ORIGINAL ARTICLE

Impact of EUS-FNA for preoperative para-aortic lymph node staging in patients with pancreatobiliary cancer

Akira Kurita, MD,[1,6] Yuzo Kodama, MD, PhD,[1] Yuji Nakamoto, MD, PhD,[2] Hiroyoshi Isoda, MD, PhD,[2] Sachiko Minamiguchi, MD, PhD,[3] Kenichi Yoshimura, PhD,[4] Katsutoshi Kuriyama, MD,[1] Yugo Sawai, MD,[1] Norimitsu Uza, MD, PhD,[1] Etsuro Hatano, MD, PhD,[5] Shinji Uemoto, MD, PhD,[5] Kaori Togashi, MD, PhD,[2] Hironori Haga, MD, PhD,[3] Tsutomu Chiba, MD, PhD[1]

Kyoto, Kanazawa, Osaka, Japan

Background and Aims: In patients with pancreatobiliary cancer, para-aortic lymph node (PALN) metastasis is considered to be the involvement beyond the regional lymph nodes, namely, distant metastasis. Effective methods for preoperative PALN staging, however, are not established. This study aimed to compare the diagnostic capability for PALN metastasis between EUS-FNA and ^{18}F-fluorodeoxyglucose positron emission tomography with CT (PET/CT).

Methods: We performed a prospective, nonrandomized, single-center trial. Between December 2010 and March 2014, 208 patients with pancreatobiliary cancer without apparent distant metastasis except for PALNs were assessed for study eligibility before surgery. Among them, 52 consecutive patients with PALN enlargement were enrolled in the study. ^{18}F-Fluorodeoxyglucose PET/CT and EUS-FNA were performed sequentially as a single combined procedure to evaluate PALN metastases. The primary outcome was to compare the diagnostic capability of EUS-FNA and PET/CT for PALN metastasis.

Results: Of 71 enlarged PALNs in the 52 patients, 30 (42.3%) were finally diagnosed as metastases in 21 patients (40.4%). Of the 21 patients with PALN metastases, preoperative EUS-FNA or PET/CT made a correct diagnosis in 20 (95.2%) or 12 (57.1%), respectively. EUS-FNA had higher sensitivity and specificity for the diagnosis of PALN metastasis (sensitivity, 96.7% [29/30]; 95% confidence interval, 82.2%-99.9%; specificity, 100% [39/39]; 95% confidence interval, 91.0%-100%) than PET/CT.

Conclusions: EUS-FNA is superior to PET/CT for preoperative PALN staging in patients with pancreatobiliary cancer. Because of the clinical benefit of EUS-FNA to reduce unnecessary surgery, it should be part of the standard preoperative examination for patients with pancreatobiliary cancer. (UMIN clinical trials registry number: 000006408.) (Gastrointest Endosc 2016;■:1-9.)

The incidence and mortality of pancreatic and biliary tract cancers are increasing worldwide. Previous studies indicate that curative surgical resection is the only treatment that achieves a good outcome. Unnecessary surgery for advanced cases, however, is disadvantageous for patients. Therefore, accurate preoperative staging is

Abbreviations: AJCC, American Joint Committee on Cancer; CA, celiac axis; CHA, common hepatic artery; CI, confidence interval; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; H&E, hematoxylin and eosin; LN, lymph node; MDCT, multidetector-row CT; NPV, negative predictive value; PALN, para-aortic lymph node; PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography with CT; PPV, positive predictive value; SMA, superior mesenteric artery; SUVmax, maximum standardized uptake value; UICC, Union for International Cancer Control; VAS, visual analog scale.

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Current affiliations: Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Kyoto, Japan (1); Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan (2); Department of Diagnostic Pathology, Kyoto University Hospital, Kyoto, Japan (3); Innovative Clinical Research Center, Kanazawa University Hospital, Kanazawa, Japan (4); Department of Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan (5); Division of Gastroenterology and Hepatology, Digestive Disease Center, Kitano Hospital, The Tazuke Kofukai Medical Research Institute, Osaka, Japan (6).

Reprint requests: Yuzo Kodama, MD, PhD, Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan.

important to determine the best treatment modality for each patient.

In addition to distant metastases to other organs, such as the liver, peritoneum, and lungs, para-aortic lymph node (PALN) metastasis has been shown to lead to an extremely poor prognosis.[1-10] Indeed, according to the current tumor-nodal-metastasis (TNM) guidelines of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), cancer spread to PALNs is considered to be involvement beyond the regional lymph nodes (LNs) in pancreatic and biliary tract cancers, namely, distant metastasis.[11,12] General rules for the study of pancreatic cancer (6th edition) by the Japan Pancreas Society also clearly define PALN involvement as a distant metastasis.[13] Thus, PALN metastasis is classified as a distant metastasis and is regarded as one of the unresectable factors. Recent reports demonstrated that such PALN metastases were found in more than 10% of surgical cases for pancreatic cancer.[9,10,14] However, because of the limited diagnostic ability using conventional imaging modalities (eg, ultrasonography, multidetector-row CT [MDCT], magnetic resonance imaging, and EUS), PALN metastasis currently is not always evaluated before surgery. To avoid unnecessary laparotomy, establishment of a new effective technology for preoperative PALN diagnosis is strongly needed.

