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# Retrospective evaluation of the feasibility of definitive chemoradiotherapy after treatment with docetaxel, cisplatin, and 5-fluorouracil in patients with esophageal squamous cell carcinoma

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**Objective:** To evaluate the safety and efficacy of definitive chemoradiotherapy (dCRT) with 5-fluorouracil and cisplatin after triple-drug combination chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (DCF) chemotherapy in patients with esophageal squamous cell carcinoma (ESCC).
**Methods:** We retrospectively evaluated 17 patients with stage II to IV ESCC who received dCRT after 3 or 4 courses of DCF chemotherapy.
**Results:** All 17 patients completed dCRT. The main grade 3 or higher acute adverse events of dCRT were anemia in 41% (7/17), neutropenia in 35% (6/17), and esophagitis in 24% (4/17) of the patients. Grade 5 radiation pneumonitis occurred in 6% (1/17). Of 13 patients with stages II or III ESCC, 11 (85%) achieved complete response (CR), and all of them were good responders to DCF chemotherapy. The recurrence rate after CR was 27% (3/11), the salvage surgery rate for residual lesions and recurrence was 100% (5/5), and the organ preservation rate was 54% (7/13). During a median follow-up time of 45 months for stages II and III ESCC, all but 2 patients who died survived disease-free.
**Conclusion:** In patients with stages II or III ESCC, dCRT after DCF chemotherapy might be a treatment option as an organ preservation strategy.

**Key words:** esophageal squamous cell carcinoma, chemoradiotherapy, organ preservation, induction chemotherapy

## Introduction

Esophageal carcinoma is a life-threatening disease for which a more effective and safe treatment than that currently available is desired. Squamous cell carcinoma (SCC) is a major pathologic type of esophageal carcinoma. Treatment strategies for stages II and III esophageal SCC (ESCC) include neoadjuvant chemotherapy or chemoradiotherapy (CRT) followed by surgery or definitive CRT (dCRT).[1-9] In Japan, following the results of the Japan Clinical Oncology Group (JCOG9907)[1] study, the standard therapy for stages II and III ESCC is neoadjuvant chemotherapy followed by surgery.

ESCC is a similar tumor to SCC of the head and neck, which is known to be sensitive to radiotherapy, and dCRT is accepted as an alternative therapy, both curative and as an organ-preserving therapy. According to the result of a prospective randomized phase 3 trial conducted by the Radiation Therapy Oncology Group (RTOG), CRT resulted in longer survival than did radiotherapy alone, and CRT was suggested as the standard non-surgical

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treatment.[6] The RTOG investigated dose escalation in a randomized trial, comparing high-dose (64.8 Gy) versus standard-dose (50.4 Gy) radiotherapy in CRT with 5-fluorouracil and cisplatin (FP). However, the high-dose arm did not show an advantage either in survival or locoregional control.[7] In Japan, a treatment schedule of 60 Gy in 30 fractions is widely used for ESCC.[8] Recently, a phase 2 study evaluated the efficacy and toxicity of a modified RTOG regimen, consisting of radiotherapy of 50.4 Gy in 28 fractions including elective nodal irradiation using a multi-field technique and concurrent chemotherapy with FP.[9] This trial achieved a positive outcome, with a median 3-year overall survival rate of 63.8%. Acute toxicity was relatively high but manageable. Late toxicity decreased when compared with the 60 Gy in 30 fractions protocol.[8]

Although the prognosis of ESCC has improved by the use of multidisciplinary therapies,[1,9] it remains unsatisfactory, and therefore, more effective chemotherapeutic regimens have been and are being investigated. Triple combination chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (DCF) chemotherapy has been reported to produce good outcomes in patients with head and neck or gastric cancer, although it tends to increase toxicity.[10-14] In some patients with head and neck cancer, DCF, as an induction chemotherapy, followed by dCRT has been suggested as a treatment option, but the merits of this induction chemotherapy are still controversial.[10-13,15] DCF chemotherapy has also been researched in the treatment of ESCC.[16-24] DCF chemotherapy has the advantage of resulting in a marked tumor shrinkage but can cause severe toxicity such as neutropenia. In Japan, recent studies have focused on neoadjuvant chemotherapy with DCF due to good short-term outcomes in patients with stages II or III ESCC.[25-28]

At our institute, treatment strategies for ESCC are decided by an esophageal cancer board consisting of surgeons, physicians, radiation oncologists, pharmacists, and nurses. We have applied DCF chemotherapy as neoadjuvant chemotherapy, and the patients treated with neoadjuvant DCF chemotherapy have then received surgery in most cases. However, some patients refuse surgery and decide to receive dCRT after DCF chemotherapy due to an improvement or resolution their symptoms such as dysphagia. Patients are only administered dCRT after being properly informed and their having consented. The standard therapy for patients with stage IV ESCC is chemotherapy with FP; however, we administer DCF chemotherapy as an induction therapy for those patients with only a few distant metastases, and/or those who have suffered from severe symptoms due to bulky disease, and/or those who had a rapidly progressing disease. Although these treatment strategies of dCRT after DCF chemotherapy are exceptional, the benefits for the patients are yet unknown.

