Benefit of Neoadjuvant Chemotherapy for Siewert Type II Esophagogastric Junction Adenocarcinoma

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Abstract. *Aim: Our objective was to clarify if preoperative chemotherapy was associated with improved survival in Japanese patients with Siewert type II adenocarcinoma of the esophagogastric junction. Patients and Methods: We retrospectively reviewed the medical records of 86 patients with Siewert type II adenocarcinoma who underwent R0 resection at the Kitasato University between 1997 and 2013. Cox regression analysis using a backward stepwise selection method was performed to identify independent prognostic factors for relapse-free survival (RFS). Results: The median age was 67 years. The male:female ratio was 74:12. Right thoracic, left thoracic and transhiatal approaches were performed in 10, 10 and 66 patients, respectively, and perioperative transfusion in 16 patients. Preoperative chemotherapy was administered to 19 patients; out of these, 13 received chemotherapy using the DCS regimen (docetaxel 40 mg/m^2, day 1; cisplatin 60 mg/m^2, day 1; S-1 80-120 mg/body, days 1-14; every 28 days). A median of three cycles of preoperative DCS chemotherapy were used. Histological responses of 1b, 2, 3 and unknown grades were obtained in three, three, four and three patients, respectively. The 5-year RFS rate was 55%, and the median follow-up period was 36 months. Cox regression analysis regarding RFS identified (y)pN1-3 [hazard ratio (HR)=4.44; 95% confidence interval (CI)=1.98-11.27], performance of perioperative transfusion (HR=4.71; 95% CI=1.69-11.88) and no preoperative chemotherapy (HR=3.75; 95% CI=1.22-14.26) as significant and independent indicators of poor prognosis. Conclusion: Preoperative chemotherapy using DCS is potentially beneficial for Japanese patients with Siewert type II adenocarcinoma. Further prospective clinical studies are required to confirm our findings.*

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The incidence of adenocarcinoma of the esophagogastric junction (AEG) is rising in both Western countries (1, 2) and Japan (3-5). Siewert *et al*. proposed a classification system for AEG, and discussed the characteristics and treatment of AEG according to disease type. The authors proposed that patients with type I AEG should be treated similarly to patients with distal esophageal cancer, whereas patients with type II and III AEG should undergo transhiatal total gastrectomy, lower esophagectomy, lower mediastinal lymph-node dissection and extended (D2) lymph-node dissection comparable to that performed in patients with gastric cancer (6). Conversely, in a study in which more than half of the patients had Siewert type II AEG, esophagectomy was associated with better outcomes than gastrectomy (7). In Japanese patients, Sasako *et al*. reported that a left thoracoabdominal approach did not improve survival after an abdominal-transhiatal approach and led to increased morbidity in patients with adenocarcinoma of the gastric body or cardia with esophageal invasion extending for ≤30 mm (mostly Siewert type II or III AEG) (8).

More recently, the use of preoperative chemoradiotherapy has improved the survival of patients with potentially curable esophageal or esophagogastric junction cancer (9). In Korea, where D2 lymph-node dissection is routinely performed, postoperative chemoradiotherapy has not been found to improve disease-specific survival in patients with curatively-resected gastric or esophagogastric junction cancer (10). In terms of chemotherapy, perioperative chemotherapy (11) or postoperative chemotherapy (12-14) has been reported to be effective in the treatment of potentially curable gastric and esophagogastric junction cancer. Because surgery for esophagogastric junction cancer requires an invasive procedure using the thoracic and abdominal approach, a high rate of

postoperative complications and reduced performance status have resulted in the administration of postoperative chemotherapy with sub-optimal dose intensity. Neoadjuvant chemotherapy is a promising strategy to ensure that patients with AEG receive adequate dosage.

However, the above-mentioned trials were not conducted exclusively for patients with esophagogastric junction cancer, and it remains unclear whether or not preoperative chemotherapy provides benefits for Japanese patients with Siewert type II AEG. The aim of the present study was to clarify if preoperative chemotherapy was associated with better survival outcomes in patients with Siewert type II AEG in Japan.

