

# EFSUMB Guidelines on Interventional Ultrasound (INVUS), Part IV EUS-guided Interventions: General aspects and EUS-guided sampling (Long Version)

## EFSUMB Leitlinien interventioneller Ultraschall (INVUS), Teil IV Endosonografisch gestützte Interventionen: allgemeine Aspekte und endosonografisch gestützte Materialgewinnung (Langversion)

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### Key words

- guideline
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- quality indicators
- adverse events

### Bibliography

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### Abstract

The fourth part of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) Guidelines on Interventional Ultrasound describes general aspects of endoscopic ultrasound-guided diagnostic and therapeutic interventions and assesses the evidence for endoscopic ultrasound-guided sampling. Endoscopic ultrasound combines the most advanced high-resolution ultrasound imaging of lesions within the wall and in the vicinity of the gastrointestinal tract and safe and effective fine needle based tissue acquisition from these lesions. The guideline addresses the indications, contraindications, techniques, adverse events, training and clinical impact of EUS-guided sampling. Advantages and drawbacks are weighed in comparison with image-guided percutaneous biopsy. Based on the most current evidence, clinical practice recommendations are given for crucial preconditions and steps of EUS-guided sampling as well as for safe performance. Additionally, the guideline deals with the principles and reliability of cytopathological reporting in endoscopic ultrasound-guided sampling (long version).

### Introduction: Diagnostic and therapeutic EUS-guided interventions

This is the first of two guidelines (part IV and V) within the framework of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) Guidelines on Interventional Ultrasound describing endoscopic ultrasound (EUS)-guided diagnostic and therapeutic interventions. Part IV deals with the indications and clinical im-

### Zusammenfassung

Der vierte Teil der Leitlinien der European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) zur interventionellen Sonografie beschreibt allgemeine Aspekte endosonografisch gestützter diagnostischer und therapeutischer Interventionen und bewertet die Evidenz für die endosonografisch gestützte Materialgewinnung. Die Endosonografie vereint fortgeschrittene hochauflösende Ultraschallbildgebung von Läsionen in der Wand des Gastrointestinaltrakts und in dessen Umgebung mit der Möglichkeit, daraus mit Feinnadeltechniken effizient und risikoarm Material für die feingewebliche Diagnostik zu entnehmen. Die Leitlinie thematisiert Indikationen, Kontraindikationen, Techniken, unerwünschte Ereignisse, Training und klinischen Stellenwert der endosonografisch gestützten Materialgewinnung. Dabei werden Vor- und Nachteile im Vergleich zur perkutanen bildgebend gestützten Biopsie abgewogen. Auf der Grundlage der aktuellen Evidenz werden für die klinische Praxis Empfehlungen zu den entscheidenden Voraussetzungen und Schritten sowie für eine sichere Durchführung der endosonografisch gestützten Materialgewinnung gegeben. Ergänzend adressiert die Leitlinie Prinzipien und Verlässlichkeit zytopathologischer Befundung von durch endosonografisch gestützte Biopsie gewonnenem Material (Langversion).

part of EUS-guided sampling<sup>1</sup> and gives evidence-based recommendations for the safe and efficient performance of this technique based on the available evidence at the time of manuscript preparation. It is complemented by a guideline on EUS-guided therapeutic interventions (part V) [1]. Methods of guideline development are described

<sup>1</sup> Term is explained in the addendum on terminology.

in the introduction to the EFSUMB Guidelines on Interventional Ultrasound (INVUS) [2]. Levels of Evidence (LoE) and Grades of Recommendations (GoR) have been assigned according to the Oxford Centre for Evidence-based Medicine criteria (March 2009 edition) [<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009>].

### General considerations

Endoscopic ultrasound (EUS; synonym: endosonography)<sup>2</sup> represents an interdisciplinary high-performance imaging method which combines endoscopy and ultrasound by using special transducers mounted at the tip of the endoscope [3–9]. EUS facilitates the use of high-frequency scanning and advanced techniques like 3D reconstruction, color Doppler, contrast enhancement and real-time elastography in anatomical regions that are poorly accessible to transabdominal or transthoracic ultrasonography. Detailed examination of the pancreaticobiliary system and gastrointestinal (GI) tract as well as of adjacent structures (e.g. liver or mediastinum) is now feasible. Prior to 1992, EUS was solely an imaging technique, but with the introduction of EUS-guided fine-needle aspiration (EUS-FNA)<sup>3</sup> [10], it became possible to obtain a definite cytopathological or histopathological diagnosis of mediastinal, abdominal, retroperitoneal and pelvic lesions, establishing EUS-FNA as a crucial procedure. Further advances in 1996, allowed EUS-guided celiac plexus neurolysis [11], EUS-guided drainage of GI tract-adjacent fluid collections and pancreatic pseudocysts [12]. Furthermore, EUS guidance or assistance plays a crucial role in other minimally invasive drainage procedures, e.g. in obstructed biliary and pancreatic ducts [7–9, 13–16]. A first experience with endobronchial ultrasound-guided transbronchial fine-needle aspiration (EBUS-TBNA)<sup>4</sup> was reported in 2003 [17].

### Equipment and setup

EUS equipment comprises a flexible video echoendoscope with a radial or linear transducer design mounted at the tip of the endoscope. The flexible scopes are linked both with an endoscopic video processor and an ultrasound processor, allowing for simultaneous endoscopic and ultrasound imaging. Several echoendoscopes are available commercially [3–9, 18]. The endoscopic image allows for orientation and navigation in the GI tract or tracheobronchial tree to the target area, while the ultrasound image is acquired only following gas aspiration, for optimal coupling of the tissue-transducer interface. Tissue-transducer coupling may be further improved with instillation of water in the GI lumen or in the balloon surrounding the transducer to obtain better quality images [7–9, 19].

Radial and linear echoendoscopes have variable frequencies (5–12 MHz). The ultrasound examination field of radial echoendoscopes is perpendicular to the long axis of the endoscope, with obtained images often concordant with computed tomography (CT)/magnetic resonance (MR) imaging, especially in the mediastinum and the rectum [6, 19]. Initial studies mainly used radial echoendoscopes with a mechanical scanner, imaging for GI (mainly esophago-gastric and rectal) and pancreaticobiliary cancer staging (75.6% of original EUS articles up to 2001) [20]. Comparative studies (including a single randomized controlled trial [RCT]), have shown

superiority of electronic vs. mechanical radial transducers with image quality [21–23]. Radial echoendoscopes cannot be used to guide diagnostic and therapeutic interventions. Linear echoendoscopes have an ultrasound examination field in the longitudinal axis of the echoendoscope, allowing performance of needle-based diagnostic and therapeutic interventions through real-time visualization [16]. A wide variety of accessory equipment for EUS-guided interventions is commercially available [24]. For endobronchial ultrasound (EBUS), specifically designed linear echoendoscopes based on flexible bronchoscopes are available [25]. Radial and linear echoendoscopes with electronic transducers incorporate functions for the examination of vascularity with color Doppler or tissue compressibility with strain elastography [7, 19, 26–29]. Several RCTs compared the diagnostic accuracy of both types of echoendoscopes, with no advantage of either radial or linear EUS for the staging of esophago-gastric cancer [30, 31] or for the detection and staging of pancreatic cancer reported [32, 33]. A therapeutic echoendoscope with a forward-viewing 90-degree curved array at the front of the scope has a potential advantage of allowing interventions with an axial application of force during needle insertion and stenting, with comparable imaging quality and equal performance in EUS-guided drainage of pancreatic pseudocysts being reported [34–36].

EUS mini-probes, with a diameter between 2 and 3 mm, are catheter-like and are passed through the biopsy channel of a conventional endoscope. Most are mechanical radial transducers, requiring a separate driving unit between the transducer and the ultrasound processor [7, 9]. Mini-probes have a high-frequency transducer (>10 MHz). Due to their high resolution but limited penetration, these high-frequency mini-probes are used for the diagnosis and staging of small (<2 cm) esophago-gastric, colorectal and bronchial lesions (endoluminal), and in pancreaticobiliary diseases (intraductal ultrasound probes, IDUS) [37–51]. For rectal examinations, where traditionally rigid radial or linear transrectal probes are used, flexible radial and linear echoendoscopes can stage lower colorectal cancers and image inflammatory bowel disease and submucosal tumors [52–54]. A comparative study showed that the staging performance of a flexible radial echoendoscope and a rigid linear probe was equivalent [53]. Both rigid (linear and curved-array) ultrasound probes with a biopsy channel as well as flexible linear and forward-viewing echoendoscopes can be used for transrectal EUS-guided interventions [55–62].

#### Recommendation 1

Linear echoendoscopes are indispensable for EUS-guided sampling and injection treatments (LoE 5, GoR D). Strong consensus (100%).

#### Recommendation 2

For one-step EUS-guided drainage procedures, a large-channel therapeutic linear echoendoscope is recommended (LoE 5, GoR D). Strong consensus (100%).

### Patient preparation and monitoring

Patient preparation is identical to flexible endoscopy, with fasting for 6 hours and clear fluids permitted until 2 hours prior. All pre-procedural considerations of gastrointestinal endoscopy should be followed, including detailed informed consent, management of an-

<sup>2</sup> Term is explained in the addendum on terminology.

<sup>3</sup> Term is explained in the addendum on terminology.

<sup>4</sup> Term is explained in the addendum on terminology.

ticoagulation and antiplatelet therapy, indication for prophylactic antibiotics and need for sedation [63]. With EUS-guided transmural drainage procedures, carbon dioxide insufflation of the gastrointestinal lumen should be considered, in particular in the drainage of walled-off pancreatic necrosis; this minimizes the risk of gas embolism.

The American Society of Gastrointestinal Endoscopy (ASGE) has defined several evidence-based preprocedural quality indicators, including:

1. appropriate and well-documented indication,
2. obtaining and documenting of informed consent based on the discussion of specific risks associated with the particular EUS procedure,
3. performing of preprocedure history and directed physical examination,
4. assessing and documenting of the risk for adverse events,
5. administration of prophylactic antibiotics in the setting of EUS-guided sampling of pancreatic cystic lesions (PCL),
6. monitoring and documentation of sedation,
7. proper management and documentation of antithrombotic treatment,
8. preprocedural team time-out<sup>5</sup>, and
9. performing of EUS by a well-trained endosonographer [64].

EUS and EUS-guided interventions are complex and lengthy procedures, more than standard endoscopy, usually requiring more patient sedation [65, 66] but are often well tolerated, including in pediatric and elderly patients [67–70]. EUS (including EBUS) can be safely performed using conscious sedation (midazolam) perhaps combined with an opioid (fentanyl or pethidine) [71–73]. Alternatively, propofol sedation is a more efficient approach, with better patient and operator satisfaction and is increasingly used [72, 74–79]. Sedation practices vary between countries, but sedation during EUS procedures with electronic patient monitoring is standard practice. Propofol sedation has a good safety profile, especially for lengthy interventions like therapeutic EUS [72, 74–78, 80–83], but controversies surrounding the personnel administering propofol remain. These legal issues have to be resolved according to local conditions and national legislations. Endoscopist- and nurse-administered propofol sedation has been shown to be safe and effective in EUS and EUS-guided interventions (including EBUS-TBNA) in both average-risk and high-risk patients [79, 82–85]. National legal restrictions in many countries do not permit non-anesthesiologist administration of propofol. It has been established in only a few European countries, including Austria, Denmark, Germany, Greece, the Netherlands, Sweden, and Switzerland [86, 87].

### Recommendation 3

Carefully monitored conscious or deep sedation should be routinely offered to all patients undergoing EUS-guided interventions (LoE 1b, GoR B). Strong consensus (100%).

### Recommendation 4

Controlled propofol sedation should be used with due consideration of national legal regulations, and the experience and training of the medical personnel (LoE 5, GoR D). Strong consensus (100%).

<sup>5</sup> Term is explained in the addendum on terminology.

## Platforms for EUS-guided diagnostic and therapeutic interventions

Needles for EUS-guided sampling are commercially available from several manufacturers. The fine needles, size range of 25–19 Gauge (G) [16, 24, 88–90], allow needle choice based on the target lesion location, the expected diagnosis, the necessity for further procedures and examiner experience in order to maximize yield and minimize complications and costs [90, 91]. “Histology needles” include: trucut needles, needles with side fenestration and reverse bevel technology [91–98] and needles with a shark mouth-like needle tip geometry.

Therapeutic EUS-guided interventions commence with puncture of the targeted lesion for initial access, followed by therapeutic injection or a guidewire-assisted drainage procedure. A 22 G needle allows only 0.018 inch guidewires. Therefore, 19 G needles are normally used, allowing passage of stiffer 0.035 inch guidewires. Either conventional or special (smooth end to prevent guidewire shearing) access aspiration needles may be used for the initial access. Diathermic devices (needle knives or cystotomes, 6–10 French) with a round cutting tip and a stabilizing sheath allowing passage of multiple guidewires are also reported. A variety of biliary dilatation balloons (up to 8 mm diameter) and biliary endoprotheses (7, 8.5 or 10 French plastic) can be used for drainage, and covered self-expandable metallic stents have been used for pancreatic and biliary drainage [1, 13–16, 99–103].

## Indications and contraindications

EUS has evolved as a diagnostic and therapeutic procedure with substantial clinical impact, altering management in a number of patients [3, 15, 20, 64, 91, 104–107]. Appropriate (evidence-based) indications are listed in [Table 1](#), [3, 7–9, 64, 91, 108–113].

Absolute contraindications of EUS are similar to those of conventional advanced endoscopy procedures. Specific contraindications of EUS-guided sampling and therapeutic interventions are related to unacceptable risks of bleeding, infection, and perforation ([Table 2](#); section 5) [8, 9, 16, 110, 114, 115], which should be assessed prior to the intervention on an individual basis weighing procedural risk vs. clinical impact.

### Recommendation 5

As EUS is an advanced invasive procedure, it requires a proper indication, assessment of individual risks and contraindications, detailed informed consent, careful consideration of antithrombotic therapy and antibiotic prophylaxis, and a pre-interventional team time-out<sup>6</sup> (LoE 5, GoR D). Strong consensus (100%).

## Education and training in endoscopic ultrasound Preconditions for performing EUS

EUS has evolved into an advanced endoscopic procedure requiring structured training as supported by the ASGE core curriculum for EUS [116]. Certain conditions need to be attained prior to commencing an EUS program; state-of-the-art EUS equipment and accessories should be in place, previous EUS experience and training (> 12 months) with proficiency in basic EUS should be available, the presence of a multidisciplinary team with expertise in gastro-

<sup>6</sup> Term is explained in the addendum on terminology.

**Table 1** Established indications of endoscopic ultrasound.

<b>diagnostic evaluation (including EUS-guided sampling)</b>	
pancreatico-biliary disorders	obstructive jaundice/biliary stricture of unknown etiology
	suspected bile duct stones
	biliary and idiopathic acute pancreatitis (early) chronic pancreatitis
	solid and cystic focal pancreatic lesions
esophagogastroduodenal tumors	subepithelial tumors
	enlarged gastric folds/wall thickening
mediastinal diseases	primary central lung/mediastinal tumors
	mediastinal lymphadenopathy
rectal diseases	fistulas, abscesses, extraluminal tumors, subepithelial tumors
<b>staging of various cancers</b>	
upper gastrointestinal cancer	T (tumor) and N (nodal) stage, M (metastatic) stage (celiac trunk lymph nodes, left adrenal, left liver lobe, ascites, etc.)
lung cancer	T and N stage (EUS and EBUS), M stage (abdominal lymph nodes, left adrenal, left liver lobe)
rectal cancer	T and N stage
pancreatico-biliary cancers	T and N stage, M stage (left liver lobe, ascites, mediastinal lymph nodes, etc.); evaluation of resectability and vascular invasion
<b>EUS-guided therapeutic interventions</b>	
drainage procedures	transmural drainage of (per-)pancreatic and peri-intestinal fluid collections (pseudocysts, walled-off pancreatic necroses, abscesses, postoperative fluid collections)
	bile duct and gallbladder drainage
	pancreatic duct drainage
injection treatment	celiac plexus/ganglia neurolysis and block glue or coil embolization of bleeding varices, visceral pseudoaneurysms, and other vascular lesions
	ethanol-ablation of small pancreatic insulinomas
other interventions	placement of fiducials

enterology, pulmonary medicine, oncology, surgery, imaging and pathology is desired.

### Methods and models for training

Various approaches for structured training have been described. Support includes EUS textbooks and atlases, DVDs and online resources [7–9, 19, 117–122]. Computer-based simulators are a valuable option, improving trainee procedural skills before performing supervised clinical endosonographic procedures [117, 120, 123–130]. EUS-guided sampling and therapeutic intervention training with animal models and supervised hands-on may facilitate more rapid learning for clinical application and may minimize false-negative sampling in patients [117, 123, 131]. The live pig is a good animal model for EUS and EUS-guided interventions, performed under general anesthesia, endotracheal intubation and mechanical ventilatory support [132]. Studies evaluating live animal model teaching of EUS, EUS-guided sampling and EUS-guided celiac plexus neurolysis showed that visualization of anatomical landmarks and performance significantly increased after several training sessions [133–135]. A study found EUS-guided sampling performed by supervised fellows to be as safe and accurate as the results of the experienced attending operators [136]. Objective assessment tools with rating scales for various steps of EUS-guided sampling (in particular EBUS-TBNA) have

**Table 2** Indications and contraindications of EUS-guided sampling.

<b>frequent/ established indications</b>	<b>less frequent/ emerging indications</b>	<b>contraindications</b>
pancreatic solid lesions	retroperitoneal masses	absolute
pancreatic cystic lesions	mediastinal masses	no impact on patient management
lymph nodes	perianastomotic masses	lack of informed consent
subepithelial tumors	adrenal gland masses	mediastinal cysts (risk of infection)
	liver masses	relative
	ascites and peritoneal nodules	severe coagulopathy
	gastrointestinal wall thickening	continued oral anticoagulation
	bile duct strictures/lesions	continued treatment with ADP antagonists (clopidogrel, prasugrel, ticagrelor)
	kidney masses	large vessels in the expected needle track
	focal splenic lesions	

been developed to measure competency for mediastinal staging of NSCLC, which can potentially be used in other diagnostic scenarios [125, 127, 130, 137–140].

