Longitudinal and Circumferential Distributions of Dysplasia and Early Neoplasia in Barrett’s Esophagus: A Pooled Analysis of Three Prospective Studies

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INTRODUCTION: Studies have shown that dysplasia in Barrett’s esophagus (BE) has a predilection for the right hemisphere. There is limited information on the longitudinal distribution. The aim was to determine both the longitudinal and circumferential distributions of dysplasia and early neoplasia from 3 prospective studies.

METHODS: This is a pooled analysis from 3 prospective studies of patients with treatment-naive BE. Both circumferential and longitudinal locations (for BE segments greater than 1 cm) of dysplastic and early neoplastic lesions were recorded.

RESULTS: A total of 177 dysplastic and early neoplastic lesions from 91 patients were included in the pooled analysis; of which 59.3% (n = 105) were seen on high-definition white light endoscopy, 29.4% (n = 52) on advanced imaging, and 11.2% (n = 20) with random biopsies. The average Prague score was C3M5. Of 157 lesions within BE segments greater than 1 cm, 49 (34.8%) lesions were in the proximal half, whereas 92 lesions (65.2%) were in the distal half (P < 0.001). The right hemisphere of the esophagus contained 55% (86/157) of the total lesions compared with 45% (71/157) for the left hemisphere (P = 0.02). This was because of the presence of high-grade dysplasia being concentrated in the right hemisphere compared with the left hemisphere (60% vs 40%, P = 0.002).

DISCUSSION: In this pooled analysis of prospective studies, both low-grade dysplasia and high-grade dysplasia are more frequently found in the distal half of the Barrett’s segment. This study confirms that the right hemisphere is a hot spot for high-grade dysplasia. Careful attention to these locations is important during surveillance endoscopy.

INTRODUCTION
Barrett’s esophagus (BE) is the established precursor to esophageal adenocarcinoma, a cancer with increasing incidence and high mortality (1). Esophageal adenocarcinoma develops from specialized intestinal metaplasia undergoing step-wise progression to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and intramucosal adenocarcinoma (IMCA). The goal of endoscopic surveillance in BE was to detect dysplasia and early neoplasia at a stage in which it can be treated by endoscopic therapy. Barrett’s associated dysplasia can have subtle appearance with a focal and heterogenous distribution.

Previous studies have shown that dysplasia and early neoplasia in BE has a predilection to reside on certain clock-face orientations/hemispheres of the esophagus in patients who are endoscopic therapy naive (2–6). Two of these studies were retrospective in nature and suggest that dysplasia resides more commonly in the right hemisphere (clock face orientation of 12-6 o’clock) of the esophagus (2,3). The 2 prospective studies on this subject have shown variable results, with one study reporting lesions residing more often in the 2–5 o’clock position and another study reporting lesions more often found in the 12–3 o’clock position. All of these studies used previous generation endoscopy systems. In total, the number of lesions reviewed by these studies was 607, and only 3 studies included patients with BE with early neoplasia (HGD, IMCA, or T1b) (3–5).

Only a single study has examined the longitudinal distribution (proximal vs distal esophagus) of dysplasia (7) and found that
dysplasia is confined more to proximal BE segment before ablation therapy. The Ablation of Intestinal Metaplasia (AIM) Containing Dysplasia trial and the Surveillance versus Radiofrequency Ablation (SURF) trial (8,9). The AIM trial was started in early 2006 and the SURF trial was started in 2007, both predating the emergence and widespread use of the higher definition scopes that are now widely used.

The use of next generation endoscopy systems has greatly improved our diagnostic capability. Studies of colonoscopy for the adenoma detection rate have shown that newer generation technologies have increased the detection rate of polyps (10). Similarly, it is possible that with the new generation of gastroscopes, we may be finding more dysplasia in the esophagus as well. In addition to new generation endoscopes, advance imaging techniques have been created that can improve the diagnostic yield of dysplasia and early neoplasia (11–13).

It is unclear whether the observation that dysplasia is truly confined to the right hemisphere and proximal areas of a Barrett’s segment or is simply related to limitations of previous imaging and maneuverability of early generation endoscopes. Thus, the aim of this study was to examine both the circumferential/clock-face and longitudinal orientation of Barrett’s dysplasia and early neoplasia from 3 prospective studies that meticulously recorded the locations of suspected dysplastic lesions with the scope in the neutral position.

