Ann Surg Oncol (2019) 26:4754–4764
https://doi.org/10.1245/s10434-019-07744-7

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Dysphagia Score as a Predictor of Adverse Events Due to Triplet Chemotherapy and Oncological Outcomes in 434 Consecutive Patients with Esophageal Cancer

Takaomi Hagi, MD[1], Tomoki Makino, MD, PhD[1], Makoto Yamasaki, MD, PhD[1], Koji Tanaka, MD, PhD[1], Naohiro Nishida, MD, PhD[2], Daisuke Sakai, MD, PhD[2], Masaaki Motoori, MD, PhD[3], Yutaka Kimura, MD, PhD[4], Taroh Satoh, MD, PhD[2], Masaki Mori, MD, PhD[5], and Yuichiro Doki, MD, PhD[1]

[1]Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Osaka, Japan; [2]Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Osaka, Japan; [3]Department of Surgery, Osaka General Medical Center, Osaka, Japan; [4]Department of Surgery, Faculty of Medicine, Kindai University, Osaka, Japan; [5]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

ABSTRACT

Background. Dysphagia is a major symptom of esophageal cancer (EC) that significantly affects patient quality of life; however, little is known regarding its clinical impact on the treatment course in patients with EC.

Methods. This retrospective study included 434 consecutive patients with EC who received docetaxel, cisplatin, and 5-fluorouracil (DCF) chemotherapy as an initial treatment. We evaluated the relationships between the dysphagia score at diagnosis and clinicopathological factors, including DCF therapy-related adverse events, tumor response, and survival.

Results. The dysphagia scores were 0 in 208 patients (47.9%), 1 in 82 patients (18.9%), 2 in 52 patients (12.0%), 3 in 59 patients (13.6%), and 4 in 33 patients (7.6%). High ($\geq$ 3) dysphagia scores were significantly associated with high incidences of grade 3/4 febrile neutropenia (FN) (79.3 vs. 35.7%, $P < 0.001$) and diarrhea (63.0 vs. 28.1%, $P < 0.001$) compared with low ($\leq$ 2) scores. Logistic regression analysis further identified the dysphagia scores as an independent predictor of both FN and severe diarrhea during DCF chemotherapy. Furthermore, compared with low scores, high dysphagia scores were associated with a worse clinical response to chemotherapy (response rate 65.2 vs. 78.7%, $P = 0.008$) and worse 5-year overall survival (35.4 vs. 56.4%, $P = 0.001$).

Conclusions. The dysphagia score at diagnosis was an independent predictor of FN and severe diarrhea. Furthermore, this score might be useful in predicting chemotherapy response and long-term survival in patients treated with DCF.

Preoperative chemotherapy has become a standard treatment for advanced esophageal cancer (EC), based on results from the recent JCOG9907 multicenter randomized trial.[1] Previous trials reported the utility of the cisplatin plus 5-fluorouracil (CF) regimen as a neoadjuvant chemotherapy for EC;[2–4] however, that regimen led to limited response rates and survival benefits, and thus we need to establish a more powerful regimen. Recently, several phase III studies have demonstrated that the combination of docetaxel, cisplatin, and 5-fluorouracil (DCF) was an effective chemotherapy regimen for head and neck squamous cell carcinoma, as well as advanced gastric cancer.[5–7] Additionally, several trials, including a multicenter, phase I/II study,[8] demonstrated a high response with

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-019-07744-7) contains supplementary material, which is available to authorized users.

Takaomi Hagi and Tomoki Makino contributed equally as first authors.

First Received: 15 May 2019;
Published Online: 26 August 2019

T. Makino, MD, PhD
e-mail: tmakino@gesurg.med.osaka-u.ac.jp

DCF chemotherapy for EC. Furthermore, a recent randomized, phase II trial conducted by our group[9] showed a significantly prolonged recurrence-free survival (RFS) with DCF, compared with CF plus adriamycin, for treating resectable EC. Accordingly, DCF chemotherapy is becoming recognized as a useful treatment option for treating EC; however, the high incidence of severe hematological and non-hematological adverse effects associated with DCF has been clinically problematic.[5–7,9–11] In addition, the incidences of grade 3/4 febrile neutropenia (FN) and diarrhea were reported to be as high as 4.8–28.5% and 2.8–19.5%, respectively. Severe toxicities could lead to treatment delay, a reduction in chemotherapy dose, and, potentially, a worse performance status (PS) in patients. Therefore, the accurate prediction and prevention of these adverse events in multimodal treatments are urgently needed for patients with EC.

Some studies on head and neck squamous cell carcinoma revealed that enteral tube feeding and a combination of neutrophil and monocyte counts could predict the risk of DCF chemotherapy-related FN.[12,13] These factors are associated with nutritional status, which suggested that nutritional disorders before treatments might be associated with the incidence of DCF chemotherapy-related adverse events; However, few studies have focused on predictive factors of DCF chemotherapy-related adverse events for EC. Dysphagia (i.e. difficulty in swallowing food or liquid) is one of the most significant and critical symptoms observed in patients with EC. Dysphagia has a substantial impact on patient quality of life, and is typically caused by obstruction, due to an esophageal tumor, and is likely to lead to reduced oral intake, a nutritional disorder, and weight loss.[14] Several studies have classified dysphagia into five categories, according to severity, and it has been used as an endpoint in therapeutic interventions;[14–16] however, little is known about the clinical impact of dysphagia on the treatment course or outcome in patients with EC receiving multidisciplinary treatments. The present study aimed to determine the potential utility of a dysphagia score for predicting adverse events caused by DCF chemotherapy in patients with EC. We also evaluated how the dysphagia score at diagnosis impacted treatment response and long-term survival in patients with EC who received DCF chemotherapy.

