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The Impact of Surgery and Survival Prediction in Patients with Gastroenteropancreatic Neuroendocrine Tumors: A population-based cohort study

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CRediT authorship contribution statement
Zenghong Wu: Methodology, Formal analysis, Writing – original draft. Weijun Wang: Methodology, Formal analysis, Writing – original draft. Kun Zhang: Methodology, Formal analysis, Writing – original draft. Mengke Fan: provided design improvement, administrative and material support, Supervision. Rong Lin: provided design improvement, administrative and material support, Supervision.

Data availability statement
All data used in this study can be freely accessed from the SEER program (https://seer.cancer.gov/).

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The authors verify that all information and materials in the manuscript are original.

Data availability statement

All data used in this study can be freely accessed from the SEER program (https://seer.cancer.gov/).

- This study aimed to analysis the impact of surgery treatment in patients with gastroenteropancreatic neuroendocrine tumors.
- The overall survival of patients was not significant after rectum and small intestine surgery.
- There was a significant difference in overall survival after colon, pancreas, and stomach surgery on the patients.
- Metastatic patients treated with surgery did not improve their overall survival after surgery.

Abstract

Objective

This study aimed at assessing the impact of surgical treatments in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

Methods

A propensity score-matched (PSM) analysis based on data in the Surveillance, Epidemiology, and End Results (SEER) database was used to assess the efficacy of surgical treatment in patients with GEP-NETs.

Results

A total of 7,515 patients diagnosed with GEP-NETs from 2004 to 2015 were evaluated from the SEER database. There were 1,483 patients in the surgery group and 6,032 patients in the non-surgery group. Compared with patients in the surgery group, patients in the non-surgery group were inclined to receive chemotherapy (50.8 % vs. 16.7 %) and radiation (12.9 % vs. 3.7 %) as treatment options. Multivariate Cox regression analysis revealed higher rates of overall survival (OS) outcomes for GEP-NETs patients who had been subjected to surgery (hazard ratio (HR) = 0.483, 95%CI = 0.439-0.533, $p < 0.001$). Then, to reduce the impact of bias, a 1:1 PSM analysis was performed for the two groups of patients. A total of 1760 patients were assessed and each subgroup included 880 patients. In the matched population, the patients exhibited the ability to significantly benefit from surgery (HR = 0.455, 95%CI = 0.439-0.533, $p < 0.001$). The OS outcomes for radiation or chemotherapy patients who had been treated with surgery were better that those of patients who had not been treated with surgery ($p < 0.001$). In addition, it was found that the OS of patients was not significant after rectum and small intestine surgery whereas there was a significant difference in OS after colon, pancreas, and stomach surgery on the patients. Patients who had been subjected to surgery in the rectum and small intestines exhibited better therapeutic benefits.

Conclusion

Patients with GEP-NETs who are treated with surgery have better OS outcomes. Therefore, surgery is recommended for specified selected patients with metastatic GEP-NETs.

Keywords: Gastroenteropancreatic neuroendocrine tumors, SEER, propensity score matching, overall survival, surgery

Background

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous class of rare tumors that originate from the diffuse neuroendocrine system of the pancreas and gastrointestinal tract. According to the 2019 World Health Organization (WHO) classification, GEP-NETS are categorized on the basis of Ki-67 proliferation index, the primary tumor site, cell type, molecular genetic markers, and tumor differentiation.

The GEP-NETs are classified as well differentiated NETs: NET G1 (Ki-67< 3 %), NET G2 (Ki-67 3-20 %), NET G3 (Ki-67>20 %) and poorly differentiated neuroendocrine tumor carcinoma (NEC), all with Ki-67 proliferation index > 20 %[1]. Globally, there has been a steady increase in annual incidences of GEP-NETs [2], whose aggressive nature is associated with poor prognostic outcomes[3]. Even though the increased incidence may be due to improved detection and an aging population, there are other unknown contributing factors[4]. In the last few decades, the overall survival outcomes for patients with NETs have also improved. Resection of the primary tumor in metastatic GEP-NETs is still an ongoing discussion. Due to progression or intolerance to chemotherapy regimens, the available treatment options for patients with advanced GEP-NETs are often limited, therefore, combination immunotherapy is recommended for such patients[5]. For localized, non-metastatic disease, and advanced cancer patients at initial diagnosis, surgical intervention is the next best option to systemic chemotherapy, with a 5-year survival rate of 57 % for G3 GEP-NETs, and 5.2 % for small-cell tumors[6]. Surgery can be curative in patients with localized disease, even with regional lymph node disease[7]. Therefore, surgery should be considered for all patients with regional and localized GEP-NETs, but not for esophageal primaries. Overall survival (OS) outcomes are better in patients who are subjected to a combination of surgery and chemotherapy, compared with patients who are subjected to chemotherapy + radiotherapy[8].

