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Barrett's Oesophagus: Today's Mistake and Tomorrow's Wisdom in Screening and Prevention

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Keywords

Barrett's oesophagus · Oesophageal adenocarcinoma · Screening · Prevention · Endoscopy

Abstract

Background: Oesophageal adenocarcinoma (OAC) is a lethal cancer with an overall 5-year survival of <20%. Given the presence of a pre-invasive disease stage, also known as Barrett's oesophagus (BO), and the availability of minimally invasive treatments for BO-related neoplasia, it is thought that early detection is the best strategy to improve patient outcomes. Clinical guidelines recommend endoscopic screening in patients with symptoms of acid reflux and additional risk factors. This strategy is flawed by the cost and invasiveness of endoscopy as well as by the fact that a significant proportion of OAC patients deny a history of reflux symptoms. ***Summary:*** New research on the use of epidemiologic and clinical data has allowed the creation of risk-prediction algorithms to identify the population at risk. In addition, newer less-invasive devices such as transnasal endoscopy, Cytosponge, volumetric laser endomicroscopy, and volatile organic compounds are emerging as promising options to allow screening in the primary care setting. Finally, there is an opportunity to intervene at the pre-invasive stage with pharmacological strategies to reduce the risk burden. ***Key Messages:*** In this review, we provide a critical appraisal of the different screening approaches and chemopreventive strategies and a guide to readers on how to implement research evidence in clinical practice.

Introduction

Oesophageal adenocarcinoma (OAC) is the 7th most common cause of cancer-related death [1]. Barrett's oesophagus (BO) is the only known precursor to OAC with an estimated prevalence of 1–2% among the Western population [2] and a prevalence of between 8 and 24.3% among those with a known history of gastro-oesophageal reflux disease (GORD) [3, 4].

BO is thought to progress to cancer through intermediate dysplastic stages. Although the cancer risk for non-dysplastic BO is small (0.3% per patient-year) [5], once dysplasia is diagnosed, this risk increases significantly. Although guidelines recommend proactive treatment of dysplastic BO to reduce progression to cancer [6, 7], the prognosis of OAC remains poor with an average 5-year survival of 17% [1].

Rationale for Screening

The effectiveness of screening is well established for breast and colon cancer, whose mortality has approximately halved in the last 3 decades after the introduction of mammographic and colonoscopy screening, respectively [8]. There is a 3-fold rationale behind screening for OAC: (i) there is a pre-cancerous condition, (ii) BO can be resolved with minimally invasive treatments, and (iii) endoscopic therapy reduces cancer progression rates. Studies have shown that a receipt of a gastroscopy at least 1 year before the diagnosis of OAC was associated with a

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reduced risk of death from OAC (relative hazard 0.73, 95% CI: 0.57–0.93), indicating the potential role for screening and surveillance in improving patient outcomes [9]. However, subsequent research on the impact of endoscopic surveillance on OAC mortality showed contrasting results [10]. The explanation for this discrepancy is that only adequate endoscopic surveillance impacts positively on patient outcomes [11].

Identifying the Target Population for Screening

Current societal guidelines endorse selective endoscopic screening for patients deemed at high risk for OAC. The British Society of Gastroenterology (BSG) recommends screening for patients with symptomatic GORD and at least three risk factors (older age, male gender, Caucasian or positive family history) [6]. Similarly, the American College of Gastroenterology (ACG) guidelines require ≥2 risk factors, plus chronic GORD (>5 years), as a threshold for endoscopic screening [7].

However, the variable presentation of BO and OAC diminishes the efficacy of this clinical strategy. In a multicentre study from the USA, only 61% and 38%, respectively, of patients with OAC or adenocarcinoma of the cardia reported reflux symptoms >5 years before their diagnosis [12]. Similarly, among those with a diagnosis of BO, only 70% had any symptoms for >5 years and only 37% reported weekly symptoms for >5 years [12]. A recent modelling study from the USA has shown that only ~7% of OAC cases are diagnosed within endoscopic surveillance programmes [13]. Taken together, these data suggest that a symptom-based screening strategy has a modest influence on OAC mortality.

