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Optimal timing and predictors of adjuvant therapy in

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An abstract of

A thesis submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

in partial fulfillment of the requirements for the degree of

Master of Science

in Clinical Research

2025

ABSTRACT

Optimal timing and predictors of adjuvant therapy in patients with poorly differentiated pancreatic adenocarcinoma

By Mihir M. Shah

Background: Multimodal therapy, combining chemotherapy and surgical resection, is the standard of care for patients with resectable Pancreatic Ductal Adenocarcinoma (PDAC). Patients with poorly differentiated PDAC have suboptimal overall survival (OS), partly due to the limited understanding of optimal timing for return to intended oncologic therapy (RIOT) after upfront surgery. This thesis evaluates patients with poorly differentiated PDAC who undergo upfront surgical resection and assess how the timing of receipt of adjuvant chemotherapy is associated with OS.

Methods: Using the National Cancer Database, we identified poorly differentiated non-metastatic PDAC patients who received upfront surgical resection followed by adjuvant chemotherapy (2007-2016). Adjusted Cox proportional hazard models evaluated OS based on RIOT timing. Logistic regression was used to identify factors associated with RIOT.

Results: Of 3,050 included patients, 66.1% (n=1,810) did RIOT within 9 weeks and 33.9% (n=927) after 9 weeks. The median age of the study cohort was 62 years; 52% (n = 1,583) were male and 87.1% (n = 2,657) were White. Adjusted multivariable analysis (age, race, facility type, insurance status, Charlson-Deyo score, income, education, year of diagnosis, pathological T & N stage and margins) noted that patients who did RIOT within 9 weeks were associated with improved OS compared to patients who did RIOT after 9 weeks (aHR 0.90, 95%CI 0.82-0.99, p=0.03). Treatment at academic facilities was associated with lower odds of RIOT within 9 weeks compared to treatment at non-academic facilities (aOR 0.83, 95%CI 0.70-0.98, p=0.03).

Conclusion: Patients with poorly differentiated pancreatic ductal adenocarcinoma may benefit from adjuvant therapy within 9 weeks after surgical resection. Opportunities may exist in academic facilities to facilitate adjuvant therapy within 9 weeks of surgical resection.

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1. Background

Pancreatic Ductal Adenocarcinoma (PDAC) is the 6th leading cause of cancer related death worldwide.[1] In the United States, it is the 3rd leading cause of cancer-related death after lung and colon. In 2024, it was estimated that 66,440 people would be diagnosed with PDAC and 51,750 people would die of PDAC.[2] It is a lethal disease and associated with five-year survival rate of 12.8%.[3] This is due to several reasons: 1) lack of screening for prevention or early detection of PDAC[4] means that patients with newly diagnosed PDAC have non-operable disease 80% of the time;[3] 2) the current chemotherapeutic regimens available to treat PDAC are relatively ineffective in this chemo-resistant disease;[5,6] 3) significant weight loss and malnutrition related to this disease, results in decreased functionality and appetite for patients making it challenging to tolerate therapy to treat this disease.[7,8]

Without having surgery as an option, the majority of patients with PDAC (80%) are treated with systemic drug therapy as the mainstay of therapy based on National Comprehensive Cancer Center Network (NCCN) guidelines.[9] However, in patients with localized disease or non-metastatic PDAC, combination or multimodal therapy is preferred due to the systemic nature of the disease. Multimodal therapy includes a combination of surgical resection, chemotherapy or radiation therapy.[9] Surgical resection is determined based on cross-sectional imaging, where the non-metastatic patients are categorized into resectable, borderline-resectable and locally advanced unresectable PDAC.[10,11] The current standard of care for resectable or borderline-resectable disease includes a combination of chemotherapy and surgical resection (Figure 1).[9]

