

Adverse Prognostic Factors of Advanced Esophageal Cancer in Patients Undergoing Induction Therapy with Docetaxel, Cisplatin and 5-Fluorouracil

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Abstract. *Background/Aim:* The purpose of this study was to identify adverse prognostic factors for patients with advanced esophageal cancer undergoing chemotherapy with docetaxel, cisplatin and 5-fluorouracil (DCF). *Patients and Methods:* The study cohort comprised of 45 patients with advanced esophageal cancer who underwent induction DCF therapy followed by esophagectomy or chemoradiotherapy. Treatment outcomes and factors affecting early recurrence and death were analyzed. *Results:* Overall 3-year survival was 61.4%, and 3-year disease-free survival was 44.7%. Clinically evident lymph node metastasis and clinical stage were associated with recurrence within 1 year and death within 2 years. Low maximum standardized uptake value (SUV_{max}) after induction DCF therapy and small decreases in SUV_{max} from pre- to post-DCF therapy were also predictors of recurrence and poor prognosis. *Conclusion:* Induction DCF therapy may be ineffective for advanced-stage esophageal cancer and clinical lymph node metastasis ($\geq N2$, \geq stage IIIB). Moreover, small decreases in SUV_{max} DCF therapy are associated with early disease relapse and death.

Currently, treatment modalities for esophageal cancer vary according to tumor stage. In Japan, endoscopic mucosal resection and endoscopic submucosal dissection is an accepted alternative to open surgery for cancer confined to the mucosal

layer (1-3). Excision plus three-field lymph node dissection has contributed to improvement in survival rates of patients with locally advanced cancer (4). However, despite optimization of surgical treatment in high-volume centers, outcomes following resection of esophageal squamous cell carcinoma (ESCC) remain unsatisfactory (5, 6). Therefore, multimodal therapy is now frequently administered for various stages of esophageal cancer, including operable cancer (7-11). In Japan, there has been a recent trend for augmenting surgery for resectable stage II and III ESCC with preoperative neoadjuvant chemotherapy (12, 13).

Cisplatin with 5-fluorouracil (5-FU) (CF) has been a standard regimen for esophageal cancer. Docetaxel has recently been added to this combination and the resultant DCF regimen is now widely used (14-18). This combination is considered the most promising chemotherapy for advanced esophageal cancer, most studies reporting it to have good anticancer effects. However, associated adverse prognostic factors have not been reported.

In this study, possible adverse prognostic factors in patients with advanced esophageal cancer undergoing induction DCF therapy were assessed.

Patients and Methods

Prospective database for induction DCF. Since February 2010, we have treated patients with advanced esophageal cancer with induction DCF followed by surgery or definitive chemoradiotherapy and enrolled them in a prospective observational study. The eligibility criteria included the following: pathologically confirmed esophageal cancer without distinct invasion of neighboring structures (T4b: seventh edition TNM) (19); no distant metastases; no prior treatment; Eastern Cooperative Oncology Group performance status of 0 to 2; age 20-75 years; and adequate bone marrow, renal, and hepatic function (absolute neutrophil count $>2.0 \times 10^9/l$ and platelet count $>10.0 \times 10^9/l$; serum

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creatinine <1.5 mg/dl; aspartate aminotransferase and alanine aminotransferase <1.5× the upper limit of normal; and total bilirubin <1.5× the upper limit of normal). All participants provided written informed consent for inclusion and the study was approved by the Medical Ethics Committee of Dokkyo Medical University (approval number: C-234-06).

Regimen of induction DCF and following curative therapy. The DCF regimen consisted of 70 mg/m² of docetaxel infused over 1 h on day 1, followed by 70 mg/m² of cisplatin infused over 1 hour on day 1, and 700 mg/m² of 5-FU on days 1 to 5 as a 24 h continuous intravenous infusion (20). This regimen was administered at 4-week intervals, two courses being administered before curative therapy (esophagectomy or definitive chemoradiotherapy).

