Article

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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BOB CAT, a Large-Scale Evidence Review and Consensus Statements for Management of Barrett's Esophagus with No Dysplasia, Indefinite for, or Low Grade Dysplasia, based on a Delphi Process.

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ABSTRACT

Background and aims: Barrett's esophagus (BE) is a common premalignant lesion for which endoscopic 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 management strategies for BE and provided consensus recommendations for the management of patients with non-dysplastic, indefinite and low grade dysplasia (LGD).

Methods: We defined the scope and then proposed statements, searched electronic data-bases yielding 20,558 publications which were screened online and developed into the evidence-base. We used a Delphi consensus process, with an 80% agreement threshold, using GRADE 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 and 15 of the 25 *post hoc* statements.

Population endoscopic screening is not recommended except for very high risk cases of over 60's males with chronic uncontrolled reflux. A new international definition of BE was agreed. For any degree of dysplasia, at least two specialist GI pathologists are required. Risk factors for cancer include males, length of BE and , obesity. Endoscopic resection should be used for visible, nodular areas. Surveillance is not recommended if there is less than 5 years life expectancy. 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.

Conclusions: In one of the largest evidence based consensus processes 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.

[Abstract word count 264]

Keywords: BOB CAT; Esophageal Cancer; Treatment Strategy; Systematic Analysis

BACKGROUND

BE is a premalignant condition of metaplastic columnar epithelium of any histological subtype (Fitzgerald et al., 2014) that replaces the stratified squamous epithelium. BE is more common in developed countries, affecting 2% of the general adult population (Ronkainen et al., 2005) particularly in those with heartburn or undergoing an upper gastrointestinal endoscopy, (Ford et al., 2005) (Malfertheiner et al., 2005); furthermore the incidence of BE at diagnostic endoscopy has been reported to be rising independently of an increase in the number of endoscopies carried out (Coleman et al., 2011) suggesting a true increase in incidence rather than a higher detection rate. BE is strongly associated with gastro-esophageal reflux disease (GERD), suggesting that BE related adenocarcinoma develops from chronic esophagitis, through benign BE, and dysplasia (Figure 1) although the precise relationship is unclear.(Taylor and Rubenstein, 2010) (Ronkainen et al., 2011) (Erichsen et al., 2012) (Malfertheiner et al., 2012) The incidence of EA is increasing in developing countries, (Lagergren and Lagergren, 2013) (National Cancer Institute. Fast stats, 2000-2010) and it is estimated that patients with BE have at least a 1 to 5% lifetime

risk of developing esophageal adenocarcinoma (EA). (Hvid-Jensen et al., 2011), (Desai et al., 2012), (Jung et al., 2011), (Bhat et al., 2011)

The most recent guidelines from the British (Fitzgerald et al., 2014 and American societies (Spechler et al., 2011a), (Fitzgerald et al., 2014) recommended surveillance endoscopy every 2 to 5 years in patients with BE to detect early stages of the neoplastic process and early signs of high-grade dysplasia (HGD) treatable by endotherapy. (Spechler et al., 2011a), (Spechler et al., 2011b) Other published consensus papers on the topic have impacted on clinical management, but have focused on BE in general, (Spechler et al., 2011a), (Fitzgerald et al., 2014) HGD (Bennett et al., 2012b) or specific therapies. (NICE, 2010)

Endoscopic and histopathologic classification of BE dysplasia is highly variable among and within countries. This consensus specifically included members from outside the UK and USA to obtain an international viewpoint. Considering the impact of a diagnosis of non-dysplastic BE on the patient, and the cost and risk of endoscopic surveillance and the consequences of progression to invasive EA if management strategies fail, there is a need for an international consensus approach to non-dysplastic BE patients and those with LGD.

Our previously published guideline 'BAD CAT' addressed the management of high-grade dysplasia and early cancer in BE. The motivation for doing this current review was to show how poor the evidence is and highlight areas for research in non-dysplastic BE and low grade dysplasia (LGD). We analyzed risk factors, current practice, and therapies, to inform clinical practice for a world-wide audience. In addition BOBCAT was a much larger review, using GRADE and extra voting rounds. We consequently established a new international definition of BE, and we provide clear escalation and de-escalation strategies for non-

dysplastic, indefinite for dysplasia (IND) and LGD. We named this consensus the Benign

Barrett's and CAncer Taskforce consensus group 'BOB CAT'.

METHODS

The specific population under consideration consisted of adults aged 18 years or older with a diagnosis of non-dysplastic 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), which were reviewed in the previous consensus (Bennett et al., 2012b).

We used an evidence-based Delphi process (Powell, 2003), (Sinha et al., 2011) to develop consensus statements for non-dysplastic BE and LGD. The process (Bennett et al., 2012b) permitted anonymous individual feedback and changes of views during the process, together with controlled feedback of evidence regulated by the coordinator (CB) and the consensus chair (JJ). The principal steps in the process were: (1) selection of the consensus group; (2) identification of areas of clinical importance (3) systematic literature reviews to identify evidence to support each statement; (4) draft statements and discussions supported by evidence specific to each statement, by panels; (5) 3 rounds of anonymous voting and feedback, plus 3 supplementary rounds of post-hoc voting following peer reviewers' requests. The respondents were asked to choose 1 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 re-phrased the statement in a negative fashion to see if 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 prior to the next voting round.

Evidence-based discussions with key references were provided; it was the statement on which participants voted.

We defined consensus as 80% of respondents strongly agree or agree 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 less than 20% agreement, reflecting comments on the inclusion of negatively phrased statements (Figure 2). (6) GRADE assessments of the strength and quality of the evidence and strength of the recommendations. GRADE ratings were not applied when recommendations were considered to refer to universally excepted good practice rather than evidence based decision on two or more competing management strategies and these statements are identified as good practice recommendations. Treatment comparisons were given one of four GRADE scores reflecting the quality of the evidence: high-, moderate-, low-, or very low-quality evidence, (Guyatt et al., 2011) and we used GRADE to quantify the strength of recommendations as strong, or conditional (Guyatt et al., 2008a, Guyatt et al., 2008b)

Further details are listed in the online Appendix (Methods). This paper uses a similar but larger and improved methodology to that published in 2012. (Bennett et al., 2012b) However the topic being covered is distinctly different. Specifically the previous paper covered the management of BE with either HGD or locally invasive cancer whereas the topic being covered here excludes these areas totally and instead covers the management of non-dysplastic, indefinite for dysplasia (IND) and LGD in BE.

