EDITORIAL

Sampling para-aortic lymph nodes in pancreatic and biliary cancers with EUS-guided FNA: diagnostic, clinical, and therapeutic implications

Pancreatic cancer is the fourth leading cause of cancer-related mortality in the United States. Surgical resection is the only potentially curative treatment. Unfortunately, the prognosis is dismal, even after a complete resection. The probability of locoregional recurrence approaches 80% after complete resection, and long-term survival is less than 25% even for patients treated for resectable disease. The 5-year survival after pancreaticoduodenectomy is about 25% to 30% for node-negative and 10% for node-positive disease. Attempts at improving survival by extended lymphadenectomy have failed. Although this latter approach showed perioperative morbidity and mortality similar to those of standard lymphadenectomy, no long-term survival benefits were identified.[1-3] Furthermore, extended lymphadenectomy was associated with a significant increase in perioperative adverse events.[4] Thus, it is essential to identify the patient population at risk for early recurrence and to establish appropriate selection criteria for radical surgery.

Staging of pancreatic malignancy is done according to the American Joint Committee on Cancer staging TNM classification, which describes the tumor extension (T), lymph node involvement (N), and distant metastases (M) of tumors, respectively. Advances in cross-sectional imaging and EUS imaging have improved our ability to diagnose and stage pancreatic and biliary cancers. High-resolution CT with dual-phase contrast enhancement is the primary imaging modality for staging of pancreas and biliary (PB) cancers and determining the surgeon's ability to achieve a complete resection with negative tissue margins. CT is reported to have a sensitivity of 89% to 97% for pancreas cancer, although it is less effective in diagnosing small (<2 cm) lesions, with a sensitivity of 65% to 75%. In this respect, EUS is superior, with reported sensitivities of over 95% in most studies. Recent studies have found comparable results between EUS and CT and MRI for both T and N staging. This can be secondary to improved cross-sectional imaging, different staging classifications used in the various studies, and changing criteria for resectability and surgical exploration.[5] The role of functional imaging, especially 18F-fluorodeoxyglocuse positron emission tomography (FDG-PET)/CT, is still uncertain in the staging of pancreas and biliary cancers. The National Comprehensive Cancer Network (NCCN) guidelines list the possible performance of PET/CT for the detection of regional nodes and extrapancreatic metastases, although its use is still not a routine examination. The PET scans are qualitatively graded by a 5-point scale visual scoring system (I = low to V = high) for the presence and intensity of focal FDG uptake. Positive scores of IV and V yield a sensitivity of 71% and a specificity of 64% for representing definite malignancy. Glucose uptake is quantified by the standard uptake value (SUV), with an SUV above 3.5 considered indicative of malignancy. For definite assessment of a pancreatic mass, both the visual scores and the SUV value are typically considered. A receiver operating characteristic analysis of SUV values is typically performed to verify the cutoff point between benign and malignant lesions.[6] The sensitivity and specificity of FDG-PET/CT in the diagnosis and evaluation of pancreatic cancer ranges from 71% to 100% and 64% to 95%, respectively, significantly higher than those of CT scans.[7,8] The sensitivity of PET/contrast-enhanced CT in detecting local recurrence, abdominal lymph node metastasis, and peritoneal dissemination are 83.3%, 87.5%, and 83.3%, respectively. False positive results may be seen in inflammatory conditions. False negative results may be secondary to hyperglycemia and small tumor sizes (low sensitivity rate 20%-35%).[9]

When the para-aortic nodes obtained from sampling biopsy are histologically positive, radical surgery with extended lymphadenectomy and soft tissue clearance should be abandoned because of poor outcome.

Computed tomography is not sensitive for detecting nodal metastases. With a short axis dimension of 10 mm as the cutoff point, CT has a sensitivity of only 15% for detecting nodal metastases. Sensitivity increases to about 70% when a 5-mm threshold is used, but specificity drops to 65%. On the other hand, enlarged nodes may be secondary to pancreatitis, chronic liver disease, or other benign processes. The accuracy of EUS for N staging of pancreatic tumors ranges from 41% to 86%.

