

Prognostic Factors of Metastatic or Recurrent Esophageal Squamous Cell Carcinoma in Patients Receiving Three-drug Combination Chemotherapy

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Abstract. *Background:* Three-drug combination therapy based on cisplatin/fluorouracil might improve treatment efficacy for metastatic esophageal squamous cell carcinoma (ESCC), but at the risk of increasing toxicity. The study sought to identify factors associated with outcomes of metastatic ESCC in patients who were treated with three-drug combinations. *Patients and Methods:* One-hundred and thirteen patients with metastatic or recurrent ESCC who were treated with cisplatin/fluorouracil-based three-drug combination during 2000-2009 were studied. The prognostic impact of clinicopathological characteristics were evaluated by Cox proportional hazard regression analyses. *Results:* The third chemotherapeutic agents comprised of paclitaxel, docetaxel, and methotrexate in 76 (67%), 13 (12%), and 24 (21%) of patients, respectively. The overall response rate was 41%. The median overall survival (OS) was 8.5 months. Results of the Cox proportional hazard regression models showed that age ≥ 65 years, Eastern Cooperative Oncology Group performance status of 0 and 1, lymph node-only metastasis and baseline white blood cell (WBC) count $\leq 10,000/\text{mm}^3$ were significant prognostic factors for better OS. The OS curves were significantly separated by risk groups comprising of age, metastasis status and WBC count as risk factors. *Conclusion:* The identification of prognostic factors could facilitate for future design of randomized studies on the efficacy of three-drug combinations for metastatic ESCC.

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Esophageal cancer is one of the most common types of gastrointestinal cancers worldwide. Histologically, adenocarcinoma and squamous cell carcinoma are the predominant subtypes of esophageal cancer and each type responds to treatment differently (1- 4). Unlike most Western countries (5, 6), esophageal squamous cell carcinoma (ESCC) remains the most common histological subtype of esophageal cancer in Asia (7-9).

The current standard treatment for metastatic or recurrent ESCC is cisplatin combined with fluorouracil (5-FU), leading to a median survival of only six months (10, 11). More effective treatment options are, therefore, desperately needed. Although the addition of a third drug to cisplatin and 5-FU has shown survival improvement in phase III trials of metastatic gastric and gastroesophageal adenocarcinoma (12, 13), no data have proven a definite survival benefit of cisplatin-5-FU-based three-drug combinations for metastatic or recurrent ESCC at present. Trials addressing this issue are all small-scale phase II studies and with variable results.

We have previously reported that addition of methotrexate to the cisplatin and 5-FU backbone was active and with low toxicity (14). We also reported that paclitaxel plus cisplatin and 5-FU produced high activity and acceptable toxicity (15). The objective response rate and overall survival (OS) time with the methotrexate/cisplatin/5-FU and paclitaxel/cisplatin/5-FU regimens was 28% and 5 months, and 39% and 8.9 months, respectively.

Knowledge of prognostic factors from patients with metastatic or recurrent ESCC treated by cisplatin/5-FU-based three-drug combinations will facilitate better interpretation of the variable results of previously reported phase II trials. It will also add to proper trial design and selection of patient treatment. However, the prognostic factors for metastatic or recurrent ESCC have yet to be established.

To explore the potential usefulness of these cisplatin/5-FU-based regimens and identify patient groups that might

Table I. Summary of the schedule and dosage of the three-drug combination regimens.

Third drug		Cisplatin	5-FU	Cycle
Methotrexate	40 mg/m ² D1, 8, 15	35 mg/m ² 24 h D2, 9, 16	2600 mg/m ² 24 h D2, 9, 16	Every 28 days
Paclitaxel	35 mg/m ² D1, 4, 8, 11	20 mg/m ² 2 h D2, 5, 9, 12	2000 mg/m ² 24 h D5, 12	Every 21 days
Docetaxel	30-35 mg/m ² D1, 8	30-35 mg/m ² 2 h D1, 8	2000 mg/m ² 24 h D1, 8	Every 21 days

5-FU: 5-Fluorouracil.

benefit from this treatment, we examined long-term follow-up data from 113 patients treated in two sequential phase II studies and outside clinical trials using taxane/cisplatin/5-FU.

