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【 ORIGINAL ARTICLE 】

Docetaxel+Cisplatin+5-FU (DCF) Therapy as a Preoperative Chemotherapy to Advanced Esophageal Squamous Cell Carcinoma: A Single-center Retrospective Cohort Study

Yusuke Umeki[1], Hiroshi Matsuoka[1], Masahiro Fujita[1], Ai Goto[1], Akiko Serizawa[1], Kenichi Nakamura[1], Shingo Akimoto[1], Masaya Nakauchi[2], Tsuyoshi Tanaka[3], Susumu Shibasaki[1], Kazuki Inaba[2], Ichiro Uyama[2,3] and Koichi Suda[1,4]

Abstract:

Objective The aim of this study was to determine the safety and clinical efficacy of docetaxel+cisplatin+5-fluorouracil (DCF) as neoadjuvant chemotherapy (NAC).

Methods In this single-center study, patient background and treatment outcomes (NAC efficacy assessment, NAC adverse events, short-term postoperative outcomes, and one-year postoperative outcomes) in patients treated with preoperative DCF and preoperative cisplatin+5-FU (CF) were compared retrospectively.

Patients Seventeen patients diagnosed with esophageal squamous cell carcinoma (ESCC) and treated with preoperative DCF therapy and 50 patients treated with preoperative CF therapy between January 2013 and July 2019 were included in this study.

Results There were significant differences in clinical T factor and clinical stage between the CF and DCF groups ($p<0.05$). All patients in the DCF therapy group were above clinical T3 and clinical stage III. The clinical response after NAC was partial response (PR) for 23 patients (46.0%) in the CF group and 13 patients (76.5%) in the DCF group ($p=0.030$). Regarding adverse events in NAC, neutropenia, febrile neutropenia (FN), diarrhea, and stomatitis were observed more frequently in the DCF group than in the CF group ($p<0.05$). The postoperative results [overall survival (OS), recurrence-free survival (RFS), one-year OS, one-year RFS] of the DCF group were comparable to those of the CF group.

Conclusion DCF therapy has been recognized as an effective treatment option for advanced ESCC. However, the indication for DCF therapy should be chosen carefully because of the high incidence of adverse events.

Key words: esophageal squamous cell carcinoma, neoadjuvant chemotherapy

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Introduction

Esophageal squamous cell carcinoma (ESCC) often causes metastasis and recurrence and has a poor prognosis compared to other gastrointestinal cancers. ESCC is the sixth-highest cause of death due to cancer worldwide (1), with not only surgical therapies performed but also other multidisciplinary therapies, including chemotherapy and radiation therapy. In Western countries, neoadjuvant chemoradiotherapy is mainstream (2), but according to guidelines for the diagnosis and treatment of carcinoma of the esophagus

[1]Department of Surgery, Fujita Health University, Japan, [2]Department of Advanced Robotic and Endoscopic Surgery, Fujita Health University, Japan, [3]Collaborative Laboratory for Research and Development in Advanced Surgical Technology, Fujita Health University, Japan and [4]Collaborative Laboratory for Research and Development in Advanced Surgical Intelligence, Fujita Health University, Japan
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Correspondence to Dr. Hiroshi Matsuoka, mats1025@fujita-hu.ac.jp

