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Research advances in esophageal diseases: bench to bedside

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Abstract

Over the last year, significant steps have been made toward understanding the pathogenesis of esophageal diseases and translating this knowledge to clinical practice. Gastroesophageal reflux disease (GERD) is the most common outpatient diagnosis in gastroenterology and has a high prevalence in the general population. As many as 40% of patients with GERD have incomplete response to medical therapy, and the pathophysiological mechanisms underlying lack of response are now better understood. Novel medical and minimally invasive interventions are available to optimize management of GERD. Esophageal cancer, regardless of the histological subtype, has among the worst survival statistics among all malignancies. Taking advantage of technological advances in genome sequencing, the mutational spectra in esophageal cancer are now emerging, offering novel avenues for targeted therapies. Early diagnosis is another strand for improving survival. While genome-wide association studies are providing insights into genetic susceptibility, novel approaches to early detection of cancer are being devised through the use of biomarkers applied to esophageal samples and as part of imaging technologies. Dysmotility and eosinophilic esophagitis are the differential diagnoses in patients with dysphagia. New pathophysiological classifications have improved the management of motility disorders. Meanwhile, exciting progress has been made in the endoscopic management of these conditions. Eosinophilic esophagitis is still a relatively new entity, and the pathogenesis remains poorly understood. However, it is now clear that an allergic reaction to food plays an important role, and dietary interventions as well as biologic agents to block the inflammatory cascade are novel, promising fields of clinical research.

Introduction

This review highlights research advances made over the last year in esophageal diseases, with particular reference to gastroesophageal reflux disease (GERD), premalignant and malignant conditions, eosinophilic esophagitis (EoE), and motility disorders. Understanding molecular and pathophysiological mechanisms of disease is paramount to improve patient management. Recent technological advances have made it possible to uncover genetic factors involved in the etiopathogenesis and progression of disease, with the possibility to translate this into improved identification of individuals at risk and introduce molecular targeted therapies. This review will focus on how molecular research can improve patient care and on the most relevant recent clinical studies in esophageal disease.

Gastroesophageal reflux disease

In the last 10 to 20 years, GERD has placed an enormous burden on the Western world, and the prevalence in the general population varies between 20% and 30% [1,2]. A recent analysis of a large US national database revealed that GERD was the most common gastrointestinal (GI) diagnosis in an outpatient setting, accounting for almost 9 million visits in 2009 [3]. Up to 70% of patients with typical GERD symptoms (heartburn and regurgitation) have normal endoscopic findings (non-erosive reflux disease, or NERD), and approximately half of patients with NERD have negative 24-hour esophageal pH monitoring (functional heartburn) [4]. Demonstration of the causes and consequences of disease therefore can be challenging in these two groups of patients. Confocal laser endomicroscopy demonstrated microstructural

alterations of the squamous epithelium, such as an increase in the number and diameter of intrapapillary capillary loops and dilated intercellular spaces [5]. When these three parameters were combined, the specificity for a diagnosis of NERD was 100%, but the sensitivity was only 42%. Further studies are warranted to understand the possible clinical impact of confocal endomicroscopy in the management of patients with NERD.

Proton pump inhibitors (PPIs) are the most effective medical intervention for treatment of GERD [6]. However, an incomplete response to PPIs is often reported, and there is a clinical interest in trying to predict this response in clinical practice. A prospective study of 100 patients with typical GERD symptoms found that patients with low body mass index (≤25 kg/m^2), functional digestive disorders, (irritable bowel syndrome or dyspepsia), and the absence of esophagitis are more likely to experience PPI failure [7]. Accordingly, Kahrilas and colleagues [8] found that the presence of dyspepsia-like pain correlated with a lower remission rate for heartburn. Alternative treatments, including drugs that affect gastric motility, tone of the lower esophageal sphincter, and esophageal nociception, have been studied [9].

Acidic reflux has been shown to correlate with a more proximal position of the acid pocket, which is an unbuffered layer of acidic gastric juice above the gastric content. A more proximal acid pocket is more common in patients with a hiatus hernia. In a small randomized crossover study, Rohof and collaborators [10] found that azithromycin, a macrolide antibiotic with prokinetic properties, reduced the size of the hiatus hernia and lowered the position of the acid pocket, resulting in a significant reduction in the post-prandial esophageal acid exposure.

