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ORIGINAL ARTICLE

Is curative gastrectomy justified for gastric cancer with cytology positive as the only stage IV factor?

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Abstract

Aims The prognosis of patients with gastric cancer and stage IV factors is poor. However, several recent studies have identified that curative surgery followed by S-1 chemotherapy for cytology positive (CY1) only patients contributed to a better prognosis. This study was designed to compare the prognosis between curative and palliative gastrectomy followed by chemotherapy in CY1 only stage IV gastric cancer.

Methods Between 2001 and 2016, 1507 patients underwent gastrectomy for gastric cancer. Of these, 51 consecutive patients with only CY1 factor who underwent gastrectomy followed by chemotherapy were enrolled in this study.

Results (1) Twenty three (45%) patients underwent curative D2 or D2+ gastrectomy, and the remaining 28 (55%) patients underwent palliative gastrectomy, followed by S-1 based or another historical recommended chemotherapy postoperatively. (2) Compared with patients undergoing palliative gastrectomy, patients undergoing curative gastrectomy had a significantly better prognosis ($P = 0.042$; median survival time: curative vs. palliative, 22.6 months vs. 11.8 months) and a lower incidence of recurrences ($P = 0.091$). Two- and five-year overall survival rates of patients following curative gastrectomy were 48.2% and 18.2%, respectively. A multivariate analysis showed that venous invasion [$P = 0.006$; hazard ratio (HR), 3.70 (95% CI: 1.27–9.43)] and curative gastrectomy [$P < 0.005$; HR, 0.28 (95% CI: 0.12–0.87)] were independent prognostic factors.

Conclusion Curative gastrectomy followed by chemotherapy might be justified to improve the prognosis of patients with only CY1 Stage IV gastric cancer.

Keywords Cytology positive · Gastrectomy · Lymphadenectomy · Stage IV · Gastric cancer

Introduction

Gastric cancer is a major cause of death worldwide [1]. Recent advances in diagnosis, less invasive treatments, surgical techniques, perioperative management, and chemotherapy have improved the early and long-time outcomes of gastric cancer [2, 3]. Nonetheless, patients with advanced stage disease and a high incidence of stage IV factors still have a poor prognosis. Stage IV factors, such as cytology positive (CY1), peritoneal metastasis (P1), hematogenous metastasis, such as liver metastasis (H1), and paraaortic lymph node metastasis (No.16(+)), are the strongest predictor of the prognosis of gastric cancer patients, and the treatment strategy against stage IV factors is one of most important clinical issues [4–6].

Gastrectomy for the primary tumor and lymphadenectomy for regional lymph nodes are recognized as the only chance for macroscopic tumor clearance and cure for gastric cancer; the effects of such surgical resections are restricted to local control of the primary tumor [7–9] and cannot prevent recurrence due to micro-metastasis. However, if micro-metastases, such as CY1 only gastric cancer, are controlled using recent systemic chemotherapy [10–12], then macroscopic residual tumors and metastatic lymph nodes could affect the cure of gastric cancer [13].

Each stage IV factor has a different clinical behavior and tumor burden. In particular, cytology positive (CY1) is

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recognized as a clinical status of micro-metastasis and a low tumor burden at the peritoneal cavity. Indeed, stage IV gastric cancer patients with only CY1 factor following gastrectomy have been reported to have a comparatively better prognosis than those with other stage IV factors or multiple stage IV factors in Japan and Korea studies [14–17]. Therefore, Japanese treatment guidelines have indicated no established and evidence-based treatment strategy for the chemotherapy periods, the timing, the regimens, and the detailed procedure regarding gastrectomy for patients with only CY1 Stage IV gastric cancer [18, 19]. In this study, we investigated the clinical significance of gastrectomy followed by chemotherapy in CY1 only stage IV gastric cancer, with special reference to the curative intent. The results of our study may suggest that curative gastrectomy followed by chemotherapy is a feasible strategy for the better local tumor clearance and prognosis in patients with only CY1 gastric cancer.

