BMC Cancer

RESEARCH

Open Access

Clinicopathologic characteristics and prognostic factors of pure gastric neuroendocrine carcinoma patients undergoing radical surgery

Kai Zhou[1†], Xiao Hu[2†], Xuesong Yang[3†], Yan Wu[2], Ke Ji[1], Xin Ji[1], Ji Zhang[1], Xiaojiang Wu[1], ZhongWu Li[2], Anqiang Wang[1*], Yusheng Wang[4,5*] and Zhaode Bu[6*]

Abstract

Background There is a low incidence of gastric neuroendocrine carcinoma (G-NEC), but it is associated with particularly aggressive biological behaviours and poor prognosis compared with other gastric neoplasms. Our study aimed to investigate the clinicopathologic traits and prognostic factors of patients with pure gastric neuroendocrine carcinoma treated with radical surgery.

Methods We retrospectively analysed 60 patients with pure G-NEC who underwent radical gastrectomy between March 2010 and May 2019. 68 patient who underwent curative surgery for mixed gastric adenoneuroendocrine carcinoma (G-ANEC) from August 2012 to June 2022. The relationships between the clinicopathologic characteristics of pure G-NEC and overall survival (OS) and disease-free survival (DFS), as well as the comparison of pure-NEC with G-ANEC in terms of prognosis and treatment regimens, were evaluated using the Kaplan–Meier method and (or) Cox regression.

Results The gastroesophageal junction (GEJ) was the predilection site for G-NEC. Tumor location, histology, and lymph node metastasis status were independent prognostic factors for OS ($P<0.05$). Pathological T stage and the presence or absence of lymph node metastasis were independently associated variables with DFS ($P=0.019$ and $P=0.041$). Large cell neuroendocrine carcinoma (LCGNEC) did not differ statistically from the small cell neuroendocrine carcinoma (SCGNEC) ($P=0.314$) for OS, while mixed type (MGNEC) vs. LCGNEC did differ significantly ($P=0.031$). There were no significant differences in OS and DFS between etoposide and cisplatin (EP) and S-1 + oxaliplatin (SOX) / oxaliplatin + capecitabine (XELOX). The study of 106 patients found no significant impact of NEC proportion on OS ($P=0.438$) or DFS ($P=0.079$). Neoadjuvant/adjuvant chemotherapy targeting NEC versus adenocarcinoma showed no statistical difference in OS ($P=0.415$, $P=0.350$), but there was a trend toward longer survival with NEC-targeted regimen.

†Kai Zhou, Xiao Hu and Xuesong Yang contributed equally to this work.

*Correspondence:
Anqiang Wang
wanganqiang0902@163.com
Yusheng Wang
wangyusheng1972@163.com
Zhaode Bu
buzhaode@cjcrcn.org
Full list of author information is available at the end of the article

Conclusions The LCGNEC did not differ statistically from the SCGNEC for OS, while the MGNEC vs. LCGNEC were different. The prognosis of G-NEC was related to the tumor location, histology, postoperative T stage, and lymph node metastasis. For gastric neuroendocrine carcinoma, prognosis does not differ statistically by NEC proportion. Chemotherapy regimens targeting lymph node metastases with an NEC component maybe better prognosis than those focusing on the adenocarcinoma component.

Keywords Pure gastric neuroendocrine carcinoma, Clinicopathologic characteristics, Radical surgery, Overall survival time, Disease-free survival time

Introduction

By 2020, gastric cancer (GC) was the fourth most prevalent cancer in the world and the fifth main cause of cancer-related deaths [1–4]. A total of 820,000 new cases and 580,000 deaths were reported from GC in Asia, primarily in China [5]. As per China's latest statistics in 2020, among all cancers, GC has the third-highest incidence and mortality rate [6, 7]. Usually, gastric neuroendocrine carcinomas (G-NEC) do not occur, accounting for 0.1–0.6% of all GC and approximately 4.1% of all neuroendocrine tumors [8–10]. G-NEC is characterized by its low degree of differentiation, containing over 20 mitotic cells in 10 high power fields, or having a Ki-67 labelling index over 20% [10, 11]. Meanwhile, immunohistochemistry (IHC) markers synaptophysin (Syn) and chromogranin A (CgA) typically exhibit positive expression in pathological samples of G-NEC. G-NEC is characterized by tumor tissue heterogeneity, aggressive biological behavior, and inferior prognosis compared with gastric adenocarcinoma. However, only a small percentage of clinical G-NEC cases have been analyzed to date due to its low incidence rate and difficulty in diagnosis with preoperative biopsy [10, 12]. Therefore, the correlations between the clinicopathological features and prognosis have not been elucidated thoroughly, and the optimum therapeutic therapy options for pure G-NEC are not yet well established [13].

Our research aims to provide an updated review of clinicopathological features, treatments, and prognosis for 60 pure G-NEC patients eligible for radical surgical resection, and to provide a significant reference value for the therapy of these populations.

Materials and methods

Patients

A total of 244 patients were diagnosed with gastric carcinoma with neuroendocrine component undergoing surgery at Peking University Cancer Hospital from 2010 to 2022 were initially considered. We consecutively enrolled 60 patients diagnosed with pure NEC who underwent either radical total or partial gastrectomy. The inclusion criteria were as follows: 1) pure G-NEC with a neuroendocrine component of 100%; 2) radical resection; 3) negative peritoneal cytology; and 4) no distant metastasis at the time of initial surgery. The exclusion criteria were as follows: 1) patients with multiple primary neoplasms; and 2) patients in a vegetative state who died in the perioperative period. Among these patients, 38 patients with pure G-NEC who also experienced lymph node metastasis. To compare pure G-NEC with mixed gastric adenoneuroendocrine carcinoma (G-ANEC) (1%–99% for NEC or AC), we included 68 additional cases of G-ANEC with lymph node metastasis, containing only NEC and AC components, irrespective of NEC proportion. Among these patients, 41 were diagnosed with gastric mixed adenoneuroendocrine carcinoma (G-MANEC), and 27 had a neuroendocrine carcinoma component that constituted less than 30% or more than 70% of the G-ANEC. Exclusion criteria included non-curative surgical procedures, presence of distant metastasis (M1), and cases with substantial missing clinical and pathological data.

Data collection

For pure G-NEC, most of clinicopathological features including age, sex, surgical modalities, neoadjuvant chemotherapy (NAC) status, NAC regimens, tumor location, the greatest dimension, serum CEA, CA199, CA724, CA125, CA242, neuron specific enolase (NSE), adjuvant chemotherapy (AC) status, AC regimens, with or without a correct preoperative diagnosis, histology, mitotic rate, lymphatic invasion (LVI) status, nerve invasion, postoperative T stage, lymph node metastasis, postoperative TNM stage status, Syn, CgA, CD56, and Ki-67 index in IHC were retrospectively collected from the electronic medical anamnesis system (Table 1). Using the eighth categorization system developed by the American Joint Committee on Cancer/Union for International Cancer Prevention, we evaluated the clinical stage using abdominal computed tomography (CT). The review board of the cancer hospital at Peking University authorized a retrospective study conducted in accordance with the Helsinki Declaration's principles.

Table 1 Clinicopathological parameters

Parameters	No. of cases (%)
Median age (years)	63.00
Age(year)	
≤62	27(45.0)
62-70	25(41.7)
＞70	8(13.3)
Gender	
Female	11(18.3)
Male	49(81.7)
Surgical modalities	
Open surgery	7(11.7)
Laparoscopic surgery	53(88.3)
Surgical resection modalities	
Proximal gastrectomy	6(10.0)
Distal gastrectomy	14(23.3)
Total gastrectomy	40 (66.7)
Neoadjuvant chemotherapy	
Yes	29 (48.3)
No	31 (51.7)
Neoadjuvant chemotherapy regimens	
EP	11 (18.3)
IP	1(1.7)
SOX/XELOX	7 (11.7)
other	10 (16.7)
Location of tumor	
EGJ	29(48.3)
Non-EGJ	31(51.7)
Greatest dimension	
＜5cm	48(80.0)
≥5cm	12(20)
CEA (ng/mL)	
0-5	45(75.0)
＞5	10(16.7)
Missing data	5 (8.3)
CA199 (U/mL)	
0-37	55(91.7)
＞37	0 (0)
Missing data	5(8.3)
CA724 (U/mL)	
0-6.7	46 (76.7)
＞6.7	9 (15)
Missing data	5 (8.3)
CA125 (U/mL)	
0-35	42(70.0)
＞35	0 (0)
Missing data	18(30.0)
CA242 (U/mL)	
0-20	24 (40)
＞20	0 (0)
Missing data	36 (60.0)

Table 1 (continued)