^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) and FDG-PET with CT (PET/CT) are relatively new diagnostic tools for detecting not only the primary site but also metastatic sites of various cancers, including pancreatobiliary cancer.[14-20] For the diagnosis of LN metastasis, however, FDG-PET and PET/CT have not achieved satisfactory outcomes, with at most 60% to 80% accuracy, a high false-positive rate, and a low sensitivity rate.[15-17] Indeed, according to the National Comprehensive Cancer Network (NCCN) guidelines, MDCT is recommended as a standard imaging modality for the staging of pancreatic cancer, but the role of PET/CT is still uncertain. Several recent reports demonstrated the efficacy of EUS and EUS-FNA biopsy for the diagnosis of LN metastasis.[21-28] Although these reports revealed better outcomes by EUS-FNA than by FDG-PET or PET/CT for the diagnosis of LN metastasis, to date there have been no reports evaluating the usefulness of EUS-FNA in the diagnosis of PALN metastasis.

Therefore, in the present study, we prospectively compared the efficacy of EUS-FNA with that of PET/CT for PALN staging in patients with pancreatobiliary neoplasms using histology as the criterion standard.

METHODS

Patients

From December 2010 through March 2014, a total of 208 patients with pancreatobiliary cancer without apparent distant metastases were assessed for PALN enlargement by MDCT at Kyoto University Hospital, Kyoto, Japan. The PALN was defined as the LN around the abdominal aorta that was classified as No. 16 LN according to the Japanese classification.[1-10,13] Patients who had PALN enlargement with a short axis size of at least 5 mm or a long axis size of at least 8 mm were eligible for this study. As for patients with pancreatic cancer, regional LNs were defined as LNs along the common bile duct, common hepatic artery (CHA), portal vein, posterior and anterior pancreaticoduodenal arcades, and superior mesenteric vein and right lateral wall of the superior mesenteric artery (SMA) for pancreatic head cancer and as LNs along the CHA, celiac axis (CA), splenic artery, and splenic hilum for pancreatic body/tail cancer according to the TNM guidelines,[11,12] leading to the concept that PALNs are nonregional. This study was approved by the Kyoto University ethical review board, and written informed consent was obtained from all the patients.

Study design

First, a histologically proven definitive diagnosis was made for the primary tumor of the pancreatobiliary cancer in each patient. Then, patients without distant metastasis were prospectively enrolled in this PALN evaluation study. According to the National Comprehensive Cancer Network guidelines, the surgical criteria for resectable pancreatic cancer were no arterial tumor contact (CA, SMA, or CHA) and no tumor contact with the superior mesenteric vein or portal vein or 180° or less of contact without vein contour irregularity, and borderline resectable was defined as solid tumor contact with the CHA without extension to the CA or the hepatic artery bifurcation, allowing for safe and complete resection and reconstruction; solid tumor contact with the SMA of 180° or less for pancreatic head cancer; and solid tumor contact with the CA of 180° or less for pancreatic body/tail cancer. In the borderline resectable cases, neoadjuvant therapy, such as chemotherapy or chemoradiotherapy, was provided first, and subsequently resectability and study eligibility were assessed again before surgery. Information on PALN enlargement by MDCT was sent to the PET/CT or EUS/EUS-FNA investigators. ^{18}F-Fluorodeoxyglucose positron emission tomography with CT and EUS/EUS-FNA were scheduled within 2 weeks and 1 week before surgery, respectively. This tight schedule was designed to avoid an evaluation bias due to a delay between assessments. Diagnosis by PET/CT, EUS, and EUS-FNA was performed prospectively and independently, and the investigators were blinded to the results of the other imaging data or histopathology results. The final diagnosis of PALNs was confirmed by histologic evaluation of EUS-FNA or surgically resected LN specimens. Data collection was performed prospectively in consecutive patients.

Techniques and image evaluation

CT imaging. The MDCT examinations were performed using a 64-detector row scanner (Aquilion, Toshiba Medical, Tokyo, Japan). Details of the imaging procedures have been published previously.[28] The MDCT images were interpreted by a single experienced radiologist (I.H.) based on all the available clinical information and correlative conventional imaging. If a PALN was identified, the position was recorded according to the branching artery from the aorta, and the long axis and short axis were measured. All recognized PALNs with a short-axis size of at least 5 mm or a long-axis size of at least 8 mm were eligible for this study.

PET/CT imaging. Whole-body imaging was performed using a combined PET/CT scanner (Discovery ST Elite, GE Healthcare, Waukesha, Wis). Details of the imaging procedures have been published previously.[29] Positron emission tomographic scanning was prospectively interpreted and recorded by 2 board-certified radiologist/nuclear medicine physicians (one was Y.N., with >15 years of experience in PET/CT, and the other changed depending on the day). Evaluation by PET/CT was made by qualitative and quantitative methods. For the qualitative evaluation, the probability of LN metastasis was assessed on a per-node basis using the following 5-point visual scoring system, as previously reported[30]: 1, normal; 2, probably benign; 3, equivocal; 4, probably malignant; and 5, definitely malignant. Lesions scored 4 or 5 were considered PET/CT positive. For the quantitative evaluation, the maximum standardized uptake value (SUVmax) was measured if possible. If there was no abnormal FDG uptake, the SUVmax was not measured. Because we do not have a generally accepted cutoff value for SUVmax to distinguish malignant from benign, we did not use the SUVmax for this prospective analysis.

