Borrmann type IV gastric cancer should be classified as pT4b disease

Short title: Classifying Bor IV GC as pT4b disease

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Abstract

Background: The impact of macroscopic pathological features of primary tumor that could be obtained preoperatively on pT classification has not been reported so far. The aim of this study was to investigate the feasibility of incorporation of Borrmann type IV gastric cancer into the pT classification.

Materials and methods: Clinicopathologic and prognostic data of 1622 patients with advanced gastric cancer who underwent radical surgery were retrospectively studied.

Results: Of 1622 patients, 135 (8.32%) patients were classified as having Borrmann type IV gastric cancer. We first confirmed that Borrmann type IV gastric cancer was one of the independent prognostic factors for patients with advanced gastric cancer who underwent radical surgery. Interestingly, we found that overall survival of patients with Borrmann type IV gastric cancer could be clearly distinguished by pN classification and pTNM stage, but not by pT classification. Importantly, further analysis demonstrated that the prognosis of Borrmann type IV gastric cancers was homogeneous with that of pT4b cancers, but poorer than pT2, pT3, pT4a cancers. Therefore, we proposed a novel pT classification in which pT4b disease was defined as cancers that were Borrmann type IV or those that had invaded adjacent structures. Two-step multivariate analysis demonstrated that the novel pT classification was more suitable for prognostic assessment than the original classification.

Conclusions: Classifying Borrmann type IV gastric cancer as pT4b disease improves pT classification prediction of prognosis in patients with advanced gastric cancer after radical surgery.

Key words: gastric cancer, prognosis, Borrmann type, macroscopic types, pT, TNM.

Introduction

Gastric cancer is the fourth most common malignancy worldwide, and about one million new cases of gastric cancer have been estimated to occur each year.[1, 2] Although developments in diagnostic modalities have increased the diagnosis of early gastric cancer, most patients present with advanced diseases when they are diagnosed with gastric cancer. At present, penetration depth of the primary tumor (pT classification) and the number of metastatic lymph nodes (pN classification) are considered to be the most important prognostic factors in patients with advanced gastric cancer after radical surgery.[3-6] However, the pT classification and the pN classification can be only obtained accurately postoperatively. Recently, several papers reported that addition of macroscopic pathological features of primary tumor that could be obtained easily during operation, such as macroscopic serosal classification and width of serosal invasion, might improve pT classification prediction of prognosis in patients with advanced gastric cancer after radical surgery.[7,8] Unfortunately, the impact of the features that could be obtained preoperatively on pT classification has not been reported so far.

The Borrmann classification system is now widely used to classify advanced gastric cancer according to the macroscopic appearance of primary tumor. Borrmann type IV gastric cancer is characterized by a thickened and indurated gastric wall without a clear margin of tumor, which can be easily diagnosed by imaging examination or endoscopy preoperatively.[9] Borrmann type IV gastric cancer, which shows a more malignant biological behavior compared to other types of gastric cancer, has been demonstrated to be an independent factor predicting poor survival.[10-13] Nevertheless, the impact of Borrmann type IV gastric cancer on the pT classification has not been assessed. Therefore, in the present study, we retrospectively analyzed the clinicopathologic and prognostic data of 1622 patients with advanced gastric cancer after radical surgery in our center, to investigate the feasibility of

incorporation of Borrmann type IV gastric cancer into the pT classification.

Methods

All patients with gastric cancer who underwent surgery at the Department of Surgical Oncology, First Affiliated Hospital of China Medical University, from January 1980 to December 2005 were entered into a prospectively maintained database. In all, 1756 patients without distant metastasis underwent radical (R0) surgery for histologically proven advanced gastric carcinoma. A radical surgery was defined as en bloc resection of primary cancer and completed lymphadenectomy without microscopic or macroscopic residual disease according to the TNM staging system.[14] The completed lymphadenectomy referred to D2 or D3 lymphadenectomy according to Japanese gastric cancer treatment guidelines 2010 (ver. 3).[15] Among them, we excluded patients: (1) with a prior gastric surgery (23 patients), (2) without pathologic data of the TNM staging system or Borrmann types (49 patients), (3) who died in the postoperative period (the first 30 days after surgery, 20 patients), and (4) who were lost during the time of follow-up (42 patients). After these exclusions, a total of 1622 patients were enrolled into this study. All patients did not receive neoadjuvant chemotherapy.