The primary cause of gastroesophageal reflux is transient relaxation of the lower esophageal sphincter (LES). Baclofen is a $GABA_b$ agonist that inhibits LES relaxation and has a potential positive effect on both acidic and non-acidic reflux. Since baclofen has sedating properties, it could be particularly helpful to reduce nocturnal reflux. In a small randomized crossover study, Orr and colleagues [11] demonstrated that baclofen significantly reduced the number of overnight reflux events and improved several measures of sleep quality. The last two studies indicate possible medical adjuncts in patients with an incomplete response to PPIs.

Absence of acidic reflux on pH monitoring in patients who have a positive correlation between acid reflux events and symptoms (symptom index of greater than 50%) is defined as a hypersensitive esophagus. Patients with hypersensitive esophagus generally have a lower rate of response to PPI than patients with GERD, as nociception is also triggered by non-acidic or weakly acidic reflux. Viazis and colleagues [12] performed a randomized controlled trial (RCT) comparing a selective serotonin reuptake inhibitor (citalopram 20 mg/day) with placebo in 75 patients with hypersensitive esophagus. At 6 months, a significantly lower proportion of patients in the citalopram group reported persistence of symptoms compared with the placebo group (38.5% versus 66.7%). This finding gives further support to the idea that at least a proportion of GERD cases have pathophysiological mechanisms in common with functional bowel disorders.

Anti-reflux surgery is an alternative to medical therapy and generally is indicated in patients who have physiologically proven reflux but who do not wish to take life-long medication or have incomplete or no response to medical therapy [13,14]. Recently, novel endoscopic and minimally invasive surgical procedures have been investigated (Table 1). RCTs are warranted before these therapeutic interventions can be recommended routinely in clinical practice.

Barrett's esophagus and esophageal adenocarcinoma

Barrett's esophagus (BE) is characterized by a columnar metaplasia of the distal esophagus, which commonly comprises an intestinal phenotype and is the only known precursor to esophageal adenocarcinoma (EAC). Gastroesophageal reflux is the most important risk factor for the development of BE and EAC [15,16]. Other risk factors traditionally associated are shown in Table 2.

The exact pathophysiological mechanisms leading to the development of BE are not fully understood; however, it is thought that acid-related oxidative and genotoxic damage plays a significant role [17,18] in association with metabolic factors and inflammatory pathways related to the visceral adipose tissue [19].

The Hedgehog pathway, which is important during embryonic development and stem cell function, has been shown to have a role in BE development through cross-talk with the underlying stroma involving epithelial expression of the target gene SOX9 [20]. A Hedgehog inhibitor was successfully used in a rat surgical model of gastro-duodeno-esophageal reflux, in which it reduced the incidence rate of columnar metaplasia [21]. There is also evidence that *SOX9* is directly involved in esophageal carcinogenesis and can be induced by transforming growth factor-beta (TGFβ) and Notch pathways.

Table 1. Novel endoscopic and minimally invasive procedures for the management of gastroesophageal reflux disease

Technique	Methodology	Design	Number of patients	Results	Comments	Reference
Stretta	Endoscopic delivery of radiofrequency energy to the LES	Meta-analysis	1,441	Improvement of heartburn ($P = 0.001$), QoL ($P = 0.001$), and esophageal pH ($P = 0.007$)	Unclear pathophysiological mechanism. Heterogeneous results	[84]
Implanted electrical stimulator	Increase LES pressure by electrical stimulation	Cohort with 6-month follow-up	24	Improvement of symptom score ($P < 0.001$) and esophageal pH ($P < 0.001$)	Small study. Short follow-up. Laparoscopic implant required	[85]
LINX™	Sphincter augmentation by ring of magnetic beads	Cohort with 5-year follow-up	100	At least 50% reduction in esophageal pH in 64% of patients ($P < 0.001$). At least 50% improvement in QoL scores in 92% of patients	Dysphagia in 68% of patients post-op (11% and 4% at 1 and 3 years). Serious adverse events in 6%	[86]
Esophyx	Transoral incisionless fundoplication	Cohort with 24-month follow-up	42	77% and 70% of patients stopped or reduced PPI at 6 and 24 months, respectively	Low efficacy in cases with large hiatus hernia and ineffective motility	[87]

LES, lower esophageal sphincter; LINX; PPI, proton pump inhibitor; QoL, quality of life.

