Relationship between primary tumor resection for metastatic small intestine neuroendocrine tumors with survival: a propensity score-matched analysis

Haihao Yan
Second Affiliated Hospital of Nanjing Medical University
Zheng Liu (liuzheng117@126.com)
Second Affiliated Hospital of Nanjing Medical University

Research Article

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Abstract

Background

At present, it has been controversial whether primary tumor resection (PTR) can bring survival advantage to patients with metastatic small intestine neuroendocrine tumors (SI-NETs). To answer this question, we conducted a retrospective cohort study to evaluate the effect of PTR on the survival of patients with metastatic SI-NETs.

Methods

Information on SI-NENs patients from 2004 to 2015 was extracted from Surveillance, Epidemiology, and End Results (SEER) databases. Demographics, tumor characteristics, treatment, and survival were compared. Propensity score-matched (PSM) was used 1:1 in the filtered queue. Cox proportional hazard regression model was used to evaluate the correlation between surgery and treatment results.

Results

After PSM, there were 62 patients in the PTR group and 62 patients in the Non-PTR group. There was no significant difference in overall survival (OS) and cancer-specific survival (CSS) between the two treatments. Multivariate analysis showed that there was no significant difference in OS and CSS between the two groups ($p > 0.05$).

Conclusion

Our study shows that OS and CSS are comparable between patients in the PTR group and those in the Non-PTR group,which suggests that PTR should be used only when necessary. Early preventive surgery should not be advocated.

Introduction

Neuroendocrine neoplasms (NENs) are heterogeneous malignant tumors produced by specialized neuroendocrine cells. These cells can secrete hormones and neuropeptides, which can lead to characteristic clinical symptoms [1]. From a pathological point of view, there are two important types of NENs: well/moderately differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). It is essential to distinguish between these neuroendocrine tumors because they have different manifestations, prognoses, and treatment options [2,3]. Under the condition that the tumor is still limited, surgical resection is the leading way to treat NETs. For NECs, systemic treatment is usually the primary treatment, and surgery is only used in specific cases [4].

The small intestine is the most common primary NENs site of the digestive tract, accounting for about 30.8% of all digestive tract NENs. Among them, well /moderately differentiated NETs accounted for most of the small intestinal NENs. Small intestine neuroendocrine tumors (SI-NETs) are usually inert. The symptoms of patients with early SI-NETs are usually atypical and difficult to detect before the onset of related symptoms such as obstruction or bleeding and carcinoid syndrome [5].

About 30%-35% of SI-NENs patients were found to have distant metastasis at the time of diagnosis, and the most common site of metastasis was in the liver [6]. Somatostatin analogs are the current first-line therapy for metastatic SI-NETs. It can effectively control the symptoms caused by excessive hormones and effectively inhibit tumor progression. Clinical data also support the anti-proliferative effect of SSA on patients with NETs [7]. However, due to the presence of fibroblasts around the primary tumor, SI-NETs patients are prone to complications such as intestinal obstruction or intestinal ischemia caused by mesenteric fibrosis [8,9]. Once this happens, the effect of drug treatment is limited, and primary tumor resection (PTR) has a better effect on relieving the complications mentioned above.

At present, it has been controversial whether PTR can bring survival advantages to patients with metastatic SI-NENs. Several previous retrospective studies have shown that metastatic SI-NETs patients receiving PTR have a longer survival time [10–13]. However, these studies are severely limited by retrospective design and selection of patients with fewer complications and better tumor features in the surgical group. To further explore this issue, we conducted a retrospective cohort study using the Surveillance, Epidemiology, and End Results (SEER) database to further evaluate the effect of PTR on the survival time of patients with untreatable metastatic well/moderately differentiated SI-NETs. It is worth noting that due to the poor prognosis of patients with poorly differentiated small intestinal NECs, their biological behavior is quite different from well/moderately differentiated SI-NETs. The ESMO clinical practice guidelines in 2020 propose that metastatic NEC should be regarded as an absolute contraindication for surgery [14]. Therefore, we excluded patients with poorly differentiated small intestinal NEC.

Methods

Database and research population

The SEER database (www.seer.ancer.gov), which comes from cancer registries in 19 regions of the United States, represents about 28% of the population of the United States. The SEER database accurately collects information about patient demographics, tumor characteristics, the use of cancer-related treatments, and the survival time of cancer patients.

We used SEER*Stat version 8.3.9 to extract information about SI-NETs patients from 2004 to 2015 from the SEER database. The third edition of the International Classification of Oncology (ICD-O-3) is coded as C17.0-C17.3 and C17.8-C17.9. The histological code of ICD-O-3 is 8150–8157,8240–8246 and 8249. All patients' relevant demographic characteristics (age, sex, race), tumor characteristics (primary tumor site,

tumor size, lymph node metastasis, differentiation), treatment (surgery, chemotherapy, and radiotherapy), and survival information during the follow-up period up to December 31, 2015, were extracted.

The exclusion criteria were as follows: unknown surgical information, follow-up time of less than 1 month or unknown, poorly/undifferentiated tumors, multiple primary tumors, not the first tumor, unknown death information, unknow surgery information and surgery at the site of metastasis. The patients with distant metastasis were selected according to the "DerivedAJCCM,6thed (2004+)" variable. According to the "RX.Summ..Surg.Prim.Site..1998.." variable, the screened population was divided into PTR and Non-PTR groups. The flow chart of the patient selection process is shown in Fig. 1. The study exempts the agency review board because the data in the SEER database are open to the public for research and do not contain identifiable patient information.

