Prognostic significance of surgery after chemotherapy in patients with type 4 gastric cancer

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Abstract

Background

The majority of patients with type 4 gastric cancer have distant metastases with extremely poor prognosis. Consequently, considering a therapeutic strategy that improves the prognosis of these patients is clinically important. The present study aimed to assess the clinical indication and prognostic impact of surgery in patients with type 4 gastric cancer who underwent chemotherapy.

Methods

A total of 67 patients with type 4 gastric cancer who underwent chemotherapy were retrospectively enrolled. All patients were grouped into progressive disease (PD) and non-PD groups by tumor response to chemotherapy.

Results

Distant metastases occurred in 58 patients. With regard to tumor response, 16 and 51 patients had PD and non-PD, respectively. The prognosis was significantly poorer in patients with PD than in those with non-PD ($p < 0.0001$). Among 23 patients who underwent surgery after chemotherapy, 21 had a R0 resection. The presence or absence of surgery was significantly correlated with age, first-line chemotherapeutic regimen, lymph node metastasis, clinical stage, number of distant metastatic sites, peritoneal dissemination, and tumor response ($p = 0.0412$, $p = 0.0096$, $p = 0.0024$, $p = 0.0059$, $p = 0.0128$, and $p = 0.0020$, and $p = 0.0066$, respectively). Multivariate analysis selected tumor response and surgery as an independent prognostic factor ($p = 0.0001$ and $p = 0.0009$, respectively). Moreover, multivariate analysis for the surgery group demonstrated that metastatic nodal status (N0-1 vs N2-3) and residual tumor status (R0 vs R1-2) were significant independent prognostic factors ($p = 0.0258$ and $p = 0.0458$, respectively).

Conclusion

Our retrospective study suggests that surgery after chemotherapy for type 4 gastric cancer may improve the prognosis of responders with N0-1 status and a curative R0 resection.

Background

The incidence of patients with gastric cancer has been gradually decreasing in Japan [1]. However, gastric cancer is the third leading cause of cancer-related deaths worldwide [2]. Although the advancement of chemotherapy has dramatically improved survival in patients with unresectable advanced or recurrent gastric cancer, the prognosis of patients with type 4 gastric cancer remains poor. In fact, the 5-year overall survival (OS) rate of patients with type 4 gastric cancer has been reported from 12.5–27.6% [3–6]. Since type 4 gastric cancer involves diffuse infiltration as an oncological property, tumors easily invade the entire stomach. Moreover, patients with type 4 gastric cancer have a high incidence of serosal penetration and peritoneal dissemination [3–6]. In particular, prevention of peritoneal recurrence after a curative surgery is a key issue in the clinical management of patients with type 4 gastric cancer [7]. Consequently, considering the therapeutic strategy to improve the prognosis of these patients is clinically important.

According to the 2018 Japanese Gastric Cancer Treatment Guidelines, systemic chemotherapy is recommended as the first-line treatment for patients with distant metastasis [8]. Furthermore, recent studies have demonstrated the prognostic significance of conversion surgery after chemotherapy in patients with stage IV gastric cancer [9–12]. Conversely, neoadjuvant chemotherapy (NAC) has been found as a promising therapeutic strategy in patients with locally advanced gastric cancer, such as those with macroscopic type 4 tumor, large type 3 tumor, bulky lymph node metastasis, and clinically stage III [13–17]. However, the indication and prognostic significance of conversion surgery or NAC remain uncertain in patients with type 4 gastric cancer.

Therefore, the present study aimed to examine the tumor response and surgical findings after chemotherapy in patients with type 4 gastric cancer and to assess the correlation between the presence or absence of surgery and clinicopathological findings. Moreover, the indication and prognostic impact of surgery after chemotherapy were also investigated in responders.

Methods

Patients

A total of 67 patients (30 men and 37 women; age range, 30–87 years; mean age, 62.5 years) with type 4 gastric cancer who underwent chemotherapy at Kagoshima University Hospital (Kagoshima, Japan) between February 2002 and November 2019 were retrospectively enrolled. Patients with synchronous or metachronous cancer in other organs were excluded from this study. Blood examination, esophagogastroduodenoscopy, endoscopic ultrasonography, and computed tomography before chemotherapy data of all patients were also evaluated. Furthermore, 40 patients underwent staging laparoscopy before starting chemotherapy. Patients were classified and staged based on the TNM classification for gastric carcinoma [18]. The Ethics Committee of Kagoshima University approved this retrospective study (approval number: 200015).

Evaluation of tumor response

Tumor response was assessed every three cycles of chemotherapy and was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) [19]. Tumor response was categorized into progressive disease (PD) and non-PD in the present study. Survival time was defined from the date of chemotherapeutic initiation to the date of death or last follow-up.

