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Indications, results, and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline – Updated January 2017

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Appendix e1
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MAIN RECOMMENDATIONS

For pancreatic solid lesions, ESGE recommends performing endoscopic ultrasound (EUS)-guided sampling as first-line procedure when a pathological diagnosis is required. Alternatively, percutaneous sampling may be considered in metastatic disease.
Strong recommendation, moderate quality evidence.

In the case of negative or inconclusive results and a high degree of suspicion of malignant disease, ESGE suggests re-evaluating the pathology slides, repeating EUS-guided sampling, or surgery.
Weak recommendation, low quality evidence.

In patients with chronic pancreatitis associated with a pancreatic mass, EUS-guided sampling results that do not confirm cancer should be interpreted with caution.
Strong recommendation, low quality evidence.

For pancreatic cystic lesions (PCLs), ESGE recommends EUS-guided sampling for biochemical analyses plus cytopathological examination if a precise diagnosis may change patient management, except for lesions ≤ 10 mm in diameter with no high risk stigmata. If the volume of PCL aspirate is small, it is recommended that carcinoembryonic antigen (CEA) level determination be done as the first analysis.
Strong recommendation, low quality evidence.

For esophageal cancer, ESGE suggests performing EUS-guided sampling for the assessment of regional lymph nodes (LNs) in T1 (and, depending on local treatment policy, T2) adenocarcinoma and of lesions suspicious for metastasis such as distant LNs, left liver lobe lesions, and suspected peritoneal carcinomatosis.
Weak recommendation, low quality evidence.

For lymphadenopathy of unknown origin, ESGE recommends performing EUS-guided (or alternatively endobronchial ultrasound [EBUS]-guided) sampling if the pathological result is likely to affect patient management and no superficial lymphadenopathy is easily accessible.
Strong recommendation, moderate quality evidence.

In the case of solid liver masses suspicious for metastasis, ESGE suggests performing EUS-guided sampling if the pathological result is likely to affect patient management, and (i) the lesion is poorly accessible/not detected at percutaneous imaging, or (ii) a sample obtained via the percutaneous route repeatedly yielded an inconclusive result.
Weak recommendation, low quality evidence.

This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). It addresses the indications, results, and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology. A separate Technical Guideline describes the general technique of EUS-guided sampling, particular techniques to maximize the diagnostic yield depending on the nature of the target lesion, and sample processing. The target readership for the Clinical Guideline mostly includes gastroenterologists, oncologists, internists, and surgeons while the Technical Guideline should be most useful to endoscopists who perform EUS-guided sampling.

ABBREVIATIONS

CEA	carcinoembryonic antigen
CI	confidence interval
CT	computed tomography
EBUS	endobronchial ultrasound/ultrasonography
ERCP	endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
EUS	endoscopic ultrasonography/ultrasound
GI	gastrointestinal
GIST	gastrointestinal stromal tumor
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
IPMN	intraductal papillary mucinous neoplasm
LN	lymph node
MRI	magnetic resonance imaging
PCL	pancreatic cystic lesion
RCT	randomized controlled trial
SEL	subepithelial lesion

1. Introduction

The Clinical Guideline on endoscopic ultrasound (EUS)-guided sampling published in 2011 by the European Society of Gastrointestinal Endoscopy (ESGE) described the role of this technique in patient management and made recommendations on circumstances that warrant its use [1]. New evidence that has become available since then is discussed in the present update and new recommendations are issued. For the general technique of EUS-guided sampling, particular techniques to obtain the highest yield possible depending on the lesion sampled, and sample processing, readers are referred to the associated ESGE Technical Guideline.

2. Methods

The ESGE commissioned this Guideline and appointed a guideline leader (J.M.D.) who invited the listed authors to participate in the project development. The key questions were prepared by the coordinating team (J.M.D., M.P., P.H.D., C.H.) and then approved by the other members. The coordinating team formed task force subgroups, each with its own leader, who

were assigned key questions (see ▶ **Appendix e1**, available online-only in Supplementary material).

Each task force performed a systematic literature search to prepare evidence-based and well-balanced statements on their assigned key questions. The literature search was performed in MEDLINE to identify new publications since February 2011, focusing on meta-analyses and fully published prospective studies, particularly randomized controlled trials (RCTs). Retrospective analyses and pilot studies were also included if they addressed topics not covered in the prospective studies. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was adopted to define the strength of recommendation and the quality of evidence [2, 3]. Each task force proposed statements on their assigned key questions which were discussed during a meeting in Athens, June 2016. Literature searches were re-run in August 2016. This time-point should be the starting point in the search for new evidence for future updates to this Guideline. In September 2016 a draft prepared by J.M.D. and the task force leaders was sent to all group members for review. The draft was also reviewed by two external reviewers and two members of the ESGE Governing Board, and sent for further comments to the ESGE National Societies and Individual Members. After agreement on a final version, the manuscript was submitted to the journal *Endoscopy* for publication. All authors agreed on the final revised version.

This Guideline was issued in 2017 and will be considered for review in 2021, or sooner if new and relevant evidence becomes available. Any updates to the Guideline in the interim period will be noted on the ESGE website: http://www.esge.com/ esge-guidelines.html.

3. Pancreatic solid masses, cholangiocarcinoma, and ampullary lesions

3.1 Pancreatic solid masses

RECOMMENDATION

For pancreatic solid lesions, ESGE recommends performing EUS-guided sampling as first-line procedure when a pathological diagnosis is required. Alternatively, percutaneous sampling may be considered in metastatic disease.
Strong recommendation, moderate quality evidence.
In the case of negative or inconclusive results and a high degree of suspicion of malignant disease, ESGE suggests re-evaluating the pathology slides, repeating EUS-guided sampling, or surgery.
Weak recommendation, low quality evidence.

RECOMMENDATION

In patients with chronic pancreatitis associated with a pancreatic mass, EUS-guided sampling results that do not confirm cancer should be interpreted with caution.
Strong recommendation, low quality evidence.

Solid pancreatic lesions mostly include ductal adenocarcinoma but also lymphoma, neuroendocrine tumors, metastases, solid pseudopapillary tumor, and benign conditions such as autoimmune pancreatitis and focal pancreatitis.

EUS-guided sampling is increasingly applied for the diagnosis of pancreatic solid masses: a recent nationwide US study found that, between 2001 and 2009, the proportion of patients with curative-intent surgery who underwent EUS-guided sampling increased from 10 % to 45 % [4]; nevertheless, its use significantly varies between medical specialties [5]. This Guideline cannot answer the question of whether a pathological diagnosis is required in a specific patient, as multiple patient-related factors affect the decision to obtain a pathological diagnosis [6]. As a guide, two studies found that EUS-guided sampling has a significant impact on patient management:

- i) A retrospective study (100 patients) found that it had a major impact on the management of 49 patients, by permitting a decision to proceed with chemotherapy, surgery, and surveillance in 36, 5, and 8 patients, respectively [7]. Minor impact (confirmation of surgical indication) and negative/no impact were reported in 13 and 28 patients, respectively;
- ii) A prospective study (207 patients) found positive and negative impacts on the management of 136 (66 %) and 2 (1 %) patients, respectively [8].

EUS-guided sampling has become the method of choice for the pathological diagnosis of solid pancreatic masses as it is very accurate (sensitivity and specificity, 85 % – 89 % and 96 % – 99 %, respectively, according to three meta-analyses) [9 – 11], and it is an advanced staging method that allows the sampling of locoregional and distant lymph nodes (LNs), liver lesions, and small amounts of ascites undetected by other imaging techniques [12].

A single RCT (84 patients) has compared sampling guided by EUS vs. computed tomography (CT) or ultrasound: EUS-guided sampling had a higher sensitivity (84 % vs. 62 %) and diagnostic accuracy (89 % vs. 72 %) but the differences were not significant [13]. The authors suggested that this was related to a failure to meet target enrollment. Five other series [14 – 18], either prospective (n = 1) or retrospective (n = 4), compared access routes for sampling, and only the largest study found a significant difference in favor of EUS compared to CT/ultrasound-guided sampling when analyzing the diagnostic accuracy for lesions < 3 cm [18].

