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Endoscopic tissue sampling – Part 1: Upper gastrointestinal and hepatopancreatobiliary tracts. European Society of Gastrointestinal Endoscopy (ESGE) Guideline

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MAIN RECOMMENDATIONS

1 ESGE recommends that, where there is a suspicion of eosinophilic esophagitis, at least six biopsies should be taken, two to four biopsies from the distal esophagus and two to four biopsies from the proximal esophagus, targeting areas with endoscopic mucosal abnormalities. Distal and proximal biopsies should be placed in separate containers.
Strong recommendation, low quality of evidence.

2 ESGE recommends obtaining six biopsies, including from the base and edge of the esophageal ulcers, for histologic analysis in patients with suspected viral esophagitis.
Strong recommendation, low quality of evidence.

3 ESGE recommends at least six biopsies are taken in cases of suspected advanced esophageal cancer and suspected advanced gastric cancer.
Strong recommendation, moderate quality of evidence.

4 ESGE recommends taking only one to two targeted biopsies for lesions in the esophagus or stomach that are potentially amenable to endoscopic resection (Paris classification 0-I, 0-II) in order to confirm the diagnosis and not compromise subsequent endoscopic resection.
Strong recommendation, low quality of evidence.

5 ESGE recommends obtaining two biopsies from the antrum and two from the corpus in patients with suspected *Helicobacter pylori* infection and for gastritis staging.
Strong recommendation, low quality of evidence.

6 ESGE recommends biopsies from or, if endoscopically resectable, resection of gastric adenomas.
Strong recommendation, moderate quality of evidence.

7 ESGE recommends fine-needle aspiration (FNA) and fine-needle biopsy (FNB) needles equally for sampling of solid pancreatic masses.
Strong recommendation, high quality evidence.

8 ESGE suggests performing peroral cholangioscopy (POC) and/or endoscopic ultrasound (EUS)-guided tissue acquisition in indeterminate biliary strictures. For proximal and intrinsic strictures, POC is preferred. For distal and extrinsic strictures, EUS-guided sampling is preferred, with POC where this is not diagnostic.
Weak recommendation, low quality evidence.

9 ESGE suggests obtaining possible non-neoplastic biopsies before sampling suspected malignant lesions to prevent intraluminal spread of malignant disease.
Weak recommendation, low quality of evidence.

10 ESGE suggests dividing EUS-FNA material into smears (two per pass) and liquid-based cytology (LBC), or the whole of the EUS-FNA material can be processed as LBC, depending on local experience.
Weak recommendation, low quality evidence.

SOURCE AND SCOPE

This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). It provides guidance on the collection and handling of tissue samples during endoscopy of the upper gastrointestinal and hepatopancreatobiliary tracts. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was adopted to define the strength of recommendations and the quality of evidence.

1 Introduction

Adequate collection and handling of tissue samples during endoscopy is fundamental in diagnosing pathology of the digestive system. The aim of this guideline was to make evidence-based recommendations on the indications and protocols for endoscopic tissue sampling for the most common conditions in the upper and lower gastrointestinal tracts and the hepatopancreatobiliary (HPB) tract (the lower gastrointestinal tract will be covered in Part 2 and published separately).

2 Methods

The European Society of Gastrointestinal Endoscopy (ESGE) commissioned this Guideline (Guideline Committee chair, J.v.H.) and appointed a guideline leader (R.P.) who invited the listed authors to participate in the project development. After the project group had been assembled, task forces were formed to define the key questions and PICOs (population, intervention, comparator, outcome) in the upper gastrointestinal, lower gastrointestinal, and HPB domains (**Table 1 s**, see online-only Supplementary material). Literature searches and reviews of the relevant articles were performed between March and September 2020. The available evidence was graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [1]. Based on the available evidence, recommendations and suggestions were drafted and discussed with the project group during online meetings. Further details on the methodology of ESGE guideline development have been reported elsewhere [2].

In February 2021, a draft prepared by the leaders and coordinating team was sent to all group members. The manuscript was also reviewed by two independent reviewers and sent for further comments to the ESGE National Societies and individual

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ABBREVIATIONS

CMV	cytomegalovirus
ERCP	endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
EUS	endoscopic ultrasound
FGP	fundic gland polyp
FNA	fine-needle aspiration
FNB	fine-needle biopsy
GERD	gastroesophageal reflux disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
HPB	hepatopancreatobiliary
HSV	herpes simplex virus
LBC	liquid-based cytology
MALT	mucosa-associated lymphoid tissue
MAPS	management of precancerous conditions and lesions in the stomach
PICO	population, intervention, comparator, and outcome
POC	peroral cholangioscopy
PPI	proton pump inhibitor
ROSE	rapid onsite evaluation

members. After agreement on a final version, including the agreed recommendations (a summary of the upper gastrointestinal tract recommendations is given in ▶ **Table 1**), the manuscript was submitted to the journal *Endoscopy* for publication. All authors agreed on the final revised manuscript.

This Guideline was issued in 2021 and will be considered for review and update in 2026, or sooner if new and relevant evidence becomes available. Any updates to the Guideline in the interim will be noted on the ESGE website: http://www.esge.com/esge-guidelines.html.

3 Upper gastrointestinal tract

3.1 Eosinophilic esophagitis

RECOMMENDATION

ESGE recommends that, where there is a suspicion of eosinophilic esophagitis, at least six biopsies should be taken, two to four biopsies from the distal esophagus and two to four biopsies from the proximal esophagus, targeting areas with endoscopic mucosal abnormalities. Distal and proximal biopsies should be placed in separate containers.

