Efficacy of pre-operative chemotherapy with docetaxel, cisplatin, and S-1 (DCS therapy) and curative resection for gastric cancer with pathologically positive para-aortic lymph nodes

doi: 10.1002/jso.22125

Title

Efficacy of pre-operative chemotherapy with docetaxel, cisplatin, and S-1 (DCS therapy) and curative resection for gastric cancer with pathologically positive para-aortic lymph nodes

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Short Title

DCS therapy for advanced gastric cancer

Abbreviations list

PAN, para-aortic lymph node; PAND, para-aortic lymph node dissection; DCS therapy, triple combination chemotherapy with docetaxel, cisplatin, and S-1; 5-FU , 5-fluorouracil

Synopsis

We investigated the effects and survival benefits of combined pre-operative triple combination chemotherapy with docetaxel, cisplatin, and S-1 (DCS therapy) and gastrectomy with para-aortic lymph node dissection (PAND) for advanced gastric cancer with para-aortic lymph node (PAN) metastasis. Our findings suggested that this multimodal therapy is extremely effective for advanced gastric cancer with PAN metastasis compared with conventional surgical treatment of gastrectomy and PAND.

Abstract

Background: The prognosis of gastric cancer with para-aortic lymph node (PAN) metastasis is poor. We applied triple combination chemotherapy with docetaxel, cisplatin, and S-1 (DCS therapy) as pre-operative chemotherapy and investigated the outcome of the combination of this therapy and gastrectomy with para-aortic lymph node dissection (PAND).

Methods: We retrospectively identified 44 patients with pathologically positive PAN who underwent curative surgery at Kanazawa University Hospital between 1990 and 2008. Among the 44 patients, 16 received pre-operative DCS therapy and subsequent surgical resection after 2 courses of the therapy.

Results: Pre-operative DCS therapy showed high clinical response ratio (68.8%) and disease control ratio (100%). The pathological response ratio of resected specimen was 87.5%. At 2 years after surgery, the overall survival ratio was 93.8% and relapse-free survival was 75.0%. Pre-operative DCS therapy was only independent prognostic factor in multivariate analysis. Grade 3/4 toxicity was observed only in 25.0% patients who underwent DCS therapy. Surgical complication was observed in 31.3% patients, and this ratio was equal to that of patients who did not receive DCS therapy.

Conclusion: Multimodal therapy comprising combined pre-operative DCS therapy and gastrectomy with PAND was extremely effective and feasible for advanced gastric cancer with PAN metastasis.

Keywords: gastric cancer, para-aortic lymph node metastasis, pre-operative chemotherapy, para-aortic lymph node dissection

Introduction

Although the incidence of gastric cancer has decreased in recent decades, it is still one of the leading causes of cancer death in East Asia and Eastern Europe [1]. Recent improvements in therapeutic methods have considerably improved the prognosis of gastric cancer. This result is mostly attributed to the improved outcome of treatment of localized gastric cancer in relative early stage. However, the prognosis of unresectable cancers including hematological metastasis, peritoneal metastasis, and distant lymph node metastasis, such as para-aortic lymph node (PAN) metastasis, remains poor. More than 20% of patients with advanced gastric cancer develop PAN metastasis. Total resection of metastatic foci is difficult in gastric cancer with hematological or peritoneal metastasis, which should be treated with chemotherapy. Compared with the previously mentioned metastasis, lymph node metastasis can be completely resected without residual tumor; therefore, surgical intervention can improve the prognosis of patients with lymph node metastasis. Complete retrieval of these metastasized nodes is indispensable to improve the prognosis of such patients [2-6]. However, the prognosis is quite poor even after regional lymphadenectomy plus para-aortic lymph node dissection (PAND) are performed. For such patients, additional systemic chemotherapy is the potential and commonly used treatment.

Several chemotherapeutic regimens with various kinds of combinations including 5-fluorouracil (5-FU), cisplatin, irinotecan, and taxans were intensively investigated. Fluorouracil-based regimens were widely used and were the most effective chemotherapy for advanced gastric cancer. The Japanese Clinical Oncology Group 9912 Trial showed that S-1,

which is a novel orally administrated 5-FU analog, was a good alternative to continuous infusion of 5-FU for unresectable gastric cancer [7]. A multicenter phase Ⅲ trial for unresectable gastric cancer (SPIRITS trial) comparing S-1 alone with S-1 plus cisplatin yielded a significantly higher response rate and improved overall survival in patients with S-1 plus cisplatin [8]. Hence, S-1 plus cisplatin is considered as the existing standard regimen for advanced gastric cancer in Japan. Furthermore, the efficacy of triple combination regimen of ECF (epirubicin, cisplatin, and 5-FU) and DCF (docetaxel, cisplatin plus 5-FU) is reported from western countries, since these treatments are golden standard in western countries [9, 10]. Recently, a novel triple combination with docetaxel, cisplatin, and S-1 (DCS therapy) has been reported as a powerful regimen for highly advance stage gastric cancer [11-13].

