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# Endoscopic management of subepithelial lesions including neuroendocrine neoplasms: European Society of Gastrointestinal Endoscopy (ESGE) Guideline



## Authors

Pierre H. Deprez<sup>1</sup> , Leon M.G. Moons<sup>2</sup>, Dermot O'Toole<sup>3</sup>, Rodica Gincul<sup>4</sup>, Andraida Seicean<sup>5</sup>, Pedro Pimentel-Nunes<sup>6</sup>, Gloria Fernández-Esparrach<sup>7</sup>, Marcin Polkowski<sup>8</sup> , Michael Vieth<sup>9</sup>, Ivan Borbath<sup>1</sup>, Tom G. Moreels<sup>1</sup>, Els Nieveen van Dijkum<sup>10</sup>, Jean-Yves Blay<sup>11</sup>, Jeanin E. van Hooft<sup>12</sup>

## Institutions

- 1 Department of Hepatogastroenterology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium
- 2 Divisie Interne Geneeskunde en Dermatologie, Maag-, Darm- en Leverziekten, Universitair Medisch Centrum Utrecht, Utrecht, The Netherlands
- 3 Neuroendocrine Tumor Service, ENETS Centre of Excellence, St. Vincent's University Hospital and Department of Clinical Medicine, Trinity College Dublin, University of Dublin St. James's Hospital, Dublin, Ireland
- 4 Service de Gastroentérologie et Endoscopie Digestive, Hôpital Privé Jean Mermoz, Lyon, France
- 5 Regional Institute of Gastroenterology and Hepatology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
- 6 Department of Gastroenterology, Portuguese Oncology Institute of Porto; Department of Surgery and Physiology, Center for Research in Health Technologies and Information Systems (CINTESIS), Faculty of Medicine, University of Porto, Portugal
- 7 Endoscopy Unit, Institut de Malalties Digestives i Metaboliques, Hospital Clínic, Barcelona, Spain
- 8 Department of Gastroenterology, Hepatology and Clinical Oncology, Center for Postgraduate Medical Education, and Department of Oncological Gastroenterology, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland
- 9 Institut of Pathology, Friedrich-Alexander University Erlangen-Nuremberg, Klinikum Bayreuth, Bayreuth, Germany
- 10 Department of Surgery, Amsterdam UMC, Cancer Center Amsterdam, University of Amsterdam, The Netherlands
- 11 Centre Léon Bérard, Université Claude Bernard Lyon 1, Lyon, France

12 Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands

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## Appendix 1s

Supplementary material is available under <https://doi.org/10.1055/a-1751-5742>

## Corresponding author

Pierre H. Deprez, MD PhD, Hepato-gastroenterology Dpt, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Avenue Hippocrate 10, 1200 Brussels, Belgium  
pdeprez@saintluc.uclouvain.be

## MAIN RECOMMENDATIONS

1 ESGE recommends endoscopic ultrasonography (EUS) as the best tool to characterize subepithelial lesion (SEL) features (size, location, originating layer, echogenicity, shape), but EUS alone is not able to distinguish among all types of SEL.

Strong recommendation, moderate quality evidence.

**2** ESGE suggests providing tissue diagnosis for all SELs with features suggestive of gastrointestinal stromal tumor (GIST) if they are of size >20 mm, or have high risk stigmata, or require surgical resection or oncological treatment. Weak recommendation, very low quality evidence.

**3** ESGE recommends EUS-guided fine-needle biopsy (EUS-FNB) or mucosal incision-assisted biopsy (MIAB) equally for tissue diagnosis of SELs  $\geq 20$  mm in size.

Strong recommendation, moderate quality evidence.

**4** ESGE recommends against surveillance of asymptomatic gastrointestinal (GI) tract leiomyomas, lipomas, heterotopic pancreas, granular cell tumors, schwannomas, and glomus tumors, if the diagnosis is clear.

Strong recommendation, moderate quality evidence.

**5** ESGE suggests surveillance of asymptomatic esophageal and gastric SELs without definite diagnosis, with esophagogastroduodenoscopy (EGD) at 3–6 months, and then at 2–3-year intervals for lesions <10 mm in size, and at 1–2-year intervals for lesions 10–20 mm in size. For asymptomatic SELs >20 mm in size that are not resected, ESGE suggests surveillance with EGD plus EUS at 6 months and then at 6–12-month intervals.

Weak recommendation, very low quality evidence.

**6** ESGE recommends endoscopic resection for type 1 gastric neuroendocrine neoplasms (g-NENs) if they grow larger

than 10 mm. The choice of resection technique should depend on size, depth of invasion, and location in the stomach.

Strong recommendation, low quality evidence.

**7** ESGE suggests considering removal of histologically proven gastric GISTs smaller than 20 mm as an alternative to surveillance. The decision to resect should be discussed in a multidisciplinary meeting. The choice of technique should depend on size, location, and local expertise.

Weak recommendation, very low quality evidence.

**8** ESGE suggests that, to avoid unnecessary follow-up, endoscopic resection is an option for gastric SELs smaller than 20 mm and of unknown histology after failure of attempts to obtain diagnosis.

Weak recommendation, very low quality evidence.

**9** ESGE recommends basing the surveillance strategy on the type and completeness of resection. After curative resection of benign SELs no follow-up is advised, except for type 1 gastric NEN for which surveillance at 1–2 years is advised. Strong recommendation, low quality evidence.

**10** For lower or upper GI NEN with a positive or indeterminate margin at resection, ESGE recommends repeating endoscopy at 3–6 months and another attempt at endoscopic resection in the case of residual disease.

Strong recommendation, low quality evidence.

## SOURCE AND SCOPE

This Guideline is an official statement from the European Society of Gastrointestinal Endoscopy (ESGE). It covers the endoscopic diagnosis and management of subepithelial lesions (including neuroendocrine neoplasms) in the upper and lower gastrointestinal tract, describing the role of EUS, the tissue acquisition techniques, the surveillance of these lesions, and the indications and methods for endoscopic resection.

tine endoscopy and are most often found in the stomach but may be also found throughout the digestive tract. Characterization mainly depends on endoscopic ultrasonography (EUS) examination and tissue acquisition. Data on the management of these lesions are still controversial because of the lesions' rare occurrence, their considerable histopathological variety, and their usually weak malignant potential.

The European Society of Gastrointestinal Endoscopy (ESGE) commissioned this Guideline to evaluate the role of endoscopy and EUS in the workup of these lesions, the need for tissue acquisition with the advent of new fine-needle biopsy (FNB) devices and biopsy techniques, and the indications for no surveillance, surveillance, or for resection. Various endoscopic resection techniques with high technical success have recently been reported, mostly in case series or retrospective reports. However evident selection biases raise the concern of unjustified resection (of benign lesions with low risk of malignancy). It seemed therefore appropriate to deliver up-to-date guidelines for the management of SELs and NENs, to optimize diagnosis with more frequent tissue acquisition attempts, and to suggest or recommend resection only for lesions at risk of malignancy or causing symptoms. "Just because you can resect a lesion, doesn't mean you should do it."

## Introduction

Subepithelial lesions (SELs) of the gastrointestinal (GI) tract are tumors that originate from the muscularis mucosa, submucosa, or muscularis propria. The term subepithelial lesion is preferred to the term submucosal tumor, which should be reserved for those that originate from the submucosal layer. Neuroendocrine neoplasms (NENs) usually affect both the mucosa and submucosa and may involve any part of the GI tract but their behavior and management varies according to the different sites affected. SELs and NENs are usually detected during rou-

**ABBREVIATIONS**

|               |   |
|---------------|---|
| <b>CAG</b>    | chronic atrophic gastritis  |
| <b>CH-EUS</b> | contrast-enhanced harmonic endoscopic ultrasound                  |
| <b>CT</b>     | computed tomography   |
| <b>d-NEN</b>  | duodenal neuroendocrine neoplasm                                  |
| <b>ECL</b>    | enterochromaffin-like   |
| <b>EFTR</b>   | endoscopic full-thickness resection                               |
| <b>EGD</b>    | esophagogastroduodenoscopy  |
| <b>EMR</b>    | endoscopic mucosal resection                                      |
| <b>ENETS</b>  | European Neuroendocrine Tumor Society                             |
| <b>ER</b>     | endoscopic resection  |
| <b>ESD</b>    | endoscopic submucosal dissection                                  |
| <b>ESE</b>    | endoscopic submucosal excavation                                  |
| <b>ESGE</b>   | European Society of Gastrointestinal Endoscopy                    |
| <b>EUS</b>    | endoscopic ultrasonography  |
| <b>EUS-E</b>  | endoscopic ultrasonography with elastography                      |
| <b>EUS-TA</b> | endoscopic ultrasonography tissue acquisition                     |
| <b>FNA</b>    | fine-needle aspiration  |
| <b>FNB</b>    | fine-needle biopsy  |
| <b>g-NEN</b>  | gastric neuroendocrine neoplasm                                   |
| <b>GCT</b>    | granular cell tumor   |
| <b>GIST</b>   | gastrointestinal stromal tumor                                    |
| <b>GRADE</b>  | Grading of Recommendations Assessment, Development and Evaluation |
| <b>MDT</b>    | multidisciplinary team  |
| <b>MEN1</b>   | multiple endocrine neoplasia type 1                               |
| <b>MIAB</b>   | mucosal incision-assisted biopsy                                  |
| <b>MOSE</b>   | macroscopic on-site evaluation                                    |
| <b>MRI</b>    | magnetic resonance imaging  |
| <b>NEN</b>    | neuroendocrine neoplasm   |
| <b>NET</b>    | neuroendocrine tumor  |
| <b>PET</b>    | positron emission tomography                                      |
| <b>r-NEN</b>  | rectal neuroendocrine neoplasm                                    |
| <b>RCT</b>    | randomized controlled trial                                       |
| <b>ROSE</b>   | rapid on-site evaluation  |
| <b>SEL</b>    | subepithelial lesion  |
| <b>WLE</b>    | white-light endoscopy   |
| <b>ZES</b>    | Zollinger–Ellison syndrome  |

**Methods**

ESGE commissioned this Guideline (Guideline Committee Chair, J.v.H.) and appointed a guideline leader (P.D.) who invited the listed authors to participate in the project development. The key questions were prepared by the coordinating team (J.v.H., P.D.) and then approved by the other members. The coordinating team formed task force subgroups, each with its own leader, who were assigned key questions (see **Appendix 1s**, available online-only in Supplementary material).

Each task force performed a systematic literature search to prepare evidence-based and well-balanced statements on their assigned key questions. The literature search was performed in Medline and Embase for publications in English, focusing on meta-analyses and fully published prospective studies, particu-

larly randomized controlled trials (RCTs), performed in humans, up till September 2020. Retrospective analyses and pilot studies were also included if they addressed topics not covered in the prospective studies. Articles were first selected by title; their relevance was then confirmed by review of the corresponding manuscripts, and articles with content that was considered irrelevant were excluded.

All selected important articles were individually assessed and graded for level of evidence and strength of recommendation according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [1,2]. Each task force proposed statements on their assigned key questions that were discussed and voted on during virtual meetings in November 2020 and February 2021. In March 2021, a draft prepared by the subgroup leaders and coordinating team was sent to all group members. The manuscript was also reviewed by a member of the ESGE Governing Board and an external reviewer, and sent for further comments to the ESGE national societies and individual members. After agreement on a final version, the manuscript was submitted to the journal *Endoscopy* for publication. All authors agreed on the final revised manuscript.

This Guideline was issued in 2022 and will be considered for review and update in 2027 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>.

**Diagnosis of subepithelial lesions (SELs) and neuroendocrine neoplasms (NENs)****RECOMMENDATION**

ESGE does not recommend white-light endoscopy or advanced endoscopic imaging techniques for characterization of SEL subtypes.

Strong recommendation, low quality evidence.

