The Clinicopathological Features and Overall Survival of Patients With Gastric Neuroendocrine Carcinoma

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Abstract

Objectives: Gastric neuroendocrine carcinoma (GNEC) is a class of rare histological subtypes in gastric cancer (GC). This retrospective case-control study aimed to explore the clinicopathological features and overall survival (OS) of patients with GNEC.

Methods: A large population of GNEC and intestinal-type GC (IGC) patients were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. The 1:1 propensity score matching (PSM) analysis was initiated to adjust the confounders between GNEC and IGC cohorts. Kaplan-Meier (KM) plots with log-rank tests were used to compare the survival differences in GNEC versus IGC. Additionally, Cox proportional hazard regression models were adopted to characterize the prognostic factors relevant to OS of the GNEC patients.

Results: An entity of 4596 patients were collected, including 3943 (85.8%) IGC patients and 653 (14.2%) GNEC patients. The PSM analysis well-balanced all confounders in GNEC versus IGC (all $P > .05$). The KM plots showed that GNEC had significantly superior OS to IGC both before and after PSM analysis. Before PSM, the median OS was 52 (33.6-70.4) months in GNEC versus 32 (29.3-34.7) months in IGC ($P = .0015$). After PSM, the median OS was 26 (18.3-33.7) months in GNEC versus 21 (17.7-24.3) months in IGC ($P = .0039$). Stratified analysis indicated that GNEC had superior survivals to IGC in early stage patients and those who received surgery. In Cox regression analysis, age $\geq$ 60, tumor size > 50 mm, stage II-IV, T2, and N3 were independent risk factors for the GNEC patients (hazard ratio [HR]>1, $P < .05$). By contrast, year 2010 to 2015, female, and surgery were independent protective factors for these patients (HR < 1, $P < .05$).

Conclusions: GNEC has unique clinicopathological features quite different from IGC and may have a superior survival to IGC in early stage patients. The prognostic factors identified here may assist the clinicians to more individually treat these patients.

Introduction

According to cancer statistics in 2019, the estimated new cases of gastric cancer (GC) were 27 510, and estimated deaths were 11 140 in the United States.[1] This poses a significant public health problem. GC is a heterogeneous disease, different histological types usually represent distinct molecular patterns, clinical characteristics, and prognoses.[2] Among multiple histological subtypes of GC, intestinal-type GC (IGC) is characterized by definite glandular structures with intestinal phenotypes, derived from multifocal atrophies in gastric mucosa.[3] By comparison, gastric neuroendocrine carcinoma (GNEC) is a rare disease, which occupies 0.1% to 0.6% of the whole GC.[4]

In definition, GNEC constitutes the proliferation of poorly differentiated endocrine cells with distinct cellular atypia, possibly originated from dedifferentiation of adenocarcinoma cells to the endocrine cells.[5]

Based on the morphology and proliferation rate, current neuroendocrine neoplasms are classified as well differentiated

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Table 1. Characteristics of Patients in IGC Versus GNEC Before and After PSM, n (%).

