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ROUND TABLE

Role of Endoscopic Ultrasonography in the Diagnosis and Treatment of Cystic Tumors of the Pancreas

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Summary

Endoscopic ultrasound (EUS) allows high resolution imaging of the pancreas. EUS is a very useful technique for evaluating morphological features of a cystic tumors of the pancreas. These features include thick wall type, tumor protruding type, thick septal type, microcystic type, thin septal type and simple type. Malignant cystic lesions may present as a hypoechoic cystic/solid mass or as a complex cyst and are frequently associated with a dilated main pancreatic duct. There is some overlap between EUS appearances of non-neoplastic and neoplastic cystic pancreatic lesions. EUS guided FNA of cystic pancreatic lesions can play an important role in the differential diagnosis of these lesions and deciding about the need for surgery by evaluating cytology and tumor markers such as CEA in cyst fluid. There is some emerging data on EUS guided treatment of cystic pancreatic tumors by injection of alcohol.

Endoscopic ultrasound (EUS) allows high resolution imaging of the pancreas. EUS imaging prior to planned endoscopic drainage is useful for appropriate case selection to avoid complications. EUS imaging may change the planned management of up to 37% of pseudocysts prior to attempting endoscopic drainage [1]. With the development of large channel echoendoscopes, real time EUS guided trans-gastric pseudocyst drainage can be performed under EUS control [2, 3].

Beyond the application of EUS for therapy of pseudocysts, EUS has become an important modality for evaluation of cystic pancreatic tumors. This article will focus on the role of EUS for diagnosis and treatment of cystic tumors of the pancreas. Cystic neoplasms of the pancreas can be divided onto serous and mucinous. Serous cystic neoplasms (serous "microcystic" adenomas) are generally benign, and usually there is little or no risk for malignant transformation (very rare serous cystadenocarcinomas have been reported in the literature). Mucinous cystic neoplasms, on the other hand, are either malignant or, if benign, have potential for malignant transformation. Mucinous cystic neoplasms (MCNs) presenting as a cystic lesion in the pancreas include mucinous cyst adenomas or mucinous cyst adenocarcinoma. Another form of mucinous pancreatic neoplasm that may be associated with a cystic lesion is intraductal papillary mucinous neoplasm (IPMN). Ninety percent of mucinous cystic neoplasms occur in the body and tail of the pancreas while IPMNs are common in the head but can also occur in the body and tail. It is clinically important to differentiate pseudocysts from cystic neoplasms as well as serous cystic neoplasms from mucinous cystic neoplasms [4]. All mucinous neoplasms of the pancreas should be considered potentially malignant.

EUS Morphology for Cystic Pancreatic Tumors

Many authors have tried to study the morphology of pancreatic cystic tumors by EUS for differential diagnosis. Koito *et al*. [5], classified pancreatic cysts into six types to differentiate non-neoplastic from neoplastic cysts after making EUS and pathological correlation in 52 pancreatic solitary cystic tumors. These included 10 mucinous cystadenomas, 7 mucinous cystadeno-carcinomas, 5 serous cystadenomas, 10 duct ectatic mucinous cystic tumors, 5 solid and papillary epithelial neoplasms and 15 non-neoplastic cysts. The mean tumor size was 3.5 cm. These six types included: thick wall type, tumor protruding type, thick septal type, microcystic type, thin septal type and simple type. All neoplastic cysts belonged to the first four types and all non-neoplastic cysts belonged to the last 2 types. Two observers of EUS findings estimated the accuracy of EUS in making the above differentiation at 96% and 92%. To further characterize mucinous cysts tumors by EUS, Gress *et al*. [6], correlated EUS findings with surgical pathology in 35 patients.

The study included 14 mucinous cystadenocarcinomas that were more likely to be characterized by hypoechoic cystic/solid mass or a complex cyst and were more likely to be associated with a dilated main pancreatic duct. Benign mucinous duct ectasia in 6 patients was characterized by a dilated main pancreatic duct in conjunction with hyperechoic thickening of the pancreatic duct wall. Two cases of intraductal mucinous hyperplasia additionally showed a hypoechoic mass. Intraductal papillary carcinoma in 11 patients had features similar to mucinous cystadenocarcinomas but also had echogenic foci in the mass and intraductal hyperechoic lesions. Two cases of microcystic adenoma showed either a mixed hypoechoic solid/cystic mass or a complex cyst without the additional features seen in mucinous cystadenocarcinoma.