Few studies have evaluated the outcome of patients with ESCC who received dCRT after DCF chemotherapy.[29,30] We retrospectively evaluated the safety and efficacy of dCRT after DCF chemotherapy in patients with ESCC.

## Materials and Methods

*Patients*

From February 2010 through January 2014, 86 patients with stages II to IV intrathoracic ESCC received 3- to 8-course DCF as neoadjuvant or induction chemotherapy in our institute. After DCF chemotherapy, 39 patients received surgery. We followed a dCRT regimen according to the RTOG.[7,9] We administered dCRT after DCF chemotherapy with informed consent from patients with fair general health conditions and tumors that had a possibility of being controlled. Twenty-seven patients received dCRT, 12 received dose reduction or another CRT, 4 received chemotherapy alone, 1 received radiotherapy alone, and 2 received supportive care. We evaluated 17 patients who received dCRT after 3 or 4 courses of DCF chemotherapy and excluded 10 patients who were enrolled in another prospective study. Safety was evaluated for 17 patients with stages II to IV, and efficacy was evaluated for 13 patients with stages II or III (Figure 1). This retrospective study was performed in accordance with the Declaration of Helsinki, and approved by the review board of Kitasato University.

*DCF chemotherapy*

The DCF regimen consisted of: docetaxel (70－75 mg/m$^2$), given as a 1-hour intravenous infusion on day 1; cisplatin (70－75 mg/m$^2$), given as a 2-hour intravenous infusion on day 1; and 5-fluorouracil (750 mg/m$^2$/day), given as a continuous 24-hour intravenous infusion on days 1－5 of a 21-day cycle. All patients received adequate hydration and antiemetics (dexamethasone and a 5-hydroxytryptamine-3 antagonist). Dexamethasone was administered for a total of 5 days. Ciprofloxacin (200 mg orally three times a day) was given prophylactically on days 5－15. Granulocyte-colony stimulating factors (G-CSF) were used at the discretion of the clinician in charge. In principle, prophylactic G-CSF were permitted if a patient had febrile neutropenia or infection.