We mainly compared the difference in overall survival (OS) and cancer-specific survival time (CSS) between the PTR and Non-PTR groups. OS refers to the time window from diagnosis to death from various causes. CSS is defined as the time window from diagnosis to death due to SI-NETs.

Statistical analysis

We made an intergroup comparison between the PTR group and the Non-PTR group. T-test was used to analyze continuous variables, chi-square test (or Fisher's exact test) was used to analyze classified variables. The logistics regression model was used to understand the selection tendency of surgical patients, and the results were expressed by adjusted odds ratio (AORS) and corresponding 95% confidence interval (CI). We established the Kaplan-Meier survival curve, performed the log-rank test on the survival difference between the two groups, and calculated the 3-year and 5-year survival rates. We use the propensity score-matched (PSM) method to reduce this study's selection bias and confounding variables. PTR and Non-PTR groups were matched at 1:1 according to age group, gender, race, primary tumor site, tumor size, differentiation, lymph node metastasis, chemotherapy, and radiotherapy. The caliper value is set to 0.02. We also performed a subgroup analysis to determine whether the effect of surgery on survival was different in different subgroups. In addition, we used the multivariate Cox proportional hazard model to look for independent prognostic factors affecting prognosis. The results are expressed as hazard ratio (HR) and corresponding 95% CI.

SPSS25.0 (IBM Corp, Armonk, NY) was used for the chi-square test (or Fisher's exact test), t-test, logistics regression analysis, and Cox proportional hazard analysis. The Kaplan-Meier survival curve was drawn with GraphPad Prism 8.0 (San Diego, California, USA). PSM and Cox subgroup analysis was performed in R software 4.1.0 (https://www.rproject.org/). All statistical tests were based on bilateral probability, and the significance level was set to $p < 0.05$.

Result

Unmatched Groups

After screening, a total of 597 patients were included in this study. Before the match, there were 434 (72.70%) patients in the PTR group and 163 (27.30%) patients in the Non-PTR group. The total median follow-up time was 35 months. There were significant differences in most baseline characteristics between the two groups (Table 1). Among them, patients with tumor size ≤ 20mm (44.0% vs. 8.0%, $p < 0.001$), patients with tumor size > 20mm (48.8% vs. 19.6%, $p < 0.001$), patients with lymph node metastasis (79.0% vs. 22.7%, $p < 0.001$), patients with primary site in ileum (59.9% vs. 23.3%, $p < 0.001$), patients with well differentiated tumors (19.6% vs. 8.6%, $p < 0.001$) and patients with moderately differentiated tumors (64.5% vs. 30.1%, $p < 0.001$) who did not receive radiotherapy (97.0% vs. 93.3%, paired 0.038) were more common in the PTR group. A total of 208 (34.84%) patients died during the follow-up period, of which 174 (29.15%) died of SI-NENs metastasis.

Table 1
Demographic information for metastatic SI-NETs patients in unmatched group.

	No. of Patients (%)			
Variables	**Total(n = 597)**	**Non-PTR group (n = 163)**	**PTR group (n = 434)**	**P-value**
Age				0.627
Mean(SD)	61.57(12.68)	62.87(13.09)	61.08(12.50)	
Age group				0.701
≤ 60	286(47.9)	76(46.6)	210(48.4)	
> 60	311(52.1)	87(53.4)	224(51.6)	
Gender				0.452
Male	289(48.4)	82(50.9)	206(47.5)	
Female	308(51.6)	80(49.1)	228(52.5)	
Race				0.256
White	507(84.9)	134(82.2)	373(85.9)	
Other	90(15.1)	29(17.8)	61(14.1)	
Tumor size				< 0.001
≤ 20mm	204(34.2)	13(8.0)	191(44.0)	
> 20mm	244(40.9)	32(19.6)	212(48.8)	
Unknown	149(25.0)	118(72.4)	31(7.1)	
Lymph node metastasis				< 0.001
No	155(26.0)	74(45.4)	81(18.7)	
Yes	380(63.7)	37(22.7)	343(79.0)	
Unknown	62(10.4)	52(31.9)	10(2.3)	
Primary site				< 0.001
Non-Ileum	82(13.7)	32(19.6)	50(11.5)	
Ileum	298(49.9)	38(23.3)	260(59.9)	
Small intestine, NOS	217(36.3)	93(57.1)	124(28.6)	

Other: Black, American Indian, Alaska Native, Asian/Pacific Islander, unknown; NOS: Not otherwise specified; PTR: Primary tumor resection

	No. of Patients (%)			
Differentiation				< 0.001
Well differentiated	329(55.1)	49(30.1)	280(64.5)	
Moderately differentiated	99(16.6)	14(8.6)	85(19.6)	
Unknown	169(28.3)	100(61.3)	69(15.9)	
Radiation				0.038
No	573(96.0)	152(93.3)	421(97.0)	
Yes	24(4.0)	11(6.7)	13(3.0)	
Chemotherapy				0.332
No	477(79.9)	126(77.3)	351(80.9)	
Yes	120(20.1)	37(22.7)	83(19.1)	
Other: Black, American Indian, Alaska Native, Asian/Pacific Islander, unknown; NOS: Not otherwise specified; PTR: Primary tumor resection				

We used the multivariate logistics regression model to analyze the selection tendency of surgical patients in the unmatched groups. Since the SEER database does not contain information about the sequence of surgery, radiotherapy, and chemotherapy, we exclude these two variables from the model. The regression analysis results showed that women patients with the primary site in the ileum, tumor size ≤ 20mm, lymph node metastasis, and known differentiation were more likely to undergo surgery (Table 2).

