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Impact of Adjuvant Radiotherapy on Survival after Pancreatic Cancer Resection: An Appraisal of Data from the National Cancer Data Base

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Abstract

Purpose—The impact of adjuvant radiotherapy for pancreatic adenocarcinoma (PAC) remains controversial. We examined effects of adjuvant therapy on overall survival (OS) in PAC, using the National Cancer Data Base (NCDB).

Methods—Patients with resected PAC from 1998 to 2002 were queried from the NCDB. Factors associated with receipt of adjuvant chemotherapy (ChemoOnly) versus adjuvant chemoradiotherapy (ChemoRad) versus no adjuvant treatment (NoAdjuvant) were assessed. Cox proportional hazard modeling was used to examine effect of adjuvant therapy type on OS. Propensity scores (PS) were developed for each treatment arm and used to produce matched samples for analysis to minimize selection bias.

Results—From 1998 to 2002, a total of 11,526 patients underwent resection of PAC. Of these, 1,029 (8.9 %) received ChemoOnly, 5,292 (45.9 %) received ChemoRad, and 5,205 (45.2 %) received NoAdjuvant. On univariate analysis, factors associated with improved OS included: younger age, higher income, higher facility volume, lower tumor stage and grade, negative

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margins and nodes, and absence of adjuvant therapy. On multivariate analysis with matched PS, factors independently associated with improved OS included: younger age, higher income, higher facility volume, later year of diagnosis, smaller tumor size, lower tumor stage, and negative tumor margins and nodes. ChemoRad had the best OS (hazard ratio 0.70, 95 % confidence interval 0.61–0.80) in a PS matched comparison with ChemoOnly (hazard ratio 1.04, 95 % confidence interval 0.93–1.18) and NoAdjuvant (index).

Conclusions—Adjuvant chemotherapy with radiotherapy is associated with improved OS after PAC resection in a large population from the NCDB. On the basis of these analyses, radiotherapy should be a part of adjuvant therapy for PAC.

Pancreatic adenocarcinoma (PAC) remains an aggressive malignancy, with a 5-year disease-specific survival of ~5 %.¹ Surgical therapy offers the best chance of meaningful survival for those patients with tumors amenable to resection, but even then, survival rates improve to only 15–20 %, demonstrating the need for effective multimodal therapy.^{1,2} Adjuvant therapy is now standard practice after resection of PAC on the basis of results of several clinical trials, but the ideal regimen remains controversial, especially with regard to use of adjuvant radiotherapy (ART).

In the United States, adjuvant chemoradiotherapy (ChemoRad) is typically administered after PAC resection on the basis of the results of the 1985 Gastrointestinal Tumor Study Group (GITSG) randomized, prospective, multicenter clinical trial.³ Despite limited accrual of only 43 patients in 11 years, interim analysis demonstrated a significant median survival advantage for the treatment arm over the observation arm (20 vs. 11 months; $p = 0.035$), and this approach became common practice in the United States. In Europe, the European Study Group of Pancreatic Cancer (ESPAC)-1 trial, published in 2001 and updated in 2004, supported the use of adjuvant chemotherapy only (ChemoOnly), while identifying a deleterious effect of ChemoRad on overall survival (OS) after resection of PAC.^{4,5} Patients who received ChemoOnly had improved overall 5-year survival compared with those who did not (21 vs. 8 %, $p = 0.009$), and those who received ChemoRad actually did worse than those who did not (10 vs. 20 %, $p = 0.05$). This led the investigators to conclude that ChemoOnly was beneficial, while ChemoRad was detrimental for patients who underwent resection for PAC, thus establishing the standard in Europe.

The purpose of this analysis was to compare OS rates for a large, representative U.S. cohort of resected PAC patients stratified by adjuvant therapy type and adjusted for patient and provider factors affecting outcomes, using records from the National Cancer Data Base (NCDB). Our main objective was to examine the differential impact of no adjuvant therapy (NoAdjuvant) versus ChemoRad versus ChemoOnly in this NCDB cohort who underwent surgical resection for PAC. To mitigate the impact of any treatment selection biases in this observational study, we used a propensity score (PS) matching method. The PS enables us to balance observed patient characteristics across treatment groups and hence simulate the key feature of successful randomization.⁶ Typically, PS matching methods are applied for two-treatment comparisons. In the current study, we extend this approach to accommodate the comparison for more than two interventions using an innovative matching algorithm.

