A RETROSPECTIVE COHORT STUDY COMPARING NEOADJUVANT CHEMOTHERAPY VS. NEOADJUVANT CHEMORADIOTHERAPY FOR PATIENTS WITH LOCALLY ADVANCED THORACIC ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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(received 2 February 2022, accepted 13 May 2022)

Abstract

Background : Based on results from the Japan Clinical Oncology Group (JCOG) 9204 and JCOG 9907 trials, neoadjuvant-CF (cisplatin+5-fluorouracil) followed by esophagectomy with extended lymphadenectomy is the standard treatment for patients with locally advanced thoracic esophageal squamous cell carcinoma (ESCC) in Japan. Recently, however, results from the JCOG 1109 trial revealed that neoadjuvant-DCF (docetaxel+cisplatin+5-fluorouracil) provides significantly better overall survival (OS) than neoadjuvant-CF, whereas neoadjuvant chemoradiotherapy (NACRT) did not produce significantly better outcomes than neoadjuvant-CF.

Methods : We retrospectively identified 225 ESCC patients treated between December 2008 and December 2021 who received esophagectomy at Akita University Hospital. These patients were divided into neoadjuvant-CF (NAC, $n=30$) and NACRT (NACRT, $n=195$) groups before esophagectomy. Using the Kaplan-Meier method, we compared OS and disease-specific survival (DSS) between the two groups.

Results : The pathological response to treatment was significantly better in the NACRT than the NAC group. Although 5-year OS and DSS were better in the NACRT than NAC group, these differences did not reach statistical significance.

Conclusion : Among patients with locally advanced thoracic ESCC, NACRT produced a significantly better pathological response than NAC. However, NACRT did not produce significantly better long-term survival than NAC, which is consistent with the results of JCOG 1109.

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Key words: esophageal squamous cell carcinoma, prognosis, neoadjuvant treatment, chemoradiotherapy, esophagectomy

Introduction

In Asia, Africa and Central America, the predominant pathological subtype of esophageal cancer is esophageal squamous cell carcinoma (ESCC)[1,2]. Clinical trials carried out in several countries have investigated the efficacy of various neoadjuvant treatments for patients with locally advanced ESCC[3,4]. In Japan, based on the results of Japan Clinical Oncology Group (JCOG) 9204[5] and JCOG 9907[6], neoadjuvant CF (cisplatin + 5-fluorouracil) followed by esophagectomy with extended lymphadenectomy is now the standard treatment for these patients. In addition, the results of JCOG 1109[7], comparing neoadjuvant CF, neoadjuvant DCF (docetaxel + cisplatin + 5-fluorouracil) and neoadjuvant chemoradiotherapy (NACRT; CF + 41.4 Gy/23 fractions) found that neoadjuvant DCF provided significantly longer median survival time than neoadjuvant CF (DCF: not reached vs. CF: 5.6 years, HR 0.68, $p=0.006$). On the other hand, NACRT did not appear to provide a significant prolongation of median survival time as compared to CF (NACRT: 7.0 years vs. CF: 5.6 years, HR 0.84, $p=0.12$). From on these results, it appears that neoadjuvant DCF is the most appropriate neoadjuvant treatment before esophagectomy with extended lymphadenectomy for these patients.

In 2008, prior to the launch of JCOG 1109, we began using NACRT as a neoadjuvant treatment for these patients in parallel with neoadjuvant CF. In the present study, we retrospectively identified patients treated with NACRT or neoadjuvant CF followed by esophagectomy with extended lymphadenectomy and compared the survival between these two groups.

