If a significant difference was found in these numerical measurements, a receiver operating characteristics (ROC) curve analysis was performed to determine the area under the curve (AUC) and the optimal cutoff value for each measurement. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated based on such cutoff values. Statistical analysis was performed using SPSS, version 26 (IBM Corporation, Armonk, NY).

RESULTS

We investigated 1073 LNs from 20 patients, including 38 metastatic LNs. The clinicopathological characteristics are shown in Table 1.

LN Station-Based Analysis of Preoperative ^{18}F-FDG PET/CT

One patient underwent endoscopic submucosal dissection before esophagectomy; thus, we evaluated the primary tumor SUV$_{max}$ of 19 patients. The median SUV$_{max}$ of these primary tumors was 3.7 (range, 2.1–37.6).

Among the 20 patients, a total of 18 LN stations were visually positive on FDG PET/CT. Among these, 8 LN stations included metastatic LNs. The median SUV$_{max}$ of the stations including
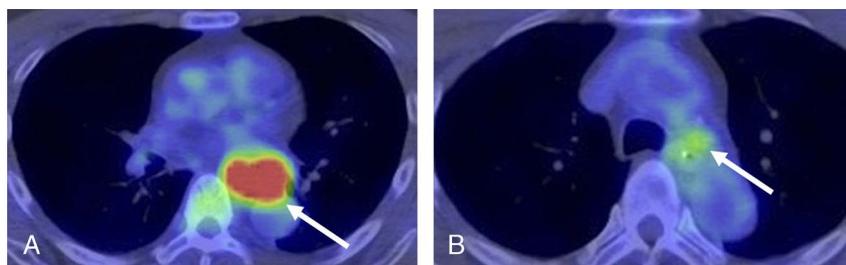
FIGURE 3. Representative false-positive FDG PET/CT finding for patient 8. **A,** The primary esophageal lesion has the SUV$_{max}$ of 17.7. **B,** A PET-positive finding is identified in the left tracheobronchial LN station with SUV$_{max}$ of 3.3, but pathologically, there is no metastatic LN.

versus not including metastatic LNs was 3.95 (range, 3.5–14.1) versus 2.45 (range, 2.0–9.0); however, this difference was not significant. We dissected a total of 331 LN stations according to the Japan Esophageal Society classification,[14] 28 of which included metastatic LNs. Based on the LN station-based analysis, the sensitivity, specificity, PPV, and NPV were 28.6%, 96.7%, 44.4%, and 93.6%, respectively. Representative images of the FDG PET/CT are shown in Figures 1 to 3.

## One-by-One LN-Based Analysis With Measurement of Dissected LNs

Table 2 shows the characteristics of the 1073 harvested LNs, including 38 metastatic LNs. Weight, shortest LN diameter, cps, and decay-corrected cps were significantly different between metastatic and nonmetastatic LNs ($P < 0.001$). The elapsed time from FDG injection until data acquisition with a well-type counter was not significantly different ($P = 0.41$).

Receiver operating characteristics curve analysis for weight, shortest LN diameter, cps, and decay-corrected cps was performed to distinguish metastatic and nonmetastatic LNs (Fig. 4). The AUC, sensitivity, specificity, PPV, and NPV of each measurement are shown in Table 3. The decay-corrected cps showed the largest AUC (0.92), and using the optimal cutoff value of 840 decay-corrected cps, 2 (5%) of 38 metastatic LNs were falsely judged as negative; one of these was 7 × 2 mm in size with 75 decay-corrected cps, and the other was 10 × 6 mm in size with 730 decay-corrected cps.

DISCUSSION

This prospective study aimed to assess the diagnostic power of FDG to detect metastatic LNs in patients with esophageal cancer. Although the LN station-based analysis of the preoperative FDG PET image showed a low sensitivity of 28.6%, the one-by-one LN-based analysis, in which the FDG uptake of individual LNs was measured by a well-type counter, showed a high sensitivity of 94.4%. The radioactivity of metastatic LNs was significantly higher than that of nonmetastatic LNs. Such high sensitivity indicates that intraoperative direct evaluation of LN FDG uptake would be useful to diagnose each individual LN, improving the decision to dissect or leave each LN located in a region with a high risk of postoperative complications.

