Am J Cancer Res 2022;12(10):4737-4750
www.ajcr.us /ISSN:2156-6976/ajcr0146658

Original Article

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

Yuqing Cheng[1*], Xinwen Zhang[1,4*], Xiaoli Zhou[1], Kequn Xu[2], Min Lin[3], Qin Huang[1,5]

Departments of [1]Pathology, [2]Oncology, [3]Gastroenterology, The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou, Jiangsu, China; [4]Graduate School of Dalian Medical University, Dalian, Liaoning, China; [5]Department of Pathology and Laboratory Medicine, Veterans Affairs Boston Healthcare System, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts, USA. [*]Equal contributors.

Received September 23, 2022; Accepted October 12, 2022; Epub October 15, 2022; Published October 30, 2022

Abstract: Gastric neuroendocrine carcinoma (NEC), including mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN), is uncommon and differences in clinicopathological features and outcomes of NEC arising in various gastric regions remain elusive. We investigated 56 consecutive NECs identified among 3961 gastrectomies performed at our center between 2005 and 2021. We then compared clinicopathological characteristics and prognosis between gastroesophageal junctional (GEJ) NECs (N=39) and gastric non-cardiac NECs (N=17). No significant difference was found between the two groups in age, gender, tumor size, mixed non-neuroendocrine carcinoma component, MiNEN, NEC type, metastatic NEC component in lymph nodes, tumor infiltrating lymphocyte, lymph node metastasis, lymphovascular or perineural invasion, intestinal metaplasia in adjacent non-neoplastic mucosa, and expression of P53, PD-L1, TTF-1, HER2, and Ki-67. However, compared to gastric non-cardiac NECs, GEJ NECs displayed a significantly higher frequency of prevalence (2.79% versus 0.66%), pT3-T4 (92.3% versus 64.7%), advanced pathological stage (IIb-IV) (76.9% versus 47.1%), and a significantly lower 5-year overall survival rate (46.1% versus 73.1%) ($P<0.05$). The GEJ location was the only independent risk factor for overall survival. In stage-stratified comparisons, patients with stage II GEJ NEC demonstrated a significantly lower 5-year survival rate than those with gastric non-cardiac NEC at the same stage. Compared to non-NECs matched for age, gender, tumor location, and pathological summary stage, GEJ NEC was associated with significantly worse prognosis. In conclusion, GEJ NEC showed deeper invasion, more advanced pathological stages, and worse prognosis than gastric non-cardiac NEC. The findings provide pathologic evidence for individualized management strategies for patients with GEJ NEC. Future studies with larger samples are needed.

Keywords: Stomach, gastroesophageal junction, neuroendocrine carcinoma, gastric carcinoma, prognosis

Introduction

Gastric neuroendocrine carcinoma (NEC) is uncommon and often combined with a non-neuroendocrine glandular component, which is termed as a mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN), if each component is ≥30% and morphologically and immunohistochemically recognizable [1]. Gastric NEC is a highly aggressive malignancy with poor prognosis [1-3]. However, there are few studies focused on clinicopathological features and prognosis of gastroesophageal junctional (GEJ) NECs due to the rarity [4, 5]. In general, GEJ carcinoma rarely arises more than 1 cm above the GEJ in Chinese patients. This uncommon carcinoma, also known as proximal gastric carcinoma or cardiac carcinoma in China, was regarded as part of esophageal adenocarcinoma and classified as Siewert II and III GEJ adenocarcinomas. The current 8th edition of the American Joint Committee on Cancer stage manual (AJCC

8) reclassified Siewert II GEJ adenocarcinoma without esophageal extension and Siewert III GEJ adenocarcinoma as gastric carcinoma [6]. Emerging evidence suggests that GEJ carcinoma displays unique clinicopathological features, such as a broader histopathological spectrum and a lower risk of nodal metastasis in early GEJ carcinoma than in early gastric non-cardiac carcinoma [7-9]. The advances in investigation of molecular pathogenesis mechanisms also uncovered characteristic genetic profiles of GEJ carcinoma, such as higher frequencies of p53 gene mutation and HER2 gene amplification [8-11]. These recent findings suggest potential existence of different clinicopathological features between GEJ and gastric non-cardiac NECs. Herein, we analyzed clinicopathologic and prognostic features of GEJ NECs in comparison with those of gastric non-cardiac NECs. We also compared patient survival outcomes between NEC and non-neuroendocrine carcinomas (non-NEC) cases matched for age, gender, tumor location, and stage.

Materials and methods

Patient selection

Electronic pathology archives were searched for the diagnosis of carcinoma in gastrectomies over the period from June 1, 2005 to December 31, 2021 in the Department of Pathology of the Changzhou No. 2 People's Hospital in the Jiangsu Province of China. Cases diagnosed as "neuroendocrine carcinoma", "small cell carcinoma", "mixed adenoneuroendocrine carcinoma", or "carcinoma with neuroendocrine differentiation" in gastric, distal esophageal, and GEJ regions were selected. Gender-, tumor location-, and pathologic stage-matched concurrent gastric non-NECs with follow-up information, and non-NEC patients with age difference within 5 years of corresponding NEC patients were randomly selected as the control group for survival outcome comparison analysis. The exclusion criteria were as follows: 1) synchronous malignancy, 2) a history of neoadjuvant therapy, 3) a palliative gastrectomy or gastrectomy with a non-R0 resection margin. Patient private identification information, such as name, phone number, and address, etc., was deleted and each case was indexed with a pathology accession number to protect patient privacy. The study protocol was approved by the Medical Ethics Committee of the Changzhou No. 2 People's Hospital in the Jiangsu Province of China (2022; KY001-01). Written informed consents from patients for the use of tumor tissues for research were obtained prior to the resection procedure.

Study and control groups

GEJ carcinoma was defined as carcinomas with epicenters located in the region of 5 cm above and 5 cm below the GEJ line. Gastric non-cardiac carcinoma referred to carcinomas with epicenters in other regions of the stomach. In difficult cases with questionable information on tumor location, endoscopic and radiologic images and reports were reviewed. Overall, the study group consisted of 56 consecutive NECs, in which 39 were classified as GEJ NEC, while 17 were gastric non-cardiac NEC. The information on survival was available for 36 GEJ NECs and 17 gastric non-cardiac NECs. The control group was selected randomly by SPSS 26.0 software and composed of non-NEC cases (1:1 matched for age, gender, tumor location, and pathologic stage, as defined above).

Clinicopathological investigation

All histology slides, including corresponding immunostains, of each eligible NEC case were retrieved and reviewed by two experienced senior pathologists to confirm the diagnosis of NEC, based on the 5th edition of the World Health Organization (WHO) diagnostic criteria for the digestive tract tumors (2019) [1]. NECs were subclassified into small and large cell types, as defined by the WHO criteria. The small cell type was diagnosed as tumor cells showing a significantly high nuclear/cytoplasmic ratio, scant cytoplasm, and hyperchromatic nuclei with fine granular chromatin and indistinct nucleoli. The large cell type demonstrated tumor cells with moderate cytoplasm, prominent nucleoli, and round or irregular nuclei [1, 2]. For NEC with both small and large cell types, the predominant type was recorded. Gastric NEC mixed with no less than 30% non-neuroendocrine carcinoma components was subclassified as MiNEN. The AJCC 8 was followed for pathologic staging [6]. Tumor-infiltrating lymphocytes in NEC were evaluated by following the guidelines proposed by the International Immuno-Oncology Biomarker Working Group

[12]. In brief, tumor-infiltrating lymphocytes were assessed within the stromal compartment of a tumor mass and scored as a percentage of the stromal area that was occupied by mononuclear inflammatory cells over the total intratumoral stromal area. Scores were averaged across the whole slide at 200 × magnification.

