



## Survival and Prognostic Factors of Patients with Advanced CY1/P0 Gastric Cancer

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### Abstract

**Introduction:** The prognosis is poor for patients with gastric cancer with positive cytologic examinations of peritoneal lavage fluid (CY1), and optimal treatment is not established. Further, the surgical strategy for patients with free cancer cells in the intraperitoneal fluid in the absence of overt peritoneal metastasis (CY1/P0) is controversial. Here, we investigated the clinical outcomes and prognostic factors of patients with CY1/P0 gastric cancer.

**Methods:** We conducted an analysis of 39 patients with CY1/P0 gastric cancer who underwent gastrectomy and analyzed the clinical characteristics of patients who survived  $\geq 3$  years after surgery.

**Results:** Large type-3 and type-4 tumors, scirrhous (sci), and infiltrative growth cancers (INFc) were associated with high recurrence rates. INFc was an independent risk factor for recurrence. Univariate analysis of overall survival (OS) showed that large type-3 and type-4 cancers, INFc, and lack of postoperative chemotherapy correlated with poor OS. Multivariate analysis showed that INFc and postoperative chemotherapy were independent prognostic factors. Univariate analysis showed that large type-3 and type-4 tumors, sci, INFc, and large tumor size correlated with poor progression-free survival (PFS). Multivariate analysis showed that INFc was an independent prognostic factor of PFS. The numbers of long-term survivors with large type-3 and type-4 cancers were significantly lower compared with those with types 1–3.

**Conclusion:** In patients with CY1/P0 gastric cancer, INF and postoperative chemotherapy were independent prognostic factors of OS. The prognosis of large type-3 and type-4 P0/CY1-gastric cancers is very poor. Therefore, such patients should be treated with multidisciplinary therapy such as neoadjuvant chemotherapy.

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### Introduction

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer-related death worldwide [1]. Patients with advanced gastric cancer have poor survival despite progress in multidisciplinary therapy [2,3]. Peritoneal dissemination (P1) is the most common metastatic pattern in gastric cancer, and the prognosis is extremely poor [4,5]. Patients with free intraperitoneal cancer cells without overt peritoneal metastasis (CY1/P0) are categorized as stage IV [6,7], and their 5-year overall survival (OS) rate after potentially curative surgery is 0–35% [8]. Peritoneal metastases arise from implantation of free peritoneal cancer cells, and CY1/P0 disease is considered a precursor of peritoneal metastasis. A positive cytologic examination of peritoneal lavage fluid (CY1) is considered a poor prognostic factor for patients with gastric cancer [9,10].

CY1 is therefore considered equivalent to distant metastasis, regardless of the presence of peritoneal metastasis. Since 1999, CY1 gastric cancer has been considered stage IV disease according to the Japanese Classification of Gastric Cancer (JCGC) stages [11]. Because peritoneal lavage cytology is available in at least 90% of hospitals in Japan, this test may have the same prognostic significance as peritoneal dissemination [12]. Moreover, the Union for International Cancer Control (UICC) has considered CY1-gastric cancer as stage IV disease since 2009 [7]. Although the prognosis of CY1 patients is poor, the optimal treatment for these patients is not established. Therefore, the aim of the current study was to identify prognostic factors by evaluating the most recent clinical outcomes of patients with CY1/P0 gastric cancer.

### Materials and Methods

#### Patients

Between 2000 and 2014, 1830 patients with histologically confirmed primary gastric cancer

**Table 1:** Patient characteristics (n = 39).

Factors	Number of patients
Age (years)	median: 73 (30 –86) ≥70: 25, <70: 14
Gender	Male: 24, Female: 15
Tumor location	U:5, M: 15, L: 19
Cross-sectional parts	Less: 12, Gre: 4, Ant: 2, Post: 2, Circ: 19
Macroscopic types	Type 1: 1, Type 2: 5, Type 3 (<80mm): 7, Type 3 (≥80mm): 14, Type 4: 12
Histology	pap: 1, tub1: 1, tub2: 11, por1: 4, por2: 13, sig: 8, muc: 1
Depth	SS: 1, SE: 34, SI: 4
Stromal volume	med: 6, int: 13, sci: 20
INF	a: 2, b: 12, c: 25
ly	ly0: 0, ly1: 5, ly2: 13, ly3: 21
v	v0: 3, v1: 24, v2: 11, v3: 1
N	N0: 2, N1: 4, N2: 6, N3a 12, N3b 15
Size	median: 105 mm (45 –194 mm) ≥100 mm: 21, <100 mm: 18
Type of gastrectomy	Distal gastrectomy: 20, Total gastrectomy: 8, Total gastrectomy+Splenectomy: 10, Total gastrectomy+Splenectomy+Colostomy: 1
Lymph node dissection	D0: 1, D1: 9, D1+: 3, D2: 26
Neoadjuvant chemo	none: 35, S-1+CDDP: 4 type 4 cases(2 course: 3, 4 course: 1)
Postop chemo	none: 5, S-1:13, S-1+CDDP: 3, S-1+PTX: 6, S-1+DOC: 6, 5'DFUR: 5, S-1+CDDP+trastuzumab: 1, second line: 11, third line: 3, fifth line: 1, sixth line: 1
Complications	anastomotic leakage: 2, anastomotic stenosis: 2, leakage of pancreatic juice: 2, pneumonia: 2, ileus: 1
Type of recurrence	P only: 16, N only: 2, bone only: 1, ovary: 1, P + lung: 1, N + bone: 1, P + liver: 1, P + N: 1, P + liver + N: 1, P + lung + liver + N: 1

