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Review Article

Clinical outcomes and endoscopic surveillance of gastroesophageal reflux disease: a review

Xiao-Bo Yang[1], Li-Fen Yu[2]

Departments of [1]Geriatrics, [2]Gastroenterology, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China

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Abstract: Gastroesophageal reflux disease (GERD) is a condition where the reflux of stomach contents causes troublesome symptoms and/or complications. The disease has been classified into oesophageal and extraoesophageal syndromes. GERD is widely recognized by clinicians due to its pathogenesis, pathological manifestations, and clinical symptoms. However, literature concerning clinical outcomes is limited and contradictory. The role of endoscopy and, in particular, of endoscopic surveillance in GERD remains controversial. Here, we review the most recent findings concerning endoscopic surveillance and prognosis in GERD.

Keywords: Gastroesophageal reflux disease, clinical outcomes, endoscopic surveillance, prognosis, risk factors

Introduction

Gastroesophageal reflux disease (GERD) is associated with troublesome symptoms and/or complications due to the reflux of stomach contents into the oesophagus. The disease has been subdivided into oesophageal and extraoesophageal syndromes. The management of the disease is currently patient-orientated, independent of endoscopic findings. Laryngitis, cough, asthma, and dental problems have recently been considered as components of GERD syndromes [1]. GERD significantly impacts quality of life, and may predispose patients to oesophageal adenocarcinoma (EAC) [2, 3]. GERD has traditionally been divided into 3 distinct categories with little transition between them: nonerosive (NERD), erosive (ERD), and Barrett's oesophagus (BE) [4-6]. However, mucosal erosions can develop in a previously NERD patient, severe damage can result from mild esophagitis, and complications such as intestinal metaplasia or adenocarcinoma can arise in a previously uncomplicated case [7]. NERD or ERD patients can develop adenocarcinoma, even in the absence of BE. In some countries, including China, ERD patients undergo initial upper gastrointestinal endoscopy. The role of endoscopy and, in particular, of endoscopic surveillance in GERD remains controversial [8, 9]. Based on the low progression rate of BE to EAC [3, 10], endoscopic and bioptic surveillance studies have not found a significant benefit over those who did not receive surveillance [11]. However, long-term treatment and monitoring of GERD patients significantly burdens the economy, raising the question of the value of these measures in patient prognosis. This review focused on the latest research progress and clinical outcomes of endoscopic surveillance in GERD.

Do NERD patients progress to ERD?

A prospective study showed only 2 of 63 NERD patients progressed to ERD during a 6-year follow-up period [12]. Another multicentre, prospective study declared that, after a 3-year endoscopic follow-up of 34 NERD patients, only 3 progressed to ERD [14]. However, Pace et al. [15] conducted a 6-month follow-up study of 33 NERD patients administered acid suppressive and/or pro-kinetic drugs, and found that 5 patients developed ERD. The well validated Los Angeles (LA) classification system for esophagitis [16] was used to study a cohort of 3894 patients with predominant heartburn, with or without esophagitis (1717 NERD, 1512 LA

grade A/B, 278 LA grade C/D, and 387 BE) under routine clinical care in Germany, Austria and Switzerland [17]. After initial treatment with esomeprazole, patients were followed for 2 years, regardless of their response. Medical therapy or endoscopy was initiated at the discretion of the primary care physician, in line with routine care. At 2 years, endoscopy with biopsy was performed according to the protocol. Twenty-five percent of patients who had NERD at baseline progressed to LA grade A/B, and 0.6% to LA grade C/D. Twenty-two percent of patients had been off medication for at least 3 months. GERD does not seem to be a categorical disease. Kawanishi [18] studied 497 patients who underwent endoscopic examination annually for 5 years, and found that esophagitis developed in 36.2% of the NERD group and in 11.3% of the control group ($P < 0.01$). In particular, individuals with hiatal hernias, without *Helicobacter pylori* infections, and those who smoked and drank alcohol were prone to develop esophagitis. Chen et al. [19] investigated the 5-year clinical course of 30 NERD patients, and found that pathological acid exposure did not alter the presence of reflux symptoms. Disease progression to ERD occurred more frequently among patients with pathological acid exposure compared to those without pathological acid exposure ($P = 0.025$).

