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Original Article

Prognostic Relevance of Recurrent Sites of Gastric Cancer Treated With Curative Resection: A Single Center Retrospective Study

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No potential conflict of interest relevant to this article was reported.

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ABSTRACT

Purpose: Gastric cancer treated with curative resection exhibits several recurrence patterns. The peritoneum is the most common site of recurrence. Some reports have indicated different prognostic influences according to the recurrence sites in other cancers, such as esophageal and colorectal cancers. This study investigated whether the recurrence sites influenced the prognosis of patients with recurrent gastric cancer.
Materials and Methods: The data of 115 patients who experienced tumor recurrence after curative gastrectomy were retrospectively reviewed. The sites of recurrence were divided into 4 groups: lymph node (LN), peritoneum, other single organs, and multiple lesions. Clinicopathological features were compared between the sites of recurrence. Prognosis after resection and recurrence were also compared.
Results: The peritoneum was the primary site of recurrence in 38 patients (33%). The tumor differentiation and pathological stages were significantly different. Survival after surgery did not show a statistically significant difference (hazard ratio [HR] of LN: 1, peritoneum: 1.083, other single organs: 1.025, and multiple lesions: 1.058; P=1.00). Survival after recurrence was significantly different (HR of LN, 1; peritoneum, 2.164; other single organs, 1.092; multiple lesions, 1.554; P=0.01), and patients with peritoneal and multiple lesion recurrences had worse prognosis. Furthermore, peritoneal recurrence seemed to occur later than that at other sites; the median times to recurrence in LN, peritoneal, other single-organ, and multiple lesions were 265, 722, 372, and 325 days, respectively.
Conclusions: The sites of gastric cancer recurrence may have different prognostic effects. Peritoneal recurrence may be less sensitive to chemotherapy and occur during the late phase of recurrence.

Keywords: Gastric cancer; Recurrence; Prognosis

INTRODUCTION

The prognosis of gastric cancer has improved owing to advancements in surgical techniques and chemotherapy [1]. Advancements in systemic chemotherapy have especially improved the prognosis of unresectable and recurrent gastric cancers, as S-1 and cisplatin treatment have shown efficacy [2,3]. New drug options for gastric cancer are the most plausible reasons

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for this prognostic improvement [4-7]. However, the prognosis for patients with recurrent gastric cancer remains poor. Therefore, novel treatment options and drugs are required.

There are several patterns of recurrent gastric cancer after curative resection, with peritoneum being the most common recurrence site [8,9]. In other cancers, such as esophageal and colorectal cancers, which also have several recurrence patterns, recurrence sites may show different prognoses [10-14]. Although some studies have investigated the prognosis of unresectable and recurrent gastric cancers, most have examined the relationship between prognosis and metastatic sites, including recurrence sites. Studies focusing only on recurrence sites are rare [15]. This study aimed to provide new insights into the treatment of recurrent gastric cancer treated with curative resection.

In this study, we hypothesized that the site of gastric cancer recurrence would also indicate prognostic differences. This study aimed to investigate whether different sites of gastric cancer recurrence after curative resection have different prognoses.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the data of patients who underwent curative gastrectomy between 2008 and 2020 at the Tochigi Cancer Center. We enrolled patients who experienced recurrence during the surveillance period.

Detection of recurrence and recurrent groups

Recurrence sites were divided into four groups: lymph node (LN), peritoneum, other single organs, and multiple lesions. LN recurrence was detected using CT, regardless of whether the lesion was local or distant. The peritoneum was also examined using computed tomography (CT), which revealed ascites or definitive peritoneal nodes. Other single organs with recurrence, such as the liver, lung, and adrenal glands, were detected by CT, irrespective of the number of recurrent lesions (single/multiple). Multiple lesions were defined as recurrences in multiple organs, such as the peritoneum, LN, and other organ. Surveillance was performed according to the Japanese Gastric Cancer Treatment Guidelines [16]: TM follow-up every three months, CT follow-up every six months, and upper gastrointestinal endoscopy follow-up after the first, third, and fifth years after surgery.

