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Received March 5, 2014; Accepted April 8, 2014

DOI: 10.3892/mco.2014.320

Abstract. To determine the efficacy of postoperative adjuvant chemotherapy with docetaxel + cisplatin + 5-fluorouracil (DCF) in lymph node metastasis-positive esophageal cancer, we retrospectively analyzed 139 patients with stage II/III (non-T4) esophageal cancer with lymph node metastasis (1-6 nodes), who did not receive preoperative treatment and underwent three-field lymph node dissection in the Juntendo University Hospital between December, 2004 and December, 2009. The tumors were histologically diagnossed as squamous cell carcinoma. The patients were divided into two groups, a surgery alone group (S group, 88 patients) and a group that received postoperative DCF therapy (DCF group, 51 patients). The disease-free and overall survival were compared between the groups and a multivariate analysis of prognostic factors was performed. The same analysis was performed for cases classified as N1 and N2, according to the TNM classification. There were no significant differences between the S and DCF groups regarding clinicopathological factors other than intramural metastasis and main tumor location. The presence of intramural metastasis, blood vessel invasion and the number of lymph nodes were identified as prognostic factors. The 5-year disease-free and overall survival were 55.8 and 57.3%, respectively, in the S group and 52.8 and 63.0%, respectively, in the DCF group. These differences were not considered to be statistically significant (P=0.789 and 0.479 for disease-free and overall survival, respectively). Although there were no significant differences in disease-free and overall survival between the S and DCF groups in N1 cases, both disease-free and overall survival were found to be better in the DCF group (54.2 and 61.4%, respectively) compared to the S group (29.6 and 28.8%, respectively) in N2 cases (P=0.029 and 0.020 for disease-free and overall survival, respectively). Therefore, postoperative adjuvant chemotherapy with DCF was shown to improve disease-free and overall survival in moderate lymph node metastasis-positive cases (N2), suggesting that the DCF regimen may be effective as postoperative adjuvant chemotherapy for patients with lymph node metastasis from esophageal cancer.

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Key words: docetaxel + cisplatin + 5-fluorouracil therapy, esophageal cancer, intramural metastasis, lymph node metastasis, postoperative adjuvant chemotherapy

Introduction

Esophageal cancer is more highly malignant compared to other gastrointestinal cancers and is associated with a high rate of lymph node metastasis and metastases distributed over a wide range (1). Three-field lymph node dissection is widely performed in Japan in an attempt to thoroughly dissect lymph nodes in highly malignant esophageal cancer and it is currently considered as the standard surgery for thoracic esophageal cancer with depth of invasion in the submucosa (SM) or greater (2). We previously reported that three-field lymph node dissection is expected to be effective in cases with ≤5 metastatic lymph nodes (3,4) and that the number of lymph node metastases is the most powerful prognostic factor for esophageal cancer, with the prognosis rapidly declining with ≥6 positive lymph nodes (3,4). The present study retrospectively analyzed the efficacy of treatment with docetaxel (TXT), cisplatin (CDDP) and 5-fluorouracil (5-FU) (DCF regimen) as postoperative adjuvant chemotherapy in patients undergoing surgery for esophageal cancer with lymph node metastasis. The patients were also grouped according to the number of metastatic nodes based on the TNM classification, in order to identify a subgroup that may benefit from DCF therapy.

Patients and methods

Patient characteristics and inclusion criteria. Of the esophageal cancer patients who underwent three-field lymph node dissection in our department between December, 2004 and

December, 2009 and were found to be pathologically positive for lymph node metastasis, a total of 139 patients were included in this study, as they fulfilled all the following criteria: i) thoracic esophageal cancer diagnosed histologically as squamous cell carcinoma; ii) pathologic stage II/III patients according to the TNM classification, excluding pT4 patients; iii) 1-6 metastatic lymph nodes (N1 or N2 according to the TNM classification); iv) no preoperative treatment (chemotherapy, radiotherapy or chemoradiotherapy); v) no residual tumor on gross examination (R0); vi) Eastern Cooperative Oncology Group performance status of 0, 1 or 2; vii) no organ function abnormalities on clinical laboratory test results (white blood cell count ≥3,000/mm^3; platelet count ≥100,000/mm^3; hemoglobin ≥10 g/dl; serum creatinine ≤1.5 mg/dl; blood urea nitrogen ≤25 mg/dl; creatinine clearance ≥50 ml/min; aspartate aminotransferase ≤100 IU/l; alanine aminotransferase ≤100 IU/l; and total bilirubin ≤1.5 mg/dl); viii) informed consent was obtained from the participants; ix) no severe underlying heart disease; and x) postoperative time to chemotherapy >2 weeks and <2 months.

