Original article

Recurrence following curative resection for gastric carcinoma

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Background: The diagnosis and treatment of recurrent gastric cancer remains difficult. The aim of this study was to determine the risk factors for recurrence of gastric cancer and the prognosis for these patients.

Methods: Of 2328 patients who underwent curative resection for gastric cancer from 1987 to 1995, 508 whose recurrence was confirmed by clinical examination or reoperation were studied retrospectively. The risk factors that determined the recurrence patterns and timing were investigated by univariate and multivariate analysis.

Results: The mean time to recurrence was 21·8 months and peritoneal recurrence was the most frequent (45·9 per cent). Logistic regression analysis showed that serosal invasion and lymph node metastasis were risk factors for all recurrence patterns and early recurrence (at 24 months or less). In addition, independent risk factors involved in each recurrence pattern included younger age, infiltrative or diffuse type, undifferentiated tumour and total gastrectomy for peritoneal recurrence; older age and larger tumour size for disseminated, haematogenous recurrence; and older age, larger tumour size, infiltrative or diffuse type, proximally located tumour and subtotal gastrectomy for locoregional recurrence. Other risk factors for early recurrence were infiltrative or diffuse type and total gastrectomy. Reoperation for cure was possible in only 19 patients and the mean survival time after conservative treatment or palliative operation was less than 12 months.

Conclusion: The risk factors for each recurrence pattern and timing of gastric cancer can be predicted by the clinicopathological features of the primary tumour. Since the results of treatment remain dismal, studies of perioperative adjuvant therapy in an attempt to reduce recurrence are warranted.

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Introduction

Gastric cancer is still the most common cause of death from cancer in Korea, despite improved prognosis as a result of early diagnosis, radical operations and the development of adjuvant therapy[1–3]. Death from gastric cancer is almost entirely due to recurrent disease, and recurrences are often found in various forms or at more than one site simultaneously. Therefore, it is difficult clinically to confirm the patterns of recurrence and to establish precise data about the relationship between patterns of recurrence and the therapeutic strategy in gastric cancer. However, clarifying the relationship between clinicopathological factors and patterns of recurrence may contribute to the choice of better treatment or follow-up programme.

This study reviewed experience with recurrent gastric cancer after curative resection and evaluated the following: (1) patterns and timing of recurrence, (2) risk factors according to patterns of recurrence, and (3) prognosis according to patterns of recurrence and mode of treatment.

Patients and methods

The records of 2328 consecutive patients who underwent potentially curative resection for gastric cancer from January 1987 to June 1995 were reviewed. All patients had histologically confirmed adenocarcinoma of the stomach without clinical or radiological evidence of distant metastases. At operation, either total or distal subtotal gastrectomy was performed depending on location and macroscopic type of gastric cancer. All patients underwent extended lymphadenectomy, and a minimum of 15 lymph nodes was retrieved. The cancer was staged according to the Union Internacional Contra la Cancrum (UICC) tumour node metastasis (TNM) classification[4].

The patients were followed closely until 31 December 1998; the median length of follow-up was 68 (range

1–144) months. Routine follow-up consisted of physical examination, laboratory tests (including estimation of carcinoembryonic antigen, CA19-9 and CA125 levels), chest radiography, abdominopelvic ultrasonography and computed tomography (CT). However, follow-up intervals were individualized according to the TNM stage of each patient. In early stages (stage IA or IB), patients were followed every 4 months during the first 2 years, and then every 6 months or yearly beyond the third year; in advanced stages (stage II or greater), follow-up was every 3 months during the first year, every 4 months during the second, and every 6 months thereafter, for a total of 5 years. Endoscopy was performed every 6 months or yearly, and other radiological studies were performed only on suspicion of recurrence.

At the time of the last follow-up, 1499 patients (64·4 per cent) were still alive, 72 (3·1 per cent) were lost to follow-up and 757 (32·5 per cent) had died from recurrence or other causes. Of 652 patients (28·0 per cent) with recurrent gastric cancer, the exact sites of failure were unknown due to incomplete data in 144.

Therefore, 508 patients whose recurrence was confirmed by clinical and radiological examination ($n = 411$) or by reoperation ($n = 97$) were entered in the study. Of these patients, recurrent cancer was pathologically proven in 197 patients (38·8 per cent).

