

Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2022



Authors

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MAIN RECOMMENDATIONS

ESGE recommends that the evaluation of superficial gastrointestinal (GI) lesions should be made by an experienced endoscopist, using high definition white-light and chromoendoscopy (virtual or dye-based).

ESGE does not recommend routine performance of endoscopic ultrasonography (EUS), computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)-CT prior to endoscopic resection.

ESGE recommends endoscopic submucosal dissection (ESD) as the treatment of choice for most superficial esophageal squamous cell and superficial gastric lesions.

For Barrett's esophagus (BE)-associated lesions, ESGE suggests the use of ESD for lesions suspicious of submucosal invasion (Paris type 0-Is, 0-IIc), for malignant lesions >20 mm, and for lesions in scarred/fibrotic areas.

ESGE does not recommend routine use of ESD for duodenal or small-bowel lesions.

ESGE suggests that ESD should be considered for en bloc resection of colorectal (but particularly rectal) lesions with suspicion of limited submucosal invasion (demarcated depressed area with irregular surface pattern or a large protruding or bulky component, particularly if the lesions are larger than 20 mm) or for lesions that otherwise cannot be completely removed by snare-based techniques.

ESGE recommends that an en bloc R0 resection of a superficial GI lesion with histology no more advanced than intramucosal cancer (no more than m2 in esophageal squamous cell carcinoma), well to moderately differentiated, with no

lymphovascular invasion or ulceration, should be considered a very low risk (curative) resection, and no further staging procedure or treatment is generally recommended.

ESGE recommends that the following should be considered to be a low risk (curative) resection and no further treatment is generally recommended: an en bloc R0 resection of a superficial GI lesion with superficial submucosal invasion (sm1), that is well to moderately differentiated, with no lymphovascular invasion, of size ≤ 20 mm for an esophageal squamous cell carcinoma or ≤ 30 mm for a stomach lesion or of any size for a BE-related or colorectal lesion, and with no lymphovascular invasion, and no budding grade 2 or 3 for colorectal lesions.

ESGE recommends that, after an endoscopically complete resection, if there is a positive horizontal margin or if resection is piecemeal, but there is no submucosal invasion and no other high risk criteria are met, this should be considered a local-risk resection and endoscopic surveillance or re-treatment is recommended rather than surgery or other additional treatment.

ESGE recommends that when there is a diagnosis of lymphovascular invasion, or deeper infiltration than sm1, or positive vertical margins, or undifferentiated tumor, or, for colorectal lesions, budding grade 2 or 3, this should be considered a high risk (noncurative) resection, and complete staging and strong consideration for additional treatments should be considered on an individual basis in a multidisciplinary discussion.

ESGE recommends scheduled endoscopic surveillance with high definition white-light and chromoendoscopy (virtual or dye-based) with biopsies of only the suspicious areas after a curative ESD.

SOURCE AND SCOPE

This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). It is an update of the previous 2015 Guideline addressing the role of endoscopic submucosal dissection (ESD) for superficial gastrointestinal lesions.

1 Introduction

This Guideline represents an update of the Guideline on the role of endoscopic submucosal dissection (ESD) for superficial gastrointestinal (GI) lesions, published by the European Society of Gastrointestinal Endoscopy (ESGE) in 2015 [1].

This evidence-based Guideline was commissioned by ESGE. It addresses major issues concerning ESD, that is, evaluation before ESD, comparison with other therapeutic strategies, namely endoscopic mucosal resection (EMR) and surgery, and management after ESD, to inform and underpin the use of this fundamental technique for the treatment of superficial GI lesions.

ABBREVIATIONS

AE	adverse event
BE	Barrett's esophagus
BLI	blue-light imaging
CE	chromoendoscopy
CI	confidence interval
CRC	colorectal cancer
CRD	complete remission of dysplasia
CRIM	complete remission of intestinal metaplasia
CRT	chemoradiotherapy
CT	computed tomography
DSS	disease-specific survival
EAC	esophageal adenocarcinoma
EGC	early gastric cancer
EMR	endoscopic mucosal resection
ER	endoscopic resection
ESD	endoscopic submucosal dissection
ESGE	European Society of Gastrointestinal Endoscopy
EUS	endoscopic ultrasonography
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HGD	high grade dysplasia
HM	horizontal margin
JES	Japan Esophageal Society
JNET	Japan NBI Expert Team
JGES	Japan Gastroenterological Endoscopy Society
LCE	Lugol chromoendoscopy
LNM	lymph node metastasis
LST	laterally spreading tumor
ME	magnification endoscopy
MRI	magnetic resonance imaging
NBI	narrow-band imaging
NICE	NBI International Colorectal Endoscopic [classification]
NPV	negative predictive value
OR	odds ratio
OS	overall survival
OTS	over-the-scope
P-CAB	potassium-competitive acid-blocker
PEECS	post-ESD electrocoagulation syndrome
PET	positron emission tomography
PICO	patients, interventions, controls, outcomes
PPI	proton pump inhibitors
PPV	positive predictive value
RFA	radiofrequency ablation
SCC	squamous cell carcinoma
USD	United States dollar
VM	vertical margin
TEM	transanal endoscopic microsurgery
WLE	white-light endoscopy

This Guideline does not address the skills and knowledge that the endoscopist should have to perform ESD, or the specific

management of antithrombotic or other medications in the periprocedural setting, or quality measurements, as these are addressed in separate guidelines [2, 3]. A companion Technical Review will be published separately, that will cover prevention strategies regarding ESD complications and detailed technical issues.

2 Methods

ESGE commissioned this Guideline and appointed a guideline leader (P.P.N.) who invited the listed authors to participate in its development. The key PICO (patients, interventions, controls, outcomes) questions were prepared by the coordinating team (P.P.N., J.v.H., M.D.R.) and then approved by the other members. The coordinating team formed organ-based task force subgroups, each with its own leader, and divided the key topics (pretreatment evaluation, treatment, management after treatment) among these task forces (see **Appendix 1 s**, 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, with a focus on articles published from January 2015 until January 2021, after the literature review of the previous ESD guideline. Searches were performed in PubMed. 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 by the level of evidence and strength of recommendation, according to the GRADE system [4, 5].

Each task force proposed statements on their assigned key questions which were discussed and voted on at a virtual meeting in February 2021. In August 2021, new relevant articles published up till that date were considered and reviewed, and a draft prepared by the leaders and coordinating team was sent to all group members. Statements were only approved when the consensus was greater than 80%. ► **Table 1** gives a complete list of statements.

The manuscript was also reviewed by two members of the ESGE Governing Board and sent for further comments to the 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.

Evidence tables created from the literature review are presented in the Supplementary Material of this Guideline (**Table 1 s**, Esophageal squamous cell carcinoma (SCC); **Table 2 s**, Barrett's esophagus (BE); **Table 3 s**, Stomach; **Table 4 s**, Duodenum; **Table 5 s**, Colorectum).

Organ-specific decision algorithms are presented in ► **Figs. 1–4**.

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>.

► **Table 1** Endoscopic submucosal dissection (ESD) for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2022. Complete list of statements.

Pretreatment evaluation

1 ESGE recommends that the evaluation of superficial gastrointestinal lesions should be made by an experienced endoscopist, using high definition white-light and chromoendoscopy (virtual or dye-based), and validated classifications when available.
Strong recommendation, high quality evidence.

2 ESGE does not recommend routine performance of endoscopic ultrasonography (EUS), computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography CT (PET-CT) prior to endoscopic resection (ER).
Strong recommendation, moderate quality evidence.

3 ESGE suggests that when suspicious features for deep submucosal invasion are present, complete staging should be considered in order to exclude stage T2/T3 or lymph node metastasis (LNM).
Weak recommendation, low quality evidence.

Therapeutic options

4 ESGE recommends ESD as the treatment of choice for most esophageal squamous cell and gastric (or junctional non-Barrett's) superficial lesions, mainly to provide an en bloc potentially curative resection with accurate pathologic staging.
Strong recommendation, moderate quality evidence.

5 ESGE suggests that ESD might also be considered for en bloc resection of noncircumferential clinically staged T1a-m3/T1b-sm1 or circumferential clinically staged T1a-m1/m2 esophageal squamous cell carcinoma (SCC)
Weak recommendation, moderate quality evidence.

6 For Barrett's esophagus (BE)-associated lesions, ESGE recommends to use endoscopic mucosal resection (EMR) for ≤ 20 mm visible lesions with low probability of submucosal invasion (Paris type 0-IIa, 0-IIb) and for larger or multifocal benign (dysplastic) lesions.
Strong recommendation, high quality evidence.

7 For BE-associated lesions, ESGE suggests to use ESD for lesions suspicious for submucosal invasion (Paris type 0-Is, 0-IIc), for malignant lesions > 20 mm, and for lesions in scarred/fibrotic areas.
Weak recommendation, low quality evidence.

8 ESGE recommends ESD for differentiated gastric lesions clinically staged as dysplastic or as intramucosal carcinomas (of any size if not ulcerated and ≤ 30 mm if ulcerated), with EMR being an alternative for Paris 0-IIa lesions of size ≤ 10 mm with low likelihood of malignancy.
Strong recommendation, moderate quality evidence.

9 ESGE suggests that gastric adenocarcinomas that are ≤ 30 mm, superficial, submucosal (sm1), and well-differentiated, or ≤ 20 mm, intramucosal, and poorly differentiated type, both without ulcerative findings, can be considered for ESD, although the decision should be individualized.
Weak recommendation, low quality evidence.

10 ESGE does not recommend routine use of ESD for duodenal or small-bowel lesions, with its use being reserved for selected cases in expert centers.
Strong recommendation, moderate quality evidence.

11 ESGE recommends polypectomy and/or EMR (en bloc or piecemeal) as the treatment of choice for most duodenal and small-bowel superficial lesions.
Strong recommendation, moderate quality evidence.

12 ESGE recommends polypectomy and/or EMR (en bloc or piecemeal) as the treatment of choice for most superficial colorectal lesions.
Strong recommendation, high quality evidence.

13 ESGE suggests that ESD should be considered for en bloc resection of colorectal (but particularly rectal) lesions with suspicion of limited submucosal invasion (demarcated depressed area with irregular surface pattern or a large protruding or bulky component, particularly if the lesions are larger than 20 mm), or for lesions that otherwise cannot be completely removed by snare-based techniques.
Weak recommendation, moderate quality evidence.

Management after ER

Esophageal SCCs

14 ESGE recommends that an en bloc R0 resection of a superficial esophageal squamous cell lesion with histology no more advanced than intramucosal m2 cancer, well to moderately differentiated, with no lymphovascular invasion, should be considered a very low risk (curative) resection and no further staging procedure or treatment is recommended.
Strong recommendation, moderate quality evidence.

15 ESGE suggests that an en bloc R0 resection of an esophageal m3 or sm1 SCC that is well to moderately differentiated and with no lymphovascular invasion, should be considered a low risk (curative) resection and no further treatment is generally recommended.
Weak recommendation, moderate quality evidence.
However, in these cases, particularly if the lesion is bigger than 20 mm, there is a real (albeit low) risk of lymph node metastasis (LNM) and complete staging is recommended with the risk from further therapy being balanced against the risk of LNM, in a multidisciplinary discussion.
Weak recommendation, low quality evidence.

16 ESGE suggests that complementary radiotherapy or chemoradiotherapy (CRT) may be considered in a multidisciplinary discussion after a curative resection of esophageal m3/sm1 SCC (particularly if > 20 mm in size).
Weak recommendation, moderate quality evidence.

BE-associated lesions

17 ESGE recommends that an en bloc R0 resection of a BE-associated superficial lesion with histology no more advanced than intramucosal cancer, well to moderately differentiated, with no lymphovascular invasion, should be considered a very low risk (curative) resection and no further staging procedure is generally recommended.
Strong recommendation, moderate quality evidence.

18 ESGE suggests that an en bloc R0 resection of a BE-associated superficial lesion with superficial submucosal invasion (sm1), and that is well to moderately differentiated, and with no lymphovascular invasion, should be considered a low risk (curative) resection and no further treatment (except for ablation of BE tissue) is generally recommended.
Weak recommendation, moderate quality evidence.
However, in these cases, there is a real (albeit low) risk of LNM, and complete staging is recommended with the risk from further therapy (surgery) being balanced against the risk of LNM, in a multidisciplinary discussion.
Weak recommendation, low quality evidence.

19 ESGE recommends ablation of all of the Barrett's mucosa after a curative or local-risk resection.
Strong recommendation, high quality evidence.

Gastric lesions

20 ESGE recommends that an en bloc R0 resection of a superficial gastric lesion with histology no more advanced than intramucosal cancer, well to moderately differentiated, with no lymphovascular invasion, should be considered a very low risk (curative) resection, independently of size if without ulceration or of lesions ≤ 30 mm if ulcerated, and no further staging procedure or treatment is generally recommended.
Strong recommendation, moderate quality evidence.

21 ESGE suggests that an en bloc R0 resection of a ≤ 30 mm gastric adenocarcinoma, with superficial submucosal invasion (sm1), that is well to moderately differentiated and with no lymphovascular invasion and no ulcer, should be considered a low risk (curative) resection and no further treatment is generally recommended.
Weak recommendation, moderate quality evidence.
However, in these cases there is a real (albeit low) risk of LNM and complete staging is recommended with the risk from further therapy (surgery) being balanced against the risk of LNM, in a multidisciplinary discussion.
Weak recommendation, moderate quality evidence.

22 ESGE suggests that an en bloc R0 resection of a ≤ 20 mm gastric intramucosal poorly differentiated carcinoma, with no lymphovascular invasion or ulcer, should be considered a low risk (curative) resection and no further treatment is generally recommended.
Weak recommendation, moderate quality evidence.
However, in these cases there is a real (albeit low) risk of LNM and complete staging is recommended with the risk from further therapy (surgery) being balanced against the risk of LNM, in a multidisciplinary discussion.
Weak recommendation, moderate quality evidence.

23 ESGE recommends that a resection of a > 30 mm gastric adenocarcinoma with superficial submucosal invasion (sm1) or with ulceration should be considered a high risk (noncurative) resection and complete staging should be done and strong consideration for additional treatments (surgery) should be given on an individual basis in a multidisciplinary discussion.
Strong recommendation, moderate quality evidence.

Duodenal/small-bowel lesions

24 ESGE suggests that, given the lack of evidence, the same post-resection criteria as in the colon should apply to the management of duodenal and small-bowel lesions, on an individual basis and with a multidisciplinary approach.
Weak recommendation, very low quality evidence.

Colorectal lesions

25 ESGE recommends that an en bloc R0 resection of a colorectal lesion with histology no more advanced than intramucosal adenocarcinoma, well to moderately differentiated, with no lymphovascular invasion, should be considered a very low risk (curative) resection and no further staging procedure or treatment is generally recommended.
Strong recommendation, high quality evidence.

26 ESGE recommends that an en bloc R0 resection of a colorectal lesion with superficial submucosal invasion (sm1), that is well to moderately differentiated and with no lymphovascular invasion and no grade 2 or 3 budding, should be considered a low risk (curative) resection, and no further treatment is generally recommended.
Strong recommendation, high quality evidence.

27 ESGE suggests that after an en bloc R0 resection of a rectal lesion meeting the single high risk criterion of submucosal invasion deeper than sm1 (well to moderately differentiated with no lymphovascular invasion and no grade 2 or 3 budding), CRT and/or surveillance might be preferred over surgery on an individual basis in a multidisciplinary approach.
Weak recommendation, very low quality evidence.

All organs

28 ESGE recommends that after an endoscopic complete resection, if there is a positive horizontal margin or if resection is piecemeal, but there is no submucosal invasion and no other high risk criteria are met, this should be considered a local-risk resection and endoscopic surveillance/re-treatment is recommended rather than surgery or other additional treatment.
Strong recommendation, moderate quality evidence.

29 ESGE recommends that when there is a diagnosis of lymphovascular invasion or deeper infiltration than sm1 or positive vertical margins or undifferentiated tumor or, for colorectal lesions, grade 2 or 3 budding, that the resection should be considered a high risk (noncurative) resection; complete staging should be done and strong consideration for additional treatments (chemoradiotherapy and/or surgery) should be given, on an individual basis in a multidisciplinary discussion.
Strong recommendation, moderate quality evidence.

Surveillance after endoscopic resection

30 ESGE recommends scheduled endoscopic surveillance with high definition white-light and chromoendoscopy (virtual or dye-based) with biopsies of only the suspicious areas after a curative ESD.
Strong recommendation, moderate quality evidence.

31 ESGE recommends that after piecemeal resection or in the presence of positive lateral margins when criteria for additional treatment are not met, a high definition chromoendoscopy (virtual and/or dye-based) with biopsies is recommended at 3–6 months.
Weak recommendation, low quality evidence.

32 For upper GI superficial lesions, ESGE suggests endoscopy at 3–6 months and then annually after a curative ESD resection or after a local-risk ESD resection without recurrence.
Weak recommendation, low quality evidence.

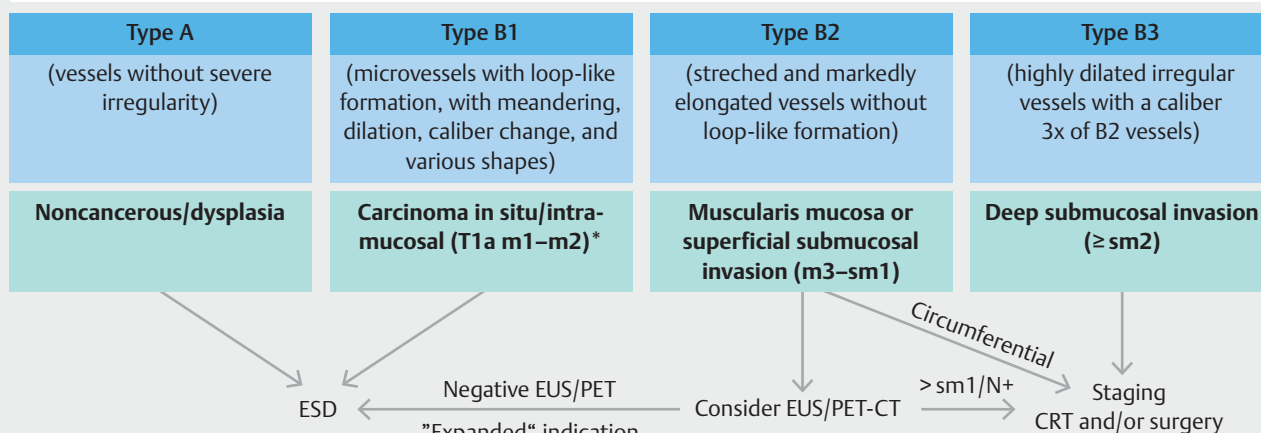
33 ESGE suggests colonoscopy at 12 months and then further surveillance in accordance with polypectomy and colorectal cancer guidelines, after a local-risk ESD resection without recurrence or after a low or very low risk (curative) ESD of a colorectal malignant lesion.
Weak recommendation, low quality evidence.

34 ESGE does not suggest routine use of EUS, MRI, CT, or PET in the follow-up after a very low or low risk (curative) endoscopic resection, but this might be considered in the cases of T1a-m3/T1b-sm1 esophageal SCC particularly if no additional treatment has been decided.
Weak recommendation, low quality evidence.

Esophageal squamous cell lesion

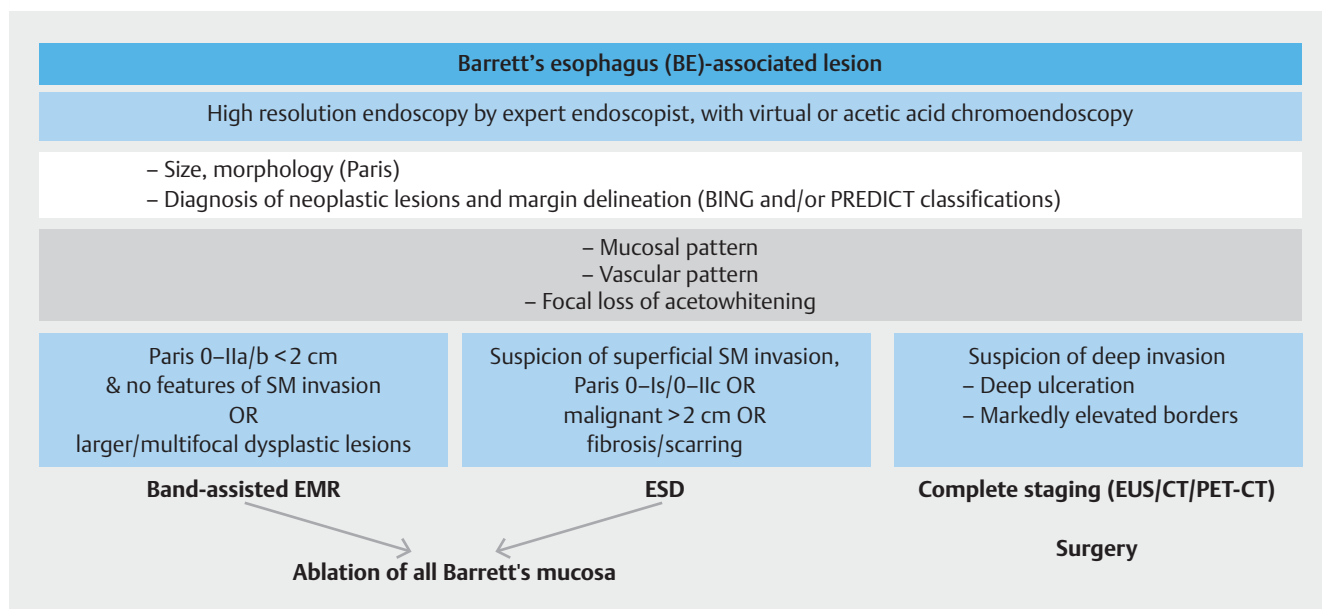
High resolution endoscopy by expert endoscopist, with virtual chromoendoscopy (dye chromoendoscopy if not available)

- Size, morphology (Paris), margin delineation
- Estimation of invasion depth (Japan Esophageal Society magnifying endoscopy classification if possible)

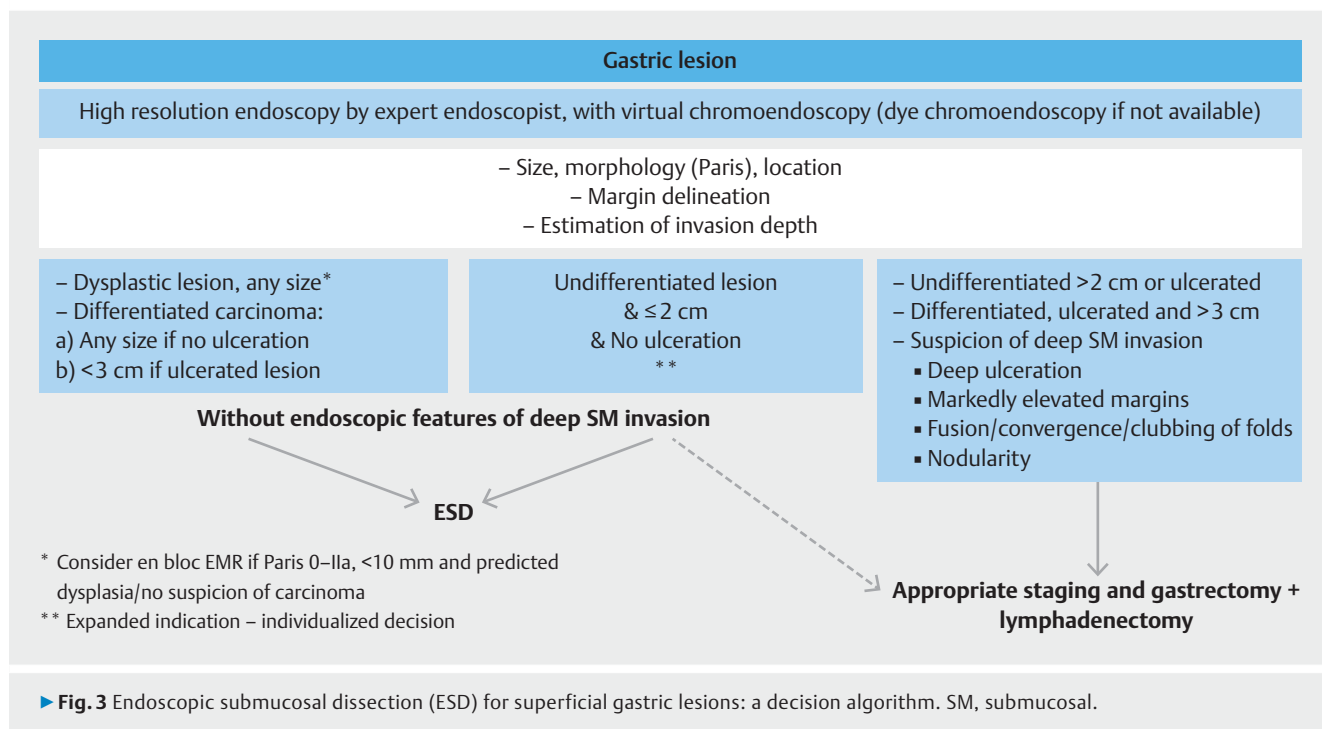


* If circumferential, "expanded" indication

► **Fig. 1** Endoscopic submucosal dissection (ESD) for superficial esophageal squamous cell cancers (SCCs): a decision algorithm. CRT, chemoradiotherapy, CT, computed tomography; EUS, endoscopic ultrasonography; PET, positron emission tomography.



► **Fig. 2** Endoscopic submucosal dissection (ESD) for Barrett's esophagus (BE)-related lesions: a decision algorithm. BING, Barrett's International NBI Group; CT, computed tomography; EMR, endoscopic mucosal resection; EUS, endoscopic ultrasonography; PET, positron emission tomography; PREDICT, Portsmouth acetic acid classification; SM, submucosal.



► **Fig. 3** Endoscopic submucosal dissection (ESD) for superficial gastric lesions: a decision algorithm. SM, submucosal.

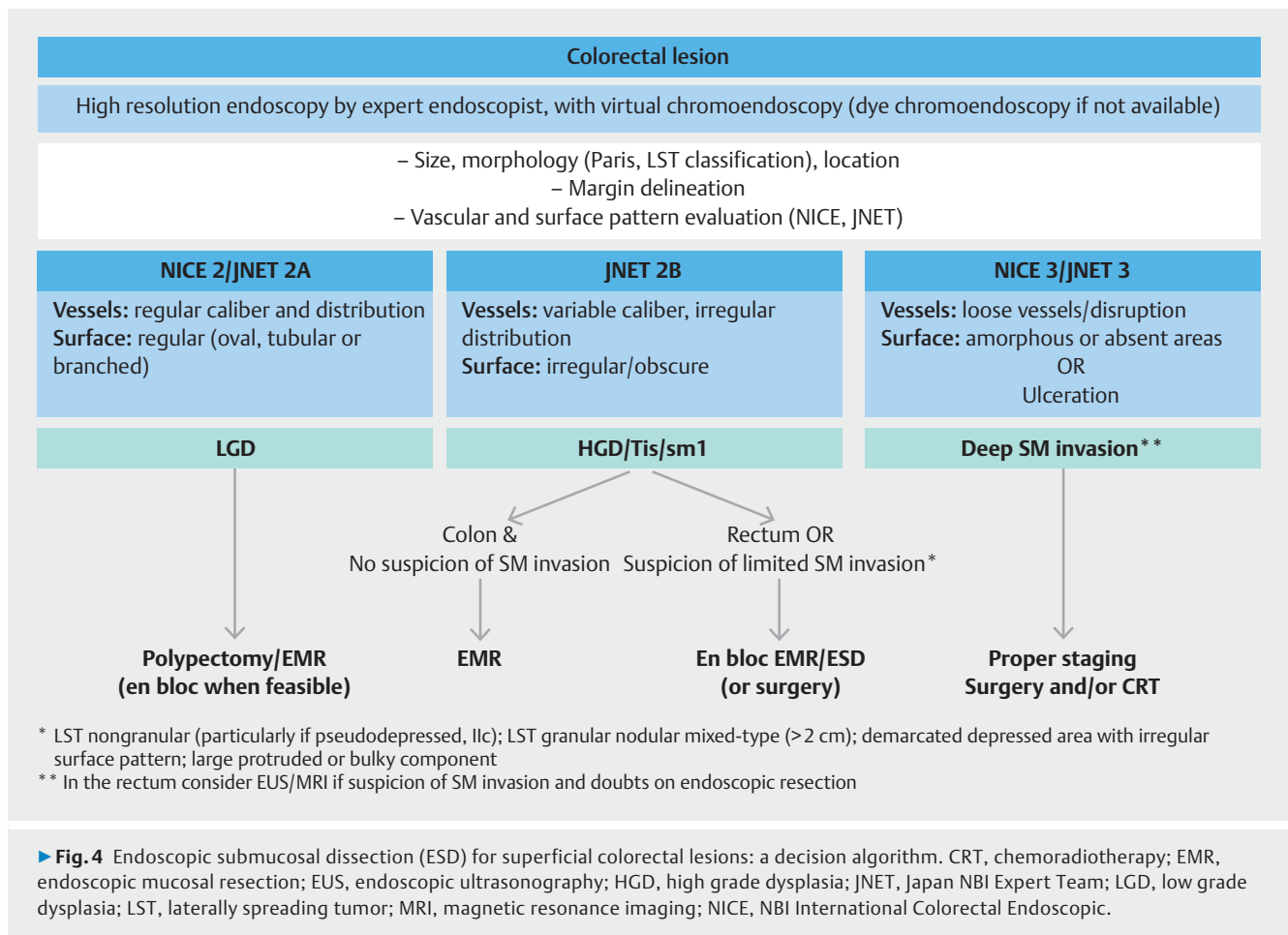
3 Pretreatment evaluation

3.1 Endoscopic evaluation

Successful curative resection of a superficial GI lesion can only be achieved by precise characterization of the lesion, optimal delineation of tumor margins, and estimation of depth of invasion, and this can only be correctly assessed by experienced endoscopists. The morphology of all visible lesions should be

RECOMMENDATION

1 ESGE recommends that the evaluation of superficial gastrointestinal lesions should be done by an experienced endoscopist, using high definition white-light and chromoendoscopy (virtual or dye-based), and validated classifications when available.
Strong recommendation, high quality evidence.



described using the Paris classification since this gives an indication of the likelihood of invasive cancer [6].

