Location, location, location: does early cancer in Barrett's esophagus have a preference?

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Background: Early cancer (high-grade dysplasia [HGD] and intramucosal carcinoma [ImCa]) associated with Barrett's esophagus (BE) may have a circumferential spatial predilection.

Objective: To describe the esophageal circumferential location of early cancer in BE.

Design and Setting: Retrospective study, single tertiary referral center.

Patients and Intervention: One hundred nineteen patients were referred for endoscopic eradication therapy for early cancer associated with BE. Endoscopic images and reports and pathology were reviewed.

Main Outcome Measurements: Circumferential location designation of early cancer in BE by using a clock-face orientation.

Results: One hundred nineteen of 131 patients referred for endoscopic eradication therapy had a location designation for their advanced histology (91.9%). There were a total of 57 patients (47.9%) with HGD and 62 patients (52.1%) with ImCa. There was a significantly higher rate of early cancer (HGD or ImCa) in the right hemisphere (12 to 6 o'clock location) compared with the left hemisphere (84.9% vs 15.1%, $P < .0001$). The highest percentage of early cancer was found in the 12 to 3 o'clock quadrant (64.7%); 71.9% of HGD and 58.1% of ImCa lesions were located in the 12 to 3 o'clock quadrant.

Limitations: Retrospective design, single center.

Conclusions: Early cancer associated with BE is far more commonly found in the right hemisphere of the esophagus (12 to 6 o'clock) with the highest rate in the 12 to 3 o'clock quadrant. These findings support enhanced scrutiny of the right hemisphere of the esophagus during surveillance and endoscopic treatment of patients with BE. (Gastrointest Endosc 2013;78:462-7.)

Abbreviations: BE, Barrett's esophagus; HGD, high-grade dysplasia; ImCa, intramucosal carcinoma.

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Barrett's esophagus (BE) is a premalignant condition of the esophagus with an annual risk of progression to esophageal adenocarcinoma that increases with progressively higher levels of dysplasia.[1-4] Despite advances in the diagnosis of esophageal adenocarcinoma, BE remains the fastest-growing cancer in the Western world, and its overall 5-year survival remains poor. Long-term cancer survival may be improved with early detection, namely the diagnosis of BE and subsequent appropriate stratification of this precursor lesion into the categories of no dysplasia, low-grade dysplasia, or high-grade dysplasia (HGD).

Endoscopic surveillance has been shown to be associated with earlier detection and improved survival of esophageal adenocarcinoma.[5,6] The current standard for BE surveillance[7] is high-resolution white light endoscopy, with careful inspection to identify and sample macroscopically visible lesions in conjunction with systematic 4-quandrant biopsy samples every 1 to 2 cm of the involved segment.

Two studies have suggested a spatial predilection of advanced histology associated with BE, with most HGD or intramucosal carcinoma (ImCa) located in the 12 to 3 o'clock or 2 to 5 o'clock wall of the esophagus.[8,9] We hypothesized that HGD and ImCa (herein, collectively termed early cancer or early neoplasia) encountered in BE are found more frequently in the right hemisphere of the esophagus (12 o'clock to 6 o'clock location). Our goal is to describe the location of early cancer arising in patients with BE who presented for their initial planned eradication endoscopy at a high-volume tertiary care referral center. A circumferential predilection of advanced histology would have implications for surveillance techniques.

Take-home Message

- Early cancer associated with BE is far more commonly found in the right hemisphere of the esophagus (84.9%), with the highest rate in the 12 to 3 o'clock quadrant.
- Enhanced scrutiny and targeted surveillance biopsy samples of the right hemisphere of the esophagus may lead to greater detection of advanced histologic lesions and will impact image-guided therapy.

METHODS

This is a retrospective review of endoscopic reports, endoscopic images, and pathology reports of patients referred for evaluation of suspected HGD or ImCa, contained within a BE endotherapy registry at the University of Pennsylvania. The study was approved by the University of Pennsylvania Institutional Review Board.

