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A Proposed New Clinical Classification of Metastatic Gastric Cancer: Pyloric and Antral Gastric Cancer

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Background: We aimed to classify metastatic pyloric/antral gastric cancer in terms of macroscopic morphology and metastatic form.

Methods: Thirty-eight patients with pyloric/antral gastric cancer were included in the study. Patients were classified according to a combination of Borrmann classification type and metastatic type, and the clinicopathological characteristics of each group were compared.

Result: Of the 38 patients, 33 (type II: 9 and type III: 24) (87%) had ulcerative gastric cancer. Ulcerative gastric cancer was classified into four groups: lymphatic only group (L+H−P−), lymphatic + hematogenous group (L+H+P−), disseminated ± lymphatic group (L±H−P+), and lymphatic + hematogenous + disseminated group (L+H+P+). In the L+H−P− group, all patients had bulky lymph nodes and serum levels of both carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were high; the condition of patients was good, and the therapeutic response was good. In the L+H+P− group, metastases other than liver metastases were rare, and serum CEA levels were high. In the L±H−P+ group, the predominant histological type was signet ring cell carcinoma; both serum CEA and CA19-9 levels were low. Patients in the L+H+P+ group had higher serum CA19-9 levels and were more prone to hematogenous metastasis to various organs; these patients had worse patient status and lower treatment response. Gastric cancer other than ulcerative type was only detected in five patients (type V: 3, type IV: 1, type I: 1).

Conclusion: Classification by a combination of macroscopic and metastatic form in pyloric/antral metastatic gastric cancer might be useful for diagnosis and treatment.

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Key words: clinical classification, metastatic gastric cancer, pyloric and antral gastric cancer

Introduction

Various classification systems for gastric cancer have been developed. For example, the Borrmann classification system categorizes gastric cancer on the basis of macroscopic findings, while Lauren's classification system, the histological classification of the World Health Organization (WHO) and the Japanese pathological classification system classifies gastric cancer on the basis of histological findings[1–4]. In addition, the Tumor-Node-Metastasis (TNM) classification system for gastric cancer correlates well with prognosis[5]. Recently, classification of gastric cancer at the molecular level has also been reported[6]. However, there are few classifications of gastric cancer that take distant metastasis into account. Yoshida et al.[7] divided stage IV gastric cancer into four categories based on whether the tumor could be technically resected; however, no studies have classified metastatic gastric cancer in terms of biological behavior. Riihimäki et al.[8] investigated the characteristics of metastases from 7,559 patients with metastatic gastric cancer but did not classify the tumors. Therefore, the development of a new classification system for metastatic gastric cancer may provide an ap-

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proach to link molecular abnormalities to various metastatic forms of gastric cancer and aid in treatment development.

Gastric mucosa, which is the origin of gastric cancer, has a pyloric gland area, a gastric gland area, and a cardiac gland area depending on the location. Therefore, gastric cancer may have different properties depending on its localization. In fact, clinical pathological differences in gastric cancer because of differences in localization have been reported[9,10].

The Borrmann classification of gastric cancer, which is easily determined by endoscopy, is widely accepted by clinicians and research physicians. This system is considered an effective classification and the classification type (type I-V) represents a valuable clinicopathological feature of gastric cancer[11–13]. The metastatic forms of gastric cancer are generally hematogenous, lymphoid, or peritoneal dissemination, as represented by the TNM staging system[5]. Therefore, in this study, we aimed to classify metastatic gastric cancer in terms of localization, macroscopic morphology, and metastatic form. Here, we report the results of classification of pyloric and antral gastric cancer using this new classification system.

Materials and Methods

In this retrospective study, 100 consecutive patients diagnosed with metastatic gastric adenocarcinoma corresponding to stage cIVB according to TNM classification from April 2012 to December 2019 at Nippon Medical School were enrolled. From this initial group of 100 patients, we extracted cases in which the center of the tumor was located in the pylorus or antrum as detected by endoscopy.

The Borrmann type (type I-V) was determined by endoscopic findings. We investigated the presence of lymphatic metastases (L) including intra-regional and extra-regional metastases in the TNM staging system, hematogenous metastases (H), and peritoneal dissemination metastases (P) by computed tomography and/or ultrasonography and/or positron emission tomography imaging. We then classified the metastatic pyloric and antral gastric cancer according to the Borrmann type and the combination of the three metastatic forms (L, H, and P). We indicated metastases as + and no metastases as −; for example, L+H+P− indicated a case with lymphatic metastases and hematogenous metastases but no peritoneal dissemination.

