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ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Dr. Tatsuo Kanda received an MD from the Niigata University School of Medicine (Japan) in 1991 and a PhD from the Graduate School of Medicine at Chiba University (Japan) in 1999. He then undertook post-doctoral training in the Departments of Pathology and Internal Medicine at Saint Louis University School of Medicine (United States) under the mentorship of Prof. Ratna B. Ray and Prof. Ranjit Ray, respectively. He returned to Japan and became an Associate Professor in the Department of Gastroenterology and Nephrology at Chiba University, Graduate School of Medicine in 2008. In his current roles as Associate Professor and Clinical Professor in the Division of Gastroenterology and Hepatology, Department of Medicine, Nihon University School of Medicine at Itabashi-ku, Tokyo, Japan, he performs clinical and basic research on hepatic and pancreatic diseases. (L-Editor: Filipodia)

AIMS AND SCOPE

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Prognostic value of pretreatment contrast-enhanced computed tomography in esophageal neuroendocrine carcinoma: A multi-center follow-up study

Yue Zhou, Ping Hou, Kai-Ji Zha, Feng Wang, Kun Zhou, Wei He, Jian-Bo Gao

ORCID number: Yue Zhou 0000-0001-7781-7228; Ping Hou 0000-0002-3932-8789; Kai-Ji Zha 0000-0002-8774-0698; Feng Wang 0000-0002-1607-6478; Kun Zhou 0000-0002-2234-3069; Wei He 0000-0001-5214-5162; Jian-Bo Gao 0000-0003-1252-7144.

Yue Zhou, Ping Hou, Kai-Ji Zha, Jian-Bo Gao, Department of Radiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

Feng Wang, Wei He, Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

Kun Zhou, Department of Thoracic Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

Corresponding author: Jian-Bo Gao, MD, PhD, Professor, Department of Radiology, The First Affiliated Hospital of Zhengzhou University, No. 1 Jianshe Road, Zhengzhou 450052, Henan Province, China. cjr_gaojianbo@163.com

Abstract

BACKGROUND
The rare incidence of esophageal neuroendocrine carcinoma (NEC) and limited treatment experience result in insufficient clinical observations and unsuitable guidelines for its management.

AIM
To investigate the prognostic value of pretreatment contrast-enhanced computed tomography (CT) characteristics in patients with esophageal NEC.

METHODS
Seventy-seven esophageal NEC patients who received contrast-enhanced CT at two hospitals were enrolled in this study from June 2014 to December 2019. The clinical features and image characteristics were recorded accordingly. Univariate survival analysis was performed using the Kaplan-Meier method and log-rank test, and multivariate analysis was carried out with a Cox proportional hazards model.

RESULTS
The multivariate analysis performed using the Cox proportional hazards model showed that N stage, adjuvant chemotherapy, and degree of enhancement were independent prognostic factors for overall survival (OS). Meanwhile, adjuvant chemotherapy was an independent prognostic factor for progression-free survival

(PFS). The hazard ratios (HRs) of N stage, adjuvant chemotherapy, and degree of enhancement (mild *vs* moderate/marked) for OS were 0.426 (P = 0.024), 3.862 (P = 0.006), and 2.169/0.809 (P = 0.037), respectively. The HR of adjuvant chemotherapy for PFS was 6.432 (P < 0.001). Adjuvant chemotherapy was significantly associated with degree of enhancement (P = 0.018).

CONCLUSION
Adjuvant chemotherapy is an independent prognostic factor for OS and PFS. Additionally, N stage and degree of enhancement are prognostic factors for OS in patients with esophageal NEC.

Key words: Esophageal neuroendocrine carcinoma; Computed tomography; Prognosis; Survival; Follow-up; Adjuvant chemotherapy

Core tip: The occurrence of esophageal neuroendocrine carcinoma (NEC) is rare. The clinical data included in the previous prognostic models are limited and imaging data are lacking. Our results demonstrate that adjuvant chemotherapy is an independent prognostic factor for overall survival and progression-free survival. In addition, N stage and degree of enhancement are prognostic factors for overall survival in patients with esophageal NEC. Furthermore, adjuvant chemotherapy is significantly associated with degree of enhancement, while degree of enhancement significantly correlates with esophageal wall thickness.

INTRODUCTION

Neuroendocrine tumors are heterogeneous tumors that secrete a variety of peptide substances and/or hormones and other bioactive substances[1]. Neuroendocrine cells are located throughout the body; thus, neuroendocrine tumors occur throughout the entire body as well. Owing to the wide distribution of neuroendocrine cells in the digestive system, the incidence of neuroendocrine tumors in this system is higher than that in other systems[2]. However, the occurrence of esophageal neuroendocrine carcinoma (NEC) is rare, with an incidence of only 0.03%-5% of reported gastro-intestinal neuroendocrine tumors; this is because the neuroendocrine system is not well developed in the esophagus[3]. The few case reports on esophageal NEC usually depict it as having the characteristics of a high-grade malignancy with poor differentiation, inadequate tumor vascularization, and common metastasis[3-5].

Pathological immunohistochemistry is of high value in the diagnosis, pathological classification, and prognosis evaluation of NEC[6]. Unlike esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), NEC can be diagnosed and classified using a grading system based on the mitotic count and Ki-67 proliferation index[7]. Esophageal NEC is entirely defined by high-grade ratings (G3) and high ratios of Ki-67[8]. The early clinical symptoms of esophageal NEC are mild or atypical, and local or distant metastases often occur at diagnosis. Surgery combined with chemoradiotherapy is considered to be the ideal treatment strategy for esophageal NEC owing to its highly invasive nature and tendency for early metastasis[9].

