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SOLICITED REVIEW

Australian clinical practice guidelines for the diagnosis and management of Barrett's esophagus and early esophageal adenocarcinoma

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Abstract

Barrett's esophagus (BE), a common condition, is the only known precursor to esophageal adenocarcinoma (EAC). There is uncertainty about the best way to manage BE as most people with BE never develop EAC and most patients diagnosed with EAC have no preceding diagnosis of BE. Moreover, there have been recent advances in knowledge and practice about the management of BE and early EAC. To aid clinical decision making in this rapidly moving field, Cancer Council Australia convened an expert working party to identify pertinent clinical questions. The questions covered a wide range of topics including endoscopic and histological definitions of BE and early EAC; prevalence, incidence, natural history, and risk factors for BE; and methods for managing BE and early EAC. The latter considered modification of lifestyle factors; screening and surveillance strategies; and medical, endoscopic, and surgical interventions. To answer each question, the working party systematically reviewed the literature and developed a set of recommendations through consensus. Evidence underpinning each recommendation was rated according to quality and applicability.

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Introduction

Barrett's esophagus (BE) is the only known precursor to esophageal adenocarcinoma (EAC), a cancer with a rapidly rising incidence. Most people with BE never develop EAC however, and most patients diagnosed with EAC have no preceding diagnosis of BE. Thus, there is uncertainty about the best way to manage this condition.

These guidelines about BE and early EAC are aimed at gastroenterologists, pathologists, surgeons and physicians, and other members of multidisciplinary teams to which patients with BE and EAC are referred. The guidelines will also be relevant to primary care practitioners and patients diagnosed with this condition. The need to develop Australian guidelines for the management of BE and early EAC was identified as a priority by a strategic partnership of clinicians, researchers, patients, and policy makers initiated by Cancer Council NSW in 2011.

Information covered by the guidelines includes:

1. Endoscopic and histological definitions of BE and early EAC
2. Prevalence, incidence, natural history, and risk factors for BE
3. Management of BE and early EAC, including modification of lifestyle factors, screening, surveillance, and medical, endoscopic, and surgical interventions.

The evidence summaries and recommendations are provided separately for BE without dysplasia and BE with dysplasia and/or early cancer, but do not extend to the management of invasive EAC. The recommendations contained herein should not override good clinical judgment. However, they do represent consensus views of expert practitioners and accord with international practices. This publication represents a summary of more extensive material hosted on the Cancer Council Australia Wiki platform[1] that explores the reasons underlying the recommendations in more detail.

Methods

Guideline development was facilitated by Cancer Council Australia, which managed the project and provided in-kind support. No external funding was received for guideline development.

The guidelines were developed by a multidisciplinary working group and used standard methodology.[2] A series of clinical questions were developed to be answered based on systematic reviews. In consultation with the working group, systematic search strategies were developed by project officers using the PICO framework and limits and exclusion criteria were pre-defined to complete the systematic review protocol. Databases searched included the Cochrane Library, PubMed, Embase, Trip Database, Econlit, National Health Service (UK) Economic Evaluation Database, the National Guideline Clearinghouse, the National Comprehensive Cancer Network and the National Institute for Health and Clinical Excellence, Scottish Intercollegiate Guidelines Network, and Canadian Medical Association. Search results were screened by project officers and relevant articles were sent to topic authors for critical appraisal with respect to level and quality of evidence, effect size, and clinical importance and relevance. The level of evidence for each article was assigned according to the National Health and Medical Research Council of Australia Evidence Hierarchy (Table 1).

Table 1 Hierarchy of evidence recommendation†

Level	Description
I	A systematic review of level II studies
II	A randomized controlled trial (intervention) or a prospective cohort study (etiology)
III-1	A pseudo-randomized controlled trial (intervention) or all or none design (etiology)
III-2	A comparative study with concurrent controls (intervention) or a retrospective cohort study (etiology)
III-3	A comparative study without concurrent controls (intervention) or a case–control study (etiology)
IV	Case series with either post-test or pre-test/post-test outcomes or a cross-sectional study

†Adapted from the National Health and Medical Research Council of Australia.

Table 2 Body of evidence recommendation†

Grade	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
Practice point	Where no good-quality evidence is available but there is consensus among expert working group members, so-called Practice points are given

†Adapted from the National Health and Medical Research Council of Australia.

Each topic author summarized the relevant body of literature and then developed recommendations. Each recommendation was assigned a grade by the working group taking into account the volume, consistency, generalizability, applicability, and clinical impact of the supporting evidence (Table 2). When there was insufficient evidence to make a specific recommendation but consensus among experts about the advisability of making a clinically relevant statement, the working group formulated "practice points" to guide clinical practice. The working group also reviewed comparable international guidelines to calibrate the recommendations.

The draft guidelines underwent public consultation in June and July 2014. Feedback was reviewed by topic authors and the working group. Subsequent changes to the draft were agreed by consensus of the working group and the final guidelines were released on August 2014. The Wiki guidelines will be reviewed annually and updated as required.

Guidelines for BE without dysplasia

What is the definition of BE and how is it described? BE is a premalignant condition of the esophagus defined as the presence of metaplastic columnar epithelium,[3]

which appears endoscopically as salmon pink mucosa extending above the gastro-esophageal junction (GEJ) and into the tubular esophagus, thereby replacing the normal stratified squamous epithelium.[3,4] An accurate diagnosis of BE depends on the endoscopic recognition of the anatomic landmarks at the GEJ and squamocolumnar junction.[5] Using the Prague C&M (circumferential and maximal) criteria proposed by the International Working Group for the Classification of Esophagitis,[6] the landmark for the GEJ is the proximal end of the gastric folds.

The metaplastic columnar mucosa can be one of three types: gastric-fundic type, cardiac type, and intestinal type.[7] There remains disagreement as to the histological features of the columnar mucosa necessary to define BE as reflected in the differing definitions given in European and American guidelines.[8–11] For the Australian guidelines, however, the presence of intestinal metaplasia with morphologically typical goblet cells was considered necessary for the diagnosis of BE.

Biopsies from the tubular esophagus containing columnar mucosa without intestinal metaplasia should be given a descriptive diagnosis (e.g. columnar mucosa without intestinal metaplasia), but it is currently recommended that these are not diagnosed as BE until the biological significance of this entity is clarified.

Intestinal metaplasia occurring in isolation at the GEJ or cardia without metaplasia in the tubular esophagus is not considered BE. It may be a precursor to carcinoma, but the risk is low and surveillance is not warranted.[12,13] However, goblet cells noted in a GEJ biopsy can be confirmed to be intestinal metaplasia in columnar-lined esophagus (CLE) if the particular biopsy fragment shows native esophageal structures such as submucosal glands and/or ducts.

Practice points. To identify patients at increased risk of neoplastic progression, BE is defined as metaplastic columnar mucosa in the tubular esophagus, with intestinal metaplasia proven histologically.

Biopsies to confirm intestinal metaplasia should be performed when any length of possible BE is seen extending above the GEJ.

The extent of BE should be described using the Prague C&M criteria.