Regarding complications, no difference was seen with respect to directly procedure-related matters such as pancreatitis, infection or bleeding. Data on long-term complications such as tumor seeding are sparse and not congruent: compared with percutaneous sampling, EUS-guided sampling harbored a lower risk of seeding (2 % vs. 16 %, approximately 3 months after sampling) in a retrospective study (89 patients) [19] while other studies, that did not routinely assess this outcome, reported no significant differences between the two access routes [16, 17]. Tumor seeding related to EUS-guided sampling is discussed in more detail in section 10.2.

With respect to cost, a study that used a decision analysis model suggested that EUS-guided sampling was less costly than percutaneous procedures, mostly because patients were assumed to be hospitalized for 24 hours following CT/ultrasound-guided sampling while EUS-guided sampling was computed as an ambulatory procedure [20]. Sensitivity analysis showed that CT/ultrasound-guided sampling total costs would need to be less than 650 US dollars for this approach to be preferred over EUS-guided sampling.

Repeat EUS-guided sampling in the case of failure or inconclusive pathological result

A retrospective study (4502 cases) found that indeterminate pathological diagnoses were made in 14 % of the cases [21]; these consisted of the "atypical" and "suspicious for malignancy" categories (one third and two thirds of cases, respectively), and these carried a malignancy risk of 79 % and 96 %, respectively. Therefore, the authors recommended classifying results "suspicious for malignancy" as malignant, to optimize the diagnostic performance of EUS-guided sampling. These results were in line with those of a meta-analysis (23 studies, 3566 cases) that found "atypical" (excluding "suspicious") results reported in 5 % of cases and carrying a malignancy risk of 58 % (range 0 – 100 %) [22]. The new terminology for pancreatobiliary cytology, including that of pancreatic cystic-appearing lesions [23], will be further discussed in the Technical part of this Guideline; it allowed reclassification of all specimens primarily classified as "atypical" and half of those primarily classified as "suspicious" into the new category "neoplastic: other" in a retrospective study (155 patients) [24].

Another useful option for increasing diagnostic accuracy is to test inconclusive samples for *KRAS* mutation: this allows reduction of the false-negative rate by approximately 50 % with a false-positive rate of approximately 10 % according to a meta-analysis (8 studies, 931 patients) [25].

Apart from sample re-evaluation, repeat EUS-guided sampling is another option that has been investigated mostly for pancreatic masses (▶ **Table 1**) [26 – 33]. Repeat EUS-guided sampling was performed at the same institution except in two studies [26, 30]; the sensitivity for diagnosing malignancy ranged from 35 % to 100 % and overall diagnostic accuracy was 78 %. Although this can be considered a rather high success rate, criteria used for assessing sensitivity and accuracy differed between studies and the selection bias for these studies is a concern. Other studies that reported on repeat EUS-guided sampling are not listed in ▶ **Table 1** because they did not allow calculation of diagnostic accuracy [34 – 36].

Finally, two retrospective studies found that, for indeterminate cytopathological diagnoses, several clinical conditions (e. g., weight loss and bile duct obstruction) were associated with a final diagnosis of malignancy. This led the authors to recommend surgery in patients with "suspicious" cytopathology and those clinical predictors if the mass was resectable, and repeat tissue sampling in patients with unresectable masses [32, 34].

EUS-guided sampling in chronic pancreatitis

In the presence of chronic pancreatitis, the sensitivity of EUS-guided sampling for the diagnosis of malignancy is significantly lower according to a retrospective and a prospective study (54 % and 74 % vs. 89 % and 91 % in the presence vs. the absence of chronic pancreatitis, respectively) [37, 38].

For the differential diagnosis between pancreatic cancer and inflammatory masses, commonly used options include EUS elastography, contrast-enhanced harmonic EUS, and repeat sampling. EUS elastography presents pooled sensitivities and specificities of 95 % – 99 % and 67 % – 76 %, respectively, according to four meta-analyses [39 – 42]. Contrast-enhanced harmonic EUS has yielded a sensitivity and specificity of 88 % and 93 %, respectively, when used for real-time quantitative assessment in a multicenter prospective trial (167 patients with chronic pancreatitis or pancreatic carcinoma) [43]. Although hypovascular lesions are strong indicators of malignancy, two recent prospective studies that compared EUS-guided sampling combined with contrast-enhanced harmonic EUS vs. EUS-guided sampling alone found no differences in accuracy for the diagnosis of solid pancreatic masses [44, 45].

In chronic pancreatitis patients with suspicion of malignancy and severe pain as main complaint, resection may also be proposed.

3.2 Biliary strictures including cholangiocarcinoma

RECOMMENDATION

ESGE suggests EUS-guided sampling for the diagnosis of indeterminate biliary strictures, either as an alternative to or in combination with endoluminal biliary sampling.
Weak recommendation, moderate quality evidence.

Two meta-analyses (6 and 20 studies, 196 and 957 patients) found that the pooled sensitivities of EUS-guided sampling for the diagnosis of malignant biliary strictures were 66 % and 80 %, and the pooled specificities were 100 % and 97 %; a higher sensitivity was reported in patients with a mass detected at EUS [46, 47]. Recent studies not included in the meta-analyses were in line with these results [48, 49].

A prospective study found that, compared with ERCP-guided sampling, the diagnostic yield of EUS-guided sampling was higher in patients with a pancreatic mass (sensitivity 100 % vs. 38 %) and similar in patients with a biliary mass (79 % sensitivity for both) or an indeterminate biliary stricture (sensitivity 80 % vs. 67 %) [50].

EUS-guided biliary sampling appears to be safe, with a pooled rate of adverse events of 1 % in the most recent meta-analysis [47]. The main concern is potential tumor seeding that has led some authors to discourage EUS-guided sampling of a hilar mass in locations where liver transplantation is offered for perihilar cholangiocarcinoma (but not sampling of distal lesions as the puncture tract is resected during surgery) [51]. According to these authors, EUS-guided sampling of LNs and other extrahepatic sites remains a very important tool for the staging of perihilar cholangiocarcinoma: in a retrospective study (47

▶ **Table 1** Value of repeat endoscopic ultrasound (EUS)-guided sampling.

First author, year	Patients, n	Study design	Indication for repeat EUS-guided sampling	Pancreas lesion (n)	Repeat EUS-guided samplings, n	Sensitivity for malignancy (n/n)	Diagnostic accuracy (n/n)
DeWitt, 2008 [26]	17	Retrospective cohort study	Benign or inconclusive diagnosis	100 % (17)	1	100 % (6/6)	59 % (10/17)
Eloubeidi, 2008 [27]	24	Retrospective cohort study	Inconclusive diagnosis	100 % (24)	1 – 3	73 % (11/15)	83 % (20/24)
Nicaud, 2010 [28]	28	Retrospective cohort study	Inconclusive diagnosis	100 % (28)	1	35 % (6/17)	61 % (17/28)
Prachayakul, 2012 [29]	15	Retrospective cohort study	Inconclusive diagnosis	53 % (8)	NR	89 % (8/9)	87 % (13/15)
Suzuki, 2013 [30]	84	Retrospective cohort study	Inconclusive diagnosis	100 % (84)	1	96 % (69/72)	96 % (77/80)
Téllez-Ávila, 2016 [31]	34	Retrospective cohort study	Benign or atypical diagnosis	100 % (34)	1	62 % (13/21)	59 % (20/34)
Alston, 2016 [32]	37	Retrospective cohort study	Inconclusive diagnosis	100 % (37)	NR	92 % (34/37)	NR
Zhang, 2016 [33]	43	Retrospective cohort study	Inconclusive diagnosis	100 % (43)	1 – 2	62 % (NR)	65 % (28/43)

NR, not reported

patients), they found, using EUS-guided sampling, malignant LNs contraindicating liver transplantation in 8 patients (17 %) [52].