Sedlack *et al*. [7] also analyzed the EUS features of 34 patients with cystic pancreatic lesions in comparison to surgical pathology after resection. Based on surgical pathology the authors classified the cysts as benign (simple cyst, pseudocyst, serous cyst-adenoma) or malignant/potentially malignant (mucinous cystadenoma, intraductal papillary mucinous tumor, cystic islet cell tumor, cyst adenocarcinoma). The authors found that the following features on EUS imaging predict a malignant or potentially malignant cystic lesion (with a sensitivity of 91%, specificity of 60% and accuracy of 72%): wall thickness of 3 mm or more, macroseptation with cystic compartments greater than 10 mm, presence of mass or intramural growth or cystic dilation of the main pancreatic duct.

Song *et al*. [8] evaluated EUS findings in 58 cystic tumors (including IPMN, mucinous cystic tumors, serous cystadenomas) and 17 pseudocysts. In univariate analysis, pseudocysts exhibited echogenic debris and parenchymal changes more often than cystic tumors. In contrast, septa and mural nodules were found more frequently in cystic tumors than pseudocysts. Serous cyst adenomas showed diverse EUS features as well as a honeycomb appearance. The authors concluded that parenchymal changes, septa and mural nodules appear to be independent predictors of differentiation between cystic tumors and pseudocysts [8].

However, the echo features on EUS of pancreatic cysts in the above study [8] and by others discussed above may not provide an absolute differentiation between cystic lesions. Ahmad *et al*. [9] tried to answer the questions: can EUS alone differentiate between malignant and benign cystic lesions of the pancreas? In their study, 48 patients had surgical/pathological correlation of EUS findings. The original EUS images were reviewed by two endosonographers who were blinded to the interpretation of the other endo-sonographer and to the surgical/pathological findings. The EUS images were assessed for the presence or absence of a wall, solid component, septae, lymphadenopathy, and number of cysts. For reviewer A, the presence of a solid component by EUS was the only statistically significant predictor of

malignancy. However, 61% of benign lesions were also interpreted as having a solid component. Reviewer B found none of the features to be a significant predictor of malignancy and when results of both reviewers were combined, even the solid component was not found to be a significant predictor of malignancy. The authors concluded that endosonographic features cannot reliably differentiate between benign and malignant cystic lesions of the pancreas after a non-diagnostic cross sectional imaging modality. This issue is also further complicated by the problem of inter-observer variability in describing cystic pancreatic lesions on EUS. The same group as above also led a multi-center study on inter-observer agreement among endosonographers for the diagnosis of neoplastic versus non-neoplastic pancreatic cyst lesions [10]. Videotapes of EUS procedures from 31 consecutive cases of a variety of histologically proven cystic tumors were chosen. The reviewers (blinded to clinical and pathology findings) reviewed each case for various features and were asked to identify each lesion as neoplastic or non-neoplastic, as well as, give a specific diagnosis for each lesion. There was fair agreement between endosonographers for diagnosis of neoplastic versus non-neoplastic lesions (k=0.24). Agreement for the presence of a solid component was moderately good (k=0.43); fair for abnormal pancreatic duct (k=0.29), debris (k=0.21) and septations (k=0.30). The agreement was slight for the presence or absence of margins (k=0.01) and abnormal pancreatic parenchyma (k=0.01). Accuracy rates of EUS for the diagnosis of neoplastic versus non-neoplastic lesions ranged from 40% to 93%.

Due to above stated problems with relying only on echo features of cystic lesions of the pancreas EUS imaging, EUS-guided FNA of pancreatic cystic lesions may provide additional information when the diagnosis or management plan based on cross section imaging (CT scan and/or MRI±MRCP), and diagnostic EUS is not readily apparent [11]. EUS guided FNA for cystic pancreatic tumors is discussed below.

EUS-Guided FNA for Cystic Pancreatic Lesions

Linear EUS allows real-time ultrasound guided fine needle aspiration pancreas [12]. Initially, there was a concern of infectious complications with EUS-FNA of pancreatic cysts. However, infectious complications can be minimized or prevented by using prophylactic antibiotics. EUS-FNA cytology analysis of the fluid aspirated from a pancreatic cystic lesion can provide additional information regarding its etiology. The success rate and accuracy of EUS-FNA cytology, however is somewhat variable among different centers.

