

Retrospective Study

Short- (30-90 days) and mid-term (1-3 years) outcomes and prognostic factors of patients with esophageal cancer undergoing surgical treatments

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Abstract

BACKGROUND

The factors influencing the prognosis of patients with esophageal cancer vary among studies and are still poorly known.

AIM

To determine the factors associated with survival in patients with esophageal cancer.

METHODS

This retrospective study included patients with esophageal cancer admitted between January 2017 and March 2020 at Heping Hospital Affiliated to Changzhi Medical College. All patients were treated according to the available guidelines. Follow-up was censored in October 2020. Univariable and multivariable Cox regression analyses were used to determine the independent risk factors for overall survival (OS).

RESULTS

In total, 307 patients were included. Their median age was 64 (range, 44-79) years, 63.5% were male, and the median disease course was 2 (0.1-36) months. The median tumor size was 3 (0-10) cm. Most patients were T3 (29.6%), N0 (70.0%). Most tumors were grade 2 (48.2%), and 87.3% were squamous cell carcinoma. The in-hospital mortality was 16.9%, the 30-day mortality was 19.9%, and the 90-day mortality was 25.4%. The cumulative OS rates at the last follow-up were 82.1% (95%CI: 67.7%-96.5%) for stage 0/I/II and 47.4% (95%CI: 16.5-78.6%) for stage

III/IVA ($P < 0.001$). The multivariable analysis showed that creatinine levels (HR = 1.02, 95%CI: 1.00-1.03, $P = 0.050$), pTNM III/IVA (HR = 4.19, 95%CI: 2.19-8.01, $P < 0.001$), adjuvant radiotherapy and/or chemotherapy (HR = 0.23, 95%CI: 0.11-0.49), and the Comprehensive Complication Index (CCI) (HR = 1.02, 95%CI: 1.004-1.03, $P = 0.011$) were independently associated with OS.

CONCLUSION

The survival of patients with esophageal cancer is poor, especially those with pTNM III/IVA. pTNM stage III/IVA, CCI, and adjuvant therapy (radiotherapy and/or chemotherapy) are independently associated with OS.

Key Words: Esophageal cancer; Survival; Prognosis; Factors; Multivariable analysis

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Core Tip: The factors influencing prognosis in esophageal cancer vary among studies and are still poorly known. Therefore, this study aimed to determine the factors related to the survival of patients with esophageal cancer. The results showed that the in-hospital mortality was 16.9%, the 30-day mortality was 19.9%, and the 90-day mortality was 25.4%. Hence, the survival of patients with esophageal cancer is poor, especially those with pTNM III/IVA disease. pTNM stage III/IVA, Comprehensive Complication Index, and adjuvant therapy (radiotherapy and/or chemotherapy) are independently associated with overall survival. These results help delineate the factors associated with poor survival in patients with esophageal cancer.

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INTRODUCTION

Esophageal cancer is the ninth cancer worldwide in terms of incidence but the sixth in mortality[1]. The most common histological subtypes of esophageal cancer include squamous cell carcinoma (SCC) and adenocarcinoma[2-5]. Worldwide, SCC comprises 90% of all esophageal cancer cases. In Western countries, the incidence of SCC is on the decline while adenocarcinoma incidence is rising; SCC is more common in Eastern Europe and Asia, while adenocarcinoma is more common in North America and Western Europe[3-5]. Most patients with esophageal cancer are > 50 years old[2,3], and both histologic subtypes are more common in men[4]. The most likely risk factors for esophageal cancer include tobacco use and excessive alcohol use (especially for the development of SCC), obesity (especially for the development of adenocarcinoma), and a history of gastroesophageal reflux disease (GERD) and/or Barrett esophagus (especially for the development of adenocarcinoma)[3,4].

