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

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This article is part of a combined publication that expresses the current view of the European Society of Gastrointestinal Endoscopy (ESGE) about endoscopic ultrasound (EUS)-guided sampling in gastroenterology, including EUS-guided fine needle aspiration (EUS-FNA) and EUS-guided trucut biopsy (EUS-TCB), of submucosal tumors, diffuse esophageal/gastric wall thickening, pancreatic solid masses and cystic-appearing lesions, mediastinal lesions unrelated to lung or esophageal cancer, cancer of the esophagus, stomach, and rectum, lymph nodes of unknown origin, adrenal gland masses, and focal liver lesions. False-positive cytopathological results and needle tract seeding are also discussed. The present Clinical Guideline describes the results of EUS-guided sampling in the different clinical settings, considers the role of this technique in patient management, and makes recommendations on circumstances that warrant its use. A two-page executive summary of evidence statements and recommendations is provided. 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.

1. Introduction

This Clinical Guideline describes the results obtained with endoscopic ultrasound (EUS)-guided sampling, describes the role of this technique in patient management, and makes recommendations on circumstances that warrant its use. 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 Technical Guideline from the European Society of Gastrointestinal Endoscopy (ESGE) [1].

2. Methods

The ESGE commissioned and funded this Guideline. The methodology was similar to that used for other ESGE Guidelines [2,3]. Briefly, subgroups were formed, each charged with a series of clearly defined key questions (see **Appendix e1**, available online). The committee chair worked with subgroup leaders to identify pertinent search terms that always included, as a minimum, "endoscopic ultrasonography" and words pertinent to specific key questions. Evidence tables were generated for each key question based on meta-analyses or randomized controlled trials (RCTs) if these were available; otherwise, case–control studies, retrospective analyses, and case series were included. The number of articles retrieved and selected for each task force is indicated in the Evidence table (see **Appendix e2**, available online). Evidence levels and recommendation grades used in this Guideline were slightly modified from those recommended by the amended Scottish Intercollegiate Guidelines Network (**Table 1**) [4]. Subgroups agreed electronically on draft proposals that were presented to the entire group for general discussion during two meetings held in 2010 and 2011. The results of that discussion were incorporated into the subsequent Guideline version and again discussed using electronic mail until unanimous agreement was reached. Searches were re-run in February 2011 (this date should be taken into account for future updates). The final draft was approved by all members of the Guideline development group; it was sent to all individual ESGE members in March 2011 and,

Table 1 Definitions of categories for evidence levels and recommendation grades used in this Guideline [4].

Evidence level	
1++	High quality meta-analyses, systematic reviews of RCTs, *or* RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, *or* RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews, *or* RCTs with a high risk of bias
2++	High quality systematic reviews of case – control or cohort studies; high quality case – control studies *or* cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case – control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2–	Case – control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Nonanalytic studies, e. g. case reports, case series
4	Expert opinion
Recommendation grade	
A	At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population *or* a systematic review of RCTs *or* a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 1– or 2+ directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from studies rated as 2++
D	Evidence level 2–, 3 or 4 *or* extrapolated evidence from studies rated as 2+

RCT, randomized controlled trial.

after incorporation of their comments, it was endorsed by the ESGE Governing Board prior to submission to *Endoscopy* for international peer review. The final revised version was approved by all members of the Guideline development group before publication.

Evidence statements and recommendations are stated in italics, key evidence statements and recommendations are in bold. This Guideline will be considered for revision in 2014, or sooner if important new 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. Summary of statements and recommendations

Submucosal tumors (SMTs)

Data from selected centers suggest that endoscopic forceps biopsy with the so-called bite-on-bite technique can provide specimens adequate for diagnosis in a substantial proportion of cases (Evidence level 2–). The diagnostic yield of EUS-guided fine needle aspiration (EUS-FNA) cytology is moderate and limited by unsatisfactory immunostaining in a substantial proportion of patients (Evidence level 2+); this may be improved by obtaining samples for cytopathological plus histopathological examinations (Evidence level 2–). The diagnostic yield of EUS-guided trucut biopsy (EUS-TCB) is similar to that of EUS-FNA (Evidence level 2+). The potential impact of EUS-guided sampling on patient management varies according to many factors including clinical presentation, SMT characteristics (size, location, and echo features), and patient physical condition (Evidence level 4).

Bite-on-bite biopsy should be the first diagnostic step at centers where satisfactory results are achieved with this technique. When bite-on-bite biopsy fails or is not attempted, EUS-guided sampling with efforts at obtaining samples for histopathological evaluation should be performed (Recommendation grade C). For selected small lesions located in the second or third EUS layer, endoscopic resection may also be considered (Recommendation grade D). EUS-guided sampling is not likely to impact management and hence is generally not indicated in patients with the following (Recommendation grade D):

- *Surgery planned because of SMT-related symptoms;*
- *SMT harboring typical echo features of a lipoma;*
- *Small (<2 cm) SMTs of the esophagus and stomach.*

Also the clinical benefit of EUS-guided sampling in patients with hypoechoic esophageal or gastric SMTs >2 cm is usually limited and should not be overstated (Recommendation grade D).

EUS-guided sampling is indicated in the following situations (Recommendation grade D):

- *SMTs with a presumptive diagnosis of unresectable gastrointestinal stromal tumor (GIST) for which treatment with tyrosine kinase inhibitors is contemplated;*
- *patient previous history of malignancy with an SMT that may be consistent with a metastasis;*
- *suspected diagnosis of lymphoma, neuroendocrine tumor, or extrinsic tumor, based on EUS, biological, or clinical criteria.*

For duodenal and colorectal SMTs, no recommendations are made due to insufficiency of data.

Diffuse esophageal/gastric wall thickening

Diagnostic accuracy of EUS-TCB for investigating diffuse esophageal/gastric wall thickening seems to be high (90%), in particular when compared with that of EUS-FNA (60%) (Evidence level 2+). In patients with diffuse esophageal/gastric wall thickening, after failure of standard biopsy techniques to establish a diagnosis, we recommend performing EUS-TCB (Recommendation grade C). In the case of technical failure of EUS-TCB, EUS-FNA could be indicated (Recommendation grade D).

Pancreatic solid masses

EUS-FNA presents a high diagnostic accuracy but a relatively low negative predictive value (NPV) for the diagnosis of pancreatic cancer. Due to this universal drawback of all sampling techniques available for the pancreas, preoperative sampling is generally not advised (i. e., for potentially resectable pancreatic tumors in operable patients). In other circumstances (e. g., neoadjuvant or palliative radio/chemotherapy), a pathological diagnosis is required; this can be obtained by sampling the primary pancreatic lesion or possible metastases (Evidence level 1+). Compared with ultrasound-guided or computed tomography (CT)-guided FNA of pancreatic masses, EUS-FNA seems to present a higher diagnostic accuracy, particularly for small lesions (Evidence level 2+). EUS-FNA can also demonstrate, in approximately 10% of patients, metastatic dissemination to distant lymph nodes, the peritoneum, or the liver that was unsuspected with other imaging techniques (Evidence level 2++). Repeat EUS-FNA in patients with a high clinical suspicion for pancreatic cancer but indeterminate or negative findings

at initial EUS-FNA allows improvement of diagnostic accuracy (Evidence level 2+).