What is the optimal tissue sampling at endoscopy for diagnosis of BE?

Intestinal metaplasia can be patchy and may not be consistently sampled with endoscopic biopsies[14] (level of evidence IV). Advancements in chromoendoscopy (methylene blue, indigo carmine, and acetic acid), endoscope digital enhancements (narrow-band imaging, i-SCAN, Fujinon intelligent chromo endoscopy), and enhanced magnification have not been shown to be superior to the currently accepted practice of random four-quadrant biopsies at 2-cm intervals[15–17] (levels of evidence I, II, IV, respectively); however, the diagnostic yield may be higher with increasing number of biopsies (level of evidence IV).[18] Jumbo biopsy forceps have not been shown to be superior to standard capacity forceps in obtaining adequate biopsy samples (level of evidence II).[19] Office-based unsedated transnasal endoscopy using pediatric biopsy forceps is well tolerated and may emerge as a cost-effective strategy (level of evidence II).[20–22]

Recommendation. Random four-quadrant biopsies at 2-cm intervals are the mainstay for tissue sampling (recommendation grade B).

Practice points. Focal abnormalities such as ulcerated or nodular lesions should be targeted with biopsies and labeled before random biopsies from the rest of the mucosa as minor biopsy-related bleeding is common and may impair endoscopic views.

Technological advancements in chromoendoscopy, digital enhancements, and enhanced magnification complement rather than replace random four-quadrant biopsies at 2-cm intervals. Biopsies obtained every 2 cm should be placed into separate jars that are labeled according to the distance from the incisors, while biopsies from the GEJ and cardia can also be specifically labeled as such.

Are there biomarkers for the diagnosis of BE?

Numerous biomarkers have been proposed to aid the diagnosis of BE. Estimates of diagnostic accuracy have been reported for tissue biomarkers, including cytokeratin profiling,[23–29] immunohistochemical biomarkers to detect goblet cells such as mucin immunostaining,[30,31] and stress response protein AG2;[32] a serum biomarker (G17[33]); and a non-endoscopic capsule sponge device to collect cytology samples for Trefoil factor 3 immunohistochemistry (TFF3)[34,35] (diagnostic accuracy level of evidence II–III-3). These studies provide insufficient evidence to recommend any biomarkers to supplement or replace standard practice use of endoscopy and histopathology due to study designs with a high risk of bias, wide variation in accuracy estimates across studies, and no comparison with current standard practice.

Recommendation. There is insufficient evidence to recommend cytokeratins, MUC, G17, or AG2 to aid BE diagnosis (grade D).

There is insufficient evidence to recommend the non-endoscopic capsule sponge device with TFF3 for BE screening (grade C).

What is the prevalence of BE in the Australian population in comparison with other populations?

Globally, the prevalence of BE is low (<5%) but is higher in selected groups such as those with gastro-esophageal reflux disease (>15%). There are no studies describing the prevalence of BE in an asymptomatic, unselected Australian population. One small study suggests a high prevalence in high-risk patient populations.[36] A data linkage study conducted in one Australian healthcare region reported prevalence rates at each of three time points as 0.42% (1990), 2.3% (1998), and 4.2% (2002).[37] International studies suggest prevalence varies significantly by ethnicity (e.g. Asians <1% prevalence) and gender (more common in males).

Which factors best predict the risk of developing BE?

Risk factors for BE have been assessed in more than 50 studies. All studies have been observational, and most have been case–control studies of variable quality. From these studies, the major risk factors identified include age,[38] male sex,[39] history of frequent gastro-esophageal acid reflux,[40] central obesity,[41] smoking,[42] and family history[43] (level of evidence III-3, IV). A few studies have conducted serological assays comparing the prevalence of anti-*Helicobacter pylori* antibodies between BE cases and controls, reporting risk reductions of about 50% for persons with

past infection with *H. pylori*.[44,45] There is no evidence that alcohol consumption or dietary or nutritional factors influence risk.[46,47]

Recommendation. Clinical assessment of a person's future risk of BE should consider their age, sex, history of gastro-esophageal acid reflux, waist–hip ratio, or other measures of central adiposity, smoking history, and family history of EAC and/or BE (grade B).

What is the incidence of neoplasia in patients with BE? Five population-based, prospective studies with large sample sizes and complete follow up of patients with uncomplicated BE with no dysplasia have reported progression rates to high-grade dysplasia (HGD) or adenocarcinoma of 2.2–2.6/1000 person-years (py) in Northern Ireland,[48,49] 3.3/1000 py in the Netherlands,[50] 1.2/1000 py in Denmark,[51] and 3/1000 py in the United Kingdom.[52] Meta-analyses of high-quality studies derived similar estimates of progression risks.[53,54]

What are the risk factors for progression from non-dysplastic BE to HGD or adenocarcinoma? Increased rates of progression from non-dysplastic BE to HGD or adenocarcinoma have been associated with patient factors (age, sex, smoking), endoscopic appearance (greater segment length), and aneuploidy[48,55–58] (level of evidence III-2). There is observational evidence that regular users of proton pump inhibitors (PPIs), non-steroidal anti-inflammatory drugs, and statins may have lower rates of progression from BE to cancer[59–64] (level of evidence: II, III-2, III-3).

Recommendation. Clinical assessment of future risk of HGD or adenocarcinoma in the setting of non-dysplastic BE should consider age, sex, smoking history, and endoscopic findings (grade C).

For which populations is screening for BE cost-effective? In line with accepted epidemiologic practice, these guidelines reserve "screening" to describe the process of identifying new cases of disease in an unselected population, whereas "surveillance" describes the systematic follow up of patients with known disease at periodic intervals as part of an early detection strategy to prevent progression to cancer.

There is no evidence to support population screening for BE. However, health economic studies generally suggest that one-off screening of 50-year-old men with gastro-esophageal reflux disease might be cost-effective. Both the cytosponge[65] and ultra-thin endoscopy[66] may be more cost-effective compared with standard endoscopic screening. General population screening, even if conducted coincident with colonoscopy screening, is not cost-effective.

What is appropriate medical systemic therapy for symptoms associated with BE? Medical systemic therapy for patients with BE aims to control symptoms and reduce the risk of complications. Uncomplicated BE is not a cause of symptoms (indeed patients with BE may have reduced sensitivity to esophageal acidification); rather these are due to the symptoms of gastro-esophageal reflux.[67] Acid suppression with PPI is the most effective systemic therapy for reflux symptoms in patients with BE and will control symptoms in most patients with a durable effect over years (level of evidence II, IV)[68–78] Higher than standard doses of PPI may be required to control symptoms in a proportion of patients (level of evidence IV).[79–81]

Recommendation. Symptomatic patients with BE should be treated with PPI therapy, with the dose titrated to control symptoms (grade C).

Are there any medical or surgical interventions that cause regression of BE? Regression of BE is defined by a reduction in the length or area of metaplastic columnar epithelium; however, the significance of regression in BE is unclear. There are insufficient data to indicate that regression leads to reduced incidence of EAC. The degree of Barrett's regression appears largest among patients undergoing anti-reflux surgery although a randomized trial comparing surgical and medical therapy found no significant differences.[76]

Combined analysis of randomized trials has not demonstrated BE regression with medical therapy[82] (level of evidence I).