For borderline-resectable PDAC, chemotherapy given prior to surgery (neoadjuvant) is considered the first-line of therapy.[7] However, for resectable disease, neoadjuvant chemotherapy or upfront surgical resection are standard of care treatment options.[7] Many academic centers prefer neoadjuvant chemotherapy because 40% of patients are unable to complete chemotherapy after surgical resection (adjuvant).[12] This is important because patients with PDAC who undergo surgical resection alone have significantly lower median overall survival (OS) compared to patients who receive a combination of chemotherapy (either in neoadjuvant or adjuvant setting) and surgical resection.[13] Hence, in order to maximize the receipt of chemotherapy in patients with resectable PDAC, many academic centers prefer chemotherapy in neoadjuvant setting. Due to the lack of randomized data (ongoing clinical trial)[14], it is reasonable for patients to undergo upfront surgical resection for resectable PDAC, as practiced by many centers world-wide, followed by adjuvant chemotherapy in patients who are able to receive it.

Despite multimodal therapy, the median OS is poor (< 2 years) in resectable PDAC.[5,15] The indicators for poor prognosis include poorly differentiated histology, lymphovascular invasion, perineural invasion, margin-positive resection, lymph node positive disease (≥stage IIB), size of the primary tumor and absence of adjuvant therapy.[16] Limited data are available on patients with poorly differentiated resectable PDAC who undergo upfront surgical resection in relation to the optimal timing of adjuvant chemotherapy. When adjuvant chemotherapy was started within 12 weeks of surgical resection in patients with PDAC, no difference in OS was noted compared to patients who started adjuvant chemotherapy after 12 weeks.[17,18] However, the study cohort in both retrospective studies was not limited to patients with poorly differentiated PDAC. Additionally, only 33.5% of PDAC patients have poorly differentiated histology making it challenging to study

this population prospectively.[19] Another study (n=7,548) analyzed the National Cancer Database (NCDB), where PDAC patients with Return to Intended Oncologic Therapy (RIOT) within 59 days (8.42 weeks) demonstrated an association with improvement in 2-year OS compared to PDAC patients with RIOT after 59 days (52.5% vs. 45.1%, p=0.02). In this study, majority of patients had either well-differentiated or moderately differentiated PDAC, highlighting the need to evaluate the optimal timing of RIOT in a cohort consisting only of patients with poorly differentiated PDAC.[20] The current NCCN guideline mentions initiating adjuvant chemotherapy only after adequate postoperative recovery and in the absence of recurrence or metastatic disease. This may be done ideally within 12 weeks based on the design parameters of randomized controlled trials.[5,9,21] Hence, the aim of this thesis is to add to the literature by analyzing a retrospective, observational database (NCDB) to evaluate patients with poorly differentiated PDAC who undergo upfront surgical resection and assess how the timing of receipt of adjuvant chemotherapy is associated with OS. The hypothesis is that these patients who receive additional (adjuvant) chemotherapy within 8 weeks of surgical resection will demonstrate an association with improved OS compared to patients who receive adjuvant therapy after 8 weeks of surgical resection.

2. Methods

2.1 Study Design

In this retrospective cohort study, the NCDB was used to identify patients with Pancreatic Ductal Adenocarcinoma (PDAC) from 2006 to 2017. The NCDB, started in 1989, is a joint initiative by the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society and is a nationwide oncology outcomes database. It contains hospital registry data, representing 72% of all newly diagnosed cancer cases in the United States with approximately 40 million records from more than 1500 CoC-accredited cancer programs. Data on all types of cancer are tracked, analyzed, and used to explore outcomes in cancer care and serve as the basis for quality improvement.[22] The STROBE guidelines were followed during manuscript preparation.[23]

2.2 Study Patients

No institutional review board approval was required, as this is a retrospective study using deidentified data from the NCDB. We selected all patients diagnosed with PDAC using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes for PDAC (8020 and 8140). For primary site, the following codes were used: 'C250', 'C251', 'C252', 'C253', 'C257', 'C258', 'C259'; **not** 'C254' (malignant neoplasm of the endocrine pancreas). Patients with poorly differentiated non-metastatic PDAC who received upfront surgical resection followed by adjuvant chemotherapy were included. Patients who received neoadjuvant therapy prior to surgical resection were excluded using the variable "systemic/surgery sequence". Patients with unknown data on the number of days between the date of initial diagnosis and the date of surgical resection and the number of days between the date of initial diagnosis and the start of systemic therapy were

excluded. Patients who received only palliative care, those with metastatic disease on clinical staging, those who received upfront radiation and those with well or moderately differentiated PDAC were excluded from the final analysis cohort. See Figure 2.

