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Relationship between T stage and survival in distantly metastatic esophageal cancer

A STROBE-compliant study

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Abstract

To shed light on the interaction between the American Joint Committee on Cancer (AJCC) T stage and M stage in the determination of the overall survival (OS) and cancer-specific survival (CSS) of esophageal carcinoma patients. Moreover, to confirm our hypothesis that tumors that metastasize to distant sites in the early T stage may reflect a more biologically aggressive disease compared with those that metastasize in more advanced T stages.

We performed a retrospective cohort study with patients who were pathologically diagnosed with esophageal cancer between 2004 and 2014 in the surveillance epidemiology and end results (SEER) database. The primary study variables were the T and M stage, as well as their interaction terms. We performed a survival analysis of the interaction terms using unadjusted Kaplan–Meier methods and adjusted Cox proportional hazards models. Furthermore, we performed an exploratory analysis with stratification by histological type, esophageal adenocarcinoma (EAC), and esophageal squamous cell carcinoma (ESCC).

Data of 19,078 patients were retrieved from the SEER database. Unadjusted Kaplan–Meier curve indicated that patients with T2 and T3 stage had longer median OS and CSS (3 months and 4 months, respectively) than with T1 stage in distantly metastatic esophageal cancer (M1 stage). Multivariate analysis revealed a significant interaction between the T stage and M stage when determining the OS and CSS of esophageal cancer ($P < .001$). Using T1M0 as a reference, patients with T1M1 had significantly worse OS and CSS than those with T2M1 and T3M1 stage ($P < .001$). A similar pattern was also observed among patients with EAC and ESCC.

Our analysis suggests that the T1 stage predicts worse survival compared with T2 and T3 stage in distantly metastatic esophageal cancer and might be a surrogate for biologically aggressive disease, indicating that those patients should receive more aggressive treatments. Our findings also encourage researchers to discover new genomic changes in this subset of tumors with the potential to uncover new prognostic markers or drug targets. Further researches on the association between T stage and survival in metastatic esophageal cancer are warranted to validate our findings.

Abbreviations: AJCC =American Joint Committee on Cancer, CI = confidence interval, CSS = cancer-specific survival, EAC = esophageal adenocarcinoma, ESCC = esophageal squamous cell carcinoma, HR = hazard ratios, OS = overall survival, SEER = surveillance, epidemiology, and end results program, TNM = tumor, node, metastasis.

Keywords: cancer-specific survival, metastatic esophageal cancer, overall survival, personalized medicine, T stage

1. Introduction

Esophageal cancer is the sixth most common cause of cancer-related death and the ninth most common type of cancer worldwide.[1] Nearly 50% of esophageal cancer patients present with distant metastasis at initial diagnosis, and the prognosis of esophageal cancer remains far from satisfactory with an overall 5-year survival rate of 5% to 20%.[1,2] Accurately predicting patients' survival is very important to ensure that the therapy is tailored to the needs of each patient and develop a reasonable follow-up plan to improve the prognosis. Thus far, many prognostic factors including depth of tumor invasion, regional lymph node involvement, distant metastasis, tumor subsite, size, histology, and differentiation grade, as well as patients' race, age, sex, performance status, and comorbidities have been identified.[1,3,4] Among these, the presence of distant metastasis and the depth of tumor invasion, represented by the M stage and T stage according to the American Joint Committee on Cancer (AJCC), are two of the most critical prognostic determinants.

Recently, a growing body of literature revealed that the metastasis might occur in the early cancer stage. For example, it had been found that breast cancer with very small size could metastasize to local lymph nodes and present a more biologically

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The dataset(s) supporting the findings of this study are available in SEER 18 program using the SEER*Stat software (version 8.3.5).

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aggressive phenotype and was proved to cause worse survival than tumors that metastasize to local lymph nodes with the larger size.[5–7] A similar trend may be easier to detect in distantly metastatic cancer because distant metastasis represents the higher ability to spread than local metastasis. Nevertheless, tumor size cannot be examined easily in distantly metastatic esophageal cancer, and we can just use the T stage instead of tumor size. Consequently, we hypothesized that esophageal cancers that metastasize to distant sites in the early T stage may reflect a more biologically aggressive phenotype and lead to worse survival than those that metastasize to distant sites in the more advanced T stages. If our hypothesis is verified to be right, it might remind us that distantly metastatic esophageal cancer patients with early T stage should receive more aggressive treatments, shorter follow-up period, and stronger supportive care than metastatic patients with more advanced T stages. Our findings might also provide a new perspective for researchers to discover new genomic changes that enable early T stage tumors to metastasize distantly, with the potential to uncover new prognostic markers or drug targets.