Most tumors are diagnosed with regional or distant metastasis, and the 5-year overall survival (OS) is 39% in patients with a localized disease compared with 4% in patients with distant metastases[3]. Local recurrence after primary treatment with definitive chemoradiation may occur in 10%-30% of the patients within the first year[2]. Increased HER2-neu expression is associated with poor survival, particularly in patients with SCC[4]. The 5-year OS rate among patients treated with neoadjuvant chemotherapy for esophageal cancer in various studies ranges from 16% to 62%[6]. A Charlson score ≥ 2 , history of myocardial infarction, and congestive heart failure may increase mortality risk following surgery for esophageal cancer[7]. Age > 70 years does not have prognostic significance after esophagectomy for esophageal cancer[8].

Some predictive models are available, but their value is limited. The Dutch nomogram is based on three variables and shows a concordance index of 0.76-0.77[9]. The POSSUM models can predict morbidity and mortality in patients undergoing gastroesophageal surgery, but they can overestimate the risks[10]. Other multivariable analysis studies reported various factors associated with poor prognosis[11-14]. However, beyond the traditional prognostic factors (*e.g.*, histological grade and TNM staging[3-5,15-19]), the factors influencing prognosis in esophageal cancer are poorly known and vary among studies. Identification of the factors that could help refine prognostication is important since two patients with the same histological grade and TNM staging can have different survival.

Therefore, this study aimed to determine the factors related to the survival of esophageal cancer. The results could help delineate the factors associated with poor survival in patients with esophageal cancer.

MATERIAL AND METHODS

Study design and patients

This retrospective study included patients with esophageal cancer admitted between January 2017 and June 2020 at the Department of Gastrointestinal Surgery of Heping Hospital Affiliated to Changzhi Medical College. This study was approved by the Ethics Committee of Heping Hospital Affiliated to Changzhi Medical College [approval number: 2020 (037), approval date: July 22, 2020]. The requirement for informed consent was waived by the committee due to the retrospective study design.

The inclusion criteria were: (1) > 18 years of age; (2) underwent surgical treatments; and (3) confirmed with esophageal cancer by postoperative pathological examination. The exclusion criteria were: (1) incomplete clinical data; and (2) follow-up < 90 days.

Treatments

Each patient was treated according to the available guidelines for the treatment of esophageal cancer[4, 5,15,16], the physicians' clinical experience, and the discussion with the patient. The treatment regimens included radiotherapy alone, chemotherapy alone (paclitaxel + cisplatin, paclitaxel + nedaplatin, oxaliplatin, tegafur/gimeracil/oteracil, oxaliplatin + docetaxel/tegafur/gimeracil/oteracil, and nedaplatin/docetaxel), and radiotherapy combined with chemotherapy.

The type of surgery was selected according to the tumor's location and size (the most important factor), infiltration depth, invasive degree, and general condition of the patients (whether they could tolerate open surgery). The surgery methods included endoscopic submucosal dissection (ESD), mediastinoscopy/laparoscopy/thoracoscopy, laparothoracoscopy combined palliative resection of esophageal cancer, laparothoracoscopy combined esophageal cancer radical operation, and open surgery. All the procedures were performed by experienced surgeons and followed standard protocols.

Follow-up

The patients were followed at 1, 3, 6, 9, 12, 18, 24, 30, 36, 48, and 72 months after the operation. For this study, follow-up was censored in October 2020. The follow-up was completed by the investigators and the medical team routinely. Routine follow-up included telephone, SMS, email, and outpatient visits. All follow-up data were extracted from the patient charts. The patients were not contacted for the purpose of this study.

Data collection

The following data were collected from the medical records: demographic data, past medical history, and concomitant diseases; site, size, stage, and type of esophageal cancer; hematological examination results within 1 week before the operation, treatment strategies, operation-related parameters, postoperative complications, Comprehensive Complication Index (CCI)[20]; survival, recurrence, and metastasis.

