CANCER DIAGNOSIS & PROGNOSIS
1: 185-191 (2021) doi: 10.21873/cdp.10025

Survival Benefit of Neoadjuvant Chemotherapy for Locally Advanced Adenocarcinoma of Esophagogastric Junction

SATOSHI SUZUKI, SHINGO KANAJI, NAOKI URAKAWA, GOSUKE TAKIGUCHI, HIROSHI HASEGAWA, YOSHIKO MATSUDA, KIMIHIRO YAMASHITA, TAKERU MATSUDA, TARO OSHIKIRI, TETSU NAKAMURA and YOSHIHIRO KAKEJI

Division of Gastrointestinal Surgery, Department of Surgery, Graduate School of Medicine, Kobe University, Kobe, Japan

Abstract. *Background/Aim: Adenocarcinoma of the esophagogastric junction (AEG) is refractory even when curative resection is followed by adjuvant chemotherapy. This study evaluated the efficacy of neoadjuvant chemotherapy (NAC) using an oral fluoropyrimidine-platinum regimen for AEG. Patients and Methods: Out of 35 patients with locally advanced AEG who underwent curative resection, 21 who underwent surgery first and 14 who received NAC were retrospectively compared in terms of survival. Results: The NAC regimens comprised of S-1 or capecitabine plus oxaliplatin or cisplatin; trastuzumab was added to six borderline resectable cases. The downstaging rate was 50% and the pathological response rate including complete response (29%) was 50%. The three-year relapse-free survival in the NAC group was significantly superior than the surgery-first group (78% vs. 22%, p=0.011). The NAC group had a significantly longer median survival time than the surgery-first group (NR vs. 29 months, p=0.032). Conclusion: NAC using an oral fluoropyrimidine-platinum regimen may provide survival benefit in AEG.*

Correspondence to: Satoshi Suzuki, Division of Gastrointestinal Surgery, Department of Surgery, Graduate School of Medicine, Kobe University, 7-5-2 Kusunoki-cho, Chuo-ku, Hyogo, Kobe 650-0017, Japan. Tel: +81 783825925, Fax: +81 783825939, e-mail: ss147@med.kobe-u.ac.jp

Key Words: Adenocarcinoma of esophagogastric junction, neoadjuvant chemotherapy, prognosis.

The incidence of adenocarcinoma of esophagogastric junction (AEG) has increased globally (1, 2). Although surgery is the mainstay of treatment for locally advanced AEG, prognosis remains poor even after complete resection (3). Therefore, multimodality approaches, such as preoperative (neoadjuvant) and postoperative (adjuvant) therapies, including chemotherapy or chemoradiation, have been developed to improve survival (4-8). Combined modality therapy is currently incorporated in treatment guidelines (9, 10), but the recommended strategies differ across countries and even centers, and the best approach has not been clearly established. In Japan, the standard treatment for resectable AEG, based on the results of clinical trials for stage II/III gastric cancer, is a primary resection followed by adjuvant chemotherapy (11-13); however, the therapeutic outcomes are unsatisfactory. A more intensive strategy to improve prognosis is required for this disease.

Neoadjuvant chemotherapy (NAC) represents an advantage over adjuvant chemotherapy because it is administered before surgery, whereas the intensive adjuvant setting is limited by the poor compliance of post-gastrectomy patients to chemotherapy during the postoperative recovery phase (14, 15). Some clinical trials and experimental studies have demonstrated the survival benefits of preoperative chemotherapy for AEG (16-18). Infusional 5-FU-based regimens such as cisplatin and fluorouracil (CS), epirubicin and cisplatin plus either fluorouracil or capecitabine (ECF/EOX), and fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) are conventionally used as preoperative and perioperative chemotherapy for AEG in Western countries (4-6), while oral fluoropyrimidine such as S-1 or capecitabine-based regimens for unresectable or recurrent gastric adenocarcinoma are generally adopted for neoadjuvant settings in Japan (18-20). However, few studies have investigated the efficacy of NAC using an oral fluoropyrimidine regimen for resectable AEG.