Here, we aimed to shed light on the interaction between the T stage and M stage to determine the overall survival (OS) and cancer-specific survival (CSS) of patients with esophageal cancer using data obtained from the Surveillance, Epidemiology, and End Results (SEER) program. Particularly, we examined whether the early T stage indicates a worse prognosis in metastatic esophageal cancer compared with other more advanced T stages.

2. Methods

2.1. Patient selection and outcome measures

The SEER program collects information about cancer incidence, diagnosis, treatment, and prognosis. It is sponsored by the National Cancer Institute and covers 34.6% of the United States population to date.[8] The SEER research data are available to the public, and our requirement to access the research data has been approved by the SEER program (username: dengji). So, informed consent was not required. We obtained data from the SEER 18 program using the SEER*Stat software (version 8.3.5). Our study was approved by the Ethics Committee of Chinese PLA General Hospital.

In accordance with the STROBE statement, we performed a retrospective cohort study with eligible patients from this population-based database: those with pathologically confirmed esophageal cancer (site codes: C15.0–C15.5, C15.8, and C15.9), age >18 years, with esophageal cancer as the first and only primary cancer, and who were diagnosed between 2004 and 2014. Information on pathological T stage was not available before 2004; cases after 2014 were not included to make provision for adequate follow-up time. Patients with unknown or incomplete data on race, marital status, TNM stage, and surgery of primary cancer were excluded. We also excluded patients whose survival time was 0 month. Those patients whose data were obtained from autopsy records, death certificates, records from hospice care agencies, or records from nursing homes were excluded, as they were unlikely to receive aggressive systematic cancer treatment.

Data on patients' demographic and clinicopathologic characteristics, treatment regimens, and survival were retrieved. The primary study outcomes were OS and CSS. Vital status was assessed to determine whether the patient was alive or dead. OS was defined as the time from the initial diagnosis to death of any cause. Cause of death was categorized as esophageal cancer–specific or non-esophageal cancer–related death. CSS was calculated from the date of initial diagnosis to the date of esophageal cancer-related death. Patients who had non-esophageal cancer–related death were censored at the date of death for CSS analysis.

2.2. Statistical analysis

The interaction term, that is, T stage and M stage, was used as the primary study variable, to explore whether there was a significant interaction between pathological T stage and M stage in predicting survival in esophageal cancer. Additional study variables included decade of diagnosis (2004–2007, 2008–2011, and 2012–2014), age at diagnosis (≤75 years or >75 years), sex (female or male), marital status, race (white, black, and others), lymph node involvement (negative or positive), tumor location, grade, histological type, and surgical treatment. Marital status was reclassified into partnered (domestic partner or married) and un-partnered (divorced, separated, single, or widowed). Tumor location was classified into 4 groups:

(1) upper esophageal cancer (cervical and upper third of the esophagus tumors; site codes, C15.0 and C15.3),
(2) middle esophageal cancer (thoracic and middle third of the esophagus tumors; site codes, C15.1 and C15.4),
(3) lower esophageal cancer (abdominal and lower third of the esophagus tumors; site codes, C15.2 and C15.5), and
(4) not reported (site codes, C15.8 and C15.9).

Eligible patients' demographic and clinicopathologic characteristics by M Stage were compared using the Chi-square test or Kruskal–Wallis H test. Survival outcomes were estimated using the Kaplan–Meier method and compared using log-rank statistics. We used multivariable Cox proportional hazards regression to adjust for potential confounding covariates to calculate the adjusted hazard ratios (HR) and associated 95% confidence interval (CI). We did not include chemotherapy and radiotherapy in the analysis as the overall sensitivities for chemotherapy and radiotherapy were 68% and 80%, respectively.[9]

The overall presence of interaction between the T stage and M stage was explored using the Wald test. Pairwise comparisons were performed between different combinations of the T stage and M stage to determine the presence of significant survival differences. We performed an exploratory analysis with stratification by histological type, esophageal squamous cell carcinoma (ESCC), and esophageal adenocarcinoma (EAC) in accordance with the AJCC staging system. Moreover, the EAC and ESCC have different tissues of origin, risk factors, and high incidence areas and display considerable geographic variations. Hence, they were considered as different disease entities.[1,10] Two-sided *P* values less than .025 were considered significant. SPSS 23.0 (SPSS Inc. Chicago, IL) software was used to perform all statistical analyses.

3. Results

3.1. Descriptive statistics

In total, 19,078 patients who met the eligibility criteria were identified from the SEER database. The median follow-up time was 16 months (interquartile range [IQR]: 7–38) in M0 patients and 7 months (IQR: 3–14) in M1 patients. In total, 78.1% of patients died at the last contact, and 68.5% died due to

Table 1

Demographic and clinicopathologic characteristics of patients by M stage.