**SELs**

Most SELs are asymptomatic and detected incidentally on endoscopy performed for unrelated reasons. Symptomatic cases present as GI bleeding and subsequent iron-deficiency anemia, and sometimes as abdominal pain related to obstruction of the GI lumen by a tumor located near the cardia, pylorus, ileocecal valve, or rectum [3]. Whereas their endoscopic aspect is generally characterized by small (<20 mm) rounded protuberances with normal overlying mucosa, there are very few specific characteristics that will identify SEL subtypes that can be observed using conventional white-light endoscopy. Some lesions may present with a central depression or umbilication. As far as color is concerned, most have normal-looking overlying mucosa, but some lesions may be more yellowish or whitish, others more reddish. The consistency of a SEL can be assessed using a closed biopsy forceps as a poking device, with the pillow or cushion sign considered 98% specific

for lipoma diagnosis [4]. Large lesion size, growth during follow-up, or the presence of a (bleeding) ulceration may be signs suspicious of malignant transformation [5]. No comparative studies are available on the use of magnifying endoscopy or chromoendoscopy in the endoscopic diagnosis of SELs, probably because of the limited use of those techniques in these lesions that usually have normal overlying mucosa.

SELs are most frequently found in the stomach followed by esophagus, duodenum, and large intestine. Location appears important in the clinical diagnosis, for example leiomyomas are most often found in the lower two-thirds of the esophagus, and gastrointestinal stromal tumors (GISTs) are the most frequent tumor in the stomach. The different types of SEL addressed by the present Guideline are described in ►Table 1. Asymptomatic SELs with features suggestive of varices, pancreatic rests (small umbilicated SELs in the antrum), or lipoma do not need any further workup or resection, and will therefore not be further discussed in this Guideline.

MicroGISTs (<10 mm), and miniGISTs (10–20 mm) are observed in up to 20% of individuals in autopsy series [6]. This is in marked contrast to the low incidence of overtly malignant GISTs of larger size; this is reported to be close to 1.1 per million in most studies, but few of those studies are based on a systematic registry [7]. Of note, these small tumors are not included in most registries since their natural history is still unclear. GISTs are characterized by a wide variety of mutations, in the receptor tyrosine kinases KIT or PDGFRA, which are mutually exclusive [8–10]. If a biopsy or resection is performed, it is important that a dedicated multidisciplinary tumor board should evaluate the utility of genomic characterization (this is mandatory if a medical treatment is proposed) [7].

## NENs

Neuroendocrine tumors (NETs) can involve any part of the GI tract but their behavior and management varies according to the site affected. The term neuroendocrine neoplasm (NEN) is now preferred, as it encompasses both well-differentiated NETs and poorly differentiated neuroendocrine carcinomas that share common histologic, immunophenotypic, and ultrastructural neuroendocrine features. Asymptomatic NENs of the GI tract are increasingly discovered incidentally because of the expanding use of endoscopy especially as part of screening for upper and lower GI neoplasms [11]. Other NENs result in functional symptoms from overexpression or secretion of peptides or hormones, causing a specific set of symptoms or clinical syndrome (e.g., gastrinomas or carcinoid syndrome).

Endoscopically NENs are usually found as a rounded lesion, often with a lighter (yellow) or darker (red) color as compared to the surrounding mucosa. In the stomach NENs can present as multifocal subepithelial lesions. These are usually diagnosed by standard mucosal biopsy techniques [12]. There is a stark contrast between the usually aggressive nature of esophageal NENs (often high grade small-cell type in nature) and the mostly more indolent nature of gastric NENs, so that NENs from each GI site warrant separate discussion (►Table 2). Pathological classification should be performed in accordance with the staging and grading systems of the Union for International Cancer

Control (UICC) and the European Neuroendocrine Tumor Society (ENETS) [13].

## Role of EUS in detection and characterization of SELs

### RECOMMENDATION

ESGE recommends endoscopic ultrasonography (EUS) as the best tool to characterize SEL features (size, location, originating layer, echogenicity, shape), but EUS alone is not able to distinguish among all types of SEL.

Strong recommendation, moderate quality evidence.

EUS can distinguish SELs from extrinsic compression (92% sensitivity) and is able to determine their layer of origin, size, echogenicity, and margins [14]. The reported accuracy for identification of SEL originating layer in one prospective and three retrospective studies was 63%–74.6%; this was higher (82.6%–100%) for SELs originating from the submucosal layer [15–18]. Lesion size was measured with a 87% accuracy compared to resected specimens, with limitations in the case of large lesions beyond the ultrasound penetration distance [19].

EUS features are pathognomonic for lipoma and varices, and suboptimal for other types of SEL (accuracies 43%–67%) [20]. The reported EUS accuracy is 77%–89% for GIST diagnosis [20], 50%–100% for NEN [17,21], 57%–61% for ectopic pancreas (related to heterogeneous layer origin), and 37.5%–82.6% for leiomyoma [16,20] (because of common features with GIST). The accuracy for differential diagnosis of small gastric SELs by EUS is, however, poor and ranges from 45.5% to 48.0% [21]. Most of the incorrect EUS diagnoses involved hypoechoic lesions originating in the fourth echo-layer, and specifically low grade GISTs misdiagnosed as leiomyomas [19]. Inhomogeneity, hyperechogenic spots, marginal halo, and higher echogenicity as compared with the surrounding muscle layer appeared more frequently in GIST than in leiomyoma; two of these features distinguished them with 89.1% sensitivity and 85.7% specificity [22]. EUS digital analysis with grayscale and histograms may show higher and more uniform echogenicity in GISTs compared to leiomyomas [23]. Retrospective studies demonstrate a better global accuracy using artificial intelligence (90% vs. 53% for SELs  $\geq 20$  mm and 86.3% vs. 73.2% for SELs  $< 20$  mm) [24]. Miniprobe EUS gave better results, but no comparison study with conventional EUS exists. One prospective and three retrospective studies showed that, for GISTS, size of  $> 30$ –40 mm and heterogeneous echogenicity (echogenic foci or cystic space) are predictive for intermediate/high malignant risk with 80%–92% sensitivity [19,22,25,26]. In two retrospective studies, the detection rate on computed tomography (CT) compared to EUS was 69% vs. 85.3% (with CT there was a higher detection rate for SELs  $> 10$  mm) [27,28]. The CT accuracy for specific diagnosis was lower than in EUS (50.9% vs. 64.2%) [20]; in lesions  $> 27$  mm CT showed improved delineation of malignant features.

► Table 1 Types of subepithelial lesion (SEL) in the gastrointestinal (GI) tract.

| SEL type                           | Originating layer | Echogenicity   | Size, mm | Border                         | Location in gastro-intestinal (GI) tract             |
|------------------------------------|-------------------|--|----------|--------------------------------|--|
| Duplication cyst                   | 3rd/ external     | Anechoic, without Doppler signal   |          | Sharp, sometimes with 5 layers | Any  |
| Varices                            | 3rd               | Anechoic, with Doppler signal  |          | Sharp, serpiginous shape       | Any  |
| Lymphangiomas                      | 3rd               | Anechoic with internal septa, without Doppler signal   |          | Sharp                          | Any  |
| Granular cell tumor                | 2nd, 3rd          | Hypoechoic, higher echogenicity compared to the muscle layer<br>Heterogeneous  | <20      | Variable                       | Esophagus  |
| Gastric inflammatory fibroid polyp | 2nd, 3rd          | Hypoechoic<br>Homogeneous<br>Polypoid  | 8–18     | Indistinct                     | Antrum<br>Small bowel                                |
| Neuroendocrine neoplasms           | 2nd, 3rd          | Hypoechoic/intermediate hypo-echogenicity/ hyperechoic   |          | Sharp                          | Stomach<br>Small bowel<br>Rectum                     |
| Ectopic pancreas                   | 3rd, 4th          | Hypoechoic<br>Heterogeneous echotexture, with cysts or ducts inside<br>Central umbilication                            | <5–20    | Indistinct                     | Antrum up to 88%<br>Gastric body<br>Duodenum 16%     |
| Leiomyoma                          | 2nd/4th           | Hypoechoic, similar to the muscle layer, lower than for GIST<br>Homogeneous<br>Rarely multiloculated or leiomyomatosis | Varies   | Sharp                          | Esophagus or stomach or anywhere in the GI tract     |
| GIST low risk                      | 2nd/4th           | Hypoechoic<br>Heterogeneous<br>Hypervascular   | <30      | Sharp when benign              | Esophagus 5%<br>Stomach<br>Small intestine<br>Rectum |
| GIST, high risk                    | 2nd/4th           | Hypoechoic<br>Heterogeneous, with cystic space or echogenic foci   | >30      | Irregular                      | Esophagus 5%<br>Stomach<br>Small intestine<br>Rectum |
| Lymphoma                           | 2nd, 3rd, 4th     | Hypoechoic   | Varies   | Irregular                      | Gastric<br>Small intestine                           |
| Schwanomma                         | 4th               | Hypoechoic<br>Homogeneous, sometimes with marginal halo  |          | Sharp                          | Gastric body   |
| Glomus tumor                       | 3rd/4th           | Hypo-/hyperechoic<br>Hypervascular, with internal echo   | Varies   | Sharp                          | Any  |
| Endometriosis                      | 4th, 5th          | Hypoechoic<br>Heterogeneous,<br>Might extend into the rectovaginal septum  | 20–50    | Irregular                      | Rectum<br>Sigmoid colon                              |
| Lipoma                             | 3rd               | Hyperechoic<br>Homogeneous   | Varies   | Sharp                          | Any  |
| Brunner gland hyperplasia          | 2nd or 3rd        | Iso-/hyperechoic<br>Homogeneous<br>Sometimes with duct inside  |          | Sharp                          | Duodenal bulb  |
| Metastasis                         | Any               | Hypoechoic   |          | Irregular                      | Any  |

GIST, gastrointestinal stromal tumor.

► **Table 2** General classification of gastrointestinal (GI) neuroendocrine neoplasms (NENs).