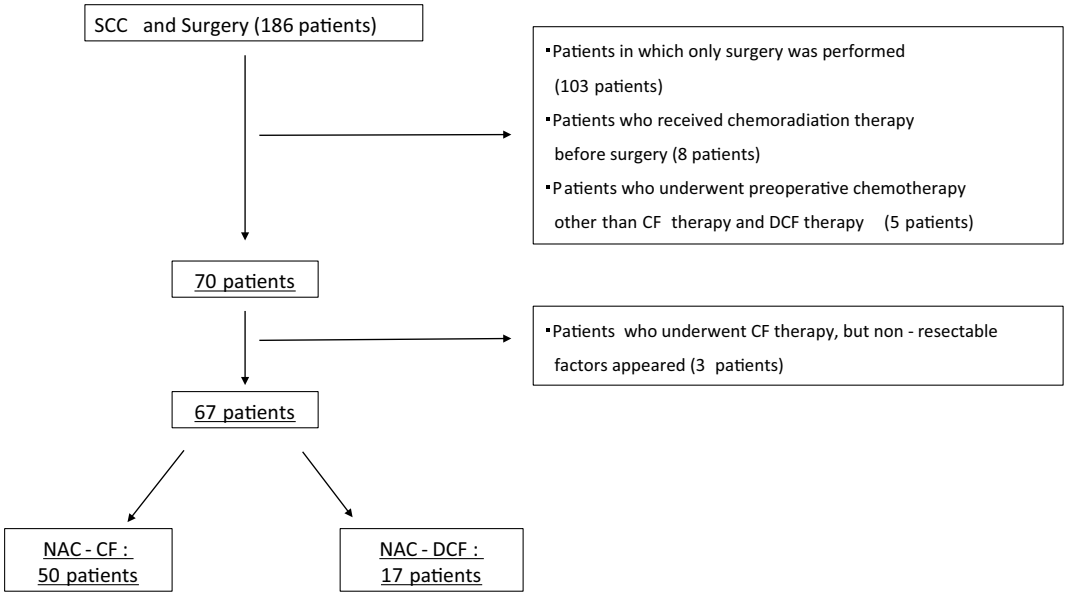

Figure 1. **Flowchart of patient selection.**

in Japan, the recommendation is to perform neoadjuvant chemotherapy (NAC) only for cases of clinical stage II or III ESCC (3).

The JCOG 9907 trial conducted by the Japan Clinical Oncology Group (JCOG) was a randomized trial comparing a preoperative adjuvant chemotherapy group with a postoperative adjuvant chemotherapy group for resectable stage II or III esophageal cancer. The five-year overall survival (OS) rate was 43% in the postoperative adjuvant chemotherapy group and 55% in the preoperative adjuvant chemotherapy group (p=0.04) (4). Based on the results of JCOG 9907, preoperative cisplatin plus 5-fluorouracil (CF) is currently considered the standard of care in Japan. However, while JCOG 9907 showed that CF was effective for clinical T1, T 2, and stage II patients, it was not sufficiently effective for clinical T3 and stage III patients.

Konishi et al. reported that CF is effective in patients with clinical stage II ESCC but may be less effective in patients with clinical stage III or T3 disease (5). As an alternative, several reports have described good results by adding docetaxel to CF (DCF) therapy (6-12). In addition, a treatment combining additives docetaxel+cisplatin+S-1 was reported with good results, showing a clinical response rate of 76%, and a pathological response rate of 33% (Grade 2/3) (13). However, some reports have described more adverse events occurring with DCF therapy than with CF therapy (14). In particular, neutropenia and febrile neutropenia (FN) occur frequently and are often difficult to manage in practice.

At our institution, DCF therapy is actively performed for cases of more advanced ESCC and for relatively young patients with a good organ function. To examine the safety and clinical effects of DCF therapy as NAC for ESCC, we retrospectively compared the outcomes of cases treated with DCF and CF.

Materials and Methods

Patients characteristics

Among the 186 patients diagnosed with ESCC between January 2013 and July 2019, 70 received CF or DCF as NAC, excluding 103 patients who underwent surgery alone without preoperative treatment, 8 who underwent preoperative radiation therapy, and 5 who underwent preoperative chemotherapy other than CF or DCF. Among the 70 patients who underwent NAC (53 with CF and 17 with DCF), 3 who received preoperative CF had non-resectable factors during NAC. After excluding these 3 patients, a total of 67 (50 with CF therapy and 17 with DCF therapy) were retrospectively reviewed (Fig. 1).

The clinical and pathological stages were evaluated based on the eighth edition of TNM classification (15). The clinical response [complete response (CR)/partial response (PR)/stable disease (SD)] and adverse events of NAC were evaluated based on the Response Evaluation Criteria in Solid Tumors (RESIST) (16) and Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (17), respectively. The tumor location, residual tumor, cancer curativity, and pathological response were evaluated based on the Japanese classification of esophageal cancer, 11th edition (18). Clavien-Dindo (CD) classification was used for perioperative complications (19).

This study was conducted under the approval of the ethics committee of Fujita Medical University in accordance with the Declaration of Helsinki. The test registration number is HM20-146.

NAC

We perform CF or DCF therapy as NAC for ESCC cases of clinical stage ≥II judged to be resectable. Adaptation of

Table 1. Patient Characteristics.