Patients and Methods

Patients

This study was approved by the Ethics Committee of Akita University School of Medicine (#2617), and all experiments were performed in accordance with the Helsinki Declaration. All study participants provided informed written consent. We retrospectively identified 566 patients who received esophagectomy for esophageal cancer at Akita University Hospital between December 2008 and December 2021. Among these, we excluded 341 patients who had up-front esophagectomy, salvage esophagectomy or esophagectomy for other histological subtypes (Figure 1). The remaining 225 ESCC patients were analyzed in the present study. For analysis, these patients were further divided into neoadjuvant CF (NAC; $n=30$) and NACRT ($n=195$) groups. We then used the Kaplan-Meier method to compared overall survival (OS) and disease specific survival (DSS) between the two groups. The clinical tumor stages of all the patients were decided by a cancer board composed of radiologists, oncologists, gastroenterologists, and surgeons based on the results of blood tests, upper gastrointestinal endoscopy, CT and $^{[18F]}$FDG-PET. Clinical and pathological stages were determined according to the latest 8th edition of TNM classification of Malignant Tumours by the UICC[8].

Neoadjuvant treatment

The dosages used for NAC were identical to those used in JCOG 9204[5], JCOG 9907[6] and JCOG 1109[7]. Briefly, 80 mg/m^2 cisplatin was administrated on day 1, and 800 mg/m^2 5-fluorouracil were continuously administered over each 24-hour period on days 1-5. This protocol was repeated twice with at least a 3-week interval in between. The regimen for NACRT was administration of the same doses of NAC concurrently with radiation. A representative radiation field for a middle thoracic ESCC patient is shown in Figure 2. External body radiation was delivered by anterior and posterior opposite-beam interpolation using a 10 MV X-ray beam at 1.8 Gy/day for 5 days each week to a total amount of 41.4 Gy in 23 fractions. Radiation fields were limited to the esophageal primary lesion with craniocaudal 3-cm margins and to clinically metastatic lymph nodes without elective nodal area radiation. All radiation plans were made by certificated radiation oncologists with three-dimensional conformal radiotherapy planning based on simulation

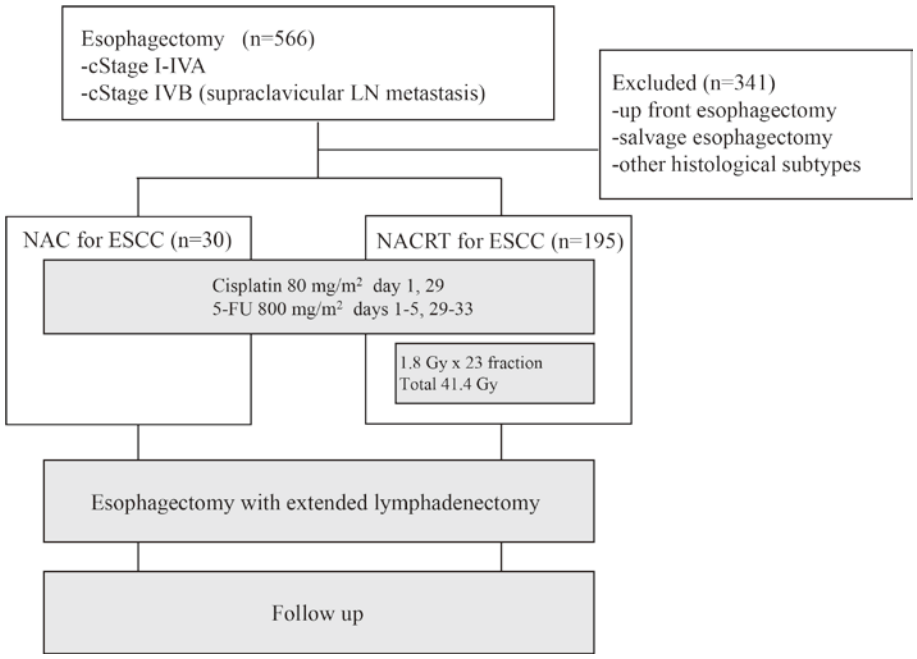

Figure 1. Study design of this randomized, retrospective cohort study. Thirty patients were treated with neoadjuvant CF (NAC group) while 195 patients were treated with NACRT (NACRT group) before esophagectomy.

CT. Grading of adverse events associated with the NAC or NACRT was according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. When a patient experienced a severe adverse event or showed obvious progressive disease after the first course of NAC and was therefore judged to be intolerant or nonresponsive, the second course of NAC was canceled, and esophagectomy was performed after an adequate non-dosing period.

