RESEARCH

Tumor size and perineural invasion predict outcome of gastric high-grade neuroendocrine neoplasms

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Abstract

A new subcategory, grade 3 neuroendocrine tumors, is incorporated into the grading system of pancreatic neuroendocrine neoplasms in the 2017 WHO classification in order to differentiate grade 3 neuroendocrine tumors from neuroendocrine carcinomas. The 2019 WHO classification extends the concept of grade 3 neuroendocrine tumors to gastrointestinal high-grade neuroendocrine neoplasms. However, there is still limited study focusing on the gastric grade 3 neuroendocrine tumors and gastric neuroendocrine carcinomas. We retrospectively enrolled 151 gastric high-grade neuroendocrine neoplasms patients, who underwent radical resection from January 2007 to December 2015. Clinicopathologic and prognostic features were studied. The Surveillance, Epidemiology, and End Results (SEER) database was used to verify the prognostic determinants found in the Zhongshan cohort. Neuroendocrine carcinomas showed a higher Ki67 index and higher mitotic count than grade 3 neuroendocrine tumors. We identified 109 (72.2%) patients with neuroendocrine carcinomas, 12 (7.9%) patients with grade 3 neuroendocrine tumors, and 30 (19.9%) patients with mixed neuroendocrine-non-neuroendocrine neoplasms. Although neuroendocrine carcinomas demonstrated higher Ki67 index ($P = 0.004$) and mitoses ($P = 0.001$) than grade 3 neuroendocrine tumors, their prognosis after radical resection did not demonstrate significant differences ($P = 0.709$). Tumor size, perineural invasion, and TNM stage were independent prognostic factors of gastric high-grade neuroendocrine neoplasms.

Key Words

- gastric high-grade neuroendocrine neoplasms
- grade 3 neuroendocrine tumors
- surgical resected
- prognosis

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Introduction

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a group of rare neoplasms, which are reported since the 1900s. The 2010 WHO classification categorized GEP-NENs into three groups mainly according to its proliferative activity (1). The prognosis of high-grade GEP-NENs, also known as grade 3 GEP-NENs, was much worse than that of grade 1 neuroendocrine tumors (G1 NET) and grade 2 neuroendocrine tumors (G2 NET) (2, 3, 4). However, the 2010 WHO classification was challenged after several studies reported that some cases of high-grade GEP-NENs also presented a well-differentiated pattern (5, 6). NORDIC study also reported heterogeneity in high-grade GEP-NENs (7). Thus, the concept of grade 3 neuroendocrine tumor (G3 NET) was proposed and investigated in GEP-NENs. Several studies on GEP-NENs reported that G3 NET showed a worse prognosis than G1/G2

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NET but better prognosis than neuroendocrine carcinoma (NEC), and NEC presented a higher Ki67 index than G3 NET (8, 9). 2018 IARC separated G3 NET from high-grade neuroendocrine neoplasms (NENs) in the gastrointestinal (GI) tract according to previous studies on GEP-NENs (10, 11). 2019 WHO classification included the G3 NET subgroup into the categories of gastric neuroendocrine neoplasms (gNENs) (12).

However, Coriat *et al.* (13) found that the gastric-originated neoplasms accounted for 8–24% in G3 NET and 7–8% in NEC in several major studies on GEP-NENs. The investigation on gastric high-grade neuroendocrine neoplasms were usually mixed with intestinal, pancreatic, and lung NEC. Fang *et al.* (14) reported that the prognosis of GEP-NENs significantly differed by deriving site (range of 3-year OS rate, 48.5–90.2%). However, there are still limited studies focusing on stomach investigating the difference between gastric G3 NET and NEC. Besides, only few studies investigate the prognostic determinants of resected high-grade gNENs in the Asian population (15, 16, 17). Our study aims to investigate the prognostic difference between gastric G3 NET and NEC and find out the prognostic determinants of resected high-grade gNENs.