Methods

Patients and surgical procedures

Between 2001 and 2016, 1507 consecutive gastric cancer patients underwent gastrectomy for gastric cancer at the Department of Surgery, Kyoto First Red Cross Hospital. Of all 1507 patients, 298 patients had single or multiple stage IV factors. Specifically, 152 patients had P1CY1 factors, 48 patients had only H1 factor, 51 patients had only CY1 factor, 3 patients had only No.16(+) factor, 33 patients had P1CY1H1 factors, 6 patients had P1CY1No.16(+) factors, 2 patients had H1CY1 factors, 1 patient had H1No.16(+) factors, 1 patient had CY1No.16(+) factors, and 1 patient had P1CY1H1No.16(+) factors. In this study, 51 consecutive patients with only CY1 stage IV factor who underwent gastrectomy followed by chemotherapy were analyzed retrospectively.

Patients underwent preoperative assessments including gastric endoscopy, computed tomography (CT) scans, and laboratory tests. Based on the preoperative diagnosis, all patients were preoperatively scheduled for curative gastrectomy and lymphadenectomy, mainly according to the Japanese guidelines for the treatment of gastric cancer [20]. When only CY1 stage IV factor was positive during surgery, whether to perform curative or palliative gastrectomy was preoperatively scheduled by each operator, and each patient was informed prior to surgery because there was no established and evidence-based strategy [18, 19].

As a result, 23 (45%) patients underwent curative D2 or D2+ (D2 $\underline{\leq}$) gastrectomy, and the remaining 28 (55%) patients underwent palliative gastrectomy. In the D2 dissection, the perigastric lymph nodes and all second-tier lymph nodes were completely retrieved. Depending on the location of the tumor, lymphadenectomy was added along the distal side of the splenic artery (no. 11d) and at the splenic hilum (no. 10), together with splenectomy or splenectomy with distal pancreatectomy [21].

Cytological examination was routinely performed after the laparotomy, prior to manipulation of the tumor using 100 ml of saline. Saline was introduced into the Douglas pouch and collected after gentle stirring. Cytological smears were prepared from centrifuged deposits and were examined by at least two experienced pathologists after Papanicolaou and Giemsa staining. The cytology, resected tumor specimens, and retrieved lymph nodes were examined and evaluated based on Japanese classifications of gastric cancer [21] and the TNM staging manual [22]. Histological types were classified as differentiated (papillary adenocarcinoma or moderately or well-differentiated adenocarcinoma) or undifferentiated (poorly differentiated or undifferentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous adenocarcinoma) [21].

Treatments following gastrectomy

All 51 patients underwent S-1 based or another historically recommended chemotherapy postoperatively. Forty-five patients (88.2%, 45/51) received S-1 alone or an S-1-based chemotherapy such as S-1 plus cisplatin or S-1 plus taxane [11, 23, 24]. Of the remaining six patients, two patients received weekly paclitaxel, one patient received methotrexate plus 5-fluorouracil, one patient received isovoline plus 5-fluorouracil, and two patients received uracil-tegafur. Chemotherapy was continuously performed until patients survived for more than 5 years without recurrences or until patients preferred to be followed without chemotherapy due to various reasons including disease progression. None of the patients received neoadjuvant chemotherapy, adjuvant radiotherapy, or chemoradiotherapy. All patients were examined in the outpatient clinic, in which abdominal ultrasound, CT and measurements of carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9) levels were performed every 1–3 months after surgery.

Statistical analysis

The χ^2 test and Fisher's exact probability test were performed for categorical variables, whereas the Student's t test and Mann–Whitney U test for unpaired data of continuous variables were performed to compare the clinicopathological characteristics between the two groups. Survival curves were estimated using the Kaplan–Meier method, and statistical differences were examined using the log-rank test. Univariate and multivariate survival analyses were performed using the

likelihood ratio test of the stratified Cox proportional hazards model. $P < 0.05$ was considered statistically significant.

Results

Clinicopathological characteristics of CY1 only stage IV gastric cancer patients

The clinical characteristics of 51 consecutive patients with only CY1 stage IV gastric cancer were as follows. Of 51 patients, preoperatively, one patient was staged as cStage I, 8 patients as cStage II, and 42 patients as cStage III. The study group consisted of 37 male and 14 female patients with a median age of 67 years (range 23–85 years). Thirty-three patients underwent total gastrectomy, 15 patients underwent distal gastrectomy, 2 patients underwent remnant gastrectomy, and 1 patient underwent pancreatoduodenectomy (Table 1).

