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Invited Review

Endoscopic Ultrasound-Guided Fine-Needle Aspiration (EUS-FNA) in Gastroenterology

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SUMMARY

Endoscopic ultrasound (EUS) is recognized as a useful diagnostic modality in detecting lesions in the pancreas, gastrointestinal tract, periluminal and pancreaticobiliary lymph nodes, the spleen, as well as in outlining their locoregional extent. EUS-guided fine-needle aspiration (FNA) has signaled the beginning of a new era for the capabilities of EUS, because it enables the biological characterization of the lesion, thereby rendering patient management more efficient. This review focuses on the vast variety of EUS-FNA applications (according to different anatomical sites), their advantages and contribution to the diagnosis of deep-seated lesions (such as those of the pancreas, biliary tract and lymph nodes), as well as on their drawbacks and limitations. Technical issues such as training difficulties and future developments are also discussed.

Key words: EUS, EUS-FNA, pancreatic cancer, pancreatic neuroendocrine tumors, pancreatic cysts, IPMT, autoimmune pancreatitis, foregut cysts, mediastinal masses, mediastinal lymphadenopathy, stromal tumors, GIST, liver lesions, adrenal masses, ascites, EUS-FNA complications.

INTRODUCTION

Over the last twenty years, endoscopic ultrasound (EUS) has been proven to be an indispensable diagnostic modality in gastroenterology since it displays both periluminal and intramural lesions of the GI tract in detail. High-resolution images of the GI wall and the organs in its vicinity are produced because of the use of high-frequency (5-10MHz) ultrasound probes and their proximity to the lesion. The addition of Doppler imaging has further enhanced the application of EUS in the characterization of vascular structures and hemodynamics.

It is, however, the introduction of linear echoendoscopes, which enable EUS-guided fine-needle aspiration (FNA) with real-time control, (the continuous visualization of the needle) that has broadened the spectrum of indications; at the same time, the procedure has become reliable and safe. This remarkable ability to acquire cytologic material under direct visualization opens a whole new dimension in the usefulness of the technique because it offers an opportunity for a prompt and accurate diagnosis.[1,2] Since the availability of the first linear-array echoendoscopes by Pentax Precision Instruments in 1991, there has been a clear and progressive improvement in the these instruments as well as in the needle design, with the result that a vast variety of lesions may now be approached using this technique. Basically, EUS-FNA involves passing an 19 to 25-gauge (most commonly a 22-gauge) stainless steel, aspiration needle through the working channel of an echoenoscope under real-time guidance, into an EUS visualized mass, lesion, lymph node, lesion within another organ, or fluid collection.[3]

Based on the operating characteristics of EUS-FNA reported in the literature, the overall cellular yield from the organ targets is 86%-98%, while sensitivity ranges from 77%-95%, specificity 96%-100% and accuracy 79%-97%, in the diagnosis of malignant neoplasms.[2] The different statistical results reflect the dependency of the technique on the operator's experience; the greater the experience the higher the probability of detecting a tu-

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mor, especially in lesions smaller than 2 cm in size. Experience is even more important in EUS-FNA, a supplementary method that enhances the positive predictive value of the EUS. Equally essential factors in increasing the diagnostic yield of samples, is the cytopathologist's experience (particularly, the ability to diagnose malignancy in well-differentiated tumors)[2] and his/her presence during the procedure, enabling an on-site assessment of the cellular adequacy of the specimens obtained and also permitting a highly accurate preliminary diagnosis of potential malignancy. In addition, on-site evaluation of EUS-FNA helps obtain samples for ancillary examinations such as immunohistochemical analysis, bacterial cell cultures, flow cytometry and gene rearrangement studies for unsuspected cases of lymphoma[2] Indeed, cytopathologic feedback during EUS-FNA increases the diagnostic yield by 10-15%[3]