Construction of tissue microarray, immunohistochemical staining, fluorescence in situ hybridization (FISH), ebstein barr virus (EBV) detection

For making a tissue microarray paraffin block, we used a hollow needle to remove one tissue core, 2 mm in diameter, from a representative tumor cell-rich area in a formalin-fixed paraffin-embedded tumor tissue block of each gastric NEC case. Under a routine protocol, a microarray tissue block was then cut at 4 μm in thickness and subjected to routine hematoxylin eosin and immunohistochemical stains.

For immunohistochemistry, tissue sections were routinely immunostained with the DAKO PharmDx Link 48 Autostainer for PD-L1 (22C3, Dako, Carpentaria, CA), MLH1 (ES05, DAKO, Dako, Carpentaria, CA), PMS2 (EP51, Dako, Carpentaria, CA), MSH2 (FE11, Dako, Carpentaria, CA), MSH6 (EP49, Dako, Carpentaria, CA), and the Ventana Benchmark GT autostainer for HER2 (4B5, Ventana, Tucson, USA), Ki-67 (30-9, Ventana, Tucson, USA), P53 (MX008, Maxim, Fuzhou, China), and TTF-1 (SPT24, Maxim, Fuzhou, China). PD-L1 expression was assessed by the combined positive score (CPS), which was calculated by dividing the number of tumor cells and immune cells with at least partial membranous PD-L1 staining by the number of viable tumor cells counted, and multiplied by 100 [13]. A CPS of 1 or greater was regarded as PD-L1 positive. Strong diffuse nuclear staining in over 60% of tumor cells or complete absence of tumor cell staining was considered as positive for aberrant P53 gene expression. Any nuclear immunoreactivity in tumor cells was deemed as positive for MLH1, PMS2, MSH2, and MSH6 gene expression. When more than 5% tumor cell nuclei were positive for TTF-1 gene expression, the case was diagnosed to be TTF-1-positive. HER2 immunostain was evaluated for NEC and non-NEC components separately and graded with a score of 0, 1+, 2+, or 3+, according to the American Society of Clinical Oncology guideline [14]. For cases with a HER2 immuinostain score of 2+, a fluorescence *in situ* hybridization (FISH) test was performed to assess HER2 gene amplification with a commercial dual-color HER2 probe kit (IBP, Guangzhou, China), according to the manufacturer's protocol. The criterion for HER2 positivity was based on an immunostaining score of 3+ or HER2 gene amplification determined by the FISH test for cases with an immunostain score of 2+. Appropriate positive and negative controls were included in each immunostain run or FISH test.

The presence of EBV in NECs was assessed with the EBER chromogenic *in situ* hybridization (CISH) test. This was performed manually on an unstained tissue microarray section in 3 μm thickness, using a probe complementary to the EBV-encoded RNA (Zhongshan Jinqiao, Beijing, China). The hybridization signal was detected with an anti-digoxigenin antibody-horseradish peroxidase conjugate and counterstained with hematoxylin. A known EBV-positive nasopharyngeal carcinoma tumor section was included in each run as the positive control.

Patient survival investigation

Patient survival investigation was carried out via a review of the patient's electronic medical record, or telephone interview by the authors to the patient or patient family members. The number of overall survival months after gastrectomy was calculated from the date of surgical resection to the date of last follow-up interview or patient death of all causes. The calculated total number of survival days was rounded up to the number of survival months after surgery.

Statistical analysis

Clinicopathological features, including patient age, gender, tumor size, mixed non-NEC component, MiNEN, pathological tumor stage, pathological summary stage, lymphovascular invasion, perineural invasion, lymph node metastasis, NEC type, metastatic NEC component in a lymph node, tumor infiltrating lymphocyte, intestinal metaplasia in adjacent non-neoplastic mucosa, immunohistochemical profile, and overall survival outcome were statistically ana-

lyzed and compared between groups. Comparisons of categorical variables were determined with the Chi-square test. Continuous values, such as patient age and tumor size, were compared with the Student's *t* test or Mann-Whitney test, as appropriate. Overall survival rates were estimated with the Kaplan-Meier method with a log rank test. The reverse Kaplan-Meier method was used to calculate the follow-up time. A Cox proportional hazards model was used in the multivariate survival analysis for independent risk factors of overall survival. $P<0.05$ was considered to be statistically significant. All statistical analyses were performed with IBM SPSS Statistics version 26.0 (IBM, Armonk, NY, USA).

Results

Among 3961 consecutive gastrectomies for carcinomas, 56 (1.41%, 56/3961) gastric carcinomas were diagnosed as NECs, in which 39 (0.98%, 39/3961) epicentered in the GEJ region, and 17 (0.43%, 17/3961) were in gastric non-cardiac regions. None of the epicenters of GEJ NEC tumors located 1 cm above the GEJ line. Statistically, NEC significantly more frequently occurred in the GEJ region (2.79%, 39/1397) than in any other gastric non-cardiac region (0.66%, 17/2564) (P<0.001).

Clinicopathological characteristics

As shown in **Table 1**, there was no significant difference in patient mean age, gender, tumor size, NEC type, mixed non-NEC component, MiNEN, and tumor infiltrating lymphocyte. Although GEJ NEC showed higher frequencies of lymph node metastasis (71.8% versus 58.8%), lymphovascular invasion (76.9% versus 52.9%), and perineural invasion (35.9% versus 23.5%) than gastric non-cardiac NEC, the difference did not reach a statistically significant level (P=0.339, 0.073, 0.362, respectively). For cases with lymph node metastasis, there was no significant difference in prevalence of the presence of an NEC component in metastatic lymph nodes between the two groups, as also in the immunohistochemical expression of Ki-67, PD-L1, P53, HER2, and TTF-1 genes. However, the proportions of tumor stage T3-T4 (92.3% versus 64.7%) and pathological summary stage IIb-IV (76.9% versus 47.1%) were significantly higher in the GEJ NEC group than in the gastric non-cardiac NEC group (P=0.029, 0.028, respectively) (**Table 1**). None of the patients with gastric NECs had a clinical history of autoimmune gastritis nor relevant histopathological features in gastrectomy specimens.

Histopathological analysis

Microscopically, the proportion of the NEC large cell type (83.9%, 47/56) was higher than that of the small cell type (16.1%, 9/56). MiNEN was diagnosed in 14 (25%, 14/56) NECs. A non-NEC adenocarcinoma component was observed in 33 NECs with a range of 1% to 70% of the estimated tumor volume with various morphologies, such as tubular, papillary, poorly cohesive/signet ring cell, and mucinous adenocarcinomas. Most non-NEC components were located in the superficial layer of a tumor, except for 5 cases in which both non-NEC adenocarcinoma and NEC components co-existed in the same layer of the gastric wall. An NEC component of gastric NEC was identified in metastatic lymph nodes of 36 (64.3%, 36/56) cases, and absent in only 2 cases (**Figure 1**). The percentage of tumor infiltrating lymphocytes in the stromal compartment ranged from 0% to 50% (median: 5%).