The main patterns of recurrence were recorded as the first site of detectable failure at the time of diagnosis, and patients were divided into three groups: locoregional, peritoneal and haematogenous (disseminated) recurrence. The criteria and the number of patients according to each recurrence pattern are shown in *Table 1*. Lymph nodes included the regional nodes (perigastric, left gastric, common hepatic, coeliac and hepatoduodenal lymph nodes) as well as retropancreatic, mesenteric and paraaortic nodes. The determination of locoregional recurrence was made by endoscopy, ultrasonography, CT or reoperation. Peritoneal recurrence was determined by ultrasonography, CT, barium enema, intravenous pyelography and reoperation, as well as the appearance of clinical signs such as ascites, rectal shelf, intra-abdominal mass, abdominal wound or drain site mass, intractable intestinal obstruction or obstructive uropathy. Haematogenous recurrence was determined by chest radiography, ultrasonography, CT, scintigraphy or pathological diagnosis.

Table 1 Patterns of recurrence in gastric cancer

	Alone	Combined
Locoregional	98 (19·3)	165 (32·5)
Anastomosis or stump	54 (10·6)	80 (15·7)
Lymph nodes	34 (6·7)	68 (13·4)
Adjacent organ	10 (2·0)	13 (2·6)
Peritoneal	172 (33·9)	223 (43·9)
Haematogenous	133 (26·2)	174 (34·3)
Liver	75 (14·8)	96 (18·9)
Lung	26 (5·1)	35 (6·9)
Bone	26 (5·1)	34 (6·7)
Brain	5 (1·0)	8 (1·6)
Testis	1 (0·2)	1 (0·2)
Extra-abdominal nodes*	22 (4·3)	24 (4·7)

Values in parentheses are percentages. *Supraclavicular, inguinal or axillary lymph nodes

Statistical analysis

The relationships between the recurrence patterns and variable clinicopathological factors were compared, with special reference to the length of time to recurrence and the prognosis. Statistically significant differences were analysed with the two-tailed χ^2 test and Student's t test. The risk factors that influence patterns and timing of recurrence were determined by means of logistic regression analysis. Forward stepwise selection with a likelihood ratio test was used for selecting variables. The odds ratio (OR) in logistic regression analysis was defined as the ratio of the probability that an event will occur to the probability that it will not occur.

The prognostic power of covariates was expressed by calculation of a relative risk or OR with 95 per cent confidence intervals. $P < 0{\cdot}05$ was considered statistically significant. All statistical analyses were carried out with the SPSS for Windows (SPSS, Chicago, Illinois, USA) program.

Results

Patterns of recurrence

The main patterns of recurrence in 508 patients are shown in *Fig. 1*. Of these, 403 patients had only one recurrence pattern and 83 (16·3 per cent) had two or more sites of recurrence at the time of diagnosis. As a single pattern, peritoneal recurrence (33·9 per cent) was observed most frequently, followed by haematogenous (26·2 per cent) and locoregional (19·3 per cent) recurrence. The most common combined pattern was locoregional recurrence with peritoneal recurrence in 42 patients (8·3 per cent). Extra-abdominal lymph node metastases such as supraclavicular, inguinal or axillary nodes were found in 22 patients (4·3 per cent). As shown in *Table 1*, the highest incidence of locoregional recurrence was in the anastomosis or stump in 80 patients (15·7 per cent), followed by lymph nodes in 68 patients (13·4 per cent). The most common site of

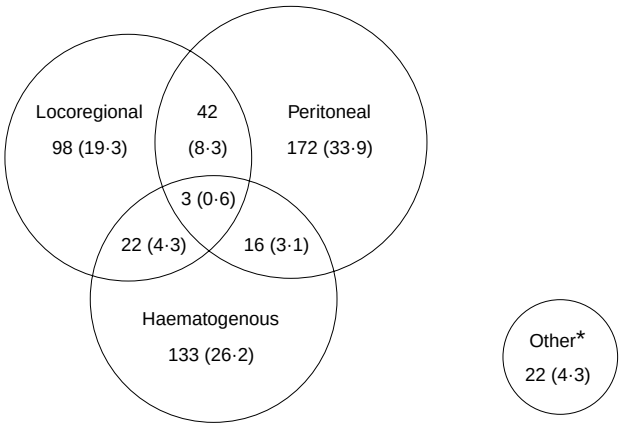

Fig. 1 Patterns of recurrence in 508 patients after curative resection. Values in parentheses are percentages. *Recurrence at the extra-abdominal lymph nodes

