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# Diagnosis and management of Barrett esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

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## MAIN RECOMMENDATIONS

**MR1** ESGE recommends the following standards for Barrett esophagus (BE) surveillance:
– a minimum of 1-minute inspection time per cm of BE length during a surveillance endoscopy
– photodocumentation of landmarks, the BE segment including one picture per cm of BE length, and the esophagogastric junction in retroflexed position, and any visible lesions
– use of the Prague and (for visible lesions) Paris classification
– collection of biopsies from all visible abnormalities (if present), followed by random four-quadrant biopsies for every 2-cm BE length.
Strong recommendation, weak quality of evidence.

**MR2** ESGE suggests varying surveillance intervals for different BE lengths. For BE with a maximum extent of ≥ 1 cm and < 3 cm, BE surveillance should be repeated every 5 years. For BE with a maximum extent of ≥ 3 cm and < 10 cm, the interval for endoscopic surveillance should be 3 years. Patients with BE with a maximum extent of ≥ 10 cm should be referred to a BE expert center for surveillance endoscopies.
For patients with an irregular Z-line/columnar-lined esophagus of < 1 cm, no routine biopsies or endoscopic surveillance are advised.
Weak recommendation, low quality of evidence.

**MR3** ESGE suggests that, if a patient has reached 75 years of age at the time of the last surveillance endoscopy and/or the patient's life expectancy is less than 5 years, the discontinuation of further surveillance endoscopies can be considered.
Weak recommendation, very low quality of evidence.

**MR4** ESGE recommends offering endoscopic eradication therapy using ablation to patients with BE and low grade dysplasia (LGD) on at least two separate endoscopies, both confirmed by a second experienced pathologist.
Strong recommendation, high level of evidence.

**MR5** ESGE recommends endoscopic ablation treatment for BE with confirmed high grade dysplasia (HGD) without visible lesions, to prevent progression to invasive cancer.
Strong recommendation, high level of evidence.

**MR6** ESGE recommends offering complete eradication of all remaining Barrett epithelium by ablation after endoscopic resection of visible abnormalities containing any degree of dysplasia or esophageal adenocarcinoma (EAC).
Strong recommendation, moderate quality of evidence.

**MR7** ESGE recommends endoscopic resection as curative treatment for T1a Barrett's cancer with well/moderate differentiation and no signs of lymphovascular invasion.
Strong recommendation, high level of evidence.

**MR8** ESGE suggests that low risk submucosal (T1b) EAC (i. e. submucosal invasion depth ≤ 500 µm AND no [lympho] vascular invasion AND no poor tumor differentiation) can be treated by endoscopic resection, provided that adequate follow-up with gastroscopy, endoscopic ultrasound (EUS), and computed tomography (CT)/positron emission tomography-computed tomography (PET-CT) is performed in expert centers.
Weak recommendation, low quality of evidence.

**MR9** ESGE suggests that submucosal (T1b) esophageal adenocarcinoma with deep submucosal invasion (tumor invasion > 500 µm into the submucosa), and/or (lympho)vascular invasion, and/or a poor tumor differentiation should be considered high risk. Complete staging and consideration of additional treatments (chemotherapy and/or radiotherapy and/or surgery) or strict endoscopic follow-up should be undertaken on an individual basis in a multidisciplinary discussion.
Strong recommendation, low quality of evidence.

**MR10 a** ESGE recommends that the first endoscopic follow-up after successful endoscopic eradication therapy (EET) of BE is performed in an expert center.
Strong recommendation, very low quality of evidence.

**b** ESGE recommends careful inspection of the neo-squamocolumnar junction and neo-squamous epithelium with high definition white-light endoscopy and virtual chromoendoscopy during post-EET surveillance, to detect recurrent dysplasia.
Strong recommendation, very low level of evidence.

**c** ESGE recommends against routine four-quadrant biopsies of neo-squamous epithelium after successful EET of BE.
Strong recommendation, low level of evidence.

**d** ESGE suggests, after successful EET, obtaining four-quadrant random biopsies just distal to a normal-appearing neo-squamocolumnar junction to detect dysplasia in the absence of visible lesions.
Weak recommendation, low level of evidence.

**e** ESGE recommends targeted biopsies are obtained where there is a suspicion of recurrent BE in the tubular esophagus, or where there are visible lesions suspicious for dysplasia.

Strong recommendation, very low level of evidence.

**MR11** After successful EET, ESGE recommends the following surveillance intervals:

– For patients with a baseline diagnosis of HGD or EAC:
at 1, 2, 3, 4, 5, 7, and 10 years after last treatment, after which surveillance may be stopped.
– For patients with a baseline diagnosis of LGD:
at 1, 3, and 5 years after last treatment, after which surveil-

**ABBREVIATIONS**

| | |
|---|---|
| **AAC** | acetic acid chromoendoscopy |
| **AE** | adverse event |
| **APC** | argon plasma coagulation |
| **BE** | Barrett esophagus |
| **BE-IND** | indefinite for dysplasia in a patient with BE |
| **CE IM** | complete eradication of intestinal metaplasia |
| **CT** | computed tomography |
| **EAC** | esophageal adenocarcinoma |
| **EET** | endoscopic eradication therapy |
| **EMR** | endoscopic mucosal resection |
| **ER** | endoscopic resection |
| **ESD** | endoscopic submucosal dissection |
| **ESGE** | European Society of Gastrointestinal Endoscopy |
| **EUS** | endoscopic ultrasound |
| **GERD** | gastroesophageal reflux disease |
| **HGD** | high grade dysplasia |
| **IHC** | immunohistochemistry |
| **IM** | intestinal metaplasia |
| **LNM** | lymph node metastasis |
| **MDM** | methylated DNA marker |
| **NBI** | narrow-band imaging |
| **NLR** | neutrophil-to-lymphocyte ratio |
| **NSAID** | nonsteroidal anti-inflammatory drug |
| **OR** | odds ratio |
| **PDT** | photodynamic therapy |
| **PET** | positron emission tomography |
| **PPI** | proton pump inhibitor |
| **RFA** | radiofrequency ablation |
| **TTF-3** | Trefoil-factor 3 |
| **WLE** | white-light endoscopy |

**SCOPE AND PURPOSE**

This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). It is an update of the previous (2017) Position Statement on the endoscopic management of Barrett esophagus.

## 1 Introduction

In 2017, the European Society of Gastrointestinal Endoscopy (ESGE) published their first Position Statement on the endoscopic management of Barrett esophagus (BE) [1]. The purpose of that document was to optimize patient management according to the best scientific evidence, and to harmonize the diagnosis and care for patients with BE.

Since the publication of the Position Statement, new evidence has emerged on various aspects of BE management. Therefore, the 2017 Position Statement on the endoscopic management of BE was updated, using a systematic review methodology. Additional recommendations were formulated on the screening, surveillance, and management of BE. The aim of this document is to deliver a practical guide, even when supporting evidence is weak [2].

## 2 Methods

The ESGE commissioned this Guideline (Guideline Committee Chair, K.T.) and appointed a Guideline Leader (B.W.). In October 2021, an invitational email to join the guideline group was sent out to several key opinion leaders in the field of BE and BE-related neoplasia. Individual ESGE members were informed about this Guideline revision and were asked to apply if they were interested in contributing to the Guideline. Seven individual members (E.C., M.B.*, R.E.P., A.R., G.F.-E., M.J., and F.B.-S.) were selected based on their expertise and scientific output. Finally, a guideline group was formed comprising of 20 members.

All guideline group members reviewed all of the statements in the 2017 ESGE Position Statement on the endoscopic management of BE to identify statements on which new evidence had emerged since its date of publication, and determine which statements could be retained. In addition, all guideline group members were asked to identify potential new areas to be covered in the revised guideline. In total, six statements from the 2017 Position Statement on the endoscopic management of BE were retained. These statements are listed in ▶ **Table 1**.

Six taskforces were created, based on the input of the guideline group members: chemoprevention, screening and case finding, surveillance, pathology sampling and risk stratification, treatment, and management after endoscopic treatment. A taskforce leader was appointed for each of these (M.D.-R., M.C.W.S., R.B., M.d.P., O.P., and R.E.P., respectively) and group members were assigned to one or more taskforces (**Appendix 1 s**, see online-only Supplementary Material).

* M.B. represented the Société Française d'Endoscopie Digestive

▶ **Table 1** Statements preserved from the 2017 ESGE Position Statement on the endoscopic management of Barrett esophagus (BE) [1].

| | |
|---|---|
| 1 | The diagnosis of BE is made if the distal esophagus is lined with columnar epithelium with a minimum length of 1 cm (tongues or circular) containing intestinal metaplasia at histopathological examination |
| 2 | The diagnosis of any degree of dysplasia (including "indefinite for dysplasia") in BE requires confirmation by an expert gastrointestinal (GI) pathologist |
| 3 | Patients with a diagnosis of "indefinite for dysplasia" confirmed by a second expert GI pathologist should be managed with optimization of antireflux medication and repeat endoscopy at 6 months. If no definite dysplasia is found in subsequent biopsy samples (including if the biopsies are again classified as "indefinite for dysplasia"), then the surveillance strategy should follow the recommendation for nondysplastic BE |
| 4 | Patients with LGD on random biopsies confirmed by a second expert GI pathologist should be referred to a BE expert center. A surveillance interval of 6 months after confirmed LGD diagnosis is recommended.<br>i) If no dysplasia is found at the 6-month endoscopy, the interval can be broadened to 1 year. After two subsequent endoscopies negative for dysplasia, standard surveillance for patients with nondysplastic BE can be initiated.<br>ii) If a confirmed diagnosis of LGD is found in the subsequent endoscopies, endoscopic ablation should be offered. |
| 5 | Prophylactic endoscopic therapy (such as ablation therapy) for non-neoplastic BE should not be performed |
| 6 | All patients with a BE ≥ 10 cm, a confirmed diagnosis of LGD, HGD, or early cancer should be referred to a BE expert center for surveillance and/or treatment.<br>A BE expert center should meet the following requirements:<br>(i) annual case load of ≥ 10 NEW patients with endoscopic treatment for HGD or early carcinoma per BE expert endoscopist<br>(ii) endoscopic and histologic care is provided by endoscopists and pathologists who have followed additional training in this field (either by courses or guest visits) – a minimum of 30 supervised cases of endoscopic resection and 30 cases of endoscopic ablation should be performed to acquire competence in technical skills, management pathways, and complications<br>(iii) patients with Barrett's neoplasia are discussed in multidisciplinary meetings<br>(iv) access to experienced esophageal surgery<br>(v) all patients with BE are registered prospectively in a database |

LGD, low grade dysplasia; HGD, high grade dysplasia.

The kick-off meeting for this guideline was held virtually using an online platform on November 22, 2021. Clinical questions were formulated, and subsequently translated into research questions. The research questions followed the PICO format (P, population in question; I, intervention; C, comparator; and O, outcomes of interest) where appropriate. Systematic literature searches were performed using MEDLINE, Embase, and the Cochrane library. Evidence levels and recommendation strengths were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [3]. Further details on the methodology of ESGE guidelines have been reported elsewhere [2].

The results of data extraction are available in the evidence tables viewable at the ESGE website: https://www.esge.com/assets/downloads/pdfs/guidelines/a_2176_2440_Evidence_tables.pdf. Available literature, draft recommendations, and strength of evidence were discussed during a face-to-face meeting at Schiphol Airport, Amsterdam on September 24, 2022. Subsequently, further refinement of the recommendations was carried out using an online voting platform (https://docs.google.com/forms). Voting was based upon a five-point Likert scale (1, strongly disagree; 2, disagree; 3, neither disagree nor agree; 4, agree; 5, strongly agree). All respondents were invited to leave comments supporting their votes, on the basis of which the recommendations were adjusted. In total, two iterations of the online voting process were needed to reach the final document.

