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Analysis on plausible factors related to the prognosis of stage IV esophageal cancer

Chenghui Li, PhD, Zhiqiu Wang, PhD*, Aixiong Duan, PhD, Qian Jiang, PhD

Abstract

To investigate factors related to poor prognosis of patients with stage IV esophageal cancer and to provide some bases on which proper therapeutic schemes could be formulated for stage IV esophageal cancer patients with performance status (PS) score between 0 and 2.

Clinical data of 60 patients with stage IV esophageal cancer were retrospectively analyzed, and the relationships of clinical characteristics and therapeutic methods with patients' prognosis were explored. Univariate analysis on factors possibly affecting the prognosis of patients with stage IV esophageal cancer was performed using Log-rank test, and independent risk factors for the prognosis were estimated in multivariate Cox regression analysis through embracing variables which showed statistical significance in univariate analyses.

According to univariate analysis results, nutritional status, anemia, therapeutic method, esophageal stent, and visceral metastasis were main influencing factors for the prognosis of stage IV esophageal cancer ($P < .05$). While in multivariate Cox regression analysis, visceral metastasis was revealed to be an independent risk factor for poor prognosis in patients with stage IV esophageal cancer.

Visceral metastasis is an independent risk factor for poor prognosis in patients with stage IV esophageal cancer. Optimizing therapeutic modes according to with or without combined visceral metastasis possesses certain clinical significance in prolonging survival time and in improving the quality of life among patients with stage IV esophageal cancer.

Abbreviations: AJCC = American Joint Committee on Cancer, ALB = albumin, BMI = body mass index, CT = computed tomography, DF = cisplatin+fluorouracil, ECOG = Eastern Cooperative Oncology Group, Hb = hemoglobin, OS = overall survival, PET = positron emission tomography, PNI = prognostic nutritional index, PS = performance status, PTV = planning target volume, TLC = total lymphocyte count, TNM = tumor node metastasis, TP = cisplatin+paclitaxel, UICC = Union for International Cancer Control.

Keywords: esophageal stent, prognostic nutritional index, stage IV esophageal cancer

1. Introduction

Esophageal cancer is a malignancy with strong invasiveness, poor prognosis, and high incidence. Of all its patients, about 35% have entered into advanced stage when they see a doctor, so these cases lose the opportunity to receive radical treatment and thus see unsatisfactory therapeutic effects, with a 5-year survival rate <5%.[1,2] Currently, evidence-based findings are insufficient for treating this malignancy, especially for those in advanced stages. In our research, we collected clinical data of 60 patients with stage IV esophageal cancer to retrospectively analyze the relationship of therapeutic regimens and clinical features with the cancer prognosis.

2. Materials and methods

2.1. Clinical data

Sixty patients with stage IV esophageal cancer receiving initial treatment in our department between January 30, 2013 and January 30, 2018 were collected for this study. Through biopsy for specimens from gastroscopy, the patients were pathologically confirmed as squamous cell carcinoma. Clinical staging was implemented on the basis of findings from endoscopic ultrasonography combined with enhanced computed tomography (CT) or positron emission tomography (PET)/CT, and their Eastern Cooperative Oncology Group (ECOG) score was between 0 and 2. The cases consisted of 36 men and 24 women aged between 50 and 75. Of them, 22 were no >65 years old while the others over this figure. Besides, 26 cases had lesions at neck and upper thoracic sections, and the others showed lesions at mid- and lower-thoracic sections. Before treatment, malnutrition was detected in 36 patients while the figure for anemia was 38. Of all patients, 33 underwent combined regimen of radiotherapy and chemotherapy, and the others only received chemotherapy. Stent installment was operated for 12 cases. And 38 patients simultaneously had visceral metastasis (not including distant nodal metastasis, simple bone metastasis, or cerebral metastasis),

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while the others had none. This study was supported by the Research Ethics Committee of Anqing Hospital Affiliated to Medical University of Anhui. All study subjects signed written informed consents before enrollment.

2.2. Methods

Staging criteria: According to Tumor Node Metastasis (TNM) Classification for esophageal cancer, 8th ed by Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) in 2017,[3] stage IV esophageal cancer contains T4aN1-2M0, T4bNxM0, TxN3M0, and TxNxM1.

2.3. Prognostic nutritional index

Prognostic nutritional index (PNI) is a simple index only containing 2 parameters of peripheral blood, namely serum albumin (ALB) and total lymphocyte count (TLC), and calculated via the following equation: PNI = ALB (g/L) + $5 \times$ TLC (10^9/L). PNI $\geq$45 meant normal nutritional status for patients.[4]

2.4. Diagnostic criteria for anemia

In the light of Chinese clinical practise and therapeutic methods, anemia refers to hemoglobin (Hb) <120 g/L in men and Hb <110 g/L in women.