MATERIALS AND METHODS

Patients

We retrospectively reviewed medical records and data from a database of patients with esophageal squamous cell carcinoma who received at least one cycle of DCF chemotherapy as an initial treatment from 2010 to 2017 in the Department of Gastroenterological Surgery, Osaka University Hospital. A total of 504 consecutive patients received a pathological diagnosis of esophageal squamous cell carcinoma and underwent chemotherapy with a DCF regimen, either as a neoadjuvant treatment, for resectable cases, or an induction treatment, for initially unresectable tumors during this period. We excluded 70 patients because they had undergone radiotherapy concurrent with the first cycle of DCF chemotherapy ($n = 45$), a modified DCF regimen ($n = 16$), or prior treatments ($n = 9$). The remaining 434 patients were eligible for this study. The Human Ethics Review Committee of Osaka University Graduate School of Medicine approved the protocol for this retrospective study, and each subject provided signed consent.

Dysphagia Score and Clinical Data Collection

The ability to swallow was expressed as a dysphagia score,[15,17] based on the symptoms caused by tumoral stricture, and the score was modified using the scoring method described by Mellow and Pinkas,[14] as follows: 0, able to eat a normal diet; 1, able to eat some solid food; 2, able to eat semi-solid food only; 3, able to swallow liquids only; and 4, complete dysphagia. These scores were evaluated before the DCF chemotherapy treatment, and were carefully assigned based on nutritionist and patient diet records. We defined 'no enteral nutrition' as the inability to consume at least 500 kcal/day, either orally or with enteral tube feeding, during DCF chemotherapy. For patients who could not tolerate a feeding tube due to severe dysphagia, total parenteral nutrition was provided during chemotherapy. PS was assessed according to the Eastern Cooperative Oncology Group (ECOG) PS.[18] Weight loss before any treatment was evaluated in terms of a 5-kg cut-off value, as described previously.[19] TNM staging was reclassified according to the 8th edition of the Union for International Cancer Control (UICC) TNM classification and staging system.[20] Clinical response was evaluated, based on computed tomography scan and endoscopy images acquired 10–14 days after the first day of DCF chemotherapy, according to the World Health Organization response criteria for measurable disease and the criteria of the Japanese Classification of Esophageal Cancer.[21] Clinical response was classified into the following four categories; complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), as previously described.[22] Patients who achieved CR or PR were considered responders, while, conversely, patients who achieved SD or PD were considered non-responders. We calculated the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-

lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP)-to-albumin ratio (CAR), while the prognostic nutritional index (PNI) was calculated as follows: PNI = serum albumin (g/dL) × 10 + total peripheral lymphocyte count (/mm^3) × 0.005.

Docetaxel, Cisplatin, and 5-Fluorouracil (DCF) Chemotherapy Regimen and Evaluation of Adverse Effects

The DCF regimen consisted of intravenous docetaxel (70 mg/m^2) and cisplatin (70 mg/m^2) on day 1, and a continuous intravenous infusion of 5-fluorouracil (700 mg/m^2) on days 1–5, as previously described.[23–27] This regimen was administered every 3 weeks, unless severe toxicity or PD occurred. Based on each patient's physical status or renal disorder, the dose of each agent was reduced by 20–50%, as shown in electronic supplementary Table 1. All patients were hospitalized during each cycle, and supportive care was provided for adverse events. Granulocyte colony-stimulating factor was only administered when either grade 3/4 neutropenia or grade 3 FN occurred during the first cycle of DCF chemotherapy. Antibiotics were used for suspicious infections or grade 3/4 neutropenia, as a secondary prophylactic against FN. Hematological and non-hematological toxicities were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.[28] The highest adverse event grade occurred during the first cycle of DCF chemotherapy, and chemotherapy-related deaths occurred within 30 days of the start of chemotherapy.

Statistical Analysis

The distributions of categorical and numerical variables between independent groups were compared using the Chi square and Mann–Whitney *U* tests. Continuous variables were dichotomized with cut-off values, based on the median values, and statistically significant variables detected in univariate analyses ($P < 0.05$) were further assessed in a multivariate logistic regression analyses. Overall survival (OS) was calculated from the date of the first cycle of DCF chemotherapy to the date of the last follow-up visit or death, regardless of the type of treatment that followed the first cycle of DCF chemotherapy. RFS was calculated from the date of surgery to the date of recurrence. 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 OS in univariate analyses were further assessed in multivariate Cox proportional hazard model analyses. *P*-values < 0.05 were considered to indicate statistical significance. Analyses were performed using SPSS software, version 22.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Patient Characteristics and Adverse Events during the First DCF Chemotherapy Cycle

The baseline characteristics of all 434 patients with EC who received DCF chemotherapy as an initial treatment are summarized in electronic supplementary Table 1. The dysphagia scores were 0 in 208 patients (47.9%), 1 in 82 patients (18.9%), 2 in 52 patients (12.0%), 3 in 59 patients (13.6%), and 4 in 33 patients (7.6%). Among all patients, 20 (4.6%) could not receive enteral nutrition during chemotherapy due to difficulty in inserting the transnasal tube beyond the tumoral stricture. Approximately 90% of all patients received a full dose of docetaxel and 5-fluorouracil. Overall, 327 (75.3%) patients underwent R0 resection surgery after DCF chemotherapy. Details of adverse events identified during the first cycle of DCF chemotherapy are summarized in electronic supplementary Table 2. The overall incidence rates of grade 3/4 hematological and non-hematological adverse events were 94.9% and 68.7%, respectively. Among grade 3/4 hematological adverse events, neutropenia was the most commonly observed (94.7%), followed by FN (44.9%), anemia (5.3%), and thrombocytopenia (5.3%). In contrast, the most common grade 3/4 non-hematological adverse event was hyponatremia, identified in 37.1% of patients, followed by diarrhea (35.5%), anorexia (26.5%), and nausea (17.3%). Two (0.5%) chemotherapy-related deaths were observed; one patient died of aspiration pneumonitis, and the other patient died of an hepatic disorder.

