Original article

Barrett's esophagus: results from an Italian cohort with tight endoscopic surveillance

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Abstract. *Background and aim:* Barrett's Esophagus represent a condition that predisposes to the development of esophageal adenocarcinoma. The aim of the present study was to analyze the demographic and clinical characteristics of patients with BE, to establish the presence of risk factors for this condition, and to determine the frequency of dysplastic lesions as well as the evolution towards adenocarcinoma under tight endoscopic control. *Methods:* In this study, we retrospectively collected and analyzed data from a cohort of patients with Barrett's Esophagus identified through endoscopic records of ULSS7 in Northern Italy, who underwent upper esophago-gastroduodenoscopy over a 10-year period from July 2008 to December 2020. *Results:* A total of 264 patients were identified as having BE and included in the study. Mean follow-up was 6.7 years (range: 3 months-13 years). Demographic characteristics of the study population included mean age of 62.7 years (range 33-90 years), with 62.5% of the study population being aged 60 or older, and a male predominance. Females were significantly older than males (65.7 years, range 37-90 vs 61.9 years, range 33-87, p=0.043, respectively). *Conclusions:* The present study confirms the importance of tight endoscopic control in the management of BE, favoring early detection of BE degeneration towards high grade dysplasia or adenocarcinoma. In a subset of patients with high-risk factors including male sex, cigarette smoking and heavy alcohol intake, it may be worthwhile to consider endoscopic control over time in order to detect the development of BE. (www.actabiomedica.it)

Key words: Barrett's Esophagus, esophageal adenocarcinoma, gastroesophageal reflux disease

Introduction

Barrett's Esophagus (BE), a precancerous condition that increases the risk of developing esophageal adenocarcinoma (EAC), is defined as the replacement of the normal squamous lining of the esophagus with a columnar intestinal epithelium, usually in response to long-standing, abnormal gastroesophageal reflux. Endoscopically, the normal white hue of the esophagus is substituted by a well-delimited area of salmon-colored mucosa. From a histological point of view, however, the definition differs between countries; in the United States and Europe, this condition is defined as "the presence of intestinal metaplasia at the esophageal level", that is, the recognition of mucin-producing goblet cells within the esophageal mucosa. In Japan and the United Kingdom, this condition does not necessarily include the presence of intestinal metaplasia, but includes any gastric metaplastic changes in the squamous epithelium of the esophagus, even in the absence of goblet cells(1).

The clinical significance of BE lies in its potential risk of progressing to EAC, especially in patients in whom dysplasia is found. Typically EAC develops through a metaplasia–dysplasia–carcinoma sequence, and it is estimated that the annual incidence of EAC among BE patients varies from 0.2% to 0.6%, whereas the combined incidence of high-grade dysplasia (HGD) and EAC is 0.9% to 1.0%.(2–7) Although the overall risk of progression to cancer is low (approximately 0.3% per year) in most countries, patients with BE are managed with endoscopic surveillance at regular intervals(8). This approach has been demonstrated to be effective in diagnosing cancer at an earlier stage and with better outcomes in terms of survival. BE patients are estimated to have a 30-125 times greater risk of esophageal adenocarcinoma with respect to the general population. Moreover, the incidence of this histological type of esophageal cancer is greater in Western countries, where BE is more frequent(9). Importantly, the prognosis of EAC is dismal, with a 5-year survival <15%, rendering surveillance necessary in patients with BE, who have an increased risk of developing this neoplasm.

The prevalence of BE has been estimated to be 376 per 100.000, according to a large study from the Mayo Clinic on long-segment BE comparing autopsies with endoscopic findings.(10) According to an Italian survey in a local community of 1033 adults, the prevalence of BE was 1.3%.(11), whereas an Asian meta-analysis based on four studies estimated a prevalence of BE of 0.7%.(12) More recent epidemiological studies have yielded similar data, with an estimated prevalence that is reportedly between 1.3 and 1.6% in the general population(13).

