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Comparison of Overall Survival of Gastric Neoplasms Containing Neuroendocrine Carcinoma Components with Gastric Adenocarcinoma: A Propensity Score Matching Study

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Abstract

Background Gastric neoplasms containing neuroendocrine carcinoma (NEC) components are rare malignancies with highly aggressive behavior and poor prognosis, including pure NEC and mixed tumor containing NEC components. We attempt to investigate whether there is a distinct difference in overall survival (OS) between Gastric neoplasms containing NEC components and gastric adenocarcinoma.

Methods Surgically resected gastric neoplasms containing NEC components (n = 54) and gastric adenocarcinoma (n = 600) from January 2013 to December 2019 at Peking University Cancer Hospital were retrospectively analyzed. Patients were categorized into the surgical group and the neoadjuvant group and adjusted using propensity score matching. In the two groups, gastric neoplasms containing NEC components were divided into pure NEC, mixed tumors with neuroendocrine carcinoma components less than 30% (< 30% G-HMiNEN), between 30% and 70% (G-HMiNEN) and more than 70% (> 70% G-HMiNEN). OS was compared between these groups and gastric adenocarcinoma.

Results The OS of gastric neoplasms containing neuroendocrine NEC components was poorer than that of gastric adenocarcinoma in the surgical group, whether the ratio of neuroendocrine cancer components was less than 30%, between 30% and 70%, higher than 70% or 100%. Cox multivariate regression analysis proved tumor category (neoplasms containing NEC components or gastric adenocarcinoma) to be an independent risk factor for prognosis. In patients receiving neoadjuvant therapy, however, the difference was not significant.

Conclusions Gastric neoplasms containing NEC components, regardless of the proportion of neuroendocrine carcinoma components, had poorer overall survival than gastric adenocarcinoma in patients treated with surgery directly, indicating a higher degree of malignancy than gastric adenocarcinoma.

Introduction

Gastric neoplasm containing neuroendocrine carcinoma (NEC) component is a heterogeneous subgroup of gastric cancer, with highly aggressive behavior and poor prognosis, including pure NEC and mixed tumor containing NEC components. Every year there are about 1 million new cases of gastric cancer worldwide, and gastric neoplasms containing NEC components account for about 0.1% -0.6%[1, 2]. Attributable to the lower incidence, there is few comprehensive basic and clinical research to systematically guide the treatment, making the prognosis of these tumors unsatisfactory[3–7].

According to the 2017 World Health Organization (WHO) digestive neuroendocrine tumor classification, neuroendocrine neoplasm (NEN) can be divided into three categories based on Ki-67 levels and mitotic counts (× 10 HPF): Grade 1 (G1, Ki67 ≤ 2%, Mitoses < 2), Grade 2 (G2, 3%< Ki67 ≤ 20%, 2 ≤ Mitoses ≤ 20), Grade 3 (G3, Ki67 > 20%, Mitoses > 20)[8]. Meanwhile, American joint Committee on cancer (AJCC) defines the highly differentiated NEN as neuroendocrine tumor (NET) and the poorly differentiated NEN as neuroendocrine carcinoma (NEC) based on the degree of tumor cell differentiation. Generally speaking, G1, G2, and rare well-differentiated G3 NEN belong to the NET, while poorly differentiated G3 NEN belongs to NEC[8, 9]. Gastric mixed neuroendocrine-non-neuroendocrine neoplasm (G-MiNEN) is a special type of gastric NENs, which is defined as containing more than 30% of components in both neuroendocrine and non-neuroendocrine[8], accounting for approximately 7% of all G-NENs and 25% of gastric neuroendocrine carcinomas (G-NECs)[4–6]. For those mixed tumors with neuroendocrine carcinoma components less than 30% or more than 70%, there is no uniform definition. Considering the heterogeneity of MiNEN and the malignancy degree of different components in the tumor, La Rosa et al. [10, 11] proposed to divide MiNEN

into three categories: high-grade, intermediate-grade and low-grade. High-grade MiNEN consists of NEC and carcinoma/adenoma, intermediate-grade consists of NET and carcinoma, while low-grade MiNEN consists of NET and adenoma.

Generally, the prognosis of mixed tumors is largely determined by the most malignant component. Kim et al. [12] found that G-NEC has shorter progression-free survival (PFS) in comparison to gastric adenocarcinoma. Huang et al. [13] found that the prognosis of patients with neuroendocrine cancer components above 50% is significantly poorer than that of patients below 50%. All of these studies provide evidence that tumors containing neuroendocrine cancer components may contribute to a worse prognosis. We hypothesized that if the mixed tumor contains neuroendocrine carcinoma components, its prognosis is worse than that of a pure adenocarcinoma. We sought to find researches on the overall survival (OS) comparison of G-HMiNEN and gastric adenocarcinoma but failed. Therefore, we think that the study of the comparison of the OS of G-HMiNEN and gastric adenocarcinoma will provide a valuable supplement to the current study of G-HMiNEN. In order to overcome the bias caused by the differences between the covariates in the comparison, we used propensity score matching (PSM) to match the covariates, matching important factors such as age, gender, tumor location, tumor size, pathological staging, neoadjuvant chemotherapy, and adjuvant chemotherapy between the two groups, making the research results more reliable.

