

Barrett's oesophagus: Current controversies

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Abstract

Oesophageal adenocarcinoma is rapidly increasing in Western countries. This tumour frequently presents late in its course with metastatic disease and has a very poor prognosis. Barrett's oesophagus is an acquired condition whereby the native squamous mucosa of the

lower oesophagus is replaced by columnar epithelium following prolonged gastro-oesophageal reflux and is the recognised precursor lesion for oesophageal adenocarcinoma. There are multiple national and society guidelines regarding screening, surveillance and management of Barrett's oesophagus, however all are limited regarding a clear evidence base for a well-demonstrated benefit and cost-effectiveness of surveillance, and robust risk stratification for patients to best use resources. Currently the accepted risk factors upon which surveillance intervals and interventions are based are Barrett's segment length and histological interpretation of the systematic biopsies. Further patient risk factors including other demographic features, smoking, gender, obesity, ethnicity, patient age, biomarkers and endoscopic adjuncts remain under consideration and are discussed in full. Recent evidence has been published to support earlier endoscopic intervention by means of ablation of the metaplastic Barrett's segment when the earliest signs of dysplasia are detected. Further work should concentrate on establishing better risk stratification and primary and secondary preventative strategies to reduce the risk of adenocarcinoma of the oesophagus.

Key words: Barrett's oesophagus; Gastroenterology; Endoscopy; Oesophageal adenocarcinoma; Dysplasia

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Core tip: Oesophageal adenocarcinoma is increasing in incidence especially in Western populations. Barrett's oesophagus is the identifiable pre-malignant condition which allows periodic surveillance and secondary prevention to be undertaken to reduce cancer risk. There has been recent evidence supporting earlier endoscopic intervention for dysplastic changes in Barrett's oesophagus, but the high burden of surveillance prompts increased efforts to identify individuals at highest cancer risk to concentrate resources on those patients who will derive the greatest benefit.

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INTRODUCTION

Barrett's oesophagus is an acquired oesophageal condition characterized by the presence of metaplastic columnar epithelium in the distal oesophagus which replaces normal stratified squamous mucosa^[1].

It is associated with prolonged gastro-oesophageal reflux and a risk of development of adenocarcinoma of the oesophagus^[1]. Diagnosis is made by oesophago-gastroduodenoscopy and biopsy sampling to allow histological examination of the oesophageal mucosa (Figure 1). There is a histological spectrum of appearances of the Barrett's epithelium spanning benign changes to adenocarcinoma which is classified using the Modified Vienna Criteria into one of five categories^[2] (Table 1).

Following initial diagnosis and confirmation of the histological findings^[3-6], the management of Barrett's oesophagus will include consideration of periodic surveillance of the Barrett's mucosa, measures to control gastro-oesophageal reflux, chemo-protective strategies, ablation of the metaplastic segment, endoscopic resection and surgical resection of the oesophagus.

AREAS OF DEBATE

Six decades have passed since Normal Barrett described this eponymous condition^[7], yet there are still several areas of controversy surrounding definitions, formal diagnostic criteria, the role of screening, the scope of primary and/or secondary prevention and how to undertake surveillance. The pathogenesis of Barrett's oesophagus is also debateable but will not be addressed fully in this article as the focus is clinical. The most controversial areas surround the fact that overall risk has been established but calculating individualised risk is limited as it is based on crude markers of perceived risk. Also, new evidence for earlier ablation of dysplasia has changed the goals of surveillance; the best risk modification to reduce the risk of dysplasia is not widely practiced; sampling error and pathological interpretation are subject to significant errors; and adjuncts to these methods not being widely taken up.

DEFINITIONS IN BARRETT'S OESOPHAGUS

The definition of Barrett's oesophagus is controversial. There are several definitions of Barrett's oesophagus

and without comprehensive population-based studies it is difficult to define the true incidence of the disease. Overall, it is fundamentally the presence of metaplastic columnar epithelium in the distal oesophagus.

However, other factors which are not part of the definition are oftentimes included in the requirements for consideration in surveillance including the precise location of the oesophageal landmarks, the required extent of metaplastic mucosa and the presence of intestinal metaplasia.

Different studies use different clinical end points when examining outcomes in Barrett's oesophagus. Some use cancer incidence or mortality, whereas others use the development of dysplasia (to improve study power or due to therapeutic interventions). Interventional trials may use endpoints such as macroscopic eradication of columnar mucosa, a reduction in Barrett's extent or absence of intestinal metaplasia or dysplasia on biopsies. There is also considerable variability in biopsy protocol and histological grading of biopsy findings.

SCREENING FOR BARRETT'S OESOPHAGUS

Screening identifies the possible presence of disease in asymptomatic individuals to facilitate earlier intervention and management with the aim of reducing morbidity and mortality. The criteria required for a valid screening programme are listed in Table 2.

WHAT IS THE PREVALENCE OF BARRETT'S OESOPHAGUS?

Several studies have established that the prevalence of Barrett's oesophagus in the unselected general population is between 1%-2% in European studies (Italian 1.3%, $n = 1033$ and Swedish 1.6%, $n = 1000$)^[8,9]. It is 5.6% in the United States^[10]. The factors associated with Barrett's oesophagus are gastro-oesophageal reflux disease (GORD) symptoms^[11-16], older age^[11-13], and the male gender^[11,12,17]. Studies have revealed an association with central obesity (waist to hip ratio or abdominal circumference, but less clearly to body-mass index or overall body fat content), tobacco smoking, the Caucasian race and a positive family history. Conversely, alcohol consumption does not appear to be a strong risk factor. Studies have also found potential risk factors including metabolic syndrome, type 2 diabetes mellitus, and sleep apnoea^[18-21]. It has been suggested that the difference in prevalence between the United States and Europe is due to a higher prevalence of associated risk factors (GORD, obesity, diet, smoking); and can explain the reason behind the difference in prevalence between the West and Asia or Africa^[8,22]. Nevertheless, data from meta-analyses on the difference in cancer

Table 1 Modified Vienna Criteria

Category	Description
1	No dysplasia
2	Indefinite for dysplasia
3	Low-grade intraepithelial neoplasia (low-grade adenoma/dysplasia)
4	High-grade intraepithelial neoplasia (high-grade adenoma/dysplasia, non-invasive carcinoma, or suspicion of invasive carcinoma)
5	Invasive epithelial neoplasia (intramucosal carcinoma, submucosal carcinoma, or beyond)

**Figure 1** Barrett's oesophagus on endoscopy.

incidence between countries across the world do not show a difference in cancer risk^[23]. However, there are likely to be differences between individual studies so further individualised risk stratification is needed with a possible inclusion on geographical location.

