Clinical Interventions in Aging

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ORIGINAL RESEARCH

Primary site surgery for elderly patients with distant metastatic pancreatic neuroendocrine tumor: to do or not to do?

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Objective: To investigate the effect of primary site surgery (PSS) on elderly patients (≥65 years) with pancreatic neuroendocrine tumor (pNET) distant metastasis.

Patients and methods: We reviewed Surveillance Epidemiology and the End Results database for elderly patients with distant pNET from 1973 to 2015. The variables and survival outcomes of patients with PSS were compared with that of patients with no PSS. After propensity score matching, the survival outcome was compared again between the two groups. Multivariable Cox proportional hazard model was used to identify variables associated with cancer-specific and overall survival. Four sub-groups were divided according to the age and differentiation: 1) age 65–74 years+ well or moderately differentiated; 2) age ≥75 years+ well or moderately differentiated; 3) age 65–74 years+ poorly differentiated or undifferentiated; and 4) age ≥75 years+ poorly differentiated or undifferentiated. Cancer-specific survival was compared between the patients with and without PSS in the above each group.

Results: A total of 210 elderly patients with distant pNET were finally confirmed. Of which, 148 patients did not undergo PSS, while 62 patients underwent PSS. Being female (p=0.049), locating on body/tail of pancreas (p=0.006), and well or moderately differentiated (p=0.032) were more likely received PSS. The patients underwent PSS had better survival outcomes both before and after propensity score matching. Multivariable Cox proportional hazard analysis proves PSS and higher histological grade to be protective and risk factors. PSS may improve cancer specific survival in patients of group 1), and no improvement was observed in patients of the other three sub-groups.

Conclusion: Not all elderly patients with pNET distant metastasis could benefit from PSS. Patients aged 65–74 years with well or moderately differentiated may benefit from primary lesion surgery, but should be evaluated carefully. Prospective randomized controlled trials are worth performing.

Keywords: primary site surgery, pancreatic neuroendocrine tumor, distant metastasis, elderly patients

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Introduction

As a rare neoplasm, pancreatic neuroendocrine tumor (pNET) originates from pancreatic neuroendocrine cells and may occur in various organs, including lung, gastrointestinal tract, pancreas, etc.[1,2] pNETs represent approximately 7% of all NETs and account for 1–2% of all pancreatic malignancies.[1–3] Over the past several decades, the incidence of pNET has been increasing in the United States.[4] pNETs have great variance in biological behavior. Most of the pNETs have low malignant behavior and slow growth rate, but some of them possess high ability of invasiveness.[5] Up to 60–80% of patients develop

distant metastasis during the course of this disease.[6,7] Based on the data from Surveillance Epidemiology and End Results (SEER) database from 1973 to 2015 in the current study, 50.0% of the pNET patients (4212/8422) were distant metastasis at the first diagnosis. Previous studies have revealed that the presence of distant metastatic is one of the strongest predictors for patients' survival. The 5-year survival rate (13–54%) was significantly worse than patients without liver metastasis (75–99%).[8,9]

Distant metastatic pNET requires systematic treatment, which includes somatostatin analogs (SSA), molecular targeted therapy, chemotherapy, peptide receptor radionuclide therapy (PRRT), etc.[10] Previous studies have indicated that the primary site surgery (PSS) can improve the survival of patients with distant metastatic pNET.[11,12] With the aggravation of social aging, the number of elderly cancer patients is increasing gradually. Elderly patients account for a considerable proportion of cancerous cases.[13,14] In the current study, elderly patients (≥65 years) account for 40.7% (3431/8422) of all pNET patients between 1973 and 2015 in SEER database. In the distant metastatic cases, elderly patients (≥65 years) account for 41.4% (1743/4212) in SEER database. The elderly patients have special physiological and pathological characteristics, such as more complications, poor tolerance to surgery, and high mortality after surgery.[15] Is it justifiable to perform the PSS in elderly patients with distant metastasis of pNET, which is seldom elucidated in the existing literature. We performed a study solely focusing on the elderly patients (≥65 years) with pNET distant metastasis based on the SEER database, to investigate the effect of PSS on elderly patients with pNET distant metastasis.

Patients and methods

Patient demographic and clinical data

We queried SEER database for patients with pNET from 1973 to 2015, using SEER*Stat software version 8.3.5. The data accessed from SEER are freely available. PNET was defined as including the following International Classification of Diseases for Oncology third edition (ICD-O3) codes: 8150/3, 8151/3, 8152/3, 8153/3, 8155/3, 8156/3, 8240/2, 8240/3, 8241/3, 8242/3, 8243/3, 8246/2, 8246/3, 8249/3. All pancreatic anatomical sites were included (C25.0-C25.9) in our study. Patients with stage IV pNET diagnosed between 1973 and 2015 were selected. Only the cases with diagnoses based on histological studies were included, while cases whose diagnoses relied only on autopsies or were detailed only on death certificates were excluded. A total of 8422 patients suffered pNET, and 4212 patients have distant metastasis.