Methods

Data Source

Our sample was obtained from the NCDB's Participant Use Data File (PUF) for pancreatic neoplasms. The NCDB, the largest disease-specific clinical registry in the United States, is jointly supported and managed by the American College of Surgeons' Commission on Cancer (CoC) and the American Cancer Society. Created in 1988, the NCDB contains detailed clinical, pathological, and demographic data on ~70 % of all U.S. incident cancer cases, as reported on an ongoing basis by the roughly 1,500 CoC-approved cancer programs.⁷

The Pancreatic PUF is a Health Insurance Portability and Accountability Act (HIPAA)-compliant data file containing deidentified patient-level data that thus do not identify hospitals, providers, or patients. These tumor site-specific PUFs are designed to provide CoC-approved cancer programs with a resource to review and advance the quality of care delivered to cancer patients.

Study Population

Our sample consisted of all NCDB incident cases of PAC diagnosed between 1998 and 2002, based on availability of survival data at the time of analysis. We included cases for which a primary tumor site in the pancreas could be identified. From this group, we selected cases with adequate survival data, excluding patients with missing information. We included only patients who underwent surgical resection of the primary PAC and selected patients with information available on ART and adjuvant chemotherapy. We excluded patients who had radiotherapy as their only form of adjuvant therapy, and those who died within 60 days of surgical resection.

Study Variables

Variables selected for impact on OS are listed in Table 1. Footnotes are provided to clarify those variable in need of explanation. The measures for education level, income, and urban/rural status were determined for each patient's area of residence by matching the zip code of the patient at the time of diagnosis to 2000 U.S. Census data.

Statistical Methods

Descriptive Analysis—Categorical variables were summarized as frequencies, and the median and range were reported for each continuous variable. The univariate survival analyses were conducted by associating OS with each variable individually, using both the Kaplan–Meier method (with log rank test *p* values) and a Cox proportional hazard model (yielding hazard ratios [HR], with 95 % confidence intervals [CI]). The association between the adjuvant therapy type (NoAdjuvant, ChemoOnly, and ChemoRad) and each of potential confounder variables was examined by the chi-square test for categorical covariates or ANOVA for continuous covariates.

Multivariable Analyses—Cox proportional hazard modeling was used to estimate the relative impacts of the three adjuvant therapy strategies on 5-year OS. Two Cox modeling

strategies were used to adjust for patient-level differences potentially influencing survival outcomes in this study design. The first model uses traditional multivariable regression modeling (in a nonstratified Cox model) and assumes that systematic differences across patients in the three intervention groups were adequately captured and controlled via inclusion of the potentially confounding covariates shown in Table 2. The second model was built by backward elimination with a p value of <0.05 , balancing between goodness of fit and simplicity. The start-up variable list was created from those factors in Table 2 that were statistically significant in the univariate survival analysis.

To further reduce patient selection bias in our second model, a PS method was used that was based on matching.^{7,8} Under this particular PS approach, each patient is assigned, ex post facto, a predicted probability (i.e., a PS) of having received each of the competing adjuvant therapy strategies (NoAdjuvant, ChemoRad, ChemoOnly) on the basis of a multivariable regression analysis. Each patient receiving a given intervention, e.g., ChemoRad, is matched with a patient who received ChemoOnly and a patient who received NoAdjuvant on the basis of the approximate equality of their PS across all three interventions. Under PS matching, the three patients may be regarded post hoc as having roughly the same probability distribution of having received any of the three therapeutic options (Supplementary materials). After forming the matched sample, the Cox proportional hazard model was performed, stratified by matched groups to estimate treatment effect.

This matching process reduces the effective sample size as unmatched patient data are eliminated from the analysis. For comparison purposes, the multivariable regression findings regarding the impact of these interventions on survival are presented both without and with PS adjustment. All Cox proportional hazard analyses were performed by SAS 9.2, and the PS matching algorithm was implemented by R , with the significance level set at 0.05.