Furthermore, *SOX9* expression correlated with enhanced tumor formation in a xenograft model and poor survival in patients with EAC [22].

In addition to gene expression data, the spectrum of somatic DNA mutations in EAC is being elucidated through high-throughput genome sequencing methods as part of the human genome atlas (The Cancer Genome Atlas) [23] and the International Cancer Genome Consortium [24]. Dulak and colleagues [25] published the first exome (coding regions) sequencing data on 149 EACs and normal tissue pairs and identified novel genes with recurrent mutations, including four chromatin-modifying factors (*SPG20*, *TLR4*, *DOCK2*, and *ELMO1*, the latter of which has been shown to be involved in cell invasion).

BE is generally thought to be a consequence of life-style and environmental factors, although familial clustering is reported in about 7% of individuals with BE or EAC [26]. In 2012, the first genome-wide association study (GWAS), based on 1,852 UK cases of BE and 5,172 controls, was published (Table 1). Two variants on chromosome 6p21 and 16q24 were associated with BE compared with controls [27], and their association with esophageal cancer was validated in an independent Dutch case-control study [28]. Other GWASs are currently being performed and hopefully will provide new insight into the genetic predisposition to cancer progression in BE.

The rate of progression from BE to cancer has been the focus of several publications. A recent meta-analysis and two population studies found that the cancer risk in BE is lower than previously thought (around 0.3% per year) [29-31]). Furthermore, a retrospective community-based case-control study in a population of 8,272 patients with BE found that, among the 70 EAC cases with a previous diagnosis of BE, surveillance within 3 years was not associated with a decreased risk of cancer-related death [32]. Despite the limitations of this study, including the small number of cases and the unusually high prevalence of advanced-stage disease (50%) in EAC cases with known BE, this study adds to the controversial debate surrounding the usefulness of surveillance in BE. The major limitation of endoscopic surveillance is that dysplasia and early neoplasia are often invisible at endoscopy and therefore can be missed by random sampling. Increased molecular knowledge of BE pathogenesis has allowed investigators to devise molecular imaging algorithms, which aim to enhance detection of pre-neoplastic lesions. For example, a fluorescently labeled lectin (wheat germ agglutinin), which differentially binds surface glycoprotein of dysplastic and normal cells, has been shown in proof of principle to localize areas of inconspicuous dysplasia in surgically resected esophagi [33]. Similarly, a different group of investigators identified a fluorescent peptide with high affinity for neoplastic cells, which, in combination with confocal laser endomicroscopy, could be used to image early EAC. Further *in vivo* data are required to determine the usefulness of this approach in routine endoscopic surveillance [34].

The limitation of surveillance strategies, together with the dramatic increase in the incidence of EAC seen over

Table 2. Risk factors associated with Barrett's esophagus, esophageal adenocarcinoma, and esophageal squamous cell carcinoma in recent studies

