International Journal of Clinical Oncology (2019) 24:60–67
https://doi.org/10.1007/s10147-018-1336-x

ORIGINAL ARTICLE

Phase II feasibility study of preoperative concurrent chemoradiotherapy with cisplatin plus 5-fluorouracil and elective lymph node irradiation for clinical stage II/III esophageal squamous cell carcinoma

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Received: 7 June 2018 / Accepted: 6 August 2018 / Published online: 14 August 2018

Abstract

Background Preoperative chemoradiotherapy (CRT) is a standard treatment for stage II/III esophageal cancer. Preoperative chemotherapy is also considered a standard treatment for stage II/III esophageal squamous cell carcinoma (ESCC) in patients who undergo radical lymph node dissection. We conducted a feasibility study of preoperative CRT with cisplatin plus 5-fluorouracil (CF) and elective lymph node irradiation followed by esophagectomy with radical lymph node dissection in patients with stage II/III ESCC.

Methods Patients with clinical stage II/III, excluding T4, ESCC (International Union Against Cancer TNM classification system, 6th edition) were eligible. Chemotherapy comprised two courses of CF infusion repeated after 4-weeks. Radiation therapy was concurrently administered to the primary tumor, metastatic lymph nodes, and regional lymph nodes at a dose of 41.4 Gy. After the completion of CRT, transthoracic esophagectomy with 2–3 fields lymphadenectomy was performed. The primary endpoint was the completion rate of protocol treatment with R0 resection.

Results Thirty-one eligible patients were enrolled. During CRT, the most common grade 3 or 4 toxicities were leukopenia (65%), neutropenia (65%), anemia (13%), thrombocytopenia (13%), febrile neutropenia (13%), anorexia (16%), esophagitis (16%) and hyponatremia (16%). Thirty patients (96.8%) underwent surgery. One patient received palliative chemotherapy because of appearance of lung metastasis during CRT. The completion rate of protocol treatment was 93.5% (29/31). There was one treatment-related death after surgery. Pathological complete response was achieved in 42% (13/30).

Conclusion Preoperative CRT with CF and elective lymph node irradiation showed an acceptable toxicity and promising activity especially in ESCC.

Keywords Esophageal cancer · Preoperative chemoradiotherapy · Elective lymph node irradiation · Clinical trial · Phase II

Introduction

Esophageal cancer, a highly aggressive malignancy, is often refractory to current therapeutic approaches and has a poor outcome. Worldwide, almost 450,000 new cases of esophageal cancer are diagnosed annually—it is the eighth most common cancer and the sixth most common cause of cancer-related mortality [1]. In Japan, esophageal cancer was responsible for 11,700 deaths in 2015, accounting for 6% of the country's total cancer deaths [2]. Various multimodality combined therapies have been investigated to improve local and distant relapse rates with preoperative chemotherapy or chemoradiotherapy (CRT). The results of a recent meta-analysis suggest that preoperative therapy followed by surgery is associated with better survival than surgery alone [3–5]. Therefore, preoperative CRT is considered a standard treatment in both squamous cell cancer and adenocarcinoma. In the CROSS trial, preoperative CRT showed survival benefit compared to surgery alone [6]: paclitaxel and carboplatin were administered once per week for 5

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weeks with 41.4 Gy radiotherapy to patients with stage II/III esophageal cancer; overall survival (OS) was significantly better in the CRT arm. In contrast, in the FFCD9901 trial, preoperative CRT did not improve survival due to toxicity of the CRT arm [7]. Preoperative CRT is associated with a significant increase in perioperative complications [8, 9]. In Japan and some other Asian countries, the standard operative procedure is esophagectomy with 3-field lymphadenectomy, which includes additional nodal dissection of the neck to thoracoabdominal dissection (2-field lymphadenectomy) to improve local control and survival [10, 11]. The Japan Clinical Oncology Group (JCOG) 9907 study revealed that preoperative chemotherapy with cisplatin plus 5-fluorouracil (CF) was superior to postoperative chemotherapy in clinical stage II/III esophageal squamous cell carcinoma (ESCC). In this trial, preoperative CF produced a 5-year OS rate of 55%, a relatively good result in comparison with the survival in preoperative CRT in Western countries [12]. Still, locoregional recurrence was seen in 25% of all relapsed patients in the preoperative chemotherapy group in JCOG9907, and survival in stage III ESCC was limited (the 5-year OS rate: 52.1%). Therefore, it would be expected to see benefits from strengthening local therapy, including elective lymph node irradiation (ENI). Nevertheless, the benefit and safety of ENI in preoperative CRT is still unknown even with 2- or 3-field lymphadenectomy.