U: Upper Third; M: Middle Third; L: Lower Third; Less: Lesser Curvature; Gre: Greater Curvature; Ant: Anterior Wall; Post: Posterior Wall; Circ: Circumferential; Pap: Papillary Adenocarcinoma; Tub1: Well-Differentiated Tubular Adenocarcinoma; Tub2: Moderately Differentiated Tubular Adenocarcinoma; Por1: Solid Type Poorly Differentiated Adenocarcinoma; Por2: Non-Solid Type Poorly Differentiated Adenocarcinoma; Sig: Signet Ring Cell Carcinoma; Muc: Mucinous Adenocarcinoma; SS: Subserosa; SE: Contiguous To Serosa Or Penetrates The Serosa And Is Exposed To Peritoneal Cavity; SI: Tumor Invades Adjacent Structures; Med: Medullary Type; Int: Intermediate Type; Sci: Scirrhous Type; INF: Tumor Infiltrative Pattern; Infa: Expanding Growth; Infb: Intermediate Pattern; Infc: Infiltrative Growth; Ly: Lymphatic Invasion; Ly0: No Lymphatic Invasion; Ly1: Minimal Lymphatic Invasion; Ly2: Moderate Lymphatic Invasion; Ly3: Marked Lymphatic Invasion; V: Venous Invasion; V0: No Venous Invasion; V1: Minimal Venous Invasion; V2: Moderate Venous Invasion; V3: Marked Venous Invasion; N: Lymph Node Metastasis; N0: No Regional Lymph Node Metastasis; N1: Metastasis In 1-2 Regional Lymph Nodes; N2: Metastasis In 3-6 Regional Lymph Nodes; N3a: Metastasis In 7-15 Regional Lymph Nodes; N3b: Metastasis In 16 Or More Regional Lymph Nodes; D: Lymph Node Dissection; Postop: Postoperative; Chemo: Chemotherapy; CDDP: Cisplatin; PTX: Paclitaxel; Doc: Docetaxel; 5'DFUR: Doxifluridine; P: Peritoneum

underwent surgery at the Department of Surgery, Kurume University School of Medicine, Kurume, Japan. Peritoneal lavage cytology was principally performed for patients with tumors clinically invading the muscularispropria (cT2) or beyond, while it was omitted for tumors clinically confined to the mucosa or submucosa (cT1). Therefore, 684/1830 (37.4%) without distant metastasis underwent peritoneal lavage cytology, and 39 (5.7%) with cT2 or beyond were diagnosed as CY1/P0.

### Clinicopathological factors

Analysis of tumor recurrence and prognosis were performed to identify independent factors to predict recurrence and prognosis of the 39 patients with CY1/P0 gastric cancer who underwent gastrectomy. Nineteen clinicopathological parameters were investigated, as listed in (Table 1), including neoadjuvant chemotherapy, postoperative chemotherapy, postoperative complications, and type of recurrence. Tumor location, cross-sections of the stomach, macroscopic type, and histology, depth of tumor invasion, stromal volume, tumor infiltrative pattern (INF), lymphatic invasion (ly), venous invasion (v), and lymph node metastasis (N) were evaluated according to the 3rd English edition of the Japanese Classification of Gastric Carcinoma [6]. The types of gastrectomy and lymph node dissection (D) were evaluated according to the Japanese Gastric Cancer Treatment Guidelines 2010 (ver. 3) [13]. In the present study, macroscopic type-3 cancer (≥80 mm) was defined as large type-3 cancer.

### Long-term survival

Patient's alive ≥3 years after surgery are called long-term survivors.

### Statistical analyses

The clinical variables of patients with recurrence and long-term survivors were compared using univariate analysis and the  $\chi^2$  test. We used a logistic regression method to extract significant factors further analysis. OS and progression-free survival (PFS) rates were calculated according to the Kaplan–Meier method, and differences were evaluated using the log-rank test. Cox's proportional hazards regression model was used to identify prognostic factors for survival.  $P < 0.05$  was considered statistically significant. All statistical analyses were performed using SPSS II software (IBM Co., Armonk, NY).

## Results

### Patients' characteristics

The clinicopathological characteristics of 39 patients with CY1/P0 gastric cancer are presented in (Table 1). The median age was 73 years (range, 30-86 years) and 24 patients were male. Thirty-three patients (84.6%) had macroscopic infiltrating types that included type-3 and type-4 tumors. There were 26 patients (66.7%) with large type-3 and type-4 tumors. Twenty patients (51.3%) had scirrhous type (sci) and 25 (64.1) had infiltrative growth (INFc). The four (10.2%) patients with type-4 cancer who underwent neoadjuvant chemotherapy were