In examining the risk of development of oesophageal adenocarcinoma in the general population: a large case-control study found that the OR of developing oesophageal adenocarcinoma for patients with GORD symptoms at least once a week was 7.7 (95%CI: 5.3-11.4) compared to individuals without GORD symptoms^[24].

In summary, Barrett's oesophagus is an important health problem as it is an identifiable premalignant leading to oesophageal adenocarcinoma^[1]. There is a detectable early stage where an effective intervention would be more beneficial than at a later stage as it would reduce the risk of malignant progression.

NATURAL HISTORY OF BARRETT'S OESOPHAGUS

There is an asymptomatic but detectable early stage which offers a window for treatment. Treatment of cancer/dysplasia is more beneficial the earlier it is given^[25]. Subsequently, the natural history is now often interrupted by interventions made when dysplasia is identified^[26]. Evidence for the efficacy of various interventions (endoscopic, pharmacological and surgical) on the natural history is currently being studied.

Two specific major United Kingdom trials currently underway are: the Barrett's Oesophagus Surveillance Study (BOSS) which randomises patients to standard surveillance vs endoscopy at time of need and the Aspirin and Esomeprazole Cancer Chemoprevention Trial^[27,28] which is discussed in the section on Secondary prevention.

Nevertheless, for now, it is agreed that oesophageal adenocarcinoma develops by a multistep process where a normal stratified squamous cell in the distal oesophagus becomes metaplastic columnar epithelium under the environmental assault of gastric acid, made more likely on a background of genetic and non-modifiable risk factor predisposition^[29] and onward to neoplasia (Table 1). The process is dependent on

defective genes amongst those which control the cell cycle where genomic instability results in multiple aneuploid populations of cells; which will genetically acquire the ability to invade and metastasize^[30-32].

A number of studies have reported resolution of dysplastic changes and whilst regression to a less severe dysplastic stage may be plausible, the absence of dysplasia (which by definition is neoplastic with genetic changes) is more likely to be due to sampling error or variability in histopathological interpretation^[30,32-34]. Several papers conclude that the natural history of Barrett's oesophagus is not known with an unpredictable progression^[29]. Moreover, attempting to understand the natural history becomes more difficult on an individual patient basis as it would require consideration of genetic, environmental and behavioural factors^[35]. Despite the uncertainty, a study in Northern Ireland found that the annual risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus was 0.38% per year (when intestinal metaplasia is present) compared to 0.07% in patients without intestinal metaplasia^[36]. The lifetime risk was 5.8% in males and 3.0% in females. Overall, there are many questions surrounding the pathogenesis which require further research into.

TARGETTED SCREENING

A decision analytical model established that a one-time screening endoscopy for Barrett's oesophagus was cost-effective^[37]. Nonetheless, there is a debate on the target population for screening and most guidelines advocate targeting individuals with certain risk factors rather than the general population to maximise its yield. One of the important risk factors considered includes GORD. There is evidence lacking for the most suitable tests and potential methods for screening include endoscopy but this is generally considered to be too expensive, invasive and cumbersome where a study found that the cost of endoscopic screening in GORD patients was \$24718 per life-year saved^[38]. A similar figure (\$22200) was also arrived at in another study where the population screened incorporated a number of the key risk factors (50-year-old white men with a history of GORD)^[39,40]. Another study

Table 2 The Wilson-Jungner criteria for appraising the validity of a screening programme

The Wilson-Jungner Screening Criteria	Achieved for Barrett's oesophagus?
The condition being screened for should be an important health problem	+
The natural history of the condition should be well understood	+/-
There should be a detectable early stage	+
Treatment at an early stage should be of more benefit than at a later stage	+
A suitable test should be devised for the early stage	+
The test should be acceptable	+
Intervals for repeating the test should be determined	+/-
Adequate health service provision should be made for the extra clinical workload resulting from screening	+
The risks, both physical and psychological, should be less than the benefits	+
The costs should be balanced against the benefits	-

investigating the possibility of streamlining the number of patients requiring endoscopic surveillance has positive results. They limited the surveillance cohort after an initial endoscopy to patients with 2 cm of columnar metaplasia or more, and limited again after the second endoscopy by excluding patients without intestinal metaplasia. Results showed that when the risk was stratified in this way, the percentage requiring endoscopy was reduced by 33% and the procedure becomes cost-effective^[41].

Cytosponge

The Cytosponge is a device encased within a pill attached to a piece of string which, when swallowed, dissolves to reveal an expandable sponge which scrapes off up to 500000 cells when withdrawn up the oesophagus by the string^[42]. Whilst being withdrawn, it collects cells along the entire oesophagus rather than just point samples from endoscopy. Studies have already shown that the Cytosponge technique is able to overcome the sampling bias of endoscopy and is able to reflect the entire clonal architecture^[43].

The initial study (BEST1) of 500 patients between 50 to 70 year olds found that 99% were able to swallow the device without issues. A larger study (BEST2) was conducted involving 1110 patients with Barrett's oesophagus ($n = 647$) or GORD but not investigations for Barrett's oesophagus ($n = 463$) where both groups swallowed the Cytosponge (93.9% swallowed successfully) and underwent an endoscopy. Results showed that the Cytosponge was as accurate as endoscopy and was preferred to endoscopy in over 90% of patients^[44].