To improve survival of patients with resectable ESCC, it is necessary to develop new treatment strategies, including intensive preoperative chemotherapy or CRT followed by surgery with radical lymph node dissection. To evaluate the safety and efficacy of this treatment, we conducted a feasibility study of preoperative CRT with CF and ENI followed by esophagectomy with 2- or 3-field lymphadenectomy in patients with clinical stage II/III ESCC.

Patients and methods

Patients

Patients were enrolled in this study according to the following eligibility criteria: histologically proven squamous cell carcinoma of the thoracic esophagus; clinical stages IIA, IIB, or III excluding T4 (International Union Against Cancer TNM classification system, 6th edition,); an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1; age 20–75 years; adequate organ function. Patients were excluded for any of the following conditions: history of any previous therapy for esophageal cancer; concurrent active malignancy; active infection; serious complications that might interfere with the achievement of study objectives; pregnancy or lactation. Written informed consent was required from all patients prior to enrollment. This study was approved by the Institutional Review Board at the each site. This study is registered in UMIN-CTR, number 000004223.

Chemotherapy

Chemotherapy comprised two courses of infusion of 5-fluorouracil (1000 mg/m^2/day) on days 1–4 and a 2-h infusion of cisplatin (75 mg/m^2) on day 1, with concurrent radiotherapy. Chemotherapy was repeated every 28 days. Modification of chemotherapy was done as same as mRTOG regimen, which was definitive CRT for stage II/III ESCC [13]. We determined that the protocol treatment was completed if: (1) the patient completed two courses of chemotherapy and received 41.4 Gy of radiotherapy; (2) tumor was resected as R0 surgery.

Radiotherapy

Radiotherapy was delivered with megavoltage equipment ($\geq$ 6 MV) using a multiple-field technique. Three-dimensional treatment planning was required. The total dose was set at 41.4 Gy in 23 fractions. A 3- or 4-field technique was strongly recommended for a middle or lower thoracic esophagus tumor. An opposite field technique was permitted for an upper thoracic esophagus tumor. Primary tumor and metastatic lymph nodes were contoured as gross tumor volumes (GTV). Primary tumor, metastatic lymph nodes and regional lymph nodes were contoured as clinical target volumes (CTV), including the primary tumor with a 2-cm craniocaudal margin, metastatic lymph nodes and regional lymph nodes. The regional lymph nodes were targeted for elective irradiation, including bilateral supraclavicular fossae and superior mediastinal lymph nodes, in carcinoma of the middle or lower thoracic esophagus. Celiac axis lymph nodes were also included in carcinoma of the lower thoracic esophagus. Planning target volume (PTV) was defined as CTV plus a 1–2-cm margin in the craniocaudal direction and 0.5–1 cm margin in the lateral direction to account for respiratory organ motion and daily setup error. The reference point for radiation doses was set at the center of the PTV. Lung inhomogeneity corrections were not used. The dose to the spinal cord was maintained below 45 Gy, the percentage of pulmonary volume irradiated to > 20 Gy (V 20) was limited to < 25% and the mean dose to the heart was limited to < 40 Gy.