| GI site   | Pathology  | Incidence   | Endoscopy  | Behavior  |
|---|--|---|--|---|
| <b>Esophageal</b>   | Mostly high grade neuroendocrine carcinomas (NECs)<br>90% small-cell <sup>1</sup> , 10% large-cell<br>High mitotic index and Ki-67   | Rare (0.3% to 3.8% of all esophageal carcinomas)                | Flat or exophytic lesion, ± central ulceration<br>Mid to lower third<br>Can be multiple<br>Nodes (>50%)  | 52% survival at 3 years (median survival 45 months)   |
| <b>Gastric</b>  |  | 0.3/100 000<br>Increased over 15-fold in past 4 decades         |  |   |
| Gastric type 1 (Hypergastrinemia in autoimmune gastritis with chronic atrophic gastritis)<br>Male/female ratio (1/2.5)  | Majority well-differentiated<br>Low mitotic index and grade, low Ki-67<br>Background gastric atrophy, ECL <sup>2</sup> hyperplasia, intestinal metaplasia  | 70%–80% of all gastric NENs                                     | Small, multiple polyps or nodules (<10 to 20 mm); flat, sessile, macular, ulcerated when large   | Slow growing<br>Metastatic rate 3% to 7%<br>5-year disease-specific survival 98%–100%   |
| Gastric type 2 (Hypergastrinaemia in Zollinger–Ellison syndrome [ZES] and multiple endocrine neoplasia [MEN]-1)         | Majority well-differentiated<br>Low to intermediate mitotic index and Ki-67  | 6% of gastric NENs  | Like type 1 but thickened gastric folds (due to ZES) and often signs of high acid-related mucosal damage<br>Duodenal NEN associated (in ZES and MEN1)  | Metastasis rate 10%–30%<br>Prognosis often more related to other NENs associated with MEN1                                    |
| Gastric type 3 (Sporadic)   | Well- to poorly differentiated<br>Moderate to high mitotic index and Ki-67   | 15%–20% of gastric NENs   | Solitary, mostly antrum, sessile<br>Normal background gastric mucosa   | Metastasis rate 70%   |
| <b>Duodenal</b><br>(Gastrinomas<br>Gangliocytic paraganglioma [GCPG]<br>Nonfunctional duodenal NEN)                     | Varied pathology<br>Mostly well-differentiated<br>Ampullary periampillary more aggressive (poorly differentiated or higher grades)   | Gastrinomas, 48%<br>GCPG, 30%–40%<br>Nonfunctional NEN, 10%–20% | Gastrinomas, duodenal bulb (often occult even if nodal metastasis present), first part of the duodenum (single; if multiple, suspect MEN1)<br>GCPG, sessile single ampulla, periampillary ± ulceration<br>Nonfunctional lesions (often small sessile nodules 10–20 mm) | Gastrinomas, often metastatic (60%) even if small<br>GCPG (nodal metastasis, 30%)<br>Nonfunctional (varied)                   |
| <b>Small intestine</b><br>Majority ECL cells with serotonin production (carcinoid syndrome)<br>Nonfunctional also occur | Well-differentiated.<br>Small lesions can have metastases (node often larger than primary)   | 26% of all GI well-differentiated NENs                          | Usually <20 mm<br>>70% in ileum with distal ileum most common<br>Up to 30% multiple along small intestine<br>Small sessile or submucosal-like terminal ileal lesion  | Lymph node metastasis 36%–39%<br>Distant metastasis 64%   |
| <b>Colorectal</b>   | <i>Colonic:</i><br>Well- to poorly differentiated, moderate to high mitotic index and Ki-67; ECL origin  | Rare  | Right and transverse more common   | Metastases >50%   |
|   | <i>Rectal:</i><br>Mostly well-differentiated; occasionally higher grades; L cell (glucagon-like peptide [GLP]), pancreatic polypeptide (PP)/peptide tyrosine tyrosine (PYY) cells<br>Chromogranin A often absent | 1.04/100 000 (increasing in incidence)                          | Mid to lower rectum<br>Size usually <20 mm<br>Varied morphology (sessile, submucosal-like, umbilicated, polypoid)<br>Different pit pattern from adenomas or hyperplastic polyps at WLE or electronic chromoendoscopy   | Localized 75%–85% Survival: median overall survival 24.6 years<br>Small, localized, 5-year survival >90%<br>N1 5-year 54%–74% |

ECL, enterochromaffin-like; WLE, white-light endoscopy.

<sup>1</sup> Also known in the literature as small-cell carcinoma of the esophagus.

<sup>2</sup> ECL cells hyperplasia due to high gastrin may ultimately lead to clustering of ECL cells into small ECLoma, and eventually the development of type 1 gastric-NEN.

No data are available on EUS assessment of local recurrence after resection, except for one prospective series that showed signs of residual tissue in 1.4% of cases, but no clinical recurrence [16].

### Is there a role for EUS image enhancement techniques: contrast-enhanced harmonic EUS (CH-EUS), and endoscopic ultrasonography with elastography (EUS-E)?

#### RECOMMENDATION

ESGE suggests that CH-EUS can be used for characterization of SELs in the upper digestive tract and estimation of the malignant potential of GISTs, but it cannot replace EUS tissue acquisition. Moreover, ESGE suggests that there is insufficient evidence to recommend EUS-E in the diagnosis and management of SELs.

Weak recommendation, low quality evidence.

CH-EUS can visualize the microvascularization of SELs and improves their characterization, hyperenhancement being specific for GIST whereas hypoenhancement is specific for benign SEL. One meta-analysis [29], three prospective studies [30–32] and several retrospective studies (for example [33–36]) reported usefulness of CH-EUS and EUS-E for characterization of subepithelial lesions in the upper digestive tract. These studies enrolled only small numbers of patients; therefore, confidence in the estimate of effect is limited. They showed that hyperenhancement had sensitivities, specificities, and accuracies ranging from 81.1% to 100%, 60% to 100% and 82.2% to 98%, respectively, for diagnosing GIST. In a meta-analysis assessing the value of CH-EUS in distinguishing between GISTs and other benign SELs, with a total of 187 patients, the pooled sensitivity and specificity were 89% (95%CI 82%–93%) and 82% (95%CI 66%–92%), respectively, with an area under the receiver operating characteristic (AUROC) of 0.89 [29].

Only three nonanalytic studies reported on EUS-E for the differential diagnosis between GIST and benign SEL, showing a good sensitivity but low specificity [32, 37, 38].

Concerning further characterization of GIST, there are six reports on CH-EUS for the differential diagnosis between low grade and high grade malignancy GIST [29–31, 34, 39, 40]. These reports showed that for diagnosing high grade malignancy GIST, sensitivity ranged from 63.6% to 100% and specificity from 63% to 100%. Among those, three reports showed that irregular intratumoral vessels were a sign of high grade malignancy GIST with sensitivity and specificity from 75% to 100% and 63% to 100%, respectively [30, 31, 34], and with 83% accuracy in the only prospective study [30]. Among five studies [30, 31, 34, 37, 39] included in a meta-analysis, the pooled sensitivity and specificity of CH-EUS in distinguishing the malignant potential of GIST were 96% (95%CI 90%–99%) and 53% (95%CI 40%–66%), respectively [29].

### When is tissue required?

#### RECOMMENDATION

ESGE suggests providing tissue diagnosis for all SELs with features suggestive of GIST, if they are of size > 20 mm, or have high risk stigmata, or require surgical resection or oncological treatment.

Weak recommendation, very low quality evidence.

There is not enough evidence in the literature to suggest that EUS tissue acquisition (EUS-TA) is required from all SELs or only from those > 20 mm or with high risk stigmata [41]. The European Society for Medical Oncology [42], the Japanese GIST Guideline Subcommittee [43] and the Chinese Society of Clinical Oncology [44] recommend surgical resection when a SEL is immunohistologically diagnosed as a GIST, even when smaller than 20 mm. Therefore, tissue sampling for immunohistochemical analysis using EUS-TA or biopsy is required for a definite diagnosis of GIST before surgery or chemotherapy [5]. In contrast, the National Comprehensive Cancer Network guidelines recommend that small GISTs of < 20 mm may be periodically followed up by EUS when they lack high risk features [45]. In cases with severe bleeding when there is no contraindication to resection, biopsy should be discouraged and resection should be discussed by a multidisciplinary team (MDT).

### Which techniques of tissue acquisition should be preferred and in which order?

#### RECOMMENDATION

ESGE recommends EUS-guided fine-needle biopsy (EUS-FNB) or mucosal incision-assisted biopsy (MIAB) equally for tissue diagnosis of SELs ≥ 20 mm in size.

Strong recommendation, moderate quality evidence.

#### RECOMMENDATION

ESGE suggests using MIAB (first choice) or EUS-FNB (second choice) for tissue diagnosis of SELs < 20 mm in size.

Weak recommendation, low quality evidence.

### Mucosal incision-assisted biopsy (MIAB)

Endoscopic forceps biopsy from the mucosa overlying SELs often fails to provide tumor tissue for pathologic evaluation [46]. Therefore, special biopsy techniques have been developed such as the bite-on-bite, jumbo, and snare methods. Newer techniques involve unroofing the SEL to expose its surface, or submucosal tunneling allowing direct biopsy sampling of the tumor [47]. Several variants of this technique exist; here they are collectively referred to as MIAB [48, 49]. MIAB was evaluated in a meta-analysis of 7, mostly retrospective series including a

total of 159 patients with upper GI SELs (mean diameter 21 mm, 94.8% located in the stomach). The overall pooled diagnostic yield, defined as the rate of samples adequate for pathological diagnosis, was 89% (95%CI 82.7%–93.5%). No perforations were observed and the rate of clinically significant bleeding was 5% (95%CI 0.36%–12.9%) [50].

An MIAB variant, endoscopic submucosal dissection (ESD)-assisted deep biopsy, was evaluated in a meta-analysis of 7 prospective and retrospective series including a total of 209 patients with upper GI SELs (mean diameter 18.8 mm, 96% located in the stomach). The overall pooled diagnostic yield, defined as the rate of samples adequate for pathological diagnosis, was 95% (95%CI 84.9%–99.9%), with significant heterogeneity among the studies [51]. One case of perforation was observed, that was managed endoscopically. The rate of major bleeding was 0.07% (95%CI 0.00%–2.32%) [51].

MIAB was compared with EUS-FNA and EUS-FNB in three randomized controlled trials (RCTs) [48, 49, 52]. No significant differences in the rates of diagnostic samples or adverse events were observed; however, these RCTs were powered to detect only large differences between the compared techniques. A subgroup analysis in one of these RCTs showed advantages of MIAB over FNA for tumors <20 mm [49]. This observation was confirmed by a retrospective study of 177 patients using propensity score-matching analysis [53]. MIAB however required significantly longer procedural time compared with EUS-FNA/B [53]. The decision to perform MIAB for diagnosis should take into account the risk of bleeding and its management, and the fact that it might preclude subsequent endoscopic resection using submucosal tunneling.

#### Endoscopic ultrasonography tissue acquisition (EUS-TA)

A meta-analysis of 17 studies evaluating a total of 978 EUS-TA procedures for upper GI SELs, showed a pooled diagnostic rate of 59.9% (95%CI 54.8%–64.7%) with significant heterogeneity among the studies [54]. The studies included in this meta-analysis were published between 2004 and 2014 and evaluated mostly FNA needles or the QuickCore Tru-Cut needle. Newer FNB needles, designed to obtain histologic samples, were used in only two studies [54].

In another meta-analysis of 10 studies with 669 patients [55], comparing FNB and FNA, FNB outperformed FNA in all diagnostic outcomes evaluated: namely, adequate sample rate, optimal histologic core procurement rate, diagnostic accuracy, and number of passes needed to obtain diagnostic samples. The needles used were predominantly 22G and the evaluated FNB needle designs included reverse-bevel ProCore (Cook Medical), Acquire (Boston Scientific), and SharkCore (Medtronic). The ProCore needle was assessed in all the RCTs in the meta-analysis but the Acquire and SharkCore were assessed only in retrospective studies. None of the studies included in the meta-analysis was adequately powered to evaluate adverse events; however, the observed adverse events, mostly minor bleeding, were rare (6 cases in total, so <1%), and occurred in relation to both FNB and FNA [55]. Based on limited evidence, endoscopic biopsy or EUS-TA of a GIST is not considered tumor rupture and does not have an impact on prognosis [56].

The superiority of EUS-FNB has been corroborated by two recent large retrospective multicenter studies [57, 58]. There are no RCTs that compare the various designs and sizes of FNB needles, or the technical aspects of sampling, optimal number of needle passes, or the use of rapid or macroscopic on-site evaluation (ROSE or MOSE). Needle size (22G vs. 19G ProCore) seems to have no impact on FNB sensitivity [59], and the sensitivity of FNB (using the Acquire 22G) is significantly higher when visible white tissue cores of >4 mm in length can be identified in the specimen on on-site stereomicroscopic assessment [60].

#### What can we expect from histology beyond diagnosis?

With surgical pathology findings as the reference standard, the diagnostic accuracy of EUS-FNB histology is high (83%–100%) [61]. This is not the case with cytology [62]. The accuracy of cytology can be increased to more than 95% if the cytoblock technique is used instead of the traditional smear method [63]. Histology and the cytoblock technique are the only methods that are useful as ancillary tests for diagnostic, therapeutic, and prognostic information [54].

The choice of markers depends on the typing of the lesion after routine hematoxylin and eosin (H&E) staining. Numerous immunohistochemical and molecular markers are available, but no standard panels that are useful for all SELs. NEN markers such as chromogranin A and/or synaptophysin are recommended for diagnosis, and in rectal NENs chromogranin A may be a marker for a more unfavorable prognosis [64]. The proliferation index and/or the mitosis count are classic morphological markers for NEN, and no further tests are recommended in a routine setting [65].

