Clinicopathological features of early gastric cancer with duodenal invasion

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INTRODUCTION

Early gastric cancer (EGC), which is defined as a lesion confined to the mucosa or the submucosa, regardless of the presence of lymph node metastasis, has a good prognosis with surgical treatment. However, a small number of patients experience recurrence of EGC after resection. Sano et al. have reported that, in a study of 1475 patients with EGC treated with surgery, 1.4% experienced disease recurrence. The incidence of recurrence of EGC was shown to be significantly higher in the patient group with submucosal, node-positive and undifferentiated tumors. Furthermore, some rare cases show distant metastasis, such as in liver, lung, or bone, even though the depth of cancer invasion is confined to the mucosa. Sufficient resection margins are necessary to prevent recurrence of EGC, because inadequate resection that does not maintain surgical margins free of cancer can lead to disease recurrence. Duodenal invasion by gastric cancer is encountered in 11.9%-23.8% of all patients with cancer in the gastric antrum. However, EGC with duodenal invasion is rare amongst cases of advanced gastric cancer. There have been very few case reports of this type of cancer. Since the literature on this subject consists mostly of isolated case reports, the clinicopathological features of EGC with duodenal invasion remain unclear. We attempted to elucidate the clinicopathological features of patients with EGC extended to the duodenum, and discuss the possible mechanisms underlying this rare condition and practical surgical strategies.

PATIENTS AND CLINICOPATHOLOGICAL PRESENTATION

We reviewed 41 patients who underwent surgical resection for EGC with duodenal invasion between
Table 1 Clinicopathological data for 41 cases of EGC with duodenal invasion

| Authors       | Year (yr) | Gender | Age (yr) | Location | Type     | Size (mm) | Depth of invasion | Lymph node metastasis | Histological type | Distance of duodenal invasion (mm) | Preoperative diagnosis |
|---------------|-----------|--------|----------|----------|----------|-----------|-------------------|-----------------------|---------------------|-------------------------------|----------------------|
| Ishii         | 1975      | M      | 50       | Circ     | Depressed| 32 × 25   | m                 | -                     | Intestinal          | 7                             | ND                   |
| 47            | M         | Less   | 30 × 15  | Ele    | m         | 40 × 35   | m                 | Diffuse              | 5                   | Impossible            | ND                   |
| 1997          | 72        | M      | Ant-Less | 32 × 25 | m         | 35 × 21   | m                 | Diffuse              | 7                   | ND                             |
| 1997          | 61        | M      | Circ     | Mixed   | 30 × 15   | m         | -                 | Intestinal           | 2                   | ND                             |
| 1997          | 37        | M      | Ant-Gre  | 30 × 15 | m         | -         | -                 | -                     | -                   | -                             |
| 1995          | 73        | F      | Circ     | Elevated| 68 × 38   | m         | -                 | Intestinal           | 16                  | Possible             |
| 1996          | 76        | F      | Less     | Mixed   | 25 × 35   | m         | -                 | Intestinal           | 3                   | ND                             |
| 1996          | 2000      | ND     | LD       | Less    | 25 × 9    | m         | ND                | Diffuse              | 3                   | Impossible            |
| 1996          | 2000      | ND     | LD       | Mixed   | 30 × 13   | m         | ND                | Diffuse              | 10                  | Possible             |
| 1996          | 2000      | ND     | LD       | Elevated| 45 × 45   | m         | Intestinal        | 5                     | Impossible         |
| 1996          | 2000      | ND     | LD       | Superficial | 45 × 45    | m         | Intestinal        | 5                     | Impossible         |
| 1996          | 2000      | ND     | LD       | ND      | 30 × 15   | m         | -                 | Diffuse              | 3                   | ND                             |
| 1996          | 2000      | ND     | LD       | ND      | 30 × 15   | m         | -                 | Intestinal           | 7                   | ND                             |
| 1996          | 2000      | ND     | LD       | ND      | 120 × 102 | m         | -                 | Diffuse              | 8                   | ND                             |
| 1996          | 2000      | ND     | LD       | ND      | 55 × 24   | m         | +                 | Diffuse              | 3                   | ND                             |
| 1996          | 2000      | ND     | LD       | ND      | 5 × 50    | m         | +                 | Diffuse              | 3                   | ND                             |
| 1996          | 2000      | ND     | LD       | ND      | 40 × 38   | m         | +                 | Diffuse              | 3                   | ND                             |
| 1996          | 2000      | ND     | LD       | ND      | 80 × 65   | m         | +                 | Diffuse              | 2                   | ND                             |
| 1996          | 2000      | ND     | LD       | ND      | 68 × 37   | m         | -                 | Intestinal           | 20                  | Possible             |
| 1996          | 2000      | ND     | LD       | ND      | 30 × 15   | m         | -                 | Intestinal           | 12                  | Possible             |
| 2000          | 2000      | ND     | LD       | ND      | 30 × 12   | m         | -                 | Intestinal           | 1                   | Impossible            |
| 2000          | 2000      | ND     | LD       | ND      | 35 × 15   | m         | -                 | Intestinal           | 3                   | Impossible            |
| 2000          | 2000      | ND     | LD       | ND      | 85 × 80   | m         | -                 | Intestinal           | 38                  | Possible             |

