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ORIGINAL ARTICLE

Clinical characteristics and treatment outcomes of gastric cancer patients with isolated para-aortic lymph node involvement

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Abstract
Background Although gastric cancer with isolated para-aortic lymph node (PAN) involvement is considered an advanced disease, the clinical characteristics of it have not been comprehensively elucidated.
Patients and methods We reviewed the medical records of 1,277 patients received palliative chemotherapy with advanced gastric cancer according to metastatic sites: PAN-only metastasis, single organ metastasis other than PAN, and multiple organ metastasis. Time to other organ metastasis (TTOM) was determined only in PAN-only metastasis group as the time interval between initial diagnosis of recurrence or de novo metastasis and confirming distant metastasis beyond PAN area.
Results The median overall survival (OS) of patients with PAN-only metastasis was significantly longer than that of patients with single organ metastasis other than PAN or multiple organ metastasis (13.8 months vs. 11.4 months vs. 8.4 months; $P < 0.001$). In the PAN-only metastasis group, patients with recurrent diseases showed longer TTOM beyond the PAN area (10.7 vs. 7.7 months; $P = 0.037$) and OS (23.8 vs. 12.8 months; $P = 0.010$) than those with de novo metastatic disease and it was validated by multivariate analysis.
Conclusion Patients with isolated PAN metastasis showed an excellent prognosis compared with patients with metastasis at other sites and it was primarily evident in patients with recurrent PAN metastasis.

Keywords Advanced gastric cancer · Para-aortic lymph node · De novo metastasis · Recurrent disease

I.H. Park and S.Y. Kim contributed equally to this work.

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Introduction

Gastric cancer is the second most common cause of cancer-related mortality worldwide and the most common cancer in Korea [1, 2]. Gastric cancer is often diagnosed at advanced stages, and even when a curative resection is possible, recurrences are common, occurring in approximately 60% of treated patients [3, 4]. In the context of metastasis or recurrence, gastric cancer is rarely curable, even with chemotherapy. De novo metastatic gastric cancer and recurrent metastatic gastric cancer are currently considered to have similar clinical characteristics and prognoses and are therefore treated with similar clinical manners [5].

Among metastatic sites, para-aortic lymph nodes (PANs) have been investigated in a number of research studies. The efferent lymphatic flow from the stomach through regional lymph nodes eventually drains into PANs, which are considered the terminal nodes of the stomach. Indeed, micrometastases in PANs were detected in 6.2–33.0% of patients who had undergone PAN dissection [6, 7]. Based on those results, several clinical trials of extensive lymph node dissection have been performed (D3 or D4 dissection). However, these treatments have not provided any survival benefit compared with D2 dissection [7, 8]. Since patients with de novo PAN

metastasis have a poor prognosis even if they undergo extensive lymph node dissection (including PANs), they are not recommended for curative resection [9–11]. De novo and recurrent PAN metastasis are regarded and treated as the same disease, like other distant metastatic or recurrent sites, and few studies have directly compared the clinical course and prognosis of each disease. While most patients with recurrence or metastasis in PAN experience rapid disease progression to other sites, even after systemic chemotherapy, in some cases of PAN metastasis the disease can remain confined to the PAN area without metastasis for a considerable amount of time during treatment. In those cases, a local treatment modality including operation or radiotherapy with systemic chemotherapy can cure the disease. It is therefore important to differentiate diseases that tend to localize to the PAN from those that are likely to rapidly metastasize beyond the PAN area.

This retrospective study, we addressed the unique clinical entities of advanced gastric cancer with a single metastatic area of PAN as recurrence or de novo metastasis compared to those with other distant metastasis. We further investigated the prognostic factors of these patient groups, particularly in terms of the progression to sites beyond the PAN area and overall survival.

Patients and methods

Study population

A total of 1,335 patients were treated with palliative chemotherapy for recurrent or metastatic gastric adenocarcinoma at the Gastric Cancer Branch of the National Cancer Center in Korea between March 2000 and December 2006. Of a total 3,338 surgical cases, 301 (9.1%) cases were experienced disease recurrence after R0 resection. For this study, we excluded 58 patients who had experienced a locoregional recurrence after R0 resection such as in an anastomosis site, a gastric bed, or a regional lymph node. Our analysis focused on a group of 92 patients who had only PAN area involvement at the time of diagnosis as recurrent or de novo metastatic disease, without any evidence of other distant metastatic organs. PAN area metastasis was defined as lymph node metastasis within the upper margin of the celiac trunk and aortic bifurcation, designated as numbers 16a2, 16b1, and 16b2 and classified in the cross-sectional circumference of the abdominal aorta and inferior vena cava as preaortic, lateraortic, retroaortic, interaorticocaval, precaval, laterocaval, and retrocaval, according to the Japanese classification scheme [12, 13]. To better characterize this PAN group, we divided the entire source population into three groups: group A, patients with only PAN metastasis ($n = 92$); group B, those with a single metastatic organ site other than the PAN area ($n = 378$); and group C, those with multiple metastatic organ sites ($n = 807$).