Immunohistochemical, FISH, and CISH studies

Striking Ki-67 nuclear expression was observed in gastric NEC with a median prevalence of 70% (range: 20-90%) (**Figure 2A**). The frequency of aberrant P53 immunoreactivity was seen in 75% (42/56) of gastric NECs (**Figure 2B**). In the NEC component, HER2 1+ membranous immunopositivity was identified in only two cases, and absent in the remaining cases. In the non-NEC component, HER2 2+ was identified in 3 cases (**Figure 2C**), in which HER2 gene amplification (3.6%, 2/56) in two cases were further confirmed by a positive FISH test. At a CPS ≥1 cutoff, PD-L1 expression was positive in 21.4% (12/56) of the cases (CPS range: 1-40) (**Figure 2D**). TTF-1 nuclear immunoreactivity was seen in 7 cases (12.5%, 7/56), including 4 of 9 small cell NECs and 3 of 47 large cell NECs (**Figure 2E**). All NEC cases retained the nuclear expression of MLH1, PMS2, MSH2, and MSH6 genes (**Figure 2F**). None of the NEC cases was EBV-positive.

Post-resection survival

The median post-operative follow-up period was 77 months (range, 3-144 month). Three

Table 1. Comparison of clinicopathologic features between gastroesophageal junctional (GEJ) and gastric non-cardiac neuroendocrine carcinomas (NEC)

Clinicopathological feature	GEJ NEC (n=39), n (%)	Gastric non-cardiac NEC (n=17), n (%)	*P*
Age (year)			
Mean+/-SD	67.26+/-7.01	67.76+/-9.98	0.828
≤68	23 (59.0)	7 (41.2)	0.219
≥69	16 (41.0)	10 (58.8)	
Gender			
Male	33 (84.6)	13 (76.5)	0.725
Female	6 (15.4)	4 (23.5)	
Tumor size (cm)			
Median	5	4.5	0.781
≤5	24 (61.5)	10 (60.7)	0.848
>5	15 (38.5)	7 (39.3)	
Mixed non-neuroendocrine carcinoma component			
Absent	13 (33.3)	10 (58.8)	0.075
Present	26 (66.7)	7 (41.2)	
MiNEN			
No	29 (74.4)	13 (76.5)	0.867
Yes	10 (25.6)	4 (23.5)	
pT stage			
T1/T2	3 (7.7)	6 (35.3)	0.029
T3/T4	36 (92.3)	11 (64.7)	
Lymph node metastasis			
Absent	11 (28.2)	7 (41.2)	0.339
Present	28 (71.8)	10 (58.8)	
Pathological summary stage			
pI-IIA	9 (23.1)	9 (52.9)	0.028
pIIB-IV	30 (76.9)	8 (47.1)	
Lymphovascular invasion			
Absent	9 (23.1)	8 (47.1)	0.073
Present	30 (76.9)	9 (52.9)	
Perineural invasion			
Absent	25 (64.1)	13 (76.5)	0.362
Present	14 (35.9)	4 (23.5)	
NEC type			
Large cell	32 (82.1%)	15 (88.2)	0.854
Small cell	7 (17.9)	2 (11.8)	
Metastatic NEC component in lymph node*			
Absent	2 (7.1)	0 (0)	0.532
Present	26 (92.9)	10 (100)	
Tumor infiltrating lymphocyte			
<10%	26 (66.7)	11 (64.7)	0.887
≥10%	13 (33.3)	6 (33.9)	
Intestinal metaplasia in adjacent non-neoplastic mucosa			
Absent	9 (23.1)	1 (5.9)	0.244
Present	30 (76.9)	16 (94.1)	

Ki-67 index (%)			
<70	20 (51.3)	8 (47.1)	0.771
≥70	19 (48.7)	9 (52.9)	
PD-L1 expression			
Negative	29 (74.4)	15 (88.2)	0.418
Positive	10 (25.6)	2 (11.8)	
P53 expression			
Negative	8 (20.5)	6 (35.3)	0.401
Positive	31 (79.5)	11 (64.7)	
HER2 gene amplification			
Negative	38 (97.4)	16 (94.1)	0.519
Positive	1 (2.6)	1 (5.9)	
TTF-1 expression			
Negative	34 (87.2)	15 (88.2)	1.000
Positive	5 (12.8)	2 (11.8)	

Note: *: compared among cases with lymph node metastasis. Abbreviations: MiNEN: Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm; SD: Standard Deviation.

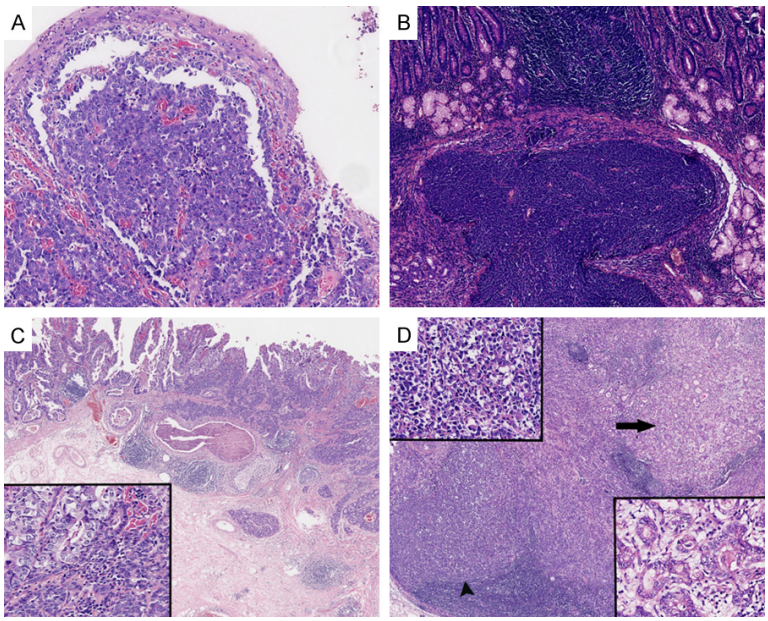

Figure 1. Histological features of gastric neuroendocrine carcinoma (NEC). (A) A representative photomicrograph of gastroesophageal junctional (GEJ) large cell NEC invaded the distal esophagus. (B) In a gastric non-cardiac small cell NEC, the tumor invaded the pyloduodenal junction submucosally. (C) An early mixed neuroendocrine non-neuroendocrine carcinoma showed the co-existence of well differentiated tubular adenocarcinoma (left) and NEC (right), the latter of which invaded deeper than the former. The transition of two components is enlarged in the insert in the left lower quadrant. (D) Both tubular adenocarcinoma (arrow) and NEC components (arrow head) of a mixed gastric NEC tumor metastasized to one lymph node, which are enlarged in the inserts in the left upper quadrant for NEC and the right lower quadrant for tubular adenocarcinoma, respectively (Hematoxylin-eosin stain, × 40 in C, D, × 100 in B, × 200 in A and the inserts of C and D).