Recommendation. There is insufficient evidence to recommend the use of acid suppressive therapy for the regression of BE (grade B).

There is insufficient evidence to recommend anti-reflux surgery for the regression of BE (grade C).

Practice point. Acid suppressive therapy and anti-reflux surgery can be used to control symptoms and heal reflux esophagitis in patients with BE. There is insufficient evidence to recommend high-dose (twice daily) acid suppressive therapy when symptom control or mucosal healing is achieved with standard dosing.

Is there a role for ablative therapy to treat BE? Various endoscopic techniques have been investigated for eradicating BE epithelium, including those that deliver focal ablation (argon plasma coagulation [APC], laser heater probe, and endoscopic mucosal resection [EMR]) and those that ablate broad fields (photodynamic therapy [PDT] and radiofrequency ablation [RFA]).

APC is a widely available monopolar electrocautery method. Randomized trials show that medically treated patients and patients with prior fundoplication can be cleared of Barrett's mucosa whereas control patients do not show significant regression.[83–85]

PDT involves administration of a photosensitizer drug (typically oral aminolevulinic acid, or IV photofrin) and subsequent exposure of the Barrett's mucosa to a laser light. Because of potentially severe skin sensitivity, the subject must remain in a darkened environment, restricting use of this technology to cooler climate countries.

RFA involves placement of a balloon catheter in the esophagus, through which radiofrequency energy is delivered allowing treatment of a 3-cm circumferential segment of the esophagus.

Side effects include chest pain, dysphagia, and stricture formation. Rare complications such as bleeding and perforation have been noted. Randomized sham-controlled studies have shown high levels of eradication of both non-dysplastic (> 90%) and dysplastic (> 90%) Barrett's mucosa.[82] Long-term follow up studies show the response is durable with the majority of patients (> 85%) maintaining complete eradication at 5 years.

Recommendation. Long-term outcome studies do not yet support ablation in patients without dysplasia (grade B).

Are there any treatments that prevent progression of BE to cancer? There is limited evidence to support preventive strategies. The choice of anti-reflux therapy (i.e. PPIs *vs* anti-reflux surgery) has not been shown to influence progression to cancer. There is interest in the use of COX inhibitors, but to date only small trials have been conducted with no clear evidence of benefit. A large randomized controlled trial is being conducted to evaluate the efficacy of aspirin to prevent the onset of cancer in patients with BE.[86] This trial is due to report in 2019.

Ablation therapies have shown benefit in randomized trials, but only in those who have already developed dysplasia. In these individuals, the risk of cancer progression appears to be reduced by approximately 50% by both PDT[87] and RFA,[88–90] but cancer risk is not eliminated. The only randomized trial[91] to evaluate ablation (APC) in non-dysplastic BE failed to show benefit for ablation.

Recommendation. Ablation of BE should remain limited to individuals with HGD in BE who are at imminent risk of developing EAC (grade B).

Practice points. The treatment of gastro-esophageal reflux with either PPIs or anti-reflux surgery has not been shown to influence progression to EAC.

There is currently no high-quality evidence supporting the use of COX inhibitors for prevention of EAC.

How frequently should patients with BE undergo endoscopy? The aim of surveillance is to detect dysplasia and early cancer for early treatment. Endoscopic surveillance in patients with BE is the current standard of practice,[8,9] although there is no evidence from randomized controlled trials for its effectiveness. There is, however, indirect evidence based on earlier stage and improved survival in EAC patients detected at surveillance, although these retrospective studies are subject to potential lead and length time bias.[92,93]

Both the British Society of Gastroenterology (BSG) and American Gastroenterological Association (AGA) have published guidelines for endoscopic surveillance of BE.[8,9] The guidelines differ in the criteria for the diagnosis of BE with both requiring a CLE but the AGA also requiring intestinal metaplasia to be present in biopsies from the CLE. This Australian guideline uses the AGA criteria for a diagnosis of BE. British and American guidelines also use the grade of dysplasia found at endoscopy to determine the timing of the subsequent surveillance endoscopy. These recommendations are based on the evidence of an increased risk of EAC with increasing degrees of dysplasia. In those with no dysplasia, the BSG guidelines also take into account the absence of intestinal metaplasia and short-segment (< 3 cm) length, both of which appear to be associated with a decreased risk of malignant progression. Both guidelines recommend biopsies of any visible lesion or mucosal irregularity and quadrantic biopsies. The BSG guidelines recommend quadrantic biopsies every 2 cm in all surveillance endoscopies. The AGA guidelines recommend Seattle protocol biopsies with quadrantic biopsies every 2 cm unless there is suspected or known dysplasia where every 1 cm is recommended. These biopsy protocols have been shown to increase the detection of advanced (high grade and early adenocarcinoma) lesions.[94,95] However, there is low adherence to the protocols[96] resulting in lower detection rates of dysplasia.[97]

The recommendations of the Australian working group for frequency of surveillance are shown in Table 3 and Figure 1. The diagnosis of BE requires intestinal metaplasia in biopsies from the CLE. Recommendations for CLE without intestinal metaplasia are discussed below.

Uncertainty regarding risk of low-grade dysplasia (LGD) progression. The optimum management of patients diagnosed with LGD is uncertain. There is considerable debate about the risks of progression to HGD or cancer in this group. Population-based studies report cancer progression rates of ~0.5% p.a.[51] In contrast, studies undertaken in academic centers in which diagnoses of LGD are made only after review by expert gastrointestinal pathologists report progression rates up to 13% p.a.[98] Importantly, in those studies, about 85% of patients diagnosed originally with LGD were down-staged to non-dysplastic BE upon expert review. Among down-staged patients, the progression rate was ~0.5% p.a.

Endoscopic surveillance in patients with CLE without intestinal metaplasia. In patients with no intestinal metaplasia or dysplasia detected in biopsies from long-segment (≥ 3 cm) CLE, endoscopic surveillance as per the protocol for long-segment BE is recommended (i.e. every 2–3 years). If there is 1 to < 3 cm of CLE without intestinal metaplasia or dysplasia, a repeat endoscopy in 3–5 years is suggested with consideration for discharge from surveillance if the repeat endoscopy with Seattle protocol biopsies again shows no intestinal metaplasia or dysplasia. In patients with CLE less than 1 cm without intestinal metaplasia or dysplasia on biopsies from the CLE, no endoscopic surveillance is suggested. If dysplasia is found in any biopsies from a CLE without intestinal metaplasia, then recommendations are as per the protocols for BE with dysplasia.

Practice points. In the absence of randomized trial evidence, the frequency of surveillance endoscopy in BE can be guided by current practice guidelines.

It is advisable to undertake endoscopic surveillance in suitable patients with BE. The frequency of surveillance is based on the presence or absence of dysplasia on previous Seattle protocol biopsies and length of BE.

A diagnosis of dysplasia (indefinite, low, and high grade) should be confirmed by a second pathologist, ideally an expert gastrointestinal pathologist.