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 (Figure 2) with a corresponding decrease in null votes by the final round.

The core group reviewed the results and after the final round, and selected and summarized 10 key groups of 30 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 references (Figure 4 Flow diagram) (Liberati et al., 2009) were available for review and inclusion.

Additional statements are provided in an online appendix (Results) to this publication and all the statements were archived: (http://mdpub.org/bobcat/index.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 intestinal metaplasia (IM) is present above the gastro-esophageal junction. 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 divide opinion. In the USA there is strong endorsement that the term 'Barrett's esophagus' should be used only for patients who have intestinal metaplasia in the esophagus. This definition of BE is at odds with current UK and Japanese (Takubo et al., 2012), (Rugge et al., 2014) opinion and the definition in updated BSG guidelines (Fitzgerald et al., 2014) which do not require IM to establish the diagnosis. Recognition of the increased risk of neoplastic progression when IM is present is acknowledged, however, in the updated BSG guidelines in that it is proposed that BE surveillance is based on risk stratification (including the presence of IM). The presence of IM 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 time scale (Harrison et al., 2007). Although other data show that a cohort of between 9- 25% of patients have never had goblet cells detected, other authors question the need for IM for the diagnosis of BE (Riddell and Odze, 2009). 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 of neoplastic progression (Hahn et al., 2009). There is also growing evidence that challenges the notion that EA is always preceded by IM, and suggesting that there is no difference in the rate of development of EA between patients with and without IM. The difference in definition clearly has the potential to greatly influence the frequency of diagnosis of BE at index endoscopy, (Westerhoff et al., 2012) and the number of patients entering into follow up and surveillance programs. (Balasubramanian et al., 2012)

There are three main caveats which should be borne in mind to ensure that this new global definition of BE is clinically meaningful that the gastro-esophageal junction is irregular, and tongues of 1cm or less may be a natural phenomenon (even if IM is present, it can occur in the cardia of the stomach); in greater than 80 to 90% of cases of BE a hiatal hernia also co-exists; and that the diagnosis must be an agreed clinico-pathological definition, but there are cases where either the pathologist of the endoscopist may be

able to overrule the other (examples of this are long segments of BE greater than 3cm, most hiatal hernias are 3cm or less, and micro-metaplasia which 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 above the gastro-esophageal junction.

2. *The optimal definition of LGD in BE includes the use of an agreed internationally-recognized criteria including increased nuclear/cytoplasmic ratio, hyperchromatic and heterochromic nuclei. Overall agreement 83.60%. 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.*

Unequivocal low grade intraepithelial neoplasia (WHO, 2010) criteria typically include preserved nuclear polarity, nuclear heterogeneity and margination, few mitoses, no atypical mitoses, 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 intra-observer variations in the diagnosis and grading of LGD and in differentiating it from reactive changes. (Kaye et al., 2009)ʼ (Haggitt, 1994) Criteria for grading foveolar and

serrated dysplasia have not been fully addressed in the literature. (Mahajan et al., 2010) '

(Kushima et al., 2005)   In the future image analysis may help to refine the criteria further.

(Sabo et al., 2006)

Diagnosis

3. *Reporting by a single pathologist is satisfactory for the diagnosis of non-dysplastic BE.*

   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 for

the diagnosis of BE is satisfactory. (Hirschowitz et al., 2013)

4. *A consensus between at least two specialist gastrointestinal (GI) pathologists is*
   required for the diagnosis of LGD. 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 than non-

dysplastic BE. It therefore generally results in a much more intensive follow-up schedule

and as newer less invasive treatment modalities such as radiofrequency ablation (RFA) gain acceptance it may soon be the trigger for definitive treatment. For this reason, it is vital that pathologists diagnose LGD accurately. Studies which have looked at pathologist interobserver agreement for the diagnosis of LGD show at best fair agreement with Kappa scores ranging from 0.15-0.4, (Sanders et al., 2012) (Wani et al., 2011b, Kerkhof et al., 2007) (increasing to κ=0.61 (0.53-0.69), when probe-based confocal laser endomicroscopy (pCLE) was employed (Gaddam et al., 2011) 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 experts many are downgraded to non dysplasia (ND). This purified dysplastic cohort then has a relatively high rate of progression. (Kaye et al., 2009) (Curvers et al., 2010) At least two studies have also shown that the chance of progression of dysplasia is proportional to the number of pathologists who agree a case is dysplastic. (Kaye et al., 2009) (Skacel et al., 2000) In the recent Amsterdam paper (Duits et al., 2014) and the SURF study, (Phoa et al., 2014) only about a quarter of LGD 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 by at least 2 GI pathologists who are at least partially specialized in gastrointestinal pathology and who are experienced in the pathology of BE. The new BSG guidelines (Fitzgerald et al., 2014) 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 indefinite for dysplasia (IND) can be used for a variety of histopathological appearances and requires consensus agreement between at least 2 GI pathologists. 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. Firstly it may refer to an epithelium, which possesses the cytological features of dysplasia (nuclear pleomorphism, hyperchromasia, loss of polarity), but features are present only in the base of the crypts and not in the surface epithelium which may be absent. Lack of surface maturation has, by convention been required for the diagnosis of dysplasia, but more recently there has been recognition of crypt dysplasia without maturation in up to 7.3% of BE cases. (Lomo et al., 2006) Secondly, 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 cut-off between normal and abnormal epithelium. It is clear that reproducibility of diagnosis of IND is poor. (Coco et al., 2010) ' (Montgomery et al., 2001)' (Sonwalkar et al., 2010)

RECOMMENDATION: we recommend two or more specialist pathologists should be involved when <u>any</u> grade of dysplasia is diagnosed.

Conditional recommendation, low quality evidence

6. A proforma (standardized reporting form) should be used to report BE. 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 non-dysplastic 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 (Zaninotto et al., 2007), (Curvers et al., 2008), (Kaye et al., 2009), (Cross et al., 1998) to improve completeness, accuracy, and reproducibly of recording and reporting the morphological features of BE. Proposed dataset/data items that could be included in a draft proforma may include: 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); p53 immunostaining.

