Chinese Journal of Cancer

Original Article

The 2002 AJCC TNM classification is a better predictor of primary small cell esophageal carcinoma outcome than the VALSG staging system

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Abstract

Small cell carcinoma of the esophagus (SCCE) is a rare and aggressive malignant tumor with a poor prognosis. The optimal disease staging system and treatment approaches have not yet been defined. This study aimed to evaluate the prediction of different staging systems for prognosis and treatment options of SCCE. We retrospectively accessed the clinicopathologic characteristics, treatment strategy, and prognosis of 76 patients diagnosed with primary SCCE between 2001 and 2011. The 1-, 2-, 3-, and 5-year overall survival rates were 58%, 31%, 19%, and 13%, respectively. Univariate analysis showed that the 2002 American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification (P = 0.002), Veterans Administration Lung Study Group (VALSG) stage (P = 0.001), predisposing factors (P < 0.001), T category (P = 0.023), and M category (P < 0.001) were prognostic factors for overall survival. Multivariate analysis showed that the 2002 AJCC TNM stage (P < 0.001) was the only independent prognostic factor for survival. The value of the area under the receiver operator characteristic (ROC) curve (AUC) of the 2002 AJCC TNM staging system was larger than that of VALSG staging system with regard to predicting overall survival (0.774 vs. 0.620). None of the single treatment regimens showed any benefit for survival by Cox regression analysis. Thus, the 2002 AJCC TMN staging system improved the prediction of SCCE prognosis; however, the optimal treatment regimen for SCCE remains unclear.

Key words Small cell carcinoma, esophagus, TNM staging, chemotherapy, radiotherapy, esophagectomy

Small cell carcinoma (SCC) is a poorly differentiated neuroendocrine tumor that most frequently arises in the lung. Extrapulmonary SCC is extremely rare and has been described in many tissues, including gastrointestinal, genitourinary, head and neck, and breast tissues[1].

The esophagus is the most frequently reported gastrointestinal site of extrapulmonary SCC. SCC of the esophagus (SCCE), characterized by McKeown[2] in 1952, is a highly aggressive malignancy that accounts for only 0.4% to 3.1% of all esophageal malignancies[3-11]. It is clinically similar to SCC of the lung, with a high frequency of early regional and distant dissemination. The standard management and prognostic factors of SCCE have not yet been defined due to the paucity of cases and poor prognosis. Some authors recommended surgery for patients with locoregional disease[12-20], whereas some recommended systemic therapy based on the success of chemoradiotherapy[6,21-24]. The present study retrospectively cross-analyzed epidemiologic data, clinical characteristics, and treatment outcomes of 76 patients with SCCE treated at Zhejiang Cancer Hospital to better define prognostic factors and therapeutic options for this dismal disease.

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doi: 10.5732/cjc.012.10161

Patients and Methods

Patient cohort and data collection

In total, 76 SCCE patients treated at Zhejiang Cancer Hospital between January 2001 and June 2011 were involved in this study. The pathologic diagnosis of SCC was determined from biopsy or resected specimens. In all cases, the histologic diagnosis of SCC was previously confirmed by the Zhejiang Pathology Quality & Control Center.

As there is no specific staging system for SCCE, the staging workup for all patients included chest radiography, upper gastrointestinal endoscopy with biopsy, endoscopic ultrasonography, and computed tomography of the chest and upper abdomen. Most patients also underwent barium esophagogram, computed tomography/magnetic resonance imaging scan of the brain, neck and abdomen, radionuclide bone scan, and bronchoscopy. Disease stage was presented according to two staging systems: (1) the 2002 American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system for esophageal cancer, and (2) the Veterans Administration Lung Study Group (VALSG) staging system for primary pulmonary SCC. The latter contains two staging categories: limited disease (LD) and extensive disease (ED). LD is defined as a disease locating within an anatomic region that can be safely encompassed within a tolerable radiation field. ED is a disease beyond locoregional boundaries, which may include malignant pleural or pericardial effusion or hematogenous metastases.

