Symptoms and Endoscopic Features at Barrett's Esophagus Diagnosis: Implications for Neoplastic Progression Risk

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Symptoms and endoscopic features at Barrett's esophagus diagnosis: implications for neoplastic progression risk

Short title: Endoscopic features and Barrett's progression risk

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STUDY HIGHLIGHTS

WHAT IS CURRENT KNOWLEDGE

- A minority of Barrett's esophagus patients will undergo neoplastic progression

- Few factors have been identified that distinguish Barrett's esophagus patients at highest risk of progression

WHAT IS NEW HERE

- No short-segment Barrett's cases developed esophageal adenocarcinoma during the study period

- Ulceration in the Barrett's segment was associated with an increased risk of neoplastic progression

- Absence of reflux symptoms is not associated with a reduced risk of malignant progression

Abstract

Introduction: Risk stratification of Barrett's esophagus (BE) patients based on clinical and endoscopic features may help to optimise surveillance practice for esophageal adenocarcinoma (EAC) development. The aim of this study was to investigate patient symptoms and endoscopic features at index endoscopy and risk of neoplastic progression in a large population-based cohort of BE patients.

Methods: A retrospective review of hospital records relating to incident BE diagnosis was conducted in a subset of patients with specialised intestinal metaplasia from the Northern Ireland BE register. Patients were matched to the Northern Ireland Cancer Registry to identify progressors to EAC or esophageal high grade dysplasia (HGD). Cox proportional hazards models were applied to evaluate the association between endoscopic features, symptoms and neoplastic progression risk.

Results: During 27,997 person-years of follow-up, 128 of 3,148 BE patients progressed to develop HGD/EAC. Ulceration within the Barrett's segment, but not elsewhere in the esophagus, was associated with an increased risk of progression (HR 1.72; 95%CI: 1.08-2.76). Long segment BE carried a significant 7-fold increased risk of progression compared with short segment BE; none of the latter group developed EAC during the study period. A reported weight loss of ≥5kg at incident BE was predictive of a doubled risk of progression to cancer, even up to 5 years post-diagnosis. Conversely, the absence of reflux symptoms was associated with a increased risk of cancer progression (HR 1.61; 95% CI: 1.05-2.46).

Conclusions: BE patients presenting with a long segment BE, Barrett's ulcer or substantial weight loss have an increased risk of progressing to HGD/EAC and should be considered for more intense surveillance. The absence of reflux symptoms at BE diagnosis is not associated with a reduced risk of malignant progression, and may carry an increased risk of progression.

Introduction

Barrett's esophagus (BE), metaplasia of the normal esophageal squamous epithelium into specialised columnar epithelium, is rising in incidence (over and above endoscopy rates) throughout the Western world.(1-3) The importance of BE lies in the fact that it is a precursor of esophageal adenocarcinoma (EAC), a tumor that has a poor prognosis.(4, 5) The opportunity for detection of BE, and potential prevention of adenocarcinoma, has led gastroenterology organisations worldwide to endorse endoscopic surveillance of BE patients.(6, 7) However, endoscopic surveillance of BE is controversial due to ongoing debate as to its cost effectiveness.(8) Identifying patients at greatest risk of neoplastic progression, which only occurs in a minority of cases,(9-11) is a key priority in order to optimise the usefulness of such surveillance programmes.

BE and EAC are both thought to result from repeated exposure to bile and gastric acid in the distal esophagus.(12) A landmark publication from a Swedish population-based case-control study demonstrated that individuals reporting weekly reflux symptoms were at a 7-fold increased risk of EAC.(13) Moreover, a dose-response relationship with frequency of symptoms was also noted.(13) However, in contrast to the link between symptoms in the general population and development of EAC, the relationship between reflux symptoms experienced at presentation of BE and subsequent risk of neoplastic progression is less certain.(14)

BE is thought to represent an adaptive response to acid-induced injury and ulceration and therefore it is not unexpected that a substantial proportion of BE patients purport to be

asymptomatic.(15) The relevance of reflux, and other, symptoms present BE at diagnosis for stratification of cancer risk and associated need for surveillance is yet to be determined. Stratification of patients for surveillance based on other endoscopic findings at BE presentation, such as esophagitis and ulceration, has also been suggested by some studies.(14, 16) However, previous studies seeking to explore the association between these findings and EAC risk in a sequential manner have been limited by relatively small numbers of outcomes or lack of adjustment for known confounders, such as the presence of low grade dysplasia.(14, 16)

The aim of this study was to examine the association between symptoms and endoscopic features in incident BE patients and their risk of neoplastic progression in a large population based cohort.