Patients exclusion criteria include (see Figure 1):

Combined with other primary tumor;

Incomplete data;

Survival month ≤1 month;

Patients with age <65 years.

Patient data collection and outcome measurement

We collected patients demographic and tumor characteristics concerning age, gender, race,primary site of tumor, histological grade, year of diagnosis, tumor size, PSS, marital status, survival months, SEER cause-specific survival, and overall survival. Cancer-specific survival was defined as the duration from diagnosis to death attributable to the pNET. Overall survival was defined as the duration from diagnosis to death from any cause.

The variables of patients with PSS were compared with that of patients with no PSS. The overall survival and cancer-specific survival were also compared with log-rank test between the two groups before and after the propensity score matching of the variables. The primary survival outcome measure was cancer-specific survival. Multivariable Cox proportional hazard model was used to identify variables associated with cancer-specific survival and overall survival before and after propensity score matching.

In order to further study the effects of PSS on different age and differentiation group, patients were further divided into four sub-groups: 1) age 65–74 years+ well or moderately differentiated; 2) age ≥75 years+ well or moderately differentiated; 3) age 65–74 years+ poorly differentiated or undifferentiated; and 4) age ≥75 years+ poorly differentiated or undifferentiated. Cancer-specific survival was compared between the patients with PSS and the patients without PSS using Kaplan–Meier survival analysis with log-rank test and multivariable Cox proportional analysis in the above each group. The cutoff value of age was identified by X-tile.[16]

The data accessed from SEER are freely available. This study does not contain any studies with human participants or animals performed by any of the authors. In addition, according to the guidelines of the government of the United States, data released through the SEER database donot require informed patient consent.

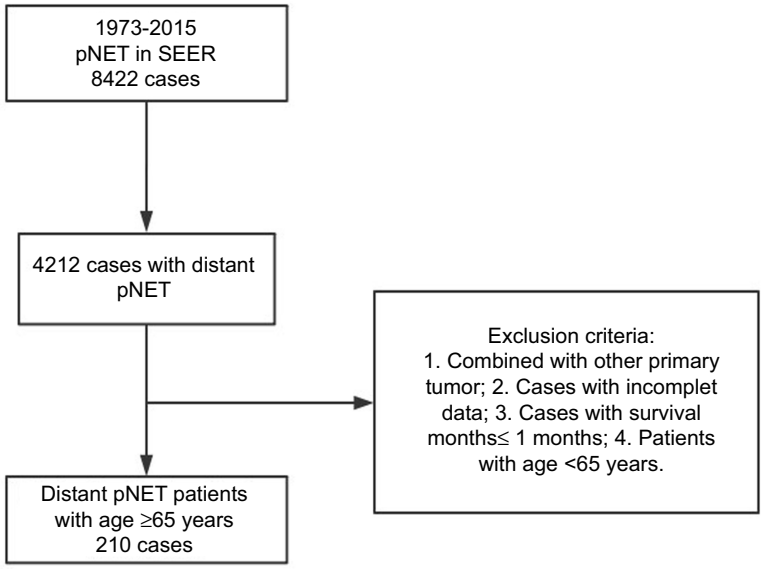

Figure 1 Patient screening process.
Abbreviations: pNET, pancreatic neuroendocrine tumor; SEER, Surveillance Epidemiology and End Results.

Statistical analyses

A two-sided $p<0.05$ was considered statistically significant and the analyses were performed by IBM SPSS Statistics 22.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 7.0 (GraphPad Software, USA). Pearson and Fisher chi-square tests were performed before and after PSM to compare the characteristics of patients with and without PSS. To balance the potential baseline confounding variables between the two groups, a propensity score matching method was performed by the "MatchIt" R package and the "nearest neighbor matching" method (ratio=1:1). Kaplan–Meier survival analysis with a log-rank test was performed to plot survival curves and to calculate the cancer-specific survival and overall survival rate. Multivariable Cox proportional hazard model was used to identify variables associated with cancer-specific survival and overall survival before and after propensity score matching. HRs were presented with 95% CI.

Result

Patient clinico-pathological features

A total of 210 patients were finally confirmed after screened out the unqualified patients. Of which, 148 elderly pNET patients with distant metastasis did not undergo PSS, while 62 patients underwent PSS. Being female (p=0.049), locating on body/tail of pancreas (p=0.006), and histological grade of well or moderately differentiated (p=0.032) were more likely received PSS (Table 1). After propensity score matching, all variables were comparable between the two groups (Table 1).

Logistic regression analysis of characteristics associated with elderly patients (≥65 years) who underwent PSS

The univariate regression analysis for PSS was performed to patients with age ≥65 years (Table 2). The variables with univariate logistic analysis $p<0.1$ were further analyzed using multivariate logistic regression. Being female (p=0.012, OR: 2.329, 95% CI: 1.204–4.503), and tumor locating at body/tail of pancreas (p=0.001, OR: 3.780, 95% CI: 1.749–8.170) were more likely received PSS, while tumor with histological grade of poorly differentiated/undifferentiated (p=0.040, OR: 0.455, 95% CI: 0.215–0.964) had decreased possibility of receipt of PSS (Table 2).