In April 2023, a draft prepared by B.W. and R.E.P. was sent to all group members. A revised version was drafted based on the feedback received. After the agreement of all group members had been obtained, the manuscript was reviewed by the ESGE Guideline Committee Chair (K.T.) and two external reviewers, and was sent for further comments to the ESGE national societies and individual members. After this, it was submitted to *Endoscopy* for publication. All participants declared any potential conflicts of interest.

## 3 Background

BE is a condition in which the distal esophagus is lined with columnar epithelium with a minimum length of 1 cm (either tongues or circumferentially) containing intestinal metaplasia (IM) on histopathologic examination (▶ **Table 1**) [1].

BE has an estimated prevalence of up to 1 %–2 % based on two large population-based studies from Europe and two systematic reviews. In those with chronic gastroesophageal reflux disease (GERD) symptoms, it may increase to 8 %–13 % [4–9], although a recent prospective screening study in patients aged 50 years or older with GERD symptoms also demonstrated a prevalence of 2 % [10]. BE is a condition predisposing to esophageal adenocarcinoma (EAC). Although the risk of progression to high grade dysplasia (HGD) or EAC is low (0.3 %–0.8 % per year [11–13]), in most countries patients with BE are managed with endoscopic surveillance at regular intervals, because the consequences of a diagnosis of invasive adenocarcinoma are severe with high lethality and treatment-associated morbidity.

## 4 Chemoprevention

**RECOMMENDATION 1**

**a** ESGE suggests a proton pump inhibitor (standard dose* once daily) for chemoprevention in patients with BE.

Weak recommendation, moderate quality of evidence.

**b** ESGE recommends against the use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) for chemoprevention.

Strong recommendation, moderate quality of evidence.

It is widely accepted that BE and EAC are related to GERD. Proton pump inhibitors (PPIs), through their acid-suppressive effects and potential antioxidant and anti-inflammatory effects, may potentially prevent carcinogenesis [15]. In patients with BE, PPIs are primarily indicated for their control of reflux symptoms. There is however increasing evidence that PPIs may have a chemopreventive effect among BE patients based on five systematic reviews including meta-analyses of observational studies and one multicenter randomized controlled trial (RCT) [16–21].

In a large meta-analysis of 12 observational studies with 155 769 subjects, PPI use was associated with a two-fold risk reduction of BE progression to HGD/EAC (odds ratio [OR] 0.47, 95 %CI 0.32–0.71) [19].

The AspECT trial enrolled 2557 BE patients who were followed up for a median of 8.9 years and received high dose (40 mg twice daily) or low dose (20 mg once daily) PPI, with or without aspirin [20]. This trial demonstrated that high dose PPI is superior to low dose PPI in the primary composite end point of time to all-cause mortality or development of HGD or EAC (time ratio [TR] 1.27, 95 %CI 1.01–1.58), with a number needed to treat of 34. In fact, combining high dose PPI with aspirin had the strongest effect compared with low dose PPI without aspirin (TR 1.59, 95 %CI 1.14–2.23), suggesting an additive effect, whereas differences in the primary end point between aspirin and no aspirin failed to reach a statistically significant difference. However, despite being well conducted, this trial did not include a no-PPI group, and used a composite end point including all-cause mortality. Therefore, based on the AspECT trial, no conclusion can be drawn about the effect of high dose PPI or aspirin on cancer progression and their use as chemopreventive agents.

Long-term PPI administration has garnered interest with regards to potential side effects; however, most associations have failed to demonstrate conclusive evidence and/or document a causal relationship. The structural and functional changes in the gastric mucosa, the increased risk of enteric infections, and the potential interference with the absorption of vitamin $B_{12}$, magnesium, and calcium are putative associations that need further confirmation [22]. In fact, these associations have recently been studied in a randomized, double-blind trial of 17 598 patients who received either PPI or placebo and were followed up for 3.01 years. This trial demonstrated no associations, except for enteric infections (OR 1.33, 95 %CI 1.01–1.75) [23]. In addition, the aforementioned AspECT trial demonstrated a favorable safety profile for high dose PPI [20].

In summary, GERD symptom control and reflux esophagitis healing are clear indications for PPI. A secondary benefit from curtailing mucosal inflammation with regard to neoplastic disease progression is plausible and studies support this contention. Further study is required to determine if the use of PPI for chemoprevention is most efficacious in patient groups at higher risk of progression (e. g. male sex, long BE segment, family history). Given the required cohort sizes to draw meaningful conclusions, these data are most likely to come from real-world data.

Other agents, such as statins, metformin, bisphosphonates, nonsteroidal anti-inflammatory drugs (NSAIDs), and ursodeoxycholic acid, have insufficient evidence for their role in chemoprevention in BE patients.

## 5 Screening and case finding

**RECOMMENDATION 2**

**a** ESGE recommends against screening for BE in an unselected population.

Strong recommendation, low quality of evidence.

**b** ESGE suggests that case finding for BE could be considered in a select population, consisting of patients ≥ 50 years of age with a history of chronic GERD symptoms, and at least one of the following risk factors (white ethnicity, male sex, obesity, smoking, having a first-degree relative with BE or EAC).

Weak recommendation, low quality of evidence.

Screening for BE or EAC in an unselected population is not recommended because of the relatively low risk in the general population, the estimated prevalence in a general population being up to 1 %–2 % [4–9], with an annual risk of progression to HGD or EAC of 0.3 %–0.8 % [11–13]. Therefore, the (cost)effectiveness of BE screening programs has been disputed [24–26]. The ESGE suggests that, if screening is considered, it should be limited to a select population with a high anticipated BE prevalence in order to be acceptable and cost-effective.

The prevalence of BE in individuals with known risk factors has recently been assessed in a systematic review and meta-analysis by Qumseya et al. [27]. BE prevalence was low (0.8 %) in individuals without GERD symptoms. A higher prevalence was found in individuals with known risk factors for BE, such as family history of BE/EAC (23 %), male sex (6.8 %), age > 50 years (6.1 %), GERD (2.3 %), and obesity (1.9 %). Also, the prevalence in patients with GERD symptoms and one additional risk factor

* Standard PPI dose for the indication "severe esophagitis" is omeprazole 40 mg or its dose equivalent (pantoprazole 40 mg, esomeprazole 40 mg, rabeprazole 20 mg, or lansoprazole 30 mg) [14].

was significantly higher (12.2 %) than in individuals with GERD symptoms alone. A positive linear relationship was shown between BE prevalence and the number of risk factors, increasing the prevalence of BE by 1.2 % for each additional risk factor. These data support the concept of case finding of BE in select individuals with GERD symptoms and at least one additional risk factor. It must be noted that approximately 50 %–60 % of all BE cases occur in patients without GERD symptoms [28, 29]. These patients will be missed when adhering to the currently suggested strategies for screening and case finding, because these all require GERD symptoms as an indication for screening. However, given the large population of individuals without GERD symptoms, all-comer screening would lead to substantial economic costs.

The cost-effectiveness of screening programs may be improved by using prediction tools that incorporate multiple risk factors (i. e. GERD symptoms, white ethnicity, obesity, male sex, age ≥ 50 years, smoking, family history) to select patients for screening. Such prediction tools have already been studied [30] but, because these were retrospective analyses, additional prospective studies using questionnaires or electronic tools are needed before clinical implementation can be considered. Finally, new screening modalities that do not require sedation may be more cost-effective than screening with standard sedated endoscopy [26]. With the implementation of such modalities, the indications for BE screening/case finding may be expanded in the future.

### 5.1 Nonendoscopic technologies

**RECOMMENDATION 3**

ESGE recommends that a swallowable nonendoscopic cell collection device such as the Cytosponge, combined with a cytopathologic assessment and biomarker Trefoil-factor 3 (TFF3) can be used as an alternative to endoscopy for case finding of BE. Other nonendoscopic technologies cannot yet be recommended.

Strong recommendation, high quality of evidence for Cytosponge, low quality of evidence for other nonendoscopic technologies.

There has been a recent emergence of minimally invasive, nonendoscopic cell sampling devices that can be administered in an office-based setting, typically by a trained nurse. Most of the evidence to date is for swallowable esophageal sampling devices that are encapsulated and expand when the capsule dissolves, such as the Cytosponge (Medtronic, Watford, UK) and EsophaCap, or an inflatable silicon balloon, such as the EsoCheck. These devices are deployed to the upper stomach and withdrawn orally, and the samples obtained are sent to a central laboratory for processing. The samples are then tested for biomarkers to assess for the presence of BE: hematoxylin and eosin (H&E) coupled with immunohistochemistry (IHC) for Trefoil-factor 3 (TFF3) is used to detect IM (Cytosponge) [10, 31, 32]; combined cytopathology and IHC for MUC2 to detect IM (EsophaCap) [33]; or a quantitative polymerase-based assay is used to detect a panel of methylated DNA markers (MDMs) to predict the presence of BE mucosa (EsophaCap and EsoCheck) [34–38].

Among these technologies, by far the largest body of evidence pertains to the Cytosponge, which has been rigorously tested in both observational case–control studies and a randomized trial in the intended screening population. A recent trial, the Barrett Esophagus Screening Trial 3 (BEST3), a multicenter, pragmatic RCT that was conducted in over 13 000 individuals from > 100 primary care practices in the UK, showed that the offer of a Cytosponge test was associated with a 10-fold higher rate of diagnosis of BE compared with usual care among a screening population reporting symptoms of reflux disease and taking a PPI [10]. As a secondary outcome, those randomized to the Cytosponge group also had more dysplastic BE (n = 5) and early stage EAC (n = 4) diagnosed, compared with usual care, suggesting that screening using the Cytosponge could lead to earlier stage disease diagnosis, although the study was not powered for this analysis. In addition, it was shown that the interpretation of TFF3 positivity could be performed in an automated manner, thereby significantly reducing pathologist workload [39]. Further, modelling studies suggest Cytosponge TFF3-based screening to be cost-effective when used on a hypothetical population of white individuals aged ≥ 50 years with acid reflux symptoms [40, 41].