Pancreas

Pancreatic lesions can be divided into two major categories: solid and cystic lesions. EUS-FNA has proven to be a highly effective modality for detecting and staging pancreatic lesions in both categories, with a reported sensitivity of 81-98% and specificity of 99-100%. The incidence of **pancreatic cancer** has been increasing over the past 40 years, becoming the second most frequent malignancy of the GI tract.[4] The 5-year cumulative survival rate is as low as 5%, while the major contributing factor to this dismal prognosis is the delay in diagnosis.[5] The objectives of EUS-FNA are to obtain the initial diagnosis for a clinically suspicious malignant neoplasm (obviating the need for surgery), for the purpose of acquiring tissue for diagnosis before surgical resection with curative intent, or initiating adjuvant chemotherapy[2] (figure1). Moreover, EUS alone is more sensitive (94%) for detecting pancreatic lesions < 3cm, than a CT scan (69%) and magnetic resonance imaging (MRI) (83%). Accuracy rates for T and N staging are 85% and 72%, respectively, for EUS alone compared with 30% and 55%, respectively, for a CT scan. In the prediction of local resectability, EUS has shown an accuracy of 93% compared with that of only 60% for CT ($p < 0.01$). The specificity of EUS is analogous to that of angiography in detecting vascular invasion, but EUS is more sensitive (86% vs. 21%; $p=0.0018$) and accurate (81% vs. 38%).[6-8] EUS-FNA is the recommended technique for the tissue sampling of pancreatic cancer as it involves only a negligible risk for peritoneal seeding, unlike percutaneous FNA.[9] A new Tru-Cut needle has recently become available for EUS-guided histological tissue analysis, providing tissue fragments up to 11 mm in length and a correct diagnosis in 87% of the successfully punctured cases. Consequently, until improved and easier-to-use versions of the needle are developed, EUS-FNA should remain the technique of choice.[10]

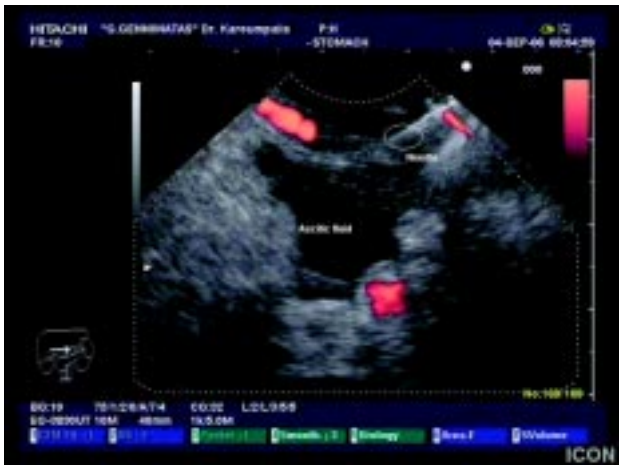

Fig. 1. EUS-FNA of a pancreatic mass lesion.

It has been well demonstrated that while EUS-FNA has excellent specificity, it sometimes lacks sensitivity. One way to improve sensitivity is to increase the number of passes required to obtain a correct diagnosis[5] Factors that influence the number of fine needle passes made during EUS-FNA include the sonographic characteristics of the lesion, pretest probability of the expected diagnosis, presence of a cytopathologist or cytotechnician during the EUS procedure and the level of cytologic expertise available. According to the only prospective study, the optimal median number of needle passes was 3.5 for the pancreas. Interestingly, the sensitivity tended to increase after each needle pass, reaching a maximum level after the seventh pass (sensitivity 86.7%, specificity 100%, positive predictive value (PPV) 100% and negative predictive value (NPV) 50%)[11] Nevertheless, some conditions, such as a recent episode of acute pancreatitis and especially chronic pancreatitis, contribute to a false negative EUS-FNA examination (thus a low negative predictive value). Notably, in a Bhutani et al[12] multicenter retrospective survey, all patients with a negative EUS had undergone at least one other imaging examination, also negative. The poor sensitivity and specificity in diagnosing pancreatic cancer in a patient with underlying chronic pancreatitis is not a problem unique to EUS because all other diagnostic modalities (CT, MRI, ERCP, PET) are also poor in detecting a malignancy superimposed on chronic pancreatitis. Although cytologic sampling of the pancreas with EUS-FNA would seem to be the ideal solution, even this approach is problematic, because dif-

ferentiating well-differentiated carcinoma from inflammatory atypia can be challenging. The use of molecular techniques may hold significant promise in this area[13-17]

