Clinicopathological features and prognosis factors for survival in elderly patients with pancreatic neuroendocrine tumor
A STROBE-compliant article

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Abstract

To investigate the features and prognosis of the elderly patients with pancreatic neuroendocrine tumor (pNET).

The patients diagnosed with pNETs between 2004 and 2014 were identified from the Surveillance Epidemiology and End Results database. The ethical approval was waived because the present study was analysis of the data from Surveillance Epidemiology and End Results database.

A total of 4608 patients with "one primary only" histologically pNETs were confirmed and 653 were older than 75 years. Cancer-specific survival (CSS) and overall survival (OS) were examined. The elderly patients (≥75 years) have disadvantage in CSS and OS compared with younger cohort. Multivariate logistic regression revealed that the elderly patients have increased poorly differentiated composition, and decreased proportion of Black patients, receipt of surgery, married status, and number of removed lymph node. Multivariate Cox regression analysis demonstrated worse differentiation. Patients of T3–4 and M1 stage were associated with poor CSS, while patients of being female, tumor locating at pancreatic body/tail, receipt of surgery, and being married were associated with better CSS in the elderly patients. Meanwhile, patients with higher histological grade and M1 stage have poor OS, while patients with the characteristics of female, being married, tumor location at pancreatic body/tail and tumor surgery have better OS. Distant metastatic elderly patients underwent primary site surgery had better CSS and OS than the patients without surgery.

The elderly patients have increased possibility of poorly differentiated tumor, and decreased proportion of Black patients, surgery of primary site, number of removed lymph node and married status. Worse differentiation and tumor metastasis were independent risk factors for both CSS and OS, while primary tumor located in body/tail of pancreas, female patients, surgery of tumor primary site, and being married were protective factors.

Abbreviations: CSS = cancer-specific survival, ICD-O3 = International Classification of Diseases for Oncology third edition, NET = neuroendocrine tumor, OS = overall survival, pNET = pancreatic neuroendocrine tumor, SEER = Surveillance Epidemiology and End Results.

Keywords: elderly cohort, pancreatic neuroendocrine tumor

1. Introduction

The neuroendocrine tumors (NETs) originate from neuroendocrine cells and may occur in many organs, including lung, gastrointestinal tract, and pancreas. Among them, gastroenteropancreatic NETs account for 65–75% of the whole body NETs.[1] Pancreatic NETs (pNETs) comprise approximately half of the gastroenteropancreatic NETs, and account for approximately <3% of all pancreatic malignancies.[2] As a rare pancreatic neoplasm with an annual incidence of 0.19/100,000–0.32/100,000,[3–5] the incidence of pNET has been rising in the United States over the past several decades.[6] A previous study exhibited that most patients with pNETs possessed the characteristics of indolent physiological behavior and longer survival time than those with other pancreatic malignancies.[7] The 5-year overall survival (OS) rates of patients with NETs were >90% both in China and the United States, and the 5-year disease-free survival rates were also similar in the Chinese and American patients: 63.6% vs. 66.9%.[7] However, pNETs are highly heterogenous tumors and may develop aggressive invasion or fatal metastasis.[8,9]

In the recent decades, owing to an increase in the aging population, the incidence of malignancies among the elderly is increasing.[10–12]

The characteristics of the elderly patients suffering from malignancies are different from those of other patients.[11,13,14] Numerous studies across various malignancies have shown that

advanced age is associated with decreased referral to specialists, increased delivery of suboptimal therapy, and increased patient refusal of therapy.[11,13,14] Thereby, the effect of the treatment in the elderly is probably worse than that in the young patients. To this day, the characteristics of the elderly cohort suffering from pNETs are poorly defined. In order to analyze the characteristics and the more effective way of treatment for elderly patients suffering from pNETs, we collected and studied the data from the Surveillance Epidemiology and End Results (SEER) database.

2. Methods

2.1. Database and patient cohort

The SEER database was searched for patients with histologically confirmed pNET from 2004 to 2014, using the SEER*Stat software version 8.3.5 (accession number: 15076-Nov2016). We defined pNET to include 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, and 8249/3. We included all the pancreatic anatomical sites (C25.0–C25.9) in our study. The patients who had 2 or more malignancies were excluded. An elderly person was defined as age ≥75 years based on the definition by the WHO.[15]

2.2. Patient data collection and outcome measurement

Variables regarding gender, race, primary site of tumor, histological grade, T stage, N stage, M stage, primary site surgery (yes or no), marital status, survival months, and cause-specific death classification were collected.

The primary outcome measure was cancer-specific survival (CSS). CSS was defined as the time elapsed from the diagnosis to death attributable to the pNET. The secondary outcome measure was OS, which was defined as the duration from the diagnosis to death from any cause. The information on systemic treatment was not provided by the SEER database.