2.5. Chemotherapy regimen

All of 60 patients received combined chemotherapy for at least 4 cycles, with 23 taking DF (cisplatin+fluorouracil) regimen while 37 bearing TP (cisplatin+paclitaxel) scheme. Specifically, of 9 patients undergoing concurrent chemoradiotherapy, 6 orally took tegafur gimeracil and oteracil potassium during radiotherapy and adopted DF regimen for consolidation chemotherapy; while the other 3 experienced TP regimen weekly during their radiotherapy and accepted TP for consolidation. Of 24 patients facing sequential chemoradiotherapy, 14 encountered TP regimen while the others bore DF scheme. Among those only receiving chemotherapy, 20 had TP and 7 took DF.

2.6. Radiotherapy plan

All of the patients experienced three-dimensional conformal or intensity modulated radiotherapy. Total prescription dose was 54 to 60 Gy, and conventionally divided into 1.8 to 2.0 Gy each time per day, 5 times a week. Relevant requirements were as follows: 95% of planning target volume (PTV) were irradiated through 100% of the above mentioned prescribed dose, with whole lungs V5 $\leq$55% to 60%, V20 $\leq$25% to 30%, V30 $\leq$18%, heart D_{mean} $\leq$30 Gy, and spinal cord D_{max} <45 Gy.

2.7. Observational index

Survival time was calculated during the period between initial chemotherapy or radiotherapy and the end date of follow-up: August 1, 2018. The influences of clinical features and therapy-related factors on prognosis were monitored.

2.8. Statistical method

SPSS 17.0 (SPSS, Inc., Chicago, IL) software was employed for statistical analyses, while Kaplan–Meier method was adopted to calculate overall survival (OS) and to plot survival curves. Log-rank tested *P* values and completed univariate prognosis analysis. And multivariate Cox regression model was applied for prognosis analysis. $P < .05$ stood for the presence of statistical significance in differences.

3. Results

3.1. Univariate analysis

Univariate analysis was conducted for sex, age, lesion location, pretreatment nutritional status, with or without anemia before therapy, anti-tumor therapeutic method, with or without esophageal stent before therapy, and with or without combined visceral metastasis.

Median survival time was compared between men (n = 36) and women (24), and the result showed no significant difference ($P = .074$), indicating sex had no obvious influence on the prognosis of stage IV esophageal cancer.

Among 60 patients, 23 were no >65 years old while 37 exceeded this figure. Comparison on median survival between the 2 groups revealed no significant difference ($P = .242$), suggesting age harbored no substantial influence on the prognosis of stage IV esophageal cancer.

Of 60 patients, 34 had lesions at mid- and lower-thoracic sections while the others at neck and upper thoracic sections. Between these 2 groups, median survival time displayed no statistical difference ($P = .579$), demonstrating the location of primary focus possessed no significant effect on the prognosis of stage IV esophageal cancer.

Before therapy, 60 patients were classified into mulnutrition (n = 36) and normal nutrition (n = 24) groups. According to comparison findings, prognosis was poorer in mulnutritional group than in normal nutrition group, and difference between the 2 groups was statistically significant ($P = .003$).

Pretreatment anemia was observed in 38 patients while the others (n = 22) had no such symptom. The prognosis in anemia group was more miserable than the other group according to their median survival, showing statistical difference between the 2 groups ($P < .001$).

Among the patients, 33 adopted combined regimen of radiotherapy with chemotherapy while the other 27 ones received only chemotherapy. In comparing median survival, combination regimen group exhibited significantly better prognosis than chemotherapy-only group ($P < .001$).

Sixty patients were divided into 2 groups according to with (n = 38) or without (22) visceral metastasis. After comparing their median survival, we saw poorer prognosis for metastasis group than that without metastasis, and the difference was statistically significant ($P < .001$).

Esophageal stent was installed for 12 of our studied patients, while the others had none. According to result from comparing median survival, cases with the stent experienced poorer prognosis than those without the stent, showing statistical difference ($P < .001$).

All of the above findings demonstrated that nutritional status, anemia, therapeutic method, esophageal stent, and visceral metastasis were major factors affecting the prognosis of stage IV esophageal cancer ($P = .003$, $P < .001$, $P < .001$, $P < .001$, $P = .002$, respectively) (Table 1 and Figs. 1–8).

3.2. Multivariate Cox regression model analysis

Multivariate Cox regression analysis embraced all of the 5 elements exhibiting significant influences on prognosis

Table 1

Univariate prognosis analysis.

