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Effect of Surgical Margins on Overall Survival in Resectable Pancreatic Cancer

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Effect of Surgical Margins on Overall Survival in Resectable Pancreatic Cancer

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B.S.

Jiangsu University

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Abstract

Effect of Surgical Margins on Overall Survival in Resectable Pancreatic Cancer

By Shuo Wang

Background Surgical resection remains the best treatment option for pancreatic ductal adenocarcinoma. However, controversy remains about the role of negative margin in resection. Using the National Cancer Data Base (NCDB), our aims were to investigate: 1) effect of surgical margins on overall survival (OS) in resected pancreatic cancer patients; 2) factors associated with margin status.

Methods Resected pancreatic adenocarcinoma cases from 2004-2013 were identified from the NCDB. Margin status was coded as negative (R0), microscopically positive (R1), and macroscopically positive (R2) from pathology reports. Univariate and multivariable logistic regression was used to assess the association between covariates and negative margin. Propensity scores (PS) were developed for each surgical margin status and used to produce matched samples for survival analysis. Cox proportional hazard modeling and Kaplan Meier plots examined the association between surgical margin status and OS.

Results Fifteen thousand one hundred nineteen patients underwent resection of pancreatic ductal adenocarcinoma. Of these, 11,596 patients (76.7%) were R0, 1,992 patients (13.2%) were R1, and 1,531 patients (10.1%) were R2. Median survival after PS matching for R0, R1 and R2 was 19.1, 13.3 and 13.8 months, respectively ($P < 0.0001$). No significant difference was found between R1 and R2 ($P = 0.0693$); however, R0 patients demonstrated better OS than R1 patients ($P < 0.0001$) (Hazard Ratio (HR) $_{R1 \text{ vs. } R0} = 1.54$, 95% confidence interval (CI): 1.38 - 1.71; $HR_{R2 \text{ vs. } R0} = 1.41$, 95% CI: 1.27 - 1.57). Factors associated with margin status included: facility type, insurance status, tumor stage, tumor size, and lymph nodes.

Conclusions For pancreatic adenocarcinoma resection, a negative surgical margin was associated with better OS. While the NCDB has limitations common to all retrospective databases, its national sample and survival status data contribute to the surgical debate related to margin status in this setting.

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BACKGROUND

Pancreatic cancer is the fourth leading cause of cancer deaths among both females and males in the United States.[1] Despite recent improvements in surgical management[2] and chemotherapy treatments,[3] pancreatic cancer remains a highly aggressive malignancy with an overall five-year survival rate about eight percent.[1] Surgical resection remains the best option for treatment, associated with prolonged survival,[4,5] however, only a minority of patients presenting with pancreatic ductal adenocarcinoma are candidates for resection.[4]

Factors that may potentially influence patient survival after surgical resection for pancreatic cancer include pathologic tumor stage, tumor grade, tumor size, surgical margin status, lymph nodal metastases, and lymphovascular invasion.[2,6-9] Of these factors, the operating surgeon can influence the extent of nodal harvest and resection margin. Based on surgical oncologic principles, complete pancreatic tumor extirpation with negative margin status should result in meaningful survival outcomes. Traditionally, frozen section has been used to assess the completeness of resection during pancreaticoduodenectomy; if the margin was positive, an additional resection of the involved margins was performed to achieve negative margins (R0).[10] However, the overall survival (OS) in previous retrospective cohort studies that pursued further resection to achieve negative margins has been inconsistent. Five previous publications compared the effect of microscopically positive margin (R1) and R0 on OS, and found an R0 margin was statistically significantly associated with improved OS outcome.[11-15] However, in the Royal North Shore Hospital study (n = 109 patients), Pang et al.[16] found R0 neck margins was associated with improved OS, but the association was not statistically significant (median OS: R1 = 23 months and R0 = 29 months, $p = 0.42$). All of these studies compared the survival of R1 patients with R0 patients with relative small sample sizes, and no study included the effect of macroscopically positive margin (R2).

METHODS

Hypothesis

The aim of the present study was to use the National Cancer Data Base (NCDB) to investigate the association of surgical margin status with overall survival in resectable pancreatic cancer. Additionally, we investigated factors that predict surgical margins status. The hypothesis was that negative (R0) margin status would be associated with improved overall survival (OS) as compared to microscopically involved (R1) or macroscopically positive (R2) margins in the context of surgically resected pancreatic adenocarcinoma.

National Cancer Data Base

The National Cancer Data Base (NCDB) is a nation-wide oncology database, which captures approximately 70% or more of newly diagnosed cases of cancer in the United Status. The NCDB is supported by the American College of Surgeons and the American Cancer Society and includes more than 1500 Commission on Cancer (CoC)-approved hospitals in the United States. Data included in the NCDB include patient demographics (e.g. age at diagnosis, insurance status, race, ethnicity, education level, and income level), tumor-related information (e.g. behavior, histology, grade, stage, and sequence number), detailed treatment information (including types of treatment, sequencing, dose and other important factors), and survival status.

Our patient population was obtained from the Pancreatic Participant Use Data File (PUF) from the NCDB. The PUF consists of de-identified patient level data designed for CoC-authorized cancer programs to analyze to advance quality care for cancer patients. Emory University was granted access to the Pancreatic PUF, which includes all incident cases of pancreatic cancer for the ten-year period 2004-2013.

Study Population

There were 309,709 cancer patients listed in the NCDB pancreatic cancer PUF from 2004 - 2013. We selected only patients with adequate and valid survival data (n = 60,512) and primary tumor site in the pancreas (n = 60,151). From this specific group, we selected patients whose

tumor behavior was invasive, whose pancreatic cancer diagnosis was either their first (sequence number = 0) or second instance (sequence number = 1) of cancer, and who received treatment at a reporting facility (n = 47,747). We then selected patients diagnosed with pancreatic adenocarcinoma by histology (n = 21,850). We excluded patients who did not undergo surgery and patients whose previous surgeries were not involving the pancreas, and we excluded patients who were missing margin status information (n = 16,719). We also excluded cases with evidence of metastatic disease as well as those with pathology stage classification T0 and Tis. Our final sample included 15,119 patients.