Screening to detect BE

7. Endoscopic screening for BE is not justified in the general population. Overall Agreement 94.2%. A+ 58.7%, A 35.5%, U 2.5%, D 1%, D+1%.

RECOMMENDATION: we suggest against screening the general population for BE endoscopically or with non-endoscopic methods.

Conditional recommendation, low quality evidence.

Endoscopic screening in the general population is not currently recommended. Markov models that have been created, albeit in 50 year old men with GERD and not the general population, have not shown an advantage to screening. (Rubenstein et al., 2007) The incidence of EA resulting from BE is too low (Bhat et al., 2011) to warrant broad population based screening. It follows that non-endoscopic screening methods, given their lower sensitivity and/or specificity are not indicated. Transnasal endoscopy has good accuracy, (Shariff et al., 2012) 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 over age 60, with GERD symptoms for 10 yrs. Overall Agreement 84%. A+ 16%, A 68%, U 8%, D 6.7%, D+ 1.3%.*

The risk of EA is strongly associated with male sex; this cancer is uncommon among women. This may be due to a lower frequency of BE among women, to a lower risk of BE progressing to EA, or both (Pohl et al., 2013). One of the largest population-based cohorts to date, including 8522 patients with BE, found that men with BE had almost a two-fold increased risk of developing esophageal adenocarcinoma, compared with women. (Bhat et al., 2011) Similar results, of an increased risk for men to progress to dysplasia or cancer, have been reported from other studies. (Badreddine et al., 2010) A meta-analysis which 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. (Yousef et al., 2008) Furthermore, work from Rubenstein et al found that the risk of EA in men less than age 50 was very low, beginning to increase after age 50 and become substantial for men after age 60 with weekly GERD symptoms. (Rubenstein et al., 2011) Also, GERD symptoms for 10 years are strongly

predictive of development of EA. (Lagergren et al., 1999) In conclusion even if the symptoms are well controlled, the length of time with GERD in this age group makes BE a clinically meaningful lesion to identify. This would suggest that men with this clinical profile should be screened. (Spechler, 2013)

RECOMMENDATION: we suggest endoscopic screening to detect BE (and for the investigation of dyspepsia) in men over age 60 with prolonged GERD (10 year or more) symptoms.

Conditional recommendation, very low quality evidence.

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). 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. (Vaughan et al., 2002) Waist–hip ratio of BE patients has been shown to correlate with the prevalence of combined LGD and HGD. (Moe et al., 2000) ˌ (Hardikar et al., 2013) Furthermore, serum levels of leptin and insulin resistance were strongly correlated with increased risk of progression to EA in BE subjects followed prospectively. (Duggan et al., 2013) A recent meta-analysis showed a consistent association (BMI and reflux independent) between parameters linked to central obesity and esophageal inflammation, metaplasia and EA. (Singh et al., 2013)

10. The risk of non-dysplastic BE progressing to dysplasia or EA is greater among men than

among women. 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 8522 patients with

BE, found that men with BE had almost a two-fold increased risk of developing EA,

compared with women. (Bhat et al., 2011) Similar results have been reported from other

studies. (Anandasabapathy et al., 2007) A meta-analysis which 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. (Yousef et al., 2008)

11. The risk of progression of BE metaplasia is related to (longer) length of BE. Overall

agreement 96%. A+ 57.3%, A 38.7%, U 4%, D 0%, D+ 0%

In a 15-year prospective study of endoscopic surveillance (Iftikhar et al., 1992)

columnar-lined esophagus was significantly longer (8 cm or more) in those who developed

dysplasia as compared with the whole group, while 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 (Menke-Pluymers et al., 1993)

The prevalence of dysplasia in long segment BE (LSBE) was 2 times greater than in short

segment BE (SSBE). (Hirota et al., 1999) The results of a multicenter cohort study (Sikkema

et al., 2011) multivariable analysis showed that amongst other factors length of BE (RR 1.11

per cm increase in length; 95% CI 1.01-1.2), was a significant predictor of progression to

HGD or EA.

Endoscopic methods in confirmed BE.

12. Endoscopic reporting should be done using a minimum dataset including a record of the length using the Prague criteria, presence and size of a hiatal hernia (HH) below and esophagitis above the BE segment. Overall agreement 82.9%. 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 intra-observer and inter-observer errors in follow up. The Prague criteria, formulated in 2006, (Sharma et al., 2006) provide a uniform set of criteria for describing BE and has excellent reliability coefficients among expert endoscopists, trainees, (Vahabzadeh et al., 2012) community- based practitioners (Alvarez Herrero et al., 2013) across continents (Lee et al., 2010) ' (Chang et al., 2009) and for the scoring of maximal circumferential and linear extent of BE (Jones et al., 2002) which may be associated with increased risk of BE and progression to EA (Balasubramanian et al., 2012). 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. (Sharma et al., 2006, Sharma et al., 2004)It is recommended that good endoscopic practice is advocated, maintained and taught as these standards lead to clinically meaningful outcomes (Harrison et al., 2007) ' (Das et al., 2008) ' (Bennett et al., 2012b).