Treatment

In our cohort, 72 patients underwent systematic or locoregional therapy, and 4 patients did not undergo any therapy (Table 1). Thirty-three patients underwent transthoracic esophagectomy with two-field or three-field lymphadenectomy, among which 32 underwent radical surgery and 1 underwent palliative surgery. A total of 625 lymph nodes were resected, with 79 metastases found pathologically. Among the patients who underwent radical surgery, 21 were treated with surgery alone, 8 with surgery plus postoperative chemotherapy, 1 with surgery plus postoperative radiotherapy, and 3 with surgery plus postoperative chemoradiotherapy. The patient who underwent palliative surgery was treated with surgery plus postoperative chemotherapy. A total of 41 patients underwent chemotherapy, including 25 who underwent it in combination with radiotherapy, surgery, or both. For chemotherapy, 33 patients were treated with etoposide plus cisplatin, 4 with paclitaxel plus cisplatin, 2 with 5-fluorouracil plus platinum, 1 with gemcitabine plus platinum, and 1 with irinotecan plus platinum. The number of cycles of chemotherapy ranged from 1 to 9, with the median cycle number being 3. Twenty-seven patients underwent radiotherapy, which was delivered by 6 MV or 10 MV photons. For postoperative therapy, radiation was delivered 2 Gy per day, 5 days per week, to a total dose of 40 Gy to 60 Gy (mean, 53 Gy). For radical therapy, radiation was delivered 2 Gy per day, 5 days per week, to a total dose of 45 Gy to 68 Gy (mean, 57.6 Gy). As an exception, one patient were treated with 14.4 Gy in 8 fractions and then abandoned treatment.

Statistical analyses

Data on patient demographics, symptoms at time of presentation, diagnosis, disease stage, treatment, and outcome were collected. All patients were followed up by telephone or mail. Overall survival (OS) was calculated from the start of treatment to the date of either death or

Table 1. The 2002 AJCC classification and treatment of 76 patients with small cell carcinoma of the esophagus (SCCE)

Treatment	AJCC classification			
	Stage I	Stage II	Stage III	Stage IV
S	1	9	9	2
R	0	3	2	4
C	0	5	1	10
S+R	0	0	0	1
S+C	1	6	1	0
R+C	1	3	3	7
S+R+C	1	1	1	0
No treatment	0	2	0	2
Total	4	29	17	26

S, surgery; R, radiotherapy; C, chemotherapy. All values are presented as number of patients.

the last follow-up. Survival was estimated using the Kaplan-Meier method, and survival curves were compared using the log-rank method. *P* values less than 0.05 were considered significant.

SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was used to analyze prognostic factors with the Cox hazard regression model. The entry factors were gender, age (≤60 years vs. >60 years), predisposing factors, size of the primary lesion (≤5 cm vs. >5 cm), location of the primary lesion, TNM classification, LD/ED stage, surgery (yes vs. no), chemotherapy (yes vs. no), and radiotherapy (yes vs. no).

Results

Cohort characteristics

From January 2001 to June 2011, 76 patients with SCCE or SCC of the gastroesophageal (GE) junction were identified, accounting for 1.28% (76 of 5,936) of all patients with esophageal malignancies at Zhejiang Cancer Hospital during that time. Complete medical records were available for all patients. The cohort characteristics are summarized in Table 2.

Tumor characteristics

Tumor characteristics are summarized in Table 3. In more than half (61%) of the cases, the tumor was located in the middle of the tissue. In 42% of the cases, the tumor size was large (>5 cm). In histologic components, 80% (61 of 76) of the cases were purely SCCE, whereas 19% (14 of 76) of the cases were mixed tumors with squamous differentiation and 1 case was SCCE with sarcomatoid differentiation. No SCCE with adenocarcinoma was found. According to the 2002 AJCC TNM staging criteria, 66% (50 of 76) of the patients presented with stages I–III disease. By the VALSG criteria, 79% (60 of 76) of patients were diagnosed with LD. The most frequent metastatic sites were the retroperitoneal lymph nodes (7/17, 41%) and liver (6/17, 35%). No patients had paraneoplasic syndromes. Only 1 patient had gastroesophageal reflux disease (GERD) before diagnosis. Of note, serum neuron-specific enolase (NSE) was higher than normal in