Strong recommendation, low quality of evidence.

Biopsies should be obtained in patients in whom eosinophilic esophagitis is a clinical possibility, even when normal mucosa is visualized. Inflammatory alterations in eosinophilic esophagitis are frequently patchy, therefore it is recommended that at least six biopsies should be obtained from at least two different locations in the esophagus, typically two to four biopsies from both the distal and proximal esophagus, depending on where most endoscopic abnormalities are visualized. The diagnostic sensitivity increases with the number of biopsies and is maximized with at least six biopsies. Esophageal biopsies should be targeted to areas of endoscopic abnormality, mainly white stipples, exudates, and longitudinal furrows, which are associated with higher eosinophil counts. In patients with symptoms, biopsies should also be taken even if the endoscopic appearance is normal, as this has been reported in up to 10 % of adult patients [3–7].

RECOMMENDATIONS

ESGE suggests, in histologically confirmed eosinophilic esophagitis, obtaining biopsies after a 6- to 12-week initial treatment course, with at least two to four biopsies from the distal esophagus and two to four biopsies from the proximal esophagus, focusing on areas with endoscopic mucosal abnormalities.

Weak recommendation, very low quality of evidence.

ESGE suggests against endoscopy and histologic assessment on an annual basis for patients who have responded to therapy and are maintained on these treatments.

Weak recommendation, very low quality of evidence.

For patients who are treated with a proton pump inhibitor (PPI), elimination diet, or steroids, the response to therapy can be assessed by means of a follow-up endoscopy after a 6- to 12-week initial course, obtaining at least six biopsies from at least two different locations in the esophagus, typically two to four biopsies from both the distal and proximal portions of the esophagus. However, there is little evidence to support this in patients who respond to therapy. For patients who respond to a PPI, elimination diet, or steroids and are maintained on these treatments, current data do not support follow-up with endoscopic and histologic assessment [3–7].

3.2 Gastroesophageal reflux disease

RECOMMENDATION

ESGE recommends against obtaining biopsies for the diagnosis of gastroesophageal reflux disease (GERD) in patients with normal endoscopic findings.

Strong recommendation, low quality of evidence.

In patients with complaints of gastroesophageal reflux, with or without PPI use, and with or without endoscopic signs of erosive esophagitis, biopsies are not recommended to confirm gastroesophageal reflux disease (GERD). For this indication,

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▶ **Table 1** Summarized recommendations for tissue sampling in the upper gastrointestinal tract.

Suspected diagnosis or indication	Number and location of biopsies	Remarks
Eosinophilic esophagitis: initial diagnosis or evaluation of therapy response	At least six biopsies, two to four biopsies from the distal esophagus and two to four biopsies from the proximal esophagus, targeting areas with endoscopic mucosal abnormalities	Place biopsies from the distal and proximal esophagus into separate containers
Gastroesophageal reflux disease	Biopsies not indicated for diagnosis	
Infectious esophagitis		
▪ Candida esophagitis	Given the high positive predictive value of white plaque-like lesions for candida, biopsies are only indicated if the results would have therapeutic consequences	Mycologic analysis only indicated for treatment resistance
▪ Viral esophagitis	Six biopsies, including from the base and the edge of esophageal ulcers	
Barrett's esophagus	In cases with endoscopic evidence of Barrett's esophagus > 1 cm, biopsies should be taken from all visible abnormalities; in addition, random four-quadrant biopsies should be collected every 2 cm within the Barrett's segment, starting from the upper end of the gastric folds	Place biopsies from any abnormalities and from each level into separate containers
Esophageal cancer and early neoplasia	At least six biopsies in cases of suspected advanced cancer Only one to two targeted biopsies for lesions that are potentially amenable to endoscopic resection	
Dyspepsia and gastritis	Two biopsies from the antrum and two from the corpus in patients where *H. pylori* is suspected If staging systems are to be used in patients with atrophy or intestinal metaplasia (e. g. OLGA, OLGIM), a biopsy in the angle should also be performed	Place biopsies from antrum and corpus in separate containers
Gastric polyps		
▪ Fundic gland polyp	Standard biopsies are not required	
▪ Hyperplastic polyp	Biopsy (or resect) if size is > 10 mm	
▪ Adenoma	Biopsy or, if endoscopically resectable, resect	
Gastric cancer and early neoplasia	At least six biopsies in cases of suspected advanced cancer Only one to two targeted biopsies for lesions that are potentially amenable to endoscopic resection For suspected linitis plastica, at least 10 bite-on-bite biopsies, targeting mucosal abnormalities	
Celiac disease	At least six biopsies from different locations in the duodenum, including two samples from the bulb	Biopsies can be collected in one container

OLGA, operative link for gastritis assessment; OLGIM, operative link on intestinal metaplasia assessment.

the sensitivity and specificity of the histologic findings have insufficient diagnostic accuracy and alternative diagnostic methods with higher sensitivity and specificity are available (e. g. reflux monitoring). Biopsies can be considered to exclude alternative diagnoses, if these are suspected based on the patient's symptoms [8–16].

3.3 Infectious esophagitis

RECOMMENDATIONS

ESGE suggests only obtaining biopsies in cases of suspected candida esophagitis if results are expected to have therapeutic consequences. Esophageal biopsies targeted at white plaque-like lesions should be sent for histologic and mycologic analysis when there is treatment resistance.
Weak recommendation, very low quality of evidence.