In cases where sampling of a suspected pancreatic cancer is indicated, we recommend EUS-FNA as the first-line procedure. If lesions suspicious for metastases are discovered during EUS staging of a suspected pancreatic cancer in patients with an otherwise resectable mass, EUS-FNA of these lesions should be performed (Recommendation grade B). In patients with a high clinical suspicion for pancreatic cancer and indeterminate or negative findings at the initial sampling procedure, including EUS-FNA, EUS-FNA (possibly repeated) is recommended (Recommendation grade C).

Pancreatic cystic-appearing lesions

Biochemical and cytopathological analyses of fluid aspirate obtained by EUS-FNA may help the differential diagnosis of pancreatic cystic-appearing lesions (Evidence level 1+). In some conditions, the cyst wall may be brushed during EUS; this technique may allow a higher diagnostic yield than FNA but it has been associated with frequent, sometimes severe, complications (including death) (Evidence level 2–).

If nonsurgical diagnosis of pancreatic cystic-appearing lesions may change patient management, EUS-FNA with determination of amylase and carcinoembryonic antigen (CEA) levels plus cytopathological examination of fluid aspirate is recommended for lesions > 2 cm in diameter (Recommendation grade B). EUS-guided cyst wall brushing may be useful in well-selected cases (Recommendation grade D).

Mediastinal lesions unrelated to lung or esophageal cancer

Transesophageal EUS-FNA is safe and accurate for the diagnosis of solid lesions located in the posterior mediastinum. For mediastinal lymph nodes, the addition of FNA to EUS slightly increases sensitivity and significantly increases specificity for diagnosing the cause of lymph node enlargement (Evidence level 1–). EUS-FNA of noncystic mediastinal lesions of unknown origin impacts patient management in > 70% of cases (Evidence level 2+). EUS-FNA of mediastinal cysts carries a risk of severe infection even if prophylactic antibiotics are administered (Evidence level 3).

We recommend transesophageal EUS-FNA for the initial work-up of solid mediastinal lesions and enlarged lymph nodes of unknown origin that are accessible to this technique (Recommendation grade B); we discourage EUS-FNA of mediastinal cysts (Recommendation grade D).

Esophageal cancer

For initial lymph node staging in esophageal cancer, EUS-FNA is more accurate than EUS alone as well as than helical CT (Evidence level 2++); it also allows diagnosis of metastases undetected at CT in the left liver lobe in approximately 5% of patients. In patients who are considered for surgical resection, EUS-FNA may impact treatment decisions by correcting the stage determined by helical CT (usually towards a higher stage) in approximately one third of cases (Evidence level 2+). The impact of adding FNA to the staging based on EUS alone remains uncertain but there is limited evidence suggesting that EUS-FNA may change the management plan based on EUS alone (Evidence level 2–). EUS-FNA has higher accuracy than integrated fluorodeoxyglucose positron emission tomography and CT (integrated FDG-PET/CT) for lymph node staging. For lymph node re-staging and for predicting complete pathological response after neoadjuvant therapy, EUS-FNA has lower accuracy than integrated FDG-PET/CT (Evidence level 2+).

For initial staging, EUS-FNA should be performed whenever the cytological result is likely to affect the decision on what treatment option to choose in a given patient (e.g., primary surgical resection, or definitive or neoadjuvant chemoradiotherapy). Integrated FDG-PET/CT is recommended only in case of incomplete EUS examination (Recommendation grade D). For re-staging after neoadjuvant therapy, integrated FDG-PET/CT is recommended (Recommendation grade C). Whether EUS-FNA should be performed to obtain cytological confirmation of integrated FDG-PET/CT findings positive for lymph node metastasis requires further studies.

Gastric cancer

EUS-FNA modifies the management of patients with a gastric cancer by demonstrating distant metastases unsuspected with other imaging techniques in 8%–15% of cases (Evidence level 2+).

In patients with gastric cancer, we recommend performing EUS-FNA of all suspected distant metastases detected during EUS examination only when it has the potential to change patient management (Recommendation grade C).

Rectal cancer

For the initial staging of rectal cancer, EUS-FNA does not have more impact on patient management than EUS alone; in patients with perirectal lesions detected at EUS and a history of cancer, EUS-FNA is useful to demonstrate or rule out cancer recurrence (Evidence level 2+).

We recommend performing EUS-FNA of perirectal lesions only when it has the potential to change patient management, i.e. mostly in patients with a previous history of cancer, and not for rectal cancer staging (Recommendation grade C).

Lymph nodes of unknown origin

EUS-FNA allows accurate determination of the nature of lymph nodes of unknown origin (Evidence level 2+).We recommend performing EUS-FNA of lymph nodes of unknown origin if these are accessible, no other significant lymph node is easily accessible (e.g., subcutaneous lymph node), and a pathological result would likely affect patient management (Recommendation grade C).

Adrenal gland masses

EUS-FNA is an accurate and safe technique for sampling left adrenal gland masses (Evidence level 2+). In patients with lung cancer and an enlarged left adrenal gland, EUS-FNA of the left adrenal gland modifies disease stage and treatment strategy in approximately half of patients (Evidence level 2+); it is recommended if a cytopathological result positive for malignancy is likely to change patient management (Recommendation grade C).

Focal solid liver lesions

Solid liver lesions may be safely sampled by EUS-FNA; the diagnostic yield and the impact on patient management are high (Evidence level 2+). We recommend performing EUS-FNA of focal liver lesions accessible to EUS-FNA if: (i) a pathological result positive for malignancy would likely affect patient management, and (ii) the lesion is poorly accessible to percutaneous FNA or it is detected de novo by EUS or it has been sampled by percutaneous FNA with a nondiagnostic result (Recommendation grade C).

False-positive cytopathological results

The incidence of false-positive cytopathological results with EUS-FNA samples ranges between 1.6% and 5.3% (Evidence level 2+). Flushing the working channel of the echoendoscope before every needle pass may reduce this risk (Evidence level 2–). The possibility of a false-positive diagnosis should be kept in mind when interpreting cytopathological results of EUS-FNA, particularly for EUS-FNA of lymph nodes in patients with luminal cancers (Recommendation grade C). We suggest flushing the working channel of the echoendoscope before every needle pass and collection of microcores to help prevent this outcome (Recommendation grade D).

Needle tract seeding

Needle tract seeding is extremely rare with EUS-FNA (Evidence level 3).

4. Digestive wall lesions

This section is devoted to circumscribed intramural solid lesions of the gastrointestinal (GI) tract, referred to as submucosal tumors (SMTs) and diffuse intramural infiltration of the GI tract presenting in the form of widespread, diffuse, GI wall thickening.

