Clinicopathologic characteristics of early gastric cancer according to specific intragastric location

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Abstract

Background: Although the incidence of early gastric cancer (EGC) continues to rise, there have been few studies on the intra-gastric distribution and locational characteristics of EGCs. In addition, there has been no attempt to visualize the intra-gastric distribution of EGCs using a merged tumor map.

Methods: We investigated the anatomic distribution of 644 cases of EGCs and analyzed the correlation between clinicopathologic findings and location by dividing areas of the stomach vertically and transversely. Merged tumor maps were generated using 310 surgically resected cases.

Results: Early gastric cancer was most commonly located in the antrum (57.5%) along the lesser curvature (37.8%). The intra-gastric distributions were similar in the merged tumor maps. Vertically, cancers of the middle third were associated with younger patient age, larger tumor size, and more frequent poorly differentiated (PD) or signet ring cell histology than cancers in other sites. Submucosal invasion was most frequently observed in the upper third. When divided transversely, tumors in the anterior or posterior wall showed more frequent PD or signet ring cell histology than those along the lesser or greater curvatures.

Conclusions: EGC is the most prevalent in the antrum along the lesser curvature and has characteristic locational features, including histologic type, invasion depth, patient age, and tumor size. These results will improve the endoscopic detection rate of EGC and help to determine endoscopic resectability.

Keywords: Stomach neoplasms, Neoplasm by site, Gastrectomy, Incidence

Background

Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related death worldwide [1]. In Korea, gastric cancer is the second most common cancer among the male population and the fourth most common cancer in the female population [2]. Early gastric carcinoma (EGC) is an invasive neoplasm confined to the gastric mucosa or submucosa irrespective of lymph node metastasis. EGC can be treated via endoscopic resection with an excellent survival rate and high quality of life for patients; thus, it is important to identify candidates for endoscopic resection [3, 4]. Endoscopic resectability is determined by various clinicopathologic factors, including tumor differentiation, tumor size, invasion depth, ulceration, and lymphovascular invasion, which vary depending on the intragastric location of EGCs [5]. However, studies of the intra-gastric distribution of EGCs or their locational characteristics have been rare [6, 7]. In addition, there have been no attempts to visualize the real distribution of EGCs using merged tumor maps.

The stomach epithelium originates from the foregut endoderm and becomes regionalized along the proximal-distal axis during development to give rise to distinct functional regions or chambers [8]. Anatomically, the stomach is classified into the cardia, fundus, body, antrum, and pylorus, as well as the lesser and greater curvatures.
Most prior studies on the locational characteristics of gastric cancers have divided the stomach into more general categories of proximal versus distal or cardiac versus non-cardiac [6, 9–12]. As the incidence of proximal gastric cancer grows globally, many studies have focused on the evaluation of characteristics of proximal gastric cancer. These studies have revealed that while proximal gastric cancer is typically more aggressive and has a poor prognosis, the most prevalent gastric cancer location is the antrum [6, 9–15]. Therefore, further knowledge regarding the clinicopathologic features of gastric cancer according to detailed intragastric location is needed to aid in selecting appropriate treatment strategies.

We investigated the anatomic distribution of EGC by generating a merged tumor map and then analyzed the correlation between clinicopathologic findings and location based on detailed segmentation of the stomach.

**Method**

**Patients and clinical data**

This retrospective study was approved by the Institutional Review Board of Kangbuk Samsung Hospital. A total of 310 gastrectomy specimens and 334 endoscopic submucosal dissection (ESD) specimens of EGC resected at Kangbuk Samsung Hospital between January 2011 and December 2014 was included. Subtotal and total gastrectomy were performed in 264 (85.2%) and 45 (14.5%) patients, respectively. One patient (0.3%) underwent a proximal gastrectomy. Clinical data including age, sex, and follow-up findings were obtained from electronic medical records.

