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ORIGINAL ARTICLE

Neoadjuvant chemoradiotherapy with docetaxel, cisplatin, and 5-fluorouracil (DCF-RT) for locally advanced esophageal squamous cell carcinoma

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Abstract

Purpose To further improve the prognosis of esophageal cancer patients, it is necessary to investigate new treatment strategies. The purposes of this study were to retrospectively assess the safety and efficacy of neoadjuvant chemoradiotherapy (CRT) with docetaxel/cisplatin/5-fluorouracil (DCF) (DCF-RT) in patients with thoracic esophageal squamous cell carcinoma (ESCC).

Methods We reviewed 30 thoracic ESCC patients who underwent neoadjuvant DCF-RT followed by esophagectomy, and evaluated the safety and efficacy of DCF-RT. DCF-RT consisted of 40 Gy radiation with two courses of intravenous DCF (docetaxel, 30 mg/m^2/day, day 1; cisplatin, 7 mg/m^2/day, day 1; 5-FU, 350 mg/m^2/day, days 1–5 and days 8–12) repeated every 2 weeks. Esophagectomy was scheduled 8–10 weeks after completion of DCF-RT.

Results Twenty-nine of thirty patients completed radiotherapy; however, 27 of 30 patients required dose reduction of the second cycle of DCF. Complete response (CR), partial response, and stable disease were observed in 7, 11, and 10 patients, respectively. The number of lymph node metastases after DCF-RT was significantly lower than that before DCF-RT ($P < 0.0001$). Among the 30 patients, pathological CR (pCR) in the primary tumor was observed in 17 patients, and pCRs in both the primary tumor and lymph nodes were observed in 14 patients. The 3-year overall survival rate was 62.2%, and that of patients who experienced pCR was 84%.

Conclusions Neoadjuvant DCF-RT was tolerable and yielded a high pCR rate in ESCC. Therefore, neoadjuvant DCF-RT may confer a survival benefit and may be a candidate neoadjuvant therapy regimen for patients with locally advanced thoracic ESCC.

Keywords Esophageal squamous cell carcinoma · Neoadjuvant chemoradiotherapy · Docetaxel · Cisplatin · 5-Fluorouracil

Introduction

In Japan, neoadjuvant chemotherapy (nCT) with cisplatin plus 5-fluorouracil (CF) followed by radical surgery has been accepted as the standard therapeutic approach for resectable esophageal squamous cell carcinoma (ESCC) based on the results of a Japan Clinical Oncology Group randomized control trial that compared pre- and postoperative CF regimen in patients with stage II/III ESCC (JCOG9907) [1]. To further improve the prognosis of patients with locally advanced ESCC, it is necessary to identify new treatment strategies. The results of two phase II studies indicated that neoadjuvant CF plus docetaxel (DCF) was well tolerated and feasible in patients with resectable ESCC [2, 3]. Furthermore, some recent studies have reported favorable outcomes associated with definitive chemoradiotherapy (CRT) with DCF (DCF-RT) for advanced ESCC [4, 5]. In continental Europe and the United States, resectable esophageal or esophagogastric-junction cancer is generally treated with neoadjuvant CRT (nCRT) based on the results of a large-scale phase III randomized control trial that compared surgery alone to surgery with preoperative paclitaxel, carboplatin, and concurrent radiotherapy (CROSS trial) [6]; however, whether nCRT followed by radical surgery is effective for Japanese ESCC patients has yet to be established. This prompted the initiation of the JCOG1109 trial, an ongoing three-arm randomized

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phase III trial comparing CF, DCF, and CRT with CF as neoadjuvant therapy for locally advanced ESCC [7]. The aims of the present study were to retrospectively assess the safety and efficacy of neoadjuvant DCF-RT followed by esophagectomy in patients with thoracic ESCC.

Patients and methods

This study was approved by the ethical committee of our institute (Approved number 24-114), and we obtained informed consent from all patients prior to enrollment. This study was also conducted in accordance with the guidelines of the Declaration of Helsinki (1964) and later versions.

