Table 2. Treatment exposure

Relative dose intensity (%)	S-1* (median dose intensity, 80 mg · m^{-2} · d^{-1} × 25 days)		Irinotecan (median dose intensity, 80 mg · m^{-2} · d^{-1} × 4 days)	
	No. of patients	%	No. of patients	%
100	65	97	58	86.6
≥90 to <100	1	1.5	0	0
≥80 to <90	0	0	0	0
≥70 to <80	0	0	8	11.9
Missing	1	1.5	1	1.5

* The maximum dose of S-1 was 120 mg · m^{-2} · d^{-1}.

rate of pathologic CR was 31.6% in the Phase I setting (16), and our result was comparable in this Phase II setting. The total response rate involving both Grade 2 (considerable response) and Grade 3 (CR) was 68.7% (46 of 67 patients), whereas that including even Grade 1a/1b (slight response) reached 100%, if evaluated in the primary cancers (Table 3). Although no cancer cells were found in 54 patients (80.6%) on colonoscopy with biopsy after chemoradiotherapy, more than half of these patients were actually confirmed to have residual disease on histopathologic examination of the resected specimens.

Safety includes incidences of adverse reactions and complications, and adverse events as acute toxicities are summarized in Table 5. Adverse events are infrequent, and there was no Grade 4 hematologic or nonhematologic toxicity. Regarding hematologic toxicity, only 3 patients had Grade 3 leukopenia and 3 had Grade 3 neutropenia. One patient with Grade 3 leukopenia concurrently had Grade 3 thrombocytopenia. Regarding nonhematologic toxicity, only 3 patients had Grade 3 diarrhea, which promptly improved after treatment with a continuous intravenous infusion. One patient had Grade 3 anorexia and nausea; treatment was withdrawn before completion at the patient's request. Activity of either dihydropyrimidine dehydrogenase or orotate phosphoribosyl transferase enzyme was not assessed in this study, but such enzyme deficiency might have been involved in the patient with Grade 3 anorexia and nausea.

Surgical procedures and pathologic findings

Of the 67 patients, 50 (74.6%) underwent sphincter-preserving surgery and 17 (25.4%) underwent abdominoperineal resection. A diverting ileostomy was created in all patients who underwent sphincter-preserving surgery. We currently perform ileostomy for patients who had sphincter-preserving surgery in case of anastomotic leakage, because we are afraid that the low anterior resection was done after radiation therapy. Such ileostomy is a transient stoma and usually reversed 6 months to a 1 year later. For patients undergoing abdominoperineal resection, the sigmoid colon was diverted.

The median number of examined lymph nodes was 19 (range, 12 to 52). Among the 67 patients, 26 were found to have lymph node metastasis: 18 (26.9%) had pathologic N1 disease (1–3 metastatic regional lymph nodes) and 8 (11.9%) had pathologic N2 disease (≥4 metastatic regional lymph nodes). The relation between the response of the primary tumor and lymph node metastasis is shown in Table 4. Downstaging of the primary tumor according to clinical T stage was confirmed in 49 patients (73.1%). Of the 37 patients evaluated to have node-positive disease before treatment, 16 (43.2%) had no pathologic evidence of lymph node metastasis. In 1 patient with a Grade 3 response of the primary tumor, 2 metastatic lymph nodes were found in the field of the inferior mesenteric artery.

In 6 of the 26 patients with lymph node metastasis, metastatic lymph nodes along the internal iliac artery and obturator foramen were recognized but were dissected by surgery. These patients all had enlarged lymph nodes in these regions on computed tomography and/or MRI before treatment. Such patients with pathologic evidence of lymph node metastasis also received six courses of postoperative adjuvant chemotherapy with S-1 (80 mg/m^2), given for 14 days, followed by 14 days of rest, and irinotecan (125 mg/m^2), given on Days 1 and 15.