Treatment and endpoints. The primary endpoint was disease-free survival and the secondary endpoints were survival rate and severity of side effects. The postoperative adjuvant chemotherapy included two courses of DCF therapy (5-FU 500 mg/m^2 on days 1-4, TXT 60 mg/m^2 on day 1 and CDDP 60 mg/m^2 on day 1).

Patient grouping and classification. The patients were divided into two groups, a surgery alone group, in which no postoperative adjuvant therapy was administered (S group, 88 patients) and a group that received postoperative DCF therapy (DCF group, 51 patients). The disease-free and overall survival were compared between the groups and a multivariate analysis of prognostic factors was conducted. The Japanese Classification of Esophageal Cancer (5) was used for clinicopathological factors and the TNM classification (7th edition) (6) of the UICC was used for staging. The patients were also classified as N1 cases (1-2 lymph node metastases) or N2 cases (3-6 lymph node metastases) according to the TNM classification; the same analyses were conducted in the S and DCF groups.

Statistical analysis. The survival rates were analyzed using the Kaplan-Meier method and tests of significance were performed using the log-rank method. The Cox regression analysis was used in the multivariate analysis of prognostic factors. In all analyses, P<0,05 was considered significant.

Results

Clinicopathological factors. The clinicopathological characteristics of the 139 patients are summarized in Table I. Except for intramural metastasis and main tumor location, there were no significant differences between the S (88 patients) and DCF (51 patients) groups regarding clinicopathological factors, including tobacco and alcohol use.

The presence of intramural metastasis and blood vessel invasion and the number of lymph nodes were identified as prognostic factors in all the patients (Table II).

Table I. Clinicopathological factors.

Factors	S group (n=88)	DCF group (n=51)	P-value
Mean age, years (range)	65.4 (44-83)	62.2 (52-76)	0.205
Gender			
Male	72	44	
Female	16	7	0.644
Tobacco use			
Yes	80	47	
No	8	4	0.720
Alcohol use			
Yes	76	47	
No	12	4	0.428
Main tumor location			
Upper thoracic	8	4	
Middle thoracic	43	36	
Lower thoracic	37	11	
Abdominal esophagus	0	0	0.036
Histological differentiation (SCC)			
High	37	26	
Moderate	48	23	
Poor	3	2	0.561
Lymph vessel invasion			
ly0	12	5	
ly1	41	14	
ly2	35	32	0.228
Venous invasion			
v0	23	11	
v1	46	22	
v2	19	18	0.212
Depth of tumor invasion			
pT1b	25	9	
pT2	23	7	
pT3	40	35	0.064
Intramural metastasis			
IM 0	84	40	
IM 1	4	11	0.001

DCF, docetaxel + cisplatin + 5-fluorouracil; S, surgery alone; SCC, squamous cell carcinoma.

Adverse events. The adverse events due to chemotherapy were evaluated based on the Common Terminology Criteria for Adverse Events v4.0 (7) and are listed in Table III. Side effects of grade 3 or higher from DCF were leukopenia in 20 patients (39.2%), nausea/vomiting in 5 patients (9.8%), diarrhea in 5 patients (9.8%) and hyponatremia in 21 patients (41.2%), all of which were manageable with appropriate measures. The treatment was completed with one course in only 5 patients,

Table II. Results of Cox regression analysis.

Covariates	P-value	Hazard ratio	95% CI
Age	0.244	1.020	
Gender	0.400	1.698	0.495-5.824
Tobacco	0.490	0.593	0.134-2.616
Alcohol	0.608	0.721	0.206-2.518
Depth of tumor invasion	0.132		
pT1b	0.360	0.366	0.042-3.152
pT2	0.335	0.558	0.170-1.826
pT3	0.063	2.558	0.952-6.877
Lymph vessel invasion	0.548	1.457	0.427-4.790
Blood vessel invasion	0.003	6.320	1.843-21.67
Intramural metastasis	0.028	0.224	0.095-0.529
No. of lymph nodes	0.0001		

CI, confidence interval.