Kaplan–Meier analysis with log-rank test, and multivariable Cox proportional hazard analysis before propensity score matching and after propensity score matching

The Kaplan–Meier analysis with log-rank test proved that PSS in distant metastatic pNET patients with age ≥65 years had better cancer-specific survival and overall survival both before and after propensity score matching (Figure 2). Multivariable Cox proportional hazard analysis was performed for all 210 patients before propensity score

Table 1 Characteristics of patients older than 65 years included in the study

Variables	Before PSM			After PSM		
	NPSS, N=148	PSS, N=62	*p*	NPSS, N=62	PSS, N=62	*p*
Age			0.265			0.091
65–75 years	95 (64.2%)	45 (72.6%)		35 (56.5%)	45 (72.6%)	
≥75 years	53 (35.8%)	17 (27.4%)		27 (43.5%)	17 (27.4%)	
Gender			0.049			0.281
Male	89 (60.1%)	28 (45.2%)		35 (56.5%)	28 (45.2%)	
Female	59 (39.9%)	34 (54.8%)		27 (43.5%)	34 (54.8%)	
Race			0.247			0.161
White	123 (83.1%)	57 (91.9%)		50 (80.6%)	57 (91.9%)	
Black	16 (10.8%)	3 (4.8%)		9 (14.5%)	3 (4.8%)	
Other	9 (6.1%)	2 (3.2%)		3 (4.8%)	2 (3.2%)	
Marital status			0.639			0.855
Married	96 (64.9%)	38 (61.3%)		36 (58.1%)	38 (61.3%)	
Unmarried	52 (35.1%)	24 (38.7%)		26 (41.9%)	24 (38.7%)	
Year of diagnosis			0.875			0.699
1973–2009	53 (35.8%)	21(33.9%)		18 (29.0%)	21 (33.9%)	
2010–2015	95 (64.2%)	41 (66.1%)		44 (71.0%)	41 (66.1%)	
Tumor site			0.006			0.517
Head	58 (39.2%)	12 (19.4%)		16 (25.8%)	12 (19.4%)	
Body/tail	62 (41.9%)	42(67.7%)		35 (56.5%)	42 (67.7%)	
Overlap	21 (14.2%)	7 (11.3%)		8 (12.9%)	7 (11.3%)	
Other	7 (4.7%)	1 (1.6%)		3 (4.8%)	1 (1.6%)	
Tumor size			0.000			0.097
≤4 cm	48 (32.4%)	21 (33.9%)		29 (46.8%)	21 (33.9%)	
>4 cm	67 (45.3%)	41 (66.1%)		31 (50.0%)	41 (66.1%)	
Unknown	33 (22.3%)	0 (0%)		2 (3.2%)	0 (0%)	
Histological grade			0.032			1.000
Well/moderately	97(65.5%)	50 (80.6%)		50 (80.6%)	50 (80.6%)	
Poorly/undifferentiated	51(34.5%)	12 (19.4%)		12 (19.4%)	12 (19.4%)	

Notes: Race: other included American Indian/AK, Native Asian/Pacific Islander. Marital status: unmarried included divorced/separated/single (never married)/unmarried or domestic partner/widowed. Tumor site: "Other" included Islets of langerhans+other specific parts of pancreas+NOS of pancreas.
Abbreviations: PSM, propensity score matching; NPSS, no primary site surgery; PSS, primary site surgery; cm, centimeter.

matching. Histological grade of poorly differentiated/undifferentiated was risk factor for both overall survival (HR: 3.062, 95% CI: 2.118–4.425, $p<0.001$) and cancer-specific survival (HR 3.641, 95% CI 2.351–5.640, $p<0.001$), and PSS was proved to be protective factor for overall survival (HR: 0.392, 95% CI: 0.252–0.612, $p<0.001$) and cancer-specific survival (HR: 0.362, 95% CI: 0.206–0.637, $p<0.001$) (see Table 3). After propensity score matching, multivariable Cox proportional hazard analysis was performed for 124 patients. Histological grade of poorly differentiated/undifferentiated was also proved to be risk factor for both overall survival (HR: 4.020, 95% CI: 2.203–7.336, $p<0.001$) and cancer-specific survival (HR: 6.574, 95% CI: 3.261–13.251, $p<0.001$), and PSS was also proved to be protective factor for overall survival (HR: 0.212, 95% CI: 0.125–0.360, $p<0.001$) and cancer-specific survival (HR: 0.210, 95% CI: 0.110–0.403, $p<0.001$). (See Table 4)

Kaplan–Meier analysis with log-rank test and multivariable Cox proportional analysis for sub-groups of elderly patients with pNET distant metastasis

Cases with PSS had a cancer-specific survival advantage comparing with cases with no PSS in the sub-group of 1)

Table 2 Logistic regression analysis of characteristics for PSS in elderly patients (≥65 years)

