Cancer Chemotherapy and Pharmacology (2019) 83:1047–1055
https://doi.org/10.1007/s00280-019-03813-6

ORIGINAL ARTICLE

Outcomes of preoperative S-1 and docetaxel combination chemotherapy in patients with locally advanced gastric cancer

Takashi Kosaka[1] · Hirotoshi Akiyama[1] · Hiroshi Miyamoto[2] · Sho Sato[2] · Yusaku Tanaka[2] · Kei Sato[2] · Chikara Kunisaki[2] · Itaru Endo[1]

Received: 5 February 2019 / Accepted: 8 March 2019 / Published online: 25 March 2019

Abstract

Purpose The therapeutic outcomes of stage III gastric cancer patient receiving D2 gastrectomy and adjuvant chemotherapy remain unsatisfactory. To improve the long-term outcomes in this population, the combination of docetaxel and S-1 (DS) therapy can be expected to be a useful regimen as neoadjuvant chemotherapy (NAC). This study aimed to prospectively evaluate the efficacy of NAC-DS for clinical stage III gastric cancer.

Methods Between January 2010 and December 2013, 26 patients were enrolled. Patients with clinical stage III gastric cancer received two courses of docetaxel 40 mg/m^2 on day 1, 15 and S-1 40 mg/m^2 bid orally on day 1–7, 15–21 every 4 weeks, followed by radical D2 gastrectomy. Short- and long-term outcomes were evaluated. This study was approved by the ethics committee of Yokohama City University, and was registered in the University Hospital Medical Information Network (UMIN) database (ID: 000011521).

Results Of 26 patients, 24 (92.3%) patients completed two courses of NAC. After NAC-DS, Grade 3 neutropenia was observed in 5 (19.2%) patients including one patient with febrile neutropenia, anemia in 1 (3.8%) patient and diarrhea in 1 (3.8%) patient. All patients underwent R0 gastrectomy and pathological response was found in 15 (57.6%) patients. Postoperatively, Clavien-Dindo grade II complication occurred in 8 (30.7%) patients and no mortality was observed. The 5-year overall survival (OS) was 57.7%, median OS was 78.7 months and recurrence free survival (RFS) was 49.0%, median RFS was 45.4 months with 66.5 months median follow-up. Pathological response (HR = 0.091, 95% CI 0.011–0.730, $p = 0.016$) and > 5% body weight loss before NAC-DS (HR = 0.133, 95% CI 0.023–0.765, $p = 0.024$) were independent risk factors for recurrence, > 5% body weight loss before NAC-DS (HR = 0.133, 95% CI 0.023–0.765, $p = 0.024$) were independent risk factors for overall survival by multivariate analysis.

Conclusions NAC-DS demonstrated acceptable toxicity with a high R0 resection rate in clinical stage III gastric cancer patients, especially in patients with good nutritional status. Further prospective study is warranted to compare the long-term outcomes between with and without NAC-DS.

Keywords Gastric cancer · Preoperative chemotherapy · S-1 · Docetaxel

Introduction

Although the incidence of gastric cancer is declining, advanced gastric cancer is the third most common cause of cancer death worldwide [1]. In Japan, the standard treatment for locally advanced gastric cancer (LAGC) is gastrectomy with D2 lymph node dissection followed by postoperative chemotherapy using S-1 for a year according to ACTS-GC trial [2]. However, follow-up study of ACTS-GC trial revealed that the efficacy of this treatment among patients with stage III disease was unsatisfactory, overall survival rates were 67.1% and 50.2% in stage IIIA and IIIB patients

✉ Takashi Kosaka
t_kosaka@yokohama-cu.ac.jp

[1] Department of Gastroenterological Surgery, Graduate School of Medicine, Yokohama City University, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan

[2] Department of Surgery, Gastroenterological Center, Yokohama City University, 4-57, Urafune-cho, Minami-ku, Yokohama 232-0024, Japan

respectively [3]. To improve the survival for stage III gastric cancer patients, some studies conducted preoperative chemotherapy [4–9]. These studies showed encouraging short- and long-term results. We also conducted a prospective single arm cohort study of neoadjuvant S-1 plus docetaxel (DS) treatment for stage III advanced gastric cancer and reported short-term outcomes [10]. The aim of this study is mainly to clarify long-term survival of patients with NAC-DS and gastrectomy.