Considering the increased availability of virtual chromoendoscopy (CE) techniques, the absence of side effects, shorter duration of the procedure, and similar or better accuracy in detecting and delineating the resection margins of lesions, as compared to dye-based CE, virtual CE (complementing high resolution white-light endoscopy [WLE]) should be the standard of care for pretreatment evaluation of superficial GI lesions [7].

3.1.1 Esophageal squamous cell carcinoma (SCC) lesions

The 2015 ESGE guideline recommended virtual CE (narrow-band imaging [NBI], blue-light imaging [BLI]) as an alternative to Lugol CE (LCE) for the detection of superficial esophageal SCC. Both methods have been proven to be more accurate than WLE alone [1]. CE provides a high diagnostic rate in evaluating the esophagus to diagnose SCC. A meta-analysis showed that NBI has comparable sensitivity to that of LCE (88% vs. 92%), but superior specificity (88% vs. 82%, $P < 0.001$) [8]. The higher specificity was confirmed in a prospective randomized trial, even when the technique was used by nonexperts [9]. A recent study compared LCE with NBI for delineation of tumor mucosal margins before endoscopic resection of SCC, and found no difference in the complete lateral resection rate [10]. Thus, virtual CE appears to be the optimal method for detection and

delineation of esophageal SCC, with the more cumbersome LCE remaining as an option.

For determining depth of invasion also, WLE appears to be suboptimal when compared to virtual CE [11]. The Japan Esophageal Society (JES) proposed a new simplified magnifying endoscopy (ME)-CE classification for estimating the depth of invasion of superficial esophageal SCC [12]. The JES classification categorized the lesions according to the type of microvessels: type A microvessels without severe irregularity correspond to noncancerous/low grade dysplastic lesions; type B microvessels with severe irregularity are suggestive of cancerous lesions. Type B is further divided into three categories: B1 corresponds to high grade intraepithelial neoplasia or intramucosal carcinoma m1 or m2; B2 to carcinoma invading the muscularis mucosae/m3 or sm1; and B3 to at least sm2 tumors. The overall accuracy of type B microvessels for predicting tumor invasion depth was 90.5% [12]. Most studies using this classification show an overall accuracy exceeding 80%–90%, and excellent interobserver agreement (over 0.85). Performance is excellent with type B1 tumors (88.6%; sensitivity 71.4%, specificity of 100%), and type B3 tumors (90.0%; sensitivity 75%, specificity 97.8%) [13, 14]. All these studies used ME-NBI, but a recent trial reported similar accuracies with ME-blue-light imaging (BLI) with concordance between ME-NBI and ME-BLI of 91.2% [15]. Based on these studies we propose that the newly developed

JES classification is useful in estimating the invasion depth of superficial SCC and, even though no study has been reported in the West, it can be considered in clinical practice.

3.1.2 Barrett's esophagus (BE)-associated lesions

Although early esophageal neoplasia in BE generally presents as subtle flat lesions that may be difficult to detect, most procedures performed with high resolution endoscopes do reveal these abnormalities to the experienced eye [16, 17]. Both virtual CE and acetic acid dye-based CE are easy to learn and interpret. Criteria have been developed in the new PREDICT classification to diagnose Barrett's neoplasia according to focal loss of acetowhitening and surface patterns of Barrett's mucosa [18]. Concerning acetic acid, a recent meta-analysis showed that pooled sensitivity, specificity, and positive and negative likelihood ratios (with 95% confidence intervals [95% CIs] shown in parentheses), for the diagnosis of high grade dysplasia (HGD) and Barrett's adenocarcinoma for all the included studies (9 studies, 1379 patients) were 0.92 (0.83–0.97), 0.96 (0.85–0.99), 25.0 (5.9–105.3), and 0.08 (0.04–0.18), respectively [19].

The BING working group developed a simple, internally validated system to identify dysplasia and esophageal adenocarcinoma (EAC) in patients with BE, based on NBI results. When images are assessed with a high degree of confidence, the system can classify neoplasia within Barrett's with >90% accuracy and a high level of interobserver agreement [20]. However, a recent study showed that its sensitivity and positive predictive value for the diagnosis of dysplasia may be low in daily practice [21].

These studies suggest that both CE methods are valuable tools with excellent performance when used by experienced observers and should be used for evaluation of Barrett's dysplasia, alone or simultaneously.

3.1.3 Stomach lesions

Diagnosis and evaluation of early gastric cancer (EGC) lesions is clearly improved by CE when compared to WLE [22]. Virtual CE with ME has high accuracy in delineating horizontal margins before ESD and performs equally well as or better than dye-based CE [23–25]. CE has also the potential for predicting EGC differentiation [26, 27]. Several studies also suggest that CE can be used for prediction of depth of invasion, with a blurry mucosal and irregular mesh pattern suggesting submucosal invasion, with a global accuracy superior to 80% [27–30]. However, no validated classification exists nor is there any study suggesting that CE is better than standard high resolution WLE for this purpose, and the decision not to endoscopically resect the lesion is still based mainly on macroscopic features of the lesion (► Fig. 3).

3.1.4 Duodenal lesions

Data are scarce on the pretherapeutic evaluation of duodenal neoplasia. In a single-center trial the ability of virtual CE to distinguish adenoma from intramucosal cancers was evaluated, with a mixed or absent pattern having 72% accuracy with moderate interobserver agreement (kappa 0.59) [31]. Endoscopic

prediction of invasion depth of early duodenal neoplasia has never been compared with that of EUS, CT, or other imaging modalities, and therefore pre-ESD staging is still based on endoscopic evaluation [32].

3.1.5 Colorectal lesions

In patients with large colorectal laterally spreading tumors (LSTs) resected endoscopically, the risk of pathological T1 cancer can be predicted on the basis of the laterally spreading tumor (LST) subclassification and tumor diameter [33]. To determine the indication for ESD or EMR, overall judgment based on the subclassification of LST, vessel, surface, and pit pattern diagnosed by means of CE observation is useful. Distinction between adenoma and adenocarcinoma can be achieved with high accuracy using high resolution endoscopy and CE observation [34, 35]. For this purpose, NICE (NBI International Colorectal Endoscopic) and JNET (Japan NBI Expert Team) classifications have been associated with high accuracy in determining the histology of the lesion [36, 37]. Thus, the indication for EMR, ESD or surgery will be made on macroscopic morphological features and on more detailed features assessed by advanced imaging techniques (see ► Fig. 4) [38, 39]. The latter were recently addressed in an ESGE guideline [40].

3.2 Endoscopic ultrasonography and other modalities

RECOMMENDATION

2 ESGE does not recommend routine performance of endoscopic ultrasonography (EUS), computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography CT (PET-CT) prior to endoscopic resection (ER).
Strong recommendation, moderate quality evidence.

RECOMMENDATION

3 ESGE suggests that when suspicious features for deep submucosal invasion are present, complete staging should be considered in order to exclude stage T2/T3 or lymph node metastasis (LNM).
Weak recommendation, low quality evidence.

3.2.1 Esophageal SCC lesions

Given the results shown with endoscopy, particularly when complemented with virtual magnifying endoscopy with chromoendoscopy (ME-CE), the role of other staging modalities, including EUS, CT, MRI, or PET-CT, is doubtful in lesions with estimated depth of invasion of T1 m3–sm1 or less.

A meta-analysis performed in 2016 confirmed the limitations of EUS in detecting submucosal invasion, with pooled sensitivity and specificity for T1 versus T2–4 tumors of 77% (95% CI 73%–80%) and 95% (95% CI 94%–96%), respectively. Among the T1 tumors, EUS had a pooled sensitivity in distinguishing between T1a and T1b of 83%–84% (95% CI 80%–88%), and a

specificity of 89% (95%CI 86%–92%) [41]. In the largest retrospective study focusing on EUS overstaging, the rate of overstaged pTis–T1a was 39.5% [42].

Several reports and a meta-analysis compared accuracy outcomes between EUS and ME-NBI, showing comparable results [43, 44]. In one of these reports, the sensitivity and accuracy of ME-NBI in distinguishing m1–m2 from m3/sm1 and from more deeply invasive SCCs was significantly higher than that of EUS ($P=0.048$ and $P=0.017$, respectively) [44]. Recent studies have emphasized the relevance of MRI and PET-CT with regard to T1 lesions, showing a high accuracy of MRI compared to EUS and CT [45,46], and a possible role for PET-CT in identifying T1a lesions when no uptake can be seen in the esophageal wall [47], but these studies need further validation. Nevertheless, since PET-CT is a standard staging method for advanced SCC, the combined use of PET-CT and high resolution CE, especially with microvascular findings of types B2 and B3, may be useful to determine whether ER is indicated for the lesion [48]. When the lesion is visible on PET, a therapeutic modality other than ER should be considered [47].

In summary, ME-CE is superior to WLE alone in estimating depth of invasion for esophageal SCC, and has at least a similar overall staging accuracy compared with EUS, without the limitations of EUS such as the risk of overstaging early endoscopically curable disease. JES type B2–B3 lesions or lesions with distinct features, such as nodular protrusion, ulceration, and depressed areas, should be considered to have the risk of submucosal invasion and are most likely to benefit from additional staging procedures such as EUS and PET-CT.

3.2.2 Barrett's esophagus (BE)-associated lesions

A meta-analysis of EUS staging of superficial esophageal adenocarcinoma (EAC) showed favorable pooled values for mucosal cancer staging, but unsatisfactory diagnostic results for EAC at the esophagogastric junction [49]. Even in lesions suspicious for malignancy (nodular or depressed lesions), resection of the lesion with histological examination had greater utility than staging by EUS [50]. Hence, EUS appears to be of limited utility in accurate staging of BE patients with high grade dysplasia (HGD) or early EAC [51]. Nevertheless, if deep submucosal invasion is suspected endoscopically, then complete staging should be performed with EUS, CT, and/or PET-CT.

3.2.3 Stomach lesions

The use of abdominal CT or PET-CT in the staging of endoscopically resectable early gastric cancer (EGC) does not have an established role because of the very low risk of distant metastasis. Moreover, perigastric adenopathy may be a nonpathological finding that can jeopardize ER. Regarding the use of these techniques in order to assess the feasibility of ESD in EGC, in recent years only a few studies have tried to use CT or PET-CT to predict the curability of EGC by ER; they have shown differing results, with an accuracy for CT scan of 60% [52] whilst PET-CT showed sensitivity, specificity, PPV, and NPV of 79%, 91%, 81%, and 89%, respectively [53].

The role of EUS in the staging of EGC is also debatable. In a recent meta-analysis, for invasion depth EUS showed sensitivity

and specificity of 0.87 (95%CI 0.86–0.88) and 0.67 (95%CI 0.65–0.70), respectively. The overall overstaging rates for m1–3 and sm1 tumors by EUS were 13.3% and 32.8%, respectively, while the overall understaging rate for sm tumors was 29.7%. The total misdiagnosis rates for EUS were 30.4% for lesions ≥ 2 cm and 20.9% for lesions < 2 cm, 27.7% for ulcerative lesions and 21.4% for nonulcerative lesions, and 22% for differentiated lesions and 26.9% for undifferentiated lesions [54]. Globally, the overall accuracy varied from 71.5% [55] to 95% [56].

It should be noted that endoscopy alone (even without CE) has almost 80% accuracy in determining curability by ER, with several prediction models described to decide between ESD or surgery, with good results published in the literature [57–59]. Moreover, ESD does not preclude the possibility of subsequent surgery and should be seen as the most definitive T-staging modality.

To conclude, EUS, CT, or PET do not add to endoscopic evaluation alone, they have significant rates of over- and understaging, and cannot be recommended routinely, particularly for lesions that are considered endoscopically resectable.

3.2.4 Colorectal lesions

A subset analysis of a multicenter randomized controlled trial (RCT) comparing CE with EUS for staging of early colorectal cancer (CRC) showed no advantage of EUS over CE, with a global accuracy of 78% for both techniques [60]. Since the 2015 guideline, four new meta-analyses have been published that address the diagnostic accuracy of EUS, CT, and MRI. Overall, with indirect comparison, no significant differences in T or N staging could be found between CT, MRI, or EUS, in the setting of a newly diagnosed rectal lesion that is being considered for endoscopic therapy. Accuracy in distinguishing T1 from T2 cancers is limited for both EUS and MRI, with a serious risk for overstaging [61–64].

Based on those studies we recommend that all colorectal lesions should be described according to laterally spreading tumor (LST) type, CE features, and location, in order to predict the risk of submucosal invasion and, hence, choose the best therapeutic option. EUS and/or MRI may have a role in the rectum when suspicious features of submucosal invasion are present. As ER might create inflammatory lymph nodes around the rectum, in these cases staging should preferably be done before any eventual resection; however, in cases with T-stage discrepancy between optical evaluation and EUS/MRI, the endoscopic evaluation should carry greater weight. Complete staging is recommended in lesions with optical features for deep submucosal invasion.

4 Therapeutic options

4.1 Esophageal SCC lesions

RECOMMENDATION

4 ESGE recommends ESD as the treatment of choice for most esophageal squamous cell and gastric (or junctional non-Barrett's) superficial lesions, mainly to provide an en bloc potentially curative resection with accurate pathologic staging.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

5 ESGE suggests that ESD might also be considered for en bloc resection of noncircumferential clinically staged T1a-m3/T1b-sm1 or for circumferential clinically staged T1a-m1/m2 esophageal squamous cell carcinoma (SCC). Weak recommendation, moderate quality evidence.

Numerous studies evaluating long-term outcomes after ESD for superficial esophageal cancer have been published since the 2015 guideline [65–67]. Following ESD for lesions limited to the epithelium (m1) or the lamina propria (m2), the 5-year disease-specific survival (DSS) and 5-year overall survival (OS) rates were reported to be 98%–100%, and 85%–95%, respectively. Thus such lesions represent an absolute indication for ER [66].

Two issues are still debated regarding T1 tumors. The first concerns the role of ER as first-line treatment for noncircumferential esophageal SCC that has preoperatively been clinically staged as cT1a-m3/T1b-sm1 (N0M0). The second concerns ESD for superficial SCC involving the entire circumference of the esophagus.

There are no available European data covering these two topics, but the most recent Japan Gastroenterological Endoscopy Society (JGES) guideline suggests that ESD is weakly recommended as first-line treatment for preoperatively clinically diagnosed cT1a-m3/T1b-sm1 noncircumferential esophageal SCC. It is also weakly recommended for clinically diagnosed cT1a superficial SCC with a major axis length ≤ 50 mm and involving the entire circumference of the esophagus, upon implementation of preventive measures for stenosis [68]. A recent study adds evidence to these recommendations, showing that almost 60% of endoscopically predicted T1a-m3/T1b-sm1 tumors involving less than three-quarters of the circumference can be cured by ER alone but if the lesion is circumferential then the ESD curability rate drops to less than 20% [69].

4.1.1 Comparison with endoscopic mucosal resection (EMR)

There is no randomized study comparing EMR with ESD for SCC, but several new European reports have confirmed the efficacy and the superiority of ESD compared to EMR already stated in the previous 2015 guideline [10, 67, 70, 71]. In a French trial, the complete resection rates for the ESD group and the EMR

group were, respectively, 97.1% versus 85% ($P < 0.01$), and the 5-year disease-free survival rates were, respectively, 95.2% versus 73.4% ($P < 0.01$) [71]. In an older meta-analysis of retrospective studies, ESD had higher en bloc and curative resection rates than EMR regardless of lesion size [72]. Thus ESD seems superior to EMR in the treatment of SCC as evidenced by significantly higher en bloc and curative resection rates and by a notably lower local recurrence rate [73].

4.1.2 Comparison with surgery

Three recent articles compared the outcomes of ESD and surgical resection for pT1 esophageal SCC, all of which were single-center, retrospective studies. A report from Shanghai [74], found fewer treatment-related deaths in patients in the ESD compared with the surgery group, although the difference was not significant (0.3% vs. 1.5%, $P < 0.186$). Furthermore, there were significantly fewer severe complications in the ESD group than in the surgical resection group (15.2% vs. 27.7%, $P < 0.001$). Post-treatment stenosis was more common in the ESD group but the difference was not significant (13.4% vs. 9.9%, $P < 0.203$). However, in the ESD compared with the surgical resection group, treatment duration and length of hospital stay were significantly shorter (49 min vs. 240 min, $P < 0.001$, and 3 days vs. 11 days, $P < 0.001$, respectively) and the cost of hospitalization was significantly lower (median 2813 US dollars [USD] vs. 10 001 USD, $P < 0.001$). There was no significant difference between the two groups in terms of all deaths, disease-specific death rates, or metastasis rates, over a median observation period of 21 months, including in the patients with T1b tumors. Similarly, a report from Korea [75] found no difference between the ESD and surgical resection groups after mean observation periods of 43 and 63 months, respectively, in terms of OS, DSS, or recurrence-free survival. Another report from Shanghai [76] that specifically addressed outcomes according to invasion depths concluded that ESD oncologic outcomes were comparable to those achieved with esophagectomy, but were associated with minimal invasion, lower cost, and lower incidence of serious adverse events. However, in sm2/sm3 tumor patients, the ESD R0 resection rates were lower than those of esophagectomy [76].

Long-term outcomes were recently analyzed in a systematic review and meta-analysis that included 3796 patients and 5 comparative studies [77]. In terms of the comparison between ESD and esophagectomy, there was no difference in the OS (86.4% vs. 81.8%; hazard ratio 0.66, 95%CI 0.39–1.11) as well as in DSS and recurrence-free survival. In addition, ESD was associated with fewer adverse events (19.8% vs. 44.0%; odds ratio 0.3, 95%CI 0.23–0.39).

ER is, therefore, considered safer and less invasive than surgical resection in patients with pT1 cancers, as well as being superior in terms of medical economics. Furthermore, patients are likely to prefer ER over surgical resection. Hence, balancing the benefits of organ preservation and the harm of postoperative complications, ESD should be recommended as first-line therapy for selected lesions (if a tumor classification no more severe than T1b-sm1 is expected).

4.1.3 Comparison with chemoradiotherapy (CRT)

In a phase II trial (JCOG9708) [78] of CRT including 72 patients with cT1N0M0 esophageal SCC, over 90 % of patients achieved a complete response, with a 4-year OS rate of 80.5 %. However, local recurrences were observed in 31 % of patients, with a 4-year DSS rate of only 52.8 %. More recently, a retrospective study of definitive CRT in 36 patients with T1bN0M0 esophageal SCC found that local and metastatic recurrences were common, with a 5-year OS rate of 86 % and a 5-year DSS rate of 59 % [79].

Data from the JCOG9708 trial [78] showed that adverse events of grade ≥ 2 included dyspnea in 11.1 %, esophagitis in 2.7 %, ischemic heart disease in 2.7 %, myocarditis in 2.7 %, and arrhythmia in 1.4 % of patients. The abovementioned recent report found grade ≥ 2 adverse events that included esophageal stenosis in 11 % and pleural effusion in 14 % of patients, with grade 4 pericardial effusion in 3 % and grade 5 pneumonia in 3 % of patients [79]. The benefit and harm profiles of ESD and CRT therefore differ.

However, the benefit-harm balance of ESD limited to patients with superficial cancers appears superior to that of CRT, reflecting the minimal invasiveness of ESD. Thus, if either ESD or CRT is indicated, we recommend ESD as the first-line treatment and CRT as a possible after-treatment option. Nevertheless, ESD is also technically feasible in patients with local failure after CRT, especially as an initial salvage treatment and as treatment for second primary lesions within the irradiation field [80].

4.2 Barrett's esophagus (BE)-associated lesions

RECOMMENDATION

6 For BE-associated lesions, ESGE recommends to use EMR for ≤ 20 mm visible lesions with low probability of submucosal invasion (Paris type 0-IIa, 0-IIb) and for larger or multifocal benign (dysplastic) lesions.
Strong recommendation, high quality evidence.

RECOMMENDATION

7 For BE-associated lesions, ESGE suggests to use ESD for lesions suspicious for submucosal invasion (Paris type 0-Ia, 0-IIc), for malignant lesions > 20 mm, and for lesions in scarred/fibrotic areas.
Weak recommendation, low quality evidence.

The efficacy of ESD in Barrett's-associated neoplasia is well established both in the East and the West, with en bloc resection rates varying around 90 %. It remains, however, very difficult to delineate Barrett's lesions since most series show a lower R0 resection for cancer (ranging between 70 % and 88 %) [70].

4.2.1 Comparison with EMR

In comparison with EMR, ESD results more frequently in R0 resection. This has been demonstrated in a Japanese retrospective study involving 13 centers that assessed long-term outcomes of EMR and ESD of lesions at the gastroesophageal junction [81]. Although potentially comparable in nature, it is however not clear how this finding translates to BE-associated neoplasia, for which the treatment mostly is a combination of resection and ablation of residual columnar epithelium at risk for recurrence, regardless of whether EMR or ESD is used [70, 82].

Since the 2015 guideline, three meta-analyses have been published that assess outcomes of ESD and compare ESD with EMR for Barrett's-associated neoplasia. Yang et al. published a meta-analysis assessing safety and efficacy of ESD for early BE neoplasia. It included 11 studies and 501 patients, with a mean lesion size of 27 mm. The en bloc resection rate was 92.9 % (95 %CI 90.3 %–95.2 %), R0 resection was however lower at 74.5 % (95 %CI 66.3 %–81.9 %), and the curative resection rate was 64.9 % (95 %CI 55.7 %–73.6 %). Perforation occurred in 1.5 % (95 %CI 0.4 %–3.0 %), bleeding in 1.7 % (95 %CI 0.6 %–3.4 %), and the reported stricture rate was 11.6 % (95 %CI .9 %–29.6 %). Recurrence was found in 0.17 % (95 %CI 0 %–0.3 %) after a mean follow-up of 22.9 months [83].

A more recent meta-analysis on comparison of esophageal ESD versus EMR included 8 studies with BE neoplasia and 3 studies combining SCC and BE [84]. Only for lesions > 20 mm, the authors found higher en bloc resection rates for ESD (OR [odds ratio] 47.25, 95 %CI 23.86–93.57; $P < 0.001$), higher curative resection rates for ESD (OR 6.16, 95 %CI 2.5–15.19; $P < 0.001$), and lower local recurrence for ESD (OR 0.19, 95 %CI 0.05–0.81; $P = 0.025$). Complication rates for perforation, bleeding, and stricture were not different between EMR and ESD. The authors suggested that lesion size should be one of the determining factors to select resection technique. Indeed, since procedure time is significantly longer for ESD, it is more cost-effective to perform EMR in most of the lesions [84].

Finally, the most recent JGES guideline for ESD/EMR for esophageal cancer included a systematic literature search and systematic review comparing ESD to EMR for BE neoplasia (with 26 studies included). The en bloc resection rate for EMR was 50 % versus 96.4 % for ESD with corresponding R0 resection rates of 39.7 % and 81.9 %. The local recurrence rate for EMR was 12.4 % and for ESD it was 2.5 %. Overall complication rates were not different between ESD and EMR. The JGES guideline concluded that, because of the higher rates of en bloc and R0 resections and a lower rate of local recurrence, ESD was recommended over EMR for the treatment of lesions that were amenable for ER [68].

However, there is most likely to be selection bias in the ESD groups and a significant length time bias. In addition, in view of the currently available ablation techniques, recurrence of 12.5 % after a combination of EMR and radiofrequency ablation (RFA) is very unlikely. In fact, multimodality endotherapy with ER and RFA has been associated with only 4 % recurrence, with all recurrences amenable to endoscopic therapy [82].

A recent study suggested a higher rate of complete remission of dysplasia (CRD) after 2 years in patients treated with ESD and subsequent ablation (85.6%) compared with patients treated with EMR and subsequent ablation (75.8%; $P < 0.01$) [85]. This was a retrospective analysis of a prospective database that included 537 patients, with 456 undergoing cap-assisted EMR and 81 ESD, followed by different ablation techniques. The data in this study are, however, confusing. The main conclusion was based on the Kaplan–Meier curve showing a higher cumulative probability at 2 years of obtaining CRD for the ESD group; however, in absolute numbers 420/537 patients (78%) in the cap-EMR group obtained CRD over a median follow-up of 11.2 years and 48/81 (59%) of the ESD group obtained CRD over a median follow-up of 1.4 years. The follow-up terms at least suggest a significant length time bias. Also the study is probably somewhat underpowered for accurate comparison: complete remission of intestinal metaplasia (CRIM) was 78.5% for cap-assisted EMR and only 40.7% for ESD but this was statistically not significant.

It is clear from the previous trial [85] that ESD does not compromise subsequent ablation. This was further illustrated by a retrospective study by Subramaniam et al. that compared the success of RFA after ESD ($n = 27$) or after EMR ($n = 43$) or RFA alone ($n = 21$), and showed no significant difference regarding CRD or CRIM [86].

A well-conducted randomized controlled trial (RCT) indicated that when lesions are amenable for both EMR and ESD, there is no clinical benefit in performing ESD. Terheggen et al. included 40 patients with single lesions that should have been amenable for either technique, including types 0-Is, 0-IIa, 0-IIc or their combinations, limited in horizontal extent to a diameter of ≤ 3 cm in the longitudinal direction or less than half of the esophageal circumference in the lateral direction, and without any endoscopic suspicion of deep infiltration into the submucosal layer. Although R0 resection rate was higher for ESD (10/17 vs. 2/17 for EMR), CRD at 3 months was not different [87]. Therefore, this trial provided evidence that ESD has little role for lesions that are clearly amenable for both EMR and ESD.

However, different situations exist with lesions that are bulkier and may be difficult to resect. If a lesion is suspicious for submucosal invasion (Paris 0-Is, 0-IIc lesions) and a deep R0 resection for accurate staging is desirable, ESD may also be indicated. Especially in elderly patients who are unfit for surgery or CRT, a radical resection may in fact still be curative albeit with a higher chance for metastasis. As indicated by the study from Terheggen et al. [87], and the meta-analysis by Yang et al. [83], ESD could be considered, particularly for larger lesions (> 2 – 3 cm). Some studies also indicate that ESD is successful in more challenging cases with nodular lesions, lesions larger than 2 cm, or with scarring (poor lifting) [88–91].

Therefore, in conclusion, in terms of need for surgery, neoplasia remission and recurrence, ESD and EMR are both highly effective for ER of early Barrett's neoplasia. ESD achieves a higher R0 resection rate, but for most patients this bears little clinical relevance, as it is more time-consuming and has the potential to cause severe adverse events [87, 92].

4.2.2 Comparison with surgery

For the 2015 ESGE guideline only three studies were found showing that for T1a EAC, ER was as effective as surgery and had a better safety profile [93–95]. Recent studies confirmed that for early BE-related EAC, ER is associated with similar DSS but with shorter hospital stays, fewer readmissions and lower 90-day mortality [96–98]. Moreover, a recent study analyzing quality of life after these two options shows that multiple measures of symptom status are better following ER when compared to surgery [99].

Hence, based on ER efficacy and its fewer and more manageable complications, ER (when combined with ablation) appears to be a viable alternative to surgery even for lesions with superficial submucosal invasion.

4.3 Stomach lesions

RECOMMENDATION

8 ESGE recommends ESD for differentiated gastric lesions clinically staged as dysplastic or as intramucosal carcinomas (of any size if not ulcerated and ≤ 30 mm if ulcerated), with EMR being an alternative for Paris 0-IIa lesions of size ≤ 10 mm with low likelihood of malignancy. Strong recommendation, moderate quality evidence.

RECOMMENDATION

9 ESGE suggests that gastric adenocarcinomas that are ≤ 30 mm, submucosal (sm1), and well-differentiated, or ≤ 20 mm, intramucosal, and poorly differentiated type, both without ulcerative findings, can be considered for ESD, although the decision should be individualized. Weak recommendation, low quality evidence.

4.3.1 Comparison with EMR

Since the publication of the first ESD guidelines, two meta-analyses including > 6000 patients and a large prospective cohort have compared efficacy and safety outcomes of EMR and ESD [100, 101, 102]. Compared with EMR, ESD is associated with significantly higher rates of en bloc and complete resection (including in lesions < 10 mm), lower recurrence, and similar post-procedural bleeding; on the other hand, it is associated with a slightly higher perforation risk and increased procedural duration. Several real-world ESD series confirm its high rates of en bloc and R0 resection ($> 90\%$), curative resection (75%–80%), low local recurrence ($< 5\%$) and acceptable rates of adverse events (post-procedural bleeding 5%–10%, perforation $< 3\%$) [102, 103]. It also seems that gastric ESD is being successfully implemented in Europe, and although published studies generally include a low number of patients, the outcomes of European series are generally comparable to those from Eastern countries [3]. Short- and long-term outcomes of ESD in cardia/esophagogastric lesions are also comparable to

those for other gastric locations although there is a trend to lower R0 and curative resection rates [81].

ESD is thus recommended as the first-line endoscopic treatment for gastric superficial lesions with a null/very low risk of LNM. These are, namely:

- a) dysplastic lesions of any size;
- b) differentiated-type adenocarcinomas, clinically staged as intramucosal (that is, without signs of deep submucosal invasion), of any size in the absence of ulceration and ≤ 3 cm in the presence of ulceration.

EMR should be considered as an alternative for elevated (0-IIa) lesions, < 10 mm, and with low likelihood of advanced histology, and provided that the endoscopist feels that en bloc R0 resection can be achieved. For undifferentiated-type adenocarcinomas clinically staged as intramucosal, ER can be considered if the lesion is < 2 cm and without ulcerative findings, although the decision should be individualized, balancing surgical risks and patient preferences (in the expanded indication for ER) [104].