Item	n	Median survival time	χ^2	P
Gender				
Male	36	9±0.639	3.196	.074
Female	24	9±0.385		
Age				
≤65	23	10±0.378	1.367	.242
>65	37	8±0.433		
Lesion location				
Mid- and lower thoracic	34	8±0.568	0.309	.579
Neck and upper thoracic	26	9±0.257		
Mulnutrition				
No	24	10±0.550	8.621	.003
Yes	36	9±0.269		
Anemia				
No	22	11±0.561	15.34	<.001
Yes	38	8±0.293		
Therapeutic method				
Radiotherapy and chemotherapy	33	10±0.446	17.471	<.001
Chemotherapy	27	8±0.228		
Visceral metastasis				
No	22	10±0.534	15.036	<.001
Yes	38	8±0.254		
Esophageal stent				
No	48	9±0.356	9.623	.002
Yes	12	7±0.385		

in univariate analysis, namely nutritional status, anemia, therapeutic method, esophageal stent, and visceral metastasis. As a result, only visceral metastasis showed statistically significant influence on patients' prognosis ($P=.032$, Table 2).

4. Discussion

Esophageal cancer shows high incidence in China, with >90% of the cases as squamous carcinoma. This malignancy sees relatively poor prognosis, because even invasion into submucosa could lead to lymphatic distant metastasis or widespread skipping metastasis regardless of the cancer stage, owing to abundant lymphoid tissues in esophageal wall.[5] Esophageal cancer mainly attacks people in remote rural regions, with evil dietary habits (like taking moldy, salted, hot, and high-salt foods) as its high risk factors. Restrained to medical conditions, patients in early stage generally ignore their choking when they eat, and when they see a doctor for the first time after developing evident symptoms, about 35% of them have been in stage IV, thus losing the opportunity for radical cure. Besides, most patients would develop mulnutrition due to difficulty in swallowing, and then their constitutions become weak, even unable to suffer systemic chemotherapy, facing extremely short survival time.[1,2]

In this study, we collected clinical data on 60 patients who were diagnosed as stage IV esophageal cancer, and then retrospectively analyzed the relationships of the patients' clinical features and therapeutic methods with their prognosis. In univariate analysis, patients' age, sex, or the location of esophageal lesion exhibited no relationship with prognosis. In comparing patients with and without anemia before therapy, we adopted Kaplan–Meier curve method to calculate OS and to plot survival curves, using Log-rank for testing, and found statistical difference between the 2 groups, indicating anemia acted as a risk factor for poor prognosis in esophageal cancer patients at advanced stage. According to current clinical researches, anemia affects not only radiotherapeutic and chemotherapeutic effects on esophageal cancer patients but also impacts the cases' quality of life and survival time.[6–8]

In recent years, many indexes have been employed to assess nutritional status, like body mass index (BMI), Glasgow

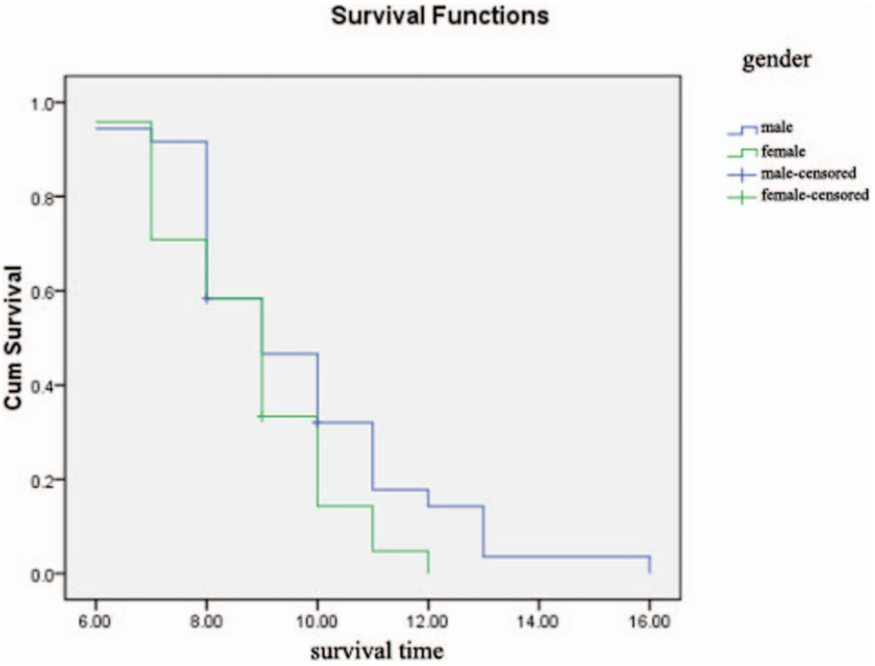

Figure 1. Overall survival curve comparison between different sexes. $P=.074$.