Surgical Margin Status

The Union for International Cancer Control applied the standard residual tumor designations in 1987.[17] An R0 status was defined as a negative margin, or the absence of gross and microscopic tumor cells at the resection margin. An R1 status was designated for a microscopic presence of tumor cells at the resection margin, whereas an R2 status was defined as the macroscopic presence of tumor cells at the resection margin. The margin status in the study was the final status of the surgical margins reported from the pathology report after resection of the primary tumor.

Statistical Analysis

Descriptive statistics for each covariate of interest in the dataset were reported for the overall patient population. We conducted univariate and multivariable logistic regression to investigate the association of selected covariates with negative margin status (R1 + R2 vs. R0).

Overall survival (OS) was calculated from the date of first surgery to the patient's death or last follow-up appointment. We performed univariate Cox proportional hazard model for the association of surgical margin status with OS. We fitted the multivariable Cox proportional hazard model for the association of surgical margin status with OS using the backward selection method with an alpha = 0.20 removal criterion. We used propensity score (PS) developed for each margin status to produce matched samples. Under the PS approach, we fitted a logistic

regression model to estimate the probability of a patient to have R0, R1, and R2 margins based on variables associated with OS, and the probability called PS. Then, we weighted the study population by treatment weighting, therefore, each patient with a given margin status, e.g., R0 margin, is matched with a R1 patient and a R2 patient of similar PS across all three margins. After weighting, we check the balance carried by standard difference with a criterion of 0.15, which was considered as negligible imbalance.[18] After forming the matched sample, we conducted Cox hazard regression to investigate the association of surgical margin status with overall survival. We generated Kaplan-Meier plots with log-rank test for both unmatched and matched samples to compare the five-year survival by margin status (R0, R1 and R2).

The analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) with software macros generated at the Winship Cancer Institute's Department of Biostatistics and Bioinformatics.[19]

RESULTS

Patient Demographics and Clinical Characteristics

A total of 15,123 patients with pancreatic ductal adenocarcinoma were identified from the NCDB, for diagnosis years 2004-2013. Supplemental Table 1 illustrates patient inclusion and exclusion criteria. Demographic data and clinical characteristics for selected patients are shown in Table 1. The mean age at diagnose for overall patients was 65.2 years (range 24 - 90 years). 48.8% of patients were female and 85.7% were White. On the basis of surgical margin status, 11,596 (76.7%) patients were defined as R0, 1,991 (13.2%) patients were defined as R1, and 1,531 (10.1%) were defined as R2. Compared with R1 and R2 patients, R0 patients, on average, were more likely to be reported at academic/ research/ integrated network cancer programs, to have neoadjuvant radiation or systemic therapy, to have surgery on total pancreas, to have smaller tumor size, to have no positive node, and to have lower tumor stage.

Survival Analyses

Univariate and multivariable Cox hazard regression for association of factors with OS were shown in Table 2. Multivariate analysis revealed that the factors associated with reduction in OS included positive margins, lack of insurance, higher Charlson-Deyo comorbidity score, absence of adjuvant radiation therapy, absence of systemic therapy, higher tumor grade, larger tumor size, presence of positive lymph nodes, having Whipple operation or having operation on total pancreatectomy with extension, and higher pathologic tumor stage. The standard difference among matched and unmatched samples are shown in Figure 1. After PS matching, the standard differences of all variables are less than 0.15. Cox hazard regression for association of surgical margin status with OS among matched sample were shown in Table 3. The results also show R0 patients were associated with better OS.

In the analysis of unmatched samples, the median OS (95% CI) for R0, R1 and R2 patients was 20.8 (20.3, 21.2), 13.2 (12.4, 13.9), and 12.9 (12.3, 13.6) months, respectively ($P < 0.0001$; log–rank test). The difference in OS between R0 and R1 patients was statistically significant ($P <$

0.0001; log–rank test). However, the difference in OS comparing R1 and R2 patients was not statistically significant (P = 0.6163; log–rank test) (Figure 2). After matching the cohort by PS, the median OS (95% CI) for R0, R1 and R2 patients was 19.1 (18.5, 19.7), 13.3 (12.2, 14.1), and 13.8 (12.8, 14.7) months, respectively (P < 0.0001; log–rank test). The multicomparable log – rank test results were similar with the unmatched sample. The difference in OS between R0 and R1 patients was statistically significant (P < 0.0001; log–rank test). However, the difference for OS comparing R1 and R2 patients was not statistically significant (P = 0.0693; log–rank test) (Figure 3).

Covariates Associated with Negative Margin Status

Univariate and multivariable logistic regression for association of covariates with margin status are shown in Table 4. Multivariable logistic regression revealed that patients who were reported at academic/ research/ integrated network cancer programs, or patients with insurance, lower Charlson-Deyo score, lower pathologic tumor stage, absence of positive regional lymph nodes, and smaller tumor size were more likely to have negative margin during surgery.

DISCUSSION

The purpose of this study was to evaluate the effect of surgical margins on OS in a large cohort of pancreatic cancer patients who underwent surgical resection and what factors might predict margin status. The data demonstrate that patients whose final margin status was defined as R0 experienced better OS compared with those whose final margin status was defined as R1 and R2. OS among R1 patients was similar to R2 patients. The data also demonstrated that for patients who were reported at academic/ research/ integrated network cancer programs, or patients with insurance, lower Charlson-Deyo score, lower pathologic tumor stage, absence of positive regional lymph nodes, and smaller tumor size were more likely to achieve R0 during the surgery.