EUS. All the EUS and EUS-FNA examinations were performed by gastroenterologists well trained in EUS using a linear array echoendoscope (GF-UCT 240-AL5, Olympus Optical Corp Ltd, Tokyo, Japan). All the examinations were performed in a standardized manner with the patients under conscious sedation using midazolam. After the probe was inserted into the stomach or duodenum, PALN stations were systemically imaged and categorized into 1 of 3 locations (above the confluence of the celiac artery, between the confluence of the celiac artery and the left renal artery, or below the confluence of the left renal artery). All the PALNs visualized by EUS were assessed regarding size (long axis and short axis), shape, border delineation, echogenicity, and homogeneity. Features of EUS regarded as malignant were as follows: short-axis diameter of at least 10 mm, round shape, sharply demarcated borders, and a central echo pattern that was homogeneous and hypoechoic.[31] EUS positive was defined as having at least 1 of these 4 features. In addition, a 5-point visual analog scale (VAS) was also recorded for roundness, echogenicity, and homogeneity (minimum 3 to maximum 15) according to previous reports.[31,32] The sum of the 5-point VAS was also assessed in association with the score and node histopathology.

EUS-FNA. After the EUS examination, EUS-FNA was performed at the same session. All the PALNs indicated by MDCT were punctured. The EUS-FNA was performed with a 22-gauge needle using suction (Expect, Boston Scientific, Natick, Mass) with at least 1 pass. A part of the obtained sample was prepared for Diff-Quik staining for rapid on-site cytology to ensure the quantity and quality of the material by an attending cytotechnologist, and the remainder was wet-fixed for Papanicolaou staining. In addition, tissue fragments were fixed in 10% neutral-buffered formalin, embedded in paraffin, and then processed as a routine tissue block. The tissue section from the cell block was stained with hematoxylin and eosin and used for immunohistochemical analysis as appropriate. The detailed positions of punctured PALNs were reported to the surgeons according to the registered location as described previously herein to avoid misidentification of resected LNs during surgery. If there were several LNs, EUS-guided tattooing was also performed toward the punctured nodes at the same session as EUS-FNA. Specimens obtained from the EUS-FNA were evaluated for both cytology and histology. Cytologic and histologic diagnoses were separately classified into 4 categories: benign or reactive change, suspicious for malignancy, malignant, and inadequate material for diagnosis. FNA positive was defined as suspicious for malignancy or malignant by either cytology or histology. Others were defined as FNA negative.

Pathologic evaluation of resected LNs. The surgically resected LNs were submitted for routine sectioning and pathologic evaluation.

Final diagnosis of PALN metastasis. The final diagnosis of PALN metastasis was made based on histologic confirmation of malignancy by EUS-FNA or surgical resection. Cytologic diagnosis was not reflected in the final diagnosis due to its relatively high false-positive rate.[33] In cases of histologic results of benign or reactive change, suspicious for malignancy, or inadequate material for diagnosis by EUS-FNA, pathologic confirmation of surgically resected LNs was required for a final diagnosis. On the other hand, considering the ethical problems, the surgery was canceled if the PALN was proved to be histologically malignant by EUS-FNA.

Statistical analysis

The primary outcome measures of the study were sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of PET/CT, EUS, and EUS-FNA for PALN staging in patients with pancreatobiliary cancer. Secondary outcome measures were the feasibility and safety of EUS-FNA and the sum of the 5-point VAS of EUS for PALN staging.

Confidence intervals (CIs) for the outcomes were calculated based on exact binominal distribution. Comparison