F: Female; M: Male; ND: Not described; Circ: Circumferential; Less: Lesser curvature; Gre: Greater curvature; Ant: Anterior; Post: Posterior; Intestinal: Papillary and tubular adenocarcinomas; m: Mucosa; sm: Submucosa; Diffuse: Poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma.

EFFECT OF TUMOR INVASION DISTANCE

Table 2 shows the results of univariate analysis of the distance of duodenal invasion from the pyloric ring in relation to eight selected variables: age, gender, gross appearance, tumor size, depth of invasion, histological type, lymph node metastasis, and preoperative diagnosis.

1975 and 2008. Thirty-eight cases were identified in the available literature using a Medline search and Japan Centra Revuo Medicina by use of the keywords “early gastric cancer” and “duodenal invasion”. Additional articles were obtained from references within the papers identified by the searches. Three cases were patients treated in our hospital. Data on age, gender, tumor location, tumor type, tumor size, depth of invasion, lymph node metastasis, histological type, and preoperative diagnosis of duodenal invasion for each patient were obtained. The clinicopathological features of the 41 reported cases are listed in Table 1. Of the 41 patients analyzed, the mean age of patients was 63.2 years (range, 44-84 years), and there was a slight male predominance, with a male-to-female ratio of 16:13. The average diameter of tumors was 51.6 mm (range, 10-130 mm). The average distance of duodenal invasion was 7.9 mm (range, 1.0-38 mm). The case with the maximal distance of duodenal invasion was one of our cases. All patients had undergone curative tumor resection. There was no lymph node metastasis in cases in which the tumor was confined to the mucosa, whereas of the 25 patients in which the tumor had invaded the submucosa, four had lymph node metastasis. There was no lymphatic or venous invasion or distant metastasis.

The Mann-Whitney U test was used to assess correlations among the mean values for each group. The Pearson χ² test was applied to qualitative variables. All values are expressed as mean ± SD. P < 0.05 was considered significant.
of duodenal invasion. The distance of duodenal invasion by EGC was 4.5 mm for depressed type tumors, 11.4 mm for elevated type tumors, 5.3 mm for tumors with a diameter < 60 mm, and 14.8 mm for tumors with a diameter > 60 mm. These results revealed a positive correlation between more extensive duodenal invasion and elevated type tumors with a size > 60 mm.

In advanced gastric cancer, the rate of metastasis to the lymph nodes was high when the distance of duodenal invasion was > 10 mm[15]. By comparison, we found lymph node metastasis in only four cases of EGC, and in each of these, invasion had reached the submucosa and the distance of duodenal invasion was < 10 mm. This result suggests that there is a strong positive correlation between the incidence of lymph node metastasis and submucosal invasion, regardless of the distance of duodenal invasion.

### PREOPERATIVE DIAGNOSIS OF EGC WITH DUODENAL INVASION

Generally, preoperative diagnosis of malignant invasion to the duodenum is difficult[8-9], because spread of gastric cancer to the duodenum is often infiltrative and invades directly through the submucosal or subserosal layer[10-12]. Most of these cases are advanced gastric cancer[13]. In EGC, gastroenteroscopic examination is a reliable technique for identifying the area of cancer infiltration[14]. It is necessary to accurately define the tumor margin in order to determine the resection line. However, it is occasionally difficult to accurately determine the margin of the tumor in the vicinity of the pyloric ring by endoscopy[15-17]. This is because the pyloric ring is a narrow lumen, making it difficult to observe the tumor, and it can be deformed by ulcers, mucosal atrophy, and metaplastic changes. Moreover, pyloric movement caused by strong peristalsis and reflux of bile prevent the satisfactory observation of the lesion on the pyloric ring[18].

