Clinical use of endoscopic ultrasound-guided fine-needle aspiration: Guidelines and recommendations from Chinese Society of Digestive Endoscopy

Prepared by EUS Academic group of Chinese Society of Digestive Endoscopy

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INTRODUCTION

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) or EUS fine-needle biopsy (EUS-FNB) is a means of facilitating specimen procurement for microscopic analysis. Diagnostic samplings (cells or tissues) successfully obtained in this manner may greatly impact patient therapeutic management.

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The guideline presented herein is based on our current understanding of the field. Various aspects of EUS-FNA (or EUS-FNB), ranging from preoperative preparation and clinical applications to major complications, are addressed. Related technologies

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with the potential to improve diagnostic accuracy are highlighted. We believe that this compilation may be helpful in clinical settings and the training of beginners.

PATIENT PREPARATION

General considerations

- Patients should provide signed informed consent before procedures, acknowledging the risks involved
- Results of EUS and other imaging tests (computed tomography [CT], magnetic resonance imaging, or ultrasound [US]) must be reviewed preliminarily by specialists in charge
- A 6–8-h period of fasting is required for patients in advance of procedures
- Patients are generally recumbent (on left side) for EUS examinations
- Such examinations are contraindicated in the event of a coagulation disorder.

Sedation during endoscopic ultrasound

- Topical pharyngeal anesthesia (*e.g.*, lidocaine) is generally administered, and a sedative/hypnotic (*e.g.*, midazolam) is appropriate to ease patient anxiety. Continuous monitoring of pulse, blood pressure, and oxygenation is also essential
- Intravenous delivery of propofol by an anesthesiologist during endoscopy is considered safe and has become the preferred method for induction and maintenance of anesthesia[1]
- General anesthesia (with endotracheal intubation) is not routinely used in this setting but may be required if propofol-induced respiratory failure should occur.[2]

CLINICAL INDICATIONS

Submucosal tumors/subepithelial lesions

Submucosal tumors are neoplasms originating below digestive tract mucosa. Subepithelial lesion (SEL) is a term coined recently to denote growths beneath the epithelium. SELs may be neoplastic or nonneoplastic in nature,[3] ectopic pancreas being one example of nonneoplastic SEL.[4]

EUS is the most accurate imaging technique for differentiating SELs and extramural distortions because information on location, size, echo pattern, and level of origin is conveyed. FNA may be performed jointly with EUS in hopes of establishing a pathologic diagnosis, a strategy proven accurate by some in pretherapeutic diagnosis of gastric SELs.[5-7] However, adequacy of sampling periodically falls short (17.7%)[6] or precludes warranted immunohistochemistry.[8]

In a recent meta-analysis, EUS-guided needle sampling was shown safe but only moderately effective in diagnosing upper gastrointestinal (GI) SELs. The choice of needle for FNA, Tru-cut biopsy, or FNB (*i.e.*, 19 gauge, 22 gauge, or 25 gauge) does not seem to alter overall diagnostic rates.[9] Furthermore, EUS-FNA is not always needed to diagnose SELs. Deep biopsy, also known as bite-on-bite or stacked forceps biopsy, is still considered the superior choice for pathologic evaluation.[10] Alternative methods available for tissue sampling include endoscopic mucosal resection, endoscopic submucosal dissection, and submucosal tunneling with endoscopic resection.[11]

Before FNA is applied, patients' symptoms and comorbid conditions must be considered, as well as certain characteristics (size, location, and echo patterns) of lesions. It may be difficult to perform EUS-FNA in some instances of small-diameter SELs (~10 mm). To stabilize SELs during FNA, Yamabe *et al.* attached a cap device to the scope tip.[12]

It has been acknowledged that EUS-FNA is particularly useful in circumstances where the pathologic diagnosis of SELs is critical but is not achievable through endoscopic forceps biopsy[6,13] as follows:

- A patient with history of malignant SELs (or other malignancy) to rule out possible metastasis
- A patient with nonresectable malignant GI stromal tumor who may benefit from EUS-FNA before initiating tyrosine kinase inhibitor therapy.

Differential diagnosis of diffuse gastric wall thickening

Gastric wall thickening is detectable by EUS, showing which layers are involved and any structural loss. It may thus help identify the fundamental cause (*i.e.*, infiltrating carcinoma, lymphoma, various metastases, eosinophilic gastroenteritis, Zollinger–Ellison syndrome, Menetrier's disease, tuberculosis, or amyloidosis). In this context, the false-negative rate for superficial biopsy is high. Deep biopsy, also known as bite-on-bite or stacked forceps biopsy, is a widely accepted alternate approach. There are few studies addressing the diagnosis of diffuse digestive wall thickening through EUS-FNA, but related data suggest a diagnostic yield of ~60%.[14]

Hence, EUS-FNA is a viable option if bite-on-bite tissue sampling is nondiagnostic.