Variables	Univariate analysis for PSS			Multivariate analysis for PSS		
	OR	95% CI	*p*	OR	95% CI	*p*
Age						
65–75 years	1 (Referent)					
>75 years	0.677	0.353–1.299	0.241			
Gender						
Male	1 (Referent)			1 (Referent)		
Female	1.832	1.007–3.333	0.048	2.329	1.204–4.503	0.012
Race						
White	1 (Referent)					
Black	0.405	0.113–1.444	0.163			
Other	0.480	0.100–2.291	0.357			
Marital status						
Married	1 (Referent)					
Unmarried	1.166	0.632–2.151	0.623			
Year of diagnosis						
1973–2009	1 (Referent)					
2010–2015	1.089	0.584–2.033	0.788			
Tumor site						
Head	1 (Referent)			1 (Referent)		
Body/tail	3.274	1.570–6.826	0.002	3.780	1.749–8.170	0.001
Overlap	1.611	0.560–4.638	0.377	1.241	0.418–3.681	0.697
Other	0.690	0.078–6.142	0.740	0.711	0.077–6.535	0.763
Histological grade						
Well/moderately	1 (Referent)			1 (Referent)		
Poorly/undifferentiated	0.456	0.223–0.934	0.032	0.455	0.215–0.964	0.040
Tumor size						
≤4 cm	1 (Referent)					
>4 cm	1.399	0.735–2.662	0.485			
Unknown			NA			

Note: Variables with univariate analysis $p<0.1$ underwent further multivariate analysis.
Abbreviation: PSS, primary site surgery.

age 65–74 years+ well or moderately differentiated ($p<0.001$) (Figure 3A). However, no differences were observed regarding cancer-specific survival in the sub-groups of 2) age ≥75 years+ well or moderately differentiated ($p=0.229$) (Figure 3B), 3) age 65–74 years+ poorly differentiated or undifferentiated ($p=0.237$) (Figure 3C), and 4) age ≥75 years+ poorly differentiated or undifferentiated ($p=0.655$) (Figure 3D). Multivariable Cox proportional analysis was performed for the four sub-groups, and PSS was an independent protective factor only in cases with age of 65–74 years and well or moderately differentiated tumors (HR 0.142, 95% CI 0.053–0.379, $p<0.001$) (supplemental materials).

Discussion

Patients with distant metastasis of pNET are often treated with comprehensive therapy, including SSA, molecular targeted therapy, chemotherapy, PRRT, etc.[10] Many studies advocate PSS in the setting of metastatic pNET for reasons that PSS can improve the control of endocrine-related symptoms, relieve the symptoms of compression and may prolong the survival time of patients.[11,12,17,18] However, with the increase of the elderly

