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The prognostic analysis of different metastatic patterns in pancreatic neuroendocrine tumors patients

A population based analysis

Sumei Wang, MD[a], Jiandong Zhang, BS[a,*], Shuye Liu, PhD[a], Jinjuan Zhang, PhD[b]

Abstract

Objective: To evaluate the prognostic value of pancreatic neuroendocrine tumors (pNETs) with different metastatic patterns.

Methods: Data of pNETs cases were extracted from the Surveillance, Epidemiology, and End Result (SEER) database. They were classified according to the different metastatic patterns. We utilized chi-square test to compare the clinical and metastasis characteristics among different groups. We used Kaplan–Meier analysis and log-rank testing for survival comparisons. Adjusted HRs with 95% CIs was calculated using Cox regression model to estimate prognostic factors. $P < .05$ was considered statistically significant.

Results: Among the 3909 patients, liver is the most metastatic organ, and isolated brain metastasis is the least common. At the same time, many patients have had multiple metastases. We studied the overall survival (OS) and cancer-specific survival (CCS) of the groups. OS: Non-organ metastasis: 5-year OS = 77.1%; Bone metastasis: median survival time (MST) = 56 m, 5-year OS = 42.7%; Liver metastasis: MST = 24 m, 5-year OS = 25.5%; Lung metastasis: MST = 14 m, 5-year OS = 33.7%; multiple metastases: MST = 7m, 5-year OS = 12.0%. CCS: Non-organ metastasis: 5-year OS = 84.2%; Bone metastasis: 5-year OS = 52.5%; Liver metastasis: MST = 27 m, 5-year OS = 28.6%; Lung metastasis: MST = 49 m, 5-year OS = 40.1%; multiple metastases: MST = 8 m, 5-year OS = 14.5%. In addition, the results showed that there were all statistical significances between the surgery and the no surgery group (all, $P < .001$). Multivariate analysis revealed that brain metastasis, multiple metastases, age over 60 years, unmarried, grade III/IV, regional/distant and no surgery were independently associated with decreased OS and CCS.

Conclusions: pNETs patients without organ metastasis had the best survival outcomes, while multiple had the worst outcomes. There were no significant differences in bone metastasis, liver metastasis and lung metastasis. Surgery was still an option for patients with metastasis.

Abbreviations: AJCC = American Joint Committee on Cancer, CCS = cancer-specific survival, HR = hazard ratio, ICD- O- 3 = International Classification of Diseases for Oncology, 3rd edition, MST = median survival time, OS = overall survival, pNETs = pancreatic neuroendocrine tumors, SEER = Surveillance, Epidemiology, and End Result.

Keywords: metastasis, pancreatic neuroendocrine tumors, surveillance epidemiology and end results database

1. Introduction

Neuroendocrine tumors (NETs) are a relatively rare but heterogeneous tumor. In recent years, its incidence has been rising. The epidemiological survey in the United States has shown that its incidence has increased 6.4 times in the past 40 years, reaching 6.98/100,000, and the pancreas is one of the most common sites of NETs.[1,2] Pancreatic neuroendocrine tumors (pNETs) may be classified as functioning or non-functioning tumors. Functioning pNETs are characterized by secretion of one or more biologically active peptides, inducing specific clinical syndromes. Secreting products include insulin, gastrin, glucagon, somatostatin, and vasoactive intestinal peptide. Non-functioning pNETs may secrete peptides, such as chromogranin A and neurotensin, and may be asymptomatic.[3]

When compared with pancreatic adenocarcinoma, pNETs are relatively slow growing but remain associated with substantial morbidity and mortality. Distant metastasis occurs in 20% to 64% of patients with pNETs at the time of diagnosis, and liver metastasis is the most common one. Distant metastasis is an important factor affecting the prognosis of patients.[4–7] However, some cases may experience a change of the metastatic pattern and involve other distant organs without involving the liver. These cases may represent a different subset of patients with different biology and prognosis and subsequently different therapeutic approach. Up to now, less is known about how metastatic pattern of pNETs patients at diagnosis relates to tumor

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[a] Department of Clinical Laboratory, [b] Department of Surgery, Third Central Hospital of Tianjin, Tianjin Key Laboratory of Artificial Cell Artificial Cell Engineering; Technology Research Center of Public Health Ministry, Tianjin, China.

