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Predictive Factors Improving Survival After Gastrectomy in Gastric Cancer Patients with Peritoneal Carcinomatosis

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Abstract

Background The aim of this study was to review prognosis following gastrectomy for gastric cancer patients with synchronous peritoneal carcinomatosis and to identify predictive factors for improving survival after gastrectomy in this setting.

Methods Records of all patients who underwent gastrectomy for gastric cancer with peritoneal dissemination in our center between 1993 and 2004 were reviewed.

Results Data of 101 patients who underwent gastrectomy for gastric cancer with peritoneal dissemination were available. Peritoneal dissemination was classified as P1, metastasis to the adjacent peritoneum in 34 patients; P2, a few scattered metastases to the adjacent peritoneum in 13 patients; and P3, numerous metastases in 54 patients. Nineteen patients sustained 21 adverse events. Overall survival was significantly improved for those in the P1 and P2 groups compared with that for the P3 group (median of 18 months and 15 months vs. 9 months; $P < 0.001$). Seven factors were significant for overall survival: peritoneal carcinomatosis, peritoneal lavage cytology, macroscopic type, resection margin, extent of lymph node dissection, curative potential of gastric resection, and chemotherapy, including perioperative and postrecurrent chemotherapy. In multivariate analysis, two factors were identified as independently associated with poor survival: P3 disease ($P = 0.002$) and absence of chemotherapy ($P = 0.009$). Univariate analysis of gastric cancer patients with P1 or P2 carcinomatosis revealed only tumor differentiation to be significant.

Conclusions Gastric cancer patients with P1/P2 carcinomatosis and well/moderately differentiated tumors are likely to have an improved survival after gastrectomy. We emphasize that patients with good performance status and P1/P2 carcinomatosis should be considered appropriate surgical candidates before embarking on palliative systemic chemotherapy alone.

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Introduction

Gastric cancer disseminates by hematogenous, lymphatic, and direct implants on peritoneal surfaces. Peritoneal dissemination is the most frequent pattern of metastasis and recurrence in patients with gastric cancer [1–3]. Patients (10–20%) investigated for potentially curative resection of gastric cancer will have peritoneal seeding at the time of abdominal examination, and some patients with gastric cancer will present with peritoneal carcinomatosis [4–6].

Traditionally, there was a mutual agreement in the oncology community that those patients with gastric peritoneal dissemination were incurable [7]. Results of published studies have indicated a median survival of about 6 months [8, 9]. Despite improvements in systemic chemotherapy, gastric cancer patients with peritoneal dissemination generally have poor survival, and although palliative systemic chemotherapy has shown encouraging tumor response rates, there has been no improvement in survival [10–12]. Positive effects of palliative gastric cancer resection on survival have been previously demonstrated in patients with peritoneal carcinomatosis [5, 6, 13–17] but surgical strategies for these patients remain controversial.

The aim of this study was to review the prognosis following gastrectomy for gastric cancer patients with synchronous peritoneal carcinomatosis and to identify predictive factors for improving the survival rate after gastrectomy in this setting.

Methods

Patients

Between January 1993 and December 2004, a total of 101 consecutive patients underwent gastrectomy for gastric cancer with peritoneal dissemination at the National Cancer Center Hospital East in Chiba, Japan. The diagnosis of peritoneal dissemination was based on the operative findings and therefore the medical records of these patients were retrospectively reviewed. Clinical, pathological, and treatment-related variables were analyzed. These included age, gender, preoperative symptoms, tumor location, tumor macroscopic type, depth of tumor invasion (T), lymph node metastasis (N), peritoneal lavage cytology (CY), peritoneal dissemination (P), pathological confirmation of peritoneal dissemination, other distant metastasis, histology, lymphatic invasion (ly), venous invasion (v), resection margins, operative procedure, lymph node dissection, curative potential of resection, chemotherapy including perioperative and postrecurrent chemotherapy, and postoperative complications. Patient follow-up lasted until death or until the cutoff date of October 1, 2008. At the cutoff date only one patient was lost to follow-up. The patient had been followed for 10 years after gastrectomy and had completed the follow-up.

