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Original Article

Analysis of prognostic factors for esophageal squamous cell carcinoma with distant organ metastasis at initial diagnosis

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Abstract

Background: Esophageal cancer is the eighth most common malignancy and sixth most fatal disease worldwide. However, it is the fourth most common cause of death in China. Although surgery is currently the recommended course of treatment, there are some patients that do not receive radical treatment due to the presence of distant organ or lymph node metastasis. There is at present no established treatment standard for esophageal cancer patients with distant organ metastasis. The purpose of this study was to investigate the prognostic factors involved in determining survival of esophageal cancer patients with distant organ metastasis at initial diagnosis, and to provide a reference for the planning of a clinical treatment strategy.

Methods: The data of 57 evaluable esophageal squamous cell carcinoma patients with distant organ metastasis at initial diagnosis were studied retrospectively. The survival rate was calculated using the Kaplan–Meier method, and the log-rank test was used to test the differences. Multivariable analysis was performed using the Cox proportion hazards model.

Results: The median survival time for all patients was 6 months (range, 1–55 months), and the 1- and 2-year survival rates were 21.1% and 11.8%, respectively. The median survival time for patients with single metastasis was 10 months with 1- and 2-year survival rates of 47.4% and 28.1%, respectively. For patients with multiple metastases, the survival duration was 5 months, with 1- and 2-year survival rates of 7.9% and 3.9%, respectively ($p < 0.001$). The 1- and 2-year survival rates with multimodality treatment were 70% and 45%, respectively, which were significantly better than chemotherapy alone (13.3% and 8.9%, respectively, $p = 0.003$) and best supportive care (5.9% and 0%, $p < 0.001$), but there was no significant difference between the latter two groups ($p = 0.061$).

Conclusion: For esophageal squamous cell carcinoma patients with distant organ metastasis upon initial diagnosis, the presence of a single metastasis appeared to favor overall survival compared to multiple metastases. Multimodality treatment may also improve patient survival, but chemotherapy alone has not been established as a favorable prognostic factor.

Keywords: esophageal neoplasms; neoplasm metastasis; prognosis; therapy

1. Introduction

Esophageal cancer has an extraordinary impact on worldwide health, with ~460,000 new diagnoses and >380,000 deaths annually.[1] It also has a significant effect on the health of Chinese people, in whom it represents the fourth most common cause of death. Surgery is currently the mainstay of esophageal cancer treatment; however, >30% of patients do not qualify for surgical resection due to advanced cancer stage or concomitant diseases.[2] Furthermore, about 18% of patients present with distant organ or lymph node metastasis and miss the opportunity for radical treatment.[3]

Although there are numerous available case reports regarding the treatment of newly diagnosed distant organ metastasis of esophageal cancer,[4,5] there is currently no established standard

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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treatment. Due to the dismal long-term patient survival rate of 0.3% at 3 years and a median survival time (MST) of 7 months,[6,7] treatment commonly includes palliative esophageal stent implantation or improvement of symptoms by palliative chemotherapy and radiotherapy.

In the present study, the clinical data of 57 esophageal squamous cell carcinoma patients with distant organ metastasis at initial diagnosis were collected and retrospectively reviewed. The outcomes were evaluated and the factors affecting prognosis were analyzed to provide reference for the planning of a clinical treatment strategy.

2. Methods

2.1. Patient characteristics

The data of 57 esophageal squamous cell carcinoma patients with distant organ metastasis at initial diagnosis, who were treated at Fujian Medical University Union Hospital, Fujian, China between January 1, 2007 and December 31, 2010, were collected. The retrospective analysis was approved by Fujian Medical University Union Hospital Institutional Review Board. All information had been anonymized and de-identified prior to its analysis. The clinical characteristics of these patients are summarized in Table 1. The patients included 47 men and 10 women (male: female ratio, 4.7:1), with a median age of 57 years (range, 37−78 years). All patients had been diagnosed with squamous cell carcinoma. Furthermore, 50 (87.7%) patients had an Eastern Cooperative Oncology Group (ECOG) score of $\leq$1. Pulmonary, hepatic, bone, brain, and gastric body metastases were diagnosed in 29 patients, 17 patients, four patients, one patient, and one patient, respectively, whereas five patients presented with multiple organ metastases.

2.2. Exclusion criteria

The exclusion criteria were as follows: (1) history of other tumors; (2) adenocarcinoma, neuroendocrine or small-cell esophageal carcinoma, or other malignant tumors of special or uncertain biological behavior; and (3) other concomitant medical condition requiring treatment.

Table 1
Clinical characteristics of 57 patients.