Several factors have been claimed to constitute risk factors for the development of BE, including non-modifiable ones like age, sex, and ethnicity, and modifiable ones including alcohol intake, cigarette smoking, excessive body weight, and long-term therapy with certain drugs such as bisphosphonates and statins. However, the most important risk factor for the development of BE is the presence of gastroesophageal reflux, which seems to constitute the main pathophysiological trigger of mucosal transformation(13–15). In a large, multicenter US study, Parasa, Sharma, and collaborators identified a set of characteristics that are able to predict development of HGD or EAC, and developed a scoring system (Progression in Barrett's Esophagus score)(16) which aids clinicians in stratifying patients according to their risk profile, therefore avoiding excessively frequent endoscopic examinations in patients with very low risk of degeneration, and optimization and strict follow-up of patients with elevated risk. According to this model, the presence of each of these factors increases the score by 9 points if male sex, 5 points if cigarette smoking, 1 point for each cm of BE's length, and 11 points for the presence of confirmed low- grade dysplasia (LGD).

Aim

The aim of the present study was to analyze the demographic and clinical characteristics of patients with BE, to establish the presence of risk factors for this condition, and to determine the frequency of dysplastic lesions as well as the evolution towards adenocarcinoma under tight endoscopic control.

Methods

In this study, we retrospectively collected and analyzed data from a cohort of patients with BE identified through endoscopic records of ULSS7 Pedemontana, Alto Vicentino Hospital, in Northern Italy, who underwent upper esophagogastroduodenoscopy over a 10-year period from July 2008 to December 2020.

Records of patients first identified in our Endoscopy register as having BE were reviewed for histological confirmation of diagnosis. Strict endoscopic and histological criteria were maintained, including columnar lined mucosa and presence of intestinal metaplasia, respectively. Following internationally recognized guidelines, diagnosis of dysplasia was confirmed by a second pathologist.

Information was collected from each patient's electronic medical records (endoscopy database and medical chart); study variables included demographic data such as age and sex, date of death (when applicable), cause of death (when applicable), as well as the following clinical information: past medical history of diabetes, hypertension, metabolic syndrome, smok-

ing/alcohol intake, body mass index, family history of upper gastrointestinal malignancy, medication use including proton-pump inhibitors, history of previous bariatric surgery and/or anti-reflux surgery, *Helicobacter pylori* infection status, date of index endoscopic evaluation, endoscopic findings including hiatal hernia, esophagitis, ulcers, length of BE, and histological findings of esophageal biopsies performed according to the Seattle protocol (4-quadrant biopsy specimens taken every 1-2 cm starting from the gastroesophageal junction) as well as gastric biopsies performed according to the Sydney protocol (2 antral biopsies, 1 biopsy from the incisura angularis, and 2 biopsies of the corpus), the latter of which are performed routinely in every esophago-gastro-duodenoscopic evaluation in the absence of contraindications. Alcohol intake was quantified as units per day and divided in 3 categories as follows: 1 unit per day, from 2-3 units per day, or more than 3 units per day.

According to established endoscopic surveillance guidelines, patients with BE ≥ 1 cm and < 3 cm, were evaluated at least at 5-year intervals, while patients with BE ≥ 3 and < 10 cm were evaluated at least every 3 years, allowing for identification of patients progressing from BE to LGD, HGD, and EAC.

For identification of predictors of progression, patients were included only when the following criteria were fulfilled:

1) a diagnosis of BE that was confirmed on both pathologic and endoscopic findings,
2) at least 2 endoscopic surveillance examinations

Histologic gastric samples are routinely analyzed and reported using the Operative Link on Gastritis Assessment (OLGA) staging system, a standardized and validated method to stratify and grade severity and distribution of atrophy which allows the classification of patients in 5 groups from stage 0 to stage IV, the latter representing the most severe or advanced stage of atrophy, involving severe depletion of gastric mucosal cells in the antrum as well as in the gastric body(17).