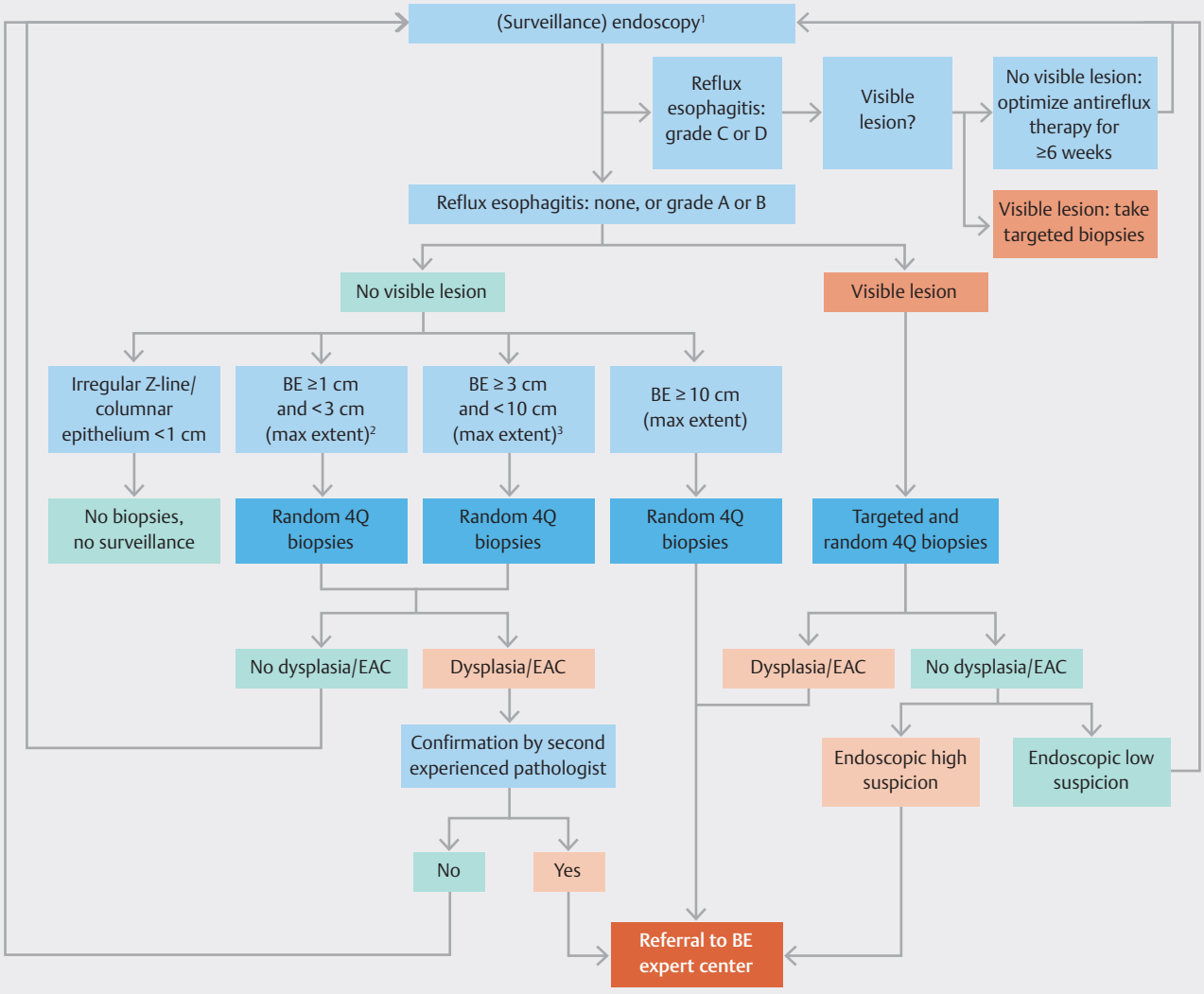
Other nonendoscopic technologies such as the EsophaCap [34, 36–38], EsoCheck [35], and Cytosponge combined with MDMs [42] have also shown significant promise, although their evidence to date has been limited to small observational studies in enriched populations. Studies to test these technologies on a screening population are ongoing.

For a further discussion of potential alternative screening and case finding modalities, please refer to **Appendix 2 s**. A detailed discussion of the effect of a positive family history of BE/EAC on the prevalence of BE is provided in **Appendix 3 s**.

## 6 Surveillance

In accordance with the 2017 ESGE Position Statement on the endoscopic management of BE, the Working Group recommends endoscopic surveillance of patients with BE [1]. However, for the individual patient, patient factors should explicitly be taken into consideration, such as co-morbidity, life expectancy, and patient preferences. The Working Group wishes to underscore that BE surveillance is only indicated if detection of dysplasia or EAC would reasonably impact a patient's management.

A flowchart showing the recommended BE surveillance intervals, biopsy practice, and when to refer a patient to a BE expert center is provided in ▶ **Fig. 1**.




▶ **Fig. 1** Flowchart of the recommended surveillance for patients with Barret esophagus (BE).
4Q, four quadrant; EAC, esophageal adenocarcinoma.
[1] Consider stopping surveillance if a patient has reached the age of 75 at the time of the last surveillance endoscopy.
[2] Surveillance interval 5 years.
[3] Surveillance interval 3 years.

## 6.1 Endoscopy equipment and (virtual) chromoendoscopy

**RECOMMENDATION 4**

**a** ESGE recommends the use of high definition endoscopy for endoscopic surveillance of BE.
Strong recommendation, low quality of evidence.

**b** ESGE suggests the use of chromoendoscopy (acetic acid and/or virtual chromoendoscopy) for endoscopic surveillance of BE.
Weak recommendation, low quality of evidence.

High definition endoscopy systems (endoscope, processor, and screen) provide superior image resolution and are widely available; however, the role of high definition endoscopy systems in BE surveillance is based on limited low quality studies. In a retrospective study, a high definition endoscopy system was superior to a standard definition system in detecting dysplastic lesions, and in detecting HGD or cancer on random and targeted biopsies [43]. Given its inferior imaging quality and limited biopsy sampling capability, transnasal endoscopy should not be used for BE surveillance.

With regard to narrow-band imaging (NBI), there are studies demonstrating a significantly higher rate of dysplasia detection with fewer biopsies when the use of NBI is compared with standard resolution white-light endoscopy (WLE) [44], but no

differences in detection rate when NBI is compared with high definition WLE with four-quadrant biopsies [45].

Acetic acid chromoendoscopy (AAC) has been studied for its usefulness to detect Barrett neoplasia in several studies [46]. Longcroft-Wheaton et al. reported on a feasibility study in which patients scheduled for BE surveillance underwent two gastroscopies 6–8 weeks apart: one regular endoscopy with random biopsies according to the Seattle protocol, and one endoscopy using AAC with AAC-targeted biopsies only. The authors found a similar dysplasia/EAC detection rate between the two protocols, with a significant reduction in the number of biopsies in the AAC arm [47]; however, larger studies are needed.

Although the evidence to support the use of (virtual) chromoendoscopy is weak, the Working Group favors its use. Currently, all of the high definition endoscopy systems are equipped with virtual chromoendoscopy, and the use of AAC is associated with very limited additional costs. An important additional advantage is that the use of virtual chromoendoscopy and AAC requires decent cleaning of the esophagus. In addition, the use of (virtual) chromoendoscopy is generally associated with an extra pull through, which translates to increased inspection time. These factors, apart from the possible intrinsic properties of (virtual) chromoendoscopy, might improve quality in BE surveillance.

Evidence that these techniques can replace the Seattle protocol in a standard surveillance setting is still lacking. Therefore, it is recommended that these techniques be used prior to and in addition to Seattle protocol biopsy sampling.

Additional considerations on the role of virtual chromoendoscopy with NBI, blue-light imaging, and i-SCAN in surveillance of patients with BE are provided in **Appendix 4s**.

## 6.2 Artificial intelligence in BE surveillance

ESGE has recently published a Position Statement on the expected value of AI in gastrointestinal (GI) endoscopy [48]. It is anticipated that AI will improve the quality of routine endoscopy. In view of the fact that many lesions are missed on referral or in daily practice [49, 50], expectations after the first pilot study to improve this outcome are high. The value of AI in BE surveillance lies not in exceeding expert performance but in raising routine practice to expert level performance. Different research groups have demonstrated high sensitivities of AI systems for detecting dysplasia/EAC during real-time endoscopy, ranging from 83.7 % to 95.4 % [51–53]. Two systematic reviews and meta-analyses have indicated high detection performances, ranging between 88 % and 96 % [54, 55]. Nonetheless, most studies are pilot feasibility studies in enriched populations, and therefore more evidence is needed before AI can be generally accepted as an adjunct to – or a replacement of – the Seattle biopsy protocol during surveillance. At the advent of the launch of commercial devices, emphasis must remain on basic endoscopy quality standards with regard to technical performance and cleaning of the esophagus: if the lesion is not adequately shown to the system because of hurried pull through, insufficient insufflation, or insufficient cleaning, AI will not be of any help.

## 6.3 Quality standards and pathology sampling

**RECOMMENDATION 5**

ESGE recommends the following standards for BE surveillance:

- a minimum of 1-minute inspection time per cm of BE length during a surveillance endoscopy
- photodocumentation of landmarks, the BE segment including one picture per cm of BE length, and the esophagogastric junction in retroflexed position, and any visible lesions
- use of the Prague and (for visible lesions) Paris classification
- collection of biopsies from all visible abnormalities (if present), followed by random four-quadrant biopsies for every 2-cm BE length.

Strong recommendation, weak quality of evidence.

The Working Group underscores the importance of adherence to the Performance Measures mentioned in the ESGE Position Paper statement on quality metrics in upper GI endoscopy [56]. In addition, endoscopy reports should be complete, including: (i) the location of the esophagogastric junction and diaphragmatic pinch; (ii) the circular and maximum extent of the BE segment, according to the Prague classification, and location of any islands proximal to the maximum BE segment extent; (iii) a description of location (in cm from the incisors and clockwise orientation) of any visible abnormality within the Barrett epithelium, in addition to lesion size (mm) and macroscopic appearance using the Paris classification; (iv) the presence or absence of erosive esophagitis using the Los Angeles classification [1].

There are no randomized controlled data supporting a minimum inspection time for BE surveillance; however, a few retrospective studies suggest an increase in dysplasia detection with longer BE inspection times [57, 58]. Even more important than inspection time is what endoscopists do during the time they are inspecting. Proper inspection includes cleaning of the esophagus, multiple pull throughs with both high definition WLE and (virtual) chromoendoscopy, as well as accurate photodocumentation of landmarks and the BE segment. If this is applied consistently, BE inspection time easily exceeds 1 minute per cm of BE length prior to biopsy taking.

Biopsy samples should be taken of all visible mucosal abnormalities. One to two biopsies, targeted on the most suspicious part of the lesion, are considered enough for lesions (Paris type 0-I, 0-II) that are potentially amenable to endoscopic resection (ER) in order to confirm the diagnosis and not compromise subsequent ER [59]. In addition, random four-quadrant biopsies should be collected every 2 cm within the Barrett segment, starting from the upper end of the gastric folds. Biopsies from each level are preferably collected in separate, marked containers. Several studies have indicated low compliance with guidelines with regard to obtaining a sufficient number of random biopsies [60–62], with lower dysplasia detection rates if

the Seattle biopsy protocol was not adhered to [63]. These studies highlight points of improvement in current practice and the importance of high quality endoscopy. These standards are key to minimizing the risk of undetected lesions and avoiding redundant repeat endoscopies that are scheduled because of nonadherence to quality guidelines. This will help to reduce the carbon footprint and environmental burden of elective endoscopy [64].

In patients with reflux esophagitis grade C or D, no random biopsies should be taken, and BE surveillance endoscopy should be repeated at least 6 weeks after optimization of antireflux therapy. However, even in the presence of severe reflux esophagitis, a careful inspection of the BE segment is warranted and targeted biopsies of suspected lesions are still recommended (▶ **Fig. 1**).

The Working Group feels that it is essential to allocate at least 30 minutes to surveillance procedures, preferably in well-sedated patients, in order to allow for adequate inspection time, photodocumentation, and biopsy sampling, increasing to 40 minutes for ultralong BE segments [58].

**RECOMMENDATION 6**

**a** ESGE recommends the use of p53 immunohistochemistry to support reproducibility of dysplasia diagnosis and aid the assessment of atypia of uncertain significance.
Strong recommendation, moderate level of evidence.

**b** ESGE does not recommend routine use of molecular biomarkers in patients with no evidence of dysplasia.
Weak recommendation, low to very low level of evidence.

The use of biomarkers on esophageal biopsies/brushing material has the potential to improve clinical decision-making, and simulation studies suggest that the introduction of biomarker-guided management strategies may be cost-effective compared with the standard of care [65–68].