Characteristics	No.(%) of patients			*P* value
	Total (N = 19,078)	M0 stage (N = 13,506)	M1 stage (N = 5572)	
Year of diagnosis				.035‡
2004–2007	6540 (34.3)	4735 (35.1)	1805 (32.4)	
2008–2011	7054 (37.0)	4884 (36.2)	2170 (38.9)	
2012–2014	5484 (28.7)	3887 (28.8)	1597 (28.7)	
Age at diagnosis				<.001
≤75	15169 (79.5)	10435 (77.3)	4734 (85.0)	
>75	3909 (20.5)	3071 (22.7)	838 (15.0)	
Sex				<.001
Female	3754 (19.7)	2847 (21.1)	907 (19.7)	
Male	15324 (80.3)	10659 (78.9)	4665 (80.3)	
Race				>0.05
Others*	1003 (5.3)	707 (5.2)	296 (5.3)	
White	16069 (84.2)	11375 (84.2)	4694 (84.2)	
Black	2006 (10.5)	1424 (10.5)	582 (10.4)	
Marital status				>0.05
Unpartnered	7757 (40.7)	5462 (40.4)	2295 (41.2)	
Partnered	11321 (59.3)	8044 (59.6)	3277 (58.8)	
Tumor location				<.001
Upper esophagus	1208 (6.3)	951 (7.0)	257 (4.6)	
Middle esophagus	3549 (18.6)	2715 (20.1)	834 (15.0)	
Lower esophagus	12423 (65.1)	8595 (63.6)	3828 (68.7)	
Not reported	1898 (9.9)	1245 (9.2)	653 (11.7)	
Histological type				<.001
Adenocarcinoma	12261 (64.3)	8475 (62.7)	3786 (67.9)	
SCC†	6817 (35.7)	5031 (37.3)	1786 (32.1)	
Grade				<.001
I	948 (5.0)	808 (6.0)	140 (2.5)	
II	6652 (34.9)	4982 (36.9)	1670 (30.0)	
III,IV	8295 (43.5)	5433 (40.2)	2862 (51.4)	
Unknown	3183 (16.7)	2283 (16.9)	900 (16.2)	
Lymph node involvement				<.001
Negative	8873 (46.5)	7099 (52.6)	1774 (31.8)	
Positive	10205 (53.5)	6407 (47.4)	3798 (68.2)	
T stage				<.001‡
T1	6419 (33.6)	4635 (34.3)	1784 (32.0)	
T2	2259 (11.8)	1879 (13.9)	380 (6.8)	
T3	7314 (38.3)	5448 (40.3)	1866 (33.5)	
T4	3086 (16.2)	1544 (11.4)	1542 (27.7)	
Surgery				<.001
Performed	6746 (35.4)	6184 (45.8)	562 (10.1)	
Not Performed	12332 (64.6)	7322 (54.2)	5010 (89.9)	

* American Indian/AK Native, Asian/Pacific Islander.

† SCC = squamous cell carcinoma (According to the seventh edition of the AJCC cancer staging manual, if a tumor is of mixed histopathologic type or is not otherwise specified, it is recorded as squamous cell carcinoma).

‡ The statistical difference here is tested by Kruskal-Wallis H test.

esophageal cancer. A descriptive analysis of the demographic and clinicopathological features of the included patients was performed, and the results are shown in Table 1. Categories of M stage significantly differed in terms of age, sex, tumor location, lymph node involvement, differentiation grade, and histological type, T stage distribution, and surgical treatment.

3.2. Interaction between the T stage and M stage

Univariate analysis showed that decade of diagnosis, age, marital status, race, lymph node involvement, T stage, M stage, tumor location, grade, histological type, and surgical treatment were significantly associated with OS and CSS of esophageal cancer (Supplemental Table 1, http://links.lww.com/MD/E231). In multivariate analysis, a significant interaction was found between the T stage and M stage when determining the OS and CSS of esophageal cancer ($P < .001$, Tables 2 and 3). An earlier decade of diagnosis, older age, male sex, unpartnered status, black race, presence of lymph node involvement, later T stage and M1 stage, lower or unknown tumor location, higher tumor grade, ESCC, and absence of surgical treatment were independently associated with worse OS and CSS. Separate Kaplan–Meier survival curves and median survival months for nonmetastatic and metastatic patients stratified by T stage are shown in Figure 1.