[*] Correspondence: Jiandong Zhang, Third Central Hospital of Tianjin, 83 Jintang Road, Hedong District, Tianjin 300170, China (e-mail: welovemedicine@163.com).

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presentation and clinical outcomes. Since knowledge of prognosis of these patterns is crucial for pre-treatment evaluation, our study aimed to describe the distant metastatic patterns, frequency of occurrence and clinical outcomes based on a large population using Surveillance, Epidemiology, and End Result (SEER) database.

2. Materials and methods

2.1. Database and patient selection

Data for this study were obtained from the SEER database of the National Cancer Institute in the United States, covering approximately 28% of the US population.[8] It is one of the most representative large clinical cancer registration databases in North America. It collects clinicopathological information and prognostic data of various cancers and is open to the world for clinical doctors' evidence-based practice and clinical oncology research. It provides valuable first-hand information. We identified patients diagnosed with pNETs that were reported to the SEER database from 2010 to 2015. Because detailed information about the site of distant metastases was not available before 2010.

ICD- O- 3[9] (International Classification of Diseases for Oncology, 3rd edition) morphology codes 8013, 8041, 8150, 8151, 8152, 8153, 8154, 8155, 8156, 8240, 8241, 8244, 8246, and 8249 were used to identify pNETs. All pancreatic anatomical sites (C25.0-C25.9) were included in this study.[4]

Patients were excluded if the pNETs was not their first primary cancer, unknown the survival months, below 18 years old, without clear metastatic status or follow-up data. Detailed information on the numbers of patients included and excluded, consequent to each of the previous criteria, is shown in Figure 1. The final analysis included a cohort of 3909 patients.

2.2. Variable definition

We included variabilities as age, sex, race, marital status, primary site, grade, stage, and cancer-directed surgery. CS Mets at Dx (metastatic status) identifies whether there is metastatic involvement of distant site(s) at the time of diagnosis. CS Mets at Dx is part of the Collaborative Stage Data Collection System (CS), and was first introduced in 2004. It is used to derive some American Joint Committee on Cancer TNM Staging System (AJCC) M values and SEER Summary Stage codes.[10] The CS Mets at Dx was introduced into yes, no and unknown. According to the records in the SEER database, patients were divided into the following 6 groups:

1. Non-organ metastasis;
2. Bone metastasis;
3. Brain metastasis;
4. Liver metastasis;

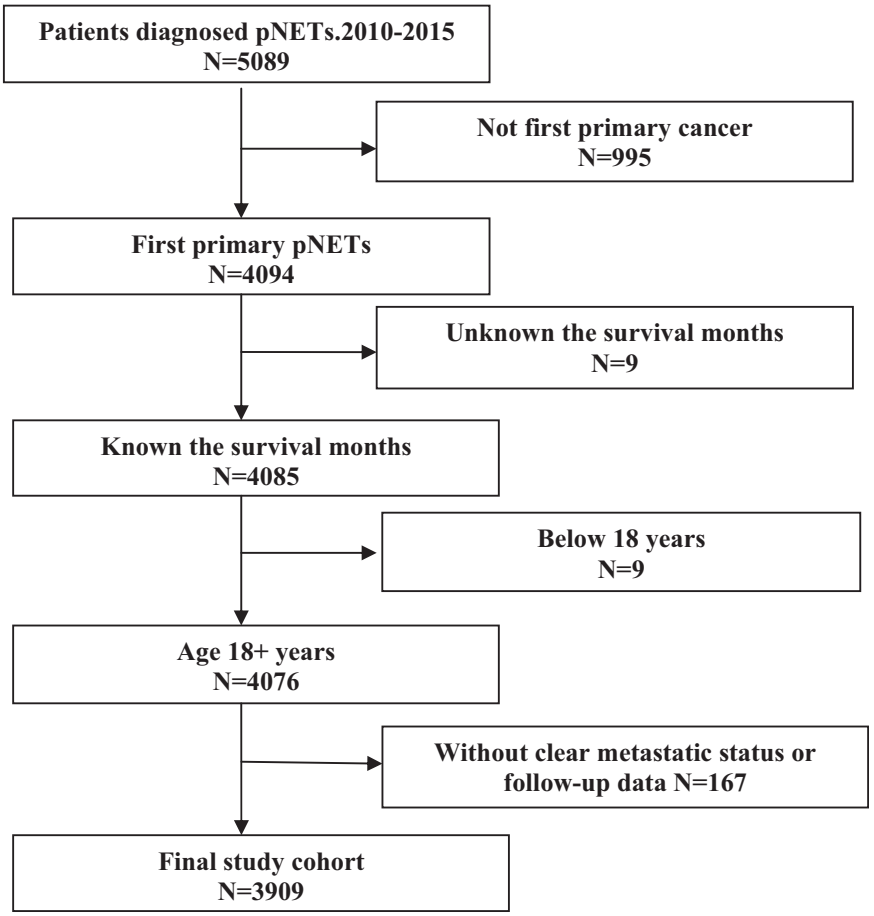

Figure 1. Flow chart of patients' cohort selection.

