

## Barrett's oesophagus

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Barrett's oesophagus is a metaplastic change of the lining of the oesophagus, such that the normal squamous epithelium is replaced by specialised or intestinalised columnar epithelium. The disorder seems to be a complication of chronic gastro-oesophageal reflux disease, although asymptomatic individuals might also be affected, and it is a risk factor for the development of oesophageal adenocarcinoma, a cancer with rapidly increasing incidence in developed societies. We review the presentation, epidemiology, and risk factors for this condition. We discuss the molecular changes necessary for the development of Barrett's oesophagus and its progression to cancer, and new strides in both the endoscopic detection of the lesion and the treatment of dysplastic disease. Also, we assess the effectiveness of efforts to screen patients at risk of Barrett's oesophagus, and whether such efforts avert cancer death. We conclude with a discussion of future directions for research, focusing on treatment of early neoplasia, and modifications of current practices to show our evolving understanding of this condition.

### Introduction

Barrett's oesophagus is a metaplastic change of the lining of the oesophageal mucosa, such that the normal squamous epithelium is replaced with specialised or intestinalised columnar epithelium.<sup>1,2</sup> Intestinal metaplasia is clinically significant because it is associated with heightened risk of oesophageal adenocarcinoma, which has substantially increased in incidence in developed populations. Barrett's oesophagus is associated with symptoms of chronic gastro-oesophageal reflux disease (GERD), such as heartburn and regurgitation.<sup>3</sup> This association led to calls for routine upper gastrointestinal endoscopy for all patients with chronic GERD to detect Barrett's oesophagus and prompt subsequent surveillance endoscopies to assess progression to cancer.<sup>4</sup> Although such an approach is intuitively appealing, how well screening and surveillance endoscopy works is uncertain, and the associated costs are large and poorly described.<sup>5</sup>

### Clinical presentation

The diagnosis of Barrett's oesophagus should satisfy two criteria.<sup>6,7</sup> First, examination by upper endoscopy should show cephalad displacement of the squamocolumnar junction. Normally, the squamocolumnar junction should coincide with the most distal extent of the tubular oesophagus (figure 1A). The intersection of the squamous epithelium of the tubular oesophagus (figure 1B) and the columnar epithelium of

the stomach is termed the Z line, because of the jagged appearance of the interface. Usually, the Z line is easily identified from the colour difference between the epithelia: normal squamous epithelium is white or very light pink, whereas columnar epithelium is salmon-coloured. In Barrett's oesophagus, salmon-coloured epithelium projects into the tubular oesophagus. These projections might present as tongues of tissue (figure 1C), or as circumferential involvement of the mucosa (figure 2), or both. The second criterion for diagnosis is intestinalised epithelium, or epithelium containing goblet cells (figure 1D), in a biopsy specimen of the tubular oesophagus. Whether identification of goblet cells in the metaplastic epithelium is necessary for diagnosis is debatable—US societies and authorities require identification<sup>6,7,8</sup> but the British Society of Gastroenterology does not.<sup>9</sup> Metaplastic tissue with or without goblet cells has been termed columnar lined epithelium. For clarity, oesophageal epithelium with the endoscopic appearance of Barrett's oesophagus, but without histological confirmation, should be termed endoscopically suspected oesophageal metaplasia.<sup>10</sup>

The length of the displaced squamocolumnar junction should be measured during endoscopy: longer than 3 cm is long-segment Barrett's oesophagus; 3 cm or shorter is short-segment Barrett's oesophagus.<sup>11,12</sup> Previously, investigators have suggested that short segments are not clinically significant, but other research has shown an increased cancer risk in even short-segment disease compared with the general population.<sup>11,13</sup> Therefore, the most common current definition of Barrett's oesophagus is salmon-coloured mucosa of any length in an oesophagus harbouring goblet cells.

Is the presence of goblet cells or intestinal metaplasia in a biopsy specimen of a normal-appearing Z line associated with an increased risk of adenocarcinoma of the oesophagus or the gastric cardia? In patients with GERD symptoms but no endoscopic evidence of Barrett's oesophagus, almost 20% had intestinal metaplasia in a biopsy sample of their Z line.<sup>14</sup> A substantial number of these patients were believed to have a squamocolumnar line that was straight and unwavering. 10–17% of patients

### Search strategy and selection criteria

We searched Medline (1950–March, 2008), the Cochrane Library (1993–March, 2008), and Embase (1966–March, 2008) using the search terms "Barrett's esophagus" or "Barrett esophagus", "specialized epithelium", "columnar-lined esophagus", and "intestinalized epithelium". We also searched for "oesophageal adenocarcinoma" and "adenocarcinoma of the esophagus" combined with the terms "prevention", "pathogenesis", "pathophysiology", "diagnosis", and "epidemiology". No language restrictions were placed on the searches. We focused on original contributions, systematic reviews, and meta-analyses published in the past 5 years, but we also included reviews, editorials, and older publications that we judged to be relevant. We searched the reference lists of selected articles identified by the search strategy. The date of the last search was November, 2008.