Deng *et al.*[9] collected clinicopathological data on patients with consecutive limited disease stage esophageal NEC who underwent esophagectomy with regional lymphadenectomy and found that prognosis of the patients was not significantly improved. However, the optimal treatment option for localized disease has not been fully established. Treatment choices in metastatic disease consist of liver surgery and/or locoregional as well as ablative therapies[10]. In 2010, the North American Society for Neuro Endocrine tumors (NANETS) recommended deviation from surgery for patients with metastatic disease to surgery for patients with local and regional diseases, and even specified radical resection for patients with metastatic diseases. The efficacies of surgery in different lymph node stages, different age groups, as well as clinical stages have not been fully established. There is need for high quality registered large sample size surgical data based on updated pathological classification and modern radiological staging to determine the benefits of primary resection according to primary site and staging. The probable advantages of metastatic surgery should also be confirmed. In this study, using data in Surveillance, Epidemiology, and End Results (SEER) database, we analyzed the efficacy of surgical

treatments in patients with GEP-NETs using a propensity score-matched (PSM) analysis.

Methods

Patients

Patients with GEP-NETs were identified from the SEER-13 registry database (1992-2018) with additional treatment data from the SEER-18 registry database (1975-2016) using NCI's SEER*Stat software (version 8.3.9). Histologic codes from the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), and site codes were used to examine patients with GEP-NETs, as previously reported. Based on histology, patients with GEP-NETs were diagnosed as merely primary malignancy. The TNM staging data were retrieved according to the following codes: Derived AJCC Stage Group, 6th Ed. (2004-2015), Derived AJCC T, 6th Ed. (2004-2015), Derived AJCC N, 6th Ed. (2004-2015), and Derived AJCC M, 6th Ed. (2004-2015). Diagnostic information could only be obtained from death certificates or autopsy reports, however, patients who had died within 1 month after the initial diagnosis were excluded from this study. Surgical procedures were performed to the primary site. Primary site surgery describes a surgical procedure that removes and/or destroys primary site tissues performed as part of the initial work-up or first course of therapy. Patients with unknown pathology before surgery were excluded from this study. The requirement for ethical approval was waived by the institutional review committee because the SEER database is freely available to global researchers. This population-based cohort study has been reported in line with the STROCSS criteria[11], Supplemental Digital Content 1, http://links.lww.com/JS9/A408 .

Study Variables

Variables such as age (from 20-24 to 85+ years), sex (female, male), race (white, black, and others (American Indian/AK Native, Asian/Pacific Islander)), tumor size (reclassified as ≤ 20, 21-40, and ≥ 41mm), SEER stage, pathology, histologic grade, surgery, radiotherapy, chemotherapy, survival months, and vital status for individual patients were extracted from the SEER database. The SEER historic stage A (1973-2015) was used for GEP-NETs staging: localized, regional, unstaged, and distant. Therapy classifications such as chemotherapy, surgery, and radiotherapy were obtained from SEER-specific records. Surgery was chosen using the SEER code "Reason no cancer-direct surgery", whereas radiotherapy and chemotherapy were assessed using "radiation recode" and "chemotherapy recode" in SEER. For tumor categories, the SEER categories scheme systematically classified the subjects into four grades: grade 1 with high discrimination (G1), moderately differentiated (G2), poorly differentiated (G3), and undifferentiated or anaplastic (G4). The site recode ICD-O-3/WHO 2008 information was used to filter patients by tumor location, including the appendix, ascending colon, cecum, descending colon, hepatic flexure,

large intestines, pancreas, rectosigmoid junction, rectum, sigmoid colon, small intestines, splenic flexure, stomach, and transverse colon. Age was reclassified as ≤ 30, 31-60, and ≥ 61 years whereas the OS outcomes were defined as the primary endpoints of this study.

