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.

Methods: A retrospective analysis was performed on patients with esophageal cancer who underwent curative esophagectomy between 2001 and 2011. Clinicopathological factors were analyzed to identify predictors of outcome.

Results: A total of 119 patients who underwent radical esophagectomy were included. The mean age was 65.2 ± 12.87 years. The 30-day postoperative mortality rate was 5.0%. Multivariate analysis demonstrated that long-lasting symptoms (p=0.0001), elevated serum calcium levels (p=0.019), higher pT and pN status, advanced stage, higher tumor grade (p=0.001, p=0.018, p=0.003, p=0.012), and lower FEV_1 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, with a mean follow-up period of 22.46 ± 1.79 months. Multivariate analysis identified pT, pN, stage, grade (p=0.012, p<0.0001, p<0.0001, p<0.0001), and tumor length (p=0.018) as independent prognostic factors.

Conclusion: Our results indicate that tumors longer than 4 cm are associated with poorer prognosis. We suggest that tumor length should be incorporated into TNM staging of esophageal carcinoma to improve patient selection for appropriate treatment strategies.

Keywords

esophageal cancer, mortality, survival, tumor length

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Introduction

Esophageal cancer is among the leading causes of cancer-related deaths worldwide. It is endemic in many regions, particularly in developing countries.[1] Surgical resection remains the primary treatment for these patients; however, the 5-year overall survival rate is approximately 20%, even when tumors are resected at early stages.[2,3] The most widely accepted prognostic factors following esophagogastrectomy include histological subtype, depth of tumor invasion (T), lymph node metastases (N), and tumor differentiation.[4-6] Although tumor length has been identified as an independent prognostic factor,[7,9] it is not included as a risk factor in the 7th edition of the American Joint Committee on Cancer TNM system.[10]

Despite advances in treatment techniques, the prognosis of esophageal carcinoma remains poor. In this study, we aimed to analyze predictive prognostic factors in patients who underwent esophagectomy without neoadjuvant therapy and to evaluate whether tumor length should be incorporated into TNM staging.

Materials and Methods

Between March 2001 and December 2011, a total of 146 patients with esophageal carcinoma underwent esophagectomy at the Thoracic Surgery Department of Ankara Numune Training and Research Hospital. Clinicopathological variables and survival data were collected via telephone interviews and patients' medical records. Survival information was available for 119 of the 146 patients.

All patients underwent physical examination, laboratory testing, upper gastrointestinal endoscopy and barium studies, flexible bronchoscopy, computed tomography (CT) scans from the neck to the upper abdomen, and radionuclide bone scans. Some patients also received positron emission tomography (PET) CT. Pulmonary and cardiac function assessments were performed to evaluate surgical tolerance.

Esophagectomy was performed via a right thoracic approach in 68 patients, via left thoracophrenotomy in 30 patients, and via a transhiatal approach in 21 patients. Three-field lymphadenectomy was performed in 59 patients, and two-field lymphadenectomy in 60 patients. Gastric tube reconstruction was performed in all patients, with intrathoracic anastomosis in 39 patients and cervical anastomosis in 80 patients. All anastomoses were hand-sewn.

Pathological examination revealed squamous cell carcinoma in 92 patients (77.3%), adenocarcinoma in 22 patients (18.5%), and adenosquamous carcinoma in 5 patients (4.2%). Tumor staging was performed according to the AJCC 7th edition guidelines. This study protocol was approved by the Medical Ethics Committee of our institution.

Statistical Analysis

Statistical analyses were performed using SPSS 11.5 for Windows (SPSS Inc., USA). Descriptive statistics were calculated for all patient characteristics and expressed as mean ± standard deviation or percentage. Categorical variables were compared using the X^2 test. Factors affecting hospital mortality were first evaluated with univariate analysis, and those with $p<0.25$ were further analyzed using multivariate logistic regression. Survival probability curves were calculated using the Kaplan-Meier method and compared by the log-rank test. Multivariate survival analyses were conducted using the Cox proportional hazards model. A p-value < 0.05 was considered statistically significant.

Results

Clinicopathologic Characteristics

Out of 146 patients, survival information was available for 119 patients, including 43 (36.1%) females and 76 (63.9%) males, resulting in a male-to-female ratio of 1.7. The mean age at diagnosis was 65.2 ± 12.87 years (range, 20–80 years). Patients' characteristics are summarized in Table 1. Esophagogastric anastomosis was cervical in 80 (67.2%) patients and intrathoracic in 39 (32.7%) patients. Sixty-three patients (52.9%) were in stage III, and 44 patients (36.9%) received adjuvant chemoradiation following surgery.