4.3.2 Comparison with surgery

Several studies have also directly compared short- and long-term outcomes of ESD and gastrectomy in the treatment of gastric superficial lesions, as summarized in four meta-analyses [105–108]. Although the majority of studies are retrospective and performed in Eastern countries, these meta-analyses have found that ESD is associated with significantly lower procedural time, length of stay, and adverse events. A significantly lower procedure-related mortality was also found in one meta-analysis [106]. Two prospective studies not included in that meta-analysis also directly compared short-term ESD and gastrectomy outcomes, with similar results [109, 110]. Concerning long-term outcomes, in the meta-analyses no differences were found in OS or DSS (DSS $> 99\%$ for both treatment groups), although ESD was associated with a significantly higher recurrence risk and lower disease-free survival. Metachronous lesions were also significantly more frequent in ESD arms (5.2%–6.0% vs. 0.4%–0.5% in gastrectomy studies), which accounts for most of the events during follow-up. However, ESD was found to have a positive impact on health-related quality of life when compared with gastrectomy [109, 111–113].

Based on these data, when the lesion appears endoscopically resectable with a predictable high curability potential, ESD appears a better option than surgery.

4.4 Duodenal and small-bowel lesions

RECOMMENDATION

10 ESGE does not recommend routine use of ESD for duodenal or small-bowel lesions, with its use being reserved for selected cases in expert centers.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

11 ESGE recommends polypectomy and/or EMR (en bloc or piecemeal) as the treatment of choice for most duodenal and small-bowel superficial lesions.

Strong recommendation, moderate quality evidence.

Rates of R0 resection for duodenal ESD are highly variable, between 19.4% in a European study [114] to 93.9% in China [115]. In all studies analyzed it seems clear that R0 resection rates are lower in the duodenum compared with other organs particularly for less experienced endoscopists [116].

Regarding safety, perforation rates are high with an incidence $> 10\%$ in different studies including in expert centers [115, 117], and reaching 15% [118] to 37.5% [119] in some of those studies. The major risk factor for delayed perforation, a dreadful complication that occurs mainly with ESD (and less with EMR), was lesion location that was distal to the ampulla of Vater [120].

4.4.1 Comparison with EMR

Available comparative data available are scarce and retrospective, but demonstrate a higher rate of R0 resection with ESD compared to EMR [114–116]. In retrospective studies whose data were compiled in a meta-analysis, ESD demonstrated a higher rate of complete resection than EMR with an OR of 1.63 but without any difference in the risk of local recurrence [116]. On the other hand, the risk of per-procedure and delayed perforation with duodenal ESD was higher than for EMR, and there was a higher risk of surgery for delayed perforation [116, 120]. Similar results were reported in Japan, although the rate of R0 resection was higher in Asian than in European studies (OR 2.16) [116]. Hybrid techniques did not show higher R0 resection rates than EMR [121].

Finally, EMR seems to remain the better therapeutic option for duodenal neoplasia because of its efficacy and safety profile, even for complex lesions, and its favorable comparison with surgery [122–124]. Moreover, the clinical benefit for the patient of achieving R0 resection has never been demonstrated for duodenal lesions, in particular because of the low incidence of invasive submucosal cancer. ESD has been proposed as an alternative when EMR is not technically feasible because of strong fibrosis after local recurrence [125].

Thus, for the moment, there are no clear indications for the use of ESD for nonampullary duodenal lesions. EMR remains the first option strategy for duodenal neoplasia since ESD is not as effective and safe as in other organs, with lower R0 resection rates than in other organs, a high perforation rate, and with no proven advantage in recurrence when compared to EMR.

4.5 Colorectal lesions

RECOMMENDATION

12 ESGE recommends polypectomy and/or EMR (en bloc or piecemeal) as the treatment of choice for most superficial colorectal lesions.

Strong recommendation, high quality evidence.

RECOMMENDATION

13 ESGE suggests that ESD should be considered for en bloc resection of colorectal (but particularly rectal) lesions with suspicion of limited submucosal invasion (demarcated depressed area with irregular surface pattern or a large protruding or bulky component, particularly if the lesions are larger than 20 mm), or for lesions that otherwise cannot be completely removed by snare-based techniques.

Weak recommendation, moderate quality evidence.

Colorectal ESD is common practice in Eastern countries, with good results and established indications [35, 126, 127]. In experienced hands en bloc and R0 resection rates can be higher than 90% [128]. In the West initial studies were disappointing even for rectal lesions, with an en bloc resection rate of only 61% and a perforation rate of 18% [129]. However, more recent studies have shown better results with 80% en bloc and 69% R0 resection rates, and an 8% complication rate (with 2% requiring emergent surgery) [130]. A recent systematic review of 109 studies on 19484 colorectal lesions treated by ESD showed rates of en bloc resection of 91%, R0 resection of 82.9%, and 2% recurrence; the rate of bleeding was 2.7% and of perforation 5.2%, and 1.1% needed surgery because of adverse events [131]. However, these results were worse in non-Asian countries.

Therefore, even though ESD is the endoscopic technique that allows a greater chance of en bloc R0 resection in the colon, its safety profile looks worse than in the esophagus and in the stomach, particularly in Western countries.

4.5.1 Comparison with EMR

Several studies and meta-analyses compared EMR versus ESD for colorectal lesions, with similar conclusions: en bloc and R0 resection rates are higher and recurrence lower with ESD, but in the ESD group the procedure is longer, and the rates of perforation, complications, and additional surgery because of complications are higher [128, 132–134]. Moreover, to our knowledge, no comparative study has addressed the difference in adenoma recurrence between ESD and piecemeal EMR (pEMR) using thermal coagulation at the end of resection, a technique that has been proven in a large randomized controlled trial (RCT) to reduce recurrence after pEMR from 21% to 5% ($P < 0.001$) with no adverse events [135]. The effectiveness of this technique in clinical practice has now been

confirmed with recurrence rates of only 1.4% in those receiving complete margin thermal ablation [136].

Thus, the question is when we should use ESD instead of EMR? A recent systematic review including 11260 colorectal ESDs showed that even in selected lesions there was only a low prevalence of the sm1 lesions that would justify the attempt at en bloc ESD resection: 15.7% of the specimens disclosed submucosal invasion with only 8% overall infiltrating less than 1000 microns and only 6% of resections being curative. The number needed to treat for avoiding one surgery was 12.5 to 16.7. The authors concluded that ESD should not be used indiscriminately in the resection of colorectal neoplasia [137].

A cost-effectiveness study comparing ESD and wide-field EMR for removing large sessile and laterally spreading lesions >20 mm showed that even for these lesions universal ESD could not be justified (the exception being high risk rectal lesions), and the best strategy would be selective ESD for the lesions suspicious for submucosal cancer [138]. The lesions at risk of submucosal invasion are: nongranular LSTs (LST-NGs), particularly if pseudodepressed 0-IIc; granular nodular mixed LSTs, particularly if more than 2 cm in size; especially lesions in the recto-sigmoid area; and those showing an irregular pattern with CE. These lesions should be considered for ESD and/or surgery [33–35, 39].

4.5.2 Comparison with surgery

Although surgery is a more definitive treatment for large and malignant polyps, and also allows lymph node resection, it is associated with a considerable burden of AEs and even mortality. In a retrospective cohort for complex nonmalignant polyps, surgery was associated with rates of 17% for significant adverse events, 3% for additional surgery, and 1% for 12-month mortality; compared with ER, length of stay and costs were greater [139]. Another study from the tertiary Veterans Affairs Medical Centers showed that a strategy of a prior attempt at ER reduced morbidity compared to laparoscopic surgery, particularly for polyps <4 cm [140]. A case-matched comparison of ESD versus laparoscopic surgery for complex polyps showed that ESD is more cost-effective than conventional segmental resection, suggesting that ESD can be offered as a colon-preserving procedure [141]. Furthermore, quality of life has been evaluated to be better after ESD compared to laparoscopy-assisted surgery [142] in one study, and costs are higher for transanal endoscopic microsurgery compared to ESD [142, 143]. Moreover, for patients with T1 CRC, prior ESD with histological en bloc resection did not adversely affect their oncologic prognosis after additional surgery [144].

However, specifically analyzing only malignant T1 polyps (and excluding benign polyps), a study using the US National Cancer Database, that was one of the largest population-based analyses of patients with T1N0M0 malignant colon polyps, showed that OS was higher in patients who underwent surgery compared with polypectomy. This finding was consistent even after adjustments between the two groups for multiple patient and tumor factors [145]. This study contradicted a systematic review and meta-analysis that found that ER should be considered as the first-line treatment for endoscopically resectable T1

colorectal cancers, and that in cases of noncurative resection, additional surgery can have comparable outcomes to primary surgery [146]. Another study showed that for colonic neoplasms, laparoscopic surgery should be considered when ESD is technically difficult, but that for rectal neoplasms, ESD is desirable even for large-sized lesions [147].

Taking all this into account, if a lesion is clearly benign, ER should be the first-line therapy, though as we have seen EMR might be a better option than ESD for these lesions. For lesions suspicious for malignancy, then ESD and/or surgery are comparable options and the decision will depend on several factors (location, size, complexity of ESD, patient preferences, center experience). The exception appears to be the rectum where ESD could have an advantage over EMR for complex high risk benign lesions and over surgery for suspicious T1 lesions.

5 Management after endoscopic resection

In this Guideline an adjustment of risk categories and terminology was deemed necessary, to reflect the different probabilities of LNM risks that depended upon the pathological characteristics of the resected tumor (see the section on **Pathological aspects**, and also ► **Table 2**).

5.1 Esophageal SCC lesions

RECOMMENDATION

14 ESGE recommends that an en bloc R0 resection of a superficial esophageal squamous cell lesion with histology no more advanced than intramucosal m2 cancer, well to moderately differentiated, with no lymphovascular invasion, should be considered a very low risk (curative) resection and no further staging procedure or treatment is recommended.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

15 ESGE suggests that an en bloc R0 resection of an esophageal m3 or sm1 SCC that is well to moderately differentiated and with no lymphovascular invasion, should be considered a low risk (curative) resection and no further treatment is generally recommended.

Weak recommendation, moderate quality evidence.

However, in these cases, particularly if the lesion is bigger than 20 mm, there is a real (albeit low) risk of LNM and complete staging is recommended, with the risk from further therapy being balanced against the risk of LNM, in a multidisciplinary discussion.

Weak recommendation, low quality evidence.

RECOMMENDATION

16 ESGE suggests that complementary radiotherapy or CRT may be considered in a multidisciplinary discussion after a curative resection of esophageal m3/sm1 SCC (particularly if >20 mm in size).

Weak recommendation, moderate quality evidence.

Among lesions in which the depth of invasion does not extend beyond the mucosal layer (T1a), those confined within m1–m2 layers are only extremely rarely associated with LNM; therefore, ER is considered curative [148, 149]. A recent meta-analysis suggests that after full evaluation, ER can be recommended as a curative treatment for patients with superficial SCC if the following conditions are met: (i) tumor size ≤20 mm; (ii) Paris 0-II macroscopic type of tumor; (iii) possible confinement of lesion to mucosa; and (iv) absence of lymphovascular invasion [150]. Lesions extending up to the muscularis mucosae or slightly infiltrating the submucosa (up to 200 µm) are also amenable to ER; however, as a whole they are associated with a greater risk of LNM. Nevertheless, if some criteria are met, ER of these lesions might also be highly likely to be curative. In fact, in a recent study no single patient with m3/sm1 cancer, high tumor differentiation, no lymphovascular invasion, and tumor length <2 cm had LNM, and none of these patients experienced recurrence [151].

About 50% of the lesions that show deeper (>200 µm) invasion into the submucosa (T1b) are associated with metastasis, and in such cases ER should be considered to be a high risk resection and patients should be treated in the same manner as those with advanced carcinomas [148, 149].

ER plus adjuvant therapy appears to be a new combination treatment for SCC invading to deep mucosa (pT1a-m3) or submucosa (pT1b). Adjuvant therapy can take the form of esophagectomy, radiotherapy, or CRT. At present, there is no clear recommendation for or against the administration of additional treatments in patients with pT1a-m3 SCC. A recent randomized trial from China studied the combination of ESD with additional radiotherapy (59.4 Gy within 2 months after ESD) in T1a SCC. In the nonradiotherapy group 3/70 patients experienced intraluminal mucosal recurrence compared with none in the radiotherapy group. No local LNM or distant metastasis occurred in either group. The 3-year cumulative recurrence-free survival was 100% in the radiotherapy group and 85.3% in the nonradiotherapy group ($P=0.04$). No severe radiation toxicities were recorded [152]. Another earlier study showed the benefit of additional radiotherapy in patients with T1a-m3/T1-sm1 tumors [153].

Is additional treatment recommended in patients with pT1b-sm1 SCC, based on histological findings following ER? Again, if no other high risk criteria are met and the tumor size is <2 cm, the risk of LNM appears low [151]. Nevertheless, the efficacy of adding CRT after ER of SCC with submucosal invasion has been reported in several retrospective trials, with a better safety profile in comparison with surgery [154–157]. The

ECOG0508 trial was a prospective nonrandomized study to confirm the efficacy of selective CRT based on findings from ER in patients with T1b sm1–2 tumors [158]. Depending on the ER findings, patients received the following: no additional treatment for patients with pT1a tumors with a negative resection margin and no lymphovascular invasion (group A); prophylactic CRT for patients with pT1b tumors with a negative resection margin or pT1a tumors with lymphovascular invasion (group B); or definitive CRT for patients with a positive vertical resection margin (group C). The 3-year overall survival rates were similar among the groups (90.7% for group B and 92.6% in all patients). Efficacy was comparable to that of surgery. The JES guidelines conclude that there is strong evidence to recommend additional treatment (mainly CRT) after ER in patients identified as meeting high risk criteria (poorly differentiated tumor, lymphovascular invasion, deep submucosal invasion), taking into account the benefit–risk balance, strength of evidence, and patient preferences [159].

Based on these studies, the present authors consider that after a low risk (curative) ER of a T1a-m3 or T1b-sm1 tumor, surveillance and/or additional radiotherapy might be considered as a preferred less aggressive additional treatment, as compared to surgery or CRT, depending on the patient's clinical status. Nevertheless, CRT might be preferred over radiotherapy alone in young and fit patients. Surgery is an option for young fit patients meeting high risk criteria (noncurative ER), particularly if there is deep submucosal invasion and lymphovascular invasion, since in these cases overall survival could be better with surgery [160, 161].

5.2 BE-associated lesions

RECOMMENDATION

17 ESGE recommends that an en bloc R0 resection of a BE-associated superficial lesion with histology no more advanced than intramucosal cancer, well to moderately differentiated, with no lymphovascular invasion, should be considered a very low risk (curative) resection and no further staging procedure is generally recommended. Strong recommendation, moderate quality evidence.

RECOMMENDATION

18 ESGE suggests that an en bloc R0 resection of a BE-associated superficial lesion with superficial submucosal invasion (sm1), and that is well to moderately differentiated, and with no lymphovascular invasion, should be considered a low risk (curative) resection and no further treatment (except for ablation of BE tissue) is generally recommended.

Weak recommendation, moderate quality evidence.

However, in these cases, there is a real (albeit low) risk of LNM, and complete staging is recommended with the risk from further therapy (surgery) being balanced against the risk of LNM, in a multidisciplinary discussion.

Weak recommendation, low quality evidence.

RECOMMENDATION

19 ESGE recommends ablation of all of the Barrett's mucosa after a curative or local-risk resection. Strong recommendation, high quality evidence.

The risk of LNM in BE-associated esophageal adenocarcinoma (EAC) appears to be lower than in SCC. For BE-associated adenocarcinomas, according to reports that analyzed the rate of LNM relative to the depth of tumor infiltration, ER appears to be curative for intramucosal carcinomas that are well or moderately differentiated and without lymphovascular invasion [72, 162–165]. Based on limited data these criteria might be extended to lesions with invasion into the submucosa ($\leq 500 \mu\text{m}$, sm1), namely to low risk tumors (well or moderately differentiated, without lymphovascular invasion), because such lesions harbor a low risk of LNM (1.4%–1.9%) that appears to be lower than the risk of surgery for most patients [165–167]. Nevertheless, for sm1 tumors, this risk should be balanced against the risk of surgery for a particular patient. For sm2/sm3 EACs, surgery is recommended since the rate of LNM appears higher than the mortality risk of surgery, although a recent retrospective study reported a very low risk of LNM with less than $1000 \mu\text{m}$ of submucosal invasion [168, 169].

When remaining Barrett's mucosa is left untreated, case series have reported recurrence of neoplasia, with rates varying from 11% to 30% [170–172]. The multicenter EURO-II study demonstrated that complete eradication of neoplasia and Barrett's mucosa can be achieved with the combination of ER and RFA in 98% and 93%, respectively (in a per-protocol analysis). The recurrence rate for neoplasia was 4% and for intestinal metaplasia it was 8% [82]. According to a recent systematic review and meta-analysis the risk for recurrence of neoplasia is significantly higher in those patients who have residual Barrett's mucosa after completion of endoscopic therapy compared with those in whom CRIM has been achieved (risk ratio [RR] 2.8, 95%CI 1.7–4.6). The pooled cumulative incidence rate of dysplasia and Barrett's adenocarcinoma recurrence was 3%

► **Table 2** Types of endoscopic resection according to endoscopic and pathological criteria (post-resection), and proposed subsequent management.

	Endoscopic	Pathological	Notes	Management
Very low risk (curative) resection Lymph node metastasis (LNM) risk < 1 %	Complete AND En bloc	<ul style="list-style-type: none"> Only dysplasia If cancer: <ul style="list-style-type: none"> Only intramucosal cancer Differentiated V0 L0 HM0 and VM0 (R0) UL0 UL1 gastric intramucosal cancer and: <ul style="list-style-type: none"> Differentiated L0 HM0 and VM0 (R0) ≤ 3 cm 	Esophageal SCC T1a-m3 has a higher risk of LNM and should not be considered as a very low risk resection (instead it should be a low risk resection)	<ul style="list-style-type: none"> Only endoscopic surveillance recommended No need for further radiological staging or surveillance
Low risk (curative) resection LNM risk < 3 %	Complete AND En bloc	<ul style="list-style-type: none"> sm1 cancer¹ and: <ul style="list-style-type: none"> Differentiated V0 L0 HM0 and VM0 (R0) UL0 Budding 0/1 (colon) Poorly differentiated gastric intramucosal cancer and²: <ul style="list-style-type: none"> V0 L0 HM0 and VM0 (R0) UL0 ≤ 2 cm 	If m3/sm1 esophageal SCC, lesion should ideally be ≤ 2 cm	<ul style="list-style-type: none"> Complete staging is recommended Further therapy generally not recommended Adjuvant therapy might be considered in esophageal SCC m3/sm1 (CRT) and in poorly differentiated intramucosal gastric cancer (surgery) Only endoscopic surveillance recommended (radiological surveillance might be considered in esophageal SCC and poorly differentiated gastric intramucosal cancer)
			If sm1 gastric cancer, lesion should be ≤ 3 cm	
Local-risk resection LNM risk < 3 % Local recurrence risk 10%–30 %	Complete AND Piece-meal	<ul style="list-style-type: none"> HM1 and VM0 (RX) and: <ul style="list-style-type: none"> Only dysplasia or intramucosal cancer Differentiated V0 L0 UL0 	If SM cancer present in the margins, it should be considered a high risk resection If only intramucosal cancer in the margins, decision should be individualized	<ul style="list-style-type: none"> Complete staging is recommended (if malignant) Endoscopy and biopsies 3–6 months after ESD and until no recurrence confirmed If recurrence and if possible, endoscopic re-treatment preferred over other treatments
			If SM cancer area not in the margins (allowing full evaluation of the SM cancer area) decision should be individualized	

► **Table 2** (Continuation)

	Endoscopic	Pathological	Notes	Management
High risk (noncurative) resection LNM risk > 3 %	Incomplete ER If complete at least one of pathological criteria must apply	<ul style="list-style-type: none"> ▪ Cancer and at least one of these criteria must apply: <ul style="list-style-type: none"> – sm2/sm3 invasion – Undifferentiated – V1 – L1 – VM1 (R1) – Budding 2/3 (colorectal) ▪ sm1 or UL1 gastric cancer and: <ul style="list-style-type: none"> – > 3 cm 	<p>If complete ER most patients will, nevertheless, be cured</p> <p>LV1 is the most important risk factor for LNM (20%–30% risk) and the strongest indication for adjuvant treatment</p> <p>If sm2 is the only high risk criterion present then in some scenarios (old and unfit patients; rectal location) the risk of further therapy might be higher than that of surveillance alone</p>	<ul style="list-style-type: none"> ▪ Complete staging is mandatory ▪ Multidisciplinary team decision recommended ▪ Strong consideration for adjuvant treatments (surgery and/or CRT in esophageal SCC and rectum) recommended

CRT, chemoradiotherapy; ER, endoscopic resection; ESD, endoscopic submucosal dissection; HM, horizontal margin; L, lymphatic invasion; LNM, lymph node metastasis; LV1, lymphovascular invasion; SCC, squamous cell cancer; SM, submucosal; UL, ulcerated; V, vascular invasion; VM, vertical margin.

¹ sm1 cancer: tumor invasion ≤ 200 μm (SCC), ≤ 500 μm (Barrett's and gastric), and ≤ 1000 μm (colon); all other criteria must apply to consider ER as a low risk resection.

² Expanded indication, individualized decision; all other criteria must apply to consider ER as a low risk resection.

(95%CI 2%–4%) after achieving CRIM and 6% (95%CI 0%–16%) after achieving CRD only [173]. Based on these studies ESGE suggests complete ablation of all of the Barrett's mucosa after ER.

5.3 Stomach lesions

RECOMMENDATION

20 ESGE recommends that an en bloc R0 resection of a superficial gastric lesion with histology no more advanced than intramucosal cancer, well to moderately differentiated, with no lymphovascular invasion, should be considered a very low risk (curative) resection, independently of size if without ulceration or of lesions ≤ 30 mm if ulcerated; and no further staging procedure or treatment is generally recommended.
Strong recommendation, moderate quality evidence.

RECOMMENDATION

21 ESGE suggests that an en bloc R0 resection of a ≤ 30 mm gastric adenocarcinoma, with superficial submucosal invasion (sm1), that is well to moderately differentiated and with no lymphovascular invasion and no ulcer, should be considered a low risk (curative) resection, and no further treatment is generally recommended.
Weak recommendation, moderate quality evidence.

However, in these cases there is a real (albeit low) risk of LNM and complete staging is recommended with the risk from further therapy (surgery) being balanced against the risk of LNM, in a multidisciplinary discussion.
Weak recommendation, moderate quality evidence.

RECOMMENDATION

22 ESGE suggests that an en bloc R0 resection of a ≤ 20 mm gastric intramucosal poorly differentiated carcinoma, with no lymphovascular invasion or ulcer, should be considered a low risk (curative) resection and no further treatment is generally recommended.
Weak recommendation, moderate quality evidence.

However, in these cases there is a real (albeit low) risk of LNM and complete staging is recommended with the risk from further therapy (surgery) being balanced against the risk of LNM, in a multidisciplinary discussion.
Weak recommendation, moderate quality evidence.

RECOMMENDATION

23 ESGE recommends that a resection of a > 30 mm gastric adenocarcinoma with superficial submucosal invasion (sm1) or with ulceration should be considered a high risk (noncurative) resection, and complete staging should be done and strong consideration for additional treatments (surgery) should be given, on an individual basis in a multidisciplinary discussion.
Strong recommendation, moderate quality evidence.

Overall, intramucosal adenocarcinomas (pT1a) have a 2%–5% incidence of LNM, while in submucosally invasive adenocarcinoma (pT1b) this risk increases to 10%–25%. However, if certain histological characteristics are met, the risk of LNM is null or minimal. This led to the proposal of criteria for curative ER,

based on three landmark studies that correlated lesion characteristics with the presence of LNM in gastrectomy specimens [174–176]. Since the publication of the first edition of this guideline, several studies have evaluated the oncological safety of endoscopic treatment. Studies have also compared the outcomes of endoscopic and surgical treatment in lesions meeting curative criteria, confirming that 5-year OS and DSS are similar between the two treatment approaches [105].

Extensive research conducted in recent years confirms that deep submucosal invasion, undifferentiated histology, size ≥ 30 mm, and lymphovascular invasion are independent risk factors for LNM, reinforcing the value of the proposed criteria for curative resection. However, some recent studies also show LNM rates for expanded criteria resections that are higher than previously reported. Of note, although the risk of LNM is almost null in Japanese studies, in studies outside of Japan this risk is higher (though still less than 4%), which may be related to differences in specimen handling [177]. It is also important to note that to date there is no convincing evidence that other independent risk factors can be used to better stratify LNM risk and refine curativeness criteria. Nevertheless, single studies have found some factors independently associated with LNM, namely: mucinous adenocarcinoma [178], muscularis mucosae invasion [179] and perineural invasion in pT1a lesions [180], submucosal invasion width >4 mm [181], and the ratio of submucosal invasion width to superficial tumor size being greater than 0.04 [182]. A meta-analysis also did not find differences in LNM rates if a submucosal invasion depth of ≤ 300 μ m was used as a cutoff as opposed to ≤ 500 μ m [177].

Taking all the above into account, the following criteria for curativeness of resection should guide management:

- a) **Curative/very low risk resection (LNM risk $<0.5\%$ – 1%):**
En bloc R0 resection; dysplastic/pT1a, differentiated lesion, no lymphovascular invasion, independent of size if no ulceration and ≤ 3 cm if ulcerated.
- b) **Curative/low risk resection (LNM risk $<3\%$):** En bloc R0 resection; lesion with no lymphovascular invasion and:
 - pT1a, predominant type is poorly differentiated or undifferentiated, size ≤ 2 cm, no ulceration; and
 - pT1b, invasion ≤ 500 μ m, differentiated, size ≤ 3 cm.
- c) **Local-risk resection (very low risk of LNM but increased risk of persistence/recurrence):**
 - Piecemeal resection or tumor-positive horizontal margin of a lesion otherwise meeting curative/very low risk criteria;
 - Provided that there is no submucosally invasive tumor at the resection margin: piecemeal resection or tumor-positive horizontal margin; pT1b; invasion ≤ 500 μ m; well-differentiated; size ≤ 3 cm; VM0.
- d) **High risk resection (noncurative):** Any lesion with any of the following:
 - positive vertical margin;
 - lymphovascular invasion;
 - deep submucosal invasion (>500 μ m from the muscularis mucosae);
 - ulceration or size >2 cm, in poorly differentiated lesions;

- size >3 cm in pT1b differentiated lesions with submucosal invasion <500 μ m, or in intramucosal ulcerative lesions.

It is also important to note that some other factors may also influence LNM risk, namely a papillary component, perineural invasion, and budding. Papillary adenocarcinoma is associated with worse short-term outcomes – higher rates of incomplete resection, submucosal invasion, and lymphovascular invasion, and thus lower rates of curative resection – but it does not have a proven independent prognostic value in lesions that meet curative criteria [183,184]. Perineural invasion is very rare in the absence of lymphatic or vascular involvement. But at present there is no convincing evidence that these three features should be included in risk stratification and management strategies.

There is also some debate on how to handle mixed-type adenocarcinomas since some studies with gastrectomy specimens found a higher risk of LNM in tumors with histological heterogeneity, even when compared with undifferentiated-type tumors [185–188]. However the prognostic value of this feature does not seem to apply in intramucosal lesions that meet curability criteria [189], and thus definitive conclusions cannot be drawn. Thus, we recommend classifying tumors according to the quantitatively predominant component ($>50\%$) into differentiated-type (which includes papillary and tubular adenocarcinoma) or undifferentiated-type (which includes poorly differentiated, signet ring cell, and mucinous adenocarcinoma if T1b). However the issue of the prognostic significance of histological heterogeneity, specifically in lesions meeting curability criteria deserves further evaluation.

It should be noted that after a high risk ER, even though surgery should always be an option, some patients who refuse surgery may have a similar prognosis to those who proceed to surgery, and this has been shown in both Eastern [190,191] and Western countries [192].

It is clear that the risk of LNM differs according to histopathological features, and that surveillance can be a better option if surgical risk exceeds LNM risk. In this context, the e-Cura scoring system has been proposed. Patients are assigned into three risk categories depending on histopathological features. The score gives 3 points for lymphatic invasion, and 1 point each for tumor size >30 mm, sm2 status, venous invasion, and positive vertical margin, and has been validated as an important decision tool after noncurative ER [193,194]. However, it is important to stress that if LNM or distant metastasis occurs, the prognosis is generally dismal, with palliative chemotherapy or best supportive care being the treatment in the majority of the cases [190]. Thus in a multidisciplinary discussion patients considering surveillance instead of surgery should be informed that, even though the absolute risk of LNM or distant metastasis is low, if it should occur, the prognosis is poor.

Regarding the issue of resection with nonevaluable or positive horizontal margins (HMx/HM1), a meta-analysis showed that the risk of persistent disease was, respectively, 10% or 36%, with no increased risk of LNM [195]. A study showed that the risk of recurrence after resection with a positive horizontal margin, which was 30% with observation only, could be

reduced to 11% when another endoscopic treatment was done as soon as 3 months after resection even when no clear lesion was seen [196].

Taking all this into account, an individualized decision for one of the following options, that balances recurrence and surgical risk, can be considered adequate: close observation, with scar biopsies taken at least in the first follow-up endoscopy; or for coagulation/ablation or re-ESD, namely resection of the ESD scar and/or coagulation of the scar before recurrence occurs; or for surgery. Given the poorer safety profile of surgery, it seems reasonable to reserve that option to endoscopically nontreatable recurrence. In the other cases, close endoscopic observation or an early endoscopic re-treatment (beginning within 3–6 months of the index ER) appear safe strategies. This scenario is considered an eCura C-1 resection in the Japanese Gastric Cancer Association guideline, and this suggested management is similar to the one recommended in that guideline [197].

