

Short-Segment Barrett's Esophagus and Adenocarcinoma

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Abstract: Barrett's esophagus is a known risk factor for the development of adenocarcinoma of the esophagus and esophagogastric junction. Based on the length of the columnar segment at endoscopy, Barrett's esophagus has been arbitrarily separated into two broad categories: long-segment and short-segment. The rapid rise in the incidence of esophageal adenocarcinoma has generated sustained research interest in this lesion. Studies have shown that although the prevalence of short-segment Barrett's esophagus is higher than that of long-segment Barrett's esophagus, the risk of developing dysplasia and adenocarcinoma may actually be lower in those patients with short segment Barrett's esophagus. Nonetheless, both dysplasia and esophageal adenocarcinoma have been reported in patients with short-segment Barrett's esophagus, making this arbitrary distinction clinically unimportant. The current surveillance guidelines remain the same for both short- and long-segment Barrett's esophagus. Another key issue is differentiating short-segment Barrett's esophagus from intestinal metaplasia of the gastric cardia. The latter is distinct from esophageal intestinal metaplasia (ie, Barrett's esophagus) and probably does not warrant surveillance.

The past three decades have seen a greater than five-fold increase in the incidence of adenocarcinoma of the esophagus and the esophagogastric junction in Western countries.¹⁻³ Esophageal adenocarcinoma now accounts for more than 50% of all esophageal cancers in the United States and Western Europe.^{2,4} The mortality rate for this malignancy is high and the mean 5-year survival rate in patients with advanced disease is less than 20%^{5,6} and less than 1% for unresectable tumors.⁶ The majority of esophageal adenocarcinomas arise in the setting of Barrett's esophagus (BE).⁷⁻⁹

Definition of BE and SSBE Esophagus

The working definition of BE as proposed by the American Gastroenterological Association Chicago workshop is the displacement of the squamocolumnar junction (SCJ or Z-line) proximal to the gastroesophageal junction (GEJ) with the presence of intestinal metaplasia.¹⁰ The goal in defining BE is the creation of a standardized method for identification of this risk factor for esophageal

Keywords

Barrett's esophagus, short-segment Barrett's esophagus, long-segment Barrett's esophagus, high-grade dysplasia, low-grade dysplasia, adenocarcinoma.

adenocarcinoma. Endoscopic criteria for the recognition of a columnar-lined distal esophagus includes the proximal displacement of the SCJ relative to the GEJ. The histologic requirement is the presence of esophageal intestinal metaplasia.

This working definition of BE has evolved over time to identify those patients with a high risk for malignant transformation. The definition of BE in the 1980s included at least 3 cm of circumferential columnar lining in the distal esophagus without any inclusion of histologic criteria.¹¹ This was a purely arbitrary restriction to exclude shorter segments of columnar epithelium in order to ensure that patients had the disease being studied and perhaps to prevent overdiagnosis of BE.^{11,12} Reports of columnar epithelium less than 3 cm with intestinal metaplasia lining the distal esophagus started appearing in the literature more than a decade ago. Spechler and colleagues¹³ reported that of 142 patients with either less than 3 cm of columnar-appearing mucosa in the distal esophagus or a normally located SCJ, 26 (18%) had intestinal metaplasia. Several other investigators have also published their experience on short segments of intestinal metaplasia in the distal esophagus.¹⁴⁻²⁰ Segments of columnar mucosa with intestinal metaplasia that were less than 2–3 cm in length started being referred to as short-segment Barrett's esophagus (SSBE). Sharma and coworkers²¹ proposed the definition of SSBE as an abnormal-appearing esophageal lining at endoscopy less than 3 cm in length with intestinal metaplasia documented on biopsy. The columnar lining seen at endoscopy may be circumferential or, more commonly, in the form of one or multiple tongues, or a combination. A distinction was made from long-segment Barrett's esophagus (LSBE) defined as at least 3 cm and intestinal metaplasia of the gastric cardia (ie, biopsies from a normally located SCJ).

