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Real-world safety and efficacy of neoadjuvant docetaxel, cisplatin, and 5-fluorouracil therapy for locally advanced esophageal squamous cell carcinoma

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Abstract

Background Neoadjuvant chemotherapy with docetaxel, cisplatin plus 5-FU (DCF) has become the new standard of care for locally advanced esophageal squamous cell carcinoma (ESCC). In a real-world setting, the efficacy, recurrence, and adverse events (AEs) remain unclear.

Methods This retrospective cohort study included 86 patients who received neoadjuvant DCF followed by esophagectomy for resectable ESCC.

Results Following neoadjuvant DCF treatment, 75 patients underwent R0 curative resection. At the median follow-up of 19.2 months, the median disease-free survival (DFS)/recurrence-free survival (RFS) was not yet reached, with estimated 3-year DFS/RFS rates of 65.2%, respectively. The incidence of primary tumor regression grading (TRG) grade 1a and pathological complete response (pCR) were 21.3% (16/75) and 14.7% (11/75), respectively. The estimated 1-year DFS/RFS rates were 93.8% for primary TRG grade 1a and 100% for pCR. Baseline elevated serum SCC-antigen levels were inversely associated with achieving primary TRG grade 1a or pCR. In 64 patients who did not achieve pCR, residual tumor cells in the lymph nodes (ypN; HR, 16.96; 95% CI, 2.11-136.12; $P < 0.01$) and Glasgow prognostic score (GPS; HR, 8.34; 95% CI, 1.73–40.31; $P < 0.01$) were independent predictors of shorter DFS/RFS. The most common grade ≥ 3 AEs were neutropenia (61.6%) and febrile neutropenia (26.7%), which were not associated with clinicopathological factors. The most common non-hematological AEs were appetite loss (9.3%), pulmonary embolism (8.1%), diarrhea (7.0%), and nausea (2.3%). Nine patients discontinued neoadjuvant DCF due to toxicities.

Conclusions Neoadjuvant DCF was effective and well-tolerated in real-world ESCC patients. Primary TRG grade 1a or pCR showed a favorable DFS/RFS, while positive ypN and GPS were independent risk factors for worse DFS/RFS.

Keywords Neoadjuvant chemotherapy, Esophageal squamous cell carcinoma, DCF

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Introduction

Esophageal cancer (EC) is the seventh most common cancer and the sixth leading cause of cancer-related deaths worldwide [1]. The 5-year overall survival (OS) rate following treatment for this aggressive malignancy remains poor, with 26% for patients diagnosed with regional disease and 47% for those with localized disease [2]. EC can be histologically classified as either esophageal squamous cell carcinoma (ESCC) or esophageal adenocarcinoma (EAC), which have distinct epidemiology, molecular profiles, and clinical features [3]. ESCC is the most prevalent histological type, accounting for approximately 85% of ECs. ESCC is associated with a higher sensitivity to radiotherapy [4], and exhibits a higher prevalence of lymphatic spread with poorer survival outcomes than EAC [3]. Thus, ESCC and EAC must be considered separate entities, indicating the need for different therapeutic strategies.

For patients with locally advanced ESCC, radical surgery is essential for cure, but the prognosis is poor due to high rates of local and distant recurrence [4–6]. Multidisciplinary neoadjuvant approaches are essential to improve prognosis by aiding in curative resection through tumor downstaging and eliminating systemic micro-metastases. Based on results of phase III landmark trials comparing the neoadjuvant chemoradiotherapy (nCRT) followed by surgery with surgery alone [4, 7, 8], the nCRT has become the standard treatment for locally advanced ESCC [9, 10]. Neoadjuvant chemotherapy (nCT) using the cisplatin plus 5-fluorouracil (CF) regimen has also been established as a standard of care, supported by phase III trial results [11, 12]. In a network meta-analysis of individual participant data from randomized controlled trials on nCT or nCRT for EC [13], both nCT and nCRT were consistently superior to surgery alone for ESCC, with no significant difference in OS between the two approaches.

Recently, in a phase III JCOG1109 NExT trial comparing the efficacy for locally advanced ESCC in three arms: (1) doublet nCT-CF regimen, (2) triplet nCT regimen composed of docetaxel, cisplatin, and 5-fluorouracil (DCF), and (3) nCRT with CF regimen as a control arm [14], the DCF regimen significantly improved OS over the CF regimen, but nCRT did not show the superiority over the nCT-CF regimen. Thus, DCF represents a new standard nCT regimen for ESCC. However, the DCF regimen showed a higher incidence of grade 3–4 adverse events (AEs), including neutropenia, febrile neutropenia, stomatitis, appetite loss, and diarrhea, compared to the CF regimen. Neoadjuvant therapy is often given to patients who are ineligible for clinical trials due to comorbidities, advanced age, or frailty. Real-world data may therefore provide valuable information for guiding therapeutic decisions regarding the nCT-DCF regimen. We conducted a retrospective observational study to assess the safety and efficacy of the nCT-DCF regimen in clinical practice and to explore clinicopathological factors associated with treatment efficacy, recurrence, and AEs for treatment optimization.

Material and method

Study population

In this single-institution retrospective study, 86 patients who received at least one cycle of DCF chemotherapy as a nCT from June 2016 to July 2023 at the Cancer Institute Hospital for the Japanese Foundation for Cancer Research (JFCR), Japan were evaluated. Key inclusion criteria were histologically confirmed, resectable, locally advanced ESCC, defined as T2 or higher (any N) or N1 or higher (any T) with M0, as nCT is the standard of care for this population in Japan [15, 16]. Clinical staging prior to nCT was determined according to the 8th edition of the American Joint Committee on Cancer (AJCC)/the Union for International Cancer Control (UICC) TNM classification [17]. Although supraclavicular lymph node metastases are classified as M1 according to the AJCC/UICC classification, the Japanese Classification of Esophageal Cancer, 12th edition, defines them as M1a for tumors in the thoracic esophagus and esophagogastric junction, making patients with these metastases eligible for radical surgery with lymph node dissection. These patients were therefore included regardless of stage IVB. According to the JCOG1109 NExT trial protocol [14], the DCF regimen (docetaxel 70 mg/m^2, cisplatin 70 mg/m^2 on day 1, and continuous 5-fluorouracil 750 mg/m^2 on days 1–5) was administered every three weeks for three cycles prior to surgery, with dose modifications for toxicity or disease progression at the clinician's discretion. Following nCT, patients with thoracic ESCC underwent subtotal esophagectomy with regional lymphadenectomy. Patients with cervical ESCC underwent cervical esophagectomy with radical cervical and mediastinal lymphadenectomy.