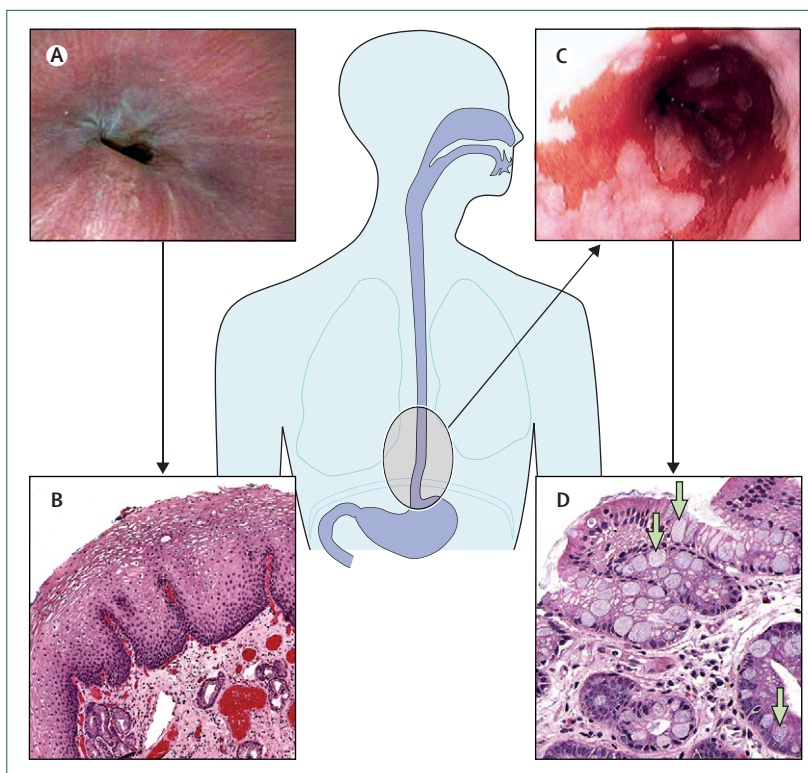
undergoing routine upper endoscopy, without endoscopic irregularity or a history of reflux symptoms, had intestinal metaplasia in a biopsy sample.<sup>15</sup> The cause and natural history of this lesion is unclear but seems to be benign, with a low rate of progression to dysplasia in the cardia.<sup>16</sup> Whether patients presenting with goblet cells or intestinal metaplasia, in an otherwise normal Z line, should routinely be entered into endoscopic surveillance programmes is also unknown. The common nature of this presentation, and the small number of oesophageal adenocarcinomas and cardia cancers, suggests that the increased risk of cancer in this population, if any, is nominal. For this reason, routine endoscopic biopsies of a normal-appearing gastro-oesophageal junction in patients with GERD symptoms are not recommended.

### Natural history

The risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus is low, about 0.5% per patient-year,<sup>17-19</sup> and most die with the disorder, not as a result of it. If Barrett's oesophagus does progress, it seems to do so through a series of cellular changes, ranging between non-dysplastic disease, low-grade dysplasia, high-grade dysplasia, and oesophageal adenocarcinoma. Patients with Barrett's oesophagus under endoscopic surveillance who develop cancer often do so without detection of each of these stages by biopsy. Whether there are problems with biopsy detection, or some patients skip from non-dysplastic disease or low-grade dysplasia to cancer, is unknown. Not surprisingly, a high level of dysplasia portends a raised risk of adenocarcinoma, such that patients with high-grade dysplasia might have cancer rates of 10% or greater per patient-year.<sup>20-22</sup>

### Epidemiology

Barrett's oesophagus is highly prevalent in the general population and especially in people with chronic reflux conditions, but in some patients the condition is asymptomatic. Policy decisions regarding endoscopic screening and understanding of the cancer risk partly depend on the prevalence of Barrett's oesophagus in the general population. In 1990, the prevalence in Olmsted County, MN, USA, was about 376 cases per 100 000 population, from almost 1000 unselected autopsies.<sup>23</sup> This number was 21-fold higher than the clinically recognised cases in the county, suggesting that many, if not most, patients with Barrett's oesophagus remained unrecognised. A rigorous Swedish study<sup>24</sup> of adults showed that the overall prevalence was 1.6%, about a third of which was long-segment disease. More than 40% of the patients with Barrett's oesophagus reported no reflux disease and the investigators were unable to consistently identify risk factors for Barrett's oesophagus in asymptomatic patients from demographic or symptom-questionnaire data. In studies of simultaneous endoscopy in healthy patients undergoing screening colonoscopy for colorectal cancer, the prevalence



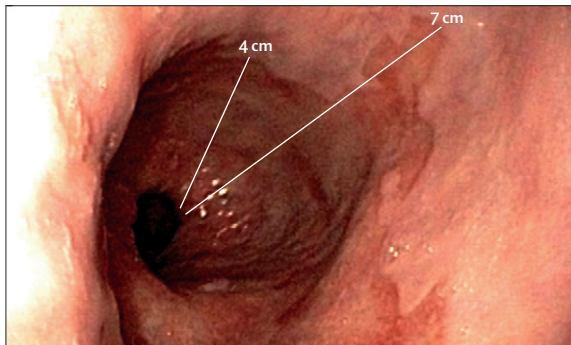
**Figure 1: Normal oesophagus versus Barrett's oesophagus**

(A) Normal appearance of squamocolumnar junction at gastro-oesophageal junction. (B) Normal oesophageal squamous mucosa. (C) Tongues of Barrett's oesophagus radiating orad from the gastro-oesophageal junction. (D) Biopsy specimen of intestinal metaplasia (arrow points to goblet cell).

ranged from 5.6% in a US midwestern population,<sup>25</sup> to 15–25% in elderly people<sup>26</sup> and veterans.<sup>27</sup>

Although the prevalence in the general population is substantial, it is much higher in patients undergoing upper endoscopy to investigate chronic reflux symptoms, at 5–15%.<sup>28-31</sup> The risk and segment length of Barrett's oesophagus increase with the amount of acid exposure in the distal oesophagus, and are both associated with the presence and size of hiatal hernias.<sup>32-35</sup> Unfortunately, symptoms of GERD are a poor predictor of Barrett's oesophagus,<sup>28,36</sup> and little or no correlation with heartburn symptom severity has been recorded.<sup>37</sup> Symptom frequency and symptom chronicity (total number of years with reflux symptoms) are, however, better predictors of the presence of disease than symptom severity.<sup>3,38</sup>

Other demographic predictors of the presence of Barrett's oesophagus in patients with chronic heartburn symptoms include sex, age, and ethnicity. Even after controlling for the severity of reflux disease, white men have increased risk of disease, as do elderly people.<sup>24,31,36</sup> The reason for this predisposition is unclear, and, so far, the genetic predeterminants of the condition remain obscure.<sup>39</sup> Other potential risk factors include tobacco use and dietary habits.<sup>32,40</sup> Unlike squamous cell carcinoma of the oesophagus, alcohol abuse and chronic tobacco use are at best minor risk factors.<sup>24,40-42</sup> Whether



**Figure 2: Circumferential and non-circumferential involvement of the distal oesophagus with Barrett's oesophagus**

The lines indicate 4 cm of circumferential involvement in the distal oesophagus, and 7 cm of maximum involvement (C4M7 segment by the Prague classification).

