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BOB CAT: A Large-Scale Review and Delphi Consensus for Management of Barrett's Esophagus With No Dysplasia, Indefinite for, or Low-Grade Dysplasia

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Abstract

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SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

We have not used the term "specialized" intestinal metaplasia as it implies intestinal metaplasia (IM) i.e. goblet cells. The term "columnar mucosa" implies columnar metaplastic replacement of the native squamous mucosa.

CONFLICT OF INTEREST

Guarantor of the article: Janusz Jankowski, MD, PhD.

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OBJECTIVES—Barrett's esophagus (BE) is a common premalignant lesion for which surveillance is recommended. This strategy is limited by considerable variations in clinical practice. We conducted an international, multidisciplinary, systematic search and evidence-based review of BE and provided consensus recommendations for clinical use in patients with nondysplastic, indefinite, and low-grade dysplasia (LGD).

METHODS—We defined the scope, proposed statements, and searched electronic databases, yielding 20,558 publications that were screened, selected online, and formed the evidence base. We used a Delphi consensus process, with an 80% agreement threshold, using GRADE (Grading of Recommendations Assessment, Development and Evaluation) to categorize the quality of evidence and strength of recommendations.

RESULTS—In total, 80% of respondents agreed with 55 of 127 statements in the final voting rounds. Population endoscopic screening is not recommended and screening should target only very high-risk cases of males aged over 60 years with chronic uncontrolled reflux. A new international definition of BE was agreed upon. For any degree of dysplasia, at least two specialist gastrointestinal (GI) pathologists are required. Risk factors for cancer include male gender, length of BE, and central obesity. Endoscopic resection should be used for visible, nodular areas. Surveillance is not recommended for <5 years of life expectancy. Management strategies for indefinite dysplasia (IND) and LGD were identified, including a de-escalation strategy for lower-risk patients and escalation to intervention with follow-up for higher-risk patients.

CONCLUSIONS—In this uniquely large consensus process in gastroenterology, we made key clinical recommendations for the escalation/de-escalation of BE in clinical practice. We made strong recommendations for the prioritization of future research.

COMMENTARY

Barrett's esophagus (BE) is a premalignant lesion of metaplastic columnar epithelium of any histological subtype (1). Even though guidelines for the management of BE (1–4) have been produced, its endoscopic and histopathologic classification, and management is highly variable among and within countries, and it is unlikely that large, well-designed trials will ever be conducted, although with some exceptions (5–7).

Given the impact of a diagnosis of nondysplastic BE on the patient, the cost, risk of endoscopic surveillance, and the consequences of progression to invasive esophageal adenocarcinoma (EA) if management strategies fail, our international BOB CAT (*B*enign *B*arrett's and *CA*ncer *T*askforce) consensus group has produced an evidence-based consensus focused on the management of nondysplastic BE, and low-grade dysplasia (LGD) specifically, to inform clinical practice for a worldwide audience.

We have established an international agreement for a definition of BE for the first time, i.e., "BE is defined by the presence of columnar mucosa* in the esophagus and it should be stated whether intestinal metaplasia (IM) is present above the gastro esophageal junction." (*see footnote) This definition amalgamates both the divergent European (non-IM allowed) (1) and the US (IM only allowed) systems (8,9). In addition, because the gastroesophageal junction is mentioned explicitly, it emphasizes how important it is to distinguish BE from the commonly associated hiatal hernia (HH) below (10). Future refinements to this

definition may, for example, include a requirement for IM in those with a predefined length of Barrett's.

BE affects 2% of the adult population (11), particularly those with heartburn and those undergoing endoscopy (12–14). BE-related EA develops from chronic esophagitis through benign BE and dysplasia (Figure 1a) (15–18), and the incidence of EA has increased in recent decades in developed countries (19,20). Although it is uncommon for BE patients to develop EA (21–24), in recent population-based studies looking at outcomes from surveillance taking into account lead time bias and length bias, surveillance of BE leads to diagnosis of EA at an earlier stage and to improved survival from EA (25) and is cost effective if undertaken every 5 years for nondysplastic BE and every 3 years for LGD in long-segment BE (26). These estimates are all predicated on the conversion rate from BE to EA being at least 0.5% per year. Indeed, the most recent guidelines from the British (1) and American societies (2) recommended surveillance endoscopy every 2–5 years in patients with BE to detect high-grade dysplasia (HGD) that is treatable by endotherapy (2,27,28). The majority of the BOB CAT group was either undecided or negative on the proposition that surveillance (with its associated potential harms and costs of surveillance) decreases mortality from EA. There are few data to guide recommendations about surveillance for non-dysplastic BE, and until these become available (7), we have produced guidance on stratification of risk for targeted surveillance in high-risk groups, including, but not limited to, age and sex, length of BE segment, and symptom duration, frequency, and severity, as well as central obesity and tobacco smoking (29).

We now have consensus on a new bidirectional pathway (see Figure 1b) to de-escalate or escalate the management of patients with lower-risk BE compared with those with potentially higher-risk BE such as indefinite for dysplasia (IND), or LGD with persistence over two endoscopies, multifocality, and long-segment BE. If not treated, in the case of LGD found on a single occasion, follow-up should be close (a more intensive 6–12-month surveillance interval) and biopsy protocols strict, as many may also have, or go on to develop, HGD. Intervention steps are highlighted in Figure 1c. The diagnosis of IND should be considered a temporary diagnosis only and should prompt further close follow-up with adequate biopsy sampling. Patients with persistent and confirmed LGD should be treated with ablative therapy, which decreases progression to neoplasia (30), and not just followed up. In all cases, the risks and benefits of surveillance should be taken into account with the patient's input, particularly in those patients with comorbidities or short life expectancy.

Future research including evaluation of genetic markers to determine cancer risk (31,32) and biomarkers of progression (33,34) may also permit selection of higher-risk groups for endoscopic surveillance or treatment. We make no recommendation to proceed with routine use of biomarkers in practice, but the adoption of these markers in specialist centers could be considered.

METHODS

The specific population under consideration consisted of adults aged ≥18 years old with a diagnosis of nondysplastic BE or LGD, but excluding those with esophagitis alone, or

invasive or advanced stages of EA. HGD, intramucosal EA (T1m or T 1a), or superficial submucosal EA (T1sm1 or T1b) were reviewed in the previous consensus (3).

We used an evidence-based Delphi process (35,36) to develop consensus statements for nondysplastic BE and LGD. This paper uses a similar but larger and improved methodology to that published in 2012 (3) that covered the management of BE with either HGD or locally invasive cancer. The present study excluded these areas totally and instead covered the management of nondysplas-tic, IND, and LGD in BE.

The process (3) permitted anonymous individual feedback and changes in views during the process, together with controlled feedback of evidence regulated by the coordinator (C.B.) and the consensus chair (J.J.). The principal steps in the process were as follows: (i) selection of the consensus group; (ii) identification of areas of clinical importance; (iii) systematic literature reviews to identify evidence to support each statement; (iv) draft statements and discussions supported by evidence specific to each statement, by panels; and (v) three rounds of anonymous voting and feedback, plus three supplementary rounds of *post hoc* voting following peer reviewers' requests. The respondents were asked to choose one of the following for each statement: agree strongly (A+), agree with reservation (A), undecided (U), disagree (D) or disagree strongly (D+). When no strong agreement was reached, we rephrased the statement in a negative manner to see whether this would provoke stronger agreement. A description of any concerns about the statement was provided from the online comments of the respondents, allowing statement chairpersons to modify statements and discussion before the next voting round. Evidence-based discussions with key references were provided; it was the statement on which participants voted. We did not use meta-analysis techniques, although we drew on evidence from existing meta-analyses.

We defined consensus as 80% of respondents strongly agreeing or agreeing with reservation. If >50% of respondents strongly agreed with the statement, it was accepted as a measure of agreement (Figure 2). With each round of the main consensus process (both the main rounds and the *post hoc* voting rounds), fewer statements received <20% agreement, reflecting comments on the inclusion of negatively phrased statements (Figure 2) (6). We used GRADE (Grading of Recommendations Assessment, Development and Evaluation) terminology to describe the strength and quality of the evidence for treatment comparisons: high-, moderate-, low-, or very low-quality evidence (37), and we used GRADE to quantify the strength of recommendations as strong or conditional (38). GRADE ratings were not applied when recommendations were considered to refer to universally accepted good practice rather than an evidence-based decision on two or more competing management strategies.

Further details are listed in Appendix 2 online (please see Supplementary Paper, Methods online).

RESULTS

We reached consensus in the final round (defined as 80% of the respondents who took part in the final voting rounds indicating that they agree strongly or agree with reservation) in

55/127 statements. Agreement among at least 50% of respondents was achieved in 90 of 102 statements in the final main voting round and in 23 of 25 in the final *post hoc* voting round (Figure 2), with a corresponding decrease in null votes by the final round.

The core group reviewed the results and, afier the final round, selected and summarized 10 key groups of 35 statements that represent clinically relevant areas in screening, diagnosis, surveillance, approaches to treatment, and prevention of progression to HGD and early EA in patients with BE. We made these selections on the basis of clinical relevance with a high degree of consensus to guide clinical practice (Figure 3).

