Barrett oesophagus

*Yonne Peters[1,8], Ali Al-Kaabi[1,8], Nicholas J. Shaheen[2], Amitabh Chak[3], Andrew Blum[3], Rhonda F. Souza[4], Massimiliano Di Pietro[5], Prasad G. Iyer[6], Oliver Pech[7], Rebecca C. Fitzgerald[5] and Peter D. Siersema[1] **

Abstract | Barrett oesophagus (BE), the only known histological precursor of oesophageal adenocarcinoma (EAC), is a condition in which the squamous epithelium of the oesophagus is replaced by columnar epithelium as an adaptive response to gastro-oesophageal reflux. EAC has one of the fastest rising incidences of cancers in Western countries and has a dismal prognosis. BE is usually detected during endoscopic examination, and diagnosis is confirmed by the histological presence of intestinal metaplasia. Advances in genomics and transcriptomics have improved our understanding of the pathogenesis and malignant progression of intestinal metaplasia. As the majority of EAC cases are diagnosed in individuals without a known history of BE, screening for BE could potentially decrease disease-related mortality. Owing to the pre-malignant nature of BE, endoscopic surveillance of patients with BE is imperative for early detection and treatment of dysplasia to prevent further progression to invasive EAC. Developments in endoscopic therapy have resulted in a major shift in the treatment of patients with BE who have dysplasia or early EAC, from surgical resection to endoscopic resection and ablation. In addition to symptom control by optimization of lifestyle and pharmacological therapy with proton pump inhibitors, chemopreventive strategies based on NSAIDs and statins are currently being investigated for BE management.

Barrett oesophagus (BE) involves the formation of a metaplastic columnar epithelium with crypt architecture (which resembles the epithelium of the intestine) from the squamous epithelium of the oesophagus, which is a reparative response to reflux-induced damage (FIG. 1). It is now widely accepted that BE is a pre-malignant condition that predisposes patients to develop oesophageal adenocarcinoma (EAC). BE is detected by endoscopy and histopathological assessment of biopsy samples and is diagnosed on the basis of the presence of intestinal metaplasia (IM). However, ongoing debate about some diagnostic features stands in the way of a comprehensive definition of BE[1–4].

The prevalence of BE in the general population is difficult to determine, as accurate population-based estimates are rare and the majority of individuals with BE are not diagnosed, although the prevalence in Western countries is ~1–2% in the general population and ~10% in populations that report acid reflux symptoms[5,6].

Epidemiological and histopathological evidence indicate that many cases of EAC arise in individuals with BE[7] by the progression of IM to dysplasia and finally to neoplasia. Given the high mortality in patients with EAC, improved diagnosis of individuals with BE or early stages of EAC could improve outcomes by enabling clinical surveillance and treatment of patients with dysplasia who are at high risk of malignant progression. The increasing knowledge of risk factors for both BE and EAC could help define clinical pathways to enable identification of individuals at high risk who could undergo endoscopic or non-endoscopic screening tests or be candidates for preventive strategies to halt BE development or progression[8,9].

In this Primer, we provide an up-to-date overview of the epidemiology and pathophysiology of BE, discuss the criteria for the diagnosis of BE and explore developments in screening and surveillance. In addition, we review the management of BE, including endoscopic eradication strategies, and the effect of the condition on the quality of life (QOL) of patients.

Epidemiology

Trends in incidence and prevalence

EAC is one of the cancers with the fastest rising prevalence in Western countries[10]. As BE is the precursor lesion in the majority of EAC cases, data suggest that the incidence and prevalence of BE are also rising. Studies of the incidence and prevalence of BE are confounded by the increasing use of gastrointestinal (GI) endoscopy; because BE is often associated with gastric reflux with no distinguishing symptoms, detection of BE is expected to increase as upper endoscopy use increases, regardless

**e-mail: peter.siersema@radboudumc.nl

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Author addresses

[1]Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, Netherlands.
[2]Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.
[3]Division of Gastroenterology and Liver Diseases, Case Western Reserve University, Cleveland, OH, USA.
[4]Department of Medicine and the Center for Esophageal Diseases, Baylor University Medical Center at Dallas and the Center for Esophageal Research, Baylor Scott and White Research Institute, Dallas, TX, USA.
[5]Medical Research Council Cancer Unit, University of Cambridge, Cambridge, UK.
[6]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA.
[7]Department of Gastroenterology, St John of God Hospital, Regensburg, Germany.
[8]These authors contributed equally: Yonne Peters, Ali Al-Kaabi

of true increases in underlying incidence[11,12]. To control for this detection bias, the proportion of upper endoscopies that result in a diagnosis of BE has been assessed, which in some studies showed a steady increase in BE diagnoses[12]. The current best estimate of the prevalence of BE in adults is 1–2%[5] (~10% in those with chronic gastro-oesophageal reflux disease (GERD) symptoms) in Western countries[13–15].

Accurate estimates of the annual risk of EAC among patients with BE are difficult to obtain, as incidence rates vary between studies. Early studies before the year 2000 usually overestimated EAC incidence (2–4% per year) in patients with non-dysplastic BE owing to publication bias and inclusion of high-risk patients[16]. Population-based studies and large meta-analyses in the past 10 years reported lower progression rates of 0.1–0.5% per patient-year[17,18], although the lower estimate might be too low, as it is possible that patients with IM of the gastric cardia or with ultra-short BE were included in these pathology registry-based studies.

Although BE is a well-established risk factor for EAC, the assumption that all patients who develop EAC go through the same reflux-induced response leading to adenocarcinoma was challenged by a retrospective analysis that found that only 46% of patients with EAC presented with endoscopic confirmation of BE and histopathological evidence of IM[7]. Furthermore, comparison of patients with EAC who had confirmed BE at presentation to those without BE suggested the existence of two EAC phenotypes with different tumour behaviour and response to therapy[7]. These findings raise the question of whether EAC always develops through the IM–dysplasia–EAC sequence.

Risk factors

Risk factors for BE include demographic, lifestyle (such as diet and weight), GERD-specific and miscellaneous risk factors (TABLE 1). GERD, obesity and smoking are responsible for ~80% of the burden of EAC[19]. When combined, these risk factors can be used to stratify risk in populations to optimize screening programmes for BE and EAC.

Demographic factors. BE is a disease with a white male predominance. After controlling for other relevant risk factors, individuals of white ethnicity are at 2–3-fold higher risk of developing BE than individuals of African descent[20,21]. The effect of Hispanic ethnicity is less clear, as some studies documented a reduced risk of developing BE[20,21], whereas others estimate a risk similar to that in the white population[22]. Although BE is reportedly uncommon in East Asians, a meta-analysis of 28 studies showed that the prevalence of histologically confirmed BE was 1.3% in East Asians[23].

The risk of developing BE is approximately twofold higher in men than in women[24]. Increasing age is an additional strong risk factor — prevalence increases by 50–100% for every decade of life in adults[11,25].

Lifestyle factors. Cigarette smoking is a moderate risk factor for the development of BE[26]. Compared with a never smoker, a current or past smoker has >50% increased risk of developing BE. Furthermore, a dose–response relationship exists, as greater cumulative pack-years of exposure result in a greater risk of BE[5,27].

Diet is also a risk factor for the development of BE. After controlling for appropriate risk factors, increasing intake of vegetables has a protective effect against BE[28]. The intake of red meat or processed meat does not seem to be associated with increased risk of BE[29]. Increased levels of nitric oxide from dietary sources can be detected in the distal oesophagus, and cell culture experiments suggest that they may contribute to BE. High levels of nitric oxide result in the formation of higher oxides of nitrogen, which might contribute to mutagenesis in epithelial cells at the gastro-oesophageal junction[30,31].

The association between alcohol use and BE risk is unclear, as some studies reported no association, whereas others reported that alcohol increased risk of BE[32]. Overall, alcohol use is not a strong risk factor, although the type of alcohol that is consumed may matter, as wine seems to be protective, whereas hard spirits augment the risk of developing BE[33].

Obesity is a strong risk factor for BE[34]. Overall, the risk of developing BE is approximately twofold higher in patients who are obese (body mass index (BMI) >30 kg/m^2) than in those who are not[34]. Furthermore, the type of obesity (that is, the distribution of fat) seems to be important; truncal obesity (the presence of large amounts of intra-abdominal fat; also known as central obesity) seems to carry an especially high risk[35]. In fact, when waist circumference is controlled for, the association between obesity and BE disappears in some studies[35]. The pathophysiological basis for this relationship is unclear but may be due to trophic hormonal effects that are associated with truncal obesity, such as increased serum levels of insulin and leptin, which have been shown to be an independent risk factor for BE[36]. In addition, truncal obesity can mechanically influence GERD through increased abdominal pressure and reduced lower oesophageal sphincter (LES) pressure[37,38]. However, because the association between obesity and BE persists even after controlling for GERD symptoms, mechanisms beyond obesity's promotion of reflux may be present[35].

GERD-specific factors. As BE is considered to be a complication of chronic GERD, it is perhaps not surprising that risk factors for gastric reflux are also strongly associated with BE. Reflux-induced injury has been linked

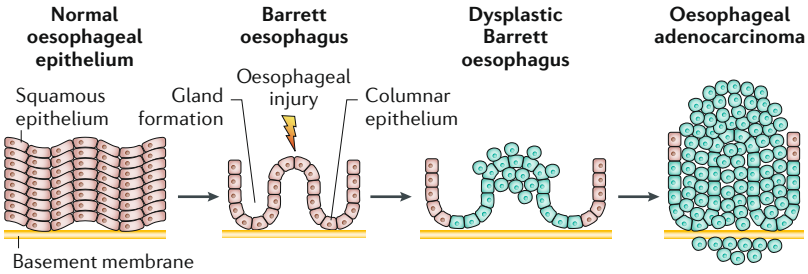

Fig. 1 | **Development and progression of Barrett oesophagus.** Oesophageal injury, mainly due to gastrointestinal reflux, might lead to Barrett oesophagus, a lesion that is characterized by replacement of the normal squamous epithelium by columnar epithelium, termed intestinal metaplasia. This pre-malignant condition might progress to dysplasia and oesophageal adenocarcinoma, which may invade the submucosa. Figure adapted from REF.[219], Springer Nature Limited.

to cellular and molecular changes in the oesophagus[39,40]. Physiological alterations that predispose to GERD are also associated with BE, including LES hypotension[41], increased gastric acid production[42] and increased bile in refluxate[43]. Symptoms of heartburn and regurgitation are strongly associated with the presence of BE, and duration of GERD symptoms may also be a risk factor for BE[44]. Although GERD is a strong risk factor for both BE and EAC, 40–50% of patients with these disorders do not report chronic reflux symptoms, suggesting that silent reflux or other risk factors are important in the pathogenesis of BE and EAC. Indeed, the prevalence of BE in individuals without frequent, chronic reflux symptoms is substantial and, in some studies, comparable to that in individuals with frequent, chronic reflux[45].

Hiatal hernia size also correlates with risk of BE[46], although whether this is solely due to the increased severity of GERD symptoms in those with bigger hiatal hernias or is due to another, not-yet-elucidated mechanism, remains unknown.

Gastric infection with *Helicobacter pylori* is negatively correlated with the presence of BE, especially for the most virulent forms of *H. pylori*[47,48]. The reduced gastric acid output that is associated with chronic *H. pylori* infection might result in a lower prevalence of BE in these patients.

Family history. Familial studies have implicated a genetic component in predisposition to BE and a family history of BE or EAC may be a strong risk factor for disease[49,50]. The prevalence of BE in individuals with a family history of BE is estimated to be 6–7.3%[49,50]. Familial aggregation must be interpreted with caution, as it could also be due to common environmental exposures, such as diet and smoking, or a genetic susceptibility to other risk factors, such as obesity or GERD. In addition, studies of heritability of these traits may be confounded by detection bias in family members, given the increased use of endoscopy in this group compared with the general population[49].

Medication. Whereas the use of NSAIDs has been strongly inversely associated with the risk of EAC, NSAID use is not associated with decreased risk of BE[51]. However, some studies suggest that use of other medications, such as statins and proton pump inhibitors[52] (PPIs), may be associated with decreased risk of developing BE.

Risk factors for progression of BE

In general, many of the risk factors for development of BE also seem to be risk factors for progression of BE to dysplasia or EAC (TABLE 1). Age is an important risk factor for progression of BE. Among patients with non-dysplastic BE, the risk of dysplasia increases by ~3.3% per year of age[53–55]. White ethnicity and male sex[53,55,56] are also associated with increased risk of progression to EAC. The length of BE (measured from the gastro-oesophageal junction (GEJ)) is similarly directly correlated with risk of progression to dysplasia and EAC[53–56]. Active reflux, smoking, BMI and waist circumference also increase the risk of progression[55].