We investigated whether there were differences in clinicopathological features such as age, sex, presence or absence of bulky lymph nodes, hematogenous metastatic organs, histology, serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) positive rate, best supportive care (BSC) only rate, and survival time of chemotherapy-treated cases between each classified group. This clinical information was obtained from the hospital records. In metastasis to lymph nodes inside and outside the region, we diagnosed lymphoadenopathy of >30 mm as bulky lymphoadenopathy. The gastric carcinomas were histologically classified using the Japanese pathological classification[4]. Because all cases were evaluated with tissue biopsy specimens, poorly differentiated adenocarcinoma (por) was not differentiated into solid type (por1) and non-solid type (por2). Positive serum CEA was defined as > 5.0 ng/mL and positive CA19-9 level was defined as > 37.0 U/mL. We determined that a patient was positive for CEA and CA19-9 if the values were above the threshold at least once during the observation period. Survival time was defined as the period from the start of treatment to death. This study was conducted in accordance with the provisions of the Helsinki Declaration and was approved by the Ethics Committee for Human Research of Nippon Medical School (No. 30-02-1077).

Statistical Analysis

Categorical variables were evaluated by the Pearson's χ^2 test and Fisher's exact test. Survival curves were created by the Kaplan-Meier method, and the log rank test was used as the significance test for each county. A P value < 0.05 was considered statistically significant. The clinical data related to the patients were input into the commercially available SPSS 22.0 software, which was used for all statistical analyses.

Results

From April 2012 to December 2019, 100 consecutive patients with metastatic gastric adenocarcinoma were enrolled in this study. Among the 100 patients, 38 had cancers in the pylorus or antrum, 42 had cancers in the corpus or fundus, 7 had cancers in the cardia, and 13 had cancers that spanned the entire area (**Fig. 1a**). In the Borrmann classification of the pyloric and antral cancers, 24 (63.2%) cases were type III, 9 (23.7%) cases were type II, 3 (7.9%) cases were type V, and only 1 case each was type I and type IV (2.6%) (**Fig. 1b**).

Type II and III Patients (Ulcerative Type)

Because type II cases (n=9) and type III cases (n=24) showed similar clinicopathological features (data not shown), we combined these together as the ulcerative

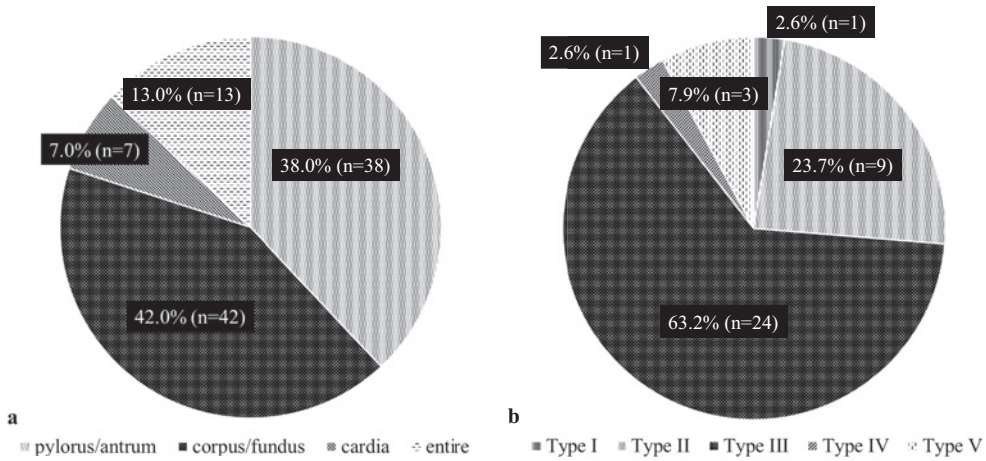

Fig. 1 Localization of total gastric cancer and the Borrmann classification of pyloric and antral gastric cancer
a: Localization of the gastric cancer in 100 patients with metastatic gastric adenocarcinoma.
b: Borrmann classification of pyloric and antral gastric cancer in 38 patients with metastatic gastric adenocarcinoma.