**Gross examination of gastrectomy specimens and generation of merged tumor map**

Fresh gastrectomy specimens were photographed after opening along the greater or lesser curvature (Fig. 1a). After fixation in 10% buffered formalin solution overnight, fixed gastrectomy specimens were photographed, and the definite tumor location and extent was determined (Fig. 1b and c). Gross characteristics including tumor location, tumor size, and EGC type were recorded. Vertical locations were recorded as gastroesophageal junction, cardia, fundus, high body, mid body, low body, antrum, and pylorus. To analyze clinicopathologic parameters, three groups were used: upper third, from the gastroesophageal junction to the high body; middle third, mid body and low body; lower third, antrum and pylorus. Transverse locations were recorded as the lesser curvature, greater curvature, anterior wall, and posterior wall. The transverse location could not be determined in cases located in the cardia, fundus, or gastroesophageal junction due to circular tumor shape.

Images of tumor maps were merged using the ImageJ program (http://imagej.net/) according to type of operation and opening method. Among 310 cases, 31 cases opened in unusual ways were excluded from the merged tumor map. Finally, 250 cases opened along the greater curvature and 29 cases opened along the lesser curvature were included. To adjust the size and position of images, the bUnwarpl plugin of ImageJ was used. After registration, the tumor area was manually labeled using the rectangular selection tool in ImageJ. The labeled images were saved individually. Then, merged stack images were created using ImageJ’s Z Project menu.

**Gross examination of endoscopic submucosal dissection specimens**

ESD specimens were photographed after fixation in 10% buffered formalin solution overnight. After applying dye to the deep and lateral resection margins, the specimens were cut at 2-mm increments and mounted on glass slides. Tumor locations were determined based on endoscopic findings. Gross characteristics including tumor location and tumor size were recorded in the same manner as for gastrectomy specimens.
Microscopic evaluation
All gastrectomy and ESD cases were microscopically reviewed to determine the histological classification, tumor differentiation, depth of invasion, presence of lymphovascular invasion, presence of perineural invasion, and presence of adenomatous background [13]. In cases with two or more EGC lesions in the same specimen, tumor characteristics (including histologic type and depth of invasion) of the EGC lesion with the deepest tumor invasion were used. Tumor stage was assigned according to the 2010 AJCC Tumor Node Metastasis staging system [1].

Statistical analysis
Data were analyzed using PASW Statistics 18 (SPSS Inc., Chicago, IL, USA) software. Crosstabs, Pearson's chi-square test, and Fisher's exact test were used as needed. Differences were regarded as statistically significant if \( P < 0.05 \).

Results
The clinicopathologic data for all 644 patients with EGC are given in Table 1. The median age was 61 (range: 29 to 87 years) and 67 years (range: 30 to 89 years) in patients who underwent gastrectomy and ESD, respectively. The mean lesion size was 3.17 cm (range: 0.2 to 14.5 cm) and 1.89 cm (range: 0.1 to 7.8 cm) in patients who underwent gastrectomy and ESD, respectively. More than half of cases had tumors located in the antrum (57.5%) (Table 2). The most common EGC location was the antrum along the lesser curvature (21.9%), followed by the anterior wall of the antrum (12.9%) and the posterior wall of the antrum (12.7%). When dividing cases into three groups according to vertical location, tumors in the upper third were most commonly located in the posterior wall, while tumors in the middle and lower third showed lesser curvature predominance (Fig. 2a). The merged tumor map with gastrectomy cases showed a hot spot in the antrum and low body along the lesser curvature (Fig. 3a). The tumor map with cases opened along the lesser curvature also revealed a hot spot in the antrum along the greater curvature with a more distal location (Fig. 3b).

