Predictors of dysplastic and neoplastic progression of Barrett's esophagus

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Background: It is unknown why some cases of Barrett's esophagus progress to invasive malignant disease rapidly while others do so more slowly or not at all. The aim of this study was to identify demographic and endoscopic factors that predict dysplastic and neoplastic progression in patients with Barrett's esophagus.

Methods: Patients with Barrett's esophagus who were assessed in 2000–2010 were assessed for inclusion in this retrospective study. Demographic and endoscopic variables were collected from an endoscopy database and the medical chart. Dysplastic and neoplastic progression was examined by time-to-event analysis. We used Cox proportional hazard regression modelling and generalized estimating equation methods to identify variables that were most predictive of neoplastic progression.

Results: A total of 518 patients had Barrett's esophagus confirmed by endoscopy and pathology and at least 2 surveillance visits. Longer Barrett's esophagus segment (≥ 3 cm) (odds ratio [OR] 1.2, 95% confidence interval [CI] 1.1–1.3) and increased age (≥ 60 yr) (OR 3.5, 95% CI 1.7–7.4) were independent predictors of progression from nondysplasia to dysplastic or neoplastic grades. Presence of mucosal irregularities (OR 8.6, 95% CI 2.4–30.4) and increased age (OR 5.1, 95% CI 1.6–16.6) were independent predictors of progression from nondysplasia to high-grade dysplasia or adenocarcinoma.

Conclusion: Increased age, longer Barrett's segment and presence of mucosal irregularities were associated with increased risk of dysplastic and neoplastic progression. In addition to dysplasia, these factors may help stratify patients according to risk of neoplastic progression and be used to individualize surveillance. More prospective studies with larger samples are required to validate these results.

Contexte : On ignore pour quelle raison certains cas d'œsophage de Barrett évoluent rapidement vers une maladie maligne envahissante, tandis que d'autres progressent lentement ou se stabilisent. Le but de cette étude était d'identifier les facteurs démographiques et endoscopiques prédicteurs d'une progression dysplasique et néoplasique chez les patients porteurs d'un œsophage de Barrett.

Méthodes : Des patients présentant un œsophage de Barrett ayant été examinés entre 2000 et 2010, ont été évalués en vue de leur participation à cette étude rétrospective. Les variables démographiques et endoscopiques ont été recueillies à partir d'une base de données endoscopiques et des dossiers médicaux. La progression dysplasique et néoplasique a été évaluée par analyse du délai de survenue de l'événement. Nous avons utilisé le modèle de la régression de Cox (risques proportionnels) et les équations d'estimation généralisée afin d'identifier les variables les plus prédictives d'une progression néoplasique.

Résultats : En tout, 518 patients présentaient un œsophage de Barrett confirmé par examen endoscopique et anatomopathologique et comptaient au moins 2 visites de surveillance. La présence de segments d'œsophage de Barrett plus longs (≥ 3 cm) (rapport des cotes [RC] 1,2, intervalle de confiance à 95 % [IC] 1,1–1,3) et un âge avancé (≥ 60 ans) (RC 3,5, IC à 95 % 1,7–7,4) ont été des prédicteurs indépendants de progression d'un grade non dysplasique vers un grade dysplasique. La présence d'irrégularités muqueuses (RC 8,6, IC à 95 % 2,4–30,4) et l'âge avancé (RC 5,1, IC à 95 % 1,6–16,6) ont été des prédicteurs indépendants de progression de la nondysplasie vers une dysplasie de haut grade ou l'adénocarcinome.

Conclusion : L'âge avancé, des segments d'œsophage de Barrett plus longs et la présence d'irrégularités muqueuses ont été associés à un risque accru de progression dysplasique et néoplasique. En plus de la dysplasie, ces facteurs peuvent faciliter la

stratification des patients selon le risque de progression néoplasique et servir à individualiser la surveillance. Il faudra procéder à d'autres études prospectives auprès d'échantillons de population plus volumineux pour valider ces résultats.

