Review

Past, present and future of Barrett's oesophagus

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Abstract

Barrett's oesophagus is a condition which predisposes towards development of oesophageal adenocarcinoma, a highly lethal tumour which has been increasing in incidence in the Western world over the past three decades. There have been tremendous advances in the field of Barrett's oesophagus, not only in diagnostic modalities, but also in therapeutic strategies available to treat this premalignant disease. In this review, we discuss the past, present and future of Barrett's oesophagus. We describe the historical and new evolving diagnostic criteria of Barrett's oesophagus, while also comparing and contrasting the British Society of Gastroenterology guidelines, American College of Gastroenterology guidelines and International Benign Barrett's and CAncer Taskforce (BOBCAT) for Barrett's oesophagus. Advances in endoscopic modalities such as confocal and volumetric laser endomicroscopy, and a non-endoscopic sampling device, the Cytosponge, are described which could aid in identification of Barrett's oesophagus. With regards to therapy we review the evidence for the utility of endoscopic mucosal resection and radiofrequency ablation when coupled with better characterization of dysplasia. These endoscopic advances have transformed the management of Barrett's oesophagus from a primarily surgical disease into an endoscopically managed condition.
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Introduction

Population studies have suggested that up to 1.6% of Europeans have Barrett's oesophagus (BO), a condition in which the native squamous epithelial lining of the distal oesophagus undergoes metaplastic change to a columnar epithelium due to chronic damage caused by gastro-oesophageal reflux disease (GORD).[1,2] Barrett's oesophagus and its predisposing condition, GORD is a major risk factor for the development of oesophageal adenocarcinoma (OAC), a highly malignant cancer which has been increasing in the Western population over the past three decades.[3–6]

Ever since the relationship between BO and OAC was established in the 1970s, there has been a rapid increase in research activity in the field of BO particularly in its diagnosis and management. The common goal among investigators is to curb the progression of this precancerous condition before incurable malignancy sets in.[7–9] However, with advancing knowledge has come misconception and controversy, particularly with regards to the definition and the diagnostic criteria of BO. Even today there remains no universally adopted definition of BO among authorities in this field.

In this review, we describe the past, present and future of BO. We further explore the evolving definition and diagnostic criteria of BO and try to understand where there is consensus and which areas still require resolution. In addition, we describe developments in therapeutic modalities and how this has the potential to impact on the mortality of OAC in the future.

Diagnosis of Barret's oesophagus

Historical perspective and evolution of the diagnostic criteria for Barrett's oesophagus

BO bears its name from the pioneering British surgeon, Norman Barrett who in 1950 published his seminal paper –

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'Chronic peptic ulcer of the oesophagus and 'Oesophagitis'' in which he described the columnar-lined oesophagus.[10,11] However, it was Wilder Tileston who first reported three cases of 'peptic ulcer of the oesophagus' in 1906 wherein he described the histology of the ulcer and adjacent epithelium which resembled a gastric ulcer in columnar epithelium.[12] Over the next four decades, disagreements regarding the distal oesophageal histology were prevalent, with some arguing that the ulcers in the distal oesophagus were not oesophageal, but gastric ulcers within an intrathoracic stomach in patients with congenital short oesophagus.[13–16] In fact, this notion was supported by Barrett in his paper in 1950.[10]

In 1953, Allison and Johnstone published an influential report rejecting Barrett's hypothesis, and suggesting that the tubular structure within the distal thorax could not be stomach since it: 1) lacked an outer peritoneal lining; 2) had musculature identical to oesophagus; 3) consisted of columnar epithelium interspersed with squamous islands; 4) lacked mucosal oxyntic cells; and 5) had mucosal glands typical of the oesophagus.[17] Subsequent reassessment of these 'gastric' ulcers by Barrett led him to acknowledge his prior misjudgement, and he published a revised report in 1957, redefining this tubular structure as 'lower oesophagus lined by columnar epithelium'.[18]

Between 1960 to the mid-1970s, there were varying histological descriptions of the columnar subtypes in the distal oesophagus including junctional (gastric cardiac epithelium), gastric-fundal, and intestinal epithelium with goblet cells.[19–21] This histologic conundrum was clarified in 1976 by Paull et al., who performed biopsies on 11 patients with a columnar-lined distal oesophagus and elucidated the presence of a histologic spectrum which from most proximal to distal comprised: columnar epithelial containing villi and goblet cells (now known as intestinal metaplasia, IM and sometimes referred to as Specialised Intestinal Metaplasia); followed by junctional epithelium; and finally, atrophic gastric fundal epithelium with chief and parietal cells.[22]

In the 1980s it was established that GORD and the presence of a hiatal hernia were risk factors for BO and it grew to be appreciated that these could distort the anatomic landmarks of the GOJ during endoscopy making a precise diagnosis difficult.[23,24] To avoid error, diagnostic criteria for BO were established by Skinner et al. who proposed that a minimum of 3 cm columnar lining is required to diagnose BO and for enrolment into clinical studies.[25] By the mid-1980s, the association between BO and OAC was well established[7–9] and it became clear that IM had a mosaic distribution with strong predisposition to dysplasia which led to IM becoming the defining feature for BO.[26,27]

In the mid-1990s, Spechler et al. challenged the conventional practice of only performing biopsies on BO ≥3 cm because he demonstrated that 18% of patients with endoscopically apparent BO measuring less than 3 cm still contained IM.[28] Furthermore, there were reports of OAC developing from BO <3 cm.[29,30] These results, coupled with the categorization of BO into short (≤3 cm) and long segments (≥3 cm) have proved essential in shaping the diagnostic criteria for BO over the years.[31]

Current diagnostic criteria for Barrett's oesophagus

The quality of endoscopic images has improved significantly with the advent of high resolution endoscopes making it easier to discern the landmarks. Today, a diagnosis of BO requires endoscopic visualization of columnar epithelium ≥1 cm above the gastro-oesophageal junction (GOJ) in addition to histological confirmation of columnar metaplasia.[32]

Endoscopic diagnosis of Barrett's oesophagus

Endoscopy remains the gold standard to diagnose BO. During endoscopy, three important landmarks need to be recognized: 1) the GOJ, 2) the diaphragmatic pinch and 3) the squamo-columnar junction (SCJ). The GOJ signals the end of the oesophagus and the start of the stomach and is best identified as the most proximal margin of the gastric folds.[33] The diaphragmatic pinch is the point at which the diaphragmatic crura constricts or 'pinches' the oesophagus and is an important landmark to denote the presence of a hiatal hernia. The SCJ is the transitional point between stratified squamous and columnar epithelial of the stomach. Visually, squamous epithelial has a pale glossy colour while columnar epithelial adopts a darker reddish appearance due to its increased vasculature. In normal oesophagus, the GOJ and SCJ coincide. However, when the SCJ lies ≥1 cm above the GOJ at the level of its most proximal extension, then this suggests the presence of BO.