Among patients with M1 stage, those with T1 stage experienced significantly worse OS and CSS compared with those with T2 and T3 stage ($P < .001$, Tables 2 and 3). Overall, patients with T2 and T3 stage had longer OS and CSS (3 months and 4 months, respectively) than those with T1 stage. There was no significant difference in CSS between patients with T1 stage

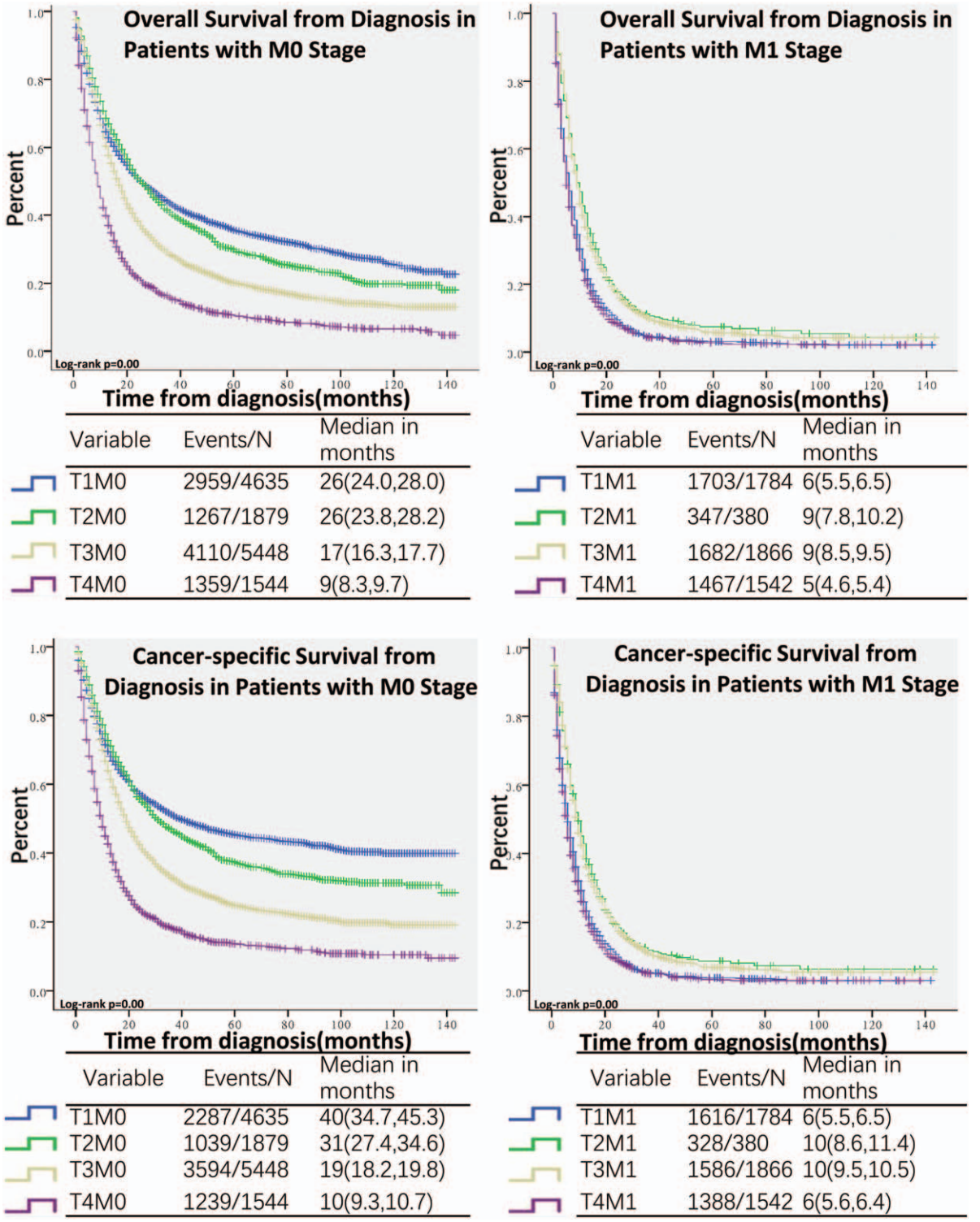

Figure 1. Separate Kaplan–Meier survival curves and median survival months (95% confidence interval) for nonmetastatic and metastatic patients stratified by T stage.

and those with T4 stage ($P > .025$, Table 3). In contrast, patients with T4 had significantly worse OS than those with T1 stage ($P < .025$, Table 2).

Among patients with M0 stage, those with T1 stage experienced significantly better OS and CSS than patients with T3 and T4 stages ($P < .001$, Tables 2 and 3). There was no significant difference in CSS and OS between patients with T1 and those with T2 stage ($P > .025$, Tables 2 and 3).

3.3. Interaction after stratification by histological type

After stratification by histological type, 12,261 patients were found to have EAC and 6817 had ESCC. A significant correlation

Table 2

Multivariable analysis of overall survival in esophageal cancer*.