In terms of direct applicability to routine practice, to date, most available evidence in this field pertains to p53 measured by IHC on esophageal biopsies or esophageal cytology material. p53 IHC is a relatively inexpensive biomarker that tightly correlates with *TP53* mutation status. p53 IHC already forms part of the existing diagnostic arsenal and can be easily integrated into routine clinical practice [69]. *TP53* is the most commonly mutated gene in EAC, occurring as early as the premalignant dysplastic stages [70]. Several studies have shown that p53 IHC can serve as an adjunct test to establish the presence of dysplasia and increase interobserver agreement [71–74]. In recent studies, the use of p53 immunostaining significantly improved interobserver agreement and the percentage of correct diagnoses among both experienced and nonexperienced BE pathologists [75–77].

In addition, p53 IHC may also help to better define the presence or absence of dysplasia in Barrett patients considered as "indefinite for dysplasia" (BE-IND) [75, 77, 78]. In a recent study, the diagnosis of BE-IND was reduced by over 40 %, and more than half of cases previously designated as BE-IND were reclassified as nondysplastic after p53 IHC slides were evaluated [77]. In a multicenter randomized crossover study, the presence of molecular biomarkers (p53 and aneuploidy) in biopsies targeted by image-enhanced endoscopy improved diagnostic accuracy for dysplasia [79]. In summary, there is now clear evidence that p53 IHC increases the reproducibility of histopathologic dysplasia diagnosis and aids in the assessment of atypia of uncertain significance in the context of BE surveillance biopsies.

Recently, a novel 3-tier 15-feature classifier (TissueCypher; Cernotics, Pittsburgh, Pennsylvania, USA) has been developed to risk stratify patients into low, intermediate, and high risk for progression. This test employs a multiplexed fluorescence imaging platform to generate quantitative and objective data on nine protein-based biomarkers implicated in different pathways that drive disease progression (company proprietary information). A recent pooled analysis of four case–control studies (552 patients) suggested that TissueCypher is predictive of progression to HGD/EAC when used as an adjunct to histopathology diagnosis and performs on a par with expert histopathology diagnosis in all BE patients. [80]. The Working Group feels that more independent studies with the gold standard as a back-to-back procedure in average-risk populations will be needed before TissueCypher can be recommended for routine clinical practice.

Other biomarkers have been investigated in the effort to identify predictors of disease behavior [81–88]. None of these are ready for implementation in clinical practice yet.

**RECOMMENDATION 7**

ESGE suggests that brushing techniques such as WATS$^{3D}$ should not be routinely used as an alternative for, or adjunct method to, conventional biopsies for tissue collection during endoscopic BE surveillance.
Weak recommendation, low level of evidence.

Tissues sampling with endoscopic brushing might have the advantage of allowing coverage of larger areas of BE epithelium compared with standard biopsies, with the potential to reduce sampling error and reduce the rate of nonadherence to the Seattle protocol. A technology recently approved and widely investigated for this purpose is the WATS$^{3D}$ (CDx Diagnostics, New York, New York, USA), a rigid endoscopic brush with long and hard bristles that allow deep transepithelial sampling coupled with tridimensional computer-assisted analysis, which consists of computerized neural network analysis of transepithelial cytology specimens to identify cytologic and histologic features suspicious for dysplasia, with subsequent evaluation by a trained pathologist in a centralized laboratory.

To date, the routine use of brushing techniques such as the one employed in the WATS$^{3D}$ technology cannot be recommended in clinical practice because of uncertainties about the clinical meaning of dysplasia detected by brushes only and the cost-effectiveness of incorporating brush sampling into BE sur-

veillance, in addition to the lack of proof that this technology could replace forceps biopsies. For a more comprehensive discussion on the topic, please refer to **Appendix 5s**.

**RECOMMENDATION 8**

ESGE does not recommend the use of nonendoscopic tools (swallowable cell collecting devices or blood-based biomarkers) for the surveillance of BE.

Weak recommendation, moderate quality of evidence for swallowable cell collecting device; low quality of evidence for blood-based biomarkers.

Pilonis et al. recently reported on a retrospective study in which the Cytosponge swallowable cell collecting device was combined with a multidimensional biomarker panel encompassing cytopathologic assessment for atypia, p53 IHC, and clinical risk factors such as length of BE, sex, and age [89]. Based on findings from a training cohort (n = 557), patients were assigned a high risk category if they were found to have atypia on cytopathologic assessment, or if cell material stained positive for p53 IHC. Moderate risk was defined by the absence of atypia or negative p53 IHC, but with the presence of a longer segment length (C ≥ 3 or M ≥ 6), and age > 60 years or male sex; low risk as not meeting the criteria for high or moderate risk. When applied in a validation cohort of 344 patients (10 % of whom had HGD on biopsies), 41 % of patients classified as high risk (31/75) were shown to have HGD/EAC on biopsies, compared with 1 % (2/185) in the low risk group. When subsequently applied onto a real-world BE surveillance cohort, not enriched for dysplasia, who underwent Cytosponge surveillance during the COVID pandemic owing to unavailability of the endoscopy service, the positive predictive value for HGD/EAC of the Cytosponge was 31 % (12/39), and 44 % (17/39) for any dysplasia [89]. Although promising, larger prospective studies are required to validate the biomarker panel and, at present, this technology cannot be recommended for clinical adoption.

Over the past few years, the blood-based neutrophil-to-lymphocyte ratio (NLR) has emerged as a potentially simple and clinically applicable biomarker for risk stratification in BE. Two retrospective observational studies have shown that the NLR correlated with a diagnosis of dysplasia and could predict progression [90, 91]. Although promising, the lack of a well-defined NLR cutoff value hinders its application in a clinical setting. Larger prospective studies with longer follow-up are required to clarify the real clinical utility of this test.

Other blood-based biomarkers such as serum glycoprotein biomarkers (complement C9, gelsolin, serum paraoxonase/arylesterase 1, serum paroxonase/lactonase 3) [92], squamous cellular carcinoma antigen [93], leucocyte telomere length (measured by quantitative PCR) [94], and genetic alteration in cell-free DNA (fractional allelic loss index) [95] have shown promise in risk stratification, but so far lack sufficient evidence for their clinical adoption in the routine surveillance of BE.

## 6.4 Surveillance intervals

**RECOMMENDATION 9**

ESGE suggests varying surveillance intervals for different BE lengths. For BE with a maximum extent of ≥ 1 cm and < 3 cm, BE surveillance should be repeated every 5 years. For BE with a maximum extent of ≥ 3 cm and < 10 cm, the interval for endoscopic surveillance should be 3 years. Patients with BE with a maximum extent of ≥ 10 cm should be referred to a BE expert center for surveillance endoscopies.

For patients with an irregular Z-line/columnar-lined esophagus of < 1 cm, no routine biopsies or endoscopic surveillance are advised.

Weak recommendation, low quality of evidence.

RCTs on optimal surveillance strategies in BE patients are lacking and the suggested cutoff levels are arbitrary. Although adequate endoscopic surveillance has been associated with improved survival from EAC [96], the cost-effectiveness of current surveillance strategies is in doubt [97, 98]. In the absence of new data, the Working Group decided to keep the previous surveillance intervals unchanged (▶ **Fig. 1**).

Current surveillance intervals are stratified by BE length and dysplasia, as these are both accepted risk factors for disease progression. This is corroborated by several recent studies, which demonstrate significantly lower rates of neoplastic progression in patients with short-segment BE compared with long-segment BE [99–101]. The cost-effectiveness of current surveillance strategies could be further improved by reducing the frequency of surveillance in low risk patients [97, 98], but identifying low risk patients remains challenging. There is a need for improved risk stratification strategies, incorporating multiple risk factors including segment length, sex, age, smoking, and previous biopsy findings [21]. Currently, several multifactorial risk estimation tools are being studied to determine the optimal surveillance interval per individual patient, but such tools cannot yet be implemented.

Patients with an irregular Z-line should be excluded from surveillance because of their low progression risk [101, 102]. There are no data on the optimal surveillance interval for patients with an ultralong BE (≥ 10 cm), but most experts adhere to a surveillance interval of 1–2 years in such cases.

In accordance with the 2017 ESGE Position Statement on the endoscopic management of BE [1], the Working Group recommends that the diagnosis of any degree of dysplasia (including "indefinite for dysplasia") in BE requires confirmation by an experienced GI pathologist (▶ **Table 1**). Patients with a diagnosis of "indefinite for dysplasia" confirmed by a second experienced GI pathologist should be managed with optimization of antireflux treatment and repeat endoscopy at 6 months. If no definite dysplasia is found in subsequent biopsy samples (including if the biopsies are again classified as "indefinite for dysplasia"), the surveillance interval should follow the recommendation for nondysplastic BE.

### 6.5 Discontinuation of surveillance

**RECOMMENDATION 10**

ESGE suggests that, if a patient has reached 75 years of age at the time of the last surveillance endoscopy and/or the patient's life expectancy is less than 5 years, the discontinuation of further surveillance endoscopies can be considered.

Weak recommendation, very low quality of evidence.

Evidence on the optimal age cutoff for endoscopic surveillance in patients with BE is very limited. In general, it is reasonable to stop surveillance in patients who are no longer fit for repeated endoscopy or who cannot tolerate the treatment modalities needed to cure esophageal dysplasia/EAC. More importantly, endoscopic surveillance should be limited to patients who are expected to benefit from treatment of BE-related dysplasia/EAC, meaning those who are not likely to die from other causes within a few years after treatment.

There is only one modelling study available about the optimal age to stop endoscopic surveillance based on sex and co-morbidity [103]. This study found that the optimal age for last surveillance is lower in women and in patients with co-morbidities, with an optimal stop-age varying between 69 years (in women with co-morbidity) and 81 years (in men without co-morbidity). However, real-world data are missing and prospective studies are needed to validate these findings.

The age cutoff of 75 years is arbitrary, and is based on average life expectancy; hence, surveillance extension up to 80 years can be considered in individual cases.

## 7 Treatment

In accordance with the 2017 ESGE Position Statement on the endoscopic management of BE [1], the working group recommends against prophylactic endoscopic therapy (such as ablation therapy) for nondysplastic BE (▶ **Table 1**).

**RECOMMENDATION 11**

ESGE recommends offering endoscopic eradication therapy using ablation to patients with BE and low grade dysplasia (LGD), on at least two separate endoscopies, both confirmed by a second experienced pathologist.

Strong recommendation, high level of evidence.

In accordance with the 2017 ESGE Position Statement on the endoscopic management of BE [1], the working group recommends that patients with low grade dysplasia (LGD) on random biopsies confirmed by a second experienced GI pathologist should be referred to a BE expert center. As a rule, upper GI endoscopy will be repeated in the expert center, because studies have shown that, in a significant proportion of patients with a referral diagnosis of flat BE with "invisible" LGD, more advanced pathology (HGD or EAC) is detected in a BE expert center when the endoscopy is repeated [49, 104, 105]. In the absence of visible lesions and more advanced pathology, a surveillance interval of 6 months after a confirmed LGD diagnosis is recommended.

(i) If no dysplasia is found at the 6-month endoscopy, the interval can be broadened to 1 year. After two subsequent endoscopies negative for dysplasia, standard surveillance for patients with nondysplastic BE can be initiated.

(ii) If a confirmed diagnosis of LGD is found in the subsequent endoscopies, endoscopic ablation can be offered (▶ **Table 1**).