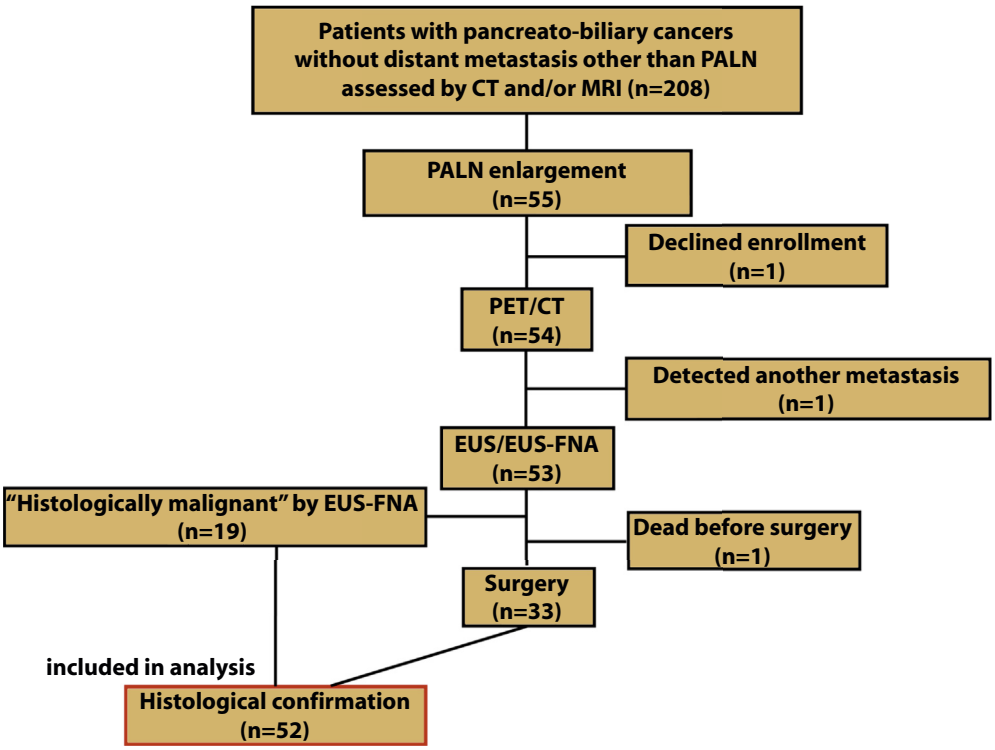

Figure 1. Flowchart of patients throughout the study. *PALN,* para-aortic lymph node; *PET/CT,* ^{18}F-fluorodeoxyglucose positron emission tomography with CT.

between diagnosing methods was performed using the McNemar test. All the *P* values were 2-sided, and $P < .05$ was considered statistically significant. All the statistical analyses were performed using JMP software, version 11.2 (SAS Institute Inc, Cary, NC).

RESULTS

Between December 2010 and March 2014, 208 patients with pancreatobiliary cancer without apparent distant metastases except for PALNs were assessed for study eligibility (Fig. 1). Fifty-five patients with PALN enlargement were eligible for the study, and informed consent was obtained from 54 patients. ^{18}F-Fluorodeoxyglucose positron emission tomography with CT was performed in these 54 patients, and other organ metastasis was detected in 1 patient, who was thus excluded from study. Then, EUS-FNA was performed in 53 patients, and surgery was cancelled for the 19 patients diagnosed as having histologically malignant PALN. Surgery was scheduled for the remaining 34 patients but was performed in only 33 patients because 1 patient died just before surgery. Eventually, 71 PALNs in 52 patients were enrolled in this study (Fig. 1). The median age of the patients was 67.5 years (range, 33-83 years). Thirty-two patients were men and 20 were women. Regarding the primary tumor, 29 patients had pancreatic ductal adenocarcinoma, 11 had intrahepatic cholangiocarcinoma, 8 had gallbladder carcinoma, 3 had bile duct carcinoma, and 1 had ampullary carcinoma. The final diagnosis of PALN metastases was made for 30 PALNs in 21 patients. Among these, 28 nodes in 19 patients were confirmed by EUS-FNA, and the remaining 2 nodes in 2 patients were confirmed by surgical resection. A schematic presentation of the locations of the PALNs is shown in Figure 2 and the Supplementary Figure (available online at www.giejournal.org).

PET/CT

Of the 71 PALNs in the 52 evaluated patients, 17 LNs (23.9%) were PET/CT positive, 16 of which were finally diagnosed as PALN metastases (Table 1). One false-positive case by PET/CT had an SUVmax of 3.9, but the surgically resected specimen revealed only a sarcoid-like reaction without cancer involvement (Fig. 3). On the other hand, the remaining 14 PALNs with final diagnoses of metastases were not detected by PET/CT (Table 1).

As for the quantitative analysis, the SUV was measured in 39 nodes of 71 PALNs. The SUVmax was significantly higher in malignant PALNs than in nonmalignant ones ($P < .0001$) (Fig. 4). Retrospective evaluation of PET/CT using a cutoff value of 1.8 resulted in a diagnostic accuracy of 80.3% (data not shown).

EUS

Of the 71 PALNs in 52 patients, 1 node was not evaluated because the target PALN could not be visualized by EUS. Of the 70 nodes visualized by EUS, 60 LNs (85.7%)