The sensitivity of the device was 79.9% which rose to 87.2% for patients with more than 3 cm of circumferential Barrett's oesophagus. It rose further again to 89.7% when the Cytosponge was swallowed twice during the study ($n = 107$). Specificity was unchanged (92.4%). The study demonstrated that the Cytosponge is safe and acceptable and comparable to other screening options^[40]; however, it was a case-control study rather than a population-based study which limits the amount generalization that can be made to a primary care population^[44]. Therefore, the BEST3 Trial is in place to investigate its use in a primary

care setting and evaluate its cost effectiveness. A small study found that 16% of 161 endoscopy referrals were suitable for triage to use of the Cytosponge^[45].

Targetted population

Cost effective identification of patients at highest risk will involve symptoms, demographics and other associated factors (as previously discussed). A meta-analysis of five case-control studies (1189 oesophageal adenocarcinoma patients and 4666 controls) revealed that patients with weekly GORD symptoms were five times more likely (OR = 4.9) to develop oesophageal adenocarcinoma than their counterparts with less frequent or no symptoms^[46]. The question remains as to whether a single (one off) screening test is appropriate or whether repetition should be undertaken. Studies show that the mean age at the time of diagnosis is approximately 55 years^[47] and whilst children may have patches of columnar epithelium in the oesophagus or distal oesophageal columnarised segments, it is rare before five years of age^[48]. This epidemiology suggests that Barrett's oesophagus is an acquired condition and provides insight into informing the age at which screening should start.

The absolute risk for development of adenocarcinoma in individuals with GORD symptoms less than once per week is very low at 0.1 to 15.4 per 100000 for men (aged 30-80 years), and 0 to 2.3 per 100000 for women (aged 30-80 years)^[49]. Over 40% of patients with oesophageal adenocarcinoma do not have a history of heartburn, and a study in 2000 found that fewer than 5% of patients with oesophageal adenocarcinoma were known to have had Barrett's oesophagus before they presented with symptoms^[24,50]. Subsequently, a targetted screening (or surveillance) programme will only detect some of the individuals at risk^[49].

The lack of utility in screening all GORD patients was echoed in the guidelines from the American Gastroenterological Association (AGA)^[6] and the American College of Physicians^[45] which state that endoscopy should be offered to patients with risk factors for adenocarcinoma. According to both guidelines, these include chronic GORD, hiatal hernia (Figure 2), age 50 years and over, male gender, Caucasian race,



Figure 2 Barrett's oesophagus extending above a hiatus hernia.

and intra-abdominal body fat distribution. Interestingly, the American College of Gastroenterology (ACG)^[3] also supports the use of endoscopy as a screening tool but only if there are GORD symptoms in the presence of alarm symptoms (dysphagia, weight loss, and signs of gastrointestinal bleeding). The British Society of Gastroenterology (BSG) also arrived at similar conclusions where it was decided that endoscopic screening is unfeasible and unjustified in an unselected population with GORD symptoms but should be considered in patients with chronic GORD and multiple risk factors (at least three of age 50 years or older, Caucasian race, male sex and obesity)^[4]. The report also mentioned that the threshold should be lowered if there is a family history of Barrett's oesophagus or oesophageal adenocarcinoma; and that life expectancy of the individual should be considered in view of screening. The National Institute of Health and Care Excellence also has guidelines on a "two-week wait referral for suspected upper gastrointestinal cancer" where endoscopy is urgently arranged for patients with the following symptoms: dysphagia or aged 55 and over with weight loss and upper abdominal pain, reflux or dyspepsia^[51].

DIAGNOSIS AND CONSIDERATION OF ENTRANCE INTO SURVEILLANCE PROGRAMMES

Controversies around the entrance into a surveillance programmes focus on the relevance of intestinal metaplasia and the minimum length of Barrett's oesophagus needed. Following endoscopic and histological diagnosis, as per the BSG, AGA, ACG and American Society for Gastrointestinal Endoscopy (ASGE)^[3-6], intestinal metaplasia is not compulsory but helpful, and patients with at least 1 cm of columnar metaplasia of the oesophagus may be considered for surveillance.

Relevance of intestinal metaplasia

There have been differences in opinion on the importance of the detection of in short (arbitrarily

defined as < 3 cm) segments when considering the management of Barrett's oesophagus.

Intestinal metaplasia is the transformation of oesophageal or stomach epithelium into that which resembles intestinal epithelium (with goblet cells identified in the sampled columnar epithelium). Its requirement for consideration of surveillance arises from a suspected lower risk of development of oesophageal adenocarcinoma in short segment Barrett's epithelium without features of intestinal metaplasia. Recommendations on surveillance based on the presence of intestinal metaplasia have not been included in previous BSG guidelines^[4] due concern that in the process to confirm intestinal metaplasia, there would be limitations from sampling errors in mucosal biopsy samples alongside some studies suggesting it does not influence cancer risk^[52]. Moreover, a studies showed that initially the rate of developing dysplasia or cancer was the same in patients with or without intestinal metaplasia^[53,54].

Furthermore, in one study which undertook a survival analysis, over 50% of those without intestinal metaplasia initially had evidence of it within 5 years and there was a cancer risk in patients where intestinal metaplasia had not been detected. The study demonstrated that a low number of biopsy samples (fewer than 8) is not enough to exclude intestinal metaplasia, especially if the segment of Barrett's oesophagus is short^[55]. It has also been demonstrated that DNA content abnormalities are comparable in both metaplastic epithelia without goblet cells and metaplastic epithelia with goblet cells; however, another study has shown that cancer is commonly found with the surrounding presence of goblet cells^[56-58]. Subsequently, a large study from Northern Ireland found that the incidence of high grade dysplasia and cancer in patients with intestinal metaplasia is five times higher than those without intestinal metaplasia (0.38% vs 0.07%)^[36,56].