Table III. Side effects of DCF therapy.

	Grade				
Toxicity	0	1	2	3	4
Low hemoglobin	37	10	4	0	0
Leukopenia	8	10	13	17	3
Thrombocytopenia	48	3	0	0	0
Nausea/vomiting	3	20	23	5	0
Diarrhea	30	6	10	5	0
Stomatitis	47	1	3	0	0
High creatinine	49	2	0	0	0
Arrhythmia	51	0	0	0	0
Infection	49	2	0	0	0
Fever	30	11	10	0	0
Hyponatremia	16	14	-	19	2

DCF, docetaxel + cisplatin + 5-fluorouracil.

and the proportion in which two courses could be completed was 47/51 (92.2%).

Survival. The 5-year disease-free survival was 55.8% in the S group and 52.8% in the DCF group, with no statistically significant difference (P=0.789) (Fig. 1A). The 5-year overall survival was 57.3% in the S group and 63.0% in the DCF group, also without a statistically significant difference (P=0.479) (Fig. 1B).

Treatment efficacy and clinicopathological factors in N1 and N2 cases. The efficacy of DCF treatment was investigated in patients divided according to the number of metastatic

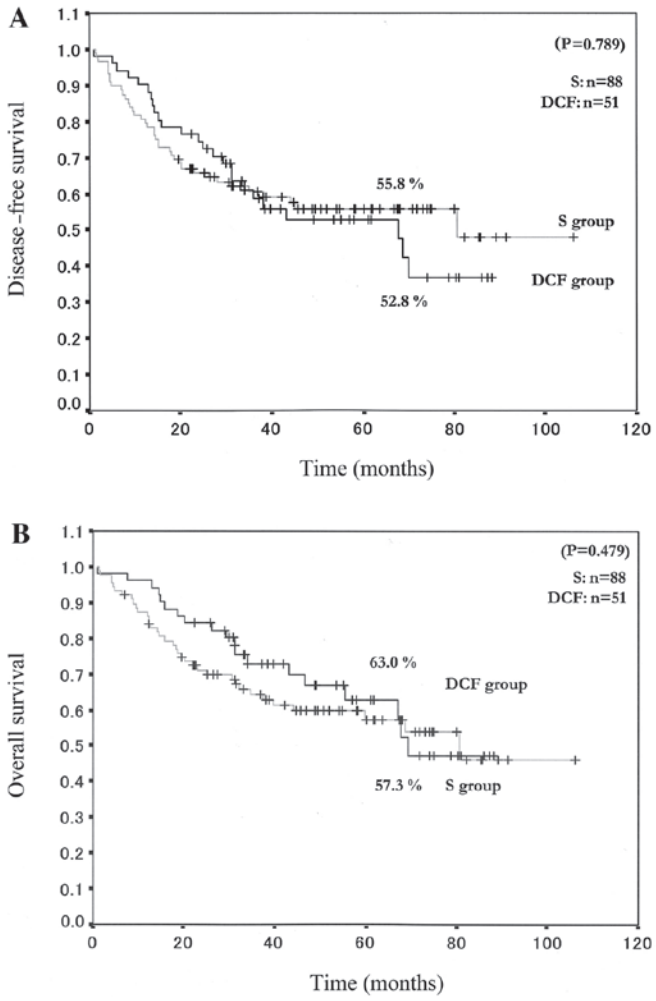

Figure 1. (A) Five-year disease-free survival in all patients. Cumulative survival rates in the S group (no postoperative adjuvant therapy) and DCF group (postoperative DCF therapy). (B) Five-year overall survival in all patients. Cumulative survival rates in the S group (no postoperative adjuvant therapy) and DCF group (postoperative DCF therapy). DCF, docetaxel + cisplatin + 5-fluorouracil; S, surgery alone.

lymph nodes (N1, 1-2 nodes; and N2, 3-6 nodes) based on the TNM classification of UICC. There were 70 N1 cases and 69 N2 cases and their clinicopathological characteristics are summarized in Tables IV and V, respectively. A significant difference between the S and DCF groups was only observed regarding the presence or absence of intramural metastases in both N1 and N2 cases.