3.3 Ampullary lesions

RECOMMENDATION
ESGE did not find sufficient evidence to recommend for or against EUS-guided sampling for the diagnosis of ampullary lesions.

The optimal management of early ampullary tumors is controversial [53, 54]. A single retrospective study (10 patients) reported a 100 % accuracy of EUS-guided sampling for distinguishing papillitis from ampullary adenocarcinoma but no case of adenoma was included in that study [55]. As malignant transformation of adenomas is frequently focal [53, 54], this is a serious concern. Another study included EUS-guided sampling of the ampulla of Vater but it did not report results specific to this technique [56].

4. Pancreatic cystic lesions

RECOMMENDATION
For pancreatic cystic lesions (PCLs), ESGE recommends EUS-guided sampling for biochemical analyses plus cytopathological examination if a precise diagnosis may change patient management, except for lesions ≤ 10 mm in diameter with no high risk stigmata. If the volume of PCL aspirate is small, it is recommended that carcinoembryonic antigen (CEA) level determination be done as the first analysis.
Strong recommendation, low quality evidence.

RECOMMENDATION
ESGE suggests performing direct wall puncture and/or *KRAS* mutation analysis in selected cases, for example if the PCL aspirate is too scant for assessment of CEA concentration. ESGE did not find sufficient evidence to recommend the analysis of other biomarkers or EUS-guided confocal laser endomicroscopy for PCLs outside of clinical trials.
Weak recommendation, low quality evidence.

PCLs are increasingly diagnosed because of the widespread use of cross-sectional imaging; in 80 % of cases, they are smaller than 10 mm [57, 58]. Incidental PCLs are associated with a 40 % increase in mortality for patients younger than 65 years and an overall increased risk of pancreatic adenocarcinoma [59]. PCLs mostly consist of pancreatic pseudocysts and epithelial cystic neoplasms, including serous cystadenomas, intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms. The two latter present a potential for malignant change and are often designated as mucinous cysts [60]. Determining whether a PCL is mucinous vs. nonmucinous and benign vs. malignant are two key clinical questions for appropriate patient management.

Samples obtained under EUS guidance may help in answering these questions by macroscopic inspection, cytopathological examination, and biochemical analyses:

- At the macroscopic level, the “string sign” is the most informative: it consists of placing a drop of PCL aspirate between the thumb and index finger and stretching it; a string length > 3.5 mm indicates a mucinous cyst [61]. In a prospective study on 98 histopathologically proven pancreatic cysts, the string sign was highly specific for diagnosis of mucinous pancreatic cysts; in particular, when string sign results and CEA concentration (≥ 200 ng/mL) were combined, diagnostic accuracy improved from 74 % and 83 %, respectively, to 89 % [62].
- Cytopathological examination of PCL aspirate was found to present a sensitivity and specificity of 54 % and 93 %, respectively, for differentiating mucinous from nonmucinous cysts in a meta-analysis (18 studies, 1438 patients) [63]. Importantly, mucin or mucin-producing cells of the gastrointestinal (GI) wall should not be misinterpreted as the mucin or epithelial cells of a mucinous cyst [64]. In mucinous cysts, the cytopathological diagnosis (together with EUS imaging features) serves to triage patients for surgery as it is strongly correlated with the risk of malignancy [60]. For example, in a retrospective study (127 resected mucinous cysts), the absolute risk of malignancy associated with the atypical, suspicious, and positive categories proposed by the Papanicolaou Society of Cytopathology guidelines was 64 %, 80 %, and 100 %, respectively [65].
- Among biochemical analyses performed on PCL aspirate, the determination of CEA is the most useful to differentiate mucinous from nonmucinous cysts: in the abovementioned meta-analysis, the sensitivity and specificity of CEA concentration at a cutoff value of 192 ng/mL were 63 % and 88 %, respectively [63]. The cutoff value is mostly based on studies that included mucinous cysts with high risk stigmata or worrisome features, as resected PCLs were used as the gold standard. Therefore, lower cutoff values have been proposed to increase test accuracy for the diagnosis of mucinous cysts [66], in particular in the most frequent clinical setting where surgical resection is not performed [67]. CEA level is not used to discriminate malignant from benign PCLs. The concentration of amylase may also be useful because a value < 250 U/L virtually excludes a pancreatic pseudocyst but a value > 250 U/L is frequently encountered in IPMNs [68].

A limitation of the abovementioned tests is that they are not feasible in a significant proportion of cases: in a prospective study (143 patients), material sufficient to perform a cytopathological and a biochemical analysis was obtained in only 31 % and 49 % of cases, respectively [69]. In another prospective study (370 patients) [70], EUS-guided aspiration was unsuccessful or retrieved enough liquid for a single test in 10 % and

38 % of the patients, respectively, with a strong correlation between the number of feasible tests and the PCL diameter. In cysts of 1 cm, it was possible to test at least one variable in 75 % of cases. In another report, a size of 1.5 cm was the minimum required to obtain fluid for at least one analysis [68] and this cutoff of ≥ 1.5 cm was chosen by the Italian Consensus Guidelines for EUS-guided sampling [71].

Specific protocols have been developed that allowed performance of three tests (pathological examination, CEA determination, and *KRAS* mutation analysis) on samples smaller than 1 mL in 80 % of cases [72]. Small volumes of PCL aspirate may also be tested for biomarkers including DNA-based biomarkers (mainly *KRAS*/*GNAS* mutation analyses, allelic loss, and concentration of DNA) and proteomic/metabolomic-derived biomarkers [73]. *KRAS* mutation analysis has been the most studied: in a meta-analysis (8 studies, 428 patients) the sensitivity and specificity of *KRAS* mutation were 47 % and 98 %, respectively, for distinguishing mucinous from nonmucinous PCLs, and 59 % and 78 %, respectively, for differentiating malignant from benign cysts [74]. Another meta-analysis (12 studies, 362 patients) found that, by adding *KRAS* mutation analysis to cytopathological examination, the sensitivity for distinguishing mucinous from nonmucinous PCLs increased from 41 % to 71 %, while specificity slightly decreased, from 99 % to 88 % [75]. Similarly, the combination of *KRAS* mutation analysis and CEA concentration has been found to increase sensitivity while maintaining specificity for discriminating mucinous from nonmucinous cysts, in large studies [76, 77]. These studies suggest that *KRAS* mutation analysis may be useful in selected cases, for example if the cyst fluid is too scant for CEA determination and cytopathological examination will likely be nondiagnostic. Commercially available tests allow a comprehensive DNA analysis of PCL aspirate, including *KRAS* mutation, but no added value has been demonstrated compared with standard of care, especially in practices where most PCLs are benign [78].

Direct sampling of the PCL wall following content aspiration has been proposed to overcome the relatively low sensitivity of fluid aspirate cytological analysis. Various instruments were used:

- The needle used for PCL aspiration: two prospective series (66 and 58 patients) reported that material adequate for pathological examination was obtained in 81 % and 65 % of cases, respectively (including material for histopathological assessment in one third of cases when a modified 22G ProCore needle was used) [79, 80]. Almost one third of PCLs with CEA values < 192 ng/mL were reclassified as mucinous; adverse events were rare (pancreatitis in one patient and no hemorrhagic episodes) [79].
- A minibiopsy forceps introduced through a 19G needle, with promising preliminary results that need to be validated in larger studies [81].
- A brush inserted through a 19G needle: this technique has mostly been abandoned because of frequent and sometimes severe adverse events including death [82, 83].

Finally, the intracystic inspection of the PCL wall has become possible using an endoscopic probe, combined or not with a confocal laser endomicroscopy probe introduced through a 19G needle. Although the interpretation of confocal endomicroscopy images is challenging, three clinical trials (total 127 patients) reported promising diagnostic accuracies, but adverse events (pancreatitis and intracystic hemorrhage) were relatively frequent (3 %, 7 %, and 9 % of cases) [84 – 86].

