Preoperative endoscopic ultrasound-guided fine needle aspiration for diagnosis of pancreatic cancer in potentially resectable patients: Is this safe?

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Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has become the preferred method for tissue acquisition in patients with pancreatic cancer and plays an important role in several proposed diagnostic and staging algorithms.[1,2] Although the diagnostic accuracy of EUS-FNA for solid pancreatic cancers is variable, a recent meta-analysis reported pooled sensitivity and specificity of 85% and 98%, respectively. When atypical or suspicious cytology were included to determine true neoplasms, the sensitivity increased to 91% with 94% specificity.[3] EUS-FNA is a relatively safe procedure with an overall complication rate of 1-2%.[2] However, some have suggested that EUS-FNA should not be performed on patients with potentially resectable pancreatic neoplasms due to concerns of needle tract tumor seeding, especially if the area of surgical resection does not include the needle tract site. EUS-FNA is typically performed with a transduodenal approach for pancreatic head masses, with the sampled duodenal region resected along with the entire pancreatic head during curative intent surgery. For pancreatic body and tail masses, EUS-FNA is performed transgastrically at an area that is not typically resected during surgery, raising concern that FNA by this method could result in an even higher risk of tumor seeding and gastric or peritoneal implantation.

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Prior to 2005, the risk of pancreatic adenocarcinoma seeding from EUS-FNA was merely theoretical. However, since that time there have been several case reports of suspected gastric wall seeding following EUS-FNA of pancreatic body and tail adenocarcinoma in patients who underwent curative central or distal pancreatectomy.[4-7] A case of peritoneal carcinomatosis following EUS-FNA biopsy (EUS-FNAB) of an intraductal papillary mucinous tumor has also been reported.[8] To the best of our knowledge, tumor seeding following EUS-FNA of a pancreatic head adenocarcinoma is yet to be reported. The absolute risk of tumor seeding from EUS-FNA of pancreatic neoplasms is unknown. Given the increasing number of EUS-FNA procedures performed for diagnosing pancreatic cancer[9] and the unclear incidence of tumor seeding, it is necessary to evaluate whether or not preoperative EUS-FNA is safe to perform in cases with potentially resectable tumors, particularly for lesions in the pancreatic body and tail.[4]

In the current issue of "Gut", Ngamruengphong *et al.* conducted a retrospective population-based study that examined the impact of preoperative EUS-FNA on overall and cancer-specific survival in patients with locoregional pancreatic cancer who had undergone curative intent surgery.[9] Although their study did not directly assess the occurrence of tumor seeding or the recurrence of pancreatic cancer, their hypothesis

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was that patient survival would be impaired if tumor dissemination occurred. The patients in the study were divided into two groups: 498 patients (24%) who underwent preoperative EUS-FNA (EUS-FNA group) and 1,536 patients (76%) who either did not receive EUS or underwent EUS without FNA (non-EUS-FNA group). The investigators used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database to obtain data including that of pathological diagnosis, tumor characteristics, and the administration of radiation therapy and chemotherapy. The majority of cases (n = 1,839, 90%) had pancreatic adenocarcinoma. Patients were followed up over a mean time period of 21 months, with 285 patient deaths (57%) occurring in the EUS-FNA group and 1,167 patient deaths (76%) occurring in the non-EUS-FNA group. The use of EUS-FNA was marginally associated with improved overall survival [hazard ratio (HR) 0.84, 95%, confidence interval (CI) 0.72 to 0.99] with statistically similar cancer-specific survival (HR 0.87, CI 0.74 to 1.03) in multivariate analysis after controlling several variables, including tumor histology, stage, grade, location, undergoing percutaneous aspiration/biopsy, and the use of radiation and chemotherapy.

The authors of the study concluded that preoperative EUS-FNA did not adversely affect overall or cancer-specific survival and is, therefore, safe to perform as part of the workup of suspicious pancreatic lesions. Their conclusions are similar to prior smaller studies that also examined the effect of preoperative EUS-FNA on overall survival in patients with pancreatic neoplasms. A single center retrospective study of 256 patients who underwent surgery with curative intent for malignant solid and cystic neoplasms determined that EUS-FNA was not associated with increased gastric or peritoneal recurrence or decreased overall survival.[10] A retrospective cohort study of 204 patients with primary pancreatic neoplasms who underwent distal pancreatectomy also reported similar rates of overall and recurrence-free survival for patients who underwent EUS-FNA as well as for those who did not.[11] Another retrospective study of 213 patients who were thought to have resectable pancreatic cancer on the basis of cross-sectional imaging findings reported significantly higher overall and relapse-free survival in patients who underwent EUS-FNA, although more patients in the FNA group underwent adjuvant chemotherapy.[12]

The authors are to be commended for this important study, which is the first large population-based study to examine if EUS-FNA has a negative impact on long-term outcomes for patients with resectable pancreatic cancer. Differentiating local disease recurrence, direct tumor extension, and local needle track tumor seeding are difficult, especially given the high relapse rate and aggressiveness of pancreatic cancer. Therefore, it is reasonable to use survival as a surrogate marker tumor for clinically significant tumor seeding. However, one must question if patient follow-up was long enough to adequately detect any tumor recurrence and mortality that resulted from tumor seeding. Tumor dissemination that results from EUS-FNA is initially low volume, and growth progression to radiographically and clinically detectable growth takes time. The reported cases of post EUS-FNA tumor seeding were diagnosed at 21 months, 22 months, 26 months, and over 36 months following surgical resection. Studies with longer follow-ups are, therefore, warranted in order to capture these recurrences. However, given the high mortality and poor overall prognosis among pancreatic cancer patients, studies with longer follow-ups will likely be difficult to obtain.

