S56

State of the art lecture: Endoscopic ultrasound (EUS) and FNA in pancreatico-biliary tumors

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Introduction

In the past few decades, there has been relatively little change in the epidemiology, therapy, or over-all survival of pancreaticobiliary tumors. However, we are now in an era where diagnostic and therapeutic paradigms are finally going beyond traditional approaches (cytology/pathology for diagnosis and cytotoxic agents for therapy) with the potential of changing the natural history of these tumors. Many of these new approaches are made possible with emerging diagnostic and interventional EUS techniques. This state-of-the-art paper will review the role of EUS-guided FNA in the diagnosis of pancreaticobiliary lesions such as pancreatic tumors, cystic and neuroendocrine tumors of the pancreas, as well as the less appreciated applications to biliary and ampullary cancers. I will also discuss the specific role of EUS-guided FNA in the staging of various pancreaticobiliary cancers. The role of EUS-guided therapies, including celiac neurolysis, cyst-gastrostomy, and delivery of anti-tumor agents via EUS-guided fine needle aspiration (FNI) will be covered in the accompanying article "FNI and Anti-tumor therapy".

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EUS-guided FNA in the diagnosis of pancreatic tumors

Pancreatic cancer

Adenocarcinoma is the fifth leading cause for cancer-related death in the United States. Despite improvements in medical and surgical therapy, the overall 5-year survival still remains at 4%. The most favorable outcome is among surgical patients with small tumors without nodal, vascular, or systemic metastasis. These patients have 5-year survivals that range up to 25%. Optimally, earlier detection and precise pre-operative staging would best stratify patients who would most likely benefit from surgery while sparing the remaining patients from exploratory or palliative-only surgery. Endoscopic ultrasound is considered as one of the most useful diagnostic procedures among the body imaging tools for detecting pancreatic cancer. EUS was shown to be superior (sensitivity 98%) to other imaging modalities, including CT, in 146 patients with pancreatic cancer [1]. With the more recent introduction of spiral CT with dual phase contrast, the detection rate for CT is improving. However, recent comparisons between dual-phase spiral CT and endoscopic ultrasound still favor EUS. The ability to obtain cytological specimen by EUS-guided FNA has overcome the difficulty in differentiating between benign vs malignant lesion seen on EUS alone. The application of EUS-guided FNA to the pancreas in particular has great clinical utility. CT or US guided percutaneous FNA are the more common methods for diagnosing pancreatic cancer. The sensitivity of percutaneous FNA ranges from 45% to 100%, with a specificity of up to 100%. However, obtaining a tissue diagnosis with CT or US guidance is limited by the ability to visualize the lesion. In a previous multicenter trial, 56% of patients with pancreatic carcinoma had CT scans which did not demonstrate a mass or revealed nonspecific enlargement of the pancreas [2]. ERCP with cytologic brushing also has a relatively low yield, with sensitivities between 30% and 56%. The over-all sensitivity, specificity, diagnostic accuracy, NPV and PPV of EUS-guided FNA for pancreatic cancer was 83%, 90%, 85%, 80% and 100%. This was superior to CT alone (without FNA): 56%, 37%, 50%, 28% and 65%, respectively (p < 0.05). There were 4 complications in 164 patients (2%), including 2 major (perforation, bleeding) and 2 minor (fever). Comparison among the four centers showed that institutions in which a cytologist was present during the procedure had a significantly higher number of passes, cytologic yield, sensitivity and diagnostic accuracy. Advantages of EUS-guided FNA include procuring a tissue diagnosis while also obtaining additional TN staging information the avoidance of additional diagnostic testing and/or surgery and the prognostic information relating to accurate TN staging. In another report from a large single-institution study of 144 pancreatic lesions undergoing EUS-guided FNA, showed a sensitivity, specificity, and diagnostic accuracy of 82%, 100%, and 85% respectively [3]. The most difficult diagnosis to make for any imaging test, including EUS-guided FNA, is the differentiation between pancreatic carcinoma and chronic pancreatitis. Contrast enhanced EUS may improve this differentiation with a recent paper showing the sensitivity increasing from 73% to 91% and specificity increasing from 83% to 93% with the addition of SonoVue intravenous constrast and power Doppler scanning [4]. With FNA the positive predictive value is almost 100%, although a negative FNA is about 85% accurate in the setting of pancreatitis. Positron emission tomography (PET) with or without CT fusion may play a role in distinguishing pancreatic cancer from chronic