Patients and methods

Between January 2010 and December 2013, 26 patients with clinical stage III gastric cancer were enrolled in this study. The eligibility criteria of patients, treatment, assessment, and follow-up were previously described [10]. These patients were given S-1 orally twice daily for a week according to the body surface area (BSA) as follows: < 1.25 m^2, 80 mg/day; 1.25–1.5 m^2, 100 mg/day; > 1.5 m^2, 120 mg/day. This was followed by a drug-free interval of 1 week. Docetaxel (40 mg/m^2) was administrated by intravenous infusion for 1 h in 100 ml normal saline on day1 and 15. Each course lasted for 1 month. All patients received 2 courses of treatment and lesions were evaluated by imaging study. Open R0 gastrectomy with D2 lymphadenectomy was performed in all patients within 4–8 weeks after chemotherapy. All patients were questioned about body weight in good health at first visit to our hospital and the weight were measured at first visit (preNAC), before surgery (postNAC) and 1 month after surgery respectively. The pathological response to treatment was classified according to the following criteria by the Japanese Gastric Cancer Association (JGCA) [11]. We evaluated therapeutic toxicity, clinical and pathological response, and additionally the overall (OS) and recurrence free survival (RFS) during 60.4 months median follow-up. This study was approved by the ethics committee of Yokohama City University, and was registered in the University Hospital Medical Information Network (UMIN) database (ID: 000011521) and all patients provided written informed consent.

Statistical analysis

OS and RFS was analyzed according to patient characteristics and were compared by the log-rank test. Some factors with significance in this univariate analysis were used for the Cox proportional hazard regression model to detect independent risk factors for recurrence. Statistical analysis was performed using SPSS® version 24.0 (SPSS, Chicago, IL, USA).

Table 1 Pretreatment characteristics of the patients

Characteristics	No. of patients (%)
Age (years)[a]	
Median	64
Range	45–78
Gender	
Male	20 (76.9)
Female	6 (23.1)
Performance status	
0	22 (84.6)
1	4 (15.4)
Lauren classification	
Intestinal	15 (57.6)
Diffuse	11 (42.3)
Tumor location	
U	11 (42.3)
M	9 (34.6)
L	5 (19.2)
Entire	1 (3.8)
Tstage[b]	
T3 (SS)	3 (11.5)
T4a (SE)	18 (69.2)
T4b (SI)	5 (19.2)
Nstage[b]	
N0	0
N1	10 (38.4)
N2	15 (57.6)
N3	1 (3.8)
Stage[b]	
IIIA	12 (46.2)
IIIB	10 (38.5)
IIIC	4 (15.3)

Results

Patient characteristics

A total of 26 patients (20 men and 6 women) with a median age of 64 years (range 45–78) were enrolled in this study. Patient characteristics are listed in Table 1. Most of patients were in good general condition (84.6% with a performance status of 0). Histologically, 15 (57.6%) patients had intestinal type and 11 (42.3%) had diffuse type adenocarcinoma. Moreover, 23 (88.5%) patients had tumors with serosal invasion and all patients were diagnosed as having lymph node metastasis according to findings of CT or MRI images.

Table 2 Toxicity during chemotherapy

Toxicity	No. of patients (%)	
	Grades 1–2	Grades 3–4
Hematological		
Neutro/leukopenia	6 (23.0)	5 (19.2)
Febrile neutropenia	–	1 (3.8)
Anemia	0	1 (3.8)
Thrombocytopenia	0	0
Non-hematological		
Alopecia	13 (50.0)	–
Anorexia	12 (46.1)	0
Nausea	2 (7.6)	0
Diarrhea	4 (15.3)	1 (3.8)
Dermatitis	4 (15.3)	0
General fatigue	8 (30.7)	0

Table 3 Pathological chemotherapeutic effect

Grade	No. of patients (%)
0	2 (7.6)
1a	9 (34.6)
1b	9 (34.6)
2	5 (19.2)
3	1 (3.8)

Treatment

A total of 50 courses of NAC-DS were administrated to 26 patients. Two patients could not continue this chemotherapy due to tumor bleeding and pyloric stenosis after one course was finished. The docetaxel dose was reduced from 40 to 35 mg/m^2 in two patients due to grade 4 neutropenia and the S-1 dose was reduced from 120 to 100 mg/day in two patients due to patients' intents. Doses of both drugs were reduced in one who had grade 3 diarrheas during one course.