Median age, y (range)	57 (37−78)
Sex (M/F), *n*	47/10
ECOG performance status, *n*	
0	19
1	31
≥2	7
Organ of metastasis (solitary-metastasis), *n*	
Lung	29 (10)
Liver	17 (5)
Bone	4 (2)
Brain	1 (1)
Gastric body	1 (1)
Multiorgan	5
Treatment, *n*	
Best supportive care	17
Chemotherapy alone	30
Surgery and chemotherapy	6
Radiotherapy and chemotherapy	4

ECOG = Eastern Cooperative Oncology Group.

2.3. Pretreatment workup and diagnosis of metastases

The pretreatment workup of all patients included a physical examination, standard laboratory tests, chest radiography, upper gastrointestinal endoscopy, barium swallow, cervical and abdominal ultrasound, chest computed tomography (CT), bone scan, and magnetic resonance imaging. Additionally, bronchoscopy was performed if considered necessary. The diagnostic criteria for metastasis were: (1) metastatic lesions pathologically confirmed by surgical or biopsy samples; (2) multiple metastases on CT or ^{18}F-fluorodeoxyglucose positron emission tomography/CT; and (3) a single metastatic lesion confirmed by two or more types of imaging modalities. The presence of a single metastatic lesion was defined as solitary metastasis (19 patients; 33.3%), whereas two or more metastatic lesions were defined as multiple metastases (38 patients; 66.7%).

2.4. Statistical analysis

All patient outcomes were evaluated in December 2011. Survival was calculated from the 1st day of treatment to the date of death or the last follow-up. The survival data were analyzed with SPSS software, version 17.0 (SPSS, Inc., Chicago, IL, USA).

Survival curves were created with the Kaplan−Meier method and compared with the log-rank test. A multivariable analysis by sex, age, ECOG score, metastasis site, number of metastases, and treatment model was performed using the Cox proportional hazards model. The relevant inspection level was bilateral, where $\alpha \leq 0.05$.

2.5. Treatment

The patients were classified into three categories by treatment method: best supportive care, chemotherapy alone, and multimodality treatment (surgery combined with chemotherapy, or radiotherapy combined with chemotherapy; Table 1). Seventeen patients received best supportive care (2 cases, esophageal stenting; 1 case, referred for gastric fistula; 1 case, traditional Chinese medicine treatment; and 13 cases, nutritional supportive treatment). Thirty patients received chemotherapy alone [6 cases, calcium folinate + ftorafur + lobaplatin or oxaliplatin; 11 cases, taxol + cisplatin (lobaplatin or oxaliplatin or nedaplatin); 4 cases, S1 + lobaplatin; 1 case, gemcitabine + cisplatin; 1 case, irinotecan + cisplatin; 3 case, single-agent Xeloda or carmofur; and 4 cases, outpatient chemotherapy]. The mean number of chemotherapy cycles was 1.8 (range, 1−9 cycles). Multimodality treatment was administered to 10 patients [6 cases, surgery + chemotherapy (5 cases, esophageal tumor resection and 1 case, esophageal tumor and concomitant solitary lung metastasis resection); 4 cases, radiotherapy + chemotherapy (1 patient underwent

hepatic metastasis resection following satisfactory control of the primary esophageal tumor)].

3. Results

3.1. Outcome analysis

At the latest follow-up, 46 patients had succumbed to the disease and 11 patients remained alive. The MST for all the patients was 6 months (range, 1−55 months) and the 1- and 2-year survival rates were 21.1% and 11.8%, respectively (Fig. 1).

The MST for patients with an ECOG score ≤1 (50/57; 87.7%) was 7 months (range, 1−55 months) with 1- and 2-year survival rates of 22.0% and 13.6%, respectively. For patients with an ECOG score ≥2 (7/57; 12.3%), the MST was 3 months (range, 1−13 months), whereas the 1- and 2-year survival rates were 14.3% and 0%, respectively, without significant heterogeneity ($p = 0.061$; Fig. 2).

The MST for solitary metastasis was 10 months (range, 1−55 months), with 1- and 2-year survival rates of 47.4% and 28.1%, respectively. For patients with multiple metastases, the MST was 5 months (range, 1−17 months), with 1- and 2-year survival rates of 7.9% and 3.9%, respectively. The difference was considered to be statistically significant ($p < 0.001$; Fig. 3).