Clinical indication of surgery

Surgery after chemotherapy was clinically indicated for patients with a performance status of 0–2, non-PD, and tumors predicted to achieve curative resection. Therefore, these patients underwent staging laparotomy or laparoscopy before gastrectomy. When patients had noncurative factors during staging laparotomy or laparoscopy, curative gastrectomy was postponed, and further chemotherapy was performed.

Evaluation of residual tumor and histological response

Residual tumor status postoperatively and the histological response of primary tumors were determined based on the Japanese classification of gastric carcinoma [20]. Accordingly, the surgical status was grouped into R0, R1, and R2 according to the presence or absence of residual tumors. The histological response was classified into grades 0, 1a, 1b, 2, and 3.

Statistical analysis

The relationship between the presence or absence of surgery and clinicopathological factors was assessed using the chi-square test, Fisher's exact test, or Wilcoxon rank-sum test. Kaplan–Meier survival curves were generated, and prognostic differences were evaluated by the log-rank test. Prognostic factors were assessed using univariate and multivariate analyses (Cox proportional hazards regression modeling). All data were analyzed using JMP14 (SAS Institute Inc., Cary, NC, USA). A p value of < 0.05 was considered statistically significant.

Results

Clinicopathological factors

Table 1 shows patients' clinicopathological factors. Among the 67 patients, 5 and 62 had clinical T3 and T4 tumors, respectively. With regard to lymph node metastasis, 23, 12, 17, and 15 patients had clinical nodal status of N0, N1, N2, and N3, respectively. Distant metastasis was observed in 58 patients, with at least peritoneal dissemination in 55 patients. Seven had more than two distant metastatic sites. Among them, 5, 5, 1, and 1 had liver metastasis, distant lymph node metastasis, ovarian metastasis, and metastasis of the small intestine, respectively.

Among 67 patients enrolled in this study, 33 and 34 underwent platinum- and taxane-based chemotherapy as a first-line regimen, respectively. Furthermore, 8 patients with positive human epidermal growth factor receptor 2 expression received trastuzumab combined with chemotherapy.

Tumor response and survival after chemotherapy

Concerning the tumor response to chemotherapy, 16 and 51 patients had PD and non-PD, respectively. Therefore, the disease control rate was 76.1% (51/67). The median survival durations of patients with PD and those with non-PD were 159 and 757 days, respectively (Fig. 1). The survival difference based on tumor response was statistically significant ($p < 0.0001$).

Surgery after chemotherapy and pathological findings

A total of 23 patients (34.3%) underwent surgery after chemotherapy. Surgical procedures and pathological findings are shown in Table 2. Twenty-two patients underwent total gastrectomy and one underwent proximal gastrectomy. Moreover, D1, D1+, and D2 lymphadenectomy was performed in 2, 6, and 15 patients, respectively. As two patients had no viable tumor cells in the primary site, the depth of tumor invasion was staged as T0. However, 1, 5, and 15 patients had a pathological T2, T3, and T4 tumors, respectively. Furthermore, 9, 2, and 12 patients had a pathological N0, N1, and N3, respectively. R0, R1, and R2 resection was performed in 21, 1, and 1 patient, respectively. Eighteen, 1, 2, and 2 patients had the histological response of grade 1a, 1b, 2, and 3, respectively.

Correlation between the presence or absence of surgery and clinicopathological factors

The mean age (± standard deviation) of the surgery ($n = 23$) and non-surgery ($n = 44$) groups was 58.0 ± 13.7 and 64.9 ± 12.6 years, respectively (Table 3). Consequently, the presence or absence of surgery was significantly correlated with age ($p = 0.0412$). Moreover, surgery was significantly associated with the first-line chemotherapeutic regimen, lymph node metastasis, clinical stage, number of distant metastatic sites, and peritoneal dissemination ($p = 0.0096$, $p = 0.0024$, $p = 0.0059$, $p = 0.0128$, and $p = 0.0020$, respectively) (Table 3). Among 23 patients in the surgery group, 22 (95.7%) had non-PD as tumor response, whereas 15 patients (34.1%) had PD among the 44 patients in the non-surgery group. Accordingly, tumor response was significantly associated with the presence or absence of surgery ($p = 0.0066$) (Table 3).

Survival assessment in both surgery and non-surgery groups

The 3-year OS rate of surgery and non-surgery groups was 56.4% and 6.2%, respectively ($p < 0.0001$) (Fig. 2).