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Endosonographic criteria for metastatic lymph nodes (LNs) include size greater than 1 cm, round shape, hypoechoic echogenicity, and distinct margins. The sensitivity of EUS for the diagnosis of metastatic adenopathy in pancreatic cancer is less than 65%. This can be related to the fact that most metastatic LNs do not have all 4 of the endosonographic features, and peritumoral inflammation and large tumor size may contribute to poor detection of adenopathy. The specificity of EUS for the diagnosis of metastatic adenopathy in pancreatic cancer is close to 70%. It is presumed that the addition of EUS-FNA to the evaluation of suggestive LNs may increase the specificity.[5]

According to the TNM guidelines and the Japanese Pancreas Society classification, the regional LNs for pancreatic head cancers include LNs along the common bile duct, common hepatic artery, portal vein, posterior and anterior pancreaticoduodenal arcades, the superior mesenteric vein, and the right lateral wall of the superior mesenteric artery; the regional LNs for pancreatic body and tail cancers include LNs along the common hepatic artery, celiac axis, splenic artery, and splenic hilum.[6] Para-aortic lymph nodes (PALNs) are not included in the regional LNs and are basically regarded as nonregional LNs for both pancreatic head and body or tail cancers. PALNs can be categorized according to their anatomic position (No. 16 LN) and the probability of metastasis in pancreas cancer. PALNs anterior to the aorta and in between the aorta and the inferior vena cava (IVC) from the celiac artery to the inferior mesenteric artery (IMA) had much higher metastatic rates than those lateral and posterior to the aorta and IVC and those anterior to the IVC (metastatic rates all <4%). These high-risk nodal regions (anterior and medial to the aorta between celiac artery and IMA) should be encompassed in the clinical target volume during any planned radiation therapy.[6]

Metastasis of PALNs in patients with PB cancers has been reported as a definite predictor of early recurrence and shorter survival term. PALN metastasis is present in more than 10% of pancreas cancer patients undergoing surgery.[10,11] Many surgeons recommend sampling and pathologic confirmation of PALNs before starting radical operation. However, the role of para-aortic lymphadenectomy remains controversial; it is invasive and is associated with surgical adverse events. Therefore, preoperative noninvasive imaging diagnosis of PALNs metastasis is very important. Kim et al[12] compared the accuracy of CT scan and MRI for detecting PALNs in patients with PB cancers; they were comparable. Features suggestive of metastatic PALNs include LN diameter larger than 5.3 mm, irregular margin, and central necrosis. To date, there have been no reports assessing the diagnostic performance of EUS-FNA for PALNs metastasis in patients with PB cancers, and comparing it with PET/CT scan in the preoperative staging of patients with PB cancers.

In this issue of *Gastrointestinal Endoscopy*, Kurita et al[13] commendably address this topic. In this prospective, nonrandomized, single-center trial, 208 patients with PB cancers without apparent distant metastases except for PALNs were assessed for study eligibility before surgery; 52 consecutive patients with PALNs enlargement were enrolled. PET/CT and EUS-FNA were performed sequentially as a single combined procedure to evaluate PALN metastasis. The authors performed PET/CT evaluation qualitatively (prospectively) by using a 5-point visual scoring system and quantitatively by using SUVmax (retrospectively, given that the authors did not initially follow a cutoff value for SUVmax to distinguish malignant from benign PALNs). The 5-point visual scoring system is an already established method and has been reported by multiple groups. Lesions scored 4 or 5 were considered PET/CT positive. On the other hand, SUVmax was significantly higher in malignant PALNs than in nonmalignant PALNs (4.6 ± 2.8 vs 1.8 ± 0.8, $P < .0001$). When a cutoff value of 1.8 was used, the diagnostic accuracy of PET/CT with SUVmax was 80.3%, which was comparable with, but not significantly higher than, the results of the visual scoring system. Of 71 enlarged PALNs in the 52 patients, 30 PALNs (42.3%) were finally diagnosed as metastases in 21 (40.4%) patients. In the 21 patients with PALN metastases, preoperative EUS-FNA made a correct diagnosis in 20 (95.2%) patients. One false negative was recorded and was thought to represent a micrometastatic lesion. No false positives were recorded. Although PET/CT made a correct diagnosis in 12 (57.1%) patients, EUS-FNA had higher sensitivity, specificity, positive predictive value, negative predictive value, and accuracy (96.7%. 100%, 100%, 97.5%, and 98.6%, respectively) for the diagnosis of PALNs metastasis than did PET/CT (53.3%, 97.6%, 94.1%, 74.1%, and 78.9%, respectively). The differences for the sensitivity and accuracy were significant ($P < .001$).