haematogenous recurrence was the liver, occurring in 96 patients (18·9 per cent) and in 75 (14·8 per cent) as the only site of recurrence. The relationship between the clinicopathological features of patients and the single pattern of recurrence is shown in *Table 2*. Age, gross and histological type of tumour, and depth of invasion were significantly different between the main patterns of recurrence ($P < 0{\cdot}001$).

Length of time to recurrence

The mean length of time to recurrence was 21·8 (range 3–120) months. For each recurrence pattern, the mean time was 27·3 months for locoregional recurrence, 18·1 months for peritoneal recurrence and 14·6 months for haematogenous recurrence ($P < 0{\cdot}001$, Student's *t* test).

The patients were divided into an early recurrence group (24 months or less) and a late recurrence group (more than

Table 2 Clinicopathological features according to single recurrence patterns

	Locoregional ($n = 98$)	Peritoneal ($n = 172$)	Haematogenous ($n = 133$)	P*
Sex				0·24
M	65 (66·3)	108 (62·8)	92 (69·2)	
F	33 (33·7)	64 (37·2)	41 (30·8)	
Mean age (years)	56·8	50·3	55·9	< 0·001
Tumour size (cm)				0·68
⩽ 4	35 (35·7)	54 (31·4)	46 (34·6)	
> 4	63 (64·3)	118 (68·6)	87 (65·4)	
Tumour location				0·37
Upper third	17 (17·3)	21 (12·2)	20 (15·0)	
Middle third	40 (40·8)	58 (33·7)	50 (37·6)	
Lower third	36 (36·7)	81 (47·1)	60 (45·1)	
Whole	5 (5·1)	12 (7·0)	3 (2·3)	
Gross type				< 0·001
Superficial	5 (5·1)	1 (0·6)	12 (9·0)	
Localized	21 (21·4)	16 (9·3)	30 (22·6)	
Infiltrative or diffuse	72 (73·5)	155 (90·1)	91 (68·4)	
Histological type				< 0·001
Differentiated	28 (28·6)	32 (18·6)	58 (43·6)	
Undifferentiated	70 (71·4)	140 (81·4)	75 (56·4)	
Depth of invasion				< 0·001
pT_1	5 (5·1)	1 (0·6)	12 (9·0)	
pT_2	24 (24·5)	16 (9·3)	27 (20·3)	
pT_3	65 (66·3)	144 (83·7)	88 (66·2)	
pT_4	4 (4·1)	11 (6·4)	6 (4·5)	
Lymph node metastasis				0·24
pN_0	21 (21·4)	27 (15·7)	26 (19·5)	
pN_1	33 (33·7)	60 (34·9)	44 (33·1)	
pN_2	31 (31·6)	53 (30·8)	33 (24·8)	
pN_3	13 (13·3)	32 (18·6)	30 (22·6)	
Type of resection				0·06
Subtotal	69 (70·4)	96 (55·8)	83 (62·4)	
Total	29 (29·6)	76 (44·2)	50 (37·6)	

Values in parentheses are percentages. pT, pathological tumour; pN, pathological node (classification). *χ^2 or Student's *t* test

