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Five-year Outcomes of Chemotherapy With Docetaxel, Cisplatin, and 5-Fluorouracil Followed by Oesophagectomy in Oesophageal Cancer

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Abstract. *Background: Preoperative chemotherapy with surgery is the most effective treatment modality in Japan for advanced oesophageal squamous cell carcinoma (OSCC). We evaluated the long-term outcomes associated with preoperative docetaxel/cisplatin/5-fluorouracil (DCF) administration followed by oesophagectomy in OSCC. Patients and Methods: Overall, 76 consecutive patients with cStage IB-IIIC OSCC were enrolled. After two cycles of preoperative DCF, oesophagectomy was performed. Survival monitoring was performed and relevant risk factors were analysed. Results: The median follow-up period was 88.3 months. The 5-year overall and recurrence-free survival rates were 51% and 43%, respectively. In the multivariable analysis, cT3 stage [hazard ratio (HR)=1.81, 95% confidence interval (CI)=1.08-6.16], incomplete chemotherapy (HR=2.35, 95% CI=1.37-4.02), poor clinical response (HR=1.82, 95% CI=1.01-3.29), and postoperative complications (HR=2.11, 95% CI=1.14-3.90) were independent predictors of poorer overall survival. Conclusion: The 5-year outcomes of preoperative DCF with oesophagectomy were favourable. Our findings can aid in the formulation of strategies aimed at improving prognosis in OSCC.*

Although oesophagectomy combined with chemotherapy and/or radiation is recognised as the most effective treatment modality for resectable oesophageal cancer, the treatment outcomes are currently unsatisfactory (1-5). In the Japanese Clinical Oncology Group 9204 (JCOG9204) trial, chemotherapy with cisplatin and 5-fluorouracil (CF) following surgery significantly improved the recurrence-free survival (RFS) rates compared to surgery alone in patients with oesophageal squamous cell carcinoma (OSCC) accompanied by lymph node metastasis (p=0.037) (6). The JCOG9907 trial demonstrated that preoperative chemotherapy with CF improved overall survival (OS) rates more effectively than did postoperative chemotherapy in patients with cStage II/III OSCC (7). Accordingly, preoperative chemotherapy followed by surgery is considered the standard treatment for resectable locally advanced OSCC, except cT1N0 disease, in Japan, and is associated with better OS rates in those with cStage II/III disease than definitive chemoradiotherapy (8).

Preoperative chemotherapy is now a popular treatment option, and several trials using different anticancer drug combinations have been conducted. Preoperative chemotherapy using CF combined with adriamycin; cisplatin, S-1 and docetaxel (DCS); and CF combined with docetaxel (DCF), is safe and effective in treatment of resectable OSCC. The 2-year OS rates associated with CF with adriamycin, DCS, and DCF were 65%, 68%, and 70%-88%, respectively, while the rates of haematological adverse events were 69%, 68%, and 78-90%, with pathological response rates were 14%-18%, 33% and 42%-51%, respectively (9-15). However, the long-term survival benefit of preoperative DCF followed by oesophagectomy remains unclarified. While some studies that investigated predictors of OS focused on associated clinicopathological factors, response, and complications, few have systematically evaluated these parameters over an extended follow-up period (15, 16).

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Therefore, this study aimed to investigate the 5-year outcomes associated with the use of preoperative DCF followed by oesophagectomy in patients with resectable locally advanced OSCC.

Patients and Methods

Study design. We retrospectively investigated patients who underwent oesophagectomy after preoperative DCF. The primary endpoint, 5-year OS, was defined as the period between chemotherapy initiation and the date of death from any cause. Five-year RFS, the secondary endpoint, was defined as the period between chemotherapy initiation and the date of recurrence or death from any cause. Data were censored at the time of the last valid assessment before the cut-off date, if events did not occur. Other data, such as those pertaining to clinicopathological response, adverse events, postoperative complications, and prognostic factors, were also properly investigated.