About 2 weeks after the second course of induction DCF, the effect of the chemotherapy was evaluated by esophagogastroduodenoscopy, computed tomography (CT) and ¹⁸F-deoxyglucose positron-emission tomography (FDG-PET)/CT. Patients with maximum standard uptake (SUV_{max}) in tumor of 2.0 or less were classified as chemo-responders and those with SUV_{max} ≥ 2.0 as chemo-non-responders (21). Definitive chemoradiotherapy (CRT) was administered to all chemoresponders and to chemo-non-responders whose cancer was judged as unresectable, whereas curative esophagectomy was performed on chemo-non-responders whose tumors were considered resectable.

Study cohort. From February 2012 through December 2014, 45 patients met the eligibility criteria. Nine patients who were classified as chemo-responders and two chemo-non-responders were treated with definitive CRT after two courses of induction DCF; these nine patients were categorized as the S-CRT group and the chemo-non-responders who underwent CRT as the R-CRT group. Curative esophagectomy was performed on 34 patients who were chemo-non-responders and had resectable cancer; they were categorized as the Surgery group.

Tumor staging. All patients were staged pretreatment by endoscopy, endoscopic ultrasonography, and FDG-PET/CT. Clinical and pathological findings were classified according to the tumor, node, metastasis classification system (TNM) (7th edition) of the International Union against Cancer (UICC) (19).

Response evaluation. About 2 weeks after completion of treatment, clinical responses were evaluated according to the criteria of the Japan Esophageal Society (22). The assessment involved repeat esophagogastroduodenoscopy by two investigators who assessed the pre- and post-treatment macroscopic findings for each tumor before and CT scans of the neck, chest and abdomen. Five-millimeter continuous scans were obtained from the neck to the pelvis after intravenous injection of contrast medium. The endoscopic and CT results were discussed by the investigators and responses of primary and target lesions (maximum of five measurable lesions per organ) were classified as follows. For target lesions: complete response (CR), complete disappearance of all clinical evidence of disease; partial response (PR), >30% decrease in target lesion size; progressive disease (PD), >20% increase in target lesion size; or stable disease (SD), increase of <20% in tumor size or of less than <30% in target lesion size. For non-target lesions (any other lesions, including primary tumor): CR, disappearance of all non-target lesions, including primary lesion undetectable on endoscopy; and incomplete response/SD, persistence of one or more non-target

lesion(s) or conditions for CR or PD not met on endoscopy; and PD, appearance of one or more new lesions or unequivocal progression of non-target lesion(s) or distinct growth of primary lesion or progression of esophageal stenosis compared with best condition during treatment. Overall responses were diagnosed based on a combination of response in target and non-target lesions and no new lesions. Responses were also evaluated on SUV_{max} in FDG-PET studies, as described above.

Histopathological responses to treatment were classified in accordance with the criteria of the Japan Esophageal Society. Briefly, the viability of residual tumor cells was assessed as follows: Grade 0, no necrosis, cellular or structural changes evident; grade 1a, necrosis or tumor comprising less than one-third of lesion, or only cellular or structural changes present in varying amounts; grade 1b, necrosis or tumor comprising no more than two-thirds of lesion; grade 2, necrosis or tumor comprising more than two-thirds of lesion with some viable tumor cells remaining; grade 3, entire lesion necrotic or replaced by fibrosis with or without granulomatous changes (no viable tumor cells seen).

Follow-up. The patients were followed-up at our clinic at least every 3 months. All patients were followed up for more than 24 months, the median follow-up from starting chemotherapy to death or last visit being 33.2 months.

Statistical analysis. Categorical analysis of variables was performed using either the Chi-squared or Fisher's exact test, as appropriate. Continuous data were compared with the Mann-Whitney *U*-test. Survival curves were plotted according to the Kaplan-Meier method and any differences were analyzed using the log-rank test. Multivariate analysis was performed using logistic regression. Differences were considered to be significant when the *p*-value was less than 0.05. All statistical analyses were carried out using R software (version 3.3.1).