Correlations between Dysphagia Score and Baseline Parameters

Table 1 shows the univariate analysis results of clinicopathological characteristics, stratified by the dysphagia score at diagnosis. Compared with a low dysphagia score (0–2), a high dysphagia score (3–4) was significantly associated with a larger tumor diameter and higher frequencies of advanced cT and cStages. In addition, body composition was different between groups; compared with the low-score group, the high dysphagia score group was significantly correlated with a worse PS, lower body weight, lower body mass index (BMI), and more

TABLE 1 Correlations between dysphagia score and clinicopathological characteristics

Characteristics	Dysphagia score		*P* value
	Low (0–2) [*n* = 342]	High (3–4) [*n* = 92]	
Age, years			
Age, years [median (range)]	67 (38–83)	69 (45–82)	0.132
Sex			
Male	300 (87.7)	78 (84.8)	0.456
Female	42 (12.3)	14 (15.2)	
Performance status			
0	190 (100.0)	152 (62.3)	< 0.001
1–2	0 (0)	92 (37.7)	
cT stage			
1–2	103 (30.1)	2 (2.2)	< 0.001
3–4	239 (69.9)	90 (97.8)	
cN stage			
0–1	267 (78.1)	66 (71.7)	0.202
2–3	75 (21.9)	26 (28.3)	
cStage			
I–II	112 (32.7)	10 (10.9)	<0.001
III–IV	230 (67.3)	82 (89.1)	
Primary tumor site			
Ut	82 (24.0)	24 (26.1)	0.676
Mt/Lt	260 (76.0)	68 (73.9)	
Largest tumor diameter, mm [median (range)]	28.3 (10.7–76.8)	34.1 (13.9–56.9)	< 0.001
Histological differentiation			
Well/moderately	276 (90.8)	71 (91.0)	0.949
Poor	28 (9.2)	7 (9.0)	
Weight loss at diagnosis, kg			
< 5	287 (83.9)	42 (45.7)	< 0.001
≥ 5	55 (16.1)	50 (54.3)	
Dose reduction of docetaxel			
No	320 (93.6)	83 (90.2)	0.268
Yes	22 (6.4)	9 (9.8)	
Dose reduction of cisplatin			
No	304 (88.9)	75 (81.5)	0.059
Yes	38 (11.1)	17 (18.5)	
Dose reduction of 5-fluorouracil			
No	324 (94.7)	83 (90.2)	0.111
Yes	18 (5.3)	9 (9.8)	
Nutritional parameters and laboratory data			
Weight, kg [median (range)]	57.5 (35.5–92.7)	51.0 (35.0–75.0)	< 0.001
BMI, kg/m^2 [median (range)]	21.1 (15.4–33.3)	19.5 (14.6–28.8)	< 0.001
WBC, mm^3 [median (range)]	6265 (2590–16,840)	7640 (3860–16,750)	< 0.001
Neutrophil count, mm^3 [median (range)]	4115 (1413–14,090)	5264 (2371–14,539)	< 0.001
Lymphocyte count, mm^3 [median (range)]	1545 (497–3734)	1577 (729–3158)	0.882
Monocyte count, mm^3 [median (range)]	420 (41–2047)	499 (52–1533)	0.002
Platelet count, 10^4/mm^3 [median (range)]	24.1 (5.4–52.2)	27.4 (11.7–63.4)	0.004
Albumin, g/dL [median (range)]	3.9 (1.9–5.0)	3.6 (2.3–4.6)	0.001
CRP, mg/dL [median (range)]	0.13 (0.04–11.51)	0.47 (0.04–10.10)	< 0.001

Data are expressed as number of patients (%) unless otherwise indicated

Ut upper thorax, *Mt/Lt* middle or lower thorax, *BMI* body mass index, *WBC* white blood cell, *CRP* C-reactive protein

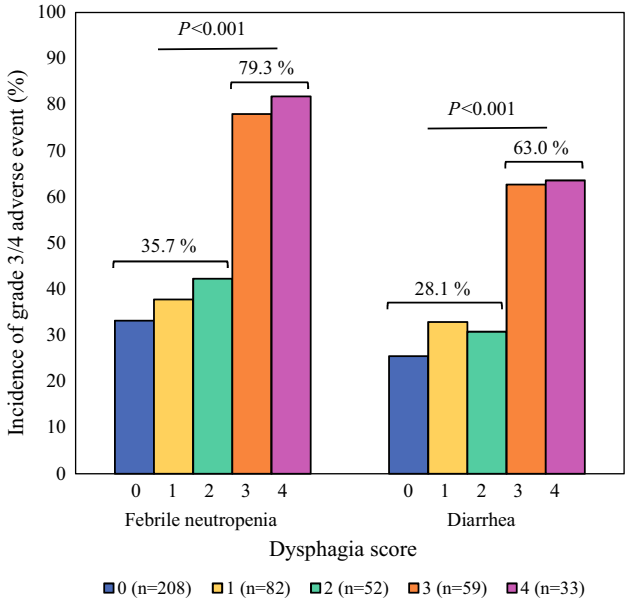

FIG. 1 Incidence of grade 3/4 febrile neutropenia and diarrhea during the first cycle of DCF chemotherapy for esophageal cancer. Patients were classified by dysphagia score. *DCF* docetaxel, cisplatin, and 5-fluorouracil

pretreatment weight loss. Among the laboratory data collected prior to chemotherapy, the dysphagia score was significantly associated with white blood cell count, neutrophil count, monocyte count, platelet count, serum albumin level, and CRP level (Table 1).