2.3. Statistical analyses

Pearson chi-squared test and multivariate logistic regression were utilized to compare the differences in the demographic and tumor characteristics between the younger (<75) and elderly patients. Multivariate Cox proportional hazards model was used to identify the factors which were independently associated with CSS and OS. The Kaplan–Meier analysis with the log-rank test was used to describe the CSS and OS. $P < 0.05$ was considered as statistically significant. All statistical analyses were performed using the IBM SPSS Statistics 22.0 (IBM, Armonk, NY).

3. Result

3.1. Clinicopathological features of the patients

A total of 6034 patients with histologically confirmed pNETs were extracted from the SEER database, and those with 2 or more malignancies were excluded. In all, 4608 patients with 1 primary-only pNETs were included, of which, 3955 were <75 years (85.8%, mean age 55.69±11.82) and 653 patients ≥75 years (14.2%, mean age 80.24±4.19). The baseline characteristics of both groups were compared using the Chi-squared analysis as shown in Table 1. Gender composition ($P = .080$), metastasis status ($P = .475$), and surgery of other region or disseminated site ($P = .052$) were compared between the 2 groups. Significant

Table 1

Chi-squared test of characteristics between elderly and younger patients.

Variables	<75 (N = 3955)	≥75 (N = 653)	P
Gender			
Male	2188 (55.3%)	325 (50.0%)	.080
Female	1767 (44.7%)	328 (50.0%)	
Race			
White	3047 (77.0%)	536 (82.1%)	.014
Black	525 (13.3%)	58 (8.9%)	
Other	354 (8.95%)	54 (8.3%)	
Unknown	29 (0.73%)	5 (0.77%)	
Tumor primary site			
Head of pancreas	1211 (30.6%)	200 (30.6%)	.048
Body or tail of pancreas	1696 (42.9%)	264 (40.4%)	
Overlapping	291 (7.36%)	37 (5.67%)	
Unknown	757 (19.1%)	152 (23.3%)	
Histological grade			
Well differentiated	1557 (39.4%)	176 (27.0%)	<.001
Moderately differentiated	451 (11.4%)	69 (10.6%)	
Poorly differentiated	225 (5.69%)	55 (8.42%)	
Undifferentiated	73 (1.85%)	15 (2.30%)	
Unknown	1649 (41.7%)	338 (51.8%)	
T stage			
T0–2	1132 (28.6%)	175 (26.8%)	.002
T3–4	1027 (26.0%)	136 (20.8%)	
Tx or NA	1796 (45.4%)	342 (52.4)	
N stage			
N0	1388 (35.1%)	243 (37.2%)	.007
N1	874 (22.1%)	109 (16.7%)	
Nx or NA	1693 (42.8%)	301 (46.1%)	
M stage			
M0	1200 (30.3%)	186 (28.5%)	.475
M1	1382 (34.9%)	243 (37.2%)	
Mx or NA	1373 (34.7%)	224 (34.4%)	
Primary site surgery			
No	1870 (47.3%)	459 (70.2%)	<.001
Yes	2073 (52.4%)	189 (28.9%)	
Unknown	12 (0.30%)	5 (0.77%)	
Resected number of regional LN resection			
None reg LN	2133 (53.9%)	493 (75.5%)	<.001
Reg LN 1–3	344 (8.70%)	28 (4.29%)	
Reg LN ≥4	1342 (33.9%)	107 (16.4%)	
Surgery of other region or disseminated site			
No	3920 (99.1%)	652 (99.8%)	.052
Yes	35 (0.88%)	1 (0.15%)	
Marital status			
Unmarried	1280 (32.4%)	274 (42.0%)	<.001
Married	2471 (62.5%)	348 (53.3%)	
Unknown	204 (5.16%)	31 (4.75%)	

LN = lymph node; Mx = uncertain M stage; NA = no information; Nx = uncertain N stage; Tx = uncertain T stage.

differences were detected regarding racial predilection ($P = .014$), tumor primary site ($P = .048$), histological grade ($P < .001$), T stage ($P = .002$), N stage ($P = .007$), primary site surgery ($P < .001$), resected number of regional lymph node ($P < .001$), and marital status ($P < .001$).

3.2. Multivariate logistic regression reveals characteristics associated with elder patients of pNETs

The differing variables between the 2 groups as revealed in the chi-squared test were selected and further analyzed using the multivariate logistic regression. The elderly patients showed decreased predilection for the Black race ($P < .001$, Odds ratio

(OR) 0.520, 95% CI 0.387–0.699), and increased possibility of poorly differentiated tumor (P=.013, OR 1.582, 95% CI 1.101–2.275), primary site surgery (P<.001, OR 0.544, 95% CI 0.397–0.747), number of resected lymph nodes (1≤n≤3:P=.017, OR 0.569, 95% CI 0.359–0.903; n≥4: P=.004, OR 0.603, 95% CI 0.427–0.850), and married status (P<.001, OR 0.654, 95% CI 0.547–0.782) (Table 2).