Meanwhile, 261 gastric cancer patients with distant metastasis (M1) who underwent surgeries during the same study period were included as a reference group for prognostic comparisons with Borrmann IV gastric cancer patients who underwent radical surgery. All patients in the reference group with distant metastasis underwent palliative operation, and did not receive neoadjuvant therapy.

Follow-up of the entire study population was conducted until death or the cutoff date (March 31, 2009) by means of outpatient clinic consultation and/or communication with patients through telephone or letter. Median and mean follow-up periods were 38 and 59.81 months (range: 1-319 months), respectively.

Of the 1622 patients, the following clinicopathologic features were obtained: age, gender, location of the primary tumor, tumor size, pT classification, pN classification, pTNM stage, histologic type, lymphovascular invasion, and Borrmann type. The pT classification, pN classification, and pTNM stage were classified according to the seventh International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) TNM staging system.[3] Borrmann type classification was classified according to the Japanese Classification of Gastric Carcinoma.[9] Borrmann type IV gastric cancer was diagnosed when the following characteristics were observed: thickened and indurated gastric wall; no obvious protruded lump or deep ulceration; hypertrophic gastric folds; narrow gastral cavity; even a leather-bottle-like stomach. (Fig. S1)

All statistical analyses were performed with the SPSS 19.0 statistical package (SPSS Inc., Chicago, IL, USA). The categorical variables were compared using a 2-tailed chi-square test. The continuous data was presented as a mean $\pm$ standard deviation (SD), and 2-tailed t test was used for the statistical comparisons. All the clinicopathologic features that were significantly associated with Borrmann type IV gastric cancer were included in the logistic regression analysis (stepwise forwards method) to identify the independent predictors of the presence of Borrmann type IV gastric cancer. Overall survival rates were determined using the Kaplan–Meier estimator, and the log-rank test was used to identify differences between the survival curves of different patient groups. Cox’s proportional hazard model was used as multivariate analysis to identify independent factors predicting patients’ prognosis. For all analyses, *P* values were 2-tailed, and only *P* values<0.05 were considered significant.

Results

Of the 1622 patients enrolled in the present study, there were 1195 men (73.7%) and 427 women (26.3%; ratio, 2.8:1), with a mean age of 58.09 $\pm$ 10.8 years (median, 59 years; range, 17–90 years).

Among these patients, 44 (2.71%) were Borrmann type I, 310 (19.11%) were Borrmann type II, 1107 (68.25%) were Borrmann type III, 135 (8.32%) were Borrmann type IV, and 26 (1.61%) were Borrmann type V. Table 1 summarizes the clinicopathologic features of the 135 patients with Borrmann type IV gastric cancer and the 1487 patients with the other types of gastric cancer. There were significant differences in age, gender, location of the primary tumor, tumor size, pT classification, pN classification, pTNM stage, lymphovascular invasion, and histologic type. Logistic regression analysis revealed that gender, location of the primary tumor, tumor size, and histologic type were the independent predictors of the presence of Borrmann type IV gastric cancer (Table 2).

Concerning prognosis, the 5-year survival rate (5-YSR) of patients with Borrmann type IV gastric cancer was significantly poorer than that of the other types of gastric cancer (Fig. 1; 5-YSR: 19.7% vs. 45.3%; $P=0.000$), but significantly better than that of those with distant metastasis (Fig. 1; 5-YSR: 19.7% vs. 7.5%; $P=0.000$). When the overall survival rates were compared as stratified by pT classification, pN classification, and pTNM stage respectively, a significant difference could be observed between patients with Borrmann type IV gastric cancer and those with other types of gastric cancer in pT2-pT4a classification, pN0-pN3a classification, and stage IIa and IIIa-IIIc disease, but not in pT4b classification, pN3b classification, and stage Ib and IIb disease (Table 3).