(5.4%, 3/56) GEJ NEC patients were lost to follow-up. Patients with GEJ NEC demonstrated a significantly lower 5-year overall survival rate (46.1%), compared to those with gastric non-cardiac NEC (73.1%) (*P*= 0.030) (**Table 2**; **Figure 3A**). By univariate analysis, significant risk factors for overall survival also included lymph node metastasis and pathological summary stage (**Table 2**; **Figure 3B** and **3C**). The GEJ location was found to be the only independent risk factor for worse overall survival (Hazards Ratio: 2.922; 95% confidence interval: 1.003-8.514, *P*= 0.049) (**Table 3**). The patients with PD-L1-positive NEC tumors demonstrated a higher 5-year overall survival rate (83.3%), compared to PD-L1-negative counterparts (44.4%); the difference almost reached a statistically significant level (*P*=0.052) (**Table 2**; **Figure 3D**). Stage-stratified comparisons were not analyzed in cases with stage I (N=5) or IV (N=3) carcinomas due to the small sample sizes. In comparison among cases with stage II NEC, the 5-year overall survival rate was significantly lower in patients with GEJ NEC (51.2%) than those with gastric

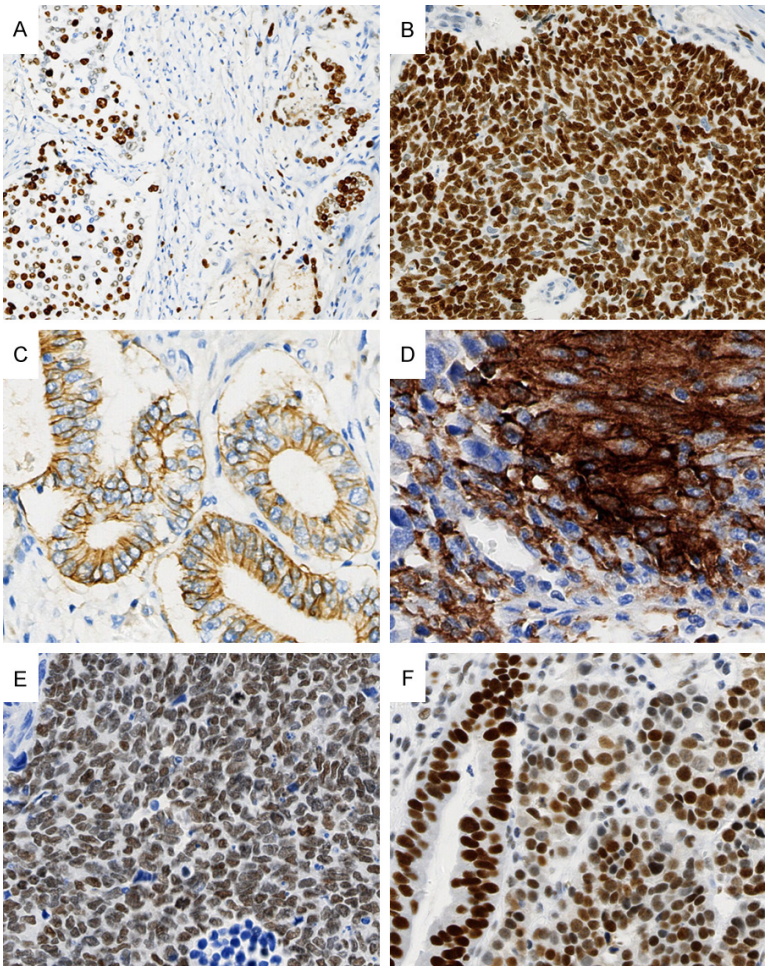

Figure 2. Representative photomicrographs of immunohistochemistry. (A) The Ki-67 proliferative index was about 70% for a mixed neuroendocrine non-neuroendocrine carcinoma. (B) A gastric NEC was diffusely strong positive for P53. (C) The adenocarcinoma component of a gastric NEC was HER2-posivie with a score of 2^{+}. (D) Tumor cells exhibited expression of PD-L1 in a gastric neuroendocrine carcinoma. (E) A small cell type gastric NEC was diffusely positive for TTF-1. (F) A gastric NEC retained the expression of MLH1 (Immunohistochemical stain, A, B, × 200, C-F, × 400).

non-cardiac NEC (83.3%) (*P*=0.046). Although the patients with stage III GEJ NEC also demonstrated a lower 5-year survival rate (46.2%) than the patients with gastric non-cardiac NEC at the same stage (75.0%), the difference did not reach a statistically significant level.

Overall survival analysis was carried out in 36 GEJ NECs, 17 gastric non-cardiac NECs, and 53 matched gastric adenocarcinoma control cases with follow-up survival information. The 5-year survival rate was significantly lower in patients with GEJ NEC (46.1%) than those with GEJ non-NEC carcinoma (61.8%) (*P*=0.046, **Figure 4**). However, patients with gastric non-cardiac NEC showed no significant difference in 5-year survival in comparison with those with gastric non-cardiac non-NEC adenocarcinoma (73.1% versus 71.9%, *P*= 0.791). There was no statistically significant difference in patient age, tumor size, prevalence of lymph node metastasis, and follow-up time between paired groups.

Discussion

In this retrospective comparison study, GEJ NECs, compared to gastric non-cardiac NECs, showed worse clinicopathological features as follows: 1) a higher frequency of pathologic tumor stages of pT3-T4; 2) a larger proportion of advanced pathological summary stages IIb-IV; and 3) a lower 5-year overall survival rate. Although this subset of gastric carcinoma is rare, GEJ NEC is fatal and requires an urgent measure for early detection, prompt resection, and active post-surgery surveillance to identify and treat early recurrence and metastasis to improve survival outcomes.

In the present study, NEC constituted only 1.41% of gastrectomies for carcinomas, which is similar to that reported recently by another institution in China [4], but is higher than that reported from Japan (0.64%) and Brazil (0.8%) [2, 15]. The discrepancy may be related to the differences in geography and patient ethnicity. Over the past decades, the incidence of gastric neuroendocrine neoplasm, including NEC, increased steadily from 1975 to 2016, according to the study in American patients, based on the United States Surveillance, Epidemiology, and End Results (SEER) database [16]. The high prevalence of NEC in our study may reflect a similar trend in China, probably due to the

Table 2. Univariate survival analysis of risk factors on overall survival in patients with gastroesophageal junctional or gastric non-cardiac neuroendocrine carcinoma

Clinicopathological feature	5-Year survival rate (%)	*P*
Age (year)		0.122
≤68	60.4	
≥69	51.2	
Gender		0.789
Male	56.3	
Female	50.8	
Tumor size (cm)		0.929
≤5	56.5	
>5	54.2	
Tumor location		0.030
Gastroesophageal junctional	46.1	
Gastric non-cardiac	73.1	
Mixed non-neuroendocrine carcinoma component		0.693
Absent	61.5	
Present	52.3	
MiNEN		0.511
No	57.8	
Yes	50.8	
pT stage		0.120
pT1-T2	85.7	
pT3-T4	49.8	
Lymph node metastasis		0.043
Absent	76.6	
Present	45.8	
Pathological summary stage		0.016
pI-IIA	83.9	
pIIB-IV	43.9	
Lymphovascular invasion		0.362
Absent	59.3	
Present	54.4	
Perineural invasion		0.491
Absent	58	
Present	52	
Neuroendocrine carcinoma type		0.908
Large cell	54.3	
Small cell	62.5	
Tumor infiltrating lymphocyte		0.434
<10%	55.6	
≥10%	55.5	
Intestinal metaplasia in adjacent non-neoplastic mucosa		0.171
Absent	35.4	
Present	61.2	
Ki-67 index (%)		0.096
<70	75	
≥70	47.1	

PD-L1 expression		0.052
Negative	44.4	
Positive	83.3	
P53 expression		0.165
Negative	90.9	
Positive	48.1	
TTF-1 expression		0.364
Negative	53.9	
Positive	71.4	

Abbreviation: MiNEN: Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm.