Materials and methods

We retrospectively searched the database of Zhongshan Hospital, Fudan University for all patients with pathologically confirmed high-grade gNENs, who underwent surgical resection from January 2007 to December 2015. This study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (B2018-157). Two experienced pathologists in gNENs (Prof Ji and Dr Xie) reviewed and confirmed the pathologic characteristics including tumor differentiation, Ki67 index, mitotic count, immunohistochemical results (CD56, chromogranin A (CgA), and synaptophysin (Syn)), and percentage of NEN components. Primary antibody of CD56 (Leica, NCL-CD56-1B6) was used at a dilution of 1:100. Primary antibody of CgA (DAKO) and Syn (DAKO) was used at a dilution of 1:200. According to 2019 WHO classification, neuroendocrine tumor (NET) was defined as well-differentiated NENs and was classified as G1 (Ki67 index < 3% or mitoses/2 mm^2 < 2), G2 (Ki67 index 3–20% or mitoses/2 mm^2 2–20), and G3 (Ki67 index >20% or mitoses/2 mm^2 > 20); NEC was defined as poorly differentiated NENs which exhibited G3 characteristics (12). In the cases of mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs), the differentiation, Ki67 index, and mitotic count were based on NENs. According to recent clinical practice guidelines (18, 19), the pTNM stages of high-grade gNENs were evaluated according to American Joint Committee on Cancer (AJCC) 8th edition staging manual for gastric adenocarcinoma (20).

The SEER database was used to verify the determinants found in the Zhongshan cohort. The cohort was retrieved according to the International Classification of Diseases for Oncology (ICD-O-3) in the database (Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub, 1973–2014 varying). The ICD-O-3 code of site was restricted to the stomach, C16.0–C16.9. The following ICD-O-3 codes of histology were selected: large cell carcinoma (8012–8013), small cell carcinoma (8041–8044), carcinoid tumor (8240), argentaffin carcinoid tumor (8241), enterochromaffin cell tumor (8242), mucocarcinoid tumor (8243), mixed adenoneuroendocrine carcinoma (8244), adenocarcinoid tumor (8245), neuroendocrine carcinoid (8246), and atypical carcinoid tumor (8249). For the data of Ki67 index and mitotic count which was not available in the SEER database, we only enrolled poorly differentiated cases into our study. We screened patients who underwent surgical resection by code of RX Summ–Surg Prim Site (1998+). We excluded patients who could not be reclassified by the latest AJCC TNM classifications for incomplete data. TNM information was retrieved by the following codes: Derived AJCC Stage Group 7th ed (2010+), Derived AJCC Stage Group 6th ed (2004+), CS tumor size (2004+), Regional nodes positive (1988+). Collected information included recode of race, tumor behavior, grade, T stage, number of positive lymph nodes, number of retrieved lymph nodes, metastatic disease, surgery, survival etc.

Statistical analysis was performed using SPSS, version 19.0 (IBM). Comparisons of characteristics between groups were performed by χ^2-test or Mann–Whitney *U*-test. Overall survival (OS)/disease-free survival (DFS) was calculated from the date of surgical intervention until the date of the last contact or date of death/recurrence. Survivals were analyzed by Kaplan–Meier curves, and comparisons were performed using log-rank test. Cox proportional hazards regression model was used to identify the prognostic factors. Statistical significance was defined as a two-sided $P < 0.05$.

Results

Clinicopathologic features of patients from Zhongshan Hospital

Total of 151 patients with high-grade gNEN were included in our study (Table 1). We identified 109 (72.2%) patients of

Table 1 Clinicopathologic features of the Zhongshan cohort.