Previous studies indicated that the one-year and three-year survival rates of patients with esophageal NEC after surgery were 88.2% and 55.9%, respectively[10,11]. However, the limited number of patients in clinical practice receiving imaging modalities for esophageal NEC restricted the prognosis evaluation in the past. Moreover, specific immunohistochemical tests must be performed in specialized hospitals. There are currently no specific criteria to evaluate patients with esophageal NEC in the American Joint Committee on Cancer (AJCC) staging system. Owing to its rarity, only

a few cases of esophageal NEC have been reported in the literature, with most focusing on the clinicopathological characteristics[1,3,6,12] and treatment[8,12,13]. Recent retrospective clinical esophageal NEC analyses have shown better postoperative survival rates with a combination of radical resection[8,13], radical lymph node dissection[1,3,6], and adjuvant therapy[13]. Yet, the clinical data included in the foregoing prognostic models are limited and imaging data are lacking. Studies involving prognosis of esophageal NEC including contrast-enhanced CT have not yet been conducted.

This study aimed to investigate the role of pretreatment contrast-enhanced computed tomography (CT) imaging and patient clinical characteristics in predicting the progression-free survival (PFS) and overall survival (OS) of patients with esophageal NEC.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board (IRB) of the First Affiliated Hospital of Zhengzhou University. Informed consent from the patients enrolled in this study was waived due to the retrospective nature of the study.

Subject Enrollment

Patients who had a confirmatory diagnosis of esophageal NEC during the period from June 2014 to December 2019 were incorporated into our database and retrospectively analyzed. We confirmed the diagnosis of esophageal NEC based on pathological and immunohistochemical specimens *via* esophagoscopy before surgery or intraoperatively. Patients who earlier had undergone a baseline pretreatment contrast-enhanced CT in our institution were enrolled in the study. The exclusion criteria were: (1) Patients who had esophageal NEC with a squamous carcinoma/adenocarcinoma component; (2) Patients who had a history of anti-tumor treatment; (3) Patients whose deaths were caused by diseases other than esophageal NEC during the follow-up; and (4) Patients who were lost to follow-up with any treatment. Finally, 77 patients (median age, 64 years; range, 42-78 years), comprised of 59 males and 24 females, were included in this study for treatment observation and subsequent follow-up investigation.

Therapies

The treatment strategies for NEC consist of esophagectomy only, chemotherapy, chemoradiotherapy, and postoperative adjuvant chemotherapy. The treatment regimen for chemotherapy and postoperative adjuvant chemotherapy included etoposide, 100 mg/m^2 intravenous, injected on days 1-5 and cisplatin 75 mg/m^2 intravenously injected on the first day of a 21-d cycle, for a total of 4-6 cycles. Patients treated with radiotherapy received a dose of 1.8 Gy per day on days 1-5, with a total dose of 60 Gy by day 33. Chemoradiotherapy regimen consisted of etoposide 50 mg/m^2 and cisplatin 20 mg/m^2 on days 1-5, and a total of 60 Gy of concurrent radiotherapy, as mentioned previously.

CT image acquisition

A baseline CT scan was obtained less than a week before treatment. All patients fasted for 6 h. Amidoamine was injected (20 mg intramuscularly) 10-15 min before the CT examination, to relax the esophageal muscle. A contrast-enhanced CT scan of the chest was performed with a 256-slice CT scanner (Revolution CT, GE Healthcare, Waukesha, WI, United States). The scan mode settings comprised of a tube voltage of 120 kV or 80 kV/140 kV by a fast kV-switching technique, tube current under Auto mA with a noise index of 8.0, slice thickness of 5 mm, gantry speed of 0.6 s per rotation, and pitch of 0.984:1. A contrast medium containing 350 mg/mL of iodine (Omnipaque; GE Healthcare, Cork, Ireland) was injected at a flow rate of 3 mL/s *via* the elbow vein. The dose of the contrast medium was calculated as 1.5 mL per kg body weight. Scanning was done when the CT value of the aortic arch reached 100 HU. The venous phase was initiated 60 s after triggering the scan.

Two radiologists (Zhou Y and Hou P) with 10 and 8 years of experience in chest and abdominal CT diagnosis, respectively, independently measured and analyzed the imaging in a blinded and randomized manner at a spectral CT workstation (Advantage of Windows, version 4.6; GE Healthcare, Waukesha, WI, United States). Basic patient information, TNM stage, tumor location, morphological subtype, esophageal wall thickness, tumor length, enhanced CT characteristics, degree of

enhancement, and average contrast-enhanced Hounsfield unit (HU) value were recorded. The degree of the enhancement was classified as mild, moderate, and marked, with the standard used for the assessment of enhancement being: Slightly enhanced, the enhancement of the nodule was close to that of adjacent muscles; moderately enhanced, enhancement slightly higher than the adjacent muscles; and markedly enhanced, enhancement markedly higher than in the muscles[13]. A round or oval region of interest (ROI) was placed according to the size and location of the tumor. Size and shape of the ROIs were consistent in the measurement. When there was a discrepancy between interpretations, a consensus was achieved by discussion.

