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

Authors

Pedro Pimentel-Nunes[1,2,*], Diogo Libânio[1,3,*], Barbara A. J. Bastiaansen[4], Pradeep Bhandari[5], Raf Bisschops[6], Michael J. Bourke[7], Gianluca Esposito[8], Arnaud Lemmers[9], Roberta Maselli[10,11], Helmut Messmann[12], Oliver Pech[13], Mathieu Pioche[14], Michael Vieth[15], Bas L. A. M. Weusten[16], Jeanin E. van Hooft[17], Pierre H. Deprez[18], Mario Dinis-Ribeiro[1,3]

Institutions

1 Department of Gastroenterology, Porto Comprehensive Cancer Center, and RISE@CI-IPOP (Health Research Network), Porto, Portugal
2 Department of Surgery and Physiology, Porto Faculty of Medicine, Portugal
3 MEDCIDS, Faculty of Medicine, University of Porto, Porto, Portugal
4 Department of Gastroenterology and Hepatology, Amsterdam Gastroenterology & Metabolism, Amsterdam University Medical Center, The Netherlands
5 Department of Gastroenterology, Queen Alexandra Hospital, Portsmouth, UK
6 Department of Gastroenterology and Hepatology, University Hospitals Leuven, TARGID, Leuven, Belgium
7 Department of Gastroenterology, Westmead Hospital, Sydney, Australia and Western Clinical School, University of Sydney, Sydney, Australia
8 Department of Medical-Surgical Sciences and Translational Medicine, Sant' Andrea Hospital, Sapienza University of Rome, Italy
9 Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, CUB Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium.
10 Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy
11 IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy
12 Department of Gastroenterology, Universitätsklinikum Augsburg, Augsburg, Bayern, Germany
13 Department of Gastroenterology and Interventional Endoscopy, St. John of God Hospital, Regensburg, Germany
14 Endoscopy and Gastroenterology Unit, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France
15 Institute of Pathology, Friedrich-Alexander University Erlangen-Nuremberg, Klinikum Bayreuth, Bayreuth, Germany
16 Department of Gastroenterology and Hepatology, St. Antonius Hospital Nieuwegein and University Medical Center Utrecht, Utrecht University, The Netherlands.
17 Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands
18 Department of Hepatogastroenterology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium

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* Joint first authors

Corresponding author
Pedro Pimentel-Nunes, MD PhD, Gastroenterology Department, Instituto Português de Oncologia, Rua Dr. Bernardino de Almeida, 4200–072 Porto, Portugal
pedronunesml@gmail.com

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

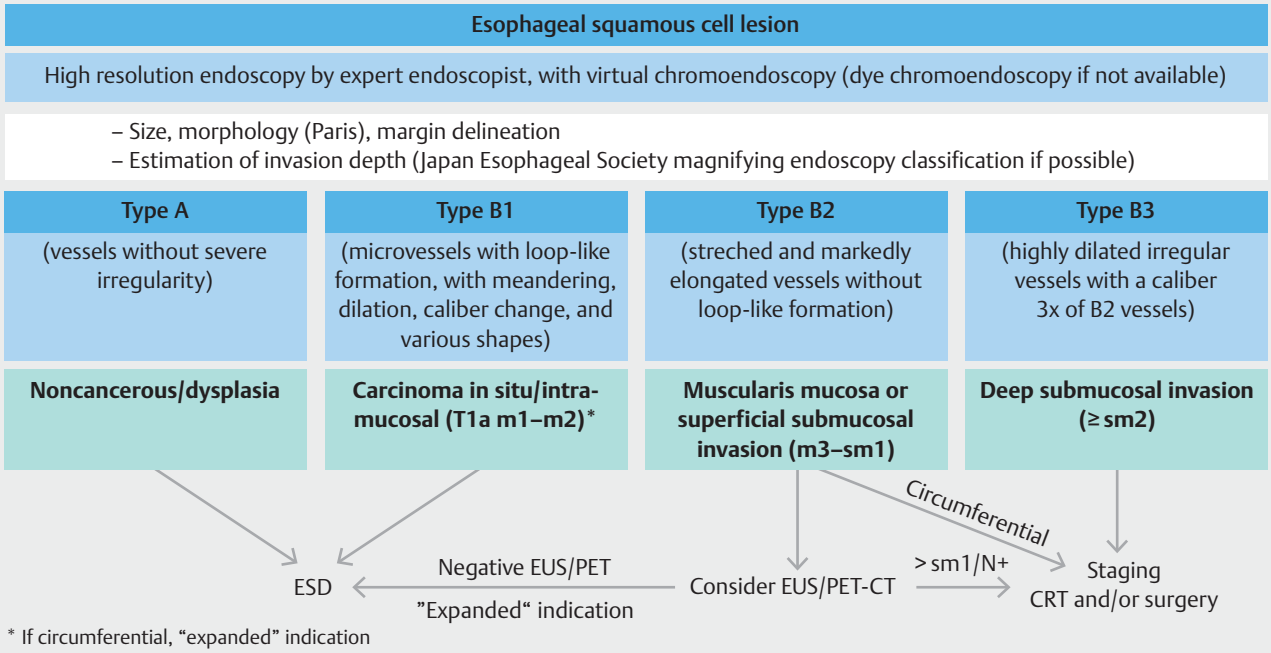
30 ESGE recommends scheduled endoscopic surveillance with high definition white-light and chromoendoscopy (virtual or dye-based) with biopsies of only the suspicious areas after a curative ESD.
Strong recommendation, moderate quality evidence.

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.

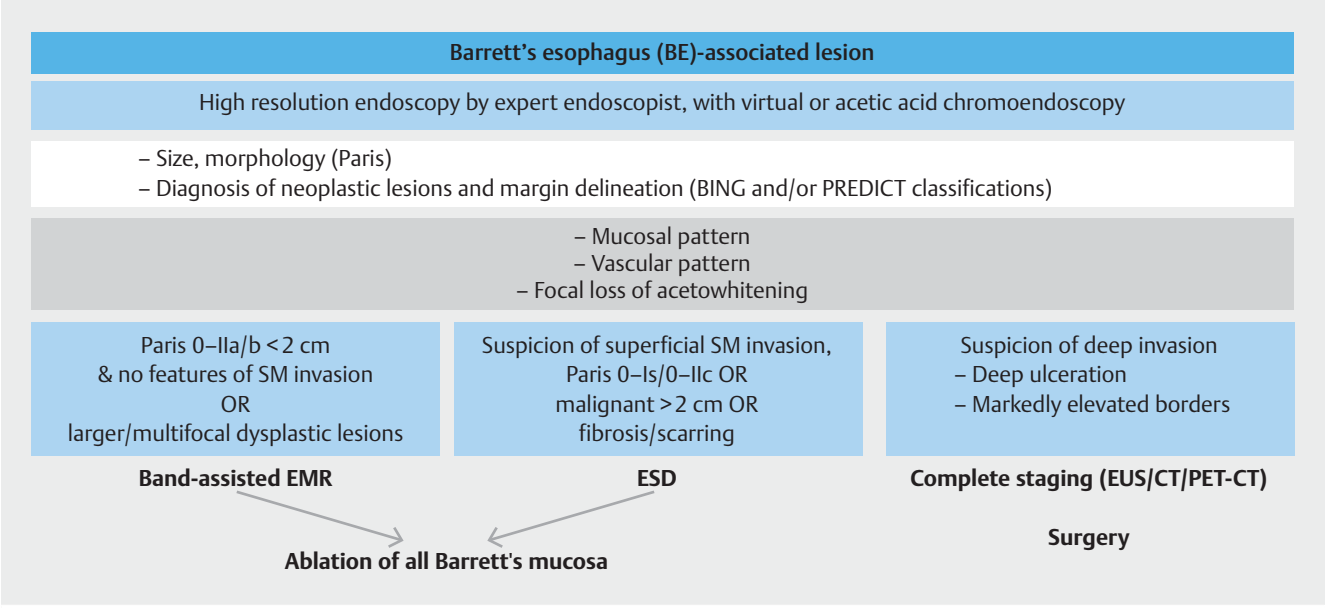
32 For upper GI superficial lesions, ESGE suggests endoscopy at 3–6 months and then annually after a curative ESD resection or after a local-risk ESD resection without recurrence.
Weak recommendation, low quality evidence.

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.

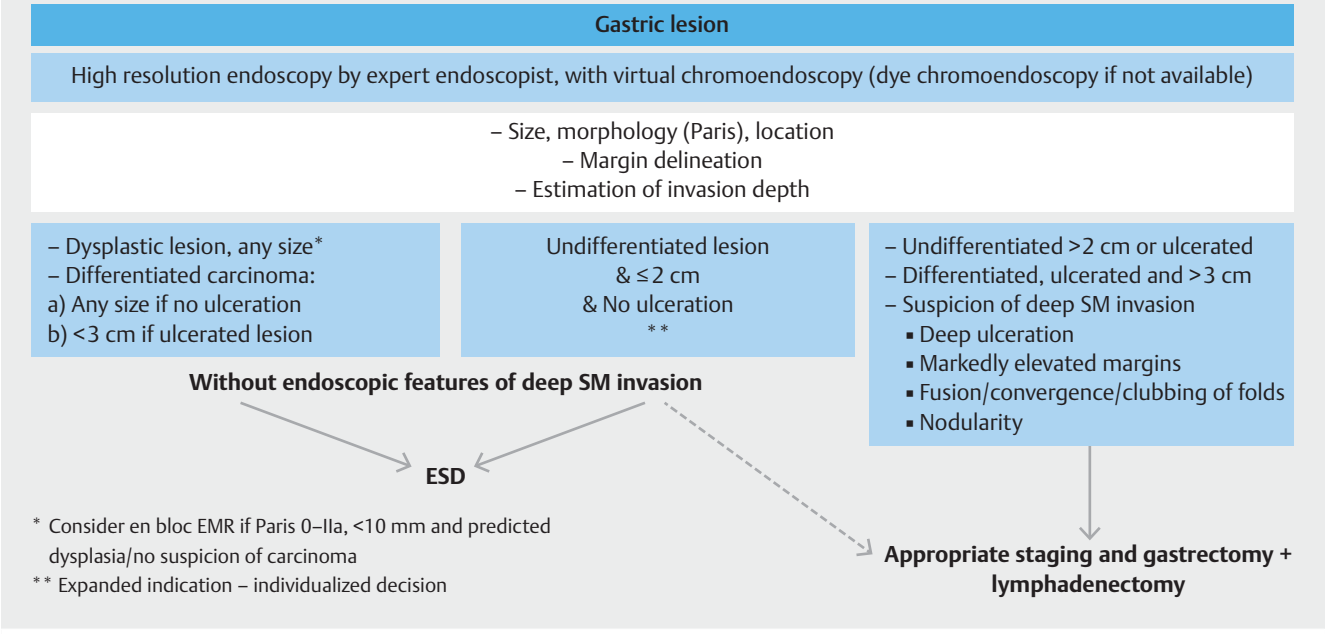
34 ESGE does not suggest routine use of EUS, MRI, CT, or PET in the follow-up after a very low or low risk (curative) endoscopic resection, but this might be considered in the cases of T1a-m3/T1b-sm1 esophageal SCC particularly if no additional treatment has been decided.
Weak recommendation, low quality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



▶ **Fig. 1** Endoscopic submucosal dissection (ESD) for superficial esophageal squamous cell cancers (SCCs): a decision algorithm. CRT, chemo-radiotherapy, 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

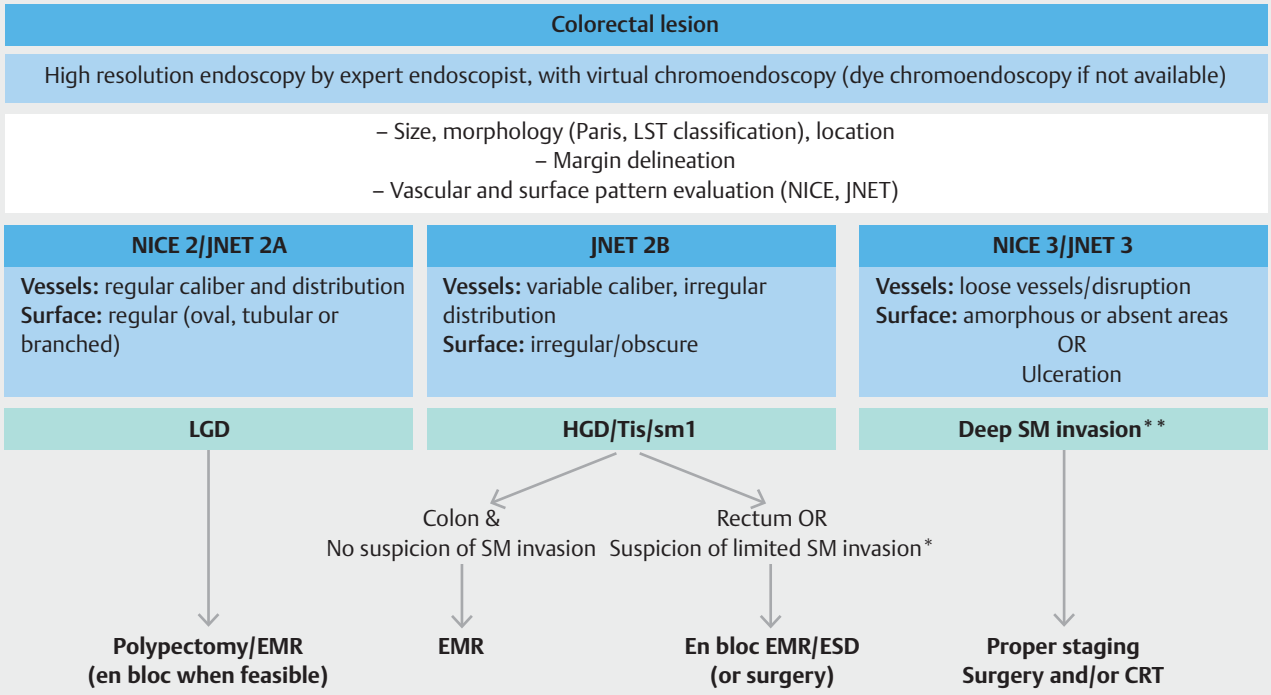
3.1 Endoscopic evaluation

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.



* LST nongranular (particularly if pseudodepressed, IIc); LST granular nodular mixed-type (>2 cm); demarcated depressed area with irregular surface pattern; large protruded or bulky component

** In the rectum consider EUS/MRI if suspicion of SM invasion and doubts on endoscopic resection

▶ **Fig. 4** Endoscopic submucosal dissection (ESD) for superficial colorectal lesions: a decision algorithm. CRT, chemoradiotherapy; EMR, endoscopic mucosal resection; EUS, endoscopic ultrasonography; HGD, high grade dysplasia; JNET, Japan NBI Expert Team; LGD, low grade dysplasia; LST, laterally spreading tumor; MRI, magnetic resonance imaging; NICE, NBI International Colorectal Endoscopic.

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/T1bsm1 (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-Is, 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 19 484 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 11 260 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 rectosigmoid 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 (≤ 500 µm, 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 µm 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	▪ Only dysplasia ▪ If cancer: – Only intramucosal cancer – Differentiated – V0 – L0 – HM0 and VM0 (R0) – UL0 ▪ UL1 gastric intramucosal cancer and: – 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)	▪ Only endoscopic surveillance recommended ▪ No need for further radiological staging or surveillance
Low risk (curative) resection *LNM risk < 3 %*	Complete AND En bloc	▪ sm1 cancer[1] and: – Differentiated – V0 – L0 – HM0 and VM0 (R0) – UL0 – Budding 0/1 (colon) ▪ Poorly differentiated gastric intramucosal cancer and[2]: – V0 – L0 – HM0 and VM0 (R0) – UL0 – ≤ 2 cm	If m3/sm1 esophageal SCC, lesion should ideally be ≤ 2 cm If sm1 gastric cancer, lesion should be ≤ 3 cm	▪ 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)
Local-risk resection *LNM risk < 3 %* *Local recurrence risk 10 %–30 %*	Complete AND Piecemeal	▪ HM1 and VM0 (RX) and: – 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 If SM cancer area not in the margins (allowing full evaluation of the SM cancer area) decision should be individualized	▪ 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

▶ **Table 2** (Continuation)

	Endoscopic	Pathological	Notes	Management
High risk (noncurative) resection *LNM risk > 3 %*	Incomplete OR If complete at least one of pathological criteria must apply	▪ Cancer and at least one of these criteria must apply: – sm2/sm3 invasion – Undifferentiated – V1 – L1 – VM1 (R1) – Budding 2/3 (colorectal) ▪ sm1 or UL1 gastric cancer and: – > 3 cm	If complete ER most patients will, nevertheless, be cured LV1 is the most important risk factor for LNM (20 %–30 % risk) and the strongest indication for adjuvant treatment 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	▪ 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 µm was used as a cutoff as opposed to ≤ 500 µm [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 µm, 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 µm; 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 µm from the muscularis mucosae);
   – ulceration or size > 2 cm, in poorly differentiated lesions;
   – size > 3 cm in pT1b differentiated lesions with submucosal invasion < 500 µm, 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 ≥ sm2 or ≥ 1000 µm (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 µm 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 ≥1000 µm 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 µm may help to reduce the incidence of unnecessary surgery after ER [206]. However, a recently published meta-analysis including 16 observational studies and 10 181 patients confirmed submucosal invasion of at least 1000 µm 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 1 mm), 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 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 ≥sm2 (submucosal ≥1000 µm) 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 ≥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 2 s** (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 2 s**), 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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References

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

[2] Veitch AM, Vanbiervliet G, Gershlick AH et al. Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. Endoscopy 2016; 48: 385–402

[3] Pimentel-Nunes P, Pioche M, Albeniz E et al. Curriculum for endoscopic submucosal dissection training in Europe: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy 2019; 51: 980–992

[4] Atkins D, Eccles M, Flottorp S et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res 2004; 4: 38

[5] Hassan C, Ponchon T, Bisschops R et al. European Society of Gastrointestinal Endoscopy (ESGE) Publications Policy – Update 2020. Endoscopy 2020; 52: 123–126

[6] Endoscopic Classification Review Group. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 2005; 37: 570–578

[7] Dekker E, Houwen B, Puig I et al. Curriculum for optical diagnosis training in Europe: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy 2020; 52: 899–923

[8] Morita FH, Bernardo WM, Ide E et al. Narrow band imaging versus lugol chromoendoscopy to diagnose squamous cell carcinoma of the esophagus: a systematic review and meta-analysis. BMC Cancer 2017; 17: 54

[9] Gruner M, Denis A, Masliah C et al. Narrow-band imaging versus Lugol chromoendoscopy for esophageal squamous cell cancer screening in normal endoscopic practice: randomized controlled trial. Endoscopy 2021; 53: 674–682

[10] Costa-Santos MP, Ferreira AO, Mouradides C et al. Is Lugol necessary for endoscopic resection of esophageal squamous cell neoplasia? Endosc Int Open 2020; 8: E1471–E1477

[11] Yu T, Geng J, Song W et al. Diagnostic accuracy of magnifying endoscopy with narrow band imaging and its diagnostic value for invasion depth staging in esophageal squamous cell carcinoma: a systematic review and meta-analysis. Biomed Res Int 2018; 2018: 8591387

[12] Oyama T, Inoue H, Arima M et al. Prediction of the invasion depth of superficial squamous cell carcinoma based on microvessel morphology: magnifying endoscopic classification of the Japan Esophageal Society. Esophagus 2017; 14: 105–112

[13] Fujiyoshi T, Tajika M, Tanaka T et al. Comparative evaluation of new and conventional classifications of magnifying endoscopy with narrow band imaging for invasion depth of superficial esophageal squamous cell carcinoma. Dis Esophagus 2017; 30: 1–8

[14] Katada C, Tanabe S, Wada T et al. Retrospective assessment of the diagnostic accuracy of the depth of invasion by narrow band imaging magnifying endoscopy in patients with superficial esophageal squamous cell carcinoma. J Gastrointest Cancer 2019; 50: 292–297

[15] Ueda T, Dohi O, Naito Y et al. Diagnostic performance of magnifying blue laser imaging versus magnifying narrow-band imaging for identifying the depth of invasion of superficial esophageal squamous cell carcinoma. Dis Esophagus 2020: doi:10.1093/dote/doaa078

[16] Pech O, Gossner L, Manner H et al. Prospective evaluation of the macroscopic types and location of early Barrett's neoplasia in 380 lesions. Endoscopy 2007; 39: 588–593

[17] Thomas T, Gilbert D, Kaye PV et al. High-resolution endoscopy and endoscopic ultrasound for evaluation of early neoplasia in Barrett's esophagus. Surg Endosc 2010; 24: 1110–1116

[18] Kandiah K, Chedgy FJQ, Subramaniam S et al. 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). Gut 2018; 67: 2085–2091

[19] Coletta M, Sami SS, Nachiappan A et al. Acetic acid chromoendoscopy for the diagnosis of early neoplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. Gastrointest Endosc 2016; 83: 57–67.e51

[20] Sharma P, Bergman JJ, Goda K et al. Development and validation of a classification system to identify high-grade dysplasia and esophageal adenocarcinoma in Barrett's esophagus using narrow-band imaging. Gastroenterology 2016; 150: 591–598

[21] Nogales O, Caballero-Marcos A, Clemente-Sanchez A et al. Usefulness of non-magnifying narrow band imaging in EVIS EXERA III video systems and high-definition endoscopes to diagnose dysplasia in Barrett's esophagus using the Barrett International NBI Group (BING) classification. Dig Dis Sci 2017; 62: 2840–2846

[22] Muto M, Yao K, Kaise M et al. Magnifying endoscopy simple diagnostic algorithm for early gastric cancer (MESDA-G). Dig Endosc 2016; 28: 379–393

[23] Uchita K, Yao K, Uedo N et al. Highest power magnification with narrow-band imaging is useful for improving diagnostic performance for endoscopic delineation of early gastric cancers. BMC Gastroenterol 2015; 15: 155

[24] Makazu M, Hirasawa K, Sato C et al. Histological verification of the usefulness of magnifying endoscopy with narrow-band imaging for horizontal margin diagnosis of differentiated-type early gastric cancers. Gastric Cancer 2018; 21: 258–266

[25] Horii Y, Dohi O, Naito Y et al. Efficacy of magnifying narrow band imaging for delineating horizontal margins of early gastric cancer. Digestion 2019; 100: 93–99

[26] Nakayoshi T, Tajiri H, Matsuda K et al. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology (including video). Endoscopy 2004; 36: 1080–1084

