Primary Tumor Surgery Improves Survival in Patients With Gastroenteropancreatic Neuroendocrine Carcinoma: A Population-Based Preliminary Study

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Research Article

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Abstract

Background: Chemotherapy has always been the primary treatment for gastroenteropancreatic neuroendocrine carcinomas (GEP-NECs), but the efficacy of surgical resection for GEP-NECs patients receiving chemotherapy is still controversial.

Methods: Information on GEP-NECs patients from 2004 to 2015 were extracted from the Surveillance, Epidemiology, and End Results (SEER) databases. Kaplan-Meier analysis and Log-rank test were used to evaluate the difference in survival rate between the surgery and the non-surgery group. Cox proportional hazard model was used to find the prognostic factors affecting overall survival (OS) time and cancer-specific survival (CSS) time.

Results: A total of 589 patients participated in our study, including 196 patients who underwent surgery and 393 patients who did not undergo surgery. Kaplan-Meier curve showed that there were significant differences in OS and CSS ($p<0.001$) between the surgery and the non-surgery group. Multivariate COX analysis showed that surgery was an independent protective factor for prolonging the duration of OS and CSS ($p < 0.001$). At the same time, through the propensity score-matched (PSM) of the original data, we also draw the same conclusion.

Conclusion: Our study preliminarily shows that for some patients with GEP-NECs, surgery for primary tumors may bring survival benefits. Compared with chemotherapy alone, surgery combined with chemotherapy can significantly prolong the survival time of patients.

Introduction

Neuroendocrine neoplasms (NENs) are a group of highly heterogeneous tumors originating from the diffuse neuroendocrine system [1]. NENs can occur in all parts of the body, among which the digestive system is the most common [2,3]. In 2019, the World Health Organization (WHO) classified NENs into well-differentiated neuroendocrine tumors (NETs), poorly differentiated neuroendocrine carcinomas (NECs), and Mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs) according to Ki-67 index and differentiation. In histopathology, the Ki-67 of poorly differentiated NECs is more than 20%, divided into small or large cell NECs [4]. The clinical manifestation, biological behavior, and prognosis of well-differentiated NETs and poorly differentiated NECs are different, and the treatment regimen is also other.

Gastroenteropancreatic neuroendocrine carcinoma (GEP-NECs) is rare in NECs with rapid progression and poor prognosis, and most of them have distant metastasis at the time of diagnosis. The incidence of GEP-NECs has increased slowly in the past few decades and is now about 7 per 100,000 persons/year [2,5,6]. GEP-NECs usually do not respond to routinely used treatments in highly differentiated NETs, such as somatostatin analogs (SSAs), sunitinib, and interferon [7]. Due to the lack of sufficient patients to conduct large phase II or III clinical trials, the evidence for GEP-NECs treatment is limited. The European Neuroendocrine Tumor Society (ENETS) [8] and the European Society of Medical Oncology (ESMO) [9]

recommend etoposide and platinum-based chemotherapy as first-line therapy. Still, other data on first-line treatment and appropriate second-line treatment are limited. It is understood that the survival time of GEP-NECs patients who only receive supportive treatment is as short as 1 month. Moreover, although some patients have received chemotherapy, the prognosis is still poor, with a median survival time of only 10-13 months [10–13]. Therefore, there is an urgent need for other treatments to prolong the survival time of patients with GEP-NECs.

Due to the highly invasive behavior and high risk of metastasis of GEP-NECs, whether surgery can bring survival benefits to these patients has been controversial. Radical surgery is generally used for localized lesions, but GEP-NECs show a high recurrence rate after surgery, limiting the application of surgery in this disease [14]. The ESMO guidelines [9] recommend that surgery should not be actively performed on localized GEP-NECs. Once the metastasis of GEP-NECs occurs, it should be regarded as the absolute contraindication of surgery. However, there is a lack of relevant research support for this proposal. Some studies have also found that primary tumor resection or liver metastasis surgery is beneficial to the survival of some patients with pancreatic NECs [15,16]. Moreover, compared with chemotherapy alone, surgery combined with chemotherapy may benefit patients [17]. Therefore, the effect of surgery on patients with GEP-NECs can not be wholly denied, even for patients with distant metastasis.

Since GEP-NECs is a rare and low incidence of carcinoma, this study chose to use the Surveillance, Epidemiology and End Results (SEER) Database (www.seer.ancer.gov) as a source of statistical data. The database, supported by the National Cancer Institute, collects information on cancer incidence, mortality, demographics, pathological features, and treatment of cancer patients from 19 regional cancer registries in the United States,which may provide complete and accurate results. Since chemotherapy is the current first-line treatment for NECs patients, the purpose of this study was to evaluate the effect of primary tumor surgery on the survival of NECs patients receiving chemotherapy.

Patients And Methods

Database and patient selection

SEER*Stat software version 8.3.8 was used to collect patient information from 2004 to 2015. According to the third edition of the International Classification of Diseases (ICD-O-3), select tumors are located in the gastrointestinal and pancreas. The specific site code is C16.0-C16.3, C16.5-C16.6, C16.8-C17.3, C17.8-C18.9, C19.9, C20.9, C24.1, C25.0-C25.2, C25.4, C25.7-C25.9. The histological codes of ICD-O-3 were large cell neuroendocrine carcinoma (8013), small cell carcinoma (8041), and neuroendocrine carcinoma (8246). Poorly differentiated and undifferentiated tumors were screened according to "differentiation" variables. This information is the same as WHO2017/2019 's definition of GEP-NECs. According to the above criteria, we initially screened 1388 patients with GEP-NECs. If the patient is less than 18 years old; if the surgical information is unknown; if it is not the only primary tumor; if the follow-up time is less than 1 month; if you do not receive chemotherapy, it will be excluded. After screening, 589 GEP-NECs patients were selected for this study.

Covariates and results

Variables extracted from the SEER database included age, gender, race, year of diagnosis, marital status, primary tumor site, tumor size, lymph node metastasis, distant metastasis, differentiation, primary tumor surgery, radiotherapy, follow-up time, and vital status.