Methods

Data collection

BE patients with specialised intestinal metaplasia (SIM) were identified from the Northern Ireland BE register, which is a population-based register of all individuals aged ≥16 years who were diagnosed with columnar-lined epithelium of the esophagus since 1993 in the province.(1) The register excludes BE cases with prevalent HGD, but retains those with indefinite or low-grade dysplasia at incident BE diagnosis. Between 1993 and 2005, 4,717 BE patients were diagnosed with SIM, of whom 3,167 (comparable in age and sex distribution to all SIM patients) underwent a hospital case note review. The hospital notes of these patients were retrospectively reviewed by one of three trained data abstractors between March 2005 and March 2010. A standardised electronic proforma in Microsoft Access was utilised to extract demographic, medical, symptom, treatment and clinical information from records corresponding to the patient's incident diagnosis of BE. The process of this case note review has been previously described for outcomes up to the end of 2008.(17) The Northern Ireland BE register has subsequently been populated with the Health and Social Care number (a unique identifier within the UK National Health Service). This allowed identification of a small number of duplicate patients (n=19, 0.6%), leaving 3,148 BE patients in the current analysis.

Confirmation of outcome diagnosis

Details of the linkage process and confirmation of BE patients who progressed to develop cancer and high grade dysplasia (HGD) in this cohort have been published elsewhere.(9) Briefly, the Northern Ireland BE register was linked to the Northern Ireland Cancer Registry to identify patients diagnosed with incident esophageal and gastric cardia adenocarcinomas or unspecified cancers of the esophagus on or before 31st December 2010. Esophageal squamous

cell carcinomas were excluded. Cases of HGD were identified from an electronic and manual review of all esophageal biopsy reports within Northern Ireland up to 31st December 2010. Only cancers or HGD diagnosed at least six months after an incident BE diagnosis were included, to minimise the potential for prevalent cancers to have influenced symptom experience and endoscopic features. The Northern Ireland BE register was matched to the General Registrar's Office in Northern Ireland to identify deaths occurring over the same time period.

Statistical analysis

Independent *t*-tests and chi-squared tests were applied to compare continuous and categorical variables, respectively, between BE patients who progressed to cancer or HGD and those who did not progress. Where the report relating to an incident BE diagnosis did not mention a symptom or endoscopic feature, for example gastrointestinal bleeding, that patient was presumed to not have experienced that symptom or feature and was recoded accordingly. Cox proportional hazards models were applied to investigate the association between reported symptoms and endoscopic features at incident BE diagnosis and the risk of progression to cancer or HGD. Assumptions for Cox proportional hazards models were checked by visual inspection of Kaplan Meier plots. Both unadjusted and adjusted models were applied, using a censor date as the date of death, date of cancer or HGD diagnosis or 31st December 2010. In adjusted models, included confounders were age, sex, presence of low-grade dysplasia, socio-economic status (reflected by area-based income deprivation quintiles), tobacco smoking status (never/former/current/unknown) and Barrett's segment length, based on *a priori* knowledge of these risk factors for EAC development. We also tested adjustment for ever use of medications including non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, proton pump inhibitors

(PPIs) and H2 antagonists but these did not significantly alter the results shown. Stratified analyses were conducted for cancer only outcomes by follow-up duration, age categories, Barrett's segment length, smoking status, PPI usage and dysplastic status. Tests for interactions were conducted using the likelihood ratio test. In addition, sensitivity analyses excluding outcomes diagnosed within one year of follow-up were conducted to minimise the likelihood of reverse causation from undetected prevalent neoplasms. All statistical analysis was conducted using Intercooled Stata Version 11 (StataCorp, Texas, USA).

Results

A total of 3,148 BE patients were followed for a mean (±SD) of 8.9 (±4.1) years (range 0.5-18.0 years). During this period, 128 patients progressed to develop HGD (n=36) or EAC (n=92). Demographic, lifestyle and clinical data of these patients are displayed in Table 1. Progressors were more likely to be male, aged 60-70 years at incident BE, have long-segment BE, low-grade dysplasia and have ever smoked tobacco compared with non-progressors. No significant differences were observed between progressors and non-progressors in terms of socio-economic status or usage of certain medications (NSAIDs, aspirin, H2 antagonists or PPIs) at their incident BE diagnosis.

