

Research Paper



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Can Patients with Pancreatic Cancer and Liver Metastases Obtain Survival Benefit from Surgery? A Population-Based Study

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Abstract

Background: Surgery for pancreatic cancer with liver metastases (PCL) is not recommended in the international guidelines, and investigation of its clinical significance in patients with PCL is very limited. This study explored whether surgery, especially synchronous resection of the primary tumor and liver metastases (SPL), could improve survival in PCL.

Methods: Data of 14,248 patients with PCL from Surveillance, Epidemiology, and End Results database was analyzed. Patients were divided into following groups: SPL, synchronous primary site, and other resection (SPO), single resection of the primary site (SPS), and no resection (NR).

Results: In this study, only 93 (0.7%) underwent SPL, 88 (0.6%) for SPO, and 232 (1.6%) for SPS. Multivariate Cox analysis showed surgical procedures of both the primary site and other sites were independent protective prognostic factors for pancreatic cancer cause-specific survival (PCSS) (all P < 0.001). Patients in the SPL group showed the most survival benefit, with a significant and gradually increased difference as compared with the SPO, SPS, and NR groups (median survival: 54, 34, 15, and 3 months, respectively, all P < 0.001). Compared with the NR group, mortalities were significant and gradually declining in the SPS, SPO, and SPL groups, with hazard ratio 0.329 (95% confidence interval [CI], 0.281 to 0.386), 0.220 (95% CI, 0.164 to 0.294), and 0.162 (95% CI, 0.118 to 0.222), respectively (all P < 0.001).

Conclusions: Surgical procedures for both primary site and other sites improved survival. SPL, particularly, showed a considerable survival benefit in well-selected patients with PCL.

Key words: Pancreatic cancer, metastases, surgical procedures, survival, SEER

Introduction

Pancreatic cancer (PC) remains one of the most aggressive malignant tumors. Although the mortality from most cancers is declining, PC moved from the fourth leading cause of cancer-related death to the third in 2016 [1]. Despite of many efforts, this rate has not improved much over the last 30 years, with a persistently low 5-year survival rate of 8% [2,3]. Compared with stages I-III, the overall survival (OS) of patients with stage IV metastatic disease (M1) was worse [4-6]. The median survival of locally advanced PC is only 6-10 months, and just 3-6 months in M1 PC [7]. Surgery is regarded as the only potentially curative method. However, once distant metastases are identified, surgery is not recommended in the guidelines [8,9].

For other malignant tumors, such as colorectal cancer, gastric cancer, and even sarcoma, there is increasing evidence that simultaneous metastasectomy can improve survival in appropriately selected patients who are in good general health and if the surgical procedures are performed carefully [10-12]. The question arises whether all patients with M1 PC should face the presently dismal outcomes. Yet, it remains controversial whether there is a survival benefit from synchronous resection of both the primary tumor as well as metastases in patients with M1 PC.

A few studies including data from six European pancreas centers have all shown a significant survival benefit, with acceptable morbidity and mortality in patients with PC and liver metastases (PCL) who underwent synchronous resection of the primary tumor and liver metastases (SPL), in comparison with patients with PCL who did not undergo resection [13,14]. Conversely, other studies have found no significant difference in survival between patients with PCL who underwent SPL and palliative bypass alone [15,16].

Up to the present, the sample sizes of patients undergoing SPL in previous studies have all been very small [13-16], with the largest sample including 69 patients in a collaboration study of six high-volume centers in Europe [14]. To reach more robust conclusions, the present study aimed to use data from a larger patient sample to investigate the clinical significance of surgery, especially SPL, in patients with PCL. We extracted data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry to systematically analyze the effect of surgery, especially SPL, on PC cause-specific survival (PCSS) in patients with PCL.

Materials and Methods

Patient selection in the SEER database

The SEER Cancer Statistics Review, which comprises the most recent statistics on cancer incidence, mortality, survival, prevalence, and lifetime risk, is published annually by the Data Analysis and Interpretation Branch of the National Cancer Institute in the United States (US). The current SEER database derives from 18 population-based cancer registries in the US [17]. It contains no identifiers and is publicly available for studies of cancer-based epidemiology. We used SEER*Stat 8.3.5 software to identify patients with a histopathologic diagnosis of PC from January 1, 2010, through December 31, 2015, with follow-up through December 31, 2017.

SEER registry patients with PC who were eligible for our study cohort included those with the following histologic type, according to the International Classification of Diseases for Oncology, Third Edition: adenocarcinoma (8140, 8141, 8144, 8210, 8211, 8255, 8260, 8263, 8310, 8401, 8440, 8450, 8470, 8480, 8481, 8503, 8574, 8576), neuroendocrine carcinoma (8246) and others (8000, 8001, 8004, 8010, 8012, 8013, 8014, 8020, 8021, 8022, 8031, 8032, 8033,

8035, 8041, 8046, 8070, 8071, 8072, 8120, 8150, 8151, 8152, 8153, 8154, 8160, 8162, 8170, 8240, 8244, 8249, 8430, 8452, 8453, 8490, 8500, 8507, 8523, 8550, 8560, and 8980).

We extracted the following data: sex, race, age at diagnosis, primary diagnosis, vear of site, pathological grade, histologic type, T stage, N stage, tumor size, insurance status, marital status, county with a bachelor's degree, county percentage county-level percentage unemployed, median household residential area, income, surgical procedure for the primary site, surgical procedure for other sites, radiotherapy, chemotherapy, SEER causespecific death classification, SEER other cause of death classification, survival months, and vital status.

In this analysis, we included only adult patients with PC and liver metastases, with TNM stage IV, according to the criteria described in the American Joint Committee on Cancer Staging Manual (7th edition). We excluded patients as follows: those with bone metastasis, lung metastasis, brain metastasis, other primary cancer, unknown surgical history, unknown bachelor's degree status, and cause of death missing/unknown or attributable to causes other than PC.

Statistical analysis

The primary endpoint of this study was PCSS. PCSS was defined as the time from the date of diagnosis to the date of death owing to PC. Baseline patient demographics and tumor characteristics were compared using the chi-square test. The PC survival rate was compared between subgroups using Kaplan-Meier analysis. All prognostic factors with P < 0.1 in Kaplan-Meier analysis were investigated using multivariate Cox analysis to identify predictors of PCSS. All statistical analyses were performed using IBM SPSS, version 22 (IBM Corp, Armonk, NY, USA). Statistical significance was set at two-sided P < 0.05.

All patients were categorized as those receiving surgery for the primary site (PSP), those who were recommended but did not undergo surgery for the primary site (RN-PSP) group, and those who were not recommended and did not have surgery for the primary site (NRN-PSP). The PSP group was divided into the SPL group, synchronous primary tumor, and other resection (SPO) groups, and no synchronous resection for other sites group also called single resection of the primary site (SPS). A surgical procedure of other sites was defined as any of the following: (1) non-primary surgical procedure for liver; (2) non-primary surgical procedure for other regional sites; (3) non-primary surgical procedure for distant lymph node(s); (4) any combination of surgical procedures for other regional sites, distant lymph node(s), and/or liver; and (5) non-primary surgical procedure performed without detail information. Apart from non-primary surgical procedures for the liver, the remaining surgical procedures for other sites were defined as other resection.

Results

Baseline patient characteristics

We identified a total of 14,248 eligible patients with PCL between 2010 and 2015, with 7,711 male and 6,537 female patients. Of these, 93 (0.7%) underwent SPL, 88 (0.6%) received SPO, 232 (1.6%) received SPS, 414 (2.9%) PSP, 320 (2.3%) RN-PSP, 13,514 (94.8%) NRN-PSP and 13,503 (94.8%) patients received no resection (NR). Mean ages of patients were 58.5 ± 12.4 (range: 25-82) years in the SPL group, 55.7 ± 13.2 (range: 20-87) years in the SPO group, 60.6 ± 12.5 (range: 20-93) years in the NR group.

In within-group comparisons, the SPL group had the highest proportion (53.8%) of body/tail site, greater frequency (36.0%) of well/moderately differentiated pathology grade, highest prevalence (41.9%) of neuroendocrine carcinoma, a greater proportion (72.0%) of T3 stage, and less (33.3%) chemotherapy, which were all statistically significant (P < 0.001). Baseline patient demographics and tumor characteristics according to different surgical procedures are described in **Table 1**.

 Table I. Baseline demographic and tumor characteristics of different surgical procedures for pancreatic cancer with liver metastases in the SEER database

Characteristic	SPL, N (%)	SPO, N (%)	SPS, N (%)	NR, N (%)	Р
	(n = 93)	(n = 88)	(n = 232)	(n = 13503)	
Sex					0.525
Male	52 (55.9)	41 (46.6)	128 (55.2)	7312 (54.2)	
Female	41 (44.1)	47 (53.4)	104 (44.8)	6191 (45.8)	
Race					0.572
White	76 (81.7)	76 (86.4)	182 (78.4)	10608 (78.6)	
Black	10 (10.8)	6 (6.8)	30 (12.9)	1847 (13.7)	
Other*	7 (7.5)	6 (6.8)	20 (8.6)	1048 (7.8)	
Age					< 0.001
<65	64 (68.8)	68 (77.3)	137 (59.1)	5552 (41.1)	
≥65	29 (31.2)	20 (22.7)	95 (40.9)	7951 (58.9)	
Year of diagnosis					0.539
2010-2011	26 (28.0)	27 (30.7)	69 (29.7)	4096 (30.3)	
2012-2013	29 (31.2)	36 (40.9)	84 (36.2)	4468 (33.1)	
2014-2015	38 (40.9)	25 (28.4)	79 (34.1)	4939 (36.6)	
Primary Site					< 0.001
Head	32 (34.4)	25 (28.4)	123 (53.0)	4899 (36.3)	
Body/Tail	50 (53.8)	45 (51.1)	70 (30.2)	4856 (36.0)	
Other	11 (11.8)	18 (20.5)	39 (16.8)	3748 (27.8)	
Grade					< 0.001
Well/Moderate	56 (60.2)	50 (56.8)	116 (50.0)	1040 (7.7)	
Poor/Anaplastic	21 (22.6)	28 (31.8)	71 (30.6)	1431 (10.6)	
Other	16 (17.2)	10 (11.4)	45 (19.4)	11032 (81.7)	