Results

Study Population

The original NCDB pancreatic PUF (1998–2007) contained 208,930 patients diagnosed with PAC. The selected time interval provided 94,385 patients meeting histologic criteria for PAC. Subsequent inclusion criteria were: primary anatomic tumor site in the pancreas could be identified ($n = 69,268$); adequate survival data ($n = 69,240$); surgical resection of the primary PAC ($n = 13,385$); information on ART ($n = 13,385$); and adjuvant chemotherapy ($n = 12,881$). We excluded patients who had received radiotherapy as their only form of adjuvant therapy ($n = 438$), and those who died within 60 days of resection ($n = 917$), leaving a final sample of 11,526 patients.

Patient and Disease Variables

Patient-related and disease-specific variables are summarized in Table 1, which also summarizes information on adjuvant therapy grouping (NoAdjuvant 45.2, ChemoOnly 8.9, and ChemoRad 45.9 %).

Univariate Analysis for Receipt of Adjuvant Treatment and OS

The univariate results for associations between patient and disease variables and type of adjuvant treatment received are provided in Table 1. Factors associated with receiving adjuvant therapy included younger patient age, male gender, having either private insurance or Medicaid, and having positive surgical margins and positive lymph nodes.

Univariate OS results by patient and disease variable are shown in Table 2. Factors associated with better OS included younger age, being female, having private insurance or Medicaid, having a higher median income, having negative surgical margins, and having negative lymph nodes. Although the proportionate distribution of patients across treatment types did not change significantly over time (Table 1), OS improved progressively (Table 2), with patients treated in 1998 experiencing the worst OS (HR 1.11, $p = 0.003$), compared with patients treated in 2002 (the final diagnosis year of our study population). Patients who received ChemoRad had better OS than the ChemoOnly patients, but worse survival than those receiving NoAdjuvant therapy (HR 1.17, $p < 0.001$).

Multivariable Analysis for Factors Associated with OS

Table 3 shows the Cox model analysis for OS without PS adjustment. Although no patient level variable had more than 12 % of observations missing and most had fewer than 5 % missing, the resulting available sample for analysis was 7,288. The impact of individual factors on survival is summarized by HR and 95 % CI. In this non-PS-adjusted analysis, use of ChemoRad was associated with a survival advantage compared with NoAdjuvant (HR 0.79, $p < 0.001$). By contrast, patients receiving ChemoOnly experienced the similar OS as NoAdjuvant patients (HR 1.08, $p = 0.108$).

In the Cox model stratified by propensity-score matched groups ($N = 1,650$), the resulting multivariable estimates were similar to those for the non-PS-adjusted Cox model shown in Table 3, but the survival benefit for ChemoRad patients was greater when compared with that of NoAdjuvant patients (HR 0.70, $p < 0.001$). Figure 1 illustrates the change of Kaplan–Meier curves before and after selection bias has been removed. There was still no significant survival difference between ChemoOnly and NoAdjuvant (HR 1.04, $p = 0.77$). Further discussion of these PS matched-sample analyses is provided in the Supplementary materials.

Discussion

The purpose of this study was to assess the value of adjuvant therapy on OS in a large cohort of patients with PAC who underwent surgical resection. The sample consisted of all incident cases of PAC over the 1998–2002 period reported to the NCDB meeting study inclusion criteria. In multivariable survival analyses that also attempted to adjust for possible treatment selection bias through PS matching methods, we demonstrated that patients who received ChemoRad experienced better OS compared with those who had ChemoOnly or NoAdjuvant; ChemoOnly OS was similar to NoAdjuvant. Novel aspects of this study include the use of the NCDB to address this question of adjuvant therapy used in resected PAC, and the novel PS matching method, which allowed us to assess three treatment arms simultaneously.