**Table 2:** Characteristics of patients with and without recurrence.

Factors	(-)	(+)	P value	HR	Multivariate HR (95 % CI)	P value
Age						
<70yrs	3	11	0.682			
>= 70yrs	8	16				
Sex						
Male	6	17	0.908			
Female	5	10				
Tumor location						
L, M	10	23	1			
U	1	4				
Cross-sectional parts						
Non-circ	7	12	474			
Circ	4	15				
Macroscopic types						
1,2,3 (< 80mm)	7	6	0.039	1.035	0.119-8.987	0.975
3 (≥80mm)	4	4	21			
Histology						
Differentiated	6	7	0.19			
Undifferentiated	5	20				
Depth						
SS, SE	9	25	0.69			
SI	2	2				
Stromal volume						
med, int	9	9	0.018	2.591	0.267-25.183	0.412
Sci	2	18				
Infiltrative pattern (INF)						
a,b	9	5	0.001	11.91	1.366-103.888	0.025
c	2	22				
Lymphatic invasion (ly)						
1,2	6	5	0.836			
3	5	15				
Venous invasion (v)						
0,1	8	18	1			
2,3	3	9				
Lymph node metastasis (N)						
N0,1,2,3a	9	15	0.25			
N3b	2	12				
Size						
< 100 mm	8	10	0.101			
>=100 mm	3	17				
Type of gastrectomy						
Distal	7	13	0.611			
Total	4	14				
Lymph node dissection						
D0, 1, 1+	4	8	984			
D2	7	19				
Neoadjuvant chemotherapy						
(-)	10	24	1			

(+)	1	3			
Postoperative chemotherapy					
(-)	1	3	1		
(+)	10	24			
Complications					
(-)	10	24	0.474		
(+)	1	7			

HR: Hazard Ratio; CI: Confidence Interval

**Table 3:** Univariate and multivariate analysis of prognostic factors associated with overall survival (OS) and progression-free survival (PFS).

Prognostic factors	OS		PFS	
	Univariate (p)	Multivariate HR (95%CI) (p)	Univariate (p)	Multivariate HR (95%CI) (p)
Age	0.8527		0.3681	
Sex	0.8389		0.8044	
Tumor location	0.1675		0.9507	
Cross-sectional parts	0.1864		0.1204	
Macroscopic types	0.0034	0.115 2.325 (0.814 – 6.641)	0.0146	0.329 0.343 (0.040 – 2.942)
Histology	0.2301		0.0832	
Depth	0.9914		0.3141	
Stromal volume	0.0603		0.0026	0.117 4.592 (0.682– 30.899)
INF	0.0011	0.015 4.302 (1.334–3.870)	0.0005	0.016 6.005 (1.391 – 25.928)
ly	0.4628		0.9512	
v	0.5700		0.9601	
N	0.0887		0.2136	
Size	0.0541		0.0195	0.806 1.150 (0.377 – 3.507)
Type of gastrectomy	0.1935		0.2519	
Lymph node dissection	0.5775		0.7384	
Neoadjuvant therapy	0.7766		0.3164	
Postoperative chemotherapy	0.0141	0.005 0.183 (0.056 – 0.595)	0.7308	
Complications	0.1587		0.2395	

OS: Overall Survival; PFS: Progression Free Survival; HR: Hazard Ratio; CI: Confidence Interval

administered S-1 + cisplatin (CDDP). Twenty-nine (74.4%) patients received S-1 or S-1 + another drug. Eleven (28.2%) patients required second-line chemotherapy, and five (12.8%) patients required third-line or additional chemotherapy after surgery. Disease recurrence in the peritoneum alone or with recurrence at another site was present in 21 (53.8%) patients.

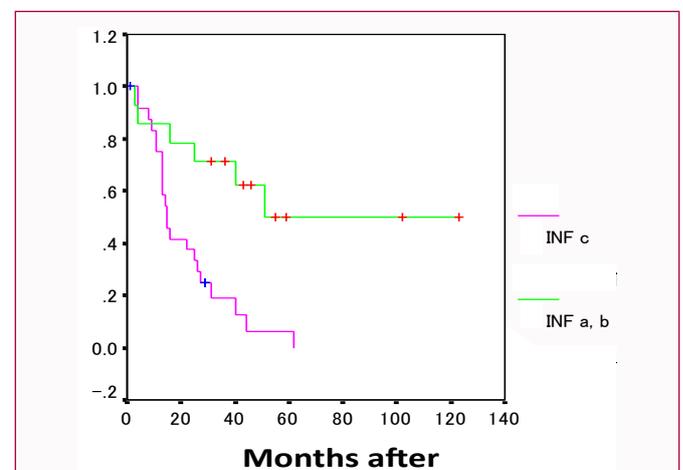
**Recurrence and clinicopathological characteristics**

Tumors recurred in 27 patients (69.2%). Univariate analysis indicated a significant association between recurrence and macroscopic type, stromal volume, and INF (Table 2). Multivariate analysis showed that recurrence significantly associated with only INF (hazard ratio [HR], 11.911; 95% confidence interval [CI], 1.366–103.888; *P* = 0.025). The recurrence rates of patients with expanding growth and intermediate pattern (INFa,b) or INFc were 35.7% (5/14) and 91.7% (22/24), respectively. The recurrence rate of patients with INFc was about two and a half times higher than those with INFa,b (*P* = 0.001).

