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ORIGINAL RESEARCH

Metastatic Esophageal Carcinoma: Prognostic Factors and Survival

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Abstract

Background Worldwide, esophageal cancer is the eighth most common cancer and the sixth leading cause of cancer-related death. At initial diagnosis, about 50% of esophageal cancer patients present with metastasis. The prognosis of metastatic esophageal cancer is poor with 5-year survival rate of less than 5%.

Methods This is a retrospective study of stage IV esophageal cancer patients registered at Clinical Oncology and Nuclear Medicine department and Oncology Center Mansoura University in the period from 2009 to 2018 inclusive. Eligibility criteria were all pathologically proven stage IV esophageal cancer patients. The medical files of patients were reviewed.

Results Most patients were ≥ 50 years (67.8%) with male predominance (76.7%). Middle third was the most common site of primary tumor (38.9%). Squamous cell carcinoma was more common with incidence of grade 3 (40%). T3-4 lesion was recorded in 61.1% and node positive in 66.7%. As regards metastasis; liver was the most common one (45.5%) followed by lung (30%). One-year survival rate was 25.6% with median survival time of 8 months. Multivariate analysis indicated that age ($p = 0.03$), site ($p = 0.04$), grade of primary tumor ($p = 0.049$), T classification ($p = 0.0038$), ECOG PS ($p = 0.046$), site ($p = 0.026$), and number of metastasis ($p = 0.04$) significantly affect prognosis while sex ($p = 0.74$) and histologic type ($p = 0.94$) do not.

Conclusion Metastatic esophageal carcinoma is a disease of poor prognosis especially in patients with the following criteria: old age, lower third location, high grade and large tumors, poor performance status, multiple sites of metastasis and presence of bone secondaries.

Keywords Esophageal cancer · Metastasis · Prognostic factors

Introduction

Worldwide, esophageal cancer (EC) is the eighth most common cancer and the sixth leading cause of cancer-related death [1]. In western country, the main histologic subtype is adenocarcinoma (AC) that arises commonly in distal esophagus or esophagogastric junction (EGJ) while in Asia, Africa, and South America, esophageal squamous cell carcinoma (SCC) is the predominant histology and arises in cervical and upper and thoracic esophagus [2]. The leading cause of cancer-related mortality is distant metastasis [3]. At initial diagnosis, about 50% of EC patients present with metastasis to organs or lymph nodes [4]. Approximately 30% of patients develop distant metastasis mostly within 6 months after radical treatment [5]. The prognosis of metastatic EC is poor with 5-year survival rate of less than 5% [6]. Liver is the most common site of EC metastasis followed by the lung, bone, and brain [7]. This study was conducted to assess survival outcome in metastatic esophageal cancer and its related prognostic factors.

Patients and Methods

This is a retrospective study of stage IV EC patients registered at Clinical Oncology and Nuclear Medicine department and Oncology Center Mansoura University in the period from 2009 to 2018 inclusive.

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Eligibility criteria were all pathologically proven stage IV EC patients either SCC or AC. Patients without positive histology or with double malignancy were excluded.

Medical files of patients were reviewed, and the following data were collected: age, sex, tumor location, T and N stage, histologic subtype, tumor grade, site and number of metastasis, ECOG performance status, treatment data, date of death, or last follow-up.

Overall survival (OS) was estimated from date of diagnosis to date of death or last follow-up.

The primary end point was overall survival. Several factors affect survival were analyzed as age sex, tumor location, T stage, histologic subtype, tumor grade, site and number of metastasis, ECOG performance status (ECOG PS), and treatment. The Institutional Review Board of Faculty of Medicine, Mansoura University approved this study.

Statistical Methods IBM SPSS was used for statistical analysis, chi square test was used as a test of significance, and $p < 0.05$ was considered significant. The Kaplan-Meier test was used for survival functions.

Results

This retrospective study included 90 patients with stage IV EC; the clinicopathological characteristics of them are summarized in Table 1. Most patients were ≥ 50 years (67.8%) with male predominance (76.7%). Middle third was the most common site of primary tumor (38.9%). SCC was more common (74.5%) with incidence of grade 3 (40%). T3-4 lesion was recorded in 61.1% and node positive in 66.7%. Eleven patients were of poor performance status so managed with best supportive care while others received palliative treatment in the form of radiotherapy or chemotherapy or both. As regards metastasis, 60% of patients presented with one site of metastasis, and liver was the most common one (45.5%) followed by lung (30%).