Surgery

Surgery was performed within 56-days from the date of finished CRT. Patients underwent thoracotomy for curative resection by total or subtotal thoracic esophagectomy. A thoracoscopic procedure for esophagectomy was permitted. Regional lymphadenectomy consisted of a 2- or 3-field

lymphadenectomy. Evaluations of residual tumor (R) were classified as follows: R0, no residual tumor; R1, suspected residual tumor or microscopic residual tumor; or R2, macroscopic residual tumor. Surgical specimens were evaluated pathologically and graded according to the proportion of tumor affected by degeneration or necrosis using a grading system by the Japanese Classification of Esophageal Carcinoma [14]: grade 0, no part of tumor affected; grade 1, less than two-thirds affected; grade 2, between two-thirds and entire tumor affected; and grade 3, no residual tumor.

Treatment assessment

As safety assessments, adverse events (AE) were graded using common terminology criteria for adverse events (CTCAE) version 3.0. Approximately 4–6 weeks after CRT, the patient was re-evaluated by CT of the chest and upper abdomen. If there was no evidence of metastatic disease, surgery should be done immediately. During the first 2 years after treatment was completed, patients were seen every 4 months. After the third year, follow-up took place every 6 months. Tumor responses were evaluated by the investigators in the patients who had measurable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0.

Statistical methods

The primary endpoint was the completion rate of protocol treatment. Completion of protocol treatment was defined as follows; (1) two cycles of preoperative chemotherapy were completed, (2) 41.4 Gy of irradiation was administered, and (3) pathologically proven R0 resection was performed within 56 days after termination of CRT. Secondary endpoints included the safety and tolerability of this CRT, evaluation of operative morbidity and mortality, and efficacy, including response rate, progression-free survival (PFS), and OS. In the present trial, the incidence of toxicities from CRT with CF and ENI seemed to increase more than with CF as a preoperative setting; the rate of treatment completion was expected to be lower than that in the JCOG9907 study (89.6%). We assumed a null hypothesis of 75% completion rate for protocol treatment, and we expected a completion rate of protocol treatment of 90%. Using a one-sided binomial test at a 10% level of statistical significance and a statistical power of at least 80%, then a minimum of 28 patients was needed. Considering dropout of a few patients, the projected sample size was 30 patients in total. Summary statistics are presented as percentages in the case of categorical variables and as medians with ranges in the case of continuous variables. The survival curve was estimated using the Kaplan–Meier method. Safety and efficacy analyses were both conducted on per protocol set population, defined as all patients enrolled in the study who received at least one dose of chemotherapy. PFS was defined as the time from the date of registration to the first documentation of disease progression, subsequent therapy, or death. OS was determined from the date of registration to the date of death from any cause or to the last confirmation of survival. Statistical data were obtained using the SPSS software package (SPSS 11.0 Inc., Chicago, IL) and the SAS software, version 9.4 (SAS institute, Cary, NC, USA).

Results

Patient characteristics

From July 2010 to June 2011, 33 patients were enrolled from four institutions. Thirty-one patients were eligible and 2 patients were ineligible because of stage changing by conference after registration to the trial (stage I and stage IV). Twenty-eight patients were men, and the median age was 63 years (range 40–73 years). Nineteen and 12 patients showed ECOG PS of 0 and 1, respectively. Twenty-one patients had T3 disease and 19 patients had clinical stage III (Table 1).

Table 1 Patient characteristics

Characteristics	No. of patients (%)	
Sex		
Male	28	(90.3%)
Female	3	(9.7%)
Age, years		
Median (range)	63 (40–73)	
ECOG performance status		
0	19	(61.3%)
1	12	(38.7%)
Site of primary tumor		
Ut	2	(6.5%)
Mt	16	(51.6%)
Lt	13	(41.9%)
Clinical T stage		
T1	6	(19.4%)
T2	4	(12.9%)
T3	21	(67.7%)
Clinical N stage		
N0	2	(6.5%)
N1	29	(93.5%)
Clinical stage		
IIA	2	(6.5%)
IIB	10	(32.2%)
III	19	(61.3%)

Treatment profile

Thirty-one patients (100%) underwent CRT and 30 patients (96.8%) underwent surgery (Fig. 1). Eleven patients required dose reduction in the second cycle (cisplatin, 5 for 25% reduction and 6 for 50% reduction; 5-fluorouracil, 6 for 25% reduction and 5 for 50% reduction) mainly due to hematological toxicity at the beginning of the second course of CRT. However, all patients were able to receive subsequent chemotherapy due to appropriate dose reduction.