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	
≤ 4 cm	68 (57.1%)
> 4 cm	51 (42.8%)
Adjuvant Treatment	
With Postoperative Chemoradiation	44 (36.9%)
Without Postoperative Chemoradiation	75 (63.1%)

Mortality

Operative mortality was defined as any death occurring within 30 days postoperatively or during the same hospitalization. In-hospital mortality was 8.4% (10/119), while the 30-day postoperative mortality rate was 5.0% (6/119). Thirty-day deaths were primarily due to anastomotic leaks (n = 2, intrathoracic), bronchopneumonia (n = 3), and multi-organ dysfunction (n = 1).

Univariate analysis revealed that high pathological T status (p=0.002), high pathological N status (p=0.043), advanced TNM stage (p=0.002), high tumor grade (p=0.017), elevated serum calcium (p=0.030), FEV_1 < 2 L (p=0.001), and longer symptom duration (p=0.001) were associated with increased mortality. Multivariate logistic regression confirmed that all these factors were independently associated with operative mortality (Table 2).

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

Variable	Univariate Analysis P-value *	Multivariable Logistic Regression Analysis OR (95% CI)	P-value
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

Postoperative Morbidity

Significant postoperative complications occurred in 39 patients (32.7%). Anastomotic leakage was observed in 8 patients (6.7%); four were intrathoracic, of whom two died due to mediastinitis. Two leakages occurred at the gastric tube staple line and required reconstructive surgery. Cervical anastomotic leaks were managed conservatively. Pulmonary complications were identified in 18 patients (15.1%), including bronchopneumonia (n = 10), pulmonary embolism (n = 2), respiratory distress syndrome (n = 1), and pleural complications (n = 5). Cardiac arrhythmias occurred in 4 patients, and wound infections were noted in 3 patients.

Survival

The 1, 3, and 5 year survival rates were 68.2%, 36.2%, and 20.1%, respectively, with a mean follow-up period of 22.46 ± 1.79 months. Univariate analysis identified T status (p<0.001), N status (p<0.001), TNM stage (p<0.001), tumor grade (p<0.001), and tumor length as significant predictors of cumulative survival (Table 3).and tumor length (p=0.011). As a continuous variable only FEV_1 (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 found tumor length greater than 4 cm was associated with high pT status (X^2 = 54.768, p<0.001) high pN status (X^2 = 14.02, p<0.001) and high TNM stage (X^2 = 44.53, p<0.001). 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 factors affecting mortality and survival in 119 patients undergoing curative esophagectomy for esophageal carcinoma. The in-hospital mortality rate was 8.4%, the 30-day postoperative mortality rate was 5.0%, and the postoperative morbidity rate was 32.7%. Although morbidity and mortality rates for esophagectomy have decreased over time, our operative mortality was relatively high, likely due to 52.9% of patients presenting with locally advanced tumors (stage III) and low FEV_1 levels, along with prolonged symptom duration and elevated serum calcium levels.

Previous studies have suggested that age between 55–69 years and

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

Variables	No. of Patients	Survival (%) 1 year	3 year	5 year	P-value*
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 Lenght					
≤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

preoperative dyspnea are independent prognostic factors for hospital mortality.[11] In contrast, age did not significantly influence mortality in our cohort. Preoperative cardiac, respiratory, and hepatic functions have also been reported as important predictors of postoperative mortality.[12,13] In our study, pathological T and N status, TNM stage, tumor grade, high serum calcium, low FEV_1, and long symptom duration were all independently associated with increased mortality. Major pulmonary complications occurred in 15.1% of patients and accounted for 50% of operative deaths, consistent with rates reported in the literature.[14,15] Regarding survival, the mean age at diagnosis was 65.2 ± 12.87 years (range 20–80), and age did not significantly affect outcomes, unlike some reports showing an inverse relationship between age and survival.[16-17] Gender, tumor location, histopathology, and adjuvant chemoradiation also did not significantly influence survival.

Tumor length emerged as an important prognostic factor. Patients with tumors ≥ 4 cm had higher T and N stages, more advanced TNM stage, and poorer survival. These results align with prior studies highlighting TNM stage and tumor grade as strong independent prognostic factors,[18,20] and with reports indicating that tumor length independently predicts survival in both adenocarcinoma and squamous cell carcinoma of the esophagus.[8,21-23] Our findings support including tumor length as a parameter in the TNM staging system for esophageal carcinoma.