Statistical Analysis

The t test or chi-square test were used to compare the basic clinical characteristics of patients in surgery and non-surgery groups. Cox multivariable regression was performed to analyze the relationships between variables with OS by calculating hazard ratios (HRs) and 95% CIs. Clinicopathologic characteristics of patient survival were analyzed by the Kaplan–Meier curve and compared using the log-rank test. To reduce the impact of baseline differences in demographic and clinical characteristics on the outcomes, the 1:1 propensity score matching (PSM) method was used to match the patients in the surgery and non-surgery groups. The PSM method confirms background differences by standardized differences. The basic principle of the propensity score is to replace multiple covariates with one score to balance the distribution of covariates between the treatment and control groups. To reduce selection bias, the confounding factors in non-randomized studies were balanced in a manner similar to randomization. The matching factors included sex, age, race, tumor location, SEER stage, tumor stage, TNM, grade, chemotherapy and radiation. The ratio value was 1 while caliper value was 0.02. Cox multivariable regression analyses were conducted using SPSS, version 23 (IBM Corp) whereas OS analyses were conducted using GraphPad Prism 8 XML project. For each analysis, $p \leq 0.05$ was the threshold for significance.

Results

Patient Characteristics

A total of 7,515 patients with GEP-NETs diagnosed between 2004 and 2015 were assessed from the SEER database. There were 1,483 patients in the non-surgery group and 6,032 patients in the surgery group (**Table 1**). Differences in characteristics between the two groups (surgery and non-surgery), including age, tumor location, SEER historic stage, chemotherapy, AJCC stage, TNM, grade, radiation, and tumor size were significant. Patients in the non-surgery group presented a higher proportion of tumor location (pancreas, 45.7 % vs. 24.8 %, $p < 0.001$; stomach, 17.3 % vs. 6.8 %, $p < 0.001$), SEER historic stage (distant, 73.2 % vs. 26.1 %, $p < 0.001$), AJCC stage (IV, 71.6 % vs. 23.4 %, $p < 0.001$), M (M1, 71.3 % vs. 23.3 %, $p < 0.001$), and CS tumor size (≥ 41, 69.6 % vs. 31.4 %, $p < 0.001$). Moreover, patients in the non-surgery group were more inclined to receive chemotherapy (50.8 % vs. 16.7 %) and radiation (12.9 % vs. 3.7 %), compared to those in the surgery group.

Comparisons of Survival Outcomes between Surgery Group and No-surgery

Group

Univariate analysis revealed that sex, age, race, tumor location, SEER historic stage, pathology type, TNM, stage, surgery, radiation, chemotherapy, and CS tumor size were significantly associated with OS outcomes. Further, all the significant factors from the multivariate Cox analysis were incorporated into the Cox regression model. After the interventional procedures, patients with GEP-NETs exhibited higher overall survival rates (HR = 0.483, 95% CI = 0.439-0.533, $p < 0.001$) (**Table 2**). The 1:1 PSM analysis was also performed between the groups of patients to reduce the impact of bias. The factors applied for PSM analysis based on significant *p*-values from univariate analysis are shown in **Table 2**. Ultimately, 1760 patients were assessed and each subgroup included 880 patients. The *p* values for all covariates were greater than 0.05, indicating that propensity scores for the two groups significantly overlapped (**Table 3)**. Multivariate analysis of propensity score-matched groups showed that sex, age, tumor location, stage, grade, and chemotherapy were significantly associated with OS (**Table 4**). Matched population analysis showed that patients could derive significant benefits from surgery (HR = 0.455, 95%CI = 0.439-0.533, $p < 0.001$). To establish the effects of surgery on GEP-NETs patients in different subgroups, the patients were stratified by particular clinical characteristics.

Subgroup Analysis after PSM

To assess the effects of surgery in patients at different stages, patients were assigned into stages I, II, III, and IV. The OS outcomes were as shown in **Figure 1A-1D** and **Table 5**. Surgery was associated with reduced risk of mortality in stage I (HR = 0.366, 95%CI = 0.246-0.545, $p < 0.001$), stage II (HR = 0.358, 95%CI = 0.233-0.551, $p < 0.001$), stage III (HR = 0.331, 95%CI = 0.185-0.592, $p < 0.001$), and stage IV (HR = 0.503, 95%CI = 0.431-0.588, $p < 0.001$). Moreover, surgery was associated with a low risk of mortality in grade I (HR = 0.484, 95%CI = 0.378-0.620, $p < 0.001$), grade III (HR = 0.448, 95%CI = 0.367-0.548, $p < 0.001$), and grade IV (HR = 0.379, 95%CI = 0.266-0.540, $p < 0.001$), however, surgery was not an independent prognostic factor for patients in grade II (**Figure 1E-1H; Table 6**). The OS outcomes for patients that had been subjected to radiation or chemotherapy and who had been treated with surgery was better than that of patients that had not been subjected to surgery ($p < 0.001$). The metastatic patients that had been treated with surgery did not exhibit marked improvements in their OS outcomes, therefore, surgery for patients with metastatic GEP-NETs should be done with caution (**Figure 2**). Then, we conducted subgroup analyses based on different tumor types. There were significant differences in colon, pancreas, and stomach surgery patients, indicating that the surgical procedures led to good prognosis (**Figure S1**, Supplemental Digital Content 2, http://links.lww.com/JS9/A409**)**. Prognostic differences between patients that had been subjected to rectum and small intestine surgery were insignificant, however, they showed a trend of benefitting from surgery.