Table 2
Logistic regression model for receiving surgery.

Variables	Adjusted OR (95% CI)	p-value
Age group		
≤ 60	Reference	
> 60	1.392(0.781–2.481)	0.262
Gender		
Male	Reference	
Female	1.799(1.022–3.168)	0.042
Race		
White	Reference	
Other	0.695(0.310–1.558)	0.377
Tumor size		
≤ 20mm	Reference	
> 20mm	0.454(0.215–0.959)	0.038
Unknown	0.038(0.017–0.086)	< 0.001
LN metastasis		
No	Reference	
Yes	5.516(3.041–10.006)	< 0.001
Unknown	0.535(0.210–1.362)	0.190
Primary site		
Non-Ileum	Reference	
Ileum	4.080(1.863–8.937)	< 0.001
Small intestine, NOS	1.508(0.723–3.145)	0.273
Differentiation		
Well differentiated	Reference	
Moderately differentiated	1.227(0.492–3.061)	0.660
Unknown	0.436(0.237–0.802)	0.008

Other: Black, American Indian, Alaska Native, Asian/Pacific Islander, unknown; NOS: Not otherwise specified; PTR: Primary tumor resection

In the unmatched groups, the median follow-up time for patients in the PTR group and the Non-PTR group was 37 months and 27 months, respectively. Survival analysis showed that PTR significantly prolonged the survival time of metastatic SI-NENs patients [3-year OS (79.6 vs. 57.3%, p < 0.001), 5-year OS (66.1% vs. 44.3%, p < 0.001), 3-year CSS (83.0% VS. 60.6%, p < 0.001), 5-year CSS (71.9% vs. 46.9%, p < 0.001)] (Table 3). Kaplan-Meier curve also showed that there were significant differences in OS (HR = 2.259, 95CI:1.639–3.114, p < 0.001) and CSS (HR = 2.539, 95CI:1.788–3.607, p < 0.001) between the two groups (Fig. 2A-2B).

Table 3
Long-term outcomes of metastatic SI-NETs patients.

Variable	PTR group	Non-PTR group	P value
Estimated 3-year OS rate			
Unmatched group	79.60%	57.30%	< 0.001
Matched group	68.80%	65.30%	0.402
Estimated 3-year CSS rate			
Unmatched group	83.00%	60.60%	< 0.001
Matched group	71.70%	66.40%	0.166
Estimated 5-year OS rate			
Unmatched group	66.10%	44.30%	< 0.001
Matched group	56.30%	51.20%	0.402
Estimated 5-year CSS rate			
Unmatched group	71.90%	46.90%	< 0.001
Matched group	62.70%	52.10%	0.166
OS: Overall survival; CSS: Cancer-specific survival			

Propensity Score–matched Groups

Based on the R-package MATCH IT, we used PSM for unmatched groups. After matching, we obtained two equal numerical groups with similar baseline characteristics, each with 62 patients. There was no significant difference between the two groups (p > 0.05) (Table 4). The histogram that matches the score shows that the two groups match well (supplementary Fig. 1).

Table 4
Demographic information for metastatic SI-NETs patients in matched group.

	No. of Patients (%)			
Variables	**Total(n = 124)**	**Non-PTR group (n = 62)**	**PTR group (n = 62)**	**P-value**
Age				0.398
Mean(SD)	62.31(12.57)	63.06(13.31)	61.55(11.83)	
Age group				1.000
≤ 60	60(48.4)	30(48.4)	30(48.4)	
> 60	64(51.6)	32(51.6)	32(51.6)	
Gender				0.589
Male	67(54.0)	32(51.6)	35(56.5)	
Female	57(46.0)	30(48.4)	27(43.5)	
Race				0.811
White	103(83.1)	52(83.9)	51(82.3)	
Other	21(16.9)	10(16.1)	11(17.7)	
Tumor size				0.523
≤ 20mm	27(21.8)	13(21.0)	14(22.6)	
> 20mm	49(39.5)	22(35.5)	27(43.5)	
Unknown	48(38.7)	27(43.5)	21(33.9)	
LN metastasis				0.772
No	64(51.6)	30(48.4)	34(54.8)	
Yes	43(34.7)	23(37.1)	20(32.3)	
Unknown	17(13.7)	9(14.5)	8(12.9)	
Primary site				0.170
Non-Ileum	30(24.2)	15(24.2)	15(24.2)	
Ileum	39(31.5)	15(24.2)	24(38.7)	
Small intestine, NOS	55(44.4)	32(51.6)	23(37.1)	

Other: Black, American Indian, Alaska Native, Asian/Pacific Islander, unknown; NOS: Not otherwise specified; PTR: Primary tumor resection

	No. of Patients (%)			
Differentiation				0.340
Well differentiated	51(41.1)	28(45.2)	23(37.1)	
Moderately differentiated	15(12.1)	5(8.1)	10(16.1)	
Unknown	58(46.8)	29(46.8)	29(46.8)	
Radiation				0.697
No	117(94.4)	59(95.2)	58(93.5)	
Yes	7(5.6)	3(4.8)	4(6.5)	
Chemotherapy				1.000
No	104(83.9)	52(83.9)	52(83.9)	
Yes	20(16.1)	10(16.1)	10(16.1)	
Other: Black, American Indian, Alaska Native, Asian/Pacific Islander, unknown; NOS: Not otherwise specified; PTR: Primary tumor resection				