Autoimmune pancreatitis (AIP) is another important clinical entity that may benefit from EUS-FNA in reaching a correct diagnosis since AIP can be mistaken for pancreatic carcinoma (figure2). In fact, in two surgical series, AIP accounted for a large proportion (19.5% and 23.4%, respectively) of pancreatic resections for presumed malignancy.[18,19] Apart from the clinical and laboratory features of AIP, US, CT, MRI and ERCP images of AIP have been described[20-25] However none of these modalities can provide an unequivocal diagnosis of AIP. Histopathologic examination remains the primary method for the differentiation of AIP from acute and chronic pancreatitis, lymphoma and cancer, while EUS-FNA has an accuracy of 85%-96% in differentiating benign from malignant pancreatic masses[26-28] Therefore, EUS-FNA might help patients with AIP (especially in the near future when specific cell and lymphocyte markers are to be used to differentiate the type of inflammatory infiltrate), avoid unnecessary surgery and thus benefit from the administration of corticosteroid therapy[29]

Pancreatic cystic lesions (figure3) encompass a wide range of histological findings, including inflammatory lesions (pseudocyst), benign lesions (simple cysts, retentional cysts, serous cystadenoma) and premalignant and malignant lesions (intraductal papillary mucinous tumor (IPMT), mucinous cystadenoma and cystadenocarcinoma). Although considered to be the most sensitive modality in detecting pancreatic cystic lesions, the accuracy of EUS in the diagnosis of neoplastic vs non-neoplastic cysts has ranged from 40% to 93%. This gap in figures is

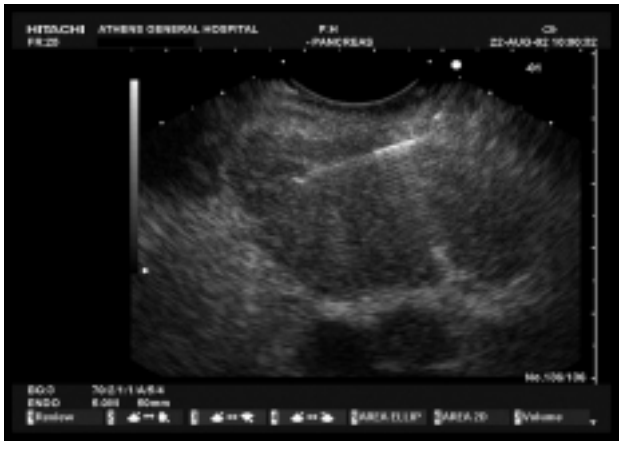

Fig. 2. EUS-FNA in a case of autoimmune pancreatitis.

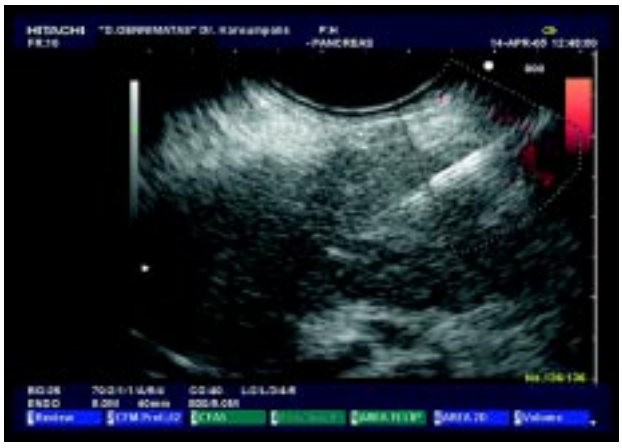

Fig. 3. EUS-FNA of serous cystadenoma.

derived from the fact that there is little more than a chance interobserver agreement among experienced endosonographers for the assessment of pancreatic cysts[30] EUS-FNA may help overcome this limitation, not so much as with the cytological analysis of the pancreatic fluid (low prognostic value), as with estimating cystic fluid tumor markers and other parameters that appear to provide new approaches to increasing the accuracy of this technique. Carcinoembryonic antigen (CEA), CA125, CA19-9, CA72-4 and amylase have been used in the hope of improving the sensitivity and specificity of the diagnosis, but their use has not yet become standard practice[31]

In a large multicenter study, Brugge et al[32] showed that the mean and median CEA concentrations for all mucinous cysts were significantly greater than the mean and median CEA concentrations for all non-mucinous cystic lesions with an optimal cut-off value of 192 ng/ml. CA72-4 is the second best discriminating marker, while very high values of amylase are only found in pseudocysts. According to Brugge's study, the determination of the cyst fluid concentration of CEA alone is highly diagnostic and more accurate than any combination of tests ($p<0.0001$).