Univariate analysis demonstrated that age, first-line chemotherapeutic regimen, lymph node metastasis (cN0-1 vs cN2-3), tumor response, and presence or absence of surgery were significantly associated with survival between surgery and non-surgery groups ($p = 0.0394$, $p = 0.0311$, $p = 0.0006$, $p < 0.0001$, and $p < 0.0001$, respectively) (Table 4). Multivariate analysis selected tumor response and surgery as an independent prognostic factor ($p = 0.0001$ and $p = 0.0009$, respectively) (Table 4).

Univariate and multivariate analyses in the surgery group alone

Univariate analysis showed that lymph node metastasis (pN0-1 vs pN2-3) and residual tumor status (R0 vs R1-2) were significantly correlated with survival in the surgery group ($p = 0.0121$ and $p = 0.0096$, respectively) (Table 5). Similarly, multivariate analysis indicated that lymph node metastasis and residual tumor status were identified as independent prognostic factors ($p = 0.0258$ and $p = 0.0458$, respectively) (Table 5).

Discussion

To date, many investigators have demonstrated that the prognosis of patients with type 4 gastric cancer is poorer than those with other macroscopic types [3–6]. Currently, surgery and/or chemotherapy are clinically introduced in patients with type 4 gastric cancer, and the novel therapeutic strategy will be expected for further prognostic improvement. However, few reports have assessed the clinical indication and prognostic impact of NAC and surgical interventions in these patients. Therefore, clinicopathological factors, tumor response to chemotherapy, presence or absence of surgery, and survival of patients with type 4 gastric cancer who underwent chemotherapy were retrospectively investigated, and the indication and prognostic significance of surgery after chemotherapy are assessed.

Patients with type 4 gastric cancer have an aggressive tumor behavior. At first, the incidence of lymph node metastasis has been reported to range from 79.5–94.0% in patients with type 4 gastric cancer [7, 21–22], whereas this study showed 60.9% even in patients who underwent chemotherapy. These results indicate the lymphatic spread of tumor cells in patients with type 4 gastric cancer. Next, patients with type 4 gastric cancer have a high incidence of peritoneal dissemination, including positive peritoneal cytology. A meta-analysis demonstrated that the odds ratio for peritoneal dissemination was 3.91 in patients with type 4 gastric cancer, compared with other macroscopic types [23]. Surprisingly, our study indicated the positive peritoneal dissemination rate of 82.1% (55/67). In this study, majority of patients underwent staging laparoscopy. The false-negative rate of staging laparoscopy for detecting peritoneal dissemination is reported to be 0–17.2% [24]. Accordingly, these findings suggest that staging laparoscopy has an important role for an accurate assessment of peritoneal dissemination in patients with type 4 gastric cancer. Staging laparoscopy would be needed to determine the therapeutic plan for these patients.

Interestingly, Kim et al. reported that the surgical curability was not a significant prognostic predictor of patients with type 4 gastric cancer in the multivariate analysis ($p = 0.187$). They concluded that the role of surgery alone was quite limited to improve the prognosis of patients with type 4 gastric cancer [7]. Recently, chemotherapy has also been selected as the initial treatment, due to the dramatic advancement of chemotherapy and potential utility of NAC, in all patients with type 4 gastric cancer. Certainly, the present study indicated a high disease control rate (76.1%) to chemotherapy. Furthermore, the prognosis was significantly better in patients with non-PD than in those with PD, and multivariate analysis showed tumor response as an independent prognostic factor. In surgical specimens, the pathological response rate of grade ≥ 1b was 21.7% (5/23). A phase II study of the preoperative chemotherapy with S-1 and cisplatin followed by gastrectomy among patients with clinically resectable type 4 and large type 3 gastric cancers showed the pathological response rate of 46.9% (23/49) [25]. Consequently, these findings support that chemotherapy is a promising tool to control tumor progression during the first process of the therapeutic strategy.

The present study showed that the pathological response rate of grade 3 was only 8.7% (1/23). Similarly, Iwasaki et al. reported that 2.0% (1/49) of patients with clinically resectable type 4 and large type 3 gastric cancer showed the pathological response of grade 3 [25]. Moreover, our study demonstrated that the prognosis of the surgery group is significantly more favorable than that of non-surgery group. Unfortunately, the 5-year OS rate of the non-surgery group was 0% (Fig. 2). As tumor cells cannot be completely eliminated with chemotherapy alone, an additional surgery may contribute to further improve the prognosis by surgically removing residual tumors in the responder group.