Characteristic	SPL, N (%)	SPO, N (%)	SPS, N (%)	NR, N (%)	Р
	(n = 93)	(n = 88)	(n = 232)	(n = 13503)	
Histology					< 0.001
Adenocarcinoma	20 (21.5)	22 (25.0)	86 (37.1)	9845 (72.9)	
Neuroendocrine	39 (41.9)	32 (36.4)	41 (17.7)	546 (4.0)	
carcinoma					
Other	34 (36.6)	34 (38.6)	105 (45.3)	3112 (23.0)	
T stage					< 0.001
Т0	0 (0.0)	0 (0.0)	0 (0.0)	119 (0.9)	
T1	4 (4.3)	3 (3.4)	10 (4.3)	337 (2.5)	
T2	17 (18.3)	15 (17.0)	41 (17.7)	3848 (28.5)	
T3	67 (72.0)	58 (65.9)	146 (62.9)	3280 (24.3)	
T4	4 (4.3)	10 (11.4)	16 (6.9)	2216 (16.4)	
TX	1 (1.1)	2 (2.3)	19 (8.2)	3703 (27.4)	
N stage					< 0.001
N0	32 (34.4)	24 (27.3)	90 (38.8)	7173 (53.1)	
N1	60 (64.5)	60 (68.2)	132 (56.9)	3904 (28.9)	
NX	1 (1.1)	4 (4.5)	10 (4.3)	2426 (18.0)	
Tumor Size					< 0.001
≤2 cm	7 (7.5)	5 (5.7)	19 (8.2)	714 (5.3)	
2-4 cm	37 (39.8)	34 (38.6)	99 (42.7)	4600 (34.1)	
>4 cm	45 (48.4)	45 (51.1)	98 (42.2)	5367 (39.7)	
Unknown	4 (4.3)	4 (4.5)	16 (6.9)	2822 (20.9)	
Insurance status					0.073
Insured	82 (88.2)	73 (83.0)	204 (87.9)	10999 (81.5)	
Medicaid	7 (7.5)	9 (10.2)	21 (9.1)	1790 (13.3)	
Uninsured/	4 (4.3)	6 (6.8)	7 (3.0)	714 (5.3)	
Unknown					
Marital status					< 0.001
Married	59 (63.4)	52 (59.1)	156 (67.2)	7210 (53.4)	
Unmarried	30 (32.3)	32 (36.4)	66 (28.4)	5662 (41.9)	
Unknown	4 (4.3)	4 (4.5)	10 (4.3)	631 (4.7)	
County % with bac	helor degree	2			0.511
Below median	37 (39.8)	40 (45.5)	90 (38.8)	5815 (43.1)	
Above median	56 (60.2)	48 (54.5)	142 (61.2)	7688 (56.9)	
County % with une	employed				0.779
Below median	40 (43.0)	43 (48.9)	107 (46.1)	6443 (47.7)	
Above median	53 (57.0)	45 (51.1)	125 (53.9)	7060 (52.3)	
County-level media	an househol	d income			0.039
Below median	41 (44.1)	41 (46.6)	91 (39.2)	6532 (48.4)	
Above median	52 (55.9)	47 (53.4)	141 (60.8)	6971 (51.6)	
Residence area	. ,	. ,	. ,		0.301
Metropolitan	88 (94.6)	80 (90.9)	215 (92.7)	12054 (89.3)	
Urban/rural	5 (5.4)	8 (9.1)	17 (7.3)	1433 (10.6)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	16 (0.1)	
Radiotherapy	. ,	· · /	. ,		< 0.001
Yes	7 (7.5)	8 (9.1)	11 (4.7)	367 (2.7)	
No/Unknown	86 (92.5)	80 (90.9)	221 (95.3)	13136 (97.3)	
Chemotherapy	` '	. /	` '	. /	< 0.001
Yes	31 (33.3)	49 (55.7)	133 (57.3)	6671 (49.4)	
No/Unknown	62 (66.7)	39 (44.3)	99 (42.7)	6832 (50.6)	

*, Other includes American Indian/Alaska Native, Asian/Pacific Islander, and unknown. SPL: synchronous resection of the primary tumor and liver metastases; SPO: synchronous primary tumor and other resection; SPS: single resection of the primary site; NR: no resection.

Effect on PCSS of surgical procedures for primary and other sites

Patients who underwent PSP had better survival (n = 13,834, 97.1%) than those who did not undergo surgery for the primary site (5-year PCSS: 33.4% vs. 0.19%, median survival: 24 vs. 3 months, P < 0.001). Five-year PCSS was 33.4% in the PSP group, 4.0% in the RN-PSP group, and 1.8% in the NRN-PSP group; survival was significantly different in Kaplan–Meier analysis (median survival: 24, 2, 3 months, respectively, P < 0.001). Surprisingly, the median survival of the RN-PSP group was significantly

shorter than that of the NRN-PSP group (P < 0.001). Moreover, for surgical procedures of other sites, 5-year PCSS was 17.5% in the liver resection group, 16.9% in the other resection group, and 2.4% in the NR group; survival was also significantly different in Kaplan–Meier analysis (median survival: 8, 11, 3 months, respectively, P < 0.001). As shown in **Table 2**, after univariate analysis and multivariate Cox analysis, surgical procedures of the primary site, surgical procedures of other sites, radiotherapy, and chemotherapy were all validated as independent protective prognostic factors for survival (all P < 0.001).

Variable	Total (n=14248)	2-year PCSS	5-year PCSS	Univariate analysis	Multivariate Cox analy	vsis
		-	-	Р	HR (95%CI)	Р
Sex				0.392		NI
Male	7711	0.071	0.032			
Female	6537	0.070	0.026			
Race				< 0.001		0.018
White	11204	0.073	0.030		Reference	
Black	1946	0.055	0.021		1.061 (1.008-1.116)	0.023
Other*	1098	0.073	0.032		0.954 (0.894-1.019)	0.161
Age				< 0.001		< 0.001
<65	5991	0.112	0.047		Reference	
≥65	8257	0.041	0.017		1.306 (1.260-1.355)	
Year of diagnosis				< 0.001		< 0.001
2010-2011	4335	0.059	0.22		Reference	
2012-2013	4729	0.076	NA		0.955 (0.916-0.997)	0.034
2014-2015	5184	0.076	NA		0.915 (0.878-0.955)	< 0.001
Primary Site				< 0.001		0.016
Head	5236	0.065	0.024		Reference	
Body/Tail	5113	0.080	0.036		1.054 (1.012-1.098)	0.011
Other	3899	0.066	0.028		1.045 (0.998-1.094)	0.020
Grade				< 0.001		< 0.001
Well/Moderate	1301	0.252	0.126		Reference	
Poor/Anaplastic	1592	0.055	0.021		1.776 (1.639-1.925)	< 0.001
Other	11355	0.052	0.019		1.525 (1.427-1.630)	< 0.001
Histology				< 0.001		< 0.001
Adenocarcinoma	10248	0.039	0.008		Reference	
Neuroendocrine carcinoma	683	0.294	0.247		0.292 (0.265-0.322)	< 0.001
Other	3317	0.084	0.047		0.893 (0.855-0.931)	< 0.001
T stage				< 0.001		0.004
TO	123	0.065	NA		Reference	
T1	360	0.092	0.038		0.829 (0.670-10.26)	0.085
T2	3993	0.069	0.029		0.819 (0.654-1.026)	0.082
T3	3656	0.098	0.041		0.769 (0.615-0.961)	0.021
T4	2314	0.060	0.023		0.781 (0.624-0.977)	0.031
TX	3802	0.052	0.021		0.838 (0.670-1.046)	0.118
N stage				< 0.001		0.100
N0	7514	0.070	0.026		Reference	
N1	4257	0.084	0.041		1.044 (1.003-1.087)	0.034
NX	2477	0.050	0.018		1.007 (0.958-1.058)	0.794
Tumor size				< 0.001		< 0.001
≤2 cm	765	0.087	0.041		Reference	
2-4 cm	4890	0.072	0.024		1.093 (0.962-1.242)	0.170
>4 cm	5664	0.076	0.036		1.214 (1.069-1.379)	0.003
Unknown	2929	0.054	0.020		1.185 (1.040-1.350)	0.011
Insurance status				< 0.001		< 0.001
Insured	11627	0.075	0.032		Reference	
Medicaid	1871	0.049	0.021		1.098 (1.041-1.157)	< 0.001
Uninsured/Unknown	750	0.051	0.010		1.181 (1.091-1.278)	< 0.001
Marital status				< 0.001		< 0.001
Married	7658	0.088	0.035		Reference	
Unmarried	5920	0.048	0.020		1.122 (1.081-1.163)	< 0.001
Unknown	670	0.080	0.044		0.982 (0.904-1.067)	0.671
County % with bachelor degree				< 0.001		0.002
Below median	6146	0.066	0.024		Reference	
Above median	8102	0.075	0.034		0.939 (0.902-0.977)	
County % with unemployed				0.007		0.738
Below median	6788	0.076	0.034		Reference	

Variable	Total (n=14248)	2-year PCSS	5-year PCSS	Univariate analysis	Multivariate Cox analysi	s
				Р	HR (95%CI)	Р
Above median	7460	0.066	0.025		0.994 (0.958-1.031)	
County-level median household income				< 0.001		0.110
Below median	6905	0.064	0.024		Reference	
Above median	7343	0.077	0.034		0.967 (0.929-1.007)	
Residence area				0.183		NI
Metropolitan	12718	0.072	0.028			
Urban/rural	1514	0.063	0.035			
Missing	16	0.125	NA			
Surgical procedure of primary site				< 0.001		< 0.001
Not recommended	13514	0.058	0.018		Reference	
Performed	414	0.492	0.334		0.390 (0.339-0.448)	< 0.001
Recommended but not Performed	320	0.049	0.040		0.910 (0.811-1.021)	0.107
Surgical procedure of other sites				< 0.001		< 0.001
No resection	13735	0.062	0.024		Reference	
Liver resection	288	0.298	0.175		0.714 (0.622-0.818)	< 0.001
Other resection	218	0.286	0.169		0.772 (0.660-0.904)	0.001
Unknown	7	NA	NA		1.261 (0.599-2.652)	0.541
Radiotherapy				< 0.001		< 0.001
Yes	405	0.132	0.027		Reference	
No/Unknown	13843	0.069	0.029		1.303 (1.174-1.447)	
Chemotherapy				< 0.001		< 0.001
Yes	7079	0.096	0.030		Reference	
No/Unknown	7169	0.046	0.028		2.477 (2.384-2.573)	

*, Other includes American Indian/Alaska Native, Asian/Pacific Islander, and unknown. PCSS: pancreatic cancer cause-specific survival; HR: hazard ratio; CI: confidence interval; NA: not applicable; NI: not included in multivariate survival analysis.