ESGE recommends obtaining six biopsies, including from the base and edge of the esophageal ulcers, for histologic analysis in patients with suspected viral esophagitis.
Strong recommendation, low quality of evidence.

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The most frequent cause of infectious esophagitis is fungal infection by *Candida* species. When associated with oropharyngeal thrush, upfront empiric antifungal treatment can be considered, as the positive predictive value of oral thrush for candida esophagitis in a patient with dysphagia reaches 77 % [17, 18]. If treatment fails or there is an absence of oropharyngeal lesions, endoscopic inspection and possible sampling of the esophageal mucosa is needed. An endoscopic diagnosis of candida esophagitis may be made by the observation of white or yellowish, plaque-like lesions (so called "cottage-cheese" plaques), and exudates on the esophageal mucosa, which are usually easily removable. White plaque-like lesions on the esophageal mucosa have a positive predictive value for candida esophagitis of 88 %–90 % [19]. The sensitivity of endoscopic biopsies with histologic assessment ranges from 54 % to 95 % [20–22]. Endoscopic biopsies with fungal culture may be needed in treatment-resistant cases.

In patients with esophageal ulcers, viral esophagitis should be suspected, most commonly caused by herpes simplex virus (HSV 1 or 2) and cytomegalovirus (CMV) [23]. In human immunodeficiency virus (HIV)-infected patients, idiopathic esophageal ulcers must also be considered in the differential diagnosis, as this has therapeutic consequences because these idiopathic esophageal ulcers are best treated with corticosteroids. Whereas HSV typically presents with ulcers in immunocompromised patients, in elderly patients it may present with vesicles and "volcano-shaped" mucosal structures. Conflicting data on the recommended number of endoscopic biopsies is possibly explained by the need to perform biopsies on the ulcer edge to observe the cytopathogenic effect of HSV and on the ulcer base for CMV [24]. Biopsies have a sensitivity of 68 %–100 % for HSV and 90 %–100 % for CMV [24–33].

Viral culture, although highly specific [24], is not available in most centers [34]. The only prospective study in the field did not observe an added diagnostic value of viral culture over routine histologic evaluation with immunohistochemical staining for CMV and HSV antigens [24]. Furthermore, the use of immunohistochemistry has not been consistently shown to improve detection of HSV and CMV [35]. Finally, routine hematoxylin and eosin staining is accurate for the diagnosis of most cases of viral esophagitis; immunohistochemical staining can be of help in selected cases.

Besides candida, HSV, and CMV esophagitis, other rare causes of infectious diagnoses should be kept in mind in the presence of esophageal ulceration, such as Epstein–Barr virus, *Leishmania*, and tuberculous esophagitis.

3.4 Barrett's esophagus

RECOMMENDATION

ESGE recommends that, in patients with endoscopic evidence of Barrett's esophagus of > 1 cm, biopsy samples should be taken from all visible mucosal abnormalities. In addition, random four-quadrant biopsies should be collected every 2 cm within the Barrett's segment, starting from the upper end of the gastric folds. Biopsies from each level should be collected in and presented to the pathologist in a separate container.

Strong recommendation, high quality of evidence.

For evidence, please refer to the existing ESGE position statement [36]. No new evidence is available on this statement.

3.5 Esophageal cancer and early neoplasia

RECOMMENDATIONS

ESGE recommends at least six biopsies are taken in cases of suspected advanced esophageal cancer.

Strong recommendation, moderate quality of evidence.

ESGE recommends taking only one to two targeted biopsies for lesions that are potentially amenable to endoscopic resection (Paris classification 0-I, 0-II) in order to confirm the diagnosis and not compromise subsequent endoscopic resection.

Strong recommendation, low quality of evidence.

High definition white-light upper gastrointestinal endoscopy using standard or virtual chromoendoscopy with biopsy is the recommended diagnostic modality for all suspected cases of esophageal cancer. Any lesion suspicious for cancer should be sampled and sent to pathology in a separate container. In cases with potentially malignant esophageal stenosis, an ultrathin endoscope should be used to complete the esophagogastroduodenoscopy and obtain tissue samples from inside the stenosis. The sensitivity of endoscopic forceps biopsies for esophageal cancer ranges from 92 % for a single biopsy to 100 % for six biopsies [37–39]. There is no role for cytology [40].

Early esophageal neoplasia is best staged and treated by endoscopic resection. Furthermore, extensive biopsy sampling can jeopardize subsequent endoscopic resection by inducing submucosal fibrosis. Therefore, where there is a suspected neoplastic esophageal lesion that is potentially amenable to endoscopic resection (Paris type 0-I or 0-II), one to two endoscopic biopsies, targeted on the most suspicious parts of the lesion, should be taken to document the presence of dysplasia or neoplasia.

Conversely, where a lesion is not amenable to endoscopic resection (esophageal stenosis, Paris type ≥ 0-III), at least six endoscopic biopsies should be obtained [41]. ▶ **Fig. 1** illustrates examples of early and advanced esophageal neoplasia.