Table 4. Univariate Cox regression analysis of continous 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: Hematochrit, WBC: White blood Count
PLT: Platelet, RDW: Red blood cell distrubition 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 Modal

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

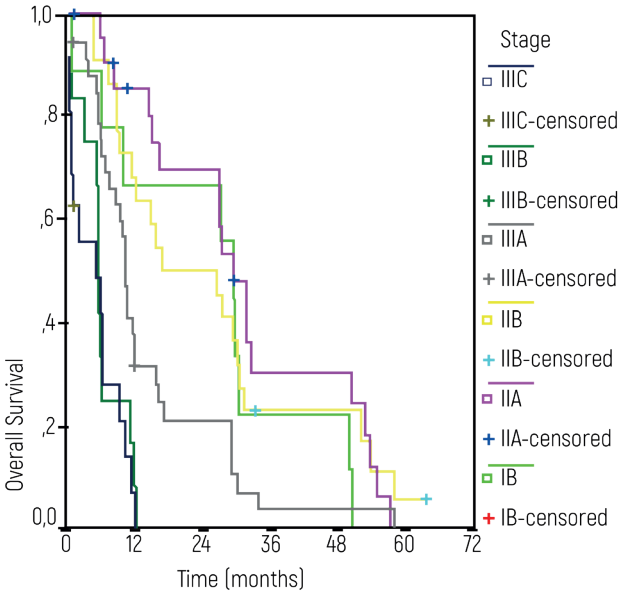

Figure 1. Survival curve based on stage of esophageal carcinoma

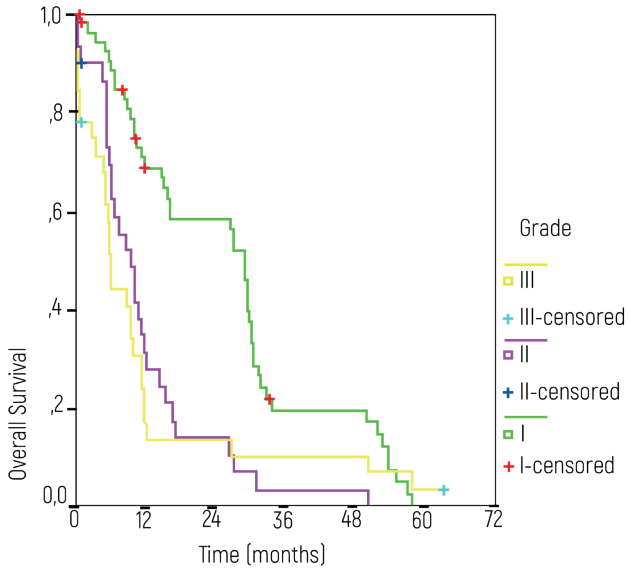

Figure 2. Survival curve based on grade of esophageal carcinoma

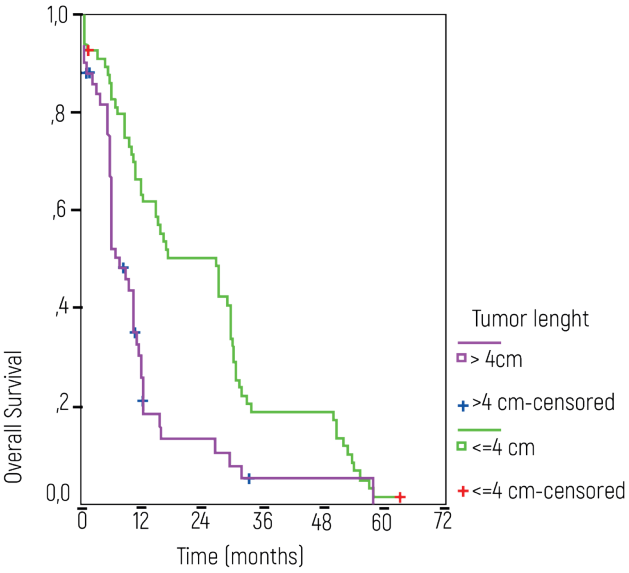

Figure 3. Survival curve based on tumor length of esophageal carcinoma.

Limitations

This study has limitations. It is retrospective, with a relatively small sample size, and mortality data were collected for all causes rather than disease-specific deaths. Additionally, only patients undergoing curative surgery were included, which may limit generalizability.

Conclusion

In conclusion, pathological T and N status, overall TNM stage, and tumor grade remain important prognostic factors in esophageal carcinoma. Moreover, tumor length ≥ 4 cm is associated with higher T and N stages, advanced TNM stage, and poorer survival, suggesting that tumor length should be incorporated into the TNM staging system as a predictive prognostic factor.

Declarations

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.

Informed Consent

Informed consent was obtained from all participants.

Conflict of Interest

The authors declare no conflicts of interest.

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Scientific Responsibility Statement

The authors declare that they are responsible for the scientific content of the article, including the study design, data collection, analysis and interpretation, manuscript preparation, and approval of the final version of the manuscript.

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