

Analysis of Prognostic Factors in Patients Undergoing Curative Surgery for Esophageal Carcinoma

Eurasian Clinical and Analytical Medicine Original Research

Prognostic Factors in Esophageal Carcinoma

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Abstract

Aim: We analyzed the clinicopathological data of patients with esophageal carcinoma who underwent curative surgery and investigated the predictive prognostic factors affecting mortality and survival.

Material and Methods: A retrospective analysis of patients with esophageal cancer who underwent curative esophagectomy between 2001 and 2011 was performed and the clinicopathological factors were analyzed.

Results: We identified a total of 119 patients who underwent radical esophagectomy. The mean age was 65.2 ± 12.87 years. The 30-day postoperative mortality was 5.0%. Multivariate analysis demonstrated that long-lasting symptoms (P = 0.0001), increased serum calcium levels (P = 0.019), high pT, high pN status, high stage, high grade (P = 0.001, P = 0.018, P = 0.003, P = 0.012) and low FEV1 levels (P < 0.0001) were associated with increased mortality. The 1, 3 and 5 year survival rates were 68.2%, 36.2% and 20.1% respectively and mean follow-up period is 2246 ± 1.79 months. Based on multivariate analysis, pT, pN, stage, grade (P = 0.012, P < 0.0001, P < 0.0001, P < 0.0001) and tumor length (P = 0.018) were independent factors for the prognosis.

Discussion: Our results showed that the tumor length greater than 4 cm were associated with poor prognosis. We suggest that for a better selection of patients for an appropriate treatment tumor length should be included in TNM staging of esophageal carcinoma.

Keywords

Esophageal Cancer; Mortality; Survival; Tumor Length

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Introduction

Esophageal cancer is one of the most causes of cancer deaths worldwide. It is endemic in many parts of the world, especially in developing countries [1]. The surgical resection is the primary treatment choice for these patients. However, the 5-year overall survival rate of esophageal carcinoma patients is approximately 20% even when the tumor is resected in the early stages [2, 3]. The mainly accepted prognostic factors in esophageal carcinoma after esophagogastrectomy are histological subtype, depth of tumor invasion (T), lymph node metastases (N), and tumor differentiation [4-6]. Although tumor length was found to be an independent prognostic factor [7-9] it was not listed as a risk factor in esophageal carcinomas in 7th edition of the American Joint Committee on cancer TNM system [10].

Despite improvements in all treatment techniques, the prognosis still remains poor. We aimed to analyze the predictive prognostic factors in esophageal carcinoma patients who underwent esophagectomy without neoadjuvant treatment whether the tumor length could be a part of TNM staging of esophageal carcinoma.

Material and Methods

One hundred and forty-six patients with esophageal carcinoma underwent an esophagectomy between March 2001 and December 2011 at Thoracic Surgery Department of Ankara Numune Teaching and Research Hospital. Clinicopathological variables and survival times were collected by telephone interview and patient's medical records. Out of 146 patients, survival information was available for 119 patients. Physical examination, laboratory tests, endoscopy and barium graphy of upper gastrointestinal system, flexible bronchoscopy, computed tomography (CT) scan from neck to upper abdomen, and radionuclide bone scans were done for all patients. Some patients received Positron Emission Tomography (PET) CT. Pulmonary and cardiac function studies were done for evaluating of surgical tolerance.

We have done esophagectomy via right thoracic approach in 68 patients, via left thoracophrenotomy in 30 patients, and via transhiatal approach in 21 patients. Three-field lymphadenectomy was performed in 59 patients and two field lymphadenectomy was performed in 60 patients. In all patients reconstruction was made with gastric tube. We performed intrathoracic anastomosis in 39 patients while cervical anastomosis was done in 80 patients. All anastomosis was done by hand sewing.

Ninety-two (77.3%) patients had squamous cell carcinoma, 22 (18.5%) patients had adenocarcinoma and 5 (4.2%) patients had adenosquamous carcinoma.

Restaging after obtaining the pathologic results were done according to AJCC 7th edition guidelines [10]. This study protocol was approved by the Medical Ethics Committee of our institution.