4.1. Submucosal tumors (SMTs)

Data from selected centers suggest that endoscopic forceps biopsy with the so-called bite-on-bite technique can provide specimens adequate for diagnosis in a substantial proportion of cases (Evidence level 2–). The diagnostic yield of EUS-guided fine needle aspiration (EUS-FNA) cytology is moderate and limited by unsatisfactory immunostaining in a substantial proportion of patients (Evidence level 2+); this may be improved by obtaining samples for cytopathological plus histopathological examinations (Evidence level 2–). The diagnostic yield of EUS-guided trucut biopsy (EUS-TCB) is similar to that of EUS-FNA (Evidence level 2+). The potential impact of EUS-guided sampling on patient management varies according to many factors including clinical presentation, SMT characteristics (size, location, and echo features) and patient physical condition (Evidence level 4).

Bite-on-bite biopsy should be the first diagnostic step at centers where satisfactory results are achieved with this technique. When bite-on-bite biopsy fails or is not attempted, EUS-guided sampling with efforts at obtaining samples for histopathological evaluation should be performed (Recommendation grade C). For selected small lesions located in the second or third EUS layer, endoscopic resection may also be considered (Recommendation grade D). EUS-guided sampling is not likely to impact management and hence is generally not indicated in patients with the following (Recommendation grade D):

- *Surgery planned because of SMT-related symptoms;*
- *SMT harboring typical echo features of a lipoma;*
- *Small (<2 cm) SMTs of the esophagus and stomach.*

Also the clinical benefit of EUS-guided sampling in patients with hypoechoic esophageal or gastric SMTs >2 cm is usually limited and should not be overstated (Recommendation grade D).

EUS-guided sampling is indicated in the following situations (Recommendation grade D):

- *SMTs with a presumptive diagnosis of unresectable gastrointestinal stromal tumor (GIST) for which treatment with tyrosine kinase inhibitors is contemplated;*
- *Patient previous history of malignancy with an SMT that may be consistent with a metastasis;*
- *Suspected diagnosis of lymphoma, neuroendocrine tumor, or extrinsic tumor based on EUS, biological, or clinical criteria.*

For duodenal and colorectal SMTs, no recommendations are made due to insufficiency of data.

The term "SMT" encompasses a variety of conditions, including non-neoplastic lesions as well as benign, premalignant, and overtly malignant neoplasms that are located in the digestive wall beneath the epithelium. Overtly malignant SMTs are rare and vastly outnumbered by GISTs that are potentially malignant. The risk that an SMT is malignant or premalignant is associated with tumor size, echo features, and anatomic location (the risk is highest for gastric SMTs and very low for esophageal SMTs) [5,6]. The studies discussed below mostly included hypoechoic SMTs of the stomach (predominantly GISTs) and it is not certain that their results can be extrapolated to SMTs involving other parts of the GI tract.

Data on the diagnostic yield of bite-on-bite (or stacked, or tunneled) biopsy are inconsistent across the literature, with reported adequacy rates ranging from 17% to 94% [7–12]. Because of these discrepant results, local experience should be used to determine the role of this potentially valuable technique in the diagnostic algorithm. More advanced techniques (e.g., "unroofing" and "keyhole" techniques) seem promising but require further evaluation [13,14]. En bloc resection of lesions <20 mm located in the second and third EUS layer is safe in experienced hands and it allows definitive pathological diagnosis [15].

EUS-FNA allows harvesting of representative material for cytopathological evaluation from most SMTs (70%–84%) (**Table 2**) [8,16–21]. However, cytological material is often insufficient for performance of the immunostaining that is required to differentiate GIST and other mesenchymal tumors. There is limited evidence to suggest that this limitation may be partly overcome by processing EUS-FNA specimens for histopathological examination [18,21,22]. EUS-TCB is not superior to EUS-FNA; however, combining both techniques improves the diagnostic yield [8,19,23]. The mitotic index, and hence the malignant potential of GIST, cannot be reliably assessed on samples obtained by EUS-guided techniques [21,23,24]. Data on the usefulness of the Ki-67 labeling index to circumvent this limitation are contradictory [22,25,26]. The above problems notwithstanding, it should be noted that when EUS-FNA or EUS-TCB provides an adequate sample, then the diagnosis is concordant with the final diagnosis in most cases. Only single cases of misdiagnoses have been reported [8,16–19,21–23].

Algorithms for the management of patients with SMTs have been proposed but none of them has been prospectively validated [19,27,28]. Also, the impact of EUS-FNA on patient management has not been evaluated. The following recommendations are based exclusively on expert opinions and data extrapolated from available studies:

1. In patients with SMT-related symptoms (e.g., bleeding, digestive obstruction), EUS-guided sampling is not likely to impact management and hence is not indicated, except for the situations described in points 3 and 5c below.
2. EUS without FNA is sufficiently accurate to diagnose lipoma [29].
3. If an intramural metastasis, lymphoma, neuroendocrine tumor, or an extrinsic tumor is suspected, EUS-FNA or EUS-TCB should be considered because the management may substantially differ from the one recommended for other SMTs. Of note, primary carcinomas of the GI wall mimicking a SMT have been reported in many EUS series [5,16,19,22].

Table 2 Diagnostic yield of various endoscopic ultrasound (EUS)-guided sampling techniques in patients with submucosal tumors*.

First author, year	Prospective/ retrospective	Patients, n	Sampling technique	Specimens†		
				Diagnostic	Insufficient for immunostaining	Nondiagnostic
Philipper, 2010 [17]	Prospective	47	FNAC	34 %	56 %	26 %
Fernández-Esparrach, 2010 [19]	Prospective	40	FNAC	53 %	18 %	30 %
Mekky, 2010 [16]	Retrospective	141	FNAC	62 %	21 %	17 %
Hoda, 2009 [8]	Retrospective	112	FNAC	62 %	22 %	16 %
Akahoshi, 2007 [18]	Prospective	53	FNAC + FNAH	79 %	0 %	21 %
Yoshida, 2009 [21]	n.r.	49	FNAC + FNAH	82 %	0 %	18 %
Turhan, 2010 [22]	Prospective	50	FNAC + FNAH	90 %	0 %	10 %
Hoda, 2009 [8]	Retrospective	15	TCB	47 %	13 %	40 %
Fernández-Esparrach, 2010 [19]	Prospective	40	TCB	55 %	5 %	40 %
Polkowski, 2009 [23]	Prospective	49	TCB	63 %	14 %	22 %
Fernández-Esparrach, 2010 [19]	Prospective	40	TCB + FNAC	78 %	n.r.	n.r.