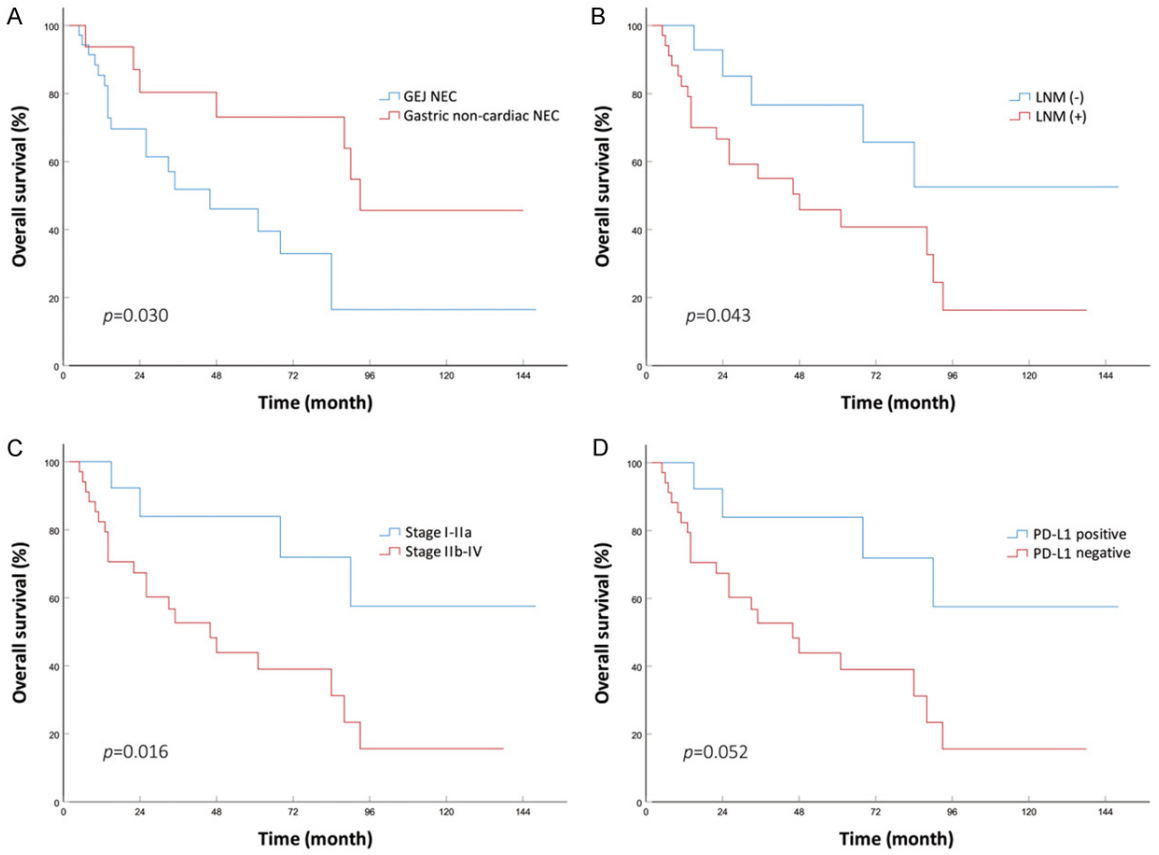

Figure 3. Kaplan-Meier overall survival curves for patients with gastric neuroendocrine carcinoma (NEC) with comparisons between gastroesophageal junctional (GEJ) and gastric non-cardiac locations (A), the presence or absence of lymph node metastasis (LNM) (B), pathology summary stages I-IIA versus IIB-IV (C), and the presence or absence of PD-L1 expression (D).

increasing awareness of NEC by pathologists and a wide availability of upper endoscopy and improved laboratory testing methods in recent years in China.

GEJ and gastric non-cardiac NECs showed bleak clinicopathologic features, such as the advanced age (mean: 67.41 years), large tumor size (median: 5 cm), a high prevalence of background intestinal metaplasia (82.1%, 46/56), a high Ki-67 index (median: 70%), and a high prevalence of aberrant P53 expression (75%, 42/56), which were comparable to the results of previous studies [2, 3, 5, 17-27]. The present study demonstrated a high prevalence of lymphovascular invasion (69.6%), perineural invasion (32.1%), lymph node metastasis (67.9%), high tumor stages pT2-T4 (94.6%), and ad-

Table 3. Cox multivariate regression analysis on overall survival in patients with gastroesophageal junctional or gastric non-cardiac neuroendocrine carcinoma

Clinicopathological feature	Hazard ratio	95% Confidence interval	*P*
Tumor location			
Gastric non-cardiac	Reference		0.049
Gastroesophageal junctional	2.922	1.003-8.514	
Lymph node metastasis			
Absent	Reference		
Present	1.684	0.364-7.794	0.505
Pathological summary stage			
pI-IIA	Reference		0.377
pIIB-IV	2.121	0.400-11.258	

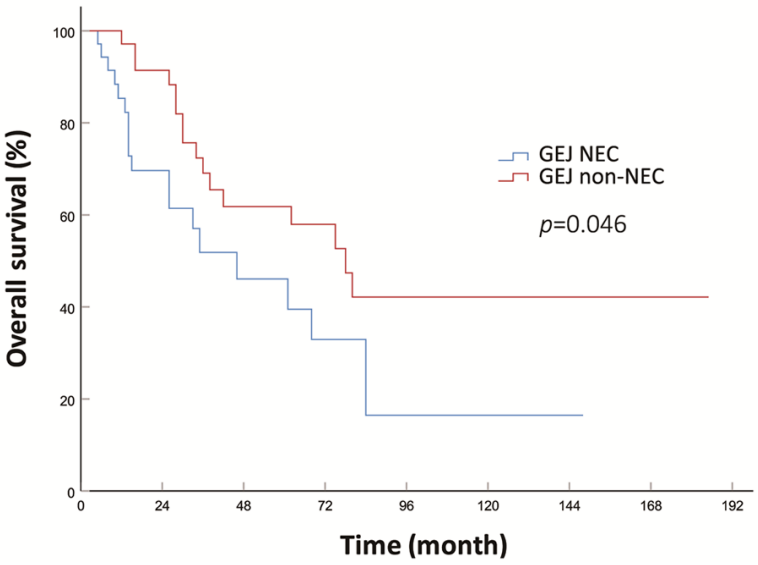

Figure 4. Comparison of Kaplan-Meier overall survival curves for patients with gastroesophageal junctional neuroendocrine carcinoma (GEJ NEC) versus those with gastroesophageal junctional non-neuroendocrine carcinoma (GEJ non-NEC).

vanced pathological stages II-IV (89.3%), which was parallel to that previously reported, ranging from 59% to 92% for lymph node metastasis, 34.3% to 78% for lymphovascular invasion, 31.4% to 58.7% for perineural invasion, 86.7% to 100% for pathology tumor stages T2-T4, 75% to 97.8% for advanced pathological stage [2, 3, 18-25, 28-30]. As expected, the 5-year survival rate (49%) of NEC in our cohort was depressing, but similar to the data (38.7% to 52.5%) reported previously from Japan, China, and United States [2, 3, 16, 21, 31].