Determination of the mitotic index in preoperative biopsy/FNA has been utilized in GISTs [66–68]. However, its reliability and prognostic importance are controversial: even when 50 high power fields (HPFs) are evaluated in EUS-FNA specimens, the mitotic index values are still lower than in the surgical specimens from the same tumors [69]. Assessment of the Ki67 protein requires less tissue than mitotic index calculation and has also been carried out in EUS-FNA samples. In 2002, Ando et al. reported that a high Ki67 index in FNA samples was associated with malignancy [70]. However, in recent retrospective EUS-FNA studies; the Ki67 levels in EUS-FNA samples led to a significant underestimation of the proliferation index compared to surgical specimens [71]. These results suggest that there is insufficient evidence to recommend Ki67 or proliferation indexes routinely in FNA specimens, but further studies with the new FNB needles are needed.

Workup for NEN requires gallium-dotatate positron emission tomography (PET)-CT and discussion of the diagnostic and/or therapeutic plan by an MDT at a center of expertise or an ENETS Center of Excellence [72, 73]. Additional anorectal EUS or pelvic magnetic resonance imaging (MRI) is advised for rectal lesions >10 mm [74].

For GIST, a mutational analysis is needed for therapeutic purposes since this analysis provides prognostic information on whether or not the GIST may be responsive to a particular therapy [7]. Once a histological diagnosis of GIST is obtained, the usual staging strategy for these tumors should be applied. The staging of GIST requires a contrast-enhanced CT scan of the abdomen and the pelvis, with a thoracic CT scan for rectal and esophageal lesions [7]. Pelvic MRI is recommended for rectal GIST. A PET scan or PET-CT is recommended if neoadjuvant treatment with imatinib is proposed by an expert MDT for locally advanced disease.

## Management: Surveillance

### RECOMMENDATION

ESGE recommends against surveillance of asymptomatic GI leiomyomas, lipomas, heterotopic pancreas, granular cell tumors, schwannomas, and glomus tumors, if the diagnosis is clear.

Strong recommendation, moderate quality evidence.

### RECOMMENDATION

ESGE suggests surveillance of asymptomatic esophageal and gastric SELs without definite diagnosis, with EGD at 3–6 months, and then at 2–3-year intervals for lesions <10 mm in size and at 1–2-year intervals for lesions 10–20 mm in size. For asymptomatic SELs >20 mm in size that are not resected, ESGE suggests surveillance with EGD plus EUS at 6 months and then at 6–12-month intervals.

Weak recommendation, very low quality evidence.

### RECOMMENDATION

ESGE suggests that for proven gastric GIST <20 mm in size, surveillance or resection are both acceptable alternatives.

Weak recommendation, very low quality evidence.

### RECOMMENDATION

ESGE suggests that for duodenal and colorectal SELs, all attempts should be made to establish a definite diagnosis to guide further decisions, since there is no evidence that surveillance is a safe option.

Weak recommendation, very low quality evidence.

### RECOMMENDATION

ESGE suggests that surveillance may be an option for type 1 gastric NENs <10 mm in size, since the risk of progression of these lesions is very low, with repeat EGD (not EUS) every 1 to 2 years. All other NENs will benefit from treatment.

Weak recommendation, low quality evidence.

All patients should preferably be managed by an MDT with expertise in SELs or NENs [45]. Management obviously depends on the precise diagnosis, namely: unknown after diagnostic procedures, completely benign, NEN, GIST with malignant potential, or malignant.

### Known diagnosis

When the diagnosis is known, benign lesions such as leiomyoma, lipoma, heterotopic pancreas, granular cell tumor, schwannoma, and glomus tumor (and others) do not warrant any kind of surveillance since the risk of malignancy/complication is anecdotal and there is no evidence that surveillance provides any benefit in those patients. On the other hand, clearly malignant diseases such as lymphoma and metastatic lesions should have individualized treatment.

If the lesion is a NEN, most patients will benefit from treatment (endoscopic or surgical) instead of surveillance [72, 73]. The only exceptions are type 1 gastric NENs smaller than 10 mm for which surveillance could be an option since the risk of progression of these lesions is very low. In these cases, most guidelines recommend surveillance with repeat endoscopy every 1–2 years [72, 75], and also for adenocarcinoma screening in the atrophic mucosa.

If a lesion is a proven GIST, then the strategy is somewhat controversial. Consideration of treatment should always be discussed with the patient in the context of a dedicated MDT since the true potential of the malignant risk of these lesions is only known after resection [76]. Nevertheless, size is an important risk factor and several studies show that gastric GISTs smaller than 20 mm have a very low risk of malignancy. In fact, several studies show that surveillance instead of treatment is a safe option for GISTs smaller than 20 or even 30 mm (considering treatment only if there is tumor growth) [77, 78], even though several societies (European Society for Medical Oncology [ESMO], Japan Society of Clinical Oncology [JSCO], Chinese Society of Clinical Oncology [CSCO]) recommend resection [42–44].

If surveillance is chosen, one must be aware of low patient compliance with long-term follow-up [78]. EUS should be recommended as the best surveillance method since there are high risk features that can only be accessed by EUS. EUS surveillance at 3–6 months, and then at 6–12-month intervals (for 20–30-mm lesions), at 1–2 years (for 10–20-mm lesions), or 2–3 years (for <10-mm lesions) could be a good strategy (even though there are no comparative studies to say which is the best surveillance strategy). For extragastric GISTs, resection is

generally recommended, independently of the size, with surveillance only being an option if the patient refuses surgery or has severe comorbidities [76].

### Unknown diagnosis

If the diagnosis is unknown, management will depend on the location, and in the stomach GIST will mostly be considered [4, 46]. NEN is unlikely, as histological biopsies are usually diagnostic for this lesion.

Lesions that are asymptomatic, hypoechoic and well-delineated (without high risk features on EUS), <20 mm in size, and located in the esophagus or stomach present a very low risk of malignancy, and surveillance seems probably the better option [46]. A retrospective study including 954 patients with this kind of lesion showed that less than 4% of the lesions increased in size during surveillance, and there were no clinical consequences for the patients [77]. A prospective multicenter study including 65 patients suggested that surveillance of this kind of lesion (even with size <30 mm) is safe, with only one patient being referred for surgery during follow-up [78]. Regarding the surveillance interval, to our knowledge, no single study has compared different strategies. Most guidelines/expert opinion suggest EUS and/or EGD in 3–6 months (to confirm stability of the lesion) and then EUS or EGD annually or biannually [46]. However, other studies suggest that a 2–3-year interval might be more appropriate and also safe, allowing better compliance of patients to the surveillance strategy [78].

Nevertheless, such lesions carry the risk that they are GISTs, with inherent potential for malignancy. Therefore, it might be appropriate to follow the strategy outlined above for known GISTs where the decision has been to not resect, with further attempts at diagnosis by means of EUS-FNB. The other option is to go for a diagnostic resection to obtain a precise diagnosis (see section **Management: Resection**).

For duodenal and colorectal lesions there is no evidence to guide recommendations or to confirm that surveillance is a safe option. Therefore we suggest that for these lesions all attempts should be made to establish a correct diagnosis that should guide further decisions.

### Management: Resection

The goal of endoscopic resection (ER) is to achieve R0 resection, with a low morbidity rate, in tumors that have not invaded regional nodes. Indications for treatment of SELs/NENs are: the risk of malignancy (GIST and NEN, and, very infrequently, granular cell tumor); symptoms such as obstruction or bleeding, which can be associated with leiomyomas, schwannomas, or lipomas; and lesions in specific locations in patients undergoing bariatric surgery.

The type of treatment and follow-up is dependent on the SEL subtype, the layer of origin, and the location in the GI tract.

## Esophagus

NENs are very rare in the esophagus, and mainly represent neuroendocrine carcinomas, which should be considered and treated similarly to esophageal adenocarcinoma and are known for their aggressive nature. Indications for endoscopic resection should follow the ESGE guidelines for adenocarcinoma if lesions are detected at an early stage [79].

Granular cell tumors can occasionally grow during follow-up, show invasion into the muscular propria, or be associated with dysphagia, and in these cases ER can be considered. The treatment strategies (EMR, ESD) depend on the size and the depth of infiltration of the esophageal wall and also on local expertise. EMR with band ligation has been shown to have a high technical success rate (100%) and R0 resection rate (90%–96%), based on retrospective case series of granular cell tumors of size <20 mm and limited to the submucosa [80, 81]. EMR should therefore be considered the first choice for treatment because of its wide availability, lower complexity, and lower cost.

The majority of SELs originating from the muscularis propria in the esophagus are leiomyomas whereas GISTs are very rare, accounting for fewer than 2% of lesions. In the case of obstructive symptoms, endoscopic full-thickness resection (EFTR) should be weighed against the risks and benefits of thoracoscopic enucleation. In the absence of a comparative study, size and access should determine the treatment strategy, with an upper size limit of 35 mm for the endoscopic approach to allow en bloc removal of the SEL [82, 83]. In the esophagus, EFTR should be performed with submucosal tunneling endoscopic dissection instead of an exposing full-thickness resection. A recent meta-analysis of 701 patients with 728 lesions, of which 90% were in the esophagus or cardia, showed rates of en bloc resection, R0 resection, and adverse events of 86% (95%CI 75%–93%), 98% (95%CI 93%–99%), and 18% (95%CI 10%–32%), respectively [84]. Another meta-analysis of 879 patients, showed almost similar results of 95% (95%CI 92%–97%), 98% (95%CI 96%–99%), and 15% (95%CI 11%–21%), respectively [85].

## Stomach

### Neuroendocrine neoplasia

#### RECOMMENDATION

ESGE recommends endoscopic resection for type 1 gastric NENs (g-NENs) if they grow larger than 10 mm. The choice of resection technique should depend on size, depth of invasion, and location in the stomach.

Strong recommendation, low quality evidence.

Gastric NENs (g-NENs) can be divided in three subtypes based on their etiological background and concurrent risk of metastasis.

**Type 1 g-NENs** develop in the background of atrophic autoimmune gastritis. These lesions are often small, multifocal,

well-differentiated, grade 1 (or low grade 2,<10%), with a low risk for metastasis (<1%). Occasionally type 1 g-NENs grow larger than 10 mm and are at risk of metastasis [86]. It is therefore recommended to resect type 1 g-NENs that are  $\geq 10$  mm in size and/or higher grade 2 (higher G2) on diagnostic histology [86, 87], although tumor grade in well-differentiated type 1 gastric NEN has not been specifically studied in this setting. Most of the studies of ER for type 1 g-NEN concerned low grade tumors of size <10 mm. An initial case series including 33 lesions, showed 100% en bloc and pathologically complete resection rates (even though 2 recurrences were observed on long-term follow-up) with no perforation and only 1 delayed bleeding [88]. Another small retrospective study has compared conventional EMR and ESD in type 1 g-NEN but was restricted to <10-mm lesions [89]. In this study of 87 lesions, ESD showed a trend to a better pathologically complete resection rate (95% vs. 83%,  $P=0.17$ ), and a trend to a higher adverse event rate (perforation 2.6%, delayed bleeding 5%), but no clear advantage regarding recurrence. Another study found no tumor recurrence during follow-up in patients with G1/G2 NEN, even with positive margins after ER (EMR or ESD), meaning that pathologically positive margins may not influence local recurrence if endoscopically the resection appears complete [90].

**Type 2 g-NENs** develop in the background of multiple endocrine neoplasia type 1 (MEN1), and the indication for local resection depends on the presence of symptoms and the presence of NEN in the duodenum and pancreas [89]. Local or limited excision can be considered, but must be tailored to the patient at multidisciplinary NEN centers of excellence.