Parameters	No. of cases (%)
NSE (ng/mL)	
0-15.2	26(43.3)
＞15.2	0 (0)
Missing data	34(56.7)
Adjuvant chemotherapy	
Yes	41(68.3)
No	19(31.7)
Adjuvant chemotherapy regimens	
EP	8(13.3)
IP	12(20.0)
SOX/XELOX	13(21.7)
Other	8 (13.3)
Preoperative correct diagnosis	
Yes	32 (53.3)
Non	28 (46.7)
Histology	
Large cell	34(56.7)
Small cell	20(33.3)
Mixed type	6 (10)
Mitotic rate (mitoses/mm^2)	
≤27	33(55.0)
＞27	25(41.7)
Missing data	2(3.3)
LVI	
Yes	28(46.7)
No	32 (53.3)
Nerve invasion	
Yes	28(46.7)
No	32(53.3)
pT	
pT0	2(3.3)
pT1	4(6.7)
pT2	7(11.7)
pT3	34(56.7)
pT4	13(21.7)
pN	
pN0	22(36.7)
pN1-3	39(63.3)
TRG grate	
0	2(3.3)
1	1(1.6)
2	9(14.8)
3	18(29.5)
Syn	
+	59(98.7)
-	0(0)
Missing data	1(1.7)
CgA	
+	42(70.0)

Table 1 (continued)

Parameters	No. of cases (%)
-	17(28.3)
Missing data	1(1.7)
CD56	
+	47(78.3)
-	12(20)
Missing data 1(1.7)	
Ki-67 index (%)	
≤65	13(21.7)
＞65	46 (76.7)
Missing data	1(1.7)
pTNM	
0/I	9(15)
II	34(56.7)
III	17(28.3)

Follow-Up

Follow-up was primarily conducted by phone or in clinics. Three months after surgery, the patients received follow-up gastroscopy, abdominal CT, chest radiography, and tumor biomarker examination at our hospital or a nearby institution, and then every three or six months thereafter. Within the first two years following surgery, the aforementioned examinations were repeated every 3–6 months and then every 6–12 months until five years had passed. OS was calculated from the start of the NAC therapy or radical surgical gastrectomy until the end of follow-up or the occurrence of any mortality. DFS was defined as the interval between the date of the initial treatment with NAC or radical gastrectomy and the date of disease recurrence, metastasis, death from any cause, or the date of the last follow-up. During this period, the patients of pure G-NEC were followed for an average duration of 45.5 months, with a range of 1 to 137 months. The patients of G-ANEC were followed for an average duration of 38.8 months, with a range of 1 to 120 months.

Statistical analysis

The SPSS 23.0 statistical package and R programming language were used to conduct the statistical study. We conducted survival studies using Kaplan–Meier and Cox proportional hazards models. In the Cox proportional hazards model, clinicopathologic traits with $P<0.10$ in univariate survival studies were included. Statistics were deemed significant at $P<0.05$. GraphPad Prism 5 was used to create the Kaplan–Meier survival curve, and SPSS 23.0 was used to run the log-rank test on the survivor data. Based on X-tile software, the ideal age, mitotic rate, and Ki-67 index cut-off values were determined.

Results

Clinical characteristics

A total of 60 participants of pure G-NEC were eventually included in our study (Fig. 1). The clinicopathological profiles of these individuals are shown in Table 1. With

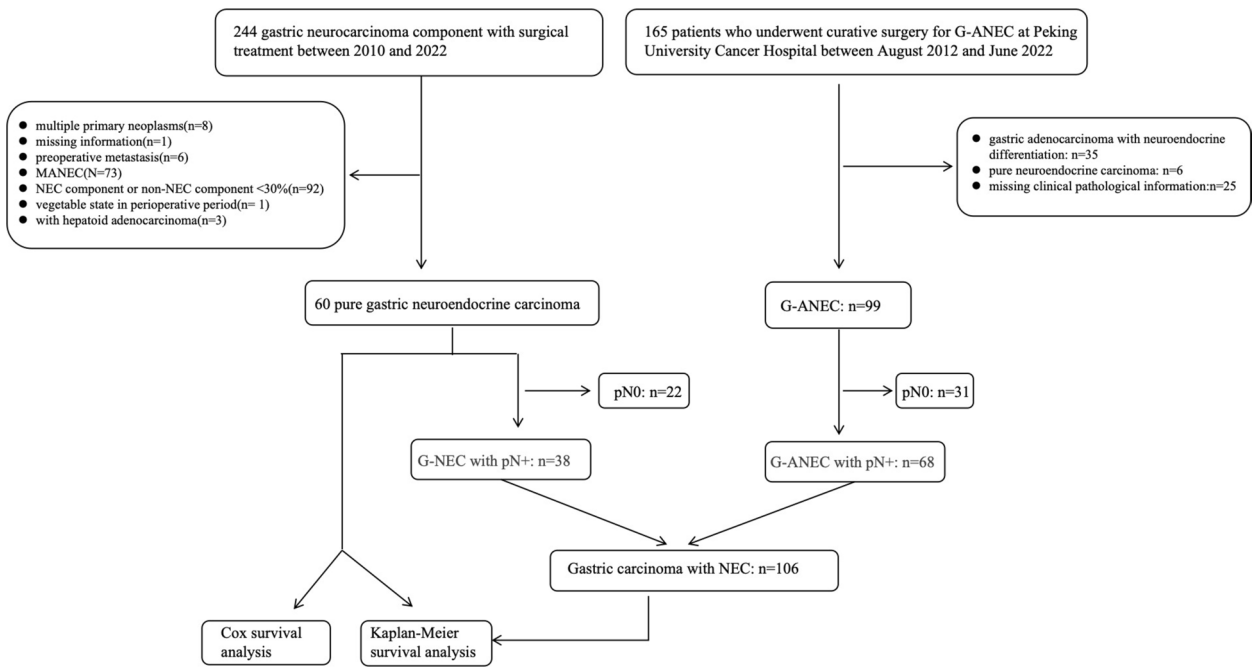

Fig. 1 Flow-chart of enrolled patients

a median age of 63 years, the ages varied from 37 to 75. The male to female ratio in the patient group was approximately 4.5:1, with 49 males (49, 81.7%) and 11 females (11, 18.3%). In terms of tumor location, the gastroesophageal junction (GEJ) (29, 48.3%) and non-GEJ (31, 51.7%) share a number of parallels. Less than 5 centimetes was the primary tumor size in 48 cases (80.0%). Before treatment, the serum carcinoembryonic antigen (CEA) level was elevated (>5 ng/ml) in 10 patients (16.7%) and normal (0–5 ng/ml) in 45 (75.0%) patients, with missing data in 5 (8.3%) patients. In 55 individuals (91.7%), the serum CA199 was measured to be within the normal reference, and the data of 8.3% of patients were missing. Similarly, 42 individuals (70%) had recorded with serum CA125 levels, and all of them had normal levels. Serum CA242 was available in 24 (40%) patients and were within the normal reference range. Serum CA724 was available for 55 patients, 46 (76.7%) were normal, and 9 (15%) showed elevated levels. The NSE was available for 26 patients, the values were within the normal reference range, and 34 were missing data. Postoperative distant metastasis occurred in 14 patients, and 12 had liver metastasis (12/14).

Pathological characteristics

All 60 tumors were diagnosed as pure G-NEC, while the overall rate of correct preoperative diagnosis was 53.3% (32/60). For postoperative pathological TNM results, nine patients (15%) had stage 0-I disease, 34 patients (56.7%) had stage II disease, and 17 patients (28.3%) had stage III disease. The LCGNEC was the most prevalent histological type (34, 56.7%), followed by the SCGNEC (20, 33.3%), and the MGNEC (6, 10.0%). The LCGNEC had an enlarged nucleus and slightly eosinophilic cytoplasm, and they were organized in sheets and solid nets for large cells. In addition, pathological karyokinesis was evident, and the chromatin was frequently granular, dense, or coarse (Fig. 2 A1). SCGNEC was arranged in a nested pattern with scant cytoplasm and densely stained, finely granular chromatin (Fig. 2 A2). Some cases exhibit the simultaneous occurrence of large cell and small cell types of neuroendocrine carcinoma (Fig. 2 A3). IHC analysis demonstrated that Syn and CgA were predominantly localized in the cytoplasm, Ki-67 in the nuclei, and CD56 on the cell membrane (refer to Fig. 2 B1-B3 for Syn, C1-C3 for CgA, D1-D3 for CD56, and E1-E3 for Ki-67). Sixty patients underwent immunohistochemical staining for Syn, 59 (98.7%) tumors were positive for Syn, and one patient had missing data. IHC staining for CgA was performed on sixty patients, 42 (70.0%) tumors were positive, and 17 (28.3%) were negative. Sixty patients were conducted in CD56 IHC staining, and 78.3% of the patients had CD56 positivity. The percent of patients with one, two, or three positive markers were 5%, 38.3%,