Do NERD and ERD progress to BE or EAC?

In a prospective study of 101 GERD patients defined by the Savary-Miller classification with stage II-III esophagitis, 9% (3/33) progressed to BE after 3-4.5 years of follow-up [20]. In another 2 year prospective study [21], 83 patients with reflux disease and mild esophagitis were monitored for the development of Barrett's metaplasia while receiving long-term therapy with proton pump inhibitors (PPIs) and cisapride. Only patients who had effective control of reflux symptoms and esophagitis were included. Twelve (14.5%) patients developed Barrett's metaplasia while receiving medical therapy. Nine of them had a short-segment BE (SSBE, length < 3 cm), and 3 had a long segment BE (LSBE, length ≥ 3 cm). Barrett's metaplasia was suspected on endoscopy and confirmed by histology. A German prospective, multicentre study enrolled 1014 dyspeptic patients [14]. After a mean follow-up period of 35 months, 47% (143/304) of previously symptomatic patients were symptom-free, and 53% (161/304) remained symptomatic or had concomitant therapy with PPIs. For follow-up endoscopy in patients of PPIs (n = 52), ERD was no longer observed in 7/12 ERD patients (58%), whereas 9% (3/34) NERD patients progressed to ERD. BE was newly diagnosed in 2 NERD patients, but could no longer be detected in 2 of 6 patients with an initial BE diagnosis.

Previous data showed that esophagitis is a necessary causal intermediary to EAC [22, 23]. Consistent with this conclusion, a large population-based cohort study from Denmark [24], including 26,194 patients, showed that 77% had ERD, and 37 developed EAC after a mean follow-up time of 7.4 years. Their absolute risk of EAC after 10 years was 0.24% (95% confidence interval [CI], 0.15%-0.32%). The incidence of cancer among ERD patients was significantly greater than that expected for the general population (standardized incidence ratio, 2.2; 95% CI, 1.6-3.0). In contrast, out of the 7655 patients with NERD, only 1 was diagnosed with EAC after 4.5 years of follow-up (standardized incidence ratio, 0.3; 95% CI, 0.01-1.5). Inflammation may therefore be an important factor in the progression from reflux to EAC [25].

Progression and regression both observed

Progression and regression between disease grades were observed in a large cohort of patients under routine clinical care [17]. BE regression was reported [26] in a prospective, multicentre study from Germany, in which only 70% of patients diagnosed with BE based on the classical histological definition of specialized intestinal columnar metaplasia maintained BE over time. In a large observational cohort in the United States over a mean follow-up period of 7 years [27], GERD progression occurred in only 11% of patients, and complications (stricture) in 2%. A total of 6215 patients were enrolled in the study, and 2721 patients completed the 5-year follow-up. Progression, regression, and stability of GERD were followed from baseline to 5 years. Only a few patients with NERD and mild/moderate ERD progressed to severe forms of ERD and even BE. Most patients remained stable or showed improvement in their esophagitis; 5.9% of the NERD patients, 12.1% of LA grade A/B patients, and 19.7% of LA grade C/D patients among whom

no BE was recorded at baseline progressed to endoscopic or confirmed BE at 5 years [28]. Progression to BE is lowest in patients with NERD, intermediate in LA grade A/B, and highest in patients with LA grade C/D. The 5-year study findings confirmed and extended the previous 2-year study findings (referred to as the ProGERD study). The observed progression of NERD to mild/moderate ERD is around 25%, but the observed regression of ERD LA grade A/B to NERD is much higher at 63%. It is possible that treatment was adjusted by the physician at 2 years in cases where esophagitis was observed, resulting in fewer patients with esophagitis at 5 years. Most GERD patients remain stable or improve over a 5-year observation period under current routine clinical care. Animal models and molecular techniques have suggested that PPIs may be effective in chemoprevention of EADC [29]. Small-scale, observational, prospective studies and retrospective analyses have confirmed the possible preventive properties of PPIs in oesophageal adenocarcinogenesis and disease progression [30, 31]. PPIs may therefore offer a relatively safe, cost-effective means of preventing oesophageal adenocarcinogenesis and disease progression [32]. For patients with unsuccessful medical treatment, a long-term, retrospective study [33] showed that anti-reflux surgery can appropriately control reflux disease, and may inhibit progression and induce regression of Barrett's metaplasia in a significant proportion of patients. The current view is that mild esophagitis tends to remain mild on follow-up, while progression from NERD to ERD, from mild to severe ERD, and from ERD to BE may occur in a small proportion of patients.

