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ORIGINAL ARTICLE

Prognostic factors for cytology-positive gastric cancer

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Abstract

Purpose Positive peritoneal lavage cytology for gastric carcinoma cells (CY1) is considered distant metastasis and is classified as Stage IV. However, patients with CY1 comprise a heterogeneous population, and their prognosis varies greatly. The prognostic factors for gastric cancer patients with CY1 were retrospectively reviewed.

Methods The participants were 80 gastric cancer patients with CY1 in our institution encountered between 2005 and 2017. Prognostic factors were analyzed using univariate and multivariate analyses.

Results The operative procedure was distal gastrectomy for 30 patients, total gastrectomy for 27 patients, staging laparoscopy for 10 patients, gastrojejunostomy for 8 patients, and probe laparotomy for 5 patients. Other distant metastases were recognized in 36 patients. A multivariate analysis revealed that other distant metastases were the strongest independent risk factor for the overall survival ($p < 0.0001$). When the cohort was limited to CY1 patients without other distant metastases, cN2–3 ($p = 0.01$), the prognostic nutritional index (PNI) < 40 ($p = 0.02$) and Type 4 ($p = 0.03$) were independent risk factors according to a multivariate analysis. The survivals of patients with cN2–3 or PNI < 40 after gastrectomy were equivalent to those with other distant metastases, as assessed by log-rank analyses.

Conclusions The prognoses of CY1 gastric cancer patients with cN2–3 or PNI < 40 were poor, even after gastrectomy.

Keywords Stomach neoplasms · Abdominal lavage cytology · Lymph node metastasis

Introduction

The number of patients who have died of gastric cancer has gradually been decreasing over the past decade in Japan [1]. However, the treatment outcomes of advanced gastric cancer patients with positive peritoneal lavage cytology for carcinoma cells, or CY1, remain poor [2]. Peritoneal dissemination develops due to floating cancer cells in the abdominal cavity that are released from the primary gastric cancer and proliferate at the peritoneal site of adherence.

To detect abdominal free cancer cells, peritoneal lavage cytology at laparotomy is the standard method in Japan. Gastric cancer with CY1 is classified as Stage IV according to the Japanese Classification of Gastric Carcinoma [3] and TNM classification by the Union for International Cancer Control [4]. However, gastric cancer patients with CY1 comprise a heterogeneous population, and the treatment and prognosis vary greatly. If there are no other non-curative factors, radical gastrectomy is an alternative according to the Japanese Gastric Cancer Guideline [5], as a phase II study showed a good prognosis after radical gastrectomy followed by adjuvant chemotherapy [6], although no confirmative studies have been reported. In addition, even if other non-curative factors exist, gastrectomy is often performed to relieve symptoms such as bleeding or stenosis. Thus, the optimum therapeutic strategy for CY1 gastric cancer has not yet been established.

In the present study, the prognostic factors for gastric cancer patients with CY1 were retrospectively reviewed. Our findings are expected to be helpful for developing a suitable new therapeutic strategy for this condition.

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Methods

Patients and data retrieval

Between 2005 and 2017, the number of patients who underwent surgery for gastric cancer was 982, including 898 patients with gastrectomy, 36 with staging laparoscopy, 30 with gastrojejunostomy, and 11 with probe laparotomy at our institution. Among them, CY1 was detected in 80 patients (8.2%). The clinical and pathological characteristics, perioperative treatment, and postoperative outcomes were retrospectively analyzed from the medical records. This study was approved by the authors' institutional review board (approval number; 02-0409).

Outcomes and definitions

Peritoneal lavage cytology was performed routinely immediately after laparotomy or at the staging laparoscopy, before manipulation of the primary tumor. When ascites existed, it was aspirated. When ascites did not exist, physiologic normal saline of 100 ml was instilled and aspirated from Douglas' pouch. Carcinoma cells on peritoneal lavage cytology were defined as CY1. Suspicious cases were defined as CY0.

The effects of the following clinical, pathological, and operative factors and perioperative treatment on the overall survival (OS) were evaluated by univariate and multivariate analyses: sex, age, preoperative serum albumin level, Onodera's prognostic nutritional index (PNI) [7], Eastern Cooperative Oncology Group Performance Status (PS) score [8], American Society of Anesthesiology (ASA) physical status classification [9], operative procedure, extent of lymph node dissection, macroscopic type of the tumor (Type 4 or not), histological classification (undifferentiated or not), clinical tumor invasion (cT), clinical lymph node metastasis (cN), liver metastasis (H), peritoneal metastasis (P), other distant metastasis (M), involvement of proximal and distal resection margin (PM, DM), residual tumor (R), and pre- and postoperative chemotherapy.

The clinicopathological findings of gastric cancer were described according to the Japanese Classification of Gastric Carcinoma 15th edition [3]. The clinical N category was determined by preoperative computed tomography (CT). A lymph node was considered positive if the longest diameter was over 1.0 cm or if it was between 0.7 and 1.0 cm and showed strong enhancement, a round shape, central necrosis, or perinodal infiltration [10]. The PNI was calculated using the following formula: $10 \times$ serum albumin (g/dl) $+ 0.005 \times$ total lymphocyte count (/mm^3) [7].