Solid pancreatic lesions

The accuracy of EUS-FNA in diagnosing pancreatic cancer is high,[15-21] making it the preferred method for pathologic diagnosis of pancreatic tumors. EUS-FNA generally provides adequate material for pathologic assessment.[22-24] According to a recent meta-analysis of pooled data, diagnostic sensitivity and specificity were 85% and 98%, respectively.[25]

EUS-FNA is appropriate in the following circumstances:

- Suspected pancreatic cancer (first choice for pathologic diagnosis)
- Preoperative assessments of patients with potentially resectable pancreatic neoplasms (whether needle tract is in surgically resected area or not)

  Ngamruengphong *et al.* recently reported outcomes of a retrospective population-based study examining the impact of preoperative EUS-FNA on overall and cancer-specific survival in patients with locoregional pancreatic cancer undergoing surgery with curative intent. In this instance, preoperative EUS-FNA bore no association with increased risk of mortality, suggesting that EUS-FNA is safe for diagnosing suspicious pancreatic lesions.[26] A smaller prior study likewise examined the effect of preoperative EUS-FNA on overall survival in patients with pancreatic neoplasms, finding no related adverse perioperative or long-term outcomes in cases with solid neoplasms after distal pancreatectomy[27]
- Nonproductive EUS-FNA attempts

  Repeated EUS-FNA is a low-risk means of reaping substantial clinical benefits.[28-30] In clinical practice, repeat EUS-FNA is especially worthwhile if initial aspiration of a suspected tumor is nondiagnostic, but other signs of malignancy, such as vascular invasion or lymphadenopathy, are evident by EUS. In addition, if US or CT served initially for guidance, use of EUS-FNA on the next attempt may increase the diagnostic yield
- Nonresectable pancreatic cancer (in examining suspected metastases during staging)
- Distinguishing autoimmune pancreatitis (AIP) from pancreatic cancer

  Histologic diagnosis of AIP typically requires larger samples to evaluate architectural elements and perform immunostains. Only surgical or core biopsies are adequate for definitive diagnosis (specimens extracted through EUS-FNA providing too little tissue).[31] Nevertheless, there is recent evidence that EUS-FNA is safe and reliable in histologic documentation of AIP.[32] The diagnostic yield is not high, but surgery may be avoided in those patients who lack distinctive features of AIP[33]
- Diagnosis of other solid pancreatic lesions (such as tuberculosis or abscess) if imaging evaluation is difficult.

Clinical reliability of endoscopic ultrasound-guided fine-needle aspiration in diagnosing pancreatic cystic lesions

Pancreatic cystic lesions (PCLs) comprise a diverse pathologic subset, with variable malignant potential.[34] Many PCLs (40%) are nonneoplastic (pseudocysts [PCs]; lymphoepithelial cyst; epidermoid, congenital, or retention cysts), but the majority are pancreatic cystic neoplasms, including intraductal papillary mucinous neoplasm, mucinous cystic neoplasm (MCN), serous cystic neoplasm, and cystic degeneration of solid tumors. The most important issues are ensuring appropriate (*i.e.*, nonexcessive) patient treatment, thus limiting patient anxiety, and determining which patients may benefit from surgery. Despite the widespread availability of cross-sectional imaging and all pertinent technologic advances, PCLs are still diagnostically challenging. CT is a good-quality initial test to be used in accordance with clinical data although its diagnostic sensitivity is <70%. Magnetic resonance cholangiopancreatography may assist in ascertaining main pancreatic duct communication.[35] However, as a minimally invasive diagnostic tool, EUS-FNA provides investigators with cyst fluid for chemical and cytologic analyses.[36,37]

Cyst fluid biochemistry and tumor markers

Cytopathology and analysis of conventional markers in cyst fluid, such as amylase, carcinoembryonic antigen (CEA), and cancer antigen (CA) 19-9, improve diagnostic capability. Of markers tested in cyst fluid, CEA (as opposed to CA 19-9, CA 72-4, or CA-125) is the most accurate index of pancreatic MCNs. In pancreatic cyst fluid, a CEA concentration of 192 ng/mL is the customary cut-point for differentiating mucinous from nonmucinous lesions.[38] Similarly, a fluid amylase level of <250 IU/L excludes the diagnosis of PC. At present, cytologic analysis of pancreatic cyst fluid confers no diagnostic benefit over radiologic findings alone.[39]

Mediastinal lesions surrounding esophagus

EUS has proved accurate in delineating middle and posterior mediastinal lesions surrounding the esophagus, and EUS-FNA is considered safe in this region. Although

the role of EUS in the staging of lung cancer is still under evaluation, the diagnostic accuracy of FNA in mediastinal lesions is excellent. Researchers have confirmed a very high accuracy of FNA in mediastinal lymph nodes.[40,41] Furthermore, in analyzing 153 EUS-FNA procedures targeting mediastinal lesions, Fritscher-Ravens *et al.*[42] reported high diagnostic sensitivity (92%), specificity (100%), and accuracy (95%). Unfortunately, EUS-FNA of cystic mediastinal lesions may culminate in severe infection that is nonpreventable through antibiotic prophylaxis. Because the results are unlikely to affect clinical decisions, caution is advised in such lesions.

If aspiration is done in more suitable regions, such as subcarinal area and pulmonary hilum, and lesion diameter is >2 cm, adequate representative samples may be anticipated for pathologic study. In contrast, sensitivity, accuracy, and sampling adequacy of EUS-FNA decline dramatically in lesions <1 cm across. The mediastinal organs maintain relatively stable positions that are seldom disturbed, so odds of serious procedural complications are minimal if sampling is properly done. Ultimately, EUS-FNA appears safe and effective for sampling of middle and posterior mediastinal lesions surrounding the esophagus.