Adjuvant therapy for resected pancreatic cancer provides patients with a survival benefit based on results of several randomized trials.^{3,8,9} The GITSG study, while small and flawed, set the standard for adjuvant therapy practices for PAC in the United States.³ The European ESPAC-1 demonstrated a survival advantage associated with adjuvant ChemoOnly and reduced survival attributable to ChemoRad.⁵ Review of other randomized trials for adjuvant therapy of resected PAC does not provide any further clarification on the role of ChemoRad versus ChemoOnly. The 2007 Charite Onkologie (CONKO-001) trial compared adjuvant gemcitabine with observation.⁸ The European Organization for Research and Treatment of Cancer (EORTC) 40891 trial did not support the benefit of ChemoRad over observation.¹⁰ The Radiation Therapy Oncology Group (RTOG) 9704 trial demonstrated no difference in OS between gemcitabine chemotherapy over 5-fluorouracil (5-FU) when combined with ART.¹¹ The most recent ESPAC-3 trial dropped the ChemoRad arm and also demonstrated no difference between 5-FU and gemcitabine ChemoOnly approaches.⁹ In summary, no existing randomized trial can definitively answer the question of the optimal adjuvant therapy approach for resected PAC.

Although at risk for selection bias, retrospective data can provide useful perspectives on questions such as this. Retrospective data may include larger samples than randomized clinical trials, and indeed it is unlikely that further, large-scale randomized trials will be launched anytime soon to study the issues addressed here. Hence, large cohort studies of the type undertaken here likely represent the best practical approach going forward to enrich the evidence base on treatment effectiveness.

Capitalizing on the NCDB PAC data set, we carried out a PS matching procedure to minimize potential bias in the sorting of patients across three treatment groups. An innovative three-way matching of these PS was performed, lowering the number of evaluable patients but improving within-group homogeneity. The sample that emerged with PS matching was still significantly larger than any previous randomized trials examining adjuvant therapy for PAC. Our matched PS multivariable results reveal an OS advantage for those patients who received ChemoRad compared with other adjuvant therapies.

Other large retrospective studies have looked at the question of ChemoRad for PAC. Several studies have assessed data from the Surveillance, Epidemiology and End Results (SEER) registry, which includes information on incident cancer cases representing about 26 % of the U.S. population.^{12–15} These studies have identified a benefit of ART when combined with adjuvant chemotherapy for PAC. A substantial limitation of these analyses is that SEER does not include specific patient-level information on the use of adjuvant chemotherapy or detail on radiation dosing. The only available option for obtaining chemotherapy-specific data on SEER patients is through analysis of the linked SEER–Medicare data base, but the latter includes only individuals who were age 65 or over and enrolled in Medicare fee for service at the time of cancer diagnosis. Although SEER data are high quality and population based, the NCDB data are also highly representative of U.S. cancer patients and include about 70 % of all incident cases nationwide.

Among analyses of the impact of adjuvant therapy on pancreatic cancer survival, only two reports (those of McDade et al. and Hsu et al.) used PS adjustments.^{15,16} McDade et al.

examined 5,676 patients from SEER between 1988 and 2005 and found an OS benefit for patients receiving ART compared with those who did not (HR 0.773; 95 % CI 0.714–0.836, $p < 0.05$)—a result notably consistent with those reported here.¹⁵ However, McDade et al. were not able to report on the impact of adjuvant chemotherapy. In contrast, we were able to assess three treatment groups (NoAdjuvant, ChemoOnly, and ChemoRad) and demonstrated superior results for ChemoRad, providing stronger support for a radiation-inclusive adjuvant strategy. The findings in our paper support those of McDade et al. and those demonstrated by GITSG, demonstrating the benefit of ChemoRad in the adjuvant therapy of PAC.

Hsu et al.¹⁶ performed Cox survival and PS analyses assessed associations with OS for 1,272 patients combined from 2 centers, using PS analysis and matched-pair analysis by treatment group (1:1) on the basis of institution, age, sex, tumor size/stage, differentiation, margin, and node positivity. They found that patients who received chemoradiotherapy had significantly better median survival than that of patients who did not receive adjuvant therapy. Again, chemotherapy alone was assessed.