Nevertheless, newly developed carcinostatics have shown remarkable proceeds; the response in gastric cancer remains limited and they mainly provide palliation or prolonged survival. Chemotherapy or radical resection severally did not produce satisfactory results. These observations indicate that novel approaches such as multimodal therapies are needed to improve the treatment outcome. However, the effect of post-operative chemotherapy remains limited despite of the recent developments [14, 15].

Recently, the efficacies of pre-operative treatment were reported in patients with locally advanced gastric cancer [16-18]. The tolerability and efficacy of these treatments were superior to those of post-operative chemotherapy. The potential benefits of pre-operative chemotherapy include these effects, reduction in cancer volume or downstaging of the tumor to make curative resection possible, extinguish micrometastasis, and furthermore assess the

sensitivity to anti-cancer drugs. Pre-operative treatment is a promising stratagem for advanced gastric cancer. Some effective pre-operative chemotherapeutic and chemoradiotherapeutic regimens have been reported in the recent years [16-18]. In these studies, the present chemotherapeutic regimens have been used together with surgical resection, but the targets of these treatments were patients with resectable cancer. These regimens may not be effective for patients with highly advance stage gastric cancer, such as PAN metastasis. Therefore, a new regimen that is powerful and safe in pre-operative setting is needed. We previously conducted Phase I study on DCS therapy in a preoperative setting for advanced gastric cancer with PAN metastasis, and the treatment was well tolerated with a quite high pathological response ratio [11].

The aim of this study was to investigate the survival benefit of gastrectomy with PAND on the heels of pre-operative DCS therapy for advanced gastric cancer patients with PAN metastasis. The survival outcome and toxicity of this multimodal therapy were examined and compared with those of conventional cases of gastrectomy accompanied with PAND.

Results

Patient characteristics

Patient demographics and tumor characteristics are summarized in Table Ⅰ. Pre-treatment clinical findings and histological features of surgical specimen (such as location, size, and depth of primary lesion; number of lymph node metastasis and PAN metastasis) did not differ between the groups. The surgical procedures were as follows: total gastrectomy in ~~18~~ 16; distal gastrectomy in 8; pancreatoduodenectomy in 3; and proximal gastrectomy in 1, respectively, in patients without pre-operative DCS therapy. In patients with pre-operative DCS therapy. the surgical procedures were as follows: total gastrectomy in ~~11~~ 9; distal gastrectomy in 6; and proximal gastrectomy in 1 respectively, All patients with pre-operative DCS therapy in present study had pathological findings suggesting presence of PAN metastasis before chemotherapy as pre-operative imaging diagnosis: 5 patients had residual cancer cells in PAN; 11 had no residual cancer cells and definite change after cancer disappearance in PAN [23]. The number of metastatic lymph node without residual cancer cells were 2-36 nodes (median 10) in all lymph nodes and 2-14 nodes (median 4) in PAN.

Adjuvant chemotherapy

The regimen of adjuvant chemotherapy in patients without pre-operative DCS therapy was altered with elapse of period. Regimen including intravenous administration of 5-FU was done in 10 patients, oral 5-FU in 11, and the other regimen in 4, 3 patients did not receive on patient's request. The regimen of adjuvant chemotherapy in patients with pre-operative DCS therapy was DCS therapy done in 2 patients, S-1 in 8, and 6 patients did not receive on

patient's request.

Adverse events from pre-operative DCS therapy

Treatment-related toxicities are shown in Table II. Toxicity of grade 3 or above, such as neutropenia (25.0%), leucopenia (18.8%), febrile neutropenia (6.3%) and diarrhea (6.3%) were observed. No patient died of treatment-related toxicities. Treatment administration was delayed in 3 of the 16 patients (18.8%), and the cause of delayed administration was neutropenia in all patients. Dose reduction was performed in 3 cases (18.8%) due to neutropenia. Two patients (12.5%) could not complete 2 courses of DCS therapy. Nevertheless, surgery was possible in all patients within 2 to 4 weeks after termination of the last chemotherapy course.

Clinical and pathological response to DCS therapy

Clinical response rates are summarized in Table III. Clinical responses according to site were as follows: primary lesion, 81.3%; and lymph node metastasis, 68.8%~~; and hepatic metastasis, 100%~~. The overall response ratio was 68.8%. The disease control ratio was 100%, and no patient had disease progression during pre-operative chemotherapy period.