Discussion

Accurate assessment of the prognosis of GEP-NETs remains a challenge because of its rarity. Further, its treatment is a complex and inconsistent process that results in unpredictability of prognostic factors and optimal treatment. The SEER database provides researchers with a large sample size to identify factors that are related to survival of patients, with a greater statistical power in studies of rare tumors, especially when using surgery, radiation, and chemotherapy data. In this study, the PSM and multivariable regression analyses revealed that surgery improves OS for GEP-NETs patients.

Studies have reported on the advantages of surgical resection in localized and locoregional disease, however, the role of surgical resection in patients with various neuroendocrine tumor types have yet to be reported. Ishida *et al.*[12] assessed the prognosis of 51 cases of gastric NEC and found that curative surgery is the sole independent prognostic factor. Similarly, another study assessed the role of surgery for high-grade pancreatic neuroendocrine carcinoma (hgPNEC) patients in a large Nordic multicenter cohort and indicated that surgery improved their survival rate, therefore, patients with metastatic hgPNEC and localized hgPNEC should be subjected to radical surgical treatment[13]. However, surgery is not recommended in some cases. A different study analyzed data for 199 esophageal small cell carcinoma (SCC) patients and found that the survival rate was better in patients who had been subjected to systemic treatment[14]. Surgery, particularly in the presence of metastatic disease, may not provide a survival advantage for most high-grade neuroendocrine carcinoma patients with colon and rectum diseases[15]. For the specified selected patients with metastatic GEP-NETs, surgery may be advantageous. For GEP-NETs with extensive hepatic metastases, liver-directed surgery was associated with prolonged survival outcomes[16]. Meanwhile, it is essential in drug development efforts and a multidisciplinary treatment approach for patients who are not candidates for surgical debulking[17,18]. The lack of data on the significance of surgical interventions is also mirrored in consensus guidelines. Therefore, multimodal treatments combined with chemotherapy and/or radiotherapy are recommended to reduce the risks of distant and local recurrence, respectively. In 2010, the recommendations of NANETS changed from surgery for patients with metastatic diseases to surgery for patients with all local and regional diseases in extrapulmonary neuroendocrine carcinomas[19]. However, the European Neuroendocrine Tumor Society (ENETS) guidelines recommend surgery of primary tumors (except stage III esophageal cancer)[20]. The National comprehensive cancer network (NCCN) recommends adjuvant chemotherapy + radical surgery for resectable lesions, chemotherapy + locoregional radiation therapy for locoregional unresectable, and chemotherapy as well as radiotherapy for selected distant metastasis sites[21].

The current steady increase in incidences of GEP-NETs may be attributed to increased cross-sectional imaging, routine monitoring, as well as endoscopic examination in clinical practice. Furthermore, it may be attributed to improvement of naming and classification of these diseases [22]. High-resolution endoscopy and advanced

radiological imaging techniques have resulted in a shift in discovery towards small-sized (≤10 mm) gastrointestinal NETs/carcinoids. Endoscopic resection is the preferred treatment approach for stomach, duodenum (despite gastrinoma) and rectum that are ≤10 mm in size, without infiltrates of muscularis propria (T1) and no vascular infiltrations (V0, L0), whereas small tumor sizes (≤ 1 cm) in the jejunum or ileum must be removed by lymph node dissection[23]. Therefore, endoscopic resection should strictly follow the indications, especially in digestive system tumors. Resection of the primary focus can improve the prognosis of low-grade metastatic NET patients[24]. Treatment options for G3 NET and NEC have not been fully established. The available treatment methods for GEP-NETs G3 include surgery, chemotherapy, neoadjuvant therapy, targeted therapy, somatostatin analogs (SSAs), peptide receptor radionuclide therapy (PRRT), and immunotherapy[25]. Treatment depends on the primary tumor site and status of metastatic organs. A previous study compared the effects of surgical treatments on pancreatic NETs G3 and NECs. It was found that OS outcomes for patients with NET-G3 were significantly better when compared with those of NEC patients[26]. Surgery with radical intent might be an effective choice for patients with GEP-NETs G3 and with locoregional disease, particularly with Ki67 value ≤ 55 %[27]. In pancreatic NEC, patients with NET G3 should probably receive the same approach to surgery of the primary and metastatic disease as NET G2 patients[28]. Tierney *et al*. showed that primary GEP-NET resection is associated with prolonged survival outcomes[29]. In this study, patients with GEP-NETs who were treated with surgery exhibited better OS outcomes and surgery was also recommended for specified selected patients with metastatic GEP-NETs.