	CF (n=50)	DCF (n=17)	p value	All patients (n=67)
Age (years)	66 [38-79]	67 [48-72]	0.444	66 [38-79]
Gender [M/F]	43/7	12/5	0.278	55/12
Location [Ce/Ut/Mt/Lt/Ae]	0/6/27/15/2	1/3/7/6/0	0.312	1/9/34/21/2
cT [2/3/4a/4b]	16/29/2/3	0/10/1/6	0.003	16/39/3/9
cN [0/1/2/3]	17/20/11/2	2/9/6/0	0.234	19/29/17/2
cStage [II/III/IVA]	22/21/7	0/10/7	0.002	22/31/14

NAC is used in cases in which the Performance Status (PS) is 0 to 2; there is a sufficient cardiac, renal, and liver function; and the patient is under 80 years old. DCF therapy in particular is indicated for patients <75 years old with a PS of 0 to 1 and clinical stage ≥III. We administered DCF therapy for the first time in August 2014. CF therapy involves cisplatin 80 mg/m^2 on day 1 and 5-fluorouracil 800 mg/m^2 on days 1 through 5. DCF therapy involves docetaxel 70 mg/m^2 and cisplatin 70 mg/m^2 on day 1 and 5-fluorouracil 750 mg/m^2 on days 1 through 5. Two courses were implemented every three to four weeks.

Surgery

Regarding the lymph node dissection area, either three-region dissection of the neck/thorax/abdomen or two-region dissection of the chest/abdomen was performed. The approach for chest manipulation was either thoracoscopic, robot-assisted, or mediastinoscopic.

Postoperative nutritional management

In our institution, we usually insert a nasopharyngeal or enterostomy catheter during surgery. Enteral nutrition is started on the third postoperative day at about 10-20 mL/h and increased gradually. On postoperative day 7, a swallowing evaluation is performed to confirm that there is no aspiration due to recurrent nerve palsy before oral intake is started. Once oral intake is stabilized, enteral nutrition is tapered in preparation for discharge.

Follow-up

After surgery, outpatient visits were made every three months for blood tests including tumor markers, every six months for contrast-enhanced computed tomography (CT), and every year for an upper gastrointestinal endoscopy. Patients with elevated tumor markers or suspected recurrence were evaluated by positron emission tomography (PET)-CT.

If PET-CT showed the accumulation in distant organs, anastomoses, or lymph nodes, the tumor was judged to have recurred. In cases of postoperative pleural or ascitic effusion, puncture drainage was performed if possible, and if cancer cells were found on cytology, recurrence was also diagnosed.

Survival rate was measured from the first date of NAC. The OS was measured to the date of death from any cause, or last follow-up, whichever occurred first. The recurrence-free survival (RFS) was measured to the date of recurrence, date of death of any cause, or last follow-up, whichever occurred first.

Statistical analyses

Comparisons of categorical variables were performed using Student's *t*-test and the χ-square test, and comparisons of continuous variables were performed using the Mann-Whitney U test. The Kaplan-Meier method was used to calculate the survival curves, and the log-rank test was used to compare the survival curves. For the calculation of long-term results (OS/RFS), the Kaplan-Meier curve was subjected to log-rank analysis. The OS and RFS were calculated from the first date of NAC. A p value of <0.05 was considered a significant difference. Statistical analyses were performed using the SPSS software program, version 27 (International Business Machines, United States of America).

Results

Patient characteristics

The median patient age was 66 (38-79) years old, and there was no marked difference between the CF and DCF groups. There was also no significant difference by gender or tumor location. There was no significant difference in clinical N factor between the two groups. However, there were significant differences in clinical T factor and clinical stage ($p<0.05$), as all patients in the DCF therapy group were above clinical T3 and clinical stage III (Table 1). The median follow-up period was 31 (5-85) months.

Preoperative assessments following NAC

Evaluations after NAC are shown in Table 2. A decrease in T factor after NAC was present in 16 (32.0%) of the 50 patients in the CF group and 10 (58.8%) of the 17 patients in the DCF group ($p<0.05$). N factors decreased in 20 patients (40.0%) in the CF group and 14 patients (82.4%) in the DCF group ($p=0.003$). Down staging was recognized in 15 patients (30.0%) in the CF group and 11 patients (64.7%) in the DCF group ($p=0.011$). The clinical response after NAC was PR for 23 patients (46.0%) in the CF group and 13 patients (76.5%) in the DCF group ($p=0.030$).