This study was approved by the ethics review board of our institution (IRB number: 2023-GB-158) and was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was described on the hospital website, and the participants were provided with the opportunity to opt out. No additional consent was required from the enrolled patients.

Assessments

We conducted a retrospective review of electronic medical records to collect data on patient characteristics, relative dose intensity of DCF regimen, grade 3 or higher treatment-related AEs, pathological response, and clinical outcomes from a patient database. Performance status (PS) was assessed according to the Eastern Cooperative Oncology Group (ECOG) PS [18]. Hematological and

non-hematological toxicities were assessed during neoadjuvant DCF chemotherapy according to the National Cancer Institute Common Terminology Criteria Common Terminology Criteria for Adverse Events version 5.0. All patients were assessed for dysphagia symptoms using a standardized dysphagia score [19]. The prognostic nutritional index (PNI), neutrophil-lymphocyte ratio (NLR), and Glasgow prognosis score (GPS) were used to assess systemic inflammatory and nutritional status at baseline prior to nCRT. PNI and NLR were calculated according to the following formula: PNI = 10 × albumin (g/dL) + 0.005 × total lymphocyte count (mm3); NLR = absolute neutrophil count/lymphocyte count. GPS is scored based on the C-reactive protein (CRP) and albumin (Alb) levels: GPS 0: CRP ≤ 10 mg/L and Alb ≥ 35 g/L, GPS 1: CRP > 10 mg/L or Alb < 35 g/L, GPS 2: CRP > 10 mg/L and Alb < 35 g/L [20]. Baseline serum SCC-antigen (Ag) levels prior to nCRT were also assessed. Surgically resected specimens were evaluated for primary tumor and lymph node status. R0 resection indicated no residual tumor, while R1/2 indicated residual tumor at the margin. Pathological evaluation included residual tumor cells in the primary tumor (ypT), residual tumor cells in the lymph nodes (ypN), and ypStage according to the AJCC/UICC classification [17]. Tumor response according to Becker grading criteria [21]. Primary tumor regression grading (TRG) was assessed based on the percentage of residual viable tumor cells in the primary tumor (grade 1a: no residual tumor, grade 1b: less than 10% residual tumor, grade 2: 10–50% residual tumor, grade 3: greater than 50% residual tumor) [21]. Major pathological response (MPR) was defined as grade 1a or 1b, and pathological complete response (pCR) was defined as no residual tumor cells in both primary tumor and lymph nodes.

Statistical analysis

To evaluate patient characteristics, summary statistics were constructed by employing frequencies and proportions for categorical variables, and medians and ranges for continuous variables. The distributions of categorical and numerical variables between groups were compared using the Fisher's exact tests and Mann–Whitney U tests. The continuous variables were compared using two-sample t-tests. Disease-free survival (DFS) was defined as the time interval from surgery to the earlier event of the first documentation of disease recurrence, second cancer, or death from any cause. DFS was censored if a patient was still alive without events at the data cutoff. Since there were no events of second cancer in the present study, the DFS corresponds to recurrence-free survival (RFS), defined as the time to recurrence or all-cause death, whichever occurred first. This analysis included patients who eventually underwent surgery, but excluded patients with R1/2 resections. Survival curves were estimated using the Kaplan– Meier method, and were compared using the log-rank test. Prognostic variables that were significantly associated with DFS/RFS in univariable analyses were further assessed in multivariable Cox proportional hazard model analyses, with the adjusted hazard ratios (HRs) and the 95% confidence intervals (CIs). Logistic regression analyses were performed to evaluate the association between clinicopathological factors—such as patient characteristics, tumor factors, the extent of nCT completion, systemic inflammatory and nutritional markers—and the risk of recurrence, non-pCR, non-TRG grade 1a, and specific AEs, estimating the odds ratios. P-values < 0.05 were considered to indicate statistical significance. All statistical analyses were performed with the JMP 14 software package (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 86 patients with ESCC received the DCF regimen as nCT at our institute during the study period. Details of baseline clinical characteristics are shown in Table 1. Overall, 75.6% of all patients were male, with a median age of 64 years (range, 40–78 years) at the start of treatment. The proportions of ECOG PS 0 and 1 were 86.0% and 14.0%, respectively. The cohort predominantly consisted of patients in clinical stages II and III, with 5.8% in stage I, 18.6% in stage II, 60.5% in stage III, and 15.1% in stage IV. Stage IVA comprised five patients, with four having clinical N3 and one having clinical T4a, while all eight stage IVB patients had supraclavicular lymph node metastases. Moreover, 89.6% of primary tumors were located in the thoracic esophagus. The dysphagia scores were 0 in 56 patients (65.1%), 1 in 22 patients (25.6%), 2 in five patients (5.8%), and 3/4 in three patients (3.5%). GPS was scored as 0 in the majority of patients (80 patients, 93.0%), while three patients (3.5%) were scored as 1, and another three patients (3.5%) were scored as 2. nCT was completed in 72 patients (83.7%), while 14 patients (16.3%) discontinued treatment, mainly due to disease progression ($n = 4$) or toxicities ($n = 9$). Among the four patients who discontinued nCT due to disease progression, three received definitive chemoradiotherapy (CRT), and one underwent curative surgery. Following nCT-DCF treatment, 78 patients (90.7%) underwent esophagectomy with regional lymphadenectomy, and 75 patients had R0 curative resection (Table 2). Eight patients did not undergo surgery, for reasons including disease progression ($n = 5$), AEs ($n = 1$), and refusal of surgery ($n = 2$). The median time from nCT to surgery was 83 days (range, 27–114 days). Adjuvant nivolumab was administered to 14 of 64 patients with pathological residual disease after R0 resection.