3.3. CSS and OS outcomes and independent factors associated with survival

Younger patients with pNETs had better survival outcomes regarding CSS and OS than the elderly, according to the Kaplan–Meier mortality analysis with log-rank test P<.001 (Fig. 1). The 3 and 5-year CSS rates were 67.3% and 58.0% in the younger cohort, and 44.6% and 35.7% in the elderly patients, respectively. Similarly, the 3 and 5-year OS rates were 64.5% and 37.7% in the younger cohort, and 54.0% and 27.7% in the elderly, respectively.

The elderly patients had worse CSS and OS rates than did the younger patients. The independent factors for CSS and OS in the

Table 2

Multivariate logistic regression analysis of clinicopathological characteristics.

Variables	OR	95% CI	P value
Race			
White	1 (Referent)		
Black	0.520	0.387–0.699	<.001
Other	0.907	0.666–1.235	.536
Unknown	1.032	0.388–2.742	.950
Tumor primary site			
Head	1 (Referent)		
Body or tail	1.006–0.818	1.237	.958
Overlap	0.711	0.485–1.041	.079
Unknown	0.970	0.762–1.234	.803
Histological grade			
Well differentiated	1 (Referent)		
Moderately differentiated	1.202	0.885–1.631	.239
Poorly differentiated	1.582	1.101–2.275	.013
Undifferentiated	1.151	0.627–2.115	.650
Unknown	1.009	0.801–1.272	.937
T stage			
T0–2	1 (Referent)		
T3–4	0.795	0.614–1.030	.082
Tx or NA	1.198	0.910–1.577	.198
N stage			
N0	1 (Referent)		
N1	0.774	0.597–1.003	.053
Nx or NA	0.848	0.656–1.098	.211
N stage			
No	1 (Referent)		
Yes	0.544	0.397–0.747	<.001
Unknown	1.916	0.639–5.740	.246
No. of removed regional LN			
$n=0$	1 (Referent)		
1≤n≤3	0.569	0.359–0.903	.017
n≥4	0.603	0.427–0.850	.004
Unknown or not applicable	0.884	0.554–1.408	.603
Marital status			
Unmarried (divorced, separated, single, widowed)	1 (Referent)		
Married	0.654	0.547–0.782	<.001
Unknown	0.695	0.460–1.049	.083

LN = lymph node; Mx = uncertain M stage; NA = no information; Nx = uncertain N stage; Tx = uncertain T stage.

elderly patients were analyzed using the multivariate Cox regression analysis (Table 3).

The results demonstrated that worse differentiation grade (moderately differentiated, P=0.034, hazard ratio (HR) 1.768, 95% confidence interval (CI) 1.044–2.995; poorly differentiated P<.001, HR 4.071, 95% CI 2.558–6.480; and undifferentiated, P<.001, HR 4.133, 95% CI 1.942–8.794), T3–4 stage (P=.023, HR 1.521, 95% CI 1.061–2.179), and tumor metastasis (M1) (P<.001, HR 2.829, 95% CI 1.975–4.053) were associated with poor CSS, whereas female gender (P=.012, HR 0.721, 95% CI 0.558–0.930), primary tumor located in body/tail of pancreas (P=.018, HR 0.706, 95% CI 0.529–0.942), surgery of tumor primary site (P<.034, HR 0.466, 95% CI 0.231–0.943), and being married (P=.023, HR 0.745, 95% CI 0.578–0.961) were associated with better CSS in the elderly patients.

Considering the independent risk factors for OS, patients with higher histological grade (poor differentiated P<.001, HR 3.138, 95% CI 2.066–4.766; undifferentiated, P=.001 ,HR 3.291, 95% CI 1.636–6.617); and metastasis status (M1) (P<.001, HR 2.204, 95% CI 1.614–3.010) have poor OS, whereas female gender (P=.011, HR 0.739, 95% CI 0.585–0.934); being married (P=.039, HR 0.783, 95% CI 0.620–0.988); tumor location in the body/tail of pancreas (P=.028, HR 0.742, 95% CI 0.569–0.968); and tumor primary site surgery (P=.02, HR 0.35, 95% CI 0.181–0.678) have better OS.

Kaplan–Meier mortality analysis with log-rank test was conducted to analyze the independent risk factors and protective factors for CSS and OS, which are shown in Figures 2–8. Patients with the characteristics of worse differentiation grade and tumor metastasis (M1) were associated with poor CSS and OS, whereas female gender, location of primary tumor in the body/tail of pancreas, surgery of tumor primary site, and being married were associated with better CSS and OS. T3–4 stage was a risk factor for CSS but not OS.