Characteristics	All cases	NEC	G3 NET	MiNEN	*P* value
Total, *n* (%)	151 (100)	109 (72.2)	12 (7.9)	30 (19.9)	
Sex, *n* (%)					0.778
Male	128 (84.8)	92 (84.4)	11 (91.7)	25 (83.3)	
Female	23 (15.2)	17 (15.6)	1 (8.3)	5 (16.7)	
Age, *n* (%)					0.949
≤65	84 (55.6)	61 (56.0)	7 (58.3)	16 (53.3)	
>65	67 (44.4)	48 (44.0)	5 (41.7)	14 (46.7)	
Tumor size, median (cm)	4.0	4.0	3.0	4.0	0.881
IQR	2.5–6.0	3.0–6.0	2.5–5.0	2.3–6.0	
Range	1.0–13.0	1.5–12.0	2.0–11.0	1.0–13.0	
Ki67 index, *n* (%)[a]					0.004
<55	53 (36.1)	34 (31.8)	9 (81.8)	10 (34.5)	
≥55	94 (63.9)	73 (68.2)	2 (18.2)	19 (65.5)	
Mitotic count, median (10 HPF)	24	26	9	24	0.001
IQR	15–36	18–39	4–17	18–33	
Range	2–74	4–74	2–34	12–62	
Positive CD56, *n* (%)	110 (72.8)	82 (75.2)	12 (100)	16 (53.3)	
Positive CgA, *n* (%)	118 (78.1)	85 (78.0)	10 (83.3)	23 (76.7)	
Positive Syn, *n* (%)	134 (88.7)	98 (89.9)	10 (83.3)	26 (86.7)	
T stage, *n* (%)					0.274
T1/T2	39 (25.8)	26 (23.9)	2 (16.7)	11 (36.7)	
T3/T4	112 (74.2)	83 (76.1)	10 (83.3)	19 (63.3)	
Lymphovascular invasion, *n* (%)					0.232
Absent	57 (37.7)	39 (35.8)	3 (25.0)	15 (50.0)	
Present	94 (62.3)	70 (64.2)	9 (75.0)	15 (50.0)	
Perineural invasion, *n* (%)					0.648
Absent	85 (56.3)	60 (55.0)	6 (50.0)	19 (63.3)	
Present	66 (43.7)	49 (45.0)	6 (50.0)	11 (36.7)	
TNM stage, *n* (%)					0.105
I	21 (13.9)	13 (11.9)	2 (16.7)	6 (20.0)	
II	37 (24.5)	30 (27.5)	0	7 (23.3)	
III	82 (54.3)	59 (54.1)	7 (58.3)	16 (53.3)	
IV	11 (7.3)	7 (6.4)	3 (25.0)	1 (3.3)	

[a]Data were available in 147 cases. The cases with missing data of Ki67 were classified by mitotic count.

NEC, 12 (7.9%) patients of G3 NET, and 30 (19.9%) patients of MiNEN. All 151 cases were type 3 g-NENs according to ENETS Consensus Guidelines for Gastroduodenal Neoplasms (21). The median age at surgery was 63 (range, 44–85), and the male/female ratio was 5.6:1. The differences in the clinicopathological characteristics of the high-grade gNENs were summarized in Table 1. The size of tumor showed no significant difference in NEC, G3 NET, and MiNEN ($P=0.881$). NEC showed higher Ki67 index ($P=0.004$) and higher mitotic count ($P=0.001$) than G3 NET. The median Ki67 index of NEC and G3 NET was 70% (range, 10–95%; IQR, 40–80%) and 30% (range, 25–65%; IQR, 25–30%), respectively. The positive rate of CD56, CgA, and Syn was 72.8, 78.1, and 88.7%, respectively.

In our study, distant metastasis was found in 11 patients at the initial diagnosis, and 6 out of 11 patients underwent radical surgery (combined resection). Totally, 7 of 151 patients underwent palliative surgery because of multiple liver metastases (5/7) and locally advanced disease (2/7). Adjuvant chemotherapy was conducted on 80 patients but a platinum-based regimen was carried out in only 37 patients.

Survival analysis and prognostic factors of Zhongshan cohort

The median follow-up duration was 34.3 months (range, 1.2–144.6 months). Seventy-three patients (48.3%) died of tumor recurrence or tumor-related complications. The overall survival of NEC, G3 NET, and MiNEN shows no significant difference (log-rank, $P=0.709$) (Fig. 1). The 5-year OS rates of stages I, II, III, and IV are 81.6, 57.5, 45.0 and 9.1%, respectively (log-rank, $P=0.001$; Fig. 2A). Survival curves are well discriminated by TNM stages.

Disease-free survival was available in 119 cases because of 7 non-radical cases and 25 incomplete follow-up cases. Overall survival and disease-free survival were investigated in univariate Cox regression and multivariate