Table 2 outlines the association between esophageal features noted at endoscopy and the risk of neoplastic progression in incident BE. Long segment Barrett's was associated with a seven-fold increased risk of progression, although segment length was unknown in approximately half of patients. Only two patients with short-segment BE progressed to HGD, with none developing EAC during the study time period. Progressors were more likely to have had a Barrett's ulcer at their incident diagnosis compared with non-progressors (HR 1.99; 95% CI: 1.26-3.15), even after adjustment for confounders (HR 1.72; 95% CI: 1.08-2.76). Other endoscopic features, including esophagitis, esophageal stricture, and presence of hiatus hernia, were unrelated to progression risk. Largely similar results were observed in analysis including only cancer progressors (Table 2).

The association between reported symptoms at incident BE diagnoses and the risk of progression is shown in Table 3. Incident BE patients reporting gastro-esophageal reflux symptoms had a reduced risk of cancer progression (HR 0.62; 95% CI: 0.41-0.95). This was

equivalent to asymptomatic patients having a 61% increased risk of EAC progression, after adjustment for confounders (HR 1.61; 95% CI: 1.05-2.46). The association was weaker when considering HGD and EAC outcomes combined. BE patients reporting ≥5kg loss in body weight at their incident diagnosis were at a significantly increased risk of cancer progression (HR 2.01; 95% CI: 1.01-3.98) compared with patients who did not report experiencing weight loss. No other reported symptoms were associated with progression risk.

A priori sensitivity and stratified analyses

As shown in Supplementary Figure 1, the magnitude of the inverse association between reflux symptoms and EAC progression risk remained consistent across strata of follow-up time, age categories, BE segment length, smoking status, PPI usage and in non-dysplastic BE at index diagnosis. Small numbers precluded meaningful sensitivity and stratified analyses for weight loss and Barrett's ulceration findings. Nevertheless, it should be noted that the direct association between a reported weight loss of ≥5kg and cancer progression remained even up to five years post-incident BE diagnosis (HR 3.09; 95% CI: 1.27-7.53).

All previously observed associations remained largely unaltered in sensitivity analyses of patients whose esophageal HGD or cancer was diagnosed at least one year after their incident BE diagnosis (Table 4).

Discussion

In the present study, based on one of the largest series of progressors from BE to HGD/EAC in the world, the presence of long-segment Barrett's carried a seven-fold increased risk of progression. Smaller, but statistically significant, increased risks of progression were also noted for patients with Barrett's ulceration and for those reporting substantial weight loss at their incident diagnosis. Gastro-esophageal reflux symptoms were associated with a decreased risk of cancer progression, while no other reported symptoms or endoscopic findings were predictive of progression in these patients.

Due to the relatively low proportion of BE patients who progress to HGD/EAC,(9) research efforts are attempting to identify factors that may streamline the entry into surveillance and its frequency. The relevance of both symptoms at presentation and endoscopic findings at BE diagnosis are of importance to clinicians when considering entry into surveillance and risk of malignant progression with individual patients.(18)

A study of 27 BE patients undergoing 24 hour esophageal pH monitoring has previously identified a strong positive correlation between the duration of acid exposure and Barrett's segment length.(19) One of the key findings from the current study was that patients with long segment BE (defined as ≥3cm) had a seven-fold increased risk of progression to HGD/EAC compared with short segment Barrett's. Our analysis was somewhat limited though, since Barrett's segment length was unknown in almost half of patients. The finding that longer segment length corresponds to increased progression risk concurs with results from several other studies(20-22) and previous reports from this cohort.(9) The lack of progression in short-

segment BE cases suggests that there would be limited benefits to entering these patients into current surveillance protocols, and that longer surveillance intervals or additional criteria for inclusion in surveillance programs may be warranted.(23)