Screening Using Prediction Scores

To help enrich the target population for screening, risk-prediction algorithms based on clinico-demographic information have been investigated such as the Michigan Barrett's oEsophagus pREdiction Tool (M-BERET), the Kunzman tool, Thrift Tool, Locke Tool, Gerson Tool, and the Nord-Trøndelag Health Study (HUNT) (Table 1). A recent study, that independently validated the performance of these prediction tools, showed that they all outperformed a symptom-based strategy in identifying BO, with an area under the curve (AuC) of 0.660–0.695 [14]. To discriminate patients harbouring BO-related neoplasia from no BO, the HUNT, M-BERET, and Kunzmann tools were comparable with an AuC of 0.796, 0.773, and 0.763, respectively. Although promising, the acceptability of prediction tools among physicians and individuals remains to be determined. Further, these prediction tools do not include family history. Given that 28% of first-degree relatives of patients with HGD or OAC have BO [15], it is important to take this into account when making clinical decisions. The BSG recommends lowering the threshold for screening in cases with a first-degree relative with BO or OAC [6]. Future research should evaluate the inclusion of family history in prediction models.

Minimally and Non-Invasive Screening Technologies

Transnasal Endoscopy

Transnasal endoscopy (TNE) uses a slim scope (<6 mm diameter) which minimizes gagging reflex, and can therefore dispense sedation. Further, the availability of portable systems with single-use devices allows compatibility with a primary care setting.

There are 2 portable TNE devices, the EndoSheath oesophagoscope and the EG-Scan system. They are both designed for inspection of the oesophagus in an office-based setting but differ in that the EndoSheath allows tissue sampling. A pilot randomized study comparing EndoSheath versus standard endoscopy showed that TNE had a sensitivity and specificity of 100%, respectively, for an endoscopic diagnosis of BO compared to standard endoscopy, but with reduced image quality and lower yield of IM on biopsies [16]. TNE however was better tolerated and preferred by the majority (60%) of patients.

Despite encouraging data on accuracy and acceptability, the main drawback of TNE is the need for an expert operator, making population-based screening difficult. In addition, 5–10% of patients fail intubation with the transnasal device, and in up to 20%, it is not possible to acquire biopsies. Hence, efforts to bring this technology into routine practice have diminished.

Cytosponge-TFF3

The Cytosponge is a minimally invasive cell sampling device that comprises a compressed mesh, encapsulated within gelatin, and tethered to a string. The Cytosponge is administered in an office-based setting typically by a nurse with a simple swallow. Upon retrieval, the Cytosponge samples up to 1 million cells, which are stained with haematoxylin and eosin and Trefoil-factor 3 (TFF3), a marker of IM [17].

A case-control study of 1,110 patients showed that Cytosponge-TFF3 had 80% sensitivity for BO, which increased to 87.2% for patients with circumferential BO ≥3 cm, and 92.4% specificity [17]. More recently, the BEST3 trial, a large multicentre RCT that randomized patients to an offer of a Cytosponge versus usual care, showed that the Cytosponge led to a 10-fold increase in BO diagnoses compared to usual care (rate ratio 10.6; 95% CI: 6.0–18.8, $p < 0.001$) [18]. Furthermore, there is evidence that automated analy-

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Table 1. Summary of parameters included in various risk-prediction tools