Adverse events of NAC-DS

Treatment-related toxicities are shown in Table 2. Grade 3 or above toxicities were neutropenia in 5 (19.2%) which included one case with grade 4 febrile neutropenia, anemia in one (3.8%) and diarrhea in one (3.8%), respectively. Administration of chemotherapeutic agents was delayed for more than 7 days in 7 courses.

Efficacy of NAC-DS

Of nine patients with measurable lesions, clinical response (CR + PR) was observed in seven patients and stable disease (SD) in two patients. The clinical evaluations of 17 (65.3%) patients without measurable lesion were nonCR-nonPD and no patient had progressive disease during NAC-DS. A total of 16 (61.5%) patients underwent open total gastrectomy (OTG) and the remaining 10 (38.5%) patients did open distal gastrectomy (ODG). The mean number of retrieved lymph nodes was 40.1 (range 7–102). In the pathological evaluation, pathological response (grade 1b–3) were observed in 15 (57.7%) patients and of these, no residual disease was observed in one (3.8%) patient (Table 3).

Surgical complication

Clavien-Dindo grade II complications were observed in 8 (30.7%) patients (2 minor anastomotic leakage, 2 ileus, 1 pancreatic fistula, 1 surgical site infection, 1 urinary tract infection and 1 anastomotic stenosis). CD grade III morbidity was not occurred in any patients enrolled in this study.

Adjuvant chemotherapy

Adjuvant chemotherapy according to ACTS-GC regimen was administrated to 13 patients and 3 patients could not complete this regimen due to Grade 2 appetite loss. Completion of adjuvant chemotherapy was observed in 10 (38.5%) patients.

Recurrence and survival

During this study, recurrences were observed in 13 (50.0%) patient as follows: peritoneal carcinomatosis (PC) in 9 (34.6%), lymph node metastasis in 1 (3.8%), pulmonary metastasis in 1, liver metastasis in 1 and erector spinae muscles metastasis in one patient. The 5-year recurrence free survival rate was 49.0%, median RFS was 45.4 months (Fig. 1a) and the 5-year overall survival rate was 57.7%, median OS was 78.7 months (Fig. 1b).

Predictive factors associated with recurrence

Univariate analysis using the log-rank test revealed that > 5% preNAC bodyweight loss (BWL) (BWL < 5%/ >5%: 5YRFS = 66.8%/25.0%, $p = 0.013$) and pathological effect (+/− : 72.2%/0.0%, $p < 0.001$) influenced recurrence free survival. Multivariate analysis using two factors whose p-factors were less than 0.05 (> 5% preNAC BWL, pathological effect) revealed that > 5% pre-NAC BWL (HR = 7.518, 95% CI 1.307–43.47, $p = 0.024$) and pathological effect (HR = 0.091, 95% CI 0.011–0.730, $p = 0.016$) were independent risk factors for recurrence (Table 4).