FNAC, fine needle aspiration cytology; FNAH, fine needle aspiration histology; n.r., not reported; TCB, trucut biopsy.
* Selected studies that included more than 25 patients, were published after 2000, and provided sufficient data. Most (84 %) submucosal tumors evaluated in these studies involved the stomach. The proportions of esophageal, duodenal and rectal tumors were 12 %, 3 %, and 1 %, respectively.
† Specimens were categorized as diagnostic (adequate for diagnosis, including immunostaining when indicated), adequate for cytological or histological evaluation but insufficient for immunostaining, and nondiagnostic. Percentages may not add to 100 % because of rounding.

4. Esophageal SMTs are rarely malignant (1 % of cases) and a pathological diagnosis is unlikely to change patient management, in particular when the tumor is < 2 cm [5,6]. Sampling of esophageal SMTs should be considered in patients with large and/or otherwise suspicious SMTs but no more specific recommendations can be provided.
5. Gastric SMTs:
   a) The management of incidental gastric SMTs < 2 cm is unlikely to be affected by EUS-FNA or EUS-TCB because such lesions harbor a very low risk of progression to clinically evident tumors and are likely more prevalent than previously thought [30 – 32]. Surveillance is a valid option in such cases [33,34].
   b) Three quarters of gastric hypoechoic SMTs > 2 cm are GISTs [17,19,23]. Most of these tumors have a very low malignant potential; however, some pose a greater risk because of high mitotic activity [17,22,23,34]. The usefulness of EUS-FNA or EUS-TCB in this setting seems limited due to the factors discussed above (limited diagnostic yield and no capability to determine the mitotic index). As laparoscopic wedge resection of the SMT represents a safe option for most patients [35], it is felt that EUS-guided sampling can be omitted in most cases and reserved only for patients who are poor surgical candidates or those with the tumor located in areas difficult to resect such as the cardia.
   c) EUS-FNA or EUS-TCB is likely to impact the management in patients with a presumptive diagnosis of unresectable GIST in whom primary treatment with tyrosine kinase inhibitors is considered and confirmation of the diagnosis and CD117 status are required [33,34].
6. For duodenal and colorectal SMTs, data are insufficient to permit recommendations but it should be kept in mind that an SMT in patients with a history of rectal cancer may indicate local recurrence [36].

4.2. Diffuse esophageal/gastric wall thickening

Diagnostic accuracy of EUS-TCB for investigating diffuse esophageal/gastric wall thickening seems to be high (90 %), in particular when compared with that of EUS-FNA (60 %) (Evidence level 2 +). In patients with diffuse esophageal/gastric wall thickening, after failure of standard biopsy techniques to establish a diagnosis, we recommend performing EUS-TCB (Recommendation grade C). In the case of technical failure of EUS-TCB, EUS-FNA could be indicated (Recommendation grade D).

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, and amyloidosis [37]. In subepithelial infiltrating tumors, standard endoscopic biopsy sampling often yields false-negative results and the diagnostic yield of bite-on-bite biopsy sampling is unknown, although this technique is commonly used [38].

At least in the stomach, EUS without sampling is relatively accurate in discriminating malignant from benign conditions: in a prospective study of 61 patients, the thickening of the submucosa and/or muscularis propria (as opposed to thickening limited to the mucosa) was the single independent predictor of malignancy; the clinical impact of this feature was high because the probability of malignancy was 95 % vs. 5 %, respectively, depending on whether deep wall layers were thickened or not [39].

Data on the diagnostic yield of EUS-FNA and EUS-TCB in patients with diffuse GI wall thickening are scarce. In a prospective study [40], the diagnostic accuracy of EUS-FNA was significantly lower for diffuse GI wall thickening as compared with all other indications and, in another large prospective study [41], the sensitivity for cancer diagnosis was only 62 %. No data about the impact of EUS-FNA for diffuse GI wall thickening have been reported. EUS-TCB holds promise as it yielded high sensitivity and accuracy for the diagnosis of cancer (84 % and 90 %, respectively) in a prospective series of 31 patients with a thickened esophageal/gastric wall

[42]. EUS-TCB significantly impacted patient management in 42% of these patients, in particular by avoiding surgery in 35% of them. These results need to be confirmed in larger studies before firm recommendations can be made.

5. Pancreatic solid masses

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EUS-FNA presents a high diagnostic accuracy but a relatively low negative predictive value (NPV) for the diagnosis of pancreatic cancer. Due to this universal drawback of all sampling techniques available for the pancreas, preoperative sampling is not generally advised (i.e., for potentially resectable pancreatic tumors in operable patients). In other circumstances (e.g., neoadjuvant or palliative radio/chemotherapy), a pathological diagnosis is required; this can be obtained by sampling the primary pancreatic lesion or possible metastases (Evidence level 1+). Compared with ultrasound-guided or computed tomography (CT)-guided FNA of pancreatic masses, EUS-FNA seems to present a higher diagnostic accuracy, particularly for small lesions (Evidence level 2+). EUS-FNA can also demonstrate, in approximately 10% of patients, metastatic dissemination to distant lymph nodes, the peritoneum, or the liver that was unsuspected with other imaging techniques (Evidence level 2++). Repeat EUS-FNA in patients with a high clinical suspicion for pancreatic cancer but indeterminate or negative findings at initial EUS-FNA allows improvement of diagnostic accuracy (Evidence level 2+).

In cases where sampling of a suspected pancreatic cancer is indicated, we recommend EUS-FNA as the first-line procedure. If lesions suspicious for metastases are discovered during EUS staging of a suspected pancreatic cancer in patients with an otherwise resectable mass, EUS-FNA of these lesions should be performed (Recommendation grade B). In patients with a high clinical suspicion for pancreatic cancer and indeterminate or negative findings at the initial sampling procedure, including EUS-FNA, EUS-FNA (possibly repeated) is recommended (Recommendation grade C).

The differential diagnosis of solid pancreatic masses includes ductal adenocarcinoma (> 85% of cases), neuroendocrine tumors, metastases, acinar cell carcinomas, lymphomas, inflammatory pseudotumors, and very rare diseases such as pancreatoblastomas and solid pseudopapillary tumors. Pancreatic solid masses suspicious for cancer may be classified into two categories: (i) masses that will not be resected because they are locally advanced, associated with metastases, or they present in patients with a poor physical condition; and (ii) potentially resectable masses. For the first category, sampling in order to obtain a definitive diagnosis is usually desirable to assist with counseling and planning palliation while, for the second category, it is generally not recommended because the results of EUS-FNA (or any other nonsurgical sampling technique) are unlikely to affect further management due to the relatively low NPV of EUS-FNA for cancer diagnosis [43]. Arguments for EUS-FNA in potentially resectable tumors include an established protocol of preoperative neoadjuvant therapy, a patient demand for a conclusive diagnosis of cancer before surgery and, lastly, exclusion of unusual tumors (e.g., lymphoma, some pancreatic metastases) that would not benefit from surgery [44].