The one-by-one LN inspection performed in this study showed high sensitivity in the identification of metastatic LNs, but the false-positive rate was relatively high. Of 1035 nonmetastatic LNs, 220 LNs (21.3%) showed a decay-corrected cps higher than the cutoff value. The false-positive rate was the highest in the subcarinal LNs (18 false-positives of 39 nonmetastatic LNs, 46.2%) followed by the main bronchus LNs (27 false-positives of 60 nonmetastatic LNs, 45.0%), where nonspecific LN inflammation tends to occur, increasing FDG uptake by activated inflammatory cells. This seems to be one of the limitations of FDG. New PET tracers, such as ^{68}Ga-labeled fibroblast activation protein inhibitors,
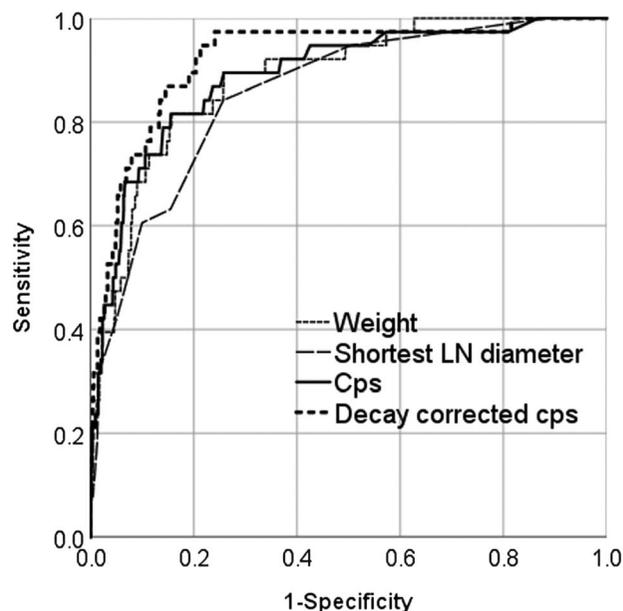
FIGURE 4. Receiver operating characteristic curves for each measurement to discriminate between metastatic and nonmetastatic LNs. Decay-corrected cps has the largest AUC (0.92).

which exhibited a high contrast between the tumor and normal tissue,[15] and [18]F L-[3-(18)F]-α-methyltyrosine (FAMT), which was reported to have high specificity in the evaluation of esophageal cancer,[16] might help overcoming this limitation of FDG.

A previous one-by-one LN study was conducted in patients with gastric cancer using the same method as in this study. In that study, 906 LNs, including 115 metastatic LNs, were investigated, resulting in 77% sensitivity and 60% specificity, and an AUC of 0.71 by ROC analysis.[17] Compared with the previous study of gastric cancer, the diagnostic ability was higher in esophageal cancer. Such difference may be attributed to the high glucose transporter (GLUT) expression and HK-II (type II hexokinase) activity in esophageal cancer.[18] In addition, a strong correlation between GLUT expression and the degree of FDG uptake measured on FDG PET images has also been reported, suggesting that the influence of other factors besides GLUT and HK-II is slight, and therefore, the interpretation of FDG uptake is straightforward.[19]

Two LNs were judged as false-negative with the optimal cutoff threshold of 840 decay-corrected cps in this study. The radioactivity of one LN was 40 cps as measured by the well-type counter and 730 decay-corrected cps with 460 minutes elapsed time, whereas that of another LN was only 3 cps as measured by the well-type counter and 75 decay-corrected cps with 509 minutes

---

TABLE 2. Characteristics of LNs (n = 1073) From 20 Patients

	With Metastasis, Median (Range), n = 38	Without Metastasis, Median (Range), n = 1035	*P**
Weight, mg	335 (39–7611)	58 (3–3954)	<0.001
Shortest LN diameter, mm	8 (3–20)	5 (1–18)	<0.001
cps	181 (3–20,216)	12 (0–1574)	<0.001
Decay-corrected cps	4753 (75–237,098)	256 (0–22,973)	<0.001
Elapsed time, min	515 (323–722)	439 (315–722)	0.413

*P value, Mann-Whitney *U* test.