Histological diagnosis of Barrett's oesophagus

Histologic criteria for BO still remain a contentious issue. The recent American College of Gastroenterology (ACG) requires biopsies confirming IM as a pre-requisite to diagnose BO.[34,35] However, the British Society of Gastroenterology (BSG) guideline stipulates that in the context of visible columnar epithelium with biopsy confirmation, IM is not a pre-requisite and hence gastric metaplasia is also regarded as a type of BO[32] (Table 1). The recent International *B*enign *B*arrett's and *CA*ncer *T*askforce (BOBCAT) consensus defines BO as presence of columnar epithelial but stipulates that it should be clearly stated whether IM is present above the GOJ.[36] The BSG and ACG difference hinges on the differential risk of malignant transformation between columnar epithelium with and without IM. The emphasis on IM as a defining feature of BO is based on increasing number of studies that have demonstrated a stronger association between IM and OAC than non-IM. For example, a study of 8522 patients with BO reported that the risk for malignant progression

Table 1
Comparison between BSG guidelines, ACG guidelines and BOBCAT consensus in the diagnosis of Barrett's oesophagus.

Diagnostic feature	British Society of Gastroenterology, 2014[32]	American College of Gastroenterology, 2016[34]	International Consensus (BOBCAT), 2015[36]
Definition	Endoscopically visible metaplastic columnar epithelial ≥1 cm above the GOJ plus biopsy confirmation of columnar metaplasia	Endoscopically visible metaplastic columnar epithelial ≥1 cm above the GOJ plus biopsy confirmation of IM	Endoscopically visible metaplastic columnar epithelial ≥1 cm above the GOJ, and pathologist should clearly state whether IM is present on biopsies above the GOJ
Endoscopic landmark for localizing GOJ	Proximal extent of the gastric folds	Proximal extent of the gastric folds	Proximal extent of the gastric folds
Reporting the extent of Barrett's oesophagus	Usage of Prague C&M criteria	Usage of Prague C&M criteria	Usage of Prague C&M criteria
Biopsy Protocol for suspected Barrett's oesophagus	Random 4 quadrant biopsies every 2 cm plus biopsy of visible lesions	Random 4 biopsies every 2 cm or 8 random biopsies to maximize IM yield. For suspected short segment BO where 8 biopsies is unattainable, a minimum of 4 biopsies/cm circumferential extent and 1 biopsy/cm Barrett's tongue is recommended	Random 4 quadrant biopsies every 2 cm plus biopsy of visible lesions
Normal Z line or Z line <1 cm from GOJ	Routine biopsy not recommended	Routine biopsy not recommended	Not discussed
Confirmation of Dysplasia	Cases of suspected dysplasia need to be confirmed by a second GI pathologist	Cases of suspected dysplasia need to be confirmed by a second GI pathologist	Cases of suspected dysplasia need to be confirmed by a second GI pathologist
Use of p53 biomarker to aid dysplasia diagnosis	Should be considered as adjunct to current diagnostic tools in the diagnosis of dysplasia	Not recommended	Not recommended for routine use, but can be considered as adjunct to aid diagnosis if done in specialist centres

BSG, British Society of Gastroenterology; ACG, American College of Gastroenterology; BOBCAT; Benign Barrett's and Cancer Taskforce, GOJ, Gastro-oesophageal junction; C&M, circumferential and maximum; IM, Intestinal Metaplasia; GI, gastrointestinal.

of IM was greater compared to gastric metaplasia (0.38%/year vs 0.07%/year, hazard ratio, HR = 3.54, 95% CI = 2.09–6.00, p < 0.01).[37] Chandrasoma et al. then showed that among 214 patients with columnar oesophagus who had biopsies taken with strict adherence to Seattle protocol, IM was noted in all patients who had dysplasia or OAC, while none of the patients with cardiac-type epithelium alone displayed dysplastic features or OAC.[38] More recently, detailed genomic analysis comparing IM and non-IM epithelium in 45 patients with BO reported a higher frequency of mutations in cancer-associated genes such as CDKN2A, WWOX, c-MYC and GATA6 in IM.[39]

However, other studies have not corroborated such findings. A retrospective analysis of 688 patients reported no significant difference in cancer risk of IM versus non-IM.[40] However, this study did not provide details regarding endoscopic findings, and whether those without IM went on to develop IM during follow-up.[40] In another study, Takubo et al. examined the mucosa adjacent to 141 cases of OAC resected endoscopically and found >70% of OAC were lying adjacent to non-IM columnar epithelial, indicating that non-IM epithelial could also harbour features for malignancy.[41] However, given that IM has a non-uniform distribution in BO, the extent of the pathological examination is critical and it is also possible that these cancers could have originated from the stomach.