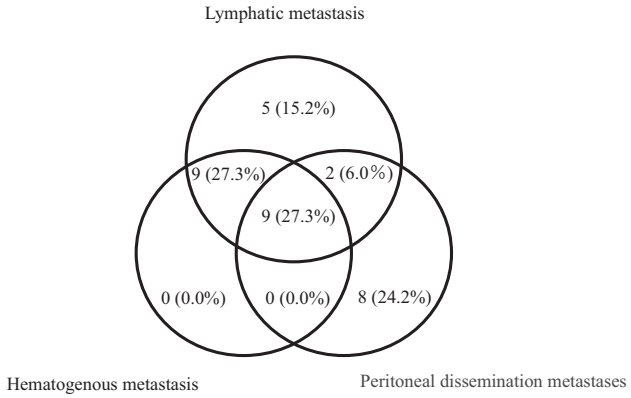

Fig. 2 Distribution of pyloric and antral ulcerative gastric cancers by metastatic type. Data are shown as n (%).

type category. We evaluated these patients according to metastatic form (L, H, P) as described in Methods and classified the patients in the following categories:

L+H−P−, n=5 (15.2%); L+H+P−, n=9 (27.3%); L−H−P+, n=8 (24.2%); L+H−P+: n=2 (6.0%); and L+H+P+: n=9 (27.3%) (**Fig. 2**). No patients were categorized as L−H+P− or L−H+P+.

Because lymphadenopathy in the L+H−P+ group was small and few, we considered that it would not be problematic to analyze the L−H−P+ and L+H−P+ groups together. Finally, we classified the patients with pyloric and antral ulcerative gastric cancer into L+H−P−, L+H+P−, L±H−P+, and L+H+P+ groups.

A significant relationship was found between the four groups and the presence or absence of bulky lymph nodes (p=0.012) (**Table 1**). All patients in the L+H−P− group showed bulky lymph node metastasis inside the region. The L+H+P+ group had significantly more hematogenous metastases outside the liver than the L+H+P− group (p=0.042).

There was more signet-ring cell carcinoma in the L±H−P+ group than in the other groups (**Table 2**). Serum CEA and CA19-9 were frequently positive in the L+H−P− group, while positive serum CEA but not CA19-9 was observed in the L+H+P− group. Both CEA and CA19-9 tended to be negative in the L±H−P+ group, and CA19-9 was positive but CEA was not in the L+H+P+ group. In addition, there was a significant relationship between the four groups and the rate at which treatment became BSC only; the BSC rate was 66.7% for the L+H+P+ group, 50.0% for the L±H−P+ group, 11.1% for the L+H+P− group, and 0.0% for the L+H−P− group (p=0.013).

The survival time of patients who received chemotherapy tended to be better in the L+H−P− group (**Fig. 3**). However, the sample size was small and there was no significant difference among groups.

Type V Patients

The endoscopic morphologies of all type V cases were submucosal infiltration-like with ulceration.

The metastatic forms of the three patients with type V were L+H+P− (n=2) and L+H−P+ (n=1). One L+H+P− case was a 74-year-old woman whose histopathology was poorly differentiated adenocarcinoma (por) > moderately differentiated tubular adenocarcinoma (tub2); bulky lymph nodes metastases to the para-aorta and mediasti-

Table 1 Clinical characteristics of patients with pyloric and antral ulcerative gastric cancer according to metastatic forms

Characteristics	Metastatic forms n (%)				
	L+H–P– n=5	L+H+P– n=9	L±H–P+ n=10	L+H+P+ n=9	*p* value
Male	4 (80.0)	4 (44.4)	9 (90.0)	6 (66.7)	0.196
Female	1 (20.0)	5 (55.6)	1 (10.0)	3 (33.3)	
Age, mean (range)	72 (61–80)	74 (65–84)	71 (57–89)	71 (52–88)	0.880
Morphology of the primary lesion					0.862
Type II	3 (60.0)	6 (66.7)	2 (20.0)	2 (22.2)	
Type III	2 (40.0)	3 (33.3)	8 (80.0)	7 (77.8)	
Bulky lymphoadenopathy					0.012
+	5 (100.0)	4 (44.4)	2 (20.0)	3 (33.3)	
–	0 (0.0)	5 (55.6)	8 (80.0)	6 (66.7)	
Hematogenous metastatic organs					
Liver	-	9 (100.0)	-	7 (77.8)	0.230
Organs other than the liver	-	1 (11.1)	-	5 (55.6)	0.042

L: lymphatic metastases, H: hematogenous metastases, P: peritoneal dissemination.