Pathological findings of surgically resected specimen are listed in Table Ⅳ. Pathological response (≥ grade1b) was observed 87.5% in primary lesion and 87.5% in lymph node metastasis. The ratio of no visible cancer cells according to site were as follows: primary lesion, 25.0%; and lymph node metastasis, 25.0%.

Surgical complication

Among patients who did not receive pre-operative DCS therapy, surgical complications

developed in 10 patients (35.7%) (Table V) as follows: 8 had anastomotic leakage, 1 had pancreatic fistulae, 1 had bleeding after surgery, and 1 had lymphatic fistulae. ~~, and 1 had peritoneal abscess~~. Among patients who received pre-operative DCS therapy, surgical complications developed in 5 patients (31.3%) as follows: 3 had pancreatic fistulae and 2 had lymphatic fistulae, respectively. The frequency of surgical complication were not different between the 2 groups. Two patients in without DCS therapy group required surgical intervention for postoperative hemorrhage and anastomotic leakage, respectively. In DCS therapy group, all complications were cured by conservative treatment. The number of complications in according to the Clavien–Dindo classification was 1 for grade I, 7 for grade II and 2 for grade III in without DCS therapy group. In DCS therapy group, the grading was 1 for grade I and 4 for grade II.

Recurrence after surgery

Relapse occurred in 24 (85.7%) of 28 patients who did not receive pre-operative DCS therapy and 5 (31.2%) of 16 patients who received pre-operative DCS therapy. In patients without DCS therapy, recurrence occurred in lymph node in 5 patients, distant organs in 7, peritoneum in 3, and in composite sites 9. In patients with pre-operative DCS therapy, the site of relapse was lymph nodes in 3 patients and liver in 2. Lymph node recurrence was observed outside the custum field of lymph node dissection, ex. porta hepatis, near the hilum of kidney or iliac lymph nodes.

Survival after surgical resection

The 2-year and 5-year overall survival ratios were 32.9% and 24.0%, respectively, in patients

who did not receive pre-operative DCS therapy, and the 2-year ratios was 93.8% in patients who received pre-operative DCS therapy. Median follow-up was 35.1 months in patients with pre-operative DCS therapy; it was longer than median overall survival in patients without DCS therapy (18.2 months). The overall survival ratio was statistically higher in patients with pre-operative DCS therapy compared with that in patients without pre-operative DCS therapy (P=0.0001) (Figure 1). The 2-year and 5-year relapse-free survival ratios were 28.7%, and 16.3%, respectively, in patients who did not undergo pre-operative DCS therapy, and the 2-year ratios was 75.0%, in patients with pre-operative DCS therapy. The relapse-free survival ratio was also statistically higher in patients with pre-operative DCS therapy (P=0.0082) (Figure 2). In survival analysis, the factors contribute to overall survival were pre-operative DCS therapy, treatment period, number of lymph node metastasis and number of PAN metastasis in univariate analysis. In multivariate analysis, pre-operative DCS therapy was only independent factor contribute to overall survival (Table Ⅵ).

Discussion

We obtained a very high clinical response ratio (68.8%) and disease control ratio (100%) with the pre-operative DCS therapy, and the pathological response ratio of resected specimen was 87.5%. The overall survival ratio was 93.8% and relapse-free survival was 75.0% at 2 years after surgery; these values were statistically higher as compared to those of patients who did not receive pre-operative DCS therapy. Pre-operative DCS therapy was only independent prognostic factor in multivariate analysis. The toxicity profile and surgical complications were acceptable and manageable. Multimodal therapy combined with pre-operative DCS therapy and gastrectomy with PAND was an extremely effective and feasible therapy for advanced gastric cancer with PAN metastasis.

Gastrectomy with lymphadenectomy is the mainstay of curative treatment for gastric cancer. Nevertheless, the appropriate degree of lymph node dissection remains controversial. The significance of curative resection in patients with positive PAN metastasis is not yet clear. A randomized trial in Japan to compare D2 lymphadenectomy alone with D2 lymphadenectomy plus PAND for gastric cancer (JCOG9501) did not suggest any difference in terms of survival between the 2 groups [24]. JCOG9501 study concluded that prophylactic PAND does not contribute to the survival benefit of resectable gastric cancer; however, this study does not deny the efficacy of therapeutic PAND. Curative resection with extended lymphadenectomy might be beneficial for patients with pathologically positive PAN metastasis. Nevertheless, limited patients gain benefit through radical dissection with PAND. Several factors indicating good prognosis of patients with PAN metastasis have been reported, including number of