The other issue surrounding the use of intestinal metaplasia in the definition is distinguishing between true Barrett's oesophagus and intestinal metaplasia of the cardia of the stomach. It is notoriously difficult to distinguish between the two on a gastro-oesophageal junction biopsy sample as the different forms of intestinal metaplasia occur at both sites and unless native oesophageal structures are seen by the histopathologist, there is a lack of reliable markers which distinguish between intestinal metaplasia of the oesophagus and cardia requiring accurate endoscopic technique when sampling this dynamic organ^[59-62].

It thus follows that although intestinal metaplasia is not a prerequisite for the definition of Barrett's oesophagus, it could and should be taken in consideration when determining the frequency and necessity of follow-up of patients as there is evidence that it affects cancer risk long term following the results of the large study from Northern Ireland^[36].

1-cm threshold and "long segment" Barrett's oesophagus

Another area of contention is the use of a 1-cm threshold. The use of 1-cm stems from studies which have shown that segments below 1 cm have very high levels of inter-observer variability, and are at very low risk of development of oesophageal adenocarcinoma, and do not show that they are at an increased risk of developing dysplasia^[63]. Therefore, they are not considered as Barrett's oesophagus but as "specialized intestinal metaplasia of the oesophagogastric junction", an irregular z-line or "ultra-short segment Barrett's oesophagus". "Long segment Barrett's oesophagus" describes metaplastic segments of 3 or more centimetres in length. Increased segment lengths have been associated with higher dysplasia and cancer risk and subsequently the presence of intestinal metaplasia is not considered a pre-requisite for either diagnosis or enrolment into surveillance programmes^[64,65].

PRIMARY PREVENTION

Some of the most important risk factors (male gender, older age) for developing Barrett's oesophagus cannot be modified which limits the scope for primary intervention to preventing GORD by maintaining a healthy weight and not smoking. However, the influence that these risk factors have on the probability of developing Barrett's needs to be investigated to ascertain whether differential efforts need to go into the respective risk factors as smoking confers a greater risk for Barrett's oesophagus in non-GORD controls.

SURVEILLANCE

Oesophageal adenocarcinoma is a tumour which tends to spread early before dysphagic symptoms become apparent with lymph node metastasis being a very poor prognostic factor. The goals of surveillance are to detect dysplasia and early cancer before distant disease has developed^[66]. Lymphatic invasion may occur very early in oesophageal tumours (when the tumour has reached the submucosa) which is one of the main reasons for the frequent presentation of advanced disease and poor prognosis^[67]. For this reason, there is immense benefit in the early detection of cancer or pre-cancer where intervention may be curative. Tumours detected within Barrett's oesophagus surveillance programmes are in general at an earlier stage than those detected *de novo*^[68].

Endoscopy is the main method of surveillance in Barrett's oesophagus with biopsy sampling using the Seattle protocol which consists of four-quadrant biopsies taken every 2 cm or every 1 cm in cases of dysplasia^[69]. The purpose of surveillance is to detect dysplasia and at present, the frequency of surveillance is generally based on the grade of dysplasia detected. Prior to surveillance, it is imperative that GORD (if

present) is medically controlled as active inflammation makes it very difficult to differentiate between dysplasia and repair. The biopsies taken should then be classed using the five-tier system of the Vienna classification^[2] (Table 1).

In most guidelines, surveillance is every 2-5 years if there is no dysplasia, every 6-12 mo for low grade dysplasia (unless an endoscopic intervention has been undertaken) and every 3 mo for high grade dysplasia with most patients undergoing endoscopic therapy rather than continued surveillance. Indefinite changes for dysplasia prompt an early repeat endoscopy (typically at 6 mo) with maximal control of reflux in the interim period to help clarify the histological features and allow more accurate interpretation. The evidence base behind the surveillance intervals arises from decision analytical models which found that surveillance every 5 years was on the only viable strategy with the greatest quality adjusted life^[69]; informing the maximal interval of 5 years. Another model found that there was little benefit of surveillance of Barrett's oesophagus patients without dysplasia as there is a low incidence of adenocarcinoma in the group. It demonstrated that if there is no dysplasia, surveillance intervals longer than 5 years are associated with costs outweighing the marginal increases in quality adjusted life years^[37].

Observer variability

Surveillance relies on histologic evaluation of dysplasia which unfortunately attracts downsides as there are pathologic limitations and diagnostic variability in assessing the presence and grading of dysplasia^[70]. This is worsened by the fact that the changes which occur as Barrett's oesophagus progresses are subtle and accompanied by a wide range of morphological patterns of atypia thus introducing intra- and inter-observer variability^[71,72]. The impact of the variability is most obvious at the lower end of the scale where it becomes challenging to differentiate regeneration from dysplasia but not the extremes where agreement is generally very high^[73]. A study into the variability found that amongst eight expert oesophageal histopathologists, there was only 60% agreement in drawing a distinction between no dysplasia detected from indefinite changes for dysplasia and low grade dysplasia^[74]. The effect is a predilection to a provisional diagnosis of indefinite changes for dysplasia. Various studies have investigated whether the variability in the diagnosis of dysplasia can be decreased but there are yet to be substantial solutions^[75]. There is clearly the need for less subjective markers to determine the risk of malignant progression Barrett's oesophagus.

BIOPSY PROTOCOL AND ADJUNCTS TO STANDARD SYSTEMATIC BIOPSY

There have been some studies examining the utility

of a systematic biopsy protocol in comparison to a random or targeted approach^[76]. One study found that four-quadrant biopsy detected dysplasia in Barrett's oesophagus in 13 times more patients than non-systematic biopsy surveillance. There is also discussion around the benefit of targeted biopsy samples where adjuncts are used alongside endoscopy to better visualise the oesophageal mucosa.