Risk factor	Disease	Methods	Number of patients	Effect size	Reference
Obesity (waist-to-hip ratio)	BE and EAC	Case-control	225 cases 675 controls	OR (highest versus lowest quartile): 2.68 (95% CI 1.57-4.55)	[88]
Heartburn	BE	Cross-sectional	1,058 cases with GERD	OR 1.5, 95% CI 1.07-2.09	[89]
Caucasian race				OR 2.4, 95% CI 1.42-4.03	
Hiatus hernia				OR 2.07, 95% CI 1.5-2.87	
Weekly GERD	BE	Cross-sectional	822 males undergoing	OR 2.33, 95% CI 1.34-4.35	[90]
Obesity (waist-to-hip ratio)			screening colonoscopy	OR per 0.10: 1.44; 95% CI 0.9-2.32	
Age				OR per 10 years: 1.53; 95% CI 1.05-2.25	
Smoking				OR per 10 pack-years: 1.09; 95% CI 1.04-1.14	
HPV	BE dysplasia and EAC	Retrospective case-control	261 patients with BE	IRR for dysplasia: 2.94; 95% CI 1.78-4.85 IRR for EAC: 2.87; 95% CI 1.69-4.86	[91]
	ESCC	Retrospective case-control	300 cases 900 controls	OR 6.4, 95% CI 4.4-9.2	[92]
Genomic variants rs9936833	BE (C allele)	GWAS	1,852 BE cases and 5,172 controls	OR 1.14, 95% CI 1.10-1.17	[27]
	EAC (C allele)	Case control	431 BE cases and 605 controls	OR 1.21, 95% CI 0.99-1.47	[28]
Genomic variant rs9257809	BE (A allele)	GWAS	1,852 BE cases and 5,172 controls	OR 1.21, 95% CI 1.13-1.28	[27]
	ESCC (G allele)	Case control	431 BE cases and 605 controls	OR 1.76, 95% CI 1.16-2.66	[28]
Heavy alcohol consumption (>30gr/day)	ESCC	Cohort	120,852 participants (107 ESCC cases)	IRR 4.61, 95% CI 2.24-9.50	[93]
Light alcohol consumption (≤1 drink/day)	ESCC	Meta-analysis	~92,000 light drinkers and ~60,000 non-drinkers	RR 1.3, 95% CI 1.09-1.56	[29]
Smoking (current)	ESCC	Cohort	120,852 participants (107 ESCC cases)	RR 2.63	[93]
Processed meat consumption	ESCC	Cohort	120,852 participants (107 ESCC cases)	HR 3.47 (95% CI 1.21-9.94)	[95]
High variety in fruit and vegetable consumption	ESCC	Cohort	452,269 participants (98 ESCC cases)	HR 0.88 (95% CI 0.79-0.97)	[96]

BE, Barrett's esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GERD, gastroesophageal reflux disease; GWAS, genome-wide association study; HPV, human papilloma virus; HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; RR, relative risk.

the last 30 years, underscores the need to find better ways to identify patients at high risk for progression and to intervene at an early stage [35]. Clinico-pathological factors are limited in their ability to predict BE behavior. Low-grade dysplasia (LGD), despite the high inter-observer variability among pathologists [36,37], and the length of BE are the only clinical parameters that have consistently been associated with cancer risk [38]. To overcome the paucity of clinical parameters for risk stratification, research has focused on the use of biomarkers [39]. A Dutch case-control study on a prospective cohort of 720 patients with BE found that aberrant p53 expression detected by immunohistochemistry confers a relative risk for neoplastic progression of 5.6 (95% confidence interval [CI] 3.1-10.3) [40]. A nested case-control study (89 cases of BE that progressed to high-grade dysplasia [HGD] or cancer and 291 non-progressors) found that a small biomarker panel comprising LGD, aneuploidy, and expression of the Aspergillus oryzae lectin predicts progression with an odds ratio (OR) of 2.99 (95% CI 1.72-5.20) for each abnormal biomarker. One of the outstanding challenges in BE is that the majority of cases are undiagnosed and hence the majority of patients with EAC present *de novo*. Endoscopic screening on a population basis is not feasible and less invasive modalities have been investigated. One of them couples a cytology collection device, Cytosponge™, with an immunochemical marker, trefoil factor 3 (TFF3), which is highly specific for cells with an intestinal phenotype. This test was devised by the Medical Research Council UK for the purpose of clinical trials [41]. This test is feasible in the primary care setting and has a diagnostic accuracy for BE comparable to other screening tests such as fecal occult blood (FOB) and cervical Papanicolaou smears. In a microsimulation model, screening 50-year-old men with GERD

symptoms with Cytosponge™ reduced mortality from EAC compared with no screening and was cost-effective compared with endoscopic screening [42]. Alternatively, a tethered capsule endomicroscopy has been devised to scan the upper gastrointestinal tract and provide three-dimensional reconstruction and microstructural images of the esophageal mucosa [43]. This uses optical frequency domain imaging, which is based on reflection of infrared light. Following the pilot study in six patients, large prospective studies are needed to confirm that this device has good acceptability and accuracy for screening for BE.