The impact of EUS-guided sampling on patient management depends significantly on the selection of PCLs sampled as well as on local guidelines: in Japan for example, the sampling of PCLs with worrisome features is considered to be contraindicated because of the fear of peritoneal seeding [60]. However, a study (243 patients) found no difference in the frequency of peritoneal seeding at 5 years following resection whether EUS-guided sampling had been performed or not [87]. Three studies evaluated the impact of EUS-guided sampling:

- A retrospective study (154 patients) found that, for the prediction of "neoplastic cysts" (a category that included mucinous cysts, cystic pancreatic ductal adenocarcinomas, cystic pancreatic neuroendocrine tumors, and solid pseudopapillary neoplasms), EUS-guided sampling increased the diagnostic yield over CT and MRI by 36 % and 54 %, respectively [88].
- A prospective study (49 patients), where information was progressively disclosed to physician experts in pancreatic diseases, found that EUS led to a change in the diagnosis and management in 30 % and 19 % of the patients, respectively; further disclosure of EUS-guided sampling results altered the diagnosis and management in an additional 39 % and 21 % of patients, respectively [89].
- A prospective study (159 patients) found that EUS-guided sampling of incidental PCLs had a major, a minor, and no impact on patient management in 48 %, 23 %, and 28 % of cases, respectively [90]. Major impact was defined as discharge rather than surgery or surgery rather than surveillance, while minor impact was defined as discharge rather than surveillance or surveillance rather than surgery.

5. Subepithelial lesions

RECOMMENDATION

ESGE suggests performing bite-on-bite biopsy as the first diagnostic procedure for subepithelial lesions (SELs). If this does not yield a diagnostic specimen, EUS-guided sampling is suggested in the following clinical situations:

- Asymptomatic hypoechoic SEL ≥ 2 cm of the stomach or gastroesophageal junction if surveillance is being considered;
- Targeted therapy of a suspected gastrointestinal stromal tumor is being considered;
- A carcinoma, neuroendocrine tumor, lymphoma, or intramural metastasis is suspected.

Weak recommendation, very low quality evidence.

RECOMMENDATION

ESGE suggests against EUS-guided sampling of SELs in the following clinical situations:

- Symptoms making resection necessary;
- Small (<2 cm) lesion located in the esophagus or stomach;
- Pathognomonic EUS appearance of a lipoma or duplication cyst;
- Patient is not a candidate for treatment.

Weak recommendation, low quality evidence)

RECOMMENDATION

ESGE suggests that, based on local expertise, advanced endoscopic techniques to obtain tissue diagnosis from SELs should be considered as an alternative to EUS-guided sampling.

Weak recommendation, low quality evidence.

RECOMMENDATION

ESGE recommends that the mitotic count or Ki67 labeling index determined on samples acquired under EUS guidance from gastrointestinal stromal tumors should not be used as evidence of low malignant potential of the tumor.

Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE recommends against sampling of esophageal subepithelial cysts.

Strong recommendation, low quality evidence.

The term "subepithelial lesion" (SEL) refers to lesions located in the deep mucosa and/or beneath the mucosa of the GI wall; they most frequently correspond to benign or premalignant neoplasms and rarely to overtly malignant tumors [91, 92]. At upper GI endoscopy, SELs are detected incidentally in 0.8% to 2% of individuals. Specific symptoms or complications are rare. Management options include surveillance, endoscopic or surgical removal, or, in selected cases of gastrointestinal stromal tumors (GISTs), targeted therapy with tyrosine kinase inhibitors. The management is determined by many factors including symptoms, patient co-morbidities and the malignant potential of the tumor. A definite diagnosis can rarely be established on the basis of imaging methods. Therefore, tissue diagnosis has the potential to influence management.

Standard or bite-on-bite forceps biopsy is often the first-line approach in patients with SELs. These techniques yielded highly variable results in 8 studies (pooled diagnostic yield 62%; range 17%–94%) (▶ **Table 2**).

▶ **Table 2** Selected series reporting the diagnostic yield of biopsy sampling of subepithelial lesions (SELs) located in the 3rd or 4th endoscopic ultrasound (EUS) layer.

First author, year	Sampling technique	Diagnostic yield* (n/n)
Hunt, 2003 [93]	Bite-on-bite technique using jumbo biopsy forceps	42% (15/36)
Cantor, 2006 [94]	Bite-on-bite technique using jumbo biopsy forceps	17% (4/23)
Zhou, 2007 [95]	Bite-on-bite technique	94% (16/17)
Sun, 2007 [96]	Bite-on-bite technique	86% (55/64)
Ji, 2009 [97]	Bite-on-bite technique using conventional biopsy forceps	38% (14/37)
Hoda, 2009 [98]	Standard technique using jumbo biopsy forceps	21% (5/24)
Komanduri, 2011 [99]	Bite-on-bite "unroofing" technique using jumbo biopsy forceps	92% (66/72)
Buscaglia, 2012 [100]	Bite-on-bite technique using jumbo biopsy forceps	59% (76/129)

* Proportion of procedures in which a diagnostic sample was obtained.

A prospective study (72 patients with a gastric SEL; median lesion size 13 mm) compared EUS-guided sampling (22 G needle plus Trucut biopsy in selected cases) vs. the "jumbo unroofing technique" which involves sampling of the tumor after exposing its surface using a jumbo biopsy forceps. EUS-guided sampling was not attempted in 42% of patients, mostly because of small tumor size. In tumors ≥2 cm the diagnostic yields of EUS-guided sampling and the unroofing technique were 72% (95% confidence interval [CI] 57%–85%) and 94% (95%CI 87%–99%), respectively [99]. Another prospective comparative study (20 patients with a gastric SEL; median lesion size 24 mm) found similar diagnostic yields with EUS-guided sampling vs. biopsy sampling using standard forceps after incision of the overlying mucosa with a needle-knife [101].

In a meta-analysis (17 studies, 978 procedures) [102], the diagnostic yield of EUS-guided sampling for upper GI SELs was 60% (95%CI 55%–65%). Most SELs were located in the stomach and measured at least 2 cm; therefore it is uncertain whether these results can be extrapolated to nongastric and/or smaller SELs. Better results have been reported in more recent studies not included in the meta-analysis (▶ **Table 3**); for example, in a retrospective study (121 patients, forward-viewing linear echo endoscope, and 19G needle) the diagnostic yield for SELs of the stomach, esophagus, duodenum and rectum was as high as 93% [103].

Determination of the mitotic index and Ki67 labeling index of GISTs is not reliable in samples obtained under EUS guidance, with a tendency to underestimate the tumor proliferative activity [105, 109]. Limited evidence suggests that block biopsy after submucosal dissection provides larger samples and a

▶ **Table 3** Recent studies on endoscopic ultrasound (EUS)-guided sampling of subepithelial lesions (SELs) not included in the meta-analysis by Zhang et al. [102].

First author, year	Tumor Location and size	Needle type and size	Diagnostic yield[1]
Larghi, 2014 [103]	Stomach (n = 96), other locations (n = 25); Mean size, 31±18 mm	Standard, 19G	93 % (113/121)
Na, 2015 [104]	Stomach ≥ 2 cm	Standard, 22G Quick-core, 19G	39 % (24/62) 78 % (70/90)
Lee, 2015 [105]	Stomach ≥ 2 cm	Procore, 22G	86 % (37/43)
Baysal, 2015 [106]	Esophagus ≥ 0.5 cm	Standard, 22G	52 % (34/65)
Lee, 2016 [107]	Stomach, ≥ 2 cm	Procore, 22G	81 % (63/78)
Han, 2016 [108]	Stomach, ≥ 1.5 cm	Standard, 22G Procore, 22G	68 % (15/22) 82 % (18/22)

* Proportion of procedures in which a diagnostic sample was obtained

more reliable determination of the mitotic count and Ki67 labeling index compared with EUS-guided sampling [110]. However, such aggressive techniques that use a knife or a snare to expose the SEL surface for biopsy sampling are inadequate for deep SELs (e. g., fourth EUS layer with protrusion to the peritoneal side) and are neither standardized nor widespread [111, 112].