Toxicity of preoperative chemoradiotherapy

The most common grade 3 or 4 toxicities were leukopenia (65%), neutropenia (65%), anemia (13%), thrombocytopenia (13%), febrile neutropenia (13%), anorexia (16%), esophagitis (16%) and hyponatremia (16%) (Table 2). All toxicities were within expectation and manageable. CRT-related deaths were not observed.

Surgery and postoperative complications

Thirty patients received subsequent surgery after completion of preoperative CRT (Table 3). One patient in whom lung metastasis was observed after preoperative CRT received palliative chemotherapy with docetaxel without surgery. All patients who had undergone surgery received 2- or 3-field lymphadenectomy (4 patients with 2-field and 26 patients with 3-field), and 29 out of 30 patients underwent R0 surgery pathologically. The median operation time was 440.5 min (range 20–860 min) and the median blood loss was 283.5 ml (range 95–900 ml). The median duration time from the beginning of the last cycle to surgery was 39 days (range 28–65 days). In all cases whose time to surgery was over 56-days, the extension was due to hospital reasons. The most common surgical complications were pleural fluid

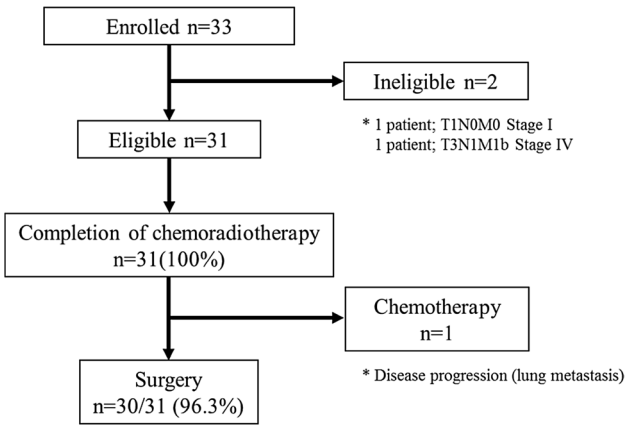

Fig. 1 Accrual and treatment summary

Table 2 Adverse events of preoperative CRT

Toxicity CTCAE ver. 3.0	No. of patients ($n=31$)				
	Grade				
	1	2	3	4	≧ Grade3 (%)
Leukopenia	0	11	17	3	20 (65%)
Neutropenia	5	6	14	6	20 (65%)
Anemia	19	6	6	0	6 (19%)
Thrombocytopenia	20	5	4	0	4 (13%)
Febrile neutropenia	–	–	4	–	4 (13%)
Fatigue	12	5	2	0	2 (6%)
Anorexia	8	12	5	0	5 (16%)
Nausea	11	6	3	0	3 (10%)
Vomiting	3	0	0	0	0 (0%)
Mucositis	7	2	1	0	1 (3%)
Esophagitis	6	19	5	0	5 (16%)
Diarrhea	5	2	0	0	0 (0%)
Creatinine	8	3	0	0	0 (0%)
Hyponatremia	21	–	6	–	6 (19%)
Others[a]	–	–	2	0	2 (6%)

CTCAE common terminology criteria for adverse events

[a]One gastric ulcer (Grade 3), one loss of consciousness (Grade 3)