**Analysis of prognosis**

Annual OS rates for years one through five were 78.9%, 50.0%, 34.3%, 18.8%, and 10.0%, respectively, and the median survival time (MST) of OS was 25 months. Annual PFS rates for years one through five were 57.1%, 45.7%, 25.8%, 14.3%, and 7.7%, respectively, and the

MST of PFS was 19 months. Clinicopathological characteristics were evaluated for their relationship with OS and PFS after surgery (Table 3). For OS, univariate analysis showed that large type-3 and type-4 cancers, INFc, and no postoperative chemotherapy correlated with

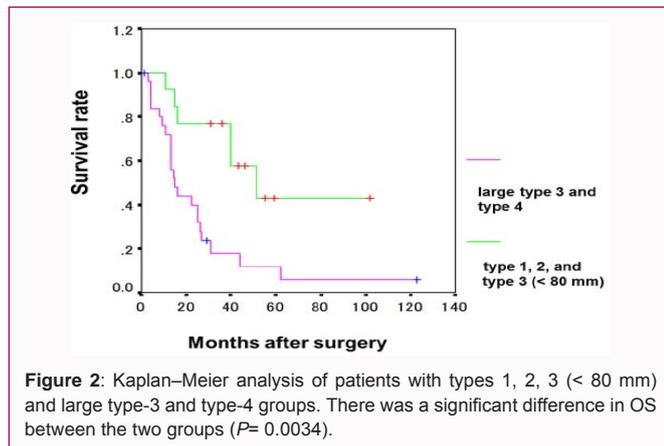


**Figure 1:** Kaplan–Meier analysis of overall survival (OS) of patients with INFa,b and INFc . There was a significant difference in OS between the two groups (*P*= 0.0011).

**Table 4:** Comparison of long-term survival ( $\geq 3$  years) stratified by patient characteristics.

Factors	Short time survival (< 3 years)	Long time survival ( $\geq 3$ years)	P
Age			
<70 yrs	9	3	1
$\geq 70$ yrs	14	8	
Sex			
Male	13	8	0.827
Female	10	4	
Tumor location			
L, M	19	12	0.329
U	4	0	
Cross-sectional parts			
Non-circ	10	7	0.632
Circ	4	0	
Macroscopic types			
1,2,3 (< 80mm)	3	9	0.001
3 ( $\geq 80$ mm)	4	20	3
Histology			
Differentiated	6	6	0.299
Undifferentiated	17	6	
Depth			
SS, SE	20	11	1
SI	3	1	
Stromal volume			
med, int	8	8	0.15
sci	15	4	
Infiltrative pattern (INF)			
a,b	4	9	0.003
c	19	3	
Lymphatic invasion (ly)			
1,2	9	6	0.797
3	14	6	
Venous invasion (v)			
0,1	14	10	0.329
2,3	9	2	
Lymph node metastasis (N)			
N0,1,2,3a	13	9	0.481
N3b	10	3	
Size			
< 100 mm	8	9	0.057
$\geq 100$ mm	15	3	
Type of gastrectomy			
Distal	10	10	0.057
Total	13	2	
Lymph node dissection			
D0, 1, 1+	8	3	0.835
D2	15	9	
Neoadjuvant chemotherapy			

(-)	21	11	1
(+)	2	1	
Postoperative chemotherapy			
(-)	4	0	0.329
(+)	19	12	
Complications			
(-)	17	10	0.837
(+)	6	2	



poor OS. For PFS, univariate analysis showed that large type-3 and type-4, sci, INFc, and large tumor size ( $\geq 100$  mm) correlated with poor PFS.

Multivariate analysis of factors with  $P < 0.05$  in univariate analysis, such as macroscopic type, INF, and postoperative chemotherapy, indicated that INF (HR, 4.302; 95% CI, 1.334–13.870;  $P = 0.015$ ) and postoperative chemotherapy (HR, 0.183; 95% CI, 0.056–0.595;  $P = 0.005$ ) were independent prognostic factors for OS. The MSTs of patients with INFa,b and INFc were 51 months and 15 months, respectively. The OS of patients with INFc was significantly lower compared with that of patients with INFa,b ( $P = 0.0011$ ) (Figure 1). The MSTs of patients who did or did not receive postoperative chemotherapy were 26 months and 4 months, respectively. The OS of patients who received postoperative chemotherapy was significantly higher compared with those who did not ( $P = 0.0141$ ).

Multivariate analysis of factors with  $P < 0.05$  in univariate analysis of PFS, such as macroscopic type, stromal volume, INF, and tumor size indicated that INF was an independent prognostic factor of PFS (HR, 6.005; 95% CI, 1.391–25.928;  $P = 0.016$ ). For PFS, the MSTs of patients with INFa,b or INFc were 36 months and 10 months, respectively. The PFS of patients with INFc was significantly lower compared with those with NFa,b ( $P = 0.0005$ ).

The MSTs for OS of patients with types 1, 2, and 3 (< 80 mm) or large type-3 and type-4 tumors were 51 months and 15 months, respectively. The OS of patients with large type-3 and type-4 tumors was significantly lower compared with those with types 1, 2, and 3 (< 80 mm) ( $P = 0.0034$ ) (Figure 2). The MSTs for PFS of patients with types 1–3 (< 80 mm) or large type-3 and type-4 were 33 months and 10 months, respectively. The PFS of patients with large type-3 and type-4 tumors was significantly lower compared with those with types 1–3 (< 80 mm) ( $P = 0.0146$ ).