The prevalence of gastric NEC with epicenter located in the GEJ region or the upper stomach is high in Chinese patients. Most Chinese studies described a prevalence of ≥40% [3, 16, 20-23, 28, 32], which is higher than that reported by Korean and Japanese investigators with a range of 17.5% to 40% [2, 19, 24, 29]. However, in two previous and present studies [28, 32], the prevalence of GEJ NEC is much higher, ranging from 50%, 57.5% to the current 69.6%. We must point out that those two Chinese institutions and our hospital are in the same East China gastric cancer endemic region where GEJ carcinoma is very common. Therefore, the high prevalence of GEJ NEC in our study may reflect geographical variation.

We showed for the first time that GEJ NEC was associated with a worse prognosis, compared to GEJ non-NEC or gastric non-cardiac NEC. Although gastric NEC is well-known as a highly aggressive carcinoma with a worse prognosis than gastric non-NEC [2, 3, 29-31], our study specifically revealed that it was GEJ NEC, not gastric non-cardiac NEC, that had worse prognosis because of high prevalence of deep invasion and advanced pathological stage than gastric non-cardiac NEC. In general, GEJ NECs at T1 stage are very rare [2-4, 22, 33, 34], as also demonstrated in our study. We did not see a single GEJ NEC case staged at pT1 and only 3 cases at pT2. The disproportionally low frequency of early GEJ NEC illustrates the difficulty in early detection by endoscopists for several reasons. First, early gastric NEC tends to be small in size and superficial without symptoms and is hard to be detected endoscopically [34]. Second, the challenging anatomy for upper endoscopy in the GEJ region often

leads to a high tumor-detection-missing rate, even in sedative endoscopy [35]. Third, GEJ NEC is highly aggressive and may develop rapidly from an invisible early stage into a large mass lesion over a short period of time, as shown in other's and our present studies with a high Ki-67 proliferation index [5, 20, 36]. Thus, a meticulous inspection of the entire GEJ mucosa at upper endoscopy is very important to reduce the missing rate and improve early diagnosis with prompt therapy.

In GEJ NEC, we showed an alarmingly high frequency of tumor deep invasion and advanced pathological stages, which correlated with a lower survival rate and worse overall survival, compared to NEC in other gastric regions. The lower survival rate and worse overall survival in Chinese patients with NEC of the upper stomach, in comparisons to that of other gastric regions, were also reported before [31, 37]. A recent study in American patients, based on the SEER database, analyzed the prognosis of gastric NEC patients and demonstrated significantly worse prognosis in patients with GEJ NEC than those with gastric non-cardiac NEC [16], as shown in our study in Chinese patients. However, there were two studies from China that reported better prognosis for patients with GEJ NEC than patients with gastric non-cardiac NEC located in the corpus or antrum [22, 25]. The discrepancy may be related to the small samples (N=43) and inclusion of non-resectable and palliative gastrectomy cases in those two reports. To exclude the potential effect of advanced stage on prognosis of the patients with GEJ NEC, we used stage-stratified and multivariate survival analyses. Our results revealed that patients with stage II or III GEJ NEC demonstrated worse prognosis than those with gastric non-cardiac NEC, although the statistically significant difference was not reached in the stage III cases, which may be related to the small sample size of gastric non-cardiac NEC cases (n=4). We demonstrated the GEJ location as the only independent risk factor for overall survival of gastric NEC patients.

At present, PD-L1 expression in gastric NEC remains unknown. We showed that gastric NEC patients with positive PD-L1 (CPS ≥1) expression in tumors demonstrated a better prognosis that almost reached a statistically significant level (P=0.052). A similar association between PD-L1 expression and the prognosis of gastric carcinoma patients has been reported before [38, 39]. However, the only one previous study on the prognostic significance of PD-L1 in gastric NEC reported a worse prognosis in gastric NEC with high expression of PD-L1 [40]. This opposite conclusion may be related to the different PD-L1 antibody and evaluation methods that they used [40]. To the best of our knowledge, our study was the first to analyze the prognostic value of PD-L1 expression in gastric NEC with the United States Food and Drug Administration (FDA)-approved PD-L1 antibody 22C3 and the widely-adopted CPS method for staining data analysis.

The major limitations of our study are several: First, as the first comparison study on the GEJ NECs and gastric non-cardiac NECs, our sample size was relatively small and future studies with larger samples, especially from other ethnic patient populations, are required for validation. Second, the inherited selection bias of a retrospective study is unavoidable. We minimized this bias in this study by collecting consecutive NEC cases for the project with controls, the number of which was limited but the controls matched for age, gender, tumor location, and stage could provide strong qualified evidence. Third, Siewert I NEC was absent in the cohort because of the rarity in the Chinese population. Future studies in western populations in which esophageal adenocarcinoma prevails are needed for validation. Finally, molecular tumorigenesis mechanism of this uncommon carcinoma was not investigated in the present study, but we plan to do it in the near future.

In summary, compared to gastric non-cardiac NEC, GEJ NEC showed more aggressive clinicopathologic features with deeper invasion depth, more cases at advanced stages, and worse prognosis.

Acknowledgements

The study was supported by a research grant from the Youth Talents Program of the Health Commission of the Changzhou City (QN201935 to Yuqing Cheng), a grant from the 14th Five-Year Healthcare High-level Talents Program of the Health Commission of the Changzhou City (2022CZBJ079 to Yuqing Cheng) and a research grant from the Recruited Foreign Talents

Program of the Science and Technology Bureau of the Changzhou City (CQ20204036 to Yuqing Cheng) in China.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Qin Huang, Department of Pathology, The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, No. 68 Gehu Road, Changzhou 213164, Jiangsu, China. Tel: +86-0519-88132677; Fax: 857-203-5623; E-mail: qinhuang0122@gmail.com

References

[1] La RS, Rindi G, Solcia E and Tang LH. Gastric neuroendocrine neoplasms. In: WHO Classification Of Tumours Editorial Board. WHO classification of tumours. Digestive system tumours. Lyon: International Agency For Research On Cancer; 2019. pp. 104-109.

[2] Ishida M, Sekine S, Fukagawa T, Ohashi M, Morita S, Taniguchi H, Katai H, Tsuda H and Kushima R. Neuroendocrine carcinoma of the stomach: morphologic and immunohistochemical characteristics and prognosis. Am J Surg Pathol 2013; 37: 949-959.

[3] Lin J, Zhao Y, Zhou Y, Tian Y, He Q, Lin J, Hao H, Zou B, Jiang L, Zhao G, Lin W, Xu Y, Li Z, Xue F, Li S, Fu W, Li Y, Xu Z, Li Y, Chen J, Zhou X, Zhu Z, Cai L, Li E, Li H, Zheng C, Li P, Huang C and Xie J. Comparison of survival and patterns of recurrence in gastric neuroendocrine carcinoma, mixed adenoneuroendocrine carcinoma, and adenocarcinoma. JAMA Network Open 2021; 4: e2114180.

[4] Hong L, Zhang Y and Liu Z. Neuroendocrine carcinoma of esophageal and gastric cardia: clinicopathologic and immunohistochemistry study of 80 cases. Oncotarget 2018; 9: 10754-10764.

[5] Zhang P, Wang W, Lu M, Zeng C, Chen J, Li E, Tan H, Yu X, Tang Q, Zhao J, Shen L and Li J. Clinicopathological features and outcome for neuroendocrine neoplasms of gastroesophageal junction: a population-based study. Cancer Med 2018; 7: 4361-4370.

[6] Ajani JA, In H, Sano Takeshi, Gaspar LE, Erasmus JJ, Tang LH, Washington MK, Gerdes H, Wittekind CW, Manseld PF, Rimmer C, Hofstetter WL and Kelson D. Stomach. In: Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Vega LM. AJCC Cancer staging manual. 8th ed. New York: Springer; 2017. pp. 211-212.