Table 3. Pathologic primary tumor response as secondary endpoint

Grade	Response to treatment	
	No. of patients	%
1a	5	7.5
1b	16	23.9
2	21	31.3
3	25	37.3

The response rate was good in 68.7% of patients, and the response rate was good or slight in 100%.

Table 4. Relation between response to treatment and lymph node metastasis

Grade	Response to treatment		
	No. of patients	No. of patients with lymph node metastasis	%
1a	5	1	20
1b	16	12	75
2	21	12	57.1
3	25	1	4

Table 5. Acute toxicity during treatment course

	Grade 1 [*n* (%)]	Grade 2 [*n* (%)]	Grade 3 [*n* (%)]	Grade 4 [*n* (%)]
Hematologic toxicity				
Leukopenia	0	10 (14.9)	3* (4.5)	0
Neutropenia	0	1 (1.5)	3 (4.5)	0
Thrombocytopenia	0	0	1* (1.5)	0
Nonhematologic toxicity				
Diarrhea	2 (3.0)	2 (3.0)	3 (4.5)	0
Anorexia/nausea	0	0	1 (1.5)	0

* One patient had leukopenia and thrombocytopenia.

Postoperative complications

Postoperative bleeding from a branch of the internal iliac vein required emergency surgery to achieve hemostasis. One patient with intestinal obstruction did not respond to conservative treatment and underwent reoperation (untethering). There were no perioperative or postoperative deaths or postoperative sequelae.

DISCUSSION

Our protocol is considered sufficiently safe, with high rates (86.6%) of completing treatment as compared with the previous studies. There was no Grade 4 toxicity, and all Grade 3 adverse events responded to conservative treatment. In the European Organisation for Research and Treatment of Cancer 22921 study, the rate of completing treatment was 82.0% in the two groups who received preoperative chemoradiotherapy (6). In the CALGB 89901 study, the incidence of Grade 3 or 4 diarrhea was 38% in patients who received preoperative chemotherapy with oxaliplatin plus 5-FU, and the percentage of patients who completed treatment was 72% (17), if we consider completing treatment to have been achieved with at least four cycles of therapy, similar to the definition we used. The recommended dose determined based on a Phase I clinical study of our regimen was thus deemed to be appropriate (16).

The low incidence of complications might be attributed primarily to the fact that the irradiated field was adequately reduced. The target volumes used for radiotherapy in this study are far smaller in comparison to those usually described in North American and European practice, where the internal iliac nodes and often the external iliac nodes are electively irradiated. We have to keep this difference in mind in determining whether we can safely use S-1 and irinotecan along with the more typical larger radiotherapy volumes used compared with the volumes used in this study. Reduced irradiated fields of our protocol can be reasoned for surgical procedures including lateral lymph node dissection, which is one of the standard surgical options in Japan.

The rate of pathologic CR in our study was 34.7%, which was clearly higher than the rates (11%–17%) in the previous studies (8, 18–21) (Table E1). In our study serial sections of tumor tissue were evaluated histopathologically. The reliability of the pathologic evaluation of CR is therefore considered higher than that in previous studies. The median number of dissected lymph nodes was 19 (range, 12–52), considered adequate for lymph node dissection. The addition of another anticancer agent to 5-FU–based chemotherapy plus radiotherapy at a dose of 45 Gy or higher was found to contribute to a higher rate of pathologic CR, consistent with the results of other studies (22, 23). The rate of pathologic CR to 5-FU/leucovorin regimens was 20% or less in most studies. In the CALGB 89901 study, in which patients also received oxaliplatin, the rate of pathologic CR improved to 25%, but serious diarrhea and a low rate of completing treatment were problems (17). With our regimen for chemoradiotherapy, the rates of completing treatment (86.6%) and of pathologic CR (34.7%) reached satisfactory levels. Such good outcomes might be attributed to increased radiosensitivity of tumor cells induced by components of S-1 or to synergism between irinotecan and tegafur (Fig. 1). UGT1A1 nucleotide polymorphisms, which are supposed to determine the sensitivity of irinotecan, were not assessed in our study. However, treatment could be completed safely, perhaps because the dose of irinotecan was lower than that used in folinic acid, 5-FU, and irinotecan regimens (88.9%).