metastatic PAN (<3 or 4) [3] and total number of metastatic lymph nodes (<11) [4]. In another report, patients with less than 15 total positive nodes and macroscopic type other than type 4 had better survival outcome with R0 resection, including PAN retrieval [5]. We already reported the efficacy of selective lymphadenectomy of subgroups of PAN according to the location of the primary tumor [6]. These patients might benefit through radical dissection accompanied with PAND. However, the key factors in subsets of patients with PAN metastasis that may provide prognostic benefits with PAND remain unknown. Moreover, it is impossible to determine the presence of remnant cancer cells in lymph nodes after pre-operative chemotherapy through imaging or intraoperative findings. Therefore, we performed systemic resection of PAN, since imaging before chemotherapy suggested the presence of metastatic foci.

The survival rate of these patients is low, and additional therapy is necessary besides curative resection to improve treatment outcome. Multimodal therapy combined with surgery and peri-operative chemotherapy currently appears to be a suitable option for resectable advanced gastric cancer. Some recent randomized trial of chemotherapy for unresectable gastric cancer failed to achieve good overall survival, in spite of good response rate and progression-free survival. It is difficult to improve the survival outcome in single-handed chemotherapy; however, this can be achieved in combination therapy including surgery and chemotherapy. ACTS-GC trial confirmed the efficacy of adjuvant chemotherapy with S-1 after D2 dissection for locally advanced gastric cancer [15]. However, the compliance of chemotherapy was low in this trial; the dose was decreased to 46.5% through the 12-month treatment schedule.

Similarly, adjuvant chemotherapy could not started in 6 of 16 patients in the present study. Tolerability is the principal concern of post-operative chemotherapy. Recent reports showed that pre-operative treatment is effective in patients with locally advanced gastric cancer [16-18], and the tolerability and efficacy of this treatment were superior to those of post-operative chemotherapy. MAGIC trial showed that peri-operative ECF therapy had significant survival benefit for operable gastric cancer [16]. Yoshikawa et al. reported the efficacy of pre-operative chemotherapy with irinotecan and cisplatin for advanced gastric cancer with PAN metastasis and/or bulky metastasis in regional lymph nodes. They reported a 3-year survival ratio of 27% and the pathological response ratio was limited to 17.0% [17]. Pathological response to preoperative chemotherapy may be a surrogate for long survival [25]. Recently, there have been novel reports on DCS therapy for unresectable gastric cancer with extremely high response rates. Sato Y et al. reported a phase Ⅱ study of DCS therapy in patients with unresectable gastric cancer who received oral S-1 (40 mg/m2 b.i.d.) on days 1 to 14 and intravenous cisplatin (60 mg/m2) and docetaxel (60 mg/m2) on day 8 every 3 weeks; their clinical response ratio was 87.1% [12]. Nakayama N et al. reported a phase Ⅰ study of DCS therapy in patients with unresectable gastric cancer patients who received oral S-1 (40 mg/m2 b.i.d.) on days 1 to 14 and intravenous cisplatin (60 to 80 mg/m2) and docetaxel (40 mg/m2) on day 1 every 4 weeks; their clinical response ratio was 69.2% [13]. Therefore, we applied DCS therapy, which is a powerful novel chemotherapy regimen, as pre-operative chemotherapy for advanced gastric cancer with PAN metastasis. In this study, the 2-year overall survival ratio was 93.8% and the pathological response ratio was 87.5%. These

findings suggest a markedly satisfactory outcome, even though poor prognosis was expected in the patient population of this study. However, Sato and Nakayama reported that although the regimens were very effective, they were too toxic to be used in a preoperative setting. Grade 3/4 neutropenia was observed in 77.4% patients by Sato Y et al. and in 42.9% patients by Nakayama et al. Treatment schedules remain a central issue in the search of a balance between good response and low toxicity. In our regimen, the dose of docetaxel and cisplatin was divided and these drugs were administered biweekly with anticipation of both decreased toxicity and preserved response.

High perioperative morbidity and mortality rates are the main concerns of surgeons in cases with extended resection after pre-operative chemotherapy. Previous reports (JCOG9501) suggested that when performed by an experienced surgeon, lymphadenectomy of regional lymph node plus PAND may be a relatively safe treatment [24]. In general, lymphadenectomy after pre-operative chemotherapy was more difficult compared to lymphadenectomy without pre-operative chemotherapy because chemotherapy results in fibrous and edematous changes in the tumour site. The tissue damage caused by pre-operative chemotherapy may be resulting to high incidence of pancreatic fistulae and lymphatic fistulae in DCS group. Lower incidence of anastomotic leakage in DCS group may be a benefit of development in surgical instruments. In this study, the morbidity rate was 31.3% and mortality rate was 0%. These rates were considered acceptable, given the efficacy of this multimodal therapy.