All patients had undergone standard imaging studies such as abdominal and pelvic computed tomography (CT) scans and a chest X-ray to determine the extent of disease. A bone scan, an ^{18}F-fluorodeoxyglucose-positron emission tomography scan or a chest CT scan was performed if needed. Cases with distant metastatic lesions at initial staging work up were classified as de novo metastatic disease. Patients were classified as recurrent cases when disease was found by biopsy or image study after complete R0 resection. For the patients with an equivocal PAN enlargement in imaging studies, PAN metastasis was confirmed by fine-needle aspiration biopsy, open biopsy, or surgical lymph node dissection. For the purpose of this study, the medical records, images, and clinical histories for each patient were reviewed, and the primary tumor characteristics, the treatment course, and the resulting outcome were determined. This study was approved by the Institutional Review Board at the Research Institute and Hospital, National Cancer Center. All information was obtained with appropriate Institutional Review Board waivers.

Treatment and assessment of efficacy

All patients received palliative chemotherapies for recurrent or de novo metastatic disease, composed of fluoropyrimidine-based or taxane-based therapies with or without platinum: 5-fluorouracil plus cisplatin ($n = 488$), capecitabine or S-1 plus cisplatin ($n = 204$), capecitabine or S-1 ($n = 89$), taxane plus cisplatin ($n = 81$), taxane plus capecitabine or S-1 ($n = 136$), oxaliplatin/5-fluorouracil/leucovorin ($n = 52$), irinotecan plus docetaxel ($n = 57$), docetaxel/5-fluorouracil plus cisplatin ($n = 58$), irinotecan plus cisplatin ($n = 46$), irinotecan/5-fluorouracil/leucovorin ($n = 28$), docetaxel ($n = 17$), weekly irinotecan ($n = 9$), and others ($n = 12$). Treatments continued until disease progression or unacceptable toxicity occurred or until patients chose to discontinue treatment. CT scans were performed every 8–12 weeks to evaluate the tumor response, which was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [14].

Statistics

A chi-square test was used to compare discrete data, and a Wilcoxon rank sum test was used to compare non-parametric variables. The time to other organ metastasis (TTOM) was only determined in patients with PAN area metastasis as the interval between diagnosis of recurrent or de novo metastatic disease to the time confirming distant metastases beyond the PAN area. Overall survival (OS) was calculated from the date of diagnosis of recurrent or de novo metastatic

Table 1 Characteristics of the entire patient pool

	Patients with a single organ metastasis in the PAN area (Group A, $N = 92$)	Patients with a single organ metastasis other than in the PAN area (Group B, $N = 378$)	Patients with multiple organ metastases (Group C, $N = 807$)	P***
Sex				0.568
Male	66 (71.7%)	251 (66.4%)	553 (68.5%)	
Female	26 (28.3%)	127 (33.6%)	254 (31.5%)	
Age (years, median, range)	58 (31–81)	57 (23–82)	57 (21–81)	0.460
ECOG performance status				0.066
0 or 1	84 (91.3%)	307 (81.2%)	663 (82.2%)	
Histology				0.136
Undifferentiated	58 (63.0%)	273 (72.2%)	537 (66.5%)	
Differentiated	34 (37.0%)	105 (27.8%)	270 (33.5%)	
Disease status				<0.001
Recurrent metastasis	24 (26.1%)	95 (25.1%)	124 (15.4%)	
De novo metastasis	68 (73.9%)	283 (74.9%)	683 (84.6%)	
Peri-operative treatment*				0.099
Chemotherapy	24 (100%)	75 (79.0%)	107 (86.3%)	
Chemoradiotherapy	0	1 (1.0%)	3 (2.4%)	
None	0	19 (20.0%)	14 (11.3%)	
Relapse-free interval** (median, months, range)	11.6 (3.6–76.9)	11.4 (3.4–93.4)	13.8 (2.0–122.9)	0.018
Number of involved organs				<0.001
1	92 (100%)	378 (100%)	0	
2	0	0	95 (11.8%)	
≥3	0	0	712 (88.2%)	
WBC ($\times 10^3/\mu$L, median)	6.5	7.4	8.0	0.004
Hemoglobin (g/dL, median)	11.0	11.2	10.9	0.196
ALP (IU/L, median)	89.0	85.5	95.0	<0.001
Albumin (g/dL, median)	4.0	3.8	3.7	<0.001
Total bilirubin (mg/dL, median)	0.4	0.4	0.5	0.060