3.4. Surgery of primary site improves CSS and OS for elderly patients with distant metastasis (M1 stage)

Total of 243 of 653 patients (37.2%) had distant metastasis and 224 patients had unknown M stage. Among the elderly patients with distant metastasis, 17 underwent primary site surgery, 225 did not undergo surgery, and for 1 patient the status was unknown. Out of 17 patients, 6 had liver metastasis, 1 bone metastasis, 1 lung metastasis, and 9 unknown. Patients who underwent surgery of primary site showed better CSS and OS than those without surgery (Fig. 9).

4. Discussion

Multivariate Cox regression analysis revealed that the worse differentiation grade, and distant metastasis (M1) were independent risk factors, whereas tumor location in the body/tail of pancreas, female patients, surgery, and being married were protective factors for both CSS and OS in the elderly cohort. The advanced T stage is also an independent risk factor for CSS, but not for OS. Surprisingly, the N stage and number of removed LN were not independent factors for prognosis.

According to our analysis, there are several possible explanations for the decreased CSS and OS in the elderly patients. First, the elderly patients possess more risk factors (worse differentiated grade) and less protective factors (surgery of tumor primary site and being married) than the younger cohort, which may partially contribute to the poor prognosis. Second, the elderly patients usually have a higher incidence of comorbidities,
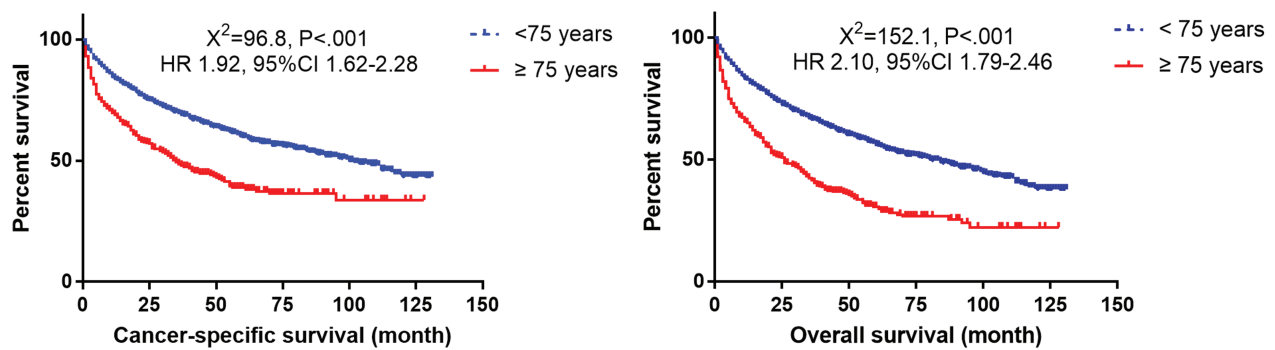
Figure 1. Survival curves with log-rank test between elderly patients (≥75) and younger patients (<75).

Table 3

Multivariate analysis of cancer-specific survival (CSS) and overall survival (OS) in elderly patients.

Variables	Cancer-specific survival			Overall survival		
	HR	95.0% CI	P	HR	95.0% CI	P
Race						
White	1 (Referent)			1 (Referent)		
Black	1.094	0.729–1.641	.665	1.229	0.863–1.752	.253
Other	1.458	0.962–2.210	.076	1.346	0.912–1.987	.135
Unknown	NA	NA	NA	0.755	0.102–5.571	.783
Gender						
Male	1 (Referent)			1 (Referent)		
Female	0.721	0.558–0.930	.012	0.739	0.585–0.934	.011
Tumor primary site						
Head	1 (Referent)			1 (Referent)		
Body or tail	0.706	0.529–0.942	.018	0.742	0.569–0.968	.028
Overlap	0.667	0.398–1.120	.125	0.732	0.458–1.172	.194
Unknown	0.989	0.737–1.327	.942	1.194	0.913–1.562	.195
Histological grade						
Well differentiated	1 (Referent)			1 (Referent)		
Moderately differentiated	1.768	1.044–2.995	.034	1.458	0.918–2.317	.110
Poorly differentiated	4.071	2.558–6.480	<.001	3.138	2.066–4.766	<.001
Undifferentiated	4.133	1.942–8.794	<.001	3.291	1.636–6.617	.001
Unknown	2.147	1.467–3.142	<.001	1.742	1.262–2.405	.001
T stage						
T0–2	1 (Referent)			1 (Referent)		
T3–4	1.521	1.061–2.179	.023	1.293	0.931–1.796	.126
Tx or NA	1.466	0.997–2.156	.052	1.247	0.878–1.769	.217
N stage						
N0	1 (Referent)			1 (Referent)		
N1	1.111	0.790–1.562	.547	1.170	0.853–1.604	.331
Nx or NA	1.366	0.975–1.913	.070	1.401	1.023–1.920	.036
M stage						
M0	1 (Referent)			1 (Referent)		
M1	2.829	1.975–4.053	<.001	2.204	1.614–3.010	<.001
Mx or NA	0.882	0.548–1.421	.606	0.837	0.550–1.275	.408
Surgery of primary site						
No	1 (Referent)			1 (Referent)		
Yes	0.466	0.231–0.943	.034	0.350	0.181–0.678	.002
Unknown	0.542	0.069–4.269	.561	0.881	0.193–4.023	.870
No. of removed regional LN						
n=0	1 (Referent)			1 (Referent)		
1≦n≦3	1.518	0.622–3.707	.359	1.642	0.706–3.820	.249
n≥4	0.798	0.348–1.829	.594	0.947	0.443–2.024	.888
Unknown or not applicable	0.903	0.490–1.667	.745	0.790	0.443–1.409	.425
Marital status						
Unmarried (divorced, separated, single, widowed)	1 (Referent)			1 (Referent)		
Married	0.745	0.578–0.961	.023	0.783	0.620–0.988	.039
Unknown	0.998	0.520–1.914	.994	1.138	0.654–1.981	.648