In the present study, the incidence of patients with non-PD among surgery group was 95.7% (22/23). Although this result indicates a close relationship between tumor response and presence or absence of surgery, the most suitable indication for surgery after chemotherapy remains to be identified in responders with type 4 gastric cancer. However, recent studies have indicated several important predictors on the prognosis based on univariate and multivariate analyses in patients with type 4 gastric cancer [6, 21]. An et al. reported that a hazard ratio of the residual tumor status (R0 vs R1) and nodal status (N0 vs N2) was 2.145 ($p < 0.001$) and 2.504 ($p < 0.001$), respectively. In the present study, multivariate analysis showed that lymph node metastasis and residual tumor status alone were independent predictors for OS in the surgery group. Accordingly, these findings may suggest that lymph node metastasis and residual tumor status are the most important factors to determine the clinical indication for the surgical strategy in patients with type 4 gastric cancer. Additionally, R0 resection rate was 91.3% (21/23) in this study. Therefore, this result shows a high surgical curability in patients with type 4 gastric cancer with an aggressive malignant behavior. Furthermore, preoperative chemotherapy might enhance the surgical curability of the clinical management for patients with type 4 gastric cancer.

The present study had several limitations. Our study was based on a retrospective analysis of a small number of populations ($n = 67$) in a single institution. Furthermore, the chemotherapeutic regimen and duration were determined based on patient's conditions or

physician's discretion. These limitations may have resulted in bias, which might have influenced several study results. Consequently, larger prospective multicenter studies with longer follow-up periods would be required to strengthen our conclusion.

Conclusions

This study suggested that surgery after chemotherapy for type 4 gastric cancer may contribute to the prognostic improvement of responders with N0-1 status and curative R0 resection.

Abbreviations

NAC: Neoadjuvant chemotherapy; OS: Overall survival; PD: Progressive disease; RECIST: Response Evaluation Criteria in Solid Tumors

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of the Kagoshima University (approval number: 200015). All patients provided written informed consent to the use and publication of their information.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TA, DM, KO, TT, KS, MN, YK, SM, HK, SY, YU, SI and TO participated in the study design. TA, DM, KO, TT, KS, MN and YK were involved in data collection and data interpretation. TA, SM, HK, SY, YU, SI and TO participated in the statistical analyses. TA wrote the manuscript. All authors read and approved the final manuscript.

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References

1. Foundation for Promotion of Cancer Research. Cancer statistics in Japan. 2017;p. 1–131.
2. Fock KM. Review article: the epidemiology and prevention of gastric cancer. Aliment Pharmacol Ther. 2014;40:250–60.
3. Kim DY, Kim HR, Kim YJ, Kim S. Clinicopathological features of patients with Borrmann type IV gastric carcinoma. ANZ J Surg. 2002;72:739–42.
4. Otsuji E, Kuriu Y, Okamoto K, Ochiai T, Ichikawa D, Hagiwara A, Yamagishi H. Outcome of surgical treatment for patients with scirrhous carcinoma of the stomach. Am J Surg. 2004;188:327–32.
5. Yook JH, Oh ST, Kim BS. Clinicopathological analysis of Borrmann type IV gastric cancer. Cancer Res Treat. 2005;37:87–91.
6. An JY, Kang TH, Choi MG, Noh JH, Sohn TS, Kim S. Borrmann type IV: an independent prognostic factor for survival in gastric cancer. J Gastrointest Surg. 2008;12:1364–9.
7. Kim EY, Yoo HM, Song KY, Park CH. Limited significance of curative surgery in Borrmann type IV gastric cancer. Med Oncol. 2016;33:69.
8. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer. 2020. [Epub ahead of print].
9. Beom SH, Choi YY, Baek SE, Li SX, Lim JS, Son T, Kim HI, Cheong JH, Hyung WJ, Choi SH, Jung M, Kim HS, Jeung HC, Chung HC, Rha SY, Noh SH. Multidisciplinary treatment for patients with stage IV gastric cancer: the role of conversion surgery following chemotherapy. BMC Cancer. 2018;18:1116.
10. Nakamura M, Ojima T, Nakamori M, Katsuda M, Tsuji T, Hayata K, Kato T, Yamaue H. Conversion Surgery for Gastric Cancer with Peritoneal Metastasis Based on the Diagnosis of Second-Look Staging Laparoscopy. J Gastrointest Surg. 2019;23:1758–66.
11. Solaini L, Ministrini S, Bencivenga M, D'Ignazio A, Marino E, Cipollari C, Molteni B, Mura G, Marrelli D, Graziosi L, Roviello F, De Manzoni G, Tiberio GAM, Morgagni P. Conversion gastrectomy for stage IV unresectable gastric cancer: a GIRCG retrospective cohort study. Gastric Cancer. 2019;22:1285–93.
12. Arigami T, Matsushita D, Okubo K, Kawasaki Y, Iino S, Sasaki K, Noda M, Kita Y, Mori S, Kurahara H, Maemura K, Yanagita S, Uenosono Y, Ishigami S, Natsugoe S. Indication and Prognostic Significance of Conversion Surgery in Patients with Liver Metastasis from Gastric Cancer. Oncology. 2020;98:273–9.
13. Tsuburaya A, Mizusawa J, Tanaka Y, Fukushima N, Nashimoto A, Sasako M, Stomach Cancer Study Group of the Japan Clinical Oncology Group. 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.
14. Coimbra FJF, de Jesus VHF, Ribeiro HSC, Diniz AL, de Godoy AL, de Farias IC, Felismino T, Mello CAL, Almeida MF, Begnami MDFS, Dias-Neto E, Riechelmann RSP, da Costa WL Jr. Impact of ypT, ypN, and Adjuvant Therapy on Survival in Gastric Cancer Patients Treated with Perioperative Chemotherapy and Radical Surgery. Ann Surg Oncol. 2019;26:3618–26.
15. Kano M, Hayano K, Hayashi H, Hanari N, Gunji H, Toyozumi T, Murakami K, Uesato M, Ota S, Matsubara H. Survival Benefit of Neoadjuvant Chemotherapy with S-1 Plus Docetaxel for Locally Advanced Gastric Cancer: A Propensity Score-Matched Analysis. Ann Surg Oncol. 2019;26:1805–13.
16. Terashima M, Iwasaki Y, Mizusawa J, Katayama H, Nakamura K, Katai H, Yoshikawa T, Ito Y, Kaji M, Kimura Y, Hirao M, Yamada M, Kurita A, Takagi M, Boku N, Sano T, Sasako M, Stomach Cancer Study Group, Japan Clinical Oncology Group. Randomized phase III trial of gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer, the short-term safety and surgical results: Japan Clinical Oncology Group Study (JCOG0501). Gastric Cancer. 2019;22:1044–52.
17. Terazawa T, Matsuyama J, Goto M, Kawabata R, Endo S, Imano M, Fujita S, Akamaru Y, Taniguchi H, Tatsumi M, Lee SW, Kurisu Y, Kawakami H, Kurokawa Y, Shimokawa T, Sakai D, Kato T, Fujitani K, Satoh T. A Phase II Study of Perioperative Capecitabine plus Oxaliplatin Therapy for Clinical SS/SE N1-3 M0 Gastric Cancer (OGSG 1601). Oncologist. 2020;25:119–208.
18. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR. AJCC Cancer staging manual. 8th ed. New York: Springer; 2017.
19. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.

20. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer. 2011;14:101–12.
21. Dong RZ, Guo JM, Zhang ZW, Zhou YM, Su Y. Prognostic impact and implications of extracapsular lymph node spread in Borrmann type IV gastric cancer. Oncotarget. 2017;8:97593–601.
22. Liang C, Chen G, Zhao B, Qiu H, Li W, Sun X, Zhou Z, Chen Y. Borrmann Type IV Gastric Cancer: Focus on the Role of Gastrectomy. J Gastrointest Surg. 2020;24:1026–32.
23. Luo Y, Gao P, Song Y, Sun J, Huang X, Zhao J, Ma B, Li Y, Wang Z. Clinicopathologic characteristics and prognosis of Borrmann type IV gastric cancer: a meta-analysis. World J Surg Oncol. 2016;14:49.
24. Fukagawa T. Role of staging laparoscopy for gastric cancer patients. Ann Gastroenterol Surg. 2019;3:496–505.
25. Iwasaki Y, Sasako M, Yamamoto S, Nakamura K, Sano T, Katai H, Tsujinaka T, Nashimoto A, Fukushima N, Tsuburaya A, Gastric Cancer Surgical Study Group of Japan Clinical Oncology Group. Phase II study of preoperative chemotherapy with S-1 and cisplatin followed by gastrectomy for clinically resectable type 4 and large type 3 gastric cancers (JCOG0210). J Surg Oncol. 2013;107:741–5.

Tables

Table 1 Clinicopathological factors ($n = 67$)

Factor	n (%)
Gender	
Male	30 (44.8)
Female	37 (55.2)
Age (years, range)	62.5 (30-87)
First-line chemotherapeutic regimen	
Platinum-based	33 (49.3)
Taxane-based	34 (50.7)
Tumor location	
Whole	29 (43.3)
Upper	18 (26.9)
Middle	11 (16.4)
Lower	9 (13.4)
Depth of tumor invasion	
cT3	5 (7.5)
cT4	62 (92.5)
Lymph node metastasis	
cN0	23 (34.3)
cN1	12 (17.9)
cN2	17 (25.4)
cN3	15 (22.4)
Clinical stage	
II	5 (7.5)
III	4 (6.0)
IV	58 (86.6)
Number of distant metastatic sites	
0	9 (13.4)
1	51 (76.1)
2–4	7 (10.4)
Peritoneal dissemination	
P0	12 (17.9)
P1	55 (82.1)
Histological type	
Differentiated	3 (4.5)
Undifferentiated	64 (95.5)