Table 3 Operative details and postoperative outcomes

	No. of patients (%)
Surgical approach	
Open thoracotomy	21 (70%)
Thoracoscopy	9 (30%)
Lymphadenectomy	
D3	26 (87%)
D2	4 (13%)
Type of resection	
R0	29 (97%)
R1	1 (3%)
Postoperative complications	
Pleural fluid	9 (30%)
Anastomotic leakage	8 (27%)
Recurrent nerve palsy	8 (27%)
Pneumonia	5 (17%)
Wound infection	5 (17%)
Chylothorax	4 (13%)
Persistent hypoxemia	5 (17%)
Acute circulatory failure	5 (17%)
Pyothorax	5 (17%)
Bronchial fistula	1 (3%)
Thrombosis (pulmonary embolism)	1 (3%)
Cerebral infarction	1 (3%)
30-days postoperative mortality	1 (3%)

(30%), anastomotic leakage (27%), recurrent nerve palsy (27%), pneumonia (17%), wound infection (17%) and chylothorax (13%). One patients died within 30-day from surgery due to cerebral infarction. Because this patient developed a mediastinal abscess after anastomotic leakage, it was characterized as a treatment-related death. With the exception of this patient, all patients with complications recovered.

Treatment outcome

Of 31 eligible patients, two patients failed to complete the protocol treatment, one due to progressive disease with lung metastasis and one due to R1 resection pathologically after esophagectomy. As a result, the completion rate of protocol treatment was 93.6% [80% confidence interval (CI) 83.7–98.2%, one-sided P value = 0.0084]. Among 18 patients who had measurable lesions, one complete and 13 partial responses were observed, giving an overall response rate of 78% (95% CI 44.1–81.4%). Most patients (77%) achieved pathological down-staging after surgery, and a pathological complete response (pCR) was achieved in 42% of the patients who underwent esophagectomy (Table 4). With a median follow-up time of 54.3 months, the estimated 3-year PFS and OS rates were 60.9% (95% CI 41.5–75.6%) and 70.8% (95% CI 51.4–83.6%), respectively (Fig. 2). Median PFS was not reached. Recurrence was seen in 9 patients (regional lymph nodes only, 2 patients; any distant metastasis, 7 patients). Local failure rate (regional recurrence plus R1-2 resection) was 9.7% (3/31), and 27.3% (3/11) in recurrent cases.

Discussion

In this multicenter trial, preoperative CRT with CF and ENI followed by esophagectomy with 2- or 3-field lymph node dissection was shown to be tolerable and demonstrated high rates of clinical and histopathological responses.

Preoperative CRT followed by surgery had earlier shown survival benefit compared to surgery in locally advanced esophageal cancer [6, 15], however, preoperative chemotherapy with CF followed by surgery significantly improved OS compared to surgery with postoperative chemotherapy in JCOG9907. Nevertheless, it was still unresolved whether preoperative CRT or preoperative chemotherapy would be preferable. Recently, the NeoRes trial has shown no additional benefits of radiotherapy over preoperative chemotherapy with CF [16]. In this trial, 11 of 24 patients (46%) in the preoperative CRT arm and 3 of 20 patients (15%) in the preoperative chemotherapy arm ($P = 0.036$) died from causes other than tumor recurrence during the first year after randomization, which seemed to be a main disadvantage of preoperative CRT. Thus, control of complications and toxicity could be the most important issue in pre- or postoperative therapy.

In our study, the frequency of adverse effects during CRT was higher than that reported in patients treated with preoperative chemotherapy with CF in the previous studies, but although the incidence of grade 3 or 4 AE is relatively high, there was no treatment interruption or discontinuation. In comparison with previous studies on preoperative CRT with CF, AE during CRT and complications after surgery seemed to be comparable, despite radical lymph node dissections.