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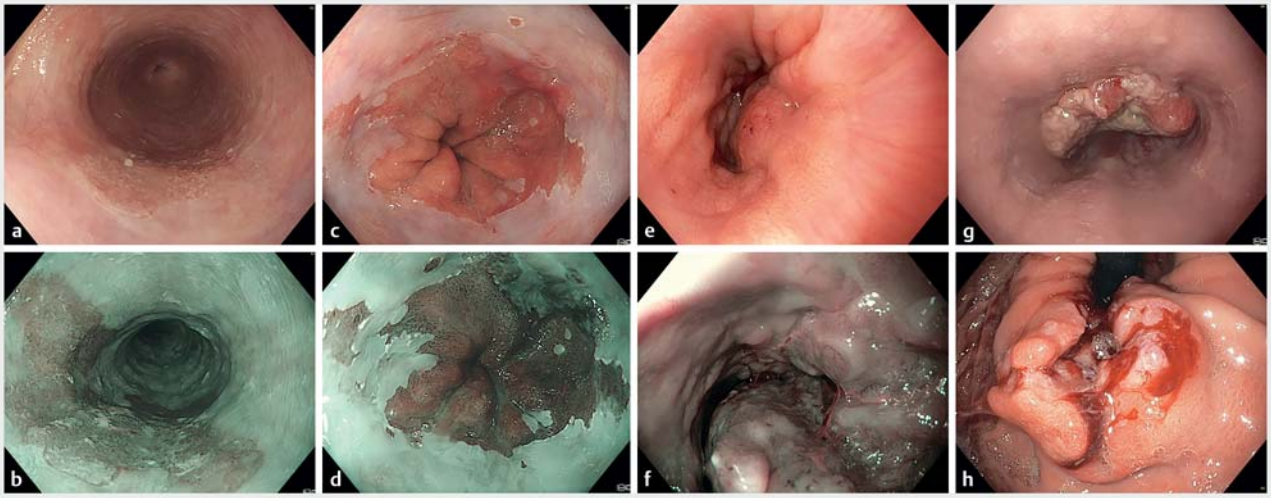

▶ **Fig. 1** Endoscopic images of esophageal neoplasia showing: **a, b** early Paris type 0-IIb squamous cell cancer from the 4–10 o'clock position on: **a** white-light endoscopy (WLE); **b** narrow-band imaging (NBI); **c, d** early Paris type 0-IIa-IIb adenocarcinoma from the 12–4 o'clock position in a short segment Barrett's esophagus on: **c** WLE; **d** NBI; **e, f** advanced esophageal squamous cell cancer on: **e** WLE; **f** NBI; **g, h** advanced distal esophageal adenocarcinoma on: **g** antegrade view; **h** retroflexed view.

3.6 Dyspepsia and gastritis

RECOMMENDATIONS

ESGE recommends obtaining two biopsies from the antrum and two from the corpus in patients with suspected *Helicobacter pylori* infection and for gastritis staging.
Strong recommendation, low quality of evidence.

ESGE recommends placing biopsies from the antrum and corpus into separate containers.
Strong recommendation, high quality of evidence.

Helicobacter pylori is a potentially curable cause of dyspepsia, peptic ulcer disease, and gastric adenocarcinoma or mucosa-associated lymphoid tissue (MALT) lymphoma. The management of *H. pylori* infection was consecutively summarized in the Maastricht/Florence Consensus Report [42]. The indications for endoscopy-based diagnosis vary according to the a priori chance of malignancy or previous treatments, and are beyond the scope of this guideline.

During such procedures, biopsies should be performed in the antrum and corpus. The need to assess both compartments is drawn from indirect evidence of the patchy distribution in the corpus in surgical specimens and that, with age and expansion of pyloric glands, a distal to proximal gastric spread of *H. pylori* occurs [43–45]. Moreover, according to the management of precancerous conditions and lesions in the stomach (MAPS) guidelines, biopsies should be taken with the purpose of staging atrophy/intestinal metaplasia as this will affect the allocation to different surveillance strategies [46]. Different containers should be used for specimens from the antrum and the corpus. A single container may be enough according to local expertise, both of the pathologists and the endoscopists, after proper training and if the endoscopic risk of extensive intestinal metaplasia is diminutive or during surveillance of individuals with known atrophic status [47]. If staging systems are to be used in patients with atrophy or intestinal metaplasia (e. g. OLGA, OLGIM), a biopsy in the angle should also be performed as described extensively in the ESGE MAPS-II guideline.

This evidence refers to the existing ESGE guideline [46]. No new evidence is available on this statement.

3.7 Gastric polyps

Gastric polyps are commonly encountered lesions during routine endoscopy. They are usually asymptomatic and non-neoplastic, and may be found sporadically or in association with polyposis syndromes. Some gastric polyps may have malignant potential. Gastric polyps can be mainly distinguished as fundic gland polyps (FGPs), hyperplastic polyps, and adenomatous polyps and can mostly be classified endoscopically based on their typical endoscopic appearance (▶ **Fig. 2**). Biopsies for classification are therefore superfluous but may be considered if in doubt and if the outcome has clinical relevance. For an endoscopically resectable polyp with the need for a histologic diagnosis, resection is preferred over biopsies, because biopsies may underestimate the neoplastic progression risk owing to sampling error.

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▶ **Fig. 2** Endoscopic images of the various types of gastric polyps: **a** fundic gland polyp; **b** hyperplastic polyp; **c** gastric adenoma (source for Fig. 2c: Dr. S. Mühldorfer).

3.7.1 Fundic gland polyps

RECOMMENDATION
ESGE does not recommend standard biopsies of fundic gland polyps.
Strong recommendation, low quality of evidence.

FGPs are the most frequently encountered gastric polyps. They are usually found in patients with chronic PPI use or in association with polyposis syndromes. A diagnosis of FGPs is often made based on the endoscopic appearance. FGPs are usually present in the fundus and gastric body. They are characterized by their small size (< 10 mm) and luminous, glossy appearance (▶ **Fig. 2a**).