Effect on **PCSS** of synchronous surgical procedure for primary and other sites

Among patients with PSP, only one had unknown surgery status for other sites; this patient was omitted from the following analyses. The 181 (43.8%) patients who received surgical procedures for other sites had better survival than the 232 (56.2%) patients who did not (5-year PCSS: 44.5% vs. 24.6%, median survival: 43 vs. 15 months, P < 0.001). As shown in **Table 3**, after univariate and multivariate Cox analyses, the synchronous surgical procedure of other sites was validated as an independent prognostic positive factor for survival (P < 0.001). Notably, radiotherapy and chemotherapy were not independent prognostic factors for survival in patients with PSP (**Table 3**).

Effect of radiotherapy/chemotherapy on PCSS in patients without surgery

The 367 (2.7%) patients without surgery who received radiotherapy (WSR) had better survival than the 13,136 (97.3%) patients without surgery who received no/unknown radiotherapy (N-WSR) (2-year PCSS: 11.2% vs. 5.5%, median survival: 6 vs. 2 months, P < 0.001) (**Table 4**). The 6671 (49.4%) patients without surgery who received chemotherapy (WSC) had better survival than the 6832 (50.6%) patients without surgery who received no/unknown chemotherapy (N-WSC) (2-year PCSS: 8.4% vs. 3.0%, median survival: 6 vs. 1 months, P < 0.001) (**Table 4**).

As shown in Table 4, after univariate analysis

and multivariate Cox analyses, radiotherapy and chemotherapy were validated as independent positive predictors of survival in patients without surgery (all P < 0.001).

Subgroup analysis of the effect on PCSS of surgical procedures for the primary site, according to the primary site

As shown in **Table 5**, Kaplan–Meier analysis and multivariate Cox analyses showed that at each primary site, including the pancreatic head, body/tail, and other sites, patients receiving PSP had better survival than those receiving RN-PSP and NRN-PSP (all P < 0.001).

Subgroup analysis of the effect on PCSS of surgical procedures for other sites, according to the primary site

As shown in **Table 5**, Kaplan–Meier and multivariate Cox analyses showed that at each primary site, including the pancreatic head, body/tail, and other sites, patients receiving NR had a worse survival than those in the liver resection and other resection groups (all P < 0.001).

Subgroup analysis of the effect on PCSS of radiotherapy in patients without surgery, according to the primary site

As shown in **Table 5**, Kaplan–Meier and multivariate Cox analyses all showed that at each primary site, including the pancreatic head, body/tail, and other sites, patients receiving WSR had better survival than those with N-WSR (all P < 0.001).

Table 3. Univariate and multivariate Cox analyses to identify predictors of pancreatic cancer cause-specific survival in patients undergoing surgical procedures of the primary site