PAN para-aortic lymph node, *ECOG* Eastern Cooperative Oncology Group, *WBC* white blood cell, *ALP* alkaline phosphatase, *AJCC* American Joint Committee on Cancer

* Perioperative treatment was only considered in patients with recurrent disease

** Relapse-free interval was determined only in patients with recurrent disease

*** P value was determined using the Wilcoxon rank sum test for non-parametric variables and the chi-square test for categorical variables

disease to the date of death or the last follow-up visit, and time to progression (TTP) was defined as the time elapsed between the date of diagnosis and tumor progression on a specific chemotherapy regimen. Relapse free interval (RFI) was defined in recurrent cases as the time interval between the date of diagnosis and the date of confirmation of recurrence. The OS, TTP, and TTOM were estimated using the Kaplan–Meier method, and the univariate effects of parameters on the OS, TTP, and TTOM were assessed using a log-rank test. Multivariate analysis using the Cox proportional hazards model was performed on all variables determined to be significant by univariate analysis such as age, sex, performance status, histologic subtype, WBC count, serum ALP, albumin, total bilirubin level, de novo metastasis, metastatic sites, and number of involved LN. All tests were two sided, and we considered a P value <0.05 statistically significant.

Results

Baseline characteristics

In this study, a total of 1,277 advanced gastric cancer patients who were received palliative chemotherapy were included except those with locoregional disease. The median age of

Table 2 Efficacy of the first-line chemotherapy

	Patients with a single organ metastasis in the PAN area (Group A, $N = 92$)	Patients with a single organ metastasis other than in the PAN area (Group B, $N = 378$)	Patients with multiple organ metastases (Group C, $N = 807$)	P**
1st line chemotherapy				0.781
Fluoropyrimidine ± cisplatin	66 (71.7%)	251 (66.4%)	522 (64.7%)	
Taxane based	14 (15.2%)	57 (15.1%)	163 (20.2%)	
Irinotecan based	10 (10.9%)	49 (12.9%)	81 (10.0%)	
Oxaliplatin/5-fluorouracil/leucovorin	1 (1.1%)	15 (4.0%)	36 (4.5%)	
Others	1 (1.1%)	6 (1.6%)	5 (0.6%)	
Response to 1st line chemotherapy				
Evaluable patients (N, %)	87 (94.6%)	302 (79.9%)	702 (87.0%)	0.001
CR + PR	49 (56.3%)*	93 (30.7%)*	241 (34.4%)*	<0.001
SD	22 (25.3%)*	130 (43.0%)*	214 (30.5%)*	
PD	16 (18.4%)*	79 (26.2%)*	247 (35.2%)*	
TTP at 1st line chemotherapy (median, months, 95% CI)	6.3 (4.7–7.9)	5.2 (4.6–5.7)	4.1 (3.7–4.4)	<0.001
OS (median, months, 95% CI)	13.8 (10.8–16.8)	11.4 (10.3–12.6)	8.4 (7.6–9.1)	<0.001

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *TTP* time to progression, *OS* overall survival, *PAN* para-aortic lymph node, *CI* confidence interval

* Proportion of evaluable patients

** P value was determined using the Wilcoxon rank sum test in non-parametric variables, the chi-square test in categorical variables, and the Kaplan–Meier method for survival analysis

the source population was 58 (range, 21–82 years), and the male-to-female ratio was 2.1:1. Of this population, 243 patients (19%) had recurrent disease, and 1,034 (81%) had de novo metastatic disease. Table 1 shows the characteristics of the three defined groups among the entire source population. There were no statistical differences among the three groups in terms of age, sex, and histological type. Although the performance status tended to be better in patients with PAN-only metastasis compared with other patients, this difference was not statistically significant ($P = 0.066$). Group C contained more patients diagnosed with de novo metastatic disease than other groups ($P < 0.001$). When we only considered patients who experienced relapse, the median relapse-free interval (RFI) after R0 resection was longer in group C ($P = 0.018$). The white blood cell (WBC) count and serum alkaline phosphatase (ALP) levels at diagnosis were significantly higher in group C than in other groups ($P = 0.004$ and $P < 0.001$, respectively). In contrast, serum albumin level was significantly lower in group C compared with the other groups ($P < 0.001$).