Statistical analysis

The continuous variables were tested for normality using the Kolmogorov-Smirnov test. The continuous variables were not normally distributed in this study and are presented as medians (ranges). Categorical and ordinal variables are presented as frequencies and percentages. Univariable and multivariable Cox regression analyses (backward) were used to determine the independent risk factors for OS. The variables with *P* values < 0.10 in the univariable analysis were included in the multivariable analysis. The Kaplan-Meier curves of OS were plotted according to the pTNM staging results. All statistical analyses were two-sided. *P* values < 0.05 were considered statistically significant. SPSS 22.0 (IBM, Armonk, NY, United States) was used for statistical analyses.

RESULTS

Characteristics of the patients

Initially, 357 patients were included according to the inclusion criteria, but 26 with missing clinical information and 24 lost to follow-up were excluded, leaving 307 patients. As shown in Table 1, the median age at diagnosis was 64 (44-79) years, 63.5% were male, median BMI was 22.2 (14.9-31.6) kg/m², median disease course was 2 (0.1-36) months, 30.9% had a history of smoking, 6.5% had a history of drinking, and 75.9% were ASA II. Table 1 also presents the biochemical characteristics of the patients.

Characteristics of the tumors and treatments

Table 2 shows the characteristics of the tumors. Most tumors were in the middle part of the esophagus (55.7%). The median tumor size was 3 (0-10) cm. Most patients were T3 (29.6%) N0 (70.0%). Most tumors were grade 2 (48.2%), and 87.3% were SCC.

Table 1 Baseline characteristics of the patients (*n* = 307)

Characteristics	Median (range) / <i>n</i> (%)
Age (yr)	64 (44, 79)
Body mass index (kg/m ²)	22.2 (14.9, 31.6)
Disease course (months)	2 (0.1, 36)
Sex (male)	195 (63.5%)
Smoking	95 (30.9%)
Drinking	20 (6.5%)
Family history of esophagus cancer	22 (7.2%)
Hypertension	112 (36.5%)
Diabetes	21 (6.8%)
Coronary heart disease	16 (5.2%)
ASA stage	
II	233 (75.9%)
III	73 (23.8%)
IV	1 (0.3%)
Hemoglobin (g/L)	141 (80, 180.4)
MCV (fl)	93.6 (71.1, 134.1)
Platelets (× 10 ⁹ /L)	213 (60.3, 445.9)
Lymphocytes (× 10 ⁹ /L)	1.56 (0.07, 7.42)
Monocytes (× 10 ⁹ /L)	0.36 (0.05, 1.01)
Neutrophils (× 10 ⁹ /L)	3.63 (1.15, 12.94)
PT (s)	13.8 (11.4, 31.9)
APTT (s)	31.4 (10.6, 51.7)
Fibrinogen (g/L)	3.79 (1.95, 6.3)
D-dimer (ng/mL)	130 (14, 3354)
Total protein (g/L)	71 (3.32, 88.1)
Albumin (g/L)	42.1 (26.1, 63.5)
Creatinine (μmol/L)	63 (36, 187)
Hematocrit (%)	46.6 (28.2, 64.5)

ASA: American Society of Anesthesiologists; MCV: Mean corpuscular volume; PT: Prothrombin time; APTT: Activated partial thromboplastin time.

Among the 307 patients, 16.6% received neoadjuvant treatments, 84.0% underwent mediastinoscopy/laparoscopy/thoracoscopy, 8.8% underwent open surgery, and 7.2% underwent ESD. An R0 resection was achieved in 99.0% of the patients. Operation time was 270 (36-485) min, and blood loss was 150 (2-1000) mL. Lymph node dissection was performed in 92.2% of the patients, and the median number of positive lymph nodes was 0 (0-8). Most patients (69.4%) received no adjuvant treatments, 2.3% received radiotherapy alone, 25.1% received chemotherapy alone, and 3.3% received radiotherapy and chemotherapy.

Table 3 presents the complications observed. Among the 307 patients, 35.5% had no complications, while 64.5% had complications. The in-hospital mortality was 16.9%, the 30-day mortality was 19.9%, and the 90-day mortality was 25.4%.