Classification of gastric cancer

Histopathological features, except peritoneal metastasis, lymph node dissection, and curative potential of resection, were evaluated according to the second English edition of the Japanese classification of gastric carcinoma published by the Japanese Gastric Cancer Association [18].

Peritoneal carcinomatosis

The second English edition of the Japanese classification of gastric carcinoma published by the Japanese Gastric Cancer Association classified peritoneal metastasis with only three grades: P0, no peritoneal metastasis; P1, peritoneal metastasis; and PX, unknown [18]. We believe that the extent of peritoneal carcinomatosis should influence the survival of gastric cancer patients with synchronous peritoneal carcinomatosis after gastrectomy. Therefore, in this study we classified peritoneal carcinomatosis according to the first edition of the General Rules for Gastric Cancer Study published by the Japanese Research Society for Gastric Cancer as follows: P0, no implants to the peritoneum; P1, cancerous implants to the region directly adjacent to the stomach peritoneum (above the transverse colon), including the greater omentum; P2, several scattered metastases to the distant peritoneum and ovarian metastasis alone; and P3, numerous metastases to the distant peritoneum [19].

Operation

Patients in this study underwent gastrectomy for gastric cancer with peritoneal dissemination. We performed D2 lymphadenectomy as our standard nodal dissection. However, we changed the type of nodal dissection in balance with other factors such as the degree of peritoneal dissemination, peritoneal lavage cytology, and lymph node metastases. D number was evaluated according to the second English edition of the Japanese classification of gastric carcinoma, and the curative potential of resection was evaluated according to this classification as follows: resection A, no residual disease with a high probability of cure (implies resection satisfying all of the following conditions: T1 or T2; N0 treated by D1–3 resection or N1 treated by D2, 3 resection; M0, P0, H0, CY0, and proximal and distal margins >10 mm); resection B, no residual disease but not fulfilling criteria for resection A; and resection C, definite residual disease [18].

Statistical analysis

The clinical characteristics of the different groups were compared using the χ^2 test. Cumulative survival analysis was performed using the Kaplan–Meier method and compared using the log-rank test. The overall survival analysis included all deaths such as in-hospital death or death from unrelated cause. A Cox regression (Cox proportional hazards model) was used for the multivariate analysis. All statistical analyses were performed using the Statistical Package for Social Sciences for Windows (SPSS Japan Inc., Tokyo, Japan). A significant difference was defined as $P < 0.05$.

Results

Descriptive data

Between January 1993 and December 2004, a total of 101 patients underwent gastrectomy for gastric cancer with peritoneal dissemination. The clinicopathological and treatment-related characteristics of the patients are given in

Table 1 Clinicopathological and treatment-related characteristics of the patients

Variables	P1 ($n = 34$)	P2 ($n = 13$)	P3 ($n = 54$)	p
Age (mean ± SD)	58.7 ± 11.1	56.7 ± 11.3	57.4 ± 12.9	NS
Gender (male/female)	22/12	9/4	32/22	NS
Location (U/M/L)	7/9/18	1/4/8	13/24/17	NS
Macroscopic type (non-type 4/type 4)	27/7	7/6	31/23	NS
T (T2/T3/T4)	1/29/4	1/10/2	0/47/7	NS
N (N0-2/N3)	23/11	12/1	41/13	NS
CY (X/0/1)	2/25/7	2/7/4	5/14/35	<0.001
Histology (differentiated/undifferentiated)	7/27	4/9	13/41	NS
Ly (0/1−3)	6/28	3/10	4/50	NS
V (0/1−3)	4/30	0/13	2/52	NS
Resection margin (negative/positive)	31/3	10/3	43/11	NS
Lymph node dissection (≥D2/<D2)	26/8	3/10	8/46	<0.001
Curative potential of gastric resection (B/C)	26/8	1/12	1/53	<0.001
Chemotherapy (including perioperative and postrecurrent) (+/−)	27/7	9/4	36/18	NS

NS not significant

Table 1. Peritoneal dissemination was classified as P1 in 34 patients (34%), P2 in 13 patients (13%), and P3 in 54 patients (53%). Ninety-six patients had peritoneal dissemination alone, whereas 5 patients had liver metastasis (P1, 2 of 34; P2, 0 of 13; P3, 3 of 54). Eighty-seven patients had pathologically confirmed peritoneal dissemination and 14 patients were diagnosed with peritoneal dissemination based on operative findings. The patients without pathological confirmation of peritoneal dissemination in each group were P1, 4 of 34; P2, 1 of 13; and P3, 9 of 54.