The patients were divided into the surgery and the non-surgery group according to whether they received primary tumor surgery or not. According to experience, we divided the age into < 60 years old or ≥ 60 years old and divided the tumor size variables into < 5cm, ≥ 5cm, and unknown size. Overall survival (OS) rate and cancer-specific survival (CSS) rate are the main results of our study. OS refers to the time from the diagnosis of GEP-NECs to death or the end of follow-up. CSS refers to the interval between the diagnosis of GEP-NECs and the death of the tumor or the last follow-up. Our study is exempt from ethical review because the SEER database is a public database and does not contain identifiable patient information.

Statistical analysis

To determine the difference between the surgery and the non-surgery group, we used the t-test to compare continuous variables and the chi-square test (or Fisher's exact test) to compare classified variables. The binary logistics regression model was used to analyze the characteristics of patients who preferred surgery, and the results were shown by odds ratio (OR) and corresponding 95% confidence interval (CI). Kaplan-Meier survival curve was established, and the log-rank test was used to analyze the survival differences between groups. We used Cox subgroup analysis to observe the effect of surgery on the survival rate of patients in different subgroups. Interaction term analyses (PINT) were performed according to age group, gender, primary site, tumor size, distant metastasis, and chemotherapy. We also used a multivariate Cox proportional hazard model to analyze independent factors affecting patient survival, and the results were expressed in terms of hazard ratio (HR) and corresponding 95%CI. In addition, the propensity score-matched (PSM) was used to reduce the selection bias and confounding variables between the surgery and the non-surgery group. 1:1 matching was performed according to age group, gender, race, primary site, tumor size, differentiation, lymph node metastasis, distant metastasis, and radiotherapy. The caliper value is set to 0.02. The survival differences between groups after matching were compared again.

We use the following software for the above analysis: SPSS25.0 (IBM Corp, Armonk, NY) for the chi-square test, t-test, logistics regression model, and multivariate Cox proportional hazard model. Kaplan-Meier survival curve and log-rank test were drawn with GraphPad Prism 8.0 (San Diego, California, USA). PSM and COX subgroup analysis are implemented in R software 4.1.0 (https://www.rproject.org/). All statistical tests are double-tailed distribution; $p < 0.05$ is considered to be significant.

Results

Demographics

After screening, a total of 589 patients were included in this study. Figure 1 shows the specific filtering process. Among them, there were 196 (33.28%) patients in the surgery group and 393 (66.72%) patients in the non-surgery group. Table 1 provides the baseline characteristics of the two groups of patients. Compared with the non-surgery group, the female (48.5% vs. 38.4%, paired 0.02), the year of diagnosis was 2004-2007 (34.7% vs. 14.0%, $p < 0.001$), the primary site was in the colorectal (64.8% vs. 41.7%, $p < 0.001$), Patients with tumor size < 5cm (42.3% vs. 32.1%, $p < 0.001$), tumor size ≥ 5 cm (50.0% vs. 34.6%, $p < 0.001$), lymph node metastasis (79.6% vs. 44.5%, $p < 0.001$), and patients without distant metastasis (15.3 vs. 5.6, $p < 0.001$) were more common in the surgery group. A total of 482 (81.83%) patients died during the follow-up period, of which 457 (77.59%) died of GEP-NECs.

Table 1
Comparison of baseline characteristics between surgery and non-surgery group in patients with GEP-NECs.

	No. of Patients (%)			
Variables	**Total(n=589)**	**Non-surgery group (n=393)**	**Surgery group (n = 196)**	**P-value**
Age				
Mean(SD)	59.12(12.67)	59.36 (13.04)	58.65 (11.92)	0.522
Age group				0.58
<60	297 (50.4)	195 (45.6)	102 (52.0)	
≥60	292 (49.6)	198 (50.4)	94 (48.0)	
Gender				0.02
Male	343 (58.2)	242 (61.6)	101 (51.5)	
Female	246 (41.8)	151 (38.4)	95 (48.5)	
Race				0.17
White	477 (81.0)	311 (79.1)	166 (84.7)	
Black	72 (12.2)	55 (14.0)	17 (8.7)	
Other*	40 (6.8)	27 (6.9)	13 (6.6)	
Year of diagnosis				<0.001
2004-2007	131 (22.2)	63 (16.0)	68 (34.7)	
2008-2011	198 (33.6)	127 (32.3)	71 (36.2)	
2012-2015	260 (44.1)	203 (51.7)	57 (29.1)	
Marital status				0.134
Married	355 (60.3)	226 (57.5)	129 (65.8)	
Unmarried	213 (36.2)	151 (38.4)	62 (31.6)	
Unknown	21 (3.6)	16 (4.1)	5 (2.6)	
Primary site				<0.001
Stomach	98 (16.6)	80 (20.4)	18 (9.2)	
Small intestine	38 (6.5)	13 (3.3)	25 (12.8)	

*Other: American Indian, Alaska Native, Asian/Pacific Islander.

	No. of Patients (%)			
Colorectum	291 (49.4)	164 (41.7)	127 (64.8)	
Pancreas	162 (27.5)	136 (34.6)	26 (13.3)	
Tumor size				<0.001
<5cm	209 (35.5)	126 (32.1)	83 (42.3)	
>5cm	234 (39.7)	136 (34.6)	98 (50.0)	
Unknown	146 (24.8)	131 (33.3)	15 (7.7)	
Lymph nodes metastases				<0.001
No	171 (29.0)	137 (34.9)	34 (17.3)	
Yes	331 (56.2)	175 (44.5)	156 (79.6)	
Unknown	87 (14.8)	81 (20.6)	6 (3.1)	
Distant metastasis				<0.001
No	52 (8.8)	22 (5.6)	30 (15.3)	
Yes	537 (91.2)	371 (94.4)	166 (84.7)	
Differentiation				0.78
Poor-differentiated	428 (72.7)	287 (73.0)	141 (71.9)	
Undifferentiated	161 (27.3)	106 (27.0)	55 (28.1)	
Radiation				0.245
No	474 (80.5)	311 (79.1)	163 (83.2)	
Yes	115 (19.5)	82 (20.9)	33 (16.8)	
*Other: American Indian, Alaska Native, Asian/Pacific Islander.				