The many important organs situated within mediastinum call for a skilled endoscopist to perform this procedure. In addition, baseline cardiorespiratory function should be evaluated beforehand, and blood oxygen saturation should be monitored during the procedure to avoid asphyxiation.

Esophageal cancer

EUS-FNA is recommended for the use in staging esophageal cancer. Its accuracy in confirming nodal and left hepatic metastases has been shown to surpass that of EUS and CT.[43-45] To evaluate esophageal cancer in the aftermath of adjuvant therapy, 18F-fluorodeoxyglucose positron emission tomography/CT remains the first choice.[46,47]

Gastric cancer

Although not a standard method of diagnosing gastric cancer, EUS-FNA is still a very important modality. FNA may help in diagnosing remote metastases, particularly if results may alter tumor staging and thereby the treatment received.[48,49]

Suspicious lymph nodes

The accuracy of FNA in lymph nodes is high.[43] If therapeutic strategy requires pathologic substantiation, and other biopsy methods are unavailable, EUS-FNA of a suspicious lymph node is recommended.

Rectal cancer

EUS-FNA is not routinely used for staging of rectal cancer. Preoperative staging is more often achieved through EUS alone, with no significant gain in accuracy by adding FNA.[50] EUS-FNA has been used to assess extramesenteric lymph nodes for early recurrence of rectal cancer.[51]

Left adrenal masses

EUS-FNA of the left adrenal gland is safe and may be useful in evaluation and staging of suspected malignancy.[52,53] This approach is recommended if treatment strategies rely heavily on pathologic diagnosis.[54]

Malignant biliary obstruction

EUS-FNA is of great use in diagnosing malignant biliary obstruction, whether from cholangiocarcinoma or pancreatic cancer.[55,56] In a prospective investigation by Weilert *et al.*, EUS-FNA proved superior to endoscopic retrograde cholangiopancreatography (ERCP) in procuring tissue from presumptive sites, especially pancreatic masses. EUS-FNA should be performed before ERCP in all patients with suspected malignant biliary obstruction.[57,58]

TECHNIQUES TO INCREASE DIAGNOSTIC YIELD

Suction technique in solid lesions

Present opinions on the use of suction during fine-needle procedures vary.[59-61] Suction may contaminate the sample with blood, clouding cytologic interpretation. EUS-FNA done without suction or by slow-pull technique seems to fare better in terms accuracy and sensitivity of cytologic diagnoses, resulting in only slight blood contamination when aspirating solid lesions.[62]

In histologic preparations, recent studies have confirmed that biopsy with (*vs.* without) suction is superior for tissue acquisition;[59] higher suction pressure seems to yield more tissue.[61,63] Biopsy by wet suction technique will also enhance tissue procurement.[64]

The quantity of tissue acquired through FNA of lymph nodes is usually good, but to reduce blood contamination, suction is not recommended.[65]

Endoscopic ultrasound-guided fine-needle aspiration with or without stylet

As indicated by prospective studies, neither the diagnostic yield in instances of malignancy nor the proportion of inadequate specimens differed in passes done with or without a stylet, regardless of specimen type (histologic or cytologic).[66-68]

Needle diameter

The high-level evidence is still lacking in terms of needle choice (19 gauge, 22 gauge, or 25 gauge) for optimal diagnostic yield. Typically, 19 gauge is applied in interventional procedures, 22 gauge is routinely used to obtain histologic (tissue) specimens, and 25 gauge has gained in popularity for cytologic evaluations since the advent of rapid on-site evaluation (ROSE). Recently, a 25-gauge needle has been widely applied in aspirating solid pancreatic masses. Although a 19-gauge needle is more successful in aspirating mucinous cyst fluid, it is difficult to manipulate in transduodenal punctures.

Rapid on-site evaluation

In analyzing the performance of both EUS technologists and cytotechnologists, neither provided reliable assessments of FNA sampling adequacy (from pancreatic masses) by gross visual inspection of specimen-bearing slides.[69] False-positive assessments occurred in 30% of samples.

ROSE of EUS-FNA specimens is considered a highly accurate approach, comparing favorably with final cytologic outcomes.[70] Conducting ROSE during EUS-FNA of pancreatic masses reportedly correlated with improved adequacy and diagnostic yield, resulting in significantly fewer inadequate samples and fewer needle passes.[71] However, the current observational data on the impact of ROSE have been conflicting. In a recently published meta-analysis, comparing EUS-FNA with and without ROSE, no statistically significant difference in diagnostic yield or proportion of patients with adequate specimens was demonstrated. Diagnostic sensitivity and specificity were also comparable for both groups.[72] In most studies, the diagnostic yield through EUS-FNA and ROSE in combination may exceed 90%. However, similar results are achievable in high-volume centers, without ROSE, making further improvement difficult to envision.[73] A multiplicity of skills is required for successful results, so ROSE alone is not the overriding factor. In hospitals with diagnostic accuracy rates <90%, ROSE is nevertheless an important consideration.[74]

Needle-pass estimates (without rapid on-site evaluation)

ROSE entails direct evaluation of smears produced at point of care in the endoscopy suite, which then aids in determining the number of passes in EUS-FNA needed for final diagnosis. However, ROSE is not an option in many centers. The endosonographer is not privy to immediate assessments and cannot guarantee that aspirates obtained are diagnostically adequate. Various studies have attempted to gauge needle passes appropriately, without benefit of ROSE. It appears that at least five to seven passes are required for pancreatic masses, three passes for lymph nodes, and only one pass for PCLs.[65,75-77]

COMPLICATIONS

Although few reports have focused on complications after EUS-FNA, published data have confirmed that related morbidity and mortality rates are relatively low, with most events qualifying as mild to moderate in severity.[78] In a systematic review conducted by Wang *et al.*, EUS-FNA was found relatively safe, marked by a very low rate of complications (~1%) and a 0.98% (107/10,941) rate of procedure-related morbidity.