Esophageal biopsies should be taken according to the Seattle protocol.

Table 3 Recommended frequency of endoscopic surveillance of patients with Barrett's esophagus

No dysplasia[†] on endoscopic assessment and Seattle protocol biopsy[‡]	
Short (< 3 cm) segment	Repeat endoscopy in 3–5 years
Long (≥ 3 cm) segment	Repeat endoscopy in 2–3 years

[†]If there has been previous low-grade dysplasia, see *low-grade dysplasia* protocol.

[‡]*Seattle protocol*—biopsy of any mucosal irregularity and quadrantic biopsies every 2 cm unless known or suspected dysplasia then quadrantic biopsies every 1 cm.

Indefinite for dysplasia on biopsy

The changes of *indefinite for dysplasia* on biopsy should be confirmed by a second pathologist, ideally an expert gastrointestinal pathologist. If *indefinite for dysplasia* is confirmed, then the following endoscopic surveillance is recommended:

1. Repeat endoscopy in *6 months* with Seattle protocol biopsies for suspected dysplasia (biopsy of any mucosal irregularity and quadrantic biopsies every 1 cm) on maximal acid suppression.
2. If repeat shows *no dysplasia*, then follow as per non-dysplastic protocol.
3. If repeat shows *low-grade* or *high-grade dysplasia* or *adenocarcinoma*, then follow protocols for these respective conditions.
4. If repeat again shows confirmed *indefinite for dysplasia*, then repeat endoscopy in 6 months with Seattle protocol biopsies for suspected dysplasia.

Low-grade dysplasia on biopsy

The changes of *low-grade dysplasia* on biopsy should be confirmed by a second pathologist, ideally an expert gastrointestinal pathologist. If *low-grade dysplasia* is confirmed, then the following endoscopic surveillance is recommended (or refer to an expert center for assessment):

1. Repeat endoscopy every *6 months* with Seattle protocol biopsies for dysplasia (biopsy of any mucosal irregularity and quadrantic biopsies every 1 cm).
2. If two consecutive 6 monthly endoscopies with Seattle dysplasia biopsy protocol show *no dysplasia*, then consider reverting to a less frequent follow up schedule.

High-grade dysplasia or adenocarcinoma on biopsy

Referral to a center that has integrated expertise in endoscopy, imaging, surgery, and histopathology.

Is surveillance cost-effective for follow up of patients with BE? A recent systematic review[99] of seven studies[100–106] found inconsistent assessments of the value of surveillance, ranging from being cost-effective to highly cost-ineffective. Hence, surveillance of all patients with non-dysplastic BE may not be cost-effective, but this may change with identification of patients at high risk of progression to EAC.

Are there groups of patients with non-dysplastic BE that require more frequent surveillance? Surveillance protocols for patients with BE are based on observational studies.[54,107] However, groups of patients may be identified with high rates of progression, and thus who may benefit from more frequent surveillance. Such groups include patients with longer segments of BE (≥ 3 cm) (level of evidence III-2),[53,54,56,107–110] as well as older patients, males, and smokers (level of evidence II, III-2).[48,55,57,111,112]

Recommendation. Patients with BE length equal to or greater than 3 cm may have intensive surveillance, possibly every 2–3 years following the Seattle protocol (grade C).

Are there groups of patients with BE that can be discharged from surveillance? There is limited high-quality evidence to address this question with certainty, although studies are in progress which may yield risk reducing modifiers (II, III-2, III-3).

Recommendation. For patients with < 1 cm of CLE that do not have evidence of intestinal metaplasia or dysplasia on Seattle protocol biopsy of the segment, endoscopic surveillance is not recommended (grade C).

Practice point. Patients with evidence of "regression" of BE (i.e. reduced CLE length or absence of intestinal metaplasia) can still continue surveillance.

Patients with significant comorbidities, or those unable to tolerate procedural intervention for dysplasia/EAC, may be considered for discharge from surveillance.

Guidelines for BE with dysplasia or early cancer

What are the endoscopic features of neoplasia (dysplasia and early cancer) within a BE segment? Because random sampling of quadrantic biopsies every 2 cm suffers from sampling error and, at times, limited adherence,[97,113] newer modalities have been proposed including chromoendoscopy, electronic image enhancement technologies, and high magnification platforms. There is limited information whether these methods can ultimately change patient management. Presently, high-resolution white light endoscopy (HR-WLE) remains the gold standard in evaluating patients with BE although the newer modalities may be used in addition to HR-WLE to

