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

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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;84:467-75.)

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

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.