

## Clinicopathological features of early gastric cancer with duodenal invasion

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### Abstract

The incidence of early gastric cancer (EGC) with duodenal invasion is extremely low, although advanced gastric cancer that arises in the antrum occasionally invades the duodenum. We investigated the clinicopathological features of EGC with duodenal invasion and provided strategies for clinical management. A Medline search was performed using the keyword "early gastric cancer" and "duodenal invasion". Additional articles were obtained from references within the papers identified by the Medline search. We revealed that EGC with duodenal invasion was of the superficial spreading type of tumor. Tumors > 60 mm in size invaded the duodenum more extensively, and the distance of duodenal invasion from the pyloric ring was further in the elevated type than in the depressed type of tumor. There was no significant difference between the length of duodenal invasion and the histological type of the tumor. Gastric cancer located adjacent to the pyloric ring, even if cancer invasion was confined to the mucosa or submucosa, was more likely to invade the duodenum. The present study reveals that the elevated type of EGC is associated with more extensive duodenal invasion when the tumor size is > 60 mm, thus highlighting the importance of identification of duodenal invasion in these cases. We also reveal that sufficient duodenal resection with a cancer-free distal surgical margin should be performed in cases of duodenal invasion.

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**Key words:** Duodenal invasion; Early gastric cancer; Gastrectomy; Superficial spreading type; Tumor differentiation

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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*<sup>[1]</sup> 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<sup>[2]</sup>. 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<sup>[3-5]</sup>. However, EGC with duodenal invasion is rare amongst cases of advanced gastric cancer<sup>[6]</sup>. 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	Age (yr)	Gender	Location	Type	Size (mm)	Depth of invasion	Lymph node metastasis	Histological type	Distance of duodenal invasion (mm)	Preoperative diagnosis
Ishii	1975	50	M	Circ	Depressed	32 × 25	m	-	Intestinal	7	ND
		47	M	Less	Elevated	30 × 15	sm	-	Intestinal	5	ND
Kuwayama <sup>[15]</sup>	1976	72	M	Ant-Less	Depressed	40 × 35	m	-	Diffuse	4	Impossible
Uchida <sup>[13]</sup>	1979	50	M	Circ	Depressed	32 × 25	m	-	Diffuse	7	ND
		61	M	ND	Mixed	35 × 21	sm	-	Intestinal	2	ND
		47	M	ND	Elevated	30 × 15	sm	-	Intestinal	5	ND
Kuwata <sup>[18]</sup>	1981	ND	ND	Less	Depressed	ND	sm	-	Diffuse	5	Impossible
		ND	ND	Gre	Elevated	ND	sm	-	Intestinal	6	Impossible
		ND	ND	Less	Elevated	ND	sm	-	Intestinal	2	Impossible
		ND	ND	Post	Mixed	ND	sm	-	Intestinal	1	Impossible
		ND	ND	Less	Mixed	30 × 15	sm	-	Intestinal	2	Impossible
		ND	ND	Less	Depressed	35 × 21	sm	-	Intestinal	1	Impossible
Kato <sup>[17]</sup>	1993	67	M	Less	Mixed	30 × 15	sm	-	Intestinal	5	Impossible
		63	F	Circ	Elevated	68 × 38	m	-	Intestinal	16	Possible
Nakazawa <sup>[9]</sup>	1994	58	M	Ant-Gre	Depressed	10 × 10	sm	-	Intestinal	3	Impossible
Boku <sup>[27]</sup>	1996	73	F	Circ	Elevated	70	sm	-	Intestinal	35	Possible
Ito <sup>[14]</sup>	1996	76	F	Less	Mixed	45 × 35	sm	-	Intestinal	25	Possible
Matsumoto <sup>[16]</sup>	2000	ND	ND	Less	Elevated	25 × 9	m	ND	Diffuse	3	Impossible
		61	M	Gre-Post	Elevated	25 × 10	sm	ND	Diffuse	10	Possible
		ND	ND	ND	Elevated	30 × 13	m	ND	Intestinal	3	Impossible
		ND	ND	ND	Elevated	65 × 23	m	ND	Intestinal	3	Impossible
Nogueira <sup>[12]</sup>	2000	ND	ND	ND	Superficial	45 × 45	sm	ND	Intestinal	5	Impossible
		ND	ND	ND	ND	ND	m	-	Diffuse	3	ND
		ND	ND	ND	ND	ND	sm	-	Intestinal	7	ND
Yasuda <sup>[23]</sup>	2000	59	F	Circ	Depressed	72 × 15	m	-	Diffuse	11	Impossible
Nakayama <sup>[37]</sup>	2001	59	F	Circ	Mixed	85 × 75	sm	-	Intestinal	38	Possible
Koufujii <sup>[29]</sup>	2003	77	M	Circ	Mixed	70 × 50	sm	-	Intestinal	2	ND
		65	M	Circ	Elevated	90 × 55	sm	-	Intestinal	2	ND
		66	F	Circ	Depressed	120 × 98	m	-	Diffuse	2	ND
		70	F	Circ	Depressed	130 × 102	m	-	Diffuse	8	ND
		58	M	Less	Depressed	55 × 24	sm	+	Diffuse	3	ND
		81	F	Gre	Depressed	30 × 20	sm	+	Intestinal	2	ND
		44	M	Less	Depressed	52 × 30	sm	-	Intestinal	5	ND
		57	F	Circ	Depressed	57 × 33	m	-	Diffuse	3	ND
		68	F	Gre	Depressed	40 × 38	sm	+	Diffuse	5	ND
		58	F	Circ	Depressed	80 × 65	sm	+	Diffuse	2	ND
Ishikawa <sup>[24]</sup>	2005	72	M	Less-Post	Elevated	68 × 37	m	-	Intestinal	20	Possible
Matsuda <sup>[6]</sup>	2007	79	F	Circ	Elevated	30 × 15	sm	-	Intestinal	12	Possible
Our case	2008	49	M	Less	Depressed	30 × 12	m	-	Intestinal	1	Impossible
		63	M	Less	Elevated	35 × 15	m	-	Intestinal	3	Impossible
		84	F	Circ	Elevated	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.