N1 cases. The 5-year disease-free survival was 69.2% in the S group and 49.1% in the DCF group; the difference was not considered significant (P=0.422) (Fig. 2A). The 5-year overall survival was 71.1% in the S group and 70.7% in the DCF group; the difference was also not significant (P=0.624) (Fig. 2B).

N2 cases. The 5-year disease-free survival was 29.6% in the S group and 54.2% in the DCF group, with a significantly better prognosis in the DCF group (P=0.029) (Fig. 3A). The 5-year overall survival was 28.8% in the S group and 61.4% in the DCF group, with a significantly better prognosis in the DCF group (P=0.020) (Fig. 3A).

Therefore, postoperative adjuvant therapy with DCF was shown to be beneficial in N2 cases.

Table IV. Clinicopathological factors in N1 cases (n=70).

Factors	S group (n=59)	DCF group (n=11)	P-value
Mean age, years (range)	65.4 (44-82)	62.2 (52-72)	0.273
Gender			
Male	50	10	
Female	9	1	0.830
Tobacco use			
Yes	51	9	
No	8	2	0.846
Alcohol use			
Yes	54	11	
No	5	0	0.542
Main tumor location			
Upper thoracic	5	3	
Middle thoracic	28	6	
Lower thoracic	26	2	
Abdominal esophagus	0	0	0.105
Histological differentiation (SCC)			
High	26	5	
Moderate	33	5	
Poor	0	1	0.062
Lymph vessel invasion			
ly0	10	0	
ly1	33	5	
ly2	16	6	0.118
Venous invasion			
v0	19	2	
v1	32	5	
v2	8	4	0.169
Depth of pathological tumor invasion			
pT1b	21	2	
pT2	18	1	
pT3	20	8	0.111
Intramural metastasis			
IM 0	56	9	
IM 1	3	2	0.040

DCF, docetaxel + cisplatin + 5-fluorouracil; S, surgery alone; SCC, squamous cell carcinoma.

Table V. Clinicopathological factors in N2 cases (n=69).

Factors	S group (n=29)	DCF group (n=40)	P-value
Mean age, years (range)	65.2 (52-83)	62.4 (51-76)	0.301
Gender			
Male	22	34	
Female	7	6	0.258
Tobacco use			
Yes	25	38	
No	4	2	0.198
Alcohol use			
Yes	26	36	
No	3	4	0.632
Main tumor location			
Upper thoracic	3	1	
Middle thoracic	15	30	
Lower thoracic	11	9	
Abdominal esophagus	0	0	0.102
Histological differentiation (SCC)			
High	11	21	
Moderate	15	18	
Poor	3	1	0.256
Lymph vessel invasion			
ly0	2	4	
ly1	8	10	
ly2	19	26	0.891
Venous invasion			
v0	4	9	
v1	14	17	
v2	11	14	0.657
Depth of pathological tumor invasion			
pT1b	5	7	
pT2	4	6	
pT3	20	27	0.987
Intramural metastasis			
IM 0	28	31	
IM 1	1	9	0.026

DCF, docetaxel + cisplatin + 5-fluorouracil; S, surgery alone; SCC, squamous cell carcinoma.

Discussion

Surgical resection is the international standard treatment for resectable stage II/III thoracic esophageal cancer and certain results have been achieved with various surgical procedures and perioperative management modifications (8-12). In Japan, satisfactory outcomes with 5-year survival rates >50% have been reported with radical surgery using thorough three-field lymph node dissection (2). However, postoperative hematogenous or lymphogenous metastasis occurs in several patients and there are limitations to the curative effect with surgical treatment alone. A multimodal approach, including postoperative adjuvant therapy, is essential to further improve treatment outcomes for patients with esophageal cancer (13,14).