Chromo-endoscopy

Chromo-endoscopy is founded on the current use of acetic acid to stain abnormal tissues during an examination of the cervix to whiten immature (young) and dysplastic cells. When acetic acid is used in the gastrointestinal tract *via* a spray catheter in the endoscope, both the oesophageal and gastric mucosae turn white (as in the cervix) but once a few minutes have passed, normal mucosa remains white whereas Barrett's mucosa transiently turns red, as does gastric columnar mucosa^[77]. Its use can be improved by the addition of indigo carmine to better visualise early gastric cancer and as a mucolytic to remove mucus obscuring the mucosa^[78]. Dysplasia may be found where there are areas of surface irregularity, changes in the vascular pattern or variability of staining.

A retrospective study ($n = 982$) involving patients with Barrett's oesophagus under surveillance found that dysplasia was detected in 41/327 (13%) patients where acetic acid was used as an adjunct vs only 13/655 (2%) in the random biopsy group^[79]. Moreover, in the initial detection of Barrett's oesophagus, targeted biopsies using acetic acid more than doubles the yield of detection (57% vs 26%)^[80]. Other studies have shown similar results for acetic acid chromo-endoscopy which was found to detect dysplasia and neoplasia better than white light endoscopy^[81], with another study showing that it requires 15 times fewer biopsies per neoplasia detected^[79]. In another study where 263 procedures were examined with neoplasia in 143, acetic acid chromo-endoscopy correctly identified 96% of these cases vs 55% with white light endoscopy.

Other dyes which have been used include methylene blue, toluidine blue, cresyl violet, crystal violet, Congo red, phenol red and Lugol's solution. Lugol's solution contains potassium iodide and iodine, both of which attach avidly to glycogen in non-keratinised squamous epithelium and so studies have found it is extremely effective for detecting squamous lesions (sensitivity 9% vs specificity 40%-95%)^[82] and it can also be used in post-ablation Barrett's oesophagus patients to distinguish between regenerative squamous epithelium and areas of residual Barrett's mucosa (which do not take up the dye). Despite its benefits, safety studies have shown that its use may cause retrosternal pain which is attenuated by sodium thiosulfate^[83]. Methylene blue is only taken up by tissue which is actively absorbing (small intestinal and colonic epithelium) and so can be used to find Barrett's mucosa (metaplastic

absorptive mucosa). Although indigo carmine is predominately used in investigating the colon by visualizing pit patterns to distinguish between different types of polyps, it can also be used to identify Barrett's oesophagus when used in conjunction with high-magnification endoscopy and Lugol's solution^[84]. Both cresyl violet and crystal violet stain cell nuclei thus aiding in identifying Barrett's metaplastic mucosa^[84,85]. Less commonly used adjuncts to endoscopy are Congo red and phenol red which are both pH indicators used to detect areas of ectopic acid secretion.

Although chromo-endoscopy offers benefits to aid in the screening or surveillance of Barrett's oesophagus, it does have a number of shortcomings that limit its use. Unfortunately, the procedure is very subjective and subject to inter-observer variability and a study found that even when blinding techniques are employed, there was no increase in the numbers of cases of Barrett's oesophagus detected and no widely accepted standardisation of their application^[86-90].

Narrow band imaging

Narrow band imaging (NBI) is an alternative technique where lights of specific blue (wavelength = 440-460 nm) and green (wavelength = 540-560 nm) wavelengths are used to enhance the detail of the mucosa and blood vessels. This works because the wavelengths correlate with the peak light absorption of haemoglobin hence will appear very dark thus improving their visibility and easing the identification of neighbouring structures.

The other methods which can be employed for surveillance of Barrett's oesophagus include endosonography [endoscopic ultrasound (EUS)], optical coherence tomography (OCT), confocal microendoscopy, auto-fluorescence endoscopy and computed virtual chromo-endoscopy (CVC).

Endoscopic ultrasound

Studies have shown that EUS to screen patients with Barrett's oesophagus is neither justified nor cost-effective but does play a role when there is high grade dysplasia or intramucosal carcinoma^[91]. Conversely, in terms of superiority, OCT is above EUS as its resolution is better as once can see the layers of the oesophageal wall can be visualised with good correlation to histologic structures thus allowing endoscopists to detect high grade dysplasia earlier. The sensitivity of detecting dysplasia was 68% and specificity was 28%^[92].

Computed virtual chromo-endoscopy

CVC enhances mucosal surface contrasts and vascular pattern variability without the use of dye as is standard in chromo-endoscopy. Its utility was demonstrated in a randomised control trial where 57 patients with Barrett's oesophagus and a history of high grade intraepithelial neoplasia/early cancer were allocated to undergo acetic acid chromo-endoscopy or CVC with

re-examination after 4-6 wk with the other procedure. The positive predictive value for the former was 39% and 37% for the latter with comparable sensitivities at 83% and 92% respectively^[92]. The study thus shows that CVC is not only useful as an adjunct but provides comparable results to conventional chromo-endoscopy in the detection of high grade dysplasia/early cancer.

Auto-fluorescence

Auto-fluorescence endoscopy is a technique incorporating a real time wide angle view allowing the endoscopist to rapidly go from standard white lighting to auto-fluorescence and to very quickly examine large areas of gastrointestinal mucosa. However, there was no clear superiority over conventional white-light imaging (whether or not it is used in conjunction with NBI)^[93]. On the other hand, confocal microendoscopy is where the resolution and contrast of imaging is augmented by eliminating out of focus light by the addition of a spatial pinhole at the confocal plane of the lens. A study determined that this method is very accurate and reliable (sensitivity 88% and specificity 96%) for the diagnosis of neoplasia^[94].