Table 3 Clinicopathological features according to recurrence time

	Early recurrence (⩽24 months) (n=368)	Late recurrence (>24 months) (n=140)	P*
Sex			0·19
M	251 (68·2)	87 (62·1)	
F	117 (31·8)	53 (37·9)	
Mean age (years)	54·3	52·1	0·17
Tumour size (cm)			0·10
⩽4	119 (32·3)	56 (40·0)	
>4	249 (67·7)	84 (60·0)	
Tumour location			0·052
Upper third	54 (14·7)	16 (11·4)	
Middle third	141 (38·3)	40 (28·6)	
Lower third	155 (42·1)	78 (55·7)	
Whole	18 (4·9)	6 (4·3)	
Gross type			<0·001
Superficial	10 (2·7)	16 (11·4)	
Localized	62 (16·8)	20 (14·3)	
Infiltrative or diffuse	296 (80·4)	104 (74·3)	
Histological type			0·013
Differentiated	115 (31·2)	28 (20·0)	
Undifferentiated	253 (68·8)	112 (80·0)	
Depth of invasion			<0·001
pT_1	10 (2·7)	16 (11·4)	
pT_2	50 (13·6)	33 (23·6)	
pT_3	287 (78·0)	85 (60·7)	
pT_4	21 (5·7)	6 (4·3)	
Lymph node metastasis			<0·001
pN_0	50 (13·6)	43 (30·7)	
pN_1	115 (31·2)	53 (37·8)	
pN_2	118 (32·1)	33 (23·6)	
pN_3	85 (23·1)	11 (7·9)	
Type of resection			<0·001
Subtotal	215 (58·4)	106 (75·7)	
Total	153 (41·6)	34 (24·3)	

Values in parentheses are percentages. pT, pathological tumour; pN, pathological node (classification). *χ^2 or Student's t test

24 months) for correlation with clinicopathological features (*Table 3*). In the early recurrence group, patients with infiltrative or diffuse type of cancer, differentiated tumour, serosal invasion, lymph node metastasis, and who had undergone total gastrectomy were common in comparison with the late recurrence group (P<0·05).

Multivariate analysis of risk factors

The independent risk factors involved in the recurrence of gastric cancer were, in order: lymph node metastasis, serosal invasion, infiltrative or diffuse type, larger tumour size (4 cm or greater), undifferentiated tumour and proximally located tumour (*Table 4*). A further multivariate analysis according to the recurrence patterns (*Fig. 2*) showed that serosal invasion and lymph node metastasis were common risk factors for all recurrence patterns. In addition, peritoneal recurrence was closely related to younger age (50 years or less), infiltrative or diffuse type, undifferentiated tumour and total gastrectomy; haematogenous recurrence was related to older age (above 50 years) and larger tumour size; while locoregional recurrence was related to older age, larger tumour size, infiltrative or diffuse type, proximally located tumour and subtotal gastrectomy. The independent risk factors for early recurrence of gastric cancer were lymph node metastasis (OR 4·988), serosal invasion (OR 3·104), infiltrative or diffuse type (OR 1·890) and total gastrectomy (OR 1·534).

Survival after recurrence

Of 508 patients, 481 died and 27 were still alive after diagnosis of recurrence. Of these 27 patients, only five were disease-free after curative reoperation; the remaining 22 are still alive with recurrent disease. Most patients died within the first year after diagnosis of recurrence and the mean survival time was 8·7 (range 2–66) months. According to the recurrence patterns, patients with peritoneal recurrence

Table 4 Logistic regression analysis of independent risk factors for recurrence of gastric cancer

	β	Odds ratio	P*
Age (⩽50 years, >50 years)	0·044	1·046 (0·868–1·258)	0·636
Sex (M, F)	0·056	1·057 (0·825–1·354)	0·659
Tumour size (⩽4 cm, >4 cm)	0·411	1·507 (1·174–1·934)	0·001
Tumour location (distal, proximal)	0·199	1·220 (1·006–1·481)	0·043
Gross type (superficial or localized, infiltrative or diffuse)	0·592	1·808 (1·483–2·205)	<0·001
Histological type (differentiated, undifferentiated)	0·328	1·387 (1·072–1·795)	0·012
Serosal invasion (none, present)	0·887	2·428 (1·825–3·229)	<0·001
Nodal metastasis (none, present)	1·345	3·838 (2·926–5·036)	<0·001
Type of resection (subtotal, total)	0·142	1.153 (0·813–1·634)	0·423
Lymph node dissection (D_2, D_3 or more)	−0·113	0·893 (0·759–1·051)	0·173

Values in parentheses are 95 per cent confidence intervals. Dependent variables (no recurrence, recurrence). *Likelihood ratio test