Dysphagia Score at Diagnosis Could Predict Adverse Effects of DCF Chemotherapy

We examined the relationship between dysphagia score and adverse events related to chemotherapy. The incidences of grade 3/4 FN and diarrhea, classified by dysphagia score, are shown in Fig. 1. Notably, the high dysphagia score group developed a significantly higher incidence of FN and diarrhea compared with the low dysphagia score group. Logistic regression analyses showed that a high dysphagia score was the only independent predictor of grade 3/4 FN (Table 2). Similarly, we identified two independent predictors of grade 3/4 diarrhea—one was a high dysphagia score and the other was enteral nutrition during chemotherapy. Notably, in the high dysphagia score group, patients who received enteral nutrition during chemotherapy developed grade 3/4 diarrhea significantly less often than those without enteral nutrition, as shown in Fig. 2.

Impact of Dysphagia Score on Chemotherapy Response and Patient Survival

We then examined the treatment response and found that patients with a high dysphagia score showed a worse response to DCF chemotherapy than those with a low dysphagia score (electronic supplementary Table 3).

The median follow-up time of all 434 patients was 26.6 months (range 0.5–103.0 months). During follow-up, 164 (37.8%) events were identified. The 3- and 5-year OS rates of all patients were 62.3% and 52.2%, respectively, while the 5-year OS rates of patients with dysphagia scores of 0, 1, 2, 3, and 4 were 56.8, 59.4, 47.9, 43.7, and 12.0%, respectively (Fig. 3a). Of note, patients with high dysphagia scores had significantly lower 5-year OS rates (35.4%) compared with patients with low dysphagia scores (56.4%) [Fig. 3b]. When we examined only patients with high dysphagia scores and cT3/4 tumors, we observed a similar result (5-year OS: 35.4 vs. 53.5%) [Fig. 3c]. Similarly, patients with high dysphagia scores had significantly worse prognoses than those with low scores, among patients with cStage III/IV (5-year OS: 33.5 vs. 52.1%) [Fig. 3e], but not among patients with cStage I/II (5-year OS: 56.3 vs. 63.9%) [Fig. 3d].

Relationship Between Dysphagia Score and Postoperative Outcomes

Esophagectomy was eventually conducted for 267 patients (78.1%) in the low dysphagia score group compared with 60 patients (65.2%) in the high dysphagia score group ($P = 0.011$). No significant difference in each postoperative complication was seen between the high and low dysphagia score group (electronic supplementary Table 4). As for OS, patients with high dysphagia scores tended to have poor prognoses compared with patients with low dysphagia scores in all patients overall (5-year OS: 43.6 vs. 60.2%) and in patients with cStage III/IV (5-year OS: 43.2 vs. 58.3%) [electronic supplementary Fig. 1a, b]. Moreover, RFS in patients with high dysphagia scores also showed tendency for poor prognoses compared with patients with low dysphagia scores in all patients overall (3-year RFS: 43.0 vs. 54.7%) and in patients with cStage III/IV (3-year RFS: 41.1 vs. 51.9%) [electronic supplementary Fig. 1c, d].

DISCUSSION

The present study showed that the dysphagia score correlated with several parameters, including PS, tumor size/stage, and nutritional/inflammatory parameters. Importantly, the dysphagia score at diagnosis was identified as an independent predictor of both FN and severe

TABLE 2 Univariate and multivariate analyses of predictive factors for grade 3/4 febrile neutropenia and diarrhea

Variables	Febrile neutropenia (Grade 3/4)				Diarrhea (Grade 3/4)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, years								
< 65	1				1			
≥ 65	1.24 (0.83–1.87)	0.300			1.39 (0.90–2.14)	0.133		
Sex								
Male	1.10 (0.63–1.94)	0.738			1			
Female	1				1.69 (0.96–2.99)	0.067		
Performance status								
0	1				1		1	
1–2	2.47 (1.67–3.67)	< 0.001	1.40 (0.88–2.21)	0.155	2.17 (1.44–3.28)	< 0.001	1.26 (0.78–2.04)	0.352
cT stage								
1–2	1				1			
3–4	1.37 (0.88–2.15)	0.164			1.61 (0.99–2.60)	0.053		
cN stage								
0–1	1				1			
2–3	1.49 (0.95–2.32)	0.088			1.33 (0.84–2.10)	0.220		
Primary tumor site								
Ut	1				1			
Mt/Lt	1.56 (0.99–2.44)	0.053			1.29 (0.81–2.07)	0.281		
Largest tumor diameter, mm								
< 30.0	1				1			
≥ 30.0	1.34 (0.89–2.02)	0.166			1.43 (0.94–2.19)	0.096		
Histological differentiation								
Well/moderately	1				1			
Poor	1.24 (0.62–2.49)	0.544			1.51 (0.75–3.07)	0.248		
BMI								
< 20	1.54 (1.05–2.27)	0.029	1.08 (0.70–1.68)	0.732	1.24 (0.83–1.85)	0.301		
≥ 20	1		1		1			
NLR								
< 2.79	1				1			
≥ 2.79	1.38 (0.94–2.02)	0.097			1.10 (0.74–1.63)	0.646		
MLR								
< 0.28	1				1.09 (0.74–1.62)	0.669		
≥ 0.28	1.44 (0.99–2.11)	0.058			1			
PLR (10^{-4})								
< 163	1				1.31 (0.88–1.95)	0.178		
≥ 163	1.28 (0.88–1.87)	0.203			1			
PNI								
< 46.6	1.42 (0.97–2.07)	0.070			1	0.732		
≥ 46.6	1				1.07 (0.72–1.59)			
CAR								
< 0.05	1				1		1	
≥ 0.05	1.32 (0.91–1.93)	0.148			1.56 (1.05–2.32)	0.027	1.12 (0.73–1.73)	0.604
Dysphagia score								
Low (0–2)	1		1		1		1	
High (3–4)	4.37 (2.69–7.10)	< 0.001	6.24 (3.15–12.36)	< 0.001	4.37 (2.69–7.10)	< 0.001	2.92 (1.63–5.22)	< 0.001