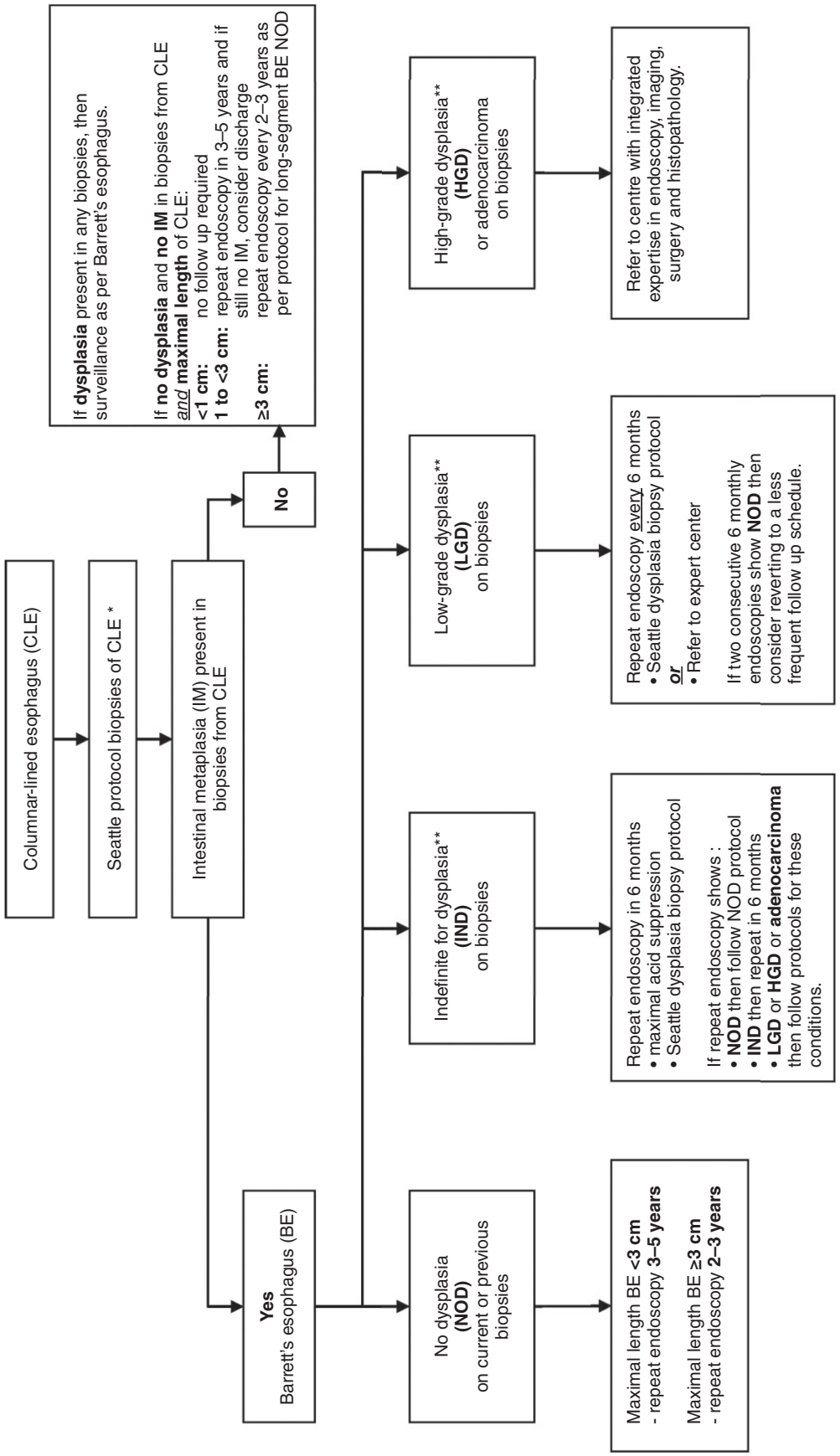

Figure 1 Decision tree for the management of Barrett's esophagus. *Seattle protocol—biopsy of any mucosal irregularity and quadrantic biopsies every 2 cm unless known or suspected dysplasia then quadrantic biopsies every 1 cm. **Dysplasia (indefinite, low, and high grade) should be confirmed by a second pathologist, ideally an expert gastrointestinal pathologist.

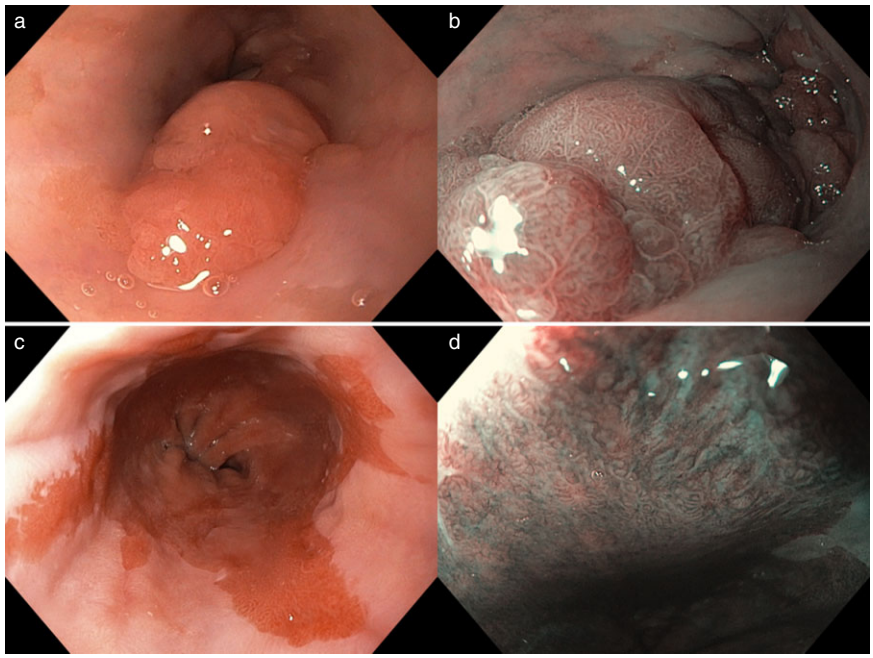

Figure 2 (a) C0M3 Barrett's esophagus containing a 2 × 1 cm (Paris 0–Is) lesion at 6 o'clock in white light and in (b) as seen with narrow-band imaging. (c) Flat C2M4 Barrett's esophagus. (d) Closer examination using narrow-band imaging reveals a focal area with irregular capillary and mucosal pattern at 12 o'clock.

improve characterization of lesions.[114] Thus, it is important to understand the gross morphological features of dysplasia and early cancer and if available, apply some of the more advanced imaging methods.

Given the inconspicuous nature of dysplasia in BE,[115] meticulous inspection and attention to subtle endoscopic anomalies using the best available imaging equipment and endoscopes are warranted. Debris and mucus should be washed off. If there is extensive peristalsis, antispasmodic agents can be used. There is some evidence that cancer preferentially occurs in the distal Barrett's segment[116] and in the 2–5 o'clock position in patients with shorter segments of BE (< 5 cm).[117]

All ulcers in BE should be monitored closely for carcinoma. Biopsies should always be taken in depressed regions and if negative, repeated after a course of PPI therapy. Visible lumps or nodules consisting of HGD suggest a more advanced lesion where more sinister pathology may be present. Suspicious lesions visualized on "white light overview" can be interrogated further with any of the enhanced imaging techniques described earlier. It is not yet clear, however, whether these modalities can replace biopsies (Fig. 2).

What is the histological definition and grading of dysplasia in patients with BE? Dysplasia is an unequivocal neoplastic transformation of the epithelial cells that is confined within the basement membrane of the metaplastic glandular tissue within which it arises. Histological features that characterize dysplasia are best identified on standard H&E-stained sections and comprise cytological changes and/or architectural changes.[118,119]

Cytological features involve nuclear changes (such as increase in size, irregular shape, increased nuclear:cytoplasmic ratio, nuclear crowding, hyperchromasia, and the presence of nucleoli) and cytoplasmic changes such as mucin depletion. Dysplastic cells exhibit increased mitotic activity, including atypical forms and surface mitoses. There is typically failure of cellular maturation toward the surface of the mucosa, although this is not always the case.[120] Goblet cell numbers are reduced and dysplastic cells may lose their normal vertical polarity.

Architectural features are irregular gland outline, variability in glandular size, gland crowding with "back-to-back" pattern, and villiform surface contour. None of these cytological or architectural features are sufficient to diagnose dysplasia in isolation. Ancillary tests (e.g. p53, AMACR and Ki67 stains) have been advocated to aid the diagnosis of dysplasia; however at present, conventional H&E examination remains the gold standard.

Grading of BE dysplasia is best performed on the H&E stain. Pathologists should report BE biopsies as fitting into one of four categories.[118,119,121–123] The rationale for this tiered approach is to stratify patients into categories of increasing risk for development of or concurrent presence of EAC. Many papers have shown an increasing risk ranging from small (negative for dysplasia) to significant (HGD).[124]

1 Negative for dysplasia
2 Indefinite for dysplasia—when the pathologist believes that the biopsy is displaying some features of true dysplasia but is unable to exclude a non-neoplastic process as the cause of the abnormality. In general, the consideration is whether the histological features are sufficient to diagnose LGD. However, in some situations the pathologist is concerned that the features may represent HGD. The concept of indefinite for HGD/adenocarcinoma has not been studied specifically; however, pathologists recognize a subgroup of indefinite for dysplasia where the cytological and/or architectural abnormality is marked but a confident diagnosis of HGD cannot be made. In some of these situations, the concern is that invasive adenocarcinoma may exist.
3 LGD—displays mild-to-moderate cytological atypia and, at

most, mild disturbance of gland architecture. The neoplastic epithelial cells are crowded, elongated, and hyperchromatic. The cells generally retain their vertical polarity.