When dividing the cases into three vertical groups according to tumor epicenter, there were differences between groups in tumor size, age, invasion depth, and histologic differentiation (Table 3). The middle third showed poorly differentiated (PD) adenocarcinoma or signet ring cell carcinoma (SRC) most frequently, while in the remaining two thirds well-differentiated (WD) adenocarcinoma was the most common histologic pattern (Table 3, Additional file 1: Table S1 and Fig. 2b). Similar distributional differences were also observed in the merged tumor maps. PD adenocarcinoma and SRC were more concentrated in the middle third (Fig. 4c and d) compared to WD and moderately differentiated (MD) tumors (Fig. 4a and b). In addition, the middle third exhibited the largest mean tumor size and the youngest mean age. Submucosal invasion was most frequently

| Table 1 | Clinicopathologic features of 644 patients with early gastric cancer |
| --- | --- | --- |
| Variables | Gastrectomy (n = 310) | Endoscopic resection (n = 334) | Total (n = 644) |
| Sex |  |  |  |
| Male | 211 (68.1) | 256 (76.6) | 467 (72.5) |
| Female | 99 (31.9) | 78 (23.4) | 177 (27.5) |
| Size (cm) |  |  |  |
| \( \leq 2 \) | 103 (33.2) | 217 (65.0) | 320 (49.7) |
| 2.1–3.0 | 78 (25.2) | 71 (21.2) | 149 (23.1) |
| > 3 | 129 (41.6) | 46 (13.8) | 175 (27.2) |
| Gross type |  |  |  |
| Elevated | 56 (18.1) | 89 (26.7) | 145 (22.5) |
| Flat | 121 (39.0) | 133 (39.8) | 254 (39.4) |
| Depressed | 133 (42.9) | 112 (33.5) | 245 (38.1) |
| pT stage |  |  |  |
| 1a | 156 (50.3) | 269 (80.5) | 425 (66.0) |
| 1b | 154 (49.7) | 65 (19.5) | 219 (34.0) |
| Histologic type |  |  |  |
| Well differentiated | 58 (18.7) | 206 (61.7) | 264 (41.0) |
| Moderately differentiated | 91 (29.4) | 99 (29.6) | 190 (29.5) |
| Poorly differentiated | 99 (31.9) | 21 (6.3) | 120 (18.6) |
| Signet ring cell carcinoma | 58 (18.7) | 5 (1.5) | 63 (9.8) |
| Mucinous adenocarcinoma | 3 (1.0) | 1 (0.3) | 4 (0.6) |
| Lymphoepithelioma-like | 1 (0.3) | 2 (0.6) | 3 (0.5) |
| Lymphatic invasion | 46 (14.8) | 23 (6.9) | 69 (10.7) |
| Vascular invasion | 5 (1.6) | 2 (0.6) | 7 (1.1) |
| Perineural invasion | 6 (1.9) | 0 (0) | 6 (0.9) |
| Adenomatous background | 15 (4.8) | 80 (24.0) | 95 (14.8) |

Data are presented as number (%)

Table 2 | Location of 644 cases of early gastric cancer |
| --- | --- | --- | --- | --- |
| Greater curvature | Lesser curvature | Anterior wall | Posterior wall | Total |
| GEJ, cardia, fundus | 4 (0.6) | 12 (1.9) | 6 (0.9) | 15 (2.3) | 37 (5.7) |
| High body | 8 (1.2) | 29 (4.5) | 8 (1.2) | 17 (2.6) | 62 (9.6) |
| Mid-body | 27 (4.2) | 52 (8.1) | 35 (5.4) | 34 (5.3) | 148 (23.0) |
| Low body | 64 (9.9) | 141 (21.9) | 83 (12.9) | 82 (12.7) | 370 (57.5) |
| Total cases | 103 (16.7) | 234 (37.8) | 132 (21.4) | 148 (24.0) |

Data are presented as number (%)

**ESD** endoscopic submucosal dissection, **GEJ** gastroesophageal junction

*The transverse location cannot be determined
observed in the upper third (Table 3). Gender, gross type, lymphovascular invasion, perineural invasion, adenomatous background, and lymph node metastasis were not significantly different according to vertical location.