Several retrospective studies have reported on the close association between the rate of pathologic CR and long-term outcomes (24, 25), but such a positive correlation between these factors has yet to be clearly shown in a prospective study. In our study overall survival is being followed up as a secondary endpoint. In addition to long-term outcomes, the relation between pathologic CR and the long-term outcome is an interesting issue. Some patients with a pathologic CR may have not required surgery, but postoperative histopathologic examinations are currently required to establish the occurrence of a pathologic CR. More than half of these patients with no cancer cells on colonoscopy with biopsy after chemoradiotherapy were actually confirmed to have residual disease on histopathologic examination of the resected specimens. It is therefore difficult to evaluate the bona fide response rate only on biopsy without surgery. New examination methods other than biopsy will hopefully be established to accurately evaluate pathologic CR before surgery.

Roels *et al.* (26) reported that the rates of recurrence in the pelvic cavity were 49% in the posterior region (presacral region), 21% in the lateral region (internal iliac lymph node region), and 12% in the inferior region (perineal region). Posterior and inferior lymph nodes can be adequately

removed by TME, whereas lateral lymph nodes were not included in the irradiated field in our study and were resected surgically. If these lateral lymph nodes had not been dissected, pelvic recurrence may have occurred. The irradiated field is thus expected to become an important issue in patients with enlarged lateral lymph nodes before treatment. The clinical significance of conventional lateral lymph node dissection has yet to be shown in clinical studies. To determine the optimal irradiated field for patients with lateral lymph node metastasis, we are now closely following local recurrence and outcomes, two other secondary endpoints of this study.

In conclusion, the regimen that we developed for preoperative treatment generated promising results. However, many issues remain unresolved, including the dose (including chemotherapy cycles), duration of chemoradiotherapy, radiation target volumes in patients with lateral lymph node metastasis, optimal concomitant agents, preoperative evaluation methods for response, role of adjuvant chemotherapy, and especially, survival benefit. To assess our regimen for locally advanced rectal adenocarcinoma, the durations of disease-/recurrence-free survival and overall survival should be carefully analyzed prospectively in Phase II trials, and then large Phase III trials might be anticipated.

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Neoadjuvant Chemoradiotherapy for Clinical Stage II-III Esophageal Squamous Cell Carcinoma

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Abstract. *Background: The clinical significance of neoadjuvant chemoradiotherapy (NACRT) for potentially resectable esophageal squamous cell carcinoma (ESCC) is unclear. Patients and Methods: Patients with clinical stage II-III ESCC were classified into an NACRT group (n=76) and surgery alone group (n=92). The prognosis and the incidence of postoperative complications were retrospectively investigated. The pathological response to NACRT and patient prognosis were also analyzed. Results: The 5-year survival rate was 47.7% in the surgery alone group and 56.5% in the NACRT group (p=0.4831). The 5-year survival rates of patients in whom NACRT was markedly effective was clearly better than that of the other patients (ineffective/slightly effective: 36.9%, moderately effective: 53.8%, markedly effective: 100%). The incidence of postoperative complications was 31.5% in the surgery alone group and 40.8% in the NACRT group (p=0.2121). Conclusion: A pathological complete response to NACRT is critical for improving the survival of patients with clinical stageII-III ESCC.*

Since the majority of patients with esophageal cancer still tend to have widespread disease at the time of detection, esophageal cancer remains one of the most difficult malignancies in the digestive tract to control by surgery alone (1). Neoadjuvant chemoradiotherapy (NACRT) has been applied for esophageal cancer, mainly at advanced stages, for the purpose of reducing the main tumor and control of microscopic metastases. However, the clinical usefulness of NACRT for potentially resectable esophageal cancer still remains controversial. Some randomized studies and meta-analyses have emphasized the superiority of the clinical results in NACRT plus surgery to those of surgery alone (2, 3), whereas other reports have shown that the difference was not significant (4-6). With regard to postoperative complications, NACRT for esophageal cancer was reported to increase their incidence (7, 8). However, others have reported that the incidence of complications was similar to that in the patients who received surgery without NACRT (9-11).