We compared the selection preference between the surgery and the non-surgery group by the binary logistics regression model. Since the SEER database does not contain information about the sequence of surgery and radiotherapy, we exclude the variable of radiotherapy in the model. Table 2 shows the result. Specifically, the regression analysis results show that female patients diagnosed from 2004 to 2007, primary site in the small intestine or colorectal, tumor size < 5cm, tumor size ≥ 5cm, lymph node metastasis, and no distant metastasis were more likely to undergo surgery.

Table 2
Logistic regression model for receiving surgery.

Variables	Adjusted OR (95% CI)	p-value
Age group		
<60	Reference	
≥60	1.154 (0.739-1.803)	0.528
Gender		
Male	Reference	
Female	1.617 (1.021-2.563)	0.041
Race		
White	Reference	
Black	0.511 (0.248-1.051)	0.068
Other*	0.912 (0.388-2.145)	0.833
Year of diagnosis		
2004-2007	Reference	
2008-2011	0.517 (0.291-0.920)	0.025
2012-2015	0.192 (0.108-0.342)	<0.001
Marital status		
Married	Reference	
Unmarried	0.635 (0.390-1.034)	0.068
Unknown	0.429 (0.123-1.495)	0.184
Primary site		
Stomach	Reference	
Small intestine	31.153 (9.352-103.773)	<0.001
Colorectum	5.616 (2.663-11.844)	<0.001
Pancreas	1.134 (0.499-2.579)	0.764
Tumor size		
<5cm	Reference	
>5cm	1.092 (0.674-1.771)	0.721

Other: American Indian, Alaska Native, Asian/Pacific Islander.

Variables	Adjusted OR (95% CI)	p-value
Unknown	0.171 (0.084-0.351)	<0.001
Lymph nodes metastases		
No	Reference	
Yes	3.803 (2.194-6.593)	<0.001
Unknown	0.297 (0.102-0.859)	0.025
Distant metastasis		
No	Reference	
Yes	0.200 (0.093-0.428)	<0.001
Differentiation		
Poor-differentiated	Reference	
Undifferentiated	1.281 (0.783-2.096)	0.323
Other: American Indian, Alaska Native, Asian/Pacific Islander.		

Influence of primary tumor resection on OS and CSS

The median survival time of all patients was 9 months. The median OS and CSS time of patients in surgery group and non-surgery group were 13 months and 8 months respectively. Survival analysis showed that surgery significantly prolonged the survival time of GEP-NECs patients [1-year OS rate (50.4% vs. 33.5%, p < 0.001), 3-year OS rate (16.2 vs. 7.1%, p < 0.001), 5-year OS rate (13.4 vs. 4.3%, P < 0.001), 1-year CSS rate (51.8% VS. 359%, p < 0.001), 3-year CSS rate (17.5% vs. 8.4%, p < 0.001), 5-year CSS rate (14.4%vs. 5.5%, p < 0.001)]. Kaplan-Meier curve also showed that there were significant differences in OS (HR=0.631, 95CI:0.527-0.755, p < 0.001) and CSS (HR=0.646, 95CI:0.537-0.777, p < 0.001) time between the two groups (Figure 2A-2B).

Subgroup analysis

Patients were divided into several subgroups according to age group, gender, primary site, tumor size, distant metastasis, and radiotherapy. Figure 3 shows the forest plots of the subgroup analysis. Our OS and CSS results show that surgery does not bring survival benefits to patients without distant metastasis. The OS and CSS time of patients in other subgroups were significantly prolonged after surgery. Our interaction test showed no significant difference in the interaction between surgery and patients in each subgroup (PINT > 0.05). The Kaplan-Meier curve also showed that the patients with localized lesions had the same time of OS (HR=0.534,95CI:0.244-1.171) and CSS (HR=0.565,95CI:0.253-1.261) after surgery as

those without surgery (Figure 4A-4B). In patients with distant metastasis, the time of OS (HR=0.714,95CI:0.591-0.864, p < 0.001) and CSS (HR=0.726,95CI:0.598-0.883, p < 0.001) were significantly prolonged after surgery (Figure 4C-4D). Moreover, the time of OS (p < 0.001) and CSS (p < 0.001) in patients with localized lesions was significantly higher than that in patients with distant metastasis (Figure 5A-5B).

Multivariable Predictors of Survival

Table 3shows the results of the multivariate Cox proportional hazard model. After adjusting the related confounding factors, surgery was an independent protective factor for prolonging the duration of OS (HR=0.561,95CI:0.440-0.716, p < 0.001) and CSS (HR=0.562,95CI:0.438-0.721, p < 0.001). In the OS and CSS cohort, black, male, primary site in the colon and rectum, and distant metastasis were independent risk factors for OS and CSS time in patients.

Table 3
Multivariate cox regression analysis of OS and CSS in patients with GEP-NECs.

Variables	OS		CSS	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age group				
<60	Reference		Reference	
≥60	1.177 (0.976-1.420)	0.089	1.148 (0.947-1.391)	0.161
Gender				
Male	Reference		Reference	
Female	0.729 (0.601-0.886)	0.001	0.742 (0.608-0.905)	0.003
Race				
White	Reference		Reference	
Black	1.635 (1.233-2.167)	<0.001	1.650 (1.236-2.202)	0.001
Other*	0.853 (0.583-1.249)	0.415	0.905 (0.618-1.327)	0.61
Year of diagnosis				
2004-2007	Reference		Reference	
2008-2011	0.887 (0.699-1.127)	0.327	0.879 (0.688-1.124)	0.305
2012-2015	0.784 (0.611-1.007)	0.056	0.786 (0.608-1.015)	0.065
Marital status				
Married	Reference		Reference	
Unmarried	1.074 (0.882-1.308)	0.478	1.090 (0.890-1.334)	0.405
Unknown	1.143 (0.683-1.912)	0.612	1.046 (0.604-1.810)	0.872
Primary site				
Stomach	Reference		Reference	
Small intestine	1.005 (0.643-1.571)	0.982	0.968 (0.610-1.536)	0.89
Colorectum	1.404 (1.072-1.840)	0.014	1.395 (1.058-1.838)	0.018
Pancreas	0.845 (0.632-1.130)	0.256	0.804 (0.596-1.083)	0.152
Tumor size				
<5cm	Reference		Reference	

Other: American Indian, Alaska Native, Asian/Pacific Islander.