In conclusion, pre-operative DCS therapy is highly active against advanced gastric cancer with PAN metastasis, and this treatment is well tolerated with less toxicity and high rate of

pathological response. The favorable results of our study have raised the hope that this multimodal therapy may improve survival outcomes for patients with advanced gastric cancer accompanied with PAN metastasis, and this approach could became a promising strategy for treating patients with advanced gastric cancer with PAN metastasis in the future. However, since a small number of patients received this multimodal therapy in this study, further evaluations with large patient populations are required.

Patients and Methods

We retrospectively identified patients with pathologically proven PAN metastasis who had undergone curative resection at our institute between 1990 and 2008. In all, 1355 patients underwent gastrectomy for gastric cancer at the Kanazawa University Hospital. Curative gastrectomy with lymphadenectomy of regional lymph node and PAN was performed in 121 patients. Of these 121 patients, 49 had pathologically proven PAN metastasis. 5 of 49 these patients had hepatic metastasis and they were excluded in this study. We included these ~~49~~ 44 patients in our study. Traditional strategy for resectable gastric cancer in pre-operative images; even if diagnosed as accompanied with PAN metastasis, was that preceding total resection of cancer focus and the subsequent adjuvant chemotherapy. From 2005, we performed DCS therapy as a preoperative chemotherapy in advanced gastric cancer patients with PAN metastasis. To 2008, we have treated ~~18~~ 16 patients of advanced gastric cancer with PAN metastasis with combined pre-operative DCS therapy and curative gastrectomy and lymphadenectomy of regional lymph node and PAN. Basically adjuvant chemotherapy was planned; the regimen was determined by the pathological effectiveness of pre-operative DCS therapy. For evaluating the efficacy of preoperative DCS therapy, patient characteristics and treatment outcome were analyzed. In addition, the survival benefit of this therapy was evaluated and compared with that of ~~31~~ 28 patients who did not receive preoperative DCS therapy.

Preoperative DCS therapy and surgery

Preoperative DCS therapy with docetaxel and cisplatin [30-35 mg/m2 an intravenous

infusion] on days 1 and 15 with hydration and S-1 [orally 40 mg/m2 twice daily (b.i.d.)] on days 1 to 14 every 4 weeks was administered, as described in a previous report [11]. Surgical resection was planned after 2 courses of preoperative DCS therapy. In patients who were judged to be candidates for curative resection, surgery was performed 2 to 4 weeks after the completion of the last course. Complete resection of primary lesion and regional lymphadenectomy plus PAND was performed. These ~~18~~ 16 patients were included in our study cohort as the DCS group. A part of patients in DCS group this were overlapped with other studies we have previously published [11, 19].

Clinical assessment of surgery and cancer status

In the present study, curative resection was defined as surgery without macroscopically evident residual cancer. Individual patient records and clinical, surgical, and pathological findings were collected from the institute database and evaluated according to the criteria of the Japanese Research Society for Gastric Cancer [20]. Surgical complications were assessed according to the Clavien-Dindo classification [21].

Clinical response and histological evaluation of surgical specimen

In all patients, computed tomography and gastrointestinal fiberscopy were preformed before surgery; furthermore, in patients who received preoperative DCS therapy, pre-chemotherapy and post-chemotherapy evaluation was performed. The objective response to chemotherapy for metastatic lesions was evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST; version 1.0) criteria and for primary lesions according to the Japanese Research Society for Gastric Cancer [22].

All resected specimens were examined by same pathologist, and the pathological response to chemotherapy was evaluated according to the criteria of the Japanese Research Society for Gastric Cancer [22]. According to the amount of necrosis or disappearance of the tumor in the estimated total amount of the lesion, the tumors were graded as 0 to 3.Here, grade 0 meant neither necrosis nor cellular or structural change was observed throughout the lesion; grade 1a meant necrosis or disappearance of the tumor was persistent in less than one-third of the whole lesion or only cellular or structural changes were visible; grade 1b meant necrosis or disappearance of the tumor was persistent in no more than two-third of the whole lesion; grade 2 meant necrosis or disappearance of the tumor was persistent in more than two-third of the whole lesion but visible tumor cells were still observed; and grade 3 meant completely necrotic lesion and/or fibrosis was observed with or without granulomatous changes, and no visible tumor cells were observed. Lymph nodes were also assessed in the same approach; lymph nodes with findings of grade 3 were assessed as the originally metastasized lymph nodes in which tumor cells were exterminated by pre-operative chemotherapy.