Results

A total of 264 patients were identified as having BE and included in the study. Mean follow-up was 6.7 years (range: 3 months-13 years). Demographic characteristics of the study population included mean age of 62.7 years (range 33-90 years), with 62.5% of the study population being aged 60 or older, and a male predominance. Females were significantly older than males (65.7 years, range 37-90 vs 61.9 years, range 33-87, p=0.043, respectively). Mean body mass index of the study population was 26.2 (range 16-57), and was not significantly different between males (26.4, range 18-38) and females (25.3, range 16-57).

A family history of esophageal or gastric cancer was present in 9.5% of the study population, without significant differences between males and females. *H. pylori* infection was found in 6.8% of patients, while 18.2% of the study population was on proton-pump inhibitor (PPI) therapy at the moment of the index endoscopy, without significant differences between genders in either case. More than half of the study population (55.8%) were either ex-smokers or active smokers, and although significantly more men declared being ex-smokers with respect to women (41.9% vs 18.8%, p=0.003), the percentage of active smokers was similar between men and women (21.6% vs 10.4, p=0.083, respectively). Daily alcohol consumption was reported in 75.6% of patients, with significant differences respectively between males and females regarding any daily amount (84.6% vs 43.8%, p=0.0001), 1 unit daily (56.8% vs 41.7%, p=0.045), 2-3 units daily (16.6% vs 2.1%, p=0.004), and more than 3 units daily (11.2% vs 0%, p=0.007).

All-cause mortality was 10.2% (27/264 patients died during the study period), with similar frequency between males and females. Sub-group analysis showed a significantly higher mortality in the long segment group (17/264, 19.5%) vs short segment group (7/264, 6.5%) and ultra-short segment group (3/264, 4.3%), p=0.002. Death in 7 (2.7%) patients was related to EAC.

Endoscopic findings at baseline included hiatal hernia in 57.2%, esophagitis in 15.5%, and peptic ulcer in 6.1% of patients, with similar distributions between sexes. Ultra-short (1-2 cm), short (<3 cm), and long (≥ 3 cm) BE was diagnosed in 70 (26.5%), 107 (40.5%), and 88 (33%) patients, respectively, with similar distribution between genders. Regarding histologic findings according to the OLGA Staging System, grade 0, I,

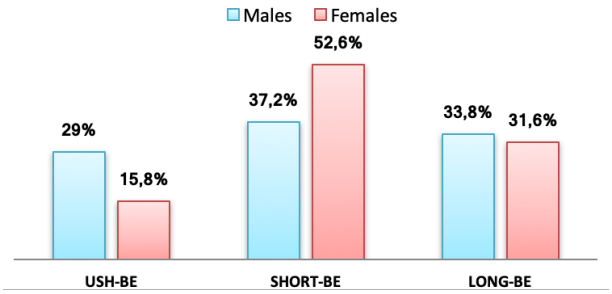

Figure 1. Distribution of BE length classified as ultra-short BE (USH-BE), short BE, and long-BE according to gender (n=264).

II-III was found in 203 (76.9%), 28 (10.6%), and 5 (1.9%) of patients, respectively, with a similar distribution between genders; information on histological grading was missing in 28/264 patients.

OLGA 0 was found in 77.1%, 72.8%, and 81.6% of patients with ultra-short, short, and long-segment BE, respectively, while OLGA I was found in 10.0%, 15.9%, and 4.6% of patients with ultra-short, short, and long-segment BE, respectively. Cases corresponding to OLGA II were seen more frequently in patients with ultra-short or short-segment BE (2.8% and 1.9%, respectively) with respect to long-segment BE, seen in only 1 patient (1.1%). The single patient with OLGA III staging was a male patient with ultra-short segment BE.