METHODS

This is a pooled analysis of patients treated at one tertiary care center (Northwell Health) from 3 separate prospective studies on advanced imaging in treatment-naïve BE undergoing surveillance examination from 9/2016–10/2019. These studies prospectively recorded the location of suspected dysplastic lesions with a high-definition gastroscope (GIF-HQ190; Olympus America, Center Valley, PA) in the neutral position (lesser curvature of the stomach in contiguity with the 3 o’clock esophageal orientation, ventral aspect of the esophagus at 12 o’clock, and the posterior esophagus at 6 o’clock). Both longitudinal and clock-face orientation locations of dysplastic lesions were recorded, immediately before biopsy or endoscopic resection, at the instruction of the endoscopist by a research coordinator while the endoscopist was performing the procedure. Longitudinal location of nontargeted Seattle protocol (SP) biopsies (biopsies taken every 1 cm in a 4-quadrant fashion) was recorded. Dysplastic lesions were defined as either LGD or early neoplasia, which included lesions with HGD, IMCA, and T1b adenocarcinoma. All data were prospectively recorded on a case report form and entered into a Research Electronic Data Capture database (REDCap, Fort Lauderdale, FL). In each of the following data sources, endoscopic evaluation was the primary method of determining lesion location. Volumetric laser endomicroscopy (VLE) was an adjunct to endoscopy. Only Northwell data were used because of (i) availability of data; (ii) all lesions were visualized with the scope in the neutral position; and (iii) high-definition white light endoscopy, narrow band imaging, and VLE were used for all examinations.

Data sources

Volumetric laser endomicroscopy with intelligent real-time segmentation NCT 03814824. In this prospective study, patients with BE underwent endoscopy with high-definition white light endoscopy, narrow band imaging, and VLE with laser marking randomized with or without intelligent real-time segmentation (an artificial intelligence platform that highlights VLE features of dysplasia). Each area of suspected dysplasia was recorded with the scope in the neutral position. Raised lesions were removed by endoscopic mucosal resection. Flat focal areas of suspected dysplasia on narrow band imaging or VLE were biopsied. Random biopsies were taken subsequently per the SP. Two GI pathologists reviewed and confirmed the pathology. All results of dysplasia were included in this pooled analysis.

Barrett’s dysplasia detection pilot trial using the NvisionVLE imaging (DDP) NCT02864043. In this study, patients with BE underwent endoscopy with high-definition white light endoscopy, narrow band imaging with near focus, and VLE with laser marking. Each area of suspected dysplasia was recorded with the scope in the neutral position. Raised lesions were removed by endoscopic mucosal resection. Flat focal areas of suspected dysplasia on narrow band imaging or VLE were biopsied. Random biopsies were taken subsequently per the SP. Two GI pathologists reviewed and independently confirmed the pathology. All results of dysplasia were included in this pooled analysis.

NVision VLE system registry NCT02215291. In this study, patients with BE underwent endoscopy with high-definition white light endoscopy, narrow band imaging with near focus, and VLE without laser marking. Each area of suspected dysplasia was recorded with the scope in the neutral position. Raised lesions were removed by endoscopic mucosal resection. Flat focal areas of suspected dysplasia on narrow band imaging or VLE were biopsied. Random biopsies were taken subsequently per the SP. Two GI pathologists reviewed and confirmed the pathology. All results of dysplasia were included in this pooled analysis.

| Table 1. Patient and lesion characteristics |
|--------------------------------------------|
| Characteristic                             |
| Total patients                             | 91 |
| Male (number, %)                           | 72  79.1% |
| Caucasian (number, %)                      | 75  82.4% |
| Barrett’s lesions                          | 177 |
| Prague Class-C (mean, range)               | 3  0–12 |
| Prague Class-M (mean, range)               | 5  0–13 |
| Segment length                             | 5  0–13 |
| Hiatal hernia (number, %)                  | None  45  29% |
| Small (0–2 cm)                             | 58  37.4% |
| Medium (2–4 cm)                            | 31  20.0% |
| Large (4+ cm)                              | 21  13.5% |
| Visible lesion on high-definition white light | 105  59.3% |
| Dysplasia grade (number, %)                | Low-grade dysplasia  51  28.8% |
|                                            | High-grade dysplasia  68  38.4% |
|                                            | Intramucosal adenocarcinoma  53  29.9% |
|                                            | T1b Adenocarcinoma  5  2.8% |