### Learning curve and minimum number of supervised procedures

Few articles address the minimum number of EUS examinations required to attain competency [116]. The efficiency and success of EUS-guided sampling are dependent on the experience of the endosonographer and the cytopathologist. Reports on the skill acquisition of individuals for EUS [141, 142] and for EUS-FNA of solid pancreatic lesions [143, 144] challenge the ASGE recommendations that comprehensive competence in all aspects of EUS requires at least 150 supervised cases, including 50 EUS-FNA [145]. A prospective evaluation of 12 months of EUS training for 12 trainees without prior experience found a large variation in skill acquisition, with nobody gaining acceptable performance in diagnostic EUS before having performed 225 examinations [141]. For EUS-FNA of solid pancreatic lesions, the sensitivity significantly and continuously increased for the first 30 cases [143]. Further observation of 3 separate periods of 100 pancreatic EUS-FNA following basic skills acquisition demonstrated further improvement in terms of a decreasing number of diagnostic needle passes<sup>7</sup> and decreasing adverse events in period 3 compared to periods 1 and 2 [144]. A 7-year experience in pancreatic EUS-FNA showed a significant correlation between years of operator experience and the mean of annual EUS examinations in the preceding 3 years with fewer needle passes [146, 147]. A similar effect of cumulative EUS-FNA experience over a 13-year period on the diagnostic accuracy of pancreatic EUS-FNA was also reported, representing a joint learning curve of both endosonographers and cytopathologists [148]. A survey of participants of a European EUS workshop found a high annual hospital case load of EUS-

<sup>7</sup> Term is explained in the addendum on terminology.

FNA but not the years of individual EUS experience to be a significant predictor of self-reported sensitivity of EUS-FNA [149]. In two gastroenterological centers, the rate of non-diagnostic specimens from EUS-FNA decreased significantly after a 1- or 2-month joint training period of cytopathologists and endosonographers [150, 151]. In another EUS center, the rate of non-diagnostic or false findings<sup>8</sup> of EUS-FNA reached an acceptable level (< 10%) at 121 and 97 examinations, respectively. This level of competency was achieved after performance of 48 EUS-FNA of mediastinal lymph nodes compared to 171 (non-diagnostic) or 186 (misdiagnosis) pancreatic EUS-FNA [152].

Similar experience has been reported in EUS-guided sampling for lung cancer staging. The performance of 4 pulmonologists improved significantly during a supervised training course. However, only 2/4 achieved the mean score of experienced endosonographers after 17 and 23 procedures. 20 EUS-guided sampling sessions were insufficient to achieve a consistently high level of competency for trainees [140]. For EBUS-TBNA, in pulmonary medicine fellows, the majority achieved the first independent successful performance of EBUS-TBNA following a training protocol (that included theoretical education and simulation sessions) after an average of 13 procedures [153]. Studies show significant variation in learning curves for EBUS-TBNA [153–160] with an acceptable 90% accuracy of EUS-TBNA achieved after performing 50–80 procedures [154–156, 160]. In a study with 9 interventional pulmonology fellows, skill improvement was ongoing for lymph node identification by EBUS and EBUS-TBNA even after 200 cases [160].

Compared with the gaining of expertise in EUS and EUS-FNA for a gastroenterologist or EBUS and EBUS-TBNA for a pulmonologist, diagnostic handling of EUS-FNA samples is simpler for experienced cytopathologists. After performing a short intensive training session, experienced general pathologists who had little prior experience with EUS-FNA demonstrated marked improvement in the reproducibility of cytological diagnoses [161]. A continuous dialog and common training of endosonographers and cytopathologists is the cornerstone of diagnostic success in EUS-guided sampling [110].

#### Recommendation 6

Education and training for EUS procedures should be performed systematically in a standardized fashion. Various learning methods should be used, including textbooks, online resources, and EUS phantoms, before performing hands-on human cases (LoE 5, GoR D). Strong consensus (100%).

#### Recommendation 7

Standardized criteria and assessment tools should be developed and applied for assessing the skills of individual trainees before credentialing competency (LoE 1b, GoR B). Strong consensus (100%).

#### Recommendation 8

At least 50 EUS-guided sampling procedures are needed in order to attain basic competency in EUS-guided interventions (LoE 5, GoR D). Strong consensus (100%).

## Quality indicators and benchmarking

The ideal benchmark for the performance of EUS-guided sampling would be the actual positive and negative predictive value of malignancy diagnosis, requiring data from surgical pathology or from long-term follow-up. Due to the increasing use of neoadjuvant treatments and practical constraints, this is not always available in clinical practice. Recent reviews and a position paper of the ASGE have proposed appropriate process and outcome measures for monitoring and benchmarking the performance of EUS procedures [64, 89, 91, 110]. With particular emphasis on EUS-guided sampling, useful quality indicators may be:

- percentage of appropriate indications for performing EUS-guided sampling based on guidelines (Table 2) [64]
- prospective documentation of adverse events after EUS-guided sampling (performance target: > 98%) [64]
- incidence of adverse events after EUS-guided sampling (performance targets: acute pancreatitis < 2%, clinically significant bleeding < 1%) [64, 89, 110]
- frequency of algorithmic EUS-guided sampling of both suspected metastatic disease (in particular lymph nodes, ascites, adrenal and liver metastases) and the primary tumor in cases, in which results of EUS staging would impact further clinical management (performance target: > 98%) [64]
- the yield of malignant diagnoses<sup>9</sup> in EUS-guided sampling of solid pancreatic masses and the sensitivity for diagnosis of pancreatic cancer (performance targets: ≥ 70% and 85%, respectively) [64, 89, 91, 110, 162]
- the percentage of adequate samples<sup>10</sup> (performance target: ≥ 85%) [64, 89, 110] and
- the frequency of inconclusive cytopathological diagnoses<sup>11</sup> (atypical, suspicious: ≤ 10%) [89, 110, 152].

Particular quality parameters for EUS-guided therapeutic interventions have not yet been established, but should be derived from those for EUS-guided sampling and advanced endoscopic and interventional procedures [64, 163].

#### Recommendation 9

Appropriate indicators should be implemented to monitor the quality of EUS-guided interventions (LoE 5, GoR D). Strong consensus (100%).

## EUS-guided sampling: Indications and clinical impact

### General indications of EUS-guided sampling

EUS has high accuracy for the diagnosis and staging of benign and malignant conditions within and outside the gastrointestinal tract [106, 107]. EUS-guided sampling relies on its ability to obtain specimens with either fine-needle aspiration (FNA) or fine-needle biopsy (FNB)<sup>12</sup> [91, 110].

First described in 1992 [10], EUS-guided sampling has become an indispensable adjunct to EUS, and has been shown to be feasible and safe in obtaining tissue diagnosis in the majority of lesions within EUS reach [164]. The practical clinical applications of EUS-

<sup>9</sup> Term is explained in the addendum on terminology.

<sup>10</sup> Term is explained in the addendum on terminology.

<sup>11</sup> Term is explained in the addendum on terminology.

<sup>12</sup> Term is explained in the addendum on terminology.

<sup>8</sup> Term is explained in the addendum on terminology.

guided sampling, validating its use in diagnostic and staging algorithms, showing it is cost-effective and showing its significant effect on patient outcome, have been dealt with in numerous articles [91, 96, 104, 110] (Table 2).

Several prospective and retrospective studies and meta-analyses have substantiated the key importance of EUS-guided sampling, particularly in suspicious nodal disease for staging, guiding treatment, and predicting outcome in non-small cell lung cancer (NSCLC) [165–170], various extrathoracic malignancies [171, 172], upper gastrointestinal cancer [173, 174], rectal cancer [58], as well as for proving recurrence of malignancy [55, 175–178]. Specimens provided by EUS can be examined by immunohistochemical and biological marker analysis to identify specific tumor characteristics for personalized treatment [179–187]. The minimally invasive characteristics of EUS-guided sampling make this the most favorable option in terms of patient acceptance, safety profile, repeatability and cost-effectiveness.

There is limited data comparing EUS-guided sampling with percutaneous (CT- or US-guided) sampling of pancreatic lesions [188–191]. Typically, the diagnostic accuracy of EUS-guided sampling is similar to that of percutaneous techniques in comparative studies [188–191]. One retrospective analysis found EUS had superior accuracy when evaluating lesions <3 cm ( $p=0.015$ ) [189]. The complication rate and patient preferences were favorable for EUS [190–192]. Importantly, one study in pancreatic cancer suggested that peritoneal seeding occurred more frequently in patients following percutaneous rather than with EUS-guided sampling [192]. One RCT did not meet enrollment targets as patients and referring physicians specifically requested EUS-guided sampling [190]. A cost-minimization analysis demonstrated that EUS-guided sampling was the better initial test and the preferred secondary test following failure of other techniques for the diagnosis of pancreatic cancer, when considering the total expected costs for a successful diagnosis [193]. Evidence from large tertiary referral centers shows that implementation of an EUS-FNA service in pancreatic cancer was accompanied by a marked cytological improvement of sample adequacy and accuracy, leading to widespread replacement of other techniques of tissue acquisition [194]. A 5-year retrospective claims analysis of Medicare patients undergoing sampling of pancreatic malignancies showed an ongoing trend towards EUS-guided sampling. However, in spite of higher costs, the application of percutaneous image-guided sampling remained prevalent in particular outside major academic and urban hospitals [195].

#### Recommendation 10

EUS-guided sampling should be considered for tissue diagnosis of lesions in or adjacent to the gastrointestinal tract when the result is likely to alter clinical management (LoE 2a, GoR B). Strong consensus (100%).

### EUS-guided sampling for primary diagnosis Solid pancreatic lesions

Solid pancreatic lesions suspected as ductal pancreatic adenocarcinoma (PDAC) are typically targets for EUS-guided sampling. Metastases and/or primary lesion sampling is indicated when the lesion is non-resectable allowing appropriate radiotherapy/chemotherapy. EUS-guided sampling of potentially resectable tumors will follow local protocols to obtain confirmation of malignancy prior to surgical intervention.

EUS has a high positive predictive value (PPV) and a fair negative predictive value (NPV) in diagnosing PDAC. Several studies report a sensitivity between 85–93% and a specificity between 96–100% (Table 3) [196–200].

With neuroendocrine tumors (second most common solid pancreatic lesion), studies report high sensitivity and diagnostic accuracy for EUS-guided sampling using immunocytochemical evaluation [201, 202]. Ki-67 grading of neuroendocrine pancreatic tumors is reliable using EUS fine-needle samples with adequate cellularity [203–205].

Other pancreatic lesions should also be considered in the differential diagnosis; solid pseudopapillary neoplasm, “mass-forming” pancreatitis, lymphoma and metastases (melanoma, kidney, breast, lung, ovarian) [206–220]. EUS-guided sampling is a reliable method to differentiate PDAC from neuroendocrine pancreatic tumors and other rare pancreatic neoplasms (non-PDAC), each with differing outcomes and alternative treatment strategies [146–148, 221].

#### Recommendation 11

In pancreatic masses, EUS-guided sampling should be preferred in potentially resectable lesions and in unresectable lesions in which percutaneous biopsy is not feasible (LoE 2b, GoR C). Strong consensus (100%).

#### Recommendation 12

EUS-guided sampling should be preferred over percutaneous biopsy in pancreatic masses prior to neoadjuvant radiotherapy/chemotherapy (LoE 2b, GoR C). Strong consensus (100%).

#### Recommendation 13

EUS-guided sampling is recommended in potentially resectable, pancreatic masses that are atypical for pancreatic ductal adenocarcinoma (LoE 3b, GoR C). Strong consensus (100%).

### Pancreatic cystic lesions

There is a wide differential diagnosis of pancreatic cystic lesions (PCL) including both benign and malignant. True pancreatic cysts should be differentiated from pseudocysts, which is not always possible based on morphological features. The most common benign true pancreatic cyst is the serous cystadenoma. Mucinous cystadenoma and branch-duct intraductal papillary mucinous neoplasm (BD-IPMN) are often thought of as being borderline for malignancy, whereas a main-duct intraductal papillary mucinous neoplasm (MD-IPMN) is at high risk for malignancy. Neuroendocrine cystic tumors and solid pseudopapillary tumors are rare [222–224].

EUS-guided sampling is performed when the other diagnostic modalities are inconclusive, if a PCL with “suspicious” features (other than an enhancing solid component) has been demonstrated, for risk-assessment of BD-IPMN, or in advanced malignant PCLs when chemotherapy is considered [225, 226]. It aims to differentiate mucinous from non-mucinous and malignant from benign lesions. For best diagnostic accuracy, EUS-FNA cytology and biochemical aspirate assays should be reviewed in combination with the EUS findings, clinical history and other imaging techniques [225, 227, 228]. A study (92 patients) of small pancreatic cysts con-

first author of meta-analysis	included studies	patients	pooled sensitivity	pooled specificity
<b>solid pancreatic lesions/pancreatic cancer</b>				
Hewitt MJ et al. 2012 [196]	33	4984	85 % (91 % <sup>1</sup> )	98 % (94 % <sup>1</sup> )
Puli SR et al. 2013 [199]	41	4766	86.8 %	95.8 %
Chen J et al. 2012 [198]	15	1860	92 %	96 %
Chen G et al. 2013 [197]	31	4840	89 % (91 % <sup>2</sup> )	96 % (94 % <sup>2</sup> )
Hébert-Magee S et al. 2013 [200] <sup>3</sup>	34	3644 (2285 pancreatic cancer)	88.6 %	99.3 %
<b>cystic pancreatic lesions/mucinous neoplasms</b>				
Thornton GD et al. 2013 [234] <sup>4</sup>	18	1438	54 %	93 %
Thosani N et al. 2010 [239] <sup>4</sup>	11	376	63 %	88 %
Suzuki R et al. 2014 [240] <sup>5</sup>	4	96	65 %	91 %
Wang QX et al. 2015 [241]	16	1024	51 % <sup>6</sup> 52 % <sup>7</sup>	94 % <sup>6</sup> 97 % <sup>7</sup>
<b>biliary strictures and gallbladder masses/cholangiocarcinoma</b>				
Navaneethan U et al. 2014 [273]	6 (5 <sup>8</sup> )	196 (146 <sup>8</sup> )	66 % (80 % <sup>8</sup> )	not included in analysis
Wu LM et al. 2011 [274]	9	284	84 %	100 %
<b>mediastinal lymph nodes/nodal lung cancer staging</b>				
Puli SR et al. 2008 [319] <sup>9</sup>	76	9310	88 %	96.4 %
Chandra S et al. 2012 [339] <sup>10</sup>	14	1658	92 %	100 %
Micames CG et al. 2007 [165] <sup>11</sup>	18	1201	83 %	97 %
Silvestri GA et al. 2013 [389] <sup>11</sup>	26	2443	89 %	100 %
Adams K et al. 2009 [166] <sup>12</sup>	14	1658	88 %	100 %
Gu P et al. 2009 [167] <sup>12</sup>	11	1299	93 %	100 %
Dong X et al. 2013 [169] <sup>12</sup>	9	1066	90 %	99 %
Silvestri GA et al. 2013 [389] <sup>12</sup>	26	2756	89 %	100 %
Zhang R et al. 2013 [168] <sup>13</sup>	8	822	86 %	100 %
Dhooria S et al. 2015 [170] <sup>14</sup>	4	425	91 %	100 %

<sup>1</sup> atypical, suspicious, and malignant, determining a positive result for malignancy;

<sup>2</sup> prospective studies only;

<sup>3</sup> referring to pancreatic adenocarcinoma, studies with various EUS-guided sampling techniques;

<sup>4</sup> mucinous vs. non-mucinous PCL;

<sup>5</sup> malignant vs. benign IPMNs;

<sup>6</sup> benign vs. malignant PCL, malignant cytology = positive for malignancy and high-grade dysplasia;

<sup>7</sup> benign vs. malignant PCL, malignant cytology = positive for malignancy and high-grade dysplasia, suspicious for malignancy, potential malignancy;

<sup>8</sup> studies with a visible mass in EUS;

<sup>9</sup> mediastinal lymph nodes, EUS-FNA;

<sup>10</sup> mediastinal lymph nodes, EBUS-TBNA;

<sup>11</sup> nodal staging of lung cancer, EUS-FNA;

<sup>12</sup> nodal staging of lung cancer; EBUS-TBNA;

<sup>13</sup> nodal staging of lung cancer, combined EBUS-TBNA and EUS-FNA;

<sup>14</sup> nodal staging of lung cancer, combined EBUS-TBNA and EUS-FNA using a EBUS scope (EUS-B-FNA).

firmed that in the absence of worrisome imaging features or high-risk stigmata (according to the international consensus guideline [225]) and high-grade atypia or malignancy in cyst-fluid aspirates, there was a 99 % predictive value for safe nonsurgical management [229]. A management strategy for asymptomatic PCLs based on risk stratification using EUS-guided sampling and cyst fluid analysis was cost-effective in comparison with a conservative follow-up or an aggressive surgical approach [230].