Table 2. Cohort characteristics of 76 patients with SCCE

Characteristic	No. of patients	Percentage (%)
Age (years)		
Median	61	
Range	41–84	
Gender		
Male	60	79
Female	16	21
Second malignancies		
No	72	95
Yes	4	5
Predisposing factors		
No	21	28
Tobacco abuse alone	12	16
Alcohol abuse alone	4	5
Tobacco and alcohol abuse	39	51
Family history		
No	61	80
Yes	13	17
Unknown	2	3
Presenting symptoms		
Dysphagia	57	75
Pain/reflux	25	33
Weight loss	36	47
Bleeding	2	3
Cerchnus	2	3
Others	1	1

Table 3. Tumor characteristics of 76 patients with SCCE

Characteristic	No. of patients	Percentage (%)
Location		
Upper/thoracic	16	21
Middle	46	61
Lower/gastroesophageal junction	14	18
Tumor length		
⩽5 cm	44	58
> 5 cm	32	42
Other histological components		
Pure small cell	61	80
Adenocarcinoma	0	0
Squamous cell	14	19
Sarcomatoid	1	1
Precursor lesion		
No	75	99
Barrett's epithelium	1	1
TNM classification		
I	4	5
II	29	38
III	17	23
IVa	10	13
IVb	16	21
T classification		
T1	8	11
T2	20	26
T3	44	58
T4	4	5
N classification		
N0	33	43
N1	43	57
Tumor extent		
Limited	60	79
Extensive	16	21
Sites of metastases at presentation[a]		
Liver	6	35
Distant lymph nodes	7	41
Lung	3	18
Bone	3	18
Pancreas	1	6
Stomach	1	6
Number of metastatic sites[a]		
1	13	76
2	4	24

[a]The number of patients with metastases is 17.

4 patients.

Overall survival

As of October 2011, equivalent to a median follow-up of 11.47 months for all patients, 23 patients (30%) were still alive, including 1 with ED and 22 with LD. The median OS of the 76 patients was 15.77 months [95% confidence interval (CI): 11.00–20.53 months]. The 1-, 2-, 3-, and 5-year OS rates were 58%, 31%, 19%, and 13%, respectively (Figure 1). The median OS for patients with LD and ED was 19.70 months (95% CI: 11.30–28.10 months) and 7.40 months (95% CI:

6.86–7.94 months), respectively (P = 0.001) (Figure 2). Patients with stage I disease had a longer survival than patients with stage II, III, or IV disease (Figure 3). The 4 patients with stage I disease all survived up to October 2011 (5, 51, 104, and 112 months). Of the patients with LD, 4 (2 with stage I, 1 with stage II, and 1 with stage III) had been free of disease for more than 5 years and were still alive at the date of the last follow-up. Two of the 4 patients with LD who were long-term survivors underwent induction chemotherapy followed by chemoradiotherapy without surgery. The other two underwent radical resection plus chemotherapy.

Univariate and multivariate analyses

Univariate analysis revealed the following factors to be predictive factors for prognosis (Table 4): ED/LD stage (χ^2 = 10.856, P = 0.001) (Figure 2), TNM classification (χ^2 = 15.179, P = 0.002) (Figure 3), T category (χ^2 = 5.146, P = 0.023) (Figure 4), M category