5.4 Duodenal and small-bowel lesions

RECOMMENDATION

24 ESGE suggests that, given the lack of evidence, the same post-resection criteria as in the colon should apply to the management of duodenal and small-bowel lesions, on an individual basis and with a multidisciplinary approach.

Weak recommendation, very low quality evidence.

Low and high risk resections are not defined in the case of duodenal or small-bowel lesions. For nonampullary duodenal neoplasia, the risk of LNM in the case of intramucosal carcinoma seems negligible [198], and the risk remains unknown in the case of submucosal invasion [199] with few cases reported. The rare cases of duodenal adenocarcinoma with submucosal invasion have been sent to surgery but the LNM status found at those surgeries is not known [122]. In the case of tumor-free margins, the recurrence rate has been 0% in most series [122]. In the case of non-free margins (with data from piecemeal resections), the risk of recurrence is not null, with studies showing large discrepancies from 1.2% [200] to 20.4% in a recent prospective study [201], and with most recurrences allowing further endoscopic treatment. Data on submucosal invasion with lymphovascular invasion, budding, or undifferentiated types are not reported in the literature. In fact, we do not know the risk of distant metastasis and LNM in the case of T1 duodenal adenocarcinoma with submucosal invasion.

Given this absence of data, and the morbidity and mortality of duodenal surgery, ESGE suggests that a decision for surgery should be based on the same criteria as in the colon, in a multidisciplinary team discussion.

5.5 Colorectal lesions

RECOMMENDATION

25 ESGE recommends that an en bloc R0 resection of a colorectal lesion with histology no more advanced than intramucosal adenocarcinoma, well to moderately differentiated with no lymphovascular invasion, should be considered a very low risk (curative) resection and no further staging procedure or treatment is generally recommended.

Strong recommendation, high quality evidence.

RECOMMENDATION

26 ESGE recommends that an en bloc R0 resection of a colorectal lesion with superficial submucosal invasion (sm1), that is well to moderately differentiated and with no lymphovascular invasion and no grade 2 or 3 budding, should be considered a low risk (curative) resection, and no further treatment is generally recommended.

Strong recommendation, high quality evidence.

RECOMMENDATION

27 ESGE suggests that after an en bloc R0 resection of a rectal lesion meeting the single high risk criterion of submucosal invasion deeper than sm1 (well to moderately differentiated with no lymphovascular invasion and no grade 2 or 3 budding), CRT and/or surveillance might be preferred over surgery on an individual basis in a multidisciplinary approach.

Weak recommendation, very low quality evidence.

Several studies and meta-analyses investigated risk factors for LNM. A meta-analysis that included 13 cohort studies with 7066 patients who only underwent radical surgery, showed that there is a significant risk of LNM with the following: submucosal invasion, that is \geq sm2 or $\geq 1000\mu\text{m}$ (OR 3.00, 95%CI 1.36–6.62; $P=0.007$); vascular invasion (OR 2.70, 95%CI 1.95–3.74; $P<0.001$); lymphatic invasion (OR 6.91, 95%CI 5.40–8.85; $P<0.001$); poorly differentiated carcinoma (OR 8.27, 95%CI 4.67–14.66; $P<0.001$); or tumor budding (OR 4.59, 95%CI 3.44–6.13; $P<0.001$) [202]. This study confirmed the results of a previous meta-analysis [203]. However, the risks of each of these factors may not be equivalent.

Isolated depth of invasion of $>1000\mu\text{m}$ in the submucosa is not a consistent independent risk factor in several studies. By itself it is probably not a strong risk factor for LNM, and how much weight to give it in decision-making about further revision surgery after ER is debatable [204]. However, it should be noted that even though in this last-mentioned study submucosal invasion was not considered an independent risk factor ($P=0.075$), the risk of LNM was 6% in the absence of the independent risk factors; a risk that might be considered higher than

the surgical risk. In fact, another study evaluating ER specimens does show by multivariate analysis that a depth of submucosal invasion $\geq 1000\mu\text{m}$ is an independent risk factor for LNM (OR 5.56, 95%CI 2.14–19.10) [205]. This is contradicted by a recent study that suggests that when no other risk factors are present choosing a cutoff depth of submucosal invasion of $>1900\mu\text{m}$ may help to reduce the incidence of unnecessary surgery after ER [206]. However, a recently published meta-analysis including 16 observational studies and 10181 patients confirmed submucosal invasion of at least $1000\mu\text{m}$ as a risk factor for LNM (OR 3.53, $P<0.001$) [207].

A positive vertical margin after ER has also been associated with local recurrence, LNM, and rescue surgery. In a recent study evaluating risk factors for an adverse prognosis after ER of T1 tumors, the variables related to surgical rescue were piecemeal resection (OR 4.48, 95%CI 1.48–13.6), infiltrated/nonevaluable resection border (OR 7.44, 95%CI 2.12–26.0), not well-differentiated histology (OR 4.76, 95%CI 1.07–20.0), vascular infiltration (OR 8.24, 95%CI 2.72–25.0), and Haggitt 4 infiltration of the submucosa (OR 5.68, 95%CI 2.62–12.3). Residual disease after ER was associated with infiltrated/nonevaluable resection border (OR 34.9, 95%CI 4.08–298), not well-differentiated histology (OR 6.67, 95%CI 1.05–50.0), and vascular infiltration of the submucosa (OR 7.61, 95%CI 1.55–37.4) [208]. So, clearly a positive vertical margin is a risk factor for residual disease and need for additional surgery and potential for LNM, as suggested by the study of Boenicke et al. This showed that in patients who underwent ER of malignant polyps followed by surgery, even though 63% of resection margins were positive (a free margin was not defined as a tumor-free extent of more than 1mm), subsequent surgical specimens showed residual carcinoma in only 2.8% but LNM in 7.6% [209]. What should be considered a positive vertical margin is, however, a matter of discussion (see section on **Pathological aspects**).

Perineural invasion was also demonstrated to be a risk factor of LNM in T1 colorectal cancer. However, there is not sufficient evidence to conclude that it has an independent role or to make any recommendation regarding perineural invasion per se [204].

Similarly to the other organs the importance of positive horizontal margins seems low in the colon, with recurrence rates after en bloc ER being as low as 2.2% when the size of the positive invaded margins is small ($<8\text{mm}$) [210]. In contrast, piecemeal resection at ESD is associated with a higher risk of recurrence, reaching 15.2% compared with 5.1% for en bloc resections with positive margins or 2.2% in the case of indeterminate margins [211]. Those recurrence rates are significantly higher than the risk of recurrence after R0 resection with free margins, evaluated to be null [212]. In all these studies a positive horizontal margin was not associated with LNM risk and so, in the absence of histological high risk factors, a “wait-and-see” policy is justified [213].

With all the above in mind, it is the present authors’ opinion that a more extensive resection accompanied by a lymph node dissection is necessary in most patients with resected T1 colorectal cancer with nonpedunculated $\geq \text{sm2}$ (submucosal

$\geq 1000\mu\text{m}$) invasion, lymphovascular invasion, poorly differentiated carcinoma, grade 2 or 3 tumor budding, or positive vertical margin. Nevertheless, we recognize that for some patients, if the only high risk criterion is $\geq \text{sm2}$ tumor, particularly in the rectum, the risk of surgery may be similar to the risk of LNM, and surveillance could be an option. Even though, as shown in a recently published meta-analysis [207], rectal location may be a risk factor for LNM (OR 1.36, $P=0.003$), the surgical options are also more aggressive than in the colon (and may imply abdominoperineal amputation) with mortality and severe morbidity rates as high as 3% and 15%, respectively [214, 215]. Moreover, in patients with high risk pT1 rectal cancer after local excision, CRT has been shown to be a safe and effective treatment alternative to revision radical resection [216, 217]. Therefore, even though based on a low level of evidence, it is the present authors’ opinion that after an en bloc R0 resection of a rectal lesion, when the single high risk criterion is submucosal invasion deeper than sm1 (i.e., the lesion is well to moderately differentiated with no lymphovascular invasion and no grade 2 or 3 budding), surveillance and/or CRT might be preferred over surgery on an individual basis in a multidisciplinary discussion.

5.6 All organs

RECOMMENDATION

28 ESGE recommends that after an endoscopic complete resection, if there is a positive horizontal margin or if resection is piecemeal but there is no submucosal invasion and no other high risk criteria are met, this should be considered a local-risk resection and endoscopic surveillance/re-treatment is recommended rather than surgery or other additional treatment.

Strong recommendation, moderate quality evidence.

As we have seen, independently of the organ (see above evidence for each organ), when complete, a resection that is piecemeal or with positive/nonevaluable horizontal margins (Rx resection), with no other poor prognosis features (including with no submucosal invasion at the margins), does not per se have an increased risk of LNM or distant metastasis [195, 201, 213]. However, in these cases, the risk of local persistence/recurrence may be as high as 30% and for this reason, such a resection should be considered a local-risk resection. Since many of these recurrences are amenable to further endoscopic treatment, it is the present authors’ opinion that endoscopic surveillance or re-treatment are better initial options than surgery or other additional treatment (with these being considered if endoscopic re-treatment is not possible or fails) [196, 201].

RECOMMENDATION

29 ESGE recommends that when there is a diagnosis of lymphovascular invasion or deeper infiltration than sm1 or positive vertical margins or undifferentiated tumor or, for colorectal lesions, grade 2 or 3 budding, that the resection should be considered a high risk (noncurative) resection; complete staging should be done and strong consideration for additional treatments (chemoradiotherapy and/or surgery) should be given, on an individual basis in a multidisciplinary discussion.
Strong recommendation, moderate quality evidence.

Again, independently of the organ (see above), the poor prognostic features are the same: undifferentiated tumor, lymphovascular invasion, deep submucosal invasion, tumor budding in the colon, or a positive vertical margin, when carcinoma is present [148,149,168,169,197,202]. In these cases, even though many patients will have no residual disease, the global LNM risk is potentially higher than the risk of further treatment. So, when one of these features is present, the ER should be considered a high risk (noncurative) resection. Complete staging should be done and strong consideration for additional treatments should be given on an individual basis, in a multidisciplinary discussion. Nevertheless, it should be noted that all these poor prognostic features do not carry the same weight, and the risk for LNM increases with the number of risk factors (with lymphovascular invasion being the strongest and deep submucosal invasion the weakest predictor for LNM). This should be taken into account in the multidisciplinary decision-making, recognizing that surveillance may be an option in some scenarios, particularly in old and unfit patients.

6 Surveillance after endoscopic resection

6.1 Endoscopic surveillance

RECOMMENDATION

30 ESGE recommends scheduled endoscopic surveillance with high definition white-light and chromoendoscopy (virtual or dye-based) with biopsies of only the suspicious areas after a curative ESD.
Strong recommendation, moderate quality evidence.

In general, close surveillance after ER is needed to detect local recurrences and metachronous lesions, since ER leaves a larger area of mucosa than does surgery and the risk of new lesions may be as high as 1%–5% per year, justifying scheduled endoscopic surveillance in every organ. As we have seen, CE increases detection, allows better characterization of lesions, can guide biopsies of irregular areas, and should be used routinely after ESD [218]. Since after a curative/R0 resection the risk of

recurrence is consistently lower than 1%–2%, routine biopsies of the ESD scar are not recommended.

The question of when to stop endoscopic surveillance has not been answered, since the majority of studies show a steady increase of metachronous lesions over time (older patients being especially at higher risk), and so the benefit of discovering or treating an early lesion should be balanced against age, comorbidities, and life-expectancy. In conclusion, the decision to stop surveillance should be individualized.

RECOMMENDATION

31 ESGE recommends that after piecemeal resection or in the presence of positive lateral margins when criteria for additional treatment are not met, a high definition chromoendoscopy (virtual and/or dye-based) with biopsies is recommended at 3–6 months.
Weak recommendation, low quality evidence.

As we have seen, in all cases and organs, the presence of horizontal margins that are positive or nonevaluable (HM1/HMx) increases local recurrence rates, with the recurrences most of the time being amenable to further endoscopic treatment if diagnosed early. In these cases, we suggest at least two endoscopies/colonoscopies with biopsies in the first 12–18 months (the first in the first 3–6 months after ER and the second depending on the organ and on the result of the first). After the first endoscopy without histologically confirmed recurrence, we then recommend the same surveillance protocol as for curative resections.

RECOMMENDATION

32 For upper GI superficial lesions, ESGE suggests endoscopy at 3–6 months and then annually after a curative ESD resection or after a local-risk ESD resection without recurrence.
Weak recommendation, low quality evidence.

6.1.1 Esophageal SCC lesions

In a recent Western report on long term follow-up after ER, the recurrence rate was 23.7% (19/80) in the endoscopic mucosal resection (EMR) group and 2.9% (2/68) in the ESD group ($P=0.002$). The median follow-up time before recurrence was 4 months (range 2–23 months), suggesting early follow-ups (at 3–6 months) and then annually [71]. Some new studies confirmed the need for close surveillance stated in the previous ESGE guideline of 2015. Even though some risk factors for recurrence have been described, such as male sex, alcohol consumption, smoking, and others, there is insufficient evidence to suggest different follow-up in these cases [219–222]. A large trial in 886 specimens found 5% had positive/nonevaluable horizontal tumor margins (HM1/HMx), with a 26.7% recurrence

rate. HM1/HMx lesions with less than 1 mm between the cancer and specimen edge were associated with substantial risk of local recurrence, and strict follow-up is recommended in these cases [223].

6.1.2 BE-associated lesions

Recurrence of intestinal metaplasia (IM) and dysplasia occurs even after complete ablation of the entire BE segment and therefore surveillance should be performed after therapy [82, 173]. It is recommended that biopsies should be taken during surveillance endoscopy at the esophagogastric junction (EGJ) and within the extent of the previous BE.

In a recent publication Cotton and co-workers built and validated a model to predict the incidence of neoplasia recurrence after initially successful RFA [224]. They used data from the United States Radiofrequency Ablation Registry and the United Kingdom National Halo Registry. According to this model, surveillance endoscopies for patients with high grade dysplasia or intramucosal adenocarcinoma should be performed at 3, 6, and 12 months and then annually, resulting in detection of unresectable cancers during surveillance at rates of less than 1/1000 endoscopies.

6.1.3 Stomach

After a curative ER, the risk of LNM is low or very low, but there is a very low risk of recurrence and a moderate risk of metachronous lesions during follow-up (10%–20%) [192, 225–231]. There is evidence that *Helicobacter pylori* eradication decreases the risk of metachronous lesions and thus eradication is recommended if the patient has active *H. pylori* infection [232]. No other strategies showed benefit in decreasing risk of metachronous lesions, but there is consistent evidence that older patients and patients with synchronous or multiple lesions at diagnosis and/or with extensive preneoplastic conditions are at higher risk [192, 225–231]. However, to date there are no data showing that these risk factors should influence surveillance intervals. Most centers perform an endoscopy 3–6 months after ESD and then annually for at least 5 years. Indeed, a study found that a surveillance interval > 12 months was associated with significantly larger and more advanced metachronous lesions, and a significantly higher proportion needed surgical treatment when compared with metachronous lesions in patients with surveillance intervals ≤ 12 months [233].

6.1.4 Colorectal lesions

RECOMMENDATION

33 ESGE suggests colonoscopy at 12 months and then further surveillance in accordance with polypectomy and colorectal cancer guidelines, after a local-risk ESD resection without recurrence or after a low or very low risk (curative) ESD of a colorectal malignant lesion. Weak recommendation, low quality evidence.

After a curative resection for T1 colorectal carcinoma, the risk of local and distant recurrences seems negligible [234, 235]. Local recurrences were found to be 0.7% at 2 years after curative treatment in 3278 patients with CRC who warranted adjuvant treatment (the majority because of N+ disease) [236]. However, the same study showed that the incidence of a second primary CRC was as high as 1.5% at 5 years [236]. From these results, Hassan et al. showed that 1-year surveillance colonoscopy was then cost-effective, allowing lesions to be found at an earlier stage than the previously recommended colonoscopy at 3 years [237].

Hence, there is no clear evidence to inform decisions on optimal post-ESD surveillance. If ESD had been performed for a good indication then it is predictable that the resected lesion will be high risk or malignant. Most authors recommend follow-up endoscopy in the first year after resection in order to verify complete removal and exclude synchronous/metachronous lesions. If technical success is confirmed, ESGE then recommends further surveillance in accordance with polypectomy and colorectal cancer surveillance guidelines [238, 239].

6.2 Other surveillance methods

RECOMMENDATION

34 ESGE does not suggest routine use of EUS, MRI, CT, or PET in the follow-up after a very low or low risk (curative) endoscopic resection, but this might be considered in the cases of T1a-m3/T1b-sm1 esophageal SCC particularly if no additional treatment has been decided. Weak recommendation, very low quality evidence.

Since the risk of LNM after a curative resection is very low (in most cases and organs < 1%–3%), there is no evidence to suggest routine radiological surveillance in these cases. The exception might be after ER of T1a-m3/T1b-sm1 esophageal SCCs since, as we have seen, the natural history of these tumors is not clearly defined.

7 Pathological aspects

A complete discussion of pathological issues and the definitions are provided in **Appendix 2s** (Pathology and definitions). ESGE recommends that patients who undergo ESD because of malignant lesions are treated by multidisciplinary teams, with the following recommendations for management, based on endoscopic and pathology reports as detailed in ► **Table 2**.

In this update of the ESD guideline, we considered four levels of risk related to ER, including two levels of “curative” ER based on different levels of LNM risk.

a) **Very low risk resection.** In this case the risk of LNM is almost null and lower than 0.5% (global LNM risk should not be higher than 1%). In general, this applies to en bloc, R0 resection of dysplasia/pT1a cancers, that are differentiated with no lymphatic and no vascular invasion (L0 and V0). In

these cases, the risk of local or distant recurrence is almost nonexistent, and only endoscopic surveillance is recommended with no further staging method or treatment.

- b) **Low risk resection.** In these cases the risk of LNM is generally very low and lower than 2% (global LNM risk should be lower than 3%). In general, this applies to en bloc, R0 resection of T1b-sm1 cancers that are differentiated, L0 and V0, and with other organ-specific characteristics. The risk of distant recurrence is low, and lower than the risks of further therapy. Although additional treatments are generally not recommended they can be considered in specific patients and scenarios, to further decrease the risk of LNM. However in all these cases, even though ER is considered “curative,” complete staging is recommended since these lesions represent true malignant disease.
- c) **Local risk resection.** This category includes piecemeal resection or where the horizontal margin is positive or unassessable (HM1 or HMx; thus Rx resection) and with no poor prognostic features for distant metastasis (including no submucosal invasion at the margins). In these cases, the risk of LNM is almost null, but the risk of local persistence/recurrence may be as high as 30% and a stricter endoscopic surveillance (and/or treatment) is recommended.
- d) **High risk resection (“noncurative”).** This includes R0 or Rx ERs but with at least one poor prognostic feature (poor differentiation, lymphovascular invasion, deep submucosal invasion, tumor budding in the colon); or R1 resection (implying a positive vertical margin [VM1]), when carcinoma is present. In these cases, even though most patients will have no residual disease, the global LNM risk is higher than 3% and in general this risk is higher than the risk of further treatment. Complete staging and additional nonendoscopic treatments are recommended in these cases (although surveillance may be an option in old and unfit patients).

It is important to note that most of this evidence comes from retrospective studies based on surgical specimens that may not have been pathologically handled and analyzed in the same manner as ER specimens. Furthermore, organ-specific considerations should be taken into account when deciding the type of ER and further decisions (see above).

Regarding what should be considered a safe VM (for more details, see **Appendix 2s**), this issue is highly controversial, particularly as regards the colon since in the other organs this is rarely reported. For the colon most Western societies recommend that a safe margin should be ≥ 1 mm [239,240]. But in fact, no validated data are available on the size of the safety margin after ER, which is why it is not mentioned in Asian guidelines [35]. In the largest meta-analysis that evaluated pathologic factors for LNM in early colorectal cancer, no increased risk was observed for a positive margin (OR 1.44, 95%CI 0.52–4.03) [202]. Moreover, in the study that most societies use to justify the 1 mm margin, residual invasive disease in the colon wall was noted in 16% with <1 mm polypectomy margin, in 21% with an indeterminate margin, and in 0% with a margin ≥ 1 mm ($P=0.009$), but this was not a risk factor for LNM [241]. Another study showed that although 63% of resection margins were

not deemed tumor-free, subsequent surgical specimens showed residual carcinoma in only 2.8% of all patients but LNM in 7.6%. However, in this study a free margin was not defined as a tumor-free extent of more than 1 mm; instead the resected specimen was only considered positive if there was lesion at the margin (R1) or limited assessability due to coagulation artefacts (Rx) [209].

Therefore, we believe that there is no evidence supporting the concept that a tumor-free margin of extent less than 1 mm should be considered a positive margin and, consequently, an indication for surgery. However, we recognize that smaller margins may increase the risk of persistent local disease (that can be recognized in the surveillance endoscopies). Therefore, in the present Guideline ESGE recommends the use of the term “preferably 1 mm,” but if the margin is smaller than 1 mm but free of tumor this should have no consequences for the clinical routine other than a stricter follow-up.

Disclaimer

The legal disclaimer for ESGE guidelines [5] applies to this Guideline.

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Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2022

Pimentel-Nunes P* ^{1,2,3}, Libânio D*, Bastiaansen B, Bhandari P, Bisschops R, Bourke MJ, Esposito G, Lemmers A, Maselli R, Messman H, Pech O, Pioche M, Vieth M, Weusten B, van Hooft JE, Deprez PH, Dinis-Ribeiro M

Abbreviations: ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; SCC: squamous cell cancer; BE: Barrett esophagus; GI: gastrointestinal; RFA: radiofrequency ablation.

Appendix 1s: Working groups and PICO Questions

Task forces

1. Esophagus (SCC, Barrett’s)

Group leader: Deprez PH

Other members: Bisschops R, Messmann H, Bhandari P

2. Stomach/junction non-Barrett’s

Group leader: Pimentel-Nunes P

Other members: Dinis-Ribeiro M, Libânio D, Esposito G

3. Duodenum/small bowel

Group leader: Pioche M

Other members: van Hooft JE

4. Colon (rectum and colon)

Group leader: Bisschops R

Other members: Lemmers A, Maselli R, Pioche M, Weusten B

5. Pathology

Group leader: Vieth M

Supplementary material

PICO questions (all organs)

A) Pretreatment Evaluation

Clinical Question:

1. Which pre-ESD staging is needed (EUS, TC, chromo-, etc.)?

PICO:

P – patients with superficial GI lesion

I – Endoscopic evaluation (HR-endoscopy)

C – Vs HR-virtual chromoendoscopy (PICO1) vs conventional CE (PICO2) vs EUS (PICO3) vs other/CT/PET (PICO 4)

O – staging accuracy

B) Treatment

Clinical questions:

1. What are the clinical indications (if any) for ESD in the different organs?
2. What are the available evidences on the efficacy/safety of ESD for each of these indications?
3. How does such efficacy/safety compare with competitive techniques (EMR, hybrid, EFTR, surgery) for each of these indications?
4. Is there any auxiliary technique (traction? Specific knife?) that leads to better ESD outcomes?

PICO:

P – patients with superficial GI lesion

I – ESD

C – Vs EMR (PICO1) vs Surgery (PICO2) vs Hybrid (PICO3) vs other/EFTR (PICO 4)

O – efficacy (curative/non-curative; R0/Rx/R1; survival); safety (bleeding/perforation/other adverse events/mortality);

PICO:

P – patients with superficial GI lesion going to be treated by ESD

I – ESD (standard knife, no traction)

C – Vs ESD (other knife) (PICO 5) Vs ESD with traction (PICO 6)

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O – efficacy (curative/non-curative; R0/Rx/R1; survival); safety (bleeding/perforation/other adverse events/mortality); speed of dissection.

C) Handling of ESD complications

Clinical question:

- 1. Can we prevent ESD complications?
- 2. What is the management of ESD complications?

PICO

P – patients with superficial GI lesion treated by ESD

I – coagulation of vessels

C – Vs no coagulation of vessels (PICO1)

O – incidence of bleeding (perforation/other adverse events/mortality);

P – patients with superficial GI lesion treated by ESD

I – closure of the scar

C – Vs no closure of the scar (PICO2)

O – incidence of bleeding (perforation/other adverse events/mortality);

P – patients with superficial GI lesion treated by ESD

I – second look

C – Vs no second look (PICO3)

O – incidence of bleeding (perforation/other adverse events/mortality);

P – patients with superficial GI lesion treated by circumferential/more than half circumferential ESD

I – no prophylatic therapy

C – Vs corticoid injection/therapy (PICO4) Vs other (PICO5)

O – incidence of stenosis;

P – patients with bleeding after ESD

I – standard (clips, injection)

C – Vs other endoscopic/hemospray (PICO6) Vs surgery (PICO7)

O – efficacy of treatment (no surgery/mortality);

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P – patients with perforation after ESD
I – standard (clips)
C – Vs other endoscopic/OTSC (PICO8) Vs surgery (PICO9)
O – efficacy of treatment (no surgery/mortality);

D) Management after treatment

Clinical questions:

1. What is the post-ESD management according to technical and histological outcomes?
2. What is the post-ESD surveillance according to technical and histological outcomes?

Importance of lateral margin (Rx resection)

P – patients treated by ESD
I – free margin
C – Vs positive margin (PICO1) Vs tangential margin (PICO2)
O – recurrence; need for surgery;

Importance of vertical margin (R1 resection)

P – patients treated by ESD
I – free margin
C – Vs positive margin (PICO1) Vs tangential (1 mm? 500 um?) margin (PICO2)
O – recurrence; LNM; need for surgery; survival (?)

Importance of tumour differentiation

P – patients treated by ESD
I – differentiated tumour
C – Vs undifferentiated/poor differentiated tumour (PICO1)
O – recurrence; LNM; need for surgery; survival (?)

Importance of depth of invasion

P – patients treated by ESD
I – mucosal tumour
C – Vs submucosal tumour sm1 (PICO1) Vs sm2 or more (PICO2)

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O – recurrence; LNM; need for surgery; survival (?)

Importance of LV invasion

P – patients treated by ESD

I – no LV invasion

C – Vs LV + (PICO1)

O – recurrence; LNM; need for surgery; survival (?)

Importance of perineural invasion

P – patients treated by ESD

I – no perineural invasion

C – Vs perineural invasion + (PICO1)

O – recurrence; LNM; need for surgery; survival (?)

Importance of budding

P – patients treated by ESD

I – no budding (0/+)

C – Vs budding ++/+++ (PICO1)

O – recurrence; LNM; need for surgery; survival (?)

According to these questions the following scenarios should be defined (per organ):

1. Low risk-resection (“curative” resection) – risk of recurrence/persistence and risk of LNM less than <1-2%
2. Local risk-resection – risk of LNM <1% but risk of recurrence/persistence >1-2%
3. High risk-resection (“non-curative”) – risk of LNM >1-2%

Surveillance after low-risk resection:

P – patients treated by ESD with a low-risk resection

I – endoscopic surveillance

C – Vs no surveillance (PICO1) Vs HR-CE surveillance (PICO2) Vs End plus CT (PICO2) Vs end plus EUS (PICO3)

O – recurrence; metachronous lesions; survival

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Surveillance/management after local-risk resection:

- P – patients treated by ESD with a local-risk resection
- I – endoscopic surveillance
- C – Vs no surveillance (PICO1) Vs HR-CE surveillance (PICO2) Vs End plus CT (PICO2) Vs end plus EUS (PICO3)
- O – recurrence; metachronous lesions; survival

If recurrence:

- P – patients treated by ESD with recurrence
- I – endoscopic retreatment
- C – Vs surgery (PICO1) Vs other/qtx/rtx (PICO2)
- O – recurrence/persistence;LNM; survival

Surveillance/management after high-risk resection:

- P – patients treated by ESD with a high-risk resection
- I – endoscopic/non invasive surveillance/management only
- C – Vs surgery (PICO1) Vs other/qtx/rtx (PICO2)
- O – recurrence; LNM; survival

Time for follow-up

Is there any evidence to suggest any particular interval for follow-up vs another?

Surveillance after low-risk resection:

- P – patients treated by ESD with a low-risk resection
- I – annual endoscopic surveillance
- C – Vs other (PICO1)
- O – recurrence; metachronous lesions; survival

Surveillance/management after local-risk resection:

- P – patients treated by ESD with a local-risk resection
- I – endoscopic surveillance at 3-6 months then annually

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C – Vs other (PICO1)
O – recurrence; metachronous lesions; survival

Surveillance/management after high-risk resection:

P – patients treated by ESD with a high-risk resection
I – endoscopic surveillance at 3-6 months then annually
C – Vs other (PICO1)
O – recurrence; LNM; survival

Other:

Pathology

1. How to manage the pos-ESD pathological sample?
2. What should be indicated in the ESD-pathological report?

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Appendix 2s: Pathology and definitions

These recommendations are valid for the entire gastrointestinal tract.

Note: the terms “dysplasia” and “intraepithelial neoplasia” can be used synonymously. In this report however the term “intraepithelial neoplasia” is used (with one exception in evaluation of the R-status).

How to manage the post-endoscopic resection pathological sample?

Tissue derived from endoscopic resections should be pinned on cork or thick paper to avoid shrinkage artefacts. Needles should not stretch the specimen but pin it down very loosely. If the gastroenterologist feels that accurate orientation is necessary, latex colours can be applied to mark the edges to allow orientation of the specimen. Alternatively, coloured needles can be used. Needle placement through a suspected lesion or too close to the edges of the specimen should be avoided, as this may hamper proper examination of lesions as well as of resection lines. Circular en bloc resections can be placed over a syringe before fixation for best results esp. in tubular esophageal specimen.

The specimen should then be placed overnight in 4% neutral buffered formalin. The specimens should completely be covered by formalin. It is important that vials are the correct size and contain enough formalin (formalin:specimen ratio = 1:17).

What should be included in the endoscopic resection pathological report?