Risk factors for GERD progression

Since long-term treatment and monitoring of GERD can significantly burden the economy, risk stratification is needed to identify patients who could most benefit from surveillance or other interventions. The following summarizes the data on several possible risk stratification factors.

Age: Studies have shown that age > 40 years is an independent risk factor for progression of GERD to BE [34]. Compared with patients age < 55 years, the risk of progression to BE among those > 75 increased by approximately 3-fold [35]. A large population-based study was conducted by Bhat et al. [36]. The mean follow-up period for the 8522 patients included for analysis was 7 years. The incidence of cancers in the whole cohort was 0.16% per year. When analyzed by age category, the highest risk of progression appeared in the 60- to 69-year age category (0.33% per year), and the lowest risk in patients younger than 50 years (0.12% per year). The group of patients who were older than 80 years showed a low risk of progression (0.17% per year). However, another study showed no independent correlation between age and BE progression to EAC [37].

Smoking: Smoking has been considered as a risk factor for EAC, doubling its overall risk [38]. Pohl et al. [37] indicated that smoking has no effect on the development of GERD or the transition from GERD to BE. However, smoking appears to increase the risk for progression from BE to cancer. The same results were reported in several European studies [35, 39, 40]. Similar to Pohl et al., Coleman et al. [40] did not find any association with the length of smoking history.

Male gender: Pohl et al. [37] confirmed prior observations [42] of a male predominance in both BE and EAC. They found that male gender increased the risk of developing BE among GERD patients for over 2-fold, and further doubled the risk for BE patients to develop cancer of high-grade dysplasia (HGD). Reasons for this phenomenon are not clear, but it can be speculated to be related to the higher incidence of smoking in male than in female patients, or to be associated with the protective effect of estrogen in GERD progression to BE and further progression to EAC [43].

Abdominal obesity: Bhat et al. [36] showed that body mass index (BMI) positively correlated with GERD progression to BE; patients with BMI > 30 had nearly doubled the risk of disease progression. However, BMI was not associated with BE progression to EAC. A meta-analysis by Singh et al. [43] found that, compared with patients with normal body habitus, patients with central adiposity had a higher risk of ERD (19 studies; odds ratio [OR], 1.87; 95% CI, 1.51-2.31) and BE (17 studies; OR, 1.98; 95% CI, 1.52-2.57). The association between central adiposity and BE persisted after adjusting for BMI (5 studies; OR, 1.88; 95% CI, 1.20-2.95).

LSBE/Low-Grade Dysplasia (LGD): LSBE is another risk factor for GERD progression [33-35]. Compared with SSBE, patients with LSBE had a 7-fold increased risk of progression to high-grade intraepithelial neoplasia or EAC [44]. Studies showed that, for patients with low-grade intraepithelial neoplasia, the cancer risk increased more than 3-fold [41, 45]. The risk of progression to high-grade intraepithelial neoplasia or EAC among BE patients with low-grade intraepithelial neoplasia was 1.4%, over 5-fold higher than BE patients without dysplasia [36].

Low fruit and vegetable intake: Case-control studies have shown a protective dose-dependent influence of fruit and vegetable intake against development of EAC [46, 47]. However, Pohl et al. [37] did not find that fruit and vegetable intake influenced development of GERD. They suggested that a high fruit and vegetable intake might protect against development of cancer in BE patients, and Kubo et al. [48] found that this protected against development of BE.