In this retrospective study, we aimed to compare the therapeutic outcomes of patients with locally advanced AEG between patients who had surgery first and patients who had surgery after NAC using an oral fluoropyrimidine-platinum regimen and to evaluate the potential benefit of NAC on prognosis.

Patients and Methods

Patients. A total of 35 patients with locally advanced AGE underwent surgery with curative intent at the Kobe University Hospital from January 2007 to December 2018. Of these, 21 patients underwent surgery first (surgery first group) and 14 patients received NAC before surgery (NAC group). We analyzed the patients' clinicopathological and treatment data extracted from medical records. The clinical stage was assessed by esophagogastroduodenoscopy (EGD) and a thoracoabdominal computed tomography (CT) scan and was diagnosed according to the Japanese classification of gastric carcinoma (21). The eligibility criteria for NAC were as follows: cT2 or deeper tumor or cN+ stage. During the NAC sessions, six patients received the SOX regimen, two received the CS regimen, and six received the XP plus trastuzumab regimen. The SOX regimen consisted of three cycles of oral S-1 (40 mg/m^2 twice daily on days 1-14, followed by a one-week rest period) and an intravenous infusion of oxaliplatin (130 mg/m^2 on day 1). The CS regimen consisted of two courses of oral S-1 (40 mg/m^2 twice daily on days 1-21, followed by a one-week rest period) and an intravenous infusion of cisplatin (60 mg/m^2 on day 8). For marginally resectable HER2-positive tumors with invasion to adjacent organs or metastases to extensive lymph nodes, XP plus trastuzumab was administered *via* two cycles of oral capecitabine (2,000 mg/m^2 twice daily on days 1-14) and intravenous cisplatin (60 mg/m^2 on day 1) plus trastuzumab (8 mg/kg during the first cycle and 6 mg/kg during the second cycle on day 1). For the patients who underwent NAC, EGD and a CT scan were repeated once each cycle of chemotherapy to evaluate the clinical response. The pathological response was evaluated based on the Japanese classification of gastric carcinoma: Grade 0, no evidence of effect; Grade 1a, viable tumor cells occupy more than 2/3 of the tumorous area; Grade 1b, viable tumor cells remain in more than 1/3 but less than 2/3 of the tumorous area; Grade 2, viable tumor cells remain in less than 1/3 of the tumorous area; Grade 3, no viable tumor cells remain (21). Adverse events associated with chemotherapy were accessed by the Common Terminology Criteria for Adverse Events (version 5.0).

Siewert type I tumors were resected by transthoracic esophagectomy with two-field lymph node dissection and gastric conduit reconstruction. Siewert type II/III tumors were resected by a transhiatal abdominothoracic lower esophagectomy and total or proximal gastrectomy with intrathoracic reconstruction. Postoperative morbidities higher than grade II on the Clavien-Dindo classification were defined as morbidities (22). Morbidities higher than grade IIIa were defined as severe. Adjuvant chemotherapy was adopted for pathological stage II/III disease in both groups. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki. This study was approved by the Institutional Review Board of the Graduate School of Medicine, Kobe University (approval number: B200093).

Table I. *Patient and tumor characteristics*.

Variables	Surgery first (n=21) n (%)	NAC (n=14) n (%)	*p*-Value
Age (years) (median, range)	73.5 (62-84)	67 (47-80)	0.071
Gender			0.652
Male	15 (71)	10 (71)	
Female	6 (29)	5 (29)	
ASA-PS			0.600
≤2	20 (95)	15 (100)	
3	1 (5)	0	
Histology			0.304
Differentiated type	15 (71)	8 (57)	
Undifferentiated type	6 (29)	6 (43)	
Tumor location			0.460
Siewert I	0	1 (7)	
Siewert II	18 (86)	11 (73)	
Siewert III	3 (14)	2 (20)	
Clinical T category*			0.007
T2	2 (10)	1 (7)	
T3	18 (86)	6 (43)	
T4	1 (5)	7 (50)	
Clinical N category*			0.100
N0	9 (43)	1 (7)	
N1	8 (38)	8 (57)	
N2	4 (19)	4 (29)	
N3	0	1 (7)	
Clinical M category*			1.000
M0	16 (100)	14 (100)	
M1	0	0	
Clinical Stage*			0.233
I	3 (13)	0	
II	14 (69)	9 (64)	
III	4 (19)	5 (36)	

ASA-PS: American Society of Anesthesiologists Physical Status; NAC: neoadjuvant chemotherapy; *according to the Japanese classification of gastric carcinoma.