Neoplastic features are rarely found in FGPs, with the exception of FGPs on the background of a polyposis syndrome. Case series of FGPs reveal low grade dysplasia (LGD) in < 1 % of FPGs [48, 49]. There have been limited case reports published on the occurrence of high grade dysplasia (HGD) and gastric carcinoma in FGPs [50–52]. Large (> 10 mm) FGPs seem to have a slightly higher risk for the presence of dysplasia or focal cancer compared with small (< 10 mm) FGPs [53]. The risk of malignant progression of sporadic or PPI-associated FGPs is very low. In cases where FGPs have atypical features, size of > 1 cm, antral location, ulceration, or unusual appearance, biopsies of the FGP can be considered.

3.7.2 Hyperplastic polyps

RECOMMENDATION
ESGE recommends taking biopsies from (or resection of) hyperplastic polyps of > 10 mm.
Strong recommendation, low quality of evidence.

Gastric hyperplastic (hyperplasiogenic) polyps are a result of chronic inflammation of the gastric mucosa, mainly due to *H. pylori* infection or autoimmune gastritis. They appear as solitary, sessile or pedunculated lesions with an eroded surface and are mainly located in the antrum (▶ **Fig. 2b**). Multiple hyperplastic polyps can also be present, usually in association with a hereditary disorder [54].

In the literature, large variations in neoplastic progression rates of gastric hyperplastic polyps are documented. Focal carcinoma can be present in 0 %–8 % of hyperplastic polyps [55–59]. The presence of a hyperplastic polyp appears to be associated with an increased risk, up to 8.5 %, of gastric cancer development in the surrounding gastric mucosa [53, 60].

Large (> 10 mm) hyperplastic polyps are more at risk of harboring dysplastic foci compared with small (< 10 mm) hyperplastic polyps [59, 61]. Recurrence rates after the resection of large hyperplastic polyps are high, up to 55 % has been described [61, 62].

3.7.3 Adenomas

RECOMMENDATION
ESGE recommends biopsies from or, if endoscopically resectable, resection of gastric adenomas.
Strong recommendation, moderate quality of evidence.

Gastric adenomas can be found sporadically or in association with familial polyposis syndrome. They appear as solitary, delineated lesions that are often eroded (▶ **Fig. 2c**). Adenomas can be distinguished as tubular, villous, or tubulovillous adenomas. Histologically, their differentiation can be intestinal or gastric. Gastric differentiation includes pyloric gland adenomas, rare foveolar adenomas, and even more rare oxyntic gland adenomas. They may occur anywhere in the stomach, although they are frequently encountered in the antrum.

Adenomas are associated with atrophic gastritis and gastric cancer development in the surrounding gastric mucosa [63–65]. According to the literature, foci of carcinoma are present in up to 38 % of adenomas [65–67]. Gastric adenomas are precancerous lesions with a risk of neoplastic progression.

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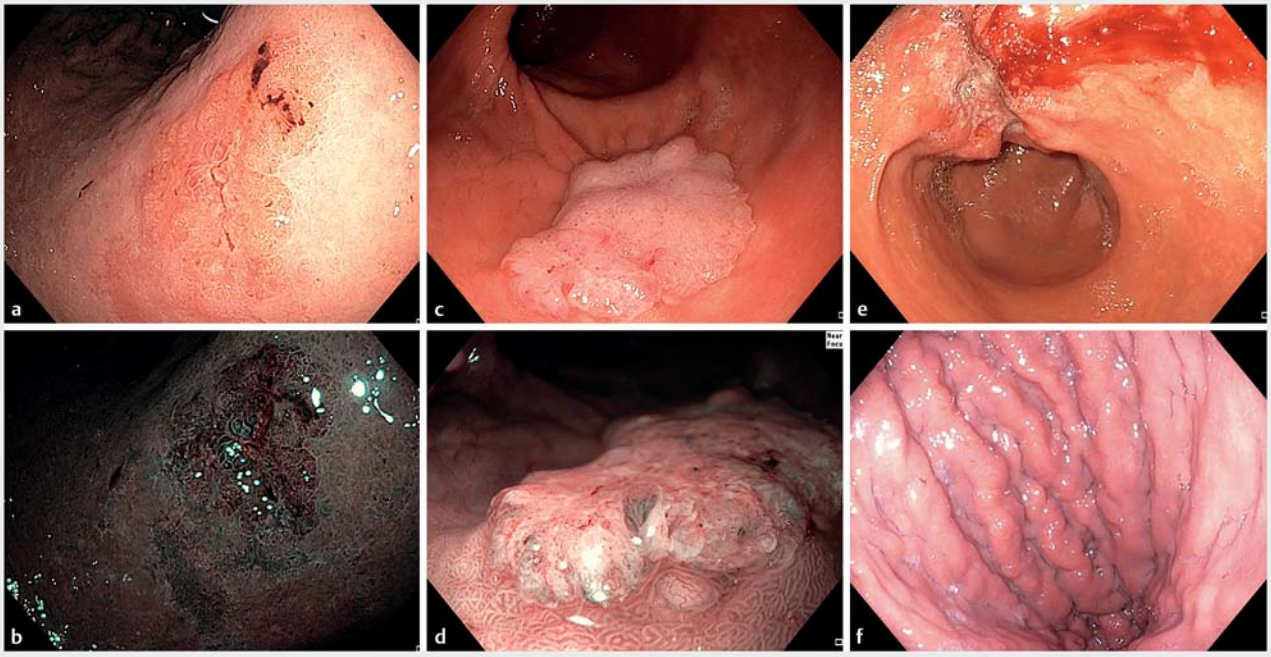

▶ **Fig. 3** Endoscopic images of gastric neoplasia showing: **a, b** early Paris type 0-IIb mucosal gastric cancer on: **a** white-light endoscopy (WLE); **b** narrow-band imaging (NBI); **c, d** early Paris type 0-IIa submucosal gastric cancer on: **c** WLE; **d** near focus with NBI; **e** advanced ulcerative gastric cancer (Borrmann type III); **f** linitis plastica (Borrmann type IV).