Statistical analysis

The significant differences in proportions between subgroups were determined with Chi-square test. Patient survival was calculated by the Kaplan-Meier method, and log rank test was used to compare survival rate among subgroups. Cox proportional model hazards regression was used for multivariate analysis. Prognosis variables of univariate significance were selected for inclusion in the multivariate model. Statistical significance was defined as a p-value of <0.05.

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Legends of the figure

Figure 1

The overall survival ratio of patients with pre-operative DCS therapy or without pre-operative DCS therapy.

The 2-year survival ratio was 32.9% in patients without pre-operative DCS therapy, 93.8% in patients who received pre-operative DCS therapy. The difference was statistically significant (P=0.0001).

Figure 2

The relapse-free survival ratio of patients with pre-operative DCS therapy or without pre-operative DCS therapy.

The 2-year survival ratio was 28.7% in patients without pre-operative DCS therapy, 75.0% in patients who received pre-operative DCS therapy. The difference was statistically significant (P=0.0082).

Legends of the table

Table1

Pre-treatment clinical findings and histological features of surgical specimen did not differ between the groups. In pre-operative DCS therapy group, metastatic lymph node without residual tumor cells were 2-36 nodes (median 10) in all and 2-14 nodes (median 4) in PAN.

Table2

Toxicity of grade 3 or above were neutropenia (25.0%), leucopenia (18.7%), febrile neutropenia (6.3%) and diarrhea (6.3%).

Table3

Clinical responses ratios were as follows: primary lesion, 81.3%; lymph node metastasis, 68.8%; overall, 68.8%. The disease control ratio was 100%.

Table4

Pathological response (≥ grade1b) was 87.5% both in primary lesion and lymph node. The ratio of grade 3 were 25.0% both in primary lesion and lymph node..

Table5

Surgical complications were developed in 10 patients (35.7%) among without pre-operative DCS therapy group, and 5 patients (31.3%) among pre-operative DCS therapy group.

Table6

The factors contribute to overall survival were pre-operative DCS therapy, treatment period, number of lymph node metastasis and PAN metastasis in univariate analysis. In multivariate analysis, pre-operative DCS therapy was only factor contribute to overall survival.

Figure 1.