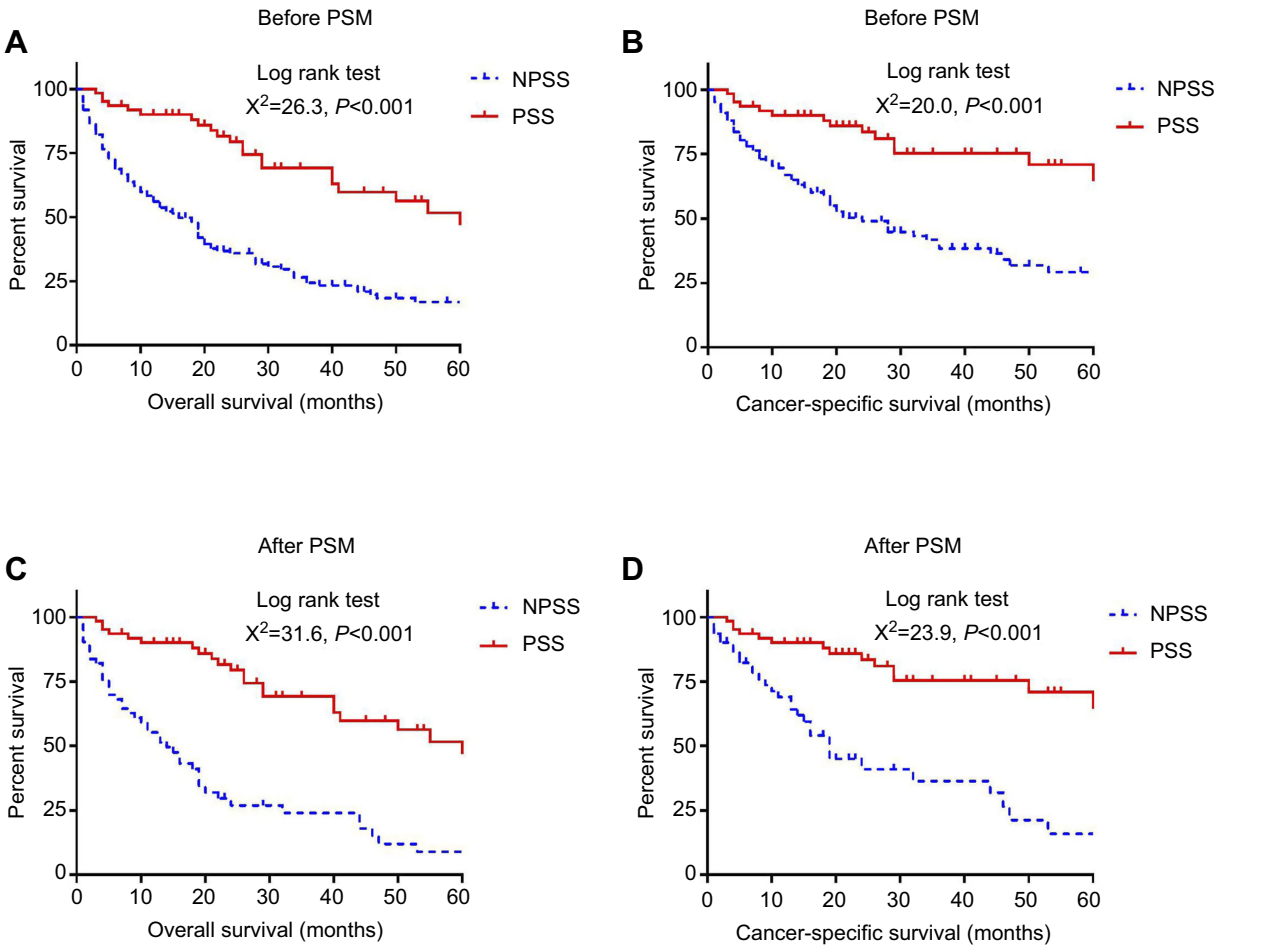

Figure 2 Overall survival and cancer-specific survival in elderly patients (≥65 years) with metastatic pNET who underwent primary site surgery (PSS) and no primary site surgery (NPSS), before and after propensity score matching (PSM).

Notes: (**A**) Kaplan–meier analysis for overall survival in elderly patients (≥65 years) who underwent PSS and NPSS before PSM; (**B**) Kaplan–meier analysis for cancer-specific survival in elderly patients (≥65 years) who underwent PSS and NPSS before PSM; (**C**) Kaplan–meier analysis for overall survival in elderly patients (≥65 years) who underwent PSS and NPSS after PSM; (**D**) Kaplan–meier analysis for cancer-specific survival in elderly patients (≥65 years) who underwent PSS and NPSS after PSM.

population, there is still few clinical evidence on the suitability of the elderly with metastatic pNET to accept PSS. The elderly patients usually have a higher incidence of comorbidities, such as chronic obstructive pulmonary disease, hypertension, coronary artery disease, and diabetes mellitus, which may increase the death rate and reduce the possibility of receipt of endocrine therapy, chemotherapy, targeted therapy, and surgery.[15] Given the absence of clinical evidence, the study focusing on the suitability of PSS for elderly patients with metastatic pNET is necessary.

In the current study, female patients are more likely to receive PSS, which may be associated with fewer comorbidities in elderly women. There are more tumors receiving PSS in the body/tail of the pancreas than in the head of the pancreas. This may be related to the fact that the complexity of surgery of pancreatic body/tail is less than that of the surgery of pancreatic head. After all, the tumors locating on the head of pancreas need pancreaticoduodenectomy, whereas the former only needs the resection of pancreatic body and tail. In addition, it is not surprising that poorly differentiated and undifferentiated tumors are less likely to undergo surgery than well-differentiated tumors, because the patients with poorly differentiated and undifferentiated tumors have worse prognosis and are more likely receiving conservative treatment options. However, the rate of PSS in the greater elderly patients (≥75 years) is not different from that in the elderly patients (65–74 years) (see Table 2).

Both before and after propensity score matching, tumor histological grade of poorly differentiation and undifferentiation is an independent risk factor for overall survival and cancer-specific survival, whereas PSS is an independent protective factor (see Tables 3, 4 and Figure 2). Then, in order to further explore whether elderly patients with metastatic pNET are suitable for PSS, a further sub-grouping of age and

Table 3 Multivariate regression analysis of characteristics for survival in elderly patients (≥65 years) before PSM

Variables	Multivariate analysis for OS			Multivariate analysis for CSS		
	HR	95% CI	*p*	HR	95% CI	*p*
Age						
65–75 years	1 (Referent)			1 (Referent)		
>75 years	1.373	0.954–1.977	0.088	1.231	0.775–1.955	0.378
Gender						
Male	1 (Referent)			1 (Referent)		
Female	1.028	0.678–1.557	0.898	0.939	0.571–1.544	0.803
Race						
White	1 (Referent)			1 (Referent)		
Black	1.367	0.726–2.572	0.333	1.333	0.621–2.859	0.460
Other	1.598	0.782–3.269	0.199	1.767	0.777–4.018	0.175
Marital status						
Married	1 (Referent)			1 (Referent)		
Unmarried	1.228	0.852–1.770	0.271	1.417	0.906–2.217	0.127
Year of diagnosis						
1973–2009	1 (Referent)			1 (Referent)		
2010–2015	0.931	0.634–1.365	0.714	1.027	0.638–1.651	0.913
Tumor site						
Head	1 (Referent)			1 (Referent)		
Body/tail	1.104	0.734–1.661	0.635	0.872	0.538–1.415	0.580
Overlap	1.226	0.692–2.171	0.485	0.859	0.422–1.749	0.676
Other	1.709	0.784–3.729	0.178	1.758	0.773–3.997	0.178
Histological grade						
Well/moderately	1 (Referent)			1 (Referent)		
Poorly/undifferentiated	3.062	2.118–4.425	0.000	3.641	2.351–5.640	0.000
Tumor size						
≤4 cm	1 (Referent)			1 (Referent)		
>4 cm	0.862	0.568–1.308	0.485	0.790	0.476–1.310	0.361
Unknown	0.798	0.463–1.375	0.416	0.812	0.423–1.558	0.531
Primary site surgery						
No	1 (Referent)			1 (Referent)		
Yes	0.392	0.252–0.612	0.000	0.362	0.206–0.637	0.000