Levels of carcinoembryonic antigen (CEA) and amylase yield a suboptimal diagnostic accuracy of 60 – 86 % for distinguishing between mucinous and non-mucinous PCLs. Levels of amylase < 250 U/L virtually exclude pseudocysts, while high levels of CEA reliably indicate the mucinous nature of a PCL [231 – 234]. Differentiation of mucinous vs. non-mucinous pancreatic cystic lesions yield varying CEA cut-off values between 30 ng/ml and > 800 ng/ml and varying diagnostic accuracies [231, 232, 235 – 238]. CEA levels are not predictive of malignancy [235]. A high CA 125-level in the cyst fluid may be helpful in differentiating mucinous cystadenoma from intraductal papillary mucinous neoplasm (IPMN)

[237]. EUS morphology, cytology and biochemical cyst-fluid analysis in 976 patients compared to 198 patients with histology or malignant cytology as the diagnostic standard demonstrated that in the prediction of a mucinous cyst, CEA was significantly more accurate (86 %) than EUS morphology (48 %) and cytology (58 %). Cytology was the most accurate test (75 %) for the diagnosis of a malignant cystic neoplasm [235]. However, the value of cytology is limited by the low cellularity of cyst fluid. The specificity of cytological diagnosis of malignant PCLs is adequate (88 – 97 %), but the sensitivity is low (51 – 65 %, **Table 3**) [234, 239 – 241]. It is suggested that high-grade atypia be defined as “positive cytology” [242, 243], but there is considerable interobserver variability for the grading of cellular atypia in pancreatic cyst fluid [244, 245]. Newer techniques, e.g. cystic fluid molecular marker assays (DNA quantity and methylation, K-ras mutation, and others) [246 – 250] and intracystic probe-based confocal laser endomicroscopy, are being developed [251, 252]. The incremental diagnostic value of molecular analysis over biochemical analysis of cyst fluid is low. For most parameters the specificity is high, but

**Table 3** Meta-analyses on the diagnostic accuracy of EUS-guided sampling of solid and cystic pancreatic lesions, biliary cancer, lung cancer and mediastinal lymphadenopathy.

the sensitivity is reported only between 20–50%. However, the combination of molecular analysis and CEA or cytology has a better performance for the diagnosis of neoplastic mucinous PCLs than either of the individual tests [248, 253, 254].

#### Recommendation 14

Biochemical, cytological, and molecular analysis of EUS aspirates from pancreatic cystic lesions may facilitate differentiation between mucinous and non-mucinous cysts and evaluation of the malignancy risk (LoE 2a, GoR B). Strong consensus (100%).

#### Biliary cancer

Several studies report successful EUS-guided sampling of gallbladder wall lesions [255–259], extrahepatic cholangiocarcinoma and indeterminate biliary strictures [255, 260–271], as well as tumors of the papilla of Vater [272], but with a wide variation in sensitivity (43–100%). In the evaluation of indeterminate biliary strictures, the NPV (29–72%) of EUS-guided sampling of biliary malignancy was poor. A meta-analysis reported a 66% sensitivity of EUS-guided sampling for the diagnosis of cholangiocarcinoma responsible for an indeterminate bile duct stricture (● Table 3) [273]. A further meta-analysis of the accuracy of EUS-guided sampling of both bile duct strictures and gallbladder masses reported a sensitivity of 84% (● Table 3) [274]. One prospective study quoted a higher sensitivity for distal than for proximal cholangiocarcinoma [269]. EUS-guided sampling proved to be successful following failed or negative ERCP-guided brushing or biopsy [261, 263–267, 273]. Comparison of EUS-guided sampling with that of ERCP-guided techniques revealed a better outcome for EUS in gallbladder cancer, biliary strictures produced by pancreatic cancer rather than cholangiocarcinoma, and in EUS-visible masses, with a combined approach considered clinically appropriate [257, 259, 262, 271, 273]. EUS-guided sampling of hilar lymph nodes may be used to diagnose and stage suspected biliary cancer [257, 258, 260, 266, 270, 275].

#### Recommendation 15

Complementary to ERCP-guided brushing and biopsy, EUS-guided sampling may be used for diagnosis of indeterminate biliary strictures and gallbladder masses (LoE 2a, GoR B). Strong consensus (100%).

#### Subepithelial gastrointestinal tumors

Differential diagnosis of gastrointestinal subepithelial tumors (SETs) includes leiomyoma, schwannoma, gastrointestinal stromal tumor (GIST), lipoma, ectopic pancreas, neuroendocrine tumor, cyst and others [276–278]. While a reliable differential diagnosis is possible on EUS features alone in some SETs, so, with the frequently occurring hypoechoic SET originating from the 4<sup>th</sup> layer (muscularis propria), i.e. GIST, leiomyoma and schwannoma, diagnosis may be problematic. In the stomach, the majority of hypoechoic SETs are GISTs, with a variable malignant risk, dependent on the size and number of mitoses per high power microscopic field. Approximately 25% of incidentally detected hypoechoic gastric SETs are benign leiomyomas or schwannomas for which surgery is unnecessary [276–278]. EUS-guided sampling combines smear cytology (SC) with immunohistochemistry for maximal di-

agnostic accuracy. The diagnostic yield remains suboptimal using standard EUS needles of various diameters, ranging from 20% [279] to 93% [280], as retrieved tissue is not always sufficient to allow immunohistochemical analysis [280–294]. The European Society of Gastrointestinal Endoscopy (ESGE) guideline on EUS-guided sampling in gastroenterology states that in hypoechoic SETs of the stomach <20 mm the usefulness of EUS-guided sampling is limited due to the moderate diagnostic yield and lacking capability to determine the mitotic index [104].

“Histology” needles, e.g. trucut needles and aspiration needles with side holes and reverse bevel technology (ProCore), have been introduced in an attempt to overcome these limitations and to retrieve a core sample suitable for immunohistochemistry. While the results obtained with trucut needles are not superior to those of standard aspiration needles (diagnostic yield 35–79%) [279, 287, 288, 295], results of an RCT (n=28 patients with SET) encourage further evaluation of the ProCore needle, with a diagnostic yield significantly higher compared with aspiration needles (75% vs. 20%) [294].

A comparison of the diagnostic yield, specimen size, and procedure time for EUS-guided sampling of upper GI SETs using a forward-viewing vs. a traditional oblique-viewing echoendoscope showed no significant differences between the echoendoscopes with regard to puncture success and diagnostic yield. Procedure time was shorter and specimens larger using the forward-viewing echoendoscope [296].

Immunohistochemical diagnosis is valuable in poor surgical candidates or with SETs located in challenging surgical positions, e.g. gastric cardia. EUS-guided sampling is beneficial in suspected non-resectable GISTs, when primary treatment with tyrosine kinase inhibitors is planned following confirmed diagnosis. Pre-treatment genotyping, evaluation of biological aggressiveness using the Ki-67 index and mitotic count, and prediction of primary resistance against Imatinib is feasible using EUS-FNA specimens [187, 297, 298]. In esophageal SETs or SETs <2 cm, EUS-guided sampling is not necessary as it is unlikely to influence management; surgical resection is not usually indicated [278]. In resectable SETs, tissue diagnosis is not necessary before surgery [278].

#### Recommendation 16

EUS-guided sampling may be used for differential diagnosis of subepithelial gastrointestinal tumors ≥20 mm in cases with high surgical risk or suspected non-resectability (LoE 2b, GoR C). Strong consensus (100%).

#### Lung cancer

In suspected lung cancer conventional techniques (bronchoscopic or percutaneous-transsthoracic biopsy) fail to establish a histological diagnosis in up to 1/3 of patients. EUS allows effective transeophageal or transbronchial guidance for sampling of centrally located lung masses or lymph nodes adjacent to the esophagus or the respiratory tract [299–306]. There is a high diagnostic yield (87.6%) for EUS-guided sampling with suspected malignant central lung mass or in the presence of a peripheral lung nodule and PET-positive mediastinal lymph nodes following at least one unsuccessful attempt at diagnostic flexible bronchoscopy or CT-guided transthoracic needle aspiration. The endosonographic approach had an accuracy of 90.1% for the diagnosis of lung cancer, thus avoiding invasive and expensive surgical procedures [304]. Subtyping of non-small cell lung cancer is the basis of persona-



lized oncological treatment and is feasible using EUS-guided sampling (including EBUS-TBNA) in 77–90.6% of cases [307–309]. The rate of non-small cell lung cancer not otherwise specified (NSCLC-NOS) was reduced by 50% in patients who underwent cell block (CB)<sup>13</sup> immunohistochemistry [307]. Furthermore, in cases with CB, a significantly higher agreement of subtyping between EUS-/EBUS fine-needle aspirates and matched biopsies compared to cases without CB (96% vs. 69%) has been shown [310]. Genotyping (e.g. molecular analysis: EGFR, KRAS, EML4-ALK rearrangement) was possible using EUS/EBUS fine-needle aspirates in 77–98.4% [180, 307–309, 311–313]. With EBUS-TBNA a minimum of four needle passes provided an adequate material for subtyping and molecular profiling of NSCLC cases [309].

#### Recommendation 17

In suspected lung cancer EUS-guided sampling (EUS-FNA, EBUS-TBNA) of centrally located mass lesions or suspicious lymph nodes is recommended to establish a definite tissue diagnosis complementing other diagnostic techniques (LoE 2b, GoR B). Strong consensus (100%).

#### Mediastinal and abdominal lymphadenopathy of unknown origin

Based on EUS morphology alone [314], confident classification as malignant or benign is achievable in 25% of lymph nodes [315, 316]. EUS-FNA has a higher accuracy than EUS features alone [317, 318]. A meta-analysis (n=9310) showed significant improvement in evaluating mediastinal lymphadenopathy with EUS-guided sampling over EUS features of lymph nodes (sensitivity 88% vs. 84.7%; specificity 96.4% vs. 84.6%) (• Table 3) [319]. The probability of malignancy is low if no EUS malignant lymph node criteria are present. Therefore, in addition to patient history, endosonographic lymph node features may facilitate endosonographic lymph node-sampling [318, 320–327].

Several studies and meta-analyses have demonstrated a high diagnostic yield and accuracy of EUS-guided sampling (EUS-FNA and EBUS-TBNA) for the evaluation of indeterminate mediastinal and abdominal lymphadenopathy, with or without a malignant disease background [170, 172, 176, 319, 323, 328–348]. Experienced cytopathologists demonstrate excellent reproducibility of cytological diagnoses on mediastinal lymph node specimens, and short, comprehensive training further improved the inter-observer agreement between the least and the most experienced [161]. The diagnostic yield of EUS-guided lymph node sampling may be significantly improved by ancillary tests (e.g. immunohistochemistry and molecular analysis) [331, 340, 342, 347, 349–358]. EUS-guided sampling (EUS-FNA, EBUS-TBNA) shows satisfactory yield for the diagnosis and subtyping of primary and recurrent malignant non-Hodgkin-lymphoma, particularly if flow cytometry, immunohistochemistry, and cytogenetic analysis are used in specimen processing. The reported diagnostic accuracies (44–96.7%) and feasibility of the WHO subclassification system (66.6–88.8%) was varied [329, 332, 340, 342, 344, 351, 354, 359–365]. Flow cytometry was a necessary complement of cytology [211, 329]. The diagnostic yield may be lower for primary diagnosis of malignant lymphoma compared with recurrent disease, and for correctly classifying Hodgkin's lymphoma

and low-grade non-Hodgkin's lymphoma compared with high-grade diffuse large B-cell lymphoma [362, 365].

EUS-guided sampling (EUS-FNA, EBUS-TBNA) of mediastinal and abdominal lymph nodes is a reliable technique for definite tissue diagnosis of stage I and II sarcoidosis, whereas bronchoscopy with mucosal and transbronchial biopsy and bronchoalveolar lavage fails in approximately 50% of cases [366–379]. CB technique as well as combining histopathological evaluation of EUS core biopsies with conventional SC both improve the diagnostic yield, reducing the false-negative rate of EUS- and EBUS-guided tissue sampling in sarcoidosis [350, 369, 372]. Stage I is more accurately diagnosed compared to stage II sarcoidosis [372, 375]. The sensitivity (54–93%) and accuracy of EUS-FNA and EBUS-TBNA are superior in comparison to bronchoscopy-related biopsy techniques [371, 373, 375, 378]. An international randomized clinical multicenter study recently compared endosonographic sampling techniques (EUS-FNA and EBUS-TBNA) of mediastinal lymph nodes with bronchoscopy using mucosal and transbronchial lung biopsy for the diagnosis of stage I/II sarcoidosis. The diagnostic yield of endosonographic sampling to detect non-caseating granuloma (80%) was significantly higher compared with bronchoscopy (53%) and bronchoalveolar lavage (54%) [373]. A meta-analysis (2097 patients, prevalence of sarcoidosis 15%) reported a diagnostic yield of 79%, a sensitivity of 84%, and a specificity of 100% for the diagnosis of sarcoidosis using EBUS-TBNA [379].

Besides sarcoidosis, granulomatous lymphadenopathy may arise from a paraneoplastic “sarcoid-like reaction”, tuberculosis, atypical mycobacteriosis, and other granulomatous diseases. Reliable tuberculosis diagnosis and differentiation from sarcoidosis is possible using endosonographic sampling techniques. Special staining, microbiological culture, and PCR are useful adjuncts to conventional cytopathological evaluation (see section 4) [336, 349, 352, 355, 357, 367, 380–386].

An RCT compared transbronchial vs. transesophageal sampling, using an ultrasound bronchoscope, for the diagnosis of mediastinal lymph nodes and other accessible lesions. There was an equal diagnostic yield and patient tolerance, but fewer anesthetic and sedative requirements, a shorter procedure time, less frequent oxygen desaturation and higher operator satisfaction in favor of transesophageal endosonographic sampling [387]. Combined transbronchial and transesophageal sampling, using an ultrasound bronchoscope, is superior compared with EBUS-TBNA alone for the diagnosis of mediastinal lymphadenopathy. The additional diagnostic gain of transesophageal sampling was 7.6% [170].

#### Recommendation 18

EUS-guided sampling (EUS-FNA, EBUS-TBNA) is recommended as the primary diagnostic technique for tissue diagnosis of mediastinal or abdominal lymphadenopathy of unknown etiology (LoE 3a, GoR B). Strong consensus (100%).

#### EUS-guided sampling for tumor staging Algorithmic approach

For tumor staging an algorithmic approach of EUS-guided sampling following the TNM classification of the respective malignant tumor is sensible. Potential sites of metastases within reach of EUS-FNA should be examined and sampled first, followed by regional lymph node stations, in which demonstration of metastatic involvement would alter management (e.g. N3- and N2-stations in NSCLC [120, 388–390] or liver hilum lymph nodes in

<sup>13</sup> Term is explained in the addendum on terminology.

unresectable hilar cholangiocarcinoma prior to liver transplantation [275]). The suspected primary tumor should be sampled last if necessary [110, 114, 391]. This systematic approach in an inverse TNM order addresses concerns that needle contamination with tumor cells from the first sampling target, from the instrumental channel or from gastrointestinal fluid could contribute to false-positive results from the subsequent targeted lesions [392–395]. Malignant cells have been identified within gastrointestinal luminal fluid in 48% of luminal cancer, and in 10% of extraluminal cancer patients undergoing EUS-FNA [393].

### Mediastinal lymph nodes

In the absence of distant metastases, mediastinal lymph node involvement is the most important factor affecting the management and outcome of patients with NSCLC [389]. Esophageal EUS has a high sensitivity and specificity for malignant lymph node infiltration when found in the posterior mediastinum, aortopulmonary, subcarinal, and periesophageal regions [112, 319, 389, 396–398]. Meta-analyses report a sensitivity and specificity of between 83–89% and 96.4–100%, respectively, for nodal staging of lung cancer by EUS-guided sampling (EUS-FNA, EBUS-TBNA) (Table 3) [166–170, 320, 339, 389]. Staging of NSCLC is an established indication for EUS-guided sampling of mediastinal lymph nodes. EUS has been shown to be more accurate than CT in defining disease stage [398–400]. EUS-guided sampling also impacts treatment choice and survival in patients with NSCLC. Patients with positive nodes were significantly more likely to receive chemotherapy and/or radiation therapy and less likely to undergo surgery compared with patients with negative node sampling. Patients with N2 or N3 disease by EUS-FNA had a significantly shorter survival time than node-negative patients. After adjusting for age, race, and sex, EUS-guided sampling was the most important predictor of survival [401]. When implementing EUS in the staging algorithm, a significant reduction (up to 70%) in unnecessary surgical exploration has been demonstrated [400, 402–404]. Staging accuracy was significantly improved, when EUS-guided sampling was performed in addition to mediastinoscopy. With the capability of EUS to detect metastatic mediastinal lymph nodes and to assess mediastinal tumor invasion, up to 16% of thoracotomies could have been avoided in one study [405].