5. Lung metastasis;
6. Multiple (metastases in at least 2 of the above sites).

Cancer-specific survival (CCS) was calculated from the date of diagnosis to the date of death related to pNETs. Death attributed to other causes was considered as censored observation.

2.3. Statistical analysis

We utilized Chi-square test to compare the clinical and metastasis characteristics among different metastatic patterns. We used Kaplan–Meier analysis and log-rank testing for survival comparisons. Adjusted hazard ratio (HR) with 95% CI was calculated using Cox regression model to estimate prognostic factors. $P < .05$ was considered statistically significant. The statistical software SPSS 21.0 was utilized for all data analyses.

3. Results

3.1. Population characteristics

Among the 3909 patients we finally selected from SEER database, 2524 (64.6%) patients had no organ metastasis, 21 (0.5%) patients were diagnosed with isolated bone metastasis, 5 (0.1%) patients were diagnosed with isolated brain metastasis, 1133 (29.0%) patients were diagnosed with isolated liver metastasis and 28 (0.7%) patients were diagnosed with isolated lung metastasis. 1187 (30.4%) patients have a single organ site of metastasis while 198 patients (5.1%) patients have multiple organ metastases. Statistically significant correlations between different baseline characteristics and different sites of metastases are shown in Table 1. There were a series of significant differences among the 6 groups including age, marital Status, primary site, grade, stage and cancer-directed surgery (all, $P < .05$).

3.2. Survival outcomes

As shown in Figure 2, we plotted Kaplan–Meier curves and used the log-rank test for survival comparisons. For both endpoints, patients without organ metastasis had the best survival outcomes, while multiple had the worst outcomes. There were no significant differences in bone metastasis, liver metastasis and lung metastasis. (OS: Non-organ metastasis: 5-year OS = 77.1%; Bone metastasis: median survival time (MST) = 56 m, 5-year OS = 42.7%; Liver metastasis: MST = 24 m, 5-year OS = 25.5%; Lung metastasis: MST = 14 m, 5-year OS = 33.7%; multiple metastases: MST = 7m, 5-year OS = 12.0%. Non-organ metastasis vs other groups: $P < .001$; bone vs liver metastasis: $P = .230$; bone vs lung metastasis: $P = .228$; bone vs multiple metastasis: $P = .001$; liver vs lung metastasis: $P = .793$; liver vs multiple metastases: $P < .001$; lung vs multiple metastases: $P = .024$) (CCS:

Table 1

Clinical and metastasis characteristics of the study population.