**Type 3 g-NENs** do not develop in the background of MEN1 or atrophic gastritis, are mostly unifocal, often G2–G3, and have a more aggressive nature with a higher reported risk of metastasis. For years, type 3 g-NENs were not considered suitable candidates for local excision. However, 10 retrospective studies with a total of 229 patients of whom 121 underwent a local excision of small type 3 g-NENs (the majority G1/G2) showed an R0 resection rate varying between 72% and 87% [91]. Only one in 121 patients developed a metastasis during follow-up. Type 3 g-NENs may therefore be candidates for endoscopic resection if they are <20 mm, show only submucosal invasion, and have a negative gallium-68 dotatoc scan beforehand [92–94].

It is not possible to extract data from these studies on which is the better resection technique. Therefore, we suggest that these cases should be discussed by an MDT at an NEN center of excellence. The ESGE guidelines on endoscopic resection for superficial adenocarcinoma should be followed [79], ideally employing the ESD technique, or surgery should be considered (wedge resection and nodal sampling as indicated following the MDT discussion).

### Lipomas

Lipomas can occur in the gastric wall but are seldom an indication for local excision. Only in the case of obstruction, bleeding or ulceration might endoscopic removal of a lipoma be considered. A systematic review described the outcome of 20 ESD procedures on giant gastric lipomas [95]. The average size of the lipomas was 40 mm (range 12–90 mm) with 80% of the

tumors located in the antrum. Three lipomas were removed by submucosal tunneling. All tumors were successfully removed en bloc and no major complications were reported. Because of significant publication bias these results should be interpreted with caution.

### Gastrointestinal stromal tumors (GISTs)

#### RECOMMENDATION

ESGE suggests considering removal of histologically proven gastric GISTs smaller than 20 mm as an alternative to surveillance. The decision to resect should be discussed in a multidisciplinary meeting. The choice of technique should depend on size, location, and local expertise. Weak recommendation, very low quality evidence.

#### RECOMMENDATION

In the presence of an indication for resection, ESGE suggests considering ER (either STER, endoscopic submucosal excavation [ESE], or EFTR) as an alternative to laparoscopic gastric wedge excision for removing a gastric GIST <35 mm in size and protruding into the gastric lumen, with a multidisciplinary meeting beforehand. Weak recommendation, very low quality evidence.

GISTs smaller than 20 mm have a predicted low risk of malignant degeneration and can be followed up with EUS. Some advocate that endoscopic resection of GISTs <20 mm can avoid the burden of repeated follow-up EUS for young patients, and some patients prefer local excision to long-term repeated follow-up with EUS. Also, GIST size <20 mm and features at EUS that are suspicious for malignant degeneration can be considered to be an indication for local excision. The upper size limit for EFTR seems to be 40 mm, although larger SELs have been removed endoscopically.

Nonmetastasized GISTs of <35 mm can be removed by local excision of the gastric wall by EFTR or laparoscopic wedge excision. The latter is currently considered to be the gold standard in different international guidelines in Western countries [7, 45, 76]. EFTR of SELs originating from the muscular propria can be divided into exposing and nonexposing techniques. With exposing techniques, the intraperitoneal cavity is exposed to gastric luminal content by an iatrogenic perforation of the gastric wall which is closed afterwards. Nonexposing techniques close the perforation by means of a mucosal flap as in the submucosal tunneling endoscopic resection (STER) procedure, or with clip closure beforehand with an over-the-scope full-thickness resection device (Ovesco). There is no direct randomized comparison between the different resection methods. A recent meta-analysis of 1292 patients from 12 mainly retrospective studies comparing laparoscopic wedge excision versus EFTR showed similar complication, hospitalization, and recurrence rates, with a similar 5-year disease-free survival [96].

A meta-analysis on the efficacy of ER of GIST of <20 mm showed a pooled R0 resection rate of 97% (95%CI 95%–99%), a complication rate of 9% (95%CI 7%–13%), and a recurrence rate of 3% (95%CI 2%–6%) [97]. Another meta-analysis on gastric STER procedures on SELs showed similar results, with an R0 resection rate within the group of en bloc resected SELs of 97.9% (95%CI 93.6%–99.3%). Gas- and inflammation-related complications were observed in 10.5% and 9.9% [98].

Exposing EFTR is associated with R0 resection rates (98.8%) similar to those of nonexposing, and a surgical conversion rate of 0.8% [99]. There is limited experience with nonexposing EFTR using the over-the-scope full-thickness resection device [100, 101] or a flat-based over-the-scope clip (Padlock) [102], showing an R0 resection rate of 50% for GIST. Endoscopic submucosal excavation (ESE) is an alternative technique which seems to be especially effective for <20 mm SELs, with R0 resection rates varying between 90% and 99% [103–106]. A few retrospective nonrandomized case series compared ESE to STER procedures, and showed equal effectiveness for both techniques, especially for SELs <15 mm [105–107]. Another study showed that despite the importance of achieving complete (R0) resection, R1 resection was not associated with recurrence if en bloc resection had been achieved [108].

### Schwannomas

Schwannomas develop from the nerve plexus near or in between the layers of the muscular propria, mainly in the gastric corpus, and are often difficult to distinguish from GISTs. Because of the low risk of malignant degeneration, excision is only indicated if they are symptomatic, for example bleeding. The same techniques as used for GIST can be applied [78, 109].

### Diagnostic excision of SELs of unknown histology originating from the muscularis propria

#### RECOMMENDATION

ESGE suggests that, to avoid unnecessary follow-up, endoscopic resection is an option for gastric SELs smaller than 20 mm and of unknown histology, after failure of attempts to obtain diagnosis.

Weak recommendation, very low quality evidence.

In some cases it is very difficult to obtain a histological diagnosis, because of small lesion size or difficult access. As it is supposed that 60% of SELs originating from gastric muscularis propria will turn out to be GISTs, this often results in biannual surveillance by EUS for lesions <20 mm in size. It is known that when a follow-up strategy is applied, patients with SELs tend to be lost to follow-up after a few rounds of investigations because of poor compliance with the EUS surveillance schedule [78]. There is no direct comparison between a strategy of follow-up with resection upon growth or malignant change, and a strategy of diagnostic excision of a SEL of unknown histology with follow-up only if indicated. The alternative of endoscopic resec-

tion instead of follow-up of a small SEL suspicious for GIST should be discussed with the patient, on a case-by-case basis.

## Duodenum

#### RECOMMENDATION

ESGE suggests choosing between EMR, ESD, and EFTR to resect nonampullary, nonfunctional duodenal NENs of <15 mm, depending on size, location, depth of invasion, and local expertise.

Weak recommendation, low quality evidence.

### NENs

The main indication for ER in the duodenum is for nonampullary, <20-mm nonfunctional duodenal NENs (d-NENs). Ampullary d-NENs and functional d-NENs exhibit a more aggressive etiology, with more synchronous lymph node and liver metastasis, and are therefore considered appropriate for oncological surgery [110–112]. G1 nonfunctional nonampullary d-NENs of <20 mm have a much lower risk of metastasis, especially if smaller than 10 mm, and removal by local excision is therefore advised [89]. However when such lesions are larger than 20 mm, the risk of metastasis increases and therefore oncological surgery is appropriate. Although there is evidence for the safety of ER for G1 d-NENs of size <15 mm [113, 114], the reported data for ER in d-NENs sized 15–20 mm are anecdotal [114].

A meta-analysis comparing local surgical resection with ER showed that margins were more often R1/Rx in the latter (15% vs. 43%). However, there were significant differences in size and depth of invasion between the lesions treated by each technique [115]. There was also considerable heterogeneity amongst the studies (which included more than 21 non-randomized reports, with 382 ERs) and various techniques had been used, including EMR (often with band ligation, circumferential incision, or traction), ESD, or EFTR. ESD tends to have a higher R0 resection rate than EMR but is associated with much greater complexity and a higher perforation rate [89, 113, 115–117]. EFTR with an over-the-scope full-thickness resection device is a promising technique, with R0 resection rates over 80%, but more experience is needed [102, 118, 119].

Band ligation without resection has also been studied for small d-NENs. A preliminary series of 8 patients treated for lesions <10 mm showed a 100% technical success, with no residual lesion confirmed at long-term follow-up (median 4.2 years) [120]. The drawback of this technique is the absence of final histological findings that could contribute information on prognosis. However, diminutive d-NENs do not show any growth during follow-up, leading some authors to advocate follow-up rather than resection of d-NENs smaller than 5 mm [121].

## GISTs

Current guidelines do not advocate ER of GIST in the duodenum because of the higher risk of malignant degeneration and metastasis [7]. However, exposing EFTR has shown good results (en bloc resection rate 100%, R0 resection rate 100%) in a series of 32 patients [122]. Further studies should determine the role of using the over-the-scope full-thickness resection device, and whether local excision can be expanded to a specific subgroup of duodenal GISTs [119]. No recommendations can be made, even for small nonclassified SELs or GISTs.

## Small intestine

All SELs originating from the mucosa, submucosa, and muscularis propria have a higher potential for an aggressive nature, which makes them unsuitable for local endoscopic excision (except for proven benign SELs such as lipomas or leiomyomas).

## Colon and rectum

### NENs

#### RECOMMENDATION

ESGE suggests using modified EMR as the first technique for removing rectal NENs <10 mm in size, and ESD or transanal endoscopic microsurgery for lesions up to 20 mm. Weak recommendation, low quality evidence.

Most colonic NENs are in the rectum (r-NEN), and they are increasingly identified at screening colonoscopy. Following current ENET guidelines, r-NENs can be resected locally if <20 mm in size [74]. Risk factors for metastasis are endoscopic features of depression or ulceration, suspicious lymph nodes at EUS or MRI, invasion of the muscularis propria, histological G2, and lymphovascular invasion [74, 123, 124]. A recent large retrospective nationwide Dutch study confirmed that no lymph node or distant metastasis could be detected that was related to endoscopically removed G1 NENs up to 20 mm in size, during a long follow-up of 11.6 years (range 4.9–26.0) [125].

Concerning the best technique for r-NEN removal, different cutoff sizes have been proposed such as EMR for lesions of <10 mm and ESD or transanal endoscopic microsurgery for lesions 10–15 mm, depending on local expertise [123, 126, 127]. For r-NENs smaller than 16 mm, a meta-analysis showed that ESD was associated with rates of 89% for complete resection, 4% for adverse events, and <1% for local recurrence [128]. The complete resection rate was better than that of conventional EMR (75%,  $P<0.001$ ) but not better than that of modified EMR (91%; band ligation, double-channel, cap-assisted, circumferential pre-cutting). Even though both ESD and modified EMR were associated with higher rates of complete resection when compared to conventional EMR, this did not translate into a lower risk of clinical recurrence. Two meta-analyses confirmed the superiority of modified EMR over conventional EMR (odds ratio [OR] for histologically complete resection 0.23, 95% CI 0.10–0.51;  $P<0.01$ ), and over ESD (OR 4.08, 95% CI 2.42–6.88;

$P<0.001$ ), with no difference in the adverse event and recurrence rates (<1%) [129, 130].

Unfortunately, small r-NENs (mostly <5 mm) are often mistaken for hyperplastic lesions and resected with cold snaring. This often (in >50% of cases) leads to incomplete resection [125]. It is unknown how often such an incomplete resection results in a significant recurrence or metastasis. EUS is recommended for most r-NENs except perhaps for very small (<5 mm) lesions that have been completely removed [131]. Salvage resection should be discussed on a case-by-case basis at centers of excellence in treating NEN. In a recent case series, a salvage ER was more effective than biopsy or EUS to detect residual r-NEN (in 38% of cases) [132]. The optimal ER technique (EMR, ESD, EFTR) for additional resection of the scar is currently unknown.