Statistical analysis

We performed statistical analyses using the free software "R." The continuous variables were analyzed with Kruskal–Wallis test, and categorical variables were analyzed with the χ^2 test. Survival analyses were conducted using Cox regression analysis and the Kaplan–Meier method with a log-rank test, comparing the 3-year overall survival (OS) after surgery and after recurrence at each site, and progression-free survival (PFS) during palliative chemotherapy. The OS after surgery was defined as the time from surgery to death from any cause. The OS after recurrence was defined as the time from recurrence to death from any cause. PFS was defined as the time from disease recurrence to the first confirmation of disease progression. A Cox proportional hazards regression model was used to calculate the hazard ratio (HR) and 95% confidence interval (95% CI) for each site of recurrence. Differences were considered statistically significant at $P<0.05$.

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Ethical consideration

This retrospective protocol was based on the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Tochigi Cancer Center. All the data used in the study was appropriately anonymized before analysis.

RESULTS

Patient characteristics

Among 868 patients who underwent curative gastrectomy for gastric cancer, 115 experienced recurrence. The peritoneum was the most common site of recurrence (n=38, 33%), followed by other single organs (n=33, 28.7%), LN (n=23, 20%), and multiple lesions (n=21, 18.3%). Regarding clinical characteristics, only pathological type and stage showed statistically significant differences among the groups. In LN and peritoneal recurrences, the proportion of the undifferentiated type was greater than that of the differentiated type, whereas the proportion of the undifferentiated type in other single-organ and multiple-lesion recurrences was lower. Pathological stage III was more predominant in LN, peritoneal, and multiple lesion recurrences than in other single-organ recurrences. Neither adjuvant nor palliative chemotherapy resulted in significant differences. Palliative chemotherapy was not initiated in patients who experienced recurrence due to poor compliance or unwillingness. Sixty-five patients with recurrence received chemotherapy (56.6%) (**Table 1**).

Survival analysis after surgery and recurrence

Fig. 1 shows the Kaplan–Meier curves for OS after surgery (**Fig. 1A**) and recurrence (**Fig. 1B**) in this study population. While each recurrence site showed almost the same prognosis (**Fig. 1A**), the OS after recurrence showed different prognoses, especially for peritoneal and multiple-lesion recurrences, which showed a significantly worse prognosis. After surgery, the HR of each recurrence site were 1 for the LN, 1.083 for the peritoneum, 1.025 for other single organs, and 1.058 for multiple lesions. After recurrence, the HR of each recurrence site were 1 for the LN, 2.164 for the peritoneum, 1.092 for other single organs, and 1.554 for multiple lesions. There was a significant difference in peritoneal recurrence.

PFS of the 1st and 2nd line palliative chemotherapy

Fig. 2 shows the PFS after the 1st and 2nd line palliative chemotherapy. There were no significant differences in PFS between both the 1st (**Fig. 2A**) and 2nd (**Fig. 2B**) lines of chemotherapy. The survival curve for the 1st line PFS at each recurrence site was similar to the OS curves after recurrence. Patients with peritoneal and multiple recurrences tended to have worse prognoses; however, these differences were not statistically significant.

Details of chemotherapy after recurrence

Table 2 shows the details of the chemotherapy regimens administered after recurrence. There were 65 patients who were treated with chemotherapy after recurrence as the 1st line of treatment. There were no significant differences in the types of chemotherapy administered between recurrence sites. Although platinum-based chemotherapy was the predominant chemotherapy for all recurrence sites, the proportion of platinum-based chemotherapy for LN recurrence was lower than that for other sites. In the second-line treatment group, 41 patients received chemotherapy. Taxan-based chemotherapy is the most commonly used treatment for these patients. No statistically significant differences were observed between the groups.