Statistical analyses

All statistical analyses were performed with SPSS 11.5 for windows (SPSS Inc., USA). Descriptive analyses were done for all patient characteristics. Results were expressed as means \pm standard deviation and percentage. χ^2 tests was used to compare categorical variables. The factors affecting hospital mortality were evaluated with univariate analyses and in case of $P < 0.25$ the factors also evaluated with multivariate logistic regression analyses. The probability curves for survival were calculated according to the Kaplan-Meier Method and compared by the log-rank test. Multivariate analyses were carried out using the Cox proportional hazard model. $p < 0.05$ was considered as statistically significant.

Results

Clinicopathologic characteristics

Out of 146 patients, survival information was available for 119 patients, including 43 (36.1%) female and 76 (63.9%) male. The male-female ratio

Table 1. Patients' demographics and tumor characteristics

Age	65.2 [20-80]
Male/female	1.7:1
Presenting Symptoms	n (%)
Dysphagia	115 (96.6%)
Odynophagia	36 (30.3%)
Regurgitation	21 (17.6%)
Weight loss	105 (88.2%)
1-5 kg	62 (52.1%)
6-10 kg	37 (31.1%)
11-15 kg	6 (5.0%)
Tumor differentiation (Grade)	
1	57 (47.9%)
2	30 (25.2%)
3	32 (26.9%)
Tumor Location	
Cervical esophagus	18 (15.2%)
Upper thoracic esophagus	20 (16.8%)
Middle thoracic esophagus	39 (32.7%)
Lower thoracic esophagus	30 (25.2%)
Gastro-esophageal junction	12 (10.0%)
Tumor depth	
pT1	7 (5.9%)
pT2	32 (26.9%)
pT3	58 (48.7%)
pT4	22 (18.5%)
Lymph nodes status	
pN0	55 (46.2%)
pN1	42 (35.0%)
pN2	22 (18.5%)
Stage	
I B	9 (7.6%)
II A	23 (19.3%)
II B	24 (20.2%)
III A	35 (29.4%)
III B	12 (10.1%)
III C	16 (13.4%)
Histological Type	
Squamous cell carcinoma	92 (77.3%)
Adenocarcinoma	22 (18.5%)
Adenosquamous carcinoma	5 (4.2%)
Tumor Length	
\leq 4 cm	68 (57.1%)
$>$ 4 cm	51 (42.8%)
Adjuvant Treatment	
With Postoperative Chemoradiation	44 (36.9%)
Without Postoperative Chemoradiation	75 (63.1%)

was 1.7. The mean age was 65.2 ± 12.87, (range 20-80) at the time of diagnosis. Patients' characteristics for the study group are summarized in Table 1. Esophagogastric anastomosis was cervical in 80 (67.2%) patients and intrathoracic in the remaining 39 (32.7%) patients. Sixty three (52.9%) patients were in stage III. Forty four (36.9%) patients received chemoradiation after surgery.

Mortality

Traditionally, operative mortality has been defined as any death, regardless of cause, occurring (1) within 30 days after surgery in or out of the hospital, and (2) after 30 days during the same hospitalization subsequent to the operation. Additionally in-hospital mortality was defined as death occurring during the hospital stay. The in-hospital mortality rate was 8.4% (10/119) where the 30-day postoperative mortality rate was 5.0% (6/119). On the other hand operative mortality was as same with in-hospital mortality rate (8.4%). Thirty day postoperative mortality was mainly due to anastomotic leaks (n = 2 the anastomosis were intrathoracic), bronchopneumonia (n = 3), multi-organ dysfunction (n = 1). According to univariate analyses of all risk factors in operative mortality, high pathological T status (P = 0.002), high pathological N status (P = 0.043), high TNM stage (P = 0.002), high grade (P = 0.017), and as a continuous variable high calcium level (P = 0.030), FEV1 level less than 2 lt (P < 0.001), and high duration of symptoms (P < 0.001) were each associated with increased mortality following esophagectomy. Also when evaluated by multivariable logistic regression analyses all these factors were independently associated with mortality (Table 2).