The past 3 decades have seen a dramatic increase in North America in the rate of esophageal adenocarcinoma (EAC).[1–3] Barrett's esophagus is a well-known premalignant esophageal condition that has the potential to progress to invasive adenocarcinoma.[4,5] Although controversial, the most accepted definition in North America for Barrett's esophagus follows the position supported by the American College of Gastroenterology: any length in the distal esophageal epithelium that can be recognized through endoscopy as columnar-type mucosa and confirmed by biopsy to have intestinal metaplasia.[6]

The key for curable management of invasive adenocarcinoma in patients with known Barrett's esophagus is the detection and eradication of cancer while it is still at an early stage. Indeed, enrolment into an endoscopic surveillance biopsy program is the current recommendation for patients with Barrett's esophagus.[6] However, not all patients with Barrett's esophagus are being identified, as their symptoms are controlled with medications and the disorder eventually progresses to EAC without their undergoing any surveillance. At present, the recommendations for the period of surveillance in patients with nondysplastic Barrett's esophagus ranges between 2 and 3 years.[6–8] Because the rate of progression from nondysplasia to cancer has been estimated to be 0.1%–0.5% per year,[9,10] most patients may not benefit from a routine endoscopic biopsy surveillance program, which makes the clinical effectiveness and cost-effectiveness of this program questionable.[11,12] On the other hand, in some patients, there is a very rapid progression to malignant disease within the 2- or 3-year period recommended for surveillance.

Given these circumstances, a risk stratification for neoplastic progression among patients with Barrett's esophagus would be more ideal and would make the surveillance program more cost-effective in the long term, as it would allow for individualization of intensive surveillance for those at high risk.

In current practice, the management of patients with Barrett's esophagus is based on the pathologic findings of the endoscopic biopsy sample. However, to be able to stratify the risk of dysplastic or neoplastic progression, additional predictors are required to identify patients at higher risk for progression. When these predictors are used in conjunction with endoscopic biopsy, they may improve the efficiency and cost-effectiveness of surveillance programs.

The aim of this study was to identify readily available demographic and endoscopic factors that can predict the progression to any dysplastic or neoplastic grade from a baseline of nondysplastic Barrett's esophagus. The primary objective was to identify the predictors of progression from nondysplastic Barrett's esophagus epithelium to high-grade dysplasia or cancer. The secondary objective was to calculate the annual incidence of each type of progression.

Methods

All patients with a diagnosis of Barrett's esophagus who were evaluated at the McGill University Health Centre, Montréal, between January 2000 and December 2010 were assessed for inclusion. We reviewed demographic and endoscopic data for each patient confirmed by endoscopy and pathology to have Barrett's esophagus. We maintained strict criteria for Barrett's esophagus: endoscopic (columnar-lined mucosa) and pathologic (intestinal metaplasia) criteria were required. For identification of predictors of progression, patients were included only when there was 1) a diagnosis of Barrett's esophagus that was confirmed on both pathologic and endoscopic findings, 2) 2 or more endoscopic surveillance visits carried out in order to assess progression status and 3) no prior history of esophageal cancer or esophageal/gastric resection.

Patients were identified through a comprehensive pathology database of the McGill University Health Centre. All patients with intestinal metaplasia of the esophagus were captured through this database. Their demographic and endoscopic findings were then obtained from both an endoscopy database and the medical chart. Demographic variables included age and sex; endoscopic variables included endoscopy date, information on hiatal hernia presence, presence of esophagitis, presence of ulcer, Barrett's segment length, presence of mucosal irregularities (nodules, irregular mucosa or polyps) and presence of stricture. Smoking, alcohol use and obesity were not included as potential variables owing to lack of adequate documentation of these variables in the older charts.

We classified patients into 3 groups based on their baseline pathologic status at the first endoscopy: 1) nondysplastic Barrett's esophagus, 2) indefinite of dysplasia or low-grade dysplasia or 3) high-grade dysplasia or EAC. To identify predictors of dysplastic and neoplastic progression, we analyzed 2 different stages of progression: from nondysplastic Barrett's esophagus to any dysplastic or neoplastic grade, and from nondysplastic Barrett's esophagus to high-grade dysplasia or EAC.

Statistical analysis

We used the statistical software program Stata 12 (StataCorp) for all analyses. We calculated the incidence rate (cases per 1000 person-years) for each type of progression outcome being investigated among the patients included in the final analysis. Length of time for progression from

nondysplastic Barrett's esophagus to premalignant/malignant lesions was initially examined by time-to-event analysis. We used Kaplan–Meier curves and log-rank tests to see the survival difference among selected categories.