Regarding esophageal histological findings at baseline, simple metaplasia without dysplasia was found in 250/264 patients (94.7%), while 14 patients (5.3%) had varying grades of dysplasia or adenocarcinoma: LGD, HGD, and adenocarcinoma arising from BE were found at baseline in 2 (1.0%), 3 (1.4%), and 9 (4.3%) patients, respectively.

Discussion

Our study confirms that male sex and increasing age (peak of frequency around the sixth decade) are the most important non-modifiable risk factors. Moreover, female patients with BE are statistically older than their male counterparts (65.7 vs 61.9, p=0.043) which may indicate that a longer exposure to risk factors is needed for BE development in women.

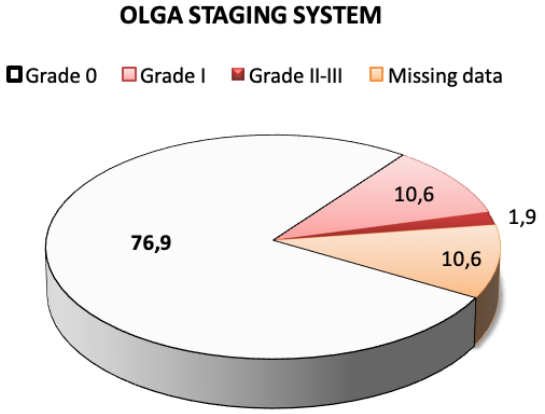

Figure 2. Distribution of BE patients with respect to severity of gastric atrophy, according to the Olga Staging system.

Regarding modifiable risk factors, smokers with reflux symptoms are three times more frequently diagnosed with BE compared with non-smokers. An interesting multi-center Italian study analyzing 339 patients with BE, 462 patients with esophagitis, and 619 controls (of which 289 GERD-negative and 339 GERD-positive past medical history) from 12 endoscopy units demonstrated a remarkably elevated correlation between BE and all smoking-related predictors in former smokers. In particular, having smoked for more than 32 years increased the risk of BE more than twice (Odds, ratio (OR) 2.44, 95% CI 1.33-4.45). The authors of this study conclude that smoking seems to be an independent determinant of BE, and, to a lesser degree, of esophagitis. Interestingly, the elevation in risk is independent from GERD and is already present in light cigarette smokers.(20) Higher smoking burden (pack-years) is associated with higher risk of BE, and duration of smoking cessation is inversely associated with the risk of BE(21). Conversely, alcohol seems not to be a strong risk factor.(13,14) This study confirms the importance of cigarette smoking as a risk factor for development of BE as well as esophageal adenocarcinoma, as more than half (55.8%) of patients with BE are active or past smokers. Previous studies have demonstrated that the duration of exposure is very important; smoking more than 20 cigarettes per day for more than 10 years increases the risk of BE, more so in Asians (3.1%) with respect to Caucasians (1.6%), as reported in a Russian study(22). Although our study included only Caucasians and in spite of the fact that

Table 1. Demographic characteristics, risk factors, and endoscopic findings of the study population according to the length of BE at baseline

	USH-BE n.69	SHORT-BE n.107	LONG-BE n. 88	p-value*
Gender M/F	60/9	77/30	70/18	0.035
Age, yr (mean ± DS) Range	60.0± 11.2 39-82	63.1± 12.8 33-90	64.4± 13.1 33-87	0.043
Cigarette smoking (%)				
- Active smokers	28.6	16.7	14.7	0.114
- Ex Smokers	32.1	32.1	45.3	0.161
Daily alcohol intake (%)				
- 1 U	62.5	47.1	53.9	0.115
- 2-3 U	19.6	12.9	9.2	0.109
- >3 U	3.6	10.6	10.5	0.111
Body Mass Index (cm/kg^2)				
- Mean ± SD	26.3±5.2	26.1±3.9	26.2±3.4	0.683
- Range	17-57	16-38	18-35	
H. pylori infection (%)	8.6	7.5	4.6	0.581
Family history of esophageal or gastric cancer (%)	14.5	8.4	6.8	0.235
PPI therapy (%)	20.0	22.4	11.5	0.384
Hiatal hernia (%)	34.8	54.2	78.4	0.0001
Esophagitis (%)	11.6	15.9	18.2	0.307
Peptic Ulcer (%)	5.8	5.6	6.8	0.923
All-cause mortality	4.3	6.5	19.3	0.002

*p values refer to ultra-short BE vs the combination of short and long BE

more detailed information of smoking habit duration was not available and the study design does not allow for risk estimation, most patients with BE have been smokers or are active smokers.