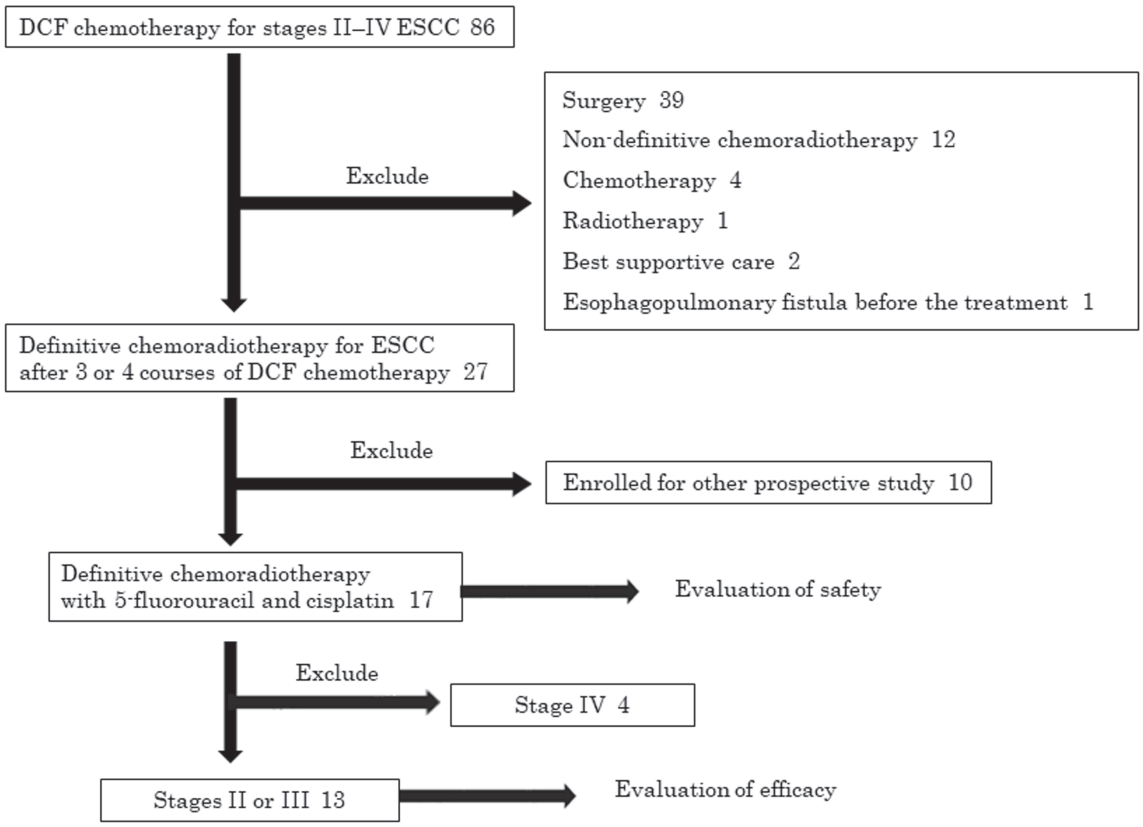


**Figure 1.** Patient selection after triple combination DCF chemotherapy. Evaluation of safety for stages II to IV and efficacy for stages II or III.

The rule of dose reduction was as follows. In principle, the dose of each drug for cycle 2 of chemotherapy was reduced by 20% or was modified at the discretion of the responsible physician for patients who had grade 3 or higher non-hematologic toxicity, or grade 4 hematologic toxicity in cycle 1. If grade 3 or higher non-hematologic toxicity persisted, or grade 4 hematologic toxicity developed, the dose of each drug was reduced by 40% for cycle 3.

*Definitive chemoradiotherapy*

Chemotherapy

The regimen of chemotherapy consisted of 5-fluorouracil (1,000 mg/m$^2$/day), given as a continuous 24-hour intravenous infusion on days 1－4 and days 29－32, and cisplatin (75 mg/m$^2$) given as a 2-hour intravenous infusion on days 1 and 29. The dosage for the first course was 100%, and the dosage for the second course was modified at the discretion of the responsible physician.

Radiotherapy

Three-dimensional conformal radiotherapy planned by a computed tomography (CT) simulator was delivered with 6 or 10 MV X-rays using multiple fields, with at least 4 ports for middle and lower thoracic tumors. The radiotherapy dose was 50.4 Gy in 28 fractions (1.8 Gy per fraction and 5 fractions per week) administered concurrently with chemotherapy. The primary tumor, metastatic lymph nodes, and regional lymph nodes were irradiated with 39.6 Gy in 22 fractions, and boost irradiation for the primary tumor, and metastatic lymph nodes was delivered with 10.8 Gy in 6 fractions. The gross tumor volume (GTV) was defined as the tumor volume before DCF chemotherapy and was delineated carefully on a simulation CT acquired after DCF (while referring to the images before DCF). This was done using either image fusion software or two monitors with the pre- and post-DCF images side by side. The clinical target volume (CTV) included the primary lesion with a 2.0 cm craniocaudal margin, metastatic lymph nodes, and regional lymph nodes. The planning target volume was defined as the CTV plus a 0.5－2.0 cm margin accounting for organ motion and setup error. Regional lymph nodes included supraclavicular lymph nodes, cervical paraesophageal lymph nodes, and mediastinal lymph nodes to the tracheal carina for upper thoracic tumors; mediastinal lymph nodes and perigastric lymph nodes for middle thoracic tumors; and mediastinal lymph nodes, perigastric lymph nodes, and celiac lymph nodes

**Table 1.** Patient characteristics

| | No. of patients (N = 17) |
|---|---|
| Age | |
| Median (range) | 65 (41－75) |
| Gender | |
| Male/Female | 13/4 |
| Performance Status (ECOG) | |
| 0/1 | 3/14 |
| Site of primary tumor | |
| Upper/Middle/Lower | 2/9/6 |
| Clinical stage (UICC 6th) | |
| IIA/IIB/III/IVA/IVB | 8/0/5/1/3 |
| T2/T3/T4 | 3/11/3 |
| N0/N1 | 8/9 |
| M0/M1a/M1b | 13/1/3 |
| Reason for administering dCRT after DCF | |
| Refusal of surgery after neoadjuvant DCF | 9 |
| Disease control after induction DCF | 6 |
| Unresectable tumor after neoadjuvant DCF | 1 |
| Difficulty in surgery due to past surgery | 1 |

ECOG, The Eastern Cooperative Oncology Group; UICC, The Union for International Cancer Control; dCRT, definitive chemoradiotherapy; DCF, docetaxel, cisplatin, and 5-fluorouracil

for lower thoracic tumors. For stage IV ESCC patients or those who had received radiotherapy for metachronous oropharyngeal carcinoma, irradiation for regional lymph nodes was omitted.

Regarding organs at risk, we attempted to restrict the volume of the lung irradiated at least 10 Gy ($V_{10}$) less than 40%, 20 Gy ($V_{20}$) less than 25%. Similarly, the mean dose to the heart was restricted to less than 40 Gy, and the maximum dose to the spinal cord was restricted to less than 48 Gy and kept as low as possible. In 3 patients, the total dose was 61.2 Gy in 34 fractions due to cervical esophagus invasion, synchronous pharyngeal carcinoma, or cervical esophageal carcinoma.