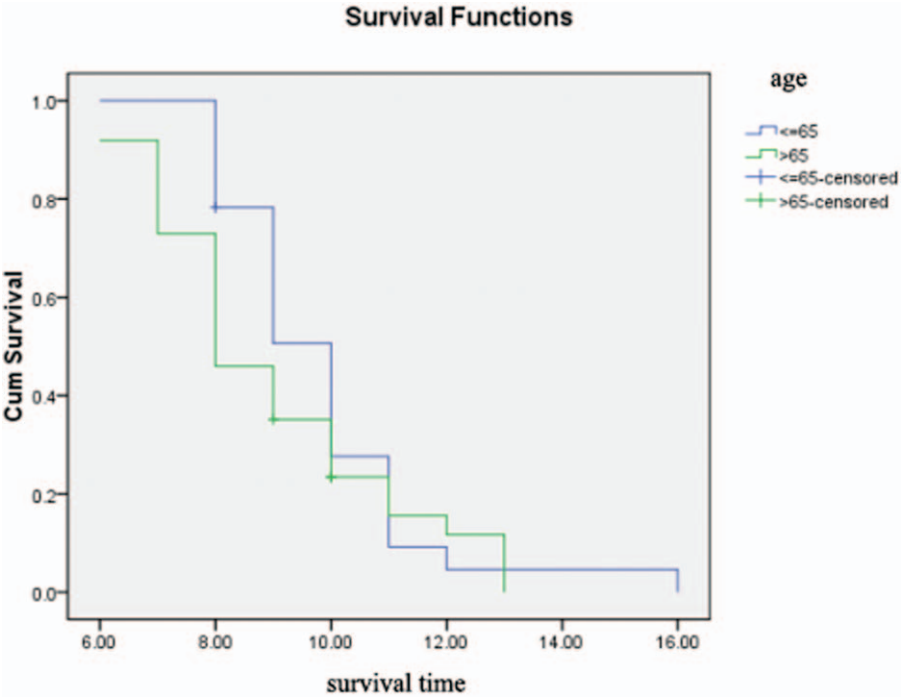

Figure 2. Overall survival curve comparison between different ages. $P = .242$.

prognosis score, and PNI. Among others, PNI represents a relatively mature one in practical application, and offers a simpler and more convenient testing method. Therefore, we employed PNI in this study to evaluate pre-therapy nutritional status for patients with stage IV esophageal cancer. As a result, of total 60 patients, 38 were malnourished while the others well-nourished. For these 2 groups, Kaplan–Meier method was applied to calculate their OS and to establish corresponding survival curves. In Log-rank test, statistical difference was detected between the groups, suggesting malnutrition functioned

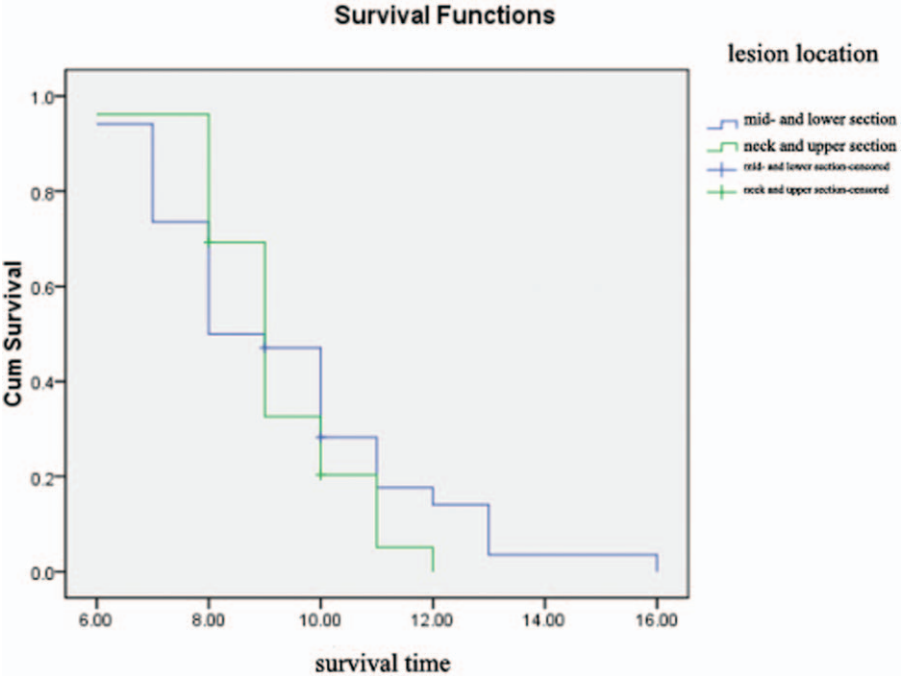

Figure 3. Overall survival curve comparison between different lesion locations. $P = .579$.