Patients

We retrospectively examined 30 thoracic ESCC patients who received neoadjuvant DCF-RT and subsequently underwent esophagectomy at Kagoshima University Hospital from January 2013 to June 2016. Disease was clinically confirmed based on the 7th UICC-TNM classification as evaluated by esophagoscopy, esophagography, computed tomography (CT), endoscopic ultrasonography (EUS), bronchoscopy, and positron emission tomography-CT (PET-CT).

Procedures

Chemotherapy consisted of two courses of intravenous DCF (docetaxel, 30 mg/m^2/day, day 1; cisplatin, 7 mg/m^2/day, day 1; 5-FU, 350 mg/m^2/day, days 1–5 and days 8–12) repeated every 2 weeks. Radiotherapy was performed using 6- or 10-MV external photon beams delivered at a daily dose of 2 Gy, five times per week for 4 weeks. The clinical target volume (CTV) included the primary tumor, metastatic lymph nodes (LNs), and regional LNs. Regional LNs included bilateral supraclavicular LNs, mediastinal LNs, and perigastric LNs. Esophagectomy was scheduled 8–10 weeks after completion of DCF-RT.

Assessment

Adverse events associated with DCF-RT were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [8]. Clinical and histopathological tumor responses were evaluated in accordance with the Japanese Classification of Esophageal Cancer by the Japan Esophageal Society [9]. To assess severity, postoperative morbidity was graded based on the Clavien–Dindo classification of surgical complications [10]. The frequency of follow-up was typically once every 3 months after esophagectomy. The median follow-up period was 45 (range 28–66) months.

The Ethics Committee of Kagoshima University approved the study, and all patients provided written informed consent to participate in all procedures associated with this study.

Statistical analysis

Continuous variables are expressed as medians. Survival curves were calculated using the Kaplan–Meier method and were compared using the log-rank test. A p value < 0.05 was considered to be statistically significant. All statistical analyses were performed using JMP10 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Patient characteristics before DCF-RT are summarized in Table 1. Patients included 25 males and 5 females, ranging in

Table 1 Patient characteristics

Variable	$n = 30$
Median age, years (range)	65 (48–76)
Sex	
Male	25 (83.3)
Female	5 (16.7)
ECOG performance status, *n* (%)	
0	33 (100)
1	0 (0)
Location, *n* (%)	
Upper	4 (13.3)
Middle	12 (40.0)
Lower	14 (46.7)
cT[a], *n* (%)	
1b	3 (10.0)
2	6 (20.0)
3	21 (70.0)
cN[a], *n* (%)	
0	3 (10.0)
1	9 (30.0)
2	10 (33.3)
3	8 (26.7)
cM[a] lymph node metastasis[b], *n* (%)	
0	29 (96.7)
1	1 (3.3)
cStage[a], *n* (%)	
I	1 (3.3)
II	6 (20.0)
III	22 (73.3)
IV	1 (3.3)

ECOG Eastern Cooperative Oncology Group

[a]UICC, 7th edition

[b]Supraclavicular lymph node metastasis

age from 48 to 76 (median 65) years. Clinical stages included stage I ($n=1$ [3.3%]), II ($n=6$ [20%]), III ($n=22$ [73.3%]), and IV (M1 LYM confined to supraclavicular LNs; $n=1$ [3.3%]).

Compliance and adverse events

Twenty-nine patients received the complete dose of 40 Gy of radiotherapy, and one patient received 34 Gy due to viral infection. Dose reduction during the second cycle of chemotherapy was required in 27 (90.0%) patients due to adverse events. Adverse events observed during DCF-RT are shown in Table 2. Grade 3 or greater hematological adverse events included leukopenia in 11 (36.7%) patients, lymphopenia in 22 (66.7%) patients, neutropenia in 7 (23.3%) patients, and febrile neutropenia in 3 (10.0%) patients. With respect to non-hematological adverse events, Grade 1 hyponatremia occurred in 22 (73.3%) patients and Grade 1–2 esophagitis occurred in 21 (70.0%) patients.

