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Endoscopic ultrasound-guided tissue sampling: European Society of Gastrointestinal Endoscopy (ESGE) Technical and Technology Review

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ABSTRACT

This Technical and Technology Review from the European Society of Gastrointestinal Endoscopy (ESGE) represents an update of the previous document on the technical aspects of endoscopic ultrasound (EUS)-guided sampling in gastroenterology, including the available types of needle, technical aspects of tissue sampling, new devices, and specimen handling and processing. Among the most important new recommendations are:

ESGE recommends end-cutting fine-needle biopsy (FNB) needles over reverse-bevel FNB or fine-needle aspiration (FNA) needles for tissue sampling of solid pancreatic lesions; FNA may still have a role when rapid on-site evaluation (ROSE) is available.

ESGE recommends EUS-FNB or mucosal incision-assisted biopsy (MIAB) equally for tissue sampling of subepithelial lesions ≥20 mm in size. MIAB could represent the first choice for smaller lesions (<20 mm) if proper expertise is available.

ESGE does not recommend the use of antibiotic prophylaxis before EUS-guided tissue sampling of solid masses and EUS-FNA of pancreatic cystic lesions.

ABBREVIATIONS

AE	adverse event
CH-EUS	contrast harmonic endoscopic ultrasound
ESGE	European Society of Gastrointestinal Endoscopy
EUS	endoscopic ultrasound
EUS-TA	EUS-guided tissue acquisition
FCM	fluorescence confocal laser microscopy
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IPMN	intraductal papillary mucinous neoplasia
LBC	liquid-based cytology
MIAB	mucosal incision-assisted biopsy
MOSE	macroscopic on-site evaluation
nCLE	needle-based confocal laser endomicroscopy
NET	neuroendocrine tumor
PCL	pancreatic cystic lesion
PICO	population, intervention, comparator, and outcome
RCT	randomized controlled trial
ROSE	rapid on-site evaluation
TTNB	through-the-needle biopsy
VOSE	visual on-site evaluation

SCOPE AND PURPOSE

This European Society of Gastrointestinal Endoscopy (ESGE) Technical and Technology Review addresses the technical aspects of endoscopic ultrasound (EUS)-guided sampling in gastroenterology, providing updated guidance on the available needles and devices, and techniques for tissue sampling.

1 Introduction

1.1 Focus and rationale

The focus of this Technical and Technology Review from the European Society of Gastrointestinal Endoscopy (ESGE) is the technical aspects of endoscopic ultrasound (EUS)-guided sampling in gastroenterology, including the available types of needle, technical aspects of tissue sampling, new devices, and specimen handling and processing.

Since the publication of the previous ESGE technical review on EUS-tissue sampling [1], several randomized controlled trials (RCTs) have been published covering many of the technical aspects and approaches to EUS-guided tissue sampling of gastrointestinal (GI) solid lesions and pancreatic cysts. Furthermore, new devices have been introduced and tested in clinical practice.

While the indications, results, and clinical impact of EUS-guided sampling are addressed in a separate Guideline from the ESGE [2, 3] and in the recent ESGE core curriculum, the target audience for this technical and technology review is endoscopists who perform EUS-guided sampling.

1.2 Methodology and development process

ESGE commissioned this technical and technology review and appointed two co-leaders (A.F. and M.A.), who invited the listed authors (the panel) to participate in the development of the project. The key questions were prepared by the two leaders in cooperation with the chair of the ESGE research committee (L.F.) and then approved by the other members. The relevant clinical questions were developed according to the PICO format, which outlined the specific patient population (P), intervention (I), comparator (C), and outcome (O) for each question. The two leaders then assigned the key questions to task force subgroups.

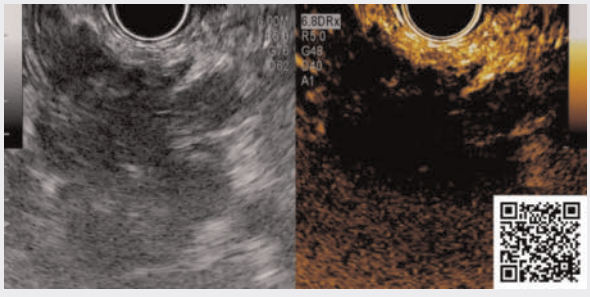
The members of the task forces, under the supervision of the task force leaders, performed a systematic literature search to prepare evidence-based statements to address their assigned key questions. The literature search was performed on the main scientific databases up until June 2024, focusing mainly on RCTs and meta-analyses of RCTs. Retrospective or nonrandomized studies were included only if they addressed topics not covered in the RCTs. The proposed statements were discussed during an online meeting in June 2024. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was adopted to define the quality of evidence and strength of recommendation [4].

The certainty of the evidence was defined as one of four grades: high, moderate, low, or very low (**Table 1s**, see online-only Supplementary material). The assessment of the strength of recommendation reflected the extent to which the panel was confident that the desirable effects of an intervention outweighed its undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended. Recommendations fell into two categories: strong or conditional.

The final draft was also reviewed by the ESGE Governing Board, and after agreement on a final version, the manuscript was submitted to the journal *Endoscopy* for publication. All authors agreed on the final revised version.

The studies included in the current Technical and Technology review used a variety of outcomes classified in five main categories: (i) diagnostic accuracy; (ii) sample adequacy and quality; (iii) safety; (iv) technical performance of the needle/device; and (v) costs. All of these outcomes were systematically analyzed and are discussed in this document, with the recommendations listed in ▶ **Table 1**. Of note, EUS-guided liver biopsy was not covered in the current document as it is the subject of another ESGE Technical and Technology review.

The gold standard for diagnostic accuracy was the histologic diagnosis on the surgical specimen for resected patients and the clinical follow-up (for at least 6 months/1 year) for nonsurgical patients. Sample adequacy and the quality of the specimen were inconsistently defined across most of the included RCTs; however, a pooled analysis was performed when a homogeneous definition was available. Adverse events (AEs) were reported in the RCTs, although none of them was primarily designed and adequately powered to evaluate safety issues. The PICOs and search strategies are shown in **Tables 2s** and **3s**, and the table of evidence is shown in **Table 4s**.



Video 1 Contrast harmonic-endoscopic ultrasound can assist in identifying the target area for tissue acquisition in solid lesions by avoiding necrotic areas, which appear avascular, and vessels. Online content viewable at: https://doi.org/10.1055/a-2524-2596

2 Advanced EUS imaging to guide tissue acquisition

RECOMMENDATION

ESGE suggests that B-mode and contrast harmonic EUS perform equally for EUS-guided tissue acquisition in patients with solid pancreatic lesions.

Conditional recommendation, low quality of evidence.

Contrast-enhanced EUS is a well-established method that combines the advantage of high resolution EUS of internal organs with the administration of ultrasound contrast agents.

Pancreatic adenocarcinoma shows a hypovascular heterogeneous pattern and less intense enhancement than the surrounding parenchyma on contrast harmonic EUS (CH-EUS), whereas neuroendocrine tumors (NETs) are typically homogeneously hyperenhancing [5]. CH-EUS may be used not only to characterize the mass, but also to suggest where to target the needle during EUS-guided tissue acquisition (EUS-TA). Indeed, CH-EUS, according to RCTs, clearly outperforms B-mode EUS in identifying the target area in solid lesions by avoiding necrotic areas, which appear avascular, and vessels [6], and in delineating the lesion [7] (▶ **Video 1**).

In spite of the above-mentioned advantages, CH-EUS-guided tissue acquisition (CH-EUS-TA) did not prove superior over B-mode EUS-TA in the routine setting for solid pancreatic lesions, as outlined in several RCTs, considered at low risk of bias, and meta-analyses [8, 9, 10, 11, 12, 13] (**Table 5s**). The panel performed a comparative meta-analysis of diagnostic accuracy between the two approaches and did not find any significant difference (relative risk [RR] 0.99, 95%CI 0.95–1.03) (**Figs. 1s** and **2s**). The quality of evidence was downgraded owing to imprecision (95%CIs crossing unity) and indirectness (owing to different contrast agents and needles being used). Therefore, a conditional recommendation with a low quality of evidence was provided that supports the equal effectiveness of the two approaches (**Table 4s**).

CH-EUS-TA could be indicated in poorly visible lesions on B-mode EUS, such as indeterminate masses in chronic pancreatitis, isoechoic lesions or suspicion of tumors in the context of acute pancreatitis. Additionally, CH-EUS allows better visualization and tissue acquisition of extravascular migratory metastases, which are identified by EUS as soft-tissue cuffs surrounding the vessel in up to 28% patients [14].

With regard to cystic pancreatic lesions, vascularized mural nodules are considered to be "high risk stigmata" for malignancy when they are ≥5 mm in size (sensitivity and specificity for high grade dysplasia/invasive carcinoma of 73%–100% and

▶ **Table 1** List of recommendations.

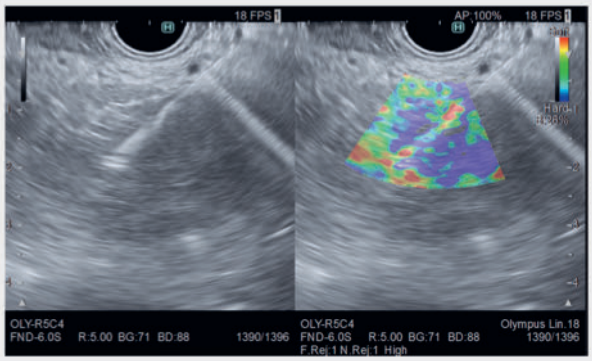
Recommendation	Strength of recommendation Quality of evidence
1 ESGE suggests that B-mode and contrast harmonic EUS perform equally for EUS-guided tissue acquisition in patients with solid pancreatic lesions	Conditional recommendation Low quality evidence
2 ESGE recommends end-cutting FNB needles over reverse-bevel FNB or FNA needles for tissue sampling of solid pancreatic lesions; FNA may still have a role when ROSE is available	Strong recommendation High quality of evidence
3 ESGE suggests using end-cutting FNB needles rather than reverse-bevel FNB or FNA needles for the histopathologic diagnosis of autoimmune pancreatitis	Conditional recommendation Very low quality of evidence
4 ESGE recommends EUS-FNB or mucosal incision-assisted biopsy (MIAB) equally for tissue sampling of subepithelial lesions ≥20 mm in size. MIAB could represent the first choice for smaller lesions (<20 mm) if proper expertise is available	Strong recommendation Moderate quality of evidence
5 ESGE suggests end-cutting FNB needles rather than reverse-bevel FNB or FNA needles for tissue sampling of lymph nodes	Conditional recommendation Very low quality of evidence
6 ESGE recommends use of the fanning technique because it improves the diagnostic accuracy of EUS-guided tissue acquisition of solid pancreatic lesions	Strong recommendation Moderate quality of evidence
7 ESGE recommends equally the wet-suction or slow-pull techniques for EUS-FNB of pancreatic masses because they provide high rates of adequate samples and tissue integrity, and reduce specimen bloodiness compared with dry suction	Strong recommendation Moderate quality of evidence
8 ESGE recommends performing two passes with end-cutting FNB needles and three passes with reverse-bevel FNB needles. At least four passes are needed with FNA needles when ROSE is not available	Strong recommendation Moderate quality of evidence
9 ESGE suggests performing EUS-TA before ERCP in jaundiced patients with pancreatic head lesions, especially when self-expandable metal stents are being used	Conditional recommendation Low quality of evidence
10 ESGE recommends the use of ROSE when EUS-FNA is performed. ROSE is not needed for EUS-FNB, particularly with end-cutting needles, of pancreatic solid lesions and submucosal lesions	Strong recommendation Moderate quality of evidence
11 ESGE recommends the use of macroscopic on-site evaluation (MOSE) for EUS-FNB of pancreatic masses because this approach leads to high diagnostic accuracy, with the need for fewer needle passes	Strong recommendation Moderate quality of evidence
12 ESGE suggests the use of glucose level over carcinoembryonic antigen (CEA) in the cystic fluid for the diagnosis of pancreatic mucinous cysts	Conditional recommendation Low quality of evidence
13 ESGE suggests EUS-guided through-the-needle biopsy (TTNB) where the histologic diagnosis may change the clinical management of the patient. TTNB should be avoided in PCLs with communication with the pancreatic duct owing to the risk of serious adverse events	Conditional recommendation Very low quality of evidence
14 ESGE suggests the use of needle-based confocal laser endomicroscopy (nCLE) to discriminate between mucinous and non-mucinous pancreatic cysts in centers with adequate expertise	Conditional recommendation Low quality of evidence
15 ESGE does not recommend the use of antibiotic prophylaxis before EUS-guided tissue sampling of solid masses and EUS-FNA of PCLs	Strong recommendation Moderate quality of evidence

ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; EUS-TA, EUS-guided tissue acquisition; FNA, fine-needle aspiration; FNB, fine-needle biopsy; PCL, pancreatic cystic lesion; ROSE, rapid on-site evaluation.