Esophagectomy

Our standard operative procedure for thoracic ESCC patients was right thoracoscopic/robot-assisted or open esophagectomy with resection of the cardiac portion of the stomach. Also performed was extended three-field lymph node dissection of the upper to lower mediastinal (involving the periesophageal region and areas around the trachea and bilateral main bronchus), abdominal (involving the perigastric region and areas around the celiac axis), and cervical (involving the bilateral periesophageal region and supraclavicular region) lymph nodes. Reconstruction commonly involved insertion of a gastric conduit via the posterior mediastinal route or retrosternal route[15-18]. Surgical complications were evaluated using the Clavien-Dindo classification[19].

Pathological response

The pathological response of the primary tumor was graded as follows using the response evaluation criteria for the effects of radiation, chemotherapy or both published by the Japanese Esophageal Society[9,10] : Grade 0, no recognized cytological or histological therapeutic effect ; Grade 1, slightly effective, with apparently viable cancer cells accounting for at least one-third of the tumor tissue ; Grade 2, moderately effective with viable cancer cells accounting for less than one-third of the tumor tissue ; and Grade 3, markedly effective, with no evidence of viable cancer cells (complete response).

Statistical analysis

To evaluate differences between the NAC and NACRT groups, the Mann-Whitney-Wilcoxon test was used for

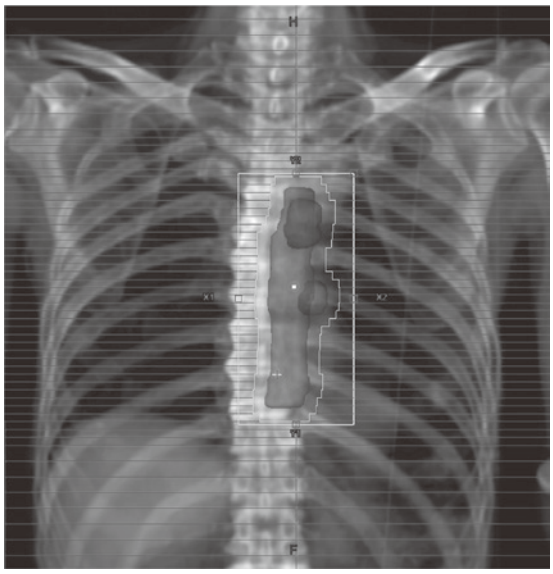

Figure 2. Representative radiation field for a middle thoracic ESCC patient. Beams eye view of the anterior field for a 69-year-old male with advanced middle thoracic ESCC staged as clinical T3N2M0. The radiation fields were limited to the primary esophageal lesion with craniocaudal 3-cm margins and clinically metastatic lymph nodes without elective nodal area radiation.

continuous variables, and the χ^2 and Fisher's exact tests were used for categorical variables. Length of survival was calculated from the first date of neoadjuvant treatment to the patient's death or date of the last clinical follow-up. Oncological outcomes, including OS and DSS, were investigated using the Kaplan-Meier method and compared using the log-rank test. In univariate and multivariate analyses, we utilized a Cox proportional hazard analysis to investigate differences between the two groups while adjusting for significant variables at a p-value <0.05. All statistical analysis were performed using JMP Pro14 (Version 14.2.0, SAS Institute Inc., Cary, NC). Values of $p<0.05$ (two-sided) were considered significant.

Results

Clinicopathological characteristics and esophagectomy after neoadjuvant treatment

The pre- and post-treatment clinicopathological characteristics of the patients in the NAC and NACRT groups are summarized in Table 1. There were no significant differences between the two groups with respect to sex, age at surgery, tumor location, cT, cM, cStage, ypT, ypN, ypM, ypStage or prognosis. However, the NACRT group showed a significantly higher rate of well-differentiated tumors ($p=0.01$), higher cN ($p=0.04$) and a greater pathological response ($p=<0.01$) than the NAC group. There were three patients in the NACRT group whose tumors were T4b (tracheobronchial or aorta) and resulted in residual tumors.