No statistical difference was observed in the mean age of the patients in each group. There were more men than women in each group (P1, 22 vs. 12; P2, 9 vs. 4; P3, 32 vs. 22) but the difference in the gender ratio of each group was not significant. The differences in tumor location, macroscopic type, T, N, histology, ly, and v of primary lesions were not significant. Resection margin status and chemotherapy (including perioperative and postrecurrent) were not significant. There were more P3-group patients with a positive CY (P1, 7 of 34; P2, 4 of 13; P3, 35 of 54), and the difference in the CY-positive ratio was significant ($P < 0.001$). Compared with the other groups, more patients in the P1 group required extensive lymphadenectomy ($P < 0.001$) and achieved the curative potential of gastric resection B ($P < 0.001$).

Eighty-two patients (81%) had no postoperative complications. The remaining 19 patients sustained 21 adverse events, including intra-abdominal abscess ($n = 3$), anastomotic leakage ($n = 3$), pancreatic fistula ($n = 7$), anastomotic stenosis ($n = 1$), wound infection ($n = 3$), small bowel obstruction ($n = 1$), cholecystitis ($n = 1$), and pneumonia ($n = 2$). One patient, who underwent gastrectomy and right hemicolectomy simultaneously, suffered from sepsis due to anastomotic leakage after colonojejunostomy and died.

Survival data

Figure 1 shows the overall patient survival after gastrectomy stratified according to the extent of peritoneal dissemination. There was a significant overall improved survival for those in the P1 and P2 groups than in the P3 group (median of 18 months and 15 months vs. 9 months; $P < 0.001$ by log-rank test). The 1-year survival for patients in the P1, P2, and P3 groups was 64.7, 69.2, and 35.2%, respectively. The 5-year survival of each group was 14.7, 15.4, and 0%, respectively. Four patients were alive at the time of follow-up, and there were 13, 7, and 2 patients who survived for 3, 5, and 10 years, respectively.

Univariate analysis of potential prognostic factors for survival

Clinicopathological and treatment-related factors were analyzed for their prognostic significance in these 101 patients. Table 2 gives the univariate analysis of the clinicopathological and treatment-related factors affecting overall survival. Seven factors were found to be significant for overall survival: P ($P < 0.001$), CY ($P = 0.002$), macroscopic type ($P = 0.017$), resection margin ($P = 0.049$), extent of lymph node dissection ($P = 0.018$), curative potential of gastric resection ($P < 0.001$), and chemotherapy, including perioperative and postrecurrent chemotherapy ($P = 0.013$). The following factors were not significant prognostic indicators for overall survival: N ($P = 0.481$), tumor differentiation ($P = 0.056$), other