Table 1 Clinicopathological characteristics in 86 patients with ESCC

Variables	No.	(%)
Age (years)		
Median (range)	64 (40–78)	
Gender		
Male	65	75.6
Female	21	24.4
ECOG PS		
PS0	74	86.0
PS1	12	14.0
BMI		
Median (range)	21.2 (14.7–27.9)	
Tumor location		
Ce	7	8.1
Ut	20	23.3
Mt	28	32.6
Lt	29	33.7
EGJ	2	2.3
cT category (AJCC/UICC-TNM 8th)*		
T1	8	9.3
T2	15	17.4
T3	62	72.1
T4	1	1.2
cN category (AJCC/UICC-TNM 8th)*		
N0	10	11.6
N1	41	47.7
N2	31	36.0
N3	4	4.7
cStage (AJCC/UICC-TNM 8th)*		
I	5	5.8
II	16	18.6
III	52	60.5
IV	13	15.1
Serum SCC-Ag (ng/ml)		
≤ 1.5	46	53.5
> 1.5	37	43.0
unknown	3	3.5
Dysphagia score		
Score 0	56	65.1
Score 1	22	25.6
Score 2	5	5.8
Score 3/4	3	3.5
GPS		
Score 0	80	93.0
Score 1	3	3.5
Score 2	3	3.5
PNI		
Median (range)	47.9 (31.4–57.9)	
NLR		
Median (range)	2.6 (0.8–9.8)	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; BMI, body mass index; GPS, Glasgow prognostic score; PNI, prognostic nutritional index; NLR, neutrophil/lymphocyte ratio

*, the 8th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC).

Patients with supraclavicular lymph node metastases were included in the study as candidates for radical resection.

Treatment efficacy

The median follow-up period was 19.2 months (range, 5.9–55.5 months). During the study period, 19 patients (25.3%) of 75 patients with R0 resection had tumor recurrence, including locoregional recurrence ($n=7$) and distant metastasis ($n=12$). The pattern of recurrence is summarized in Supplemental Table S1. The median DFS/RFS was not yet reached (95% CI, 31.8 months to not reached), with estimated 1-year and 3-year DFS/RFS rate of 76.7% and 65.2%, respectively (Fig. 1A). Among the 75 patients who underwent R0 resection, 16 (21.3%) and 15 (20.0%) achieved primary TRG grades 1a and 1b, respectively, according to the Becker grading criteria, resulting in an MPR of 41.3% (Table 2). Among the 31 patients with MPR, primary TRG grade 1a demonstrated the best DFS/RFS, with estimated 1-year and 3-year DFS/RFS rates of 93.8%, while TRG grade 1b showed moderate outcomes, with estimated 1-year and 3-year DFS/RFS rates of 85.1% and 73.0%, in the Becker grading classification (Fig. 1B). Eleven patients (14.7%) achieved pCR (Table 2). These patients had no recurrence and had better 3-year DFS/RFS rates compared to those without pCR (i.e. pathological residual disease), which was 100% versus 60.4% (Fig. 1C). In the prognostic analysis based on ypStage, the estimated 1-year and 3-year DFS/RFS rates were 100% for 26 patients with ypStage I (ypT0, ypN0 [i.e., pCR], and ypT1-2, ypN0), 69.2% and 53.6% for 44 patients with ypStage II/III, and 20.0% and 0% for 5 patients with ypStage IV (Fig. 1D). Since cervical ESCC was not included in the phase III JCOG1109 NExT trial, we analyzed the treatment efficacy in 70 patients with thoracic ESCC, excluding five patients with cervical ESCC from the 75 who underwent R0 resection. The treatment efficacy remained consistent, with a median DFS/RFS not yet reached (95% CI, 31.8 months to not reached; Supplemental Fig. S1). The estimated 1-year and 3-year DFS/RFS rates were 78.2% and 66.4%, respectively. The pCR was achieved in 11 patients (15.7%), and primary TRG grade 1a was observed in 15 patients (21.4%). The OS analysis was deemed premature, as only six patients had died during the study period.

Table 2 Treatment status and efficacy

Variables	Frequency	
	No.	(%)
Neoadjuvant treatment disposition		
Completion of neoadjuvant treatment	72	83.7
Reason for termination of neoadjuvant treatment	14	16.3
Disease progression	4	28.6
Adverse event	9	64.3
Other	1	7.1
Relative dose intensity, median (range), %		
5-FU	93.3 (62.0-100)	
CDDP	91.5 (52.7–100)	
DTX	93.3 (50.0-100)	
Surgery		
Time from the initiation of neoadjuvant to surgery		
Median (range), days	83 (27–114)	
Completion of surgery	78	90.7
Reason for non-surgery	8	9.3
Disease progression	5	62.5
Adverse event	1	12.5
Other	2	25.0
No. of harvested LNs		
Median (range)	43 (15–93)	
Residual tumor		
R0	75	96.2
R1/2	3	3.8
Adjuvant		
Adjuvant nivolumab	14	18.7
Efficacy		
Primary TRG according to the Becker criteria		
Grade 1a	16	21.3
Grade 1b	15	20.0
Grade 2	15	20.0
Grade 3	29	38.7
pCR (AJCC/UICC-TNM 8th)*	11	14.7
ypStage (AJCC/UICC-TNM 8th)*		
ypStage I	26	34.7
ypStage II	6	8.0
ypStage III	38	50.7
ypStage IV	5	6.7

Abbreviations: 5-FU, 5-fluorouracil; CDDP, cisplatin; DTX, docetaxel; LNs, lymph nodes; TRG, tumor regression grading; pCR, pathological complete response

*, the 8th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC)

Factors associated with DFS/RFS, recurrence, and pCR

There was a significant difference in baseline serum SCC-Ag levels between patients with and without pCR, but no significant differences were found in other clinical characteristics, such as age, gender, clinical stage, dysphagia score, systemic inflammatory and nutritional status, completion of nCT, and febrile neutropenia (Table 3). The elevated serum SCC-Ag levels were the only significant risk factor for non-pCR in univariable logistic regression analysis (odds ratio, 8.72; 95% CI, 1.04–72.94; $P = 0.046$; Supplemental Table S2). Similarly, the serum SCC-Ag levels were inversely correlated with primary TRG grade 1a and were the only risk factor for non-TRG grade 1a (odds ratio, 4.00; 95% CI, 1.12–18.91; $P = 0.03$; Supplemental Table S2). Since no recurrent events occurred in patients who achieved pCR, further statistical analyses including pCR could not be conducted. In 64 patients who did not achieve pCR, male gender (HR, 0.23; 95% CI, 0.08–0.62; $P < 0.01$) was an independent factor for longer DFS/RFS, while ypN (HR, 16.96; 95% CI, 2.11-136.12; $P < 0.01$) and GPS (HR for GPS2 referred to GPS0, 8.34; 95% CI, 1.73–40.31; $P < 0.01$) were independent factors for shorter DFS/RFS in multivariable Cox proportional hazard model analysis (Table 4). These factors were significantly associated with DFS/RFS in the log-rank test (Fig. 2A and Supplemental Fig. S2). They also remained independent predictors for DFS/RFS in a total of 75 patients who underwent R0 resection (Supplemental Table S3). The ypN category further stratified the PFS/RFS among patients without pCR (Fig. 2B). Recurrence was negatively associated with primary TRG grade 1a, and positively associated with ypN and high GPS levels in multivariable logistic regression analyses (Supplemental Table S4).