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Table 2. Dysplastic lesion location by longitudinal orientation comparing proximal and distal half only

| Dysplasia grade | Proximal half N = 49 | Distal half N = 92 | P value |
|-----------------|----------------------|--------------------|---------|
|                 | N        | %       | N        | %       |         |
| LGD             | 15       | 34.1 (15/44) | 29       | 65.9 (29/44) | <0.001 |
| HGD             | 15       | 28.3 (15/53) | 38       | 71.7 (38/53) | <0.001 |
| IMCA            | 18       | 45.0 (18/40) | 22       | 55.0 (22/40) | 0.2036 |
| T1b cancer      | 1        | 25.0 (1/4)   | 3        | 75.0 (3/4)   | 0.0209 |
| Early neoplasia (HGD + IMCA + T1b cancer) | 34       | 35.1 (34/97) | 63       | 64.9 (63/97) | <0.001 |
| All lesions     | 49       | 34.8 (49/141)| 92       | 65.2 (92/141)| <0.001 |

Sixteen lesions were not included in this from this analysis as they were in the middle of the Barrett’s segment. An additional 20 lesions were not included as the Barrett’s segment was less than 1 cm.

HGD, high-grade dysplasia; IMCA, intramucosal adenocarcinoma; LGD, low-grade dysplasia.

Longitudinal and circumferential orientation classification

Dysplastic lesion locations obtained from targeted biopsies or endoscopic mucosal resection were reported by longitudinal orientation and clock-face orientation. Dysplastic lesions obtained from nontargeted SP biopsies were reported by longitudinal orientation only. Longitudinal orientation was reported as the lesion residing in the proximal half or distal half. Lesions in the middle (i.e., a lesion involving both halves) or those that resided in a segment <1 cm in length (Prague class C1M1 or less) were excluded from the longitudinal analysis. Regarding clock-face orientation, the clock-face was divided into quadrants: quadrant 1 at 12–3, quadrant 2 at 3–6, quadrant 3 at 6–9, quadrant 4 at 9–12. Quadrants 1 and 2 were the right hemisphere of the esophagus, whereas quadrants 3 and 4 were the left hemisphere. If a lesion was on the border of a quadrant, it was counted to the quadrant where most lesions involved.

Institutional review board and statistics

The Zucker School of Medicine at Hofstra/Northwell Intuitional Review Board approved these studies. All authors had access to the data and reviewed the final study.

We performed post hoc power calculations to evaluate whether the study was powered to detect a difference in dysplastic lesions between the right and the left hemispheres and between the distal and proximal halves of the Barrett’s segment. The first null hypothesis was that if there would be 50% of lesions in each hemisphere, a difference of 30% between the hemispheres with 141 lesions would give the study a power of 85% at a two-sided significance level of \( \alpha = 0.05 \), assuming that the lesions were located arbitrarily. The second null hypothesis was that if there would be 50% of lesions in each half of the esophagus (distal and proximal), a difference of 33% between the halves with 141 lesions would give the study a power of 83% at a two-sided significance level of \( \alpha = 0.05 \), assuming that the lesions were located arbitrarily.

Continuous variables were described using mean and standard deviations. The categorical variables were compared using \( \chi^2 \) tests and McNemar tests for proportions as appropriate. A \( P \) value of <0.05 was considered statistically significant. All data were stored in a prospective REDCap database.

RESULTS

A total of 177 dysplastic and early neoplastic lesions from 91 patients were included in the pooled analysis; of which 59.3% (n = 105) were seen on high-definition white light endoscopy. Of the lesions not visible on high-definition white light endoscopy, 29.4% (n = 52) lesions were obtained after visualization with advanced imaging and 11.2% (n = 20) were obtained via SP biopsies. Patient characteristics are listed in Table 1. Male sex and Caucasian race represented 79% and 82% of the patient cohort, respectively. The average length was Prague C3M5. Of the total lesions, 51 (28.8%) were LGD, 68 (38.4%) were HGD, 53 (29.9%) were IMCA, and 5 (2.8%) were stage T1b adenocarcinoma.