When dividing the stomach transversely, the lesser curvature (37.8%) was the most common site for EGCs, and the greater curvature (16.7%) was the least (Table 2) common site. Tumors located in the anterior or posterior wall showed a higher frequency of PD adenocarcinoma/SRC histology than those located along the greater or lesser curvatures (Table 4). These histologic differences were not demonstrated on the merged tumor map because the frequency of tumors located along the lesser curvature was remarkably high (Fig. 4). Tumors located along the lesser curvature showed the largest tumor size and most commonly had an adenomatous background. Tumors located in the posterior wall were associated with the youngest mean age (Table 4). The remaining clinicopathologic features were not significantly different according to transverse location.

**Discussion**

This is the first study in Korea to provide detailed distribution and locational characteristics of all EGCs, including both surgically and endoscopically resected EGCs. We confirmed that the antrum (57.5%) and lesser curvature (37.8%) were the most common sites for EGCs, and the greater curvature (16.7%) was the least (Table 2) common site. Tumors located in the anterior or posterior wall showed a higher frequency of PD adenocarcinoma/SRC histology than those located along the greater or lesser curvatures (Table 4). These histologic differences were not demonstrated on the merged tumor map because the frequency of tumors located along the lesser curvature was remarkably high (Fig. 4). Tumors located along the lesser curvature showed the largest tumor size and most commonly had an adenomatous background. Tumors located in the posterior wall were associated with the youngest mean age (Table 4). The remaining clinicopathologic features were not significantly different according to transverse location.

![Fig. 2 Transverse location (a) and histologic distribution (b) of early gastric carcinoma according to vertical location. The transverse location is indicated as posterior wall (PW), greater curvature (GC), anterior wall (AW), and lesser curvature (LC) (a). The middle third shows more frequent poorly differentiated (PD) adenocarcinoma or signet ring cell carcinoma (SRC) histology compared to upper or lower thirds, which has predominant well differentiated (WD) or moderately differentiated (MD) histology (b).](image)

![Fig. 3 Merged tumor maps generated according to surgical opening along the greater (a) or lesser (b) curvatures. Tumors are most often concentrated in the antrum and low body along the lesser curvature (a). Along the greater curvature, tumors are located only in the antrum and low body, with preservation of the mid and high body (b).](image)
Studies on the locational characteristics of EGC are rare, although there have been several previous reports of locational characteristics of all gastric cancers [6, 7, 16–21]. A Chinese study, the only study including both surgically resected EGCs, divided the stomach into proximal and distal portions and revealed that proximal gastric cancer had smaller tumor size, deeper invasion than those in the lower portion, but this study included only endoscopically resected EGCs [7].

Our results present more detailed locational characteristics and include EGC cases regardless of treatment modality. These are strengths that distinguish our study from the previous studies mentioned above.

Our results showed that EGCs in the middle third longitudinally and in the anterior or posterior wall transversely were more likely to represent PD adenocarcinoma or SRC than tumors found at other sites. In a previous study comparing the locational characteristics of gastric cancer from two cohorts in Koreans and Americans, the Korean cohort more frequently had undifferentiated cancers in the upper and middle thirds than in the lower third. However, there was no significant histologic difference between longitudinal locations in the American cohort [19]. A Chinese study also reported that PD type was found more frequently in the middle third than in the upper and lower thirds [22]. Based on our results and the abovementioned previous reports, gastric cancers in the middle and upper thirds have different histologic types than those of the lower third in Asian people including Koreans. These results suggest that gastric cancers occur via different carcinogenesis pathways depending on the intra-gastric location. Further studies investigating precancerous lesions according to detailed intra-gastric location are necessary, including not only the atrophic gastritis-intestinal metaplasia-dysplasia sequence but also signet ring cell carcinoma in situ lesions.

Gastric cancers located in the upper third, especially the cardia and gastroesophageal junction, are known to have a poor prognosis independent of stage [16]. In our results, submucosal invasion was most frequently found in the upper third. Akashi et al. reported that the cardia had looser smooth muscle bundles and more frequent large lymphatics in the muscularis mucosae layer than other gastric sites, which is presumed to be one reason for more frequent submucosal invasion in the cardia [23]. Endoscopy in the mid-to-upper stomach is technically difficult, which may also result in decreased early detection [7]. However, our study and also previous reports included a small number of upper third cancers, which limits investigation of the frequent submucosal invasion seen in this area.