Safety

The most common grade ≥ 3 hematological AEs were neutropenia (61.6%) and febrile neutropenia (26.7%) (Supplemental Table S5). No clinicopathological factors were associated with grade ≥ 3 neutropenia or febrile neutropenia in logistic regression analysis (Supplemental Table S6). These AEs were also not associated with treatment efficacy or recurrence (Tables 3 and 4 and Supplemental Table S3-4). The most common non-hematological AEs were appetite loss, pulmonary embolism, diarrhea, and nausea were most frequently observed in eight patients (9.3%), seven patients (8.1%), six patients (7.0%) and two (2.3%), respectively. There were no treatment-related deaths. The median dose intensity of 5-fluorouracil, cisplatin, and docetaxel was relatively high, at 93.3% (range, 62.0-100%), 91.5% (range, 52.7–100%), and 93.3% (range, 50.0-100%), respectively (Table 2). Nine patients discontinued nCT due to toxicities: hematological toxicities in three patients, gastrointestinal toxicities and pulmonary embolism in two patients each, and renal toxicity and hematemesis in one patient each. One patient completed three cycles of nCT-DCF treatment but developed recurrent aspiration pneumonia. Due to the achievement of a clinical complete response, the patient was observed without surgery.

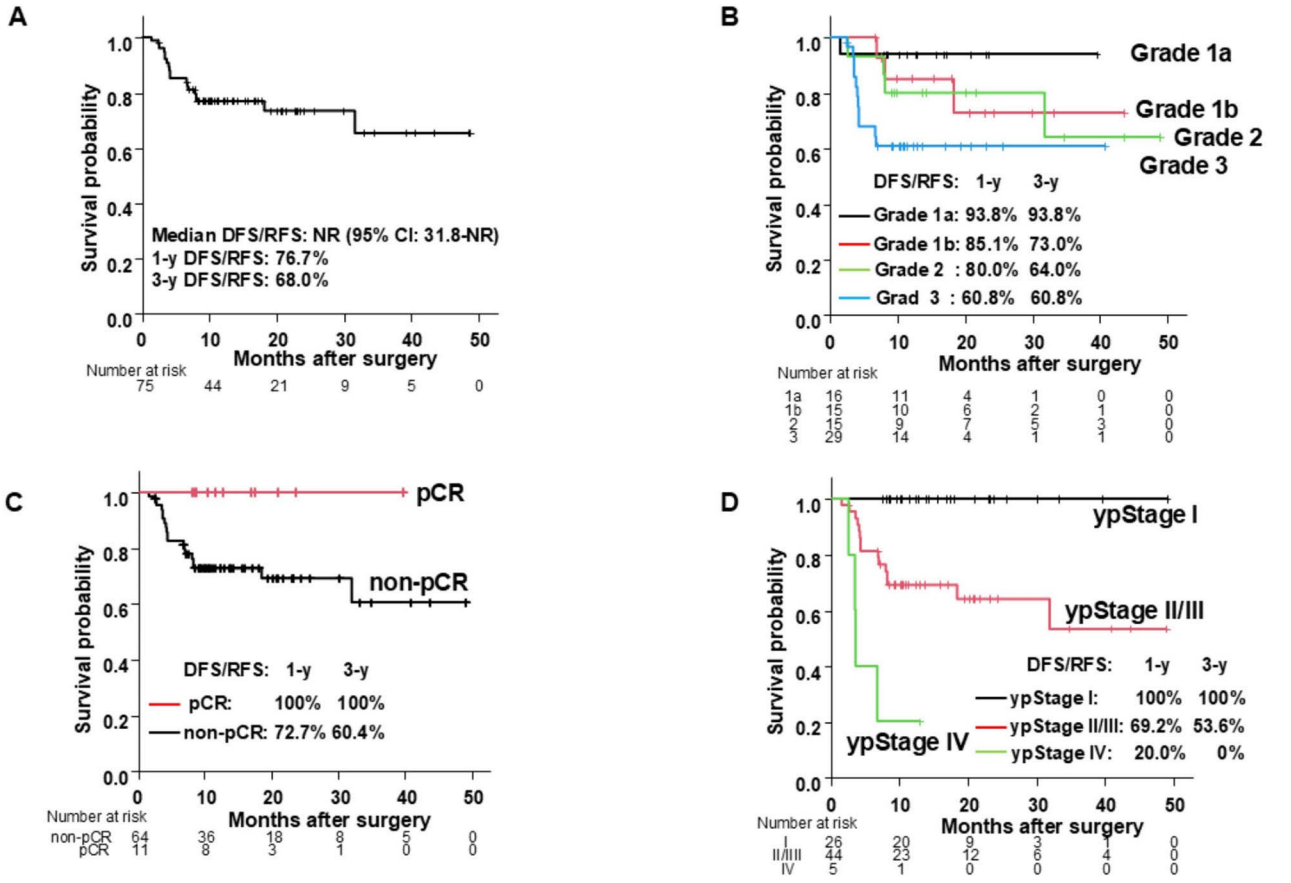

Fig. 1 DFS/RFS for 75 ESCC patients who underwent neoadjuvant DCF treatment followed by R0 curative resection (**A**), according to the Becker grading criteria (**B**), pCR (**C**), and ypStage (**D**)

Abbreviations: DFS/RFS, disease-free survival/recurrence-free survival; ESCC, esophageal squamous cell carcinoma; DCF, docetaxel, cisplatin, and 5-fluorouracil; pCR, pathological complete response; NR, not reached.