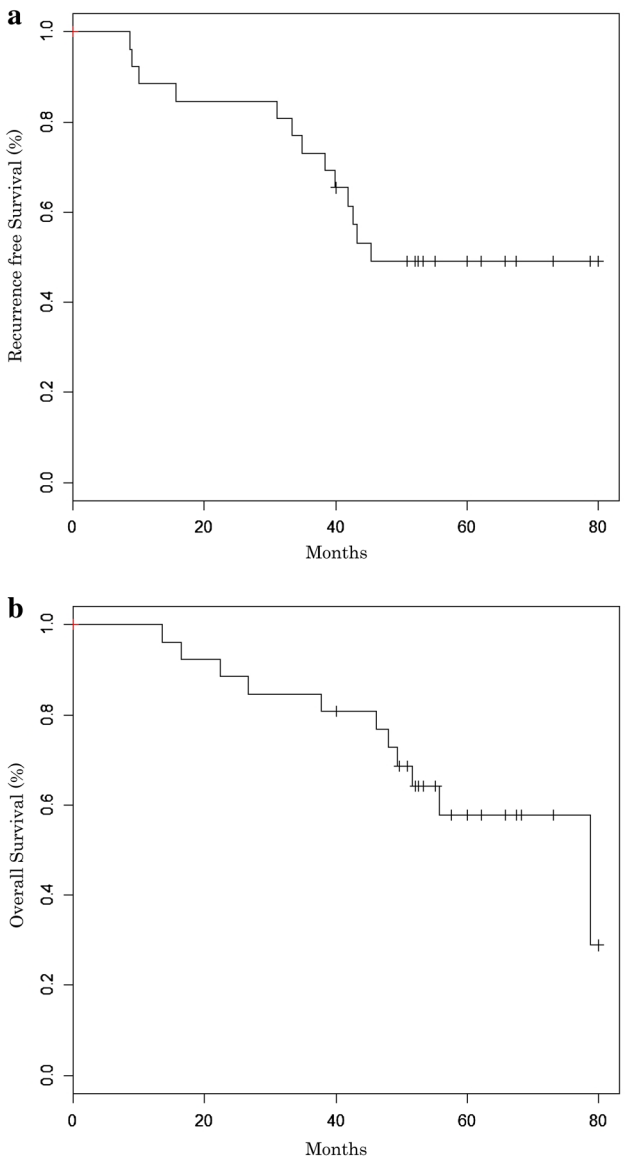

Fig. 1 **a** Recurrence free survival. The 5-year recurrence free survival rate was 49.0%, median RFS was 45.4 months. **b** Overall survival. The 5-year overall survival rate was 57.7%, median OS was 78.7 months

Predictive factors associated with overall survival

Univariate analysis revealed that > 5% pre-NAC bodyweight loss (BWL) (BWL < 5% />5%: 5YRFS = 82.5% / 33.3%, $p = 0.003$) and pathological effect (+/− : 80.0%/22.7%, $p = 0.008$) were prognostic indicator of overall survival. Multivariate analysis revealed that > 5% preNAC BWL (HR = 1.389, 95% CI 1.361–142.85, $p = 0.026$) was independent risk factor for overall survival (Table 5).

Discussion

This study reported short-term and long-term results of patients with neoadjuvant chemotherapy with S-1 and docetaxel followed by surgery after 60.4 months median follow-up.

Recurrence was unexpectedly frequent at 2 years after initial treatments in this study. In the CROSS trial, therapeutic outcomes were compared between neoadjuvant chemoradiation plus surgery and surgery alone for oesophageal or oesophagogastric junction cancer after a median follow-up of 84.1 months. Preoperative therapies mainly suppressed distant metastasis during the first 24 months [recurrence rate (%): NAC/surgery alone = 28/40] and the preventive effects of NAC gradually weakened after 24 months [recurrence rate (%): NAC/surgery alone = 11/8] [12]. NAC-DS in the present study was also effective for recurrence during first 24 months, but could not effectively suppress recurrence after 2 years. The incidence of recurrence was 15.4% within the first 24 months and 34.6% after 24 months, respectively. Two-third of recurrences was detected after 2 years from the initial treatment. These findings may suggest that NAC has an effect on the delay of growing of micro-metastasis but is less effective to diminish these lesions. In several reports concerning NAC [4–9, 13–19], median follow-up periods were about 36 months (12.6–40.9 months). Therefore, longer follow-up is necessary to confirm survival benefits of NAC for gastric cancer.

The rate of PC recurrence was 9/13 (69.2%) and it was the most frequent relapse type in the present study. PC is common recurrent pattern after curative gastrectomy for advanced gastric cancer without NAC respectively and its rates were 32.1–59.2% in previous reports [20–23] and the rate was similar, 32.9–46.4% among gastric cancer with NAC [7,]. Preoperative chemotherapy including this study could not defeat peritoneal seedings even though the principal risk factor for PC development was serosal exposure of gastric cancer lesion, which almost patients with NAC tend to have. A previous study reported that antitumoral agents were limitedly delivered to peritoneal cavity due to peritoneum-plasma barrier [13, 24] and some other studies argued that insufficient efficacy of conventional systemic chemotherapy including NAC on PC [14, 15]. The strategy focused on peritoneal lesion, for example intraperitoneal chemotherapy [16] may be needed to improve the survival results.