Pancreatic neuroendocrine tumors (PNTs) have a broad and often misleading clinical spectrum because of their small size and the production and release of various hormones. The most common tumors are carcinoid tumor, insulinoma, gastrinoma, somatostatinoma, glucagonoma. The diagnosis depends on the clinical symptoms and the identification of the hormone produced. However 15-30% of PNTs are non-functioning.[33] The precise localization of PNTs is of crucial importance, because surgical resection is the only curative treatment.[34] The ability of standard imaging studies such as transcutane-

ous US, CT and MRI to localize a PNT is poor to moderate and depends on the size of the tumor (for example, CT and MRI localize fewer than 10% of PNTs less than 1cm). Selective abdominal angiography is quite sensitive (identifying 60% of small PNTs and 73% of other PNTs) but it is relatively expensive and as an invasive procedure, has significant potential for complications.[35] Somatostatin receptor scintigraphy (SRS) can detect up to 90% of PNTs (except for insulinomas and gastrinomas which lack somatostatin receptors), but in a very raw mode, without the anatomical details needed for a accurate surgical resection. EUS, however, is highly accurate for the pre-operative localization of PNTs and is a good alternative to other invasive modalities, with sensitivity and specificity at 82% and 95%, respectively.[32] It can even identify lesions as small as 2-3 mm within the pancreas that are difficult to find by palpation during surgery. To avoid such problems, small lesions are tattooed by the endosonographer before the operation. The cytologic and histopathologic evaluation of specimens obtained by EUS-FNA can confirm the diagnosis, especially when combined with immunohistochemistry, thus enhancing the diagnostic accuracy for PNTs (83%). The PPV and NPV are 95% and 60%, respectively.[3] Thus, if a malignant lesion is found before surgery, the choice of operation is optimized, while documentation of multifocal disease by EUS and EUS-FNA will mandate a change in the therapeutic approach.

Lesions of the liver and extrahepatic biliary tree (fig.4)

EUS alone appears to be a feasible, safe and reliable modality in liver exploration (particularly of the left lobe, as there are parts of the right lobe that can not be visualized clearly due to their distance from the US probe) and it is able to identify hepatic lesions in cases where a prior CT scan had failed to detect a lesion.[36] EUS-FNA is supplementary in enhancing EUS accuracy (e.g. in a multi-institutional study, EUS-FNA increased the diagnostic accuracy in 89% of cases in which prior percutaneous FNA was non diagnostic).[37] In another study, EUS led to the early detection of hepatocellular carcinoma, resulting in its early resection.[38] Prasad et al,[39] after reviewing the records of 222 patients admitted for staging of known or suspected malignancies, demonstrated that of 21 patients who underwent EUS-FNA, 15 had positive cytologic evidence of liver metastases, five of whom had had former normal noninvasive imaging. It is worth mentioning that most of the lesions missed on CT but detected by EUS had a short-axis diameter of less than 1 cm. A median number of 2.5 passes is thought to be sufficient for reaching a definite diagnosis of a liver lesion[11]

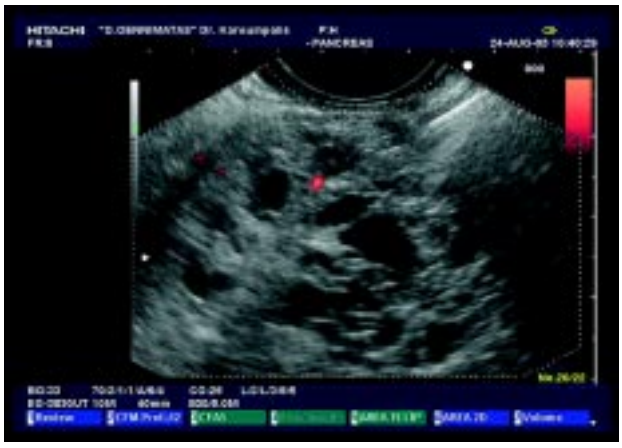

Fig. 4. EUS-FNA of an hepatic lesion.