TABLE 3. Sensitivity, Specificity, PPV, NPV, and AUC by ROC Analysis for the Measurements

	Cutoff Value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
Weight, mg	165	81.6	84.6	16.1	99.2	0.885
Shortest LN diameter, mm	5.5	84.2	74.3	6.5	99.6	0.857
cps	66	81.6	84.4	16.1	99.2	0.890
Decay-corrected cps	840	94.7	78.7	14.0	99.8	0.920

elapsed time. The shortest LN diameters were 6 mm and 2 mm, respectively. The second LN was pathologically diagnosed as micrometastasis. Among a total of 38 metastatic LNs, there were 3 LNs with micrometastasis and 3 LNs with isolated tumor cells (ITCs). A micrometastasis is defined as metastasis larger than 0.2 mm and/or more than 200 tumor cells, but not larger than 2 mm; ITC is defined as single tumor cell or small clusters of cells not more than 0.2 mm in the greatest extent.[20,21] Although 2 of 3 LNs with micometastasis and all 3 LNs with ITC were successfully judged as positive by the well-type counter measurement, 3 cps of micrometastasis is considered to be an extremely low radioactivity, which is a crucial limitation of FDG as a marker.

Radio-guided surgery, such as sentinel lymph node (SLN) navigation surgery, is used for patients with early-stage breast cancer or melanoma and plays a role in the omission of prophylactic LN dissection. Sentinel lymph node navigation surgery is based on the theory that the SLN is the first LN receiving lymphatic drainage from a primary tumor. Furthermore, in esophageal cancer, radio-guided SLN mapping has shown benefit in detecting LN metastases in early-stage cases; however, in advanced cases, multiple LN metastases can exist even with negative SLN. In addition, even in the early stages, SLNs were detected in an area extending from the cervical to the abdominal region in patients with thoracic esophageal cancer,[22] suggesting that lymphatic drainage from the primary tumor is already extended to a wide area and that the lymphatic drainage routes are complex. Therefore, in thoracic esophageal cancer, the efficacy of the SLN method is considered to be limited. We should evaluate each individual LN, especially those located in regions at high risk for postoperative complications.

Owing to the development of SLN navigation surgery, surgical procedures combined with radioactivity detection have also been developed. A drop-in gamma camera was integrated into robot-assisted laparoscopic surgery and demonstrated feasibility and efficacy.[23] Nakamura et al[24] developed a new handheld laparoscopic Compton camera for use in intraoperative FDG imaging. This new Compton camera succeeded in imaging dissected LNs and part of the primary tumor after FDG injection in patients with esophageal cancer. Although these techniques can be used for intraoperative FDG-guided surgery, careful clinical trials should be conducted to confirm their capability and accuracy in detecting metastatic LNs.

The following steps to implement FDG-guided surgery have been proposed: (1) preoperative diagnostic PET imaging, (2) intraoperative imaging, (3) ex vivo imaging, and (4) postoperative clinical PET imaging.[6,7,25] Ex vivo imaging indicates imaging of the specimen after resection, which can be measured by several methods using clinical PET, micro-PET, or a well-type counter. Our study concerns the stage of ex vivo imaging using a well-type counter. Although our study showed a significant difference in radioactivity between metastatic and nonmetastatic LNs in patients with esophageal cancer, well-type counters have higher efficiency in measuring radiation activity from samples because the samples are surrounded by the detector except for their upper

side and can be measured with minimal background. Therefore, there are still differences in measurement conditions between intraoperative imaging and the method we used in this study, related to the detector device.