[27] Ok KS, Kim GH, Park doY et al. Magnifying endoscopy with narrow band imaging of early gastric cancer: Correlation with histopathology and mucin phenotype. Gut Liver 2016; 10: 532–541

[28] Yagi K, Saka A, Nozawa Y et al. Prediction of submucosal gastric cancer by narrow-band imaging magnifying endoscopy. Dig Liver Dis 2014; 46: 187–190

[29] Kikuchi D, Iizuka T, Hoteya S et al. Usefulness of magnifying endoscopy with narrow-band imaging for determining tumor invasion depth in early gastric cancer. Gastroenterol Res Pract 2013; 2013: 217695

[30] Kobara H, Mori H, Fujihara S et al. Prediction of invasion depth for submucosal differentiated gastric cancer by magnifying endoscopy with narrow-band imaging. Oncol Rep 2012; 28: 841–847

[31] Kakushima N, Yoshida M, Yamaguchi Y et al. Magnified endoscopy with narrow-band imaging for the differential diagnosis of superficial non-ampullary duodenal epithelial tumors. Scand J Gastroenterol 2019; 54: 128–134

[32] Takahashi T, Ando T, Kabeshima Y et al. Borderline cases between benignancy and malignancy of the duodenum diagnosed successfully by endoscopic submucosal dissection. Scand J Gastroenterol 2009; 44: 1377–1383

[33] Kobayashi K, Tanaka S, Murakami Y et al. Predictors of invasive cancer of large laterally spreading colorectal tumors: A multicenter study in Japan. JGH Open 2020; 4: 83–89

[34] Bogie RMM, Veldman MHJ, Snijders L et al. Endoscopic subtypes of colorectal laterally spreading tumors (LSTs) and the risk of submucosal invasion: a meta-analysis. Endoscopy 2018; 50: 263–282

[35] Tanaka S, Kashida H, Saito Y et al. Japan Gastroenterological Endoscopy Society guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. Dig Endosc 2020; 32: 219–239

[36] Hayashi N, Tanaka S, Hewett DG et al. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. Gastrointest Endosc 2013; 78: 625–632

[37] Sumimoto K, Tanaka S, Shigita K et al. Clinical impact and characteristics of the narrow-band imaging magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. Gastrointest Endosc 2017; 85: 816–821

[38] Vosko S, Shahidi N, Sidhu M et al. Optical evaluation for predicting cancer in large nonpedunculated colorectal polyps is accurate for flat lesions. Clin Gastroenterol Hepatol 2021: doi:10.1016/j.cgh.2021.05.017

[39] Burgess NG, Hourigan LF, Zanati SA et al. Risk stratification for covert invasive cancer among patients referred for colonic endoscopic mucosal resection: A large multicenter cohort. Gastroenterology 2017; 153: 732–742 e731

[40] Bisschops R, East JE, Hassan C et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2019. Endoscopy 2019; 51: 1155–1179

[41] Luo LN, He LJ, Gao XY et al. Endoscopic ultrasound for preoperative esophageal squamous cell carcinoma: A meta-analysis. PLoS One 2016; 11: e0158373

[42] Choi J, Chung H, Lee A et al. Role of endoscopic ultrasound in selecting superficial esophageal cancers for endoscopic resection. Ann Thorac Surg 2020; 111: 1689–1695

[43] Tao Z, Yan C, Zhao H et al. Comparison of endoscopic ultrasonography and magnifying endoscopy for assessment of the invasion depth of shallow gastrointestinal neoplasms: a systematic review and meta-analysis. Surg Endosc 2017; 31: 4923–4933

[44] Mizumoto T, Hiyama T, Oka S et al. Diagnosis of superficial esophageal squamous cell carcinoma invasion depth before endoscopic submucosal dissection. Dis Esophagus 2018; 31: doi:10.1093/dote/dox142

[45] Guo J, Wang Z, Qin J et al. A prospective analysis of the diagnostic accuracy of 3 T MRI, CT and endoscopic ultrasound for preoperative T staging of potentially resectable esophageal cancer. Cancer Imaging 2020; 20: 64

[46] Qu J, Zhang H, Wang Z et al. Comparison between free-breathing radial VIBE on 3-T MRI and endoscopic ultrasound for preoperative T staging of resectable oesophageal cancer, with histopathological correlation. Eur Radiol 2018; 28: 780–787

[47] Nakajima M, Muroi H, Yokoyama H et al. (18)-F-Fluorodeoxyglucose positron emission tomography can be used to determine the indication for endoscopic resection of superficial esophageal cancer. Cancer Med 2018; 7: 3604–3610

[48] Toriyama K, Tajika M, Tanaka T et al. Clinical relevance of fluorodeoxyglucose positron emission tomography/computed tomography and magnifying endoscopy with narrow band imaging in decision-making regarding the treatment strategy for esophageal squamous cell carcinoma. World J Gastroenterol 2019; 25: 6767–6780

[49] Ishihara R, Goda K, Oyama T. Endoscopic diagnosis and treatment of esophageal adenocarcinoma: Introduction of Japan Esophageal Society classification of Barrett's esophagus. J Gastroenterol 2019; 54: 1–9

[50] Bulsiewicz WJ, Dellon ES, Rogers AJ et al. The impact of endoscopic ultrasound findings on clinical decision making in Barrett's esophagus with high-grade dysplasia or early esophageal adenocarcinoma. Dis Esophagus 2014; 27: 409–417

[51] Thota PN, Sada A, Sanaka MR et al. Correlation between endoscopic forceps biopsies and endoscopic mucosal resection with endoscopic ultrasound in patients with Barrett's esophagus with high-grade dysplasia and early cancer. Surg Endosc 2017; 31: 1336–1341

[52] Fairweather M, Jajoo K, Sainani N et al. Accuracy of EUS and CT imaging in preoperative gastric cancer staging. J Surg Oncol 2015; 111: 1016–1020

[53] Chung HW, Kim JH, Sung IK et al. FDG PET/CT to predict the curability of endoscopic resection for early gastric cancer. J Cancer Res Clin Oncol 2019; 145: 759–764

[54] Shi D, Xi XX. Factors affecting the accuracy of endoscopic ultrasonography in the diagnosis of early gastric cancer invasion depth: a meta-analysis. Gastroenterol Res Pract 2019; 2019: 8241381

[55] Lee JY, Choi IJ, Kim CG et al. Therapeutic decision-making using endoscopic ultrasonography in endoscopic treatment of early gastric cancer. Gut Liver 2016; 10: 42–50

[56] Kuroki K, Oka S, Tanaka S et al. Clinical significance of endoscopic ultrasonography in diagnosing invasion depth of early gastric cancer prior to endoscopic submucosal dissection. Gastric Cancer 2020: doi:10.1007/s10120–020–01100–5

[57] Kim EH, Park JC, Song IJ et al. Prediction model for non-curative resection of endoscopic submucosal dissection in patients with early gastric cancer. Gastrointest Endosc 2017; 85: 976–983

[58] Libanio D, Dinis-Ribeiro M, Pimentel-Nunes P et al. Predicting outcomes of gastric endoscopic submucosal dissection using a Bayesian approach: a step for individualized risk assessment. Endosc Int Open 2017; 5: E563–E572

[59] Ma X, Zhang Q, Zhu S et al. Risk factors and prediction model for non-curative resection of early gastric cancer with endoscopic resection and the evaluation. Front Med (Lausanne) 2021; 8: 637875

[60] Yamada T, Shimura T, Ebi M et al. Subset analysis of a multicenter, randomized controlled trial to compare magnifying chromoendoscopy with endoscopic ultrasonography for stage diagnosis of early stage colorectal cancer. PLoS One 2015; 10: e0134942

[61] Chan BPH, Patel R, Mbuagbaw L et al. EUS versus magnetic resonance imaging in staging rectal adenocarcinoma: a diagnostic test accuracy meta-analysis. Gastrointest Endosc 2019; 90: 196–203. e191

[62] Gao Y, Li J, Ma X et al. 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: 225–234

[63] Li XT, Sun YS, Tang L et al. Evaluating local lymph node metastasis with magnetic resonance imaging, endoluminal ultrasound and computed tomography in rectal cancer: a meta-analysis. Colorectal Dis 2015; 17: O129–135

[64] Li XT, Zhang XY, Sun YS et al. Evaluating rectal tumor staging with magnetic resonance imaging, computed tomography, and endoluminal ultrasound: A meta-analysis. Medicine (Baltimore) 2016; 95: e5333

[65] Nagami Y, Ominami M, Shiba M et al. The five-year survival rate after endoscopic submucosal dissection for superficial esophageal squamous cell neoplasia. Dig Liver Dis 2017; 49: 427–433

[66] Nishizawa T, Suzuki H. Long-term outcomes of endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. Cancers (Basel) 2020; 12: doi:10.3390/cancers12102849

[67] Oda I, Shimizu Y, Yoshio T et al. Long-term outcome of endoscopic resection for intramucosal esophageal squamous cell cancer: a secondary analysis of the Japan Esophageal Cohort study. Endoscopy 2020; 52: 967–975

[68] Ishihara R, Arima M, Iizuka T et al. Endoscopic submucosal dissection/endoscopic mucosal resection guidelines for esophageal cancer. Dig Endosc 2020; 32: 452–493

[69] Matsueda K, Matsuura N, Kanesaka T et al. Validity of endoscopic resection for clinically diagnosed T1a-MM/T1b-SM1 N0 M0 esophageal squamous cell carcinoma. Esophagus 2021: doi:10.1007/s10388–021–00814–4

[70] Probst A, Aust D, Markl B et al. Early esophageal cancer in Europe: endoscopic treatment by endoscopic submucosal dissection. Endoscopy 2015; 47: 113–121

[71] Berger A, Rahmi G, Perrod G et al. Long-term follow-up after endoscopic resection for superficial esophageal squamous cell carcinoma: a multicenter Western study. Endoscopy 2019; 51: 298–306

[72] Cao Y, Liao C, Tan A et al. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. Endoscopy 2009; 41: 751–757

[73] Guo HM, Zhang XQ, Chen M et al. Endoscopic submucosal dissection vs endoscopic mucosal resection for superficial esophageal cancer. World J Gastroenterol 2014; 20: 5540–5547

[74] Zhang Y, Ding H, Chen T et al. Outcomes of endoscopic submucosal dissection vs esophagectomy for T1 esophageal squamous cell carcinoma in a real-world cohort. Clin Gastroenterol Hepatol 2019; 17: 73–81.e73

[75] Min YW, Lee H, Song BG et al. Comparison of endoscopic submucosal dissection and surgery for superficial esophageal squamous cell carcinoma: a propensity score-matched analysis. Gastrointest Endosc 2018; 88: 624–633

[76] An W, Liu MY, Zhang J et al. Endoscopic submucosal dissection versus esophagectomy for early esophageal squamous cell carcinoma with tumor invasion to different depths. Am J Cancer Res 2020; 10: 2977–2992

[77] Yeh JH, Huang RY, Lee CT et al. Long-term outcomes of endoscopic submucosal dissection and comparison to surgery for superficial esophageal squamous cancer: a systematic review and meta-analysis. Therap Adv Gastroenterol 2020; 13: 1756284820964316

[78] Kato H, Sato A, Fukuda H et al. A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group Study (JCOG9708). Jpn J Clin Oncol 2009; 39: 638–643

[79] Murakami Y, Takahashi I, Nishibuchi I et al. Long-term results of definitive concurrent chemoradiotherapy for patients with esophageal submucosal cancer (T1bN0M0). Int J Clin Oncol 2015; 20: 897–904

[80] Nakajo K, Yoda Y, Hori K et al. Technical feasibility of endoscopic submucosal dissection for local failure after chemoradiotherapy or radiotherapy for esophageal squamous cell carcinoma. Gastrointest Endosc 2018; 88: 637–646

[81] Abe S, Ishihara R, Takahashi H et al. Long-term outcomes of endoscopic resection and metachronous cancer after endoscopic resection for adenocarcinoma of the esophagogastric junction in Japan. Gastrointest Endosc 2019; 89: 1120–1128

[82] Phoa KN, Pouw RE, Bisschops R et al. Multimodality endoscopic eradication for neoplastic Barrett oesophagus: results of an European multicentre study (EURO-II). Gut 2016; 65: 555–562

[83] Yang D, Zou F, Xiong S et al. Endoscopic submucosal dissection for early Barrett's neoplasia: a meta-analysis. Gastrointest Endosc 2018; 87: 1383–1393

[84] Han C, Sun Y. Efficacy and safety of endoscopic submucosal dissection versus endoscopic mucosal resection for superficial esophageal carcinoma: a systematic review and meta-analysis. Dis Esophagus 2020: doi:10.1093/dote/doaa081

[85] Codipilly DC, Dhaliwal L, Oberoi M et al. Comparative outcomes of cap assisted endoscopic resection and endoscopic submucosal dissection in dysplastic Barrett's esophagus. Clin Gastroenterol Hepatol 2020: doi:10.1016/j.cgh.2020.11.017

[86] Subramaniam S, Kandiah K, Chedgy F et al. The safety and efficacy of radiofrequency ablation following endoscopic submucosal dissection for Barrett's neoplasia. Dis Esophagus 2018; 31: doi:10.1093/dote/dox133

[87] Terheggen G, Horn EM, Vieth M et al. A randomised trial of endoscopic submucosal dissection versus endoscopic mucosal resection for early Barrett's neoplasia. Gut 2017; 66: 783–793

[88] Coman RM, Gotoda T, Forsmark CE et al. Prospective evaluation of the clinical utility of endoscopic submucosal dissection (ESD) in patients with Barrett's esophagus: a Western center experience. Endosc Int Open 2016; 4: E715–721

[89] Subramaniam S, Chedgy F, Longcroft-Wheaton G et al. Complex early Barrett's neoplasia at 3 Western centers: European Barrett's Endoscopic Submucosal Dissection Trial (E-BEST). Gastrointest Endosc 2017; 86: 608–618

[90] Yang D, Coman RM, Kahaleh M et al. Endoscopic submucosal dissection for Barrett's early neoplasia: a multicenter study in the United States. Gastrointest Endosc 2017; 86: 600–607

[91] Chevaux JB, Piessevaux H, Jouret-Mourin A et al. Clinical outcome in patients treated with endoscopic submucosal dissection for superficial Barrett's neoplasia. Endoscopy 2015; 47: 103–112

[92] Barret M, Cao DT, Beuvon F et al. Endoscopic submucosal dissection for early Barrett's neoplasia. United European Gastroenterol J 2016; 4: 207–215

[93] Prasad GA, Wu TT, Wigle DA et al. Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus. Gastroenterology 2009; 137: 815–823

[94] Pech O, Bollschweiler E, Manner H et al. Comparison between endoscopic and surgical resection of mucosal esophageal adenocarcinoma in Barrett's esophagus at two high-volume centers. Ann Surg 2011; 254: 67–72

[95] Das A, Singh V, Fleischer DE et al. A comparison of endoscopic treatment and surgery in early esophageal cancer: an analysis of surveillance epidemiology and end results data. Am J Gastroenterol 2008; 103: 1340–1345

[96] Marino KA, Sullivan JL, Weksler B. Esophagectomy versus endoscopic resection for patients with early-stage esophageal adenocarcinoma: A National Cancer Database propensity-matched study. J Thorac Cardiovasc Surg 2018; 155: 2211–2218.e1

[97] Raman V, Jawitz OK, Voigt SL et al. The effect of age on survival after endoscopic resection versus surgery for T1a esophageal cancer. J Thorac Cardiovasc Surg 2020; 160: 295–302.e293

[98] Smith I, Kahaleh M. Endoscopic versus surgical therapy for Barrett's esophagus neoplasia. Expert Rev Gastroenterol Hepatol 2015; 9: 31–35

[99] Reddy CA, Tavakkoli A, Chen VL et al. Long-term quality of life following endoscopic therapy compared to esophagectomy for neoplastic Barrett's esophagus. Dig Dis Sci 2020: doi:10.1007/s10620–020–06377–1

[100] Tao M, Zhou X, Hu M et al. Endoscopic submucosal dissection versus endoscopic mucosal resection for patients with early gastric cancer: a meta-analysis. BMJ Open 2019; 9: e025803

[101] Zhao Y, Wang C. Long-term clinical efficacy and perioperative safety of endoscopic submucosal dissection versus endoscopic mucosal resection for early gastric cancer: an updated meta-analysis. Biomed Res Int 2018; 2018: 3152346

[102] Suzuki H, Takizawa K, Hirasawa T et al. Short-term outcomes of multicenter prospective cohort study of gastric endoscopic resection: "Real-world evidence" in Japan. Dig Endosc 2019; 31: 30–39

[103] Tanabe S, Ishido K, Matsumoto T et al. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a multicenter collaborative study. Gastric Cancer 2017; 20: 45–52

[104] Gotoda T, Iwasaki M, Kusano C et al. Endoscopic resection of early gastric cancer treated by guideline and expanded National Cancer Centre criteria. Br J Surg 2010; 97: 868–871

[105] Abdelfatah MM, Barakat M, Ahmad D et al. Long-term outcomes of endoscopic submucosal dissection versus surgery in early gastric cancer: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2019; 31: 418–424

[106] Liu Q, Ding L, Qiu X et al. Updated evaluation of endoscopic submucosal dissection versus surgery for early gastric cancer: A systematic review and meta-analysis. Int J Surg 2020; 73: 28–41

[107] Gu L, Khadaroo PA, Chen L et al. Comparison of long-term outcomes of endoscopic submucosal dissection and surgery for early gastric cancer: a systematic review and meta-analysis. J Gastrointest Surg 2019; 23: 1493–1501

[108] Li H, Feng LQ, Bian YY et al. Comparison of endoscopic submucosal dissection with surgical gastrectomy for early gastric cancer: An updated meta-analysis. World J Gastrointest Oncol 2019; 11: 161–171

[109] Libânio D, Braga V, Ferraz S et al. Prospective comparative study of endoscopic submucosal dissection and gastrectomy for early neoplastic lesions including patients' perspectives. Endoscopy 2019; 51: 30–39

[110] Najmeh S, Cools-Lartigue J, Mueller C et al. Comparing laparoscopic to endoscopic resections for early gastric cancer in a high volume North American center. J Gastrointest Surg 2016; 20: 1547–1553

[111] Kim YI, Kim YA, Kim CG et al. Serial intermediate-term quality of life comparison after endoscopic submucosal dissection versus surgery in early gastric cancer patients. Surg Endosc 2018; 32: 2114–2122

[112] Kim SG, Ji SM, Lee NR et al. Quality of life after endoscopic submucosal dissection for early gastric cancer: a prospective multicenter cohort study. Gut Liver 2017; 11: 87–92

[113] Choi JH, Kim ES, Lee YJ et al. Comparison of quality of life and worry of cancer recurrence between endoscopic and surgical treatment for early gastric cancer. Gastrointest Endosc 2015; 82: 299–307

[114] Perez-Cuadrado-Robles E, Queneherve L, Margos W et al. Comparative analysis of ESD versus EMR in a large European series of non-ampullary superficial duodenal tumors. Endosc Int Open 2018; 6: E1008–E1014

[115] Zou J, Chai N, Linghu E et al. Clinical outcomes of endoscopic resection for non-ampullary duodenal laterally spreading tumors. Surg Endosc 2019; 33: 4048–4056

[116] Perez-Cuadrado-Robles E, Queneherve L, Margos W et al. ESD versus EMR in non-ampullary superficial duodenal tumors: a systematic review and meta-analysis. Endosc Int Open 2018; 6: E998–E1007

[117] Hoteya S, Yahagi N, Iizuka T et al. Endoscopic submucosal dissection for nonampullary large superficial adenocarcinoma/adenoma of the duodenum: feasibility and long-term outcomes. Endosc Int Open 2013; 1: 2–7

[118] Yahagi N, Kato M, Ochiai Y et al. Outcomes of endoscopic resection for superficial duodenal epithelial neoplasia. Gastrointest Endosc 2018; 88: 676–682

[119] Nonaka S, Oda I, Tada K et al. Clinical outcome of endoscopic resection for nonampullary duodenal tumors. Endoscopy 2015; 47: 129–135

[120] Inoue T, Uedo N, Yamashina T et al. Delayed perforation: a hazardous complication of endoscopic resection for non-ampullary duodenal neoplasm. Dig Endosc 2014; 26: 220–227

[121] Basford PJ, George R, Nixon E et al. Endoscopic resection of sporadic duodenal adenomas: comparison of endoscopic mucosal resection (EMR) with hybrid endoscopic submucosal dissection (ESD) techniques and the risks of late delayed bleeding. Surg Endosc 2014; 28: 1594–1600

[122] Hara Y, Goda K, Dobashi A et al. Short- and long-term outcomes of endoscopically treated superficial non-ampullary duodenal epithelial tumors. World J Gastroenterol 2019; 25: 707–718

[123] Klein A, Nayyar D, Bahin FF et al. Endoscopic mucosal resection of large and giant lateral spreading lesions of the duodenum: success, adverse events, and long-term outcomes. Gastrointest Endosc 2016; 84: 688–696

[124] Klein A, Ahlenstiel G, Tate DJ et al. Endoscopic resection of large duodenal and papillary lateral spreading lesions is clinically and economically advantageous compared with surgery. Endoscopy 2017; 49: 659–667

[125] Lupu A, Faller J, Oung B et al. Endoscopic submucosal dissection using countertraction with clips and rubber band allows safe en bloc resection of recurrent duodenal superficial lesions with intense fibrosis. Endoscopy 2020; 52: E398–E399

[126] Niimi K, Fujishiro M, Kodashima S et al. Long-term outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms. Endoscopy 2010; 42: 723–729

[127] Saito Y, Yamada M, So E et al. Colorectal endoscopic submucosal dissection: Technical advantages compared to endoscopic mucosal resection and minimally invasive surgery. Dig Endosc 2014; 26: (Suppl. 01): 52–61

[128] Russo P, Barbeiro S, Awadie H et al. Management of colorectal laterally spreading tumors: a systematic review and meta-analysis. Endosc Int Open 2019; 7: E239–E259

[129] Rahmi G, Hotayt B, Chaussade S et al. Endoscopic submucosal dissection for superficial rectal tumors: prospective evaluation in France. Endoscopy 2014; 46: 670–676

[130] Ronnow CF, Uedo N, Toth E et al. Endoscopic submucosal dissection of 301 large colorectal neoplasias: Outcome and learning curve from a specialized center in Europe. Endosc Int Open 2018; 6: E1340–E1348

[131] Fuccio L, Hassan C, Ponchon T et al. Clinical outcomes after endoscopic submucosal dissection for colorectal neoplasia: A systematic review and meta-analysis. Gastrointest Endosc 2017; 86: 74–86.e17