	No. (%) of patients							
Characteristics	Non-organ metastasis (n = 2524)	Bone metastasis (n = 21)	Brain metastasis (n = 5)	Liver metastasis (n = 1133)	Lung metastasis (n = 28)	Multiple* (n = 198)	Total (n = 3909)	P
Age								.001
< 60	1564 (62.0)	8 (38.1)	3 (60.0)	662 (58.4)	10 (35.7)	103 (52.0)	2350 (60.1)	
≥ 60	960 (38)	13 (61.9)	2 (40.0)	471 (41.6)	18 (64.3)	95 (48.0)	1559 (39.9)	
Sex								.640
Male	1356 (53.7)	14 (66.7)	3 (60.0)	636 (56.1)	14 (50.0)	107 (54.0)	2130 (54.5)	
Female	1168 (46.3)	7 (33.3)	2 (40.0)	497 (43.9)	14 (50.0)	91 (46.0)	1779 (45.6)	
Race								.080
White	1915 (75.9)	19 (90.5)	3 (60.0)	892 (78.7)	25 (89.3)	157 (79.3)	3011 (77.0)	
Black	318 (12.6)	1 (4.8)	2 (40.0)	143 (12.6)	2 (7.1)	25 (12.6)	491 (12.6)	
Others	291 (11.5)	1 (4.8)	0 (0.0)	98 (8.6)	1 (3.6)	16 (8.1)	407 (10.4)	
Marital Status								.007
Married	1993 (79.0)	17 (81.0)	1 (20.0)	876 (77.3)	25 (89.3)	154 (77.8)	3066 (78.4)	
Unmarried	399 (15.8)	1 (4.8)	2 (40.0)	198 (17.5)	2 (7.1)	35 (17.7)	637 (16.3)	
Unknown	132 (5.2)	3 (14.3)	2 (40.0)	59 (5.2)	1 (3.6)	9 (4.5)	206 (5.3)	
Primary Site								<.001
Head	766 (30.3)	5 (23.8)	2 (40.0)	320 (28.2)	12 (42.9)	57 (28.8)	1162 (29.7)	
Body	430 (17.0)	6 (28.6)	0 (0.0)	112 (9.9)	1 (3.6)	23 (11.6)	572 (14.6)	
Tail	847 (33.6)	5 (23.8)	1 (20.0)	350 (30.9)	4 (14.3)	55 (27.8)	1262 (32.3)	
Overlap	157 (6.2)	3 (14.3)	0 (0.0)	121 (10.7)	2 (7.1)	14 (7.1)	297 (7.6)	
Others	324 (12.8)	2 (9.5)	2 (40.0)	230 (20.3)	9 (32.1)	49 (24.7)	616 (15.8)	
Grade								<.001
I	1542 (61.1)	6 (28.6)90	0 (0.0)	224 (19.8)	5 (17.9)	23 (11.6)	1800 (46.0)	
II	371 (14.7)	3 (14.3)	0 (0.0)	125 (11)	2 (7.1)	13 (6.6)	514 (13.1)	
III	100 (4.0)	1 (4.8)	1 (20.0)	113 (10.0)	5 (17.9)	25 (12.6)	245 (6.3)	
IV	36 (1.4)	0 (0.0)	0 (0.0)	34 (3.0)	4 (14.3)	12 (6.1)	86 (2.2)	
Unknown	475 (18.8)	11 (52.4)	4 (80.0)	637 (56.2)	12 (42.9)	125 (63.1)	1264 (32.3)	
Stage								<.001
Localized	1518 (60.1)	0 (0.0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1519 (38.9)	
Regional	800 (31.7)	4 (19.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	805 (20.6)	
Distant	163 (6.5)	16 (76.2)	5 (100.0)	1132 (99.9)	28 (100.0)	198 (100.0)	1541 (39.4)	
Unknown	43 (1.7)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	44 (1.1)	
Cancer-directed Surgery								
Yes	1939 (76.8)	4 (19.0)	0 (0.0)	207 (18.3)	4 (14.3)	6 (3.0)	2160 (55.3)	<.001
No	551 (21.8)	17 (81.0)	5 (100.0)	913 (80.6)	24 (85.7)	192 (97.0)	1702 (43.5)	
Unknown	34 (1.3)	0 (0.0)	0 (0.0)	13 (1.1)	0 (0.0)	0 (0.0)	47 (1.2)	

* Multiple mean metastases in at least 2 of the above sites.