Of note, the complication rate for EUS-FNA of pancreatic cystic (*vs.* solid) lesions is higher by comparison. However, given the less-than-severe grades of complications and the clinical importance of this technique, the risk is acceptable.[79]

Bleeding

Severe bleeding is a rare complication of EUS-FNA, as a study based on nationwide administrative data in Japan has shown.[80] However, the incidence of severe bleeding in low-volume hospitals was shown to be 5-fold higher than rates in medium- and high-volume hospitals ($P = 0.045$),[80] supporting the notion put forth previously that complication frequencies in this setting reflect a learning curve.[81]

Bleeding risk for endoscopic ultrasound-guided fine-needle aspiration in patients given anticoagulants

The guidelines of major GI endoscopic societies list EUS-FNA as a high-risk procedure for bleeding. However, few studies have examined the risk of

bleeding for EUS-FNA of solid organs in patients who continue antithrombotic treatment. One study by Inoue *et al.* cites a low incidence of bleeding related to EUS-FNA in patients receiving antithrombotic agents. Bleeding events were few, despite aspirin or cilostazol continuation.[82] Although EUS-FNA of solid lesions during clopidogrel use similarly may not place patients at high risk of bleeding,[83] discontinuation of low-molecular-weight heparins should be considered in advance of these procedures.[84]

Tumor cell seeding

Concerns that tumor cells are seeded along needle tracks or within the peritoneum have limited the preoperative use of EUS-FNA in pancreatic cancer.[85-87] It appears that peritoneal carcinomatosis may occur with greater frequency in such patients who undergo percutaneous FNA.[88] Nevertheless, at least two investigations[88,89] have yielded evidence to refute this argument, finding no increased risk of needle-tract seeding and supporting EUS-FNA as the diagnostic method of choice in patients with potentially resectable pancreatic cancer.

Infections

Clinical infectious complications are very rare after EUS-FNA of solid lesions, with incidences of 0%–0.6% in two large prospective series.[90,91] Although EUS-FNA of PCLs has been linked to a higher rate of infection,[92] the risk is deemed acceptable as previously mentioned. Consideration should be given to the puncture of mediastinal cysts,[93] for which the rate of infection is much higher. Some infections due to mediastinal cyst aspiration are life-threatening, notably in bronchogenic cysts.[94,95]

Other rare conditions

Mediastinitis after FNA has been described in a patient with sarcoidosis.[96] Bile peritonitis also reportedly developed after an inadvertent biliary puncture during EUS-FNA,[97] and hemothorax due to FNA of an SEL (in gastric fornix) has been documented.[98] Finally, acute ectopic pancreatitis is an unusual complication both induced and diagnosed through EUS-FNA and subsequently cured through surgery.[99]

The guidelines above are based on a literature review and the consensus of endoscopic experts, hoping to be of clinical use and help train beginners. In this setting, however, clinical aspects are complex and evolving, requiring strategic modifications to meet individual needs. As technical developments and new research continue to surge, the future updates of these recommendations will follow.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Gotoda T, Okada H, Hori K, *et al.* Propofol sedation with a target-controlled infusion pump and bispectral index monitoring system in elderly patients during a complex upper endoscopy procedure. *Gastrointest Endosc* 2016;83:756-64.
2. Nayar DS, Guthrie WG, Goodman A, *et al.* Comparison of propofol deep sedation versus moderate sedation during endosonography. *Dig Dis Sci* 2010;55:2537-44.
3. Cho JW; Korean ESD Study Group. Current Guidelines in the Management of Upper Gastrointestinal Subepithelial Tumors. *Clin Endosc* 2016;49:235-40.
4. Attwell A, Sams S, Fukami N. Diagnosis of ectopic pancreas by endoscopic ultrasound with fine-needle aspiration. *World J Gastroenterol* 2015;21:2367-73.
5. Akahoshi K, Oya M, Koga T, *et al.* Clinical usefulness of endoscopic ultrasound-guided fine needle aspiration for gastric subepithelial lesions smaller than 2 cm. *J Gastrointestin Liver Dis* 2014;23:405-12.
6. Mekky MA, Yamao K, Sawaki A, *et al.* Diagnostic utility of EUS-guided FNA in patients with gastric submucosal tumors. *Gastrointest Endosc* 2010;71:913-9.
7. Turhan N, Aydog G, Ozin Y, *et al.* Endoscopic ultrasonography-guided fine-needle aspiration for diagnosing upper gastrointestinal submucosal lesions: A prospective study of 50 cases. *Diagn Cytopathol* 2011;39:808-17.
8. Hoda KM, Rodriguez SA, Faigel DO. EUS-guided sampling of suspected GI stromal tumors. *Gastrointest Endosc* 2009;69:1218-23.
9. Zhang XC, Li QL, Yu YF, *et al.* Diagnostic efficacy of endoscopic ultrasound-guided needle sampling for upper gastrointestinal subepithelial lesions: A meta-analysis. *Surg Endosc* 2016;30:2431-41.
10. Lee DS, Ahn YC, Eom DW, *et al*. Primary esophageal mucosa-associated lymphoid tissue lymphoma diagnosed by using stacked forceps biopsy. *Dis Esophagus* 2016;29:887-90.
11. Sun S, Ge N, Wang C, *et al*. Endoscopic band ligation of small gastric stromal tumors and follow-up by endoscopic ultrasonography. *Surg Endosc* 2007;21:574-8.
12. Yamabe A, Irisawa A, Bhutani MS, *et al.* Usefulness of endoscopic ultrasound-guided fine-needle aspiration with a forward-viewing and curved linear-array echoendoscope for small gastrointestinal subepithelial lesions. *Endosc Int Open* 2015;3:E161-4.
13. Fernández-Esparrach G, Sendino O, Solé M, *et al.* Endoscopic ultrasound-guided fine-needle aspiration and trucut biopsy in the diagnosis of gastric stromal tumors: A randomized crossover study. *Endoscopy* 2010;42:292-9.
14. Pellisé Urquiza M, Fernández-Esparrach G, Solé M, *et al.* Endoscopic ultrasound-guided fine needle aspiration: Predictive factors of accurate diagnosis and cost-minimization analysis of on-site pathologist. *Gastroenterol Hepatol* 2007;30:319-24.
15. Giovannini M. Contrast-enhanced endoscopic ultrasound and elastosonoendoscopy. *Best Pract Res Clin Gastroenterol* 2009;23:767-79.
16. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, *et al*. Quantitative endoscopic ultrasound elastography: An accurate method for the

