



Original article

Prediction of recurrence after curative resection of gastric carcinoma invading the muscularis propria: a multivariate analysis

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Abstract

Background. In Japan, the incidence of gastric cancer invading the muscularis propria is about 10% of all patients with gastric cancer undergoing surgical resection. Although many prognostic factors for early gastric cancer and advanced gastric cancer have been identified, there are few reports concerning prognostic factors for gastric cancer invading the muscularis propria, and the characteristics of recurrence are not well understood.

Methods. We retrospectively analyzed data on 167 patients with gastric cancer that had invaded the muscularis propria. All patients had undergone curative resection.

Results. Recurrences were evident in 37 patients (22.2%). Based on our univariate analysis, the recurrence was associated with lymph node metastases. Multivariate analysis showed that independent risk factors for recurrence were lymph node metastases and location of tumor in the upper or lower one-third of the stomach. With respect to the pattern of recurrence, 17 (46.0%) were secondary to hematogenous recurrence, 8 (21.6%) to peritoneal dissemination, and 6 (16.2%) to a local recurrence in the remnant stomach and in regional lymph nodes. Most deaths occurred during the second year after surgery, and approximately two-thirds of all patients (64.8%) died within 3 years after surgery.

Conclusion. In patients with the risk factors of lymph node metastases and tumor in the upper or lower one-third of the stomach, lymph node dissection and postoperative adjuvant therapy are vital to try to prevent recurrences, especially during the first 2 years after surgery.

Key words Gastric carcinoma · Muscularis propria · Recurrence · Lymph node metastasis

and early gastric cancer (EGC) as that confined to the mucosa or submucosa, regardless of the presence or absence of lymph node metastases. In Japan, the incidence of gastric cancer invading the muscularis propria (pm gastric cancer) accounts for about 10% of all patients with gastric cancer undergoing surgical resection [1,2]. The pm gastric cancer is usually treated by curative resection [3], and the 5-year survival rate for patients with pm gastric cancer was reported to be between 70% and 80%, a value between that for EGC and AGC [4,5]. Although pm gastric cancer belongs to the category of AGC, it is considered to be an intermediate stage between EGC and AGC [6], and the biological characteristics of pm gastric cancer are different from those of AGC [7].

Recurrences of gastric cancer are likely to take a variety of forms and to be manifested in different organs, and the rate of recurrence increases in proportion to the degree of depth of invasion, even after curative resection for gastric cancer [8–10]. Although many prognostic factors for EGC and AGC have been identified [9,11], there are few reports concerning prognostic factors for pm gastric cancer, and the characteristics of recurrence are not well understood. For early detection and more effective treatment of recurrent disease, it is important to fully understand the relevant characteristics. We examined the clinicopathological characteristics of patients with pm gastric cancer in relation to recurrence.

Introduction

In Japan, advanced gastric cancer (AGC) is defined as that extending into or beyond the muscularis propria,

Patients and methods

Patients

From 1965 to 1998, curative resection for 2437 Japanese patients with primary gastric cancer was done at the Second Department of Surgery at Kyushu University Hospital (Fukuoka, Japan). The present study is based

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on analysis of the data on 167 patients (6.9%) with pm gastric cancer treated by resection. Recurrence was defined as cases in which recurrence was clearly the cause of death. The following patients were excluded: (1) those with cancers of other organs; and (2) those with distant metastasis, peritoneal dissemination, or adjacent organ involvement. Standardized procedures were used: gastric resection was done after determining a resection line 3 cm away from the macroscopic edge

for a localized tumor, and 6 cm away from the macroscopic edge for an infiltrative tumor [12]. All patients were examined clinically and pathologically with respect to the factors listed in Table 1. Pathological diagnosis and classification were evaluated according to the General rules for the gastric cancer study in surgery and pathology of the Japanese Research Society for Gastric Cancer [13]. Lymph nodes in groups 1, 2, and 3 are referred to as n1, n2 and n3, respectively, based on

Table 1. Comparison of clinicopathological factors in patients with gastric cancer invading the muscularis propria with recurrence (–) and without recurrence (+)