73%–85%, respectively) and a "worrisome feature" when their size is <5 mm [15]. CH-EUS is helpful for assessing vascularity and differentiating mural nodules from nonenhancing mucin plugs, with a reported sensitivity and specificity of 88% and 79%, respectively [16].

Elastography determines the stiffness of the lesion and pancreatic adenocarcinoma tends to show high stiffness owing to the desmoplastic reaction of the tissue. While elastography can be a useful tool for tissue characterization, there is limited evidence on its use to target tissue sampling. Indeed, despite the promising results of a preliminary report [17], elastography-guided fine-needle aspiration (FNA) from the hardest (blue) part of the pancreatic mass (▶ **Fig. 1**), which is considered to have the highest suspicion of malignancy, proved not to have added utility over conventional EUS-FNA (sensitivity 90% vs. 93%) [18].

No data on the use of these ancillary techniques to target EUS-TA in extrapancreatic lesions are available.



▶ **Fig. 1** Endoscopic ultrasound images showing elastography-guided fine-needle biopsy of a pancreatic lesion; the needle was targeted to the "blue" area of the lesion, which represents an area with higher stiffness that is more likely to be neoplastic.

3 Needle choice for the sampling of solid lesions

3.1 Available needle types

In the last three decades, the evolution of needles has undergone a remarkable change and they are still constantly under development, with the design of innovative tips allowing for larger histologic specimens with preserved tissue architecture, and the use of tissue for genomic profiling and organoid development, which are very important in the era of oncologic personalized medicine. As a result, the current era has seen a decisive shift from FNA to fine-needle biopsy (FNB) needles, with the former's role now mainly restricted to interventions for pancreaticobiliary access and pancreatic cysts [19].

EUS-FNA needles have limitations that are well known: their diagnostic performance is dependent on a cytopathologist to render a rapid on-site evaluation (ROSE); no histologic core tissue is possible (this is especially relevant to differentiate pancreatic cancer from autoimmune pancreatitis or chronic pancreatitis); and insufficient tissue is obtained for risk stratification to tailor anticancer therapy.

Reverse-bevel EUS-FNB needles were developed in 2011 (EchoTip ProCore; Cook Medical, Indiana, USA). They consisted of an opening at the side of the needle, with a hollow reverse-bevel architecture, which allows cutting of the tissue during backward retraction of the needle [20]. Multiple studies, including RCTs and meta-analyses, have been published comparing reverse-bevel FNB needles with standard EUS-FNA needles, with the former not having been able to establish their superiority with respect to diagnostic accuracy over the latter [21, 22]. These meta-analyses showed that both needles had similar diagnostic accuracy and sample adequacy, but ProCore FNB needles required fewer passes to establish the diagnosis (mean difference −1.2 and −0.32, respectively) [21, 22].

Subsequently, newer "third generation" EUS needles were developed, known as "end-cutting" needles. These needle types have shown excellent diagnostic accuracy (>90%), even without ROSE, and are not associated with an increased incidence of AEs [23].

Currently, four needle-tip geometries are available.

3.1.1 Franseen type

The Franseen type, which has three symmetrically distributed needle points and cutting edges (Acquire, Boston Scientific, Marlborough, USA; EchoTip AcuCore, Cook Medical, Indiana, USA; SonoTip TopGain, Medi-Globe, Germany).

The Acquire is made of cobalt–chromium and is available in 19G, 22G, and 25G sizes. The new version, the Acquire S, has a taper-point stylet to ease needle penetration. The EchoTip AcuCore EUS-FNB needle was introduced in 2024. It is made of cobalt–chromium combined with a spring-coiled sheath to enhance its flexibility; it is available only in the 22G size. The SonoTip TopGain needle is made of stainless steel, with a nitinol stylet, and has a laser engraving over the needle length for better visibility; it is available in 19G, 22G, and 25G sizes.

3.1.2 Fork-tip type

The fork-tip type has two protruding asymmetrical sharp points and six distal cutting edges (SharkCore, Medtronic, Minneapolis, USA) [24]. SharkCore needles, available in 19G, 22G, and 25G, are made of stainless steel and contain a nitinol stylet. They use a Beacon delivery system (Medtronic, Minneapolis, USA), allowing for needle removal from the sheath, maintaining the sheath in the echoendoscope.

3.1.3 Three-prong asymmetric tip

The three-prong asymmetric tip has one tip longer than the other two (Trident, Microtech, Nanjing, China). The Trident needle is made of cobalt–chromium, has laser etched markings for enhanced needle echogenicity, and it is available in 19G, 22G, and 25G sizes.

3.1.4 Menghini tip

The Menghini tip is characterized by a tapered continuous cutting edge (ProCore, Cook Medical, Indiana, USA; EZ Shot 3 Plus, Olympus, Tokyo, Japan; Sonopsy CY, Hakko Medical, Nagano, Japan). The 20G ProCore has a forward-facing bevel, antegrade core trap technology, and ReCoil stylet. The automatic recoiling pattern of the latter helps the technicians to easily manage the stylet, minimizing contamination [25]. The EZ Shot 3 Plus is made of nitinol with a side hole and a multilayer coil metal sheath, and is available in 19G, 22G, and 25G sizes. The Sonopsy CY is a 21G needle with a sharpened stylet that is directly connected to the plunger of the aspiration syringe and retracted while activating the aspiration.

3.2 EUS-FNA vs. EUS-FNB

RECOMMENDATION

ESGE recommends end-cutting FNB needles over reverse-bevel FNB or FNA needles for tissue sampling of solid pancreatic lesions; FNA may still have a role when ROSE is available.

Strong recommendation, high quality of evidence.

ESGE suggests using end-cutting FNB needles rather than reverse-bevel FNB or FNA needles for the histopathologic diagnosis of autoimmune pancreatitis.

Conditional recommendation, very low quality of evidence.

Based on previous meta-analyses that did not show a significant difference in terms of diagnostic accuracy between FNA and FNB ProCore needles [21,22], the latest ESGE Guidelines on tissue sampling recommended FNB and FNA equally in patients with pancreatic solid lesions with only a weak recommendation for end-cutting FNB needles when the aim is to obtain core tissue [2].

Data across previous RCTs were incorporated in two network meta-analyses, performed by Han et al. and Gkolfakis et al. [26, 27]. Han et al. evaluated data from 29 RCTs and showed that 22G fork-tip FNB needles had the best performance in terms of pooled diagnostic accuracy, followed by the 22G Olympus needle and the 22G Franseen needle (Boston Scientific) [26]. Similarly, Gkolfakis et al. showed that Franseen and fork-tip FNB needles were the best ranked needles, especially in the 22G size [27]. Additionally, 25G Franseen or fork-tip needles did not outperform 22G reverse-bevel needles; of note, FNA needles seemed to still be competitive when ROSE was available, providing similar results to FNB in this specific setting [27].

The panel updated the literature search of the above mentioned meta-analyses, and the main characteristics of the 19 RCTs [28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46] that compared end-cutting FNB needles with each other or with FNA/reverse-bevel FNB needles in patients with pancreatic solid lesions are listed in the ▶ **Table 2**. The panel confirmed the results of the previous network meta-analysis [27], with Franseen and fork-tip FNB clearly outperforming FNA and reverse-bevel FNB (Franseen vs. reverse-bevel, RR 1.2,

▶ **Table 2** Randomized controlled trials comparing different end-cutting FNB needles with each other or versus FNA/FNB needles with reverse-bevel design for tissue sampling of pancreatic masses.

Author, year country	Study design	Number of patients	Age, years; sex, male, n (%)	Needle used	ROSE	Accuracy	Adequacy
Ardengh, 2020 Brazil	Cross over RCT	FNA: 20	65 9 (45)	22G	No	15/20	19/20
		FNB: 20		20G forward-facing bevel		18/20	20/20
Ashat, 2020 USA	Parallel RCT	Franseen: 39	66 56 (42)	22G	Yes	36/39	38/39
		Fork-tip: 36	64 56 (42)	22G		34/36	35/36
Asokkumar, 2019 Singapore	Cross over RCT	FNA: 20	64 16 (44)	22G	Yes	18/20	20/20
		FNB: 20		22G Franseen		18/20	19/20
Bang, 2017 USA	Cross over RCT	FNA: 46	68 28 (61)	22G	Yes	37/46	38/46
		FNB: 46		22G Franseen		43/46	45/46
Bang, 2018 USA	Cross over RCT	Franseen: 50	71 28 (56)	22G	Yes	48/50	48/50
		Fork-tip: 50		22G		46/50	46/50
Bang, 2021 USA	Parallel RCT	Fork-tip: 31	64 17 (55)	22G	No	30/31	31/31
		Menghini: 33	68 20 (61)	22G		25/33	33/33
		Franseen: 32	70 14 (44)	22G		30/32	32/32
		Reverse bevel: 33	71 18 (53)	22G		22/33	28/33
Chen, 2021, Canada	Parallel RCT	Fork-tip: 115	70 65 (57)	22/25G	Yes	106/115	110/115
		FNA: 120	69 58 (48)	22/25G		112/120	112/120

▶ **Table 2** (Continuation)

Author, year country	Study design	Number of patients	Age, years; sex, male, n (%)	Needle used	ROSE	Accuracy	Adequacy
Cho, 2020 Korea	Parallel RCT	Reverse bevel: 43	64 26 (61)	25G	No	34/43	32/43
		Forward-facing bevel: 45	64 22 (49)	20G		40/45	41/45
Crino, 2020 Italy	Parallel RCT	Fork-tip: 96	66 64 (67)	22/25G	No	91/96	94/96
		Reverse bevel: 96	64 46 (48)	22/25G		80/96	89/96
Igarashi, 2019 Japan	Cross over RCT	Menghini: 30	74 11 (37)	21G	No	27/30	27/30
		Reverse bevel: 30		22G		27/30	27/30
Kandel, 2020 USA	Cross over RCT	Fork-tip: 50	68 25 (50)	19/22G	Yes	50/50	50/50
		FNA: 50		25G		50/50	50/50
Karsenti, 2020 France	Cross over RCT	Franseen: 60	69 27 (45)	22G	No	52/60	60/60
		Forward-facing bevel: 60		20G		40/60	49/60
Mendoza Ladd, 2022 USA	Parallel RCT	Fork-tip: 22	NR NR	22G	No	NR	22/22
		Franseen: 33		22G		NR	33/33
Mizukawa, 2020 Japan	Cross over RCT	Menghini: 97	68 63 (65)	21G	Yes	86/97	93/97
		FNA: 97		22G		71/97	89/97
Mohamadnejad, 2023 Iran	Parallel RCT	Franseen: 57	60 36 (63)	22G	No	54/57	NR
		Three-prong tip: 57	61 32 (56)	22 3G		56/57	NR
Oh, 2021 Korea	Parallel RCT	25G Franseen: 70	66 39 (56)	25G	No	68/70	70/70
		22G Franseen: 70	62 40 (57)	22G		70/70	70/70
Oppong, 2021 UK	Cross over RCT	Fork-tip: 108	69 57 (53)	22/25G	No	85/108	97/108
		FNA: 108		22/25G		69/108	99/108
Tomoda, 2021 Japan	Cross over RCT	25G Franseen: 88	71 45 (51)	25G	Yes	76/88	79/88
		22G Franseen: 88		22G		79/88	82/88
Yousri, 2022 Egypt	Parallel RCT	Franseen: 50	58 28 (56)	22G	No	49/50	NR
		FNA: 50	58 29 (58)	22G		45/50	NR

FNA, fine needle aspiration; FNB, fine needle biopsy; RCT, randomized controlled trial; ROSE; Rapid On-Site Evaluation.