The histopathological diagnosis of an endoscopic resection specimen is the basis for the clinical decision on whether the endoscopic resection has been curative or whether the patient needs to undergo further ablative therapy or surgical resection. All specimen should be measured in three dimensions after fixation and the size of the tumor should be also given in micrometer or millimeter or centimeter according to the local recommendations. Thus, the report on the specimen needs to include all the relevant information needed to make that decision incl. risk factors such as lymphatic vessel permeation or poorly differentiated areas (given as percentage of the whole tumor). This information varies throughout the gastrointestinal tract, because of location, type of epithelium, different staging modalities, and tumor aggressiveness. For all neoplasms, however, the following risk factors have to be reported: lymphatic vessel permeation, blood vessel permeation, budding (mandatory due to different staging systems and lacking worldwide acceptance, graded according to the budding consensus IBTCC 2016), perineural invasion, resection margin involvement (HM=horizontal margin, VM=vertical margin), as well as typing and grading of neoplasia according to the WHO classification. Perineural invasion is, however, mainly identified in deeply invasive carcinomas and its presence should not be expected in early cancers. Information on the distance towards the basal margin (in micrometers) should be included in every report.

Notably, the WHO classification refers to mucosal carcinomas only in the upper gastrointestinal tract and the anal canal. In the colorectum, only tumors that have penetrated through the muscularis mucosae are considered malignant (invasive). A diagnosis of carcinoma in situ should only be made for lesions originating from

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squamous epithelium. In contrast to the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) TNM system, the term “carcinoma in situ” therefore should be avoided for lesions originating from columnar epithelium, as the criteria for diagnosis have not been fully established and differentiation from high grade dysplasia is infeasible. Notably almost all diagnoses of lesions termed carcinoma in situ are in fact mucosal carcinomas of the gastro-intestinal tract. The WHO doesn’t recommend to use the term mucosal carcinoma in the colorectum. The reasons are not logical, nor validated at all but are perpetuated in the Western World. In Japan the entity of colorectal mucosal carcinoma has been established well. Due to the discrepancy to the WHO classification pathologists are encouraged to give an explaining comment when the term “mucosal carcinoma” is used in the colorectum. Elsewhere in the gastrointestinal tract it is supported to be used by the WHO classification.

When is an endoscopic resection specimen removed completely?

In operation specimen safety margins depend on the organ. Even the circumferential margin in the colorectum needs to be mentioned (CRM) since it is known when safety margins are less than recommended that there is a higher risk for recurrence. Nevertheless, a case with less than the recommended safety margin (e.g. in a case of diffuse gastric cancer with a safety margin less than 10 cm) the case can be R0. This means type of cancer and organ influence the safety margin and this affects mainly the planning of an operation in cases with advanced cancer. In endoscopic resections the discussion about such safety margins is obsolete since the risk for recurrence and metastasis does not apply to mucosal carcinoma or minute infiltration to the submucosal layer (definition depending on the organ) (table LNM risk). Otherwise, an operation needs to be recommended due to a higher risk for recurrence and metastasis. On general: the larger the safety margin the more positive it is for the outcome. Nevertheless, even mucosal carcinoma can show features of higher risk for recurrence and metastasis such as lymphatic vessel permeation or/ and high scores in budding or/ and foci of poor differentiation, etc... . In such cases interdisciplinary individual decisions how to proceed are necessary.

Most of the Western guidelines (**Shaukat A, Kaltenbach T, Dominitz JA, Robertson DJ, Anderson JC, Cruise M, Burke CA, Gupta S, Lieberman D, Syngal S, Rex DK. Endoscopic Recognition and Management Strategies for Malignant Colorectal Polyps: Recommendations of the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2020 Nov;159(5):1916-1934.e2. doi: 10.1053/j.gastro.2020.08.050. Epub 2020 Nov 4. PMID: 33159840**) prefer a safety margin of 1mm in endoscopic resections. The present guideline states that is “preferable” to have 1mm safety margin. But in fact, there are no validated data available on the span of the safety margin in endoscopic resections. This is the reason why Asian guidelines (**Tanaka S, Kashida H, Saito Y, Yahagi N, Yamano H, Saito S, Hisabe T, Yao T, Watanabe M, Yoshida M, Saitoh Y, Tsuruta O, Sugihara KI, Igarashi M, Toyonaga T, Ajioka Y, Kusunoki M, Koike K, Fujimoto K, Tajiri H. Japan Gastroenterological Endoscopy Society guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. Dig Endosc. 2020 Jan;32(2):219-239. doi: 10.1111/den.13545. Epub 2019 Dec 27. PMID: 31566804**) don’t mention it. Therefore, in the present guideline the ESG recommends to use the term “preferably” 1mm. At the level of the Horizontal margin (HM) often

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the 1mm is met but not at the Vertical margin (VM) but no consequences are drawn in clinical routine other than follow-up.

Noteworthy, that it is obsolete to state a R0 situation when low grade intraepithelial neoplasia or high-grade intraepithelial neoplasia found at a margin but no carcinoma. The intraepithelial neoplasia is just the margin of the carcinoma but not an own entity that can be seen independent from the carcinoma.

Esophagus

In the esophagus two different types of epithelium may give rise to two different forms of neoplasia: squamous cell neoplasia and neoplasia of columnar epithelium (Barrett’s).

Squamous cell neoplasia appears to be more aggressive than Barrett’s neoplasia. Furthermore, squamous cell neoplasia tends to show “lateral spread” along the basal cell layer with an overlaying “normal” squamous cell layers. About two thirds of cases show this type of lateral cancer spread, extending 2mm or more with overlying completely normal squamous epithelium. Endoscopic detection of lateral cancer spread is extremely difficult. Its clinical relevance is still unknown but the finding should be reported and could explain the so called field carcinogenesis.

The report of squamous cell neoplasia should include grading of neoplasia, e.g. low grade intraepithelial neoplasia, high grade intraepithelial (carcinoma in situ), mucosal carcinoma, invasive squamous cell carcinoma. Information on keratinization is optional. In the case of verrucous carcinoma this should be stated explicitly since verrucous carcinomas do not metastasize in general. In invasive carcinomas information on the depth of infiltration is mandatory. Depth should be classified according to the Japanese guidelines on esophageal cancer, and subdivided into m1 (=carcinoma in situ, high grade intraepithelial neoplasia), m2 (=microinvasive carcinoma into the tunica propria), and m3 (=invasion into muscularis mucosae). Depth of submucosal invasion should be classified as invasion into the upper third (sm1), middle third (sm2), or lower third (sm3). A correct estimation of thirds of submucosal invasion can only be made on surgical specimens and cannot be made on endoscopic resections. Therefore, the maximum depth of submucosal invasion (in micrometers [microns, μm]) should be measured. In this setting, sm1 invasion is restricted to cancer invasion at equal to or less than 200 micrometers (≤200 μm).

Barrett’s neoplasia is also subdivided into low grade intraepithelial neoplasia, high grade intraepithelial neoplasia, and carcinoma. Because of the double muscularis mucosae, two different classification systems are available to substage depth of infiltration following the anatomical structures (those of Westerterp et al. [216] and of Vieth et al. [217]). However, this discrepancy appears to be largely irrelevant, as the clinical impact of tumor substaging is limited in mucosal carcinomas. Hence, substaging of mucosal cancers cannot be regarded as mandatory, while invasion depth of submucosal tumors should be subdivided into thirds as described above (sm1–sm3). When the maximum depth of submucosal invasion is measured (in micrometers), the limit for sm1 in Barretts’s carcinoma is to be seen at equal to or less

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than 500 micrometers ($\leq 500\mu\text{m}$) measured from the bottom fibre of the muscularis mucosae downwards. Also, the width of submucosal invasion should be given in micrometers. Probably early and focal submucosal invasion represents a prognosis comparable to that of mucosal carcinoma [74].

Stomach

Neoplasms of the stomach are subdivided into low grade intraepithelial neoplasia, high grade intraepithelial neoplasia, and carcinoma. Carcinoma is subdivided into mucosal carcinoma (m-type) and submucosal carcinoma (sm1 –sm3). The limit for sm1 is given as equal to or less than 500 micrometers ($\leq 500\mu\text{m}$). The report should type the carcinomas according to the WHO classification and according to the Laurén classification (intestinal type, diffuse type, and poorly cohesive). Information on pathological findings in the adjacent non-neoplastic gastric mucosa (e.g. gastritis status) should be provided. Notably, the type of differentiation should also be given and not to be mixed up with grading into gastric or intestinal. Gastric differentiations include foveolar type, pyloric gland type and oxyntic gland type of neoplasia or mixed forms also to be seen with intestinal differentiations. Gastric differentiations can be seen in more than 60% of advanced gastric carcinomas and probably around 10% of early gastric carcinomas. The prognosis seems to be the same for intestinal and gastric differentiated neoplasms with one exception: oxyntic gland neoplasms never metastazise and it is questioned whether oxyntic gland neoplasms can progress to carcinoma at all. Some cases with clear submucosal invasions are published but these cases are very rare. The usual criteria of intestinal type of neoplasia cannot be applied to gastric type of neoplasia because nuclear polymorphism is mainly absent and neoplastic cells show more subtle and uniform morphology, instead.

Duodenum/small bowel

For the small bowel there are no clear recommendations in the literature that are distinct from those for the stomach, probably because of the small number of primary small-bowel carcinomas. Therefore, probably, the same rules as those for grading and evaluating depth of infiltration in the stomach apply. That means there is the possibility of mucosal carcinoma of the small bowel (m-type) and the upper third of the submucosa is defined as equal to or less than 500 micrometers ($\leq 500\mu\text{m}$). Special attention should be paid at the papilla since adenomas here can show an invasive component in the depth of the pancreatic duct and may require resection of the pancreatic head. Special attention should be also paid for papillary lesions on the basis that a main-duct type of intraductal papillary mucinous neoplasia (IPMN) of the pancreas can sometimes protrude into the lumen of the small bowel.

Large bowel

Neoplasms of the colorectum are subdivided into low grade intraepithelial neoplasia, high grade intraepithelial neoplasia, and carcinoma. As already pointed out above, carcinomas at this site have penetrated through the muscularis mucosae and they are

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subdivided into sm1–sm3, accordingly. In sessile lesions, depth of infiltration should additionally be measured (in micrometers from the deepest fibre of the muscularis mucosae), and the limit for sm1 has to be defined as equal to or less than 1000 micrometers ($\leq 1000\mu\text{m}$). In pedunculated lesions, the stalk always represents the upper third of the submucosal layer. For prognostic stratification of depth of submucosal invasion in pedunculated lesions, the Haggitt levels should be mentioned in the pathology report. Haggitt levels 1 and 2 represent low risk lesions, whereas Haggitt level 3 with infiltration of the stalk of the polyp may be seen as a lesion with a higher risk of lymph node metastasis, esp. when the depth of invasion reaches 3mm or more. The original manuscript by Rodger Haggitt shows up to 6% (check!!!!) lymph node metastasis when the invasion reached Haggitt level 3 into the stalk. But these numbers have to be interpreted carefully, since the patient number was rather small for all Haggitt levels in that particular publication.

Since standardization of grading of single tumor cells at the invasive front have been reached 2016 (ITBCC international consensus) and validated in subsequent publications it is considered nowadays as an independent marker for tumor aggressiveness, particularly in colorectal cancers but also for all other gastrointestinal carcinomas, and should be included in the report. Special tumor types, such as medullary or micropapillary carcinoma, have been identified and should be reported. Immunohistochemistry may be helpful in differential diagnosis and may also be applied to identify patients with Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]) [218]. In contrast to the WHO classification of gastrotinestinal tumors mucinous carcinomas still require prognostic testing of the microsatellites. The studies the WHO classification based the decision not to test are based on two studies incl stage 4 tumors and thus the results are biased a lot since in stage 4 tumors a risk stratification makes almost no sense, anymore. In this situation a comment should be given why testing for microsatellites has been carried out in mucinous carcinomas (other than stage 4 tumors).

All carcinomas must be classified according to the AJCC/UICC TNM system.

ESGE recommendations for mandatory data to be shown in the conclusion of endoscopic/pathology reports

Before ESD

- Exact location [organ, distance, position]
- Paris classification
- Ulceration (Y/N)
- Size [mm]
- Inclusion of images is mandatory, preferably within the endoscopic report

Examples:

Esophagus, 25cm from incisors, IIc, ulc–, 15mm

Stomach, distal lesser curvature, IIc+a, ulc–, 30mm

Colon, rectum, granular LST, 30mm

ESD

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- Exact location
- Paris classification
- Ulceration (Y/N)
- Size [mm]
- En bloc versus piecemeal
- Inclusion of images is mandatory, preferably within the endoscopic report

Examples:

Esophagus, 25 cm from incisors, IIc, ulc–, 15 mm

Stomach, distal lesser curvature, IIc+a, ulc–, 30 mm, en bloc

Colon, rectum, granular LST, 30 mm, piecemeal

Pathology

- Maximal histology observed and differentiation if applicable [well/moderate versus poorly]
- Size [mm] [we recommend to include HGD in the complete measurement; and this size will determine the attitude]
- Horizontal margin [negative if no neoplasia is present in at least 1 mm, HM0; positive for carcinoma, HM1c, or dysplasia, HM1dh (for high grade dysplasia), HM1dl (for low grade dysplasia)]
- Vertical margin [negative, VM0 (preferably > 1 mm) or positive, VM1; only applicable for carcinoma]
- Maximum depth of invasion sm [taken from the lowest fibre of the muscularis mucosae; in Barrett’s be aware of duplicated muscularis mucosae]
- Lymphatic and/or venous infiltration [L0, L1; V0, V1]
- Complete resection or not [R0, RX, R1]
 - R0 (complete), if en bloc, and horizontal and vertical margins negative (HM0 & VM0)
 - RX (non-assessable), if en bloc or piecemeal, and horizontal margin positive (HM1) and vertical margin negative (VM0)
 - R1, if vertical margin positive (VM1)

Examples:

Well-differentiated carcinoma, 30 mm, HM0, VM0, R0

Well-differentiated carcinoma, 20 mm, HM1 d, VM0, sm 450 µm, L0, V0, Rx

Poorly differentiated carcinoma, 15 mm, HM0, VM0, R0

Tumor budding

In experienced hands grading of budding always had a prognostic relevance. Since the IBTCC consensus 2016 an easy reproducible and prognostically relevant grading system has been introduced and should thus be reported as bd 1, bd2 or bd3. Please note, that there is no bd 0 !

Supplementary material

Multidisciplinary recommendation

ESGE recommends that patients are seen in multidisciplinary teams, with the following recommendations based on endoscopic and pathology reports.

Low risk resection (i.e., low risk for local or distant recurrence; no further immediate therapy is required) is defined as:

- R0, and no poor prognosis features <cutoff invasion, and L0 and V0

High risk resection (i.e., high risk for distant recurrence; further measures are required; case-by-case follow-up): is defined as:

- R0 or RX but at least one poor prognosis feature; or R1

Local risk resection (i.e., with risk for local recurrence) is defined as:

- RX and no poor prognosis features for distant metastasis

Competing interests: None

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Supplementary material

Evidence Tables

Table 1s: Esophageal squamous cell carcinoma

Table A pico 3. Research/PICO question: Is virtual chromoendoscopy better in staging accuracy than HR-endoscopy?

First author, year	Study design , study objective	Intervention	Participants	Outcomes	Results	Level of evidence
Kim 2017	Retrospective	ME-NBI before resection (IPCL classification B1-2-3)	70 pts (43 T1a, 27 T1b)	Overall accuracy of ME-NBI for estimating depth of invasion of SESCC	Overall accuracy 78.6%. Sensitivity and specificity of type B2 for tumors invading into m3 or sm1 were 94.4% and 73.1%, respectively, while those of type B3 for tumors invading into sm2 were 75.0% and 97.8%, respectively. Interobserver agreement was excellent (κ = 0.86, 95%CI: 0.76-0.95).	Low
Fujiyoshi 2017	Prospective	ME-NBI, (New classification vs. Inoue’s or Arima’s classifications),	151 pts	Assessment of sensitivity and specificity, concordance rates	The specificity for classifying invasive depth as epithelium (EP)/lamina propria mucosae (LPM)	Moderate

Supplementary material

		before endoscopic or surgical resection			confined was higher with the new classification than with Inoue's classification (0.512 vs. 0.349; P = 0.02) and Arima's classification (0.512 vs. 0.279; P < 0.01). However, the sensitivity was lower (0.902 vs. 1.000; P < 0.01) compared with Arima's classification. The concordance rates of three evaluators (κ values) were 0.52 for the new classification, 0.50 for Inoue's classification, and 0.23 for Arima's classification	
Oyama 2017	Prospective	New JES classification and prediction of invasion depth	211 pts	Accuracy of type B microvessels to estimate tumours depth	The overall accuracy of type B microvessels in estimating tumor invasion depth was 90.5 %	High
Katada 2019	Retrospective	Role of ME-NBI JES classification	256 pts	Assessement of tumour invasion	The PPV of diagnosis according to the JES	Moderate

Supplementary material

		compared to WLI, pre-ESD		depth	classification was 93% for EP/LPM, 65% for MM/SM1, and 77% for SM2 ME-NBI enhanced the diagnostic accuracy of the depth of invasion in patients with S-ESCC	
Tanaka 2020	Retrospective	Role of ME-NBI in type B2 vessels	248 pts, 78 with B2 lesions	Optimal size (<4mm) of B2 vessels to detect T1a-MM or deeper invaion	to predict T1a-MM or deeper invasion, B2-Broad had a sensitivity, specificity, positive predictive value, and negative predictive value of 61%, 98%, 95%, and 79%, respectively.	Moderate
Kimura 2020	Retrospective	Role of JES classification in B2 types os SESCCs	104 lesions Type B2	Over and understaging risk with B2 type	Type B2 area <6 mm and Type B2 vessels around erosion were significantly associ-ated with overdiagnosis, while distinct features (protruding or depressed area) were significantly associated with	Moderate

Supplementary material

					underdiagnosis. Adjusted by these misdiagnosis factors, PPV significantlyimproved from 38% to 65% (P < 0.01)	
Ueda 2020	Retrospective	Accuracy of magnifying blue laser imaging for depth of invasion	160 SESCOs	WLI vs M-BLI and ME-NBI accuracy	Significant differences were found between WLI and WLI + M-BLI or WLI + M-NBI (P = 0.006 and P = 0.021, respectively). The concordance of intrapapillary capillary loops between M-BLI and M-NBI was 91.2%.	Moderate
Yu 2018	Meta-analysis	ME-NBI diagnostic accuracy analysis.	10 studies, 207 pts with T1 lesions	WLI vs ME-NBI accuracy	In the differentiation for invasion depth staging, ME-NBI is superior to WLI and has a similar diagnostic rate compared with HF-EUS	Low

ME-NBI= magnifying endoscopy with narrow band imaging
Pubmed search: From January 2015 UP to November 2020
Table A pico 3. Research/PICO question: Is EUS better in staging accuracy than HR-endoscopy or than MRI/CT or PET-CT

Supplementary material

First author, year	Study design , study objective	Intervention	Participants	Outcomes	Results	Level of evidence
EUS accuracy						
Luo 2016	Meta-analysis	Diagnostic accuracy of EUS before resection	44 studies (2880 pts)	Staging accuracy	The pooled sensitivity and specificity of T1 were 77% (95%CI: 73 to 80) and 95% (95%CI: 94 to 96). Among the T1 patients, EUS had a pooled sensitivity in differentiating T1a and T1b of 84% (95%CI: 80 to 88) and 83% (95%CI: 80 to 86), and a specificity of 91% (95%CI: 88 to 94) and 89% (95%CI: 86 to 92).	Moderate
Luu 2017	Retrospective	Diagnostic accuracy of EUS before resection	139 patients with clinical stage I or II A esophageal cancer undergoing esophagectomy	Staging accuracy	Preoperative EUS matched the final surgical pathology in 73/139 patients for a concordance rate of 53%. Twenty-nine patients (21%) were under-staged by EUS; of those, 19 (14%) had unrecognized nodal disease.	Low
Choi 2020	Retrospective	Diagnostic accuracy of EUS before resection	532 pts with SCC, 321 superficial (42 pT1s, 115 pT1a, 165 pT1b)	Staging accuracy, focus on overstaging	Accuracy rates, sensitivity, specificity, positive predicted value, and negative predicted value for selecting cT1a by EUS were 82.3%, 60.5%, 91.5%, 74.8%, and 84.7% respectively.	Moderate

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					The rate of overstaged pTis-T1a was 39.5%. In multivariable analysis, tumor size (>2 cm), poor differentiation, protruding gross type, and use of conventional EUS (vs. miniprobe) were associated factors for overstaging of pTis-T1a.	
EUS vs. ME-NBI						
Lee 2014	Retrospective	Comparison EUS vs ME-NBI	45 pts	Differentiation of mucosal from submucosal SCC	ME-NBI and EUS had overall accuracies of 76.1% and 84.8%, respectively, in distinguishing mucosal from non-mucosal cancers When both ME-NBI and EUS suggested a mucosal depth of lesion invasion, the frequency of mucosal cancer in the final histopathology was 94%	Low
Ishihara 2017	Systematic review and meta-analysis	EUS vs ME vs non-ME for depth invasion assesement	14 studies	Differentiation of invasion depth EP/LPM vs. MM/SM1 vs. ≥ SM2	ME demonstrated very low NLR, and is thus a reliable modality for confirming deep cancer invasion, while EUS showed a high positive likelihood ratio, thus a suitable modality for confirming that a cancer is limited to the surface.	Moderate

Supplementary material

					Combined use of these two modalities should be recommended	
Tao 2017	Systematic review and meta-analysis	EUS vs ME-NBI for depth invasion assesement	754 pts, 7 prospective studies	R0 resection rates and procedure times	Comparable performance he sensitivity and specificity of EUS for the diagnosis of the depth of invasion of gastrointestinal cancers were 0.75 (95% CI 0.69–0.81) and 0.84 (95% CI 0.79–0.88), respectively. In comparison, the sensitivity and specificity for ME were 0.74 (95% CI 0.67–0.69) and 0.85 (95% CI 0.80–0.89), respectively.	Moderate
Mizumoto 2018	Retrospective	EUS vs ME-NBI	174 pts (124 T1a, 50 T1b)	Staging accuracy in differentiating EP/LPM from MM/SM	Sensitivity and accuracy of ME-NBI in distinguishing EP/LPM from MM/SM1 and more deeply invasive SESCOs is significantly higher than those of EUS (P = 0.048 and P = 0.017, respectively)	Moderate
EUS vs CT or MRI in T1 lesions						
Qu 2018	Prospective	EUS vs r-VIBE MRI,	43 pts with SCC	Staging accuracy compared with	Accuracy of staging on r-VIBE is higher in T1/2 than in T3/4 Accuracy of EUS was 100% and 68.2% for T1/T2 and T3/T4	Low

Supplementary material

				postoperative stage	stage	
Guo 2020	Prospective	EUS vs CT vs MRI	63 pts with SCC 45 T1-T2 vs 28 T3-4 out of 74pts	Staging accuracy, gold standart	Compared to CT, MRI showed significantly higher accuracy for both the readers (96% vs 82%, p = 0.003, for MRI vs CT, respectively). Further, MRI outperformed EUS with higher specificity (59% vs 93%, p = 0.0015, for EUS vs MRI respectively), and accuracy (81% vs 96%, p = 0.002, for EUS vs MRI, respectively)	Low

Pubmed search: From January 2015 UP to November 2020

Supplementary material

Table B pico 5. Research/PICO question: Is there any auxiliary technique (specific knife?) that leads to better ESD outcomes

First author, year	Study design , study objective	Intervention	Participants	Outcomes	Results	Level of evidence
Esaki 2020	Multicenter retrospective study	ESD with scissor-type of knife (Clutch Cutter) versus conventional knife (various types) in ESCC	48 pts scissor-type 114 pts conventional knives	Procedure time, efficacy and safety	Procedure time scissors versus conventional: 44.0 min vs 66.5 min Similar efficacy and safety	Low: cohort bias (endoscopists switched from conventinal to scissor-type)

Pubmed search:
From January 2015 UP to April 2020
x studies
Relevant studies selected and present in the tables above.

Supplementary material

Table A pico 1. Research/PICO question: Is Virtual Chromoendoscopy better in staging than HR-endoscopy						
First author, year	Study design , study objective	Intervention	Participants	Outcomes	Results	Level of evidence
Koike 2015	RCT	ESD with hookknife with or without wire traction	40 pts (39 ESCC, 1 BE cancer) 20 pts per group	Disection time, number and volume of injections	Wire traction vs conventional: - time 19.8 vs 31.8 min (p=0.044) - number of injections and injection volume also significantly less	Moderate
Xie 2017	Case-matched comparative study (prospective)	ESD with Needle knife, IT-2 knife and hook knife, with or without traction	100 pts (ESCC), 50 pts per group	Disection time, Muscularis propria injuries	Wire traction vs conventional: - time 22.0 vs 26.5 min (P0.018) only for lesions <50% of circumference, no difference in lesions >50% - mp injuries: 10 vs 30% (P=0.007)	Moderate
Jacques 2017	Prospective series	ESD by unexperienced European endoscopists	62 lesions, mixed ESCC and BE, using hybrid knife or dual knife	Efficacy and safety	Successful, no perfs,	Low

Supplementary material

Kitagawa 2018	Prospective series	ESD with IT-nano with traction (clip and wire)	103 pts (ESCC)	Efficacy and safety	Very successful, no perfs, no delayed bleeds	Low
Zhang 2019	Prospective series	Snare and clips ESD				Low
Yoshida 2020	RCT multicenter	ESD with and without clip-and-wire	240 pts (ESCC), after exclusions 117 conventional, 116 traction	Procedure duration time	Traction versus conventional ESD: Procedure time 44,5 min vs 60.5 min (P<0.001). No adverse events in traction group	High
Su 2020	Meta-regression of RCTs	ESD with and without traction (clip and wire), for esophagus, stomach and colon	The two RCTs by Yoshida and Koike included	R0 resection rates and procedure times	R0 resection rates were equal, traction was associated with shorter duration	

Pubmed search:
From January 2015 UP to April 2020
x studies
Relevant studies selected and present in the tables above.

Supplementary material

Table C pico 3. Research/PICO question: usefulness of a second look endoscopy for the prevention of delayed bleeding

First author, year	Study design , study objective	Intervention	Participants	Outcomes	Results	Level of evidence
Mochizuki 2015	Multicenter RCT	Second look (n=130) 1 day after gastrc ESD vs no second look (n=132)	Pts undergoing gastric ESD	Post-ESD bleeding	Second Look vs no SL Post-ESD bleeding: 5.4% vs 3.8%	high
Jee 2016	Multicenter RCT	Second look (n=110) 1 day after gastrc ESD vs no second look (n=110)	Pts undergoing gastric ESD	Post-ESD bleeding	Second Look vs no SL Post-ESD bleeding: 6.4% vs 1.8%	high
Kim 2017	Systematic review	Second looko vs no second look after gastric ESD		Post-ESD bleeding	No effect	high

Pubmed search:
From January 2015 UP to April 2020
x studies
Relevant studies selected and present in the tables above.