We used age-adjusted Cox regression models to estimate risk factors for progression. For multivariate modelling, we applied an empirical estimation in which all the independent variables were examined for their covariate effects. We analyzed demographic and endoscopic characteristics using the low-risk category as the referent group. Two-sided p values < 0.05 were considered to be statistically significant. Owing to the nature of the data and availability at multiple observations per patient, we used generalized estimating equation models to calculate how the progression at an index visit was predictive from the variables of the previous visit. We examined all independent variables to estimate their covariate influence in order to identify factors that were most predictive of progression.

Results

From January 2000 to December 2010, 1054 patients with intestinal metaplasia of the esophagus were identified in the pathology database. A total of 303 patients were excluded because there was no documentation of columnar-lined mucosa on endoscopy or we were unable to locate the endoscopy report, leaving 751 patients who were confirmed to have both pathologic and endoscopic diagnosis of Barrett's esophagus. Of the 751, 518 had 2 or more surveillance visits and were thus eligible for the progression analysis.

Baseline demographic and endoscopic characteristics of the 518 patients are shown in Table 1. Among the 518, 458 had Barrett's esophagus without any degree of dysplasia, and in 60, the disorder had progressed to any dysplastic grade or cancer. The incidence of progression to any dysplastic grade or cancer was 19.8 cases per 1000 person-years (95% confidence interval [CI] 14.2–27.6).

Table 1. Baseline characteristics of patients with Barrett's esophagus

Characteristic	No. (%) of patients			
	All patients n = 518	Nondysplastic n = 458	Indefinite of dysplasia/ low-grade dysplasia n = 33	High-grade dysplasia/EAC n = 27
Age, yr				
< 60	263 (50.8)	240 (52.4)	15 (45.4)	8 (29.6)
≥ 60	255 (49.2)	218 (47.6)	18 (54.5)	19 (70.4)
Sex				
Male	372 (71.8)	319 (69.7)	28 (84.8)	25 (92.6)
Female	146 (28.2)	139 (30.3)	5 (15.2)	2 (7.4)
Hiatal hernia				
No	209 (40.3)	187 (40.8)	11 (33.3)	11 (40.7)
Yes	143 (27.6)	124 (27.1)	11 (33.3)	8 (29.6)
Missing	166 (32.0)	147 (32.1)	11 (33.3)	8 (29.6)
Esophagitis				
No	269 (51.9)	234 (51.1)	17 (51.5)	18 (66.7)
Yes	83 (16.0)	77 (16.8)	5 (15.2)	1 (3.7)
Missing	166 (32.0)	147 (32.1)	11 (33.3)	8 (29.6)
Ulcer				
No	318 (61.4)	281 (61.4)	18 (54.5)	19 (70.4)
Yes	34 (6.6)	30 (6.6)	4 (12.1)	0 (0.0)
Missing	166 (32.0)	147 (32.1)	11 (33.3)	8 (29.6)
Length of Barrett's esophagus segment, cm				
< 3	49 (9.4)	40 (8.7)	5 (15.2)	4 (14.8)
≥ 3 cm	98 (18.9)	81 (17.7)	8 (24.2)	9 (33.3)
Missing	371 (71.6)	337 (73.6)	20 (60.6)	14 (51.9)
Mucosal irregularities				
No	338 (65.2)	305 (66.6)	20 (60.6)	13 (48.1)
Yes	14 (2.7)	6 (1.3)	2 (6.1)	6 (22.2)
Missing	166 (32.0)	147 (32.1)	11 (33.3)	8 (29.6)
Stricture				
No	341 (65.8)	301 (65.7)	21 (63.6)	19 (70.4)
Yes	11 (2.1)	10 (2.2)	1 (3.0)	0 (0.0)
Missing	166 (32.0)	147 (32.1)	11 (33.3)	8 (29.6)

EAC = esophageal adenocarcinoma.

High-grade dysplasia or EAC developed in 10 patients, with an overall progression rate of 5.5 cases per 1000 person-years (95% CI 2.9–10.3).