Survival

The 1-year cumulative OS rates were 93.7% (95%CI: 88.3%-99.1%) for stage 0/I/II and 72.4% (95%CI: 57.7%-87.1%) for stage III/IVA. The 2-year cumulative OS rates were 87.8% (95%CI: 79.1%-96.5%) for stage 0/I/II and 60.2% (95%CI: 41.6%-78.8%) for stage III/IVA. The 3-year cumulative OS rates were 85.5% (95%CI: 74.7%-96.3%) for stage 0/I/II and 56.9% (95%CI: 36.8%-77.0%) for stage III/IVA. The

Table 2 Treatment related information (*n* = 307)

Variables	Median (range) / <i>n</i> (%)
Tumor location	
Upper	15 (4.9%)
Middle to upper	21 (6.8%)
Middle	171 (55.7%)
Middle to lower	43 (14.0%)
Lower	57 (18.6%)
Tumor diameter (cm)	3 (0, 10)
T stage	
Tis	30 (9.8%)
1a	4 (1.3%)
1b	69 (22.5%)
2	75 (24.4%)
3	91 (29.6%)
4a	36 (11.7%)
4b	2 (0.7%)
N stage	
0	215 (70.0%)
1	61 (19.9%)
2	28 (9.1%)
3	3 (1.0%)
G stage	
0	30 (9.8%)
1	21 (6.8%)
1-2	73 (23.8%)
2	148 (48.2%)
2-3	24 (7.8%)
3	11 (3.6%)
pTNM	
0	30 (9.8%)
I	108 (35.2%)
II	71 (23.1%)
III	87 (28.3%)
IVA	11 (3.6%)
Pathological type	
Squamous cell carcinoma	268 (87.3%)
Intraepithelial neoplasia	30 (9.8%)
Adenocarcinoma	8 (2.6%)
Signet-ring cell carcinoma	1 (0.3%)
Neoadjuvant radiotherapy and/or chemotherapy	51 (16.6%)
Surgery	
Mediastinoscopy/ laparoscopy/thoracoscopy	258 (84.0%)

Thoracotomy/laparotomy	27 (8.8%)
Endoscopic submucosal dissection	22 (7.2%)
Resection	
R0	304 (99.0%)
R1	3 (1.0%)
Operation time (min)	270 (36, 485)
Intraoperative blood loss (mL)	150 (2, 1000)
Lymph node dissection	283 (92.2%)
Postoperative treatment	
None	213 (69.4%)
Radiotherapy alone	7 (2.3%)
Chemotherapy alone	77 (25.1%)
Radiotherapy + chemotherapy	10 (3.3%)
Number of metastatic lymph nodes	0 (0, 8)

Table 3 Postoperative complications, recurrence, metastasis, and mortality (n = 307)

Variables	Median (range) / n (%)
Clavien-Dindo stage	
None	109 (35.5%)
I	27 (8.8%)
II	121 (39.4%)
IIIa	28 (9.1%)
IIIb	4 (1.3%)
IV	4 (1.3%)
IVa	8 (2.6%)
IVb	6 (2.0%)
CCI, median (range)	20.9 (0, 96.6)
Anastomotic leakage	75 (24.4%)
Secondary operation	7 (2.3%)
Hypoalbuminemia	88 (28.7%)
Pulmonary infection	68 (22.1%)
Recurrence	11 (3.6%)
Metastasis	21 (6.8%)
In-hospital mortality	52 (16.9%)
30-day mortality	61 (19.9%)
90-day mortality	78 (25.4%)

CCI: Charlson comorbidity index.

cumulative OS rates at the last follow-up were 82.1% (95%CI: 67.7%-96.5%) for stage 0/I/II and 47.4% (95%CI: 16.5%-78.6%) for stage III/IVA. The Kaplan-Meier analysis shows that the differences in survival were significant ($P < 0.001$) (Figure 1).