2.3 Variables and Comparison Groups

Independent variables in this analysis included patient demographic and pathological tumor factors. Patient demographic factors included age, race (white, black and others), facility type (academic/research vs. non-academic) and insurance status (private vs. Medicare/Medicaid/other government/not insured); these were treated as unordered categorical variables. Neighborhood-level education and median household income were defined using ZIP code–level estimates. Education was classified into quartiles based on the percentage of adults in the patient's ZIP code without a high school diploma (<7%, 7% to 12.9%, 13% to 20.9%, and ≥21%). Median household income was categorized into quartiles according to ZIP code (<$38,000, $38,000 to $47,999, $48,000 to $67,999, and ≥$68,000). The Charlson Deyo (CD) score (0 vs. ≥1) was treated as an ordered categorical variable. The year of diagnosis was categorized (2006–2010 vs. 2011–2017) based on the PRODIGE 4/ACCORD 11 trial published in 2011, which demonstrated improved OS with FOLFIRINOX compared to gemcitabine.[24] Pathological tumor features included margin status (positive vs. negative) which was treated as an unordered categorical variable and pathological T and M staging which were treated as ordered categorical variables. Timing to Return to Intended Oncologic Therapy (RIOT) was treated as an ordered categorical variable. The year of diagnosis was defined as the year when cancer was clinically or histologically confirmed, based on the Facility Oncology Registry Data Standards (FORDS) definition. Time interval was defined as time between definitive surgical procedure and start of adjuvant chemotherapy. Patients

were right-censored at the time of death or last known follow-up, with survival time calculated from the date of diagnosis. Dichotomizing the RIOT time interval at 5, 6, 7, 8, 9, 10, 11, 12 and 16 weeks was evaluated to assess the impact on OS.

2.4 Statistical Analysis

Descriptive statistics were used to summarize patient demographics and tumor characteristics. Univariate and multivariable analyses utilizing Cox proportional hazard models were used to explore OS based on timing to RIOT (primary aim). In the multivariable Cox proportional hazard model, patient characteristics (age, sex, race, facility type, insurance status, CD score, median household income, education and year of diagnosis) and tumor characteristics (margin status and pathological T and N staging) were initially considered for model inclusion. Then a backward selection method was used for multivariable analysis with an alpha level of removal of >/=0.2. To identify factors associated with RIOT (secondary aim), a binary logistic regression model was used to assess patient demographics and tumor factors associated with RIOT within the optimal time interval based on our exploratory analyses. A $p<0.05$ was accepted to indicate a statistically significant association. All analyses were performed using SAS 9.4 (SAS Institute Inc.).

3. Results

3.1 Patient Demographics and Tumor Characteristics

We reviewed de-identified data for 585,239 patients with pancreatic cancer from the NCDB between 2006 and 2017. Following the application of selection criteria (Figure 2), 3,050 patients were included in the final analysis. The cohort predominantly consisted of White patients (n=2,657, 87.1%), with 65.4% having a CD score of 0 (n=1,995). A majority of patients (n= 2,124, 69.6%) were diagnosed between 2011 and 2017. Regarding insurance status, 38.7% (n=1,181) had private insurance, while the remaining 61.3% (n=1,869) were either insured through Medicare/Medicaid/other government programs or uninsured. Advanced tumor stage (pT3-4) was observed in 85.4% (n=2,441) patients, with nodal involvement (pN1) in 72.6% (n = 2,059) patients. Negative surgical margins were reported in 77.9% (n = 2,375) patients. The median time from diagnosis to surgery was 2.4 (IQR 0.4-4.1) weeks (Table 1). The median time from surgery to adjuvant therapy was 7.8 (IQR 6-10) weeks. On a median follow-up of 13 (IQR 9.6-18.4) weeks, 87% of patients (n=2,653) died, while the remaining 13% (n=397) were right-censored (alive or lost to follow-up).