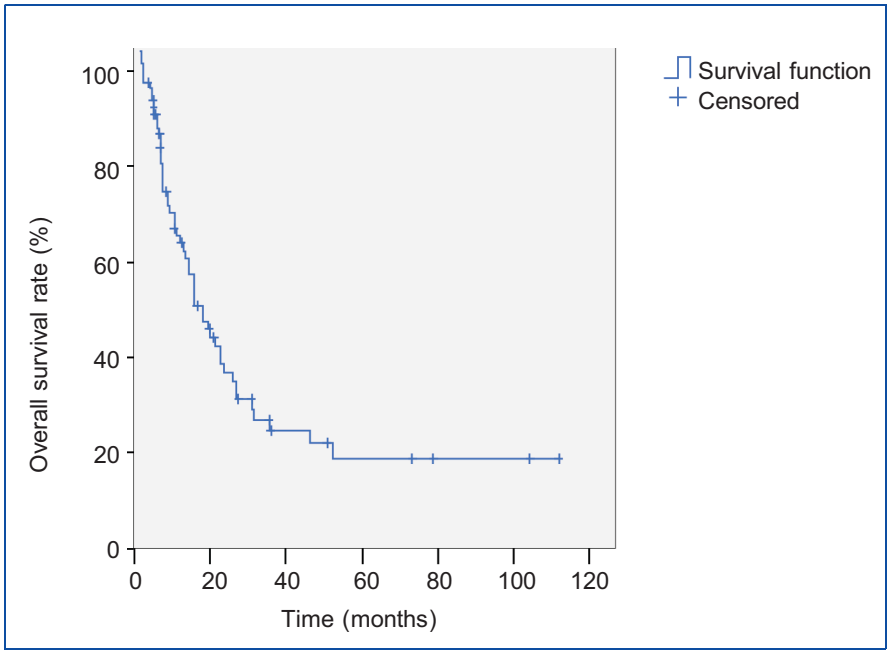

Figure 1. **Survival curves for the patient cohort with small cell carcinoma of the esophagus (SCCE).** Median overall survival (OS) is 15.77 months.

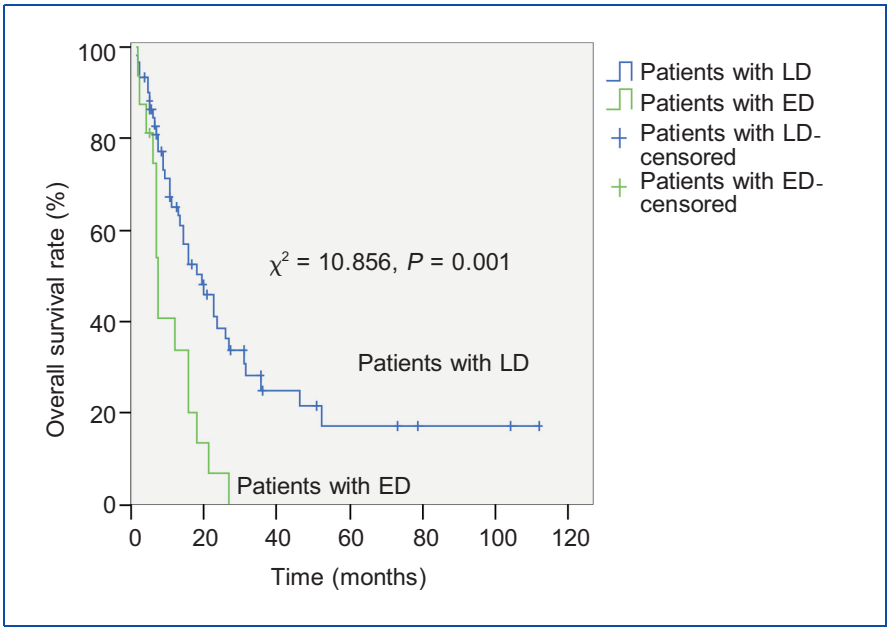

Figure 2. **Survival curves for patients with limited disease (LD) and extensive disease (ED).** Median OS of patients with ED is shorter than that of patients with LD (7.4 months vs. 19.7 months, P = 0.001).

(χ^2 = 9.832, P = 0.002) (Figure 5), and predisposing factors such as alcohol abuse (χ^2 = 23.064, P < 0.001) (Figure 6). Other clinicopathologic features, such as gender, size of the primary lesion (≤5 cm vs. >5 cm),