Of note, only 24.3% of the study population declares to refrain from drinking alcohol, and males are significantly twice as likely to declare being active drinkers (any amount of daily alcohol intake), moderate drinkers (1-3 units daily), and heavy drinkers (> units per day). Although large meta-analyses have failed to demonstrate an association between alcohol consumption and BE, except for Asian heavy drinkers, alcohol does exert a direct noxious effect on the esophageal mucosa, which predisposes to acid-related injury.(23) Alcohol, especially if intake is of 20 g/day or greater might be an important risk factor for BE development in males in the presence of hiatal hernia. (24,25)

Although infection with *H pylori*, which causes destruction of acid-producing gastric mucosa, has been advocated as a protective factor for BE, infection has been reported in a variable percentage of patients with BE, ranging from 5.2% to 43.3%(26). Reportedly, however, eradication of *H pylori* does not seem to increase the risk of developing either BE nor esophageal carcinoma.(27) An extensive meta-analysis including 84717 BE patients and 390749 controls showed that infection with *H. pylori* reduces the risk of BE; OR = 0.68 (95% CI: 0.58-0.79, P < 0.001). Subgroup analysis revealed risk reduction in Asia OR = 0.53 (95% CI:

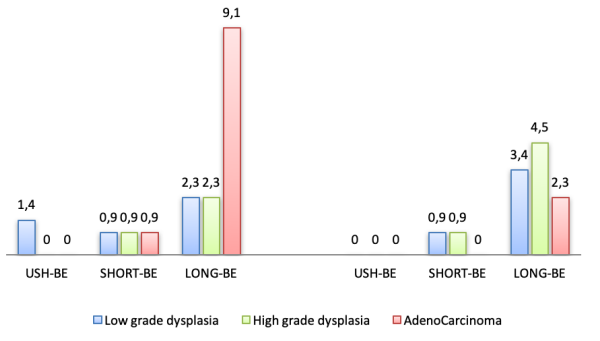

Figure 3. Histological dysplastic/neoplastic findings according to length of BE segment at baseline (left panel) and at follow-up (right panel).

0.33-0.84, P = 0.007), Australia OR = 0.56 (95% CI: 0.39-0.80, P = 0.002), Europe OR = 0.77 (95% CI: 0.60-0.98, P = 0.035), and North-America OR = 0.59 (95% CI: 0.47-0.74, P <0 .001). The risk was significantly reduced for dysplastic BE, OR = 0.37 (95% CI: 0.26-0.51, P < 0.001) for non-dysplastic BE, OR = 0.51 (95% CI: 0.35-0.75, P =0.001), and for long segment BE, OR = 0.25 (95% CI: 0.11-0.59, P = 0.001) in case of *H pylori* infection(28). In our study population, *H pylori* infection was present in 6.8% of cases, which is, on average, lower than the overall prevalence of *H pylori* in our general population and the population that undergoes EGDS evaluation for all causes at our institution. In a local study of 266 dyspeptic patients evaluated with EGDS, *H. pylori* infection was present in 114 subjects (42%)(29).