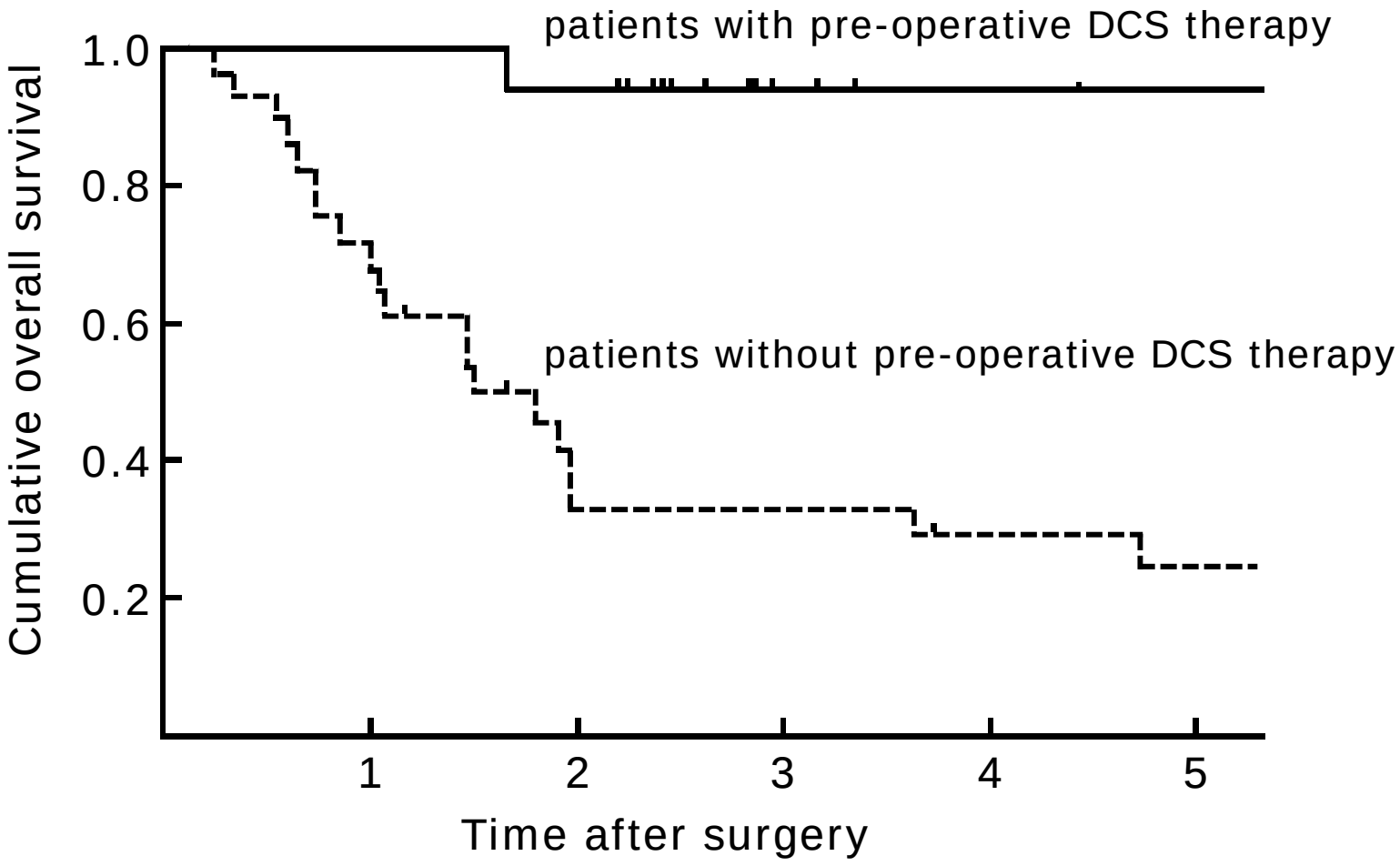

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Figure 2.

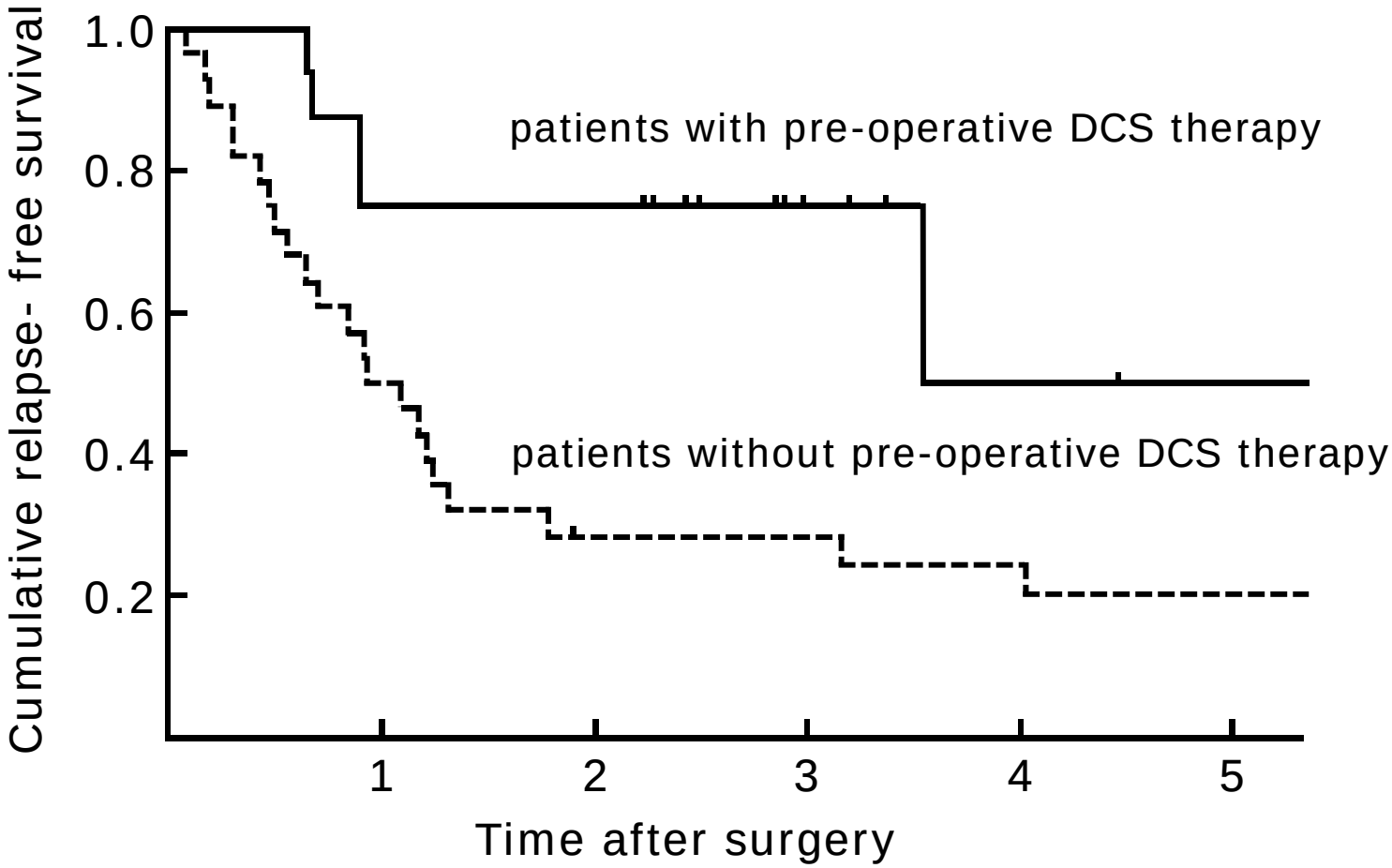

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Table Ⅰ. Patient characteristics