Table 1 Comparison of clinicopathological factors between patients with curative D2 ≤ gastrectomy and palliative gastrectomy in CY1 only stage IV gastric cancer

	Number	Gastrectomy		*P* value
		Curative (D2 ≤)	Palliative	
Total	51	23	28	
Age (years)				
< 75	40	18 (78%)	22 (79%)	0.752
75 ≤	11	5 (22%)	6 (21%)	
Gender				
Female	14	7 (30%)	7 (25%)	0.906
Male	37	16 (70%)	21 (75%)	
Histological type				
Differentiated	10	2 (9%)	8 (29%)	0.091
Undifferentiated	41	21 (91%)	20 (71%)	
Macroscopic appearance				
Type 4	27	12 (52%)	15 (54%)	0.921
Non-type 4	24	11 (48%)	13 (46%)	
Lymphatic invasion				
Negative	1	1 (4%)	0 (0%)	0.450
Positive	50	22 (96%)	28 (100%)	
Venous invasion				
Negative	8	2 (10%)	6 (21%)	0.268
Positive	43	21 (100%)	22 (79%)	
pT categories				
T1–3	2	0 (0%)	2 (7%)	0.494
T4	49	23 (100%)	26 (93%)	
pN categories				
Negative	3	2 (9%)	1 (4%)	0.582
Positive	48	21 (91%)	27 (96%)	
JCGC/TNM cStage				
I	1	1 (4%)	0 (0%)	0.982
II	8	3 (13%)	5 (18%)	
III	42	19 (83%)	23 (82%)	
Gastrectomy				
Distal	15	8 (35%)	7 (25%)	0.869
Total	33	13 (57%)	20 (71%)	
Remnant	2	1 (4%)	1 (4%)	
PD	1	1 (4%)	0 (0%)	

P values were calculated by chi-square or Fisher's exact test

PD pancreatoduodenectomy

Comparison of clinicopathological factors between patients with curative D2 ≤ gastrectomy and palliative gastrectomy in CY1 only stage IV gastric cancer

Next, we compared the clinicopathological factors between patients with curative D2 ≤ gastrectomy and palliative gastrectomy in CY1 only stage IV gastric cancer. There was no difference in clinical factors such as age, sex, cStage, and gastrectomy between both groups. Regarding pathological factors such as histology, macroscopic appearance, lymphatic invasion, venous invasion, depth of invasion, and the presence of lymph node metastasis, there was no difference between both groups (Table 1).

Univariate and multivariate analyses using the Cox's proportional hazard model in CY1 only stage IV gastric cancer

Compared with CY1 only stage IV patients undergoing palliative gastrectomy, patients undergoing curative D2 ≤ gastrectomy had a significantly better prognosis [$P = 0.042$; curative D2 ≤ gastrectomy vs. palliative < D2 gastrectomy: median survival time (MST), 632 days (22.6 months) vs. MST, 330 days (11.8 months)] (Fig. 1) and tended to have a lower incidence of recurrences ($P = 0.091$; curative

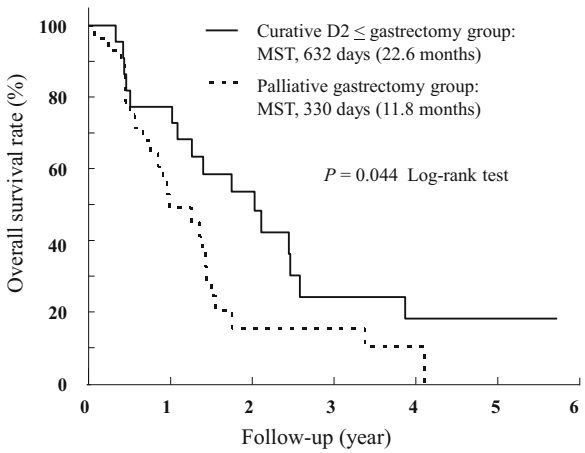

Fig. 1 Comparison of survival curves between patients with curative D2 ≤ gastrectomy and palliative gastrectomy in CY1 only Stage IV gastric cancer. Compared with CY1 only stage IV patients undergoing palliative gastrectomy, patients undergoing curative D2 ≤ gastrectomy had a significantly better prognosis. Two- and 5-year OS rates of patients following curative gastrectomy were 48.2% and 18.2%, respectively. MST, median survival time; OS, overall survival.