3.8 Gastric cancer

RECOMMENDATIONS

ESGE recommends at least six biopsies in cases of suspected advanced gastric cancer.
Strong recommendation, moderate quality of evidence.

ESGE recommends taking only one to two targeted biopsies for lesions that are potentially amenable to endoscopic resection (Paris classification 0-II) to confirm the diagnosis and allow subsequent endoscopic resection.
Strong recommendation, low quality of evidence.

High definition upper gastrointestinal endoscopy with biopsy is the recommended diagnostic modality for all suspected cases of gastric neoplasia. Any lesion suspicious of neoplasia should be sampled and sent to pathology in a separate container.

Early gastric neoplasia is best staged and treated by endoscopic resection. Furthermore, extensive biopsy sampling can jeopardize subsequent endoscopic resection by inducing scarring and submucosal fibrosis. Therefore, for suspected neoplastic gastric lesions that are potentially amenable to endoscopic resection, the number of endoscopic biopsies should be limited. One large retrospective study showed that two endoscopic biopsies yielded a 92.5 % diagnostic accuracy for early gastric neoplasia [68]. Therefore, two biopsies targeted on the most suspicious parts of the lesion should be taken to document the presence of dysplasia or neoplasia. Conversely, for lesions not amenable to endoscopic resection (Paris classification 0-I or 0-III, ulcerated lesions > 3 cm) where surgery or oncologic treatments will be requested, although three endoscopic biopsies will yield a 98.3 % sensitivity, at least six endoscopic biopsies should be obtained, in order to assess the expression of potential biomarkers, such as Her2neu [41, 69]. ▶ **Fig. 3** illustrates examples of early and advanced gastric neoplasia.

RECOMMENDATIONS

ESGE suggests obtaining at least 10 bite-on-bite biopsies in cases of suspected gastric linitis plastica, targeting mucosal abnormalities.
Weak recommendation, low quality of evidence.

ESGE suggests that, where there are negative biopsies and a persisting suspicion of gastric linitis plastica, endoscopy with more extensive biopsies can be repeated. Endoscopic ultrasound (EUS) may be used to target biopsies or fine-needle aspiration/biopsy (FNA/B) of the most affected part of the stomach.
Weak recommendation, low quality of evidence.

Obtaining a histologic diagnosis of gastric linitis plastica (diffuse gastric cancer) can be challenging because tumor cells

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are diffusely spread in the gastric submucosa and stroma, and the mucosa is often normal. Where there is a radiologic or endoscopic suspicion of linitis plastica (presence of large folds, gastric stenosis, circumferential thickening of at least one segment, lack of stomach distensibility, or thickening of the third hyperechogenic layer on endoscopic ultrasound [EUS]) [70], it is advisable to obtain at least 10 bite-on-bite biopsies of the areas that appear most abnormal [71, 72]. If biopsies are negative, these can be repeated to obtain more tissue. As for *CDH1* patients, the Cambridge protocol could be used [71, 72].

In addition, EUS can be used to identify the most affected area of the stomach and to guide target biopsies or fine-needle aspiration/biopsy (FNA/B). FNA of the gastric wall or suspicious lymph nodes has been reported to be helpful in some cases, although data are scarce [73–75]. Other possibilities for obtaining tissue samples from the submucosa, such as submucosal tunneling or prior endoscopic resection of overlying normal mucosa, have been described but evidence on the efficacy and safety of these techniques is very limited [76].

3.9 Celiac disease

RECOMMENDATION

ESGE recommends at least six biopsies from different locations in the duodenum, including two samples from the duodenal bulb, in patients with a suspicion of celiac disease. Biopsies can be collected in the same container.
Strong recommendation, high quality of evidence.

Celiac disease is characterized by typical histologic changes. Mucosal changes appear mostly in the proximal part of the small intestine and may be patchy. Therefore, mucosal changes may be missed if insufficient biopsies are obtained. Studies have demonstrated that in patients with ultrashort celiac disease, pathology may be confined to the duodenal bulb [77]. Including biopsies from the bulb increases the diagnostic yield of endoscopic biopsies for the diagnosis of celiac disease. ESGE adheres to the advice from the World Gastroenterology Organisation and American College of Gastroenterology, namely to obtain at least six biopsies from different sites in the small bowel, including two biopsies from the duodenal bulb, in patients with a suspicion of celiac disease based on endoscopy or serology [78–83].

This represents agreement between merged guidelines [78, 79]. No new evidence is available on this statement.

4 Hepatopancreatobiliary tract

4.1 Liver

Tissue sampling is often required for solid liver lesions or parenchymal liver disease. For both indications, the method of choice is a percutaneous approach, which has been well established and provides core samples for histologic diagnosis. EUS-guided biopsy may be considered in specific situations, such as anatomical issues, failure of percutaneous biopsy, or concomitant indications for EUS. For example, EUS-guided liver biopsy has recently been increasingly used for patients in whom diagnostic EUS is being performed to exclude extrahepatic biliary obstruction [84], evaluate esophageal varices, or perform portal pressure gradient measurement.

