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TOPIC HIGHLIGHT

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Natural history of Barrett's esophagus

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Abstract

The natural history of Barrett's esophagus (BE) is difficult to quantify because, by definition, it should describe the course of the condition if left untreated. Pragmatically, we assume that patients with BE will receive symptomatic treatment with acid suppression, usually a proton pump inhibitor, to treat their heartburn. This paper describes the development of complications of stricture, ulcer, dysplasia and adenocarcinoma from this standpoint. Controversies over the definition of BE and its implications in clinical practice are presented. The presence of intestinal metaplasia and its relevance to cancer risk is discussed, and the need to measure the extent of the Barrett's epithelium (long and short segments) using the Prague guidelines is emphasized. Guidelines and international consensus over the diagnosis and management of BE are being regularly updated. The need for expert consensus is important due to the lack of randomized trials in this area. After searching the literature, we have tried to collate the important studies regarding progression of Barrett's to dysplasia and adenocarcinoma. No therapeutic studies yet reported show a clear reduction in the development of cancer in BE. The effect of pharmacological and surgical intervention on the natural history of Barrett's is a subject of ongoing research, including the Barrett's Oesophagus Surveillance Study and the aspirin and esomeprazole cancer chemoprevention trial with interesting results. The geographical variation and the wide range of outcomes highlight the difficulty of providing an individualized risk profile to patients with BE. Future studies on the interaction of genome wide abnormalities in Barrett's and their interaction with environmental factors may allow individualization of the risk of cancer developing in BE.

Key words: Barrett's esophagus; Columnar lined esophagus; Dysplasia; Adenocarcinoma; Gastroesophageal reflux; Surgery

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INTRODUCTION

Barrett's esophagus (BE) is commonly defined as the replacement of esophageal squamous epithelium with metaplastic columnar epithelium, from the gastroesophageal junction proximally, that has been visualized endoscopically and confirmed histologically[1-3]. The importance of the diagnosis of BE lies in the fact that it is known to increase the future risk of developing adenocarcinoma[4]. The presence of BE is also associated with patients who have a more severe degree of acid and bile reflux compared to patients with gastro-esophageal reflux

disease without Barrett's columnar lining in their esophagus[5,6]. This has implications in their clinical management.

There is debate about the degree to which intestinal metaplasia (IM) of the columnar-lined esophagus increases the risk of esophageal adenocarcinoma, and some observers have included the presence of IM in the definition of BE[3,7]. Some authorities, however, do not specify IM as they believe its absence is only a reflection of sampling error and that it will invariably be present if meticulously searched for[8-10]. It is clear that the presence of IM is common in patients who have no other diagnostic criteria of BE[1,11], and without a consistent endoscopic abnormality the diagnosis of IM on biopsy only may have no clinical relevance. Patients with BE have a range of histological abnormalities including gastric metaplasia (fundic and/or body) and non specialized IM, often with a mosaic of different cell types spread across the epithelium.

SYMPTOMS

Patients with BE usually present with symptoms of gastroesophageal reflux disease (GERD) or its complications[12]. Amongst a cohort of 309 BE patients described by Rudolph *et al*[13], 98.6% reported a history of heartburn or acid regurgitation spanning at least a decade or more. Lieberman *et al*[14] further confirmed the correlation between a long history of GERD and the presence of BE. Also, patients with uncomplicated BE seem to have less symptoms than those who have esophagitis without BE[6]. Patients with BE have a greater frequency and severity of defective anti-reflux mechanisms[15].

Symptom correlation with onset or progression of BE is very poor. This could be due to the observation that patients with BE have an alteration in their pain perception and thus repeated reflux events and associated tissue injury remain asymptomatic to the patient[16]. In a prospective non randomized study of 35 patients with low grade dysplasia (LGD) in BE, only 63% had typical symptoms of GERD and 15% had no predominant symptom[17]. Also, up to 40% of patients with BE-associated esophageal adenocarcinoma do not have reflux symptoms[18]. Only a minority of patients with reflux symptoms develop BE. In a large prospective study of GERD patients followed up for several years, BE was found in 11% of the studied population of 6250 patients[19], and in the recent LOTUS trial BE was diagnosed in 10.8% of a population of 554 patients with chronic reflux symptoms[20].