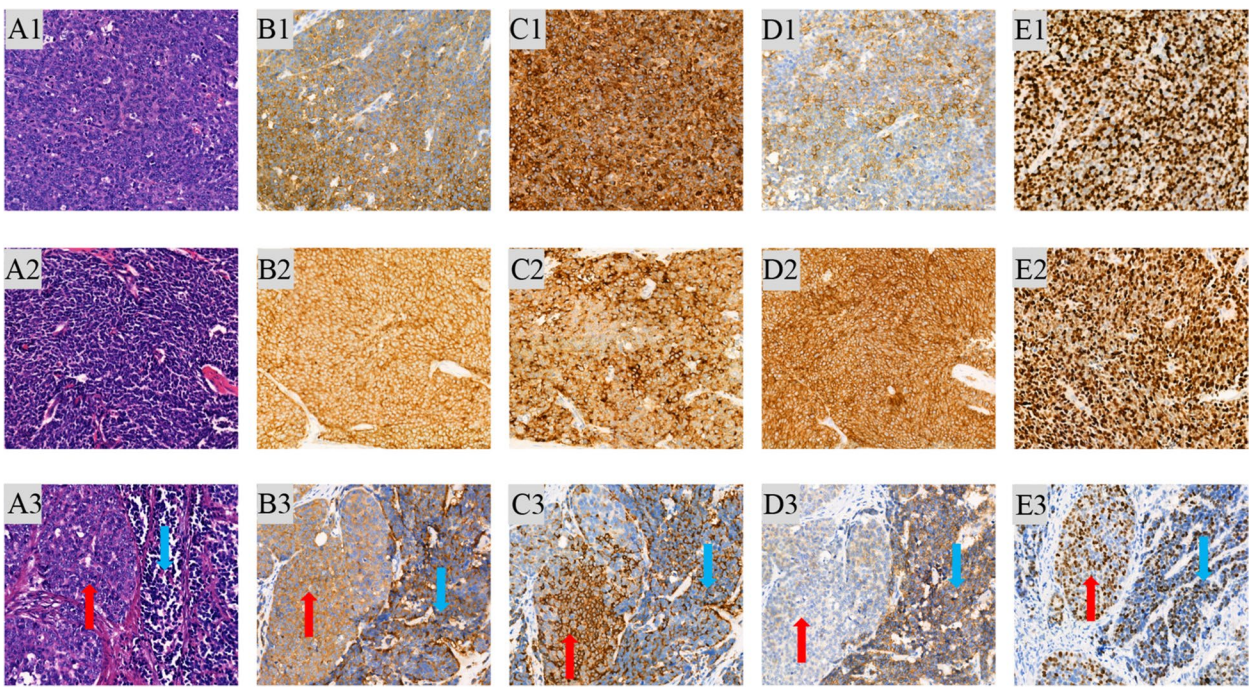

Fig. 2 Histologic and immunohistochemical features of large-cell, small-cell G-NEC, and large and small cell mixed type G-NEC. Al Large cell G-NEC. A2 Small cell G-NEC. A3 Large and small cell mixed type of G-NEC. For large cell G-NEC: B1 Syn; C1 CgA; D1 CD56; E1 Ki-67. For small cell G-NEC: B2 Syn; C2 CgA; D2 CD56, E2 Ki-67. For Large and small cell mixed type of G-NEC. B3 Syn; C3 CgA; D3 CD56; E3 Ki-67

and 55%, respectively. A high Ki-67 index (>65%) and a low Ki-67 index (≤65%) were dichotomized. A high Ki-67 index was observed in 46 (76.7%) patients, and a low Ki-67 index was observed in 13 (21.7%) patients. In addition, we also dichotomized the mitotic rate into ≤27/mm^2 and >27/mm^2. The former included 33 patients (55.0%), whereas the latter included 25 patients (41.7%). Twenty-eight (46.7%) patients had lymphatic invasion (LVI). Twenty-eight (46.7%) patients had never experienced invasion (Table 1). The metastasis rates of lymph nodes in tumour stage I, II and III were 22.2% (2/9), 55.9% (19/34), and 100% (17/17), respectively.

Treatment regimens

There was a significant preponderance of laparoscopic surgery (53, 88.3%) over open surgery (7, 11.7%). All patients underwent radical gastrectomy, including 40 cases of total gastrectomy (66.7%), 14 cases of distal gastrectomy (23.3%), and 6 cases of proximal gastrectomy (10%). Twenty-nine (48.3%) patients received NAC, while 11 (18.3%) patients received etoposide and cisplatin (EP), 7(11.7%) patients were given S-1+oxaliplatin (SOX) and oxaliplatin+capecitabine (XELOX), and 1 patient received cisplatin+irinotecan (IP). 41 patients (68.3%) received adjuvant chemotherapy (AC). SOX and XELOX ($n=13$), IP ($n=12$), EP ($n=8$), and other regimens ($n=8$) were the AC regimens (Table 1).

Survival and correlation with clinicopathological factors

On univariate OS analysis, age ($P=0.026$, Fig. 3A), NAC regimens ($P=0.006$, Fig. 3B), tumor site ($P=0.036$, Fig. 3C), histology ($P=0.093$, Fig. 3D), LVI ($P=0.055$, Fig. 3E), nerve invasion ($P=0.023$, Fig. 3F), lymph node metastases ($P<0.001$, Fig. 3H), and postoperative TNM

