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Chemoradiation Therapy Sequencing for Resected Pancreatic Adenocarcinoma in the National Cancer Data Base

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Abstract

Background—Pancreatic adenocarcinoma (PAC) has low overall survival (OS) rates and high recurrence rates following surgical resection. The role for preoperative radiation therapy (prRT) for PAC versus postoperative RT (poRT) remains uncertain. The authors used the National Cancer Data Base (NCDB) to report prRT outcomes for the largest multi-institutional patient cohort to date.

Methods—NCDB data were obtained for all patients who underwent resection and external beam radiation (RT) for PAC from 1998–2002. Patients with metastatic (M1) disease, intraoperative RT, RT both before and after surgery, missing OS or missing RT variables were excluded. Univariate (UV) and Multivariate (MV) analysis were run using treatment characteristics, tumor characteristics and patient demographics. The difference in patients' known characteristics was described by a Chi-square test or ANOVA.

Results—5414 patients were identified. 277 received prRT and 5137 received poRT. Overall, 92.9% received chemotherapy and 7.1% received RT alone. 56% (2990/5307) of patients were AJCC 5th ed. stage III. Median tumor size was 3 cm (range: 0–9.9). 82% (199/244) of prRT patients had negative surgical margins; 72% (3383/4699) of poRT patients had negative margins. 41% (71/173) of prRT were lymph node (LN) positive; 65% (3159/4833) of poRT were LN positive. Median OS for prRT patients was 18 months (95% CI 18–19) and for poRT patients, 19 months (95% CI 17–22).

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Conclusions—PrRT was associated with lower stage, higher rates of negative margins and lower rates of lymph node positivity at resection. However, there was no significant difference in median OS versus the poRT group.

Introduction

Pancreatic Adenocarcinoma (PAC) remains a cancer with a dismal prognosis despite significant advances in surgical technique, radiation delivery and chemotherapy. Five-year overall survival (OS) rates for newly diagnosed pancreatic cancer patients have improved little over the past decade and remain at less than 5%¹. The only hope for cure is successful surgical resection, yet only approximately 15-20% of patients are considered resectable at presentation². Of those successfully resected, local or distant recurrence occurs in up to 80% of patients despite adjuvant therapy.

In these initially resectable patients, multimodality therapy generally consists of resection followed by 5-Fluorouracil (5-FU) or Gemcitabine (Gem) with or without radiotherapy (RT). This regimen has improved median and 5-year overall survival (OS) compared with surgery alone,³ but adjuvant therapy is not completed in approximately 25% of patients^{4,5}. In an attempt to encourage completion of all phases of multimodality therapy, a few small retrospective and non-randomized prospective studies have been undertaken to evaluate the use of initial chemoradiation at diagnosis, but very little has been published in this area⁵⁻¹⁰.

Due to this lack of data, initial chemoradiotherapy (CRT) is only used in specific circumstances: up-front CRT is used in some patients with borderline resectable disease¹¹ and as palliative treatment in patients not deemed surgical candidates. Over the last thirty years, the possible role of preoperative systemic therapy in resectable patients has been a subject of debate, as this treatment sequence has demonstrated improved morbidity and/or mortality in esophageal and rectal cancers¹²⁻¹⁴. Given this potential benefit of completed therapy and improved survival outcomes, a role exists for a randomized study to evaluate the role of neoadjuvant therapy in PAC; the aim of this study was to use the large National Cancer Data Base (NCDB), which contains detailed patient-linked data on approximately 70% of newly-diagnosed cancer cases in the U.S., to provide a rationale for this trial in the future.

Materials and Methods

National Cancer Data Base

The National Cancer Data Base (NCDB) contains approximately 70% of newly-diagnosed cancer cases in the U.S. and at 26 million patient records; it is 2.5 times larger than the widely utilized Surveillance, Epidemiology and End Results (SEER) database. It provides patient-linked treatment information that is unavailable in the SEER database outside of SEER-Medicare linked data. The NCDB is maintained 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 available is extensive and includes extensive patient demographics (including insurance status, county of residence, ethnicity, age and others) tumor characteristics, pathologic characteristics, survival data,

treatment center type, and detailed treatment information (including sequencing, types of treatments, treatment intent, dose and other important factors), although some variables remain optional for data entry. Overall survival is calculated as the number of months between the date of diagnosis and the date on which the patient was last contacted or died.