Debate exists about whether IM is a risk factor for malignant progression. A large, population-based cohort study demonstrated a substantially higher annual EAC risk in patients with IM than in those without IM (0.38% versus 0.07%; HR 3.54, 95% CI 2.09–6.00, $P < 0.001$)[57], although another study found that IM did not increase the risk of malignant progression[58]. The presence of dysplasia is a major risk factor for progression to EAC[59,60]. Furthermore, there is uncertainty among pathologists about the histopathological diagnosis of low-grade dysplasia[60] (LGD). The annual risk of malignant progression is 5.2–9.1% in patients with LGD that was confirmed by an expert pathologist[60,61]. A meta-analysis estimated that the risk of EAC is 6.6% per annum in patients with high-grade dysplasia (HGD), but considerably higher rates (up to 28%) have been reported in therapeutic studies[62–64].

Mechanisms/pathophysiology

Pathogenesis

BE occurs as a result of epithelial injury in the distal oesophagus, which is caused by reflux of acid, bile and other noxious substances, and a subsequent reparative response. Reflux-induced damage is usually repaired by regeneration of squamous cells, but in some individuals, the squamous epithelium in the distal oesophagus is replaced by a differentiated columnar epithelium (that is, IM)[65]. Similarly to gastric and intestinal mucosa, BE has a glandular structure comprising crypts that contain stem cells that are located approximately one-third of the distance from the base of the crypts. There are various cell lineages within the metaplastic columnar lining of BE, including columnar cells that strongly express the mucins *MUC1* and *MUC5AC* and the trefoil family member *TFF1*; mucus-secreting cells that express *MUC6*, *TFF2* and *TFF3*; and goblet cells that express *MUC2* and *MUC3*, which are similar to the epithelial cell types that are present in the intestine[66,67].

Exposure to gastric refluxate, which frequently contains bile acids from duodeno-gastro-oesophageal reflux, is associated with increased oxidative stress, activation of inflammatory mediators and DNA damage in cells of BE[68]. The resulting inflammatory infiltrate is accompanied by changes in the expression of key genes that are involved in cell fate and development, including *BMP4, PTGS2, SHH*, the caudal-type homeobox genes *CDX1* and *CDX2*, *Notch* and *SOX9* (REFS[69–73]).

Table 1 | **Selected risk factors for BE and EAC**

Risk factor	Association with BE (OR (95% CI))[a]	Association with EAC (OR (95% CI))[a]	Refs[b]
Male sex	2.0 (1.8–2.2)	2.2 (1.8–2.5)	24,53–55
White ethnicity	+	+	20,22,33
Increased age	1.0 (1.0–1.1)	1.0 (1.0–1.1)[c]	11,25,53–55
Presence of GERD symptoms	2.9 (1.9–4.5)	7.7 (5.3–11.4)	14,44
Hiatal hernia size	3.9 (3.0–5.1)	Unknown	46
BMI (per unit increase)	1.0 (0.9–1.0)	1.0 (0.9–1.2)[c]	34,35,55
Waist circumference ratio (per 5 cm increase)	1.2 (1.0–1.3)	2.1 (1.3–3.2)	35
Cigarette smoking	1.4 (1.2–1.7)	1.5 (1.1–2.0)[c]	26,55,56,229
Alcohol intake	1.1 (0.6–1.8)	1.1 (0.8–1.5)[c]	55,230
Helicobacter pylori infection	0.7 (0.6–0.8)	0.5 (0.4–0.7)	47,48,231
NSAID use	1.0 (0.8–1.3)	0.7 (0.5–1.0)[c]	51,55
Family history of GERD, BE or EAC	+	+	49,50

BE, Barrett oesophagus; BMI, body mass index; EAC, oesophageal adenocarcinoma; GERD, gastro-oesophageal reflux disease. + indicates positive for risk factor. [a]Odds ratios for family history are not available and in the case of white ethnicity, they depend on the population that is used for comparison. [b]If a recent meta-analysis has been published, it is preferentially listed. [c]Odds ratio for factors associated with progression of BE to EAC.

Several hypotheses exist about the cellular origins of BE, although consensus is lacking[65] (FIG. 2a). For example, BE may develop by transdifferentiation of mature oesophageal squamous cells to columnar epithelial cells, or IM may result from differentiation of immature progenitor cells (transcommitment). Although the various models seem to be distinct, they may not be mutually exclusive and the formation of BE may involve a combination of these processes.

Transdifferentiation of oesophageal squamous cells. BE may develop by direct transdifferentation of oesophageal squamous cells into metaplastic columnar cells[74]. Indirect transdifferentiation, in which the squamous cell first dedifferentiates into a transitional cell that then differentiates into a columnar cell, has also been proposed in the setting of GERD[65]. In transdifferentiation, the reflux-induced inflammatory environment (mediated by prostaglandin E_2 (PGE_2), nuclear factor-κB (NF-κB), TNF and other molecules) leads to increased sonic hedgehog signalling and decreased Notch signalling (FIG. 2b).

The transcription factor CDX2 is an important contributor to the transdifferentiation of squamous cells into IM (FIG. 2b). Selective overexpression of *Cdx2* from the *Krt14* promoter in the mouse oesophagus and forestomach induces a glandular phenotype in the squamous-cell-lined oesophagus, which is characterized by reduced basal keratinocyte proliferation, reduced barrier function and the presence of transitional cells with secretory features[72]. In patients with reflux-related symptoms, CDX2 expression was detected in oesophageal biopsy samples with IM but not in those without IM[75]. However, other factors probably contribute to IM, as it does not occur in transgenic mice overexpressing *Cdx2* (REF.[72]).

Overexpression of the TGFβ family member *Bmp4* in mice induced a columnar phenotype in the epithelium at the squamocolumnar junction (SCJ), which contained glands that were positive for phosphorylated SMAD1 (pSMAD1), pSMAD5 and/or pSMAD8 but lacked expression of the IM markers CDX2 and MUC2 (REF.[69]). In another mouse model of BE (caused by surgically induced reflux), high levels of pSMAD1, pSMAD5 and/or pSMAD8, CDX2 and MUC2 were observed in columnar epithelial cells[69]. This study demonstrated that a non-specialized columnar epithelium may be an intermediate stage in the formation of a specialized IM, in which the downstream BMP targets pSMAD1, pSMAD5 and/or pSMAD8 are required as cofactors to activate the transcriptional activity of CDX2. However, other signalling pathways may also be involved in this process (FIG. 2b).

Transcommitment of progenitor cells. Despite some evidence for transdifferentiation, reprogramming of immature pluripotent stem cells (that is, transcommitment) is perhaps a more likely explanation for the multiple different cell types observed in BE. BE was initially thought to result from migration of columnar epithelial cells from the gastric cardia in response to tissue damage[76]. However, in animal studies, a columnar epithelium still develops in a damaged oesophageal mucosa that is separated from the gastric mucosa by a normal squamous epithelium[77], which is not consistent with this hypothesis. Evidence exists for migration of progenitor cells (marked by expression of the stem cell marker LGR5) from the gastric cardia to the distal oesophagus in a Notch1-dependent manner in a mouse model of BE (induced by chronic inflammation due to oesophageal overexpression of IL-1β)[78]. IL-1β overexpression was sufficient to induce IM, dysplasia and cancer, which was accelerated by dietary bile acids. The molecular similarity between EAC and chromosomally unstable gastric cancer, and the resemblance between BE-associated EAC and normal gastric mucosa in their chromatin structure, is further (indirect) evidence for the gastric origin of BE[79,80].

Another hypothesis is that stem cells in oesophageal submucosal glands undergo transcommitment to form a columnar epithelium. In this model, the columnar epithelium and the submucosal glands are a morphological continuum and different clones of immature stem cells are reprogrammed to differentiate into BE[81,82]. In the porcine oesophagus, submucosal glands contain a population of pluripotent stem cells that can differentiate into both squamous epithelium and columnar epithelium. Interestingly, these pluripotent stem cells proliferate in response to injury, which is also observed in oesophageal submucosal glands in humans[83,84]. In support of this model, single-cell transcriptomics of oesophageal cells from biopsy samples of patients with BE and healthy individuals identified a cell population in BE that expresses the stem cell factors olfactomedin 4 (OLFM4) and LEFTY1 and had a transcription profile that substantially overlaps with that of oesophageal submucosal gland cells[85].

Studies in mice suggest that BE may develop from the proximal migration of dormant stem cells or transitional epithelium progenitor cells that are present at the SCJ. In this model, BE develops through competition

between stem cells in the squamous epithelium and residual embryonic stem cells at the SCJ for stem cell niches. In p63-deficient adult mice that lack stratified epithelia, embryonic KRT7$^+$p63$^-$ stem cells from the SCJ proliferate in response to damage to the squamous epithelium, which leads to oesophageal metaplasia[86]. In fact, a histologically distinct multilayered transition zone at the SCJ is present in both mice and humans and contains KRT5$^+$KRT7$^+$p63$^+$ basal progenitor cells, overlaid by luminal KRT7$^+$ cells[71]. A surgically induced reflux model and a *Cdx2*-overexpression mouse model with lineage tracing showed that BE-type metaplasia arises from this transitional epithelium[71].

Other sources of these progenitor cells include resident stem cells in the basal layer of the oesophagus or multipotent bone-marrow-derived stem cells[87,88],