Postoperative Morbidity

Significant postoperative complications occurred in 39 (32.7%) patients. Anastomotic leakage was identified in a total of 8 (6.7%) patients. Four of them were intrathoracic and two of these patients died because of mediastinitis. In the other two patients the leakage was from the linear staple line of gastric tube and they underwent surgery for reconstruction of the gastric tube. The other anastomoses were in the cervical region and we treated these patients conservatively. Significant pulmonary complications were observed in 18 (15.1%) patients with bronchopneumonia (n = 10), pulmonary embolism (n = 2), respiratory distress syndrome (n=1), and pleural complication (n = 5). Other postoperative complications were cardiac arrhythmias (n=4) and wound infections (n=3).

Survival

The 1, 3 and 5 year survival rates were 68.2%, 36.2% and 20.1% respectively and mean follow-up period was 22.46 ± 1.79 months. Table 3 shows the clinicopathological variables affecting the cumulative survival rates by the univariate analysis. The factors affecting survival rate were T status (P < 0.001), N status (P < 0.001), stage (P < 0.001), grade (P < 0.001),

and tumor length (P = 0.011). As a continuous variable only FEV1 (P < 0.001), was affecting the survival rate (Table 4). Among these significant variables evaluated by the univariate analysis, independent prognostic factors of poor prognosis as determined by multivariate analyses were high pT (P = 0.012), high pN (P < 0.001), high TNM stage (P < 0.001), high grade (P < 0.001), and tumor length > 4 cm (P = 0.018), (Table 5). We also

Table 3. Clinicopathological variables influencing the cumulative survival rates by the univariate analysis.

Variables	No. of Patients	Survival [%]			P-value*
		1 year	3 year	5 year	
Sex					
Female	43	61.5	38.6	30.9	0.326
Male	76	74.7	47.1	36.5	
T Status					
T1	7	85.7	57.1	42.9	< 0.001*
T2	32	79.6	69.2	58.8	
T3	58	74.8	42.4	3.3	
T4	22	36.7	5.2	5.2	
N Status					
N0	55	88.5	70.4	57.9	< 0.001*
N1	42	71.6	31.8	23.1	
N2	22	22.7	4.5	NC	
Stage					
IB	9	77.8	66.7	66.7	< 0.001*
IIA	23	95.2	85.4	69.4	
IIB	24	90.9	68.2	50.0	
IIIA	35	72.3	31.4	21.0	
IIIB	12	25.0	0.0	0.0	
IIIC	16	27.8	0.0	0.0	
Tumor Location					
Servical esophagus	18	71.4	31.2	25.7	0.594
Upper esophagus	20	65.5	29.8	29.8	
Middle esophagus	39	80.8	54.9	42.2	
Lower esophagus	30	64.6	35.9	26.3	
GEJ	12	69.8	49.2	31.2	
Grade					
I	57	88.6	68.8	58.4	< 0.001*
II	30	62.3	27.7	13.8	
III	32	44.2	17.0	13.6	
Pathology					
SCC	92	69.8	44.4	34.2	0.540
ADC	22	67.4	43.3	33.7	
ADSC	5	80.0	60.0	40.0	
Tumor Length					
≤4	68	82.9	61.8	50.4	0.011*
>4	51	52.4	18.4	13.1	
Adjuvant Treatment					
With CRT	44	69.8	34.9	25.6	0.250
Without CRT	75	70.2	50.2	40.5	

SCC: Squamous cell carcinoma ADC: Adenocarcinoma NC: Not Calculated ADSC: Adenosquamous carcinoma CRT: Chemoradiation GEJ:Gastroesophageal Junction * Statistically significant P < 0.05

Table 2. Statistical Association of Preoperative and Postoperative Variables with 30-day postoperative mortality

Variable	Univariate Analysis	Multivariable Logistic Regression Analysis	P-value
	P-value *	OR (95% CI)	
T status	0.002*	2.885 (1.566-5.313)	0.001*
N status	0.043*	2.915 (1.199-7.087)	0.018*
Stage	0.002*	2.426 (1.355-4.343)	0.003*
Grade	0.017*	3.152 (1.292-7.691)	0.012*
Calcium	0.030*	3.300 (1.218-8.942)	0.019*
FEV1(lt)	P < 0.001*	0.000 (0.000-0.175)	0.0001*
Symptoms duration (day)	P < 0.001*	0.091 (0.099-1.006)	0.0001*

OR: Odds Ratio, CI: confidence interval, * statistically significant p<0.05

found tumor length greater than 4 cm was associated with high pT status ($\chi^2 = 54.768, P < 0.001$) high pN status ($\chi^2 = 14.02, P < 0.001$) and high TNM stage ($\chi^2 = 44.53, P < 0.001$).