Table 2. Preoperative Assessments Following Neoadjuvant Chemotherapy.

	CF (n=50)	DCF (n=17)	p value	All patients (n=67)
Down stage of T factor [Yes/No]	16/34	10/7	0.023	26/41
Down stage of N factor [Yes/No]	20/30	14/3	0.003	34/33
Down stage [Yes/No]	15/35	11/6	0.011	26/41
Clinical response [PD/SD/PR]	6/21/23	0/4/13		6/25/36
Clinical response [PD·SD/PR]	27/23	4/13	0.030	31/36

Table 3. Adverse Events of Neoadjuvant Chemotherapy.

Adverse event		CF (n=50)	DCF (n=17)	p value
Hematologic toxicity	n, (%)			
Neutropenia		7 (14)	13 (76.5)	0.012
Febrile neutropenia		1 (2)	9 (52.9)	0.002
Anemia		0	1 (5.9)	0.254
Thrombocytopenia		3 (6)	0	0.409
Renal dysfunction		1 (2)	1 (5.9)	0.446
Hyponatremia		4 (8)	3 (17.6)	0.243
Hyperkalemia		1 (2)	1 (5.9)	0.446
Hypokalemia		3 (6)	0	0.409
Non-hematologic toxicity	n, (%)			
Diarrhea		3 (6)	5 (29.4)	0.021
Nausea/vomiting		6 (12)	3 (17.6)	0.410
Anorexia		8 (16)	6 (35.3)	0.092
Stomatitis		3 (6)	6 (35.3)	0.006

Adverse events of NAC

Table 3 shows the incidence rate of adverse events (CTCAE Grade 3 or above) of NAC. For hematologic toxicity, significant differences in the occurrence rates between the CF group and the DCF group were neutropenia (14.0% vs. 76.5%, p=0.012) and FN (2.0% vs. 52.9%, p=0.002). There was no significant difference between the two groups in the occurrence rate of anemia, thrombocytopenia, renal dysfunction, hyponatremia, hyperkalemia, or hypokalemia. For nonhematologic toxicity, significant differences between the CF and DCF group were seen in the occurrence of diarrhea (6.0% vs. 29.4%, p=0.021) and stomatitis (6.0% vs. 35.3%, p=0.006). The occurrence rate of anorexia tended to be high in the DCF therapy group (p=0.092). The occurrence rate of nausea/vomiting did not show a significant difference between the two groups.

Operative findings and short-term outcomes

Table 4 shows the surgical and short-term outcomes. The median operative time was 724 min, and the median blood loss was 162 mL in all cases, with no significant differences observed between the CF and DCF groups. R0 resection was achieved in 42 cases (84%) of the CF group and 11 cases (64.7%) of the DCF group (p=0.219). Morbidity (CD classification grade III and above) was found in 12 cases (24%) in the CF group and 6 cases (35.3%) in the DCF group, showing no significant difference. The rate of a histological response (grade ≥1b) was 22% in the CF group and 35.3% in the DCF group (p=0.219). In addition, there was no significant difference between the two groups in the duration of hospital stay after surgery, pathological T factors, pathological N factors, or pathological stages.

One-year postoperative results

No significant difference in the OS or RFS was noted between the CF and DCF groups (Fig. 2). In addition, the 1-year OS was 90% in the CF group and 88.2% in the DCF group (p=0.904), and the 1-year RFS was 68% in the CF group and 52.9% in the DCF group (p=0.173) (Fig. 3).

Discussion

To determine the safety and clinical efficacy of preoperative DCF in our setting, we compared patients who received preoperative CF therapy with those who received preoperative DCF therapy. There are some reports of better clinical and pathological responses to preoperative DCF than to preoperative CF (20, 21). In our study, the clinical response was significantly higher in the DCF group than in the CF group, but there was no significant difference in the pathological response between the two groups. Although preoperative DCF was applied to more advanced cases, there were significantly more cases with down-staging in the DCF group than in the CF group in terms of T and N factors. The postoperative results (OS, RFS, and one-year OS and

Table 4. Operative Results and Short-term Outcomes.