gastrectomy vs. palliative gastrectomy: 57% (13/23) vs. 87% (23/28)). Two- and 5-year overall survival (OS) rates of patients undergoing curative D2 ≤ gastrectomy were 48.2% and 18.2%, respectively. Regarding the causes of death, among 23 patients undergoing curative D2 ≤ gastrectomy, 13 patients died of recurrences. Of 10 patients without recurrences, three patients died of other diseases. Among 28 patients undergoing palliative < D2 gastrectomy, 23 patients died of recurrences. Of the five patients without recurrences, two patients died of other diseases, and three patients died of unknown causes, which might be highly indicative of recurrences.

As a prognostic factor in CY1 only stage IV gastric cancer, univariate and multivariate analyses using the Cox's proportional hazard model demonstrated that being male and venous invasion were independent poor prognostic factors [$P = 0.006$; HR, 3.70 (95% CI: 1.27–9.43)]. Moreover, curative D2 ≤ gastrectomy was an independent better prognostic factor [$P < 0.005$; HR, 0.28 (95% CI 0.12–0.87)] (Table 2).

Discussion

This study demonstrated that CY1 only stage IV gastric cancer patients who underwent gastrectomy with curative gastrectomy with D2 lymphadenectomy followed by chemotherapy had a better prognosis than those with palliative gastrectomy. Furthermore, this study clearly identified that curative gastrectomy and venous invasion were independent prognostic factors in CY1 only stage IV gastric cancer patients. These results strongly indicated that curative gastrectomy with standard lymphadenectomy followed by chemotherapy might be justified to improve the prognosis of CY1 only stage IV gastric cancer, and venous invasion could be specifically targeted in an effort to improve the prognosis, suggesting an indication for more intensive postoperative chemo- and/or molecular-targeted therapy.

Various reports have shown the better prognostic effect of curative gastrectomy with standard lymphadenectomy for stage IV patients with only CY1 factor. Kodera et al. reported on the long-term follow-up results of 47 consecutive patients with only CY1 factor who underwent curative gastrectomy with standard D2 lymphadenectomy followed by adjuvant S-1 chemotherapy (CCOG0301 study). MST was 23.5 months (705 days). Two- and 5-year OS rates were 46% and 26%, respectively [14]. Oh et al. also investigated the long-term results and prognostic factors of 37 consecutive patients with only CY1 stage IV factor. As a result, MST was 15.0 months. Two- and 5-year OS rates were 45.9% and 0%, respectively [15]. Bando et al. reported that the 5-year OS rate was 26.6% in 120 consecutive patients with only CY1 factor who underwent

Table 2 Univariate and multivariate analyses using the Cox's proportional hazard model in CY1 only stage IV gastric cancer

Variables	Univariate[a]		Multivariate[b]	
	P value	HR	95% CI	*P* value
Age				
≥ 75 vs. < 75	0.357	1.789	0.519–6.173	0.357
Gender				
Male vs. Female	0.024	2.873	1.230–6.711	0.015
Histological type (JCGC)				
Undifferentiated vs. Differentiated.	0.903	2.070	0.776–5.525	0.146
Macroscopic appearance				
Type 4 vs. non-type 4	0.960	1.690	0.783–3.647	0.181
Lymphatic invasion				
Positive vs. negative	0.926	1.483	0.520–4.232	0.462
Venous invasion				
Positive vs. negative	0.014	3.704	1.270–9.434	0.006
pT-stage				
T4 vs. T1–3	0.384	1.846	0.145–23.57	0.636
pN-stage				
N3 vs.N0–2	0.944	1.923	0.600–6.165	0.271
Lymphadenectomy				
Curative (D2 ≤) vs. palliative	0.042	0.275	0.118–0.865	0.003

HR hazard ratio, *CI* confidence interval

[a] Kaplan and Meier method, and the statistical significance was determined by log-rank test

[b] Multivariate survival analysis was performed using Cox's proportional hazard model

gastrectomy with lymphadenectomy followed by adjuvant S-1- or S-1-based chemotherapy [16]. More recently, Kano et al. reported the long-term results of 36 consecutive patients with only CY1 factor. MST was 22.3 months (669 days). Two- and 5-year OS rates were 38.9% and 17.8%, respectively [17]. Our study reproducibly proved that curative gastrectomy with standard lymphadenectomy followed by chemotherapy improved the prognosis of CY1 only stage IV gastric cancer [MST, 632 days (22.6 months); 2-year-OS, 48.2%; 5-year-OS, 18.2%)]. Thus, curative gastrectomy with standard lymphadenectomy for stage IV patients with only CY1 factor could be justified for improving the prognosis.