Screening studies for BE in asymptomatic subjects[21,22] use the definition of BE which relies on the endoscopic appearance of salmon pink mucosa plus the microscopic diagnosis of IM. In the absence of a defined endoscopic abnormality, they use the term specialized IM of the esophagogastric junction. The introduction of the presence of IM and the circular reasoning of assuming that any IM defines BE has created a degree of confusion in the clinical epidemiology of this condition. The abnormality of BE which has a clinical relevance has been the endoscopic diagnosis of columnarization. When this columnarization is > 3 cm long, the likelihood that this is a hiatus hernia diminishes. When IM is found, the risk of cancer is considered greater, and, any patient with > 3 cm length of BE is likely to eventually show IM on surveillance endoscopy even if the first series of biopsies are negative. Thus an overemphasis on the presence of IM is very unhelpful. Therefore, the endoscopic finding should be the primary recorded abnormality, supported by histology.

Endoscopic features should be reported according to the Prague C and M criteria described by Sharma *et al*[23] with precise definitions of endoscopic abnormalities, including the tongues, the circumferential extent and the position and extent of the associated hiatus hernia. The criteria include assessment of the circumferential (C) and maximum (M) extent of the endoscopically visualized BE segment, as well as endoscopic landmarks. This is very useful for long-term follow-up of individual patients and for standardizing results in clinical trials. The data in almost all of the studies reported in this review have not been recorded within the standards of the Prague classification, but future studies should uphold this current standard.

Onset of diagnosis and observation on natural history of BE over time

BE develops in the distal esophagus following tissue injury due to GERD. It is believed to be an acquired condition because of its association with more severe forms of GERD, its prevalence in older patients[24] and the evidence from animal models[25]. Two theories have been proposed for the evolution of BE.

Progressive theory: Amongst the proposed theories for the evolution of BE, the progressive theory is the most supported. Microscopic changes first start in the squamocolumnar junction in the form of a change from neutral to acid mucin production and formation of goblet cells. This is then subsequently visible as a columnar lined esophagus of varied length depending on the duration and severity of reflux[26]. Thereafter, the segment length and the degree of differentiation of cells progresses according to the stimulus to which it is exposed. BE may occur after resection of the lower esophagus as observed by Hamilton *et al*[27] and also in the upper esophagus as seen in patients who have survived cancer resections for BE-induced adenocarcinoma[28].

Instantaneous field change theory: Most patients with BE do not demonstrate a significant increase in the length of the affected segment with time[24,29]. This observation and the lack of good evidence for the progression of BE led to an alternative hypothesis suggested by Cameron *et al*[24]. This instantaneous field change theory proposed that in response to a specific reflux injury, there is immediate change in the lining of the esophagus of a certain length which then remains constant. However, there is in-

creasing evidence to suggest that there is progression of BE (with regard to segment length and de-differentiation) with time[30-32], and that long segment BE has more severe acid exposure than short segment BE[33].

Male Caucasians (non-Hispanic whites) in the age range 60-70 years have consistently been shown to have a higher incidence of BE[34,35]. Not surprisingly, the prevalence of BE, particularly the long segment type, is low in East Asians[36]. Also, although BE is considered to affect the elderly, this trend seems to be changing. In a retrospective analysis of 7220 patients with BE, the mean age of diagnosis of BE had decreased between the years 1990 and 2005, with an increase in newly diagnosed BE patients below the age of 50 years[37]. Guardino *et al*[38] also found that 25% of BE patients from their 837 patients registry were younger than 50 years of age. These differences in the demographics of patients with BE has not been explained by any study yet although it has implications in surveillance programs. Future studies need to address the influence of increased availability of endoscopy, lower threshold for health-seeking behavior and increasing obesity in Western countries with the increased prevalence/incidence of BE in these countries.