LN=lymph node; Mx=uncertain M stage; NA=no information; Nx=uncertain N stage; Tx=uncertain T stage.
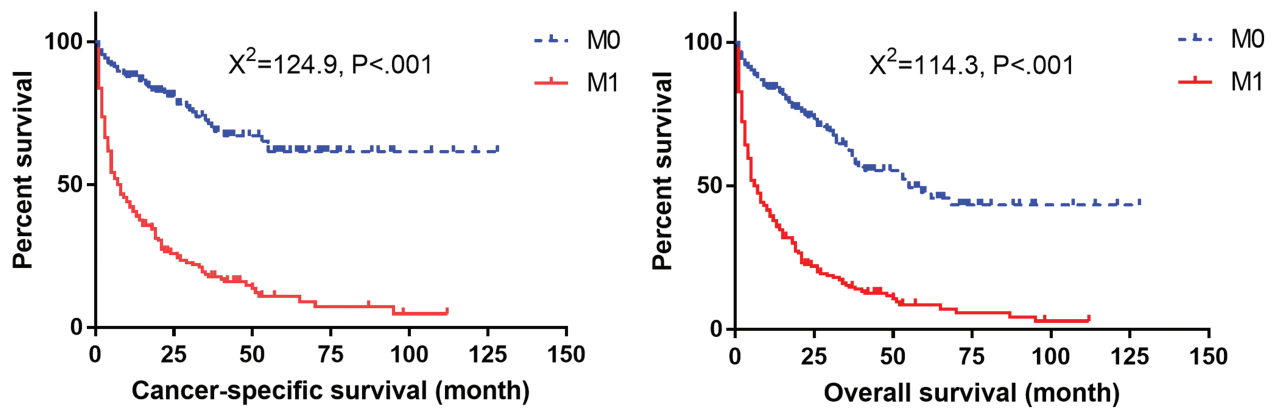
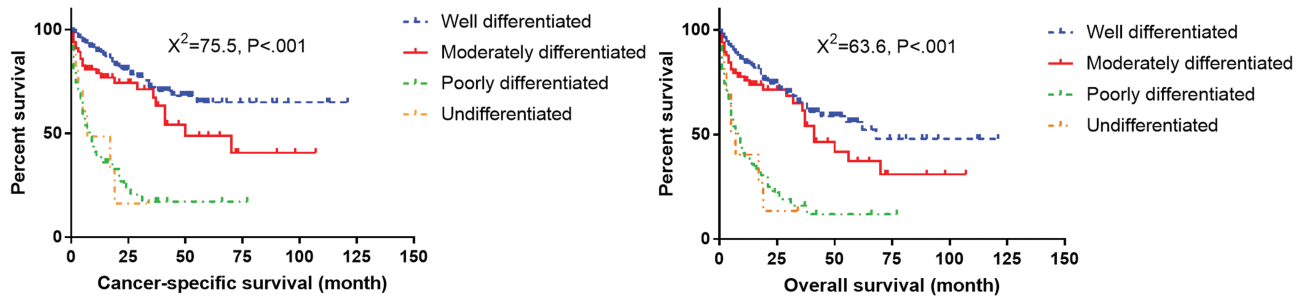**Figure 2.** Survival curves with log-rank test for different M stage in elderly patients.