Nwogu et al[8] reported that a limitation of the gamma probe was detecting FDG uptake in LNs located close to the primary tumor because it is difficult to differentiate incoming gamma rays of LNs from those of the primary tumor. A representative handheld probe designed to detect 511-keV gamma rays shows a 15-mm full width at half maximum (FWHM) at a distance of 1 cm and 47-mm FWHM at a distance of 5 cm from the point source in air.[26] Lymph nodes located within the FWHM of the primary tumor cannot be differentiated from the primary tumor. Even when LNs are located outside the FWHM of the primary tumor, higher radioactivity over thresholds, which are widely used at ranges of 1.5 to 3.0 times to the background, are needed for differentiation.[8,9] This is one of the limitations of the measurement method that uses probe-type detectors. In addition, background radioactivity from physiological uptake and LN movement caused by pulmonary respiration and heart pulsations can also confound the radioactivity measurements. To overcome these difficulties, new imaging devices will be necessary. For example, a large field of view would enable us to easily differentiate between LN and physiological uptake based on the contour of neighboring organs, while real-time imaging would allow tracking LN activity even if the LN moves according to the surrounding organ movements.

CONCLUSIONS

This prospective study compared pathological LN diagnosis with LN station-based findings on preoperative FDG PET images and with the radioactivity of each dissected LN after FDG injection in patients with esophageal cancer. The measurements of radioactivity after decay time correction for each LN showed the highest diagnostic accuracy compared with other LN measurements, namely, radioactivity without decay time correction, LN weight, and the shortest LN diameter. The remarkable improvement in the sensitivity obtained using individual LN radioactivity suggests that FDG is a potentially useful marker for navigation surgery in esophageal cancer, which may decrease the prevalence of severe complications.

REFERENCES

1. Ando N, Ozawa S, Kitagawa Y, et al. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. *Ann Surg*. 2000;232:225–232.
2. Tachibana M, Kinugasa S, Yoshimura H, et al. Clinical outcomes of extended esophagectomy with three-field lymph node dissection for esophageal squamous cell carcinoma. *Am J Surg*. 2005;189:98–109.
3. Tsurumaru M, Kajiyama Y, Udagawa H, et al. Outcomes of extended lymph node dissection for squamous cell carcinoma of the thoracic esophagus. *Ann Thorac Cardiovasc Surg*. 2001;7:325–329.
4. Nishihira T, Hirayama K, Mori S. A prospective randomized trial of extended cervical and superior mediastinal lymphadenectomy for carcinoma of the thoracic esophagus. *Am J Surg*. 1998;175:47–51.

5. van Vliet EP, Heijenbrok-Kal MH, Hunink MG, et al. Staging investigations for oesophageal cancer: a meta-analysis. *Br J Cancer*. 2008;98:547–557.

6. Povoski SP, Hall NC, Murrey DA Jr, et al. Multimodal imaging and detection approach to ^{18}F-FDG-directed surgery for patients with known or suspected malignancies: a comprehensive description of the specific methodology utilized in a single-institution cumulative retrospective experience. *World J Surg Oncol*. 2011;9:152.

7. Murrey DA Jr, Bahnson EE, Hall NC, et al. Perioperative (18)F-fluorodeoxyglucose-guided imaging using the Becquerel as a quantitative measure for optimizing surgical resection in patients with advanced malignancy. *Am J Surg*. 2009;198:834–840.

8. Nwogu C, Fischer G, Tan D, et al. Radioguided detection of lymph node metastasis in non-small cell lung cancer. *Ann Thorac Surg*. 2006;82: 1815–1820.

9. Cohn DE, Hall NC, Povoski SP, et al. Novel perioperative imaging with ^{18}F-FDG PET/CT and intraoperative ^{18}F-FDG detection using a handheld gamma probe in recurrent ovarian cancer. *Gynecol Oncol*. 2008;110: 152–157.