Supplementary material

Table C pico 4. Research/PICO question: steriods for stricture prevention

First author, year	Study design , study objective	Intervention	Participants	Outcomes	Results	Level of evidence
Wakahara 2016	RCT for best timing of steroid injections post ESD	ESD followed by steroid injection (triamcinolon) to prevent strictures Randomization between weekle and bi-weekly injections	Patients after ESD of >75% of circumference 33 pts in total - 15 weekly - 15 bi-weekly - 3 excluded	Duration of treatment - stricture rate - number of dilations - number of steroid injections - complications	Weekly vs bi-weekly Duration: 37.0 vs 34,2 days Number of strictures and number of dilations similar Less injections in bi-weekly group	moderate
Muzitani 2015	RCT oral steriods vs local injection					Trial in progress
Nagami 2016	Matched case controll study	Steroid injection (dexamethason / triamcinolon)	From a cohort of 305 cases (461 lesions), prosensity score matching: 28 patients with and 28 without steroid injection after ESD	Stricture rate	With vs without steroid injection: - stricture rate 10.7% vs 35.7% (P=0.035)	Moderate

Supplementary material

			Either triamcinolon once, or dexamethason repeated 2 times per week (1-6 times) ESD 70-75% of circumference			
Takahashi 2015	RCT	Single dose of triamcinolon injection after ESD of >75% of civrumference, vs no injection	32 pts, 16 with steroid injection, 16 without	Stricture rate Number of dilations (Diameter of stricture)	Steriod injection vs no injection: - strictures: 62,5% vs 87,5% (P=0.22) - number of dilations: 6.1 vs 12.5 (P=0.04) - minimal stricture diameter: 11.0 vs 7.1 mm (P=0.008)	Moderate (primary endpoin NS; possibly type 2 error).
Yamaguchi 2011	Retrospective cohort study	Oral steroids 30mg/d started on day 3, tapered with 5mg/d each week Only EBD on	Patients withs ESCC with ESD of >3/4 circumference: Oral steriods: n=21	Stricture rate Number of dilations needed to resolve dysphagia	Oral steriods vs pre-emptive EBD Strictures: 1/19 vs 7/22 (P<0.05 Number or dilations:	low

Supplementary material

		indication vs pre-emptive balloon dilation: twice weekly for 8 weeks	Pre-emptive balloon dilation: n=22		15,6 vs 1,7 (P<0.0001)	
Sato 2013	Retrospective cohort study	Oral steroids 30mg/d started on day 3, tapered with 5mg/d each week Pre-emptive balloon dilation: in case of resistance EBD each week, in case endoscope couldn't pass: EBD twice weekly	Complete circumferential ESD Oral steriods + balloon dilation: n=10 Pre-emptive balloon dilation: n=13	Number of EBD sessions Duration of EBD therapy	Oral steriods + EBD versus EBD alone Number of EBD: 13,8 vs 33,5 (P<0.001) Duration in months: 4,8 vs 14,2 (P=0.005)	low
Zhou 2017	Retrospective cohort	oral steriods: 30mg starting on D3, tapered with 5mg for 14 d.	ESD>50% of circumference, Oral prednisone	Stricture rate Number of EBD	Oral steriods versus no steroids Stricture rate	

Supplementary material

		EBD only on demand	n=13 No steriods n=10		23.1% vs 80% (P<0.05) Number of EBD 0.69 vs 13.5 (P<0.05)	
Chu 2019	Retrospective cohort	Intralesional steroid injection (single treatment triamcinolon 80-120mg) + oral steroids (starting on D3, 2 weeks of 30mg/d, tapering with 5mg/d per week) Versus No steroids	ESD>2/3 of circumference Local+oral steriods: n=34 No steriods: n=36	Stricture rate Numer of EBD	Steriods versus no steriods Stricture rate: 14.7% vs 52.8% (P=0.001) Number of EBD 0.2 vs 3.3 (P=0.001)	Low
Kadota 2020	retrospective	Full circumferential ESD Injection triamcinolone	26 patients with cirvumferential ESD	Stricture rate Refractory strictures (6 or more EBD)	Stricture rate 62% Refractory: 38% Unimproved: 12%	low

Supplementary material

		50-100mg once, followed by oral prednisone 30mg/d tapered in 8 weeks		Unimproved strictures		
Yamashita 2019	Small animal study	Injection of triamcinolone in musc propria after endoscopic resection			Abcesses observed	Very low
Yang 2019	Network meta-analysis		Studies using - no prevention - long-tern oral steriods - medium term oral steriods - short term oral steriods - single dose steriod injections - repeated steroid injections - topical superficial steroids - combined injection and	Stricture rates Number of dilation sessions needed	Steriods better than no steroids, both in terms of stricture rates as well as number of dilations needed Long-term oral steroids probably most efficacious. Short term and medium term orals steroids and single steroid injection might be as efficacious, with fewer complications No increase in complications	High (for effectiveness of steroids in general)

Supplementary material

			oral steroids - pre-emptive EBD			
Iizuka 2018	Retrospective cohort studies	Oral steroids after circumferential ESD: - conventional: 30mg for 2 week, 25mg for 2 weeks, tapered by 5mg each week - modified group: 30mg for 3 weeks, tapered with 5mg every 3 weeks	22 pts with circumferential ESD - conventional group: n=11 - modified group: n=11	Stricture rate Number of dilations	Conventional (short) vs modified (long): - stricture rate: 82% vs 36,4% (P=0.04) - number of dilations: 19.4 vs 6.2 Complications: - candida esophagitis (modified group) - oral herpes infection - steroid myopathy (modified group)	
Kataoka 2014	Retrospective cohort study	Oral steroids after semicircular or circumferential ESD Short course of prednisone: 30mg on D2: 1	Oral steroids: n=17 No steroids: n=16	Stricture rate Number of EBD	Oral steroids vs no profylaxis: - stricture rate: 17,6% vs 68,7% (P<0.01) - number of EBD: 4.6 vs 8.1 (P<0.01)	Low

Supplementary material

		week 30mg, 1 week 20mg, 1 week 10mg				
		No oral steroids				

Pubmed search:
From January 2015 UP to April 2020
x studies
Relevant studies selected and present in the tables above.

Table C pico 5. Research/PICO question. Other measures for prevention of post-ESD strictures

First author, year	Study design , study objective	Intervention	Participants	Outcomes	Results	Level of evidence
Chai 2018	RCT for prevention of post-ESD strictures	ESD followed by stent placement plus or minus polyglycolic acid sheet covering. Stentremoval: stent + PGA: 4w Stent only: 8w	70 ts with lesions >3/4 of circumference and length >3cm. 66 evaluable patients	Strictures (<diameter<1cm); Time to stricture, number of dilations needed	Stent + PGA vs no PGA - Strictures: 20,5% vs 46,9% (P=0.024) - Number of dilations: 4 vs 6 (P=0.007)	Moderate (no blinding for results / stricture assessment or dilation
Wen 2016	RCT	Botulin toxin injection versus no treatment after ESD	67 pts with ESCC >50% of circumference Botox: n=33 No TX: n=34	Stricture rate Number of dilations	Botox vs no Tx - strictures: Per protocol 6.1% vs 32.4% ITT 11.4% vs 37.8% P<0.05	Moderate (no blinding for results / treatment)

Supplementary material

					- number of dilations 1.5 vs 2.8 (P<0.05)	
Li 2019	Prospective series	Self-dilation with balloon after cESD	8 pts with circumferential ESD	Stricture rate	1 patient (12.5%) developed stricture, resolved after 3 endoscopic ballon dilations	low

Pubmed search:
From January 2015 UP to April 2020
x studies
Relevant studies selected and present in the tables above.

Supplementary material

Table C pico 8 and 9. Research/PICO question: management of perforations during esophageal ESD						
First author, year	Study design , study objective	Intervention	Participants	Outcomes	Results	Level of evidence
Noguchi 2017	Retrospective series	Conservative management of perf after esophageal ESD	Pts undergoing esophageal ESD complicated by perforation: N=9		No esophagecomy needed. Direct clip closure in 6/9. Drainage for pleural effusion in 2.	Very low
Yamamoto 2019	review				Acute perfs reported in 1.5-5.0% No systematic evidence, only case series: - small perfs might be managed by conservative measures without closure - most reports on clip closure - few reports on PGA (ref 58-60), SEMS, and OTSC for large perfs (ref 61,62) Delayed perfs are rare but can be serious,	

Supplementary material

					with successful SEMS in some cases, but need for esophagectomy in half of the cases (ref 63, 64)	
Matsuda 2015	Case report				2 cases of delayed perforation (at D6 and D10), treated with esophagectomy	Very low
Omae 2018	Case report				1 case of delayed perf after BE ESD (1 day after ESD), successfully managed by endoscopic senting	Very low

Pubmed search:
From January 2015 UP to April 2020
x studies
Relevant studies selected and present in the tables above.

Supplementary material

Table C pico extra. Research/PICO question: use of CO2 for esophageal ESD.

First author, year	Study design , study objective	Intervention	Participants	Outcomes	Results	Level of evidence
Maeda 2016	RCT	ESD using CO2 or air insufflation	46 patients CO2: n=24 Air: n=22	Mediastinal emphysema on CT immediately after and 1 day after ESD Air in digestive tract VAS post-operative	CO2 versus air Mediastinal emphysema - immediately after: 17% vs 55% (P=0.012) - next day: 8.3% vs 32% (P=0.066) Volume of air in digestive tract: (808 mL vs 1173 mL, P = 0.013) VAS scores for pain not different	Moderate (no blinding described)

Pubmed search:
From January 2015 UP to April 2020
x studies
Relevant studies selected and present in the tables above.

Supplementary material

Table 2s: Barrett’s esophagus

Table X. Research/PICO question.

First author, year	Study design , study objective	Intervention	Participants	Outcomes	Results	Level of evidence
Qumseya BJ, Dig Liver Dis. 2018 May;50(5):438-445.	Meta-Aanalysis, overstaging by EUS?	EUS	Barrett-Ca (T1a and T1b)	Rate of overstaging and accuracy	pooled false negative rate was 9.2% [95%CI: 4.7-17.3%], p<0.01 accuracy of was low at 74.6% [58.7-85.8%], p=0.004	moderate
Bartel MJ, Gastrointest Endosc. 2017 Aug;86(2):292-298	Retrospective cohort study	EUS	Barrett with HGIN and adenocarcinoma	rate of over-staging related EUS	Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for patient selection to endoscopic (T1aN0 or less) or surgical therapy with EUS TN staging were 50%, 93%, 40%, 95%, and 90%, respectively.	moderate
Qumseya BJ, Gastrointest Endosc. 2015 Apr;81(4):865-74.e2	Meta-Aanalysis	EUS	Patients with BE and HGD or esophageal adenocarcinoma (EAC)	Pooled proportion of patients with advanced EAC identified by EUS	proportion of patients with advanced disease detected on EUS was 14% (95% confidence interval, 8%-22%; P < .0001).	moderate
Thota PN, Surg Endosc. 2017 Mar;31(3):1336-1341		EUS	BE with HGD or early esophageal adenocarcinoma		EMR resulted in change in diagnosis with upstaging in 21 % (32/151) and downstaging in 29 % (44/151) IMC on EMR, EUS findings were T1a in 23.6 % (9/38), upstaged in 18.4 % (7/38) and downstaged in 57.8 % (22/38). EUS accurately identified EMR histology in all submucosal cancers.	moderate
Coletta M, Gastrointest Endosc. 2016	Meta-Analysis	Acetic Acid Staining	Barrett and early Neoplasia	Accuracy of acetic acid staining for detection od	For the diagnosis of HGD/EC, the pooled	moderate

Supplementary material

Jan;83(1):57-67				neoplasia	sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR-) for all included studies (9 studies, 1379 patients) were 0.92 (95% confidence interval [CI], 0.83-0.97), 0.96 (95% CI, 0.85-0.99), 25.0 (95% CI, 5.9-105.3), and 0.08 (95% CI, 0.04-0.18), respectively.	
Sharma P, Gastroenterology. 2016 Mar;150(3):591-8.	Prospective cohort study	NBI	Patients with Barrett’s esophagus and neoplasia	Accuracy of NBI to identify patients with dysplasia	To identify patients with dysplasia: 85% overall accuracy, 80% sensitivity, 88% specificity, 81% positive predictive value, and 88% negative predictive value	moderate
Kandiah K, Gut. 2018 Dec; 67(12):2085-2091	Prospective cohort study	Acetic Acid Staining	Images with Barrett and neoplasia	Develop a training tool for AA staining	application of PREDICT (Portsmouth acetic acid classification) by endoscopists improved the sensitivity and negative predictive value (NPV) from 79.3% and 80.2% to 98.1% and 97.4%, respectively (p<0.001).	moderate
Lipman G,	Prospective	i-scan and acetic	Patients with	assess the effect of	accuracy of the I-SCAN	moderate

Supplementary material

Endoscopy. 2017 Dec;49(12):1219-1228.	Cohort study	acid staining	dysplastic Barrett’s	magnification endoscopy with I-SCAN (Pentax, Tokyo, Japan) and acetic acid (ACA) on dysplasia detection in BE	classification system for BE dysplasia improved with I-SCAN magnification from 69 % to 79 % post-ACA (<i>P</i> = 0.01).	
Everson MA, Gastrointest Endosc. 2019 Feb;89(2):247-256.	Prospective Cohort study	i-scan OE vs white light			improvements in accuracy (79.9% vs 66.7%), sensitivity (86.3% vs 83.4%), and specificity (71.2% vs 53.6%) of dysplasia detection. PPV improved (62%-76.6%), as did NPV (67.7%-78.5%).	moderate
Subramaniam S, Gastrointest Endosc. 2020 Feb;91(2):310-320	Prospective Cohort study	BLI for identification of Barrett’s neoplasia	Images with Barrett and neoplasia	Develop a training tool for a new BLI classification	pretraining sensitivity (85.3%) improved significantly to 95.7% post-training with a good level of agreement (κ = .67).	moderate
De Groof AJ, Gastrointest Endosc. 2020 May;91(5):1050-1057.	Prospective Cohort study	BLI and LCI for delineation of Barrett’s neoplasia	Images with Barrett’s neoplasia	Assess the effect of BLI and LCI for delineation of Barrett’s neoplasia	Significantly better	low
Nogales O, Dig Dis Sci. 2017 Oct;62(10):2840-2846.	Prospective Evaluation of a retrospective database of images	NBI (Evaluation of BING classification)	Images with Barrett’s neoplasia		Dysplasia prediction had an accuracy of 81.1%, sensitivity of 48.4%, and a specificity of 91%	low
Surveillance after curative endoscopic resection: Barrett esophagus						
Cotton CC, Gastroenterology. 2018Aug;	Retrospective Evaluation of prospective	Follow-up endoscopy	Patients with Barrett’s neoplasia after	model the incidence of neoplastic recurrence, validate the model in an independent cohort, and propose evidence-based	patients with high-grade dysplasia or intramucosal adenocarcinoma, we propose surveillance endoscopy at 0.25, 0.5, and 1 year after CEIM, then annually	moderate

Supplementary material

155(2):316-326.e6.	registry data		RFA	surveillance intervals		
Sawas T, Gastrointest Endosc. 2019 May;89(5):913-925.e6.	Meta-Analysis	Follow-up endoscopy	Patients with Barrett’s neoplasia after completed endoscopic eradication therapy	dysplasia recurrence risk after successful eradication of neoplasia with EET	Risk for recurrence is significantly higher in patients who achieved complete remission of dysplasia but not CR of intestinal metaplasia (RR, 2.9; 95% CI, 1.66-5)	moderate
Krishnamoorthi R, Gastrointest Endosc. 2016 Jun;83(6):1090-1106.e3.	systematic review and meta-analysis	Follow-up endoscopy	Patients with Barrett’s esophagus after ablation	Recurrence of IM and dysplasia/adenocarcinoma	Pooled IRs of recurrent IM, dysplastic BE, and HGD/EAC after radiofrequency ablation were 9.5% (95% CI, 6.7-12.3), 2.0% (95% CI, 1.3-2.7), and 1.2% (95% CI, .8-1.6) per patient-year, respectively	moderate
Guthikonda A, Am J Gastroenterol. 2017 Jan;112(1):87-94.	Retrospective cohort study	Follow-up endoscopy	Patients treated with RFA for dysplastic BE.	rates and risk factors for recurrence, dysplastic recurrence, and invasive adenocarcinoma after CE-IM	Of the 306 eligible patients undergoing RFA, 218 achieved CE-IM. 52 (24%) experienced recurrence of IM or Barrett's-associated neoplasia over 540.6 person-years (incidence rate 9.6%/year). Thirty (58%) of these achieved second CE-IM; 4 (1.8% of total, 7.7% of recurrences) ultimately progressed to invasive adenocarcinoma (incidence rate 0.65%/year). Longer Prague M was a strong risk factor for invasive adenocarcinoma (rate ratio of 1.34/cm). Most dysplastic recurrences were in the cardia, and the majority were not visible but detected on random biopsies.	moderate

Supplementary material

Pubmed search:
From January 2015 UP to April 2020
x studies
Relevant studies selected and present in the tables above.

Virtual **chromoendoscopy** by using optical enhancement improves the detection of **Barrett's** esophagus-associated neoplasia.
Everson MA, Lovat LB, Graham DG, Bassett P, Magee C, Alzoubaidi D, Fernández-Sordo JO, Sweis R, Banks MR, Wani S, Esteban JM, Ragunath K, Bisschops R, Haidry RJ.Everson MA, et al. Gastrointest Endosc. 2019 Feb;89(2):247-256.e4. doi: 10.1016/j.gie.2018.09.032. Epub 2018 Oct 3.Gastrointest Endosc. 2019. PMID: 30291849

Acetic acid-guided biopsies in **Barrett's** surveillance for neoplasia detection versus non-targeted biopsies (Seattle protocol): A feasibility study for a randomized tandem endoscopy trial. The ABBA study.
Chedgy F, Fogg C, Kandiah K, Barr H, Higgins B, McCord M, Dewey A, De Caestecker J, Gadeke L, Stokes C, Poller D, Longcroft-Wheaton G, Bhandari P.Chedgy F, et al. Endosc Int Open. 2018 Jan;6(1):E43-E50. doi: 10.1055/s-0043-120829.

International development and validation of a classification system for the identification of **Barrett's** neoplasia using acetic acid **chromoendoscopy**: the Portsmouth acetic acid classification (PREDICT).
Kandiah K, Chedgy FJQ, Subramaniam S, Longcroft-Wheaton G, Bassett P, Repici A, Sharma P, Pech O, Bhandari P.Kandiah K, et al. Gut. 2018 Dec;67(12):2085-2091. doi: 10.1136/gutjnl-2017-314512.

Impact of advanced endoscopic imaging on **Barrett's** esophagus in daily clinical practice.
Beg S, Mensa M, Fullard M, Finerty E, Richman P, Leahy A.Beg S, et al. Gastrointest Endosc. 2018 May;87(5):1189-1194. doi: 10.1016/j.gie.2017.09.012.

Systematic assessment with I-SCAN magnification endoscopy and acetic acid improves dysplasia detection in patients with **Barrett's** esophagus.

Supplementary material

Table X. Research/PICO question.

1. What are the clinical indications (if any) for ESD in Barrett’s esophagus ?

2. What are the available evidences on the efficacy/safety of ESD for each of these indications?

3. How does such efficacy/safety compare with competitive techniques (EMR, hybrid, EFTR, surgery) for each of these indications?

First author, year	Study design , study objective	Intervention	Participants	Outcomes	Results	Level of evidence
Codipilly 2020 [1]	Retrospective analysis of prospective database AIM : to compare histological outcomes of ESD versus cEMR followed by ablation	cEMR versus ESD in Barrett neoplasia	537 patients undergoing cap-EMR (n=456) or ESD (n=81) followed by different ablation techniques. Patients who underwent both or chemoradiation were excluded	Complete remission for dysplasia on biopsy and time to complete remission for dysplasia Rate of complications	420/537 (78%) of c-EMR and 48/81 (59%) of ESD CRD achieved CRD. The Kaplan-Meier curve demonstrates that the 2-year cumulative probability of CRD is lower in cEMR patients compared to ESD patients (75.8% versus 85.6%). Univariate analysis showed lower odds of achieving CRD in cEMR patients (HR: 0.41; 95% CI: 0.31-0.54; p<0.01). There seem to be a lentgth time bias in this study. No difference in CRIM, although absolute number better for cEMR (78.5% versus 40.7%) Bleeding : cEMR 0.4% ,	Moderate

Supplementary material

					ESD 2.5%. No perforations. Strictures 3.8% in cEMR 5.9% in ESD	
Han 2020 [2]	Systematic review and meta-analysis	ESD versus EMR	8 studies BE neoplasia, 3 studies combination of SCC and BE neoplasia	RO resection rate Local recurrence Procedure duration complications	Higher en bloc resection rate for ESD (OR 47.25 (95% CI 23.86-93.57) p< 0.0001 Higher curative resections for ESD (OR 6.16 95% CI 2.5-15.19) p< 0.0001 Local recurrence lower for ESD OR 0.19 95% CI 0.05-0.81) p=0.025 ONLY FOR LESIONS > 20 mm Procedure time longer for ESD WMD 87.06 95% CI 13.87-160.25 p=0.02 Perforations not higher for ESD in BE OR 2.94 95% CI 0.72-12.03 Bleeding : no significant difference OR 0.4 95% CI 0.13-1.23 Stricture rate : no difference OR 1.2 95% CI 0.73-1.96	Moderate Publication bias detected
Tomizawa 2020 [3]	Retrospective case series	ESD	32 patients BE neoplasia 12/32 as salvage therapy	The primary endpoint of this study was the rate of en-bloc	No difference in en-bloc resection or RO resection between salvage and primary ESD	Very low level

Supplementary material

				resection in salvage vs. non- salvage treatments.		
Ishihara 2020 [4]	Japanes guideline including literature search and systematic review for ESD versus EMR for BE adenocarcinoma	ESD versus EMR	26 articles	En bloc resection RO resection Local recurrence complications	En bloc : EMR 50% ESD 96.4% RO resection EMR 39.7% and ESD 81.9% Local recurrence : EMR 12.4% , ESD 2.5% with possible length time bias Complications : EMR 9.3%, ESD 10.5% Conclusion : Compared with EMR, ESD had higher rates of en bloc and RO resections and a lower rate of local recurrence. The rates of procedural adverse events (post- procedural bleeding, perforation, and stenosis) were roughly equal. ESD is therefore strongly recommended over EMR for the radical resection of superficial esophageal adenocarcinomas suitable	Moderate level : selection bias in ESD group , lenth time bias

Supplementary material

					for endoscopic treatment.	
Abe 2019[5]	Retrospective study, 13 centres	to assess the long-term outcomes and metachronous cancer in Japanese patients with adenocarcinoma at the gastroesophageal junction after ER based on our criteria for the risk of lymph node metastasis.	EMR n= 51 ESD n=321	Not clearly predefined	positive lateral margin was statistically more significant in EMR compared with ESD (49.0% vs 7.5%, P < .01), no signicican difference for deep margin. The en bloc resection rate and the R0 resection rate in the EMR and ESD group were 60.8% and 99.1% and 49.0% and 87.9%, respectively p<0.01. All local recurrence developed in patients undergoing non-R0 ER. Five-year cumulative incidences of local recurrence were 13% and .5% in the EMR and ESD group, respectively. (P < .01).	Low level Selection and length time bias.
Subramaniam 2018[6]	Retrospective single center	RFA after ESD versus RFA after EMR	ESD n=27 EMR n=43 RFA alone n=21	Complications CRD CRIM	Complications : EM 9.3%; ESD 7.4% CRD : ESD 96.3%, EMR 88.4%, RFA 100%	Very low lever Retrospective case series, potential

Supplementary material

					CRIM : ESD 85.2%; EMR 81.4%, RFA 90.5%	selsection and length time bias.
Yang 2018 [7]	Meta-analysis	ESD in Barrett	11 studies, 501 patients	Efficacy and safety	en bloc resection was 92.9% (95% CI, 90.3%-95.2%). R0 (complete) 74.5% (95% CI, 66.3%-81.9%) curative resection rates 64.9% (95% CI, 55.7%-73.6%) Perforation 1.5% 95% CI, .4%-3.0% Bleeding 1.7% (95% CI, .6%-3.4%) stricture rate was 11.6% (95% CI, .9%-29.6%). Recurrence : 0.17% (95% CI, 0%- .3%) FATER 22.9 months	High level evidence
Subramaniam 2017[8]	Retrospective multicenter study	ESD in Barrett in more challenging indications	143 ESD in 124 patients, nodular lesions or flat > 2 cm or scarred	Efficacy and safety	The en-bloc resection rate was 90.8% and R0 resection rate 79% in this series. The overall adverse event rate was 3.5% (1.4% bleeding, 0% perforation, and 2.1% stricture formation). The	Low level, although clinically important regarding the possible indication for ESD

Supplementary material

					expanded curative resection rate was 65.8%, reflecting the R0 resection rate and proportion of cases with more advanced disease. Submucosal cancer was identified as a significant factor affecting the R0 resection rate.	
Yang 2017[9]	Retrospective multicenter	ESD in Barrett		En bloc resection RO resection Safety Remission neoplasia	En bloc resection : 96% RO resection : 70% Safety : 3 bleeding; 1 perforation Remission: 100%	Very low level
Coman 2016[10]	Prospective cohort	ESD in BE	36 Patients with cancer, after EMR with positive lateral margin or nodularity with HGD. 14 patients with previous therapy	En bloc and RO resection safety	En bloc resection 100% RO resection : 81% Safety: 22% 1 bleeding 7 strictures	low level
Barret 2016[11]	Retrospective cohort	ESD in BE lesions > 10 mm or elevated	35 pt	RO resection for CA En bloc resection RO resection for HGD complications	RO resection for CA: 72.4% En bloc resection : 88.9% Curative resectionCA : 65.5% curative resection for HGD : 51.4%	Low level

Supplementary material

					Complications : 11.1% , 3 perforations; strcture 5.6%	
Terheggen 2017[12]	RCT	ESD versus EMR	ESD n=20 EMR n= 20 Lesions should be amenable for both techniques Inclusion : BE with endoscopically visible single neoplastic superficial lesion of type 0–Is, 0–IIa, 0–IIc or their combinations while biopsies of the remaining BO did not show any neoplastic changes. ► Limitation of the horizontal extent to a diameter of ≤3 cm in the longitudinal direction or less than half of the	Primary outcome was R0 resection; secondary outcomes were complete remission from neoplasia, recurrences and adverse events (AEs).	RO ESD : 10/17 vs EMR 2/17 (p=0.01) Complete remission at 3 months : ESD 15/16; EMR 16/17 Recurrent ACE : ESD 1/17; EMR 0/17 SAE: ESD 2/17, EMR 0/17	High quality : this trial provided evidence that ESD has no place in lesions that are clearly ameneble for both EMR and ESD. There is no further research needed to define this.

Supplementary material

			<p>oesophageal circumference in the lateral direction.</p> <p>► No endoscopic suspicion of massive infiltration into the submucosal layer and no additional neoplastic lesions according to endoscopic appearance.</p> <p>Exclusion :</p> <p>previous endoscopic or surgical treatment</p> <p>► neoplastic lesions that do not meet the inclusion criteria, particularly flat lesions (type 0–IIb) and additional areas of HGIN or AC.</p>			
Probst 2015[13]	Prospective cohort	ESD in Barrett and SCC	ESD Barrett n=87 Tertiary referral	Feasibility Safety	En bloc resection : 95.4% RO resection : 83.9% Curative resection : 72.4%	Low level

Supplementary material

					Recurrence : 2.4% Strictures : 11.7% Bleeding 0.9%	

Pubmed search:

From January 2015 UP to 7/12/2020

x studies

Relevant studies selected and present in the tables above.

(ESD AND Barrett) AND (("2015/01/01"[Date - Publication] : "3000"[Date - Publication]))

Terheggen G, Horn EM, Vieth M, Gabbert H, Enderle M, Neugebauer A, et al. A randomised trial of endoscopic submucosal dissection versus endoscopic mucosal resection for early Barrett’s neoplasia. Gut. 2017 May 1;66(5):783–93. **this trial provided evidence that ESD has no place in lesions that are clearly amaneble for both EMR and ESD. There is no further research needed to define this.**

Yang D, Zou F, Xiong S, Forde JJ, Wang Y, Draganov PV. Endoscopic submucosal dissection for early Barrett’s neoplasia: a meta-analysis. Gastrointest Endosc. 2018;87(6):1383–93 A recent meta-analysis that demonstrated feasibility and relative success and low AE among patients undergoing ESD for early EAC. This study included data from both Asian and North American and European populations, which is important given the early adoption of ESD (and thus greater expertise) in the East compared to the West.

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Comparative Outcomes of Cap Assisted Endoscopic Resection and Endoscopic Submucosal Dissection in Dysplastic Barrett’s Esophagus D. Chamil Codipilly, Lovekirat Dhaliwal, Meher Oberoi, Parth Gandhi, Michele L. Johnson, Ramona M. Lansing, W.Scott Harmsen, Kenneth K. Wang, Prasad G.

Iyer PII: S1542-3565(20)31551-2 DOI: <https://doi.org/10.1016/j.cgh.2020.11.017> Reference: YJCGH 57609 To appear in: *Clinical Gastroenterology and Hepatology*

Accepted Date: 10 November 2020

Efficacy and safety of endoscopic submucosal dissection versus endoscopic mucosal resection for superficial esophageal carcinoma: a systematic review and meta-analysis. Han C, Sun Y. Dis Esophagus. 2020 Sep 7:doaa081. doi: 10.1093/dote/doaa081. Online ahead of print. : B **SUGGESTION FOR ESD > 20 mm maybe causes local recurrence, but we do not know how this relates to a lenth time bias in follow-up and the add on therapy of ablation. It may be that ESD is performed on smaller lesions at start, explaining the lower stricture rate ...**

[Endoscopic submucosal dissection \(ESD\) for Barrett's esophagus \(BE\)-related early neoplasia after standard endoscopic management is feasible and safe.](#)
Tomizawa Y, Friedland S, Hwang JH.Endosc Int Open. 2020 Apr;8(4):E498-E505. doi: 10.1055/a-0905-2465. Epub 2020 Mar 23.

Endoscopic submucosal dissection/endoscopic mucosal resection guidelines for esophageal cancer. Ishihara R, Arima M, Iizuka T, Oyama T, Katada C, Kato M, Goda K, Goto O, Tanaka K, Yano T, Yoshinaga S, Muto M, Kawakubo H, Fujishiro M, Yoshida M, Fujimoto K, Tajiri H, Inoue H; Japan Gastroenterological Endoscopy Society Guidelines Committee of ESD/EMR for Esophageal Cancer. Dig Endosc. 2020 May;32(4):452-493. doi: 10.1111/den.13654.

Japanese guideline

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The safety and efficacy of radiofrequency ablation following endoscopic submucosal dissection for Barrett's neoplasia. Subramaniam S, Kandiah K, Chedgy F, Meredith P, Longcroft-Wheaton G, Bhandari P. Dis Esophagus. 2018 Mar 1;31(3). doi: 10.1093/dote/dox133. **This study although low level evidence provides data on the safety and efficacy of subsequent ablation after ESD, not being different from EMR. This is an important issue with regard to the safety of the entire treatment package and not ESD alone.**

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Early esophageal cancer in Europe: endoscopic treatment by endoscopic submucosal dissection. Probst A, Aust D, Märkl B, Anthuber M, Messmann H. *Endoscopy*. 2015 Feb;47(2):113-21. doi: 10.1055/s-0034-1391086. Epub 2014 Dec 5.