In the last 5 to 10 years, the biggest advance in the management of BE and early EAC has been the advent of endoscopic therapy. This generally comprises endoscopic resection (ER) for early neoplasia and ablative techniques for the eradication of inconspicuous dysplasia. Currently, radiofrequency ablation (RFA) is the ablative technique with the best safety and efficacy profile [44]. Endoscopic treatment has allowed patients with HGD or early cancer to be shifted away from the surgical pathway [45]. Data from a large UK registry including 335 patients with HGD or intramucosal cancer treated with RFA in combination with ER if required, showed a 12-month eradication rate for neoplasia of 86% and a rate of complete eradication of intestinal metaplasia of 62% [46]. Even though these efficacy data are lower than those reported in well-controlled prospective series [47,48], they represent outcomes from real-life clinical scenarios and therefore indicate that this new therapeutic paradigm is feasible and effective in routine practice. However, it is clear that continued endoscopic follow-up of these patients is required as some patients will need further endoscopic or surgical therapy for persistent or recurrent disease. An expert consensus review in 2012 recommended endoscopic therapy over surgery for the treatment of HGD and T1m esophageal and junctional adenocarcinoma [49].

On the other hand, most patients with EAC present with advanced disease requiring neoadjuvant oncological therapy followed by surgery. There are intensive treatment regimens associated with significant morbidity and mortality, particularly in older patients with coexisting medical problems. Therefore, better predictors of outcome than radiological estimates of pre-treatment are required to help patients and clinicians make management decisions. In patients with established EAC, a panel of three immunohistochemical markers – EGFR, TRIM44, and SIRT2 – can split patients with EAC into two prognostic groups, which are independent of clinical stage, with a hazard ratio for adverse survival of 1.2 (95% CI 1.03 to 1.4) for each positive biomarker [50].

Squamous dysplasia and squamous cell carcinoma

From a global perspective, esophageal squamous cell carcinoma (ESCC) is still the most common esophageal malignancy [51]. Risk factors recently associated with ESCC are listed in Table 1. A recent GWAS on over 2,000 cases and 2,000 controls found nine new susceptibility loci for ESCC, of which two showed significant interaction with alcohol drinking, suggesting that the etiology of this cancer is multifactorial and that multiple genes interact with strong environmental risk factors [52].

Two recent studies have investigated prognostic factors in ESCC. A GWAS found that a single-nucleotide polymorphism in a gene coding for a zinc transporter (*SLC39A6*) is associated with worse survival with a hazard ratio for death of 1.3 (95% CI 1.19-1.43) [53]. Another predictor of clinical disease behavior is p53 expression, and a meta-analysis of 28 studies found that normal p53 expression or maintenance of wild-type *p53* gene correlated with high response to chemotherapy-based treatments and a high rate of complete pathological response to neo-adjuvant chemoradiotherapy [54]. Two additional ESCC tumor markers have recently been identified. The protein tyrosine kinase 6 (*PTK6*) is epigenetically downregulated in ESCC and its tumor suppressor function was validated by proliferation and migration in *in vitro* assays and in a xenograft model [55]. In another study, a lipid raft protein, FLOT1, was found to be overexpressed in ESCC cell lines and tissue samples, where it acts as a promoter of proliferation and cell motility and an inhibitor of apoptosis [56]. Future work will be required to establish whether these markers can be used clinically to predict disease behavior or target molecular therapy in the clinic.

Similarly to EAC, early diagnosis of ESCC is important not only because it ensures higher survival rates compared with standard therapeutic interventions (chemo-radiotherapy with or without surgery) but also because it opens the possibility to offer patients minimally invasive endoscopic treatment. A large retrospective cohort study of 570 patients with early ESCC treated with endoscopic resection showed a 90% 5-year survival rate in patients with disease confined within the lamina propria (LPM); however, the survival rate dropped to 70% when muscularis mucosae (MM) or the submucosa (SM) was involved [57]. In keeping with this, the cumulative 5-year metastasis rate in patients with LPM, MM, SM1, and SM2 disease were 0.4, 8.7, 7.7, and 36%, respectively. This highlights a fundamental difference between early EAC and early ESCC, whereby involvement of MM is compatible with endoscopic therapy in EAC but not in ESCC. However, squamous

dysplasia is often inconspicuous at endoscopy; therefore, advanced imaging modalities are needed to flag suspicious areas. One of these is chromoendoscopy using Lugol's iodine, which exploits the lower affinity of iodine to dysplastic compared to normal epithelium [58]. An alternative way to image dysplastic tissue is molecular imaging. Periostin is an adhesion molecule highly expressed in the ESCC tumor microenvironment. Wong and colleagues [59] used a fluorescently labelled antibody against periostin in combination with near-infrared endoscopy to image esophageal neoplasia in a cancer mouse model that resembles ESCC.