Results

Characteristics of patients. The mean patient age was 64.6 years. There were 40 men and five women (ratio 8:1). The predominant histological type was squamous cell carcinoma (n=43), the remaining two tumors were adenocarcinomas. Twenty-one tumors were located in the mid-thoracic, 14 in the lower, and 10 in the upper thoracic esophagus. Most tumors had invaded to the adventitia or beyond (T3 or T4a) and lymph node metastases were detected in 39 patients (86.7%). Clinical stages were as follows: seven stage II, 37 stage III, and one stage IV.

Clinical response to DCF therapy. CR, PR, SD, and PD were achieved in two (4.4%), 32 (71.1%), nine (20%), and two (4.4%) cases, respectively. The clinical response rate (cRR; CR plus PR) was 75.6% and the disease control rate (DCR; CR, PR, and SD) 95.6%.

Relationship between clinical response to DCF therapy and type of curative therapy. Patient characteristics according to curative therapy received are shown in Table

I. Age, sex, tumor location, depth of tumor invasion, nodal status, and tumor stage did not differ between the three treatment groups. The relationship between clinical responses after induction chemotherapy and curative therapy received were as follows: CR and PR occurred in one (11.1%) and eight (88.9%) patients, respectively, in the S-CRT group. PR, SD, and PD occurred in 25 (73.5%), eight (23.5%), and one (2.9%) patient, respectively, in the Surgery group. SD and PD each occurred in one patient in the R-CRT group. The responses rates in the curative therapy groups were 100%, 73.5%, and 0%, respectively. Clinical response was significantly related to type of curative therapy ($p < 0.0001$).

Outcomes after curative therapy. Nine patients in the S-CRT group achieved CR, whereas both patients in the R-CRT group had PD. Pathology-assessed outcomes in the 34 patients in the Surgery group were: Grade 0: 1, grade 1a: 23, grade 1b: 3, grade 2: 3, and grade 3: 4. Twenty-five patients had no residual tumor (R0) (73.5%), six had suspicion of residual tumor or microscopic residual tumor (R1) (17.6%), and three macroscopic residual tumor (8.8%).

Survival. The overall survival (OS) and disease-free survival (DFS) of the 45 patients are shown in Figure 1. Three-year OS was 53.6% and 3-year DFS 42.2%. OS and DFS according to curative therapy are shown in Figure 2. In the S-CRT group, 3-year OS was 77.8%, whereas 3-year DFS was 66.7%. In the Surgery group, 3-year OS was 46.1% and 3-year DFS was 38.2%. The two patients in the R-CRT group died within 1 year.

Factors affecting recurrence within 1 year and death within 2 years in the whole patient cohort. Adverse prognostic factors are summarized in Table II. Clinical lymph node metastases $\geq N2$, clinical stage $\geq III B$, and high SUV_{max} after induction DCF therapy were found to be significantly associated with recurrence within 1 year and death within 2 years. Small decreases in SUV_{max} from pre- to post-induction DCF therapy were also associated with poor prognosis. However, none of these were independent prognostic factors according to multivariate logistic regression (data not shown).

Factors affecting recurrence within 1 year and death within 2 years in patients underwent esophagectomy. Adverse prognostic factors in patients who underwent esophagectomy are summarized in Table III. Clinical lymph node metastases $\geq N2$, clinical stage $III B$ or higher, and post-chemotherapy SUV_{max} affected recurrence within 1 year and death within 2 years in this group. However, these factors were not independent prognostic factors according to multivariate logistic regression (data not shown).

Table I. Patients characteristics according to type of curative therapy received.

Factor	S-CRT group (n=9)	Surgery group (n=34)	R-CRT group (n=2)	p-Value
Age, years	68.2±5.9	64±10.3	62.0±2.0	NS
Gender				0.2577
Male	9	30	1	
Female	0	4	1	
Location				0.1658
Upper	4	6	0	
Middle	3	16	2	
Lower	2	12	0	
Depth of tumor invasion				0.8203
T1b	0	1	0	
2	0	1	0	
3	2	27	1	
4a	7	5	1	
Lymph node metastasis				0.3215
N0	1	5	0	
1	5	12	0	
2	2	12	0	
3	1	5	2	
Stage				0.2651
II	1	6	0	
III	7	28	2	
IV	1	0	0	

S-CRT: Sensitive-chemoradiotherapy; R-CRT: resistant-chemoradiotherapy; NS: not significant.