Subjects

Consecutive patients diagnosed with BE by biopsy-proven HGD or ImCa between December 1997 and May 2010 who were referred for endoscopic eradication therapy to a single provider (G.G.G.) at an endoscopy referral center were considered for analysis. BE was defined as the presence of intestinal metaplasia (specialized columnar epithelium, characterized by acid-mucin containing goblet cells) anywhere in the tubular esophagus and/or esophagogastric junction. HGD was defined by hyperchromaticity and a nuclear-to-cytoplasmic ratio of $>50\%$. ImCa was defined as the presence of adenocarcinoma without invasion into the submucosa. Invasive adenocarcinoma denoted the presence of invasion deep to the submucosa. The histopathologic criteria followed that set forth in the Vienna classification.[10] HGD and ImCa were confirmed on histopathology from slide review of prior biopsy samples (by an expert GI pathologist at the University of Pennsylvania) and/or endoscopic resection or additional biopsy samples. Only a subject's first endoscopy (EGD) for planned eradication therapy was considered in the present analysis.

Data collection and location determination

Data collected included patient demographics; concomitant use of proton pump inhibitor therapy; endoscopic and histologic characteristics of BE, including segment length (short segment defined as <3 cm vs long segment defined as ≥ 3 cm); and presence of HGD or ImCa. Additionally, endoscopic reports and images were examined for notation that delineated the location of the target visible lesion. All location determinations found within the endoscopic report were made by the single examining endoscopist, with the endoscope in a neutral position and the patient in the left lateral decubitus position.

A clock-face orientation of the esophageal lumen with the endoscope in the patient (with the lesser curve of the stomach in contiguity with the 3 o'clock esophageal orientation, ventral aspect of esophagus at 12 o'clock, and posterior esophagus at 6 o'clock) was used to characterize the lesion. Examples of various macroscopic lesions and their clock-face designations are demonstrated in Figure 1. If the endoscopic report did not designate a location of the visible lesion, the endoscopic images were reviewed retrospectively to assign a location of the target lesion ($n = 12$, 10.0%). It was standard practice of the endoscopist to capture endoscopic images of the Barrett's segments in white light and narrow-band imaging in the neutral endoscope position. In instances where there was no visible lesion, the examining endoscopist obtained biopsy samples from each quadrant, labeled in separate specimen containers; the pathology reports from these patients was reviewed to assign a quadrant location of the nonvisible early cancer.

The location designation was further aggregated into quadrant designations as follows: 12 to 3 o'clock, 3 to 6 o'clock, 6 to 9 o'clock, and 9 to 12 o'clock. The lesions were subsequently classified into right and left hemisphere locations (right hemisphere, 12 to 6 o'clock lesions; left hemisphere, 6 to 12 o'clock). Cases in which a lesion spanned 2 or more quadrants were noted in the analysis,