With respect to adverse events, the review of a nationwide Japanese database (1135 patients) found that severe bleeding complicated EUS-guided sampling of SELs in 0.4 % of cases [113]. In the meta-analysis mentioned above, severe adverse events, excluding bleeding, were reported in 0.3 % of cases and included one death; most of the included studies were retrospective [102]. Because the EUS needle may inadvertently traverse the tumor, tumor cell spillage is a theoretical risk but it has not been investigated (tumor rupture during surgery is an adverse prognostic factor in GIST) [114].

The impact of EUS-guided sampling on patient management was analyzed in a single retrospective series of 65 patients with gastric SELs ≥ 2 cm: a specimen adequate for diagnosis was obtained in 37 patients (57 %) using a 19G Trucut needle, and this changed the original management plan based on clinical information in 18 patients (28 %) [115]. Various algorithms incorporating EUS-guided sampling have been proposed for the management of SELs, but they have not been validated [116]. Although available evidence does not permit strong recommendations, it is felt that EUS-guided sampling of a SEL is likely to influence patient management in the following situations:

1. Asymptomatic hypoechoic gastric tumor ≥ 2 cm if surveillance is considered as an alternative to tumor resection.
   a) Esophageal SELs are rarely malignant (1 % of cases) [92]; however, obtaining tissue diagnosis should be considered in lesions ≥ 2 cm before surveillance is started in selected cases, especially in young patients.
   b) Most gastric hypoechoic SELs ≥ 2 cm evaluated in EUS or surgical series are GISTs [92, 117, 118]. Although most of these tumors have a very low malignant potential, some pose a greater risk [118]. As this risk cannot be reliably assessed on samples acquired under EUS guidance [109], and laparoscopic wedge resection represents a safe option for most patients, it is felt that EUS-guided sampling can be reserved for poor surgical candidates or patients with the tumor located in surgically difficult areas such as the cardia. Tissue diagnosis seems especially important for cardia SELs as in this area leiomyomas outnumber GISTs [119].
2. Large tumor with a presumptive diagnosis of GIST in a patient in whom primary targeted drug therapy is considered because of concerns about tumor resectability (i. e., definitely unresectable tumors or tumors that are potentially resectable but with a risk of significant morbidity and/or extensive resection) [120]. In such cases, confirmation of a GIST diagnosis is required before therapy.
3. The tumor has an atypical EUS appearance and/or there is a suspicion of carcinoma, neuroendocrine tumor, lymphoma, or metastasis to the GI wall.

On the other hand, it is felt that EUS-guided sampling of a SEL is unlikely to influence patient management in the following situations:

1. Symptoms making resection necessary (e. g., bleeding).
2. EUS features typical of a lipoma or a duplication cyst.
3. Hypoechoic, asymptomatic, small (< 2 cm) SELs located in the esophagus or stomach: these SELs present a very low risk of malignancy or of progression to clinically significant tumors [92]. In a retrospective study of incidental upper GI SELs (954 patients; mean follow-up 47 months), the SEL size increased in < 4 % of cases [121]. Furthermore, data on the diagnostic performance of EUS-guided sampling of small SELs are limited.
4. The patient is not a candidate for treatment.

For duodenal and colorectal SELs, data are insufficient to permit recommendations.

6. Diffuse esophageal/gastric/rectal wall thickening

RECOMMENDATION

In patients with diffuse esophageal/gastric/rectal wall thickening, after failure of standard biopsy techniques, ESGE suggests performance of EUS-guided sampling aiming at a core biopsy. Flow cytometry should be performed if a GI lymphoma is suspected. Newly developed biopsy techniques under optical endoscopic guidance should be considered as an alternative.

Weak recommendation, low quality evidence.

Diffuse GI wall thickening is predominantly observed in the stomach and, less frequently, in the esophagus and rectum. Malignant causes include linitis plastica and, less frequently, lymphoma or diffuse metastasis. Benign causes are multiple, including eosinophilic infiltration, Zollinger–Ellison syndrome, Ménétrier's disease, amyloidosis, and newly recognized entities such as IgG4-related disease [122, 123]. Data on the endoscopic sampling of infiltrating, as opposed to mass-forming, subepithelial lesions are scarce.

Standard as well as bite-on-bite biopsy sampling using jumbo biopsy forceps often yields false-negative results [93, 124]. Therefore, new techniques are regularly being reported to optimize tissue acquisition, such as the combination of miniprobe EUS with bite-on-bite biopsy sampling through a double-channel endoscope, or the tunneling bloc biopsy which involves endoscopic submucosal dissection [125, 126]. Interestingly, the former technique provided a definitive diagnosis in 29 of 36 patients (81 %) with no severe complications reported in a retrospective study [126].

The use of a standard 22G needle for EUS-guided sampling of GI wall thickening has yielded disappointing results: with this needle, the intramural location of the target lesion was the only variable independently associated with an incorrect diagnosis in a prospective study (n = 213) [127]. Better results have been reported with larger needles aiming at collecting core samples for histopathological examination from GI wall thickening: using a standard or Procore 19G needle, a correct diagnosis was obtained in 11 of 13 patients (85 %) (2 cases of linitis plastica were misdiagnosed) [128, 129]. These results are very preliminary but they tend to confirm the high (90 %) diagnostic accuracy reported with the currently discontinued EUS Trucut biopsy needle in a prospective series of 31 patients [130].

The possibility of a GI lymphoma should always be evaluated in patients with GI wall thickening as, in such cases, similarly to those of nodal lymphomas, samples should be preserved in conditions that will allow the application of ancillary methods (e. g., flow cytometry, analysis of gene rearrangement). In a retrospective study (n = 39), adding flow cytometry to cytopathological examination increased the diagnostic accuracy for GI lymphoma from 69 % to 82 % [131].

Finally, a new application for EUS-guided sampling of the GI wall has recently been reported: in patients with severe gastroparesis, EUS-guided sampling of the antral muscularis propria using a 19G needle provided samples adequate for assessment of the loss of the interstitial cells of Cajal in 11 of 13 patients (81 %); the correlation between results obtained with surgical and endoscopic specimens was good [132].

7. Esophageal, gastric, and rectal luminal cancers

7.1 Esophageal cancer

RECOMMENDATION

For esophageal cancer, ESGE suggests performing EUS-guided sampling for the assessment of regional LNs in T1 (and, depending on local treatment policy, T2) adenocarcinoma and of lesions suspicious for metastasis such as distant LNs, left liver lobe lesions, and suspected peritoneal carcinomatosis.

Weak recommendation, low quality evidence.

Current guidelines recommend EUS for all patients with esophageal cancer who are candidates for surgical resection [133, 134]. This is related to the higher sensitivity (balanced by a lower specificity) of EUS for N staging compared with CT and 18F-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET), according to two meta-analyses (36 articles each for EUS, 2180 and 2360 patients) [135, 136]. In the specific setting of adenocarcinoma of the gastroesophageal junction, the accuracy of EUS for N staging was higher than that of CT in a recent prospective cohort (77 % vs. 71 %, respectively) [137].

EUS-guided sampling may target LNs that are not perituMoral (the sampling needle should not enter the tumor), either regional or distant, as well as metastases:

- Regional LNs dictate the N stage and this influences treatment only in patients with T1 adenocarcinoma, as neoadjuvant therapy is recommended for all patients with a resectable esophageal cancer except T1N0 adenocarcinomas [138, 139]. Controversy exists about whether adenocarcinoma of clinical stage T2N0M0 should be treated preoperatively as approximately 20 %–30 % of these patients actually have T1N0M0 disease [139]. Some authors have also proposed using the results of EUS-guided sampling of LNs to modify the target contour of radiation therapy, but this approach has not been validated [140].
- Distant LNs indicate stage IV disease and thus contraindicate resection. In this respect it is important to note that celiac LNs are considered to be regional LNs according to the current 2010 TNM staging system (regional LNs extend from periesophageal cervical LNs to celiac LNs) [141]. The American Joint Committee on Cancer has clarified that some nodal chains in this large area are partially regional and partially distant: supraclavicular, pulmonary ligament, hilar tracheo-

bronchial, and diaphragmatic LNs include regional LNs close to the esophagus and distant LN that are further from the esophagus [141].