Discussion

DCF is currently used to treat patients with advanced esophageal cancer and is reportedly very effective (23, 24). However, it has a high incidence of adverse events (15, 25). Therefore, administration should be avoided in patients in whom it will likely be ineffective. We therefore investigated possible adverse prognostic factors associated with induction DCF therapy in this series.

Neoadjuvant chemotherapy followed by esophagectomy is currently the mainstay of treatment for stage II and III esophageal cancer (13). However, esophagectomy for advanced esophageal cancer is very invasive and has a high incidence of postoperative morbidity and mortality (26, 27), thus quality of life after surgery may be poor (28). CRT is the second therapeutic modality to consider for resectable esophageal cancer (12). Although the quality of life after chemoradiotherapy varies, organ preservation is the greatest advantage over esophagectomy provided CR is achieved. At our Institution, curative therapy (esophagectomy or chemoradiotherapy) is selected according to the clinical effect of induction chemotherapy. We consider FDG-PET findings to be a useful aid in making therapy decisions (21). In this study, the 3-years OS for the whole cohort was

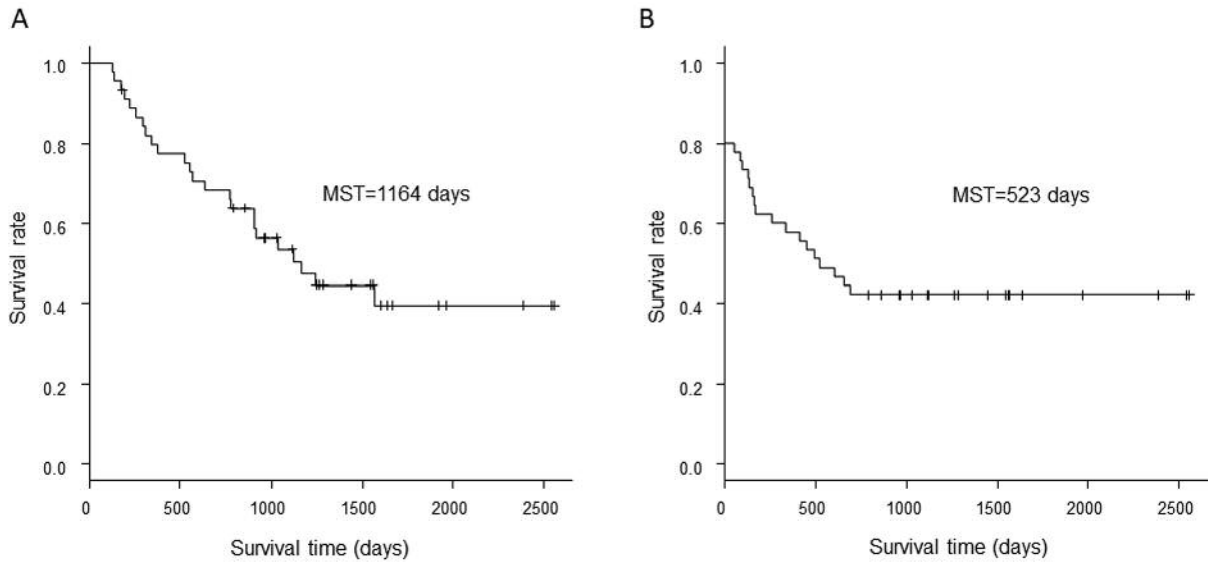


Figure 1. Survival curves after induction chemotherapy with docetaxel, cisplatin, 5-fluorouracil. A: Overall survival of the 45 patients. B: Disease-free survival. MST: Median survival time.