This study has a few limitations. First, since only tumor maps of surgically resected cases were used in the merging processes of tumor maps, the merged tumor

### Table 3 Clinicopathological features according to the vertical location of early gastric cancer

| Variables | Upper third (n = 64, 9.9%) | Middle third (n = 210, 32.6%) | Lower third (n = 370, 57.5%) | P-value |
|-----------|---------------------------|-------------------------------|----------------------------|---------|
| Size (cm) | 2.77 ± 2.09               | 2.96 ± 2.06                  | 2.21 ± 1.54                | < 0.001 |
| Age (years) | 63.56 ± 12.46           | 60.28 ± 11.70                | 64.24 ± 11.11              | < 0.001 |
| Sex | | | | 0.249 |
| Male | 52 (81.3) | 149 (71.0) | 266 (71.9) | |
| Female | 12 (18.8) | 61 (29.0) | 104 (28.1) | |
| pT stage | | | | 0.001 |
| 1a | 30 (46.9) | 134 (63.8) | 261 (70.5) | |
| 1b | 34 (53.1) | 76 (36.2) | 109 (29.5) | |
| Gross type | | | | 0.263 |
| Elevated | 18 (28.1) | 40 (19.0) | 87 (23.5) | |
| Flat | 27 (42.2) | 91 (43.3) | 136 (36.8) | |
| Depressed | 19 (29.7) | 79 (37.6) | 147 (39.7) | |
| Histologic type<sup>a</sup> | | | | < 0.001 |
| WD | 29 (46.0) | 67 (32.1) | 168 (46.0) | |
| MD | 16 (25.4) | 47 (22.5) | 127 (34.8) | |
| PD / Signet ring cell carcinoma | 18 (28.6) | 95 (45.4) | 70 (19.2) | |
| Lymphatic invasion | 6 (9.4) | 21 (10.0) | 42 (11.4) | 0.823 |
| Venous invasion | 0 (0) | 3 (1.4) | 4 (1.1) | 0.628 |
| Perineural invasion | 1 (1.6) | 1 (0.5) | 4 (1.1) | 0.658 |
| Adenomatous background | 12 (18.8) | 30 (14.3) | 53 (14.3) | 0.636 |
| Lymph node metastasis<sup>b</sup> | 2 (5.4) | 12 (9.3) | 20 (12.2) | 0.420 |

Data are presented as number (%) or mean ± standard deviation. SD, standard deviation; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.

<sup>a</sup>Mucinous adenocarcinoma and carcinoma with lymphoid stroma were excluded from this analysis.

<sup>b</sup>Lymph node metastasis was analyzed in only 310 gastrectomy specimens.

first attempt to visualize EGC frequency by creating merged tumor maps reflecting the actual location and extent of EGCs. Additional multi-center experiments with more tumor maps, including endoscopically resected cases, will be helpful in creating a Korean EGC map.
**Fig. 4** Tumor distribution by tumor differentiation. Tumor maps are merged according to surgical opening along greater (a, c) or lesser (b, d) curvatures. The highest concentrations of well and moderately differentiated adenocarcinoma (a, b) are located in a lower part than most poorly differentiated adenocarcinomas and signet ring cell carcinomas (c, d).