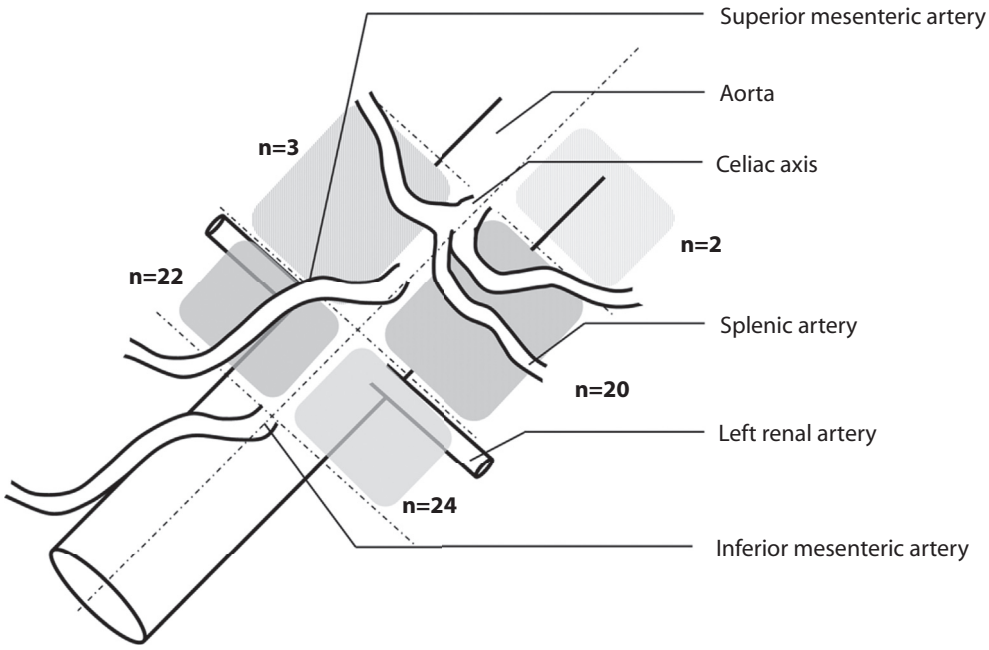

Figure 2. Schematic presentation of the locations of the para-aortic lymph nodes.

TABLE 1. Diagnosis of PALNs by PET/CT

	Final diagnosis of PALNs, n		
PET/CT result	**Malignant**	**Nonmalignant**	**Total**
Positive	16	1	17
Negative	14	40	54
Total	30	41	71

PALN, Para-aortic lymph node; *PET/CT,* ^{18}F-fluorodeoxyglucose positron emission tomography with CT.

were EUS positive, 28 of which were finally diagnosed as PALN metastases. As to the EUS features for malignant LN, only 20% of PALN metastases (n = 6) had all 4 malignant EUS features of size, shape, border, and echo pattern. On the other hand, the sum of the 5-point VAS was positively correlated with malignant findings in PALN histology (Table 2). Para-aortic lymph nodes with a sum of the 5-point VAS of 10 or greater tended to be malignant, with an accuracy of 70%.

EUS-FNA

In addition to the 1 patient whose PALN was not visualized by EUS, EUS-FNA could not be performed in another patient owing to the interposition of an artery. Finally, EUS-FNA was successfully performed for 69 nodes (97.2%) without any procedure-related morbidity and mortality. The median number of passes by EUS-FNA was 2 (1 pass in 31 nodes, 2 passes in 29 nodes, 3 passes in 8 nodes, and 4 passes in 1 node). FNA positive was observed in 29 nodes (42.0%), including 28 histologically malignant and 1 histologically suspicious for malignancy (Table 3). In the 1 case that was suspicious for malignancy, surgical resection confirmed the histology as very well-differentiated tubular adenocarcinoma. There was no false-positive case. On the other hand, a false-negative was found in only 1 case, in which the surgically resected LN specimen revealed micrometastasis (Fig. 5).

Regarding the quality of the specimens, inadequate material for diagnosis occurred in 10.1% (7/69) or 1.4% (1/69) of cytologic or histologic specimens, respectively. Evaluable specimens were obtained from 98.6% of LNs (68/69).

Comparison of diagnostic capability for PALNs between EUS-FNA and PET/CT

Table 4 shows the sensitivity, specificity, PPV, NPV, and accuracy of EUS-FNA and PET/CT for preoperative PALN staging in patients with pancreatobiliary cancer. EUS-FNA showed 96.7% sensitivity (95% CI, 82.8%-99.9%) and 100% specificity (95% CI, 91.0%-100%), whereas PET/CT showed 53.3% sensitivity (95% CI, 34.3%-71.7%) and 97.6% specificity (95% CI, 87.1%-99.9%). The diagnostic capability of EUS-FNA for PALNs had higher sensitivity, specificity, PPV, NPV, and accuracy compared with PET/CT.

Direct benefit of preoperative staging by EUS-FNA

EUS-FNA led to a correct diagnosis in 1 false-positive and 7 false-negative cases by PET/CT. Of the 52 patients, including 21 with a final diagnosis of PALN metastasis, preoperative EUS-FNA and PET/CT identified 20 and 12 patients with PALN metastasis, respectively, with significantly higher sensitivity by EUS-FNA (P = .01). This finding indicated that by using EUS-FNA, unnecessary laparotomy