Patients. We retrospectively reviewed the medical records of patients with resectable thoracic OSCC who received preoperative DCF between October 2008 and April 2015 at The Jikei University Hospital. The inclusion criteria were: cStage I, II, and III (excluding T1N0) thoracic OSCC according to the Union for International Cancer Control [seventh edition (17)]; age under 85 years; no prior treatment; Eastern Cooperative Oncology Group performance status score of 0, 1 or 2; and normal haematological and biochemical data. This study was approved by the local Ethics Committee of The Jikei University Hospital (approval number 24-004 and 28-054), and written informed consent was obtained from all patients prior to enrolment.

Patients were evaluated by oesophagogastroduodenoscopy (OGD), computed tomography, and magnetic resonance imaging for clinical staging before and after chemotherapy. All clinical and pathologic findings were classified according to tumour invasion, regional lymph node metastasis, and distant metastasis status following the guidelines of the Union for International Cancer Control (17) and Japanese Classification of Esophageal Cancer (JCEC 10th edition) (18).

Treatment procedure. The following chemotherapy regimen was employed: Docetaxel administered at a dosage of 60 mg/m^2/hour intravenously (*i.v.*) on day 1, cisplatin administered at a dosage of 70 mg/m^2/hour *i.v.* on day 1, and 5-fluorouracil administered continuously at a dosage of 600 mg/m^2/day using an infusion pump over 5 days (120 h). The regimen was repeated every 4 weeks. The protocol was scheduled twice before oesophagectomy. The drug dose was reduced by 20% in patients aged older than 76 years or those with grade 3 non-haematological or grade 4 haematological adverse events during the first course. Patients who had febrile neutropenia during the first course received prophylactic granulocyte colony-stimulating factor (G-CSF) during the second course. The second course was cancelled in patients with progressive disease and grade 4 non-haematological adverse events during the first course.

The patients underwent transthoracic oesophagectomy with two- or three-field lymphadenectomy according to the treatment guidelines in Japan (19). The stomach was used as an oesophageal substitute for reconstruction. When the stomach could not be used, the reconstruction was performed using the jejunum or colon.

Table I. *Patient characteristics*.

	Value
Age, years	
Mean±SD (range)	69.7±7.6 (44-85)
Gender, n (%)	
Male	70 (92%)
Female	6 (8%)
Tumour location, n (%)	
Upper thorax	7 (9%)
Middle thorax	37 (49%)
Lower thorax	32 (42%)
Performance status score, n (%)	
0	54 (71%)
1	17 (22%)
2	5 (7%)
Histology, n (%)	
Squamous cell carcinoma	76 (100%)
cT, n (%)	
1a	0 (0%)
1b	6 (8%)
2	12 (16%)
3	58 (76%)
cN, n (%)	
0	8 (11%)
1	47 (61%)
2	17 (22%)
3	4 (6%)
cStage, n (%)	
IB	1 (1%)
IIA	7 (9%)
IIB	15 (20%)
IIIA	33 (44%)
IIIB	13 (17%)
IIIC	7 (9%)
Chemotherapy dose, n (%)	
Complete	45 (59%)
Incomplete	31 (41%)
Clinical response, n (%)	
Complete response	5 (7%)
Partial response	32 (42%)
Stable disease	38 (50%)
Progressive disease	1 (1%)
Thoracic surgical procedure, n (%)	
Open	59 (78%)
Thoracoscopy	17 (22%)
Lymphadenectomy, n (%)	
3-Field	66 (87%)
2-Field	10 (13%)
Surgical complications (>Grade 3a), n (%)	
Yes	19 (25%)
No	57 (75%)

SD: Standard deviation.