Methods

Patients selection

We retrospectively collected patients diagnosed with gastric NENs and underwent radical resection at Peking University Cancer Hospital, Beijing, from January 2013 to December 2019. The inclusion criteria were as follows. (1) those pathologically confirmed pure NEC or tumor components contain NEC; (2) those without distant metastases and underwent R0 resection; (3) those who follow up for more than 5 years. Patients with incomplete clinical information were excluded from further analysis. We also precluded those dead during the perioperative period. Patients with gastric adenocarcinoma undergoing radical surgery were randomly selected for PSM analyses.

Follow-up

We followed the patients at least twice a year. Serum tumor markers test, gastroscope, and computed tomography (CT) scans were used to reexamine patients after surgery. Depending on the patients' status, Magnetic resonance imaging (MRI) and Positron emission tomography & computed tomography (PET-CT) were also considered. The follow-up lasted more than 5 years.

Diagnosis And Classification

We re-evaluated the diagnosis and classification of G-HMiNEN. Mixed tumors with neuroendocrine carcinoma components less than 30% or more than 70% were also included in this study, which were defined as < 30%G-HMiNEN and > 70%G-HMiNEN, respectively. To make the study more convincing, we also included pure NEC cases for comparison. All neuroendocrine tumors were identified, diagnosed, and classified by two independent pathologists in accordance with 2019 WHO classification of tumors[8]. The tumor staging involved in the study was referred to the AJCC 8th Edition TNM Staging Guidelines[9]. All possible disagreements were discussed in our study group.

Definition Of Variables And Groups

In this study, patients were divided into the surgical group and the neoadjuvant group based on whether they had received neoadjuvant therapy before surgery. Patients in the surgery group were assessed by the pTNM staging system, while patients in the neoadjuvant treatment group were assessed by the ypTNM staging system. OS refers to the time from surgery to the last follow-up, the time of death, or the end of follow-up (e.g., loss of follow-up or other cause of death).

Propensity Score Matching

To accurately compare the prognosis of G-HMiNEN and gastric adenocarcinoma, we employed PSM to balance the differences between the two groups. Logistic regression models were used to estimate propensity scores based on gender, age, tumor location, tumor size, pathological staging, neoadjuvant chemotherapy, and adjuvant chemotherapy. According to the 0.2 caliper width, 1:4 nearest neighbor matching was performed. Chi-square test and Mann-Whitney U test were used to further verify the matching results.

Statistical analysis

All statistical analyses were performed using SPSS 22.0 statistical software (IBM, United States). Chi-square test and Mann-Whitney U test were used for statistical analysis of categorical variables and continuous variables, respectively. Kaplan-Meier method was used for the comparison of OS. The log-rank test was used to compare survival rates. $P < 0.05$ was regarded as the threshold of significance.

Results

Patient selection and PSM results

Between 2013 and 2019, a total of 180 patients with gastric carcinomas containing neuroendocrine cancer components underwent radical resection at Peking University Cancer Hospital, of which 55 were pure NEC and the remaining 125 were mixed tumors. Finally, 54 patients were included in our study (NEC: 15, < 30%G-HMiNEN: 15, G-HMiNEN: 20, > 70%G-HMiNEN: 4) (Fig. 1). Of included patients, a total of 22 patients received neoadjuvant therapy. We also randomly selected 600 patients with gastric adenocarcinoma who underwent radical surgery and followed up for more than 5 years. Among them, 381 patients received neoadjuvant therapy, and the remaining 228 patients were treated with surgery directly.

Prior to the OS comparison, PSM was performed to ensure that there were no significant statistical differences in patient gender, age, tumor location, tumor size, pathological staging, neoadjuvant chemotherapy, and adjuvant chemotherapy between the two groups. Details before and after the match are shown in Table 1.