The MST for best supportive care was 5 months (range, 1−17 months), with 1- and 2-year survival rates of 5.9% and 0%, respectively. For chemotherapy alone, the MST was 7 months (range, 1−25 months) with 1- and 2-year survival rates of 13.3% and 8.9%, respectively. For multimodality treatment, the MST was 15.5 months (range, 5−55 months) with 1- and 2-year survival rates of 70% and 45%, respectively. The survival duration with multimodality treatment was superior to that with best supportive therapy ($\chi^2 = 15.402$, $p < 0.001$) and chemotherapy alone ($\chi^2 = 8.446$, $p = 0.003$). However, there was no statistically significant difference between chemotherapy alone and best supportive care ($\chi^2 = 3.509$, $p = 0.061$; Fig. 4, Table 2).

There were no statistically significant differences in survival time with multimodality treatment of surgery combined with chemotherapy, or radiotherapy combined with chemotherapy ($\chi^2 = 2.106$, $p = 0.147$; Fig. 5). The multifactorial analysis revealed that the number of metastases and multimodality treatments were independent prognostic factors and

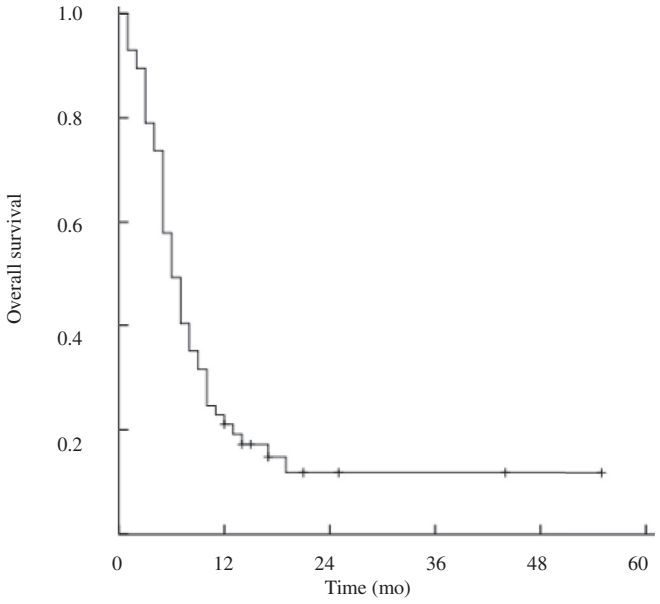

Fig. 1. Overall survival curve for all patients.

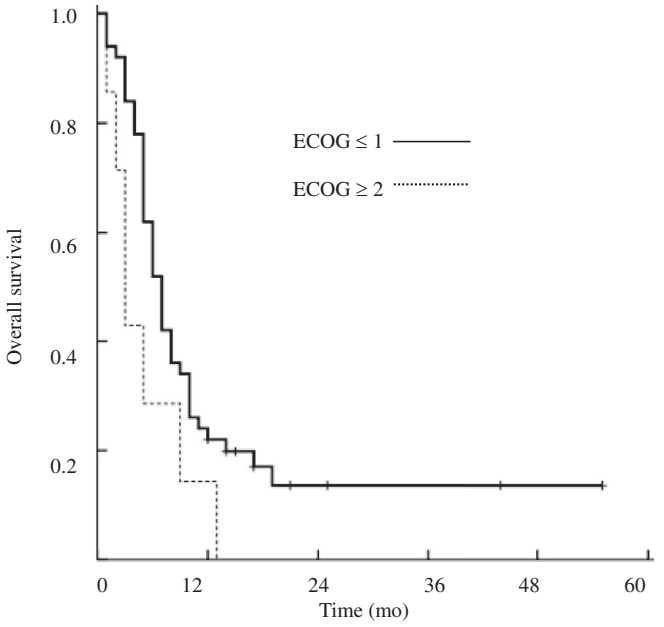

Fig. 2. Overall survival curve for ECOG score, $p = 0.061$. ECOG = Eastern Cooperative Oncology Group.

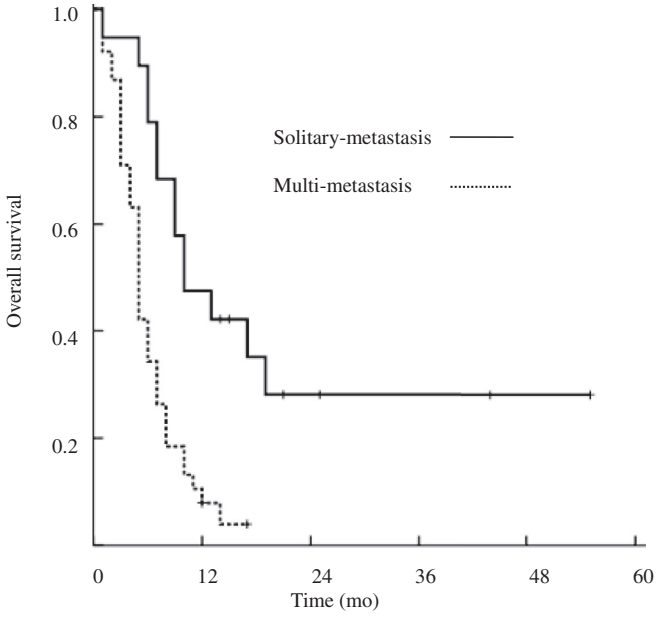

Fig. 3. Overall survival curve for solitary-metastasis and multi-metastasis, $p < 0.001$.