Statistical analyses. Statistical comparisons between the two groups were performed with the Mann-Whitney *U*-test for continuous variables and with the Chi-square test and Fisher's exact test for categorical variables, as appropriate. Overall survival (OS) was defined as the period from the date of surgery to death from any cause or the last follow-up date. Relapse-free survival (RFS) was defined as the period from the date of surgery to recurrence or death. The cumulative survival rate was estimated using the Kaplan-Meier method, and were compared using the log-rank test. *p*-Values <0.05 were considered statistically significant. All statistical analyses were performed using JMP statistical software, ver. 14 (SAS, Cary, NC, USA).

Results

Clinicopathological characteristics did not differ significantly between the two groups in terms of gender, American Society of Anesthesiologists Physical Status (ASA-PS), and tumor

Table II. *Neoadjuvant chemotherapy-related adverse events.*

Toxicities	Grade 1	Grade 2	Grade 3	Grade 4	% Grade ≥3
Hematologic					
Leukopenia	0	2	1	1	14
Neutropenia	0	2	1	1	14
Thrombocytopenia	0	0	0	2	14
Anemia	0	0	0	0	0
AST	1	0	0	0	0
ALT	0	0	0	0	0
Total bilirubin	0	0	0	0	0
Creatinine	0	1	0	0	0
Non-hematologic					
Anorexia	0	0	0	0	0
Nausea	0	1	0	0	0
Vomiting	0	0	0	0	0
Diarrhea	0	2	0	0	0
Stomatitis	0	0	0	0	0
Fatigue	0	0	0	0	0
Neurosensory	0	0	0	0	0
Febrile neutropenia	0	0	1	0	7

AST: Aspartate transaminase; ALT: alanine transaminase.

location, although the surgery first group tended to have a higher median age (p=0.071, Table I). The NAC group had a more advanced cT category than the primary surgery group (p=0.007). Likewise, the cN category tended to be more advanced in the NAC group (p=0.100). Table II shows the adverse events of NAC in the 14 patients. Grade 3 or 4 adverse events recorded during NAC included leukopenia (14%), neutropenia (14%), thrombocytopenia (14%), and febrile neutropenia (7%) in four total patients; no chemotherapy-related deaths occurred. A total of 71% of patients completed the planned courses of NAC. The therapeutic outcomes are presented in Table III. There was no significant difference in the operative procedure. R0 resection was achieved in all 35 patients. The (y)pT and (y)pStage categories in the NAC group were significantly less advanced than those in the surgery first group (p=0.014 and p=0.019, respectively). A clinical downstage effect of NAC was observed in seven patients (50%), and no patients exhibited disease progression. The pathological response of the primary tumor was distributed as follows: grade 1a in seven patients, grade 1b in one patient, grade 2 in two patients, and grade 3 in four patients; thus, the response rate was 50% (7 of 14 patients). Of the six patients who received additional trastuzumab, three (50%) downstaging and two (33%) pathological grade 3 responses were obtained. Adjuvant chemotherapy was continued for six patients in each group. The NAC group had a significantly lower rate of recurrence than the surgery first group (21% *vs*. 62%, p=0.019). Postoperative morbidities are summarized in Table IV. Grade II or higher morbidities were observed in 10 patients (48%) in surgery first group and 8 patients (57%) in NAC group (p=0.58). Grade III or higher morbidities were observed in 8 patients (38%) in surgery first group and 3 patients (21%) in NAC group (p=0.25). The median follow-up period was 39.5 months. NAC was significantly associated with superior three-year relapse-free survival (RFS) compared to surgery first [78% (95% confidence interval (CI)=0.39-0.94) *vs*. 22% (95%