Duodenal invasion by EGC was diagnosed preoperatively by esophagogastroduodenoscopy (EGD) or barium meal examination in only eight cases (Table 1). The mean distance of duodenal invasion was 24.3 mm in the group in which a preoperative diagnosis was possible, whereas it was 3.6 mm in the group in which a preoperative diagnosis was not possible. There was a significant difference between the two groups (Table 2). In these cases, the distance of duodenal invasion was greater for elevated or mixed type tumors > 10 mm in diameter. Of the nine cases in which the distance of duodenal invasion was > 10 mm, there was only one case in which a preoperative diagnosis of duodenal invasion was not possible. By comparison, no case could be diagnosed preoperatively where the distance of duodenal invasion was < 10 mm. These results suggest that a preoperative diagnosis of duodenal invasion is related to tumor type and size. Kuwata et al[18] have reported that radiological diagnosis of duodenal invasion is more useful in the elevated type than in the depressed type of tumor, and that the compression method gives a more accurate diagnosis than the double-contrast method. Furthermore, despite extensive preoperative examination, determination of the tumor margin is often not possible in patients with a superficial spreading type of gastric cancer[19-22]. Thus, a satisfactorily precise diagnostic approach to assess the extent of tumor invasion has not been established.

### MECHANISMS OF DUODENAL INVASION BY EGC

The border between the stomach and the duodenum is not clinically obvious. Brunner's glands can be considered as the start of the duodenum for the clinicopathological assessment of duodenal invasion by gastric cancer[23]. When gastric cancer directly invades the mucosal layer, the Brunner's glands remain intact, even when surrounded by cancer cells[3]. For this reason, it is thought that Brunner's glands prevent direct cancer invasion from the gastric mucosa to the duodenal mucosa. In a study of 141 patients with gastric carcinoma with duodenal invasion, there was only one case of intramucosal carcinoma[3]. In the case of a lesion caused by an ulcer, it is speculated that destruction of the mucosal structure of the duodenum by an ulcer located in the pylorus allowed gastric cancer to invade the duodenum[24]. In another case in which endoscopic mucosal resection (EMR) had been performed previously for gastric cancer in the area of the pyloric ring, it is thought that destruction of the gastroduodenal mucosal microanatomy by EMR allowed carcinoma cells to invade the duodenal mucosa[25].

The superficial spreading type of EGC is characterized by wide and superficial spreading activity of the...
The indistinct tumor margins characteristic of superficial spreading tumors in EGC can lead to discrepancies in tumor area between surgical findings and pathological diagnosis. Kasakura et al. have reported that, despite extensive preoperative examination, determination of the tumor margin was not possible in 26 of 59 patients with superficial spreading cancer. Furthermore, the number of metastatic lymph nodes was greater than with the common tumor type. Accordingly, gastrectomy with extensive lymph node dissection with wide and sufficient surgical margin seems to be a most appropriate treatment for the superficial spreading type of EGC, including those cases with duodenal invasion. Based on these findings, treatment of superficial spreading type EGC, in which the distal margin is near the pyloric ring, should focus on attaining a satisfactory margin from the tumor.

| Characteristics                        | Superficial spreading type | Small-sized type | P value |
|----------------------------------------|---------------------------|-----------------|---------|
| Number of cases (%)                    | 10 (27.0)                 | 27 (73.0)       | 0.001   |
| Age (yr)                               | 68.7 ± 8.1                | 60.4 ± 12.2     | 0.048   |
| Gender                                 |                           |                 |         |
| Male                                   | 3                         | 13              |         |
| Female                                 | 7                         | 6               |         |
| Gross appearance                       |                           |                 |         |
| Depressed                              | 3                         | 12              | 0.281   |
| Elevated                               | 5                         | 8               |         |
| Depth of invasion                      |                           |                 | 0.614   |
| Mucosa                                 | 5                         | 11              |         |
| Submucosa                              | 5                         | 16              |         |
| Histological type                      |                           |                 | 0.847   |
| Intestinal                             | 7                         | 18              |         |
| Diffuse                                | 3                         | 9               |         |
| Lymph node metastasis                  |                           |                 | 0.773   |
| Negative                               | 9                         | 19              |         |
| Positive                               | 1                         | 3               |         |
| Length of duodenal invasion (mm)       | 16.3                      | 5.4             | 0.044   |
| Preoperative diagnosis of duodenal invasion |                       |                 | 0.003   |
| Possible                               | 5                         | 3               |         |
| Impossible                             | 0                         | 12              |         |

CONCLUSION

Gastric cancer located adjacent to the pyloric ring, even if cancer invasion is confined to the mucosal or submucosal layer, has the potential for duodenal invasion, and surgeons should be aware of this possibility. The present study indicates that EGC of the elevated type with a tumor size > 60 mm correlates positively with more extensive duodenal invasion. Our findings highlight the importance of identification of duodenal invasion by pre- and intra-operative closed observation, and reveal that the resection line in cases of duodenal invasion should be performed with a cancer-free margin.
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