Patients and Methods

AEG definition. AEG was defined as adenocarcinoma that had invaded the esophagogastric junction with a tumor epicenter located ≤5 cm from the junction. Tumors were classified according to the Siewert classification as follows: type I, tumor epicenter located 1-5 cm above the esophagogastric junction; type II, tumor epicenter located 1 cm above to 2 cm below the esophagogastric junction; and type III, tumor epicenter located 2-5 cm below the esophagogastric junction. The location of the epicenter was comprehensively evaluated based on findings obtained from the patient after oral administration of barium and upper gastrointestinal endoscopy. In patients who received preoperative chemotherapy, tumor classification was based on their characteristics prior to chemotherapy.

Patients and clinicopathological evaluation. We retrospectively reviewed the medical records of 86 patients with Siewert type II AEG who had undergone R0 resection at our institute between January 1997 and October 2013. The median follow-up period was 36 (interquartile range=23-58) months.

Tumor stage was classified according to the 7th edition of the International Union Against Cancer TNM staging system (15). Adenocarcinoma was histologically classified according to the definitions of the Japanese Classification of Gastric Carcinoma (16). Well- and moderately differentiated tubular adenocarcinomas and papillary adenocarcinomas were classified as differentiated-type adenocarcinoma; poorly-differentiated adenocarcinomas, signet-ring cell carcinomas and mucinous carcinomas were classified as undifferentiated-type adenocarcinoma.

Log-rank plot analysis was performed to determine the threshold value for tumor size regarding the prediction of relapse-free survival. We calculated *p*-values and relative risks by means of prognostic analysis using the log-rank method, classifying tumor size at 5-mm intervals. The highest relative risk was considered as the critical point in this analysis.

Perioperative transfusion (POT) was defined as allogeneic blood transfusion performed during surgery or within the first two postoperative days, as previously reported (17).

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of Kitasato University School of Medicine. The requirement for informed consent was waived because the study was of retrospective design.

Surgical procedures. Surgical procedures were determined on the basis of tumor depth and the extent of esophageal and gastric invasion. For patients with tumors that exhibited substantial esophageal invasion, a right thoracic approach (RTA) was used to perform subtotal esophagectomy and mediastinal lymph-node dissection through a right thoracotomy, and gastric conduit reconstruction was performed through a laparotomy. Esophagogastric anastomosis was performed in the thoracic cavity (Ivor-Lewis approach) or in the neck (McKeown approach). For patients with tumors that exhibited substantial gastric invasion, a left thoracic approach (LTA) through a left thoracotomy and laparotomy and a transhiatal approach (THA) after wide splitting of the esophageal hiatus were used to perform total gastrectomy, distal esophagectomy, D2 lymph-node dissection and lower mediastinal lymph-node dissection. For cT1 cancer, proximal gastrectomy and jejunal interposition or esophagogastric anastomosis using a THA were performed if possible. Because video-assisted thoracoscopic esophagectomy was performed through an RTA in only three patients, these patients were included for analysis in the RTA group.

Chemotherapy. Preoperative chemotherapy was administered to patients with marginally resectable disease or cStage IV disease. For these patients, a combination of docetaxel, cisplatin and S-1 (DCS) was commonly used. The treatment schedule for DCS was as follows: 40 mg/m^2 docetaxel, day 1; 60 mg/m^2 cisplatin, day 1; 80-120 mg S-1, days 1-14; every 28 days (18). The histological response of the primary tumor was evaluated according to the Japanese Classification of Gastric Carcinoma (16). Postoperative adjuvant chemotherapy was generally given to adenocarcinoma patients with pStage II or III disease. For these patients, S-1 monotherapy was commonly used (12, 13).

Survival analysis. Overall survival (OS) in patients who had received preoperative chemotherapy was defined as the time from the date of starting chemotherapy to the date of death from any cause; OS in patients who had not received preoperative chemotherapy was defined as the time from the date of surgery to the date of death from any cause; data on surviving patients were censored at the last follow-up. Relapse-free survival (RFS) in patients who had received preoperative chemotherapy was defined as the time from the date of starting chemotherapy to the date of relapse or death from any cause; RFS in patients who had not received preoperative chemotherapy was defined as the time from the date of surgery to the date of relapse or death from any cause; data on surviving patients without relapses were censored at the last follow-up.