Table III. *Therapeutic outcomes.*

Variables	Surgery first (n=21) n (%)	NAC (n=14) n (%)	p-Value
Surgical approach			0.165
Abdominal	20 (95)	11 (79)	
Abdominothoracic	1 (5)	3 (21)	
R status			1.000
0	16 (100)	14 (100)	
1/2	0	0	
(y)pathological T category*			0.014
T0	0	4 (29)	
T1	0	2 (14)	
T2	2 (10)	0	
T3	13 (62)	7 (50)	
T4	6 (29)	1 (7)	
(y)pathological N category*			0.277
N0	4 (19)	7 (50)	
N1	6 (29)	3 (21)	
N2	6 (29)	2 (14)	
N3	5 (24)	2 (14)	
(y)pathological M category*			0.647
M0	20 (95)	13 (93)	
M1	1 (5)	1 (7)	
(y)pathological Stage*			0.019
0	0	4 (29)	
I0	2 (14)		
II	8 (38)	4 (29)	
III	12 (57)	3 (21)	
IV	1 (5)	1 (7)	
Clinical downstaging			
Present		7 (50)	
Absent		7 (50)	
Pathological response			
Grade 1a		7 (50)	
Grade 1b		1 (7)	
Grade 2a		1 (7)	
Grade 2b		1 (7)	
Grade 3		4 (29)	
Adjuvant chemotherapy			0.303
Present	6 (29)	6 (43)	
Absent	15 (71)	8 (57)	
Recurrence	13 (62)	3 (21)	0.019
Hematogenous	5 (24)	1 (7)	
Lymphogenous	5 (24)	1 (7)	
Dissemination	1 (5)	1 (7)	
Locoregional	2 (10)	0	

NAC: Neoadjuvant chemotherapy; R: residual tumor; (y): classification after initial multimodality treatment; *according to the Japanese classification of gastric carcinoma.

Table IV. *Postoperative morbidities*.

Event	Grade I	Grade II	Grade III	Grade IV	% Grade ≥III
Surgery first (n=21)					
Anastomotic leakage	0	0	3	0	14
Pancreatic fistula	0	2	3	0	14
Ileus	0	0	1	0	5
Reflux esophagitis	0	0	0	0	0
Pneumonia	0	1	0	0	0
Atelectasis	0	0	0	0	0
Venous thromboembolism	0	1	0	0	0
NAC (n=14)					
Anastomotic leakage	0	0	2	0	14
Pancreatic fistula	0	0	0	0	0
Ileus	0	0	0	0	0
Reflux esophagitis	0	1	0	0	0
Pneumonia	0	1	1	0	5
Atelectasis	0	3	0	0	0
Venous thromboembolism	0	0	0	0	0

Grade: Clavien-Dindo classification; NAC: neoadjuvant chemotherapy.

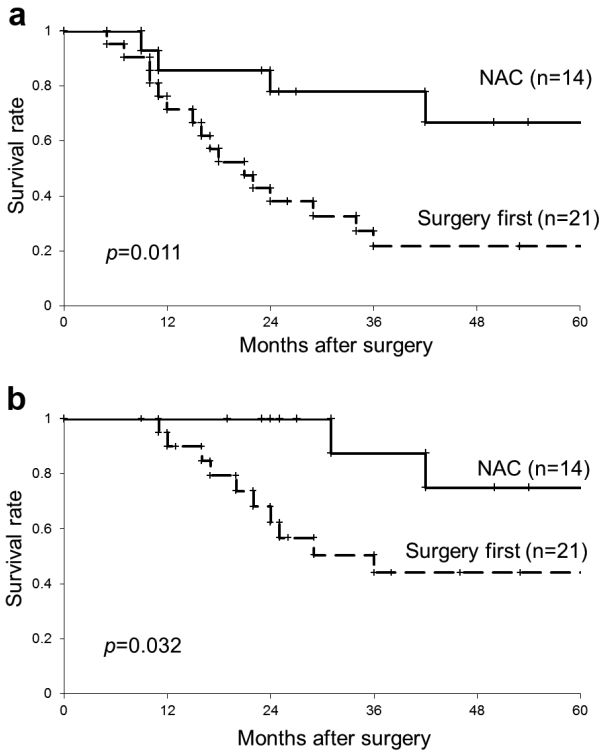

Figure 1. *Kaplan-Meier survival curves of patients with AEG treated with surgery first and with NAC. (A) Relapse-free survival. (B) Overall survival.*

CI=0.03-0.40), p=0.011, Figure 1a]. The overall survival (OS) was significantly longer in the NAC group than in the surgery first group [median survival, not reached (95% CI=0.45-1.00) *vs*. 29 months (95% CI=0.21-0.68), p=0.032, Figure 1b].