Table 1
Patient characteristics before and after propensity matching in all patients with NEC components

Patient Characteristics	Unmatched comparison			Matched comparison		
	Patients with NEC components (n = 54)	Gastric adenocarcinoma (n = 600)	*P* value	Patients with NEC components (n = 45)	Gastric adenocarcinoma (n = 146)	*P* value
Age (year), mean ± SD	64.5 ± 8.5	57.4 ± 10.9	< 0.001	63.0 ± 8.3	62.3 ± 9.0	0.624
Gender (male/female)	42/12	504/96	0.238	37/8	122/24	0.833
BMI, mean ± SD	24.0 ± 3.8	23.5 ± 3.4	0.333	23.6 ± 3.9	23.6 ± 3.5	0.937
Neoadjuvant therapy			< 0.001			0.249
Yes	19 (35.2)	372 (62.0)		19 (42.2)	76 (52.1)	
No	35 (64.8)	228 (38.0)		26 (57.8)	70 (47.9)	
Adjuvant therapy						0.404
Yes	47 (87.0)	449 (74.8)	0.045	38 (84.4)	115 (78.8)	
No	7 (13.0)	151 (25.2)		7 (15.6)	31 (21.2)	
Tumor location			< 0.001			0.802
Upper third	36 (66.7)	224 (37.3)		32 (71.1)	94 (64.4)	
Middle third	13 (24.1)	66 (11.0)		8 (17.8)	33 (22.6)	
Lower third	5 (9.3)	294 (49.0)		5 (11.1)	19 (13.0)	
Entire	0 (0.0)	16 (2.7)		0 (0.0)	0 (0.0)	
Tumor size			0.102			0.409
< 5 cm	32 (59.3)	420 (70.0)		29 (63.4)	102 (69.9)	
≥5 cm	22 (40.7)	180 (30.0)		16 (25.6)	44 (30.1)	
Type of gastrectomy			< 0.001			0.104
Total gastrectomy	44 (81.5)	243 (40.5)		36 (80.0)	92 (63.0)	
Distal gastrectomy	5 (9.3)	292 (48.7)		5 (11.1)	28 (19.2)	
Proximal gastrectomy	5 (9.3)	65 (10.8)		4 (8.9)	26 (17.8)	

Patient Characteristics	Unmatched comparison			Matched comparison		
	Patients with NEC components (n = 54)	Gastric adenocarcinoma (n = 600)	*P* value	Patients with NEC components (n = 45)	Gastric adenocarcinoma (n = 146)	*P* value
Surgical procedure			0.002			< 0.001
Open	54 (100.0)	510 (85.0)		45 (100.0)	116 (79.5)	
Laparoscopic	0 (0.0)	90 (15.0)		0 (0.0)	30 (20.5)	
T stage			< 0.001			< 0.001
T1	2 (3.7)	186 (28.0)		1 (2.2)	32 (21.9)	
T2	10 (18.5)	54 (9.0)		9 (20.0)	8 (5.5)	
T3	24 (44.4)	141 (23.5)		20 (44.4)	44 (30.1)	
T4	18 (33.3)	237 (39.5)		15 (33.3)	62 (42.5)	
N stage			0.017			0.228
N0	15 (27.8)	268 (44.7)		14 (41.1)	54 (37.0)	
N1	12 (22.2)	94 (15.7)		10 (22.2)	25 (17.1)	
N2	15 (27.8)	88 (14.7)		12 (26.7)	23 (15.8)	
N3	12 (22.2)	150 (25.0)		9 (20.0)	44 (30.1)	
TNM stage			0.033			0.629
I	8 (14.8)	188 (31.3)		8 (17.8)	35 (24.0)	
II	17 (31.5)	135 (22.5)		13 (28.9)	35 (24.0)	
III	29 (53.7)	277 (46.2)		24 (53.3)	76 (52.1)	

NEC: neuroendocrine carcinoma;

Patients with NEC components: NEC, < 30% high grade MiNEN, high grade MiNEN and > 70% high grade MiNEN

Comparison of OS between all patients with NEC components and patients with gastric adenocarcinoma

PSM was performed on all patients with NEC components, including pure NEC patients and mixed tumor patients (Table 1). As a result, 45 patients with NEC components and 146 patients with gastric adenocarcinoma were matched. The proportion of patients receiving neoadjuvant therapy was 42.2% and 52.1% (Table 1, p = 0.249), respectively, with no statistical difference. Apparently, patients with NEC components had a poorer OS than that of gastric adenocarcinoma (Fig. 2a, p = 0.0424). To investigate whether neoadjuvant therapy had an effect on OS, patients in the surgical and neoadjuvant groups were analyzed separately (Supplement Table 1–2). The results showed that the OS of patients with NEC components was still poorer than that of gastric adenocarcinomas in the surgical group (Fig. 2b, p = 0.0347). While there was no significant difference between the patients receiving neoadjuvant therapy (Fig. 2c, p = 0.5396).