| Characteristics | Before PSM (N = 4596) | | | After PSM (N = 1002) | | |
	IGC n = 3943 (85.8)	GNEC n = 653 (14.2)	P	IGC n = 501 (50)	GNEC n = 501 (50)	P
Diagnosis year			<.001			.563
2004 to 2009	1875 (47.6)	239 (36.6)		201 (40.1)	210 (41.9)	
2010 to 2015	2068 (52.4)	414 (63.4)		300 (59.9)	291 (58.1)	
Age (y)			<.001			.665
<60	760 (19.3)	246 (37.7)		147 (29.3)	140 (27.9)	
60 to 80	2302 (58.4)	339 (51.9)		295 (58.9)	293 (58.5)	
>80	881 (22.3)	68 (10.4)		59 (11.8)	68 (13.6)	
Gender			<.001			.652
Male	2515 (63.8)	343 (52.5)		304 (60.7)	297 (59.3)	
Female	1428 (36.2)	310 (47.5)		197 (39.3)	204 (40.7)	
Race			<.001			.261
White	2300 (58.3)	500 (76.6)		359 (71.7)	360 (71.9)	
Black	590 (15)	100 (15.3)		76 (15.2)	89 (17.8)	
Others	1053 (26.7)	53 (8.1)		66 (13.2)	52 (10.4)	
Tumor size (mm)			.573			.411
≤50	2124 (53.9)	344 (52.7)		251 (50.1)	238 (47.5)	
>50	1819 (46.1)	309 (47.3)		250 (49.9)	263 (52.5)	
Stage			<.001			.668
I	1731 (43.9)	349 (53.4)		219 (43.7)	216 (43.1)	
II	779 (19.8)	76 (11.6)		82 (16.4)	72 (14.4)	
III	568 (14.4)	44 (6.7)		46 (9.2)	43 (8.6)	
IV	865 (21.9)	184 (28.2)		154 (30.7)	170 (33.9)	
Tumor depth			<.001			.582
T1	1254 (31.8)	343 (52.5)		217 (43.3)	227 (45.3)	
T2	1767 (44.8)	183 (28)		170 (33.9)	156 (31.1)	
T3	571 (14.5)	52 (8)		55 (11)	49 (9.8)	
T4	351 (8.9)	75 (11.5)		59 (11.8)	69(13.8)	
LN metastasis			<.001			.627
N0	1938 (49.2)	421 (64.5)		282 (56.3)	280 (55.9)	
N1	1429 (36.2)	202 (30.9)		181 (36.1)	191 (38.1)	
N2	433 (11)	26 (4)		35 (7)	26 (5.2)	
N3	143 (3.6)	4 (0.6)		3 (0.6)	4 (0.8)	
Distant metastasis			<.001			.143
M0	3299 (83.7)	484 (74.1)		367 (73.3)	346 (69.1)	
M1	644 (16.3)	169 (25.9)		134 (26.7)	155 (30.9)	
LN examined			<.001			.061
0	884 (22.4)	426 (65.2)		264 (52.7)	280 (55.9)	
1 to 15	1515 (38.4)	139 (21.3)		154 (30.7)	133 (26.5)	
16 to 29	1050 (26.6)	50 (7.7)		61 (12.2)	50 (10)	
>29	494 (12.5)	38 (5.8)		22 (4.4)	38 (7.6)	
Surgery			<.001			.337
No	740 (18.8)	247 (37.8)		202 (40.3)	217 (43.3)	
Yes	3203 (81.2)	406 (62.2)		299 (59.7)	284 (56.7)	
Radiotherapy			<.001			.641
No	3133 (79.5)	615 (94.2)		459 (91.6)	463 (92.4)	
Yes	810 (20.5)	38 (5.8)		42 (8.4)	38 (7.6)	
Chemotherapy			<.001			.646
No/unknown	2276 (57.7)	464 (71.1)		315 (62.9)	322 (64.3)	
Yes	1667 (42.3)	189 (28.9)		186 (37.1)	179 (35.7)	

Abbreviations: GNEC, neuroendocrine carcinoma; IGC, intestinal-type gastric cancer; LN, lymph node; PSM, propensity-score matching.

neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinoma (NEC).[6] In the World Health Organization classification, the nomenclature for grade 3 NETs was altered to "NEC," including small cell carcinoma and large cell NEC.[6]

GNEC has poorly differentiated morphology and larger proliferation rates than the well differentiated NETs.[6] Several recent studies focusing on this kind of tumor have revealed that GNEC was highly aggressive and liable to invade adjacent lymph
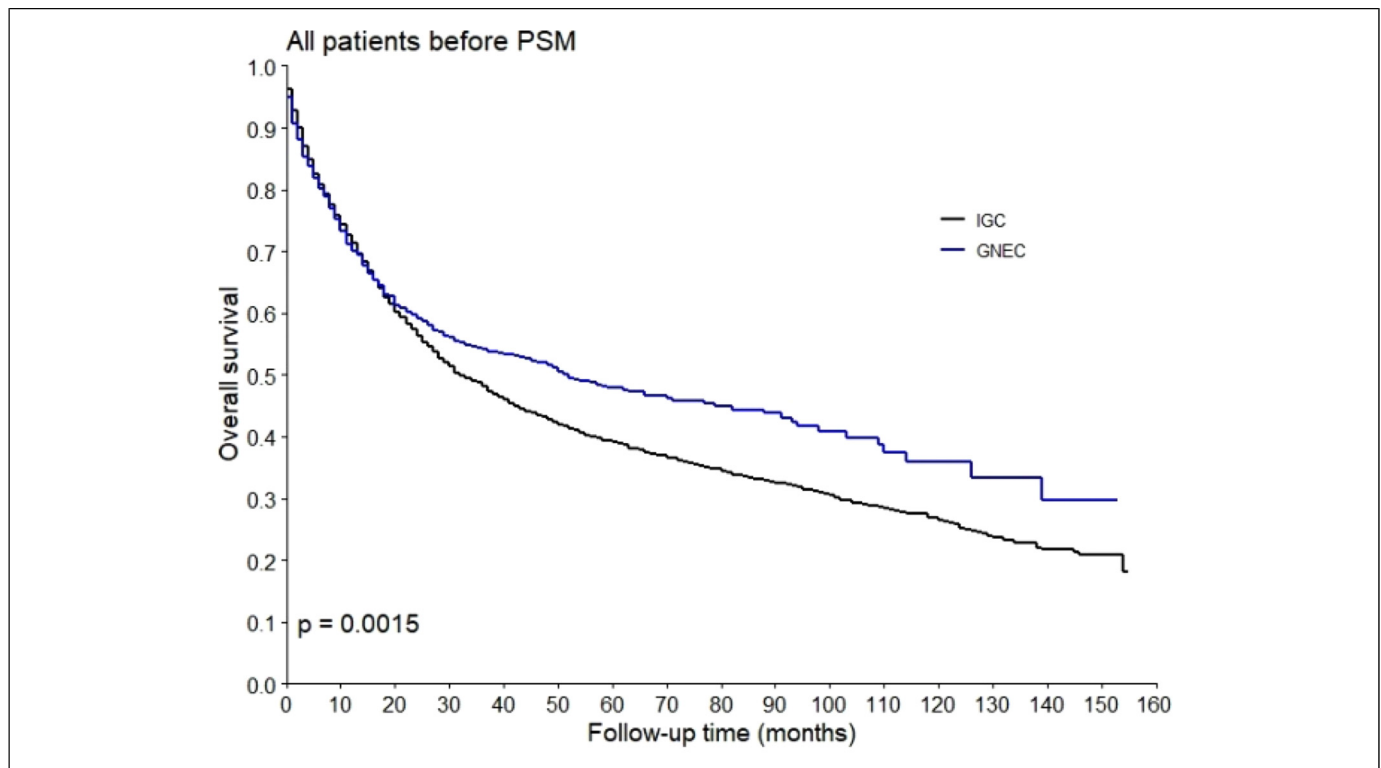
Figure 1. The OS of patients with IGC versus GNEC before PSM, $P < .05$.
Abbreviations: GNEC, neuroendocrine carcinoma; IGC, intestinal-type gastric cancer; OS, overall survival; PSM, propensity-score matching.