The total median follow-up time of the matched population was 33.5 months, while the median follow-up time of patients in the PTR and Non-PTR groups was 35 months and 27 months, respectively. Survival analysis showed that the survival time of patients in the PTR group and the Non-PTR group was comparable [3-year OS (68.8 vs. 65.3%, p = 0.402), 5-year OS (56.3% vs. 51.2%, p = 0.402), 3-year CSS (71.7% vs. 66.4%, p = 0.166), 5-year CSS (62.7% vs.52.1%, p = 0.166)] (Table 3). Kaplan-Meier curve and Log-rank test also showed that there was no significant difference in OS (HR = 1.257, 95CI:0.723–2.188, p = 0.402) and CSS (HR = 1.506, 95CI:0.831–2.729, p = 0.166) between the two groups (Fig. 2C-2D).

Subgroup Analysis And Multivariate Survival Predictors

In order to further observe the effect of surgery on the survival rate of each subgroup, we performed a COX subgroup analysis of the entire cohort (Fig. 3). The results showed that in terms of OS, surgery was not found to prolong the survival time of patients in each subgroup. In terms of CSS, we found that surgery can bring survival benefits to patients ≤ 60 years (HR = 0.342,95CI:0.145–0.805). Similar results were obtained by the Kaplan-Meier curve and Log-rank test (Fig. 4A-4B).

Finally, to test whether surgery is a predictor of survival after matching, we established a multivariate COX proportional hazard model. After adjusting the related variables such as age group, gender, race, primary site, tumor size, differentiation, lymph node metastasis, chemotherapy, and radiotherapy, we found that surgery was not an independent factor affecting OS (HR = 0.730, 95CI:0.400–1.300, p = 0.307) and CSS (HR = 0.600, 95CI:0.310–1.200, p = 0.128) in patients with metastatic SI-NETs (Fig. 5A-5B).

Discussion

This study evaluated the prognosis of patients with metastatic SI-NETs treated with PTR. The results showed that compared with patients who did not receive PTR treatment, patients who received PTR treatment did not find an increase in survival time after PSM. Further subgroup analysis also showed that only the CSS of patients ≤ 60 years was prolonged, and no more benefits were found in PTR in other subgroups. Multivariate COX proportional hazard model also found that PTR was not a prognostic factor for OS and CSS in patients with metastatic SI-NETs.

SI-NETs usually have a good prognosis. Even if distant metastasis occurs, SI-NETs patients still have a reasonable survival rate compared with other gastrointestinal malignant tumors [15,16]. However, although the progress of SI-NETs is slow, their clinical manifestations are not common benign tumors. Primary tumor and lymph node metastasis can cause mesenteric fibrosis, mesenteric contraction, and beaded changes of blood vessels, resulting in partial or complete obstruction, mesenteric ischemia, and colic. According to statistics, the probability of the above complications in SI-NETs is as high as 50%, which dramatically affects patients' quality of life [8,9]. PTR is currently recognized as a better treatment to alleviate the complications related to intestinal obstruction in SI-NETs.

Due to the lack of randomized controlled trials, there is no accurate conclusion on the best time for surgical treatment of metastatic SI-NETs patients and whether surgery can bring survival benefits to patients. Both the 2017 ENETS and NANETS guidelines recommend active resection of primary tumors and regional diseases in patients with metastatic SB-NETs to avoid local complications and possibly prolong the survival of patients [17,18]. However, the evidence of these guidelines is based on retrospective studies and will inevitably be severely limited by retrospective design and selection bias. For example, patients with fewer complications and better tumor characteristics are more likely to receive surgery. In comparison, those with more complications or more severe conditions are more likely to receive systematic treatment. Therefore, it is difficult to determine that surgical resection itself is the main factor leading to prolonged survival.

A single-center retrospective cohort study in Sweden attempted to reduce selection bias through PSM. The study compared the prognosis of patients who underwent early primary tumor resection (within 6 months after diagnosis) with those without resection or delayed resection (6 months after diagnosis). The results showed that there was no difference in OS between the two groups [median OS (7.9 years vs. 7.6 years, HR = 0.98, 95%CI: 0.70–1.37, p = 0.93), and opposed prophylactic resection [19]. Our results are similar to those in Sweden, but some differences need to be explained. First of all, although the Swedish study included many patients and included detailed indicators related to the prognosis of the disease, the cohort of the study only came from a single-center, which lacked representativeness and credibility, which limited the promotion of promotion the results. Second, the primary purpose of this study is to explore whether prevention surgery can bring survival benefits to asymptomatic patients. However, the study does not exclude patients who receive surgical resection of metastatic sites, which reduces the credibility of the results because radical surgery at the metastatic site may also prolong the survival time of patients

[20]. Third, this study only explored the impact of prophylactic resection on OS. Some patients may die from causes other than the tumor. We do not know the effect of surgery on prolonging CSS. Our study chose the SEER database based on the American population as the data source, and the study cohort is representative.