The influence of the extent of BE on its natural history is controversial. Patients with short segment BE were not considered to be predisposed to esophageal adenocarcinoma, and hence were often excluded from earlier studies of the natural history of BE[39-44]. Rudolph *et al*[13], however, did not observe an association between segment length of BE and the risk of carcinoma in their cohort of 309 patients with BE. In their study, 32 patients with high grade dysplasia (HGD) progressed to cancer and 8 patients developed adenocarcinoma directly from benign BE, giving an overall incidence of 3.4/100 patient years (1184 years of follow-up). The length of BE, also did not influence the symptomatology of their patients significantly[13]. More recent studies have observed a strong relationship between length of BE and development of adenocarcinoma and dysplasia[32,45]. The demographic data for both short and long segment BE are similar, indicating that these are a continuum of the same process[46]. The site of malignant degeneration also seems to depend on the anatomical configuration of the esophagogastric junction because cancer tends to occur in the right lateral quadrant of the esophagus in patients with BE[47]. This is supported by Prasad *et al*[48] who have comprehensively studied the current evidence of various predictors that may be useful in determining the progression of BE, including clinical and demographic factors, endoscopic factors, pathologic factors and molecular biomarkers.

DEVELOPMENT OF COMPLICATIONS

Esophagitis

Erosive esophagitis occurs along with BE in a similar frequency to those symptomatic GERD patients without BE. Zaninotto *et al*[45] demonstrated esophagitis in 19% of BE patients. BE can be present in nearly 27% of patients with erosive esophagitis, and its diagnosis may be missed due to the presence of inflammation. Therefore, repeat evaluation should be considered after complete healing of esophagitis[49].

The degree and extent of inflammation is variable. Fitzgerald *et al*[50] showed that most patients without macroscopic evidence of esophagitis had microscopic evidence of inflammation with T cell, neutrophil and eosinophil infiltration. They also showed a higher degree of inflammation and interleukin-8 cytokine expression in proximal compared with distal BE[51]. This proximal part of the columnar lined esophageal segment is known to be the area with the greatest risk of inflammatory complications such as stricture formation.

Stricture

In early retrospective series, strictures were present in up to 100% of cases[52] but in prospective series, stricture rates of 15%-40% are found. They occur within the distal esophagus most frequently near the squamocolumnar junction[53].

Ulceration

The development of ulceration within the columnar lined segment can occur in up to 60% of cases. They may be found incidentally or may present with complications such as bleeding[16] in up to 50%, or more rarely with perforation into the mediastinum[54], or fistula formation. Fistulation due to erosion through the esophageal wall into adjacent structures has been reported into the aorta[55], pericardium[56] and respiratory tree[57].

Dysplasia

During the development of adenocarcinoma there is a gradual increase in dysplastic features of the epithelium through LGD and HGD culminating in invasive cancer[58]. The reported incidence of dysplasia varies with different publications and is generally around 2%-5%[43,59-63]. Studies on the natural history of patients with dysplasia in BE are summarized in Table 1.

LGD: In prospective studies, LGD is more commonly seen than HGD[13,45]. This can progress to HGD/cancer, regress or remain static for several years[43,58-60]. HGD is frequently found in specimens containing adenocarcinoma indicating that adenocarcinoma develops from HGD[44].

The time it takes to progress from dysplasia to adenocarcinoma is highly variable with some rapidly developing adenocarcinoma, some having LGD for long periods[68,69] and some progressing from LGD to HGD[43,57-59]. Regression from HGD to LGD and HGD/LGD to absence of dysplasia is also variable. In the majority of patients, LGD is relatively stable and does not tend to progress to invasive adenocarcinoma when observed in the short term[43,59]. However, when compared to patients with no dysplasia, those with LGD have a significantly higher risk of progressing to cancer/HGD[61-67]. For patients with a