In addition, our findings demonstrated that the presence of Barrett's ulceration, but not ulceration elsewhere in the esophagus, increased the risk of progression to HGD/EAC. Because our study is large, it builds upon observations from previous smaller studies, affording greater specificity of findings. In an Australian study of 353 BE patients, of whom 13 progressed to HGD/EAC over a 20 year follow-up period, the combined presence of severe esophagitis, nodularity, Barrett's ulceration and/or stricture was deemed to elevate the risk of progression in age- and sex-adjusted analysis.(16) A small study reported by Switzer-Taylor e*t al* (2008), in which 9 esophageal cancers were detected amongst a sample of 212 BE patients during 13 years of follow-up, noted that half of progressors had ulceration at their index endoscopy.(24) A Dutch study of 713 patients, incorporating 26 progressors, found BE 'irregularities' (incorporating erosions, ulcers and nodules) to carry a non-significant 2-fold increased risk of progression in multivariate models, while esophagitis was a determinant of progression.(14) A recent report from the North-Eastern Italian BE register also noted ulceration or nodularity to be associated with a heightened risk of HGD/EAC in analysis of 22 progressors.(25)

Case-control studies have identified that reflux symptoms in the general population are linked with esophageal carcinogenesis.(12, 26, 27) That is consistent with the well-established role of reflux in BE development.(28, 29) By contrast, asymptomatic BE patients in the current study were found to be at greater risk of EAC progression, and whom a recent review

highlighted to have an unknown prognosis.(30) In turn, these findings point to the presence of reflux symptoms at the time of diagnosis of BE diagnosis as being inversely associated with progression risk. It is highly unlikely that this reflects a 'true' decreased risk, since mechanistic evidence supports the carcinogenic effects of chronic acid exposure in Barrett's cell lines, such as inflammation and induction of chromosomal aneuploidy,(31) which is predictive of BE progression risk.(32)

Rather, it is more plausible that a poor correlation exists between patient perception of reflux and actual refluxate in the esophagus. Symptoms of gastro-esophageal reflux disease are not predictive of BE presence,(33) and it has long been known that there is reduced esophageal acid sensitivity in columnar versus squamous mucosa.(34) A small pain-stimulation study has also demonstrated that BE patients are hyposensitive to heat in both the normal squamous and the metaplastic epithelium of their esophagus compared with normal controls,(35) hence may be less likely to report symptoms. Our results suggested this was not reflective of age disparities in symptom recognition, as has been postulated by others.(36, 37) The relationship between symptoms and acid exposure is an important area for further research, since our findings suggest that subjectively reported symptoms would not be useful in stratifying high-risk BE patients for surveillance. Moreover, our results also raise questions over symptom control being the desired endpoint in BE management, as has been highlighted by Sarela and colleagues.(38) Asymptomatic patients may still require anti-acid treatments.

In addition, we observed that weight loss of ≥5kg in BE patients was associated with a significantly increased risk of progression. It is unlikely that such weight loss was reflecting subclinical disease, or the development of more aggressive tumors amongst BE progressors,

since progression risk remained elevated up to five years after BE diagnosis. Such substantial weight loss could reflect prior overweight/obesity, which is a known risk factor for esophageal adenocarcinoma.(12, 39) It is important for future prospective studies to distinguish the intent, nature and timing of weight loss. This is necessary to avoid detracting from the public health message that individuals should maintain a normal body weight in order to reduce their risk of developing EAC.(39, 40)

Our study has several strengths, including its large size and population-based setting in the Northern Ireland BE register, providing generalisability to all BE patients in the province. Although information was collected retrospectively, it was retrieved from hospital case notes relating to a patient's incident BE diagnosis. Therefore, this is the largest study to date that has investigated endoscopic findings and symptom experiences and progression risk in a sequential manner. In addition, we were able to control for a number of known confounders in our analysis.

There are some limitations to our analysis. It is possible that some patients did not report all of their symptoms to clinicians in order for them to be recorded in the case notes. The potentially subjective nature of symptoms reporting means that results for reflux symptoms and weight loss should be interpreted with caution. Our analysis of Barrett's segment length was relatively crude as we did not have exact length in cm for most patients and length was unknown for a considerable proportion. It is also plausible that there may be some residual confounding from unaccounted variables in our analysis.

In conclusion, BE patients presenting with long segment Barrett's, Barrett's ulceration or substantial weight loss have an increased risk of progressing to HGD/EAC and should be considered for more intense surveillance. The absence of reflux symptoms at diagnosis is not associated with a reduced risk of malignant progression, and may carry an increased risk of progression.