In Japan, the clinical significance of NACRT for resectable advanced esophageal squamous cell carcinoma (ESCC) still remains controversial. In this study, we retrospectively evaluated the usefulness of NACRT for clinical stage II-III (cStageII-III) ESCC. We also examined the relationship between NACRT and the development of postoperative complications.

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Key Words: Esophageal squamous cell carcinoma, neoadjuvant chemoradiotherapy, pathological response, complication, prognosis.

Patients and Methods

Patients. An esophagectomy was performed in 168 patients with cStageII-III ESCC between 1998 and 2007 in the Department of Surgery and Science at Kyushu University, Japan. Among these patients, NACRT had been performed for 76 patients, while surgery alone was indicated for 92 patients. For cStageII-III patients, NACRT was principally administered between 1998 and 2002. However, since NACRT was found to demonstrate no substantial survival benefit, surgery without neoadjuvant therapy was performed between 2003 and 2007. Therefore, this study is retrospective, without randomization, but is based on historical controls.

The clinicopathological backgrounds according to the administration of NACRT are shown in Table I. There were some differences in the clinical backgrounds between the two groups: the incidence of clinical T1b was significantly lower in the NACRT group than in the surgery alone group ($p<0.05$). The incidence of pathological T1 and pathological N (+) was also significantly lower in the NACRT group than in that of surgery alone ($p<0.05$ and $p<0.0005$, respectively). The pathological stage (pStage) was significantly more advanced in the NACRT group than in that of surgery alone ($p<0.05$). There were no differences in factors such as age, gender, location of the tumor, clinical N factor, cStage and curability.

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Table I. *Clinicopathological background according to NACRT.*

Factor		NACRT, n (%) No (n=92)	NACRT, n (%) Yes (n=76)	*p*-Value
Gender	Male	80 (87.0)	62 (81.6)	0.3375
	Female	12 (13.0)	14 (18.4)	
Age, years (mean)		63.6	62.6	0.5165
Location of tumor	Upper	12 (13.0)	14 (18.4)	0.4012
	Middle	40 (43.5)	36 (47.4)	
	Lower	40 (43.5)	26 (34.2)	
Clinical T factor	cT1b	10 (10.9)	1 (1.3)	0.0183*
	cT2	30 (32.6)	20 (26.3)	
	cT3	52 (56.5)	55 (72.4)	
Clinical N factor	cN (–)	38 (41.3)	36 (47.4)	0.4307
	cN (+)	54 (58.7)	40 (52.6)	
Clinical stage	II	53 (57.6)	41 (53.9)	0.6342
	III	39 (42.4)	35 (46.1)	
Pathological T factor	pT1	22 (23.9)	3 (3.9)	0.0010*
	pT2, 3	65 (70.7)	70 (92.1)	
	pT4	5 (5.4)	3 (3.9)	
Pathological N factor	pN (–)	27 (29.3)	44 (57.9)	0.0002*
	pN (+)	65 (70.7)	32 (42.1)	
Pathological stage	I	12 (13.0)	2 (2.6)	0.0469*
	II, III	73 (79.3)	69 (90.8)	
	IV	7 (7.6)	5 (6.6)	
Curability	Curative	77 (83.7)	67 (88.2)	0.4107
	Non-curative	15 (16.3)	9 (11.8)	

*A significant difference was observed between the two groups.