4.1.1 Liver tumors

RECOMMENDATION

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

For solid liver masses that are suspicious for malignancy or metastases, histologic tissue sampling can be necessary to decide on further patient management. Generally, tissue sampling of these lesions is performed percutaneously. However, recently, there have been reports on the use of EUS-FNA to sample solid liver masses suspicious for malignancy, with high specimen adequacy and diagnostic accuracy [85]. Although this indication for EUS-FNA is relatively new and not yet clearly defined, one may consider it in cases where lesions are poorly accessible or not detected by percutaneous imaging, or if percutaneous sampling has repeatedly yielded an inconclusive result.

4.1.2 Parenchymal liver disease

RECOMMENDATION

ESGE suggests, where EUS-guided sampling is indicated, the use of larger caliber needles (19G FNA or FNB needles) in cases of suspected parenchymal liver disease.
Weak recommendation, low quality evidence.

EUS-guided liver biopsy has been increasingly used, especially in patients in whom diagnostic EUS is being performed to exclude extrahepatic biliary obstruction. Newer indications may include patients with unknown liver disease undergoing endoscopic evaluation of esophageal varices or portal pressure gradient measurement. Generally, liver biopsy requires histologic evaluation of a specimen of a minimum size and number of portal tracts, making proper needle selection important. A number of studies have evaluated and compared the use of differently sized FNA needles and FNB. Samples adequate for histopathologic evaluation were acquired more often with 19 G FNA needles or FNB, compared with smaller sized needles. Factors such as the technique of biopsy may contribute to the tissue yield rather than the needle itself [86–96].

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4.2 Pancreatic solid masses

RECOMMENDATIONS

ESGE recommends FNA and FNB needles equally for sampling of solid pancreatic masses.
Strong recommendation, high quality evidence.

ESGE suggests using newer generation FNB needles (with forward-facing bevels, fork tip, or crown tip) when the aim is to obtain core tissue (e.g. neuroendocrine neoplasia, need for tumor genotype profiling) and when rapid onsite evaluation (ROSE) is not available.
Weak recommendation, moderate quality evidence.

Since the 2017 ESGE guideline on EUS-guided sampling [97], a number of randomized trials and six meta-analyses comparing FNA and FNB sampling in pancreatic masses have been published. These publications support the recommendation from 2017 that FNA and FNB are recommended equally for the sampling of pancreatic masses [98–114]. Overall, the diagnostic yield does not differ between FNA and FNB needles [110, 113], but some studies indicate that the sample adequacy for histologic evaluation is higher when using FNB compared with FNA needles [99, 100, 111, 112]. There is some evidence suggesting that the use of FNB results in more tissue and higher diagnostic accuracy with fewer needle passes than FNA [98–101, 104–106, 109, 111, 114], which may be relevant in cases where core tissue is required for diagnosis or genetic profiling, or when rapid onsite evaluation (ROSE) is not available. The handling of specimens is addressed below. Technical aspects of EUS-guided tissue sampling are described in the 2017 ESGE clinical guideline [97].

4.3 Bile ducts

The majority of biliary strictures are malignant (70%–80%), with a limited number of causes (i.e. cholangiocarcinoma, pancreatic cancer, gall bladder carcinoma, metastatic disease, or lymphoma). A benign etiology may also be found in 20%–30%, with a much broader differential diagnosis (e.g. IgG4 disease, primary sclerosing cholangitis, infection, post-trauma or post-surgery, and vasculitis, among others) [115]. Early diagnosis of biliary strictures is important for achieving optimal patient outcomes and avoiding unnecessary surgical procedures. The etiology of most biliary strictures can be diagnosed after a basic work-up including transabdominal imaging, endoscopic retrograde cholangiopancreatography (ERCP) with standard transpapillary tissue sampling, or EUS-FNA/B in cases of suspected pancreatic malignancy. Those cases in which this basic work-up is non-diagnostic are referred to as indeterminate biliary strictures.

4.3.1 Indeterminate biliary strictures

RECOMMENDATIONS

ESGE suggests performing peroral cholangioscopy (POC) and/or EUS-guided tissue acquisition in indeterminate biliary strictures. For proximal and intrinsic strictures, POC is preferred. For distal and extrinsic strictures, EUS-guided sampling is preferred, with POC where this is not diagnostic.
Weak recommendation, low quality evidence.

ESGE suggests that performing POC with visually guided biopsies provides the highest chance of confirming malignancy.
Weak recommendation, moderate quality evidence.

Studies have demonstrated a high sensitivity (75%–94%) and diagnostic accuracy (79%–94%) for EUS-guided sampling in indeterminate strictures, which is much higher than the sensitivity (49%–60%) and diagnostic accuracy (60%–61%) for ERCP-guided brush cytology [116–118].

For peroral cholangioscopy (POC), meta-analyses have reported a sensitivity of 72%–94% and a specificity of 87%–99% for cholangioscopy-guided biopsies in indeterminate strictures [119–123]. The sensitivity and accuracy of POC were proved to be higher than those of ERCP in indeterminate strictures in a randomized study [124]. It suggested that POC may be preferable for proximal and intrinsic strictures, whereas EUS-guided tissue sampling may be preferable for distal and extrinsic strictures [124, 125].