TABLE 2 continued

Variables	Febrile neutropenia (Grade 3/4)				Diarrhea (Grade 3/4)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Enteral nutrition during chemotherapy								
Yes	1		1		1		1	
No	5.25 (1.73–15.98)	0.001	1.03 (0.30–3.55)	0.963	11.46 (3.30–39.76)	< 0.001	4.20 (1.13–15.66)	0.032
Weight loss at diagnosis, kg								
< 5	1		1		1			
≥ 5	1.64 (1.06–2.56)	0.028	0.77 (0.45–1.33)	0.346	1.51 (0.97–2.37)	0.071		

OR odds ratio, *CI* confidence interval, *Ut* upper thorax, *Mt/Lt* middle or lower thorax, *BMI* body mass index, *NLR* neutrophil-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *PNI* prognostic nutritional index, *CAR* C-reactive protein-to-albumin ratio

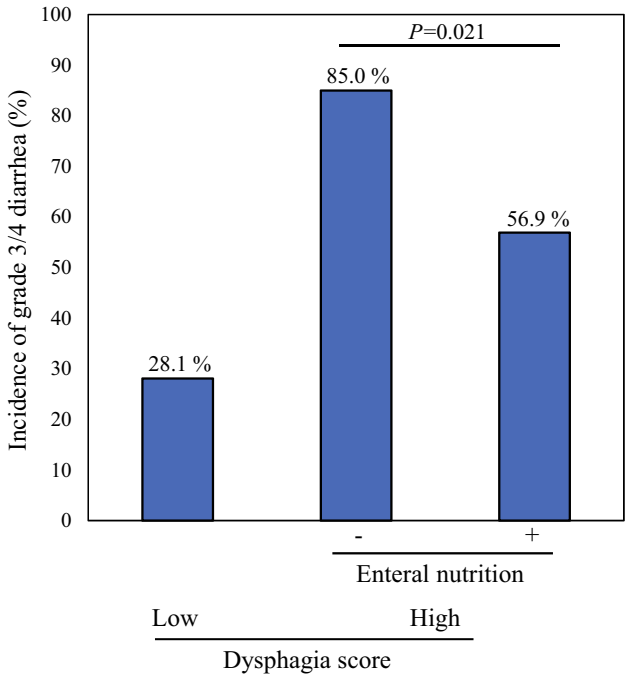

FIG. 2 Incidence of grade 3/4 diarrhea during the first cycle of DCF chemotherapy for esophageal cancer. Patients were classified by dysphagia severity (low: 0–2 vs. high: 3–4), and by the presence/absence of an enteral nutrition intervention. *DCF* docetaxel, cisplatin, and 5-fluorouracil

diarrhea development during DCF chemotherapy. The dysphagia score might also be useful in predicting the response to DCF chemotherapy and the long-term survival of patients with EC undergoing DCF chemotherapy. To our knowledge, this study was the first to report the clinical significance of the dysphagia score in a large series of patients with EC who underwent DCF chemotherapy as the initial treatment.

In the present study, the dysphagia score, a simple, easy scale for assessing the patient's quality of life at presentation, was significantly associated with weight loss at presentation and also with nutritional parameters, including body weight, BMI, and serum albumin. All of these parameters were lower in patients with high dysphagia scores than in those with low scores. This association was remarkable when patients were classified into groups, i.e. those who could eat at least semi-solid food (dysphagia scores 0–2) and those who could swallow, at most, only liquids (dysphagia scores 3–4). According to the ESPEN guidelines, patients are likely to experience severe weight loss when they cannot eat for more than 1 week, or their estimated energy intake is < 60% of their energy requirement for more than 1–2 weeks.[29] Thus, a potential method for evaluating patient nutritional statements might be to differentiate between dysphagia scores of 0–2 and 3–4.

The incidences of grade 3/4 FN and diarrhea, two major adverse events in DCF chemotherapy, were 44.9% and 35.5%, respectively. These incidences were relatively higher than those reported previously in several phase II or III studies.[5–7,11] However, other previous studies that targeted unselected patients in actual community settings reported incidences of FN and diarrhea similar to those found in our study, despite the fact that they used smaller drug doses (i.e. cisplatin 60 mg/m^2, docetaxel 60 mg/m^2, and 5-fluorouracil 600–700 mg/m^2 on days 1–4)0.[12,13] This discrepancy between clinical trial data and real-life data arose partly from the different backgrounds of the patient cohorts. Indeed, the large series of patients in the present study included the entire population of patients with EC treated at our institute, thus representing a real-life cohort of patients with EC.