Table 4. Univariate analysis for the prognosis of 76 patients with SCCE

Characteristic	No. of patients	Survival rate (%)			MST (months, 95% CI)	χ^2	P
		1-year	2-year	3-year			
Gender						0.021	0.884
Male	60	60.8	18.8	11.8	15.767 (11.399–20.134)		
Female	16	47.7	19.1	19.1	12.000 (0.000–26.710)		
Age (years)						0.286	0.593
≤60	37	54.8	25.8	25.8	13.433 (7.708–19.159)		
> 60	39	61.8	14.2	0.0	17.933 (12.695–23.172)		
Predisposing factors						23.064	<0.001
No abuse	21	66.5	26.6	17.7	15.933 (7.763–24.104)		
Tobacco abuse alone	12	56.3	25.0	25.0	14.500 (6.174–22.826)		
Alcohol abuse alone	4	0.0	0.0	0.0	4.600 (1.823–7.377)		
Tobacco and alcohol abuse	39	60.9	12.6	6.3	17.933 (10.813–25.054)		
Location						1.964	0.375
Upper	16	46.7	15.6	0.0	10.633 (2.621–18.646)		
Middle	46	63.5	25.3	20.3	15.933 (8.696–23.171)		
Lower	14	57.1	8.3	8.3	13.433 (1.135–25.731)		
Tumor length (cm)						2.707	0.100
≤5	44	66.6	22.1	22.1	20.100 (13.384–26.816)		
> 5	32	47.7	15.3	5.1	12.000 (7.161–16.839)		
TNM classification						15.179	0.002
I	4	100.0	100.0	100.0	–		
II	29	68.1	21.6	21.6	–		
III	17	61.9	15.5	7.7	–		
IVa/IVb	10/16	40.4	0.0	0.0	–		
T classification						6.758	0.080
T1	8	83.3	50.0	50.0	31.733		
T2	20	50.2	23.5	23.5	14.367 (7.102–21.631)		
T3	44	61.0	16.1	5.4	15.933 (9.628–22.239)		
T4	4	25.0	0.0	0.0	5.233 (3.469–6.997)		
N classification						2.600	0.107
N0	33	59.9	31.2	31.2	15.767 (7.255–24.278)		
N1	43	57.2	10.8	3.6	14.500 (10.068–18.932)		
M classification						9.832	0.002
M0	50	68.3	30.6	21.0	19.700 (10.779–28.621)		
M1	26	40.4	0.0	0.0	7.467 (4.342–10.591)		
Tumor extent						10.856	0.001
Limited	60	65.2	25.1	17.2	19.700 (11.297–28.103)		
Extensive	16	33.9	0.0	0.0	7.400 (6.861–7.939)		
Surgery						2.009	0.156
Yes	30	70.3	29.6	15.8	18.000 (5.573–30.427)		
No	46	50.9	10.8	10.8	15.667 (9.343–21.991)		
Chemotherapy						1.022	0.312
Yes	43	59.4	20.1	20.1	15.967 (10.593–21.341)		
No	33	56.5	17.3	6.5	14.367 (7.524–21.209)		
Radiotherapy						0.812	0.367
Yes	29	62.5	19.1	19.1	15.933 (9.869–21.998)		
No	47	55.5	19.2	7.2	14.367 (10.729–18.004)		

MST, median survival time.

location of the primary lesion, macroscopic tumor type, and treatment option, did not show a significant association with prognosis ($P > 0.05$). By multivariate analysis, TNM classification ($\chi^2 = 14.709$, $P < 0.001$) was the only independent factor for the prediction of prognosis (Table 5).

Two staging systems in predicting survival

The correlations between the results of the two staging systems were evaluated, and the prognostic accuracy of each staging system was assessed for the whole group using the receiver operator characteristic (ROC) method and by estimating the area under the curve (AUC). The AUC for the 2002 AJCC TNM staging system was larger than that of the VALSG staging system with regard to predicting survival (0.774 vs. 0.620, Table 6), suggesting that the 2002 AJCC TNM staging system is superior to the VALSG staging system in predicting SCCE prognosis. Of note, brain metastases