Variables	OS		CSS	
>5cm	1.174 (0.950-1.452)	0.138	1.188 (0.955-1.477)	0.121
Unknown	0.971 (0.753-1.253)	0.821	0.982 (0.756-1.276)	0.893
Lymph nodes metastases				
No	Reference		Reference	
Yes	1.158 (0.928-1.446)	0.194	1.167 (0.930-1.465)	0.183
Unknown	1.133 (0.837-1.534)	0.418	1.078 (0.787-1.475)	0.64
Distant metastasis				
No	Reference		Reference	
Yes	2.329 (1.572-3.452)	<0.001	2.259 (1.514-3.372)	<0.001
Differentiation				
Poor-differentiated	Reference		Reference	
Undifferentiated	1.089 (0.885-1.340)	0.421	1.094 (0.884-1.353)	0.408
Primary tumor surgery				
No	Reference		Reference	
Yes	0.561 (0.440-0.716)	<0.001	0.562 (0.438-0.721)	<0.001
Radiation				
No	Reference		Reference	
Yes	0.864 (0.680-1.099)	0.234	0.842 (0.657-1.079)	0.175
Other: American Indian, Alaska Native, Asian/Pacific Islander.				

Propensity score-matched

After the PSM of the original cohort, two groups of equal numerical cohorts with balanced variables were produced, and there were 140 patients in each group. **Supplementary Table S1** showed the baseline characteristics of patients in the cohort after matching, and there was no significant difference between most of the variables between the two groups ($p > 0.05$). The histogram that matches the score shows that the two groups fit well (**Supplementary Figure S1**).

After matching, the median OS time of patients in the surgery and the non-surgery group was 8 months and 12 months, and the median CSS time was 9 months and 13 months. The Kaplan-Meier curve still showed that the surgery significantly prolonged the time of OS (HR=0.720, 95CI:0.555-0.933, p=0.008)

and CSS (HR=0.709, 95CI:0.545-0.922, p=0.006) (Figure 6A-6B). Multivariate Cox proportional hazard model also showed that surgery was still an independent protective factor for prolonging the duration of OS (HR=0.536, 95CI:0.389-0.740, p<0.001) and CSS (HR=0.517, 95CI:0.373-0.716, p < 0.001)(Table 4).

Table 4
Multivariate cox regression analysis of OS and CSS in patients with GEP-NECs after PSM.

Variables	OS		CSS	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age group				
<60	Reference		Reference	
≥60	1.003 (0.760-1.324)	0.981	0.971 (0.733-1.287)	0.839
Gender				
Male	Reference		Reference	
Female	0.600 (0.454-0.792)	<0.001	0.618 (0.467-0.819)	0.001
Race				
White	Reference		Reference	
Black	1.974 (1.244-3.133)	0.004	1.998 (1.255-3.181)	0.004
Other*	0.734 (0.416-1.295)	0.285	0.758 (0.429-1.339)	0.34
Year of diagnosis				
2004-2007	Reference		Reference	
2008-2011	0.745 (0.533-1.042)	0.086	0.720 (0.512-1.011)	0.058
2012-2015	0.636 (0.442-0.915)	0.015	0.620 (0.429-0.897)	0.011
Marital status				
Married	Reference		Reference	
Unmarried	1.027 (0.767-1.374)	0.86	0.989 (0.736-1.328)	0.939
Unknown	0.824 (0.374-1.813)	0.63	0.714 (0.306-1.664)	0.435
Primary site				
Stomach	Reference		Reference	
Small intestine	0.904 (0.448-1.824)	0.779	0.955 (0.471-1.937)	0.899
Colorectum	1.293 (0.808-2.070)	0.285	1.327 (0.822-2.142)	0.247
Pancreas	0.841 (0.507-1.396)	0.503	0.837 (0.500-1.402)	0.499
Tumor size				
<5cm	Reference		Reference	

PSM: Propensity score-matched; Other: American Indian, Alaska Native, Asian/Pacific Islander.

Variables	OS		CSS	
>5cm	1.168 (0.878-1.554)	0.285	1.166 (0.873-1.558)	0.298
Unknown	0.872 (0.546-1.394)	0.568	0.882 (0.551-1.414)	0.603
Lymph nodes metastases				
No	Reference		Reference	
Yes	1.249 (0.890-1.753)	0.199	1.235 (0.877-1.741)	0.227
Unknown	1.129 (0.651-1.957)	0.667	1.152 (0.663-2.002)	0.616
Distant metastasis				
No	Reference		Reference	
Yes	2.288 (1.232-4.247)	0.009	2.247 (1.209-4.173)	0.01
Differentiation				
Poor-differentiated	Reference		Reference	
Undifferentiated	1.096 (0.815-1.473)	0.543	1.079 (0.799-1.456)	0.621
Primary tumor surgery				
No	Reference		Reference	
Yes	0.536 (0.389-0.740)	<0.001	0.517 (0.373-0.716)	<0.001
Radiation				
No	Reference		Reference	
Yes	0.829 (0.573-1.200)	0.32	0.848 (0.584-1.230)	0.385
PSM: Propensity score-matched; Other: American Indian, Alaska Native, Asian/Pacific Islander.				

Discussion

NECs are rare in the digestive tract and usually occurs in the form of small cell lung cancer (SCLC) in the lungs. Due to the similarities between GEP-NECs and SCLC in pathological and clinical features, there is little evidence to support the recommendations of GEP-NECs treatment. Therefore, the current recommendations for treating GEP-NECs are based on the analogy of SCLC [18]. Etoposide and platinum-based chemotherapy is the current first-line therapy for patients with GEP-NECs. Whether surgery can improve the prognosis of these patients is still controversial. To more accurately evaluate the therapeutic effect of surgery on GEP-NECs patients, our study included all patients who had received chemotherapy. As far as we know, this is the most extensive study focusing on the survival outcome of GEP-NECs patients undergoing surgery.