Statistical analyses

Univariate and multivariate analyses to identify prognostic factors for the OS were carried out using Cox's proportional hazards model. The OS was shown on Kaplan–Meier curves and was compared using the log-rank test. The OS was defined as the interval from the date of operation to the date of death from any cause. Surviving patients were censored at the date that they were last known to be alive. p values of less than 0.05 were defined as significant. All analyses were performed using JMP software program (version 11.0.0 for Windows; SAS Institute Inc., Cary, NC, USA).

Results

Patients' characteristics

The 80 patients' characteristics, both resected and unresected, are shown in Table 1. Those characteristics indicated that 36 patients had other distant metastases, including 32 with peritoneal metastases, 3 with hepatic metastases, 3 with paraaortic lymph node metastases, and 1 with skin metastases, including overlapping patients.

Operative procedure

For CY1 gastric cancer, the indication for resection was left to the surgeons' policy, according to the trend at the time, as no strong evidence of gastrectomy had been established. Resection was not performed for 23 patients, including 11 with staging laparotomy, 8 with gastrojejunostomy, and 4 with probe laparotomy. Staging laparotomy was performed to confirm peritoneal metastasis in six patients, as a routine check before neoadjuvant chemotherapy (clinical trial) in four patients, and to make a decision regarding conversion surgery in one patient. Probe laparotomy was performed due to pancreas invasion in three patients and peritoneal seeding in two patients (one patient had both). No patients were converted to secondary resection after primary gastrojejunostomy. Distal and total gastrectomy was performed for 30 and 27 patients, respectively. Standard lymph node dissection with D2 was selected for 31 patients, while limited lymph node dissection < D2 was selected for 26 patients. Of those 57 gastrectomized patients, 7 had a macroscopic residual tumor (R2 resection). Gastrectomy in the current series was performed with open laparotomy, not via a laparoscopic approach.

Chemotherapy

Before the operation, intensive chemotherapy for unresectable cancer was administered for six patients, including S-1 + cisplatin (SP) for three patients, S-1 alone for two

Table 1 Clinical, operative, and pathological characteristics of 80 gastric cancer patients with CY1

Sex	male/female	64/16
Age (years)	median (range)	68 (34–91)
Albumin (g/dl)	median (range)	3.6 (2.3–4.7)
PNI	median (range)	43 (25–59)
PS	0/1/2/3/4	66/3/3/6/2
ASA	1/2/3	8/65/7
Operative procedure	distal gastrectomy/total gastrectomy/staging laparoscopy/gastrojejunostomy/probe laparotomy	30/27/10/8/5
Lymph node dissection*	<D2/≥D2	26/31
Macroscopic type	0–I/1/2/3/4/5	1/1/12/26/35/5
Histological classification	pap/tub/por/sig/muc/other	2/19/46/5/6/2
HER2	0/1/2(FISH-)/2(FISH+)/3/unknown	6/13/4/2/1/54
Clinical depth of tumor invasion (cT)	2/3/4a/4b	6/29/29/16
Pathological depth of tumor invasion (pT)*	1b/2/3/4a/4b	1/1/4/42/9
Lymphatic invasion (Ly)*	0/1a/1b/1c	3/10/19/25
Venous invasion (V)*	0/1a/1b/1c	8/17/17/15
Clinical lymph node metastasis (cN)	0/1/2/3a/3b	29/21/23/6/1
Bulky N	no/yes	72/8
Pathological lymph node metastasis (pN)*	0/1/2/3a/3b	6/4/9/16/22
Hepatic metastasis (H)	0/1	77/3
Peritoneal metastasis (P)	0/1	48/32
Other distant metastasis (M)	1(LYM)/1(SKI)	3/1
H1, P1, M1(LYM), or M1(SKI)	no/yes	44/36
Resection margin (PM1 or DM1)*	negative/positive	49/8
Residual tumor	1/2	50/30
Preoperative chemotherapy	no/yes	65/15
Postoperative chemotherapy	no/yes	19/61

PNI Onodera's prognostic nutritional index, *PS* Eastern Cooperative Oncology Group performance status, *ASA* American Society of Anesthesiologists physical status, *HER2* human epidermal growth factor receptor 2, *FISH* fluorescence in situ hybridization

Clinical and pathological findings are written according to the Japanese Classification of Gastric Carcinoma 15th edition, *for only resected cases, $n = 57$