In total, 20,558 records of publications (Figure 4, flow diagram) (39) were available for review and inclusion.

Additional statements are provided in Appendix 2 online (Results) to this publication and all statements were archived: (http://www.mdpub.org/bobcat/results.php).

Statement agreement

Definition of BE—1. BE is defined by the presence of columnar mucosa in the esophagus, and it should be stated whether IM is present above the gastroesophageal junction. STATEMENT ENDORSED, overall agreement 88%. A+, 49.3%, A, 38.7%, U, 4%, D, 5.3%, D+, 2.7%.

Recommendation

Good practice includes the adoption of internationally accepted pathology criteria for both benign and dysplastic BE.

Good practice recommendation.

The definition and hence diagnostic criteria for BE remains controversial, varies worldwide, and continues to be divided in opinion. In the United States, there is strong endorsement that the term “Barrett’s esophagus” should be used only for patients who have IM in the esophagus. This definition of BE is at odds with current UK and Japanese (8,40) opinion and with the definition in updated British Society of Gastroenterology (BSG) guidelines (1) that do not require IM to establish the diagnosis. The BSG guidelines do acknowledge the increased risk of neoplastic progression when IM is present, in that it is proposed that BE surveillance is based on risk stratification (including the presence of IM). The presence of IM (i.e goblet cells) can be limited by sampling error in mucosal biopsies but can virtually always be identified in endoscopically visible columnar metaplasia provided a sufficient number of biopsies are taken over a sufficient timescale (10). Although other data show that a cohort of between 9 and 25% of patients have never had goblet cells detected, other authors question the need for IM for the diagnosis of BE (41). Defining IM by the morphological identification of mucosal goblet cells has now been shown to be problematic, as there is evidence that the non-goblet columnar epithelium may be intestinalized, showing similar molecular abnormalities as goblet cell epithelium, and with similar risk for neoplastic progression (42). There is also growing evidence that challenges the notion that EA is always preceded by IM, and suggests that there is no difference in the rate of development of EA between patients with and those without IM. The difference in definition

clearly has the potential to greatly influence the frequency of diagnosis of BE at index endoscopy (43), and the number of patients entering into follow-up and surveillance programs (44).

There are three main caveats that should be borne in mind to ensure that this new global definition of BE is clinically meaningful: the gastroesophageal junction is irregular and tongues of ≤1 cm may be a natural phenomenon (even if IM is present, it can occur in the cardia of the stomach); in >80–90% of cases of BE a HH also coexists; and that the diagnosis must be an agreed clinicopathological definition. However, there are cases in which either the pathologist or the endoscopist may be able to overrule the other. Examples of this are long segments of BE >3 cm (most HH are ≤3 cm) or micrometaplasia that can be missed endoscopically but picked up by the pathologist.

In conclusion, BE is a combined endoscopic and pathological diagnosis; BE is defined by the endoscopic presence of columnar mucosa of the esophagus, and the pathology report should state whether IM is present or absent in the tissue samples taken from the above gastroesophageal junction.

2. The optimal definition of LGD in BE includes the use of an agreed upon internationally recognized criteria including increased nuclear/cytoplasmic ratio and hyperchromatic and het-erochromic nuclei. STATEMENT ENDORSED, overall agreement 83.6%. A+, 21.9%; A, 61.7%; U, 7.8%; D, 7.8%; D+, 0%.

Recommendation

Good practice includes the adoption of internationally accepted pathology criteria for both benign and dysplastic BE.

Good practice recommendation.

The criteria for unequivocal low-grade intraepithelial neo-plasia (45) typically include preserved nuclear polarity, nuclear heterogeneity and margination, few mitoses, no atypical mitoses, and decreased numbers of transition to adjacent glandular epithelium. Architectural changes are absent or minimal in LGD but may include irregular growth patterns, parallel tubules, minimal gland distortions, no single cell budding, no significant branching of glands, no solid or cribriform patterns, and normal lamina propria. There are intraobserver variations in the diagnosis and grading of LGD and in differentiating it from reactive changes (46,47). Criteria for grading foveolar and serrated dysplasia have not been fully addressed in the literature (48,49). In the future, image analysis may help refine the criteria further (50).

Diagnosis

3. The single reporting of biopsies for routine diagnosis of benign Barrett's is satisfactory. STATEMENT ENDORSED, overall agreement 80.8%. A+, 30.4%; A, 50.4%; U, 13.6%; D, 4%; D+, 1.6%.

Recommendation

We recommend that for benign BE a single pathologist report is satisfactory for management.

Good practice recommendation.

The evaluation of routine biopsies by a single specialist (in BE) histopathologist, i.e. single reporting, for the diagnosis of BE is satisfactory (51).

4. A consensus between at least two specialist gastrointestinal (GI) pathologists is required for the diagnosis of LGD. STATEMENT ENDORSED, overall agreement 90.8%. A+, 48.7%; A, 42.1%; U, 3.9%; D, 5.3%; D+, 0%.

The diagnosis of LGD is potentially a watershed in the natural history of BE, as most studies have shown that it indicates a much higher chance of progression compared with nondysplastic BE. It therefore generally results in a much more intensive follow-up schedule with treatment modalities such as radiofrequency ablation (RFA). For this reason, it is vital that pathologists diagnose LGD accurately. Studies that have looked at pathologist interobserver agreement for the diagnosis of LGD show at best fair agreement, with κ-scores ranging from 0.15 to 0.4 (52–54), and increasing to κ=0.61 (0.53–0.69), when probe-based confocal laser endomicroscopy was employed (55). However, as differentiation between LGD and HGD is difficult, agreement for the presence of dysplasia vs. no dysplasia may be considerably better than this. Nevertheless, several studies have shown that when LGD is diagnosed by general pathologists, the progression rate is low and that when these cases are reviewed by specialist GI pathologists, many are downgraded to no dysplasia. At least two studies have also shown that the chance of progression of dysplasia is proportional to the number of pathologists who agree that a case is dysplastic. This purified dysplastic cohort then has a relatively high rate of progression (46,56,57). In the recent Amster-dam paper (58) and the SURF (SUrveillance vs. RadioFrequency ablation) study (30), only approximately a quarter of LGD cases were confirmed after specialist review by a panel and there was a clear difference in progression rates. For these reasons, it is recommended that the initial diagnosis of dysplasia is agreed upon by at least two GI pathologists who are specialized in gastrointestinal pathology and who are experienced in the pathology of BE. The new BSG guidelines (1) actually go slightly further and recommend that “Given the important management implications for a diagnosis of dysplasia, we recommend that all cases of suspected dysplasia are reviewed by a second GI pathologist, with review in a cancer center if intervention is being considered.” For follow-up biopsies in patients who already have an established consensus diagnosis of dysplasia at the same institution, it could be argued that this requirement could be relaxed, although there are no data to support this either way.

5. In BE, the diagnosis of IND can be used for a variety of histo-pathological appearances and requires consensus agreement between at least two specialist GI pathologists. STATEMENT ENDORSED, overall agreement 80%. A+, 37.3%; A, 42.7%; U, 14.7%; D, 4%; D+, 1.3%.

The meaning of such a diagnosis in a pathology report can be several fold but where there are some features of the epithelium and glands which are suspicious for dysplasia the term

‘indefinite for dysplasia’ may be useful in the interim. First it may refer to an epithelium that possesses the cytological features of dysplasia (nuclear pleomorphism, hyperchromasia, loss of polarity), but the features are present only in the base of crypts and not in the surface epithelium. Lack of surface maturation has, by convention, been required for the diagnosis of dysplasia, but more recently there has been recognition of crypt dysplasia with surface maturation in up to 7.3% of BE cases (59). Second, regenerative changes may mimic dysplasia, whereby there is a constellation of cytological atypical features, evidenced by an often marked increase in mitotic figures, nuclear pleomorphism, and loss of cell polarity, associated with inflammation, but a retained architecture and no sharp cutoff between normal and abnormal epithelium. Technical factors may also make a definitive assessment of the tissue impossible. It is clear that reproducibility of diagnosis of IND is poor (60–62), and there is no evidence pointing to an optimal number of pathologists required for an IND diagnosis, but all cases of dysplasia require consensus review by at least 2 specialist GI pathologists.

Recommendation

We recommend two or more specialist GI pathologists should be involved when any grade of dysplasia is diagnosed.

Conditional recommendation, low-quality evidence.

6. A proforma (standardized reporting form) should be used to report BE. STATEMENT ENDORSED, overall agreement, 83.9%. A+, 46%; A, 37.9%; U, 14.5%; D, 1.6%; D+, 0%.

Recommendation

Using a proforma for pathology reporting in nondysplastic BE is good practice.

Good practice recommendation.

The use of a proforma report is strongly recommended in the setting of BE, at least for the reporting of biopsies from the index endoscopy (46,63–65) to improve completeness, accuracy, and reproducibly of recording and reporting the morphological features of BE. Proposed data set/data items that could be included in a draft proforma may include the following: the number of biopsies per cm (including levels); mucosal subtypes—e.g., squamous, columnar, mosaic, presence or absence of reflux esophagitis; IM presence or absence; active or chronic inflammation, with grading into mild/moderate/severe; presence of native structures; Vienna neoplasia category (1: no dysplasia, 2: IND, 3: LGD, 4: HGD, 5: invasive EA); and p53 immunostaining.

