Barrett esophagus frequency and predictors of dysplasia or cancer in Barrett esophagus

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Abstract. – OBJECTIVE: Identifying factors associated with an increased risk for dysplasia and cancer development among patients with Barrett esophagus would aid better patient care and improve risk stratification approaches. This study aimed at examining the frequency of Barrett esophagus and factors predicting the presence of dysplasia and cancer among patients with Barrett esophagus.

PATIENTS AND METHODS: Adult patients that underwent upper gastrointestinal endoscopic examination for gastroesophageal complaints were screened in this retrospective, cross-sectional study; and patients diagnosed with Barrett esophagus were included in the analysis. Frequency of dysplasia/cancer and its predictors were examined.

RESULTS: Among 10,404 endoscopic examinations performed during the study period, 143 patients (1.4%) were diagnosed with Barrett esophagus. Among patients with Barrett esophagus, the frequency for high-grade dysplasia, low-grade dysplasia, and adenocarcinoma was 2.8%, 2.1%, and 1.4%, respectively. On multivariate analysis, age ≥55 years (OR, 11.1 [95%CI: 2.0-61.4], p=0.006) and long segment Barrett esophagus (OR, 5.7 [95%CI: 1.2-27.8], p=0.031) emerged as significant independent predictors for dysplasia/cancer.

CONCLUSIONS: Frequency of Barrett esophagus in our population seems to be different than figures reported from different geographical regions. Advanced age and long Barrett segment on endoscopic examination are associated with the presence of concomitant dysplasia/cancer on pathological examination. Larger studies with prospective methodology are warranted.

Key Words: Barrett esophagus, Dysplasia, Esophageal cancer, Upper gastrointestinal endoscopy.

Introduction

Chronic gastroesophageal reflux disease (GERD) is already known as an established risk factor for the development of Barrett esophagus, along with obesity, advanced age, male gender, and Caucasian ethnicity. Barrett esophagus is defined as the presence of metastatic columnar epithelium in distal esophagus to any extent, instead of its normal stratified squamous epithelial lining.

The presence of Barrett esophagus with intestinal metaplasia is the only histological type that has been clearly linked to esophageal cancer. Esophageal cancer is still associated with poor survival, necessitating close surveillance for Barrett esophagus.

It is hard to identify the true prevalence of Barrett esophagus; therefore, it is unclear. A screening study identified 6.8% frequency among patients that underwent colonoscopy simultaneously with screening upper gastrointestinal endoscopy. On the other hand, figures from Turkey for patients with dyspeptic complaints or reflux symptoms are far lower and data for cancer prevalence are lacking. There may be geographical differences in epidemiology and course of Barrett esophagus. Identification of the factors associated with increased risk for dysplasia and cancer development would not only aid better and individualized patient care and follow-up, but also improve the understanding of the disease process and risk stratification algorithms. So far, several studies with different methodologies have examined the predictors for unfavorable progression of Barrett esophagus, and identified longer segment, advanced age, mucosal irregularities, male gender, longstanding GERD, increased hiatal hernia size, nodularity and visible endoscopic lesions, lifestyle, medications, molecular markers, abdominal obesity, caffeine intake, smoking, and presence of esophagitis as potential predictors. However, these findings need to be validated and confirmed with the data of patient groups from different geographical regions.
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This study aimed at examining the frequency of Barrett esophagus among patients that underwent upper gastrointestinal endoscopy for dyspeptic complaints, and frequencies of dysplasia and cancer among patients diagnosed with Barrett esophagus as well as factors predicting presence of dysplasia and cancer.

Study Design

Adult patients that underwent upper gastrointestinal endoscopic examination between January 2010 and September 2018 for dyspeptic complaints, epigastric pain, or symptoms suggestive of GERD were screened for this retrospective cross-sectional study, and the patients diagnosed with Barrett esophagus were included in the analyses. Patients younger than 18 years, pregnant women, and patients with known malignant disease or patients who were diagnosed with squamous cell carcinoma of esophagus or other gastric cancers during the endoscopic examination were excluded.