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. Overall agreement 93.4%. A+ 55.3 %, A 38.2%, U 3.9%, D 2.6%, D+ 0%

In practice, clinicians who initially assess BE patients may have limited experience in the management of BE or may have either a medical or surgical training. In patients diagnosed with esophago-gastric cancer, 8-10% have had endoscopies in the 3 years preceding diagnosis; these studies include both squamous and adenocarcinoma. (Yalamarthi et al., 2004), (Chadwick et al., 2014) For early (stage 0/1) esophago-gastric cancer, 34% had not been recognized in the preceding endoscopies, particularly those located in the upper esophagus (Chadwick et al., 2014). 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% (Yalamarthi et al., 2004). 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 minute per centimeter of BE detected more patients with endoscopically suspicious lesions (54.2% vs 13.3%), and there was a trend toward a higher detection rate of neoplasia (40.2% vs 6.7%). Indeed, there was a direct correlation between the endoscopists' mean inspection time per centimeter of BE and the detection of patients with neoplasia. (Gupta et al., 2011) This is in line with the well known finding that adenoma detection rate among colonoscopists (a key performance indicator) is related to colonoscope withdrawal time, with withdrawal times in excess of 6 minutes showing higher rates of detection. (Barclay et al., 2006) 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 to 65 at the specialist unit. (Cameron et al., 2014) It was noted that only 57% of the referring endoscopists had used high definition endoscopy (which is now recommended for BE surveillance) (Fitzgerald et al., 2014) and 14% narrow band imaging. While 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 neoplasia often presents as subtle flat Paris Type II-b lesions (Pech et al., 2007) which can be easily missed if inspection is not careful. The 'Seattle' protocol (Levine et al., 2000) involves visual inspection and multiple biopsies from lesions and at 1- to 2-cm intervals throughout the BE segment. This protocol is safe and leads to an increase in the detection of early neoplasia. (Fitzgerald et al., 2001), (Abela et al., 2008) However, non-adherence to BE biopsy guidelines is associated with significantly decreased dysplasia detection. (Abrams et al., 2009), (Peters et al., 2008b, Das et al., 2008), (Ramus et al., 2008), (Curvers et al., 2008) Although a 4 quadrant 2 cm Seattle protocol for systematic biopsy is accepted as a standard for BE surveillance, (Fitzgerald et al., 2014) it is often not adhered to in practice (Peters et al., 2008b) which may lead to reduced diagnosis of neoplasia. (Abela et al., 2008)

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

RECOMMENDATION: we suggest 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. (Spechler et al., 2011a) High resolution endoscopes (HRE) 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 (Wolfsen et al., 2008). 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 non-dysplastic BE patients, routine surveillance (versus no surveillance) was not supported in this consensus:

15. *Among patients with non-dysplastic BE, endoscopic surveillance according to recommended guidelines decreases mortality from EA (compared to no surveillance). 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 endoscopic surveillance can result in earlier detection of EA; however, it is unclear whether surveillance at such intervals results in an overall survival benefit in the population. BE-associated EAs detected through surveillance endoscopies were associated with low-stage disease and improved survival compared with non-surveillance detected cancers. (Corley et al., 2002)ˑ (Aldulaimi et al.,

2005) ʼ (Wong et al., 2010)   In contrast, most EAs found in a non-surveillance cohort were invasive (more than T1) at index endoscopy. (Wong et al., 2010)ʼ (Grant et al., 2013)

In terms of survival benefit, even though surveillance enables detection of EA at an earlier stage, it does not significantly influence overall survival. (Sontag, 2001) , (Corley et al., 2013), (Macdonald et al., 2000)   One of the largest retrospective studies (Solaymani-Dodaran et al., 2013) reported an annual mortality rate from EA of only 0.14%. A meta-analysis of 51 studies which included 14,109 patients (Sikkema et al., 2010) found an annual rate of mortality of 0.3% due to EA. In a population-based cohort study, (Anderson et al., 2003) 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 versus no surveillance for reduction of mortality from EA, we did not achieve consensus on statements examining intervals for surveillance.

16. *Surveillance of non-dysplastic 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 or older, white race, male sex, obesity and symptoms). Overall agreement 96%. A+ 57.3%, A 38.7%, U 4%, D 0%, D+ 0%.*

There are currently no tightly defined and accepted criteria to differentiate those with non-dysplastic BE and a higher risk of progression from those at lower risk, and there are no

data available yet from RCTs which 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 segment, and symptom duration, frequency and severity. The study by Bhat in 2011,(Bhat et al., 2011) stated that "the risk of cancer was statistically significantly elevated in patients with versus without specialized intestinal metaplasia (SIM)at index biopsy (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. (Nunobe et al., 2007) On the other hand these data also imply that if goblet cells are present BE has a risk for malignant transformation that is considered to be around 0.12 % per year but due to the low frequency this now calls into question the rationale for ongoing surveillance in any patients who have BE without dysplasia. (Hvid-Jensen et al., 2011) No conclusive surveillance strategies can be drawn up at the moment.

RECOMMENDATION: we make no recommendations about surveillance for non-dysplastic BE, but i*f 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 less than 5 years life expectancy as evidence by the strong disagreement in the following statement.

17. *Among patients with non-dysplastic BE who have less than a 5-year life expectancy, endoscopic surveillance, compared with no surveillance, decreases mortality from EA. 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 non-dysplastic BE in patients with a life expectancy of 5 years or less.*
> *Conditional recommendation, low quality evidence.*

The risk of malignant progression over a 5-year interval, in patients with BE, appears low. (Martinek et al., 2008) ' (Bhat et al., 2011) ,(Conio et al., 2003) When compared with patients with other esophageal disorders, and the general population, rates of esophageal cancers (both squamous cell carcinomas and EA) and extra-esophageal cancers were similar. Estimated 10-year survival rates among the BE, other esophageal disorders and the general population were similar. (Eckardt et al., 2001) Mortality from EA was only 4.7% in one other study. (Anderson et al., 2003) Bronchopneumonia and ischemic heart disease are more common causes of death in patients with BE than EA and the rate of esophageal cancer deaths that might be impacted by BE surveillance is only ~1 in 380 patient years of follow-up. (Moayyedi et al., 2008) ' (Solaymani-Dodaran et al., 2005) ' (Cook et al., 2007) In a single-center, prospective cohort study in 1239 patients with BE, EA accounted overall for less than 3% of all deaths at 5-years. (Caygill et al., 2012) Surveillance incurs costs and patients under surveillance have a lower quality of life. (Garside et al., 2006) In patients

with multiple co-morbidities or short life expectancy, the risks and benefits should be discussed with the patient prior to enlisting for surveillance.