Table 2 Surgical procedures and pathological findings ($n = 23$)

Factor	n (%)
Surgical procedure	
Total gastrectomy	22 (95.7)
Proximal gastrectomy	1 (4.3)
Lymph node dissection	
D1	2 (8.7)
D1+	6 (26.1)
D2	15 (65.2)
Depth of tumor invasion	
pT0 (no viable tumor cells)	2 (8.7)
pT1	0 (0.0)
pT2	1 (4.3)
pT3	5 (21.7)
pT4	15 (65.2)
Lymph node metastasis	
pN0	9 (39.1)
pN1	2 (8.7)
pN2	0 (0.0)
pN3	12 (52.2)
Residual tumor status	

R0	21 (91.3)
R1	1 (4.3)
R2	1 (4.3)
Histological response	
Grade 1a	18 (78.3)
Grade 1b	1 (4.3)
Grade 2	2 (8.7)
Grade 3	2 (8.7)

Table 3 Correlation between the presence or absence of surgery and clinicopathological factors

	Treatments (%)		
Factor	Surgery group (n = 23)	Non-surgery group (n = 44)	p value
Gender			0.0724
Male	14 (60.9)	16 (36.4)	
Female	9 (39.1)	28 (63.6)	
Age (years)	58.0 ± 13.7	64.9 ± 12.6	0.0412
First-line chemotherapeutic regimen			0.0096
Platinum-based	6 (26.1)	27 (61.4)	
Taxane-based	17 (73.9)	17 (38.6)	
Tumor location			0.7804
Whole/upper	17 (73.9)	30 (68.2)	
Middle/lower	6 (26.1)	14 (31.8)	
Depth of tumor invasion			1.0000
cT3	2 (8.7)	3 (6.8)	
cT4	21 (91.3)	41 (93.2)	
Lymph node metastasis			0.0024
cN0–1	18 (78.3)	17 (38.6)	
cN2–3	5 (21.7)	27 (61.4)	
Clinical stage			0.0059
II–III	7 (30.4)	2 (4.5)	
IV	16 (69.6)	42 (95.5)	
Number of distant metastatic sites			0.0128
0	7 (30.4)	2 (4.5)	
1	14 (60.9)	37 (84.1)	
2–4	2 (8.7)	5 (11.4)	
Peritoneal dissemination			0.0020
P0	9 (39.1)	3 (6.8)	
P1	14 (60.9)	41 (93.2)	
Histological type			1.0000
Differentiated	1 (4.3)	2 (4.5)	
Undifferentiated	22 (95.7)	42 (95.5)	
Tumor response to chemotherapy			0.0066
PD	1 (4.3)	15 (34.1)	
non-PD	22 (95.7)	29 (65.9)	

PD progressive disease

Table 4 Univariate and multivariate analyses of survival in all patients ($n = 67$)

	Univariate analysis			Multivariate analysis		
Independent factor	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Gender			0.1768			
Female	1.000	reference				
Male	0.679	0.387–1.191				
Age (years)			0.0394			0.1814
< 70	1.000	reference		1.000	reference	
≥ 70	1.832	1.030–3.258		1.500	0.828–2.719	
First-line chemotherapeutic regimen			0.0311			0.7941
Platinum-based	1.000	reference		1.000	reference	
Taxane-based	0.529	0.296–0.944		1.086	0.586–2.013	
Tumor location			0.2102			
Whole/upper	1.000	reference				
Middle/lower	1.453	0.810–2.605				
Depth of tumor invasion			0.3233			
cT3	1.000	reference				
cT4	1.803	0.560–5.803				
Lymph node metastasis			0.0006			0.5769
cN0–1	1.000	reference		1.000	reference	
cN2–3	2.728	1.543–4.823		1.207	0.623–2.340	
Peritoneal dissemination			0.1301			
P0	1.000	reference				
P1	1.933	0.823–4.539				
Histological type			0.8089			
Differentiated	1.000	reference				
Undifferentiated	0.865	0.266–2.807				
Tumor response to chemotherapy			< 0.0001			0.0001
non-PD	1.000	reference		1.000	reference	
PD	6.604	3.360–12.982		4.123	1.990–8.540	
Surgery			< 0.0001			0.0009
Absence	1.000	reference		1.000	reference	
Presence	0.178	0.084–0375		0.229	0.096–0.547	

CI confidence interval, *PD* progressive disease

Table 5 Univariate and multivariate analyses of survival in the surgery group alone ($n = 23$)