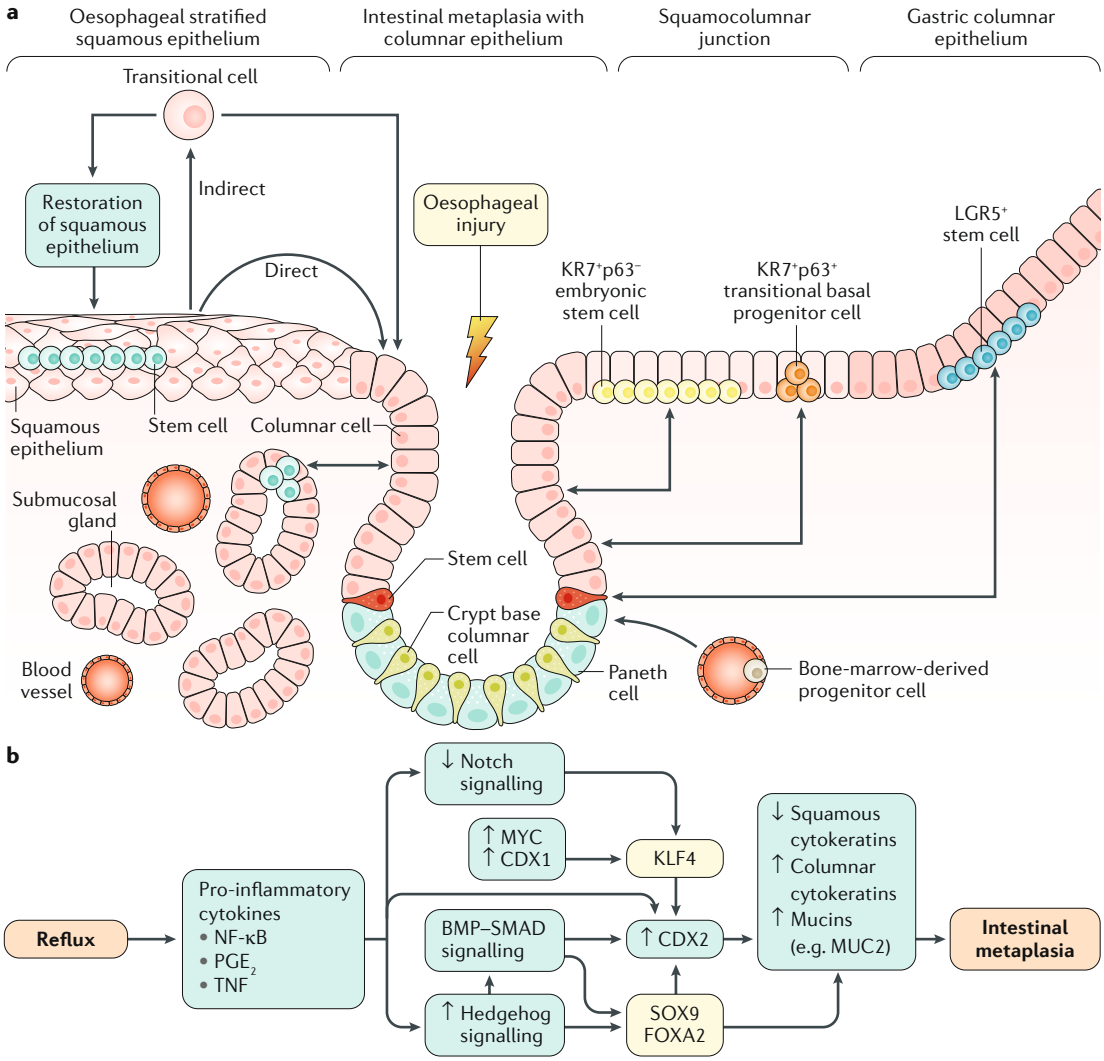

Fig. 2 | **Pathogenesis of Barrett oesophagus. a** | Pathogenetic mechanisms in Barrett oesophagus (BE). Various cell types have been proposed to give rise to intestinal metaplasia (the replacement of oesophageal squamous epithelium by intestinal columnar epithelium in response to oesophageal injury, typically by gastric reflux) in BE, which can progress to oesophageal adenocarcinoma. Intestinal metaplasia can arise by transdifferentiation of squamous cells, directly or via a transitional cell, or by migration of bone-marrow-derived progenitor cells to the mucosa. Furthermore, various stem cells, including residual embryonic stem cells, submucosal gland stem cells or gastric cardia stem cells, or progenitor cells, including gastro-oesophageal junction or basal squamous progenitor cells, can undergo transcommitment. The pathogenetic mechanisms might act separately or in combination to give rise to the BE lesion. **b** | Molecular mediators of transdifferentiation in BE. Reflux-induced oesophageal injury leads to inhibition of Notch signalling and increased expression of MYC and the homeobox protein CDX1, which promote transdifferentiation by decreasing levels of squamous epithelium cytokeratins and increasing levels of columnar epithelium cytokeratins and mucins[73]. The transcription pathways mediating these changes are unclear, although KLF4 expression seems to be upregulated, which is linked to increased transcription of *CDX2* and *MUC2* (REF.[227]). Furthermore, reflux activates Hedgehog signalling in squamous epithelial cells, leading to secretion of sonic hedgehog (SHH). SHH induces BMP4 expression in stromal fibroblasts, which in turn activates BMP4–SMAD1/SMAD5/SMAD8 (BMP–SMAD) signalling in squamous cells and thereby increases CDX2 and MUC2 expression (REF.[228]). BMP and SHH also upregulate the transcription factors SOX9 and FOXA2, which in turn can upregulate the levels of CDX2 and MUC2 (REF.[228]). NF-κB, nuclear factor-κB; PGE_2, prostaglandin E_2.

although robust evidence from clinical studies for either of these sources is very limited.

These models of BE pathogenesis have mostly been studied using surgically induced reflux or transgenic mouse models of BE, which have multiple limitations that must be considered when translating these results to humans[89].

Germline susceptibility and environmental factors. Susceptibility to BE is probably a composite effect of environmental risk factors, various germline and somatic genetic variants and epigenetic variants. Genetic and other analyses have identified a multitude of genetic polymorphisms and humoral factors (such as circulating levels of various cytokines) that are associated with risk of development and progression of BE[90–92]. Genome-wide association studies (GWASs) showed that germline genetic susceptibility factors constitute ~35% of the heritability of BE and ~25% of EAC[93]. Furthermore, GWASs showed that a polygenic component underlies disease risk in unrelated individuals with BE or EAC and that a substantial proportion of single-nucleotide polymorphisms (SNPs) overlap in individuals with BE or EAC, which suggests a shared genetic basis of susceptibility[93]. These SNPs are in or near genes that regulate oesophageal development (for example, *FOXF1* and *FOXP1*), ion transport (cystic fibrosis transmembrane conductance regulator (*CFTR*)) and immune regulation (the major histocompatibility complex genes and the antioxidant microsomal glutathione *S*-transferase 1)[94,95]. Another GWAS explored the association between several well-known epidemiological risk factors for BE (GERD, cigarette smoking and BMI) and seven SNPs that are implicated as risk factors for BE[96]. Only a SNP in *FOXP1* combined with at least weekly reflux symptoms modified the risk of developing BE and EAC[96]. An analysis of a large number of SNPs identified multiple risk-modifying polymorphisms. Individuals with obesity (BMI ≥30 kg/m^2) and an rs491603-AA genotype had a threefold increased likelihood of BE compared with those with BMI <25 kg/m^2. Risk of BE in individuals with a history of heavy smoking and an rs11631094-AA genotype at chromosome 15p14 was 50% that of light smokers[90]. Smoking status and rs13429103, and recurrent GERD symptoms and three SNPs (rs12465911, rs2341926 and rs13396805), affected the risk of EAC (OR ~2.0)[90]. These findings need to be validated in future studies.

Malignant progression in BE

The transformation of BE to dysplasia and then to EAC requires accumulation of genetic and epigenetic alterations at an early stage, which enable metaplastic cells to acquire the core physiological capabilities of tumour cells[97]. These acquired features include generation of their own mitogenic signals (generally through oncogene activation), resistance to growth inhibitory signals (generally through inactivation of tumour suppressor genes), avoidance of apoptosis, immortalization, vascularization, invasion of adjacent structures and metastasis to distant structures, reprogramming of energy metabolism and evasion of tumour-destroying immune cells[97]. The acquisition of these core capabilities is facilitated by genomic instability (which can be reflected by aneuploidy and whole-genome doubling), somatic driver and passenger mutations and a tumour-promoting, inflammatory microenvironment (that is, oxidative stress)[97,98]. This conceptual framework can be useful to classify the numerous acquired genetic alterations described during malignant progression of BE into the major carcinogenic capabilities[99].

Pathways for malignant progression. Whole-exome sequencing of DNA extracted from areas of BE adjacent to EAC has revealed a somatic mutation frequency of 1.3–5.4 mutations per Mb of DNA in non-neoplastic metaplasia[100–102], which is higher than that in prostate or breast carcinomas. The mutation pattern was indicative of genomic damage caused by oxidative stress, most likely due to GERD. Mutations in *TP53* are early shared mutations in tumour development, as they are found in both EAC and adjacent (high-risk) non-dysplastic BE[100]. Although the mutational load in EAC is high, many somatic mutations, such as those in *ARID1A* and *SMARCA4*, were also present in biopsy samples from non-dysplastic BE that did not progress to HGD or EAC (low risk). These early-occurring passenger mutations contribute to increased clonal expansion and changes in clonal diversity[102], whereas the acquisition of a driver mutation pushes the cell towards cancer[103]. Analysis of BE without dysplasia suggests that the level of genetic diversity at baseline remains constant over time and is associated with an increased risk of malignant progression in BE[101,102,104].

Only a minority of tumours progress along this traditional pathway of stepwise loss of function of *TP53* and other tumour suppressor genes (such as *CDKN2A* and *SMAD4*) followed by oncogene amplification and the development of genomic instability (FIG. 3).

Whole-exome sequencing and whole-genome sequencing studies have identified other pathways to malignancy, involving alterations in large regions of the genome, which can arise at any stage and accelerate malignant progression[100,102,105,106]. In fact, the frequency of whole-genome duplication suggests that a substantial proportion of tumours in Barrett metaplasia might develop through the genome duplication pathway. In this pathway, *TP53* mutations occur first, followed by whole-genome duplication in dysplastic tissues and then genomic instability and oncogene amplification in cancerous tissues[98,100] (FIG. 3).

Other genomic events, such as chromothripsis (chromosome shattering), kataegis (localized regions of hypermutation) and breakage–fusion–bridge (chromosome breakage followed by fusion and bridge formation), may also be mechanisms of malignant progression in BE. Although the understanding of their role in progression is incomplete, the presence of these genomic catastrophes in BE with HGD and in EAC suggests that multiple mechanisms are involved in the rapid progression[105,106].

Diagnosis, screening and prevention

Diagnosis

Endoscopy is the gold-standard test for a diagnosis of BE. Upper endoscopy is indicated in patients >50 years of age who have new-onset symptoms of reflux or dyspepsia and at any age if these symptoms persist despite

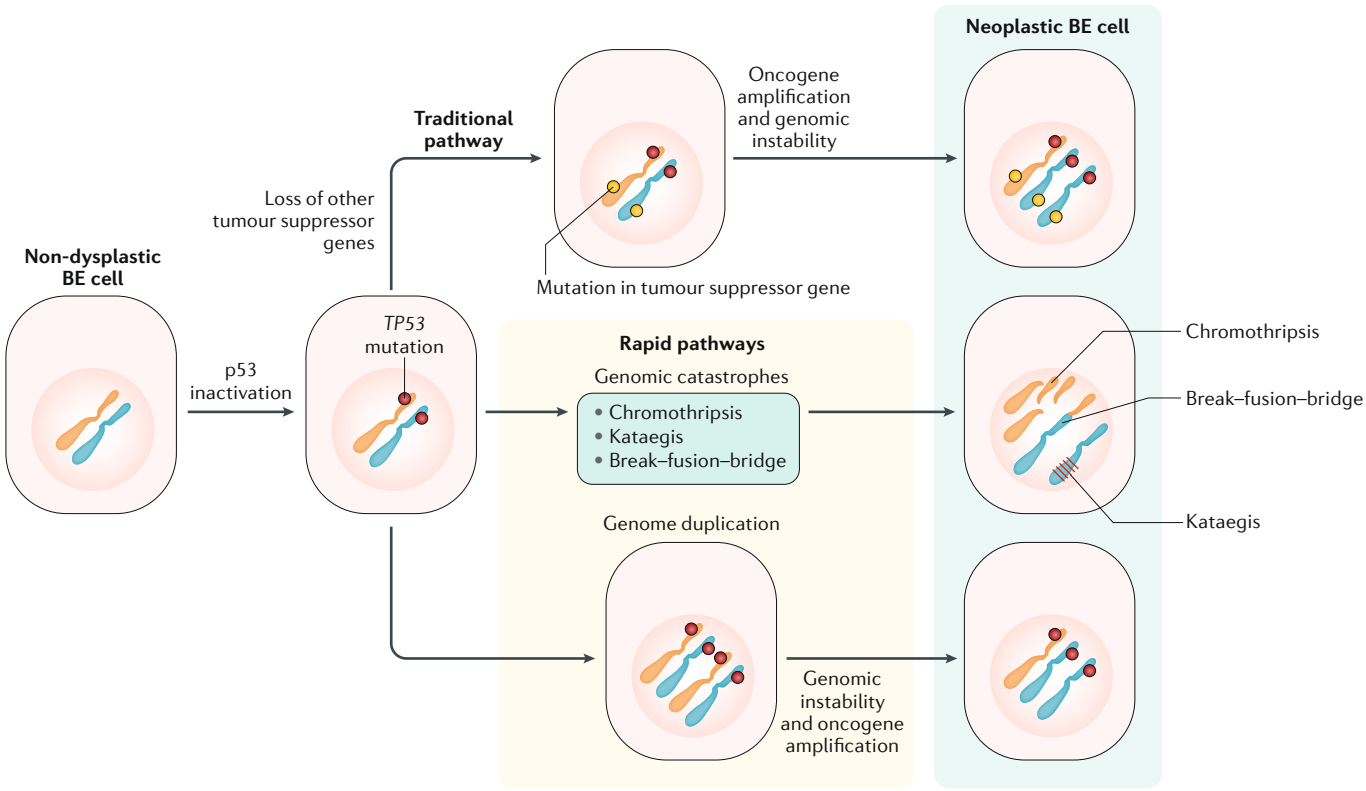

Fig. 3 | **Mechanisms of malignant progression in Barrett oesophagus.** Non-dysplastic cells in Barrett oesophagus (BE) first acquire mutations in *TP53* that inactivate p53. In the traditional pathway, stepwise accumulation of loss-of-function mutations in other tumour suppressor genes occurs next, followed by oncogene amplification and genomic instability, which eventually lead to cancer formation. Conversely, in the genome-doubling pathway, *TP53*-mutant non-dysplastic cells in BE undergo whole-genome duplication to form dysplastic tissues, which progress to oesophageal adenocarcinoma by genomic instability and oncogene amplification. Rapid progression to malignancy can also occur by chromothripsis (chromosome shattering), kataegis (localized regions of hypermutation) and breakage–fusion–bridge.

initial medical management or in the presence of alarm symptoms (that is, dysphagia, persistent vomiting, weight loss, upper GI bleeding or anaemia)[107,108]. A BE diagnostic yield of 3–12% was obtained in patients who were referred with GERD or dysphagia[13–15]. The final diagnosis of BE is made by synthesis of endoscopic and histopathological evidence of columnar-lined epithelium (FIG. 4). Although diagnosis seems straightforward, there continues to be debate about the precise endoscopic and histopathological criteria (FIG. 5; TABLE 2).