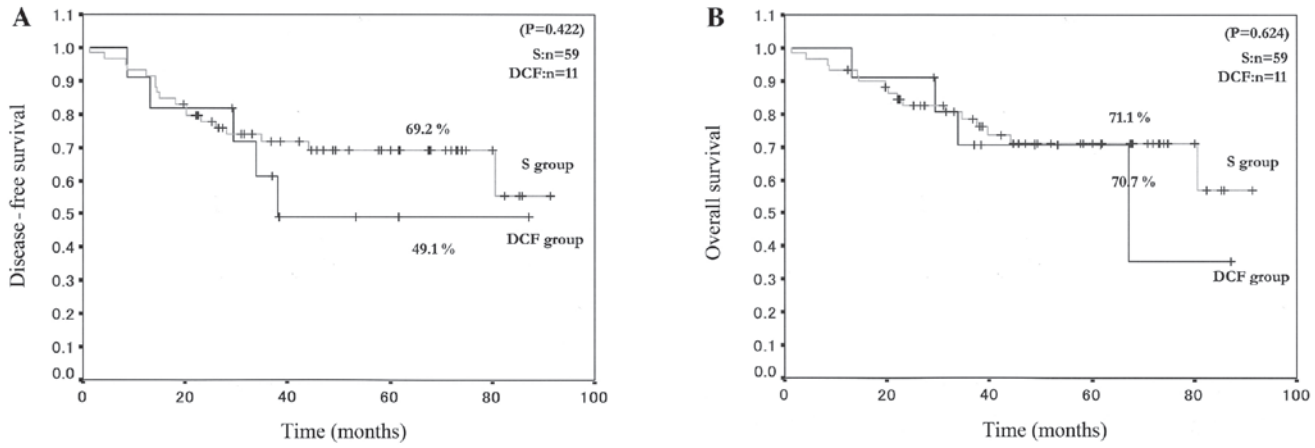

Figure 2. (A) Five-year disease-free survival in all N1 cases. Cumulative survival rates in the S group (no postoperative adjuvant therapy) and DCF group (postoperative DCF therapy) in N1 cases. (B) Five-year overall survival in all N1 cases. Cumulative survival rates in the S group (no postoperative adjuvant therapy) and DCF group (postoperative DCF therapy) in N1 cases. DCF, docetaxel + cisplatin + 5-fluorouracil; S, surgery alone.

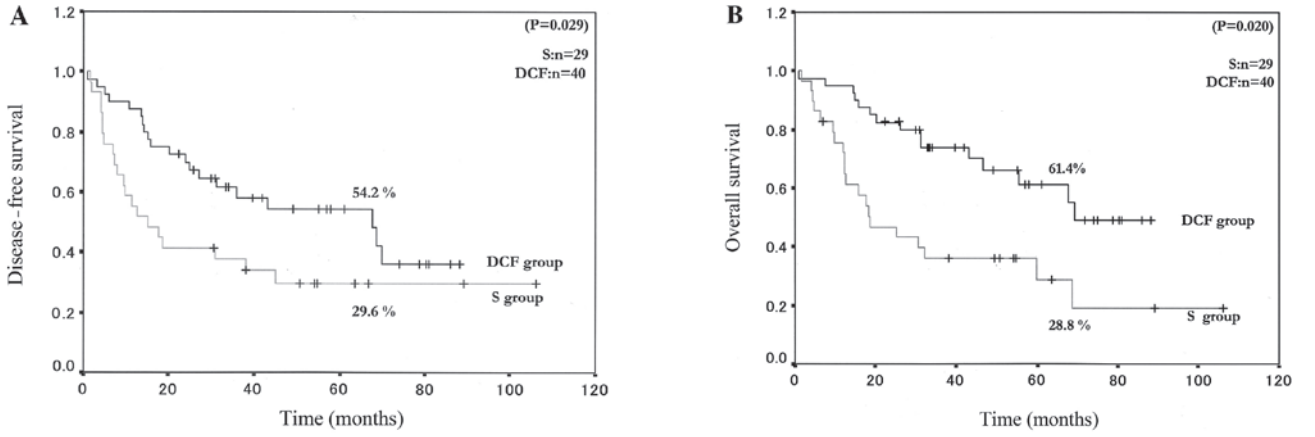

Figure 3. (A) Five-year disease-free survival in all N2 cases. Cumulative survival rates in the S group (no postoperative adjuvant therapy) and DCF group (postoperative DCF therapy) in N2 cases. (B) Five-year overall survival in all N2 cases. Cumulative survival rates in the S group (no postoperative adjuvant therapy) and DCF group (postoperative DCF therapy) in N2 cases. DCF, docetaxel + cisplatin + 5-fluorouracil; S, surgery alone.