Table 2
Univariate and multivariate analyses of survival after PSM in mixed tumor surgical group

Patient Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (year)	0.961	0.925–0.998	0.039	1.022	0.976–1.069	0.345
Gender			0.643			
female	1	1				
male	0.807	0.333–1.956				
BMI	1.052	0.952–1.162	0.324			
Adjuvant therapy			0.001			0.139
Yes	1	1		1	1	
No	12.324	2.939–51.666		15.936	0.405-626.747	
Tumor location			0.263			
Upper third	1	1				
Middle third	1.107	0.475–2.581				
Lower third	0.384	0.115–1.281				
Tumor size			< 0.001			0.005
< 5 cm	1	1		1	1	
≥5 cm	4.296	2.142–8.615		3.438	1.460–8.094	
Tumor category			0.024			0.007
Gastric adenocarcinoma	1	1		1	1	
<30%G-HMiNEN + G-HMiNEN + > 70%G-HMiNEN	2.273	1.117–4.626		3.181	1.370–7.385	
Type of gastrectomy			0.120			
Total gastrectomy	1	1				
Distal gastrectomy	0.220	0.052–0.929				
Proximal gastrectomy	0.911	0.373–2.223				
Surgical procedure			0.499			
Open	1	1				
Laparoscopic	0.737	0.304–1.785				

The data of TNM_III had a collinearity relation with the data of Adjuvant therapy, so it was deleted from the multivariate cox regression analysis

Patient Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
T stage			0.009			0.501
T1	1	1		1	1	
T2	4.048	0.676–24.230		0.913	0.125–6.660	
T3	11.239	2.504–50.453		0.406	0.040–4.129	
T4	8.865	2.034–38.638		0.296	0.033–2.636	
N stage			0.001			0.196
N0	1	1		1	1	
N1	5.262	1.412–19.614		1.878	0.153–23.038	
N2	4.372	1.315–14.541		1.121	0.110-11.452	
N3	9.613	3.176–29.095		2.989	0.313–28.528	
TNM stage			0.002			0.623
I	1	1		1	1	
II	10.251	2.125–49.443		0.731	0.209–2.554	
III	13.117	3.088–55.726		-	-	
The data of TNM_III had a collinearity relation with the data of Adjuvant therapy, so it was deleted from the multivariate cox regression analysis						

Comparison of OS between patients with pure NEC and patients with gastric adenocarcinoma

In pure NEC group, PSM was also performed, and finally, 13 NEC cases and 46 gastric adenocarcinoma cases were successfully matched. The proportion of patients receiving neoadjuvant therapy in the two groups was 57.1% and 62.0% (Supplement Table 3, p = 0.742), respectively. OS in patients with pure NEC was also poorer than that of patients with gastric adenocarcinoma (Fig. 3a, p = 0.0150). We also evaluated the OS according to the neoadjuvant therapy status, the result was similar to that of all patients with NEC component. In the surgery group, the OS of patients with pure NEC was significantly poorer than that of patients with gastric adenocarcinoma (Fig. 3b, p = 0.0260), however, there was no significant difference in the neoadjuvant group (Fig. 3c, p = 0.9857). Detail patient characteristics before and after PSM in surgical group and neoadjuvant group were shown in Supplement Table 4–5.

Comparison of OS between patients with mixed tumors containing NEC components and patients with gastric adenocarcinoma

In the group of patients with mixed tumors containing NEC components, 32 cases were successfully matched with 101 gastric adenocarcinoma cases after PSM, with neoadjuvant therapy ratio of 34.4% and 41.6% (Supplement Table 6, p = 0.468), respectively. Significant differences in OS were also observed when compared with the OS of gastric adenocarcinoma (Fig. 4a, p = 0.0484). As with the pure NEC group, the OS of patients with mixed tumors containing NEC components was also poorer than that of gastric adenocarcinoma in the surgery group (Fig. 4b, p =

0.0198, Supplement Table 7), but there was still no significant difference in the neoadjuvant group (Fig. 4c, p = 0.9885, Supplement Table 8).

From the above results we can infer that in the surgical group, both pure NEC and mixed tumors patients had a poorer prognosis than that of gastric adenocarcinoma. To further explore the prognostic factors, Cox regression analysis was performed on matched patients in the surgical group of mixed tumors (Table 2). In univariate analysis, age, adjuvant therapy, tumor size ≥ 5 cm, tumor category (gastric adenocarcinoma or mixed tumor containing NEC components), T stage, N stage, and TNM stage are considered to be important factors affecting prognosis. Multivariate analysis identified tumor size ≥ 5 cm and tumor category as independent risk factors.

Comparison of OS between patients with mixed tumors containing different proportions of NEC components and patients with gastric adenocarcinoma in the surgery group

To investigate whether the level of NEC components had an effect on overall survival in the surgical group, < 30% G-HMiNEN, G-HMiNEN and > 70%G-HMiNEN were compared with gastric adenocarcinoma and found that even the group with the lowest content of NEC, < 30% G-HMiNEN group had a poorer OS than adenocarcinoma (Fig. 5a). And in the G-HMiNEN and > 70%G-HMiNEN groups with higher NEC content, the OS was also worse than that of gastric adenocarcinoma as speculated (Fig. 5b & 5c). Detailed clinical information after matching was shown in Supplement Table 9–11.