The BSG guidelines argues for a broader diagnostic criteria to encompass columnar metaplasia with or without IM because IM detection is prone to sampling error and because understanding of the cellular and molecular basis for malignant risk continues to evolve.[42] The Seattle protocol which incorporates 4-quadrant biopsies every 1–2 cm provides a rigorous and reliable method for obtaining adequate biopsies for BO diagnosis; however, this protocol is not strictly adhered to in clinical practice. A Dutch study showed that adherence to the Seattle protocol was 79% for BO up to 5 cm, but decreased to 30% for BO lengths 10–15 cm.[43] Similar findings were reported in a large study of 2245 patients where only 51% of BO diagnosis adhered to the protocol.[44] In a comparative study designed to determine the optimal number of oesophageal biopsies for IM, investigators showed that the diagnostic yield for IM increases with the number of biopsies.[45] When the number of biopsies increased from 4, to 8 and to ≥16, diagnostic accuracy for IM increased from 34.7% to 67.9% and to 100%, respectively.[45] These conclusions have led to the latest ACG recommendation of obtaining at least 8 random biopsies on suspected Barrett's column during index endoscopy to maximize diagnostic yield.[34] While obtaining ≥16 biopsies would achieve 100% accuracy, this would not only be time consuming, but might also increase the risk of post-biopsy haemorrhage as well as the increased cost of processing biopsy.

In practical terms, the three definitions are consistent. The newly published European position statement agrees with the statements defined here, however, similar to the ACG, it requires IM for diagnosis.[35] Whilst the BSG guideline includes all histologically confirmed metaplasia in the definition, the clinical follow-up for any individual patient is determined by the risk of cancer progression and aside from dysplasia two of the strongest risk factors are segment length[46,47] and presence of IM. A recent study by Pohl et al. showed that the annual risk of cancer progression of long ($\geq$3 cm), short ($\geq$1 to $\leq$3 cm) and ultra-short ($\leq$1 cm) BO varied considerably, with the risk being 0.22%, 0.03% and 0.01%, respectively.[46] Hence, for patients with short segments (<3 cm) without IM, it is recommended that the procedure is repeated to ensure that there is indeed columnar mucosa within the oesophagus (and that this has not been mistaken for a hiatus hernia) and to repeat biopsies for IM. In patients with a short segment of gastric-type epithelium the risks of surveillance are thought to outweigh the benefits in view of the low risk for cancer progression.[46] All three guidelines support the use of the proximal gastric folds as the landmark for delineating the GOJ. Similarly, all three guidelines endorse the application of the Prague C&M criteria (grading system for BO according to its circumferential extent (C value, in cm), and the maximum length of BO tongues (M value, in cm)) when reporting BO length since it has good inter-observer reliability (r = 0.72) for BO $\geq$ 1 cm.[48]

Confirmation of dysplasia

Dysplasia is a biomarker for cancer risk in BO and is graded according to the Vienna classification.[49] However, there remains substantial inter-observer variability with regards to the grading of dysplasia between pathologists. In a Dutch study where two gastrointestinal (GI) pathologists retrospectively reviewed 293 BO specimens with a prior diagnosis of low−grade dysplasia (LGD), only 27% had 'true' LGD, while the remaining 73% were downgraded to non-dysplasia (ND) or indefinite-for-dysplasia (IND).[50] Following histologic review, patients with confirmed LGD were shown to have a higher risk for cancer progression (9.1%/patient-year) compared to those who were downgraded to ND (0.6%/patient-year) and IND (0.9%/patient-year).[50] Recently, a study comparing pathologist from the United States and Europe showed poor inter-observer agreement when diagnosing LGD (k = 0.11, 95% CI 0.004−0.15).[51] As the grading of dysplasia invariably dictates management strategies, unsurprisingly all three guidelines require that the diagnosis of dysplasia is confirmed by two GI pathologists.[32,34,36]

Histologic confirmation of dysplasia thus remains the only acceptable predictor for cancer progression; however, it is prone to sampling bias and high inter-observer variability. Alternative biomarkers, in particular p53 expression has emerged as a possible adjunct to improve risk stratification of BO. Sikkema et al. showed that p53 protein overexpression was a more powerful predictor of progression to high-grade dysplasia (HGD) or OAC irrespective of histology (HR 6.5; 95% CI 2.5−17.1) compared to a diagnosis of LGD (HR 3.6; 95% CI 1.6−8.1).[52] More recently, an analysis of >12,000 biopsies from 635 patients with BO showed that aberrant p53 expression (p53 overexpression or loss of p53 expression which can occur with a truncating mutation of the p53 gene) was associated with increased cancer risk, and furthermore the risk was higher for BO with loss of p53 expression (adjusted relative risk, RR[a] 14.0, 95% CI 5.3−37.2) compared to BO with p53 overexpression (RR[a] 5.6, 95% CI 3.1−10.3).[53] Furthermore, immunohistochemistry for p53 detection had good inter-observer reliability.[53] Therefore, although p53 staining has not yet reach mainstream clinical use, its use could allow more accurate risk stratification of BO into higher risk groups who will require more intensive surveillance.

Future diagnostic strategies for Barrett's oesophagus

Technologies for diagnosing BO have advanced over the years with a number of technologies aimed to better characterize dysplasia in secondary care (confocal and volumetric laser endomicroscopy). However, whether these modalities actually increase dysplasia detection has not been proven. Since the majority of Barrett's is undiagnosed, technologies have also been developed for diagnosing BO more readily in primary care (tethered capsule endomicroscopy, transnasal endoscopy and Cytosponge).

Confocal Laser Endomicroscopy

Confocal Laser Endomicroscopy (CLE) is a powerful imaging modality that combines endoscopy and microscopy to obtain high resolution and magnified images of the GI mucosa. CLE comes in the form of a probe-based system (pCLE) where a probe is passed through a port within the endoscope. An endoscope-based CLE (eCLE) previously existed, however, this system is no longer available on the market. CLE is based on the principle of tissue illumination by a blue laser (488 nm), with detection of fluorescence reflecting off tissues aided by the application of fluorescein which is excited by the laser.[54,55] CLE can achieve subcellular resolution up to 250 µm depth with 500−1000× magnification.[56] This permits in-vivo tissue evaluation at endoscopy and can effectively distinguish non-dysplastic, dysplastic and neoplastic epithelium.[57,58]

Trials for pCLE have been promising wherein addition of pCLE to white light endoscopy (WLE) and narrow band imaging (NBI, an endoscopic technology that uses light of shorter wavelength to allow better visualization of mucosal abnormalities and vascular patterns associated with dysplasia)[59] have reported increased sensitivity of detection of neoplasia from 45.0% to 75.8% (p = 0.01).[60] Further, the use of autofluorescence imaging (AFI, a technology that detects abnormal tissue architecture by exploiting fluorescence

off oesophageal mucosa) with pCLE to detect any grade of dysplasia in real-time ('optical biopsy') has been shown to have a sensitivity of 96.4% sensitivity compared to 57.1% sensitivity for AFI with NBI.[61] While CLE is promising the interpretation requires specialist training and expertise in interpretation therefore its use is currently restricted to academic hospitals. Current work is underway to define criteria for diagnosing dysplasia that could be adopted across studies.