In the 5th trial of the Japan Clinical Oncology Group (JCOG9204) (15), the efficacy of postoperative adjuvant chemotherapy with CDDP 80 mg/m^2 on day 1 and 5-FU 800 mg/m^2 on days 1-5 (FP therapy, 2 courses) was prospectively investigated in patients with esophageal squamous cell carcinoma diagnosed as stage II/III on postoperative pathological examination. Comparing the postoperative chemotherapy group of 122 patients and the surgery alone group of 120 patients, the 5-year overall survival was 61 and 52%, respectively, with no significant difference between the groups (P=0.13). However, the disease-free survival was significantly better in the postoperative chemotherapy compared to that in the surgery alone group (55 vs. 45%, respectively; P=0.037) and a recurrence prevention effect was observed (15). This effect was particularly significant in patients with pathologically confirmed metastasis-positive lymph nodes (P=0.041); no recurrence prevention effect was observed in patients with pathologically confirmed metastasis-negative lymph nodes (15).

From those results, it was hypothesized that postoperative adjuvant chemotherapy is a meaningful approach to preventing recurrence in patients with lymph node metastasis, with FP therapy recommended for preventing postoperative metastasis (16).

FP therapy was previously reported to exert a stable effect, with response rates of 30-40% in previous phase II trials (17,18) and is currently widely used as the standard treatment (19,20). Additional phase II trials using various combination treatments centered on CDDP and 5-FU have been conducted in other countries as well (21-27), although no regimen exceeding FP in efficacy has yet been established (28).

In our department, we focused on DCF therapy, which is reported to have treatment outcomes exceeding those of FP therapy in the head and neck and gastric cancer fields (29,30), and have used it since 2004. From the analysis of survival by number of metastatic lymph nodes, we also investigated which cases may still benefit from three-field lymph node dissection and have concluded that a positive effect from three-field lymph node dissection may be expected in cases with ≤5 metastatic lymph nodes (3,4). Therefore, we conducted the present study with the aim of determining i) whether DCF therapy is beneficial and ii) which patient subgroups among patients with lymph node metastasis may benefit from DCF as postoperative adjuvant chemotherapy.

No significant difference was observed in the 5-year disease-free or overall survival between the S and DCF groups when considering the entire patient sample. In addition, when patients were grouped by the number of metastatic lymph nodes, no significant difference was observed in the 5-year disease-free or overall survival between the S and DCF groups in N1 cases, which may be attributed to the good effect of surgical dissection, leaving little room for postoperative adjuvant chemotherapy to display any benefit.

However, in the N2 cases, the treatment outcomes regarding both disease-free and overall survival were significantly better in the postoperative DCF therapy group compared to the S group, with a disease-free survival of 54.2 vs. 29.6% and an overall survival of 61.4 vs. 28.8%, respectively (P=0.029 and 0.020, respectively). The efficacy of postoperative DCF therapy was thus shown in these patients. Among the underlying factors, intramural metastases, which are considered to be an indicator of malignancy, were present at a significantly higher rate in the DCF group; however, the recurrence prevention effect of DCF therapy is considered to extend beyond the results expected solely based on this malignancy factor.

Massive fluid loading and diuresis are required to protect the kidneys in patients receiving DCF or FP and hospitalization for treatment is essential. The toxicity profile is considered to be acceptable and the treatment completion rate is high, with a completion rate for FP therapy in the JCOG9204 trial of 75% (15) and a DCF completion rate in this study of 90.3%. From the abovementioned findings it may be concluded that DCF therapy is useful as postoperative adjuvant chemotherapy for moderate lymph node metastasis-positive patients, suggesting its value as postoperative adjuvant chemotherapy for patients with intramural metastasis.

The development of novel multimodal therapies is essential to further improve the prognosis of esophageal cancer patients and DCF therapy is considered to be a viable option in the postoperative adjuvant chemotherapy setting for patients with lymph node metastasis from esophageal cancer.

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