ER of more proximal colonic NENs has rarely been described [133], with surgical resection being the main therapy. The finding of neuroendocrine hyperplasia within random colonic biopsies has been described, and particularly the “microcarcinoids” found in inflammatory bowel disease, which are not thought to be aggressive and might be a response to inflammation [134].

### GISTs

GISTs account for 0.6% of all rectal neoplasia [135] and are also rare in the colon. Small hard nodules, <10 mm in diameter, are found incidentally during rectal examination but large tumors have clinical similarities with rectal adenocarcinoma. There are no data on endoscopic removal of these tumors, even in the largest series of colorectal EFTR, in which the only SELs treated by this technique were NENs [136].

## Follow-up

#### RECOMMENDATION

ESGE recommends basing the surveillance strategy on the type and completeness of resection. After curative resection of benign SELs no follow-up is advised, except for type 1 gastric NEN for which surveillance at 1–2 years is advised.

Strong recommendation, low quality evidence.

#### RECOMMENDATION

For lower or upper GI NEN with a positive or indeterminate margin at resection, ESGE recommends repeating endoscopy at 3–6 months and another attempt at endoscopic resection in the case of residual disease.

Strong recommendation, low quality evidence.

## RECOMMENDATION

ESGE suggests a new attempt at endoscopic or surgical resection after noncurative resection of a GIST. If this is not feasible, the tumor is considered as a locally advanced tumor and guidelines on the management of advanced GIST should be applied.

Weak recommendation, low quality evidence.

After resection, surveillance strategies will depend on the diagnosis and completeness of resection. Again, clearly benign lesions do not require any kind of surveillance. For malignant lesions surveillance will depend on the diagnosis.

After complete ER of a NEN (without criteria for additional treatment) surveillance is generally recommended [72]. For type I gastric NENs (that generally present recurrent behavior), the US National Comprehensive Cancer Network (NCCN) guidelines recommend EGD every 6–12 months in the first 3 years and annually thereafter [137]. For type 2 and 3 gastric NENs (less recurrent) annual endoscopic surveillance is enough (and the surveillance interval could probably be extended). At any surveillance, biopsies/resection of new lesions should be performed. For duodenal and colorectal NENs, annual endoscopy is also generally recommended (as well as other imaging and serological markers, depending on the stage). The exception might be completely resected small r-NENs with size <10 mm, G1–G2 grading, no muscularis propria invasion, and no lymph node metastasis; these might not require regular surveillance [74]. In the common scenario of a patient with a previously resected polyp in whom histology shows a NEN with positive margins (without other risk features), recent guidelines suggest repeating endoscopy at 3–6 months since there is a real risk of persistent/recurrent disease [138]. If the scar shows residual tumor, another endoscopic treatment should be performed. If the scar does not show macroscopic recurrence/residual tumor, biopsies should be taken to exclude microscopic disease.

For other NENs (G3 grading, tumors >20 mm), follow-up is suggested every 4–6 months in the first year and thereafter at least annually. Even though there is not a specific protocol for surveillance, ENETS recommends colonoscopy, EUS, and MRI for rectal evaluation, and CT or MRI for liver metastasis and dosage of serum chromogranin A [74].

After complete resection of a GIST, local recurrence is not an issue (after R0 surgical resection, recurrences are mainly hepatic or peritoneal) and generally only imaging methods (e.g. CT) are recommended for surveillance [76]. Nevertheless, since the natural history of this tumor after ER is not clearly known, an endoscopy at 6–12 months after ER and then in 2–3 years might be an option for early detection of local recurrence that might be amenable to further treatments.

After incomplete resection of a GIST, reoperation to obtain a R0 resection is recommended [43, 76]. If this is not feasible, the tumor is considered as a locally advanced tumor and guidelines on the management of advanced GIST should be applied in a multidisciplinary assessment [43, 76].

## Disclaimer

The legal disclaimer for ESGE guidelines [2] applies to this Guideline.

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## Competing interests

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## References

- [1] Atkins D, Eccles M, Flottorp S et al. Systems for grading the quality of evidence and the strength of recommendations I: Critical appraisal of existing approaches The GRADE Working Group. *BMC Health Serv Res* 2004; 4: 38
- [2] Dumonceau J-M, Hassan C, Riphauw A et al. European Society of Gastrointestinal Endoscopy (ESGE) Guideline Development Policy. *Endoscopy* 2012; 44: 626–629
- [3] Nishida T, Kawai N, Yamaguchi S et al. Submucosal tumors: Comprehensive guide for the diagnosis and therapy of gastrointestinal submucosal tumors. *Dig Endosc* 2013; 25: 479–489
- [4] Menon L, Buscaglia JM. Endoscopic approach to subepithelial lesions. *Ther Adv Gastroenterol* 2014; 7: 123–130
- [5] Akahoshi K, Oya M, Koga T et al. Current clinical management of gastrointestinal stromal tumor. *World J Gastroenterol* 2018; 24: 2806–2817
- [6] Agaimy A, Wünsch PH, Hofstaedter F et al. Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. *Am J Surg Pathol* 2007; 31: 113–120
- [7] Casali PG, Abecassis N, Aro HT et al. Gastrointestinal stromal tumors: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; 29: iv68–iv78

[8] Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumors: origin and molecular oncology. *Nat Rev Cancer* 2011; 11: 865–878

[9] Boikos SA, Stratakis CA. The genetic landscape of gastrointestinal stromal tumor lacking KIT and PDGFRA mutations. *Endocrine* 2014; 47: 401–408

[10] Rossi S, Gasparotto D, Toffolatti L et al. Molecular and clinicopathologic characterization of gastrointestinal stromal tumors (GISTs) of small size. *Am J Surg Pathol* 2010; 34: 1480–1491

[11] Dasari A, Shen C, Halperin D et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol* 2017; 3: 1335–1342

[12] Felder S, Jann H, Arsenic R et al. Gastric neuroendocrine neoplasias: manifestations and comparative outcomes. *Endocr Relat Cancer* 2019; 26: 751–763

[13] Rindi G. The ENETS guidelines: the new TNM classification system. *Tumori* 2010; 96: 806–809

[14] Rösch T, Kapfer B, Will U et al. Accuracy of endoscopic ultrasonography in upper gastrointestinal submucosal lesions: a prospective multicenter study. *Scand J Gastroenterol* 2002; 37: 856–862

[15] Bialek A, Wiechowska-Kozłowska A, Pertkiewicz J et al. Endoscopic submucosal dissection for treatment of gastric subepithelial tumors (with video). *Gastrointest Endosc* 2012; 75: 276–286

[16] He G, Wang J, Chen B et al. Feasibility of endoscopic submucosal dissection for upper gastrointestinal submucosal tumors treatment and value of endoscopic ultrasonography in pre-operation assess and post-operation follow-up: a prospective study of 224 cases in a single medical center. *Surg Endosc* 2016; 30: 4206–4213

[17] Chen H-T, Xu G-Q, Teng X-D et al. Diagnostic accuracy of endoscopic ultrasonography for rectal neuroendocrine neoplasms. *World J Gastroenterol* 2014; 20: 10470–10477

[18] Li Q-L, Zhang Y-Q, Chen W-F et al. Endoscopic submucosal dissection for foregut neuroendocrine tumors: an initial study. *World J Gastroenterol* 2012; 18: 5799–5806

[19] Rösch T, Lorenz R, Dancygier H et al. Endosonographic diagnosis of submucosal upper gastrointestinal tract tumors. *Scand J Gastroenterol* 1992; 27: 1–8

[20] Kim SY, Shim K-N, Lee J-H et al. Comparison of the diagnostic ability of endoscopic ultrasonography and abdominopelvic computed tomography in the diagnosis of gastric subepithelial tumors. *Clin Endosc* 2019; 52: 565–573 doi:10.5946/ce.2019.019

[21] Karaca C, Turner BG, Cizginer S et al. Accuracy of EUS in the evaluation of small gastric subepithelial lesions. *Gastrointest Endosc* 2010; 71: 722–727

[22] Kim GH, Park DY, Kim S et al. Is it possible to differentiate gastric GISTs from gastric leiomyomas by EUS? *World J Gastroenterol* 2009; 15: 3376–3381

[23] Khan S, Zhang R, Fang W et al. Reliability of endoscopic ultrasound using miniprobes and grayscale histogram analysis in diagnosing upper gastrointestinal subepithelial lesions. *Gastroenterol Res Pract* 2020; 2020: 6591341

[24] Minoda Y, Ihara E, Komori K et al. Efficacy of endoscopic ultrasound with artificial intelligence for the diagnosis of gastrointestinal stromal tumors. *J Gastroenterol* 2020; 55: 1119–1126

[25] Brand B, Oesterhelweg L, Bimmoeller KF et al. Impact of endoscopic ultrasound for evaluation of submucosal lesions in gastrointestinal tract. *Dig Liver Dis* 2002; 34: 290–297

[26] Chen T-H, Hsu C-M, Chu Y-Y et al. Association of endoscopic ultrasonographic parameters and gastrointestinal stromal tumors (GISTs): can endoscopic ultrasonography be used to screen gastric GISTs for potential malignancy? *Scand J Gastroenterol* 2016; 51: 374–377

[27] Ra JC, Lee ES, Lee JB et al. Diagnostic performance of stomach CT compared with endoscopic ultrasonography in diagnosing gastric subepithelial tumors. *Abdom Radiol N Y* 2017; 42: 442–450

[28] Okten RS, Kacar S, Kucukay F et al. Gastric subepithelial masses: evaluation of multidetector CT (multiplanar reconstruction and virtual gastroscopy) versus endoscopic ultrasonography. *Abdom Imaging* 2012; 37: 519–530

[29] Tang JY, Tao KG, Zhang LY et al. Value of contrast-enhanced harmonic endoscopic ultrasonography in differentiating between gastrointestinal stromal tumors: A meta-analysis. *J Dig Dis* 2019; 20: 127–134 doi:10.1111/1751-2980.12710

[30] Sakamoto H, Kitano M, Matsui S et al. Estimation of malignant potential of GI stromal tumors by contrast-enhanced harmonic EUS (with videos). *Gastrointest Endosc* 2011; 73: 227–237

[31] Zhao Y, Qian L, Li P et al. The diagnostic value of endoscopic ultrasonography and contrast-enhanced harmonic endoscopic ultrasonography in gastrointestinal stromal tumors. *Endosc Ultrasound* 2016; 5: 111–117

[32] Tsuji Y, Kusano C, Gotoda T et al. Diagnostic potential of endoscopic ultrasonography-elastography for gastric submucosal tumors: A pilot study. *Dig Endosc* 2016; 28: 173–178

[33] Kannengiesser K, Mahlkne R, Petersen F et al. Contrast-enhanced harmonic endoscopic ultrasound is able to discriminate benign submucosal lesions from gastrointestinal stromal tumors. *Scand J Gastroenterol* 2012; 47: 1515–1520

[34] Yamashita Y, Kato J, Ueda K et al. Contrast-enhanced endoscopic ultrasonography can predict a higher malignant potential of gastrointestinal stromal tumors by visualizing large newly formed vessels. *J Clin Ultrasound JCU* 2015; 43: 89–97

[35] Pesenti C, Bories E, Caillol F et al. Characterization of subepithelial lesions of the stomach and esophagus by contrast-enhanced EUS: A retrospective study. *Endosc Ultrasound* 2019; 8: 43–49

[36] Kamata K, Takenaka M, Kitano M et al. Contrast-enhanced harmonic endoscopic ultrasonography for differential diagnosis of submucosal tumors of the upper gastrointestinal tract. *J Gastroenterol Hepatol* 2017; 32: 1686–1692

[37] Ignee A, Jenssen C, Hocke M et al. Contrast-enhanced (endoscopic) ultrasound and endoscopic ultrasound elastography in gastrointestinal stromal tumors. *Endosc Ultrasound* 2017; 6: 55–60