The technique of EUS guided FNA of pancreatic cysts at our center is as follows. We puncture unilocular cysts or the largest locule (that is also closest to the echoendoscope) in a multiloculated lesion. Intravenous antibiotics are used during the procedure followed by oral antibiotics for 5-7 days. Color Doppler is always used to rule out major vessels in the projected needle path. Once the cyst or a large locule is punctured with the needle, we attempt to aspirate the entire cyst contents (or the entire locule that is entered in case of a multilocular lesion) and completely collapse the cyst (Figure 1). We then move the needle back and forth in the bed of the cystic lesion to pick up any cells in the cyst wall. If due to technical reasons, the needle during an FNA is displaced and has to be withdrawn, then a fresh pass is made with a new sterile needle to minimize the risk of infection. EUS FNA can also be performed for solid lesions or a solid component associated with a cystic lesion as this approach can help maximize the chance of making a positive diagnosis (Figure 2).

In the study by Brandwein *et al*. [13], EUS-guided FNA was only 50% sensitive for evidence of malignancy in cystic pancreatic tumors. In another study [7], the accuracy of EUS-FNA cytology for diagnosing malignant or potentially malignant pancreatic cystic lesion was 55%. Although the specificity of EUS-FNA was 100%, but the sensitivity was only 27%. Another group has reported better