use of non-steroidal anti-inflammatory drugs (NSAID) is associated with a decreased risk of Barrett's oesophagus is also unclear, although some cohort and case-control data suggest that the prevalence is diminished by past chronic NSAID exposures. Such data are, however, susceptible to confounding by other unmeasured health habits, and a recent attempt to show a protective effect of inhibitors of cyclo-oxygenase 2 (coxibs) against cancer, in a Barrett's oesophagus population, was unsuccessful.<sup>43</sup>

### Pathogenesis

Whether Barrett's oesophagus is hereditary is unknown. Several reports suggest that a higher proportion of first-degree relatives of patients with Barrett's oesophagus have the condition than might be expected by chance,<sup>39,44</sup> but no gene has been identified and such data are probably subject to detection bias. The risk of both Barrett's oesophagus and oesophageal adenocarcinoma has long been known to be related to body-mass index (BMI). Increasing BMI is also associated with a statistically significant rise in the risk of GERD symptoms and erosive oesophagitis,<sup>45</sup> progressively heightening the risk of GERD complications,<sup>15</sup> and even a small rise in BMI increases the probability of reflux symptoms.<sup>46</sup> A cross-sectional study estimated that visceral abdominal tissue was on average 1.5-fold greater in patients with Barrett's oesophagus than in controls.<sup>47</sup> Case-control studies also showed the importance of central adiposity in development of the condition.<sup>48,49</sup> A population-based case-control study recorded a strong association between Barrett's oesophagus and increasing waist-to-hip ratio.<sup>49</sup> In fact, when the researchers controlled for this ratio, the association between BMI and Barrett's oesophagus was almost completely attenuated, suggesting that the high risk of disease from increased BMI was mediated through central adiposity.

How might central obesity contribute to the development of Barrett's oesophagus? One explanation is that patients with central obesity are predisposed to hiatal hernia.<sup>50,51</sup> Additionally, intragastric pressure increases with obesity, a factor promoting reflux. Perhaps more compelling is a possible hormonal explanation. Patients with central

obesity have high concentrations of insulin and insulin-like growth factor 1 (IGF1), which promote cell proliferation and determine cell differentiation. The patients also have different adipokine profiles. These peptides are active in mediating cell inflammation and apoptosis.

In view of the increased prevalence of the condition in patients with chronic reflux, some have postulated that the initiating event might be an initial erosive reflux episode, denuding the oesophagus of normal epithelium and allowing it to become repopulated with columnar epithelium. In dogs,<sup>52</sup> high acid output produced by repeated histamine injections resulted in epithelial metaplasia and Barrett's oesophagus formation. Clinical studies have confirmed the presence of severe GERD in patients with the condition.<sup>53</sup> In general, these patients have greater decreases in lower oesophageal sphincter pressures and more oesophageal dysmotility than do patients with erosive oesophagitis or non-erosive disease, and more than 90% have substantially abnormal pH tests.<sup>53</sup> Other workers report that patients with Barrett's oesophagus have long exposure to caustic concentrations of gastric acid (pH<3.0 or 2.0),<sup>54</sup> high proximal extent of acid reflux in long-segment disease,<sup>34</sup> and high frequency of hiatal hernias (76% in Barrett's oesophagus vs 36% in reflux patients).<sup>32</sup> Bile in the stomach and bile reflux, which is usually associated with acid reflux, is more common in Barrett's oesophagus patients than in other forms of GERD.<sup>55</sup>

These studies suggest the possibility of a synergy between acid and bile in the development of Barrett's oesophagus, although bile without acid does not seem to contribute.<sup>56</sup> Supporting this hypothesis, laboratory studies in oesophageal cells showed that short exposures to bile acids and low pH resulted in oxidative stress and DNA damage.<sup>57</sup> These alterations might underlie the development of Barrett's oesophagus and tumour progression. Animal models show that anatomic alteration, leading to pathological amounts of acid and bile reflux, culminates in the development of specialised epithelium in the tubular oesophagus.<sup>58,59</sup> Continued epithelial injury results in cancer development in many of these animals.

Another important environmental factor might be *Helicobacter pylori* infection. Such infection might decrease intragastric acidity by generating large amounts of ammonia, or cause severe corpus gastritis with destruction of parietal cells and thereby reduce acid output, or both.<sup>60</sup> Infection with CagA<sup>+</sup> strains of *H pylori* is associated with high grades of gastric inflammation and increased propensity to develop gastric atrophy and intestinal metaplasia.<sup>61</sup> Especially in east Asia, but also in the USA and Europe, coexisting *H pylori* infection has protected from the development of erosive oesophagitis and even Barrett's oesophagus.<sup>62</sup> The diminishing prevalence of *H pylori* infection in developed countries is temporally associated with an increased incidence of GERD complications, including Barrett's oesophagus.<sup>63</sup>