Screening to detect BE

7. Endoscopic screening for BE is not justified in the general population. STATEMENT ENDORSED, overall agreement 94.2%. A+, 58.7%; A, 35.5%; U, 2.5%; D, 1.7%; D+, 1.7%.

Recommendation

We suggest against screening the general population for BE endoscopically or with nonendoscopic methods.

Conditional recommendation, low-quality evidence.

Endoscopic screening in the general population is not currently recommended. Markov models that have been created, although in 50-year-old men with gastroesophageal reflux disease (GERD) and not in the general population, have not shown an advantage to screening (66). The incidence of EA resulting from BE is too low (21) to warrant broad population-based screening. It follows that nonendoscopic screening methods, given their lower sensitivity and/or specificity, are not indicated. Transnasal endoscopy has good accuracy (67), but it needs to be validated outside tertiary centers, and population screening for BE is still controversial.

8. Endoscopic screening for BE is recommended to decrease the risk of death from esophageal adenocarcinoma in men >60 years old with GERD symptoms for 10 years. STATEMENT ENDORSED, overall agreement 84%. A+, 16%; A, 68%; U, 8%; D, 6.7%; D +, 1.3%.

Recommendation

We suggest endoscopic screening to detect BE (and for the investigation of dyspepsia) in men >60 years old with prolonged GERD (≥10 years) symptoms.

Conditional recommendation, very low-quality evidence.

Men with BE have almost a twofold increased risk of developing esophageal adenocarcinoma as compared with women (21). This may be due to a lower frequency of BE among women, a lower risk of BE progressing to EA, or both (21,68). Similar results, of an increased risk for men to progress to dysplasia or cancer, have been reported from other studies (69). A meta-analysis that pooled results from 47 reports of cancer incidence in BE also noted that men with BE were approximately twice as likely as women to progress to EA (70). Furthermore, work from Rubenstein *et al.* (71) found that the risk of EA in men < age 50 years was very low, increases after age 50 years, and becomes substantial among men after the age of 60 years, with weekly GERD symptoms. In addition, GERD symptoms for 10 years are strongly predictive of development of EA (72). In conclusion, even if the symptoms are well controlled, the length of time with GERD in the >60 year age group makes BE a clinically meaningful lesion to identify. This would suggest that men with this clinical profile should be screened (73).

Risk factors

There are accepted risk factors in BE for progression to EA.

9. The risk of progression of BE metaplasia to HGD or EA is related to central obesity (measured by waist circumference, waist–hip ratio, or visceral abdominal fat area). STATEMENT ENDORSED, overall agreement 86.6%. A+, 18.5%; A, 68.1%; U, 10.1%; D, 3.4%; D,+ 0%.

Cross-sectional studies have shown some association between measures of abdominal fat and biomarkers of progression (74). The waist–hip ratio of BE patients has been shown to correlate with the prevalence of combined LGD and HGD (75,76). Furthermore, serum

levels of leptin and insulin resistance were strongly correlated with increased risk of progression to EA in BE subjects followed up prospectively (77). A recent meta-analysis showed a consistent association (body mass index and reflux independent) between parameters linked to central obesity and esophageal inflammation, metaplasia, and EA (78).

10. The risk of nondysplastic BE progressing to dysplasia or EA is greater among men than among women. STATEMENT ENDORSED, overall agreement 94.4%. A+, 49.2%; A, 45.2%; U, 4.8%; D, 0.8%; D+, 0%. One of the largest population-based cohorts to date, including 8,522 patients with BE, found that men with BE had almost a twofold increased risk of developing EA as compared with women (21). Similar results have been reported from other studies (79). A meta-analysis that pooled results from 47 reports of cancer incidence in BE noted that men with BE were approximately twice as likely as women to progress to cancer (70).

11. The risk of progression of BE metaplasia is related to the (longer) length of BE. STATEMENT ENDORSED, overall agreement 96%. A+, 57.3%; A, 38.7%; U, 4%; D, 0%; D+, 0%.

In a 15-year prospective study of endoscopic surveillance (80), columnar-lined esophagus was significantly longer (≥8 cm) in those who developed dysplasia as compared with the whole group, whereas no patient with a columnar-lined esophagus of <8 cm was found to develop dysplasia or EA. Doubling of the length of BE increased the risk of development of EA by a factor of 1.7 (81). The prevalence of dysplasia in long-segment BE was 2 times greater than in short-segment BE (82). The results of a multivariable analysis from a multicenter cohort study (29) showed that among other factors, length of BE (relative risk 1.11 per cm increase in length; 95% confidence interval 1.01–1.2) was a significant predictor of progression to HGD or EA.

Endoscopic methods in confirmed BE

12. Endoscopic reporting should be carried out using a minimum data set including a record of the length using the Prague criteria, and the presence and size of a HH below and esophagitis above the BE segment. STATEMENT ENDORSED, overall agreement 92.5%. A+, 50%; A, 42.5%; U, 4.2%; D, 2.5%; D+, 0.8%.

An objective scoring system for measuring the length of BE and associated esophagitis needs to be used to avoid intraobserver and interobserver errors in follow-up. The Prague criteria, formulated in 2006 (83), provide a uniform set of criteria for describing BE and has excellent reliability coefficients among expert endoscopists, trainees (84), and community-based practitioners (85) across continents (86,87) and for the scoring of maximal circumferential and linear extent of BE (88) that may be associated with increased risk of BE and progression to EA (44). Objective landmarks should be formally recorded during BE surveillance (please see Supplementary Paper online). In addition, it is vital to identify the size of the HH below in order to avoid false classification of the BE where no BE or a much smaller BE segment exists in reality (83,89). It is recommended that good endoscopic practice is advocated, maintained, and taught, as these standards lead to clinically meaningful outcomes (3,10,90).

13. Surveillance and biopsy of BE should be performed by experienced endoscopists, with the availability of and training in appropriate techniques and tools, used according to standard protocols and with sufficient time allowed for careful inspection. STATEMENT ENDORSED, overall agreement 93.4%. A+, 55.3%; A, 38.2%; U, 3.9%; D, 2.6%; D+, 0%.

Recommendation

Strong research recommendations.

Further studies are needed on the optimal pathways of management in BE using risk factors and biomarkers to test systematic protocols for biopsy collection, in particular the optimum number and the optimal setting for BE surveillance (e.g., dedicated lists, specialist centers).

In patients diagnosed with esophagogastric cancer, 8–10% have had endoscopies in the 3 years preceding diagnosis; these studies include both squamous and adenocarcinoma (91,92). For early (stage 0/1) esophagogastric cancer, 34% had not been recognized in the preceding endoscopies, particularly those located in the upper esophagus (92). Among patients in whom no abnormality had been noted (definitely missed cancers: 7.2%), endoscopist error was determined to have been the failure in 73% (91). A recent study has shown that among patients with BE examined by 11 endoscopists at 5 tertiary referral centers, those endoscopists with average BE inspection times longer than 1 min per cm of BE detected more patients with endoscopically suspicious lesions (54.2% vs. 13.3%), and there was a trend toward a higher detection rate for neoplasia (40.2% vs. 6.7%). Indeed, there was a direct correlation between the endoscopists' mean inspection time per cm of BE and the detection of patients with neoplasia (93). This is in line with the finding that the key performance indicator of adenoma detection rate among colonoscopists is related to colonoscope withdrawal time, with withdrawal times in excess of 6 min showing higher rates of detection (94). In another recent study of 69 patients referred to a specialist unit with dysplastic BE, only 29 had a visible mucosal abnormality found by the referring endoscopist compared with 65 at the specialist unit (95). It was noted that only 57% of the referring endoscopists had used high-definition endos-copy (which is now recommended for BE surveillance) (1) and 14% had used narrow band imaging. Although this was interpreted as indicating that all dysplastic BE should be examined in referral centers, it is not clear whether examination time could have had an influence in the difference in findings. Indeed, BE early neo-plasia often presents as subtle flat Paris type II-b lesions (96) that can be easily missed if inspection is not careful. All these findings suggest that surveillance of BE should be done in a careful and systematic manner, although there is no clear evidence available to confidently recommend specialized referral units or clinics for BE (97), or that centralized BE surveillance services or dedicated surveillance lists can reduce variation in treatment, change management, or improve adherence to local guidelines. Dedicated lists would potentially allow adequate time to examine BE segments, use adjunctive techniques that may improve neoplasia detection in a surveillance setting (98), and carry out systematic protocolized biopsies as well as targeted biopsies of visible abnormalities.

The "Seattle" protocol (99) involves visual inspection and multiple biopsies from lesions and at 1–2 cm intervals throughout the BE segment. This protocol is safe and leads to an increase in the detection of early neoplasia (100,101). However, nonadherence to BE biopsy

guidelines is associated with significantly decreased dysplasia detection (64,90,101–104). Although a 4-quadrant 2-cm Seattle protocol for systematic biopsy is accepted as a standard for BE surveillance (1), it is not the only tested method for randomly harvesting biopsies and for prospective follow-up to detect cancer development (please see Supplementary Paper).