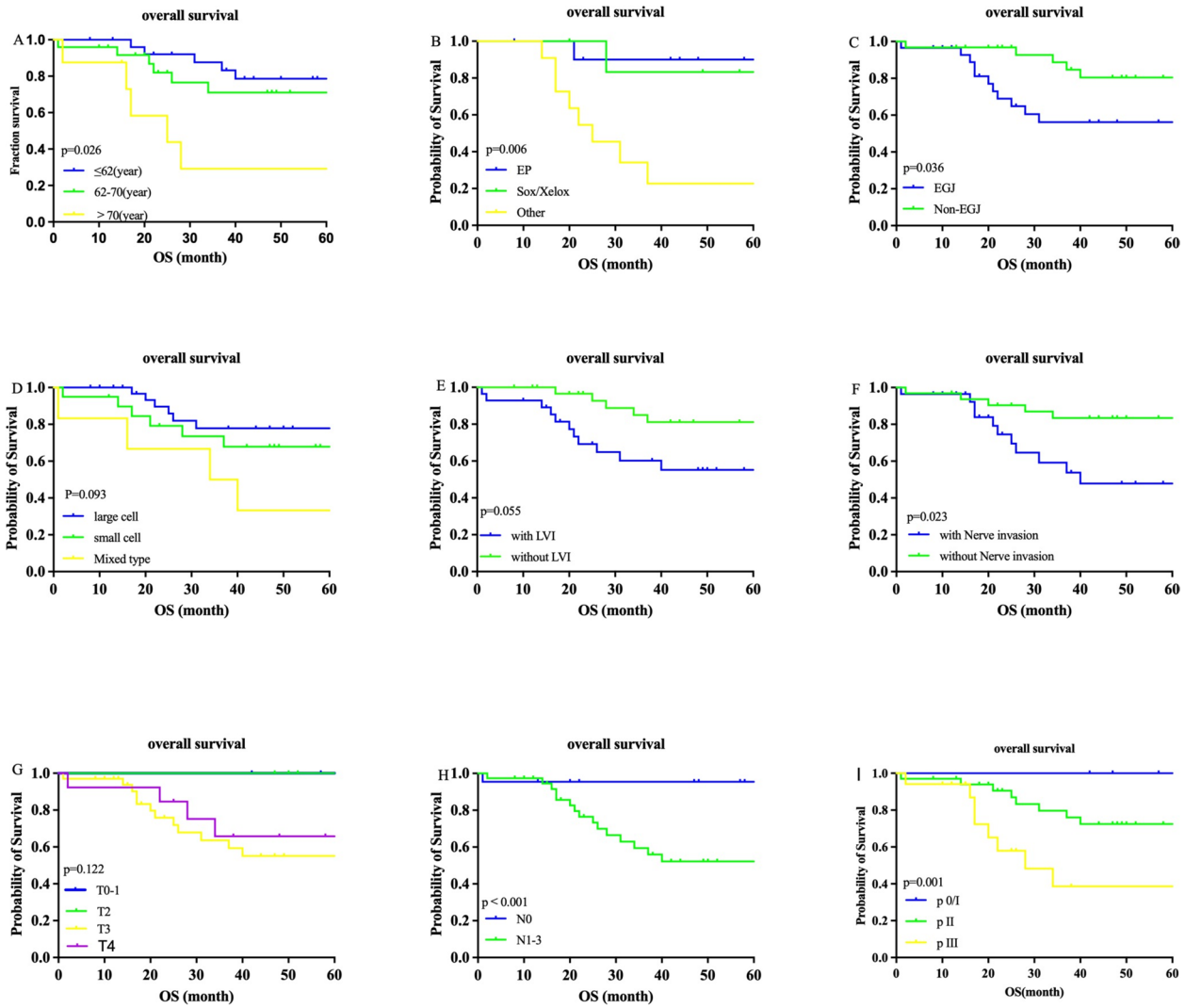

Fig. 3 Univariate Kaplan–Meier survival analyses of overall survival time

stage ($P=0.001$, Fig. 3I) were significant predictors of survival ($P<0.1$). There is no statistically significant difference in OS between different pT stages ($P=0.122$, Fig. 3G). Moreover, those who received EP or SOX/XELOX as NAC did not show statistical significance for OS ($P=0.303$). IP was categorized with the other treatments. EP and SOX/XELOX were statistically different from other regimens ($P=0.004$ and $P=0.060$). The LCGNEC was not statistically different from the SCGNEC ($P=0.314$), while the MGNEC was significantly different from the LCGNEC ($P=0.031$). A multivariate analysis of overall survival revealed that tumor site, histology, and the presence or absence of lymph node metastases were independent predictive factors ($P<0.05$, Fig. 4). The 1-, 3-, and 5-year OS rates for TNM stage 0-I patients were all 100%. Patients with TNM stage II had 1-, 3-, and 5-year OS rates of 97.1%, 79.7%, and 72.5%, respectively. Patients with TNM stage III had 1-, 3-, and 5-year OS rates of 94.1%, 38.6%, and 38.6%, respectively (Table 2).

On univariate DFS analysis, surgical modalities ($P=0.029$, Fig. 5A), AC presence or absence ($P=0.04$, Fig. 5B), mitotic rate ($P=0.03$, Fig. 5C), LVI ($P=0.01$, Fig. 5D), nerve invasion ($P=0.009$, Fig. 5E), pT ($P=0.07$, Fig. 5F) lymph node metastatic presence or absence ($P=0.014$, Fig. 5G), and postoperative TNM stage ($P=0.026$, Fig. 5H) were significant predictors ($P<0.1$). Postoperative T stage and lymph node metastasis status were independent predictive predictors ($P=0.019$ and $P=0.041$) according to multivariate DFS analysis (Fig. 6). The 1-, 3-, and 5-year DFS rates for TNM stage 0-I patients were all 100%. The 1-, 3-, and 5-year OS rates for TNM stage II patients were 87.8%, 77.1%, and 77.1%, respectively. Patients with TNM stage III had 1-, 3-, and 5-year OS rates of 80%, 38.4%, and 38.4%, respectively (Table 2).

Comparison of pure-NEC and G-ANEC in terms of prognosis and treatment regimens

The results indicate that the proportion of NEC components in the primary tumor (≤30%, 31%–70%, 71%–99%, 100%) of 106 patients is not a poor factor affecting OS and DFS ($P>0.05$, Figs. 7A, B). There was no statistical difference in OS between G-NEC and G-ANEC patients ($P=0.592$, Fig. 7C). Moreover, there was no statistical difference in OS among different neoadjuvant

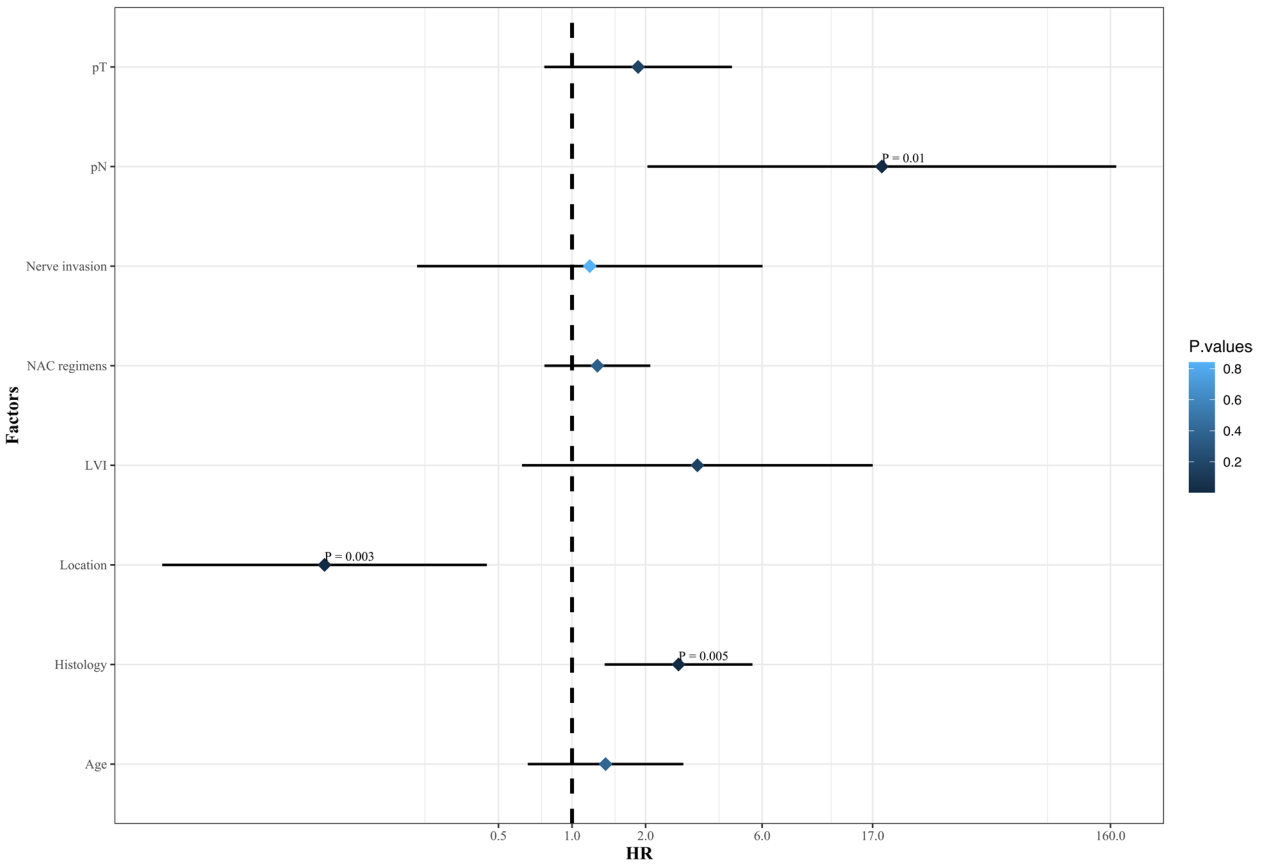

Fig. 4 Forest plot of multivariate overall survival analysis

Table 2 Univariate overall survival time and disease-free survival time disease-free analysis of clinical and pathological factor

Factors	OS				DFS			
	1-year survival rate (%)	3-year survival rate (%)	5-year survival rate (%)	*P* values	1-year survival rate (%)	3-year survival rate (%)	5-year survival rate (%)	*P* values
Age(year)				0.026				0.858
≤62	100.0	87.6	78.6		85.0	75.9	70.5	
62-70	96.0	71.1	71.1		91.3	75.9	75.9	
〉70	87.5	29.2	29.2		85.7	85.7	85.7	
Gender				0.879				0.832
Female	100.0	77.1	77.1		81.8	81.8	68.2	
Male	95.9	72.6	67.5		89.0	75.8	75.8	
Surgical modalities				0.352				0.029
Open surgery	98.1	74.8	70.2		50.0	50.0	50.0	
Laparoscopic surgery	85.7	57.1	57.1		92.1	80.5	77.6	
Surgical resection modalities				0.345				0.054
Proximal gastrectomy	100.0	62.5	-		100.0	83.3	-	
Distal gastrectomy	100.0	90.9	81.8		78.6	53.0	44.2	
Total gastrectomy	95.0	69.1	69.1		89.2	86.2	86.2	
Neoadjuvant chemotherapy				0.278				0.870
Yes	100.0	66.1	62.0		89.1	78.0	72.0	
No	93.5	81.4	76.9		86.2	77.3	77.3	
Neoadjuvant chemotherapy regimens				0.006				0.249
EP	100.0	90.0	90.0		100.0	90.0	78.8	
SOX/XELOX	100.0	83.3	83.3		100.0	85.7	85.7	
Other(IP)	100.0	34.1	22.7		70.0	60.0	60.0	
Location of tumor				0.036				0.814
EGJ	96.6	56.2	56.2		89.3	81.2	81.2	
Non-EGJ	96.8	88.7	80.4		86.2	74.4	70.0	
Greatest dimension				0.586				0.210
〈5cm	95.8	71.8	66.6		86.8	73.9	70.6	
≥5cm	100.0	79.5	79.5		90.9	90.9	90.9	
CEA (ng/mL)				0.706				0.067
0-5	95.6	74.6	69.0		85.6	72.0	68.6	
〉5	100.0	77.8	77.8		100.0	100.0	100.0	
CA724(U/mL)			0.601					0.344
0-6.7	95.7	74.9	72.1		86.0	74.6	71.2	
〉6.7	100.0	75.0	60.0		100.0	87.5	87.5	
Adjuvant chemotherapy				0.392				0.040
Yes	100.0	74.2	71.2		82.3	70.2	66.7	
NO	89.5	72.7	65.4		100.0	94.1	94.1	
Adjuvant chemotherapy regimens				0.321				0.620
EP	87.5	87.5	87.5		100.0	87.5	75.0	
IP	100.0	60.0	60.0		83.3	69.4	69.4	
SOX/XELOX	100.0	90.0	90.0		76.9	57.0	57.0	
Other	100.0	58.3	43.8		71.4	71.4	71.4	
Preoperative correct diagnosis 0.697 0.372								
Yes	96.9	70.3	70.3		90.2	81.9	76.8	
No	100.0	76.8	68.0		84.4	71.3	71.3	
Histology				0.093				0.783
Large cell	100.0	77.9	77.9		81.7	73.8	73.8	
Small cell	95.0	73.5	67.9		76.0	76.0	76.0	