|                                 | American College of Gastroenterology <sup>7</sup>   | American Society for Gastrointestinal Endoscopy <sup>8</sup>  | American Gastroenterological Association <sup>9</sup>   | British Society of Gastroenterology <sup>9</sup>  |
|---------------------------------|---|---|---|---|
| Date                            | 2008  | 2006  | 2005  | 2005  |
| Clinical presentation           | Visible columnar epithelium and histological confirmation from tubular oesophagus, excluding intestinal metaplasia of the cardia  | Intestinal metaplasia of distal tubular oesophagus of any length  | ..  | Visible columnar epithelium and histological confirmation of columnar tissue  |
| Screening of patients with GERD | Usefulness remains to be established; recommendations should be individualised to the patient   | Consider for patients with chronic long-standing GERD   | Might be useful for patients aged over 50 years and with heartburn symptoms   | Not for patients with chronic heartburn; screen patients presenting with alarm features associated with chronic reflux (eg, dysphagia, recurrent vomiting, weight loss, or anaemia)   |
| Diagnosis                       | Histological confirmation of intestinal metaplasia from biopsies of abnormal-appearing oesophageal mucosa   | Histological confirmation of intestinal metaplasia from biopsies, followed by classification of biopsy specimens as carcinoma, high-grade dysplasia, low-grade dysplasia, indefinite dysplasia, or no dysplasia   | Histological confirmation of Barrett's oesophagus in biopsy specimens   | Histological confirmation of columnar (but not necessarily intestinalised) metaplasia from biopsy specimens of visibly abnormal epithelium above the gastro-oesophageal junction  |
| Surveillance                    |   |   |   |   |
| No dysplasia                    | Two oesophageal examinations with biopsy within 1 year and follow up with endoscopy every 3 years   | Two consecutive oesophageal examinations within 1 year and follow up with endoscopy every 3 years   | Assess within 1 year and if no dysplasia, defer for 5 years or until cancer therapy is not possible or life expectancy is limited   | Surveillance every 2 years, if appropriate  |
| Indefinite dysplasia            | ..  | Repeat biopsy after 8 weeks of acid suppression, if evidence of acute inflammation due to gastro-oesophageal acid reflux  | ..  | Assess with extensive biopsies after course of proton pump inhibitors and return to routine surveillance, if no definite dysplasia at 6 months  |
| Low-grade dysplasia             | Treat based on highest grade of dysplasia seen on two oesophageal examinations within 6 months, with pathologist's confirmation, and follow up with endoscopy every year until dysplasia is absent on two subsequent examinations   | Follow up after 6 months with concentrated biopsies in area of dysplasia; follow up every 12 months thereafter if dysplasia persists  | Assess in 1 year and re-examine every year if dysplasia is confirmed by two pathologists (if there is disagreement about the presence of dysplasia then re-examine in 2 years)  | Extensive biopsy after intensive acid suppression for 8–12 weeks; surveillance every 6 months if dysplasia persists; surveillance intervals of 2–3 years if regression occurs on two sequential examinations                    |
| High-grade dysplasia            | Document any mucosal irregularities, repeat oesophageal examination with biopsy within 3 months, with pathologist's confirmation, to eliminate the possibility of cancer; follow up with endoscopic mucosal resection in the case of any mucosal irregularity; then intensive endoscopic surveillance every 3 months or an intervention, such as oesophagectomy or ablation, in the case of flat mucosa | Diagnosis should be confirmed by a pathologist; surgical candidates can choose to have surgery or endoscopic therapy; follow up patients who choose surveillance every 3 months for 1 year with several large biopsies every 1 cm along oesophagus; after 1 year without cancer detection, surveillance duration can be lengthened, provided dysplastic changes are absent on two subsequent examinations | Diagnosis should be confirmed by two pathologists; patients should be treated with surgical resection or endoscopic therapy; surveillance can be offered provided follow up with endoscopy is every 3 months with a minimum of eight biopsies every 2 cm along the oesophagus | Oesophagectomy recommended if changes persist after intensive acid suppression, if confirmed by two pathologists, and if patient considered fit for surgery; if unfit for surgery, use endoscopic ablation or mucosal resection |
| Therapy                         | Control symptoms of GERD  | ..  | Lifestyle modifications to decrease cancer risk   | Dose-escalation of proton pump inhibitors until satisfactory symptom response and healing   |
| Biopsy sampling                 | Quadrant biopsies every 2 cm in columnar segment  | Several systematic biopsies; biopsy of any macroscopic lesions; consider jumbo forceps (especially for dysplasia) and general approach of quadrant biopsies every 2 cm  | Random biopsies; four specimens every 1–2 cm; additional specimens from mucosal abnormalities; jumbo forceps not recommended for surveillance   | Quadrant biopsies every 2 cm in columnar segment and biopsies of any visible lesions  |

GERD=gastro-oesophageal reflux disease.

**Table: Guidelines for the evaluation and management of Barrett's oesophagus**

However, poorly described host factors are probably also important because many patients will develop severe recurrent erosive disease but not Barrett's oesophagus. The dramatic metaplastic changes in the intercellular protein composition of the tight junctions in the epithelium result in a more acid-resistant lining in Barrett's oesophagus patients than in healthy individuals.<sup>64</sup> Therefore, development of the condition might actually represent short-term adaption, by decreasing the complications of chronic reflux such as bleeding and structuring.

The molecular changes underlying the morphological change of Barrett's oesophagus are being elucidated.

Polymorphisms in genes that are important in the inflammatory response (including cytokine polymorphisms), DNA repair, and chemical detoxification are associated with the presence or progression of the condition.<sup>65–67</sup> Since the heritability is weak and does not correspond to any commonly recognised patterns, the condition is probably a polygenic trait rather than a single gene mutation. Studies assessing gene expression in Barrett's oesophagus compared with squamous tissue suggest that different cellular pathways are activated in metaplasia.<sup>68–70</sup> For example, the *CDX2* gene seems to be important in differentiation of gastrointestinal cells,<sup>68</sup> and

transgenic animals induced to overexpress this gene develop aberrant intestinal metaplasia, whereas knockouts actually show abnormal islands of squamous tissue in the small intestine. Some data suggest that epigenetic changes are partly responsible for abnormal genetic expression that might spur the development of Barrett's oesophagus. For example, demethylation of the promoter regions of *CDX2* might allow expression of this gene in a previously quiescent cell line, inducing intestinalised differentiation of the progeny cells.<sup>69</sup> Such a mechanism might be a link between genetic mechanisms and environmental exposures. For example, epithelial exposure to duodenal contents affects the expression of *Cdx2* in animal models.<sup>70</sup>

The progenitor cell from which Barrett's oesophagus develops is unclear. Candidates include progenitor cells resident in the submucosal glands or the interbasal layer of the epithelium, bone-marrow-derived stem cells, or transdifferentiated squamous cells.<sup>71</sup> A multilayer epithelium with cell markers of both squamous and columnar epithelium might precede the disease.<sup>72</sup> Animal models show that Barrett's oesophagus can develop in the absence of directly contiguous columnar epithelium,<sup>58</sup> which makes migration of columnar cells seem less probable.