	Overall		Pairwise	
Variable	**HR (95%CI)**	***P* Value**	**HR(95%CI)**	***P* Value**
Year of diagnosis		<.001		
2004–2007	1.00 [Reference]			
2008–2011	0.88 (0.85–0.92)			
2012–2014	0.82 (0.79–0.86)			
Age at diagnosis		<.001		
≤75	1.00 [Reference]			
>75	1.43 (1.38–1.49)			
Sex		<.001		
Female	1.00 [Reference]			
Male	1.18 (1.13–1.23)			
Race		<.001		
Others	1.00 [Reference]			
White	1.08 [1.00–1.16)			
Black	1.24 (1.14–1.35)			
Marital status		<.001		
Unpartnered	1.00 [Reference]			
Partnered	0.84 (0.81–0.86)			
Tumor location		<.001		
Upper esophagus	1.00 [Reference]			
Middle esophagus	1.22 (1.13–1.31)			
Lower esophagus	1.21 (1.12–1.30)			
Not reported	1.32 (1.21–1.43)			
Histological type		0.011		
SCC	1.00 [Reference]			
Adenocarcinoma	0.95 (0.91–0.99)			
Grade		<.001		
I	1.00 [Reference]			
II	1.24 (1.14–1.36)			
III,IV	1.50 (1.37–1.63)			
Unknown	1.11 (1.01–1.22)			
LNs involvement		<.001		
Negative	1.00 [Reference]			
Positive	1.17 (1.13–1.21)			
Surgery		<.001		
Not Performed	1.00 [Reference]			
Performed	0.42 (0.40–0.43)			
T stage		<.001		
M stage		<.001		
T stage*M stage†		<.001		
T stage and M stage‡		<.001		
T1M0	1.00 [Reference]		1.00 [Reference]§	
T2M0	0.96 (0.90–1.03)		0.94 (0.88–1.00)§	.067
T3M0	1.27 (1.21–1.34)		1.24 (1.18–1.31)§	<.001
T4M0	1.66 (1.55–1.78)		1.63 (1.53–1.75)§	<.001
T1M1	2.26 (2.12–2.41)		1.00 [Reference]‖	
T2M1	1.70 (1.52–1.90)		0.76 (0.68–0.86)‖	<.001
T3M1	1.79 (1.67–1.91)		0.80 (0.75–0.86)‖	<.001
T4M1	2.47 (2.30–2.64)		1.09 (1.01–1.17)‖	.023

* CI = confidence interval; HR = hazard ratio; LNs = lymph nodes.

† To determine whether there was significant interaction between tumor pathological T stage and M stage in predicting OS in esophageal cancer, we defined an interaction term (T stage*M stage).

‡ When the variable T stage and M stage were included, the variables T stage, M stage and their interaction term T stage*M stage were removed from the Cox model.

§ Reference group: T1M0.

‖ Reference group: T1M1.

between T stage and M stage in predicting both OS and CSS was also identified ($P < .001$) among patients with EAC and those with ESCC, respectively.

Among patients with M1 stage, those with T1 stage also experienced significantly worse OS and CSS than those with T2 and T3 stages ($P < .025$, Tables 4 and 5) in 2 subgroups. In patients with ESCC, those with T1 stage experienced significantly better OS and CSS than those with T4 stage ($P < .025$, Tables 4 and 5). In patients with EAC, no significant difference was observed in CSS and OS between patients with T1 stage and those with T4 stage.

Among patients diagnosed with ESCC with M0 stage, no significant difference was observed in OS and CSS between patients with T1 stage and those with T3 stage ($P > .025$, Tables 4

Table 3

Multivariable analysis of the cancer-specific survival in esophageal cancer[*].

	Overall		Pairwise	
Variable	**HR(95%CI)**	***P* value**	**HR(95%CI)**	***P* value**
Year of diagnosis		<.001		
2004–2007	1.00 [Reference]			
2008–2011	0.87 (0.84–0.91)			
2012–2014	0.81 (0.78–0.85)			
Age at diagnosis		<.001		
≤75	1.00 [Reference]			
>75	1.35 (1.30–1.41)			
Sex		<.001		
Female	1.00 [Reference]			
Male	1.16 (1.11–1.22)			
Race		<.001		
Others	1.00 [Reference]			
White	1.07 [1.00–1.16)			
Black	1.22 (1.12–1.34)			
Marital status		<.001		
Unpartnered	1.00 [Reference]			
Partnered	0.84 (0.81–0.87)			
Tumor location		<.001		
Upper esophagus	1.00 [Reference]			
Middle esophagus	1.21 (1.18–1.43)			
Lower esophagus	1.19 (1.10–1.29)			
Not reported	1.30 (1.19–1.43)			
Histological type		.02		
SCC	1.00 [Reference]			
Adenocarcinoma	0.95 (0.91–1.00)			
Grade		<.001		
I	1.00 [Reference]			
II	1.30 (1.18–1.43)			
III,IV	1.60 (1.45–1.76)			
Unknown	1.16 (1.05–1.28)			
LNs involvement		<.001		
Negative	1.00 [Reference]			
Positive	1.21 (1.17–1.26)			
Surgery		<.001		
Performed	1.00 [Reference]			
Not Performed	0.41 (0.39–0.43)			
T stage		<.001		
M stage		<.001		
T stage*M stage [†]		<.001		
T stage and M stage [‡]		<.001		
T1M0	1.00 [Reference]		1.00 [Reference][§]	
T2M0	1.00 (0.93–1.08)		0.97 (0.90–1.05)[§]	.432
T3M0	1.39 (1.31–1.47)		1.33 (1.26–1.41)[§]	<.001
T4M0	1.88 (1.75–2.02)		1.82 (1.82–1.96)[§]	<.001
T1M1	2.61 (2.46–2.79)		1.00 [Reference][‖]	
T2M1	1.97 (1.75–2.22)		0.76 (0.68–0.86)[‖]	<.001
T3M1	2.05 (1.91–2.19)		0.80 (0.75–0.86)[‖]	<.001
T4M1	2.83 (2.63–3.04)		1.09 (1.01–1.17)[‖]	.026