Table 4 Response of preoperative CRT

Clinical response						
Response	Patients with measurable lesion ($n = 18$)		Patients without measurable lesion ($n = 13$)		Total % ($n = 31$)	
CR	1	6%	4	31%	5	16%
PR	13	72%	–	–	13	42%
(IR/)SD	2	11%	9	69%	11	35%
PD	2	11%	0	0%	2	6%
CR + PR	14	78%	4	31%	18	58%
Pathological response						
Response	No. of patients	%				
Grade1	6	19				
Grade2	11	35				
Grade3	13	42				
pCR	13	42				

CR complete response, *PR* partial response, *IR* incomplete response, *SD* stable disease, *PD* progressive disease, *pCR* pathological complete response

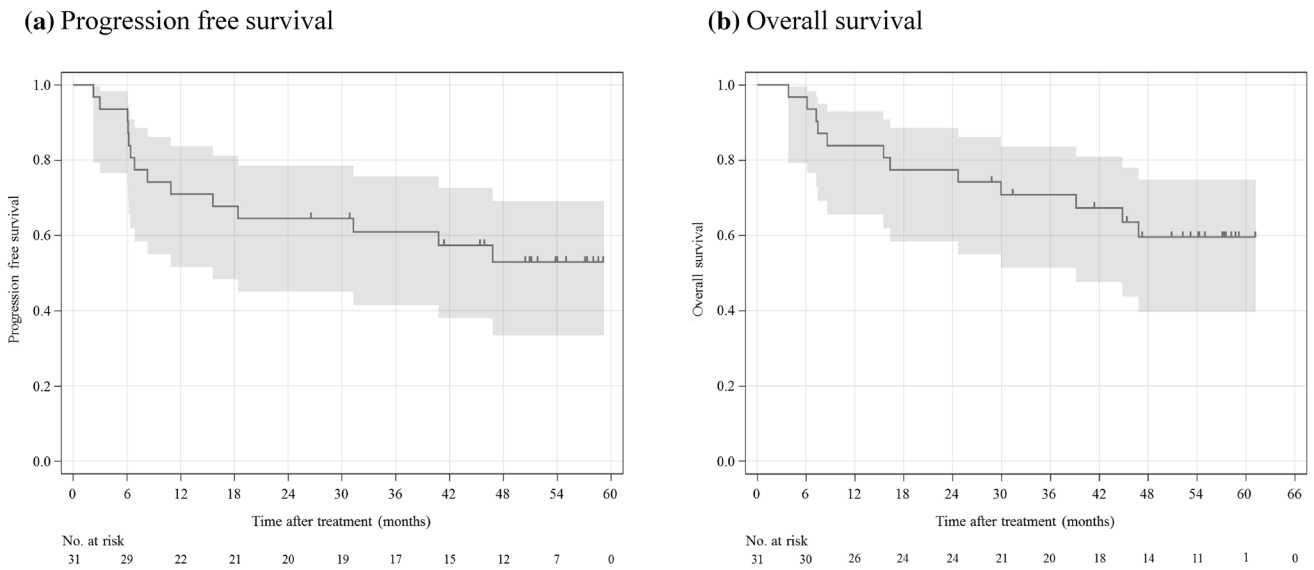

Fig. 2 Progression-free survival and overall survival for all eligible patients. Kaplan–Meier estimates of **a** progression-free survival and **b** overall survival. The estimated 3-year progression-free survival and overall survival were 60.9 and 70.8%, respectively

One patient died within 30 days after surgery in this trial, but this patient had uncontrolled diabetes and needed insulin therapy. He completed preoperative CRT with no severe AE before surgery but suffered anastomotic leakage and mediastinal abscess after surgery. Subsequently, he suffered tracheal perforation and cerebral infarction, and died of cerebral infarction. Control of postoperative complications is still a major issue. In this study, anastomotic leakage (27%), pneumonia (17%) and chylothorax (13%) were observed, which were slightly higher than the AE in the CROSS trial. We suggest that exposure of peri-gastric and celiac lymph nodes to ENI may be the cause of the relatively higher incidence of anastomotic leakage. These lymph nodes may reduce the blood flow in the anastomosis site. Since decreasing the range of ENI may reduce anastomotic leakage, we are omitting prophylactic radiotherapy to peri-gastric and celiac lymph nodes in further phase III trial, named NExT trial [17]. The toxicities during chemoradiotherapy and after surgery seemed to be generally manageable, and the threshold rate of completion of the protocol treatment, which was 60% in the study design, was achieved (the completion rate of protocol treatment was 93.6%, 80% CI 83.7–98.2%), and thus meets the primary endpoint. Another issue should be discussed: the surgical procedure in this trial, which was esophagectomy with radical, 2- or 3-field, lymph node dissection, was different from that in the CROSS trial or other Western trials. Though intensive local therapy, such as CRT with ENI and esophagectomy with 2- or 3-field lymph node dissection, was administered in this trial, the operative mortality and morbidity were not increased compared to those in the CROSS trial.