*Assessment of safety and efficacy*

Adverse events of DCF chemotherapy and of dCRT were evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. Adverse events of dCRT were divided into acute and late. The acute phase was defined within 90 days after starting dCRT, and late phase was defined more than 90 days after. The completion status of dCRT was also evaluated.

Treatment outcomes of DCF chemotherapy and of dCRT were evaluated to assess efficacy according to the RECIST (Response Evaluation Criteria in Solid Tumours), version 1.1.[31] Primary tumors were evaluated by endoscopy as non-target lesions, and lymph node metastasis was evaluated by CT. After complete response (CR) confirmation, endoscopy and CT were repeated every 3 months during the first year, every 4 months during the second and third years, and every 6 months thereafter in principle. The follow-up period and survival time were defined as from the date of starting DCF chemotherapy to the date of the last contact with living patients or the date of death.

Moreover, we compared the outcome of dCRT in good responders to DCF chemotherapy and poor responders. We defined patients whose both primary tumor and lymph node metastasis had shrunk with DCF chemotherapy as good responders and the others as poor responders.

## Results

*Patients*

The demographic characteristics are shown in Table 1. The median age was 65 years (range, 41－75). There were 13 men (76%) and 4 women (24%). The Eastern Cooperative Oncology Group performance status was 0 in 3 patients (18%) and 1 in 14 (82%). The site of the primary tumor was the upper thoracic portion of the

esophagus in 2 patients (12%), the middle esophagus in 9 (53%), and the lower esophagus in 6 (35%). The clinical stage according to the 6th edition of the tumor-node-metastasis classification of the Union for International Cancer Control was stage IIA in 8 patients (47%), stage III in 5 (29%), stage IVA in 1 (6%), and stage IVB in 3 (18%). Three patients had T4 tumor, 2 had bronchus invasion, and 1 had aorta invasion. One patient with M1a disease had celiac lymph node metastasis. Three patients had M1b disease, 1 had bone metastases, and 2 had abdominal distant lymph node metastases. At the initial diagnosis, 11 patients had tumors estimated as resectable.

The reasons for administering dCRT after DCF chemotherapy were the refusal of surgery after neoadjuvant chemotherapy with DCF in 9 patients and as an additional treatment for disease control after induction chemotherapy with DCF in 6 patients (4 patients with distant metastases and 2 patients with T4 disease). One patient had an attempted esophagectomy after neoadjuvant chemotherapy with DCF, but the tumor was not resected due to surrounding tissue adhesion despite visible tumor shrinkage after neoadjuvant chemotherapy with DCF. And 1 patient was judged as having difficulty in surgery due to past surgery.

*Safety*

Adverse events associated with DCF chemotherapy are shown in Table 2. Fifteen patients received 3 courses of DCF, and 2 patients received 4 courses. The dose was reduced from the second course of DCF chemotherapy in 7 patients (41%) and from the third course in 1 patient (6%). The main grade 3 or higher adverse events were neutropenia in 15 patients (88%), febrile neutropenia in 7 patients (41%), hyponatremia in 4 patients (24%), and oral mucositis, hypokalemia, and hypocalcemia in 3 patients for each disease (18%).

The median interval from starting the final course of DCF to starting dCRT was 38 days (range, 25－66). The performance status before starting dCRT was 0 in 13

**Table 2.** Adverse events associated with DCF chemotherapy (N = 17)

| Toxicity | NCI-CTCAE grade, version 4.0 | | | | | Grade 3/4 (%) |
|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | |
| Neutropenia | 0 | 0 | 2 | 2 | 13 | 88 |
| Anemia | 0 | 6 | 11 | 0 | 0 | 0 |
| Thrombocytopenia | 6 | 8 | 3 | 0 | 0 | 0 |
| Febrile neutropenia | 10 | 0 | 0 | 7 | 0 | 41 |
| Fatigue | 5 | 6 | 4 | 2 | 0 | 12 |
| Lethargy | 14 | 3 | 0 | 0 | 0 | 0 |
| Weight loss | 15 | 1 | 1 | 0 | 0 | 0 |
| Anorexia | 2 | 6 | 7 | 2 | 0 | 12 |
| Nausea | 4 | 5 | 8 | 0 | 0 | 0 |
| Vomiting | 7 | 6 | 4 | 0 | 0 | 0 |
| Dysgeusia | 9 | 6 | 2 | 0 | 0 | 0 |
| Hiccups | 15 | 1 | 1 | 0 | 0 | 0 |
| Cheilitis | 11 | 2 | 3 | 1 | 0 | 6 |
| Oral mucositis | 5 | 3 | 6 | 3 | 0 | 18 |
| Esophagitis | 17 | 0 | 0 | 0 | 0 | 0 |
| Constipation | 5 | 7 | 4 | 1 | 0 | 6 |
| Diarrhea | 8 | 4 | 3 | 2 | 0 | 12 |
| Hypoalbuminemia | 0 | 10 | 7 | 0 | 0 | 0 |
| Total bilirubin increase | 13 | 4 | 0 | 0 | 0 | 0 |
| AST increase | 12 | 5 | 0 | 0 | 0 | 0 |
| ALT increase | 11 | 5 | 1 | 0 | 0 | 0 |
| Serum creatinine increase | 13 | 4 | 0 | 0 | 0 | 0 |
| Hyponatremia | 2 | 11 | 0 | 4 | 0 | 24 |
| Hypokalemia | 10 | 4 | 0 | 3 | 0 | 18 |
| Hypocalcemia | 3 | 5 | 6 | 3 | 0 | 18 |