For NACRT, 30-42 Gy of radiation for the primary tumor and metastatic lymph nodes was administered preoperatively. The chemotherapy regimen was low-dose cisplatin and 5-fluorouracil (5-FU) (cisplatin: 5 mg/m^2/day, 5-FU: 250 mg/m^2/day, administered on weekdays, repeated every 3-4 weeks).

Staging of the tumor and pathological effectiveness of NACRT. The staging of the tumor and the effects of NACRT were assessed based on the criteria in the Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus by the Japanese Society for Esophageal Diseases (12). The details of pathological evaluations are as follows: markedly effective (grade 3), all cancer cells were destroyed with no evidence of viable cancer cells; moderately effective (grade 2), most (more than two-thirds) of the cancer cells were damaged, despite the continued presence of viable cancer cells. In this study, slightly effective cases (grade 1) and ineffective cases (grade 0) were regarded as ineffective. The pStage was determined not only based on the viable cancer cells but also on the scar tissue affected by NACRT.

We compared the clinicopathological features, as well as the prognosis, of the patients according to the effects of NACRT. We divided the patients into two groups, those whose pathological effects were grade 3 (n=16) and those who were grade 0-2 (n=60), because the outcome of the patients was clearly different between the groups.

Statistical analysis. The differences in distribution frequencies among the groups were evaluated using Fisher's exact test or unpaired *t*-test. The survival curves were plotted according to the Kaplan-Meier method and any differences were analyzed using the log-rank test. Differences were considered to be significant if the *p*-value was less than 0.05.

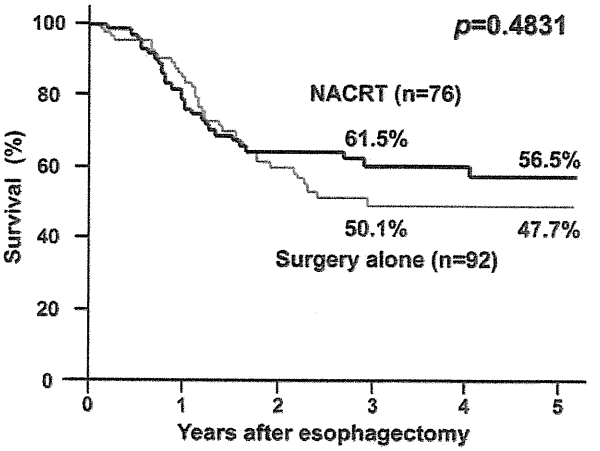

Figure 1. *The survival curves of cStageII-III ESCC patients in the surgery alone group and in the NACRT group. The 5-year survival rate was 56.5% in the NACRT group and 47.7% in the surgery alone group, which was not significantly different (p=0.4831).*

Results

Outcome of NACRT in patients with cStageII-III ESCC. The survival curves of cStageII-III ESCC patients in the surgery alone group and the NACRT group are shown in Figure 1. The 3-year and 5-year survival rate was 61.5% and 56.5% in the NACRT group and 50.1% and 47.7% in the surgery alone group (p=0.4831). As shown in Figure 2, there were no significant differences in the prognosis between the patients in the surgery alone group and the NACRT group, regardless of disease stage (cStageII, p=0.7387, cStageIII, p=0.4370).

Pathological effects of NACRT and prognosis. Among the 76 patients who received NACRT, grade 3 and grade 2 responses were observed in 16 (21.1%) and 26 patients (34.2%), respectively. In the other 34 (44.7%) patients, the pathological effects of NACRT were grade 0/1.

No significant differences were observed with regard to clinical background between the patients with grade 0-2 and grade 3 responses (Table II). The survival of patients whose pathological effects were grade 3 was clearly better than those with grade 2 or grade 0/1: the 5-year survival rate was 100%, 53.8% and 36.9%, respectively (Figure 3). The log-rank test was inapplicable because no events were observed in the patients with grade 3 responses.