Table 1 Barrett's esophagus: Development of dysplasia

Author	Patients with BE	Dysplasia at diagnosis	Patient years follow up	New LGD	New HGD	New dysplasia incidence (%)
Miros *et al*[43]	81	13	290	10	1	7.5
Katz *et al*[59]	102	5	563	19	4	4.1
O'Connor *et al*[60]	136	Excluded	570	24	4	4.9
Basu *et al*[61]	138	3	405	7	0	1.7
Alcedo *et al*[63]	155	Excluded	3875	83	12	2.7
Ferraris *et al*[64]	187	5	562	5	2	2.1
Weston *et al*[65]	108	Excluded	362	-	5	1.4
Oberg *et al*[66]	140	Excluded	946	44	4	5.0
Sharma *et al*[67]	618	-	2546	156	22	7.14

LGD: Low grade dysplasia; HGD: High grade dysplasia; BE: Barrett's esophagus.

Table 2 Barrett's esophagus: Outcome of series exclusively following up high grade dysplasia

Author and year	Patients	Follow-up (yr)	HGD to cancer	Cancer/ patient years
Schnell *et al*[73], 2001	79	7.3	12	2
Rastogi *et al*[75], 2008	236	–	69	6.5
Weston *et al*[76], 2000	15	3	6	13

HGD: High grade dysplasia.

diagnosis of LGD, the cumulative risk of progressing to HGD or carcinoma was reported as 85.0% in 109.1 mo compared with 4.6% in 107.4 mo for patients with non-dysplastic BE ($P < 0.0001$). The incidence of HGD or cancer was 13.4% per patient per year for patients with LGD[70].

In patients with BE, dysphagia/odynophagia and nausea/vomiting were associated with a higher risk of development of dysplasia[71]. We do not know the risk factors in patients with LGD which predispose to development of cancer, and are unable to individualize the interval for surveillance endoscopy.

HGD: HGD, similarly, has a variable course with both regression and rapid progression well documented[58,72-76] (Table 2). Most will have HGD for several years before progressing to adenocarcinoma[73,74]. Also, an intensive surveillance program can still miss adenocarcinoma in HGD patients[74].

The presence of nodularity in HGD increases the likelihood that there will be submucosal invasion, and the recommendation is that all such lesions should, at a minimum, be removed by endoscopic resection, if not by esophagectomy[75-80]. The work of Manner *et al*[78] shows that most HGD lesions with nodularity can still be resected completely by endoscopic resection, but if the depth of submucosal invasion is beyond the upper third (into the SM3 level), lymph node involvement becomes a possibility. Hence the endoscopic appearance of nodularity alone raises the risk of an underlying cancer being present. The natural history of cancer evolution is variable and patients need to be managed by individualized assessment.

Resected specimens of esophagectomy for HGD variably confirm the presence of invasive adenocarcinoma[8,81,82], but this often quoted statistic fails to give a useful overview of the likelihood of cancer. In follow-up studies, cancer frequency in HGD patients ranged from 2%-13%. Table 2 describes the range of incidence of cancer in patients with HGD. It is important to remember while reviewing these studies that dysplastic/neoplastic changes are frequently localized within the segment, and are not a field change[44]. Therefore areas of HGD or cancer may be missed on initial biopsy, and are only detected on follow-up biopsy, leading to apparent rapid progression.

Series in specialized centers which attract tertiary referrals are very selective. Such is the Seattle group of Levine *et al*[83] who studied 70 patients undergoing prospective surveillance. Twelve patients were found to have invasive cancer on early follow-up (mean 2 mo). Fifteen progressed to cancer over a mean of 27 mo, while 43 remained stable or regressed during a mean of 30 mo follow-up. Such tertiary referral centers do not provide a useful guide to the management of the full range of community observed dysplastic BE and may skew practice.

Adenocarcinoma

Adenocarcinoma of the esophagus and gastroesophageal junction is amongst the fastest growing cancers in the Western world[84,85], and is thought to be due to the increased incidence of GERD and its complications in this population. It may be important to note the recent epidemiological study of Pohl *et al*[86] who studied the Surveillance Epidemiology and End Results database of the National Cancer Institute of USA 1973-2006. They found the incidence of esophageal adenocarcinoma to have plateaued. Whether this is true in Europe has not been reported.