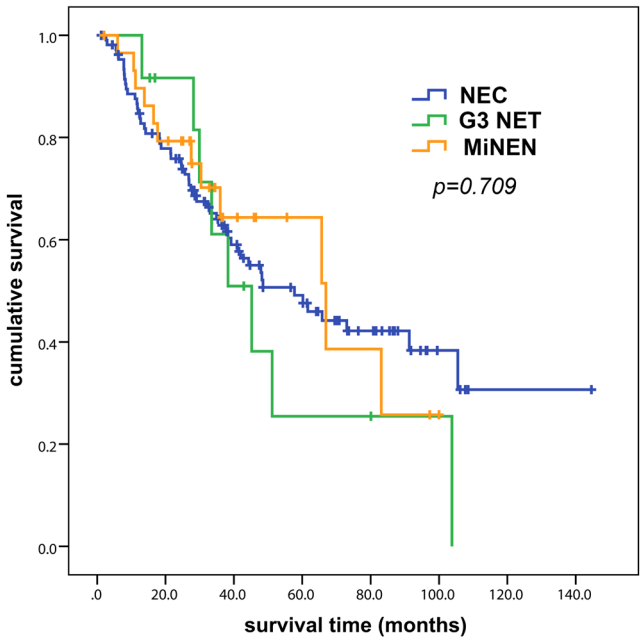

Figure 1
Kaplan–Meier curves of overall survival of NEC, G3 NET, and MiNEN patients from the Zhongshan cohort ($P = 0.709$, log-rank test).

Cox regression analysis. Univariate Cox regression analysis showed differentiation was not a significant prognostic factor of high-grade gNENs in OS ($P=0.227$) and DFS ($P=0.143$) (Table 2). Tumor with adenocarcinoma components did not demonstrate significant impact on OS ($P=0.538$) and DFS ($P=0.705$). T stage ($P=0.019$ OS; $P=0.018$, DFS) and N stage ($P=0.058$, OS; $P=0.112$, DFS) showed potential influence on OS and DFS. Tumor size ($P=0.020$, OS; $P=0.016$, DFS), perineural invasion ($P=0.007$, OS; $P=0.022$, DFS) and TNM stage ($P=0.001$, OS; $P=0.002$, DFS) proved to be prognostic factors. Platinum-based adjuvant chemotherapy demonstrated beneficiat in overall survival ($P=0.025$). Multivariate Cox regression analysis showed that tumor size ($P=0.044$, OS; $P=0.026$, DFS), perineural invasion ($P=0.016$, OS; $P=0.030$, DFS) and TNM stage ($P < 0.001$, OS; $P=0.003$, DFS) were independent prognostic factors of gastric high-grade neuroendocrine neoplasms (Table 3).

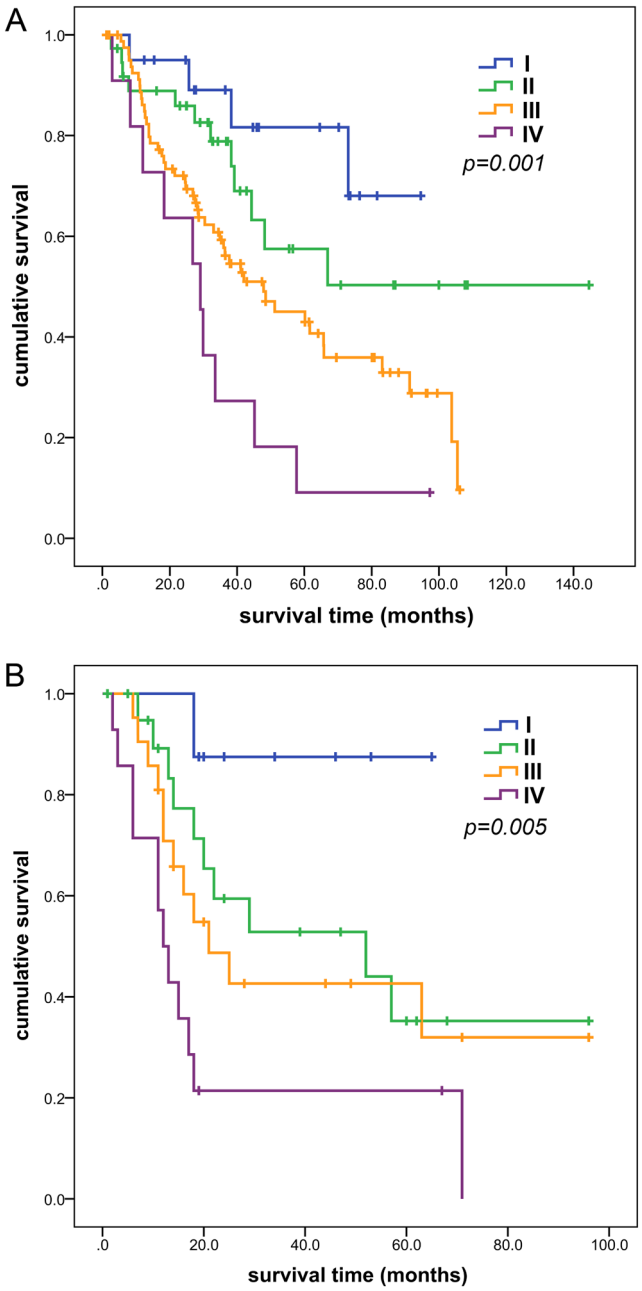

Figure 2
(A) Kaplan–Meier curves of overall survival of patients from the Zhongshan cohort ($P = 0.001$, log-rank test). (B) Kaplan–Meier curves of overall survival of patients from SEER cohort ($P = 0.005$, log-rank test).