Cox regression analysis using the backward stepwise selection method was performed to identify the independent prognostic factors among the various variables [age, sex, pN category (pN0/1-3), pT category (pT0-2/3), tumor size, preoperative chemotherapy (yes/no), POT (yes/no) and thoracotomy (yes/no)] for OS and RFS. Survival analysis was performed using the Kaplan–Meier and log-rank tests. All calculations were performed using JMP® 10 (SAS Institute Inc., Cary, NC, USA), and *p*-values of less than 0.05 were considered as indicating statistical significance.

Results

Patients' characteristics. The clinicopathological features of the patients are detailed in Table I. The median patient age was 67 (range=31-81) years. The male:female ratio was 74:12. RTA, LTA and THA were performed in 10, 10 and 66 patients, respectively. POT was undertaken in 16 patients.

The median tumor size was 4.5 cm. Log-rank plot analysis revealed that the cutoff value for tumor size was 2.5 cm (p=0.027; relative risk=2.22).

Chemotherapy. Preoperative chemotherapy was administered to 19 patients; of these patients, 13 received chemotherapy using the DCS regimen. The median number of cycles of preoperative chemotherapy using this regimen were three (range=1-6). Chemotherapy using an S-1-based regimen other than DCS was administered to four patients [docetaxel + S-1 in one, irinotecan + S-1 in one, cisplatin + S-1 in one, and paclitaxel + cisplatin + S-1 in one]. Chemotherapy involving the irinotecan-plus-cisplatin regimen was administered to one patient and the capecitabine with cisplatin plus trastuzumab regimen was administered to one patient with an HER2-positive tumor. No toxic deaths associated with chemotherapy were recorded. The histological responses of the primary tumor for the patients who received preoperative chemotherapy using the DCS regimen were as follows: Grade 1b in three, grade 2 in three, grade 3 in four and unknown in three. Postoperative chemotherapy was administered to 26 patients. Of these, 22 received chemotherapy with S-1.

Survival analysis. Out of the 83 patients, 20 had recurrence. The first sites of recurrence and number of patients involved were as follows: peritoneum, three; mediastinal lymph nodes, three; abdominal lymph nodes, three; liver, four; lung, three; bone, one; brain, one; and local sites, three (including one patient with simultaneous recurrence of abdominal lymph-nodes and peritoneum). The 5-year OS and RFS rates were 63% and 55%, respectively (Figure 1). For OS, Cox regression analysis involving the backward stepwise selection method revealed that the performance of preoperative chemotherapy was not selected as a covariate (Table II). Kaplan–Meier curves and the log-rank test revealed that preoperative chemotherapy was not a significant prognostic factor (Figure 2a). However, for the RFS rate, Cox regression analysis using the backward stepwise selection method revealed that (y)pN1-3 [hazard ratio (HR)=4.44; 95% confidence interval (CI)=1.98-11.27; p<0.001), performance of POT (HR=4.71; 95% CI=1.69-11.88; p=0.004), and no preoperative chemotherapy (HR=3.75; 95% CI=1.22-14.26; p=0.020) were found to be the significant and independent indicators of poor prognosis (Table III; Figure 2b-d).

Table I. *Clinicopathological features of patients with Siewert type II cancer.*

Median age (range), years	67 (31-81)
Gender	
Male	74
Female	12
Histological type	
Differentiated-type adenocarcinoma	61
Undifferentiated-type adenocarcinoma	24
Unknown	1
Tumor depth (histological)	
(y)pT0	4
(y)pT1	22
(y)pT2	16
(y)pT3	44
Nodal stage (histologial)	
(y)pN0	43
(y)pN1	18
(y)pN2	13
(y)pN3	12
Pathological stage	
0	3
IA	20
IB	9
IIA	12
IIB	6
IIIA	15
IIIB	10
IIIC	11
Median tumor size (IQR), cm	4.5 (2.5-6.2)
POT	
Yes	16
No	70
Approach	
RTA	10
LTA	10
THA	66
Preoperative chemotherapy	
Yes	19
No	67
Postoperative chemotherapy	
Yes	26
No	60
Median no. (IQR) dissected lymph nodes	31 (17-46)

Discussion

In the current analysis, we found that neoadjuvant chemotherapy could potentially provide survival benefits for patients with Siewert type II AEG. We also found that POT and lymph-node metastasis were significantly associated with poor survival.