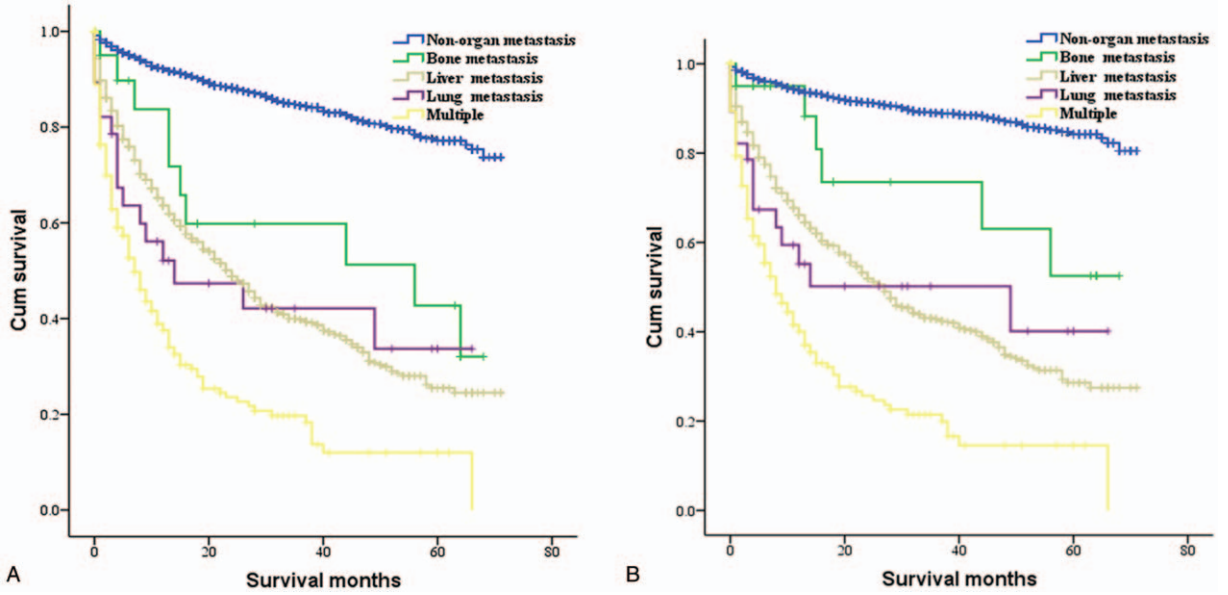

Figure 2. Kaplan–Meier curves and Log-rank test for overall survival (A) and cancer-specific survival (B) according to different metastasis.

Non-organ metastasis: 5-year OS = 84.2%; Bone metastasis: 5-year OS = 52.5%; Liver metastasis: MST = 27 m, 5-year OS = 28.6%; Lung metastasis: MST = 49 m, 5-year OS = 40.1%; multiple metastases: MST = 8 m, 5-year OS = 14.5%. Non-organ metastasis vs other groups: $P < .001$; bone vs liver metastasis: $P = .045$; bone vs lung metastasis: $P = .085$; bone vs multiple metastases: $P = .001$; liver vs lung metastasis: $P = .945$; liver vs multiple metastases: $P < .001$; lung vs multiple metastases: $P = .019$). Because of the very small number of patients with isolated brain metastasis (5 patients), they were not included in this analysis. MST will not be calculated with mortality less than 50%.

In addition, we studied the OS and CCS of Non-organ metastasis, Liver metastasis and multiple metastases based on whether or not cancer-directed surgery was performed (Fig. 3). The results showed that there were all statistical significances between the surgery and the no surgery groups (all, $P < .001$).

3.3. Multivariate analysis using the Cox hazard regression model

Moreover, we conducted multivariate analysis with Cox hazard regression model (Table 2) to evaluate the impact of different metastatic patterns and baseline characteristics on OS and CCS. As was shown, brain metastasis, multiple metastases, age over 60 years, unmarried, grade III/IV, regional/distant and no surgery were independently associated with decreased OS and CCS.

4. Discussion

This is the largest study to date use the SEER database to evaluate the prognostic value of different metastatic patterns among patients with pNETs. Previous studies showed that 40% to 80% pNETs patients are already metastatic at the time of diagnosed, the more frequent site is the liver (40%–93%), followed by the bone (12%–20%) and lung (8%–10%).[11] Consistent with these studies, our results showed that liver was the most common metastatic site in all pNETs. While we did not find any studies on the incidence of isolated organ metastasis of the pNETs patients. In addition, some pNETs patients developed more than 1 metastatic site, and few studies have reported on the multiple metastases in these patients. Our study expanded the multiple metastases group. Results showed that 5.1% patients have multiple organ metastases. Brain is the least common distant metastatic organ in pNETs patients.

Understanding the prognostic outcome of a metastatic pattern rather than another may be helpful for informed discussions with patients about the overall prospects of the disease; moreover, it may help to develop a systematic treatment strategy for the disease. The presence of a single liver metastasis is associated with better survival, as shown by Frilling et al.[12] Other studies showed that the presence of liver metastases also has a negative impact on the prognosis,[13,14] and the extension of pNETs liver metastases is correlated to long-term survival.[15,16] While our studies showed that without organ metastasis had the best survival outcomes, multiple had the worst outcomes. There were no significant differences in bone metastasis, liver metastasis and lung metastasis. Because of the less sample for all studies, we need further research. Some pNETs patients developed more than one metastatic site, and few studies have reported on the multiple metastases in these patients. In our study, multiple metastases achieving to 5.1% and have the worst outcomes. Multivariate analysis using the Cox hazard regression model showed that patients with brain metastasis or multiple metastases were independently associated with decreased OS and CCS.