differentiation of solid pancreatic masses. *Gastroenterology* 2010;139:1172-80.
17. Napoleon B, Alvarez-Sanchez MV, Gincoul R, *et al.* Contrast-enhanced harmonic endoscopic ultrasound in solid lesions of the pancreas: Results of a pilot study. *Endoscopy* 2010;42:564-70.
18. Khalid A, Nodit L, Zahid M, *et al.* Endoscopic ultrasound fine needle aspirate DNA analysis to differentiate malignant and benign pancreatic masses. *Am J Gastroenterol* 2006;101:2493-500.
19. Maluf-Filho F, Kumar A, Gerhardt R, *et al.* Kras mutation analysis of fine needle aspirate under EUS guidance facilitates risk stratification of patients with pancreatic mass. *J Clin Gastroenterol* 2007;41:906-10.
20. Pellise M, Castells A, Gines A, *et al*. Clinical usefulness of KRAS mutational analysis in the diagnosis of pancreatic adenocarcinoma by means of endosonography-guided fine-needle aspiration biopsy. *Aliment Pharmacol Ther* 2003;17:1299-307.
21. Iglesias-Garcia J, Lariño-Noia J, Domínguez-Muñoz JE. When to puncture, when not to puncture: Pancreatic masses. *Endosc Ultrasound* 2014;3:91-7.
22. Voss M, Hammel P, Molas G, *et al.* Value of endoscopic ultrasound guided fine needle aspiration biopsy in the diagnosis of solid pancreatic masses. *Gut* 2000;46:244-9.
23. Iglesias-Garcia J, Dominguez-Munoz E, Lozano-Leon A, *et al.* Impact of endoscopic ultrasound-guided fine needle biopsy for diagnosis of pancreatic masses. *World J Gastroenterol* 2007;13:289-93.
24. Papanikolaou IS, Adler A, Wegener K, *et al.* Prospective pilot evaluation of a new needle prototype for endoscopic ultrasonography-guided fine-needle aspiration: Comparison of cytology and histology yield. *Eur J Gastroenterol Hepatol* 2008;20:342-8.
25. Hewitt MJ, McPhail MJ, Possamai L, *et al.* EUS-guided FNA for diagnosis of solid pancreatic neoplasms: A meta-analysis. *Gastrointest Endosc* 2012;75:319-31.
26. Ngamruengphong S, Swanson KM, Shah ND, *et al*. Preoperative endoscopic ultrasound-guided fine needle aspiration does not impair survival of patients with resected pancreatic cancer. *Gut* 2015;64:1105-10.
27. Beane JD, House MG, Coté GA, *et al.* Outcomes after preoperative endoscopic ultrasonography and biopsy in patients undergoing distal pancreatectomy. *Surgery* 2011;150:844-53.
28. Kim EY. Role of repeated endoscopic ultrasound-guided fine needle aspiration for inconclusive initial cytology result. *Clin Endosc* 2013;46:540-2.
29. Téllez-Ávila FI, Martínez-Lozano JA, Rosales-Salinas A, *et al.* Repeat endoscopic ultrasound fine needle aspiration after a first negative procedure is useful in pancreatic lesions. *Endosc Ultrasound* 2016;5:258-62.
30. Mitchell RA, Stanger D, Shuster C, *et al*. Repeat endoscopic ultrasound-guided fine-needle aspiration in patients with suspected pancreatic cancer: Diagnostic yield and associated change in access to appropriate care. *Can J Gastroenterol Hepatol* 2016;2016:7678403.
31. Morishima T, Kawashima H, Ohno E, *et al.* Prospective multicenter study on the usefulness of EUS-guided FNA biopsy for the diagnosis of autoimmune pancreatitis. *Gastrointest Endosc* 2016;84:241-8.
32. Kanno A, Ishida K, Hamada S, *et al.* Diagnosis of autoimmune pancreatitis by EUS-FNA by using a 22-gauge needle based on the International Consensus Diagnostic Criteria. *Gastrointest Endosc* 2012;76:594-602.
33. Iwashita T, Yasuda I, Doi S, *et al*. Use of samples from endoscopic ultrasound-guided 19-gauge fine-needle aspiration in diagnosis of autoimmune pancreatitis. *Clin Gastroenterol Hepatol* 2012;10:316-22.
34. Lennon AM, Wolfgang C. Cystic neoplasms of the pancreas. *J Gastrointestinal Surg* 2013;17:645-53.
35. Jones MJ, Buchanan AS, Neal CP, *et al*. Imaging of indeterminate pancreatic cystic lesions: A systematic review. *Pancreatology* 2013;13:436-42.
36. Nakai Y, Isayama H, Itoi T, *et al.* Role of endoscopic ultrasonography in pancreatic cystic neoplasms: Where do we stand and where will we go? *Dig Endos* 2014;26:135-43.
37. Thornton GD, McPhail MJ, Nayagam S, *et al*. Endoscopic ultrasound guided fine needle aspiration for the diagnosis of pancreatic cystic neoplasms: A meta-analysis. *Pancreatology* 2013;13:48-57.
38. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, *et al.* Diagnosis of pancreatic cystic neoplasms: A report of the cooperative pancreatic cyst study. *Gastroenterology* 2004;126:1330-6.
39. Shirley LA, Walker J, Krishna S, *et al.* Routine cyst fluid cytology is not indicated in the evaluation of pancreatic cystic lesions. *J Gastrointest Surg* 2016;20:1581-5.
40. Tournoy KG, Praet MM, Van Maele G, *et al*. Esophageal endoscopic ultrasound with fine-needle aspiration with an on-site cytopathologist: High accuracy for the diagnosis of mediastinal lymphadenopathy. *Chest* 2005;128:3004-9.
41. Bhutani MS, Hawes RH, Hoffman BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration for diagnosis of malignant lymph node invasion. *Gastrointest Endosc* 1997;45:474-9.
42. Fritscher-Ravens A, Soehendra N, Schirrow L, *et al*. Role of transesophageal endosonography-guided fine-needle aspiration in the diagnosis of lung cancer. *Chest* 2000;117:339-45.
43. Keswani RN, Early DS, Edmundowicz SA, *et al.* Routine positron emission tomography does not alter nodal staging in patients undergoing EUS-guided FNA for esophageal cancer. *Gastrointest Endosc* 2009;69:1210-7.
44. Marsman WA, Brink MA, Bergman JJ, *et al.* Potential impact of EUS-FNA staging of proximal lymph nodes in patients with distal esophageal carcinoma. *Endoscopy* 2006;38:825-9.
45. Eloubeidi MA, Wallace MB, Reed CE, *et al*. The utility of EUS and EUS-guided fine needle aspiration in detecting celiac lymph node metastasis in patients with esophageal cancer: A single-center experience. *Gastrointest Endosc* 2001;54:714-9.
46. Cerfolio RJ, Bryant AS, Ohja B, *et al*. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. *J Thorac Cardiovasc Surg* 2005;129:1232-41.
47. Anderegg MC, de Groof EJ, Gisbertz SS, *et al*. 18F-FDG PET-CT after neoadjuvant chemoradiotherapy in esophageal cancer patients to optimize surgical decision making. *PLoS One* 2015;10:e0133690.
48. Araujo J, Bories E, Caillol F, *et al*. Distant lymph node metastases in gastroesophageal junction adenocarcinoma: Impact of endoscopic ultrasound-guided fine-needle aspiration. *Endosc Ultrasound* 2013;2:148-52.
49. Hassan H, Vilmann P, Sharma V. Impact of EUS-guided FNA on management of gastric carcinoma. *Gastrointest Endosc* 2010;71:500-4.
50. Harewood GC, Wiersema MJ, Nelson H, *et al.* A prospective, blinded assessment of the impact of preoperative staging on the management of rectal cancer. *Gastroenterology* 2002;123:24-32.
51. Gleeson FC, Clain JE, Rajan E, *et al*. EUS-FNA assessment of extramesenteric lymph node status in primary rectal cancer. *Gastrointest Endosc* 2011;74:897-905.
52. DeWitt J, Alsatie M, LeBlanc J, *et al*. Endoscopic ultrasound-guided fine-needle aspiration of left adrenal gland masses. *Endoscopy* 2007;39:65-71.
53. Chang KJ, Erickson RA, Nguyen P. Endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration of the left adrenal gland. *Gastrointest Endosc* 1996;44:568-72.
54. Uemura S, Yasuda I, Kato T, *et al*. Preoperative routine evaluation of bilateral adrenal glands by endoscopic ultrasound and fine-needle aspiration in patients with potentially resectable lung cancer. *Endoscopy* 2013;45:195-201.
55. Onda S, Ogura T, Kurisu Y, *et al.* EUS-guided FNA for biliary disease as first-line modality to obtain histological evidence. *Therap Adv Gastroenterol* 2016;9:302-12.
56. Tummala P, Munigala S, Eloubeidi MA, *et al*. Patients with obstructive jaundice and biliary stricture ± mass lesion on imaging: Prevalence of malignancy and potential role of EUS-FNA. *J Clin Gastroenterol* 2013;47:532-7.
57. Weilert F, Bhat YM, Binmoeller KF, *et al.* EUS-FNA is superior to ERCP-based tissue sampling in suspected malignant biliary obstruction: Results of a prospective, single-blind, comparative study. *Gastrointest Endosc* 2014;80:97-104.
58. DeWitt J, Misra VL, Leblanc JK, *et al.* EUS-guided FNA of proximal biliary strictures after negative ERCP brush cytology results. *Gastrointest Endosc* 2006;64:325-33.
59. Puri R, Vilmann P, Saftoiu A, *et al.* Randomized controlled trial of