[132] De Ceglie A, Hassan C, Mangiavillano B et al. Endoscopic mucosal resection and endoscopic submucosal dissection for colorectal lesions: A systematic review. Crit Rev Oncol Hematol 2016; 104: 138–155

[133] Fujiya M, Tanaka K, Dokoshi T et al. Efficacy and adverse events of EMR and endoscopic submucosal dissection for the treatment of colon neoplasms: a meta-analysis of studies comparing EMR and endoscopic submucosal dissection. Gastrointest Endosc 2015; 81: 583–595

[134] Arezzo A, Passera R, Marchese N et al. Systematic review and meta-analysis of endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal lesions. United European Gastroenterol J 2016; 4: 18–29

[135] Klein A, Tate DJ, Jayasekeran V et al. Thermal ablation of mucosal defect margins reduces adenoma recurrence after colonic endoscopic mucosal resection. Gastroenterology 2019; 156: 604–613 e603

[136] Sidhu M, Shahidi N, Gupta S et al. Outcomes of thermal ablation of the mucosal defect margin after endoscopic mucosal resection: A prospective, international, multicenter trial of 1000 large nonpedunculated colorectal polyps. Gastroenterology 2021; 161: 163–170 e163

[137] Fuccio L, Repici A, Hassan C et al. Why attempt en bloc resection of non-pedunculated colorectal adenomas? A systematic review of the prevalence of superficial submucosal invasive cancer after endoscopic submucosal dissection Gut 2018; 67: 1464–1474

[138] Bahin FF, Heitman SJ, Rasouli KN et al. Wide-field endoscopic mucosal resection versus endoscopic submucosal dissection for laterally spreading colorectal lesions: a cost-effectiveness analysis. Gut 2018; 67: 1965–1973

[139] Keswani RN, Law R, Ciolino JD et al. Adverse events after surgery for nonmalignant colon polyps are common and associated with increased length of stay and costs. Gastrointest Endosc 2016; 84: 296–303.e291

[140] Patel M, Haque M, Kohli D et al. Endoscopic resection reduces morbidity when compared to surgery in veterans with large and complex colorectal polyps. Surg Endosc 2020: doi:10.1007/s00464–020–07482-y

[141] Gamaleldin M, Benlice C, Delaney CP et al. Management of the colorectal polyp referred for resection: A case-matched comparison of advanced endoscopic surgery and laparoscopic colectomy. Surgery 2018; 163: 522–527

[142] Nakamura F, Saito Y, Haruyama S et al. Short-term prospective questionnaire study of early postoperative quality of life after colorectal endoscopic submucosal dissection. Dig Dis Sci 2017; 62: 3325–3335

[143] Nam MJ, Sohn DK, Hong CW et al. Cost comparison between endoscopic submucosal dissection and transanal endoscopic microsurgery for the treatment of rectal tumors. Ann Surg Treat Res 2015; 89: 202–207

[144] Yamashita K, Oka S, Tanaka S et al. Preceding endoscopic submucosal dissection for T1 colorectal carcinoma does not affect the prognosis of patients who underwent additional surgery: a large multicenter propensity score-matched analysis. J Gastroenterol 2019; 54: 897–906

[145] Lowe D, Saleem S, Arif MO et al. Role of endoscopic resection versus surgical resection in management of malignant colon polyps: A National Cancer Database analysis. J Gastrointest Surg 2020; 24: 177–187

[146] Yeh JH, Tseng CH, Huang RY et al. Long-term outcomes of primary endoscopic resection vs surgery for T1 colorectal cancer: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2020; 18: 2813–2823.e2815

[147] Inoue T, Koyama F, Kuge H et al. Short-term outcomes of endoscopic submucosal dissection versus laparoscopic surgery for colorectal neoplasms: An observational study. J Anus Rectum Colon 2018; 2: 97–102

[148] Moon JY, Kim GH, Kim JH et al. Clinicopathologic factors predicting lymph node metastasis in superficial esophageal squamous cell carcinoma. Scand J Gastroenterol 2014; 49: 589–594

[149] Sgourakis G, Gockel I, Lang H. Endoscopic and surgical resection of T1a/T1b esophageal neoplasms: a systematic review. World J Gastroenterol 2013; 19: 1424–1437

[150] Xu W, Liu XB, Li SB et al. Prediction of lymph node metastasis in superficial esophageal squamous cell carcinoma in Asia: a systematic review and meta-analysis. Dis Esophagus 2020: doi:10.1093/dote/doaa032

[151] Ye B, Zhang X, Su Y et al. The possibility of endoscopic treatment of cN0 submucosal esophageal cancer: results from a surgical cohort. Surg Endosc 2020: doi:10.1007/s00464–020–07420-y

[152] Zhang Y, Liu L, Wang Q et al. Endoscopic submucosal dissection with additional radiotherapy in the treatment of T1a esophageal squamous cell cancer: randomized controlled trial. Endoscopy 2020; 52: 1066–1074

[153] Hisano O, Nonoshita T, Hirata H et al. Additional radiotherapy following endoscopic submucosal dissection for T1a-MM/T1b-SM esophageal squamous cell carcinoma improves locoregional control. Radiat Oncol 2018; 13: 14

[154] Ikeda A, Hoshi N, Yoshizaki T et al. Endoscopic submucosal dissection (ESD) with additional therapy for superficial esophageal cancer with submucosal invasion. Intern Med 2015; 54: 2803–2813

[155] Kawaguchi G, Sasamoto R, Abe E et al. The effectiveness of endoscopic submucosal dissection followed by chemoradiotherapy for superficial esophageal cancer. Radiat Oncol 2015; 10: 31

[156] Suzuki G, Yamazaki H, Aibe N et al. Endoscopic submucosal dissection followed by chemoradiotherapy for superficial esophageal cancer: Choice of new approach. Radiat Oncol 2018; 13: 246

[157] Yoshimizu S, Yoshio T, Ishiyama A et al. Long-term outcomes of combined endoscopic resection and chemoradiotherapy for esophageal squamous cell carcinoma with submucosal invasion. Dig Liver Dis 2018; 50: 833–838

[158] Minashi K, Nihei K, Mizusawa J et al. Efficacy of endoscopic resection and selective chemoradiotherapy for stage I esophageal squamous cell carcinoma. Gastroenterology 2019; 157: 382–390.e383

[159] Kitagawa Y, Uno T, Oyama T et al. Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal Society: part 1. Esophagus 2019; 16: 1–24

[160] Koterazawa Y, Nakamura T, Oshikiri T et al. A comparison of the clinical outcomes of esophagectomy and chemoradiotherapy after noncurative endoscopic submucosal dissection for esophageal squamous cell carcinoma. Surg Today 2018; 48: 783–789

[161] Tsou YK, Lee CH, Le PH et al. Adjuvant therapy for pT1a-m3/pT1b esophageal squamous cell carcinoma after endoscopic resection: Esophagectomy or chemoradiotherapy? A critical review. Crit Rev Oncol Hematol 2020; 147: 102883

[162] Hirasawa K, Kokawa A, Oka H et al. Superficial adenocarcinoma of the esophagogastric junction: long-term results of endoscopic submucosal dissection. Gastrointest Endosc 2010; 72: 960–966

[163] Yoshinaga S, Gotoda T, Kusano C et al. Clinical impact of endoscopic submucosal dissection for superficial adenocarcinoma located at the esophagogastric junction. Gastrointest Endosc 2008; 67: 202–209

[164] Alvarez Herrero L, Pouw RE, van Vilsteren FG et al. Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: study based on endoscopic resection specimens. Endoscopy 2010; 42: 1030–1036

[165] Manner H, May A, Pech O et al. Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. Am J Gastroenterol 2008; 103: 2589–2597

[166] Manner H, Pech O, Heldmann Y et al. Efficacy, safety, and long-term results of endoscopic treatment for early stage adenocarcinoma of the esophagus with low-risk sm1 invasion. Clin Gastroenterol Hepatol 2013: quiz e645 11: 630–635

[167] Manner H, Pech O, Heldmann Y et al. The frequency of lymph node metastasis in early-stage adenocarcinoma of the esophagus with incipient submucosal invasion (pT1b sm1) depending on histological risk patterns. Surg Endosc 2015; 29: 1888–1896

[168] Manner H, Wetzka J, May A et al. Early-stage adenocarcinoma of the esophagus with mid to deep submucosal invasion (pT1b sm2–3): the frequency of lymph-node metastasis depends on macroscopic and histological risk patterns. Dis Esophagus 2017; 30: 1–11

[169] Benech N, O'Brien JM, Barret M et al. Endoscopic resection of Barrett's adenocarcinoma: Intramucosal and low-risk tumours are not associated with lymph node metastases. United European Gastroenterol J 2021; 9: 362–369

[170] Larghi A, Lightdale CJ, Ross AS et al. Long-term follow-up of complete Barrett's eradication endoscopic mucosal resection (CBE-EMR) for the treatment of high grade dysplasia and intramucosal carcinoma. Endoscopy 2007; 39: 1086–1091

[171] Fleischer DE, Overholt BF, Sharma VK et al. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. Endoscopy 2010; 42: 781–789

[172] Peters FP, Kara MA, Rosmolen WD et al. Endoscopic treatment of high-grade dysplasia and early stage cancer in Barrett's esophagus. Gastrointest Endosc 2005; 61: 506–514

[173] Sawas T, Alsawas M, Bazerbachi F et al. Persistent intestinal metaplasia after endoscopic eradication therapy of neoplastic Barrett's esophagus increases the risk of dysplasia recurrence: meta-analysis. Gastrointest Endosc 2019; 89: 913–925 e916

[174] Gotoda T, Yanagisawa A, Sasako M et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000; 3: 219–225

[175] Hirasawa T, Gotoda T, Miyata S et al. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. Gastric Cancer 2009; 12: 148–152

[176] Nakahara K, Tsuruta O, Tateishi H et al. Extended indication criteria for endoscopic mucosal resection of early gastric cancer with special reference to lymph node metastasis–examination by multivariate analysis. Kurume Med J 2004; 51: 9–14

[177] Abdelfatah MM, Barakat M, Othman MO et al. The incidence of lymph node metastasis in submucosal early gastric cancer according to the expanded criteria: a systematic review. Surg Endosc 2019; 33: 26–32

[178] Chu YN, Yu YN, Jing X et al. Feasibility of endoscopic treatment and predictors of lymph node metastasis in early gastric cancer. World J Gastroenterol 2019; 25: 5344–5355

[179] Lee SH, Choi CW, Kim SJ et al. Risk factors for lymph node metastasis in mucosal gastric cancer and re-evaluation of endoscopic submucosal dissection. Ann Surg Treat Res 2016; 91: 118–126

[180] Choi KK, Bae JM, Kim SM et al. The risk of lymph node metastases in 3951 surgically resected mucosal gastric cancers: implications for endoscopic resection. Gastrointest Endosc 2016; 83: 896–901

[181] Ma DW, Lee SJ, Kook MC et al. The suggestion of revised criteria for endoscopic resection of differentiated-type submucosal gastric cancer. Ann Surg Oncol 2020; 27: 795–801

[182] Choi JY, Park YS, Jung HY et al. Identifying predictors of lymph node metastasis after endoscopic resection in patients with minute submucosal cancer of the stomach. Surg Endosc 2015; 29: 1476–1483

[183] Kim TS, Min BH, Kim KM et al. Endoscopic submucosal dissection for papillary adenocarcinoma of the stomach: low curative resection rate but favorable long-term outcomes after curative resection. Gastric Cancer 2019; 22: 363–368

[184] Lee HJ, Kim GH, Park DY et al. Endoscopic submucosal dissection for papillary adenocarcinoma of the stomach: is it really safe? Gastric Cancer 2017; 20: 978–986

[185] Chen JN, Wang QW, Zhang QW et al. Poorly differentiated is more significant than signet ring cell component for lymph node metastasis in mixed-type early gastric cancer: a retrospective study from a large-volume hospital. Surg Endosc 2020: doi:10.1007/s00464–020–07532–5

[186] Seo HS, Lee GE, Kang MG et al. Mixed histology is a risk factor for lymph node metastasis in early gastric cancer. J Surg Res 2019; 236: 271–277

[187] Lee IS, Lee S, Park YS et al. Applicability of endoscopic submucosal dissection for undifferentiated early gastric cancer: Mixed histology of poorly differentiated adenocarcinoma and signet ring cell carcinoma is a worse predictive factor of nodal metastasis. Surg Oncol 2017; 26: 8–12

[188] Lee JH, Choi IJ, Han HS et al. Risk of lymph node metastasis in differentiated type mucosal early gastric cancer mixed with minor undifferentiated type histology. Ann Surg Oncol 2015; 22: 1813–1819

[189] Takizawa K, Ono H, Yamamoto Y et al. Incidence of lymph node metastasis in intramucosal gastric cancer measuring 30 mm or less, with ulceration; mixed, predominantly differentiated-type histology; and no lymphovascular invasion: a multicenter retrospective study. Gastric Cancer 2016; 19: 1144–1148

[190] Takizawa K, Hatta W, Gotoda T et al. Recurrence patterns and outcomes of salvage surgery in cases of non-curative endoscopic submucosal dissection without additional radical surgery for early gastric cancer. Digestion 2019; 99: 52–58

[191] Yamada S, Hatta W, Shimosegawa T et al. Different risk factors between early and late cancer recurrences in patients without additional surgery after noncurative endoscopic submucosal dissection for early gastric cancer. Gastrointest Endosc 2019; 89: 950–960

[192] Libanio D, Pimentel-Nunes P, Afonso LP et al. Long-term outcomes of gastric endoscopic submucosal dissection: Focus on metachronous and non-curative resection management. GE Port J Gastroenterol 2017; 24: 31–39

[193] Hatta W, Gotoda T, Oyama T et al. A scoring system to stratify curability after endoscopic submucosal dissection for early gastric cancer: "eCura system". Am J Gastroenterol 2017; 112: 874–881

[194] Hatta W, Gotoda T, Oyama T et al. Is the eCura system useful for selecting patients who require radical surgery after noncurative endoscopic submucosal dissection for early gastric cancer? A comparative study Gastric Cancer 2018; 21: 481–489

[195] Figueiredo PC, Pimentel-Nunes P, Libanio D et al. A systematic review and meta-analysis on outcomes after Rx or R1 endoscopic resection of superficial gastric cancer. Eur J Gastroenterol Hepatol 2015; 27: 1249–1258

[196] Jeon MY, Park JC, Hahn KY et al. Long-term outcomes after noncurative endoscopic resection of early gastric cancer: the optimal time for additional endoscopic treatment. Gastrointest Endosc 2018; 87: 1003–1013.e1002

[197] Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2020: doi:10.1007/s10120–020–01042-y

[198] Hirashita T, Ohta M, Tada K et al. Prognostic factors of non-ampullary duodenal adenocarcinoma. Jpn J Clin Oncol 2018; 48: 743–747

[199] Goda K, Kikuchi D, Yamamoto Y et al. Endoscopic diagnosis of superficial non-ampullary duodenal epithelial tumors in Japan: Multicenter case series. Dig Endosc 2014; 26: (Suppl. 02): 23–29

[200] Kuroki K, Sanomura Y, Oka S et al. Clinical outcomes of endoscopic resection for superficial non-ampullary duodenal tumors. Endosc Int Open 2020; 8: E354–E359

[201] Probst A, Freund S, Neuhaus L et al. Complication risk despite preventive endoscopic measures in patients undergoing endoscopic mucosal resection of large duodenal adenomas. Endoscopy 2020; 52: 847–855

[202] Choi JY, Jung SA, Shim KN et al. Meta-analysis of predictive clinicopathologic factors for lymph node metastasis in patients with early colorectal carcinoma. J Korean Med Sci 2015; 30: 398–406

[203] Bosch SL, Teerenstra S, de Wilt JH et al. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy 2013; 45: 827–834

[204] Ronnow CF, Arthursson V, Toth E et al. Lymphovascular infiltration, not depth of invasion, is the critical risk factor of metastases in early colorectal cancer: retrospective population-based cohort study on prospectively collected data, including validation. Ann Surg 2020: doi:10.1097/SLA.0000000000003854

[205] Kawachi H, Eishi Y, Ueno H et al. A three-tier classification system based on the depth of submucosal invasion and budding/sprouting can improve the treatment strategy for T1 colorectal cancer: a retrospective multicenter study. Mod Pathol 2015; 28: 872–879

[206] Han J, Hur H, Min BS et al. Predictive factors for lymph node metastasis in submucosal invasive colorectal carcinoma: a new proposal of depth of invasion for radical surgery. World J Surg 2018; 42: 2635–2641

[207] Ebbehoj AL, Jorgensen LN, Krarup PM et al. Histopathological risk factors for lymph node metastases in T1 colorectal cancer: meta-analysis. Br J Surg 2021: doi:10.1093/bjs/znab168

[208] Cubiella J, Gonzalez A, Almazan R et al. pT1 Colorectal cancer detected in a colorectal cancer mass screening program: treatment and factors associated with residual and extraluminal disease. Cancers (Basel) 2020; 12: doi:10.3390/cancers12092530

[209] Boenicke L, Fein M, Sailer M et al. The concurrence of histologically positive resection margins and sessile morphology is an important risk factor for lymph node metastasis after complete endoscopic removal of malignant colorectal polyps. Int J Colorectal Dis 2010; 25: 433–438

[210] Kim JY, Han SJ, Jung Y et al. The relationship between local recurrence and positive lateral margin after en bloc resection of colorectal neoplasm. Scand J Gastroenterol 2018; 53: 1541–1546

[211] Makazu M, Sakamoto T, So E et al. Relationship between indeterminate or positive lateral margin and local recurrence after endoscopic resection of colorectal polyps. Endosc Int Open 2015; 3: E252–257

[212] Yamada M, Saito Y, Takamaru H et al. Long-term clinical outcomes of endoscopic submucosal dissection for colorectal neoplasms in 423 cases: a retrospective study. Endoscopy 2017; 49: 233–242

[213] Backes Y, de Vos Tot Nederveen Cappel WH, van Bergeijk J et al. Risk for incomplete resection after macroscopic radical endoscopic resection of T1 colorectal cancer: A multicenter cohort study. Am J Gastroenterol 2017; 112: 785–796

[214] Chen K, Cao G, Chen B et al. Laparoscopic versus open surgery for rectal cancer: A meta-analysis of classic randomized controlled trials and high-quality nonrandomized Studies in the last 5 years. Int J Surg 2017; 39: 1–10

[215] Wu Q, Wei M, Ye Z et al. Laparoscopic colectomy versus open colectomy for treatment of transverse colon cancer: A systematic review and meta-analysis. J Laparoendosc Adv Surg Tech A 2017; 27: 1038–1050

[216] Jeong JU, Nam TK, Kim HR et al. Adjuvant chemoradiotherapy instead of revision radical resection after local excision for high-risk early rectal cancer. Radiat Oncol 2016; 11: 114

[217] Sasaki T, Ito Y, Ohue M et al. Postoperative chemoradiotherapy after local resection for high-risk T1 to T2 low rectal cancer: Results of a single-arm, multi-institutional, phase II clinical trial. Dis Colon Rectum 2017; 60: 914–921

[218] Barbeiro S, Libanio D, Castro R et al. Narrow-band imaging: Clinical application in gastrointestinal endoscopy. GE Port J Gastroenterol 2018; 26: 40–53

[219] Kim GH, Min YW, Lee H et al. Risk factors of metachronous recurrence after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. PLoS One 2020; 15: e0238113

[220] Sawada G, Niida A, Uchi R et al. Genomic landscape of esophageal squamous cell carcinoma in a Japanese population. Gastroenterology 2016; 150: 1171–1182

[221] Uno K, Koike T, Kusaka G et al. Risk of metachronous recurrence after endoscopic submucosal dissection of esophageal squamous cell carcinoma. Dis Esophagus 2017; 30: 1–8

[222] Urabe Y, Kagemoto K, Nakamura K et al. Construction of a risk model for the development of metachronous squamous cell carcinoma after endoscopic resection of esopahageal squamous cell carcinoma. Esophagus 2019; 16: 141–146

[223] Fukuda H, Ishihara R, Shimamoto Y et al. Effect of horizontal margin status and risk of local recurrence after endoscopic submucosal dissection for superficial esophageal cancer. JGH Open 2020; 4: 160–165

[224] Cotton CC, Haidry R, Thrift AP et al. Development of evidence-based surveillance intervals after radiofrequency ablation of Barrett's esophagus. Gastroenterology 2018; 155: 316–326.e316

[225] Brito-Goncalves G, Libanio D, Marcos P et al. Clinicopathologic characteristics of patients with gastric superficial neoplasia and risk factors for multiple lesions after endoscopic submucosal dissection in a Western country. GE Port J Gastroenterol 2020; 27: 76–89

[226] Okada K, Suzuki S, Naito S et al. Incidence of metachronous gastric cancer in patients whose primary gastric neoplasms were discovered after Helicobacter pylori eradication. Gastrointest Endosc 2019; 89: 1152–1159.e1151

[227] Park WY, Lee SJ, Kim YK et al. Occurrence of metachronous or synchronous lesions after endoscopic treatment of gastric epithelia dysplasia- impact of histologic features of background mucosa. Pathol Res Pract 2018; 214: 95–99

[228] Yang HJ, Kim SG, Lim JH et al. Novel risk stratification for metachronous recurrence after curative endoscopic submucosal dissection for early gastric cancer. Gastrointest Endosc 2018; 87: 419–428.e413

[229] Yang HJ, Kim SG, Lim JH et al. Surveillance strategy according to age after endoscopic resection of early gastric cancer. Surg Endosc 2018; 32: 846–854

[230] Moon HS, Yun GY, Kim JS et al. Risk factors for metachronous gastric carcinoma development after endoscopic resection of gastric dysplasia: Retrospective, single-center study. World J Gastroenterol 2017; 23: 4407–4415

[231] Abe S, Oda I, Suzuki H et al. Long-term surveillance and treatment outcomes of metachronous gastric cancer occurring after curative endoscopic submucosal dissection. Endoscopy 2015; 47: 1113–1118

[232] Pimentel-Nunes P, Libanio D, Marcos-Pinto R et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy 2019; 51: 365–388

[233] Hahn KY, Park JC, Kim EH et al. Incidence and impact of scheduled endoscopic surveillance on recurrence after curative endoscopic resection for early gastric cancer. Gastrointest Endosc 2016; 84: 628–638.e621

[234] Oka S, Tanaka S, Saito Y et al. Local recurrence after endoscopic resection for large colorectal neoplasia: a multicenter prospective study in Japan. Am J Gastroenterol 2015; 110: 697–707

[235] Yoshii S, Nojima M, Nosho K et al. Factors associated with risk for colorectal cancer recurrence after endoscopic resection of T1 tumors. Clin Gastroenterol Hepatol 2014; 12: 292–302.e293

[236] Green RJ, Metlay JP, Propert K et al. Surveillance for second primary colorectal cancer after adjuvant chemotherapy: an analysis of Intergroup 0089. Ann Intern Med 2002; 136: 261–269

[237] Hassan C, Pickhardt PJ, Zullo A et al. Cost-effectiveness of early colonoscopy surveillance after cancer resection. Dig Liver Dis 2009; 41: 881–885

[238] Hassan C, Antonelli G, Dumonceau JM et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2020. Endoscopy 2020; 52: 687–700

[239] Benson AB, Venook AP, Al-Hawary MM et al. NCCN guidelines insights: Colon Cancer, version 2, 2018. J Natl Compr Canc Netw 2018; 16: 359–369

[240] Shaukat A, Kaltenbach T, Dominitz JA et al. Endoscopic recognition and management strategies for malignant colorectal polyps: Recommendations of the US Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2020; 115: 1751–1767

[241] Butte JM, Tang P, Gonen M et al. Rate of residual disease after complete endoscopic resection of malignant colonic polyp. Dis Colon Rectum 2012; 55: 122–127

Thieme

Supplementary material

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 prophilatic 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);

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 (?)