Diagnosis of SSBE

The key factor in recognizing SSBE at endoscopy is to clearly define, identify, and record the SCJ in relation to the GEJ. The SCJ is formed by the juxtaposition of the pale squamous epithelium and the red, velvet-like columnar mucosa. This landmark is easily identified endoscopically. Localization of the GEJ, however, is more challenging. Many investigators have considered the proximal margin of the gastric folds to be a reliable marker of the GEJ which should be determined with minimal inflation of the distal esophagus as overinflation may flatten the gastric folds.²² The distance between the proximally displaced margin of the SCJ and GEJ is currently the best measure available to grade the length of Barrett's mucosa. Biopsies should then be obtained from this area of columnar lining of the distal esophagus (endoscopically suspected SSBE) to document

intestinal metaplasia. On the other hand, if the SCJ and GEJ coincide and are at the same level, the entire esophagus is lined by squamous epithelium and endoscopic evidence of BE is absent. If biopsies are obtained in this setting and reveal intestinal metaplasia, it is not SSBE, rather intestinal metaplasia of the gastric cardia.

Improving the Diagnosis Rates of SSBE

Only a fraction of patients with endoscopically suspected SSBE are proven to have intestinal metaplasia on biopsy. This yield has ranged from 25% to 61%^{19,23,24} and increases as the length of endoscopic Barrett's increases.^{19,24,25} Possible reasons for this would be that intestinal metaplasia is either absent in the columnar segment or present in a patchy distribution that is missed by random biopsies. In a study by Jones and coworkers,²⁶ it was shown that more than 20% of patients with suspected SSBE on initial endoscopy (but no intestinal metaplasia on biopsies) had evidence of intestinal metaplasia (ie, proven SSBE) on repeat endoscopy. This highlights the shortcomings of standard endoscopy with random biopsies and therefore alternate techniques that can better confirm SSBE would be beneficial (increasing the yield of intestinal metaplasia).

Chromoendoscopy with methylene blue has been used, albeit with inconsistent results. Wo and colleagues²⁷ showed that the results of methylene blue-directed biopsy in detecting intestinal metaplasia were similar to those with conventional biopsy. Conversely, Sharma et al²⁸ showed that methylene blue chromoendoscopy significantly increased the detection of intestinal metaplasia (42% to 61%) with fewer biopsies required in patients with suspected SSBE (≥ 1 cm of columnar-appearing mucosa) to document intestinal metaplasia. Differences in the methodology of staining may account for the discrepancy in the results using chromoendoscopy in BE. Magnification chromoendoscopy and narrow-band imaging are other novel techniques that have recently been shown by some investigators to be useful tools in increasing the detection rate of intestinal metaplasia in patients with endoscopically suspected BE.²⁹⁻³¹ Immunohistochemical staining techniques have been used to identify patterns specific for BE and to help differentiate intestinal metaplasia in the distal esophagus (ie, SSBE) from intestinal metaplasia of the gastric cardia. Use of a cytokeratin 7 and 20 pattern, which is sensitive and specific for LSBE,³² has shown conflicting results when used to differentiate SSBE from intestinal metaplasia of the gastric cardia,³²⁻³⁴ limiting its utility in routine clinical practice. Thus, although a number of new endoscopic and immunohistochemical techniques are under investigation to increase the diagnosis rates of SSBE, at this time standard upper endoscopy with biopsy remains the gold standard.