Volumetric laser endomicroscopy

Optical coherence tomography (OCT) relies on the principle of backscattering of light to produce high resolution images. A new generation OCT, Volumetric Laser Endomicroscopy (VLE) is an emerging technology that incorporates a rotating optical laser probe centred within a transparent balloon. A laser (wavelength 1350 nm) emanating from the probe in a helical fashion, with an automated pullback, circumferentially scans 6 cm of the distal oesophagus up to 3 mm depth to produce cross-sectional images of the oesophagus up to the submucosal layer.[62] A case series of 6 patients with long segment BO who underwent both WLE with NBI at index endoscopy, followed-up by VLE with targeted biopsies within 6 months showed that VLE led to upstaging of disease status, allowing these patients to qualify for ablative therapy.[63] The requirement for a gold standard for these studies can lead to difficulty in determining which is superior.

A tethered-capsule endomicroscopy device has also been designed which utilises optical frequency domain imaging technology to generate 3D, microscopic images of the oesophageal wall at 30 μm lateral, and 7 μm axial resolution.[64] The capsule is swallowed and then withdrawn upon reaching the stomach. During transit, cross-sectional images of the oesophagus are acquired and the images are reconstructed to produce a 3D representation of the entire oesophagus.[64] A feasibility study on 7 healthy volunteers and 6 volunteers with BO showed that this procedure is safe whilst also producing high quality subsurface images that are easily missed on WLE.[64]

This technology opens up new avenues for BO imaging as it not only can be used as a screening modality, but could also detect architectural abnormalities of mucosa and submucosa which could indicate dysplasia.[64] The ease of performing the procedure with minimal training required, coupled with the ability of the capsule to be disinfected and reused might make it cost-effective and feasible as a screening tool in primary care. Although promising, larger studies assessing the accuracy of VLE imaging and histopathologic correlation are necessary prior to adopting this technology into routine practice.

Transnasal endoscopy

Transnasal endoscopy (TNE) has emerged as a possible alternative to transoral endoscopy for diagnosing BO.

Major endoscope companies (Fujinon, Pentax, Olympus, Vision Sciences) have produced 'ultrathin' endoscopes with a slimmer diameter (5—6 mm) than the standard endoscope, whilst also containing a working channel (up to 2 mm diameter) which allows for biopsies. A portable and disposable transnasal endoscope (E.G. Scan™, Intro-Medic, Seoul, South Korea) has also been developed and when compared to traditional endoscopy, was shown to have reasonable level of agreement of detecting BO (k = 0.617, 95% CI 0.378—0.860).[65] More recently, a transnasal endoscope with a disposable sheath (TNE-5000 with Endosheath, Vision Science, NY, USA) has been developed which protects the scope from contact with body fluids and circumvents the need for decontamination. In a pilot cross-over randomised controlled trial (RCT), Endosheath technology had a 100% sensitivity and specificity for obtaining an endoscopic diagnosis of BO, and a 66.7% and 100% sensitivity and specificity, respectively, for obtaining a histologic diagnosis of BO when compared to transoral endoscopy.[66] The advantages of TNE includes: 1) better patient tolerance and acceptability, 2) better safety profile (no need for sedation) and 3) suitability for use in primary care (E.G. Scan™).[66,67] It could also be cost-effective as it can be performed by technicians after sufficient training and does not require post-procedural vital sign monitoring.[67] Despite its many advantages, limitations of TNE include failure of intubation (due to narrow nasal canal) and epistaxis (up to 5%).[67] Although transoral endoscopy remains the standard for upper GI endoscopy, the many advantages of TNE is a promising tool for BO screening in primary care. It is not recommended for surveillance as the field of view, image quality and size of biopsies are not optimal for detection of dysplasia.

Cytosponge and Trefoil Factor-3

The Cytosponge is a cell sampling device that comprises a small compressed mesh within a gelatin capsule (Fig. 1).[68] The capsule is swallowed and disintegrates upon reaching the stomach to release a 3 cm-diameter spherical mesh that is withdraw by pulling the string which

Figure 1. The Cytosponge expanded (left) and encapsulated (right). Reproduced with permission from Kadri et al.[68]

then samples the entire length of the oesophagus, collecting up to one-million cells.[42] Immunohistochemistry for Trefoil Factor-3 (TFF3), a protein which is over-expressed in BO, is then performed on paraffin-embedded cytologic specimens as an objective diagnostic biomarker which is scored as positive or negative.[69]

The BEST-1 feasibility study evaluated the use of Cytosponge-TFF3 to diagnose BO and showed that it was applicable in primary care and although not the primary outcome, had a promising specificity of 93.8% and sensitivity of 73.3% for detecting BO ≥1 cm. For segments ≥2 cm, the specificity and sensitivity were 93.5% and 90.0%, respectively.[68] The subsequent BEST-2 study which enrolled 1110 participants in a case-control design to enable assessment of sensitivity and specificity, reported 79.9% sensitivity for Cytosponge-TFF3 to detect BO increasing to 87.2% for BO circumferential segment ≥3 cm.[70] The specificity for BO was 92.4%.[70] These figures are comparable to the current colorectal cancer screening programme using faecal occult blood test (FOBT) which has a sensitivity and specificity range of 6.2–83.3% and 65–99%, respectively.[71]

The BEST-3 study will begin recruitment in early 2017 with the aim of comparing the use of the Cytosponge-TFF3 with standard care (lifestyle advice, acid-suppressing medications and, Helicobacter Pylori eradication) against standard care alone in patients with reflux disease in the primary care setting. This study is designed to assess whether Cytosponge-TFF3 could lead to increased detection of BO in primary care and to evaluate the health economics of this approach. It is hoped that this study will provide pivotal information regarding the development of a comprehensive and cost-effective screening programme for BO.