Table 2 (continued)

Factors	OS				DFS			
	1-year survival rate (%)	3-year survival rate (%)	5-year survival rate (%)	*P* values	1-year survival rate (%)	3-year survival rate (%)	5-year survival rate (%)	*P* values
Mixed type	83.3	50.0	33.3		100.0	75.0	75.0	
Mitotic rate (mitoses/mm^2)				0.226				0.030
≤27	93.9	67.0	63.3		93.3	83.7	83.7	
＞27	100.0	79.5	73.9		80.0	67.1	61.5	
LVI				0.055				0.010
Yes	100.0	60.2	55.2		76.0	61.9	55.7	
No	100.0	85.0	81.1		96.8	89.1	89.1	
Nerve invasion				0.023				0.009
Yes	96.4	59.2	47.8		77.2	52.7	52.7	
No	96.9	83.5	83.5		96.7	89.3	89.3	
pT				0.122				0.070
T0-1	100.0	100.0	100.0		100.0	100.0	100.0	
T2	100.0	100.0	100.0		100.0	100.0	100.0	
T3	97.1	63.7	55.2		81.5	74.5	74.5	
T4	92.3	65.8	65.8		90.9	58.4	43.8	
pN				＜0.001				0.014
pN0	95.5	95.5	95.5		100.0	100.0	94.4	
pN1-3	97.4	59.5	52.2		80.3	62.1	62.1	
pTNM				0.001				0.026
0/I	100.0	100.0	100.0		100.0	100.0	100.0	
II	97.1	79.7	72.5		87.8	77.1	77.1	
III	94.1	38.6	38.6		80.0	38.4	38.4	
Cga				0.564				0.405
+	95.2	69.9	63.3		84.4	75.2	71.2	
-	100.0	80.4	80.4		94.1	79.9	79.9	
CD56				0.532				0.296
+	95.7	71.9	66.8		90.9	80.7	77.3	
-	100.0	77.8	77.8		75.0	60.0	60.0	
Ki-67 index (%)				0.563				0.455
≤65	100.0	74.1	74.1		92.3	83.9	83.9	
＞65	95.7	72.8	67.3		86.0	75.0	71.6	

chemotherapy regimens (EP/IP, SOX/XELOX, and others) used in the 106 patients ($P=0.291$, Fig. 7D). This study categorized the neoadjuvant chemotherapy regimens into those targeting adenocarcinoma (AC) and NEC, and the univariate analysis showed no statistical difference in OS between the two groups among the 106 patients included ($P=0.415$, Fig. 7E), yet the survival curve suggests a trend towards longer survival in the group treated with the NEC-targeted regimen compared to the AC-targeted regimen. There was a statistical difference in OS among different adjuvant chemotherapy regimens (EP/IP, SOX/XELOX, and others) ($P=0.044$, Fig. 7F), but the survival curves indicated no significant difference in OS between the EP/IP and SOX/XELOX groups. Similarly, categorizing the adjuvant chemotherapy regimens into those targeting AC and NEC, univariate analysis revealed no statistical difference in overall survival between the two groups ($P=0.350$, Fig. 7G). The survival curve suggested a trend towards longer survival in the NEC-targeted regimen group compared to the AC-targeted regimen group for adjuvant chemotherapy. Further investigation into patients with lymph node metastases containing NEC components showed no statistical difference in OS among different adjuvant chemotherapy regimens (EP/IP, SOX/XELOX, and others) ($P=0.647$, Fig. 7H). There was no statistical difference in OS between the two groups (targeting AC and targeting NEC for adjuvant chemotherapy regimens) ($P=0.351$,

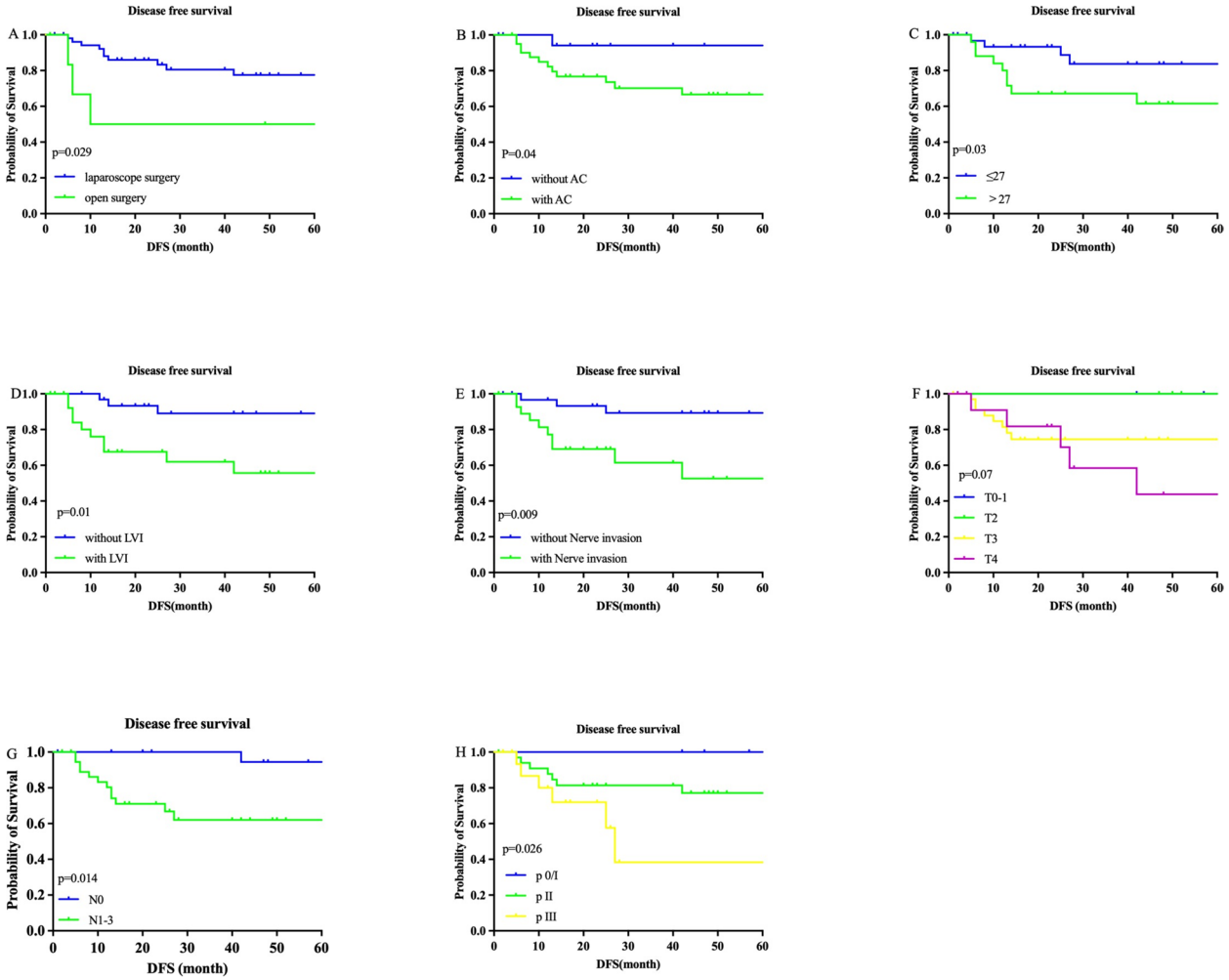

Fig. 5 Univariate Kaplan–Meier survival analyses of disease-free survival time

Fig. 7I), yet the survival curve indicates a trend towards longer survival in the NEC-targeted regimen group compared to the AC-targeted regimen group.