Follow-ups

The therapeutic efficacy was assessed 12 wk after surgery by a CT examination. Patients who were treated with chemotherapy and/or radiotherapy also underwent a CT enhancement examination after every three cycles, from the beginning of the treatment for the first 12 cycles and every four cycles thereafter. All patients underwent clinical follow-up through an outpatient service or a telephone communication (every 12 wk) until death or the end of the study. The PFS and OS were fixed as the main endpoints. PFS was the period from the end of treatment to the disease progression, or the last follow-up in the case of no progression. The OS was defined as the period from the date of diagnosis to death from any cause.

Statistical analysis

Statistical analyses were performed using SPSS 21.0 statistical software (SPSS Inc., Chicago, IL, United States). All continuous variables are presented as medians. For survival analysis, patients were put into two subgroups based on a threshold (median value) of continuous variables. Data were analyzed by the Kaplan-Meier methods for univariate analysis, and then significant variables were included in the multivariate step-wise forward Cox regression. The Spearman correlation was applied for the correlation between clinical factors and imaging characteristics. The significance level for all tests was 5% (two-sided).

RESULTS

Patient characteristics

Seventy-seven esophageal NEC patients were enrolled in this study from June 2014 to December 2019. The basic and CT characteristics are summarized in Table 1. The median PFS and OS times were 6.2 (range, 0.3-45) mo and 12.6 (range, 0.9-64.8) mo, respectively. There were three cases with censored data, and the rate of loss to follow-up was 2.5% and 1.2% for PFS and OS, respectively. The 1-, 3-, and 5-year PFS rates were 64.2%, 23.9%, and 0%, respectively. The 1-, 3-, and 5-year OS rates were 67.1%, 38.3%, and 10.9%, respectively.

Univariate survival analysis

As outlined in Table 2 and Figure 1, the log-rank test was used to analyze clinical factors and CT characteristics. We found that adjuvant chemotherapy was a prognostic factor for PFS and OS. The PFS and OS rates for patients who underwent adjuvant chemotherapy for 1, 3, and 5 years were 95.4%, 76.9%, and 38.4%, and 73.6%, 40.2%, and 13.4%, respectively. The median PFS times were 20.5 mo (95%CI: 12.5–28.5) and 2 mo (95%CI: 0-4.2) for patients treated with and without adjuvant chemotherapy, respectively ($P < 0.001$, hazard ratio [HR] = 0.155, 95%CI: 0.061-0.398). The median OS times of patients treated with and without adjuvant chemotherapy were 32 mo (95%CI: 18.6-45.4) and 4 mo (95%CI: 0-9.8) ($P = 0.035$, HR = 0.412, 95%CI: 0.176-0.967), respectively.

Additionally, N stage and degree of enhancement were significant OS-related prognostic factors ($P = 0.04$ and $P = 0.042$, respectively). Patients with lymph node metastases or mild CT enhancement tended to have a shorter OS. In addition, patients treated without adjuvant chemotherapy also showed a shorter OS. At the same time, patients who underwent adjuvant chemotherapy exhibited longer PFS times. Typical cases of patients are depicted in Figures 2 and 3.

Multivariate survival and correlation analysis

Multivariate analysis performed with Cox proportional hazards models showed that N stage, adjuvant chemotherapy, and degree of enhancement were independent

Table 1 Basic clinical factors and computed tomography characteristics of the patients

Variable	Statistics, *n* (%)
Gender	
Male	53 (69)
Female	24 (31)
Median age (yr)[1]	64 (42-78)
Morphological subtype	
Medullary type	34 (44)
Mushroom type	31 (40)
Ulcer type	12 (16)
Narrowing type	18 (23)
Tumor length (mm)[1]	39.9 (10-118.9)
Tumor location	
Upper segment esophagus	5 (6)
Middle segment esophagus	45 (58)
Lower segment esophagus	27 (35)
Clinical symptom	
Progressive dysphagia	48 (62)
Abdominal/retrosternal pain	15 (20)
Loss of appetite	12 (15)
Fever	2 (3)
Immunohistochemical result	
CK	57 (74)
CgA	25 (32)
Syn	63 (82)
NSE	22 (29)
Ki-67 (%)[1]	80 (40-95)
Thickness of esophageal tumor wall (mm)[1]	11 (2-27.93)
Treatment strategy	
Esophagectomy only	9 (12)
Chemotherapy	1 (1)
Chemo radiotherapy	1 (1)
Postoperative adjuvant chemoradiotherapy	67 (87)
Progression-free survival (mo)[1]	6.2 (0.3-45)
Overall survival (mo)[1]	12.6 (0.9-64.8)

Except where indicated, data are numbers of patients, with percentages in parentheses.

[1]Data are medium values, and numbers in parentheses are ranges. CK: Cytokeratin; CgA: Chromogranin A; Syn: Synaptophysin; NSE: Neuron-specific enolase.

prognostic factors for OS, while adjuvant chemotherapy was an independent prognostic factor for PFS. The HRs of N stage, adjuvant chemotherapy, and degree of enhancement (mild *vs* moderate/marked) for OS were 0.426 (*P* = 0.024, 95%CI: 0.203-0.895), 3.862 (*P* = 0.006, 95%CI: 1.483-10.058), and 2.169/0.809 (*P* = 0.037, 95%CI: 0.827-5.689/0.285-2.296), respectively. The HR of adjuvant chemotherapy for PFS was 6.432 (*P* < 0.001, 95%CI: 2.514-16.485) (Table 3).