Pathological response rate (PRR) was one of the predictive factors for recurrence but not for overall survival in the present study. In the recent literatures [4–9, 25–28], PRR widely varied 17–87.5% and the significance of pathological response on survival in AGC patients receiving NAC was also controversial [27, 29–33]. Several tumor regression

Table 4 Predictive factors associated with recurrence

	n	Univariate		Multivariate	
		5Y-RFS (%)	*p* value	HR (95% CI)	*p* value
Age			0.305		
< 70	16	39.4			
> 70	10	57.1			
Sex			0.587		
Male	20	52.1			
Female	6	33.3			
ASA score			0.320		
1	12	50.0			
2	14	42.9			
PreNAC BWL > 5%			0.013	7.518 (1.307–43.47)	0.024
0	14	66.8			
1	12	25.0			
PreNAC PNI < 45			0.259		
0	18	41.2			
1	8	60.0			
PreNAC c-stage			0.267		
IIIA	12	66.7			
IIIB-	14	35.7			
G3 adverse event during NAC			0.499		
0	19	42.5			
1	7	57.1			
PostNAC BWL > 3%			0.367		
0	15	57.8			
1	11	34.1			
PostNAC PNI < 45			0.873		
0	13	45.4			
1	13	40.4			
Operation			0.948		
OTG	16	48.6			
ODG	10	43.8			
Surgical morbidity			0.957		
0	18	46.2			
1	8	50.0			
Lauren classification			0.189		
Intestinal	15	55.4			
Diffuse	11	34.1			
p-effect			< 0.001	0.091 (0.011–0.730)	0.016
0	11	0.0			
1	15	72.2			
POM1 BWL > 5%			0.113		
0	10	30.0			
1	16	59.1			
POM1 PNI < 43			0.184		
0	12	65.6			
1	14	33.3			
Adjuvant chemotherapy			0.911		
0	16	46.4			
1	10	43.0			

Table 5 Predictive factors associated with overall survival

	n	Univariate		Multivariate	
		5Y-RFS (%)	*p* value	HR (95% CI)	*p* value
Age			0.840		
< 70	16	58.9			
> 70	10	60.0			
Sex			0.373		
Male	20	67.5			
Female	6	33.3			
ASA score			0.333		
1	12	61.7			
2	14	57.1			
PreNAC BWL > 5%			0.003	1.389 (1.361–142.85)	0.026
0	14	82.5			
1	12	33.3			
PreNAC PNI < 45			0.809		
0	18	61.2			
1	8	58.3			
PreNAC c-stage			0.139		
IIIA	12	83.3			
IIIB-	14	41.7			
G3 adverse event during NAC			0.459		
0	19	53.8			
1	7	71.4			
PostNAC BWL > 3%			0.602		
0	15	66.7			
1	11	50.9			
PostNAC PNI < 45			0.559		
0	13	69.2			
1	13	51.3			
Operation			0.765		
OTG	16	61.9			
ODG	10	56.0			
Surgical morbidity			0.984		
0	18	59.3			
1	8	62.5			
Lauren classification			0.715		
Intestinal	15	57.1			
Diffuse	11	63.6			
p-effect			0.008		
0	11	22.7			
1	15	80.0			
POM1 BWL > 5%			0.303		
0	10	48.0			
1	16	68.8			
POM1 PNI < 43			0.432		
0	12	61.7			
1	14	57.1			
Aduvant chemotherapy			0.531		
0	16	53.6			
1	10	70.0			

scales were used in these studies, the threshold line divided responder and non-responder was defined as less than 10% residual cancer cells in whole body of tumor by Becker regression criteria [34], 50% by Mandard et al. [35] and 67% by JCGC criteria [11]. Pathological response should be assessed with standardized criteria and the value of it as surrogate marker for survival and indicator for postoperative adjuvant chemotherapy after NAC should be evaluated in the further trial.

Another prognostic factor in this study was > 5% preoperative body weight loss (BWL) which was the one of agreed diagnostic criteria for cachexia of malignant disease [36, 37]. Some studies showed that pretreatment BWL is the important malnutritional index and could serve the useful predictor of survival in gastric, esophageal, and head/neck cancers [38–41]. The mechanism seemed to be that malnutrition impaired immune response including anti-tumoral immunity and caused inflammatory activity and postoperative complications. A study showed the severe BWL was associated with decreased survival in patients receiving chemotherapy [38] and another study reported that patients with > 10% preoperative BWL had better OS than those with surgery plus adjuvant chemotherapy [41]. Patients with > 5% preoperative BWL might not benefit from preoperative chemotherapy in this study and whether these patients should undergo NAC or other strategies such as straightforward gastrectomy or nutritional intervention should be discussed in further analysis.