- Metastases in the left liver lobe or collections of malignant pleural fluid unsuspected at CT were diagnosed by EUS-guided sampling in 3 % – 5 % of patients in a prospective and a retrospective study (total 207 patients) [142, 143]. However, this prevalence may not apply to a standard patient population as a larger study reported detection of liver metastases by EUS-guided sampling in only 2 of 953 patients (0.2 %), evident in both cases on PET-CT [144].

Compared with EUS alone, EUS-guided sampling was slightly more accurate (87 % vs. 74 %) for LN staging in a prospective blinded study of 76 patients that used surgical pathology as gold standard [145]. In that study, EUS-guided sampling was performed sequentially in the celiac, perigastric, and periesophageal area on all detected LNs until suspicious cells were found on the smear or no additional LNs were found. Obstructive tumors were dilated if necessary. These data tended to confirm those of a retrospective study from the same authors [146]. As EUS-guided sampling of all LNs is demanding, these authors reported that, using a modified set of indicators for LN malignant involvement, EUS-guided sampling could be avoided in almost half of the patients (those with ≥ 6 or no criteria for malignant involvement of LNs), maintaining accuracy and reducing costs [147]. Other authors have not confirmed these data. No other comparison of EUS alone versus EUS-guided sampling is available (a meta-analysis of 44 studies reported a higher sensitivity and specificity of EUS-guided sampling vs. EUS alone for esophageal cancer staging but it was flawed) [148].

The true impact of EUS-guided sampling on patient management is difficult to measure because treatment decisions are guided not only by the presence of LNs or distant metastases but also by many other factors, including patient performance status and tumor location, histology, and infiltration depth (T-stage). Moreover, old studies are no longer relevant as staging definitions, recommendations for treatment, and surgical techniques have evolved [139, 141]. Recent studies have aimed to define the impact of EUS-guided sampling:

- In a retrospective study (798 patients), EUS, supplemented by guided sampling if indicated, altered management decisions in only 11 % of patients, 97 % of these having a CT diagnosis of Tx/possible, T1 (early), or T4b disease [144]. The authors calculated that the risk of EUS (esophageal perforation) outweighed potential benefit (alteration of management) in patients with a tumor staged as T2 – T4a at CT scan (72 % of the patients in that study).
- A retrospective study (145 patients) found that EUS added little information about the resectability of esophageal cancer after thoracoabdominal CT and ultrasonography of the neck had been performed [149].
- EUS-guided sampling may detect metastases unsuspected at CT but the impact of this has likely been overestimated as mentioned above [142, 143].

With respect to the cost – effectiveness of EUS-guided sampling in esophageal cancer staging, studies mentioned in the 2011 ESGE Guideline are no longer relevant because they were based on hypotheses (resectability depending on celiac LN status) that have become obsolete [138, 139, 141].

RECOMMENDATION

For LN restaging and for predicting complete pathological response after neoadjuvant therapy, integrated FDG-PET-CT is recommended over EUS, and EUS-guided sampling should only be considered in highly selected cases.
Weak recommendation, low quality evidence.

Following neoadjuvant therapy, EUS-guided sampling may be performed to determine whether there is a compelling reason not to offer surgical resection, such as liver metastasis or distant malignant LNs. A prospective comparative study (48 patients) showed a lower accuracy for N staging of EUS-guided sampling vs. integrated FDG-PET-CT (78 % vs. 93 %) [150]. The authors suggested that FDG-PET-CT and CT may be used to provide targets for sampling as results are often falsely positive. More recently, the same group of authors reported a retrospective study (107 patients) in which EUS-guided sampling yielded a sensitivity and accuracy for N0 restaging of 82 % and 68 %, respectively [151]. However, 10 of 17 patients restaged as N1 indeed had N0 disease at surgery. As restaging was used to avoid offering surgery in patients with distant malignant disease, this could be a major problem of the technique. Another group of authors reported that EUS-guided sampling of distant LNs (supraclavicular, cervical, superior mediastinum, aorticocaval) was performed in 12 of 65 patients who had EUS for restaging, and it impacted treatment in four cases [152]. No surgical pathology was available in these cases.

RECOMMENDATION

ESGE suggests against stricture dilation for EUS/EUS-guided sampling except in exceptional cases where patient management, as assessed by a multidisciplinary team, is likely to be affected by the sampling results.
Weak recommendation, low quality evidence.

In at least 10 % – 46 % of patients [144, 153], esophageal tumors cannot be traversed by an echoendoscope without stricture dilation. Esophageal perforation has been associated with stricture dilation in 0 – 24 % of cases [154, 155]. EUS-guided sampling following stricture dilation has mostly been performed to assess malignant involvement of celiac LNs and it has been suggested to be an accurate technique [156]; however celiac LN malignant involvement is no longer considered to be a distant metastasis [138, 139, 141].

A retrospective study (46 patients) found that all patients with a nonmetastatic nontraversable esophageal tumor had T3 or T4 disease, and the authors suggested that neoadjuvant

therapy may thus be offered without the need even for EUS [153]. Similar conclusions were reached in the study mentioned earlier [144]: among 81 patients with an impassable tumor, none had N0 disease that would have made neoadjuvant therapy unnecessary. Although a single perforation (0.1 %) occurred in the whole cohort, using decision theory, the authors concluded that the risks of EUS outweighed its benefits in patients with impassable tumors.

7.2 Gastric cancer

RECOMMENDATION

In gastric cancer, ESGE recommends against EUS-guided sampling of local LNs and suggests EUS-guided sampling of distant LNs if it may impact treatment decisions. It should also be considered for other lesions suspected to be distant metastases.
Weak recommendation, low quality evidence.

In patients with gastric cancer, the main utility of EUS-guided sampling is to avoid unnecessary surgery by demonstrating distant metastasis. Malignant involvement of distant intra-abdominal LNs (e. g., retropancreatic, mesenteric, and para-aortic LNs) or of mediastinal LNs distant from the primary tumor is indicative of metastatic disease that qualifies the patient for palliation rather than resection with curative intent [157]. The impact of EUS-FNA in the preoperative evaluation of gastric carcinoma has been reported in three studies:

- A prospective series of 62 patients: EUS-guided sampling was performed in 12 patients (19 %), demonstrating distant metastases in 8 patients (13 %); of these 3 patients had metastases suspected on CT and/or percutaneous ultrasound (actual impact on patient management, 8 %) [158].
- A retrospective series of 234 patients: EUS-guided sampling was performed in 81 patients (35 %), demonstrating distant metastases in 38 patients (16 %) (61 % had the primary tumor in the cardia); of these, 4 patients had metastases suspected on CT (actual impact on patient management, 15 %) [159].
- A retrospective series of 100 patients: EUS detected perigastric fluid in 21 patients, of whom 15 had peritoneal carcinomatosis confirmed by laparoscopy (n = 12) or EUS-guided sampling (n = 3) (actual impact on patient management, 3 %). However, in 7 of the 79 patients (8 %) not showing the presence of ascites, peritoneal implants were identified by exploratory laparoscopy-laparotomy [160].

7.3 Rectal cancer

RECOMMENDATION

In rectal cancer staging, ESGE suggests against EUS-guided sampling of local LNs. In patients with a history of rectal cancer, ESGE suggests EUS-guided sampling of perirectal masses if it may impact treatment decisions.
Weak recommendation, low quality evidence.

For the preoperative evaluation of rectal cancer, the impact of EUS-guided sampling has been formally analyzed in a single, prospective, study (41 patients): EUS-guided sampling added almost no relevant information to EUS alone as both modalities had similar accuracies, except for a lower sensitivity of EUS-guided sampling (52 % vs. 74 %), likely because most perirectal LNs detected at EUS during rectal cancer staging are malignant [161]. More recently, a retrospective study found that, in 19 patients who had EUS-guided sampling for rectal cancer staging, the result was positive for malignancy in 12 cases; however, accuracy could not be calculated as gold standard pathology was not available for all cases [162].