Figure 3. Survival curves with log-rank test for different histological grade in elderly patients.
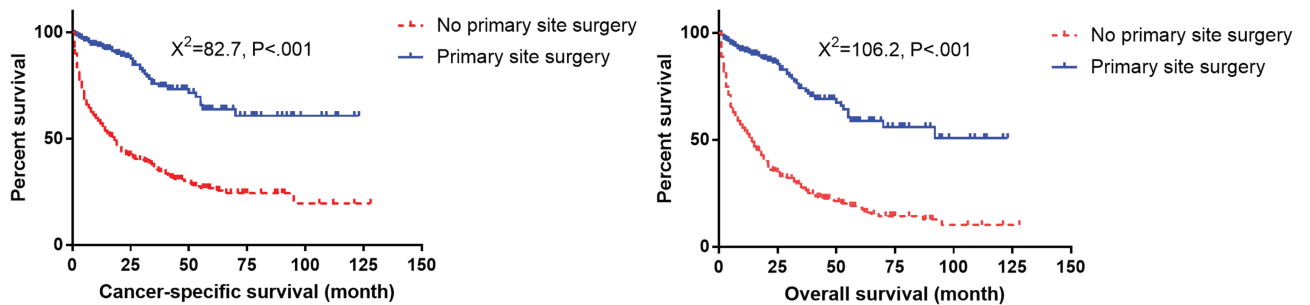

Figure 4. Survival curves with log-rank test for different surgery status in elderly patients.
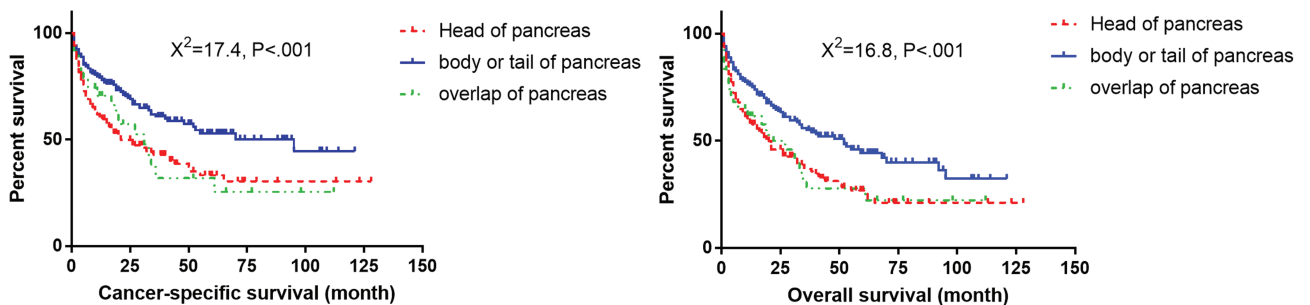

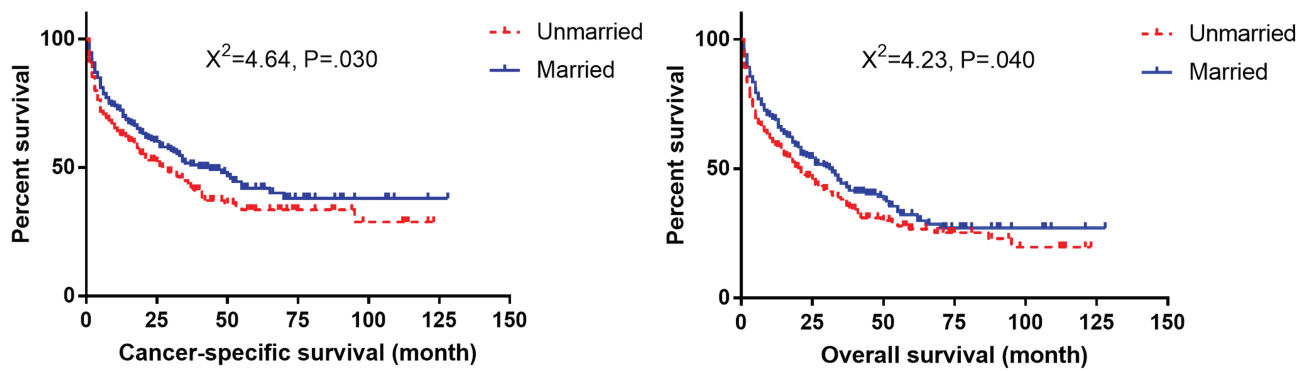**Figure 5.** Survival curves with log-rank test for different tumor location in elderly patients.

