Association Between Length of Barrett's Esophagus and Risk of High-grade Dysplasia or Adenocarcinoma in Patients Without Dysplasia

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BACKGROUND & AIMS: **It is not clear whether length of Barrett's esophagus (BE) is a risk factor for high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) in patients with nondysplastic BE. We studied the risk of progression to HGD or EAC in patients with nondysplastic BE, based on segment length.**

METHODS: **We analyzed data from a large cohort of patients participating in the BE Study—a multicenter outcomes project comprising 5 US tertiary care referral centers. Histologic changes were graded as low-grade dysplasia, HGD, or EAC. The study included patients with BE of documented length without dysplasia and at least 1 year of follow-up evaluation (n = 1175; 88% male), and excluded patients who developed HGD or EAC within 1 year of their BE diagnosis. The mean follow-up period was 5.5 y (6463 patient-years). The annual risk of HGD and EAC was plotted in 3-cm increments (≤3 cm, 4–6 cm, 7–9 cm, 10–12 cm, and ≥13 cm). We calculated the association between time to progression and length of BE.**

RESULTS: **The mean BE length was 3.6 cm; 44 patients developed HGD or EAC, with an annual incidence rate of 0.67%/y. Compared with nonprogressors, patients who developed HGD or EAC had longer BE segments (6.1 vs 3.5 cm; $P < .001$). Logistic regression analysis showed a 28% increase in risk of HGD or EAC for every 1-cm increase in BE length ($P = .01$). Patients with BE segment lengths of 3 cm or shorter took longer to develop HGD or EAC than those with lengths longer than 4 cm (6 vs 4 y; $P =$ nonsignificant).**

CONCLUSIONS: **In patients with BE without dysplasia, length of BE was associated with progression to HGD or EAC. The results support the development of a risk stratification scheme for these patients based on length of BE segment.**

Keywords: BEST Study; Esophageal Cancer; Screening; Surveillance; Intestinal Metaplasia.

Esophageal adenocarcinoma (EAC) is the most rapidly increasing incident cancer in the Western world, with a dismal 5-year survival rate of less than 20%.[1] Barrett's esophagus (BE), a well-established premalignant condition for EAC, is characterized by metaplastic transformation of squamous to columnar-type epithelium containing goblet cells (intestinal metaplasia) on histologic evaluation.[2,3] The progression to adenocarcinoma is believed to occur through a sequence of changes involving nondysplastic BE (NDBE), low-grade dysplasia (LGD), and high-grade dysplasia (HGD), before final progression to EAC.[3]

At present, the degree of dysplasia remains the most widely used risk-stratification tool for determining surveillance intervals and the management of patients with BE.[4] Upper-gastrointestinal endoscopy with random 4-quadrant biopsy specimens every 1 to 2 cm is endorsed by various gastroenterology societies for surveillance of patients with BE because there is evidence from retrospective studies suggesting that endoscopic surveillance is associated with a diagnosis of EAC at an earlier stage along with improved survival.[2,3] According to the current guidelines for BE management, diagnosis of NDBE requires surveillance endoscopies every 3 to 5 years.[5] Nevertheless, the timing of endoscopic surveillance has implications on cost-effectiveness and resource use given the lack of clear data on cause-specific mortality related to BE and the low rate of

Abbreviations used in this paper: BE, Barrett's esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SD, standard deviation.

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progression of BE to EAC, particularly in NDBE patients.[6–9] Until molecular biomarkers are identified and validated as adjunctive tools for risk stratification, knowledge of other clinical and endoscopic features that accurately could risk-stratify patients with NDBE and identify target subgroups at risk for progression to HGD/EAC could facilitate more rational tailoring of endoscopic surveillance.

The length of Barrett's segment has the potential to serve as an endoscopic marker for risk of malignant progression and thus indirectly aid in the determination of optimal surveillance strategies. Studies evaluating Barrett's length as a predictor of progression to HGD/EAC have shown inconsistent results. Although data from retrospective and prospective cohort studies have shown an increased risk of progression to EAC with increasing Barrett's length, the studies have been limited by inclusion of prevalent cases of HGD/EAC, inclusion of patients with high-risk visible lesions, small sample sizes, and lack of adjustment for baseline dysplasia.[10–16]

We hypothesized that segment length would predict progression to HGD/EAC in NDBE patients. The aim of this study was to determine the annual incidence rates of progression to the combined end point of HGD/EAC in patients with NDBE stratified by the Barrett's segment length.