Masses and strictures in the extrahepatic biliary tree often represent a diagnostic challenge, as they are usually regarded as being a minefield for all imaging techniques due to the difficulties in distinguishing between benign and malignant lesions.[11] For example, in ERCP, even if the clinical features and cholangiographic appearances of bile duct strictures suggest malignancy, it is not possible to distinguish between primary cholangiocarcinoma, pancreatic adenocarcinoma, metastatic disease or lymphoma. Furthermore, treatment options are becoming increasingly dependent on pathological diagnosis.[40] Histological confirmation of malignancy allows one to manage patients with pancreaticobiliary malignancy more appropriately and to choose between the surgical, chemotherapeutic and radiotherapeutic options. Brush cytology during ERCP, although easy and convenient to perform, has a low sensitivity for malignant bile strictures ranging from 30% to 69%.[41] Even adapting methods such as FNA or forceps biopsy, the yield of tissue sampling in ERCP remains far from ideal.

On the other hand, EUS visualizes the bile duct very well and it is used to detect and aid in the differential diagnosis of bile duct masses or strictures[41] EUS has undoubtedly improved the accuracy of local staging of tumors, because by using Doppler imaging one can identify if there is invasion of neighboring vascular structures, which are important determinants of resectability.[42] Hilar lesions are often small or diffusely infiltrating and can be hard to detect and/or sample. In a prospective study, Fritscher-Ravens et al. reported that EUS-FNA may aid in the diagnosis of hilar cholangiocarcinomas, when standard methods of tissue diagnosis are inconclusive The overall diagnostic accuracy, sensitivity and spe-

cificity rates were 91%, 89%, and 100%, respectively, while the NPV was lower (67%). In 20% of the patients, EUS-FNA led to a major change in management, avoiding a planned surgery.[43] Erickson and Garza also found that performing EUS with FNA as the initial modality for evaluation of obstructive jaundice obviates the need for approximately 50% of ERCPs and substantially reduces costs ($1007-$1313 per patient).[44] Concerning the gallbladder, EUS-FNA may be used to take samples in order to rule out malignant neoplasms, but further studies are necessary to demonstrate the cytologic features and the safety of performing FNA of gallbladder lesions[2]

Spleen

In general, FNA of the spleen has proven to be useful in the detection of malignant non-Hodgkin's lymphoma, metastatic carcinoma, sarcoidosis, infectious conditions and extramedullary hematopoiesis. There is only preliminary experience in the use of EUS-FNA in the spleen, which suggests that it might allow the detection of unsuspected neoplasms, the determination of a preoperative diagnosis of splenic lesions, or both. Further studies are needed to determine the safety and efficacy of this modality in the detection of splenic lesions.[2]

Gastrointestinal tract

For GI tract lesions, EUS is particularly helpful in determining the origin of the lesion: for example, whether it arises in the wall or is caused by an extrinsic lesion compressing the GI lumen.[45] EUS can also identify the layer of the luminal wall from which the lesion arises, providing information on the extent and the borders of the lesion as well as on its cytology when EUS-FNA is used. Therefore, EUS-FNA permits preoperative determination of the depth of tumor invasion (T staging), and of the N status, providing valuable information regarding the TNM staging of GI tract malignant neoplasms, including those of the esophagus, stomach, colorectal and anal tumors[46-52] Specifically, EUS-FNA has been shown to be of great value in the following areas:

Foregut cysts

One of the major differential diagnoses for a patient with a posterior mediastinal lesion that might manifest with dysphagia, is a foregut cyst, which includes an esophageal reduplication cyst and a bronchogenic cyst. The differentiation between esophageal reduplication and bronchogenic cysts can be based on the presence of the complete muscle wall, the type of epithelial lining and the results of EUS imaging. An esophageal reduplication cyst is a rare developmental anomaly that clinically and radiologically can mimic a neoplasm. Cytologic features are not pathognomonic for the diagnosis of a foregut cyst, but they can be used to rule out a malignant neoplasm and help to support the diagnosis of a foregut cyst when used in combination with EUS findings[2]

Gastrointestinal stromal tumors (GISTs)