This study has some limitations. First, data on various surgical aspects, such as surgical approach and time were unavailable from the SEER database. Second, the Ki-67 and mitotic index factors, which are key for tumor classification in the SEER database, were not considered in tumor classification in this study. Furthermore, several important prognostic factors, such as relapse free survival, microvascular invasion, vascular resection performed, R0/R1 resection, antitumor immune responses, organ-specific and peptide receptor radionuclide therapy were not taken into consideration in this study. Surgical procedures for neuroendocrine tumors, such as radical resection, volume reduction, and palliative resection have various meanings. Due to limited data, the procedures were not assessed in this study, which may have resulted in bias. There are differences in the nature of surgery, such as obstruction or bleeding, curative resection, palliation, or unmeasured confounders, which may cause bias when used in PSM. Finally, since guidelines and pathology assessments have changed over time, it is unclear what the effects of treatment changes were in our study groups, which should be investigated further. Finally, the SEER database did not offer data on comorbidity, therefore, we could not assess the effects of comorbidity on OS outcomes, which may result in bias.

Conclusion

Patients with GEP-NETs who had been treated with surgery exhibited better OS

outcomes and surgery is also suitable for the specified selected patients with metastatic GEP-NETs.

Provenance and peer review
Not commissioned, externally peer-reviewed.

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Figure 1: Overall survival analysis of GEP-NETs patients in different stages and grades. A. Stage I; B. Stage II; C. Stage III; D, Stage IV; E. Grade I; F. Grade II; G, Grade III; H. Grade IV.

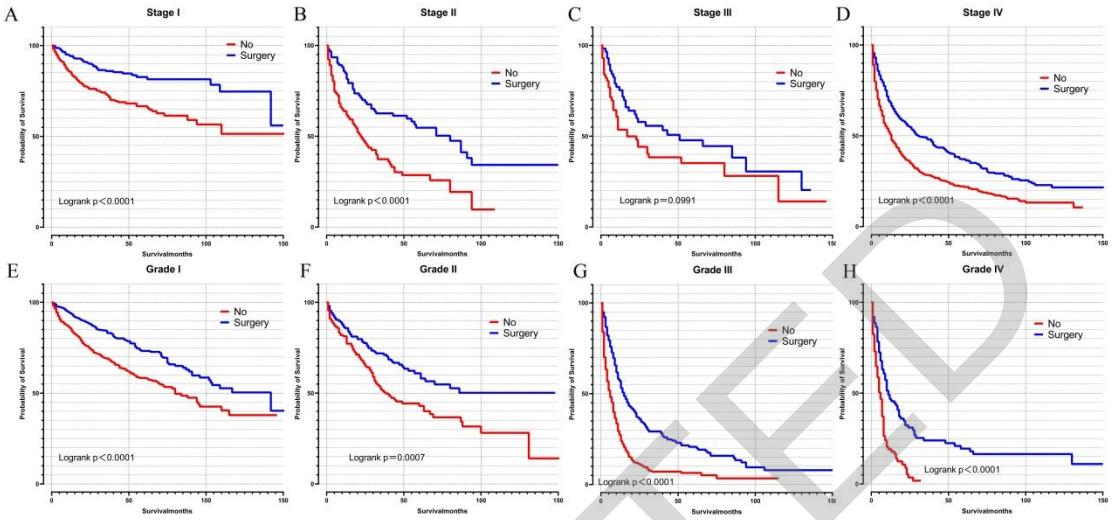

Figure 2: Overall survival analysis of GEP-NETs patients in different subgroups. A. Radiation; B. Chemotherapy; C. Metastasis.