Note that PALN metastasis was found in 21 of the 208 (10.1%) patients with PB cancers. This percentage is comparable to the percentage of PALNs metastasis noted in the literature and further highlights that inoperable cancer caused by PALNs metastasis is not rare and should not be ignored. This has implications for the choice of the best treatment modalities (surgery, neoadjuvant or adjuvant therapy, or a combination). When the PALNs obtained from biopsy samples are histologically positive, radical surgery with extended lymphadenectomy and soft tissue clearance should be abandoned because of poor outcome.[14]

According to the NCCN guidelines, pancreatic cancer is subcategorized into resectable (no vascular or regional spread), borderline resectable (regional spread into vessels or other organs that would make surgery difficult but not impossible), locally advanced (not metastatic but with invasion into structures, making curative surgery impossible), and metastatic (surgically incurable because of spread to distant sites). Adjuvant therapy (chemotherapy, radiation therapy, or both) is an integral part of definitive treatment of resectable pancreatic carcinoma.[15] Randomized controlled trials have suggested that adjuvant chemotherapy (gemcitabine or 5-FU) improve disease-free survival, overall survival (OS), and 5-year OS.[16-18] The role

of adjuvant chemoradiation, specifically in the subgroup of patients with positive resection margins, is still debatable. However, given that the 5-year survival of this group is 10% with surgery alone and 25% with the addition of adjuvant therapy, preoperative neoadjuvant chemotherapy has been proposed. A systematic review and meta-analysis of 111 studies (56 phase 1-2 trials) demonstrated that in patients with initially resectable tumors, resection frequencies and survival after neoadjuvant therapy are similar to those in patients with primarily resected tumors and adjuvant therapy. Approximately one third of patients with initially staged nonresectable tumors would be expected to have resectable tumors after neoadjuvant therapy, with survival comparable with that in patients with initially resectable tumors. Thus, patients with locally nonresectable tumors should be included in neoadjuvant protocols and subsequently re-evaluated for resection.[19] According to the results of a recent study presented at the 2016 Gastrointestinal Cancers Symposium,[20] better outcomes (superior median and 5-year OS) are noted when adjuvant or neoadjuvant therapy is performed at high-volume tertiary care centers. Contributing factors to the survival benefit include, among others, multidisciplinary management (pancreas tumor board), accurate staging, use of guidelines and treatment algorithms, staffing, and advanced surgical techniques.

Because preoperative identification of PALNs may preclude surgery, meticulous survey of this region is critical during staging of all pancreatic tumors. The authors are to be congratulated on their pursuit of such a challenging and evolving topic. The data presented serve as a hypothesis generated for further large clinical trials, preferably in prospective fashion, to further investigate the best imaging modality for detecting PALNs in patients with PB cancers.

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Abbreviations: EUS, endoscopic ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; PB, pancreatico-biliary; CT, computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography–computed tomography; FDG, fludeoxyglucose; SUV, standard uptake value.

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