Endoscopic diagnosis. During endoscopic examination, the BE segment is inspected with high-definition white-light (HD-WL) endoscopy and a targeted biopsy of visible mucosal lesions is performed. In the Seattle protocol, random four-quadrant biopsy samples are obtained every 2 cm, starting from the upper end of the gastric folds[1–3,109]. The minimum length of a columnar-lined epithelium (circumferential or maximum length of the BE segment) for an endoscopic diagnosis of BE is the subject of debate (TABLE 3). The guidelines of the American Gastroenterology Association, Cancer Council Australia and the Japanese Society of Gastroenterology do not indicate a minimum segment length[1,110,111], whereas those of the American College of Gastroenterology (ACG), the British Society of Gastroenterology and the European Society of Gastrointestinal Endoscopy require a columnar epithelium that is clearly visible endoscopically and ≥1 cm in length (measured from the GEJ) for a diagnosis of BE[2,3,109]. The minimum length cut-off stems mostly from the high interobserver variability in diagnosis of sub-centimetric BE and the very low cancer risk associated with ultra-short BE[2,112,113].

Quality indicators have been published to guide physicians in endoscopic diagnosis and in judging the appropriateness of diagnosis and management of BE[114]. These indicators include careful delineation of endoscopic landmarks (diaphragmatic pinch and GEJ) and use of the Prague classification for measuring the length of BE[115] (FIG. 4). Adherence to quality indicators and to the Seattle biopsy protocol led to a 2–3-fold higher rate of dysplasia diagnosis[116,117].

Pathological diagnosis. Debate also exists about histopathological criteria for a BE diagnosis — in particular, whether the presence of specialized IM with goblet cells is required. The guidelines of all the major societies agree that IM is a diagnostic prerequisite, although some guidelines accept that short BE segments may be columnar-lined epithelium without the presence of IM (TABLE 3). Furthermore, IM can be missed owing to insufficient sampling, as the yield of IM correlates

directly with the number of endoscopic biopsy samples obtained[118]. However, although IM might not be essential for a BE diagnosis in all guidelines, routine surveillance for short-segment BE (<3 cm in length) without IM (confirmed by two endoscopies) is not recommended by any Western society owing to a very low cancer risk in the absence of IM[57]. In addition, in some guidelines, cases with tongues of columnar-lined oesophagus <1 cm in length (that is, an irregular SCJ or Z-line) should not be routinely biopsied and an incidental finding of IM within an irregular Z-line is not an indication for routine surveillance and should be diagnosed as IM of the gastric cardia, not BE. IM of the gastric cardia is a common finding in routine endoscopy (up to 18% of all upper endoscopies)[119], has a different epidemiology from BE and EAC (a lower male:female ratio and an association with *H. pylori* infection) and has a very low cancer risk[11,119].

Staging. Progression from BE to EAC occurs through a morphological continuum of progressive derangement of cytological features (such as variably sized and enlarged nuclei, rounded nuclei, loss of polarity and prominent nucleoli) and the development of glandular architecture (complex budding or branching of glands and back-to-back glands). According to the Vienna classification, GI epithelial neoplasia is classified as indefinite for dysplasia (that is, dysplasia that cannot be confidently identified or ruled out), LGD, HGD, non-invasive carcinoma and suspicion of invasive carcinoma[120]. To date, dysplasia remains the best available marker of cancer risk in patients with BE, although there is considerable inter-observer and intraobserver variability in the interpretation of dysplasia (TABLE 2). The Vienna classification has improved the agreement among pathologists in staging early neoplasia in the oesophagus, although the cytological and architectural changes in LGD can be subtle and agreement among pathologists remains very low ($\kappa = 0.11$)[121]. The Seattle biopsy protocol clearly detects more dysplasia than ad hoc random biopsies[122], although sampling error is inevitable as this protocol samples <5% of the BE epithelium[118]. The role of computer-assisted or brush biopsies for increasing the yield of dysplasia is currently being assessed[123].

Most LGD cases and up to one-third of HGD cases are invisible by standard white-light endoscopy. Consequently, considerable effort has been dedicated to developing novel imaging modalities to improve detection of early neoplasia, although convincing evidence that these modalities can improve diagnosis of BE is still lacking. A multicentre, randomized, crossover trial compared narrow-band imaging (in which light of specific wavelengths is used to improve the resolution of the surface mucosa) with targeted biopsies to standard high-definition endoscopy with targeted and random biopsies[124]. Although narrow-band imaging diagnosed a higher proportion of areas with dysplasia than did standard endoscopy (30% versus 21%, $P = 0.01$), this did not translate into a diagnostic benefit in the per-patient analysis[124]. Other imaging techniques, such as acetic acid chromoendoscopy, confocal laser endomicroscopy and volumetric laser endomicroscopy, are being evaluated (reviewed elsewhere[125]). In summary, a thorough endoscopic examination with high-definition endoscopy, strict adherence to basic quality indicators and allowing sufficient time for mucosal cleaning and inspection

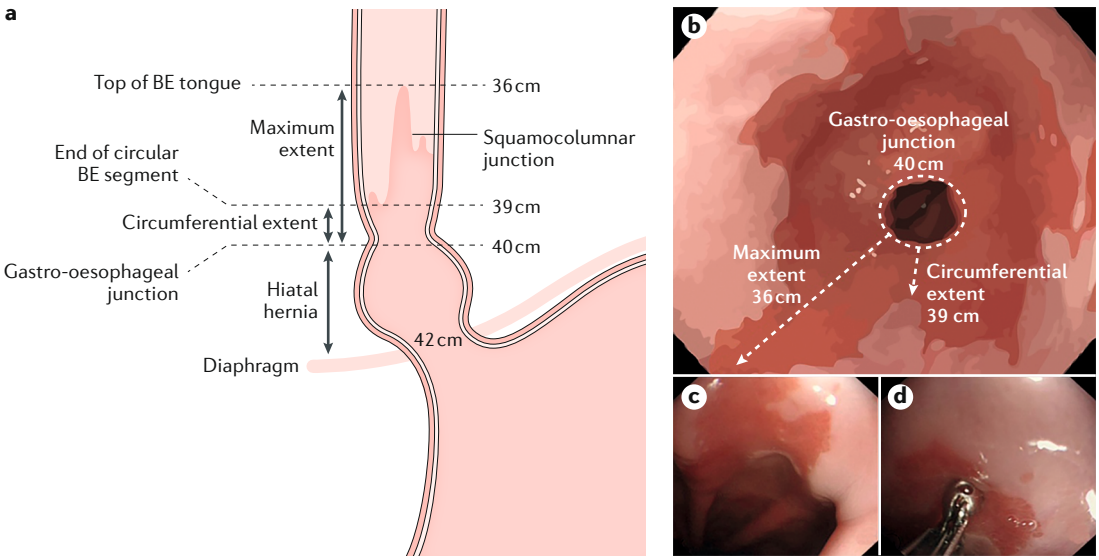

Fig. 4 | **Endoscopic diagnosis of Barrett oesophagus.** Endoscopic criteria for a diagnosis of Barrett oesophagus (BE) are described in the Prague classification (REF.[115]). **a**,**b** | The lower measurement boundary is formed by the most proximal extent of the gastric folds, at the gastro-oesophageal junction. The two upper measurement boundaries are marked by the proximal margin of the circumferential BE segment (circumferential extent) and the proximal margin of the longest tongue-like BE segment (maximum extent). In these panels, the Prague classification is C1M4. **c** | A short segment of columnar-epithelium-lined oesophagus can be difficult to size endoscopically. **d** | Measurement of BE segment length using open biopsy forceps (usually 6 mm maximum open size). In this case, the segment length was measured as 1 cm (Prague classification: C0M1). Image in part **b** courtesy of I. Koutroubakis, on behalf of the Annals of Gastroenterology, Annals of Gastroenterology, Greece.

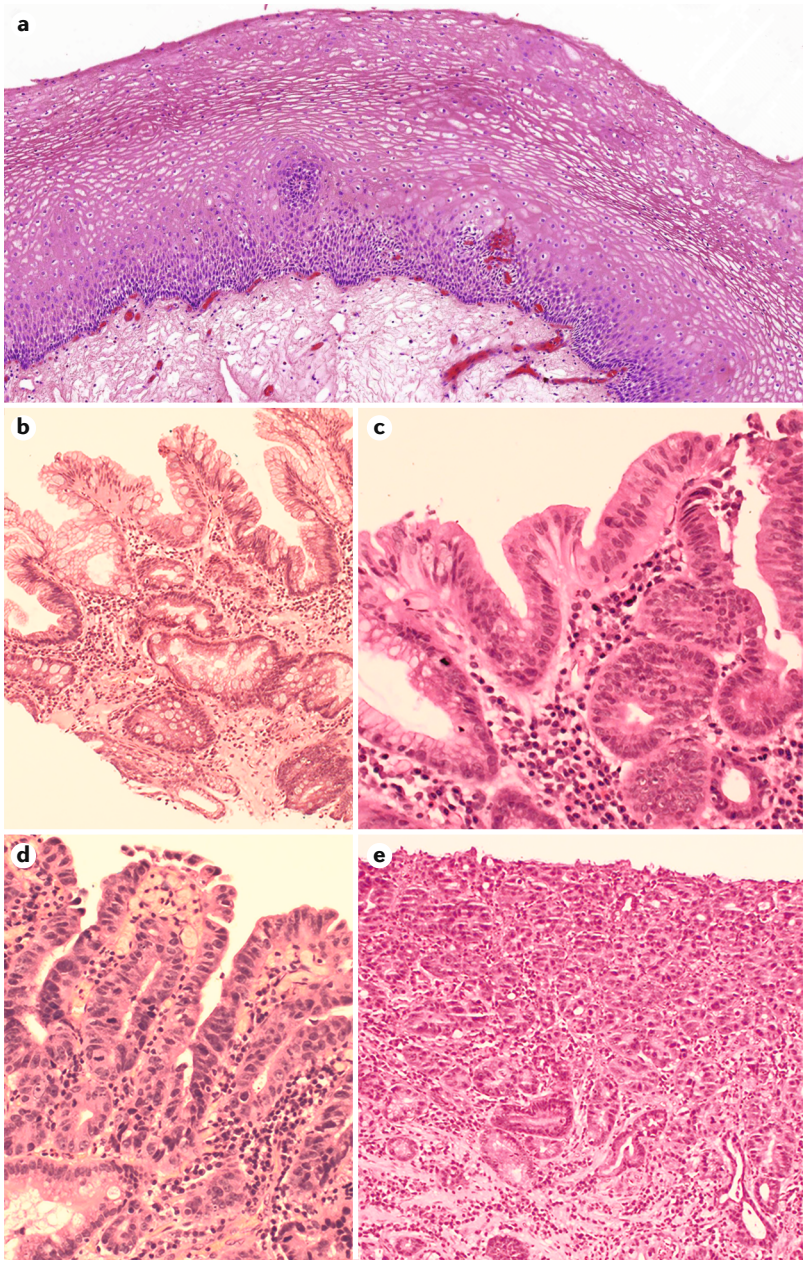

Fig. 5 | **Histopathological features of Barrett oesophagus.** Progression from squamous epithelium to intestinal metaplasia, dysplasia and oesophageal adenocarcinoma (see TABLE 2 for detailed description of these stages). **a** | Normal oesophageal squamous epithelium. Magnification ×4. **b** | Intestinal metaplasia containing goblet cells: intestinalized columnar-lined epithelium, normal cytology and normal surface maturation (nuclear:cytoplasmic ratio of surface epithelium is lower than basal cells). Magnification ×10. **c** | Low-grade dysplasia: mild architectural changes, surface maturation disrupted (stratification) and mild, diffuse cytological abnormalities (for example, enlarged hyperchromatic nuclei, mitotic activity and normal cell polarity). Magnification ×20. **d** | High-grade dysplasia: marked architectural changes, no surface maturation and marked cytological abnormalities (for example, enlarged nuclei, loss of cell polarity, mitotic activity and atypical mitoses). Magnification ×20. **e** | Oesophageal adenocarcinoma: marked architectural changes with crowded irregular glands showing marked cytological abnormalities with enlarged nuclei, loss of cell polarity, mitotic activity and atypical mitoses. Lamina propria and submucosa invasion is present. Magnification ×10. Staining in all panels is with haemotoxylin and eosin. Image in part **a** courtesy of R. S. van der Post, Radboud University Medical Centre, Netherlands. Images in parts **b**–**e** courtesy of M. O'Donovan, Cambridge University Hospital, UK.

seem to be the key elements for maximizing detection of dysplasia in routine practice.