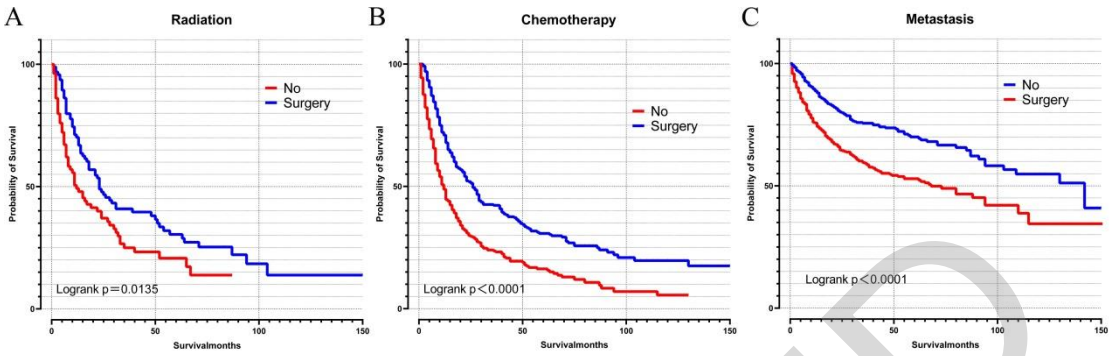

Table 1: Demographic and clinicopathological characteristics of patients in surgery and non-surgery groups before propensity score matching
Table 2: Univariate and multivariate Cox regression analyses for overall survival of the GEP-NETs patients before propensity score matching
Table 3: Demographic and clinicopathological characteristics of patient's surgery and non-surgery groups after propensity score matching
Table 4: Multivariate Cox regression analysis for overall survival of GEP-NETs patients after propensity score matching
Table 5: Comparisons of overall survival outcomes between stage-matched patients in surgery and non-surgery groups
Table 6: Comparisons of overall survival between grade-matched patients in surgery and non-surgery groups

Table 1: Demographic and clinicopathological characteristics of patients in surgery and non-surgery groups before propensity score matching

Items	No-Surgery (N=1483)	Surgery (N=6032)	P-value
Age			
20-29	15 (1.0%)	124 (2.1%)	<0.001
30-59	554 (37.4%)	2644 (43.8%)	
60+	914 (61.6%)	3264 (54.1%)	
Race			
Black	223 (15.0%)	802 (13.3%)	0.346
Other	96 (6.5%)	386 (6.4%)	
Unknown	10 (0.7%)	36 (0.6%)	
White	1154 (77.8%)	4808 (79.7%)	
Tumor location			
Colon	156 (10.5%)	1499 (24.9%)	<0.001
Pancreas	678 (45.7%)	1496 (24.8%)	
Rectum	230 (15.5%)	611 (10.1%)	
Small Intestine	162 (10.9%)	2018 (33.5%)	
Stomach	257 (17.3%)	408 (6.8%)	
SEER historic stage			
Distant	1086 (73.2%)	1575 (26.1%)	<0.001
Localized	267 (18.0%)	2281 (37.8%)	
Regional	130 (8.8%)	2176 (36.1%)	
Chemotherapy			
No	730 (49.2%)	5023 (83.3%)	<0.001
Yes	753 (50.8%)	1009 (16.7%)	
Stage			
I	263 (17.7%)	1948 (32.3%)	<0.001
II	91 (6.1%)	1110 (18.4%)	
III	67 (4.5%)	1565 (25.9%)	
IV	1062 (71.6%)	1409 (23.4%)	
T			
T0	7 (0.5%)	0 (0%)	<0.001
T1	385 (26.0%)	1585 (26.3%)	
T2	229 (15.4%)	1116 (18.5%)	
T3	260 (17.5%)	2322 (38.5%)	
T4	212 (14.3%)	980 (16.2%)	
TX	390 (26.3%)	29 (0.5%)	
N			
N0	766 (51.7%)	2964 (49.1%)	<0.001
N1	474 (32.0%)	2428 (40.3%)	
N2	8 (0.5%)	610 (10.1%)	
N3	0 (0%)	1 (0.0%)	
NX	235 (15.8%)	29 (0.5%)	

M			
M0	425 (28.7%)	4625 (76.7%)	<0.001
M1	1058 (71.3%)	1407 (23.3%)	
Grade			
Grade I	522 (35.2%)	3725 (61.8%)	<0.001
Grade II	219 (14.8%)	1067 (17.7%)	
Grade III	546 (36.8%)	945 (15.7%)	
Grade IV	196 (13.2%)	295 (4.9%)	
Radiation			
No	1292 (87.1%)	5808 (96.3%)	<0.001
Yes	191 (12.9%)	224 (3.7%)	
Survival months			
Mean (SD)	25.4 (28.9)	49.6 (33.6)	<0.001
Status			
Alive	398 (26.8%)	4190 (69.5%)	<0.001
Death	1085 (73.2%)	1842 (30.5%)	
CS tumor size			
≤20	172 (11.6%)	2488 (41.2%)	<0.001
21-40	279 (18.8%)	1647 (27.3%)	
≥41	1032 (69.6%)	1897 (31.4%)	