Discussion

G-NEC is an aggressive disease that is rising in incidence. Meanwhile, its long-term survival rates have stagnated over the past decades [14]. Previous case reports and case series were insufficient, and the data collection and data processing were unsatisfactory in revealing the clinical characteristics, therapies, and prognosis of pure NEC. Current studies have highlighted that there is inadequate awareness among physicians about the clinical manifestations, therapies, and prognoses of G-NEC. In most cases, G-NEC is detected at a very advanced stage, and has a poor prognosis [2]. Therefore, we completed an overview analysis of 60 patients undergoing radical surgical resection for pure G-NEC. The results provide a basis for the clinical manifestations, prognoses, and case management of G-NEC.

Preoperative diagnosis of G-NEC is notoriously difficult. In our study, only 53.3% of pure G-NEC patients obtained an accurate preoperative pathological diagnosis. Usually, the superficial layer of G-NEC is covered by non-neoplastic mucosa, and the biopsy position is too superficial [15]. In addition, the high heterogeneity is another contributing factor, for example, differences in tumor cell growth rates, invasive capabilities, and tumor microenvironments among individuals. Immunostaining with neuroendocrine markers is necessary to achieve a definitive diagnosis and boost the differential diagnosis rate of G-NEC. Nevertheless, Syn, CgA, and CD56 are well-recognized markers for it. Theoretically, the G-NEC IHC staining was positive for at least one of them [13, 16]. In our study, diagnostic confirmation of G-NEC appears to be most sensitive by Syn, followed by CD56 and CgA. Ishida and colleagues reported that Syn was observed to

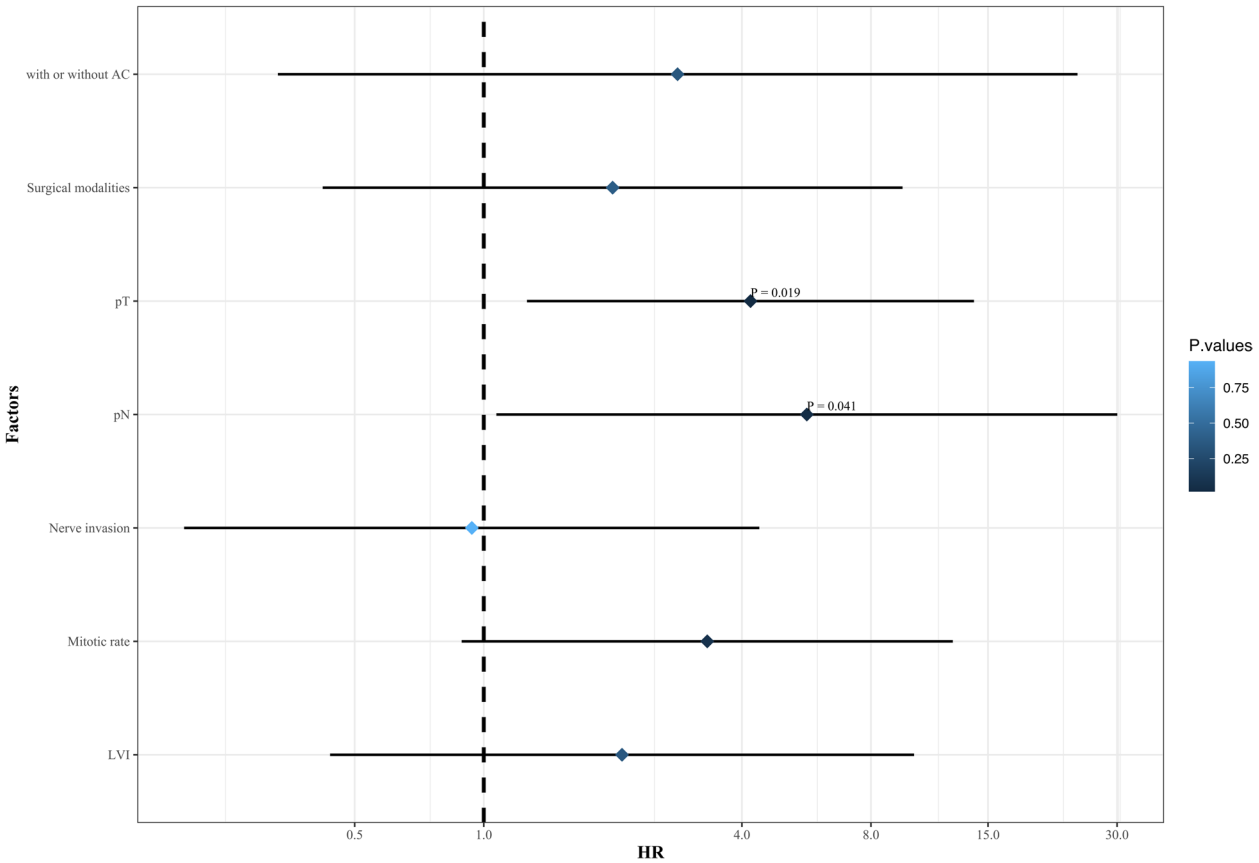

Fig. 6 Forest plot of multivariate disease-free survival time

be the most sensitive marker, diffusely positive in 94% of 51 patients, followed by CgA (86%) and CD56 (47%). In another retrospective study conducted by Xie, the rate of Syn positive expression was the highest (98%, 130/132), followed by CgA (64%, 84/132) and CD56 (60%, 74/132) [16]. In agreement with previous studies, Syn and CgA could identify 96% of the G-NEC [17, 18]. Therefore, to improve the accuracy of preoperative diagnosis, we propose that that Syn can be used as a routine immunohistochemical indicator if the preoperative biopsy reveals poorly differentiated carcinoma.

From a microscopically cytological morphology perspective, G-NEC can be morphologically divided into large or small cell types [12, 18, 19]. However, in our study, we divided G-NEC into three categories: large-cell G-NEC (LCGNEC), small-cell G-NEC (SCGNEC) and large and small cell mixed type (MGNEC). However, to the best of our knowledge, this is the first study to include a relatively high number of MGNEC, which have been reported in the digestive system. No statistically significant differences in OS were discovered between LCGNEC and SCGNEC types. The conclusions of Ishida and Deng were in agreement with ours, in which they suggested that was not associated LCGNEC and SCGNEC types with OS [13, 14]. However, after controlling for potential confounding factors, we observed by multivariate Cox regression that histologic subclassification was an independent risk factor determining the OS of patients with pure G-NEC. The longest OS was LCGNEC, followed by SCGNEC, and the shortest OS was MGNEC. Therefore, due to the small number of samples employed in the three studies, further investigation is needed to confirm our conclusion. In addition, our study identified that tumor location was an independent risk factor for OS. Compared with non-GEJ of G-NEC, GEJ of G-NEC had a worse outcome. Evidence from Cheng and colleagues' study supported this finding. They found that GEJ of G-NEC showed a deeper depth of invasion, more advanced pathological stages, and worse prognosis than non-GEJ of G-NEC [20]. However, some academic perspectives differed [21, 22]. The difference in OS between GEJ of G-NEC and non-GEJ of G-NEC was not statistically significant. Different findings from our own can be explained by the following reasons. First, patients who underwent noncurative resection or who did not undergo resection were included in their