patients, and capecitabine + cisplatin (XP) for one patient. Neoadjuvant chemotherapy for resectable cancer was administered for nine patients, including SP for seven patients and S-1 alone for two patients. Postoperative chemotherapy was administered for 61 patients. The first-line chemotherapy after operation contained S-1 alone for 25 patients (including 1 unresected and 4 R2 resection patients), SP for 17 patients (including 10 unresected and 1 R2 resection patients), paclitaxel for 5 patients, docetaxel for 2 patients, XP for 2 patients, S-1 + oxaliplatin for 1 patient, S-1 + paclitaxel for 1 patient, XP + trastuzumab for 1 patient, ramucirumab + paclitaxel for 1 patient, irinotecan + cisplatin for 1 patient, irinotecan for 1 patient, UFTE for 1 patient, and S-1 + intravenous and intraperitoneal paclitaxel for 1 patient. The median duration of S-1 chemotherapy was 9 months (range 0.3–28 months). Fifteen out of 25 patients ceased S-1 chemotherapy within 12 months because of progressive disease in 10 patients, adverse events in 2 patients, patients' rejection in 2 patients, and a poor general condition in 1 patient. The median number of SP chemotherapy courses was 3 (range 1–13). The reasons for discontinuation of SP chemotherapy were progressive disease in nine patients, stable disease in three patients, adverse events in one patient, a poor general condition in one patient, and physicians' judgement in three patients. Nineteen patients did not receive chemotherapy because of a poor general condition in five patients, poor oral intake in four patients, old age in three patients, comorbidity in three patients, cancer progression in two patients, patient's rejection in one patient, and unknown reason in one patient.

The prognosis

At the time of the analysis, 69 patients (86%) had died, and the median follow-up period of the 11 surviving patients was 60 months. The cause of death was known in 59 patients: gastric carcinoma in 53 patients (90%), pneumonia in 2 patients, cardiac failure in 2 patients, cerebral infarction in

1 patient, and other carcinoma in 1 patient. The 5-year OS rate was 11% ($n=7$). Those seven patients were all resected cases without other distant metastases than CY1. They showed no sign of cancer relapse after surgery. One of them died of cerebral infarction 71 months after surgery, but the remaining 6 patients were alive for 60–126 months.

Among the 50 patients who received gastrectomy without macroscopic residual tumor (R1 resection), cancer relapse was recognized in 37 patients by postoperative CT. The metastatic sites were peritoneum for 31 patients, lymph nodes for 5 patients (4 in paraaortic lymph nodes, 1 in hepatic hilar lymph nodes), liver for 5 patients, bone for 4 patients, and pleura for 4 patients (including duplication). The five patients who developed lymph node metastases had cN2–3 preoperatively.

Univariate and multivariate analyses for CY1 patients (entire CY1 cohort)

Univariate analyses were performed for 80 patients with CY1. In these analyses, the serum albumin level (< 3.5 vs. ≥ 3.5), PNI (< 40 vs. ≥ 40), macroscopic type (Type 4 vs. non-Type 4), cN (2–3 vs. 0–1), bulky N, peritoneal metastasis (P1), distant metastases (M1) other than CY1, and absence of postoperative chemotherapy were significantly correlated with a poor OS (Table 2). A multivariate analysis conducted with the significant factors of PNI, macroscopic type, cN, M1 other than CY1, and postoperative chemotherapy revealed that Type 4, cN2–3, M1 other than CY1, and absence of postoperative chemotherapy were independent risk factors for death. Of those factors, M1 other than CY1 was the strongest independent prognostic factor ($p < 0.0001$).

Univariate and multivariate analyses for CY1 patients without other distant metastases (CY1 alone cohort)

As patients with M1 other than CY1 had a significantly worse prognosis than those with CY1 alone, univariate analyses were performed for the 44 patients with CY1 without other distant metastases. In these analyses, the serum albumin level (< 3.5 vs. ≥ 3.5), PNI (< 40 vs. ≥ 40), ASA (3 vs. 1–2), macroscopic type (Type 4 vs. non-Type 4), and cN (2–3 vs. 0–1) were significantly correlated with a poor OS (Table 3). A multivariate analysis conducted with these significant factors of PNI, ASA, macroscopic type, and cN revealed that PNI < 40, Type 4, and cN2–3 were independent risk factors for death.

Table 2 Univariate and multivariate analyses for CY1 patients

Variables		*n*	MST (months)	Univariate analysis			Multivariate analysis		
				HR	95% CI	*p*	HR	95% CI	*p*
Sex	male/female	64/16	13.2/13.6	0.85	0.48–1.62	0.60			
Age (years)	≥ 70/< 70	38/42	14.3/11.5	0.98	0.61–1.59	0.95			
Albumin (g/dl)	< 3.5/≥ 3.5	32/48	9.7/15.8	**1.84**	**1.13–2.98**	**0.02**			
PNI	< 40/≥ 40	24/56	8.2/15.8	**2.01**	**1.19–3.33**	**0.01**	1.58	0.91–2.71	0.10
PS	1–3/0	14/66	9.7/15.2	1.80	0.94–3.20	0.08			
ASA	3/1–2	7/73	9.0/13.8	2.32	0.95–4.84	0.06			
Macroscopic type	Type 4/non-Type 4	35/45	11.5/15.2	**1.71**	**1.04–2.80**	**0.03**	**1.80**	**1.08–3.00**	**0.02**
Histological classification	undifferentiated/other	52/28	11.5/17.3	1.56	0.95–2.62	0.08			
cT	4/1–3	45/35	12.7/15.2	0.98	0.61–1.59	0.93			
cN	2–3/0–1	30/50	10.0/15.5	**2.02**	**1.20–3.36**	**0.01**	**1.88**	**1.11–3.15**	**0.02**
Bulky N	yes/no	8/72	7.9/14.3	**3.00**	**1.13–6.71**	**0.03**			
pP	1/0	32/48	10.5/17.3	**2.46**	**1.48–4.12**	**0.001**			
H1, P1, M1(LYM), or M1(SKI)	yes/no	36/44	10.4/19.7	**2.72**	**1.63–4.60**	**0.0001**	**3.50**	**2.00–6.24**	**< 0.0001**
Resection	no/yes	23/57	10.4/15.5	1.65	0.95–2.77	0.08			
Residual tumor (R)	2/1	30/50	10.0/15.8	**1.96**	**1.17–3.23**	**0.01**			
Preoperative chemo	no/yes	65/15	14.3/8.2	0.80	0.45–1.53	0.48			
Postoperative chemo	no/yes	19/61	5.4/15.4	**2.15**	**1.22–3.63**	**0.01**	**2.68**	**1.47–4.95**	**0.003**