Table 4. Univariate Cox regression analysis of continuous variables that can affect survival rates.

Variables	Relative risk	95% Confidence Interval	P-value*
Age	0.999	0.984 - 1.014	0.859
Symptoms duration (day)	1.001	0.999 - 1.002	0.443
Calcium	1.355	0.976 - 1.881	0.069**
Sedimentation	1.006	0.997 - 1.014	0.197**
Hgb	1.024	0.934 - 1.122	0.614
Hematocrit	1.008	0.975 - 1.043	0.631
WBC	1.000	0.924 - 1.081	0.991
PLT	1.000	0.999 - 1.002	0.612
Fibrinogen	1.000	0.999 - 1.002	0.646
RDW	1.002	0.937 - 1.071	0.961
LDH	1.001	0.999 - 1.002	0.263
FEV1lt	0.612	0.481 - 0.778	< 0.001*

Hgb: Hemoglobin, Hct: Hematocrit, WBC: White blood Count
 PLT: Platelet, RDW: Red blood cell distribution width,
 LDH: lactate dehydrogenase activity, * statistically significant P < 0.05
 **P < 0.25 was considered sufficient,

Table 5. Multivariate Analysis of Prognostic factors for Cumulative Survival Using Cox's Proportional Hazard Model

Variables	Hazard ratio	95% Confidence Interval	P-value
Stage	1.501	1.222 - 1.844	< 0.001*
FEV1 lt	0.725	0.853 - 1.730	0.244
Grade	1.498	1.056 - 1.720	< 0.001*
Tumor length cm	1.123	0.851 - 1.435	0.018*
pT	1.451	1.029 - 2.048	0.012*
pN	2.146	1.617 - 3.088	< 0.001*
Calcium	1.225	0.870 - 1.725	0.246
Sedimentation	1.004	0.996 - 1.013	0.351

* Statistically significant P < 0.05

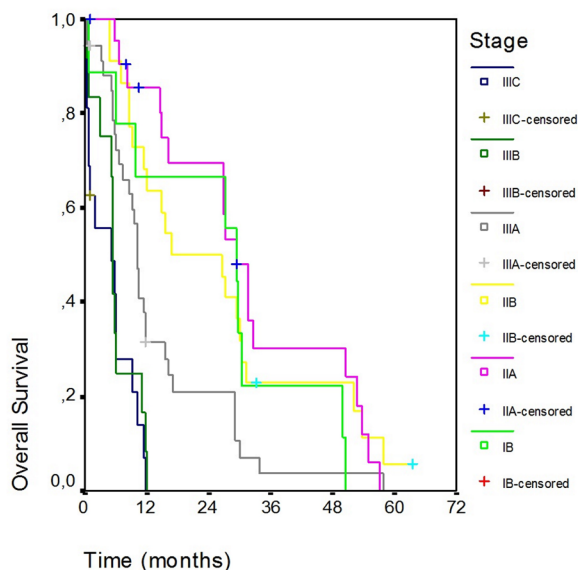


Figure 1. Survival curve based on stage of esophageal carcinoma

Cumulative survival curves in terms of stage, grade and tumor length are shown in Figures 1, 2, 3 respectively.

Discussion

In this study we analyzed the factors affecting the mortality and survival data in 119 patients undergoing curative esophagectomy for esophageal carcinoma. Our analysis demonstrated an 8.4% in-hospital mortality rate, a 5.0% 30-day postoperative mortality rate and a 32.7% postoperative morbidity rate after esophagectomy. Morbidity and mortality rates have decreased over time for esophagectomies performed for cancer. Recently Merkow et al. suggested that age between 55-69 years, and presence of preoperative dyspnea were found to be independently prognostic factors for hospital mortality [11]. But age was not found to be related with increased mortality in our study. Furthermore preoperative cardiac, respiratory and hepatic functions were found to be related with postoperative mortality in several studies [12, 13]. In the current study, T status, N status, stage, grade, and as a continuous variable high calcium level, low FEV 1 level, and high duration of symptoms were each associated with increased mortality. On the other hand our operative mortality rate (8.4 %) was high because 52.9% of the patients had locally advanced tumor (stage III) with a low FEV1 and in these patients duration of symptoms and serum calcium levels were expected to be high.