Tools	GORD	Age	Obesity	Smoking	Gender	Anti-reflux medication	Others
M-BERET [33]	Yes (weekly)	Yes (50–59, 60–69, 70–79)	Waist-to-hip ratio (per 0.10 increments)	Yes (per 10-pack years)	Male	–	–
GERSON tool [34]	Heartburn Odynophagia Nocturnal pain Dysphagia	Yes (per 10 years)	–	–	Male	–	Ethnicity
HUNT [35]	Yes (yes or no)	Yes (<50, 50–59, 60–69, ≥70)	BMI (<30 or ≥30)	Smoking (ever or never)	Male	–	–
Locke [36]	Yes (>5 years) Dysphagia Psychosomatic symptom score	Yes (no specified range)	–	–	Male	Yes	–
Thrift [37]	Yes	Yes (per 5 years)*	BMI (<25, 25–29.9, ≥30)	Yes (current, former, or never)	Male	Yes	Education
Kunzmann [38]	Presence of oesophageal conditions GORD BO HH or HH surgery Oesophageal stricture or fundoplication Acid-suppressing medications (none or any)	Yes (50–55, 55–60, 60–65, 65+)	BMI (<25, 25 to <30, 30 to <35, >35)	Yes (current, former, or never)	Male	Yes (as part of oesophageal conditions)	–

GORD, gastro-oesophageal reflux disease; BMI, body mass index; HH, hiatal hernia. *Model was created using the Study of Digestive Health from Brisbane, Australia, which included all patients with BO or dysplasia aged 18–79 years.

sis of Cytosponge specimens using a machine learning framework could reduce the pathologists' workload by 57% and reduce the impact on the health service of a Cytosponge screening programme for BO or OAC [19].

Capsule Volumetric Laser Endomicroscopy

Optical coherence tomography (OCT) is an imaging technology that produces high-resolution cross-sectional imaging using backscattering of light. Volumetric laser endomicroscopy (VLE), a second-generation OCT technology, has emerged as a tool to diagnose BO. VLE has been engineered into a tethered capsule that can be swallowed and generate cross-sectional images of the oesophagus upon withdrawal [20]. A small pilot study on 7 healthy volunteers and 6 patients with BO demonstrated the feasibility and safety of this device. Although promising, the complexity of the imaging output makes this device not ideal for screening in primary care until image interpretation is streamlined by software analysis. More recently, a fully automated computer-aided detection (CAD) algorithm has been combined with balloon-based VLE technology in the surveillance setting achieving an AuC of 0.93 for high-grade dysplasia [21]. This suggests that CAD could be combined in the future with VLE capsules to facilitate image interpretation.

Volatile Organic Compounds

Volatile organic compounds (VOC) are metabolites of human gut flora and can be detected on exhalation. A recent diagnostic validation study among 163 patients with OAC or gastric adenocarcinoma and 172 controls have shown that mass spectrometric analysis of VOC successfully differentiated neoplasia from other benign oesophageal conditions with a sensitivity and specificity of >80% [22]. A different technology using the "electric nose" (e-nose) showed that among a cohort of 129 patients with BO and 273 controls with GORD, oesophagitis, and hiatal hernia, the e-nose was able to discriminate patients with ≥3 cm BO from controls with a sensitivity of 96% and a specificity of 74% [23]. Although promising, these technologies still require further validation in a primary care population.

Chemoprevention

Chemoprevention refers to the use of natural, synthetic, or pharmacological agents to prevent or suppress the initial phases of disease pathogenesis tumorigenesis or to arrest or reverse the progression of premalignant conditions into invasive disease. The mechanism by which BO develops is not entirely understood, although it is thought that acid reflux leads to chronic inflammation and activation of various transcription factors involved in cell differentiation and migration [24]. In mice, there is evidence that basal progenitor cells at the squamous-columnar junction can differentiate into intestinal-type epithelium upon injury and activation of CDX2 [25]. A recent breakthrough study that utilized multiomic profiling of single human cells across the gastro-oesophageal junction showed that BO cells most closely resembled cells from the gastric cardia, and migration of these cells into the oesophagus causes BO [26].

Acid Inhibition

Studies evaluating the use of acid suppressants to prevent the development of BO among patients with GORD are scant. Further, reflux oesophagitis and BO is thought to be caused also by bile acids in the refluxate, and therefore the role of acid suppressants alone in preventing BO remains uncertain [6]. At present, societal guidelines have only recommended acid suppressants for symptomatic control of reflux, and not for chemoprevention of BO [6, 7].