3.2 Demographic and Tumor Characteristics associated with Overall Survival

On univariate analysis, RIOT within 9 weeks, age, facility type, insurance status, CD score, year of diagnosis, pathologic T and N staging and margin status were associated with improved OS (Table 2). On multivariable analysis, RIOT within 9 weeks remained significantly associated with improved OS (aHR 0.90, 95%CI 0.82–0.99, p=0.03). Similar results were observed in two other multivariable models: 1) Patients who did RIOT within 8 weeks vs. those who did RIOT after 8

weeks (aHR 0.89, 95%CI 0.82–0.98, p=0.015) and 2) Patients who did RIOT within 7 weeks vs. those who did RIOT after 7 weeks (aHR 0.9, 95%CI 0.82–0.99, p=0.029). No association with OS was observed in multivariable models comparing patients who did RIOT within 5, 6, 12 and 16 weeks vs. those who did RIOT after these time points following upfront surgery (Supplementary Table 2). Other factors on multivariable analysis associated with improved OS included treatment at academic/research facility compared to the non-academic facility (aHR 0.83, 95%CI 0.76–0.91, p<0.001), year of diagnosis between 2011 and 2017 compared to 2006–2011 (aHR 0.84, 95%CI 0.76–0.93, p=0.001), pathologic T1-2 stage compared to T3-4 stage (aHR 0.75, 95%CI 0.66–0.86, p<0.001), pathologic N0 stage compared to N1 stage (aHR 0.71, 95%CI 0.64–0.79, p<0.001) and negative surgical margins compared to positive margins (aHR 0.69, 95%CI 0.62–0.78, p<0.001). Factors associated with worse OS included Black race compared to White (aHR 1.29, 95%CI 1.1–1.52, p=0.002), and a CD score of 1 compared to 0 (aHR 1.12, 95%CI 1.02–1.24, p=0.016) (Table 3).

3.3 Demographic and Tumor Characteristics associated with RIOT (≤ 9 weeks)

Following surgical resection, 66.1% (n=1,810) of patients were able to RIOT within 9 weeks, while 33.9% (n=927) patients were able to RIOT after 9 weeks (Table 1). On univariate analysis, age below the median (OR 1.21, 95%CI 1.04–1.42, p=0.016), median household income quartile ($48,000-$67,999: OR 1.21, 95%CI 1.04–1.42, p=0.016; $38,000-$47,999: OR 1.21, 95%CI 1.04–1.42, p=0.016; Ref. ≥$68,000) and private insurance (OR 1.25, 95%CI 1.06-1.47, p=0.008) were associated with higher odds of RIOT within 9 weeks (Table 4). On multivariable analysis, treatment at a non-academic facility was associated with higher odds of RIOT within 9 weeks compared to treatment at an academic/research facility (aOR 1.18, 95%CI 1.01–1.38, p=0.03)

(Table 5). Patients with a median household income of $48,000–$67,999 (aOR 0.72, 95%CI 0.56–0.91, p=0.007) and $38,000–$47,999 (aOR 0.66, 95%CI 0.50–0.86, p=0.003) were associated with lower odds of RIOT within 9 weeks compared to those in the highest income quartile (≥$68,000). The odds of RIOT within 9 weeks were not significantly different for patients in the lowest income quartile (<$38,000) compared to those in the highest income quartile (≥$68,000) (aOR 0.86, 95%CI 0.61–1.21, p=0.383).

4. Discussion

The primary aim of this study was to evaluate the optimal timing of RIOT and its association with OS in patients with poorly differentiated PDAC who underwent upfront surgical resection. The secondary aim was to evaluate factors associated with timely RIOT in poorly differentiated PDAC. The analysis determined that 9 weeks is the optimal time cut-off for RIOT, before which patients may benefit from initiating adjuvant therapy. Patients with RIOT within 9 weeks demonstrated an association with improved OS compared to patients with RIOT after 9 weeks. Treatment at a non-academic facility was associated with higher odds of RIOT within 9 weeks compared to treatment at an academic/research facility.