ENDOSCOPIC SURVEILLANCE

INTERVALS

Non-dysplastic (no dysplasia detected)

The BSG, ASGE and AGA are all in agreement on the management which follows for each biopsy category^[3-6]. If biopsies show non-dysplastic Barrett's oesophagus (no dysplasia detected), surveillance (every 2-5 years) is offered following a discussion about its benefits and risks. The Barrett's segment length is incorporated into guidelines too. Australian and British guidelines state that endoscopy should be repeated 3-5 years if the maximal length is less than 3 cm, and every 2-3 years if above or equal to 3 cm^[4,95]. The AGA and ACG does not delineate surveillance for no dysplasia detected by segment length (3-5 years for all lengths); however, the latter differentiates the number of biopsies by segment length (4 biopsies for every 2 cm of segment length, or at least 8 biopsies if the segment is less than 2 cm at the initial exam) which should reduce sampling error for detection of intestinal metaplasia^[53].

Indefinite changes for dysplasia, Low grade dysplasia, High grade dysplasia and Adenocarcinoma

If biopsies are indefinite for dysplasia, American and British guidelines emphasise maximal acid suppression with a PPI to reduce the misleading effects of reflux oesophagitis on the oesophageal mucosa. After adequate acid suppression (BSG and Australian guidelines: 6 mo; ACG: 3-6 mo), further biopsies should be taken using the Seattle biopsy protocol and if they are still indefinite, the diagnosis should be confirmed by an expert oesophageal histopathologist. If the diagnosis is clarified with classification to another

group on the second biopsy, the appropriate pathway (no dysplasia detected, low grade dysplasia, high grade dysplasia, adenocarcinoma) should be taken.

If low grade dysplasia or high grade dysplasia/intramucosal carcinoma is seen, the findings must be confirmed with an expert oesophageal histopathologist and the Seattle protocol used to obtain further systematic biopsies (due to the risk of sampling error and confirm the degree of dysplasia) with endoscopic resection of any mucosal irregularities. Guidelines from the United States and the United Kingdom recommend that low grade dysplasia patients are given the option of either surveillance every six months or endoscopic eradication. For high grade dysplasia/intramucosal carcinoma patients, guidelines recommend an intervention to the dysplastic mucosa at this time due to the risk of an occult carcinoma or disease progression^[64,96]. Although endoscopic eradication is recommended for high grade dysplasia, endoscopic surveillance is advocated in some units. The evidence comes from a study over a period of 20 years where of 75 patients with high grade dysplasia underwent surveillance over an average of 7.3 years, and 12 developed adenocarcinoma which was curable by ablation in all but 1 who was lost to follow-up^[97]. In another study of 45 patients with diagnosed cancer from high grade dysplasia, 13 were detected at the initial endoscopy whereas 32 were found during surveillance and of the 32, only one patient had metastatic disease when first seen on surveillance^[98].

Patients who are found to have frank oesophageal adenocarcinoma need to undergo staging investigations with a frank discussion on possible treatment options. The radical options include chemo-radiotherapy, radiotherapy, an oesophagectomy or endoscopic resection/ablation of disease confined to the mucosa. Quality of life is slow to return after an oesophagectomy and not regained in patients surviving less than 2 years^[99].

Unfortunately, abiding by comprehensive systematic biopsy protocols is very challenging because there is a substantial time and resource implication to taking multiple biopsies including time to process and interpret results. Moreover, there is no widely utilised system for targeted biopsies.

SURVEILLANCE-DETECTED CANCERS

Overall, studies have already demonstrated that survival rates are markedly better in patients with Barrett's oesophagus where endoscopic surveillance has detected oesophageal adenocarcinoma compared to patients not undergoing surveillance^[100-105]. Despite the potential for the findings from these studies to be explained away with lead time and length time biases, the findings were maintained even after correcting for these biases. Nevertheless, there are costs associated with surveillance including the small morbidity associated with surveillance and biopsy, the resource use and associated anxiety. There are

also the limitations associated with surveillance programmes in their goals of detecting dysplasia and early cancer. There is an ongoing randomised control trial (BOSS Trial) comparing survival rates in 3400 patients with Barrett's oesophagus in a standardised 2-year endoscopic surveillance group vs an "at need endoscopy" group^[27]. Results from the study will contribute towards the settling the debate on the need and benefit of surveillance to cancer incidence or survival.

SECONDARY PREVENTION

Unfortunately, the incidence of Barrett's oesophagus and oesophageal adenocarcinoma are on the rise^[46].

Medical control of reflux

Acid suppression with PPIs is a fundamental part of the management of patients with Barrett's oesophagus, and PPIs have been shown to be superior to histamine receptor antagonists^[106]. It is known that PPI use relieves symptoms associated with GORD but its effect on the risk of progression to cancer is not known. It has been postulated that if PPI treatment could reduce the stage of dysplasia or the length of Barrett's mucosa, it would contribute to a reduction in the cancer risk^[107,108]. At present, studies show that PPI use promotes squamous re-epithelialization next to and on top of Barrett's mucosa but does not cause regression hence surveillance would still be necessary^[109-111].

Chemoprevention

There are data that suggest that non-steroidal anti-inflammatory drugs (NSAIDs, particularly aspirin and COX inhibitors) and statins reduce the risk of malignant progression which was seen in a study of 570 Barrett's oesophagus patients who were investigated across 4.5 years^[112]. The study demonstrated that the use of both pharmacological agents together had an additive protective effect. These findings and suggestions have been replicated in several other studies supporting the potential implementation of chemoprevention into guidelines^[113-118] including one which found that aspirin chemoprevention was more effective and less expensive than endoscopic surveillance alone^[119]. However, there are data which suggest the opposite or discuss it in general^[120-122]. Table 3 summarises all the studies^[113,115-117,121,123]. Nevertheless, at present, the BSG, AGA and ACG guidelines do not recommend chemoprevention.

Anti-reflux surgery

Anti-reflux surgery (fundoplication) has been shown to offer some benefits to patients with Barrett's oesophagus which is mostly symptomatic relief^[124-127]. However, at present, there is conflicting evidence with some studies (including meta-analyses) showing that anti-reflux surgery does not reduce the risk or incidence of adenocarcinoma but others do show a

lower cancer risk^[128-130].