Table 2 shows the longitudinal distribution of dysplasia and early neoplasia. Twenty patients were excluded from this analysis because the Barrett’s segment was 1 cm or less. Of 157 lesions, 49

Table 3. Dysplastic lesion location by clockface orientation

| Dysplasia grade | Quadrant 1 | Quadrant 2 | Quadrant 3 | Quadrant 4 | P value |
|-----------------|------------|------------|------------|------------|---------|
|                 | n        | %        | n        | %        | n        | %        | n        | %        |         |
| LGD             | 7        | 17.9 (7/39) | 11       | 28.2 (11/39) | 11       | 28.2 (11/39) | 10       | 25.6 (10/39) | 0.31 |
| HGD             | 18       | 30.0 (18/60) | 18       | 30.0 (18/60) | 9        | 15.9 (9/60)   | 15       | 25.0 (15/60)  | 0.68 |
| IMCA            | 16       | 30.2 (16/53) | 13       | 24.5 (13/53) | 10       | 18.9 (10/53)  | 14       | 26.4 (14/53)  | 0.80 |
| T1b cancer      | 0        | 0 (0/5)   | 3        | 60.0 (3/5)   | 0        | 0 (0/5)   | 2        | 40.0 (2/5)   | 0.80 |
| All lesions     | 41       | 26.1 (41/157) | 45       | 28.7 (45/157) | 30       | 19.1 (30/157) | 41       | 26.1 (41/157) | 0.65 |

HGD, high-grade dysplasia; IMCA, intramucosal adenocarcinoma; LGD, low-grade dysplasia.
Table 4. Dysplastic lesion location by stratified by the right or left hemisphere of the esophagus

| Dysplasia grade                  | All lesions N = 157 | Right hemisphere (quadrant 1 and 2) N = 86 | Left hemisphere (quadrant 3 and 4) N = 71 |
|----------------------------------|---------------------|-------------------------------------------|------------------------------------------|
|                                 | n  | %     | n  | %     | n  | %     | P value |
| LGD                              | 39 | 25%   | 21 | 25%   | 18 | 24%   | 0.33    |
| HGD                              | 60 | 40%   | 24 | 40%   | 36 | 40%   | 0.002   |
| IMCA                             | 53 | 34%   | 24 | 28%   | 29 | 33%   | 0.17    |
| T1b cancer                       | 5  | 3%    | 2  | 2%    | 3  | 4%    | 0.36    |
| Early neoplasia (HGD + IMCA + T1b cancer) | 118 | 76%   | 50 | 68%   | 68 | 76%   | 0.001   |
| All lesions                      | 157| 100%  | 71 | 100%  | 86 | 100%  | 0.02    |

HGD, high-grade dysplasia; IMCA, intramucosal adenocarcinoma; LGD, low-grade dysplasia.

dysplastic lesions (31.2%) were in the proximal half, whereas 92 lesions (58.6%) were in the distal half (P < 0.001). Sixteen lesions (10.2%) were in the middle or involved both the proximal and distal halves and thus were not included in the analysis. All lesions were more likely to be in the distal half of the Barrett’s segment versus the proximal (65.2% vs 34.8%, P < 0.001). Both LGD and early neoplasia (HGD, IMCA, and T1b) were more likely to be in the distal half of the Barrett’s segment versus the proximal (65.9% vs 34.1%, P < 0.001 and 64.9% vs 35.1%, P < 0.001, respectively).

Table 3 shows the distribution of dysplasia and early neoplasia by clock-face orientation. The 20 dysplastic lesions obtained by SP biopsies were excluded from the analysis because this information is not available. There was no difference in location between the 4 quadrants regarding total dysplasia (Q1 26.1% vs Q2 28.7% vs Q3 19.1% vs Q4 26.1%; P = 0.65). Table 4 compares the right and left hemispheres for circumferential location of dysplasia and early neoplasia. The right hemisphere of the esophagus contained 55% (86/157) of all lesions compared with 45% (71/157) for the left hemisphere (P = 0.02). The right hemisphere contained 57.6% of early neoplasia (HGD/IMCA/T1b lesions) (68/118) vs 42.4% (50/118) in the left hemisphere (P = 0.001). LGD was evenly distributed with 46.2% (18/39) in the right hemisphere and 53.8% (21/39) in the left hemisphere (P = 0.33).

**DISCUSSION**

In this study, we examined the longitudinal and circumferential distributions of dysplasia and early neoplasia based on 3 prospective studies that recorded the location of suspected dysplasia targets with the scope in the neutral position. This study used high-definition white light endoscopy, advanced imaging, and random biopsies to locate lesions and thus provides a complete picture of the longitudinal and the circumferential location of dysplasia.