Eosinophilic esophagitis

EoE is a relatively recently described clinico-pathological entity characterized by symptoms of esophageal dysfunction and microscopic esophageal eosinophilia (>15 eosinophils/high-power field), which persists after a 2-month course of PPI and when other causes of eosinophilia have been excluded. The American guidelines for the management of EoE were recently issued [60]. Patients with EoE may have one of more of the following endoscopic findings – rings, strictures, narrow caliber, furrows, plaques, or mucosal pallor – and up to 93% may have at least one of these features in prospective studies. However, the overall diagnostic accuracy based on the endoscopic appearance is poor; sensitivity ranges between 15% and 48%; therefore, histological corroboration is mandatory [61]. However, it is often challenging to distinguish between EoE and GERD. First, they can present with similar symptoms, second, mucosal eosinophilia is a common finding in GERD, and finally, patients with negative pH monitoring and symptoms and histological findings suggestive of EoE can have symptomatic and histological resolution when treated with a PPI. This has been confirmed by a recent RCT in which patients with symptoms of esophageal dysfunction and esophageal eosinophilia were randomly assigned to either topical fluticasone 440 μg twice daily or esomeprazole 40 mg once daily [62]. Although PPI treatment correlated with a better symptomatic response (dysphagia score) compared with topical steroid among patients who had normal pH monitoring, there was no statistical difference in the histologic response, and a resolution of eosinophilia was seen in 33% and 19% of patients, respectively. Another RCT showed better rates of symptomatic and histologic response (68% and 63%, respectively) with higher doses of topic fluticasone (880 μg twice daily); however, esophageal candidiasis occurred in about a quarter of cases [63]. To help distinguish between EoE and GERD, tissue biomarkers have been studied. A recent case-control study tested four immunohistochemistry markers and found that the combination of major basic protein (MBP) and eotaxin-3 together with the eosinophil count had an area under curve for a diagnosis of EoE of 0.99 [64]. Improved understanding of the pathogenesis of EoE has led to development of new alternative treatment to steroids and PPI [65]. EoE is triggered by a Th2 allergic reaction to food, which involves release of eotaxin-3 and interleukins (IL) 5 and 13 that, in turn, induces eosinophil trafficking in the esophagus. Promising results have recently been obtained with treatment of pediatric and adult EoE patients with a six-food elimination diet (SFED) (milk, soy, nuts, fish, eggs, and wheat) for 6 weeks followed by progressive reintroduction every 2 weeks, while monitoring histologic and symptom scores. In a prospective cohort of 50 patients, SFED led to a complete histologic response in 64% of patients, and up to 78% showed at least 50% reduction in the eosinophil count, and there was a symptomatic response in 94% of patients [66]. When foods were reintroduced, the most common relapse triggers were wheat (60% of cases) and milk (50% of cases). Similar results were found in another cohort study with long-term follow-up, where remission of symptoms could be maintained for up to 3 years [67]. Of note, both studies showed that conventional allergy tests (serum IgE and skin prick test) have limited value with low sensitivity values. On the downside, the SFED is a lengthy process and the rate of compliance to the reintroduction process in clinical practice may be even lower outside research protocols. However, the advantage compared with other dietary interventions, such as elemental diet, is the improved quality of life, although comparative studies are lacking. Of note, elemental diet, which was shown to be very effective in pediatric patients [68], did not improve symptoms of EoE in a small adult cohort despite improving histological scores [69].

Biological agents are currently being tested with the intent of blocking the molecular cascade responsible for the allergenic process. A large RCT that compared three different doses of an anti-IL-5 antibody (reslizumab) with placebo in a pediatric cohort showed improvement of the histologic score in all treatment groups; however, significant symptomatic benefit was lacking [70]. Similar results were obtained with a different anti-IL-5 antibody in a small cohort study [71].