nodes (LNs), spread to distant organs, diminishing the hope of curative surgery.[7] The clinical manifestations engendered by cancer metastasis were abdominal distension and belly pain.[8] A previous study has reported that the prognosis of GNEC was worse than that of gastric adenocarcinoma.[9] Tumor size, stage, location, and treatment were significantly associated with the prognosis of GNEC patients.[8] However, the survival differences between GNEC and IGC have not been clarified yet. Understanding these differences is important for prognosis evaluation and tailored treatment strategies.

With the help of the Surveillance, Epidemiology, and End Results (SEER) database, we designed this retrospective case-control study to comprehensively compare the overall survival (OS) of patients with IGC versus GNEC. We aimed to determine the clinicopathological characteristics and survival outcomes of these 2 histological subtypes of GC. We also identified the prognostic factors of GNEC, which may help the doctors to acquire a deeper insight into this rare disease and optimize its therapeutic strategy.

Materials and Methods

Subjects

All the patients were recruited from the Incidence-SEER 18 registries Custom Database (with additional treatment fields), which was submitted in November 2018. We initiated the data collection via SEER*Stat version 8.3.9 software. The patients' information

released by the SEER database is publicly available and completely anonymous, so our study need not informed patient consent. Since the patients cannot be identified, our study was exempt from the review of research ethics board.

Case Selection and Inclusion Criteria

The inclusion criteria were briefed as follows: (1) the year of diagnosis was confined from 2004 to 2015; (2) the primary site was stomach; (3) GC was the first or only cancer diagnosis; (4) the ICD-O-3 (International Classification of Disease for Oncology-3) histology codes were listed below, 8012 to 8013 (large cell carcinoma), 8041 to 8044 (small cell carcinoma), 8244 (mixed adeno-NEC), 8246 (NEC), and 8144 (adenocarcinoma, intestinal type). These subtypes except 8144 were designated as GNEC. Histology code 8144 was regarded as a common reference subtype. The patients with diagnosis from death certificates or autopsy were excluded. We also excluded the cases with unknown table variables.

Table Variables

The patients' clinical variables included year of diagnosis, age at diagnosis, sex, race, tumor size, American Joint Committee on Cancer (AJCC) stage, Tumor, Node, Metastasis (TNM) stage, regional nodes examined, surgery, radiotherapy, chemotherapy, survival months, and vital status recode. Among these variables, age was treated as a triple variable, which was divided into <60,

60 to 80, and >80 years old. Tumor size was categorized as a binary variable: ≤50 mm and >50 mm. Regional nodes examined were divided into 0, 1 to 15, 16 to 29, >29 LNs.

Outcome Evaluation

In this study, OS was our concerned outcome, which was calculated as the period from cancer diagnosis to death by any cause. The patients were censored if they were alive on the date of last follow-up.

Statistical Methods

The entire cohort was dichotomized into IGC and GNEC. As for clinicopathological characteristics between the two comparison groups, categorical variates were analyzed by Chi-square or Fisher exact test. The differences in baseline characteristics between IGC and GNEC patients were adjusted by 1:1 propensity score matching (PSM) analysis. The factors involved in PSM were diagnosis year, age, gender, race, AJCC stage, T/N/M stage, LN examined, surgery, radiotherapy, and chemotherapy. The caliper value in PSM analysis was 0.01. The PSM was completed by R version 4.1.0 with MatchIt package. The survival curves were drawn by Kaplan-Meier (KM) method. The patients' survival differences were evaluated by log-rank test. The prognostic factors possibly associated with OS were identified by Cox proportional hazard models. Subgroup analyses highlighted the survival differences in IGC versus GNEC by univariate Cox regression models. A

Table 2. Comparison of the Patients' Median OS Before PSM (N = 4596).