The associations between the clinicopathological parameters and CT characteristics

Table 2 Univariate analysis of clinical factors and computed tomography characteristics of the patients

Variable	n	PFS				OS			
		Median (mo)	95%CI	χ^2	P value	Median (mo)	95%CI	χ^2	P value
Gender				1.647	0.199			2.417	0.12
Male	53	21.5	7-36			36	22-50		
Female	24	15.3	8-22.6			20.5	10.8-30.1		
Age				0.029	0.865			0.007	0.932
< 64 yr	35	15	14-16			27.7	6.1-49.3		
≥ 64 yr	42	28.8	5-52.6			28.8	13.3-44.3		
Tumor length				1.257	0.262			2.551	0.11
< 40 mm	41	21.5	12.8-30.2			45	13.4-76.6		
≥ 40 mm	36	15	3.8-26.2			20.5	0-43.1		
Ki-67				0.035	0.851			0.001	0.977
< 80%	20	15.3	10.3-20.3			28.8	12.6-45		
≥ 80%	57	15	4.1-26			32	17.4-46.6		
T stage				0.351	0.554			0.46	0.498
cT1-2	33	20.5	11.6-29.5			28.8	5.6-52		
cT3-4	44	15.3	3.3-27.3			27.7	10.4-45		
N stage				2.708	0.1			3.876	0.04[a]
Absent	30	21.5	18.8-24.2			40.6	14.9-66.3		
Present	47	15	5.9-24.1			20.5	1-40		
M stage				0.862	0.353			2.974	0.085
Absent	49	15.3	5.6-25			20.5	12.4-28.6		
Present	28	15	0-33.2			36	28.5-43.5		
Tumor location				0.148	0.929			1.642	0.44
Upper segment	5	28.8	2.9-38.8			28.8	16.2-41.4		
Middle segment	45	20.5	8.3-32.7			21.5	6.2-36.8		
Lower segment	27	15.3	0-41.6			36	12.2-59.8		
Morphological subtype				3.29	0.349			5.285	0.152
Medullary type	34	15.3	0-37.9			28.8	2.7-54.9		
Mushroom type	31	40.6	2-79.2			40.6	3.6-77.6		
Ulcer type	12	21.5	0-47.3			21.5	0-44		
Narrowing type	18	15	13.3-16.7			20.5	6.5-34.5		
Wall thickness				0.294	0.588			3.041	0.081
< 11 mm	38	20.5	12-29			28.8	2.9-54.7		
≥ 11 mm	39	15	0-32.6			27.7	4.7-50.7		
Surgery				0.008	0.928			0.037	0.847
Performed	47	21.5	10.3-32.7			27.7	12.2-43.3		
None	30	15	6.4-23.6			32	11.4-52.6		
Adjuvant chemotherapy				20.057	< 0.001[a]			4.465	0.035[a]
Performed	67	20.5	12.5-28.5			32	18.6-45.4		
None	10	2	0-4.2			4	0-9.8		
Tumor margin				0.006	0.941			0.195	0.658

Well-defined	67	20.5	12.5-28.5			27.7	15.6-39.8		
Ill-defined	10	14.3	0-29.4			23.9	16.2-41.4		
Necrosis				0.14	0.708			0.207	0.649
Absent	72	20.5	12.2-28.8			27.7	15.2-40.2		
Present	5	15	0-35.4			20.8	16.2-41.4		
Enhanced homogeneity				0.503	0.478			0.006	0.94
Homogeneous	7	20.5	12.3-28.7			28.8	16-41.6		
Heterogeneous	70	15	3.6-26.4			18.4	16.2-41.4		
Degree of enhancement				5.114	0.078			4.968	0.042[a]
Mild enhancement	12	14.7	5.1-24.3			15.3	0.5-30.1		
Moderate enhancement	30	28.7	16-41.5			32	0-64		
Marked enhancement	35	28.8	9.6-48			43	22.7-63.3		

[a]Statistically significant. OS: Overall survival; PFS: Progression-free survival.

Table 3 Multivariate analysis of clinical factors and computed tomography characteristics of the patients

Variable	B	Wald	*P* value	HR	95%CI
PFS					
Adjuvant chemotherapy (Performed *vs* none)	1.861	15.075	< 0.001	6.432	2.514-16.485
OS					
N stage (Absent *vs* present)	-0.853	5.079	0.024	0.426	0.203-0.895
Adjuvant chemotherapy (Performed *vs* none)	1.351	7.658	0.006	3.862	1.483-10.058
Degree of enhancement (Mild *vs* moderate/marked)	0.774/-0.212	6.581	0.037	2.169/0.809	0.827-5.689/0.285-2.296

OS: Overall survival; PFS: Progression-free survival; HR: Hazard ratio.

are displayed in Table 4. We initially investigated the clinical factors between the patients with or without adjuvant chemotherapy and found that adjuvant chemotherapy was significantly associated with the degree of enhancement (*P* = 0.018). Thereafter, we explored the correlation of N stage and degree of enhancement. We found that the degree of enhancement significantly correlated with the esophageal wall thickness (*P* = 0.029). Meanwhile, N stage was positively associated with tumor length (*P* = 0.018), T stage (*P* = 0.003), M stage (*P* < 0.001), and esophageal wall thickness (*P* = 0.015).