Surgery remains the only curative treatment for pNETs. Surgical resection is usually performed when all tumors can be completely resected or if debulking of more than 90% of tumor burden can be achieved. It remains unknown however, if cancer-directed surgery is beneficial in the setting of distant metastases. The guidelines of both the European Neuroendocrine Tumor Association and North American Neuroendocrine Tumor Association currently do not recommend routine surgical resection in patients with distant metastasis since the available

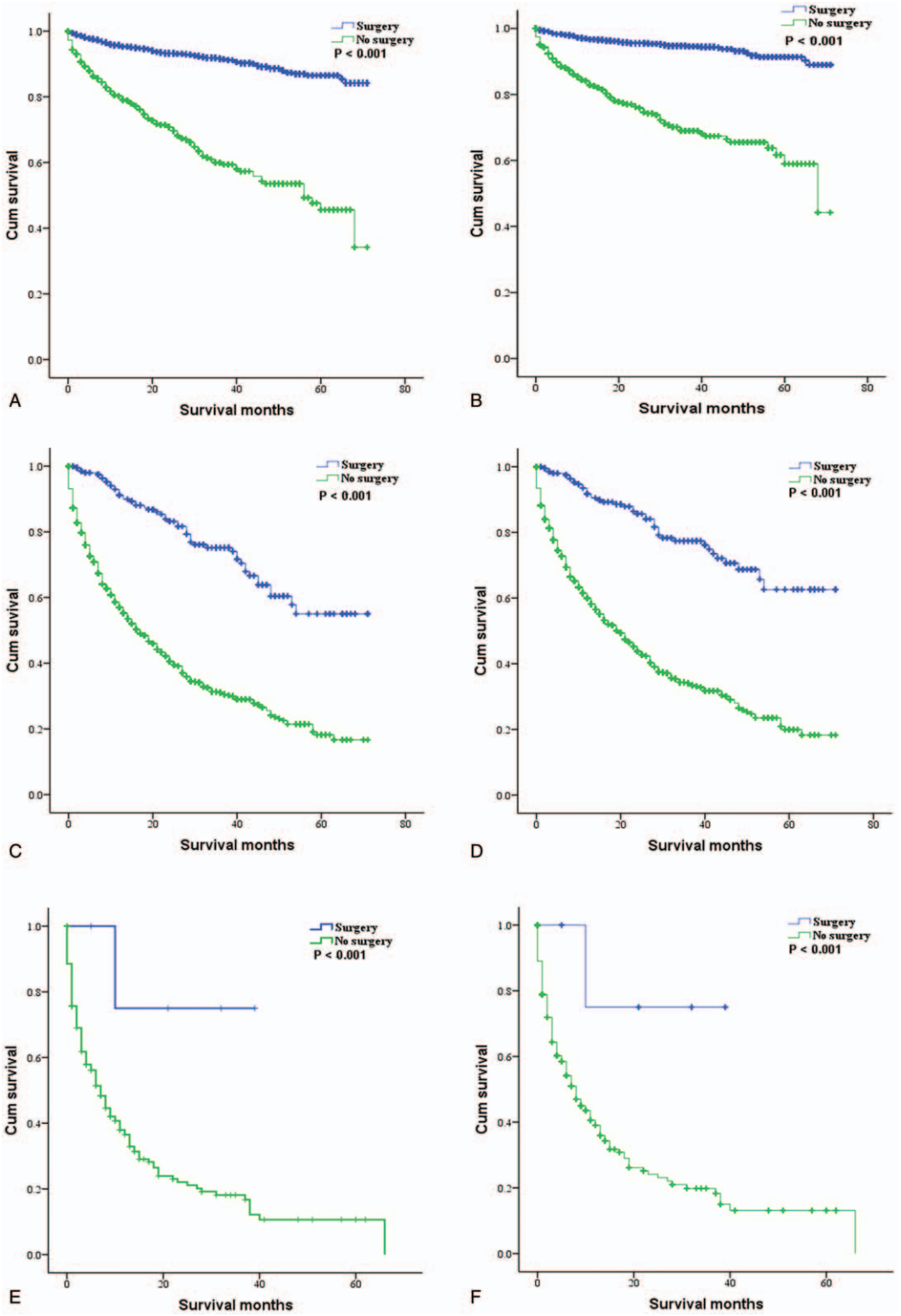

Figure 3. Kaplan–Meier curves and Log-rank test for OS and CCS based on whether or not cancer-directed surgery was performed: (A) OS of non-organ metastasis; (B) CCS of Non-organ metastasis; (C) OS of liver metastasis; (D) CCS of liver metastasis; (E) OS of multiple metastasis; (F) CCS of multiple metastasis. CCS = cancer-specific survival, OS = overall survival.