For patients with LGD, the risk of progression to HGD/EAC is between 9.2 % and 13.4 % per patient per year [106–108]. A risk factor for progression is confirmation of the LGD diagnosis by at least one experienced GI pathologist [106, 107, 109]. Therefore, independent confirmation of the LGD diagnosis by an experienced GI pathologist should always be obtained. It has also been shown that the diagnosis of LGD on two or more endoscopies is associated with a higher risk for progression [109, 110]. Aberrant p53 expression is also associated with increased risk of progression; however, whether patients with a single diagnosis of LGD plus p53 aberrant expression would benefit from endoscopic eradication therapy (EET) is a point for further study. Whether multifocal LGD diagnosed on a single endoscopy is a risk factor has not been confirmed up to now [109].

Regarding the preferred method of ablation in the context of BE-related neoplasia in general, radiofrequency ablation (RFA) is the ablation method most extensively studied. RFA has proven to be safe and effective in several large prospective randomized and non-randomized studies [111–115]. Alternative treatment methods are argon plasma coagulation (APC), hybrid APC, and cryoablation (cryoballoon and cryospray). Studies have demonstrated inferior outcomes compared to RFA with APC and cryospray (56 %–79 % complete eradication of intestinal metaplasia [CE IM], 9 %–13 % strictures for APC [116, 117]; 41 %–61 % CE IM, 3 % strictures for cryospray [118–120]) and outcomes comparable to RFA for hybrid APC and cryoballoon ablation (87 % CE IM, 4 % strictures for hybrid APC [121]; 91 % CE IM, 12 % strictures for cryoballoon [122]).

Several studies have demonstrated that RFA of BE with confirmed LGD can significantly reduce the progression rate to HGD and/or EAC [113, 123, 124]. In two multicentric prospective randomized studies comparing RFA with surveillance, the risk of progression was reduced by up to 25 % [113, 123]. In contrast to the European and the US multicenter trials, a French study showed surprisingly high rates of progression of 13.5 % in the RFA arm compared with 26.2 % in the surveillance group [125]. The reason for this discrepancy might be the low rate of 35 % CE IM in the RFA arm compared with the US and European studies with CE IM rates of 77.4 % and 91 %, respectively [113, 123] and the wide range of expertise in the technology among the recruiting centers in the French trial.

The effect of cryoablation and ablation with APC in patients with LGD has been investigated in non-randomized prospective multicenter studies, which have demonstrated a protective effect of ablation against progression [122, 126]. In the US cryo-

ablation study, there was no progression in 29 patients with LGD within 12 months [122], and, in the Polish APC study, with 71 patients, no progression was observed within 2 years [126].

In specialized BE centers, close surveillance of patients with LGD does however appear to be a valid alternative to ablation in individual cases. Pouw et al. reported on the long-term follow-up of patients who were initially included in the previously mentioned RCT on RFA versus surveillance for patients with confirmed LGD [124]. During an additional follow-up time of 40 months, a total of 23/68 patients (34%) who were randomized to the surveillance arm progressed to HGD/EAC. Of these 23 patients, 22 were free of dysplasia after EET with RFA, with or without ER. In one patient, an esophagectomy was performed after ER of a poorly differentiated submucosal cancer. The esophagectomy specimen revealed no residual cancer, nor positive lymph nodes.

**RECOMMENDATION 12**

ESGE recommends endoscopic ablation treatment for BE with confirmed HGD without visible lesions, to prevent progression to invasive cancer.

Strong recommendation, high level of evidence.

The risk of progression from flat HGD to cancer is not clear. Two RCTs have been performed in patients with BE without visible lesions, and a diagnosis of HGD. One study randomized 63 patients to either RFA (n = 42) or sham treatment (n = 21) and reported eradication rates for IM of 73.8% and for dysplasia of 81% [123]. Among patients with HGD, 19.0% of those in the control group progressed to cancer, compared with 2.4% of those in the ablation group ($P = 0.04$). At 5-year follow-up of this study, the incidence of dysplasia recurrence after initial eradication of IM after RFA, was 7.3 per 100 person-years for patients with baseline HGD [127]. The second study randomized 208 patients with HGD to treatment with photodynamic therapy (PDT; n = 138) versus PPI only (n = 70). Eradication of HGD was achieved in 77% of the treatment group and 38% of the surveillance group, with progression to cancer in 13% of patients in the PDT group versus 28% in the control group ($P = 0.006$) [128]. The 5-year follow-up of this study demonstrated cancer progression in 15% of the PDT group, versus 29% of the control group ($P = 0.004$) [129]. These results suggest that ablation of flat BE with HGD significantly decreases the risk of progressing to cancer.

Different studies have studied ablation techniques to eradicate BE with dysplasia, including HGD. Two meta-analyses have demonstrated that ablation of BE is effective and safe. One systematic review and meta-analysis assessed the use of RFA and, in a total of 3802 patients, of whom 31% had HGD, eradication of all dysplasia was achieved in 85% of patients, with an annual progression risk to cancer of 0.4% [130]. Esophageal stricture was the most common adverse event (AE), being reported in 5% of patients. Another systematic review and meta-analysis evaluated cryoablation. A total of 405 patients with dysplasia, including HGD, were included. In the high quality studies, a pooled proportion of eradication of dysplasia of 91.3% and a pooled proportion of eradication of IM of 71.6% were found [131]. AEs were reported in 12.2% patients.

**RECOMMENDATION 13**

ESGE recommends offering complete eradication of all remaining Barrett epithelium by ablation after endoscopic resection of visible abnormalities containing any degree of dysplasia or EAC.

Strong recommendation, moderate quality of evidence.

It has been shown that the rate of recurrence or metachronous HGD and/or EAC is up to 20%–35% after successful ER of focal lesions [117, 132, 133]. Because of this high risk of subsequent lesions, most expert centers follow the two-step strategy of ER of all visible lesions, followed by ablation of the remaining at-risk BE.

There is a lot of evidence on the effectiveness of ablation of residual BE after ER [116, 121, 134, 135]. In addition, endoscopic BE ablation is associated with few AEs. Moreover, the risk of recurrence is significantly higher if only ER is performed compared with ER followed by APC or RFA. Despite robust evidence, one should bear in mind that the majority of studies mix patients with a visible lesion and patients with flat dysplasia.

In BE centers with experience in BE management, close surveillance after ER of a dysplastic lesion/EAC in BE appears to be a valid alternative to ablation in patients who are frail or have multiple co-morbidities. A Dutch study reported on the follow-up of 94 patients with untreated residual BE (median C2M5) after ER of a lesion with LGD, HGD, or EAC [136]. During a median follow-up period of 21 months, 17 patients (18%) developed HGD or EAC: all were curatively treated endoscopically and none progressed to advanced cancer. Therefore, for all individual patients, the benefit of ablation after ER of a BE lesion should be weighed against the risks (especially strictures), costs, and the burden to the patient.

**RECOMMENDATION 14**

**a** ESGE recommends the use of 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.

**b** ESGE suggests the use of endoscopic submucosal dissection (ESD) for lesions suspicious for submucosal invasion (Paris type 0-Is, 0-IIc), for malignant lesions of > 20 mm, and for lesions in scarred/fibrotic areas.

Weak recommendation, low quality of evidence.

Recommendation 14 is derived from "Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2022" [137]. For further discussion and supportive evidence, please refer to that guideline.

**RECOMMENDATION 15**

ESGE recommends endoscopic resection as curative treatment for T1a Barrett's cancer with well/moderate differentiation and no signs of (lympho)vascular invasion. Strong recommendation, high level of evidence.

Low risk intramucosal (T1a) cancer arising in BE, with well or moderate differentiation and no (lympho)vascular invasion, is associated with a low risk of lymph node metastasis (LNM). Local ER can therefore be considered as curative treatment, with a very favorable safety profile [138]. Furthermore, endoscopic treatment carries a minimal risk of complications compared with invasive surgery [138].

No randomized trials have been performed comparing ER and surgery for the treatment of low risk T1a cancer [139]; one meta-analysis is available [140]. This study included seven studies involving 870 patients, 510 treated endoscopically and 360 treated with esophagectomy. The meta-analysis showed that there was no significant difference between endoscopic therapy and esophagectomy in the neoplasia remission rate (relative risk [RR] 0.96), or overall survival rates at 1 year (RR 0.99), 3 years (RR 1.03), and 5 years (RR 1.00). Endoscopic therapy was associated with a higher dysplasia recurrence rate (RR 9.50) and fewer major AEs (RR 0.38).

**RECOMMENDATION 16**

ESGE suggests that low risk submucosal (T1b) esophageal adenocarcinoma (i. e. submucosal invasion depth ≤ 500 µm AND no [lympho]vascular invasion AND no poor tumor differentiation) can be treated by endoscopic resection, provided that adequate follow-up with gastroscopy, endoscopic ultrasound (EUS), and computed tomography (CT)/positron emission tomography-computed tomography (PET-CT) is performed in expert centers.
Weak recommendation, low quality of evidence.

It has been demonstrated, in several retrospective cohort studies, that the risk of LNM for T1b EAC with an infiltration depth into the submucosa of up to 500 µm and without any other risk factors (poor differentiation grade [G3], lymph [L1] or blood vessel infiltration [V1]) is very low and usually below the mortality rate of esophagectomy in experienced centers [141–145]. A recent publication by Nieuwenhuis et al., with a median follow-up of 29 months, reported an annual risk of 0.7 % for metastases in low risk T1b EAC [146]. In older studies, the risk for LNM was around 2 % [141–143]. Therefore, ER can be considered curative treatment and esophagectomy is not necessary.

However, oncologic staging at the time of diagnosis and follow-up including gastroscopy (to detect local recurrence), EUS (to detect LNM at an early, yet curable, stage), and CT/PET-CT is mandatory in these patients. Given the low incidence of LNM in this patient population, the fact that not all patients are surgical candidates, and ethical considerations regarding patient preference, a prospective randomized study comparing endoscopic treatment with esophagectomy will not be feasible. In all available retrospective studies, cancer-specific survival is however similar for T1b EAC treated endoscopically or surgically, suggesting no clear benefit of surgical resection over ER for low risk T1b EAC [147].

**RECOMMENDATION 17**

ESGE suggests that mucosal (T1a) esophageal adenocarcinoma with (lympho)vascular invasion and/or poor tumor differentiation should be considered as high risk. Complete staging and consideration of additional treatments (chemotherapy and/or radiotherapy and/or surgery) or strict endoscopic follow-up should be undertaken on an individual basis in a multidisciplinary discussion. Weak recommendation, very low level of evidence.

Data on the clinical impact of high risk T1a EACs are scarce. High risk T1a is defined as the presence of poor differentiation grade and/or (lympho)vascular invasion in the resection specimen. Only small retrospective cohort studies are available, reporting a risk for LNM of around 20 % [138, 146, 148, 149]. In a recent multicenter retrospective study, lymph node and/or distal metastases were diagnosed in 5/25 patients (20 %) after ER and follow-up for high risk T1a EAC, with a medium interval between ER and the detection of metastases of 31 months [146]. Therefore, complete oncologic staging with gastroscopy, EUS, and CT/PET-CT at the time of diagnosis, and discussion in a multidisciplinary team meeting is recommended. Depending on patient characteristics and patient preference, chemotherapy and/or radiotherapy and/or surgery, or a conservative approach consisting of an intensified follow-up with gastroscopy, EUS, and CT/PET-CT in the setting of an expert center can be considered.

**RECOMMENDATION 18**

ESGE suggests that submucosal (T1b) esophageal adenocarcinoma with deep submucosal invasion (tumor invasion > 500 µm into the submucosa), and/or (lympho) vascular invasion, and/or a poor tumor differentiation should be considered high risk. Complete staging and consideration of additional treatments (chemotherapy and/or radiotherapy and/or surgery) or strict endoscopic follow-up should be undertaken on an individual basis in a multidisciplinary discussion.