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Table 1. Patients characteristics

Characteristics	Total	Recurrent sites				
		Lymph nodes	Peritoneum	Other organs	Multiple lesions	P-value
No. of patients	115 (100.0)	23 (20.0)	n=38 (33.0)	n=33 (28.7)	n=21 (18.3)	
Median age (yr)	68	68	65	70	69	0.304
Sex						0.907
Male	76 (66.1)	14 (60.9)	25 (65.8)	22 (66.7)	15 (71.4)	
Female	39 (33.9)	9 (39.1)	13 (34.2)	11 (33.3)	6 (28.6)	
ASA PS						0.650
1	75 (65.2)	17 (73.9)	25 (65.8)	19 (57.6)	14 (66.7)	
2–3	40 (34.8)	6 (26.1)	13 (34.2)	14 (42.4)	7 (6.1)	
Pathological type						<0.001
Differentiate	44 (38.3)	4 (17.4)	12 (31.6)	16 (48.5)	12 (57.1)	
Undifferentiate	59 (51.3)	16 (69.6)	25 (65.8)	13 (39.4)	5 (23.8)	
Others	12 (10.4)	3 (13.0)	1 (2.6)	4 (12.1)	4 (19.0)	
Median blood loss (g)	264	310	309	202	252	0.144
Median surgery time (min)	191	221	185	187	220	0.784
Surgical approaches						0.252
Open	101 (87.8)	21 (91.3)	36 (94.7)	28 (84.8)	16 (76.2)	
Laparoscopic	12 (10.4)	1 (4.3)	2 (5.3)	5 (15.2)	4 (19.0)	
With thoracotomy	2 (1.7)	1 (4.3)	0 (0.0)	0 (0.0)	1 (4.8)	
Surgical procedures						0.196
Distal	49 (42.6)	12 (52.2)	11 (28.9)	15 (45.5)	11 (52.4)	
Total	66 (57.4)	11 (47.8)	27 (71.0)	18 (54.5)	10 (47.6)	
pStage						0.038
I	5 (4.3)	2 (8.7)	1 (2.6)	1 (3.0)	1 (4.8)	
II	26 (22.6)	1 (4.3)	7 (18.4)	15 (45.5)	3 (14.3)	
III	81 (70.4)	20 (87.0)	29 (76.3)	16 (48.5)	16 (76.2)	
IV	3 (2.6)	0	1 (2.6)	1 (3.0)	1 (4.8)	
Adjuvant chemotherapy						0.122
Yes	75 (65.2)	11 (47.8)	29 (76.3)	20 (60.6)	15 (71.4)	
No	28 (24.3)	12 (52.2)	9 (23.7)	13 (39.4)	6 (28.6)	
Palliative chemotherapy						0.175
Yes	65 (56.5)	17 (73.9)	20 (52.6)	15 (45.5)	13 (61.9)	
No	50 (43.5)	6 (26.1)	18 (47.4)	18 (54.5)	8 (38.1)	
Her2 status						0.610
Positive	12 (10.4)	3 (13.0)	3 (7.9)	5 (15.2)	1 (4.8)	
Negative	58 (50.4)	12 (52.2)	21 (55.3)	15 (45.5)	10 (47.6)	

The peritoneum was the most common site of recurrence (n=38, 33%), followed by other single organs (n=33, 28.7%), lymph node (n=23, 20%), and multiple lesions (n=21, 18.3%). Regarding clinical characteristics, only pathological type and stage showed statistically significant differences among the groups. Values are presented as number of patients (%).
ASA PS = American Society of Anesthesiologists Physical Status.

Time to recurrence and survival time after recurrence

Fig. 3 shows the median time to recurrence (blue columns) and the median survival time after recurrence (orange columns). The median times to LN, peritoneal, other single-organ, and multiple lesion recurrences were 265, 722, 372, and 325 days, respectively. The median survival time was 442 days after LN recurrence, 185 days after peritoneal recurrence, 467 days after other single-organ recurrences, and 195 days after multiple lesion recurrences.