data supporting this strategy are sparse.[17,18] Our findings show that patients with no organ metastasis, liver metastasis and multiple metastases had better survival than those without surgery. A previous study[19] examined the impact of primary tumor resection on pNETs with unresectable multifocal LM among 43 patients and demonstrated that primary tumor resection predicted improved survival. The 5-year survival rates in the study among operated and non-operated patients were

Table 2

Results of multivariate analysis using the Cox hazard regression model.

Characteristics	OS		CCS	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Metastasis				
Non-organ metastasis	1.00 (reference)		1.00 (reference)	
Bone metastasis	0.994 (0.518–1.907)	.985	0.691 (0.301–1.584)	.382
Brain metastasis	3.920 (1.567–9.808)	.004	4.043 (1.608–10.166)	.003
Liver metastasis	1.126 (0.887–1.429)	.329	1.127 (0.877–1.448)	.351
Lung metastasis	0.979 (0.570–1.683)	.940	0.951 (0.534–1.694)	.864
Multiple	1.873 (1.414–2.481)	<.001	1.871 (1.393–2.512)	<.001
Age				
< 60	1.00 (reference)		1.00 (reference)	
≥ 60	1.759 (1.555–1.989)	<.001	1.605 (1.405–1.834)	<.001
Sex				
Male	1.00 (reference)		1.00 (reference)	
Female	0.898 (0.795–1.014)	.082	0.900 (0.789–1.027)	.118
Race				
White	1.00 (reference)		1.00 (reference)	
Black	1.103 (0.924–1.318)	.279	1.107 (0.914–1.340)	.298
Others	1.089 (0.882–1.344)	.428	1.146 (0.916–1.434)	.232
Marital status				
Married	1.00 (reference)		1.00 (reference)	
Unmarried	1.207 (1.022–1.426)	.026	1.214 (1.016–1.451)	.033
Unknown	1.019 (0.780–1.331)	.890	0.996 (0.743–1.334)	.976
Primary site				
Head	1.00 (reference)		1.00 (reference)	
Body	0.824 (0.670–1.014)	.067	0.816 (0.651–1.024)	.079
Tail	0.818 (0.697–0.960)	.014	0.785 (0.659–0.935)	.007
Overlap	0.817 (0.644–1.035)	.094	0.785 (0.608–1.013)	.062
Others	0.996 (0.846–1.172)	.960	0.971 (0.816–1.157)	.744
Grade				
I	1.00 (reference)		1.00 (reference)	
II	1.256 (0.965–1.634)	.090	1.424 (1.055–1.924)	.021
III	3.733 (2.974–4.684)	<.001	4.266 (3.302–5.510)	<.001
IV	3.634 (2.638–5.004)	<.001	4.322 (3.064–6.095)	<.001
Unknown	2.090 (1.733–2.519)	<.001	2.410 (1.939–2.994)	<.001
Stage				
Localized	1.00 (reference)		1.00 (reference)	
Regional	2.793 (2.131–3.662)	<.001	5.377 (3.650–7.920)	<.001
Distant	4.417 (3.217–6.064)	<.001	9.361 (6.156–14.234)	<.001
Unknown	2.079 (1.206–3.584)	.008	3.397 (1.703–6.772)	.001
Cancer-directed surgery				
Yes	1.00 (reference)		1.00 (reference)	
No	2.808 (2.307–3.417)	<.001	3.062 (2.442–3.840)	<.001
Unknown	2.218 (1.273–3.864)	.005	2.771 (1.543–4.975)	.001

82% and 50%, respectively. Compared to that study, the 5-year survival rate in this cohort was much shorter (OS: 55.0% and 18.2%, CCS: 62.6% and 19%) and may be the source of heterogenicity regarding systemic therapies. Most patients (74%) in the previous study[19] received peptide receptor radionuclide therapy (PRRT) and systemic therapy.