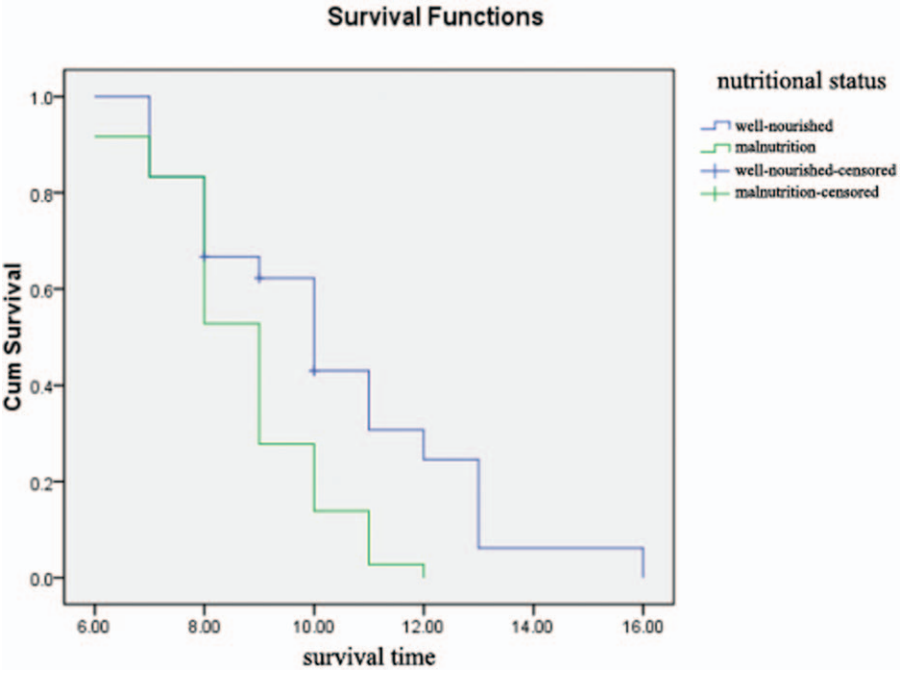

Figure 4. Overall survival curve comparison between different nutritional statuses. $P = .003$.

as a risk factor for poor prognosis among patients with advanced esophageal cancer. Up to now, accumulating documents have confirmed that among esophageal cancer patients, malnutrition significantly increases adverse responses to chemotherapy and is also a trigger of poor prognosis.[4,6,8]

Treatment for stage I esophageal cancer mainly relies on surgery, while for patients with stage II and III cancer, universally accepted approach refers to comprehensively multi-disciplinary mode combining radiotherapy, chemotherapy, and surgery.[9,10] As for cases with stage IV esophageal cancer, whether local