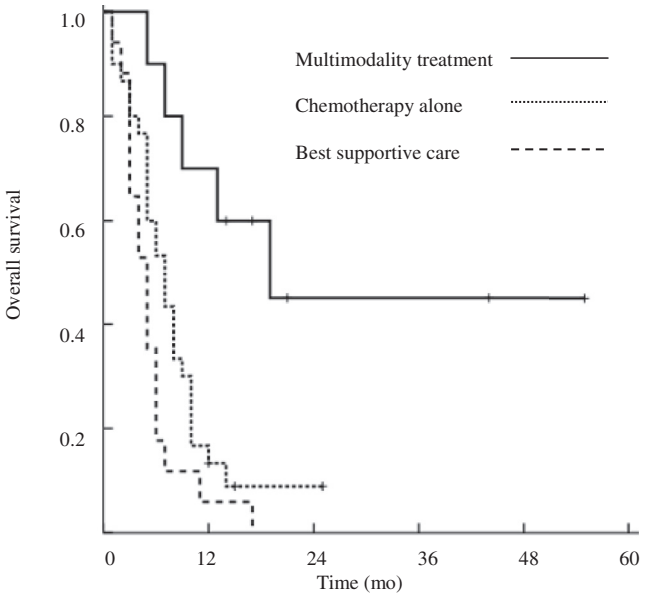

Fig. 4. Overall survival curve for different treatment methods, the best supportive care, chemotherapy alone, and multimodality treatment (multimodality treatment vs. chemotherapy alone: $\chi^2 = 8.446$, $p = 0.003$; multimodality treatment vs. best supportive care: $\chi^2 = 15.402$, $p < 0.001$; and chemotherapy vs. best supportive care: $\chi^2 = 3.509$, $p = 0.061$).

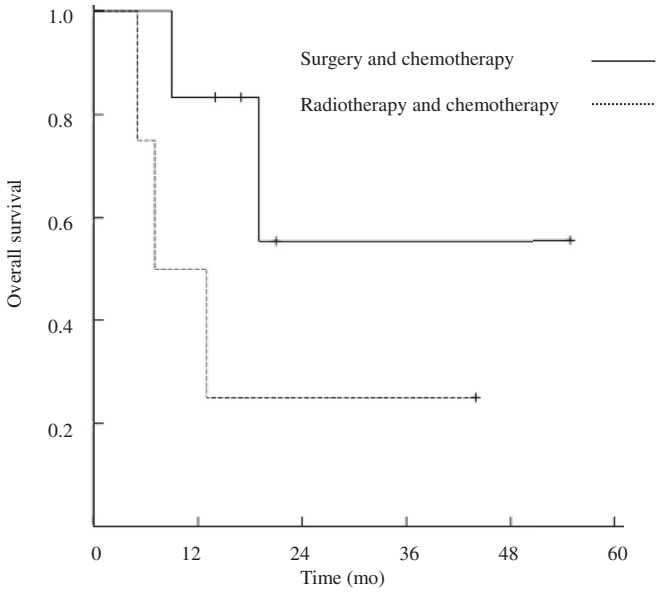

Fig. 5. Overall survival curve for multimodality treatment, $p = 0.147$.

the proportion hazards were 2.259 [(95% confidence interval (CI): 1.081−4.717] and 0.506 (95% CI: 0.347−0.738), respectively.

4. Discussion

Esophageal cancer is one of the most common malignancies occurring worldwide and is associated with a dismal prognosis. Despite advances in surgical techniques, radiotherapy technology, and novel chemotherapeutic agents widely used over the past few years, the 5-year survival rate remains 20−30%.[8] Local recurrence and distant metastasis are the main causes of treatment failure. Upon development of distant metastasis, treatment is difficult and the prognosis is poor, with an MST of 6 months, as demonstrated in this study, and 1- and 2-year survival rates of only 21.1% and 11.8%, respectively.

Table 2
Survival in patients.