Discussion

Patients with locally advanced cancer often experience disease recurrence after surgery alone; therefore, nCRT or nCT is recommended as an adjunct to surgery [9, 10, 15, 16]. The neoadjuvant therapeutic strategy varies by region. In Japan, the phase III JCOG1109 NExT trial showed that the nCT-DCF regimen had a survival benefit over the nCT-CF regimen, but there was no survival benefit of nCRT over nCT-CF regimen [14]. Clinical trials rigorously select patients based on specific criteria, but real-world settings include diverse patients with varying characteristics and conditions, potentially affecting treatment outcomes. Thus, the findings of clinical trials may not always be generalizable to all patients in real-world clinical settings, highlighting the importance of confirming clinical feasibility. Importantly, almost all previous studies on the DCF regimen used different schedules from the JCOG1109 NExT trial, including variations in dosage, frequency of administration, or the combination of different regimens for analysis [22–28]. In contrast, the present study adhered to the standard DCF regimen outlined in the JCOG1109 NExT trial, providing data on the efficacy, recurrence, and safety of the standard DCF as nCT in a real-world setting. Additionally, the present study investigated clinical factors that predict treatment efficacy, recurrence, and AEs to optimize treatment, as few studies have explored these aspects in the nCT-DCF regimen.

This real-world study in patients with ESCC showed that nCT-DCF treatment achieved comparable rates of R0 resection, pCR, and estimated 3-year DFS/RFS to those observed in the JCOG1109 NExT trial [14]. In addition, our results were consistent with a previous observational study [29], supporting the use of nCT-DCF regimen in clinical practice. Patients achieving pCR after nCRT have better survival and lower recurrence risks than those who do not in locally advanced ESCC [30–33]. However, the prognosis of pCR after nCT, especially with the DCF regimen, is not well-established [23–29, 34–36]. The present study showed that patients who achieved pCR had no recurrence and exhibited better DFS/RFS compared to those with pathological residual disease. Although primary TRG grade 1a correlated with a favorable DFS/RFS and the absence of recurrence, this grading

Table 3 Association between clinicopathological factors and pCR/MPR

	pCR			Primary TRG grade 1a		
Variables	**Negative (%)**	**Positive (%)**	***P* value**	**Negative (%)**	**Positive (%)**	***P* value**
Age (years)			0.24			0.78
Age ≥ 70	15 (93.8)	1 (6.3)		13 (81.2)	3 (18.8)	
Age < 70	49 (83.1)	10 (17.0)		46 (78.0)	13 (22.0)	
Gender			0.48			0.64
Male	46 (83.6)	9 (16.4)		44 (80.0)	11 (20.0)	
Female	18 (90.0)	2 (10.0)		15 (75.0)	5 (25.0)	
ECOG PS			0.62			0.49
PS 0	56 (86.2)	9 (13.9)		52 (80.0)	13 (20.0)	
PS 1	8 (80.0)	2 (20.0)		7 (70.0)	3 (30.0)	
BMI			0.82			0.69
Median (range)	21.2 (17.2–27.9)	22.6 (14.7–26.8)		21.3 (17.2–27.9)	21.1 (14.7–26.8)	
Tumor location			0.68			0.33
Ce / Ut	18 (85.7)	3 (14.3)		17 (81.0)	4 (19.1)	
Mt	21 (80.8)	5 (19.2)		18 (69.2)	8 (30.8)	
Lt / EGJ	25 (89.3)	3 (10.7)		24 (85.7)	4 (14.3)	
cT category (AJCC/UICC-TNM 8th)*			0.20			0.50
T1	5 (62.5)	3 (37.5)		5 (62.5)	3 (37.5)	
T2	12 (92.3)	1 (7.7)		10 (76.9)	3 (23.1)	
T3 / T4a	47 (87.0)	7 (13.0)		44 (81.5)	10 (18.5)	
cN category (AJCC/UICC-TNM 8th)*			0.81			0.79
N0	8 (80.0)	2 (20.0)		8 (80.0)	2 (20.0)	
N1	29 (87.9)	4 (12.1)		27 (81.8)	6 (18.2)	
N2 / N3	27 (84.4)	5 (15.6)		24 (75.0)	8 (25.0)	
cStage (AJCC/UICC-TNM 8th)*			0.08			0.05
I	3 (60.0)	2 (40.0)		3 (60.0)	2 (40.0)	
II/III	51 (85.0)	9 (15.0)		46 (76.7)	14 (23.3)	
IV	10 (100)	0 (0)		10 (100)	0 (0)	
Serum SCC-Ag (ng/ml)			0.01			0.03
SCC > 1.5	31 (96.9)	1 (3.1)		29 (90.6)	3 (9.4)	
SCC ≤ 1.5	32 (78.1)	9 (22.0)		29 (70.7)	12 (29.3)	
GPS			0.52			0.58
Score 0	60 (85.7)	10 (14.3)		56 (80.0)	14 (20.0)	
Score 1	2 (66.7)	1 (33.3)		2 (66.7)	1 (33.3)	
Score 2	2 (100)	0 (0)		1 (50.0)	1 (50.0)	
PNI (median: 47.9)			0.95			0.94
≥ median	35 (85.4)	6 (14.6)		32 (78.1)	9 (22.0)	
< median	28 (84.9)	5 (15.2)		26 (78.8)	7 (21.2)	
NLR (median: 2.35)			0.55			0.24
≥ median	41 (87.2)	6 (12.8)		39 (83.0)	8 (17.0)	
< median	23 (82.1)	5 (17.9)		20 (71.4)	8 (28.6)	
Dysphagia score			0.21			0.31
Score 0	40 (80.0)	10 (20.0)		37 (74.0)	13 (26.0)	
Score 1	19 (95.0)	1 (5.0)		18 (90.0)	2 (10.0)	
Score 2	2 (100)	0 (0.0)		2 (100)	0 (0)	
Score 3/4	3 (100)	0 (0.0)		2 (66.7)	0 (0)	
Neutropenia			0.99			0.89
Grade ≥ 3	35 (85.4)	6 (14.6)		32 (78.1)	9 (22.0)	
Grade < 3	29 (85.3)	5 (14.7)		27 (79.4)	7 (20.6)	
Febrile neutropenia			0.14			0.16
Grade ≥ 3	18 (94.7)	1 (5.3)		17 (89.5)	2 (10.5)	
Grade < 3	46 (82.1)	10 (17.9)		42 (75.0)	14 (25.0)	
Neoadjuvant treatment			0.55			0.24