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  $\chi^2$  test was applied to qualitative variables. All values are expressed as mean  $\pm$  SD. *P* < 0.05 was considered significant.

## 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

**Table 2** Clinicopathological characteristics of EGC with duodenal invasion

Characteristics	No. of patients	Length of duodenal invasion (mm)	P value
Age (yr)			0.276
< 60	13	7.2	
> 60	16	11.7	
Gender			0.029
Male	16	5.3	
Female	13	15.2	
Gross appearance			0.046
Depressed	16	4.3	
Elevated	15	10.9	
Tumor size (mm)			0.049
< 60	23	5.3	
> 60	12	14.8	
Depth of invasion			0.836
Mucosa	16	8.3	
Submucosa	25	7.6	
Histological type			0.088
Intestinal	28	9.1	
Diffuse	13	5.1	
Lymph node metastasis			0.006
Negative	32	8.9	
Positive	4	3	
Preoperative diagnosis of duodenal invasion			0.001
Possible	8	24.3	
Impossible	16	3.6	

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<sup>[7]</sup>. 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<sup>[8,9]</sup>, because spread of gastric cancer to the duodenum is often infiltrative and invades directly through the submucosal or subserosal layer<sup>[10-12]</sup>. Most of these cases are advanced gastric cancer<sup>[13]</sup>. In EGC, gastroenteroscopic examination is a reliable technique for identifying the area of cancer infiltration<sup>[14]</sup>. 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<sup>[15-17]</sup>. 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<sup>[15]</sup>.

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.*<sup>[18]</sup> 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<sup>[19-22]</sup>. 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<sup>[3,13]</sup>. When gastric cancer directly invades the mucosal layer, the Brunner's glands remain intact, even when surrounded by cancer cells<sup>[3]</sup>. 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<sup>[3]</sup>. 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<sup>[25]</sup>. 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<sup>[24]</sup>.