The strengths of the current study include its data source (NCDB), large sample, use of propensity adjustment, and the further matching of the PS to achieve more homogeneous comparison groups. Limitations of our work include the retrospective nature of our data and the selection of data from an earlier time period (1998 to 2002), as these included the cases for which survival data were available. We did not have comorbidity data available because this information was added to NCDB only in more recent years. We cannot comment on the exact nature of the chemotherapy or on comorbid conditions of the patients examined; thus, as with any population study analysis, selection bias may play a substantial role in our defining our findings. Importantly, only 8.9 % of the patients received ChemoOnly. The time period was a transitional period for the use of the three treatment arms assessed. Perhaps the ChemoOnly patients had more comorbid conditions precluding them from receiving concomitant radiotherapy and worsening their survival. It is also important to note that both 5-FU and gemcitabine were used during this time period in the adjuvant setting for PAC, but NCDB data do not provide detail on specific agents. However, the ESPAC-3 trial demonstrated that there was no difference in survival between groups receiving ChemoOnly with 5-FU versus gemcitabine.

This study is the first to demonstrate, using a large national database, an OS advantage for resected PAC patients who received adjuvant therapy consisting of both chemotherapy and radiotherapy over those who received no adjuvant therapy or adjuvant chemotherapy alone. It is also the first to use matched PS to examine the value of these specific approaches, and the first (in the pancreatic cancer domain) to make this assessment between three treatment groups as opposed to two groups (adjuvant therapy vs. no adjuvant therapy). Given the shifting paradigm toward increasing preoperative therapy strategies, this question of optimal adjuvant treatment continues to evolve, especially with new response data to FOFIRINOX, a more aggressive chemotherapy regimen.^{17–21} In light of the conflicting conclusions from existing randomized trials, our findings support the use of combination radiotherapy and chemotherapy as adjuvant therapy for patients who undergo surgical resection of pancreatic ductal adenocarcinoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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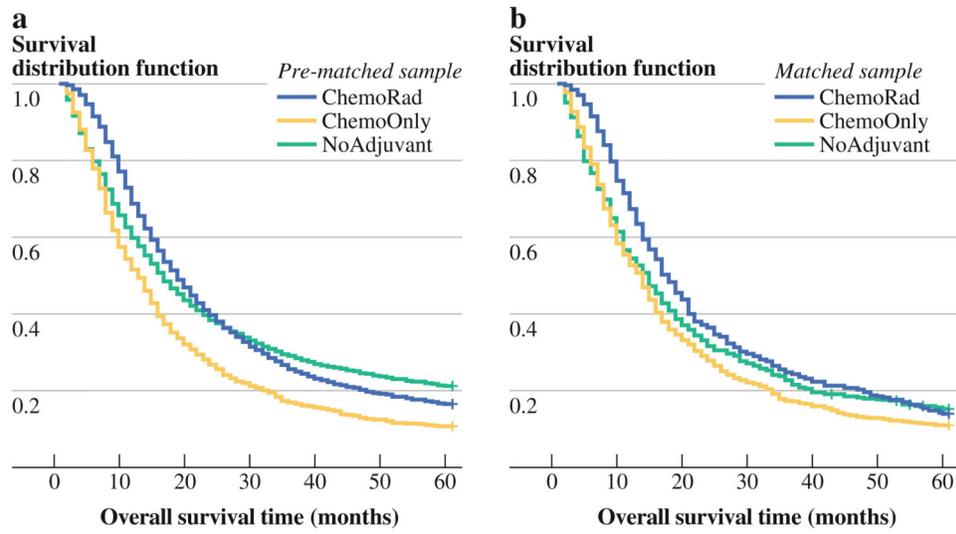


Fig. 1. Kaplan–Meier survival curves for the three therapy groups (*heavy line* NoAdjuvant, *light line* ChemoOnly, *hatched line* ChemoRad) for both the prematched sample ($n = 7,288$, *left*) and one of matched samples ($n = 1,650$, *right*). Note the overlap between the NoAdjuvant and ChemoRad groups before propensity score matching, which disappears after matching

Table 1
Univariate analysis of factors according to type of adjuvant therapy received in patients with pancreatic adenocarcinoma from the National Cancer Data Base, 1998–2002 (N = 11,526)