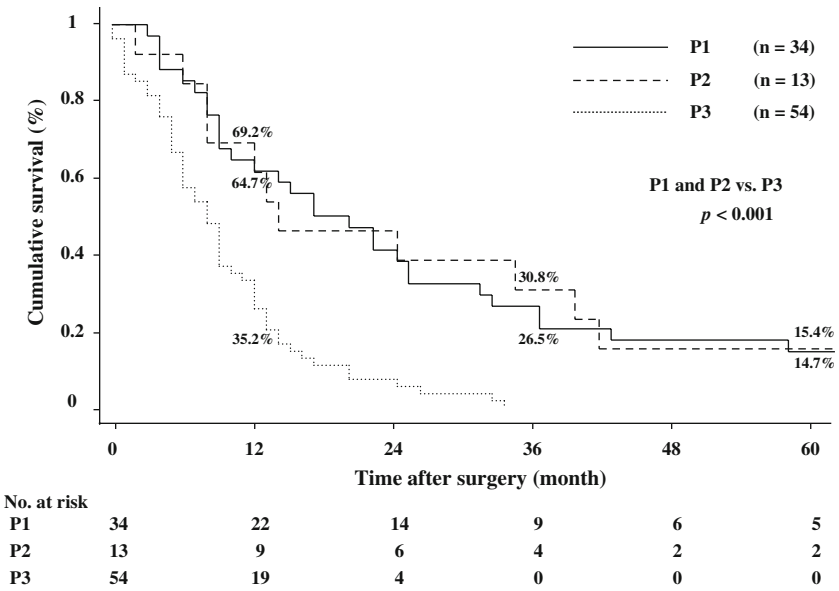

Fig. 1 Overall survival after gastrectomy for gastric cancer patients with peritoneal carcinomatosis. The prognostic significance for the degree of peritoneal dissemination was $P < 0.001$

Table 2 Univariate analysis of the clinicopathological and treatment-related factors affecting overall survival

Variable	Patients (*n*)	Median survival (months)	Survival rate (%)		*P*
			1 year	3 year	
Total	101	11	48.5	12.9	
P					
P1–2	47	18	66.0	27.7	<0.001
P3	54	9	33.3	0.0	
CY					
CY0	46	17	65.2	21.7	0.002
CY1	46	8	30.4	6.5	
Macroscopic type					
Non-type 4	66	13	53.0	18.2	0.017
Type 4	35	10	40.0	2.9	
Resection margin					
Negative	84	13	51.2	15.5	0.049
Positive	17	9	35.3	0.0	
Lymph node dissection					
≥D2	37	15	62.2	21.6	0.018
<D2	64	10	40.6	7.8	
Curative potential of gastric resection					
B	28	18	67.9	32.1	<0.001
C	73	10	41.1	5.5	
Chemotherapy (including perioperative and postrecurrent)					
+	72	13	58.3	13.9	0.013
−	29	7	27.6	10.3	

distant metastases ($P = 0.367$), neoadjuvant chemotherapy ($P = 0.210$), adjuvant chemotherapy ($P = 0.256$), and pathological confirmation of peritoneal dissemination ($P = 0.307$).

Multivariate analysis for survival

In the multivariate analysis of overall survival, two factors were identified to be independently associated with

Table 3 Multivariate analysis of clinicopathologic and treatment-related factors affecting survival

Variable	Hazzard ratio	95% CI	*P*
P (P1 and P2 vs. P3)	2.347	1.372–4.016	0.002
CY (CY0 vs. CY1)	1.378	0.845–2.248	NS
Macroscopic type (non-type 4 vs. type 4)	1.354	0.856–2.141	NS
Resection margin (negative vs. positive)	1.627	0.900–2.941	NS
Lymph node dissection (≥D2 vs. <D2)	1.200	0.728–1.979	NS
Curative potential of gastric resection (B vs. C)	1.169	0.601–2.276	NS
Chemotherapy (including perioperative and postrecurrent) (+ vs. −)	1.858	1.165–2.963	0.009

P peritoneal carcinomatosis; *CY* peritoneal lavage cytology

improved survival: P3 disease (hazard ratio = 2.347; 95% confidence interval = 1.372-4.016; $P = 0.002$), and absence of chemotherapy, including perioperative and postrecurrent chemotherapy (hazard ratio = 1.858; 95% confidence interval = 1.165-2.963; $P = 0.009$) (Table 3).