A chemopreventive role for acid suppressants to reduce cancer progression of BO appears more likely. A meta-analysis that included 7 observational studies and >2,800 patients showed that PPI use was associated with a 71% reduction in risk of OAC or HGD among patients with BO (adjusted OR 0.29; 95% CI: 0.12–0.79) [27]. Interestingly, however, a study from Denmark showed that PPI use was not associated with any cancer-preventive properties [28]. The AspECT trial randomized patients with BO to either low- (20 mg) or high-dose (80 mg) esomeprazole [29]. The primary endpoint was a composite of progression to HGD or OAC, disease-specific mortality, and all-cause mortality. Although high-dose PPI was not associated with a reduction of disease-specific endpoints, there was a significant protective effect against the composite endpoint including all-cause mortality. This trial did not have an arm without PPI, and therefore it was not designed to assess the overall chemopreventive role of PPI, which, based on retrospective studies, still appears likely. However, considering the potential side effects related to long-term PPI therapy, a tailored approach is advocated [30]. While it seems reasonable to use low-dose PPI in most BO patients, life-long high-dose PPI is discouraged. In younger patients with BO, objective evidence of reflux should be sought and alternative reflux controlling strategies discussed in case of positive results.

Aspirin and Non-Steroidal Anti-Inflammatory Drugs

Some clinical studies have demonstrated the potential benefit of aspirin or NSAIDs as a chemopreventive agent for BO (Table 2). However, a pooled analysis from 6 case-control studies using multivariable logistic regression and random-effects meta-analytic model, which compared aspirin and NSAIDs use among 1,474 patients with BO and controls (2,256 population-based controls 2018 GORD controls), showed that regular NSAIDs or daily

Table 2. Studies of aspirin or NSAIDs for chemoprevention of BO and OAC

Reference	Design	Size	Medication	Adjusted odds ratio (95% CI)
Barrett's oesophagus				
Anderson et al. [39]	Case-control	244 cases 260 controls	Aspirin Non-aspirin NSAIDs	≥1 year before study: **0.58 (0.35-0.96)** ≥1 year before study: **0.48 (0.26-0.90)**
Omer et al. [40]	Case-control	434 cases 434 controls	Aspirin	Versus controls: **0.59 (0.36-0.99)**
Thrift et al. [29]	Pooled analysis from 6 case-control studies	1,474 cases 4,274 controls 2,256 population-based controls 2,018 GORD controls	Aspirin (at least weekly) Non-aspirin NSAIDs (at least weekly)	Versus population-based controls: ns Versus GORD controls: ns Versus population-based controls: ns Versus GORD controls: ns
Oesophageal adenocarcinoma				
Liao et al. [41]	Pooled analysis (5 case-control, 1 cohort)	1,226 cases 5,314 controls	Aspirin (at least weekly) Non-aspirin NSAIDs (at least weekly) Any NSAIDs (daily use)	Versus controls: **0.77 (0.59-0.99)** Versus control: ns Versus control: **0.56 (0.43-0.73)**
Zhang et al. [31]	Meta-analysis (6 cohorts and 3 case-control)	605 cases (HGD or OAC) 4,841 controls	Aspirin Non-aspirin NSAIDs Any NSAIDs	Subgroup analysis of 5 studies: **0.63 (0.43-0.94)** Subgroup analysis of 3 studies: **0.50 (0.32-0.78)** All 9 studies: **0.64 (0.53-0.77)**
Jankowski et al. [27]	RCT (AspECT)	2,557 patients Primary outcome: composite of time to all-cause mortality, OAC, or HGD, whichever occurred first	4 groups (1) low-dose PPI, no aspirin (2) high-dose PPI, no aspirin (3) low-dose PPI and aspirin (4) high-dose PPI and aspirin	High- versus low-dose PPI: **TR 1.27 (1.01-1.58)** Aspirin versus no aspirin: ns Aspirin + high-dose PPI versus no aspirin + low-dose PPI: **TR 1.59 (1.14-2.23)** Aspirin + high-dose PPI versus high-dose PPI alone: **TR 1.38 (0.98-1.94)**

BO, Barrett's oesophagus; OAC, oesophageal adenocarcinoma; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton-pump inhibitors; TR, time-ratio; RCT, randomized controlled trial; COX, cyclooxygenase; mRNA, messenger RNA; HGD, high-grade dysplasia; APC, adenomatous polyposis coli; ns, not significant; BD, twice daily.