Endoscopic and Pathological Examination

A diagnosis of Barrett esophagus was made with both endoscopic examination and pathological examination findings. Endoscopic examinations were done using Exera-II CV 180 series or Exera-II CV 190 series devices (Olympus, Japan). Under white light endoscopic examination, a salmon color change was considered characteristic appearance of Barrett esophagus. Barrett esophagus was suspected when squamocolumnar junction was located ≥ 1 cm proximal to the gastroesophageal junction and optical chromoendoscopy was performed with narrow band imaging. A Barrett esophagus segment of ≥ 3 cm and < 3 cm was defined as long segment and short segment Barrett esophagus, respectively. Multiple biopsies were obtained from suspected regions. No biopsy was taken from apparently normal Z line or irregular Z line extending < 1 cm to the esophagus.

Statistical Analysis

Statistical Package for Social Sciences version 21.0 (SPSS, IBM Corp., Armonk, NY, USA) was used for data analysis. To test the normality of continuous variables, hypothesis tests and graphical methods were used; and Student’s t-test or Mann-Whitney U test was used for intergroup comparisons of continuous data, where appropriate. For intergroup comparisons of dichotomous data, Pearson’s Chi-square test or Fisher’s Exact test was used, where appropriate. Logistic regression was used for multivariate analysis of the potential predictors for cancer or dysplasia on pathological examination. Receiver Operating Characteristic (ROC) curves were used to identify optimal cut-off values for age to be incorporated in multivariate analysis. A p-value < 0.05 was considered statistically significant.

Results

A total of 10,404 endoscopic examinations were performed during the study period. Among them, 143 (1.4%) were diagnosed with Barrett esophagus; in addition, 4 (0.04%) had high grade dysplasia, 3 (0.03%) had low-grade dysplasia, and 2 (0.02%) had adenocarcinoma. The frequency for high grade dysplasia, low grade dysplasia, adenocarcinoma was 2.8%, 2.1%, and 1.4%, respectively, among patients diagnosed with Barrett esophagus.

Table I compares Barrett esophagus patients with or without dysplasia/cancer based on pathological examination in terms of demographical and clinical characteristics. An optimal cut-off point of 55 years was found through ROC analysis (AUC: 0.671, p=0.087) with 0.78 sensitivity and 0.72 specificity. Figure 1 shows Receiver Operating Characteristics (ROC) curve for age to predict the presence of dysplasia/cancer on pathological examination. Dysplasia/cancer was more frequent among patients ≥ 55 years of age (p=0.004); however, the difference did not reach statistical significance for gender, Barrett length (short or long segment), or hernia presence (p > 0.05 for all). On multivariate analysis, age ≥ 55 years (OR, 11.1 [95%CI: 2.0-61.4], p=0.006) and a long segment Barrett esophagus (OR, 5.7 [95%CI: 1.2-27.8], p=0.031) emerged as significant independent predictors of dysplasia/cancer on pathological examination, among patients with Barrett esophagus.

Follow-up of Patients with Dysplasia/Cancer

Table II summarizes the characteristics of nine patients diagnosed with dysplasia/cancer. All patients were male and intestinal metaplasia was the
only type identified in Barrett esophagus patients diagnosed with dysplasia/cancer.

**Discussion**

This study demonstrated a relatively low frequency of Barrett esophagus among patients who received upper gastrointestinal endoscopic examination for dyspeptic complaints, and Barrett length and advanced age emerged as significant independent predictors of dysplasia/cancer on pathological examination. This study is among the few examples of its kind examining the predictors of dysplasia/cancer with a cross-sectional design.

A previous study by Anandasabapathy et al. with a similar retrospective cross-sectional design with the present study, examined 109 patients who were diagnosed with Barrett esophagus and demonstrated the risk factors for the presence of high/low grade dysplasia and adenocarcinoma on pathological examination; and identified duration of reflux symptoms (≥20 years), longer Barrett segment (≥3 cm), hernia size and male gender as indicators for higher pathological grade. Similarly, Barrett length emerged as a significant predictor for unfavorable pathological findings in the present study. On the other hand, the present study is inconsistent with the study of Anandasabapathy et al. in the fact that age did not emerge as a predictor; however, that study did not perform an analysis with an age cut-off value. In our study, although age did not emerge as a predictor when included as a continuous variable, the optimal cut-off point identified (55 years) emerged as a significant predictor. This finding actually may be considered in line with the findings of that previous study, which found the duration of GERD as a significant predictor.