Clinical response

Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were observed in 7 (23.3%), 11 (36.7%), 10 (33.3%), and 2 (6.7%) patients, respectively. The clinical response rate (CR and PR) was 60.0% and the disease control rate (CR, PR, and SD) was 93.3%. The number of LN metastases before and after DCF-RT was 4.1 ± 0.5 and 0.77 ± 0.5, respectively, and that after DCF-RT was significantly lower than that before DCF-RT ($p < 0.0001$).

Surgical outcomes and postoperative morbidity and mortality

Surgical outcomes, postoperative morbidity, and mortality are shown in Table 3. Median time from completion of DCF-RT to surgery was 60 (range 34–111) days. Median operative time was 586 (range 378–848) min and median blood loss was 283 (range 0–1000) mL. Twenty-nine of the thirty patients underwent subcutaneous reconstruction after neoadjuvant CRT. The median number of dissected LNs was 24 (range, 5–55). Postoperative morbidities included anastomotic leakage in 9 (30.0%) patients, arrhythmia in 5 (16.7%) patients, recurrent nerve palsy in 4 (13.3%) patients, pneumonia in 2 (6.7%) patients, pleural effusion in 2 (6.7%) patients, and chylothorax in 2 (6.7%) patients. No patients underwent reoperation, and there was one in-hospital death.

Histopathological changes

Histopathological changes resulting from DCF-RT are shown in Table 4. *T* and *N* scores could be downstaged in 23 of 30 (76.7%) and 24 of 27 (88.9%) patients, respectively. Stage could be downstaged in 28 of 30 (93.3%) patients. Pathologic complete resection (R0) was achieved in 28 (93.3%) patients, while microscopic residual disease

Table 2 Adverse events experienced by patients who received neoadjuvant chemoradiotherapy

Adverse events	Patients ($n=30$)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4, n (%)
Hematological toxicities					
Leukopenia	5	9	11	0	11 (36.7)
Lymphopenia	0	2	18	2	22 (66.7)
Neutropenia	5	10	7	0	7 (23.3)
Anemia	6	3	0	0	0 (0)
Thrombocytopenia	3	3	1	0	1 (3.3)
Febrile neutropenia	0	0	3	0	3 (10.0)
Non-hematological toxicities					
Anorexia[a]	5	5	4	0	4 (13.3)
Nausea	5	4	3	0	3 (10.0)
Radiation pneumonia	2	2	1	0	1 (3.3)
Viral infection	0	0	3	0	3 (10.0)
Diarrhea	0	1	1	0	1 (3.3)
Hepatotoxicity	0	1	0	1	1 (3.3)
Hyponatremia	22	0	1	0	1 (3.3)
Catheter-related infection	0	0	1	0	1 (3.3)
Thromboembolic event	0	0	1	0	1 (3.3)
Esophagitis	3	18	0	0	0 (0)
Candida infection	0	1	0	0	0 (0)

[a]Five cases were excluded because they underwent naso-gastric tube insertion due to esophageal stenosis

Table 3 Surgical outcomes and postoperative morbidity and mortality

	n = 30
Median interval between NACRT and esophagectomy, days (range)	60 (34–111)
Median operative time, min (range)	586 (378–848)
Median blood loss, g (range)	283 (50–1000)
No. of dissected lymph nodes	
Median (range)	24 (5–55)
Surgical approach, *n* (%)	
Right thoracotomy	26 (86.7)
Transhiatal lower esophagectomy	1 (3.3)
Blunt (mediastinoscopic)	3 (10.0)
Route of reconstruction, *n* (%)	
Subcutaneous	29 (96.7)
Inferior mediastinal	1 (3.3)
Organ used for reconstruction, *n* (%)	
Stomach	26 (86.7)
Colon	3 (10.0)
Jejunum	1 (3.3)
Postoperative complications (CD Grade ≥ I), *n* (%)	
Anastomotic leakage	9 (30.0)
Arrhythmia	5 (16.7)
Recurrent nerve palsy	4 (13.3)
Pneumonia	2 (6.7)
Pleural effusion	2 (6.7)
Chylothorax	2 (6.7)
Surgical site infection	1 (3.3)
Anastomotic stenosis	1 (3.3)
Reoperation, *n* (%)	0 (0)
In-hospital death, *n* (%)	1 (3.3)