95%CI 1.1–1.4; Franseen vs. FNA, RR 1.2, 95%CI 1.0–1.3; fork-tip vs. reverse-bevel, RR 1.2, 95%CI 1.0–1.3; and fork-tip vs. FNA, RR 1.1, 95%CI 1.0–1.2). Therefore, end-cutting needles, such as Franseen and fork-tip FNB needles, should be preferred over FNA and reverse-bevel needles, particularly when ROSE is not available.

The quality of evidence was rated as high because the literature was based on a large number of RCTs, without evidence of heterogeneity, indirectness, publication bias, inconsistency, or imprecision (**Table 4s**). Therefore, a strong recommendation with a high quality of evidence supported the comparison among the different needle types for pancreatic solid lesions.

The histologic diagnosis of autoimmune pancreatitis represents a great challenge for endoscopists given the need to obtain high quality core tissue for the final diagnosis [47]. The development of EUS-FNB needles has generated a great deal of

interest in the field; however, although FNB needles are supposed to improve tissue capture, previous meta-analyses found only a suboptimal diagnostic accuracy, up to 63% with FNB, although this was significantly superior to that of FNA [48]. Of note, this meta-analysis included mainly studies using reverse-bevel FNB needles as only a few reports using end-cutting needles were available at that time.

The panel updated the meta-analysis including only FNB needles and found 12 noncomparative series, with 496 patients [49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60]. The characteristics of the included studies are reported in **Table 6s**.

The overall diagnostic accuracy rate of EUS-FNB in these patients was 75% (95%CI 66%–83%) (**Fig. 3s**), with superiority of end-cutting FNB over reverse-bevel FNB (80% [95%CI 70%–90%] vs. 49% [95%CI 21%–67%]; *P*<0.001). FNB provided International Consensus Diagnostic Criteria (ICDC) level 1 histologic diagnosis in 47% of cases (38%–57%) and level 2 in 23% (16%–30%). Specifically, FNB provided a rate of definitive histopathology in those patients without a diagnosis with other criteria as high as 77% (95%CI 63%–91%). Therefore, the panel concluded that EUS-FNB with end-cutting needles should be preferred over FNA or other FNB needles in the diagnostic management of autoimmune pancreatitis. The quality of evidence was downgraded because the meta-analysis was based on nonrandomized observational studies and because of inconsistency (high heterogeneity in the estimates) and indirectness (indirect comparison between different needles) (**Table 4s**). Therefore, a conditional recommendation with a very low quality of evidence was provided that supported the use of end-cutting needles in patients with autoimmune pancreatitis.

RECOMMENDATION

ESGE recommends EUS-FNB or mucosal incision-assisted biopsy (MIAB) equally for tissue sampling of subepithelial lesions ≥20 mm in size. MIAB could represent the first choice for smaller lesions (<20 mm) if proper expertise is available.

Strong recommendation, moderate quality of evidence.

ESGE suggests end-cutting FNB needles rather than reverse-bevel FNB or FNA needles for tissue sampling of lymph nodes.

Conditional recommendation, very low quality of evidence.

In terms of data on EUS-TA for lymph nodes and subepithelial lesions, data are somewhat scarce. A meta-analysis of 10 studies, of which six were RCTs, comparing FNA versus FNB for subepithelial lesions showed FNB to be superior in terms of pooled sample accuracy (95% vs. 81%; *P* = 0.007), histologic core (90% vs. 65%; *P*<0.001), diagnostic accuracy (odds ratio [OR] 4.1, 95%CI 2.5–6.8) with a lower mean number of passes (mean difference −0.75) [61].

The same group recently published a network meta-analysis comparing all the available techniques to sample subepithelial lesions [62]. Based on eight RCTs [63, 64, 65, 66, 67, 68, 69, 70] (**Table 7s**), the authors found that EUS-FNB was significantly superior to EUS-FNA in terms of sample adequacy (RR 1.2, 95%CI 1.1–1.5), and appeared to be the best technique (surface under cumulative ranking [SUCRA] score 0.90), followed by mucosal incision-assisted biopsy (MIAB; SUCRA 0.83), whereas endoscopic bite-on-bite biopsy showed the poorest performance. Interestingly, when considering lesions <20 mm, MIAB (a group of newer techniques involving unroofing the subepithelial lesion to expose its surface or submucosal tunneling allowing direct biopsy sampling of the lesion), but not EUS-FNB, showed significantly higher accuracy rates compared with EUS-FNA (RR 1.7, 95%CI 1.0–2.9) and ranked as the best intervention in this specific subset of lesions. As observed with solid pancreatic lesions, when ROSE was available, no difference between EUS-FNB, EUS-FNA, and MIAB was observed [62].

Therefore, as already outlined in the previous ESGE guidelines [71], the panel recommend the use of EUS-FNB or MIAB for tissue sampling of subepithelial lesions in the GI tract. MIAB could represent the first choice in the subset of smaller lesions (<2 cm); however, owing to the risk of bleeding and complications, and the more challenging technical characteristics, MIAB should be performed in centers with high case volume and adequate expertise. The quality of evidence was downgraded because of high imprecision in the estimates owing to wide 95%CIs crossing unity or failure to reach the optimal information size. Therefore, a strong recommendation with a moderate quality of evidence was provided (**Table 4s**).

As already observed with solid pancreatic lesions, a meta-analysis clearly showed that end-cutting FNB needles outperform EUS-FNA in terms of diagnostic accuracy for tissue sampling of lymph nodes (OR 1.9, 95%CI 1.2–3.0), whereas no difference was observed in the sensitivity analysis comparing reverse-bevel FNB versus FNA (OR 1.0, 95%CI 0.5–1.5) [72]. Of note, a recent large prospective Italian series of lymph nodes sampled with 22G Franseen or 25G fork-tip FNB needles showed an overall sensitivity, specificity, and accuracy of 96%, 100%, and 97%, respectively [73].

The panel updated the meta-analysis [72], including 10 studies [74, 75, 76, 77, 78, 79, 80, 81, 82, 83] that directly compared EUS-FNB versus EUS-FNA for tissue sampling of lymph nodes (**Table 8s**). Diagnostic accuracy was similar between FNB and FNA (OR 1.5, 95%CI 0.9–2.5) (**Fig. 4s**); however, FNB performed with end-cutting needles clearly outperformed FNA (pooled accuracy with end-cutting FNB needles, 89%; OR 1.9, 95%CI 1.2–3.0).

Therefore, the panel concluded that EUS-FNB with end-cutting needles could be the best option in these patients, although further data from RCTs are needed. The quality of evidence was downgraded because the meta-analysis was based mainly on nonrandomized observational studies and because of inconsistency (high heterogeneity in the estimates), risk of bias in the literature, and imprecision in the estimates (**Table 4s**). Therefore, a conditional recommendation with a very low quality of evidence was provided.

4 Sampling techniques

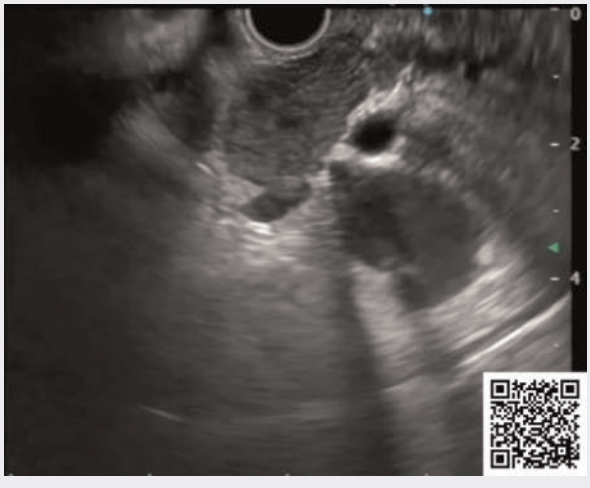
4.1 Fanning

RECOMMENDATION
ESGE recommends use of the fanning technique because it improves the diagnostic accuracy of EUS-guided tissue acquisition of solid pancreatic lesions.
Strong recommendation, moderate quality of evidence.

The fanning technique allows sampling of multiple areas within the same lesion with a single needle pass by changing the needle's direction with the up/down deflection wheel (big wheel) or the elevator [84, 85] (▶ **Video 2**). To increase the efficacy of fanning, it is suggested that the direction of the puncture be changed after withdrawing the needle at the proximal limit of the tumor. Despite not being widely investigated, two RCTs have demonstrated that, compared with the standard technique, the fanning technique results in higher diagnostic accuracy, a lower number of passes to establish the diagnosis, and a higher percentage of patients in whom a diagnosis is achieved with just the first pass, yet with no difference in terms of technical failure or complication rates [84, 85]. A change in the direction of the needle (i. e. fanning the needle into the lesion) can also be obtained by torquing the scope, with results similar to those of the "classic" fanning technique [86, 87] (**Table 9s**). The fanning technique also seems equivalent to sampling using contrast-harmonic EUS guidance [13], but without requiring the additional cost of contrast.

Notably, all of the available studies included only pancreatic solid lesions, and the role of the fanning technique in non-pancreatic lesions has not been investigated. Intuitively, the fanning technique is also supposed to acquire a sample more representative of the whole tumor, allowing an advantage even for molecular analyses, despite not yet being adequately investigated.

The panel then performed a meta-analysis of the four RCTs [84, 85, 86, 87] that compared fanning versus standard FNA/FNB and found a significant superiority of fanning for accuracy (RR 1.21, 95%CI 1.11–1.31) (**Fig. 5s**, part A), which was confirmed when excluding the torque technique (RR 1.27, 95%CI 1.16–1.38) (**Fig. 5s**, part B). The quality of evidence was downgraded owing to indirectness related to different sampling techniques (suction vs. no suction vs. slow pull) in the included RCTs (**Table 4s**). Therefore, a strong recommendation with a moderate quality of evidence was provided.



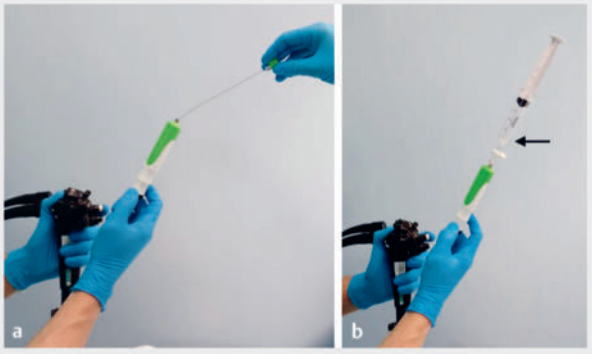
Video 2 Demonstration of the fanning technique.
Online content viewable at:
https://doi.org/10.1055/a-2524-2596

4.2 Aspiration techniques

RECOMMENDATION
ESGE recommends equally the wet-suction or slow-pull techniques for EUS-FNB of pancreatic masses because they provide high rates of adequate samples and tissue integrity, and reduce specimen bloodiness compared with dry suction.
Strong recommendation, moderate quality of evidence.