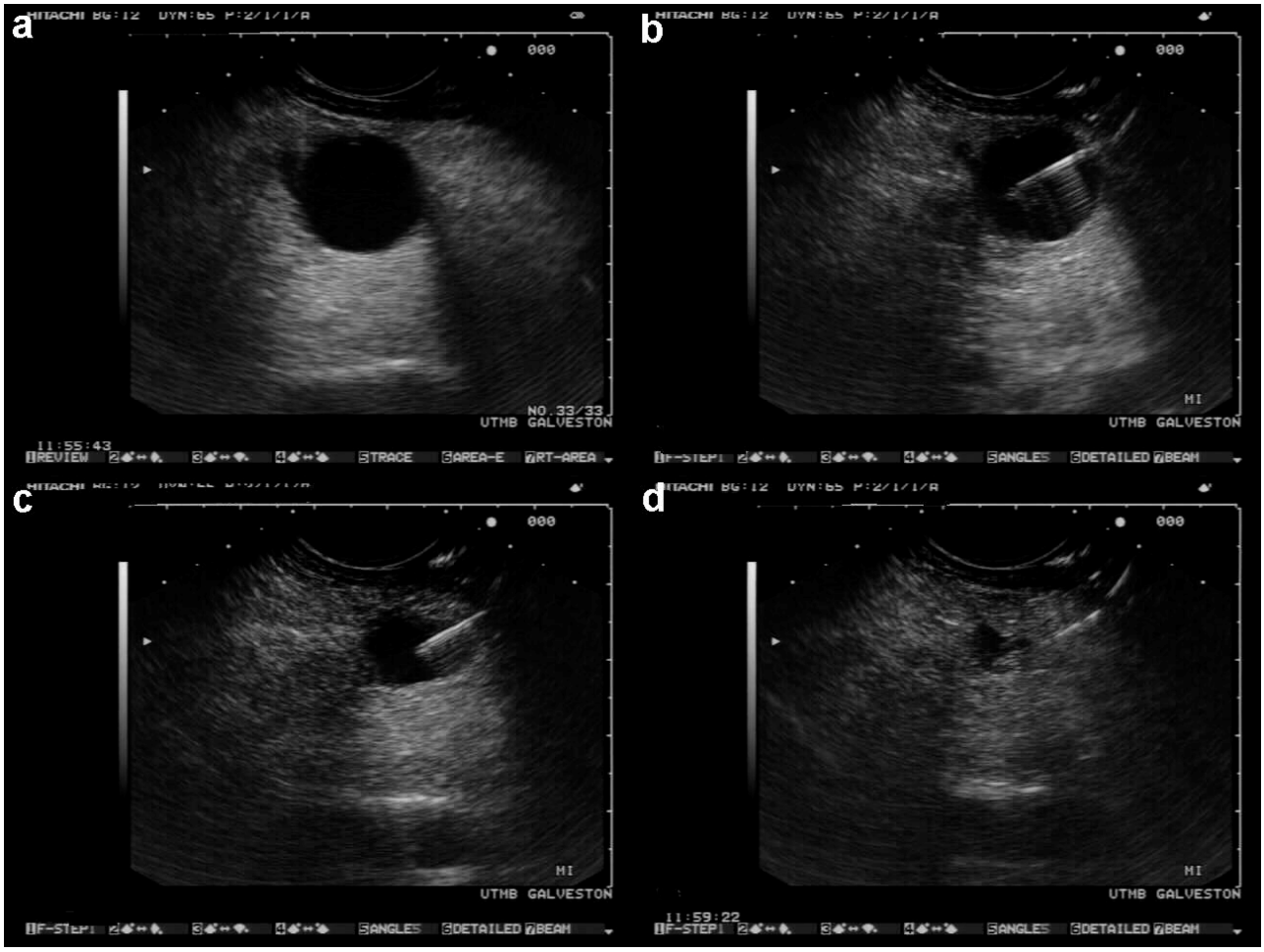

Figure 1. a. Unilocular cystic lesion in pancreatic body as imaged with a linear echoendoscope in a woman with no symptoms attributable to this lesion. **b.** Linear EUS guided puncture of the cystic pancreatic lesion shown in Figure 1a. **c, d.** Progressive decrease in the size of the cystic lesion as cyst fluid is aspirated. Cytopathology revealed mucinous cyst adenoma.

results with EUS-guided FNA to indicate where a pancreatic cystic lesion needs surgery [14]. In this study by Frossard *et al*. [14] data from a series of 127 consecutive patients with pancreatic cystic lesions were prospectively studied. EUS imaging and EUS guided FNA was performed in all patients. EUS provided a tentative diagnosis in 113 cases (89%). EUS FNA cytology provided a diagnosis in 98 cases (77%). When the results of EUS and EUS guided FNA were compared with the final diagnosis in 67 cases, EUS correctly identified 49 cases (73%) and EUS FNA correctly identified 65 cases (97%). The sensitivity, specificity, positive predictive value and negative predictive value of EUS-guided FNA to indicate whether the lesion needed surgery in this study were 97%, 100%, 100% and 95% respectively, corresponding values for EUS imaging alone were 71%, 30%, 49% and 40% respectively. For the diagnosis of IPMN another approach and application of EUS guided FNA is EUS guided puncture of the dilated pancreatic duct and aspiration of pancreatic duct fluid. Maire *et al*. [15] performed this technique in 19 patients and the cytology material was interpreted as positive in 4 cases (21%) and noninformative in 15. Lai *et al*. [16] also performed EUS guided FNA of dilated pancreatic ducts in 12 patients with no procedure related complications. Cytology was diagnostic in 9 of 12 patients (six with intraductal papillary mucinous tumor).

Since the results of EUS guided FNA cytology for pancreatic cystic tumors have been variable, many groups have attempted to look at tumor markers in the aspirated cyst

fluid. The tumor markers that are being studied by some centers, include carcinoembryonic antigen (CEA), CA 19-9, CA 72-4, CA 15-3 [17]. In the study by Frossard *et al*. [14] CA 19-9 value greater than 50,000 U/mL in the cyst fluid had a 15% sensitivity and 81% specificity to distinguish mucinous cysts from other cystic lesions, whereas it had an 86% sensitivity and 85% specificity to distinguish cystadenocarcinoma from other cystic lesions. A large multicenter study (Cooperative Pancreatic Cyst Study) was just published that investigated the value of various tumor markers in pancreatic cyst fluid collect by EUS [18]. In this cooperative study the results of EUS imaging, cyst fluid cytology and various cyst fluid markers (CEA, CA 72-4, CA 125, CA 19-9 and CA 15-3) were prospectively collected and compared with histology as the final diagnostic "gold standard". Three hundred and forty one patients underwent EUS with FNA of a pancreatic cystic lesion. Out of these 112 patients underwent surgery with final diagnosis of mucinous tumors in 68, serous tumors in 7, inflammatory cysts in 27, endocrine tumors in 5 and 5 other lesions. Receiver operating curve analysis was performed of the tumor markers and it was demonstrated that a cut-off of 192 ng/mL for CEA in the cyst fluid demonstrated the greatest area under the curve (0.79) for the differentiation of mucinous versus non-mucinous cystic lesions. The accuracy of CEA (88 of 111) of 79% was significantly greater than the accuracy of EUS morphology 51% or cytology 59% ($P<0.05$). There was no combination of tests that provided greater accuracy than CEA alone ($P<0.0001$) and the authors concluded that cyst fluid CEA was the most accurate test (among the tested markers) for the diagnosis of mucinous cystic lesions of the pancreas.