Prevalence of SSBE

The reported prevalence of SSBE has varied in different studies, reflecting the population evaluated, the definition of SSBE used, and the rigor of the endoscopy/biopsy protocol. Spechler and colleagues¹³ reported that 26 of 142 patients undergoing endoscopy for any indication had intestinal metaplasia in the region of the GEJ. In 9 patients, however, the SCJ and GEJ were at the same level, while in 17 patients the columnar epithelium extended less than 3 cm into the distal esophagus. Thus, 12% of patients (n=17) actually had SSBE. Weston and coworkers¹⁴ found an 8% prevalence of SSBE (defined as a length ≤ 2 cm) in patients undergoing upper endoscopy for any indication. Similarly, Chalasani and associates¹⁷ showed an 8% prevalence of SSBE defined as columnar mucosa extending less than 2.5 cm in the distal esophagus with histological evidence of intestinal metaplasia. Other investigators have also reported an SSBE prevalence of 2–8%.^{20,35,36} All of these studies reporting the prevalence of SSBE included patients referred for upper endoscopy for any indication including symptoms of gastroesophageal reflux. More recently, Westhoff et al³⁷ detected a prevalence of 8.5% for SSBE versus 4.8% for LSBE in patients undergoing endoscopy for reflux symptoms. Other studies have reported the prevalence of intestinal metaplasia at the GEJ without recognizing the difference between SSBE and intestinal metaplasia of the gastric cardia.^{25,38,39} Hence careful scrutiny is necessary when reviewing studies discussing the prevalence of SSBE, and patients with intestinal metaplasia of the gastric cardia should be identified separately from those who have intestinal metaplasia in the distal esophagus. Some other recent studies have evaluated the prevalence of BE (both SSBE and LSBE) in asymptomatic subjects without gastroesophageal reflux symptoms. Rex and coworkers⁴⁰ found a 5.5% prevalence of SSBE in patients referred for a colonoscopy (when offered an upper endoscopy examination). The prevalence of SSBE was not different between patients who had heartburn versus those who did not (5.7% vs 5.24%). In a similar study of patients undergoing flexible sigmoidoscopy (when screened for the presence of BE), the rate of SSBE was 17.3% compared to 7.3% for LSBE.⁴¹ Thus, the prevalence of SSBE appears to be higher than that of LSBE and varies with the demographics and the symptom profile of the patients being evaluated.

SSBE and Dysplasia

The natural history of SSBE is not clearly understood. Although both dysplasia and adenocarcinoma can be associated with SSBE, the exact rates of progression are

not known. There is also no conclusive evidence that SSBE can regress. Whether acid suppression can lead to a reduction in the length or reduce the incidence of dysplasia in SSBE is also controversial.

Both low-grade dysplasia (LGD) and high-grade dysplasia (HGD) have been detected in SSBE patients. Sharma and colleagues¹⁶ found that 5 of 59 patients with SSBE had LGD on initial endoscopy. They prospectively followed 32 patients for a mean period of 36.9 months and 5 patients developed dysplasia—3 with LGD and 2 with HGD. The prevalence of LGD was 8.5% with the incidence for dysplasia being 5.7% per year. Weston and coworkers¹⁵ reported a similar prevalence of dysplasia in SSBE (8.1%)—5 patients with LGD and 1 with HGD. LGD developed in 2 out of 26 patients followed for a mean of 18.6 months. Conio and colleagues⁴² reported a 9.4% prevalence of LGD in SSBE. In a study of 30 patients with SSBE followed for a mean of 4.2 years, 4 developed LGD while none had HGD.⁴³ Other authors have not found any dysplasia in patients with SSBE.^{14,19} Thus, the overall prevalence of dysplasia in SSBE, mainly LGD, appears to range from 0% to 10%, whereas LGD has been shown to develop in these patients during follow-up at a rate of approximately 4–5% per year. The major limitations of these studies are the relatively small number of patients and short durations of follow-up. Larger population-based studies that follow patients over longer time periods are needed to unravel the actual prevalence and incidence of dysplasia in SSBE. Until then, it is sufficient to say that both LGD and HGD can be prevalent in SSBE patients, as well as develop during follow-up.