Duration of reflux symptoms: Severe reflux symptoms are an important risk factor for progression of BE to EAC. The majority of precancerous lesions leading to EAC are BE (62%, 118/189) [45]. Pathological acid reflux is a prerequisite for development of EAC [49]. This conclusion has been confirmed by many cohort studies [37, 45, 50, 51]. Lagergren et al. [45] demonstrated that frequency, severity, and duration of symptoms correlated with an increased risk of EAC. Patients with GERD symptoms had a 7.7-fold risk of developing EAC. The risk is even higher when the symptoms occur at night, up to 11-fold compared to the asymptomatic population. Prolonged, severe reflux symptoms may increase the risk of EAC by approximately 43.5 times.

Hiatal hernia: Hiatal hernia is the only risk factor that is strongly associated with development of GERD and is considered as a major component of GERD pathogenesis, albeit with more restraint and in a more mechanistic construct [52, 53].

H. pylori infection. H. pylori infection has been reported to decrease the risk of BE [54] and its progression to cancer, possibly as a result of reduced acid secretion in H. pylori -associated corpus predominant gastritis [55]. However, Pohl et al. [37] did not reveal a statistically significant association. They observed an overall trend suggesting some protective influence of H. pylori infection on both the progression to BE and to cancer. Recently, a meta-analysis [56] including 16 cohort studies showed no significant effect of H. pylori infection on the development of GERD in the long term. H. pylori eradication therapy was recommended, since H. pylori infection is a major cause of acute and chronic gastritis and peptic ulcer diseases, and has been established as a definite etiologic factor for gastric cancer.

Overall, age, male gender, smoking, increased BMI, LSBE/LGD, low fruit and vegetable intake, duration of reflux symptoms, and presence of a hiatal hernia were risk factors for cancer/HGD. The role of H. pylori infection remains controversial.

Endoscopic surveillance and follow-up

As has been mentioned, GERD is progressive with time in a consistent minority of patients. Patients with BE have a 30-50-fold increased risk of early-stage EAC compared to those without BE [57]. BE patients may need periodic reassessment of disease severity, off treatment, and/or screening for BE throughout their life.

BE is defined as the condition in which the stratified squamous epithelium that normally lines the distal oesophagus is replaced by endoscopically visible metaplastic columnar epithelium that is pre-disposed to cancer development. For decades, this disease was defined by the endoscopically visible appearance of a >3 cm proximal displacement of the squamocolumnar junction, which is now termed LSBE. This is in contrast to SSBE, where various definitions have been proposed, such as a length of at least 1 cm [58, 59]. It has been reported that the gastric cardia and intestinal metaplasia of the gastroesophageal junction (IMGEJ) account for 10-15% [60, 61] of the normal population. In the United States, 401 patients with BE and 86 patients with IMGEJ were followed for a median interval of 7 or 8 years, respectively [62]. No patient with IMGEJ progressed to EAC, while the BE subjects had a cumulative 7% risk of progression to EAC by 10 years, and an increased risk of death from EAC (standardized mortality ratio 9.62). In this large, popula-

tion-based cohort with long-term follow-up, subjects with IMGEJ had distinct demographic and clinical characteristics compared to those with BE. A prospective (training) study was conducted with a cohort of 1603 patients who underwent endoscopy to identify risk factors and develop a risk prediction model [63]. Two prediction models were identified and validated for columnar lined epithelium and intestinal metaplasia ≥ 2 cm. Both models have fair prediction accuracies and can select out the approximately 20% of individuals unlikely to benefit from investigation for BE. Such prediction models have the potential to generate significant cost-savings for BE screening among the symptomatic population.

Endoscopic surveillance intervals

The incidence of EAC in Western countries has rapidly increased over the past few decades [64]. The American Gastroenterological Association guideline suggests that endoscopic surveillance should be performed at 3-5 years intervals in patients with BE without dysplasia [65]. One population-based cohort study by Hvid-Jensen et al. [45] in 2011 identified 11,028 patients with BE and analyzed their data for a median period of 5.2 years. Presence of LGD in the index endoscopy is associated with a 0.51% incidence of adenocarcinoma. In contrast, the incidence among patients without dysplasia was 0.1%. BE is a strong risk factor for EAC, but the absolute annual risk of 0.12% is much lower than the assumed risk of 0.5%, which is the basis for current surveillance guidelines. Recently, Gaddam et al. [66] conducted a large cohort, multicentre study showing that the stable persistence of BE without dysplasia over several endoscopic examinations identified patients at a very low risk of progression to EAC. They support that surveillance intervals should be lengthened or surveillance should be discontinued among patients with persistent, non-dysplastic BE. This study should help inform future decisions on surveillance intervals in BE patients without dysplasia [67].