Covariate	Adjuvant therapy N (Row %)				P*	
	Level	Total	NoAdjuvant	ChemoOnly		ChemoRad
Age at diagnosis	50 years	2,690	1,075 (39.96)	254 (9.44)	1,361 (50.59)	<0.001
	50–65 years	3,039	1,142 (37.58)	289 (9.51)	1,608 (52.91)	
	65–75 years	3,911	1,776 (45.41)	367 (9.38)	1,768 (45.21)	
Gender	>75 years	1,886	1,212 (64.26)	119 (6.31)	555 (29.43)	<0.001
	Male	5,854	2,517 (43)	527 (9)	2,810 (48)	
White race	Female	5,670	2,686 (47.37)	502 (8.85)	2,482 (43.77)	0.209
	No	1,398	658 (47.07)	129 (9.23)	611 (43.71)	
Median income, 2000 ^a	Yes	10,128	4,547 (44.9)	900 (8.89)	4,681 (46.22)	<0.001
	<\$30,000	1,372	666 (48.54)	139 (10.13)	567 (41.33)	
Insurance type	\$30,000–\$34,999	1,892	913 (48.26)	179 (9.46)	800 (42.28)	<0.001
	\$35,000–\$45,999	3,117	1,406 (45.11)	273 (8.76)	1,438 (46.13)	
	>\$46,000	4,575	1,983 (43.34)	385 (8.42)	2,207 (48.24)	
Facility type ^b	Uninsured	294	151 (51.36)	25 (8.5)	118 (40.14)	<0.001
	Medicaid	424	172 (40.57)	44 (10.38)	208 (49.06)	
	Private/other	8,619	3,763 (43.66)	769 (8.92)	4,087 (47.42)	
Facility volume ^c	Medicare	1,619	850 (52.5)	145 (8.96)	624 (38.54)	<0.001
	CCP	1,049	411 (39.18)	128 (12.2)	510 (48.62)	
	CCCP	4,288	1,673 (39.02)	406 (9.47)	2,209 (51.52)	
Year of diagnosis	ARCP	6,189	3,121 (50.43)	495 (8)	2,573 (41.57)	<0.001
	n	11,526	5,205	1,029	5,292	
Year of diagnosis	Mean	45.24	52.11	38.68	39.76	0.117
	Median	18.5	21	15	17	
Year of diagnosis	1998	1,991	929 (46.66)	180 (9.04)	882 (44.3)	0.117
	1999	2,086	928 (44.49)	178 (8.53)	980 (46.98)	
	2000	2,255	1,009 (44.75)	178 (7.89)	1,068 (47.36)	
	2001	2,463	1,119 (45.43)	214 (8.69)	1,130 (45.88)	

Adjuvant therapy N (Row %)						<i>P</i> *
Covariate	Level	Total	NoAdjuvant	ChemoOnly	ChemoRad	
Primary site	2002	2731	1,220 (44.67)	279 (10.22)	1,232 (45.11)	
	Head	9224	3,918 (42.48)	769 (8.34)	4,537 (49.19)	<0.001
	Body	649	307 (47.3)	70 (10.79)	272 (41.91)	
	Tail	1,389	828 (59.61)	176 (12.67)	385 (27.72)	
Tumor size	Body/tail	264	152 (57.58)	14 (5.3)	98 (37.12)	
	25 mm	3,616	1,667 (46.1)	242 (6.69)	1,707 (47.21)	<0.001
	25–35 mm	2,730	1,114 (40.81)	232 (8.5)	1,384 (50.7)	
	35–45 mm	1,783	750 (42.06)	168 (9.42)	865 (48.51)	
Stage ^d	>45 mm	2,061	1,052 (51.04)	224 (10.87)	785 (38.09)	
	I	2,274	1,431 (62.93)	97 (4.27)	746 (32.81)	<0.001
	II	2,046	938 (45.85)	145 (7.09)	963 (47.07)	
	III	5,044	1,724 (34.18)	444 (8.8)	2,876 (57.02)	
Grade	IV	1,493	586 (39.25)	285 (19.09)	622 (41.66)	
	Unspecified	1,739	1,074 (61.76)	128 (7.36)	537 (30.88)	<0.001
	I	1,374	750 (54.59)	92 (6.7)	532 (38.72)	
	II	4,809	1,900 (39.51)	431 (8.96)	2,478 (51.53)	
Surgical margin positive	III/IV	3,604	1,481 (41.09)	378 (10.49)	1,745 (48.42)	
	No	7,861	3,781 (48.1)	606 (7.71)	3,474 (44.19)	<0.001
LN positive	Yes	2,631	943 (35.84)	286 (10.87)	1,402 (53.29)	
	No	4,494	2,459 (54.72)	305 (6.79)	1,730 (38.5)	<0.001
	Yes	5,931	2,165 (36.5)	603 (10.17)	3,163 (53.33)	
	No	7,615	3,657 (48.02)	701 (9.21)	3,257 (42.77)	<0.001
No. of examined LNs > 12	Yes	3,050	1,191 (39.05)	239 (7.84)	1,620 (53.11)	