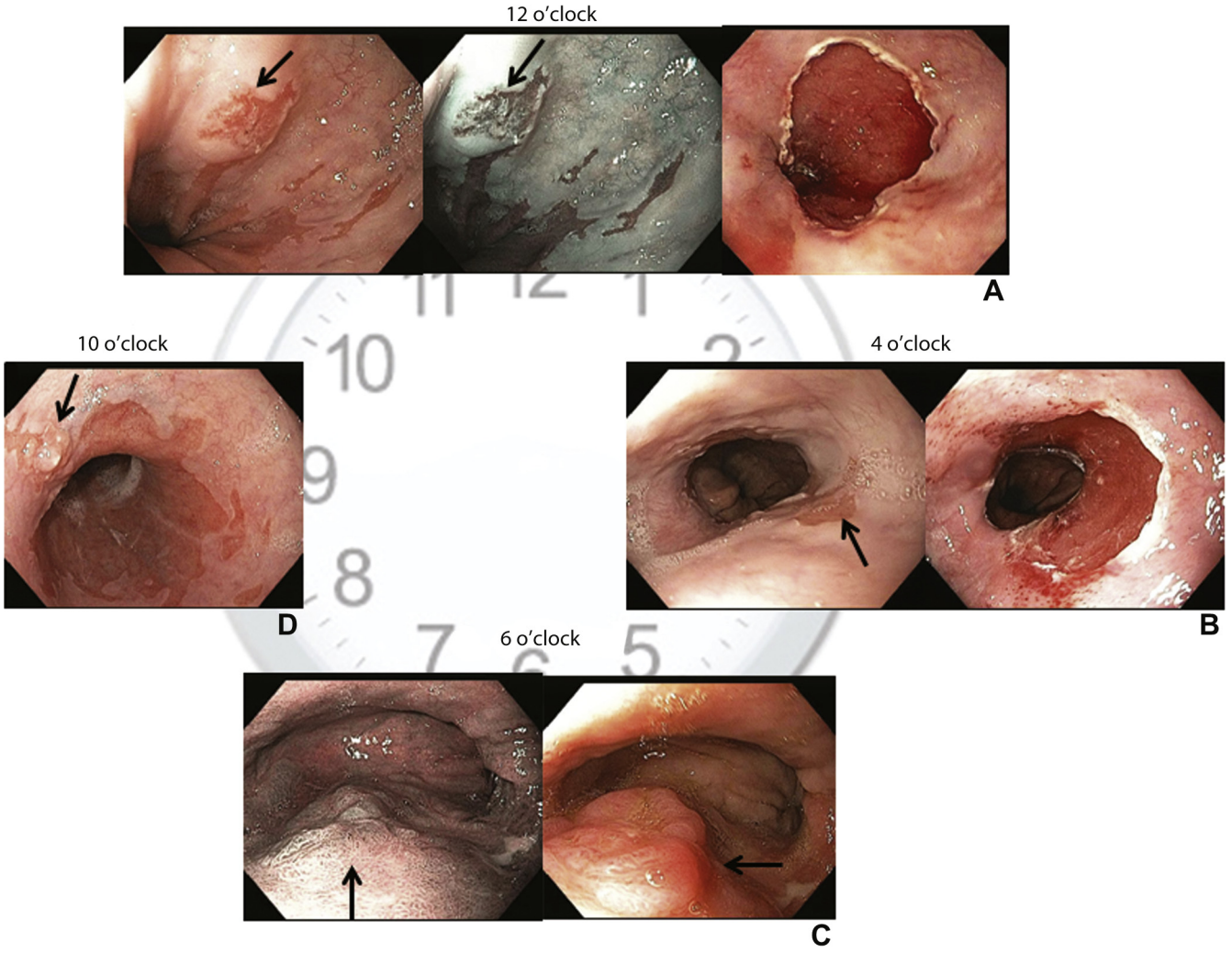

Figure 1. Examples of clock-face distribution of early cancer in BE. **A,** Mucosal irregularity and nodularity at 12 o'clock (*arrows*) visualized in high-definition white light and narrow-band imaging with post-EMR defect. **B,** Mucosal irregularity at 4 o'clock (*arrow*) with a wide-area confluent mucosal resection defect. **C,** Large nodule spanning two adjacent quadrants and both hemispheres but centered at 6 o'clock (*arrow*) visualized by using narrow-band imaging and high-definition white light. **D,** Subtle nodule at the 10 o'clock (*arrows*) position that subsequently underwent EMR.

and the central portion of the lesion was used to designate its predominance in the right or left hemisphere.

The type of endoscopic resection (snare ligation, cap ligation, or multiband mucosectomy) performed and adverse events of bleeding and perforation were also collected within the BE endotherapy registry. However, these factors were not the focus of this study.

Endoscopic eradication therapy

All eradication therapy in this cohort of patients was performed by a single endoscopist, and the type of eradication therapy used was determined by the endosocopist. All procedures were performed on an outpatient basis with the patient under conscious sedation or deep sedation administered by an anesthesia provider. Endoscopy was performed with a 160 or 180 series endoscope (Olympus, Inc, Center Valley, PA). Once available, narrow-band imaging was used to further interrogate the BE mucosa. The squamocolumnar junction was examined en face and in retroflexed views with both high-definition white light (once available with the HD180 Olympus endoscopes) and narrow-band imaging. Chromoendoscopy was not used during the study time frame.

