Endoscopic Ultrasound and Pancreatic Cystic Lesions-Diagnostic and Therapeutic Applications

Won Jae Yoon¹, William R. Brugge²*

¹Gastrointestinal Unit, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA; ²Harvard Medical School; Gastrointestinal Unit, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

Abstract:
Pancreatic cystic lesions are being detected with an increasing frequency. Endoscopic ultrasound (EUS) provides both diagnostic and therapeutic means for pancreatic cystic lesions. Detailed imaging and EUS-guided fine-needle aspiration provide additional information on pancreatic cystic lesions. EUS-guided pseudocyst drainage has advantages over conventional drainage modalities. EUS-guided cyst ablation is a promising therapeutic modality.

Keywords:
endosonography; pancreatic cyst

INTRODUCTION

Pancreatic cystic lesions (PCLs) are being detected more frequently, at least partly because of the increased use of cross-sectional imaging.¹ The reported prevalence of PCLs ranges from 1.2% to 19.6% in image-based studies.²⁻⁴ In the past, 80%⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻˓—and therapeutic applications of EUS to PCLs.

DIAGNOSTIC APPLICATIONS OF EUS TO PCLs

When faced with PCLs, cystic neoplasms must be differentiated from pseudocysts. The diagnosis of a pseudocyst is primarily based on a patient history compatible with pancreatitis, with additional information from laboratory and imaging features.⁷ However, clinicians should always remember that patients with PCNs may also present with pancreatitis, and that patients with a pseudocyst may have no apparent history suggestive of pancreatitis.⁷

Sahani et al.¹⁰ simply but usefully classified PCLs based on imaging morphological features: (1) unilocular (pseudocysts, IPMNs, unilocular macrocystic serous cystadenoma, and lymphoepithelial cysts); (2) microcystic (SCNs); (3) macrocystic (MCNs and IPMNs); and (4) cysts with a solid component (MCNs, IPMNs, cystic neuroendocrine neoplasms, SPNs, ductal adenocarcinoma with cystic degeneration, and metastasis).

With its widespread availability and ability to detect cystic lesions, computed tomography (CT) is an excellent diagnostic tool for PCLs.¹¹ Magnetic resonance (MR) imaging with MR cholangiopancreatography is widely used given its ability to demonstrate the relationship between a PCL and the pancreatic duct.¹⁰ There are some characteristic imaging features of PCNs. For example, one can readily diagnose SCN when a central scar with calcification is observed on a cross-sectional image.¹² Other features diagnostic of SCNs are the honey-combed or microcystic appearance of the...
lesions, MCNs are diagnosed based on their unilocular or macrocystic appearance.\textsuperscript{13} Peripheral calcification on CT is also specific for MCNs.\textsuperscript{14} For main-duct IPMNs, the cystic dilation of the main pancreatic duct is a characteristic finding. Filling defects that may represent mucinous or papillary tumors may be noted.\textsuperscript{15} In branch-duct IPMNs, the branch ducts are cystically dilated and communicate with the main pancreatic duct.\textsuperscript{15} MR imaging can also be used to differentiate IPMN from chronic pancreatitis. In a report comparing the MR imaging features of IPMN and those of chronic pancreatitis, pancreatic duct dilatation without stricture as well as bulging ampulla, nodule in a duct, grape-like cyst shape, and nodule in a cyst were all specific for IPMNs.\textsuperscript{16} Image findings of main pancreatic duct involvement, cyst diameter > 3 cm, and the presence of mural nodules are associated with malignant IPMNs.\textsuperscript{17}

In EUS, the findings typical of SCNs are multiple small, anechoic areas and thin septations (Fig. 2).\textsuperscript{18} MCNs appear as fluid-filled, thin-walled, septated cavities.\textsuperscript{19} EUS findings of IPMNs include the dilation of the main pancreatic duct or branch duct with or without mural nodules and intraluminal contents.\textsuperscript{19} In one report that compared EUS findings with the surgical histopathology of IPMNs, the presence of a dilated main pancreatic duct, solid lesions, pancreatic ductal filling defects, or thickened septa within any cyst in EUS was associated with malignancy.\textsuperscript{20} Kubo \textit{et al.}\textsuperscript{21} revealed that for IPMNs, the marked dilatation of the main pancreatic duct (≥10 mm) in main-duct IPMNs and large tumors (>40 mm) with irregular septa in branch-duct IPMNs in EUS were both associated with malignancy. In contrast, mural nodules >10 mm in height in EUS were associated with malignancy in both types of IPMN (Fig. 3-5). A cyst diameter >30 mm is one of the factors that predict malignant branch-