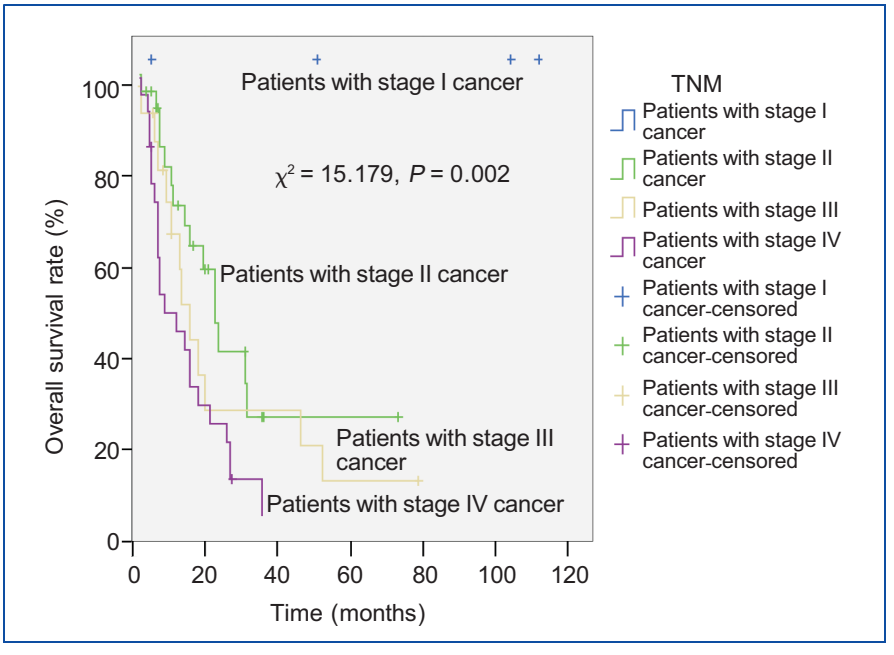

Figure 3. **Survival curves for patients with different TNM classification.** Patients with stage I cancer were all alive compared to patients with stage II, III, or IV cancer ($P = 0.002$).

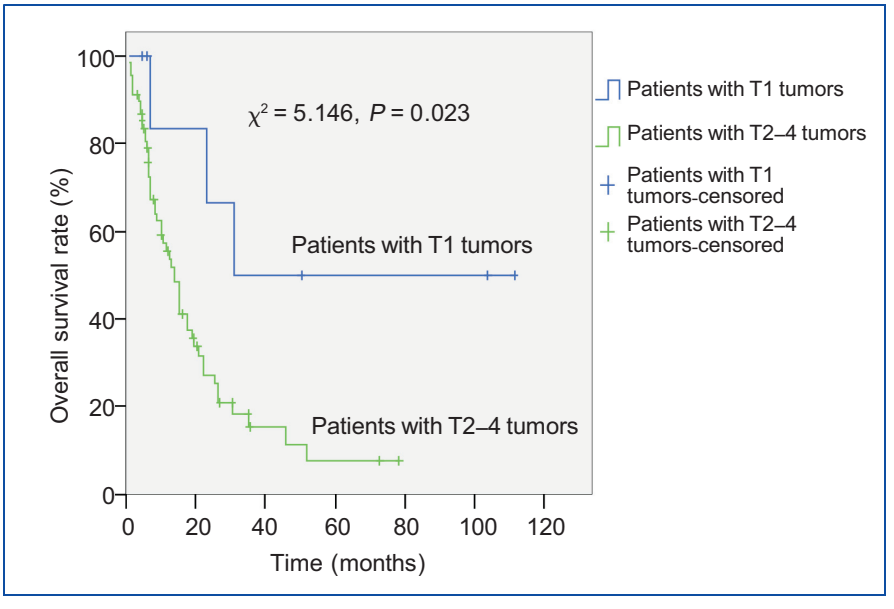

Figure 4. **Survival curves for patients with T1 and T2–4 tumors.** Median OS of patients with T1 tumors is longer than that of patients with T2–4 tumors (31.7 months vs. 14.5 months, $P = 0.023$).