Therapy for Barrett's oesophagus

Treatments for BO have evolved considerably over the past twenty years and have altered the clinical rationale for detection of Barrett's. Traditionally, oesophagectomy was the only option for high-grade dysplasia and carcinoma; however, with advancing technology, endoscopic therapy has become the mainstay treatment for BO. We begin by describing the brief history of oesophagectomy, followed by discussion on the current (surveillance, radiofrequency ablation and endoscopic resection) and future (cryotherapy and chemoprevention) management strategies for BO.

Historical treatment for Barrett's oesophagus – oesophagectomy

Oesophagectomy still remains the only definitive therapy for invasive OAC. Although surgical outcomes have improved over the years, oesophagectomy still remains a challenging procedure as patients often have multiple existing co-morbidities and so it is not without risks. The transthoracic oesophagectomy (Ivor Lewis oesophagectomy, ILO) is considered the gold standard procedure and was first performed by Ivor Lewis in 1944 on a patient who had OAC of the distal oesophagus.[72] He performed a laparotomy to mobilize the stomach and a left-sided thoracotomy for resecting the oesophagus.[72] Although there are variations to the standard oesophagectomy including a transhiatal approach, the Ivor Lewis procedure is often preferable as it permits better visualization of abdominal contents and allows for wide margins of lymph node dissection.[73]

With the success of laparoscopic surgery during the late 1980s, Watson et al. reported two cases of minimally invasive oesophagectomy (MIO) by utilising laparoscopic means for gastric mobilization, followed by a thoracoscopic approach for oesophageal resection and anastomosis, achieving excellent results with shorter hospital stay and convalescence.[74] A recent phase 3 RCT (MIRO trial) comparing open ILO to MIO reported favourable short-term outcomes for MIO with lower post-operative morbidity (37 vs 67, p = 0.0001) and pulmonary complications (18 vs 31, p = 0.037), but no difference in 30-day mortality between groups.[75] More recently, robotic-ILO is gaining popularity since it provides magnified images and better freedom of movement via wristed motions compared to laparoscopic approach.[76] However, more studies are needed to assess the safety and outcomes of robotic-ILO compared to open or MIO.

Current management for Barrett's oesophagus

Surveillance and endoscopic therapy

Algorithms for the management of flat and nodular BO, with or without dysplasia are shown (Figs. 3 and 4). For
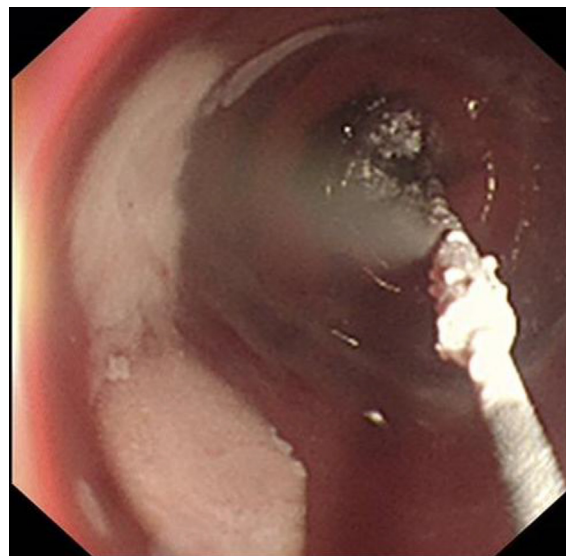

Figure 2. Cryotherapy using the Coldplay cryoballoon system (C2 Therapeutics/Pentax Medical).
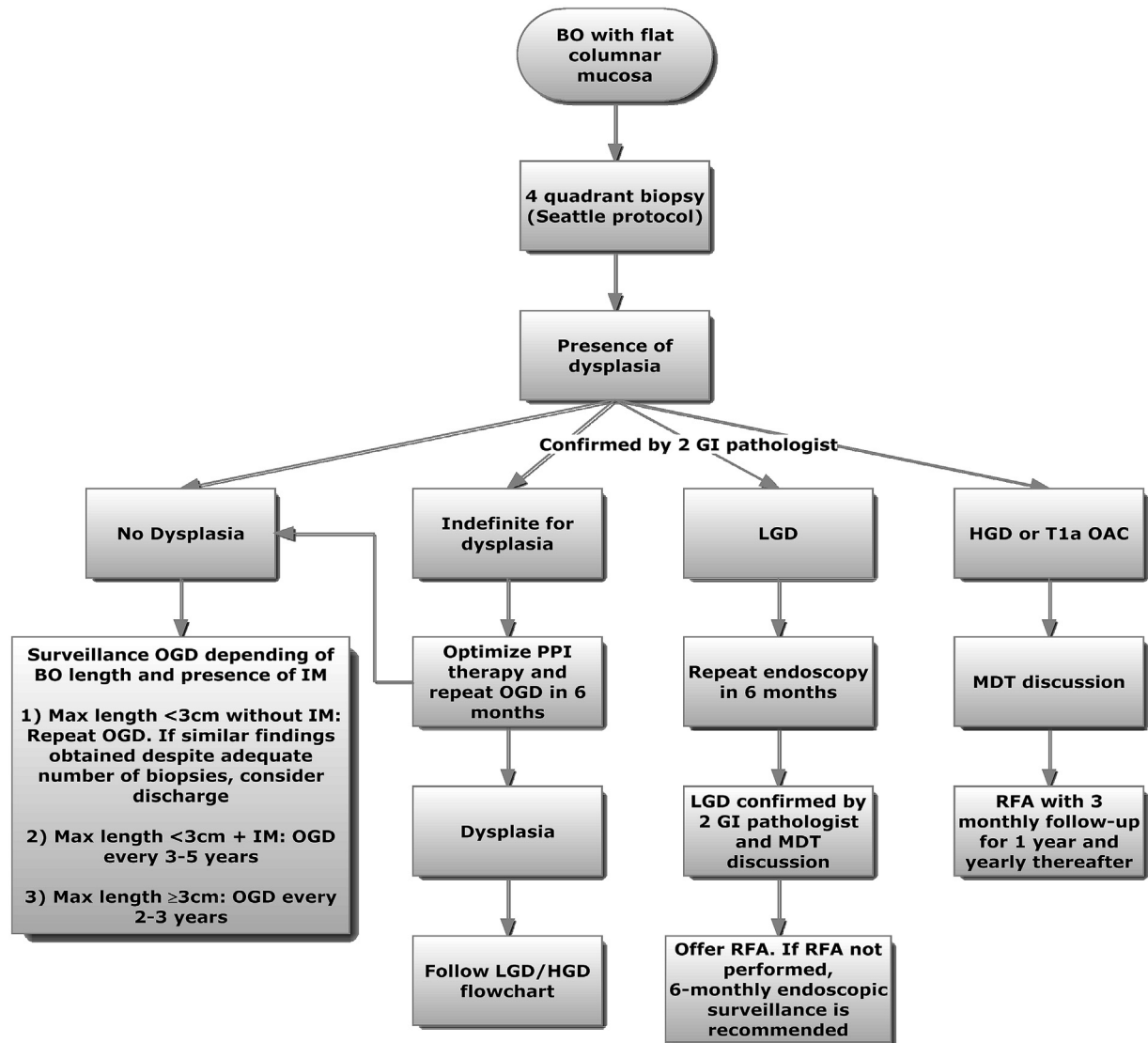
Figure 3. Algorithm for management of Barrett's oesophagus with flat mucosa (non-nodular). BO; Barrett's oesophagus, GI; Gastrointestinal, PPI; Proton Pump inhibitor, OGD; Oesophagogastroduodenoscopy, IM; Intestinal metaplasia, LGD; Low grade dysplasia, HGD; High grade dysplasia, RFA: Radiofrequency ablation, MDT; Multidisciplinary team.