Participant Use Files (PUF) are de-identified data sets distributed to individual CoC-approved cancer programs for analysis. Emory University was awarded alpha-test user site status with access to the Pancreatic PUF containing incident cases for the 5-year period 1998-2002. Although this time period was chosen because adequate five-year survival data was available, using this time period also eliminated some variability in types of chemotherapy and radiation delivery as this was well before extensive stereotactic body radiotherapy (SBRT) and FOLFIRINOX use. The use and publication of these data are subject to review by the NCDB.

Patient Selection

From 94,385 patients in the NCDB pancreatic cancer PUF from 1998-2002, we selected only patients with survival data available (n=94,344) and a primary tumor site in the exocrine pancreas (n=69,240). Further, we selected only patients who underwent surgery on the primary site (n=13,571). In order to select the most homogeneous group of patients who received CRT, we included only patients who underwent External Beam Radiation Treatment (n=5639). AJCC 5th edition Stage IV includes patients with T4 N0 M0 tumors in addition to node positive and metastatic patients, so only clinical M0 patients were included and pathological M1 patients were excluded (n=5513). We then selected patients who had received CRT either before or after surgery, but not both. This left a total of 5414 analyzable patients.

Statistical Analysis

Statistical analysis was conducted using SAS Version 9.3. Descriptive statistics were reported for the overall patient population and for the preoperative (prRT) and postoperative (poRT) groups. Differences between the groups were assessed using the Chi-square test for categorical covariates or ANOVA for continuous covariates. Kaplan-Meier survival analysis was used to generate overall survival curves and estimate median survival with 95% confidence intervals for each group.

Univariate survival analysis was performed for therapy sequence (prRT vs. poRT) and the following covariates: chemotherapy use, days elapsed from diagnosis to start of treatment, surgical margin status, lymph node (LN) positivity, number of LN's examined, tumor size (mm), stage, grade, patient age at diagnosis, race, sex, facility type and facility volume. Facility volume was calculated as the total number of resected pancreatic cases in a given facility during the year 1998-2002, and facility types were designated as Community Cancer Programs (CCP), Comprehensive Community Cancer Programs (CCCCP) or NCI-designated Cancer Centers/Academic Comprehensive Care Program (NCI/ARCP). Staging was primarily the AJCC 5th edition guidelines, which explains why some stage III and stage IV patients were included, as they were M0 and resected. Although the majority of these

patients received chemo, it was included as a covariate due to its potentially strong clinical impact.

Covariates that had a significant unadjusted association with overall survival or therapy sequence in the univariate analysis were included in the multivariable survival model. The covariates chosen for multivariate analysis were chemotherapy use, days elapsed from diagnosis to date of first treatment, surgical margin, LN status, tumor size, grade, number of LN examined, age, facility type and facility volume. Stage was excluded to prevent collinearity since it was based on both LN status and tumor size, which were also included in the model. A separate model was run including stage to confirm that there was no contribution of stage aside from LN status and tumor size, with no change in results. The multivariate survival analysis was run using a Cox proportional hazards model and entering the covariates using a backward variable selection method with an $\alpha=.05$ removal criteria. Therapy sequence was forced in the model.

Two multivariate logistic regression models were also fit for margin negativity and LN positivity including therapy sequence, chemotherapy use, days elapsed from diagnosis to date of first treatment, number of LN's examined, tumor size (mm), grade, patient age, facility type, and facility volume. Again, backwards selection was used with an $\alpha=.05$ removal criteria.