EMR techniques used during the study time frame included cap ligation and snare ligation (including the commercially available multiband mucosectomy device, Duette, Cook Medical, Bloomington, IN) or a combination of EMR techniques. Endoscopic ultrasound was not routinely used before EMR, unless otherwise clinically indicated. All patients were counseled on the risks and benefits of endoscopic and surgical therapy, and all patients provided written informed consent for endoscopic therapy.

Statistical analysis

Data were analyzed with SPSS, version 20 (IBM Corp, Armonk, NY). Descriptive and univariate statistics were

used. A χ^2 test was used to compare the distribution of lesions in the right and left hemispheres.

RESULTS

One hundred thirty-one patients with BE with HGD or ImCa presenting for their first endoscopic eradication were identified. Of the 131 subjects with early cancer (HGD or ImCa) in BE, 119 had an identifiable location designation for their advanced histology (91.9%). No lesion location designation was discernible for the remaining 12 patients despite review of the endoscopic report, pathology report, or available endoscopic images (ImCa in 4, HGD in 7, invasive cancer in 1) (Fig. 2). The characteristics of the 119 patients in our cohort are shown in Table 1. The mean age of the patients was 67.7 ± 11.5 years, and most subjects were white men. All patients referred for endoscopic eradication therapy were on proton pump inhibitor therapy. There were a total of 57 patients (47.9%) with HGD and 62 patients (52.1%) with ImCa.

The localization distribution of HGD and ImCa is shown in Table 2 and Figure 3. The highest percentage of early cancer (HGD or ImCa) was found in the 12 to 3 o'clock quadrant (64.7%) followed by the 3 to 6 o'clock quadrant (38.7%) (percentages not mutually exclusive because 30 patients had lesions with confluent involvement of 2 or more quadrants: 18 with HGD and 12 with ImCa). Of the 30 patients that had lesions with confluent involvement of 2 or more quadrants, the predominant hemisphere of the lesion was the right hemisphere in 19 and the left hemisphere in 11; 71.9% of HGD and 58.1% of ImCa lesions were located in the 12 to 3 o'clock quadrant, followed by the 3 to 6 o'clock quadrant (HGD, 31.6%; ImCa, 45.2%). One hundred one patients (84.9%) had early cancer in the right hemisphere (HGD, 48 [84.2%]; ImCa, 53 [85.4%]). A significantly higher rate of early cancer occurred in the right hemisphere (12 to 6 o'clock location) compared with the left hemisphere (84.9% vs 15.1%, $P < .0001$).

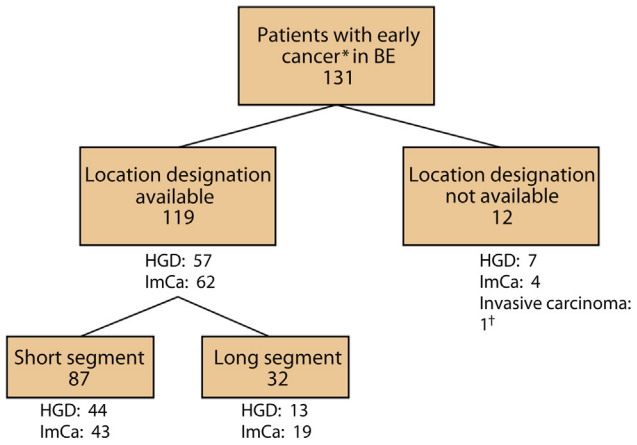

Figure 2. Study flow diagram. Short-segment BE defined as ≤3 cm. *Early cancer includes HGD and ImCa. †Endoscopic images were not available for review.