14. High-resolution endoscopy with targeted biopsies in experienced hands is an effective tool for the diagnosis of BE neoplasia. STATEMENT ENDORSED, overall agreement 89.2%. A+, 24.2%; A, 65%; U, 8.3%; D, 2.5%; D+, 0%.

Recommendation

We suggest the use of high-resolution endoscopy with targeted biopsies in expert centers only.

Conditional recommendation, low-quality evidence.

Endoscopic surveillance of BE should be performed using high-resolution white-light endoscopy (2). High-resolution endoscopes (HREs) that have a resolution of 1,000,000 pixels have greatly improved the ability to visualize subtle mucosal abnormalities in BE and appear to have higher sensitivity for detecting progression to early neoplastic lesions in BE (105). HRE is recommended but requires training and experience in its use (particularly in lesion recognition) in all settings, which is most likely to be achieved in expert centers. Ideally, only those with training and experience in the use of HRE should undertake HRE-visualized biopsies.

Surveillance and surveillance intervals

For the purposes of reducing mortality from EA in nondysplas-tic BE patients, routine surveillance (vs. no surveillance) was not supported in this consensus.

15. Among patients with nondysplastic BE, endoscopic surveillance according to recommended guidelines decreases mortality from EA (compared with no surveillance). STATEMENT *NOT* ENDORSED, overall agreement 38.5%. A+, 13.1%; A, 25.4%; U, 33.6%; D, 21.3%; D+, 6.6%.

Multiple observational studies have demonstrated that BE-associated EAs detected through surveillance endoscopies were associated with low-stage disease compared with nonsurveillance-detected cancers (106,107). In contrast, most EAs found in a nonsurveillance cohort were invasive (more than T1) at index endoscopy (108,109). However, in terms of survival benefit, even though surveillance enables detection of EA at an earlier stage, it is unclear whether it significantly influences survival (110–112), or whether surveillance at defined intervals results in an overall survival benefit in the population.

One of the largest retrospective studies (113) reported an annual mortality rate from EA of only 0.14%. A meta-analysis of 51 studies that included 14,109 patients (114) found an annual rate of mortality of 0.3% due to EA. In a population-based cohort study (115), the overall mortality rate in patients with BE was similar to that of an age- and sex-matched control population. EA accounted for only a small proportion of deaths in these patients, most deaths being due to other causes. From these data and similar results of many other

studies not cited, EA is an uncommon cause of death in patients with BE, and the mortality rate due to EA is low, whether or not patients undergo endoscopic surveillance.

In the absence of agreement on surveillance vs. no surveillance for reduction of mortality from EA, we did not achieve consensus on statements examining intervals for surveillance.

16. Surveillance of nondysplastic BE, to decrease the risk of death from EA, should be targeted at high-risk groups (defined using composite risk factors including, but not limited to, age ≥50 years, white race, male sex, obesity, and symptoms). STATEMENT ENDORSED, overall agreement 82.7%. A+, 29.3%; A, 53.3%; U, 12%; D, 5.3%; D+, 0%.

There are currently no tightly defined and accepted criteria to differentiate those with nondysplastic BE and a higher risk of progression from those at lower risk, and there are no data available yet from randomized controlled trials (RCTs) that demonstrate benefits from scheduled surveillance in terms of a decrease in mortality due to EA. In the absence of this information, the decision to carry out surveillance should be based on risk of progression of BE and should include evaluation of factors known to place patients at higher risk of progression. These include, but are not limited to, age and sex, length of the segment, central obesity, and symptom duration, frequency, and severity. The influence of IM is unclear; the study by Bhat *et al.* (21) in 2011 stated that the risk of cancer was statistically significantly elevated in patients with, vs. without IM at index biopsy i.e. “(0.38% per year vs. 0.07% per year; hazard ratio [HR]=3.54, 95% CI=2.09 to 6.00, P .001).” Analyzing the literature evidence indicates that it is unclear that goblet cells precede all EAs in the distal esophagus (116). On the other hand, the available data also imply that if goblet cells are present, BE has a risk for malignant transformation that is considered to be ~0.12% per year, but because of the low frequency this now calls into question the rationale for ongoing surveillance in any patients who have BE without dysplasia (22). The lack of definitive evidence means that no conclusive surveillance strategies can be drawn up at the moment.

Recommendation

We make no recommendations about surveillance for nondysplas-tic BE, but, if undertaken, surveillance should be directed at high-risk groups.

Conditional recommendation, low-quality evidence.

If surveillance is carried out, the surveillance cycle should stop in patients with <5 years of life expectancy, as evidenced by the strong disagreement in the following statement.

17. Among patients with nondysplastic BE who have <5-year life expectancy, endoscopic surveillance, compared with no surveillance, decreases mortality from EA. STATEMENT *NOT* ENDORSED, overall agreement 7.6%. A+, 3.4%; A, 4.2%; U, 12.7%; D, 35.6%; D+, 44.1%.

Recommendation

We suggest against surveillance of nondysplastic BE in patients with a life expectancy of ≤5 years.

Conditional recommendation, low-quality evidence.

The risk of malignant progression over a 5-year interval in patients with BE appears low (21,117,118). When compared with patients with other esophageal disorders, and the general population, rates of esophageal cancers (both squamous cell carcinomas and EA) and extraesophageal cancers were similar. Estimated 10-year survival rates among patients with BE, those with other esophageal disorders, and the general population were similar (119). Mortality from EA was only 4.7% in one other study (115). In contrast, in another study, patients with BE had excess mortality compared with age and sex-matched controls from the general population; however in the BE patients, bronchopneumonia and ischemic heart disease were more common causes of death than EA, and the rate of esophageal cancer-related deaths that might be affected by BE surveillance is only ~1 in 380 patient-years of follow-up (120–122). In a single-center, prospective cohort study in 1,239 patients with BE, EA accounted overall for <3% of all deaths at 5 years (123). Surveillance incurs costs, and patients under surveillance have a lower quality of life (124). In patients with multiple comorbidities or short life expectancy, the risks and benefits should be discussed with the patient before enlisting for surveillance.

We examined the evidence for the benefits of surveillance in patients with LGD in the following statement:

18. There are almost no data on different surveillance intervals or its effects among only individuals with LGD. STATEMENT ENDORSED, overall agreement 89.3%. A+, 25.4%; A, 63.9%; U, 7.4%; D, 3.3%; D+, 0%.

There was no agreement in our consensus for surveillance intervals in LGD in BE. We make no recommendations for practice.

Recommendation

Strong research recommendation: further data are needed on appropriate surveillance intervals in LGD.

There are almost no data on different surveillance intervals or on its effects in unselected populations of LGD (118). The only study to date powered to evaluate the influence of surveillance on cancer mortality, among all patients with BE, found no substantial reduction in mortality for surveillance within 3 years (111). Recent data from large registries, which combined surveillance with RFA, have suggested lower-than-expected rates of progression to cancer; however, these studies lacked comparator populations of patients not in surveillance and did not assess mortality (30,125,126).

Management strategies

19. Endoscopic ablation therapy should not be offered routinely to patients with nondysplastic BE. STATEMENT ENDORSED, overall agreement 92.4%. A+, 58.8%; A, 33.6%; U, 1.7%; D, 0.8%; D+, 5%.

Recommendation

We suggest against ablation therapy in benign BE. Conditional recommendation, low quality of evidence.

There are no large studies with long-term follow-up that provide evidence that endoscopic nondysplastic BE ablation decreases the risk of malignant transformation along with an assessment of risks of harm and the need for further surveillance after ablation (127). In addition, studies with follow-up after ablation indicate that no ablation technique can achieve 100% BE ablation (128–132), and neosquamous epithelium after ablative treatment may still contain buried glands (133) that could be associated with progression to cancer (134). Furthermore, prophylactic BE ablation does not appear to be cost effective (135).

20. Patients with BE with LGD on a single occasion (confirmed by at least two specialist GI pathologists), without higher risk features (including multifocality, long segment), should be managed with continued more frequent (6–12 months) surveillance (provided the patient is fit for endoscopy and is not already undergoing therapy). STATEMENT ENDORSED, overall agreement 88%. A+, 17.3%; A, 70.7%; U, 6.7%; D, 4%; D, 1.3%.

Overall, the majority of patients diagnosed with LGD do not progress to HGD/EA. The overall rate of progression as reported by Wani *et al.* (52) was 0.44% per year from LGD to EA and 1.83% per year to HGD or EA combined. LGD is subject to a high degree of interobserver variability and is challenging to diagnose in the setting of inflammation. LGD may be overcalled and often does not get confirmed on subsequent review by additional specialist GI pathologists, as demonstrated in a Dutch study (58) in which 73% of cases that were initially diagnosed with LGD were down-staged to either non-dysplastic BE or IND.