## Diagnosis

### Standard endoscopic screening

Endoscopy is the suggested method for diagnosis, but the results need to be confirmed by histological examination of an endoscopic biopsy specimen. Other methods such as barium study or CT do not have sufficient sensitivity for detection. Patients with chronic reflux symptoms should be screened for Barrett's oesophagus by upper endoscopy only after the patient has been on acid suppression with a proton pump inhibitor for at least 4 weeks. Although pretreatment with a proton pump inhibitor will reduce the probability of identifying erosive oesophagitis during the examination, inflammation of the distal oesophagus can obscure Barrett's oesophagus. As much as 12% of short-segment disease can be missed because of severe erosive oesophagitis.<sup>73</sup> During this endoscopy, the length of the displaced squamocolumnar junction should be measured. The proximal squamocolumnar junction extension is often circumferential, but especially in the case of short-segment disease, it can be tongues of columnar mucosa. To identify the most distal extent of the Barrett's oesophagus, the most proximal end of the gastric folds should be identified endoscopically. Additionally, the mucosal capillary loops have a characteristic pattern that can be recognised on narrow-band endoscopy.<sup>74</sup>

An international working group proposed and validated an endoscopic classification system for Barrett's oesophagus.<sup>75</sup> The Prague C and M criteria assess the circumferential (C) and maximum (M) extent of the endoscopically visualised Barrett's oesophagus segment, above the gastro-oesophageal junction, assessed with

minimum insufflation (figure 2). The overall inter-observer reliability coefficient for the assessment of the C and M extent was 0.95 and 0.94, respectively. The overall reliability coefficient for endoscopic recognition of Barrett's oesophagus of 1 cm or more was moderate (0.72), but only fair (0.22) for Barrett's oesophagus of less than 1 cm.

The diagnosis should be confirmed by random biopsies throughout the length of the suspected Barrett's oesophagus to identify intestinal metaplasia with goblet cells from samples stained with haematoxylin and eosin. In cases of uncertainty, alcian blue pH 2.5 stain will reveal goblet cells.<sup>76</sup> Some workers<sup>77</sup> suggest that eight random biopsies should be done to enhance the probability of identifying intestinal metaplasia. Histological confirmation of disease varies with the length of columnar-appearing mucosa identified at endoscopy, with suspected short-segment disease confirmed in only about 25% of cases and long-segment disease confirmed in 44–80% of cases.<sup>78</sup> More than 20% of patients without confirmation of intestinal metaplasia at initial endoscopy have it at later endoscopy,<sup>79</sup> probably because of sampling error or interim development of intestinal metaplasia after the first examination.

Unfortunately, the reliability of the histological grading of Barrett's oesophagus is poor. The agreement between pathologists of the degree of dysplasia is often poor to moderate ( $\kappa=0.2-0.6$ ), and only marginally improved by education.<sup>80,81</sup> Much of this difficulty is caused by the small size of the biopsy samples provided for review, lack of consensus on boundaries demarcating degrees of dysplasia, and the difficulty of discerning the degree of dysplasia in patients with concurrent inflammation of the oesophagus, which is often the case in those with chronic reflux symptoms.

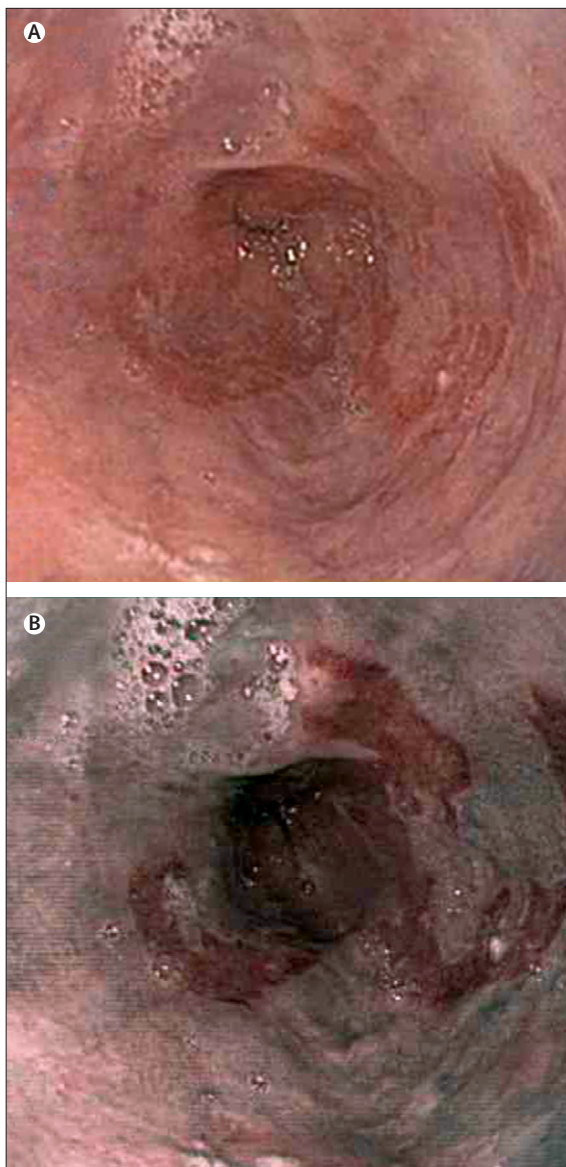
Debate continues about the usefulness of endoscopic screening programmes, which are designed to identify patients with Barrett's oesophagus from among those with chronic GERD, and endoscopic surveillance programmes, which are designed to monitor patients with Barrett's oesophagus for progression to cancer. Several professional organisations have released guidelines endorsing screening and surveillance endoscopy, which provide suggested intervals for periodic endoscopies (table). Proponents of these guidelines draw attention to the rapid increase in the incidence of oesophageal adenocarcinoma, the strong evidence associating chronic GERD symptoms with the presence of Barrett's oesophagus, and the increased risk of cancer. However, sceptics point to the enormous number of patients with chronic reflux symptoms who would need to be screened, the small absolute risk of cancer in individual patients with GERD, the expense of the screening test, and the unproven nature of the intervention.<sup>2</sup>

Despite no direct evidence in favour of endoscopic screening and surveillance, this practice is common in the USA and the UK.<sup>82</sup> The cost-effectiveness of

endoscopic screening and surveillance is unknown, and depends on poorly described factors such as the accuracy of the test to diagnose Barrett's oesophagus, the risk of cancer in patients with the condition, and the cost of endoscopy and histological analysis.<sup>83,84</sup> One analysis suggested that, although one screening endoscopy was highly cost-effective, subsequent surveillance endoscopies in patients whose biopsies showed only Barrett's oesophagus with no dysplasia were very cost-ineffective, adding only a few extra days of life expectancy at an extra cost of thousands of US dollars.<sup>85</sup>