<u>According to these questions the following scenarios should be defined (per organ):</u>

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%

<u>Surveillance after low-risk resection:</u>

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

<u>Surveillance/management after high-risk resection:</u>

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?

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 2 mm 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 (≤500 µm) 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 (≤500 µm). 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 (≤500 µm). 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 (≤1000 µm). 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, 25 cm from incisors, IIc, ulc–, 15 mm

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

Colon, rectum, granular LST, 30 mm

ESD

Supplementary material

- 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 reproducable 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 !

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

- **References**

- **1** Atkins D, Best D, Eccles M et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004; 328: 1490
- **2** Dumonceau JM, Hassan C, Riphaus A et al. European Society of Gastrointestinal Endoscopy (ESGE) Guideline Development Policy. Endoscopy 2012; 44: 626-629 Epub 2012 Feb 27 DOI: 10.1055/s-0031-1291747.
- **3** Higuchi K, Koizumi W, Tanabe S et al. Current management of esophageal squamous-cell carcinoma in Japan and other countries. Gastrointest Cancer Res 2009; 3: 153-161
- **4** [Anonymous]. Japanese Classification of Esophageal Cancer, 10th edition: part I. Esophagus. 2009. 6 1-25
- **5** Tajima Y, Nakanishi Y, Tachimori Y et al. Significance of involvement by squamous cell carcinoma of the ducts of esophageal submucosal glands. Analysis of 201 surgically resected superficial squamous cell carcinomas. Cancer 2000; 89: 248-254
- **6** Natsugoe S, Baba M, Yoshinaka H et al. Mucosal squamous cell carcinoma of the esophagus: a clinicopathologic study of 30 cases. Oncology 1998; 55: 235-241
- **7** Bollschweiler E, Baldus SE, Schroder W et al. High rate of lymph-node metastasis in submucosal esophageal squamous-cell carcinomas and adenocarcinomas. Endoscopy 2006; 38: 149-156
- **8** Kanzaki H, Ishihara R, Ohta T et al. Randomized study of two endo-knives for endoscopic submucosal dissection of esophageal cancer. Am J Gastroenterol 2013; 108: 1293-1298
- **9** Toyonaga T, Man-i M, East JE et al. 1,635 Endoscopic submucosal dissection cases in the esophagus, stomach, and colorectum: complication rates and long-term outcomes. Surg Endosc 2013; 27: 1000-1008

Supplementary material

- **10** Kawahara Y, Hori K, Takenaka R et al. Endoscopic submucosal dissection of esophageal cancer using the Mucosectom2 device: a feasibility study. Endoscopy 2013; 45: 869-875
- **11** Fujinami H, Hosokawa A, Ogawa K et al. Endoscopic submucosal dissection for superficial esophageal neoplasms using the stag beetle knife. Dis Esophagus 2014; 27: 50-54
- **12** Yamashina T, Ishihara R, Uedo N et al. Safety and curative ability of endoscopic submucosal dissection for superficial esophageal cancers at least 50 mm in diameter. Dig Endosc 2012; 24: 220-225
- **13** Yamashita T, Zeniya A, Ishii H et al. Endoscopic mucosal resection using a cap-fitted panendoscope and endoscopic submucosal dissection as optimal endoscopic procedures for superficial esophageal carcinoma. Surg Endosc 2011; 25: 2541-2546
- **14** Mochizuki Y, Saito Y, Tsujikawa T et al. Combination of endoscopic submucosal dissection and chemoradiation therapy for superficial esophageal squamous cell carcinoma with submucosal invasion. Exp Ther Med 2011; 2: 1065-1068
- **15** Takahashi H, Arimura Y, Masao H et al. Endoscopic submucosal dissection is superior to conventional endoscopic resection as a curative treatment for early squamous cell carcinoma of the esophagus (with video). Gastrointest Endosc 2010; 72: 255-264 (264.e 251–252)
- **16** Repici A, Hassan C, Carlino A et al. Endoscopic submucosal dissection in patients with early esophageal squamous cell carcinoma: results from a prospective Western series. Gastrointest Endosc 2010; 71: 715-721
- **17** Chaves DM, Maluf Filho F, de Moura EG et al. Endoscopic submucosal dissection for the treatment of early esophageal and gastric cancer – initial experience of a western center. Clinics (Sao Paulo) 2010; 65: 377-382
- **18** Teoh AY, Chiu PW, Yu Ngo DK et al. Outcomes of endoscopic submucosal dissection versus endoscopic mucosal resection in management of superficial squamous esophageal neoplasms outside Japan. J Clin Gastroenterol 2010; 44: e190-e194
- **19** Nonaka K, Arai S, Ishikawa K et al. Short term results of endoscopic submucosal dissection in superficial esophageal squamous cell neoplasms. World J Gastrointest Endosc 2010; 2: 69-74
- **20** Ono S, Fujishiro M, Niimi K et al. Long-term outcomes of endoscopic submucosal dissection for superficial esophageal squamous cell neoplasms. Gastrointest Endosc 2009; 70: 860-866
- **21** Fujishiro M, Yahagi N, Kakushima N et al. Endoscopic submucosal dissection of esophageal squamous cell neoplasms. Clin Gastroenterol Hepatol 2006; 4: 688-694
- **22** Oyama T, Tomori A, Hotta K et al. Endoscopic submucosal dissection of early esophageal cancer. Clin Gastroenterol Hepatol 2005; 3: 67-70
- **23** Hoteya S, Matsui A, Iizuka T et al. Comparison of the clinicopathological characteristics and results of endoscopic submucosal dissection for esophagogastric junction and non-junctional cancers. Digestion 2013; 87: 29-33
- **24** Neuhaus H, Terheggen G, Rutz EM et al. Endoscopic submucosal dissection plus radiofrequency ablation of neoplastic Barrett's esophagus. Endoscopy 2012; 44: 1105-1113
- **25** Hirasawa K, Kokawa A, Oka H et al. Superficial adenocarcinoma of the esophagogastric junction: long-term results of endoscopic submucosal dissection. Gastrointest Endosc 2010; 72: 960-966

Supplementary material

- **26** Yoshinaga S, Gotoda T, Kusano C et al. Clinical impact of endoscopic submucosal dissection for superficial adenocarcinoma located at the esophagogastric junction. Gastrointest Endosc 2008; 67: 202-209
- **27** Kakushima N, Yahagi N, Fujishiro M et al. Efficacy and safety of endoscopic submucosal dissection for tumors of the esophagogastric junction. Endoscopy 2006; 38: 170-174
- **28** Chevaux JB, Piessevaux H, Jouret-Mourin A et al. Clinical outcome in patients treated with endoscopic submucosal dissection for superficial Barrett's neoplasia. Endoscopy 2015; 47: 103-112
- **29** Higuchi K, Tanabe S, Azuma M et al. A phase II study of endoscopic submucosal dissection for superficial esophageal neoplasms (KDOG 0901). Gastrointest Endosc 2013; 78: 704-710
- **30** Arantes V, Albuquerque W, Freitas Dias CA et al. Standardized endoscopic submucosal tunnel dissection for management of early esophageal tumors (with video). Gastrointest Endosc 2013; 78: 946-952
- **31** Isomoto H, Yamaguchi N, Minami H et al. Management of complications associated with endoscopic submucosal dissection/endoscopic mucosal resection for esophageal cancer. Dig Endosc 2013; 25: 29-38
- **32** Sato H, Inoue H, Kobayashi Y et al. Control of severe strictures after circumferential endoscopic submucosal dissection for esophageal carcinoma: oral steroid therapy with balloon dilation or balloon dilation alone. Gastrointest Endosc 2013; 78: 250-257
- **33** Chaves DM, Moura EG, Milhomem D et al. Initial experience of endoscopic submucosal dissection in Brazil to treat early gastric and esophagheal cancer: a multi-institutional analysis. Arq Gastroenterol 2013; 50: 148-152
- **34** Lee CT, Chang CY, Tai CM et al. Endoscopic submucosal dissection for early esophageal neoplasia: a single center experience in South Taiwan. J Formos Med Assoc 2012; 111: 132-139
- **35** Kikuchi OMH, Matsueda K, Yamamoto H. Endoscopic submucosal dissection for treatment of patients aged 75 years and over with esophageal cancer. ISRN Gastroenterol 2012; DOI: 10.5402/2012/671324.
- **36** Ishii N, Uchida S, Itoh T et al. Endoscopic submucosal dissection with a combination of small-caliber-tip transparent hood and flex knife for superficial esophageal neoplasia. Is it safe for elderly patients? . Surg Endosc 2010; 24: 2110-2119
- **37** Ishihara R, Iishi H, Takeuchi Y et al. Local recurrence of large squamous-cell carcinoma of the esophagus after endoscopic resection. Gastrointest Endosc 2008; 67: 799-804
- **38** Probst A, Aust D, Markl B et al. Early esophageal cancer in Europe: endoscopic treatment by endoscopic submucosal dissection. Endoscopy 2015; 47: 113-121
- **39** Linghu E, Feng X, Wang X et al. Endoscopic submucosal tunnel dissection for large esophageal neoplastic lesions. Endoscopy 2013; 45: 60-62
- **40** Farhat S, Chaussade S, Ponchon T et al. Endoscopic submucosal dissection in a European setting. A multi-institutional report of a technique in development. Endoscopy 2011; 43: 664-670
- **41** Coda S, Trentino P, Antonellis F et al. A Western single-center experience with endoscopic submucosal dissection for early gastrointestinal cancers. Gastric Cancer 2010; 13: 258-263

Supplementary material

- **42** Motohashi O, Nishimura K, Nakayama N et al. Endoscopic submucosal dissection (two-point fixed ESD) for early esophageal cancer. Dig Endosc 2009; 21: 176-179
- **43** Li QL, Yao LQ, Zhou PH et al. Submucosal tumors of the esophagogastric junction originating from the muscularis propria layer: a large study of endoscopic submucosal dissection (with video). Gastrointest Endosc 2012; 75: 1153-1158
- **44** Gong W, Xiong Y, Zhi F et al. Preliminary experience of endoscopic submucosal tunnel dissection for upper gastrointestinal submucosal tumors. Endoscopy 2012; 44: 231-235
- **45** Shi Q, Zhong YS, Yao LQ et al. Endoscopic submucosal dissection for treatment of esophageal submucosal tumors originating from the muscularis propria layer. Gastrointest Endosc 2011; 74: 1194-1200
- **46** Katada C, Muto M, Momma K et al. Clinical outcome after endoscopic mucosal resection for esophageal squamous cell carcinoma invading the muscularis mucosae – a multicenter retrospective cohort study. Endoscopy 2007; 39: 779-783
- **47** Makuuchi H. Endoscopic mucosal resection for mucosal cancer in the esophagus. Gastrointest Endosc Clin N Am 2001; 11: 445-458
- **48** McCulloch P, Ward J, Tekkis PP. Mortality and morbidity in gastro-oesophageal cancer surgery: initial results of ASCOT multicentre prospective cohort study. BMJ 2003; 327: 1192-1197
- **49** Karl RC, Schreiber R, Boulware D et al. Factors affecting morbidity, mortality, and survival in patients undergoing Ivor Lewis esophagogastrectomy. Ann Surg 2000; 231: 635-643
- **50** Shitara K, Muro K. Chemoradiotherapy for treatment of esophageal cancer in Japan: current status and perspectives. Gastrointest Cancer Res 2009; 3: 66-72
- **51** Shimizu Y, Kato M, Yamamoto J et al. EMR combined with chemoradiotherapy: a novel treatment for superficial esophageal squamous-cell carcinoma. Gastrointest Endosc 2004; 59: 199-204
- **52** Ciocirlan M, Lapalus MG, Hervieu V et al. Endoscopic mucosal resection for squamous premalignant and early malignant lesions of the esophagus. Endoscopy 2007; 39: 24-29
- **53** Kodama M, Kakegawa T. Treatment of superficial cancer of the esophagus: a summary of responses to a questionnaire on superficial cancer of the esophagus in Japan. Surgery 1998; 123: 432-439
- **54** Katada C, Muto M, Manabe T et al. Local recurrence of squamous-cell carcinoma of the esophagus after EMR. Gastrointest Endosc 2005; 61: 219-225
- **55** Cao Y, Liao C, Tan A et al. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. Endoscopy 2009; 41: 751-757
- **56** Alvarez Herrero L, Pouw RE, van Vilsteren FG et al. Safety and efficacy of multiband mucosectomy in 1060 resections in Barrett's esophagus. Endoscopy 2011; 43: 177-183
- **57** Deprez PH, Bergman JJ, Meisner S et al. Current practice with endoscopic submucosal dissection in Europe: position statement from a panel of experts. Endoscopy 2010; 42: 853-858
- **58** Goda K, Singh R, Oda I et al. Current status of endoscopic diagnosis and treatment of superficial Barrett's adenocarcinoma in Asia-Pacific region. Dig Endosc 2013; 25: 146-150

Supplementary material

- **59** Komanduri S, Deprez PH, Atasoy A et al. Barrett's esophagus: treatments of adenocarcinomas I. Ann N Y Acad Sci 2011; 1232: 248-264
- **60** Liu L, Hofstetter WL, Rashid A et al. Significance of the depth of tumor invasion and lymph node metastasis in superficially invasive (T1) esophageal adenocarcinoma. Am J Surg Pathol 2005; 29: 1079-1085
- **61** Prasad GA, Wu TT, Wigle DA et al. Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus. Gastroenterology 2009; 137: 815-823
- **62** Alvarez Herrero L, Pouw RE, van Vilsteren FG et al. Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: study based on endoscopic resection specimens. Endoscopy 2010; 42: 1030-1036
- **63** Buskens CJ, Westerterp M, Lagarde SM et al. Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. Gastrointest Endosc 2004; 60: 703-710
- **64** Sepesi B, Watson TJ, Zhou D et al. Are endoscopic therapies appropriate for superficial submucosal esophageal adenocarcinoma? An analysis of esophagectomy specimens. J Am Coll Surg 2010; 210: 418-427
- **65** Stein HJ, Feith M, Bruecher BL et al. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. Ann Surg 2005; 242: 566-573 (discussion 573-565)
- **66** Westerterp M, Koppert LB, Buskens CJ et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch 2005; 446: 497-504
- **67** Abraham SC, Krasinskas AM, Correa AM et al. Duplication of the muscularis mucosae in Barrett esophagus: an underrecognized feature and its implication for staging of adenocarcinoma. Am J Surg Pathol 2007; 31: 1719-1725
- **68** Barbour AP, Jones M, Brown I et al. Risk stratification for early esophageal adenocarcinoma: analysis of lymphatic spread and prognostic factors. Ann Surg Oncol 2010; 17: 2494-2502
- **69** Dunbar KB, Spechler SJ. The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. Am J Gastroenterol quiz 863 2012; 107: 850-862
- **70** Pech O, May A, Manner H et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology 2014; 146: 652-660 (e651)
- **71** Peters FP, Brakenhoff KP, Curvers WL et al. Histologic evaluation of resection specimens obtained at 293 endoscopic resections in Barrett's esophagus. Gastrointest Endosc 2008; 67: 604-609
- **72** Pech O, Gossner L, Manner H et al. Prospective evaluation of the macroscopic types and location of early Barrett's neoplasia in 380 lesions. Endoscopy 2007; 39: 588-593
- **73** Tharavej C, Hagen JA, Peters JH et al. Predictive factors of coexisting cancer in Barrett's high-grade dysplasia. Surg Endosc 2006; 20: 439-443
- **74** Manner H, May A, Pech O et al. Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. Am J Gastroenterol 2008; 103: 2589-2597
- **75** Sgourakis G, Gockel I, Lang H. Endoscopic and surgical resection of T1a/T1b esophageal neoplasms: a systematic review. World J Gastroenterol 2013; 19: 1424-1437

Supplementary material

- **76** Pech O, Behrens A, May A et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut 2008; 57: 1200-1206
- **77** Larghi A, Waxman I. State of the art on endoscopic mucosal resection and endoscopic submucosal dissection. Gastrointest Endosc Clin N Am 2007; 17: 441-469
- **78** Ono S, Fujishiro M, Niimi K et al. Predictors of postoperative stricture after esophageal endoscopic submucosal dissection for superficial squamous cell neoplasms. Endoscopy 2009; 41: 661-665
- **79** Mizuta H, Nishimori I, Kuratani Y et al. Predictive factors for esophageal stenosis after endoscopic submucosal dissection for superficial esophageal cancer. Dis Esophagus 2009; 22: 626-631
- **80** Yamaguchi N, Isomoto H, Nakayama T et al. Usefulness of oral prednisolone in the treatment of esophageal stricture after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. Gastrointest Endosc 2011; 73: 1115-1121
- **81** Hashimoto S, Kobayashi M, Takeuchi M et al. The efficacy of endoscopic triamcinolone injection for the prevention of esophageal stricture after endoscopic submucosal dissection. Gastrointest Endosc 2011; 74: 1389-1393
- **82** Deprez PH. Esophageal strictures after extensive endoscopic resection: hope for a better outcome?. Gastrointest Endosc 2013; 78: 258-259
- **83** Pech O, Bollschweiler E, Manner H et al. Comparison between endoscopic and surgical resection of mucosal esophageal adenocarcinoma in Barrett's esophagus at two high-volume centers. Ann Surg 2011; 254: 67-72
- **84** Das A, Singh V, Fleischer DE et al. A comparison of endoscopic treatment and surgery in early esophageal cancer: an analysis of surveillance epidemiology and end results data. Am J Gastroenterol 2008; 103: 1340-1345
- **85** Thomas T, Gilbert D, Kaye PV et al. High-resolution endoscopy and endoscopic ultrasound for evaluation of early neoplasia in Barrett's esophagus. Surg Endosc 2010; 24: 1110-1116
- **86** Anonymus. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 2005; 37: 570-578
- **87** Pohl J, May A, Rabenstein T et al. Comparison of computed virtual chromoendoscopy and conventional chromoendoscopy with acetic acid for detection of neoplasia in Barrett's esophagus. Endoscopy 2007; 39: 594-598
- **88** Longcroft-Wheaton G, Duku M, Mead R et al. Acetic acid spray is an effective tool for the endoscopic detection of neoplasia in patients with Barrett's esophagus. Clin Gastroenterol Hepatol 2010; 8: 843-847
- **89** Fortun PJ, Anagnostopoulos GK, Kaye P et al. Acetic acid-enhanced magnification endoscopy in the diagnosis of specialized intestinal metaplasia, dysplasia and early cancer in Barrett's oesophagus. Aliment Pharmacol Ther 2006; 23: 735-742
- **90** Inoue H, Rey JF, Lightdale C. Lugol chromoendoscopy for esophageal squamous cell cancer. Endoscopy 2001; 33: 75-79
- **91** Lee CT, Chang CY, Lee YC et al. Narrow-band imaging with magnifying endoscopy for the screening of esophageal cancer in patients with primary head and neck cancers. Endoscopy 2010; 42: 613-619
- **92** Takenaka R, Kawahara Y, Okada H et al. Narrow-band imaging provides reliable screening for esophageal malignancy in patients with head and neck cancers. Am J Gastroenterol 2009; 104: 2942-2948

Supplementary material

- **93** Mannath J, Subramanian V, Hawkey CJ et al. Narrow band imaging for characterization of high grade dysplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. Endoscopy 2010; 42: 351-359
- **94** Curvers WL, Bohmer CJ, Mallant-Hent RC et al. Mucosal morphology in Barrett's esophagus: interobserver agreement and role of narrow band imaging. Endoscopy 2008; 40: 799-805
- **95** Fitzgerald RC, di Pietro M, Ragunath K et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 2014; 63: 7-42
- **96** Lal N, Bhasin DK, Malik AK et al. Optimal number of biopsy specimens in the diagnosis of carcinoma of the oesophagus. Gut 1992; 33: 724-726
- **97** Lee IS, Park YS, Lee JH et al. Pathologic discordance of differentiation between endoscopic biopsy and postoperative specimen in mucosal gastric adenocarcinomas. Ann Surg Oncol 2013; 20: 4231-4237
- **98** Thosani N, Singh H, Kapadia A et al. Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: a systematic review and meta-analysis. Gastrointest Endosc 2012; 75: 242-253
- **99** Sgourakis G, Gockel I, Lyros O et al. Detection of lymph node metastases in esophageal cancer. Expert Rev Anticancer Ther 2011; 11: 601-612
- **100** May A, Gunter E, Roth F et al. Accuracy of staging in early oesophageal cancer using high resolution endoscopy and high resolution endosonography: a comparative, prospective, and blinded trial. Gut 2004; 53: 634-640
- **101** Larghi A, Lightdale CJ, Memeo L et al. EUS followed by EMR for staging of high-grade dysplasia and early cancer in Barrett's esophagus. Gastrointest Endosc 2005; 62: 16-23
- **102** Pech O, Gunter E, Dusemund F et al. Value of high-frequency miniprobes and conventional radial endoscopic ultrasound in the staging of early Barrett's carcinoma. Endoscopy 2010; 42: 98-103
- **103** Pech O, May A, Gunter E et al. The impact of endoscopic ultrasound and computed tomography on the TNM staging of early cancer in Barrett's esophagus. Am J Gastroenterol 2006; 101: 2223-2229
- **104** Pech O, Gunter E, Dusemund F et al. Accuracy of endoscopic ultrasound in preoperative staging of esophageal cancer: results from a referral center for early esophageal cancer. Endoscopy 2010; 42: 456-461
- **105** Rampado S, Bocus P, Battaglia G et al. Endoscopic ultrasound: accuracy in staging superficial carcinomas of the esophagus. Ann Thorac Surg 2008; 85: 251-256
- **106** Young PE, Gentry AB, Acosta RD et al. Endoscopic ultrasound does not accurately stage early adenocarcinoma or high-grade dysplasia of the esophagus. Clin Gastroenterol Hepatol 2010; 8: 1037-1041
- **107** Pouw RE, Heldoorn N, Alvarez Herrero L et al. Do we still need EUS in the workup of patients with early esophageal neoplasia? A retrospective analysis of 131 cases. Gastrointest Endosc 2011; 73: 662-668
- **108** Moriya H, Ohbu M, Kobayashi N et al. Lymphatic tumor emboli detected by D2–40 immunostaining can more accurately predict lymph-node metastasis. World J Surg 2011; 35: 2031-2037
- **109** Ishii N, Horiki N, Itoh T et al. Endoscopic submucosal dissection with a combination of small-caliber-tip transparent hood and flex knife is a safe and effective treatment for superficial esophageal neoplasias. Surg Endosc 2010; 24: 335-342