Multivariable analysis of OS

Table 4 shows that creatinine levels ($P = 0.020$), tumor size ($P = 0.002$), T3-4 ($P = 0.003$), N1-3 ($P < 0.001$),

Table 4 Univariable and multivariable Cox regression analyses of overall survival

	Univariable			Multivariable		
	HR	95%CI	P	HR	95%CI	P
Age	1.018	0.979, 1.059	0.377			
Sex						
Female	ref					
Male	1.020	0.58, 1.796	0.945			
Body mass index						
< 28	ref					
≥ 28	1.912	0.816, 4.478	0.136			
Smoking	1.185	0.663, 2.118	0.567			
Drinking	0.916	0.285, 2.942	0.882			
Family history of esophagus cancer	1.372	0.545, 3.452	0.501			
Hypertension	0.939	0.530, 1.663	0.829			
Diabetes	1.898	0.810, 4.449	0.140			
Hemoglobin	0.987	0.971, 1.004	0.125			
D-dimer	1.000	0.999, 1.001	0.782			
Albumin	1.004	0.945, 1.067	0.897			
Creatinine	1.020	1.003, 1.036	0.020	1.016	1, 1.032	0.050
Tumor diameter	1.244	1.083, 1.429	0.002			
T stage						
Tis/0-2	ref			ref		
3-4	2.327	1.331, 4.068	0.003	1.869	0.98, 3.564	0.058
N stage						
0	ref					
1-3	2.869	1.659, 4.962	< 0.001			
G stage						
< 2	ref					
≥ 2	1.990	1.062, 3.73	0.032			
pTNM stage						
0/I/II	ref			ref		
III/IVA	4.117	2.349, 7.213	< 0.001	4.189	2.190, 8.012	< 0.001
Pathological type						
Squamous cell carcinoma	ref					
Others	0.616	0.222, 1.711	0.353			
Received preoperative radiotherapy or chemotherapy	1.157	0.592, 2.261	0.669			
Operation method						
ESD/endoscopy/thoracoscopy/laparoscopy	ref					
Thoracotomy/laparotomy	0.867	0.312, 2.405	0.784			
Lymph node dissection	3.622	0.500, 26.255	0.203			
Postoperative radiotherapy and/ or chemotherapy	0.449	0.225, 0.897	0.023	0.234	0.112, 0.488	< 0.001
Number of metastatic lymph nodes	1.277	1.109, 1.471	0.001			
CCI	1.029	1.014, 1.044	< 0.001	1.018	1.004, 1.032	0.011

HR: hazard ratio; CI: confidence interval; ESD: Endoscopic submucosal dissection; CCI: Comprehensive Complication Index.

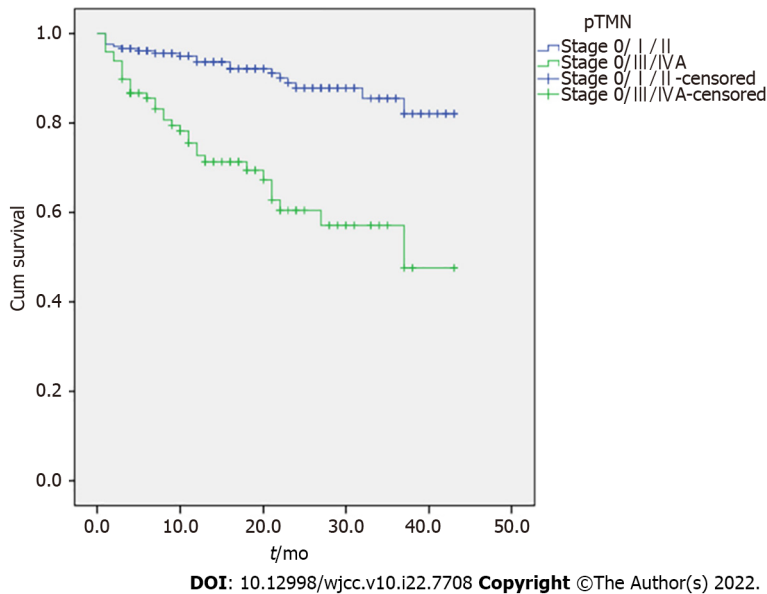


Figure 1 Kaplan-Meier curve of overall survival according to the pTNM stage.