In order to accurately describe the effect of PTR on the prognosis of patients with metastatic SI-NETs, we excluded patients who received surgical treatment at the metastatic site. In addition, we also discussed the effect of PTR on OS and CSS in patients with metastatic SI-NETs. Even so, our survival analysis also showed that PTR did not bring significant survival benefits to patients with metastatic SI-NETs, both for OS and CSS. Our subgroup analysis showed that PTR could bring significant CSS improvement to patients under 60 years of age. Age is indeed an important prognostic factor. Compared with the elderly, young people have more substantial physiological reserves and can withstand invasive treatment, lower surgical risk, and are more likely to tolerate surgery-related complications. All these may lead to better surgical results for young patients.

In the real world, PTR is widely used in SI-NETs patients with tumor load symptoms. As recorded in the SEER database, more than 70% of metastatic SI-NETs patients have received PTR. The 2020 ESMO Clinical practice guidelines, based on the results of the Swedish study [19], recommend only those patients with symptoms associated with tumor load to undergo tumor debulking surgery at the primary site [14]. However, the manifestations of tumor load include carcinoid syndromes such as flushing and diarrhea and intestinal obstruction and colic caused by mesenteric fibrosis. At present, SSA treatment has been proved to control the symptoms of carcinoid syndrome and delay the progression of the disease to avoid surgery and related risks. Therefore, combined with our study and Swedish study results, we believe that carcinoid syndrome is not suitable for active surgical treatment. In the absence of randomized controlled trials, PTR should only be used in related manifestations such as intestinal obstruction or intestinal ischemia caused by primary tumor and surrounding fibrosis that SAA cannot alleviate consistent with the 2018 NCCN clinical practice guidelines. Furthermore, active early preventive surgery should not be advocated. Our view is also similar to that of the 2018 NCCN Clinical practice Guide [21]. It should still be noted that the treatment of metastatic SI-NETs should be multidisciplinary, and surgical treatment of this disease should be evaluated by experienced gastroenterological surgeons and specialists in various departments.

We admit that there are some limitations to this study. First of all, our study is based on the retrospective design of the SEER database, and logistics regression analysis shows that there is a bias in the choice of surgery. We try to use the propensity score matching method to reduce the selection bias, but the hidden, unknown bias factors may still exist and lead to confusion. Second, the SEER database lacks information that can reflect the general condition of patients, such as comorbidity index and PS score, which may affect our judgment of patient survival rate. However, CSS excludes deaths from causes other than cancer, so the lack of this information does not affect our CSS results. Third, the SEER database contains some unknown data about tumor size and differentiation. In order to obtain more sample size, we did not choose to exclude these unknown data, but it may also affect our results. Fourth, SSA, molecular targeted

therapy, and peptide receptor radionuclide therapy (PRRT) are commonly used to treat metastatic SI-NETs. Recently, a German study found that PRRT combined with surgical treatment can bring significant survival benefits to SI-NETs patients [22]. Unfortunately, due to the lack of these data in the SEER database, we cannot compare whether surgery combined with other treatments is more beneficial to improve the prognosis of SI-NETs patients.

Overall, our results show that for patients with metastatic SI-NETs, the results of OS and CSS are comparable between the PTR group and the Non-PTR group. Therefore, PTR should only be used in related manifestations such as intestinal obstruction or intestinal ischemia caused by primary tumor and surrounding fibrosis that SAA cannot alleviate. Similarly, early preventive surgery should not be advocated. However, in order to seek high-quality evidence, prospective randomized controlled trials are still needed in the future to verify the effect of surgical treatment on the survival time of patients with metastatic SI-NETs.

Data Availability Statement

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

Declarations

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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