DISCUSSION

Esophageal NEC is a rare malignant tumor of the esophagus, which exists independently or mixed with squamous cell carcinoma and adenocarcinoma[1-3]. The principal clinical manifestations are non-specific dysphagia, including choking sensation, chest pain, emaciation, hematemesis, and black stool. Ectopic hormone secretion may occur, such as antidiuretic hormone, with corresponding clinical symptoms[1-5]. Esophageal NEC is radically different from squamous cell carcinoma and adenocarcinoma in biological behavior, tumor response, and prognosis[9]. Most of the patients were in the middle and late stages with a poor prognosis owing to the highly invasive characteristics. It is easy to misdiagnose because of the non-specific clinical findings and imaging manifestations. Immunohistochemistry markers for esophageal NEC include Ki-67 index (used for grading), synaptophysin (Syn), CD56, chromogranin A(CgA), and neuron specific enolase (NSE)[7,8]. Combined detection of multiple markers is beneficial for a definite diagnosis. Although Ki-67 index can be used as an indicator of tumor cell proliferation clinically, a median value of 80% in this

Table 4 Association of clinical factors and computed tomography characteristics

Variable	Adjuvant chemotherapy			Variable	Degree of enhancement				Variable	N stage		
	Performed	None	P value		Mild	Moderate	Marked	P value		Absent	Present	P value
Gender			0.933	Gender				0.677	Gender			0.862
Male	46 (66)	7 (70)		Male	25 (71)	4 (36)	24 (77)		Male	21 (70)	32 (68)	
Female	24 (34)	3 (30)		Female	10 (29)	7 (64)	7 (23)		Female	9 (30)	15 (32)	
Age			0.299	Age				0.431	Age			0.769
< 64 yr	32 (48)	3 (30)		< 64 yr	18 (51)	4 (36)	13 (42)		< 64 yr	13 (43)	22 (47)	
≥ 64 yr	35 (52)	7 (70)		≥ 64 yr	17 (49)	7 (64)	18 (58)		≥ 64 yr	17 (57)	25 (53)	
Tumor length				Tumor length				0.352	Tumor length			0.018[a]
< 40 mm	37 (55)	4 (40)	0.375	< 40 mm	20 (57)	7 (64)	14 (45)		< 40 mm	21 (70)	20 (43)	
≥ 40 mm	30 (45)	6 (60)		≥ 40 mm	15 (43)	4 (36)	17 (55)		≥ 40 mm	9 (30)	27 (57)	
T stage			0.243	T stage				0.839	T stage			0.003[a]
cT1-2	27 (40)	6 (60)		cT1-2	15 (43)	5 (45)	13 (42)		cT1-2	19 (63)	14 (30)	
cT3-4	40 (60)	4 (40)		cT3-4	20 (57)	6 (55)	18 (58)		cT3-4	11 (37)	33 (70)	
N stage[a]			0.942	N stage				0.942	M stage			< 0.001[a]
Absent	26 (39)	4 (40)		Absent	14 (47)	5 (45)	11 (35)		Absent	27 (90)	22 (47)	
Present	41 (61)	6 (60)		Present	21 (45)	6 (55)	20 (65)		Present	3 (10)	25 (53)	
M stage			0.132	M stage				0.255	Wall thickness			0.015[a]
Absent	40 (60)	9 (90)		Absent	25 (71)	6 (55)	18 (58)		< 11 mm	20 (67)	18 (38)	
Present	27 (40)	1 (10)		Present	10 (29)	5 (45)	13 (42)		≥ 11 mm	10 (33)	29 (62)	
Wall thickness			0.532	Wall thickness				0.029[a]	Surgery			0.203
< 11 mm	34 (61)	4 (40)		< 11 mm	20 (57)	9 (82)	9 (29)		Performed	9 (30)	21 (45)	
≥ 11 mm	33 (39)	6 (60)		≥ 11 mm	15 (43)	2 (18)	22 (71)		None	21 (70)	26 (55)	
Enhanced homogeneity			0.916	Enhanced homogeneity				0.122	Enhanced homogeneity			0.165
Homogeneous	6 (9)	1 (10)		Homogeneous	5 (14)	1 (9)	1 (3)		Homogeneous	1 (3)	6 (13)	
Heterogeneous	61 (91)	9 (90)		Heterogeneous	30 (86)	10 (91)	30 (97)		Heterogeneous	29 (97)	41 (87)	
Degree of enhancement			0.018[a]	Surgery				0.91	Degree of enhancement			0.726