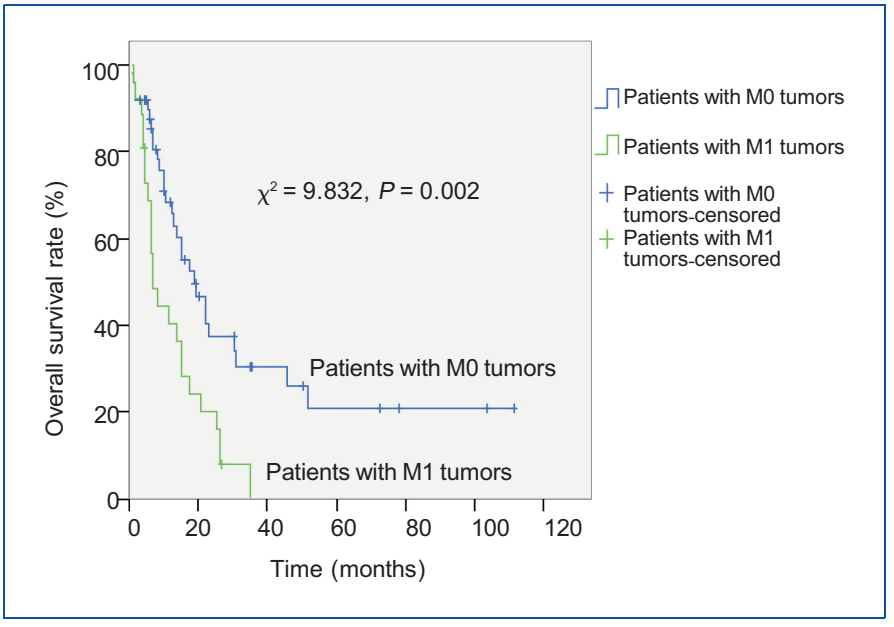

Figure 5. **Survival curves for patients with M0 and M1 tumors.** Median survival time of patients with M0 tumors is longer than that of patients with M1 tumors (19.7 months vs. 7.47 months, P = 0.002).

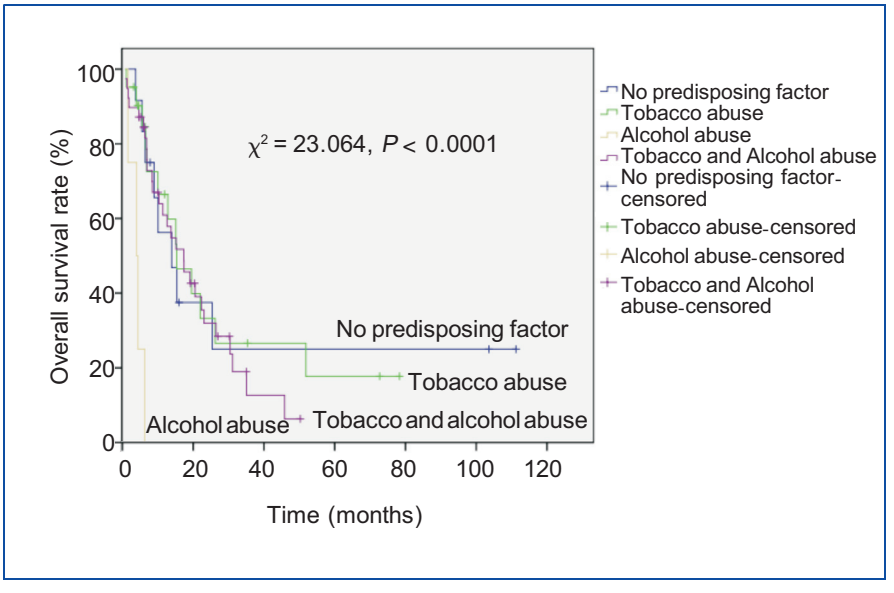

Figure 6. **Survival curves for patients with different predisposing factors.** Alcohol abuse patients had a shorter survival than patients with other predisposing factors (median survival time$_{(alcohol\ abuse)}$ = 4.6 months, P < 0.001).

were observed in only 1 patient during the follow-up period.