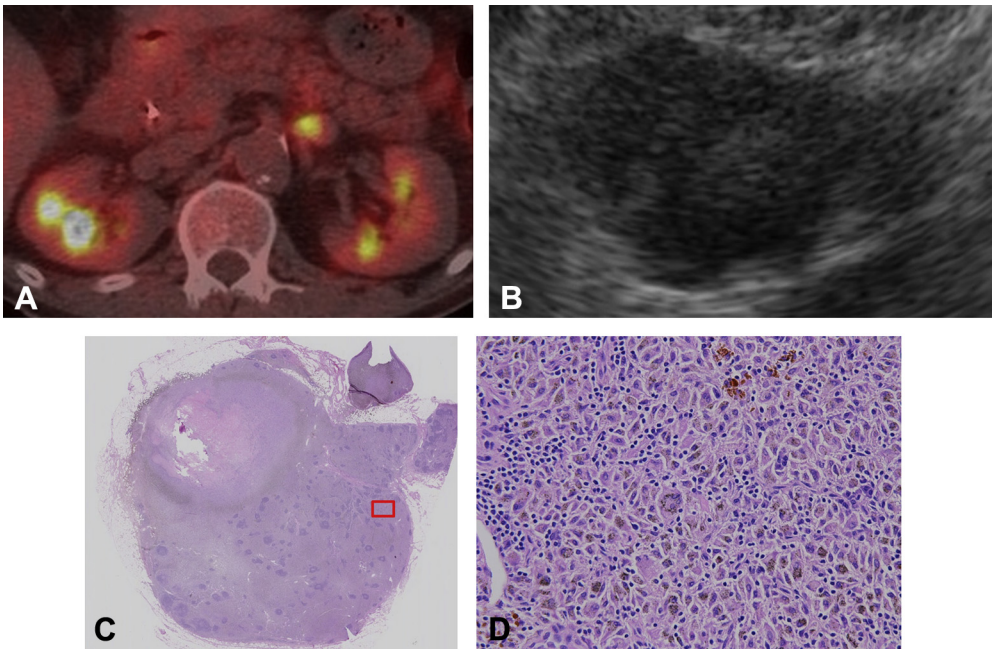

Figure 3. A, ^{18}F-Fluorodeoxyglucose positron emission tomography with CT showed strong ^{18}F-fluorodeoxyglucose uptake in the para-aortic lymph node (PALN), with a maximum standardized uptake value of 3.9. **B,** EUS showed the PALN to be malignant, 13 × 20 mm, oval, sharply demarcated, and low echoic, with a homogeneous echo pattern. **C** and **D,** Resected enlarged lymph node with histologic findings of a sarcoid-like reaction. The lymph node was occupied by non-necrotizing epithelioid granuloma (H&E, orig. mag. × 40). The area in the red box in part C is magnified in part D.

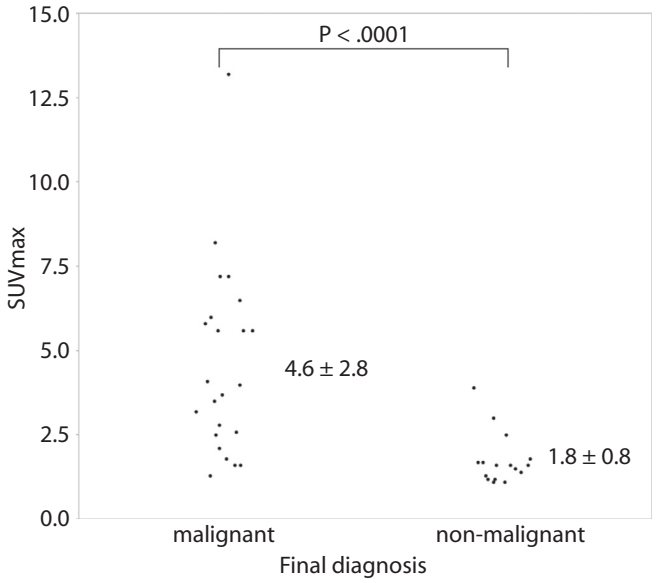

Figure 4. Correlation between maximum standardized uptake value (SUVmax) and the final diagnosis of para-aortic lymph nodes.

could be avoided in 8 patients. Indeed, 7 patients did not have a laparotomy in the present study.

DISCUSSION

This prospective study demonstrates that the diagnostic accuracy of EUS-FNA (98.6%) is higher than that of PET/CT (78.9%) for the preoperative PALN staging of pancreatobiliary cancer. Based on its significant clinical benefit of reducing unnecessary laparotomy, EUS-FNA for PALNs should be added to the standard preoperative examinations for pancreatobiliary cancer.

TABLE 2. Association between the sum of the 5-point VAS for EUS and PALN histology

	VAS score			
	3-6	7-9	10-12	13-15
PALNs, n	9	31	20	10
Malignant nodes, n (%)	0	9 (29.0)	11 (55)	10 (100)

VAS, Visual analog scale; *PALN,* para-aortic lymph node.

For preoperative staging of various cancers, the PET/CT is reported to be useful for detecting not only the primary site but also metastatic sites. During the past decade, the clinical efficacy of EUS-FNA has been highlighted compared with that of PET/CT, especially for the diagnosis of LN metastases. For example, Larsen et al[27] reported the preoperative LN diagnosis of 11 PALNs in patients with GI cancer using EUS and EUS-FNA with accuracies of 77% and 85%, respectively. Chen and Eloubeidi[18] and Annema et al[20] reported that EUS-FNA yielded a correct diagnosis in 98.8% and 77.8% of patients with malignant mediastinal/peri-intestinal LNs, respectively.[18,20] Although it is well-recognized that preoperative PALN staging is crucially important in patients with pancreatobiliary cancer, there has been no report on evaluation by EUS-FNA. In the

TABLE 3. Cytologic and histologic diagnosis of PALNs by EUS-FNA

Diagnosis category	Final diagnosis of PALNs, n		
	Malignant (n = 30)	Nonmalignant (n = 39)	Total (N = 69)
Cytology by EUS-FNA			
Malignant	25	0	25
Suspicious	1	0	1
Benign	1	35	36
Inadequate	3	4	7
Histology by EUS-FNA			
Malignant	28	0	28
Suspicious	1	0	1
Benign	1	38	39
Inadequate	0	1	1

PALN, Para-aortic lymph node.