**Table 4** Clinicopathological features according to the transverse location of early gastric cancer

| Variables                     | Greater curvature | Lesser curvature | Anterior wall | Posterior wall | P-value |
|-------------------------------|-------------------|------------------|---------------|---------------|---------|
| Size (cm)                     | 2.02 ± 1.23       | 2.81 ± 2.13      | 2.55 ± 1.79   | 2.28 ± 1.45   | 0.001   |
| Age (years)                   | 64.72 ± 11.56     | 63.26 ± 11.17    | 62.74 ± 0.89  | 60.59 ± 12.65 | 0.036   |
| Sex                           |                   |                  |               |               | 0.343   |
| Male                          | 79 (76.7)         | 172 (73.5)       | 88 (66.7)     | 105 (70.9)    |         |
| Female                        | 24 (23.3)         | 62 (26.5)        | 44 (33.3)     | 43 (29.1)     |         |
| pT stage                      |                   |                  |               |               | 0.171   |
| 1a                            | 66 (64.1)         | 169 (72.2)       | 82 (62.1)     | 96 (64.9)     |         |
| 1b                            | 37 (35.9)         | 65 (27.8)        | 50 (37.9)     | 52 (35.1)     |         |
| Gross type                    |                   |                  |               |               | 0.275   |
| Elevated                      | 31 (30.1)         | 46 (19.7)        | 28 (21.2)     | 30 (20.3)     |         |
| Flat                          | 40 (38.8)         | 88 (37.6)        | 57 (43.2)     | 61 (41.2)     |         |
| Depressed                     | 32 (31.1)         | 100 (42.7)       | 47 (35.6)     | 57 (38.5)     |         |
| Histologic type<sup>a</sup>   |                   |                  |               |               | 0.041   |
| WD                            | 49 (48.5)         | 111 (47.6)       | 43 (32.8)     | 49 (33.6)     |         |
| MD                            | 36 (35.6)         | 61 (26.2)        | 42 (32.1)     | 45 (30.8)     |         |
| PD / Signet ring cell carcinoma | 16 (15.9)   | 61 (26.2)        | 46 (35.1)     | 52 (35.6)     |         |
| Lymphatic invasion            | 14 (13.6)         | 20 (8.5)         | 15 (11.4)     | 15 (10.1)     | 0.545   |
| Venous invasion               | 1 (1.0)           | 1 (0.4)          | 3 (2.3)       | 2 (1.4)       | 0.448   |
| Perineural invasion           | 0 (0)             | 2 (0.9)          | 2 (1.5)       | 1 (0.7)       | 0.638   |
| Adenomatous background        | 13 (12.6)         | 46 (19.7)        | 15 (11.4)     | 16 (10.8)     | 0.047   |
| Lymph node metastasis<sup>b</sup> | 6 (15.0)  | 6 (5.6)          | 9 (11.1)      | 12 (14.0)     | 0.201   |

Data are presented as number (%) or mean ± standard deviation
SD standard deviation, WD well differentiated, MD moderately differentiated, PD poorly differentiated
<sup>a</sup>Mucinous adenocarcinoma and carcinoma with lymphoid stroma were excluded from this analysis
<sup>b</sup>Lymph node metastasis was analyzed in only 310 gastrectomy specimens
maps in this study reflected only the locations of surgically resected EGC cases rather than entire EGCs. Second, this study included no information about lymph node metastasis status after ESD procedures, tumor recurrence status, or patient survival.

Conclusion
In conclusion, EGC was most commonly located in the antrum along the lesser curvature in Koreans. Younger patient age, larger tumor size, and more frequent PD adenocarcinoma and SRC were observed in the middle third on vertical location analysis. Submucosal invasion was most frequently observed in the upper third. Regarding transverse locations, anterior and posterior wall tumors showed more frequent PD adenocarcinoma and SRC. These location-specific features may be helpful in determining treatment options for patients with EGC.

Additional file

**Additional file 1:** Table S1. Transverse location and histologic differentiation according to vertical location. (DOCX 15 kb)

**Abbreviations**
EGC: Early gastric carcinoma; ESD: Endoscopic submucosal dissection; MD: Moderately differentiated; PTD: Poorly differentiated; PTD: Proximal, transitional, and distal; SRC: Signet ring cell carcinoma; WD: Well differentiated

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**Availability of data and materials**
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors’ contributions**
SWC supervised the entire study and participated in study design and coordination. KK, YC, JHS, DHK, IGD, HJL, SID, SA, and HWL performed most of the experiments. KK performed statistical analyses and drafted the manuscript. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**
This retrospective study was approved by the Institutional Review Board of the experiments. KK performed statistical analyses and drafted the manuscript.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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