There are some limitations in this study. This study was single arm with small sample size and held in single institute. Moreover, methods to evaluate tumor stage before NAC in respect to the diagnostic modalities whether PETCT, EUS were adopted or not and the indication of postoperative chemotherapy was not clearly defined. Although we inquired all patients about body weight in good health at first presentation, the values were not measured precisely and might be uncertain.

In conclusion, the results of the current study indicate that the NAC-DS demonstrated acceptable toxicity with a high R0 resection rate in clinical stage III gastric cancer patients, especially in patients with good nutritional status. However, a well-designed phase III trial with long follow-up should be conducted to confirm the therapeutic effect of NAC-DS for gastric cancer to confirm the efficacy of this treatment.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136(5):E359–E386
2. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K, ACTS-GC Group (2007) Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357(18):1810–1820
3. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y (2011) Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 29(33):4387–4393
4. Park I, Ryu MH, Choi YH, Kang HJ, Yook JH, Park YS, Kim HJ, Jung HY, Lee GH, Kim KC, Kim BS, Kang YK (2013) A phase II study of neoadjuvant docetaxel, oxaliplatin, and S-1 (DOS) chemotherapy followed by surgery and adjuvant S-1 chemotherapy in potentially resectable gastric or gastroesophageal junction adenocarcinoma. Cancer Chemother Pharmacol 72(4):815–823
5. Hirakawa M, Sato Y, Ohnuma H, Takayama T, Sagawa T, Nobuoka T, Harada K, Miyamoto H, Sato Y, Takahashi Y, Katsuki S, Hirayama M, Takahashi M, Ono M, Maeda M, Takada K, Hayashi T, Sato T, Miyanishi K, Takimoto R, Kobune M, Hirata K, Kato J (2013) A phase II study of neoadjuvant combination chemotherapy with docetaxel, cisplatin, and S-1 for locally advanced resectable gastric cancer: nucleotide excision repair (NER) as potential chemoresistance marker. Cancer Chemother Pharmacol 71(3):789–797
6. Oki E, Emi Y, Kusumoto T, Sakaguchi Y, Yamamoto M, Sadanaga N, Shimokawa M, Yamanaka T, Saeki H, Morita M, Takahashi I, Hirabayashi N, Sakai K, Orita H, Aishima S, Kakeji Y, Yamaguchi K, Yoshida K, Baba H, Maehara Y (2014) Phase II study of docetaxel and S-1 (DS) as neoadjuvant chemotherapy for clinical stage III resectable gastric cancer. Ann Surg Oncol 21(7):2340–2346
7. Yoshikawa T, Morita S, Tanabe K, Nishikawa K, Ito Y, Matsui T, Fujitani K, Kimura Y, Fujita J, Aoyama T, Hayashi T, Cho H, Tsuburaya A, Miyashita Y, Sakamoto J (2016) Survival results of a randomised two-by-two factorial phase II trial comparing neoadjuvant chemotherapy with two and four courses of S-1 plus cisplatin (SC) and paclitaxel plus cisplatin (PC) followed by D2 gastrectomy for resectable advanced gastric cancer. Eur J Cancer 62:103–111
8. Migita K, Nashimoto A, Yabusaki H, Matsuki A, Aizawa M (2016) Efficacy of neoadjuvant chemotherapy with docetaxel, cisplatin and S-1 for resectable locally advanced gastric cancer. Int J Clin Oncol 21(1):102–109
9. Sasaki K, Onodera S, Otsuka K, Satomura H, Kurayama E, Kubo T, Takahashi M, Ito J, Nakajima M, Yamaguchi S, Miyachi K, Kato H (2017) Validity of neoadjuvant chemotherapy with docetaxel, cisplatin, and S-1 for resectable locally advanced gastric cancer. Med Oncol 34(8):139
10. Kosaka T, Akiyama H, Makino H, Takagawa R, Kimura J, Ono H, Kunisaki C, Endo I (2014) Preoperative S-1 and docetaxel combination chemotherapy in patients with locally advanced gastric cancer. Cancer Chemother Pharmacol 73(2):281–285
11. Japanese Gastric Cancer Association (2011) Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 14(2):101–112
12. Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, van Laarhoven HWM, Nieuwenhuijzen GAP, Hospers GAP, Bonenkamp JJ, Cuesta MA,