Four main different aspiration techniques have been described: no-suction, slow-pull, dry-suction, and wet-suction techniques (including a modified wet-suction technique) (▶ **Fig. 2**). The no-suction technique just requires removal of the stylet before lesion puncture, with no application of negative pressure. The slow-pull technique consists of a slow retraction of the stylet while performing the to-and-fro movements within the lesion, which appears to apply low negative pressures to the needle tip. Suction techniques require removing the stylet and using a syringe with a 5-, 10-, or 20-mL negative pressure attached to the needle to provide a greater negative pressure than the slow-pull technique. The wet-suction technique also requires flushing of the needle with saline before performing the puncture to apply the negative pressure onto a fluid that has no expandability and, therefore, precisely transmits it to the tip of the needle [88].

Despite a wide literature on the topic, there is no striking evidence to suggest the unequivocal superiority of one suction technique over any another. Outcomes commonly evaluated in available studies were sample adequacy, cellularity, and tissue integrity/core procurement. Several meta-analyses showed that the wet-suction technique ranked as the best technique in terms of diagnostic accuracy [89, 90, 91]. Similarly, the wet-suction technique is ranked as the best technique regarding adequacy, followed equally by the slow-pull and dry-suction techniques, with the no-suction technique being inferior for this outcome. On the other hand, the no-suction and slow-pull techniques provided very low blood contamination compared with the wet-suction and dry-suction techniques [92, 93]. In addition, wet-suction seems better than the dry-suction tech-



▶ **Fig. 2** The different techniques for tissue sampling include: **a** the slow-pull technique, consisting of a slow retraction of the stylet while performing to-and-fro movements within the lesion, which appears to apply low negative pressures to the needle tip; **b** the wet-suction technique, which requires removal of the stylet and flushing of the needle with saline before performing the puncture so that, when negative pressure is applied to a fluid, which has no expandability, this is precisely transmitted to the tip of the needle.

nique regarding blood contamination. Notably, the impact of blood contamination has been inherited from FNA studies as it could impair cytologic evaluation. In contrast, it should not impact the assessment of histologic samples or the capability to retrieve high quality histologic tissue [94]. Furthermore, most studies evaluated only pancreatic solid lesions, with a few lymph nodes and submucosal tumors included, and subgroup analyses were not performed in the meta-analyses.

The panel updated the meta-analysis of RCTs comparing different techniques for tissue sampling with EUS-FNB of pancreatic solid lesions and found 10 RCTs [33, 44, 94, 95, 96, 97, 98, 99, 100, 101] (**Table 10s**).

As outlined in a previous network meta-analysis [89], the no-suction technique was significantly inferior to the other techniques in terms of sample adequacy (RR 0.85, 95%CI 0.08–0.92 vs. slow pull; RR 0.85, 95%CI 0.78–0.92 vs. dry suction; RR 0.83, 95%CI 0.76–0.90 vs. modified wet suction), although it led to less blood contamination of samples. The highest tissue integrity was observed with modified wet suction (RR 1.36, 95%CI 1.06–1.75 vs. dry suction) and the highest rate of blood contamination was observed with dry suction (RR 1.44, 95%CI 1.15–1.80 vs. slow pull). Altogether, this evidence favors using the wet-suction technique, with the slow-pull technique considered a valuable alternative to be used intuitively for hypervascular pancreatic lesions or where cytologic evaluation is required. With any suction technique, it is recommended to neutralize residual negative pressure in the needle before withdrawing it from the target lesion to avoid contamination of the sample by GI fluid.

Data on nonpancreatic lesions are scarce. The trial by Crinò et al. found a higher rate of tissue core retrieval with the wet-suction rather than slow-pull technique in the subgroup of nonpancreatic lesions (67% vs. 48%), although the significance threshold (adjusted for multiplicity) was not reached, probably because the RCT was underpowered for this subgroup analysis [94]. It is likely that the application of suction may have a greater impact on the quantity of tissue aspirated into the needle in softer tissues, such as nonpancreatic lesions, rather than stiff pancreatic masses, like adenocarcinoma.

The panel downgraded the quality of evidence to moderate owing to indirectness related to the different study designs and different FNB needles used in the individual studies (**Table 4s**). Therefore, a strong recommendation with a moderate quality of evidence was provided.

4.3 Number of to-and-fro movements

The number of to-and-fro movements, also called the "number of actuations," is the number of back-and-forth movements performed inside a lesion within the same needle pass. Most studies reported performing 10–15 actuations, but only a few have specifically investigated this topic and only in pancreatic solid lesions, reporting scanty and heterogeneous data that are difficult to standardize.

An RCT comparing 40 versus 20 actuations performed with a 22G side-fenestrated needle showed no benefit in doing more movements [102]. A recent RCT performed with FNA needles demonstrated similar accuracy with 10, 15, and 20 actuations when suction was applied, but with higher blood contamination with 20; in contrast, 10 actuations were associated with lower accuracy if no suction was used [103]. The authors concluded that 10 or 15 to-and-fro movements should be performed with and without suction.

Two crossover RCTs using a 22G Franseen needle compared different numbers of actuations. The first study demonstrated a slightly, though not significantly, higher accuracy with 15 actuations compared with five; however, 15 actuations were better than five regarding the area of the tissue core retrieved [104]. Conversely, the second study demonstrated that three actuations provided similar results to 12 in terms of diagnostic accuracy and microscopic histologic quantity, but with less blood contamination [105].

Finally, a large retrospective study raised concerns about an increased risk of AEs when performing more than 15 actuations during EUS-FNA [106], although, considering its retrospective design, the results of this study should be interpreted with caution.

Given the paucity of data and the discordant results of the RCTs, which tested different numbers of actuations, thereby making it impossible to standardize the data, the panel decided to refrain from providing a statement on this topic. Intuitively, the number of actuations should also depend on the lesion size. In fact, each to-and-fro movement should ideally cross the entire diameter of the tumor. Consequently, in the case of small lesions, the range of movement would be very small, and increasing the number of actuations could result in a better sample. In contrast, the range of movement in large masses is extended, so allowing for a reduction in the number of to-and-for movements.

4.4 Number of passes

RECOMMENDATION

ESGE recommends performing two passes with end-cutting FNB needles and three passes with reverse-bevel FNB needles. At least four passes are needed with FNA needles when ROSE is not available.

Strong recommendation, moderate quality of evidence.

Overall, several meta-analyses have demonstrated that, compared with FNA, FNB needles can reduce the number of passes required to achieve a diagnosis [21, 107, 108, 109, 110, 111]; however, most of the studies available in the literature reported the diagnostic yield of EUS-TA in relation to the cumulative number of passes or reported partial data on each pass outcome, and only a limited number of studies performed a per-pass analysis with a pre-established (or established on ROSE) number of passes [36, 45, 84, 96, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122]. Notably, most studies employing FNA needles used ROSE during EUS-guided sampling.

With the above-mentioned limitation, based on specifically designed studies, when ROSE is unavailable, to achieve a diagnostic yield of approximately 90%, four passes should be performed with an FNA needle and three with a reverse-bevel needle. With the advent of new end-cutting FNB needles, it seems that the number of required passes could be further lowered; in fact, when using 22G Franseen [122, 123] or fork-tip needles [36], two passes increased diagnostic yield compared with one and reached the plateau, thereby suggesting that two passes might be sufficient. A slight advantage of performing a third pass was observed using 22G three-prong asymmetric tip [45] and 25G fork-tip needles [36].

These findings were also observed in a recent meta-analysis of 19 RCTs that demonstrated, using any FNB needle, a pooled diagnostic accuracy of 78% (95%CI 73%–84%), 87% (95%CI 83%–91%), 92% (95%CI 88%–95%), 89% (95%CI 81%–96%), and 96% (95%CI 95%–97%) with one, two, three, four, and five passes, respectively, with significant benefit for performing up to three passes. Subgroup analysis of end-cutting needles (Franseen and fork-tip) demonstrated a pooled accuracy of 80% (95%CI 74%–87%), 87% (95%CI 79%–94%), and 91% (95%CI 84%–97%) with one, two, and three passes, respectively, with no benefit from adding the third pass [124] (▶ **Table 3**).

Most of the reported studies included patients with pancreatic solid lesions; however, two to three passes with an end-cutting needle seem sufficient even for submucosal lesions and lymph nodes [73, 120].

The panel downgraded the quality of evidence to moderate owing to the indirectness related to different availability of ROSE/macroscopic on-site evaluation (MOSE) across the RCTs (**Table 4s**).

Finally, with the progressive advent of molecular analyses to aid personalized treatments and considering the need to also retrieve material for this precise aim, additional passes, apart from the diagnostic ones, could be considered. Although the aforementioned meta-analysis [124] found higher adequacy with three passes, even using end-cutting FNB needles, probably owing to the higher quality of tissue samples, promising data show that two passes are not different from three passes in terms of the quantity of retrieved DNA and RNA for molecular analyses [125]. Nonetheless, the standard technique for EUS-TA should also be established based on the center's and endoscopists' individual experiences, as most of the published

▶ **Table 3** Comparison of numbers of needle passes for tissue sampling of pancreatic masses.

Outcomes	Number of passes	Number of RCTs	Number of patients	OR (95%CI); I^2
Any FNB needle				
Diagnostic accuracy	Two vs. one	9	1159	1.9 (1.4–2.7); 50%
	Three vs. two	9	1159	1.6 (1.2–2.1); 0%
	Three vs. one	8	1045	3.2 (2.0–5.3); 61%
	Four vs. three	4	398	1.1 (0.7–1.8); 0%
Tissue adequacy	Two vs. one	6	1072	2.1 (1.6–2.8); 36%
	Three vs. two	5	962	1.9 (1.3–2.8); 61%
	Three vs. one	5	962	4.1 (2.9–5.9); 50%
End-cutting FNB needles				
Diagnostic accuracy	Two vs. one	6	674	1.8 (1.2–2.6); 0%
	Three vs. two	5	411	1.4 (0.9–2.2); 0%
Tissue adequacy	Two vs. one	4	434	2.2 (1.7–2.9); 0%
	Three vs. two	3	544	3.0 (2.0–4.5); 0%

FNB, fine-needle biopsy OR, odds ratio.

literature represents standards in high volume centers with experienced endosonographers and pathologists.

4.5 EUS-guided tissue acquisition in jaundiced patients needing biliary stenting

RECOMMENDATION

ESGE suggests performing EUS-TA before ERCP in jaundiced patients with pancreatic head lesions, particularly when self-expandable metal stents are being used.

Conditional recommendation, low quality of evidence.

For patients with obstructive jaundice due to an unresectable pancreatic head tumor, given the concurrent need for cyto/histologic confirmation that is mandatory before chemotherapy, performing both the EUS and ERCP procedures during the same session may represent a valuable option. ERCP is however more widely available than EUS, and relieving bile duct obstruction is commonly considered more clinically urgent than tissue acquisition for establishing a pathologic diagnosis [126]. Therefore, in most instances, biliary stenting frequently precedes EUS-TA; however, some concerns have been raised regarding the impact of biliary stents on the diagnostic accuracy of EUS-TA, likely owing to poor visualization of the lesion from acoustic shadowing, reverberation, and/or surrounding inflammation associated with the stent [127, 128, 129]. Additionally, these studies seem to suggest that plastic or self-expandable metal stents (SEMSs) could have a dissimilar effect because of differences in their material and diameter.

Table 11s shows the data from the studies that have assessed the impact of the presence of a biliary stent on the diagnostic performance of EUS-FNA/FNB of masses in the pancreatic head [128, 129, 130, 131, 132, 133, 134]. As reported in the meta-analysis by Facciorusso et al. [135], only SEMSs showed an impact on decreasing the diagnostic accuracy of EUS-TA (OR 0.5, 95%CI 0.2–1.0), whereas plastic stents had no impact (OR 0.9, 95%CI 0.5–1.5), with the pooled accuracy of EUS-FNB after placement of a plastic stent around 85% [135]. Therefore, the panel concluded with a conditional recommendation, based on retrospective studies, in favor of performing EUS-TA before ERCP in patients with jaundice due to pancreatic head masses, particularly if SEMSs are to be used.