Table 2: Univariate and multivariate Cox regression analyses for overall survival of the GEP-NETs patients before propensity score matching

Characteristics	Univariate		Multivariate	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Sex				
Female	Reference		Reference	
Male	1.205 (1.120-1.296)	＜0.001	1.197 (1.112-1.289)	＜0.001
Age				
≤30	Reference		Reference	
31-60	1.570 (1.056-2.336)	0.026	1.098 (0.737-1.636)	0.645
≥61	2.950 (1.988-4.376)	＜0.001	1.956 (1.316-2.906)	0.001
Race				
Black	Reference		Reference	
White	1.089 (0.977-1.214)	0.122	0.851 (0.762-0.950)	0.004
Other	0.893 (0.746-1.070)	0.221	0.750 (0.626-0.900)	0.002
Tumor location				
Colon	Reference		Reference	
Pancreas	0.645 (0.586-0.710)	＜0.001	0.826 (0.735-0.929)	0.001
Rectum	0.722 (0.636-0.819)	＜0.001	0.955 (0.833-1.094)	0.504
Small Intestine	0.409 (0.367-0.454)	＜0.001	0.742 (0.654-0.843)	＜0.001
Stomach	1.010 (0.890-1.147)	0.875	0.976 (0.848-1.124)	0.736
SEER historic stage				
Distant	Reference		Reference	
Localized	0.184 (0.166-0.205)	＜0.001	0.706 (0.511-0.975)	0.035
Regional	0.348 (0.319-0.379)	＜0.001	1.004 (0.787-1.282)	0.972
Stage				
I	Reference		Reference	
II	1.982 (1.716-2.290)	＜0.001	1.094 (0.874-1.368)	0.433
III	2.022 (1.767-2.313)	＜0.001	1.037 (0.788-1.363)	0.797
IV	6.296 (5.616-7.059)	＜0.001	2.357 (1.679-3.308)	＜0.001
T			Not selected	
T1	Reference			
T2	1.460 (1.278-1.667)	＜		

		0.001		
T3	1.987 (1.778-2.220)	< 0.001		
T4	3.687 (3.294-4.127)	< 0.001		
N				
N0	Reference		Reference	
N1	1.389 (1.279-1.508)	< 0.001	1.038 (0.937-1.150)	0.473
N2	3.828 (3.474-4.218)	< 0.001	1.364 (1.212-1.535)	<0.001
M				
M0	Reference		Not selected	
M1	4.014 (3.729-4.321)	< 0.001		
Grade				
Grade I	Reference		Reference	
Grade II	1.743 (1.557-1.950)	< 0.001	1.417 (1.264-1.589)	<0.001
Grade III	6.714 (6.151-7.328)	< 0.001	4.120 (3.713-4.571)	<0.001
Grade IV	8.092 (7.181-9.120)	< 0.001	4.558 (3.992-5.203)	<0.001
Surgery				
No	Reference		Reference	
Yes	0.251 (0.233-0.271)	< 0.001	0.483 (0.439-0.533)	<0.001
Radiation				
No	Reference		Not selected	
Yes	2.601 (2.305-2.934)	< 0.001		
Chemotherapy			Not selected	
No	Reference			
Yes	3.549 (3.296-3.822)	< 0.001		
CS tumor size (mm)				
≤20	Reference		Reference	
21-40	1.912 (1.709-2.139)	< 0.001	1.022 (0.907-1.151)	0.725
≥41	3.610 (3.276-3.979)	< 0.001	1.130 (1.008-1.267)	0.036

Table 3: Demographic and clinicopathological characteristics of patient's surgery and non-surgery groups after propensity score matching

Items	No-Surgery (N=880)	Surgery (N=880)	P-value
Age			
20-29	8 (0.9%)	9 (1.0%)	0.938
30-59	348 (39.5%)	353 (40.1%)	
60+	524 (59.5%)	518 (58.9%)	
Race			
Black	116 (13.2%)	129 (14.7%)	0.668
other	71 (8.1%)	69 (7.8%)	
White	693 (78.8%)	682 (77.5%)	
Tumor location			
Colon	158 (18.0%)	132 (15.0%)	0.37
Pancreas	341 (38.8%)	362 (41.1%)	
Rectum	124 (14.1%)	131 (14.9%)	
Small Intestine	147 (16.7%)	134 (15.2%)	
Stomach	110 (12.5%)	121 (13.8%)	
SEER historic stage			
Distant	522 (59.3%)	498 (56.6%)	0.376
Localized	233 (26.5%)	259 (29.4%)	
Regional	125 (14.2%)	123 (14.0%)	
Chemotherapy			
No	523 (59.4%)	560 (63.6%)	0.0778
Yes	357 (40.6%)	320 (36.4%)	
Stage			
I	225 (25.6%)	255 (29.0%)	0.443
II	92 (10.5%)	91 (10.3%)	
III	57 (6.5%)	56 (6.4%)	
IV	506 (57.5%)	478 (54.3%)	
T			
T1	250 (28.4%)	277 (31.5%)	0.44
T2	133 (15.1%)	139 (15.8%)	
T3	216 (24.5%)	205 (23.3%)	
T4	281 (31.9%)	259 (29.4%)	
N			
N0	450 (51.1%)	465 (52.8%)	0.75
N1	295 (33.5%)	288 (32.7%)	
N2	135 (15.3%)	127 (14.4%)	
M			
M0	376 (42.7%)	405 (46.0%)	0.179
M1	504 (57.3%)	475 (54.0%)	
Grade			
Grade I	381 (43.3%)	397 (45.1%)	0.869