The estimated risk of developing adenocarcinoma in BE varies widely (Table 3). The reasons cited for this observation are the surveillance program in place, the biopsy protocol and sampling error, publication bias and geographical variation[87-100].

Some commentators raised the possibility that determination of cancer incidence in BE suffered particularly from reporting bias where positive studies were more likely to be published and smaller population groups tended to have a higher cancer incidence. This may be true of American series but Jankowski *et al*[101] contended that this was not the case for European studies where there is a more normal (Gaussian) distribution of cancer incidence and population study size.

The recent very large prospective study by de Jonge *et al*[100] however, seems to show a lower rate of progression to cancer than the previous smaller European studies (Table 3).

There may be a sex difference in cancer risk in patients with BE[100,102]. Falk *et al*[102] have shown that Barrett's segment length was greater in men than in women

Table 3 Barrett's esophagus: Development of adenocarcinoma

Author and year	Patients	Years follow-up	Cancers	% cancer/ patient years
American series				
Spechler *et al*[87], 1984	105	3	2	0.6
Sprung *et al*[88], 1984	84	4	4	1.2
Cameron *et al*[89], 1985	104	8	2	0.23
Achkar *et al*[90], 1988	62	3	1	0.6
Williamson *et al*[39], 1991	176	3	5	1
Drewitz *et al*[91], 1997	170	5	4	0.48
Streitz *et al*[92], 1998	149	3	7	1.37
Katz *et al*[59], 1998	102	5	4	0.71
Weston *et al*[65], 1999	108	3.3	5	1.39
Rudolph *et al*[13], 2000	309	3.8	40	3.4
Sharma *et al*[67], 2006	618	4.12	12	0.47
European and others series				
Robertson *et al*[93], 1988	56	3	3	1.79
Van der Veen *et al*[94], 1989	155	4	4	0.59
Hameeteman *et al*[40], 1989	50	5	5	2
Miros *et al*[43], 1991	81	3.6	3	1
Iftikar *et al*[41], 1992	102	4	4	1
Sánchez *et al*[95], 1995	46	3.6	2	0.96
Wright *et al*[96], 1996	166	3	6	1.2
Ferraris *et al*[64], 1997	88	3	3	1.25
Bujanda Fernández de Piérola *et al*[97], 1999	46	3.5	2	1.2
Basu *et al*[61], 2004	138	2.9	2	0.5
Oberg *et al*[66], 2005	140	5.8	3	0.74
Aldulaimi *et al*[98], 2005	506	9	13	4
Lim *et al*[62], 2007	356	11	25	0.62
Zaninotto *et al*[45], 2007	397	1.5	3	0.5
Gatenby *et al*[99], 2009	217		17	2.68
Alcedo *et al*[63], 2009	386	4.2	19	0.5
de Jonge *et al*[100], 2010	42 207	15	2709	0.43

(mean, 5.06 ± 4.2 cm *vs* 4.05 ± 3.27 cm, $P = 0.003$). Of 839 patients with BE, there were 114 cases of HGD or cancer (96 men, 18 women). Women were less likely to have HGD or cancer than men (odds ratio, 0.52; 95% confidence interval, 0.31-0.88; $P = 0.015$). There were 13 new cases of HGD or cancer (11 men, 2 women) during a mean follow-up of 4.72 years, with an incidence of 1 in 179 patient-years of follow-up for women and 1 in 91 patient-years of follow-up for men.

Accurate risk estimation is critically important to the economics of surveillance and other interventions to prevent carcinoma in BE patients, and thus to the specification of optimal clinical management policies.

Although many observers believe that the presence of IM in BE raises the cancer risk, it is now clear that cancer can occur without IM being detected[8,103,104]. Comparison of rates of malignant degeneration are made more complex because some authors (such as Oberg *et al*[66]) exclude all dysplastic patients at the start of the observation period while many others include all patients and document the subsequent cancer rate.