Our study showed 1-year survival rate of 25.6% with median survival time of 8 months (Fig. 1).

As regards prognostic factors, multivariate analysis indicated that age ($p = 0.03$), site ($p = 0.04$) and grade of primary tumor ($p = 0.049$), T classification ($p = 0.0038$), ECOG PS ($p = 0.046$), site ($p = 0.026$), and number of metastasis ($p = 0.04$) significantly affect prognosis while sex ($p = 0.74$) and histologic type ($p = 0.94$) do not. We found that patient age of ≥ 50 years, lower third tumor, grade3, ECOG PS of 3, T3-4, multiple sites of metastasis, and presence of bone secondaries were associated with significantly poorer survival (Table 2).

Table 1 Clinicopathological characteristics of 90 patients

Variable	No. (%)
1. Age (years)	29 (32.2)
Median 62	61 (67.8)
< 50	
≥ 50	
2. Sex	69 (76.7)
Male	21 (23.3)
Female	
3. Site of primary tumor	30 (33.3)
1. Upper third	35 (38.9)
2. Middle third	25 (27.8)
3. Lower third	
4. Histologic type	67 (74.5)
SCC	23 (25.5)
AC	
5. Tumor grade	54 (60)
1–2	36 (40)
3	
6. T classification	35 (38.9)
T1-2	55 (61.1)
T3-4	
7. Regional nodal classification	30 (33.3)
N0	60 (66.7)
N1	
8. Site of metastasis	41 (45.6)
Liver	27 (30)
Lung	13 (14.4)
Lymph node	9(10)
Bone	
9. Number of metastatic sites	54 (60)
1 site	36 (40)
≥ 2 sites	
10. ECOG PS	79 (87.8)
≤ 2	11 (12.2)
3	
11. Treatment	79 (87.3)
Yes	11 (12.2)
No	

Discussion

Distant metastasis is still the major cause of treatment failure and death in EC, despite recent advances in its diagnosis and treatment [8]. Prognostic factors that related to patients and the disease itself are multiple; knowing these parameters allow for better stratification of high-risk groups [9].

The median age of our group was 62 years comparable with that reported by Tepper et al. [10] but slightly higher