A large review (28 studies involving 4225 patients in total) of the performance of EUS-FNA in differentiating benign vs. malignant pancreatic masses found median figures for sensitivity, specificity, NPV, and diagnostic accuracy of 83% (range, 54%–95%), 100% (range, 71%–100%), 72% (range, 16%–92%) and 88% (range, 65%–96%), respectively [43]. The wide ranges reported above may be related to the use of varying definitions to classify cytopathological results as benign or malignant as well as to the exclusion of nondiagnostic specimens in some studies. New techniques including contrast-enhanced EUS and elastosonoendoscopy [45–47], DNA analysis [48], and K-*ras* mutation determination on FNA aspirates [49–51], are being developed to increase the NPV of EUS-FNA (72% in this review). In patients with indeterminate or negative findings at initial EUS-FNA and a high clinical suspicion for pancreatic cancer, repetition of EUS-FNA is strongly advised: a retrospective review of 24 consecutive patients showed that repeating EUS-FNA facilitated determination of the true status of disease in 20 patients (84%) with inconclusive findings at initial EUS-FNA [52]; another prospective study showed that EUS-FNA repeated up to three times increased sensitivity for cancer diagnosis from 68% to 92% [53]. Both studies used rapid on-site evaluation for the initial and subsequent EUS-FNA.

For the diagnosis of pancreatic neuroendocrine tumors, high sensitivity and diagnostic accuracy have been reported in two large retrospective studies that used immunocytochemistry for analyzing EUS-FNA samples [54,55]. EUS-FNA helped in assessment of the malignant behavior of pancreatic neuroendocrine tumors and was able to predict 5-year survival [56,57]. Determination of Ki-67 expression in EUS-FNA samples seems to be well correlated with that measured in surgical specimens and with the patient prognosis [58,59]. Metastatic lesions may also be demonstrated by EUS-FNA: in a series of 114 consecutive patients with focal pancreatic lesions identified on CT, EUS-FNA allowed demonstration of metastases of an extrapancreatic cancer in 11% of cases [60]. Finally, in cases suspicious for autoimmune pancreatitis or pancreatic lymphoma where pancreas sampling is indicated, specific techniques (namely, EUS-TCB and flow cytometry) may be useful [27,61].

Data comparing EUS-FNA vs. percutaneous CT- or ultrasound-guided FNA of pancreatic masses are limited [62–65]. In the single RCT available to date, 84 patients underwent CT- or ultrasound-guided FNA (n = 43) vs. EUS-FNA (n = 41) of a solid pancreatic mass [63]. EUS-FNA had numerically higher sensitivity and diagnostic accuracy than CT/ultrasound-FNA (84% vs. 62% and 89% vs. 72%, respectively) but the difference was not statistically significant. Three other series retrospectively evaluated 70, 149 and 1050 FNA procedures [62,64,65]. Only the largest study showed a significant difference, with a higher accuracy of EUS-FNA compared with CT/ultrasound-guided FNA for masses < 3 cm [65]. In addition, a cost-minimization study has demonstrated that EUS-FNA is the best initial test and the preferred secondary method after a failed alternative sampling procedure for the diagnosis of suspected pancreatic cancer [66].

An important advantage of EUS-FNA over the percutaneous route is the presumed lower risk of peritoneal seeding [67] and the ability to provide supplemental staging information by sampling of: (i) lymph node metastases in the celiac, lumboaortic, retroduodenopancreatic, and superior mesenteric regions, (ii) small hepatic lesions missed at other imaging modalities [68], and (iii) small pockets of previously undetected ascites [69]; all these sites when positive for malignancy indicate a poor prognosis, with an impact on patient management [70]. In a prospective study, 12% of 99 operable patients were found by EUS-FNA to have metastasis in lymph nodes (n = 6), liver (n = 4), ascites (n = 1), and retroperitoneum (n = 1) that were unsuspected at ultrasound/CT [71]. The percutaneous technique may still be indicated in patients who

are at risk for sedation-related complications and in those with surgically altered upper GI anatomy [72].

6. Pancreatic cystic-appearing lesions

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Biochemical and cytopathological analyses of fluid aspirate obtained by EUS-FNA may help the differential diagnosis of pancreatic cystic-appearing lesions (Evidence level 1+). In some conditions, the cyst wall may be brushed during EUS; this technique may allow a higher diagnostic yield than FNA but it has been associated with frequent, sometimes severe, complications (including death) (Evidence level 2–).

If nonsurgical diagnosis of pancreatic cystic-appearing lesions may change patient management, EUS-FNA with determination of amylase and carcinoembryonic antigen (CEA) levels plus cytopathological examination of fluid aspirate is recommended for lesions >2 cm in diameter (Recommendation grade B). EUS-guided cyst wall brushing may be useful in well-selected cases (Recommendation grade D).

Pancreatic fluid collections mostly consist of benign cystic neoplasms with or without a malignant potential (namely, intraductal papillary mucinous neoplasm [IPMN] and mucinous cystadenoma [MCA], or serous cystadenomas, respectively), inflammatory pseudocysts, and malignant cysts such as mucinous cystadenocarcinomas (MCAC). In a large multicenter study, the accuracy of EUS morphology for differentiating between MCA/MCAC and nonmucinous lesions was low (51%) [73]. The analysis of CEA in fluid aspirate yielded a higher accuracy in a pooled analysis (**Table 3**) [74]. The measurement of amylase level is also useful because a value <250 U/L virtually excludes pancreatic pseudocyst. Nevertheless, the value of all of these analyses is limited by: (i) a relatively low sensitivity for distinguishing MCA/MCAC from serous cystadenomas and pseudocysts, and (ii) the requirement for a minimum of 1 mL of liquid to perform the analysis, a demand that is not feasible with lesions <1 cm in diameter. The usefulness of other analyses, including total DNA, K-*ras* mutation, and proteomic analysis on fluid aspirate is currently being investigated [75–77].

The analysis of biochemical markers is complemented by cytopathological examination of the aspirate. Cytopathological examination yields a sensitivity of approximately 50% for the diagnosis of malignancy [74]. EUS-guided fluid aspiration may be complemented by cyst wall brushing if a 19-G needle is used (the lesion has to be >2 cm in diameter and those located in the head of the pancreas or the uncinate process are difficult to reach due to the rigidity of the needle). In the two controlled studies of EUS-guided cyst wall brushing reported to date in full-text papers [78,79], brushing had a higher sensitivity than FNA for the cytopathological diagnosis of intracellular mucin in identical patients (62% vs. 23%, respectively; $P=0.001$) and it was superior for detecting diagnostic cells (73% vs. 36%, respectively; $P=0.08$) and mucinous cells (50% vs. 18%, respectively; $P=0.016$). However, a final diagnosis was not available for all patients in these studies, and this technique is not widely used, possibly due to potential complications: in three prospective studies involving a total of 73 patients, morbidity associated with cyst wall brushing was 9.5% and two patients required hospitalization due to post-procedure pancreatitis [78,80,81]. One procedure-related death has also been reported [79]. Some authors recommend cyst wall brushing in selected patients, namely in those with prior inconclusive FNA who have cysts suspicious for malignant transformation or in those who are poor surgical candidates and are considered for cyst ablation techniques [78].