Esophageal EUS and EBUS in combination allow targeting of nearly all relevant mediastinal lymph node locations [406–409]. Several studies and meta-analyses have shown that this combined approach improves lymph node staging, compared with either technique used alone [168, 170, 389, 390, 404, 410–418]. A 21% increase in sensitivity for mediastinal nodal staging in proven or suspected lung cancer is achieved by performing combined endobronchial and esophageal endosonography-guided sampling compared with the esophageal approach alone (pooled data from 7 studies), and a 13% increase compared with EBUS-TBNA alone (pooled data from 9 studies) [390]. The accuracy of a combined endosonographic approach was significantly higher than PET-CT alone (90.0% vs. 73.6%) [415]. A comparison of two different approaches to combined endosonographic mediastinal staging of potentially operable lung cancer (EBUS first vs. esophageal EUS first) found no differences in efficacy and patient satisfaction. However, EBUS-guided sampling was the more efficient primary procedure [416]. Guidelines produced co-operatively by the ESGE, the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS) recommend the combination of EBUS-TBNA and transesophageal EUS-FNA (using either a gastrointestinal echoendoscope or alternatively an ultrasound bronchoscope

pe=EUS-B-FNA) for the staging of patients with suspected or proven NSCLC and offer differentiated evidence-based recommendations for the use of endosonography for the diagnosis and staging of NSCLC in various clinical situations [390, 419–421].

Both esophageal EUS and EBUS have also been successfully used for the assessment of tumor spread to mediastinal lymph nodes (M1 disease) in a variety of extra-thoracic malignant disease [171, 328, 335, 337, 422–426]. In particular, the usefulness of EUS-guided sampling has been reported in the staging of patients with gastric cancer, pancreatic cancer, breast cancer, head and neck cancer, colorectal cancer, and lymphoma [173, 174, 361, 427–431]. A meta-analysis (n=533 patients) showed a sensitivity of 85% and a specificity of 99% of EBUS-TBNA for the diagnosis of mediastinal lymph node metastases of extra-thoracic malignancies [172].

Esophageal cancer staging requires the detection and differential diagnosis of thoracic as well as abdominal lymph nodes (see next paragraph for the latter). The clinical impact of EUS-guided sampling is profound. EUS-FNA of mediastinal lymph nodes for the N staging of esophageal cancer is more sensitive and accurate than EUS alone and significantly impacts therapeutic decisions (e.g. surgical strategy) [432–434]. In most cases EUS demonstrates a more advanced stage than CT, resulting in greater non-surgical management than if the EUS stage had been identical or less advanced [435]. There are limitations to EUS-guided sampling; it is not always technically feasible (peritumoral lymph nodes, stenotic tumors), it may increase the complication rate, it increases procedure costs [436], and with cancer cell contamination of the gastrointestinal lumen and the working channel of the echoendoscope, there is a risk of false-positive cytopathological diagnosis (see section 5) [392–394].

EUS-FNA was demonstrated to be accurate and sensitive when restaging patients as N0 after neoadjuvant chemo-radiotherapy, thus guiding critical treatment decisions [437]. However, the restaging accuracy of EUS-FNA (78%) was found to be significantly inferior to that of PET/CT (93%), which is also superior with respect to predicting complete pathological response [438].

### Abdominal lymph nodes

Previous studies have shown high accuracy and clinical impact of EUS-guided sampling of celiac lymph nodes in esophageal cancer staging [439–441]. According to the current TNM classification, malignant celiac lymph nodes are no longer assigned M1a classification, and together with cervical and mediastinal lymph node metastasis, are included in the N category [442], with EUS-guided sampling only being useful in selected cases.

In addition to EUS-guided sampling of mediastinal lymph nodes, sampling of abdominal lymph nodes in gastric cancer may alter staging classification. Malignant involvement of distant lymph nodes (e.g. retropancreatic, mesenteric, para-aortic, mediastinal) is indicative of metastatic disease and resigns the patient to palliative care [173, 174].

EUS-guided sampling is not recommended for the staging of rectal cancer; it does not alter management compared to standard EUS alone. Most perirectal lymph nodes are malignant and are not suitable to be sampled because of the risk of traversing the primary tumor [443, 444]. In patients with previous surgery and suspicion of cancer recurrence, EUS-guided sampling is useful for detecting perirectal or perianastomotic malignancy with greater accuracy than imaging alone [55].

### Adrenal glands and liver masses

EUS-guided sampling of adrenal masses can provide valuable information for the staging of lung cancer and other malignancies. Particularly in lung cancer, 30–80% of adrenal masses are adenomas [445]. Sampling from the left adrenal gland is viable and safe; sampling from the right adrenal gland has also been reported. The diagnostic yield of EUS-guided sampling ranges from 76–100%. Further management is altered in approximately 50% of lung cancer patients [446–458].

EUS and EUS-guided sampling are superior to CT for detecting small liver metastases [459, 460], and a 7-point scoring system (PPV 88%) may be used to target EUS-guided sampling of these liver lesions [460]. The diagnostic yield is reported between 80–98% with a substantial effect on clinical management [461–467]. Liver metastases are meaningful targets of EUS-guided sampling when the primary malignancy cannot be sampled due to intervening structures or if not detectable. EUS examination of the liver is incomplete, is limited to the left lobe, the proximal part of the right lobe and the hilum and should be considered complementary but not as an alternative to the other imaging techniques.

### Other metastatic locations and diagnosis of recurrent malignant disease

EUS and EUS-guided sampling may play a pivotal role in the detection and diagnosis of disease recurrence or late distant spread of gastrointestinal cancer [391]. A high accuracy with clinical impact of EUS-guided sampling has been shown in establishing recurrent malignancy following curative treatment [55, 175–178, 215, 359, 365, 427, 468], and metastatic disease, in particular affecting the pancreas [147, 206, 212, 213, 215], spleen [469, 470], pelvis [59, 61, 471], and peritoneal space [466, 472–483].

#### Recommendation 19

Combined EUS-guided sampling (EBUS-TBNA and EUS-FNA) is recommended for complete nodal staging of non-small cell lung cancer (LoE 1a, GoR A). Strong consensus (100%).

#### Recommendation 20

EUS-guided sampling (EBUS-TBNA, EUS-FNA) may be used in mediastinal nodal and metastatic staging of other malignancies (LoE 3a, GoR B). Strong consensus (100%).

#### Recommendation 21

EUS-guided sampling may be used for the detection of recurrence of malignancies (LoE 3b, GoR C). Strong consensus (100%).

#### Recommendation 22

When biopsy of suspected metastatic lesions for staging purposes is contemplated, penetration of the primary tumor should be avoided (LoE 5, GoR D). Strong consensus (100%).

#### Recommendation 23

In cases with suspected distant and/or nodal metastases, algorithmic sampling should be performed beginning with the potentially most advanced metastatic site and following an inverse TNM order (LoE 5, GoR D). Strong consensus (100%).

### EUS-guided sampling: Needle choice, sampling techniques and other factors influencing diagnostic yield



#### Choice of needle type and diameter

There are four types of needles commercially available for EUS-guided sampling: standard aspiration needles (19 G, 22 G, 25 G for EUS-FNA; 21 G and 22 G for EBUS-TBNA), aspiration needles with a core trap and reverse bevel technology (19 G, 20 G, 22 G, 25 G), aspiration needles with a shark mouth needle tip geometry (19 G, 22 G, 25 G), and trucut needles (19 G).

#### EUS-guided fine-needle aspiration for cytopathological processing

Standard aspiration needles were originally designed to obtain cellular material for cytopathological examinations [110, 484, 485]. The cytological yield and diagnostic accuracy, in studies using predominantly 22 G aspiration needles, are reported to be high for solid pancreatic lesions and metastatic lymph nodes, satisfactory for biliary mass lesions, but only moderate for gastrointestinal SETs and PCLs (Table 3) [104, 110, 486, 487]. Currently, the 22 G aspiration needle is most widely used, with increased utilization of 25 G aspiration needles particularly for sampling and cytopathological evaluation of pancreatic lesions and lymph nodes [149, 488, 489].

#### 22 G vs. 25 G aspiration needles

Meta-analyses demonstrate slight superiority of the 25 G over the 22 G aspiration needle for EUS-FNA of solid pancreatic lesions [490, 491]. In one meta-analysis of EUS-FNA of pancreatic and various peri-pancreatic lesions (8 prospective, 3 non-randomized and 5 randomized studies), 25 G needles performed marginally better (difference of 12%) with regard to the number of adequate needle passes in comparison to 22 G needles. There was no significant advantage with regard to sensitivity (25 G: 91%, 22 G: 78%), specificity (both needle types: 100%), needle visibility, diagnostic yield, number of needle passes or complication rates between 22 G and 25 G needles [490]. A further meta-analysis (5 prospective studies, 3 RCTs) reported a significantly higher sensitivity when using the 25 G vs. the 22 G needle for EUS-FNA of solid pancreatic lesions (25 G: 93% vs. 22 G: 85%). No significant differences were observed between needle diameters with regard to specificity (25 G: 97% vs. 22 G: 100%), accuracy (25 G: 98% vs. 22 G: 97%), and needle malfunction (25 G: 15.7% vs. 22 G: 12.8%) [491]. The most likely reason for the superiority of the 25 G aspiration needle is that needle passage may be easier when in a position requiring tight angulation of the tip of the echoendoscope (e.g. transduodenal access to pancreatic head lesions) and in very firm lesions (pancreatic cancer) [492–495]. This superiority was most pronounced for lesions located in the uncinate process of the pancreatic head [493]. Cross-over from the 22 G needle to the 25 G needle was more often needed for lesions in the uncinate process than elsewhere in the pancreas [494]. The quality of cytological smears is superior and bloody contamination is less pronounced with 25 G compared with 22 G needles [493, 496]. Further comparison of 22 G and 25 G EUS-FNA needles in solid and cystic pancreatic masses [497] and in solid pancreatic and non-pancreatic masses [498] found no significant differences between needle diameters with diagnostic accuracy [497, 498]. However, in one study 25 G needles were easier to manipulate with fewer procedure-related complications (3.2% vs. 10.6% with the 22 G needle) [497]. In contrast, the other multicenter study reported a significantly better performance of the 22 G

needle in terms of visibility of the needle tip and performance of the procedure [498]. A further study demonstrated equivalency of 25 G needles and 22 G needles in lymph node biopsies, a non-significant advantage of 25 G needles in solid pancreatic lesions and a non-significant advantage of 22 G needles in SETs [494]. This agrees with two studies showing similar diagnostic yields for 22 G needles and 25 G needles for EUS-FNA of various non-pancreatic lesions and lymph nodes, but a higher yield of the 25 G aspiration needle for pancreatic lesions [291, 499]. In conclusion, the advantage of the 25 G needle appears to be limited to pancreatic lesions, in particular within the pancreatic head.

A new algorithmic approach for needle choice (EUS-FNA: 25 G transduodenally, 22 G all other routes; EUS-guided treatment: flexible 19 G transduodenally, all other routes standard 19 G) was tested prospectively. Compared with the prior protocol (EUS-FNA 22 G or 25 G at the preference of the examiner; all therapeutic interventions: standard 19 G), the new algorithmic approach significantly reduced the technical failure rate from 10.9% to 1.8% [495].

### 19 G vs. 22 G and 25 G aspiration needles

There is limited data comparing the performance of the 19 G aspiration needle with aspiration needles of a smaller diameter. There was no difference in diagnostic accuracy by intention-to-treat analysis between the 19 G and the 22 G aspiration needle, but the 19 G was superior to the 22 G needle in terms of the amount of cellular material and diagnostic accuracy by per-protocol analysis (following exclusion of 5 technical failures, all with pancreatic head lesions). Further analysis favored the 19 G aspiration needle for sampling of lesions within the pancreatic body and tail [500]. In a large retrospective analysis from an experienced center (n=548) of EUS-guided diagnostic and therapeutic interventions, significantly more technical failures were observed with 19 G vs. 22 G and 25 G needles (19.7% vs. 8.8%) and with transduodenal vs. other access routes (24.4% vs. 5.2%) [495]. These findings are in agreement with two studies showing that EUS-FNA of lesions within the uncinate process may not be possible using the stiff 19 G aspiration needles [501, 502]. A flexible 19 G aspiration needle has been shown to be effective for procuring aspirates from pancreatic head lesions even by the transduodenal route [495, 503, 504]. Equipotency of the flexible 19 G aspiration needle and the 25 G aspiration needle in terms of on-site diagnosis, technical failure and adverse events has been demonstrated [504].

### 21 G vs. 22 G aspiration needles for EBUS-TBNA

A meta-analysis of 5 studies (n = 1720 patients) did not reveal significant differences in the diagnostic yield, sample adequacy, or the mean number of needle passes between the 21 G and 22 G needles during EBUS-TBNA [505].

### EUS-guided tissue acquisition for histopathological processing

With increasing requirements of histopathological, immunohistochemical and molecular biological diagnosis [506, 507], three types of “histology needles” have been developed to facilitate acquisition of core cylinders suitable for histopathological examination: trucut needles [92, 93, 508, 509], aspiration needles with a side fenestration (core trap) and reverse bevel technology [95, 97, 510, 511] and aspiration needles with a shark mouth design. Acquisition of tissue suitable for histopathological processing is also possible with standard aspiration needles, not just

with “histology needles” [96, 104, 110, 484, 485, 512, 513]. The diagnostic yield for histological material is dependent on the needle diameter.

### 25 G standard aspiration needle

Only a limited number of reports describing the use of a 25 G aspiration needle for obtaining samples suitable for histopathological processing are available. For solid pancreatic lesions, histological yields are reported at 44% (1 needle pass) [504], and 81% (2 or 4 needle passes) [514]. In a randomized cross-over trial, 72% (low negative suction pressure) and 90% (high negative suction pressure) of specimens obtained with 25 G aspiration needles from solid pancreatic lesions were adequate for histopathological processing. 25 G aspiration with high suction pressure was significantly more likely to provide an accurate diagnosis [515].

### 22 G standard aspiration needle

Studies using standard 22 G aspiration needles reported material suitable for histological diagnosis in 28% [516], 68% [517], 73% [291], 79% [493], 80% [217], 81% [518], 82% [283, 519], 84% [519, 520], 87% [521], 89% [522], 92% [205], 96% [523] to 98% [463] (for details, see 96, 110, 485, 486). In a study of factors influencing the success of EUS-FNA, the chance of acquiring adequate material for histopathologic evaluation was significantly higher for 22 G aspiration needles (73%) than for 25 G aspiration needles (61%) [291]. Some authors advocate using a high negative suction pressure (30 ml to 50 ml) to facilitate procurement of histological material [516, 518, 523]. Histological and immunohistochemical diagnosis using the 22 G aspiration needle is reported particularly for gastrointestinal SETs [281, 283, 293], neuroendocrine pancreatic and other rare pancreatic tumors [205, 340, 521], liver tumors [463] and autoimmune pancreatitis [217].

### 19 G standard aspiration needle

In several studies using the standard 19 G aspiration needle, an adequate histological sample was obtained in 79% [524], 88% [504], 89% [361], 94.7% [503] 97.5% [525] to 100% [332, 369] (for details, see [96, 485]). To overcome the technical limitations of transduodenal puncture, removing the stylet before insertion of the needle into the working channel of the echoendoscope [525] or using a flexible nitinol needle [503] was advocated. Compared with a 25 G aspiration needle, histological core procurement was significantly better with a flexible 19 G aspiration needle (88% vs. 44%). However, specimens supplied by the 19 G needle were more often significantly contaminated with blood (severe blood contamination, 36% vs. 4%) [504]. Using 19 G aspiration needles, it is possible to achieve histological material appropriate to diagnose and subtype malignant lymphoma (immunohistochemistry, flow cytometry, cytogenetic assessments) [361], diagnose stage I sarcoidosis [369], autoimmune pancreatitis [216] and parenchymal liver disease [513, 526, 527], differentiate GISTs from other types of gastrointestinal SET [280, 290], and grade pancreatic neuroendocrine tumors (Ki-67) [204].

### 19 G trucut needle

A 19 G trucut needle with a 20 mm tissue tray and a spring-loaded mechanism for endosonographic applications was first reported in 2002 [92, 93]. Results comparing the yield of EUS-guided trucut biopsy to standard aspiration needles have been unfavorable. Several technical limitations (rigidity, mechanical friction of the spring-loaded firing mechanism, technically demanding use, no fanning in multiple trajectories through the le-

sion possible, minimal diameter of the target lesions of approximately 20 mm) cause the diagnostic yield and accuracy to vary with no obvious advantage over standard aspiration needles (for details, see [96, 110, 484, 485]). Due to these drawbacks and the high cost of the needle platform, EUS-guided trucut biopsy has not prevailed in clinical practice. The ability to obtain a specific diagnosis by immunohistochemistry is significantly higher with EUS-guided trucut biopsy compared with EUS-FNA [94].

#### ProCore needles

Promising results using a 19 G aspiration needle with a lateral opening near the needle tip (core trap) and reverse bevel technology (ProCore) were reported for EUS-guided biopsy in various mass lesions and lymph nodes, with the sample quality being adequate for histological assessment in 89.5% of cases [95]. ProCore needles are available with diameters of 19 G, 20 G, 22 G and 25 G. A high single-pass rate of 88.5% adequate histological samples with the 22 G ProCore needle from pancreatic masses (mainly transduodenal biopsy) has been demonstrated [97]. A further study using the 22 G ProCore needle for EUS-guided biopsy of various pancreatic and non-pancreatic mass lesions reported a similar yield of 83% adequate histological core samples [528]. However, a tissue core with material sufficient for cytopathological assessment was obtained in only 53% of small solid pancreatic lesions ( $\leq 20$  mm) [529] and in 46% of PCLs [530]. A high single-pass diagnostic yield was reported for EUS-guided sampling of solid pancreatic lesions with the 25 G ProCore needle but with histological core material provided in only 32% [511]. A further study using the 25 G ProCore needle reported diagnostic specimens in only 60.4% of EUS-guided biopsies of solid masses, lymph nodes and thickened gastric wall, with histological specimens provided in only 40.5% [531].