The cumulative incidence of progression to dysplastic or neoplastic lesions by age and by length of the Barrett's esophagus segment is shown in Figure 1 and Figure 2, respectively. The cumulative incidence of progression to high-grade dysplasia/EAC by age and by presence of mucosal irregularities is shown in Figure 3 and Figure 4, respectively.

Univariate analyses of the effect of potential factors on progression from nondysplastic Barrett's esophagus to any dysplastic or neoplastic grade showed that length of the Barrett's esophagus segment of 3 cm or greater was a significant predictor of progression (p = 0.03). Presence of ulcer (p = 0.01) and presence of mucosal irregularities (p = 0.001) were significant predictors of progression from nondysplastic Barrett's esophagus to high-grade dysplasia/EAC.

Multivariate Cox regression analyses showed that only length of the Barrett's esophagus segment of 3 cm or greater was an independent predictor of progression from nondysplastic Barrett's esophagus to any dysplastic or neoplastic grade (hazard ratio [HR] 2.2, 95% CI 1.1–4.7) (Table 2). The presence of mucosal irregularities was an independent predictor of progression from nondysplasia to high-grade dysplasia/EAC (HR 4.6, 95% CI 1.1–18.3) (Table 3). Other factors carried no predictive value for dysplastic or neoplastic progression.

Generalized estimating equation analysis gave almost identical results to the Cox regression analyses. Length of the Barrett's esophagus segment of 3 cm or greater (odds ratio [OR] 1.2, 95% CI 1.1–1.3) and increased age (≥ 60 yr) (OR 3.5, 95% CI 1.7–7.4) were the only independent predictors of progression to any dysplastic and neoplastic grade (Table 4). Presence of mucosal irregularities (OR 8.6, 95% CI 2.4–30.4) and increased age (OR 5.1,

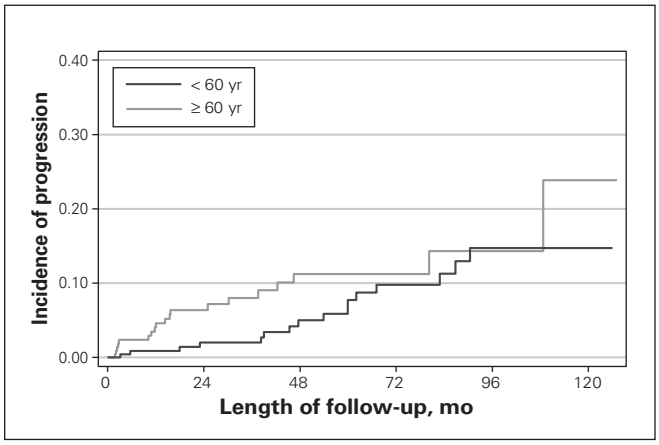

Fig. 1. Cumulative incidence of progression from nondysplastic Barrett's esophagus to dysplastic or neoplastic grades by age. There was no difference between age groups (p = 0.1).

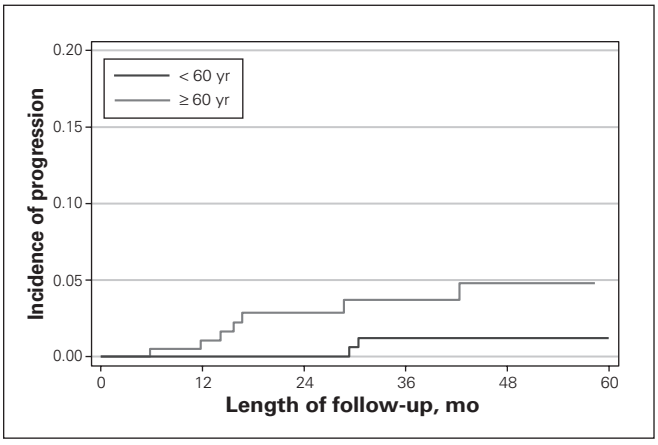

Fig. 3. Cumulative incidence of progression from nondysplastic Barrett's esophagus to high-grade dysplasia or esophageal adenocarcinoma by age. There was no difference between age groups (p = 0.07).