### Clinical characteristics of long-term survivors

There were 12 (30.8%) long-term survivors. Long-term survival

was associated with macroscopic type and INF (Table 4). The rates of long-term survivors with INFa,b cancers or INFc cancers were 69.2% (9/13) and 13.6% (3/22), respectively. The percentages of long-term survivors with types 1–3 of small cancers (< 80 mm) or large type-3 and type-4 cancers were 75.0% (9/12) and 13.0% (3/23), respectively. The percentage of long-term survivors with large type-3 and type-4 tumors was significantly lower compared with those with types 1–3 (< 80 mm) ( $P = 0.001$ ). The rate of long-term survivors with INFc was significantly lower than for those with INFa,b cancers ( $P = 0.003$ ) (Table 5). The patient with a type-4 tumor among long-term survivors was administered two courses of S-1+CDDP neoadjuvant chemotherapy and postoperative chemotherapy, including intraperitoneal chemotherapy combined with intravenous chemotherapy (IP/IV) and hyperthermia until the sixth line. One patient with a large type-3 tumor (108 mm) received postoperative chemotherapy, including DOC+CDDP+S-1 (DCS) until the third line. However, both patients died because of recurrence in the peritoneum.

## Discussion

Although the prognosis of CY1 patients is poor, the optimal treatment for these patients has not been established. In the present study, we investigated the clinical outcomes and prognostic factors of 39 patients with CY1/P0 gastric cancer, and identified INF and postoperative chemotherapy as independent prognostic factors for OS. Moreover, INF was found to be an independent prognostic factor for PFS. The percentage of long-term survivors with large type-3 and type-4 tumors was significantly lower compared with those with types 1–3 (< 80 mm). The therapeutic strategy was thought to be very important for CY1/P0 gastric cancer patients with an infiltrative growth pattern such as large type-3 and type-4 tumors to improve prognosis.

According to the Japanese Classification of Gastric Carcinoma, CY should be performed immediately after laparotomy in all patients with gastric carcinoma, except in those with a T1 tumor [6]. Available evidence [9,10,12] suggests that oncologists consider the prognosis of CY1 to be dismal. Fukagawa et al. [12] reported that the 5-year OS rate among 88 patients with CY1/P0 gastric cancer is 7.8%, and five patients experienced recurrence-free survival. Mezhir [9] reported a 5-year OS rate <10% for patients with M1 Cyt+ (corresponding to CY1/P0 here). In the present study, the 5-year OS rate of the 39 CY1/P0 cases was 10%. Further, postoperative chemotherapy was an independent prognostic factor of OS. Yamashita et al. [14] reported that long-term postoperative adjuvant therapy contributed to a 5-year OS rate of >20% in 35 patients with CY1 and no other stage IV factors (P0H0CY1). Mezhir et al. [9] found that macroscopic peritoneal dissemination is associated with a dismal prognosis (e.g. no survivors >5 years), indicating that the clinical significance of surgical resection of the primary tumor is not established. CY1 is defined as M1 in

**Table 5:** Clinicopathological features of long-term survivors with CY1 and no other stage IV factor (n = 12).

Age	Sex	NAC	Location	Macro	Size (mm)	Surgery	T	N	INF	History	Postoperative Chemotherapy	Recurrence	Observed term (M)	Death
70	M	No	MUL	3	80	T+S/D2	SE	3a	b	muc	5'DFUR+PSK	free	123	Alive
79	F	No	MLU	2	140	D/D0	SI 2	2	b	por1	5'DFUR	free	102	Alive
75	M	No	LM	3	66	D/D2	SE	3b	c	tub1	S-1,S-1+PTX,S-1+DOC P	lung	40	Dead
49	M	Yes	MUL	4	194	T+S/D2	SE	3a	c	por2	S-1+Doc,PTX+Cis	p	44	Dead
											S-1+PTXiv,ip+hyperthermia, Cis+CPT-11,DOC+Cis,PTX+Cis			
73	M	No	LD	3	73	D/D2	SE	2	b	tub2	S-1	free	55	Alive
73	M	No	LM	3	63	D/D2	SE	2	b	tub2	S-1+Doc, S-1+Cis P,	lung, H, N	40	Dead
65	F	No	LM	3	108	D/D2	SE	3b	c	sig	S-1+Doc, S-1,DCS	P	62	Dead
63	F	No	L	2	53	D/D2	SE	1	a	tub2	S-1+PTX, S-1	free	59	Alive
70	M	No	L	2	94	D/D1	SE	3a	b	sig	S-1+Doc, S-1, Cis+CPT-11	P	51	Dead
69	M	No	LD	3	76	D/D1	SE	3a	b	tub2	S-1+Cis+trastuzumab	free	36	Alive
72	M	No	LD	2	70	D/D2	SE	2	b	sig	S-1	free	46	Alive
74	F	N0	ML	1	82	D/D2	SE	3b	a	pap	S-1	free	43	Alive

NAC: Neoadjuvant Chemotherapy; T: Depth Of Tumor Invasion; M: Months; M: Male; F: Female; D: Duodenum; T+S: Total Gastrectomy+Splenectomy; D: Distal Gastrectomy; PSK: Protein-Bound Polysaccharide Kureha; Cis: Cisplatin; IV: Intravenous; Ip: Intraperitoneum; CPT-11: Irinotecan; P: Peritoneum; H: Liver; N: Lymph Node Metasta

the latest Japanese treatment guidelines for gastric cancer, which recommends palliative surgery as an option [6].