Efficacy of chemotherapy and prognostic factors for survival

Of all patients considered, 1,091 could be assessed for tumor response according to RECIST criteria with measurable lesions. Although various chemotherapeutic regimens were used as first therapy treatments, more than 50% of patients in each group received fluoropyrimidine-based chemotherapies. Among the evaluated patients, 383 (35.1%) achieved an objective response [complete response (CR) + partial response (PR)], 366 patients (33.5%) displayed stable disease (SD), and 342 patients (31.3%) experienced disease progression (PD) (Table 2). There was a significant difference in overall response rate among the three analyzed groups: patients with PAN metastasis alone (group A) showed a higher response rate (CR + PR) {56.3% [95% confidence interval (CI), 45.3–66.9%]} than did group B [30.7% (95% CI, 25.6–36.3%)] or group C [34.4% (95% CI, 30.8–37.9%); $P < 0.001$].

All patients were evaluated for survival. With a median follow-up period of 40.2 months (range, 11.9–91.6 months), the median TTP and the median OS of the entire patient pool were 4.4 months (95% CI, 4.1–4.6 months) and 9.7 months (95% CI, 9.1–10.4 months), respectively. Comparing survival among the three groups, we found that patients with PAN metastasis alone showed prolonged TTP from first-line chemotherapy treatment [6.3 months (95% CI, 4.7–7.9 months) vs. 5.2 months (95% CI, 4.6–5.7 months) vs. 4.1 months (95% CI, 3.7–4.4 months); $P < 0.001$] and OS [13.8 months (95% CI, 10.8–16.8 months) vs. 11.4 months (95% CI, 10.3–12.6 months) vs. 8.4 months (95% CI, 7.6–9.1 months); $P < 0.001$] (Table 2; Fig. 1). The 3-year OS rates of those three groups were as

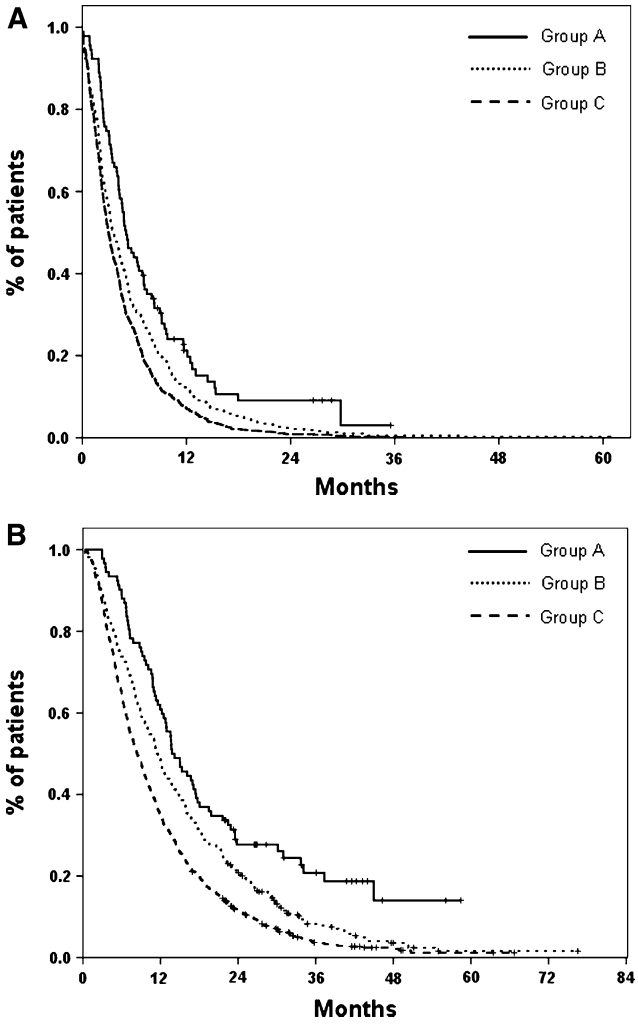

Fig. 1 Time to progression for the first-line chemotherapy and overall survival curves of the three subgroups: Group A, patients with a single organ metastasis in the PAN area; Group B, patients with a single organ metastasis other than the PAN area; and Group C, patients with multiple organ metastases. **a** Time to progression at the first-line chemotherapy ($P < 0.001$), **b** overall survival ($P < 0.001$)

follows: group A, 12.0% (95% CI, 6.1–20.4%); group B, 5.6% (95% CI, 3.5–8.4%); and group C, 2.2% (95% CI, 1.3–3.5%). We performed a Cox proportional hazard analysis for OS for all patients (Table 3). Univariate analysis showed that the following factors were found statistically significant for OS; de novo metastatic disease, poor performance status of ECOG ≥2, increased WBC count, higher serum ALP level, lower serum albumin level, and poorly differentiated pathologic type. In addition, metastasis to only the PAN area was a good prognostic factor for prolonged survival compared with disease that had metastasized to other sites [HR 2.05 (95% CI, 1.61–2.61); $P < 0.001$] and even compared with single organ site metastases other than the PAN area [HR 1.51 (95% CI, 1.17–1.94); $P = 0.002$]. All factors except serum ALP level and de novo metastatic disease were also statistically significant in a multivariate analysis (Table 3).