Submucosal tumors, such as GISTs, cannot be detected by brush sampling or forceps biopsy, (the latter has a false-negative rate as high as 5%). However, EUS-FNA is being used increasingly for the diagnosis of GIST, because of its accuracy in obtaining sufficient samples under EUS guidance and simultaneously demarcating the size, the site and the extent of the lesion.[2] Some of these features are useful in determining the malignant potential of this tumor. The major pitfall with EUS-FNA and GIST is the aspiration of muscle cells from the wall of the GI tract or from a smooth muscle tumor[53] Since the definite differentiation of GISTs from other spindle-cell lesions influences subsequent therapy, distinguishing these lesions is important. Some immuno-histochemical stains including c-kit (CD 117), CD34, SMA, muscle-specific actin and S-100 may be used to differentiate GISTs from muscle cells, smooth muscle tumors and rare tumors, such as solitary fibrous tumors of the GI tract.[2]

MALT lymphoma

EUS is useful in determining the characteristic wall thickness of the GI tract, as well as in the prognosis and therapeutic response of MALT lymphomas.[54,55] The diagnosis of GI MALT lymphomas using EUS-FNA is more difficult, as it is not always possible based on morphologic features only and requires a high degree of clinical suspicion and ancillary studies, including flow cytometry and immunoglobulin analysis and gene rearrangements or both[2]

Ascites

The presence and the consequent tissue diagnosis of ascites due to metastatic disease in cases of known or suspected gastrointestinal malignancies is of great importance for patient management and assessing the prognosis. In patients with peritoneal carcinomatosis, ascites is the most common finding (49-60%), while the cytology is reported to be positive in 64% of cases.[56-59] Nguyen et al[60] showed that EUS-FNA may serve both purposes, as it is a more sensitive test for detecting peritoneal fluid than CT or transabdominal US, and also that ascitic fluid can be aspirated simultaneously for cytologic analysis (figure 5). On EUS, a small amount of fluid, long before the term 'ascites' has any clinical notion, is typically seen as a triangu-

lar anechoic area. In Nguyen's study, EUS-FNA sensitivity, specificity, and diagnostic accuracy were 50%, 100%, and 58%, respectively. The mean volume of ascites aspirated during EUS-FNA was far less than 50 cc (7.4 cc), which is considered to be adequate for cytologic examination, thus explaining the low sensitivity rates. No complications were reported, however, malignant seeding into the ascites through the needle tract may happen. This is why the fluid must be aspirated first, before the suspected tumor, in order to avoid possible needle contamination, and the site of needle penetration must not involve the tumor. As a result, EUS-FNA appears to be a safe and efficient diagnostic method of identifying patients with malignant ascites, thus greatly affecting further patient management (for example, precluding surgery).

Trucut biopsy

There are some limitations arising with EUS-FNA, such as small biopsy samples of destroyed tissue architecture that diminish diagnostic sensitivity in GI stromal tumors,lymphomas and well differentiated lesions containing desmoplasia. In addition, 'on-site' cytologic adequacy assessment is not easily available and may be hampered by the presence of blood and benign epithelial cells, calling for further biopsies Larger-caliber cutting needles, which can obtain bigger specimens, (preserving tissue architecture thus allowing histologic rather than cytologic examination) have been developed. The Trucut Biopsy (TCB) needle, which can be used with linear echoendoscopes, has recently been introduced. The assembly consists of a spring-loaded mechanism attached to the handle and of disposable 19-gauge needle along with an 18 mm specimen tray. Initial studies, despite their methodological drawbacks (lack of large patient numbers, of randomization or of a standard protocol), suggest the superior diagnostic accuracy of EUS-TCB vs. EUS-FNA for submucosal tumors and lymphomas. EUS-TCB seems to require fewer needle passes than EUS-FNA, especially for solid lesions of the pancreas, while recent data focuses on the contribution of EUS-TCB tissue sampling in autoimmune pancreatitis and cystic pancreatic tumors.[60] The use of EUS-TCB might obviate the presence of an "on-site" cytologist, and decrease procedure time and minimize cost. Still a serious disadvantage of the device remains its inability to acquire an adequate specimen from lesions that require a great degree of echoendoscope tip deflection (transduodenal approach). In such cases, either the needle extension from the accessory channel is precluded, or there is a laggard advancement of the cutting sheath over the specimen tray, inhibiting the acquisition of a diagnostic sample[61] Until future properly conducted studies determine the overall diagnostic accuracy and safety and design modifications for instrument improvements take place, EUS-TCB and EUS-FNA devices should not be considered as complementary but rather as competing methods.