TABLE 1. Demographics

Characteristic	
Total N	119
Mean age, y	67.7 ± 11.5
Male gender	97 (81.5%)
Race	
White	90 (75.6%)
Black	2 (1.7%)
Hispanic	1 (0.8%)
Unknown	26 (21.8%)
PPI therapy	119 (100%)
Barrett's characterization	
Mean segment length, cm (± SD)	3.35 ± 2.93
Short segment (<3 cm)	87 (73.1%)
Long segment (≥3 cm)	32 (26.9%)
HGD	57 (47.9%)
ImCa	62 (52.1%)

PPI, proton pump inhibitor; *HGD,* high-grade dysplasia; *ImCa,* intramucosal carcinoma.

DISCUSSION

In this study we found that early cancer associated with BE is far more commonly found in the right hemisphere of the esophagus (12 to 6 o'clock), with the highest rate in the 12 to 3 o'clock quadrant. This study included patients with any length of BE and those with and without macroscopically visible lesions. These findings applied to both HGD and ImCa.

Two studies have examined the spatial predilection of dysplasia in BE.[8,9] In 2007, Pech et al[8] evaluated macroscopic characteristics (Paris classification) and the spatial location of lesions in 344 patients with BE with HGD or ImCa. Although these characteristics were not the primary focus of their study, they incidentally found that 48% of all early cancer lesions were found in the 12 to 3 o'clock quadrant of the esophagus. In 2012, Kariyawasam et al[9] reported on 75 patients with BE segments ≤ 5 cm containing a visible lesion with HGD or ImCa. Of the 80 distinct lesions, 53.8% were centered on the 2 to 5 o'clock arc of the esophagus. Our study confirms this predilection of early neoplasia to these regions and expands on those studies by the striking predominance of 84.9% of lesions in the 12 to 6 o'clock hemisphere of the esophagus. These findings thus

TABLE 2. Localization distribution* of HGD and ImCa associated with Barrett's esophagus

	12 to 3 o'clock	3 to 6 o'clock	6 to 9 o'clock	9 to 12 o'clock
HGD (n = 57)	41 (71.9%)	18 (31.6%)	11 (19.3%)	7 (12.3%)
ImCa (n = 62)	36 (58.1%)	28 (45.2%)	7 (11.3%)	6 (9.7%)
Total (n = 119)	77 (64.7%)	46 (38.7%)	18 (15.1%)	13 (10.9%)

Percentages represent proportions of total HGD, ImCa, or all patients with a designation in the specific quadrant.
HGD, high-grade dysplasia; *ImCa,* intramucosal carcinoma.
*Thirty patients (18 with HGD, 12 with ImCa) had more than 1 location designation (ie, confluent involvement of adjacent quadrants) and therefore percentages are not mutually exclusive.

provide further support for enhanced scrutiny of the right hemisphere of the esophagus during surveillance and endoscopic treatment of patients with BE.

These findings should also be interpreted in the context of the concept of inspection time in surveillance for BE. As recently described by Gupta et al,[11] detection of lesions in BE is directly related to the time inspecting the columnar lined segment. Our findings support that inspection should be emphasized at the right hemisphere of the esophagus where advanced lesions occur with considerably higher frequency.

Our study differs from previous studies in several ways. First, the *primary* outcome of this study was to describe the circumferential location of early neoplasia in BE. Second, we included patients with and without macroscopically visible lesions. Those patients without macroscopically visible lesions had biopsy samples taken from each quadrant in separately labeled pathology containers. Therefore, even in the absence of visible lesions, there is a predilection for flat advanced lesions to be located in the right hemisphere. Finally, designation of all clock-face locations was performed by a single expert endoscopist, thereby limiting variability.