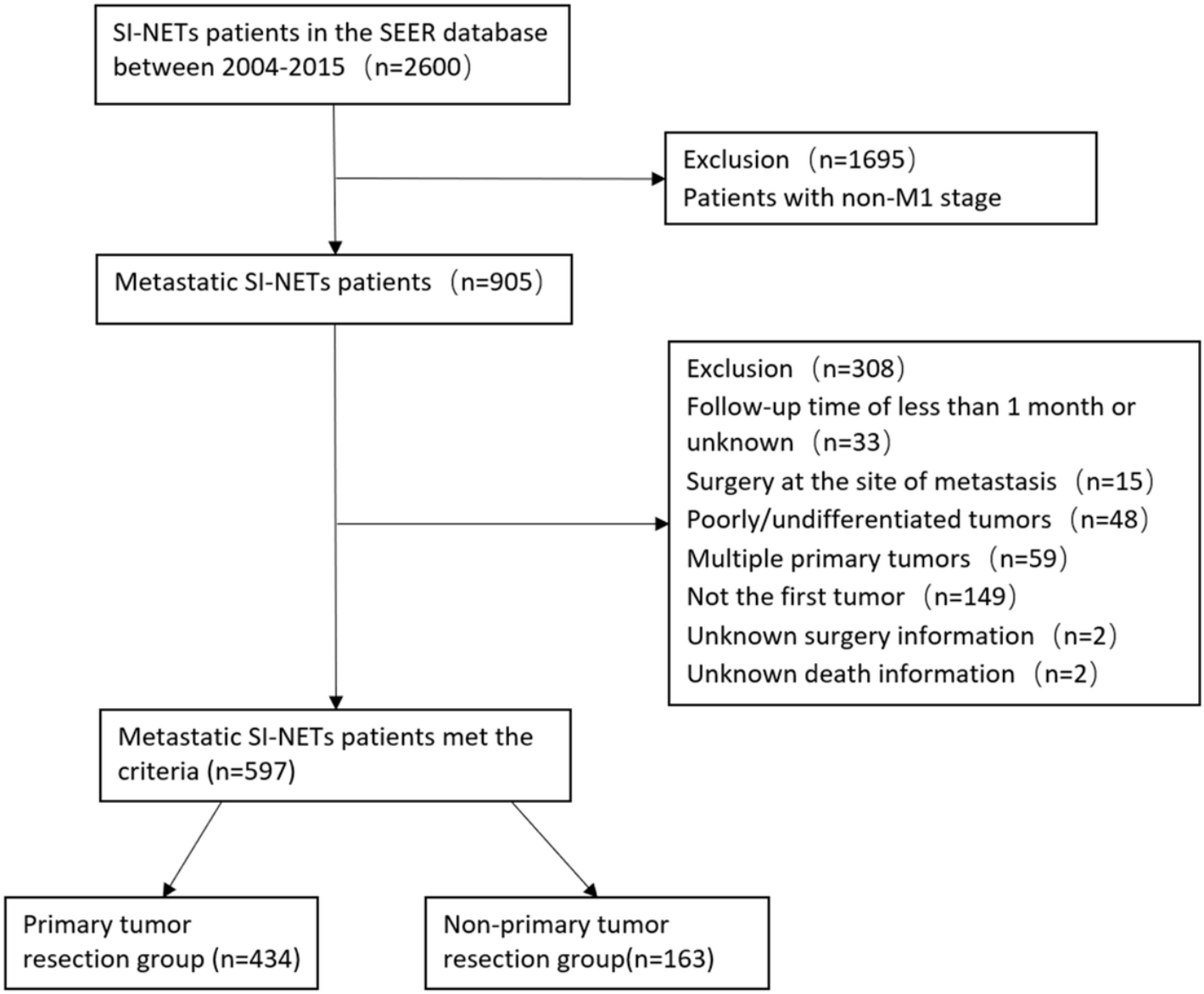

Figure 1

Flow diagram of eligible patients diagnosed with metastatic SI-NETs.