Not P 1R (6% C) P Maic 221 0.05 0.244 N Maic 122 0.05 0.244 N Rece 0.792 N1 White 3.4 0.485 0.204 N Site 0.485 0.204 N N Maic 46 0.485 0.204 N N Alge 0.272 0.014 0.014 N N Alge 0.260 1.406 (1.07-1.1846) N N N 2012-011 142 0.575 N N N N 2012-015 142 0.575 N N N N 2012-015 NA 0.260 (257.897) 0.016 N N N 1044/1 Molerate 182 0.271 0.077 0.260 (257.897) 0.011 N N N Muich Molerate 120 0.673 0.474 2.262 (1.42.949) 0.001	Variable	Total (n=413)	2-year PCSS	5-year PCSS	Univariate analysis	Multivariate Cox analys	is
See 0.5% 0.5% 0.5% 0.5% Fanale 10 0.5% 0.244		()	5	5	P	HR (95%CI)	Р
Make Fearable1020.4500.3440.3	Sex				0.858		NI
Fands92.00.3240.3240.722NWhich340.4450.340.4450.340.445Other0.4850.340.4870.1410.141Other0.4800.4800.4870.1410.141Sat0.4800.4870.1410.1410.141Sat0.1420.1420.1410.1410.141Sat0.1420.1430.1410.1410.141Sat0.1420.1430.1410.1410.141Sat0.1420.1430.1410.1460.141Sat0.1410.1410.1410.1410.141Sat0.1420.1410.1410.1410.141Sat0.1420.1410.1420.1420.141Sat0.1420.1420.1420.1420.141Sat0.1420.1420.1420.1420.141Sat0.1420.1420.1420.1420.141Sat0.1420.1420.1420.1410.141Sat0.1420.1420.1420.1410.141Sat0.1420.1420.1420.1410.141Sat0.1420.1420.1420.1410.141Sat0.1420.1420.1420.1410.141Sat0.1420.1420.1420.1410.141Sat0.1420.1420.1420.1410.141Sat0.14	Male	221	0.050	0.344			
RecUNALUN	Female	192	0.485	0.324			
White340.4840.34Black640.4850.34Chiler'330.4880.409Aler6016.67Stat2090.370.4856.67Stat2090.370.4856.67Stat1200.350.4856.67Stat1200.350.341.04Stat1200.350.340.04202-20731240.49N0.29202-20731440.49N0.29202-20731440.200.670.67202-20731460.49N0.29202-20731550.630.660.67202-20731550.630.4670.56204/Tail1550.630.4670.56204/Tail1520.730.172.52204/Tail1200.220.1742.52204/Adachaic1200.230.070.67204/Saccintonia1200.330.470.221211240.430.470.220.511240.490.320.320.540.321250.470.570.570.541261270.520.540.571261280.570.570.541261290.520.570.541261290.520.570.541261290.52 <td< td=""><td>Race</td><td></td><td></td><td></td><td>0.782</td><td></td><td>NI</td></td<>	Race				0.782		NI
Bick, Other*30.4880.4990.4970.405<	White	334	0.494	0.334			
Other"300.490.700.400.700.401Net were were were were were were were we	Black	46	0.485	0.304			
Age	Other*	33	0.498	0.409			
</td <td>Age</td> <td></td> <td></td> <td></td> <td>< 0.001</td> <td></td> <td>0.014</td>	Age				< 0.001		0.014
2651440.350.201.468 (1.07)-1.549)Var of digmo0.3540.3640.374N2010-20131490.469NANA2014-20151420.59NANA2014-20151420.500.4050.677 (0.52,0.897)0.011Eddy Tail1650.6330.4050.567 (0.52,0.897)0.011Eddy Tail1660.330.4050.568 (0.57,0.897)0.011Eddy Tail1620.2720.764Reference-Wall/Modeate2200.720.764Reference-Vord/Anaplate2200.720.764Reference-Wall/Modeate2200.720.764Reference-Vord/Anaplate2200.720.764Reference-Mathematic excisiona1220.830.67Reference-Vord/Anaplate1220.730.77Reference-Tatage0.020.524 (0.16.0.33-0.3200.936Tatage-0.520.16.0.33-0.3210.936-Tatage-0.1640.5250.1640.9350.936Tatage-0.1640.5250.560.9350.936Tatage-0.560.570.560.570.56Tatage-0.560.570.560.570.57Tatage-0.570.570.560.570.57Tat	<65	269	0.579	0.405		Reference	
Yar of diagnosisUSNA2012-201514200.469NA2012-201514200.515NAFinary Sile	≥65	144	0.335	0.210		1.406 (1.071-1.846)	
2010-2013 142 0.464 0.87 2014-2015 142 0.451 NA Primary Site - - 0.067 0.513 Na Bioly Train Site - - 0.067 0.513-0.67 Na Bioly Train Site - - 0.067 0.513-0.67 Na Sold Site Site Site Site Site Site Site Site	Year of diagnosis				0.394		NI
2012-2015) 142 0.439 NA Finary Sile V 5 142 0.518 NA Finary Sile V 5 142 0.518 NA Finary Sile V 5 142 0.519 NA Finary Sil	2010-2011	122	0.466	0.287			
2014-2015) 142 0,51 NA Frinary Site V 500 0,520 0,520 0,500 0,530 0,500	2012-2013	149	0.499	NA			
Primary Site	2014-2015	142	0.515	NA			
Haad1900.2340.2100.4070.050-0070.016Other6.80.5860.4870.676	Primary Site				< 0.001		0.019
Body TailInfé0.630.4050.0670.071Char60.560.570.9770.016Grade220.740.660.570.9770.016Pory Anaplastic1200.2720.1742451.772Other1200.2720.1742451.7720.001Histology1.7271.790.0790.0051.7720.0010.005Histology1.7720.9700.676.670.001Adenozarinoma1220.8330.4570.5280.5160.001Other1730.9710.520.5160.570.570.97Targe10.4530.3520.5410.9320.510.97Targe10.6550.551.0560.970.92130.520.570.3521.0560.3520.9260.73.1450.962140.520.510.3521.0560.350.920.75.1450.92150.9210.550.550.9260.73.1450.920.930.16140.520.510.3520.470.950.930.101150.4210.550.4210.4560.580.930.101140.550.4270.3520.3610.4660.85.3.930.101150.4290.550.4770.3520.3670.3670.367140.550.4370.466	Head	180	0.324	0.210		Reference	
Other686.3860.4870.0860.350.9870.016Grade2220.6730.476KaferanceWall/Moderate2220.730.476KaferanceWall/Moderate0.001Dorly Anaplatica170.3200.1881.2751.2452(7.373.1)0.001Other170.3200.0871.2452(7.373.1)0.001Matsology1280.3200.0970.2421.074.03.030.001Naucoendocrine carcinoma1280.330.3270.2520.161.03.900.001Other1730.6910.3280.2520.2520.161.03.900.001Tagge70.6130.6270.6260.3520.3620.36212730.4780.3620.3621.054 (0.330363.4)0.9621370.4270.5120.3520.2620.2620.2640.362140.4630.5520.3570.4620.3720.3620.314150.4280.5150.3570.4760.4320.432150.5220.5150.3571.174 (0.865.155)0.3150.342170.4550.3570.3441.460 (0.863.494)0.101170.4570.3570.3471.460 (0.863.494)0.101170.4570.3570.3471.460 (0.865.194)0.311170.4570.3570.3471.460 (0.865.194)0.31117 <td>Body/Tail</td> <td>165</td> <td>0.633</td> <td>0.405</td> <td></td> <td>0.697 (0.503-0.967)</td> <td>0.031</td>	Body/Tail	165	0.633	0.405		0.697 (0.503-0.967)	0.031
Grade	Other	68	0.586	0.487		0.566 (0.357-0.897)	0.016
Well/Moderate2420.6730.476ReferencePory/Anaplastic120.2720.1742.425 (L743.313)<0.001	Grade				< 0.001		< 0.001
Pary Anglastic1200.2720.3742.425 (1.774.3.31)<0.001Other710.3200.1841.772 (1.392.6.39)0.005Histology0.0010.001Histology1120.8330.4570.252 (0.161.0.394)0.001Neuroendocine carcinoma1120.8330.4570.252 (0.161.0.394)0.001Other1730.6310.4570.252 (0.161.0.394)0.001Tatage0.0010.4510.0220.471170.6350.652Reference0.93017730.4780.2960.203.0.314)0.902180.5270.2870.906 (0.273.3.145)0.902170.4780.2920.2860.902 (0.273.3.145)0.902180.5270.2870.906 (0.273.4.145)0.202170.4780.9020.2870.902 (0.273.4.145)0.902180.5270.2870.902 (0.273.4.145)0.902170.910.9260.5270.926 (0.273.4.145)0.926170.9260.5270.2870.902 (0.273.4.145)0.281180.5270.2871.174 (0.864.1597)0.316190.2480.3201.184 (0.860.3599)0.101190.2490.3100.3211.866 (0.853.934)0.101100.4240.3100.2811.863 (0.869.3994)0.101100.4240.3100.3211.863 (0.869.3994)<	Well/Moderate	222	0.673	0.476		Reference	
Other710.3200.1881.72 (1.19.2.489)0.005Histology	Poor/Anaplastic	120	0.272	0.174		2.425 (1.774-3.313)	< 0.001
Histology	Other	71	0.320	0.188		1.772 (1.190-2.639)	0.005
Adencarinoma1280.2370.097ReferenceNeuroendocrino carcinoma1730.6910.3280.541 (0.392-0747)<0.001	Histology				< 0.001		< 0.001
Neurondocrine carcinoma1120.8330.4570.2520.1250.1250.1270.001T stage.0.4710.4710.4710.4710.4710.1711.1710.1710.1710.1710.1710.1710.1711.1710.1711.1710.1711.1710.1711.1710.1711.1710.1711.1710.1711.171	Adenocarcinoma	128	0.237	0.097		Reference	
Ohler 173 0.691 0.228 0.511 (0.392-07/47) <0.001 Tstage	Neuroendocrine carcinoma	112	0.833	0.457		0.252 (0.161-0.394)	< 0.001
Tstage 0.47 0.475 0.471 T0 0.63 NA NA T1 0.63 0.635 Reference T2 73 0.478 0.298 1.054 (0.330.362) 0.990 T3 0.71 0.527 0.257 0.256 (0.378.314) 0.962 T4 0.0 0.527 0.257 0.256 (0.378.314) 0.902 TA 0.0 0.527 0.257 0.256 (0.378.314) 0.902 Tstage 0.162 0.104 2.136 (0.58.314) 0.902 Natge 0.156 0.104 2.136 (0.58.314) 0.248 Natge 0.550 0.357 Reference 0.162 Natge 0.501 0.321 1.174 (0.864.1.597) 0.343 Stamp 0.520 0.515 Reference 0.343 Stamp 0.520 0.515 Reference 0.101 Unknown 126 0.460 0.341 1.660 (0.863.9.396) 0.117 Uninswerd/Unknown <td>Other</td> <td>173</td> <td>0.691</td> <td>0.328</td> <td></td> <td>0.541 (0.392-0.747)</td> <td>< 0.001</td>	Other	173	0.691	0.328		0.541 (0.392-0.747)	< 0.001
100NANAT1170.6350.635ReferenceT20.6350.6350.6350.6470.54(0.330.3.62)0.900T32710.5120.3521.026(0.336.3.134)0.902TA200.5270.2870.926(0.273.3.145)0.902TX220.1560.3070.926(0.273.3.145)0.902TX220.1560.3570.926(0.273.3.145)0.902Nsige	T stage	_			0.002		0.471
11170.6350.635NetterenceT2730.4780.2981.056 (0.330.3.62.)0.930T32710.5120.3521.026 (0.330.3.62.)0.962T4300.5270.2870.926 (0.273.145)0.902T4220.1560.1042.196 (0.578.839)0.248Nage220.5610.337ReferenceN10.550.357Reference0.375Tumor Size0.2040.1601.74 (0.864.1597)0.305X2 cm310.5620.515Reference24 cm130.5620.515Reference24 cm130.5620.3841.866 (0.869.394)0.101Vancown1880.5730.3841.866 (0.869.394)0.101Unknown1880.5730.3841.866 (0.869.394)0.101Unknown1880.5730.3471.866 (0.869.394)0.101Unknown1880.5730.3471.866 (0.869.394)0.101Unknown1890.3920.2471.866 (0.869.394)0.101Unknown1890.3920.3471.866 (0.869.394)0.101Unknown1890.3920.3471.866 (0.869.394)0.101Unknown170.463NA1.924 (0.400.421)0.561Unknown180.3920.3710.3511.924 (0.400.421)Unknown180.6940.2670.35	10	0	NA	NA			
12730.4780.2981.0540.054 (0.330-3.35c)0.930T30.5120.3520.2671.026 (0.330-3.145)0.962T420.1610.9270.2870.926 (0.273-3.145)0.902TX220.1610.1042.195 (0.578-3.145)0.902Nstage		17	0.635	0.635		Reference	
132/10.5120.5220.5251.026 (0.336-3.134)0.966T4300.5270.2870.926 (0.273.3.145)0.902TX20.1560.1042.195 (0.278.3.139)0.248N stage-0.067Reference0.162N12520.5010.3321.174 (0.864.1.507)0.075NX150.1620.3321.174 (0.864.1.507)0.075Tumor Size-0.0011.870 (0.940.3.21)0.07524 cm310.5620.515Reference24 cm1860.5730.3841.863 (0.869.3.996)0.11024 cm1880.5730.3841.863 (0.869.3.996)0.1101msurace status1254 (0.460.3.42)0.6581.254 (0.460.3.42)0.658Insurard3590.5050.347NIInsurard170.463NAUninsured/Unknown170.463NAUninsured/Unknown180.2670.3010.351 (0.134.0.922)0.034Unknown180.2811.173 (0.884.1.556)0.2670.049Reference0.4970.409Reference0.089Unknown1670.4580.285Reference0.081Courty % with unemployed1260.4680.2681.129 (0.830.1.57)0.031Below median1900.5400.2680.709 (0.516.4.975)0.034Below median1910.4	12	73	0.478	0.298		1.054 (0.330-3.362)	0.930
14300.52/0.28/0.29/0.72/3.145/0.902TX220.1560.1620.1590.780.162N stage1460.5050.357Reference	13	271	0.512	0.352		1.026 (0.336-3.134)	0.965
IA220.1680.1042.199 (0.598.5.39)0.248Nstage05050.357Reference	14	30	0.527	0.287		0.926 (0.273-3.145)	0.902
Nage 0.062 0.062 0.062 0.162 N0 146 0.505 0.37 Reference N1 252 0.501 0.332 1.74 (0.864.1.597) 0.305 N1 15 0.240 0.160 1.870 (0.940.3.721) 0.305 S2 cm 13 0.562 0.515 Reference - 24 cm 170 0.430 0.280 1.866 (0.885.3.934) 0.101 V4 cm 188 0.573 0.384 1.863 (0.889.3.934) 0.101 V4 cm 188 0.573 0.384 1.863 (0.889.3.934) 0.101 V4 cm 170 0.831 0.116 1.254 (0.460.3.421) 0.658 Insured 859 0.575 0.247 0.463 1.75 (0.885-1.556) 0.461 Insured/Unknown 27 0.463 NA - 0.411 Unknown 18 0.469 0.440 0.510 (0.134.0.22) 0.324 Unknown 18 0.524 0.371	TX	22	0.156	0.104	0.0/7	2.195 (0.578-8.339)	0.248
N0 146 0.505 0.537 Reference N1 252 0.501 0.332 1.174 (0.8641.597) 0.305 NX 15 0.240 0.160 1.870 (0.940.3.721) 0.075 Tumor Size . 0.001 Reference	N stage	144	0 505	0.057	0.067	D (0.162