Treatment evaluation. The clinical response to chemotherapy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) (20). Although primary oesophageal tumours are defined as non-measurable lesions according to

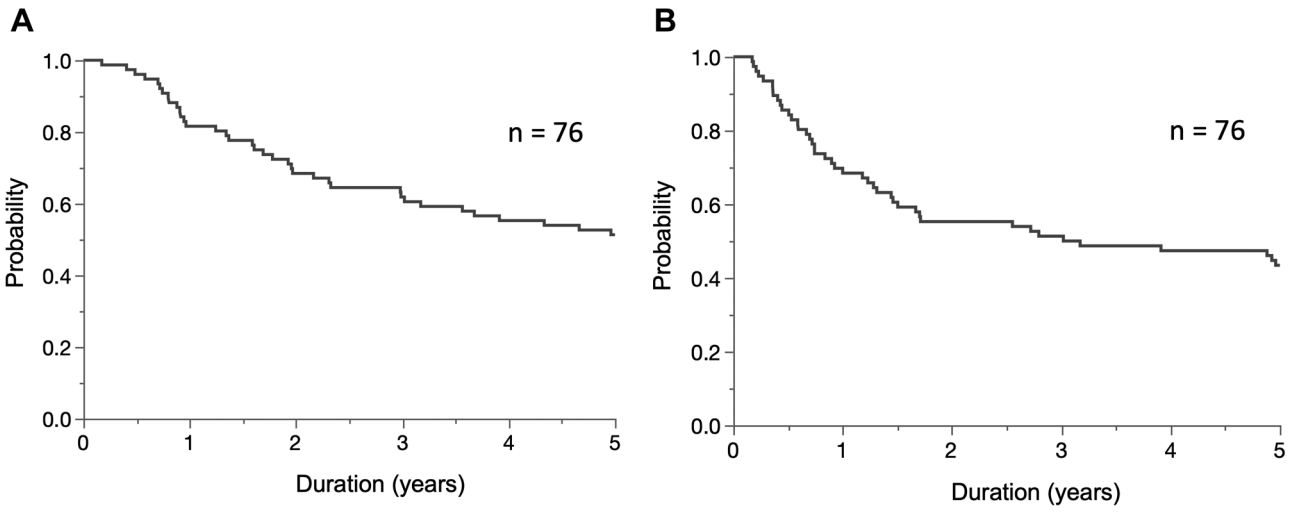

Figure 1. *Overall (A) and recurrence-free (B) survival in 76 patients with thoracic oesophageal squamous cell carcinoma who underwent preoperative docetaxel/cisplatin/5-fluorouracil therapy followed by surgery.*

RECIST criteria, patients may have measurable lesions. Thus, the overall responses of patients with no measurable lesions were evaluated using OGD according to the JCEC guidelines (18), as follows: Complete response (CR), disappearance of the primary tumour; partial response (PR), remarkable improvement in the primary tumour; progressive disease (PD), prominent progression of the primary tumour or appearance of a new lesion; stable disease (SD), absence of any changes.

Pathological response to preoperative chemotherapy was classified into five categories according to JCEC guidelines (18), as follows: Grade 0, ineffective: absence of a recognisable cytological or histological therapeutic effect; grade 1, slightly effective: 1a, viable cancer cells accounted for two-thirds or more of the tumour tissue; 1b, viable cancer cells accounted for one-third to two-thirds of the tumour tissue; grade 2, moderately effective: viable cancer cells accounted for less than one-third of the tumour tissue; and grade 3, markedly effective: absence of apparent viable cancer cells. Adverse events were assessed by the Common Terminology Criteria for Adverse Events, version 4.0 (21).

Postoperative follow-up with CT was scheduled every 3 to 4 months. Patients who were available for at least a 5-year follow-up period were included in this study.

Statistical analysis. JMP 14 software (SAS Institute, Cary, NC, USA) was used for the statistical analyses. All quantitative data are expressed as the mean±standard deviation. Survival rates were estimated using the Kaplan–Meier method. Univariate and multivariate analyses of OS were performed using Cox proportional hazard models. Univariate predictors with *p*-values lower than 0.10 were included in the multivariable analysis. Statistical significance was considered at a level of 0.05.