4 HGD—typically displays both architectural abnormality and severe cytological atypia. Aberrant architectural features include glandular crowding, branching or budding glands, villiform, cribriform, micropapillary, or cystically dilated crypt patterns. Cytological features include complete loss of cell polarity, rounded enlarged nuclei with irregular-thickened nuclear membranes, and conspicuous nucleoli. Typical and atypical mitotic figures are readily identified at all levels within the glands, as well as on the luminal surface.

Grading of dysplasia is subject to significant interobserver variability,[125–127] especially LGD. Interobserver agreement among general histopathologists ranges from kappa values of 0.14 to 0.32. Specialist gastrointestinal histopathologists have better agreement (kappa 0.48–0.69).[128] When a diagnosis of LGD made by a general histopathologist is reviewed by an expert panel, the diagnosis is most often down-graded to "negative for dysplasia."

These data support the notion that all cases of BE diagnosed as dysplasia (indefinite, low, or high grade) should be reviewed by at least one expert GI pathologist.

What are the histological features of early adenocarcinoma of the esophagus? Early adenocarcinoma refers to invasion into mucosa or superficial submucosa, but not deeper (T1 in the current TNM system). Adenocarcinoma exists when there is invasion beyond the basement membrane of the epithelium. The histological features identifying that invasion has occurred include:[129,130]

1 Single neoplastic cells or small clusters of neoplastic cells in the lamina propria.
2 Complex architectural patterns characterized by solid growth patterns, tight cribriform growth pattern, glands with acute angulation in at least one part of their outline, and a pattern of anastomosing fusion of small glands.
3 Neoplastic cells invading overlying squamous epithelium.
4 Desmoplastic stromal reaction.

Significant interobserver variability exists between pathologists in the separation of HGD from early invasive adenocarcinoma in biopsy specimens.[131] Recent studies have identified a variety of histological patterns that predict invasive adenocarcinoma including solid or cribriform growth patterns, ulceration of dysplastic epithelium, abundant neutrophils within dysplastic epithelium, dilated neoplastic glands containing necrotic debris, and dysplastic glandular epithelium being incorporated into squamous epithelium. The risk of adenocarcinoma is increased with number of features present.[132]

The histological report of EMRs should include data that are important for clinical management, particularly the identification of patients who should be considered for esophagectomy. These are discussed in greater detail in the guidelines for reporting esophageal and gastro-esophageal carcinomas provided by the Royal College of Pathologists of Australasia.[133]

What are the best modalities for accurately staging early EAC? Early EACs are those defined as intramucosal adenocarcinoma (T1a) or superficial submucosal adenocarcinoma (T1b).[114] A more comprehensive subclassification of early esophageal cancers has been proposed with mucosal disease and submucosal disease divided into three categories, respectively (m1-3/4 and sm1-3) based on depth of invasion.

Options for staging of early EAC include:

1 Endoscopic biopsy
2 Endoscopic resection (ER) (also known as EMR)
3 Endoscopic ultrasound (EUS) with or without fine-needle aspirate (FNA)
4 Positron emission tomography-computerized tomography (PET-CT), once the diagnosis of cancer has been confirmed

Endoscopic biopsy is useful but is subject to sampling error. ER is superior to biopsy and results in a change in diagnosis in up to 50% of patients with dysplasia or adenocarcinoma (level of evidence IV).[134–137] Moreover, ER allows improved pathological staging of HGD and T1m and T1sm adenocarcinoma as compared with biopsy and EUS (level of evidence IV)[136,138] (Fig. 3). Rates of adverse events following ER, such as perforation, bleeding, and stricturing, are low when performed at expert centers (level of evidence IV).[138–140] EUS is not accurate for determining the stage of early EAC, especially distinguishing T1m from T1sm tumors. It is useful for differentiating T1 and >T1 stages (level of evidence IV).[141,142] EUS and EUS guided FNA (EUS-FNA) are superior to CT for locoregional lymph node staging (level of evidence IV).[143,144]

Recommendations. ER is the most accurate staging modality for early EAC for suitable lesions and where appropriate expertise is available (grade D).

EUS can be used prior to ER when deeper invasion is considered likely, particularly for lesions with ulcerated or depressed morphology (grade D).

FDG-PET or PET/CT is not routinely indicated in staging early EAC. It is best used for the staging of distant metastases or in cases of suspected more advanced local disease (grade D).

What is the appropriate management of LGD in patients with BE? Recent studies suggest that when the diagnosis of LGD is agreed on by two or more expert pathologists, the risk of progression to neoplasia is higher than previously reported (level of evidence III-2).[88,98,145] British and American guidelines recommend increased frequency of surveillance.[8,9] Endoscopic ablation with a range of methods is associated with lower rates of progression to cancer (level of evidence IV).[146] In particular, an RCT reported that RFA in patients with confirmed LGD have significantly lower rates of progression to cancer or HGD, although as yet there is no evidence of an overall survival benefit (level of evidence II).[88]

Recommendations. The diagnosis of LGD should be confirmed by a second pathologist, ideally an expert gastrointestinal pathologist (grade C).

In patients with confirmed LGD, it is advised to perform rigorous high-definition endoscopy or refer to an expert centre for assessment (grade C).

In patients with confirmed LGD, intensified endoscopic surveillance is required. Endoscopic ablation may be considered

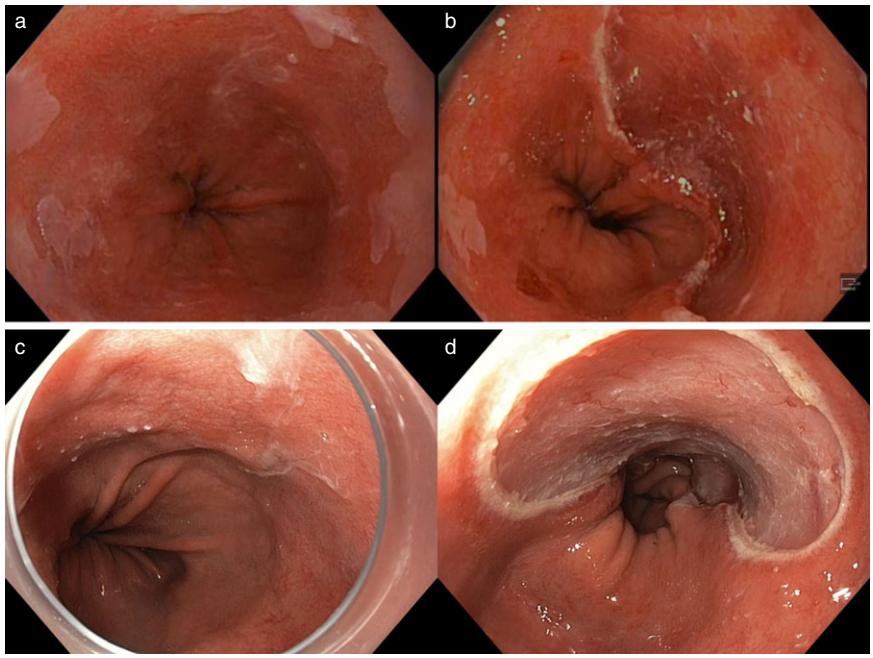

Figure 3 (a) C3M4 Barrett's esophagus. After careful inspection, a focal abnormality was noted at 2 o'clock. (b) Focal endoscopic mucosal resection was performed for staging confirming high-grade dysplasia. (c) C7M8 Barrett's esophagus. Using a distal attachment cap for improved visualization, nodular lesion with slight depression (Paris 0–IIa+IIc) noted at 12–2 o'clock. (d) This area is completely excised by endoscopic mucosal resection. Histology confirmed Barrett's esophagus with high-grade dysplasia and focal area of intramucosal adenocarcinoma (M1-T1a).