5 On site evaluation

5.1 Rapid on-site evaluation (ROSE)

RECOMMENDATION

ESGE recommends the use of ROSE when EUS-FNA is performed. ROSE is not needed for EUS-FNB, particularly with end-cutting needles, of pancreatic solid lesions and submucosal lesions.

Strong recommendation, moderate quality of evidence.

ROSE is a cytomorphologic diagnostic procedure that allows assessment of the adequacy of the material obtained during individual biopsy passes within a few minutes, in or near to the endoscopy suite (on-site). Once the tissue has been acquired, the section obtained is printed onto a glass side, stained, and observed under a microscope by the cytopathologist. The sampling is repeated until the cytopathologist deems the specimen obtained to be adequate [136].

ROSE may be performed by a cytopathologist, a pathology trainee, or a cytotechnologist. Given the low availability of these professional figures, training endosonographers to evaluate the specimen themselves has been proposed as a potential solution. In the prospective double-blind RCT by Savoy et al., well-trained endosonographers had inferior abilities compared with a cytopathologist in terms of identifying specimen adequacy ($P = 0.004$) and making a preliminary estimate of malignancy ($P<0.001$) in various lesions (lymph nodes, pancreas, and liver specimens) [137]. In a more recent RCT, which exclusively analyzed pancreatic solid lesions, the sensitivity and accuracy of ROSE by the endosonographer for malignancy were high (93% and 88%, respectively), with a shorter procedural duration, as well as fewer needle passes in the ROSE versus non-ROSE group [138]. Zhang et al. compared ROSE performed by endoscopists in 97 patients to 97 patients without ROSE in a RCT [139]. Self-ROSE improved the diagnostic accuracy ($P<0.001$) and sensitivity ($P<0.001$) compared to the non-self-ROSE group, with an acceptable consistency between endoscopist and pathologist in the cytopathologic diagnosis ($P<0.05$) and in the sample adequacy rate ($P<0.001$) [139]. In the prospective study by Eloubeidi et al. [140], an excellent agreement between ROSE and the final cytology was demonstrated. Of the 300 lesions initially reported as malignant on ROSE, 294 (98%) remained malignant on the final cytology, while only 2% of the lesions initially reported as being benign on ROSE were upgraded to malignant or suspicious for malignancy in the final cytology report. Scant cellularity was the most frequently reported reason for discrepancies, followed by the need for consultation with other specialists, the need for ancillary studies, intraobserver variability, and challenging diagnoses [140].

Given the rapid advance of artificial intelligence (AI) in the medical field, Lin et al. [141] reported the validation of an AI-based model (ROSE-AI model) to substitute for manual ROSE during EUS-FNA; it demonstrated strong performance in

detecting cancer cells, achieving an accuracy rate of 83% in the internal validation dataset and a comparable result of 89% in the external validation dataset [141].

The cost-effectiveness of ROSE is still under debate. In the cost-analysis study by Wani et al. [142], EUS-FNB of pancreatic and nonpancreatic solid lesions appeared a more cost-effective strategy than EUS-FNA with ROSE. On the other hand, in a study aimed at assessing the cost-efficacy of ROSE performed during EUS-FNA of several different GI lesions, EUS-FNA with ROSE was associated with a significant cost-effectiveness benefit, resulting in savings of almost $252 per case of EUS-FNA when ROSE was applied. The economic savings attributed to ROSE were owing to a lower rate of inadequate specimens and fewer EUS-FNA sessions needed to achieve the final pathologic diagnosis [143]. In a retrospective study by the same group, the cost-effectiveness analysis was not different between EUS-FNB and EUS-FNA with ROSE in GI lesions [144]. Therefore, the authors concluded that the choice of strategy depends on availability and local expertise.

As demonstrated in previous meta-analyses [145, 146], the inclusion of ROSE in EUS-FNA improves sample adequacy for pathologic evaluation and enhances the diagnostic performance of the procedure. In particular, the aforementioned network meta-analysis demonstrated that EUS-FNA with ROSE leads to similar diagnostic outcomes as compared with EUS-FNB, even with highly performing end-cutting needles, both in pancreatic solid lesions [27] and subepithelial lesions [62]. On the other hand, conflicting results are reported in the literature concerning EUS-FNA of lymph nodes [147].

ROSE may not be routinely and widely available; it is especially present in high volume tertiary care centers. In a global survey published in 2016 [148], ROSE was used by 98% of American endosonographers and only by 48% of European and 55% of Asian respondents.

As previously reported, the development of end-cutting FNB needles led to very high adequacy and accuracy rates, thereby limiting the need for ROSE, as outlined in several studies and in a large multicenter RCT enrolling 771 patients with solid pancreatic masses, which found comparable diagnostic accuracies (96% with ROSE and 97% without ROSE; $P = 0.40$), but with a significantly shorter mean sampling procedural time (18 [SD 9] vs. 12 [SD 6] minutes; $P < 0.001$) [149]. Similar results were also reported in the recent meta-analysis of eight studies (2147 patients), where the difference in terms of sample adequacy of solid pancreatic lesions was not statistically significant between EUS-FNB alone versus EUS-FNB + ROSE [150]. The diagnostic accuracy was superior in the EUS-FNB + ROSE group ($P = 0.03$); however, when considering only the new FNB needles, this difference did not reach statistical significance ($P = 0.56$). The same results were observed in the setting of subepithelial lesions, where the above network meta-analysis showed that ROSE did not improve the diagnostic yield of EUS-FNB [62].

Nowadays, with the advancement of digital imaging technology, there is the possibility of an expert cytopathologist evaluating FNA specimens remotely. In 2014 Khurana et al. demonstrated that telecytopathology on-site evaluation of EUS-FNA of pancreatic lesions reduced the nondiagnostic rate, especially for solid lesions [151]. A more recent study by Machado et al. demonstrated the feasibility of a low-cost instant messenger smartphone application for evaluating specimens of EUS-FNA of pancreatic solid lesions in terms of sample adequacy, with the possibility of an initial diagnosis of malignancy in 61% of samples [152]. Telecytopathology offered by high volume centers may in the future serve as an effective substitute for on-site evaluation, overcoming the issue of a shortage of cytopathologists.

The studies comparing the diagnostic outcomes of EUS-FNB with ROSE versus EUS-FNB without ROSE are reported in **Table 12s** [79, 149, 153, 154, 155, 156, 157, 158].

As reported in the study by Facciorusso et al. [150], the meta-analysis of the two RCTs [79, 149] that compared the two approaches showed no difference (OR 1.1, 95%CI 0.3–3.9), with moderate evidence of heterogeneity ($I^2 = 49\%$).

The high level of indirectness, related to the different study designs (one of the RCTs was a subanalysis of an RCT) and different FNB needles used, led to downgrading of the quality of evidence to moderate (**Table 4s**). Therefore, a strong recommendation with a moderate quality of evidence was provided.

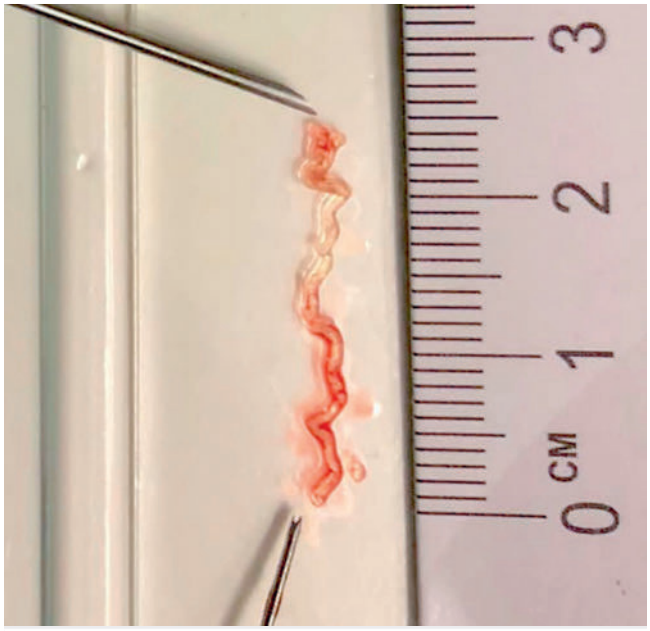
5.2 Macroscopic on-site evaluation (MOSE) and visual on-site evaluation (VOSE)

RECOMMENDATION

ESGE recommends the use of MOSE for EUS-FNB of pancreatic masses because this approach leads to high diagnostic accuracy, with the need for fewer needle passes. Strong recommendation, moderate quality of evidence.

Other techniques have been implemented for assessing the quality of tissue samples during EUS procedures. MOSE, introduced by Iwashita et al. [159], involves evaluating the presence of a macroscopically visible core (a whitish or yellowish tissue fragment) in the sample dispensed onto a glass slide; if it is ≥4 mm, it predicts the presence of a histologic core (▶ **Fig. 3**). MOSE has been evaluated with both FNA [160] and FNB needles [123], demonstrating excellent diagnostic parameters for both techniques. Moreover, according to a recent noninferiority RCT [123], MOSE can significantly reduce the number of needle passes in patients with pancreatic and nonpancreatic solid lesions, with an accuracy that is not inferior to that of EUS-FNB with three needle passes. Sundaram et al. showed that, when end-cutting EUS-FNB needles were used for the evaluation of solid pancreatic lesions, no difference in sensitivity, specificity, or diagnostic accuracy was detected between ROSE and MOSE [161].

Visual on-site evaluation (VOSE) might represent an easy alternative to MOSE, consisting of assessing the EUS sample fully expelled into a graduated formalin vial, which is shaken to better visualize the presence of a macroscopically visible core. In the prospective single-center study by Stigliano et al. [162], the endoscopist evaluated the presence of a macroscopic visible core, the color (white or red/mixed) and the blood contam-



▶ **Fig. 3** Macroscopic on-site evaluation (MOSE) involves evaluating for the presence of a macroscopically visible core (a whitish or yellowish tissue fragment) in the sample after it has been dispensed onto a glass slide.

ination; the authors found that a VOSE "red-mixed specimen" was associated with a higher probability of histologic adequacy.

VOSE and MOSE are quick and simple procedures performed by the endosonographer in the endoscopy room, without the need for other professional figures, making them highly cost-effective; however, in comparison with ROSE, they do not provide quality information or a preliminary diagnosis.

A recent meta-analysis by Mohan et al. showed a pooled accuracy of FNA and/or FNB specimens in yielding a pathologic diagnosis by MOSE of 91% (95%CI 89%–93%), pooled sensitivity of 92% (95%CI 89%–94%), and pooled specificity of 99% (95%Ci 97%–100%), which was also confirmed in the subgroup analysis that was restricted to end-cutting FNB needles [163]. Based on the single RCT by Mangiavillano et al. [123], no difference was observed in terms of diagnostic accuracy between EUS-FNB with MOSE versus without MOSE (RR 1.02, 95%CI 0.95–1.10). The panel therefore decided to downgrade the quality of evidence owing to imprecision (wide 95%CIs crossing unity and failure to reach the optimal information size) (**Table 4s**). Therefore, a strong recommendation with a moderate quality of evidence was provided.

Given the very limited published data on the use of VOSE, the panel decided to refrain from providing a statement on VOSE.

5.3 Digital confocal laser microscopy

Ex vivo fluorescence confocal laser microscopy (FCM) represents a new digital tool allowing for real-time microscopic assessment of fresh unfixed biologic specimens. Its main advantage, especially in the field of EUS-FNB, is the fact that it produces digital histologic images without any need for conventional slide preparation. Its application could lead to shorter procedures, fewer needle passes, and a lower risk of AEs, while at the same time obviating the need for ROSE.