Patients and Methods

Patient population. From January 2000 to December 2009, a total of 240 patients with metastatic or recurrent ESCC were treated with chemotherapy as first-line treatment at National Taiwan University Hospital, Taipei, Taiwan. Among them, 127 patients were treated with cisplatin/5-FU doublets and 113 patients with cisplatin/5-FU-based triplets. The latter group of patients became the cohort of the current report. There were three different patient subgroups in the study cohort: (i) those treated with methotrexate/cisplatin/5-FU combination and enrolled in a prospective phase II trial (14), (ii) those treated with paclitaxel/cisplatin/5-FU combination and enrolled in a prospective phase II trial (15), and (iii) those who were not enrolled in clinical trials but were treated with either paclitaxel or docetaxel/cisplatin/5-FU combinations. For subgroup (i) and subgroup (ii), the inclusion/exclusion criteria of enrolling patients in the two phase II trials have been reported (14, 15). For subgroup (iii), patients were selected for treatment with three-drug combinations according to the criteria which were used for the prior two phase II trials. In brief, patients were required to have adequate bone marrow reserves (defined as minimum white blood cell (WBC) count of 4,000/mm³ and platelet count of 10,000/mm³), adequate liver function (aspartate transaminase and alanine transaminase 3.5-times the upper limits of reference values, and total bilirubin 2.0 mg/dl), and adequate kidney function (serum creatinine 1.5 mg/dl), and fair performance status [Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0-2].

Three-drug combination therapy comprised of cisplatin and 5-FU plus methotrexate, paclitaxel, or docetaxel. The schedule and dosage details of the regimens are summarized in Table I. In brief, when methotrexate was the third drug, methotrexate, cisplatin and 5-FU were administered weekly for three weeks every 28 days; when paclitaxel was the third drug, paclitaxel and cisplatin were administered twice a week and 5-FU was administered weekly for two weeks every 21 days; when docetaxel was the third drug, docetaxel, cisplatin and 5-FU were administered weekly for two weeks every 21 days. Appropriate medications were given before administration of the three chemotherapeutic agents and appropriate antiemetics were given before administration of cisplatin. Treatment was continued until disease progression or intolerable toxicities occur.

Survival and response analyses. OS was calculated from the date of the start of three-drug combination chemotherapy for metastatic or

recurrent ESCC to the date of death or the last follow-up date. Survival data were available through February 2011. After a median follow-up of 9.7 months (range=3.5 to 27.0 months), only nine patients (8%) were still alive. The potential prognostic factors were gender, age, ECOG PS, recurrent or *de novo* metastatic status, extent of metastasis (lymph node-only vs. visceral), history of radiotherapy to the primary site, baseline hemoglobin level, WBC count, and platelet count.

The Kaplan-Meier method and log-rank test were used to estimate and compare OS among the three groups as previously reported (16). The pre-treatment laboratory parameters were dichotomized into categorical variables, namely hemoglobin ≥ 10.0 g/dl vs. < 10.0 g/dl; WBC count $\geq 10,000/\text{mm}^3$ vs. $< 10,000/\text{mm}^3$; and platelet count $\geq 400,000/\text{mm}^3$ vs. $< 400,000/\text{mm}^3$. In order to determine the relative contribution of various factors to OS, univariate and multivariate analyses were carried out *via* log-rank test and Cox proportional-hazards analysis (17), respectively.

Response Evaluation Criteria in Solid Tumors 1.0 (RECIST 1.0) (18) and World Health Organization (WHO) criteria (19) were used to evaluate tumor response. All tests were two-tailed and a *p*-value of < 0.05 was considered to indicate statistical significance. All statistical analyses were conducted with SPSS version 17.0 (SPSS, Chicago, IL, USA).

Results

Characteristics of the study population. The study group comprised of 113 patients with metastatic or recurrent ESCC. Patient and clinicopathological characteristics are shown in Table II. The majority of patients were male (94%), had visceral metastases (65%), and had an ECOG PS score of 0 or 1 (82%). All patients received cisplatin and 5-FU plus one of the three additional chemotherapeutic agents as first-line chemotherapy. The third chemotherapeutic agent included paclitaxel in 76 (67%), docetaxel in 13 (12%), and methotrexate in 24 (21%) patients.