endoscopic ultrasound-guided fine-needle sampling with or without suction for better cytological diagnosis. *Scand J Gastroenterol* 2009;44:499-504.
60. Lee JK, Choi JH, Lee KH, *et al.* A prospective, comparative trial to optimize sampling techniques in EUS-guided FNA of solid pancreatic masses. *Gastrointest Endosc* 2013;77:745-51.
61. Kudo T, Kawakami H, Hayashi T, *et al.* High and low negative pressure suction techniques in EUS-guided fine-needle tissue acquisition by using 25-gauge needles: A multicenter, prospective, randomized, controlled trial. *Gastrointest Endosc* 2014;80:1030-7.e1.
62. Chen JY, Ding QY, Lv Y, *et al.* Slow-pull and different conventional suction techniques in endoscopic ultrasound-guided fine-needle aspiration of pancreatic solid lesions using 22-gauge needles. *World J Gastroenterol* 2016;22:8790-7.
63. Matsubayashi H, Matsui T, Yabuuchi Y, *et al.* Endoscopic ultrasonography guided-fine needle aspiration for the diagnosis of solid pancreaticobiliary lesions: Clinical aspects to improve the diagnosis. *World J Gastroenterol* 2016;22:628-40.
64. Attam R, Arain MA, Bloechl SJ, *et al.* Wet suction technique (WEST): A novel way to enhance the quality of EUS-FNA aspirate. Results of a prospective, single-blind, randomized, controlled trial using a 22-gauge needle for EUS-FNA of solid lesions. *Gastrointest Endosc* 2015;81:1401-7.
65. Wallace MB, Kennedy T, Durkalski V, *et al.* Randomized controlled trial of EUS-guided fine needle aspiration techniques for the detection of malignant lymphadenopathy. *Gastrointest Endosc* 2001;54:441-7.
66. Abe Y, Kawakami H, Oba K, *et al.* Effect of a stylet on a histological specimen in EUS-guided fine-needle tissue acquisition by using 22-gauge needles: A multicenter, prospective, randomized, controlled trial. *Gastrointest Endosc* 2015;82:837-44.e1.
67. Rastogi A, Wani S, Gupta N, *et al.* A prospective, single-blind, randomized, controlled trial of EUS-guided FNA with and without a stylet. *Gastrointest Endosc* 2011;74:58-64.
68. Wani S, Early D, Kunkel J, *et al.* Diagnostic yield of malignancy during EUS-guided FNA of solid lesions with and without a stylet: A prospective, single blind, randomized, controlled trial. *Gastrointest Endosc* 2012;76:328-35.
69. Nguyen YP, Maple JT, Zhang Q, *et al.* Reliability of gross visual assessment of specimen adequacy during EUS-guided FNA of pancreatic masses. *Gastrointest Endosc* 2009;69:1264-70.
70. Eloubeidi MA, Tamhane A, Jhala N, *et al.* Agreement between rapid and final cytologic interpretations of EUS-guided FNA specimens: Implications for the endosonographer and patient management. *Am J Gastroenterol* 2006;101:2841-7.
71. Iglesias-Garcia J, Dominguez-Munoz JE, Abdulkader I, *et al.* Influence of on-site cytopathology evaluation on the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of solid pancreatic masses. *Am J Gastroenterol* 2011;106:1705-10.
72. Kong F, Zhu J, Kong X, *et al.* Rapid on-site evaluation does not improve endoscopic ultrasound-guided fine needle aspiration adequacy in pancreatic masses: A meta-analysis and systematic review. *PLoS One* 2016;11:e0163056.
73. Wyse J, Rubino M, Iglesias Garcia J, *et al.* Onsite evaluation of endoscopic ultrasound fine needle aspiration: The endosonographer, the cytotechnologist and the cytopathologist. *Rev Esp Enferm Dig* 2017;109. doi: 10.17235/reed.2017.4473/2016. [Epub ahead of print].
74. Iglesias-Garcia J, Lariño-Noia J, Abdulkader I, *et al.* Rapid on-site evaluation of endoscopic-ultrasound-guided fine-needle aspiration diagnosis of pancreatic masses. *World J Gastroenterol* 2014;20:9451-7.
75. Petrone MC, Arcidiacono PG. Basic technique in endoscopic ultrasound-guided fine needle aspiration for solid lesions: How many passes? *Endosc Ultrasound* 2014;3:22-7.
76. Varadarajulu S, Jhala NC. Cytopathology: A dying art or something that a gastroenterologist should know? *Gastrointest Endosc* 2012;76:397-9.
77. Lim LG, Lakhtakia S, Ang TL, *et al.* Factors determining diagnostic yield of endoscopic ultrasound guided fine-needle aspiration for pancreatic cystic lesions: A multicentre Asian study. *Dig Dis Sci* 2013;58:1751-7.