Regarding the prognostic factors of CY1 only stage IV gastric cancer, two groups have reported the clinical issue of Borrmann type 4 factor [15, 25]. Noda et al. reported that type 4 factor was associated with poor prognosis (MST, 12.2 months; 5-year OS, 6.3%). There was no prognostic difference between patients with and without gastrectomy in CY1 only stage IV gastric cancer. Oh et al. also reported that type 4 was an independent poor prognostic factor [15]. In our study, although type 4 factor was not an independent poor prognostic factor, there was no prognostic difference between curative D2 ≤ gastrectomy and palliative gastrectomy in type 4 stage IV patients with only CY1 factor ($P = 0.344$). However, in non-type 4 cancer, patients with curative D2 ≤ gastrectomy tended to have a better prognosis ($P = 0.081$). Therefore, in the future, further strategies need be established for this issue, given the results of recent clinical trials such as JCOG 0210 and JCOG 0501, which investigated the prognostic significance of preoperative S-1 plus cisplatin followed by gastrectomy for type 4 cancer [26].

The most striking finding in our study was that the venous invasion was an independent poor prognostic factor for CY1 only gastric cancer. Previously, Oh also reported the venous invasion as an independent poor prognostic factor in CY1 only gastric cancer [15]. Several previous studies have demonstrated that venous invasion was a risk factor for hematogenous recurrence and a poor prognostic factor [27, 28], and a risk factor for chemoresistance [29] in gastric cancer. In this study, the incidence of recurrence tended to be higher in patients with venous invasion than in those without ($P = 0.144$). However, there were no significant differences between patients with and without venous invasion in peritoneal recurrence ($P = 0.785$), hematogenous recurrence ($P = 0.711$), and local or lymph node recurrences ($P = 0.732$). However, we suggest that venous invasion could be a surrogate biomarker for an indication of more intensive chemo- and/or molecular-targeted therapy in order to improve the prognosis of stage IV patients with only CY1 factor.

Concerning other prognostic factors in CY1 only gastric cancer, Kano proved that N3b was an independent poor prognostic factor. Previously, we indicated that the prognosis of N3b patients was poorer than that of N3a patients despite the better local tumor clearance by radical lymphadenectomy [30]. Accordingly, putative N3b patients with only CY1 factor may also need further strategies such as chemotherapy without gastrectomy or a neoadjuvant chemotherapy plus curative gastrectomy with lymphadenectomy for responder patients [17]. Regarding the potential role of neoadjuvant chemotherapy for only CY1 factor, there have been no definite reports, although the strategy might be promising. Further studies would be warranted using staging laparoscopy to detect only CY1 factor followed by preoperative chemotherapy.

Our study had a limitation because the results were retrospectively demonstrated. The long accrual period of the retrospective analysis at a single institute may have meant possible variations of the treatment. Namely, until definitive clinical guidelines for surgery and adjuvant chemotherapy were established in Japan [18, 19], confounding treatment effects may not have been completely negligible. Therefore, a prospective observational study using several large cohorts and/or a nationwide clinical database study may be needed to validate the significance of curative gastrectomy with standard lymphadenectomy for CY1 only gastric cancer.

Author contribution Shuhei Komatsu, Yasuhiro Shioaki, Hirotaka Furuke, Atsuki Ohta, Ryota Tsuji, Sachie Tanaka, Tatsuya Kumano, Ken-ichiro Imura, Katsumi Shimomura, Jun Ikeda, Fumihiro Taniguchi, Yasuo Ueshima, Chol Joo Lee, Eiichi Deguchi, Eito Ikeda, Eigo Otsuji performed the research and analyzed the data, and Shuhei Komatsu wrote the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This study did not include any experiments on animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethics approval This study was institutionally approved by Kyoto First Red Cross Hospital.

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