Discussion

Extrapulmonary small cell carcinoma is very uncommon, accounting for only 2.5% to 5.9% of all small cell carcinomas[1,25]. The clinical features of SCCE are basically identical to those of squamous cell carcinoma, with the major symptoms being progressive dysphagia, retrosternal pain, and loss of body weight. SCCE does not produce identifiable paraneoplasic syndromes, which have, in contrast, been well reported in small cell lung cancer[12]. Accordingly, paraneoplasic syndromes were not observed in our patient cohort. Furthermore, SCCE is characterized by high malignancy and early metastasis. At initial diagnosis, metastases are reported in 31% to 90% of cases[4,13,26,27]. In our study, 57% (43 of 76) of patients had regional lymph node metastasis and 34% (26 of 76) had distant metastases. An exception is brain metastases, which are common with small cell lung cancer but are rare with SCCE. Accordingly, only one patient from our cohort developed

Table 5. Multivariate Cox regression analysis for the prognosis of 76 patients with SCCE

Variable	*P*	RR (95% CI)
TNM classification	<0.001	1.749 (1.300–2.353)
Surgery	0.949	–
Chemotherapy	0.329	–
Radiotherapy	0.122	–
Location	0.689	–
Length	0.790	–
Predisposing factor	0.456	–
Extent disease	0.228	–

RR, relative risk; CI, confidence interval.

Table 6. Area under the curve statistics

Test result variable	Area	Standard error	Asymptotic significance	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
ED/LD	0.620	0.066	0.099	0.491	0.748
TNM	0.774	0.058	<0.001	0.660	0.887

ED, extensive disease; LD, limited disease. Extend (ED/LD) and TNM respectively have at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

brain metastases, and no patients had to undergo prophylactic cranial irradiation. In our study, the median OS was longer than that of other studies[28-30]. This is possibly because more of the patients in our cohort underwent therapy at early stages of disease. Patients with LD and early-stage disease (by the 2002 AJCC TNM staging system) had longer survival than patients with ED and late-stage disease.

The diagnosis of SCCE ultimately depends on histopathologic examinations, as the clinical presentation can be cryptic[10,31]. Esophagoscopic biopsy is the most frequently used method for diagnosis. Immunohistochemistry is also informative for diagnosis. Although NSE, which is found in neuroendocrine cells, is a good marker for SCCE diagnosis in tumor tissue, NSE in blood serum has been rarely observed[32-34]. Likewise, in our study, NSE levels in the blood remained low in most cases.

The standard therapy for SCCE has not yet been established. Patients with stage I disease survive longer after either chemoradiotherapy or radical surgery, making transthoracic esophagectomy with lymphadenectomy the option of choice for patients with early-stage cancer. For patients with advanced cancer, the most common systemic therapy is a cisplatin-based chemical regimen with concurrent or sequential radical radiotherapy. Ultimately, treatment is based on patient status, tumor stage, and other factors. Previous reports have suggested that SCCE should be considered a systemic disease and treated as such; however, no individual treatment regimens showed any survival benefit by Cox analysis in our cohort. This suggests that the use of combined treatments should be considered for this intractable malignancy for future studies.

Song *et al*.[35] suggested that clinical stage is an independent prognostic factor by multivariate analysis. In our cohort, the 2002 AJCC TNM classification was the only independent factor identified in multivariate analysis for predicting prognosis. Because this study included patients who did and did not undergo surgery, the newer 2009 AJCC TNM staging system was not used, as it is primarily targeted to patients who undergo surgery. The AUC of the 2002 AJCC TNM staging system, with regard to predicting the survival status, suggested that the TNM staging system is more accurate than the VALSG staging system for predicting the prognosis of SCCE. Interestingly, our data also showed that patients with alcohol abuse had worse prognosis than patients with other predisposing factors, including heavy smoking combined with alcohol abuse.

Our study is retrospective because the rarity of this neoplasia makes randomized trials infeasible. Multicenter network is needed in future studies.

In summary, SCCE is a relatively rare and fatal tumor for which a standard treatment has yet to be established. Detection of SCCE at early stages, regardless of the staging system used to diagnose the patient, is a good prognosis factor for survival. Although the 2002 AJCC TNM staging system was more sensitive than the VALSG staging system for predicting survival status, we recommend using both staging systems in clinical practice. Our data also confirm that brain metastases are uncommon in esophageal SCC and that prophylactic cranial irradiation is not routinely necessary.

Acknowledgment

This work was supported by a grant from the Zhejiang Provincial Natural Science Foundation (No. Y2080749).

Received: 2012-06-24; revised: 2012-08-17; accepted: 2012-09-09.

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