Subsequently, we compared the overall survival according to pT classification, pN classification, and pTNM stage in the 135 patients with Borrmann IV gastric cancer. For pN classification, there were significant prognostic differences in survival among patients with different classifications (Table 3; $P=0.000$). For pTNM stage, there were also significant differences in survival among patients with different stages (Table 3; $P=0.000$). However, for pT classification, significant differences in survival could not be observed among patients with different classifications (Table 3; $P=0.242$). We also

compared the overall survival according to pT classification, pN classification, and pTNM stage in the 1475 patients with other types of gastric cancer. We found that there were significant prognostic differences in survival among patients with different pT classifications, different pN classifications, and different pTNM stages (Table 3, $P=0.000$ for all three comparisons).

Since there was no difference in overall survival among pT2, pT3, pT4a, and pT4b patients with Borrmann type IV gastric cancer, we compared the prognosis of all 135 patients with Borrmann type IV gastric cancer with that of pT2, pT3, pT4a, and pT4b patients with other types of gastric cancer, respectively. Interestingly, as Fig. 2 shows, the prognosis of patients with Borrmann type IV gastric cancer was similar to that of pT4b patients with other types of gastric cancer (5-YSR: 19.7% vs. 20.6%; $P=0.898$) but significantly poorer than that of pT2, pT3 and pT4a patients with other types of gastric cancer ($P=0.000$ for all the three comparisons). We also compared the overall survival of all pT4b patients with that of pT2, pT3, pT4a patients with Borrmann type IV gastric cancer, respectively. We found that the prognosis of pT4b patients was similar to that of pT2, pT3, pT4a patients with Borrmann type IV gastric cancer, respectively (Fig. 3; $P=0.207$, $P=0.772$, $P=0.891$, respectively).

Based on these results, we proposed a novel pT classification, in which pT4b classification disease was defined as cancers that were Borrmann type IV or invaded adjacent structures. The survival curves according to each of the T classifications were well separated both in the UICC/AJCC pT classification and in the novel pT classification (Fig. 4; $P=0.000$ for both). To explore which pT classification was more suitable for prognostic assessment, we performed 2-step multivariate analysis for survival of patients with radical surgery. Univariate analysis of prognostic factors suggested that age, location of the primary tumor, tumor size, UICC/AJCC pT classification, pN classification, histologic type, lymphovascular invasion, Borrmann type, and the novel pT classification were significantly correlated

with patient prognosis (Table 4). In step 1 multivariate analysis, all the significant prognostic factors in the univariate analysis were considered except for the novel pT classification. We found that age, location of the primary tumor, pT classification, pN classification, lymphovascular invasion, and Borrmann type were independent factors predicting patients' prognosis (Table 5). When the novel pT classification was also considered in step 2 multivariate analysis, it replaced the UICC/AJCC pT classification as one of the most important prognostic factors (Table 5).

Discussion

Since the Borrmann classification system was developed in 1926, it has been generally accepted and widely adopted. It is widely reported that Borrmann type IV gastric cancer is an independent factor predicting poor survival for patients with advanced gastric cancer.[10-13] Nevertheless, the feasibility of incorporation of Borrmann type IV gastric cancer into the pT classification has not been investigated. The findings of the present study suggest that Borrmann type IV gastric cancer should be classified as pT4b disease.

In this study, we found that overall survival of patients with Borrmann type IV gastric cancer could be clearly distinguished by pN classification and pTNM stage, but not by pT classification, suggesting that pT classification of the UICC/ AJCC TNM staging system needs improvement. Importantly, our data demonstrated that the prognosis of Borrmann type IV gastric cancers was homogeneous with that of pT4b cancers. Therefore, we proposed a novel pT classification, in which in which pT4b classification disease was defined as cancers that were Borrmann type IV or invaded adjacent structures. By using 2-step multivariate analysis, we confirmed that the novel pT classification was superior to the UICC/AJCC pT classification in prediction of prognosis in patients with advanced gastric cancer after radical surgery.