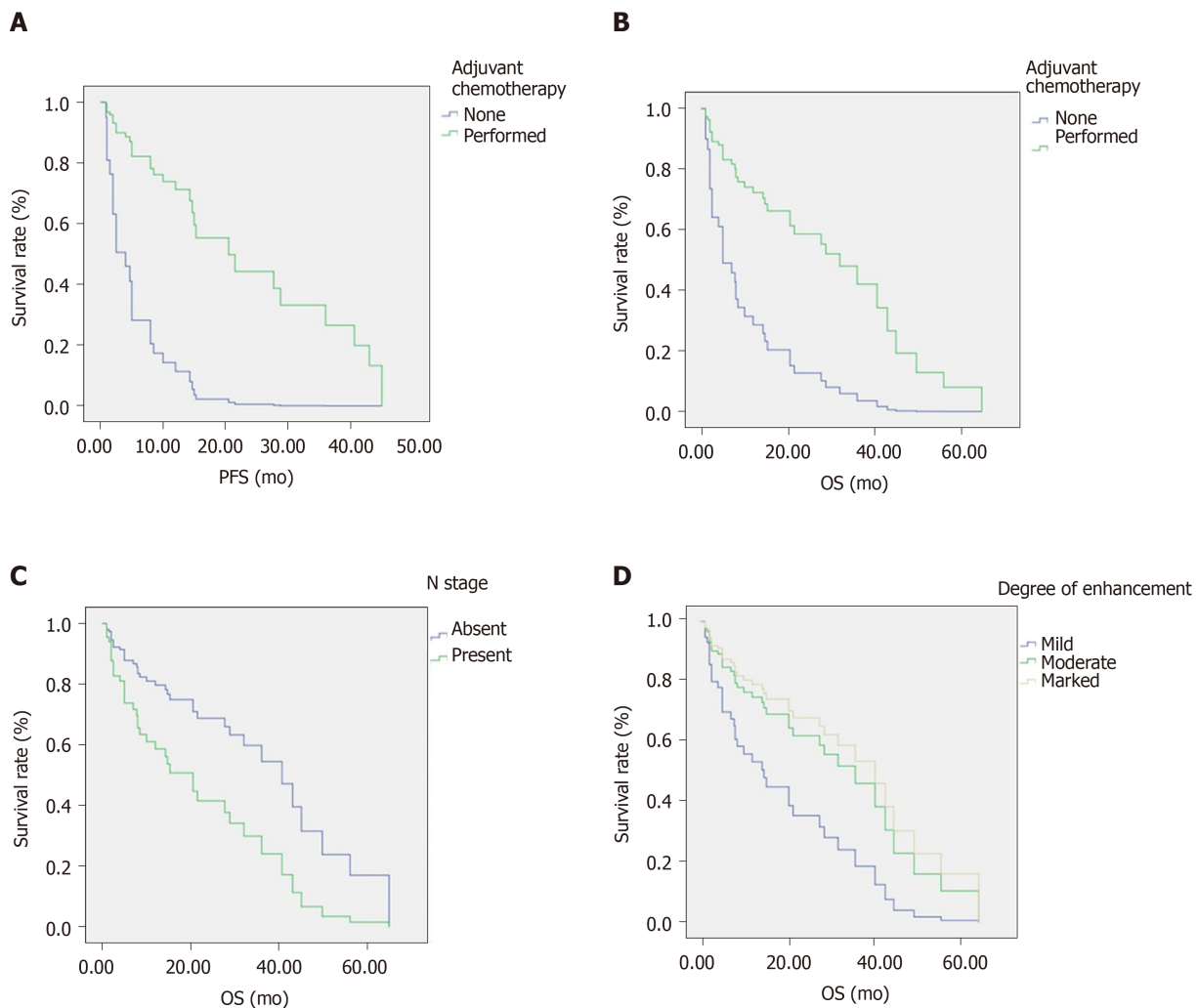| Mild	12 (18)	0	Performed	21 (60)	7 (64)	19 (61)	Mild	5 (16)	6 (12)
Moderate	22 (33)	8 (80)	None	14 (40)	4 (36)	12 (39)	Moderate	11 (37)	20 (43)
Marked	33 (49)	2 (20)					Marked	14 (47)	21 (45)

[a]Statistically significant.

study indicates the high malignancy of esophageal NEC[10,11]. Currently, treatment strategies mainly include surgery and comprehensive treatment with combined chemotherapy and/or radiotherapy[8,12,13].

It is acknowledged that CT, magnetic resonance imaging (MRI), and ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) are commonly applied to determine malignancy or metastases at present. Their combined use could, however, be of clinical value, with FDG-PET detecting malignancy or possible metastases, and CT and MRI confirming or excluding their presence and precisely determining the location, and significantly improve the ability to quantitatively assess the functional imaging characteristics in the tumor[14-17]. High-resolution CT is widely used to identify the locations and relationships of surrounding organs and to assess distant metastases of esophageal lesions due to cost-effective advantage and low radiation exposure at the first diagnosis[18]. Currently, owing to the low incidence of esophageal NEC, there are still no esophageal NEC survival analysis reports on imaging features supported by a large amount of data. In view of this, we designed this study to explore the application of pretreatment clinical features and contrast-enhanced CT-defined characteristics as significant prognostic biomarkers for the survival of patients with esophageal NEC. Our results demonstrated that adjuvant chemotherapy is an independent prognostic factor for OS and PFS. Moreover, N stage and degree of enhancement are prognostic factors for OS in patients with esophageal NEC. In addition, adjuvant chemotherapy was significantly associated with degree of enhancement, while degree of enhancement significantly correlated with esophageal wall thickness.