Mezhir et al. [9] reported a median disease-specific survival for P1 of 0.8 years, and 1.3 years for CY1/P0. Kanazawa et al. [15] demonstrated that the MST by group was 34.5 months for CY1/P0, 34.3 months for CY0/P1, and 19.3 months for CY1/P1, with the OS in CY1/P0 and CY0/P1 groups being significantly longer than in the CY1/P1 group. These studies indicate that the prognosis of patients with CY1/P0 gastric cancer is better than that of patients with P1 gastric cancer [9,15]. Our patients with CY1/P0 gastric cancer included two (5.1%) who survived >5 years with no evidence of recurrence, and one patient who has survived for 10 years and 3 months. Fukagawa et al. [12] reported recurrence-free patients with CY1 advanced gastric cancer who underwent gastrectomy, and showed that five (5.7%) of the 88 patients survived for more than 5 years without evidence of recurrence, indicating that surgery might serve as a promising strategy. In our hospital, surgery was selected as the first-line therapy of patients with CY1/P0 gastric cancer, except four patients with type-4 disease who underwent neoadjuvant chemotherapy using S-1 and CDDP. However, only one patient survived for more than 3 years.

The optimal treatment strategy for CY1/P0 gastric cancer is controversial. Available evidence suggests that the findings of peritoneal lavage cytology are a strong prognosticator. For example, the median survival times of patients with positive cytology range between 10.5–14.8 months after gastrectomy [16,17]. Okabe et al. [18] reported that neoadjuvant chemotherapy is effective for patients with CY1 and an MST of 43.2 months following neoadjuvant therapy. Kodera et al. [19] found that adjuvant chemotherapy with S-1 is effective (MST of 23.5 months). In our present study, the MST of patients with CY1/P0 disease who underwent postoperative chemotherapy using S-1 was 27.0 months. We believe therefore that gastrectomy with adjuvant S-1 might improve survival. Most of our long-term survivors were administered S-1 postoperatively, and 29 patients received postoperative S-1 or S-1 + another drug. Further, of the 12 long-term survivors, after surgery, three patients were administered S-1 only, and six patients were administered S-1 + PTX

or + DOC. Adjuvant monotherapy with S-1 or taxane is acceptable and efficient for preventing peritoneal recurrence. In our experience, nine (75.0%) of 12 long-term survivors were administered S-1 or taxane postoperatively. Kanazawa et al. [15] reported the efficacy of adjuvant chemotherapy with S-1 followed by DOC after R1 resection for CY1/P0 gastric cancer. According to the results of their study, this adjuvant chemotherapy is safe and well tolerated and has the potential to improve OS (MST = 34.5 months). Therefore, based on the evidence cited, we consider S-1 or S-1 + taxane effective adjuvant chemotherapy to be effective for CY1/P0 gastric cancer after surgery.

The development of novel chemotherapeutic regimens for intraperitoneal chemotherapy will be challenging. Peritoneal dissemination is among the most important and difficult therapeutic targets in patients with gastric cancer [20]. Although, current treatment outcomes are disappointing for surgery and systemic therapy, intraperitoneal chemotherapy in combination with intravenous chemotherapy shows promise [21]. The rationale for such treatment is based on the slow absorption of paclitaxel from the peritoneum into the body, which maintains a high concentration in the peritoneum [22,23]. Therapy using IP/IV paclitaxel + S-1 to treat patients with gastric cancer with macroscopic peritoneal metastasis achieves an MST of 17.6 months and 1-year survival rate >77.1% [21], which is consistent with the results reported here for patients with CY1/P0 disease.

IP/IV therapy may be feasible for patients with CY1 gastric cancer and for those with preperitoneal dissemination. An alternate strategy for CY1 or peritoneal dissemination might increase the response rate as preoperative chemotherapy. Recently, potent chemotherapy in the form of DCS was administered to patients with advanced gastric cancers, and achieved the conversion of CY1 to CY0 [24]. Salvage gastrectomy may serve as an option for patients with CY1 gastric cancer. For example, such salvage surgery after IP/IV paclitaxel + S1 therapy improved survival compared with standard chemotherapy such as S1/Cisplatin [25]. The MST of patients with severe peritoneal metastasis and as cites receiving salvage surgery after IP/IV paclitaxel + S1 therapy was 26.4 months [25]. This compares with 17.3 months

for patients with large type-3 and type-4 cancer receiving S-1 + CDDP followed by gastrectomy [26].

In the present study, we treated four patients with type-4 disease who were administered S-1 + CDDP, and only one survived beyond 3 years. One patient with type-4 disease among the 12 long-term survivors received neoadjuvant therapy using S-1 + CDDP, and IP/IV paclitaxel + S-1 + hyperthermia after surgery. One of the three long-time survivors of large type-3 disease received postoperative DCS therapy. Recently, Ishigami et al. [27,28] reported that intravenous and intraperitoneal paclitaxel combined with S-1 is very effective for patients with P1 and/or CY1. In their phase II trial, the MST and 1-year survival rate was 22.5 months and 78%, respectively, and peritoneal cytology results turned negative in 24 of 28 patients [27]. This treatment strategy is now under investigation in a phase III randomized control trial of S-1 plus intravenous and intraperitoneal paclitaxel versus S-1 plus cisplatin for gastric cancer with peritoneal metastasis (PHOENIX-GC trial).