Clinical and pathological findings are written according to the Japanese Classification of Gastric Carcinoma 15th edition. Bold letters indicate statistical significance

PNI Onodera's prognostic nutritional index, *PS* Eastern Cooperative Oncology Group performance status, *ASA* American Society of Anesthesiologists physical status, *MST* median survival time, *HR* hazard ratio, *CI* confidence interval

Univariate and multivariate analyses for CY1 patients with R1 resection (R1 resection cohort)

In addition, univariate and multivariate analyses were performed for the 50 patients with CY1 with R1 resection. This population included patients with CY1P0 or CY1P1 who underwent gastrectomy leaving no macroscopic residual tumor. In univariate analyses, the PNI (< 40 vs. ≥ 40), macroscopic type (Type 4 vs. non-Type 4), cN (2–3 vs. 0–1), pP (1 vs. 0), and absence of postoperative chemotherapy were significantly correlated with a poor OS (Table 4). A multivariate analysis conducted with these significant factors of PNI, macroscopic type, cN, pP, and postoperative chemotherapy revealed that Type 4, cN2–3, and pP1 were independent risk factors for death.

Subgroup survival analyses by PNI

Given the above-mentioned results, log-rank survival analyses were performed for the following 3 groups: patients who underwent gastrectomy with PNI ≥ 40 and CY1 without any other distant metastasis (PNI ≥ 40 Group, $n = 24$); patients who underwent gastrectomy with PNI < 40 and CY1 without any other distant metastasis (PNI < 40 Group, $n = 12$); and patients with CY1 and other distant metastases (Other M1 Group, $n = 36$). The Kaplan–Meier curves are shown in Fig. 1. The OS of the PNI ≥ 40 Group (3- and 5-year OS rates and MST: 46, 27%, and 31.6 months, respectively) was significantly better than that of the PNI < 40 Group (3- and 5-year OS rates and MST: 17, 8%, and 10.9 months, respectively; $p = 0.006$). The OS of the PNI < 40 Group was as poor as that of the Other M1 Group (3- and 5-year OS rates and MST: 6, 0%, and 10.4 months, respectively; $p = 0.30$).

Subgroup survival analyses by macroscopic type

Log-rank survival analyses were performed for the following 3 groups: patients who underwent gastrectomy with non-Type 4 tumor and CY1 without any other distant metastasis (Non-Type 4 Group, $n = 21$); patients who underwent gastrectomy with Type 4 tumor and CY1 without any other distant metastasis (Type 4 Group, $n = 15$); and the Other M1 Group. The Kaplan–Meier curves are shown in Fig. 2. The OS of the Non-Type 4 Group (3- and 5-year OS rates and MST: 55, 38%, and 41.8 months, respectively) was significantly better than that of the Type 4 Group (3- and 5-year OS rates and MST: 13, 0%, and 17.3 months, respectively; $p = 0.03$). The OS of the Type 4 group was still better than that of the Other M1 Group ($p = 0.02$).

Subgroup survival analyses by cN

Log-rank survival analyses were performed by the following 3 groups: patients who underwent gastrectomy with cN0–1 and CY1 without any other distant metastasis (cN0–1 Group, $n = 21$); patients who underwent gastrectomy with cN2–3 and CY1 without any other distant metastasis (cN2–3 Group, $n = 15$); and the Other M1 Group. The Kaplan–Meier curves are shown in Fig. 3.

Table 3 Univariate and multivariate analyses for CY1 patients without other distant metastases

Variables		*n*	MST (months)	Univariate analysis			Multivariate analysis		
				HR	95% CI	*p*	HR	95% CI	*p*
Sex	male/female	39/5	17.3/32.0	1.15	0.52–6.07	0.52			
Age (years)	≥ 70/< 70	25/19	19.7/22.0	1.67	0.83–3.58	0.15			
Albumin (g/dl)	< 3.5/≥ 3.5	17/27	14.3/24.6	**2.01**	**1.05–3.99**	**0.05**			
PNI	< 40/≥ 40	13/31	9.0/28.3	**2.62**	**1.27–5.24**	**0.01**	**2.93**	**1.18–6.69**	**0.02**
PS	1–3/0	5/39	13.2/22.0	1.43	0.48–3.39	0.48			
ASA	3/1–2	5/39	9.0/24.6	**3.45**	**1.12–8.85**	**0.03**	0.96	0.27–3.20	0.95
Macroscopic type	Type 4/non-Type 4	19/25	17.3/28.3	**2.19**	**1.07–4.56**	**0.03**	**2.34**	**1.10–5.12**	**0.03**
Histological classification	undifferentiated/other	26/18	13.2/28.3	1.58	0.80–3.26	0.19			
cT	4/1–3	22/22	24.6/16.6	0.77	0.39–1.52	0.46			
cN	2–3/0–1	18/26	13.0/31.6	**2.63**	**1.26–5.47**	**0.01**	**2.94**	**1.36–6.38**	**0.01**
Resection	no/yes	8/36	11.5/22.0	1.34	0.50–3.08	0.53			
Preoperative chemo	no/yes	34/10	22.0/20.5	0.79	0.37–1.88	0.58			
Postoperative chemo	no/yes	10/34	11.6/22.2	1.86	0.85–3.80	0.12			