Grade II	155 (17.6%)	155 (17.6%)	
Grade III	256 (29.1%)	243 (27.6%)	
Grade IV	88 (10.0%)	85 (9.7%)	
Radiation			
No	786 (89.3%)	801 (91.0%)	0.262
Yes	94 (10.7%)	79 (9.0%)	
Survival months			
Median [Min, Max]	36.0 [1.00, 153]	19.0 [1.00, 153]	
CS tumor size			
≥41	547 (62.2%)	537 (61.0%)	0.87
21-40	182 (20.7%)	190 (21.6%)	
≤20	151 (17.2%)	153 (17.4%)	

Table 4: Multivariate Cox regression analysis for overall survival of GEP-NETs patients after propensity score matching

Characteristics	**Multivariate**	
	HR (95% CI)	***P*-value**
Sex		
Female	Reference	
Male	1.323 (1.165-1.502)	＜0.001
Age		
≤30	Reference	
31-60	1.034 (0.549-1.948)	0.917
≥61	1.956 (1.316-2.906)	0.113
Tumor location		
Colon	Reference	
Pancreas	0.794 (0.663-0.951)	0.012
Rectum	0.882 (0.710-1.095)	0.256
Small Intestine	0.626 (0.494-0.793)	＜0.001
Stomach	0.747 (0.589-0.946)	0.016
Stage		
I	Reference	
II	1.823 (1.384-2.403)	＜0.001
III	1.894 (1.387-2.588)	＜0.001
IV	3.283 (2.657-4.057)	＜0.001
Grade		
Grade I	Reference	
Grade II	1.339 (1.093-1.640)	0.005
Grade III	4.875 (4.038-5.885)	＜0.001
Grade IV	5.835 (4.639-7.340)	＜0.001
Surgery		
No	Reference	
Yes	0.455 (0.400-0.518)	＜0.001
Chemotherapy		
No	Reference	
Yes	0.845 (0.726-0.983)	0.029

Table 5: Comparisons of overall survival outcomes between stage-matched patients in surgery and non-surgery groups

Stage	**OS Events N**	**HRs (95%CI)**	***P*-value**
Stage I (n=480)	122		
Surgery		0.366 (0.246-0.545)	＜0.001
No-surgery		Reference	
Stage II (n=183)	109		
Surgery		0.358 (0.233-0.551)	＜0.001
No-surgery		Reference	
Stage III (n=113)	68		
Surgery		0.331 (0.185-0.592)	＜0.001
No-surgery		Reference	
Stage IV (n=984)	698		
Surgery		0.503 (0.431-0.588)	＜0.001
No-surgery		Reference	
Stage I-IV (n=1760)	997		
Surgery		0.455 (0.400-0.518)	＜0.001
No-surgery		Reference	

P value was adjusted by a multivariate Cox proportional hazard regression model.

Table 6: Comparisons of overall survival between grade-matched patients in surgery and non-surgery groups

Grade	OS Events N	HRs (95%CI)	*P*-value
Grade I (n=778)	276		
Surgery		0.484 (0.378-0.620)	＜0.001
No-surgery		Reference	
Grade II (n=310)	147	Not selected	
Surgery			
No-surgery			
Grade III (n=499)	425		
Surgery		0.448 (0.367-0.548)	＜0.001
No-surgery		Reference	
Grade IV (n=173)	149		
Surgery		0.379 (0.266-0.540)	＜0.001
No-surgery		Reference	
Grade I-IV (n=1760)	997		
Surgery		0.455 (0.400-0.518)	＜0.001
No-surgery		Reference	

P value was adjusted by a multivariate Cox proportional hazard regression model.