NACRT and postoperative complications. Table III shows the postoperative complications and hospital mortality of each

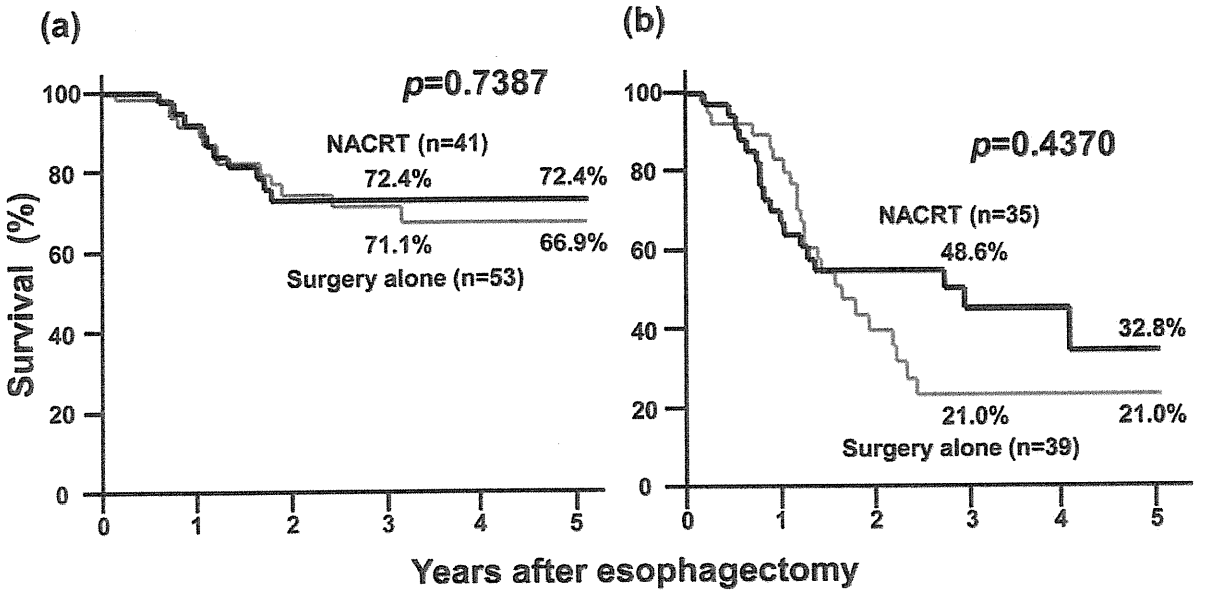

Figure 2. *The survival curves of cStageII (a) and cStageIII (b) ESCC patients in the surgery alone group and the NACRT group. The 5-year survival rates were not significantly different (cStageII: p=0.7387, cStageIII: p=0.4370).*

group. The incidence of postoperative complications was 31.5% in the surgery alone group and 40.8% in the NACRT group (p=0.2121). Pulmonary complications developed in 12.0% of patients in the surgery alone group and in 19.7% of patients in the NACRT group (p=0.1621). Anastomotic leakage developed in 17.4% of the surgery alone patients and in 25.0% of the NACRT patients (p=0.2268). Regarding in-hospital mortality, there were no significant differences between the groups: the incidence was 3.3% in the surgery alone group and 0% in the NACRT group (p=0.1122).

Discussion

For surgically resectable esophageal cancer, whether or not NACRT actually increases long-term survival remains controversial. Urba *et al.* (4) reported that in randomized trial, NACRT *versus* surgery alone for patients with potentially resectable esophageal carcinoma did not demonstrate a statistically significant survival difference. Burmeister *et al.* (5) reported that NACRT with cisplatin and 5-FU did not significantly improve progression-free or overall survival for patients with resectable esophageal cancer compared with surgery alone, however, the subgroup analysis showed that patients with ESCC had better progression-free survival with NACRT than did those with non-squamous carcinomas. In randomized trials in Western countries, the patients usually have different pathological types (*i.e.* adenocarcinoma and ESCC). No clearly recommended protocols have so far been established regarding either the radiation dose and field, or the chemotherapy regimen for the treatment of surgically resectable esophageal cancer. We therefore need to pay careful attention when we introduce new treatments based on evidence from Western countries to our practice in Japan. In this study, there was no significant difference between the patients with and without NACRT, thus suggesting that