Clinicopathologic features and prognostic factors of SEER data

We enrolled 65 patients with poorly differentiated gNEC from SEER database (Supplementary Table 1, see section on supplementary materials given at the end of this article). In SEER data set, the median follow-up duration was 18 months (range, 1.0–121.0 months). OS rates of 1-, 3-, and 5-year were 91.6, 63.2, and 43.4%, respectively. Overall survival is discriminated by TNM stages ($P=0.005$) (Fig. 2B). Cox regression analysis shows that TNM stages ($P=0.026$) are associated with overall survival (Table 4).

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Table 2 Univariate analysis of overall survival and disease-free survival in Zhongshan data set.

Characteristics	Overall survival		Disease-free survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Tumor size (cm)				
≤4	1.000		1.000	
>4	1.730 (1.092–2.741)	0.020	1.983 (1.138–3.457)	0.016
Adenocarcinoma components				
Absent	1.000		1.000	
Present	1.168 (0.712–1.916)	0.538	1.117 (0.630–1.981)	0.705
Differentiation				
Well differentiated	1.000		1.000	
Poorly differentiated	0.662 (0.339–1.293)	0.227	0.525 (0.222–1.242)	0.143
Ki67 index[a]				
<55	1.000		1.000	
≥55	1.051 (0.649–1.701)	0.840	0.729 (0.416–1.278)	0.270
T stage				
T1/T2	1.000		1.000	
T3/T4	2.163 (1.138–4.112)	0.019	2.384 (1.157–4.910)	0.018
Lymphatic metastases				
N0	1.000		1.000	
N1	1.696 (0.810–3.552)	0.161	1.833 (0.754–4.459)	0.181
N2	1.927 (0.943–3.938)	0.072	2.056 (0.845–5.004)	0.112
N3	2.084 (0.975–4.452)	0.058	2.189 (0.833–5.754)	0.112
Lymphovascular invasion				
Absent	1.000		1.000	
Present	1.535 (0.936–2.517)	0.090	1.377 (0.772–2.456)	0.278
Perineural invasion				
Absent	1.000		1.000	
Present	1.886 (1.188–2.996)	0.007	1.914 (1.096–3.342)	0.022
Adjuvant chemotherapy				
Negative	1.000		1.000	
Positive	0.957 (0.602–1.522)	0.852	1.090 (0.616–1.930)	0.767
Type of regimen[b]				
Platinum-based	1.000		1.000	
Others	2.204 (1.104–4.399)	0.025	1.048 (0.517–2.122)	0.897
TNM stage				
I	1.000		1.000	
II	1.820 (0.584–5.673)	0.302	3.627 (0.811–16.215)	0.092
III	3.476 (1.250–9.664)	0.017	5.945 (1.421–24.867)	0.015
IV	6.870 (2.147–21.980)	0.001	13.095 (2.534–67.670)	0.002

[a]Data were available in 147 cases; [b]Adjuvant chemotherapy was carried out in 80 cases. Platinum-based regimens included EP, IP, EOX, XELOX, DOS, etc. Other types of regimens included S-1, capecitabine, etc.

Table 3 Multivariate analysis of overall survival and disease-free survival in the Zhongshan data set.

Characteristics	Overall survival		Disease-free survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Tumor size (cm)				
≤4	1.000		1.000	
>4	1.623 (1.014–2.597)	0.044	1.973 (1.086–3.583)	0.026
Differentiation				
Well differentiated	1.000		1.000	
Poorly differentiated	0.988 (0.489–1.999)	0.974	1.076 (0.402–2.879)	0.884
Perineural invasion				
Absent	1.000		1.000	
Present	1.973 (1.114–2.887)	0.016	1.948 (1.067–3.557)	0.030
TNM stage				
I/II	1.000		1.000	
III	1.863 (1.033–3.360)	0.039	1.625 (0.829–3.183)	0.157
IV	4.545 (1.973–10.472)	<0.001	5.621 (1.818–17.385)	0.003

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Table 4 Cox regression analysis of overall survival in the SEER cohort.