7. Mediastinal lesions unrelated to lung or esophageal cancer

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Transesophageal EUS-FNA is safe and accurate for the diagnosis of solid lesions located in the posterior mediastinum. For mediastinal lymph nodes, the addition of FNA to EUS slightly increases sensitivity and significantly increases specificity for diagnosing the cause of lymph node enlargement (Evidence level 1–). EUS-FNA of noncystic mediastinal lesions of unknown origin impacts patient management in >70% of cases (Evidence level 2+). EUS-FNA of mediastinal cysts carries a risk of severe infection even if prophylactic antibiotics are administered (Evidence level 3).

We recommend transesophageal EUS-FNA for the initial work-up of solid mediastinal lesions and enlarged lymph nodes of unknown origin that are accessible to this technique (Recommendation grade B); we discourage EUS-FNA of mediastinal cysts (Recommendation grade D).

The posterior mediastinum is accessible by transesophageal EUS-FNA; in this location, lesions most frequently consist of enlarged lymph nodes. Endosonographic criteria have been proposed to establish the benign or malignant nature of lymph nodes [82]. In a meta-analysis of 76 noncomparative, retrospective or prospective cohort series that used either EUS-FNA or EUS to investigate mediastinal lymph nodes, it was found that compared with EUS, EUS-FNA had a slightly higher sensitivity (88% vs. 85%) and a significantly higher specificity (96% vs. 85%) for diagnosing the cause of lymph node enlargement [83]. Compared with alternative techniques available for sampling the mediastinum, EUS-FNA 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 [84]. We recommend mediastinoscopy or CT-guided biopsy as second-line approaches.

The ability of EUS-FNA to diagnose lymph node metastases deriving from cancers located outside of the mediastinum and the lungs has been demonstrated in two case series involving patients with breast cancer or pancreatic/periampullary cancers [85,86]. Lymphoma has been diagnosed with a high accuracy (96%) in a prospective series of 104 patients with lymph nodes of unknown origin (50 patients had lymph nodes located in the

Table 3 Biochemical analyses for the diagnosis of cystic-appearing pancreatic lesions.

Cutoff	Diagnosis	Sensitivity, %	Specificity, %	Accuracy, %
Amylase <250 U/L	SCA, MCA, MCAC	44	98	65
CEA <5 ng/mL	SCA, pseudocyst	50	95	67
CEA >800 ng/mL	MCA, MCAC	48	98	79

CEA, carcinoembryonic antigen; SCA, serous cystadenoma; MCA, mucinous cystadenoma; MCAC, mucinous cystadenocarcinoma.
Adapted with permission from van der Waaij et al. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointest Endosc 2005; 62: 383–389.

mediastinum and 48 had a lymphoma) [87]. The diagnosis of lymphoma is frequently missed at cytopathological examination of EUS-FNA samples; this can be remedied by subjecting EUS-FNA specimens to flow cytometry or by on-site isolation of whitish fragments for histopathological examination [88]. EUS-FNA is also very useful for the diagnosis of infectious and inflammatory diseases affecting the mediastinum, including extrapulmonary tuberculosis and sarcoidosis [89,90]. It has been suggested that using a 19-G needle to obtain a core biopsy was useful in the latter condition [91]. In a prospective series of 60 patients suspected of having tuberculosis in an area endemic for the disease [92], EUS-FNA of isolated mediastinal lymph nodes had a diagnostic yield of 93 %.

Concerning mediastinal cysts, EUS-FNA has been associated with severe infectious complications despite the administration of prophylactic antibiotics [93 – 97], and it is unlikely to impact patient management. Therefore, the indication of EUS-FNA in mediastinal cysts requires a careful consideration of the balance between benefits and risks in each patient.

The impact of EUS-FNA on the management of patients with posterior mediastinal lesions was analyzed in five studies that involved 444 patients in total (one prospective [98], four retrospective [99 – 102]). Globally, the proportion of mediastinal lesions with a final diagnosis of malignancy and the impact on patient management were in the range of 56 % – 64 % and 70 % – 87 % of cases, respectively. Definitions of impact on management varied between studies but most frequently consisted of avoidance of surgery. Hirdes et al. emphasized the risk of a negative impact on patient management related to inadequate or false-negative EUS-FNA samples (this affected 7 % of their patients) [100]. In that study, a mean cost reduction of 472 € per patient was observed by using EUS-FNA compared with alternative diagnostic procedures, and complications (nonfatal perforations) were reported in 0.9 % of patients. Three of the five studies cited above specifically reported on the impact of EUS-FNA in patients investigated for mediastinal lesions of unknown origin (n = 109), as opposed to the staging of a known malignancy [98,99,101]. The final diagnosis for the mediastinal lesions was a malignancy in 30 % – 72 % of patients and EUS-FNA had an impact on patient management in 73 % – 94 % of them, most frequently by guiding therapy and avoiding surgery.

8. Esophageal cancer

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For initial lymph node staging in esophageal cancer, EUS-FNA is more accurate than EUS alone as well as than helical CT (Evidence level 2++); it also allows diagnosis of metastases undetected at CT in the left liver lobe in approximately 5 % of patients. In patients who are considered for surgical resection, EUS-FNA may impact treatment decisions by correcting the stage determined by helical CT (usually towards a higher stage) in approximately one third of cases (Evidence level 2+). The impact of adding FNA to the staging based on EUS alone remains uncertain but there is limited evidence suggesting that EUS-FNA may change the management plan based on EUS alone (Evidence level 2 –). EUS-FNA has higher accuracy than integrated fluorodeoxyglucose positron emission tomography and CT (integrated FDG-PET/CT) for lymph node staging. For lymph node re-staging and for predicting complete pathological response after neoadjuvant therapy, EUS-FNA has lower accuracy than integrated FDG-PET/CT (Evidence level 2+).

For initial staging, EUS-FNA should be performed whenever the cytological result is likely to affect the decision on what treatment option to choose in a given patient (e.g., primary surgical resection, or definitive or neoadjuvant chemoradiotherapy). Integrated FDG-PET/CT is recommended only in case of incomplete EUS examination (Recommendation grade D). For re-staging after neoadjuvant therapy, integrated FDG-PET/CT is recommended (Recommendation grade C). Whether EUS-FNA should be performed to obtain cytological confirmation of integrated FDG-PET/CT findings positive for lymph node metastasis requires further studies.