TREATMENT OF DYSPLASIA

In the past, an oesophagectomy was the preferred option for the management of dysplasia in Barrett's oesophagus but nowadays, it can be managed using endoscopic techniques such as ablation or resection. Ablative therapy uses energy to destroy the Barrett's mucosa (without damaging the deeper oesophageal wall) but does not provide a tissue sample.

The most commonly used endoscopic ablative therapy is radiofrequency ablation (RFA) and studies demonstrate that patients with low- and high-grade dysplasia treated with RFA were less likely to undergo malignant progression of their disease than controls^[129]. A meta-analysis looking into the efficacy of radiofrequency ablation found that 91% of patients across 20 studies had complete eradication of dysplastic Barrett's mucosa^[130]. However, recurrence is an issue as a study of 246 patients with high grade dysplasia or intramucosal carcinoma found that despite initial eradication in 80% of cases, neoplastic recurrence was at 25% by 5 years and metaplastic recurrence was 50% by 4 years^[131]. Until recently the role of endoscopic ablation of low grade dysplasia was controversial, but this has changed with the recently published outcomes from the SURF study (Surveillance vs Radiofrequency Ablation)^[132].

This randomized control trial which compared surveillance with radio-frequency ablation for low grade dysplasia. The trial was undertaken at 9 Barrett treatment centres in Europe where eligible patients had confirmed low grade dysplasia Barrett's oesophagus (seen on endoscopy within the previous 18 mo). Patients were excluded if they had previous endoscopic treatment for Barrett's oesophagus, a history of high grade dysplasia or adenocarcinoma, active secondary malignancy, an estimated life expectancy of less than 2 years, and who were under 18 years or over 85 years. Randomization was in 1:1 ratio into either the ablation group or the endoscopic surveillance (control) group.

The trial found that the ablation resulted in a reduced risk of neoplastic progression (high grade dysplasia or adenocarcinoma) over 3 years of follow-up [high grade dysplasia: 1.5% ablation group ($n = 1$) vs 26.5% control group ($n = 18$), $P < 0.001$; and adenocarcinoma: 1.5% ablation group ($n = 1$) vs 8.8% control group ($n = 6$), $P = 0.03$]^[132]. The number needed to treat to prevent one case of high grade dysplasia was 4.0 and adenocarcinoma was 13.6. Moreover, the dysplasia and intestinal metaplasia were completely eradicated and remained so in the majority of patients in the ablation group. The data effectively suggests that ablative treatment is superior to endoscopic surveillance in patients with Barrett's oesophagus and low grade dysplasia. Nevertheless, no patient in the control group had unresectable cancer or cancer-related death.

Table 3 Studies investigating chemoprevention in Barrett's oesophagus

Ref.	Type	Sample size	Chemo-prevention	Effect on risk	Overall
Nguyen <i>et al</i> ^[113] , 2010	Cohort	812	NSAID and aspirin	Filled NSAID/aspirin prescriptions were associated with a reduced risk of oesophageal adenocarcinoma (adjusted incidence density ratio, 0.64; 95%CI: 0.42-0.97) Filled statin prescriptions were associated with a reduction in EAC risk (0.55; 95%CI: 0.36-0.86)	Reduces risk
Corley <i>et al</i> ^[115] , 2003	Meta-analysis of 9 studies	1813	NSAID and aspirin	Protective association between any use of aspirin/NSAID and oesophageal adenocarcinoma (OR = 0.57; 95%CI: 0.47-0.71) Intermittent (OR = 0.82; CI: 0.67-0.99) and frequent medication use were protective (OR = 0.54; 95%CI: 0.43-0.67) Any use was protective against both oesophageal adenocarcinoma (OR = 0.67; 95%CI: 0.51-0.87) and squamous cell carcinoma (OR = 0.58; 95%CI: 0.43-0.78)	Reduces risk
Alexandre <i>et al</i> ^[116] , 2012	Meta-analysis of 2 studies	1382	Statin	Pooled effect size of 0.53 (95%CI: 0.36-0.78, $P = 0.001$, $I^2 = 0\%$) for risk of oesophageal adenocarcinoma with prior statin use	Reduces risk
Alexandre <i>et al</i> ^[116] , 2012	Meta-analysis of 3 studies	35214	Statin	Pooled effect size of 0.86 (95%CI: 0.78-0.94, $P = 0.001$, $I^2 = 0\%$) for risk of oesophageal adenocarcinoma with prior statin use	Reduces risk
Beales <i>et al</i> ^[117] , 2012	Case-control	85	Statin	Regular statin use was associated with a significantly lower incidence of oesophageal adenocarcinoma (OR = 0.45, 95%CI: 0.24-0.84) After NSAID/aspirin confounding correction: OR = 0.57, 95%CI: 0.28-0.94	Reduces risk
Heath <i>et al</i> ^[121] , 2007	Randomised control trial	100	NSAID (celecoxib)	No difference in the proportion of biopsy samples with dysplasia or cancer between treatment groups in either the low-grade (median change with celecoxib = -0.09); or high-grade (median change with celecoxib = 0.12) stratum	No effect
Singh <i>et al</i> ^[123] , 2013	Meta-analysis of 13 studies	9285	Statin	A 28% reduction in the risk of oesophageal adenocarcinoma among patients who took statins (adjusted OR = 0.72; 95%CI: 0.60-0.86)	Reduces risk

NSAID: Non-steroidal anti-inflammatory drug.

Endoscopic resection of specific lesions has been successfully reported (and the resected tissue can be examined by the pathologist). Resection of the entire or circumferential Barrett's mucosa is not recommended due to the risk of stricture formation. It has been reported that complete eradication of high grade dysplasia/early cancer or Barrett's mucosa was achieved in 95% and 89% of patients respectively and the remaining Barrett's mucosa may be treated with ablative therapy^[133].

Nevertheless, there are issues around current ablative therapies which include not having an examinable sample; having to wait for the epithelium to regenerate before repeat sampling can take place and the risk of buried dysplastic or neoplastic cells and glands which have the potential to progress undetected. Moreover, there are risks associated with the procedure itself (pain, bleeding, perforation and stricturing), difficulty in interpreting the sampled findings, and undemonstrated long-term outcomes^[134].