Unexpectedly, the current data showed the OS for R1 and R2 patients was similar. This may be due to the biology of the tumor at time of resection. Maybe the tumor has spread beyond the tumor itself to other parts of the pancreas or other organs.[11] Therefore, even though surgery was done, the patient may still do poorly because the tumor is simply more biologically aggressive.

The current results validate the findings of several similar previous retrospective cohort studies. In the University of South Florida study (n = 85 patients), Hernandez et al.[11] found R0 status was statistically significantly associated with improved OS (median OS: R1 = 13 months and R0 = 21 months, $p = 0.02$). Similar to our finding, this study also showed that patients with higher tumor stage were more likely to have R1 margin status ($P < 0.0001$). In the Emory University Hospital study (n = 382 patients), Lad et al.[15] found that positive frozen section neck margin (R1) was statistically significantly associated with decreased OS (median OS: R0 = 17.3 months and R1 = 11.1 months, $p = 0.013$). In another University of South Florida study (n = 408 patients), Mathur et al.[12] also found permanent R0 margin resection was statistically significantly associated with improved OS (median OS: R1 = 12 months and R0 = 20 months, $p < 0.001$). In a multi-center study (n = 1,327 patients), Kooby et al.[13] found R0 margin was statistically significantly associated with improved OS (median OS: R1 = 13.7 months and R0 = 22.8 months,

$p < 0.001$). This study also found that patients with larger tumor size, more node-positive disease, and incidence of perinerual invasion were more likely to have a positive R1. In the University Hospital Dresden study (n = 216 patients), Nitschke et al.[14] found R0 patients were statistically significantly associated with improved OS (median OS: R1 = 12 months and R0 = 29 months, $p < 0.001$). Similar to our current finding, Nitschke et al.[14] reported patients with more advanced stage malignancies were more likely to have positive margin ($P < 0.0001$). Our finding is in contrast to the result of Pang et al.[16] who also found R0 neck margins was associated with improved OS in the Royal North Shore Hospital study (n = 109 patients), but the result was not statistically significant (median OS: R1 = 23 months and R0 = 29 months, $p = 0.42$).

In conclusion, the present study confirms the hypothesis that R0 status is associated with improved OS among resectable pancreatic cancer patients. Patients who were reported at academic/ research/ integrated network cancer programs, or patients with insurance, lower Charlson-Deyo score, lower pathologic tumor stage, absence of positive regional lymph nodes, and smaller tumor size were more likely to achieve R0 during the surgery.

Potential limitations

Our current findings should be interpreted with caution due to inherent limitations of large retrospective cohort study designs. Additionally, the data may have been miscoded, introducing a reporting bias. Although our study population was significantly larger than the sample size in previous studies, our sample represents only a fraction of the total patients available in NCDB, and the NCDB data are not population-based. Patients with missing values of surgical margin status, tumor characteristics information, and patients who didn't get treatment at a reporting facility were excluded, thus we may have introduced selection bias into the analysis. However, we applied PS to produce matched samples to minimize selection bias and the weighted analyses demonstrated the same results for OS differences based on margin status.

FUTURE DIRECTIONS

Future studies may focus on the effect of different type of surgery and additional therapy (e.g., chemotherapy or systemic therapy), given before or after surgery, on the OS among resectable pancreatic cancer patients.

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TABLES

Table 1. Demographic Data and Clinical Characteristics for Selected Patients, the NCDB, 2004 - 2013 (N = 15,119)

Variable	All patients (n = 15,119)	R0 patients (n = 11,596)	R1 patients (n = 1,992)	R2 patients (n = 1,531)
Age at diagnosis, years ± SD	65.2 ± 10.6	65.2 ± 10.6	65.3 ± 10.5	64.7 ± 10.5
Sex				
Male	7,743 (51.2)	5,846 (50.4)	1,082 (54.3)	815 (53.2)
Female	7,376 (48.8)	5,750 (49.6)	910 (45.7)	716 (46.8)
Race				
White	12,954 (85.7)	9,953 (85.8)	1,720 (86.3)	1,282 (83.7)
Black	1,505 (10.0)	1,144 (9.9)	180 (9.0)	181 (11.8)
Other	478 (3.2)	351 (3.0)	73 (3.7)	54 (3.5)
Missing	182 (1.2)	148 (1.3)	19 (1.0)	15 (1.0)
Facility type[2]				
CCCP/CCP/Other	5,290 (35.0)	3,968 (34.2)	742 (37.2)	580 (37.9)
ARCP/INCP	9,675 (64.0)	7,504 (64.7)	1,239 (62.2)	932 (60.9)
Missing	154 (1.0)	124 (1.1)	11 (0.6)	19 (1.2)
Insurance type				
Not insured	448 (3.0)	317 (2.7)	65 (3.3)	66 (4.3)
Private insurance	6,089 (40.3)	4,666 (40.2)	798 (40.1)	625 (40.8)
Government insurance	8,319 (55.0)	6,403 (55.2)	1,102 (55.3)	814 (53.2)
Missing	263 (1.7)	210 (1.8)	27 (1.4)	26 (1.7)
Median income[3]				
< $30,000	1,817 (12.0)	1,388 (12.0)	225 (11.3)	204 (13.3)
≥ $30,000, < $36,000	2,609 (17.3)	2,000 (17.2)	339 (17.0)	270 (17.6)
≥ $36,000, < $46,000	4,012 (26.5)	3,077 (26.5)	543 (27.3)	392 (25.6)
≥ $46,000	5,934 (39.2)	4,571 (39.4)	782 (39.3)	581 (37.9)
Not available	747 (4.9)	560 (4.8)	103 (5.2)	84 (5.5)
No high school degree[4]				
≥ 29%	2,282 (15.1)	1,734 (15.0)	282 (14.2)	266 (17.4)
≥ 20, < 29.0%	3,404 (22.5)	2,605 (22.5)	446 (22.4)	353 (23.1)
≥ 14, < 20.0%	3,460 (22.9)	2,633 (22.7)	486 (24.4)	341 (22.3)
< 14%	5,225 (34.6)	4,063 (35.0)	675 (33.9)	487 (31.8)
Not available	748 (4.9)	561 (4.8)	103 (5.2)	84 (5.5)
Living area				
Metro	11,597 (76.7)	8,890 (76.7)	1,548 (77.7)	1,159 (75.7)
Urban	2,480 (16.4)	1,924 (16.6)	308 (15.5)	248 (16.2)
Rural	318 (2.1)	241 (2.1)	42 (2.1)	35 (2.3)
Missing	724 (4.8)	541 (4.7)	94 (4.7)	89 (5.8)
Charlson-Deyo Score				
0	10,192 (67.4)	7,860 (67.8)	1,284 (64.5)	1,048 (68.5)
1	3,871 (25.6)	2,950 (25.4)	551 (27.7)	370 (24.2)
2	1,056 (7.0)	786 (6.8)	157 (7.9)	113 (7.4)
Radiation therapy				
No radiation therapy	8,668 (57.3)	6,826 (58.9)	1,008 (50.6)	834 (54.5)
Neoadjuvant therapy	961 (6.4)	833 (7.2)	74 (3.7)	54 (3.5)
Adjuvant therapy	5,257 (34.8)	3,777 (32.6)	874 (43.9)	606 (39.6)
Neoadjuvant and adjuvant therapy	20 (0.1)	13 (0.1)	5 (0.3)	2 (0.1)
Missing	213 (1.4)	147 (1.3)	31 (1.6)	35 (2.3)