Variable	Recurrence (–) (n = 130)	Recurrence (+) (n = 37)	P value
Age (years)	60.3 + 12.6*	59.5 + 11.2	NS
Sex			
Male	95	24	
Female	35	13	NS
Tumor size (cm)	4.68 + 2.26 ^a	4.98 + 1.68	NS
Operative procedure			
Partial	102	31	
Total	26	4	
Unknown	2	2	NS
Location of tumor			
Upper (C)	26	5	
Middle (M)	45	7	
Lower (A)	59	25	NS
Location of tumor			
Lesser curvature	35	12	
Greater curvature	21	4	
Anterior wall	35	10	
Posterior wall	29	9	
Circumferential	10	2	NS
Peritoneal dissemination			
Negative	130	37	
Positive	0	0	
Liver metastases			
Negative	130	37	
Positive	0	0	
Borrmann type			
I	9	2	
II	37	19	
III	21	5	
IV	2	0	
Other	61	11	NS
Histologic findings			
Differentiated	75	21	
Undifferentiated	55	16	NS
Lymphatic involvement			
Negative	61	12	
Positive	44	15	
Unknown	25	10	NS
Vascular involvement			
Negative	77	20	
Positive	21	5	
Unknown	32	12	NS
Lymph node metastasis			
Negative	75	13	
Positive	55	24	P < 0.05

NS, Not significant

^amean + SD

lymph node metastasis. Lymph node dissection was classified as follows: D1, complete removal of group 1 lymph nodes alone; D2, complete removal of group 1 and 2 lymph nodes; and D3, complete removal of group 1, 2, and 3 lymph nodes.

Statistical analysis

Clinicopathological data were stored in an IBM 4381 mainframe computer. The BMDP Statistical Package Program (BMDP, Los Angeles, CA, USA) was used for all statistical analysis [14]. BMDP 4F and 3S programs were used for the χ^2 test and Mann-Whitney rank-sum tests to compare data on groups of patients with pm gastric cancer. The BMDP 1L program was used to apply the Kaplan-Meier method for analysis of survival time, and to test for the equality of survival curves using Generalized Wilcoxon analysis. The BMDP P2L program was used for simultaneous multivariate adjustment of all covariates by the Cox regression analysis forward stepwise model [15]. The level of significance was $P < 0.05$.

Results

Clinicopathological factors

Table 1 shows the clinicopathological data for 130 recurrence-free post-surgery patients and 37 patients who died after a recurrence. There were no significant differences between the variables of age and sex. When the entire stomach was involved, the two groups differed significantly with respect to lymph node metastases.

Risk factors

To determine which of the many covariates was the most significant with respect to recurrence for patients with pm gastric cancer, all of the factors listed in Table 2 were subjected to Cox regression analysis. The independent risk factors for recurrence were lymph node metastases and location of tumor in the upper or lower one-third of the stomach.

Table 2. Cox regression analysis of data for patients with gastric cancer invading the muscularis propria

Covariate	<i>P</i> value	Relative risk
Lymph node metastases (negative, positive)	<0.01	3.6766
Location of tumor (middle, upper and lower)	<0.01	0.153

Recurrence patterns

Data for the 37 patients who died as a result of recurrence were analyzed with respect to the pattern of recurrence (Table 3). Recurrence was detected at multiple sites in 5 patients. Of the 37 gastric cancer-related deaths, 17 (46.0%) were secondary to hematogenous recurrence, 8 (21.6%) were secondary to peritoneal dissemination, and 6 (16.2%) were secondary to a local recurrence in the remnant stomach or anastomosis and recurrence in the regional lymph nodes; for 11 patients (29.7%), data were indefinite regarding organs most involved in the recurrence. In patients with pm gastric cancer, hematogenous recurrence was twice as frequent as peritoneal recurrence. Of the 17 patients with a hematogenous recurrence, there was metastasis to the liver in 9, to the lung in 3, to the brain in 4, and to the bone in 2.

Survival time after operation

Recurrent deaths were most frequent during the second year after surgery, and approximately two-thirds of all patients (64.8%) died within 3 years after surgery (Fig. 1). The 10-year survival rates were 100% for those without recurrence and 18.9% for those with recurrence; the difference was significant (data not shown).

Discussion

Recurrence was mainly classified as of hematogenous or peritoneal patterns. Hematogenous recurrence is presumed to occur when cancer cells released from the primary site enter the vessel system and are transported to the organ, where the cells attach and proliferate [16]. Peritoneal recurrence is considered to be established by tumor cells' infiltration of the gastric wall and dissemination to the peritoneum. Hematogenous recurrence is the predominant means of recurrence in patients with ECG [9], and peritoneal recurrence is predominant for

Table 3. Site of recurrence after curative resection of gastric cancer invading the muscularis propria in 37 patients

Site of recurrence	Number of patients (%)
Hematogenous	17 (46.0)
Liver	9
Lung	3
Bone	2
Brain	4
Peritoneum	8 (21.6)
Local and lymph node	6 (16.2)
Other, unknown	11