pancreatitis [5,6], although results are somewhat disparaging [7–9]. EUS-guided FNA of pancreatic lesions is also worthwhile in patients with a prior negative tissue diagnosis by ERCP or CT of the abdomen. Gress et al. reported his experience with EUS-guided FNA of pancreatic mass lesion in 102 patients who had negative cytological tissue diagnosis by ERCP sampling or CT-guided FNA [10]. Among those patients, 57 of the 61 patients (93.4%) with a final diagnosis of pancreatic cancer had positive cytology results for adenocarcinoma by EUS-guided FNA. The false positive results were zero.

There have been several papers written regarding the clinical and economic outcomes of EUS/FNA. One single center study compared the management and survival of 136 patients with pancreatic cancer between the pre and post EUS eras [11]. EUS detected carcinomas that were either not seen or only possibly seen by CT in 34% and there were 75% fewer required operations for diagnosis. The median survival without liver metastases was also longer during the EUS period (102 versus 205 days; p < 0.02, log-rank test) probably attributable, in part, to lead-time bias. The economic impact of EUS-guided FNA was addressed in an earlier series of 44 consecutive patients who underwent EUS with or without FNA as part of their pancreatic cancer evaluation [12]. Surgery and further diagnostic testing were avoided in 41% and 57% of patients respectively. A substantial cost saving of $ 3300 per patient was calculated. In a series of 216 consecutive patients, the use of EUS with EUS-guided FNA as the initial approach to patients with obstructive jaundice was studied by Erickson et al [13]. EUS/FNA proved useful not only as a diagnostic and staging modality, but also served in directing the need for subsequent therapeutic endoscopic retrograde cholangiopancreatography (ERCP), saving approximately $1007 to $1313 per patient. In addition, if EUS/ EUS-guided FNA were not utilized at all, an extra $2200 would be spent per patient. EUS-guided FNA of the pancreas unlike CT-guided FNA can be preformed during the initial endosonographic procedure. The overall complication rate of EUS-guided FNA was reported to be 0.5%-2.9%.

We believe that all patients thought to have operable disease based on initial CT imaging should undergo EUS ± FNA prior to surgical intervention (see Clinical Algorithm in Fig.1). At the same time, considering the possibility of a false negative result (up to 20%, especially in the setting of chronic pancreatitis), we believe that surgical intervention should not be precluded in a patient with a high suspicion of resectable pancreatic carcinoma and a negative FNA cytology.

In the near future, EUS/FNA will go beyond cytology diagnosis to assess for molecular and/or genetic alterations within the tumor tissue. This is now possible with such techniques as cDNA microarrays which can screen for hundreds of genes simultaneously [14]. Using cDNA microarray, investigators can evaluate specific tumors for chemoresistance-related genes. One such study will have been presented at this year's DDW [15].