DISCUSSION

Reports on esophageal and colon cancers have shown that the prognosis of recurrent tumors shows different clinical courses according to the recurrence sites [10-12,17-19]. However, such data on gastric cancer has been scarcely reported. Some studies have investigated the prognosis of patients with unresectable and recurrent gastric cancer. However, studies focusing solely on recurrent gastric cancer are rare. This study investigated whether the recurrence site influences

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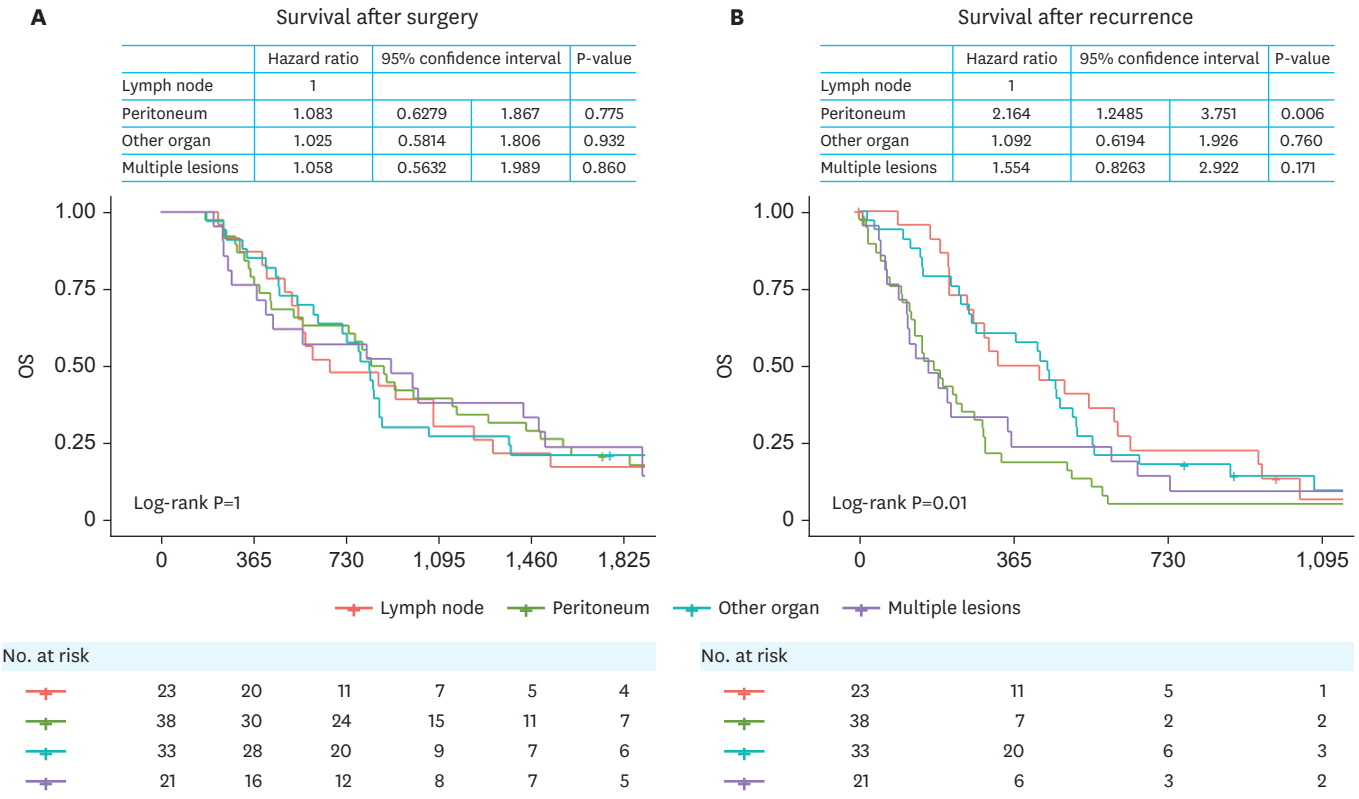