N1 22 0.501 0.332 1.174 (0.884-1.597) 0.305 NX 15 0.240 0.160 1.870 (0.940-3.721) 0.075 Tumor Size .001 0.343 ≤ 2 cm 31 0.562 0.515 Reference ≤ 4 cm 170 0.430 0.280 1.863 (0.885-3.930) 0.101 ≤ 4 cm 170 0.430 0.281 1.863 (0.869-3.996) 0.101 Unknown 24 0.231 0.116 1.863 (0.885-3.930) 0.101 Unknown 28 0.573 0.384 1.863 (0.869-3.996) 0.101 Insured 188 0.573 0.384 1.863 (0.885-3.930) 0.101 Unknown 24 0.231 0.116 0.251 0.658 Insured 359 0.505 0.347 0.171 0.171 Maridi status 7 0.463 N 0.041 Maridi status 617 0.497 0.340 Reference 0.041 Maridi status 627 0.497 0.351 0.351 0.351 <th< td=""><td>NU</td><td>146</td><td>0.505</td><td>0.357</td><td></td><td>Reference</td><td>0.005</td></th<>	NU	146	0.505	0.357		Reference	0.005
NX 15 0.240 0.100 1.870 (0.940.2/21) 0.007 Tumor Size 0.01 Reference 0.343 ≤ 2 cm 31 0.562 0.515 Reference 0.101 ≤ 4 cm 170 0.430 0.280 0.866 (0.885.3.934) 0.101 ≤ 4 cm 188 0.70 0.342 0.866 (0.885.3.934) 0.101 Unknown 24 0.231 0.161 1.254 (0.460.3.421) 0.658 Insured 359 0.505 0.347 1.254 (0.460.3.421) 0.658 Insured/Unknown 17 0.463 NA 1 1 1 Marited 37 0.392 0.281 1.173 (0.885.1556) 0.267 Unknown 188 0.769 0.401 86 0.810 0.351 (0.134.0.922) 0.034 Unknown 188 0.524 0.454 0.285 Reference 393 Unknown 167 0.448 0.285 Reference 393 Elow median 190 0.522 0.409 Reference 393 <t< td=""><td>NI</td><td>252</td><td>0.501</td><td>0.332</td><td></td><td>1.174 (0.864-1.597)</td><td>0.305</td></t<>	NI	252	0.501	0.332		1.174 (0.864-1.597)	0.305
Initialized 0.001 0.043 2 cm310.5620.515Reference2.4 cm1700.4300.2801.866 (0.885-3.934)0.101> 4 cm1880.5730.3841.863 (0.869-3.996)0.110Unknown240.2310.1161.254 (0.460-3.421)0.658Issurace status $$		15	0.240	0.160	0.001	1.870 (0.940-3.721)	0.075
24 cm 31 0.362 0.37 Neterine 24 cm 170 0.430 0.280 1.863 (0.869.3.934) 0.101 >4 cm 188 0.573 0.384 1.863 (0.869.3.934) 0.101 Unknown 24 0.231 0.116 1.254 (0.460.3.421) 0.658 Insurance status . 0.392 0.281 . . NI Insured 359 0.505 0.447 . . 0.041 Maricad 37 0.392 0.281 Maried 7 0.463 NA .<	1 umor Size	01	0.5(2	0.515	0.001	D - (0.343
24 cm 170 0.430 0.20 1.800 0.800 0.801 0.101 24 cm 188 0.573 0.384 1.863<(0.805-3.994)	S2 cm	31 170	0.562	0.515		Reference	0 101
A fun 188 0.53 0.534 1.685 (0.505-3.596) 0.110 Unknown 24 0.231 0.116 1.254 (0.460-3.421) 0.658 Insurace status 0.231 0.347 NI NI Insured 359 0.505 0.347 Status	2-4 cm	170	0.450	0.280		1.866 (0.865-3.934)	0.101
Dirklowin 24 0.29 0.10 1.254 (0.400-3.421) 0.038 Insured 359 0.505 0.347 NI Insured 37 0.392 0.281 . . . Mariad 37 0.392 0.281 . <td>24 CIII</td> <td>166</td> <td>0.373</td> <td>0.364</td> <td></td> <td>1.003 (0.009-3.990)</td> <td>0.110</td>	24 CIII	166	0.373	0.364		1.003 (0.009-3.990)	0.110
Instruct Status 0.505 0.47 N1 Medicaid 359 0.505 0.347		24	0.251	0.116	0 226	1.234 (0.460-3.421)	0.050 NI
Instruct 359 0.302 0.342 Medicaid 37 0.392 0.281 Uninsured/Unknown 17 0.463 NA Marital status 0.051 0.051 0.041 Married 267 0.497 0.340 Reference Unmarried 128 0.448 0.281 1.173 (0.885-1.556) 0.267 Unknown 128 0.769 0.844 0.281 1.073 (0.885-1.556) 0.267 County % with bachelor degree 128 0.448 0.281 0.351 (0.134-0.922) 0.303 Below median 167 0.448 0.285 Reference 0.304 Above median 167 0.448 0.285 Reference 1.39 Above median 167 0.448 0.285 Reference 1.39 Above median 190 0.522 0.409 Reference 0.343 Below median household incow 173 0.428 0.268 Reference 1.29 (0.830-1.577) 0.344 Below median 173 0.428 0.268 Reference 1.312	Insurance status	250	0 505	0.247	0.230		111
Meridad 57 0.392 0.201 Uninsured/Unknown 17 0.463 NA 0.411 Marital status 0.497 0.340 Reference 0.011 Unmarried 267 0.497 0.340 Reference 0.267 Unmarried 128 0.488 0.281 $0.310, 0134.0.922$ 0.034 Unknown 128 0.4488 0.281 $0.321, 0134.0.922$ 0.034 County % with bachelor degree 0.4488 0.285 Reference 0.080 Below median 167 0.448 0.285 Reference 0.392 Above median 167 0.448 0.285 Reference 0.439 Below median 190 0.522 0.409 Reference 0.349 Above median 90 0.482 0.268 0.271 0.392 Below median 173 0.428 0.268 Reference 0.394 Above median 173 0.428 0.286 $0.709 (0.516.0.975)$ 0.914	Medicoid	27	0.303	0.347			
Initial status 0.400 NAMarital status 0.497 0.340 ReferenceUnmarried128 0.448 0.281 1.173 ($0.885-1.556$) 0.267 Unknown18 0.769 0.684 0.351 ($0.134-0.922$) 0.034 County % with bachelor degree 0.684 0.351 ($0.134-0.922$) 0.034 Below median167 0.448 0.285 ReferenceAbove median167 0.448 0.285 ReferenceBelow median167 0.448 0.285 ReferenceAbove median100 0.522 0.409 ReferenceAbove median190 0.522 0.409 ReferenceAbove median190 0.522 0.409 ReferenceAbove median190 0.522 0.409 ReferenceAbove median190 0.522 0.409 ReferenceAbove median193 0.428 0.268 0.201 Below median173 0.428 0.268 0.709 ($0.516-0.975$)Residence area 0.709 0.709 ($0.516-0.975$) 0.911 Metropolitan283 0.507 0.339 0.111 Metropolitan30 0.507 0.329 0.001 Urban/rural30 0.592 0.246 ReferenceSpr.232 0.392 0.246 Reference	Uningured /Unknown	17	0.392	0.201 NA			
Married 267 0.497 0.340 Reference Unmarried 128 0.448 0.281 1.173 (0.885-1.556) 0.267 Unknown 18 0.769 0.684 0.351 (0.134-0.922) 0.034 County % with bachelor degree 0.042 0.351 (0.134-0.922) 0.034 Below median 167 0.448 0.285 Reference Above median 246 0.524 0.371 0.767 (0.570-1.033) County % with unemployed 246 0.522 0.409 Reference Above median 190 0.522 0.409 Reference 0.034 Above median 190 0.522 0.409 Reference 0.034 Above median 190 0.522 0.409 Reference 1.129 (0.830-1.537) 1.129 (0.830-1.537) County-level median household income 203 0.468 0.268 Reference 1.129 (0.830-1.537) Below median 173 0.428 0.268 0.709 (0.516-0.975) 1.129 (0.830-1.537) <td< td=""><td>Marital status</td><td>17</td><td>0.405</td><td>INA</td><td>0.051</td><td></td><td>0.041</td></td<>	Marital status	17	0.405	INA	0.051		0.041
Marine 20 0.477 0.487 0.486 Reference Unmarried 128 0.448 0.281 1.173 (0.885-1.556) 0.267 Unknown 18 0.769 0.684 0.351 (0.134-0.92) 0.034 County % with bachelor degree 0.042 0.042 0.080 Below median 167 0.448 0.285 Reference 0.080 Above median 246 0.524 0.371 0.767 (0.570-1.033) - County % with unemployed 190 0.522 0.409 Reference 0.439 Below median 190 0.522 0.409 Reference 0.034 Above median 190 0.522 0.409 Reference 0.034 Below median 190 0.522 0.409 Reference - 0.034 Below median 190 0.428 0.268 0.709 (0.516-0.975) - Reference - - 1.173 (0.88-1.550 0.034 - - - 1.173 (0.89.1.537) - - - - - - - -	Married	267	0.497	0.340	0.001	Reference	0.041
Contraction 120 0.440 0.201 1.175 (0.000-1.500) 0.034 Unknown 18 0.769 0.684 0.351 (0.134-0.922) 0.034 County % with bachelor degree 0.042 0.042 0.080 Below median 167 0.448 0.285 Reference 100 Above median 246 0.522 0.409 Reference 0.439 Below median 190 0.522 0.409 Reference 0.034 Above median 190 0.522 0.409 Reference 1129 (0.830-1.537) 0.39 County % with unemployed 223 0.468 0.268 1.129 (0.830-1.537) 0.34 Below median household income 233 0.428 0.268 Reference 0.034 Below median 173 0.428 0.268 0.709 (0.516-0.975) 1129 Residence area 173 0.428 0.268 0.709 (0.516-0.975) 1129 Metropolitan 383 0.507 0.339 0.707 1129 Urban/rural 30 0.323 0.277 112	Unmarried	128	0.448	0.281		1 173 (0 885-1 556)	0.267
County % with bachelor degree 0.000 0.002 0.002 0.002 Below median 167 0.448 0.285 Reference 0.042 0.080 Above median 246 0.524 0.371 0.040 0.6767 (0.570-1.033) 0.439 Below median 246 0.522 0.409 Reference 0.439 Below median 190 0.522 0.409 Reference 0.034 Above median 233 0.468 0.268 1.129 (0.830-1.537) 0.034 Below median household income 233 0.428 0.268 Reference 0.034 Below median 173 0.428 0.268 0.709 (0.516-0.975) 0.034 Below median 240 0.540 0.386 0.709 (0.516-0.975) 0.11 Metropolitan 383 0.507 0.339 0.277 V V Virban/rural 30 0.323 0.277 0.011 0.011 SPS 232 0.392 0.246 Reference 0.011	Unknown	120	0.769	0.684		0.351 (0.134-0.922)	0.034
Below median 167 0.448 0.285 Reference Above median 26 0.524 0.371 0.767 (0.570-1.033) County % with unemployed 0.522 0.409 Reference Below median 190 0.522 0.409 Reference Above median 223 0.468 0.268 1.129 (0.830-1.537) County-level median household income 0.0268 Reference Below median 173 0.428 0.268 Reference Above median 173 0.428 0.268 Reference Above median 173 0.428 0.268 0.709 (0.516-0.975) Residence area 0.500 0.386 0.709 (0.516-0.975) Wetropolitan 383 0.507 0.339 0.77 Urban/rural 30 0.323 0.277	County % with bachelor degree	10	0.705	0.004	0.042	0.001 (0.104-0.022)	0.080
Above median 167 0.450 0.205 Reference Above median 246 0.371 0.767 (0.570-1.033) County % with unemployed	Below median	167	0 448	0.285	0.012	Reference	0.000
Note including International of the instance International of the instance County % with unemployed 0.610 0.631 0.6409 Below median 190 0.522 0.409 Reference Above median 223 0.468 0.268 1.129 (0.830-1.537) County-level median household income 0.439 0.002 0.001 Below median 173 0.428 0.268 Reference Above median 240 0.540 0.386 0.709 (0.516-0.975) Residence area 173 0.428 0.268 NI Metropolitan 383 0.507 0.339 NI Urban/rural 30 0.323 0.277 10.011 SPS 232 0.392 0.246 Reference	Above median	246	0.524	0.203		0 767 (0 570-1 033)	
Below median 190 0.522 0.409 Reference Above median 223 0.468 0.268 1.29 (0.80-1.537) County-level median household income 0.002 0.034 Below median 173 0.428 0.268 Reference Above median 240 0.540 0.386 0.709 (0.516-0.975) Residence area 0.104 NI Metropolitan 383 0.507 0.339 Urban/rural 30 0.323 0.277 Synchronous surgical procedure	County % with unemployed	210	0.021	0.071	0.040	0.707 (0.070 1.000)	0 439
Above median 223 0.428 0.626 0.102 0.1129 (0.830-1.537) County-level median household income 0.002 0.034 Below median 173 0.428 0.268 Reference Above median 240 0.540 0.386 0.709 (0.516-0.975) Residence area NI Wetropolitan 383 0.507 0.339 Urban/rural 30 0.323 0.277 0.011 SPS 232 0.392 0.246 Reference	Below median	190	0.522	0.409		Reference	
County-level median household income 0.020 0.034 Below median 173 0.428 0.268 Reference Above median 240 0.540 0.386 0.709 (0.516-0.975) Residence area 0.104 NI Metropolitan 383 0.507 0.339 Urban/rural 30 0.323 0.277 Synchronous surgical procedure	Above median	223	0.468	0.268		1.129 (0.830-1.537)	
Below median 173 0.428 0.268 Reference Above median 240 0.540 0.386 0.709 (0.516-0.975) Residence area NI Metropolitan 383 0.507 0.339 Urban/rural 30 0.323 0.277 Synchronous surgical procedure < SPS 232 0.392 0.246	County-level median household income				0.002		0.034
Above median 240 0.540 0.386 0.709 (0.516-0.975) Residence area 0.104 NI Metropolitan 383 0.507 0.339 Urban/rural 30 0.323 0.277 Synchronous surgical procedure < SPS 232 0.392 0.246	Below median	173	0.428	0.268		Reference	
Residence area 0.104 NI Metropolitan 383 0.507 0.339 Urban/rural 30 0.323 0.277 Synchronous surgical procedure < SPS 232 0.392 0.246	Above median	240	0.540	0.386		0.709 (0.516-0.975)	
Metropolitan 383 0.507 0.339 Urban/rural 30 0.323 0.277 Synchronous surgical procedure < <0.001 SPS 232 0.392 0.246 Reference	Residence area	-			0.104		NI
Urban/rural 30 0.323 0.277 Synchronous surgical procedure <0.001 0.011 SPS 232 0.392 0.246 Reference	Metropolitan	383	0.507	0.339	-		
Synchronous surgical procedure <0.001 0.011 SPS 232 0.392 0.246 Reference	Urban/rural	30	0.323	0.277			
SPS 232 0.392 0.246 Reference	Synchronous surgical procedure				< 0.001		0.011
	SPS	232	0.392	0.246		Reference	