Table 3 (continued)

	pCR			Primary TRG grade 1a		
Variables	**Negative (%)**	**Positive (%)**	***P* value**	**Negative (%)**	**Positive (%)**	***P* value**
Completion	54 (84.4)	10 (15.6)		49 (76.6)	15 (23.4)	
Termination	10 (90.9)	1 (9.1)		10 (90.9)	1 (9.1)	
No. of harvested LNs (median: 43)			0.71			0.53
≥ median	33 (86.8)	5 (13.2)		31 (81.6)	7 (18.4)	
< median	31 (83.8)	6 (16.2)		28 (75.7)	9 (24.3)	

Abbreviations: pCR, pathological complete response; MPR, major pathological response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BMI, body mass index; GPS, Glasgow prognostic score; PNI, prognostic nutritional index; NLR, neutrophil/lymphocyte ratio

*, the 8th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC).

system for the primary tumor was not an independent factor for DFS/RFS. The estimated 3-year DFS/RFS rates were 100% in patients with ypStage I, including those with pCR and those with negative lymph node metastasis with ypT1-2. In addition, six patients with ypT3-4, ypN0 also had favorable outcomes, with estimated 1-year DFS/RFS rates of 100% and 3-year DFS/RFS rates of 75.0%. These findings highlight the importance of lymph node metastasis status in addition to primary TRG grade 1a. In fact, positive ypN was an independent predictor for recurrence and shorter DFS/RFS, consistent with previous studies [23, 24, 27, 29]. Moreover, even in patients who did not achieve pCR, the presence of ypN was associated with worse DFR/RFS. The ypN category could also provide meaningful subclassifications for DFR/RFS, suggesting its critical role in recurrence after neoadjuvant DCF therapy followed by curative surgery. The accurate identification of patients at high risk of recurrence remains challenging, but ypN status could improve individual assessment of recurrence risk and guide further treatment decisions.

Systemic inflammatory response and nutritional status, driven by host-tumor interactions, are closely linked to tumor progression [37]. Assessment tools of a systemic inflammatory response have potential as prognostic markers in both palliative and curative settings for various malignancies, including ESCC [37, 38]. However, most studies on recurrence risk have focused on clinicopathological characteristics rather than systemic status of patients. In the present study, systemic inflammatory and nutritional status, including GPS [37–41], PNI [42], NLR [37, 43], and dysphagia score [44], were evaluated along with clinicopathological characteristics to assess the efficacy and toxicities of nCT-DCF treatment. GPS, combining CRP and albumin, was useful in identifying patients at higher risk of recurrence, with high GPS levels being independent predictive factors for shorter DFS/RFS. GPS showed no impact on the dose intensity of the DCF regimen or grade ≥ 3 febrile neutropenia. Only six of 75 patients had a GPS score of 1 or 2. Previous studies have shown that abnormal GPS levels can identify patients with a poor prognosis in locally advanced EC, even though low albumin or abnormal GPS levels are rare in this population [45, 46]. GPS may serve as a clinically accessible predictive marker for recurrence and shorter DFS/RFS but not for AEs.

Tumor-related proteins produced by cancer cells can be secreted into the bloodstream and used as noninvasive tumor markers in clinical settings. The serum SCC-Ag is a widely used marker for estimating prognosis in ESCC [47, 48], but few studies have investigated its relationship with the therapeutic effect of nCT [49]. The levels of serum SCC-Ag were negatively associated with pCR and primary TRG grade 1a, as only one out of 32 patients with elevated serum SCC-Ag achieved pCR, and three achieved primary TRG grade 1a. The baseline serum SCC-Ag levels may guide the selection of patients with ESCC who are unlikely to benefit from nCT. We assessed the association between treatment efficacy and changes in serum SCC-Ag levels after cycle 1 or cycle 3 of DCF treatment from baseline (Supplemental Table S7). Changes in SCC levels were not associated with pCR, primary TRG grade, or ypStage. Similarly, no association was found between changes in systemic inflammatory and nutritional markers, such as GPS, PNI, and NLR, after DCF treatment and treatment efficacy (data not shown). Gender differences may also influence the efficacy, outcome, and toxicities of systemic treatments. Consistent with results of the present study, an individual data network meta-analysis found that males tend to benefit more from nCT than females in EC [50]. Another study suggested that males may have a better PFS with three courses of DCF compared to two courses in ESCC [51]. However, there are conflicting results, with some studies suggesting that females may have a positive impact on prognosis [52–54]. Of note, gender was not associated with recurrence in logistic regression analysis. Women represented only 23% of the study population, potentially affecting these findings.

Adjuvant nivolumab has become the standard of care for EC patients who undergo R0 resection after nCRT without achieving a pCR [9], based on the phase III Checkmate 577 trial [55]. Although the efficacy of adjuvant nivolumab following nCT and surgery has not been

Table 4 Cox proportional hazard model analyses for DFS/RFS in 64 patients who did not achieve pCR