Note: Variables with univariate analysis $p<0.1$ underwent further multivariate analysis.
Abbreviations: OS, overall survival; CSS, cancer-specific survival; PSM, propensity score matching.

differentiation was performed. The reason for choosing 75 years for further grouping is that WHO stipulates that the older elderly are over 75 years old.[15] In addition, X-tiles are also used to determine the cutoff value of age. From the results of the present study, patients with age ≥65 years with poorly differentiated and undifferentiated pNETs are not suitable to receive PSS. For well and moderately differentiated metastatic pNETs, only those aged 65–74 are suitable for PSS, while those aged ≥75 are not suitable for PSS, because there is no difference in cancer-specific survival between PSS and no PSS patients. The physical condition of the patients with age≥75 years is worse than that of other patients, and their physical state, surgical tolerance, and antineoplastic immunity are decreased. These may be the explanation of the fact that even accepting PSS does not improve cancer-specific survival for cases with age ≥75 years and histological grade of well and moderately differentiation.

It should be pointed out that selection bias may exist in the present study. Firstly, patients who have not undergone surgery may be too ill to perform surgery. Secondly, it is impossible to

Table 4 Multivariate regression analysis of characteristics for survival in elderly patients (Table 4: Multfter PSM)

Variables	Multivariate analysis for OS			Multivariate analysis for CSS		
	HR	95% CI	*p*	HR	95% CI	*p*
Age						
65–75 years	1 (Referent)			1 (Referent)		
>75 years	1.442	0.852–2.442	0.173	1.224	0.648–2.311	0.533
Gender						
Male	1 (Referent)			1 (Referent)		
Female	1.591	0.880–2.877	0.125	1.378	0.688–2.758	0.366
Race						
White	1 (Referent)			1 (Referent)		
Black	1.371	0.602–3.124	0.452	1.031	0.377–2.817	0.953
Other	2.705	0.959–7.628	0.060	3.864	1.340–11.143	0.012
Marital status						
Married	1 (Referent)			1 (Referent)		
Unmarried	1.309	0.750–2.288	0.344	1.370	0.694–2.703	0.364
Year of diagnosis						
1973–2009	1 (Referent)			1 (Referent)		
2010–2015	0.909	0.482–1.714	0.769	0.931	0.413–2.100	0.863
Tumor site						
Head	1 (Referent)			1 (Referent)		
Body/tail	0.649	0.347–1.214	0.176	0.664	0.303–1.456	0.307
Overlap	0.694	0.288–1.670	0.414	0.530	0.164–1.706	0.287
Other	0.423	0.129–1.384	0.155	0.602	0.167–2.171	0.438
Histological grade						
Well/moderately	1 (Referent)			1 (Referent)		
Poorly/undifferentiated	4.020	2.203–7.336	0.000	6.574	3.261–13.251	0.000
Tumor size						
≤4 cm	1 (Referent)			1 (Referent)		
>4 cm	1.058	0.618–1.813	0.836	1.087	0.548–2.157	0.811
Unknown	0.701	0.114–4.324	0.702	1.070	0.162–7.080	0.944
Primary site surgery						
No	1 (Referent)			1 (Referent)		
Yes	0.212	0.125–0.360	0.000	0.210	0.110–0.403	0.000

Note: Variables with univariate analysis $p<0.1$ underwent further multivariate analysis.
Abbreviations: OS, overall survival; CSS, cancer-specific survival; PSM, propensity score matching.

determine whether the two groups are completely balanced in other treatments (such as SSA, chemotherapy, molecular targeted therapy or PRRT, etc.) due to the lack of other treatment information. In addition, there are other limitations that need to be addressed. First, there is a lack of information related to surgery. We can not obtain the duration of surgery, blood loss, complications, and so on. Secondly, the number of patients administrated in the study was relatively small, especially after further divided sub-groups. Thirdly, we can not know the exact reason for the surgery due to the lack of relevant information.