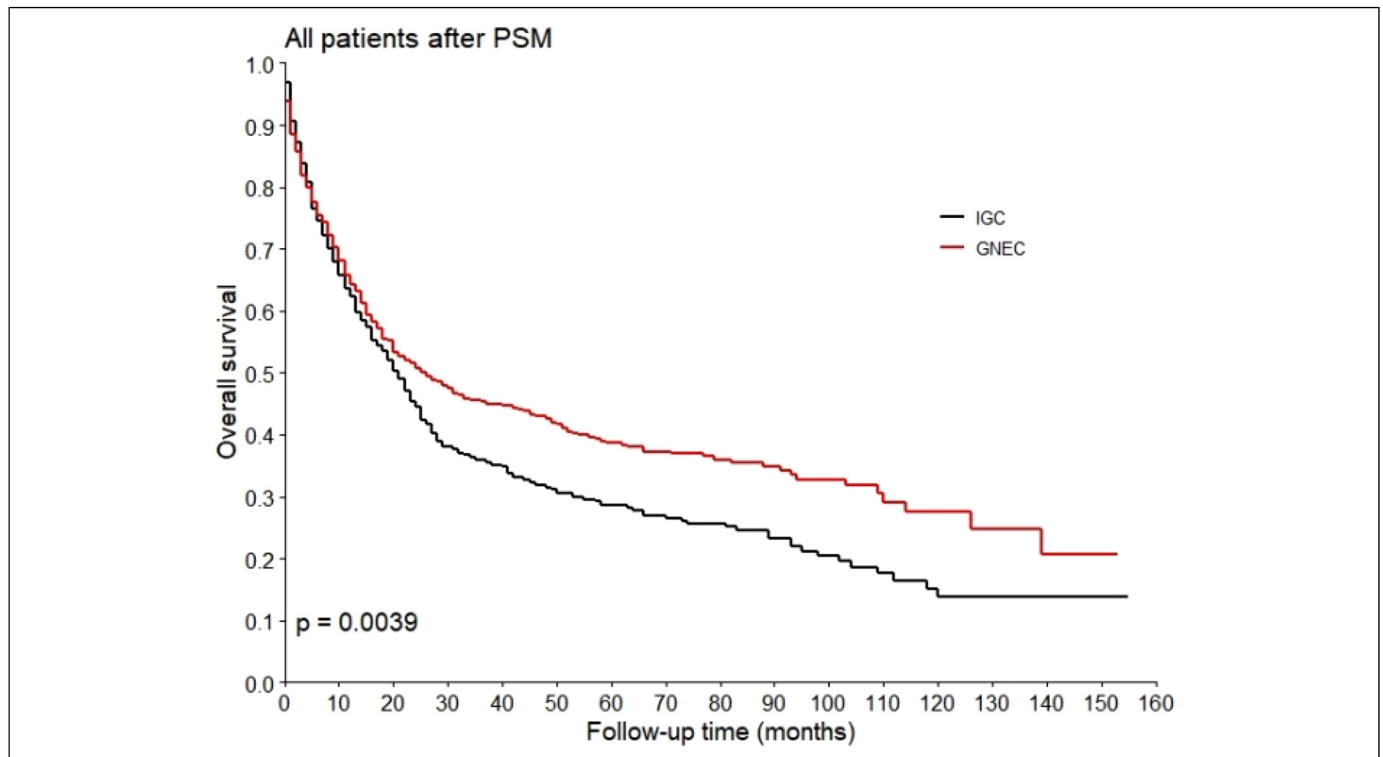| Before PSM	Patients, n	Median OS 95% CI, months
IGC	3943	32 (29.3-34.7)
GNEC	653	52 (33.6-70.4)
P value		.0015

Abbreviations: CI, confidence interval; GNEC, neuroendocrine carcinoma; IGC, intestinal-type gastric cancer; OS, overall survival; PSM, propensity-score matching.

forest plot was produced to indicate the influence of each prognostic factor on the patients' OS. Additional statistics were performed on SPSS version 25.0 software. All statistical tests were 2-sided, and $P < .05$ was deemed statistically significant.

Results

Patient Characteristics

As a whole, 4596 patients were finally collected in our study, including 3943 (85.8%) IGC patients and 653 (14.2%) GNEC patients. In the cohort before PSM, significant differences between IGC and GNEC can be seen in all the variates ($P < .001$) except tumor size ($P = .573$). In demographic statistics, the GNEC patients seem relatively younger (age < 60: 37.7%

Figure 2. The OS of patients with IGC versus GNEC after PSM, $P < .05$.
Abbreviations: GNEC, neuroendocrine carcinoma; IGC, intestinal-type gastric cancer; OS, overall survival; PSM, propensity-score matching.