NACRT neoadjuvant chemoradiotherapy, *CD* Clavien–Dindo classification

Table 4 Pathological effects of neoadjuvant chemoradiotherapy

Variable	ypN0	ypN1	ypN2	*n* = 30 (%)
ypT[a], *n* (%)				
0	14	3	0	17 (56.7)
1	1	0	1	2 (6.7)
2	3	0	1	4 (13.3)
3	2	3	1	6 (20.0)
4	0	1	0	1 (3.3)
ypN[a], *n* (%)				
0				20 (66.7)
1				7 (23.3)
2				3 (10.0)
ypM[a] lymph node metastasis[b], *n* (%)				
0				30 (100)
1				0 (0)
ypStage[a], *n* (%)				
0				14 (46.7)
I				4 (13.3)
II				5 (16.7)
III				7 (23.3)
Downstaging (yes/no), *n* (%)				28 (93.3)/2 (6.7)
Residual tumor, *n* (%)				
R0				28 (93.3)
R1				2 (6.7)
Pathological grade of primary tumor, *n* (%)				
Grade 1				10 (33.3)
Grade 2				3 (10.0)
Grade 3				17 (56.7)

[a]UICC, 7th edition

[b]Supraclavicular lymph node metastasis

(R1) was observed in 2 (6.7%) patients. Grade 3, 2, and 1 responses in primary tumors were observed in 17 (56.7%), 3 (10.0%), and 10 (33.3%) patients, respectively. Among the 30 patients, pCRs in both the primary tumor and lymph nodes were observed in 14 (46.7%) patients. The 3-year overall survival (OS) rate of the pCR subset was 84%, and these patients were also disease free.

Survival and patterns of postoperative recurrence

The outcomes of patients who underwent neoadjuvant DCF-RT and subsequent esophagectomy are shown in Fig. 1. The median observation period was 45 (range 27–66) months after initial treatment. The 3-year OS rate was 62.2%, while the 3-year disease-free survival (DFS) rate was 61.4%. The 3-year OS rates for patients who experienced pCR and non-pCR were 84.4% and 43.3%, respectively ($P = 0.0063$) (Fig. 2).

Discussion

In this study, neoadjuvant DCF-RT resulted in high rates of downstaging and pCR, and favorable outcomes for patients with thoracic ESCC. In this study, the pCR rate was 47%, and the 3-year OS rate was 62.2%. CF therapy was established as the standard regimen in Japan by the JCOG 9907 trial, in which the pCR rate was 5% and the 5-year OS rate was 55% [1]. In the CROSS trial, the pCR rate was 49% and median OS was 81.6 months among SCC patients [11], and in the most recent randomized controlled trial that compared nCT with nCRT for thoracic esophageal cancer, nCRT resulted in a 42% pCR rate and a 56% 3-year OS rate among patients with SCC [12]. A phase II study that evaluated docetaxel-based nCRT reported a pCR rate of 47% and a 3-year OS rate of 59% [13], and a phase I/II study reported a pCR rate of 49% and a 3-year OS rate of 37% [14]. The pCR rate of 47% in the present study is one of the highest pCR rates