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Supplementary material

Table 3s: Stomach

Table 1 - Efficacy and safety of EMR vs ESD in the treatment of gastric superficial lesions

First author, year, journal	Study design, aim	Participants	Intervention / comparator	Outcomes	Results [95% CI / p-value)	Level of evidence
Tao M, 2019, BMJ Open ²	SR/MA Compare outcomes of EMR and ESD	18 studies 6723 patients	ESD vs EMR	En-bloc (13 studies) R0 (11 studies) Post-procedural bleeding (15 studies) Perforation (16 studies) Curative (6 studies) Local recurrence (12 studies)	OR 9.00 [6.66-12.17] OR 8.43 [5.04-14.09] OR 1.26 [0.88-1.80] OR 2.55 [1.48-4.39] OR 2.92 [1.85-4.61] OR 0.18 [0.09-0.34]	2
Zhao Y, 2018, BioMed Res Int ³	SR/MA Compare outcomes of EMR and ESD	18 studies 7325 patients	EMR (n=3596) vs ESD (n=3799)	En-bloc (13 studies) * R0 (9 studies) * Bleeding (12 studies) Perforation (13 studies) Operative time (8 studies) Curative Local recurrence (11 studies)	56% vs 93%, OR 0.10 [0.09-0.13] 52% vs 92%, OR 0.14 [0.12-0.17] 7.0% vs 7.2%, OR 0.79 [0.47-1.35] 1.2 vs 3.2%, OR 0.37 [0.24-0.57] MD: -49.9 minutes [-71.6; -28.1] NR 5.2 vs 0.2%, OR 14.9 [7.3-30.7]	2
Tanabe S, 2017, Gastric cancer ⁸⁷	Prospective multicentric cohort, compare outcomes of EMR and ESD	12647 patients	ESD (n=10259) vs EMR (n=2355)	En-bloc En-bloc R0 Surgery for bleeding Surgery for perforation Curative 5Y OS (standard/ expanded/ non- curative resection) 5Y DSS (standard/ expanded/ non-curative resection)	94.5% vs 66.8%, p<0.01 86.0% vs 48.2%, p<0.01 0.3% vs 0.4%, p=0.23 0.3% vs 0.4%, p=0.54 75.1% vs 44%, p<0.01 91.6% / 90.3% / 86.5% 99.7% / 99.6%/ 98.7%	3

SR/MA – Systematic Review/Meta-Analysis; EMR – Endoscopic Mucosal Resection; CI – Confidence Interval; R0 – Histological complete resection; MD – Mean Difference; OS – Overall survival; DSS – Disease-specific survival; NR – not reported. * For lesions <10mm (4 studies), EMR achieved en-bloc resection in 68.8% (vs 94.9% ESD) and R0 in 48.9% (vs 96.1% ESD).

Supplementary material

Table 2 – Studies comparing ESD and gastrectomy outcomes in gastric superficial lesions

First author, year, journal	Participants	Exposure / intervention	Outcomes	Results [95% CI / p value]	Level of evidence
Systematic reviews / meta-analysis					
Liu Q, 2020, Int J Surg ⁷	18 retrospective studies (1 western from Lithuania); 5993 patients	ESD vs gastrectomy	Procedural time (6 studies) Hospital stay (12 studies) Procedure-related death (12 studies) Overall AE (17 studies) R0 (11 studies) Curative (9 studies) Local recurrence (8 studies) Metachronous (7 studies) Overall survival (13 studies) Disease-specific survival (3 studies) Disease-free survival (5 studies) Recurrence-free survival (2 studies)	MD -128 min, p=0.001 MD -7.1 days, p<0.001 OR 0.21 [0.07-0.68] 7.6% vs 15.9%, OR 0.47 [0.34-0.63] 90.6% vs 99.7%, OR 0.07 [0.03-0.14] 91.7% vs 99.7%, OR 0.06 [0.01-0.27] 2.3% vs 0.2%, OR 4.83 [2.27-10.26] 7.1% vs 0.4%, OR 14.26 [6.80-29.91] HR 0.92 [0.71-1.19] HR 0.73 [0.36-1.49] HR 4.58 [2.79-7.52], lower in ESD HR 1.99 [1.38-2.87], lower in ESD	2
Gu L, 2019, J Gastrointest Surg, ⁸	13 retrospective studies (all Eastern); 4986 patients.	ESD vs gastrectomy	Overall survival (13 studies) Disease-specific mortality (3 studies) Disease-free survival (10 studies) Non-metachronous GC (12 studies) Metachronous GC (11 studies)	96.3% vs 96.3%, RR 0.90 [0.68-1.19] 0.35% vs 0.92%, RR 0.40, [0.15-1.03] 90.2% vs 97.1%, RR 3.40 [2.39-4.84] 3.8% vs 0.7%, RR 4.94 [3.04-8.03] 5.2% vs 0.5%, RR 8.64 [5.00-14.95]	2
Li H, 2019, World J Gastrointest Oncol ⁹	14 retrospective studies (all Eastern); 5112 patients	ESD vs gastrectomy	Procedural time (4 studies) Hospital stay (7 studies) Post-procedural AEs (13 studies) Recurrence (9 studies) Overall survival (6 studies) Event-free survival (6 studies)	MD -140 min, p<0.001 MD -5.4 d, p<0.001 OR 0.39 [0.28-0.55] OR 9.24 [5.94-14.36] HR 0.51 [0.26-1.00] HR 1.59 [0.66-3.81]	2

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Abdelfatah, 2019, Eur J Gastro Hepatol ⁶	13 retrospective studies (all Eastern), 6739 patients	ESD vs gastrectomy	5Y overall survival (11 studies) Disease-specific survival (3 studies) Disease-free survival (6 studies) Recurrence (10 studies) Recurrence-free survival (4 studies) Metachronous (10 studies)	96% vs 96%, OR 0.96 [0.74-1.25] 99.4% vs 99.2%, OR 0.69 [0.16-2.87] 95.9% vs 98.5%, OR 1.86 [0.57-6.06] 1.4% vs 0.4%, OR 2.50 [1.32-4.74] 92.4% vs 98.3%, OR 0.17 [0.06-0.49] 6.0% vs 0.4%, OR 10.09 [5.97-17.06]	2
Prospective studies (not included in meta-analysis)					
Libânio D, 2019, Endoscopy ¹⁰	253 patients (Portugal)	ESD (n=153) vs gastrectomy (n=101)	Procedural time Hospital stay Severe AEs Surgical reintervention Quality-of-life	72 vs 164 minutes, p<0.001 3 vs 16 days, p<0.001 8% vs 22%, p<0.05 1% vs 11%, p<0.05 Better in ESD	3
Najmeh S, 2016, J Gastrointest Surg ¹¹	67 patients (USA)	ESD (n=30) vs laparoscopic gastrectomy (n=37)	R0 Hospital stay Severe AEs	87% vs 89%, p=1.00 2 vs 7 days, p<0.0001 3.3% vs 21.2% p=0.4	3
Retrospective studies in selected populations (not included in meta-analysis)					
Park JC, 2018, Surg Endosc ⁸⁸	493 patients with undifferentiated early gastric cancer	ESD (n=111) vs gastrectomy (n=382); 81 matched pairs Follow-up 48 and 60 months, respectively	Recurrence Local recurrence LNM/distant metastasis Median disease-free survival Overall survival	12% vs 1%, p=0.001 9% vs 1%, p<0.05 1.8% vs 0%, p=ns 91 vs 118 months, p<.05 after match 97 vs 114 months, p=0.85 after matching	3
Lim JH, 2019, Surg Endosc ⁸⁹	1147 patients with undifferentiated early gastric cancer	ESD (n=126) vs surgery (n=1021)	Overall survival Disease-free survival	Similar including in propensity matching Significantly lower in ESD group due to metachronous	3

CI – Confidence Interval; MD – mean difference; AEs – Adverse Events; R0 – Histological complete resection; OR – Odds Ratio; HR – Hazard ratio; GC – Gastric cancer; RR – Risk Ratio; DSM – Disease-specific mortality

Supplementary material

Table 3 - Studies evaluating endoscopic preventive measures to reduce bleeding

First author, year, journal	Study design; intervention studied	Participants	Exposure / intervention	Outcomes	Results	Level of evidence
Traction						
Su YF, 2020, Endoscopy ⁴⁶	SR/MA of RCTs; traction	5 gastric studies, 922 gastric ESD	Traction-assisted ESD vs conventional	PPB	4.4% vs 4.3%, OR 1.01 [0.51-2.00]	1
Suzuki S, 2016, GIE ⁹⁰	Retrospective propensity matched; traction.	238 pts; 43 matched pairs	Dental floss+clip vs conventional	PPB (matched)	4.7% vs 4.7%, p=1.0	3
Closure of resection scar						
Goto O, 2020, Gastroint Endosc ⁹¹	Prospective, single-arm. Mucosal closure.	30 patients (50% under AT)	Mucosal closure with endoscopic suturing	PPB	3/30 (10%)	6
Shielding / spraying of the resection scar						
Kikuchi D, 2019, Endosc Int Open ⁴²	Retrospective cohort. PGA+FG.	123 patients under AT	PGA+FG shielding (n=38) vs controls (n=85)	PPB Hemostasis (SLE)	1/38 (2.6%) vs 12/85 (14.1%), p=0.047 6/38 (15.8%) vs 35/85 (41.2%), p=0.02	3
Wang J, 2020, Surg Endosc ⁹²	Retrospective, propensity matched, cohort; PFS	332 pts; 115 matched pairs	PFS vs coagulation of visible vessels	Massive bleeding PPB (>24h)	5.2% vs 8.7%, p=0.30 1.7% vs 2.6%, p=0.65	3
Hwang JJ, 2018, J Dig Dis ⁹³	RCT. Surgicell.	157 patients	PPI vs H2RA+surgicell	PPB	16.7% vs 8.1%, p=0.35	2
Kawata N, 2018, Gastric Cancer ⁴¹	RCT. PGA + FG.	84 patients under AT	PGA (n=38) vs control (n=47)	PPB	5.8% vs 20.8%, p=0.04	3
Hahn KY, 2018, J Gastroent Hepato ^{l94}	Prospective, single-arm. Hemostatic powder	44 patients under AT or size ≥40mm	Hemostatic powder	PPB	4/44 (9.1%)	6
Tanaka S, 2017, J Gastroent Hepato ^{l95}	RCT. Coagrasper vs new hemostatic forceps	66 patients	Coagrasper vs FD-Y0007	Hemostasis time AEs	57 vs 25 seg, p<0.001 PPB 0 vs 0%, p=ns	2+
Horikawa Y, 2016, Digestion ⁹⁶	Prospective cohort; knife coagulation.	80 lesions (40 pairs)	Coagulation-forceps vs knife-coagulation	Major bleeding Procedure-time	Non-significant Reduced by 15% in knife group	3
Tan ES, Dig Surg, 2016 ⁹⁷	Retrospective cohort; FG spray.	397 lesions	FG (96) vs controls (301)	PPB	0% vs 6%, p=0.03 (univariate)	4
Nakanishi H, 2016, PLoS One ⁹⁸	Retrospective cohort; Pre-ESD gastric lavage.	760 patients (148 lavage, 612 control)	Pre-ESD gastric lavage (1L water) vs controls	PPB (matched)	2.8% vs 9.2%, p=0.04	3
Uraoka T, 2016, Gastroint Endosc ⁹⁹	Prospective, single-arm. Spraying of peptide.	47 patients, 51 lesions	Synthetic peptide solution	PPB	1/51 (2.0%)	6
Tsuji Y, 2015, GIE ⁴⁰	Retrospective cohort. PGA+FG on PPB	86 lesions with high-bleeding risk	PGA+FG vs historical controls	PPB	3/45 (6.7%) vs 9/41 (22%), p=0.041	4

Supplementary material

Second-look endoscopy						
Libânio D, 2016, Gastroint Endosc ²⁷	SR/MA. SLE.	7 studies (3 RCTS)	SLE vs no SLE	PPB	4.4% vs 2.9%, OR 1.34 [0.85-2.12]	2
Kim EH, 2017, J Gastroent Hepatol ⁴⁷	SR/MA. SLE.	16 studies (4 RCTS)	SLE vs no SLE Hemostasis on SLE	PPB PPB	OR 1.27 [0.80-2.00] OR 3.40 [1.87-6.18]	2
CO2 insufflation						
Baniya R, 2017, Clin Endosc ⁴³	SR/MA. CO2.	4 RCTs, 391 patients	CO2 vs air insufflation	PPB	7.1% vs 13.2%, OR 0.51 [0.22-1.19]	1

SR/MA – Systematic review/meta-analysis; PPB – post-procedural bleeding; OR – odds ratio; AT – antithrombotic therapy; PGA+FG – polyglycolic acid sheets + fibrin glue; SLE – second-look endoscopy; PFS – porcine fibrin sealant; PPI – proton-pump inhibitor; H2RA – histamin-2 receptor antagonist;

Supplementary material

Table 4 – Lymph-node metastasis rate according to histological features

	Lesion characteristics	LNM / total (95% CI)
Original / landmark studies that originated standard and expanded curative criteria		
Gotoda <i>et al</i> ⁵⁰	pT1a, differentiated*§, ≤30mm, LV- (regardless of ulceration**)	0/1230 (0-0.3%)
	pT1a, differentiated, UL-, any size	0/929 (0-0.4%)
	pT1b ≤500µm, ≤30mm, LV-	0/145 (0-2.5%)
	pT1a, ≤20mm, undifferentiated***§, UL-	0/141 (0-2.6%)
Hirasawa <i>et al</i> ⁵¹		0/310 (0-1.2%)
Nakahara et al ⁵²	pT1a or pT1b ≤30mm, UL-, LV-	0/422 (0-2.6%)
Recent studies evaluating LNM rates in lesions meeting curative criteria		
Abdelfatah <i>et al</i> , 2018 ¹⁰⁰ (meta-analysis)	Standard criteria	6/3025 (0.2%)
	Expanded criteria	68/9798 (0.7%)
	Ex-1. pT1a, differentiated, ≤3cm, LV-, regardless of UL	16/2814 (0.57%)
	Ex-2. pT1a, differentiated, UL-, LV-, regardless of size	8/3004 (0.27%)
	Ex-3. pT1a, undifferentiated, ≤2cm, UL-	25/972 (2.57%)
	Ex-4. pT1b ≤500µm, differentiated, ≤3cm, LV-	8/315 (2.5%)
Abdelfatah <i>et al</i> , 2019 ⁵⁸ (meta-analysis)	pT1b ≤500µm, differentiated, ≤3cm, LV-	45/1507 (3%)
	Japanese studies	0/389 (0%)
	Studies outside of Japan	45/1118 (4.0%)
Hanada <i>et al</i> , 2019 ¹⁰¹ (USA)	Expanded indication	3/40 (7.5%)
Pessorrusso <i>et al</i> , 2019 (Brazil) ¹⁰²		3/104 (2.9%) #
Probst <i>et al</i> ¹⁰³ , 2017		1/84 (1.2%)

*Includes well and moderately-differentiated tubular adenocarcinomas and papillary adenocarcinomas (D-AC); ** Ulceration was defined as active ulceration or scarring from previous ulceration (converging folds, deformity of the muscularis propria or fibrosis in the submucosal or deeper layers). *** Includes poorly-differentiated carcinomas (PD-AC) and signet-ring cell carcinomas (SRC); s § A tumor with both D-AC and PD-AC/SRC should be classified according to the predominant (>50%) type, although there is some evidence that mixed-type AC may harbor a different risk of LNM (see main text). # All of them expanded-criteria 3 (undifferentiated)

Supplementary material

Table 5 - Studies evaluating outcomes after non-curative endoscopic resection

First author, year	Study design	Participants	Intervention	Outcomes	Results	EL
Single-arm studies evaluating LNM incidence and its risk factors in gastrectomy specimens after non-curative endoscopic resection						
Kang HY, 2019, J Gastrointest Surg ¹⁰⁴	Retrospective	140 patients with NCR	Gastrectomy after ESD	LNM Independent RF for LNM	12% L+ (OR 5.8), V+ (OR 5.7)	3
Kim HJ, 2019, PLoS One ¹⁰⁵	Retrospective	113 patients with NCR (including HM1)	Gastrectomy after ESD	Residual tumor / LNM Independent RF for LNM	20% / 12% (3% if LV-) L+, VM+	3
Akaike H, 2019, World J Surg Oncol ¹⁰⁶	Retrospective	861 patients with NCR	Gastrectomy after ESD	LNM incidence Incidence according to the n ^o of risk factors (SM2, UL+ >30mm; undiff and >20mm; L+ /V+)	12.7% 0-1 risk factor: 0.8% 2/3/4 RF: 15.1% / 33.9% / 50%	3
Zhao B, 2019, J Gastrointest Surg ⁸²	SR/MA	9 studies (1720 patients with NCR)	Gastrectomy after ESD	LNM Incidence RF for LNM	5.3-11% SM2 (OR 3.4), VM1 (OR 2.3), L+ (OR 11), V+ (OR 2.8)	2
Niwa H, 2018, PLoS One ¹⁰⁷	Retrospective	47 patients with NCR (including HM1)	Gastrectomy after ESD eCura scoring	Residual cancer eCura 0-1	19% (9/47; 6 local, 4 LNM) 0%	3
Hatta W, 2017, Am J Gastroenterol ⁸⁵	Retrospective	1101 patients with NCR	Gastrectomy after ESD	LNM incidence Independent RF for LNM eCura validation	9.4% >30mm (OR 2), L+ (OR 4), V+ (OR 1.6), VM1 (OR 1.8), SM2 (OR 1.7, p=0.065) Low 2.5%; Med 6.7%; High 22.7%	3
Goto A, 2017, Eur J Gastro Hepatol ¹⁰⁸	Retrospective	101 patients with NCR	Gastrectomy after ESD	LNM RF for LNM	9 / 101 (10%) ≥500µm and LV+	3
Kawata N, Surg Endosc, 2017 ¹⁰⁹	Retrospective	323 ptatients with NCR	Gastrectomy after ESD	LNM incidence Independent RF for LNM	9.3% LV+ (OR 8.6)	3
Single-arm studies evaluating surveillance outcomes after non-curative endoscopic resection						
Takizawa K, 2019, Digestion ⁸³ and Yamada S, 2019, Gastrointest Endosc ⁸⁴	Retrospective,	905 patients with NCR (all HM0)	Follow-up	5Y cancer recurrence Recurrence management RF for early recurrence (>2 Y) RF for late recurrence (>2 Y)	3.2% (3 intragastric, 7 LNM, 15 distant metastasis, 2 incomplete data) 1 re-ESD; 12 surgery; 6 CxT; 11 BSC L+ (HR 8.56, p=.003) V+ (HR 4.5, p.039); L+ (HR 3.6, p=0.07)	3
Hatta W, 2017, Am J Gastroenterol ⁸⁵	Retrospective	1101 patients with NCR	Follow-up	5Y-DFS according to eCura risk category	Low 99.6%; Med 96%; High 90%	3
Comparison of outcomes (follow-up vs surgery) in patients with non-curative resection						
Kim HJ, 2019, PLoS	Retrospective	288 pts with NCR	Surveillance (175) vs	5Y OS	89% vs 94%, p=0.26	3

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One ¹⁰⁵		(175 surveillance, 113 surgery)	surgery (113)	5Y DSS 5Y DFS Metachronous	98% vs 100%, p=0.48 74% vs 98%, p<0.001 9.7% vs 0.9%, p<0.05	
Kang HY, 2019, J Gastrointest Surg ¹⁰⁴	Retrospective	311 patients with NCR	Surveillance (171) vs surgery (140)	5Y OS 5Y DSS	89% vs 96% p.04 97% vs 98% p=0.94	3
Esaki M, 2019, Dig Dis ¹¹⁰	Retrospective	1969 patients with NCR	Surveillance vs surgery	5Y -OS 5Y-DSS	<70Y: 84% vs 96.9% 70-79Y: 78.3% vs 90.4% ≥80Y: 84.7% vs 74% <70Y: 99% vs 99.6% 70-79Y: 99% vs 97.7% ≥80Y: 95% FUP, 99%	3
Li D, 2019, Surg Endosc ¹¹¹	SR/MA	10 studies (4225 patients with NCR)	Surgery vs follow-up	5Y OS 5Y DSS	92% vs 76.3% (OR 3.5, 2.9-4.2) 99% vs 96% (OR 3.9, 2.5-6.4)	2
Jeon MY, 2018, Gastroint Endosc ¹¹²	Retrospective	512 ptatients with NCR (including HM1/VM1 in follow-up group)	Observation vs surgery	Overall mortality DSS Local recurrence Distant metastasis	8.6% vs 2.6% 86% vs 97%, p=0.03 4% vs 0% 0% vs 0.8%	3
Hatta W, 2018, Gastric cancer ⁸⁶ and Hatta W, 2017, J Gastroenterol ¹¹³	Retrospective	1969 patients with NCR (all HM0)	Surveillance (905) vs surgery (1064)	5Y-OS 5Y-DSS Low-risk eCura Med-risk eCura High-risk eCura	75.2% vs 92.6%, p<0.01 97.5% vs 98.8%, p=0.01 DSS 99.6 vs 99.7%, p=ns No differences between FUP/surg Higher cancer recurrence (HR 3.13, p=0.02)	3
Yano T, 2018, Surg Endosc ¹¹⁴	Retrospective	231 patients with NCR (Includes HM1/VM1 in the FUP group)	FUP (113) vs gastrectomy (118)	5Y OS 5Y DFS Cancer mortality	96 vs 73%, p<0.001 (no differences if >75y) 93 vs 100%, p=0.01 (no differences if >75y) 4.4% vs 0%	3
Toyokawa T, 2016, Surg Endosc ¹¹⁵	Retrospective	167 pts with NCR (HM1 included in FUP)	Gastrectomy (100) vs follow-up (67)	Cancer mortality	2/100 (2%) vs 2/67 (3%)	3

NCR – Non-curative resection; LNM – Lymph node metastasis; RF – Risk Factors; L+ - Lymphatic invasion; V+ - Vascular invasion; HM1 – Positive horizontal margin; LV- - Without lymphovascular invasion; VM1 – Positive vertical margin; SM2 – deep submucosal invasion (>500µm); UL+ - With ulcerative findings; SR/MA – Systematic review and meta-analysis; BSC – Best supportive care; CxT – Chemotherapy; DFS – Disease-free survival; OS – Overall Survival; DSS – Disease-specific Survival; DFS – Disease-free survival

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Table 6 – Management after gastric ESD

Criteria			LNM risk
Curative criteria (very-low risk resection)	En-bloc, R0, LV-	Dysplasia/pT1a and Differentiated and Any size (if UL-) or ≤3cm (if UL+)	<0.5%
Low-risk resection	En-bloc, R0, LV-	- pT1a, poorly-differentiated and ≤2cm and UL- OR - pT1b ≤500μm, differentiated, ≤3cm	<3%
Local-risk resection	Piecemeal or HM1 and LV-	- Dysplasia - pT1a, differentiated, any size (UL-) or ≤3cm (UL+) - pT1b ≤500μm, differentiated, UL- **	<0.5%
High-risk resection	Not meeting curative or low-risk resection criteria	Low risk *** (0-1 point)	~2.5%
		Intermediate risk *** (2-4 points)	~6.7%
		High-risk *** (5-7 points)	~22.7%

* But increased risk of local recurrence and further treatment may be necessary; ** provided that there is no SM invasive tumor at the level of invaded horizontal margin; *** eCura classification: 3 points for lymphatic invasion; 1 point each for tumor ≥30mm, >SM2, vascular invasion, positive vertical margin

Supplementary material

Supplementary table 1 – European / Western studies reporting gastric ESD outcomes published since 2015

First author, year, journal	Study design, country	Participants	Outcomes and results	Level of evidence
Manta R, 2020, J Clin Med	Multicentric case series, Italy	296 patients	En-bloc 97.7% / R0 91.1% / curative 72% AE 10% (perforation 1%, PPB 5%; death 0%)	6
Ruiz AC, 2020, Rev Esp Enf Dig ¹¹⁶	Prospective case series; Spain	35 patients	En-bloc 86% / curative 77% / recurrence 11.4%	6
Kim Y, 2020, Scand J Gastro ¹¹⁷	Retrospective case series; UK	35 patients (37 lesions)	En-bloc 57% / Curative 19% / recurrence 23%	6
Pagano N, 2019, Eur Rev Med. Pharmacol Sci ¹¹⁸	Retrospective case series. Italy	28 lesions	R0 79% / curative 79%	6
Tate DJ, 2019, Gastrointest Endosc ¹¹⁹	Prospective case series; Australia	121 patients, 135 lesions	En-bloc 94.8% / R0 87% / curative 79% PPB 5.2% / perforation 1.5%	6
Costa RS, 2019, GE Port J Gastroenterol ¹²⁰	Retrospective case series; Portugal	114 lesions	En-bloc 96% / R0 88% / Curative 83% / recurrence 5% AEs 13% (PPB 10.5%, perforation 0.9%) Metachronous 16% (100% re-ESD)	6
Mocker L, 2019, EIO ¹²¹	Retrospective case series; Germany	26 lesions	En-bloc 100% / R0 81% / curative 73% AEs 8%	6
Catalano F, 2019, Updates Surg ¹²²	Retrospective case series; Italy	60 lesions	En-bloc 93% / R0 88% / curative 87% AEs 8.3%	6
Santos-Antunes J, 2018, UEG Journ ¹²³	Retrospective case series; Portugal	169 lesions	R0 93% / curative 92%	6
Libânio D, 2019, Endoscopy ¹⁰	Prospective cohort; Portugal (2015-2017)	153 lesions	R0 90% / curative 79% Severe AEs 8% / Surgery due to AEs 1%	3
Libânio D, 2017, GE Port J Gastroenterol ⁶⁹	Retrospective case series; Portugal (2005-2014)	164 patients (2005-2014)	En-bloc 95% / R0 94% / curative 84% AEs 13% (PPB 8%; laceration/perforation 3%)	6
Probst A, 2017, Endoscopy ¹⁰³	Retrospective case series; Germany	179 patients, 191 lesions	En-bloc 94.8% (standard), 89% expanded; R0 90% (standard), 74% expanded AEs: perforation 1%; PPB 6.3%; stricture 2%; mortality 1.1% Local recurrence: 0% standard; 4.8% expanded	
Aslan F, Scand J, 2015 ¹²⁴	Retrospective series; Turkey	95 pts, 100 lesions	En-bloc 93% / R0 92%	
Petruziello L, 2018, UEGJ	Retrospective series; Italy	70 lesions	En-bloc 97% / R0 66% Severe AEs 3%	

R0 – Histological complete resection; AEs – Adverse Events; PPB – post-procedural bleeding

Supplementary material

Supplementary table 2 - Outcomes of ESD in esophago-gastric junction lesions

First author, year, journal	Study design, aim	Participants	Intervention / comparator	Outcomes	Results	Level of evidence
Liu, S, Surg Endosc, 2020 ¹²⁵	Retrospective cohort, ESD outcomes	209 patients (192 ESD, 17 ESTD)	ESD (n=192) or ESTD (n=17)	En-bloc / R0 / curative Complications Recurrence 5Y-DSS	87% / 79% / 73.7% 2.8% 4.3% 98.4%	3
Kim HJ 2018, Surg Endosc ¹²⁶	Retrospective cohort, compare long-term ESD and surgery outcomes	66 patients	ER (ESD 36, EMR 2) vs surgery	Recurrence (after R0 resection) 5Y OS 5Y DFS	5.3% vs 1/28, p=0.50 93.3% vs 92.9%, p=0.28 88.0 vs 100%, p=0.07	3
Kim JK, 2018, Surg Endosc ¹²⁷	Retrospective case series, ESD outcomes	48 patients	ESD	En-bloc / R0 / curative PPB / perforation	96% / 77% / 71% 8% / 4%	6
Gong EJ, 2017, Gastric cancer ¹²⁸	Retrospective cohort; compare long-term ESD and surgery outcomes	79 patients	ESD (n=40) vs surgery (n=39)	5Y OS Cancer death Adverse events	94 vs 97%, p=0.4 0% vs 0% 10% vs 18%, p=0.3	3
Gong EJ, 2016, Dig Dis Sci ¹²⁹	Retrospective case series; ESD outcomes	88 patients	ESD	Median time En-bloc / R0 / curative Adverse events 5Y OS / 5Y DSS	40 min 89% / 83% / 60% 10% 97% / 100%	6
Jang YS, 2015, Medicine (Baltimore) ¹³⁰	Retrospective case series; ESD outcomes	82 patients	ESD	En-bloc / R0 / curative PPB / perforation	87% / 79% / 66% 6% / 1%	6
Park CH, Dig Liver Dis, 2015 ¹³¹	SR/MA Outcomes EGJ	6 studies, 3559 patients	ESD	En-bloc / R0 Stricture Recurrence after curative resection	98.6% / 87% 6.9% 0%	2

ESD – Endoscopic Submucosal Dissection; ESTD – Endoscopic Submucosal Tunneling Dissection; R0 – Histological complete resection; DSS – Disease-Specific Survival; ER – Endoscopic Resection; OS – Overall Survival; DFS – Disease-Free Survival; ns – non-significant; PPB – Post-procedural bleeding; SR/MA – Systematic review and meta-analysis

Supplementary material

Supplementary Table 3 – Endoscopic predictors of non-curative endoscopic submucosal dissection (ESD)