Characteristics	HR (95% CI)	*P* value
Sex		
Male	1.000	
Female	0.892 (0.441–1.803)	0.750
Age (year)		
≤65	1.000	
>65	1.482 (0.759–2.892)	0.249
Race		
White	1.000	
Black	0.994 (0.404–2.442)	0.989
Other	0.850 (0.238–3.039)	0.802
Tumor size (cm)		
≤4	1.000	
>4	1.029 (0.458–2.311)	0.944
TNM stage		
I/II	1.000	
III/IV	2.272 (1.105–4.672)	0.026

Discussion

In our study, the heterogeneity of gNENs was investigated. NEC demonstrated a higher Ki67 index and mitoses than G3 NET. Although their pathologic features were partially different, NEC and G3 NET showed a similar prognosis after radical resection (Fig. 1). Differentiation failed to predict the prognosis of high-grade gNENs either in OS or DFS (Table 3). Meanwhile, tumor size, perineural invasion, TNM stages were independent prognostic factors of resected high-grade gNENs.

Previous study on GEP-NENs reported that G3 NET accounted for 18–31% of the G3 NENs (8, 9, 22). Our results demonstrated that the rate of G3 NET was 7.9% in high-grade gNENs. In recent years, researchers realized that tumor heterogeneity was an important influence factor of prognosis and therapeutic sensitivity. Several studies have reported the heterogeneity of high-grade GEP-NENs. Basturk *et al.* (8) and Heetfeld *et al.* (9) found that the Ki67 index or mitotic count of GEP-NEC was significantly higher than that of G3 GEP-NET. In our study, with the data focusing on high-grade gNENs, we also found that NEC showed a higher Ki67 index and mitotic count than G3 NET. Regarding the prognosis, Heetfeld *et al.* (9) investigated 204 cases of high-grade GEP-NENs, 17 patients of gNEN included, and found that the median overall survival of G3 NET was significantly higher than that of NEC. Afterwards, Milione *et al.* (22) studied 136 cases of G3 GEP-NEN, 28 patients of gNEN included, and demonstrated that NEC had a worse prognosis than G3 NET. However, the percentage of gNENs in these studies was relatively limited. So, based on one of the major Chinese centers of GI carcinomas, our study focused on the characteristics of resected gastric G3 NET and NEC and the prognostic factors of high-grade gNENs. Not consistent with the previous studies, our results showed that the overall survival of patients with resected gastric NEC and G3 NET has no significant difference. One of the possible reasons might be that patients in our study received radical resection and gNENs were investigated together with other GEP-NENs in some previous studies. Fang *et al.* (3) demonstrated that the prognosis of GEP-NENs of different sites varied significantly. Similarly, Milione *et al.* (22) suggested that midgut and/or hindgut sites of origin correlated with a worse survival when compared with the origin of the foregut. Therefore, the difference in surgical prognosis of gastric G3 NET and NEC needs further investigation by a larger cohort.

In our study, we confirmed the prognostic role of tumor size and perineural invasion in high-grade gNENs (15, 23). As to the Ki67 index and prognosis, several retrospective studies indicated that the Ki67 index was an important prognostic factor of high-grade GEP-NENs (7, 9, 22, 23). However, a prospective study put forward that the Ki67 index had limited prognostic value (24). In our study, the Ki67 index did not show significant correlation with prognosis. It seems that the significance of the Ki67 index to prognosis needs to be further investigated in high-grade gNENs.

In our study, adjuvant chemotherapy did not demonstrate benefit on OS ($P=0.852$) and DFS ($P=0.767$). This was probably because some chemotherapy regimens in our study did not use platinum drugs, resulting in poor efficacy. One reason was that standard care of chemotherapy was not confirmed by large-scale clinical trial around 2010 (25). Therefore, we further investigated the efficacy of platinum drugs. The platinum-based adjuvant chemotherapy demonstrated benefit on OS ($P=0.025$), which confirmed the results of previous studies (9, 22).