To date, several studies have examined the predictors for progression of Barrett esophagus to higher pathological grades over time. A recent study with 518 patients diagnosed with Barrett esophagus identified longer Barrett’s esophagus segment, increased age (≥60 years), and the presence of mucosal irregularities as independent predictors for progression to higher pathological grades. Again, another study included 318

**Table I.** Comparison between the period March/April 2020 (Group 1A) and the same period in 2019 (Group 1B).

<table>
<thead>
<tr>
<th></th>
<th>Dysplasia/Cancer present (n=9)</th>
<th>Dysplasia/Cancer absent (n=134)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean±SD)</td>
<td>55.3±12.1</td>
<td>47.4±13.6</td>
<td>0.087</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age≥55 (n=44)</td>
<td>7 (15.9%)</td>
<td>37 (84.1%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Age&lt;55 (n=99)</td>
<td>2 (2.0%)</td>
<td>97 (98.0%)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n=107)</td>
<td>9 (8.4%)</td>
<td>98 (91.6%)</td>
<td>0.112</td>
</tr>
<tr>
<td>Female (n=36)</td>
<td>0 (0.0%)</td>
<td>36 (100.0%)</td>
<td></td>
</tr>
<tr>
<td>Barrett length</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short (n=95)</td>
<td>3 (3.2%)</td>
<td>92 (96.8%)</td>
<td>0.061</td>
</tr>
<tr>
<td>Long (n=48)</td>
<td>6 (12.5%)</td>
<td>42 (87.5%)</td>
<td></td>
</tr>
<tr>
<td>Hernia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent (n=99)</td>
<td>7 (7.1%)</td>
<td>92 (92.9%)</td>
<td>0.772</td>
</tr>
<tr>
<td>Present (n=44)</td>
<td>2 (4.5%)</td>
<td>42 (95.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Unless otherwise stated, data presented as n (%).
non-dysplastic Barrett esophagus patients and 301 patients with Barrett esophagus accompanied with low grade dysplasia, and patients were followed for a mean duration of 5.3 years. In that study, Barrett esophagus length, presence of nodularity, and low-grade dysplasia at baseline emerged as significant predictors for progression to esophageal carcinoma. Another recent retrospective study on 460 patients identified age, caffeine intake, and low-grade dysplasia as risk factors for progression to high grade dysplasia or esophageal cancer but also demonstrated that statin or SSRI usage reduced the risk. A 2018 meta-analysis with 20 studies, more than 1,200 events, and almost 75,000 patients, identified advanced age, male sex, current or past smoking, higher Barrett segment length, and low-grade dysplasia as predictors for progression; and use of proton pump inhibitors or statins emerged as protective factors. In several small-sized studies, few biomarkers, such as aneuploidy and p53 loss of heterozygosity, were found to be associated with progression. Although several factors such as Barrett length, age, and low-grade dysplasia consistently found to be associated with poor outcomes over time, other potential predictors vary across studies owing to the use of different methodologies and assessments. Based on such findings, algorithms and even computer models have been developed using clinical, endoscopic, and molecular predictors for progression; however, they all need further development and validation.

GERD is a common and ever-increasing problem in the Western world. A 2014 meta-analysis found that GERD prevalence was estimated between 18.1-27.8% and 8.8-25.9%, in North America and Europe, respectively. On the other hand, rates in East Asia were relatively lower (2.5-7.8%). However, such rates may be underestimated given the fact that many people use over-the-counter GERD medications. Previous studies showed a similar population prevalence in Turkey; thus, it can be considered as a high prevalence country. Prevalence of GERD was estimated to be 20% in a study conducted by Bor et al. Another nation-wide population-based study estimated 19.1% GERD prevalence in Turkey.

Barrett esophagus is a clinically imported complication of GERD; however, there are variations in the reported figures for its prevalence, possibly due to differences in methodologies. For example, some studies were conducted in patients with GERD symptoms or any dyspeptic symptoms, and some were done with healthy individuals. In Western countries with estimated high prevalence of GERD, the reported prevalence estimates of Barrett esophagus are also relatively high among individuals with gastrointestinal complaints, mostly ranging between 8.6-50%, although a figure as low as 0.08% has also been reported from Spain. In contrast, the present study found a low prevalence rate (1.4%) among patients with dyspeptic complaints in a country that can be considered to have high prevalence of GERD. This is in line with the figures previously reported from Turkey. In a study by Yilmaz et al, a low prevalence of Barrett esophagus (0.4%) was found among 18,766 patients who underwent upper gastrointestinal endoscopy for general symptoms. In another study by Bayrakci et al, Barrett esophagus rate was 2% among 160 patients who underwent endoscopy for GERD symptoms. Such a difference between Turkey and Western countries may be explained by differences in certain risk factors such as eating habits, obesity prevalence, and H. pylori prevalence.