Results

Patient Demographics and Treatment Characteristics

After applying the above criteria, 5414 analyzable patients remained. 5.1% (277) received prRT and 94.9% (5137) received poRT. Median age was 64 (range 20-88), 53.1% were male and 89.4% were Caucasian. All patients underwent surgical resection and prRT or poRT +/- chemotherapy; 92.9% received concurrent chemo-RT and 7.1% received RT alone. All patients were pathologic and clinical M0, but overall stage was not reported for 2.0% of patients. 793 patients were AJCC 5th edition stage I, 1002 stage II, 2990 were stage III, and 522 were stage IVa. 64.5% were LN positive. Median tumor size was 3 cm (range: 0-9.9), and 72.5% overall had negative surgical margins. Full results can be seen in Table 1.

Covariate Association with Radiation/ Surgery Sequence

The association of individual covariates with therapy sequence can be seen in Table 2. Preoperative RT was significantly associated with higher rates of chemotherapy use, lower stage, and treatment at an Academic/ Research (ARCP) facility. Preoperative RT was also significantly associated with higher rates of negative margins and negative LN status.

Lymph Node and Margin Status

At resection, 82% (199/244) of prRT patients had negative surgical margins while 72% (3383/4699) of poRT patients had negative margins. 41% (71/173) of prRT were LN positive at resection while 65% (3159/4833) of poRT patients were LN positive.

On multivariate logistic regression to predict LN status (Table 3a), there was significantly lower odds of LN positivity at resection in the prRT group (OR 0.45 [95% CI 0.31-0.65]; $p<.$

001) and in those with smaller tumors (OR 0.73 [95% CI 0.60-0.88]; $p=.001$) and with lower grade tumors (OR 0.74 [95% CI 0.59-0.92]; $p=.007$).

On multivariate logistic regression for negative margin status (Table 3b), there was a significantly higher odds of negative margins in the prRT group (OR 1.71 [95% CI 1.17-2.52]; $p=.006$) in addition to those with smaller tumors (OR 1.95 [95% CI 1.59-2.41]; $p<.001$). There was a lower odds of negative margins in those not receiving chemotherapy (OR 0.71 [95% CI 0.55-0.91]; $p=.007$).

Survival Analysis

In Kaplan-Meier survival analysis (Figure 1), there was no significant difference between overall survival in the two groups; median OS was 18 months (95% CI 18-19) for prRT and 19 months (95% CI 17-22) for poRT.

In multivariate Cox regression analysis (Table 4), radiation therapy sequencing was still not a statistically significant predictor of survival ($p=.077$). Predictors of poor OS included receiving no chemotherapy (HR 1.16 [95% CI 1.02-1.34]; $p=.03$) and older age (HR 1.04 [95% CI 1.03-1.06]; $p<.001$). Increased OS was associated with negative margins (HR 0.75 [95% CI 0.70-0.82]; $p<.001$), negative LN status (HR 0.67 [95% CI 0.62-0.72]; $p<.001$), smaller tumor size (HR 0.67 [95% CI 0.60-0.75]; $p<.001$), lower grade tumors (HR 0.55 [95% CI 0.49-0.63]; $p<.001$), greater number of LN's examined at resection (HR 0.96 [95% CI 0.94-0.98]; $p<.001$) and higher facility volume (HR 0.99 [95% CI 0.99-1.00]; $p=.009$). The complete results of the MV analysis can be found in Table 3b.

Discussion

Although the use of prRT has been associated with an improvement in morbidity and/or mortality in other neoplasms, including rectal and esophageal cancer, its use in PAC remains controversial. In an attempt to improve OS in PAC, a few small, single-institutional prospective and retrospective studies have examined the use of preoperative chemoradiation followed by resection in borderline resectable PAC. Some of these studies evaluating neoadjuvant therapy in selected patients have had promising results in improving resectability, with resection rates as high as 89% following re-staging after chemoradiation and R0 resections as high as 47% in these cases^{5,15}. Additionally, tri-modality therapy (surgical resection, chemotherapy and RT) has been associated with decreased locoregional recurrence in PAC¹⁶⁻¹⁸, where even with R0 resections nearly 80% of patients were found to have evidence of microscopic cells left in situ at the surgical site¹⁹. Generally, resectable patients undergo surgery and then adjuvant chemoradiation in the United States. However, as many as 25% of patients undergoing resection do not complete postoperative therapy, either due to operative morbidity or disease progression. Given this large percentage, the use of prRT in selected patients may increase the opportunities to complete all three phases of tri-modality therapy. The purpose of this study was to analyze and report data from the largest published group of patients receiving prRT for PAC to date and thus provide a rationale for further studies of prRT in PAC.