Patient characteristics		without DCS therapy	DCS therapy	P value
No. of patients		28	16	
SEX	male/female	17/11	13/3	0.142
Age-yr	range (median)	31-78 (58)	42-78 (61)	0.533
Clinical findings (before starting therapy)				
Tumor location	U/M/L	7/7/14	6/3/7	0.583
Tumor size-cm	range (median)	2.5-15 (7.2)	4.0-10 (5.5)	0.234
Depth of tumor invasion	T2/T3/T4	9/12/7	6/5/5	0.922
Borrmann macroscopic type	1/2/3/4	0/8/16/4	0/2/14/0	0.112
~~Hepatic metastasis~~	~~positive/negative~~	~~3/28~~	~~2/13~~	~~0.709~~
Histological findings				
Histological type	differentiated/undifferentiated	14/14	11/5	0.116
Histological findings of lymph nodes				
Number of metastatic lymph nodes	range (median)	2-67 (13)	5-49 (12)	0.591
without residual cancer cells	range (median)	-	2-36(10)	-
Number of metastatic PAN	range (median)	1-24 (4)	3-19 (3)	0.217
without residual cancer cells	range (median)	-	2-14(4)	-

Table Ⅱ. Adverse events from chemotherapy

Adverse events	grade 1	grade 2	grade 3	grade 4	incidence	incidence of grade3/4
Hematological Toxicities						
leucopenia	0	4	2	1	43.8%	18.8%
neutropenia	0	2	3	1	37.5%	25.0%
anemia	3	0	0	0	18.8%	0%
Nonhematological Toxicities						
nausea/vomiting	4	4	0	0	50%	0%
diarrhea	0	0	1	0	6.3%	6.3%
~~gastric hemorrhage~~	~~0~~	~~0~~	~~0~~	~~0~~	~~5.5%~~	~~5.5%~~
febrile neutropenia	-	-	1	0	6.3%	6.3%

Table Ⅲ. Clinical response to DCS therapy

Clinical response	No. of patients	PD	SD	PR	CR
Primary lesion	16	0	3	13	0
Lymph node	16	0	5	11	0
~~liver~~	~~2~~	~~0~~	~~0~~	~~2~~	~~0~~
overall	16	0	5	11	0

Table Ⅳ. Pathological response to DCS therapy

Pathological response	No. of patients	Grade 0	Grade 1a	Grade 1b	Grade 2	Grade 3
Primary lesion	16	0	2	2	8	4
Lymph node	16	0	2	3	7	4
~~liver~~	~~2~~	~~0~~	~~0~~	~~0~~	~~1~~	~~1~~

Table Ⅴ. Surgical complication

	without pre-operative DCS therapy (n=28)		with pre-operative DCS therapy (n=16)	
	number	incidence	number	incidence
Morbidity	10	35.7%	5	31.3%
pancreatic fistulae	1	3.6%	3	18.8%
lymphatic fistulae	1	3.6%	2	12.5%
anastomotic leakage	8	28.6%	0	0%
bleeding after surgery	1	3.6%	0	0%
~~peritoneal abscess~~	~~0~~	~~0%~~	~~0~~	~~0%~~
Mortality	0	0%	0	0%

Table VI. Survival analysis

	overall survival		
	univariate analysis	multivariate analysis	
	P	Hazard ratio (95% CI)	P
pre-operative DCS therapy (- vs. +)	0.001	0.061 (0.006 - 0.581)	0.015
treatment period (-1999 vs. 2000-)	0.002	0.858 (0.247 – 2.988)	0.810
adjuvant chemotherapy (- vs. +)	0.177	-	-
Borrmann macroscopic type (2/3 vs. 4)	0.078	-	-
histological type (intestinal vs. diffuse)	0.149	-	-
No. of lymph node metastasis (≤11 vs. 12<)	0.048	3.143 (0.737 – 13.397)	0.122
No. of PAN metastasis (≤3 vs. 4<)	0.003	1.472 (0.258 – 1.472)	0.663