Fig. 1. Kaplan-Meier curves of survival after surgery and survival after recurrence. (A) Survival after surgery and (B) survival after recurrence.
OS after recurrence showed different prognoses, especially for peritoneal and multiple lesion recurrences, which showed a significantly worse prognosis.
OS = overall survival.

the prognosis of patients with gastric cancer treated with curative gastrectomy to shed further light on this oncological phenomenon. The results showed that the prognosis after surgery was not different at each recurrence site; however, in the survival analysis after recurrence, there was a statistical difference among each recurrent site. The prognosis of peritoneal and multiple lesion recurrences was worse than that of other recurrence sites. This novel finding in gastric cancer research should be acknowledged by clinicians.

In this study, the peritoneum was the most common site of recurrence, consistent with previous reports on gastric cancer recurrence sites [8,9]. In general, peritoneal recurrence appears to be less sensitive to chemotherapy than other recurrence sites because the peritoneum has a large area and fewer connections with the blood vessels and lymphatic chains. Additionally, the peritoneum–plasma barrier prevents effective drug delivery from the systemic circulation into the peritoneal cavity [20]. In this study, we performed PFS analysis to investigate chemotherapeutic sensitivity based on recurrence sites. The PFS analysis did not reach statistical significance; however, we presume that it showed a trend of having a comparatively high HR in peritoneal recurrence and a survival curve under other recurrence sites. Cases of multiple lesion recurrences included 14 peritoneal recurrences, accounting for over 50% of multiple recurrence cases. Therefore, the prognostic behavior of multiple lesional recurrences was similar to that of peritoneal recurrences in this study.

In contrast to the PFS analysis, the analysis of survival after recurrence showed a significant difference, indicating that the peritoneum had the worst prognosis among those of

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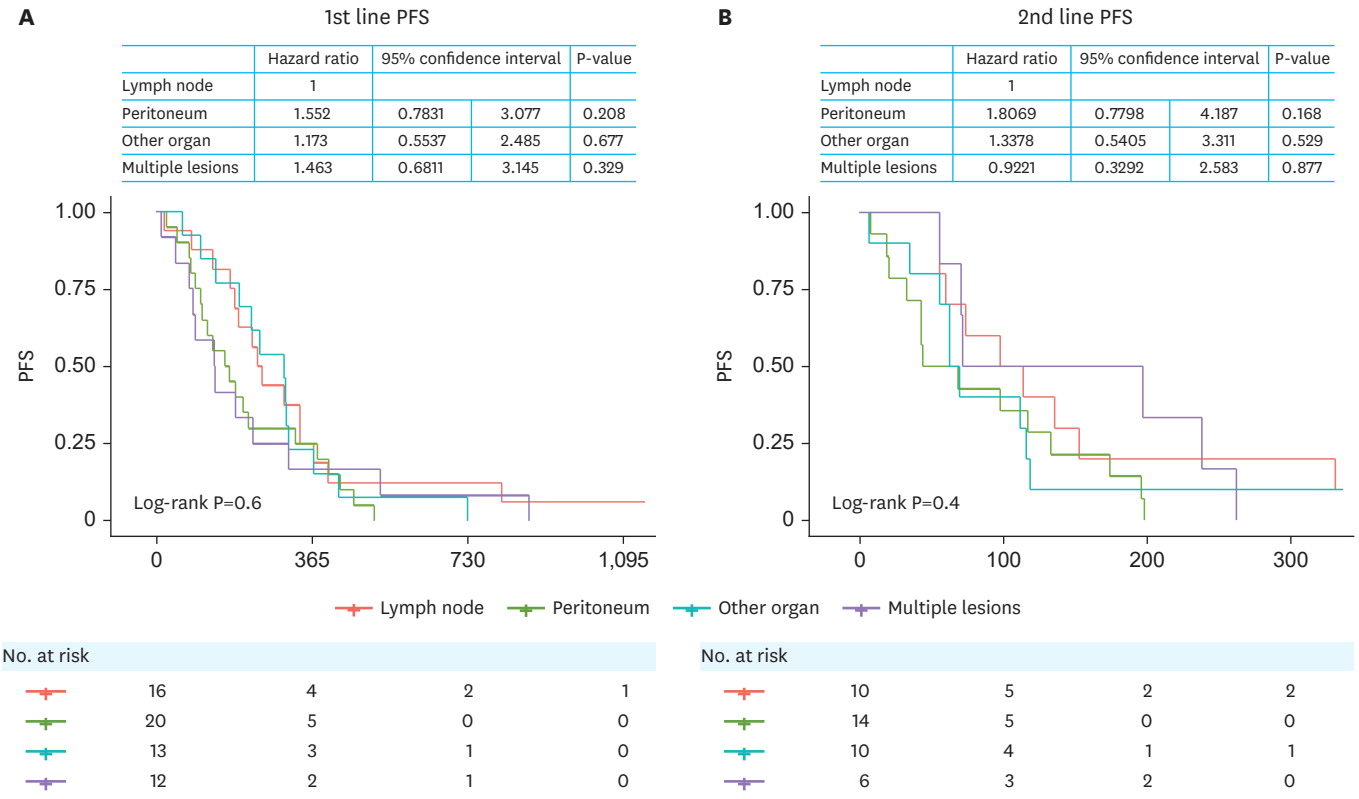