	Univariate analysis			Multivariate analysis		
Independent factor	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Gender			0.2919			
Female	1.000	reference				
Male	0.551	0.182–1.669				
Age (years)			0.4174			
< 70	1.000	reference				
≥ 70	1.715	0.466–6.310				
First-line regimen of chemotherapy			0.2868			
Platinum-based	1.000	reference				
Taxane-based	0.405	0.077–2.135				
Tumor location			0.0733			
Whole/upper	1.000	reference				
Middle/lower	3.567	0.887–14.346				
Tumor size (mm)			0.9096			
< 100	1.000	reference				
≥ 100	0.932	0.279–3.118				
Depth of tumor invasion			0.1734			
pT0–3	1.000	reference				
pT4	2.482	0.671–9.187				
Lymph node metastasis			0.0121			0.0258
pN0–1	1.000	reference		1.000	reference	
pN2–3	5.517	1.452–20.959		4.786	1.209–18.954	
Residual tumor status			0.0096			0.0458
R0	1.000	reference		1.000	reference	
R1–2	13.672	1.891–98.872		7.655	1.039–56.423	

CI confidence interval

Figures

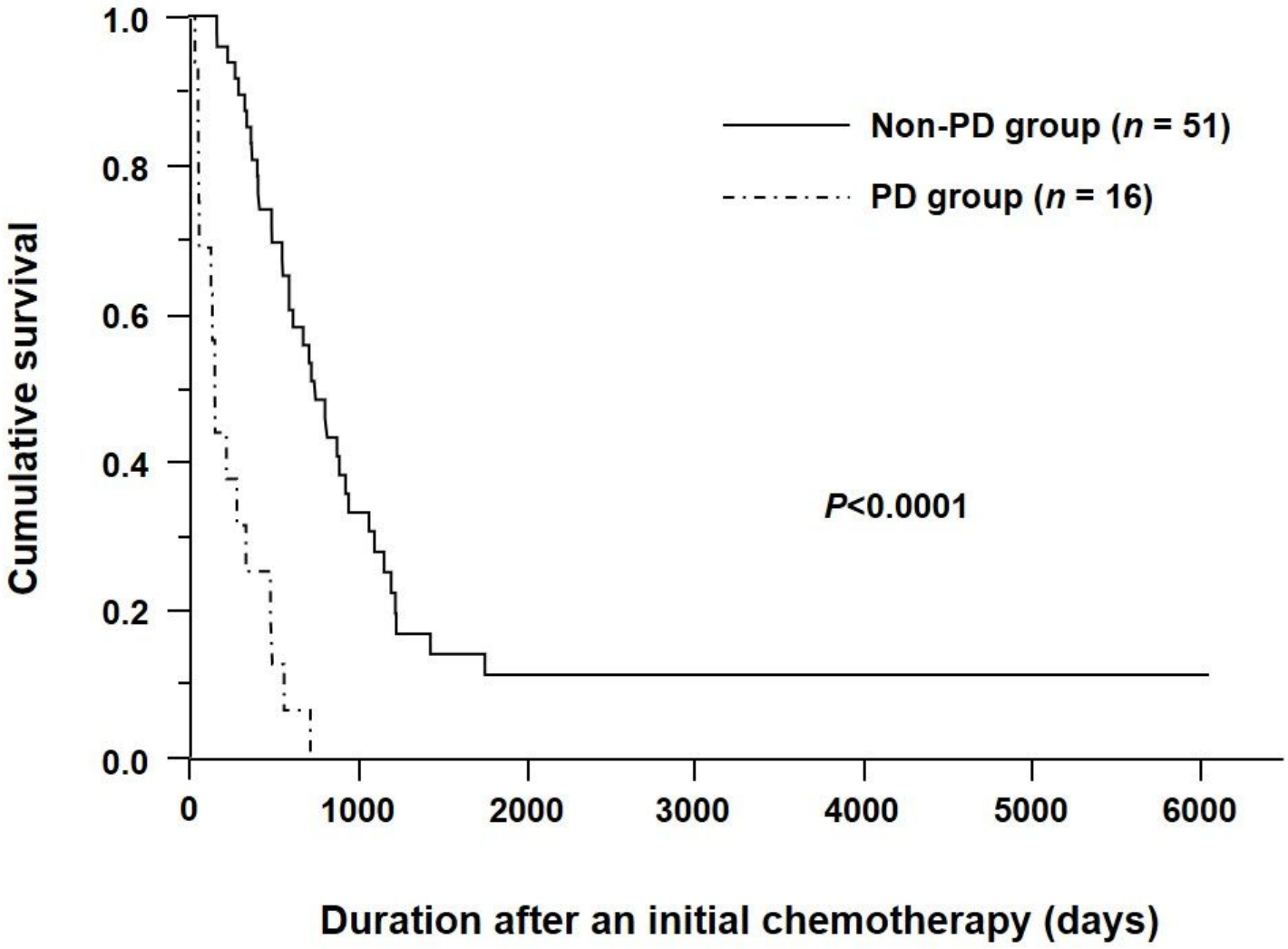

Figure 1

Kaplan–Meier survival curves based on tumor response. Survival of patients with PD was significantly poorer than in those with non-PD ($p < 0.0001$).

