Original article

Histological differences in the invasion of advanced esophageal and gastric carcinoma beyond the esophago-gastric junction

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Abstract

Background. The esophago-gastric junction (EGJ) has several unique anatomical and histological features. We investigated the histological differences between esophageal squamous cell carcinoma with invasion of the gastric wall (esophageal group of patients) and gastric carcinoma with invasion of the esophageal wall (gastric group of patients).

Methods. Thirty-six patients in the esophageal group and 83 patients in the gastric group were histologically examined in regard to the mode of invasion. The pattern of tumor invasion beyond the EGJ was classified as continuous or discontinuous.

Results. The discontinuous pattern was more frequently seen in the esophageal group than in the gastric group. In the gastric group, however, the distance invaded beyond the EGJ was significantly greater in tumors with the discontinuous pattern than in those with the continuous pattern ($P < 0.01$). Gastric mucosal invasion at the EGJ was not seen in 36% of the esophageal group, whereas tumor infiltration into the esophageal mucosal layer at the tip beyond the EGJ was found in 60% of the gastric group. The incidence of invasion deeper than the muscularis propria in the gastric and esophageal groups was 18% and 58%, respectively ($P < 0.0001$).

Conclusion. The histological characteristics of esophageal or gastric carcinoma beyond the EGJ should be taken into consideration in diagnosis and surgical procedures.

Key words Gastric cancer · Esophageal cancer · Invasion · Esophago-gastric junction

Introduction

The esophagus is situated in the mediastinum and the stomach in the abdomen; the histologically squamous epithelium of the esophagus gives way to the columnar epithelium of the stomach at the esophago-gastric junction (EGJ). Therefore, the EGJ has several unique ana-

tomical features. Some squamous cell carcinomas arising from the lower esophagus invade the gastric wall, and, conversely, some gastric adenocarcinomas invade the esophageal wall. It is important to examine the characteristics of invasion of these tumors, because the surgical approach depends on the extent of tumor invasion [1–4].

The purpose of the present study was to elucidate the histological difference between esophageal squamous cell carcinoma with invasion of the gastric wall and gastric adenocarcinoma with invasion of the esophageal wall.

Patients and methods

Thirty-six patients with advanced squamous cell carcinoma of the esophagus which had invaded the stomach (esophageal group) and 83 patients with advanced adenocarcinoma of the stomach which had invaded the esophagus (gastric group) were enrolled in this study. We defined advanced carcinomas as tumors deeper than the submucosa. All patients had undergone resection at the First Department of Surgery, Kagoshima University Hospital, between 1980 and 1996. In the 36 patients in the esophageal group, the right thoraco-abdominal approach was used in 18, the left thoraco-abdominal approach in 13, the transhiatal approach in 4, and the abdominal approach in 1. In the 83 patients in the gastric group, the left thoraco-abdominal approach was used in 53, and the abdominal approach in 30. None of the patients had received radiation therapy or chemotherapy. Early-stage carcinomas were excluded, because the pattern of invasion was confined to the mucosa or submucosa.

The resected specimens were treated in a standard fashion throughout the period of the study. To this end, they were fixed on a board after being stretched as far as possible, and the extent of tumor infiltration beyond the

Fig. 1. **a** Gastric carcinoma with continuous spreading pattern. Cancer cells have infiltrated massively at the tip of the esophago-gastric junction (EGJ). **b** Esophageal carcinoma

with discontinuous spreading pattern. Scattered cancer cells have infiltrated at the tip (*arrow heads*, scattered cancer cells). **a,b** Hematoxylin and eosin staining, $\times 40$

EGJ, as well as the distance from the center of the tumor to the EGJ, were measured. Where the EGJ had been destroyed by tumor, the extent of invasion beyond the EGJ was estimated on the basis of the assumed location of the EGJ on the resected specimens. The specimens were then fixed in 10% formalin, cut serially into 4-mm-thick slices, and embedded in paraffin for sectioning into 4- μ m-thick slices, which were stained with hematoxylin and eosin. The depth of tumor invasion, lymph node metastasis, vessel invasion, and histological type were examined by microscopy. The tumor depth at the tip beyond the EGJ and the spreading pattern were also examined. The spreading pattern of the tumor beyond the EGJ was classified into two types; a continuous pattern in which cancer cells infiltrated massively at the tip, and a discontinuous pattern in which scattered cancer cells infiltrated at the tip of the EGJ (Fig. 1).

Pathological data were evaluated in accordance with the tumor-node-metastasis classification of the International Union Against Cancer [5]. All data were statistically evaluated using the χ^2 test and Student's *t*-test. A *P* value of less than 0.05 was considered to be significant.