Table 2 Clinicopathological characteristics of patients with pyloric and antral ulcerative gastric cancer according to metastatic forms

Characteristics	Metastatic forms n (%)				
	L+H–P– n=5	L+H+P– n=9	L±H–P+ n=10	L+H+P+ n=9	*p* value
Histopathological type					
tub1	1 (20.0)	4 (44.4)	2 (20.0)	1 (11.1)	0.460
tub2	3 (60.0)	6 (66.7)	4 (40.0)	3 (33.3)	0.490
por	2 (40.0)	3 (33.3)	9 (90.0)	6 (66.7)	0.058
sig	1 (20.0)	0 (0.0)	8 (80.0)	2 (22.2)	0.001
muc	0 (0.0)	1 (11.1)	3 (30.0)	0 (0.0)	0.188
Serum tumor marker					
CEA positive	4 (80.0)	9 (100.0)	2 (20.0)	3 (33.3)	0.001
CA19-9 positive	4 (80.0)	2 (22.0)	3 (30.0)	8 (88.9)	0.011
Therapy					
BSC	0 (0.0)	1 (11.1)	5 (50.0)	6 (66.7)	0.013
Chemotherapy	5 (100.0)	8 (88.9)	5 (50.0)	3 (33.3)	

L: lymphatic metastases, H: hematogenous metastases, P: peritoneal dissemination, tub1: well-differentiated tubular adenocarcinoma, tub2: moderately differentiated tubular adenocarcinoma, por: poorly differentiated adenocarcinoma, sig: signet-ring cell carcinoma, muc: mucinous adenocarcinoma, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, BSC: best supportive care.

num as well as lung and bone metastases were also found. The serum tumor markers were CEA-negative and CA19-9-positive, and treatment was BSC only because of the patient's poor general condition.

The other L+H+P– case was a 64-year-old man whose histopathology was por; the patient showed intraregional lymph node metastasis and liver metastasis. Serum tumor markers were CEA-positive and CA19-9-positive. The patient received chemotherapy and the survival time was 14 months.

The L+H–P+ case was a 76-year-old man with bulky intraregional lymph node metastasis and peritoneal dissemination. The histopathology of this case was por and sig, and both tumor markers were positive. The patient was treated with chemotherapy and had a survival time of 5.7 months (**Table 3**).

Type IV Patient

The type IV case was a 45-year-old man with L+H–P+ metastatic form. There was no bulky lymph node metastasis; the histopathology was por and serum CEA and

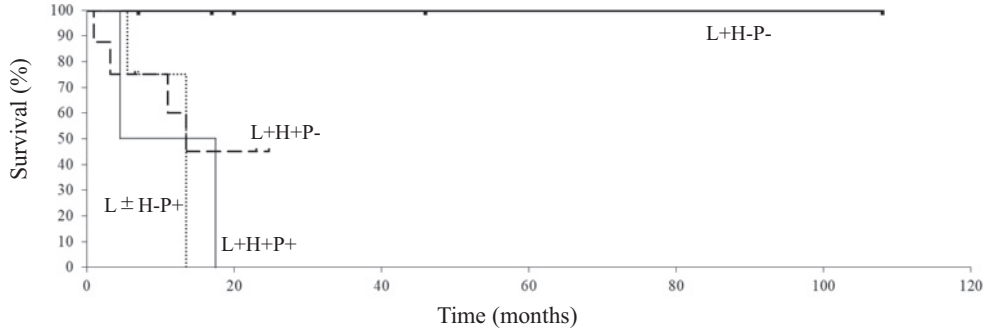

Fig. 3 Kaplan-Meier curve for overall survival of patients with pyloric and antral ulcerative gastric cancer who received chemotherapy stratified according to metastatic forms. No significant differences were found in overall survival among the groups (L+H–P– vs. L+H+P–, P = 0.077; L+H+P– vs. L±H–P+, P = 0.78; L±H–P+ vs. L+H+P+, P = 0.12). The survival time of chemotherapy patients tended to be better in the L+H–P– group compared with the other groups.