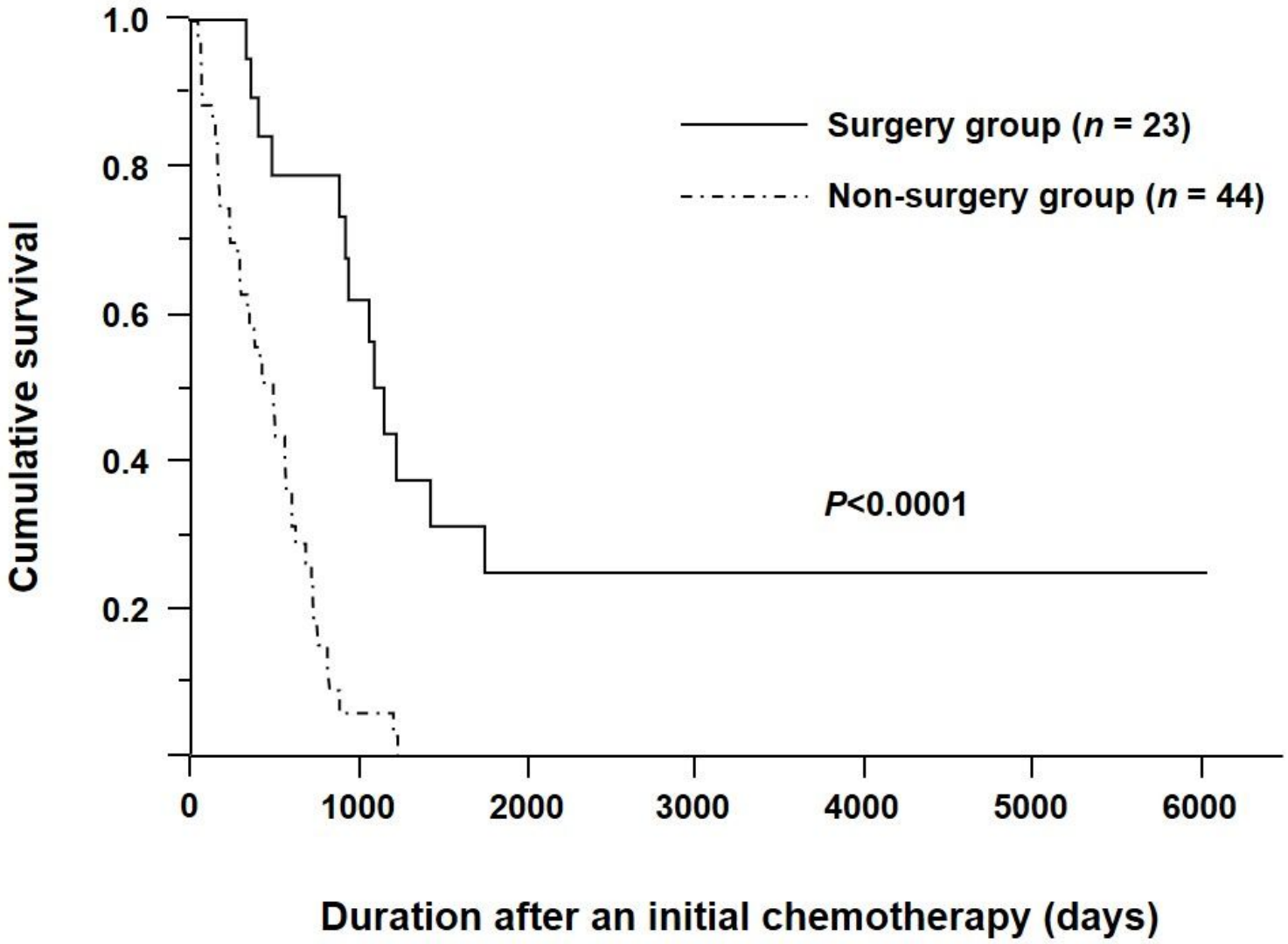

Figure 2

Kaplan–Meier survival curves based on the presence or absence of surgery. Survival of the non-surgery group was significantly poorer than that of the surgery group ($p < 0.0001$).