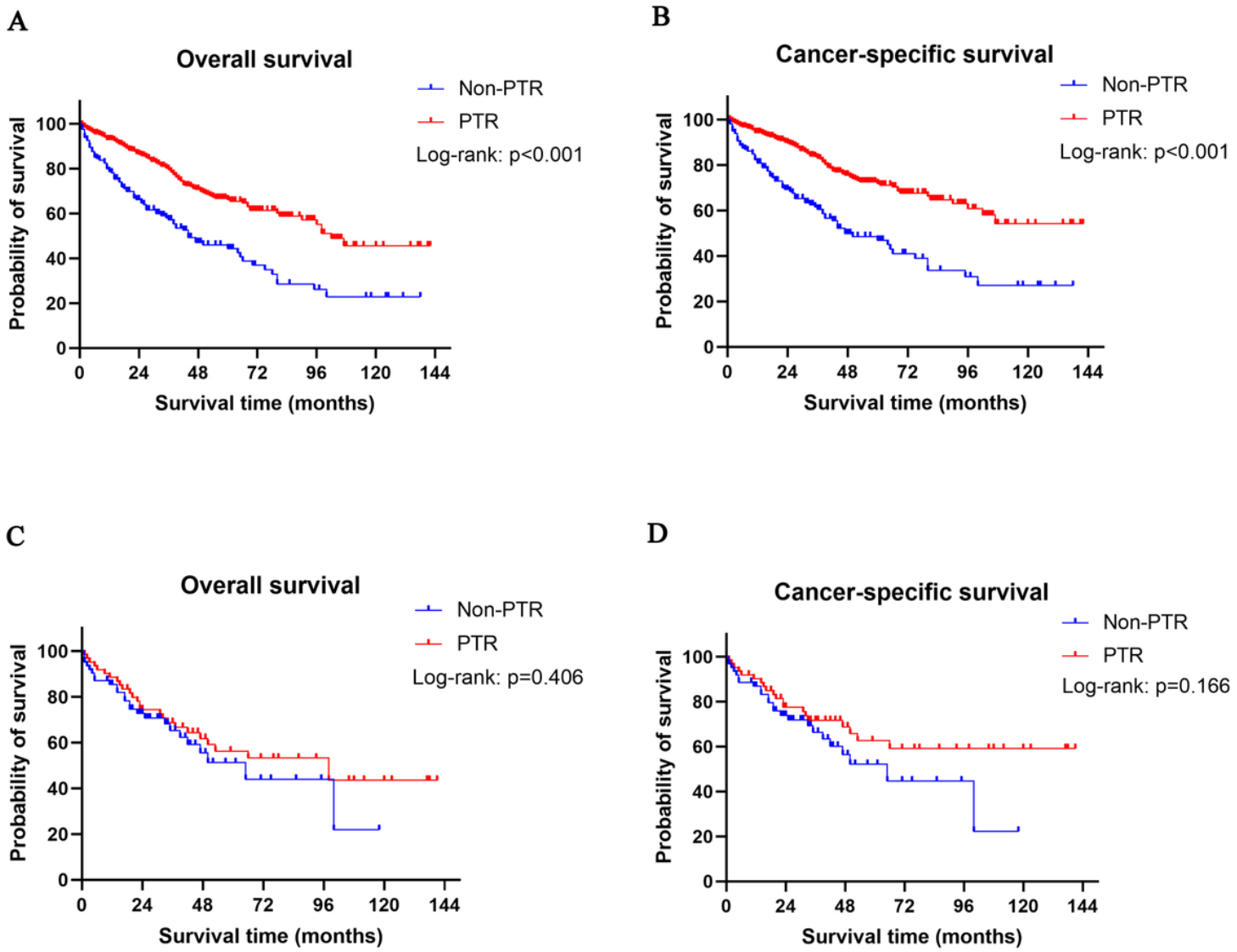

Figure 2

Kaplan-Meier curves according to treatment. (A)OS of metastatic SI-NETs before matched. (B)CSS of metastatic SI-NETs before matched. (C) OS of metastatic SI-NETs after matched. (D) CSS of metastatic SI-NETs before matched.