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any role in the study design, collection, analysis or interpretation of data or the writing of the report.

Table 1. Descriptive characteristics of patients at their index Barrett's esophagus diagnosis.

Characteristics	Non-progressors (n =3,023)	Progressors (n=128)	P-value
Mean age at Barrett's diagnosis (years)	62.0 ± 14.1	62.1 ± 11.5	0.98
Age group (years)			
16-<40	195 (6.5)	4 (3.1)	
40-<50	432 (14.3)	14 (10.9)	
50-<60	681 (22.5)	31 (24.2)	0.006
60-<70	753 (24.9)	49 (38.3)	
70-<80	643 (21.3)	24 (18.8)	
≥80	319 (10.5)	6 (4.7)	
Sex			
Male	1,881 (62.2)	99 (77.3)	0.001
Female	1,142 (37.8)	29 (22.7)	
Barrett's segment length			
Short, <3cm	323 (10.7)	2 (1.6)	
Long, ≥3cm	1,316 (43.5)	71 (55.5)	0.001
Unknown	1,384 (45.8)	55 (43.0)	
Presence of dysplasia*			
Yes	182 (6.0)	31 (24.2)	
No	2,602 (86.1)	83 (64.8)	<0.001
Unknown	239 (7.9)	14 (11.0)	
Income deprivation quintile			
I (Most deprived)	638 (21.1)	28 (21.9)	
II	598 (19.8)	33 (25.8)	0.23
III	531 (17.6)	22 (17.2)	
IV	521 (17.2)	14 (10.9)	
V (Least deprived)	460 (15.2)	23 (18.0)	
Unknown	275 (9.1)	8 (6.2)	
Smoking status			
Never	1,394 (46.1)	47 (36.7)	
Former	619 (20.5)	33 (25.8)	0.001
Current	712 (23.5)	44 (34.4)	
Unknown	298 (9.9)	4 (3.6)	
Ever use of medications			
NSAIDs	212 (7.0)	8 (6.3)	0.74
Aspirin	495 (16.4)	15 (11.7)	0.16
H2 Antagonists	437 (14.5)	23 (18.0)	0.27
PPIs	1,378 (45.6)	58 (45.3)	0.95

*Low grade or indefinite dysplasia; NSAIDs: Non-steroidal anti-inflammatory drugs; H2 Antagonists; PPIs: Proton pump inhibitors.

Table 2. Endoscopic features at incident BE diagnosis and risk of neoplastic progression.

Risk factors	Non-progressors (n =3,020)	All Progressors (n=128)	Unadjusted Hazard ratio (95% CI)	P trend	Adjusted Hazard ratio (95% CI)	P trend	EAC Progressors (n=92)	Adjusted Hazard ratio (95% CI)	P trend
Length of Barrett's									
Short (<3cm)	323 (10.7)	2 (1.5)	1.00		1.00		0 (0.0)	/	/
Long (≥3cm)	1,314 (43.5)	71 (55.5)	8.24 (2.02-33.58)	0.004	7.10 (1.74-29.04)	0.003	53 (57.6)		
Unknown	1,383 (45.8)	55 (43.0)	6.23 (1.52-25.56)		5.82 (1.42-23.94)		39 (42.4)		
Barrett's ulcer									
No/unknown	2,748 (91.0)	106 (82.8)	1.00		1.00		75 (81.5)	1.00	
Yes	272 (9.0)	22 (17.2)	1.99 (1.26-3.15)	0.003	1.72 (1.08-2.76)	0.02	17 (18.5)	1.83 (1.07-3.13)	0.03
Esophagitis*									
No/unknown	1,760 (58.3)	83 (64.8)	1.00		1.00		56 (60.9)	1.00	
Yes	1,260 (41.7)	45 (35.2)	0.74 (0.52-1.07)	0.11	0.77 (0.53-1.12)	0.18	36 (39.1)	0.97 (0.63-1.49)	0.88
Esophageal stricture seen									
No/unknown	2,811 (93.1)	115 (89.8)	1.00		1.00		83 (90.2)	1.00	
Yes	209 (6.9)	13 (10.2)	1.56 (0.88-2.78)	0.13	1.65 (0.92-2.95)	0.09	9 (9.8)	1.59 (0.79-3.21)	0.19
Hiatus hernia									
No/unknown	1,283 (42.5)	56 (43.8)	1.00		1.00		41 (44.6)	1.00	
Yes	1,737 (57.5)	72 (56.3)	0.90 (0.63-1.28)	0.56	0.95 (0.67-1.36)	0.79	51 (55.4)	0.92 (0.60-1.39)	0.68