Cystic neoplasms

EUS can be helpful in distinguishing cystic neoplasms from pancreatic pseudocyst, although even here, the specificity is not perfect [16]. The more problematic discernment is between serous and mucinous cysts, with the latter considered pre-malignant. The interobserver agreement for the interpretation of cystic lesions in the pancreas is quite low. The interobserver agreement on 31 pancreatic cyst cases among eight expert endosonographers was shown to be "fair" between endosonographers for diagnosis of neoplastic versus non-neoplastic lesions (kappa = 0.24) [17]. Agreement for individual types of lesions was moderately good for serous cystadenomas (kappa = 0.46) but fair for the remainder. Accuracy rates of EUS for the diagnosis of neoplastic versus non-neoplastic lesions ranged from 40% to 93%. Thus, EUS imaging alone is often inadequate for the clinical management of these patients. EUS-guided FNA of cystic contents can be analyzed for cytology, biochemistry and tumor markers. Since cytology is a relatively insensitive test, cyst fluid tumor markers such as CEA have been employed to improve the sensitivity for the detection of malignancy. Cyst fluid CEA values are uniformly low in serous cystadenomas, higher in mucinous lesions, and markedly elevated in mucinous cystadenocarcinomas [18]. A recent cooperative group study examined a battery of tumor markers from pancreatic cysts (CEA, CA 72–4, CA 125, CA 19–9, and CA 15–3) among 341 patients (112 with surgical resection). The final diagnosis of the cystic lesions were 68 mucinous, 7 serous, 27 inflammatory, 5 endocrine, and 5 other. Receiver operator curve analysis of the tumor markers demonstrated that cyst fluid CEA (optimal cutoff of 192 ng/mL) demonstrated the greatest area under the curve (0.79) for differentiating mucinous vs. nonmucinous cystic lesions. The accuracy of CEA (88 of 111, 79%) was significantly greater than the accuracy of EUS morphology (57 of 112, 51%) or cytology (64 of 109, 59%) (P < 0.05). There was no combination of tests that provided greater accuracy than CEA alone (P < 0.0001). We routinely send cyst fluid for cytology, amylase and CEA. Pseudocysts have very high amylase levels, often over 50,000 IU/L, with a normal CEA and benign cytology. Serous cystadenomas will usually have benign cytology, normal CEA and amylase. Mucinous cystadenomas usually differ from serous cystadenoma in having a high CEA. Mucinous cystadenocarcinoma classically will have malignant cytology, a low amylase, and a markedly elevated CEA. Whereas the cytology from the fluid of malignant cysts may be non-diagnostic. We have found that targeting any solid component, including the cyst wall, may enhance the yield on FNA cytology [19].
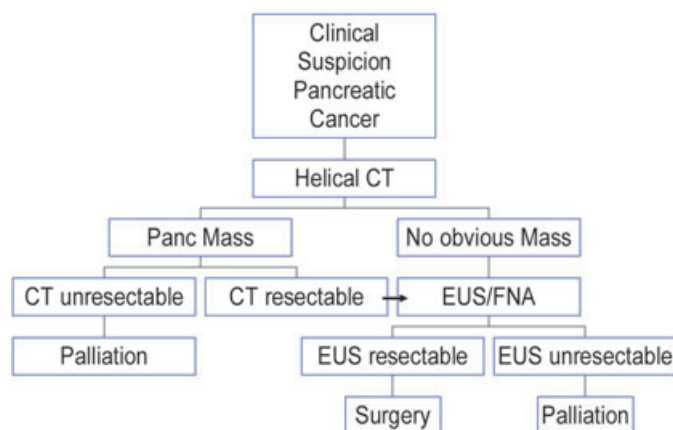

Fig. 1 Algorithm for Diagnosis and Staging of Pancreatic Cancer.

Endocrine tumors

EUS is very accurate in the detection of neuroendocrine tumors of the pancreas.

Zimmer et al reported their results in localizing and staging neuroendocrine tumors of the foregut in 40 patients examined by EUS, somatostatin receptor scintigraphy (SRS), computed tomography (CT), magnetic resonance imaging (MRI) and transabdominal ultrasound (US) [20]. EUS showed the highest sensitivity in localizing insulinomas compared with SRS, US, CT and MRI. They suggested that US and EUS should be the first-line diagnostics if insulinoma has been proven by a fasting test. Further diagnostic procedures were unnecessary in most cases. Further diagnostics such as CT or MRI to search for distant metastases are necessary in large tumors or local invasive tumors. For gastrinomas, EUS has the highest accuracy to detect or exclude pancreatic gastrinomas, but fails to detect extrapancreatic gastrinomas in about 50%. The combination of EUS and SRS may give complementary information. They recommended that the first-line diagnostics in gastrinoma patients should be SRS and CT or MRI. If no metastases are detected, EUS should be the next preoperative imaging procedure. In nonfunctional neuroendocrine tumors, EUS provides the best information on local tumor invasion and regional lymph node involvement. EUS has also been shown to be cost effective in the preoperative localization of pancreatic endocrine tumors [21] largely because of reductions in the number of diagnostic angiograms and venous sampling procedures performed. The more specific utility of EUS-guided FNA in these patients was recently reported [22] and shown to be helpful. In addition, EUS may also be useful in marking these subtle lesions using EUS-guided fine needle "tattooing" prior to surgery to assist in intra-operative localization [23].