Results

Patient characteristics. In total, 76 patients who underwent preoperative DCF followed by surgery were included. The cohort predominantly comprised male patients (92%), and the median patient age was 69.7 years (range=44-85 years). Half of the tumours were located in the middle thorax (49%). Notably, 76% of patients had cT3 tumours, and 89% showed lymph node metastasis. All patients were clinically diagnosed with stage I to III disease; of these, 70% had stage III disease. The two scheduled courses of preoperative chemotherapy were completed in 59% of the study cohort (Table I).

Outcomes. The median follow-up period was 88.3 months. The 1-, 3-, and 5-year OS rates were 82%, 62% and 51%, respectively, while the corresponding RFS rates were 70%, 51%, and 43%, respectively (Figure 1).

Clinical response. Details on the clinical response to DCF are shown in Table I. CR, PR, SD, and PD were clinically observed in five (7%), 32 (42%), and 38 (42%) cases, and one (1%) case, respectively. CR or PR was observed in 49% of the cases.

Adverse events. The most commonly observed haematological adverse events associated with DCF were grade 3/4 neutropenia (n=49, 65%) and white blood cell count reduction (n=48, 63%), followed by grade 3 febrile neutropenia (n=25, 33%). Meanwhile, with respect to nonhaematological adverse events, grade 4 hyponatraemia and anorexia were observed in three patients (4%) and one patient (1%), respectively. In total, four patients (5%) developed nonhaematological grade 4 adverse events during the first course of DCF, and eventually the second course was cancelled. No treatment-related mortality was observed (Table II).

Table II. *Incidence of adverse events*.

	Grade 3, n	Grade 4, n	Grade 3/4, n (%)
Haematological			
Neutrophil count decrease	26	23	49 (65%)
White blood cell decrease	28	20	48 (63%)
Febrile neutropenia	25	0	25 (33%)
Platelet count decrease	3	0	3 (4%)
Anaemia	3	0	3 (4%)
Non-haematological			
Hyponatremia	24	3	27 (36%)
Anorexia	24	1	25 (33%)
Acute kidney injury	20	0	20 (26%)
Nausea/vomiting	18	0	18 (24%)
Diarrhoea	8	0	8 (11%)

Postoperative morbidity and mortality. Overall, 19 patients developed grade 3a or more postoperative complications (Clavien–Dindo classification) (22). The most frequently observed complications were anastomotic leak (8%), pneumonia (8%), and recurrent nerve palsy (7%). One patient died within 30 days after surgery (1%).

Histological findings. Grade 3, 2, 1b, 1a, and 0 pathologically responses were observed in eight (11%), 12 (16%), 10 (13%), 40 (52%), and six (8%) patients, respectively. R0 resection (complete resection) was achieved in 64 patients (84%), and R1 (microscopic residual disease) and R2 (macroscopic residual disease) in five (7%) and seven patients (9%), respectively (Table III).

OS predictors. In the multivariable analysis, cT stage 3, incomplete chemotherapy, poor clinical response, and postoperative complications greater than grade 3a were independent predictors of poorer OS (Table IV).

The correlation between the relative dose intensity (RDI) of preoperative DCF and OS is demonstrated in Figure 2. Patients were divided into three groups based on the actual-to-planned dosage ratio, *i.e.* the optimal dosage, 80-99% dosage, or ≤79% dosage. RDI was significantly positively correlated with OS across the three groups ($p<0.001$).

Discussion

This study, which as far as we are aware is the first to report on the 5-year outcomes associated with preoperative DCF followed by radical oesophagectomy in OSCC, identified incomplete preoperative chemotherapy with DCF and postoperative complications as significant independent prognostic factors.

In Japan, preoperative CF followed by oesophagectomy is the standard treatment modality for advanced thoracic

Table III. *Histological outcomes*.