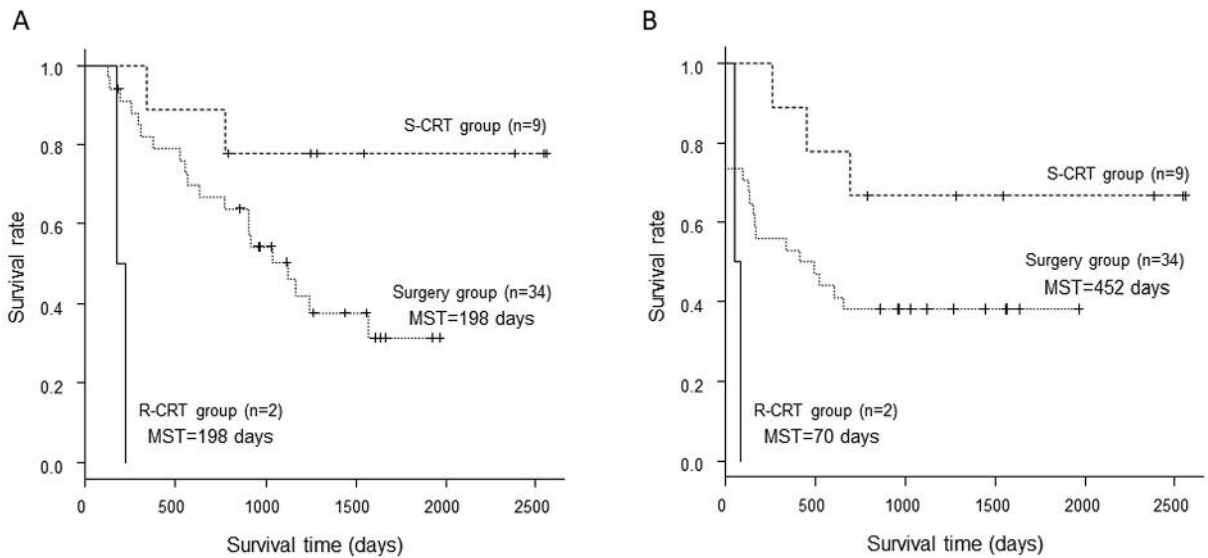


Figure 2. Survival curves according to curative therapies received. A: Overall survival of the 45 patients ($p < 0.0001$). B: Disease-free survival ($p = 0.0142$). MST: Median survival time, NA: not applicable.

53.6%. Given that this included 15 patients with stage IIIC and IV disease, we consider this result acceptable. Survival of the nine patients who underwent CRT after being identified as chemo-responders was significantly superior to that of the patients who underwent surgery. Thus, selection of radical therapy according to response to induction DCF therapy is a useful guide to individualizing treatment.

We found that clinical lymph node metastases N2 or higher, stage IIIB or higher, and higher SUV_{max} after induction DCF therapy were associated with recurrence within 1 year. Moreover, these attributes were associated with death within 2 years, as were small decreases in SUV_{max} .

Clinical evidence of lymph node metastases has been accepted as a definitive prognostic factor for esophageal

Table II. Factors affecting recurrence within 1 year and death within 2 years in the whole patient cohort.

Factor	Relapse within 1 year			Death within 2 years		
	No (n=26)	Yes (n=19)	<i>p</i> -Value	No (n=30)	Yes (n=15)	<i>p</i> -Value
Age, years	65.7	62.9	0.2645	64.6	64.3	0.9110
Gender, n			0.9150			0.7373
Male	23	17		27	13	
Female	3	2		3	2	
Location, n			0.9447			0.5698
Upper	6	4		8	2	
Middle	11	9		13	7	
Lower	9	6		9	6	
Depth of tumor invasion			0.4995			0.7827
1b	0	1		1	0	
2	1	0		1	0	
3	21	14		23	12	
4a	4	4		5	3	
Lymph node metastasis, n			0.0094			0.0010
0	6	0		6	0	
1	12	4		15	1	
2	6	10		6	10	
3	2	5		3	4	
Stage, n			0.0030			0.0193
IIA	6	0		6	0	
IIB	0	1		1	0	
IIIA	10	1		10	1	
IIIB	3	9		4	8	
IIIC	6	8		8	6	
IV	1	0		1	0	
Tumor response, n			0.3274			0.0906
CR	1	0		1	0	
PR	21	12		25	8	
SD	3	6		3	6	
PD	1	1		1	1	
Rate of SUV _{max} decrease, %	63.1	48.3	0.2281	65.2	40.1	0.0465
SUV _{max} after ICT	5.1	8.1	0.0421	4.6	9.7	0.0036