A surveillance endoscopy in unifocal LGD does provide the opportunity to determine whether there is progression, persistence, or regression. In cases of persistence (i.e., LGD present at a second, confirmatory endoscopy) (136), there is evidence to suggest that these patients may be at higher risk, as the “SURF” study (30) demonstrated that persistence of LGD over time in the control group was predictive of progression. In such patients, the risks and benefits of therapy need to be carefully evaluated. In cases of regression where LGD is no longer found on the subsequent endoscopy, continued surveillance is warranted to ensure that there is no further dysplasia. However, there is some uncertainty in these cases as to whether this is due to true regression, an issue of sampling error, interobserver variability among pathologists, or removal of the dysplastic foci by the tissue sampling. These issues underscore the need for detailed endoscopic examination (provided the patient is fit for endoscopy and is not already undergoing therapy), re-review of dysplasia by at least 2 specialist GI pathologists, and need for additional means of risk stratification (30). Risk stratification is needed to identify the subset of patients who are likely to progress and for whom there is a likely benefit from ablation therapy and in whom the risks of the therapy are warranted. In an unselected group of patients with LGD, these risks may outweigh the benefits. Therefore, patients with BE with LGD confirmed by at least two specialist GI pathologists should have a repeat endoscopy to confirm the findings, with recent guidelines recommending a broad 8-week to 12-month interval depending on the society e.g. Société Française d’Endoscopie Digestive (SFED), American Gastroenterological Association (AGA), American Society for Gastrointestinal Endoscopy (ASGE), British Society of Gastroenterology (BSG). If LGD confirmed by at least 2 specialist GI pathologists is found on a single occasion only (confirmed by repeat endoscopies) and without higher risk features (multifocal-ity, long segment, and so on), surveillance should be continued at 6–12-month

intervals to permit frequent sampling because they may fall into the persistent LGD group. The options should be discussed with each patient to enable an acceptable decision.

Recommendation

We suggest that patients with LGD on a single occasion (confirmed by at least 2 specialist GI pathologists) should be managed with continued more frequent (intensive, 6–12-month) surveillance (provided the patient is fit for endoscopy and is not already undergoing therapy). Patients who have confirmed absence of LGD after two consecutive endoscopic evaluations can revert to routine surveillance rather than intensive surveillance.

Conditional recommendation, low-quality evidence.

21. Absence of dysplasia in two subsequent consecutive endoscopic evaluations, after an initial diagnosis of LGD in BE, identifies a cohort of patients who are at low risk to progress to dysplasia or EA and can continue routine surveillance rather than intensive surveillance. STATEMENT ENDORSED, overall agreement 90.7%. A+, 21.3%; A, 69.3%; U, 6.7%; D, 0%; D+, 2.7%.

BE predisposes to the development of EA. Studies have reported a great variation in the progression rate to HGD or EA in the presence of confirmed LGD between 0.84 and 9.1% per year (29,52,58,137). One recent study (138) reported that patients with multifocal LGD were associated with an increased risk of developing HGD and EA, but Wani *et al.* (52) in 2011 reported no association for multifocal LGD for either dysplastic progression or even persistence of LGD at repeat endoscopy. It is clear that if a patient is diagnosed with dysplasia (confirmed by at least 2 specialist GI pathologists), they should have a repeat endo-scopy to confirm the findings (at the interval described above, i.e., 8 weeks to 12 months). If the repeat endoscopy shows that the dysplasia is still absent after two further endoscopies (at 6–12-month intervals), the patients appear to be at lower risk of developing EA comparable to patients who have not been diagnosed with LGD. Intervention in these patients can be “de-escalated” to continued routine surveillance rather than intensive BE surveillance, as supported by studies (118) including that by Duits *et al.*(58) that showed reduced risk of developing EA in the absence of persistent LGD.

22. Patients with BE with multifocal LGD (confirmed by at least two specialist GI pathologists) have an increased risk for progression of neoplasia compared with those with focal LGD. STATEMENT ENDORSED, overall agreement 86.7%. A+, 30.7%; A, 56%; U, 13.3%; D, 0%; D+, 0%.

For discussion, see under statement 23.

23. Patients with BE with LGD (confirmed by at least two specialist GI pathologists) that persists have an increased risk for progression of neoplasia compared with those with LGD at a single endoscopy. STATEMENT ENDORSED, overall agreement 89.3%. A+, 28%; A, 61.3%; U, 9.3%; D, 1.3%; D+, 0%.

The absolute risk of neoplastic progression (to HGD or EA) in BE patients with LGD has been controversial. Some studies have shown none or minimal increase in risk, whereas

others have demonstrated significant increase in risk. Similarly, the patient phenotypic characteristics of LGD in BE (e.g., focal vs. multifo-cal, short segment vs. long segment, persistent over time vs. intermittent (i.e., found at a second confirmatory endoscopy (136) at a surveillance interval of 6–12 months), consensus pathological agreement, and so on) have variably been described as important in predicting progression (29), while Wani *et al.* (52) followed up more than 200 patients with BE and LGD for >6 years (mean) and found that none of these variables predicted histological progression. There are several studies that indicate that patients with persistent, multifocal LGD in a longer segment of BE are more likely to progress to EA (131,136) and Thota *et al.* (138) found a correlation between multifocality of LGD and progression of neoplasia (EA) in a single-center experience of over 1,500 patient-years and a 6% decreased likelihood of dysplastic regression per 1 cm increase in BE length. Moreover, recently, Phoa *et al.* (30) in a large RCT demonstrated that persistence of LGD over time and length of BE was predictive of progression in the control group. A rigorously stratified subset of patients with LGD with a consensus diagnosis of LGD by an expert panel of specialist GI pathologists may demonstrate a higher risk of progression of neoplasia as demonstrated in a recent retrospective histological and clinical study of LGD in the Netherlands. These patients with confirmed LGD had a signifi-cantly higher rate of progression to HGD/EA (9.1% per patient-year compared with 0.6% per patient-year among those initially diagnosed with LGD but then downgraded to nondysplastic BE and 0.9% for those downgraded to IND).

24. Patients with BE with LGD (confirmed by at least two specialist GI pathologists) and higher-risk features (multifocality, segment length, persistence) should be offered treatment options including ablative therapies. STATEMENT ENDORSED, overall agreement 89.3%. A+, 36%; A, 53.3%; U, 9.3%; D, 1.3%; D+, 0%.

For discussion, see below statement 25, and discussion following statement 23.

25. Ablative therapy (with scheduled follow-up) decreases the progression of neoplasia in BE with LGD (confirmed by at least two specialist GI pathologists) and with risk factors (persistence, long BE segment, multifocality). STATEMENT ENDORSED, overall agreement 88%. A+, 30.7%; A, 57.3%; U, 9.3%; D, 2.7%; D+, 0%.

Recommendation

We suggest that patients with LGD (confirmed by at least two specialist GI pathologists) and higher risk features (multifocality, segment length, persistence) should be offered treatment options including ablative therapies, as ablative therapy decreases the progression to EA.

Conditional recommendation, moderate-quality evidence.

Ablation of BE in patients with only LGD remains controversial because of the lack of reproducible data on cancer risk or clarity as to the clinical features that confer increased risk in BE patients with LGD. Some data suggest a lower rate of progression of LGD (21,22,139) that would suggest that an unselected group of patients with LGD diagnosed with LGD do not progress to HGD/EA and may gain little benefit from ablation therapy and its potential for adverse effects (140). However, LGD on initial biopsy is an indicator of the

potential for disease progression, and a registry with over 1,000 patients reported that LGD present on the index endoscopy was associated with a rate of progression to HGD/EA of 6.5% per year, and 3.1% when tertiary referrals were excluded (137). Risk stratification (including specialist GI pathologist consensus review) would help to identify the subset of patients with LGD for whom there is a likely benefit from ablation therapy, balanced against the potential risks of such therapies. However, in high-quality studies that have evaluated neoplasia progression in BE patients with LGD, ablation therapy has consistently improved outcomes by reducing neoplastic progression (to EA). Indirect evidence would suggest that in high-risk patients with LGD (multifocality, segment length, persistence) escalating intervention to ablative therapy to decrease the risk of progression to EA should be considered.

There is evidence from RCTs and case studies that the durability of LGD eradication is long lasting. However, in these studies there is increased recognition of buried dysplasia presenting later as advanced cancer, thus justifying complete eradication of the BE with a wide area method (e.g., RFA) if focal eradication with ER was the initial therapy and BE remains. In the “SURF” RCT of surveillance vs. radiofrequency ablation (30) of participants with confirmed LGD, RFA significantly reduced neoplastic progression to HGD/EA as compared with continued surveillance of BE with LGD (control arm). Histological progression decreased from 26.5% (control) to 1.5% (RFA). However, after follow-up, 10% of patients had recurrent BE, suggesting that continued surveillance is mandatory. The most common adverse event in the treatment group was stricture (7.4%). It should be noted that some have commented that these progression rates are higher than the reported rates of LGD progression in studies from other countries, suggesting possible variability in populations with BE and LGD or in the diagnosis. However, the original RCT of RFA (131) also demonstrated improvement in outcomes in those with LGD undergoing BE ablation that was durable (132). Thus, ablation of BE with LGD is supported by two high-quality RCTs. Although the best clinical marker(s) for predicting neoplastic progression in BE with LGD remains unclear, ablation of the lesion is associated with improved outcomes in reduced neoplastic progression in a subset of patients with LGD. The options should be discussed with each patient to enable an acceptable decision.