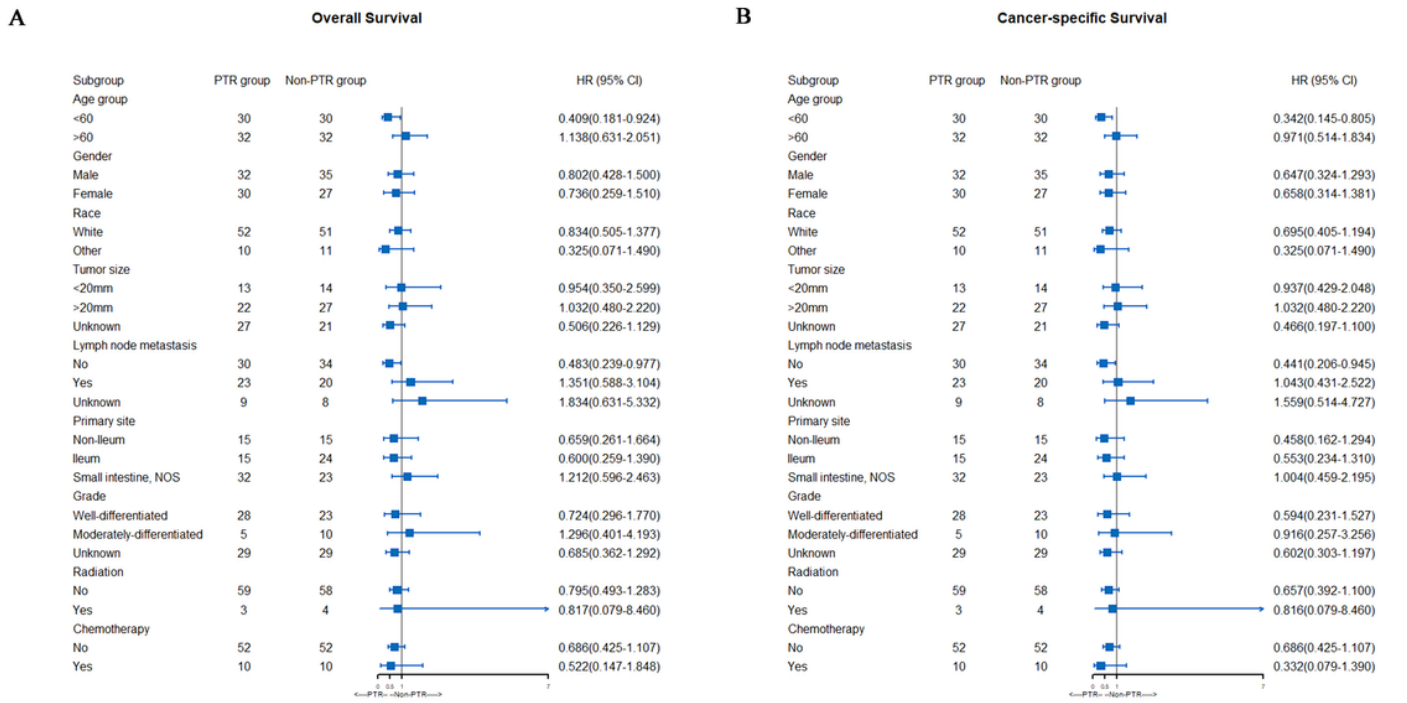

Figure 3

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

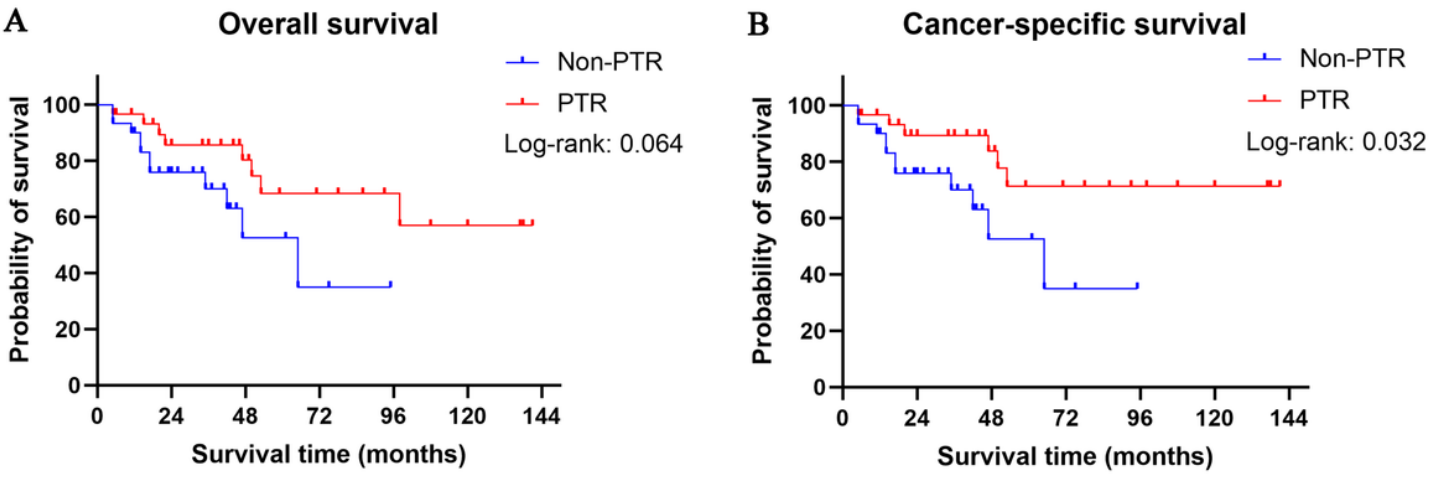

Figure 4

Kaplan-Meier curves of (A) OS and (B) CSS according to treatment in age ≤60 subgroup.

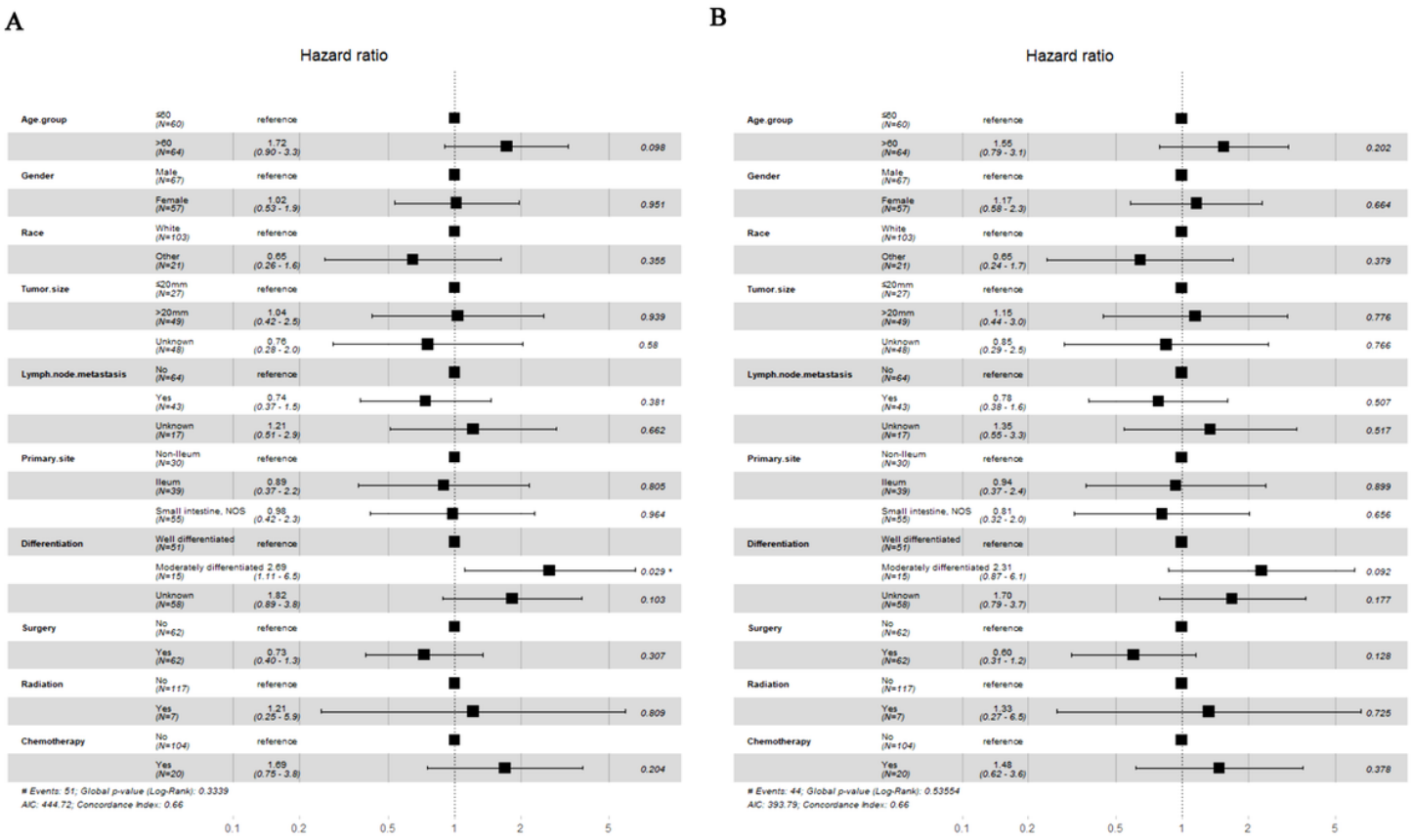

Figure 5

Forest plots summarize the HR and 95% CI of (A) OS and (B) CSS according to treatment in the multivariate COX proportional hazard model. Supplementary Figure 1. The histograms of propensity scores for the raw and matched case and controls.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigureS1.tiff