Previous studies reported that TNM stage[1,3,6,19] and adjuvant therapy[8,12,13] of esophageal NEC were closely related to the risk of death in patients with esophageal NEC, which is partly consistent with our findings. Studies also confirmed that earlier clinical stage tends to yield better survival outcomes for esophageal NEC[8,12,13]. We considered that CT imaging plays an important role in pre-treatment staging, and provides information on tumor blood supply and enhancement features. This study emphasized that clinical features and CT characteristics can be used as variables for survival analysis. Thus, we mainly selected indicators related to the TNM stage, morphological features, and enhancement characteristics of the tumor. The clinical and CT imaging prognostic biomarkers can be used by clinical workers to quantify the risk of death of patients and improve the development of post-treatment monitoring protocols.
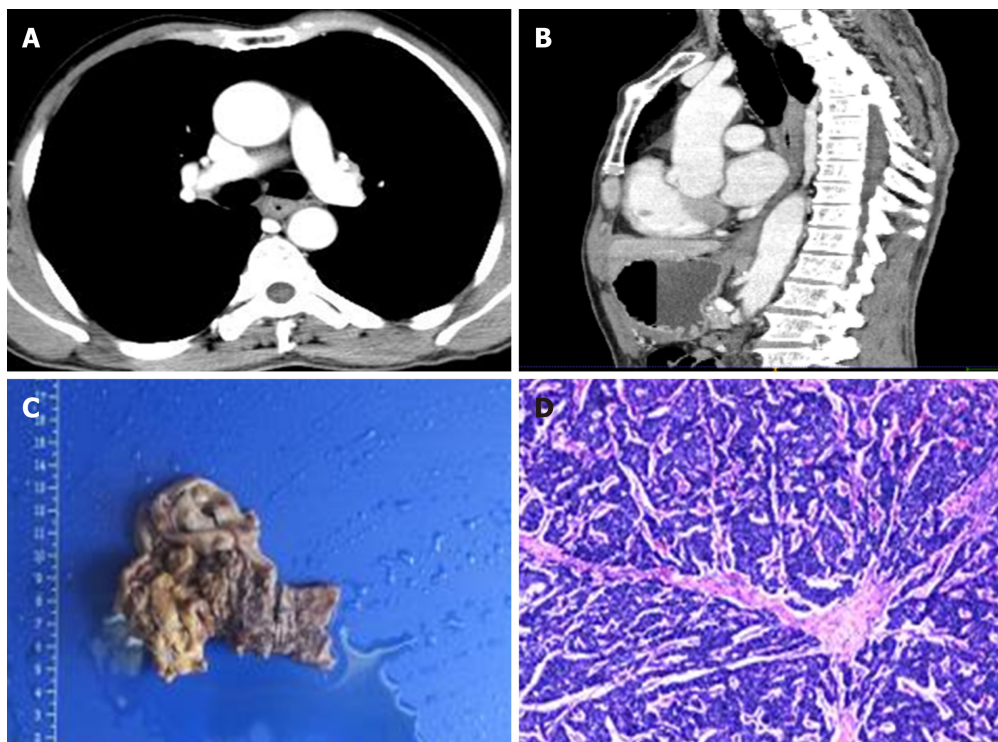
Figure 1 Kaplan-Meier univariate analysis. A and B: Progression-free survival (A) and overall survival (OS) (B) according to adjuvant chemotherapy; C and D: OS according to N stage (C) and degree of enhancement (D). OS: Overall survival; PFS: Progression-free survival.

Although surgery and adjuvant therapy have been shown to extend survival, treatment strategy for esophageal NEC has not been described systematically. Currently, the same AJCC guidelines for esophageal squamous cell carcinoma /adenocarcinoma are used for diagnosis and treatment[20]. Previous studies have demonstrated that surgery can extend the survival of esophageal NEC patients[21]. However, recent studies have shown that surgery may benefit only patients with early stage disease[6,13]. The combination with systemic adjuvant chemo-radiotherapy yields better survival than surgery alone, which has an important role in controlling metastasis and residual lesions. Our study considered that adjuvant chemotherapy was an independent risk factor for recurrence and death, which is consistent with previous research results. With adjuvant chemotherapy, the duration of PFS and OS was improved, which reaffirmed the role of adjuvant chemotherapy in esophageal NEC treatment.
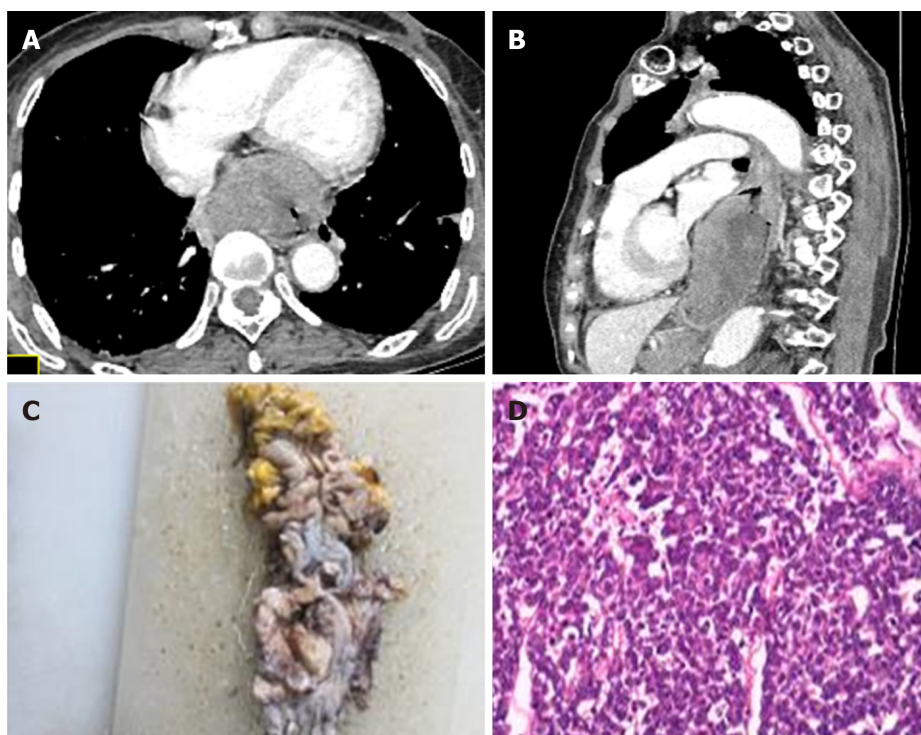
Contrast-enhanced CT scan is an effective method to evaluate the abundance of tumor blood supply. After contrast agent injection, most of the esophageal NEC exhibited marked heterogeneous enhancement, and necrosis could be seen in some larger cases. Blood supply to esophageal NEC appears to be similar to that of stomach, hepatic, pancreatic NEC, *etc*. This may be related to the high malignancy and poor differentiation of neuroendocrine NEC[22-24]. This study concluded that there are associations between clinical factors and CT characteristics. Degree of enhancement substantially correlated with adjuvant chemotherapy and esophageal wall thickness. Meanwhile, N stage was positively associated with tumor length, T stage, M stage, and esophageal wall thickness. We inferred that if the blood supply to the tumor is relatively rich, it is likely to manifest a low differentiation and common lymph node or distant metastases. Therefore, the patients would be sensitive to adjuvant chemotherapy.