Discussion

In all G-NENs, the tumor containing NEC components is a special type, including pure NEC and mixed tumor containing NEC components. The incidence of these tumors is extremely low, but they are more invasive and have a poorer prognosis than the well-differentiated G-NENs[4, 5].

In previous studies, Kim et al. found that in patients who did not receive neoadjuvant chemotherapy, progression-free survival (PFS) of pure G-NEC was poorer than that of gastric adenocarcinoma, while PFS of G-HMiNEN was not significantly different from that of gastric adenocarcinoma[12] PFS is an important indicator for evaluating prognosis, in many cases, it can reflect the trend of OS. In our research, we regard the tumors containing NEC components as a whole and found that the OS of these tumors was poorer than that of adenocarcinoma in the surgical group, in addition, the comparison result of pure G-NEC cases was similar to Kim's, while the OS of mixed tumors was also poorer than that of gastric adenocarcinoma, whether the ratio of neuroendocrine cancer components was less than 30%, between 30% and 70%, or higher than 70%. Cox multivariate regression analysis was performed and the tumor category was proved to be an independent risk factor for prognosis. This suggests that the prognosis of gastric mixed carcinoma with NEC components is substantially different from that of gastric adenocarcinoma, even a small percentage (< 30%) of G-NEC components can also impair prognosis, which challenge the cut-off value of 30%.

The proportion of each component must theoretically be higher than 30% was set in 1987[14]. It largely avoids the overdiagnosis of MiNEN in tumors with only focal neuroendocrine marker expression and no corresponding morphological changes. Besides, it also prevents clinicians from dealing with these rare neoplasms too often without guidelines[15]. Nevertheless, it is now being questioned by more and more scholars. The components in mixed tumors are not evenly distributed. For large tumors, the randomness of biopsy and postoperative pathological sampling will make the proportion of each component fluctuate greatly, it is difficult to describe the proportion of each component precisely[15]. Park et al. found that the prognosis of patients with only 10%-30% of NEC was

significantly poorer than that of patients with less than 10%. Even a small proportion of malignant components can affect prognosis[3]. Researches on the molecular mechanism of pathogenesis show that NEC components and adenocarcinoma components have similar genomic abnormalities, similar losses of heterozygosity (LOH) and mutations at multiple loci and key oncogenes, such as TP53, APC, and RB genes. All these results imply that the two components in the mixed tumor may have a common origin[16–23]. Therefore, we propose to consider mixed tumors containing both neuroendocrine marker expression and corresponding morphological characteristics as a whole, rather than defining them based on the definition of 30% for both tumor components. For mixed tumors that have only focal neuroendocrine marker expression and no morphological neuroendocrine carcinoma characteristics, no positive effect on prognosis was found in gastric adenocarcinoma[24, 25], bile duct carcinomas[26], colorectal adenocarcinoma[27, 28], but in the study of gastroesophageal junction adenocarcinoma, Koppert et al[29]. reported a positive result. Although none of these patients were involved in our study, but based on the findings of other scholars, we still recommend treating it as adenocarcinoma.

Previously, MAGIC research has confirmed the efficacy of neoadjuvant chemotherapy in gastric adenocarcinoma[30]. However, van der Veen et al. reported that neoadjuvant chemotherapy could not benefit the survival of patients with mixed tumors containing G-NEC components[31]. In our study, among patients receiving neoadjuvant therapy, no significant difference in OS between mixed tumor and gastric adenocarcinoma was observed. The possible reason is that we used the ypTNM staging system to perform PSM in the neoadjuvant group. Under the same ypTNM stages, patients with better efficacy tended to have poorer clinical TNM (cTNM) stages. Therefore, we speculated that the difference of OS between mixed tumor and gastric adenocarcinoma was diminished owning to the tumor staging downgrade of gastric adenocarcinoma. Furthermore, neoadjuvant chemotherapy may aggravate genomic instability and induce transdifferentiation of adenocarcinoma components to NEC components[27], which will further diminish the effect of neoadjuvant therapy. The benefit of neoadjuvant therapy is still undefined, and more clinical trials are needed to prove it.

This study also has its limitations. AS a retrospective study, although we performed PSM in advance, selection bias cannot be completely avoided. In addition, since the exact proportion of each component in the mixed tumor could not be obtained, we could not determine whether there is a cutoff value for diagnosis in the mixed tumor with NEC component less than 30%, so we could only treat all mixed tumors with NEC component as a whole. Moreover, because it is a single-center study, we have a limited number of cases, so we could not directly compare the prognosis of < 30% G-HMiNEN, G-HMiNEN and > 70%G-HMiNEN after PSM.