Comparative data on the efficacy of “histology needles” is expanding. Comparing the 22 G ProCore needle and a 22 G aspiration needle in EUS-guided sampling of solid pancreatic mass lesions, the diagnostic yield or quality of the histologic core did not differ significantly [510]. Further RCTs comparing the performance of standard 22 G aspiration needles and ProCore needles confirmed similar accuracy of both needles in the diagnosis of solid pancreatic masses [532–534], with a lower number of needle passes needed for a diagnostically adequate sample with a 22 G core needle biopsy [532, 533]. Conversely, one study reported a better histological sample for the standard aspiration needle [534]. A further prospective study found a significantly lower capacity for diagnosis and more technical difficulties and failures with the 22 G ProCore needle [535]. A retrospective comparative study reported similar performance of both needle types with a non-significant trend to a higher per-pass adequacy for the ProCore needle [536]. Only one RCT, comparing the performance of the 22 G standard aspiration needle with that of the 22 G ProCore needle in SETs, found a significant advantage of the ProCore needle in terms of improved capacity to obtain histological core samples and a higher diagnostic sufficiency rate [294].

A meta-analysis ( $n = 1617$ ; including 641 cases with pancreatic mass lesions) compared the performance of the ProCore and standard needles for EUS-guided sampling of pancreatic and other lesions and found no significant difference in diagnostic adequacy or accuracy, histological core tissue procurement or mean number of passes to diagnosis. There was no difference observed between the 19, 22 or 25 G needles for any of the outcome parameters [537].

A retrospective study suggested superiority of 21 G aspiration needles over 22 G aspiration needles in characterizing benign mediastinal lesions and subtyping NSCLC when using histopathological assessment of EBUS-TBNA samples [538].

#### Recommendation 24

In a referral EUS center it is advisable to have needles of different size available, and the choice among different needles should be made considering the anatomical location and the type of the target lesion and the preferred mode of processing of the material (LoE 2b, GoR C). Strong consensus (100%).

#### Recommendation 25

22 G aspiration needles have a high diagnostic yield, low risk of adverse events, and good technical performance, and therefore should be regarded as the current standard for EUS-guided sampling (LoE 2a, GoR B). Strong consensus (100%).

#### Recommendation 26

25 G aspiration needles are not inferior to 22 G aspiration needles with respect to cytological yield (LoE 1a, GoR A). The use of 25 G needles should be considered in particular for EUS-guided transduodenal sampling of pancreatic head lesions (LoE 2a, GoR C). Strong consensus (100%).

#### Recommendation 27

Due to a high rate of technical failure, the use of nonflexible 19 G needles is not recommended for transduodenal sampling of pancreatic head masses (LoE 2b, GoR B). Strong consensus (100%).

### Factors influencing the yield of EUS-guided sampling Features of the target lesion

The hypocellular character of the PCL aspirate renders the diagnostic yield and accuracy of EUS-guided sampling of PCLs considerably lower than in the case of solid pancreatic lesions (► Table 3).

For gastrointestinal SETs the diagnostic yield of EUS-guided sampling (specific diagnosis) is approximately 34% [286] to 82% [283], with most studies reporting a yield of 52–63% [278]. The sensitivity of EUS-FNA is influenced by size ( $> 10$  cm), location (duodenal), shape (irregular), and unclear layer of origin; all significantly associated with inadequate tissue yield and with non-diagnostic cytology samples [284].

Data on the influence of the size and site of solid pancreatic lesions on EUS-FNA accuracy are conflicting. In five studies of patients with solid pancreatic tumors, the sensitivity and diagnostic accuracy of EUS-FNA were correlated with tumor size [148, 539–542]. In the two largest cohorts, sensitivity and accuracy were significantly lower for tumors  $< 10$  mm [148, 541], the cut-off values of the other three studies being 20 mm [539], 25 mm [542] and 30 mm [540], respectively. Other studies did not show any association between the diagnostic performance characteristics of EUS-guided sampling and the diameter of the target lesion [152, 189, 291, 543, 544]. One study found the false-negative rate and the number of passes required for diagnosis to be higher in pancreatic tumors  $> 30$  mm compared with tumors  $\leq 30$  mm

[545]. Two studies reported tumor location in the body or tail to be associated with greater EUS-FNA sensitivity [148, 542]. In other studies, the anatomical location of pancreatic tumors was not predictive for the diagnostic yield and accuracy of EUS-guided sampling [540, 541, 544].

The diagnostic accuracy of EUS-FNA for pancreatic cancer is considerably hampered in patients with chronic pancreatitis [546–550].

There are inconsistent results in studies evaluating the influence of biliary stents on EUS-FNA performance characteristics. In two retrospective studies, EUS-FNA was found to be accurate and safe in the diagnosis of pancreatic cancer, independent of the presence of a plastic or self-expanding metallic biliary stent [545, 551]. In another study, there was no significant difference in the diagnostic yield of EUS-FNA between patients without biliary stents and those with stents placed >1 day prior to EUS-FNA. Patients with stents placed immediately before EUS-FNA were significantly more likely to have indeterminate cytopathological results [552]. A further report suggested a significantly lower accuracy of EUS-FNA for pancreatic head malignancy in patients with prior biliary stenting [553].

## Sampling technique

### Fanning technique

Large malignant tumors, lymph node metastases and inflammatory lymph nodes may develop necrosis, in particular centrally. Malignant lymph node infiltration may be focal and commences in the peripheral cortical zone. This suggests that EUS-FNA of the periphery of the lesion increases the diagnostic yield, but this is not supported by a study where aspiration from the edge of the lymph node did not increase the likelihood of a correct diagnosis [554]. Sampling of all parts of solid lesions and lymph nodes (“fanning technique”) is recommended by the ESGE guidelines on EUS-guided sampling in gastroenterology [96]. According to the results of an RCT, fanning with a needle through multiple areas of a solid pancreatic lesion is not more accurate than a traditional approach where only a single area is targeted. However, significantly fewer passes are required when using the fanning technique to establish a diagnosis [555].

### Recommendation 28

The fanning technique should be applied in EUS-guided sampling to increase sample adequacy (LoE 2b, GoR C). Strong consensus (100%).

### Suction

Traditionally, negative suction pressure using a 5 ml or 10 ml syringe is used to facilitate EUS-guided tissue acquisition. Alternatively, the fine-needle capillary sampling technique [556] or slow removal of the stylet (“slow-pull technique”) [528] may be used to draw cells up into the needle lumen. Applying suction to the needle may increase the cellular yield of the aspirate but, at the same time, potentially increases artifacts and contamination by blood. Applying high negative pressure suction has been suggested to facilitate procurement of core tissue in EUS-FNA and EBUS-TBNA [283, 516, 518, 523, 557, 558]. In the United States, routine use of suction was preferred by 85.5% of EUS-FNA practitioners for the sampling of solid lesions, and by 67% for the sampling of lymph nodes [489]. There is controversial data on the use of suction in non-pancreatic and pancreatic EUS-guided sam-

pling. An experimental study revealed that continuous suction using a 10 ml syringe rather than intermittent suction or suction using 20 ml or 30 ml syringes provided optimal cellularity in EUS-FNA of a mediastinal lymph node [559]. A further experimental study evaluated suction forces of traditional and side-hole aspiration needles of all 3 available diameters using 50 ml negative pressure, 20 ml negative pressure and the slow-pull technique. Suction forces increased with a larger needle diameter as well as with larger aspiration volume. The slow-pull technique generated a weak negative suction pressure of 1.4–4.8% of that generated with a 20 ml syringe (needle diameter dependent), with the time to reach the maximum negative pressure also being needle diameter-dependent (with a 20 ml syringe: 19 G: 4 s, 22 G: 11 s; 25 G: 80 s) [560].

An RCT demonstrated that EUS-guided lymph node sampling with suction compared with the fine-needle capillary technique did not improve the likelihood of correct diagnosis, but, due to excessive bloody contamination, provided smears of significantly poorer quality [554]. This contradicts a further RCT (n=52) with solid lesions, 66% lymph nodes. EUS-FNA with suction provided a greater number of cytological slides and a higher sensitivity and NPV without increasing the blood contamination [561]. For EBUS-TBNA of mediastinal lymph nodes, no difference in adequacy, diagnosis, or quality between suction and no suction was demonstrated in an RCT [562]. With various pancreatic and non-pancreatic targets (49% lymph nodes), no difference in suction versus capillary sampling in terms of quality and diagnostic accuracy was found [556].

For sampling of pancreatic masses using 22 and 25 G aspiration needles, one RCT favored EUS-guided fine-needle sampling with 10 ml suction. Cytological samples in the suction group were associated with a significantly higher cellularity, diagnostic yield, sensitivity, and accuracy compared with those in the non-suction group. However, blood contamination of slides was greater in the suction group [563]. In a multicenter study, no suction, 10 ml suction, and 20 ml suction were compared in EUS-guided sampling of solid pancreatic lesions using a 22 G aspiration needle in a prospective randomized fashion. The sample adequacy and accuracy were significantly better with 20 ml suction (87.5% and 86.2%, respectively) compared with 10 ml suction (76.1% and 69.0%, respectively) and no suction (45.4% and 49.4%, respectively) [564]. A retrospective study compared the slow-pull technique with suction in the sampling of solid pancreatic lesions. The slow-pull technique resulted in significantly less contamination with blood and higher sensitivity for the diagnosis of malignant tumors only when a 25 G aspiration needle was used. No significant differences between the two techniques were observed in this study when a 22 G aspiration needle was used [542].

### Recommendation 29

For aspiration of cysts and fluid collections, negative pressure suction is recommended (LoE 5, GoR D). Strong consensus (100%).

### Recommendation 30

For sampling of solid pancreatic lesions, negative pressure suction should be considered (LoE 1b, GoR A). Strong consensus (100%).

**Recommendation 31**

In lymph nodes and other highly vascularized solid lesions, sampling without applying suction should be considered (LoE 2b, GoR C). Strong consensus (100%).

**Use of a stylet**

The use of a stylet is intended to prevent clogging of the needle lumen and contamination of the aspirate by blood and gastrointestinal wall tissue, to express the aspirated material from the needle and to stabilize the needle. A removable stylet is included in all commercially available aspiration needle platforms and is recommended for use by manufacturers. In the United States, this stylet is used by the majority of EUS-FNA practitioners [489].

No advantage of using a stylet in terms of specimen quality and diagnostic yield has been demonstrated [565–569]. An RCT suggested a lower proportion of adequate samples and a higher probability for blood contamination in needle passes using a stylet compared with needle passes performed without a stylet [565]. A multicenter RCT reported non-inferiority of performing 22 G EUS-FNA of various solid lesions without a stylet compared with using a stylet with respect to the acquisition rate of histological specimens (55.5% vs. 55.0%) [570].

**Recommendation 32**

Aspiration needles may be used with or without a stylet with the same diagnostic yield (LoE 1b; GoR A). Strong consensus (100%).

**Number of needle passes**

The number of passes is determined based on the results of on-site cytopathological evaluation, should this be available (ROSE)<sup>14</sup> [96, 571, 572]. As an alternative to ROSE-guided sampling, a high number ( $\geq 7$ ) of needle passes is thought to be a predictor of a high diagnostic sensitivity of EUS-FNA [149]. If ROSE is not available, 69% of endosonographers in the United States will perform 3–5 needle passes, and 29% will perform 6 or more needle passes [489]. In Europe, 58.6% of endosonographers perform  $\leq 3$  needle passes for diagnosis of lymphadenopathy, and 44.6% ( $\geq 25$  mm) or 48.8% ( $< 25$  mm) for the diagnosis of pancreatic lesions [149]. In patients with pancreatic and non-pancreatic lesions, the diagnostic accuracy with  $\geq 3$  needle passes was significantly higher than that with  $\leq 3$  needle passes (90% vs. 78%) [291]. In Germany, 84% of endosonographers select the number of needle passes depending on visual assessment of aspirates [488].

**Pancreatic lesions**

ROSE study results indicate that the diagnosis of a solid pancreatic lesion using standard aspiration needles may require 5–7 passes [573–575]. When using a 25 G aspiration needle for sampling of a solid pancreatic lesion, 2–4 needle passes were adequate for good diagnostic accuracy [499, 514, 515, 576]. Using a standard 22 G aspiration needle, 1–2 needle passes were sufficient to achieve a high diagnostic yield and accuracy in 92% of cases with solid pancreatic lesions [521].

<sup>14</sup> The terms “number of passes” and ROSE are explained in the addendum on terminology.

Negative predictive factors for the number of diagnostic EUS-FNA needle passes include the following: intratumoral anechoic foci, well-differentiated pancreatic cancer, neuroendocrine tumor, co-existence of chronic pancreatitis, benign final diagnosis, pancreatic head location, diameter of the lesion (conflicting data) and prior attempts for tissue diagnosis [144, 148, 547, 573, 577, 578].

In the case of PCLs with no solid component, a single pass and complete cyst fluid aspiration should be performed to prevent cyst infection [96]. In the case of PCLs with a solid component, the diagnostic yield is significantly higher for  $\geq 2$  needle passes (78%) compared to one needle pass (44%) [579].

**Non-pancreatic lesions**

In the case of lymph nodes, liver metastases and adrenal lesions, a lesser number of needle passes is sufficient to provide a high diagnostic yield. Approximately 3 needle passes were sufficient for EUS-FNA and EBUS-TBNA of lymph nodes [499, 554, 573, 575, 580]. One study indicated that 5 needle passes is optimum for the cytopathological diagnosis of lymph nodes [574]. For liver lesions, 2–3 needle passes are adequate [461, 463, 573]. There is no evidence-based data to suggest an optimal number of needle passes in gastrointestinal subepithelial, adrenal, or other lesions.

**Recommendation 33**

If ROSE is not available, the number of needle passes should be based on gross visual inspection of the obtained material and the type of target lesion (LoE 2b, GoR C). Strong consensus (100%).

**Targeted sampling**

EFSUMB guidelines recommend the use of contrast-enhanced endoscopic ultrasound (CE-EUS) and of EUS-elastography to facilitate differential diagnosis of solid pancreatic lesions, PCLs and lymph nodes [581, 582]. CE-EUS and EUS-elastography are appropriate to demonstrate avascular and soft areas (necrosis) within solid tumors and lymph nodes. It is speculated that tumor necrosis reduces the diagnostic yield of EUS-guided sampling of large malignant tumors [555]. Furthermore, it has been shown for gastrointestinal SET and large lymph nodes that EUS-guided puncture of necrosis may promote infection [114].

**Lymph nodes**

A reliable classification of benign and malignant lymph nodes is an important prerequisite for the correct prognosis and treatment guidance of malignancy. B-mode and color Doppler criteria lack good sensitivity and specificity for lymph node characterization, importantly overlooking focal metastatic infiltrations of small lymph nodes [583, 584].

CE-EUS improved the specificity in diagnosing benign lymph nodes, compared to B-mode EUS, but did not improve the identification of malignant lymph nodes in the mediastinum and abdomen [585]. Evaluation of CE-EUS enhancement patterns demonstrated an improvement in sensitivity and specificity, compared with B-mode EUS [586].

EUS-elastography, currently strain elastography, has been shown to increase the discriminatory ability of normal EUS criteria, and to improve the specificity of lymph node staging in gastrointestinal malignancy [29, 582]. A meta-analysis calculated a sensitivity of 88% and specificity of 85% with EUS-elastography for differentiating between benign and malignant lymph nodes [587]. EUS-

elastography has the potential to further improve the accuracy of EUS-FNA in nodal staging [29, 582, 588]. EFSUMB guidelines suggest using EUS-elastography for identifying suspicious lymph nodes and/or harder lymph node regions as targets of EUS-guided sampling [582]. There are no prospective studies comparing B-mode-guided and elastography-guided EUS-FNA in the staging of malignant lymph nodes.

### Solid pancreatic lesions

The NPV of EUS-FNA for the diagnosis of PDAC is relatively low, estimated at 72% [196] and 58.5% [589]). The percentage of the cytopathological diagnostic category “atypical” with a malignancy rate of 25–100% (mean 58%) in follow-up amounts to 1–14% (mean 5.3%) in pancreatic EUS-FNA [152, 590–593]. Therefore, guidelines advise against preoperative sampling of potentially resectable solid pancreatic mass lesions in operable patients unless there is high suspicion of a diagnosis other than PDAC (non-PDAC), particularly autoimmune pancreatitis [104, 594, 595]. Even with detailed preoperative diagnostic evaluation, the incidence of benign disease following pancreatoduodenectomy for presumed PDAC is 5–13%, with 30–43% being focal autoimmune pancreatitis [595]. In specialized tertiary referral centers for EUS-FNA, 13% [148] to 21% [194] of focal pancreatic lesions referred for cytopathological diagnosis turn out to be benign, often focal chronic and autoimmune pancreatitis. In the case of solid pancreatic neoplasms, 12% to 25% turn out to be non-PDAC (e.g. neuroendocrine tumors, pancreatic metastases, mesenchymal tumors, lymphoma, solid pseudopapillary neoplasia) [146, 148, 194, 596]. The ratio of non-PDAC to PDAC is inversely related to the diameter of the tumor. In EUS-FNA of solid pancreatic lesions (n=996), 77.5%, 41.3% and 19.2% of solid pancreatic lesions measuring <10 mm, 10–20 mm, and >20 mm, respectively, turned out to be non-PDAC or benign [148]. A diagnosis of focal pancreatitis or non-PDAC will significantly affect the management and outcome of the patient, allowing watchful waiting for low-risk cystic neoplasias and small G1 neuroendocrine tumors, non-surgical treatment for mass-forming autoimmune pancreatitis, lymphoma and some metastases, and organ-preserving surgery for small neuroendocrine tumors. The selection of patients for EUS-guided sampling with a high suspicion of a diagnosis other than PDAC is of pivotal importance to avoid unnecessary pancreatic head resection with inherent morbidity and mortality [512].