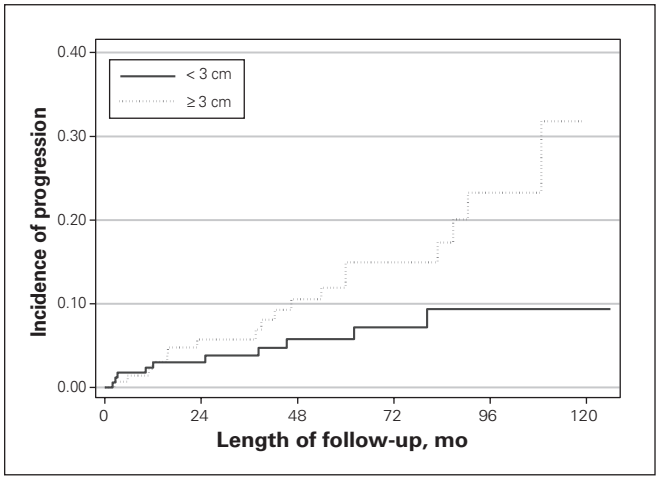

Fig. 2. Cumulative incidence of progression from nondysplastic Barrett's esophagus to dysplastic or neoplastic by length of Barrett's esophagus segment. Longer length was a significant predictor of progression (p = 0.03).

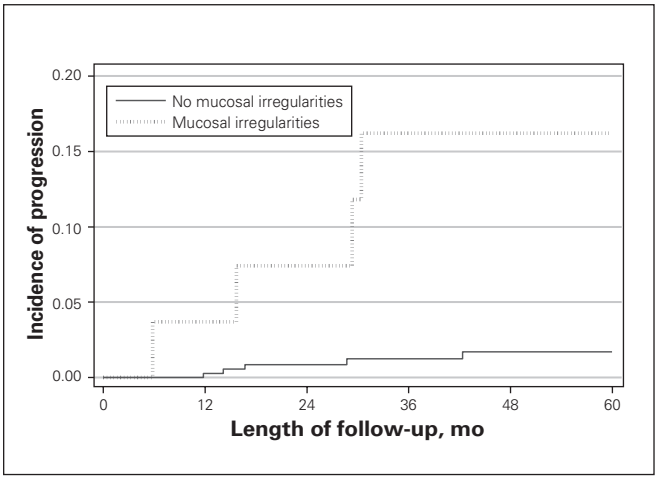

Fig. 4. Cumulative incidence of progression from nondysplastic Barrett's esophagus to high-grade dysplasia or esophageal adenocarcinoma by presence of mucosal irregularities. Presence of mucosal irregularities was a significant predictor of progression (p = 0.001).

Table 2. Multivariate analysis of potential risk factors for progression from nondysplastic Barrett's esophagus to dysplastic or neoplastic grades (Cox regression)

Variable	HR (95% CI)
Age, yr	
< 60	1.0
≥ 60	1.9 (0.9–3.9)
Length of Barrett's esophagus segment, cm	
< 3	1.0
≥ 3	2.2 (1.1–4.7)

CI = confidence interval; HR = hazard ratio.

Table 3. Multivariate analysis of potential risk factors for progression from nondysplastic Barrett's esophagus to high-grade dysplasia or esophageal adenocarcinoma (Cox regression)

Variable	HR (95% CI)
Age, yr	
< 60	1.0
≥ 60	3.2 (0.8–12.6)
Mucosal irregularities	
No	1.0
Yes	4.5 (1.1–18.3)
Ulcer	
No	1.0
Yes	3.6 (0.9–14.6)

CI = confidence interval; HR = hazard ratio.

Table 4. Multivariate analysis of potential risk factors for progression (generalized estimating equation analysis)

	OR (95% CI)	
Variable	Progression to any dysplasia	Progression to high-grade dysphasia/EAC
Age, yr		
< 60	1.0	1.0
≥ 60	3.5 (1.7–7.4)	5.1 (1.6–16.6)
Sex		
Female	1.0	1.0
Male	2.1 (0.8–5.6)	2.6 (0.6–11.1)
Hiatal hernia		
No	1.0	1.0
Yes	0.8 (0.5–1.3)	0.9 (0.5–1.3)
Esophagitis		
No	1.0	1.0
Yes	0.6 (0.3–1.4)	1.2 (0.4–3.2)
Ulcer		
No	1.0	1.0
Yes	1.9 (0.9–4.5)	0.9 (0.2–1.17)
Mucosal irregularities		
No	1.0	1.0
Yes	3.3 (0.8–13.8)	8.6 (2.4–30.4)
Length of Barrett's esophagus segment, cm		
< 3	1.0	1.0
≥ 3	1.2 (1.1–1.3)	1.1 (0.9–1.17)

CI = confidence interval; EAC = esophageal adenocarcinoma; OR = odds ratio.