Discussion

The present study demonstrated that the OS and RFS were significantly superior in patients who received NAC with an oral fluoropyrimidine-platinum regimen compared to those who underwent primary resection for locally advanced AEG.

A global standard regimen for AEG consists of a fluoropyrimidine plus a platinum compound. In addition, the ToGA trial demonstrated that the addition of trastuzumab to a combination of cisplatin plus capecitabine or infusional 5-FU improved both the response rate and the OS for HER 2-positive tumors (23). The 5-FU continuous intravenous infusion regimen for AEG is commonly administered in Western countries. Differing chemotherapy regimens might also contribute to divergent results (24). In a recent network meta-analysis of clinical trials for AEG, patients who received three fluoropyrimidines such as 5-FU, capecitabine, and S-1 had similar overall and progression-free survivals (25). In the present study, which included six patients (43%) who were administered trastuzumab, chemotherapy using oral fluoropyrimidine S-1 or capecitabine had a 50% histological response rate of grade 1b or higher and achieved a pCR rate of 28.6%, which was rather higher than the previous reports of 0-17.2% in 5-FU-based regimens (26). Oral fluoropyrimidines are generally more convenient than infusional 5-FU in clinical practice. In particular, S-1-based regimens had a lower incidence of adverse events, such as less febrile neutropenia and toxicity in Western patients, compared to regimens that included 5-FU (25). Grade 3 or higher leukopenia (21% and 27%), neutropenia (39% and 51%) and thrombopenia (3% and 2%) were recorded for the ECF/ECX and FLOT arms in the FLOT-AOI trial, respectively (6). In this study cohort, grade 3 or higher leukopenia, neutropenia, and thrombopenia each occurred in 14% of patients, and no severe non-hematological toxicity was observed. Thus, an oral fluoropyrimidine-platinum regimen seems to have a manageable and acceptable safety profile for clinical use in NAC settings.

Based on previous results including the MAGIC trial and the FLOT4-AIO trial in Western countries, perioperative chemotherapy is now a standard treatment for patients with resectable AEG (4, 6). Although perioperative chemotherapy may be more intensive compared with preoperative chemotherapy theoretically, it is unclear whether improved survival results from NAC or adjuvant chemotherapy. In the MAGIC trial, only 55% of patients in the perioperative chemotherapy group were administered postoperative chemotherapy. This may imply that the preoperative portion mainly influenced the efficacy of the perioperative treatment.

Similarly, postoperative chemotherapy was administered to 55-60% of the patients in the FLOT-AIO trial, implicating a larger role of preoperative chemotherapy. Chemoradiotherapy is reported to be superior to chemotherapy in terms of the local control rate in Western countries (7). However, the local recurrence rate was very low in AEG in Japan and Korea, likely because of D2 lymph node dissection and ensuring resection margins by intraoperative frozen sections (27, 28). The ARIST trial, which was conducted in Korea, failed to prove the additional effect of postoperative radiotherapy to adjuvant chemotherapy for resected gastric cancer. Furthermore, the survival benefit of additional radiotherapy to chemotherapy remains a matter of debate (26).

Accurately diagnosing the AEG stage is crucial for decision-making for therapeutic strategies, but the diagnostic accuracy of the T and N categories by endoscopy and imaging is limited (29). The assessment of nodal metastasis is particularly difficult, and the clinical stage of AEG tends to be underdiagnosed, as has been previously reported (30). For example, the negative predictive value (pathological node negative/clinical node negative) of gastric cancer was reported to be only 47.8% (31). We could accurately diagnose only 44.4% (4/9) of nodes as negative in the surgery first group. Lymph node metastasis is a strong predictor of survival in AEG (2). In light of these findings, we adopt NAC for node-positive tumors or cT2 or deeper tumors that have a high possibility of nodal metastasis. This aggressive implementation of NAC is one plausible explanation why the pCR rate was relatively high and the therapeutic outcomes of patients who received NAC were favorable in this study cohort.