[38] Kim SH, Yoo IK, Kwon C-I et al. Utility of EUS elastography in the diagnosis of gastric subepithelial tumors: a pilot study (with video). *Gastrointest Endosc* 2020; 91: 172–177.e2

[39] Park HY, Jeon SW, Lee HS et al. Can contrast-enhanced harmonic endosonography predict malignancy risk in gastrointestinal subepithelial tumors? *Endosc Ultrasound* 2016; 5: 384–389 doi:10.4103/2303-9027.195871

[40] Lee HS, Cho CM, Kwon YH et al. Predicting malignancy risk in gastrointestinal subepithelial tumors with contrast-enhanced harmonic endoscopic ultrasonography using perfusion analysis software. *Gut Liver* 2019; 13: 161–168

[41] Akahoshi K, Oya M, Koga T et al. Clinical usefulness of endoscopic ultrasound-guided fine needle aspiration for gastric subepithelial lesions smaller than 2 cm. *J Gastrointest Liver Dis* 2014; 23: 405–412

[42] ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014; 25: (Suppl. 03): iii21–26 doi:10.1093/annonc/mdu255

[43] Nishida T, Hirota S, Yanagisawa A et al. Clinical practice guidelines for gastrointestinal stromal tumor (GIST) in Japan: English version. *Int J Clin Oncol* 2008; 13: 416–430 doi:10.1007/s10147-008-0798-7

[44] Li J, Ye Y, Wang J et al. Chinese consensus guidelines for diagnosis and management of gastrointestinal stromal tumor. *Chin J Cancer Res Chung-Kuo Yen Cheng Yen Chiu* 2017; 29: 281–293 doi:10.21147/j.issn.1000-9604.2017.04.01

[45] von Mehren M, Kane JM, Bui MM et al. NCCN guidelines insights: Soft tissue sarcoma, version 1.2021. *J Natl Compr Canc Netw* 2020; 18: 1604–1612 doi:10.6004/jnccn.2020.0058

[46] Dumonceau J-M, Deprez PH, Jenssen C et al. Indications, results, and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline – Updated January 2017. *Endoscopy* 2017; 49: 695–714

[47] Cho JW, Korean ESD Study Group. Current guidelines in the management of upper gastrointestinal subepithelial tumors. *Clin Endosc* 2016; 49: 235–240

[48] Sanaei O, Fernández-Esparrach G, De La Serna-Higuera C et al. EUS-guided 22-gauge fine needle biopsy versus single-incision with needle knife for the diagnosis of upper gastrointestinal subepithelial lesions: a randomized controlled trial. *Endosc Int Open* 2020; 8: E266–E273

[49] Osoegawa T, Minoda Y, Ihara E et al. Mucosal incision-assisted biopsy versus endoscopic ultrasound-guided fine-needle aspiration with a rapid on-site evaluation for gastric subepithelial lesions: A randomized cross-over study. *Dig Endosc* 2019; 31: 413–421

[50] Dhaliwal A, Kolli S, Dhindsa BS et al. Clinical efficacy and safety of mucosal incision-assisted biopsy for the diagnosis of upper gastrointestinal subepithelial tumors: A systematic review and meta-analysis. *Ann Gastroenterol* 2020; 33: 155–161 doi:10.20524/aog.2020.0460

[51] Dhaliwal A, Kolli S, Dhindsa BS et al. Diagnostic yield of deep biopsy via endoscopic submucosal dissection for the diagnosis of upper gastrointestinal subepithelial tumors: a systematic review and meta-analysis. *Ann Gastroenterol* 2020; 33: 30–37 doi:10.20524/aog.2019.0444

[52] Zoundjiekpon V, Falt P, Fojtik P et al. Endosonography-guided fine-needle aspiration versus “key-hole biopsy” in the diagnostics of upper gastrointestinal subepithelial tumors. A prospective randomized interventional study. *Biomed Pap Med Fac Univ Palacky Olomouc Czechoslov* 2020; 164: 63–70

[53] Minoda Y, Chinen T, Osoegawa T et al. Superiority of mucosal incision-assisted biopsy over ultrasound-guided fine needle aspiration biopsy in diagnosing small gastric subepithelial lesions: a propensity score matching analysis. *BMC Gastroenterol* 2020; 20: 19

[54] Zhang X-C, Li Q-L, Yu Y-F et al. Diagnostic efficacy of endoscopic ultrasound-guided needle sampling for upper gastrointestinal subepithelial lesions: a meta-analysis. *Surg Endosc* 2016; 30: 2431–2441

[55] Facciorusso A, Sunny SP, Del Prete V et al. Comparison between fine-needle biopsy and fine-needle aspiration for EUS-guided sampling of subepithelial lesions: a meta-analysis. *Gastrointest Endosc* 2020; 91: 14–22.e2

[56] Nishida T, Hølmebak T, Raut CP et al. Defining tumor rupture in gastrointestinal stromal tumor. *Ann Surg Oncol* 2019; 26: 1669–1675

[57] Trindade AJ, Benias PC, Alshelleh M et al. Fine-needle biopsy is superior to fine-needle aspiration of suspected gastrointestinal stromal tumors: a large multicenter study. *Endosc Int Open* 2019; 7: E931–E936

[58] de Moura DTH, McCarty TR, Jirapinyo P et al. EUS-guided fine-needle biopsy sampling versus FNA in the diagnosis of subepithelial lesions: a large multicenter study. *Gastrointest Endosc* 2020; 92: 108–119.e3

[59] Hedenström P, Marschall H-U, Nilsson B et al. High clinical impact and diagnostic accuracy of EUS-guided biopsy sampling of subepithelial lesions: a prospective, comparative study. *Surg Endosc* 2018; 32: 1304–1313

[60] Okuwaki K, Masutani H, Kida M et al. Diagnostic efficacy of white core cutoff lengths obtained by EUS-guided fine-needle biopsy using a novel 22G franseen biopsy needle and sample isolation processing by stereomicroscopy for subepithelial lesions. *Endosc Ultrasound* 2020; 9: 187–192

[61] Kim GH, Ahn JY, Gong CS et al. Efficacy of endoscopic ultrasound-guided fine-needle biopsy in gastric subepithelial tumors located in the cardia. *Dig Dis Sci* 2020; 65: 583–590

[62] Kim GH, Cho YK, Kim EY et al. Comparison of 22-gauge aspiration needle with 22-gauge biopsy needle in endoscopic ultrasonography-guided subepithelial tumor sampling. *Scand J Gastroenterol* 2014; 49: 347–354

[63] Gilani SM, Muniraj T, Aslanian HR et al. Endoscopic ultrasound-guided fine needle aspiration cytology diagnosis of upper gastrointestinal tract mesenchymal tumors: Impact of rapid onsite evaluation and correlation with histopathologic follow-up. *Diagn Cytopathol* 2021; 49: 203–210

[64] Kim J, Kim JY, Oh EH et al. Chromogranin A expression in rectal neuroendocrine tumors is associated with more aggressive clinical behavior and a poorer prognosis. *Am J Surg Pathol* 2020; 44: 1496–1505

[65] Zhang H, Liu Q. Prognostic indicators for gastrointestinal stromal tumors: A review. *Transl Oncol* 2020; 13: 100812

[66] Larghi A, Fuccio L, Chiarello G et al. Fine-needle tissue acquisition from subepithelial lesions using a forward-viewing linear echoendoscope. *Endoscopy* 2014; 46: 39–45

[67] Polkowski M, Gerke W, Jarosz D et al. Diagnostic yield and safety of endoscopic ultrasound-guided trucut corrected biopsy in patients with gastric submucosal tumors: a prospective study. *Endoscopy* 2009; 41: 329–334

[68] Kataoka M, Kawai T, Ikemiyagi H et al. Clinicopathological characteristic and clinical handling of the patients with 2 cm or less gastric GISTs. *SpringerPlus* 2013; 2: 469

[69] Ricci R, Chiarello G, Attili F et al. Endoscopic ultrasound-guided fine needle tissue acquisition biopsy samples do not allow a reliable proliferation assessment of gastrointestinal stromal tumours. *Dig Liver Dis* 2015; 47: 291–295

[70] Ando N, Goto H, Niwa Y et al. The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis. *Gastrointest Endosc* 2002; 55: 37–43

[71] Seven G, Kochan K, Caglar E et al. Evaluation of Ki67 index in endoscopic ultrasound-guided fine needle aspiration samples for the assessment of malignancy risk in gastric gastrointestinal stromal tumors. *Dig Dis Basel Switz* 2021; 39: 407–414

[72] Oberg K, Couvelard A, Delle Fave G et al. ENETS consensus guidelines for standard of care in neuroendocrine tumours: Biochemical markers. *Neuroendocrinology* 2017; 105: 201–211

[73] O'Toole D, Grossman A, Gross D et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: Biochemical markers. *Neuroendocrinology* 2009; 90: 194–202 doi:10.1159/000225948

[74] Ramage JK, De Herder WW, Delle Fave G et al. ENETS consensus guidelines update for colorectal neuroendocrine neoplasms. *Neuroendocrinology* 2016; 103: 139–143

[75] Delle Fave G, Kwekkeboom DJ, Van Cutsem E et al. ENETS consensus guidelines for the management of patients with gastroduodenal neoplasms. *Neuroendocrinology* 2012; 95: 74–87

[76] Landi B, Blay J-Y, Bonvalot S et al. Gastrointestinal stromal tumours (GISTs): French Intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO). *Dig Liver Dis* 2019; 51: 1223–1231

[77] Song JH, Kim SG, Chung SJ et al. Risk of progression for incidental small subepithelial tumors in the upper gastrointestinal tract. *Endoscopy* 2015; 47: 675–679 doi:10.1055/s-0034-1391967

[78] Kushnir VM, Keswani RN, Hollander TG et al. Compliance with surveillance recommendations for foregut subepithelial tumors is poor: results of a prospective multicenter study. *Gastrointest Endosc* 2015; 81: 1378–1384

[79] Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015; 47: 829–854

[80] Kumar S, Chandrasekhara V, Kochman ML et al. Ligation-assisted endoscopic mucosal resection for esophageal granular cell tumors is safe and effective. *Dis Esophagus* 2020; 33: doaa027

[81] Lu W, Xu M-D, Zhou P-H et al. Endoscopic submucosal dissection of esophageal granular cell tumor. *World J Surg Oncol* 2014; 12: 221

[82] Ye L-P, Zhang Y, Mao X-L et al. Submucosal tunnelling endoscopic resection for the treatment of esophageal submucosal tumors originating from the muscularis propria layer: an analysis of 15 cases. *Dig Liver Dis* 2013; 45: 119–123

[83] Zhang Y, Peng J-B, Mao X-L et al. Endoscopic resection of large ( $\geq 4$  cm) upper gastrointestinal subepithelial tumors originating from the muscularis propria layer: a single-center study of 101 cases (with video). *Surg Endosc* 2021; 35: 1442–1452

[84] Peng W, Tan S, Huang S et al. Efficacy and safety of submucosal tunneling endoscopic resection for upper gastrointestinal submucosal tumors with more than 1-year follow-up: a systematic review and meta-analysis. *Scand J Gastroenterol* 2019; 54: 397–406

[85] Lv X-H, Wang C-H, Xie Y. Efficacy and safety of submucosal tunneling endoscopic resection for upper gastrointestinal submucosal tumors: a systematic review and meta-analysis. *Surg Endosc* 2017; 31: 49–63

[86] Grozinsky-Glasberg S, Thomas D, Strosberg JR et al. Metastatic type 1 gastric carcinoid: a real threat or just a myth? *World J Gastroenterol* 2013; 19: 8687–8695

[87] Tsolakis AV, Rakousi A, Vujasinovic M et al. Gastric neuroendocrine neoplasms type 1: A systematic review and meta-analysis. *World J Gastroenterol* 2019; 25: 5376–5387