Judging from the common sense, patients undergoing surgery should be in better physical conditions and are more likely to receive a variety of treatment options. The no prolonged survival time after surgery may be more indicative of the ineffectiveness of PSS for these patients. Patients in the three sub-groups (age ≥75 years+ well or moderately differentiated, age 65–74 years+ poorly differentiated or undifferentiated, and age ≥75 years+ poorly differentiated or undifferentiated) did not have a better prognosis after surgery, which suggests that patients of these three sub-groups are less likely to benefit from

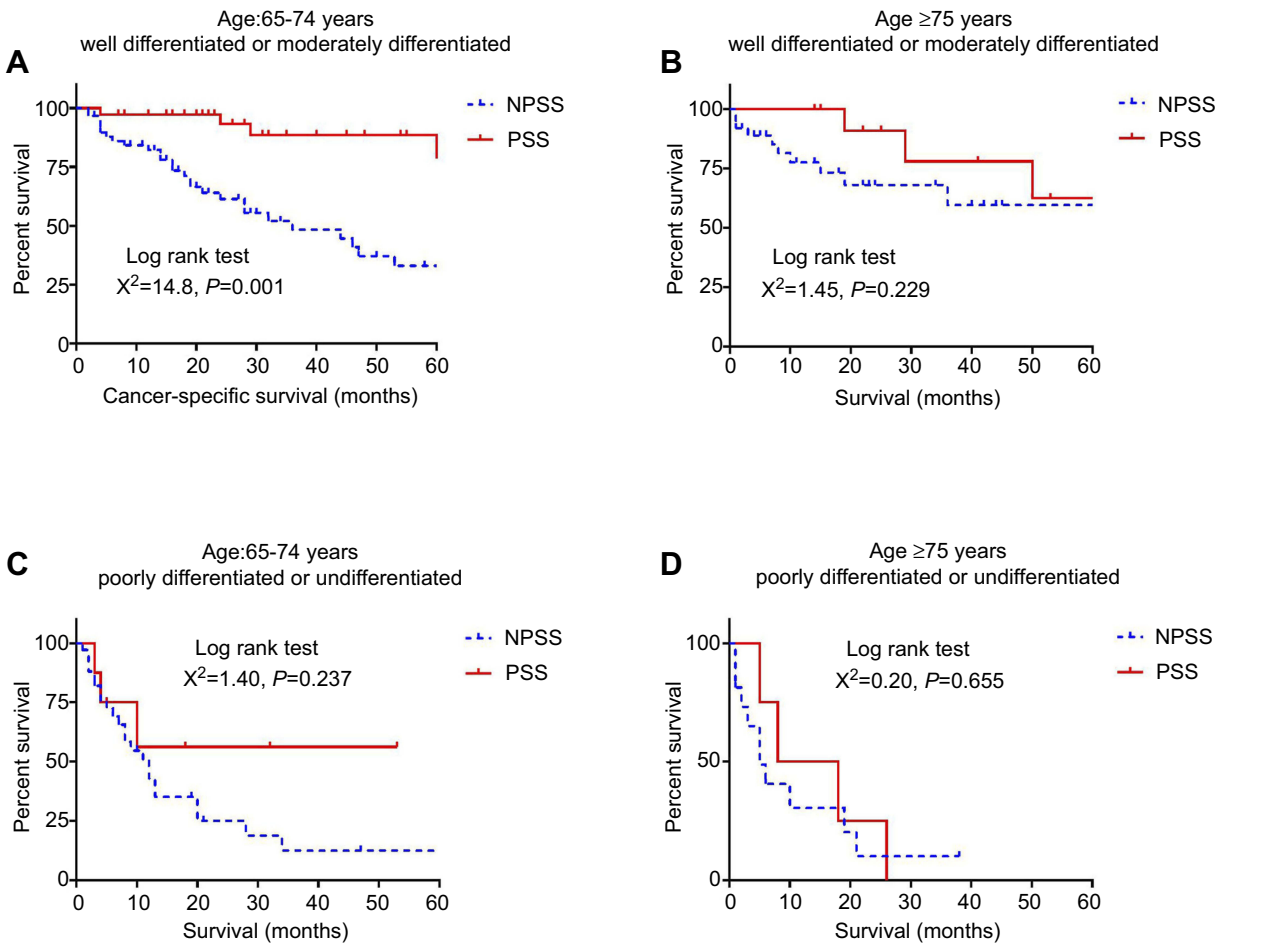

Figure 3 Kaplan–Meier analysis of cancer-specific survival for elderly patients (≥65 years) in sub-groups.
Notes: (**A**) Kaplan–meier analysis for cancer-specific survival in patients with age between 65 and 74 years and tumor of well or moderately differentiation; (**B**) Kaplan–meier analysis for cancer-specific survival in patients with age ≥75 years and tumor of well or moderately differentiation; (**C**) Kaplan–meier analysis for cancer-specific survival in patients with age between 65 and 74 years and tumor of poorly differentiation or undifferentiation; (**D**) Kaplan–meier analysis for cancer-specific survival in patients with age ≥75 years and tumor of poorly differentiation or undifferentiation.

PSS. Patients in the sub-group of age 65–74 years+ well or moderately differentiated achieved a prolonged survival after surgery. However, given the possible existing selection bias, the prolonged survival after surgery may not be entirely attributed to surgery. Careful evaluation should be performed before surgery and various treatment options should be in consideration. In a word, the results of this study have some implications for the treatment of these patients, but prospective randomized controlled studies are still necessary for concluding a decision of surgery.