Blaisse RJB, Busch ORC, Ten Kate FJW, Creemers GM, Punt CJA, Plukker JTM, Verheul HMW, Bilgen EJS, van Dekken H, van der Sangen MJC, Rozema T, Biermann K, Beukema JC, Piet AHM, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A, CROSS study group (2015) Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 16(9):1090–1098

13. Kurokawa Y, Hamakawa T, Miyazaki Y, Takahashi T, Yamasaki M, Miyata H, Nakajima K, Takiguchi S, Mori M, Doki Y (2015) Preoperative systemic and intraperitoneal chemotherapy consisting of S-1, cisplatin and docetaxel in patients with marginally resectable gastric cancer. Anticancer Res 35(4):2223–2228
14. Kobayashi D, Kodera Y (2017) Intraperitoneal chemotherapy for gastric cancer with peritoneal metastasis. Gastric Cancer 20(Suppl 1):111–121
15. An JY, Kim HI, Cheong JH, Hyung WJ, Kim CB, Noh SH (2013) Pathologic and oncologic outcomes in locally advanced gastric cancer with neoadjuvant chemotherapy or chemoradiotherapy. Yonsei Med J 54(4):888–894
16. Kitayama J, Ishigami H, Yamaguchi H, Yamashita H, Emoto S, Kaisaki S, Watanabe T (2014) Salvage gastrectomy after intravenous and intraperitoneal paclitaxel (PTX) administration with oral S-1 for peritoneal dissemination of advanced gastric cancer with malignant ascites. Ann Surg Oncol 21(2):539–546
17. Yoshikawa T, Sasako M, Yamamoto S, Sano T, Imamura H, Fujitani K, Oshita H, Ito S, Kawashima Y, Fukushima (2009) Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. NBr J Surg 96(9):1015–1022
18. Oyama K, Fushida S, Kinoshita J, Makino I, Nakamura K, Hayashi H, Nakagawara H, Tajima H, Fujita H, Takamura H, Ninomiya I, Kitagawa H, Tani T, Fujimura T, Ohta T (2012) 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. J Surg Oncol 105(6):535–541
19. 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 (2013) 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 107(7):741–745
20. Spolverato G, Ejaz A, Kim Y, Squires MH, Poultsides GA, Fields RC, Schmidt C, Weber SM, Votanopoulos K, Maithel SK, Pawlik TM (2014) Rates and patterns of recurrence after curative intent resection for gastric cancer: A United States multi-institutional analysis. J Am Coll Surg 219(4):664–675
21. Chang JS, Kim KH, Keum KC, Noh SH, Lim JS, Kim HS, Rha SY, Lee YC, Hyung WJ, Koom WS (2016) Recursive partition analysis of peritoneal and systemic recurrence in patients with gastric cancer who underwent D2 gastrectomy: Implications for neoadjuvant therapy consideration. J Surg Oncol 114(7):859–864
22. Kawamura Y, Satoh S, Umeki Y, Ishida Y, Suda K, Uyama I (2016) Evaluation of the recurrence pattern of gastric cancer after laparoscopic gastrectomy with D2 lymphadenectomy. Springerplus 5(1):821
23. Aoyama T, Yoshikawa T, Hayashi T, Kuwabara H, Mikayama Y, Ogata T, Cho H, Tsuburaya A (2012) Risk factors for peritoneal recurrence in stage II/III gastric cancer patients who received S-1 adjuvant chemotherapy after D2 gastrectomy. Ann Surg Oncol 19(5):1568–1574
24. Jacquet P, Sugarbaker PH (1996) Peritoneal-plasma barrier. Cancer Treat Res 82:53–63
25. Tsuburaya A, Mizusawa J, Tanaka Y, Fukushima N, Nashimoto A, Sasako M, Stomach Cancer Study Group of the Japan Clinical Oncology Group (2014) 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 101(6):653–660
26. Wang Y, Yu YY, Li W, Feng Y, Hou J, Ji Y, Sun YH, Shen KT, Shen ZB, Qin XY, Liu TS (2014) A phase II trial of Xeloda and oxaliplatin (XELOX) neo-adjuvant chemotherapy followed by surgery for advanced gastric cancer patients with para-aortic lymph node metastasis. Cancer Chemother Pharmacol 73(6):1155–1161