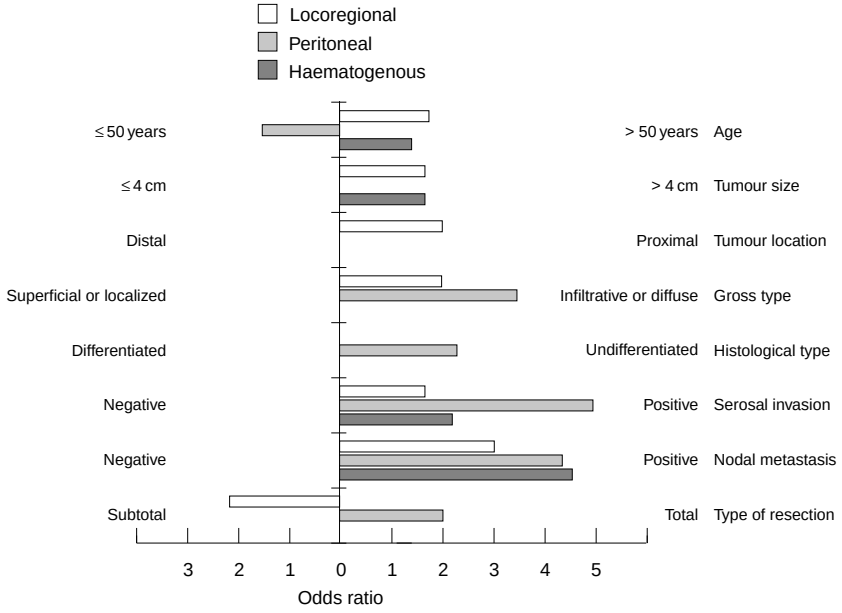

Fig. 2 Independent risk factors according to recurrent pattern by logistic regression analysis ($P < 0{\cdot}05$)

Table 5 Treatment for recurrent gastric cancer and mean survival time related to treatment

Type of treatment	No. of patients	Mean survival (months)
Conservative treatment*	411 (80·9)	8·3
Laparotomy only	25 (4·9)	6·7
Bypass procedure	24 (4·7)	8·5
Palliative resection	29 (5·7)	11·6
Curative resection	19 (3·7)	21·6

Values in parentheses are percentages. *With or without chemotherapy or radiation therapy

died most quickly (mean 6·4 months), followed by those with haematogenous (9·4 months) and locoregional (11·0 months) recurrence. Nineteen patients in whom curative resection was possible survived the longest, with a mean of 21·6 months. However, the mean survival time after non-curative or palliative surgery was less than 12 months (*Table 5*).

Discussion

The disagreement in the literature on recurrence patterns is probably related to the patient cohorts undergoing evaluation, the time at which recurrence was determined, and the methods for determining recurrence patterns. There have been many studies based on autopsy findings, but autopsies reveal only the end patterns of failure[5–7]. Gunderson and Sosin[8] reported a reanalysis of the reoperation series performed by Wangensteen *et al.*[9] at the University of Minnesota, in which patients had a second-look laparotomy after resection of the primary tumour. This type of analysis might be valuable because it can demonstrate the early modes of recurrence rather than simply showing diffuse metastatic disease at autopsy. However, routine second-look surgery has not proven to be a worthwhile procedure in gastric cancer because it can allow for an earlier diagnosis but does not improve the patient's prospects of recovery following treatment[10,11].

In this study, the recurrence patterns were based on clinical or radiological examination, and there may be some underestimation of the exact sites of recurrence. However, the results confirmed that recurrence after curative resection for gastric cancer occurred mostly within the first 2 years after operation in patients with an advanced stage of gastric cancer. Only 26 patients (5·1 per cent) had documented recurrence from early gastric cancer, and the recurrence patterns were haematogenous recurrence ($n = 12$), locoregional recurrence ($n = 5$), peritoneal recurrence ($n = 1$), or a combined pattern ($n = 8$). This study also demonstrated that intra-abdominal spread of the tumour (locoregional, liver or peritoneal recurrence) was the major feature of both single and multicomponent recurrence. Extra-abdominal, haematogenous or lymphatic spread without intra-abdominal metastases occurred rarely.

In two autopsy studies, the rate of locoregional recurrence following potentially curative resection was 40–80 per cent[6,12], but more recent series have suggested a higher incidence of peritoneal recurrence; Japanese researchers have reported that peritoneal surfaces and the liver were the major sites of treatment failure after D_2 or D_3 resection[13,14].