EUS-guided FNA in the staging of pancreatic cancer

Although EUS has historically been superior to CT or MR in staging pancreatic cancer, this may no longer be the case. A recent review analyzed the pooled data among 4 comparative studies and still showed superiority of EUS to helical CT in detection of pancreatic tumor (97% vs 73%), in accuracy for respectability (91% vs 83%), and sensitivity for vascular invasion (91% vs 64%) [24]. However, with even newer imaging modalities such as contrast-enhanced multi-detector row helical CT (MDR-CT), which allows for 3-dimensional maximum intensity projection (MIP) and volume rendered images (VRI), the vascular staging of pancreatic cancer by CT will likely surpass that of EUS [25,26]. In addition, the fusion of CT with PET may give additional distant staging information. However, EUS-guided FNA will continue to play an important role for staging pancreatic cancer in sampling metastatic lymph nodes, liver lesions, and ascites. The economic impact of EUS-guided FNA in the preoperative staging of patients with pancreatic head adenocarcinoma was clearly demonstrated in a decision analysis model [27]. The use of EUS-guided FNA prevented 16 surgeries per 100 patients compared to 8 per 100 patients if CT-guided FNA was performed for non-peritumoral lymph nodes. If the frequency of non-peritumoral lymph nodes was > 4% then EUS-guided FNA is the least costly procedure ($ 15,938) vs ($ 16,378) for CT-FNA and ($18,723) for surgery. According to a multivariate analysis, lymph node metastasis, intra-

pancreatic perineural invasion, and portal vein invasion are significant prognostic factors in patients with pancreatic cancer after curative resection [28]. In a multi-center study 171 patients underwent EUS-gduied FNA of 192 lymph nodes (46 benign, 146 malignant) [29]. When comparing EUS-guided FNA with EUS size criteria (£ 10mm = benign), the sensitivity (90% versus 91%, P = n.s.) and accuracy (92% versus 83%, P = n.s.) for EUS-guided FNA were similar whereas the specificity was superior to that of EUS size criteria alone (100% versus 47%, p < .001). Not only can EUS-guided FNA improve the specificity of lymph node metastasis with cytologic confirmation, most recently FNA has been used to detect genetic alterations in cytologic negative nodes [30]. Although there was no significant difference in overall survival rates between the pathological node-negative and -positive patients, overall survival of the patients with nodes-negative for the mutated K-ras gene were significantly better than that of the patients with genetically metastasis-positive nodes (p < 0.001). These findings suggest that detection of K-ras gene mutations in lymph nodes may be clinically useful to stratify patients who may be at higher risk for recurrence after curative resection.

Liver metastasis

EUS was not traditionally thought to be clinically applicable in imaging the liver imaging. However, both prospective [31] and retrospective [32] studies have shown the ability of EUS to detect lesions not seen on CT and the ability to safely perform EUS-guided FNA on the same procedure. EUS-guided FNA should be considered when a liver lesion is poorly accessible to percutaneous FNA or when US or CT-guided FNA fail to make a diagnosis. If EUS detects a liver lesion de novo in the setting of staging pancreatic cancer, EUS-guided FNA should be attempted first, even prior to taking biopsies of the primary pancreatic tumor. Liver lesions have a much higher cytologic yield (less needle passes requires, less inflammatory and fibrotic reaction) and give the highest staging information.