Patients and Methods

Patients

The BE Study (BEST) is a multicenter outcomes project that includes 5 tertiary care referral centers with an interest in BE. These include the Veterans Affairs Medical Center (Kansas City, MO), the Southern Arizona Veterans Affairs Health Care System (Tucson, AZ), the Cleveland Clinic (Cleveland, OH), the Veterans Affairs Medical Center (Portland, OR), and the Bethesda Naval Medical Center (Bethesda, MD). The study was approved by the institutional review board at each institution.

Patients diagnosed with BE at each of the participating centers were identified and entered into a Microsoft Access database (Microsoft Corp, Redmond, WA) at each center. Information regarding demographics (age, sex, and ethnicity), endoscopy results (date of procedure, presence of hiatal hernia, and BE length), and histologic diagnosis at each endoscopic procedure was collected. Data on the use of proton pump inhibitors (PPIs), aspirin/nonsteroidal anti-inflammatory drug (NSAID) use, and family history were recorded. The duration of follow-up evaluation for each patient was calculated from the time of initial diagnosis of BE (ie, from the first endoscopy) to the most recent endoscopy with biopsy. The time of occurrence of HGD and EAC was documented in the database, which allowed for the recording of prevalent and incident cases of HGD and EAC. Patients diagnosed with HGD or EAC at least 1 year after the first endoscopic evaluation with a biopsy that showed NDBE were defined as incident cases. Patients diagnosed with HGD or EAC within 1 year of their diagnosis of BE were considered prevalent cases.

The inclusion criteria for this study were as follows: patients who met the standardized definition of BE, that is, the presence of columnar-lined mucosa in the distal esophagus of any length at endoscopy and the presence of NDBE on histology, and a follow-up period of at least 1 year from the time of initial diagnosis.

Exclusion criteria for this analysis were as follows: (1) prevalent cases of HGD and EAC, (2) presence of visible lesions in the Barrett's segment, and (2) columnar-lined mucosa in the distal esophagus with no intestinal metaplasia on histology.

Endoscopy, Surveillance, and Histopathology

All participating centers used the same standardized definition of BE (ie, columnar-lined mucosa in the distal esophagus and intestinal metaplasia on histology). The length of BE was recorded in centimeters. The length was calculated by measuring the distance from the anatomic gastroesophageal junction to the most proximally displaced squamocolumnar junction. Because enrollment of patients began before the establishment of the Prague C&M classification, this was not uniformly available in all patients. The presence or absence and the size of the hiatal hernia were recorded. At the time of initial endoscopy and during surveillance visits, each patient underwent biopsies of the Barrett's segment. The biopsy protocol was not standardized a priori as part of the study protocol between the participating centers. However, each center followed a biopsy protocol of at least 4-quadrant biopsy specimens every 2 cm with either a standard or jumbo biopsy forceps. Histopathology assessment of biopsy specimens was reported using established criteria for NDBE, HGD, and EAC.[17,18] These were as reported by experienced gastroenterology pathologists at each of the tertiary sites. The worst histologic grade identified in each endoscopy was recorded as the overall histologic grade for that procedure. Pathology reports were reviewed by a local experienced pathologist at each site. Review of dysplasia and EAC slides by a second local expert pathologist was performed as part of routine clinical practice at each site. Central reading of all pathology specimens was not performed in this study. The endoscopic surveillance intervals were not standardized a priori as part of the study protocol. However, each center followed the recommendations of the published guidelines.[3]

Data Management and Statistical Analysis

The study coordinators at each center collected patient information and data entry was performed for the earlier-stated variables. A database of all BE patients was created at each center and each patient was provided with a unique identification number. All patient identifiers were deleted in compliance with the Health Information Portability and Accountability Act regulations. Data sets from each center then were merged into the main study database at the Veterans Affairs Medical Center in Kansas City. This was performed using Microsoft Access for Windows 2007 (Microsoft Corp). All collected and merged data were compared and reconciled for accuracy.

The follow-up interval for each patient with NDBE was calculated as the time interval between the first endoscopy showing NDBE and the most recent follow-up endoscopy with biopsy. The number of patients developing HGD/EAC was calculated. The annual risk of progression to a combined end point of HGD/EAC with 95% confidence intervals (CIs) was calculated for 5 different categories of BE length: 3 cm or less, 4 to 6 cm, 7 to 9 cm, 10 to 12 cm, and 13 cm or more.

In addition, to identify the specific threshold Barrett's length at which progression to HGD/EAC occurs, the annual risk of HGD/EAC was calculated for every centimeter length of NDBE above and below the threshold length. The time to