[*] CI = confidence interval; HR = hazard ratio; LNs = lymph nodes.

[†] To determine whether there was significant interaction between tumor pathological T stage and M stage in predicting OS in esophageal cancer, we defined an interaction term (T stage*M stage).

[‡] When the variable T stage and M stage were included, the variables T stage, M stage and their interaction term T stage*M stage were removed from the Cox model.

[§] Reference group: T1M0.

[‖] Reference group: T1M1.

and 5), while patients with T2 had significantly better OS and CSS ($P < .001$, Tables 4 and 5). Patients with T4 stage had significantly worse OS and CSS compared with those with T1 stage ($P < .001$, Tables 4 and 5).

Among patients diagnosed with EAC with M0 stage, those with T1 stage had better OS and CSS than those with T3 and T4 stages ($P < .001$, Tables 4 and 5). Patients with T1 stage had significantly better CSS ($P < .025$, Table 5) than those with T2 stage, but no significant difference in OS between them was detected ($P > .025$, Table 4).

4. Discussion

This study aimed to explore possible significant interaction between the AJCC T stage and M stage in the determination of the OS and CSS of patients with distantly metastatic esophageal

Table 4

Multivariate analysis of the overall survival in esophageal cancer by histological type*.

	Squamous cell carcinoma				Adenocarcinoma			
T stage and M stage †	Overall HR(95%CI)	*P* Value	Pairwise HR(95%CI)	*P* Value	Overall HR(95%CI)	*P* Value	Pairwise HR(95%CI)	*P* Value
T1M0	1.00 [Reference]	<.001	1.00 [Reference]		1.00 [Reference]	<.001	1.00 [Reference]	
T2M0	0.80 (0.72,0.89)		0.80 (0.71,0.88)‡	<.001	1.09 (1.00,1.18)		1.04 (0.95,1.13)‡	.375
T3M0	1.03 (0.95,1.11)		1.03 (0.95,1.12)‡	.47	1.46 (1.37,1.56)		1.38 (1.29,1.48)‡	<.001
T4M0	1.56 (1.42,1.71)		1.56 (1.42,1.72)‡	<.001	1.68 (1.52,1.85)		1.61 (1.46,1.77)‡	<.001
T1M1	1.97 (1.78,2.18)		1.00[Reference]		2.49 (2.29,2.71)		1.00[Reference]	
T2M1	1.52 (1.22,1.89)		0.76 (0.61,0.95)§	.018	1.85 (1.61,2.11)		0.77 (0.67,0.88)§	<.001
T3M1	1.51 (1.35,1.69)		0.77 (0.67,0.87)§	<.001	1.99 (1.83,2.16)		0.83 (0.76,0.90)§	<.001
T4M1	2.32 (2.09,3.45)		1.17 (1.03,1.31)§	.012	2.61 (2.39,2.85)		1.06 (0.97,1.15)§	.227

* CI = confidence interval; HR = hazard ratio.

† Adjusted for sex, age at diagnosis, decade of diagnosis, race, marital status, lymph node involvement, grade, surgery, and tumor location.

‡ Reference group: T1M0.

§ Reference group: T1M1.

cancer. We hypothesize that tumors that metastasize to distant sites in the early T stage might reflect more biologically aggressive disease and consequently result in worse survival than those that metastasize to distant sites in more advanced T stages. After adjusting for known and available prognostic factors, a significant interaction was found between the T stage and M stage when determining the OS and CSS of esophageal cancer ($P < .001$). Patients with T1 stage experienced significantly worse OS and CSS than those with T2 and T3 stage in metastatic esophageal cancer ($P < .001$). A similar pattern was also observed among patients with metastatic EAC and ESCC. In contrast, such a piecewise relationship between the T stage and survival was not observed in patients with nonmetastatic disease. These results supported our hypothesis.