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

18. There are almost no data on different surveillance intervals or its effects among only persons with LGD. Overall agreement 89.3%. A+24%, 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 is almost no data on different surveillance intervals or its effects in unselected populations of LGD. (Conio et al., 2003) 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 three years. (Corley et al., 2013) Recent data from large registries, which combined surveillance with radiofrequency ablation, 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. (Haidry et al., 2013) , (Gupta et al., 2013) , (Phoa et al., 2014)

Management strategies

19. Endoscopic ablation therapy should not be offered routinely to patients with non-

dysplastic BE. 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 which provide evidence that endoscopic non-dysplastic BE ablation decreases the risk of malignant transformation along with an assessment of risks of harm and the need for further surveillance after ablation. (Li et al., 2008) Also, studies with follow up after ablation indicate that no ablation technique can achieve 100% BE ablation (Manner et al., 2006), (Manner et al., 2011), (Madisch et al., 2005), (Shaheen et al., 2009), (Shaheen et al., 2011), and neo-squamous epithelium after ablative treatment may still contain buried glands (Gray et al., 2011) that could be associated with progression to cancer. (Hage et al., 2006) Also, prophylactic BE ablation does not appear to be cost- effective. (Hur et al., 2012)

20. Patients with BE with LGD on a single occasion (confirmed by at least 2 specialist GI

pathologists), without higher risk features (including multi-focality, long segment.)

should be managed with continued more frequent (6 to 12 months surveillance)

(providing the patient is fit for endoscopy and not already undergoing therapy).

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.(Wani et al., 2011c) 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

expert gastrointestinal pathologists as demonstrated in a Dutch study (Duits et al., 2014) where 73% of cases that were initially diagnosed with LGD were downstaged to either non dysplastic BE or IND.

A surveillance endoscopy in unifocal LGD does provide the opportunity to determine if there is progression, persistence, or regression. In cases of persistence (i.e. LGD present at a second, confirmatory endoscopy, (Abdalla et al., 2014) there is evidence to suggest these patients may be at higher risk and may consider the benefit of therapy to warrant the risk of therapy, as the SURF study (Phoa et al., 2014) demonstrated, persistence of LGD over time was predictive of progression in the control group. 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 due to is true regression, an issue of sampling error, inter-observer variability among pathologists, or removal of the dysplastic foci by the tissue sampling. These issues underscore the need for detailed endoscopic examination, (providing the patient is fit for endoscopy and not already undergoing therapy), re-review of dysplasia by at least 2 expert gastrointestinal pathologists and need for additional means of risk stratification. (Phoa et al., 2014) Risk stratification is needed to identify the subset of patients who are likely to progress and for whom the 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 2 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 (SFED, AGA, ASGE, 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 (multi-focality, long segment, etc.) surveillance should be continued at 6 -12 months intervals, to permit frequent sampling because they may fall into the persistent LGD group. An unselected group with LGD may gain little benefit from ablation therapy as the risks of therapy may outweigh the benefits. 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 (6 to 12 months surveillance) (providing the patient is fit for endoscopy and not already undergoing therapy).

Patients who have confirmed absence of LGD after 2 consecutive endoscopic evaluations can revert to routine surveillance rather than intensive surveillance.

Conditional recommendation, low quality evidence.

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21. Absence of dysplasia in 2 subsequent consecutive endoscopic evaluations, after an initial diagnosis of LGD in BE, identifies a cohort of patient who are at low risk to progress to dysplasia or EA and can continue routine surveillance rather than intensive surveillance. 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 confirmed LGD between 0.84 to 9.1% per year (Duits et al., 2014)ˑ (Picardo et al., 2014, Wani et al., 2011b, Sikkema et al., 2011) One recent study (Thota et al., 2014) reported that patients with multi-focal LGD was associated

with an increased risk of developing HGD and EA, but Wani in 2011 (Wani et al., 2011b) reported no association for multi-focal 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 endoscopy to confirm the findings, with recent guidelines recommending a broad 8 week to 12 month interval depending on the society (SFED, AGA, ASGE, BSG). If the repeat endoscopy shows the regression of dysplasia a further endoscopy should be performed and if dysplasia is still absent the patients appear to be at lower risk of developing EA, comparable to patients that have not been diagnosed with LGD. These patients can continue routine rather than intensive surveillance as supported by studies (Conio et al., 2003) including that by Duits (Duits et al., 2014) which showed reduced risk of developing EA in the absence of persistent LGD.

22. *Patients with BE with multi-focal LGD (confirmed by at least 2 GI pathologists) have an increased risk for progression of neoplasia compared with those with focal LGD. 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 2 GI pathologists) that persists, have an increased risk for progression of neoplasia compared to those with LGD at a single endoscopy. Overall agreement 89.3%. A+ 36%, A 53.3%, 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 increased in risk whereas

others have demonstrated significant increase in risk. Similarly, the patient phenotypic characteristics of LGD in BE (e.g., focal vs. multi-focal, short-segment vs. long-segment, persistent over time vs. intermittent, (i.e. found at a second confirmatory endoscopy, (Abdalla et al., 2014) at a surveillance interval of 6 to 12 months, consensus pathological agreement, etc.) have variably been described as important in predicting progression (Sikkema et al., 2011). Wani and colleagues followed more than 200 patients with Barrett 's and LGD for greater than 6 years (mean) and found none of these variables predicted histological progression. There are several studies which indicate that patients with persistent, multifocal LGD in a longer segment of BE are more likely to progress to EA (Shaheen et al., 2009), (Abdalla et al., 2014)and Thota et al. found a correlation between multifocality of LGD and progression of neoplasia (EA) in a single center experience of over 1500 patient-years and a 6% decreased likelihood of dysplastic regression per 1 cm increase in BE length. Moreover, recently Phoa, et al, in a large RCT (Phoa et al., 2014), 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 may demonstrated 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 significantly higher rate of progression to HGD/EA (9.1% per patient-year compared to 0.6% per patient-year among those initially diagnosed with LGD but then downgraded to non dysplastic BE and 0.9% for those downgraded to IND).

24. *Patients with BE with LGD (confirmed by at least 2 GI pathologists) and high-risk features (multifocality, segment length, persistence) should be offered treatment*

options including ablative therapies. Overall agreement 89.3%. A+ 36%, A 53.3%, U

9.3%, D 1.3%, D+ 0%.