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; ICT: induction chemotherapy; SUV_{max}: maximum standardized uptake value.

cancer (29). In this study, lymph node status before induction chemotherapy was associated with recurrence and prognosis. Patients with many metastatic lymph nodes tended to still have detectable lymph node metastases after two courses of induction chemotherapy (data not shown). Yasuda *et al.* reported that lymph node status according to FDG-PET after neoadjuvant chemotherapy, not the effects on the primary tumor, is a critical criterion for evaluating prognosis (30). Even after DCF therapy, it seems that multiple lymph node metastases do not completely resolve; this may be linked with disease recurrence after curative treatments and poor prognosis.

In this series, 34 out of 45 patients (75.6%) underwent esophagectomy and relapse occurred within 1 year in 16 of

them. Clinical lymph node metastases N2 or higher, stage IIIB or higher, and high SUV_{max} after induction DCF therapy were associated with recurrence and death.

Our findings indicate that two courses of DCF therapy is insufficient for patients with lymph node metastases N2 or higher and stage IIIB or higher, who clearly require more potent therapy. The JCOG1109, NExT study is currently in progress in Japan (31). This is a three-armed, randomized, controlled trial is designed to assess the superiority of preoperative DCF and of CRT with CF over CF alone for OS in patients with locally advanced esophageal cancer. Three courses of DCF therapy at 3-week intervals and CRT with CF may prove to be more effective. DCF-RT is reportedly a promising therapy for

Table III. Factors affecting recurrence within 1 year and death within 2 years in patients who underwent esophagectomy.

Factor	Relapse within 1 year			Death within 2 years		
	No (n=18)	Yes (n=16)	p-Value	No (n=22)	Yes (n=12)	p-Value
Age, years	65.2	62.6	0.4037	63.8	64.3	0.8747
Gender, n			0.3467			0.6465
Male	15	15		19	11	
Female	3	1		3	1	
Location, n			0.5666			0.8445
Upper	2	4		4	2	
Middle	9	7		11	5	
Lower	7	5		7	5	
Depth of tumor invasion, n			0.4892			0.7589
1b	0	1		1	0	
2	1	0		1	0	
3	15	12		17	10	
4a	2	3		3	2	
Lymph node metastasis, n			0.0239			0.0019
0	5	0		5	0	
1	8	4		11	1	
2	3	9		3	9	
3	2	3		3	2	
Stage, n			0.0030			0.0246
IIA	5	0		5	0	
IIB	0	1		1	0	
IIIA	8	1		8	1	
IIIB	2	9		3	7	
IIIC	3	8		5	4	
Tumor response, n			0.4172			0.1556
PR	14	11		18	7	
SD	3	5		3	5	
PD	1	0		1	0	
Rate of SUV _{max} decrease, %	53.1	52.4	0.9618	57.8	43.4	0.3351
SUV _{max} after ICT	6.6	7.2	0.7296	5.7	9	0.0374

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; ICT: induction chemotherapy; SUV_{max}: maximum standardized uptake value.

advanced esophageal cancer (32). These more potent therapies and new agents such as immune checkpoint inhibitors administered as induction therapy may achieve better outcomes (33).

A previous study found that pre-chemotherapy FDG uptake by PET is not a significant predictor of response (34). However, low SUV or large decreases in SUV after chemotherapy are reportedly predictors of response (35). In the present study, high SUV and small decreases in SUV after two courses of DCF were found to be useful for predicting disease recurrence and death. Thus, additional therapy (*e.g.* CRT or additional courses of DCF) should be considered for such patients.

In conclusion, two courses of induction DCF therapy and subsequent esophagectomy and CRT may be ineffective in patients with esophageal cancer and clinical

lymph node metastases N2 or higher and stage IIIB or higher. Stronger multimodality therapy should be considered for such patients. Moreover, early disease relapse and death are of deep concern in patients with small decreases in SUV on FDG-PET after DCF therapy. Additional therapy should also be considered for these patients.

Conflicts of Interest and Funding

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