Previous studies have shown that the median survival time of GEP-NECs patients receiving chemotherapy is only 10-13 months [10–13], and up to 85% of patients have metastasis at the time of diagnosis [11,19]. The above result is similar to our results, which show that the median survival time of patients in the entire cohort is 9 months, and 91.17% of patients have distant metastasis. We found that surgery at the primary site could prolong the median OS and CSS time and increase the 1, 3 and 5-year survival rates in patients with GEP-NECs. Subgroup analysis also showed that surgery could bring survival benefits to patients in most subgroups. Further multivariate Cox proportional hazard model confirmed that surgery was an independent protective factor affecting the prognosis of patients. We also used the PSM method, and after adjusting other variables, we can still observe the improvement of surgical treatment on the survival time of patients. However, it is worth noting that our subgroup analysis found that surgery can bring survival benefits to patients with distant metastasis, but not in patients with localized lesions, which is contrary to our assumption. We further analyze the possible causes of this phenomenon. On the one hand, patients with localized lesions have a longer survival time than patients with distant metastasis. However, due to the high recurrence rate of tumors after surgery [14], the improvement of prognosis of these patients may be limited in the relatively long survival time. The tumor with distant metastasis progressed rapidly, and the survival time of patients was short. Surgery to the primary tumor may delay the time of tumor invasion and reduce the source of metastatic tumors, thus prolonging the survival time of these patients. On the other hand, the number of patients with localized lesions in our study is too small, which to some extent affects the authenticity of the results of our subgroup analysis.

At present, there are few studies on the surgical treatment of GEP-NECs. The current guidelines [8,9,20] do not recommend active surgery for GEP-NECs patients, especially for metastatic diseases. Our research also reflects this result. We found that although the number of diagnosed GEP-NECs patients increased gradually from 2004 to 2015, the proportion of patients undergoing primary tumor surgery decreased. Even so, our analysis supports the benefits of surgery. A recent retrospective study also supports our results [15]. The study analyzed data from 201 GEP-NECs and MiNENs patients treated in eight university hospitals in northern Europe between 2007 and 2015. Patients with localized lesions have significantly prolonged survival after surgery, while carefully selected patients with metastatic diseases can also benefit from the surgery.

Due to the extremely low incidence of GEP-NECs, there are few epidemiological reports [21]. Our Cox model shows that black men have a lower survival rate than white women. However, this result is not apparent, which may be related to the differences in genetic characteristics and economic conditions of different races. Our Cox model also found that tumors with primary colorectal tumors had a worse prognosis, similar to the results of a retrospective study in northern Europe [11]. The study included 252 patients with gastrointestinal NECs and found that patients with colorectal NECs had a poor prognosis compared with gastric NECs. Another small retrospective study explored the effect of surgery on colorectal NECs [12]. The results showed that the surgical resection of the primary site had nothing to do with the prognosis of local or metastatic diseases, thus negating the effect of the operation. Our study shows that although colorectal NECs are a factor for poor prognosis, surgery can still prolong the survival time of these

patients. The differences in the results of different studies may be related to the differences in patient groups and selection deviations.

The Ki-67 index is an important index of NENs grade and prognosis. Generally speaking, the lower the Ki-67 index, the worse the prognosis. The Nordic study [11] also analyzed the relationship between the Ki-67 index and the prognosis of gastrointestinal NECs. It is reported that among NECs patients who received first-line platinum chemotherapy, patients with Ki-67 < 55% had a lower remission rate after chemotherapy than those with Ki-67 ≥ 55% (15% vs. 42% P < 0.001), but patients with Ki-67 < 55% had a longer survival (14 months vs.10 months, p < 0.001). Another European multicenter retrospective study further confirmed the relationship between the Ki-67 index and tumor prognosis and chemotherapy remission rate [22]. Due to the lack of Ki-67 index data in the SEER database, it is difficult to answer the difference in the effect of surgery on patients with different Ki-67 indexes. Because patients with Ki-67 < 55% respond poorly to chemotherapy, they may be more suitable for other treatments such as surgery. Therefore, further research and evaluation are still needed in the future.

At present, randomized controlled trials (RCT) are the best way to reduce selection bias. However, due to the rarity of GEP-NECs and the moral and profit problems faced by participants, it is always tricky for RCT related to GEP-NECs to proceed smoothly. In this case, retrospective studies are the only source of evidence to guide GEP-NECs treatment. We have made some efforts to describe the impact of surgery on patient survival, such as using multivariate Cox model to find prognostic factors, using subgroup analysis to evaluate the role of surgery in a specific population, using PSM to reduce selection bias, and adjust confounding factors. Therefore, the benefits of surgery in this study are unlikely to be entirely the result of confounding factors.

There are some limitations to this study. First, our study was based on a retrospective design of the SEER database, and logistics regression analysis confirmed that specific patients did prefer surgery. Because surgeons are more likely to operate on patients with higher performance, higher remission, and fewer complications, in this study, we try to use the Cox model and PSM to reduce selection bias. However, unknown factors may still lead to confusion of results. Second, the SEER database lacks essential information, such as clinical symptoms, detailed chemotherapy regimens, performance status, the timing of surgery, surgical margin, recurrence, and treatment of recurrence. We admit that the lack of this information may affect our judgment. Third, the SEER database contains some unknown data about tumor size and lymph node metastasis, affecting our results. Finally, the SEER database comes from the United States, and it is not clear whether our results are suitable for other people. Moreover, our study is limited to part of the population in the United States, so it is necessary to conduct more extensive clinical trials to clarify the role of surgery in the multidisciplinary management of GEP-NECs. Due to the above limitations, our results do not fully support surgical treatment for patients with GEP-NECs. But it does suggest that some patients can benefit from surgery, even if there is metastatic disease.

Overall, our study preliminarily shows that for some patients with GEP-NECs, surgery for primary tumors may bring survival benefits. Compared with chemotherapy alone, surgery combined with chemotherapy

can significantly prolong the survival time of patients. However, due to the limitations of our research, large-scale prospective studies are still needed to verify our findings in the future.

Declarations

Data Availability Statement

Publicly available datasets were analyzed in this study. This data can be found here: (https://seer.cancer.gov/).

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Not applicable.

Author Contributions

HY and ZL: conceive this study. HY: collect and analyze data. HY: consult the relevant literature and write manuscripts. All the authors contributed to this article and approved the submitted version.