The UICC/AJCC TNM staging system is used to determine treatment options for advanced gastric cancer patients worldwide.[16,17] However, the pT classification and the pN classification can be only obtained accurately postoperatively. On the contrary, Borrmann type IV gastric cancer can be easily diagnosed by imaging examination preoperatively.[18] Considering the prognostic value of Borrmann type IV gastric cancer and its impact on the UICC/AJCC pT classification, we speculate that Borrmann type IV gastric cancer may be an indicator of receiving neoadjuvant chemotherapy and intraoperative intraperitoneal chemotherapy. We plan to test this speculation in our future researches.

In addition to being utilized for deciding treatment options, the UICC/AJCC TNM staging system is usually utilized for patient stratification during experimental design to assess treatment effect.[19,20] However, few studies have considered the importance of the equal distribution of patients with Borrmann type IV gastric cancer between the experimental group and control group when they design a study. For example, Nakajima et al.[21] conducted a randomized controlled trial to compare the survival of patients with pT2-3 classification gastric cancer treated by radical surgery alone or radical surgery followed by uracil–tegafur. They reported a significant survival benefit of postoperative adjuvant chemotherapy, which increased the 5-year survival rate by 11%. However, the study did not state whether the distribution of patients with Borrmann type IV between the experimental group and control group was equal. If it was not, we think the results reported by Nakajima et al. should be further analyzed considering the significant differences in prognosis that were observed between patients with Borrmann type IV gastric cancer and those with other types of gastric cancer in pT2-3 classification in the present study. Furthermore, under this condition, the novel pT classification proposed by us may be more suitable for patient stratification to assess the treatment effect.

In this study, we found that patients with Borrmann type IV gastric cancer were characterized by

young age, female predominance, large tumor sizes, tumor occupying the entire stomach, undifferentiated histologic type, lymphovascular invasion, advanced pT classification, advanced pN classification, and advanced pTNM stage in patients with radical surgery. Logistic regression analysis revealed that gender, location of the primary tumor, tumor size, and histologic type were the independent predictors of the presence of Borrmann type IV gastric cancer. These findings are in agreement with previous reports[10-13] and shows that Borrmann type IV gastric cancer has more aggressive biologic behaviors compared to other types of gastric cancer, which should be considered as a special subset of advanced gastric cancer. In addition, we noticed that 8.32% of advanced gastric cancer was Borrmann type IV in the present study, whereas those reported by previous studies ranged from 9% to 18%.[11, 13, 22, 23] The reason for the relatively lower proportion of Borrmann type IV gastric cancer reported by us might be that only patients who underwent radical surgery were included in the present study.

A recent study by Yang et al., in which patients who did not undergo radical surgery were included, demonstrated that the survival of patients with Borrmann type IV gastric cancer was similar to those with distant metastasis (M1), and they suggested that Borrmann type IV gastric cancer should be classified as stage IV disease.[10] On the contrary, in the present study, we found that the prognosis of patients with Borrmann type IV gastric cancer who underwent radical surgery was significantly better than that of patients with distant metastasis. Therefore, according to our results, patients with Borrmann type IV gastric cancer should not be classified as stage IV disease when they underwent radical surgery.

There are some limitations in the present study. First, although we compared the prognosis between patients with Borrmann type IV gastric cancer and patients with other types of gastric cancer

stratified by pT classification, pN classification, and pTNM stage to investigate the prognostic value of Borrmann type IV gastric cancer in as much detail as possible, we could not compare overall survival between these two groups stratified by "any T + any N" classification because of the limited number of patients with Borrmann type IV gastric cancer in the present study. Second, our conclusion resulted from a Chinese monoinstitutional study in 1622 patients. Therefore, larger studies with multicentric data such as Surveillance Epidemiology and End Results (SEER) database should be performed to confirm our results.

Conclusions

In summary, we investigated the feasibility of incorporation of Borrmann type IV gastric cancer into the pT classification, and found that Borrmann type IV gastric cancer should be classified as pT4b disease. However, our conclusion just resulted from a Chinese monoinstitutional study in 1622 patients, and larger studies with multicentric data such as Surveillance Epidemiology and End Results (SEER) database should be performed to confirm our results.

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Figure legends

Fig. 1. Comparison of survival curves between patients with Borrmann type IV gastric cancer and with other types of gastric cancer, and those with distant metastasis.