Firstly, preoperative chemotherapy was demonstrated to be beneficial for patients with Siewert type II AEG. In many Western countries, based on the results of the MAGIC trial (11), perioperative chemotherapy is now a standard treatment for patients with gastric and esophagogastric junction cancer. More recently, findings from the CROSS trial indicated that preoperative chemoradiotherapy is beneficial in the treatment of esophageal or esophagogastric junction cancer (9). The ARTIST trial, in which adjuvant chemoradiotherapy was compared to adjuvant chemotherapy, for patients with curatively, resected gastric or esophagogastric junction cancer, was conducted in Korea. Although it was a trial

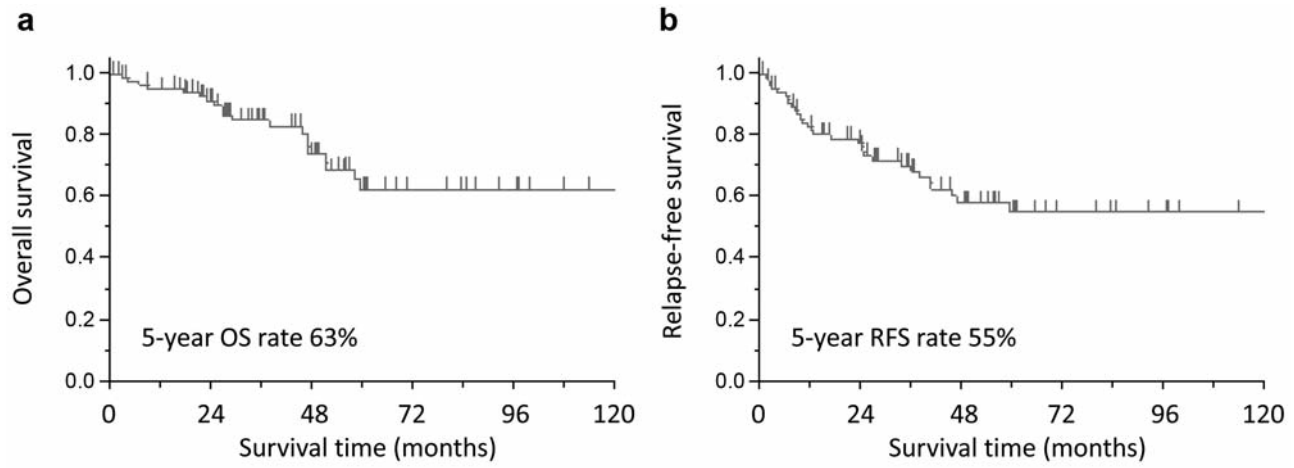

Figure 1. *Kaplan–Meier curves for overall (a) and relapse-free (b) survival for patients with the Siewert type II adenocarcinoma of the esophagogastric junction.*