Despite these advances in endoscopy and standardization of diagnostic approaches, EAC is detected in 20–25% of patients with non-dysplastic or LGD BE within 1 year of a BE diagnosis, indicating that initial endoscopy frequently misses dysplasia and EAC[126]. The number of patients with EAC who present at the time of or shortly after an initial diagnosis of BE greatly exceeds the number of incident cancers, which demonstrates the importance of early diagnosis of BE and related neoplasias.

Prevention

Modifiable risk factors. Strategies to minimize the effect of risk factors, such as GERD, obesity and smoking, might reduce the incidence of BE and related neoplasias and are likely be more effective than pharmacological chemoprevention[9]. In 2018, the World Cancer Research Fund (WCRF), in collaboration with the American Institute of Cancer Research, published a series of recommendations on diet, physical activity and weight management for cancer prevention[127]. Although recreational and occupational physical activity are associated with ~35% lower risk of BE and EAC[128,129], this association varies greatly among studies and the lack of a dose–response relationship warrants careful interpretation of these findings. Diet also seems to have a role in the prevention of BE development and progression. In a study comparing patients with GERD, non-dysplastic BE, dysplastic BE or EAC, adherence to the WCRF recommendations for high fruit and low processed meat consumption was 5–6-fold lower in the advanced disease group (dysplasia and EAC) than in the less advanced disease group (GERD and BE)[130]. In two case–control studies of the population of Northern Ireland, high dietary levels of vitamin D directly correlated with increased risk of EAC (OR 1.99, 95% CI 1.3–3.86)[131], whereas high magnesium intake protected against reflux oesophagitis (OR 0.31, 95% CI 0.11–0.87) and BE (OR 0.29, 95% CI 0.12–0.71)[132]. A vitamin-D-restricted diet is not a viable chemopreventive strategy given the protective effect of vitamin D against other types of cancer, including colorectal, breast, prostate and some haematological malignancies[133]. Conversely, a diet rich in magnesium might be an interesting component of a preventive strategy, as magnesium has well-established anti-inflammatory properties and is associated with a reduced risk of oesophagitis and BE in a retrospective study[132,134].

Primary chemoprevention. PPIs, NSAIDs and statins are the most promising classes of drugs for primary chemoprevention of BE. Acid-suppression therapy using PPIs is commonly prescribed for patients with BE to reduce heartburn symptoms, although whether these drugs reduce cancer risk in BE is debated and most GI societies currently recommend acid-suppression therapy for symptom control but not for primary chemoprevention. Long-term adverse effects have been increasingly reported in low-quality retrospective studies (reviewed elsewhere[135]), whereas long-term follow-up data from

Table 2 | **Histopathological features of BE**

Stage	Histopathology features[a]	Interobserver agreement (κ value)	HGD and EAC risk per 100 person-years (95% CI)
NDBE	• Intestinalized columnar-lined epithelium • Normal cytology • Normal surface maturation (nuclear:cytoplasmic ratio of surface epithelium is lower than basal cells)	0.58–0.73 (REFS[232,233])	• EAC: 0.33 (0.28–0.38)[234,b] • HGD/EAC: 0.26 (0.22–0.31)[17]; 0.68 (0.61–0.74)[18]
IND	• Normal architecture • Normal surface maturation • Mild cytological abnormalities	0.15–0.21 (REFS[232,233,235])	• EAC: 0.8 (0.5–0.12)[236] • HGD/EAC: 1.4 (1.0–1.9)[236]
LGD	• Mild architectural changes • Surface maturation disrupted (stratification) • Mild, diffuse cytological abnormalities (such as enlarged, hyperchromatic nuclei, mitotic activity and normal cell polarity)	0.11–0.32 (REFS[121,232,233])	• EAC: 0.54 (0.32–0.76)[237,b]; 2.51 (1.46–3.99)[61] • HGD/EAC: 1.73 (0.99–2.47)[237,b]; 5.18 (4.32–8.10)[61]
HGD	• Marked architectural changes • No surface maturation • Marked cytological abnormalities (such as enlarged nuclei, loss of cell polarity, mitotic activity and atypical mitoses)	0.43–0.76 (REFS[121,232])	• EAC: 6.6 (5.0–8.5)[62,b]
EAC	• Marked architectural changes: carcinoma invades through basement membrane • No surface maturation • Marked cytological abnormalities (such as enlarged nuclei, loss of cell polarity, mitotic activity and atypical mitoses)	0.61–0.82 (REFS[235,238])	NA

BE, Barrett oesophagus; EAC, oesophageal adenocarcinoma; HGD, high-grade dysplasia; IND, indefinite for dysplasia; LGD, low-grade dysplasia; NA, not applicable; NDBE, non-dysplastic Barrett oesophagus. [a]Histopathology features are from REF.[239]. [b]Meta-analysis.

the SOPRAN and LOTUS prospective trials confirm that PPIs are generally safe as maintenance therapy[136]. The two main rationales for using potent acid suppression for chemoprevention are the inhibition of carcinogenesis by reduction in inflammatory pathways[137] and the suppression of the pro-proliferative effects of intermittent acid exposure, which is supported by in vitro data[138,139]. In a meta-analysis of seven observational studies that included 2,813 patients with BE, PPI use was associated with a 71% reduction in cancer risk (adjusted OR 0.29, 95% CI 0.12–0.79)[140] and a weak dose–response relationship was present, despite considerable heterogeneity among studies. However, a subsequent nationwide study of the Danish population assessing the effect of PPIs in 9,883 patients with BE did not show any cancer-protective effect. In the multicentre, two-by-two, factorial, randomized AspECT trial, 2,557 patients with BE received either low-dose or high-dose esomeprazole, with or without 300 mg aspirin[141]. Whereas high-dose PPI did not affect the occurrence of dysplasia or EAC, it delayed all-cause mortality (time ratio (TR) 1.36, 95% CI 1.01–1.82). Although the effect on all-cause mortality is difficult to explain, the similar rate of adverse events for the two PPI doses provides additional evidence for the safety of high-dose PPI. The association between PPI use and a decreased risk of progression in BE, and the possibility that inflammation may promote progression to neoplasia, validates once-daily PPI therapy, even in patients without reflux symptoms.

Aspirin and cyclooxygenase 2 (COX2) inhibitors have also been evaluated for potential chemoprevention, given the role of COX2 in inflammation and neoplastic progression. In a pooled analysis of >1,200 individuals with EAC and >5,000 population-based controls, users of aspirin and non-aspirin NSAIDs had a 32% lower risk of EAC than controls (OR 0.68, 95% CI 0.56–0.83) and there was a dose–response relationship[142]. In a meta-analysis of nine observational studies that included 5,446 participants, aspirin and non-aspirin NSAID use was associated with a reduced risk of EAC and HGD among individuals with BE (relative risk (RR) 0.64, 95% CI 0.53–0.77)[143]. In the AspECT trial, aspirin alone did not delay death compared with no aspirin (TR 1.25, 95% CI 0.92–1.70), although there was a small effect in delaying development of HGD (TR 1.51, 95% CI 1.00–2.29) but not EAC (TR 1.02, 95% CI 0.64–1.64). The combination of aspirin and high-dose PPI had the strongest effect in delaying all-cause mortality, EAC and HGD (TR 1.59, 95% CI 1.14–2.23)[141], although this benefit required compliance with high-dose PPI and aspirin treatment for >10 years.

Statins can be chemopreventive independently of their lipid-lowering activity, as they reduce cell proliferation and induce apoptosis in oesophageal cells by inhibition of RAS farnesylation and ERK and AKT signalling pathways[144]. In a case–control study of 303 individuals with BE and 909 control individuals, statin use was associated with 43% lower risk of BE (OR 0.57, 95% CI 0.38–0.87)[145] and the effect was much stronger among obese individuals (OR 0.26, 95% CI 0.09–0.71). These results were confirmed in another smaller case–control study of 123 individuals with BE and 268 control individuals in eastern England, which showed a similar protective effect of statins against BE (OR 0.62, 95% CI 0.37–0.93) and a greater protective effect with the combination of statins and aspirin (OR 0.43, 95%

CI 0.21–0.89)[52]. Similarly, in another case–control study of 311 individuals with EAC and 856 matched controls, statin use was inversely related to EAC development (OR 0.65, 95% CI 0.47–0.91)[146]. Interestingly, the lack of a protective effect with other lipid-lowering drugs in two of these studies[145,146] indicates that this protective effect is specific to statins.

Prospective studies are required to confirm these findings. Despite these promising results, chemoprevention is not currently recommended by society guidelines, but its use should probably be re-considered in future revisions of guidelines[1–3,109].

Screening

Patients with EAC have a dismal prognosis (5-year survival = 15%), and >40% of patients are diagnosed with EAC after it has metastasized[147]. However, a prior diagnosis of BE before a cancer diagnosis is associated with detection of the tumour at an earlier stage and improved survival[148]. Although BE is a known precursor of EAC, in daily practice >90% of patients with EAC never had prior endoscopy and EAC is usually diagnosed when symptoms develop, outside a programme of BE surveillance[148].

The fact that endoscopic therapy has become the standard of care for dysplasia or EAC in patients with BE, together with the recent developments in minimally invasive (non)endoscopic screening techniques for BE, means that screening for EAC and its precursor BE potentially fits the WHO criteria for screening (Supplementary Box 1) and might decrease EAC-related mortality. To date, upper endoscopy combined with biopsy sampling is the only screening method for BE that is approved by most societies.

Target populations. Before 2010, chronic GERD was the only criterion for entry in endoscopic screening programmes. For example, the first guideline from the ACG recommended endoscopic screening for anyone with >5 years of reflux symptoms[149]. Although these guidelines correctly recognize GERD symptoms as a major risk factor for BE, they fail to include other easily identifiable predisposing conditions (such as smoking, poor diet and obesity) that are available for risk stratification. Furthermore, the substantial prevalence of BE in patients without GERD casts doubt on whether a GERD-centric screening strategy can substantially influence persistently poor EAC outcomes[6,45].

In the past decade, professional societies have developed a more multifaceted approach to screening recommendations, such that the target population for BE screening parallels the characteristics of the population at highest risk of developing EAC (TABLE 4). Although guidelines vary, current recommendations are to consider screening by conventional upper endoscopy in patients with chronic, frequent gastro-oesophageal reflux symptoms and the presence of several other risk factors[1–4,109]. After an initial negative endoscopy, the risk of developing BE in patients with chronic GERD is low[150]. Therefore, one-time endoscopy could reassure patients with GERD without endoscopic evidence of BE that the risk of developing BE in the future is extremely low. Although an absolute age cut-off for BE screening is not recommended, it is important to consider the overall life expectancy of the patient and explain the implications of a diagnosis of BE before screening is conducted. General population screening for BE is currently not recommended in any society guidelines.

Risk models. A risk model was created from the US Veteran's Administration database, using cigarette smoking, age, waist:hip ratio and GERD symptoms as predictive variables for BE, and substantially improved prediction of the presence of BE compared with a model using GERD symptoms alone (area under the curve (AUC) = 0.61 versus 0.72)[151]. This score was validated in a case–control study in four independent data sets and showed similar results[152]. Attempts to improve prediction models using genetic variants that are known to be associated with BE or other humoral biomarkers, such as serum leptin or interleukin levels, are underway but are not yet ready for clinical use[90,153].

Table 3 | **Criteria for diagnosis of BE**

Society	Year	Endoscopic criterion	Histological criterion	Ref.
AGA	2011	Columnar epithelium extending for any length above the GEJ into the tubular oesophagus	Intestinal metaplasia	1
ASGE	2012	Salmon or pink colour, in contrast to the light-grey appearance of the oesophageal squamous mucosa	Specialized intestinal metaplasia	4
BSG	2014	Distal oesophageal mucosa replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (≥1 cm) above the GEJ	Columnar metaplasia (columnar-lined epithelium, regardless of the presence or absence of intestinal metaplasia)	3
ACG	2016	Extension of salmon-coloured mucosa into the tubular oesophagus for ≥1 cm proximal to the GEJ	Specialized intestinal metaplasia	2
JSG	2016	Columnar epithelium that continues from the stomach to oesophagus for any length	Columnar metaplasia (columnar-lined epithelium, regardless of the presence or absence of intestinal metaplasia)	110
ESGE	2017	Distal oesophagus lined with columnar epithelium with a minimum length of 1 cm (tongues or circular)	Specialized intestinal metaplasia	109

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; ASGE, American Society for Gastrointestinal Endoscopy; BSG, British Society of Gastroenterology; ESGE, European Society of Gastrointestinal Endoscopy; GEJ, gastro-oesophageal junction; JSG, Japanese Society of Gastroenterology.