Conclusions

Our study demonstrated that gastric neoplasms with NEC components, regardless of the proportion of neuroendocrine carcinoma components, have poorer overall survival than gastric adenocarcinoma, indicating a higher degree of malignancy than gastric adenocarcinoma. Therefore, for this type of tumor, we should adopt more aggressive and powerful treatment than gastric adenocarcinoma to improve the prognosis of patients.

Abbreviations

AJCC
American joint Committee on cancer
CT
Computed tomography
G-HMiNEN

Gastric mixed neuroendocrine-non-neuroendocrine neoplasm
G-NEC
Gastric neuroendocrine carcinoma
HPF
High power field
MiNEN
Mixed neuroendocrine-non-neuroendocrine neoplasm
NEC
Neuroendocrine carcinoma
NEN
Neuroendocrine neoplasm
NET
Neuroendocrine tumor
MRI
Magnetic resonance imaging
OS
Overall survival
PET-CT
Positron emission tomography & computed tomography
PFS
Progression-free survival
PSM
Propensity score matching
WHO
World Health Organization

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Peking University Cancer Hospital and the patients' written consent was also obtained.

Consent for publication

Written informed consent for publication was obtained and stored in Peking University Cancer Hospital

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JC and AWdesigned the study and wrote the manuscript. KJ helped with data management and statistical analysis. ZB and JJ performed project administration.

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Figures

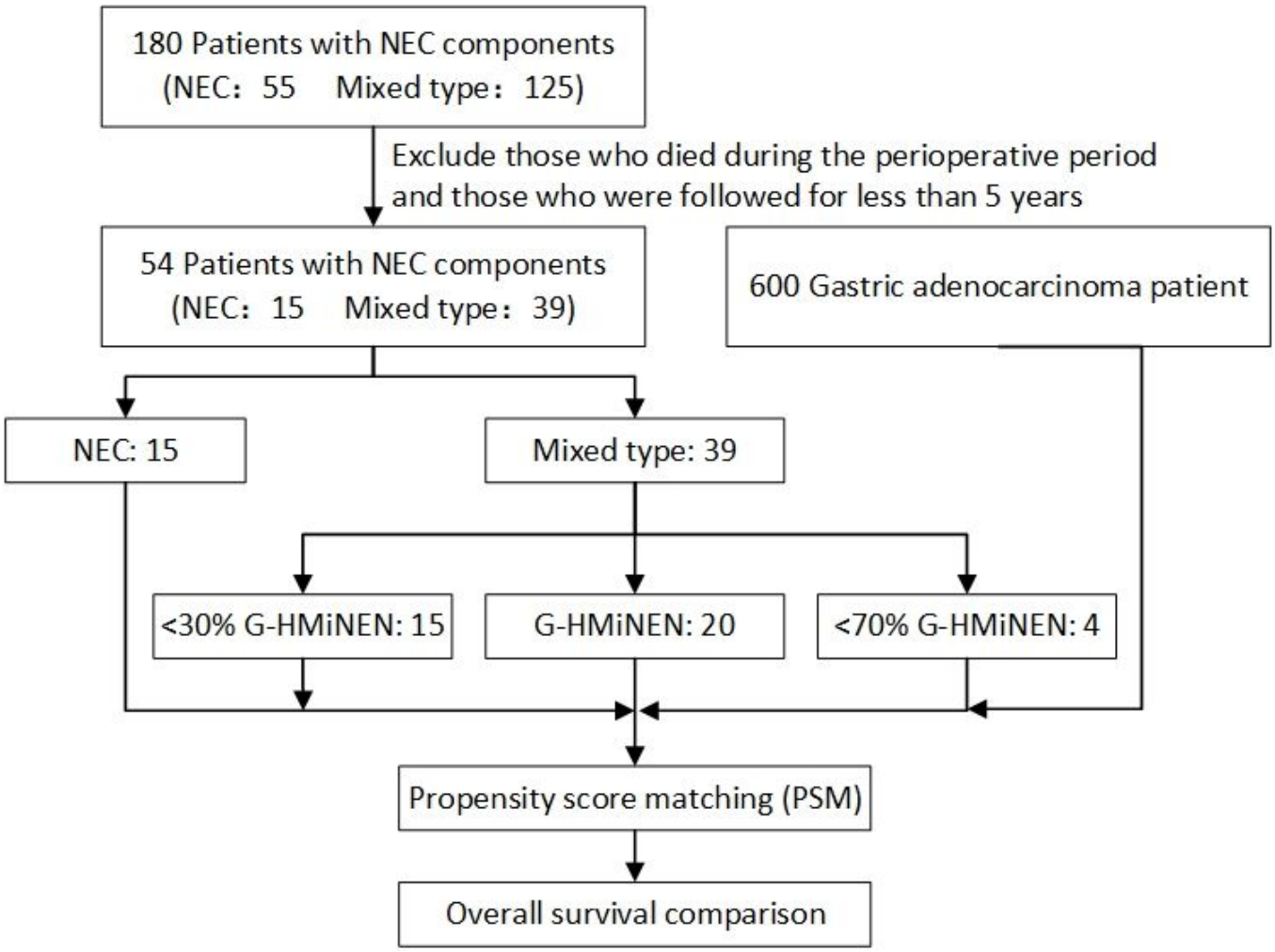

Figure 1

Flow chart of patient enrollment.