	MST, mo (range)	1-y survival (%)	2-y survival (%)	*p*
Metastasis number				<0.001
Solitary	10 (1−55)	47.4	28.1	
Multiple	5 (1−17)	7.9	3.9	
ECOG score				0.061
≤1	7 (1−55)	21.6	13.3	
≥2	3 (1−13)	14.3	0	
Treatment				
Best supportive care	5 (1−17)	5.9	0	<0.001[a]
Chemotherapy alone	7 (1−25)	13.3	8.9	0.003[b]
Multimodality treatment	15.5 (5−55)	70	45	0.061[c]
Total	6.5 (1−55)	20.7	11.6	

ECOG = Eastern Cooperative Oncology Group; MST = median survival time.
[a] Multimodality treatment vs. best supportive care.
[b] Multimodality treatment vs. chemotherapy alone.
[c] Chemotherapy vs. best supportive care.

It was previously reported that the survival time of patients with advanced cancer is correlated with their performance status.[9] In the present study, the survival of patients with an ECOG score ≤1 was superior to that of patients with an ECOG score ≥2, with an almost statistically significant difference ($p = 0.061$). Therefore, aggressive treatment is recommended for esophageal cancer patients with distant metastases who exhibit a good performance status.[10] Sanchez-Munoz et al[11] reported that, by improving the performance status through nutritional support, the survival of patients with an initially poor performance status may be improved when combined with antitumor therapy.

Teo et al[12] reported that the prognosis of nasopharyngeal carcinoma with a solitary distant metastasis was distinctly superior to that prognosis for patients with multiple metastases; however, there was no similar report on esophageal cancer. To the best of our knowledge, the present study was the first to demonstrate that the survival duration of esophageal cancer with a solitary distant metastasis was distinctly superior to that with multiple distant organ metastases ($p < 0.001$). The multiple factor analysis indicated that the presence of multiple metastases was an independent prognostic factor with the mortality risk being 2.259 times that of solitary metastasis (95% CI: 1.081−4.717). This suggested that, even in patients with advanced esophageal cancer, solitary metastasis was considered to be a favorable prognostic factor as opposed to multiple metastases. Furthermore, upon multivariable analysis, the metastatic site was not found to be an independent prognostic factor, indicating that, regardless of the location, esophageal cancer with a solitary metastasis should be treated aggressively to improve the outcome of such patients in clinical practice.

Systemic chemotherapy is widely accepted as the standard treatment of patients with distant organ metastasis, despite the fact that the number of Phase III clinical trials demonstrating that chemotherapy alone may enhance the survival benefit of patients with esophageal cancer is currently limited.[13] The present study demonstrated that, compared to the survival rate of patients with best supportive care, the survival with chemotherapy alone was almost statistically significantly different ($p = 0.061$). This may be attributed to the following reasons: (1) inadequate intensity of chemotherapy and unified chemotherapy regimens; the mean number of chemotherapy cycles was 1.8 and as many as six different chemotherapeutic regimens were used in all the patients who received chemotherapy alone; and (2) the number of case studies was too limited to achieve statistical significance. Thus, regarding distant organ metastasis of esophageal cancer, the effect of chemotherapy alone requires further investigation, particularly for patients with a good performance status. However, the appropriate combination of chemotherapy regimens and the number of chemotherapeutic cycles require confirmation by further clinical studies.

The present study revealed that survival with multimodality treatment (surgery or radiotherapy combined with chemotherapy) was superior to that with chemotherapy alone or best supportive care. A multifactorial analysis identified multimodality treatment as an independent factor affecting prognosis, with a mortality risk ratio of 0.506 (95% CI: 0.347−0.738). This indicated that, on the basis of chemotherapy, the treatment of primary esophageal lesions may improve the survival of esophageal cancer patients with distant organ metastasis.[14]

With regards to multimodality treatment, the difference in survival between surgery combined with chemotherapy and radiotherapy combined with chemotherapy was not statistically significant ($p = 0.147$), suggesting that either surgery or radiotherapy as a local treatment may be feasible for newly diagnosed distant organ metastasis from esophageal cancer.[15] However, due to the limited number of cases receiving multimodality treatment, our results require confirmation through the accumulation of more cases and further prospective clinical trials.

In addition, in two different patterns of local multimodality treatment groups, one patient in each group achieved long-term survival following surgical resection of the metastatic lesions following satisfactory control of the primary esophageal tumor, indicating that the treatment of metastatic lesions, synchronous, or asynchronous, may help improve survival.[16,17]

In conclusion, our study indicated that the number of metastatic lesions and multimodality treatment are independent prognostic factors in esophageal cancer with distant organ metastasis at initial diagnosis, with solitary metastasis being associated with a favorable prognosis. Furthermore, multimodality treatment may improve the survival of such patients. However, the benefit of chemotherapy alone requires further investigation.

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