Our study has several important limitations. This study was based on retrospective data collected at a single center. The NAC regimen was not standardized, few patients were included, and the median follow-up period was short. Although some limitations were present, oral fluoropyrimidine-platinum regimen had low toxicity and convenience for AEG patients. A larger and well-designed prospective clinical trial is warranted to confirm our results.

In conclusion, NAC using an oral fluoropyrimidine-platinum regimen potentially provides survival benefits over a surgery-first approach in patients with locally advanced AEG. This approach for AEG should be considered from the perspective of therapeutic efficacy and clinical convenience.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Study conception and design: SS and YK. Acquisition of data: GT, HH, YM, KY, and TM. Analysis and interpretation of data: SK, NU, TO and TN. Drafting of manuscript: SS and YK. Final approval of the version to be published: YK.

References

1 Hur C, Miller M, Kong CY, Dowling EC, Nattinger KJ, Dunn M and Feuer EJ: Trends in esophageal adenocarcinoma incidence and mortality. Cancer *119(6)*: 1149-1158, 2013. PMID: 23303625. DOI: 10.1002/cncr.27834

2 Yamashita H, Seto Y, Sano T, Makuuchi H, Ando N, Sasako M and Japanese Gastric Cancer Association and the Japan Esophageal Society: Results of a nation-wide retrospective study of lymphadenectomy for esophagogastric junction carcinoma. Gastric Cancer *20(Suppl 1)*: 69-83, 2017. PMID: 27796514. DOI: 10.1007/s10120-016-0663-8

3 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2019. CA Cancer J Clin *69(1)*: 7-34, 2019. PMID: 30620402. DOI: 10.3322/caac.21551

4 Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ and MAGIC Trial Participants: Perioperative chemotherapy *versus* surgery alone for resectable gastroesophageal cancer. N Engl J Med *355(1)*: 11-20, 2006. PMID: 16822992. DOI: 10.1056/NEJMoa055531

5 Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Genève J, Lasser P and Rougier P: Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol *29(13)*: 1715-1721, 2011. PMID: 21444866. DOI: 10.1200/JCO.2010.33.0597

6 Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, Kopp HG, Mayer F, Haag GM, Luley K, Lindig U, Schmiegel W, Pohl M, Stoehlmacher J, Folprecht G, Probst S, Prasnikar N, Fischbach W, Mahlberg R, Trojan J, Koenigsmann M, Martens UM, Thuss-Patience P, Egger M, Block A, Heinemann V, Illerhaus G, Moehler M, Schenk M, Kullmann F, Behringer DM, Heike M, Pink D, Teschendorf C, Löhr C, Bernhard H, Schuch G, Rethwisch V, von Weikersthal LF, Hartmann JT, Kneba M, Daum S, Schulmann K, Weniger J, Belle S, Gaiser T, Oduncu FS, Güntner M, Hozaeel W, Reichart A, Jäger E, Kraus T, Mönig S, Bechstein WO, Schuler M, Schmalenberg H, Hofheinz RD and FLOT4-AIO Investigators: Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel *versus* fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet *393(10184)*: 1948-1957, 2019. PMID: 30982686. DOI: 10.1016/S0140-6736(18)32557-1

7 van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A and CROSS Group: Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med *366(22)*: 2074-2084, 2012. PMID: 22646630. DOI: 10.1056/NEJMoa1112088

8 Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM and Martenson JA: Chemoradiotherapy after surgery

compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med *345(10)*: 725-730, 2001. PMID: 11547741. DOI: 10.1056/NEJMoa010187

9 Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D and ESMO Guidelines Committee: Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol *27(suppl 5)*: v50-v57, 2016. PMID: 27664261. DOI: 10.1093/annonc/mdw329