especially where LGD is definite, multifocal, and present on more than one occasion. This decision needs to be individualized based on discussion of risk and benefits with the patient (grade B).

What are the goals of treatment of HGD in patients with BE? There is no high-level evidence that directly answers this question, and so the guidelines are based on expert opinion. As HGD is prone to both over- and under-staging, the first goal of management is to confirm the diagnosis.

Once HGD has been confirmed, the goal of treatment is to prevent the progression to malignancy through the removal of dysplastic tissue. More specifically, the goals of treatment are:

1 The removal of all dysplastic tissue[114]
2 The removal of all Barrett's metaplasia if possible[114]
3 Preservation of normal swallowing/nutrition
4 Minimization of morbidity due to the eradication technique
5 Confirmation of the diagnosis of HGD (i.e. exclusion of malignancy) through examination of resected tissue (endoscopically or surgically), where possible
6 Continued follow up in patients who have had endoscopic therapy[114]

There is no management strategy that perfectly fulfils all these criteria. Current practice favors endotherapy (ER or ablation) over surveillance or esophagectomy for HGD/T1a cancer, although no randomized control trials have compared the two modalities directly. All patients should be discussed at a multidisciplinary meeting.

Practice point. The confirmation of HGD should act as a trigger for definitive treatment.

What is the best endoscopic treatment for HGD in patients with BE? ER alters histological grade or local T stage in 48% of patients and reduces esophagectomy rates by providing an effective local therapy. ER has a high success rate (94%) for complete Barrett's excision in short-segment BE (level of evidence IV).[139] RFA has been shown to completely eradicate HGD in 81% of patients at 1 year of follow up versus 19% complete eradication in patients undergoing endoscopic surveillance alone. Similar outcomes are reported following RFA at 2 and 3 years of follow up with 95% and 96% complete eradication, respectively (level of evidence II)[89,90] (Fig. 4).

Recommendations. ER should be considered for patients with intramucosal adenocarcinoma or HGD and visible/nodular lesions (grade D).

RFA should be considered for patients with HGD within flat segments of BE. RFA is not appropriate in patients with visible abnormalities; these should be treated by ER. RFA may be the preferred treatment strategy over ER for patients with long-segment BE or circumferential Barrett's due to a lower rate of stricture formation (grade B).

Practice point. It is advisable to refer patients with BE and dysplasia or early EAC to tertiary referral centers for management.

What is the best endoscopic management of early EAC? Early EAC comprises the histological tumor classification of T1a (invasion into the mucosa) and T1b (invasion into submucosa but not muscularis propria). The depth of invasion can be further stratified based on mucosal (m1–m3/m1–m4) or submucosal (sm1–sm3) involvement.[123,147] ER is the most accurate T staging modality for early EAC (level of evidence IV)[137,139]

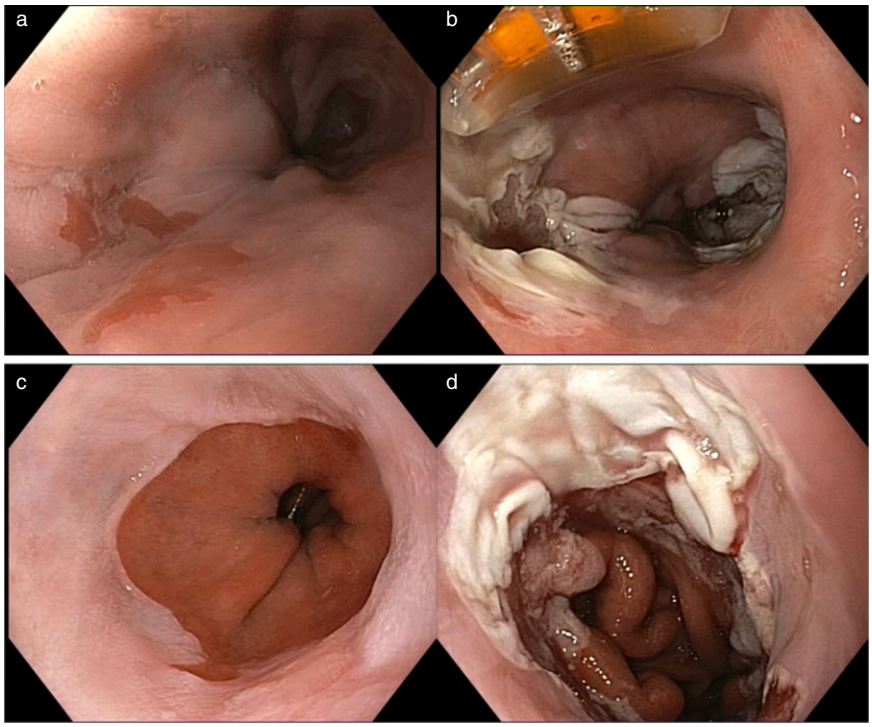

Figure 4 (a) C5M7 Barrett's esophagus with high-grade dysplasia previously treated by endoscopic mucosal resection and radiofrequency ablation—residual disease remaining at 7 o'clock proximally and 12–4 o'clock distally. (b) Focal radiofrequency ablation to sites of residual Barrett's mucosa. (c) C2M4 Barrett's esophagus previously treated by radiofrequency ablation for flat high-grade dysplasia. (d) Residual Barrett's mucosa is treated by focal radiofrequency ablation.

(Fig. 5). The risk of lymph node involvement with T1a and T1b early EAC is 1.3–2.5% and 12–31%, respectively.[148–151] Unlike locally advanced or node-involving disease, early EAC can often be cured with surgical or endoscopic approaches. Endoscopic treatment is less morbid and expensive than esophagectomy, and is organ preserving.[152] ER is effective for T1a early EAC when performed in experienced centers. Selected patients with T1b early EAC may benefit from ER if esophagectomy is not indicated (levels of evidence II, III-2, IV).[153–157]

Recommendations. All lesions and visible abnormalities should be staged by focal ER (grade D).

If ER of early EAC is planned, ER is appropriate in most cases. Ablative therapies should not be used as primary endoscopic therapy for early EAC (grade C).