Table II. *Clinical background according to the pathological effect of NACRT.*

Factor		Effect of NACRT, n (%) Grade 0-2 (n=60)	Grade 3 (n=16)	*p*-Value
Gender	Male	49 (81.7)	13 (81.3)	>0.9999
	Female	11 (18.3)	3 (18.8)	
Age, years (mean)		61.7	66.2	0.1009
Location of tumor	Upper	10 (16.7)	4 (25.0)	0.6197
	Middle	30 (50.0)	6 (37.5)	
	Lower	20 (33.3)	6 (37.5)	
Clinical T factor	cT1b	1 (1.7)	0 (0)	0.7824
	cT2	15 (25.0)	5 (31.3)	
	cT3	44 (73.3)	11 (68.8)	
Clinical N factor	cN (-)	28 (46.7)	8 (50.0)	>0.9999
	cN (+)	32 (53.3)	8 (50.0)	
Clinical stage	II	30 (50.0)	11 (68.8)	0.2602
	III	30 (50.0)	5 (31.3)	
Curability	Curative	51 (85.0)	16 (100.0)	0.1906
	Non-curative	9 (15.0)	0 (0)	

No significant differences were observed between the two groups.

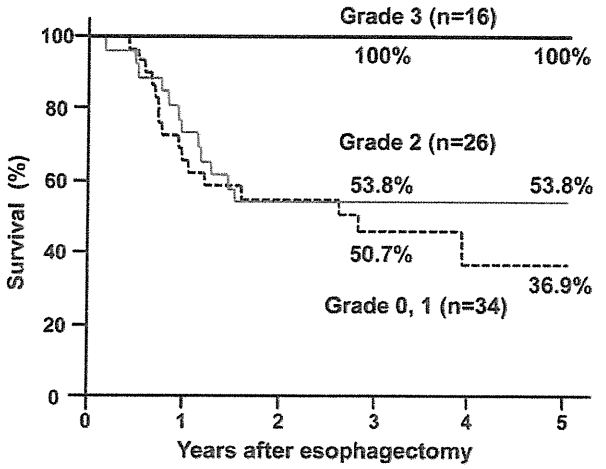

Figure 3. *Overall survival after esophagectomy according to the pathological effectiveness of NACRT in patients with ESCC who underwent NACRT. Each grade indicates the pathological effectiveness (grade 0, 1: ineffective or slightly effective; grade 2: moderately effective; and grade 3: markedly effective). The 5-year survival rate of patients in whom the response to NACRT was grade 3 (100%) was clearly better than that of patients whose pathological response was grade 2 (53.8%), or grade 0/1 (36.9%).*

Table III. *Mortality and morbidity according to NACRT.*

Factor		NACRT, n (%)		*p*-Value
		No (n=92)	Yes (n=76)	
Morbidity	(–)	63 (68.5)	45 (59.2)	0.2121
	(+)	29 (31.5)	31 (40.8)	
Pulmonary complication	(–)	81 (88.0)	61 (80.3)	0.1621
	(+)	11 (12.0)	15 (19.7)	
Anastomotic leakage	(–)	76 (82.6)	57 (75.0)	0.2268
	(+)	16 (17.4)	19 (25.0)	
Mortality	(–)	89 (96.7)	76 (100)	0.1122
	(+)	3 (3.3)	0 (0)	

No significant differences were observed between the two groups.

NACRT has no clinical significance for patients with cStageII-III ESCC. However, the incidence of clinical T1b was significantly lower in the NACRT group than in the surgery alone group. As a result, this incidence may have affected the clinical results of NACRT in this study.