Strong recommendation, low quality of evidence.

High risk features for T1b EAC are deep submucosal tumor invasion (> 500 µm), the presence of poor differentiation grade, and (lympho)vascular invasion in the resection specimen. Several retrospective studies are available on the risk of LNM after ER of high risk T1b EAC [144, 146, 150, 151]. In these studies, LNM rates ranging between 0 and 31 % have been reported. Data suggest that the risk increases with an increasing number of risk factors in the resection specimen [148, 150, 152].

Complete staging with EUS and CT/PET-CT at the time of diagnosis is crucial to identify patients with synchronous LNM. In the absence of these (i. e. for pT1bN0M0 disease), the decision on further management should be guided by patient characteristics (co-morbidity, surgical risk) and patient preference. After discussion in a multidisciplinary team meeting, chemotherapy and/or radiotherapy and/or surgery, or a conservative approach consisting of intensified follow-up with EGD, EUS, and CT/PET-CT in the setting of an expert center can be considered.

In an ongoing European multicenter prospective cohort study (NCT03222635), the conservative approach consisting of intensive follow-up by gastroscopy, in addition to EUS every 3 months in the first 2 years and every 6 months in years 3–5 after ER, combined with repeated CT/PET-CT at 12 months is being evaluated. Interim analysis after a median follow-up duration of 22 months showed LNM in 6/120 patients (5 %) [153]. All these patients could be treated by rescue therapy (esophagectomy with or without neoadjuvant chemoradiotherapy or a selective surgical resection of the affected lymph nodes). This study has a predefined follow-up period of 5 years and the final results are awaited. Nevertheless, these results suggest that this strategy of watchful waiting after ER of high risk T1b EAC might select patients in need of invasive (surgical) treatment, while preventing unnecessary surgery in the majority of patients.

▶ **Fig. 2** provides an algorithm for the management of patients with BE and dysplasia or EAC.

### 7.1 Tumor budding

Tumor buds are usually defined as isolated single cancer cells or clusters of up to four cancer cells located at the invasion front (peritumoral budding) or within the tumor (intratumoral budding). Tumor budding has prognostic significance in several carcinomas [154].

The assessment of tumor buds could help identify high risk patients who had initially been treated by ER but who might benefit from more extended therapy or close follow-up. Data on tumor budding in EAC are very sparse. The studies are small, retrospective, and use different definitions and criteria for the quantification of tumor budding. Nevertheless, they indicate a positive correlation between tumor budding and aggressive clinical behavior [155–160]. Owing to the lack of solid data, ESGE does not however recommend routine use of tumor budding in the assessment of endoscopically treated EAC.

## 8 Management after endoscopic eradication therapy of BE

**RECOMMENDATION 19**

ESGE recommends adequate acid suppression treatment during and after endoscopic eradication therapy of BE.

Strong recommendation, very low quality of evidence.

Acid reflux is the driving force in the initial development of BE and adequate acid suppression treatment is therefore considered a cornerstone of patient management after eradication of BE [127, 135, 161–172], even though controlled studies in the post-EET surveillance context are lacking. Based on the available evidence, no recommendation can be made on the optimal PPI dose, or as to whether fundoplication is a more appropriate treatment in select patients. Based however on common practice in BE expert centers, we recommend double-dose PPI (equivalent to omeprazole 40 mg b. i. d.) during EET. During follow-up, the dose may be adjusted based on patient symptoms while maintaining mucosal healing. Fundoplication after EET has only been described in two small retrospective series [173, 174]. As fundoplication can result in adequate reflux control, the risks and benefits of surgical reflux management may be discussed with patients as an alternative to a lifelong PPI.

**RECOMMENDATION 20**

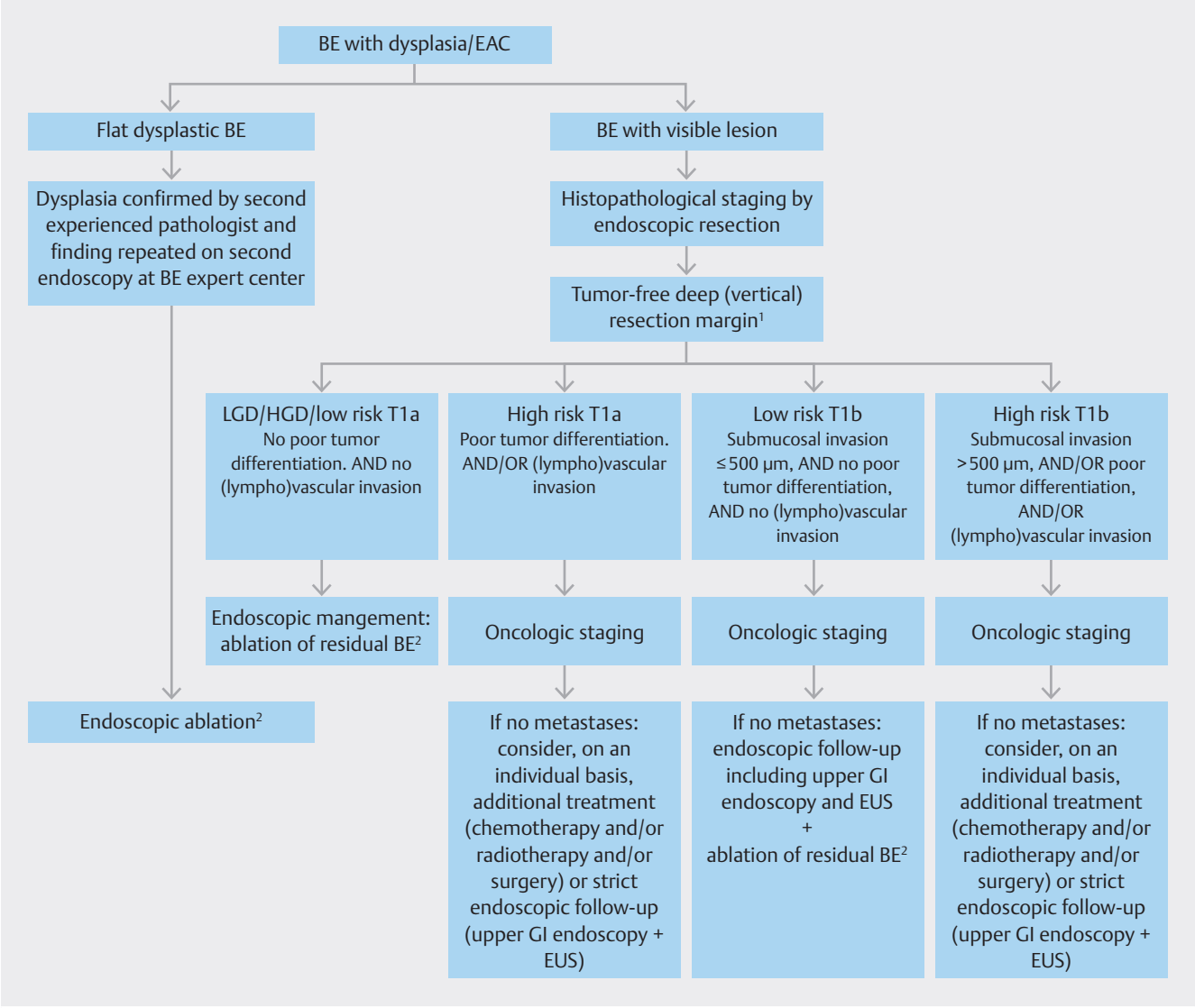
**a** ESGE recommends that the first endoscopic follow-up after successful EET of BE is performed in an expert center.

Strong recommendation, very low quality of evidence.

**b** ESGE recommends careful inspection of the neo-squamocolumnar junction and neo-squamous epithelium with high definition white-light endoscopy and virtual chromoendoscopy during post-EET surveillance, to detect recurrent dysplasia.

Strong recommendation, very low level of evidence.

*Recommendation 20 is continued on the next page.*




▶ **Fig. 2** Flowchart showing the recommended treatment of Barret esophagus (BE)-related neoplasia.
EAC, esophageal adenocarcinoma; LGD, low grade dysplasia; HGD, high grade dysplasia; GI, gastrointestinal; EUS, endoscopic ultrasound.
[1] For cases with a tumor-positive deep (vertical) resection margin: discuss in a multidisciplinary team meeting, and strongly consider nonendoscopic additional treatment.
[2] In selected cases, strict endoscopic follow-up can be considered (please refer to the text).

**c** ESGE recommends against routine four-quadrant biopsies of neo-squamous epithelium after successful EET of BE.
Strong recommendation, low level of evidence.

**d** ESGE suggests, after successful EET, obtaining four-quadrant random biopsies just distal to a normal-appearing neo-squamocolumnar junction to detect dysplasia in the absence of visible lesions.
Weak recommendation, low level of evidence.

**e** ESGE recommends targeted biopsies are obtained where there is a suspicion of recurrent BE in the tubular esophagus, or where there are visible lesions suspicious for dysplasia.
Strong recommendation, very low level of evidence.

Successful EET is defined as the absence of visible residual BE epithelium after EET. Four-quadrant biopsies just below (<5 mm) the neo-squamocolumnar junction are generally obtained at this point to rule out persisting invisible dysplasia.

Retrospective cohort analyses have indicated that the risk of dysplasia/EAC recurrence following successful EET varies

between 1% and 2% [127, 161, 172, 173, 162, 164–166, 168–171]. Because the majority of recurrences are detected within the first 2 years after EET, it is desirable to perform the first follow-up in an expert center, to allow adequate inspection and detection of residual or recurrent BE and/or dysplasia [115, 127, 175, 176]. Careful inspection of the tubular esophagus and neo-squamocolumnar junction are critically important to detect any recurrent BE or dysplastic lesions. High resolution WLE is recommended to increase dysplasia detection. Likewise, although no studies are available that have formally assessed the use of virtual chromoendoscopy during post-EET surveillance, studies have reported that small areas of columnar mucosa in the tubular esophagus are more readily detected when using virtual chromoendoscopy [177].

The diagnostic yield of biopsies obtained just distal to a normal-appearing neo-squamocolumnar junction has been examined in long-running prospective studies from expert centers. In the largest series reporting on follow-up after EET of BE with dysplasia, all high grade recurrences were detected as visible lesions during endoscopy [170]. Endoscopically invisible recurrences in the cardia were found in about 1% of patients. Given that the diagnostic yield of biopsies appears to be minimal in expert hands, random quadrant biopsies of the proximal cardia have been abandoned in some expert centers [178]. However, as the neo-squamocolumnar junction can be difficult to assess endoscopically and because this is a site where visible and invisible recurrences can occur, we recommend that, in centers with no expertise in EET, quadrant biopsies are taken just distal to the neo-squamocolumnar junction to rule out invisible dysplasia, which may require additional treatment or stricter follow-up [170, 176, 179].

IM at the neo-squamocolumnar junction detected during post-EET surveillance is of no clinical relevance, as this finding is not reproducible between patient visits, nor does it portend an increased risk of recurrent neoplasia [170, 178, 180]. IM in a normal-appearing neo-squamocolumnar junction therefore does not warrant additional treatment or stricter follow-up.

ESGE recommends against obtaining routine four-quadrant biopsies from the neo-squamous epithelium if there are no visible abnormalities. High quality studies have shown that the diagnostic yield of these biopsies is very low [165, 170, 177]. Routine four-quadrant biopsies do however add to the costs and have a negative impact on the environmental footprint; they should therefore be avoided [64].