Median OS was 8.5 [95% confidence interval (CI)=7.5-9.5] months. The one-, two- and five-year survival rates were 24.8%, 5.3%, and 0%, respectively. The survival curve of the whole patient cohort is shown in Figure 1. The median OS was 11.5 (95% CI=2.7-20.3) months, 8.9 (95% CI=8.1-9.7) months, and 5.6 (95% CI 4.0-6.4) months for patients who received docetaxel, paclitaxel and methotrexate, respectively. The median OS was 7.5 (95% CI=5.7-9.3) months for patients enrolled into prospective phase II trials, and the median OS was 9.2 months (95% CI=7.6-10.8) for patients

Table II. Demographic and clinicopathological characteristics of the 113 patients in this study.

Variable	Patient number (%)
Gender	
Male	106 (93.8)
Female	7 (6.2)
Age (years)	
<65	83 (73.5)
≥65	30 (26.5)
ECOG PS	
0	21 (19.1)
1	72 (65.5)
2	16 (14.5)
3	1 (0.9)
Metastatic pattern	
<i>De novo</i>	60 (53.1)
Recurrent	53 (46.9)
Lymph node only metastasis ^{a,b}	
Present	73 (65.2)
Absent	39 (34.8)
RT to primary site	
Yes	40 (35.4)
No	73 (64.6)
Third chemotherapy drug with cisplatin and 5-fluorouracil	
Docetaxel	13 (11.5)
Paclitaxel	76 (67.3)
Methotrexate	24 (21.2)

ECOG PS: Eastern Cooperative Oncology Group performance status, RT: radiotherapy. ^aLymph node-only metastasis included patients who only had either regional, supraclavicular, cervical, celiac or para-aortic lymph node recurrence or metastasis. ^bOne patient had only localized recurrence without lymph node or visceral involvement.

who were not enrolled into clinical trials. The survival of the patients who were enrolled in clinical trials and those who were not enrolled in clinical trials was not statistically different ($p=0.117$).

Univariate and multivariate analyses of potential prognostic factors. Table III is a summary of univariate analyses of clinical variables. There were no significant prognostic factors. Nonetheless, there was a trend for statistical significance for variables such as age, lymph node-only metastasis, ECOG PS, hemoglobin, and WBC count.

All variables with a p -value less than 0.15 in the univariate analyses were included in the multivariate analysis model. As shown in Table IV, advanced age [hazard ratio (HR)=0.44, 95% CI=0.27-0.74, $p=0.002$], ECOG PS (HR=0.55, 95% CI=0.31-0.97, $p=0.039$), and lymph node-only metastasis (HR=0.60, 95% CI=0.38-0.93, $p=0.023$) became significantly good prognosticators. On the other hand, WBC count higher than 10,000/mm³ became a significant poor prognosticator

Table III. Univariate analyses of prognostic factors of survival.

Characteristic	Categories	Median survival (months)	p -Value
Gender	Male	8.0	0.236
	Female	12.5	
Age (years)	≥65	10.1	0.053
	<65	8.0	
ECOG PS	0 and 1	8.9	0.081
	2 and 3	6.0	
Metastatic pattern	Recurrent	8.7	0.365
	<i>De novo</i>	8.5	
Lymph node-only metastasis	Yes	9.2	0.081
	No	8.0	
RT to primary site	Yes	8.7	0.406
	No	8.1	
Hemoglobin (g/dl)	≥10	9.0	0.056
	<10	7.0	
WBC (mm ³)	≥10,000	7.5	0.141
	<10,000	9.0	
Platelets (mm ³)	≥400,000	8.7	0.710
	<400,000	8.1	

ECOG PS: Eastern Cooperative Oncology Group performance status, RT: radiotherapy, WBC: white blood cell.

Table IV. Prognostic factors for overall survival in the Cox proportional hazard model.

Variable	Hazard ratio	95% CI	p -Value
Age ≥65 years	0.44	0.27-0.74	0.002*
ECOG PS 0 or 1	0.55	0.31-0.97	0.039*
Lymph node-only metastasis	0.60	0.38-0.93	0.023 *
Hemoglobin ≥10 g/dl	0.82	0.47-1.45	0.499
WBC ≥10,000/mm ³	2.13	1.33-3.41	0.002*

CI: Confidence interval, ECOG PS: Eastern Cooperative Oncology Group performance status, WBC: white blood cell. * p -Value less than 0.05.