Despite continuous technological progress in the field of CT Scan and FDG-PET scanning, EUS is still recognized as the most accurate imaging method for initial locoregional staging in esophageal cancer [103]. Consequently, it is recommended that patients who have no distant metastases on CT (and/or FDG-PET) should undergo EUS [104,105]. Whether adding EUS-FNA to this standard staging algorithm significantly changes treatment decisions has not been well studied. Although many studies reported excellent sensitivity (88 % – 100 %), specificity (100 %), and accuracy (87 % – 100 %) of EUS-FNA for detection of lymph node metastases [106 – 109], these studies were retrospective, focused mostly on celiac lymph nodes, had high potential for selection bias, and relied on an imperfect gold standard [103]. The only study that overcame these limitations was a prospective blinded comparison conducted in 76 consecutive patients in whom pathological evaluation of resected lymph nodes was available (**Table 4**) [110]. The accuracy of EUS-FNA for lymph node staging (87 %) was higher than that of EUS alone (74 %; $P = 0.01$) or that of helical CT (51 %; $P < 0.001$).

EUS-FNA may affect patient management mostly by providing cytopathological confirmation of metastasis to regional lymph nodes, to nonregional lymph nodes (mostly celiac) or to distant sites. The true impact of EUS-FNA on patient management is difficult to measure because treatment decisions are guided not only by the presence of lymph node or distant metastases but also by many other factors including patient performance status and tumor location, histology, and infiltration depth (T-stage). In addition, management algorithms vary between institutions [110,111]. Finally, it is often difficult to separate the impact of EUS-FNA from that of EUS alone, and the difference in lymph node staging accuracy between EUS alone and EUS-FNA, albeit statistically significant, is relatively small [110]. Despite these reservations, there is evidence to suggest that EUS-FNA changes the management plan based on EUS alone:

Test	Sensitivity (95 %CI)	Specificity (95 %CI)	Accuracy (95 %CI)
EUS	71 % (56 % – 83 %)	79 % (59 % – 92 %)	74 % (62 % – 83 %)
EUS-FNA	83 % (70 % – 93 %)	93 % (77 % – 99 %)	87 % (77 % – 94 %)
Helical CT	29 % (17 % – 44 %)	89 % (72 % – 98 %)	51 % (40 % – 63 %)

CI, confidence interval; EUS, endoscopic ultrasound; FNA, fine needle aspiration; CT, computed tomography

* Data from a prospective blinded study in 76 consecutive patients with pathological verification [110].

Table 4 Performance characteristics of various techniques in the detection of lymph node metastases from esophageal carcinoma*. Both EUS-FNA and EUS alone were more sensitive and more accurate than was helical CT.

- The prospective study by Vazquez-Sequeiros et al. discussed above found that EUS-FNA (but not EUS alone) was able to significantly modify tumor stage determined by helical CT (usually towards a higher stage) in 38% of patients but the study did not directly assess the impact of EUS-FNA on patient management [110].
- In two series (one prospective and one retrospective) that involved a total of 307 patients, demonstration by EUS-FNA of lymph node metastases distant from the primary cancer changed the management plan in 7%–12% of patients [71,107].
- Metastases to the left liver lobe (median size, 5 mm) or collections of malignant pleural fluid unsuspected at CT were diagnosed by EUS-FNA in 3%–5% of patients in a prospective and a retrospective study that together included a total of 207 patients [71,112].
- EUS-FNA has also been used in a prospective study to select the surgical approach in patients with a resectable distal esophageal carcinoma and mediastinal lymph nodes visualized on EUS: EUS-FNA changed the management in 23% of 48 patients, by allocating patients with positive lymph nodes to transthoracic esophagectomy, and those without demonstrated malignant lymph node involvement to transhiatal resection that offers limited capability of lymph node removal [113].

Integrated FDG-PET/CT has been compared with EUS-FNA for initial lymph node staging in a retrospective study that involved 57 patients with lymph node metastasis confirmed at pathological examination [114]. EUS was significantly more sensitive than FDG-PET/CT for diagnosing lymph node metastasis (86% vs. 44%, $P<0.0001$). Of note, FNA had been performed to confirm lymph node metastasis suspected on the basis of EUS criteria in approximately one third of cases only. These data confirm those of a prospective study that showed that the addition of FDG-PET to EUS and CT did not change patient management if a complete EUS examination had been performed [115].

After chemoradiotherapy, the accuracy of lymph node staging by EUS-FNA (78%) was found in a prospective study of 48 patients to be similar to that of CT (78%) and significantly lower than that of integrated FDG-PET/CT (93%; $P=0.04$) [116]. The latter method was also superior in predicting complete pathologic response.

9. Gastric cancer

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EUS-FNA modifies the management of patients with a gastric cancer by demonstrating distant metastases unsuspected with other imaging techniques in 8%–15% of cases (Evidence level 2+).

In patients with gastric cancer, we recommend performing EUS-FNA of all suspected distant metastases detected during EUS examination only when it has the potential to change patient management (Recommendation grade C).

In patients with gastric cancer, malignant involvement of distant intra-abdominal lymph nodes (e.g., retropancreatic, mesenteric, and para-aortic lymph nodes) or of mediastinal lymph nodes distant from the primary tumor is indicative of a metastatic disease that qualifies the patient for palliation rather than resection with curative intent. In a prospective series of 62 patients with gastric cancer who were fit for surgery, EUS-FNA was performed for staging purposes in 12 patients (19%); it demonstrated the presence of metastases in 8 patients (13%) [71]. After exclusion of three patients with metastases suspected by CT and/or percutaneous ultrasound, the actual clinical impact of EUS-FNA was 8%. A more recent, retrospective, study involved 234 consecutive patients referred for management of a gastric cancer; 81 (35%) had EUS-FNA targeting 99 lesions that were suspicious for distant metastases according to echo features and locations [104]. Most (79%) lesions sampled consisted of mediastinal lymph nodes. Overall, 38 patients had distant metastases demonstrated by EUS-FNA (23 [61%] had the primary tumor in the cardia). After exclusion of four patients with liver metastases suspected at CT, EUS-FNA was judged by a board of surgeons to change patient management in 34 patients (15%) by avoiding unnecessary surgery.

10. Rectal cancer

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For the initial staging of rectal cancer, EUS-FNA does not have more impact on patient management than EUS alone; in patients with perirectal lesions detected at EUS and a history of cancer, EUS-FNA is useful to demonstrate or rule out cancer recurrence (Evidence level 2+).

We recommend performing EUS-FNA of perirectal lesions only when this has the potential to change patient management, i.e. mostly in patients with a previous history of cancer, and not for rectal cancer staging (Recommendation grade C).

In the preoperative staging of rectal cancer, a single study has assessed the potential impact of EUS-FNA [117]. It showed that EUS-FNA added almost no relevant information to EUS alone: therapy decisions made by a colorectal surgeon after sequential disclosure of, first, the results of EUS alone and, secondly, the results of EUS-FNA, were identical in 79 of 80 patients who were evaluated prospectively. In that study, all non-juxtatumoral lymph nodes that were detected at EUS were sampled; 41 patients (51%) actually underwent EUS-FNA. Indeed, sensitivity, specificity, and diagnostic accuracy of N staging by EUS alone or EUS-FNA were similar except for a lower sensitivity of EUS-FNA (52% vs. 74%). The negligible impact of EUS-FNA could be related to the close correlation of T and N stages in rectal cancer and the fact that most perirectal lymph nodes detected at EUS during rectal cancer staging are malignant.