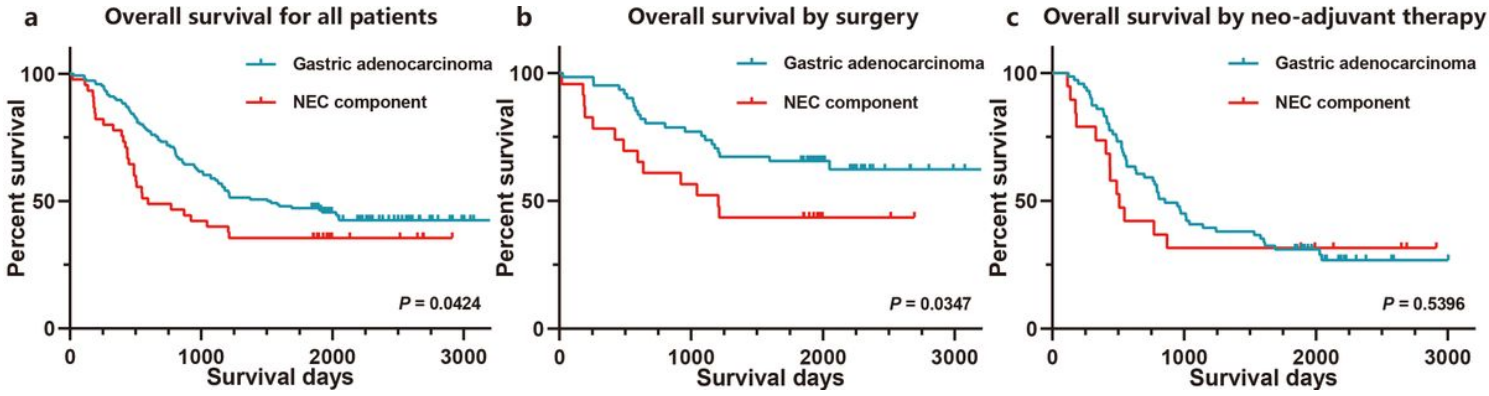

Figure 2

Comparison of overall survival of gastric neoplasms containing neuroendocrine carcinoma components with gastric adenocarcinoma. a. Overall survival for all patients. b. Overall survival in surgical groups. c. Overall survival in neo-adjuvant groups.

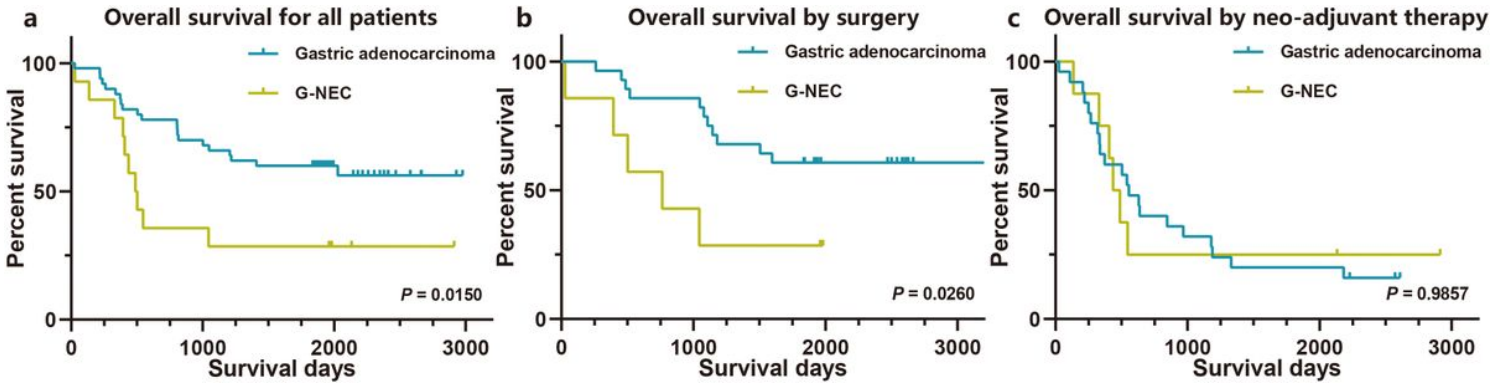

Figure 3

Comparison of overall survival of gastric neuroendocrine carcinoma (NEC) with gastric adenocarcinoma. a. Overall survival for all patients. b. Overall survival in surgical groups. c. Overall survival in neo-adjuvant groups.