Table 1. Demographic Data and Clinical Characteristics for Selected Patients, the NCDB, 2004 - 2013 (N = 15,119) (Contined)

Variable	All patients (n = 15,119)	R0 patients (n = 11,596)	R1 patients (n = 1,992)	R2 patients (n = 1,531)
Systemic therapy				
No systemic therapy	3,986 (26.4)	3,045 (26.3)	507 (25.5)	434 (28.3)
Neoadjuvant therapy	976 (6.5)	844 (7.3)	78 (3.9)	54 (3.5)
Adjuvant therapy	6,868 (45.4)	5,191 (44.8)	970 (48.7)	707 (46.2)
Neoadjuvant and adjuvant therapy	413 (2.7)	323 (2.8)	59 (3.0)	31 (2.0)
Missing	2,876 (19.0)	2,193 (18.9)	378 (19.0)	305 (19.9)
Tumor grade				
I	1,275 (8.4)	996 (8.6)	156 (7.8)	123 (8.0)
II	7,074 (46.8)	5,423 (46.8)	944 (47.4)	707 (46.2)
III/IV	5,432 (35.9)	4,083 (35.2)	763 (38.3)	586 (38.3)
Unspecified	1,338 (8.8)	1094 (9.4)	129 (6.5)	115 (7.5)
Tumor size (mm)				
≤ 20	2,598 (17.2)	2,210 (19.1)	213 (10.7)	175 (11.4)
> 20, ≤ 30	4,869 (32.2)	3,838 (33.1)	641 (32.2)	390 (25.5)
> 30, ≤ 40	3,798 (25.1)	2,852 (24.6)	511 (25.7)	435 (28.4)
> 40	3,337 (22.1)	2,326 (20.1)	565 (28.4)	446 (29.1)
Not given	517 (3.4)	370 (3.2)	62 (3.1)	85 (5.6)
Operation type[5]				
Distal	1,962 (13.0)	1,514 (13.1)	240 (12.0)	208 (13.6)
Whipple	9,370 (62.0)	7,150 (61.7)	1,289 (64.7)	931 (60.8)
Total pancreatectomy	688 (4.5)	563 (4.9)	69 (3.5)	56 (3.7)
Total pancreatectomy with extenstion	3,099 (20.5)	2,369 (20.4)	394 (19.8)	336 (21.9)
LN positive[6]				
Yes	9,631 (63.7)	7,017 (60.5)	1,497 (75.2)	1,117 (73.0)
No	5,088 (33.7)	4,284 (36.9)	448 (22.5)	356 (23.3)
Unknown	400 (2.6)	295 (2.5)	47 (2.4)	58 (3.8)
Pathologic stage (AJCC 7th)				
T1	1,047 (6.9)	947 (8.2)	53 (2.7)	47 (3.1)
T2	2,377 (15.7)	2,026 (17.5)	190 (9.5)	161 (10.5)
T3	10,426 (69.0)	7,816 (67.4)	1524 (76.5)	1,086 (70.9)
T4	510 (3.4)	249 (2.1)	135 (6.8)	126 (8.2)
Tx	769 (5.0)	558 (4.8)	90 (4.5)	111 (7.3)

[1]*P* were calculated using chi, square test for categorical variables and ANOVA tests for continuous variables

[2]CCCP/CCP, comprehensive community/community Cancer Program; ARP/INCP, academic/research/integrated network Cancer Program (includes NCI, designated comprehensive cancer centers)

[3]Median household income in patients' area of residence by matching the zip code at the time of diagnosis against files derived from year 2000 US Census data and categorized by quartiles

[4]Percent of no high school degree in patients' area of residence at the time of diagnosis against files derived from year 2000 US Census data and categorized by quartiles among all US zip codes

[5]Total pancreatomy with extension included total pancreatoduodenectomy and subtotal gastrectomy or duodenectomy and extended pancreatoduodenectomy

[6]LN, lymph node

Table 2. Univariate and Multivariable Cox Hazard Regression for Association of Factors with Overall Survival, the NCDB, 2004 - 2013 (N = 15,119)