	Univariable			Multivariable		
Variables	**HR**	**(95% CI)**	***P* value**	**HR**	**(95% CI)**	***P* value**
Age (years)						
Age ≥ 70 vs. < 70	1.11	0.37–3.35	0.86			
Gender						
Male vs. female	0.38	0.15–0.96	0.04	0.23	0.08–0.62	< 0.01
ECOG PS						
PS0 vs. PS1	0.68	0.20–2.33	0.54			
BMI (median: 21.2)						
≥ vs. < median	0.52	0.20–1.33	0.17			
Tumor location						
Ce / Ut	reference					
Mt	0.70	0.25–2.02	0.51			
Lt / EGJ	0.39	0.12–1.24	0.11			
cT category (AJCC/UICC-TNM 8th)*						
T1	0.84	0.19–3.69	0.82			
T2	0.25	0.03–1.88	0.18			
T3 / T4a	reference					
cN status (AJCC/UICC-TNM 8th)*						
Negative vs. positive	1.61E-09	0-NA	1.00			
ypT category (AJCC/UICC-TNM 8th)*						
T0	0.54	0.07–4.20	0.55			
T1	0.42	0.13–1.34	0.15			
T2	0.75	0.21–2.70	0.66			
T3 / T4a	reference					
ypN status (AJCC/UICC-TNM 8th)*						
Negative vs. positive	14.12	1.85-108.02	0.01	16.96	2.11-136.12	0.01
TRG						
Grade 1a	0.49	0.06–3.82	0.50			
Grade 1b	0.38	0.10–1.37	0.14			
Grade 2	0.47	0.14–1.52	0.21			
Grade 3	reference					
MPR						
Positive vs. negative	0.33	0.11–0.99	0.04	0.240	0.05–1.08	0.06
Serum SCC-Ag (ng/ml)						
SCC > 1.5 vs. ≤ 1.5	2.05	0.79–5.32	0.14			
GPS						
Score 0	reference			reference		
Score 1	4.20×10^{-9}	0-NR	1.00	4.30×10^{-8}	0-NR	1.00
Score 2	8.37	1.87–37.54	< 0.01	8.34	1.73–40.31	< 0.01
PNI (median: 47.9)						
≥ vs. < median	0.81	0.33–2.01	0.65			
NLR (median: 2.35)						
≥ vs. < median	0.55	0.22–1.37	0.20			
Dysphagia score						
Score 0	0.66	0.08–5.24	0.69			
Score 1	0.49	0.06–3.96	0.51			
Score 2	1.12×10^{-8}	0-NA	1.00			
Score 3/4	reference					
Neutropenia						
Grade ≥ 3 vs. Grade < 3	1.16	0.47–2.89	0.75			
Febrile neutropenia						
Grade ≥ 3 vs. Grade < 3	0.64	0.21–1.93	0.43			
Neoadjuvant treatment						

Table 4 (continued)

	Univariable			Multivariable		
Variables	**HR**	**(95% CI)**	***P* value**	**HR**	**(95% CI)**	***P* value**
Completion vs. termination	1.14	0.33–3.91	0.84			
No. of harvested LNs (median: 43)						
≥ vs. < median	1.12	0.44–2.82	0.81			
Adjuvant treatment						
Yes vs. no	1.86	0.70–4.91	0.21			

Abbreviations: HR, hazard ratio; pCR, pathological complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BMI, body mass index; TRG, tumor regression grade; MPR, major pathological response; GPS, Glasgow prognostic score; PNI, prognostic nutritional index; NLR, neutrophil/lymphocyte ratio; NR, not reached

*, the 8th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC).

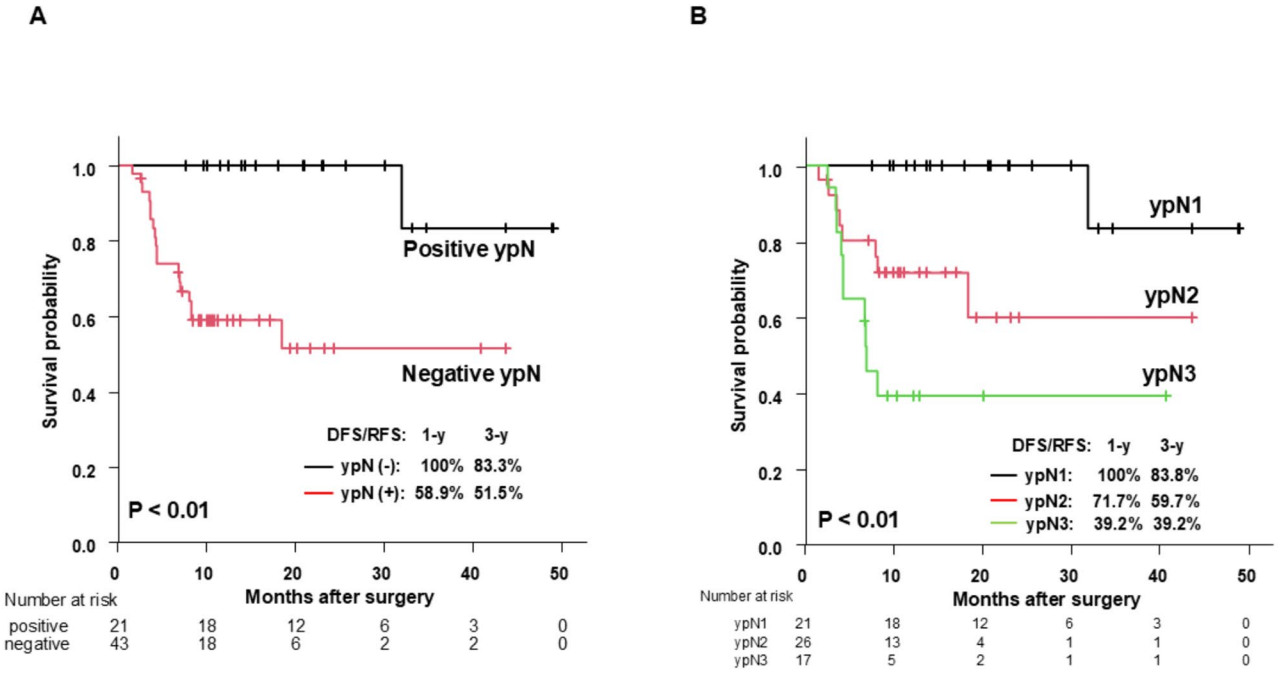

Fig. 2 DFS/RFS for 64 ESCC patients who did not achieve pCR according to the ypN status (**A**) and ypN category (**B**)
Abbreviations: DFS/RFS, disease-free survival/recurrence-free survival; ESCC, esophageal squamous cell carcinoma; pCR, pathological complete response

proven, 14 out of 64 patients with pathological residual disease after R0 resection received adjuvant nivolumab in the present study, with 13 of whom had positive ypN. In terms of treatment-related AEs with potential immunological etiologies, nine patients (64.3%) experienced AEs of any grade, and four patients (28.6%) had grade ≥ 3 AEs. The most common AEs included hypothyroidism, colitis, hepatitis, adrenal insufficiency, arthritis, myocarditis, and hemolytic anemia, each occurring in two patients (14.3%), while one patient (7.1%) experienced adrenal insufficiency, arthritis, myocarditis, and hemolytic anemia. No treatment-related deaths were observed, and adjuvant nivolumab therapy following neoadjuvant DCF and surgery was deemed safely manageable. The recurrence pattern showed that 63.2% of patients with recurrence had distant metastases. Adjuvant nivolumab therapy did not reduce locoregional recurrence compared to placebo in the Checkmate 577 trial but did reduce distant recurrence, with a median distant metastasis-free survival of 28.3 months vs. 17.6 months [56]. These results suggest that adjuvant nivolumab may reduce distant metastasis. Further research is needed to determine the benefits of adjuvant nivolumab for patients at high risk of recurrence after nCT followed by surgery.