Potential prognostic factors for survival in the P1/P2 groups

Patients evaluated at P3 stage had no hope for prolonged survival after gastrectomy. Therefore, we analyzed clinicopathological and treatment-related factors for prognostic significance in 47 patients evaluated at P1 or P2 stage. Table 4 gives the univariate analysis of clinicopathological and treatment-related factors of gastric carcinoma patients with P1/P2 carcinomatosis. Gender ($P = 0.498$), preoperative symptoms ($P = 0.188$), tumor location ($P = 0.449$), macroscopic type ($P = 0.173$), T ($P = 0.459$), N ($P = 0.612$), other distant metastases ($P = 0.886$), pathological confirmation of peritoneal carcinomatosis ($P = 0.142$), CY ($P = 0.333$), resection margin ($P = 0.315$), extent of lymph node dissection ($P = 0.883$), operative procedure ($P = 0.830$), curative potential of gastric resection ($P = 0.402$), neoadjuvant chemotherapy ($P = 0.306$), adjuvant chemotherapy ($P = 0.467$), and chemotherapy, including perioperative and postrecurrent chemotherapy ($P = 0.433$), were not significant prognostic indicators for overall survival. Tumor differentiation was the only factor that was found to be significant for overall survival ($P = 0.048$) (Fig. 2).

Discussion

Gastrectomy has been performed in our hospital for gastric cancer patients with either isolated peritoneal carcinomatosis with curative intent or disseminated peritoneal carcinomatosis with palliative intent. Despite several positive reports of palliative resection [5, 6, 13–17] and in the absence of any evidence provided so far on the efficacy of systemic chemotherapy for the selected group of patients, accepting patients with peritoneal dissemination for resection may seem controversial. Indeed, the current opinions on the standard of care for these patients are polarized: chemotherapy with or without resection.

There are several classifications that describe the quantitative prognostic indicators of peritoneal dissemination for gastric cancer [20, 21]. In this study we classified peritoneal dissemination according to the first edition of the General Rules for Gastric Cancer Study [19]. Univariate analysis of clinicopathological and treatment-related factors affecting overall survival of patients with peritoneal dissemination revealed seven significant factors: P, CY, macroscopic type, resection margin, extent of lymph node dissection, curative potential of gastric resection, and chemotherapy, including perioperative and postrecurrent chemotherapy. The results of the multivariate analysis indicated that P and chemotherapy, including perioperative and postrecurrent chemotherapy, were identified as independently associated with improved survival. We observed a postoperative morbidity rate of 19% and mortality rate of 1%, which were comparable with those observed in a previous report on surgery for advanced gastric cancer [14, 22–25]. These survival results and surgical risk for what is regarded as an incurable disease are very encouraging, especially for patients with P1/P2-graded peritoneal dissemination. From a surgeon's perspective, we believe that emphasis should be placed on stringent patient selection to identify the most optimal surgical candidates and to avoid futile aggressive treatment.

Furthermore, the univariate analysis of clinicopathological factors affecting overall survival in gastric cancer patients at P1 or P2 stage carcinomatosis revealed only tumor differentiation to be significant. In this setting, chemotherapy, including perioperative and postrecurrent chemotherapy, was not predictive for improving survival after gastrectomy ($P = 0.433$). In addition, curability and nodal dissection were not significant factors. Therefore, when patients with P1/P2 undergo resection, extent of

Table 4 Univariate analysis of clinicopathological and treatment-related factors of gastric carcinoma patients with P1/P2 carcinomatosis

Variable	Patients (*n*)	Median survival (months)	Survival rate (%)		*p*
			1 year	3 year	
Total	47	18	66.0	27.7	
Macroscopic type					
Non-type 4	35	21	65.7	34.3	0.173
Type 4	12	15	66.7	8.3	
T					
Non-T4	41	23	70.7	29.3	0.459
T4	6	10	33.3	16.7	
N					
<N3	35	18	68.6	28.6	0.612
≥N3	12	15	58.3	25.0	
Other distant metastasis					
−	45	18	64.4	28.9	0.886
+	2	26	100.0	0.0	
Pathological confirmation of peritoneal dissemination					
−	5	32	100.0	40.0	0.142
+	42	15	61.9	26.2	
CY					
CY0	32	25	71.9	31.3	0.197
CY1	11	11	45.5	27.3	
Tumor differentiation					
Well/moderately	11	33	100.0	45.5	0.048
Poorly	36	13	55.6	22.2	
Lymph node dissection					
≥D2	29	18	58.6	27.6	0.883
<D2	18	18	77.8	27.8	
Operative procedure					
Nontotal gastrectomy	19	18	63.2	31.6	0.830
Total gastrectomy	28	18	67.9	25.0	
Curative potential of gastric resection					
B	27	21	66.7	33.3	0.402
C	20	15	65.0	20.0	
Neoadjuvant chemotherapy					
−	44	18	68.2	29.6	0.306
+	3	10	33.3	0.0	
Adjuvant chemotherapy					
−	23	15	60.9	30.4	0.467
+	24	25	70.8	25.0	
Chemotherapy (including perioperative and postrecurrent)					
−	11	13	54.6	27.3	0.433
+	36	23	69.4	27.8	