The guidelines of the American Society of Clinical Oncology reported that age (≥ 65 years), PS (≥ 2), serum albumin (< 35 g/L), a prior FN episode, and comorbidities were independent predictors of FN;[30] however, those

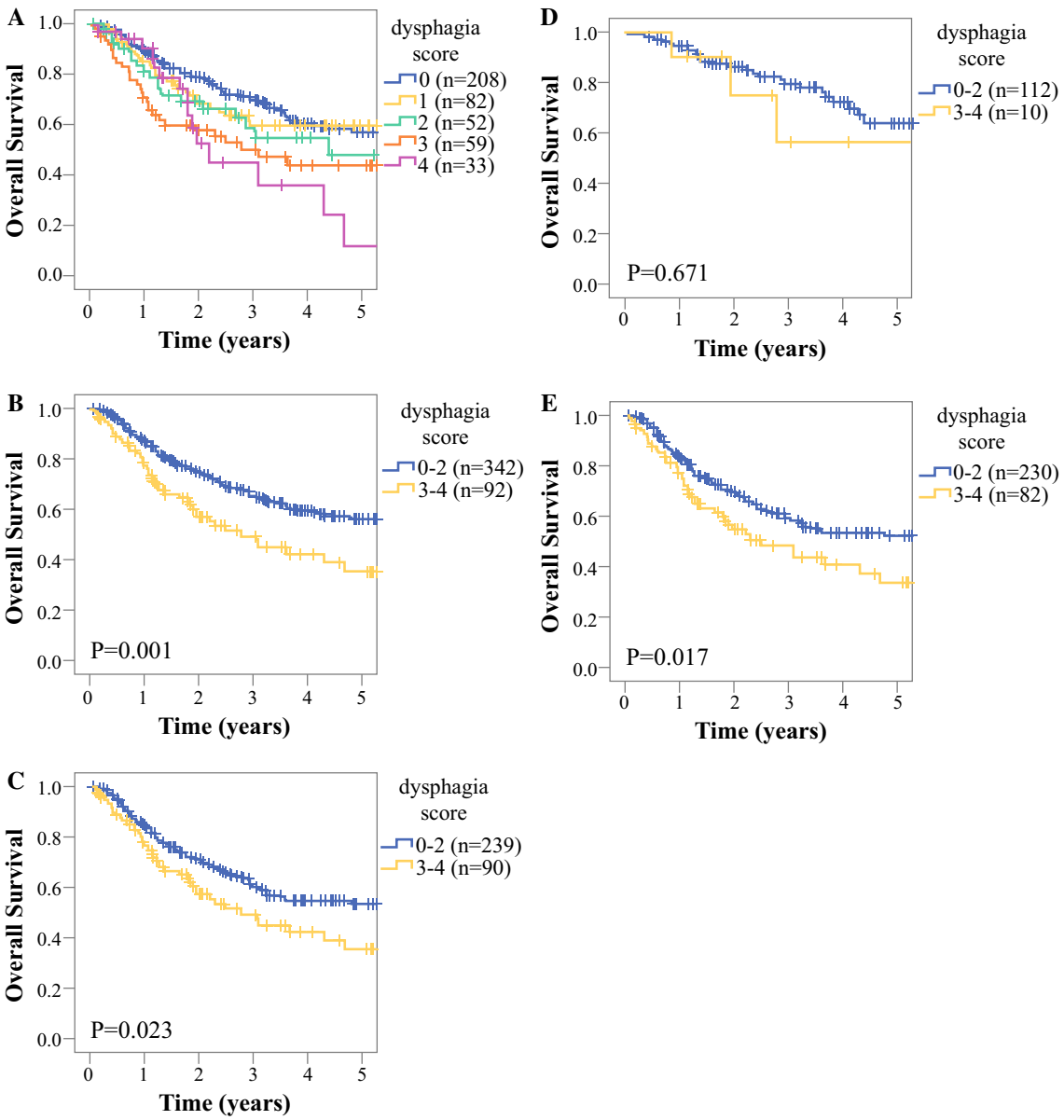

FIG. 3 Overall survival curves during DCF chemotherapy for esophageal cancer. Patients were stratified by (**a**) dysphagia score, and **b**–**e** dysphagia severity (low: 0–2 vs. high: 3–4). Survival curves are shown for (**b**) all patients, **c** the cT3/4 subgroup, **d** the cStage I/II subgroup, and **e** the cStage III/IV subgroup. *DCF* docetaxel, cisplatin, and 5-fluorouracil

associations were mainly based on studies on breast and lung cancer treated with different regimens of chemotherapy, not gastrointestinal cancers or EC. In our study, the dysphagia score at diagnosis was found to be an independent predictor of both FN and severe diarrhea. To explain these results, a nutritional disorder caused by severe dysphagia might be closely associated with immunological hypofunction.[31] Deterioration of the immune system in patients with EC can lead to the development of FN, when neutropenia occurs during chemotherapy. Second, a lack of oral intake or enteral nutrition can cause intestinal mucosa atrophy and disrupt the gut microbial flora.[32] Sonis reported that a mucosal barrier injury due to chemotherapy was closely associated with gut mucosal damage, which led to severe diarrhea or fever.[33,34] Interestingly, weight loss at diagnosis, an objective nutritional parameter, was not a risk factor for either FN or diarrhea, in the present study. This finding suggested that the ability to swallow at diagnosis, or the need for enteral nutrition during chemotherapy, had a greater influence on adverse effects than a pretreatment nutritional disorder. Our data revealed that the absence of enteral nutrition (i.e. only parenteral nutrition treatment)

during DCF chemotherapy was an independent risk factor for grade 3/4 diarrhea, but not for FN. In fact, in the high dysphagia score group, the presence of an enteral nutrition intervention during chemotherapy significantly lowered the incidence of grade 3/4 diarrhea. In addition, when all patients were divided into two subgroups of latter and former according to the period, the latter half group with more frequent enteral nutrition interventions for severe dysphagia tended to have a lower incidence of severe diarrhea than those in the former half group (data not shown). These data implied that enteral nutrition interventions, via a feeding tube, could restore damaged or atrophic mucosa in the intestine, to some extent, even within a short time after starting chemotherapy. Miyata et al. reported that in patients with EC who exhibited poor oral intake, enteral nutrition support during neoadjuvant chemotherapy significantly reduced the occurrence of severe neutropenia.[35] Although Miyata et al. did not mention the incidence of FN, that finding supported our hypothesis that an enteral nutrition intervention might lower the risk of adverse events related to DCF chemotherapy in patients with high dysphagia. Moreover, other interventions used during neoadjuvant chemotherapy, such as the synbiotics used by Motoori et al. for patients with EC, also reduced adverse events, including FN and diarrhea.[36] Taken together with our current results, these data suggested that interventions might be beneficial for patients with EC who have high dysphagia scores, i.e. patients who were predicted to be at high risk of DCF chemotherapy-induced adverse events.