Biopsies are recommended for histopathologic correlation where there is suspicion of recurrent BE in the tubular esophagus or where there are visible lesions suspicious for dysplasia. Ablation history, biopsy location, and endoscopic assessment should be clearly documented on the histopathology requisition form to aid histopathologic assessment.

**RECOMMENDATION 21**

After successful EET, ESGE recommends:

**a** using the term “recurrence of BE” where there is endoscopic evidence of columnar epithelium in the tubular esophagus – intestinal metaplasia in a normal-appearing neo-squamocolumnar junction should not be considered recurrence of BE

**b** using the term “recurrence of dysplasia” where biopsies show low or high grade dysplasia, and “recurrence of cancer” where biopsies show cancer.

Strong recommendation, very low quality of evidence.

Successful EET is defined as a situation in which the esophagus does not show any visible BE (either circumferential, or tongues or islands of columnar epithelium), in combination with a normal-appearing Z-line without any visible abnormalities, after EET has been applied.

Harmonized definitions of recurrence after EET of BE are key in clinical practice and in research settings. Recurrence risks for BE or dysplasia can only be reliably communicated with patients if the definition of recurrence is defined unequivocally in the literature. The definitions proposed here are grounded in clinical relevance, either provoking stricter follow-up or additional treatment.

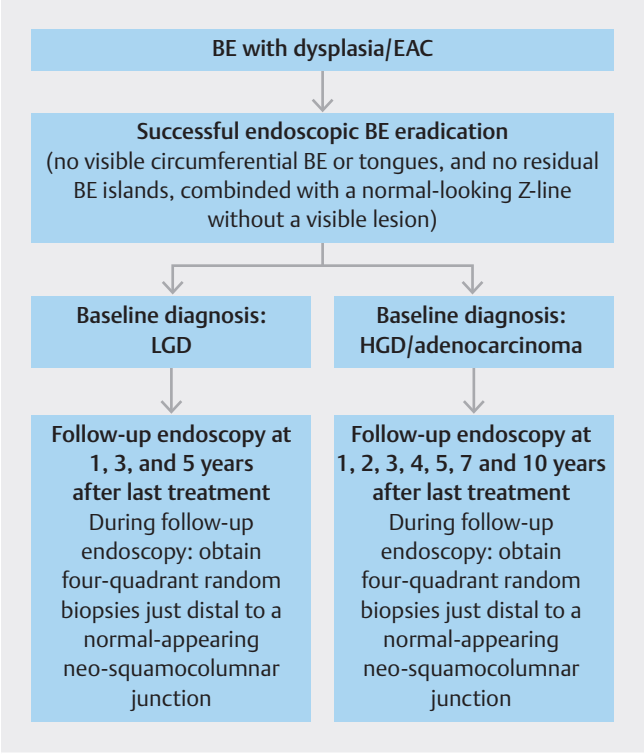
**RECOMMENDATION 22**

After successful EET, ESGE recommends the following surveillance intervals:

- For patients with a baseline diagnosis of HGD or EAC: at 1, 2, 3, 4, 5, 7, and 10 years after last treatment, after which surveillance may be stopped.
- For patients with a baseline diagnosis of LGD: at 1, 3, and 5 years after last treatment, after which surveillance may be stopped.

Strong recommendation, low quality of evidence.

Cotton and co-workers have reported model projections for optimal surveillance based on baseline diagnoses during the first 5 years after successful EET [181]. For patients with HGD or EAC as their baseline diagnosis, surveillance visits after 0.25, 0.5, 1, 2, 3, 4, and 5 years after achieving complete eradication of IM were recommended. For patients with LGD as their baseline diagnosis, surveillance visits after 1 and 3 years were advised. Two recent nationwide studies on long-term efficacy of EET have reported low recurrence risks during long-term surveillance after successful treatment for Barrett-related dysplasia/EAC [115, 170]. The majority of recurrences were detected in the first 2 years after successful treatment, varying between (on average) 12 and 31 months after treatment [115, 170, 175, 176, 179], leading to our recommendation for less aggressive surveillance in the first year after successful EET (▶ **Fig. 3**).




▶ **Fig. 3** Flowchart showing the recommended management after endoscopic eradication therapy (EET) for Barret esophagus (BE)-related neoplasia.
EAC, esophageal adenocarcinoma; LGD, low grade dysplasia; HGD, high grade dysplasia.

There are no data available that address the issue of an upper age limit for post-EET BE surveillance. Late recurrences are rare and mortality risk due to causes other than EAC can be substantial in this patient population [115, 127, 170, 175]. Therefore, it is likely that the clinical return of long-term post-EET surveillance declines with age; however, at this moment, an exact age cutoff is neither supported nor refuted by the literature. The guideline working group feels that age alone should not drive post-EET surveillance decisions in healthy individuals and using age as the sole factor for post-EET surveillance decision-making is crude and insufficient. In determining whether post-EET surveillance should be offered, patients and clinicians should discuss and individualize management decisions depending on the anticipated benefits and competing health concerns. ESGE recommends surveillance may be safely stopped 5 years after successful treatment of BE with LGD, and 10 years after successful treatment of BE with HGD/EAC.

## 9 Centralization

In accordance with the 2017 ESGE Position Statement on the endoscopic management of BE [1], the working group recommends referring all patients with BE ≥ 10 cm, a confirmed diagnosis of LGD, HGD, or early cancer to a BE expert center for surveillance and/or treatment. A BE expert center should meet the following requirements: (i) annual case load of ≥ 10 NEW patients with endoscopic treatment for HGD or early carcinoma per BE expert endoscopist; (ii) endoscopic and histologic care is provided by endoscopists and pathologists who have followed additional training in this field (either by courses or guest visits) – a minimum of 30 supervised cases of ER and 30 cases of endoscopic ablation should be performed to acquire competence in technical skills, management pathways, and complications; (iii) patients with BE dysplasia/cancer are discussed in multidisciplinary meetings with gastroenterologists, surgeons, oncologists, and pathologists; (iv) access to experienced esophageal surgery; (v) all patients with BE are registered prospectively in a database (▶ **Table 1**).

## Disclaimer

The legal disclaimer for ESGE guidelines [182] applies to this guideline.

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### Competing interests

M. Barret has received consultancy fees from Medtronic (2019 to 2023) and Fujifilm (2023), consultancy and research funding from Pentax (2021 to 2022), and fees for training programs from Olympus (2022 to 2023). M. di Pietro has received consultancy fees from Medtronic (2018 to date); the Cytosponge was developed by his institution but he does not have a share in the patent. M. Dinis-Ribeiro has received consultancy fees from Medtronic (2021) and Roche (2022), and a research grant from Fujifilm (2021 to 2022); he is Co-Editor-in-Chief of *Endoscopy*. G. Fernández-Esparrach has received speaker's fees from Medtronic (2023). R. Fitzgerald is a co-founder and shareholder (<3%) in Cyted Ltd, but is not an employee and does not receive funding or consultancy fees. She is a trustee of the charity Heartburn Cancer UK (HCUK) who have provided patient input and funded mobile units for delivery of heartburn check clinics as part of a research programme called DELTA; her research was funded by The UK Medical Research Council (MRC) who have licensed Cytosponge technology and assays to Medtronic in 2014. M. Jansen has received speaker's fees from Medtronic (2018 to date). O. Pech has received speaker's fees from Fujifilm (2012 to 2022), Boston Scientific (2012 to date), and Medtronic (2015 to date). R.E. Pouw has received speaker's fees from Pentax Medical (2022, 2023) and consultancy fees from Medtronic and MicroTech Europe (both ongoing). M.C.W. Spaander has received research support from Lucid (Esocheck) (2020 to 2023) and Capsulomics (2022 to 2023). B.L.A.M. Weusten has received financial research support, and consultancy and lecture fees from Pentax Medical (2019 to date), and financial research support from Aqua Medical Inc. (2020 to 2022).R. Bisschops, F. Baldaque-Silva, E. Coron, M. Jovani, I. Marques-de-Sa, A. Rattan, W.K. Tan, K. Triantafyllou, E.P.D. Verheij, and P.A. Zellenrath declare that they have no conflict of interest.

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# Supplementary material

Appendix 1s

Taskforces and taskforce members

| taskforce | | | | | |
|---|---|---|---|---|---|
| **chemoprevention** | **screening and case finding** | **surveillance** | **pathology sampling and risk stratification** | **treatment** | **management after treatment** |
| M.D-R.* | M.D-R. | I.M-D. | R.B. | M.D-R. | E.C. |
| I.M-D. | I.M-D. | R.B.* | M.d.P.* | O.P.* | O.P. |
| M.S. | M.S.* | E.C. | R.F. | M.B. | M.B. |
| R.F. | R.F. | M.d.P. | M.Jo. | R.P. | R.P.* |
| A.R. | A.R. | M.S. | F.B-S. | G.F-E. | G.F-E. |
| M.Jo. | M.Jo. | A.R. | M.Ja. | F.B-S. | M.Ja. |
| P.Z. | P.Z. | | K.T. | | E.V. |

*Taskforce leaders are indicated with **

**Supplementary material**

Appendix 2s

# Screening and case finding

## Emerging modalities for the purpose of BE screening or case finding, without the need for sedation.

### Non-endoscopic technologies

In addition to non-endoscopic cell sampling devices, other non-invasive technologies that are being developed include devices to detect volatile organic compounds (VOC). Examples are the electronic nose device [1] and VOC technology using selected ion flow tube mass spectrometry [2,3]. These devices have shown promise, but further studies are needed. Plasma-based detection of VOC to diagnosed EAC are also emerging, but only confined to small pilot studies [4]. Other plasma-based detection technologies, such as detection of circulating microRNAs [5–7] or other protein markers (e.g. BMP5 [8], Squamous Cellular Carcinoma Antigen [9], and L1-cell adhesion molecule [10]) also have potential, but larger prospective studies are warranted. Multi Cancer Early Detection Tests (MCEDs) have not been shown to detect pre-invasive BE [11,12].

### Trans-nasal endoscopy

Trans-nasal endoscopy (TNE) is an alternative endoscopic technique in which an ultra-thin endoscope (outer diameter <6mm) is inserted through the nose, in an unsedated patient in the sitting position.

The diagnostic accuracy of unsedated TNE (uTNE) and conventional endoscopy (cEGD) was assessed in a systematic review and meta-analysis [13]. A total of eight prospective studies were included with a total of 623 patients who underwent both uTNE and cEGD. Results showed a pooled sensitivity and specificity of uTNE for detecting columnar epithelium of 98% (95% CI 83–100%) and 99% (95% CI 82–100%) respectively. For detection of intestinal metaplasia in biopsies pooled sensitivity and specificity were 89% (95% CI 78–95%) and 93% (95% CI 71–98%) respectively. There were no adverse effects and the technical success rate was 89-100%. A meta-analysis of 34 studies with 6,659 patients demonstrated a comparable technical success rate (94.0% and 97.8% respectively) for both TNE and cEGD, with a significantly higher proportion of patients preferring TNE [14]. In general, patient acceptance of TNE appears to be high [15,16], and uTNE is associated with significantly lower direct and indirect costs compared to cEGD [17].

Limitation of TNE is the limited resolution of the imaging and the smaller biopsy sampling capability. TNE may thus be used as a preliminary triage testing modality to enrich the population that can be further assessed using conventional endoscopy for adequate inspection and acquisition of multiple, larger, surveillance biopsies to detect dysplasia. TNE should not be used for routine BE surveillance.