		CF (n=50)	DCF (n=17)	p value	All patients (n=67)
Operative time (min)		724 [487-1,110]	748 [409-877]	0.922	724 [409-1,110]
Blood loss (mL)		161.5 [28-1,225]	163 [21-956]	0.911	162 [21-1,225]
Residual tumor [R0/R1/R2]		42/6/2	11/5/1	0.219	53/11/3
Curativity [A/B/C]		30/14/6	7/8/2	0.430	37/22/8
Complications*	n, (%)	12 (24.0)	6 (35.3)	0.351	18 (26.9)
Death within post operative 30 days	n, (%)	0 (0)	0 (0)	-	0 (0)
Postoperative hospital stay (days)		30.5 [15-90]	32 [11-118]	0.829	30 [11-118]
pT [1/2/3/4a]		9/14/26/1	2/3/12/0	0.583	11/17/38/1
pN [0/1/2/3]		15/21/11/3	4/7/2/4	0.203	19/28/13/7
pStage [I/II/III/IVA]		4/16/27/3	1/4/8/4	0.238	5/20/35/7
Histological response [0-1a/1b-3]		39/11	11/6	0.219	50/17

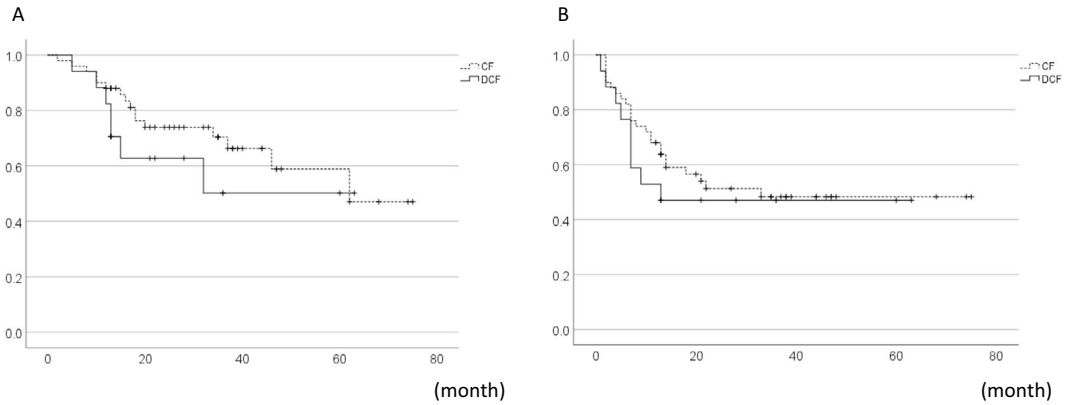

Figure 2. (A) No significant difference in the overall survival between CF and DCF groups (p=0.256). (B) No significant difference in the recurrence-free survival between CF and DCF groups (p=0.400).

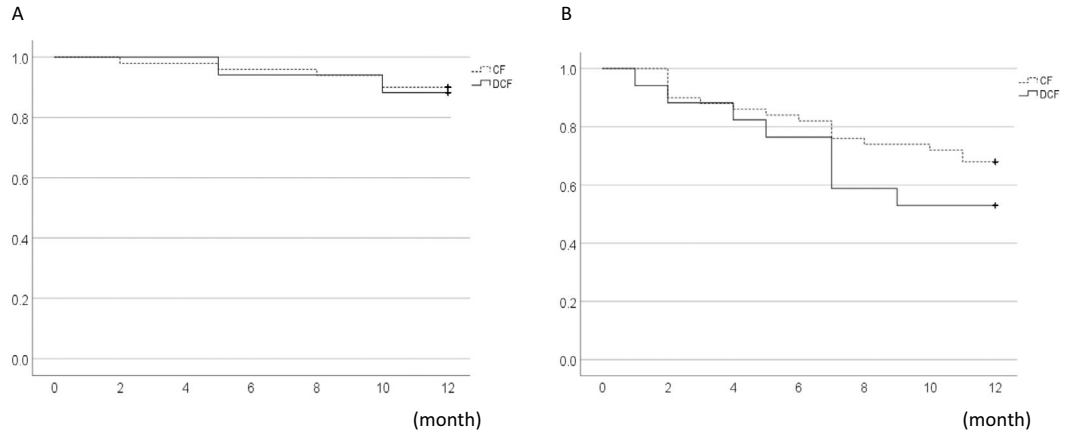

Figure 3. (A) No significant difference in the 1-year overall survival between CF and DCF groups (p=0.904). (B) No significant difference in the 1-year recurrence-free survival between CF and DCF groups (p=0.173).