To the best of our knowledge, this is the first study to systematically confirm that tumors that metastasize to distant sites in the early T1 stage were associated with worse outcomes than those that metastasize to distant sites in the T2 and T3 stage. David et al[11] performed a multivariable Cox proportional hazards model using 12,683 patients with metastatic esophageal cancer from American National Cancer Database to confirm whether definitive dose radiotherapy to primary tumor can improve OS; Similarly, patients with T1 stage experienced significantly worse OS than those with T2 and T3 stage, but this result was not mentioned and explained in this study. Here, we attempted to use systematic statistical methods to confirm the trend mentioned in Jennifer et al's study.[5] We tried to explain this phenomenon using the following facts or hypotheses. Esophageal cancer is transformed from the squamous epithelium dysplasia or metaplastic columnar epithelium.[1,10,12] Esophageal cancer initially spreads into the submucosa and then infiltrates upward, downward, and the entire layers and metastasize mainly via the lymphatic pathway.[13] Lymphatic channels are distributed in all layers below the basement membrane of the epithelium and drain into the regional lymph nodes or directly into the thoracic duct.[14] If the esophageal cancer penetrates the lymphatic vessels, then spreads, and survives in distant sites when they invade the lamina propria, muscularis mucosa, or the submucosa instead of the deeper layers like the muscularis propria, esophageal fibrous membrane, these esophageal cancers may be a surrogate for biological aggressiveness and consequently lead to worse survival. But when esophageal cancer invaded periesophageal tissues (T4 stage), there are much more regional tumor burden than T1 stage in metastatic esophageal cancer, so T1 stage was associated with better survival compared with T4 stage among patients with M1 disease.

This finding has important implications for researchers to identify the underlying mechanisms of the phenomenon. The

Table 5

Multivariate analysis of the cancer-specific survival in esophageal cancer by histological type*.

	Squamous cell carcinoma				Adenocarcinoma			
T stage and M stage †	Overall HR(95%CI)	*P* Value	Pairwise HR(95%CI)	*P* Value	Overall HR(95%CI)	*P* Value	Pairwise HR(95%CI)	*P* Value
T1M0	1.00 [Reference]	<.001	1.00 [Reference]		1.00 [Reference]	<.001	1.00 [Reference]	
T2M0	0.78 (0.70,0.89)		0.78 (0.69,0.88)‡	<.001	1.19 (1.08,1.31)		1.12 (1.02,1.24)‡	.019
T3M0	1.05 (0.97,1.15)		1.05 (0.96,1.15)‡	.271	1.67 (1.55,1.80)		1.54 (1.42,1.66)‡	<.001
T4M0	1.67 (1.51,1.85)		1.66 (1.50,1.84)‡	<.001	2.00 (1.81,2.22)		1.88 (1.69,2.09)‡	<.001
T1M1	2.15 (1.93,2.39)		1.00[Reference]		3.02 (2.76,3.30)		1.00[Reference]	
T2M1	1.67 (1.33,2.10)		0.76 (0.60,0.96)§	.022	2.25 (1.95,2.59)		0.77 (0.67,0.88)§	<.001
T3M1	1.66 (1.47,1.87)		0.77 (0.68,0.88)§	<.001	2.38 (2.18,2.60)		0.82 (0.75,0.90)§	<.001
T4M1	2.55 (2.27,2.84)		1.17 (1.03,1.32)§	.015	3.13 (2.85,3.45)		1.05 (0.96,1.15)§	.281

* CI = confidence interval; HR = hazard ratio.

† Adjusted for sex, age at diagnosis, decade of diagnosis, race, marital status,lymph node involvement, grade, surgery, and tumor location.

‡ Reference group: T1M0.

§ Reference group: T1M1.

conventional view about cancer spread is that cancer gains metastatic ability as a result of an accumulation of mutations as they grow,[6] In most esophageal cancers, this process might happen when the cancer has invaded the deeper areas.[14] However, the distant metastasis rate (M1 patients) were 27.8%, 16.8%, 25.5%, and 49.9% for patients of T1, T2, T3, and T4 respectively. These data indicate that esophageal cancers of T1 stage have similar or even higher distant metastasis ability as that of T2 and T3 stage. Several studies have also suggested that the acquisition of metastatic potential may occur early in cancer development for some tumors.[6,7] In some patients with colon cancer, nearly all mutations required for metastasis were present within the primary tumor potentially at the time of cancer initiation.[15] Similarly, in ESCC, some of the missense mutations in the TP53 gene have contributed to the invasion and metastasis.[16] A previous study revealed that TP53 mutations might occur very early in ESCC progression, even in squamous dysplasia, the precursor lesions of ESCC.[12] These findings agree with our study that some esophageal cancers might have some distinct important molecular mutations that can result in early metastasis and biological aggressiveness in the early T stage of cancer development and lead to worse survival (this might be one of the mechanisms of our hypothesis). Hence, further studies are needed to uncover these molecular mutations that enable T1 stage tumors to distantly metastasize, which might aid in the discovery of new genomic changes in this subset of tumors or new prognostic markers or drug targets.