Patients with high dysphagia scores also showed a lower response rate to DCF chemotherapy, as well as a worse prognosis. Although the specific cause remains unclear, high dysphagia scores were correlated with larger, more advanced tumors. Therefore, these patients might have developed chemoresistance due to insufficient drug delivery inside the tumor, tumor heterogeneity, or local hypoxia, which are often associated with large tumors. Immunity deterioration, due to malnutrition, could also be correlated with resistance to treatments, including chemotherapy. Although the dysphagia score clearly reflected tumor size and cT stage, the subgroup analysis of patients with similar tumor stages (cT3/4 or cStage III/IV) also showed significant differences in survival between the high versus low dysphagia score groups. Moreover, although the result was not significant, a similar tendency was observed in a subgroup analysis that only included patients who underwent surgery. In gastric adenocarcinoma, dysphagia at presentation was reported to be an independent prognostic factor, together with tumor size, T stage, and N stage.[37,38] Additionally, Deans et al. reported that weight loss associated with dysphagia was significantly correlated with survival in patients with gastroesophageal cancer.[39] However, differences in survival might partly arise due to an increased rate of severe adverse events, which can lead to reduced doses or even discontinuation of chemotherapy. Moreover, although causes of death other than EC were not assessed in the present study, severe dysphagia has a high potential of complicating aspiration pneumonia, which could increase mortality.

This study had several potential limitations. First, it was a single institution, retrospective study, therefore a potential selection bias could have influenced the results. Second, the inclusion criteria in this study did not define subsequent therapies, including the number of DCF chemotherapy cycles, other treatment regimens, and surgical treatments. Although all of those treatments could have influenced patient survival, the rates of patients who subsequently received surgery were similar between the high and low dysphagia score groups (83.7 vs. 86.8%, $P = 0.267$). Third, we only focused on adverse events that occurred during the first cycle of DCF chemotherapy, and did not evaluate those of subsequent cycles. Although previous studies have reported that the risk of adverse events was highest during the first cycle of treatment,[40] the limited time frame of our analysis might have led to a somewhat underestimated risk of chemotherapy-related adverse events. In addition, other nutritional parameters, such as daily energy intakes before presentation,[41] were not evaluated in the present study. Future studies should evaluate whether improvements in the dysphagia score, using various treatments, are related to oncological outcomes or the incidence of adverse events.

CONCLUSIONS

We showed that a high dysphagia score at diagnosis was an independent risk factor for both FN and severe diarrhea during DCF chemotherapy for EC. The dysphagia score might also be a useful marker in predicting both the response to chemotherapy and survival in patients undergoing DCF chemotherapy as an initial treatment for EC.

DISCLOSURE Takaomi Hagi, Tomoki Makino, Makoto Yamasaki, Koji Tanaka, Naohiro Nishida, Daisuke Sakai, Masaaki Motoori, Yutaka Kimura, Taroh Satoh, Masaki Mori, and Yuichiro Doki have no conflicts of interest to declare.

REFERENCES

1. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol*. 2012;19(1):68–74.
2. Allum WH, Stenning SP, Bancewicz J, et al. Long-term results of a randomized trial of surgery with or without preoperative