Analysis for patients with PAN metastasis alone

In patients with PAN metastasis alone, the OS was significantly affected by disease status at first palliative chemotherapy, i.e., recurrent disease or de novo metastatic disease. The median OS for patients with recurrent PAN metastasis and those with de novo PAN metastasis were 23.8 months (95% CI, 11.0–36.6 months) and 12.8 months (95% CI, 10.3–15.2 months), respectively ($P = 0.010$). The 3-year OS was 35.9% (95% CI, 7.1–42.2%) and 13.1% (95% CI, 3.3–18.2%), respectively ($P = 0.028$) (Fig. 2a). Even after adjusting for other factors, disease status at diagnosis remained a significant factor for OS [HR 2.97 (95% CI, 1.36–6.49); $P = 0.007$] (Table 4). We therefore analyzed these patients according to disease status (Table 5).

With a median follow-up of 13.6 months (range, 2.9–64.4 months), 39 (57.4%) patients with de novo PAN metastasis and 10 (41.7%) patients with recurrent PAN metastasis experienced a metastasis to distant sites other than the PAN area ($P = 0.236$) during their clinical course. Although the overall response rate to first-line chemotherapy was similar between the two groups, the complete response (CR) rate was higher in the recurrent PAN metastasis group than in the de novo PAN metastasis group (4.4 vs. 20.8%; $P = 0.026$). Patients with recurrent PAN metastasis tended to have better TTP in response to first-line chemotherapy than those with de novo PAN metastasis (median TTP 8.7 vs. 5.3 months; $P = 0.115$) (Fig. 2b). In addition, patients with recurrent PAN metastasis showed longer TTOM beyond PAN than those with de novo metastatic disease (median TTOM 10.7 vs. 7.7 months; $P = 0.037$) (Fig. 2c). According to the Cox proportional hazard analysis, de novo metastatic disease was significantly correlated with shorter TTOM [HR 2.21 (95% CI, 1.09–4.51)]. Other factors, including ECOG performance status [HR 1.33 (95% CI, 0.47–3.71)], WBC count [HR 1.02 (95% CI, 0.92–1.12)], serum ALP [HR 0.99 (95% CI, 0.98–1.00)], serum albumin level [HR 0.64 (95% CI, 0.39–1.04)], histology [HR 1.83 (95% CI, 0.95–3.55)], and number of involved LN ≥ 4 [HR 1.18 (95% CI, 0.63–2.21)] were not significant for TTOM.

Of 38 patients who did not experience metastasis to other sites, 13 (34.2%) patients achieved durable remission, and their median TTP was 38.2 months (range, 13.6–64.4 months). Of those, seven patients were in the de novo metastasis group and six were in the recurrent group (Table 6). Ten patients received one chemotherapeutic regimen, with a median number of cycles of chemotherapy of 11.5. Three patients with de novo metastasis of PAN were able to undergo curative gastrectomy with lymphadenectomy.

Table 3 Analysis of prognostic factors affecting overall survival for the entire patient pool

Variables	Univariate		Multivariate*	
	HR (95% CI)	*P***	HR (95% CI)	*P***
Age (cont)	1.00 (0.99–1.01)	0.321	–	–
Male versus female	0.97 (0.86–1.10)	0.627	–	–
ECOG performance status ≥2 versus <2	2.42 (1.98–2.96)	<0.001	2.06 (1.68–2.54)	<0.001
Histology, undifferentiated versus differentiated	1.24 (1.09–1.40)	0.001	1.22 (1.07–1.39)	0.003
Increased WBC count (cont')	1.05 (1.03–1.07)	<0.001	1.04 (1.02–1.05)	<0.001
Increased serum ALP level (cont')	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	0.322
Decreased serum albumin level (cont')	1.67 (1.50–1.86)	<0.001	1.50 (1.33–1.69)	<0.001
Increased total bilirubin level (cont')	1.01 (0.99–1.02)	0.357	–	–
De novo metastasis vs. recurrent metastasis	1.36 (1.14–1.63)	0.001	1.03 (0.87–1.22)	0.734
Group				
Single organ site metastasis in the PAN area	1.00		0.55 (0.43–0.71)	<0.001
Single organ site metastasis other than in the PAN area	1.51 (1.17–1.94)	0.002		
Multiple organ site metastases	2.05 (1.61–2.61)	<0.001		

Age, WBC count, serum ALP, albumin, and total bilirubin level were continuous variables