The present study also found that the incidence of locoregional recurrence was the lowest among the recurrence patterns. The site most prone to locoregional recurrence was the anastomosis or stump (15·7 per cent) following distal subtotal ($n = 70$) or total ($n = 10$) gastrectomy; the next was the lymph nodes (13·4 per cent), mostly at the mesenteric or para-aortic nodes rather than the regional lymph nodes. This may be due to routine D_2 or D_3 lymph node dissection. It is therefore possible that extended lymphadenectomy with intraoperative frozen-section examination of the resection margins may further decrease the incidence of locoregional recurrence in gastric cancer after curative resection.

There have been several studies of the relationship between recurrence patterns, time to recurrence and clinicopathological features[15–21]. Borrmann type III or IV, poorly differentiated tumours, as well as tumours with serosal invasion, adjacent tissue invasion or free intraperitoneal cancer cells, have been reported to be associated with a high risk of subsequent peritoneal spread[17–20]. It has also been reported that haematogenous recurrence, in particular liver recurrence, develops more frequently from Borrmann type I or II and well differentiated tumours[21], so that the incidence of haematogenous recurrence is relatively higher in cases of early gastric cancer[22,23].

From the logistic regression analysis, serosal invasion and lymph node metastasis were common risk factors for all recurrence patterns: serosal invasion was the highest risk factor for peritoneal recurrence, and lymph node metastasis for haematogenous recurrence. It was noteworthy that age was a different risk factor according to the recurrence pattern: younger age was a risk factor for peritoneal recurrence, whereas older age was a risk factor for haematogenous and locoregional recurrence. Differentiated tumour was predominant in haematogenous recurrence, but was not an independent risk factor for this type of recurrence in the multivariate analysis.

Furthermore, lymph node metastasis was the most significant risk factor for recurrence of gastric cancer, as well as the early recurrence of tumour. Recent studies[24,25] have disclosed that the number of metastatic lymph nodes is an important prognostic factor in gastric cancer. Siewert *et al.*[26] also reported that lymph node ratio and residual tumour are the major independent prognostic factors in patients with resected gastric cancer, and that extended lymph node dissection is the most important factor determining long-term survival in patients with stage II gastric cancer.

A number of factors, including a low rate of resectability, poor patient tolerance for treatment, frequent postoperative morbidity and mortality after operation, and an overall dismal prognosis, lead to pessimism when faced with recurrent gastric cancer[27]. The prognosis of recurrent gastric cancer in the present series was generally poor with a mean survival time of 8·7 months. Patients with peritoneal or haematogenous recurrence mostly died within 10 months after diagnosis of recurrence. Furthermore, the proportion of operations for recurrence and the prospects of a secondary cure were extremely limited. Of 508 patients, curative resection of locoregionally recurrent cancer was possible in only 19 patients (3·7 per cent), and only five patients (1·0 per cent) remained disease-free. Removal of metastatic tumour at the abdominal wound, drain site, extra-abdominal lymph nodes, or in the peritoneal cavity with or without adjuvant treatment has not been shown to be effective in prolonging survival time.

A review of clinical trials suggests that no single method of treatment can efficiently address all variants of gastric cancer spread, and that no improvement in the results obtained in recurrence of gastric cancer can be expected. At present, therefore, prevention or reduction of the frequency of recurrence is probably more important than the early detection of recurrence.

Treatment should start with complete resection of the primary tumour, including an adequate resection margin and extended lymphadenectomy to reduce the incidence of locoregional failure. Based on the high rate of peritoneal recurrence in this study, surgery alone is seen to be an inadequate treatment for cure. The results of several randomized trials have demonstrated that intraperitoneal chemotherapy in normothermic or hyperthermic patients tends to improve survival rates and decrease the incidence of peritoneal failure compared with surgery alone[28–31]. For patients with a high risk of peritoneal recurrence, intraperitoneal chemotherapy may thus be a valuable adjuvant at operation or early in the postoperative period.

In conclusion, the patterns and timing of recurrence varied with the characteristics of primary gastric cancer. As the prognosis of patients with recurrence was very poor, the selection of postoperative adjuvant therapy in systemic (intravenous or intra-arterial) and/or regional (intraperitoneal) based on the predicted risk of each recurrence pattern may be a reasonable approach to improve the prognosis of gastric cancer.

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