Five patients had recurrences at multiple sites

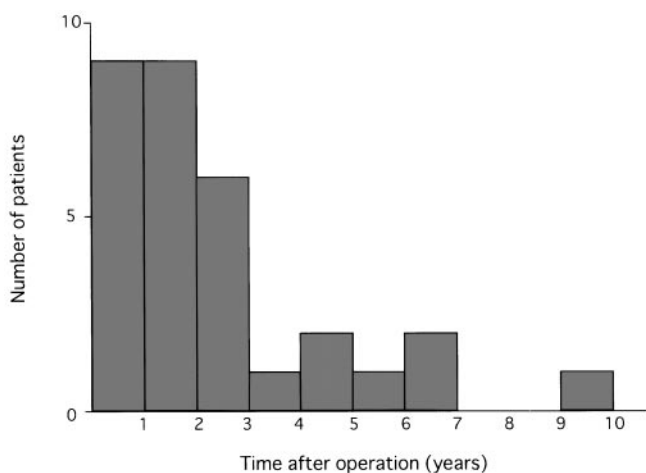


Fig. 1. Histogram of numbers of patients who died of recurrence each year for 10 years after curative resection of gastric carcinoma

patients with an advanced stage of gastric cancer of the undifferentiated tissue type [11]. Our study showed that hematogenous recurrence pattern was twice as frequent as peritoneal recurrence in patients with pm gastric cancer, and that independent risk factors were lymph node metastasis and tumor location.

As pm gastric cancer is not exposed to the serosal surface, further development of the cancer can be attributed to vessel invasion. Maehara et al. [17] found the concomitant presence of lymph node metastasis with peritoneal dissemination or liver metastasis and suggested that lymphatic progression was related to both types of metastasis. Imada et al. [18] reported the breakthrough of cancer cells in a lymph node and infiltration into the area surrounding the lymph node in metastatic lymph nodes in gastric cancer. All these findings suggested a possible role of lymphatic spread in peritoneal dissemination. Because of these risk factors for peritoneal tumor spread, the intraoperative use of intraperitoneal chemotherapy [19] is required, with detection of free peritoneal tumor cells in peritoneal lavage fluid, using immunocytochemistry [20] and the reverse transcriptase-polymerase chain reaction [21]. Subsequent adjuvant therapy may be indicated for patients at high risk of further cancer spread or occult metastases, in patients with a tumor showing aneuploidy [22], *p53* abnormality [23], or extensive neovascularization [24].

Tumors with lymph node metastasis had a high rate of lymphatic and vascular involvement [25]. On multivariate analysis, lymph node metastases is an important prognostic factor in both EGC [9] and AGC [11]. The lymphatic system plays an important role in the spread of gastric cancer [26,27]. With regard to lymph node dissection, extended lymph node dissection was not a

significant prognostic factor on univariate analysis; however, this factor was prognostically significant on multivariate analysis [28,29]. Adachi et al. [30] reported that patients with extended lymph node dissection survived longer than did those with limited lymph node dissection, and the degree of lymph node dissection was an independent prognostic factor on multivariate analysis of data for patients with recurrence of gastric cancer. Although the importance of lymphadenectomy still remains controversial [29,31,32], our view is that radical lymphadenectomy is indicated for patients with gastric cancer invading the muscularis propria with lymph node metastases.

The location of the tumor is clearly related to the prognosis of gastric cancer. Tumors in the middle-third of the stomach are more likely to be cured by surgical resection (resulting in longer survival time for the patient [33]) than tumors located in the upper-third and lower-third of the stomach. This phenomenon may be attributed to findings that tumors in the upper-third of the stomach invade the esophagus [34,35], while those in the lower-third invade the duodenum [36].

It was noteworthy that the recurrence was not influenced by the macroscopic appearance. The pm gastric cancer has been classified as either being of the Borrmann type or the EGC type, depending on the macroscopic appearance [3,37]. The Borrmann type tends to grow expansively, with higher rates of vascular vessel invasion and lymph node metastases, resulting in a poor prognosis [37]. The EGC type cancer also results in recurrence, and may metastasize in the same manner as the Borrmann type. It must also be emphasized that, although the macroscopic appearance is an important prognostic factor, it does not necessarily determine the survival time for patients with recurrence.

In conclusion, lymph node metastases and location of tumor are important predictors of recurrence after curative resection for pm gastric cancer. In patients with these risk factors, lymph node dissection should be done and postoperative adjuvant therapy should be prescribed in an attempt to prevent recurrence, especially during the first 2 years after surgery, even when a curative resection is done.

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