ECOG Eastern Cooperative Oncology Group, *WBC* white blood cell, *ALP* alkaline phosphatase, *PAN* para-aortic lymph node, *HR* hazard ratio, *CI* confidence interval

* Including variables: histology, WBC, ALP, albumin, initial disease status, single PAN metastasis

** *P* value was determined from a Cox proportional hazards regression model

Four patients in the de novo metastasis group and three patients in the recurrent group achieved durable remission through chemotherapy alone. Two patients in the recurrent group received radiotherapy in the PAN area as consolidation therapy after the first palliative chemotherapy resulted in a partial response. One patient achieved durable remission after radiotherapy to the PAN area after the patient failed to respond to second-line palliative chemotherapies because the disease was still confined to the same area.

Discussion

This study characterized features of the prognosis and clinical course of a patient population with gastric cancer with isolated PAN involvement either in synchronous or in metachronous setting. We have shown that metastatic gastric cancer patients with PAN involvement alone had better survival than those with other sites metastasis. This is consistent with the fact that PAN metastasis alone indicates a relatively small tumor burden and that involvement of multiple organ sites is known to be a poor prognostic factor in recurrent or metastatic gastric cancer [15–17]. Indeed, we found that patients with multiple organ metastases experienced decreased survival compared with individuals with a single organ metastasis, including to the PAN area (8.4 vs. 12.1 months; $P < 0.001$). However, we found that patients with PAN involvement alone experienced increased survival compared with patients with metastasis in a single area other than PAN or patients with multiple metastatic sites. This prognostic significance of PAN involvement alone remained significant after adjusting for other potential prognostic factors. This result should be interpreted cautiously because patients with metastases in a single area other than PAN are highly heterogeneous in terms of metastatic sites, which may contribute to controversial results regarding the prognostic role of the number of metastatic organ sites [15–19]. Several studies have reported that metastatic organ sites such as the bone, peritoneum, and liver show prognostic significance in patients with recurrent or metastatic gastric cancer [15–17, 20, 21].

A previous study [5] showed no difference in survival between patients with recurrent disease and patients with de novo metastatic disease. This result was consistent with our analyses when we only considered patients with metastases to areas other than PAN. Interestingly, we found that the group of patients with PAN involvement alone showed heterogeneous clinical courses and prognoses according to their disease status, i.e., de novo or recurrent metastasis. Patients with recurrent PAN metastasis showed prolonged TTP in response to first-line chemotherapy and experienced significantly longer survival than those with de novo PAN metastasis. These differences in survival remained significant after adjusting for other clinical factors. Among recurrent cases, there was a positive relation between RFI and survival even in small number of recurrent cases in PAN