Patients with T1a adenocarcinoma on endoscopic work-up should be offered ER in preference to esophagectomy (grade D). Selected patients with T1b early EAC may also be offered ER but only if esophagectomy is not indicated (grade D).

Following resection of early EAC the remaining Barrett's mucosa should be eradicated. Barrett's eradication options include complete ER, RFA, cryotherapy, and APC (grade C).

Following resection of early EAC, the patient should undergo regular and careful surveillance examinations (grade C).

Practice point. ER of early EAC should be performed in referral centers that have integrated expertise in endoscopy, imaging, surgery, and histopathology.

Careful and dedicated endoscopic interrogation of all Barrett's mucosa is advised.

After successful endoscopic treatment for BE neoplasia, how frequently should patients undergo endoscopy? There is no high-level evidence that directly answers this question, and so the guidelines are based on expert opinion. Following endoscopic treatment for BE with neoplasia, patients should be considered for three monthly surveillance endoscopies with Seattle protocol to confirm clearance of disease. Once clearance has been achieved, consider six monthly endoscopic surveillance for 1 year, then annually. Higher risk patients may require closer surveillance endoscopy after clearance of BE neoplasia is achieved (i.e. initially six monthly for a year). ER of mucosal irregularities (nodules, depressed areas) in the squamous epithelium should be considered to clarify possible recurrent or metachronous intramucosal adenocarcinoma from subsquamous glands.

Practice point. Consider three monthly surveillance endoscopy with Seattle protocol during the endoscopic treatment phase to confirm clearance of intramucosal adenocarcinoma and residual BE. Once clearance has been achieved, consider six monthly endoscopic surveillance for 1 year, then annually.

Higher risk patients may require closer surveillance endoscopy after clearance of BE neoplasia is achieved (i.e. initially three monthly for a year). ER of any nodularity in the squamous epithelium should be considered to clarify possible recurrent or metachronous cancer from subsquamous glands.

What endoscopic surveillance protocol should be followed for patients with HGD? Surveillance is generally not indicated for patients with HGD and therapeutic intervention must be considered instead.

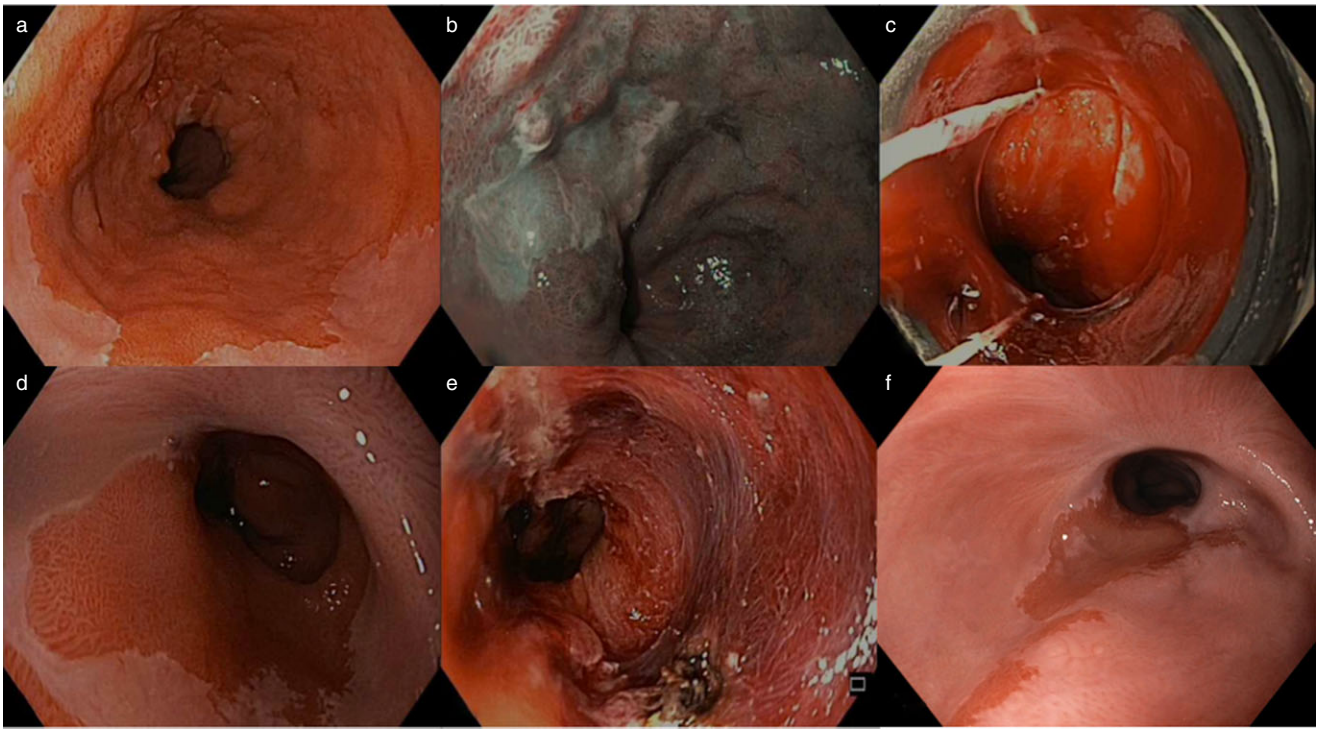

Figure 5 (a) C4M5 Barrett's esophagus with diffuse nodular mucosa between 9 and 2 o'clock. (b) Close up examination using narrow-band imaging discloses irregular mucosa with abnormal capillary and pit patterns. (c) The abnormal area is removed by multiband mucosectomy; this revealed intramucosal adenocarcinoma (T1a). (d) On progress examination at 6 weeks neosquamous epithelium is seen in the area of excision. (e) Further, stepwise complete endoscopic resection for the residual Barrett's mucosa is performed resulting in a hemi-circumferential mucosal defect. (f) Six weeks following the previous resection there is extensive neo-squamous re-epithelialization of the distal esophagus. A small residual segment of Barrett's mucosa remains. The patient had low-grade dysphagia from this stricture that was easily treated with Savary dilation.

How effective is endoscopic management compared with surgical management for HGD in patients with BE? There are no randomized controlled trials comparing surgery with endoscopic treatments for HGD. Evidence therefore comes largely from non-randomized retrospective studies. These studies report that endoscopic treatment of HGD provides similar outcomes to surgery with regard to overall survival and cancer-related mortality (level of evidence III-2).[153,158–162] In addition, the studies tend to report that compared with surgery, endoscopic treatments result in less morbidity but higher rates of local recurrence (level of evidence III-2).[153,158–162]

Recommendation. Patients with HGD in BE should be managed in centers with high-volume experience of the condition. The treatment and follow up should occur in those specialist centers (grade C).

Practice points. Patients with HGD in BE can be discussed at a multidisciplinary team meeting at a specialist centre.

Endoscopic treatment will be the first-line treatment option for the majority of patients with HGD in BE. There will be a group of patients for whom endoscopic treatment is not appropriate or successful and they will be best treated with surgery in a specialist centre.

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