Supplementary material

- **110** Larghi A, Lightdale CJ, Ross AS et al. Long-term follow-up of complete Barrett's eradication endoscopic mucosal resection (CBE-EMR) for the treatment of high grade dysplasia and intramucosal carcinoma. Endoscopy 2007; 39: 1086-1091
- **111** Peters FP, Kara MA, Rosmolen WD et al. Endoscopic treatment of high-grade dysplasia and early stage cancer in Barrett's esophagus. Gastrointest Endosc 2005; 61: 506-514
- **112** Fleischer DE, Overholt BF, Sharma VK et al. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. Endoscopy 2010; 42: 781-789
- **113** Ell C, May A, Pech O et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointest Endosc 2007; 65: 3-10
- **114** Bennett C, Vakil N, Bergman J et al. Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi process. Gastroenterology 2012; 143: 336-346
- **115** Bedi AO, Kwon RS, Rubenstein JH et al. A survey of expert follow-up practices after successful endoscopic eradication therapy for Barrett's esophagus with high-grade dysplasia and intramucosal adenocarcinoma. Gastrointest Endosc 2013; 78: 696-701
- **116** Chung IK, Lee JH, Lee SH et al. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. Gastrointest Endosc 2009; 69: 1228-1235
- **117** Gotoda T, Jung HY. Endoscopic resection (endoscopic mucosal resection/endoscopic submucosal dissection) for early gastric cancer. Dig Endosc 2013; 25: 55-63
- **118** Lian J, Chen S, Zhang Y et al. A meta-analysis of endoscopic submucosal dissection and EMR for early gastric cancer. Gastrointest Endosc 2012; 76: 763-770
- **119** Park YM, Cho E, Kang HY et al. The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and metaanalysis. Surg Endosc 2011; 25: 2666-2677
- **120** Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011; 14: 113-123
- **121** Gotoda T, Iwasaki M, Kusano C et al. Endoscopic resection of early gastric cancer treated by guideline and expanded National Cancer Centre criteria. Br J Surg 2010; 97: 868-871
- **122** Gotoda T, Yanagisawa A, Sasako M et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000; 3: 219-225
- **123** Ahn JY, Jung HY, Choi KD et al. Endoscopic and oncologic outcomes after endoscopic resection for early gastric cancer: 1370 cases of absolute and extended indications. Gastrointest Endosc 2011; 74: 485-493
- **124** Park CH, Shin S, Park JC et al. Long-term outcome of early gastric cancer after endoscopic submucosal dissection: expanded indication is comparable to absolute indication. Dig Liver Dis 2013; 45: 651-656
- **125** Takekoshi T, Baba Y, Ota H et al. Endoscopic resection of early gastric carcinoma: results of a retrospective analysis of 308 cases. Endoscopy 1994; 26: 352-358

Supplementary material

- **126** Hiki Y, Shimao H, Mieno H et al. Modified treatment of early gastric cancer: evaluation of endoscopic treatment of early gastric cancers with respect to treatment indication groups. World J Surg 1995; 19: 517-522
- **127** Uedo N, Iishi H, Tatsuta M et al. Longterm outcomes after endoscopic mucosal resection for early gastric cancer. Gastric Cancer 2006; 9: 88-92
- **128** Nagano H, Ohyama S, Fukunaga T et al. Indications for gastrectomy after incomplete EMR for early gastric cancer. Gastric Cancer 2005; 8: 149-154
- **129** Gotoda T. A large endoscopic resection by endoscopic submucosal dissection procedure for early gastric cancer. Clin Gastroenterol Hepatol 2005; 3: 71-73
- **130** Takeuchi Y, Uedo N, Iishi H et al. Endoscopic submucosal dissection with insulated-tip knife for large mucosal early gastric cancer: a feasibility study (with videos). Gastrointest Endosc 2007; 66: 186-193
- **131** Facciorusso A, Antonino M, Di Maso M et al. Endoscopic submucosal dissection vs endoscopic mucosal resection for early gastric cancer: A meta-analysis. World J Gastrointest Endosc 2014; 6: 555-563
- **132** Tanabe S, Ishido K, Higuchi K et al. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a retrospective comparison with conventional endoscopic resection in a single center. Gastric Cancer 2014; 17: 130-136
- **133** Pimentel-Nunes P, Mourao F, Veloso N et al. Long-term follow-up after endoscopic resection of gastric superficial neoplastic lesions in Portugal. Endoscopy 2014; 46: 933-940
- **134** Abe N, Gotoda T, Hirasawa T et al. Multicenter study of the long-term outcomes of endoscopic submucosal dissection for early gastric cancer in patients 80 years of age or older. Gastric Cancer 2012; 15: 70-75
- **135** Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. J Gastroenterol 2006; 41: 929-942
- **136** Lee DW, Jeon SW. Management of complications during gastric endoscopic submucosal dissection. Diagn Ther Endosc 2012; 2012: 624835
- **137** Takizawa K, Oda I, Gotoda T et al. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection--an analysis of risk factors. Endoscopy 2008; 40: 179-183
- **138** Jeon SW, Jung MK, Kim SK et al. Clinical outcomes for perforations during endoscopic submucosal dissection in patients with gastric lesions. Surg Endosc 2010; 24: 911-916
- **139** Kim HS, Lee DK, Baik SK et al. Endoscopic mucosal resection with a ligation device for early gastric cancer and precancerous lesions: comparison of its therapeutic efficacy with surgical resection. Yonsei Med J 2000; 41: 577-583
- **140** Etoh T, Katai H, Fukagawa T et al. Treatment of early gastric cancer in the elderly patient: results of EMR and gastrectomy at a national referral center in Japan. Gastrointest Endosc 2005; 62: 868-871
- **141** Choi KS, Jung HY, Choi KD et al. EMR versus gastrectomy for intramucosal gastric cancer: comparison of long-term outcomes. Gastrointest Endosc 2011; 73: 942-948
- **142** Chiu PW, Teoh AY, To KF et al. Endoscopic submucosal dissection (ESD) compared with gastrectomy for treatment of early gastric neoplasia: a retrospective cohort study. Surg Endosc 2012; 26: 3584-3591
- **143** Zeng YK, Yang ZL, Peng JS et al. Laparoscopy-assisted versus open distal gastrectomy for early gastric cancer: evidence from randomized and nonrandomized clinical trials. Ann Surg 2012; 256: 39-52

Supplementary material

- **144** Zhang CD, Chen SC, Feng ZF et al. Laparoscopic versus open gastrectomy for early gastric cancer in Asia: a meta-analysis. Surg Laparosc Endosc Percutan Tech 2013; 23: 365-377
- **145** Jung H, Bae JM, Choi MG et al. Surgical outcome after incomplete endoscopic submucosal dissection of gastric cancer. Br J Surg 2011; 98: 73-78
- **146** Kwon HY, Hyung WJ, Lee JH et al. Outcomes of laparoscopic gastrectomy after endoscopic treatment for gastric cancer: a comparison with open gastrectomy. J Gastric Cancer 2013; 13: 51-57
- **147** Choi J, Kim SG, Im JP et al. Endoscopic prediction of tumor invasion depth in early gastric cancer. Gastrointest Endosc 2011; 73: 917-927
- **148** Choi J, Kim SG, Im JP et al. Comparison of endoscopic ultrasonography and conventional endoscopy for prediction of depth of tumor invasion in early gastric cancer. Endoscopy 2010; 42: 705-713
- **149** Ezoe Y, Muto M, Uedo N et al. Magnifying narrowband imaging is more accurate than conventional white-light imaging in diagnosis of gastric mucosal cancer. Gastroenterology 2011; 141: 2017-2025 e2013
- **150** Nagahama T, Yao K, Maki S et al. Usefulness of magnifying endoscopy with narrow-band imaging for determining the horizontal extent of early gastric cancer when there is an unclear margin by chromoendoscopy (with video). Gastrointest Endosc 2011; 74: 1259-1267
- **151** Repici BE, Kim GH, Park do Y et al. Acetic acid-indigo carmine chromoendoscopy for delineating early gastric cancers: its usefulness according to histological type. BMC Gastroenterol 2010; 10: 97
- **152** Taghavi SA, Membari ME, Eshraghian A et al. Comparison of chromoendoscopy and conventional endoscopy in the detection of premalignant gastric lesions. Can J Gastroenterol 2009; 23: 105-108
- **153** Cardoso R, Coburn N, Seevaratnam R et al. A systematic review and meta-analysis of the utility of EUS for preoperative staging for gastric cancer. Gastric Cancer 2012; 15: 19-26
- **154** Mocellin S, Marchet A, Nitti D. EUS for the staging of gastric cancer: a meta-analysis. Gastrointest Endosc 2011; 73: 1122-1134
- **155** Ajani JA, Bentrem DJ, Besh S et al. Gastric cancer, version 2.2013: featured updates to the NCCN Guidelines. J Natl Compr Canc Netw 2013; 11: 531-546
- **156** Probst A, Pommer B, Golger D et al. Endoscopic submucosal dissection in gastric neoplasia – experience from a European center. Endoscopy 2010; 42: 1037-1044
- **157** Folli S, Morgagni P, Roviello F et al. Risk factors for lymph node metastases and their prognostic significance in early gastric cancer (EGC) for the Italian Research Group for Gastric Cancer (IRGGC). Jpn J Clin Oncol 2001; 31: 495-499
- **158** Son SY, Park JY, Ryu KW et al. The risk factors for lymph node metastasis in early gastric cancer patients who underwent endoscopic resection: is the minimal lymph node dissection applicable? A retrospective study. Surg Endosc 2013; 27: 3247-3253
- **159** Soetikno R, Kaltenbach T, Yeh R et al. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. J Clin Oncol 2005; 23: 4490-4498
- **160** Ohgami M, Otani Y, Kumai K et al. [Laparoscopic surgery for early gastric cancer]. Nihon Geka Gakkai Zasshi 1996; 97: 279-285
- **161** Yamao T, Shirao K, Ono H et al. Risk factors for lymph node metastasis from intramucosal gastric carcinoma. Cancer 1996; 77: 602-606

Supplementary material

- **162** Hirasawa T, Gotoda T, Miyata S et al. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. Gastric Cancer 2009; 12: 148-152
- **163** Choi MK, Kim GH, Park DY et al. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a single-center experience. Surg Endosc 2013; 27: 4250-4258
- **164** Kosaka T, Endo M, Toya Y et al. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: A single-center retrospective study. Dig Endosc 2013; DOI: 10.1111/den.12099.
- **165** Horiki N, Omata F, Uemura M et al. Risk for local recurrence of early gastric cancer treated with piecemeal endoscopic mucosal resection during a 10-year follow-up period. Surg Endosc 2012; 26: 72-78
- **166** Sekiguchi M, Suzuki H, Oda I et al. Risk of recurrent gastric cancer after endoscopic resection with a positive lateral margin. Endoscopy 2014; DOI: 10.1055/s-0034–1364938.
- **167** Ahn JY, Jung HY, Choi JY et al. Natural course of noncurative endoscopic resection of differentiated early gastric cancer. Endoscopy 2012; 44: 1114-1120
- **168** Yokoi C, Gotoda T, Hamanaka H et al. Endoscopic submucosal dissection allows curative resection of locally recurrent early gastric cancer after prior endoscopic mucosal resection. Gastrointest Endosc 2006; 64: 212-218
- **169** Oda I, Gotoda T, Sasako M et al. Treatment strategy after non-curative endoscopic resection of early gastric cancer. Br J Surg 2008; 95: 1495-1500
- **170** Yoon H, Kim SG, Choi J et al. Risk factors of residual or recurrent tumor in patients with a tumor-positive resection margin after endoscopic resection of early gastric cancer. Surg Endosc 2013; 27: 1561-1568
- **171** Kato M, Nishida T, Yamamoto K et al. Scheduled endoscopic surveillance controls secondary cancer after curative endoscopic resection for early gastric cancer: a multicentre retrospective cohort study by Osaka University ESD study group. Gut 2013; 62: 1425-1432
- **172** Mitsuhashi T, Lauwers GY, Ban S et al. Post-gastric endoscopic mucosal resection surveillance biopsies: evaluation of mucosal changes and recognition of potential mimics of residual adenocarcinoma. Am J Surg Pathol 2006; 30: 650-656
- **173** Nonaka S, Oda I, Tada K et al. Clinical outcome of endoscopic resection for nonampullary duodenal tumors. Endoscopy 2015; 47: 129-135
- **174** Abbass R, Rigaux J, Al-Kawas FH. Nonampullary duodenal polyps: characteristics and endoscopic management. Gastrointest Endosc 2010; 71: 754-759
- **175** Alexander S, Bourke MJ, Williams SJ et al. EMR of large, sessile, sporadic nonampullary duodenal adenomas: technical aspects and long-term outcome (with videos). Gastrointest Endosc 2009; 69: 66-73
- **176** Conio M, De Ceglie A, Filiberti R et al. Cap-assisted EMR of large, sporadic, nonampullary duodenal polyps. Gastrointest Endosc 2012; 76: 1160-1169
- **177** Matsumoto S, Miyatani H, Yoshida Y. Endoscopic submucosal dissection for duodenal tumors: a single-center experience. Endoscopy 2013; 45: 136-137
- **178** Jung JH, Choi KD, Ahn JY et al. Endoscopic submucosal dissection for sessile, nonampullary duodenal adenomas. Endoscopy 2013; 45: 133-135

Supplementary material

- **179** Repici A, Pellicano R, Strangio G et al. Endoscopic mucosal resection for early colorectal neoplasia: pathologic basis, procedures, and outcomes. Dis Colon Rectum 2009; 52: 1502-1515
- **180** Zorzi M, Senore C, Da Re F et al. Quality of colonoscopy in an organised colorectal cancer screening programme with immunochemical faecal occult blood test: the EQuIPE study (Evaluating Quality Indicators of the Performance of Endoscopy). Gut 2014; DOI: 10.1136/gutjnl-2014–307954.
- **181** Moss A, Bourke MJ, Williams SJ et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. Gastroenterology 2011; 140: 1909-1918
- **182** Hassan C, Repici A, Sharma P et al. Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. Gut 2015; DOI: 10.1136/gutjnl-2014–308481.
- **183** Moss A, Williams SJ, Hourigan LF et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. Gut 2015; 64: 57-65
- **184** Bosch SL, Teerenstra S, de Wilt JH et al. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy 2013; 45: 827-834
- **185** Horiuchi Y, Chino A, Matsuo Y et al. Diagnosis of laterally spreading tumors (LST) in the rectum and selection of treatment: characteristics of each of the subclassifications of LST in the rectum. Dig Endosc 2013; 25: 608-614
- **186** Uraoka T, Saito Y, Matsuda T et al. Endoscopic indications for endoscopic mucosal resection of laterally spreading tumors in the colorectum. Gut 2006; 55: 1592-1597
- **187** Saito Y, Yamada M, So E et al. Colorectal endoscopic submucosal dissection: Technical advantages compared to endoscopic mucosal resection and minimally invasive surgery. Dig Endosc 2014; 26: 52-61
- **188** Kim ES, Cho KB, Park KS et al. Factors predictive of perforation during endoscopic submucosal dissection for the treatment of colorectal tumors. Endoscopy 2011; 43: 573-578
- **189** Arezzo A, Passera R, Saito Y et al. Systematic review and meta-analysis of endoscopic submucosal dissection versus transanal endoscopic microsurgery for large noninvasive rectal lesions. Surg Endosc 2014; 28: 427-438
- **190** Repici A, Hassan C, De Paula Pessoa D et al. Efficacy and safety of endoscopic submucosal dissection for colorectal neoplasia: a systematic review. Endoscopy 2012; 44: 137-150
- **191** Niimi K, Fujishiro M, Kodashima S et al. Long-term outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms. Endoscopy 2010; 42: 723-729
- **192** Hisabe T, Nagahama T, Hirai F et al. Clinical outcomes of 200 colorectal endoscopic submucosal dissections. Dig Endosc 2012; 24: 105-109
- **193** Takeuchi Y, Ohta T, Matsui F et al. Indication, strategy and outcomes of endoscopic submucosal dissection for colorectal neoplasm. Dig Endosc 2012; 24: 100-104
- **194** Lee EJ, Lee JB, Lee SH et al. Endoscopic submucosal dissection for colorectal tumors – 1,000 colorectal ESD cases: one specialized institute's experiences. Surg Endosc 2013; 27: 31-39

Supplementary material

- **195** Repici A, Hassan C, Pagano N et al. High efficacy of endoscopic submucosal dissection for rectal laterally spreading tumors larger than 3 cm. Gastrointest Endosc 2013; 77: 96-101 DOI: 10.1016/j.gie.2012.08.03.
- **196** Rahmi G, Hotayt B, Chaussade S et al. Endoscopic submucosal dissection for superficial rectal tumors: prospective evaluation in France. Endoscopy 2014; 46: 670-676
- **197** Oka S, Tanaka S, Kanao H et al. Current status in the occurrence of postoperative bleeding, perforation and residual/local recurrence during colonoscopic treatment in Japan. Dig Endosc 2010; 22: 376-380
- **198** Terasaki M, Tanaka S, Shigita K et al. Risk factors for delayed bleeding after endoscopic submucosal dissection for colorectal neoplasms. Int J Colorectal Dis 2014; 29: 877-882
- **199** Saito Y, Uraoka T, Yamaguchi Y et al. A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). Gastrointest Endosc 2010; 72: 1217-1225
- **200** Kudo S, Tamura S, Nakajima T et al. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. Gastrointest Endosc 1996; 44: 8-14
- **201** Kato S, Fujii T, Koba I et al. Assessment of colorectal lesions using magnifying colonoscopy and mucosal dye spraying: can significant lesions be distinguished?. Endoscopy 2001; 33: 306-310
- **202** Bianco MA, Rotondano G, Marmo R et al. Predictive value of magnification chromoendoscopy for diagnosing invasive neoplasia in nonpolypoid colorectal lesions and stratifying patients for endoscopic resection or surgery. Endoscopy 2006; 38: 470-476
- **203** Matsuda T, Fujii T, Saito Y et al. Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms. Am J Gastroenterol 2008; 103: 2700-2706
- **204** Hayashi N, Tanaka S, Hewett DG et al. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. Gastrointest Endosc 2013; 78: 625-632
- **205** Hayashi N, Tanaka S, Kanao H et al. Relationship between narrow-band imaging magnifying observation and pit pattern diagnosis in colorectal tumors. Digestion 2013; 87: 53-58
- **206** Fernandez-Esparrach G, Ayuso-Colella JR, Sendino O et al. EUS and magnetic resonance imaging in the staging of rectal cancer: a prospective and comparative study. Gastrointest Endosc 2011; 74: 347-354
- **207** Hurlstone DP, Brown S, Cross SS et al. High magnification chromoscopic colonoscopy or high frequency 20 MHz mini probe endoscopic ultrasound staging for early colorectal neoplasia: a comparative prospective analysis. Gut 2005; 54: 1585-1589
- **208** Gall TM, Markar SR, Jackson D et al. Mini-probe ultrasonography for the staging of colon cancer: a systematic review and meta-analysis. Colorectal Dis 2014; 16: 1-8
- **209** Urban O, Kliment M, Fojtik P et al. High-frequency ultrasound probe sonography staging for colorectal neoplasia with superficial morphology: its utility and impact on patient management. Surg Endosc 2011; 25: 3393-3399
- **210** Haggitt RC, Glotzbach RE, Soffer EE et al. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. Gastroenterology 1985; 89: 328-336

Supplementary material

- **211** Nivatvongs S, Rojanasakul A, Reiman HM et al. The risk of lymph node metastasis in colorectal polyps with invasive adenocarcinoma. Dis Colon Rectum 1991; 34: 323-328
- **212** Beaton C, Twine CP, Williams GL et al. Systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early colorectal cancer. Colorect Dis 2013; 15: 788-797
- **213** Butte JM, Tang P, Gonen M et al. Rate of residual disease after complete endoscopic resection of malignant colonic polyp. Dis Colon Rectum 2012; 55: 122-127
- **214** Tominaga K, Nakanishi Y, Nimura S et al. Predictive histopathologic factors for lymph node metastasis in patients with nonpedunculated submucosal invasive colorectal carcinoma. Dis Colon Rectum 2005; 48: 92-100
- **215** Choi DH, Sohn DK, Chang HJ et al. Indications for subsequent surgery after endoscopic resection of submucosally invasive colorectal carcinomas: a prospective cohort study. Dis Colon Rectum 2009; 52: 438-445
- **216** Westerterp M, Koppert LB, Buskens CJ et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch 2005; 446: 497-504 (Epub 2005 Apr 19)
- **217** Vieth M, Schubert B, Lang-Schwarz K et al. Frequency of Barrett's neoplasia after initial negative endoscopy with biopsy: a long-term histopathological follow-up study. Endoscopy 2006; 38: 1201-1205
- **218** Pox C, Aretz S, Bischoff SC et al Update 2019. Leitlinienprogramm Onkologie der AWMF; Deutschen Krebsgesellschaft e.V; Deutschen Krebshilfe e.V. [S3-guideline colorectal cancer version 1.0]. https://www.awmf.org/uploads/tx_szleitlinien
- /021-007OLl_S3_Kolorektales-Karzinom-KRK_2019-01.pdf
- **219** Coman RM, Gotoda T, Draganov PV. Training in endoscopic submucosal dissection. World J Gastrointest Endosc 2013; 5: 369-378
- **220** Hotta K, Oyama T, Akamatsu T et al. A comparison of outcomes of endoscopic submucosal dissection (ESD) For early gastric neoplasms between high-volume and low-volume centers: multi-center retrospective questionnaire study conducted by the Nagano ESD Study Group. Intern Med 2010; 49: 253-259
- **221** Draganov PV, Gotoda T, Chavalitdhamrong D et al. Techniques of endoscopic submucosal dissection: application for the Western endoscopist?. Gastrointest Endosc 2013; 78: 677-688
- **222** Draganov PV, Coman RM, Gotoda T. Training for complex endoscopic procedures: how to incorporate endoscopic submucosal dissection skills in the West?. Expert Rev Gastroenterol Hepatol 2014; 8: 119-121
- **223** Imagawa A, Okada H, Kawahara Y et al. Endoscopic submucosal dissection for early gastric cancer: results and degrees of technical difficulty as well as success. Endoscopy 2006; 38: 987-990
- **224** Gotoda T, Friedland S, Hamanaka H et al. A learning curve for advanced endoscopic resection. Gastrointest Endosc 2005; 62: 866-867
- **225** Kakushima N, Fujishiro M, Kodashima S et al. A learning curve for endoscopic submucosal dissection of gastric epithelial neoplasms. Endoscopy 2006; 38: 991-995
- **226** Oda I, Odagaki T, Suzuki H et al. Learning curve for endoscopic submucosal dissection of early gastric cancer based on trainee experience. Dig Endosc 2012; 24: 129-132