Molecular analysis of cyst fluid obtained by EUS may provide even better diagnostic information prior to surgery in the future. Two recent preliminary studies were presented recently [19, 20]. In the first study [19] the authors tried to look at mutational allelotyping of aspirated free-floating DNA to predict the biological behavior of cystic pancreatic neoplasms. In this early study, the authors found multiple allelic losses at critical sites associated with K-*ras* mutations in the malignant cysts that was significantly different when compared to premalignant cysts ($P<0.007$) and benign cysts ($P<0.001$). Another study [20] reported at the same time at Digestive Disease Week (DDW 2004) looked at pancreatic cancer associated gene expression biomarkers from FNA samples in neoplastic solid and cystic pancreatic masses and compared it to normal pancreas, as well as chronic pancreatitis, and showed promising results with ability to differentiate the pancreatic neoplasm from benign pancreatic conditions as well as determine the need for surgery. These studies are very promising and we eagerly await more research and results in this direction.

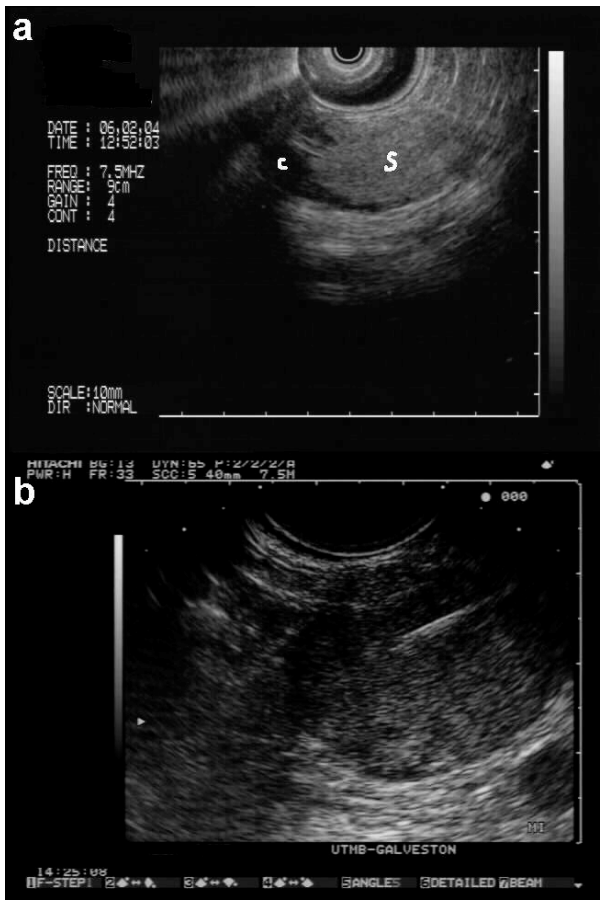

Figure 2. a. A mixed solid (S) and cystic lesion (C) in the pancreatic body. **b.** Linear EUS guided FNA was performed of the solid portion of the lesion in Figure 2a. Cytopathology revealed intraductal papillary mucinous neoplasm.

The ability of EUS to precisely target the pancreas in a minimally invasive way has also opened up possibilities for EUS guided anti-tumor therapy [21]. EUS-guided anti-tumor therapy may also be applied to cystic pancreatic tumors and early results of EUS guided alcohol injection into pancreatic cystic tumors were recently reported [22]. In this on going study, 24 patients have undergone EUS guided ethanol lavage of cystic pancreatic tumors with dilute alcohol (5-80%) for 3-5 minutes and removed by aspiration. On follow up imaging in 8 patients 5 out of 8 had resolution of the cystic lesion and the cystic lesion was persistent in 3 patients. Three patients underwent surgical resection with surgical pathology demonstrating epithelial denudation without evidence of pancreatitis. These results are very interesting and we await further studies in this area.

Conclusions

In conclusion, EUS imaging and EUS-FNA can play an important role in the evaluation of pancreatic cystic lesions. The decision to proceed with EUS FNA of a cystic lesion of the pancreas after diagnostic EUS should be decided on a case to basis after evaluating the clinical impact of the EUS FNA [23]. If the cytology of cyst fluid is non-diagnostic, CEA levels in the cyst fluid appears to be the most promising tumor marker at this time. In the future, molecular markers in cyst fluid may further increase the information obtained from EUS FNA of cystic lesions of the pancreas. There is potential for EUS guided therapy of cystic pancreatic tumors by EUS guided ethanol lavage.

Keywords Biopsy, Fine-Needle; Endosonography; Pancreatic Cyst; Pancreatic Neoplasms

Abbreviations CA: carbonic anhydrase; CEA: carcinoembryonic antigen; IPMN: intraductal papillary mucinous neoplasm; MCN: mucinous cystic neoplasm

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