Figure 6. Survival curves with log-rank test for different marital status in elderly patients.
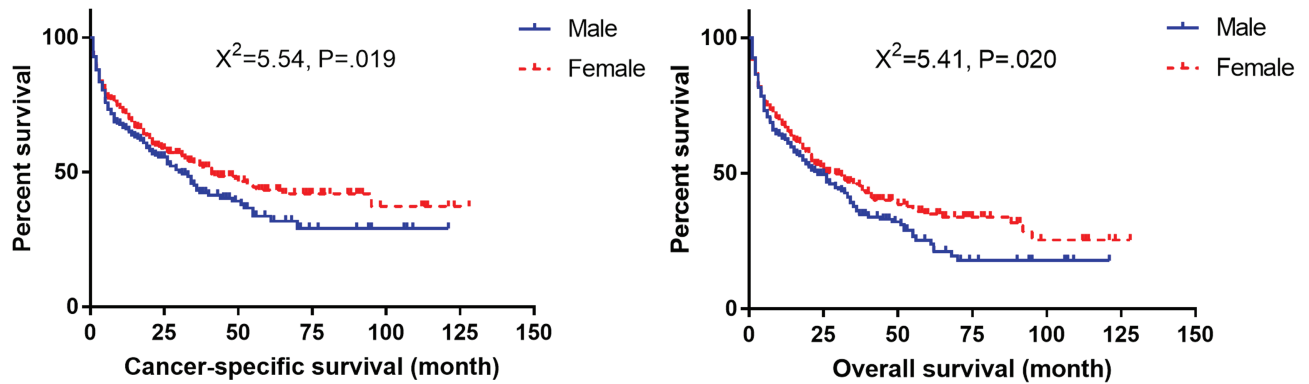

Figure 7. Survival curves with log-rank test for gender distribution in elderly patients.

such as chronic obstructive pulmonary disease, hypertension, coronary artery disease, and diabetes mellitus.[15] These comorbidities would increase the nontumor-related death and reduce the possibility of surgery. Last, elderly patients are less likely to receive adjuvant chemotherapy, such as endocrine therapy, chemotherapy, or targeted therapy, in spite of a higher proportion of worse differentiated tumors.[15]

Liver is the most common metastatic site for pNETs. Up to 60–90% of patients develop neuroendocrine liver metastasis during the course of the disease and the presence of distant metastasis is one of the strongest predictors for survival. Previous studies have

Figure 8. Survival curves with log-rank test for T stage in elderly patients.

revealed that the 5-year survival rate (13–54%) was significantly worse in patients with distant metastasis than in those without (75–99%).[16–18] The patients with distant metastasis are mainly treated using systemic treatment, including surgery of the primary foci and/or metastasis, chemotherapy, endocrine therapy, and targeted therapy. Surgery of the primary tumor is still controversial regarding the patients with distant metastasis, especially for the elderly patients.[16–18] Bettini et al[19] have demonstrated that the benefit of resecting primary tumors was to prevent symptoms arising from the tumors, such as biliary or gastrointestinal obstruction and symptoms from functional tumors. No differences in progression free survival between the two groups were detected. However, in the studies from Bertani et al, a survival benefit was detected in patients undergoing primary site surgery for metastatic disease. The authors proposed that the resection of the primary tumor may enhance the efficacy of systemic therapy, even in the absence of complications or symptoms.[20,21] A recent retrospective study by Citterio et al[22] reveals similar results. In our study, 243 of 653 patients (37.2%) showed distant metastasis, of which, 6 had liver metastasis, 1 bone metastasis, 1 lung metastasis, and 9 unknown. Out of 243 patients, 17 underwent primary site surgery, whereas 225 did not, and the status was unknown in 1 patient. The results revealed that distant metastasis proved to be an independent risk factor for both CSS and OS. Patients who underwent surgery of the primary site had better CSS and OS than those who did not. However, due to the fewer cases and multitude of the metastatic organs in present study, further research is needed to confirm the benefit of primary tumor surgery in the elderly patients with distant metastasis.
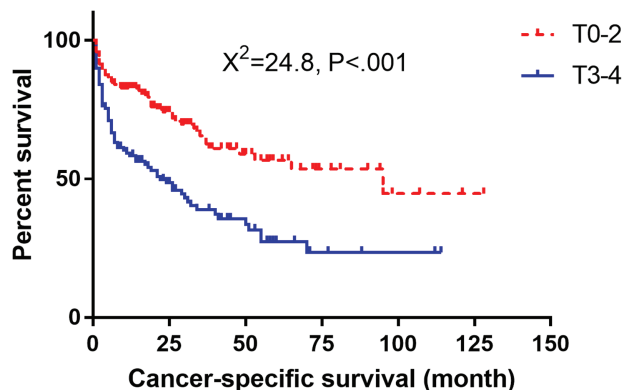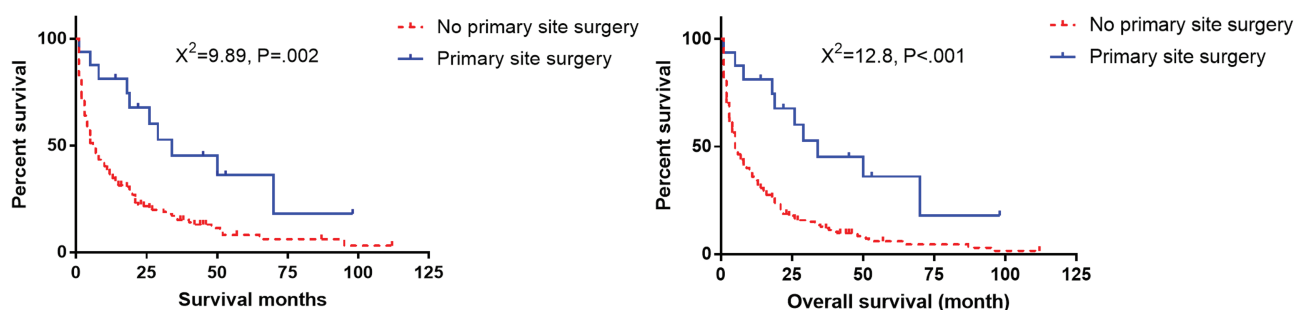
Figure 9. Survival curves with log-rank test for surgery of primary site in elderly patients with distant metastasis.