*Incorporates patients recorded as having esophagitis or ulceration in an area of the esophagus other than their Barrett's segment.
Adjustments: age groups (16-<40/40-<50/50-<60/60-<70/70-<80/≥80 years), sex (male/female), presence of low grade dysplasia (yes/no/unknown), income deprivation quintile (I/II/III/IV/V/unknown), Barrett's segment length (long/short or unknown) (except Length of Barrett's analysis), smoking status (never/former/current/unknown).

Table 3. Reported symptoms at incident BE diagnosis and risk of neoplastic progression.

Risk factors	Non-progressors (n =3,020)	All Progressors (n=128)	Unadjusted Hazard ratio (95% CI)	P trend	Adjusted Hazard ratio (95% CI)	P trend	EAC Progressors (n=92)	Adjusted Hazard ratio (95% CI)	P trend
Presence of reflux									
No/unknown	1,392 (46.1)	57 (44.5)	1.00		1.00		45 (48.9)	1.00	
Yes	1,628 (53.9)	71 (55.5)	0.85 (0.60-1.21)	0.36	0.76 (0.53-1.09)	0.13	47 (51.1)	0.62 (0.41-0.95)	0.03
GI bleeding									
No/unknown	2,652 (87.8)	115 (89.8)	1.00		1.00		80 (87.0)	1.00	
Yes	368 (12.2)	13 (10.2)	0.97 (0.54-1.72)	0.91	0.95 (0.54-1.70)	0.88	12 (13.0)	1.26 (0.68-2.34)	0.46
Anaemia									
No/unknown	2,630 (87.1)	112 (87.5)	1.00		1.00		78 (84.8)	1.00	
Yes	390 (12.9)	16 (12.5)	1.14 (0.67-1.92)	0.63	1.25 (0.72-2.14)	0.43	14 (15.2)	1.45 (0.80-2.64)	0.22
Dysphagia									
No/unknown	2,357 (78.0)	97 (75.8)	1.00		1.00		70 (76.5)	1.00	
Yes	663 (22.0)	31 (24.2)	1.10 (0.74-1.65)	0.64	1.21 (0.80-1.82)	0.36	22 (23.5)	1.20 (0.74-1.95)	0.45
Nausea & vomiting									
No/unknown	2,194 (72.7)	94 (73.4)	1.00		1.00		64 (69.6)	1.00	
Yes	826 (27.3)	34 (26.6)	1.02 (0.69-1.51)	0.92	1.06 (0.71-1.57)	0.79	28 (30.4)	1.26 (0.80-1.97)	0.31
Weight loss									
No/unknown	2,620 (86.7)	108 (84.4)	1.00		1.00		76 (82.6)	1.00	
Yes, <5kg/unknown	205 (6.8)	8 (6.3)	1.04 (0.50-2.12)		0.96 (0.46-2.00)		6 (6.5)	1.03 (0.44-2.40)	
Yes, >5kg	195 (6.5)	12 (9.4)	1.81 (0.99-3.28)	0.08	1.65 (0.89-3.05)	0.17	10 (10.9)	2.01 (1.01-3.98)	0.07
Epigastric pain									
No/unknown	1,852 (61.3)	75 (58.6)	1.00		1.00		55 (59.8)	1.00	
Yes	1,168 (38.7)	53 (41.4)	1.04 (0.73-1.47)	0.85	0.99 (0.70-1.42)	0.97	37 (40.2)	0.95 (0.63-1.46)	0.83

GI Bleeding: Gastrointestinal bleeding.
Adjustments: age groups (16-<40/40-<50/50-<60/60-<70/70-<80/≥80 years), sex (male/female), presence of low grade dysplasia (yes/no/unknown), income deprivation quintile (I/II/III/IV/V/unknown), Barrett's segment length (long/short or unknown), smoking status (never/former/current/unknown).

Table 4. Endoscopic features and reported symptoms and risk of neoplastic progression at least one year after incident BE diagnosis.