The pCR rate was 42%, which is markedly higher than the 5% reported for preoperative chemotherapy with CF in the JCOG 9907 study and comparable with preoperative CRT in other studies [6, 15, 18, 19]. It is unclear whether pCR is a surrogate marker for survival. In the NeoRes trial, the pCR was much higher in a preoperative CRT (28%) group than in a chemotherapy (9%) group, but survival was the same in the two groups. So it is important to monitor not only pCR rate but also long-term survival in both types of treatments. The efficacy of preoperative ENI is unclear, so we conducted this study. In this study, the local failure rate (regional recurrence plus R1-2 resection) was 9.7%, which is slightly lower than the approximately 12% reported for preoperative chemotherapy with CF in the JCOG 9907 study and previously reported for preoperative CRT [12, 15]. In addition, in previous report, even in patients with clinical T1N0 thoracic esophageal cancer who received surgery, they often had pathological tracheobronchial lymph node metastasis [20]. Patients with no lymph node metastasis clinically may have occult lymph node metastasis and complete dissection of tracheobronchial and neck lymph node is difficult. Therefore, preoperative ENI may be meaningful for patients with resectable EC.

Some small trials on preoperative chemotherapy have used triplet chemotherapy, which resulted in increased toxicity without significant survival benefits. However, a higher antitumor activity of preoperative chemotherapy with docetaxel, cisplatin and 5-fluorouracil (DCF) was recently reported in several phase II studies. A phase II trial on perioperative chemotherapy with DCF for esophageal and gastric adenocarcinoma showed 10% pCR among 43 patients [21].

Hara et al. reported that preoperative chemotherapy with DCF for ESCC was well tolerated and the pCR rate was 17% (7/41) [22]. Stahl et al. reported on preoperative CRT compared with chemotherapy in locally advanced adenocarcinoma of esophagogastric cancer [23]. Although this trial was closed early due to poor accrual and because statistical significance was not achieved, the 3-year survival favored the CRT arm (47.4% vs. 27.7%). On the other hand, the Neo-Res trial has not shown a benefit of preoperative CRT. After all, these problems may be solved by conducting a direct comparison between preoperative chemotherapy and CRT. There is an urgent need to address this clinical question in some regions where squamous cell carcinoma is dominant.

Some limitations are present in this trial. The trial was done in a small number of selected institutions and in selected patients. Only results from squamous cell cancer patients with short follow-up time were shown. These results should be evaluated in a large-scale phase III trial.

In conclusion, we found that preoperative CRT with CF and ENI was feasible in patients with resectable ESCC. As these results demonstrated a highly promising antitumor activity, we are now proceeding with a three-arm randomized phase III trial comparing chemotherapy with CF, with DCF and CRT with CF and ENI as a preoperative therapy for locally advanced ESCC [24]. We are quite confident that this confirmatory trial along these lines will prove very valuable.

Acknowledgements We express our appreciation to Mr. Nagai, Ms. Tada, Ms. Usami, Ms. Sakamoto, Ms. Ayabe, and Ms. Shinogi for data collection and management.

Funding This study was also supported by National Cancer Center Research and Development Funds (23-A-16, 23-A-18 and 26-A-4).

Compliance with ethical standards

Conflict of interest No author has any conflict of interest.

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