Familial clusters of BE and EAC have been observed, and an autosomal dominant transmission inheritance with relatively high penetrance has been proposed(30) However, the population-attributable fraction of familial cancer for esophageal tumors, i.e. the proportion of tumors that is related to familial clustering, is about 1%.(31) This proportion is small, but the familial risk among offspring from an affected parent is quite high, about 4-fold, suggesting the contribution of heritable factors(32,33). Family history of gastric cardia cancer has been reported as a risk factor for developing esophageal (squamous and adenocarcinoma subtypes), as well as cardial and non-cardial gastric cancer(34). Microsatellite instability and familial clustering of gastric tumors may suggest a genetic predisposition for a subset of gastric tumors, albeit this association has not yet been demonstrated for BE or esophageal adenocarcinoma(35). In a US case-control study in males affected with BE, however, no significant differences were observed in the proportion of subjects with several specific malignancies in first- or second-degree relatives between patients with and without BE.(36) In a large, multicentric Italian study, although researchers did not find evidence of an association between family history of cancer and the diagnosis of BE, they do report an association between the occurrence of esophageal/gastric cancer at an early age (before 50 years of age) among BE relatives, suggesting a possible genetic contribution in the onset of these tumors.(31) In an original and interesting study in the US, where all male patients scheduled for colonoscopy underwent upper endoscopy as well and in which family history of cancer was studied, researchers found an increased risk for BE associated with a family history of esophageal cancer or colorectal cancer(37). In our study population, almost 10% of patients had a family history of gastric or esophageal cancer, suggesting a common predisposition for developing mucosal phenotypic as well as genotypic alterations. Even more remarkably, family history of gastric cancer is found in over 8% of females with BE.

Regarding endoscopic findings of patients with BE at baseline, hiatal hernia was found in almost 60% of patients, which is in line with several studies which have reported the association between both conditions. Moreover, our study shows a significantly greater frequency of hiatal hernia in patients with long-segment BE (78.2%), with respect to patients with short-segment or ultra-short segment BE (54.2% and 35.7%, respectively) (p=0.0001), and the increasing length of BE parallels the increase in frequency of hiatal hernia. In a large meta-analysis comprising over 4000 patients, the presence of hiatal hernia was associated with an increased risk of BE of any length, even after adjusting for clinically significant confounders; the strongest association was found between hiatal hernia and long-segment BE.(38) In another large-scale case-control study from the Mayo clinic analyzing over 110,000 patients with BE, researchers found that patients with hiatal hernia have significantly higher odds of having associated BE, regardless of the grade of dysplasia.(39) Moreover, in a prospective US study following patients with BE, hiatal hernia size, for hernia of 3 or more cm, was associated to BE progression to multifocal HGD or adenocarcinoma(40).

Although traditionally gastroesophageal reflux disease has been divided into non-erosive GERD, erosive GERD, and BE, the latter may coexist with visible endoscopic erosive esophagitis. In our study population, any-grade esophagitis was found in approximately 15%, with similar distribution between sexes. Whereas both erosive esophagitis and BE are expressions of gastroesophageal reflux disease, identifying which patients with erosive esophagitis will develop BE is still not possible, and the presence of both erosive esophagitis and BE in an individual patient does

not seem to alter prognosis. Moreover, although data from the medical literature on the natural history of this disease are limited and mainly retrospective, they seem to indicate that both non-erosive reflux disease (NERD) and mild esophagitis tend to remain as such with time and the progression from NERD to erosive reflux disease (ERD), from mild to severe ERD and from ERD to BE may occur in a small proportion of patients, ranging from 0 to 30%, 10 to 22% and 1 to 13% of cases, respectively.(41)

BE was of 3 cm or more in length in more than 70% of our study population. Although ultra-short segment BE is associated with a reduced risk of dysplasia and adenocarcinoma with respect to short and long BE, nonetheless, this population still benefits from endoscopic surveillance, as lesions, even advanced ones such as adenocarcinoma, can develop from ultra-short segment BE. The large number of patients, who need to undergo endoscopic surveillance to detect one cancer has raised questions about the value of surveillance endoscopy in patients with short segment or ultra-short segment of BE.(18) However, in our experience, 30% of patients have ultra-short BE at diagnosis, don't represent an excessive burden, and warrant surveillance due to the progression to dysplasia and esophageal adenocarcinoma in 1.4% of cases, respectively. The other aspect potentially regarding both short and, especially ultra-short BE lies in the reported regression of intestinal metaplasia or at least the non-progression to dysplasia or adenocarcinoma after procedures that reduce gastroesophageal reflux(42–44).