Despite valuable findings above, there are several limitations in our study. SEER does not provide organ metastases information except brain, bone, liver and lung and there are few cases in some groups. It also has no information on when patients underwent surgery or metastasis after surgery. Due to the absence of information on chemotherapy or targeted therapy included in the SEER database, their effects on survival could not be evaluated. However, one could assume that the impact of adjuvant therapies on survival reported in SEER is low, since most effective therapies such as transarterial (chemo-) embolization, somatostatin-or radiolabeled somatostatin analogues as well as targeted therapy are newer treatment modalities that have only recently been used.[20]

5. Conclusion

In conclusion, in this study we have analyzed the tumor characteristics and survival times of the pNETs patients with different metastatic patterns. Results show that pNETs patients without organ metastasis had the best survival outcomes, while multiple had the worst outcomes. There were no significant differences in bone metastasis, liver metastasis and lung metastasis. Cancer-directed surgery is valuable not only for the patients without organ metastasis, but also for the liver metastasis and multiple metastasis patients. Of course, further research is needed.

Author contributions

Data curation: Jinjuan Zhang.
Methodology: Jinjuan Zhang.
Supervision: Shuye Liu.
Writing – original draft: Sumei Wang.
Writing – review & editing: Jiandong Zhang.

References

[1] Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol 2017;3:1335–42.
[2] Fang C, Wang W, Zhang Y, et al. Clinicopathologic characteristics and prognosis of gastroenteropancreatic neuroendocrine neoplasms: a multicenter study in South China. Chin J Cancer 2017;36:51.
[3] Giuseppe Nigri , Niccolò Petrucciani , Tarek Debs , et al. Treatment options for PNET liver metastases: a systematic review. World J Surg Oncol 2018;16:142.
[4] Luo G, Javed A, Strosberg JR, et al. Modified staging classification for pancreatic neuroendocrine tumors on the basis of the American Joint Committee on Cancer and European Neuroendocrine Tumor Society Systems. J Clin Oncol 2017;35:274–80.
[5] Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, et al. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). Ann Oncol 2010;21:1794–803.
[6] Pavel M, O'Toole D, Costa F, et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology 2016;103:172–85.
[7] Foulfoin M, Graillot E, Adham M, et al. Treatment of metastatic pancreatic neuroendocrine tumors: relevance of ENETS 2016 guidelines. Endocr Relat Cancer 2017;24:71–81.
[8] Surveillance, Epidemiology and End Results Program. About the SEER Program. Available at: http://seer.cancer.gov/about [access date June 25, 2016].
[9] Fritz A, Percy C, Jack A, et al. International Classification of Disease for Oncology. 3rd ed.Geneva, Switzerland: World Health Organization; 2000.
[10] Zhou H, Zhang Y, Wei X, et al. Racial disparities in pancreatic neuroendocrine tumors survival: a SEER study. Clin Res Cancer Med 2017;6:2745–56.
[11] Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? J Hepatol 2007;47:460–6.
[12] Frilling A, Li J, Malamutmann E, et al. Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. Br J Surg 2009;96:175–84.
[13] Norton JA. Endocrine tumours of the gastrointestinal tract. Surgical treatment of neuroendocrine metastases. Best Pract Res Clin Gastroenterol 2005;19:577–83.
[14] Madeira I, Terris B, Voss M, et al. Prognostic factors in patients with endocrine tumours of the duodenopancreatic area. Gut 1998;43:422–7.
[15] Yu F, Venzon DJ, Serrano J, et al. Prospective study of the clinical course, prognostic factors, causes of death, and survival in patients with long-standing Zollinger-Ellison syndrome. J Clin Oncol 1999;17:615–30.
[16] Que FG, Nagorney DM, Batts KP, et al. Hepatic resection for metastatic neuroendocrine carcinomas. Am J Surg 1995;10:36–43.
[17] Kulke MH, Anthony LB, Bushnell DL, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas 2010;39:735–52.
[18] Pavel M, Baudin E, Couvelard A, et al. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology 2012;95:157–76.
[19] Bertani E, Fazio N, Botteri E, et al. Resection of the primary pancreatic neuroendocrine tumor in patients with unresectable liver metastases: possible indications for a multimodal approach. Surgery 2014;155:607–14.
[20] Rossi RE, Massironi S, Conte D, et al. Therapy for metastatic pancreatic neuroendocrine tumors. Ann Transl Med 2014;2:8.