Table 3. Comparison of the Patients' Median OS After PSM (N = 1002).

| After PSM	Patients, n	Median OS 95% CI, months
IGC	501	21 (17.7-24.3)
GNEC	501	26 (18.3-33.7)
P value		.0039

Abbreviations: CI, confidence interval; GNEC, neuroendocrine carcinoma; IGC, intestinal-type gastric cancer; OS, overall survival; PSM, propensity-score matching.

vs 19.3%), more female (47.5% vs 36.2%), and more white race (76.6% vs 58.3%) than the IGC patients. With respect to tumor features, the GNEC cohort shows more stage I (53.4% vs 43.9%) and stage IV (28.2% vs 21.9%) disease, more T1/4,

N0, M1. Treatments also appear different in IGC versus GNEC groups. LN examined = 0 is significantly higher in GNEC than in IGC group (65.2% vs 22.4%, $P < .001$). Surgery, radiotherapy, and chemotherapy are less frequently used in GNEC than in IGC group. In the cohort after PSM, we achieve a group of 1002 patients, including 501 IGC and 501 GNEC patients. No significant difference in clinical variables is observed between IGC and GNEC in the matched cohort (all $P > .05$). The clinicopathological characteristics of IGC versus GNEC are summarized in Table 1.

Survival Analysis Before PSM

With the cohort before PSM, we compared the survival difference in IGC versus GNEC. The KM plot showed that the OS of GNEC was significantly superior to IGC (Figure 1, $P < .05$).
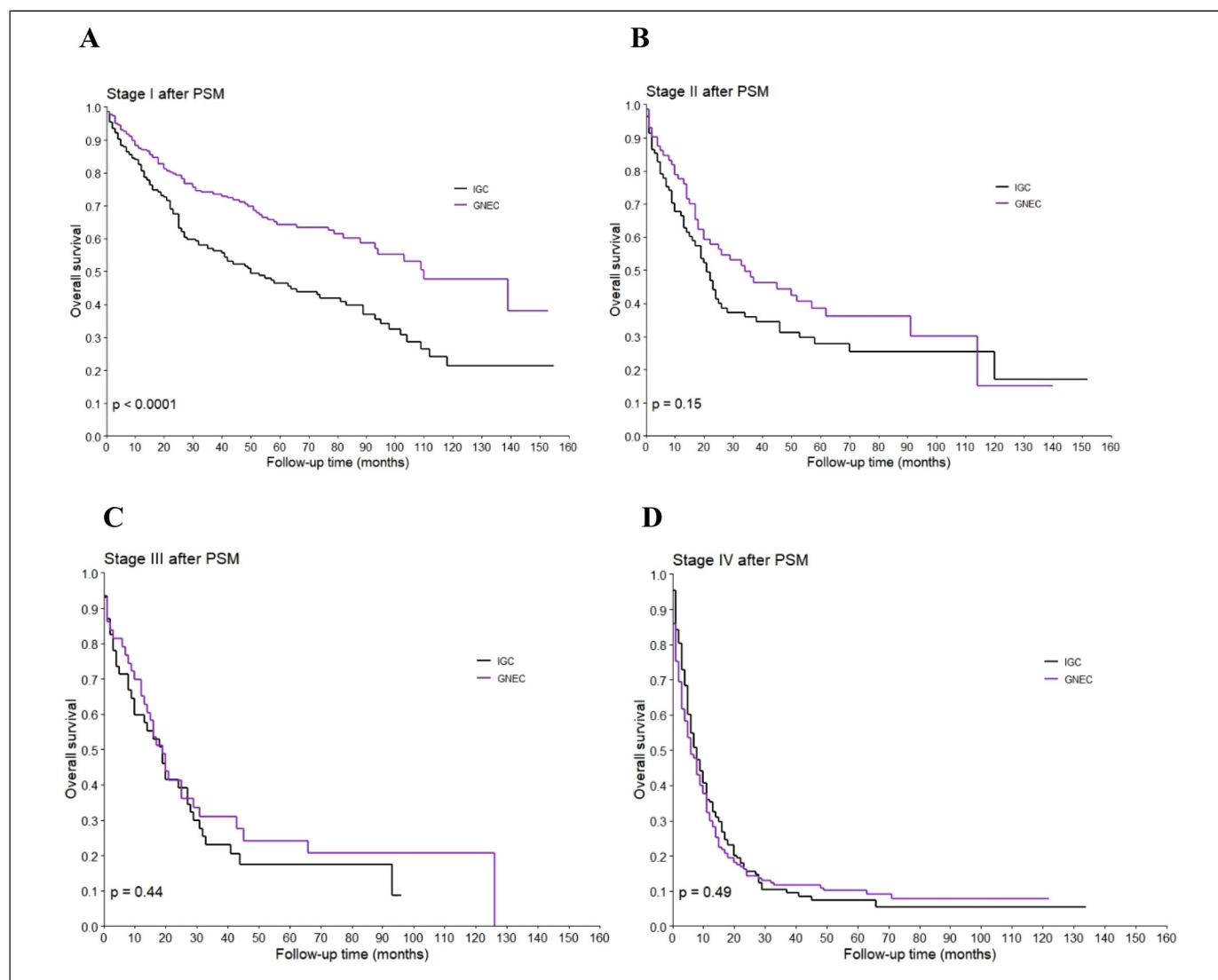
Figure 3. The OS of GNEC versus IGC stratified by Tumor, Node, Metastasis (TNM) stage. (A) stage I: $P < .05$; (B) stage II: $P > .05$; (C) stage III: $P > .05$; (D) stage IV: $P > .05$.
Abbreviations: GNEC, neuroendocrine carcinoma; IGC, intestinal-type gastric cancer; OS, overall survival; PSM, propensity-score matching.
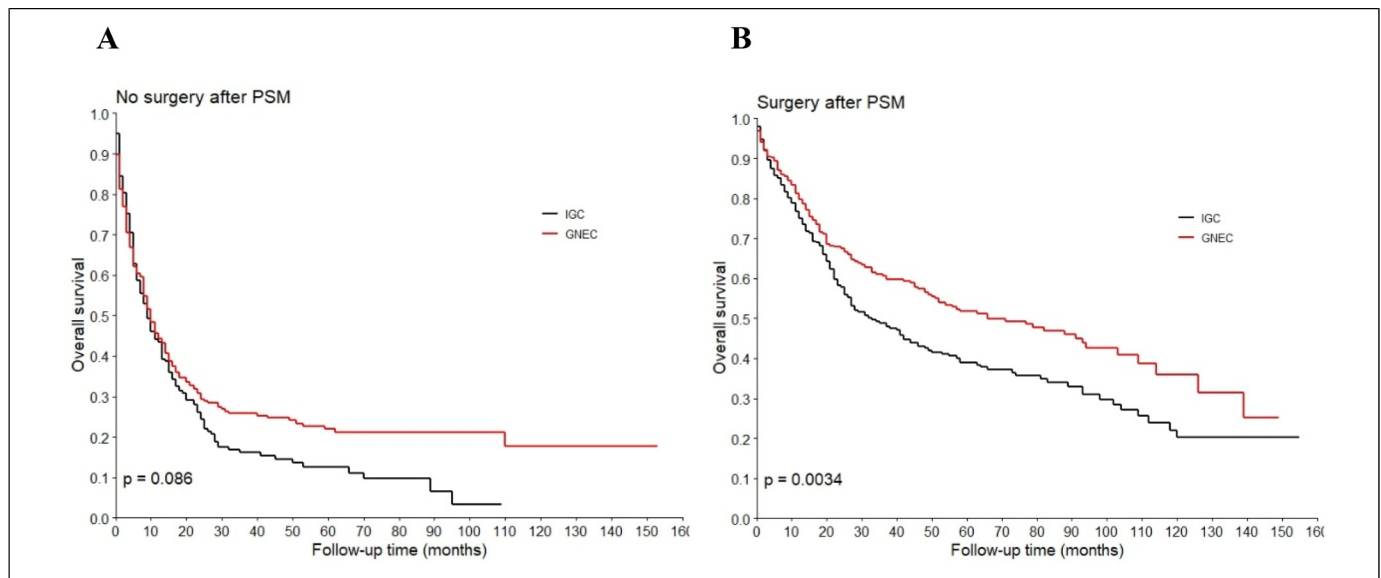
Figure 4. The OS of GNEC versus IGC stratified by surgery. (A) no surgery: $P > .05$; (B) surgery: $P < .05$.
Abbreviations: GNEC, neuroendocrine carcinoma; IGC, intestinal-type gastric cancer; OS, overall survival.