Clinical and pathological findings are written according to the Japanese Classification of Gastric Carcinoma 15th edition. Bold letters indicate statistical significance

PNI Onodera's prognostic nutritional index, *PS* Eastern Cooperative Oncology Group performance status, *ASA* American Society of Anesthesiologists physical status, *MST* median survival time, *HR* hazard ratio, *CI* confidence interval

Table 4 Univariate and multivariate analyses for CY1 patients with R1 resection

Variables		*n*	MST (months)	Univariate analysis			Multivariate analysis		
				HR	95% CI	*p*	HR	95% CI	*p*
Sex	male/female	42/8	17.3/13.1	0.78	0.37–0.92	0.56			
Age (years)	≥ 70/< 70	27/23	16.6/15.8	1.26	0.68–2.42	0.46			
Albumin (g/dl)	< 3.5/≥ 3.5	17/33	12.7/18.2	1.65	0.86–3.09	0.13			
PNI	< 40/≥ 40	15/35	9.0/22.0	**2.42**	**1.24–4.57**	**0.01**	1.92	0.88–4.05	0.10
PS	1–3/0	9/41	10.7/17.3	1.82	0.82–3.68	0.13			
ASA	3/1–2	5/45	9.0/17.3	2.61	0.88–6.37	0.08			
Macroscopic type	Type 4/non-Type 4	22/28	15.4/21.4	**2.15**	**1.13–4.15**	**0.02**	**2.25**	**1.15–4.52**	**0.02**
Histological classification	undifferentiated/other	29/21	15.8/19.7	1.27	0.68–2.40	0.48			
cT	4/1–3	27/23	18.2/13.2	0.80	0.43–1.49	0.48			
cN	2–3/0–1	21/29	13.0/19.7	**2.37**	**1.21–4.63**	**0.01**	**2.31**	**1.16–4.59**	**0.02**
Operative procedure	total/distal gastrectomy	24/26	13.2/19.7	1.35	0.73–2.51	0.34			
Lymph node dissection	<D2/D2	20/30	15.0/17.3	1.39	0.74–2.57	0.30			
pP	1/0	14/36	12.6/22.0	**2.28**	**1.11–4.52**	**0.03**	**3.04**	**1.39–6.66**	**0.01**
Resection margin	positive/negative	7/43	26.1/15.8	0.89	0.34–1.99	0.80			
Preoperative chemo	no/yes	40/10	17.3/10.0	0.82	0.40–1.93	0.63			
Postoperative chemo	no/yes	13/37	8.2/18.2	**2.14**	**1.07–4.07**	**0.03**	2.20	0.96–4.86	0.06

Clinical and pathological findings are written according to the Japanese Classification of Gastric Carcinoma 15th edition. Bold letters indicate statistical significance

PNI Onodera's prognostic nutritional index, *PS* Eastern Cooperative Oncology Group performance status, *ASA* American Society of Anesthesiologists physical status, *MST* median survival time, *HR* hazard ratio, *CI* confidence interval

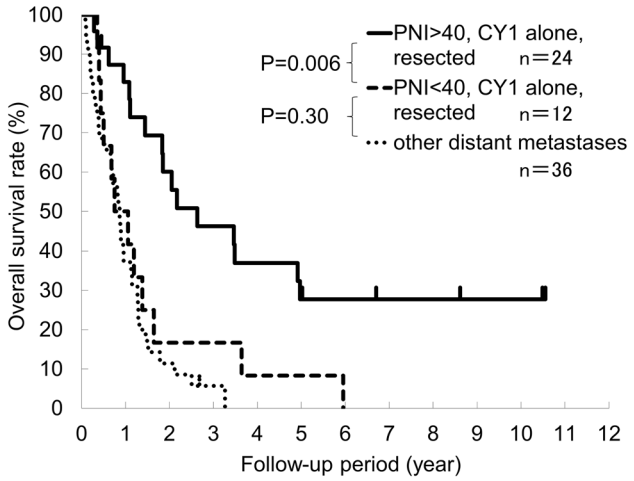

Fig. 1 Kaplan–Meier curves of three subgroups: patients who underwent gastrectomy with PNI ≥ 40 and CY1 without any other distant metastasis; patients who underwent gastrectomy with PNI < 40 and CY1 without any other distant metastasis; and patients with CY1 and other distant metastases