Competing Interests

The authors have declared that no competing interest exists.

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Figures

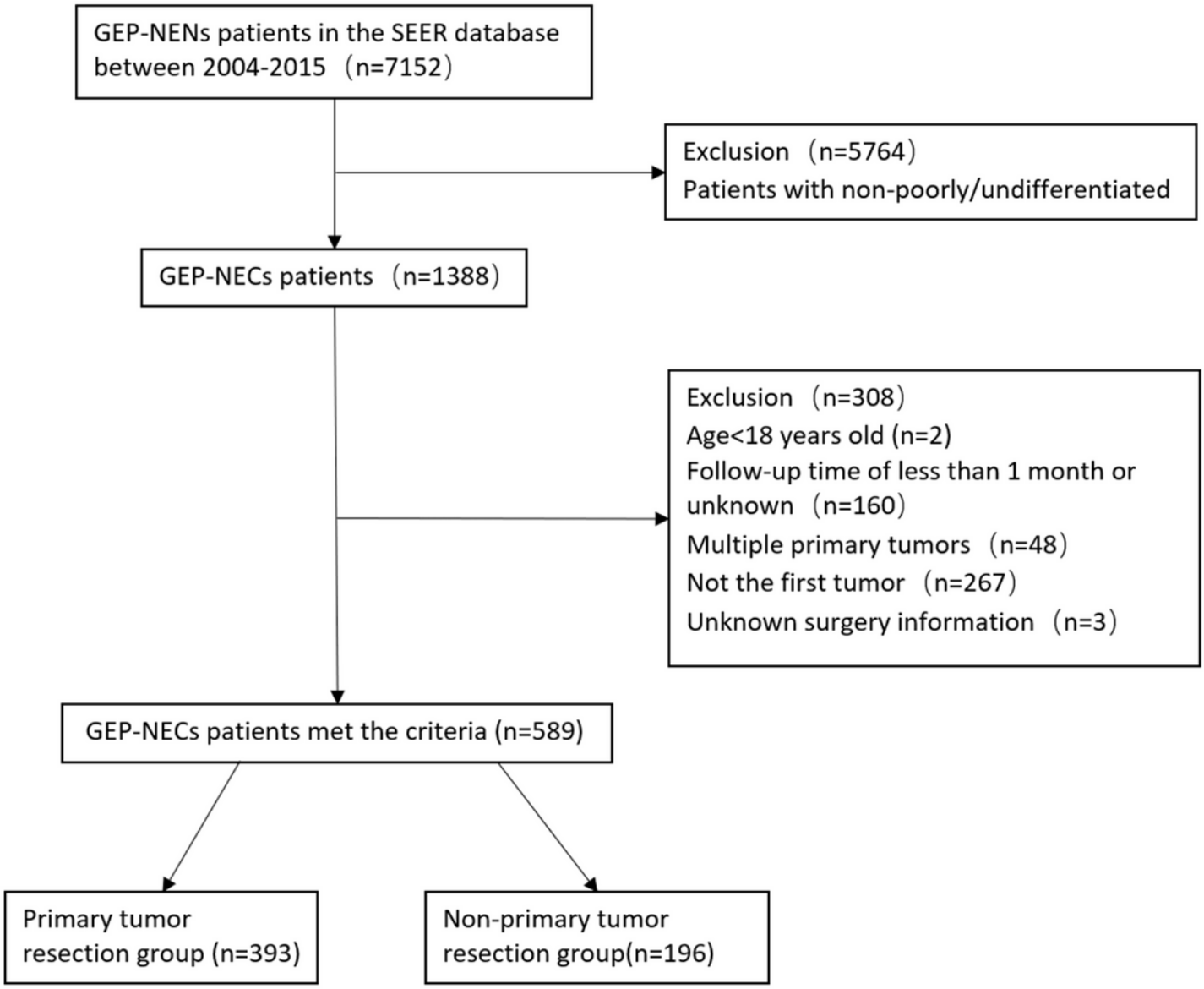

Figure 1

Flow diagram of eligible patients diagnosed with GEP-NECs.

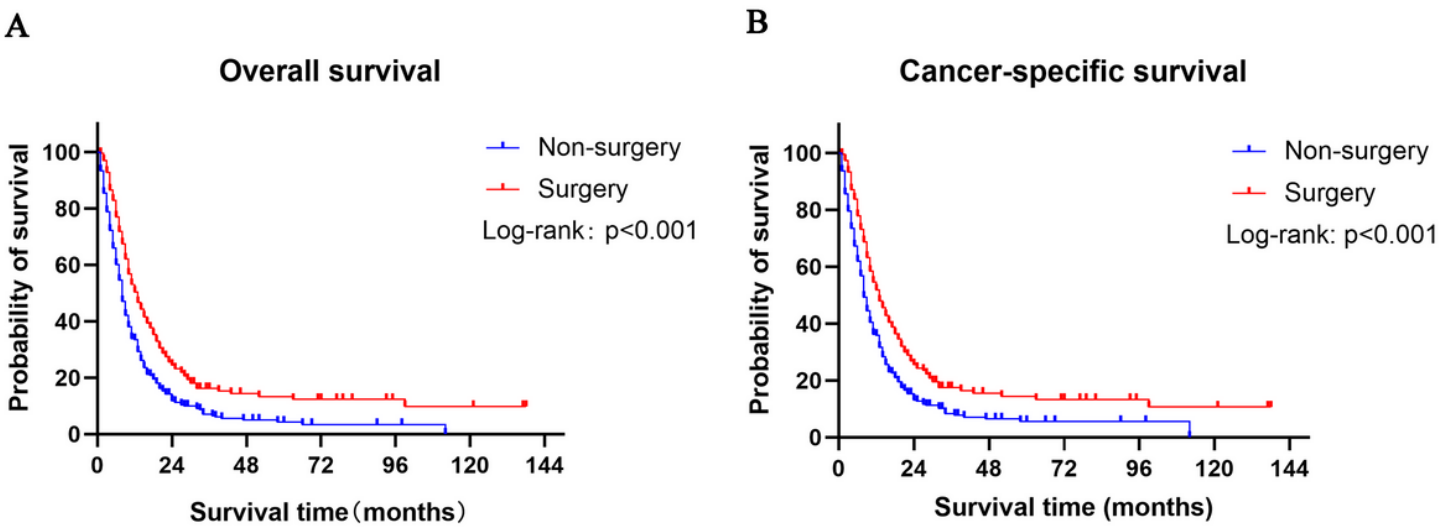

Figure 2

Kaplan-Meier curves according to treatment. (A)OS of GEP-NECs. (B)CSS of GEP-NECs.