Parameter	Subgroup	Number of patients (%)
pT	0	7 (9%)
	is	1 (1%)
	1a	2 (2%)
	1b	15 (20%)
	2	10 (13%)
	3	32 (42%)
	4a	3 (4%)
	4b	6 (8%)
pN	0	25 (33%)
	1	23 (30%)
	2	16 (21%)
	3	12 (16%)
pStage	0	7 (9%)
	IA	4 (6%)
	IB	4 (6%)
	IIA	9 (12%)
	IIB	12 (16%)
	IIIA	13 (17%)
	IIIB	9 (12%)
	IIIC	17 (23%)
	Unknown	1 (1%)
Pathological response	0	6 (8%)
	1a	40 (52%)
	1b	10 (13%)
	2	12 (16%)
	3	8 (11%)
Residual tumour	R0	64 (84%)
	R1	5 (7%)
	R2	7 (9%)

OSCC. However, the treatment outcomes remain unsatisfactory (5-year OS rate 55%, 5-year RFS rate 44%, and clinical preoperative CF response rate 38%) (6, 7). Although some studies have shown more favourable 2- or 3-year OS and RFS rates in association with preoperative DCF than CF, the long-term effect has not been thoroughly investigated (11, 13-15). In the current study, DCF did not show a survival advantage in terms of 5-year OS and RFS compared to the values observed in the JCOG9907 trial (51% and 43% *vs.* 55% and 44%, respectively); additionally, our study included a larger number of cases with advanced-stage disease and older patients than the JCOG9907 trial (7). DCF, therefore, may be more effective than CF. Yamashita *et al*. reported favourable 5-year OS and RFS rates of 77% and 58%, respectively, in association with DCF (23). However, their result cannot be compared to that of the present study owing to differences in the DCF regimen and treatment modality used after chemotherapy; nonetheless, DCF can be a candidate in multimodal therapy for OSCC.

The RDI is defined as the ratio of the planned dose intensity to the actual dose intensity received. Patients who received chemotherapy with a planned RDI had more

Table IV. *Predictors of overall survival in the multivariate analysis.*

Factor		Univariate analysis			Multivariate analysis*		
		HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age	Per increment	1.02	0.98-1.05	0.3870			
cT stage	3 *versus* 2, 1	1.81	1.03-3.17	0.0369	1.81	1.04-3.14	0.0356
cN stage	3, 2, 1 *versus* 0	2.07	0.92-4.65	0.0767	2.12	0.95-4.72	0.0651
Complete chemotherapy	No *versus* Yes	2.08	1.02-4.25	0.0441	2.35	1.37-4.02	0.0019
Adverse event >Grade 3	Yes *versus* No	1.06	0.54-2.08	0.8612			
Clinical response	SD, PD *versus* CR, PR	1.64	0.93-2.91	0.0888	1.82	1.01-3.29	0.0430
Postoperative complications >Grade 3a	Yes *versus* No	2.29	1.21-4.35	0.0109	2.11	1.14-3.90	0.0174
Pathological response	0, 1a *versus* 3, 2, 1b	1.08	0.64-1.85	0.7608			

CI: Confidence intervaI; CR: complete response; HR: hazard ratio; PD: progressive disease; PR: partiaI response; SD: stable disease. *Univariate variables with $p<0.1$ were included in the multivariable model.

favourable clinical outcomes than those with a lower RDI in malignant lymphoma or breast cancer (24, 25). In the present study, a low RDI (incomplete chemotherapy) was among the independent predictors of poorer OS. To the best of our knowledge, the RDI associated with preoperative chemotherapy for oesophageal cancer has not been addressed previously. Postoperative complications were also identified as independent OS predictors. Kataoka *et al*. reported that postoperative complications may worsen OS after surgery, which our results are consistent with (26). Therefore, preoperative DCF without postoperative complications may be beneficial in improving survival outcomes.