 

# Supplementary material

## Video capsule endoscopy

Esophageal capsule endoscopy (ECE) is feasible in an outpatient clinical setting and accepted by more than 95% of participants [15]. In a prospective study, ECE identified 14 out of 21 BE patients (sensitivity, 67%) and 58 out of 69 patients without BE (specificity, 84%) [18]. The positive predictive value for BE was 22% and the negative predictive value was 98%. Other studies showed that ECE has a moderate sensitivity and specificity for BE diagnosis in patients with GERD, and, therefore, EGD remains the modality of choice for evaluation of suspected BE [19,20]. Future generations of esophageal capsules with higher frame speed are currently studied, which might improve the results of ECE [21]. However, based on an economic modelling study, ECE is not cost effective when used for BE case finding in patients with chronic GERD symptoms [22]

A pilot study showed that Magnet Assisted Capsule Endoscopy (MACE) is also feasible and safe [23]. Accuracy of esophageal lesions was comparable to EGD. There was a difference in technical success of 94% for MACE versus 100% with EGD. Despite a rapid transit through the esophagus in some cases, the gastroesophageal junction was visualized in 100% and the Z- line in 91.5%. Patient comfort scores demonstrated a preference for MACE over EGD [23]. Further research is needed before this technique can be implemented.

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## Supplementary material


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## Supplementary material

Appendix 3s

# Screening and case finding

## Familial BE: The effect of a positive family history of BE/EAC on the prevalence of BE.

A common definition of familial BE (FBE) is that of having at least one first degree relative (that is, parents, full siblings, or offspring) with BE/EAC [1]. Some studies have also included second degree relatives (uncles, aunts, nephews, nieces, grandparents, grandchildren, half-siblings, and double cousins) in the definition of familial BE/EAC [2–5]. Genetic studies suggest that familial BE/EAC has an autosomal dominant inheritance with incomplete penetrance [6–8]. Initial studies have started identifying susceptibility variants for familial BE/EAC [9–11]. Family history has already been incorporated in some risk prediction models for BE [12], and it is recommended to obtain it carefully in patients at risk for BE or with a first diagnosis of BE/EAC and to update it regularly at follow up visits.

In one of the earliest studies in the US, a family history of BE/EAC was histologically confirmed in 7.3% of probands with BE/EAC [4]. Two other European studies found similar results [5,13]. Four studies offered endoscopy to first-degree relatives of patients with BE/EAC and found a prevalence ranging from 8% to 44% [3,14–16]. A meta-analysis that pooled the results of these studies found a BE/EAC prevalence of 23.4% (95%CI 13.7%, 37.2%) among patients with family history of BE/EAC [17]. However, it should be noted that this meta-analysis may overestimate the true risk of familial BE/EAC, because it seems that most of its results are driven by the two smaller studies, which have flawed designs [14–16]. The other two studies included in the meta-analysis are larger and have a somewhat better design, and either do not report an increased risk from family history compared to controls [15], or suggest presence of an increased risk only in patients with a "non-isolated" family history of BE/EAC [3]. Another more recent meta-analysis that incorporated additional clinical and epidemiological studies, found an overall pooled prevalence of a positive family history of BE/EAC among patients with BE of 8.8% (95%CI 5.5, 13.8) [1]. In the same meta-analysis, the pooled prevalence of a positive family history of BE/EAC among patients with EAC was 4.4% (95%CI 2.2, 8.7), while the pooled prevalence of family history of EAC in patients with EAC was 2.3% (95%CI 1.3, 3.9) [1]. Hence, having a family history of BE/EAC has been recognized as a risk factor that can potentially influence screening strategies. One of the first and most quoted studies, found a 12-fold increase in the risk of BE/EAC among people with positive family history [2]. However, more recent clinical/epidemiological studies suggest a 2.6- to 5-fold increased risk [10,13,18]. A recent meta-analysis that included 14 studies comprising 16,189 patients, found that patients with family history positive for BE/EAC were three times more likely to have BE (relative risk [RR] 3.26; 95%CI 1.43, 7.4) and two times more likely to have esophageal adenocarcinoma (RR 2.19; 95%CI 1.14, 4.21) compared to individuals without family history [1]. At present, only two retrospective studies have considered whether patients with BE and FBE have a higher rate of progression to HGD/EAC, and give conflicting answers [13,19].

When considering the presence of FBE, it should be noted that a substantial percentage of self-reported positive family history for BE/EAC are not confirmed at chart review [4,13]. Therefore, whenever possible, self-reported family history should be documented to better assess the risk for each patient. Indeed, a

 

## Supplementary material

recent meta-analysis found that results of studies that included only confirmed family history had more substantial outcomes compared to studies where family history was only self-reported but not confirmed [1].

Finally, most of available studies consider family history only as a dichotomous yes/no variable. Two studies took into account the number of positive relatives and concluded that among multiplex families (i.e. probands with BE/EAC and at least two relatives positive for BE/EAC) median age of cancer diagnosis was significantly younger compared to duplex (i.e. probands with BE/EAC and only one relative positive for BE/EAC) and non-familial kindreds [20,21]. Hence, individuals who are members of multiplex FBE pedigree, may be considered for screening at an earlier age compared to the general population even in the absence of other risk factors, while patients with only one other family member may be considered for screening in the presence of other risk factors similar to the general population.

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## Supplementary material

Appendix 4s

# Surveillance

## Additional considerations on the role of NBI, blue light imaging, and i-SCAN in surveillance of patients with BE

Wolfsen et al. conducted a prospective, blinded, tandem endoscopy study that compared NBI with standard resolution white light endoscopy (WLE) in patients with BE undergoing surveillance for previously detected dysplasia and showed a significantly higher rate of dysplasia detection (57% for NBI vs 43% for standard) with fewer biopsies (4.7 per patient vs to 8.,5 respectively; $p < 0.001$) for NBI [1]. More recently, Sharma et al. conducted a multicenter, randomized, crossover trial comparing high-definition(HD) WLE and NBI for the detection of IM and dysplasia [2]. During HD-WLE, 4 quadrant biopsies every 2 cm were taken in addition to targeted biopsies of visible lesions. During NBI, only targeted biopsies were obtained. Using NBI only, more areas of dysplasia (LGD/HGD/EAC) were identified (HD-WLE: 67 (21%) vs NBI: 81 (30%), p=0.01), but no difference was found in the proportion of areas with HGD and EAC detected by HD-WLE or NBI. In addition, on a patient based analysis, no differences were found in the detection of dysplasia between HD-WLE with 4 quadrant biopsies and NBI with only targeted biopsies. Of note, all endoscopies were performed in BE expert centers [2]. In a video-based prospective cohort study, 44 endoscopists (22 academic and 22 community) viewed 25 standardized videos with (13) or without (12) visible lesions [3]. Video clips were created to start with HD-WLE followed by NBI to mirror clinical practice. Compared to the gold standard, participants identified 72% of lesions using HD-WLE and 69% of lesions using NBI [3].

Although there is no study examining the role of Blue Light Imaging (BLI) in dysplasia detection, it can be assumed that BLI performs similar to NBI, because of the same optical principle with the use of comparable wave lengths to enhance mucosal and vascular features.

In a retrospective study using selected images of 41 BE patients, Everson et al. showed an increase in accuracy of dysplasia/EAC detection in all seven trainees and in 6 out of 7 experts when using i-SCAN Optical Enhancement compared to HD-WLE (i-SCAN OE vs HD-WLE: 76% vs 63% for trainees, and 84% vs 77% for experts) [4].

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## Supplementary material


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## Supplementary material

Appendix 5s

# Surveillance

## Additional considerations on the role of brushing techniques (in particular of WATS3D) in surveillance of patients with BE

There are 3 multicentre RCTs and 3 meta-analysis investigating the potential role of WATS3D for detection of dysplasia in comparison to standard Seattle protocol biopsies.

Vannalaganti et al [1] included 160 patients from 16 American centres that were either referred for BE surveillance or endoluminal treatment of visible neoplasia. Patients were randomized to undergo forceps biopsies first or WATS3D first, followed by the other modality. The results showed an additional detection of 23 cases of dysplasia, leading to an absolute increase in dysplasia detection of 14.4% when WATS 3D was used as an adjunct. A similar study was recently conducted in Europe (n=172), with the important difference that this trial allowed inclusion of only patients with a known history of LGD or HGD and after removal of all visible lesions by expert endoscopists [2]. The primary endpoint was concordance between forceps biopsies and WATS for detecting HGD/EAC. A total of 51 patients were diagnosed with HGD/EAC, of which 21 patients (12%) were diagnosed on both modalities, 18 patients (10%) were detected by WATS3D only and 12 (7%) were diagnosed by standard biopsies only. In the per-protocol analysis, excluding patients with insufficient samples, no significant difference in detection rate was found. A third RCT by Demeester et al [3] randomized patients between WATS and forceps biopsies. The patient population included routine referrals, BE patients with and without known dysplasia. The study did not show a difference in detecting intestinal metaplasia between biopsies (19.6%) and WATS (22.7%, P=.2). There was no difference in detection of dysplasia. Surprisingly, even within a controlled research setting non-compliance for biopsies was high and significantly larger than for WATS (27.5% vs 7%, respectively; P < .01).

There are three meta-analyses published on the topic. Qumseya et al. [4] analysed data from 7 studies and demonstrated that the use of WATS3D as an adjunct to Seattle protocol biopsies led to the following pooled relative risk (RR) for neoplasia detection in comparison to biopsies alone: RR 1.7 (95% confidence interval [CI] 1.43–2.03, P < 0.001) for any dysplasia; RR 1.88 (95 %CI 1.28– 2.77), P = 0.001 for HGD/EAC; RR 1.5 (95% CI 1.14–1.99), P = 0.004 for LGD only. Considering each modality separately, dysplasia was detected in 106 patients using biopsies and 103 patients using WATS without a significant difference in dysplasia detection between the two modalities. Codipilly et al. [5] looked primarily at the incremental yield of WATS over biopsies to diagnose dysplasia (including all types from indefinite through early cancer), when per definition biopsies were negative for dysplasia. This analysis included 3206 patients in 7 studies. The biopsy dysplasia rate of 15.9% was increased by 7.2% by WATS. For the secondary outcome for detection of HGD/EAC, the biopsy detection rate of 2.3% was increased by 2.1%. Notably, WATS3D was negative in 62.5% of cases where biopsies identified dysplasia. The third metanalysis showed that WATS in adjunct to biopsies led a 1.62 relative increase in detection of BE (measured as RR −1.62, 95% CI 1.28 to 2.05, p<0.0001) and to a 2.05 relative increase in the detection rate of dysplasia (95% CI 1.42 to 2.98, p=0.0001) with a NNT of 50 patients [6].

 

## Supplementary material

Overall these studies indicate that, although WATS significantly increases dysplasia detection as an adjunct to Seattle protocol in a high risk population, dysplasia is also missed by WATS3D. The latter therefore cannot replace the current gold standard. However, from the study in routine population it may be argued that WATS may be able to serve as a replacement because of better adherence to protocol recommendation. In addition, the clinical significance of this increased dysplasia detection remains uncertain. Data from endoscopic follow-up to ascertain biopsy histology in patients with dysplasia based solely on WATS3D are needed to determine the clinical significance of WATS3D only dysplasia, especially for LGD and the implications in terms of long term outcome. Finally, cost implications are also important. To that aspect, Singer et al studied the cost effectiveness of WATS as an adjunct technique. Between 320-337 people would need to be screened to with WATS in addition to standard biopsies to avoid one cancer and between 328-367 to avoid one cancer related death, leading to a ICER of 71,395 $/ QALY [7]. In Europe the threshold for cost-effectiveness usually varies between 30,000-50,000 euros whereas in the former American study this was 100,00-150,000 $.

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