26. Management of indefinite for dysplasia in BE should require an agreed consensus diagnosis by at least 2 specialist GI pathologists. Follow up with intense sampling by endoscopic biopsies within 12 months should be undertaken, after increased acid suppressive therapy, to downgrade or upgrade the lesion. STATEMENT ENDORSED, overall agreement 92%. A+, 33.3%; A, 58.7%; U, 6.7%; D, 1.3%; D+, 0%.

Recommendation

We suggest that patients with the diagnosis of IND (confirmed by at least 2 specialist GI pathologists) should be re-biopsied within 1 year to detect prevalent neoplasia and should have their acid suppression (usually with a proton pump inhibitor (PPI)) increased.

Conditional recommendation, very low-quality evidence.

Note that the diagnosis of IND should be considered as an interim diagnosis only. Further endoscopic surveillance (after acid-suppressive therapy and within 1 year or sooner) is required to up- or downgrade the dysplasia after careful biopsy sampling/*endoscopic resection (ER). (*We have used ER throughout as the standard term as it is interchangeable with endoscopic mucosal resection but more accurately descriptive of the technique.)

Follow-up is recommended because of uncertainty about the nature of the lesions classified as IND (141). Some follow-up studies have shown increased likelihood of progression to higher grades of neoplasia (61,62), but this seems to be only in the first year, representing prevalent cases (142). The risk appears higher in patients with multifocal IND (143) but is similar to a population with nondysplastic BE when the diagnosis of “IND” (rather than LGD) has been confirmed by a consensus panel of two (56) or six specialist GI pathologists (58).

It has been suggested (without supporting evidence) that patients with “regenerative” changes and inflammatory infil-tration require increased acid suppression with PPI therapy before rebiopsy (1,61). It is not clear what the interval for re-endoscopy and biopsy should be: the BSG guidelines suggest 6 months (by consensus rather than evidence). However, the finding that increased incidence of cancer occurs in the first year (142) suggests that a 6–12-month interval is reasonable. These data suggest that all cases of “IND” should be rebiopsied within 1 year to detect prevalent neoplasia. Although evidence is lacking, those with inflammatory infiltration and regenerative changes should have their acid suppression (usually with a PPI) increased.

27. ER should not be offered routinely to patients with nondys-plastic BE. STATEMENT ENDORSED, overall agreement 96.7%. A+, 59.2; A, 37.5%; U, 2.5%; D, 0%; D+, 0.8%.

For discussion see statement 29.

Recommendation

We suggest against using ER in patients with nondysplastic BE and no visible lesion (harms outweigh benefits).

Conditional recommendation, low-quality evidence.

28. BE patients with visible lesions in the BE segment should undergo ER to stage the lesion. STATEMENT ENDORSED, overall agreement 87.6%. A+, 46.3%; A, 41.3%; U, 9.1%; D, 3.3%; D+, 0%.

For discussion see statement 29.

Recommendation

We suggest that patients with a visible lesion in nondysplastic BE (as well as visible lesions in BE with LGD or IND) should undergo ER (followed by ablation if HGD or intramucosal cancer is detected) over simple biopsies.

Strong recommendation, low-quality evidence for nondysplastic BE; moderate-quality evidence for LGD.

29. ER of visible endoscopic lesions in diagnosed LGD should be carried out to enable accurate histological assessment. STATEMENT ENDORSED, overall agreement 94.7%. A +, 74.4%; A, 20%; U, 5.3%; D, 0%; D+, 0%.

Recommendation

We recommend that in the case of BE-visible lesions in diagnosed LGD (or IND), ER should be followed by ablation if HGD or intra-mucosal cancer is detected, rather than continued surveillance. Strong recommendation, moderate-quality evidence for LGD.

A biopsy finding of LGD in BE, especially if multifocal, carries a higher risk of progression to HGD or cancer compared with benign BE (61,143,144). Hence, the finding of endoscopically visible lesions is especially significant in the setting of biopsy-detected LGD as they may contain HGD or invasive cancer. ER of visible lesions (nodules and irregularities visualized by conventional endoscopy, without obvious signs of invasion) in previously confirmed LGD with the diagnosis confirmed by at least two specialist GI pathologists should be carried out to enable accurate histological assessment, as ER may result in a change in the diagnosis of LGD. Wani *et al.* (145) reported on a series of 138 BE patients, including 15 (10.9%) with LGD, 87 (63%) with HGD, and 36 (26.1%) EA patients; visible lesions were seen in 114 (82.6%) patients. ER resulted in a change in diagnosis for 43 (31.1%) patients (upgrade 14 (10.1%), downgrade 29 (21%)). The report of that study states that “For patients diagnosed with LGD on biopsies (n=15), ER resulted in downstaging for two (13.3%) cases and upstaging for five (33.3%) cases. Visible lesions were noted for eight (53.3%) of cases.” The most common adverse effects due to ER are bleeding, scarring (leading to stricture), and risk of perforation (146). In case of suspicious areas or raised lesions within the BE segment, ER is able to not only provide a true tissue diagnosis, including the character and extent of a potential abnormality (2), but also be a treatment approach with curative intent if early cancer is detected (147). In contrast to ER, ablative treatment approaches alone, such as RFA, destroy the tissue without being able to gain a pathology specimen, and should therefore not be used in case of suspicious or raised lesions within the BE segment.

In the event that visible lesions in LGD assessed with ER detects HGD or T1a cancer, this should be treated by an appropriate ablation or treatment method if detected (3,28).

There are no studies that have specifically looked at benign BE in which nodules or depressed areas have been detected, but, if examination reveals these types of abnormalities, indirect evidence, as it is related to patients with dysplasia, suggests that ER should be used as neoplasia may be present (125,145,148). Macroscopic surface abnormalities should be graded using the Paris modification of the Japanese system for classification of early gastric neoplasia (149).

Flat type 2b lesions are the most common among patients with dysplasia referred for high-resolution endoscopy at expert centers (96). Two studies have shown that the risk of malignancy unsuspected on initial biopsy is greatest with polypoid (type 1) or depressed (type 2c or 3) lesions (96,150).

Molecular markers of dysplasia and progression

30. Aberrant p16, p16 methylation, or p16 loss in nondysplastic BE is associated with an increased risk of progression to LGD. STATEMENT ENDORSED, overall agreement 80%. A+, 13.3%; A, 66.7%; U, 19.2%; D, 0.8%; D+, 0%.

There is evidence that p16 hypermethylation is an early predictor of progression in BE, especially for LGD. “Patients who progressed from baseline pathology to HGD or cancer had higher prevalence of hypermethylation in their initial esophagus biopsies compared with those who did not progress for p16 (100 vs. 33%; *P*=0.008)” (151). p16 is not the only marker studied for aberrant methylation; others include HPP1, RUNX3, AKAP12, CDH13, SST, TAC1, and NELL1, (152) and their utility as predictive biomarkers has been studied (153).

31. Aberrant p53, p53 mutation, or p53 loss in nondysplastic BE is associated with an increased risk of developing dysplasia. STATEMENT ENDORSED, overall agreement 87.7%. A+, 26.2%; A, 61.5%; U, 10.7%; D, 0.8%; D+, 0.8%.

There is extensive evidence that p53 overexpression is a predictor of progression in BE, especially for LGD (154–161) and that p53 overexpression is caused by mutations that lead to a hypersta-ble p53 protein overexpression (that greatly lengthen its half-life). When this overexpression is detected by immunohistochemistry, it is an excellent predictor of progression in all BE (162).

We further examined whether p53 abnormal staining is useful as an adjunct to the histopathological assessment of dysplasia and its utility as a progression marker. The following two statements (32 and 33) did not reach consensus, and the reasons cited were lack of clarity in the association between dysplasia, progression and p53 immunoreactivity, and readiness for clinical application. We therefore recommend that further research should be conducted to determine the role of these biomarkers and their clinical utility.

32. p53 aberrant expression combined with histopathological assessment of LGD is more accurate than histopathological assessment alone in specialist centers. STATEMENT *NOT* ENDORSED, overall agreement 40%. A+, 12%; A, 28%; U, 38.7%; D, 18.7%; D+, 2.7%.

33. p53 aberrant expression combined with histopathological assessment is not useful for the histopathological assessment of dysplastic progression in nondysplastic BE. STATEMENT *NOT* ENDORSED, overall agreement 38.7%. A+, 12%; A, 26.7%; U, 44%; D, 13.3%; D+, 1.3%.

Recommendation

Strong research recommendation. Test the utility of these markers as adjuncts in the histological assessment of dysplasia, and as methods of risk stratification.

Prevention of progression

Chemoprevention with aspirin (acetylsalicylic acid; ASA), statins, or diet was not agreed upon in this consensus (see Appendix 2 online, Results).

34. The use of PPIs (compared with no therapy or histamine receptor type 2 antagonists) is associated with a decrease in progression from benign BE metaplasia to BE neoplasia (dysplasia and EA). STATEMENT *NOT* ENDORSED, overall agreement 53.3%. A+, 10.8%; A, 42.5%; U, 20.8%; D, 23.3%; D+, 2.5%.