In the present study, 37 patients (43.0%) who did not meet the eligibility criteria for the JCOG1109 NExT trial were included. The exclusion reasons included patients over the age of 75, those with cervical ESCC, cT4 disease, renal impairment, low white blood cell count, a history of treatment for other cancers, and those with multiple cancers (Supplemental Table S8) [14]. Notably, their relative dose intensity of DCF, adverse events during DCF treatment, surgical outcomes, and treatment efficacy with DCF were similar to those observed in the overall patient cohort (Supplemental Fig. S3 and Supplemental Table S8). However, DCF treatment was discontinued due to

toxicities in nine of 86 patients (10.5%), indicating that not all patients are suitable for the DCF regimen because of its high incidence of AEs. Additionally, in a real-world study of 1,074 surgically resectable advanced ESCC patients who were propensity score-matched, no survival advantage of DCF over CF was observed in patients aged 76 years or older [57]. Therefore, careful patient selection is crucial for the nCT-DCF regimen. Of the 86 patients who received nCT-DCF, 77 (89.5%) received prophylactic granulocyte colony-stimulating factor (G-CSF) or pegfilgrastim from the end of DCF administration at cycle 1 to prevent neutropenia. However, grade ≥ 3 neutropenia and febrile neutropenia were common. There were no clinicopathological factors associated with grade ≥ 3 neutropenia or febrile neutropenia. Administering pegfilgrastim on day 3 reduced grade 4 neutropenia to 8.7%, with no febrile neutropenia in EC patients [58], and starting G-CSF on day 3 decreased grade 3–4 neutropenia and febrile neutropenia compared to day 7 in head and neck cancer patients [59]. Early administration of G-CSF or pegfilgrastim may be beneficial.

The present study had several limitations. First, it was conducted at a single institute, with treatment regimens determined by attending physicians. In addition, considering the nature of a retrospective study, there is a potential for selection bias. Second, the relatively small sample size limits definitive conclusions and additional analyses. As most patients (76.7% of all patients) received the DCF regimen after it was established as the standard regimen based on the results of the JCOG 1109 NExT trial, the follow-up period was relatively short, hampering OS analysis. An individual-patient data analysis of 3,154 ESCC patients who underwent nCT and surgery, including 1,046 with the DCF regimen, showed that RFS can serve as a surrogate endpoint for OS [60]. Additionally, a meta-analysis on trials for resectable EC concluded that DFS is a valid surrogate endpoint for OS in neoadjuvant, perioperative, or adjuvant settings [61]. Therefore, the findings of DFS/RFS in the present study would be crucial for treatment decisions regarding neoadjuvant DCF treatment. Although the estimated 3-year DFS/RFS rate in the present study was similar to that observed in the JCOG1109 NExT trial, the relatively short median follow-up time of 19.2 months limits the reliability of the 3-year DFS/RFS rate estimation. However, the estimated 1-year DFS/RFS rate of 76.7% was also similar to that in the JCOG1109 NExT trial, suggesting that the results of the JCOG1109 NExT trial are reproducible in real-world clinical practice. Longer-term follow-up is needed to evaluate the long-term efficacy of DCF treatment. Third, non-hematological AEs were not fully captured in the retrospective study, possibly leading to lower incidence compared to the clinical trial. Longer-term follow-up and larger sample sizes are required for further analysis to assess the long-term efficacy of DCF treatment.

In conclusion, real-world data demonstrate the efficacy and safety of neoadjuvant DCF treatment in clinical practice. Achieving primary TRG grade 1a or pCR has favorable DFS/RFS, while elevated baseline serum SCC-Ag levels are a negative predictor of primary TRG grade 1a or pCR. Conversely, positive ypN and GPS are independent predictors for worse DFS/RFS.

Abbreviations

DCF	docetaxel, cisplatin plus 5-FU
ESCC	esophageal squamous cell carcinoma
AEs	adverse events
DFS	disease-free survival
RFS	recurrence-free survival
TRG	tumor regression grading
GPS	Glasgow prognostic score
EC	Esophageal cancer
OS	overall survival
EAC	esophageal adenocarcinoma
nCRT	neoadjuvant chemoradiotherapy
nCT	neoadjuvant chemotherapy
CF	cisplatin plus 5-fluorouracil
AJCC	American Joint Committee on Cancer: UICC: Union for International Cancer Control
PS	performance status
ECOG	Eastern Cooperative Oncology Group
PNI	prognostic nutritional index
NLR	neutrophil-lymphocyte ratio: MPR: major pathological response
pCR	pathological complete response
DFS	disease-free survival
RFS	recurrence-free survival
HR	hazard ratio
CI	confidence interval

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

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Author contributions

Conception and design: A.Ooki.; acquisition of data: M.T.; analysis and interpretation of data: M.T., A.Ooki.; writing, review: A.Ooki.; revision of the manuscript: M.T., H.O., A.Ooki., M.O., S.F., A.Okamura., J.K., Y.I., K.Y., S.U., T.W., E.S., M.W., K.Y., K.C.; administrative, technical, or material support: M.T., H.O., A.Ooki., M.O., S.F., A.Okamura., J.K., Y.I., K.Y., S.U., T.W., E.S., M.W., K.Y., K.C.; study supervision: A.Ooki.

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Data availability

The data used for this study, although not available in a public repository, will be made available to other researchers upon reasonable request.

Declarations

Ethics approval and consent to participate

This study involves human participants and was approved by the Certified Review Board at the Cancer Institute Hospital of Japanese Foundation for Cancer Research (IRB number: 2023-GB-158). The protocol was described on the hospital website, and subjects were provided the opportunity to opt-out; therefore, no additional consent was required from patients.

Consent for publication

Consent for publication was obtained from the patients.

Competing interests

The authors declare no competing interests.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this study.

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