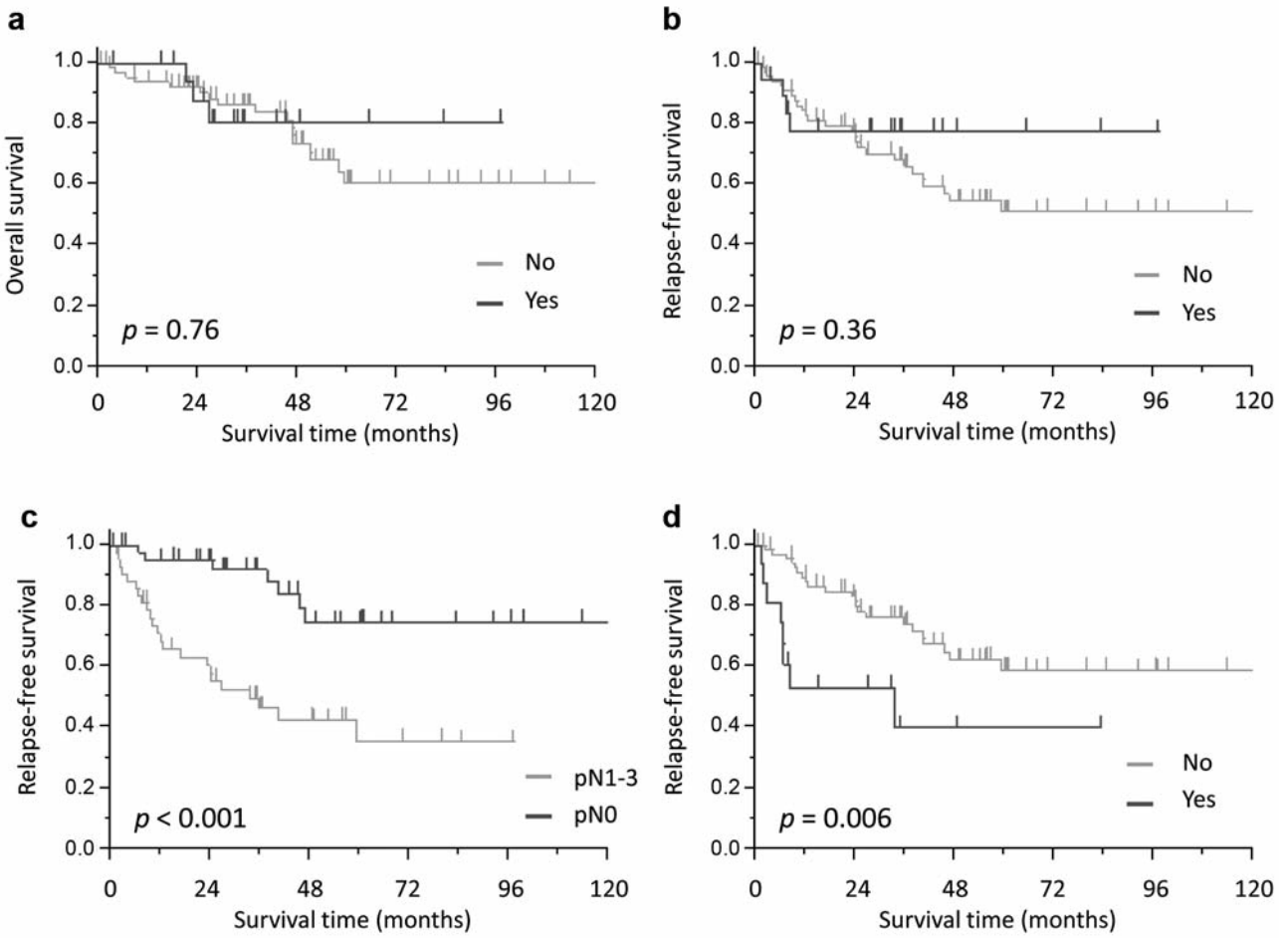

Figure 2. *Kaplan–Meier curves with p-values (log-rank test) for overall survival (OS) according to the performance of preoperative chemotherapy (a) and for relapse-free survival (RFS) according to the performance of preoperative chemotherapy (b), pN category (c) and the performance of perioperative transfusion (d).*

Table II. *Cox regression analysis for overall survival in patients with type II EGJ cancer.*

Category	Classification	Number of patients	Hazard ratio	95% CI	*p*-Value
pN	pN0	43	Reference		0.007
	pN1-3	43	4.42	1.47-16.36	
Thoracotomy	Yes	20	3.01	1.14-7.95	0.027
	No	66	Reference		
POT	Yes	16	4.71	1.69-11.88	0.046
	No	70	Reference		

CI: Confidence interval, pN: pathological lymph node metastasis according to TNM classification 7th edition. POT: perioperative allogeneic blood transfusion.

Table III. *Cox regression analysis for relapse-free survival in patients with type II EGJ cancer.*

Category	Classification	Number	Hazard ratio	95% CI	*p*-Value
pN	pN0	43	Reference		<0.001
	pN1-3	43	4.44	1.98-11.27	
POT	Yes	16	4.71	1.69-11.88	0.004
	No	70	Reference		
Preoperative chemotherapy	Yes	19	Reference		0.020
	No	67	3.75	1.22-14.26	

CI: Confidence interval, pN: pathological lymph node metastasis according to TNM classification 7th edition. POT: perioperative allogeneic blood transfusion.

involving postoperative therapy, it did not demonstrate a significant improvement in disease-free survival with the addition of chemoradiotherapy. Chemoradiotherapy is superior to chemotherapy in terms of local control rate. D2 lymph-node dissection contributes to the control of local recurrence; however, it is not as widely performed in Western countries as in Korea and Japan. Consequently, preoperative chemoradiotherapy has been proven to be beneficial in Western countries, but not in Korea. The fact that preoperative chemoradiotherapy is effective in Western countries may not necessarily lead to the application of the same treatment strategy in Japan.