Fig. 2. Kaplan-Meier curves of 1st line PFS and 2nd line PFS. (A) 1st line PFS and (B) 2nd line PFS.
The behavior of the survival curve for the 1st line PFS at each recurrence site was similar to that of the OS curves after recurrence. Peritoneal and multiple recurrences tended to show worse prognoses; however, the difference was not statistically significant.
PFS = progression-free survival; OS = overall survival.

Table 2. Detail of chemotherapy after recurrence

Variables	Recurrent sites				
	Lymph nodes with chemo (n=17)	Peritoneum with chemo (n=20)	Other organs with chemo (n=15)	Multiple lesions with chemo (n=13)	P-value
First Line					0.739
Platinum-based	11 (64.7%)	16 (80.0%)	12 (80.0%)	9 (69.2%)	
Platinum with Tmab	3 (17.4%)	3 (15.0%)	2 (13.3%)	1 (7.7%)	
Taxan	1 (5.9%)	1 (5.0%)	1 (6.7%)	2 (15.4%)	
Other	2 (11.8%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	
Second Line					0.632
Taxan-based	10 (100.0%)	12 (85.7%)	9 (81.8%)	5 (83.3%)	
Platinum-based	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	
Other	0 (0.0%)	1 (7.1%)	2 (18.2%)	1 (16.7%)	

There were no significant differences in the types of chemotherapy administered between recurrence sites.

other recurrence sites. This result may be attributed to the discrepancy in the palliative chemotherapy rate in the groups; the peritoneum had a comparatively lower chemotherapy rate after recurrence. It may also be that patients with peritoneal recurrence were not in a good physical condition, which caused poor compliance to chemotherapy. In addition, although the results were not statistically significant, the possibility of low chemotherapeutic sensitivity for peritoneal recurrence should be considered. We presume that the peritoneum showed a significantly poor survival for the reasons mentioned above.

With regard to the type of chemotherapy administered after recurrence, each recurrence site received almost the same amount of chemotherapy. Platinum-based chemotherapy is

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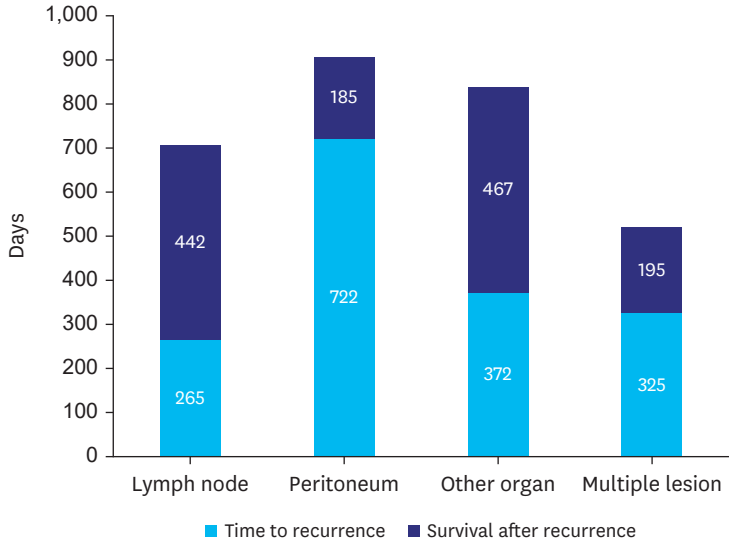