Contrast-enhanced ultrasound (CEUS) and CE-EUS are able to discriminate hypovascular PDAC from other iso- and hypervascular solid pancreatic lesions (non-PDAC) with an accuracy >85% [581, 597]. Interobserver agreement has been shown to be moderate to excellent for CE-EUS in characterizing solid pancreatic lesions [598–600]. A meta-analysis reported sensitivity and specificity of CE-EUS to diagnose PDAC at 94% and 89%, respectively [601]. When there is a high suspicion of non-PDAC, patients with solid pancreatic mass lesions which are hypervascular or isovascular in comparison with the surrounding pancreatic parenchyma should be referred to pretherapeutic EUS-guided sampling. In iso- or hypervascular pancreatic masses with a negative sampling result, PDAC is unlikely. Conversely, negative results of EUS-guided sampling of solid pancreatic lesions which are hypovascular on CE-EUS should be considered false-negative, thus requiring repeat sampling or proceeding directly to surgery [600, 602]. An RCT demonstrated that CE-EUS-guided FNA of solid pancreatic lesions is more efficient than conventional EUS-FNA with fewer needle passes required to obtain a diagnostic sample [603].

EUS-elastography has a high sensitivity, but only a moderate specificity for differentiating malignant from benign solid pancreatic lesions [29]. Meta-analyses report a sensitivity of 95–97% (qualitative elastography: 98–99%; quantitative elastography using the hue histogram: 85–96%) and a specificity of 67–76% (qualitative elastography: 69–74%; quantitative elastography: 64–76%) [604–608]. Chronic pseudotumor pancreatitis can be differentiated from PDAC by a difference in elastography appearance. Malignancy can be excluded with an NPV of >90%, if the lesion has soft elastographic features [29]. One study evaluating the performance of EUS-elastography for differentiating between PDAC and inflammatory masses found high sensitivity (for qualitative and quantitative elastography: 99% and 92%, respectively), high diagnostic odds ratios (130 and 24.7, respectively) and moderate specificity (for qualitative and quantitative elastography: 76% and 68%, respectively) [609]. EUS-elastography excludes rather than confirms a malignant pancreatic mass, and will not replace EUS-guided sampling. Used as a complementary technique to EUS, CE-EUS and EUS-FNA, it potentially may increase the yield of EUS-FNA and reduce unnecessary sampling [29, 604–607].

Combined CE-EUS and EUS-elastography had a high PPV of 96.2% and an NPV of 71.4% in the differentiation of hypovascular and hard pancreatic masses suggestive of PDAC [610]. EFSUMB guidelines recommend that in the case of persisting strong clinical suspicion of pancreatic cancer with inconclusive or negative EUS-guided sampling, a hard focal lesion on elastography and/or a hypovascular lesion on CEUS and or CE-EUS indicates the need for repeat EUS-FNA or referral to surgery [582]. Repeat EUS-guided sampling in inconclusive cases, where pancreatic cancer remains likely, is able to establish a diagnosis in the majority of patients (82–84%) [611, 612].

### Cystic pancreatic lesions

The presence of epithelial mural nodules, thick walls, and septa has been shown to be highly predictive for malignancy in BD-IPMN [613, 614]. International and European guidelines recommend surgical treatment of BD-IPMN in particular if enhancing nodules or “positive cytology” has been verified [225, 227]. Targeted biopsy of the cyst wall and solid components has a significant incremental diagnostic value over cyst-fluid aspiration alone for the diagnosis of mucinous and malignant cystic neoplasms [579, 615, 616] and is recommended by the ESGE guideline on EUS-guided sampling in gastroenterology [96].

EUS and CE-EUS significantly improve the discrimination and characterization of mural nodules in IPMN in comparison with B-mode EUS and CT [617–620], suggesting that CE-EUS may facilitate EUS-guided sampling of solid components in PCLs.

### Subepithelial gastrointestinal tumors

Differential diagnosis of hypoechoic gastric SETs by EUS and other imaging techniques is difficult [110, 277, 278, 290, 621]. Preliminary findings suggest that CE-EUS can discriminate GISTs (hypervascular) from benign lesions (leiomyoma, lipoma: hypovascular) [622]. GISTs with an intermediate and high risk of malignancy present with highly irregular vascular patterns and avascular necrotic areas [621, 623, 624]. The selection of hypovascular hypoechoic SETs, presumed not to be GISTs, for EUS-guided tissue acquisition with immunohistochemical phenotyping would help to prevent unnecessary surgery in 20% of asymptomatic patients with hypoechoic SETs of the stomach [277, 278, 621].



**Recommendation 34**

Contrast-enhanced EUS and/or EUS-elastography may be used to guide and target EUS-guided sampling of lymph nodes (LoE 2a), solid pancreatic masses (LoE 2a), pancreatic cystic lesions (LoE 2b) and gastrointestinal subepithelial tumors (LoE 3b) (GoR C). Strong consensus (100%).

**Recommendation 35**

In addition to the aspiration of cyst fluid, the cyst wall and solid components, if present, should be sampled in pancreatic cystic lesions (LoE 2b, GoR B). Strong consensus (100%).

## EUS-guided sampling: Processing and evaluation of specimens



### Techniques for expelling a specimen from the needle

Techniques for expelling specimens are related to the needle system used. Most commercially available aspiration needles are based on the original Vilmann-Hancke system, consisting of a steel needle with a stylet, a metal spiral sheath, and a biopsy handle [625]. There are three different techniques for expelling a specimen: 1. Air flushing: the needle is flushed with an empty 5 ml syringe, and the specimen is collected in a saline-filled Petri dish or a saline- or formalin-filled vial. 2. Saline flushing: the needle is flushed with a saline-filled 5 ml syringe. 3. Extrusion with the stylet: the stylet is reinserted slowly into the needle, and the specimen is expelled gently droplet by droplet onto glass slides, into a vial or Petri dish containing saline, a preservation-solution or a fixative. There is minimal evidence with regard to the method which is more effective. No differences between air flushing and stylet reinsertion with regard to the number of diagnostic specimens, overall accuracy and specimen quality were found in an RCT, but smears were bloodier following stylet use for expelling of the sample [563]. A combination of both approaches is possible [626]; use of the stylet method first followed by the air or saline flushing method is associated with a high diagnostic yield [627]. Practical aspects have to be taken into account. Gentle expelling of material from the needle using a stylet prevents splattering of the aspirated material. Controlled release of precise quantities of material onto slides is possible, and high-quality smears with minimal thick layer, air-drying or clotting artefacts may be prepared. It is better to forcefully expel some material from the needle by flushing. If the CB technique, standard histopathological processing, or thin-layer preparations are intended, flushing the needle content with air directly into the preservation or fixation fluid is most effective [628, 629].

Trucut needles have a 20 mm tissue tray [93]. The tissue core may be separated from the tray using a scalpel, a needle, or by wash-out in formalin solution.

**Recommendation 36**

Material can be expelled from EUS aspiration needles using the stylet, by spraying with air on slides, or by flushing the needle with saline (LoE 2b, GoR B). Strong consensus (100%).

**Recommendation 37**

Controlled release of the material onto slides using the stylet is the preferred method despite more blood contamination (LoE 5, GoR D). Strong consensus (100%).

## Methods for specimen preparation and processing

Optimizing specimen handling and processing may reduce non-diagnostic EUS-guided sampling [517, 630]. The handling of specimens depends on the diagnostic methods used and the final cytopathological evaluation.

### Cytopathology: conventional smears and liquid-based preparations

For cytological analysis specimens should be smeared onto slides (smear cytology, SC) or incorporated into special preservation solutions (liquid-based cytology, LBC) for further handling. Smearing techniques are described elsewhere [628, 629]. A smear may be wet-fixed or air-dried. The decision on the fixation technique determines the subsequently used staining methods. For Papanicolaou staining, wet fixation with 95% alcohol (spray fixation, immersion) is preferred. Air-dried specimens are suitable for nearly all methods particularly Romanowsky stains (e.g. May-Gruenwald-Giemsa, Diff Quick, or Hemacolor). Air-dried specimens but not wet-fixed specimens are suitable for further immunocytological staining [628, 629, 631].

The direct smearing technique requires controlled release of the specimen from the needle. Particularly with wet fixation immediate smearing is important to avoid drying artifacts of the specimen [628, 632].

LBC is based on ultracentrifugation and monolayer preparation using partially automated systems (e.g. ThinPrep, SurePath). Major advantages are independence from individual smearing techniques, purification and concentration of cellular material, and ability to perform ancillary testing. Disadvantages are filtering-induced cell loss, removal of potentially diagnostic relevant extracellular background, disintegration of cellular clusters and increased cost. Prospective comparative trials demonstrate that LBC (e.g. ThinPrep) was less sensitive with material obtained by EUS-/EBUS-guided sampling from lymph nodes and pancreatic lesions compared with traditional SC [350, 633, 634]. A further RCT suggested that LBC may serve as a complementary preparation technique if blood contamination of smears is abundant [634].

### Histopathology: cell block and core tissue preparation

In general, histopathological processing including paraffin-embedding, microtome-sectioning, and staining is possible with small coherent tissue cores embedded in a formalin fixative or with CB. A wide variety of ancillary diagnostic techniques (immunohistochemistry, molecular analysis) may be performed on histopathologically processed material [110, 285, 517, 521, 628, 629, 631, 632, 635 – 637].

CB is increasingly used. After preparation, the specimen is processed using standard histopathological methods. CB may be prepared from any cell suspension (e.g. liquid aspirates, needle rinses, or specimen in preservative solutions for LB). Pellets of artificially aggregated cells are obtained by using repeated centrifugation and/or special cell capturing gels [629 – 631, 638].

Small core particles obtained with aspiration needles or “histology needles” can be directly delivered into formalin solution for fixation followed by standard histopathological processing [95, 332,

517, 630, 639, 640]. Alternatively, core particles may be isolated from samples expressed on glass slides or preservation solutions by the stylet method before further cytopathological processing ("split-up" method). For isolation sharp instruments like needle tips or scalpels can be used. If the needle load is split for cytopathological and histopathological examination, gross visual examination is reasonably accurate [285, 521, 641]. Tissue fragments appear white or discolored within the red cylinder of coagulated blood [332]. The gross visual assessment of histological material from solid pancreatic lesions using a 22 G aspiration needle by the EUS examiner was unsuccessful in only 13.5% of cases [521]. The split method for cytopathological and histopathological evaluation does not interfere with the cytology result [642].

## Cytopathological evaluation of specimens

### Cytopathological vs. histopathological evaluation

In most cases of PDAC and lymph node metastases, cytopathological evaluation alone is adequate to establish a diagnosis of malignancy. The diagnostic accuracy of cytology obtained by EUS-FNA for pancreatic cancer, biliary cancer, and malignant mediastinal lymphadenopathy is at least reasonable (Table 3). The diagnostic sensitivity of EUS-FNA cytology is highly dependent on the proficiency and experience of the cytopathologist evaluating the specimen [152, 161] and to a lesser extent on the availability of ROSE (see sub-section below).

In a number of clinical settings and target lesions, it is tissue architecture, immunohistochemistry and molecular analysis rather than cellular features that are essential for accurate pathological assessment [636, 637]. For benign diseases, e.g. autoimmune pancreatitis [209, 216], differential diagnosis of SET (GIST vs. leiomyoma or schwannoma) [94, 280, 288, 290, 295, 298], subtyping of NSCLC and malignant lymphoma [310, 332, 361, 424, 538], diagnosis of rare tumors [221, 340, 521], grading of neuroendocrine tumors [203–205], molecular profiling of solid tumors [180–184, 186, 307–309, 311–313, 517, 643, 644] and differential diagnosis of mediastinal lymph node metastases [94, 340, 356], a core sample is preferred to a cytological aspirate [110]. Immunohistochemistry and molecular analysis will become increasingly important to allow personalized oncological treatment [180–184, 186, 307–309, 311–313, 517, 643]. Direct histopathological processing of material obtained with 22 G EUS-FNA has been shown to preserve the tumor tissue architecture in 68% of diagnostic cases compared to 28% with the standard cytopathological approach including the CB technique. In this retrospective comparative study, the histological core tissue was more suitable for immunohistochemical and molecular studies [517].

### A complementary approach: combining cytopathological and histopathological assessment

There are two reasonable strategies to achieve high diagnostic accuracy in EUS-guided sampling, without the attendance of a cytopathologist: combining cytopathological and histopathological evaluation [94, 148, 291, 345, 350, 521, 641, 645, 646], or relying on core tissue or CB material for histopathological assessment [95, 97, 216, 332, 361, 369, 503, 517, 524, 639, 640, 647, 648]. 55.8% of the participants of a European EUS workshop described routine collection of material for histopathological analysis. Routine isolation of small tissue cores for histopathological preparation is independently associated with the self-reported sensitivity of EUS-FNA [149]. Several studies have shown an incremental yield of combining SC with the CB technique or histological core assessment in terms of diagnostic yield and accuracy [148, 291,

345, 350, 520, 521, 645, 646, 649]. A multicenter study using a 22 G aspiration needle demonstrated significantly better accuracy (87.5%) and sensitivity (82.9%) for combined histopathological and cytopathological analysis in pancreatic tumors than the accuracy and sensitivity of cytology (77.6% and 68.1%, respectively) or histology (71.4% and 60%, respectively) alone [521]. Studies combining cytological assessment of samples obtained with EUS-FNA and core tissue obtained with EUS-TCB from the same lesion also showed a slightly improved outcome (see [96, 110, 486]). For most indications, cytopathological and histopathological assessment should be used in a complementary manner rather than exclusively. Cytopathological methods perform better for the evaluation of nuclear and cellular characteristics, while histopathological assessment of CB and core samples are advantageous over cytopathological assessment in cases in which immunohistochemistry is able to establish a diagnosis, e.g. in non-PDAC, gastrointestinal SETs, rare benign diseases, and lymphadenopathy [94, 148, 216, 221, 281, 283, 290, 310, 332, 340, 354, 356, 361, 369, 372, 650].

### Specimen handling for diagnosis of infectious diseases

Suspected infectious disease (e.g. abscesses, tuberculosis or atypical mycobacteriosis) requires specific handling of the aspirate. Diagnosis of lymph node tuberculosis and differentiation from other granulomatous and mycobacterial disease is a challenge; transesophageal EUS and EBUS may demonstrate tuberculous etiology of mediastinal lymphadenopathy with features such as hyperechoic foci, heterogeneous appearance or patchy anechoic and hypoechoic areas [324, 326]. Microbiological cultures are possible if samples are placed in saline, whereas a polymerase chain reaction (PCR) amplifying mycobacterial DNA requires the specimen to be placed in formalin [349, 352]. A moderate to high accuracy of SC including the Ziehl-Neelsen stain for acid-fast bacteria alone for the diagnosis of tuberculosis, and its differentiation from sarcoidosis or histoplasmosis has been shown [349, 367, 380, 382, 385, 386, 651]. Some limitations of cytopathological diagnosis have been reported; in a study of EUS-guided sampling of mediastinal lymphadenopathy, where granulomatous disease was prevalent in 206/281 patients, diagnosis was possible in 76 tuberculosis and 7 sarcoidosis patients only. The etiology was uncertain in the remainder of patients (59.7%) [652]. Further studies showed significantly higher sensitivity of PCR vs. microbiological culture and/or SC, and of microbiological culture vs. SC [352, 355, 357, 653]. In a meta-analysis of 7 prospective and 7 retrospective studies, the overall diagnostic yield of EBUS-TBNA for the diagnosis of mediastinal tuberculous lymphadenitis was 80% with the culture positive rate (54%) being significantly higher than the SC positive rate (33%) [654].

#### Recommendation 38

The processing of specimens obtained by EUS-guided sampling varies according to the cytopathological or histopathological methods used for diagnosis (LoE 2b, GoR C). Strong consensus (100%).

#### Recommendation 39

Tissue fragments can be effectively isolated from the whole sample after gross visual examination without impairing the cytopathological result (LoE 2b, GoR B). Strong consensus (100%).

**Recommendation 40**

Without rapid on-site cytopathological evaluation, the combination of cytopathological and histopathological processing seems to provide the most reliable results (LoE 2b, GoR B). Strong consensus (100%).

**Recommendation 41**

Specimens obtained with EUS-guided sampling can be used for special ancillary studies including microbiological culture, biochemical analysis, immunocytochemistry, immunohistochemistry, and molecular analysis (LoE 2b, GoR B). Strong consensus (100%).

**Recommendation 42**

Liquid-based techniques may be used complementary to traditional smearing for cytopathological evaluation of specimens (LoE 2b, GoR C). Broad agreement (90%).