non-dysplastic BO, both the ACG and BSG recommend endoscopic surveillance (Table 2). However, the BOBCAT consensus does not recommend surveillance, but if surveillance is undertaken, suggests that it should be targeted at high risk patients stratified according to patient demographics, BO length, frequency and severity of symptoms (Table 2). However, there is currently no clinically adopted algorithm for a risk stratification approach due to paucity of data and this is an area which requires further research. A recent paper describes a risk-stratification panel comprising clinical factors (age, waist-to-hip ratio and BO segment length) and molecular biomarkers applied to a Cytosponge sample (glandular atypia, Aurora Kinase A, and p53). A risk stratification calculator can then be used to risk stratify BO with dysplasia.[77] Such approaches are promising and as more data become available, future surveillance programme will likely be based upon risk stratification using biomarkers.

BO is considered indefinite for dysplasia when pathologists are unable to accurately delineate dysplastic features from inflammatory atypia.[78] For such cases, PPI optimization with repeat OGD in 6 months is recommended.[32] If no dysplasia is found on follow-up, then surveillance should follow non-dysplastic BO.

As discussed earlier cases of LGD should be confirmed by a second GI pathologist with a repeat endoscopy in 6 months. Additionally, the ACG recommends aggressive PPI for LGD followed by repeat endoscopy in 6 months since PPI may lead to downgrading of dysplastic status.[79] If repeat endoscopy confirms LGD, ablative therapy should be offered.[34] Radiofrequency ablation (RFA) is the ablative therapy of choice and is performed via a balloon catheter
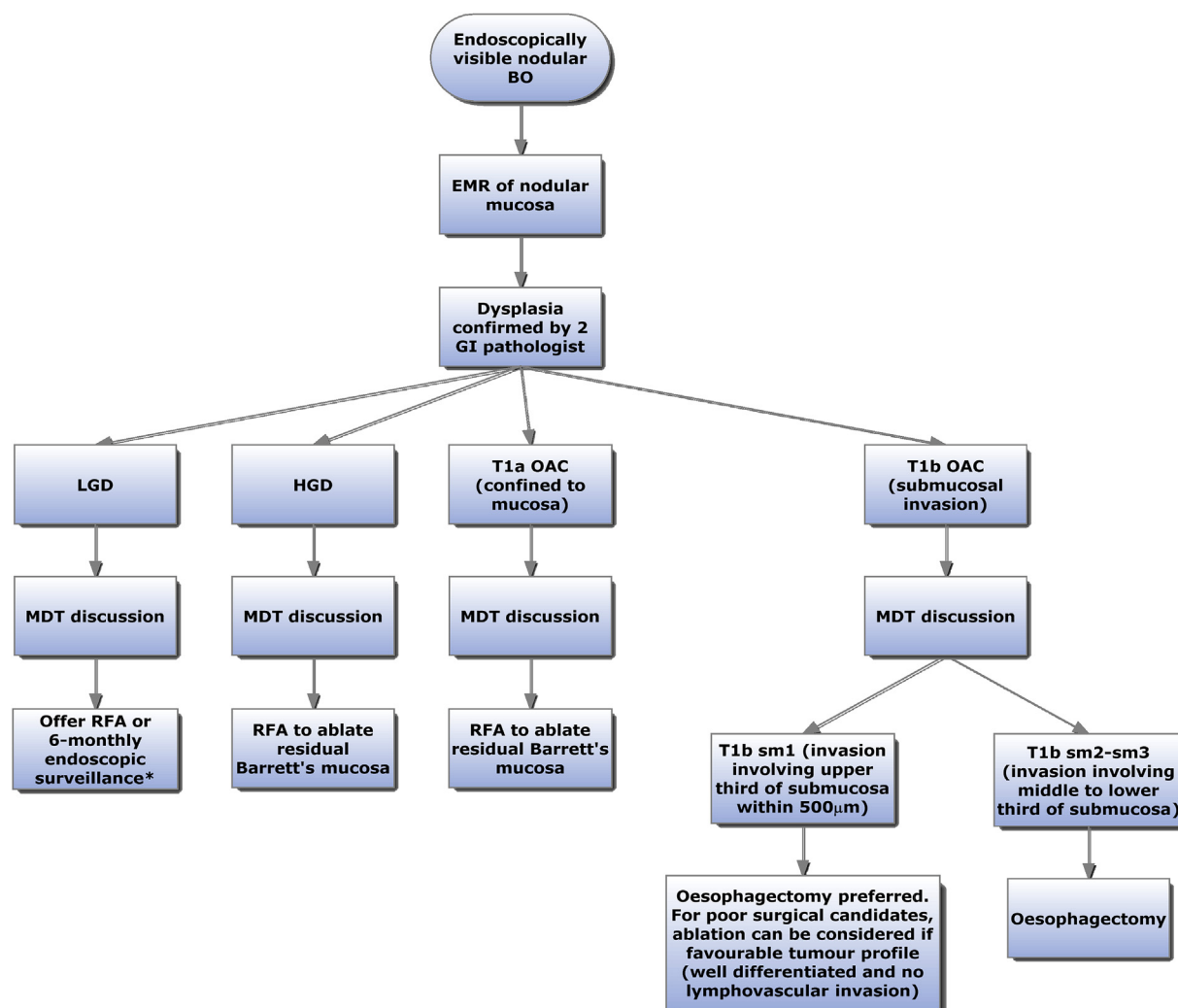
Figure 4. Algorithm for management of Barrett's oesophagus with endoscopically visible nodular lesion. *Data for management of LGD with nodular lesion treated with EMR is limited. However, a similar management strategy to that of flat LGD can be considered. BO; Barrett's oesophagus, EMR; Endoscopic mucosal resection, GI; Gastrointestinal, LGD; Low grade dysplasia, RFA; Radiofrequency ablation, HGD; High grade dysplasia, MDT; Multidisciplinary team, OAC; Oesophageal adenocarcinoma, sm; submucosa.