SSBE and Adenocarcinoma

The relationship between LSBE and esophageal adenocarcinoma has been well described in the literature. Adenocarcinoma has also been reported to develop in patients with SSBE. One of the earliest reports was by Schnell and colleagues,⁴⁴ who documented 4 cases of adenocarcinoma arising in tongues of intestinal metaplasia in the distal esophagus smaller than 2 cm. Hamilton and coworkers⁷ studied 61 consecutive resected esophagogastric specimens with adenocarcinoma and noted that the majority of the Barrett's cancers occurred in cases with 5 cm or less of Barrett's mucosa. In another study of resected surgical esophagogastric specimens, BE was detected in 10 of 24 junction adenocarcinomas and in five of those specimens the length of BE was less than 3 cm.⁸ Thus, patients with relatively short segments of BE accounted for the majority of esophagogastric cancer.

A few cases of esophageal adenocarcinoma have also been reported to develop in patients with SSBE during follow-up. In a prospective follow-up of 32 patients

with SSBE over a mean of 36.9 months, Sharma et al¹⁶ reported 1 patient who progressed to cancer over a 2-year period. In another prospective series evaluating the effect of BE segment length on the risk of neoplastic progression in BE, a total of 309 patients with BE were followed.⁴⁵ Of 83 patients with SSBE followed for a total of 279.8 patient-years, seven cases of cancer were detected. However, not all series have reported cancer development in SSBE patients. In a series of 74 patients with SSBE prospectively followed over a mean of 18.6 months, no cancers were seen.¹⁵ O'Connor and colleagues⁴³ followed 30 SSBE patients over a mean period of 4.2 years and none developed adenocarcinoma. The 2 patients who did develop cancer had LSBE. Summation of the series involving prospective follow-up of patients with SSBE reveals that approximately eight incidence cases of adenocarcinoma have been diagnosed over an estimated 620 patient-years. It should however be noted that seven of 8 cases of cancer were reported from a single tertiary center, raising a question of referral bias. The incidence appears to be lower than that of adenocarcinoma in LSBE patients, which is reported to range from 1 in 52 to 1 in 441 patient-years.⁴⁶⁻⁵² Thus, although adenocarcinoma can develop in SSBE patients, most studies show that the absolute risk is small and less than that of LSBE patients. However, as the majority of the studies involving prospective follow-up have been of short duration and include a relatively small number of patients, it is difficult to ascribe the real magnitude of cancer risk in patients with SSBE. The current surveillance guidelines for patients with SSBE remain the same as for patients with LSBE⁵³; however, this remains controversial as surveillance endoscopy has not been proven to improve outcomes in SSBE patients.¹⁰

Is the Length of BE Important?

Whether the length of the columnar-lined esophagus is a risk factor in the development of dysplasia and subsequent cancer is a matter of ongoing debate. Iftikhar and associates⁵⁰ prospectively followed patients with BE defined as columnar-lined esophagus extending circumferentially at least 5 cm above the GEJ (confirmed by histology). In this study, those patients who developed dysplasia had a significantly longer BE segment compared to the entire group, and no patient with a BE length less than 8 cm was found to have dysplasia or adenocarcinoma. Along the same lines, another study⁵⁴ showed that there was a significant relationship between the length of columnar-lined esophagus and cancer—a doubling of the BE length resulted in a 1.7-fold increase in the risk of cancer. The definition of BE in this study was greater than 3 cm of columnar epithelium above the distal end of the tubular esophagus. Similarly, another study⁵⁵ demonstrated that

a BE length longer than 10 cm was a risk factor for the development of adenocarcinoma. A few other studies have also shown that the length of BE is related to the development of HGD and adenocarcinoma.^{56,57} However, it is worth mentioning that the majority of these studies included patients with longer lengths of BE while the concept of SSBE was still evolving. Contrary to the above findings, Rudolph and coworkers⁴⁵ concluded in their study that the segment length of BE was not significantly related to the risk of cancer. More importantly, they also observed that the risk of adenocarcinoma in patients with SSBE was not significantly lower than that in patients with longer segments. After excluding patients with HGD at baseline, a nonsignificant trend was seen whereby a 5-cm difference in segment length was associated with a 1.7-fold increase in cancer risk. Nonetheless, a trend for increasing cancer incidence has been noted in all series as the length of BE increases.