The results of this study coupled with those of the studies cited above[8,9,11] should guide management. It is well established that patients with BE who comply with a structured endoscopic surveillance program have earlier detection of esophageal adenocarcinoma and improved survival compared with those not undergoing surveillance.[5,6] Systematic study of biopsy samples can increase the yield of both low-grade dysplasia and HGD as compared with randomly studied biopsy samples.[12] Advanced imaging techniques beyond high-resolution white light endoscopy and narrow-band imaging, including magnification endoscopy, chromoendoscopy, and confocal endomicroscopy, have been proposed to increase the efficiency and accuracy of endoscopic surveillance, although current guidelines do not recommend the routine use of any of these technologies. The predilection of early neoplasia in BE to the right hemisphere of the esophagus supports that endoscopic examinations should scrutinize and sample from these areas with added rigor.

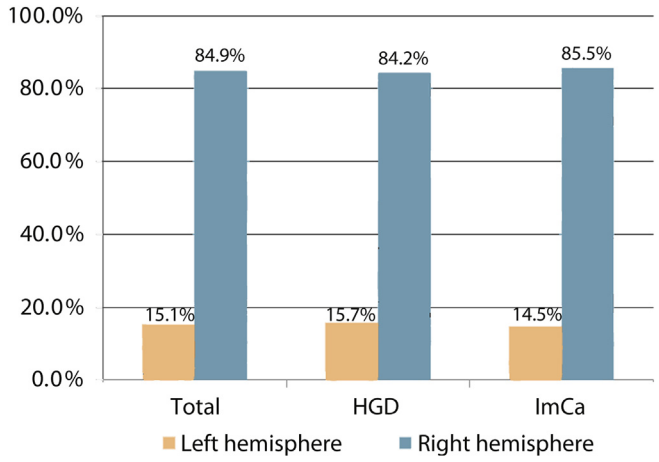

Figure 3. Hemisphere distribution of early cancer in BE (with HGD and ImCa). In those 12 cases where a lesion encompassed both hemispheres, the central point of the lesion was used to determine the predominant hemisphere involved.

Although it is not entirely clear why neoplasia in BE has a predilection for the right hemisphere of the esophagus, several theories have been proposed. The increased number of right hemisphere lesions may be representative of a detection bias because of the more favorable visualization and biopsy sampling of this area. Katsube et al[13] described an increased prevalence of mucosal breaks in the right hemisphere of the esophagus in those with Los Angeles Class A or B reflux esophagitis. Edebo et al[14] demonstrated that histologic mucosal changes (thicker basal cell layer and more intercellular space dilatation) in patients with nonerosive reflux disease and visible mucosal erosions in patients with erosive reflux disease occur most frequently (60%) at the 3 o'clock position. This is consistent with the location of early cancer in BE described in this and prior studies.

This study has several limitations. All data were collected at a specialized endoscopy referral center, and therefore the results may not be applicable to other practice settings. Given its retrospective nature, this study is subject to the biases inherent to retrospective observational studies. Although most location determinations were made by

the endoscopist at the time of the endoscopy, in 10% of cases the location determination was retrospectively assigned by review of the endoscopic images. This may lead to misclassification bias if lesions were rotated. However, we believe this influence was generally limited given the few patients in which this occurred and the consistent practice of the endoscopist to photo document the targeted areas of esophagus in both white light and narrow-band imaging in en face views with the endoscope in the neutral position. Therefore, every endoscopic report contained a set of images in the endoscope-neutral position, thereby limiting the variability in the images. The study population mainly comprised white men; however, this reflects the demographics of those patients with BE. Additionally, we did not routinely characterize BE by using the Prague Classification, which is now routinely used to endoscopically describe BE.[15]

Notwithstanding these limitations, this study's strength is that all endoscopies were performed and location determined by a single endoscopist, thereby decreasing interobserver variability. Our study includes both macroscopic and microscopic advanced lesions. Finally, the primary outcome of the study is circumferential location of early cancer in BE, and it is the largest study to date to have this primary outcome.

In conclusion, BE with HGD or ImCa has a predilection for the 12 to 6 o'clock hemisphere of the esophagus. Detailed inspection and targeted surveillance of biopsy samples in this region may lead to greater detection of advanced histologic lesions and will impact image-guided therapy.

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