Supplementary material

- **227** Kato M, Gromski M, Jung Y et al. The learning curve for endoscopic submucosal dissection in an established experimental setting. Surg Endosc 2013; 27: 154-161
- **228** Herreros de Tejada A. ESD training: A challenging path to excellence. World J Gastrointest Endosc 2014; 6: 112-120
- **229** Jung HY. Endoscopic resection for early gastric cancer: current status in Korea. Dig Endosc 2012; 24: 159-165
- **230** Rosch T, Sarbia M, Schumacher B et al. Attempted endoscopic en bloc resection of mucosal and submucosal tumors using insulated-tip knives: a pilot series. Endoscopy 2004; 36: 788-801
- **231** Kakushima N, Hirasawa K, Morita Y et al. Terminology for training of endoscopic submucosal dissection. Dig Endosc 2012; 24: 133-135
- **232** Ribeiro-Mourao F, Pimentel-Nunes P, Dinis-Ribeiro M. Endoscopic submucosal dissection for gastric lesions: results of an European inquiry. Endoscopy 2010; 42: 814-819
- **233** Dinis-Ribeiro M, Pimentel-Nunes P, Afonso M et al. A European case series of endoscopic submucosal dissection for gastric superficial lesions. Gastrointest Endosc 2009; 69: 350-355
- **234** Catalano F, Trecca A, Rodella L et al. The modern treatment of early gastric cancer: our experience in an Italian cohort. Surg Endosc 2009; 23: 1581-1586
- **235** Repici A, Zullo A, Hassan C et al. Endoscopic submucosal dissection of early gastric neoplastic lesions: a western series. Eur J Gastroenterol Hepatol 2013; 25: 1261-1264 DOI: 10.1097/MEG.0b013e328364b492.
- **236** Schumacher B, Charton JP, Nordmann T et al. Endoscopic submucosal dissection of early gastric neoplasia with a water jet-assisted knife: a Western, single-center experience. Gastrointest Endosc 2012; 75: 1166-1174
- **237** Probst A, Golger D, Anthuber M et al. Endoscopic submucosal dissection in large sessile lesions of the rectosigmoid: learning curve in a European center. Endoscopy 2012; 44: 660-667
- **238** Thorlacius H, Uedo N, Toth E. Implementation of endoscopic submucosal dissection for early colorectal neoplasms in Sweden. Gastroenterol Res Pract 2013; 2013: 758202
- **239** Spychalski M, Dziki A. Safe and efficient colorectal endoscopic submucosal dissection in European settings: Is successful implementation of the procedure possible?. Dig Endosc 2015; 27: 368-373 DOI: 10.1111/den.12353.
- **240** Spychalski M, Zelga P, Dziki A. Key factors in achieving successful endoscopic dissection of rectal tumors: early results of 33 consecutive rectal endoscopic submucosal dissections in Polish academic center. Surg Laparosc Endosc Percutan Tech 2015; 25: 173-177 DOI: 10.1097/SLE.0000000000000111.
- **241** Lang GD, Konda VJ, Siddiqui UD et al. A single-center experience of endoscopic submucosal dissection performed in a Western setting. Dig Dis Sci 2015; 60: 531-536
- **242** Bialek A, Pertkiewicz J, Karpinska K et al. Treatment of large colorectal neoplasms by endoscopic submucosal dissection: a European single-center study. Eur J Gastroenterol Hepatol 2014; 26: 607-615

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	Overal 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 endosocpic 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 SESCCs	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 ⅡA 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

Supplementary material

					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 assessement	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 assessement	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 SESCCs 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 stantard	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 knifes	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 ondergoing 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 ondergoing 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 dysplasis	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 (*P* = 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 R0 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

			oesophageal circumference in the lateral direction. ▸ **No endoscopic suspicion of massive infiltration** into the submucosal layer and no additional neoplastic lesions according to endoscopic appearance. Exclusion : **previous** endoscopic or surgical **treatment** ▸ neoplastic lesions that do not meet the inclusion criteria, particularly flat lesions (type 0–IIb) and additional areas of HGIN or AC.			
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.

Yang D, Othman M, Draganov PV. Endoscopic mucosal resection vs endoscopic submucosal dissection for Barrett's esophagus and colorectal neoplasia. Clin Gastroenterol Hepatol. 2019;17(6):1019– 28. REVIEW

Draganov PV, Wang AY, Othman MO, Fukami N. AGA Institute clinical practice update: endoscopic submucosal dissection in the United States. Clin Gastroenterol Hepatol. 2019;17(1):16–25.e1. expert review

Supplementary material

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

Long-term outcomes of endoscopic resection and metachronous cancer after endoscopic resection for adenocarcinoma of the esophagogastric junction in Japan. Abe S, Ishihara R, Takahashi H, Ono H, Fujisaki J, Matsui A, Takahashi A, Goda K, Kawada K, Koike T, Takeuchi M, Tsuji Y, Hirasawa D, Oyama T. Gastrointest Endosc. 2019 Jun;89(6):1120-1128. doi: 10.1016/j.gie.2018.12.010. Epub 2018 Dec 18.

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.**

Supplementary material

Complex early Barrett's neoplasia at 3 Western centers: European Barrett's Endoscopic Submucosal Dissection Trial (E-BEST). Subramaniam S, Chedgy F, Longcroft-Wheaton G, Kandiah K, Maselli R, Seewald S, Repici A, Bhandari P. Gastrointest Endosc. 2017 Oct;86(4):608-618. doi: 10.1016/j.gie.2017.01.027. Epub 2017 Jan 31.

Endoscopic submucosal dissection for Barrett's early neoplasia: a multicenter study in the United States. Yang D, Coman RM, Kahaleh M, Waxman I, Wang AY, Sethi A, Shah AR, Draganov PV. Gastrointest Endosc. 2017 Oct;86(4):600-607. doi: 10.1016/j.gie.2016.09.023. Epub 2016 Sep 28.

Prospective evaluation of the clinical utility of endoscopic submucosal dissection (ESD) in patients with Barrett's esophagus: a Western center experience. Coman RM, Gotoda T, Forsmark CE, Draganov PV.

Endoscopic submucosal dissection for early Barrett's neoplasia. Barret M, Cao DT, Beuvon F, Leblanc S, Terris B, Camus M, Coriat R, Chaussade S, Prat F. United European Gastroenterol J. 2016 Apr;4(2):207-15. doi: 10.1177/2050640615608748. Epub 2015 Sep 24.

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.

REFERENCES

1 Codipilly DC, Dhaliwal L, Oberoi M, Gandhi P, Johnson ML, Lansing RM, Harmsen WS, Wang KK, Iyer PG. Comparative Outcomes of Cap Assisted Endoscopic Resection and Endoscopic Submucosal Dissection in Dysplastic Barrett's Esophagus. Clin Gastroenterol Hepatol 2020; Im Internet: https://linkinghub.elsevier.com/retrieve/pii/S1542356520315512

2 Han C, Sun Y. Efficacy and safety of endoscopic submucosal dissection versus endoscopic mucosal resection for superficial esophageal carcinoma: a systematic review and meta-analysis. Dis Esophagus 2020;

3 Tomizawa Y, Friedland S, Hwang JH. Endoscopic submucosal dissection (ESD) for Barrett's esophagus (BE)-related early neoplasia after standard endoscopic management is feasible and safe. Endosc Int Open 2020; 08: E498–E505

4 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. Endoscopic submucosal dissection/endoscopic mucosal resection guidelines for esophageal cancer. Dig Endosc 2020; 32: 452–493

5 Abe S, Ishihara R, Takahashi H, Ono H, Fujisaki J, Matsui A, Takahashi A, Goda K, Kawada K, Koike T, Takeuchi M, Tsuji Y, Hirasawa D, Oyama T. Long-term outcomes of endoscopic resection and metachronous cancer after endoscopic resection for adenocarcinoma of the esophagogastric junction in Japan. Gastrointest Endosc 2019; 89: 1120–1128 Im Internet: https://pubmed.ncbi.nlm.nih.gov/30576649/

Supplementary material

6 Subramaniam S, Kandiah K, Chedgy F, Meredith P, Longcroft-Wheaton G, Bhandari P. The safety and efficacy of radiofrequency ablation following endoscopic submucosal dissection for Barrett's neoplasia. Dis Esophagus 2017; 31: 1–7 Im Internet: https://academic.oup.com/dote/article/31/3/dox133/4683665

7 Yang D, Zou F, Xiong S, Forde JJ, Wang Y, Draganov P V. Endoscopic submucosal dissection for early Barrett's neoplasia: a meta-analysis. Gastrointest Endosc 2018; 87: 1383–1393 Im Internet: https://pubmed.ncbi.nlm.nih.gov/28993137/

8 Subramaniam S, Chedgy F, Longcroft-Wheaton G, Kandiah K, Maselli R, Seewald S, Repici A, Bhandari P. Complex early Barrett's neoplasia at 3 Western centers: European Barrett's Endoscopic Submucosal Dissection Trial (E-BEST). Gastrointest Endosc 2017; 86: 608–618

9 Yang D, Coman RM, Kahaleh M, Waxman I, Wang AY, Sethi A, Shah AR, Draganov P V. Endoscopic submucosal dissection for Barrett's early neoplasia: a multicenter study in the United States. Gastrointest Endosc 2017; 86: 600–607 Im Internet: http://dx.doi.org/10.1016/j.gie.2016.09.023

10 Roxana Coman AM, Gotoda T, Forsmark CE, Draganov P V. Prospective evaluation of the clinical utility of endoscopic submucosal dissection (ESD) in patients with Barrett's esophagus: a Western center experience. Im Internet: http://dx.doi.org/

11 Barret M, Cao DT, Beuvon F, Leblanc S, Terris B, Camus M, Coriat R, Chaussade S, Prat F. Endoscopic submucosal dissection for early Barrett's neoplasia.

12 Terheggen G, Horn EM, Vieth M, Gabbert H, Enderle M, Neugebauer A, Schumacher B, Neuhaus H. A randomised trial of endoscopic submucosal dissection versus endoscopic mucosal resection for early Barrett's neoplasia. Im Internet: http://gut.bmj.com/

13 Andreas Probst A, Aust D, Märkl B, Anthuber M, Messmann H, Probst A. Early esophageal cancer in Europe: endoscopic treatment by endoscopic submucosal dissection. Endoscopy 2014; 47: 113–121 Im Internet: http://dx.doi.org/

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 Hepatol[94]	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 Hepatol[95]	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

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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 *et al* [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 *et al* [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 *et al*, 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 *et al, 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 *et al,* 2019[101] (USA)	Expanded indication	3/40 (7.5%)
Pessorrusso *et al,* 2019 (Brazil)[102]		3/104 (2.9%) #
Probst *et al*[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 nº 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

Supplementary material

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%, *p*= 0.024 specificity 90.0% *vs* 60.7%, *p*= 0.024 sensitivity 92.3% vs 90.9%, *p*= 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 radio; 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

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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

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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
Pessorrusso 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** ECG	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

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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, *Pathol* Oncol Res [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;

References

1. Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2020.
2. Tao M, Zhou X, Hu M, et al. Endoscopic submucosal dissection versus endoscopic mucosal resection for patients with early gastric cancer: a meta-analysis. BMJ Open 2019;9:e025803.
3. Zhao Y, Wang C. Long-Term Clinical Efficacy and Perioperative Safety of Endoscopic Submucosal Dissection versus Endoscopic Mucosal Resection for Early Gastric Cancer: An Updated Meta-Analysis. Biomed Res Int 2018;2018:3152346.
4. Suzuki H, Takizawa K, Hirasawa T, et al. Short-term outcomes of multicenter prospective cohort study of gastric endoscopic resection: 'Real-world evidence' in Japan. Dig Endosc 2019;31:30-39.
5. Tanabe S, Ishido K, Matsumoto T, et al. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a multicenter collaborative study. Gastric Cancer 2017;20:45-52.
6. Abdelfatah MM, Barakat M, Ahmad D, et al. Long-term outcomes of endoscopic submucosal dissection versus surgery in early gastric cancer: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2019;31:418-424.
7. Liu Q, Ding L, Qiu X, et al. Updated evaluation of endoscopic submucosal dissection versus surgery for early gastric cancer: A systematic review and meta-analysis. Int J Surg 2020;73:28-41.

Supplementary material

8. Gu L, Khadaroo PA, Chen L, et al. Comparison of Long-Term Outcomes of Endoscopic Submucosal Dissection and Surgery for Early Gastric Cancer: a Systematic Review and Meta-analysis. J Gastrointest Surg 2019;23:1493-1501.
9. Li H, Feng LQ, Bian YY, et al. Comparison of endoscopic submucosal dissection with surgical gastrectomy for early gastric cancer: An updated meta-analysis. World J Gastrointest Oncol 2019;11:161-171.
10. Libânio D, Braga V, Ferraz S, et al. Prospective comparative study of endoscopic submucosal dissection and gastrectomy for early neoplastic lesions including patients' perspectives. Endoscopy 2019;51:30-39.
11. Najmeh S, Cools-Lartigue J, Mueller C, et al. Comparing Laparoscopic to Endoscopic Resections for Early Gastric Cancer in a High Volume North American Center. J Gastrointest Surg 2016;20:1547-53.
12. Kim YI, Kim YA, Kim CG, et al. Serial intermediate-term quality of life comparison after endoscopic submucosal dissection versus surgery in early gastric cancer patients. Surg Endosc 2018;32:2114-2122.
13. Kim SG, Ji SM, Lee NR, et al. Quality of Life after Endoscopic Submucosal Dissection for Early Gastric Cancer: A Prospective Multicenter Cohort Study. Gut Liver 2017;11:87-92.
14. Choi JH, Kim ES, Lee YJ, et al. Comparison of quality of life and worry of cancer recurrence between endoscopic and surgical treatment for early gastric cancer. Gastrointest Endosc 2015;82:299-307.
15. Uchita K, Yao K, Uedo N, et al. Highest power magnification with narrow-band imaging is useful for improving diagnostic performance for endoscopic delineation of early gastric cancers. BMC Gastroenterol 2015;15:155.
16. Makazu M, Hirasawa K, Sato C, et al. Histological verification of the usefulness of magnifying endoscopy with narrow-band imaging for horizontal margin diagnosis of differentiated-type early gastric cancers. Gastric Cancer 2018;21:258-266.
17. Horii Y, Dohi O, Naito Y, et al. Efficacy of Magnifying Narrow Band Imaging for Delineating Horizontal Margins of Early Gastric Cancer. Digestion 2019;100:93-99.
18. Figueiroa G, Pimentel-Nunes P, Dinis-Ribeiro M, et al. Gastric endoscopic submucosal dissection: a systematic review and meta-analysis on risk factors for poor short-term outcomes. Eur J Gastroenterol Hepatol 2019;31:1234-1246.
19. Fairweather M, Jajoo K, Sainani N, et al. Accuracy of EUS and CT imaging in preoperative gastric cancer staging. J Surg Oncol 2015;111:1016-20.
20. Chung HW, Kim JH, Sung IK, et al. FDG PET/CT to predict the curability of endoscopic resection for early gastric cancer. J Cancer Res Clin Oncol 2019;145:759-764.
21. Shi D, Xi XX. Factors Affecting the Accuracy of Endoscopic Ultrasonography in the Diagnosis of Early Gastric Cancer Invasion Depth: A Meta-analysis. Gastroenterol Res Pract 2019;2019:8241381.
22. Lee JY, Choi IJ, Kim CG, et al. Therapeutic Decision-Making Using Endoscopic Ultrasonography in Endoscopic Treatment of Early Gastric Cancer. Gut Liver 2016;10:42-50.

Supplementary material

23. Kuroki K, Oka S, Tanaka S, et al. Clinical significance of endoscopic ultrasonography in diagnosing invasion depth of early gastric cancer prior to endoscopic submucosal dissection. Gastric Cancer 2020.
24. Lan Z, Hu H, Mandip R, et al. Linear-array endoscopic ultrasound improves the accuracy of preoperative submucosal invasion prediction in suspected early gastric cancer compared with radial endoscopic ultrasound: A prospective cohort study. J Gastroenterol Hepatol 2020;35:118-123.
25. Ono S, Fujishiro M, Yoshida N, et al. Thienopyridine derivatives as risk factors for bleeding following high risk endoscopic treatments: Safe Treatment on Antiplatelets (STRAP) study. Endoscopy 2015;47:632-7.
26. Horikawa Y, Mizutamari H, Mimori N, et al. Effect of Continued Administration of Low-dose Aspirin for Intraoperative Bleeding Control in Gastric Endoscopic Submucosal Dissection. Digestion 2019;100:139-146.
27. Libânio D, Costa MN, Pimentel-Nunes P, et al. Risk factors for bleeding after gastric endoscopic submucosal dissection: a systematic review and meta-analysis. Gastrointest Endosc 2016;84:572-86.
28. Libânio D, Dinis-Ribeiro M, Pimentel-Nunes P, et al. Predicting outcomes of gastric endoscopic submucosal dissection using a Bayesian approach: a step for individualized risk assessment. Endosc Int Open 2017;5:E563-e572.
29. Nishizawa T, Suzuki H, Akimoto T, et al. Effects of preoperative proton pump inhibitor administration on bleeding after gastric endoscopic submucosal dissection: A systematic review and meta-analysis. United European Gastroenterol J 2016;4:5-10.
30. Choi CW, Kang DH, Kim HW, et al. High Dose Proton Pump Inhibitor Infusion Versus Bolus Injection for the Prevention of Bleeding After Endoscopic Submucosal Dissection: Prospective Randomized Controlled Study. Dig Dis Sci 2015;60:2088-96.
31. Lee BE, Kim GH, Song GA, et al. Continuous Infusion versus Intermittent Dosing with Pantoprazole for Gastric Endoscopic Submucosal Dissection. Gut Liver 2019;13:40-47.
32. Ishido K, Tanabe S, Azuma M, et al. Comparison of oral and intravenous lansoprazole for the prevention of bleeding from artificial ulcers after endoscopic submucosal dissection for gastric tumors: a prospective randomized phase II study (KDOG 0802). Surg Endosc 2018;32:2939-2947.
33. Yoon JH, Kim YJ, Lee KN, et al. Effect on Bleeding Prevention of an Intravenous Proton Pump Inhibitor During the Fasting Period After Endoscopic Submucosal Dissection: a Prospective, Randomized, Double-Blind, Placebo-Controlled Trial. J Gastrointest Surg 2019.
34. Martin, Zhou Y, Meng CX, et al. Vonoprazan vs proton pump inhibitors in treating post-endoscopic submucosal dissection ulcers and preventing bleeding: A meta-analysis of randomized controlled trials and observational studies. Medicine (Baltimore) 2020;99:e19357.
35. Gao H, Li L, Zhang C, et al. Comparison of efficacy of pharmacological therapies for gastric endoscopic submucosal dissection-induced ulcers: a systematic review and network meta-analysis. Expert Rev Gastroenterol Hepatol 2020;14:207-220.
36. Jiang X, Li J, Xie J, et al. Histamine2-Receptor Antagonists, Proton Pump Inhibitors, or Potassium-Competitive Acid Blockers Preventing Delayed Bleeding After Endoscopic Submucosal Dissection: A Meta-Analysis. Front Pharmacol 2019;10:1055.
37. Jaruvongvanich V, Poonsombudlert K, Ungprasert P. Vonoprazan versus proton-pump inhibitors for gastric endoscopic submucosal dissection-induced ulcers: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2018;30:1416-1421.

Supplementary material

38. Liu C, Feng BC, Zhang Y, et al. The efficacy of vonoprazan for management of post-endoscopic submucosal dissection ulcers compared with proton pump inhibitors: A meta-analysis. J Dig Dis 2019;20:503-511.
39. Takizawa K, Oda I, Gotoda T, et al. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection--an analysis of risk factors. Endoscopy 2008;40:179-83.
40. Tsuji Y, Fujishiro M, Kodashima S, et al. Polyglycolic acid sheets and fibrin glue decrease the risk of bleeding after endoscopic submucosal dissection of gastric neoplasms (with video). Gastrointest Endosc 2015;81:906-12.
41. Kawata N, Ono H, Takizawa K, et al. Efficacy of polyglycolic acid sheets and fibrin glue for prevention of bleeding after gastric endoscopic submucosal dissection in patients under continued antithrombotic agents. Gastric Cancer 2018;21:696-702.
42. Kikuchi D, Iizuka T, Makino S, et al. Utility of autologous fibrin glue and polyglycolic acid sheet for preventing delayed bleeding associated with antithrombotic therapy after gastric ESD. Endosc Int Open 2019;7:E1542-e1548.
43. Baniya R, Upadhaya S, Khan J, et al. Carbon Dioxide versus Air Insufflation in Gastric Endoscopic Submucosal Dissection: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Endosc 2017;50:464-472.
44. Kim SY, Chung JW, Park DK, et al. Efficacy of carbon dioxide insufflation during gastric endoscopic submucosal dissection: a randomized, double-blind, controlled, prospective study. Gastrointest Endosc 2015;82:1018-24.
45. Takada J, Araki H, Onogi F, et al. Safety and efficacy of carbon dioxide insufflation during gastric endoscopic submucosal dissection. World J Gastroenterol 2015;21:8195-202.
46. Su YF, Cheng SW, Chang CC, et al. Efficacy and safety of traction-assisted endoscopic submucosal dissection: a meta-regression of randomized clinical trials. Endoscopy 2020;52:338-348.
47. Kim EH, Park SW, Nam E, et al. Role of second-look endoscopy and prophylactic hemostasis after gastric endoscopic submucosal dissection: A systematic review and meta-analysis. J Gastroenterol Hepatol 2017;32:756-768.
48. Ding X, Luo H, Duan H. Risk factors for perforation of gastric endoscopic submucosal dissection: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2019;31:1481-1488.
49. Kim JH, Nam HS, Choi CW, et al. Risk factors associated with difficult gastric endoscopic submucosal dissection: predicting difficult ESD. Surg Endosc 2017;31:1617-1626.
50. Gotoda T, Yanagisawa A, Sasako M, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000;3:219-225.
51. Hirasawa T, Gotoda T, Miyata S, et al. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. Gastric Cancer 2009;12:148-52.
52. Nakahara K, Tsuruta O, Tateishi H, et al. Extended indication criteria for endoscopic mucosal resection of early gastric cancer with special reference to lymph node metastasis--examination by multivariate analysis. Kurume Med J 2004;51:9-14.