5 Miscellaneous

5.1 Biopsy handling, technical aspects

RECOMMENDATIONS

ESGE suggests that mucosal biopsy specimens are released into labelled containers containing adequate amounts of tissue fixation fluid (10% buffered formalin).
Weak recommendation, low quality of evidence.

ESGE recommends obtaining biopsies for microbial testing or fresh biopsy material first, before the biopsy forceps has come into contact with any tissue fixation fluid.
Strong recommendation, low quality of evidence.

ESGE suggests obtaining possible non-neoplastic biopsies before sampling suspected malignant lesions to prevent intraluminal spread of malignant disease.
Weak recommendation, low quality of evidence.

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Proper biopsy handling is of paramount importance in maximizing clinical return and maintaining endoscopy quality standards. Mucosal biopsy specimens should be gently released into labelled biopsy containers containing adequate amounts of tissue fixation fluid. Fixation stops cellular autolysis and prepares tissues for embedding and sectioning. Although a range of fixatives are available for specific downstream purposes (for example glutaraldehyde for electron microscopy studies in cases of pediatric failure to thrive), in general 10 % buffered formalin is the fixative of choice for mucosal biopsies. This is compatible with point-of-care molecular (panel) sequencing tests and the global standard for antigen retrieval in immunohistochemical studies. Comparative studies examining other fixatives in standard endoscopy practice are not available.

If tissue material for microbial testing is required, this should be secured first. If fresh biopsy material is required, for example for molecular testing or enzymatic studies, this should not be obtained with biopsy forceps that have come into contact with any tissue fixation fluid. Studies have suggested that, in some cases, biopsy instrumentation may facilitate intraluminal spread of malignant disease, indicating that, where possible, non-neoplastic biopsies should be secured before any suspected malignant lesions are sampled.

Direct communication with histopathology staff is encouraged to improve quality standards and ensure that specimens are handled in line with institutional practices. For example, work-up of endoluminal resection specimens and essential pathology requisition details are best discussed within the context of multidisciplinary team meetings and benefit greatly from alignment between endoscopy and histopathology staff [126, 127].

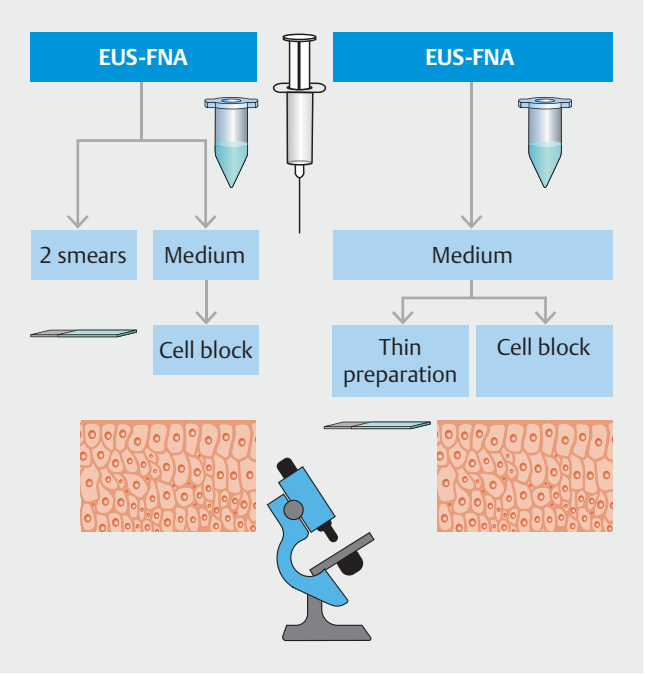
5.2 Type of biopsy forceps

RECOMMENDATION

ESGE suggests the use of a standard cold biopsy forceps, because there is too little benefit in terms of histopathologic outcome to recommend the use of a jumbo biopsy forceps.

Weak recommendation, moderate quality of evidence.

Various studies have examined the impact of biopsy forceps design on tissue adequacy in a pathologist-blinded fashion. Different types of biopsy forceps are available, with serrated jaws, oval beaks, different jaw sizes, and with a spike to be able to contain two biopsies within the cups of the forceps. Jumbo biopsy forceps sample about three times the surface area compared with standard cold biopsy forceps, but importantly do not consistently provide deeper specimens. Despite variations in the designs of different biopsy forceps and their claimed benefits, studies agree that there are no reproducible differences in tissue adequacy or clinically relevant histopathologic outcome [128–131].



▶ **Fig. 4** Diagram of the preparation of tissue specimens obtained by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) into smears and a cell block, or alternatively into liquid-based cytology with a thin preparation as the first step and a cell block as the second step.

5.3 Preparation of EUS-FNA material

RECOMMENDATION

ESGE suggests dividing EUS-FNA material into smears (two per pass) and liquid-based cytology (LBC), or the whole of the EUS-FNA material can be processed as LBC, depending on local experience.

Weak recommendation, low quality evidence.

Adequate preparation of FNA samples and dedicated training of cytotechnologists and pathologists are the prerequisites for achieving optimal results. Cytologic tissue can be evaluated using smears or liquid-based cytology (LBC), or both. LBC material can be further processed as thin preparations and/or cell blocks.

Depending on the practical experience of the involved pathology personnel, EUS-FNA material could be divided into smears (two per pass) and a cell block for additional evaluation. Alternatively, the whole of the EUS-FNA material can be processed as LBC, with a thin preparation as the first step and a cell block as the second step (▶ **Fig. 4**) [132–138].

Disclaimer

The legal disclaimer for ESGE guidelines [139] applies to this Guideline.

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Competing interests

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