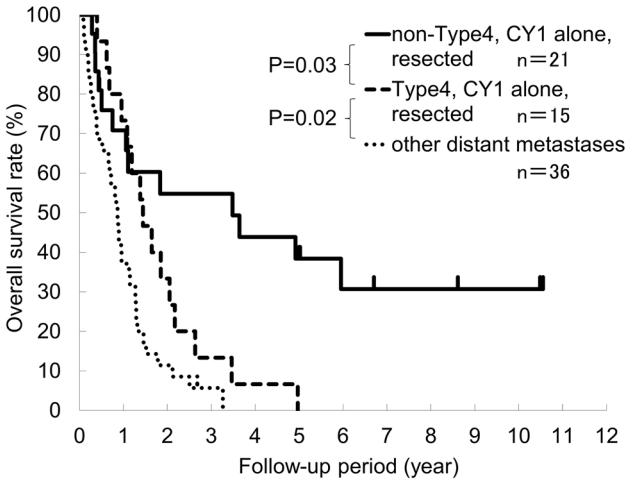

Fig. 2 Kaplan–Meier curves of three subgroups: patients who underwent gastrectomy with non-Type 4 tumor and CY1 without any other distant metastasis; patients who underwent gastrectomy with Type 4 tumor and CY1 without any other distant metastasis; and patients with CY1 and other distant metastases

The OS of the cN0–1 Group (3- and 5-year OS rates and MST: 52, 33%, and 41.6 months, respectively) was significantly better than that of the cN2–3 Group (3- and 5-year OS rates and MST: 9, 0%, and 13.2 months, respectively; $p = 0.002$). The OS of the cN2–3 Group was as poor as that of the Other M1 Group ($p = 0.28$).

Discussion

CY1 is classified as distant metastasis both in the Japanese Classification of Gastric Carcinoma [3] and in the TNM classification [4], and its prognosis is poor. In the

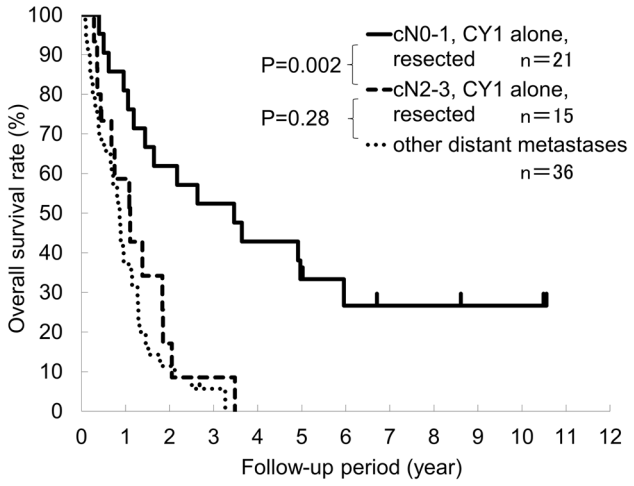

Fig. 3 Kaplan–Meier curves of three subgroups: patients who underwent gastrectomy with cN0–1 and CY1 without any other distant metastasis; patients who underwent gastrectomy with cN2–3 and CY1 without any other distant metastasis; and patients with CY1 and other distant metastases

Japanese gastric cancer registry in 2009 [2], the 5-year OS for CY0 was 66.9%, while that for CY1 was 13.1%. However, considering the results of CCOG 0301 [6], which showed that the MST and 5-year OS rate of the patients with CY1 (including resectable peritoneal metastasis) was 23.2 months and 26%, respectively, the Japanese Gastric Cancer Treatment Guidelines additionally recommend radical gastrectomy followed by S-1 chemotherapy for gastric cancer with CY1 but no other residual disease [5]. Recently, Yoshida et al. [11] classified Stage IV gastric cancer into four categories. CY1P0 gastric cancer is classified in Category 1, and the recommended treatment is primary tumor resection with or without neoadjuvant chemotherapy. In contrast, some retrospective studies have shown that aggressive surgical resection is not associated with any survival benefit for gastric cancer with CY1, even in the absence of peritoneal dissemination [12, 13]. Thus, the strategy for treating CY1 gastric cancer patients has been confusing, as a patient being CY1 alone does not seem to be sufficient grounds for deciding on a certain therapeutic procedure.

Regarding gastric cancer patients with CY1 and other distant metastases, the treatment had also been controversial, as volume reduction operations have seemed to be beneficial for the OS. However, the REGATTA trial showed no survival benefit associated with such operations for advanced gastric cancer with a single non-curable factor, including liver, peritoneum, or para-aortic lymph node (16a1/b2) metastases [14]. Therefore, gastrectomy for those patients is no longer selected except for symptomatic cases, such as patients with pyloric stenosis and bleeding.

Given this confusion regarding the optimum strategy for CY1 gastric cancer, the current study was conducted in a heterogeneous population of both resected and unresected patients. Univariate and multivariate analyses showed that cN2–3 with ≥3 swelling lymph nodes on preoperative CT was a significant prognostic factor for the entire CY1 cohort, the CY1-alone cohort, and the R1 resection cohort. The log-rank survival analyses showed that the prognoses of patients with cN2–3 CY1 who underwent gastrectomy were as poor as those with other distant metastases.