95% CI 1.6–16.6) were the only significant independent predictors of progression to high-grade dysplasia/EAC.

Discussion

In this study, we examined 2 different types of dysplastic and neoplastic progression in patients with Barrett's esophagus. Consistent with previous studies,[13,14] we found that most patients remained in a nondysplastic condition over a median follow-up period of almost 5 years. However, for those who progressed from nondysplastic Barrett's esophagus to any dysplastic or neoplastic grade, only a longer Barrett's esophagus segment and age 60 years or more were independent predictors. Presence of mucosal irregularities and age 60 years or more were independent predictors of progression from nondysplastic Barrett's esophagus to high-grade dysplasia/EAC. This suggests that patients with these risk factors should perhaps be prioritized for shorter intervals of surveillance, and those deemed at low risk based on our findings could perhaps undergo surveillance at longer intervals.

Age as a risk factor for dysplastic and neoplastic progression of Barrett's esophagus is considered controversial, as it has been reported in some studies[15,16] but not in others.[17–19] In the present study, age was an independent predictor in the generalized estimating equation model but not in the multivariate Cox regression analysis. However, in Cox regression, the HR was greater than 1, which suggests that age likely has some impact, albeit not statistically significant. This is likely a type II error that would have become significant in the multivariate analysis if we had had a larger sample.

Sex did not play a significant role in dysplastic or neoplastic progression in the current study. There is disagreement in the literature about the role of sex in progression of Barrett's esophagus.[16,19,20] Nevertheless, a higher male to female ratio among patients with EAC[21] may possibly be explained by the finding that Barrett's esophagus develops at a younger age in men than in women.[21,22]

Length of the Barrett's esophagus segment is frequently described as a risk factor for malignant progression; the longer the segment, the greater the risk of progression.[23,24] In our study, patients with a Barrett's epithelial segment of 3 cm or greater were more likely to progress to dysplastic and neoplastic grades than those with a length less than 3 cm. However, this factor was not a significant predictor of progression to high-grade dysplasia/EAC. This may have been due to the small number of patients who progressed on this path. This suggest that patients with a longer Barrett's esophagus segment should undergo more intense surveillance. However, surveillance of patients with a shorter Barrett's esophagus segment should not be limited.

In previous studies, the presence of a hiatal hernia was more common among patients who progressed to dysplastic

or neoplastic grades than among those who did not progress owing to disruption of the physiologic antireflux barrier, which creates a greater probability of dysplastic and neoplastic progression.[17,25] The presence of a hiatal hernia was not significant enough to serve as an independent predictor in our study and that by Sikkema and colleagues.[26] One possible reason for this discrepancy is the lack of documentation of hiatal hernia in endoscopy reports.

Esophagitis can play an important role in dysplastic and neoplastic progression, as the underlying inflammation may increase the possibility of abnormal proliferation and neoplastic mutation.[27] In the current study, esophagitis was not a strong predictor of progression. One possible reason for this is the aggressive treatment of esophagitis with proton pump inhibitors, which reduce the inflammatory process while at the same time reducing progression. Similarly, complications of esophagitis such as esophageal ulcers and strictures were not significant predictors of progression. Their role in dysplastic and neoplastic progression in patients with Barrett's esophagus is controversial. Some studies[28,29] showed that patients with esophageal ulcers or strictures were more likely to progress to high-grade dysplasia and cancer than those without, whereas the study by Sikkema and colleagues[26] showed no link. In the current study, neither factor was an independent predictor of dysplastic or neoplastic progression.