DCF, docetaxel, cisplatin, and 5-fluorouracil; NCI-CTCAE, National Cancer Institute's Common Terminology Criteria for Adverse Events; AST, aspartate

patients (76%) and 1 in 4 patients (24%). All 17 patients successfully completed dCRT. The median overall treatment time of radiotherapy was 40 days (range, 38－50), and the median day of starting the second course of chemotherapy was day 29 (range, 29－36). The second course of chemotherapy was completed in all patients before the final day of radiotherapy. The chemotherapy dose in dCRT was reduced during the second course of treatment in 8 patients (47%). The reasons for dose reduction were delayed resolution of neutropenia in 7 patients and an increased serum creatinine level in 1 patient. Table 3 shows the adverse events of dCRT after DCF chemotherapy. The main acute adverse events of grade 3 or higher were anemia in 7 patients (41%), neutropenia in 6 (35%), esophagitis in 4 (24%), and hyponatremia in 3 patients (18%). One patient died of radiation pneumonitis as a late adverse event. The onset of this adverse event was 4 months from starting radiotherapy. The patient transiently responded to steroid pulse therapy and steroid maintenance therapy. However, radiation pneumonitis worsened again 9 months after starting radiotherapy, and the patient died. No other patients had grade 3 or higher late adverse events.

*Efficacy*

The median follow-up for the 17 patients with stages II to IV was 35 months (range, 6－55) and for the 13 patients with stages II or III, it was 45 months (range, 13－55). Figure 2 shows the clinical course in patients with stages II or III ESCC. Among these 13 patients, 2 patients had

**Table 3.** Adverse events associated with chemoradiotherapy (N = 17)

| Toxicity | NCI-CTCAE grade, version 4.0 | | | | | | | Grade 3/4/5 (%) |
|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | NA | |
| Acute adverse events (≤90 days after starting dCRT) | | | | | | | | |
| Neutropenia | 2 | 3 | 6 | 4 | 2 | 0 | | 35 |
| Anemia | 0 | 3 | 7 | 6 | 1 | 0 | | 41 |
| Thrombocytopenia | 1 | 10 | 3 | 2 | 1 | 0 | | 18 |
| Febrile neutropenia | 17 | 0 | 0 | 0 | 0 | 0 | | 0 |
| Infection | 15 | 0 | 1 | 1 | 0 | 0 | | 6 |
| Malaise | 8 | 6 | 3 | 0 | 0 | 0 | | 0 |
| Anorexia | 1 | 9 | 4 | 2 | 0 | 0 | 1 | 12 |
| Nausea | 3 | 9 | 4 | 1 | 0 | 0 | | 6 |
| Vomiting | 11 | 5 | 1 | 0 | 0 | 0 | | 0 |
| Oral mucositis | 15 | 1 | 0 | 1 | 0 | 0 | | 6 |
| Esophagitis | 1 | 3 | 9 | 4 | 0 | 0 | | 24 |
| Dermatitis | 5 | 8 | 3 | 1 | 0 | 0 | | 6 |
| Diarrhea | 13 | 4 | 0 | 0 | 0 | 0 | | 0 |
| Total bilirubin increase | 13 | 4 | 0 | 0 | 0 | 0 | | 0 |
| Creatinine increase | 0 | 9 | 7 | 1 | 0 | 0 | | 6 |
| AST increase | 13 | 4 | 0 | 0 | 0 | 0 | | 0 |
| ALT increase | 14 | 3 | 0 | 0 | 0 | 0 | | 0 |
| Hyponatremia | 10 | 4 | 0 | 3 | 0 | 0 | | 18 |
| Hypokalemia | 6 | 8 | 1 | 1 | 1 | 0 | | 12 |
| Hypocalcemia | 2 | 11 | 2 | 2 | 0 | 0 | | 12 |
| Hyperkalemia | 14 | 2 | 0 | 1 | 0 | 0 | | 6 |
| Late adverse events (>90 days after starting dCRT) | | | | | | | | |
| Esophagus-related | 15 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Pneumonitis | 0 | 13 | 2 | 0 | 0 | 1 | 1 | 6 |
| Pleural effusion (non-malignant) | 4 | 12 | 0 | 0 | 0 | 0 | 1 | 0 |
| Pericardial effusion (non-malignant) | 2 | 0 | 14 | 0 | 0 | 0 | 1 | 0 |
| Cardiac disorder | 9 | 6 | 1 | 0 | 0 | 0 | 1 | 0 |
| Gastrointestinal disorder | 10 | 6 | 0 | 0 | 0 | 0 | 1 | 0 |