grade ≥ 2 ($P = 0.032$), pTNM III/IVA ($P < 0.001$), adjuvant therapy ($P = 0.023$), number of positive lymph nodes ($P < 0.001$), and CCI ($P < 0.001$) were associated with OS in the univariable analyses. The multivariable analysis showed that the creatinine levels (HR = 1.02, 95%CI: 1.00-1.03, $P = 0.050$), pTNM III/IVA (HR = 4.19, 95%CI: 2.19-8.01, $P < 0.001$), adjuvant radiotherapy and/or chemotherapy (HR = 0.23, 95%CI: 0.11-0.49), and the CCI (HR = 1.02, 95%CI: 1.004-1.03, $P = 0.011$) were independently associated with OS.

DISCUSSION

The factors influencing prognosis in esophageal cancer are still poorly known and vary among studies. Therefore, this study aimed to determine the factors related to the survival of patients with esophageal cancer. The results show that the survival of patients with esophageal cancer is poor, especially those with pTNM stage III/IVA. pTNM stage III/IVA, CCI, and adjuvant therapy (radiotherapy and/or chemotherapy) are independently associated with OS. This indicates that early clinical stage, fewer postoperative complications, and adjuvant therapy might be related to a better prognosis in patients with esophageal cancer after surgery. This study showed that the CCI is an independent risk factor affecting prognosis, indicating that postoperative nursing care to reduce postoperative complications might be helpful to improve the survival rate, while many surgeons tend to focus on surgery instead of postoperative nursing. Science-based postoperative management to reduce complications is also very important.

In this study, the 3-year cumulative OS rates were 85.5% for stage 0/I/II and 56.9% for stage III/IVA. This is consistent with the literature, as the studies indicate that a more advanced disease is associated with poorer survival[3-5,15-18]. Regarding the adjuvant treatments, this association is not surprising since the efficacy of adjuvant treatments to prevent recurrence and metastasis, and improve survival is the reason for giving adjuvant therapy in the first place[3-5,15,16,21]. Regarding the CCI, Bernardi *et al* [22] showed that patients with esophageal cancer who completed their treatment plan had a lower CCI than those who eventually dropped out, affecting the prognosis. Yamashita *et al*[23] and Aoyama *et al* [24] showed that the CCI was correlated with the prognosis of patients who undergo curative resection of esophageal carcinoma.

Nevertheless, a wide variety of other factors are associated with esophageal cancer prognosis in various studies. The Dutch nomogram is based on three variables independently associated with esophageal carcinoma: T stage, number of positive lymph nodes, and lymph node involvement[9]. The POSSUM score is a complex scoring system designed to determine the short-term postoperative mortality and includes 19 clinical, biochemical, and operative variables independently associated with prognosis[10]. Kawakita *et al*[25] showed that C-reactive protein levels and platelet distribution width

could predict survival in patients with esophageal cancer. In esophageal SCC, which was the main histological subtype in the present study, Kim *et al*[26] showed that only the CCI was associated with survival, supporting the present study. In the study by Hauge *et al*[19], only the pTNM stage was independently associated with OS, supporting the present study. Hauge *et al*[19] also suggested that patients with R0 resection and who received adjuvant therapy had a better survival than the other subgroups of patients, but, in the present study, the number of patients with R1 resection was too small for subgroup analyses. A large meta-analysis (171 studies and 73629 patients) indicated that the factors associated with OS were the pT stage, pN stage, perineural invasion, circumferential resection margin, poor tumor grade, and a high neutrophil-to-lymphocyte ratio[27]. The differences among studies are highly dependent upon the study populations, data available for analysis (especially retrospective studies, local practice, and the treatment periods). However, specific factors identified by multiple studies might be considered more reliable, but validation studies are necessary from multiple centers.