In a prospective cross-sectional US study analyzing 158 newly diagnosed adult BE patients, BE length (3 cm or more) correlated with hiatal hernia length ($r=0.67$, $p<0.001$) and heartburn duration ($r=0.36$, $p<0.001$), while no correlation was found with body mass index and lifestyle habits(45), although the study was not large enough to detect differences in a population with a tendency to obesity.

In our study population, BE length significantly correlated with age, being more frequent in patients over age 60 ($p=0.043$), and with the presence of hiatal hernia ($p=0.0001$). Relevantly, 10% of the study population already had EAC (developed on BE) when diagnosis of BE was first made, of whom most patients (8/9) had long segment BE whereas a single case of EAC was found upon diagnosis of short-segment BE. Almost all patients with ultra-short BE had no dysplasia/neoplasia, with the exception of a single case of LGD which was initially found on a patient with ultra-short BE but not confirmed at follow-up endoscopy. First of all, this information reinforces the observation that ultra-short segment BE has a low probability of progression towards dysplasia/EAC, as found elsewhere(18). Secondly, the single case that was found with LGD probably represents inflammation (reactive cardial mucosa) in coexisting esophagitis or gastric foveolar dysplasia; it is widely known that inflammation might erroneously lead to upgrading of metaplastic lesions. Another possibility is the regression of LGD on ultra-short segment BE, which has been described with the use of PPI or with surgical correction of hiatal hernial and improvement of gastroesophageal reflux(19). At follow-up progression of BE was observed in 11 (4.2%) patients, with development of LGD, HGD, or EAC, with low frequency of progression observed in not only ultra-short segment BE, but in short segment BE as well. When followed in time, with tight endoscopic surveillance according to international guidelines at 2–3 year intervals, a fraction of patients with long segment BE patients which is not disdainable progresses towards LGD, HGD or EAC, notwithstanding PPI therapy, which is routinely prescribed after diagnosis of BE.

In a prospective study following 108 patients with BE for a mean of 39.9 ±-20.8 months and a total of 361.8 patient-years, 5 patients developed multifocal HGD and five developed EAC, for an incidence of 1 per 71.9 patient-years for either diagnosis. Researchers found that progression to multifocal HGD/adenocarcinoma was associated with hiatal hernia ($p = 0.02$), the length of BE ($p = 0.001$), the presence of dysplasia at diagnosis ($p < 0.001$) or anytime during surveillance ($p < 0.001$). Stepwise logistic regression analysis revealed progression to multifocal HGD or adenocarcinoma was significantly and independently associated with presence of dysplasia at diagnosis ($p < 0.0001$) or anytime during follow-up ($p < 0.03$), hiatal hernia size ($p < 0.02$, for hernia > or =3 cm), and length of BE ($p = 0.009$, >2 cm).(40)

A German study analyzing 1017 patients with newly diagnosed EAC found that 573 (56%) had long-

segment, 240 (24%) short-segment, and 204 (20%) ultra-short-segment BE. Using base-case estimates for the prevalence of BE among the general German and US population, researchers report that the annual cancer transition rates for patients with long, short, and ultra-short BE were 0.22%, 0.03%, and 0.01%, respectively, and conclude that in order to detect one cancer, 450 patients with long-segment BE would need to undergo annual surveillance endoscopy; in short segment and ultra-short segment, the corresponding numbers of patients would be 3440 and 12,364(18). However, in a UK study analyzing cases of LGD and HGD on BE, 100 consecutive cases of EAC, and 100 cases of non-dysplastic BE over the study period, Barrie and coworkers found that almost 20% of all dysplasia in BE occurs in BE < 1 cm, and over 40% occurs in BE < 3 cm. Similarly, 20% of EAC occurs within 1 cm of the gastroesophageal junction and 40% occur within 3 cm.(46)