Fig. 3. Median time to recurrence and median survival after recurrence.
The median time to peritoneal recurrence was longer than that of other recurrence sites. However, the survival time after peritoneal and multiple-lesion recurrences was shorter than that at other sites.

the dominant treatment in the 1st line chemotherapy. According to the Japanese Gastric Cancer Treatment Guidelines, platinum-based chemotherapy is the dominant first-line chemotherapy [16]. In both the 1st and 2nd lines of chemotherapy, there were no statistically significant differences among the recurrence sites. Therefore, the treatment strategies appear to be almost equal for each recurrence site. Based on this observation, the recurrence sites may have different chemotherapeutic sensitivities.

The recurrence time should also be noted. The median time to peritoneal recurrence was longer than that of other recurrence sites. However, the survival time after peritoneal and multiple-lesion recurrences was shorter than that at other sites. These data indicate that peritoneal recurrence tends to occur later than that at other sites and is difficult to detect in the early phase. Although it is not clear whether early detection of recurrent tumors can improve prognosis, the prognosis of peritoneal recurrence would be different if early detection was possible [21,22]. Multiple studies have reported on the detection of early-stage cancers involving factors such as liquid biopsies and new treatment strategies, such as the intra-abdominal administration of anticancer drugs. Although several studies have been conducted, innovative surveillance methods and new useful biomarkers have not yet been identified. Some new techniques, such as ctDNA detection, have shown promising results in some cancers but are not significantly sensitive to gastric cancer. As many studies have revealed that the detection of peritoneal metastasis or recurrence remains difficult, it is believed that new technologies or new drug treatments are required to improve recurrent gastric cancer, especially peritoneal recurrence.

This study has several limitations that should be considered. First, it was based on single-center retrospective data; therefore, the sample size was relatively small. In future studies, multicenter prospective data should be collected to reduce bias. Secondly, the duration of the study was relatively long. Chemotherapy for gastric cancer has improved in recent years [2,4,6]. In recent decades, molecular-targeted drugs and immune checkpoint inhibitors have been developed [7]. These drugs improve the prognosis of gastric cancer. However, this

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study could not be considered due to the small number of patients. Therefore, the results of this study do not accurately reflect the present or future prognosis of recurrent gastric cancer. Finally, although there are several treatment options for recurrent esophageal and colorectal cancers, the recommended treatment for recurrent gastric cancer is limited. For example, patients with only cervical recurrence of esophageal cancer may undergo resection. Moreover, metastatic liver recurrent colorectal cancer can be resected. However, there is no alternative treatment for recurrent gastric cancer except systemic chemotherapy [16]. Although some reports have shown the prognostic efficacy of resection of metastatic liver gastric cancer, the evidence is too vague to recommend surgical treatment for many patients with recurrent gastric cancer, similar to those with recurrent esophageal and colorectal cancers, who can benefit from surgical resection of recurrent tumors [23-25].

In conclusion, gastric cancer may have different prognoses depending on the site of recurrence. Therefore, patients with peritoneal recurrence may be less sensitive to chemotherapy. Peritoneal recurrence may also occur in the late phase. The early detection of peritoneal recurrence may improve the prognosis of these patients. The development of new biomarkers for detecting peritoneal recurrence in the early phase, along with stronger and less toxic chemotherapy, is required.

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