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

25. Ablative therapy (with scheduled follow up) it decreases the progression of neoplasia

in BE with LGD (confirmed by at least 2 expert GI pathologist) and with risk factors

(persistence, long BE segment, multifocality).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 2

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 increase risk in BE patients with LGD. However, in high quality studies that have evaluated neoplasia progression in patients with BE LGD, ablation therapy has consistently improved outcomes by reducing neoplastic progression (to EA). Indirect evidence would suggest considering a policy of diagnostic endoscopic resection (ER) in patients with LGD and endoscopically visible lesions in BE followed by ablation therapy. in BE followed by ablation therapy. There

is some 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 versus radiofrequency ablation (Phoa et al., 2014) of participants with confirmed LGD, RFA significantly reduced neoplastic progression to HGD/EA, as compared to continued surveillance of BE with LGD (control arm). Histological progression decreased from 26.5% (control) to 1.5% (RFA). However during follow up, 10 % of patients had recurrent BE, suggesting continued surveillance is mandatory. However after follow up, 10 % of patients had recurrent BE, suggesting 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 the diagnosis or populations with BE and LGD. However, the original RCT of RFA (Shaheen et al., 2009) also demonstrated improvement in outcomes in those with LGD undergoing BE ablation which was durable (Shaheen et al., 2011) Thus ablation of BE with LGD is supported by two high quality RCTs. While 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.

These findings need to be tempered with other data suggesting a lower rate of progression of LGD (Hvid-Jensen et al., 2011, Bhat et al., 2011) (Wani et al., 2011a) which would suggest that overall, the majority of patients diagnosed with LGD do not progress to HGD/EA and may gain little benefit from ablation therapy. However LGD on initial biopsy is

an indicator of the potential for disease progression and a registry with over 1000 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. (Picardo et al., 2014) Risk stratification (including expert GI pathologist consensus review) is needed to identify the subset of patients with LGD for whom the 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. The options should be discussed with each patient to enable an acceptable decision.

26. *Management of IND in BE should require review and agreed consensus diagnosis by at least 2 gastrointestinal pathologists and follow up endoscopic biopsies within 12 months after increased acid suppressive therapy. Overall agreement 92%. A+33.5 %, 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 PPI) increased.

Conditional recommendation, very low quality evidence

Note: the diagnosis of IND should be considered as an interim diagnosis only. Further endoscopic surveillance (after acid suppressive therapy and within one year or sooner) is required to up- or down- grade the dysplasia after careful biopsy sampling/*ER.

*We have used ER throughout as the standard term as is interchangeable with endoscopic mucosal resection (EMR) but more accurately descriptive of the technique.

Follow up is recommended because of uncertainty about the nature of the lesions classified as IND. (Schlemper et al., 2000) Some follow up studies have shown increased likelihood of progression to higher grades of neoplasia, (Montgomery et al., 2001), (Sonwalkar et al., 2010) but this seems to be only in the first year, representing prevalent cases (Horvath et al., 2014). The risk appears higher in patients with multifocal IND (Younes et al., 2011) but is similar to a population with non-dysplastic BE when the diagnosis of 'IND' (rather than LGD) has been confirmed by a consensus panel of 2 (Curvers et al., 2010) or 6 expert GI pathologists. (Duits et al., 2014)

It has been suggested (without supporting evidence) that patients with 'regenerative' changes and inflammatory infiltration require increased acid suppression with proton pump inhibitor (PPI) therapy before re-biopsy. (Fitzgerald et al., 2014) (Montgomery et al., 2001) 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 (Horvath et al., 2014) suggests that a 6-12 month interval is reasonable. These data suggest that all cases of 'IND' should be re-biopsied 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. *Routine ER should not be offered routinely to patients with non-dysplastic BE. Overall agreement 96.7%. A+ 59.2, A 37.5%, U 2.5%, D 0%, D+ 0.8%.*

For discussion see 29.

> *RECOMMENDATION: we suggest against ER in patients with non-dysplastic BE and no visible lesion (harms outweigh benefits)*
>
> *Conditional recommendation, low quality evidence*

28. BE patients with visible lesions in the BE segment should have ER to stage the lesion.

Overall agreement 87.6%. A+ 46.3%, A 41.3%, U 9.1%, D 3.3%, D+ 0%.

For discussion see 29.

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

> RECOMMENDATION: we suggest patients with a visible lesion in non-dysplastic BE (as well visible lesions in BE with LGD or IND), should have ER (followed by ablation if HGD or intramucosal cancer is detected) over simple biopsies.
>
> Strong recommendation, low quality evidence for non-dysplastic BE; moderate quality evidence for LGD.

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 2 expert GI pathologists should be carried out to enable accurate histological assessment. ER may result in a change of diagnosis of LGD. Wani (Wani et al., 2013) reported a series of one-hundred and thirty-eight BE patients LGD 15 (10.9 %), HGD 87 (63 %), EA 36 (26.1 %)) were included; 114 (82.6 %) patients had visible lesions. ER resulted in a change of 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. (Pech et al., 2006)

In case of suspicious areas or raised lesions within the BE segment, ER is able to not only to provide a true tissue diagnosis including the character and extent of a potential abnormality (Spechler et al., 2011a), but also to be a treatment approach with a curative intent if early cancer is detected. (Ell et al., 2000) 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 is detected. (Bennett et al., 2012b), (Bennett et al., 2012a)

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, since it is related to patients with dysplasia, suggests that ER should be used as neoplasia may be present. (Pech et al., 2014), (Haidry et al., 2013), (Wani et al., 2013) Macroscopic surface abnormalities should be graded using the Paris modification of the Japanese system for classification of early gastric neoplasia. (Endoscopic Classification Review, 2005)

A biopsy finding of LGD in BE, especially if multifocal, carries a higher risk of progression to HGD or cancer than benign BE. (Montgomery et al., 2001), (Srivastava et al., 2007), (Younes et al., 2011) ER may result in a change of diagnosis of LGD. Flat type 2b lesions are the commonest seen among patients with dysplasia referred for high resolution

endoscopy at expert centers (Pech et al., 2007). 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. (Pech et al., 2007)' (Peters et al., 2008a)

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RECOMMENDATION: we recommend that ER should be followed by ablation if HGD or intramucosal cancer is detected, rather than continued surveillance.