We found no statistically significant benefit or detriment in OS for the 277 patients receiving prRT, even when other tumor and patient characteristics were controlled for. It is important to note that there is no intent-to-treat analysis, and it is likely that many of the patients with progressive disease on neoadjuvant therapy were not included in this survival analysis. Regardless, there was a significant association between prRT and a higher rate of negative margins and negative LN status, both on univariate analysis and in our multivariate logistic regression model predicting for margin and LN status. It is also likely that many of these patients receiving preoperative therapy were at high volume academic centers, which has been shown to have an influence on treatment for pancreatic cancer²⁰. It is possible that this may impact the rate of negative margins and negative lymph nodes. It should also be considered that this conclusion is hindered by the inability to perform an intention to treat analysis on these patients, and those with preoperative therapy may have had additional time to allow patient selection for resectability.

Previous studies have examined the role of prRT in borderline resectable patients, and have found a clear advantage to prRT both in increasing resectability and in OS in these patients. One large study of 132 potentially resectable patients who received preoperative chemoradiation followed by pancreaticoduodenectomy demonstrated successful R0 resections in nearly 90% of patients and all resected patients completing tri-modality therapy²¹. Our study, although larger than any previously reported prRT group, is significantly different in that we were unable to differentiate borderline resectable patients from initially resectable patients or patients who may have received prRT for other reasons. This is a significant limitation since we were unable to differentiate borderline resectable patients either by receipt of venous resection or by T-staging, since the patients analyzed were staged using AJCC 5th edition staging. However, our findings are consistent with previous retrospective analyses, which have demonstrated varying results of either comparable or better OS for patients receiving prRT^{6,9,22}. Previous prospective studies were abandoned due to a lack of survival benefit in the neoadjuvant 5-FU or Gemcitabine therapy groups. Lymph node status has also been consistently correlated with OS in PAC^{7,23-25}. Those patients with positive lymph node status at presentation are often not deemed surgical candidates due to spread of disease, but some of these patients may have more responsive disease and be rendered resectable by prRT. By providing prRT, it is possible that these patients will “self-select” towards resection, and those with rapidly progressive disease will be spared the unnecessary morbidity of a pancreaticoduodenectomy.

These findings are limited by inherent limitations of a large retrospective data base design. These include limited patient data on co-morbidities, individual physician treatment nuances and patient selection, in addition to possible miscoding or reporting bias. A recent study linked data reported to the NCDB for breast and colorectal cancer with insurance claims data and found approximately 85% of staging and treatment characteristics were correctly reported²⁶.

Additionally, although the cohort may seem large compared to previous studies, it is still a rather select subgroup of the large number of patients available in the NCDB. There are no data available to explain the rationale for prRT in these patients. Patients undergoing prRT may have had initially more advanced or complicated disease or may have been treated on

clinical trials, thus introducing a strong potential for a selection bias. Furthermore, our analysis included patients eligible for both resection and RT, but a lack of co-morbidities and performance status information introduces a critical unknown into the study. The tendency towards selecting riskier patients with larger, more complicated tumors or significant patient comorbidities for prRT could mask a potential survival benefit for pre-operative delivery of adjuvant therapy. Additionally, many centers may employ postoperative radiation only in patients with worse prognostic factors, such as positive margins or positive lymph node status and this selection bias may play a role in the margin status of this patient population. Still, in the NCDB cohort, only 13.3% of resected patients received chemotherapy alone, indicating this effect may be negligible.