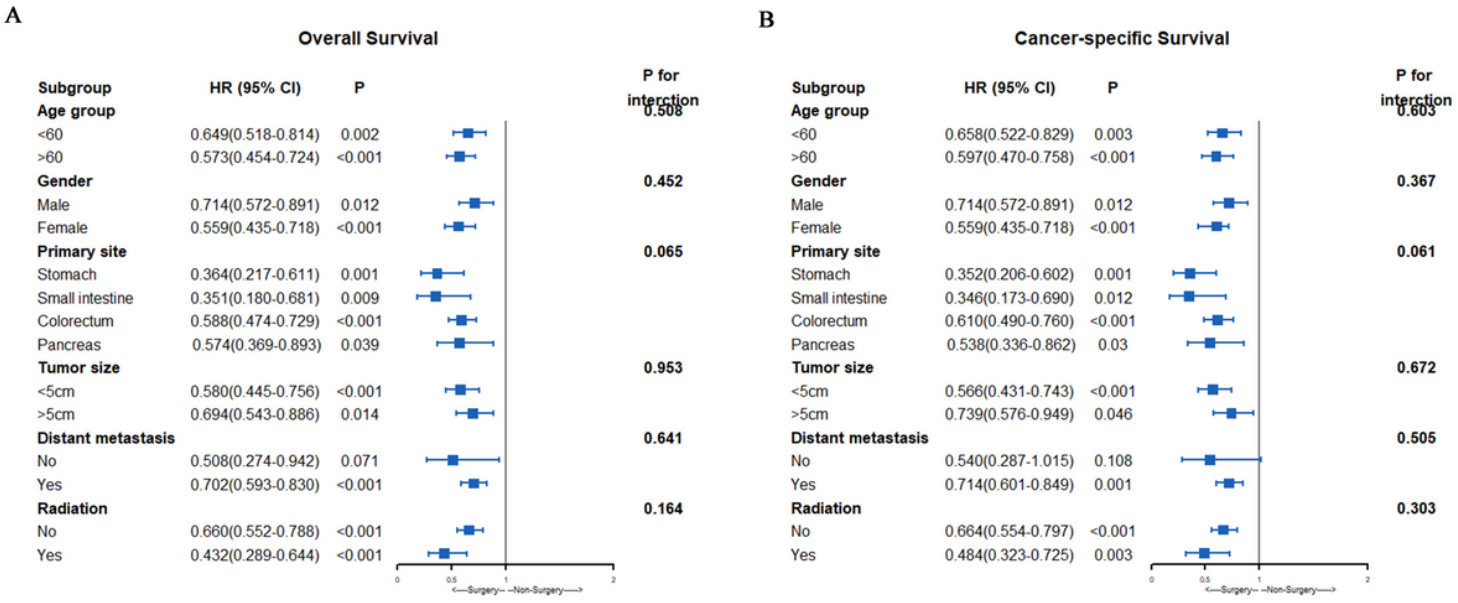

Figure 3

Forest plots summarize the HR and 95% CI of (A) OS and (B) CSS according to treatment in the Cox subgroup analyses.