Kano et al. [29] found that macroscopic type and residual tumor status were independent prognostic factors for patients with gastric cancer. After combining these two factors, no significant difference in survival was observed between CY1 patients with type-4 tumors who underwent R1 or R2 resection. In contrast, there was a significant difference in survival between CY1 patients without type-4 tumors who underwent R1 or R2 resection [29]. In our present study, the number of long-term survivors with type 4 and large type-3 cancers was significantly lower compared with that of long-term survivors with other macroscopic types.

INFc is an independent predictor of poor prognosis. However, INF is determined by pathological examination of the resected stomach after surgery, and it is therefore difficult to accurately determine INF status before surgery. In the current study, the number of patients with large type-3 and type-4 tumors with INFc was 22 (84.6%). Conversely, there were only three patients with INFc among those with types 1, 2, and small type-3 disease (23.1%). Univariate analysis showed that large type-3 and type-4 gastric cancers were associated with high recurrence rates and poor prognosis for OS and PFS. However, multivariate analysis did not indicate that macroscopic type was an independent prognostic factor of disease recurrence.

Kano et al. [29] reported that gastrectomy should be avoided for treating patients with type-4 tumors with overt peritoneal metastasis or with positive peritoneal cytology. In Kano's previous series, 22 patients with type-4 tumors underwent staging laparoscopy, and 10 (45.4%) were diagnosed with overt or occult peritoneal disease [29]. The information provided by CY is therefore essential for determining the therapeutic strategy for patients with type-4 gastric cancer. Therefore, we recommend that staging laparoscopy should be included among the first procedures performed. In our present study, the prognosis of patients with CY1 with large type-3 and type-4 tumors was extremely poor, even when an R1 resection was performed. Miki et al. [30] reported that staging laparoscopy reveals peritoneal metastasis in 36.3% of patients with large type-3 and type-4 gastric cancers without clinically evident factors that indicate incurable disease such as malignant ascites and/or distant metastasis.

Patients with type-4 or large (tumor diameter  $\geq 8$  cm) type-3 gastric cancer are considered suitable candidates for staging laparoscopy because of the high incidence of peritoneal metastasis. Staging laparoscopy is considered to be a useful tool in detecting unsuspected

peritoneal metastasis not observed by other diagnostic imaging such as abdominal ultrasonography or abdominal computed tomography [29]. Patients with cM0 type-4 and large type-3 gastric cancers are considered suitable candidates for staging laparoscopy [29]. Because the prognosis of patients with large type-3 and type-4 cancers with CY1/P0 is very poor, they likely require staging laparoscopy. Further, neoadjuvant chemotherapy such as DCS or IP/IV paclitaxel should be considered for treating patients with CY1 gastric cancer even without overt peritoneal dissemination.

The present study has some limitations. First, this was a retrospective investigation with patients treated at a single institution during a 15-year period (2000–2014), and the diagnostic modalities, operative procedures, and pre- and postoperative adjuvant therapy varied. Nevertheless, our study provides compelling evidence indicating that patients with large type-3 and type-4 CY1/P0 gastric cancer require multidisciplinary therapy such as neoadjuvant chemotherapy, using DCS and IP/IV paclitaxel.

## Conclusion

INF and postoperative chemotherapy are independent prognostic factors for OS in gastric cancer patients. Moreover, INF is also an independent prognostic factor for PFS. However, INF is only determined postoperatively by pathological examination of the resected stomach. Macroscopic type is not an independent prognostic or recurrence factor. Univariate analysis showed that large type 3 and type 4 cancers are associated with a high recurrence rate and poor prognosis in terms of both OS and PFS. Moreover, the number of large type 3 and type 4 cases with INFc was very high. Therefore, these cases are considered to require multidisciplinary therapy, including neoadjuvant chemotherapy.

## References

1. International Agency for Research on Cancer WHO. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence 2012.
2. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med.* 2007; 357: 1810–1820.
3. Yamashita K, Sakuramoto S, Kikuchi S, Katada N, Kobayashi N, Watanabe M. Validation of staging systems for gastric cancer. *Gastric Cancer.* 2008; 11: 111–118.
4. Bringand C, Arviex C, Gilly FN, Glehen O. Treatment of peritoneal carcinomatosis in gastric cancers. *Dig Dis.* 2004; 22: 366–373.
5. Isobe Y, Nashimoto A, Akazawa K, Oda I, Hayashi K, Miyashiro I, et al. Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. *Gastric Cancer.* 2011; 14: 301–316.
6. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3<sup>rd</sup> English edn. *Gastric Cancer.* 2011; 14: 101–112.
7. Sobin L, Gospodarowicz M, Wittekind C. TNM classification of malignant tumours. 7<sup>th</sup> edn. New York; Wiley-Blackwell. 2009.
8. Leake PA, Cardoso R, Seevaratnam R, Lourenco L, Helyer L, Mahar A, et al. A systematic review of the accuracy and utility of peritoneal cytology in patients with gastric cancer. *Gastric Cancer.* 2012; 15: 27–32.
9. Mezhir JJ, Shah MA, Jacks LM, Brennan MF, Coit DG, Strong VE. Positive peritoneal cytology in patients with gastric cancer: natural history and outcome of 291 patients. *Ann Surg Oncol.* 2010; 17: 3173–3180.
10. Lee SD, Ryu KW, Eom BW, Lee JH, Kook MC, Kim YW. Prognostic significance of peritoneal washing cytology in patients with gastric cancer. *Br J Surg.* 2012; 99: 397–403.

11. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 2nd English Edition. *Gastric Cancer*. 1998; 1: 10–24.
12. Fukagawa T, Katai H, Saka M, Morita S, Sasajima Y, Taniguchi H, et al. Significance of lavage cytology in advanced gastric cancer patients. *World J Surg*. 2010; 34: 563–568.
13. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines?. 2010 (ver. 3). *Gastric Cancer*. 2011; 14: 113–123.
14. Yamashita K, Ushiku H, Katada N, Hosoda K, Moriya H, Mieno H, et al. Reduced preoperative serum albumin and absence of peritoneal dissemination may be predictive factors for long-term survival with advanced gastric cancer with positive cytology test. *Eur J Surg Oncol*. 2013; 39: 1309–1316.
15. Kanazawa Y, Kato S, Fujita I, Onodera H, Uchida E. Adjuvant chemotherapy with S-1 followed by docetaxel for gastric cancer and CY1P0 peritoneal metastasis after relatively curative surgery. *J Nippon Med Sch*. 2013; 80: 378–383.
16. Cabalag CS, Chan ST, Kaneko Y, Duong CP. A systematic review and meta-analysis of gastric cancer treatment in patients with positive peritoneal cytology. *Gastric Cancer*. 2015; 18: 11–22.
17. De Andrade JP, Mezhir JJ. The critical role of peritoneal cytology in staging of gastric cancer: an evidence-based review. *J Surg Oncol*. 2014; 110: 291–297.
18. Okabe H, Ueda S, Obama K, Hosogi H, Sakai Y. Induction chemotherapy with S-1 plus cisplatin followed by surgery for treatment of gastric cancer with peritoneal dissemination. *Ann Surg Oncol*. 2009; 16: 3227–3236.
19. Kodera Y, Ito S, Mochizuki Y, Kondo K, Koshikawa K, Suzuki N, et al. A phase II study of radical surgery followed by postoperative chemotherapy with S-1 for gastric carcinoma with free cancer cells in the peritoneal cavity (CCOG0301 study). *Eur J Surg Oncol*. 2009; 35: 1158–1163.
20. Yamashita K, Sakuramoto S, Kikuchi S, Katada N, Kobayashi N, Watanabe M. Surgical resection of stage IV gastric cancer and prognosis. *Anticancer Res*. 2007; 27: 4381–4386.
21. Yamaguchi H, Kitayama J, Ishigami H, Emoto S, Yamashita H, Watanabe T. A phase 2 trial of intravenous and intraperitoneal paclitaxel combined with S-1 for treatment of gastric cancer with macroscopic peritoneal metastasis. *Cancer*. 2013; 119: 3354–3358.
22. Francis P, Rowinsky E, Schneider J, Hakes T, Hoskins W, Markman M. Phase I feasibility and pharmacologic study of weekly intraperitoneal paclitaxel: a Gynecologic Oncology Group pilot study. *J Clin Oncol*. 1995; 13: 2961–2967.
23. Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med*. 2006; 354: 34–43.
24. Koizumi W, Nakayama N, Tanabe S, Sasaki T, Higuchi K, Nishimura K. A multicenter phase II study of combined chemotherapy with docetaxel, cisplatin, and S-1 in patients with unresectable or recurrent gastric cancer (KDOG0601). *Cancer Chemother Pharmacol*. 2012; 69: 407–413.
25. Kitayama J, Ishigami H, Yamaguchi H, Yamashita H, Emoto S, Kaisaki S, et al. Salvage gastrectomy after intravenous and intraperitoneal paclitaxel (PTX) administration with oral S-1 for peritoneal dissemination of advanced gastric cancer with malignant ascites. *Ann Surg Oncol*. 2014; 21: 539–546.
26. Iwasaki Y, Sasako M, Yamamoto S, Nakamura K, Sano T, Katai H, et al. Phase II study of preoperative chemotherapy with S-1 and cisplatin followed by gastrectomy for clinically resectable type 4 and large type 3 gastric cancer (JCOG0210). *J Surg Oncol*. 2013; 107: 741–745.
27. Ishigami H, Kitayama J, Kaisaki S, Hidemura M, Kato K, Otani T, et al. Phase II study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer with peritoneal metastasis. *Ann Oncol*. 2010; 21: 67–70.
28. Ishigami H, Kitayama J, Otani K, Kamei T, Soma D, Miyato H, et al. Phase I pharmacokinetic study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer. *Oncology*. 2009; 76: 311–314.
29. Kano Y, Kosugi S, Ishikawa T, Otani T, Muneoka Y, Sato Y, et al. Prognostic significance of peritoneal lavage cytology at three cavities in patients with gastric cancer. *Surgery*. 2015; 158: 1581–1589.
30. Miki Y, Tokunaga M, Tanizawa Y, Bando E, Kawamura T, Terashima M. Staging laparoscopy for patients with cM0, type 4, and large type 3 gastric cancer. *World J Surg*. 2015; 39: 2742–2747.