Efforts have been made to supplant conventional endoscopy for screening of patients who have chronic GERD. Balloon cytology, independently of endoscopy, has been done with a disappointing yield of diagnostic goblet cells in only 24% of 63 patients.<sup>86</sup> A more abrasive balloon might generate a higher yield. Another alternative to upper endoscopy is small calibre, transnasal endoscopy. In this approach, endoscopy is done on an unsedated patient with a 5–6 mm instrument passed through the nares, into the pharynx, and down into the oesophagus. In a randomised crossover study<sup>87</sup> of 121 patients undergoing endoscopy for screening and surveillance of Barrett's oesophagus, the prevalence of disease was similar between conventional endoscopy (26%) and unsedated small-calibre endoscopy (30%); the level of agreement between the two approaches was moderate ( $\kappa=0.591$ ). Each method detected four cases of low-grade dysplasia, with concordance in one case, despite the fact that the small-calibre endoscope extracted smaller tissue samples. More than 70% of the patients preferred small-calibre endoscopy, which can eliminate the need for monitoring, recovery time, loss of work time, and an accompanying driver. One difficulty with this approach is the absence of adequate tissue sampling for histological confirmation of the diagnosis.

Another method under assessment is capsule endoscopy. A specialised capsule has been designed to obtain large numbers of photographs (up to 14/s) from both ends of the capsule, as it passes through the oesophagus. In a single-centre prospective study<sup>88</sup> of 90 patients undergoing screening or surveillance for Barrett's oesophagus, capsule endoscopy was 67% sensitive and 84% specific for identification, diagnosing 14 of 21 cases who were confirmed by biopsy. Sensitivity for short-segment and long-segment disease was similar. However, the diagnostic accuracy of this non-invasive technique is limited by excessive debris or bubbles obscuring the Z line, and the small number of frames in which the gastro-oesophageal junction is clearly visible. Somewhat improved operating characteristics of capsule endoscopy were seen in 89 patients by French investigators,<sup>89</sup> who reported excellent specificity and negative predictive value, but suboptimum sensitivity. In its current state, the technique might not be cost-effective compared with standard endoscopy for the detection of Barrett's oesophagus in patients with chronic GERD.<sup>90,91</sup>



**Figure 3:** Endoscopic (A) white light and (B) narrow-band imaging of non-dysplastic Barrett's oesophagus. Small islands and tongues are clearly seen in B.

One way to increase the diagnostic effectiveness and cost-effectiveness of conventional endoscopic screening and surveillance would be to improve the accuracy of the examination. Random biopsy samples cover only a small portion of the lesion. Techniques are being developed to optically scan large areas of mucosa for possible neoplasia accurately and effectively to identify suspicious areas for further characterisation.

#### Advanced endoscopic imaging

Chromoendoscopy is a simple technique involving the application of chemical agents to improve the characterisation of mucosal surfaces either by selective uptake (vital staining with methylene blue or Lugol's

solution) or enhancement of mucosal surface pattern (contrast staining with indigo carmine and acetic acid). Of these stains, methylene blue is the most popular, staining non-dysplastic intestinal metaplasia blue but not binding to the mucosa if there is high-grade dysplasia or cancer present.<sup>92</sup> Results have been mixed, and prospective cross-over studies have shown methylene blue chromoscopy to be no better, and in some cases worse, than random four-quadrant biopsies for the detection of dysplasia.<sup>93,94</sup> Problems associated with this technique include difficulty in achievement of complete and even coating of the mucosa, the additional time required for dye spraying, and an inability to detect superficial vascular patterns. Contrast agents such as crystal violet, indigo carmine, and acetic acid enhance the detection of mucosal patterns when they are combined with high-resolution endoscopy,<sup>95</sup> but are not used widely.

Another technique to scan large areas of the mucosa for possible neoplasia is narrow-band imaging. This technique improves contrast by narrowing the band of white light, filtering it into two major colours (blue and green) which are then better absorbed by blood vessels in the mucosa and submucosa (figure 3). Narrow-band imaging combined with high-resolution endoscopy produces detailed images of the mucosal and vascular surface patterns within the Barrett's oesophagus segment, and identifies characteristic patterns for non-dysplastic intestinal metaplasia, high-grade dysplasia, and early cancer.<sup>96</sup> In a study of 51 patients with the condition,<sup>97</sup> seven of whom had high-grade dysplasia, the sensitivity of narrow-band imaging for detecting non-dysplastic intestinal metaplasia was 93.5% and for detection of high-grade dysplasia, an irregular or distorted pattern was 100% sensitive and 98.7% specific. Narrow-band imaging was unable to distinguish intestinal metaplasia from low-grade dysplasia. However, a Dutch study<sup>98</sup> failed to show that the addition of either narrow-band imaging or vital staining to standard endoscopy improved the identification of dysplasia.

Another technique to improve standard endoscopy is autofluorescence, which uses blue light to detect naturally occurring fluorescence from tissue. Neoplastic mucosa in Barrett's oesophagus tends to appear blue-violet, whereas non-dysplastic tissue appears green.<sup>99</sup> Hence, narrow-band or autofluorescence imaging, in combination with standard endoscopy, might provide accurate visualisation of inapparent or subtle mucosal abnormalities associated with high-grade dysplasia or cancer, without the inconvenience or mess of chromoendoscopy.

Optical coherence tomography produces high-resolution cross-sectional images of tissue *in vivo*. The technique is analogous to ultrasound imaging, but uses infrared light rather than acoustic energy, and has a ten-fold higher resolution than does high-frequency ultrasound, though the maximum depth of optical coherence tomography is lower than with ultrasound imaging.<sup>100</sup> In a prospective double-blind study<sup>101</sup> of 33 patients, the technique had an

accuracy of 78% for the detection of dysplasia in patients with Barrett's oesophagus. However, the diagnostic accuracy for the four academic endoscopists ranged from 56% to 98%.<sup>101</sup> Laser confocal microscopy can magnify the mucosa more than 1000-fold and actually image cellular structures. In a study of 63 patients with Barrett's oesophagus and associated neoplasia,<sup>102</sup> laser confocal microscopy had an accuracy of 97.4% for detection of neoplasia. Potentially, these new techniques could provide true optical biopsy specimens and decrease or eliminate the need for processing and interpretation of mucosal biopsy specimens.