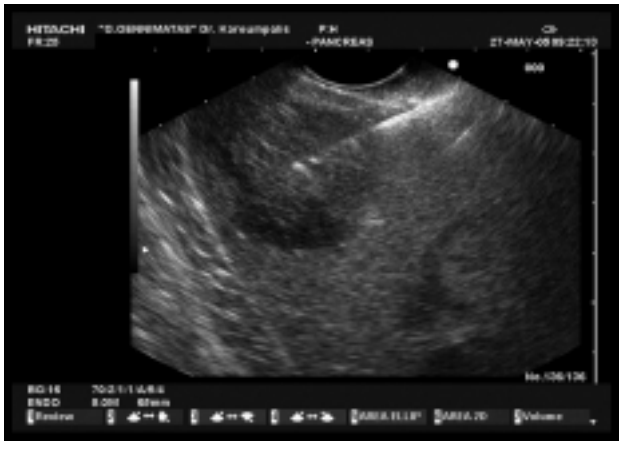

Fig. 5. EUS-FNA of perihepatic ascitic fluid.

Complications

A variety of complications have been reported with respect to EUS-FNA (Table 1). The overall complication rate of EUS-FNA appears to be 1-2%.[62-64] The major complications reported with EUS-FNA are infections of cystic lesions,[65-68] bleeding,[68-70] pancreatitis,[63,69,70] and duodenal perforation[62] Clinically significant bacteremia after EUS with and without FNA is low and in the range of that observed in other studies of diagnostic upper endoscopy (0-8%).[71-73] The rate of demonstrable bacteremia is maximal during and shortly after the endoscopic examination and diminishes rapidly within the following 30-240 minutes[1] Thus, it seems reasonable to recommend prophylactic administration of antibiotics, at best, for a selected group of patients at high risk for endocarditis according to the current guidelines[1] Because of the demonstrated risk of infecting cystic lesions, intravenous broad- spectrum antibiotics, often followed by a few days of oral antibiotics, are usually administered when carrying out EUS-FNA of cystic lesions and EUS-FNA of any lesion through the colon[74-77] Infection of pancreatic cystic lesions seems to have been substantially eliminated by prophylactic antibiotic use, however severe mediastinal infections still do occur, primarily when these lesions are sampled in this manner before knowing that they are truly cystic.[67,68,77-79]

Table 1. Complications of EUS-FNA [2]

Type of complication	Percentage (%)
General series	
Overall	0 -2
Aspiration pneumonia	0.3
Bacteremia (non-skin contaminant)	0 -4
Hemorrhage-extraluminal, none serious	1.3
Pancreatitis	2.6
Pancreas	
Minor	6.3
Major with no additional complications at 30 days	1
Death due to bleeding	0.8
Hemorrhage	1.6
Pancreatitis	1.2 -2
Tumor seeding of needle tract	2,2
Infection of pancreatic cysts [without preprocedure antibiotic prophylaxis]	14
Infection of pancreatic cysts [with antibiotic prophylaxis]	0
Mediastinum	
Mediastinitis after EUS-FNA of mediastinal cyst	25
Fever resolving on antibiotics after mediastinal node EUS-FNA	1.2
Liver	
Overall	0 -4.8
Bleeding-self limited	0.5 -4.8
Death-sepsis after liver EUS-FNA with occluded biliary stent	0.5
Fever	1
Pain	1
Spleen	
Self limited abdominal pain	8.3

Training in EUS-FNA

EUS-FNA should not be performed without a solid background in general diagnostic EUS. The American Society for Gastrointestinal Endoscopy (ASGE) currently recommends a total of 150 EUS procedures, 75 of which are pancreaticobiliary. However, due to the limited number of slots available in EUS training programs and the time and cost involved in the acquisition of additional training, in practice, some endosonographers do perfect their EUS-FNA technique through experience and self-education, after basic training in EUS.[4] The current ASGE guideline for training in pancreatic EUS-FNA suggests that 'the trainee be competent to perform diagnostic pancreaticobiliary EUS and have done at least 25 supervised EUS-FNAs of pancreatic lesions.[78] Knowing when to perform EUS-FNA is as important as being able to carry out the procedure. Animal and mechanical models and short courses may help in the development of initial EUS-FNA skills but this cannot substitute for supervised experience gained under the guidance of an experienced endosonographer.[79-81]

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