Our study had several limitations. First and most importantly, this was a retrospective single-center study, which may lead to unaccounted biases. Data of Ki67 index were not available in four patients and these patients were diagnosed with G3 NENs by mitotic count. Secondly, SEER database lacked several tumor characteristics such as the Ki67 index and mitotic count. The cohort we selected from the SEER database only contained NEC patients while 9.9% of Zhongshan cases were G3 NET patients. As a result, we could not compare NEC with G3 NET in the SEER cohort. Thirdly, we enrolled a small number of patients with gastric G3 NET because of the rarity, and further investigation was needed to clarify the difference between

G3 NET and NEC. Nevertheless, surgery is still the main primary treatment for both locoregional G3 NET and NEC. Despite these limitations, we carried out a focused study on resected gastric high-grade gNENs, and the prognostic determinants were explored. We believe that the 2019 WHO classification on gastric G3 NET and NEC needs further verification by clinical and genomic dimensions in the future.

Conclusion

High-grade gNENs demonstrate heterogeneity in clinicopathologic features. G3 NET and NEC show different characteristics in morphology, Ki67 index, and mitotic count. However, the prognosis of G3 NET and NEC has no significant difference after radical resection. Tumor size, perineural invasion, and TNM stage are prognostic determinants of high-grade gNENs.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-21-0017.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

1 Bosman FT, Carneiro CF & Hruban RH. *WHO Classification of Tumors of the Digestive System*. Lyon: IARC Press, 2010.
2 Rindi G, Azzoni C, La Rosa S, Klersy C, Paolotti D, Rappel S, Stolte M, Capella C, Bordi C & Solcia E. ECL cell tumor and poorly differentiated endocrine carcinoma of the stomach: prognostic evaluation by pathological analysis. *Gastroenterology* 1999 **116** 532–542. (https://doi.org/10.1016/s0016-5085(99)70174-5)
3 Fang C, Wang W, Feng X, Sun J, Zhang Y, Zeng Y, Wang J, Chen H, Cai M, Lin J, *et al.* Nomogram individually predicts the overall survival of patients with gastroenteropancreatic neuroendocrine neoplasms. *British Journal of Cancer* 2017 **117** 1544–1550. (https://doi.org/10.1038/bjc.2017.315)
4 Yachida S, Vakiani E, White CM, Zhong Y, Saunders T, Morgan R, de Wilde RF, Maitra A, Hicks J, Demarzo AM, *et al.* Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors. *American Journal of Surgical Pathology* 2012 **36** 173–184. (https://doi.org/10.1097/PAS.0b013e3182417d36)
5 Scoazec J-Y, Couvelard A, Monges G, Leteurtre E, Belleannee G, Guyetant S, Duvillard P, Danjoux M, Parot X & Lepage C. Well-differentiated grade 3 digestive neuroendocrine tumors: myth or reality? The PRONET Study Group. *Journal of Clinical Oncology* 2012 **30** 4129–4129. (https://doi.org/10.1200/jco.2012.30.15_suppl.4129)
6 Velayoudom-Cephise FL, Duvillard P, Foucan L, Hadoux J, Chougnet CN, Leboulleux S, Malka D, Guigay J, Goere D, Debaere T, *et al.* Are G3 ENETS neuroendocrine neoplasms heterogeneous? *Endocrine-Related Cancer* 2013 **20** 649–657. (https://doi.org/10.1530/ERC-13-0027)
7 Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, Dueland S, Hofsli E, Guren MG, Ohrling K, *et al.* Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Annals of Oncology* 2013 **24** 152–160. (https://doi.org/10.1093/annonc/mds276)
8 Basturk O, Yang Z, Tang LH, Hruban RH, Adsay V, McCall CM, Krasinskas AM, Jang KT, Frankel WL, Balci S, *et al.* The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. *American Journal of Surgical Pathology* 2015 **39** 683–690. (https://doi.org/10.1097/PAS.0000000000000408)
9 Heetfeld M, Chougnet CN, Olsen IH, Rinke A, Borbath I, Crespo G, Barriuso J, Pavel M, O'Toole D, Walter T, *et al.* Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. *Endocrine-Related Cancer* 2015 **22** 657–664. (https://doi.org/10.1530/ERC-15-0119)
10 Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, Busam KJ, de Krijger RR, Dietel M, El-Naggar AK, *et al.* A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Modern Pathology* 2018 **31** 1770–1786. (https://doi.org/10.1038/s41379-018-0110-y)
11 Kloppel G. Neuroendocrine neoplasms: dichotomy, origin and classifications. *Visceral Medicine* 2017 **33** 324–330. (https://doi.org/10.1159/000481390)
12 WHO Classification of Tumours Editorial Board. *WHO Classification of Tumours of the Digestive System*. Lyon: IARC Press, 2019.
13 Coriat R, Walter T, Terris B, Couvelard A & Ruszniewski P. Gastroenteropancreatic well-differentiated grade 3 neuroendocrine tumors: review and position statement. *Oncologist* 2016 **21** 1191–1199. (https://doi.org/10.1634/theoncologist.2015-0476)
14 Fang C, Wang W, Zhang Y, Feng X, Sun J, Zeng Y, Chen Y, Li Y, Chen M, Zhou Z, *et al.* Clinicopathologic characteristics and prognosis of gastroenteropancreatic neuroendocrine neoplasms: a multicenter study in South China. *Chinese Journal of Cancer* 2017 **36** 51. (https://doi.org/10.1186/s40880-017-0218-3)
15 Park JY, Ryu MH, Park YS, Park HJ, Ryoo BY, Kim MG, Yook JH, Kim BS & Kang YK. Prognostic significance of neuroendocrine components in gastric carcinomas. *European Journal of Cancer* 2014 **50** 2802–2809. (https://doi.org/10.1016/j.ejca.2014.08.004)
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. *European Journal of Surgical Oncology* 2016 **42** 1464–1470. (https://doi.org/10.1016/j.ejso.2016.08.004)
17 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 Journal of Gastroenterology* 2017 **23** 516–524. (https://doi.org/10.3748/wjg.v23.i3.516)