Some reports have mentioned that lymph node metastasis is associated with a poor prognosis for CY1P0 gastric cancer. cN3 (vs. cN0–2) was shown to be a significant independent indicator for an unfavorable OS by multivariable analyses among CY1P0 patients [10, 15, 16]. Furthermore, Kano et al. [17] showed that pN3b (vs. pN0–3a) was associated with an extremely poor prognosis. Saito et al. [18] indicated that the prognosis of CY1P0 patients without pathological lymph node metastasis was good, whereas that of those with pathological lymph node metastasis was extremely poor. Fukuchi et al. [16] noted that patients without serosal invasion may have CY1, and such patients occasionally develop recurrence in both the lymph nodes and peritoneum. These findings suggest that the progression of CY1 gastric cancer is associated with lymph node metastasis. Indeed, our data showed that cN2–3 patients developed lymph node metastasis after R1 gastrectomy more frequently (24%) than cN0–1 patients (0%).

We also performed a univariate analysis by dividing lymph node metastasis into cN0 vs. cN1–3 categories and cN0–2 vs. cN3 categories, but both failed to show a significant association with the survival (data not shown). Bulky N, which indicates nodal involvement of ≥3 cm or at least 2 adjacent tumors ≥1.5 cm surrounding the celiac artery and its branches, is also said to have a poor prognosis [19] and was recently described in the gastric cancer treatment algorithm under the latest Japanese Gastric Cancer Treatment Guideline [5]. Our results showed the significant association of bulky N with a worse survival in the entire CY1 cohort by a univariate analysis, but there were only eight bulky N patients in the entire CY cohort, two in the CY1-alone cohort, and three in the R1 resection cohort. Therefore, cN2–3 seems to be a more practical indicator for the OS than bulky N. Pathological N can be assessed objectively and is still viewed as a determinant of the OS, along with cN categories. However, this factor is only available after an operation, while cN can be assessed before an operation. We therefore consider cN to be a useful predictor of the prognosis before an operation.

Type 4 tumors were also reported to have an extremely poor prognosis compared to non-Type 4 tumors [20, 21]. Kano et al. [22] found by a multivariate analysis that Type 4 tumor, R2 resection, lymph node metastasis, and

postoperative chemotherapy were independent prognostic factors. Our multivariate analyses also showed that Type 4 tumors were associated with a worse OS in the entire CY1 cohort, in the CY1-alone cohort, and in the R1 resection cohort than non-Type 4 tumors. However, the log-rank test showed that the prognoses of patients with Type 4 tumors and CY1 who underwent gastrectomy were significantly better than those with other distant metastases.

In addition to the oncological factors, PS0–1 is reported to be associated with a prolonged OS for advanced gastric cancer [23], but the current study did not show the same result, as most cases (86%) were associated with the criterion of PS0–1 Previous studies have demonstrated the association between the serum albumin level and the survival in gastric cancer patients [24, 25]. The PNI, which is calculated using the serum albumin level, was originally used to evaluate the risk of postoperative complications and mortality in gastrointestinal tract surgery, and it has become a powerful prognostic parameter for various types of cancer [7]. Our findings also suggested that low serum albumin levels (< 3.5 mg/dl) and a low PNI (< 40) were poor prognostic factors. The results of log-rank survival analyses suggested that the prognoses of patients with a PNI < 40 were as poor as those with other distant metastases.

The CCOG 0301 study included R1 resection and S-1 chemotherapy for 1 year for CYP0 or CYP1 patients [6]; however, no satisfactory postoperative adjuvant chemotherapy regimen for gastric cancer patients with CY1 has been established. In our series, 25 patients received S-1 chemotherapy, but 60% of them stopped S-1 within 1 year mainly because of progressive disease. The univariate analyses showed the survival benefit of postoperative chemotherapy for the entire CY1 cohort and the R1 resection cohort, but failed to show any such benefit for the CY1-alone cohort. More discussion is needed to develop effective regimens for CY1 patients.

Our univariate analyses failed to show a survival benefit of gastrectomy for patients with CY1 with or without other distant metastases. However, the results of log-rank survival analyses by subgroups suggest that surgical resection will be beneficial for the OS if we select patients with CY1 alone and with a PNI > 40, non-Type 4, or cN0–1. In contrast, the survival rates of resected patients with CY1 alone and a PNI < 40 or cN2–3 were equivalent to those of patients with other distant metastases. This finding suggests that aggressive surgical resection may not provide any survival benefit for CY1 patients with a PNI < 40 or cN2–3, even in the absence of other distant metastases. A prospective study in a larger series of patients is needed to clarify the optimum treatment strategy for CY1 gastric cancer.

The present study has several potential limitations. First, this study was limited by its retrospective nature. A selection bias may have influenced the survival data. Second, this study was conducted at a single institution in a relatively small number of patients. Third, clinical lymph node metastasis is not clearly defined in the Japanese Classification of Gastric Carcinoma or TNM classification. We referred to the previously described definition [10], but this approach may differ among institutions and physicians.