27. Wang X, Zhao L, Liu H, Zhong D, Liu W, Shan G, Dong F, Gao W, Bai C, Li X (2016) A phase II study of a modified FOLFOX6 regimen as neoadjuvant chemotherapy for locally advanced gastric cancer. Br J Cancer 114(12):1326–1333
28. Ito S, Sano T, Mizusawa J, Takahari D, Katayama H, Katai H, Kawashima Y, Kinoshita T, Terashima M, Nashimoto A, Nakamori M, Onaya H, Sasako M (2017) A phase II study of preoperative chemotherapy with docetaxel, cisplatin, and S-1 followed by gastrectomy with D2 plus para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis: JCOG1002. Gastric Cancer 20(2):322–331
29. Kurokawa Y, Shibata T, Sasako M, Sano T, Tsuburaya A, Iwasaki Y, Fukuda H (2014) Validity of response assessment criteria in neoadjuvant chemotherapy for gastric cancer (JCOG0507-A). Gastric Cancer 17(3):514–521
30. Tahara T, Shibata T, Okubo M, Yoshida D, Kawamura T, Horiguchi N, Ishizuka T, Nagasaka M, Nakagawa Y, Ohmiya N (2017) Histological evaluations of primary lesions are independently associated with prognosis in patients with gastric cancer who receive neoadjuvant chemotherapy. Oncol Lett 13(6):4892–4896
31. Heger U, Bader F, Lordick F, Burian M, Langer R, Dobritz M, Blank S, Bruckner T, Becker K, Herrmann K, Siewert JR, Ott K (2014) Interim endoscopy results during neoadjuvant therapy for gastric cancer correlate with histopathological response and prognosis. Gastric Cancer 17(3):478–488
32. Fujitani K, Mano M, Hirao M, Kodama Y, Tsujinaka T (2012) Posttherapy nodal status, not graded histologic response, predicts survival after neoadjuvant chemotherapy for advanced gastric cancer. Ann Surg Oncol 19(6):1936–1943
33. Schmidt T, Sicic L, Blank S, Becker K, Weichert W, Bruckner T, Parakonthun T, Langer R, Büchler MW, Siewert JR, Lordick F, Ott K (2014) Prognostic value of histopathological regression in 850 neoadjuvantly treated oesophagogastric adenocarcinomas. Br J Cancer 110(7):1712–1720
34. Becker K, Mueller JD, Schulmacher C, Ott K, Fink U, Busch R, Böttcher K, Siewert JR, Höfler H (2003) Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. Cancer 98(7):1521–1530
35. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, Roussel A, Jacob JH, Segol P, Samama G (1994) Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathol Correlat Cancer 73(11):2680–2686
36. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, Jatoi A, Kalantar-Zadeh K, Lochs H, Mantovani G, Marks D, Mitch WE, Muscaritoli M, Najand A, Ponikowski P, Rossi Fanelli F, Schambelan M, Schols A, Schuster M, Thomas D, Wolfe R, Anker SD (2008) Cachexia: a new definition. Clin Nutr 27(6):793–799
37. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE (2011) Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 12(5):489–495
38. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, Cohen MH, Douglass HO Jr, Engstrom PF, Ezdinli EZ, Horton J,

Johnson GJ, Moertel CG, Oken MM, Perlia C, Rosenbaum C, Silverstein MN, Skeel RT, Sponzo RW, Tormey DC (1980) Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med 69(4):491–497
39. Langius JA, Bakker S, Rietveld DH, Kruizenga HM, Langendijk JA, Weijs PJ, Leemans CR (2013) Critical weight loss is a major prognostic indicator for disease-specific survival in patients with head and neck cancer receiving radiotherapy. Br J Cancer 109(5):1093–1099
40. van der Schaaf MK, Tilanus HW, van Lanschot JJ, Johar AM, Lagergren P, Lagergren J, Wijnhoven BP (2014) The influence of preoperative weight loss on the postoperative course after esophageal cancer resection. J Thorac Cardiovasc Surg 147(1):490–495
41. Liu X, Qiu H, Kong P, Zhou Z, Sun X (2017) Gastric cancer, nutritional status, and outcome. Onco Targets Ther 10:2107–2114