Table 3 Clinicopathological characteristics of patients with pyloric and antral gastric cancer according to Borrmann type (I, IV, V) and metastatic forms

	Type V		Type IV	Type I
	L+H+P– n=2	L+H–P+ n=1	L+H–P+ n=1	L+H–P+ n=1
Male	1 (50.0)	1 (100.0)	1 (100.0)	0 (0.0)
Female	1 (50.0)	0 (0.0)	0 (0.0)	1 (100.0)
Age, mean (range)	69 (64–74)	76	45	65
Bulky lymphoadenopathy				
+	1 (50.0)	1 (100.0)	0 (0.0)	0 (0.0)
–	1 (50.0)	0 (0.0)	1 (100.0)	1 (100.0)
Hematogenous metastatic organs				
Liver	2 (100.0)	-	-	-
Organs other than the liver	1 (50.0)	-	-	-
Histopathological type				
tub1	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
tub2	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
por	2 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)
sig	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
muc	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CEA positive	1 (50.0)	1 (100.0)	1 (100.0)	1 (100.0)
CA19-9 positive	2 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
Therapy				
BSC	1 (50.0)	0 (0.0)	1 (100.0)	0 (0.0)
Chemotherapy	1 (50.0)	1 (100.0)	0 (0.0)	1 (100.0)
OS of chemotherapy case (months)	14	5.7	-	8.5

Data are shown as n (%). L: lymphatic metastases, H: hematogenous metastases, P: peritoneal dissemination, tub1: well-differentiated tubular adenocarcinoma, tub2: moderately differentiated tubular adenocarcinoma, por: poorly differentiated adenocarcinoma, sig: signet-ring cell carcinoma, muc: mucinous adenocarcinoma, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, BSC: best supportive care, OS: overall survival.

CA19-9 were both positive. The patient's condition was poor, and treatment was BSC only (**Table 3**).

Type I Patient

The type I case was a 65-year-old woman. The lesion was a 20 mm ridge type, but the base of the ridge was covered with normal mucosa like a submucosal tumor. The histopathology was well-differentiated tubular adenocarcinoma (tub1) and the metastatic form was

L+H−P+, with intraregional lymphadenopathy, paraaortic lymphadenopathy, and marked cancerous ascites. Both serum CEA and CA19-9 were positive; the patient received chemotherapy and had a survival time of 8.5 months (**Table 3**).

Discussion

In this report, we aimed to classify pyloric and antral gastric cancers according to macroscopic morphology and metastatic form. With this classification method, pyloric and antral gastric cancer can be theoretically divided into 35 groups, but in this study, the 38 patients were divided into 8 groups. In this study, no case had metastatic forms of L−H+P− and L−H+P+. The result that no patients showed L−H+P+ metastatic forms was similar to the report by Riihimäki et al.[8] that showed that the combination of hematogenous metastasis and peritoneal metastasis was rare in 7,559 patients with metastatic gastric cancer. Of particular interest, the ulcerative type, which accounts for about 90% of pyloric and antral gastric cancer, was classified into four groups: L+H−P−, L+H+P−, L±H−P+, and L+H+P+. We believe that the new classification method might be useful, as each of these four groups had different clinical pathological characteristics and our analyses suggested that prognosis and therapeutic effects might differ between groups.

Of the four groups, the most interesting group is the L+H−P− group, which showed metastases only to the lymph nodes inside and outside the region. This group, which accounted for about 15% of ulcerative type pyloric and antral cancers and 5% of the total gastric cancer cases, had bulky lymph node metastasis of 30 mm or more inside the region in all cases. The histopathological types of this group were mostly tub2 and por, and both serum CEA and CA19-9 levels in this group were often elevated. Patients in this group were in good general condition and showed positive results with chemotherapy, with a relatively good prognosis. The treatment strategy of this group might involve chemotherapy as the center of treatment; in some cases, conversion surgery[14], which is defined as the use of chemotherapy followed by surgical resection with curative intent of a tumor that was previously considered unresectable, might be considered after chemotherapy.

In the L+H+P− group, which accounts for about 27% of the ulcerative type pyloric and antral cancers and 9% of all gastric cancers, all cases had liver metastases but few hematogenous metastases to other organs. Most of the histological types in this group were tub2 and tub1, and serum CEA levels in this group were high. The general condition of the patients was good, and the survival time with chemotherapy was approximately 1 year, which was approximately the current median survival time[15–17]. As a treatment strategy for this group, if the metastases are limited to intraregional lymph nodes and resectable liver metastases, radical surgery as well as chemotherapy might be considered.