RFS) of the DCF group were comparable to those of the CF group. These findings suggest that DCF therapy was indeed effective in improving the prognosis.

The survival rate in clinical stage III patients was comparable between the two groups (Supplementary Material 1), but a comparison of clinical stage IV patients showed that the DCF group performed better than the CF group (Supplementary Material 2), although there was no statistically significant difference between the two groups. The results for clinical T3 and T4 patients were also analyzed. Clinical T3

patients showed comparable results in the two groups (Supplementary Material 3), whereas clinical T4 patients showed better results in the DCF group than in the CF group (Supplementary Material 4), although the difference was again not statistically significant. These results suggest that preoperative DCF may be more effective than CF in highly advanced ESCC patients.

Regarding the surgical outcomes, complications of CD grade ≥III were frequently observed in the DCF group (35.3%), but there was no significant difference when compared to the CF group (24.0%). The postoperative hospital stay was 32 days in the DCF group vs. 30.5 days in the CF group (p=0.829), and no perioperative deaths were observed in either group. Takeuchi et al. reported that complications of CD grade ≥III were observed in 38.0% of patients who underwent esophagectomy after DCF therapy (22). Akiyama et al. concluded that the safety of thoracoscopic esophagectomy after DCF therapy is comparable to that of thoracoscopic surgery after CF therapy (20).

In terms of adverse events, neutropenia and FN were observed more frequently in the DCF group than in the CF group. Ojima et al. reported that CTCAE Grade ≥3 neutropenia was observed in 56% of patients in the DCF group but 0% of the CF group (23). Ohkura et al. reported that CTCAE Grade ≥3 adverse events were observed in 48.9% of patients in the DCF group, and FN was observed in 21.7% of the patients. Furthermore, prophylactic administration of pegfilgrastim reduced the rate of FN to 3.0% (24). In addition, according to the European Organization for Research and Treatment of Cancer (EORTC) guidelines, prophylactic granulocyte-colony stimulating factor (G-CSF) is recommended for use with chemotherapy typically accompanied by FN in more than 20% of patients (25). In our department, G-CSF is administered to patients with neutrophil counts of ≤1500, and prophylactic administration of G-CSF to the DCF group may reduce the risk of neutropenia and adverse events of FN. The planned administration of G-CSF may allow for a well-tolerated introduction of the second course without a reduction in the dose of the drug. Since prophylactic administration of G-CSF was not performed in this study, the introduction of prophylactic administration of G-CSF should be considered in the future.

In the present study, nonhematological adverse events, such as diarrhea, anorexia, and stomatitis, were also quite frequent in the DCF group (29.4-35.3%). Because of the potential impact on perioperative mortality and morbidity, it is important to strictly manage gastrointestinal adverse events during preoperative chemotherapy to prevent dehydration and malnutrition. Thus, it was recognized that DCF therapy can be an effective treatment option for advanced esophageal cancer by improving the accuracy of planned supportive care during the chemotherapy phase.

Since this was a retrospective study, the number of patients studied was small, and the patient background was not complete; these factors should be considered when interpreting the findings of the study. In our institution, preoperative DCF therapy is the treatment of choice for highly advanced ESCC, but the final choice of regimen is left to the judgement of the attending physician and the patient. One limitation associated with the present study is therefore the presence of regimen selection bias. Whether or not preoperative DCF therapy should be applied to earlier clinical stage II patients and what the optimal duration of treatment should be have not yet been clarified. It is also true that DCF therapy is associated with many adverse events, such as diarrhea and stomatitis, as well as hematological adverse events, such as neutropenia and FN. There is some concern that these adverse events may worsen the nutritional status of patients, leading to increased perioperative complications and perioperative mortality. Therefore, we believe that patients undergoing preoperative DCF therapy require more careful management, including enhanced nutritional support.

In the present study, there were no cases of perioperative mortality that could be attributed to NAC. Recently, nivolumab, an immune checkpoint PD-1 inhibitor, has been reported to be effective in the treatment of unresectable or recurrent esophageal cancer, and is expected to be a second-line treatment for these conditions (26). In addition, preoperative treatment with nivolumab in addition to DCF and CF has been investigated (27). The safety and efficacy of nivolumab as a preoperative treatment will continue to be evaluated in the future.

The authors state that they have no Conflict of Interest (COI).

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