Recommendation

Strong research recommendation for more data from the aspirin esomeprazole chemoprevention trial (AspECT) and chemopreven-tive trials of PPIs in patients with BE.

There is no evidence from high-quality prospective trials (RCTs) that PPI use prevents progression of BE to neoplasia, but there is scientific plausibility (prevention of injury leading to mutational events and neoplasia) (163). Cohort studies demonstrate that the use of PPIs decreased neoplasia development (164–167). Systematic reviews (168,169) have reported a strong inverse association between PPI use and the risk of EA or HGD in patients with BE.

Surgical therapies for prevention of progression

Antireflux surgery offers an alternative to PPIs in the treatment of GERD: it corrects lower esophageal sphincter failure and associated HH and controls abnormal gastric and duodenal reflux in 80–90% of patients.

35. Rates of progression to dysplasia or cancer in patients with BE are similar when comparing medical management with fundoplication. STATEMENT ENDORSED, overall agreement 86.6%. A+, 28.6%; A, 58%; U, 10.1%; D, 2.5%; D+, 0.8%.

Surgical management of reflux (fundoplication) in GERD patients, with or without BE, can provide long-term control of symptoms and esophageal pH (170). Some cohort studies suggest that effective antireflux surgery may reduce the risk of progression (171–176). However, in a study of 101 patients, there was no difference in the development of HGD comparing acid suppression (5%) and fundoplication (3%) after a median follow-up of 5 and 6 years, respectively (177). A meta-analysis (178) comparing antireflux surgery to PPI in patients with BE demonstrated a similar incidence of progression to dysplasia or cancer. However, a systematic review of 25 reports that included long-term follow-up of medically and surgically treated BE patients found that, overall, there was an increased incidence of EA in medically treated patients (179).

No difference in the incidence of EA was seen in one follow-up study of an RCT, and this study concluded that surgery alone will not prevent EA or remove the need for antisecretory medication (180,181). Recently, it was shown that progression to cancer after antireflux surgery is mainly related to late recurrence of reflux (182,183).

Recommendation

We suggest against antireflux surgery beyond establishing reflux control in patients with BE and we suggest using medical therapies over surgical therapies for preventing progression to dysplasia or cancer in patients with BE.

Conditional recommendation, moderate quality of evidence.

Note that patients placing a lower value on potential complications from surgery and a higher value on avoiding daily medications may opt for surgical approaches. Patients should be counselled that acid suppression medications may need to be used on a long-term basis after surgery.

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Supplementary Material

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Barrett's esophagus (BE) is strongly associated with gas-troesophageal reflux disease (GERD), suggesting that BE-related adenocarcinoma develops from chronic esophagitis, through benign BE, and dysplasia.
- The evidence for current practice for diagnosis of BE and low-grade dysplasia (LGD) in BE is poor.

WHAT IS NEW HERE

- We reviewed over 20,000 papers in an international consensus group. We highlight areas for research in nondysplastic BE and LGD to inform clinical practice for a worldwide audience.
- We analyzed risk factors, current practice, and therapies. We made strong recommendations for the prioritization of future research.
- We made key clinical recommendations for the escalation/de-escalation of BE in clinical practice. Population endoscopic screening is not recommended, and screening should target only very high-risk cases of males aged >60 years with chronic uncontrolled reflux. A new international definition of BE was agreed upon. Management strategies for indefinite dysplasia (IND) and LGD were identified, including a de-escalation strategy of surveillance for lower-risk patients and escalation to intervention with follow up for high-risk patients.

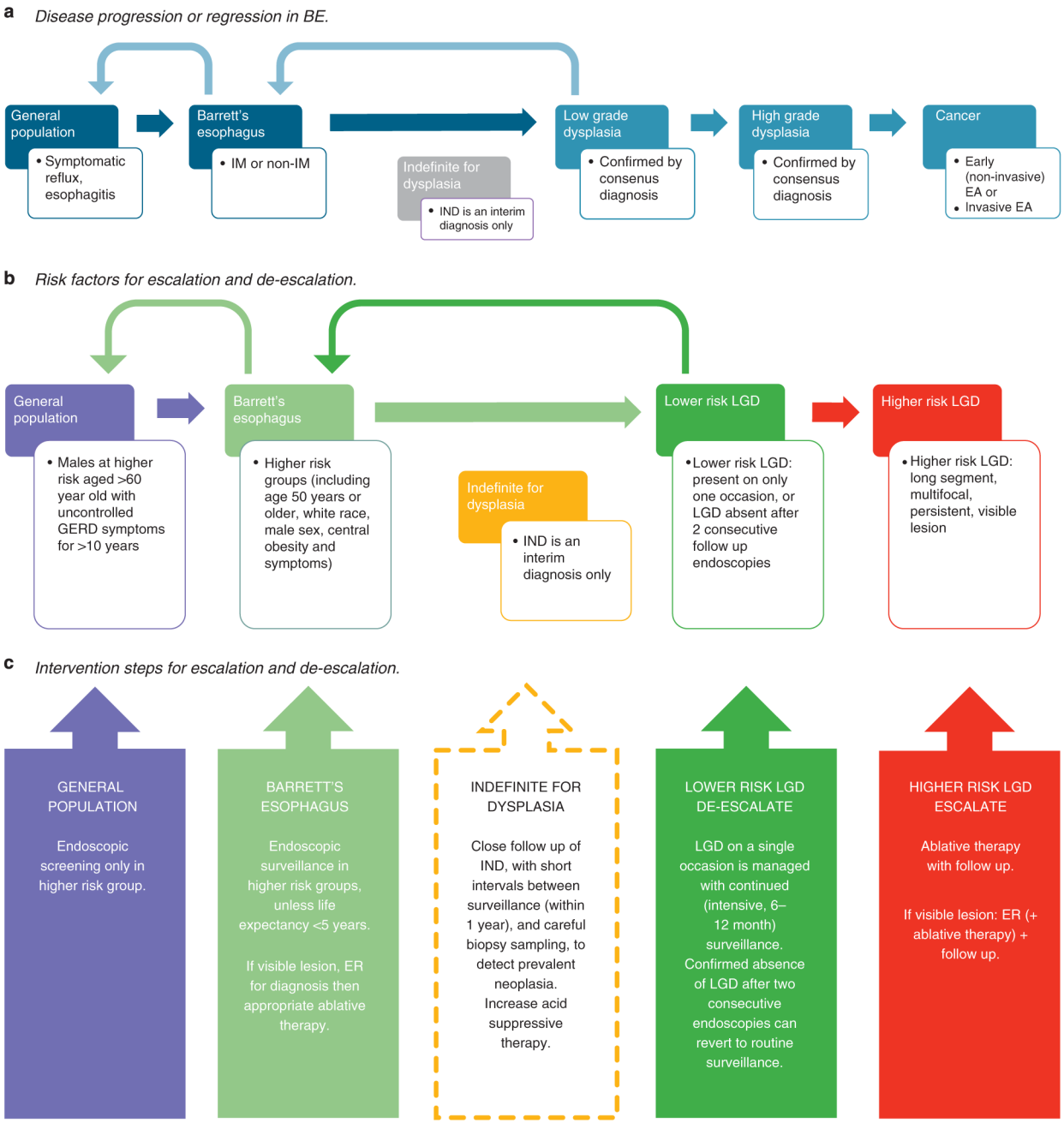

Figure 1.

(**a**) Disease progression or regression in BE. The development pathway of BE from esophagitis to metaplasia, dysplasia, and to esophageal adenocarcinoma (EA). Complete regression of BE to normal epithelium after proton pump inhibitor therapy or anti-reflux surgery is rare. Indefinite for dysplasia is not an intermediate step in the pathogenesis of EA. It is an interim diagnosis that pathologists use when the biopsies show some features of dysplasia, but due to inflammation or ulceration one cannot definitively rule out epithelial regeneration as the cause of atypia. (**b**) Risk factors for escalation and de-escalation. Risk factors in non-dysplastic BE and low-grade dysplasia (LGD) are indicators for the escalation

or de-escalation patient management. Lower-risk BE is de-escalated, compared with escalation for those with potentially higher-risk BE such as indefinite for dysplasia (IND), or LGD with persistence over two en-doscopies, multifocality, visible lesions, and long-segment BE. (**c**) Intervention steps for escalation and de-escalation. BE with LGD, diagnosed by consensus of at least two specialist GI pathologists, and lower-risk features can be de-escalated to management by close follow-up (6–12 months surveillance), and after two consecutive endoscopies can revert to routine surveillance rather than intensive surveillance. In BE with higher-risk features (including long segment, persistent, or multifocal), management is escalated to ablative therapy with scheduled follow-up and endoscopic resection (ER) to stage the lesion (followed by appropriate therapy and follow-up) if visible lesions are seen. IND is an interim diagnosis only and should be intensively followed up.