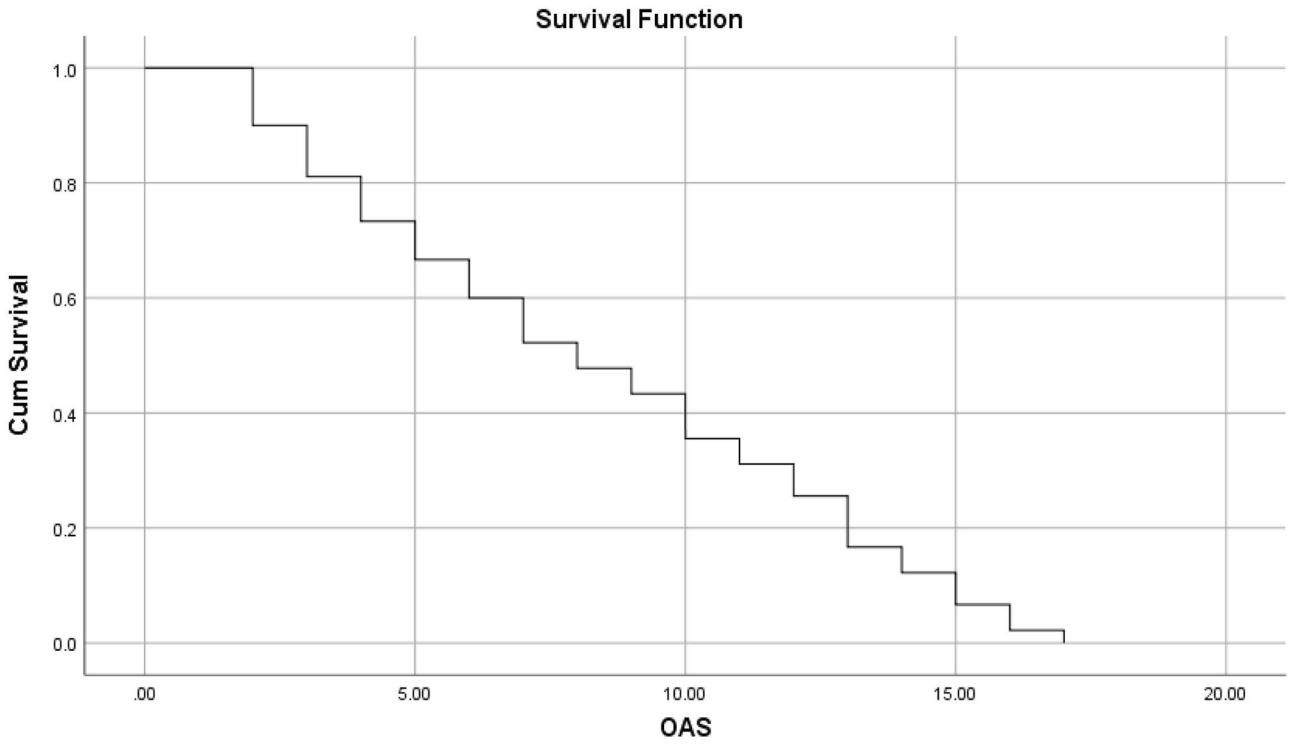

Fig. 1 Overall survival curve

that mentioned by Noronha et al. [11]. There was male predominance (76.7%) that is consistent with others [12–14].

As suspected in African countries, SCC was most common and arose from upper two third of esophagus [15].

Wu SG et al. [16] reported lymph node–positive disease in 65.9% of patients with metastatic EC similar to our finding. Similarly to some previous studies, we found that liver was the most common site of distant metastasis [7, 17], while Suzuki et al. [18] showed different pattern where distant lymph node was the most frequent site of metastasis.

One-year overall survival rate was 25.6% with median survival time of 8 months comparable with other studies [1, 19, 20]

In our study, older age was associated with bad prognosis as reported by others [21, 22]. However, Chen WW et al. [23] and Okuda et al. [24] found that older age had better prognosis. They explained their finding by difference between younger and older patients in the frequency of (1) loss of the deleted esophageal cancer 1 gene (DEC1) which is an esophageal tumor-suppressor gene located on long arm of chromosome 9(9q) and (2) mutation in tumor-suppressor gene p53.

As our results, it was reported that high tumor size and poor cellular differentiation are associated with high mortality [21, 22, 25, 26].

We found that poor performance status and lower third esophageal tumor had poor survival while gender and histologic type were not similar to previous studies [22, 23, 27]. But Haefner et al. [28] found that performance status did not affect survival.

In this study, patients with distant lymph node metastasis had the best survival while those with bone metastasis had the worst one as mentioned by others [29–31]. Some reported that bone metastasis in EC was associated with leukocytosis and hypercalcemia that may provoke rapid disease progression [32, 33]. However, Tanaka et al. [34] observed no significant difference in survival for different sites of metastasis.

We also found that not only site of metastasis significantly affect survival but also number of metastatic sites. Multiple sites of metastasis had poorer survival comparable with previous finding [16]. But Blank et al. [35] found the number of metastases was not a significant prognostic factor for survival.

Table 2 Multivariate analysis of prognostic factors

Variable	*N*(1-year survival)	*p* value
1. Age (years) < 50 ≥ 50	8/29(27.6%) 10/61(16.4%)	0.03
2. Sex Male Female	19/76(25%) 4/14(28.6%)	0.74
3. Site of primary tumor 1. upper third 2. middle third 3. lower third	12/30(40%) 7/35(20%) 3/25(12%)	0.04
4. Histologic type SCC AC	17/67(25.4%) 6/23(26%)	0.94
5. Tumor grade 1–2 3	18/54(33.3%) 5/36(13.9%)	0.049
6. T classification T1-2 T3-4	12/35(34.3%) 8/55(14.5%)	0.0038
7. Site of metastasis Liver Lung Lymph node Bone	8/41(19.5%) 4/27(14.8%) 7/13(53.8%) 1/9(11.1%)	0.026
8. Number of metastatic sites 1 site ≥ 2 sites	16/54(29.6%) 4/36(11.1%)	0.04
9. ECOG PS ≤ 2 3	33/79(41.7%) 1/11(9%)	0.046

Conclusion

Metastatic esophageal carcinoma is a disease of poor prognosis especially in patients with the following criteria: old age, lower third location, high-grade and large tumors, poor performance status, multiple sites of metastasis, and presence of bone secondaries.

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