\begin{figure}[h]
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\includegraphics[width=\textwidth]{image1}
\caption{Simple unilocular cyst undergoing fine needle aspiration.}
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\begin{figure}[h]
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\includegraphics[width=\textwidth]{image2}
\caption{Microcystic serous cystadenoma.}
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\begin{figure}[h]
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\includegraphics[width=\textwidth]{image3}
\caption{Complex multilocular cyst consistent with a benign intraductal papillary mucinous neoplasm.}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{image4}
\caption{Intraductal papillary mucinous neoplasm with mural nodule (histologically, high-grade dysplasia).}
\end{figure}
duct IPMNs. Some EUS-based studies reported different cutoff values of cyst diameters that predict malignant branch-duct IPMNs. However, considerable variability among the measurements of the PCL size among EUS, CT, and MR imaging has been reported. Zhong et al. recently indicated that most echogenic lesions detected during EUS of PCLs are mucous. The authors concluded that mucous is usually hypoechoic compared with adjacent soft tissue, with a smooth edge and a hyperechoic rim.

EUS-FNA is another powerful tool in the diagnosis of PCLs. It provides the specimens for cyst fluid analysis and cytology. Pseudocysts are usually high in cyst fluid amylase and low in cyst fluid carcinoembryonic antigen (CEA). Cyst fluid CEA is useful for identifying mucinous PCLs. A cyst fluid CEA level of 192 ng/mL was highly accurate for the diagnosis of mucinous PCLs. Increasing the cutoff value of the cyst fluid CEA level increases the diagnostic specificity at the cost of sensitivity. In addition to amylase and other tumor markers, the cyst fluid analyses of DNA, interleukin-1β, and microRNA have been reported.

EUS can be used as a platform to deliver high-resolution imaging probes into PCLs. Konda et al. reported the feasibility of needle-based confocal laser endomicroscopy (nCLE) during the EUS-FNA of pancreatic lesions. CLE is a novel imaging technology that uses a low-power laser to obtain the in vivo histology of the gastrointestinal mucosa. In the study, a nCLE miniprobe was introduced through a 19-G FNA needle. Technical feasibility was achieved in 94% of the cases. Good to very good quality images were obtained in 56% of the cases.

**Figure 5.** Malignant intraductal papillary mucinous neoplasm with a thickened wall.

The reported treatment success rates for EUS-guided pseudocyst drainage are very high, ranging between 82% and 100%. The complications of EUS-guided pseudocyst drainage include pneumoperitoneum, bleeding, stent migration, perforation, and infection.

EUS-guided pancreatic cyst ablation is another example of the therapeutic application of EUS to PCLs. Under EUS guidance, a cystic lesion is punctured, aspirated, and injected with a cytotoxic agent, which may result in the ablation of the cyst epithelium.

Ethanol was the first cytotoxic agent to be used for this purpose. In a previous study, ethanol with concentrations ranging from 5% to 80% was injected into the PCLs of 25 patients under EUS guidance. Complete resolution of PCLs was observed in 8 patients. Histologic evidence of epithelial ablation was documented in 5 patients who underwent resection. No complication was reported. A prospective, randomized, multicenter trial comparing the lavage of PCLs with 80% ethanol to the lavage with saline was conducted. Ethanol lavage resulted in a greater mean percentage of cyst surface area decrease. The overall pancreatic cyst resolution rate was 33.3%. A review of the histology of 4 resected specimens demonstrated that no epithelial ablation occurred in 1 saline lavage case, whereas 50% to 100% epithelial ablation occurred in three ethanol lavage cases. The complication rates were similar in both groups. Long-term follow-up results of patients from this study showed that in 9 patients, follow-up CTs demonstrated no evidence of cyst recurrences performed after a median follow-up period of 26 months.

EUS-guided ethanol lavage with paclitaxel injection (EUS-ELPI) for pancreatic cysts was recently introduced. To summarize the procedure, the cyst is aspirated under EUS guidance, lavaged with 99% ethanol, and injected with paclitaxel (concentration of 3 mg/mL). The volume of
injected paclitaxel is the same as that of the aspirated cyst fluid. A study on 52 patients who underwent EUS-ELPI for PCLs was reported in 2011. There were 29 patients who showed complete response, 6 partial response, and 12 persistent PCLs. In 4 patients who underwent resection, histopathology revealed variable epithelial ablation extents of 0%, 25%, 40%, and 100%. A small cyst volume was the only independent factor associated with complete response. The reported complications were fever without bacteremia (n = 1), abdominal discomfort for 2 weeks (n = 1), pancreatitis (n = 1), pericystic spillage (n = 1), and splenic vein obliteration with collateral formation (n = 1). Another potential therapeutic application of EUS is EUS-guided radiofrequency ablation. This method is currently at the experimental level and can be later be applied as an ablation tool for benign tumors in the upper gastrointestinal tract and pancreas.

CONCLUSIONS

The application of EUS in the evaluation of PCLs is rapidly expanding. Novel cyst fluid markers for the diagnosis of PCLs and the differentiation of benign and malignant PCNs play critical roles in providing a highly accurate diagnosis. In the near future, several new applications using therapeutic EUS to manage cystic lesions of the pancreas are expected.

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