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Variable	Total (n=413)	2-year PCSS	5-year PCSS	Univariate analysis	Multivariate Cox analysis	
				Р	HR (95%CI)	Р
SPL	93	0.683	0.497		0.544 (0.373-0.793)	0.009
SPO	88	0.551	0.391		0.656 (0.461-0.934)	0.033
Radiotherapy				0.513		NI
Yes	26	0.498	0.249			
No/Unknown	387	0.491	0.337			
Chemotherapy				0.001		0.056
Yes	213	0.414	0.228		Reference	
No/Unknown	200	0.580	0.451		1.365 (0.992-1.878)	

*, Other includes American Indian/Alaska Native, Asian/Pacific Islander, and unknown. PCSS: pancreatic cancer cause-specific survival; HR: hazard ratio; CI: confidence interval; SPL: synchronous resection of the primary tumor and liver metastases; SPO: synchronous primary tumor and other resection; SPS: single resection of the primary site; NA: not applicable; NI: not included in multivariate survival analysis.

Table 4. Univariate and multivariate Cox analyses to identify predictors of pancreatic cancer cause-specific survival in patients receiving no resection

Variable	Total (n=13503)	2-year PCSS	5-year PCSS	Univariate analysis	Multivariate Cox analysis	
		-	-	Р	HR (95%CI)	Р
Sex				0.298		NI
Male	7312	0.057	0.022			
Female	6191	0.056	0.016			
Race				0.004		0.019
White	10608	0.059	0.021		Reference	
Black	1847	0.045	0.013		1.059 (1.006-1.116)	0.030
Other*	1048	0.059	0.019		0.950 (0.889-1.016)	0.133
Age				< 0.001		< 0.001
<65	5552	0.088	0.029		Reference	
≥65	7951	0.035	0.013		1.295 (1.247-1.344)	
Year of diagnosis				< 0.001		0.001
2010-2011	4096	0.046	0.014		Reference	
2012-2013	4468	0.061	NA		0.962 (0.921-1.004)	0.077
2014-2015	4939	0.062	NA		0.922 (0.883-0.963)	< 0.001
Primary Site				< 0.001		0.004
Head	4899	0.054	0.016		Reference	
Body/Tail	4856	0.061	0.023		1.062 (1.019-1.107)	0.005
Other	3748	0.050	0.019		1.069 (1.020-1.121)	0.005
Grade				< 0.001		< 0.001
Well/Moderate	1040	0.163	0.055		Reference	
Poor/Anaplastic	1431	0.034	0.008		1.708 (1.569-1.859)	< 0.001
Other	11032	0.050	0.018		1.476 (1.379-1.581)	< 0.001
Histology				< 0.001		< 0.001
Adenocarcinoma	9845	0.036	0.007		Reference	
Neuroendocrine carcinoma	546	0.391	0.062		0.298 (0.269-0.330)	< 0.001
Other	3112	0.172	0.030		0.911(0.872-0.951)	< 0.001
T stage				< 0.001		0.006
ТО	119	0.060	NA		Reference	
T1	337	0.064	0.012		0.855 (0.689-1.064)	0.156
Τ2	3848	0.059	0.025		0.809 (0.643-1.018)	0.070
Τ3	3280	0.063	0.016		0.761 (0.606-0.956)	0.019
T4	2216	0.052	0.018		0.769 (0.612-0.968)	0.025
TX	3703	0.050	0.021		0.829 (0.660-1.040)	0.106
N stage				< 0.001		0.183
N0	7173	0.060	0.019		Reference	
N1	3904	0.056	0.022		1.037 (0.996-1.081)	0.079
NX	2426	0.048	0.017		0.998 (0.949-1.050)	0.950
Tumor Size				< 0.001		< 0.001
≤2 cm	714	0.065	0.021		Reference	
2-4 cm	4600	0.058	0.014		1.102 (0.966-1.258)	0.148
>4 cm	5367	0.058	0.024		1.228 (1.076-1.400)	0.002
Unknown	2822	0.052	0.020		1.183 (1.033-1.354)	0.015
Insurance status				< 0.001		< 0.001
Insured	10999	0.060	0.021		Reference	
Medicaid	1790	0.041	0.015		1.094 (1.036-1.154)	0.001
Uninsured/Unknown	714	0.043	0.007		1.164 (1.074-1.262)	< 0.001
Marital status				< 0.001		< 0.001
Married	7210	0.071	0.024		Reference	
Unmarried	5662	0.038	0.014		1.116 (1.075-1.158)	< 0.001

Variable	Total (n=13503)	2-year PCSS	5-year PCSS	Univariate analysis	Multivariate Cox analysis	
				Р	HR (95%CI)	Р
Unknown	631	0.061	0.025		1.000 (0.919-1.089)	0.997
County % with bachelor degree				< 0.001		0.003
Below median	5815	0.053	0.016		Reference	
Above median	7688	0.060	0.023		0.941 (0.903-0.980)	
County % with unemployed				0.008		0.688
Below median	6443	0.062	0.023		Reference	
Above median	7060	0.052	0.017		0.992 (0.956-1.030)	
County-level median household income	2			< 0.001		0.182
Below median	6532	0.053	0.018		Reference	
Above median	6971	0.060	0.022		0.972 (0.932-1.013)	
Residence area				0.696		NI
Metropolitan	12054	0.056	0.018			
Urban/rural	1433	0.058	0.030			
Missing	16	0.125	NA			
Radiotherapy				< 0.001		< 0.001
Yes	367	0.112	0.009		Reference	
No/Unknown	13136	0.055	0.020		1.330 (1.194-1.483)	
Chemotherapy				< 0.001		< 0.001
Yes	6671	0.084	0.024		Reference	
No/Unknown	6832	0.030	0.014		2.509 (2.413-2.608)	

*, Other includes American Indian/Alaska Native, Asian/Pacific Islander, and unknown. PCSS: pancreatic cancer cause-specific survival; HR: hazard ratio; CI: confidence interval; NA: not applicable; NI: not included in multivariate survival analysis.

Subgroup analysis of the effect on PCSS of chemotherapy in patients without surgery, according to the primary site

As shown in **Table 5**, Kaplan–Meier and multivariate Cox analyses all showed that at each primary site, including the pancreatic head, body/tail, and other sites, patients receiving WSC had better survival than those with N-WSC (all P < 0.001).

Subgroup analysis of the effect on PCSS of histology

As seen in **Table 6**, the 5-year PCSS was significantly different and gradually declined in the following groups: 49.7% in the SPL group, 39.1% in the SPO group, 24.6% in the SPS group, and 1.9% in the NR group (P < 0.001) (**Figure 1A**). The SPS, SPO, and SPL groups showed significantly and gradually longer median survival of 15, 34, and 54 months, respectively, compared with 3 months for the NR group (all P < 0.001) (**Table 6**). Compared with the NR group, mortalities were significantly and gradually declining in the SPS, SPO, and SPL groups, with hazard ratio (HR) 0.329 (95% confidence interval [CI], 0.281-0.386), 0.220 (95% CI, 0.164-0.294), and 0.162 (95% CI, 0.118-0.222), respectively (all P < 0.001) (**Table 6**).