A new finding in our study is that dysplasia and early neoplasia is found more frequently in the distal half of the esophagus compared with the proximal half. This differs from the only other report on the longitudinal location of dysplasia in BE (7). Although that study is well performed and combines 2 prospective trials, only 58.8% (157/267) of the included patients had sufficient information that allowed for calculation of the longitudinal distribution of dysplastic lesions, which could influence their results because of missing data bias. The findings of our study are aligned with data from acid physiology studies. The distal esophagus is exposed to more acid reflux both in amount and time versus the proximal esophagus (14–16). Therefore, with repeated acid reflux insults, mucosal damage is greater in the distal esophagus versus the proximal esophagus. Thus, physiology studies support our study showing the distal esophagus has more dysplasia versus the proximal esophagus. Moreover, this is further supported by a study showing that esophageal cancer within a Barrett’s segment occurs more commonly in the distal third of the Barrett’s segment (17).

Our study confirms previous reports regarding circumferential location of early neoplasia (HGD/IMCA/T1b adenocarcinoma) in BE that it tends to reside in the right hemisphere of the esophagus (2–6). Previous studies did not evaluate the location of LGD, and our study shows that LGD is evenly distributed in the right and left hemispheres. Physiology studies also support this finding. Studies have shown an increase in mucosal breaks in the right hemisphere in the esophagus in those with Grade A or B reflux esophagitis (18). In addition, histologic changes in patients with esophageal reflux disease occurs most frequently in the right hemisphere (19).

Understanding where dysplasia may be located in a Barrett’s segment is important for clinical care. Some studies suggest that dysplasia may be missed on surveillance endoscopy in BE (20,21) because of its focal nature. Rigorous examination or oversampling of certain hot zones for dysplasia may help overcome this. In addition, relatively new to BE surveillance is the wide area transepithelial (WATS) brush (22,23). This brush has been shown to increase dysplasia yield versus pinch biopsies (24). Ensuring the brush generously samples these hot zones may be a technique to increase dysplasia detection.

We believe that our study has notable strengths. First, the data were collected in a prospective fashion and careful attention was given to identification of the longitudinal and circumferential orientations of the target with the scope in the neutral position. Second, in 2 of the studies, VLE laser markings were performed of the dysplastic area to allow further visual confirmation of location. Third, this is the first study to examine the circumferential and longitudinal location of low-grade dysplasia, which may be managed differently than early neoplasia. Finally, dysplastic lesions are located using high-definition white light endoscopy, advanced imaging, and random biopsies, allowing for a longitudinal analysis of dysplastic lesions. This study does have...
limitations. The average Prague class was only C3M5. Thus, these data may not be applicable for ultra-long segments of BE. Second, these studies were performed in one tertiary care hospital and thus may not be applicable to a community setting. Nevertheless, almost all of these patients were referred to our center by community physicians. Finally, although these studies were VLE-based studies, this study is applicable to the general Barrett’s population, given most lesions (70%) were found on high-definition white light endoscopy (59.3%) and random biopsies (11.2%).

In conclusion, this study has provided detailed longitudinal and circumferential location of dysplasia and early neoplasia. It has confirmed previously circumferential data on neoplasia and provided new insight into longitudinal location of dysplasia and early neoplasia. Dysplasia and early neoplasia is more frequently located in the right hemisphere and distal half of the Barrett’s segment. Careful attention to these hot spots is important during surveillance endoscopy.

CONFLICTS OF INTEREST
Guarantor of the article: Arvind J. Trindade, MD.
Specific author contributions: A.J.T.: Conception and design. K.L.R., S.I., N.M., M.J.M., A.J.T.: Analysis and interpretation of the data. K.L.R., S.I., N.M., A.J.T., M.J.M., A.K., C.L.L., P.I.: Drafting of the article.
Financial support: None to report.
Potential competing interests: A.J.T.: Consultant for Olympus America and Pentax Medical Research Support from Ninepoint Medical. C.L.L.: Research Support from Ninepoint Medical. P.I.: Research funding from C2 Therapeutics, Nine Point Medical, Exact Sciences, Consultant: Medtronic, CSA Medical.

Study Highlights

WHAT IS KNOWN

✓ Dysplasia is a precursor to esophageal cancer in Barrett’s esophagus.
✓ Dysplasia is located more commonly in the right hemisphere of the esophagus.
✓ There are limited data on the longitudinal location of dysplasia and early neoplasia.

WHAT IS NEW HERE

✓ In this pooled analysis of 3 prospective studies, dysplasia and early neoplasia were more common in the distal half of Barrett’s segments.

TRANSITIONAL IMPACT

✓ This may impact surveillance protocols in surveillance of Barrett’s esophagus.

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