The current study is notable for its larger size and control for various clinical confounders. However, several shortcomings were noted. A significantly higher number of patients in the EUS-FNA group received chemotherapy and radiation therapy compared to patients in the non-EUS group. Adjuvant therapy has been suggested as a way to eliminate malignant cells that may have seeded following FNA.[4] Although the use of chemotherapy and radiation therapy were controlled in multivariate analysis, the use of chemotherapy or radiation therapy may have eradicated any tumor tract seeding that resulted from EUS-FNA. Additionally, most of the tumors in the current study occurred at the pancreatic head that is thought to be at a theoretically lower risk of tumor seeding from FNA, since the needle path is typically resected. Only 75 (15%) patients who underwent EUS-FNA had a pancreatic body/tail lesion. While multivariate Cox regression analysis determined no difference in overall or cancer-specific survival for lesions in the pancreatic body/tail versus the head, the study may not have been powered enough to examine the risks of performing FNA specifically at this location. A larger proportion of patients in this study also underwent partial gastrectomy as part of their curative surgery (57% in the EUS/FNA group, compared to 8% and 32% in prior similar studies). This may have resulted in resection of the area of gastric wall through which FNA was performed,

which is the area of most concern for tumor seeding and gastric wall implantation in patients who undergo transgastric EUS-FNA. It is unknown as to how many of the patients who underwent transgastric EUS-FNA had partial gastrectomy. The FNA needle size, number of needle passes, and performances of EUS-FNAB were also not recorded; so, the impact of these variables on tumor seeding and overall mortality remains unclear.

One of the concerns regarding the use of preoperative EUS-FNA, in addition to causing tumor seeding, is that the development of post EUS-FNA complications may delay or preclude surgical resection. In this study, 2.2% of the patients developed post EUS-FNA pancreatitis requiring hospitalization. No patients developed post EUS-FNA hemorrhage, perforation, or infection. This is similar to prior reported complication rates of EUS-FNA.[13,14] As the current study only included patients who underwent curative intent surgery, it is unknown whether any of the patients who underwent preoperative EUS-FNA were unable to undergo surgery due to resulting complications and were, therefore, not included in this study. However, in a smaller retrospective study of patients with resectable pancreatic cancer who did and did not undergo preoperative EUS-FNA, all patients who underwent preoperative EUS-FNA patients were able to undergo curative surgery.[12] Although patient morbidity resulting from EUS-FNA is low and does not seem to hinder the ability to undergo surgery, the potential for resulting complications should still be taken into consideration when deciding whether or not to perform EUS-FNA on patients who are candidates for curative resection.

In this study, the use of EUS (both with and without FNA) was associated with improved overall survival on multivariate analysis (HR 0.77, 95%, CI 0.67 to 0.87) after adjusting for variables, including patient age, stage of cancer, tumor location, pathology, grade, year of diagnosis, and the administration of chemotherapy and radiation therapy. This is consistent with a prior retrospective study of 8,616 patients with pancreatic adenocarcinoma (610 of whom underwent EUS with or without FNA for tumor evaluation and staging) that noted improved median survival for patients who underwent EUS versus patients who did not. In a Cox proportional hazards model that adjusted for tumor stage, curative-intent surgery, chemotherapy, radiation therapy, and comorbidity scores, the receipt of EUS was an independent predictor of improved survival (HR 0.71; 95%, CI 0.63-0.79).[15] While EUS itself is not a therapeutic procedure and, therefore, cannot confer a survival advantage, performing EUS may improve survival by improving preoperative staging that would more appropriately identify patients who would benefit from curative resection or adjuvant therapy. The current study did not compare the survival rates for patients who underwent EUS with FNA with those patients who underwent EUS alone; so, the additional survival benefit of performing FNA in addition to EUS is unclear.

The authors in this study have sought to address whether or not transgastric and transduodenal EUS-FNA negatively impacts overall survival in patients with resectable pancreatic cancer. Although their study has several limitations and additional studies are warranted to definitively establish the long-term risks of preoperative EUS-FNA, especially in patients with body/tail lesions or patients who do not receive perioperative chemoradiation therapy, endoscopists should feel more secure about the safety of conducting preoperative EUS-FNA. Tumor seeding in these cases appears to be either rare occurrence or of little clinical significance. The next question to be addressed is whether EUS-FNA needs to be performed in these cases at all. The most recent American Society for Gastrointestinal Endoscopy (ASGE) guidelines suggest that tissue diagnosis is not necessary before proceeding with surgical resection when EUS suggests resectable pancreatic cancer; however, this is controversial.[16] Advocates for performing EUS-FNA in cases of high pretest likelihood of operable cancer argue that this may help to establish a definitive diagnosis, exclude more rare tumors,[17] and may alter preoperative staging and preclude surgery in some cases.[18] Future studies should be conducted to elaborate upon the most appropriate indications for preoperative EUS and/or FNA in patients with a high clinical suspicion of resectable disease. Until then, physicians should continue to make the decision on a case-by-case basis with a multidisciplinary approach.

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