Table II. Summary of nine patients diagnosed with dysplasia/cancer.

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Age/Sex</th>
<th>Barrett length</th>
<th>Hernia</th>
<th>Diagnosis</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57/M</td>
<td>Short</td>
<td>Absent</td>
<td>LGD</td>
<td>No intervention, lost to follow-up.</td>
</tr>
<tr>
<td>2</td>
<td>33/M</td>
<td>Long</td>
<td>Present</td>
<td>LGD</td>
<td>RF, alive without disease.</td>
</tr>
<tr>
<td>3</td>
<td>58/M</td>
<td>Long</td>
<td>Absent</td>
<td>LGD</td>
<td>No intervention, lost to follow-up.</td>
</tr>
<tr>
<td>4</td>
<td>56/M</td>
<td>Long</td>
<td>Absent</td>
<td>HGD</td>
<td>EMR resulted in cure, lost to follow-up.</td>
</tr>
<tr>
<td>5</td>
<td>69/M</td>
<td>Long</td>
<td>Present</td>
<td>HGD</td>
<td>RFx2, progressed to stage IV disease, died.</td>
</tr>
<tr>
<td>6</td>
<td>66/M</td>
<td>Short</td>
<td>Absent</td>
<td>HGD</td>
<td>RFx4 resulted in cure, alive without disease.</td>
</tr>
<tr>
<td>7</td>
<td>62/M</td>
<td>Short</td>
<td>Absent</td>
<td>HGD</td>
<td>EMR identified intramucosal Adeno Ca, RFx2 resulted in cure, alive without disease.</td>
</tr>
<tr>
<td>8</td>
<td>59/M</td>
<td>Long</td>
<td>Absent</td>
<td>Adenocarcinoma</td>
<td>Surgical resection, alive without disease.</td>
</tr>
<tr>
<td>9</td>
<td>38/M</td>
<td>Long</td>
<td>Absent</td>
<td>Adenocarcinoma</td>
<td>Surgical resection, lost to follow-up.</td>
</tr>
</tbody>
</table>

M, male; LGD, low grade dysplasia; HGD, high grade dysplasia; RF, radiofrequency ablation; EMR, endoscopic mucosal resection.
In the present study, adenocarcinoma rate was 1.4% among patients diagnosed with Barrett esophagus and 0.02% among whom had endoscopy for dyspeptic symptoms. This study also provided the dysplasia rates among these patients. Previously, no data were present regarding the frequency of Barrett-related dysplasia and adenocarcinoma in Turkish population. Findings of this study underscore the differences between various geographical locations in terms of the progression and course of upper gastrointestinal conditions from simple gastrointestinal complaints to the development of Barrett esophagus and possible dysplasia and cancer. Such information may give clues for developing more accurate algorithms to predict serious upper gastrointestinal conditions; possibly including certain geographical factors may result in improvements. In addition, our findings support current evidence on the prognostic role of Barrett length and age – or indirectly the duration of GERD symptoms – in the development of higher pathological grades including cancer.

Limitations

The main limitation of the present study is its retrospective and cross-sectional design, and findings do not give an idea about the timely course of pathological changes. Another limitation may be considered the relatively small sample size.

Conclusions

Our findings demonstrate a difference in the frequency of Barrett esophagus in our geographical location when compared to Western societies. In addition, Barrett length and advanced age appears to be important indicators for the presence of dysplasia/cancer among patients with Barrett esophagus. Further large-scale studies will shed light on the course of these upper gastrointestinal conditions.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Approval

The study was performed according to the principles of the Declaration of Helsinki and the protocol was approved by the local ethics committee (Acibadem Mehmet Ali Aydinlar University, Ethics Committee for the Evaluation of Medical Studies; No. 2022-06/38; date: March 25, 2022).

Informed Consent

Informed consent was not required since the study was retrospective; all information is presented anonymously, and no private data of patients are presented in the manuscript. However, an informed consent for the intervention (not for the study) had been received from the patient at the time of intervention.

Authors’ Contributions

All authors contributed to the study conception and design. Statistical analysis was designed and performed by Nurten Turkel-Kucukmetin. Material preparation and data collection were performed by all authors. The first draft of the manuscript was written by Nurten Turkel-Kucukmetin, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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