Overall, tools that incorporate risk factors for BE and EAC could be used to identify high-risk patients and improve population screening. However, the development of minimally invasive screening tools may reduce the need for these BE risk scores by enabling more widespread screening.

Minimally invasive screening tools. Upper endoscopy is invasive, expensive and not suitable for widespread use. Therefore, a need exists for a safe, effective, minimally invasive screening method that is acceptable to patients. Several alternatives are currently being investigated[154,155] (FIG. 6), although only the ACG guidelines suggest an alternative to upper endoscopy, unsedated transnasal endoscopy (TNE)[2].

Despite a narrower working channel and smaller biopsy sample size, TNE has comparable clinical effectiveness (in terms of participation rates, yield, safety, tolerability and patient preference) to upper endoscopy and has lower direct and indirect costs[156–158]. Disposable silicone sheaths to enable reuse of the endoscope without reprocessing (Endosheath) or completely disposable transnasal capsules (EG Scan) provide more options for TNE, although biopsies are not always possible[159]. In addition, TNE can be performed by non-physicians and outside of hospitals, which could further reduce costs and increase access[160].

Novel minimally invasive techniques are in development and showed promising results in case–control studies but are not yet ready for clinical application (Supplementary Table 1). An imaging-based method, oesophageal capsule endoscopy (ECE), enables direct non-invasive visualization of the oesophagus, although biopsies are not possible[161]. In a meta-analysis assessing the accuracy of ECE for BE detection in 618 patients, pooled sensitivity and specificity were 77% and 86%, respectively[162], although the studies included in the analysis reported conflicting results about the diagnostic ability of ECE.

Collecting cells from the oesophagus for histopathological analysis without acquiring images offers an alternative approach to endoscopy to screen for BE. The most studied non-endoscopic cytological device for BE screening is an encapsulated sponge device attached to a string (Cytosponge)[8]. This device, combined with measuring trefoil factor 3 (TFF3; a cellular marker of intestinalization), has shown promising accuracy and acceptability in clinical studies[8,13] and is now being evaluated in a cluster-randomized trial of 13,000 patients in primary care; further biomarkers can be used to assess for the presence of dysplasia[163]. A similar approach using non-endoscopic cell collection devices (for example, inflatable balloons and capsule sponges) combined with a panel of methylated DNA or microRNA (miRNA) markers also showed promise for non-endoscopic detection of BE, but the results of larger studies are awaited[164–167]. Although copious quantities of cells are collected, a drawback of these non-endoscopic cell collection devices is the limited control over their passage through the oesophagus and the possible failure to retrieve cells from the GEJ.

Biomarker detection in the breath (using an electronic nose device to detect volatile organic compounds) or in blood (detection of miRNAs) is an attractive method for screening, as it is non-invasive, provides results quickly and is fairly inexpensive[168], although few studies of this method have been published to date.

Cost-effectiveness. All published modelling studies have assessed the cost-effectiveness of BE screening in white men >50 years of age who have chronic reflux symptoms[169] and have assumed a BE prevalence of 10% and a rate of progression to EAC of 0.5% (which may be higher than current estimates) in this population. These studies have mostly found that screening with standard upper endoscopy is cost-effective compared with no screening and decreases EAC incidence by 15–25% in this population (incremental cost-effectiveness ratios (ICERs) were less than US$50,000 in most studies). Data on cost-effectiveness of screening with TNE are somewhat limited, but ICERs of US$55,000 and US$28,000 have been reported[169,170]. Other (mostly older) studies did not use endoscopic therapy for the treatment of BE-related dysplasia or mucosal (stage T1a) EAC in the models, which may underestimate the positive effect of screening[171,172]. In addition, participation rates and direct and indirect costs were not included in estimates, and unreliable assumptions (such as 100% participation) were made. Newer, minimally invasive screening technologies (such as capsule sponge-based techniques[173]) are reported to be cost-effective in individuals with reflux symptoms (Supplementary Table 1), but cost-effectiveness at the population level has not been assessed to date.

Table 4 | **Recommended populations for BE screening**

Society	Year	Screening population	Ref.
AGA	2011	Multiple risk factors (≥50 years of age, male sex, white ethnicity, chronic GERD symptoms, hiatal hernia and obesity (elevated body mass index and intra-abdominal distribution of body fat))	1
ASGE	2012	Multiple risk factors (male sex, white ethnicity, >50 years of age, increased duration of reflux symptoms, smoking, obesity and family history of BE)	4
BSG	2014	Chronic GERD symptoms with ≥3 risk factors (50 years of age, white ethnicity, male sex, obesity and first-degree relative with BE or EAC)	3
ACG	2016	Men with either >5 years GERD and/or with more than weekly symptoms and ≥2 risk factors (>50 years of age, central obesity (waist circumference >102 cm or WHR >0.9), white ethnicity, smoking and first-degree relative with BE or EAC)	2
ESGE	2017	Longstanding GERD symptoms (>5 years) and multiple risk factors (≥50 years of age, white ethnicity, male sex, obesity and first-degree relative with BE or EAC)	109

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; ASGE, American Society of Gastrointestinal Endoscopy; BE, Barrett oesophagus; BSG, British Society of Gastroenterology; EAC, oesophageal adenocarcinoma; ESGE, European Society of Gastrointestinal Endoscopy; GERD, gastro-oesophageal reflux disease; WHR, waist:hip ratio.

Management

Strategies for the management of BE depend on the staging of the disease. Endoscopic treatment is indicated for patients with BE who have LGD, HGD, mucosal EAC and 'low-risk' submucosal EAC (FIG. 7) and is preferred

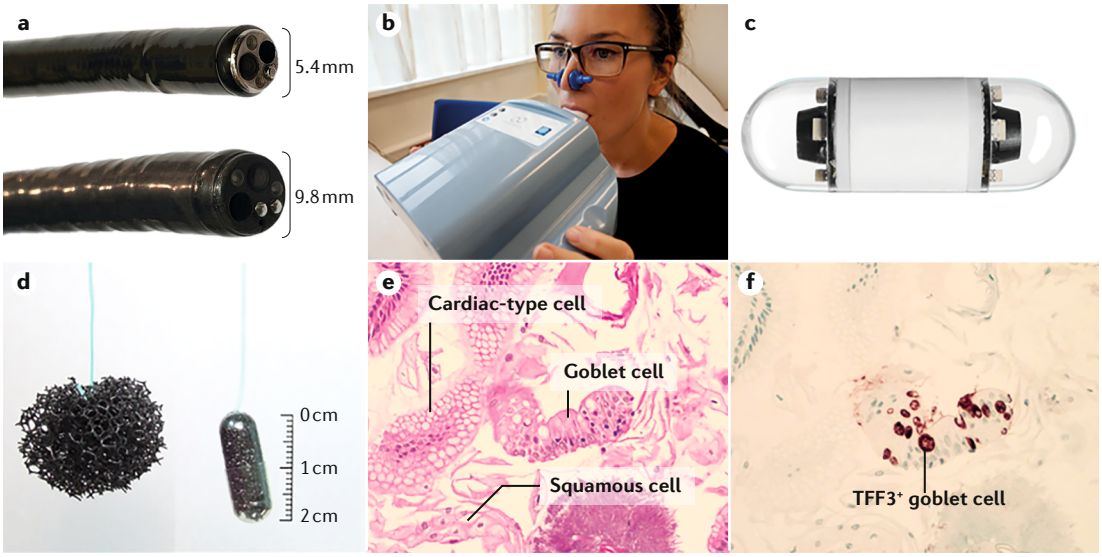

Fig. 6 | **Screening techniques for Barrett oesophagus. a** | Standard upper endoscope (Pentax EG29 (bottom)) and transnasal endoscope (Pentax EG16 (top)). **b** | Electronic nose. **c** | Capsule endoscopy. **d** | Cytosponge sampling device (expanded (left) and unexpanded (right)). **e**,**f** | A positive Cytosponge test shown by haemotoxylin and eosin staining (part **e**) and trefoil factor 3 (TFF3) immunohistochemistry (part **f**), with positive staining of the gland groups with goblet cells but not of cardiac-type mucosa and squamous epithelial cells. Magnification ×20 in parts **e** and **f**.

over surgical treatment. Management begins with careful inspection of the dysplastic BE segment and endoscopic resection of all visible lesions to enable adequate staging, followed by ablative therapy of the remaining BE[3,109,174]. Ablation should not be used as a primary treatment of early cancer in BE or endoscopically visible lesions, as the target mucosa is destroyed and histological staging is not possible after this treatment. In the absence of visible mucosal irregularities, endoscopic ablation without resection is sufficient.

Endoscopic treatment of non-dysplastic BE is not indicated, as risk of progression to HGD or EAC is too low to justify treatment. Any ablative therapy in patients with non-dysplastic BE is associated with costs and potential complications and therefore should not be performed outside controlled studies. Instead, endoscopic surveillance of patients with non-dysplastic BE is recommended in all available guidelines[3,109,174].

Surveillance

The aim of surveillance in patients with BE is to improve patient outcomes by detection of dysplasia or EAC at an early stage to ensure effective treatment. The efficacy of current surveillance strategies in reducing mortality in patients with BE compared with the general population is debated[148,175]. A meta-analysis demonstrated that surveillance was associated with diagnosis of earlier-stage EAC[59]. Furthermore, all-cause mortality was lower for cancers that are detected during surveillance than for cancers that were detected outside surveillance programmes. However, the benefit of lower mortality was eliminated after adjustment for lead-time and length-time biases.

The surveillance intervals are risk stratified by the presence and grade of dysplasia and, in European society guidelines, by the length of the BE segment (TABLE 5). Endoscopic surveillance with HD-WL endoscopy and histopathological evaluation of biopsy samples is now considered the standard of care. In some centres, several other advanced imaging methods (described earlier) are used for surveillance in clinical practice, although their routine use in patients with BE is not supported by scientific evidence or recommended by clinical guidelines.

The cost-effectiveness of surveillance in all patients with BE is the subject of debate. Many gastroenterologists argue that only patients at high risk of malignant progression should be included in a surveillance programme. An easy scoring system was developed that can identify patients at high risk of malignant progression[56], which identified male sex, smoking, BE length and baseline-confirmed LGD as significantly associated with progression to EAC. A similar model combining age, male sex and BE length could predict 71% of HGD and EAC cases[176]. Further prospective studies are needed to validate these models.

Endoscopic resection

Endoscopic mucosal resection. Patients with BE lesions containing dysplasia or superficial early EAC should undergo endoscopic mucosal resection (EMR) as the initial diagnostic and therapeutic procedure (FIG. 8). EMR provides a tissue specimen that can be evaluated for prognostic factors, such as dysplasia grade, differentiation grade, infiltration depth, vascular invasion and completeness of the resection. In a retrospective study, histopathological assessment of EMR tissue samples changed the diagnosis in ~50% of patients owing to the large tissue sample obtained with EMR[177].