In Japan, a recent randomized trial of postoperative adjuvant chemotherapy with cisplatin and 5-FU *versus* neoadjuvant chemotherapy for cStageII-III ESCC (JCOG 9907) rendered a dramatic change in the daily practice of esophageal surgery (13). Preoperative chemotherapy with cisplatin and 5-FU followed by surgery improved overall survival without additional serious adverse events in the treatment for cStage II-III ESCC. Preoperative chemotherapy with cisplatin and 5-FU is, therefore, regarded as a new standard treatment for cStage II-III ESCC. However, preoperative cisplatin and 5-FU-induced down-staging and R0 resection were reported to be less beneficial in cStage III than in cStage II disease. This suggests that a more powerful preoperative treatment than the cisplatin and 5-FU regimen may be necessary for patients with cStage III ESCC. We retrospectively evaluated the effectiveness of NACRT as a treatment for cStage II-III ESCC in this study. However, we need to make efforts to conduct further prospective randomized trials including NACRT in order to clarify its usefulness.

In terms of the long-term survival after NACRT followed by surgery for esophageal cancer, the response to NACRT has been reported to be the most important factor. Swisher *et al.* (14) emphasized that pathologic response is an independent risk factor for survival and proposed revision of the esophageal cancer staging system to accommodate pathologic response following NACRT. However, factors associated with pathological complete response are still unclear. We had previously performed a multivariate analysis, and the depth of invasion was found to be an independent factor associated with the clinical response to NACRT (15). In this study, no differences were observed in the background between the patients with grade 3 and those with grade 0-2 responses. It is thought to be clinically difficult to predict the effect of NACRT before treatment.

Regarding anticancer drugs, combination chemotherapy using cisplatin and 5-FU with radiation has been proven to be superior to radiation alone according to the RTOG 85-01 study (16). Our previous study supported the idea that preoperative cisplatin and 5-FU administration improved patient prognosis, as well as the response to NACRT (15). Thus, in this study, we focused on the patients who received cisplatin and 5-FU regimens as NACRT in order to avoid a mixture of subjects having different treatment backgrounds.

The current study examining NACRT did not reveal NACRT to be associated with postoperative complications, including pulmonary complications. However, we have reported the clinical results of esophagectomy for 1,000 cases with esophageal cancer in our institute, and we found preoperative radiotherapy to be an independent risk factor for postoperative pulmonary complications (1). Regarding the mechanism of this increase in postoperative complications, suppression of immune function has been reported to be significant (17). In our previous report, multiple immunological measures in patients with esophageal cancer revealed that preoperative treatment induced significant reductions in the total lymphocyte count, phytohemagglutinin response, and natural killer cell activity, as well as a significant gradual decrease in the CD^{4+}/CD^{8+} ratio (18). It has also been reported that NACRT for patients with ESCC results in the suppression of T-lymphocyte functions (19). Since NACRT

induces a pronounced influence on the immune function, perioperative immunonutritional management might play a key role in reducing postoperative complications after NACRT.

NACRT for esophageal cancer must be associated with improvement in patient survival. Our current study strongly supports the notion that the patients who achieve pathological complete response show a better prognosis than non-responders, suggesting that strict determination of the indications for NACRT is important in order to avoid performing unnecessary NACRT. One approach to improving the outcome after NACRT is the use of molecular biological assessment of particular characteristics of the tumor. To identify biomarkers that predict the response of esophageal cancer to NACRT, gene expression analysis of pretreatment cancer biopsies from patients with esophageal cancer has been demonstrated to be significant (20).

The current study confirms that achievement of a pathological complete response is the most significant factor underlying the efficacy of NACRT. It is important not only to clarify the most useful diagnostic strategy for prediction of the effectiveness of NACRT, but also to identify the molecular markers associated with the effects of NACRT.

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