Several studies have confirmed the presence of mucosal irregularities, including nodules, nodular mucosa and polypoid lesions, to be associated with a higher risk of progression to high-grade dysplasia and EAC.[30–32] In the present study, the presence of mucosal irregularities was an independent predictor of progression from nondysplastic Barrett's esophagus to high-grade dysplasia/EAC only and not of progression to any dysplastic or neoplastic grade. This may have been due to the presence of nodules, which can increase the risk of high-grade dysplasia or EAC specifically. Another possible reason may be the frequent use of endoscopic mucosal resection instead of conventional biopsy of a large suspicious area that might include a focus of cancer or high-grade dysplasia.

Limitations

The retrospective nature of our study and the lack of strict control over different variables are disadvantages compared to a prospective study. In addition, endoscopy reports were missing for some patients and/or for some visits for different patients. The retrospective nature of the study also made the identification of lifestyle and clinical variables challenging and sometimes impossible. We were unable to investigate the role of smoking, alcohol or obesity owing to poor documentation of these variables in the older charts; in addition, the pattern of these variables may be modified at the time of diagnosis of Barrett's esophagus. There is also the possibility of recall bias, as most of our patients received the diagnosis several years ago. Furthermore, we were unable to address the role of molecular markers in progression of Barrett's esophagus because of the retrospective nature of the study and the fact that these molecular markers were not routinely tested at our institution. Some patients have no symptoms and may progress to the dysplastic or even neoplastic stage without being identified until the late neoplastic stage. These patients may be difficult to identify or stratify for risk as they are asymptomatic and will not undergo any kind of investigation. They will not benefit from risk stratification. Another limitation is the lack of a standardized biopsy protocol at our institution, and some endoscopists performed surveillance biopsies without following the proper guidelines. In general, this lack of attention to protocol reduces the chance of detecting dysplasia or cancer in patients with Barrett's esophagus, and this may have reduced the overall number of patients with progression in our cohort. There is also the possibility that some patients who had follow-up visits in our centre may have moved to another city, progressed, sought medical advice in other centres or a different city, or died, and some may have simply withdrawn from the surveillance program offered to them. These factors may have affected the results.

Conclusion

Our study has shown that a longer length of the Barrett's esophagus segment, increased patient age and the presence of mucosal irregularities are all predictive of neoplastic progression of Barrett's esophagus. These factors may be used together with the pathologic grade to individualize the frequency of surveillance based on the estimated risk. However, more prospective studies with larger samples are required to validate these results.

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Competing interests: None declared.

Contributors: S. Alnasser and L. Ferri designed the study. S. Alnasser, R. Agnihotram, M. Martel and S. Mayrand acquired the data, which S. Alnasser, R. Agnihotram and E. Franco analyzed. S. Alnasser and R. Agnihotram wrote the article, which L. Ferri revised and all authors reviewed and approved for publication.

References

1. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;83:2049-53.
2. El-Serag HB, Mason AC, Petersen N, et al. Epidemiological differences between adenocarcinoma of the oesophagus and adenocarcinoma of the gastric cardia in the USA. *Gut* 2002;50:368-72.
3. Blot WJ, Devesa SS, Kneller RW, et al. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991;265:1287-9.

4. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006;101:1900-20.
5. Overholt BF, Lightdale CJ, Wang KK, et al. Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. *Gastrointest Endosc* 2005;62:488-98.
6. Wang KK, Sampliner RE; Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol* 2008;103:788-97.
7. Boyer J, Laugier R, Chemali M, et al. French Society of Digestive Endoscopy SFED guideline: monitoring of patients with Barrett's esophagus. *Endoscopy* 2007;39:840-2.
8. Fitzgerald RC, Di Pietro M, Ragunath K, et al.; British Society of Gastroenterology. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut* 2014;63: 7-42.
9. O'Connor JB, Falk GW, Richter JE. The incidence of adenocarcinoma and dysplasia in Barrett's esophagus: report on the Cleveland Clinic Barrett's Esophagus Registry. *Am J Gastroenterol* 1999;94: 2037-42.
10. Drewitz DJ, Sampliner E, Garewal HS. The incidence of adenocarcinoma in Barrett's esophagus: a prospective study of 170 patients followed 4.8 years. *Am J Gastroenterol* 1997;92:212-5.
11. Provenzale D, Schmitt C, Wong JB. Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. *Am J Gastroenterol* 1999;94:2043-53.
12. Garside R, Pitt M, Somerville M, et al. Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling. *Health Technol Assess* 2006; 10:1-142, iii-iv.
13. Reid BJ, Blount PL, Feng Z, et al. Optimizing endoscopic biopsy detection of early cancers in Barrett's high-grade dysplasia. *Am J Gastroenterol* 2000;95:3089-96.
14. Schnell TG, Sontag SJ, Chejfec G, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. *Gastroenterology* 2001;120:1607-19.
15. Gopal DV, Lieberman DA, Magaret N, et al. Risk factors for dysplasia in patients with Barrett's esophagus (BE): results from a multicenter consortium. *Dig Dis Sci* 2003;48:1537-41.
16. Gatenby PA, Caygill CP, Ramus JR, et al. Barrett's columnar-lined oesophagus: demographic and lifestyle associations and adenocarcinoma risk. *Dig Dis Sci* 2008;53:1175-85.
17. Avidan B, Sonnenberg A, Schnell TG, et al. Hiatal hernia size, Barrett's length, and severity of acid reflux are all risk factors for esophageal adenocarcinoma. *Am J Gastroenterol* 2002;97:1930-6.
18. De Jonge PJ, Steyerberg EW, Kuipers EJ, et al. Risk factors for the development of esophageal adenocarcinoma in Barrett's esophagus. *Am J Gastroenterol* 2006;101:1421-9.
19. Oberg S, Wenner J, Johansson J, et al. Barrett esophagus: risk factors for progression to dysplasia and adenocarcinoma. *Ann Surg* 2005; 242:49-54.
20. Bani-Hani K, Sue-Ling H, Johnston D, et al. Barrett's oesophagus: results from a 13-year surveillance programme. *Eur J Gastroenterol Hepatol* 2000;12:649-54.
21. Van Soest EM, Dieleman JP, Siersema PD, et al. Increasing incidence of Barrett's oesophagus in the general population. *Gut* 2005; 54:1062-6.
22. Van Blankenstein M, Looman CW, Johnston BJ, et al. Age and sex distribution of the prevalence of Barrett's esophagus found in a primary referral endoscopy center. *Am J Gastroenterol* 2005;100:568-76.
23. Iftikhar SY, James PD, Steele RJ, et al. Length of Barrett's oesophagus: an important factor in the development of dysplasia and adenocarcinoma. *Gut* 1992;33:1155-8.
24. Weston AP, Sharma P, Mathur S, et al. Risk stratification of Barrett's esophagus: updated prospective multivariate analysis. *Am J Gastroenterol* 2004;99:1657-66.
25. Weston AP, Badr AS, Hassanein RS. Prospective multivariate analysis of clinical, endoscopic, and histological factors predictive of the development of Barrett's multifocal high-grade dysplasia or adenocarcinoma. *Am J Gastroenterol* 1999;94:3413-9.
26. Sikkema M, Looman CW, Steyerberg EW, et al. Predictors for neoplastic progression in patients with Barrett's esophagus: a prospective cohort study. *Am J Gastroenterol* 2011;106:1231-8.
27. Moons LM, Kusters JG, Bultman E, et al. Barrett's oesophagus is characterized by a predominantly humoral inflammatory response. *J Pathol* 2005;207:269-76.
28. Montgomery E, Bronner MP, Greenson JK, et al. Are ulcers a marker for invasive carcinoma in Barrett's esophagus? Data from a diagnostic variability study with clinical follow-up. *Am J Gastroenterol* 2002;97:27-31.
29. Hillman LC, Chiragakis L, Clarke AC, et al. Barrett's esophagus: macroscopic markers and the prediction of dysplasia and adenocarcinoma. *J Gastroenterol Hepatol* 2003;18:526-33.
30. Buttar NS, Wang KK, Sebo TJ, et al. Extent of high-grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. *Gastroenterology* 2001;120:1630-9.
31. Thurberg BL, Duray PH, Odze RD. Polypoid dysplasia in Barrett's esophagus: a clinicopathologic, immunohistochemical, and molecular study of five cases. *Hum Pathol* 1999;30:745-52.
32. Arnold GL, Mardini HE. Barrett's esophagus-associated polypoid dysplasia: case report and review of the literature. *Dig Dis Sci* 2002; 47:1897-900.