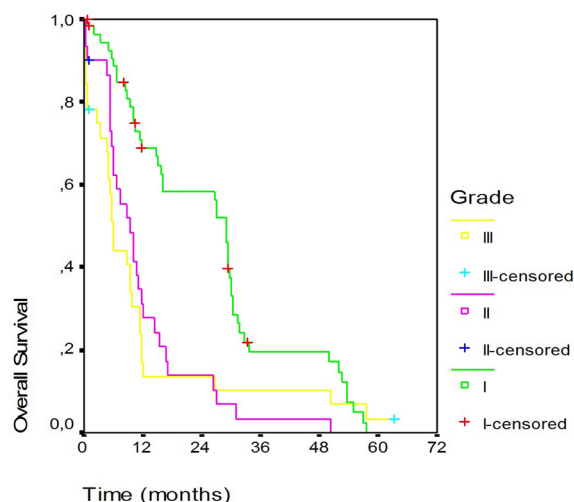


Figure 2. Survival curve based on grade of esophageal carcinoma

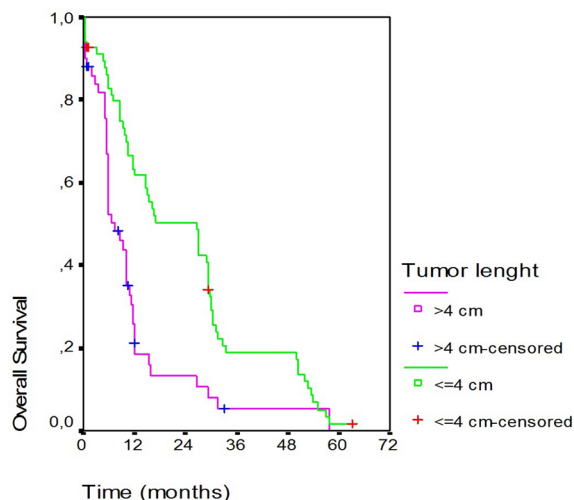


Figure 3. Survival curve based on tumor length of esophageal carcinoma.

Major pulmonary complications occurred in 15.1% of our patients and were responsible for 50% of operative mortality. This rate of pulmonary morbidity is similar to that reported in the literature [14, 15].

The mean age at diagnosis in our patients was 65.2 ± 12.87 , ranging from 20 to 80 years. In several studies age was found to be inversely associated with the survival rate [16, 17]. But in our study age did not influence the survival.

In this study gender ($P = 0.326$), tumor location ($P = 0.594$), pathology ($P = 0.540$) and adjuvant chemoradiation ($P = 0.250$) didn't influence the survival statistically. On the other hand tumor length was found to have a significant correlation with other tumor characteristics such as patients with tumor length ≥ 4 cm had high T stage, worse N stage, high TNM stage and poor survival. In many studies it has been shown that overall TNM stage and grade are strong independent prognostic factors in esophageal cancer [18- 20]. Also in the literature there are some reports stating that tumor length was an independent predictive factor for survival in adenocarcinoma or squamous cell carcinoma of esophagus [21-24]. The results of our study also showed tumor length could be a part of TNM staging of esophageal carcinoma.

As a retrospective study, there were some limitations. The sample size was small and we used mortality from all causes instead of disease specific deaths. Additionally we enrolled the patients who had only curative surgery.

In conclusion, our results confirm the importance of pT and pN, overall TNM stage and grade for the prognosis. Furthermore esophageal tumor length ≥ 4 cm was significantly associated with high pT stage, worse lymph stage, high overall TNM stage and poor survival. In this regard esophageal tumor length should be included in TNM staging system as a predictive prognostic factor.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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