TABLE 4. Diagnostic values for PALN staging by EUS-FNA and PET/CT

	EUS-FNA (n = 69)	PET/CT (n = 71)	*P* value*
Sensitivity	96.7 (82.8-99.9)	53.3 (34.3-71.7)	<.001
Specificity	100 (91.0-100)	97.6 (87.1-99.9)	1.00
Predictive value			
Positive	100 (88.1-100)	94.1 (71.3-99.9)	
Negative	97.5 (86.4-99.9)	74.1 (60.4-85.0)	
Accuracy	98.6 (92.2-100)	78.9 (67.6-87.7)	<.001

Values are given as percentage (95% confidence interval).
PALN, Para-aortic lymph node; *PET/CT;* ^{18}F-fluorodeoxyglucose positron emission tomography with CT.
*McNemar test *P* value; 2 cases were excluded for calculating *P* values because of inability to perform EUS-FNA in these cases.

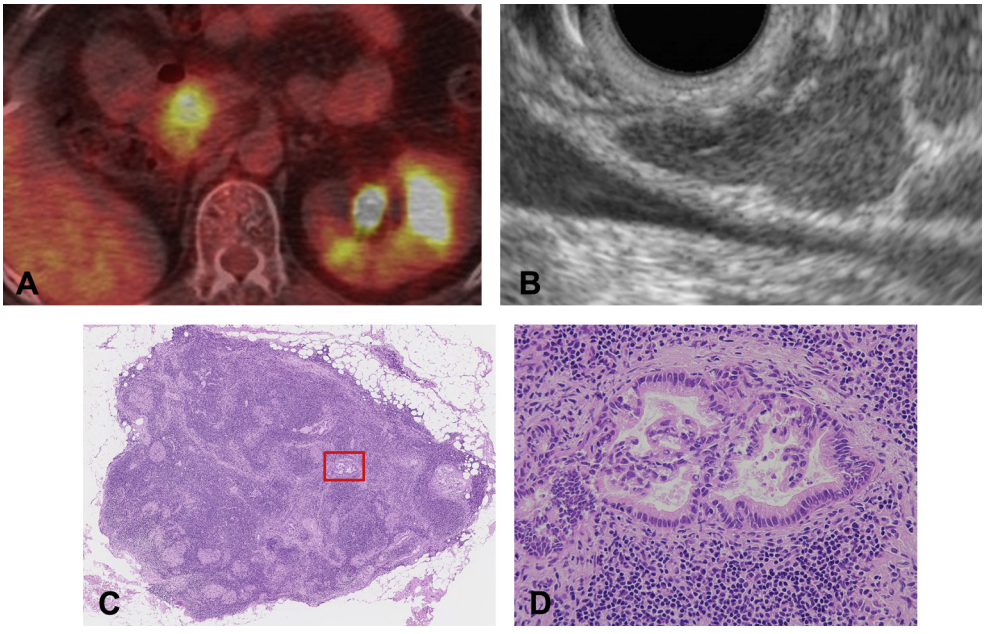

Figure 5. A, ^{18}F-Fluorodeoxyglucose positron emission tomography with CT revealed no abnormal uptake in the para-aortic lymph node (PALN). **B,** EUS revealed the PALN to be 8 × 18 mm, oval, not well demarcated, and low echoic, with a homogeneous echo pattern. **C** and **D,** Micrometastasis of adenocarcinoma observed in the resected lymph node. The total size of the scattered small glands of adenocarcinoma was 2314 μm (H&E, orig. mag. × 40). Most of the resected lymph node comprised normal lymphocytes. The area in the red box in part C is magnified in part D.

present study, therefore, we assessed the diagnostic performance of EUS-FNA for PALN metastases and obtained 96.7% sensitivity, which is comparable with previous studies of mediastinal/peri-intestinal LNs. Furthermore, this is the first study, to our knowledge, that prospectively compared EUS-FNA with PET/CT in the preoperative staging of pancreatobiliary cancer.

In this study, the diagnostic accuracy of PET/CT for PALN metastases in patients with pancreatobiliary cancer was 78.9%. In general, detecting small lesions (especially <1 cm) by PET/CT is thought to be difficult because of its low spatial resolution. The present study also showed that a PALN with a short-axis diameter of at least 10 mm is more accurately diagnosed than is a PALN with a short-axis diameter less than 10 mm by PET/CT, although the difference between the 2 groups was not statistically significant (data not shown). These results indicate that EUS-FNA had higher diagnostic accuracy than PET/CT (98.6% vs 78.9%), and, indeed, there were no patients in whom PET/CT detected PALN metastasis that

was negative by EUS-FNA. However, the specificity for the diagnosis by PET/CT was 97.6%, which was comparable with that of EUS-FNA. Therefore, PET/CT may still have an important role for PALN staging in cases in which the PALN is not visualized by EUS or when it is technically difficult to perform EUS-FNA.

Previous reports demonstrated that EUS is effective for distinguishing malignant LNs from benign LNs.[27,31] According to the previous data, we defined EUS positive as having at least 1 of 4 malignant EUS features for LN diagnosis, and we assessed the efficacy of EUS for PALN staging. As a result, the diagnostic values of sensitivity, specificity, PPV, NPV, and accuracy of EUS were lower than those of EUS-FNA, confirming the superiority of EUS-FNA to EUS. Indeed, the sensitivity, specificity, PPV, NPV, and accuracy of EUS were 93.3%, 20.0%, 46.7%, 80.0%, and 51.4%, respectively. On the other hand, the sum of the 5-point VAS was well correlated with the histologically malignant findings in PALNs, suggesting that there is room for improvement in the establishment of an objective EUS diagnostic system for LN metastasis.