dissection and curability should not be taken into consideration. Well/moderately differentiated gastric cancer patients with P1 or P2 had a median survival of 25 months, a 3-year survival of 45.5%, and a 5-year survival of 27.3%. These results emphasize that patients in this setting should be considered for better surgical indication.

The median survival time of patients in the P3 group was 9 months. The SPRITS trial by Koizumi et al. [12] showed a median survival time of about 13 months in patients treated with S-1 plus cisplatin for unresectable or recurrent advanced gastric cancer. It is difficult to determine the benefits of tumor reduction surgery in such patients.

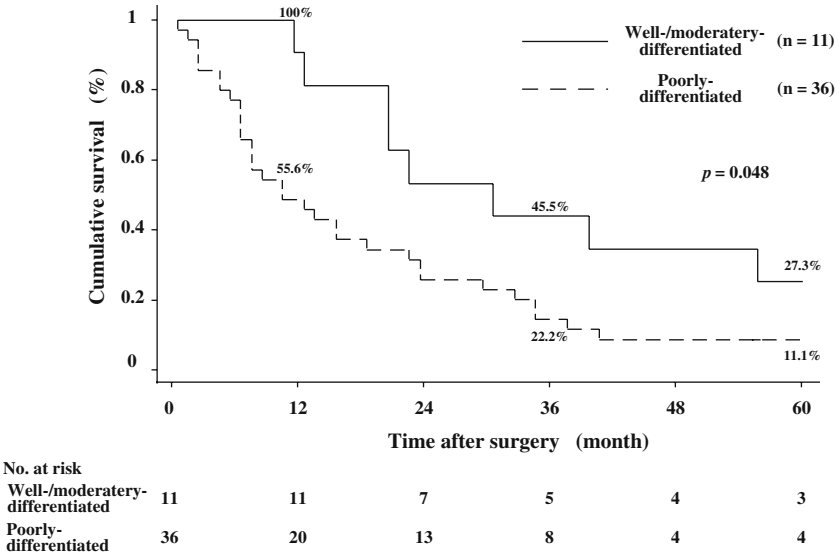

Fig. 2 Overall survival after gastrectomy for gastric cancer patients with peritoneal carcinomatosis (P1 or P2). The prognostic significance for tumor differentiation was $P = 0.048$

It appears that the most important prognostic factors for survival are localization and few peritoneal disseminations. Whether P1/P2 carcinomatosis implies merely the quantity of tumor cells, lower malignancy of the cancer itself, or potency of complete reduction needs further discussion. Indeed, multivariate analysis did not show that curability was not a significant prognostic factor in this study. Nevertheless, these groups of patients should at least be considered appropriate surgical candidates.

The current study had several limitations. This was a retrospective study and therefore the patients might have received a variety of treatments, including palliative or curative resection with or without neoadjuvant and/or adjuvant and palliative chemotherapy. Indeed, the patients with a more advanced degree of peritoneal dissemination had more palliative resection. The chemotherapy regimens were changed a lot. The patients without chemotherapy were in the earlier part of the study, and the patients treated with several regimens were in later period. Among seven patients who lived more than 5 years after surgery, three patients did not undergo postoperative chemotherapy. However, it was difficult to evaluate the effects of chemotherapy in detail.

In conclusion, the present study indicated that gastric cancer patients with P1/P2 carcinomatosis and well/moderately differentiated tumors are likely to have improved survival after gastrectomy. Reduction surgery may have a role in gastric cancer with minimal peritoneal dissemination. We emphasize that patients with good performance status and P1/P2 carcinomatosis should be considered appropriate surgical candidates before embarking on palliative systemic chemotherapy alone.

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