[7] Huang Q, Cheng Y, Chen L, Mingzhan D, Wang Y, Xu G, Shi J, Fan X, Zhou X, Zhang Y, Guo L, Liu T, Zhou D, Mashimo H, Gold JS and Zou X. Low risk of lymph node metastasis in 495 early gastric cardiac carcinomas: a multicenter clinicopathologic study of 2101 radical gastrectomies for early gastric carcinoma. Mod Pathol 2018; 31: 1599-1607.

[8] Huang Q, Read M, Gold JS and Zou XP. Unraveling the identity of gastric cardiac cancer. J Dig Dis 2020; 21: 674-686.

[9] Huang Q, Sun Q, Fan XS, Zhou D and Zou XP. Recent advances in proximal gastric carcinoma. J Dig Dis 2016; 17: 421-432.

[10] Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014; 513: 202-209.

[11] Cancer Genome Atlas Research Network; Analysis Working Group: Asan University; BC Cancer Agency; Brigham and Women's Hospital; Broad Institute; Brown University; Case Western Reserve University; Dana-Farber Cancer Institute; Duke University; Greater Poland Cancer Centre; Harvard Medical School; Institute for Systems Biology; KU Leuven; Mayo Clinic; Memorial Sloan Kettering Cancer Center; National Cancer Institute; Nationwide Children's Hospital; Stanford University; University of Alabama; University of Michigan; University of North Carolina; University of Pittsburgh; University of Rochester; University of Southern California; University of Texas MD Anderson Cancer Center; University of Washington; Van Andel Research Institute; Vanderbilt University; Washington University; Genome Sequencing Center: Broad Institute; Washington University in St. Louis; Genome Characterization Centers: BC Cancer Agency; Broad Institute; Harvard Medical School; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University; University of North Carolina; University of Southern California Epigenome Center; University of Texas MD Anderson Cancer Center; Van Andel Research Institute; Genome Data Analysis Centers: Broad Institute; Brown University:; Harvard Medical School; Institute for Systems Biology; Memorial Sloan Kettering Cancer Center; University of California Santa Cruz; University of Texas MD Anderson Cancer Center; Biospecimen Core Resource: International Genomics Consortium; Research Institute at Nationwide Children's Hospital; Tissue Source Sites: Analytic Biologic Services; Asan Medical Center; Asterand Bioscience; Barretos Cancer Hospital; BioreclamationIVT; Botkin Municipal Clinic; Chonnam National University Medical

School; Christiana Care Health System; Cureline; Duke University; Emory University; Erasmus University; Indiana University School of Medicine; Institute of Oncology of Moldova; International Genomics Consortium; Invidumed; Israelitisches Krankenhaus Hamburg; Keimyung University School of Medicine; Memorial Sloan Kettering Cancer Center; National Cancer Center Goyang; Ontario Tumour Bank; Peter MacCallum Cancer Centre; Pusan National University Medical School; Ribeirão Preto Medical School; St. Joseph's Hospital &Medical Center; St. Petersburg Academic University; Tayside Tissue Bank; University of Dundee; University of Kansas Medical Center; University of Michigan; University of North Carolina at Chapel Hill; University of Pittsburgh School of Medicine; University of Texas MD Anderson Cancer Center; Disease Working Group: Duke University; Memorial Sloan Kettering Cancer Center; National Cancer Institute; University of Texas MD Anderson Cancer Center; Yonsei University College of Medicine; Data Coordination Center: CSRA Inc.; Project Team: National Institutes of Health. Integrated genomic characterization of oesophageal carcinoma. Nature 2017; 541: 169-175.

[12] Hendry S, Salgado R, Gevaert T, Russell PA, John T, Thapa B, Christie M, van de Vijver K, Estrada MV, Gonzalez-Ericsson PI, Sanders M, Solomon B, Solinas C, Van den Eynden GGGM, Allory Y, Preusser M, Hainfellner J, Pruneri G, Vingiani A, Demaria S, Symmans F, Nuciforo P, Comerma L, Thompson EA, Lakhani S, Kim SR, Schnitt S, Colpaert C, Sotiriou C, Scherer SJ, Ignatiadis M, Badve S, Pierce RH, Viale G, Sirtaine N, Penault-Llorca F, Sugie T, Fineberg S, Paik S, Srinivasan A, Richardson A, Wang Y, Chmielik E, Brock J, Johnson DB, Balko J, Wienert S, Bossuyt V, Michiels S, Ternes N, Burchardi N, Luen SJ, Savas P, Klauschen F, Watson PH, Nelson BH, Criscitiello C, O'Toole S, Larsimont D, de Wind R, Curigliano G, André F, Lacroix-Triki M, van de Vijver M, Rojo F, Floris G, Bedri S, Sparano J, Rimm D, Nielsen T, Kos Z, Hewitt S, Singh B, Farshid G, Loibl S, Allison KH, Tung N, Adams S, Willard-Gallo K, Horlings HM, Gandhi L, Moreira A, Hirsch F, Dieci MV, Urbanowicz M, Brcic I, Korski K, Gaire F, Koeppen H, Lo A, Giltnane J, Rebelatto MC, Steele KE, Zha J, Emancipator K, Juco JW, Denkert C, Reis-Filho J, Loi S and Fox SB. Assessing tumor-infiltrating lymphocytes in solid tumors: a practical review for pathologists and proposal for a standardized method from the international immuno-oncology biomarkers working group: part 2: TILs in melanoma, gastrointestinal tract carcinomas, non-small cell lung carcinoma and mesothelioma, endometrial and ovarian carcinomas, squamous cell carcinoma of the head and neck, genitourinary carcinomas, and primary brain tumors. Adv Anat Pathol 2017; 24: 311-335.

[13] Kulangara K, Zhang N, Corigliano E, Guerrero L, Waldroup S, Jaiswal D, Ms MJ, Shah S, Hanks D, Wang J, Lunceford J, Savage MJ, Juco J and Emancipator K. Clinical utility of the combined positive score for programmed death ligand-1 expression and the approval of pembrolizumab for treatment of gastric cancer. Arch Pathol Lab Med 2019; 143: 330-337.

[14] Bartley AN, Washington MK, Ventura CB, Ismaila N, Colasacco C, Benson AB 3rd, Carrato A, Gulley ML, Jain D, Kakar S, Mackay HJ, Streutker C, Tang L, Troxell M and Ajani JA. Her2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. Arch Pathol Lab Med 2016; 140: 1345-1363.

[15] Ramos MFKP, Pereira MA, Arabi AYM, Mazepa MM, Dias AR, Ribeiro U Jr, Zilberstein B and Nahas SC. Gastric mixed neuroendocrine non-neuroendocrine neoplasms: a western center case series. Med Sci (Basel) 2021; 9: 47.

[16] Hu P, Bai Ja, Liu M, Xue J, Chen T, Li R, Kuai X, Zhao H, Li X, Tian Y, Sun W, Xiong Y and Tang Q. Trends of incidence and prognosis of gastric neuroendocrine neoplasms: a study based on SEER and our multicenter research. Gastric Cancer 2020; 23: 591-599.

[17] Morita M, Taguchi K, Kagawa M, Nakanoko T, Uehara H, Sugiyama M, Ota M, Ikebe M, Sugimachi K, Esaki T and Toh Y. Treatment strategies for neuroendocrine carcinoma of the upper digestive tract. Int J Clin Oncol 2020; 25: 842-850.