Fig. 2. Comparison of survival curves between patients with Borrmann type IV gastric cancer and pT2 patients with other types of gastric cancer (a), between patients with Borrmann type IV gastric cancer and pT3 patients with other types of gastric cancer (b), between patients with Borrmann type IV gastric cancer and pT4a patients with other types of gastric cancer (c), and between patients with Borrmann type IV gastric cancer and pT4b patients with other types of gastric cancer (d).

Fig. 3. Comparison of survival curves between pT4b patients and pT2 patients with Borrmann type IV gastric cancer (a), between pT4b patients and pT3 patients with Borrmann type IV gastric cancer (b), between pT4b patients and pT4a patients with Borrmann type IV gastric cancer (c).

Fig. 4. (a), Survival curves according to the UICC/AJCC pT classification. (b), Survival curves according to the novel pT classification.

Table 1. Comparison of clinicopathologic features between Borrmann type IV gastric cancer and other type gastric cancer.

Factors	Borrmann type IV (%)	Other Borrmann types (%)	<i>P</i> value
Age (year) ^a	56.13±11.79	58.26±10.72	0.029
Gender			0.000
Male	81(60)	1114(74.9)	
Female	54(40)	373(25.1)	
Location			0.000
Upper 1/3	10(7.4)	230(15.5)	
Middle 1/3	17(12.6)	223(15)	
Lower 1/3	65(48.1)	982(66.2)	
Entire	43(31.9)	49(3.3)	
Tumor size (cm) ^a	7.57±3.45	5.29±2.29	0.000
pT classification			0.000
T2	11(8.1)	323(21.7)	
T3	64(47.4)	735(49.4)	
T4a	46(34.1)	338(22.7)	
T4b	14(10.4)	91(6.1)	
pN classification			0.000
N0	27(20)	469(31.5)	
N1	17(12.6)	340(22.9)	
N2	38(28.1)	327(22)	
N3a	32(23.7)	262(17.6)	
N3b	21(15.6)	89(6)	
pTNM stage			0.000
Ia	4(3)	148(10)	
IIa	14(10.4)	307(20.6)	
IIb	20(14.8)	288(19.4)	
IIIa	28(20.7)	278(18.7)	
IIIb	41(30.4)	327(22)	
IIIc	28(20.7)	139(9.3)	
Histologic type			0.000
Differentiated	17(12.6)	562(38.3)	
Undifferentiated	118(87.4)	906(61.7)	
Lymphovascular invasion			0.003
No	82(63.6)	1053(75.4)	
Yes	47(36.4)	343(24.6)	

^a 2-tailed t test

Table 2. Logistic regression analysis of clinicopathologic features correlated with Borrmann type IV gastric cancer.

Factors	RR	95% CI	<i>P</i> value
Gender			0.015
Male			
Female	1.716	1.110-2.652	
Location			0.000
Entire			
Upper 1/3	0.122	0.052-0.285	
Middle 1/3	0.207	0.101-0.427	
Lower 1/3	0.164	0.091-0.296	
Tumor size	1.256	1.164-1.354	0.000
Histologic type			0.000
Differentiated			
Undifferentiated	3.719	2.090-6.618	

Abbreviations: RR, relative risk; CI, confidence interval.

Table 3. Comparison of overall survival according to Borrmann type stratified by the TNM staging system and according to the TNM staging system stratified by Borrmann type respectively.

	Borrmann type IV			Other Borrmann types			<i>P</i> value ^c
	N	5-YSR(%)	<i>P</i> value ^a	N	5-YSR(%)	<i>P</i> value ^b	
pT classification			0.242			0.000	
T2	11	27.3		323	66		0.023
T3	64	22.9		735	45.7		0.000
T4a	46	16.9		338	32.2		0.008
T4b	14	14.3		91	20.6		0.106
pN classification			0.000			0.000	
N0	27	38.9		469	68		0.012
N1	17	29.4		340	50		0.037
N2	38	24.6		327	34.8		0.028
N3a	32	0		262	24		0.000
N3b	21	10.3		89	8.9		0.262
pTNM stage			0.000			0.000	
Ib	4	50		148	75.4		0.539
IIa	14	28.6		307	73.2		0.000
IIb	20	45		288	48.3		0.859
IIIa	28	20.4		278	37.6		0.018
IIIb	41	12.6		327	21.7		0.004
IIIc	28	3.6		139	17.7		0.006

Abbreviations: 5-YSR, 5 year survival rate.