Data are presented as n (%) unless otherwise indicated
NoAdjuvant no adjuvant chemotherapy, *ChemoOnly* chemotherapy only, *ChemoRad* adjuvant chemoradiotherapy, *LN* lymph node, *CoC* Commission on Cancer
 Bold values (*p* < 0.05) are statistically significant

*The parametric *p* value is calculated by ANOVA for numerical covariates and Chi-square test for categorical covariates

^aThe measures for urban/rural status, income, and education level were determined for each patient's area of residence by matching the zip code of the patient at the time of diagnosis to 2000 U.S. Census data

^bCCCPCommunity Cancer Program, CCCPComprehensive Community Cancer Programs, ARCPAcademic/Research Cancer Program, all as defined by the CoC

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Defined as total number of pancreatic adenocarcinoma analytical cases in a given facility (regardless of facility type) over the 1998–2002 observation period within a given CoC-designated facility type (e.g., CCP), a cancer program was high volume if its number of analytical cases over the 1998–2002 period was at or above the median for all programs nationwide; similarly, a cancer program was considered low volume if its case load was below the median of all programs within that facility type

^pStage reflects the AJCC 5th ed.

Table 2

Univariate analysis of factors influencing overall survival in resected patients with pancreatic adenocarcinoma from the National Cancer Data Base, 1998 to 2002 (N = 11,526)

Covariate	Level	HR	95 % CI Low	95 % CI High	HR p value
Adjuvant therapy	ChemoRad	1.170	1.120	1.224	<0.001
	ChemoOnly	1.592	1.479	1.714	<0.001
	NoAdjuvant	-	-	-	-
Age at diagnosis	50 years	0.606	0.566	0.648	<0.001
	50-65 years	0.780	0.732	0.832	<0.001
	65-75 years	0.856	0.806	0.910	<0.001
	>75 years	-	-	-	-
Gender	Male	1.049	1.006	1.094	0.025
	Female	-	-	-	-
White race	No	0.963	0.902	1.028	0.259
	Yes	-	-	-	-
Median income, 2000	<\$30,000	1.166	1.089	1.248	<0.001
	\$30,000-\$34,999	1.121	1.054	1.191	<0.001
	\$35,000-\$45,999	1.067	1.013	1.124	0.015
	>\$46,000	-	-	-	-
	Uninsured	0.900	0.782	1.037	0.146
Insurance type	Medicaid	0.768	0.678	0.869	<0.001
	Private/other	0.821	0.774	0.871	<0.001
	Medicare	-	-	-	-
Facility type	CCP	1.231	1.144	1.325	<0.001
	CCCP	1.171	1.120	1.224	<0.001
	ARCP	-	-	-	-
Facility volume (unit = 50)		0.943	0.927	0.959	<0.001
	Year of diagnosis				
	1998	1.106	1.036	1.182	0.003
	1999	1.071	1.003	1.143	0.041
	2000	1.038	0.974	1.107	0.252
	2001	1.016	0.954	1.081	0.626