First author, year, journal	Study design	Participants	Outcomes	Results (95% CI / p-value)
Choi JM, 2015, Surg Endosc ¹³²	Retrospective	164 early gastric cancer (EGC)	Predictors for undifferentiated histology	endoscopic size >10 mm (OR 1.81; 95% CI 1.12–2.92; P = 0.016) depressed type (OR 2.85; 95% CI 1.56–5.21; P<0.001) whitish discoloration (OR 19.64; 95% CI 6.98–55.25; P<0.001) nodularity (OR 2.83; 95% CI 1.59–5.05; P<0.001)
Libânio D, 2017, Endosc Int Open ²⁸	Retrospective	245 ESD	Predictors for non-curative ESD	polypoid (OR 5.22; 95% CI 1.58-17.25; p=0.01) depressed morphology (OR 2.1; 3 95% CI 0.93-4.88; p=0.01) lesion size ≥ 20mm (OR 2.91; 95% CI 1.40-6.07; p<0.01)
Nam HS, 2018, Plos One ¹³³	Retrospective	596 early gastric cancer (EGC)	Predictors for non-curative ESD	lesion size > 20 mm (OR 3.714, 95% CI, 2.103–6.556, p < 0.001) ulceration (OR 3.538, 95% CI, 1.571–7.965, p = 0.002) nodularity (OR 2.967, 95% CI, 1.689–5.211, p < 0.001) depression (OR 1.806, 95% CI, 1.034–3.153, p = 0.038) Location at mid third (OR 7.135, 95% CI, 3.106–16.388, p<0.001) Location at upper third (OR 4.155, 95% CI, 1.732–9.962, p<0.001)
Kim SJ, 2017, Surg Endosc ¹³⁴	Retrospective	532 ESD	Predictors for non-curative ESD	elevated type (OR 2.5; 1.2–5.3; p=0.021), redness (OR 2.7; 95% CI 1.1–6.6; p=0.029) discoloration (OR 16.1; 95% CI 2.4–105.9; p=0.004) elevation (OR 17.2; 95% CI 2.0–146.7 p=0.009) fusion of convergent folds (OR 12.9; 95% CI 3.9–42.1; p<0.001) irregular surface (OR 17.8; 95% CI 5.6–56.8; p < 0.001)
Kim Y, 2016, J Gastric Cancer ¹³⁵	Retrospective	756 ESD	Predictors for non-curative ESD	lesion size of > 2.0 cm (OR 2.51; 95% CI 1.36-4.62; P=0.003) Location at upper-third (OR 4.68; 95% CI 2.59-8.43; P<0.001)
Choi IJ, 2016, Gut and Liver ¹³⁶	Prospective	737 ESD	short-term outcomes of ESD treatment	posterior wall location (OR 3.3; 95% CI 1.068–10.364 p=0.0381) lesion size >3 cm (OR28.654; 95% CI 7.053–116.411; p<0.0001) ulceration (OR 14.076; 95% CI 2.236–88.612; p=0.0048)
Kim EH, 2016, Gastrointestinal Endoscopy ¹³⁷	Retrospective	1639 ESD	Predictors for non-curative ESD	Lesion size >20mm (OR 2.674; 95% CI 1.999-3.575; p<0.001) location at upper-third (OR 2.034; 95% CI 1.325-3.123; p=0.001) presence of ulcer (OR 2.413; 95% CI 1.375-4.234; p=0.002) fusion of folds (OR 2.931; 95% CI 1.633-5.262; p<0.001) absence of nodularity (OR 1.855; 95% CI 1.395-2.468; p<0.001) spontaneous bleeding (OR 2.496; 95% CI 1.727-3.607; p<0.001)
Ohara Y, 2016, Surg Endosc ¹³⁸	Prospective	398 ESD	Predictors for non-curative ESD	lesion size >20mm (OR 3.31; 95% CI 1.74–6.29; P = 0.0003) elevated or depressed (OR 4.37; 95% CI 1.88–9.88; P = 0.0008)

Supplementary material

Supplementary Table 4 – Endoscopic ultrasonography for the assessment of deep invasion in early gastric cancer

First author, year, journal	Study design	Participants	Intervention / comparator	Outcomes	Results
Kuroki K, 2020, Gastric cancer ²³	Retrospective	1598 pts 2001 EGC	EUS vs histology	EUS-M/SM1 EUS-SM2	Accuracy 95%, sensitivity 98%, specificity 69%, PPV 97%, NPV 79%
Cheng J, 2017, Surg Endosc ¹³⁹	Retrospective	195 pts 205 GC	EUS vs histology	M/SM1 SM2	Accuracy of the model 89.86%
Fairweather M, 2015, Journal of Surgical Oncology ¹⁹	Retrospective	10 EGC 39GC	EUS vs histology	Discriminate between EGC and advanced GC	Accuracy 77.5%; sensitivity 74.4%; specificity 80.0%; PPV 93.5%; NPV 44.4%
Takamaru H, 2019, Gut and Liver ¹⁴⁰	Retrospective	259 pts 278 EGC	EUS vs histology	EUS-SM2	Sensitivity 73.7%; specificity 74.4%; accuracy 74.1%
Kim SJ, 2017, Scandinavian ¹⁴¹	Retrospective	266 pts 273 EGC	EUS vs histology	SM1 and SM2 discrimination	Accuracy 83.9%
Kim J, 2018, Surg Endosc ¹⁴²	Retrospective	6084 pts	EUS vs histology	Discriminate between T1a and advanced GC	Accuracy 75.0%; Sensitivity 67.4%; Specificity 82.5%; PPV 79.4%; NPV 71.7%
Kim TY, 2018, Surg Endosc ¹⁴³	Retrospective	345 pts 345 GC	EUS vs histology	Predicting deep invasion of GC	Accuracy 83.5%; Sensitivity 84.0%; Specificity 83.3%; PPV 60.7%; NPV 94.4%
Lan Z, 2019, J Gastroenterol and Hepatol ²⁴	Prospective	72 pts	Linear EUS vs Radial EUS vs histology	Comparison between linear EUS and radial EUS for submucosal invasion prediction	Linear EUS vs Radial EUS Accuracy 90.9% vs 69.2%, <i>p</i> = 0.024 specificity 90.0% vs 60.7%, <i>p</i> = 0.024 sensitivity 92.3% vs 90.9%, <i>p</i> = 0.902
Lee JY, 2016, Gut and Liver ²²	Retrospective	380 pts 393 GC	EUS vs histology	EUS for predicting deep invasion	Accuracy 71.5%; sensitivity 66.9%; specificity 86.8%; PPV 94.4%; NPV 44.1%.
Park J, 2016, Medicine ¹⁴⁴	Retrospective	236 GC	EUS vs histology	EUS for predicting deep invasion in ulcerative EGC	Accuracy 72.5%; Sensitivity 73.5%; Specificity 71.6%; PPV 66.4%; NPV 78%

EGC= early gastric cancer; EUS= endoscopic ultrasonography; PPV= positive predictive value; NPV= negative predictive value

Supplementary material

Supplementary table 5 - Pharmacological measures investigated to reduce post-procedural bleeding

First author, year, journal	Study design; aim	Participants	Exposure / intervention	Outcomes	Results	Level of evidence
Vonoprozan vs proton-pump inhibitors						
Shunsuke Y, 2020, Endosc Int Open ¹⁴⁵	Prospective, single-arm; Efficacy of vonoprazan.	49 patients under continued AT	Vonoprazan 20mg id for 4 weeks	PPB	1/49 (2.0% [0.4-10.7%])	6
Martin BS, 2020, Medicine (Baltimore) ³⁴	SR/MA. Compare vonoprazan and PPI on PPB.	13 studies (8 RCTs), 1510 participants	Vonoprazan (10-20mg) vs PPI (different PPIs)	PPB (7 studies)	3.7% vs 6.1%, OR 0.66 [0.32-1.35]	2
Gao H, 2020, Expert Rev Gastroenterol Hepatol	SR/MA. Compare different therapies.	21 studies	PPI vs P-CAB Others vs P-CAB	PPB PPB	RR 1.02 [1.00-1.05] * RR 1.05 [1.03-1.07] *	2
Jiang X, 2019, Front Pharmacol ³⁶	SR/MA. Vonoprazan vs PPI	16 RCTs	Vonoprazan monotherapy ps PPI monotherapy (5 RCTs)	PPB	OR 0.70 [0.33-1.47]	1
Liu C, 2019, J Dig Dis ³⁸	RS/MA. Vonoprozan vs PPI	14 studies, 1328 patients	Vonoprazan vs PPI	PPB	0.69, p=ns	2
Jaruvongvanich V, 2018, Eur J Gastro Hep ³⁷	SR/MA. Vonoprazan vs PPI on PPB	6 studies, 461 patients	Vonoprazan vs PPI	PPB	OR 0.79 [0.18-3.49]	2
Different PPI regimens						
Yoon JH, 2019, J Gastrointest Surgery ³³	Double-blind RCT. Effect iv PPI on early bleeding	235 patients, 195 analyzed	Pantoprazole 40mg iv id vs placebo (48h after ESD). Oral PPI after 48h for both groups.	Major bleed Minor bleed	3.7% vs 2.3%, p 0.58 8.3% vs 5.8%, p 0.51	2
Lee BE, 2019, Gut Liver ³¹	RCT. Impact of PPI schedule on PPB	401 patients	Pantoprazol infusion vs bolus	Significant IPB PPB	25% vs 24%, p=0.42 11.7% vs 10.2%, p=0.37	2
Ishido K, 2018, Surg Endosc ³²	RCT. Lanso iv vs oral	304 patients (152 each group)	OD lanso bid vs IV lanso bid	PPB Hemostasis on SLE	11.2% vs 14%, p=0.49 11.2% vs 12%, p<0.001 for non-inferior	2
Nishizawa T, 2016, UEG Journal ²⁹	SR/MA. Effect of pre-procedural PPI.	4 studies, 406 patients	Pre-ESD PPI vs control	PPB	9/201 (4.5%) vs 13/205 (6.3%) RD -2.7% (-0.7%; +1.7%)	2
Choi CW, 2015, Dig Dis Sci	RCT. Impact of PPI schedule on PPB	273 patients	PPI continuous infusion vs iv bolus bid	High-risk stigmata PPB	16.0% vs 15.4%, p=1.0 9.4 vs 7.3%, p=0.66	2
Other medications						
Pittayanon R, 2018, J Gastroenterol Hepatol ¹⁴⁶	SR/MA. Mucoprotectives on PPB.	8 studies, 934 patients	PPI vs PPI+ mucoprotective	PPB	RR 0.58 [0.17-1.99]	2

* Non-significant difference on sensitivity analysis (abstracts excluded); AT – Antithrombotic treatment; PPB – Post-procedural bleeding; P-CAB – Potassium-Competitive Acid Blockers; PPI – Proton-pump inhibitor; SR/MA – Systematic Review/Meta-analysis; RCT – Randomized-controlled trial; RR – risk ratio; OR – Oss ratio; SLE – Second-look endoscopy

Supplementary material

Supplementary table 6 - Studies evaluating other interventions to improve ESD outcomes

First author, year, journal	Study design; intervention studied	Participants	Exposure / intervention	Outcomes	Results	Level of evidence
Oh KH, 2017, J Dig Dis ¹⁴⁷	RCT; fasting period	101 patients	Short-fasting (1d) vs long-fasting (2d)	Pain; nausea PPB	No differences 4% vs 0%, p=0.15	2
Kishida Y, Surg Endosc, 2018 ¹⁴⁸	Retrospective; steroids	132 patients resection ≥3/4	Steroid (oral or local) vs no steroid	Stricture rate	39% vs 28%	3
Jung DH, 2015, Endoscopy ¹⁴⁹	RCT. Pre-ESD PPI.	156 patients	Pre-procedural PPI vs control	Moderate to severe pain	44.9% vs 62.8%, p<0.05	2
Harada H, 2019, WJG ¹⁵⁰	Retrospective. Continued LDA	597 patients	Continued LDA vs LDA interruption	PPB	Single-LDA: 10.7% vs 10.3% p>0.99 DAPT: 23.1% vs 5.0%, p=0.14	3
Horikawa Y, 2019, Digestion ²⁶	Retrospective cohort, propensity-matched; LAD	293 patients (50 matched pairs)	Continued LDA vs no LDA	Median IPB* PPB	1 (0-4) vs 0 (0-5), p=0.71 2.0% vs 2.0%, p=1.00	3
Jaruvongvanich V, Ann Gastroenterol, 2018 ¹⁵¹	SR/MA. Continued LDA.	5 studies, 700 patients	Continued (n=266) vs interrupted (n=434)	PPB Thrombotic events	OR 1.81 [0.85-3.83] 0% vs 2.1%, p=0.02	

RCT – randomized-controlled trial; PPB – post-procedural bleeding; PPI – proton-pump inhibitor; LDA – low-dose aspirin; DAPT – double antiplatelet therapy; IPB – number of intraprocedural bleeding episodes; SR/MA – systematic review / meta-analysis; * requiring use of hemostatic forceps

Supplementary table 7 - Studies evaluating preventive measures to reduce perforation

First author, year	Study design , intervention	Participants	Intervention / comparator	Outcomes	Results	Level of evidence
Suzuki S, 2016, GIE ⁹⁰	Retrospective. Traction.	238 pts (43 matched pairs)	Dental floss+clip vs conventional	Perforation (matched)	2.3 vs 2.3%, p=ns	3
Baniya R, 2017, Clin Endosc ⁴³	SR/MA. CO2.	4 RCTs, 391 patients	CO2 vs air insufflation	Perforation	1.6% vs 4.0%, OR 0.39 [0.10-1.57]	1
Su YF, 2020, Endoscopy ⁴⁶	SR/MA of RCTs; traction	5 gastric studies, 922 gastric ESD	Traction-assisted ESD vs conventional	Perforation	0.5% vs 2.0%, OR 0.30 [0.09-1.05]	1

Supplementary material

Supplementary table 8 - Studies evaluating risk factors and management/outcomes of perforation

First author, year	Study design, study aim	Participants	Exposure / intervention	Outcomes	Results	Level of evidence
Ding X, 2019, Eur J Gastroenterol Hepatol ⁴⁸	SR/MA. Risk factors for perforation	18 studies	Risk factors for perforation	Incidence Liver disease Upper third Resection >20mm Submucosal invasion Procedure >2 hours Depressed/flat Piecemeal resection	596/22272 (2.6%) OR 1.98 [1.02-3.85] OR 3.62 [2.83-4.65] OR 1.42 [1.03-1.96] OR 3.05 [1.80-5.18] OR 4.12 [1.63-10.39] OR 1.59 [1.25-2.01] OR 3.88 [2.69-5.60]	2
Yamamoto Y, 2017 Gastroenterol Res Pract ¹⁵²	Retrospective. Incidence and risk factors for delayed perforation; management.	1158 patients	Management	Incidence of delayed perforation Management	5/1158 (0.42%); all <24h after All treated conservatively	3
Suzuki H, WJG, 2015 ¹⁵³	Retrospective; management of delayed perforation	4943 patients; 7 with delayed perforation	Management	Incidence Management	7/4943 (0.1%); median 11h 3 surgery, 4 conservative, 0 death Gastric tube (OR 11)	
Kim HJ, Surg Endosc, 2016 ¹⁵⁴	Retrospective. Perforation outcomes.	3821 patients	Management	Incidence Management	2.4% (visible 82%, clinically 18%) Visible perforation – immediate closure with endoclips, success 97%; 2 pts surgery Clinically suspected – Abs, fasting – all success without surgery	6

Supplementary material

Supplementary table 9 - Studies evaluating incidence and risk factors for LNM in early gastric cancer

First author, year	Study design; country	Participants	Outcomes	Results	EL
Surgical series outside Japan					
Chu Y-N, 2019, World Journal Gastro ⁵³	Retrospective; China	1262 pts with EGC	LNM incidence Independent RF for LNM	14.4% (0% standard; 1.3% expanded) SM2 (OR 2), LVI (OR 16), mucinous AC (OR 3)	3
Hanada Y, 2019, Clin Gastroenterol Hepatol ¹⁰¹	Retrospetive; USA	176 patients with EGC	LNM incidence RF for LNM	20.5% (0% standard; 7.5% expanded) pT1b (OR 3.9), LV+ (OR 4.6)	3
Abdelfatah M, 2019, Surg Endosc ⁵⁸	SR/MA (non-Japanese studies)	19 studies, 1507 patients with T1b expanded criteria; 1118 non-Japan	LNM incidence RF for LNM	45/1118 (4.0%) pT1b ≤300µm 2.5%; pT1b ≤500µm 2.8%, p=ns	2
Pessorusso F, 2018, Gastrointest Endosc ¹⁰²	Retrospective (Brazil)	389 patients with EGC; 135 with criteria for ER	LNM incidence (overall)	53/389 (13.6%) Standard 0%; expanded 2.9%	3
Abdelfatah M, 2018, Gastrointest Endosc	SR/MA (China, Korea)	12 studies, 9798 patients (9678 from China, Korea)	LNM incidence	73 / 9678 (0.75%) Standard 6 / 2540 (0.24%); expanded 67 / 7138 (0.94%)	2
Gu L, 2018, J Gastrointest Surg ¹⁵⁵	Retrospective (China)	1029 patients with EGC	LNM Independent RF for LNM	22% Depressed , size, T1b, LV+, undifferentiated	3
Oh SY, 2017, Ann Surg ¹⁵⁶	Retrospective (Korea)	1003 patients with pT1a EGC	LNM incidence RF for LNM	1.8% Undifferentiated (3.2% vs 0.4%, p<0.001))	3
Lee SH, 2016, Ann Surg Treat Res ⁵⁴	Retrospective (Korea)	1191 patients with pT1a EGC	LNM incidence Independent RF for LNM	3.5% (0.6% standard; 1.8% expanded) MsM invasion (OR 4.9), UL+ (OR 2), UD-histology (OR 4.2)	3
Wang H, 2016, Chin J Cancer Res ¹⁵⁷	Retrospective (China)	386 patients with pT1a EGC	LNM incidence Independent RF	10.4% (0% standard; 8.7% expanded) Undifferentiated (OR 3.8)	3
Zheng Z, 2016, BMC Cancer ¹⁵⁸	Retrospective (China)	597 patients with EGC	LNM incidence Independent RF	9.7% Age <50yrs , undifferentiated, UL+, LV+, invasion depth	3
Choi AH, 2016, Gastroint Endosc ¹⁵⁹	Retrospective (USA)	923 patients with pT1a	LNM incidence	7.8% (5.2% Asian-Pacific Islanders; 7.0% Hispanics; 9.7% whites; 10.9% blacks)	3
Feng H, 2016, Scand ¹⁶⁰	Retrospective (China)	576 patients with differentiated EGC	LNM incidence Independent RF for LNM	38/576 (6.6%) Size ≥30mm OR 1.5, pT1b OR 2.9, UL+ OR 2.5, LV+ OR 4.4	3
Feng F, 2015, J Gastrointest Surg ¹⁶¹	Retrospective (China)	503 patients with EGC	LNM incidence Independent RF for LNM	80/503 (15.9%) Size ≥20mm, G2/G3, pT1b, LV+	3

Supplementary material

Choi KK, 2016, Gastroint Endosc ⁵⁵	Retrospective (Korea)	3951 patients with pT1a	LNM incidence Independent RF LNM	101/3951 (2.6%) – 0.3% standard; 0.4% expanded Larger tumor (OR 1.25), undifferentiated (OR 7.5), L+ (OR 20.6), P+ (OR 23.4), UL+ (OR 4.1)	3
Zhao BW, 2015, PLoS One ¹⁶²	Retrospective (China)	205 patients with EGC	LNM incidence Independent RF for LNM	52/205 (25.4%) ≥3cm (OR 2.4), T1b (OR 3.1), UD (OR 4.1), V+ (OR 6.8)	3
Fang WL, 2015, <i>Pathol Oncol Res</i> ¹⁶³	Retrospective (China)	391 patients with EGC	LNM incidence Independent RF for LNM	T1a 4.9%, T1b 21.4% T1a: Diffuse-type; L+; T1b: L+	3
Surgical series (Japan)					
Abdelfatah M, 2019, Surg Endosc ⁵⁸	SR/MA	19 studies, 1507 patients with T1b expanded criteria	LNM incidence (Japan)	0/389 (0%)	2
Abdelfatah M, 2018, Gastrointest Endosc	SR/MA	12 studies, 9798 patients (3 studies, 3145 patients from Japan)	LNM incidence	1/3145 (0.03%) – standard 0/485 (0%); expanded 1/2660 (0.04%)	2

LNM – Lymph Node Metastasis; EGC – Early Gastric Cancer; RF – Risk Factors; SM2 – invasion depth ≥500µm; OR – Odds ratio; LVI – Lymphovascular invasion; AC – adenocarcinoma; SR/MA – Systematic review and meta-analysis; ns – non-significant; ER – Endoscopic resection; MsM – Muscularis Mucosae; UL+ - with ulcerative findings; UD – Undifferentiated;

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Supplementary material

Table 4s: Duodenum

1: Literature available on the evolution of the prognosis of duodenal neoplasia

First author, year	Study design, participants (n)	Intervention	Outcome (intervention vs. study arm)	Remarks	Evidence level
Goda K et al. Dig Endosc 2014[2], Japan	163 intramucosal carcinomas 10 submucosal carcinomas		No data on lymph node risk Only endoscopic prediction of histology 10 % LNM ??? in the discussion but not in the results		Low
Hirashita T et al. JJCO 2018[1], Japan	Retrospective 25 duodenal adenocarcinoma		10 Intramucosal carcinoma → no LNM 0 Submucosal carcinoma		Low
Zenali M et al. Hum Pathol 2013.[65]	4 T1 adenocarcinoma no differentiation between intramucosal and submucosal		5.9% of lymph nodes metastasis.		Low
Oka S et al. J Clin Gastro 2003.[66]	17 tumours in 15 patients 10 FAP and 7 sporadic		No data on the depth of invasion		Low
Toba T et al. J Gastroenterol 2018.[63]	67 lesions mixing high grade dysplasia and adenocarcinoma		Expression of MUC5AC in adenocarcinomas	Mixing high grade dyplasia and cancers	Low
Hara et al.WJG 2019[37].	54 mucosal cancers 2/3 submucosal cancers		No data on the risk of lymph nodes		Low
Fujisawa et al. Gastroenterol Endosc 1995. Article in Japanese not on	166 pT1a adenocarcinomas		No lymph nodes 5.3% of lymph nodes in submucosal cancers ????? cited in other papers from Japanese guys		Low

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Nagatani K et al. Endosc Digest 1993. Article in japanese	40 pT1 adenocarcinomas		No lymph nodes		Low
Takahashi T et al. Scand J Gastro 2009. [67]	2 cases of well differentiated adenocarcinoma		No recurrence in 18 months of follow up		Low
Yoshimura M et al. Hepatogastroenterology 2010.[5]	Only in situ carcinoma no invasive ones		NBI diagnosis of duodenal adenocarcinoma was based on in situ lesions and not on invasive submucosal adenocarcinomas		Very poor

Other papers on duodenal adenocarcinoma but without data on the invasion depth[68,69]
Old papers evaluating incidence of cancers in duodenal lesions[70]
Papers on endoscopic resections of duodenal adenomas without precise description of duodenal adenocarcinomas[18,71–73]
Reviews on duodenal lesions [74,75][3]

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Results of ESD in the duodenum

First author, year	Study design, participants (n)	Intervention	Outcome (intervention vs. study arm)	Remarks	Evidence level
Kuroki K et al.EIO 2020[25]	7 procedures Retrospective design		14% of perforations 14% of delayed bleedings		Very low
Lupu et al. Endoscopy 2020[22].	Case report ESD with traction for duodenal recurrence		No perforation R0		Very low
Kato et al. EIO 2019.[26]	174 patients		84.4 % R0, 12.7% perforations	Analysis of technical difficulty and risks	Very low
Hara et al. World J Gastro 2019[37].			73% R0 45% perforations 0 perforation/136 EMR		low
Oung B et al. Video GIE 2019[23]	Case report ESD with traction for duodenal NET.		No perforation R0		Very low
Dohi et al. Dig Endosc 2019[27].	13 esd with scissors		R0 > 95%		

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Tashima T et al. Endoscopy 2018[40].	50 ESD cases Prospective interventional study	Systematic closure of the defect with OTSC	R0 88% 2.1% of delayed perforations after systematic closure with OTSC		Prospective study
Yahagi N. et al GIE 2018.[28]	174 ESD and 146 EMR	Retrospective monocentric comparative study	ESD: R0 85%, perforation 15.5%, delayed bleeding 5.2%; EMR: R0 82%, perforation 0.68%, delayed bleeding 1.4%	(defect clip / string+clip closure) (same period 2010-2017 ref 22)	low
Perez Cuadrado Robles E et al.EIO 2018[15]	37 tumors resected with ESD		16.7% of perforation 44% of R0 resection only	Low R0 rate High rate of perforation	Very low
Goda Y et al. Min Invas Ther 2018.[39]	29 patients	Retrospective comparison conventional ESD and traction ESD with or/and without OTSC closure	Less perforation in the second arm		Very low many bias Few data
Ojima et al. J Gastrointestin Surg 2018.[54]	Retrospective comparison of LECS versus ESD 50 cases of ESD		4% strictures 16% perforation 6% delayed bleedings	LECS > ESD in R0 resection rate and adverse events	low
Zou et al. Surgical Endosc 2018.[76]	retrospective study ESD (n=33) vs EMR (n=21)		R0 ESD 93.9% vs EMR 38.1% recurrence ESD 0% vs EMR 19%	delayed perforation ESD 9%	very low
Hoteya et al. Dig endosc 2015.[41]	63 patients	Retrospective comparison of risk factors of delayed bleedings	31.3% of perforations 87.3% of R0 resections 17.5% delayed bleeding		Low

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Nonaka S et al. Endoscopy 2015[29]	8 cases		1 perforation		Very low
Ishii N et al. ACG case report 2015[77].	16 cases	Retrospective Not comparative	81% R0 6.3 % of perforation		Very low
Yamamoto et al.Dig ENdosc 2014[78]	30 patients	retrospective	90% R0 10% perforations		Low
Matsumoto et al. World Journal of gastro 2014.[57]	15 ESD 31 EMR	retrospective	Perforation 20% >> EMR 0 recurrence versus 1/31 EMR		

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Supplementary material

Table 5s: Colorectum

TABLE : risk of surgery for colorectal lesions [4,5]				
	LAPAROSCOPIC		OPEN	
	Transverse	Rectal	Transverse	Rectal
MORTALITY	0,5 % (4/811)	3,1%	0,5% (4/776)	3,2%
Anastomotic leakage	1,8% (15/815)	8,4 %	2,8% (23/811)	6,7%
Bleeding	2,5% (16/649)	5,7%	2,9% (16/546)	4,4%
Wound infection	4% (25/624)	8,9 %	4,9% (29/584)	10,1%
Abdominal infection/peri-anal wounds	2,1% (9/422)	2,3%	2,3 % (10/427)	16,2%

Supplementary material

Table X. Research/PICO question.

Which pre-ESD staging is needed :

P – patients with rectal lesions suspicious for cancer

I – EUS

C – Vs CT vs MRI

O – staging accuracy for T and N stage

First author, year	Study design , study objective	Intervention	Participants	Outcomes	Results	Level of evidence
Chan , 2019 [1]	Meta-analysis	MRI versus EUS fo staging, real head to head comparison, surgical pathology as a reference standard	234 patients 6 Studies directly comparing the accuracy of EUS and MRI performed in the same patient for staging	diagnostic test accuracy of EUS and MRI in the staging of rectal cancer. Secondary objectives were to compare sensitivity and specificity of EUS and MRI	T stage : EUS superior: AUC 0.87 vs 0.82 for RI (p=0.0001) N staging : no difference EUS AUC 0.90 vs MRI AUC 0.86. However MRI superior to EUS for T2 staging (MRI	High quality

Supplementary material

			rectal cancer with surgical pathology as the reference standard were included	in T and N staging, as a composite and individual stages.	AUC 0.92 vs EUS AUC 0.82 p=0.005). after excluding studies using an endorectal coil, EUS was significantly superior to MRI in overall T, T1, T3, and N staging (P < .01 for all). MRI remained superior to EUS in T2 staging (P Z .01).	
Li et al 2016[2]	Meta-analysis	MRI, EUS of CT for T staging rectal cancer with histology as a reference standard	89 studies 9141 patient MRI : 62 studies 3887 pt EUS 32 studies 6659 pt CT 9 studies 407	Diagnostic accuracy for T staging	No significant difference in accuracy for T staging between CT, EUS or MRI. Nothing mentioned on N stage and not focused on early disease.	Moderate quality

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			patients			
Gao et al 2019[3]	Systematic review	MRI, CT, EUS or ERUS for rectal cancer N staging	Quality assessment of 7 systemic reviews (SRs) with 353 studies. EUS : 4 SRs CT: 3 SRs MRI : 5 SRs ERUS : 2SRs	Diagnostic accuracy for N staging	EUS : sensitivity, 0.64 (95% CI 0.57–0.72); specificity, 0.78 (95% CI 0.75–0.80); CT : sensitivity, 0.63 (95% CI 0.54–0.73); specificity, 0.72 (95% CI 0.67–0.78); MRI : sensitivity 0.69 (95% CI 0.63–0.77), spêcificity 0.76 (95% CI 0.73–0.79) ERUS : sensitivity 0.57 (95% CI 0.53–0.62), specificity 0.80 (95% CI 0.77–0.83)	High quality

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					MRI : higher sensitivity than ERUS for indirect comparison	
Li et al 2015[4]	Meta-analysis	MRI, CT, EUS or ERUS for rectal cancer N staging	123 studies with 8302 patients MRI : 55 studies / 2845 pt EUS : 71 studies / 5152 pt CT 27 studies /1616 pt	Diagnostic accuracy for N staging	MRI : sensitivity (0.76 95% CI (0.70, 0.81))/ specificity 0.77 95% CI (0.72-0.81) EUS : sensitivity 0.63 (95% CI (0.58-0.68) specificity 0.80 95% CI (0.77-0.83) CT : sensitivity 0.70 95% CI (0.59-0.79), specificity 0.75 (0.6-0.81) No significant differences	High quality

Supplementary material

Pubmed search:
From January 2015 UP to April 2020
x studies
Relevant studies selected and present in the tables above.

- ¹ Chan BPH, Patel R, Mbuagbaw L, Thabane L, Yaghoobi M. EUS versus magnetic resonance imaging in staging rectal adenocarcinoma: a diagnostic test accuracy meta-analysis. *Gastrointest Endosc* 2019; 90: 196-203.e1 Im Internet: <https://pubmed.ncbi.nlm.nih.gov/31004599/>
- ² Li XT, Zhang XY, Sun YS, Tang L, Cao K. Evaluating rectal tumor staging with magnetic resonance imaging, computed tomography, and endoluminal ultrasound A meta-analysis. *Med (United States)* 2016; 95
- ³ Gao Y, Li J, Ma X, Wang J, Wang B, Tian J, Chen G. The value of four imaging modalities in diagnosing lymph node involvement in rectal cancer: an overview and adjusted indirect comparison. *Clin Exp Med* 2019; 19 Im Internet: <https://pubmed.ncbi.nlm.nih.gov/30900099/>
- ⁴ Li XT, Sun YS, Tang L, Cao K, Zhang XY. Evaluating local lymph node metastasis with magnetic resonance imaging, endoluminal ultrasound and computed tomography in rectal cancer: A meta-analysis. *Color Dis* 2015; 17: O129–O135 Im Internet: <https://pubmed.ncbi.nlm.nih.gov/25628186/>