containing a bipolar electrode array which delivers thermal energy onto targeted tissue. RFA can be delivered by circumferential ablation (Halo[360] system) or focal ablation (Halo[90] system). A RCT comparing RFA versus sham-therapy for dysplasia showed that RFA was associated with lower rate of dysplastic progression (3.6% vs 16.3%, p = 0.03) and cancer development (1.2% vs 9.3%, p = 0.045) than controls with a good safety profile.[80] RFA was also associated with complete eradication of LGD in 90.5% versus 22.7% in the sham-controlled group (p < 0.001).[80] More recently, a RCT which compared RFA versus surveillance for LGD showed that RFA led to 25% reduction in risk of progression to HGD/IMC.[81] Results from these trials have led to the BSG, ACG and BOBCAT consensus recommending RFA for treating LGD.[32,34,36]

For HGD or IMC, nodular lesions should be removed with endoscopic mucosal resection (EMR) followed by RFA of remaining BO[32] (Fig. 4). RFA post-EMR is

recommended as the risk of developing metachronous neoplasia within 5 years after EMR is 14.5%.[82] A recent study also reported favourable outcomes for eliminating residual BO using a modified Argon Plasma Coagulation (APC, an ablative technique using ionized argon gas) system.[83] Patients with residual BO ≥1 cm post-EMR for early neoplasia were treated with Hybrid-APC (fluid injection into submucosa before ablation) and achieved histological remission of BO in 78% (39/50) of cases.[83]

For neoplasia staged as T1b (invasion into submucosa), oesophagectomy is preferred since up to 22% of submucosal tumour will inherently have regional lymph node metastases.[84] However, poor surgical candidates with stage T1b sm1 tumour (invasion of submucosa but confined to upper 3rd submucosal layer within 500 μm) but with low risk tumour profile (well differentiated tumour without lymphovascular invasion); endoscopic therapy can be offered as an alternative.[85,86] The current BSG recommendations for

Table 2
Comparison between BSG, ACG and BOBCAT consensus on the management of Barrett's oesophagus.

Degree of dysplasia at index endoscopy		British Society of Gastroenterology (BSG)[32]	American College of Gastroenterology (ACG)[34]	International consensus (BOBCAT)[36]
No dysplasia		- Evaluate patient fitness and obtain informed consent - BO length <3 cm without IM: Repeat OGD and if IM absent, consider discharge - BO length <3 cm with IM: OGD in 3—5 years - BO length ≥3 cm: OGD every 2—3 years	- Evaluate patient fitness and obtain informed consent - Repeat OGD with biopsy in 3—5 years	- Routine surveillance not recommended, but if undertaken, it should be targeted at high risk patients of which risk stratifications is based on age, sex, BO length, central obesity, duration, frequency and severity of symptoms, smoking status (influence of IM on surveillance is unclear) - No surveillance if life expectancy <5 years
Indefinite for dysplasia		Confirmation by 2 GI pathologists. Optimize PPI, and repeat OGD in 6 months	Confirmation by 2 GI pathologists. Optimize PPI and repeat OGD (interval not specified)	Confirmation by 2 GI pathologists. Optimize PPI, and repeat OGD within 12 months
LGD	Flat mucosa	Optimize PPI and repeat OGD in 6 months. If repeat OGD confirms LGD (by 2 GI pathologist) offer RFA. If RFA not undertaken, then 6-monthly surveillance is recommended	Optimize PPI and repeat OGD (interval not specified). If repeat OGD confirms LGD (by 2 GI pathologist) offer RFA. If RFA not undertaken, then yearly surveillance	Optimize PPI and repeat OGD in 6—12 months. If repeat OGD confirms LGD (by 2 GI pathologist) offer RFA.
	Nodular	EMR to obtain optimal histopathological staging. If LGD confirmed, offer RFA of remaining BO or 6 monthly surveillance[a]	EMR to obtain optimal histopathological staging. If LGD confirmed, offer RFA of remaining BO or 6 monthly surveillance[b]	EMR to obtain optimal histopathological staging. If HGD or IMC present, offer RFA of remaining BO
HGD or T1a stage (IMC)	Flat mucosa	Confirmation by 2nd GI pathologist. If HGD confirmed, then RFA	Confirmation by 2nd GI pathologist. If HGD confirmed, then RFA	Confirmation by 2nd GI pathologist. If HGD confirmed, then RFA[97]
	Nodular	EMR of nodule. If histopathological confirmation of HGD/IMC, then RFA of remaining BO epithelium	EMR of nodule. If histopathological confirmation of HGD/IMC, then RFA of remaining BO epithelium	EMR of nodule. If histopathological confirmation of HGD/IMC, then RFA of remaining BO epithelium[97]
OAC	T1b sm1	Oesophagectomy is preferred. If poor surgical candidates, EMR + RFA can be considered if low risk tumour profile	Oesophagectomy is preferred. If poor surgical candidates, EMR + RFA can be considered if low risk tumour profile	Oesophagectomy is preferred. If poor surgical candidates, EMR + RFA can be considered if low risk tumour profile[97]
	≥T1b sm2	Oesophagectomy	Oesophagectomy	Oesophagectomy