10 Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Besh S, Chao J, Das P, Denlinger C, Fanta P, Fuchs CS, Gerdes H, Glasgow RE, Hayman JA, Hochwald S, Hofstetter WL, Ilson DH, Jaroszewski D, Jasperson K, Keswani RN, Kleinberg LR, Korn WM, Leong S, Lockhart AC, Mulcahy MF, Orringer MB, Posey JA, Poultsides GA, Sasson AR, Scott WJ, Strong VE, Varghese TK Jr, Washington MK, Willett CG, Wright CD, Zelman D, McMillian N, Sundar H and National comprehensive cancer network: Esophageal and esophagogastric junction cancers, version 1.2015. J Natl Compr Canc Netw *13(2)*: 194-227, 2015. PMID: 25691612. DOI: 10.6004/jnccn.2015.0028

11 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 and ACTS-GC Group: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med *357(18)*: 1810-1820, 2007. PMID: 17978289. DOI: 10.1056/NEJMoa072252

12 Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim YH, Noh SI, Cho JY, Mok YJ, Kim YH, Ji J, Yeh TS, Button P, Sirzén F, Noh SH and CLASSIC trial investigators: Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet *379(9813)*: 315-321, 2012. PMID: 22226517. DOI: 10.1016/S0140-6736(11)61873-4

13 Yoshida K, Kodera Y, Kochi M, Ichikawa W, Kakeji Y, Sano T, Nagao N, Takahashi M, Takagane A, Watanabe T, Kaji M, Okitsu H, Nomura T, Matsui T, Yoshikawa T, Matsuyama J, Yamada M, Ito S, Takeuchi M and Fujii M: Addition of docetaxel to oral fluoropyrimidine improves efficacy in patients with stage iii gastric cancer: interim analysis of JACCRO GC-07, a randomized controlled trial. J Clin Oncol *37(15)*: 1296-1304, 2019. PMID: 30925125. DOI: 10.1200/JCO.18.01138

14 Kodera Y, Ishiyama A, Yoshikawa T, Kinoshita T, Ito S, Yokoyama H, Mochizuki Y, Ito H, Tsuburaya A, Sakamoto J, Nakao A and Chubu Clinical Cancer Group: A feasibility study of postoperative chemotherapy with S-1 and cisplatin (CDDP) for gastric carcinoma (CCOG0703). Gastric Cancer *13(3)*: 197-203, 2010. PMID: 20820990. DOI: 10.1007/s10120-010-0559-y

15 Takahari D, Hamaguchi T, Yoshimura K, Katai H, Ito S, Fuse N, Kinoshita T, Yasui H, Terashima M, Goto M, Tanigawa N, Shirao K, Sano T and Sasako M: Feasibility study of adjuvant chemotherapy with S-1 plus cisplatin for gastric cancer. Cancer Chemother Pharmacol *67(6)*: 1423-1428, 2011. PMID: 20809123. DOI: 10.1007/s00280-010-1432-8

16 Allum WH, Stenning SP, Bancewicz J, Clark PI and Langley RE: Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol *27(30)*: 5062-5067, 2009. PMID: 19770374. DOI: 10.1200/JCO.2009.22.2083

17 Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, Vynnychenko I, Garin A, Lang I and Falcon S: Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol *28(9)*: 1547-1553, 2010. PMID: 20159816. DOI: 10.1200/JCO.2009.25.4706

18 Hosoda K, Yamashita K, Katada N, Moriya H, Mieno H, Sakuramoto S, Kikuchi S and Watanabe M: Benefit of neoadjuvant chemotherapy for Siewert type II esophagogastric junction adenocarcinoma. Anticancer Res *35(1)*: 419-425, 2015. PMID: 25550582.