Novel chemotherapeutic combinations for PAC are emerging and are now being tested, including the recent advent of FOLFIRINOX. A recent European study using neoadjuvant Docetaxel-based chemoradiation demonstrated excellent pathological response and an improvement in survival⁷. In addition, advances in highly conformal stereotactic body radiotherapy (SBRT) are providing impressive rates of control in unresectable pancreatic patients and have acceptable toxicity endpoints^{27,28}. The role of SBRT in resectable pancreatic adenocarcinoma is unknown but is currently being examined. It is clear that there is a role for prRT in selected borderline resectable patients, but given that we have demonstrated no inferior OS in patients receiving prRT, the role of prRT with updated chemotherapeutics, modern radiotherapy delivery techniques and predictive genetic markers may be worth pursuing. This study provides unique data that serves as essential preliminary data for additional prospective studies examining the role of prRT in the management of PAC.

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Figure 1. Kaplan-Meier survival estimates are shown for patients who undergo radiation therapy before surgery versus those who have radiation therapy after surgery.

Table 1Patient Demographics and Clinicopathologic Characteristics (*n*=5414)

	%
<i>Patient Demographics</i>	
Male sex	53.1%
White race	89.4%
Age at diagnosis	64 yrs (20-88) *
<i>Clinical Characteristics</i>	
AJCC 5 th Edition Stage (all M0):	
Stage I	14.6%
Stage II	18.5%
Stage III	55.2%
Stage IV	9.6%
Missing	2.0%
Tumor Grade:	
Undetermined	10.5%
I	10.4%
II	46.7%
III/IV	32.4%
Surgical Margin Positive	27.5%
Lymph Node (LN) Positive	64.5%
Tumor Size	30 mm (0-989) *
<i>Treatment Characteristics</i>	
Radiation Therapy Before Surgery (prRT)	5.1%
Radiation Therapy After Surgery (poRT)	94.9%
Received Chemotherapy	92.9%
>12 LN examined	32.3%
Facility Type [†] :	
CCP	10.2%
CCCP	42.7%
NCI/ ARCP	47.0%

* Median (Range)

[†] CCP = Comprehensive Cancer Program, CCCP= Comprehensive Community Cancer Program, NCI/ ARCP = National Cancer Institute-designated Program/ Academic Comprehensive Care Program

Table 2

Univariate Association of Covariates with Therapy Sequence

	<u>PrRT n=277</u>		<u>PoRT n=5137</u>		<u>p-value</u> [*]
	<u>n</u>	<u>%</u>	<u>n</u>	<u>%</u>	
<i>Patient Demographics</i>					
Male sex	145	52.3%	2732	53.2%	0.786
White race	243	89.3%	4531	89.4%	0.987
Age at diagnosis					.077
	<= 50	51 18.4%	694	13.5%	
	50-65	116 41.9%	2150	41.9%	
	65-75	86 31.0%	1699	33.1%	
	>75	24 8.7%	594	11.6%	
<i>Clinical Characteristics</i>					
AJCC 5 th Edition Stage (all M0):					<.001
Stage I	81	31.9%	712	14.1%	
Stage II	52	20.5%	950	18.8%	
Stage III	68	26.8%	2922	57.8%	
Stage IV	53	20.9%	469	9.3%	
T-stage:					<.001
T0/T1/T2	109	41.1%	1492	29.5%	
T3/T4	99	58.9%	3570	70.5%	
Tumor Grade:					<.001
Undetermined	108	39.0%	463	9.0%	
I	22	7.9%	539	10.5%	
II	84	30.3%	2442	47.5%	
III/IV	63	22.7%	1693	33.0%	
Surgical Margin Positive	45	18.4%	1316	28.0%	.001
Lymph Node (LN) Positive	71	41.0%	3159	65.4%	<.001
Tumor Size (mm)					.774
	<= 20	37 18.0%	958	20.7%	
	>20 to <=30	70 34.0%	1500	32.3%	
	>30 to <= 40	53 25.7%	1117	24.1%	
	>40	46 22.3%	1063	22.9%	
<i>Treatment Characteristics</i>					
Received Chemotherapy	267	97.1%	4694	92.7%	.006
Facility Type [†] :					<.001
CCP	16	5.8%	537	10.5%	
CCCP	75	27.1%	2239	43.6%	
NCI/ ARCP	186	67.1%	2361	46.0%	
Facility Volume ^β	44 (1-323)		19 (1-350)		<.001