As mentioned previously, we achieved excellent diagnostic results using EUS-FNA for PALN staging, with high sensitivity (96.7%), specificity (100%), and accuracy (98.6%). This result yielded a clinical benefit for preventing patients with PALN metastasis from undergoing unnecessary surgical interventions. Only 1 patient in this study was understaged by EUS-FNA (false-negative) owing to micrometastasis in a very small part of the PALN. At present, such a micrometastatic lesion is undetectable with any type of diagnostic modality and is a big challenge for the future. More importantly, there were no false-positives obtained by EUS-FNA in this study. This is extremely important from the viewpoint that a patient without PALN metastasis should not miss an opportunity for surgery because of misdiagnosis using EUS-FNA.

There are some limitations to this study. First, the analysis was performed without randomization. To minimize bias, however, we prospectively assessed all consecutive patients by performing PET/CT and EUS/EUS-FNA in a sequential manner without knowledge of each result. Second, this study was performed at a single center, and the sample size was relatively small. Only 1 case had a false-positive by PET/CT, and 1 case had a false-negative by EUS-FNA. To obtain more solid data, a larger number of patients is required. Third, there was little evidence to support the size criteria of PALNs by MDCT (short axis $\geq$5 mm or long axis $\geq$8 mm) for this study. This might have resulted in selection bias. Of the 153 patients who did not fulfill the size criteria of PALNs, however, laparotomy revealed that only 2 patients had inoperable disease because of peritoneal dissemination but none had PALN metastasis. This indicates that the size criteria for identifying enlarged LNs by MDCT seem to be adequate, although further studies are required. Fourth, in 19 patients who were FNA positive, the final diagnosis of PALN metastasis was made only by EUS-FNA without confirming the pathology of the surgically resected specimen. This might be problematic for evaluation of the diagnostic performance of EUS-FNA. Considering that cell block–based histologic analysis with hematoxylin and eosin staining or appropriate immunohistochemical analysis had high diagnostic accuracy, we decided that performing a laparotomy in patients with cell block–based histologic confirmation of PALN metastasis would not be ethically acceptable.

In conclusion, we found that EUS-FNA is superior to PET/CT for preoperative PALN staging in patients with pancreatobiliary cancer. EUS-FNA could reduce the number of unnecessary laparotomies and, thus, should be added as a routine preoperative examination for pancreatobiliary cancer.

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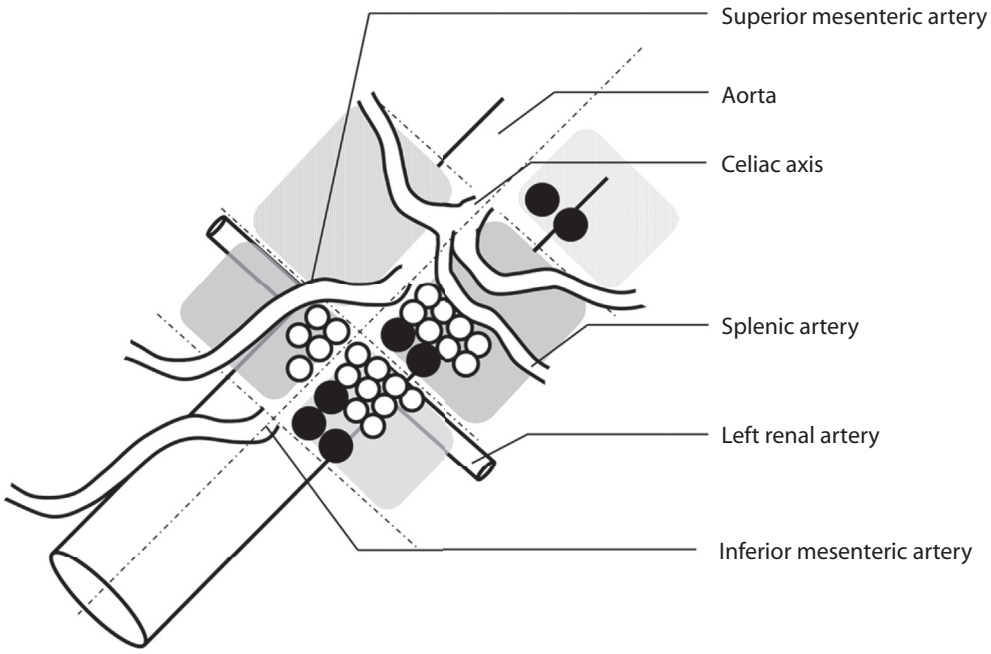

Supplementary Figure. The detailed locations of para-aortic lymph nodes (PALNs) in patients with pancreatic cancer. White circles (◯) and black circles (●) demonstrate PALNs in patients with cancer located in the pancreatic head and body/tail, respectively. Note that there were no PALNs around the celiac axis, suggesting that all the PALNs were nonregional.