Previous studies have reported the impact of race and ethnicity on tumors in recent years. African American patients are associated with poor OS in various tumors.[23,24] The study by Zhou et al[23] revealed that African American patients had a more advanced tumor stage at the time of diagnosis comparing to others. Additionally, they are more likely to be in the disadvantaged socioeconomic status (an economic, and sociological combined total measure), and tend to cluster in low-quality hospitals.[23] Moreover, Yao[5] and Dasari's[25] studies revealed similar results. However, we did not observed the difference in CSS and OS between African Americans and Caucasians. This may be explained by the present study focusing on elderly patients rather than all age groups. A lower proportion of African American patients was observed in the elderly cohort than among the younger patients in our results.

To analyze the influence of tumor location, a Pearson chi-squared test regarding baseline variables was performed to compare the patients with tumor located on the pancreatic head and body/tail. Well and moderately differentiated tumors account for 68.4% in the pancreatic head group, and 89.9% in the body and tail tumor group ($\chi^2 = 20.6$, $P < .001$). Nineteen percent of patients in the pancreatic head tumor group and 44.5% of patients in the latter group accepted surgery of the primary tumor ($\chi^2 = 33.9$, $P < .001$). Additionally, 17.3% of patients in the pancreatic head tumor group and 30.8% of patients in the latter group have more resected number of regional lymph nodes ($\chi^2 = 16.6$, $P = .001$). The patients with tumors located at body and tail of pancreas are likely to have better differentiated status, receipt of surgery, and more resected number of regional lymph nodes, which may contribute to better CSS and OS.

Undoubtedly, patients with malignancies are usually troubled by high levels of psychological distress, which is more common in unmarried patients.[26,27] Greater psychological distress can prolong the function of cortisol and lead to cytokine-mediated inflammation. These changes can disturb the normal immune function, and they have been recognized as the risk prognostic factors in patients with malignancies.[28,29] Previous studies have reported that married patients obtain more care, encouragement, and economic support from spouses and have a better socioeconomic status than the unmarried patients.[30] This better psychological and socioeconomic status explains better outcomes in the married cohort.[23,30–32] However, the exact mechanisms of marital status still need further investigation.

The present study revealed that females had better CSS and OS among the elderly patients. Kaplan RM has reported that sex has a potential interaction with marital status in a general population and the effect of marital status on survival outcomes varied by gender in some cancers.[32] Therefore, we performed the chi-squared test between the male and female patients in the elderly cohort, and the preliminary results showed that female patients of married status were lesser than their male counterparts (36.3% vs. 70.7%, $\chi^2 = 86.64$, $P < .001$). Further, Cox analysis showed that female patients have better survival outcome both in married and unmarried subgroups, which signified that the benefits in female patients on the prognosis had other underlying etiologies, rather than the marital status.

There are several limitations for this study. First, other variables, such as performance status, comorbidities, Ki-67, and surgical information (duration, blood loss, and postoperative complication) were not captured in the SEER database. Second, administration of adjuvant therapies (chemotherapy, targeted therapy, and endocrine therapy) may have contributed to a better analysis. However, this information is not provided in the SEER database.

5. Conclusion

Elderly patients showed increased possibility of poorly differentiated tumor, and decreased proportion of African American patients, receipt of surgery, number of resected lymph nodes, and married status. Poor differentiation and M1 stage were independent risk factors for both CSS and OS, while tumor location at the body/tail of pancreas, female patients, receipt of surgery, and being married were protective factors. Advanced T stage was also an independent risk factor for CSS, but not for OS.

Author contributions

Conceptualization: Gang Li, Maolin Tian, Yuntao Bing, Hangyan Wang, Bin Jiang, Chunhui Yuan, Dianrong Xiu.
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