The superficial spreading type of EGC is characterized by wide and superficial spreading activity of the

**Table 3** Clinicopathological characteristics of EGC with duodenal invasion for superficial spreading and small-sized types

Characteristics	Superficial spreading type	Small-sized type	P value
Number of cases (%)	10 (27.0)	27 (73.0)	
Age (yr)	68.7 ± 8.1	60.4 ± 11.2	0.031
Gender			0.048
Male	3	13	
Female	7	6	
Gross appearance			0.281
Depressed	3	12	
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	

cancer compared with a more limited depth of vertical invasion<sup>[25]</sup>. According to Yasui *et al*<sup>[26]</sup>, EGC is classified as a superficial spreading type of tumor when the product of the longest diameter of the tumor and the diameter perpendicular to it is > 25 cm<sup>2</sup>. Our study has revealed that gastric cancer with duodenal invasion is most often the superficial spreading type. Relations between the superficial spreading tumor and duodenal invasion of EGC may refer to multiple occurrence of cancer<sup>[27]</sup>. Previous authors have reported that the superficial spreading type accounted for 5.46%-11.0% of all EGC<sup>[19-22]</sup>, whereas it accounted for 27.0% of EGC cases with duodenal invasion (Table 3). Duodenal invasion was more extensive in superficial spreading cancer lesions (16.3 mm) than in small-sized cancer lesions (5.4 mm). In both of these groups, there was no significant difference in the gross appearance, depth of invasion, histological type, or the incidence of lymph node metastasis. Taken together, these results suggest that the superficial spreading type of gastric cancer adjacent to the pyloric ring may have the potential to invade the duodenum.

## STRATEGY FOR SURGICAL TREATMENT OF EGC WITH DUODENAL INVASION

The outcome of surgical treatment for EGC is generally considered to be satisfactory<sup>[1,28]</sup>. If EGC is treated with the appropriate surgical strategy, the outcome of treatment is excellent, even in patients with duodenal invasion<sup>[29]</sup>. However, Kakeji *et al*<sup>[30]</sup> analyzed 95 patients with duodenal invasion by gastric cancer, including advanced cases, and found that tumor spread into the duodenum was limited to within 2 cm in 76% of the patients and to within 3 cm in 81% of the patients. Therefore, for patients with advanced

gastric cancer with duodenal invasion, gastrectomy with resection of 3-4 cm of the duodenum and sufficient lymph node dissection is recommended.

Recent advances in endoscopic and laparoscopic surgery now offer a better quality of life to patients with EGC<sup>[31]</sup>. Although the 5-year survival rate for EGC is ≥ 90%<sup>[32]</sup>, complete surgical extirpation of gastric cancer with a sufficient resection margin from the tumor, and removal of metastatic lymph nodes, is necessary for good prognosis in all EGC cases, including those with duodenal invasion<sup>[1,29,31,32]</sup>. Previous reports have revealed that the prognosis of gastric cancer patients is affected mostly by depth of invasion, followed by lymph node metastasis and tumor location<sup>[33,34]</sup>. Tumor size in gastric cancer is a reliable prognostic factor that might be a suitable candidate for use in the staging system<sup>[35]</sup>. However, tumor size is not an independent prognostic factor<sup>[36]</sup>. Tumor diameter > 3.5 cm has been identified as an independent factor for the occurrence of lymph node metastasis<sup>[33]</sup>. Our review revealed that many cases of EGC with duodenal invasion had larger tumors, with an average diameter of 51.6 mm, than cases without duodenal invasion. Among the cases of EGC with duodenal invasion, there was no cancer recurrence because suitable surgical resection had been performed. It is necessary for surgeons to identify a suitable resection line for the distal margin for preoperative diagnosis of duodenal invasion. In cases in which there is further extension of the tumor toward the duodenum, it may be necessary to determine a resection line using intraoperative EGD<sup>[37]</sup>.

The indistinct tumor margins characteristic of superficial spreading tumors in EGC can lead to discrepancies in tumor area between surgical findings and pathological diagnosis<sup>[20,22]</sup>. Kasakura *et al*<sup>[19]</sup> 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<sup>[21]</sup>. 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.

## 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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