Cox regression analysis involving the backward stepwise selection method revealed that preoperative chemotherapy was not selected as a covariate for OS. This is probably because almost all patients with recurrence who had received preoperative chemotherapy died after a certain period, while some who had not received preoperative chemotherapy survived for a longer period after recurrence. This means that patients with recurrence who have not received preoperative chemotherapy may have a tendency to respond more favorably to a multi-disciplinary therapy compared with to who have received preoperative chemotherapy. On the other hand, R0 resection is reportedly associated with better survival outcomes than R1 or R2 resection (6, 19), and preoperative chemotherapy has been reported to potentially increase the R0 resection rate (11, 20). Therefore, we believe that preoperative chemotherapy may ultimately be beneficial. In addition, the patients who received preoperative chemotherapy included patients with initially unresectable advanced AEG and a poor prognosis. This may be another reason for preoperative chemotherapy not being selected as a covariate for OS.

In our current analysis, only 12% of the patients had local recurrence as a first recurrent site. On the other hand, 40% of the patients had hematogenous recurrence and 36% had distant lymph-node recurrence as a first recurrent site. Actually, the largest retrospective case series in Japan for Siewert type II tumors revealed that the local recurrence rate was very low, and that the most common type of recurrence was hematogenous (19). In other words, numerous patients with Siewert type II AEG had a distant recurrent site that could not be covered by radiotherapy. Only intensive chemotherapy was able to control these recurrences. To

maintain dose intensity, this chemotherapy should be administered preoperatively rather than postoperatively.

Secondly, POT was found to be one of the independent indicators of poor prognosis in the present study. The deleterious effects of transfusion-associated immunomodulation have long been debated. Allogeneic leukocytes are thought to play a key role in the transfusion-associated immunomodulation effect, and so leukocyte depletion could be effective in inhibiting such immunomodulation (21). However, controversy exists regarding cancer recurrence caused by leukocyte depletion (22, 23). In any case, patients with Siewert type II AEG should undergo meticulous surgery to avoid POT.

Thirdly, lymph-node metastasis was shown to be one of the independent indicators of poor prognosis in our study. With respect to lymph-node dissection for AEG, a number of studies have been published (19, 24, 25). All these studies have reported that the therapeutic effects of lymph-node dissection at stations 1, 2, 3 and 7, as defined in the Japanese Classification of Gastric Carcinoma (16), were excellent. Conversely, the therapeutic efficacy of dissection of the mediastinal or para-aortic lymph-nodes has been reported to be not so good. A prospective multi-center study regarding the efficacy of mediastinal and para-aortic lymph-node dissection for esophagogastric junction cancer is currently ongoing; it is supported by the Japanese Gastric Cancer Association and the Japan Esophageal Society (UMIN000013205). It is anticipated that the study will provide strong evidence in support of lymph-node dissection in the treatment of esophagogastric junction cancer. In any case, patients with Siewert type II AEG have higher recurrence rates and require intensive chemotherapy. Despite progress in diagnostic techniques, lymph-node metastasis is difficult to diagnose preoperatively. Presurgical techniques for detecting metastatic lymph nodes are required.

Our study had several important limitations. The analysis was based on retrospective data collection at a single center. Treatment policies were not necessarily standardized, and the demographic characteristics of the patients varied considerably. In particular, an LTA was not used after the results of the JCOG9502 study had been reported (8). Regimens and the indications for preoperative chemotherapy were also not standardized. The median follow-up period was as short as 36 (inter quartile range=23-58) months; thus, there is a possibility that in some cases, disease events could still have occured and were missed during the short follow-up period.

In conclusion, preoperative chemotherapy using the DCS regimen potentially provides therapeutic benefits for Japanese patients with Siewert type II AEG. Further prospective clinical validations are required to confirm our findings.

Conflicts of Interest

None declared.

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