Figure 2 A typical case of esophageal neuroendocrine carcinoma. A: Axial contrast-enhanced computed tomography image of a 67-year-old man with mildly enhanced esophageal neuroendocrine carcinoma in the middle segment of the esophagus (cT2N0M0). The patient showed a good treatment effect from postoperative adjuvant chemoradiotherapy with 26.13 mo and 35.6 mo of progression-free survival and overall survival, respectively; B: Sagittal-enhanced image of the patient. The tumor was 20 mm in length and exhibited marked enhancement; C: Pathological specimen of the patient; D: Histological image of the patient. Hematoxylin and eosin staining at × 10 magnification.

This study had several shortcomings. First, CT has limitations for accurate TN staging due to poor soft-tissue contrast to exactly reveal the invasion of the specific layer and lymph node characteristic. The TNM stage was evaluated in our study not by CT, but by pathology. Second, the enhanced level of the tumor was set based on the enhancement degree contrast to the adjacent muscles. However, this is likely to be inevitably influenced by subjective factors based on the observer. Moreover, the retrospective nature of the study restricted the availability of other functional imaging parameters. Additional imaging modalities, such as radiomics features, can provide information on different aspects of tumor characteristics, which can be crucial in predicting tumor prognosis. Furthermore, immunoscoring the lymphocytic infiltration is a perfect complement to the tumor prognosis judgment system nowadays[25]. Combined analysis will further improve the tumor prognosis evaluation.

In conclusion, our findings show that adjuvant chemotherapy is an independent prognostic factor for OS and PFS. In addition, N stage and degree of enhancement are prognostic factors for OS in patients with esophageal NEC.

Figure 3 A typical case of esophageal neuroendocrine carcinoma. A: Axial contrast-enhanced computed tomography image of a 75-year-old man with markedly enhanced esophageal neuroendocrine carcinoma in the middle segment of the esophagus (cT4N2M0). The patient showed a poor treatment effect from chemoradiotherapy with 3.6 mo and 8 mo of progression-free survival and overall survival, respectively; B: Sagittal-enhanced image of the patient. The tumor was 94.46 mm in length and exhibited moderate enhancement; C: Pathological specimen of the patient; D: Histological image of the patient. Hematoxylin and eosin staining at × 10 magnification.

ARTICLE HIGHLIGHTS

Research background

The occurrence of esophageal neuroendocrine carcinoma (NEC) is rare, with an incidence of only 0.03-5% of reported gastrointestinal neuroendocrine tumors. Esophageal NEC usually has characteristics of a high-grade malignancy with poor differentiation, inadequate tumor vascularization, and common metastases.

Research motivation

The clinical data included in the foregoing prognostic models are limited, and imaging data are lacking. Studies involving prognosis of esophageal NEC including contrast-enhanced computed tomography (CT) have not yet been conducted.

Research objectives

This study aimed to investigate the role of pretreatment contrast-enhanced CT imaging and patient clinical characteristics in predicting the progression-free survival and overall survival of patients with esophageal NEC.

Research methods

Seventy-seven esophageal NEC patients who received contrast-enhanced CT at two hospitals were enrolled in this study. The clinical features and image characteristics were recorded accordingly. The univariate survival analysis was performed by the Kaplan-Meier method and log-rank test, and the multivariate analysis was carried out with a Cox proportional hazards model.

Research results

The multivariate analysis showed that N stage, adjuvant chemotherapy, and degree of enhancement were independent prognostic factors for overall survival. Meanwhile adjuvant chemotherapy was an independent prognostic factor for progression-free survival. Adjuvant chemotherapy was significantly associated with degree of enhancement.

Research conclusions

Adjuvant chemotherapy is an independent prognostic factor for overall survival and progression-free survival. Additionally, N stage and degree of enhancement are prognostic factors for overall survival in patients with esophageal NEC.

Research perspectives

CT has limitations for accurate TN staging due to poor soft-tissue contrast to exactly reveal the invasion of the specific layer and lymph node characteristic. The enhanced level of the tumor is influenced by subjective factors based on the observer. Additional imaging modalities, such as radiomics features, can provide information on different aspects of tumor characteristics in predicting tumor prognosis.

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