Variables related to esophagectomy after neoadjuvant treatment are summarized in Table 2. The number of dissected lymph nodes was significantly smaller in the NACRT group ($p=<0.01$), and the number of days between neoadjuvant treatment and esophagectomy was significantly greater in the NACRT group ($p=<0.01$). There were no significant differences in any other factors.

Adverse events and reasons of discontinuation of neoadjuvant treatments

Adverse events and the reasons for discontinuation of neoadjuvant treatments are summarized in Table 3. The NACRT group had a significantly higher rate of Grade 3 and 4 leukopenia ($p=<0.01$) and neutropenia ($p=<0.01$) than the NAC group. The completion rate in the NAC group was 76.7%, while the completion rate in the NACRT group was 88.2%. In the NAC group, treatments of 7 patients (23.3%) were discontinued before the second course of NAC, whereas treatments of 23 patients (11.8%) were discontinued before the second NAC course in the NACRT group. Although the primary reason of discontinuation in the NACRT group was leukopenia (4.6%), discontinuation in the NAC group was primarily due to progression of their ESCC (16.7%).

5-year survival analysis

Kaplan-Meier analysis of survival among the 225 pa-

Table 1. Pre- and post-treatment clinicopathological features of ESCC patients

Characteristics	Neoadjuvant chemotherapy (n=30) N (%)	Neoadjuvant chemoradiotherapy (n=195) N (%)	p
Sex			0.94
Female	4 (13.3%)	27 (13.9%)	
Male	26 (86.7%)	168 (86.1%)	
Age at surgery, median (min-max)			0.11
	63 (47-78)	65 (41-77)	
Tumor location			0.46
Upper	3 (10.0%)	38 (19.5%)	
Middle	16 (53.3%)	94 (48.2%)	
Lower	11 (36.7%)	63 (32.3%)	
Differentiation			0.01*
Well	0	35 (20.0%)	
Moderate	22 (73.3%)	135 (50.0%)	
Poor	8 (26.7%)	25 (30.0%)	
cT			0.08
1	3 (10.0%)	8 (4.1%)	
2	5 (16.7%)	12 (6.2%)	
3	22 (73.3%)	172 (88.2%)	
4a	0	3 (1.5%)	
cN			0.04*
0	9 (30.0%)	23 (11.8%)	
1	16 (53.3%)	115 (59.0%)	
2	5 (16.7%)	54 (27.7%)	
3	0	3 (1.5%)	
cM (supraclavicular LN metastasis)			0.90
Positive	3 (10.0%)	21 (10.8%)	
Negative	27 (90.0%)	174 (89.2%)	
cStage (UICC-TNM8th)			0.38
I	2 (6.7%)	7 (3.6%)	
II	10 (33.3%)	38 (19.5%)	
III	15 (50.0%)	127 (65.1%)	
IVA	0	2 (1.0%)	
IVB (supraclavicular LN metastasis)	3 (10.0%)	21 (10.8%)	
Pathological response			<0.01*
0	7 (23.3%)	0	
1	20 (66.7%)	62 (31.8%)	
2	2 (6.7)	88 (45.1%)	
3 (complete response)	1 (3.3%)	45 (23.1%)	
ypT			0.10
0	2 (6.7%)	54 (27.8%)	
1	7 (23.3%)	28 (14.4%)	
2	3 (10.0%)	29 (15.0%)	