Conditional recommendation, low quality evidence

</div>

Molecular markers of dysplasia and progression

30. Aberrant p16, p16 methylation or p16 loss in non-dysplastic BE is associated with an increased risk of progression to LGD. Overall agreement 80%. A+13.3%, A66.7%, U19.2%, 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)". (Wang et al., 2009) p16 is not the only marker studied for aberrant methylation and others include HPP1, RUNX3, AKAP12, CDH13, SST, TAC1, NELL1, (Jin et al., 2009) and which have also been replicated in another study.   (Sato et al., 2008)

31. Aberrant p53, p53 mutation or p53 loss in non-dysplastic BE is associated with an increased risk to develop dysplasia. 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 (Bian et al., 2001), (Campomcnosi et al., 1996), (Carlson et al., 2002), (Cawley et al., 1998), (Doak et al., 2003), (Flejou et al., 1999), (Shi et al., 1999), (Sikkema et al., 2009b, Sikkema et al., 2009a) and that p53 overexpression is caused by mutations that lead to a hyperstable 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. (Kastelein et al., 2013)

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 done 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. Overall agreement 40%. A+ 12%, A 28%, U 38.7%, D 17.7%, D+ 2.7%.

33. p53 aberrant expression combined with histopathological assessment is not useful for the histopathological assessment of dysplastic progression in non-dysplastic BE. 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, statins or diet was not agreed in this consensus (see online appendix, Results).

34. *The use of PPI's (compared to no therapy or histamine receptor type 2 antagonists (H2RA)s is associated with a decrease in progression from benign BE metaplasia to BE neoplasia (dysplasia and EA). 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) trial.*

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). (Umansky et al., 2001) Cohort studies demonstrate the use of PPIs decreased neoplasia development. (El-Serag et al., 2004) , (Hillman et al., 2004) , (Hillman et al., 2008) , (Nguyen et al., 2009) A systematic review (Islami et al., 2009) 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.

Anti-reflux surgery offers an alternative to PPIs in the treatment of GERD: it corrects lower esophageal sphincter failure, 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 to fundoplication. Overall agreement 86.6%. A+ 28.6%, A 58%, U 10.1%, D 2.5%, D+ 0.8%.

Some cohort studies suggest that effective anti-reflux surgery may reduce the risk of progression. (Gurski et al., 2003) , (Zehetner et al., 2010) , (Zaninotto et al., 2012) 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. (Parrilla et al., 2003) A meta-analysis (Corey et al., 2003) comparing anti-reflux 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. (Chang et al., 2007)

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 anti-secretory medication. (Spechler et al., 2001) (Lodrup et al., 2014) Recently it has been shown that progression to cancer after anti-reflux surgery is mainly related to late recurrence of reflux. (Lagergren et al., 2010) , (Lofdahl et al., 2011) , (Lofdahl et al., 2013)

RECOMMENDATION: we suggest against anti-reflux 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 recommendations, moderate quality of evidence

Note: 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.

DISCUSSION

In our *post hoc* voting rounds, we agreed a universal definition of BE i.e. "BE is defined by the presence of specialized columnar mucosa in the esophagus and it should be stated whether intestinal metaplasia (IM) is present above the gastroesophageal junction." This definition may help future research and audit by amalgamating both the divergent European (non-IM allowed) and the U.S. (IM only allowed) systems. (Rugge et al., 2014) The true malignant potential of BE with or without IM is presently unknown and our new definition and requires that the pathology report should state whether IM is present or absent in the tissue samples taken from above the gastro-esophageal junction (GOJ), which is a departure from the U.S requirement for IM to be present. (McNally, 2015) In addition because the GOJ is mentioned explicitly for the first time it emphasizes how important it is to distinguish BE from the commonly associated HH below. However in order to make the definition more robust for the clinic, further refinements may require IM to be present up to a certain length to help differentiate BE from columnar tissue taken from HH.

We recommend that consensus be required from least two specialist GI pathologists for the diagnosis of dysplasia (of any grade, including 'IND') which is in accordance with the new BSG guidelines. (Fitzgerald et al., 2014) This may have short term resource implications for extra histopathology staff but longer term the increased accuracy will lead to better long term management and greater efficiency. There is no evidence pointing to an optimal number of pathologists required, but evidence indicates accuracy increases with up to 3 experts involved. (Sanders et al., 2012), (Duits et al., 2014), (Coco et al., 2010),(Montgomery et al., 2001), (Sonwalkar et al., 2010)

The format and content of the proposed pathology proforma for BE requires further clarification. We recommend the proforma such as the example proposed in the BSG guidelines in 2014 (Fitzgerald et al., 2014) as good practice but if adopted, the individual features would have to be chosen by GI pathology experts.

There is currently no case for population screening for BE to reduce the risk of death from EA. We were unable to agree a policy of endoscopic screening except in very high risk groups such as males over 60 with poorly controlled GERD >10 years. EA is relatively rare in women, and demographic groups who are less at risk of EA, therefore endoscopic investigation would usually be employed in these groups only in the context of investigations of dyspepsia, to permit diagnosis and treatment of other conditions causing GERD symptoms (e.g., gastritis).

Although it is uncommon for BE patients to develop EA, (Bhat et al., 2011, Hvid-Jensen et al., 2011) 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 improved survival from EA(Bhat et al., 2014) and is cost-effective if undertaken every 5 years for non-dysplastic BE and every 3 years for LGD, in long-segment BE. (Kastelein et al., 2014) We did not perform cost effectiveness analyses of regular surveillance in these scenarios, but cost-effectiveness is unlikely if the prevalence rates of cancer in BE is less than 0.5 per year.

We now have very strong agreement on stratification of risk for targeted surveillance in high risk groups , including, but not limited to: age and sex, length of segment, and

symptom duration, frequency and severity. Whether or not non-dysplastic BE patients are followed up with routine surveillance to decrease their risks of death from EA, should not be determined solely on the basis of presence or absence of IM. There was agreement that longer length BE has a greater risk of progression to EA amongst other factors, (Sikkema et al., 2011) including obesity and tobacco smoking. Appreciation of risk factors in BE could potentially be developed into a quantitative score comparable to the acute physiology and chronic health evaluation (APACHE) risk classification of severely ill adult patients, to help physicians to determine each patient's need, and the most appropriate interval to return for endoscopic surveillance. The risks and benefits of surveillance should be taken into account with the patient's input particularly in those patients with co-morbidities or short life expectancy.