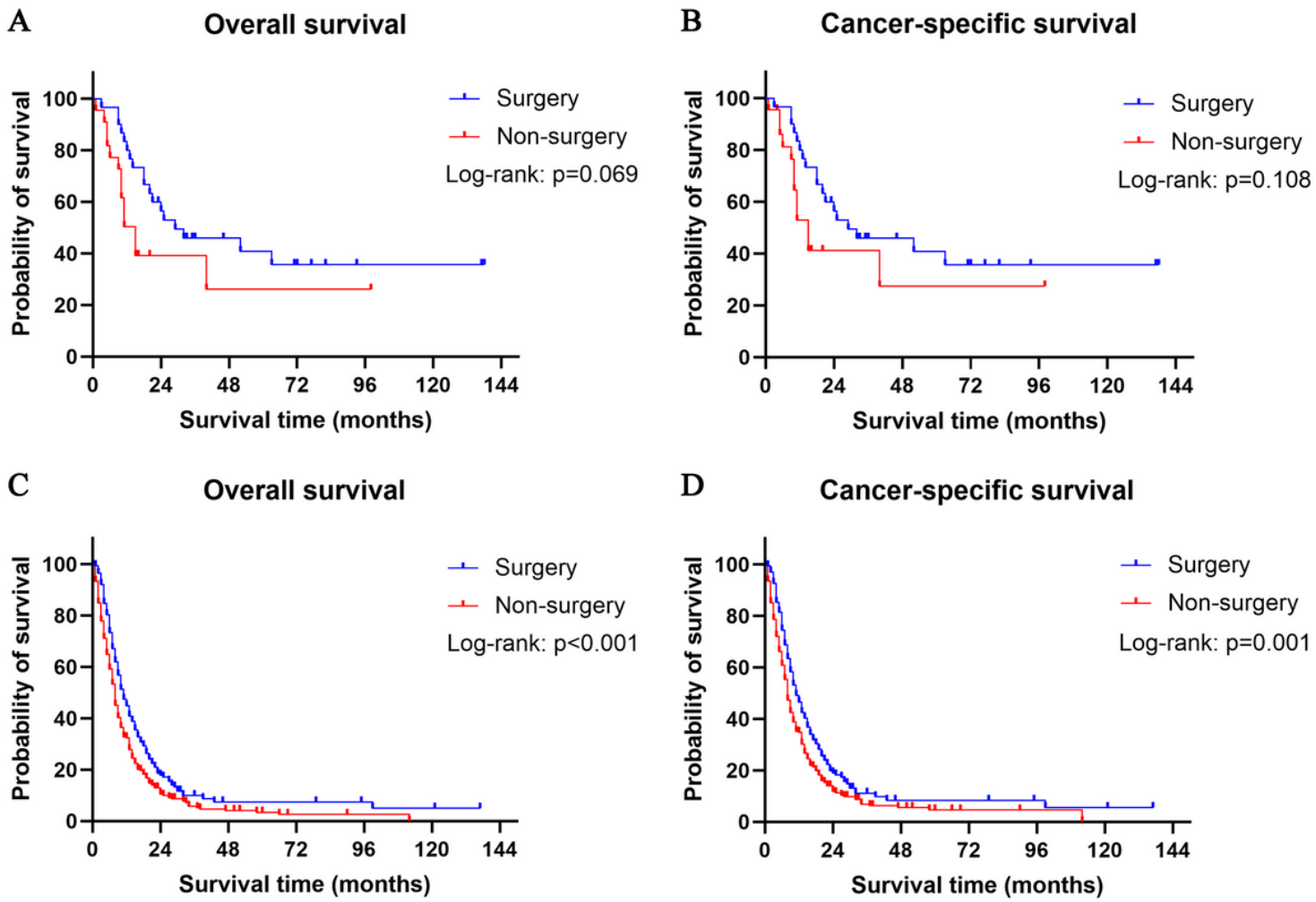

Figure 4

Kaplan–Meier survival curves for (A) overall survival and (B) cancer-specific survival in GEP-NECs patients with localized lesions in surgery and non-surgery group. Kaplan–Meier survival curves for (C) overall survival and (D) cancer-specific survival in GEP-NECs patients with distant metastasis in surgery and non-surgery group.

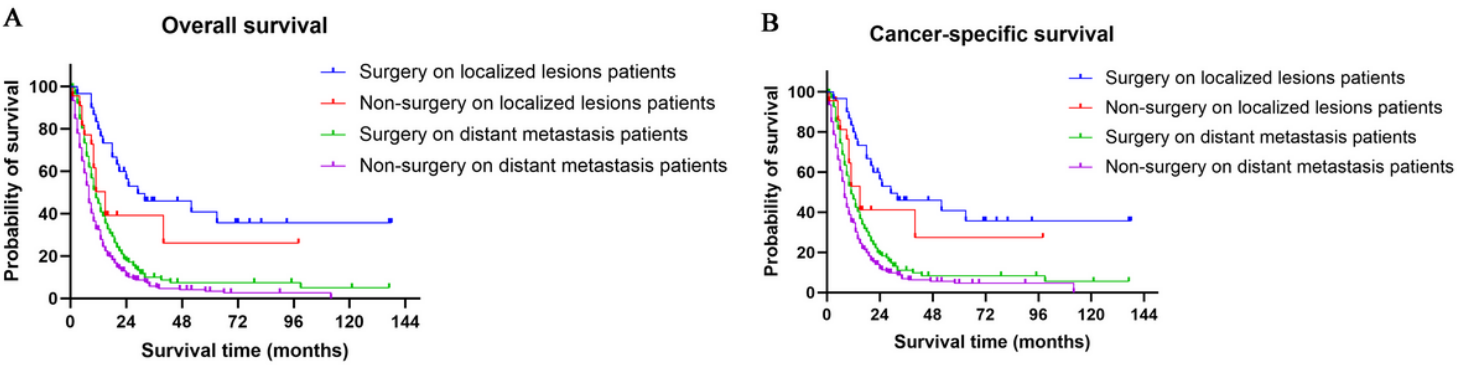

Figure 5

Kaplan–Meier survival curves for (A) overall survival and (B) cancer-specific survival in GEP-NECs patients.

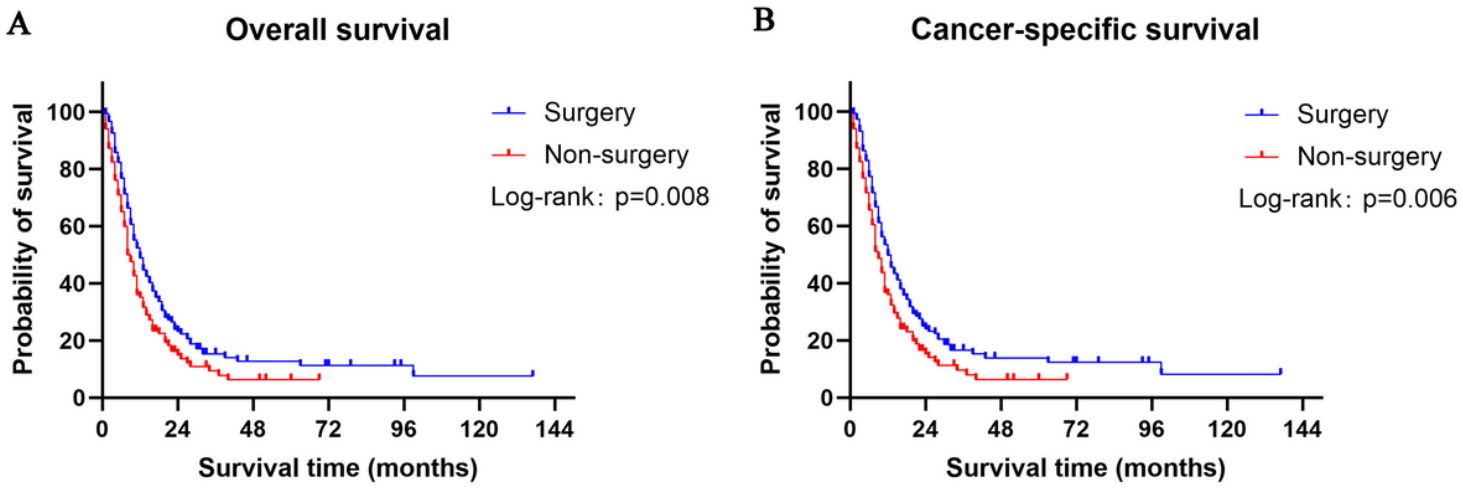

Figure 6

Kaplan-Meier curves according to treatment after PSM. (A)OS of GEP-NECs. (B)CSS of GEP-NECs.

Supplementary Files

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- FigureS1.tiff
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- TableS1.docx