Conclusion

Not all elderly patients with distant metastatic pNET could benefit from PSS. Patients aged 65–74 with well or moderately differentiated tumor may benefit from primary lesion surgery, but should be evaluated carefully and in consideration of various treatment options. Patients aged ≥75 years with well or moderately differentiated tumor, and patients aged ≥65 years with poorly differentiated and undifferentiated tumor may not benefit from PSS. Prospective randomized controlled trials are worth performing.

Ethical approval

This study does not contain any studies with human participants or animals performed by any of the authors. In addition, according to the guidelines of the government of the United States, data released through the SEER database does not require informed patient consent.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Multivariate regression analysis of characteristics for cancer-specific survival in patients with age 65–74 years+ well or moderately differentiated

Variables	Multivariate analysis for CSS		
	HR	95% CI	*p*
Gender			
Male	1 (Referent)		
Female	1.887	0.794–4.485	0.151
Race			
White	1 (Referent)		
Black	0.676	0.183–2.492	0.556
Other	0.919	0.111–7.615	0.937
Marital status			
Married	1 (Referent)		
Unmarried	1.677	0.736–3.823	0.219
Year of diagnosis			
1973–2009	1(Referent)		
2010–2015	2.286	0.944–5.534	0.068
Tumor site			
Head	1 (Referent)		
Body/tail	0.963	0.398–2.329	0.933
Overlap	1.266	0.415–3.863	0.679
Other	2.908	0.816–10.367	0.100
Tumor size			
≤4 cm	1(Referent)		
>4 cm	1.835	0.822–4.096	0.138
Unknown	0.620	0.216–1.782	0.375
Primary site surgery			
No	1 (Referent)		
Yes	0.142	0.053–0.379	0.000

Table S2 Multivariate regression analysis of characteristics for cancer-specific survival in patients with age ≥75 years+ well or moderately differentiated

Variables	Multivariate analysis for CSS		*p*
	HR	95% CI	
Gender			
Male	1 (Referent)		
Female	1.899	0.270–13.335	0.519
Race			
White	1 (Referent)		
Black			
Other	28.922	1.998–418.6	0.014
Marital status			
Married	1 (Referent)		
Unmarried	0.582	0.103–3.289	0.582
Year of diagnosis			
1973–2009	1(Referent)		
2010–2015	0.408	0.097–1.719	0.222
Tumor site			
Head	1 (Referent)		
Body/tail	2.483	0.447–13.785	0.307
Overlap			
Other	17.690	0.918–340.8	0.057
Tumor size			
≤4 cm	1 (Referent)		
>4 cm	0.166	0.036–0.764	0.037
Unknown	1.213	0.179–8.215	0.843
Primary site surgery			
No	1 (Referent)		
Yes	1.150	0.130–10.165	0.900

Table S3 Multivariate regression analysis of characteristics for cancer-specific survival in patients with age 65–74 years+ poorly differentiated or undifferentiated

Variables	Multivariate analysis for CSS		*p*
	HR	95% CI	
Gender			
Male	1 (Referent)		
Female	1.143	0.349–3.746	0.825
Race			
White	1 (Referent)		
Black	3.047	0.748–12.406	0.120
Other	0.656	0.066–6.505	0.719
Marital status			
Married	1 (Referent)		
Unmarried	1.444	0.520–4.014	0.481
Year of diagnosis			
1973–2009	1 (Referent)		
2010–2015	0.802	0.304–2.118	0.656
Tumor site			
Head	1 (Referent)		
Body/tail	0.914	0.330–2.531	0.863
Overlap	0.719	0.168–3.090	0.658
Other	0.760	0.068–8.540	0.824
Tumor size			
≤4 cm	1 (Referent)		
>4 cm	0.841	0.302–2.341	0.740
Unknown	0.986	0.285–3.413	0.983
Primary site surgery			
No	1 (Referent)		
Yes	0.621	0.174–2.218	0.463

Table S4 Multivariate regression analysis of characteristics for cancer-specific survival in patients with age ≥75 years+ poorly differentiated or undifferentiated

Variables	Multivariate analysis for CSS		*p*
	HR	95% CI	
Gender			
Male	1 (Referent)		
Female	0.640	0.141–2.898	0.563
Race			
White	1 (Referent)		
Black			
Other	8.373	1.036–67.700	0.046
Marital status			
Married	1 (Referent)		
Unmarried	1.562	0.316–7.708	0.584
Year of diagnosis			
1973–2009	1 (Referent)		
2010–2015	0.380	0.064–2.266	0.288
Tumor site			
Head	1 (Referent)		
Body/tail	2.483	0.447–13.785	0.307
Overlap			
Other	17.690	0.918–340.8	0.057
Tumor size			
≤4 cm	1 (Referent)		
>4 cm	0.458	0.119–1.766	0.257
Unknown	5.879	0.296–116.8	0.245
Primary site surgery			
No	1 (Referent)		
Yes	0.469	0.091–2.407	0.364