Future research including evaluation of genetic markers to determine cancer risk (Nicholson and Jankowski, 2009) , (Cronin et al., 2011) and biomarkers of progression (Rubenstein et al., 2005) (Rubenstein, 2014) 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 given the high levels of agreement, the adoption of these markers in specialist centers could be considered. The problem is that while in the main voting round people were very compelled by the association of for example p53 with dysplasia and cancer progression, in the *post hoc* voting rounds when we tried to dissect out the specific clinical utility of p53, the agreement fell apart because of weak specific evidence.

If undertaken, endoscopic surveillance of a patient with BE should be carried out in a careful and systematic manner to assess extent, histological features and risk factors, to guide subsequent management. Currently most BE surveillance endoscopies do not adhere to the empirical principles of good endoscopic practices; adequately trained staff, dedicated lists, and adequate biopsies taken. In the latter issue there is still disagreement as to whether Seattle is the only adequate method. We narrowly missed reaching consensus on the optimum number of biopsies to be taken during surveillance endoscopies in non-dysplastic BE being 2 per cm of BE length (76% overall agreement) and we make a strong research recommendation that further research is needed to identify the number of biopsies to detect progression for use as a quantitative metric.

Dedicated lists can allow adequate time to examine BE segments, to use adjunctive techniques which may improve neoplasia detection in a surveillance setting(Tholoor et al., 2014) and to carry out systematic protocolized biopsies as well as targeted biopsies of visible abnormalities. However, while a single center study (Anagnostopoulos et al., 2006) reported that establishing a specialist BE clinic reduced variation in treatment, changed management and improved adherence to local guidelines, there is no clear evidence yet that that specialized referral units for BE, centralized BE surveillance services dedicated surveillance lists can be confidently recommended. Statements on surveillance intervals in non-dysplastic BE and unselected populations of LGD were not agreed, probably reflecting lack of confidence in the data rather than the empirical recommendations of any guidelines (Garside et al., 2006), (Barritt and Shaheen, 2008) cited.

We now have consensus on a new bi-directional pathway to de-escalate or escalate the risk of patients with low risk BE compared with those with potentially higher risk BE such

as IND, or LGD with persistence over 2 endoscopies, multifocality, and long-segment BE. Patients with persistent and confirmed LGD should be treated by ablative therapy, which decreases progression to neoplasia (Phoa et al., 2014), and not just followed up. If not treated, in the case of LGD found on a single occasion, follow up should be close and biopsy protocols strict, as many may also have, or go on to develop HGD. The diagnosis of IND should be considered a holding diagnosis only and prompt further close follow up with adequate biopsy sampling.

Routine ER or routine endoscopic ablation therapy was not accepted as a strategy for non-dysplastic BE as the risk of harms outweighs any benefits. In the event of visible lesions in non-dysplastic BE and in all cases of dysplasia (LDG, IND) we recommend ER followed by an appropriate ablation method, as this offers a route of intervention to diagnose and treat early neoplasia. The SURF trial (Phoa et al., 2014) found that RFA was associated with a reduction in disease progression in patients with LGD confirmed by an expert panel of pathologists. It is unclear if these results can be generalized to routine management of patients with LGD. (Almond et al., 2014) There is some evidence that radiofrequency ablation (RFA), with or without endoscopic resection of BE containing confirmed LGD is long lasting. [4](Phoa et al., 2014)   However there is the increased recognition of buried dysplasia presenting later as advanced cancer, but in most cases this recurrence occurs in small islands or tongues; this would suggest a policy of continued endoscopic surveillance post-eradication with careful sampling to detect recurrence or progression of disease, but there is no evidence to recommend what surveillance intervals should be employed.

There was strong agreement that rates of progression to dysplasia or cancer in patients with BE are similar when comparing medical management to fundoplication. The studies are underpowered for patients with BE; however, there are no obvious reasons to conclude that the comparative efficacies of medical and surgical therapy differ for symptom control between BE patients and GERD patients. (Attwood et al., 2008) There are adverse events and considerable costs associated with surgical therapies compared with PPI therapy and patients may need to continue with PPI medication after surgery. (Lodrup et al., 2014) Fundoplication should not be offered to GERD patients, with or without BE, with the intent of reducing the risk of progression to BE or EA.

Our multidisciplinary international group has developed consensus to help the practicing clinician with the diagnosis and management of BE. There are a number of other potential limitations of this study; namely that we did not use meta-analysis techniques in a more rigorous approach to evaluating the literature, although we drew on evidence from existing meta-analyses, and some geographical areas (Africa, South America, Far Eastern and Middle Eastern countries, Russia), were underrepresented, despite our efforts for wide recruitment. There was some uncertainty in the voting process. In the intermediate voting round, Round 2, many participants registered a null vote and we saw a lack of a consistent downward progression in null (neither agree nor disagree votes) for some statements which may have been due to development and referencing of the statements reflecting the difficulty in obtaining scientifically valid studies about this condition. Other voters used the 'neither agree nor disagree' option to indicate true equipoise. Commenting and rigorous editing and refinement reduced the uncertainty by the final round. The relatively poor quality of data relating to BE is emphasized by 8 statements included in this summary having

low or very low levels and 3 having moderate levels of evidence quality. However, it is

unlikely that large, well-designed randomized trials will ever be done, although the

comparison of therapeutic interventions such as aspirin and different PPI doses will be

reported in the AspECT trial (a phase III, randomized study of aspirin and esomeprazole

chemoprevention in BE metaplasia) and BOSS (Barrett's Oesophagus Surveillance Study)

addresses scheduled endoscopic surveillance versus 'at need' endoscopic surveillance.

In conclusion, the process we employed and the large number of reviewers probably

reflects expert opinion better than in any traditional guideline or consensus processes and

represents the most far-reaching, inclusive, and informative consensus process on

evaluation and management of BE and LGD published to date. We made strong research

recommendations to prioritize future research and in particular we provide for the first time

an agreed global definition of BE together with a pathway of escalation and de-escalation of

indefinite dysplasia or LGD.

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