The median OS of GNEC was 52 (33.6-70.4) months, but that of IGC was 32 (29.3-34.7) months (Table 2, $P = .0015$). This result demonstrates that GNEC may have a better survival than IGC in the patients before PSM.

Survival Analysis After PSM

The 1:1 PSM was used to reduce the baseline differences in clinicopathological characteristics between the 2 histologic subtypes. All confounding factors were well-balanced between the 2 comparison groups after PSM. The KM plot indicated that difference of OS in IGC versus GNEC was still significant after PSM ($P < .05$, Figure 2). To be concrete, the median OS was 21 (17.7-24.3) months in IGC versus 26 (18.3-33.7) months in GNEC (Table 3, $P = .0039$). Apparently, GNEC showed a superior prognosis to IGC histology after PSM analysis.

Stratified Analysis by TNM Stage

A stratified analysis by stage would make the OS comparison in IGC versus GNEC more specific. We initiated further subgroup analysis with the matched cohort according to the TNM stage. The survival curve presented that OS of GNEC was significantly superior to that of IGC only in stage I patients ($P < .05$). By contrast, no significant survival difference was found between GNEC and IGC patients in stage II–IV ($P > .05$). Hence the prognosis of GNEC seemed better than IGC only in stage I patients. The KM plots of OS comparison in IGC versus GNEC stratified by TNM stage are displayed in Figure 3.