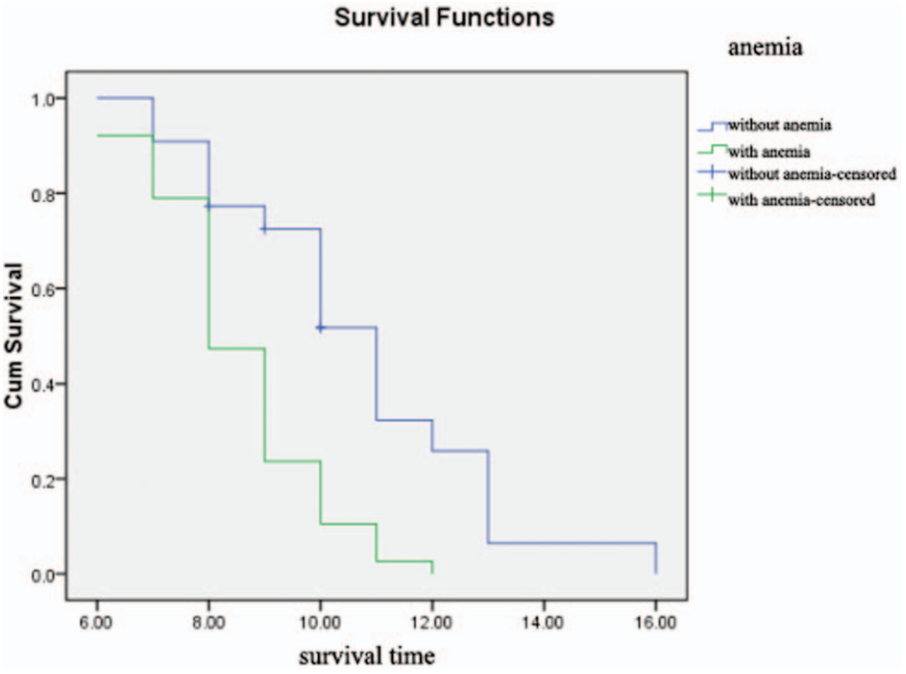

Figure 5. Overall survival curve comparison between with and without anemia. $P < .001$.

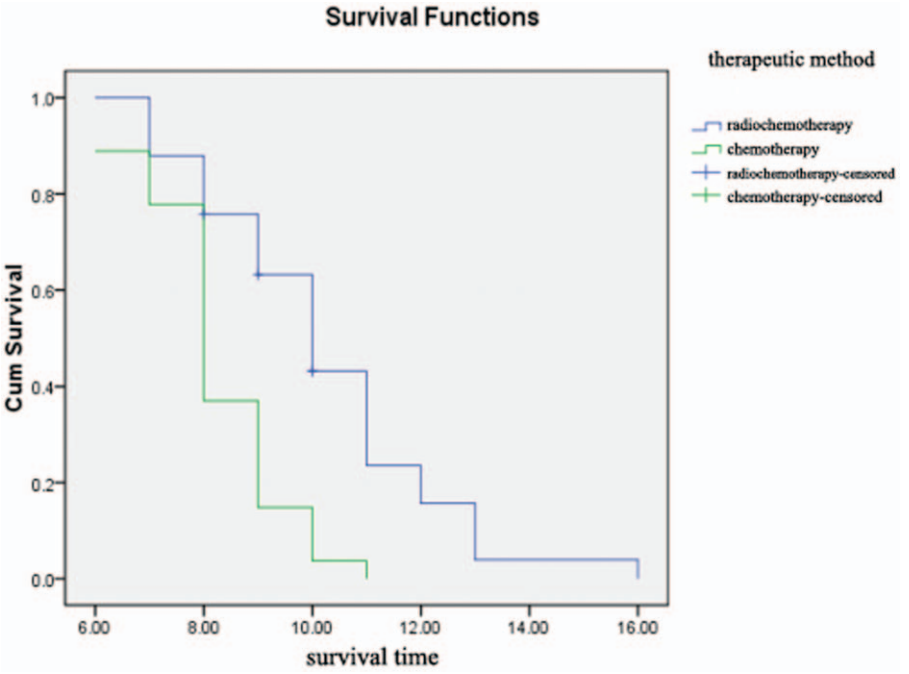

Figure 6. Overall survival curve comparison between different therapeutic methods. $P < .001$.

radiotherapy or esophageal stent should be adopted to alleviate patients' difficulty in eating and whether these applications could prolong patients' survival have been discussed by Lyu et al.[11] In their retrospective research on stage IV esophageal cancer, the scholars compared therapeutic effects between concurrent radiochemotherapy and chemotherapy alone. As a result, median survival time reached 14 months in concurrent radiochemotherapy group and 11 months in chemotherapy-alone group, with statistical difference, manifesting concurrent radiochemotherapy could significantly prolong median survival for patients with stage IV esophageal cancer. Among 60 patients with advanced esophageal cancer in this study, 33 adopted extra radiotherapy for esophageal lesions, and only 9 of them received concurrent radiochemotherapy while the others underwent sequential radiotherapy and chemotherapy. According to corresponding analysis, median survival time reached 10 months among patients