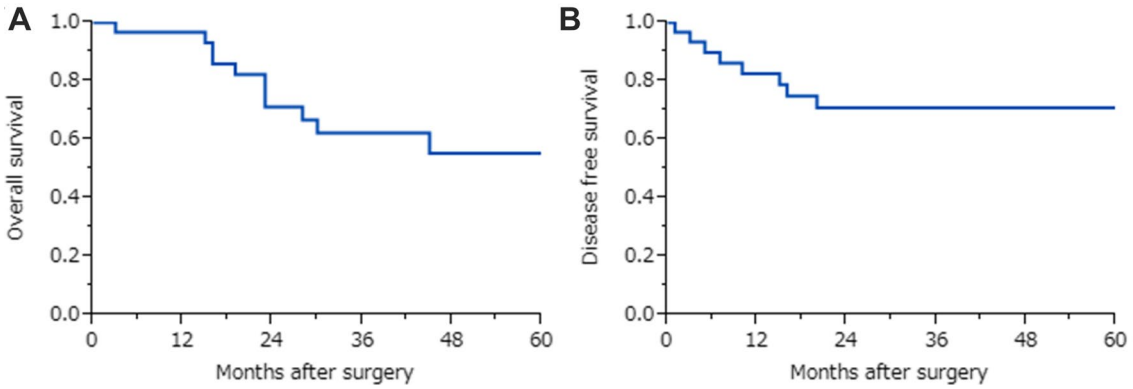

Fig. 1 Overall survival (**A**) and disease-free survival (**B**) curves for patients who received neoadjuvant DCF-RT followed by esophagectomy

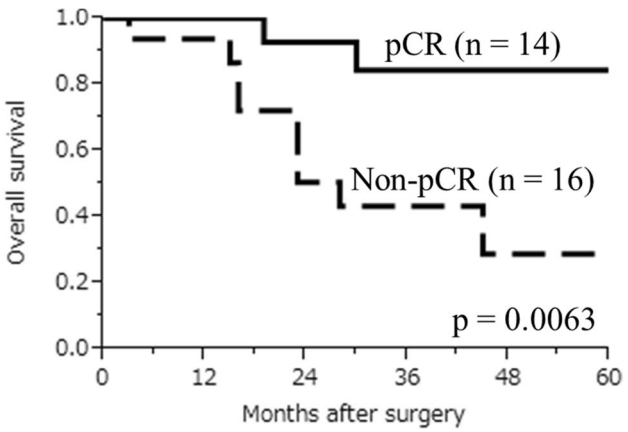

Fig. 2 Overall survival curve according to pathological response

reported thus far. After a median follow-up of 45 months, the 3-year OS rate among patients who achieved a pCR was 84%, and these patients remain disease-free. Some studies have reported that a pCR following nCRT is associated with improved outcomes, including lower rates of local recurrence and improved survival, in patients with locally advanced esophageal cancer [15–17]. Therefore, pCR after nCRT could be a relevant prognostic factor in esophageal cancer.

We scheduled surgery 8–10 weeks after the completion of DCF-RT; however, the optimal interval between the end of nCRT and surgery has not been identified. A nationwide retrospective study in the Netherlands that included 3,102 esophageal or junctional cancer patients reported that an interval of > 12 weeks was associated with higher pCR rates, but not with increased intraoperative and postoperative complications [18]. Two studies that included > 200 esophageal or junctional cancer patients reported that intervals of > 45 days or > 64 days were associated with higher pCR rates, without surgical morbidity [19, 20]. However, a recent meta-analysis of five studies and one additional study reported that the interval between end of nCRT and surgery for esophageal cancer did not affect pCR rate [21, 22].

Although DCF-RT was tolerable, the incidence of anastomotic leakage in the present study was high compared to that of the JCOG9907 study [23]. While few studies have addressed the impact of nCRT on the incidence of anastomotic leakage, the rates associated with upfront surgery and nCRT in recent reports from Western countries have ranged from 0 to 30% and 2.9 to 22.0%, respectively, with no statistically significant differences between the two procedures [11, 24–27]. The wide CTV range from the cervical to perigastric regions in the present study may have contributed to the high incidence of anastomotic leakage.

This study had some limitations. First, the DCF-RT regimen used in this study was based on a biweekly DCF regimen used in stage IVB or recurrent esophageal cancer (JCOG0807) [28] and a regimen consisting of low-dose CF combined with 40 Gy of concurrent radiotherapy as neoadjuvant CRT in ESCC [29]; however, dose limits were not tested. A phase I study should be performed to optimize the DCF-RT regimen. Second, this study was conducted at a single institute, did not have a comparator arm, and included a small number of patients. A multicenter, randomized controlled trial is required to clarify the feasibility of neoadjuvant DCF-RT.

In conclusion, the present study demonstrated that neoadjuvant DCF-RT was tolerable and yielded a high pCR rate in resectable thoracic ESCC. Therefore, neoadjuvant DCF-RT may confer a survival benefit and may be a candidate neoadjuvant therapy regimen for patients with resectable ESCC.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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