Unlike in Western countries, Asian countries including China have a high burden of oesophageal squamous cell carcinoma [68]. Although the prevalence of GERD is increasing, the prevalence of BE and EAC has remained low in most Asian countries [69]. Oesophageal cancer remains the fourth most common fatal cancer in China [70], and its overall incidence remained relatively stable in both urban and rural areas during a 20 year interval (1989 to 2008) [71]. The age standardized incidence noted in the cancer registration decreased from 39.5/100,000 in 1989 to 23.0/100,000 in 2008 in all areas (AAPC = -3.3%, 95% CI: -2.8--3.7). The trend had no change in urban areas, and a 2.1% average annual decrease was observed in rural areas. A major reason of the decreased and stable incidence is that upper endoscopic examination is available, easily accessible, and familiar throughout China. The guideline proposed by the Chinese Society of Gastroenterology [72] highlights the significance of endoscopic surveillance and biopsy. It states that BE patients with no dysplasia should have an endoscopic follow-up once every 2 years. For BE with LGD, a follow-up endoscopy should be performed every 6 months in the first year and, if no progress of dysplasia is seen, endoscopic and biopsy surveillance should be continued at 1-year intervals.

Progress in endoscopic technologies

Early detection of premalignant HGD is essential to improve outcomes in BE patients and prevent progression to invasive malignancy [73]. Unfortunately, dysplastic lesions and early-stage EAC can be endoscopically indistinguishable from non-dysplastic tissue. A number of advanced imaging technologies have emerged during the last decade to overcome this problem. Some of these, such as high-definition white light endoscopy (HD-WLE) and dye- or equipment-based chromoendoscopy, are designed to detect areas of abnormality, whereas other imaging modalities are better suited to tissue characterization (magnifying endoscopy with chromoendoscopy) and histological confirmation (confocal laser endomicroscopy [CLE] and endocytoscopy) [74].

Based on a meta-analysis [75], advanced imaging techniques such as chromoendoscopy or virtual chromoendoscopy significantly increase the diagnostic yield for identification of dysplasia or cancer by 34% in patients with BE compared with conventional white-light endoscopy. Bertani et al. [76] compared the incidence of dysplasia detection obtained by HD-WLE or by

probe-based CLE (pCLE) in a cohort of 100 patients with BE, and found that dysplasia can be more frequently detected by pCLE than by HD-WLE. It is likely that the higher dysplasia detection capabilities of pCLE could improve the efficacy of BE surveillance programs.

CLE is a novel endoscopic technique that has emerged as an important tool in the in-vivo visualization and detailed assessment of the mucosal layer and subcellular structures in BE [77]. Current guidelines recommend 4-quadrant random biopsies for identification of HGD in BE [78]. However, Gupta et al. [79] showed that, because of the relatively low sensitivity and negative predictive value, CLE may currently not replace standard biopsy techniques for the diagnosis of HGD/EAC in BE.

Expert commentary

GERD is a multifaceted (spectrum) clinical problem. In a consistent minority, GERD is progressive with time. Acid suppressant therapy is likely the main reason why most GERD patients remain stable or improve. This review of recent research found the risk of malignant progression among patients with BE to be lower than previously reported, suggesting that currently recommended routine medical care and surveillance strategies may be cost-effective. The incidence of oesophageal cancer has remained relatively stable in China over the past 20 years, possibly due to accessible upper endoscopic examinations.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Li-Fen Yu, Department of Gastroenterology, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Ruijin Second Road 197, Shanghai 200025, China. E-mail: yu-lifen@hotmail.com

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