Currently, the VivaScope 2500M-G4 microscope (MAVIG GmbH, Munich, Germany) has been evaluated in a limited number of studies. Briefly, the specimen obtained after the first needle pass is placed directly in a dedicated scaffold and, after a minimum amount of preparation, is put between two dedicated microscope slides and placed in the imaging device that, using a dedicated algorithm, converts the acquired image information into colors that resemble hematoxylin and eosin (H&E) staining [164]. In a prospective study that enrolled 81 patients undergoing EUS-FNB of solid pancreatic lesions, FCM accurately predicted the adequacy of the tissue sample in 96% of the samples, while there was significant agreement between FCM evaluation and the final histologic assessment (Cohen's *k* coefficient 0.95, 95%CI 0.89–1.01), with 100% sensitivity and 67% specificity [164].

In a more recent multicenter study, the validity of digital FCM was evaluated by comparing the interobserver agreement between FCM and standard histologic analysis [165]. The digital images from FCM and digitalized paired whole-slide images from 25 consecutive patients with pancreatic EUS-FNB were sent to 10 international expert pathologists, with a high interobserver agreement demonstrated (Cohen's *k* 0.79, 95%CI 0.65–0.92) [165]. Based on these studies, FCM could be of value in improving the real-time assessment of pancreatic solid lesions, although the high costs limit its applicability currently.

6 Tissue acquisition for pancreatic cystic lesions

6.1 Cyst fluid cytology and molecular analysis

RECOMMENDATION

ESGE suggests the use of glucose level over carcinoembryonic antigen (CEA) in the cystic fluid for the diagnosis of pancreatic mucinous cysts.

Conditional recommendation, low quality of evidence.

Accurate diagnosis and risk stratification for the development of malignancy in pancreatic cystic lesions (PCLs) are challenging. An unacceptable number of patients with PCLs with worrisome features that, according to guidelines, should undergo surgical resection are eventually diagnosed with benign disease on final histologic examination of the resection specimen [166]. In order to avoid unnecessary surgery, effective methods to better diagnose and subclassify PCLs are highly warranted.

EUS characteristics alone are usually insufficient to make a diagnosis, but there are some occasions where they are relevant (e. g. classic features of a pseudocyst in the correct clinical circumstances). EUS alone is also accurate in identifying serous cystic neoplasms, especially when honeycombing is present in a lesion with clear noncommunication with the pancreatic duct.

For most other lesions, there will be a need for sampling of the most suspicious aspect of the cyst, such as a mass or nodule, and this should be conducted as for a solid lesion. For those lesions without a clear suspicious target but where sampling has been deemed necessary, direct sampling is performed from fluid within the cyst. The use of adjunctive devices such as confocal microscopy and through-the-needle biopsy (TTNB) forceps are discussed separately.

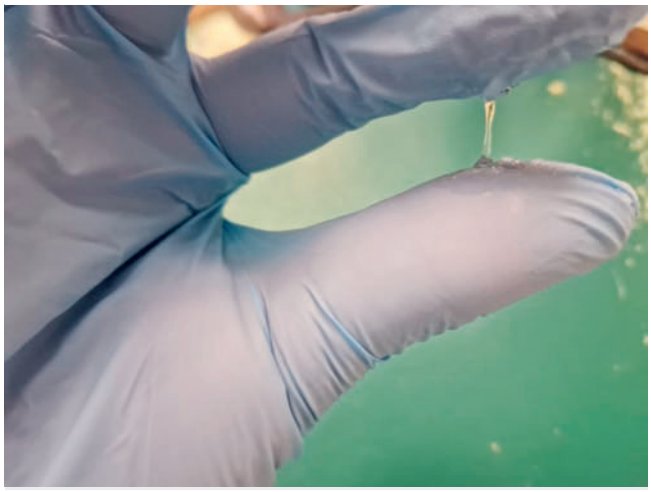
The technique involves using a standard FNA needle, as opposed to a biopsy needle, and most operators prefer either a 22G or 19G FNA needle. If a mucinous cyst is suspected, then a 19G needle is preferable, as the fluid can be very thick and requires a large needle channel for successful aspiration; however, 19G needles are more challenging in areas such as the uncinate process. If possible, the whole cyst should be aspirated to dryness in a single pass but, in multiloculated lesions, targeting of the largest cystic component and full aspiration is acceptable.

The needle should be positioned in the center of the cyst and the tip observed during aspiration to prevent contact with the cyst wall as it collapses. This should ensure complete aspiration and reduces any abrasion of the cyst wall by the tip of the needle. EUS-guided cyst FNA is low risk, but AEs such as bleeding, infection, cyst rupture, and pancreatitis have all been described. The overall risk was reported to be between 2% and 6% in a previous meta-analysis [167].

Cyst fluid assessment is comprised of its descriptive appearance and measurement of various components of the fluid, with the most common being cytology, and levels of carcinoembryonic antigen (CEA), amylase, and glucose. Few studies have examined the value of the cyst fluid appearance, although most endosonographers give a subjective description of the fluid viscosity at aspiration. The most objective measure of this is the "string sign," which involves placing a droplet of the aspirate between the thumb and index finger of a gloved hand and then separating the fingers (▶ **Fig. 4**). A positive string sign is where the "string" stretches to 1 cm and persists for >1 second [168]. This has been assessed prospectively and is specific, but not very sensitive [169].

Several tumor markers have been investigated to try to determine which cystic lesions are more likely to be mucinous, as well as those at highest risk of malignant transformation. Initial studies showed the most accurate results using CEA, and a cutoff of 192 ng/mL gave an area under the curve (AUC) of 0.79 [170]. More recent studies have shown that lower levels of CEA in the aspirate may be more accurate [171, 172]. One of the biggest issues is the lack of use of a standardized assay for measurement in different institutions, leading to the variance in the accuracy for the different reported cutoffs. It is worth noting that high CEA levels have also been found in inflammatory cysts [172].

Measurement of the cyst fluid amylase is a potentially useful adjunct. A raised amylase level suggests communication of the cyst with the pancreatic duct, with levels <250 U/L largely excluding pseudocysts [173]. A highly elevated amylase level is associated with pseudocysts, but has also been seen in mucinous lesions [172].



▶ **Fig. 4** The string sign is shown during endoscopic ultrasound-guided fine-needle aspiration of a pancreatic cystic lesion. This test involves placing a droplet of the aspirate between the thumb and index finger of a gloved hand and then separating the fingers. A positive string sign is where the "string" stretches to 1 cm and persists for >1 second.

More recently there has been interest in inexpensive, widely available markers that might reflect the level of metabolic activity within a cystic lesion. In initial studies, a lower glucose level in the cyst fluid aspirate was reported to have a high sensitivity for diagnosing mucinous cysts, whether sent to the laboratory or performed using point-of-care glucometers [174]. A recent meta-analysis showed that a cyst fluid glucose level <50 mg/dL had a sensitivity of 91% and specificity of 91% when sent to the laboratory and 90% and 84%, respectively, when using point-of-care glucometers [175]. There are two studies that have examined the utility of combining glucose and CEA levels, with one showing improved accuracy [176] and the other showing no additional benefit of CEA over glucose alone [177]. A more recent study examined the lactate level within cyst aspirates and showed significantly lower levels in mucinous cysts. Glucose had superior operating characteristics to both CEA and lactate in this study [178].

Examination of the cellular content in a pancreatic cyst aspirate is perhaps one of the oldest methods used to try to determine the nature of the lesion. The sensitivity of cyst fluid cytology is generally poor owing to the low cellular yield in the fluid aspirate. One meta-analysis showed a pooled sensitivity of 63% (95%CI 56%–70%) and a specificity of 88% (95%CI 83%–93%) [179]. This was also reflected in the high positive likelihood ratio (4.5) and low negative likelihood ratio (0.5). This means that cytology is only reliable if a positive diagnosis is made as false positives, especially for advanced changes, are uncommon, but negative cytology cannot currently exclude a mucinous lesion or even malignancy.

Within a pancreatic cyst fluid aspirate, there are other sources of information that are currently being investigated. These include assessment for the presence of genetic mutations, such as *KRAS* and *GNAS*, which appear to have a high specificity for

mucinous cysts [180]. Other studies have used next-generation sequencing to create a genetic profile for the cyst, combining the presence of different gene mutations [180]. Differing expression of mucin proteins in proteomic studies has suggested higher risk patterns, but this needs confirmation. Similarly, exploration of proteomics, metabolomics, and the microbiome may improve the accuracy of fluid sampling [181]. These areas are not currently widely available clinically and remain within the realm of exploratory research. **Table 13s** shows the outcomes of seven meta-analyses published in the last 5 years [175, 177, 182, 183, 184, 185, 186].

Glucose level showed similar specificity and significantly higher sensitivity as compared with CEA; molecular analyses led to very good results, but the high costs and the limited availability represent major concerns with their use. Therefore, a weak recommendation, with a low quality of evidence, in favor of the use of glucose levels was provided, because it was based on nonrandomized studies. The use of CEA might have a complimentary role, although whether their combined use would increase significantly the diagnostic accuracy is still uncertain.

6.2 Through-the-needle biopsy (TTNB)

RECOMMENDATION

ESGE suggests EUS-TTNB where the histologic diagnosis may change the clinical management of the patient. TTNB should be avoided in PCLs with communication with the pancreatic duct owing to the risk of serious AEs. Conditional recommendation, very low quality of evidence.

TTNB is performed by a new device that enables retrieval of histologic tissue, comprising epithelium and stroma, from the cystic wall or septa [187]. The through-the-needle microforceps biopsy technique has shown promising results for the diagnosis and subclassification of pancreatic cysts, enabling immunohistochemical, as well as high quality molecular diagnostic examination, far more accurately when compared with EUS-FNA [188, 189, 190, 191]. Moreover, a good interobserver agreement among pathologists has been demonstrated [192].

There are currently two commercially available devices: the Moray Micro forceps (US Endoscopy, Mentor, Ohio, USA) and the Micro Bite forceps (MTW Endoskopie Manufaktur, Germany), with the former most extensively tested in the published studies.

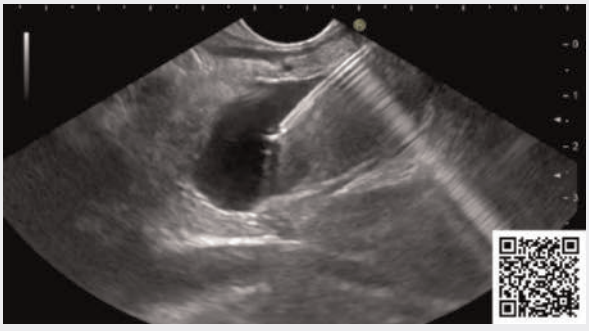
The Moray Micro forceps has a length of 230 cm, a sheath diameter of 0.8 mm, and a jaw opening width of 4.3 mm [193]. The single-use biopsy forceps can be passed through a standard 19G FNA needle. The jaws of the forceps are flat with multiple sharp teeth. The micro forceps can either be preloaded in the needle or introduced after the cyst has been punctured by a 19G needle and the stylet removed. When the transducer is positioned in the second part of the duodenum with the endoscope tip flexed, it may be difficult to advance the micro biopsy forceps through the needle owing to resistance from within a bent needle. If resistance is experienced, slight, repetitive, gentle opening and closing of the forceps during introduction through the needle reduces the friction and often helps overcome this problem. In addition, aspirating some of the fluid before TTNB ensures an amount of "nonblood-contaminated" fluid, as some minor bleeding is often observed after TTNB. Moreover, the fluid aspiration reduces the cystic wall tension and may facilitate grabbing tissue into the jaws of the microforceps [194]. Following cyst puncture and forceps introduction, the jaws of the forceps are easily visualized under real-time EUS guidance. The jaws are opened, and the forceps advanced anteriorly to the needle tip to touch the cyst wall. The forceps should then be closed, while maintaining a slight pressure, and then retracted, while showing "tenting" of the wall lining. Observed "tenting" of the wall lining on EUS is usually a good predictor of an adequate sample; if this tenting effect is not experienced, the procedure should be repeated until the desired effect is seen or alternatively until clear resistance is felt when the biopsy forceps is retracted (▶ **Video 3**).