The most common EMR technique involves the use of a multiband ligation device and a dedicated snare that can be advanced through the working channel with the

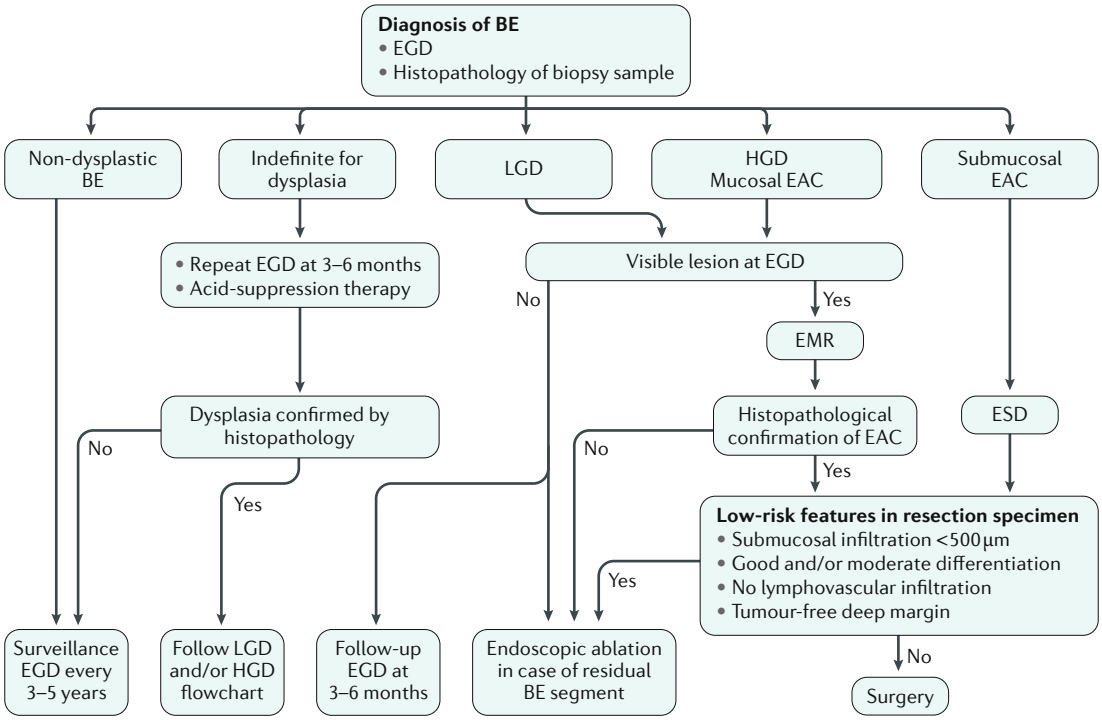

Fig. 7 | **Algorithm for management of non-dysplastic and dysplastic Barrett oesophagus.** In cases of Barrett oesophagus (BE) confirmed by oesophagogastroduodenoscopy (EGD) and histopathological assessment of biopsy samples, BE is staged as non-dysplastic, indefinite for dysplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD) or mucosal oesophageal adenocarcinoma (EAC), or submucosal EAC. For lower-grade disease (non-dysplastic or indefinite for dysplasia), surveillance at various intervals is recommended. For higher-grade disease with lesions visible by EGD, endoscopic mucosal resection (EMR) followed by ablation of the residual BE segment is recommended. In case of no visible lesion, endoscopic ablation is recommended in patients without life-limiting comorbidity, otherwise strict surveillance is warranted. Endoscopic submucosal dissection (ESD) may be considered in selected cases of EAC (with poorly lifting tumours, >15 mm or lesions at risk of submucosal invasion). If the endoscopic resection does not fulfil low-risk criteria, surgery is needed.

ligation device in place. EMR is an advanced endoscopic procedure that requires training by an experienced endoscopist in high-volume centres. A case series from the UK demonstrated that EMR in the upper GI tract was associated with a substantially higher mortality and perforation rate when performed by less experienced endoscopists[178]. Therefore, current society guidelines recommend that BE-associated EAC should be treated only in expert centres (centres with ten or more new cases with early neoplasia per year, access to experienced oesophageal surgery teams and prospective data collection for all BE cases)[109].

The largest case series of EMR in 1,000 patients with BE who have mucosal EAC demonstrated excellent long-term complete remission rates of neoplasia (93.8%) after follow-up of almost 5 years[179]. The reported complication rate was only 1.5%, although neoplastic recurrence rate is a problem in endoscopic treatment (14.5% in this series). As all patients were in a follow-up programme, recurrences were diagnosed at an early stage, making endoscopic re-treatment feasible in almost all cases.

Endoscopic submucosal dissection. Endoscopic submucosal dissection (ESD) enables en bloc resection of lesions of any size that invade the mucosa and submucosa. Although ESD is safe and effective in experienced hands, it is technically demanding and requires intensive training. In several prospective case series, complete resection (R0) rates of BE-associated EAC were 38.5–79% and stricture rates were up to 60%[180,181]. A prospective randomized series comparing EMR and ESD in 40 patients with mucosal BE-associated EAC found no significant difference in complete remission rates[182]. However, EMR is still the treatment of choice in current society guidelines[181]. Indications for ESD include bulky lesions that cannot be removed by EMR and suspicion of submucosal infiltration.

Complications of endoscopic therapy. The major complications of endoscopic resection include severe bleeding, perforations and strictures. Although ESD is technically more challenging than EMR and has a steeper learning curve, the complication rates are low in experienced hands. Bleeding is one of the most common complications of endoscopic therapy (<0.5% for EMR and 0.9–6.7% for ESD)[179,183]. Perforations after EMR and ESD occur in up to 5% of treated patients[179,182]. Stricture formation after EMR is related to the extent of resection and is minimal if <50% of the circumference is resected[184]. Complications of endoscopic therapy can usually be successfully treated during the same endoscopic procedure using endoscopic

bleeding control techniques, clip or stent placement or dilatation.

Endoscopic ablation

Radiofrequency ablation. The high rate of confirmed LGD progression to EAC is the reason why endoscopic ablation is recommended as an alternative to frequent endoscopic follow-up (FIG. 8). In radiofrequency ablation (RFA), thermal ablation of the mucosa is performed using an electromagnetic current. In a multicentre, sham-controlled study (the AIM Dysplasia trial), complete eradication of BE was achieved in 91% of patients and of dysplasia in 98% of patients after 3-year follow-up[63,185]. These results were confirmed in a randomized clinical trial of RFA versus PPIs and endoscopic follow-up[186]; ablation reduced the risk of progression to HGD by 25% and to EAC by 7.4% over 3-year follow-up.

Complete ablation of the residual BE epithelium after endoscopic resection of neoplastic lesions can significantly reduce recurrence rates[178]. RFA of the residual BE epithelium is the current treatment standard and has been evaluated extensively (>100 peer-reviewed articles and >250,000 patients treated worldwide). In the Euro-2 prospective multicentre trial of endoscopic resection followed by RFA in 132 patients with BE and HGD or early EAC, complete remission rates for neoplasia and IM were 98% and 93%, respectively[187,188]. Most current society guidelines therefore recommend endoscopic resection combined with RFA as the treatment of choice in patients with HGD and early BE-associated EAC[3,109,174].

Cryoablation. Cryoablation is one of the newest techniques for ablation of BE, and two approaches are available. Endoscopic spray cryotherapy involves spraying either liquid nitrogen or rapidly expanding carbon dioxide gas over the BE segment. Cryoballoon ablation involves expanding a balloon at the level of the BE segment and then a focal spray ablation is performed. Both methods destroy the target mucosa by rapid freezing of the tissue. Data regarding the treatment of dysplasia and EAC in patients with BE using cryoablation are limited. However, complete eradication of dysplasia and complete ablation of BE mucosa have been reported in 87–96% and 57–96% of patients, respectively[188,189]. Cryoablation was also effective in patients with BE and early EAC, with complete remission in 75% of these patients, including those in whom other endoscopic treatments failed[188,189].

Table 5 | **Recommendations for BE surveillance and management**

Society (year)	Non-dysplastic BE	Indefinite for dysplasia	LGD	HGD	Ref.
AGA (2011)	EGD every 3–5 years	Not specified	• EGD every 6–12 months • Consider endoscopic eradication therapy	• EGD every 3 months • Endoscopic eradication therapy rather than surveillance or surgery	1
ASGE (2012)	• EGD every 3–5 years • Consider no surveillance • Consider ablation in select cases	Repeat EGD with maximal acid suppression	• Repeat EGD in 6 months to confirm LGD • EGD every year • Consider endoscopic therapy	• EGD every 3 months (only patients who are not candidates for endoscopic or surgical treatment) • Consider endoscopic treatment • Consider surgical consultation	4
BSG (2014)	• Irregular Z-line: no surveillance • BE <3 cm without IM: no surveillance • BE <3 cm with IM: EGD every 3–5 years • BE ≥3 cm: EGD every 2–3 years • Consider no surveillance on the basis of patient's fitness and risk of progression	Repeat EGD at 6 months with maximal acid suppression	• Surveillance: EGD every 6 months • Ablation cannot be recommended routinely	• Mucosal irregularity: EMR • Endoscopic therapy is preferred over oesophagectomy or surveillance	3
ACG (2016)	EGD every 3–5 years	• Repeat EGD at 3–6 months after optimization of acid suppression • Persistent indefinite for dysplasia: EGD after 1 year	• Endoscopic treatment (patients without life-limiting comorbidity) • EGD every 12 months	Endoscopic treatment (patients without life-limiting comorbidity)	2
ESGE (2017)	• BE <1 cm: no surveillance • BE 1–3 cm: EGD every 5 years • BE 3–10 cm: EGD every 3 years • BE ≥10 cm: referral to BE expert centre • Consider discharge for patients with limited life expectancy and advanced age	Repeat EGD at 6 months with optimization of anti-reflux medication	• Repeat EGD at 6 months • If persistent LGD: endoscopic ablation	• Repeat EGD • Visible irregularity: EMR • Persistent HGD: ablation • No dysplasia: repeat EGD 3 months	109

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; ASGE, American Society of Gastrointestinal Endoscopy; BE, Barrett oesophagus; BSG, British Society of Gastroenterology; EGD, oesophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ESGE, European Society of Gastrointestinal Endoscopy; HGD, high-grade dysplasia; IM, intestinal metaplasia; LGD, low-grade dysplasia.

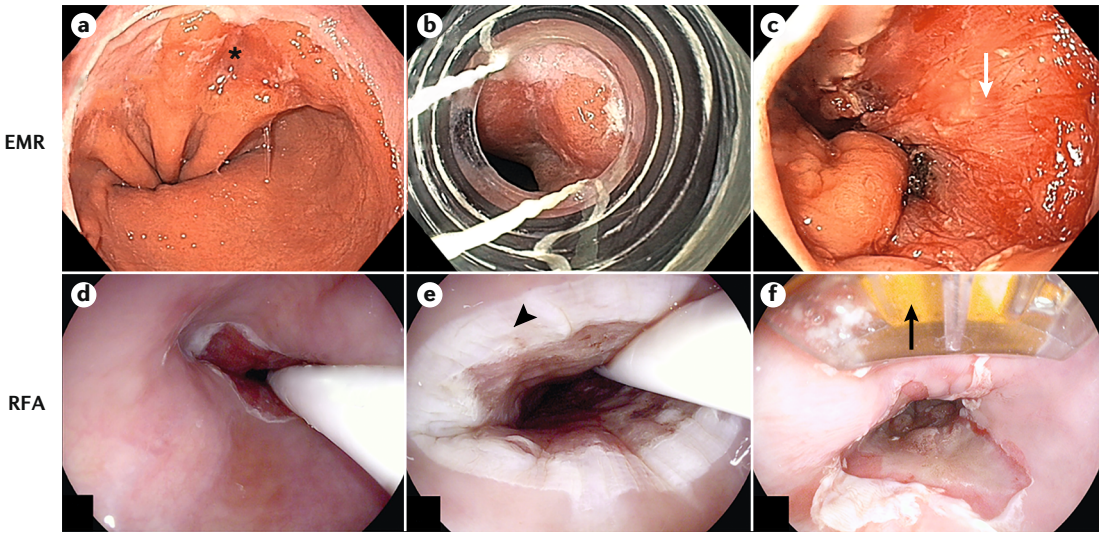

Fig. 8 | **Endoscopic approaches for treatment of Barrett oesophagus.** Endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA) of early Barrett oesophagus (BE)-associated oesophageal adenocarcinoma. **a** | BE with visible lesion (asterisk). **b** | EMR, starting with suction of the lesion into the cap. **c** | Complete endoscopic resection (white arrow). **d** | A circumferential RFA balloon is positioned in the BE segment. **e** | Whitish discoloration (arrowhead) is the immediate effect after treatment with circumferential RFA. **f** | Application of focal RFA (black arrow) to residual islands of BE.

Argon plasma coagulation. Argon plasma coagulation (APC), one of the earliest thermal ablation techniques used for BE eradication, involves passing a high-frequency electric current through ionized argon gas applied to a lesion. APC can achieve remission of BE in most patients after initial APC treatment[190]. In a prospective randomized trial, APC ablation of the BE epithelium that remained after successful endoscopic resection of mucosal EAC significantly reduced the rate of recurrent or metachronous neoplasia compared with surveillance[187]. Hybrid APC combines submucosal fluid injection and APC with a higher-frequency electric current than for conventional APC, which seems to result in a more effective ablation with fewer strictures owing to the protective effect of the submucosal fluid cushion[191]. A major downside of APC is the operator dependency, the larger number of sessions (than other ablative therapies) that are needed to achieve complete eradication of the BE epithelium and the fairly high risk of residual islands of metaplasia. Nonetheless, APC is substantially less expensive than RFA and cryoablation.