**Recommendation 43**

For the diagnosis of tuberculosis, smear cytology including Ziehl-Neelsen stains should be combined with the microbiological culture of specimens transferred into sterile saline, and PCR amplification of mycobacterial DNA using formalin-fixed specimens (LoE 2b, GoR B). Strong consensus (100%).

**On-site assessment of the adequacy of specimens****Rapid on-site cytopathological evaluation**

ROSE is reported to be used in the majority of centers in the United States [162, 489], but on-site cytopathological service is not routinely available in Europe [149, 488]. The availability of on-site cytopathological evaluation was considered by the participants of an international EUS workshop to be a significant predictor of EUS-FNA yield and accuracy [149]. Positive assessments of the role of ROSE for EUS-FNA of solid pancreatic lesions and for EUS-FNA and EBUS-TBNA of lymph nodes have been documented [148, 379, 553, 573, 612, 633, 655–664]. A study reported that the introduction of ROSE decreased the need of repeat EUS-FNA of pancreatic lesions by 50% (5.8% to 2.9%) [665]. Mathematical models predict that any sampling policy using ROSE would achieve high adequacy rates with fewer needle passes than sampling policies using a fixed number of needle passes, in particular when the per-pass adequacy rate is low [571, 572]. An RCT showed that ROSE during EBUS-TBNA significantly decreased the number of needle passes and was associated with a significantly lower need for (EBUS-guided) TBNA of further target lesions (11% vs. 57%). However, the sensitivity and accuracy of lung cancer diagnosis did not differ between the ROSE group and the non-ROSE group [663]. Similar results were reported from a multicenter RCT comparing EUS-FNA of solid pancreatic lesions with and without ROSE. ROSE-assisted EUS-FNA required fewer needle passes (4 vs. 7). However, there was no difference observed between the two groups with regard to yield of malignancy, adequacy, accuracy, sample quality, adverse events, procedure time, need for repeat procedures and costs [663a]. A high concordance of preliminary on-site interpretation and final cytopathological diagnoses has been shown [656, 662, 666, 667]. A

significantly higher degree of concordance between on-site and final cytopathological diagnosis is reported for unequivocal diagnosis of malignancy (98.9%) vs. non-malignancy (67.2%) [656]. Other studies have suggested that ROSE is not essential for high diagnostic yield and accuracy of EUS-FNA [96, 110, 668–670]. With EUS-FNA performed in a study where 554 lesions were assessed, 2 centers used immediate on-site cytopathology and 2 did not. The results did not differ with or without ROSE [164]. In a study of 381 consecutive cases of pancreatic EUS-FNA, ROSE offered no benefit in reducing the non-diagnostic rate [671]. EUS-FNA with ROSE vs. EUS-FNA without ROSE has not been compared in a prospective randomized study. Most EUS-FNA studies include only a single cohort. Only five studies with EUS-FNA of pancreatic lesions used a 2-cohort design with head-to-head comparison of adequacy and accuracy of ROSE vs. non-ROSE [672]. These studies have been included in a meta-analysis, showing that ROSE was associated with a significant 10% improvement of the per-case adequacy rate only in studies with a low adequacy rate (<90%). No significant impact of ROSE on diagnostic yield, accuracy or number of needle passes was observed [672]. A second meta-analysis including 68 single-cohort and 2 two-cohort studies (ROSE vs. non-ROSE, >10 cases) reported adequacy of EUS-FNA of solid pancreatic masses; ROSE was associated with a low, statistically significant advantage of adequacy rates (2.3%). This was independent of whether ROSE was performed by a cytopathologist, a cytology technician, or a gastroenterologist. Studies without ROSE used an average of 0.6 fewer needle passes per case (2.6 vs. 3.2). In non-ROSE studies the adequacy rate decreased with increasing needle passes, but for ROSE studies, the per-case adequacy was not correlated with the number of needle passes [673]. A further meta-analysis included 34 studies (3644 patients, 2285 PDAC) evaluating EUS-FNA for PDAC. Per-case adequacy was non-significantly higher in ROSE studies than in studies without ROSE. In a multivariate analysis ROSE was the only significant determinant of EUS-FNA accuracy [200]. The largest meta-analysis assessing the diagnostic performance of EUS-FNA of solid pancreatic lesions (33 studies with 4984 patients) demonstrated significantly lower heterogeneity among studies with a cytopathologist present on-site, but advantages over studies without ROSE in terms of sensitivity (88% vs. 80%) and the diagnostic odds ratio (relative DOR for no on-site cytopathologist, 0.36) did not reach statistical significance [196].

Conflicting results from two trials regarding the role of ROSE for the prediction of sample adequacy and accuracy in EUS-FNB using the ProCore needle have been documented. The prospective study compared a histological yield of 2 vs. 4 passes with a 25 G ProCore needle. Irrespective of the number of needle passes performed, the diagnostic adequacy of CB was lower compared with ROSE of material obtained with the first ProCore needle pass (81% vs. 100%) [514]. The retrospective study used a 22 G ProCore needle to sample various gastrointestinal lesions with satisfactory accuracy (83%). ROSE of the core specimen had an excellent specificity and PPV (100%). However due to insufficient cytopathological samples, the sensitivity (65%) and NPV (39%) were low [674]. Combining EUS-FNA (for ROSE) with EUS-guided ProCore biopsy (for histology) for non-pancreatic EUS-guided sampling increased procedure time (and costs) but not diagnostic accuracy [675]. ROSE has no value for the prediction of the diagnostic adequacy of EUS-guided core biopsy (EUS-FNB). Gross visual assessment of the core particles is more meaningful (see subsection on gross visual inspection below) [524].

In summary, ROSE has the potential to optimize the trade-off between needle passes and per-case adequacy for EUS-FNA of solid pancreatic lesions. However, the benefit of ROSE is relatively small and has to be balanced against the cost and time expenditure of a permanent on-site cytopathology service [575, 676–678]. The ESGE guideline on learning, techniques, and complications of EUS-guided sampling in gastroenterology recommends implementation of ROSE preferentially during the learning phase of EUS-FNA and at centers with an adequacy rate of EUS-guided sampling below 90% [96]. Telecytopathological rapid assessment of EUS-FNA/EBUS-TBNA samples could be a suitable time-effective alternative to maintaining an on-site cytopathological service in the endoscopy suite [679–684].

### Gross visual inspection and ROSE performed by the endosonographer

In the absence of ROSE, gross visual assessment of a sample to assess the adequacy of EUS-guided sampling is possible [685]. Studies show conflicting levels of ability of endosonographers and trained EUS and cytology assistants to assess slide adequacy and to differentiate malignant and benign specimens. With SC, one study suggested that visual adequacy assessment of smears from EUS-FNA of solid pancreatic lesions by cytology technicians or trained EUS technicians is unreliable, and the agreement with final cytopathologic adequacy assessment is only fair ( $\kappa$  0.20 and 0.19, respectively). There was a tendency to overestimate the amount of cytopathological material, but it should be noted that no formal staff training was given [686]. The ability of trained endosonographers to assess slide adequacy compared with a cytotechnologist was evaluated. In the determination of adequacy, differentiation of suspicious and malignant vs. benign specimens, no endosonographer was equivalent to the cytotechnologist [687]. Two studies compared performance parameters of EUS-FNA over two consecutive periods with conflicting results. In the first period, ROSE was performed by trained endosonographers, in the second period by a cytopathologist. One study showed comparable performance in both periods [688], while the other study showed significant improvement by cytopathologist-performed ROSE in terms of inconclusive, inadequate samples and diagnostic accuracy [689]. However, in a multicenter study the assessment by the EUS examiner of adequacy of the macroscopic specimen was unsuccessful only in 7% (cytology) and 13.5% (histology), resulting in a high diagnostic yield of EUS-guided sampling of solid pancreatic lesions with only 1.88 passes using a 22 G needle [521]. In a prospective evaluation of the visual assessment of core particles obtained with a 19 G Pro-Core needle, a core length of  $\geq 4$  mm is an indicator for an adequate histological sample and for a high overall, histological and cytological diagnostic yield [524].

All these studies lack information on the type and intensity of formal cytopathological training. Further studies have demonstrated the improved ability of endosonographers, following completion of structured training, to smear and stain slides, to operate a microscope [690], to judge the adequacy of a cytological specimen confidently [691], and to differentiate benign and malignant smears with an accuracy of 89% [692]. ROSE performed by an experienced endosonographer may be reliable, but requires completion of an intensive structured training program. Formal cytopathological training should be incorporated in EUS training programs.

### Recommendation 44

Rapid on-site cytopathological assessment does not substantially improve the diagnostic yield of malignancy or generally reduce the number of needle passes. In centers with an adequacy rate  $< 90\%$ , ROSE may improve the adequacy of EUS-guided sampling (LoE 2a, GoR C). Strong consensus (100%).

### Recommendation 45

Rapid on-site cytopathological assessment may be used to guide the number of needle passes, provide a reliable immediate diagnosis of malignancy, and assess the need for ancillary studies (LoE 2b, GoR C). Strong consensus (100%).

### Reporting and reliability of cytopathology in EUS-guided sampling

#### Cytopathological reporting

Several different classification systems are used as a basis for cytopathology reporting in EUS-guided sampling. In most cytopathological laboratories, the diagnostic categories for EUS cytology follow a Bethesda-like system (introduced originally for reporting gynecological, thyroid, and breast cytology): unsatisfactory, benign, atypical, suspicious, and positive for malignancy<sup>15</sup> [590, 693]. Based on a standard nomenclature for FNA [694], the Papanicolaou Society of Cytopathology has developed guidelines on standardized terminology and nomenclature for pancreatobiliary cytopathology, recommending a six-tiered system of diagnostic categories: non-diagnostic, negative, atypical, neoplastic, suspicious, and positive<sup>16</sup>. The category “neoplastic” is unique for pancreatic cytopathology, including benign neoplasms (serous cystadenoma) as well as premalignant mucinous cysts, neuroendocrine tumors and solid-pseudopapillary neoplasias [695].

The inconclusive and ill-defined diagnostic categories “atypical” and “suspicious for malignancy”<sup>17</sup> are inconsistently conveyed. In the USA, the usage and relative distribution of atypical and suspicious categories in EUS-FNA samples varied widely [591]. Several studies categorize suspicious or atypical findings as a malignant diagnosis (“positive”). Others interpret either category or atypical findings as representing a negative or inadequate sample. As a consequence, different combinations of diagnostic categories to define a malignant result lead to variable receiver-operator curves [589, 591, 592]. Therefore, comparison of study results of diagnostic performance parameters should be made with caution, particularly as the definition of the quality of specimens (i.e. adequacy, contamination, bloodiness) varies between cytopathologists (see the meta-analysis of EUS-FNA of solid pancreatic lesions [196], **Table 3**). Insufficient adherence to standardized nomenclature in cytopathological reporting hampers individual patient management and is a substantial obstacle for the comparison of results between centers and studies [629, 695].

#### Reliability of negative (“benign”) results and findings positive for malignancy/ neoplasia

A few studies have analyzed the reproducibility of cytopathological diagnoses of specimens obtained by EUS-guided sampling. A good-to-excellent diagnostic agreement between experienced

<sup>15</sup> Terms are explained in the addendum on terminology

<sup>16</sup> Terms are explained in the addendum on terminology

<sup>17</sup> Terms are explained in the addendum on terminology

cytopathologists was documented for the assessment of aspirations from mediastinal lymph nodes and masses [161, 405, 696], in the Ki-67 labelling index for grading of neuroendocrine pancreatic tumors [697], and in the assessment of core samples obtained with a ProCore needle [97, 531]. Fair to moderate interobserver agreement was described for the grading of pancreatic cancer [698], grading of atypia in PCLs [243–245], and classification of the subtype in NSCLC [699].

For clinical decision-making it is important to understand that there is still a significant risk of malignancy with negative findings in EUS-guided sampling, which is considerably high for PCLs, solid pancreatic lesions in patients with underlying chronic pancreatitis, indeterminate biliary strictures, and gastrointestinal SETs. The major cause for false-negative diagnoses of EUS-guided sampling is sampling error, whereas interpretative error is rare [110, 263, 486, 546, 547, 589, 591, 700–705].

The specificity and PPV of cancer diagnosis by EUS-FNA have been estimated at 100%. However, the gold standard was not surgical histology. In studies with good reference standards and long follow-up, false-positive findings have been reported for EUS-guided sampling in 1.1–5.3% when only cases with a positive cytopathological result were considered, and in 7.8% if suspicious cytopathology results were included. False-positive rates seem to be higher in luminal compared with extra-luminal (e.g. pancreatic) primary cancer [392, 706, 707]. False-positive findings may result from procedure-related factors, e.g. traversal of a neoplastic area, needle contamination with tumor cells [394, 395], or inadvertent aspiration of cancer cell-contaminated luminal fluid. Tumor cells within gastrointestinal luminal fluid are present in 48% of luminal cancers, and in 10% of extraluminal (pancreatic) cancers undergoing EUS-guided sampling [393]. A further source of a false-positive result is cytopathological misinterpretation, often occurring when the differential diagnosis includes entities with similar cytological morphologies (cellular mimicry), when reactive inflammatory epithelial alterations are misinterpreted as neoplastic, and/or when a distinct diagnosis is not expected e.g. in rare neoplasms [110, 486, 589, 700–702, 705, 706, 708, 709].

### Malignancy risk associated with inconclusive findings

Studies have evaluated the malignancy risk associated with inconclusive diagnostic cytopathological categories for EUS-guided sampling of pancreatic lesions. The suspicious category is associated with an 80–96% risk of neoplastic or malignant final diagnosis, whereas the atypical category carries a markedly variable and significantly lower malignancy risk [591, 592, 710]. A meta-analysis of the occurrence and outcome of the atypical category in EUS-guided sampling of solid pancreatic lesions included a total of 23 studies, of which 12 had complete outcome data [590]. The atypical category was reported between 1–14% (mean, 5.3%), with the risk of malignancy associated with the atypical category ranging between 25–100% (mean 58%). Significant heterogeneity was observed, with acknowledgement for a need of standardization of reporting and management of atypical categories in pancreatic EUS-FNA [590]. Heterogeneity can be partially explained by variability of the experience and disposition of the cytopathologist to commit to a malignant diagnosis [152, 590, 710]. Performing ancillary studies decreases an inconclusive diagnosis by >50%, demonstrated by a meta-analysis for K-ras gene mutation analysis in specimens obtained by EUS-guided sampling of solid pancreatic masses [711]. Several studies have evaluated clinical predictors associated with a high likelihood of a neoplastic diagnosis following an atypical cytopathological di-

agnosis in pancreatic EUS-FNA. These predictors (e.g. presence of a mass, weight loss, obstructive jaundice, CA 19–9) can be used to adapt management of patients with inconclusive cytopathological diagnoses: ancillary testing, watchful waiting, repeat EUS-guided sampling, alternative diagnostic techniques, or initiation of a specific treatment [593, 705, 712–714]. Repeat EUS-guided sampling in patients with high clinical suspicion of malignancy has been shown to yield a conclusive and correct diagnosis in 73–84% of cases with primarily inconclusive cytopathological diagnosis of first EUS-guided sampling [593, 611, 612, 714, 715].

### Recommendation 46

A standardized and validated classification system should be used for cytopathology reporting in EUS-guided sampling (LoE 5, GoR D). Strong consensus (100%).

### Recommendation 47

After inconclusive cytopathological results, the use of ancillary studies and/or repeat EUS-guided sampling should be weighed against the clinical background of patient history, clinical and laboratory data, EUS morphology, results of other imaging tests and follow-up (LoE 2b, GoR B). Strong consensus (100%).

## Adverse events of EUS-guided interventions and their prevention



### General considerations

EUS-guided sampling (including EBUS-TBNA) is a safe diagnostic technique. Severe adverse events are rare. There is no evidence that needle size or needle type affects morbidity of EUS-guided sampling [96, 114, 490, 716]. A systematic review of complications of 51 EUS-FNA studies including 10 941 patients describes an overall complication rate of 0.98% [717]. The complication rate was significantly higher in 31 prospective studies (1.72%) than in 20 retrospective studies (0.64%), indicating an underestimation in retrospective studies. Complications include post-procedural pain (34%), acute pancreatitis (34%), fever and infectious complications (16%), bleeding (13%), bowel perforation (2%) and bile leaks (1%). The procedure-related mortality was estimated at 0.02% [717]. A pooled adverse events rate of 0.36% (serious adverse events in 0.14%; no fatalities) was shown in a systematic review of 190 studies for intrathoracic endosonographic sampling (n = 16 181; EUS-FNA and EBUS-TBNA) [718]. A nationwide survey in the Netherlands reported a 0.15% serious adverse events rate (mortality 0.04%) of endosonographic sampling for pulmonary indications (14 075 EUS-FNA and 2675 EBUS procedures). Poor performance status was the most important risk factor for fatal outcomes [719]. A nationwide survey of the Japan Society for Respiratory Endoscopy (n = 7345 cases) showed a 1.23% overall complication rate and a 0.01% mortality rate of EBUS-TBNA [720]. The frequency of complications reported for EBUS-TBNA from the American College of Chest Physicians Quality Improvement Registry, Evaluation, and Education (AQUIRE) prospective database (n = 1317) was 1.44% [661]. The morbidity of EUS-guided therapeutic interventions is considerably higher than EUS-guided sampling, with the risk and type

of complications depending on the type of procedure [115, 721, 722] (see part V of INVUS guidelines [1]).