In the L±H−P+ group, which accounts for approximately 30% of ulcerative pyloric and antral cancers and approximately 10% of total gastric cancers, the histological types were por and sig, and both serum CEA and CA 19-9 levels were often negative. The increased frequency of sig type in this group of patients, in which peritoneal dissemination was the main metastatic process, was similar to the report by Riihimäki et al., who found that the diffuse type (signet ring) of the Lauren's classification had more peritoneal dissemination than the intestinal type[8]. One review reported that 40% of patients with stage IV gastric cancer were positive for CEA and CA19-9[18], but interestingly, the positivity rate in this group was low, at about 20%. In fact, a few reports showed that both CEA and CA19-9 are associated with peritoneal dissemination compared with hematogenous metastasis and lymph node metastasis[18]. The general condition of the patients in this group was rather poor, and half of the cases were treated with BSC only. The median survival time of patients treated with chemotherapy in this group was approximately 1 year. The current results for this group were inadequate, and the combination of systemic and intraperitoneal chemotherapy, as studied in the Phoenix study[19], might be useful in the future.

In the L+H+P+ group, which accounts for about 27% of ulcerative pyloric and antral cancer cases and 9% of total gastric cancer cases, patients often had hematogenous metastasis not only to the liver but also to multiple organs. Histological type was often por and serum CA19-9 level was high. The general condition of patients was poor, and approximately 70% of the treatments were BSC only. The median survival time of patients treated with chemotherapy was short, at approximately 4.5 months. These patients had a very poor prognosis, and the current therapeutic effects were insufficient, so new drugs or treatment strategies should be pursued for this patient group. According to the annual report of the Japanese Gastric Cancer Association nationwide registry in 2009, approximately 52% (n=183) of patients with unresectable gastric cancer (n=355) had peritoneal dissemination, and peritoneal recurrence (n=1,283) was the most common

cause of death in patients with resectable gastric cancer (n=13,002)[20]. In this study, cases of peritoneal dissemination (L±H−P+ and L+H+P+ groups), which accounted for 57.5% of ulcerative gastric cancer cases, were in poor general condition and were less responsive to chemotherapy than those without peritoneal dissemination. Therefore, the treatment of peritoneal dissemination, a poor prognostic factor, may be one of the key points in the treatment of gastric cancer.

The Cancer Genome Atlas (TCGA) Consortium recently classified gastric cancer into four molecular types: microsatellite instability high type, Epstein-Barr virus positive type, genome stable type, and chromosome unstable type[6]. There is a possibility that the genome-stable type, which is histopathologically considered to be diffuse-type, corresponds to the L±H−P+ group in this study. However, whether the four groups of ulcerative-type gastric cancer in this study correspond to the four groups of TCGA is not yet known, and further investigation is required.

Because the sample size of type V, IV, and I groups was too small, it will be necessary to accumulate more cases for additional study to determine the clinical features of these patient groups.

At present, the clinical application of this classification is still limited, but it is expected to have several clinical applications in the treatment of ulcerative gastric cancer, which accounts for 90% of unresectable pyloric and antral cancers. In diagnosis, the metastatic pattern might be estimated to some extent from the general condition of the patient, the positive pattern of serum CEA/CA19-9 levels, and the histopathological type of gastric cancer. For example, if the patient shows a poor general condition, serum CEA/CA19-9 levels of −/−, and histopathological type sig, the metastatic form of this case might be L±H−P+. In therapy, the following clinical applications might be expected. The L+H−P− and L+H+P− groups might be considered for radical surgery after chemotherapy according to current guidelines[21−23], depending on the situation (L+H−P− group: significant response to chemotherapy; L+H+P− group: localized liver and lymph node metastases by chemotherapy). On the other hand, in the L±H−P+ and L+H+P+ groups, it might be desirable to develop powerful therapies, especially for peritoneal dissemination. However, this classification has not yet been established, and future studies are needed to formally determine its clinical application.

The limitations of this study are that this was a retrospective study and the number of samples was small. In the future, prospective studies with an increased number of samples will be required. In addition, gastric cancer in the corpus and cardia as well as the pyloric and antral region should be examined.

In conclusion, here we established a classification system by a combination of macroscopic and metastatic form in pyloric and antral metastatic gastric cancer, which might be useful for diagnosis and treatment of pyloric/antral gastric cancer patients.

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Conflict of Interest: The authors declare that they have no conflicts of interest.

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