Table 1. Continued

Characteristics	Neoadjuvant chemotherapy (n=30) N (%)	Neoadjuvant chemoradiotherapy (n=195) N (%)	p
3	16 (53.3%)	74 (38.2%)	
4a	2 (6.7%)	6 (3.1%)	
4b (residual tumor)	0	3 (1.5%)	
ypN			0.08
0	12 (40.0%)	109 (56.2%)	
1	9 (30.0%)	58 (29.9%)	
2	6 (20.0%)	22 (11.3%)	
3	3 (10.0%)	5 (2.6%)	
ypM (supraclavicular LN metastasis)			0.59
positive	3 (10.0%)	14 (7.2%)	
negative	27 (90.0%)	181 (92.8%)	
ypStage (UICC-TNM8th)			0.45
I	7 (23.3%)	71 (36.4%)	
II	5 (16.7%)	37 (19.0%)	
IIIA	3 (10.0%)	25 (12.8%)	
IIIB	9 (30.0%)	40 (20.5%)	
IVA	3 (10.0%)	8 (4.1%)	
IVB	3 (10.0%)	14 (7.2%)	
Prognosis			0.16
Alive	14 (46.7%)	121 (62.1%)	
Alive after recurrence	2 (6.7%)	16 (8.2%)	
Deceased with ESCC	10 (33.3%)	47 (24.1%)	
Deceased with another Cancer	0	3 (1.5%)	
Deceased with other diseases	4 (13.3%)	8 (4.1%)	

tients is shown in Figure 3. The median follow-up period for censored cases was 60 months. The 5-year OS rate was 61.0% in the NACRT group and 53.9% in the NAC group (Figure 3A). The 5-year DSS rate was 68.5% in the NACRT group and 60.1% in the NAC group (Figure 3B). Although NACRT group tended to have greater rates of 5-year OS and DSS than the NAC group, the differences did not reach statistical significance.

Prognostic factors affecting 5-year OS

The results of univariate and multivariate analyses of the 5-year OS among all 225 patients are summarized in Table 4. Univariate analysis showed that sex (male vs female), pathological response (Grade 2-3 vs Grade 0-1), cT (T3-4 vs. T1-2), cStage (Stage III-IV vs Stage I-II), ypT (T3-4 vs. T0-2), ypN (N2-3 vs. N0-1) and ypStage (Stage III-IV vs Stage I-II) are all significant prognostic factors affecting 5-year OS. On the other hand, whether a patient received NAC or NACRT was not a significant factor affecting 5-year OS. Multivariate analysis considering the seven factors affecting 5-year OS as well as neoadjuvant treatment showed that sex (male vs female), cT (T3-4 vs T1-2) and ypN (N2-3 vs. N0-1) are independent prognostic factors affecting 5-year OS. The hazard ratio for NAC vs. NACRT was 1.10 (95%CI 0.46-1.80, p=0.78).

Discussion

In this study, we showed that NACRT produced a sig-

Table 2. Variables related to esophagectomy after neoadjuvant treatment

Variables	Neoadjuvant chemotherapy (n=30)	Neoadjuvant chemoradiotherapy (n=195)	p
Operative procedure			0.19
Open	21 (70.0%)	112 (57.4%)	
Thoracoscopic and robot-assisted	9 (30.0%)	83 (42.6%)	
Organ for reconstruction			0.59
Stomach	29 (96.7%)	178 (91.3%)	
Colon and small intestine	1 (3.3%)	17 (8.7%)	
Reconstructive route			0.44
Posterior mediastinal	23 (76.7%)	129 (66.1%)	
Retrosternal	4 (13.3%)	46 (23.6%)	
Subcutaneous	3 (10.0%)	20 (10.3%)	
Operative duration (min)	549 (383-963)	583 (386-928)	0.08
Blood loss (mL)	527.5 (170-1,588)	483 (78-3,366)	0.50
Dissected lymph nodes	66.5 (24-109)	49 (8-97)	<0.01*
Lymph nodes metastasis	0 (0-16)	1 (0-18)	0.02*
Days between neoadjuvant treatment and esophagectomy	30.5 (22-55)	38 (21-175)	<0.01*
Days of hospital stay after esophagectomy	24.5 (18-82)	26 (16-89)	0.17
Anastomotic leakage (CD>1)			0.41
Positive	2 (6.7%)	23 (11.8%)	
Negative	28 (93.3%)	172 (88.2%)	
Pneumonia (CD>3)			0.42
Positive	2 (6.7%)	7 (3.6%)	
Negative	28 (93.3%)	188 (96.4%)	
Recurrent nerve palsy (CD>1)			0.25
Positive	6 (20.0%)	59 (30.3%)	
Negative	24 (80.0%)	1,136 (69.7%)	