(HR=2.13, 95% CI=1.33-3.41, $p=0.002$). Hemoglobin remained a non-significant factor.

Prognostic modelling by risk factors. Since more than 80% of patients were of ECOG 0 or 1 status, we chose pre-treatment patient characteristics that are more evenly distributed (age, lymph node or visceral metastasis, and WBC count), as risk factors to see how survival was influenced. Patients were stratified into three groups: zero or one risk factor, two risk factors, and three risk factors, and the median survival was 11.0, 8.0, and 3.9 months, respectively ($p=0.001$, Figure 2). Cox regression analyses showed that the effect of treatment (taxanes *vs.* non-taxane) did not significantly influence the OS in each risk group (p for interaction=0.69).

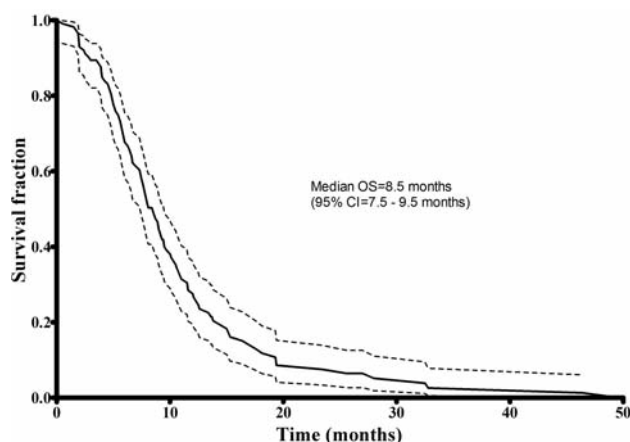


Figure 1. Kaplan-Meier survival curve of overall survival (OS) of the study cohort with 95% confidence intervals (CI).

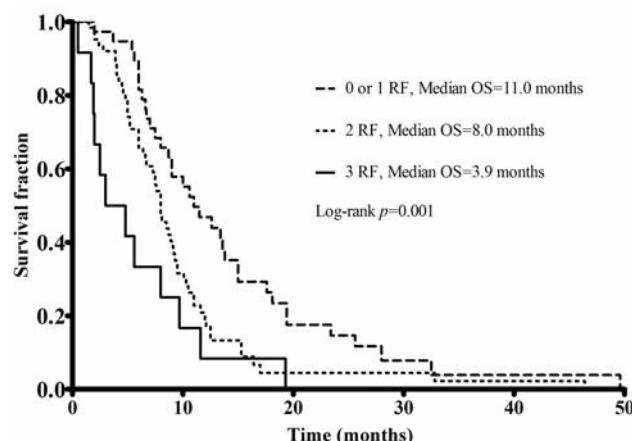


Figure 2. Kaplan-Meier overall survival (OS) curves of patients with different numbers of risk factors (RF). The risk factors are age younger than 65 years, visceral metastasis, and white blood cell count over 10,000/mm³.

No clinical characteristics associated with tumor response. Response to three-drug combination treatment could not be evaluated in five patients. The overall response rate among the 108 patients for whom response could be evaluated was 41% (95% CI=35-50%). The response rate among patients who received taxanes and methotrexate was 42% (95% CI=31-52%) and 35% (95% CI=12-58%), respectively, with a non-significant difference ($p=0.62$). Among the patients who responded to first-line chemotherapy, the median OS for those treated with taxanes and methotrexate as the third drug were 11.0 and 11.6 months, respectively. In multivariate logistic analysis, none of the clinical characteristics significantly predicted a clinical response after three-drug combination therapy (data not shown).

Discussion

Prognostic factors are critical to the management of patients and in designing appropriate clinical trials. In this study, we evaluated the prognostic factors for survival in a cohort of patients with recurrent and metastatic ESCC who had been treated with cisplatin/5-FU-based three-drug combination regimens. This analysis identified age ≥ 65 years, ECOG PS 0 or 1, lymph node-only metastasis, and WBC count $<10,000/\text{mm}^3$ as independent prognostic factors for better OS. To the best of our knowledge, this is the largest cohort to date to only include patients with metastatic or recurrent ESCC who were all treated by three-drug combination chemotherapy as first-line treatment.