### Management

Barrett's oesophagus is associated with a decreased quality of life compared with the general population.<sup>103</sup> Patients misunderstand and overestimate the cancer rates associated with their condition.<sup>104</sup> A US study<sup>105</sup> showed that in patients diagnosed with Barrett's oesophagus, despite a life-expectancy similar to age-matched and sex-matched controls, their life-insurance premiums increased by more than 100%. Patients considering endoscopy screening for the condition should be informed of these risks before the procedure.

Cohort studies show that most patients with Barrett's oesophagus do not progress past non-dysplastic disease or transient low-grade dysplasia.<sup>20</sup> In most long term studies, fewer than 10% of patients progress to high-grade dysplasia or cancer.<sup>20</sup> For this reason, the consensus among recommending organisations is that patients with non-dysplastic disease or low-grade dysplasia should be managed conservatively, with periodic surveillance endoscopy.<sup>7,9</sup>

Substantial debate surrounds the most appropriate management for patients with high-grade dysplasia, since they are at considerably increased risk of the disease progressing to cancer, with yearly rates of 4%, 2.2%, and 11.8% in some studies.<sup>20,106,107</sup> As a result, intervention is often considered in this population. Three strategies are in common use: surgical oesophagectomy, observation with frequent surveillance endoscopy, and endoscopic therapy.

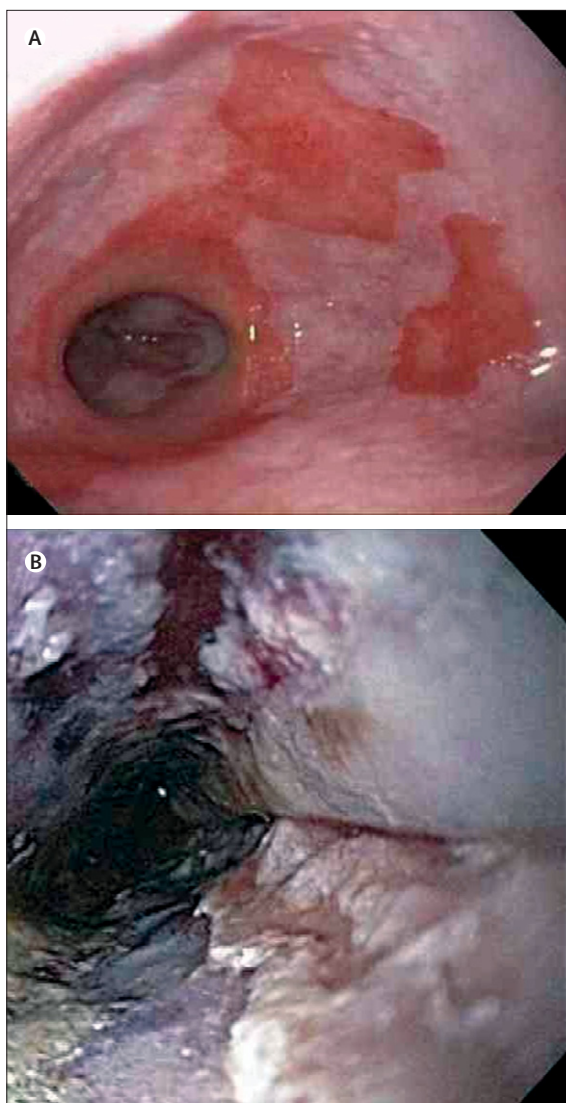
Proponents of surgery note the high risk of previously undetected microscopic foci of cancer, which are identified in the resection specimens of patients undergoing oesophagectomy; surgical series have reported occult cancer rates in such specimens of 10–50%.<sup>108,109</sup> However, the preoperative biopsy protocols are not well described in these studies, and other authorities have questioned the definition of invasive cancer.<sup>110</sup> Also, oesophagectomy is highly operator-dependent. By contrast with expert centres, in which mortality rates are 5% or lower,<sup>111,112</sup> oesophagectomy can carry a high morbidity and mortality, with reported 30-day mortality as high as 20% in low-volume centres.<sup>113</sup> Thus, some centres have used an alternative strategy featuring frequent surveillance endoscopy (every 3 months for 1 year, twice a year for 1 year, and yearly thereafter), with intervention reserved

for patients progressing to frank carcinoma. In 75 patients managed with this strategy for a mean of 7·8 years, 84% did not develop carcinoma.<sup>20</sup> In the remaining 16%, early detection allowed successful intervention in almost all. Only one patient, who was lost to follow-up for several years, developed metastatic cancer.

Perhaps the one most rapidly evolving area in the care of patients with Barrett's oesophagus is endoscopic therapy, either by endoscopic resection of the inner lining of the oesophagus (endoscopic mucosal resection or endoscopic submucosal dissection), or ablation of the inner lining of the oesophagus. All these methods rely on the seminal observation that destruction of the lining of the oesophagus, accompanied by high-dose acid suppression, usually results in regenerated squamous epithelium.<sup>114,115</sup> Although the malignant potential of this neosquamous epithelium is not completely understood, it seems that this reversion results in a substantially decreased risk of oesophageal adenocarcinoma.<sup>21</sup> Endoscopic therapies to ablate the epithelium are multipolar electrocoagulation,<sup>116</sup> laser therapy,<sup>117</sup> argon plasma coagulation,<sup>118,119</sup> photodynamic therapy,<sup>120,121</sup> cryotherapy with sprayed liquid nitrogen,<sup>122</sup> and radiofrequency wave ablation.<sup>123</sup> Comparison of these therapies is insufficient to recommend one above another, and the relative probability of developing cancer after treatment has not been assessed. Photodynamic therapy (figure 4), in which a photosensitising agent is given before laser treatment of the oesophagus, has proved to reduce the risk of cancer in patients with high-grade dysplasia by more than 50%, from 28% to 13%, in a multicentre randomised sham-controlled trial.<sup>21</sup> Radiofrequency wave ablation has been shown to eradicate both non-dysplastic<sup>124</sup> and high-grade dysplastic<sup>125</sup> Barrett's oesophagus very effectively. Endoscopic resection of some or all of the Barrett's oesophagus tissue might be used before ablation to remove nodular disease, or as a stand-alone therapy.<sup>126,127</sup>

The best management for Barrett's oesophagus with high-grade dysplasia is dependent on the patient's characteristics and preferences, and local expertise. In patients with multiple comorbidities, endoscopic ablation or endoscopic surveillance might result in the best life expectancy. In young patients with extensive, multifocal high-grade dysplasia, surgical intervention or endoscopic therapy might be preferable to intensive endoscopic surveillance. In view of the few data to compare the management strategies, a dogmatic approach to the management of high-grade dysplasia is not advisable.