Of note, in this study, creatinine levels were independently associated with the prognosis of esophageal cancer, but the *P*-value was borderline, and it is unknown whether including more patients would tip the balance one way or the other. Creatinine levels have been reported to be independently associated with prognosis in gynecological[28,29] and colorectal[30] cancers, but no previous studies have reported such an association in esophageal cancer. Further study is required to clarify this issue.

This study has limitations. First, it was a retrospective study, and some data were not collected (*e.g.*, the patients' postoperative nutritional status, which is known to influence prognosis[31]). In addition, the follow-up data were from the charts, and there is a possibility of unreported events. Second, the factors related to recurrence-free survival (RFS) could not be analyzed due to incomplete data. Third, it was a single-center study, and it is unknown whether the results are valid externally.

CONCLUSION

In conclusion, the pTNM stage, CCI, and postoperative radiotherapy and/or chemotherapy are independently associated with OS. The survival of patients with pTNM III/IVA disease is worse than that of patients with pTNM I/II disease. Fewer complications and adjuvant therapy are associated with better survival.

ARTICLE HIGHLIGHTS

Research background

Esophageal cancer is the ninth cancer worldwide in terms of incidence but the sixth in mortality. The prognosis of esophageal cancer is poor.

Research motivation

The factors influencing the prognosis of patients with esophageal cancer vary among studies and are still poorly known. Some predictive models are available, but their value is limited.

Research objectives

This study aimed to determine the factors related to the survival of patients with esophageal cancer.

Research methods

This retrospective study included patients with esophageal cancer admitted between January 2017 and March 2020 at Heping Hospital Affiliated to Changzhi Medical College. All patients were treated according to the available guidelines. Follow-up was censored in October 2020. Univariable and multivariable Cox regression analyses were used to determine the independent risk factors for overall survival (OS).

Research results

Among 307 patients, the in-hospital mortality was 16.9%, the 30-day mortality was 19.9%, and the 90-day mortality was 25.4%. The patients showed a cumulative OS rate at the last follow-up of 82.1% (95%CI: 67.7%-96.5%) for stage 0/I/II and 47.4% (95%CI: 16.5%-78.6%) for stage III/IVA (*P* < 0.001). Creatinine levels (HR = 1.02, 95%CI: 1.00-1.03, *P* = 0.050), pTNM III/IVA (HR = 4.19, 95%CI: 2.19-8.01, *P* < 0.001), adjuvant radiotherapy and/or chemotherapy (HR = 0.23, 95%CI: 0.11-0.49), and the Comprehensive Complication Index (CCI) (HR = 1.02, 95%CI: 1.004-1.03, *P* = 0.011) were independently associated with OS.

Research conclusions

The survival of patients with esophageal cancer is poor, especially those with pTNM III/IVA. pTNM

stage III/IVA, CCI, and adjuvant therapy (radiotherapy and/or chemotherapy) are independently associated with OS. These results could help manage patients by identifying those needing closer follow-up.

Research perspectives

These results could help delineate the factors associated with poor survival in patients with esophageal cancer. Identification of the factors that could help refine prognostication is important since two patients with the same histological grade and TNM staging can have different survival. These results should be validated in large cohorts of patients from multiple centers.

FOOTNOTES

Author contributions: Shi MK contributed to conceptualization, methodology, data curation and analysis, writing (original draft), and visualization; Mei YQ contributed to writing (review and editing) and supervision; Shi JL contributed to writing (review and editing), acquisition of data, and supervision; all authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of Heping Hospital Affiliated to Changzhi Medical College (approval number: 2020 (037), approval date: July 22, 2020).

Informed consent statement: The requirement for informed consent was waived by the committee due to the retrospective study design.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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