	Univariate Analysis		Multivariate Analysis[1]	
Variable	HR (95% CI)[2]	P - value	HR (95% CI)[2]	P – value[3]
Margin Status				
R0	Ref		Ref	
R1	1.64 (1.56, 1.73)	**< 0.001**	1.58 (1.48, 1.69)	**< 0.001**
R2	1.62 (1.52, 1.71)	**< 0.001**	1.48 (1.37, 1.60)	**<0.001**
Facility type[4]				
CCCP/CCP/Other	Ref		Ref	
ARCP/INCP	0.94 (0.90, 0.97)	**< 0.001**	0.90 (0.85, 0.94)	**< 0.001**
Insurance type				
Not insured	Ref		Ref	
Private insurance	0.85 (0.76, 0.95)	**0.005**	0.91 (0.79, 1.05)	0.182
Government insurance	1.07 (0.96, 1.19)	0.248	1.02 (0.88, 1.19)	0.749
Median income[5]				
< $30,000	Ref		Ref	
≥ $30,000, < $36,000	0.93 (0.87, 1.00)	**0.045**	0.89 (0.82, 0.98)	**0.015**
≥ $36,000, < $46,000	0.90 (0.84, 0.95)	**< 0.001**	0.90 (0.82, 0.99)	**0.024**
≥ $46,000	0.81 (0.76, 0.86)	**< 0.001**	0.88 (0.79, 0.97)	**0.011**
No high school degree[6]				
≥ 29%	Ref		Ref	
≥ 20, < 29.0%	0.99 (0.94, 1.05)	0.814	1.10 (1.01, 1.19)	**0.026**
≥ 14, < 20.0%	0.90 (0.85, 0.96)	**< 0.001**	0.99 (0.90, 1.08)	0.792
< 14%	0.84 (0.79, 0.89)	**< 0.001**	0.98 (0.89, 1.08)	0.653
Living area				
Metro	Ref		Ref	
Urban	1.09 (1.04, 1.15)	**< 0.001**	1.06 (0.99, 1.13)	0.107
Rural	1.09 (0.96, 1.23)	0.167	0.90 (0.77, 1.06)	0.198
Charlson-Deyo Score				
0	Ref		Ref	
1	1.10 (1.06, 1.15)	**< 0.001**	1.07 (1.01, 1.13)	**0.016**
2	1.37 (1.28, 1.47)	**< 0.001**	1.29 (1.18, 1.41)	**< 0.001**
Radiation therapy				
No radiation therapy	Ref		Ref	
Neoadjuvant therapy	0.84 (0.78, 0.91)	**< 0.001**	1.10 (0.93, 1.30)	0.286
Adjuvant therapy	0.77 (0.74, 0.80)	**< 0.001**	0.85 (0.80, 0.90)	**< 0.001**
Neoadjuvant and adjuvant therapy	0.76 (0.47, 1.24)	0.277	0.76 (0.39, 1.50)	0.432
Systemic therapy				
No systemic therapy	Ref		Ref	
Neoadjuvant therapy	0.72 (0.66, 0.78)	**< 0.001**	0.76 (0.65, 0.88)	**< 0.001**
Adjuvant therapy	0.64 (0.61, 0.67)	**< 0.001**	0.62 (0.58, 0.66)	**< 0.001**
Neoadjuvant and adjuvant therapy	0.58 (0.51, 0.65)	**< 0.001**	0.55 (0.46, 0.67)	**< 0.001**
Tumor grade				
I	Ref		Ref	
II	1.29 (1.20, 1.39)	**< 0.001**	1.21 (1.10, 1.33)	**< 0.001**
III/IV	1.64 (1.52, 1.76)	**<0 .001**	1.53 (1.40, 1.68)	**< 0.001**
Tumor size (mm)				
≤ 20	Ref		Ref	
> 20, ≤ 30	1.40 (1.32, 1.48)	**< 0.001**	1.29 (1.19, 1.41)	**< 0.001**
> 30, ≤ 40	1.54 (1.45, 1.63)	**< 0.001**	1.36 (1.25, 1.48)	**< 0.001**
> 40	1.82 (1.72, 1.93)	**< 0.001**	1.61 (1.47, 1.75)	**< 0.001**
Operation type[7]				
Distal	Ref		Ref	
Whipple	1.14 (1.08, 1.21)	**< 0.001**	1.15 (1.07, 1.24)	**< 0.001**
Total pancreatectomy	1.03 (0.93, 1.14)	0.61	1.16 (1.02, 1.32)	**0.027**
Total pancreatectomy with extenstion	1.19 (1.11, 1.27)	**< 0.001**	1.17 (1.07, 1.27)	**< 0.001**

Table 2. Univariate and Multivariable Cox Hazard Regression for Association of Factors with Overall Survival, the NCDB, 2004 – 2013 (N = 15,119) (continued)

	Univariate Analysis		Multivariate Analysis[1]	
Variable	HR (95% CI)[2]	P - value	HR (95% CI)[2]	P – value[3]
LN positive[8]				
Yes	Ref		Ref	
No	0.62 (0.60, 0.65)	**< 0.001**	0.66 (0.63, 0.70)	**< 0.001**
Pathologic stage (AJCC 7th)				
T1	Ref		Ref	
T2	1.56 (1.43, 1.71)	**< 0.001**	1.09 (0.95, 1.25)	0.208
T3	1.83 (1.69, 1.98)	**< 0.001**	1.20 (1.06, 1.36)	**0.004**
T4	2.90 (2.56, 3.28)	**< 0.001**	1.63 (1.37, 1.95)	**<0.001**

[1]The sample size of multivariate cox hazard regression was 9,166 after removing all the missing value. The backward selection with an alpha level of removal of 0.20 was used, and age at diagnosis, sex and race were removed.