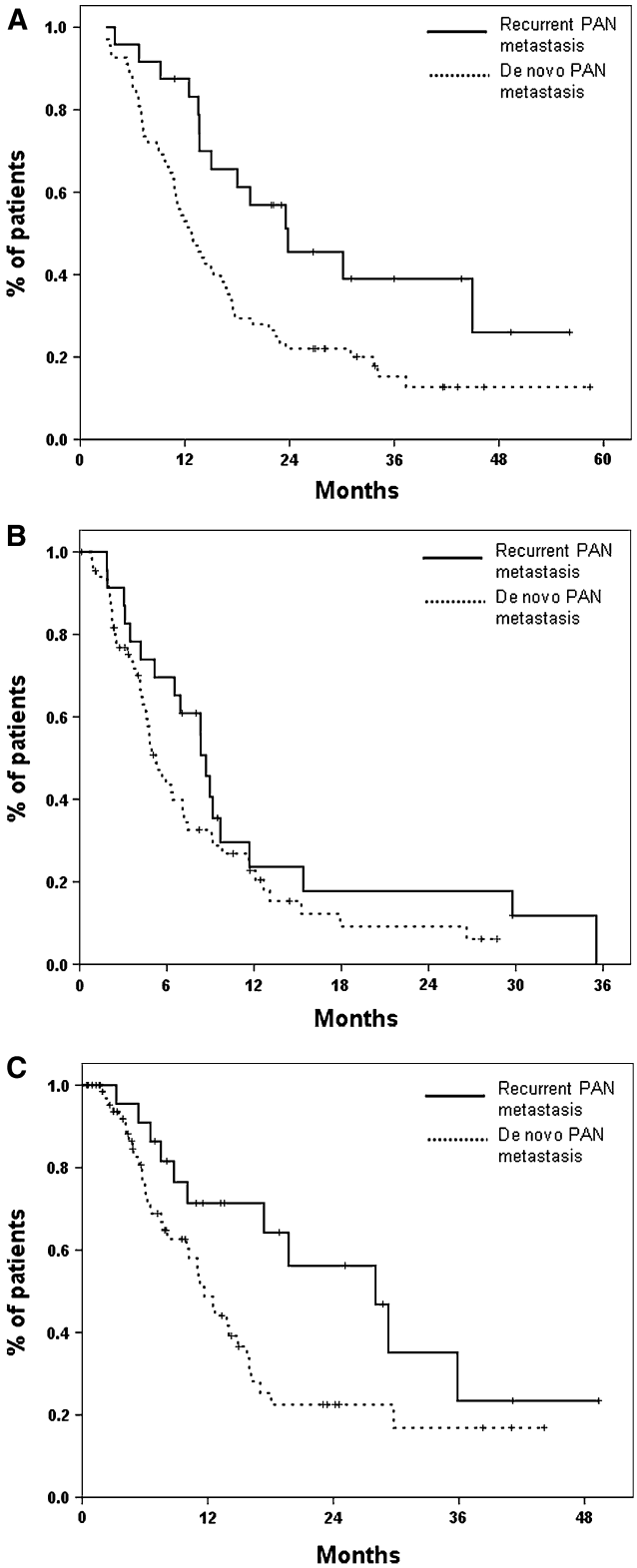

Fig. 2 Overall survival, time to progression at the first-line chemotherapy, and time to other organ metastasis curves beyond the para-aortic lymph node area according to disease status in patients with only para-aortic lymph node metastasis. **a** Overall survival ($P = 0.010$), **b** Time to progression at the first-line chemotherapy ($P = 0.155$), **c** Time to other site metastasis from diagnosis ($P = 0.037$)

only metastasis group. Indeed, the OS in patients with de novo metastatic PAN involvement alone did not differ from the OS of patients with a single area metastasis other than PAN (12.8 vs. 11.4 months; $P = 0.104$). Furthermore, during their clinical course, patients with recurrent PAN metastases experienced disease progression to other distant sites beyond the PAN much more slowly than did those with de novo PAN metastasis. More patients experienced disease progression to other sites beyond the PAN area from the de novo metastatic group than from the recurrent group. These distinctive clinical courses and prognoses in patients with recurrent PAN metastasis compared with patients with de novo PAN metastasis could be attributed to the differences in tumor burden based on the absence of primary gastric tumors or differences in tumor biology such as the differential metastatic potential of cancer cells. Similar responses to chemotherapy suggest that recurrent and de novo PAN metastatic tumors have similar chemosensitivities.

Since patients with either de novo or recurrent metastatic gastric cancer have very poor prognoses [5], it is very exciting to find that patients with recurrent PAN metastasis alone experienced favorable treatment outcomes and long-term survival. Although only a small proportion of patients with gastric cancer showed PAN-only metastasis, this population is notable because patients can be cured of the disease through palliative chemotherapy and may benefit from additional local therapy, even if chemotherapy is ineffective. For these reasons, the treatment strategy for patients with solitary PAN metastasis should be individualized according to the characteristics of the disease. Recently, Sun et al. [22] reported that gastric cancer patients with abdominal lymph node metastasis at the time of recurrence showed a median survival of 11.4 months when they received upfront radiotherapy to recurrent abdominal lymph node sites with or without sequential chemotherapy, although they had a median survival of 4.8 months when not treated with radiotherapy ($P = 0.002$). These investigators suggested that radiotherapy provides a survival benefit to recurrent gastric cancer patients with isolated abdominal lymph node involvement. However, that retrospective, non-randomized study did not provide information regarding palliative chemotherapy, and therefore did not consider the influence of chemotherapy on survival after recurrence. In addition, the fact that more than half of the patients in the radiation group experienced other distant metastases beyond the abdominal lymph node area or anastomotic recurrence suggests that radiation therapy as the first-line treatment is not an ideal treatment for these patients. Instead, systemic chemotherapy should be considered the standard treatment to control PAN disease as well as systemic micrometastases that might exist beyond the PAN area. Given that systemic metastasis beyond PAN area appeared after the substantial period from the date of diagnosis according to our data, local therapy

Table 4 Analysis of prognostic factors affecting OS in patients with para-aortic lymph node metastasis alone