NCI-CTCAE, National Cancer Institute's Common Terminology Criteria for Adverse Events; NA, not available; dCRT, definitive chemoradiotherapy; AST, aspartate aminotransferase; ALT, alanine aminotransferase

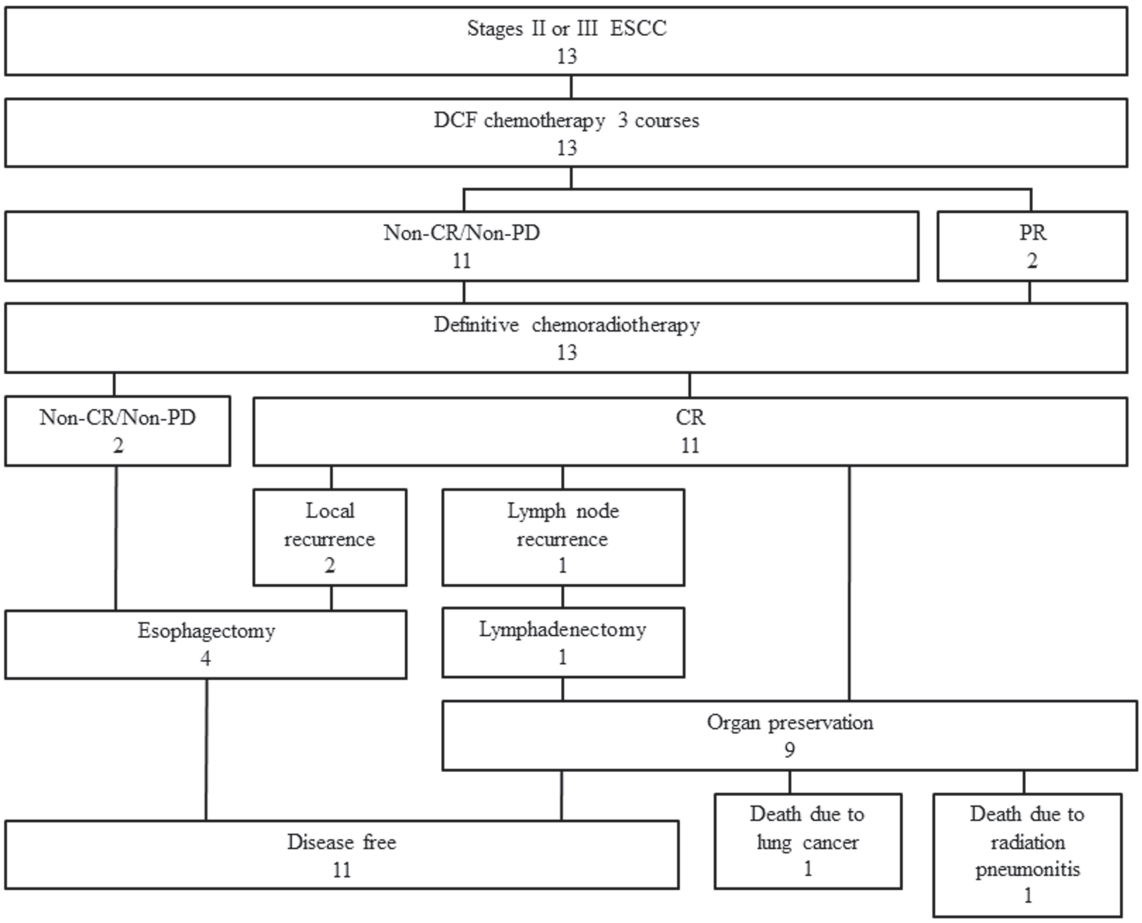


**Figure 2.** Clinical courses of 13 patients with stages II or III ESCC who had received dCRT after triple combination DCF chemotherapy. CR, complete response; PR, partial response; Non-CR/Non-PD, non-complete response/non-progressive disease