A few studies have compared the prevalence and incidence of dysplasia and cancer between SSBE and LSBE patients.^{15,36} Weston and colleagues showed that the prevalence and incidence of dysplasia was significantly higher in LSBE compared to SSBE patients and that a BE length of 3 cm or more was associated with progression of unifocal HGD to multifocal HGD and/or cancer.^{15,58} Similarly Hirota and associates³⁶ found that the prevalence of dysplasia in LSBE patients was twice that seen in SSBE patients. In summary, the length of BE appears to be a risk factor in the development of dysplasia and cancer, and there is some evidence suggesting that the risk may be significantly lower in SSBE compared to LSBE patients.

Is SSBE Different From Intestinal Metaplasia of the Gastric Cardia?

The motility of the esophagus, movement with respiration, flattening of the gastric folds with air insufflation, hiatal hernia, and erosive esophagitis all make the task of identifying the GEJ challenging. This difficulty in precisely localizing the GEJ can result in an incorrect diagnosis of SSBE, especially if biopsies are obtained in the region of the GEJ without identifying an area of columnar lining in the esophagus. Distinguishing SSBE (ie, esophageal intestinal metaplasia) from intestinal metaplasia of the gastric cardia may have important clinical implications. Although controversial, a diagnosis of SSBE potentially commits the patient to surveillance endoscopy and biopsy,⁵³ whereas, based on current available data, surveillance is not proposed by many investigators for intestinal metaplasia of the gastric cardia.^{10,36} Significant age, ethnic, and gender differences have been noted between these patient groups (SSBE and intestinal metaplasia of the gastric cardia).⁵⁹ Pereira and colleagues¹⁹

showed that reflux symptoms and erosive esophagitis were more frequent in patients with SSBE than in those with intestinal metaplasia of the gastric cardia and more men than women had SSBE, whereas more women than men had intestinal metaplasia of the gastric cardia. Similarly, Hackelsberger and colleagues³⁸ showed that while patients with SSBE were more likely to be men with evidence of reflux symptoms, erosive esophagitis, and no *Helicobacter pylori* infection, intestinal metaplasia of the gastric cardia was associated with older age, *H. pylori* gastritis, and intestinal metaplasia elsewhere in the stomach. More importantly, the prevalence and incidence of dysplasia in intestinal metaplasia of the gastric cardia are significantly lower than in SSBE.⁵⁹ Thus, based on the current available evidence, SSBE and intestinal metaplasia of the gastric cardia appear to be two different clinical entities.

Conclusions

To summarize, SSBE refers to endoscopic segments of columnar lining less than 3 cm in length and confirmed to harbor intestinal metaplasia by biopsy. Its recognition requires careful delineation of the SCJ and GEJ. SSBE is a distinct clinical entity from intestinal metaplasia of the gastric cardia, as evidenced by the higher prevalence and incidence of dysplasia in SSBE, as well as differences in patient demographics and symptom profile. LGD, HGD, and adenocarcinoma have been reported in patients with SSBE. Although the actual prevalence and incidence of dysplasia and cancer in SSBE patients are difficult to estimate due to limitations in the published series, they appear to be lower than the prevalence and incidence seen in LSBE patients. The length of BE clearly appears to be a risk factor in dysplasia and cancer development but the exact cut-off length is not known. Future research should focus on developing a simple grading system for BE with length as a continuous variable, which would be clinically more relevant than just dividing BE into two broad categories, short and long BE. Larger population-based studies with longer duration of follow-up are required to accurately identify the risk factors for dysplasia and cancer associated with SSBE. Identifying the exact length at which the risk of cancer significantly increases would help to risk-stratify BE patients. Those patients with SSBE at a high risk for neoplastic progression that may benefit from endoscopic surveillance or aggressive therapy should be identified.

Acknowledgment

The authors acknowledge support from the Veterans Affairs Medical Center, Kansas City, Mo.

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