Ascites

The utility of EUS/FNA was evaluated for detection and aspiration of scant ascites among patients undergoing EUS for diagnosis and staging of GI malignancies [33]. Eighty-five patients (15% of a series of 571 patients) were found to have ascites by EUS. Pre-EUS CT identified ascites in only 18% of patients with ascites on EUS. 31 of the 85 patients underwent EUS-guided FNA paracentesis and in 5 patients, malignant ascites was diagnosed by EUS-guided FNA. The clinical impact was high in these patients as surgery was avoided.

EUS-guided FNA in biliary lesions

Diagnosis and staging of cholangiocarcinoma

EUS-guided FNA is now being used to diagnose and stage cholangiocarcinoma. In one case series, 10 patients with bile duct strictures at the hepatic hilum, diagnosed by CT and/or ERCP, underwent EUS-guided FNA. Adequate material was obtained in nine patients [34]. Cytology revealed cholangiocarcinoma in seven and hepatocellular carcinoma in one. One benign inflammatory lesion identified on cytology proved to be a false-negative finding by frozen section. Metastatic locoregional hilar lymph nodes were detected in two patients, and in one patient the celiac and

para-aortic lymph nodes were aspirated to obtain tissue proof of distant metastasis. In a retrospective series of 238 patients with suspected or known biliary strictures, EUS-guided FNA obtained a tissue diagnosis in 12/26 (46%) patients, which were negative on cytology, or had a unsuccessful ERCP [35]. There were no complications. These studies suggest that EUS with FNA is safe, and effective in evaluating proximal biliary strictures. When used in combination with ERCP, it helps distinguish benign from malignant strictures, and facilitates a definitive diagnosis by increasing tissue yield.

Diagnosis and staging of ampullary cancer

Conventional abdominal imaging studies such as CT, MRI, and transabdominal ultrasound frequently fail to detect ampullary lesions. EUS is a sensitive modality for detecting and staging ampullary tumors. Accurate staging may be affected by biliary stenting, which is frequently performed in these patients with obstructive jaundice. Combined data from two centers reported the accuracy of ampullary tumor staging with multiple imaging modalities in patients with and those without endobiliary stents [36]. Fifty consecutive patients with ampullary neoplasms were preoperatively staged by EUS plus CT (37 patients), MRI (13 patients), or angiography (10 patients) over a 3.5 year period. Twenty-five of the 50 patients had a transpapillary endobiliary stent present at the time of endosonographic examination. EUS was shown to be more accurate than CT and MRI in the overall assessment of the T stage of ampullary neoplasms (EUS 78%, CT 24%, MRI 46%). No significant difference in N stage accuracy was noted between the three imaging modalities (EUS 68%, CT 59%, MRI 77%). EUS T stage accuracy was reduced from 84% to 72% in the presence of a transpapillary endobiliary stent. This was most prominent in the understaging of T2/T3 carcinomas. More recently, a retrospective study was published in which the role of EUS-guided FNA in the diagnosis and staging of ampullary lesions has reported [37]. EUS-guided FNA was performed in 20 of 27 (74%) patients with suspected ampullary tumors. EUS-guided FNA made the initial ampullary tissue diagnosis in 7 patients (adenocarcinoma-5, adenoma-1, neuroendocrine tumor-1). In addition, EUS-guided FNA resulted in a change of the diagnosis from adenoma to adenocarcinoma in one patient. In 1 patient, EUS-guided FNA diagnosed a liver metastasis not seen on CT. Overall, EUS-guided FNA provided new histologic information in 9/27 patients (33%).

Conclusions

EUS-guided FNA is extremely useful in the diagnosis and staging of pancreaticobiliary lesions such as pancreatic cancers, cystic tumors, neuroendocrine neoplasms, ampullary and cholangiocarcinomas. In addition, this technique has now been extended to therapeutic modalities such as celiac nerve block, cyst-gastrostomy and delivery of anti-tumor agents (see associated article on FNI).

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S60