chemotherapy in esophageal cancer. *J Clin Oncol*. 2009;27:5062–7.
3. Kelsen DP, Winter KA, Gunderson LL, et al. Radiation Therapy Oncology Group; USA Intergroup. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. *J Clin Oncol*. 2007;25:3719–25.
4. Yamasaki M, Miyata H, Miyazaki Y, et al. Perioperative therapy for esophageal cancer. *Gen Thorac Cardiovasc Surg*. 2014;62:531–40.
5. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med*. 2007;357:1705–15.
6. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med*. 2007;357:1695–704.
7. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol*. 2006;24:4991–4997.
8. Yamasaki M, Miyata H, Tanaka K, et al. Multicenter phase I/II study of docetaxel, cisplatin and fluorouracil combination chemotherapy in patients with advanced or recurrent squamous cell carcinoma of the esophagus. *Oncology*. 2011;80:307–13.
9. Yamasaki M, Yasuda T, Yano M, et al. Multicenter randomized phase II study of cisplatin and fluorouracil plus docetaxel (DCF) compared with cisplatin and fluorouracil plus Adriamycin (ACF) as preoperative chemotherapy for resectable esophageal squamous cell carcinoma (OGSG1003). *Ann Oncol*. 2017;28:116–20.
10. Hara H, Tahara M, Daiko H, et al. Phase II feasibility study of preoperative chemotherapy with docetaxel, cisplatin, and fluorouracil for esophageal squamous cell carcinoma. *Cancer Sci*. 2013;104:1455–60.
11. Yokota T, Kato K, Hamamoto Y, et al. Phase II study of chemoselection with docetaxel plus cisplatin and 5-fluorouracil induction chemotherapy and subsequent conversion surgery for locally advanced unresectable oesophageal cancer. *Br J Cancer*. 2016;115:1328–34.
12. Shimanuki M, Imanishi Y, Sato Y, et al. Pretreatment monocyte counts and neutrophil counts predict the risk for febrile neutropenia in patients undergoing TPF chemotherapy for head and neck squamous cell carcinoma. *Oncotarget*. 2018;9:18970–84.
13. Takenaka Y, Cho H, Yamamoto M, et al. Incidence and predictors of febrile neutropenia during chemotherapy in patients with head and neck cancer. *Support Care Cancer*. 2013;21:2861–8.
14. Mellow MH, Pinkas H. Endoscopic laser therapy for malignancies affecting the esophagus and gastroesophageal junction: analysis of technical and functional efficacy. *Arch Intern Med*. 1985;145:1443–6.
15. Knyrim K, Wagner HJ, Bethge N, et al. A controlled trial of an expansile metal stent for palliation of esophageal obstruction due to inoperable cancer. *N Engl J Med*. 1993;329:1302–7.
16. Watkinson AF, Ellul J, Entwisle K, et al. Esophageal carcinoma: initial results of palliative treatment with covered self-expanding endoprostheses. *Radiology*. 1995;195:821–7.
17. Maunoury V, Brunetaud JM, Cochelard D, et al. Endoscopic palliation for inoperable malignant dysphagia: long term follow up. *Gut*. 1992;33:1602–7.
18. Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649–55.
19. Yang CJ, Roh JL, Choi KH, et al. Pretreatment dysphagia inventory and videofluorographic swallowing study as prognostic indicators of early survival outcomes in head and neck cancer. *Cancer*. 2015;121:1588–98.
20. Brierley J, Gospodarowicz M, Wittekind C. TNM classification of malignant tumors. 8th ed. Oxford: Wiley-Blackwell; 2017.
21. Japan Esophageal Society. Japanese classification of esophageal cancer, 11th Edn: part II and III. *Esophagus*. 2017;14:37–65.
22. Makino T, Yamasaki M, Tanaka K, et al. Metabolic tumor volume change predicts long-term survival and histological response to preoperative chemotherapy in locally advanced esophageal cancer. *Ann Surg*. 2018. https://doi.org/10.1097/sla.0000000000002808.
23. Hashimoto T, Makino T, Yamasaki Y, et al. The pattern of residual tumor after neoadjuvant chemotherapy for locally advanced esophageal cancer and its clinical significance. *Ann Surg*. 2019. https://doi.org/10.1097/sla.0000000000003129.
24. Makino T, Yamasaki M, Tanaka K, et al. Importance of positron emission tomography for assessing the response of primary and metastatic lesions to induction treatments in T4 esophageal cancer. *Surgery*. 2017;162:836–45.
25. Makino T, Yamasaki M, Tanaka K, et al. Utility of initial induction chemotherapy with 5-fluorouracil, cisplatin, and docetaxel (DCF) for T4 esophageal cancer: a propensity score-matched analysis. *Dis Esophagus*. 2018;31(4):130.
26. Makino T, Miyata H, Yamasaki M, et al. Utility of response evaluation to neo-adjuvant chemotherapy by 18F-fluorodeoxyglucose-positron emission tomography in locally advanced esophageal squamous cell carcinoma. *Surgery*. 2010;148(5):908–18.
27. Makino T, Doki Y, Miyata H, et al. Use of (18)F-fluorodeoxyglucose-positron emission tomography to evaluate responses to neo-adjuvant chemotherapy for primary tumor and lymph node metastasis in esophageal squamous cell carcinoma. *Surgery*. 2008;144(5):793–802.
28. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Bethesda, MD: National Cancer Institute; 2017.
29. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr*. 2017;36:11–48.
30. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2013;20:794–810.
31. Bistrian BR, Blackburn GL, Vitale J, et al. Prevalence of malnutrition in general medical patients. *JAMA*. 1976;235(15):1567–70.
32. EA Deitch. Bacterial translocation: the influence of dietary variables. *Gut*. 1994;35(1 Suppl):S23–7.
33. Sonis ST. The pathobiology of mucositis. *Nat Rev Cancer*. 2004;4:277–84.
34. van der Velden WJ, Herbers AH, Netea MG, et al. Mucosal barrier injury, fever and infection in neutropenic patients with cancer: introducing the paradigm febrile mucositis. *Br J Haematol*. 2014;167:441–52.
35. Miyata H, Yano M, Yasuda T, et al. Randomized study of clinical effect of enteral nutrition support during neoadjuvant chemotherapy on chemotherapy-related toxicity in patients with esophageal cancer. *Clin Nutr*. 2012;31:330–6.
36. Motoori M, Yano M, Miyata H, et al. Randomized study of the effect of synbiotics during neoadjuvant chemotherapy on adverse events in esophageal cancer patients. *Clin Nutr*. 2017;36:93–9.
37. Stephens MR, Lewis WG, White S, et al. Prognostic significance of alarm symptoms in patients with gastric cancer. *Br J Surg*. 2005;92:840–6.
38. Sánchez-Bueno F, Garcia-Marcilla JA, Perez-Flores D, et al. Prognostic factors in a series of 297 patients with gastric

adenocarcinoma undergoing surgical resection. *Br J Surg*. 1998;85:255–60.
39. Deans DA, Tan BH, Wigmore SJ, et al. The influence of systemic inflammation, dietary intake and stage of disease on rate of weight loss in patients with gastro-oesophageal cancer. *Br J Cancer*. 2009;100:63–9.
40. Crawford J, Dale DC, Kuderer NM, et al. Risk and timing of neutropenic events in adult cancer patients receiving chemotherapy: the results of a prospective nationwide study of oncology practice. *J Natl Compr Cancer Netw*. 2008;6:109–18.
41. Andreyev HJ, Norman AR, Oates J, et al. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer*. 1998;34:503–9.