[2]HR, hazard ratio; CI, confidence interval

[3]Log, rank P, value

[4]CCCP/CCP, comprehensive community/community Cancer Program; ARP/INCP, academic/research/integrated network Cancer Program (includes NCI, designated comprehensive cancer centers)

[5]Median household income in patients' area of residence by matching the zip code at the time of diagnosis against files derived from year 2000 US Census data and categorized by quartiles

[6]Percent of no high school degree in patients' area of residence at the time of diagnosis against files derived from year 2000 US Census data and categorized by quartiles among all US zip codes

[7]Total pancreatomy with extension included total pancreatoduodenectomy and subtotal gastrectomy or duodenectomy and extended pancreatoduodenectomy

[8]LN, lymph node

Table 3. Cox Hazard Regression1 for Association of surgical margin status with Overall Survival among matched sample[1], the NCDB, 2004 – 2013 (N = 15,119)

Surgical margin	N	HR (95% CI)[2]	P-value	Type 3[3]
R0	7,043	Ref		**< 0.001**
R1	1,233	1.54 (1.38, 1.71)	**< 0.001**	
R2	891	1.41 (1.27, 1.57)	**< 0.001**	

[1]The sample size after propensity score matching is 9166
[2]HR, hazard ratio; CI, confidence interval
[3]Type 3 P-value

Table 4. Univariate and Multivariable Logistic Regression for Association of Covariates with Margin Status, the NCDB, 2004 – 2013 (N = 15,119)

	R0	R1+R2	Univeraite Analysis	Multivaraite Analysis[1]
Variable	N	N	OR (95%CI)[2]	OR (95%CI)[2]
Facility type[4]				
CCCP/CCP/Other	3,968	1,322	Ref	Ref
ARCP/INCP	7,504	2,171	0.87 (0.80, 0.94)	0.85 (0.76, 0.94)
Insurance type				
Not insured	317	131	Ref	Ref
Private insurance	4,666	1,423	0.74 (0.60, 0.91)	0.72 (0.54, 0.94)
Government insurance	6,403	1,916	0.72 (0.59, 0.89)	0.73 (0.56, 0.96)
Median income[5]				
< $30,000	1,388	429	Ref	Ref
≥ $30,000, < $36,000	2,000	609	0.99 (0.86, 1.13)	1.04 (0.84, 1.30)
≥ $36,000, < $46,000	3,077	935	0.98 (0.86, 1.12)	1.02 (0.84, 1.24)
≥ $46,000	4,571	1,363	0.96 (0.85, 1.09)	0.94 (0.78, 1.14)
No high school degree[6]				
≥ 29%	1,734	548	Ref	Ref
≥ 20, < 29.0%	2,605	799	0.97 (0.86, 1.10)	0.95 (0.80, 1.13)
≥ 14, < 20.0%	2,633	827	0.99 (0.88, 1.12)	1.01 (0.84, 1.22)
< 14%	4,063	1,162	0.91 (0.81, 1.02)	0.88 (0.72, 1.07)
Living area				
Metro	8,890	2,707	Ref	Ref
Urban	1,924	556	0.95 (0.86, 1.05)	0.98 (0.85, 1.13)
Rural	241	77	1.05 (0.81, 1.36)	1.03 (0.73, 1.44)
Charlson-Deyo Score				
0	7,860	2,332	Ref	Ref
1	2,950	921	1.05 (0.96, 1.15)	1.08 (0.97, 1.21)
2	786	270	1.16 (1.00, 1.34)	1.23 (1.03, 1.48)
Prior radiation therapy				
Yes	846	135	Ref	Ref
No	10,603	3,322	0.51 (0.42, 0.61)	0.82 (0.57, 1.20)
Prior syetemic therapy				
Yes	1,167	222	Ref	Ref
No	8,236	2,618	0.60 (0.52, 0.70)	0.77 (0.59, 1.02)
Tumor grade				
I	996	279	Ref	Ref
II	5,423	1,651	1.09 (0.94, 1.25)	1.01 (0.83, 1.22)
III/IV	4,083	1,349	1.18 (1.02, 1.37)	1.02 (0.83, 1.24)
Tumor size (mm)				
≤ 20	2,210	388	Ref	Ref
> 20, ≤ 30	3,838	1,031	1.53 (1.35, 1.74)	1.66 (1.37, 2.00)
> 30, ≤ 40	2,852	946	1.89 (1.66, 2.15)	1.85 (1.52, 2.24)
> 40	2,326	1,011	2.48 (2.17, 2.82)	2.24 (1.85, 2.72)
Operation type[7]				
Distal	1,514	448	Ref	Ref
Whipple	7,150	2,220	1.05 (0.93, 1.18)	1.07 (0.92, 1.25)
Total pancreatectomy	563	125	0.75 (0.60, 0.94)	0.69 (0.51, 0.93)
Total pancreatectomy with extenstion	2,369	730	1.04 (0.91, 1.19)	0.95 (0.80, 1.14)
LN positive[8]				
Yes	7,017	2,614	Ref	Ref
No	4,284	804	0.50 (0.46, 0.55)	0.61 (0.54, 0.68)
Pathologic stage (AJCC 7th)				
T1	947	100	Ref	Ref
T2	2,026	351	1.64 (1.30, 2.07)	0.92 (0.65, 1.32)
T3	7,816	2,610	3.16 (2.56, 3.90)	1.72 (1.24, 2.38)
T4	249	261	9.92 (7.58, 12.99)	6.25 (4.20, 9.30)

1The sample size of multivariate logistic regression was 9167 after removing all the missing value.
2OR, odds ratio; CI, confidence interval
3OR P- value
4CCCP/CCP, comprehensive community/community Cancer Program; ARP/INCP, academic/research/integrated network Cancer Program (includes NCI-designated comprehensive cancer centers)
5Median household income in patients' area of residence by matching the zip code at the time of diagnosis against files derived from year 2000 US Census data and categorized by quartiles
6Percent of no high school degree in patients' area of residence at the time of diagnosis against files derived from year 2000 US Census data and categorized by quartiles among all US zip codes
7Total pancreatomy with extension included total pancreatoduodenectomy and subtotal gastrectomy or duodenectomy and extended pancreatoduodenectomy
8LN, lymph node