19 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 and 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 *22(5)*: 1044-1052, 2019. PMID: 30827001. DOI: 10.1007/s10120-019-00941-z

20 Tokunaga M, Sato Y, Nakagawa M, Aburatani T, Matsuyama T, Nakajima Y and Kinugasa Y: Perioperative chemotherapy for locally advanced gastric cancer in Japan: current and future perspectives. Surg Today *50(1)*: 30-37, 2020. PMID: 31612329. DOI: 10.1007/s00595-019-01896-5

21 Japanese Gastric Cancer Association: Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer *14(2)*: 101-112, 2011. PMID: 21573743. DOI: 10.1007/s10120-011-0041-5

22 Dindo D, Demartines N and Clavien PA: Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg *240(2)*: 205-213, 2004. PMID: 15273542. DOI: 10.1097/01.sla.0000133083.54934.ae

23 Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK and ToGA Trial Investigators: Trastuzumab in combination with chemotherapy *versus* chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet *376(9742)*: 687-697, 2010. PMID: 20728210. DOI: 10.1016/S0140-6736(10)61121-X

24 Springfeld C, Wiecha C, Kunzmann R, Heger U, Weichert W, Langer R, Stange A, Blank S, Sisic L, Schmidt T, Lordick F, Jäger D, Grenacher L, Bruckner T, Büchler MW and Ott K: Influence of different neoadjuvant chemotherapy regimens on response, prognosis, and complication rate in patients with esophagogastric adenocarcinoma. Ann Surg Oncol *22(Suppl 3)*: S905-S914, 2015. PMID: 26001861. DOI: 10.1245/s10434-015-4617-x

25 Ter Veer E, Ngai LL, Valkenhoef GV, Mohammad NH, Anderegg MCJ, van Oijen MGH and van Laarhoven HWM: Capecitabine, 5-fluorouracil and S-1 based regimens for previously untreated advanced oesophagogastric cancer: A network meta-analysis. Sci Rep *7(1)*: 7142, 2017. PMID: 28769123. DOI: 10.1038/s41598-017-07750-3

26 Petrelli F, Ghidini M, Barni S, Sgroi G, Passalacqua R and Tomasello G: Neoadjuvant chemoradiotherapy or chemotherapy for gastroesophageal junction adenocarcinoma: A systematic review and meta-analysis. Gastric Cancer *22(2)*: 245-254, 2019. PMID: 30483986. DOI: 10.1007/s10120-018-0901-3

27 Yamashita H, Katai H, Morita S, Saka M, Taniguchi H and Fukagawa T: Optimal extent of lymph node dissection for Siewert type II esophagogastric junction carcinoma. Ann Surg *254(2)*: 274-280, 2011. PMID: 21772128. DOI: 10.1097/SLA.0b013e3182263911

28 Lee J, Lim DH, Kim S, Park SH, Park JO, Park YS, Lim HY, Choi MG, Sohn TS, Noh JH, Bae JM, Ahn YC, Sohn I, Jung SH, Park CK, Kim KM and Kang WK: Phase III trial comparing capecitabine plus cisplatin *versus* capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol *30(3)*: 268-273, 2012. PMID: 22184384. DOI: 10.1200/JCO.2011.39.1953

29 Rice TW, Gress DM, Patil DT, Hofstetter WL, Kelsen DP and Blackstone EH: Cancer of the esophagus and esophagogastric junction-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin *67(4)*: 304-317, 2017. PMID: 28556024. DOI: 10.3322/caac.21399

30 Seevaratnam R, Cardoso R, McGregor C, Lourenco L, Mahar A, Sutradhar R, Law C, Paszat L and Coburn N: How useful is preoperative imaging for tumor, node, metastasis (TNM) staging of gastric cancer? A meta-analysis. Gastric Cancer *15(Suppl 1)*: S3-18, 2012. PMID: 21837458. DOI: 10.1007/s10120-011-0069-6

31 Fukagawa T, Katai H, Mizusawa J, Nakamura K, Sano T, Terashima M, Ito S, Yoshikawa T, Fukushima N, Kawachi Y, Kinoshita T, Kimura Y, Yabusaki H, Nishida Y, Iwasaki Y, Lee SW, Yasuda T, Sasako M and Stomach Cancer Study Group of the Japan Clinical Oncology Group: A prospective multi-institutional validity study to evaluate the accuracy of clinical diagnosis of pathological stage III gastric cancer (JCOG1302A). Gastric Cancer *21(1)*: 68-73, 2018. PMID: 28194522. DOI: 10.1007/s10120-017-0701-1

Received March 12, 2021
Revised April 30, 2021
Accepted May 7, 2021