10. Orsaria P, Chiaravalloti A, Fiorentini A, et al. PET probe-guided surgery in patients with breast cancer: proposal for a methodological approach. *In Vivo*. 2017;31:101–110.

11. Schreurs LM, Smit JK, Pavlov K, et al. Prognostic impact of clinicopathological features and expression of biomarkers related to ^{18}F-FDG uptake in esophageal cancer. *Ann Surg Oncol*. 2014;21:3751–3757.

12. Kobayashi M, Kaida H, Kawahara A, et al. The relationship between glut-1 and vascular endothelial growth factor expression and ^{18}F-FDG uptake in esophageal squamous cell cancer patients. *Clin Nucl Med*. 2012;37: 447–452.

13. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC cancer staging manual: esophagus and esophagogastric junction. *Ann Surg Oncol*. 2010;17: 1721–1724.

14. Japan Esophageal Society. Japanese classification of esophageal cancer, 11th edition: part II and III. *Esophagus*. 2017;14:37–65.

15. Kratochwil C, Flechsig P, Lindner T, et al. ^{68}Ga-FAPI PET/CT: tracer uptake in 28 different kinds of cancer. *J Nucl Med*. 2019;60:801–805.

16. Sohda M, Kato H, Suzuki S, et al. ^{18}F-FAMT-PET is useful for the diagnosis of lymph node metastasis in operable esophageal squamous cell carcinoma. *Ann Surg Oncol*. 2010;17:3181–3186.

17. Okumura Y, Aikou S, Onoyama H, et al. Evaluation of ^{18}F-FDG uptake for detecting lymph node metastasis of gastric cancer: a prospective pilot study for one-to-one comparison of radiation dose and pathological findings. *World J Surg Oncol*. 2015;13:327–327.

18. Tohma T, Okazumi S, Makino H, et al. Relationship between glucose transporter, hexokinase and FDG-PET in esophageal cancer. *Hepatogastroenterology*. 2005; 52:486–490.

19. Meyer HJ, Wienke A, Surov A. Associations between GLUT expression and SUV values derived from FDG-PET in different tumors—a systematic review and meta analysis. *PLoS One*. 2019;14:e0217781.

20. Hermanek P, Hutter RV, Sobin LH, et al. International Union Against Cancer. Classification of isolated tumor cells and micrometastasis. *Cancer*. 1999;86: 2668–2673.

21. Sobin LH, Gospodarowicz MK, Wittekind CH, eds. *TNM Classification of Malignant Tumours*. 7th ed. Hoboken, NJ: Wiley-Blackwell; 2009: 13–15.

22. Takeuchi H, Fujii H, Ando N, et al. Validation study of radio-guided sentinel lymph node navigation in esophageal cancer. *Ann Surg*. 2009;249:757–763.

23. Meershoek P, van Oosterom MN, Simon H, et al. Robot-assisted laparoscopic surgery using DROP-IN radioguidance: first-in-human translation. *Eur J Nucl Med Mol Imaging*. 2019;46:49–53.

24. Nakamura Y, Shimazoe K, Takahashi H, et al. Development of a novel handheld intra-operative laparoscopic Compton camera for ^{18}F-fluoro-2-deoxy-2-d-glucose-guided surgery. *Phys Med Biol*. 2016;61:5837–5850.

25. Povoski SP, Hall NC, Murrey DA Jr, et al. Feasibility of a multimodal ^{18}F-FDG-directed lymph node surgical excisional biopsy approach for appropriate diagnostic tissue sampling in patients with suspected lymphoma. *BMC Cancer*. 2015;15:378.

26. Heuveling DA, Karagozoglu KH, Van Lingen A, et al. Feasibility of intraoperative detection of sentinel lymph nodes with 89-zirconium-labelled nanocolloidal albumin PET-CT and a handheld high-energy gamma probe. *EJNMMI Res*. 2018;8:15.