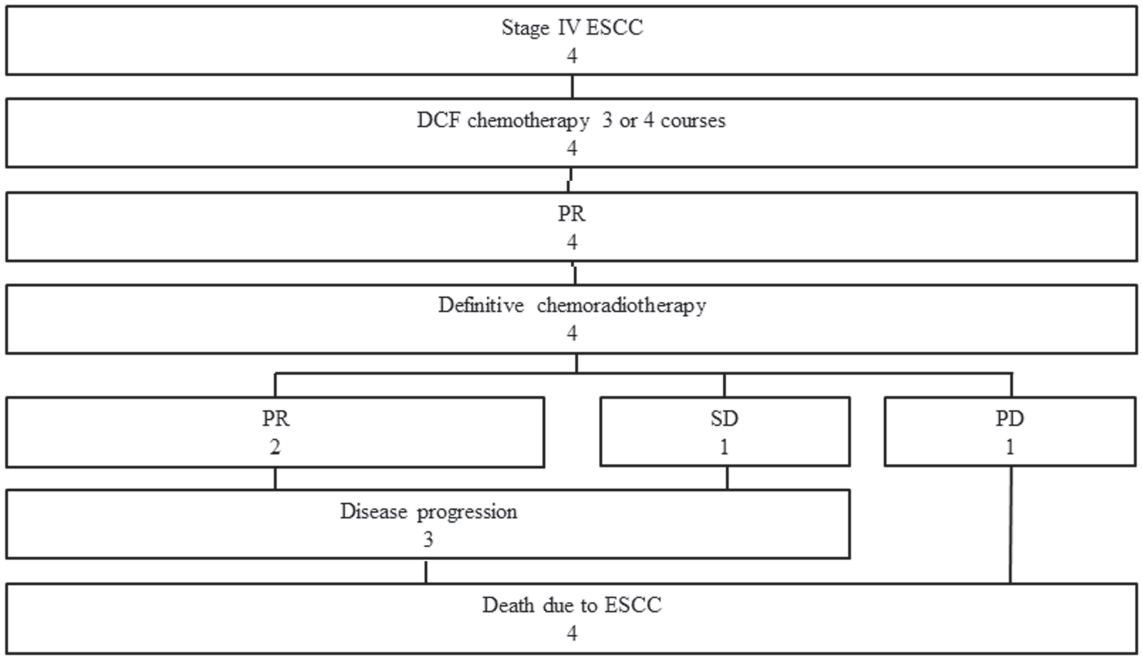


**Figure 3.** Clinical courses of 4 patients with stage IV ESCC who received dCRT after triple combination DCF chemotherapy. PR, partial response; SD, stable disease; PD, progressive disease

a partial response (PR) to DCF chemotherapy, and 11 patients had non-complete response/non-progressive disease (Non-CR/Non-PD). The response to subsequent dCRT was CR in 11 patients and Non-CR/Non-PD in 2 patients. Salvage surgery was performed in 2 patients with Non-CR/Non-PD to dCRT and 3 patients who had recurrence after CR to dCRT. With a median follow-up of 32 months (range, 22－46) after surgery, the patients in this cohort had no recurrence. One patient died of radiation pneumonitis, and 1 patient died of metachronous lung cancer. The other patients are alive, well, and without disease progression. The esophagus was preserved in 7 of 13 patients (Figure 2). In patients with stages II or III ESCC, the rate of CR to dCRT after DCF chemotherapy was 85% (11/13). The recurrence rate after CR was 27% (3/11), the rate of salvage surgery for residual lesions or recurrence was 100% (5/5), and the organ preservation rate was 54% (7/13).

In analysis of efficacy of dCRT and the degree of response to DCF chemotherapy, 11 of 12 good responders to DCF chemotherapy achieved CR to dCRT. Only 1 patient defined as poor responder resulted in Non-CR/Non-PD.

All 4 patients with stage IV ESCC had PR to DCF chemotherapy. The response to subsequent dCRT was PR in 2 patients, stable disease (SD) in 1, and progressive disease (PD) in 1 patient. All 4 patients died of progressive ESCC. The median survival time was 11 months (range, 6－21) (Figure 3).

*Salvage surgery*

Salvage surgery (esophagectomy with lymph node dissection) was performed on 2 patients without CR after dCRT and 2 patients who had local recurrence. The median interval from the completion of dCRT to salvage surgery in those 4 patients was 6 months (range, 4－8). For 1 patient who had supraclavicular lymph node metastasis outside the irradiation field 2 years after completion of dCRT, a lymphadenectomy was performed as salvage surgery. Adverse events of salvage surgery were anastomotic stenosis, anastomotic leakage, pleural injury, massive pleural effusion, and bronchitis in 1 patient each. However, all the adverse events were manageable.