Two of the prognostic factors, lymph node-only metastasis and PS, were similar with a previous study (20). In the present study, our prognostic model based on age, extent of

metastasis, and WBC count was able to identify three risk groups with significantly different median OS. The median OS for patients with zero or one, two, and three risk factors were 11.0, 8.0, and 3.9 months, respectively. However, as compared with Polee *et al.* (20), two of the pre-treatment clinical variables were different (age and WBC count), suggesting that metastatic or recurrent ESCC may need to be managed differently, as opposed to treating esophageal cancer homogenously.

In the present study, the OS for patients with a clinical response after three-drug combination therapy were numerically similar despite the different third-drug component, echoing the finding of others (20). However, none of the clinical pre-treatment clinicopathological characteristics were able to predict response to three-drug combination treatment. Future work could focus on the identification of molecular markers predictive of response to three-drug combination chemotherapy.

The toxicities and side-effects of paclitaxel and methotrexate as the third drug combination treatment have been reported elsewhere (14, 15). The most common grade 3 or 4 non-hematological toxicity in patients treated by paclitaxel as the third drug was diarrhea (14.2% of all patients) and hematological grade 3 or 4 toxicity for leukopenia, neutropenia, and thrombocytopenia were 29.4%, 36.8%, and 5.8%, respectively. In patients treated with methotrexate as the third drug, the most common grade 3 or 4 non-hematological toxicity was mucositis (27% of all patients). Hematological grade 3 or 4 toxicities were 46% and 54% for leukopenia and thrombocytopenia, respectively.

We were surprised to find advanced age to be a good prognosticator. This result implies that elderly patients

should not be totally ruled out in future trials examining the efficacy of three-drug combination therapy of metastatic or recurrent ESCC. However, it is also possible that the tumor biology of ESCC in patients of advanced age differs from that in younger patients with the disease. For example, certain studies have shown that the frequency of loss of the deleted in esophageal cancer 1 gene (*DEC1*), an esophageal tumor-suppressor gene located on the long arm of chromosome 9 (9q), differs between younger and older patients with ESCC, indicating that the *DEC1* gene might play a role in the differences in response to treatment between young and old patients with ESCC (21-23). Furthermore, Okuda *et al.* demonstrated that the frequency of mutations in the tumor-suppressor gene *p53* also differed significantly between younger and older patients with ESCC, with the prognosis favoring patients who are older (24). Studies on the differences in molecular biological characteristics between younger and older patients with ESCC are needed to determine whether these factors play a role in response to treatment.

The current study has several limitations. Firstly, the study was a retrospective analysis based on patients enrolled in two prospective phase II studies and those treated outside a clinical trial setting. However, in order to minimize the heterogeneity of these patients, we included only patients who had been enrolled and treated according to very similar inclusion and exclusion criteria. The second limitation is that the majority of patients had good PS, which may stem from two-thirds of our patients being participants of clinical trials. Although this may indicate a selection bias, the data obtained from clinical trials were more reliable than medical records collected retrospectively. Lastly, the status of second-line treatment in each treatment arm as the accessibility of taxanes may not be as free as methotrexate as second-line treatment—may impact the interpretation of our study result. Nonetheless, a recent review by Thallinger *et al.* on second-line treatments of esophageal cancer suggested that the second-line treatments had low response rates and variable efficacy (25). Moreover, analyses gathered from multiple first-line esophageal cancer clinical trials had suggested that the drug of second-line treatment is not a prognostic factor for OS (26). Therefore, we believe the impact of second-line treatments on OS is limited in our study.

In summary, three-drug combination chemotherapy is feasible in selected patients with metastatic or recurrent ESCC. Advanced age is not a poor prognostic factor, whereas leukocytosis and multiple visceral metastases are poor prognostic factors. The prognostic factors identified in our study could facilitate the progress of randomized studies (*e.g.* paclitaxel or docetaxel/cisplatin/5-FU *vs.* cisplatin/5-FU) to provide definitive evidence of the efficacy of three-drug combination chemotherapy regimens as treatment for patients with metastatic or recurrent ESCC.

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