[88] Chen WF, Zhou PH, Li QL et al. Clinical impact of endoscopic submucosal dissection for gastric neuroendocrine tumors: a retrospective study from mainland China. *ScientificWorldJournal* 2012; doi:10.1100/2012/869769

[89] Kim HH, Kim GH, Kim JH et al. The efficacy of endoscopic submucosal dissection of type I gastric carcinoid tumors compared with conventional endoscopic mucosal resection. *Gastroenterol Res Pract* 2014; 2014: 253860

[90] Jung HJ, Hong SJ, Han JP et al. Long-term outcome of endoscopic and surgical resection for foregut neuroendocrine tumors. *J Dig Dis* 2015; 16: 595–600 doi:10.1111/1751-2980.12279

[91] Exarchou K, Howes N, Pritchard DM. Systematic review: management of localised low-grade upper gastrointestinal neuroendocrine tumours. *Aliment Pharmacol Ther* 2020; 51: 1247–1267 doi:10.1111/apt.15765

[92] Min B-H, Hong M, Lee JH et al. Clinicopathological features and outcome of type 3 gastric neuroendocrine tumours. *Br J Surg* 2018; 105: 1480–1486

[93] Li Y-L, Qiu X-D, Chen J et al. Clinicopathological characteristics and prognosis of 77 cases with type 3 gastric neuroendocrine tumours. *World J Gastrointest Oncol* 2020; 12: 1416–1427

[94] Hirasawa T, Yamamoto N, Sano T. Is endoscopic resection appropriate for type 3 gastric neuroendocrine tumors? Retrospective multicenter study. *Dig Endosc* 2021; 33: 408–417

[95] Ingason AB, Theodors A, Agustsson AS et al. Giant gastric lipoma successfully removed by endoscopic submucosal dissection: case report and systematic review. *Scand J Gastroenterol* 2018; 53: 1018–1024

[96] Wang C, Gao Z, Shen K et al. Safety and efficiency of endoscopic resection versus laparoscopic resection in gastric gastrointestinal stromal tumours: A systematic review and meta-analysis. *Eur J Surg Oncol* 2020; 46: 667–674

[97] Zhang Q, Gao L-Q, Han Z-L et al. Effectiveness and safety of endoscopic resection for gastric GISTs: a systematic review. *Minim Invasive Ther Allied Technol* 2018; 27: 127–137

[98] Cao B, Lu J, Tan Y et al. Efficacy and safety of submucosal tunneling endoscopic resection for gastric submucosal tumors: a systematic review and meta-analysis. *Rev Espanola Enfermedades Dig* 2021; 113: 52–59

[99] Antonino G, Alberto M, Michele A et al. Efficacy and safety of gastric exposed endoscopic full-thickness resection without laparoscopic assistance: a systematic review. *Endosc Int Open* 2020; 8: E1173–E1182

[100] Meier B, Schmidt A, Glaser N et al. Endoscopic full-thickness resection of gastric subepithelial tumors with the gFTRD-system: a prospective pilot study (RESET trial). *Surg Endosc* 2020; 34: 853–860

[101] Hajifathalian K, Ichkhianian Y, Dawod Q et al. Full-thickness resection device (FTRD) for treatment of upper gastrointestinal tract lesions: the first international experience. *Endosc Int Open* 2020; 8: E1291–E1301

[102] Kappelle WFW, Backes Y, Valk GD et al. Endoscopic full-thickness resection of gastric and duodenal subepithelial lesions using a new, flat-based over-the-scope clip. *Surg Endosc* 2018; 32: 2839–2846

[103] Jin X-F, Gai W, Du R-L et al. Multiband mucosectomy versus endoscopic submucosal dissection and endoscopic submucosal excavation for GI submucosal tumors: short and long term follow-up. *BMC Cancer* 2019; 19: 893

[104] Zhang J-S, Ye L-P, Wang C-Y et al. Endoscopic submucosal enucleation of small gastric gastrointestinal stromal tumors with cross-shaped incision: report of sixty-nine cases. *Hepatogastroenterology* 2012; 59: 440–443

[105] Xiu H, Zhao C-Y, Liu F-G et al. Comparing about three types of endoscopic therapy methods for upper gastrointestinal submucosal tumors originating from the muscularis propria layer. *Scand J Gastroenterol* 2019; 54: 1481–1486

[106] Chen Y, Wang M, Zhao L et al. The retrospective comparison between submucosal tunneling endoscopic resection and endoscopic submucosal excavation for managing esophageal submucosal tumors originating from the muscularis propria layer. *Surg Endosc* 2020; 34: 417–428

[107] Xu H-W, Zhao Q, Yu S-X et al. Comparison of different endoscopic resection techniques for submucosal tumors originating from muscularis propria at the esophagogastric junction. *BMC Gastroenterol* 2019; 19: 174

[108] Zhu Y, Xu M-D, Xu C et al. Microscopic positive tumor margin does not increase the rate of recurrence in endoscopic resected gastric mesenchymal tumors compared to negative tumor margin. *Surg Endosc* 2020; 34: 159–169

[109] Zhai Y-Q, Chai N-L, Li H-K et al. Endoscopic submucosal excavation and endoscopic full-thickness resection for gastric schwannoma: five-year experience from a large tertiary center in China. *Surg Endosc* 2020; 34: 4943–4949

[110] Lee SW, Sung JK, Cho YS et al. Comparisons of therapeutic outcomes in patients with nonampullary duodenal neuroendocrine tumors (NADNETs): A multicenter retrospective study. *Medicine (Baltimore)* 2019; 98: e16154

[111] Vanoli A, La Rosa S, Klersy C et al. Four neuroendocrine tumor types and neuroendocrine carcinoma of the duodenum: Analysis of 203 cases. *Neuroendocrinology* 2017; 104: 112–125

[112] Gincul R, Ponchon T, Napoleon B et al. Endoscopic treatment of sporadic small duodenal and ampullary neuroendocrine tumors. *Endoscopy* 2016; 48: 979–986

[113] Kim GH, Kim JI, Jeon SW et al. Endoscopic resection for duodenal carcinoid tumors: a multicenter, retrospective study. *J Gastroenterol Hepatol* 2014; 29: 318–324

[114] Hatta W, Koike T, Iijima K et al. The risk factors for metastasis in non-ampullary duodenal neuroendocrine tumors measuring 20 mm or less in diameter. *Digestion* 2017; 95: 201–209

[115] Dasari BVM, Al-Shakhsir S, Pawlik TM et al. Outcomes of surgical and endoscopic resection of duodenal neuroendocrine tumours (NETs): A systematic review of the literature. *J Gastrointest Surg* 2018; 22: 1652–1658

[116] Oono Y, Shinmura K, Hori K et al. Endoscopic submucosal resection using a ligation device without injection for duodenal neuroendocrine tumors. *Surg Endosc* 2019; 33: 2008–2014

[117] Nishio M, Hirasawa K, Ozeki Y et al. Short- and long-term outcomes of endoscopic submucosal dissection for non-ampullary duodenal neuroendocrine tumors. *Ann Gastroenterol* 2020; 33: 265–271

[118] Klemm N, Lu-Cleary D, Chahal D et al. Endoscopic management of diminutive duodenal neuroendocrine tumors. *J Gastrointest Cancer* 2020; 52: 448–453

[119] Bauder M, Schmidt A, Caca K. Endoscopic full-thickness resection of duodenal lesions—a retrospective analysis of 20 FTRD cases. *United Eur Gastroenterol J* 2018; 6: 1015–1021

[120] Khara HS, Shovlin GJ, Johal AS et al. Endoscopic banding without resection (BWR) technique for treatment of diminutive neuroendocrine tumors in the duodenum. *Endosc Int Open* 2019; 7: E302–E307 doi:10.1055/a-0684-9563

[121] Exarchou K, Moore AR, Smart HL et al. A “watch and wait” strategy involving regular endoscopic surveillance is safe for many patients with small, sporadic, grade 1, non-ampullary, non-functioning duodenal neuroendocrine tumours. *Neuroendocrinology* 2020; doi:10.1159/000511613

[122] Ren Z, Lin S-L, Zhou P-H et al. Endoscopic full-thickness resection (EFTR) without laparoscopic assistance for nonampullary duodenal subepithelial lesions: our clinical experience of 32 cases. *Surg Endosc* 2019; 33: 3605–3611 doi:10.1007/s00464-018-06644-3

[123] de Mestier L, Lorenzo D, Fine C et al. Endoscopic, transanal, laparoscopic, and transabdominal management of rectal neuroendocrine tumors. *Best Pract Res Clin Endocrinol Metab* 2019; 33: 101293

[124] Zhou X, Xie H, Xie L et al. Factors associated with lymph node metastasis in radically resected rectal carcinoids: a systematic review and meta-analysis. *J Gastrointest Surg* 2013; 17: 1689–1697

[125] Kuiper T, van Oijen MGH, van Velthuysen MF et al. Endoscopically removed rectal NETs: a nationwide cohort study. *Int J Colorectal Dis* 2021; 36: 535–541

[126] Chen T, Yao L-Q, Xu M-D et al. Efficacy and safety of endoscopic submucosal dissection for colorectal carcinoids. *Clin Gastroenterol Hepatol* 2016; 14: 575–581

[127] Bang BW, Park JS, Kim HK et al. Endoscopic resection for small rectal neuroendocrine tumors: comparison of endoscopic submucosal resection with band ligation and endoscopic submucosal dissection. *Gastroenterol Res Pract* 2016; 2016: 6198927

[128] Zhang H-P, Wu W, Yang S et al. Endoscopic treatments for rectal neuroendocrine tumors smaller than 16 mm: a meta-analysis. *Scand J Gastroenterol* 2016; 51: 1345–1353

[129] Pan J, Zhang X, Shi Y et al. Endoscopic mucosal resection with suction vs. endoscopic submucosal dissection for small rectal neuroendocrine tumors: a meta-analysis. *Scand J Gastroenterol* 2018; 53: 1139–1145

[130] Zheng J-C, Zheng K, Zhao S et al. Efficacy and safety of modified endoscopic mucosal resection for rectal neuroendocrine tumors: a meta-analysis. *Z Gastroenterol* 2020; 58: 137–145

[131] Ramage JK, Valle JW, Nieveen van Dijkum EJM et al. Colorectal neuroendocrine neoplasms: areas of unmet need. *Neuroendocrinology* 2019; 108: 45–53

[132] Stier MW, Chapman CG, Shamah S et al. Endoscopic resection is more effective than biopsy or EUS to detect residual rectal neuroendocrine tumor. *Endosc Int Open* 2021; 9: E4–E8

[133] Xu M, Wang X-Y, Zhou P-H et al. Endoscopic full-thickness resection of colonic submucosal tumors originating from the muscularis propria: an evolving therapeutic strategy. *Endoscopy* 2013; 45: 770–773

[134] Yoon YS, Cho YB, Park KJ et al. Surgical outcomes of Korean ulcerative colitis patients with and without colitis-associated cancer. *World J Gastroenterol* 2015; 21: 3547–3553

[135] Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol* 2006; 23: 70–83

[136] Zwager LW, Bastiaansen BAJ, Bronzwaer MES et al. Endoscopic full-thickness resection (eFTR) of colorectal lesions: results from the Dutch colorectal eFTR registry. *Endoscopy* 2020; 52: 1014–1023

[137] Clark OH, Benson AB, Berlin JD et al. NCCN Clinical practice guidelines in oncology: Neuroendocrine tumors. *J Natl Compr Cancer Netw JNCCN* 2009; 7: 712–747

[138] Scherübl H, Cadiot G. Early gastroenteropancreatic neuroendocrine tumors: Endoscopic therapy and surveillance. *Visc Med* 2017; 33: 332–338