Regarding PPI therapy, in our study population, only 18.2% of patients were receiving therapy at baseline. This can be explained by the fact that up to 55% of patients with BE may be asymptomatic. The mainstay of GERD therapy including BE, acid suppression with PPIs, which was introduced after diagnosis, has been associated with a significant reduction in the risk of developing HGD and cancer in patients with BE.(47–49) Although theoretically, PPIs protect from progression of BE both in terms of BE length and development of dysplasia/adenocarcinoma, evidence that long-term PPI therapy might be associated with regression of metaplasia is lacking. In a US study analyzing 1342 BE patients of whom 505 (37.6%) experienced BE regression, no difference was seen between regressing and non-regressing groups with respect to PPI use.(19)

As expected, most patients with BE had no or very early stages of gastric atrophy, as demonstrated histologically by OLGA grading system (87.5% of patients had OLGA grades 0 or I). Few patients had OLGA II or III stages of gastric mucosa atrophy (4 and 1, respectively); this can be explained by the fact that biopsy sampling is observer-dependent and often oriented towards areas with more visible atrophy, while functional tests including the Gastropanel are able to more accurately account for gastric function, which may be conserved despite initial mucosal atrophy(50–53). In fact, mucosal atrophy is oftentimes patchy, with isles of conserved architecture and function, necessary for acid production and thus responsible for alterations leading to BE. These data confirm the importance of a healthy, acid-producing stomach in the genesis of BE, although it is possible that a few patients in whom some grades of gastric atrophy was found represent cases in which BE developed before gastric atrophy ensued, when acid production was still conserved.

In a long-term follow-up study of 236 veteran patients with BE, the cumulative incidence of dysplasia at 10 years was 21% for the patients who received PPI therapy compared to 58% for the patients who did not(54). In an update of this study that included 344 patients, subjects who were given a prescription for PPIs had a significant reduction in the risk of developing HGD and cancer, with a hazard ratio of 0.43 (95% CI: 0.21–0.83)(48). In an Australian study of 350 BE patients followed for a median of 4.7 years, patients who delayed using PPIs for ≥2 years after the diagnosis of BE had a significantly increased risk for developing LGD (hazard ratio 5.6, 95% CI: 2.0–15.7) and for developing HGD or EAC (hazard ratio 20.9, 95% CI: 2.8–158)(49). Finally, a study of 540 Dutch patients with BE followed for a median of 5.2 years found that PPI use was associated with a 75% reduction in the risk of neoplastic progression(47).

Although BE alone, that is, in the absence of HGD/EAC, does not have an impact on a subject's survival or lifespan, in our study the presence of long-segment BE was associated with higher mortality rates with respect to subjects with short or ultra-short segment BE, probably constituting a surrogate marker for central obesity, older age, and cigarette smoking, all independent risk factors for cardiovascular-related mortality.

Conclusion

The present study confirms the importance of tight endoscopic control in the management of BE, favoring early detection of BE degeneration towards HGD or adenocarcinoma. Although traditionally it

has been considered that patients with hiatal hernia should not undergo endoscopic surveillance, in a subset of patients with high-risk factors including male sex, cigarette smoking, and heavy alcohol intake, it may be worthwhile to consider endoscopic control over time to detect the development of BE.

Abbreviations: BE, Barrett's Esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma; ERD, erosive reflux disease; HGD, high grade dysplasia; LGD, low grade dysplasia; NERD, non-erosive reflux disease; OR, odds ratio; OLGA, Operative Link on Gastritis Assessment; PPI, proton-pump inhibitors.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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