nificantly better pathological response than NAC, though it did not significantly improve 5-year survival compared to NAC. We recently reported that among 94 cStage III patients treated with NACRT followed by esophagectomy with extended lymphadenectomy[18], 5-year and 10-year OS were 57.6% and 41.4%, respectively. In the JCOG 9907 trail[6], although the 5-year OS rate in the neoadjuvant-CF group was 55%, that group was composed of 82 clinical Stage II patients and 82 clinical Stage III patients. This means that the cStage III patients treated with NACRT in the present study had a better 5-year OS rate (57.6%) than the combined Stage II and III patients treated with neoadjuvant-CF in the JCOG 9907 trail. In the JCOG 1109[7] trial, the pathological complete response (pCR) rate was higher with NACRT than with neoadjuvant DCF (NACRT : 43.5%, neoadjuvant DCF : 21.9%, neoadjuvant CF : 2.2%). This indicates NACRT provides more powerful local control than neoadjuvant DCF. However, it was also reported that patients treated with NACRT experienced more deaths from diseases other than ESCC. Consequently, median survival time was not significantly prolonged with

Table 3. Adverse events and reasons for discontinuation of neoadjuvant treatments

Characteristic	Neoadjuvant chemotherapy (n=30)	Neoadjuvant chemoradiotherapy (n=195)	p
Leukopenia			<0.01*
Grade 0-2	30 (100%)	125 (64.1%)	
Grade 3-4	0	70 (35.9%)	
Neutropenia			<0.01*
Grade 0-2	30 (100%)	160 (82.0%)	
Grade 3-4	0	35 (18.0%)	
Anemia			0.44
Grade 0-2	30 (100%)	186 (95.4%)	
Grade 3-4	0	9 (4.6%)	
Thrombopenia			0.81
Grade 0-2	30 (100%)	190 (97.5%)	
Grade 3-4	0	5 (2.5%)	
Hyponatremia			0.53
Grade 0-2	27 (90%)	184 (94.4%)	
Grade 3-4	3 (10.0%)	11 (5.6%)	
Neoadjuvant treatment completion			0.08
Completed	23 (76.7%)	172 (88.2%)	
Not completed	7 (23.3%)	23 (11.8%)	
Reason of discontinuation			
Progressive disease	5 (16.7%)	0	
Renal dysfunction	1 (3.3%)	5 (2.6%)	
Leukopenia	0	9 (4.6%)	
Febrile neutropenia	0	2 (1.0%)	
Thrombopenia	0	1 (0.5%)	
Hyponatremia	0	3 (1.5%)	
Gastric ulcer	1 (3.3%)	1 (0.5%)	
Osteomyelitis	0	1 (0.5%)	
Rejection	0	1 (0.5%)	

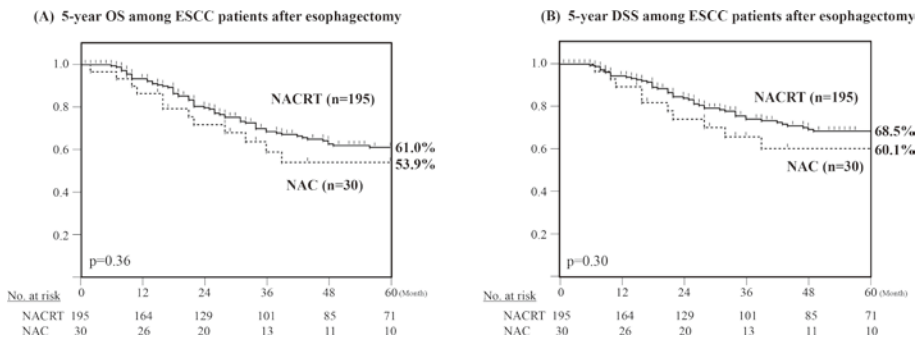

Figure 3. Kaplan-Meier curves showing the 5-year OS (A) and DSS (B) in the NAC and NACRT groups. Although 5-year OS and DSS were both better in the NACRT than NAC group, these differences did not reach statitical significance.