Esophageal motility disorders

Esophageal motility disorders are the most common cause of esophageal symptoms after GERD. They classically include achalasia, diffuse esophageal spasm (DES), hypertensive lower esophageal sphincter (LES), and nutcracker esophagus (NE). The advent of high-resolution esophageal pressure topography has enhanced the characterization of these conditions and,

in 2008, the Chicago Classification was developed to refine the diagnostic criteria. A recent iteration of this classification was published in 2012 [72]. The main innovations of the Chicago Classification are the subclassification of achalasia into three types, which impacts on clinical management, and the introduction of two additional diagnoses: esophagogastric outflow obstruction and hypercontractile esophagus [73]. Tsutsui and colleagues [74] looked at the association of globus with motility disorders. Globus is one of the atypical symptoms of GERD but frequently fails to respond to PPI. The authors found that, among 119 patients with globus non-responsive to PPI, abnormal esophageal motility was found in nearly 50% of cases [74]. About 2 out of 3 had ineffective esophageal motility and 1 out of 3 was equally divided among achalasia, NE, and DES. Whereas the therapeutic algorithm for achalasia is well defined, treatment of other conditions remains challenging, and medical therapy often proves disappointing and surgery helpful only in well-selected groups [75]. In a small RCT with a crossover design that included 22 patients with NE and DES, Botox (Allergan, Inc., Irvine, CA, USA) injection 2 and 7 cm above the esophagogastric junction (EGJ) was beneficial compared with placebo; however, only 30% of patients maintained response at 1 year [76]. Similarly, results of Botox injection in patients with achalasia are short-lived; there is almost universal recurrence at 2 years [75]. An alternative endoscopic treatment for achalasia is pneumatic dilatation (PD), which mechanically and permanently disrupts muscle fibers. A recent retrospective series of 301 patients undergoing PD showed an 82% remission rate at 1 year but a 2% perforation rate [77]. Kaplan-Meier analysis, in which symptomatic relapse after first PD and need of additional therapy (PD or other) were considered as treatment failures, demonstrated that 59% and 40% of the patients maintain remission at 5 and 10 years, respectively. A meta-analysis of 36 studies compared outcomes of PD and surgical myotomy and found that surgery guarantees longer rates of remission (76% and 79% at 5 and 10 years, respectively) but with a perforation rate that was twice that of PD [78]. Probably the most exciting advance in the management of patients with motility disorders is the recent introduction of a novel minimally invasive endoscopic technique, called per-oral esophageal myotomy (POEM). This involves the creation of a submucosal tunnel with an ESD approach from the mid esophagus until beyond the EGJ, division of the inner muscle layer with an endoscopic knife and closure of the mucosal entry with clips. POEM was first performed in Japan in 2008 by Haruhiro Inoue, and several hundred cases have been completed in Eastern and Western countries. Recent case series confirmed that POEM is effective in both relieving symptoms and improving esophageal physiology [79-81], regardless of whether the patients received endoscopic therapy. A multicenter study of 70 patients showed symptomatic remission at 6 and 12 months in 89% and 82% of patients, respectively, and a significant reduction of the mean lower esophageal pressure from 28 to 9 mm Hg [82]. A non-randomized cohort study compared the perioperative outcomes of POEM and Heller's myotomy and found that complication rate, length of stay, and pain scores were similar between the two techniques, although POEM had shorter operative time and lower estimated blood loss [83]. Longer follow-up data are needed to determine the long-term benefit of this technique.

Abbreviations

BE, Barrett's esophagus; CI, confidence interval; DES, diffuse esophageal spasm; EAC, esophageal adenocarcinoma; EGJ, esophago-gastric junction; EOE, eosinophilic esophagitis; ER, endoscopic resection; ESCC, esophageal squamous cell carcinoma; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GWAS, genome-wide association study; HGD, high-grade dysplasia; IL, interleukin; LES, lower esophageal sphincter; LGD, low-grade dysplasia; LPM, lamina propria; MM, muscularis mucosae; NE, nutcracker esophagus; NERD, non-erosive reflux disease; PD, pneumatic dilatation; POEM, per-oral esophageal myotomy; PPI, proton pump inhibitor; RCT, randomized controlled trial; RFA, radiofrequency ablation; SFED, six-food elimination diet; SM, submucosa; TFF3, trefoil factor 3.

Disclosures

Rebecca C Fitzgerald holds a patent for the Cytosponge™ technology (UK trademark number 2537681) and for TFF3 as biomarker for detecting Barrett's esophagus (A813/2479).

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