Our findings, which might also influence clinical treatments, reinforces the fact that patients with T1 stage metastatic esophageal cancer should receive more aggressive treatments, shorter follow-up period, and stronger supportive care than those with T2 and T3 stage. For instance, combination chemotherapies consisting of fluoropyrimidine/platinum should be given to these patients if their condition permits. In some cases, the third agent, such as epirubicin or docetaxel was added to the fluoropyrimidine/platinum-containing chemotherapy, which had been proved to improve patients' prognosis.[17] Similarly, another previous study highlighted that the use of definitive radiotherapy dose ($\geq$5040 cGy) in the treatment of primary tumor can improve the condition of patients with newly diagnosed metastatic esophageal cancer.[11] Hence, Adding the third agent to the regular chemotherapy or a higher radiotherapy dose could be considered in the treatment of primary tumor in this setting.

In addition, our result indicated that the prognosis of patients with esophageal cancer had been improved as the decade of diagnosis progressed over time, possibly thanks to the advances in medical technology and clinical practice in recent years. We also demonstrated that partnered patients have superior overall and esophageal cancer-specific survival compared to unpartnered patients, which highlights the importance of social support in the care of patients with esophageal cancer.[18] Furthermore, we also found the patients of the Black race had a worse prognosis than the patients of the White race and the other race in which 90% was the Asian race, which is consistent with the previous scientific evidence.[4,19] Inadequate health care access and insurance coverage for the Blacks are major factors that contributed to racial and ethnic disparities,[4] which also indicates the importance of social support in esophageal cancer.

Finally, several limitations in this study need to be considered. First, our study was retrospective in nature. There is a potential for miscoding of study variables in the SEER database. However, miscoding would always be random, which is unlikely to introduce systematic misclassification bias.[5] Second, the SEER database does not provide data on essential tumor characteristics (e.g., human epidermal growth factor receptor 2), individual variables like performance status, comorbidities, etc. Thus, our multivariable Cox analyses could not adjust for these potential confounding variables. Third, the detailed information about cancer therapy was not available in the SEER database; hence, whether these results were caused by undertreatment of metastatic patients with T1 stage remains unclear. Despite that, we have excluded those patients whose data were obtained from autopsy records, death certificates, records from hospice care agencies, or records from nursing homes, who could not receive aggressive cancer treatment. Importantly, our results remained significant after adjusting for decades of diagnosis as a surrogate for the type of therapy. Fourth, although a large initial study population was used, only a few patients were included in each subgroup after stratifying by T stage, M stage, and histological type, yielding limited statistical power. Fifth, patients diagnosed with T1 stage cancer from 2010 to 2014 were classified into T1a and T1b subgroups based on the 7th edition of the TNM staging system. As only a few patients had T1a stage, it prevented us from exploring whether metastatic cancer patients with T1a stage had worse survival than those with T1b stage. Sixth, patients with M1 stage cancer diagnosed from 2004 to 2009 were classified into M1a and M1b subgroups based on the 6th edition of the TNM staging system; as only a few patients had M1a stage. This prevented us from determining whether there is an intermediate effect of T stage on survival between T1M1a vs T2M1a and T3M1a, relative to the difference between the T1M1b vs T2M1b and T3M1b patients, and that of T1M0 vs T2M0 and T3M0 patients.

Despite these limitations, the large, diverse, and population-based esophageal cancer cohort from the SEER database was the most satisfactory cohort we can obtain to prove our hypothesis. Our results should be treated cautiously, and further research regarding the association between the T stage and survival in metastatic esophageal cancer should be conducted to validate our findings.

5. Conclusion

Our analysis suggests that the T1 stage predicts worse survival compared with T2 and T3 stage in metastatic esophageal cancer and may be a surrogate for biologically aggressive disease, indicating that those patients should receive more aggressive treatments. Our findings also encourage researchers to discover new genomic changes in this subset of tumors with the potential to uncover new prognostic markers or drug targets. Further researches regarding the association between T stage and survival in metastatic esophageal cancer are warranted to validate our findings.

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Author contributions

Conception and design: Jianqing Deng, Bo Wang. Collection and assembly of data: Jianqing Deng, Zhipeng Ren. Data analysis and interpretation: Jianqing Deng, Xiangyang Chu. Manuscript writing: all authors. All authors contributed toward data

analysis, Manuscript revision, and agreed to be accountable for all aspects of the work.

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