In patients with perirectal lesions detected at EUS and a history of cancer (in the colorectum or elsewhere), EUS-FNA allowed detection of cancer relapse with a high diagnostic accuracy in a prospective and a retrospective series that included 84 patients in total [36,118]. In both studies, EUS-FNA was more accurate than EUS alone in diagnosing malignancy recurrence, at 92% vs. 69% in the largest study ($P<0.01$) [118]. The latter study also found that EUS-FNA had a considerable impact on patient management in 26% of cases.

11. Miscellaneous

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11.1. Lymph nodes of unknown origin

EUS-FNA allows accurate determination of the nature of lymph nodes of unknown origin (Evidence level 2+). We recommend performing EUS-FNA of lymph nodes of unknown origin if these are accessible, no other significant lymph node is easily accessible (e.g., subcutaneous lymph node), and a pathological result would likely affect patient management (Recommendation grade C).

A prospective study has reported a 98% diagnostic accuracy of EUS-FNA (using a 19-G needle) in 104 patients who had lymph

nodes of unknown origin located in the mediastinum or abdomen and which were accessible to EUS-FNA [87]. Subclassification of lymphoma was possible for 44 (92 %) of the 48 patients diagnosed with this condition. A retrospective study analyzed the results of EUS-FNA for enlarged periportal lymph nodes in 64 patients without identifiable malignancy or liver disease [119]. A malignancy (metastatic carcinoma or non-Hodgkin's lymphoma/chronic lymphocytic leukemia) was diagnosed in 19 % of patients. Specific techniques of EUS-FNA and of sample preservation are useful in this indication (see Technical Guideline for details) [1]. No data on the impact of EUS-FNA in this indication has been published so far.

11.2. Adrenal gland masses

EUS-FNA is an accurate and safe technique for sampling left adrenal gland masses (Evidence level 2+). In patients with lung cancer and an enlarged left adrenal gland, EUS-FNA of the left adrenal gland modifies disease stage and treatment strategy in approximately half of patients (Evidence level 2+); it is recommended if a cytopathological result positive for malignancy is likely to change patient management (Recommendation grade C).

EUS-FNA of the left adrenal gland has been reported by a few centers and, more recently, EUS-FNA of the right adrenal gland has been reported by two centers [120 – 122]. No significant procedure-related complications have been reported to date. The diagnostic yield of EUS-FNA ranged between 76 % and 100 % in the largest series published, which included 24 – 85 patients [121,123 – 125]. Finally a study looked at the impact of EUS-FNA of left adrenal gland masses in unselected patients with established or suspected lung cancer; it showed a modification in TNM staging by EUS-FNA results in 70 % of cases whereas treatment changed in 48 % [126].

11.3. Focal solid liver lesions

Solid liver lesions may be safely sampled by EUS-FNA; the diagnostic yield and the impact on patient management are high (Evidence level 2+). We recommend performing EUS-FNA of focal liver lesions accessible to EUS-FNA if: (i) a pathological result positive for malignancy would likely affect patient management, and (ii) the lesion is poorly accessible to percutaneous FNA or it is detected de novo by EUS or it has been sampled by percutaneous FNA with a nondiagnostic result (Recommendation grade C).

EUS imaging of the liver is currently limited to the left lobe, the proximal part of the right lobe, the hilum, and part of the intrahepatic biliary tract, with variations related to the type of echoendoscope used and patient anatomy [127,128].

A prospective study in 41 patients who had solid liver lesions visible at EUS showed that a specimen adequate for pathological examination could be obtained in most cases (98 %) with an acceptable morbidity rate (5 %; all complications were minor) [129]. Sensitivity and NPV for the diagnosis of malignancy were 94 % and 78 %, respectively. Of note, these results were obtained by combining cytopathological and histopathological examination of microcores.

Two retrospective series included a total of 244 EUS-FNA procedures for solid liver lesions visible at EUS; the diagnostic yield was in the range of 80 % – 90 %, including cases where ultrasound- or CT-guided FNA had failed to yield a diagnosis [68,130]. In one study, one death was reported (mortality rate 0.6 %), due to cholangitis in a patient who was suspected to have an occluded biliary stent at the time of EUS. In both retrospective studies, EUS-FNA had an impact on clinical management in approximately 90 % of the patients who had a EUS-FNA sample positive for malignancy. No prospective study has compared percutaneous with EUS-guided FNA.

11.4. False-positive cytopathological results

The incidence of false-positive cytopathological results with EUS-FNA samples ranges between 1.6 % and 5.3 %. (Evidence level 2+). Flushing the working channel of the echoendoscope before every needle pass may reduce this risk (Evidence level 2 –). The possibility of a false-positive diagnosis should be kept in mind when interpreting cytopathological results of EUS-FNA, particularly for EUS-FNA of lymph nodes in patients with luminal cancers (Recommendation grade C). We suggest flushing the working channel of the echoendoscope before every needle pass and collection of microcores to help prevent this outcome (Recommendation grade D).

In a retrospective review of 188 patients who underwent surgery after having had a cytopathological result positive for malignancy at EUS-FNA, a false-positive diagnosis was identified in two pancreatic and one lymph node sample (false-positive rate 1.6 %) [131]. Interpretation errors were identified in two of the three cases. Gleeson et al. reported an incidence of false-positive cytopathological results of 5.3 % by matching 377 EUS-FNA and surgical samples [132]. Discordant results were blindly assessed by three cytopathologists: reasons for false-positive results included epithelial cell contamination and pathological misinterpretation. Recently, in an ex vivo experiment, smears were prepared after sham EUS-FNA performed with an echoendoscope that had just been used in 13 patients with esophageal cancer (without FNA); the sham EUS-FNA was done either after extensive flushing of the working channel (n = 5) or not (n = 8). Neoplastic cells were detected on smears prepared from 6 of the 8 samples (75 %) obtained by sham EUS-FNA without flushing the working channel and in none of the 5 samples obtained by sham EUS-FNA after flushing the working channel [133]. In a prospective study performed in 140 patients, malignant cells were found in the luminal fluid aspirated through the echoendoscope suction channel in 48 % of patients with luminal tumors (not influenced by FNA) and in 10 % of patients after EUS-FNA of pancreatic tumors [134].

11.5. Needle tract seeding

Needle tract seeding is extremely rare with EUS-FNA (Evidence level 3).

Only three cases of needle tract seeding have been reported to date following EUS-FNA, with metastases located in the gastric or esophageal wall [135 – 137]. As discussed above, the risk of peritoneal seeding from pancreatic cancer could be lower after EUS-guided compared with percutaneous FNA [67].

Use of this guideline

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 these statements, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance with these recommendations. ESGE Guidelines are intended to be an educational device for providing 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.

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