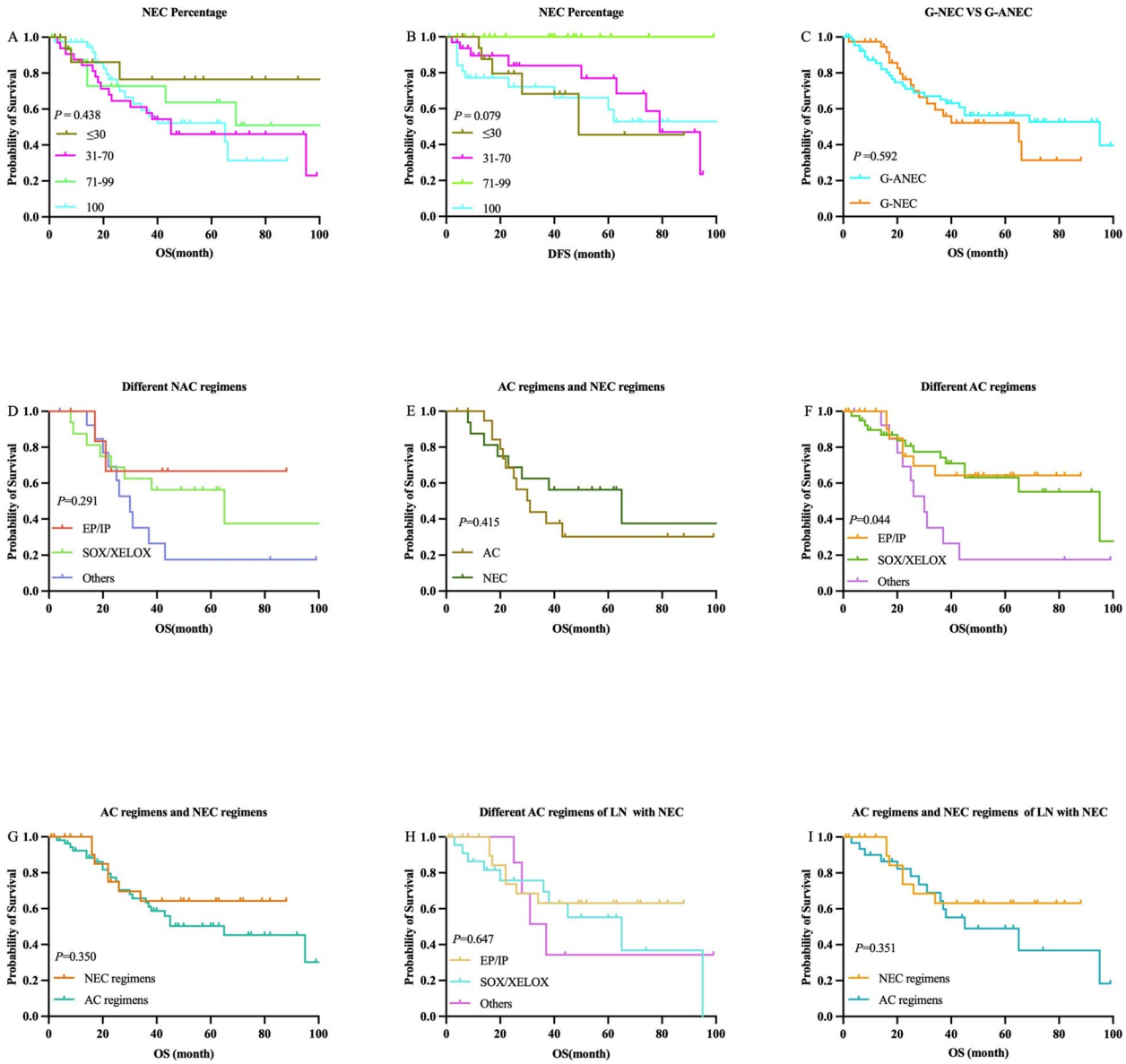

Fig. 7 Univariate survival analysis of 106 cases of pure-NEC and G-ANEC with lymph node metastasis. In the titles of Figures F and H, "AC" refers to adjuvant chemotherapy regimens, while in other titles, "AC" denotes adenocarcinoma

studies. Second, their studies included some patients who had gastric mixed adeno-neuroendocrine carcinoma (G-MiNEN). In addition, T stage was an independent risk factor for OS but not DFS. Lymph node metastasis was not only the most influential factor in determining the OS, but also the DFS. In accordance with relevant findings, there was a statistically significant difference between OS and DFS based on TNM stage [22]. These results suggested the prognostic value of TNM staging proposed by ENETS [23]. Contrary to that, Xu and associates found that tumor stage was not related to the prognosis by including 43 patients who were received radical surgeries [24]. This conclusion may be attributed to the small sample size of both studies, and some patients of Xu had a follow-up time less than 5 years, thus further validation is warranted.

After reviewing the relevant literature, there has been little progress in the treatment of G-NEC. According to our data, the presence or absence of NAC and AC were not independent risk factors for OS and DFS. According to a number of studies, systemic chemotherapy may show some survival improvements [25, 26]. In the Ma study, for instance, it was claimed that giving NAC significantly improved OS [27]. However, a sizeable

percentage of their analysis included individuals with MiNEN and clinical TNM stage IV. Nonetheless, our research indicated that NAC regimens could potentially affect OS. The influence of EP or SOX/XELOX on prognosis was pretty similar, and no statistically significant variance in OS or DFS was detected between the two patient groups. When we analyzed pure G-NEC and G-ANEC with lymph node metastases collectively, the results were consistent; However, the survival curve indicated a trend toward longer survival in the group receiving the NEC-targeted regimen compared to the AC-targeted regimen. Surprisingly, the response rates of patients receiving the EP/IP and SOX/XELOX regimens for OS were comparable in other investigations, which reached the same conclusions [27]. Several studies have demonstrated that SOX/XELOX cannot improve patient survival, whereas EP can [24, 28]. However, for the regimen of G-MANEC, the National Comprehensive Cancer Network (NCCN) Guidelines have suggested treating gastrointestinal mixed tumors according to the adenocarcinoma protocol rather than the neuroendocrine tumor protocol [29]. Some scholars have suggested that the NEC component may dictate the clinical behavior and outcomes of G-MANEC, hence recommending treatment strategies based on the NEC component [30]. Others believe that the treatment of metastatic MiNEN should theoretically target the metastatic tumor component rather than relying on the characteristics of the primary lesion [31]. Therefore, there is currently controversy over treatment approaches for both pure G-NEC and G-MANEC. Unfortunately, the sample size is too insufficient to draw any firm conclusions. This necessitates further validation through multicenter prospective clinical trials and a deeper investigation into the origins of adenocarcinoma and neuroendocrine carcinoma components within G-NEC and G-MANEC. Such research could potentially provide a foundational basis for treatment strategies.

Our study contains limitations that must be acknowledged. The investigation was conducted retrospectively and only at a single institution. Second, the sample size is small, and the conclusions may be biased. Thirdly, only R0 individuals were included in our analysis, and little is known about certain patients with stage IV G-NEC. Finally, the observed findings in our study may be influenced by confounding bias, indicating a need for additional scrutiny via propensity score matching analysis when comparing pure G-NEC with G-ANEC. Notwithstanding these limitations, a relatively high number of patients with pure G-NEC, rigorous statistical methodologies, and well-established clinicopathological characteristics are needed to make our results more persuasive.

Conclusion

Our findings suggest that Syn might serve as a potential auxiliary marker in routine immunohistochemical analysis for preoperative biopsy revealed a poorly differentiated gastric adenocarcinoma. The LCGNEC did not differentiate statistically from the SCGNEC for OS, while MGNEC has a worse prognosis compared to LCGNEC and SCGNEC. The prognosis of G-NEC is influenced by factors such as the tumor of location, its histology the pathological T stage, and the presence of lymph node metastasis. For gastric neuroendocrine carcinoma, there is no statistical difference in prognosis among tumors with varying proportions of NEC, suggesting that even minimal NEC elements may exert critical biological influence. Both neoadjuvant and adjuvant chemotherapy regimens aimed at treating lymph node metastases with NEC component tend to have a better prognosis than those targeting adenocarcinoma component. However, the retrospective nature of this study, as well as the limited sample size, restricts causal inference, and prospective trials and more in-depth clinical studies are needed to confirm therapeutic superiority.

Abbreviations

G-NEC	Gastric neuroendocrine carcinoma
G-ANEC	Mixed gastric adenoneuroendocrine carcinoma
OS	Overall survival time
DFS	Disease-free survival time
GEJ	Gastroesophageal junction
EP	Etoposide and cisplatin
SOX	S-1 + oxaliplatin
XELOX	Oxaliplatin + capecitabine
GC	Gastric cancer
Syn	Synaptophysin
CgA	Chromogranin A
NAC	Neoadjuvant chemotherapy
NSE	Neuron specific enolase
AC	Adjuvant chemotherapy
LVI	Lymphatic invasion
CT	Computed tomography
LCGNEC	Large-cell G-NEC
SCGNEC	Small-cell G-NEC
MGNEC	Large and small cell mixed type of G-NEC

Acknowledgements

We would like to thank the reviewers for their helpful remarks.

Authors' contributions

Conceptualization : AQW, ZDB, YSW Data curation : KZ, XH, XSY, KJ Formal analysis: KZ, XSY Funding acquisition: AQW, ZDB Investigation: KZ, XH Methodology: KZ, XSY Project administration: AQW, ZDB Resources: ZDB, ZWL, YSW, XJ, JZ, XJW Software: KZ, XH Supervision: AQW, ZDB, ZWL Validation: KZ, XH, XSY, AQW Visualization: KZ, XH Writing – original draft: KZ Writing –review & editing: AQW, WY, ZDB, YSW All authors reviewed the manuscript.

Funding

This study was supported by National Key Research and Development Program of China (No.2023YFF1204700, branch No.2023YFF1204702), the National Nature Science Foundation of China (No.82173151), Capital's Funds For Health Improvement and Research (No.CFH 2022–4-1025), Science Foundation of Peking University Cancer Hospital (PY202329), Clinical Medicine Plus X—Young Scholars Project, Peking University, the Fundamental Research Funds for the Central Universities (PKU2024LCXQ022), Clinical Research Fund For Distinguished Young Scholars of Peking UniversityCancer Hospital (QNJJ202306).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This research was approved by the Ethics Committee of the Peking University Cancer Hospital. Written informed consent was obtained from participating patients.

Consent for publication
NA.

Competing interests
The authors declare no competing interests.