Stratified Analysis by Surgery

Given patients receiving surgery and those not receiving surgery were analyzed together, but analyzing them separately might be more appropriate, because surgery was the only way to cure GC, so we initiated the stratified analysis by surgery. As illustrated in the KM plots below, the survival curve of GNEC was not significantly different from IGC in the cohort not receiving surgery after PSM (Figure 4A, $P > .05$). By contrast, the OS of GNEC was significantly better than IGC in the cohort receiving surgery after PSM (Figure 4B, $P < .05$). Obviously, GNEC presented a superior survival to IGC in the patients who received surgery.

Subgroup Analyses by Forest Plot

We produced a forest plot to demonstrate the more vivid subgroup analyses. It revealed that in some subgroups, such as TNM stage I, T1, N0, M0, LN examined = 0 to 15, receiving surgery, no radiotherapy, no/unknown chemotherapy, the GNEC showed a significantly better OS than IGC in the patients after PSM (hazard ratio [HR] <1, $P < .05$). These results suggest that GNEC subtype may become a positive prognostic indicator for survival in patients with these features. The forest plot of subgroup analysis is available in our supplementary file.

Identify Prognostic Factors for Patients With GNEC

To further investigate the possible variables associated with the OS of GNEC patients, we adopted univariate and multivariate Cox regression models to identify prognostic factors. In univariate Cox regression analysis, except race, LN examined, and radiotherapy ($P > .05$), all other variables were significantly associated with the OS of these patients ($P < .05$). In multivariate Cox regression analysis, age ≥ 60, tumor size > 50 mm, stage II-IV, T2, and N3 were identified as independent adverse prognostic factors (HR > 1, $P < .05$). By contrast, year 2010 to 2015, female, and surgery were independent protective factors for favorable prognosis (HR < 1, $P < .05$). The detailed results of prognostic factors were listed in Table 4.

Table 4. Cox Proportional Hazards Regression Models for OS of the GNEC Patients (N = 653).

Characteristics	Univariate Cox		Multivariate Cox	
	HR (95% CI)	P value	HR (95% CI)	P value
Diagnosis year				
2004 to 2009	Reference		Reference	
2010 to 2015	0.641 (0.515-0.799)	<.001	0.721 (0.572-0.908)	.005
Age (y)				
<60	Reference		Reference	
60 to 80	1.748 (1.364-2.24)	<.001	1.522 (1.175-1.972)	.001
>80	3.34 (2.383-4.68)	<.001	2.284 (1.601-3.261)	<.001
Gender				
Male	Reference		Reference	
Female	0.482 (0.385-0.603)	<.001	0.574 (0.451-0.731)	<.001
Race				
White	Reference		Reference	
Black	1.041 (0.772-1.402)	.794	1.094 (0.801-1.496)	.571
Others	1.134 (0.767-1.675)	.529	1.318 (0.876-1.982)	.185
Tumor size (mm)				
≤50	Reference		Reference	
>50	2.346 (1.881-2.926)	<.001	1.389 (1.09-1.77)	.008
Stage				
I	Reference		Reference	
II	2.919 (2.042-4.174)	<.001	2.08 (1.271-3.406)	.004
III	4.583 (3.086-6.805)	<.001	3.57 (2.023-6.298)	<.001
IV	9.064 (6.949-11.824)	<.001	3.807 (1.714-8.455)	.001
Tumor depth				
T1	Reference		Reference	
T2	1.882 (1.456-2.433)	<.001	1.562 (1.12-2.18)	.009
T3	2.573 (1.786-3.709)	<.001	1.052 (0.659-1.68)	.832
T4	4.869 (3.574-6.632)	<.001	1.265 (0.856-1.87)	.238
LN metastasis				
N0	Reference		Reference	
N1	2.486 (1.984-3.116)	<.001	1.181 (0.879-1.586)	.27
N2	3.542 (2.303-5.446)	<.001	1.163 (0.654-2.069)	.608
N3	11.066 (4.052-30.224)	<.001	5.641 (1.765-18.023)	.004
Distant metastasis				
M0	Reference		Reference	
M1	5.789 (4.62-7.253)	<.001	1.593 (0.805-3.149)	.181
LN examined				
0	Reference		Reference	
1 to 15	0.898 (0.687-1.174)	.431	0.822 (0.549-1.23)	.34
16 to 29	1.275 (0.883-1.84)	.196	1.011 (0.595-1.717)	.969
>29	1.051 (0.664-1.663)	.832	0.751 (0.444-1.271)	.286
Surgery				
No	Reference		Reference	
Yes	0.315 (0.254-0.392)	<.001	0.455 (0.323-0.64)	<.001
Radiotherapy				
No	Reference		Reference	
Yes	1.201 (0.805-1.792)	.37	1.384 (0.872-2.194)	.168
Chemotherapy				
No	Reference		Reference	
Yes	2.674 (2.148-3.328)	<.001	0.827 (0.624-1.098)	.189

Abbreviations: CI, confidence interval; GNEC, neuroendocrine carcinoma; HR, hazard ratio; OS, overall survival; LN, lymph node.