The CR/PR rates in the current study were slightly lower than those observed in previous studies (15, 16). These differences may be attributed to the different regimens used. Watanabe *et al*. reported that patients with CR/PR following preoperative chemotherapy may have longer survival durations than those with SD/PD. In our multivariate analysis, SD/PD was an independent predictor of poorer OS, consistent with the previous study (hazard ratio=2.69, 95% confidence interval=1.18-6.47, $p=0.04$) (15).

Docetaxel leads to severe bone marrow suppression even when administered as monotherapy. The incidence of DCF-related haematological adverse events was higher than that related to CF use. In this study, the rate of grade 3/4 neutropenia (65%) was higher than previously observed (5-18%) in patients treated with CF; however, the value was not as high as that noted in previous DCF studies (78-90%) (9, 15). This may be attributed to differences in the DCF regimens employed. Although the use of prophylactic G-CSF for preoperative DCF is controversial in Japan, the American Society of Clinical Oncology recommends its administration for myelosuppression (27, 28). In fact, among those in whom grade 4 leucopenia developed in the first course, the second course of DCF was completed using prophylactic G-CSF without grade 4 adverse events.

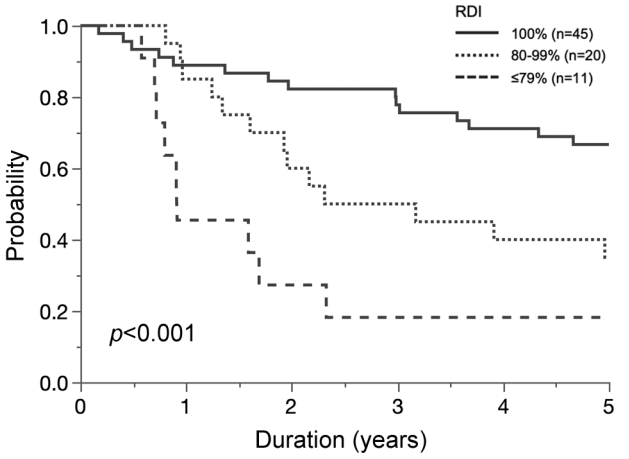

Figure 2. *Overall survival stratified by relative dose intensity (RDI).*

The incidence of severe complications of grade 3a or higher in the current study (25%) was not higher than that recorded in the nationwide database in Japan (42-43%) (29). Hara *et al*. reported that preoperative chemotherapy is not associated with increases in the rates of surgical complications; our outcomes support this (13).

In North America and Europe, preoperative chemoradiotherapy followed by oesophagectomy for oesophageal and junctional cancer was shown to yield favourable survival data; however, the associated high postoperative mortality of 4% may not be easily acceptable in Japan (4). A three-arm randomised trial focusing on preoperative therapy, comprising, CF, DCF, and chemoradiotherapy, which aims to demonstrate the efficacy and safety of preoperative treatment for advanced OSCC is currently underway in Japan (30).

The study has some potential limitations. Firstly, it had a small sample size, and a single-centre, single-arm design.

Secondly, the sample predominantly comprised elderly men. Thirdly, we used a non-standardised DCF regimen. The strength of this study is the fact that only patients who were followed-up for longer than 5 years were enrolled; therefore, the results are relevant and add significantly to the existing knowledge on optimal preoperative chemotherapy.

In conclusion, the current study demonstrated that preoperative DCF followed by oesophagectomy may offer favourable 5-year outcomes for patients with OSCC. These results may prove helpful in the formulation of strategies aimed at improving the prognosis of OSCC. However, further appropriate evidence-based clinical trials are required to confirm the efficacy and safety of the regimen.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this article.

Authors' Contributions

Yuichiro Tanishima: Design of the study, collection and analysis of data, and drafting of the article. Katsunori Nishikawa: Revision of the article. Yasuhiro Arakawa: Collection of data. Akira Matsumoto: Collection of data. Yujiro Tanaka: Collection of data. Norio Mitsumori: Collection of data. Katsuhiko Yanaga: Revision of the article and final approval of the article.

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