Overall health outcomes in BE patients

A very important issue for patients with BE is to understand that the natural history of BE is for the patient to suffer chronic GERD symptoms usually for a lifetime and to need a lifelong strategy of symptomatic care. This may be by medication or by antireflux surgery. They may also be subject to regular planned endoscopic surveillance. The need for surveillance is not the subject of this article *per se*. The true value of surveillance must be assessed in each geographical and economic environment. Such a study is the BE surveillance study in the United Kingdom (BOSS trial)[105] which will address this for the United Kingdom population and will also highlight the patients' own perceptions of the necessity for repeated endoscopic examination.

Studies of the true natural history of BE without therapy are not reported because every case series is given some form of therapy. Most patients are offered lifelong proton pump inhibitors (PPI) which are effective in symptom control. However, their ability to prevent complications, either benign or malignant has not been studied in controlled clinical trials.

Most reported studies on the outcome of reflux control by drugs or antireflux surgery are relatively short-term. Studies of open antireflux surgery have previously been compared with H2 receptor antagonist treatment and suggested better control of symptoms and prevention of complications of BE in patients who underwent antireflux surgery[106]. However, acid suppression with PPI is more effective than H2 receptor antagonists, and the recent studies in the LOTUS trial have compared laparoscopic antireflux surgery with dose adjusted esomoprezole (often given 20 mg *bid*). Three-year results from the LOTUS trial[20] have suggested that antireflux surgery is as efficacious in symptomatic control of BE as medical management, without significant operative or postoperative complications.

Interfering with the natural history of BE especially where treatments are directed at cancer prevention also is not the subject of this paper *per se*. It requires well controlled studies which are sparse. The aspirin and esomeprazole cancer chemoprevention trial in the United Kingdom[107-110] is looking at the issue of dose-response of esmoprezole with or without aspirin on overall survival (both cancer and cardiovascular related).

Some authors have suggested that there might be a benefit from antireflux surgery in prevention of cancer, but there are no controlled studies on this topic. Case series and cohort studies have been reviewed by Chang *et al*[108]. They found 25 publications with original data reports and their analysis supports this hypothesis but no conclusions can be drawn. Oberg *et al*[66] looked specifically at 140 patients in a surveillance program, of whom 46 had undergone antireflux surgery and none developed adenocarcinoma or HGD. In patients treated with antireflux surgery, the risk of developing LGD was reduced 2.3-fold compared with patients receiving conventional acid suppression therapy[66]. Whether a competent antireflux repair can indeed reduce the rate of malignant progression in patients with BE is still unclear, and further studies are needed to clarify this issue. Rossi *et al*[17] reported regression from LGD to BE in 63% patients with PPI and in 94% of those who had antireflux surgery ($P = 0.03$).

Other forms of cancer prevention now proposed are ablation of dysplastic BE which again will require long-term prospectively controlled studies. Early ablation studies used Argon beam plasma coagulation which indicated potential efficacy in controlling the progression of HGD to cancer; 86% of patients studied responded to this treatment with a follow-up evaluation over 7 years[109]. Recently, radiofrequency ablation has been introduced, which is a balloon-based technology that provides more easily standardized tissue destruction. This, when combined with endoscopic mucosal resection may dramatically alter the natural history of dysplastic BE[110,111].

Some authors contend that survival rates of patients with BE are virtually identical to those of age- and sex-matched control populations[87], and it is important to appreciate that, notwithstanding the increased risk of developing esophageal adenocarcinoma, the absolute risk of death from this tumor is small. In a cohort of 166 BE patients in the Netherlands with 1440 patient-years of follow-up, 79 patients died but only 2 of the deaths were due to esophageal carcinoma[42]. Most patients with BE die from causes unrelated to their esophageal disease[112,113], and reducing the risk of adenocarcinoma can produce no more than a small effect on overall life expectancy. Long term studies[105,107] are eagerly awaited to guide future understanding of BE.

Understanding the natural history of BE in an individual patient requires an estimate of risk based on the geographical variations of disease progression, and an individualized assessment of patient characteristics, race, obesity, *etc*. Presenting such a risk assessment in context is important for patients so that they have a balanced perspective of risk.

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