In a retrospective cohort study of 316 patients with primary rectal cancer, extramesenteric LN metastasis (M1 stage) was diagnosed by EUS-guided sampling in 41 patients (13 %). In 23 patients (7 %) the preoperative proof of extramesenteric LN metastases outside resection margins or standard radiation fields resulted in upstaging and affected treatment planning [163].

In patients with a history of colorectal cancer, a retrospective study (58 patients with suspected recurrence of rectal or colon cancer, confirmed in 69 % of them) showed a sensitivity and specificity for the diagnosis of recurrent cancer of 95 % and 100 %, respectively [164].

8. Mediastinal and abdominal lymphadenopathy of unknown origin

RECOMMENDATION

For lymphadenopathy of unknown origin, ESGE recommends performing EUS-guided (or alternatively endobronchial ultrasound [EBUS]-guided) sampling if the pathological result is likely to affect patient management and no superficial lymphadenopathy is easily accessible.
Strong recommendation, moderate quality evidence.

Endosonographic criteria have been proposed to establish the benign or malignant nature of LNs [165]. For mediastinal LNs, a meta-analysis (76 noncomparative, retrospective, or prospective cohort series; 9310 patients) showed that EUS-guided sampling had a slightly higher sensitivity (88 % vs. 85 %) and a significantly higher specificity (96 % vs. 85 %) than EUS for diagnosing the cause of LN enlargement [166]. Compared with alternative techniques available for sampling the mediastinum, EUS-guided sampling is safer and less invasive: CT-guided biopsy has

been associated with pneumothorax in a high percentage of cases, and mediastinoscopy is a surgical, thus more invasive, procedure [167]. We recommend mediastinoscopy or CT-guided biopsy as second-line approaches. For intra-abdominal lymphadenopathy of unknown origin, fewer studies have been reported but these showed that EUS-guided sampling is feasible and safe in a majority of patients. For example, in a prospective study (142 patients with nondiagnostic or unfeasible percutaneous image-guided sampling), EUS-guided sampling was successful in 92 % of the patients and it yielded a diagnosis in 91 % of them [168].

Specific techniques of EUS-guided sampling (e. g., to obtain a core biopsy) and of sample processing (e. g., cell block technique, molecular studies) are particularly important for the evaluation of LNs of unknown origin; these are discussed in the Technical part of this Guideline. For example, flow cytometry is essential to increase the diagnostic yield for lymphoma [169], and polymerase chain reaction assays permit a diagnosis of mycobacterial infection and of multiple drug resistance weeks ahead of cultures [170, 171].

For the diagnosis of stage I/II pulmonary sarcoidosis, two RCTs (404 patients) found a higher diagnostic yield from EUS/EBUS-guided sampling of mediastinal LNs, compared with bronchoscopy-guided sampling [172, 173]; these results were in line with those of prior nonrandomized comparative studies [174, 175]. The difference in diagnostic yield in favor of EUS/EBUS-guided sampling is more important for stage I than stage II disease (stage I represents mediastinal and/or hilar lymphadenopathy while in stage II, lymphadenopathy is accompanied by lung involvement) [172, 175]. For mycobacterial infections, including tuberculosis, not diagnosed by routine methods EUS-guided sampling of mediastinal or abdominal LNs is highly accurate [168, 176]. Finally, for a complete diagnosis of lymphomas including subclassification, a relatively large amount of material may be required for morphologic, immunophenotypic, genotypic, and molecular analysis and this has traditionally made hematologists/oncologists prefer surgical excision [177]. However, in a large, retrospective, study (240 patients with thoracic or abdominal LNs measuring a mean of 26 × 39 mm) where a 19G needle was used [178], the sensitivity for diagnosing lymphoma was 97 % and subclassification was possible for 91 % of the patients. Other studies have reported lymphoma subclassification in lower proportions of cases [179, 180]. With EBUS-guided sampling, diagnostic accuracies of 91 % – 97 % have been reported for the diagnosis of lymphoma, according to a meta-analysis [181].

Studies of the clinical impact of EUS-guided sampling were limited to the mediastinal location. In a retrospective study that included 145 patients with LNs sampled for disease diagnosis as opposed to staging of malignancy, EUS-guided sampling had an impact on patient management in 85 % of cases; cost-savings of 472 € per patient were calculated, mainly because of avoided mediastinoscopy but this was likely an underestimate [182]. These results are in accordance with the results of other retrospective (n = 4) and prospective (n = 1) studies showing that EUS-guided sampling of mediastinal lymphadenopathy of unknown etiology substantially reduces the need for mediastinoscopy and thoracoscopy and establishes indications for specific medical treatments [183 – 187].

9. Solid liver masses and parenchymal liver disease

RECOMMENDATION

In the case of solid liver masses suspicious for metastasis, ESGE suggests performing EUS-guided sampling if the pathological result is likely to affect patient management, and (i) the lesion is poorly accessible/not detected at percutaneous imaging, or (ii) a sample obtained via the percutaneous route repeatedly yielded an inconclusive result.

Weak recommendation low quality evidence.

RECOMMENDATION

In the case of suspected parenchymal liver disease, ESGE suggests considering EUS-guided sampling using a 19G needle in highly selected cases.

Weak recommendation, low quality evidence.

Noninvasive techniques for liver imaging including CT and MRI present a suboptimal sensitivity for the detection of liver metastases, in particular those < 10 mm [188, 189]. In a prospective comparison of 26 patients, EUS detected more liver metastases than CT and it allowed characterization of lesions that were too small to be characterized at CT [190]. However, EUS examination of the liver should be considered complementary to but not as an alternative to the other imaging techniques because it permits examination of only a part of the liver.

No prospective study has compared percutaneous vs. EUS-guided sampling of solid liver masses. In a retrospective study (332 patients) [191], the accuracy of EUS-guided sampling for the diagnosis of liver metastases was 94 % (38 % of samples were diagnosed as malignant). Compared to CT-detected lesions, EUS-detected lesions were significantly smaller (median long axis, 9 mm). A complex algorithm based on EUS features allowed discrimination of benign from malignant liver lesions with a positive predictive value of 88 %; this may help to guide the decision whether or not to perform EUS-guided sampling. Another study included 23 patients in whom ultrasound-guided percutaneous biopsy was unsuccessful because of poor accessibility, absence of mass visualization, presence of ascites, or a sample inadequate for pathological diagnosis: EUS-guided sampling was feasible in 21 (93 %) patients and it yielded an accurate diagnosis in 19 (83 %) patients [192].

With respect to the impact of EUS-guided sampling, a retrospective study (77 patients) reported a change in the management of 38 (49 %) patients [193].

In patients with diffuse liver disease, EUS-guided liver sampling using a 19 G aspiration needle has been proposed mostly

for patients who already have an indication for upper GI endoscopy. In two prospective series (total 141 patients) a specimen adequate for pathological diagnosis was obtained in 98 % and 91 % of cases [194, 195]. In another study, samples obtained under EUS guidance were larger and contained a similar or higher number of complete portal triads than specimens obtained by percutaneous or transjugular liver biopsy [196].

The potential morbidity of EUS-guided sampling in the liver should be taken into account: in a meta-analysis (51 studies, 10 941 patients), this location carried the third highest morbidity rate (2.3 %), exceeded only by ascites (3.6 %) and PCLs (2.8 %) [197]. Duodenal perforations and death have been reported [191, 198]. The absolute and relative contraindications to percutaneous liver biopsy (e. g., peliosis hepatis, suspected hemangioma, ascites) should therefore be respected, so mainly the possibility of a different needle tract and better lesion visibility are indications for EUS-guided sampling.

10. Miscellaneous

10.1 False-positive pathological result for malignancy

RECOMMENDATION

The possibility of a false-positive malignant diagnosis should be kept in mind when interpreting cytopathological results of EUS-guided sampling, particularly in patients with a cancer in the GI lumen.