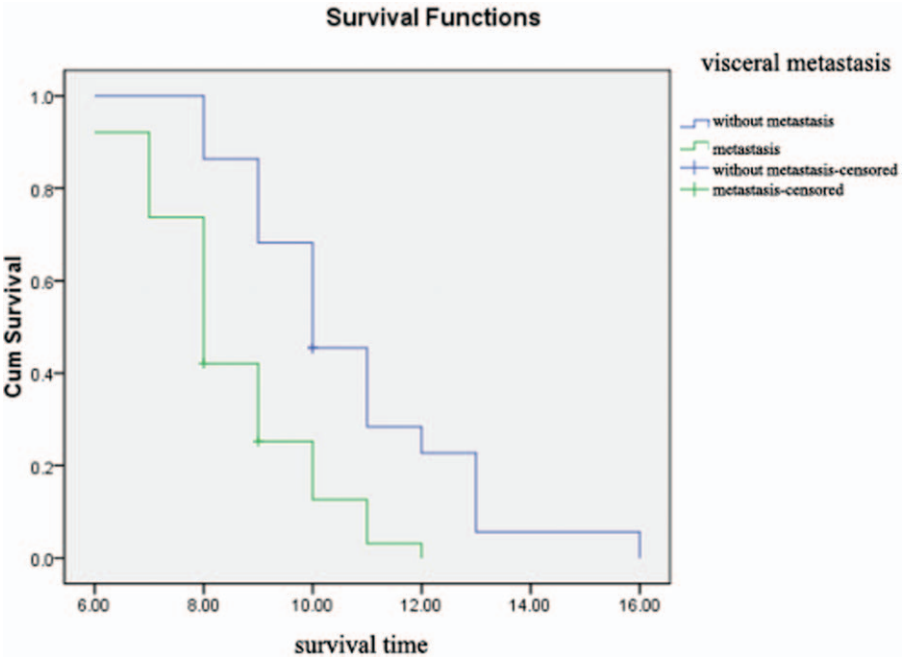

Figure 7. Overall survival curve comparison between with and without visceral metastasis. $P < .001$.

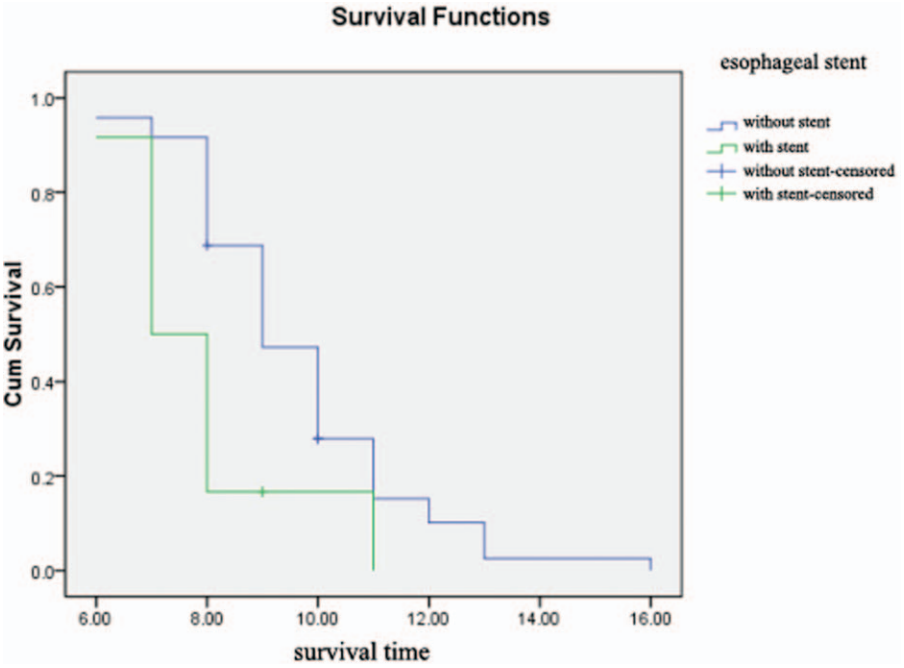

Figure 8. Overall survival curve comparison between with and without esophageal stent. $P = .002$.

experiencing additional radiotherapy, and the figure was merely 8 months in those taking chemotherapy alone, showing statistical difference. Such findings suggested radiotherapy regimen could improve survival time for cases with stage IV esophageal cancer. Local radiotherapy can solve the problem of eating obstruction, and then further improve patients' nutritional status, thus benefiting their survival. In that way, whether local installation of esophageal stent could also improve patients' survival still should be probed, considering that such operation similarly relieves difficulty in swallowing. In the retrospective study by Lu et al[12] on esophageal cancer, the incidence rate of esophageal fistula was compared between chemoradiotherapy combined with stent installation and chemoradiotherapy alone. As a result, such incidence rate achieved 87.5% in the group adopting stent and only 2.6% in the group without stent, showing statistically significant difference. Moreover, in their study, median survival time was 6 months in combination group and up to 16 months in the latter group, suggesting higher morbidity of esophageal fistula and higher mortality due to stent installation. In 12 cases with esophageal stent in our research, 10 showed chest pain, 6 developed esophageal fistula, and 3 had massive hemorrhage. Among 6 patients taking simultaneous radiotherapy, 5 developed esophageal fistula while 2 showed massive hemorrhage, with a median survival time of 7 months. And median survival was 9 months in the group without stent, exhibiting statistical difference between the groups with and without the stent. In other words, our findings also supported that median survival was obviously lower in stent group than in the group without stent, and that patients' living quality was dramatically decreased in stent group as well. Yu et al[8] compared the influences on patients' nutritional status between stent installation, nasal feeding, and gastrostomy feeding during chemoradiotherapy. Consequently, the degrees of chest pain and ALB decrease were dramatically higher in patients adopting stent installation than in other groups, indicating that esophageal stent was unsuitable during chemoradiotherapy. In the present study, we observed a similar incidence rate of esophageal fistula to that in the research by Lu et al.[12] And numerous studies have demonstrated that stent installation in esophageal cancer patients not only reduces their living quality but also possibly shortens their survival

Table 2

Multivariate COX regression analysis.