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Covariate	Level	HR	95 % CILow	95 % CIHigh	HR p value
	2002	-	-	-	-
Primary site	Head	1.297	1.122	1.499	<0.001
	Body	1.120	0.946	1.326	0.189
	Tail	0.844	0.720	0.988	0.035
	Body/tail	-	-	-	-
Tumor size	25 mm	0.913	0.857	0.973	0.005
	25-35 mm	1.143	1.070	1.221	<0.001
	35-45 mm	1.228	1.142	1.321	<0.001
	>45 mm	-	-	-	-
Stage	I	0.365	0.338	0.394	<0.001
	II	0.606	0.563	0.652	<0.001
	III	0.822	0.773	0.874	<0.001
	IV	-	-	-	-
Grade	Unspecified	0.365	0.339	0.393	<0.001
	I	0.410	0.380	0.443	<0.001
	II	0.764	0.729	0.801	<0.001
	III/IV	-	-	-	-
Surgical margin positive	No	0.654	0.623	0.687	<0.001
	Yes	-	-	-	-
LN positive	No	0.579	0.553	0.606	<0.001
	Yes	-	-	-	-
No. of examined LNs > 12	No	0.958	0.913	1.005	0.076
	Yes	-	-	-	-

Table 3
Multivariable proportional hazard model without propensity score adjustment (N = 7,288)

Covariate	Level	HR	95 % CI Low	95 % CI High	HR, p value
Age at diagnosis	50 y	0.689	0.632	0.751	<0.001
	50–65 y	0.791	0.731	0.857	<0.001
	65–75 y	0.886	0.821	0.955	0.002
	>75 y	–	–	–	–
Median income, 2000	<\$30,000	1.170	1.077	1.272	<0.001
	\$30,000–\$34,999	1.089	1.010	1.174	0.027
	\$35,000–\$45,999	1.025	0.963	1.092	0.441
	>\$46,000	–	–	–	–
Year of diagnosis	1998	1.078	0.993	1.171	0.073
	1999	1.026	0.947	1.112	0.524
	2000	1.020	0.942	1.104	0.628
	2001	0.935	0.867	1.009	0.085
	2002	–	–	–	–
Facility volume (unit = 50)		0.962	0.941	0.983	<0.001
Facility type ^a	CCP	1.104	1.002	1.217	0.047
	CCCP	1.064	1.002	1.131	0.044
	ARCP	–	–	–	–
Primary site	Head	1.160	0.958	1.405	0.128
	Body	1.172	0.938	1.465	0.162
	Tail	0.930	0.751	1.151	0.505
	Body/tail	–	–	–	–
Tumor size	25 mm	0.733	0.677	0.794	<0.001
	25–35 mm	0.884	0.815	0.959	0.003
	35–45 mm	0.942	0.863	1.029	0.187
	>45 mm	–	–	–	–
Stage	I	0.592	0.520	0.674	<0.001
	II	0.809	0.715	0.916	<0.001
	III	0.806	0.732	0.886	<0.001

Covariate	Level	HR	95 % CI Low	95 % CI High	HR p value
Grade	IV	-	-	-	-
	Unspecified	0.441	0.395	0.492	<0.001
	I	0.455	0.413	0.501	<0.001
	II	0.768	0.725	0.813	<0.001
	III/IV	-	-	-	-
Surgical margin positive	No	0.709	0.668	0.753	<0.001
	Yes	-	-	-	-
LN positive	No	0.724	0.641	0.818	<0.001
	Yes	-	-	-	-
	No	1.109	1.046	1.175	<0.001
Adjuvant therapy	Yes	-	-	-	-
	ChemoRad	0.784	0.739	0.831	<0.001
	ChemoOnly	1.076	0.977	1.186	0.139
	No adjuvant therapy	-	-	-	-

The model was built by backward elimination with a staying p value of <0.05. The starting list contains all variables that demonstrated significance at the 0.05 level in <T2>Table 2 HR hazard ratio, CI confidence interval, LN lymph node, ChemoOnly chemotherapy only, ChemoRad adjuvant chemoradiotherapy

^aCCCPCommunity Cancer Program, CCCPComprehensive Community Cancer Programs, ARCPAcademic/Research Cancer Program, all as defined by the Commission on Cancer