### Adverse events

#### Perforation

The majority of perforations associated with EUS-guided sampling are caused by the gastrointestinal passage of the echoendoscope and not the sampling procedure. The large diameter and longer rigid tip of the gastrointestinal echoendoscope increases the risk of perforation of the upper gastrointestinal tract in comparison with conventional video gastroscopes. Multicenter surveys and studies report perforation rates of 0.03–0.15% [722–726]. The risk of duodenal perforation is higher than esophageal perforation [114, 722]. A specific risk factor for esophageal perforation is esophageal cancer with luminal narrowing [722, 725].

#### Acute pancreatitis

The frequency of acute pancreatitis following EUS-FNA of pancreatic lesions is between 0.19–2.35% [114]. A systematic review reported acute pancreatitis (mild in 75%) occurring in 0.44% of patients following EUS-FNA of solid or cystic focal pancreatic lesions [717]. Pancreatitis risk is higher in patients with PCLs than in patients with solid pancreatic lesions [114, 717].

#### Intra- and extraluminal hemorrhage

Severe bleeding following EUS-FNA is a rare event occurring in 14/10 941 patients (0.13%) included in a review of 51 EUS-FNA trials [717]. One study reported clinically asymptomatic extraluminal bleeding in 3/227 patients with normal clotting parameters (1.3%) [727]. If extraluminal and intraluminal bleeding occurs following EUS-FNA, this is mild in most cases. A Japanese registry study reported an incidence of severe bleeding requiring endoscopic treatment or transfusion following EUS-FNA of pancreatic lesions of 0.23% [728]. There are three reports in the literature of fatal bleeding following pancreatic EUS-FNA [114]. There is indirect evidence that EUS-FNA of PCLs may cause a higher risk of bleeding compared with EUS-FNA of solid pancreatic lesions [717, 721, 729–731]. There is limited information on the effect of acetyl salicylic acid (ASA), other inhibitors of platelet aggregation, non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and low molecular weight heparin (LMWH) on the bleeding risk of EUS-FNA. Results of one study suggest that there is no increased bleeding risk during EUS-FNA for patients taking ASA or NSAIDs, but a possible risk for patients receiving prophylactic LMWH [732]. One study of patients undergoing transbronchial lung biopsy showed that clopidogrel, especially when combined with ASA, greatly increased bleeding risk [733]. However, in 12 patients taking clopidogrel (in 8 patients combined with ASA), EBUS-TBNA proved to be safe without any serious bleeding events [734]. Guidelines suggest discontinuing oral anticoagulants, heparin and LMWHs in therapeutic dosages as well as ADP-antagonists before EUS-guided sampling, whereas withdrawal of ASA is recommended only before EUS-FNA of PCLs [96, 716, 735–737]. Most centers check platelet count and global coagulation parameters before performing EUS-FNA. Despite limited evidence for distinct cut-off values, a platelet count < 50 000/ml and an international normalized ratio (INR) > 1.5 are regarded as contraindications to EUS-guided sampling. There is no data regarding needle size, needle type, number of needle passes or other technical factors related to bleeding risk following EUS-guided sampling.

#### Recommendation 48

In patients on antiplatelets and/or anticoagulants, a risk assessment balancing thromboembolic events versus bleeding should be performed prior to EUS-/EBUS-guided diagnostic and therapeutic interventions (LoE 5, GoR D). Strong consensus (100%).

#### Recommendation 49

Decision on suspension of antiplatelet drugs and/or anticoagulants or delay of the procedure should be made based on an individual risk assessment (LoE 5, GoR D). Strong consensus (100%).

### Fever and infection

Bacteremia following upper as well as lower gastrointestinal tract EUS-FNA is a rare event [738–741]. In large series 0.4–1.0% of patients experienced febrile episodes following EUS-FNA for solid pancreatic masses [518, 742, 743]. For endosonographic sampling of mediastinal lesions, studies report an overall frequency of major infectious complications in 0.07% of patients [718]. Serious infectious complications have been reported following EUS-FNA of mediastinal cysts [114, 718], ascites [474], perirectal cysts [61], as well as of PCLs and (peri-) pancreatic fluid collections [164]. An in-vitro study confirms that EUS-FNA of sterile cystic lesions always causes transmucosal microbial contamination [744]. Of 909 patients who underwent EUS-FNA of PCLs, the overwhelming majority of patients received peri-interventional antibiotics (93.7%), and the overall rate of cyst infection was estimated at 0.55% [717]. The incidence of infectious complications in studies that used antibiotic prophylaxis was low (0–1.4%), suggesting a protective effect [530, 579, 725, 731, 745–748]. However, a retrospective comparative study showed no protective effect of peri-interventional antibiotic treatment [749], and there is a lack of prospective comparative studies. Despite the lack of convincing evidence, several guidelines recommend peri-interventional antibiotic treatment for EUS-FNA of PCLs [96, 716, 735]. Due to potentially catastrophic consequences of mediastinal infection, guidelines and reviews regard EUS-FNA of mediastinal cysts to be contraindicated [96, 114, 716, 718, 735]. By contrast, EBUS-TBNA of mediastinal cysts seems to carry an acceptable risk [750]. A few reports on infectious complications following EUS-FNA of mediastinal lymph nodes (sarcoidosis and tuberculosis) [718, 719, 751–753] and of SETs [114, 290, 295] do not support performing peri-interventional antibiotics on a regular basis. Infectious complications after EUS-FNA of (peri-) rectal lesions are rare [58, 62, 741, 754, 755], not justifying peri-interventional antibiotics.

#### Recommendation 50

Transesophageal EUS-guided sampling of cystic mediastinal lesions should be avoided due to the high risk of infection (LoE 4, GoR C). Strong consensus (100%).

#### Recommendation 51

Peri-interventional antibiotic treatment is recommended for EUS-guided sampling of cystic lesions and fluid collections as well as in EUS-guided drainage procedures (LoE 5, GoR D). Strong consensus (100%).

**Table 4** 11 cases of needle track seeding or peritoneal dissemination following EUS-FNA [763 – 773].

Reference	Target	EUS-FNA details	Complication	Outcome
Hirooka Y et al. 2003 [763]	malignant pancreatic IPMN pT1pN0cM0	transgastric, 22 G needle, number of needle passes: not reported	peritoneal carcinomatosis 20 months following EUS-FNA	death 25 months following EUS-FNA
Shah JN 2004 [771]	perigastric lymph node metastasis (malignant melanoma)	transgastric, 22 G needle	gastric wall metastasis 6 months following EUS-FNA	surgery, further follow-up not reported
Paquin SC et al. 2005 [764]	pancreatic tail cancer pT1pN0cM0	transgastric, 22 G needle, 5 needle passes	gastric wall metastasis 21 months following EUS-FNA	palliative chemotherapy, death 12 month after diagnosis
Doi S et al. 2008 [772]	mediastinal lymph node metastasis (gastric cancer)	transesophageal, 19 G needle, 1 needle pass	esophageal wall metastasis 21 months following EUS-FNA	successful radiation treatment
Ahmed K et al. 2011 [766]	cystic pancreatic body cancer pT2pN0cM0	transgastric, needle diameter not reported, "multiple" needle passes	gastric wall metastasis nearly 4 years following EUS-FNA	death due to another malignant disease
Chong A et al. 2011 [765]	cystic pancreatic tail cancer pT2pN0cM0	transgastric, 22 G needle, 2 needle passes	gastric wall metastasis 26 months following EUS-FNA	non-resectable, further follow-up not reported
Katanuma A et al. 2012 [767]	solid pancreatic cancer pT2pN0cM0	transgastric, 22 G needle, 4 needle passes	gastric wall metastasis 22 months following EUS-FNA	surgery, further follow-up not reported
Anderson B et al. 2013 [773]	celiac lymph node metastasis of pancreatic head cancer	not reported	transmural metastasis of the gastroesophageal junction	not reported
Virgilio E et al. 2014 [768]	solid pseudopapillary neoplasia of the pancreas	not reported	delayed rupture of the solid pseudopapillary neoplasia into peritoneal cavity (20 days following EUS-FNA, probably due to infection)	not reported
Minaga K et al. 2015 [769]	solid pancreatic cancer pT3pN0pM0 R0	transgastric, 22 G needle, 3 needle passes	12 mm subepithelial gastric wall metastasis 8 months following EUS-FNA	surgery, further follow-up not reported
Tomonari A et al. 2015 [770]	solid pancreatic cancer pT3pN0pM0 R0	transgastric, 22 G needle, 2 needle passes	32 mm subepithelial gastric wall metastasis 28 months following EUS-FNA	surgery, further follow-up not reported

### Tumor cell seeding and needle track metastasis

Several studies agree that EUS-guided sampling for malignant solid and cystic pancreatic tumors and for cholangiocarcinoma is not a risk factor for the development of peritoneal seeding, tumor recurrence, or decreased survival [756 – 762]. The risk of peritoneal seeding following biopsy of pancreatic cancer appears to be significantly lower with EUS-FNA compared to percutaneous FNA [191, 192]. However, 11 individual cases of tumor cell seeding caused by EUS-guided sampling of malignant pancreatic neoplasia (n = 8, in 4 cases cystic tumors) [763 – 770] and of lymph node metastases (n = 3) [771 – 773] suggest cautious use of EUS-guided sampling (Table 4).

#### Recommendation 52

Tumor cell dissemination along the needle track following EUS-guided sampling is an exceptionally rare event. Preoperative EUS-guided sampling of pancreatobiliary malignancies is not associated with increased risk of postoperative recurrence, decreased overall survival or decreased cancer-specific survival (LoE 2c, GoR B). Strong consensus (100%).

### Miscellaneous complications

There are reports of bile peritonitis following EUS-FNA of the gallbladder or of the liver in patients with biliary obstruction

[462, 774, 775], of pneumothorax following transesophageal EUS-FNA of mediastinal lymph nodes [305], pneumoperitoneum following EUS-FNA of a pancreatic tumor [776], and of pancreatic duct leak caused by EUS-FNA of pancreatic mass lesions [777, 778]. One case of phlegmonous gastritis following EUS-FNA has been reported [779]. Two cases of a hypertensive crisis induced by EUS-FNA of retroperitoneal paraganglioma or adrenal pheochromocytoma have been documented [780, 781].

### Risk factors for complications

There is limited data linking complication rates of EUS-FNA with specific target lesions. Data from a systematic review confirmed that EUS-FNA is exceptionally safe for mediastinal lesions (n = 1310; complication rate: 0.38%), abdominal masses (n = 381; 0.26%) and adrenal glands (n = 81; 0%). Procedure-related morbidity seems to be higher for pancreatic lesions (n = 8246; 1.03%), liver lesions (n = 344; 2.33%) and perirectal lesions (n = 193; 2.07%) [717]. For sampling of mediastinal lymph nodes, in a systematic review of 190 studies including 16 181 patients, a higher frequency of adverse events (predominantly infectious complications) was reported in patients investigated with EUS-FNA (0.30%) than in those where EBUS-TBNA was performed (0.05%). Complications predominantly occurred in patients with cystic mediastinal lesions and sarcoidosis but were rare in lung cancer patients [718]. Several studies of the risk of EUS-FNA (particularly bleeding, infection, acute pancreatitis, and postopera-

tive complications) demonstrated that this was higher in PCLs than in solid pancreatic lesions [96, 717, 731, 756]. The incidence of adverse events after EUS-FNA of solid pancreatic lesions was significantly increased in small tumors ( $\leq 20$  mm) and in neuroendocrine pancreatic tumors [782].

Several studies have shown that performing EUS with or without EUS-guided sampling and ERCP in a single session is safe [783 – 790]. Prior biliary stenting has no influence on the risk of adverse events of EUS-guided sampling of suspected pancreatic cancer [552]. One study reported adverse events of EUS-guided sampling in patients with obstructive jaundice drained with plastic stents vs. self-expandable metal stents (SEMS) occurring more often in patients with plastic stents [791].

Observations from high-volume centers suggest that complications are more frequent in the learning phase of examiners [144, 164, 639]. Japanese centers reported that the rate of severe bleeding in low-volume hospitals was significantly higher than that in medium and high-volume hospitals (0.48% vs. 0.10%) [728].

#### **Recommendation 53**

EUS-guided sampling of solid lesions is a low-risk procedure. EUS-guided sampling of pancreatic cystic lesions has a higher frequency of adverse events compared to solid pancreatic lesions (LoE 2a, GoR B). Strong consensus (100%).

#### **Recommendation 54**

EUS-guided sampling and ERCP may be safely performed in a single session (LoE 2b, GoR B). Strong consensus (100%).

#### **Recommendation 55**

Any complications of EUS-guided sampling and therapeutic interventions should be documented in a standardized format in every center. The incidence of adverse events should be monitored and used as a quality indicator (LoE 5, GoR D). Strong consensus (100%).



## Addendum: Important terms used in this guidelines on EUS-guided sampling are defined and explained in

### o Table 5



**Table 5** EUS-guided interventions: definitions of important terms

Technical terms	
Cell block (CB)	Preparation of small artificial tissue fragments, clots, or cell pellets from cellular material obtained by (EUS-/EBUS-guided) fine-needle aspiration for histopathological processing (usually formalin-fixation, paraffin embedding, sectioning and staining) and evaluation. Various techniques are used for CB preparation.
Endoscopic ultrasound (EUS)	For the purpose of this guideline, the term endoscopic ultrasound is used to describe all procedures using flexible and rigid endoluminal ultrasound probes within the upper and lower gastrointestinal tract and the tracheobronchial tree. The term endosonography is used synonymously.
EUS-guided sampling	All EUS-guided procedures aiming at retrieval of tissue or fluids for cytopathological, histopathological, biochemical, microbiological, and molecular evaluation. The term embraces transintestinal EUS-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) techniques using standard aspiration needles as well as transintestinal EUS-guided fine-needle biopsy (EUS-FNB) techniques using special needles designed for the procurement of tissue cores. The terms endosonographic sampling and EUS-guided tissue acquisition are used synonymously.
Fine-needle	Needles with an outer diameter of up to 1.0 mm (18 Gauge)
Needle pass	One complete process of (EUS-guided) needle sampling from insertion of the needle into the target lesion to its withdrawal including several to-and-fro movements within the lesion. Usually several needle passes are performed in order to get sufficient material from one lesion.
Rapid on-site evaluation (ROSE)	Immediate cytopathological evaluation of specimens during the procedure at the site of EUS-guided sampling aiming at improvement of the diagnostic yield, optimization of the number of needle passes required for diagnosis, and providing a preliminary diagnosis.
Team time-out	Time-out of the entire endoscopy team just prior to the start of an advanced endoscopic procedure (e. g. EUS-guided interventions), including verification of patient identity, procedure to be performed, informed consent, pre-interventional imaging, necessary equipment, implants, individual risk assessment, and special requirements (e. g., preprocedure antibiotic administration). a checklist may be used for verification.
Outcome definitions in EUS-guided sampling	
Specimen adequacy	Percentage of specimens in which the material is representative for the target lesion and sufficient for cytopathological or histopathological preparation; the term may be used on a per-pass basis and a per-case basis. The terms "satisfactory" and "adequate" sometimes are used synonymously to describe representative and diagnostically sufficient samples.

**Table 5** (Continuation)

Diagnostic yield	Percentage of samples for which tissue diagnosis is possible; the term is usually defined on a per-case basis.
Diagnostic accuracy	Percentage of sampled cases with a tissue diagnosis that corresponds to the final diagnosis (diagnostic gold standard varying between studies); usually, non-diagnostic (inadequate and inconclusive) cases are excluded from analysis.
Rate of inconclusive (indeterminate) specimens	Percentage of sampled cases with the diagnostic categories "atypical" or "suspicious".
<b>Diagnostic categories in cytopathology</b> (based on the nomenclature and terminology of the Papanicolaou Society of Cytopathology [694, 695] and the Bethesda system for reporting in non-gynecologic cytopathology [693]) <sup>18</sup>	
Non-diagnostic	Specimen providing no diagnostically useful information about the sampled lesion (e. g. cellular material not representative of the target, scant cellularity or acellularity, aspirate containing only contaminants from the needle track, aspirate containing only necrotic material, severe contamination (e. g. blood), poor cellular preservation or inadequate preparation precluding cyto-/histopathological evaluation). The term "unsatisfactory" is used synonymously.
Negative (for malignancy)	Specimen containing adequate cellular material with respect to the sampled lesion without any criteria of malignancy.
Benign	The Bethesda classification uses the category "benign" instead of "negative", if there are sufficient criteria to establish a specific benign diagnosis (including benign neoplasms) [693].
Atypical	Specimen containing adequate cellular material with respect to the sampled lesion with features not consistent with normal or reactive cellular changes, but insufficient to classify them as neoplastic or malignant.
Neoplastic	Specimen containing adequate cellular material with respect to the sampled lesion with features diagnostic of a distinct benign or premalignant/low-grade malignant neoplasm. This term is unique for the six-tiered terminology of the guidelines of the Papanicolaou Society of Cytopathology for pancreaticobiliary cytology [694, 695].
Suspicious (for malignancy)	Specimen containing adequate cellular material with respect to the sampled lesion with features raising a strong suspicion for malignancy, but being qualitatively or quantitatively insufficient for a conclusive diagnosis of a (specific) malignant neoplasm.
Positive (for malignancy), malignant	Specimen containing adequate cellular material with respect to the sampled lesion displaying unequivocal features of a (specific) malignant neoplasm.

<sup>18</sup> For detailed definitions, explanations and examples see the guidelines of the Papanicolaou Society of Cytopathology [694, 695] and the guidelines of the College of American Pathologists [693]. In clinical practice, these terms are not consistently used.

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