Supplementary material

53. Chu YN, Yu YN, Jing X, et al. Feasibility of endoscopic treatment and predictors of lymph node metastasis in early gastric cancer. World J Gastroenterol 2019;25:5344-5355.
54. Lee SH, Choi CW, Kim SJ, et al. Risk factors for lymph node metastasis in mucosal gastric cancer and re-evaluation of endoscopic submucosal dissection. Ann Surg Treat Res 2016;91:118-26.
55. Choi KK, Bae JM, Kim SM, et al. The risk of lymph node metastases in 3951 surgically resected mucosal gastric cancers: implications for endoscopic resection. Gastrointest Endosc 2016;83:896-901.
56. Ma DW, Lee SJ, Kook MC, et al. The Suggestion of Revised Criteria for Endoscopic Resection of Differentiated-Type Submucosal Gastric Cancer. Ann Surg Oncol 2020;27:795-801.
57. Choi JY, Park YS, Jung HY, et al. Identifying predictors of lymph node metastasis after endoscopic resection in patients with minute submucosal cancer of the stomach. Surg Endosc 2015;29:1476-83.
58. Abdelfatah MM, Barakat M, Othman MO, et al. The incidence of lymph node metastasis in submucosal early gastric cancer according to the expanded criteria: a systematic review. Surg Endosc 2019;33:26-32.
59. Kim TS, Min BH, Kim KM, et al. Endoscopic submucosal dissection for papillary adenocarcinoma of the stomach: low curative resection rate but favorable long-term outcomes after curative resection. Gastric Cancer 2019;22:363-368.
60. Lee HJ, Kim GH, Park DY, et al. Endoscopic submucosal dissection for papillary adenocarcinoma of the stomach: is it really safe? Gastric Cancer 2017;20:978-986.
61. Chen JN, Wang QW, Zhang QW, et al. Poorly differentiated is more significant than signet ring cell component for lymph node metastasis in mixed-type early gastric cancer: a retrospective study from a large-volume hospital. Surg Endosc 2020.
62. Seo HS, Lee GE, Kang MG, et al. Mixed Histology Is a Risk Factor for Lymph Node Metastasis in Early Gastric Cancer. J Surg Res 2019;236:271-277.
63. Lee IS, Lee S, Park YS, et al. Applicability of endoscopic submucosal dissection for undifferentiated early gastric cancer: Mixed histology of poorly differentiated adenocarcinoma and signet ring cell carcinoma is a worse predictive factor of nodal metastasis. Surg Oncol 2017;26:8-12.
64. Lee JH, Choi IJ, Han HS, et al. Risk of lymph node metastasis in differentiated type mucosal early gastric cancer mixed with minor undifferentiated type histology. Ann Surg Oncol 2015;22:1813-9.
65. Takizawa K, Ono H, Yamamoto Y, et al. Incidence of lymph node metastasis in intramucosal gastric cancer measuring 30 mm or less, with ulceration; mixed, predominantly differentiated-type histology; and no lymphovascular invasion: a multicenter retrospective study. Gastric Cancer 2016;19:1144-1148.
66. Brito-Goncalves G, Libanio D, Marcos P, et al. Clinicopathologic Characteristics of Patients with Gastric Superficial Neoplasia and Risk Factors for Multiple Lesions after Endoscopic Submucosal Dissection in a Western Country. GE Port J Gastroenterol 2020;27:76-89.
67. Okada K, Suzuki S, Naito S, et al. Incidence of metachronous gastric cancer in patients whose primary gastric neoplasms were discovered after Helicobacter pylori eradication. Gastrointest Endosc 2019;89:1152-1159 e1.

Supplementary material

68. Park WY, Lee SJ, Kim YK, et al. Occurrence of metachronous or synchronous lesions after endoscopic treatment of gastric epithelia dysplasia- impact of histologic features of background mucosa. Pathol Res Pract 2018;214:95-99.
69. Libânio D, Pimentel-Nunes P, Afonso LP, et al. Long-Term Outcomes of Gastric Endoscopic Submucosal Dissection: Focus on Metachronous and Non-Curative Resection Management. GE Port J Gastroenterol 2017;24:31-39.
70. Yang HJ, Kim SG, Lim JH, et al. Novel risk stratification for metachronous recurrence after curative endoscopic submucosal dissection for early gastric cancer. Gastrointest Endosc 2018;87:419-428.e3.
71. Yang HJ, Kim SG, Lim JH, et al. Surveillance strategy according to age after endoscopic resection of early gastric cancer. Surg Endosc 2018;32:846-854.
72. Moon HS, Yun GY, Kim JS, et al. Risk factors for metachronous gastric carcinoma development after endoscopic resection of gastric dysplasia: Retrospective, single-center study. World J Gastroenterol 2017;23:4407-4415.
73. Abe S, Oda I, Suzuki H, et al. Long-term surveillance and treatment outcomes of metachronous gastric cancer occurring after curative endoscopic submucosal dissection. Endoscopy 2015;47:1113-8.
74. Fan F, Wang Z, Li B, et al. Effects of eradicating Helicobacter pylori on metachronous gastric cancer prevention: A systematic review and meta-analysis. J Eval Clin Pract 2020;26:308-315.
75. Zhao B, Zhang J, Mei D, et al. Does Helicobacter pylori Eradication Reduce the Incidence of Metachronous Gastric Cancer After Curative Endoscopic Resection of Early Gastric Cancer: A Systematic Review and Meta-Analysis. J Clin Gastroenterol 2020;54:235-241.
76. Hahn KY, Park JC, Kim EH, et al. Incidence and impact of scheduled endoscopic surveillance on recurrence after curative endoscopic resection for early gastric cancer. Gastrointest Endosc 2016;84:628-638.e1.
77. Kim JL, Kim SG, Kim J, et al. Clinical Outcomes of Metachronous Gastric Cancer after Endoscopic Resection for Early Gastric Cancer. Gut Liver 2020;14:190-198.
78. Choi KS, Kim SH, Kim SG, et al. Early Gastric Cancers: Is CT Surveillance Necessary after Curative Endoscopic Submucosal Resection for Cancers That Meet the Expanded Criteria? Radiology 2016;281:444-453.
79. Figueiredo PC, Pimentel-Nunes P, Libanio D, et al. A systematic review and meta-analysis on outcomes after Rx or R1 endoscopic resection of superficial gastric cancer. Eur J Gastroenterol Hepatol 2015;27:1249-58.
80. Choi YK, Kim DH, Gong EJ, et al. Comparison Between Redo Endoscopic Treatment and Surgery in Patients with Locally Recurrent Gastric Neoplasms. J Gastrointest Surg 2019.
81. Jeon MY, Park JC, Hahn KY, et al. Long-term outcomes after noncurative endoscopic resection of early gastric cancer: the optimal time for additional endoscopic treatment. Gastrointest Endosc 2018;87:1003-1013 e2.
82. Zhao B, Zhang J, Zhang J, et al. Risk Factors Associated with Lymph Node Metastasis for Early Gastric Cancer Patients Who Underwent Non-curative Endoscopic Resection: a Systematic Review and Meta-analysis. J Gastrointest Surg 2019;23:1318-1328.

Supplementary material

83. Takizawa K, Hatta W, Gotoda T, et al. Recurrence Patterns and Outcomes of Salvage Surgery in Cases of Non-Curative Endoscopic Submucosal Dissection without Additional Radical Surgery for Early Gastric Cancer. Digestion 2019;99:52-58.
84. Yamada S, Hatta W, Shimosegawa T, et al. Different risk factors between early and late cancer recurrences in patients without additional surgery after noncurative endoscopic submucosal dissection for early gastric cancer. Gastrointest Endosc 2019;89:950-960.
85. Hatta W, Gotoda T, Oyama T, et al. A Scoring System to Stratify Curability after Endoscopic Submucosal Dissection for Early Gastric Cancer: "eCura system". Am J Gastroenterol 2017;112:874-881.
86. Hatta W, Gotoda T, Oyama T, et al. Is the eCura system useful for selecting patients who require radical surgery after noncurative endoscopic submucosal dissection for early gastric cancer? A comparative study. Gastric Cancer 2018;21:481-489.
87. Tanabe S, Hirabayashi S, Oda I, et al. Gastric cancer treated by endoscopic submucosal dissection or endoscopic mucosal resection in Japan from 2004 through 2006: JGCA nationwide registry conducted in 2013. Gastric Cancer 2017;20:834-842.
88. Park JC, Lee YK, Kim SY, et al. Long-term outcomes of endoscopic submucosal dissection in comparison to surgery in undifferentiated-type intramucosal gastric cancer using propensity score analysis. Surg Endosc 2018;32:2046-2057.
89. Lim JH, Kim J, Kim SG, et al. Long-term clinical outcomes of endoscopic vs. surgical resection for early gastric cancer with undifferentiated histology. Surg Endosc 2019;33:3589-3599.
90. Suzuki S, Gotoda T, Kobayashi Y, et al. Usefulness of a traction method using dental floss and a hemoclip for gastric endoscopic submucosal dissection: a propensity score matching analysis (with videos). Gastrointest Endosc 2016;83:337-46.
91. Goto O, Oyama T, Ono H, et al. Endoscopic hand-suturing is feasible, safe, and may reduce bleeding risk after gastric endoscopic submucosal dissection: a multicenter pilot study (with video). Gastrointest Endosc 2020;91:1195-1202.
92. Wang J, Wu Q, Yan Y, et al. Effectiveness of fibrin sealant as hemostatic technique in accelerating ESD-induced ulcer healing: a retrospective study. Surg Endosc 2020;34:1191-1199.
93. Hwang JJ, Hong SJ, Han JP, et al. Efficacy of Surgicel® (Fibrillar) for preventing bleeding after endoscopic submucosal dissection for gastric epithelial tumors. J Dig Dis 2018;19:657-663.
94. Hahn KY, Park JC, Lee YK, et al. Efficacy of hemostatic powder in preventing bleeding after gastric endoscopic submucosal dissection in high-risk patients. J Gastroenterol Hepatol 2018;33:656-663.
95. Tanaka S, Toyonaga T, Morita Y, et al. Efficacy of a new hemostatic forceps during gastric endoscopic submucosal dissection: A prospective randomized controlled trial. J Gastroenterol Hepatol 2017;32:846-851.
96. Horikawa Y, Toyonaga T, Mizutamari H, et al. Feasibility of Knife-Coagulated Cut in Gastric Endoscopic Submucosal Dissection: A Case-Control Study. Digestion 2016;94:192-198.
97. Tan ES, Wang H, Lua GW, et al. Fibrin Glue Spray as a Simple and Promising Method to Prevent Bleeding after Gastric Endoscopic Submucosal Dissection. Dig Surg 2016;33:455-61.

Supplementary material

98. Nakanishi H, Kurosaki M, Takahashi Y, et al. Pretreatment Gastric Lavage Reduces Postoperative Bleeding after Endoscopic Submucosal Dissection for Gastric Neoplasms. PLoS One 2016;11:e0149235.
99. Uraoka T, Ochiai Y, Fujimoto A, et al. A novel fully synthetic and self-assembled peptide solution for endoscopic submucosal dissection-induced ulcer in the stomach. Gastrointest Endosc 2016;83:1259-64.
100. Abdelfatah MM, Barakat M, Lee H, et al. The incidence of lymph node metastasis in early gastric cancer according to the expanded criteria in comparison with the absolute criteria of the Japanese Gastric Cancer Association: a systematic review of the literature and meta-analysis. Gastrointest Endosc 2018;87:338-347.
101. Hanada Y, Choi AY, Hwang JH, et al. Low Frequency of Lymph Node Metastases in Patients in the United States With Early-stage Gastric Cancers That Fulfill Japanese Endoscopic Resection Criteria. Clin Gastroenterol Hepatol 2019;17:1763-1769.
102. Pessorrusso FCS, Felipe-Silva A, Jacob CE, et al. Risk assessment of lymph node metastases in early gastric adenocarcinoma fulfilling expanded endoscopic resection criteria. Gastrointest Endosc 2018;88:912-918.
103. Probst A, Schneider A, Schaller T, et al. Endoscopic submucosal dissection for early gastric cancer: are expanded resection criteria safe for Western patients? Endoscopy 2017;49:855-865.
104. Kang HJ, Chung H, Kim SG, et al. Synergistic Effect of Lymphatic Invasion and Venous Invasion on the Risk of Lymph Node Metastasis in Patients with Non-Curative Endoscopic Resection of Early Gastric Cancer. J Gastrointest Surg 2019.
105. Kim HJ, Kim SG, Kim J, et al. Clinical outcomes of early gastric cancer with non-curative resection after pathological evaluation based on the expanded criteria. PLoS One 2019;14:e0224614.
106. Akaike H, Kawaguchi Y, Shiraishi K, et al. Validity of additional surgical resection by comparing the operative risk with the stratified lymph node metastatic risk in patients with early gastric cancer after endoscopic submucosal dissection. World J Surg Oncol 2019;17:136.
107. Niwa H, Ozawa R, Kurahashi Y, et al. The eCura system as a novel indicator for the necessity of salvage surgery after non-curative ESD for gastric cancer: A case-control study. PLoS One 2018;13:e0204039.
108. Goto A, Nishikawa J, Hideura E, et al. Lymph node metastasis can be determined by just tumor depth and lymphovascular invasion in early gastric cancer patients after endoscopic submucosal dissection. Eur J Gastroenterol Hepatol 2017;29:1346-1350.
109. Kawata N, Kakushima N, Takizawa K, et al. Risk factors for lymph node metastasis and long-term outcomes of patients with early gastric cancer after non-curative endoscopic submucosal dissection. Surg Endosc 2017;31:1607-1616.
110. Esaki M, Hatta W, Shimosegawa T, et al. Age Affects Clinical Management after Noncurative Endoscopic Submucosal Dissection for Early Gastric Cancer. Dig Dis 2019;37:423-433.
111. Li D, Luan H, Wang S, et al. Survival benefits of additional surgery after non-curative endoscopic resection in patients with early gastric cancer: a meta-analysis. Surg Endosc 2019;33:711-716.

Supplementary material

112. Jeon MY, Park JC, Hahn KY, et al. Long-term outcomes after noncurative endoscopic resection of early gastric cancer: the optimal time for additional endoscopic treatment. Gastrointest Endosc 2018;87:1003-1013.e2.
113. Hatta W, Gotoda T, Oyama T, et al. Is radical surgery necessary in all patients who do not meet the curative criteria for endoscopic submucosal dissection in early gastric cancer? A multi-center retrospective study in Japan. J Gastroenterol 2017;52:175-184.
114. Yano T, Ishido K, Tanabe S, et al. Long-term outcomes of patients with early gastric cancer found to have lesions for which endoscopic treatment is not indicated on histopathological evaluation after endoscopic submucosal dissection. Surg Endosc 2018;32:1314-1323.
115. Toyokawa T, Ohira M, Tanaka H, et al. Optimal management for patients not meeting the inclusion criteria after endoscopic submucosal dissection for gastric cancer. Surg Endosc 2016;30:2404-14.
116. Canete Ruiz A, Arribas Anta J, Alvarez-Nava Torrego T, et al. Endoscopic submucosal dissection for gastric epithelial lesions: long-term results in a Spanish cohort. Rev Esp Enferm Dig 2020;112:189-194.
117. Kim Y, Kuan JY, Ratcliffe E, et al. Long-term follow-up of endoscopic submucosal dissection of gastric dysplasia and early neoplasia in a United Kingdom Caucasian population - a tertiary centre experience. Scand J Gastroenterol 2020;55:18-26.
118. Pagano N, Frazzoni L, La Porta M, et al. Endoscopic submucosal dissection for superficial premalignant and malignant epithelial neoplasms of the digestive tract: a real-life experience in Italy. Eur Rev Med Pharmacol Sci 2019;23:8354-8359.
119. Tate DJ, Klein A, Sidhu M, et al. Endoscopic submucosal dissection for suspected early gastric cancer: absolute versus expanded criteria in a large Western cohort (with video). Gastrointest Endosc 2019;90:467-479 e4.
120. Costa RS, Ferreira A, Leal T, et al. Endoscopic Submucosal Dissection for the Treatment of Superficial Epithelial Gastric Neoplasia in a Portuguese Centre. GE Port J Gastroenterol 2019;26:90-98.
121. Mocker L, Hildenbrand R, Oyama T, et al. Implementation of endoscopic submucosal dissection for early upper gastrointestinal tract cancer after primary experience in colorectal endoscopic submucosal dissection. Endosc Int Open 2019;7:E446-E451.
122. Catalano F, Mengardo V, Trecca A, et al. The impact of experience on short- and long-term outcomes on gastric ESD: a western series. Updates Surg 2019;71:359-365.
123. Santos-Antunes J, Baldaque-Silva F, Marques M, et al. Real-life evaluation of the safety, efficacy and therapeutic outcomes of endoscopic submucosal dissection in a Western tertiary centre. United European Gastroenterol J 2018;6:702-709.
124. Aslan F, Alper E, Cekıc C, et al. Endoscopic submucosal dissection in gastric lesions: the 100 cases experience from a tertiary reference center in West. Scand J Gastroenterol 2015;50:368-75.
125. Liu S, Chai N, Lu Z, et al. Long-term outcomes of superficial neoplasia at the esophagogastric junction treated via endoscopic submucosal dissection and endoscopic submucosal tunnel dissection: a cohort study of a single center from China. Surg Endosc 2020;34:216-225.
126. Kim HJ, Chung H, Shin SK, et al. Comparison of long-term clinical outcomes between endoscopic and surgical resection for early-stage adenocarcinoma of the esophagogastric junction. Surg Endosc 2018;32:3540-3547.

Supplementary material

127. Kim JK, Kim GH, Lee BE, et al. Endoscopic submucosal dissection for esophagogastric junction tumors: a single-center experience. Surg Endosc 2018;32:760-769.
128. Gong EJ, Kim DH, Ahn JY, et al. Comparison of long-term outcomes of endoscopic submucosal dissection and surgery for esophagogastric junction adenocarcinoma. Gastric Cancer 2017;20:84-91.
129. Gong EJ, Kim do H, So H, et al. Clinical Outcomes of Endoscopic Submucosal Dissection for Adenocarcinoma of the Esophagogastric Junction. Dig Dis Sci 2016;61:2666-73.
130. Jang YS, Lee BE, Kim GH, et al. Factors Associated With Outcomes in Endoscopic Submucosal Dissection of Gastric Cardia Tumors: A Retrospective Observational Study. Medicine (Baltimore) 2015;94:e1201.
131. Park CH, Kim EH, Kim HY, et al. Clinical outcomes of endoscopic submucosal dissection for early stage esophagogastric junction cancer: a systematic review and meta-analysis. Dig Liver Dis 2015;47:37-44.
132. Choi JM, Kim SG, Yang HJ, et al. Endoscopic predictors for undifferentiated histology in differentiated gastric neoplasms prior to endoscopic resection. Surg Endosc 2016;30:89-98.
133. Nam HS, Choi CW, Kim SJ, et al. Preprocedural prediction of non-curative endoscopic submucosal dissection for early gastric cancer. PLoS One 2018;13:e0206179.
134. Kim SJ, Choi CW, Kang DH, et al. Preoperative predictors of beyond endoscopic submucosal dissection indication or lymphovascular invasion in endoscopic resection for early gastric cancer. Surg Endosc 2018;32:2948-2957.
135. Kim YI, Kim HS, Kook MC, et al. Discrepancy between Clinical and Final Pathological Evaluation Findings in Early Gastric Cancer Patients Treated with Endoscopic Submucosal Dissection. J Gastric Cancer 2016;16:34-42.
136. Choi IJ, Lee NR, Kim SG, et al. Short-Term Outcomes of Endoscopic Submucosal Dissection in Patients with Early Gastric Cancer: A Prospective Multicenter Cohort Study. Gut Liver 2016;10:739-48.
137. Kim EH, Park JC, Song IJ, et al. Prediction model for non-curative resection of endoscopic submucosal dissection in patients with early gastric cancer. Gastrointest Endosc 2017;85:976-983.
138. Ohara Y, Toshikuni N, Matsueda K, et al. The superficial elevated and depressed lesion type is an independent factor associated with non-curative endoscopic submucosal dissection for early gastric cancer. Surg Endosc 2016;30:4880-4888.
139. Cheng J, Wu X, Yang A, et al. Model to identify early-stage gastric cancers with deep invasion of submucosa based on endoscopy and endoscopic ultrasonography findings. Surg Endosc 2018;32:855-863.
140. Takamaru H, Yoshinaga S, Takisawa H, et al. Endoscopic Ultrasonography Miniature Probe Performance for Depth Diagnosis of Early Gastric Cancer with Suspected Submucosal Invasion. Gut Liver 2019.
141. Kim SJ, Choi CW, Kang DH, et al. Factors associated with the efficacy of miniprobe endoscopic ultrasonography after conventional endoscopy for the prediction of invasion depth of early gastric cancer. Scand J Gastroenterol 2017;52:864-869.