[18] Zheng H, Zhao Y, He Q, Hao H, Tian Y, Zou B, Jiang L, Qiu X, Zhou Y, Li Z, Xu Y, Zhao G, Xue F, Li S, Fu W, Li Y, Zhou X, Zhu Z, Chen J, Xu Z, Cai L, Li E, Li H, Xie J, Zheng C, Lu J, Li P and Huang C. Multi-institutional development and validation of a nomogram to predict recurrence after curative resection of gastric neuroendocrine/mixed adenoneuroendocrine carcinoma. Gastric Cancer 2021; 24: 503-514.

[19] Choi NY, Kim BS, Oh ST and Yook JH. Comparative outcomes in patients with small- and large-cell neuroendocrine carcinoma (NEC) and mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) of the stomach. Am Surg 2021; 87: 631-637.

[20] Sun L, Zhang J, Wang C, Zhao S, Shao B, Guo Y, Liu Y and Sun Y. Chromosomal and molecular pathway alterations in the neuroendocrine carcinoma and adenocarcinoma components of gastric mixed neuroendocrine-nonneuroendocrine neoplasm. Mod Pathol 2020; 33: 2602-2613.

[21] Shen C, Chen H, Chen H, Yin Y, Han L, Chen J, Tang S, Yin X, Zhou Z, Zhang B and Chen Z. Surgical treatment and prognosis of gastric neuroendocrine neoplasms: a single-center experience. BMC Gastroenterol 2016; 16: 111.
[22] Liu DJ, Fu XL, Liu W, Zheng LY, Zhang JF, Huo YM, Li J, Hua R, Liu Q and Sun YW. Clinicopathological, treatment, and prognosis study of 43 gastric neuroendocrine carcinomas. World J Gastroenterol 2017; 23: 516.
[23] Xie J, Zhao Y, Zhou Y, He Q, Hao H, Qiu X, Zhao G, Xu Y, Xue F, Chen J, Su G, Li P, Zheng CH and Huang CM. Predictive value of combined preoperative carcinoembryonic antigen level and Ki-67 index in patients with gastric neuroendocrine carcinoma after radical surgery. Front Oncol 2021; 11: 533039.
[24] Ishida S, Akita M, Fujikura K, Komatsu M, Sawada R, Matsumoto H, Saegusa J, Itoh T, Kakeji Y and Zen Y. Neuroendocrine carcinoma and mixed neuroendocrine-non-neuroendocrine neoplasm of the stomach: a clinicopathological and exome sequencing study. Hum Pathol 2021; 110: 1-10.
[25] Han D, Li YL, Zhou ZW, Yin F, Chen J, Liu F, Shi YF, Wang W, Zhang Y, Yu XJ, Xu JM, Yang RX, Tian C, Luo J and Tan HY. Clinicopathological characteristics and prognosis of 232 patients with poorly differentiated gastric neuroendocrine neoplasms. World J Gastroenterol 2021; 27: 2895-2909.
[26] Koh J, Nam SK, Kwak Y, Kim G, Kim KK, Lee BC, Ahn SH, Park DJ, Kim HH, Park KU, Kim WH and Lee HS. Comprehensive genetic features of gastric mixed adenoneuroendocrine carcinomas and pure neuroendocrine carcinomas. J Pathol 2021; 253: 94-105.
[27] Ali AS, Langer SW, Federspiel B, Hjortland GO, Grønbæk H, Ladekarl M, Welin S, Weber Vestermark L, Arola J, Osterlund P, Knigge U, Sørbye H, Micke P, Grimelius L, Grönberg M and Tiensuu Janson E. PD-L1 expression in gastroenteropancreatic neuroendocrine neoplasms grade 3. PLoS One 2020; 15: e0243900.
[28] Wu C, Bao W, Rao Q, Wang X, Shen Q, Wei J, Dai Y and Zhou X. Clinicopathological features and prognosis of gastric mixed adenoneuroendocrine carcinoma. Int J Clin Exp Pathol 2018; 11: 1499-1509.
[29] Kim BS, Park YS, Yook JH and Kim BS. Comparison of relapse-free survival in gastric neuroendocrine carcinoma (WHO grade 3) and gastric carcinoma. Therap Adv Gastroenterol 2017; 10: 407-415.
[30] Chen J, Wang A, Ji K, Bu Z and Ji J. Comparison of overall survival of gastric neoplasms containing neuroendocrine carcinoma components with gastric adenocarcinoma: a propensity score matching study. BMC Cancer 2020; 20: 777.
[31] Xie JW, Lu J, Lin JX, Zheng CH, Li P, Wang JB, Chen QY, Cao LL, Lin M, Tu RH and Huang CM. Different long-term oncologic outcomes after radical surgical resection for neuroendocrine carcinoma and adenocarcinoma of the stomach. Oncotarget 2017; 8: 57495-57504.
[32] Nie L, Li M, He X, Feng A, Wu H and Fan X. Gastric mixed adenoneuroendocrine carcinoma: correlation of histologic characteristics with prognosis. Ann Diagn Pathol 2016; 25: 48-53.
[33] Tomita Y, Seki H, Matsuzono E, Kobayashi Y, Sogabe S, Sugai N, Fujita J and Suzuki A. Early gastric mixed neuroendocrine-non-neuroendocrine neoplasm with early poor prognosis after endoscopic submucosal dissection: a case report. DEN Open 2021; 2: e10.
[34] Zhu X, Jing H and Yao T. Clinical characteristics of early neuroendocrine carcinoma in stomach. Medicine (Baltimore) 2019; 98: e16638.
[35] Chen Z, Liu L, Tu J, Qin G, Su W, Geng X, Chen X, Wu H and Pan W. Improvement of atropine on esophagogastric junction observation during sedative esophagogastroduodenoscopy. PLoS One 2017; 12: e0179490.
[36] Lee YI, Jeon HK, Im JW, Oh SY, Kim KB and Kim B. Primary gastric small cell carcinoma: a case identified as a large subepithelial tumor from invisible state in 6 months. Clin Endosc 2019; 52: 76-79.
[37] Xie JW, Lu J, Wang JB, Lin JX, Chen QY, Cao LL, Lin M, Tu RH, Huang ZN, Lin JL, Zheng CH, Li P and Huang CM. Prognostic factors for survival after curative resection of gastric mixed adenoneuroendocrine carcinoma: a series of 80 patients. BMC Cancer 2018; 18: 1021.
[38] Pereira MA, Ramos MFKP, Dias AR, Ribeiro R, Cardili L, Zilberstein B, Cecconello I, Ribeiro U Jr, de Mello ES and de Castria TB. Scoring systems for PD-L1 expression and their prognostic impact in patients with resectable gastric cancer. Virchows Arch 2021; 478: 1039-1048.
[39] Sughayer MA, Dabbagh TZ and Battah AH. PD-L1 expression is a favorable prognostic marker in gastric carcinoma. Appl Immunohistochem Mol Morphol 2020; 28: 748-754.
[40] Yang MW, Fu XL, Jiang YS, Chen XJ, Tao LY, Yang JY, Huo YM, Liu W, Zhang JF, Liu PF, Liu Q, Hua R, Zhang ZG, Sun YW and Liu DJ. Clinical significance of programmed death 1/programmed death ligand 1 pathway in gastric neuroendocrine carcinomas. World J Gastroenterol 2019; 25: 1684-1696.