One of the more novel approaches to ablation involves the use of cryotherapy where tissue is rapidly cooled by liquid nitrogen spray or carbon dioxide gas. Studies demonstrate success rates which are comparable to aforementioned ablative techniques in the treatment of Barrett's oesophagus with high-grade dysplasia (complete eradication of dysplasia in 87%-96% of treated patients and complete eradication of intestinal metaplasia in 57%-96% of treated

patients). This success has also been replicated in early-stage oesophageal adenocarcinoma where mucosal cancer was completely eradicated in 75% of patients which included patients that were unsuccessful with other therapies. Cryotherapy is generally tolerated well by patients according to studies but these studies tend to have small sample sizes and short periods of follow-up so the need for more robust studies remains^[135].

FUTURE DEVELOPMENTS

As mentioned earlier, many institutions are not able to undertake full Seattle biopsy protocol systematic biopsies. There are adjuncts but their use is limited because they are only used in specialist institutions in the context of research projects and there is a lack of recommendation in the guidelines.

Biomarkers

The endoscopic detection of Barrett's oesophagus and grading of dysplasia are not as reliable as they could be. The need for reliable biomarkers is critical in being able to distinguish Barrett's oesophagus patients who are at risk of developing oesophageal adenocarcinoma^[136,137]. The number of publications discussing a potential biomarker for Barrett's oesophagus have increase exponentially over the last 30 years from 1 in 1981 to 1069 in total in 2011 which reflects the fact that Barrett's oesophagus needs a

Table 4 Summary of molecular biomarkers predicting malignant progression

Biomarker	Phase	Sample size	End-point
Biomarker panels			
8-gene methylation panel	3	195	High grade dysplasia/adenocarcinoma
DNA content abnormalities and loss of heterozygosity	4	243	Adenocarcinoma
Expert low grade dysplasia, aneuploidy, <i>Aspergillus oryzae</i> lectin	3	380	Adenocarcinoma
DNA content abnormalities			
Aneuploidy/tetraploidy	4	322	Adenocarcinoma
Tumour suppressor loci			
p53 loss of heterozygosity	4	256	Adenocarcinoma
p53 staining	4	48	High grade dysplasia/adenocarcinoma
Epigenetics			
P16 methylation	3	53	HD/adenocarcinoma
Proliferation			
Mcm2	3	27	Adenocarcinoma
Clonal diversity			
Clonal diversity measures	4	239	Adenocarcinoma
Cell cycle markers			
Cyclin A	3	48	High grade dysplasia/adenocarcinoma
Cyclin D1	3	307	Adenocarcinoma
Serum biomarkers			
Leukocyte telomere length	4	300	Adenocarcinoma
Selenoprotein P	4	361	Adenocarcinoma

clinically validated prognostic tool such as an effective biomarker to aid in defining risk.

The Early Detection Research Network has recommended five phases of study before a biomarker can be used clinically^[138]. Phase 1 is exploratory to identify markers, phase 2 is for the development of a clinical assay, phase 3 is for retrospective validation, phase 4 is for prospective validation and phase 5 is to test the biomarker on the population with the disease. At present, most biomarkers are in phase 3 and 4. Preclinical studies have been successful in detecting certain biomarkers which contribute to the malignant progression of Barrett's oesophagus but their widespread clinical use is very limited by differences in reproducibility, low sample sizes and the need for multi-centre prospective studies^[139-141]. Table 4 is a summary of the biomarkers studied to date^[137,142].

Overall, the desire to predict which Barrett's oesophagus patients will progress to oesophageal adenocarcinoma is palpable but remains a target and not a reality. The ideal biomarker as with all potential screening options should be cost-effective, minimally invasive, easily administered and have comparable or superior outcomes to what biopsies currently offer. More work is necessary to ensure that successful biomarkers are smoothly translated into widespread clinical practice.

Metabolomics

Metabolomics is the scientific study of the set of metabolites present within an organism, cell, or tissue and they could play a role in the discovery for a biomarker in Barrett's oesophagus as they are key players in biological systems which are disrupted in disease^[143]. A study using urinary metabolomics found that it was possible to separately distinguish Barrett's

oesophagus and oesophageal adenocarcinoma from controls as they had different urinary signatures^[143]. This suggests that urinary metabolomics and other may have a future role in the pursuit of a non-invasive screening option for Barrett's oesophagus.

Virtual biopsies

Studies have worked on trying to differentiate squamous and columnar epithelia based on their electrical characteristics using electrical impedance *via* a probe^[144]. The aim is to reduce discrepancy from inter- and intra-observer variability by having an objective measurement to categorise the epithelium. Magnification endoscopy provides an even more detailed image by optically enlarging the mucosal surface area and studies found that low and high grade dysplasia were consistently identified in Barrett's using this technique but missed using standard endoscopy alone^[145]. Confocal laser endomicroscopy (CLE) is a novel technique combining standard white light endoscopy with confocal laser microendoscopy^[146]. CLE has demonstrated a high diagnostic value for digestive diseases including Barrett's oesophagus^[147-151].

CONCLUSION

Progress has been made in further understanding Barrett's oesophagus since it was first described in 1950. It is a large and increasing health problem with multiple modifiable risk factors, yet there remain several unanswered questions regarding a formal definition, diagnostic criteria, and screening and surveillance needs and methods. Although endoscopy with systematic biopsy and standard pathological examination is currently the mainstay of screening and surveillance for Barrett's oesophagus,

there is still the need for a more cost-effective, less invasive, less cumbersome and more reliable way to conduct diagnosis, screening and surveillance. Primary prevention of Barrett's oesophagus and adenocarcinoma is also of huge interest and potential with studies focussing on the medical treatment of reflux, chemoprevention and anti-reflux surgery.

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