Risk factors	Non-progressors (n =2,976)	All Progressors (n=114)	Adjusted Hazard ratio (95% CI)	P trend	EAC Progressors (n=83)	Adjusted Hazard ratio (95% CI)	P trend
Length of Barrett's							
Short (<3cm)	321 (10.8)	2 (1.8)	1.00		0 (0.0)	/	/
Long (≥3cm)	1,291 (43.4)	68 (59.7)	7.00 (1.71-28.64)	0.007	51 (61.4)		
Unknown	1,364 (45.8)	44 (38.6)	4.72 (1.14-19.53)		32 (38.6)		
Barrett's ulcer							
No/unknown	2,712 (91.1)	94 (82.5)	1.00		67 (80.7)	1.00	
Yes	264 (8.9)	20 (17.5)	1.70 (1.04-2.79)	0.04	16 (19.3)	1.89 (1.08-3.30)	0.03
Esophagitis*							
No/unknown	1,732 (58.2)	76 (66.7)	1.00		51 (61.4)	1.00	
Yes	1,244 (41.8)	38 (33.3)	0.74 (0.49-1.10)	0.14	32 (38.6)	0.97 (0.61-1.53)	0.89
Esophageal stricture seen							
No/unknown	2,768 (93.0)	106 (93.0)	1.00		78 (94.0)	1.00	
Yes	208 (7.0)	8 (7.0)	1.18 (0.57-2.43)	0.66	5 (6.0)	0.99 (0.40-2.47)	0.98
Hiatus hernia							
No/unknown	1,261 (42.4)	48 (42.1)	1.00		36 (43.4)	1.00	
Yes	1,715 (57.6)	66 (57.9)	0.96 (0.66-1.39)	0.82	47 (56.6)	0.92 (0.59-1.44)	0.72
Presence of reflux							
No/unknown	1,353 (45.5)	48 (42.1)	1.00		39 (47.0)	1.00	
Yes	1,623 (54.5)	66 (57.9)	0.82 (0.56-1.20)	0.30	44 (53.0)	0.66 (0.42-1.03)	0.07
GI bleeding							
No/unknown	2,623 (88.1)	102 (89.5)	1.00		72 (86.7)	1.00	
Yes	353 (11.9)	12 (10.5)	1.03 (0.56-1.88)	0.92	11 (13.3)	1.35 (0.71-2.57)	0.36
Anaemia							
No/unknown	2,603 (87.5)	101 (88.6)	1.00		71 (85.5)	1.00	
Yes	373 (12.5)	13 (11.4)	1.11 (0.61-2.02)	0.63	12 (14.5)	1.36 (0.72-2.57)	0.35
Dysphagia							
No/unknown	2,321 (78.0)	89 (78.1)	1.00		65 (78.3)	1.00	
Yes	655 (22.0)	25 (21.9)	1.08 (0.69-1.69)	0.75	18 (21.7)	1.07 (0.63-1.81)	0.80
Nausea & vomiting							
No/unknown	2,166 (72.8)	83 (72.8)	1.00		57 (68.7)	1.00	
Yes	810 (27.2)	31 (27.2)	1.11 (0.73-1.68)	0.62	26 (31.3)	1.34 (0.84-2.14)	0.22
Weight loss							
No/unknown	2,585 (86.9)	97 (85.1)	1.00		70 (84.3)	1.00	
Yes, <5kg/unknown	200 (6.7)	6 (5.3)	0.83 (0.36-1.90)		4 (4.8)	0.77 (0.28-2.14)	
Yes, >5kg	191 (6.4)	11 (9.7)	1.78 (0.93-3.39)	0.17	9 (10.8)	2.08 (1.01-4.27)	0.12
Epigastric pain							
No/unknown	1,819 (61.1)	67 (58.8)	1.00		49 (59.6)	1.00	
Yes	1,157 (38.9)	47 (41.2)	0.98 (0.67-1.43)	0.91	34 (41.0)	0.97 (0.62-1.52)	0.90

*Incorporates patients recorded as having esophagitis or ulceration in an area of the esophagus other than their Barrett's segment.
Adjustments: age groups (16-<40/40-<50/50-<60/60-<70/70-<80/≥80 years), sex (male/female), presence of low grade dysplasia (yes/no/unknown), income deprivation quintile (I/II/III/IV/V/unknown), Barrett's segment length (long/short or unknown) (except Length of Barrett's analysis), smoking status (never/former/current/unknown).