Complications of endoscopic ablation. Patients often experience chest pain after thermal ablation. Stricturing is the most common complication of RFA (occurring in 5–14% of patients)[192]. EMR before RFA may increase this stricture rate. In the AIM Dysplasia trial, bleeding after RFA occurred in one patient (<1%) and was probably a result of anticoagulant therapy[185]. If ablative therapy does not destroy all metaplastic epithelium, the partially ablated mucosa may heal with an overlying layer of neosquamous epithelium to produce subsquamous IM (SSIM). Most patients with BE and neoplasia seem to have SSIM[193], as the overlying squamous epithelium hides this SSIM from endoscopic detection and might protect it from RFA. The clinical relevance of SSIM is still uncertain, but these buried glands may have malignant potential[194].

Stepwise endoscopic resection

Recurrence of EAC can also be prevented by complete stepwise endoscopic resection of the neoplastic lesion and the entire BE segment. In a study of stepwise radical resection with long-term follow-up (median 76 months), complete remission rates at the last follow-up endoscopy were 95% for IM and 97% for neoplasia[195]. However, the main disadvantage of this approach is the high stricture rate (>50%). In a meta-analysis comparing a two-step approach (focal EMR followed by RFA) and stepwise radical resection, complete remission rates were similar but the complication rate was significantly higher for the stepwise approach (strictures 33.5% versus 10.2%; bleeding 7.5% versus 1.1%; perforation 1.3% versus 0.2%)[196]. Owing to these excellent results and the lower rate of adverse events, the two-step approach is the recommended treatment strategy in all society guidelines[3,109].

Managing submucosal EAC in BE

EAC that infiltrates the submucosa is associated with a substantially increased risk of lymph node metastasis[197]. Tumours that infiltrate the upper third of the submucosa (TNM (tumour, node, metastasis) stage pT1sm1; invasion depth ≤500 μm) have a lymph node metastasis risk of 0–21%, whereas risk increases to 36–54% when the tumour invades deeper layers of the submucosa (pT1sm2 or pT1sm3)[198,199].

Endoscopic therapy can be safely performed in so-called low-risk submucosal EAC (that is, Tsm1 tumour, invasion depth ≤500 μm, good to moderate differentiation with no lymphovascular invasion and diameter <20 mm) in patients with BE[198,199]. In a case series of 67 patients with submucosal BE-associated EAC who were treated by endoscopic resection, only one patient developed a lymph node metastasis[199], representing a risk of 1.5%, which is below the usual mortality for oesophagectomy.

Thus, these data suggest that endoscopic treatment of low-risk T1sm1 BE-associated EAC can be recommended as an alternative to oesophagectomy.

Follow-up after endoscopic therapy

Endoscopic follow-up after endoscopic treatment is mandatory owing to the frequent recurrence of BE and dysplasia[3,109,174]. However, evidence-based data about surveillance intervals are very limited and recommendations are typically based on expert opinions[2,4]. The incidence of neoplastic recurrence after complete eradication of IM has been modelled, which has yielded evidence-based suggested surveillance intervals[200]. For patients with LGD, surveillance endoscopy at 1-year and 3-year follow-up are recommended. For patients with HGD or mucosal adenocarcinoma, surveillance endoscopies at 3-month, 6-month and 1-year follow-up after complete remission should be performed, and annually thereafter. The implementation of this surveillance schedule seems to be feasible and protects well against invasive adenocarcinoma[200].

Quality of life

A diagnosis of BE affects various domains of QOL, increases health-care costs, affects health-care utilization and health behaviour and carries the potential for morbidity. Decreased QOL is usually due to GERD symptoms and concern about carrying a pre-malignant condition[201].

QOL in non-dysplastic BE

Symptoms. A validated QOL score specifically for patients with BE does not exist. However, in numerous studies, the severity and frequency of GERD symptoms are associated with physical pain and reduced social, emotional and physical functioning[202,203]. Both generic and GERD-specific QOL scores are substantially reduced in individuals with BE compared with the general population but are comparable to those of individuals with GERD[204–206]. As patients with BE are a subset of those with GERD in most studies, they likely had similar symptoms and thus may not represent the total BE population[204–206]. Therefore, symptom control by PPIs seems to be an important factor in maximizing QOL but alone is not sufficient[205].

Labelling effect and psychological burden. A diagnosis of a potentially life-threatening disease may adversely affect patient QOL independent of the disease's biological effects (labelling effect)[207,208]. Studies assessing the potential psychological consequences of living with BE did not show differences among patients with BE and those with GERD[206]. By contrast, increased anxiety and depression scores (using the Hospital Anxiety and Depression Scale), both before and after endoscopic surveillance, have been shown in patients with BE compared with patients with GERD symptoms undergoing endoscopy[209,210].

Burden of endoscopic surveillance. Although it has been shown to be safe, upper endoscopy is an invasive procedure that is not well tolerated by all individuals[211]. In a questionnaire study of 180 patients with BE, the majority (59%) reported the procedure as burdensome and experienced distress beforehand[212]. A follow-up study showed that patients with BE with and without nonspecific upper GI symptoms experienced less discomfort, pain and overall burden during a surveillance endoscopy than patients without BE who were undergoing a diagnostic endoscopy owing to nonspecific upper GI symptoms[209]. Patients who interpreted their risk of developing EAC as high had higher levels of procedural discomfort and seemed to have worse strategies for coping with surveillance endoscopies[212]. Thus, elevated impact of event scores may be associated with anxiety concerning the physical burden of the upper endoscopy but also with the worry about cancer risk, which is usually followed by subsequent relief from a negative test.

Cancer risk perception and cancer worries. Patients with BE may feel psychologically burdened by the threat of developing EAC, which may negatively affect their QOL[213]. Misperception of cancer risk can have important psychological consequences and may affect screening-related health behaviour[214]. Perceptions of cancer risk vary widely in patients with BE. In two studies, ~60% of patients with BE underestimated their numerical annual risk of EAC (annual risk 0.1–0.2%)[215,216]. By contrast, two studies reported that the majority of the 134 patients with BE overestimated their 1-year cancer risk (mean perceived risk 6% and 13.6%)[217,218] and were willing to accept low success rates and high risks of complications to undergo endoscopic therapy[218]. Overestimating EAC risk is associated with more reflux symptoms, lower QOL scores and worse illness perceptions[216,217]. Risk perceptions did not correlate with endoscopic surveillance attendance[215,217]. Nonetheless, patients' knowledge of cancer risk seems to be insufficient and it is questionable whether patients with BE are provided with enough information about their diagnosis, their cancer risk and the role of surveillance and treatment.

QOL in dysplastic BE or early EAC

A diagnosis and (surgical) treatment of dysplasia and EAC, regardless of the stage, have a major impact on patients and their QOL[219,220]. Endoscopic therapy for dysplasia and early EAC is less invasive and beneficial in terms of procedural risk and long-term symptoms compared with oesophagectomy[63]. As endoscopic treatment has become standard of care, the risk of disease recurrence and the burden of subsequent surveillance must also be considered. Two consecutive studies showed that patients with early Barrett neoplasia treated endoscopically have better QOL in both physical and mental domains of the 36-Item Short Form Survey (SF-36) and fewer EAC-related symptoms compared with those treated surgically[221,222]. By contrast, fear of cancer recurrence seems to be higher in patients endoscopically treated for BE-associated EAC, despite excellent 5-year survival[222,223].

QOL following RFA of dysplastic BE was assessed in the AIM Dysplasia trial[63,220]. Eradication of dysplastic BE reduced worry of cancer recurrence, depression scores and impact on daily work and family life

compared with persistent BE (sham procedure)[220]. QOL was particularly improved in patients with complete eradication of dysplasia and BE. These improvements seem to be secondary to a decrease in patients' perceived risk of cancer[220].

Outlook

Since the initial description of BE in 1950, progress has been made in understanding of BE pathogenesis and extensive research has yielded improvements in endoscopic diagnosis and management of BE and the identification of dysplasia in BE. However, many challenges and opportunities in clinical practice and research still remain (Supplementary Box 2).

Pathophysiology

To improve understanding of BE pathogenesis, further research is needed on the different inflammatory processes that lead to IM and malignant progression. The majority of patients with chronic GERD do not develop BE. Thus, the molecular factors that contribute to the development of IM need to be further investigated. Although various models of BE pathogenesis speculate about the cellular origin of metaplastic cells, none of these models explains all aspects of BE; thus, alternative pathogenic mechanisms or even a combination of mechanisms may more fully explain BE pathogenesis. Another outstanding question is whether BE is an intermediate stage in the development of all EACs[7], which could be addressed by studies in experimental models and of Barrett metaplasia in patients.

Diagnosis

Although upper endoscopy and histopathology are the gold standard for diagnosis, consensus about various criteria, such as the minimum length of the oesophageal columnar epithelium and the presence of IM, is necessary to obtain a more precise, universal definition of BE. However, this consensus cannot occur independently of efforts to establish an accurate and reliable cancer risk stratification model for BE.

In addition, the optimal management strategy in patients with dysplasia is unclear owing to difficulties in detecting and diagnosing dysplasia. Novel imaging modalities might improve the detection of dysplasia, but none seem to be ready for clinical application at present. As histological diagnosis of dysplasia is affected by intraobserver and interobserver variability[121], more objective markers are needed to determine the risk of malignant progression in BE. Artificial intelligence may help in optimizing endoscopic and histopathological evaluation of BE and dysplasia in BE in the future.

Screening

Early detection and prevention of BE may be the best strategy to combat the increasing incidence of EAC, as BE is a well-defined precursor lesion and effective endoscopic treatment for dysplasia and early EAC is available. Although conventional endoscopy has been the focus of past research on screening methods, it is not feasible as a primary screening method owing to cost and invasiveness. Tools that incorporate risk factors for BE and EAC are available to enrich the population suitable for screening, but they have important limitations. Importantly, although strong risk factors for BE, including GERD symptoms, age, white ethnicity, male sex, waist circumference and smoking, have been identified, chronic GERD symptoms are still most commonly used to select individuals for endoscopic screening. A more sophisticated risk stratification model for clinical practice and a cost-effective, accurate, minimally invasive or serum-based screening test that is acceptable to both patients and providers are needed. Although several promising modalities have been evaluated, randomized, well-powered studies of the appropriate populations are needed to confirm their ability to identify BE and reduce EAC-related burden. Another important question is whether screening should be offered to individuals at high risk of BE or to the general population.

Surveillance

Screening for BE will be beneficial only if it is coupled with effective surveillance. However, current endoscopic surveillance of BE has numerous limitations. Although the risk of developing EAC is substantially increased in patients with BE, the vast majority of these patients never progress to HGD or EAC[18]. Therefore, in addition to identifying high-risk patients, patients with BE at low risk of malignant progression must be identified to spare them the risks and costs of unnecessary surveillance and intervention. However, despite extensive research to establish risk factors for malignant progression, most guidelines base surveillance intervals on the presence and extent of dysplasia. Stratification of patients with BE based on age, segment length, a history of persistent non-dysplastic BE or additional factors may be a first step towards a more personalized surveillance approach[18,56,224]. The efficacy and cost-effectiveness of surveillance is currently being assessed in an ongoing large, randomized trial comparing standard surveillance and 'at need' endoscopy[225].

Prevention

Substantial progress has been made in the prevention and management of BE. The available evidence suggests that maintenance therapy with PPIs for reflux disease is safe, when clinically appropriate. The protective effect of aspirin and high-dose PPI seems to be small and mostly related to a reduction in nonspecific causes of mortality (such as cardiovascular events), whereas their independent chemopreventive effect on EAC unfortunately remains far less certain. Statins are promising agents, and the retrospective data seem to support future prospective trials.

Management

Endoscopic resection and RFA are effective treatments that have high eradication rates for BE and dysplasia. Endoscopic follow-up after endoscopic treatment is mandatory to detect recurrence of BE or dysplasia. As many studies have probably overestimated the risk of recurrence by including IM at the GEJ as a BE diagnosis[223], the priority in research is to define

recurrent disease after treatment to support the development of evidence-based recommendations about the surveillance intervals.

Promising alternative ablative therapies are in development; for example, success rates with cryoablation (cryospray or cryoballoon) are encouraging, with a safety profile comparable to RFA. However, additional prospective trials of cryoablation are needed before it can substitute for RFA. Direct comparison of these ablation modalities in multicentre trials is ongoing. Nevertheless, cryoablation will likely be useful as a second-line treatment for patients who fail to respond to RFA[226].

QOL

Patients with BE may not be sufficiently knowledgeable about their diagnosis, associated cancer (recurrence) risk and the benefits and drawbacks of surveillance to make fully informed decisions about surveillance strategies and treatment options. Providing information to all newly diagnosed patients with BE may improve disease-specific knowledge and may be helpful for engaging patients in shared decision-making to affect health behaviour and QOL[3].

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