## Discussion

In Japan, neoadjuvant chemotherapy followed by surgery has become the standard treatment for stages II and III ESCC.[1] On the other hand, dCRT has improved the outcome in patients with stages II or III ESCC.[8-9] In recent years, attention has focused on neoadjuvant chemotherapy with DCF due to reported good short-term outcomes.[25-28] Because DCF chemotherapy results in considerable tumor shrinkage and dysphagia often resolves, a small number of patients refuse planned surgery after DCF chemotherapy and request dCRT instead. Although there has been a possible increase in the use of dCRT after DCF chemotherapy as a treatment option for patients with ESCC, few studies have assessed the safety and efficacy of dCRT after DCF chemotherapy.[29,30]

DCF chemotherapy can cause severe toxicity,[10,11,13,14] and therefore the feasibility of dCRT might be affected adversely. We examined patients with ESCC who received dCRT after DCF chemotherapy and retrospectively evaluated its safety and efficacy. In the present study, adverse events of DCF chemotherapy were similar to or more severe, but adverse events following dCRT were comparable to those reported previously,[7,9] and all patients completed dCRT. Although prolongation of the initial treatment time could become a disadvantage of this strategy, it may lead to an improved performance status before dCRT (compared to that before DCF chemotherapy). Improvement of symptoms such as dysphagia may also contribute to better tolerability of the second treatment. Moreover, adequate dose reduction of chemotherapy and supportive care for adverse events would play an important role to complete dCRT after DCF chemotherapy.

There are some important considerations regarding radiotherapy after DCF. Because CT images for radiotherapy planning were obtained after DCF chemotherapy, some lesions were not easily apparent. Therefore, we carefully determined the target volume by referring to images obtained before DCF chemotherapy. In patients with resectable ESCC, tumor volume reduction caused by DCF chemotherapy did not always lead to a reduced radiotherapy treated volume. dCRT after DCF chemotherapy is a more aggressive treatment compared with dCRT as an initial treatment, further caution is required with doses and irradiated volume of organs at risk. To reduce cardiotoxicity, a multiple-field technique is used in modern radiotherapy.[9,32] Lung irradiated volume should also be minimized because there are concerns that radiotherapy after treatment with docetaxel may increase the risk of interstitial pneumonitis.

In this study, grade 5 radiation pneumonitis occurred in 1 patient. That patient had a T4 primary tumor and multiple lymph node metastases spread extensively in the craniocaudal direction. Although CT images before DCF chemotherapy of the patient presented slight interstitial changes of the lung, these findings did not

change after DCF. The volume of the lung irradiated at ≥20 Gy ($V_{20}$) was <25%, and the volume of the lung irradiated at ≥10 Gy ($V_{10}$) was slightly higher than 40%. Another factor, which possibly increased the irradiated lung volume is the oblique 2-port boost irradiation field. The GTV was distributed among both the left and right sides over the vertebral bodies. Therefore, it was difficult to avoid the spinal cord and the beam angle increased to more than 45 degrees, and the beam crossed the long course. In patients with multiple lesions distributed extensively in the craniocaudal direction or on the left and right sides of vertebral bodies, there may be extensive irradiation of the organ at risk, and especial caution is required.

The CR rate of dCRT after DCF chemotherapy was 85% and comparable to the CR rate of dCRT (70.6%) as the initial treatment in a past report.[9] Salvage surgery was performed in 5 patients successfully. Five of 11 patients (45%) who achieved disease-free survival had received salvage surgery suggests that the timing for salvage treatment after dCRT is an important consideration. The treatment strategy of ESCC is the result of a multidisciplinary approach. That discussion in the esophageal cancer board and the cooperation of surgeons, radiation oncologists, and medical oncologists is important to determine the optimal treatment for each patient.

This study was retrospective and of a small, heterogeneous cohort. Therefore, further prospective studies are needed to confirm the safety and efficacy of dCRT after DCF to thoroughly evaluate its feasibility as a treatment strategy.

Among the 13 patients with stage II/III ESCC, all of the 11 patients who achieved CR to dCRT were good responders to DCF chemotherapy, and poor responder could not achieve CR. The degree of response to DCF chemotherapy may, therefore, be used as a surrogate marker of the response to dCRT.[33-35] To evaluate the efficacy and safety of chemoradiotherapy in responders to DCF chemotherapy, we have initiated "chemoselection as a strategy for organ preservation in clinical stage II/III ESCC: a phase II study of induction chemotherapy with DCF, followed by chemoradiotherapy" (Clinical Trials Registry No. UMIN000008086). The abbreviated name of this study is the CROC (chemoradiotherapy oriented by response to chemotherapy) trial.

In conclusion, dCRT after DCF chemotherapy in patients with ESCC might be a feasible treatment. In particular, for patients with stages II or III ESCC, dCRT after DCF chemotherapy might be a treatment option worth considering as an organ preservation strategy.

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