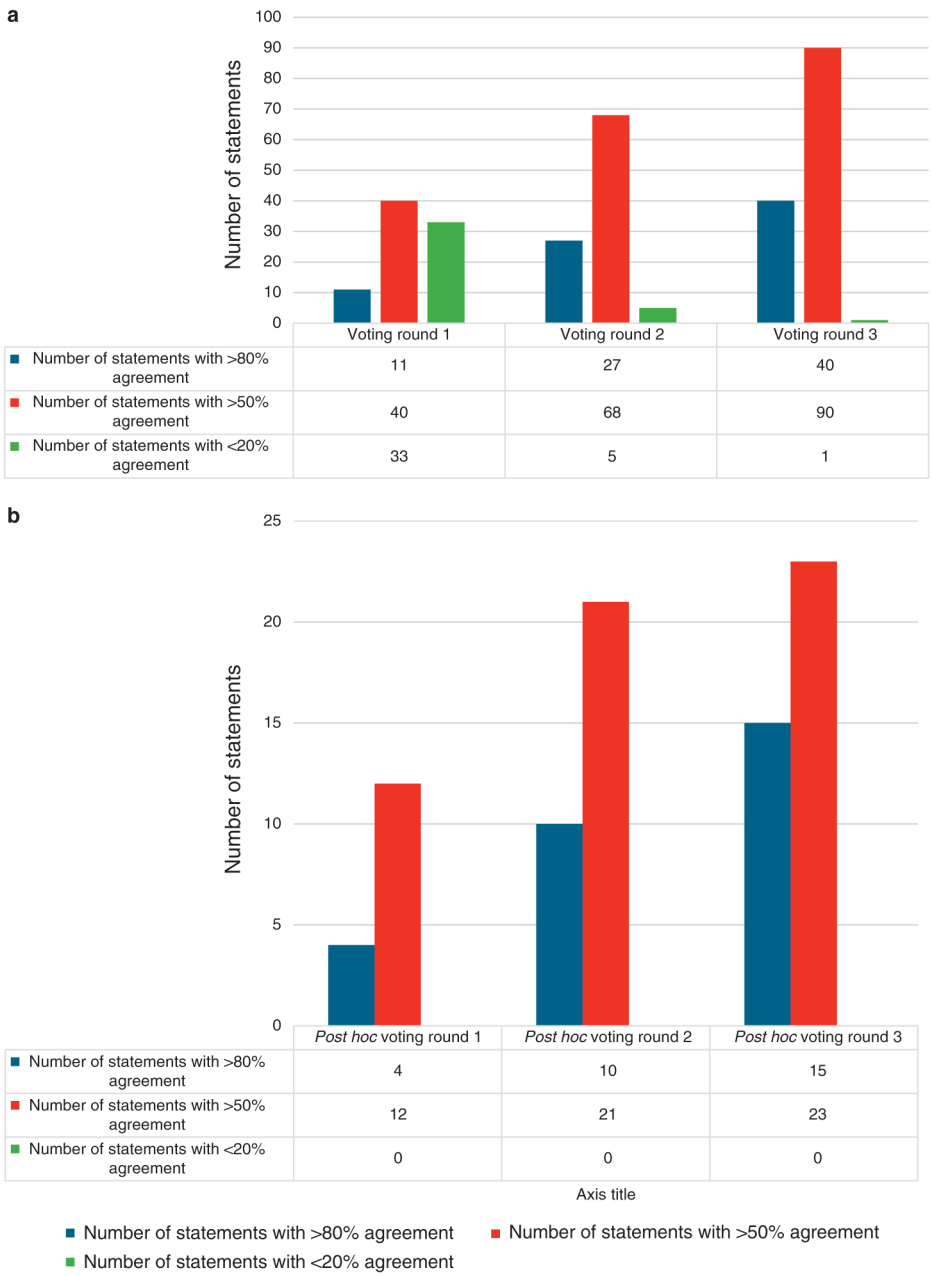

Figure 2.

Statement agreement at each round of consensus voting. (**a**, **b**) The proportion of statements achieving consensus with each round of voting. Iterative changes to the statement, discussion, and supporting evidence at interim rounds resulted in increasing agreement with successive rounds. (**a**) Agreement during the main voting rounds; (**b**) agreement during the three *post hoc* voting rounds that were a continuation of the main review with new statements informed by top-up literature searches.

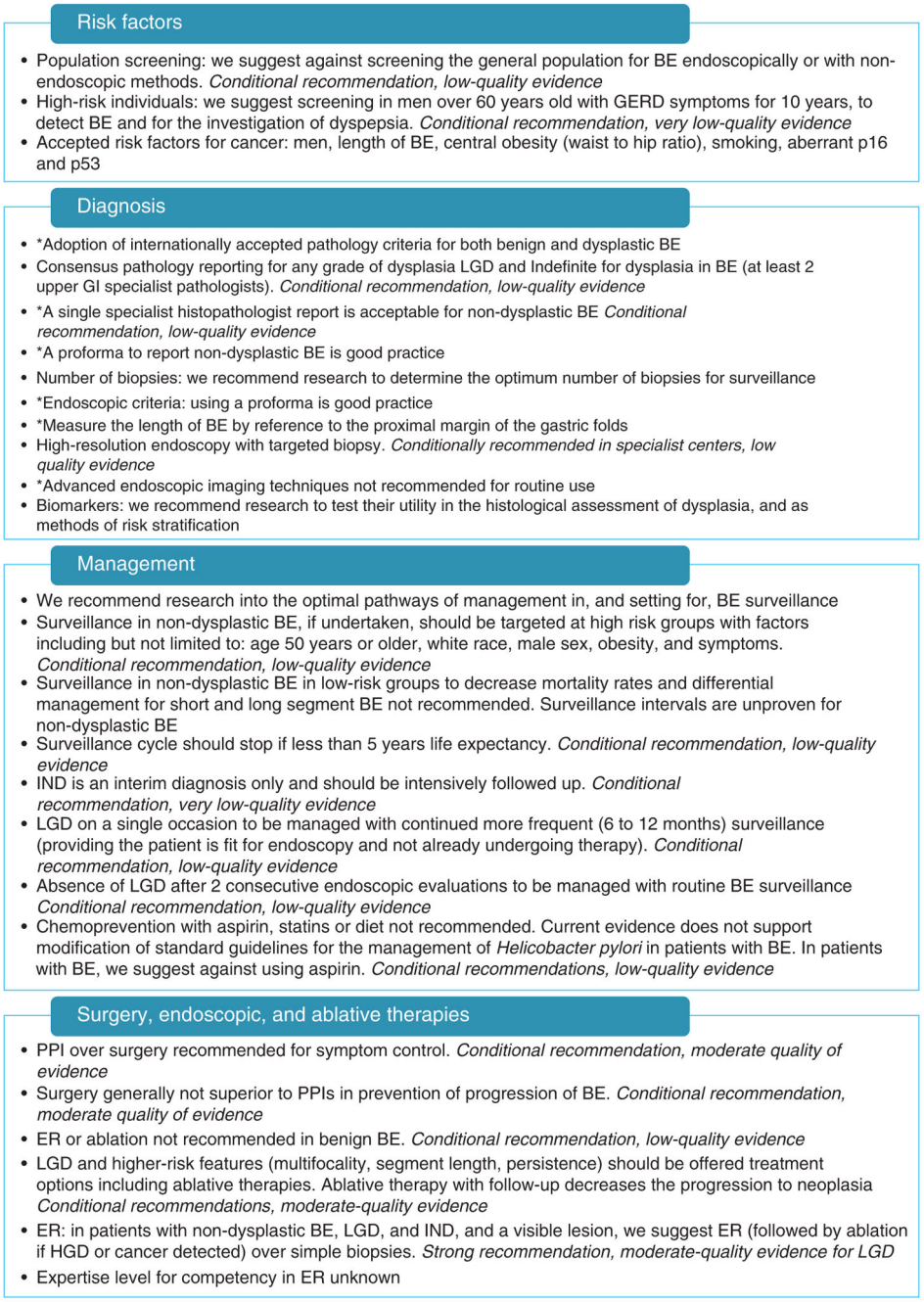

Figure 3.

Recommendations for the management of nondysplastic Barrett's esophagus (BE) and/or low-grade dysplasia (LGD). *Good practice statements—not GRADED, for details of GRADE (Grading of Recommendations Assessment, Development and Evaluation) ratings and good practice category, see main text. ER, endoscopic resection; GERD, gastroesophageal reflux disease; GI, gastrointestinal; HGD, high-grade dysplasia; IND, indefinite dysplasia; PPI, proton pump inhibitor.

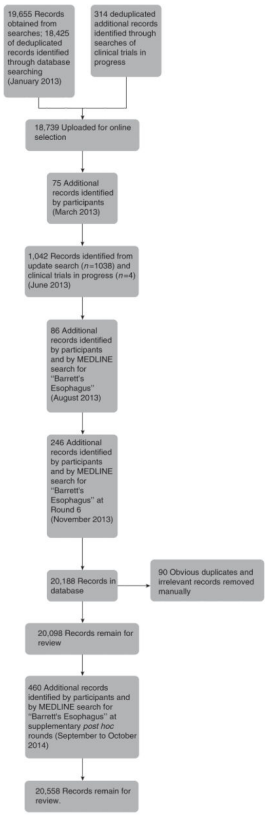

Figure 4.

Study flow diagram of the results of the search and the process of screening and selecting studies for inclusion in the main database for this large-scale literature review.