LGD; Low grade dysplasia, HGD; High grade dysplasia, IMC; Intramucosal carcinoma, OAC; oesophageal adenocarcinoma OGD; oesophagogastroduodenoscopy, BO; Barrett's oesophagus, RFA; Radiofrequency ablation, GI; Gastrointestinal.
[a] There is limited data and no optimal recommendation regarding the management of LGD diagnosed on EMR specimens of nodular BO. However, a similar management strategy to that of flat LGD should be considered.
[b] The ACG recommendation for LGD diagnosed on nodular EMR specimens of nodular BO is based on expert opinion only due to the paucity of data surrounding this clinical entity.

HGD, T1a and T1b tumours are similar to that of the ACG and BOBCAT consensus.[34,36]

Future therapeutic options for Barrett's oesophagus

EMR and RFA combination have proven to be a highly effective treatment for dysplastic BO; however, cryotherapy is a new technology which is being evaluated. Here, we also discuss the possible role of chemoprevention in BO.

Cryotherapy

Cryotherapy involves the use of a cryogen, usually liquid nitrogen or cold carbon dioxide (CO_2) to induce tissue damage. The CryoSpray Ablation device (CSA Medical) allows endoscopic delivery of liquid nitrogen while the Polar Wand (GI Supply) and Coldplay cryoballoon system (C2 Therapeutics/Pentax Medical, Fig. 2) delivers cold CO_2. Both systems cause freezing and thawing of Barrett's mucosa, resulting in apoptosis and subsequent sloughing of dead epithelial followed by regrowth of neo-squamous epithelial.[87] Early data for cryotherapy has demonstrated it to be safe and effective, achieving up to 87% eradication of all forms of dysplasia (97% for HGD), and 3% stricture rate which were easily treated with balloon dilation.[88] More recently Canto et al. also showed high success rate for eradication of HGD with CO_2 therapy (Cryoballoon), achieving 94% eradication at 1 year follow-up, with better success for

treatment naïve patients than as rescue therapy for those treated unsuccessfully with other forms of ablative therapy (100% vs 91%, respectively).[89] Despite promising results for cryotherapy, larger trials with direct comparison to RFA are necessary prior to adopting this procedure into clinical practice.

Role of chemoprevention

In BO, prolonged gastric acid reflux can lead to DNA strand breaks, oxidative damaged and increased cellular proliferation, processes which could promote carcinogenesis.[90–92] A recent prospective cohort study which investigated 540 patients with known BO with a median 5.2 years follow-up showed that proton-pump inhibitors (PPI), but not Histamine-2 receptor antagonist, was associated with a 79% decreased cancer risk (HR = 0.21, 95% CI 0.07–0.66).[93] More recently, a meta-analysis of 7 studies with >2800 patients showed that PPI was associated with 71% reduction in cancer risk (adjusted OR 0.29; 95% CI 0.12–0.79).[94] Interestingly however, a population based study of 9883 Danish patients with a median 10.2-year follow-up showed no protective effect of PPI on the incidence of HGD or OAC.[95] In fact, this study showed that longer-term use of PPI was associated with higher risk of HGD or OAC.[95] As the role of PPI as a chemopreventive agent is not well substantiated, established guidelines has only recommended PPI to be used for symptomatic control only.[32,34,36]

There has been some indirect evidence that aspirin or other non-steroidal anti-inflammatory (NSAIDs) has a chemopreventive role. A pooled analysis of observational studies showed a 40% reduction in cancer risk among patients taking aspirin or other NSAIDS.[96] However, even if there is a true reduction, its use may be offset by the potential for an increased risk of GI or intracranial haemorrhage. Current societal guidelines do not recommend routine use of aspirin/NSAIDs as chemoprevention for OAC due to its potential side effects and the lack of level-1 evidence. However, the AspECT trial, a RCT designed and powered to assess the benefits of high or low-dose PPI with or without aspirin in reducing risk of OAC in BO has recently completed recruitment, and the results of this study are awaited.

Conclusion

There have been significant advances in the field of BO not only in diagnosis, but also in the different endoscopic imaging and therapeutic modalities for BO. Although minor variations between the BSG, ACG and BOBCAT statements exist, these societal recommendation do achieve consensus in many domains, such as the reporting of BO (Prague C&M criteria) and IM, endoscopic landmarks, diagnosis and grading of dysplasia, and treatment strategies

for dysplastic Barrett's. Currently, surveillance forms the mainstay of BO management with surveillance intervals varying depending on the grade of dysplasia. However, the future of surveillance in BO is gradually migrating towards risk stratifying those at higher risk for cancer progression based on risk factors and biomarkers in order to prioritise those patients with highest risk for cancer with endoscopic therapy. Finally, in order to diagnose more BO and have any chance of reducing the population mortality from OAC a better strategy for diagnosis in primary care is required. The development of novel tests such as the Cytosponge-TFF3 test, capsule-tethered VLE, and transnasal endoscopy are an important step toward achieving this goal.

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Conflict of interest

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