The tissue obtained should be visually inspected and the procedure repeated until at least two optimal biopsies have been acquired. It has been shown that extraction of more than two biopsies does not increase the sensitivity, but raises the risk of AEs [195].

The endoscopist should be aware of the risks associated with the procedure and try to minimize the intracystic needle time after obtaining an adequate number of samples. Following the retraction of the instruments, the lesion and the surrounding area should be re-examined to exclude any AEs, such as intracystic hemorrhage, although the latter is self-limited in almost all cases.

After retraction of the micro biopsy forceps, the small specimen is placed onto a small paper disc and finally introduced into a cassette [196].

According to the recently published evidence-based international Kyoto guidelines [15], there are no established indications for EUS-TTNB, and it seems too early to reach any definitive conclusions. It was demonstrated that TTNBs can substantially change the clinical management strategy in patients with



Video 3 Demonstration of the "tenting effect" during through-the-needle biopsy.
Online content viewable at:
https://doi.org/10.1055/a-2524-2596

PCLs in 12%–19% of cases, mostly by providing the diagnosis of a serous cyst adenoma in an oligocystic or unilocular cyst, and so leading to discontinuation of follow-up [188]. As a general principle, EUS-TTNB should be performed only in patients who are fit for surgery, with a clear indication for biopsy, and where the biopsy diagnosis may change the clinical management of the patient [15].

Because EUS-TTNB offers the chance to evaluate a microhistologic sample of the cyst wall, the key advantage of the procedure is gained when the histotype of the cyst is unknown, as typically happens in the case of unilocular/oligocystic PCLs. This cyst "morphology" may encompass a wide spectrum of PCLs, ranging from the more common intraductal papillary mucinous neoplasia (IPMN), serous cystadenoma, or mucinous cystadenoma to more rare conditions, including NETs [197, 198] or schwannomas [199, 200].

The accurate definition of a PCL is crucial for the management of the patient as, for example, large mucinous cysts, unlike serous cystadenomas, are frequently indicated for resection. In contrast, whether EUS-TTNB will play a role in the evaluation of a PCL's dysplasia grade remains doubtful. In fact, as a general principle, biopsy is not the way to define the grade of dysplasia because of its variability within the same lesion and its patchy distribution along the cystic wall, thereby producing a risk of a false-negative result owing to inadequate sampling [201].

Several meta-analyses have reported very high technical success rates of 90% and 100% for TTNB, and high sensitivity and specificity of around 80%, which are superior to standard FNA cytology [202, 203, 204].

Limiting factors include the lack of epithelium in non-mucinous cysts, but also denudation of the cyst wall, which may yield false-negative results. Moreover, as previously commented, the evaluation of dysplasia warrants cautious interpretation as the biopsies represent only a portion of the cyst wall and the results may be falsely negative. Therefore, any high risk features, such as a thickened cyst wall, nodules, or solid parts, should be targeted if possible.

AEs associated with the procedure range from 2% to 23%, and the rate seems higher compared with the standard EUS-FNA procedure [205, 206]. The most common AE reported is intracystic hemorrhage, which is defined as hyperechoic changes in the cystic lumen following the tissue acquisition; however, all published cases have been mild and, in most cases, without any clinical implications [207]. Infections are rarely seen after EUS-TTNB of pancreatic cysts and a multicenter, retrospective, propensity-score matched study demonstrated that antibiotic prophylaxis does not influence the infection rate, which appears to be very low [208]. EUS-TTNB can also cause acute pancreatitis, probably owing to destruction of the cyst wall, edema of the adjacent normal pancreatic tissue architecture, microclot passage into the main pancreatic duct, and leakage of the pancreatic juice. In a recently published meta-analysis, the pooled AE rate for pancreatitis was shown to be around 3% (95%CI 1.8%–4.5%) [207]. Most pancreatitis events had a mild clinical course; however, the reported rate of serious AEs was around 1.1% (95%CI 0.4%–2.7%), mainly due to severe pancreatitis [202]. Serious concerns about the use of TTNB were raised by a prospective Danish study that reported an AE rate of 10%, including a case of death due to post-TTNB pancreatitis [188].

A large multicenter publication that included 506 patients found age (OR 1.3, 95%CI 1.1–2.1), number of TTNB passes (from OR 2.2 [95%CI 1.3–4.3] to OR 3.2 [95%CI 2.0–6.3] with increasing number of passes), complete aspiration of the cyst (OR 0.6, 95%CI 0.3–1.0), and diagnosis of IPMN (OR 4.2, 95%CI 2.3–7.7) to be independent predictors of AEs [209]. No preventive measures have been clearly demonstrated to reduce the risk of pancreatitis, although Kovacevic et al. observed a decreasing trend in the incidence of pancreatitis when using prophylactic rectal indomethacin/diclofenac [188]. Future studies are needed to evaluate the role of rectal nonsteroidal anti-inflammatory drugs (NSAIDs) or aggressive hydration in minimizing the risk of pancreatitis after TTNB.

Table 14s reports the available meta-analyses assessing TTNB performance in patients with PCLs [202, 203, 204, 205, 206, 207, 210]. In all of these studies, TTNB clearly outperformed cytology in terms of diagnostic accuracy (ORs ranging from 3.4 [95%CI 1.3–9.0] to 9.4 [5.7–15.4]). Moreover, a recent network meta-analysis of retrospective studies found TTNB to be the best technique to differentiate mucinous cysts and to identify the malignant nature of a PCL (superiority index 13, 95%CI 5–17) [211].

The panel provided a conditional recommendation with a very low quality of evidence favoring the use of TTNB in PCL patients, because the evidence was based only on retrospective studies and owing to the high risk of imprecision (failure to reach the optimal information size) (**Table 4s**).

6.3 Confocal laser endomicroscopy

RECOMMENDATION

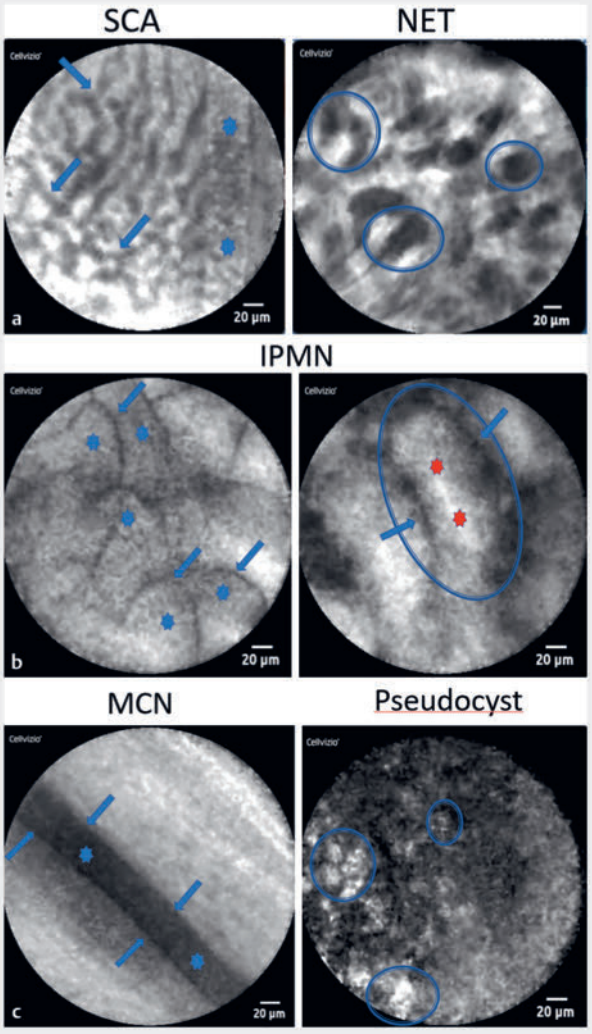
ESGE suggests the use of needle-based confocal laser endomicroscopy (nCLE) to discriminate between mucinous and non-mucinous pancreatic cysts in centers with adequate expertise.

Conditional recommendation, low quality of evidence.

Over the last decade, needle-based confocal laser endomicroscopy (nCLE) has emerged as a promising technology to overcome the limitations of EUS-FNA in the characterization of PCLs. nCLE enables real-time imaging of tissue and vascular structures.

Cellvizio I.V.E. (Mauna Kea Company, Paris, France) is a confocal laser imaging device adapted for imaging through a bundle of optical fibers, assembled with other miniaturized elements, called a Confocal Miniprobe, to allow real-time imaging of the internal microstructure of tissues (▶ **Fig. 5**).

Prior to each procedure, the AQ-Flex probe is inserted into the 19G FNA needle in lieu of the stylet and advanced until the probe is positioned with the tip aligned 1 mm beyond the needle tip and then secured with a special locking device. After EUS-guided puncture, the FNA needle should be carefully posi-



▶ **Fig. 5** Appearances of some of the different patterns observed during needle confocal laser endomicroscopy of pancreatic cystic lesions. **a** A serous cystadenoma (SCA), with the superficial vascular network seen as multiple interconnected black vessels (arrows) and big vessels (stars), in which moving red cells (small black points) are seen moving in the fluorescein-filled vessel, which appears white, and neuroendocrine tumor (NET) with irregular clusters of dark cells (blue ovals). **b** A pancreatic intraductal papillary mucinous neoplasia (IPMN) contains small papillary projections (stars) and one large papilla (blue oval) with a vascular core (red star), and the visible epithelial border (arrows). **c** A mucinous cystadenoma (MCN) with the epithelial border (blue star) and its limits marked (arrows), and a pancreatic pseudocyst, with inflammatory cells that can be seen moving in the liquid (blue ovals).

tioned within the cyst. A soft contact between the nCLE probe and the epithelium of the cyst is necessary to obtain relevant images. After image acquisition, fluid aspiration for cytology, tumor markers, and/or DNA, and/or TTNB can be performed.

Based on expert opinion, it can be recommended to minimize catheter manipulation and to stop the examination as soon as specific nCLE criteria are observed, and systematically when the potentially examinable area inside the cyst has been checked. The recommended imaging time is <10 minutes (ideally <6 minutes) to decrease the risk of pancreatitis [212].

Some concerns were previously raised concerning the reproducibility of nCLE results [213]; however, three other studies conducted with blinded reviewers reported an almost perfect interobserver agreement (>0.60) for mucinous lesions, serous cystadenomas, and pseudocysts [214, 215, 216]. Intraobserver reliability was addressed by two trials using the INDEX-study population [215, 216] and was reported for all nCLE criteria as substantial, kappa ranging from 0.68 to 0.78, for nCLE-naïve blinded reviewers (n = 6) and as almost perfect, kappa ranging from 0.85 to 0.91, among six blinded nCLE experts (experience >30 nCLE cases) [216].

The main AE reported in the studies was post-procedural acute pancreatitis (with only one severe case reported). The highest rate was reported in the DETECT study (7%), which combined Spyglass cystoscopy and nCLE imaging in the same procedure [217]. These rates are comparable to the pooled pancreatitis rate of 1.6% (95%CI 0.6%–3.8%) and global AE pooled rate of 5.5% (95%CI 0.9%–13.6%) associated with EUS-guided FNA for PCLs performed using a 19G needle [167].

A French health economic evaluation of nCLE for the diagnosis of PCLs showed nCLE to be cost-effective for the therapeutic management of PCLs for serous cystadenoma [218]. This analysis showed that the addition of nCLE to EUS-FNA resulted in a reduction of 23% in the total rate of surgical intervention, which translated to a reduction in clinical costs of 13% [218].