Variables	Univariate		Multivariate*	
	HR (95% CI)	*P***	HR (95% CI)	*P***
De novo metastasis versus recurrent metastasis	2.97 (1.36–6.49)	0.007	2.39 (1.07–5.32)	0.034
Age (cont)	1.01 (0.99–1.03)	0.516	–	–
Sex (male)	1.22 (0.73–2.04)	0.444	–	–
ECOG performance status ≥2 versus <2	0.94 (0.41–0.22)	0.890	–	–
Histology, undifferentiated versus differentiated	1.12 (0.68–1.82)	0.662	–	–
Number of involved LN ≥ 4	1.01 (0.62–1.63)	0.971	–	–
Increased WBC count (cont')	1.02 (0.94–1.10)	0.695	–	–
Elevated serum ALP level (cont')	0.99 (0.98–1.00)	0.051	1.00 (0.98–1.01)	0.412
Decreased serum albumin level (cont')	2.09 (1.42–3.07)	<0.001	1.80 (1.20–2.71)	0.004
Increased total bilirubin level (cont')	0.94 (0.31–2.88)	0.909	–	–

Age, WBC count, serum ALP, albumin, and total bilirubin level were continuous variables

ECOG Eastern Cooperative Oncology Group, *LN* lymph node, *WBC* white blood cell, *ALP* alkaline phosphatase, *HR* hazard ratio, *CI* confidence interval

* Including variables: initial disease status, ALP, albumin

** *P* value was determined from the Cox proportional hazards regression model

Table 5 Characteristics according to disease status in patients with PAN metastasis alone

Variables	De novo metastasis group (*N* = 68)	Recurrent group (*N* = 24)	*P**
Sex			0.242
Male	51 (75%)	15 (62.5%)	
Female	17 (25%)	9 (37.5%)	
Age (year, median, range)	58 (36–71)	58 (31–81)	0.386
ECOG performance status			
0 or 1	64 (94.1%)	20 (83.3%)	0.107
Number of metastatic LN (median, range)	4 (2–17)	2 (1–14)	0.001
WBC ($\times 10^3/\mu$L, median)	7.7	6.0	0.003
ALP (IU/L, median)	15 (22.1%)	10 (41.7%)	0.063
Albumin (g/dL, median)	3.9	4.2	0.002
Total bilirubin (mg/dL, median)	0.4	0.5	0.061
1st line chemotherapy			0.538
Fluoropyrimidine based	44 (64.7%)	16 (66.7%)	
Taxane based	15 (22.1%)	6 (25%)	
Response to 1st line chemotherapy			
CR	3 (4.4%)	5 (20.8%)	0.095
PR	32 (47.1%)	9 (37.5%)	
SD	17 (25.0%)	6 (25.0%)	
PD	14 (20.6%)	2 (8.3%)	
Not evaluable	3 (4.4%)	2 (8.3%)	
Time to progression at 1st line chemotherapy (median month, 95% CI)	5.3 (4.1–6.4)	8.7 (7.9–9.6)	0.155
Metastasis to other sites beyond the PAN area	39 (57.4%)	10 (41.7%)	0.236
Time to other site metastasis beyond the PAN (median month, 95% CI)	7.7 (3.2–12.1)	10.7 (2.1–20.7)	0.037
Overall survival (median months, 95% CI)	12.8 (10.3–15.2)	23.8 (11.0–36.6)	0.010

ECOG Eastern Cooperative Oncology Group, *LN* lymph node, *WBC* white blood cell, *ALP* alkaline phosphatase, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *PAN* para-aortic node, *CI* confidential interval

* *P* value was determined using the Wilcoxon rank sum test for non-parametric variables and the chi-square test for categorical variables

could be considered as consolidation or salvage therapy if their diseases are still confined to the local area with systemic chemotherapy.

In conclusion, this retrospective study has shown that gastric cancer patients with PAN involvement alone experience better survival after palliative chemotherapy with or

Table 6 CR of patients after palliative treatment

	Sex	Group	Treatment	No. of chemotherapeutics	No. of cycles of chemotherapy	TTP (months)
1	M	De novo meta	C	1	4	35.1
2	M	Recur	C	1	31	55.3
3	M	De novo meta	C + S	1	35	50.0
4	M	De novo meta	C	1	6	29.0
5	F	Recur	C	2	12	38.2
6	F	Recur	C + R	3	51	64.4
7	M	De novo meta	C + S	2	34	52.8
8	M	De novo meta	C	1	11	33.4
9	M	De novo meta	C + S	1	21	48.7
10	F	Recur	C	1	6	13.6
11	M	Recur	C + R	1	12	50.8
12	M	Recur	C + R	1	10	30.8
13	F	De novo meta	C	1	12	36.1

CR complete response, *C* chemotherapy, *S* surgical treatment, *R* radiotherapy, *PFS* progression free survival

without local treatment such as surgery or radiotherapy than patients with single-area metastases in areas other than the PAN or patients with multiple site metastases, and this is mainly confined in patients with recurrent PAN involvement. Recurrent gastric cancers with isolated PAN metastases are more likely to be limited to an initial disease site for long clinical courses with palliative chemotherapy. Further large-scale randomized trials will help to determine the best treatment strategy for these patients.

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