18 Pavel M, Oberg K, Falconi M, Krenning EP, Sundin A, Perren A, Berruti A & ESMO Guidelines Committee. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2020 **31** 844–860. (https://doi.org/10.1016/j.annonc.2020.03.304)
19 Division of Digestive Diseases & 2020 Chinese Consensus on the Pathological Diagnosis of Gastrointestinal and Pancreatic Neuroendocrine Neoplasms Experts Group. Chinese consensus on the pathological diagnosis of G and pancreatic neuroendocrine neoplasms experts G. *Chinese Journal of Pathology* 2021 **50** 14–20. (https://doi.org/10.3760/cma.j.cn112151-20200805-00623)
20 Amin MB, Edge S & Greene FL. *AJCC Cancer Staging Manual*, 8th ed. New York: Springer, 2017.
21 Delle Fave G, Kwekkeboom DJ, Van Cutsem E, Rindi G, Kos-Kudla B, Knigge U, Sasano H, Tomassetti P, Salazar R, Ruszniewski P, *et al*. Enets consensus guidelines for the management of patients with gastroduodenal neoplasms. *Neuroendocrinology* 2012 **95** 74–87. (https://doi.org/10.1159/000335595)
22 Milione M, Maisonneuve P, Spada F, Pellegrinelli A, Spaggiari P, Albarello L, Pisa E, Barberis M, Vanoli A, Buzzoni R, *et al*. The clinicopathologic heterogeneity of grade 3 gastroenteropancreatic neuroendocrine neoplasms: morphological differentiation and proliferation identify different prognostic categories. *Neuroendocrinology* 2017 **104** 85–93. (https://doi.org/10.1159/000445165)
23 Shen C, Chen H, Chen H, Yin Y, Han L, Chen J, Tang S, Yin X, Zhou Z, Zhang B, *et al*. Surgical treatment and prognosis of gastric neuroendocrine neoplasms: a single-center experience. *BMC Gastroenterology* 2016 **16** 111. (https://doi.org/10.1186/s12876-016-0505-5)
24 Walter T, Tougeron D, Baudin E, Le Malicot K, Lecomte T, Malka D, Hentic O, Manfredi S, Bonnet I, Guimbaud R, *et al*. Poorly differentiated gastro-entero-pancreatic neuroendocrine carcinomas: are they really heterogeneous? Insights from the FFCD-GTE national cohort. *European Journal of Cancer* 2017 **79** 158–165. (https://doi.org/10.1016/j.ejca.2017.04.009)
25 Paulson AS & Bergsland EK. Systemic therapy for advanced carcinoid tumors: where do we go from here? *Journal of the National Comprehensive Cancer Network* 2012 **10** 785–793. (https://doi.org/10.6004/jnccn.2012.0078)

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