Author details
[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Center of Gastrointestinal Cancer, Peking University Cancer Hospital & Institute, Beijing 100142, China. [2]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Pathology, Peking University Cancer Hospital & Institute, Beijing 100142, China. [3]Department of Gastrointestinal Surgery, Peking University Shenzhen Hospital, Shenzhen 518036, China. [4]Department of Oncology Digestive, First Hospital of Shanxi Medical University, Shanxi, China. [5]Department of Digestive, Shanxi Province Cancer Hospital/ Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences/Cancer Hospitalaffiliated to, Shanxi Medical Universityaq, Shanxi, China. [6]State Key Laboratory of Holistic Integrative Management of Gastrointestinal Cancers, Center of Gastrointestinal Cancer, Peking University Cancer Hospital & Institute, Beijing 100142, China.

Received: 26 November 2023 Accepted: 17 March 2025
Published online: 03 April 2025

References

1. Ilic M, Ilic I. Epidemiology of stomach cancer. World J Gastroenterol. 2022;28(12):1187–203.
2. Talavera-Urquijo E, Wijnhoven BPL. Evolution of laparoscopic gastrectomy for cancer in the East and West. Chin J Cancer Res. 2022;34(6):579–86.
3. Li S, Shan F, Zhang X, Li Y, Sun Y, Tang L, Wu Q, Yang W, Yang J, An Y et al. Chinese quality control indices for standardized diagnosis and treatment of gastric cancer (2022 edition). Chin J Cancer Res. 2022;34(6):623–632.
4. Kim SG, Eom BW, Yoon HM, Kim CG, Kook MC, Kim YW, Ryu KW. Recent updates and current issues of sentinel node navigation surgery for early gastric cancer. Chin J Cancer Res. 2021;33(2):142–9.
5. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49.
6. Health Commission Of The People's Republic Of China N: National guidelines for diagnosis and treatment of gastric cancer 2022 in China (English version). Chin J Cancer Res. 2022;34(3):207–237.
7. Chen J, Bu Z, Ji J. Comments on National guidelines for diagnosis and treatment of gastric cancer 2022 in China (English version). Chin J Cancer Res. 2022;34(5):453–5.
8. Modlin IM, Lye KD, Kidd M. Carcinoid tumors of the stomach. Surg Oncol. 2003;12(2):153–72.
9. Xie J, Chen P, Xie H, Sun Y, Huang Z, Wei R, Miao Z, Wang Q, Zhang SD, Wong KH, et al. Exploration of gastric neuroendocrine carcinoma (GNEC) specific signaling pathways involved in chemoresistance via transcriptome and in vitro analysis. Comput Struct Biotechnol J. 2020;18:2610–20.
10. Iwamoto M, Gotoda T, Noda Y, Esaki M, Moriyama M, Yoshida N, Takayama T, Kobayashi H, Masuda S. Gastric Neuroendocrine Carcinoma with Rapid Progression. Intern Med. 2020;59(10):1271–6.
11. Lin JP, Zhao YJ, He QL, Hao HK, Tian YT, Zou BB, Jiang LX, Lin W, Zhou YB, Li Z, et al. Adjuvant chemotherapy for patients with gastric neuroendocrine carcinomas or mixed adenoneuroendocrine carcinomas. Br J Surg. 2020;107(9):1163–70.
12. Matsui K, Jin XM, Kitagawa M, Miwa A. Clinicopathologic features of neuroendocrine carcinomas of the stomach: appraisal of small cell and large cell variants. Arch Pathol Lab Med. 1998;122(11):1010–7.
13. Ishida M, Sekine S, Fukagawa T, Ohashi M, Morita S, Taniguchi H, Katai H, Tsuda H, Kushima R. Neuroendocrine Carcinoma of the Stomach: Morphologic and Immunohistochemical Characteristics and Prognosis. Am J Surg Pathol. 2013;37(7):949–59.
14. Deng Y, Chen X, Ye Y, Shi X, Zhu K, Huang L, Zhang S, Ying M, Lin X. Histological characterisation and prognostic evaluation of 62 gastric neuroendocrine carcinomas. Contemp Oncol (Pozn). 2016;20(4):311–9.
15. Zhu X, Jing H, Yao T. Clinical characteristics of early neuroendocrine carcinoma in stomach: A case report and review of literature. Medicine (Baltimore). 2019;98(30): e16638.
16. Xie JW, Sun YQ, Feng CY, Zheng CH, Li P, Wang JB, Lin JX, Lu J, Chen QY, Cao LL, et al. Evaluation of clinicopathological factors related to the prognosis of gastric neuroendocrine carcinoma. Eur J Surg Oncol. 2016;42(10):1464–70.
17. Shia J, Tang LH, Weiser MR, Brenner B, Adsay NV, Stelow EB, Saltz LB, Qin J, Landmann R, Leonard GD, et al. Is nonsmall cell type high-grade neuroendocrine carcinoma of the tubular gastrointestinal tract a distinct disease entity? Am J Surg Pathol. 2008;32(5):719–31.
18. Jiang SX, Mikami T, Umezawa A, Saegusa M, Kameya T, Okayasu I. Gastric large cell neuroendocrine carcinomas: a distinct clinicopathologic entity. Am J Surg Pathol. 2006;30(8):945–53.
19. Mastracci L, Rindi G, Grillo F, Solcia E, Campora M, Fassan M, Parente P, Vanoli A, La Rosa S. Neuroendocrine neoplasms of the esophagus and stomach. Pathologica. 2021;113(1):5–11.
20. Cheng Y, Zhang X, Zhou X, Xu K, Lin M, Huang Q. Differences in clinicopathology and prognosis between gastroesophageal junctional and gastric non-cardiac neuroendocrine carcinomas: a retrospective comparison study of consecutive 56 cases from a single institution in China. Am J Cancer Res. 2022;12(10):4737–50.
21. Liu DJ, Fu XL, Liu W, Zheng LY, Zhang JF, Huo YM, Li J, Hua R, Liu Q, Sun YW. Clinicopathological, treatment, and prognosis study of 43 gastric neuroendocrine carcinomas. World J Gastroenterol. 2017;23(3):516–24.
22. Han D, Li YL, Zhou ZW, Yin F, Chen J, Liu F, Shi YF, Wang W, Zhang Y, Yu XJ, et al. Clinicopathological characteristics and prognosis of 232 patients with poorly differentiated gastric neuroendocrine neoplasms. World J Gastroenterol. 2021;27(21):2895–909.
23. Rindi G, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, Erikssson B, Falchetti A, Falconi M, Komminoth P, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch. 2006;449(4):395–401.
24. Xu X, Li J, Han X, Shi C, Jin D, Lou W. Clinical characteristics and prognostic factors of patients with gastric neuroendocrine carcinoma treated with radical surgery. Chin Med J (Engl). 2014;127(13):2419–22.
25. Sorbye H, Strosberg J, Baudin E, Klimstra DS, Yao JC. Gastroenteropancreatic high-grade neuroendocrine carcinoma. Cancer. 2014;120(18):2814–23.
26. Casas F, Ferrer F, Farrús B, Casals J, Biete A. Primary small cell carcinoma of the esophagus: a review of the literature with emphasis on therapy and prognosis. Cancer. 1997;80(8):1366–72.
27. Ma F, Wang B, Xue L, Kang W, Li Y, Li W, Liu H, Ma S, Tian Y. Neoadjuvant chemotherapy improves the survival of patients with neuroendocrine carcinoma and mixed adenoneuroendocrine carcinoma of the stomach. J Cancer Res Clin Oncol. 2020;146(8):2135–42.
28. Brandi G, Paragona M, Campana D, Brighi N, Bondi A, Pantaleo MA, Corbelli J, Barbera MA, Biasco G. Good performance of platinum-based chemotherapy for high-grade gastroenteropancreatic and unknown primary neuroendocrine neoplasms. J Chemother. 2018;30(1):53–8
29. Gurzu S, Fetyko A, Bara T, Banias L, Butiurca VO, Bara T Jr, Tudorache V, Jung I. Gastrointestinal mixed adenoneuroendocrine carcinoma (MANEC): An immunohistochemistry study of 13 microsatellite stable cases. Pathol Res Pract. 2019;215(12): 152697.
30. Zhang P, Li Z, Li J, Li J, Zhang X, Lu Z, Sun Y, Li Y, Zhou J, Wang X, et al. Clinicopathological features and lymph node and distant metastasis patterns in patients with gastroenteropancreatic mixed neuroendocrine-non-neuroendocrine neoplasm. Cancer Med. 2021;10(14):4855–63.

31. Lim SM, Kim H, Kang B, Kim HS, Rha SY, Noh SH, Hyung WJ, Cheong JH, Kim HI, Chung HC, et al. Prognostic value of (18)F-fluorodeoxyglucose positron emission tomography in patients with gastric neuroendocrine carcinoma and mixed adenoneuroendocrine carcinoma. Ann Nucl Med. 2016;30(4):279–86.

Publisher's Note