^a Comparison of overall survival according to pT classification, pN classification, and pTNM stage in 135 patients with Borrmann type IV gastric cancer respectively.

^b Comparison of overall survival according to pT classification, pN classification, and pTNM stage in 1487 patients with other type gastric cancer respectively.

^c Comparison of overall survival according to Borrmann type stratified by pT classification, pN classification, and pTNM stage in 1622 patients with advanced gastric cancer respectively.

Table 4. Univariate analysis of prognostic factors for patients with advanced gastric cancer who underwent radical surgery.

Factors	n	5-YSR (%)	<i>P</i> value ^a
Age			0.001
≤60 years	903	45.1	
>60 years	719	40.8	
Gender			0.920
Male	1195	43.2	
Female	427	43.3	
Location			0.000
Entire	86	16.8	
Upper 1/3	240	33.4	
Middle 1/3	241	48.5	
Lower 1/3	1052	46.4	
Tumor size			0.000
≤4 cm	584	51.6	
>4 cm	989	38.4	
UICC/AJCC pT classification			0.000
T2	334	64.6	
T3	799	43.9	
T4a	384	30.4	
T4b	105	19.8	
pN classification			0.000
N0	496	66.4	
N1	357	49	
N2	365	33.8	
N3a	294	21.3	
N3b	110	9	
Histologic type			0.008
Differentiated	579	47.4	
Undifferentiated	1024	40.4	
Lymphovascular invasion			0.000
No	1135	48.7	
Yes	390	28	
Borrmann type			0.000
Other types	1487	45.3	
Type IV	135	19.7	
Novel pT classification			0.000
T2	323	66.0	
T3	735	45.7	
T4a	338	32.2	
T4b	226	20.3	

Abbreviations: 5-YSR, 5 year survival rate; UICC, International Union Against Cancer; AJCC, American Joint Committee on Cancer.

^a *P* value was determined by log-rank test

Table 5. Two-step multivariate analysis of prognostic factors for patients with advanced gastric cancers who underwent radical surgery.

	Step 1 ^a		Step 2 ^b			
Factors	HR	95%CI	<i>P</i> value	HR	95%CI	<i>P</i> value
Age			0.000			0.000
≤60 years						
>60 years	1.324	1.167-1.503		1.325	1.167-1.503	
Location			0.000			0.000
Entire						
Upper 1/3	0.991	0.728-1.349		0.945	0.706-1.264	
Middle 1/3	0.623	0.456-0.849		0.597	0.445-0.801	
Lower 1/3	0.630	0.476-0.834		0.602	0.464-0.781	
UICC/AJCC pT classification			0.000			
T2						
T3	1.375	1.141-1.657				
T4a	1.590	1.298-1.948				
T4b	2.237	1.685-2.970				
pN classification			0.000			0.000
N0						
N1	1.465	1.214-1.767		1.469	1.218-1.772	
N2	1.958	1.628-2.356		1.935	1.608-2.328	
N3a	2.821	2.327-3.420		2.807	2.316-3.404	
N3b	5.208	4.017-6.750		5.282	4.086-6.829	
Lymphovascular invasion			0.004			0.002
No						
Yes	1.230	1.067-1.418		1.245	1.080-1.434	
Borrmann type			0.006			
Other types						
Type IV	1.384	1.097-1.745				
Novel pT classification						0.000
T2						
T3				1.370	1.132-1.658	
T4a				1.573	1.276-1.939	
T4b				2.312	1.828-2.924	

Abbreviations: HR, hazard ratio; CI, confidence interval; UICC/AJCC, International Union Against Cancer/American Joint Committee on Cancer.

^a, Step 1, with consideration of all significantly important prognostic factors in univariate analysis, except for the novel pT classification

^b, Step 2, with consideration of all significantly important prognostic factors in univariate analysis, including the novel pT classification

Figure 1

Figure 2

Figure 3

Figure 4