78. Wang KX, Ben QW, Jin ZD, *et al.* Assessment of morbidity and mortality associated with EUS-guided FNA: A systematic review. *Gastrointest Endosc* 2011;73:283-90.
79. Tarantino I, Fabbri C, Di Mitri R, *et al.* Complications of endoscopic ultrasound fine needle aspiration on pancreatic cystic lesions: Final results from a large prospective multicenter study. *Dig Liver Dis* 2014;46:41-4.
80. Hamada T, Yasunaga H, Nakai Y, *et al.* Severe bleeding and perforation are rare complications of endoscopic ultrasound-guided fine needle aspiration for pancreatic masses: An analysis of 3,090 patients from 212 hospitals. *Gut Liver* 2014;8:215-8.
81. Eloubeidi MA, Tamhane A. EUS-guided FNA of solid pancreatic masses: A learning curve with 300 consecutive procedures. *Gastrointest Endosc* 2005;61:700-8.
82. Inoue T, Okumura F, Sano H, *et al.* Bleeding risk of endoscopic ultrasound-guided fine-needle aspiration in patients undergoing antithrombotic therapy. *Dig Endosc* 2017;29:91-6.
83. Trindade AJ, Hirten R, Slattery E, *et al.* Endoscopic ultrasound-guided fine-needle aspiration of solid lesions on clopidogrel may not be a high-risk procedure for bleeding: A case series. *Digestive Endosc* 2016;28:216-9.
84. Kien-Fong Vu C, Chang F, Doig L, *et al.* A prospective control study of the safety and cellular yield of EUS-guided FNA or Trucut biopsy in patients taking aspirin, nonsteroidal anti-inflammatory drugs, or prophylactic low molecular weight heparin. *Gastrointest Endosc* 2006;63:808-13.
85. Paquin SC, Gariépy G, Lepanto L, *et al.* A first report of tumor seeding because of EUS-guided FNA of a pancreatic adenocarcinoma. *Gastrointest Endosc* 2005;61:610-1.
86. Chong A, Venugopal K, Segarajasingam D, *et al.* Tumor seeding after EUS-guided FNA of pancreatic tail neoplasia. *Gastrointest Endosc* 2011;74:933-5.
87. Ahmed K, Sussman JJ, Wang J, *et al.* A case of EUS-guided FNA-related pancreatic cancer metastasis to the stomach. *Gastrointest Endosc* 2011;74:231-3.
88. Micames C, Jowell PS, White R, *et al.* Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA *vs.* percutaneous FNA. *Gastrointest Endosc* 2003;58:690-5.
89. Ngamruengphong S, Xu C, Woodward TA, *et al.* Risk of gastric or peritoneal recurrence, and long-term outcomes, following pancreatic cancer resection with preoperative endosonographically guided fine needle aspiration. *Endoscopy* 2013;45:619-26.
90. Wiersema MJ, Vilmann P, Giovannini M, *et al.* Endosonography-guided fine-needle aspiration biopsy: Diagnostic accuracy and complication assessment. *Gastroenterology* 1997;112:1087-95.
91. Al-Haddad M, Wallace MB, Woodward TA, *et al.* The safety of fine-needle aspiration guided by endoscopic ultrasound: A prospective study. *Endoscopy* 2008l; 40:204-8.
92. Williams DB, Sahai AV, Aabakken L, *et al.* Endoscopic ultrasound guided fine needle aspiration biopsy: A large single centre experience. *Gut* 1999;44:720-6.
93. Mahady SE, Moss A, Kwan V. EUS-guided drainage of a mediastinal collection complicating FNA of a bronchogenic cyst. *Gastrointest Endosc* 2011;73:1306-8.
94. Annema JT, Veseliç M, Versteegh MI, *et al.* Mediastinitis caused by EUS-FNA of a bronchogenic cyst. *Endoscopy* 2003;35:791-3.
95. Wildi SM, Hoda RS, Fickling W, *et al.* Diagnosis of benign cysts of the mediastinum: The role and risks of EUS and FNA. *Gastrointest Endosc* 2003;58:362-8.
96. Bohle W, Zoller WG. Mediastinitis after EUS-FNA in a patient with sarcoidosis – Case report with endosonographic features and review of the literature. *Z Gastroenterol* 2014;52:1171-4.
97. Di Matteo F, Shimpi L, Gabbrielli A, *et al.* Same-day endoscopic retrograde cholangiopancreatography after transduodenal endoscopic ultrasound-guided needle aspiration: Do we need to be cautious? *Endoscopy* 2006;38:1149-51.
98. Kawakami H, Kuwatani M, Kubo K, *et al.* Huge hemothorax caused by endoscopic ultrasound-guided fine-needle aspiration of a submucosal tumor of the gastric fornix. *Endoscopy* 2015;47 Suppl 1 UCTN:E69-70.
99. Attwell A, Sams S, Fukami N. Induction of acute ectopic pancreatitis by endoscopic ultrasound with fine-needle aspiration. *Clin Gastroenterol Hepatol* 2014;12:1196-8.