Results

The greatest average ($\pm$ SD) tumor diameters in the gastric and esophageal groups were 66 ± 5 mm and 69 ± 26 mm, respectively. The incidence of T2 tumor in the gastric group was significantly higher than that in the esophageal group. Age, sex, lymph node metastasis, distant metastasis, and vessel invasion did not differ between the two groups (Table 1). The histologic type in the esophageal group was well-differentiated squamous

cell carcinoma in 12 lesions, moderately differentiated squamous cell carcinoma in 18 lesions, and poorly differentiated squamous cell carcinoma in 6 lesions. In the gastric group, all lesions were classified histologically into two types: differentiated (papillary, tubular) and undifferentiated adenocarcinoma (poorly differentiated, signet-ring cell, mucinous, miscellaneous). Fifty-two lesions were differentiated adenocarcinomas and 31 were undifferentiated adenocarcinomas.

The mean distance between the center of the tumor and the EGJ was 13 ± 14 mm in the gastric group, and 16 ± 15 mm in the esophageal group. The mean distance between the EGJ and the tumor margin beyond the EGJ was 20 ± 13 mm in the gastric group and 20 ± 14 mm in the esophageal group. Significant differences between the two groups regarding the distance between the tumor center and the EGJ, or the distance between the EGJ and tumor margin, were thus not found.

When the pattern of tumor invasion beyond the EGJ was examined, 7 (8.4%) of the 83 patients in the gastric group and 9 (25.0%) of the 36 patients in the esophageal group showed a discontinuous pattern. A significant difference was found between the two groups in this respect ($P < 0.05$). With regard to the relationship between spreading pattern and histology in gastric group, 48 of the 52 patients with differentiated adenocarcinoma showed the continuous pattern and the remaining 4 patients showed the discontinuous pattern. In undifferentiated adenocarcinomas, the number of patients with the continuous and discontinuous patterns was 28 and 3, respectively. No significant relationship was found between the spreading pattern of tumor invasion and histologic type in the gastric group. Similarly, the spreading pattern of tumor invasion was not related to the histological type in esophageal carcinoma.

Table 1. Clinicopathological features in 119 patients

	Gastric group (<i>n</i> = 83)	Esophageal group (<i>n</i> = 36)	<i>P</i>
Age (years), mean $\pm$ SD	66 $\pm$ 11	61 $\pm$ 8	NS
Sex			NS
Male/Female	68/15	30/6	
Major axis (mm), mean $\pm$ SD	66 $\pm$ 5	69 $\pm$ 26	NS
Tumor depth (pT)			<0.0001
pT2	53	3	
pT3	24	23	
pT4	6	10	
Lymph node metastases (pN)			NS
pN0	20	11	
pT1	63	25	
Distant metastases (pM)			NS
pM0	48	22	
pM1	35	14	
Vessel invasion			NS
Negative	10	9	
Positive	73	27	

NS, Not significant

Table 2. Spreading pattern and distance invaded beyond the EGJ

	Gastric group (<i>n</i> = 83)	Esophageal group (<i>n</i> = 36)	<i>P</i>
Spreading pattern			
Continuous	76 (91.6%)	27 (75%)	<0.05
Discontinuous	7 (8.4%)	9 (25%)	
Distance invaded beyond the EGJ (mm) ^a			
Continuous spreading	22 (15)	17 (13)	NS
Discontinuous spreading	42 (39)*	25 (14)	

* $P < 0.01$ versus continuous spreading in gastric group

EGJ, Esophago-gastric junction

^a Values are medians (SD)

The distance of tumor invasion beyond the EGJ was not significantly different in the two groups. In the gastric group, however, the tumor invasion distance from the EGJ was significantly greater in tumors with a discontinuous spreading pattern than in those with a continuous spreading pattern (42 ± 39 vs 22 ± 15 mm) ($P < 0.01$) (Table 2).

We assessed whether or not the tumor beyond the EGJ involved the mucosal layer. Mucosal invasion was found in 97.6% of the gastric group (81/83 patients), and in 63.9% of the esophageal group (23/36 patients). The rate was significantly higher in the gastric group than in the esophageal group ($P < 0.0001$). The layer of tumor invasion at the tip beyond the EGJ was examined. Although the layer of tumor invasion at the tip penetrated into the mucosa in 60.2% of patients in the gastric group (50/83 patients), none of the patients in the esophageal group had mucosal invasion at the tip. On the other

hand, the percentage of tumors with invasion deeper than the muscularis propria at the tip was 18.1% in the gastric group and 58.3% in the esophageal group ($P < 0.0001$) (Table 3).