FIGURES AND FIGURE LEGENDS

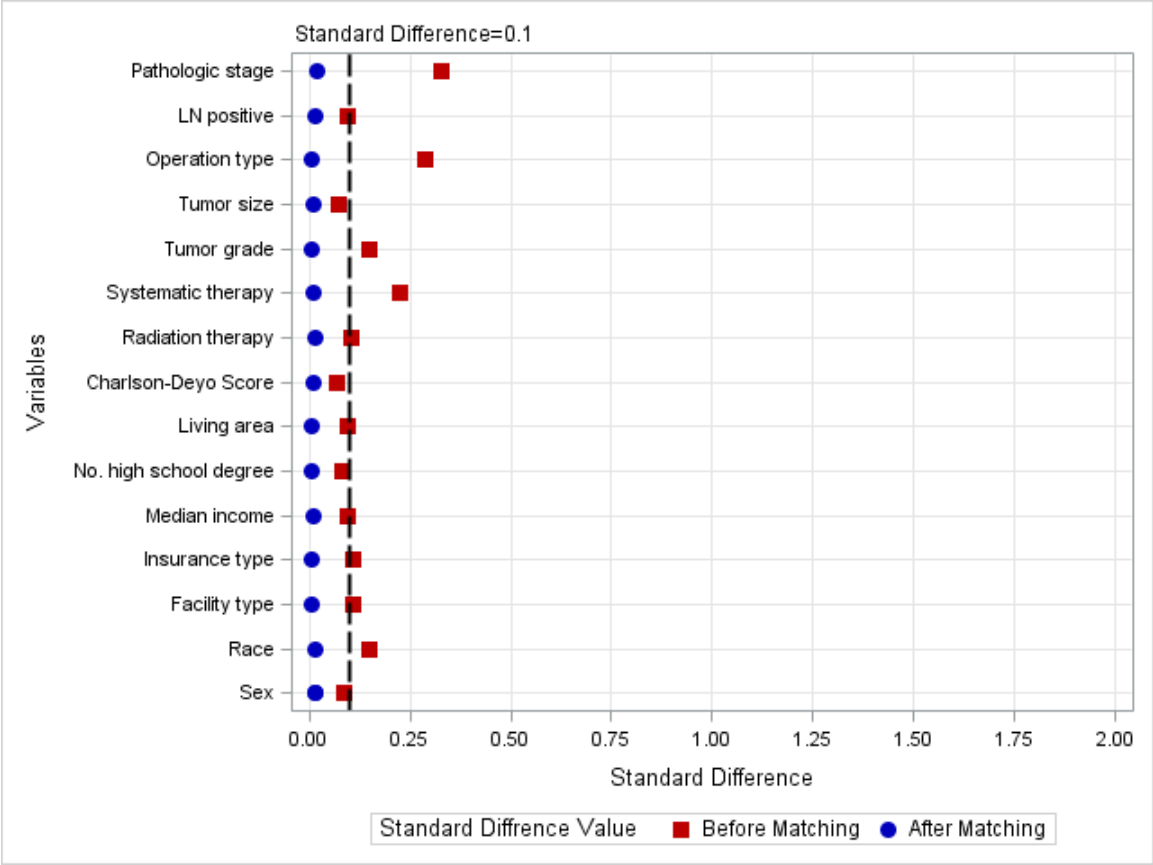
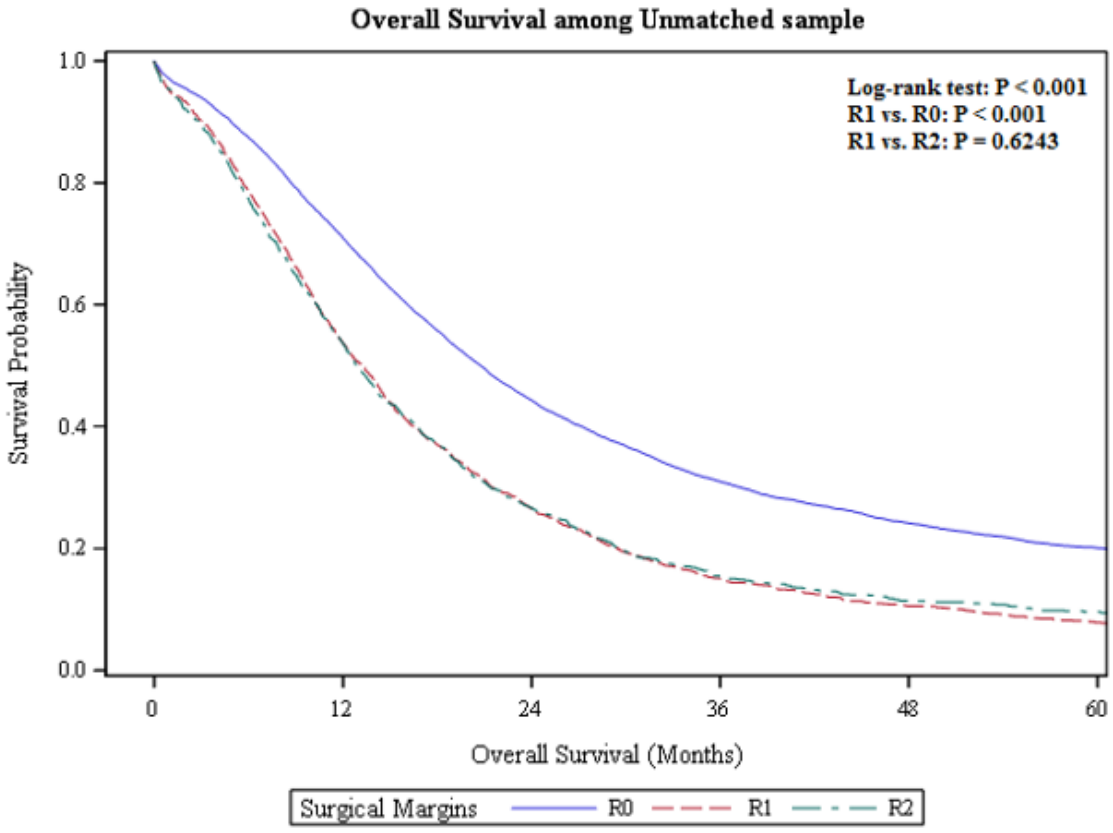
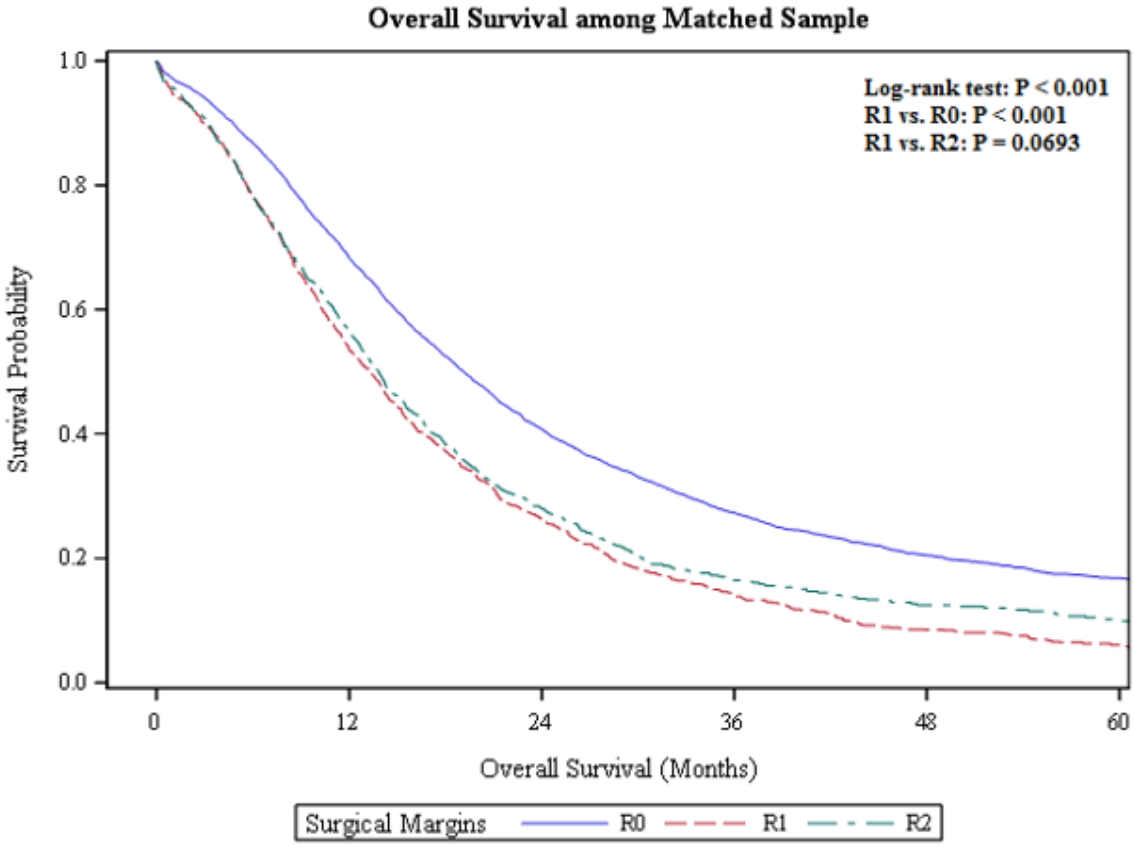