* Bold print denotes statistical significance. The p-value was calculated using ANOVA for facility volume and chi-squared test elsewhere.

[†] CCP = Comprehensive Cancer Program, CCCP= Comprehensive Community Cancer Program, NCI/ ARCP = National Cancer Institute-designated Program/ Academic Comprehensive Care Program

^β Median (Range)

Table 3**Multivariate Logistic Regression Predicting Lymph Node and Margin Positivity**

Table 3a. Multivariate Logistic Regression Predicting LN Positivity				
		Odds Ratio (95% CI)	OR P-value	Type 3 P-value *
Therapy Sequence	PrRT	0.45 (0.31 – 0.65)	<.001	<.001
	PoRT	1.0	-	
Tumor size (mm):	<= 20	0.73 (0.60 – 0.88)	0.001	<.001
	>20 to <=30	0.92 (0.77 – 1.10)	0.352	
	>30 to <= 40	1.05 (0.87 – 1.27)	0.613	
	>40	1.0	-	
Grade:	Undetermined	0.74 (0.57 – 0.95)	0.017	0.001
	I	0.74 (0.59 – 0.92)	0.007	
	II	1.04 (0.90 – 1.21)	0.580	
	III/IV	1.0	-	
LN Examined at Resection		1.07 (1.06 – 1.08)	<.001	<.001
Table 3b. Multivariate Logistic Regression Predicting Margin Negativity				
Therapy Sequence	PrRT	1.71 (1.17 – 2.52)	0.006	0.006
	PoRT	1.0	-	
Any chemotherapy	No	0.71 (0.55 – 0.91)	0.007	0.007
	Yes	1.0	-	
Tumor size (mm)	<= 20	1.95 (1.59 – 2.41)	<.001	<.001
	>20 to <=30	1.39 (1.17 – 1.66)	<.001	
	>30 to <= 40	1.21 (1.00 – 1.45)	0.050	
	>40	1.0	-	
Age (per 5 years)		0.96 (0.93 – 1.00)	0.025	0.025

* Bold print denotes statistical significance

Table 4

Multivariate Survival Analysis for All Patients

		Hazard Ratio (95% CI)	HR P-value	Type 3 P-value
Therapy Sequence	PrRT	1.20 (0.98 – 1.48)	0.077	0.077
	PoRT	1.0	-	
Any chemotherapy	No	1.16 (1.02 – 1.34)	0.030	0.030
	Yes	1.0	-	
Margin Positive	No	0.75 (0.70 – 0.82)	<.001	<.001
	Yes	1.0	-	
LN positive	No	0.67 (0.62 – 0.72)	<.001	<.001
	Yes	1.0	-	
Tumor size (mm)	<= 20	0.67 (0.60 – 0.75)	<.001	<.001
	>20 to <=30	0.81 (0.73 – 0.89)	<.001	
	>30 to <= 40	0.94 (0.85 – 1.04)	0.264	
	>40	1.0	-	
Grade	Undetermined	0.62 (0.53 – 0.71)	<.001	<.001
	I	0.55 (0.49 – 0.63)	<.001	
	II	0.79 (0.73 – 0.85)	<.001	
	III/IV	1.0	-	
LN Examined (per 5)		0.96 (0.94 – 0.98)	<.001	<.001
Age (per 5 years)		1.04 (1.03 – 1.06)	<.001	<.001
Facility Volume (per 10 patients)		0.99 (0.99 – 1.00)	0.009	0.009

*Bold print denotes statistical significance