Supplementary material

142. Kim J, Kim SG, Chung H, et al. Clinical efficacy of endoscopic ultrasonography for decision of treatment strategy of gastric cancer. Surg Endosc 2018;32:3789-3797.
143. Kim TY, Yi NH, Hwang JW, et al. Morphologic pattern analysis of submucosal deformities identified by endoscopic ultrasonography for predicting the depth of invasion in early gastric cancer. Surg Endosc 2019;33:2169-2180.
144. Park JS, Kim H, Bang B, et al. Accuracy of endoscopic ultrasonography for diagnosing ulcerative early gastric cancers. Medicine (Baltimore) 2016;95:e3955.
145. Yoshii S, Yamada T, Yamaguchi S, et al. Efficacy of vonoprazan for the prevention of bleeding after gastric endoscopic submucosal dissection with continuous use of antiplatelet agents. Endosc Int Open 2020;8:E481-e487.
146. Pittayanon R, Martel M, Barkun A. Role of mucoprotective agents in endoscopic submucosal dissection-derived ulcers: A systematic review. J Gastroenterol Hepatol 2018;33:1948-1955.
147. Oh KH, Lee SJ, Park JK. Optimal duration of fasting period after endoscopic submucosal dissection for gastric epithelial neoplasia: A prospective evaluation. J Dig Dis 2017;18:445-452.
148. Kishida Y, Kakushima N, Takizawa K, et al. Effects of steroid use for stenosis prevention after wide endoscopic submucosal dissection for gastric neoplasm. Surg Endosc 2018;32:751-759.
149. Jung DH, Youn YH, Kim JH, et al. Factors influencing development of pain after gastric endoscopic submucosal dissection: a randomized controlled trial. Endoscopy 2015;47:1119-23.
150. Harada H, Suehiro S, Murakami D, et al. Feasibility of gastric endoscopic submucosal dissection with continuous low-dose aspirin for patients receiving dual antiplatelet therapy. World J Gastroenterol 2019;25:457-468.
151. Jaruvongvanich V, Sempokuya T, Wijarnpreecha K, et al. Continued versus interrupted aspirin use and bleeding risk after endoscopic submucosal dissection of gastric neoplasms: a meta-analysis. Ann Gastroenterol 2018;31:344-349.
152. Yamamoto Y, Nishisaki H, Sakai H, et al. Clinical Factors of Delayed Perforation after Endoscopic Submucosal Dissection for Gastric Neoplasms. Gastroenterol Res Pract 2017;2017:7404613.
153. Suzuki H, Oda I, Sekiguchi M, et al. Management and associated factors of delayed perforation after gastric endoscopic submucosal dissection. World J Gastroenterol 2015;21:12635-43.
154. Kim HJ, Chung H, Jung DH, et al. Clinical outcomes of and management strategy for perforations associated with endoscopic submucosal dissection of an upper gastrointestinal epithelial neoplasm. Surg Endosc 2016;30:5059-5067.
155. Gu L, Chen M, Khadaroo PA, et al. A Risk-Scoring Model for Predicting Lymph Node Metastasis in Early Gastric Cancer Patients: a Retrospective Study and External Validation. J Gastrointest Surg 2018;22:1508-1515.
156. Oh SY, Lee KG, Suh YS, et al. Lymph Node Metastasis in Mucosal Gastric Cancer: Reappraisal of Expanded Indication of Endoscopic Submucosal Dissection. Ann Surg 2017;265:137-142.

Supplementary material

157. Wang H, Zhang H, Wang C, et al. Expanded endoscopic therapy criteria should be cautiously used in intramucosal gastric cancer. Chin J Cancer Res 2016;28:348-54.
158. Zheng Z, Zhang Y, Zhang L, et al. A nomogram for predicting the likelihood of lymph node metastasis in early gastric patients. BMC Cancer 2016;16:92.
159. Choi AH, Nelson RA, Merchant SJ, et al. Rates of lymph node metastasis and survival in T1a gastric adenocarcinoma in Western populations. Gastrointest Endosc 2016;83:1184-1192.e1.
160. Feng H, Wang Y, Cao L, et al. Lymph node metastasis in differentiated-type early gastric cancer: a single-center retrospective analysis of surgically resected cases. Scand J Gastroenterol 2016;51:48-54.
161. Feng F, Sun L, Xu G, et al. Is It Reasonable to Treat Early Gastric Cancer with Mucosal Infiltration and Well Differentiation by Endoscopic Submucosal Resection? J Gastrointest Surg 2015;19:2111-9.
162. Zhao BW, Chen YM, Jiang SS, et al. Lymph Node Metastasis, a Unique Independent Prognostic Factor in Early Gastric Cancer. PLoS One 2015;10:e0129531.
163. Fang WL, Huang KH, Lan YT, et al. The Risk Factors of Lymph Node Metastasis in Early Gastric Cancer. Pathol Oncol Res 2015;21:941-6.

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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 monocentic 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		

References

[1] Hirashita T, Ohta M, Tada K, u. a. Prognostic factors of non-ampullary duodenal adenocarcinoma. Jpn J Clin Oncol 2018; 48: 743–747
[2] Goda K, Kikuchi D, Yamamoto Y, u. a. Endoscopic diagnosis of superficial non-ampullary duodenal epithelial tumors in Japan: Multicenter case series. Dig Endosc Off J Jpn Gastroenterol Endosc Soc 2014; 26 Suppl 2: 23–29
[3] Tsuji S, Doyama H, Tsuji K, u. a. Preoperative endoscopic diagnosis of superficial non-ampullary duodenal epithelial tumors, including magnifying endoscopy. World J Gastroenterol 2015; 21: 11832–11841
[4] Kikuchi D, Hoteya S, Iizuka T, u. a. Diagnostic algorithm of magnifying endoscopy with narrow band imaging for superficial non-ampullary duodenal epithelial tumors. Dig Endosc Off J Jpn Gastroenterol Endosc Soc 2014; 26 Suppl 2: 16–22
[5] Yoshimura N, Goda K, Tajiri H, u. a. Endoscopic features of nonampullary duodenal tumors with narrow-band imaging. Hepatogastroenterology 2010; 57: 462–467
[6] Azih LC, Broussard BL, Phadnis MA, u. a. Endoscopic ultrasound evaluation in the surgical treatment of duodenal and peri-ampullary adenomas. World J Gastroenterol 2013; 19: 511–515

Supplementary material

[7] Park J-S, Seo D-W, Song TJ, u. a. Usefulness of white-light imaging-guided narrow-band imaging for the differential diagnosis of small ampullary lesions. Gastrointest Endosc 2015; 82: 94–101
[8] Ridtitid W, Schmidt SE, Al-Haddad MA, u. a. Performance characteristics of EUS for locoregional evaluation of ampullary lesions. Gastrointest Endosc 2015; 81: 380–388
[9] Patel V, Jowell P, Obando J, u. a. Does ampullary adenoma size predict invasion on EUS? Does invasion on EUS predict presence of malignancy? Endosc Int Open 2016; 4: E1313–E1318
[10] Ito K, Fujita N, Noda Y. Endoscopic diagnosis and treatment of ampullary neoplasm (with video). Dig Endosc Off J Jpn Gastroenterol Endosc Soc 2011; 23: 113–117
[11] Rösch T, Kapfer B, Will U, u. a. Accuracy of endoscopic ultrasonography in upper gastrointestinal submucosal lesions: a prospective multicenter study. Scand J Gastroenterol 2002; 37: 856–862
[12] Will U, Fueldner F, Mueller A-K, u. a. A prospective study on endoscopic ultrasonography criteria to guide management in upper GI submucosal tumors. Pol Przegl Chir 2011; 83: 63–69
[13] Pih GY, Kim DH. Endoscopic Ultrasound-Guided Fine Needle Aspiration and Biopsy in Gastrointestinal Subepithelial Tumors. Clin Endosc 2019; 52: 314–320
[14] Yasuda K, Nakajima M, Kawai K. Endoscopic ultrasonography in the diagnosis of submucosal tumor of the upper digestive tract. Scand J Gastroenterol Suppl 1986; 123: 59–67
[15] Pérez-Cuadrado-Robles E, Quénéhervé L, Margos W, u. a. Comparative analysis of ESD versus EMR in a large European series of non-ampullary superficial duodenal tumors. Endosc Int Open 2018; 6: E1008–E1014
[16] Pérez-Cuadrado-Robles E, Quénéhervé L, Margos W, u. a. ESD versus EMR in non-ampullary superficial duodenal tumors: a systematic review and meta-analysis. Endosc Int Open 2018; 6: E998–E1007
[17] Hoteya S, Yahagi N, Iizuka T, u. a. Endoscopic submucosal dissection for nonampullary large superficial adenocarcinoma/adenoma of the duodenum: feasibility and long-term outcomes. Endosc Int Open 2013; 1: 2–7
[18] Marques J, Baldaque-Silva F, Pereira P, u. a. Endoscopic mucosal resection and endoscopic submucosal dissection in the treatment of sporadic nonampullary duodenal adenomatous polyps. World J Gastrointest Endosc 2015; 7: 720–727
[19] Matsumoto S, Miyatani H, Yoshida Y. Endoscopic submucosal dissection for duodenal tumors: a single-center experience. Endoscopy 2013; 45: 136–137
[20] Jung JH, Choi KD, Ahn JY, u. a. Endoscopic submucosal dissection for sessile, nonampullary duodenal adenomas. Endoscopy 2013; 45: 133–135
[21] Zou J, Chai N, Linghu E, u. a. Clinical outcomes of endoscopic resection for non-ampullary duodenal laterally spreading tumors. Surg

Supplementary material

Endosc 2019; 33: 4048–4056
[22] Lupu A, Faller J, Oung B, u. a. Endoscopic submucosal dissection using countertraction with clips and rubber band allows safe en bloc resection of recurrent duodenal superficial lesions with intense fibrosis. Endoscopy 2020;
[23] Oung B, Walter T, Hervieu V, u. a. Nonampullary duodenal subepithelial neuroendocrine tumor removed R0 by endoscopic submucosal dissection with double clips and rubber band traction. VideoGIE Off Video J Am Soc Gastrointest Endosc 2019; 4: 570–573
[24] Basford PJ, George R, Nixon E, u. a. Endoscopic resection of sporadic duodenal adenomas: comparison of endoscopic mucosal resection (EMR) with hybrid endoscopic submucosal dissection (ESD) techniques and the risks of late delayed bleeding. Surg Endosc 2014; 28: 1594–1600
[25] Kuroki K, Sanomura Y, Oka S, u. a. Clinical outcomes of endoscopic resection for superficial non-ampullary duodenal tumors. Endosc Int Open 2020; 8: E354–E359
[26] Kato M, Sasaki M, Mizutani M, u. a. Predictors of technical difficulty with duodenal ESD. Endosc Int Open 2019; 7: E1755–E1760
[27] Dohi O, Yoshida N, Naito Y, u. a. Efficacy and safety of endoscopic submucosal dissection using a scissors-type knife with prophylactic over-the-scope clip closure for superficial non-ampullary duodenal epithelial tumors. Dig Endosc Off J Jpn Gastroenterol Endosc Soc 2019;
[28] Yahagi N, Kato M, Ochiai Y, u. a. Outcomes of endoscopic resection for superficial duodenal epithelial neoplasia. Gastrointest Endosc 2018; 88: 676–682
[29] Nonaka S, Oda I, Tada K, u. a. Clinical outcome of endoscopic resection for nonampullary duodenal tumors. Endoscopy 2015; 47: 129–135
[30] Inoue T, Uedo N, Yamashina T, u. a. Delayed perforation: a hazardous complication of endoscopic resection for non-ampullary duodenal neoplasm. Dig Endosc Off J Jpn Gastroenterol Endosc Soc 2014; 26: 220–227
[31] He G, Wang J, Chen B, u. a. Feasibility of endoscopic submucosal dissection for upper gastrointestinal submucosal tumors treatment and value of endoscopic ultrasonography in pre-operation assess and post-operation follow-up: a prospective study of 224 cases in a single medical center. Surg Endosc 2016; 30: 4206–4213
[32] Li Q-L, Zhang Y-Q, Chen W-F, u. a. Endoscopic submucosal dissection for foregut neuroendocrine tumors: an initial study. World J Gastroenterol 2012; 18: 5799–5806
[33] Shroff SR, Kushnir VM, Wani SB, u. a. Efficacy of Endoscopic Mucosal Resection for Management of Small Duodenal Neuroendocrine Tumors. Surg Laparosc Endosc Percutan Tech 2015; 25: e134-139
[34] Kim GH, Kim JI, Jeon SW, u. a. Endoscopic resection for duodenal carcinoid tumors: a multicenter, retrospective study. J Gastroenterol Hepatol 2014; 29: 318–324
[35] Klein A, Nayyar D, Bahin FF, u. a. Endoscopic mucosal resection of large and giant lateral spreading lesions of the duodenum: success,

Supplementary material

adverse events, and long-term outcomes. Gastrointest Endosc 2016; 84: 688–696
[36] Hoteya S, Furuhata T, Takahito T, u. a. Endoscopic Submucosal Dissection and Endoscopic Mucosal Resection for Non-Ampullary Superficial Duodenal Tumor. Digestion 2017; 95: 36–42
[37] Hara Y, Goda K, Dobashi A, u. a. Short- and long-term outcomes of endoscopically treated superficial non-ampullary duodenal epithelial tumors. World J Gastroenterol 2019; 25: 707–718
[38] Tashima T, Nonaka K, Kurumi H, u. a. Successful traction-assisted endoscopic submucosal dissection using dental floss and a clip for a huge superficial nonampullary duodenal epithelial tumor with severe fibrosis (with video). JGH Open Open Access J Gastroenterol Hepatol 2019; 3: 179–181
[39] Goda Y, Mori H, Kobara H, u. a. Efficacy of sufficient operation view by ring-shaped thread counter traction for safer duodenal ESD. Minim Invasive Ther Allied Technol MITAT Off J Soc Minim Invasive Ther 2018; 27: 327–332
[40] Tashima T, Ohata K, Sakai E, u. a. Efficacy of an over-the-scope clip for preventing adverse events after duodenal endoscopic submucosal dissection: a prospective interventional study. Endoscopy 2018; 50: 487–496
[41] Hoteya S, Kaise M, Iizuka T, u. a. Delayed bleeding after endoscopic submucosal dissection for non-ampullary superficial duodenal neoplasias might be prevented by prophylactic endoscopic closure: analysis of risk factors. Dig Endosc Off J Jpn Gastroenterol Endosc Soc 2015; 27: 323–330
[42] Mori H, Ayaki M, Kobara H, u. a. Suitable closure for post-duodenal endoscopic resection taking medical costs into consideration. World J Gastroenterol 2015; 21: 5281–5286
[43] Fukuhara S, Kato M, Iwasaki E, u. a. Management of perforation related to endoscopic submucosal dissection for superficial duodenal epithelial tumors. Gastrointest Endosc 2020; 91: 1129–1137
[44] Nishizawa T, Akimoto T, Uraoka T, u. a. Endoscopic string clip suturing method: a prospective pilot study (with video). Gastrointest Endosc 2018; 87: 1074–1078
[45] Otowa Y, Kanaji S, Morita Y, u. a. Safe management of laparoscopic endoscopic cooperative surgery for superficial non-ampullary duodenal epithelial tumors. Endosc Int Open 2017; 5: E1153–E1158
[46] Irino T, Nunobe S, Hiki N, u. a. Laparoscopic-endoscopic cooperative surgery for duodenal tumors: a unique procedure that helps ensure the safety of endoscopic submucosal dissection. Endoscopy 2015; 47: 349–351
[47] Ichikawa D, Komatsu S, Dohi O, u. a. Laparoscopic and endoscopic co-operative surgery for non-ampullary duodenal tumors. World J Gastroenterol 2016; 22: 10424–10431
[48] Kyuno D, Ohno K, Katsuki S, u. a. Laparoscopic-endoscopic cooperative surgery is a safe and effective treatment for superficial nonampullary duodenal tumors. Asian J Endosc Surg 2015; 8: 461–464

Supplementary material

[49] Takimoto K, Imai Y, Matsuyama K. Endoscopic tissue shielding method with polyglycolic acid sheets and fibrin glue to prevent delayed perforation after duodenal endoscopic submucosal dissection. Dig Endosc Off J Jpn Gastroenterol Endosc Soc 2014; 26 Suppl 2: 46–49
[50] Doyama H, Tominaga K, Yoshida N, u. a. Endoscopic tissue shielding with polyglycolic acid sheets, fibrin glue and clips to prevent delayed perforation after duodenal endoscopic resection. Dig Endosc Off J Jpn Gastroenterol Endosc Soc 2014; 26 Suppl 2: 41–45
[51] Valli PV, Mertens JC, Sonnenberg A, u. a. Nonampullary Duodenal Adenomas Rarely Recur after Complete Endoscopic Resection: A Swiss Experience Including a Literature Review. Digestion 2017; 96: 149–157
[52] Tomizawa Y, Ginsberg GG. Clinical outcome of EMR of sporadic, nonampullary, duodenal adenomas: a 10-year retrospective. Gastrointest Endosc 2018; 87: 1270–1278
[53] Probst A, Freund S, Neuhaus L, u. a. Complication risk despite preventive endoscopic measures in patients undergoing endoscopic mucosal resection of large duodenal adenomas. Endoscopy 2020;
[54] Ojima T, Nakamori M, Nakamura M, u. a. Laparoscopic and Endoscopic Cooperative Surgery Versus Endoscopic Submucosal Dissection for the Treatment of Low-Risk Tumors of the Duodenum. J Gastrointest Surg Off J Soc Surg Aliment Tract 2018; 22: 935–940
[55] Abbass R, Rigaux J, Al-Kawas FH. Nonampullary duodenal polyps: characteristics and endoscopic management. Gastrointest Endosc 2010; 71: 754–759
[56] Alexander S, Bourke MJ, Williams SJ, u. a. EMR of large, sessile, sporadic nonampullary duodenal adenomas: technical aspects and long-term outcome (with videos). Gastrointest Endosc 2009; 69: 66–73
[57] Matsumoto S, Yoshida Y. Selection of appropriate endoscopic therapies for duodenal tumors: An open-label study, single-center experience. World J Gastroenterol WJG 2014; 20: 8624–8630
[58] Hara Y, Goda K, Dobashi A, u. a. Short- and long-term outcomes of endoscopically treated superficial non-ampullary duodenal epithelial tumors. World J Gastroenterol 2019; 25: 707–718
[59] Nagata K, Shimizu M. Pathological evaluation of gastrointestinal endoscopic submucosal dissection materials based on Japanese guidelines. World J Gastrointest Endosc 2012; 4: 489–499
[60] Lauwers GY, Ban S, Mino M, u. a. Endoscopic mucosal resection for gastric epithelial neoplasms: a study of 39 cases with emphasis on the evaluation of specimens and recommendations for optimal pathologic analysis. Mod Pathol Off J U S Can Acad Pathol Inc 2004; 17: 2–8
[61] Schlemper RJ, Riddell RH, Kato Y, u. a. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000; 47: 251–255
[62] Yoshida M, Shimoda T, Abe M, u. a. Clinicopathological characteristics of non-ampullary duodenal tumors and their phenotypic classification. Pathol Int 2019; 69: 398–406
[63] Toba T, Inoshita N, Kaise M, u. a. Clinicopathological features of superficial non-ampurally duodenal epithelial tumor; gastric phenotype of histology correlates to higher malignant potency. J Gastroenterol 2018; 53: 64–70

Supplementary material

[64] Mitsuishi T, Hamatani S, Hirooka S, u. a. Clinicopathological characteristics of duodenal epithelial neoplasms: Focus on tumors with a gastric mucin phenotype (pyloric gland-type tumors). PloS One 2017; 12: e0174985
[65] Zenali M, Overman MJ, Rashid A, u. a. Clinicopathologic features and prognosis of duodenal adenocarcinoma and comparison with ampullary and pancreatic ductal adenocarcinoma. Hum Pathol 2013; 44: 2792–2798
[66] Oka S, Tanaka S, Nagata S, u. a. Clinicopathologic features and endoscopic resection of early primary nonampullary duodenal carcinoma. J Clin Gastroenterol 2003; 37: 381–386
[67] Takahashi T, Ando T, Kabeshima Y, u. a. Borderline cases between benignancy and malignancy of the duodenum diagnosed successfully by endoscopic submucosal dissection. Scand J Gastroenterol 2009; 44: 1377–1383
[68] Michelassi F, Erroi F, Dawson PJ, u. a. Experience with 647 consecutive tumors of the duodenum, ampulla, head of the pancreas, and distal common bile duct. Ann Surg 1989; 210: 544–556
[69] Onkendi EO, Boostrom SY, Sarr MG, u. a. 15-year experience with surgical treatment of duodenal carcinoma: a comparison of periampullary and extra-ampullary duodenal carcinomas. J Gastrointest Surg Off J Soc Surg Aliment Tract 2012; 16: 682–691
[70] Galandiuk S, Hermann RE, Jagelman DG, u. a. Villous tumors of the duodenum. Ann Surg 1988; 207: 234–239
[71] Lépilliez V, Chemaly M, Ponchon T, u. a. Endoscopic resection of sporadic duodenal adenomas: an efficient technique with a substantial risk of delayed bleeding. Endoscopy 2008; 40: 806–810
[72] Navaneethan U, Lourdusamy D, Mehta D, u. a. Endoscopic resection of large sporadic non-ampullary duodenal polyps: efficacy and long-term recurrence. Surg Endosc 2014; 28: 2616–2622
[73] Klein A, Ahlenstiel G, Tate DJ, u. a. Endoscopic resection of large duodenal and papillary lateral spreading lesions is clinically and economically advantageous compared with surgery. Endoscopy 2017; 49: 659–667
[74] Basford PJ, Bhandari P. Endoscopic management of nonampullary duodenal polyps. Ther Adv Gastroenterol 2012; 5: 127–138
[75] Lim C-H, Cho Y-S. Nonampullary duodenal adenoma: Current understanding of its diagnosis, pathogenesis, and clinical management. World J Gastroenterol 2016; 22: 853–861
[76] Zou J, Chai N, Linghu E, u. a. Clinical outcomes of endoscopic resection for non-ampullary duodenal laterally spreading tumors. Surg Endosc 2019; 33: 4048–4056
[77] Ishii N, Akiyama H, Suzuki K, u. a. Safety and Efficacy of Endoscopic Submucosal Dissection for Non-Ampullary Duodenal Neoplasms: A Case Series. ACG Case Rep J 2015; 2: 146–149
[78] Yamamoto Y, Yoshizawa N, Tomida H, u. a. Therapeutic outcomes of endoscopic resection for superficial non-ampullary duodenal tumor. Dig Endosc Off J Jpn Gastroenterol Endosc Soc 2014; 26 Suppl 2: 50–56

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

Supplementary material

			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

Supplementary material

					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 (072-0.81) 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/