Strong recommendation, moderate quality evidence.

In four studies that used surgical specimens as gold standard, specimens obtained under EUS guidance yielded a false-positive malignant pathological result in 1.1 % – 5.4 % of cases [199 – 202]. A single study considered pathological results “suspicious for malignancy” and “atypical” as positive for malignancy [199]; in two studies, including results “suspicious for malignancy” as indicative of malignancy would have increased the false-positive rates to 3.8 % and 7.2 % [200, 202]. False-positive pathological results may result from sample contamination or interpretive error at pathological examination; each of these causes accounted for half of the errors in the largest study [200]. In that study, false-positives were significantly more frequent in nonpancreatic vs. pancreatic EUS-guided sampling (15 % vs. 2.2 %).

Malignancies in the GI lumen have a high propensity to contaminate the echoendoscope and the sampling needle: in a prospective study (140 patients), malignant cells were found in the fluid aspirated through the echoendoscope after sampling in 52 % vs. 7 % of patients with a luminal vs. an extraluminal cancer [203]. These data were confirmed by another smaller prospective study [204].

In an ex vivo experiment, smears were prepared after sham EUS-guided sampling performed with an echoendoscope that had just been used in 13 patients with esophageal cancer (without sampling); the sham EUS-guided sampling was done either after extensive flushing of the working channel (n = 5) or not (n = 8). Among the specimens obtained by sham EUS-guided sampling without flushing the working channel, 75 % contained carcinoma cells, while none of the 5 samples obtained after flushing had tumor cell contamination [205].

10.2 Needle tract seeding

RECOMMENDATION

Needle tract seeding is extremely rare with EUS-guided sampling but it may impair individual patient survival.

Moderate quality evidence.

Several comparative cohort studies found no increased risk of peritoneal seeding, gastric wall metastasis, or postoperative recurrence whether preoperative EUS-guided sampling had been performed or not for pancreatic cancer, IPMN, or cholangiocarcinoma [87, 206, 207]. No difference was found also in terms of overall and cancer-specific survival for patients with resected pancreatic cancer [4] and cholangiocarcinoma [206] Shortcomings of these studies included a retrospective design and a relatively short follow-up period.

From 2003 to 2016, only 14 cases of needle tract seeding following EUS-guided sampling have been reported [208 – 211]. Metastases were located in the gastric or esophageal wall in 12 cases and in the peritoneum in 2 cases. Most cases (n = 11) complicated EUS-guided sampling of pancreatic lesions. As metastases are usually located alongside the needle tract, resectable tumors located in the pancreatic body or tail are of the most concern as the transgastric needle tract is not resected in such cases.

These ESGE guidelines represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability. Further controlled clinical studies may be needed to clarify aspects of the statements, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance to these recommendations. ESGE guidelines are intended to be an educational device to provide information that may assist endoscopists in providing care to patients. They are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment.

Competing interests

S. Carrara has provided consultancy to Boston Scientific (since 2016) and to Olympus (since 2015). L. Czakó has received honoraria from Olympus (2014 to 2016). P. H. Deprez has provided consultancy to Boston Scientific and Olympus (both 2015 to 2017). P. Fockens has provided consultancy to Fujifilm, Olympus, Medtronic, Cook, and Boston Scientific (from 2016/2017). R. F. Havre has been provided by Samsung Medison

with the use of an ultrasound scanner for research, from March to December 2017; he is a member of the Norwegian Society of Gastroenterology (since 2006). C. Jenssen's department received a research grant of 4000€ from Novartis (2012 to 2015). A. Larghi has provided consultancy to Boston Scientific (2016 to 2017). J. E. van Hooft has received lecture fees from Medtronic (2014 to 2015) and consultancy fees from Boston Scientific (2014 to 2016); her department has received research grants from Cook Medical and Abbott (both 2014 to 2017). P. Vilmann provides consultancy to MediGlobe (from 1991 to 2019). G. P. Aithal, P. G. Arcidiacono, P. Bastos, J.-M. Dumonceau, G. Fernández-Esparrach, A. Ginès, C. Hassan, J. Iglesias-Garcia, M. Polkowski, and G. Vanbiervliet have no competing interests.

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Appendix e1. Indications, results, and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline – Updated January 2017

▶ **Appendix e1** Key questions and task forces

Key questions	Task force (leader in bold)
Task force I Biliopancreatic solid masses (including papilla)	**Vanbiervliet, G**; van Hooft, JE; Dumonceau, J-M; Iglesias-Garcia, J; Jenssen, C; Fockens, P; Arcidiacono, P
▪ How does EUS-guided sampling compare with percutaneous FNA (diagnostic accuracy, NPV, complications, costs)?	
▪ Compare diagnostic accuracy of EUS-guided sampling in presence vs. absence of chronic pancreatitis, alone vs. combined with contrast enhancement, with elastography	
▪ What is the diagnostic accuracy of repeat EUS-guided sampling?	
▪ What to do in the case of an inconclusive cytopathological result?	
▪ What are the indications for EUS-guided sampling?	
▪ PSC, Klatskin etc	
▪ What is the impact of EUS-guided sampling on patient management?	
Task force II Pancreatic cystic lesions	**Deprez, PH**; Hassan, C; Fernández-Esparrach, G; Havre, RF
▪ What are the indications for EUS-guided sampling of a pancreatic collection?	
▪ How do diagnostic accuracy of marker dosage, cyst wall brushing, EUS-FNA, and EUS-guided confocal laser endomicroscopy compare?	
▪ Role of molecular markers	
▪ What is the impact of EUS-guided sampling on patient management?	
Task force III Submucosal tumors	**Polkowski, M**; Gines, À; Bastos, P
▪ What are the diagnostic yield, accuracy, and complications of endoscopic forceps biopsy, EUS-guided sampling (EUS-FNA and EUS-FNB), and newer techniques (ESD, submucosal tunneling, full-thickness resection with closure) in patients with submucosal tumors?	
▪ When is EUS-guided sampling indicated and not indicated in patients with submucosal tumors?	
▪ What is the impact of EUS-guided sampling on patient management?	
Task force IV Diffuse esophageal/gastric/rectal wall thickening	**Larghi, A**; Carrara, S
▪ What are the yields of bite-on-bite biopsies, and EUS-guided sampling?	
▪ What is the impact of EUS-guided sampling on patient management?	
▪ When to perform EUS-guided sampling?	
▪ What is the impact of EUS-guided sampling on patient management?	
Task force V Esophageal, gastric and rectal luminal cancers	**Iglesias-Garcia, J**; Vanbiervliet, G; Vilmann, P; Aithal, GP; Czako, L
▪ How do performance/safety/cost of EUS, EUS-guided sampling, and best competing technique compare for primary lymph node staging and restaging?	
▪ What are the indications for EUS-guided sampling in staging (and restaging) and its impact on patient management?	
▪ Should stenotic tumors be dilated to allow for complete staging +/–EUS-guided sampling?	
▪ Particular point for perirectal masses in patients with a history of rectal cancer: how do EUS, EUS-guided sampling, and best competing technique compare?	
▪ What is the impact of EUS-guided sampling on patient management?	

▶ **Appendix e1** (Continuation)

Key questions	Task force (leader in bold)
Task force VI Mediastinal/abdominal lymphadenopathy of unknown origin, miscellaneous	**Jenssen, C;** Carrara, S
▪ What are the yield, indications, and impact of EUS-guided sampling for mediastinal and abdominal lymphadenopathy of unknown origin?	
▪ What is the impact of EUS-guided sampling on patient management in the case of solid focal liver lesions?	
▪ What is the incidence of false-positive cytology results for cancer?	
▪ How frequent and relevant is needle-tract seeding with EUS-guided sampling compared with percutaneous imaging-guided sampling?	
▪ What is the impact of EUS-guided sampling on patient management?	

FNA, fine needle aspiration; NPV, negative predictive value; PSC, primary sclerosing cholangitis; FNB, fine needle biopsy; ESD, endoscopic mucosal dissection