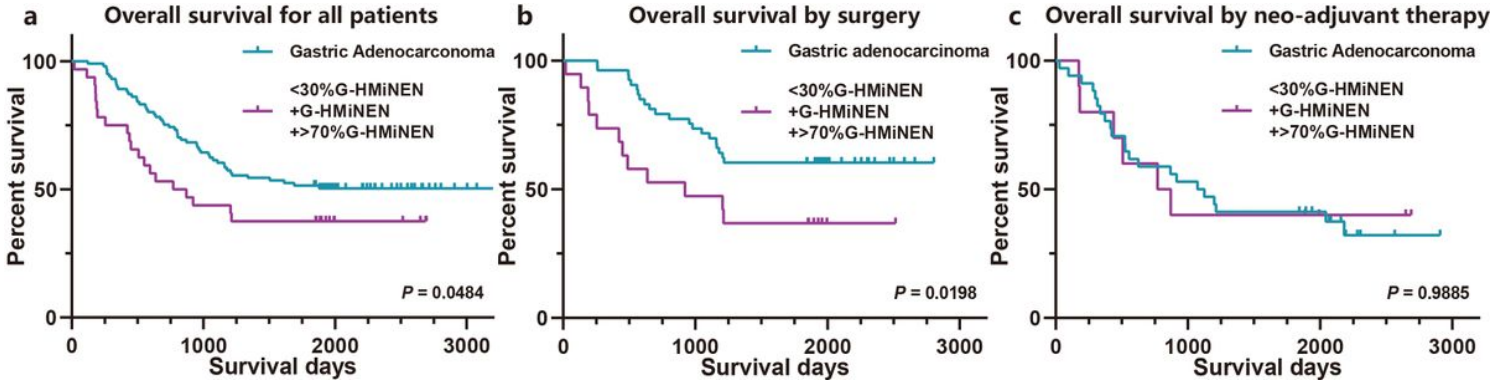

Figure 4

Comparison of overall survival of gastric mixed tumors containing neuroendocrine carcinoma components with gastric adenocarcinoma. a. Overall survival for all patients. b. Overall survival in surgical groups. c. Overall survival in neo-adjuvant groups.

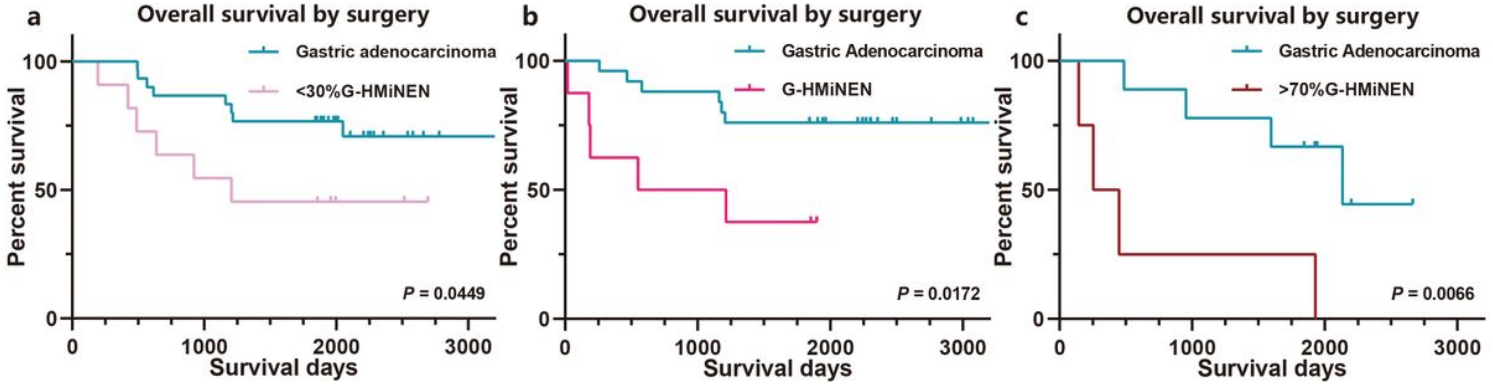

Figure 5

OS comparison between mixed tumors with different NEC content and gastric adenocarcinoma in surgical group. a. Overall survival comparison between <30%G-HMiNEN and gastric adenocarcinoma. b. Overall survival comparison between G-HMiNEN and gastric adenocarcinoma. c. Overall survival comparison between >70%G-HMiNEN and gastric adenocarcinoma.

Supplementary Files

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- SupplementTable.docx