Table 4. Univariate and multivariate analyses of 5-years OS

Variable	*n*	Univariate Hazard Ratio (95%CI)	*p*	Multivariate Hazard Ratio (95%CI)	*p*
Age					
Under 65	106	1.00			
65 and older	119	1.26 (0.80-2.00)	0.32		
Sex					
Female	31	1.00		1.00	
Male	194	4.95 (0.06-0.64)	<0.01*	5.35 (1.66-17.24)	<0.01*
Tumor differentiation					
Not poorly	191	1.00			
Poorly	34	0.79 (0.41-1.54)	0.49		
Neoadjuvant treatment					
NACRT	195	1.00		1.00	
NAC	30	1.33 (0.72-2.47)	0.37	1.10 (0.46-1.80)	0.78
Pathological response					
Grade 2-3	136	1.00		1.00	
Grade 0-1	89	2.28 (1.44-3.61)	<0.01*	1.62 (0.87-3.01)	0.13
Number of dissected LN					
<49	110	1.00			
>50	115	0.81 (0.51-1.28)	0.37		
Tumor location					
Upper	41	1.00			
Middle and Lower	184	1.25 (0.67-2.33)	0.48		
cT					
T1-2	27	1.00		1.00	
T3-4	198	5.23 (1.28-21.44)	0.02*	5.65 (1.19-26.86)	0.03*
cN					
N0-1	164	1.00			
N2-3	61	1.11 (0.67-1.83)	0.67		
cM (supraclavicular LN)					
Negative	201	1.00			
Positive	24	1.75 (0.94-3.25)	0.08		
cStage					
I-II	57	1.00		1.00	
III-IV	168	2.32 (1.19-4.52)	0.01*	1.27 (0.61-2.62)	0.52
ypT					
T0-2	123	1.00		1.00	
T3-4	102	2.10 (1.32-3.33)	<0.01*	1.12 (0.62-2.01)	0.71
ypN					
N0-1	189	1.00		1.00	
N2-3	36	3.45 (2.12-5.59)	<0.01*	2.97 (1.60-5.52)	<0.01*
ypM (supraclavicular LN)					
Negative	208	1.00			
Positive	17	1.83 (0.88-3.81)	0.11		
ypStage					
I-II	120	1.00		1.00	
III-IV	105	2.01 (1.26-3.20)	<0.01*	1.01 (0.56-1.82)	0.97

CI : confidence interval, *Considered significant,

NACRT as compared neoadjuvant CF. Although in the present study the rate of patients dying from with other diseases was lower in that NACRT than the NAC group, the results of JCOG 1109 highlights the need to pay close attention to other diseases as well as recurrence when following patients treated with NACRT followed by esophagectomy with extended lymphadenectomy. In the present study, the pCR rate was 23.1%, which is slightly more that half the pCR rate reported from JCOG 1109. Although the cT status of patients in JCOG 1109 have not been reported, the reason for the difference may be the fact that 90% of patients in the present study were cT3 or higher.

In the present study, the number of dissected lymph nodes was significantly lower in the NACRT than the NAC group, which is consistent with the finding reported in JCOG 1109[7]. We suggest the reason for this result may be that both metastatic and healthy lymph nodes are scarred by the radiation.

The main limitations of the present study are its retrospective nature and the small number of patients in the NAC group. Because the number of NAC group was low, it is important that we continue to accumulate treatment results for these patients so as to produce more reliable survival curves.

In summary, our findings show that NACRT provided a significantly better pathological response than NAC. However, NACRT did not produce significantly better long-term survival than NAC, which is consistent with the earlier finding in JCOG 1109.

Disclosure : All authors state that they have no conflict of interest to disclose.

Abbreviations
ESCC : esophageal squamous cell carcinoma
NAC : neoadjuvant chemotherapy
NACRT : neoadjuvant chemoradiotherapy
CF : Cisplatin + 5-Fluorouracil
DCF : Docetaxel + Cisplatin + 5-Fluorouracil

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