Discussion

At present, due to the rarity and high heterogeneity of neoplasms, the clinical features and prognosis of GNEC still remain poorly understood.[10] Luckily, the SEER database has provided a sufficient number of patients with rare cancers for us to clarify this issue. In this study, we retrospectively analyzed the clinicopathological features and OS of 653 GNEC patients, and compared with 3943 IGC patients. Our results suggest that GNEC patients have distinct clinical characteristics and are more likely to involve the younger female white race. After balancing the baseline characteristics

in IGC versus GNEC patients by PSM, the OS of GNEC is superior to that of IGC. The subgroup survival analyses also indicate that GNEC has a superior prognosis to IGC in early stage patients. The Cox regression analyses have identified several independent prognostic factors associated with the OS of those GNEC patients.

The clinical characteristics and survival outcomes of GNEC and IGC have been investigated by some previous studies. A research group has initiated a separate analysis of 2546 patients with high-grade gastrointestinal NEC. Their median survival was 38 (31-45) months for localized cancer, and 5 months (95% CI, 4.7-5.4 months) for M1 stage patients.[6] But this study was not specifically targeting GNEC. To be further, the Ishida's research investigated the prognosis of 51 GNEC cases. The median OS was 21 months, and the 5-year survival rate was 10.0% for such patients underwent palliative resection.[11] However, the power of analysis in this study is limited by its small sample size, significant bias from confounders, and inadequate follow-up. Regarding the survival outcome of IGC patients, a recent study has collected 4376 such patients from the SEER database. In its results, the mean survival time for early IGC was 62 months.[12] Comparatively, our study has extracted a large sample size from the SEER database. We have comprehensively compared the OS of GNEC with IGC. In the cohort after PSM, the median OS is 21 (17.7-24.3) months in IGC versus 26 (18.3-33.7) months in GNEC, $P <$ .05. Thus, GNEC may have a superior prognosis to IGC according to our PSM analysis.

Although the KM plot of matched cohort indicates that GNEC has a superior prognosis to IGC, the tumor stage may well affect the survival difference between the 2 comparison groups. A recent study has revealed an increased risk of cancer relapse and death from GC with increasing tumor stage.[13] In our study, GNEC displays a superior survival to IGC in stage I patients. However, the survival difference becomes insignificant in stage II-IV patients. Furthermore, we also stratified the survival differences between GNEC and IGC by surgery. In the results, GNEC presented a significantly better OS than IGC in the patients who received surgery. So surgery should be recommended for the patients with early stage GNEC.

With regard to the prognostic factors for GNEC, a latest study has explored the recent epidemiological trends of this disease, and also established a nomogram to evaluate the prognosis of such patients. In the results, grade, T, and N staging were significantly related to the survival of GNEC.[14] Concordantly, our Cox regression analyses have also identified older age, large tumor size, and advanced TNM stage as independent risk factors for OS in GNEC. The patients with these risk factors should be of great concern. On the other hand, another recent report has retrospectively investigated the clinical data of 132 Chinese patients with GNEC, in order to characterize the potential factors affecting their prognosis. Its survival analyses of those patients revealed that tumor size, N stage, mitotic index, radical surgery, and adjuvant chemotherapy were independent predictors for the patients' survival.[15]

Particularly, the patients who received radical resection showed the best prognosis in GNEC.[15] Consistent with this report, our study has also identified surgery as an independent protective factors for the GNEC patients. Hence our study further supports the recommendation of surgery for these patients.

There are some limitations in our study. First, this is a retrospective study with inherent selection bias, the clinical characteristics are quite different in the 2 comparison groups.[16] So we have used the PSM analysis to lessen the baseline differences from nonrandom assignments. Second, given the heterogeneity of GNEC, its prognosis is also significantly impacted by the clinical settings.[17] Regrettably, the current SEER database is lack of some crucial data which are "neuroendocrine cancer-specific." The staging according with the specific staging system, the Ki67 value and other features (systemic medical treatments) cannot be retrieved by the SEER database. Third, even after PSM, some latent variables in clinicopathological features of different patients may also engender cryptic bias.[18]

To the best of our knowledge, this is the first large population-based study to analyze the clinicopathological characteristics and prognosis in IGC versus GNEC patients. Our major strength lies in a large sample size, rigorous inclusion criteria, and PSM to minimize the nonrandom bias, highlighting the prognostic factors of GNEC.

Conclusion

The present study has demonstrated that GNEC differs significantly from IGC with respect to clinicopathological features. After PSM analysis, GNEC showed a superior survival to IGC in early stage patients. The prognostic factors identified in our study may assist the clinicians to more individually treat these patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

Ethics Statement

The SEER data contain no identifiers and are publicly available, so ethical approval was exempt for our study.

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