Does chemoprevention have a role in the prevention of Barrett's oesophagus development or the progression of Barrett's oesophagus to dysplastic disease? Since epidemiological studies show that patients on chronic use of NSAIDs have about half the rate of oesophageal cancer, compared with the general public,<sup>128</sup> NSAID use has been postulated to diminish the incidence of Barrett's oesophagus or at least delay its progression to cancer. Unfortunately, a recently reported randomised controlled



**Figure 4:** Endoscopic photograph of Barrett's oesophagus (A) before and (B) 2 days after photodynamic therapy. Substantial mucosal necrosis caused by photodynamic therapy is seen in B.

trial of 200 mg each day of celecoxib—a COX-2-selective NSAID—in patients with Barrett's oesophagus, and either low-grade or high-grade dysplasia, did not show a protective effect against disease progression.<sup>43</sup> Substantial observational data suggest that chronic acid suppression with proton pump inhibitors delays progression to dysplasia in patients with Barrett's oesophagus.<sup>129,130</sup> However, no convincing prospective data exist, and what the optimum dose of acid-suppression drugs should be is unclear. Furthermore, since Barrett's oesophagus is most frequently discovered during endoscopy for chronic GERD symptoms, and because these symptoms often need proton pump inhibitors for effective control, such maintenance treatment will be prescribed irrespective of concerns for chemoprevention. So far, high-dose treatment with proton pump inhibitors, in excess of that

needed to control symptoms, has not been shown to decrease cancer risk, and use of supratherapeutic doses solely for chemoprevention is not warranted.

Antireflux procedures are done in patients with GERD who are either intolerant or incompletely responsive to medical therapy. Do these surgical procedures decrease the risk of cancer, compared with chronic acid suppression with drugs, in patients with Barrett's oesophagus? Although the data are divided on this topic, on balance, antireflux surgery should not be pursued as an antineoplastic measure. 101 patients with Barrett's oesophagus were randomised to either antireflux surgery or acid-suppression drugs, and at a mean follow-up of 5 years there was no difference in the rate of disease progression between the groups.<sup>131</sup> Similarly, a meta-analysis of cancer outcomes with surgical and drug-based treatment of Barrett's oesophagus concluded that there was no difference between the groups.<sup>132</sup> However, important details about the type and success of surgery, the rigour of the medical management, and factors regarding patient selection, might not be taken account of in such analyses.

### Future directions

The best strategy of care for patients with Barrett's oesophagus needs further elucidation. Perhaps most important is the need for risk stratification. Presently, we cannot adequately predict which patients in the large group with chronic heartburn will have the condition, and perhaps more importantly, which patients will progress from Barrett's oesophagus to dysplasia and cancer. The use of histology from endoscopic biopsy samples to assess the degree of dysplasia and risk of cancer is far from perfect, and poorly reproducible. The test for screening and surveillance, upper endoscopy, is expensive, and must be delivered in specialised centres. The population at risk of Barrett's oesophagus—ie, those with chronic heartburn symptoms—is enormous, but oesophageal adenocarcinoma, although increasing in frequency, still has a low incidence.<sup>133</sup> A further complication is that up to 40% of individuals developing cancer have negligible reflux symptoms.<sup>134</sup>

Although this situation might seem bleak, exciting developments suggest that care will improve. Extensive efforts to understand the pathogenesis of oesophageal adenocarcinoma have led to the discovery of potential biomarkers of disease progression, such as *TP53* mutations, aneuploidy, cyclin A immunopositivity, and expression of  $\alpha$ -methylacyl coenzyme A racemase.<sup>135–137</sup> Initial work in nested case-control studies suggests that some of these biomarkers might prove much more sensitive and specific for cancer risk than traditional histology.<sup>138</sup> No reliable biomarker to chart disease progression has been identified, and the operating characteristics of these biomarkers are not yet fully elucidated. However, a panel of biomarkers might eventually provide adequate prognostic information to target patients at high risk, and perhaps just as importantly,

eliminate those at very low risk from further endoscopies and other care. Screening and surveillance will also evolve, as improved instrumentation allows easier and less costly endoscopic assessment.

Ultimately, the development of a less-invasive biomarker, such as a serum or sputum test, might make endoscopic screening obsolete. Since some patients will repeatedly acquire severe erosive disease without developing Barrett's oesophagus, identification of the genes that predispose patients with oesophageal mucosal damage to repopulate the epithelium with columnar tissue would be of great use. Studies to define allele prevalence of candidate genes are underway. Such genetic information might also help to identify which patients with chronic heartburn are at risk for Barrett's oesophagus and cancer.

Improved endoscopic therapies will probably continue to reduce the need for surgical oesophagectomy in patients with dysplastic disease. As ablative techniques become less toxic and better tolerated, data might become available to suggest that their application in non-dysplastic disease both decreases cancer risk and reduces costs because of the diminished need for surveillance endoscopy. Improvement in understanding of potential primary and secondary chemoprevention of Barrett's oesophagus might lead to appropriate treatment with NSAIDs, acid suppression, and other drugs. A large European study<sup>139</sup> to define the role of low-dose aspirin and proton pump inhibitors, in combination and separately, might delineate the roles of these drugs and best dosing.

### Contributors

Both authors participated in conception and writing of the article. Section headings were divided between the authors, and each author undertook the relevant searches and wrote the assigned sections. NS collated the sections, and both authors revised and approved the final version of the article.

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