Compared with the NR group, there had increasingly improved survival benefits of 2-year PCSS for SPS, SPO, and SPL among adenocarcinoma, neuroendocrine carcinoma, or other groups (all P < 0.05) (**Table 6, Figure 1B-D**). Moreover, compared with the NR group, mortalities were significantly and gradually declining for SPS, SPO, and SPL among the adenocarcinoma, neuroendocrine carcinoma, or other

groups (all *P* < 0.05) (**Table 6**).

Compared with the neuroendocrine carcinoma group, those who receiving SPS, SPO, SPL, or NR all had gradually worse PCSS for other histology and adenocarcinoma groups (all P < 0.05) (**Table 6, Figure 2A-D**). Moreover, compared with the neuroendocrine carcinoma group, mortalities were all significantly and gradually increased for other histology and adenocarcinoma groups receiving SPS, SPO, SPL, or NR (all P < 0.05) (**Table 6**).

Subgroup analysis of the effect on PCSS of combined surgery and adjuvant therapy

Compared with patients receiving no/unknown adjuvant therapy, there were no significant differences in survival for chemoradiotherapy and chemotherapy with no/unknown radiotherapy among the SPL, SPO, or SPS groups in Kaplan–Meier and multivariate analyses with Cox regression (all P > 0.05) (**Table 6**).

Compared with patients receiving no/unknown adjuvant therapy, those with NR had increasingly improved survival benefits for radiotherapy with no/unknown chemotherapy, chemotherapy with no/unknown radiotherapy, and chemoradiotherapy (median survival: 1, 3, 6, and 8 months, respectively, all P < 0.001) (**Table 6**). Moreover, compared with patients receiving no/unknown adjuvant therapy, mortalities was significantly and gradually declining for the radiotherapy with no/unknown chemotherapy, chemotherapy with no/unknown chemotherapy, and chemoradiotherapy groups, with HR 0.569 (95% CI, 0.462-0.699, P < 0.001), 0.394 (95% CI, 0.379-0.408, P < 0.001), and 0.332 (95% CI, 0.292-0.377, P < 0.001), respectively (**Table 6**).

Table 5. Univariate and multivariate Cox analyses of pancreatic cancer cause-specific survival according to primary site

Variable	Total	Median survival (months)	2-year PCSS	5-year PCSS	Univariate analysis	Multivariate Cox analysis	
		· · ·			P	HR (95%CI)	Р
Surgical procedure of primary site	e						
Primary Site:							
Head	5236	3			< 0.001		< 0.001
Performed	181	13	0.322	0.209		Reference	
Recommended but not performed	1 95	2	0.037	NA	< 0.001	3.615 (2.759-4.737)	< 0.001
Not recommended	4960	3	0.056	0.016	< 0.001	2.681 (2.249-3.197)	< 0.001
Body/Tail	5113	3			< 0.001		< 0.001
Performed	165	38	0.633	0.405		Reference	
Recommended but not performed	l 100	2	0.061	0.037	< 0.001	5.749 (4.275-7.730)	< 0.001
Not recommended	4848	3	0.061	0.022	< 0.001	4.926 (3.952-6.141)	< 0.001
Other	3899	2			< 0.001		< 0.001
Performed	68	53	0.586	0.487		Reference	
Recommended but not performed	l 125	1	0.050	NA	< 0.001	5.872 (3.947-8.735)	< 0.001
Not recommended	3706	2	0.057	0.019	< 0.001	5.197 (3.644-7.414)	< 0.001
Surgical Procedure of Other Sites							
Primary Site:							
Heada	5235	3			< 0.001		< 0.001
Not performed	5022	3	0.058	0.019		Reference	
Liver resection	125	8	0.239	0.140	< 0.001	0.519 (0.426-0.633)	< 0.001
Other resection	88	8	0.196	0.103	< 0.001	0.549 (0.436-0.691)	< 0.001
Body/Tail ^b	5111	3			< 0.001		< 0.001
Not performed	4926	3	0.069	0.028		Reference	
Liver resection	106	11	0.372	0.229	< 0.001	0.395 (0.314-0.497)	< 0.001
Other resection	79	13	0.382	0.245	< 0.001	0.376 (0.287-0.492)	< 0.001
Other ^c	3895	2			< 0.001		< 0.001
Not performed	3787	2	0.060	0.024		Reference	
Liver resection	57	7	0.283	0.136	< 0.001	0.513 (0.383-0.687)	< 0.001
Other resection	51	11	0.298	0.201	< 0.001	0.413 (0.299-0.568)	< 0.001
<i>Radiotherapy</i> ^d							
Primary Site:							
Head	4899	3			< 0.001		< 0.001
Yes	173	6	0.103	NA		Reference	
No/Unknown	4726	3	0.052	0.018		1.431 (1.225-1.673)	
Body/Tail	4856	3			< 0.001		< 0.001
Yes	111	5	0.122	0.030		Reference	
No/Unknown	4745	2	0.060	0.023		1.439 (1.184-1.750)	
Other	3748	2			< 0.001		< 0.001
Yes	83	8	0.121	NA		Reference	
No/Unknown	3665	2	0.053	0.019		1.736 (1.377-2.190)	
Chemotherapy ^d							
Primary Site:							
Head	4899	3			< 0.001		< 0.001
Yes	2453	7	0.077	0.018		Reference	
No/Unknown	2446	1	0.031	0.014		2.572 (2.422-2.731)	
Body/Tail	4856	3			< 0.001		< 0.001
Yes	2579	6	0.088	0.028		Reference	
No/Unknown	2277	1	0.031	0.017		2.540 (2.390-2.699)	
Other	3748	2			< 0.001		< 0.001
Yes	1639	6	0.089	0.029		Reference	
No/Unknown	2109	1	0.027	0.012		2.456 (2.291-2.632)	

^a, Excluding one patient in whom surgical procedures of other sites was unknown. ^b, Excluding two patients in whom surgical procedures of other sites was unknown. ^c, Excluding four patients in whom surgical procedures of other sites was unknown. ^d, Patients who did not undergo resection. PCSS: pancreatic cancer cause-specific survival; HR: hazard ratio; CI: confidence interval; NA: not applicable.

Discussion

Current therapeutic approaches for patients with M1 PC are palliative and mainly based on tumor cell targeting. Some palliative chemotherapies' for patients with M1 PC have recently been established, such as the use of fluorouracil, leucovorin, irinotecan,

and oxaliplatin (FOLFIRINOX) or gemcitabine with nab-paclitaxel, which have shown an increased median OS of 11 and 8.5 months, respectively, compared with 6.7-7 months for single gemcitabine [5]; nevertheless, the survival outcome of patients with M1 PC remains poor.



Figure 1. Survival curves in patients with pancreatic cancer and liver metastases treated with different surgical procedures. (A) Overall: $\chi^2 = 113.429$, P < 0.001; (B) Adenocarcinoma: Log rank $\chi^2 = 84.148$, P < 0.001; (C) Neuroendocrine carcinoma: Log rank $\chi^2 = 74.889$, P < 0.001; (D) Other: Log rank $\chi^2 = 220.033$, P < 0.001. SPL: synchronous resection of the primary tumor and liver metastases; SPO: synchronous primary tumor and other resection; SPS: single resection of the primary site; NR: no resection.

Palliative resection for advanced pancreatic cancer is controversial. Tachezy et al. deemed that palliative resection for M1 PC was not advisable because of its lack of survival benefit (5.1 months [n = 22] vs. 5.8 months [n = 46]) and higher surgery-related morbidity (59% vs. 33%, P = 0.035) and mortality (27% vs. 7%, P = 0.049), compared with bypass surgery [18]. Macroscopically complete resection has been demonstrated to be one of the most important and protective prognostic factors for survival; however, the performance of additional vessel resections and/or synchronous metastasis resections should be carefully weighed to avoid increasing morbidity and mortality caused by these surgical procedures [19-21].

International guidelines do not recommend surgery for PC when distant metastasis has occurred [1,9]. Our outcomes showed that SPS was associated with significantly improved survival compared with no resection. The present rationale for proposing SPS in patients with PC and metastatic disease has been revisited in subgroup analyses. McKenzie et al. revealed significant survival benefits of 4.7 months in patients with M1 PC receiving SPS (median survival: 6.3 months, n = 92) compared with those who did not receive surgical resection (median survival: 1.6 months, n = 2606) [22].



Figure 2. Survival curves in patients with pancreatic cancer and liver metastases treated with different histology. (A) SPL: $\chi^2 = 19.873$, P < 0.001; (B) SPO: Log rank $\chi^2 = 14.658$, P < 0.001; (C) SPS: Log rank $\chi^2 = 47.873$, P < 0.001; (D) NR: Log rank $\chi^2 = 634.958$, P < 0.001. Abbreviations: SPL: synchronous resection of the primary tumor and liver metastases; SPO: synchronous primary tumor and other resection; SPS: single resection of the primary site; NR: no resection.

Likewise, although synchronous resection for patients with PC and oligometastatic disease is controversial and not recommended in the international guidelines [1,9], with the increasing surgical safety of pancreatic and liver resection and unceasing pursuit for better survival in patients with M1 PC, SPL in carefully selected patients with PCL is being increasingly considered. Small studies, including case reports, have described the use of aggressive "curative" SPL in selected patients with PCL [10,23,24].

Two studies showed no survival benefit in PCL patients who underwent SPL, as compared with

palliative bypass alone (median survival: 5.9 [n = 22] vs. 5.6 [n = 66] months; median survival: 6 [n = 11] vs. 4 [n = 22] months; all P > 0.05, respectively) [15,16].

Conversely, a previous study revealed significant survival benefits of 5.5 months in PCL patients who received SPL as compared with NR (median survival: 11.4 [n = 11] vs. 5.9 [n = 118] months; P = 0.0384) [13]. A retrospective multicentral analysis in six European pancreas centers reported that the median OS of patients after SPL tended to be significantly longer than in those with NR (median survival: 14.5 [n = 69] vs. 7.5 [n = 69] months; P < 0.001) [14].