Table 3. DOs and DON'Ts in screening and chemoprevention of BO and OAC

Screening
DOs
Screen patients with multiple risk factors for OAC
Investigate the family history of patients with GORD as a means to identify those at higher risk for BO or OAC
Consider the use of alternative screening technologies such as Cytosponge or transnasal endoscopy depending on local availability
DON'Ts
Endoscope all patients with gastro-oesophageal reflux symptoms
Chemoprevention
DOs
Consider aspirin in the presence of BO and other cardiovascular risk factors
Consider low-dose PPI as chemoprevention in patients with BO regardless of symptoms
DON'Ts
Use high-dose PPI as routine strategy to reduce the cancer risk in BO
Use aspirin in all patients with BO

aspirin was not associated with the risk of BO [31]. This study indicates that there is a lack of evidence on the protective effect of aspirin and non-aspirin NSAIDs against the development of BO.

Progression of BO to OAC is thought to involve cyclooxygenase-2 (COX-2), an enzyme involved in inflammation, and there are reports that COX-2 mRNA expression in BO patients progressing to cancer is higher than non-progressors [32]. A meta-analysis of 9 observational studies showed that exposure to any type of COX inhibitors was associated with a 36% risk reduction in developing HGD or OAC (adjusted RR 0.64; 95% CI: 0.53–0.77) [33]. A subgroup analysis of 5 studies that reported duration of medication use and risk of HGD or OAC showed that COX inhibitor use for ≥1 year was associated with a significantly lower risk of neoplastic progression (adjusted RR 0.54; 95% CI: 0.36–0.79) compared to <1 year (adjusted RR 0.67; 95% CI: 0.46–0.97) [33].

The AspECT trial also assessed the effectiveness of aspirin on BO progression [29]. The study showed that aspirin had no protective effect against the composite endpoint (TR 1.24; 95% CI: 0.98–1.57). The effect of PPI and aspirin, however, seemed to be additive, and taking both high-dose PPI and aspirin was superior to low-dose PPI and no aspirin (TR 1.59; 95% CI: 1.14–2.23). Interestingly, however, for cancer-specific outcomes, there was no difference in the development of HGD or OAC among aspirin users versus no aspirin. Taken together, the AspECT study suggests that the chemopreventive effect of PPI and aspirin may be related to the reduction in all-cause mortality, but not cancer-specific mortality. Therefore, the indication for aspirin should be based on the perceived risk of a patient, based on the presence of other risk factors for cardiovascular disease, including obesity and smoking.

Statins

There are limited studies evaluating the effect of statin on the prevention of BO among those with GORD; however, there have been several observational studies that have suggested a role of statin for the prevention of progression of BO. A meta-analysis of 13 observational studies showed that statin use is associated with a 41% reduction in risk of OAC among those with BO (adjusted OR 0.59; 95% CI: 0.45–0.78), although the number-needed-to-treat to prevent 1 case of OAC in patients with BO was 389 [34]. Overall, there remains a lack of definitive evidence for use of statins in BO [6, 7].

Conclusion

Significant progress has been made over the last decade in the definition of screening and chemopreventive strategies for BO to OAC. Non-invasive or minimally invasive techniques are intensively being investigated as alternatives to endoscopy for low-cost screening. It is now clear that GORD remains a strong risk factor for OAC, but is not the only determinant of the individual's risk. Finally, increasing understanding about the role of pharmacological interventions to reduce this risk is being achieved. We present in Table 3 an evidence-based list of DOs and DON'Ts to inform daily practice. In the future, more research is required to better define indications and modalities for screening and chemoprevention.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

W.K.T. drafted and critically appraised the manuscript. M.d.P. revised and critically appraised the manuscript. Both authors approved the final version of the manuscript.

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