Conclusions

We retrospectively analyzed the prognostic factors for cytology-positive gastric cancer patients. The prognoses of patients with other distant metastases were significantly poorer than those of patients without other distant metastases. Univariate and multivariate analyses of the CY1 population without other distant metastases showed that a PNI < 40, Type 4, and cN2–3 were significantly correlated with a poor OS. The log-rank analyses demonstrated that CY1 patients with a PNI < 40 or cN2–3 had significantly worse prognoses than those with a PNI > 40 or cN0–1, equivalent to those with other distant metastases.

Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest.

References

1. Cancer Information Service, National Cancer Center, Japan. Cancer Registry and Statistics. https://ganjoho.jp/reg_stat/statistics/dl/index.html#mortality Accessed 1 Apr 2018.
2. Japanese Gastric Cancer Association. The Japanese gastric cancer registry in 2009. http://www.jgca.jp/entry/iganhtml/doc/2009_report.pdf Accessed 1 Apr 2018.
3. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma, the 15th edition (in Japanese). Tokyo: Kanehara; 2017.
4. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours, the eighth edition. Oxford: Wiley Blackwell; 2017.
5. Association Japanese Gastric Cancer. Gastric Cancer Treatment Guidelines, 5th ed. Tokyo: Kanehara; 2018 (**in Japanese**).
6. 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;35:1158–63.
7. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients (in Japanese with English abstract). Nihon Geka Gakkai Zasshi (J Jpn Surg Society). 1984;85:1001–5.
8. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol. 1982;5:649–55.
9. American Society of Anesthesiologists. ASA physical status classification system. https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system Accessed 1 Apr 2018.

10. Lee SD, Ryu KW, Eom BW, Lee JH, Kook MC, Kim YW, et al. Prognostic significance of peritoneal washing cytology in patients with gastric cancer. Br J Surg. 2012;99:397–403.
11. Yoshida K, Yamaguchi K, Okumura N, Tanahashi T, Kodera Y. Is conversion therapy possible in stage IV gastric cancer: the proposal of new biological categories of classification. Gastric Cancer. 2016;19:329–38.
12. Nakagohri T, Yoneyama Y, Kinoshita T, Konishi M, Inoue K, Takahashi S. Prognostic significance of peritoneal washing cytology in patients with potentially resectable gastric cancer. Hepatogastroenterology. 2008;55:1913–5.
13. Nishikawa K, Fujitani K, Endo S, Kawada J, Hirao M, Hamakawa T, et al. Is gastrectomy for CY1 gastric cancer truly essential? [abstract]. In 90th Annual Meeting of the Japanese Gastric Cancer Association program: 2018 Mar 7–9: Yokohama. Japan: Abstract PP230.
14. Fujitani K, Yang HK, Mizusawa J, Kim YW, Terashima M, Han SU, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol. 2016;17:309–18.
15. Yamamoto M, Kawano H, Yamaguchi S, Egashira A, Minami K, Taguchi K, et al. Comparison of neoadjuvant chemotherapy to surgery followed by adjuvant chemotherapy in Japanese patients with peritoneal lavage cytology positive for gastric carcinoma. Anticancer Res. 2015;35:4859–63.
16. Fukuchi M, Mochiki E, Ishiguro T, Ogura T, Sobajima J, Kumagai Y, et al. Prognostic factors for gastric cancer with cancer cells in the peritoneal cavity. Anticancer Res. 2016;36:2481–5.
17. Kano K, Aoyama T, Maezawa Y, Nakajima T, Ikeda K, Yamada T, et al. The survival and prognosticators of peritoneal cytology-positive gastric cancer patients who received upfront gastrectomy and subsequent S-1 chemotherapy. Int J Clin Oncol. 2017;22:887–96.
18. Saito H, Kihara K, Kuroda H, Matsunaga T, Tatebe S, Ikeguchi M. Surgical outcomes for gastric cancer patients with intraperitoneal free cancer cell, but no macroscopic peritoneal metastasis. J Surg Oncol. 2011;104:534–7.
19. Tsuburaya A, Mizusawa J, Tanaka Y, Fukushima N, Nashimoto A, Sasako M. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis. Br J Surg. 2014;101:653–60.
20. Noda S, Yashiro M, Toyokawa T, Morimoto J, Shinto O, Muguruma K. Borrmann's macroscopic criteria and p-Smad2 expression are useful predictive prognostic markers for cytology-positive gastric cancer patients without overt peritoneal metastasis. Ann Surg Oncol. 2011;18:3718–25.
21. 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(3):563–8.
22. 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;158:1581–9.
23. Nishimura T, Iwasa S, Nagashima K, Okita N, Takashima A, Honma Y, et al. Irinotecan monotherapy as third-line treatment for advanced gastric cancer refractory to fluoropyrimidines, platinum, and taxanes. Gastric Cancer. 2017;20:655–62.
24. Crumley AB, Stuart RC, McKernan M, McMillan DC. Is hypoalbuminemia an independent prognostic factor in patients with gastric cancer? World J Surg. 2010;34:2393–8.
25. Chen XL, Xue L, Wang W, Chen HN, Zhang WH, Liu K, et al. Prognostic significance of the combination of preoperative hemoglobin, albumin, lymphocyte and platelet in patients with gastric carcinoma: a retrospective cohort study. Oncotarget. 2015;6:41370–82.