Table 15s reports the data of five meta-analyses that assessed the diagnostic performance of nCLE in patients with PCLs [206, 219, 220, 221, 222]. The pooled sensitivity and specificity ranged between 82% and 90%, and 91% and 99%, respectively, with a reported pooled AE rate ranging from 1% to 5%, mostly due to pancreatitis. As reported in the meta-analysis by Facciorusso et al. [219], the OR for diagnostic accuracy of nCLE compared with EUS-FNA was 3.9 (95%CI 1.6–9.8). The aforementioned network meta-analysis [211] concluded that, for centers with relevant expertise and facilities, EUS-guided nCLE and EUS-guided TTNB are better choices for the diagnosis of PCLs (OR 88 [95%CI 29–214] and OR 40 [95%CI 11–104], respectively). Moreover, the indirect comparison between the two procedures reported in the meta-analysis by Kovacevic et al. [206] showed a slightly higher diagnostic yield with nCLE. Therefore, a conditional recommendation with a low quality of evidence was provided in favor of the use of nCLE, because it was based on nonrandomized studies.

7 Antibiotic prophylaxis

RECOMMENDATION
ESGE does not recommend the use of antibiotic prophylaxis before EUS-guided tissue sampling of solid masses and EUS-FNA of PCLs.
Strong recommendation, moderate quality of evidence.

Whether antibiotic prophylaxis should be administered prior to EUS-guided tissue sampling remains controversial. Incidence rates of bacteremia are reported to be low after EUS, with or without FNA, of cystic or solid lesions along the upper GI tract and for solid rectal lesions [223].

The American Society of Gastrointestinal Endoscopy (ASGE) published a guideline on antibiotic prophylaxis for GI endoscopy in 2015 that recommended against prophylaxis for solid lesions, while prophylaxis for EUS-guided sampling of cystic lesions (both pancreatic and mediastinal) was still recommended [223]. In 2017, the ESGE published a technical guideline on EUS-guided tissue sampling, confirming the indication for antibiotic prophylaxis for PCLs only, but with a low quality of evidence [1].

Over the past years, new evidence regarding antibiotic prophylaxis for EUS-guided tissue sampling of pancreatic cysts has been published. In 2020, Colan-Hernandez et al. published a randomized, noninferiority, double-blind, placebo-controlled clinical trial investigating whether EUS-FNA of pancreatic cysts without antibiotic prophylaxis increased the infection rate as compared with EUS-FNA with antibiotic prophylaxis [224]. They found that the risk of infections related to the procedure was overall very low (<1%) and was not increased when antibiotic prophylaxis was not used (OR 0.3, 95%CI 0.01–8.3) [224]. This finding was confirmed by two systematic reviews and meta-analyses, including six studies (the RCT and five retrospective series), which confirmed the very low incidence of infectious AEs (<1%), with no difference between the two groups [225, 226]. **Table 16s** reports the studies comparing antibiotic prophylaxis versus no prophylaxis before EUS-FNA of PCLs [106, 224, 227, 228, 229, 230].

Based on the available evidence, the panel recommended against the use of antibiotic prophylaxis in patients with PCLs undergoing EUS-guided sampling with complete aspiration of the cyst. A strong recommendation with a moderate quality of evidence was provided because of the risk of imprecision (wide CIs crossing unity and failure to reach the optimal information size) (**Table 4s**).

Very limited evidence is available about TTNB and the indication for prophylactic antibiotics. A retrospective propensity score-matched study reported one infectious event (1%) in the antibiotic prophylaxis group versus 2% in the control group [208]. Despite this preliminary evidence, further studies are needed to provide a definitive statement on the need for antibiotic prophylaxis before TTNB of PCLs.

8 Specimen handling and processing

Techniques used to process EUS-guided samples include conventional smears, cytospins, liquid-based cytology (LBC), and formalin-fixed paraffin-embedded tissue (specifically, cell blocks and biopsies). Cytologic methods (conventional smears, cytospins, and LBC) assess individual cells or clusters of cells, whereas histology (cell blocks and biopsies) allows assessment of intact fragments of tissue, including the architectural arrangements of cells and their relationship to surrounding tissues.

The technique of choice varies upon the nature of the lesion (solid or cystic), the type of needle used (FNA or FNB needle), the need to perform ROSE during the procedure, and the practical experience and expertise of the involved pathology personnel.

For solid lesions or for mural nodules of cystic lesions, the specimen obtained with an FNA needle can be partly spread onto glass slides (conventional smears) and partly collected in a vial containing saline or fixative. Glass slides must be fixed immediately by spray fixation or immersion in 95% alcohol for Papanicolaou or H&E staining; alternatively, they can be allowed to dry for Giemsa or Diff quick stain if ROSE is required. If ROSE is not required, the entire sample can be collected in the vial without conventional smear preparations. If the sample is collected fresh in saline solution, it should be rapidly transported to the laboratory and prepared to limit cell degeneration.

Whatever the medium, in the pathology laboratory, macroscopically visible tissue fragments and blood clots measuring >2 mm must be removed and processed separately in a paraffin block as a conventional biopsy, which requires formalin fixation. The remaining sample or its entirety, if no tissue fragments or blood clots are present, can be processed as LBC and/or cell blocks, the former technique requiring alcohol-based fixation, the latter 10% buffered formalin.

Alcohol-based fixatives are indicated for LBC (the two most common types being Cytolyt for ThinPrep and Cytorich Red for SurePath), which markedly attenuate the background elements, such as blood, mucus, and necrosis, but guarantee perfect cellular details. The residual LBC specimen can also be processed as a cell block, with subsequent formalin fixation.

To obtain a cell block, the sample is spun down with a centrifuge and the cellular material is concentrated into a cell button that is agglutinated and then processed as a routine histology specimen. There are several methods of agglutinating the cell pellet for embedding, the choice depending on which technique is available in the laboratory [231]. Sometimes no agglutination is necessary when large, clotted material is acquired with an FNA needle.

When using an FNB needle, the sample is generally corpuscolated with macroscopically visible tissue fragments that can be collected in formalin and processed as a conventional histologic biopsy, even if there can be differences among the various needle sizes and types in term of specimen volume [232]. If tissue fragments are not visible or are very small (e. g. ≤2 mm), a cell block technique can be employed to avoid loss of material.

If ROSE is required, instead of smearing part of the sample onto glass slides, touch-imprint cytology can be performed [233]: tissue fragments are gently pushed and partially spread between two glass slides to avoid smashing, in this way slides suitable for cytologic examination are obtained. Tissue fragments should then be picked up and collected in formalin.

For cystic lesions, even if ROSE is not indicated, the liquid sample can be smeared onto glass slides (see above), especially if it is viscous/mucinous, or it can be entirely collected fresh and sent immediately to the pathology laboratory, where it can be processed undiluted with the cytospin technique. This is a cell concentration method using centrifugal force to isolate, concentrate, and deposit a monolayer of cells onto a circular area on a slide. Cytospin preparations maintain the background, such as necrotic debris and mucin, but samples that have undergone transportation stress, such as exposure to abnormally high or low temperatures, may yield poor quality cells with low overall viability. Alternatively, the liquid sample can be collected in an alcohol-based fixative for LBC or in 10% buffered formalin for cell block preparation.

When dealing with pancreatic cyst fluid, the liquid should be triaged according to its quantity. Triage of aspirated PCLs requires an integrated multidisciplinary approach that involves clinical evaluation, radiologic assessment, cyst fluid biochemistry, and molecular/genetic testing, as well as cytologic evaluation. In general, if it is ≤0.5 mL, it is sent fresh for biochemical analysis or collected in ethanol for molecular studies, avoiding cytologic examination. If >0.5 mL, an aliquot of fluid can be submitted for cytologic examination and processed as described above. Each ancillary test requires at least 0.3 mL [234]. An EUS-TTNB will be processed as a standard histology specimen.

All of cytospins, conventional smears, and LBC, as well as formalin-fixed paraffin-embedded tissue (cell blocks and biopsies) allow for further studies (immunohistochemical stains and molecular analysis), although cell blocks and any biopsies, which have been formalin fixed, are considered optimal for immunohistochemistry and additionally allow direct comparison of the same cells between multiple analyses [235, 236].

Regarding processing techniques for EUS-FNA samples, the superiority of LBC over conventional smears is controversial; however, as shown in a recent meta-analysis [237], combining LBC with conventional smears showed a significantly higher pooled sensitivity compared with conventional smears alone and LBC alone for the clinical evaluation of pancreatic lesions. The combination of LBC and cell blocks has also been shown to significantly improve diagnostic accuracy, indicating that these specimen processing techniques complement each other [238].

With regard to solid lesions around the digestive tract, as demonstrated in the study by Huang et al. [239], the combination of cytologic and histologic specimen processing methods also contributes additional diagnostic efficacy to EUS-FNA in solid lesions of the digestive tract. As for PCLs, it was demonstrated that the diagnostic yield of an EUS-FNA sample improved when the endosonographer processed the specimen by spreading it onto glass slides, instead of collecting it directly into the liquid medium for LBC [240]; in contrast, with regards to the presence of mucus, cell block assessment appears superior to direct smears [241].

With regard to genomic analysis, there is limited literature on sample adequacy for molecular testing and genomic sequencing for pancreatic ductal adenocarcinoma obtained via EUS-FNA versus EUS-FNB. Comprehensive genomic profiling using next-generation sequencing has become an approved diagnostic test and has been successfully performed on FNA and FNB samples, including cell blocks, in several smaller studies [242, 243, 244]. Tumor surface area and tumor cellularity are essential parameters in determining sample adequacy for molecular testing: up to 2000 cells and 30% tumor cellularity may be necessary to perform comprehensive genomic analysis, but analysis can be successful at <10% tumor cellularity [243]. Mohamad et al. found that FNB was more likely to result in sufficient tissue sampling for genomic and molecular testing [245]. They demonstrated that sample adequacy for molecular testing was achieved in 71% of patients who underwent FNB compared with 32% of patients who underwent FNA (P<0.001).

In the absence of exact guidelines for material processing, each institution should thoroughly evaluate the optimal preparation method of EUS-FNA/FNB samples, considering that pathologists must fill the gap between the high technology endosonographer apparatus and the low/no technology sample preparation tools that they use [246]. Consequently, collaboration between endoscopists and pathologists is critical for success, with an understanding that cytologic and histologic processing techniques often complement each other, but tissue pieces >2 mm need to be processed for histology. Sample processing techniques should be selected according to an individual center's experience and expertise, bearing in mind that samples processed histologically are optimal for immunohistochemistry, are more likely to be adequate for molecular analyses, and may be necessary to make certain diagnoses requiring intact tissue architecture.

Disclaimer

ESGE Technical and Technology Reviews represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply in all situations and should be interpreted case by case in the light of specific clinical situations and resource availability. Further controlled clinical studies may be needed to clarify aspects of the statements, particularly in the absence of high quality of evidence, and revision may be necessary as new data appear.

ESGE Technical and Technology Reviews are intended to be an educational device to provide information that may assist endoscopists in providing care to patients. They are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any treatment.

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Conflict of Interest

L. Archibugi has received consultancy fees from Boston Scientific (2024). M. Arvanitakis has provided consultancy and received support for courses from Pentax and Boston Scientific (both 2024 to present). S. Carrara has received consultancy fees from Olympus and Boston Scientific (both 2022 to 2024). C. Fabbri has provided consultancy to Boston Scientific (2020 to present) and Steris (2024). J. Iglesias-Garcia has received speaker's and advisor fees from Fujifilm (2022 to present), Boston Scientific (2016 to present), and Medi-Globe (2021 to present). J. Leeds has received speaker's and advisor fees from Medtronic, Boston Scientific, Olympus, and Viatris (2015 to present); course support from Boston Scientific, Medtronic, Olympus, and Cook Medical (2018 to present); he is Secretary of the Pancreatic Society of Great Britain and Ireland (2022 to present). B. Napoleon has received fees for teaching from Olympus, Boston Scientific, and MaunaKea (all 2018 to present). P. Vilmann has provided consultancy to Medi-Globe (1992 to present). S.F. Crinò, J. Dhar, A. Facciorusso, A. Fornelli, L. Fuccio, P. Gkolfakis, B. Haugk, I.S. Papanikolaou, A. Seicean, P.M.C. Stassen, and T.C. Tham declare that they have no conflict of interest.

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