Discussion

In Asian countries, including Japan, the vast majority of esophageal neoplasms are, histologically, squamous cell carcinomas, in contrast to the high incidence of adenocarcinoma of the esophagus in Western countries [6,7]. The area between the lower esophagus and stomach is special both anatomically and histologically. Clinically, in carcinoma of the esophagus with gastric wall invasion, the resected area of the stomach is problematic, because reconstruction is usually performed using a gastric tube. When gastric cancer invades the esophageal

Table 3. Depth of invasion of the tumor at the place where the tumor extended beyond the EGJ

	Gastric group (<i>n</i> = 83)	Esophageal group (<i>n</i> = 36)	<i>P</i>
Mucosal invasion of tumor at the EGJ			<0.0001
Positive	81	23	
Negative	2	13	
Depth of invasion of tumor at the tip ^a			<0.0001
Mucosa	50	0	
Submucosa	18	15	
Muscularis propria or deeper	15	21	

^aTip refers to tip beyond the EGJ

Fig. 2. Schema of tumor invasion and its length. Gastric carcinoma invades the mucosal and/or submucosal layer of the esophagus. However, esophageal cancer invades a layer deeper than the submucosa. In gastric carcinoma, the distance of tumor invasion was longer in the discontinuous than in the continuous spreading pattern. *Striped areas*, muscularis propria; *black ellipses*, cancer cells

wall, it is difficult to choose appropriate surgical methods; namely, whether to take the abdominal or thoracoabdominal approach depends on the distance that the tumor has penetrated beyond the EGJ [8–11]. In this context, it is necessary to examine the histological features of carcinomas of the esophagus or stomach with invasion beyond the EGJ.

In the present study, we paid special attention to the spreading pattern of tumor invasion beyond the EGJ. We found notable differences in the spreading pattern between esophageal carcinoma with gastric invasion and gastric carcinoma with esophageal invasion. First, the discontinuous pattern was more frequently seen in the esophageal group than in the gastric group. However, the distance of tumor invasion beyond the EGJ was not significantly different between patients with a continuous pattern or a discontinuous pattern in the esophageal group. On the other hand, in the gastric group, the distance of tumor invasion beyond the EGJ was significantly greater in tumors with the discontinuous pattern than in those with the continuous pattern. Secondly, tumor involvement of the mucosal layer beyond the EGJ was found in all patients, with two excep-

tions in the gastric group. Furthermore, tumor infiltration at the tip beyond the EGJ was most frequently found in the mucosal layer in the gastric group. In the esophageal group, cancer cells at the tip beyond the EGJ mainly infiltrated into a layer deeper than the submucosa (Fig. 2).

Kuwano et al. [12] reported that the pattern of the gastric involvement of esophageal squamous cell carcinoma could be grouped into four types; gastric involvement via metastases in the perigastric lymph node, gastric intramural metastasis, direct invasion of the gastric wall by esophageal squamous cell carcinoma, and intraepithelial spread of esophageal cancer to the gastric epithelium. In their study, only 3 of 32 patients had intraepithelial spread of esophageal cancer to the gastric epithelium. Esophageal cancer almost never invaded the gastric mucosa, but gastric cancer readily invaded the esophageal epithelium. This seems to be related to differences in the lymphatic system between the esophagus and stomach. We examined the intramural lymphatic system draining the distal esophagus and gastric cardia, using a dye injection procedure [13]. When the dye was injected into the esophageal wall

within 2 cm superior to the EGJ, a few lymphatics were delineated, not only in the esophageal wall but also in the gastric wall. Many descending lymphatics from the distal esophagus extended obliquely downward and drained into the serosa through the muscle layer, and entered the lymphatics of the cardia. When the dye was injected into the wall of the cardia within 2 cm inferior to the EGJ, lymphatics were delineated not only in the gastric wall but also in the esophageal wall. Mucosal lymphatics extending from the esophageal to the gastric wall were few in number compared with those extending from the gastric to the esophageal wall. These results are in accord with the clinical findings of the present study.

In particular, in deciding on the appropriate surgical approach, it is important to assess esophageal invasion by gastric cancer as precisely as possible during preoperative diagnosis. Endoscopic ultrasonography is a useful tool to estimate esophageal invasion [14–16]. However, when only a few scattered cancer cells infiltrated only one or two layers (the mucosa or submucosa, or both), it was difficult to diagnose the extent of esophageal invasion. Furthermore, because the spreading pattern of tumor invasion was not related to the histologic type, it was difficult to judge the spreading pattern by preoperative histological diagnosis using biopsy specimens. Histological examination using frozen sections obtained during surgery is essential for deciding the operative safety margin.

Here, we have demonstrated differences in spreading patterns and in layers of tumor infiltration between esophageal carcinoma with gastric invasion and gastric carcinoma with esophageal invasion. It may be clinically useful to understand the characteristic invasion patterns in the diagnosis of and surgical approaches to such tumors.

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