Variables in the equation

							95.0% CI for Exp(*B*)	
	B	**SE**	**Wald**	**df**	**Sig.**	**Exp(*B*)**	**Lower**	**Upper**
Mulnutrition	−0.589	0.460	1.635	1	0.201	0.555	0.225	1.368
Anemia	−0.363	0.445	0.665	1	0.415	0.695	0.291	1.665
Therapeutic method	−0.182	0.399	0.207	1	0.649	0.834	0.382	1.822
Esophageal stent	−0.296	0.376	0.617	1	0.432	0.744	0.356	1.556
Visceral metastasis	−0.878	0.409	4.604	1	0.032	0.416	0.186	0.927

Notes: *B* = partial regression coefficient, CI = confidence interval, df = degree of freedom, Exp (i) = hazard ratio, SE = standard error, Sig. = significance.

period. Therefore, we recommend that esophageal stent should be cautiously adopted among patients preparing for chemoradiotherapy.

Stage is a main influencing factor for the prognosis of all solid tumor patients. Focusing on patients with stage IV esophageal cancer, a study from Japan explored whether visceral metastasis could affect patients' prognosis.[13] Accordingly, among esophageal cancer patients receiving chemoradiotherapy for T4 and/or M1, the prognosis was obviously better in cases without M1 than those with M1. And in our research, median survival time was 8 months in patients with visceral metastasis and 10 months in those without metastasis, showing statistical difference, which also implied that visceral metastasis represented an adverse effector on prognosis among patients with stage IV esophageal cancer.

In the present study, Cox risk regression mode also encompassed all of the 5 components into analysis, which exhibited significant influences on patients' prognoses in univariate analysis, namely anemia, therapeutic method, visceral metastasis, and esophageal stent. And relevant result presented that only visceral metastasis was related to poor prognosis among patients with stage IV esophageal cancer. Lacking significant impact for the other 4 aspects in multivariate analysis might be explained by the fact that as treatments begin to take effects and tumors shrink, anemia, and mulnutrition before therapy might be corrected to a certain degree. As for the impact of extra radiotherapy added in treatment on patients' prognosis, some existing researches claimed that concurrent chemoradiotherapy could elevate the survival of patients with stage IV esophageal cancer when compared with chemotherapy alone. In our study, among 33 patients receiving chemoradiotherapy, only 9 adopted concurrent chemoradiotherapy, while 6 cases with esophageal stent took radiotherapy; all of these mentioned individuals developed severe complications which significantly affected median survival time of the patients adopting chemoradiotherapy. Therefore, the influence of radiotherapy on the survival of patients with stage IV esophageal cancer could not been determined yet, which need to be further explored by prospective studies with larger sample sizes. Until now, only retrospectively clinical researches have ever discussed the impact of esophageal stent installation on the prognosis of esophageal cancer patients, lacking findings from prospective studies. Since in our research only 12 patients had esophageal stent, a small number for analysis, we could not statistically regarded the stent as a risk factor for poor prognosis. But esophageal stent installation did obviously increase the incidence rate of esophageal fistula and chest pain, gravely affecting patients' living quality.

In the current study, both univariate and multivariate analyses indicated visceral metastasis as an independent risk factor for poor prognosis of patients with stage IV esophageal cancer. Hence, we should proceed thorough evaluation on patients showing poor prognosis, and discretely consider whether active comprehensive therapeutic regimen could be employed. For stage IV esophageal cancer patients with PS score between 0 and 2 and free from visceral metastasis, we recommend concurrent chemoradiotherapy or sequential radiotherapy and chemotherapy; and esophageal stent installation should be avoided among patients preparing for chemoradiotherapy. Optimizing therapeutic mode possesses certain clinical significance in prolonging survival time and in improving patients' living quality among cases with stage IV esophageal cancer.

Author contributions

Conceptualization: Chenghui Li.
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Visualization: Qian Jiang.
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Writing – review & editing: Chenghui Li, Zhiqiu Wang.

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