Table 6. Univariate and multivariate Cox analyses to evaluate pancreatic cancer cause-specific survival with histology and combined therapies

Variable	Total	Median survival	2-vear PCSS	5-year PCSS	Univariate	Multivariate Cox	
		(months)	, ,	5	analysis	analysis	
					Р	HR (95%CI)	Р
Total	13916	3			< 0.001		< 0.001
No resection	13503	3	0.057	0.019		Reference	
SPS	232	15	0.392	0.246	< 0.001	0.329 (0.281-0.386)	< 0.001
SPL	93	54	0.683	0.497	< 0.001	0.162 (0.118-0.222)	< 0.001
SPO	88	34	0.551	0.391	< 0.001	0.220 (0.164-0.294)	< 0.001
Histology							
Adenocarcinoma	9973	3			< 0.001		< 0.001
No resection	9845	3	0.036	0.006		Reference	
SPS	86	9	0.191	0.065	< 0.001	0.495 (0.394-0.621)	< 0.001
SPL	20	8	0.343	NA	< 0.001	0.360 (0.215-0.614)	< 0.001
SPO	22	11	0.333	0.133	< 0.001	0.361 (0.224-0.581)	< 0.001
Neuroendocrine carcinoma	658	21			< 0.001		< 0.001
No resection	546	15	0.391	0.172		Reference	
SPS	41	NA	0.863	0.549	< 0.001	0.290 (0.173-0.486)	< 0.001
SPL	39	NA	0.873	0.665	< 0.001	0.193 (0.103-0.363)	< 0.001
SPO	32	NA	0.746	0.607	< 0.001	0.278 (0.152-0.506)	< 0.001
Other	3285	1			< 0.001		< 0.001
No resection	3112	1	0.062	0.030		Reference	
SPS	105	15	0.367	0.283	< 0.001	0.312 (0.244-0.398)	< 0.001
SPL	34	43	0.673	0.443	< 0.001	0.191 (0.115-0.318)	< 0.001
SPO	34	24	0.486	0.312	< 0.001	0.251 (0.158-0.400)	< 0.001
SPS	232	15			0.472 ^a		0.705
No/Unknown	97	15	0.420	0.352		Reference	
Chemoradiotherapy	9	18	0.444	NA	0.839	1.084 (0.493-2.382)	0.841
Chemotherapy*	124	15	0.362	0.178	0.423	1.152 (0.826-1.607)	0.403
Radiotherapy#	2	-	-	-			
SPL	93	54			0.182 ^b		0.198
No/Unknown	60	NA	0.749	0.589		Reference	
Chemoradiotherapy	5	23	0.400	NA	0.615	1.480 (0.342-6.401)	0.600
Chemotherapy*	26	42	0.321	NA	0.071	1.838 (0.945-3.576)	0.073
Radiotherapy#	2	-	-	-			
SPO	88	33			0.340 ^c		0.353
No/Unknown	38	53	0.673	0.438		Reference	
Chemoradiotherapy	7	34	0.536	0.357	0.662	1.266 (0.426-3.768)	0.671
Chemotherapy*	42	16	0.436	0.355	0.145	1.577 (0.849-2.929)	0.149
Radiotherapy#	1	-	-	-			
No resection	13503	3			< 0.001		< 0.001
No/Unknown	6736	1	0.029	0.015		Reference	
Chemoradiotherapy	271	8	0.119	0.011	< 0.001	0.332 (0.292-0.377)	< 0.001
Chemotherapy*	6400	6	0.083	0.025	< 0.001	0.394 (0.379-0.408)	< 0.001
Radiotherapy#	96	3	0.091	NA	< 0.001	0.569 (0.462-0.699)	< 0.001

*, No/unknown radiotherapy. *, No/unknown chemotherapy. *, Analysis did not include the radiotherapy group because there were only two patients who received radiotherapy. b, Analysis did not include the radiotherapy group because there were only two patients who received radiotherapy. -, Analysis did not include the radiotherapy group because there were only two patients who received radiotherapy. -, Analysis did not include the radiotherapy group because there were only two patients who received radiotherapy. -, Analysis did not include the radiotherapy group because there was only one patient who received radiotherapy. PCSS: pancreatic cancer cause-specific survival; HR: hazard ratio; CI: confidence interval; SPL: synchronous resection of the primary tumor and liver metastases; SPO: synchronous primary tumor and other resection; SPS: single resection of the primary site; NA: not applicable.

This study showed that surgical procedures of both the primary site and other sites were independent positive prognostic factors for survival. On the one hand, a good survival effect was seen in this study in that the SPS group had a 12-month increase in median survival compared with the NR group (P < 0.001). On the other hand, the median survival of the liver resection and other resection groups had 5- and 6-month increased survival in comparison with the NR group, respectively (all P <0.001). Furthermore, regardless of whether the primary site was at the head, body/tail, or another location, resection of both the primary site and of other sites all significantly improved survival as compared with the NR group.

In this study, the SPL group showed the best survival benefit, with a significant and gradual increase in median survival of 20, 39, and 51 months, respectively, compared with the SPO, SPS, and NR groups (all P < 0.001). The mortality risk in the NR group was the highest, over six times that of the SPL group, nearly five times that of the SPO group, and over three times that of the SPS group. The median survival of the SPL group in this study was superior

to that of the abovementioned studies [13-16]. This difference may be owing to many factors including patients' performance status, surgical skills, perioperative management, management of operative indications, and in this study high rate of neuroendocrine carcinoma patients.

This study found that, among different histology groups, the neuroendocrine carcinoma group had the best survival for those who receiving SPS, SPO, SPL, or NR. On the contrary, the adenocarcinoma group had the worst survival. On the other hand, patients receiving SPL had a 29.7%, 42.4%, and 48.2% gradual increase in 2-year PCSS compared with whose receiving NR in adenocarcinoma, other histology, and neuroendocrine carcinoma groups respectively. In the study, we identified a total of 683 eligible PCL patients with neuroendocrine carcinoma. Fortunately, some of them, 112 (16.4%) received surgery, 39 (5.7%) underwent SPL, 32 (4.7%) received SPO, and 41 (6.0%) had SPS. PCL patients with neuroendocrine carcinoma after SPS, SPO, SPL were associated with gradual improved 5-year PCSS (54.9%, 60.7%, and 66.5%, respectively).

Another interesting finding of our study is that survival also improved in the other resection group. The median survival of the SPO group showed a 31-month increase compared with that of the NR group (P < 0.001). This finding is similar to a report by Shrikhande et al. that synchronous resection of interaortocaval lymph nodes (n = 9) and peritoneal metastases (n = 9) showed 7- and 21.1-month increase of median survival, respectively, compared with NR (n = 118) [13]. Because of improved survival owing to adjuvant therapy, this is recommended for patients who have PC with or without surgical resection in the international guidelines [1,9]; however, it is not mentioned as a treatment regimen for patients with M1 PC who receive synchronous multivisceral resection. Furthermore, clinical studies concerning the curative effect of adjuvant therapy in patients with M1 PC who receive synchronous multivisceral resection is very limited. Reportedly, postoperative chemotherapy and radiotherapy have no apparent influence on survival in patients with M1 PC who undergo synchronous multivisceral resection [19,22]. The conclusions of this study were consistent with the abovementioned outcomes; even chemoradiotherapy did not significantly prolong postoperative survival. It is worth investigating why the addition of adjuvant therapy in patients with M1 PC who receive synchronous multivisceral resection is not associated with improved prognosis.

We found that the RN-PSP group had an even worse survival than the NRN-PSP group. This may be owing to patients' heavy psychological burden, rejecting surgery, or a lack of palliative therapy.

Our study had several limitations. First, surgery-related morbidity and mortality are not included in the SEER database. Second, recurrence data were unknown. Third, the data for radiation or chemotherapy were denoted "No/Unknown"; this is somewhat unclear and means that in the analysis, we did not have a patient group that did not receive either therapy. Fourth, it is clear that all patients had liver metastasis without metastasis to other common sites, such as bone, lung, and brain; however, whether patients had an uncommon metastatic disease is unknown. Fifth, the sequence concerning chemotherapy and surgery was unavailable. Sixth, details of chemotherapy including medications and dosage were not provided. Finally, detailed information on liver metastases was unavailable, including tumor size, number, and site.

To our best knowledge, the sample sizes of patients with PCL who underwent SPL, SPO, and SPS in this study may be the largest to date. We revealed that surgical procedures of both the primary site and other sites were independent protective predictors for survival in patients with PCL. Among the different treatment regimens, SPL in particular provided a considerable survival benefit. Besides, adjuvant therapies were not associated with improved postoperative survival in patients with PCL.

According to recent evidence, several guiding principles should be followed when performing SPL in patients with PCL. Surgical procedures should be carried out at a high-volume PC center by a multidisciplinary team including surgeons experienced in procedures involving the pancreas, liver, and so on; also, patients should have good performance status, no invasion of the adjacent vessels, and resectability in limited liver metastases.

Further studies may be required, to develop qualification criteria for which PC center is qualified to perform SPL and operative indications for which patients with PCL are appropriate for SPL. In this population-based study, among 14,248 patients with PCL, only 93 (0.7%) received SPL, with a satisfactory 5-year PCSS (49.7%). In the future, it can be expected that increasingly more well-selected patients could benefit from SPL.

Abbreviations

PC: pancreatic cancer; PCL: pancreatic cancer with liver metastases; SPL: synchronous resection of the primary tumor and liver metastases; SPO: synchronous primary tumor and other resection; SPS: single resection of the primary site; NR: no resection; PCSS: pancreatic cancer cause-specific survival; PSP: receiving surgery for the primary site; RN-PSP: recommended but did not undergo surgery for the primary site; NRN-PSP: not recommended and did not have surgery for the primary site; WSR: without surgery who received radiotherapy; N-WSR: without surgery who received no/unknown radiotherapy; WSC: without surgery who received chemotherapy; N-WSC: received no/unknown chemotherapy; SEER: Surveillance, Epidemiology, and End Results; HR: hazard ratio; CI: confidence interval; OS: overall survival; NA: not applicable; NI: not included in multivariate survival analysis.

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Competing Interests

The authors have declared that no competing interest exists.

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