Figure1. Standard Difference among Matched and Unmatched Samples



Surgical Margins	N	Event	Censored	Median Survival (95% CI)
R0	11,596	8,706	2890	20.8 (20.3, 21.2)
R1	1,992	1,756	236	13.2 (12.4, 13.9)
R2	1,531	1,314	217	12.9 (12.2, 13.6)

Figure 2. Overall survival among unmatched sample stratified by margin status (N = 15,119)



Surgical Margins	N	Event	Censored	Median Survival (95% CI)
R0	7,042	5,123	1,919	19.1 (18.5, 19.7)
R1	1,233	1,090	143	13.3 (12.2, 14.1)
R2	891	744	147	13.8 (12.8, 14.7)

Figure 3. Overall survival among matched sample stratified by margin status (N = 9,166)

APPENDICES

Supplemental Table 1. Patient Selection/Exclusion Diagram

Selection and Exclusion Criteria	Sample Size	Excluded
NCDB Pancreatic PUF Cancer Cases 2004 - 2013	309,709	-
Exclude missing and invalid survival outcome	60,512	293,197
Include Primary site in pancreas[1]	60,151	361
Include tumor behavior of invasive	58,554	1,597
Include sequence number as (0, 1)	49,274	9,280
Include patients received treatment at a reporting facility	47,747	1,527
Include ICD-O-3 in 8140[2]	22,604	25,143
Include diagnostic confirmation = histology	21,850	754
Include surgery of primary site in pancreas	17,224	4,626
Exclude missing surgical margin status	16,719	505
Exclude M1 disease	15,179	1,540
Exclude pathology T0 and Tis	15,119	60

[1]Primary site in head of pancreas, body of pancreas, tail of pancreas, pancreatic duct, other specified parts of pancreas, overlapping lesion of pancreas, or pancreas
[2]8140 refer to adenocarcinoma