Several retrospective studies analyzed the association between timing of RIOT and OS.[17,18,25] Analysis of patients with stage 1 and 2 PDAC (n=7,548) noted that patients who had RIOT before 28 days (HR 1.17, 95%CI 1.02-1.35, p=0.03) and after 59 days (HR 1.09, 95%CI 1.02-1.17, p=0.008) had worse OS compared to patients who had RIOT between 28 and 59 days following surgical resection.[25] In another multi-institutional study using the central pancreatic consortium database (n=488), similar OS was noted in PDAC patients with RIOT within 12 weeks compared to patients with RIOT after 12 weeks on univariate analysis (24.3 vs. 28.5 months, p = 0.79).[17] On multivariable analysis, patients with RIOT, regardless of timing, were noted to have improved OS compared to patients who did not RIOT (≤12 weeks: HR 0.5, 95%CI 0.34-0.82, p<0.01; >12 weeks: HR 0.48, 95%CI 0.29-0.8, p<0.01; reference: surgery only). The authors concluded that patients who did not RIOT within 12 weeks of surgical resection still remained appropriate candidates for multimodal therapy. Unlike these two studies, we limited our analysis to PDAC

patients with poorly differentiated histology and noted that RIOT within 9 weeks was associated with improved OS.

Poorly differentiated tumor grade has been recognized as an independent prognostic factor for PDAC and is associated with early recurrence and worse OS.[26,27] In a single US-based institutional analysis of patients with resected PDAC (n=957), higher odds of early recurrence were noted in patients with poorly differentiated tumors in surgical pathology compared to well/moderately differentiated tumors (OR 1.66, 95%CI 1.1-2.5, p=0.016).[28] In another single-center analysis of patients with resected PDAC (n=510), disease-free survival was compared in patients who received adjuvant therapy to those who did not receive adjuvant therapy.[19] In a subgroup analysis of patients with poorly differentiated PDAC, a significant improvement in median disease-free survival was associated with receipt of adjuvant therapy compared to no adjuvant therapy (22 vs. 12 months, p<0.0001). This association was not significant in a subgroup of patients with well-differentiated PDAC (p=0.25). Our study focused on OS as the main outcome as it is clinically meaningful due to the overall prognosis of PDAC. We noted that the timing of RIOT is also an important prognostic factor in these patients due to its impact on OS. Improved OS was noted in patients with poorly differentiated PDAC with RIOT within 9 weeks compared to RIOT after 9 weeks. These data highlight the importance of both receipt and timing of RIOT in patients with poorly differentiated PDAC.

Several studies have identified factors associated with RIOT in patients with PDAC.[29–31] In an NCDB analysis (2004-2016) by Mickel et al., male sex compared to female (OR 1.24, p<0.001), CD score of 0 (OR 1.9, p<0.001) and 1 (OR 1.7, p=0.001) compared to ≥2, negative surgical

margins compared to positive margins (OR 1.1, p=0.048) and treatment at academic institutions compared to community hospital (OR 1.3, p=0.001) were associated with improved odds of RIOT.[31] In contrast to this study, we assessed factors associated with RIOT within 9 weeks in poorly differentiated PDAC and noted that patients receiving treatment at non-academic facilities were associated with higher odds of RIOT within 9 weeks compared to patients receiving treatment at academic facilities. One potential barrier to obtaining treatment in a timely fashion at an academic center may be delays in referrals from a non-academic center, or delays in obtaining appointments for further care, including adjuvant therapy.[32] Distance to treating facility, or outcomes based on rural vs. other geographic areas of residency were not included in the analyses. In addition, examining access to care based on having private insurance vs. government or no insurance at all may not provide sufficient nuance to identify how or if payor type might impact timely receipt of RIOT. Our analysis noted an improved OS in patients receiving treatment at academic facilities compared to non-academic facilities. Our study highlights the complex interaction between the treatment facility, RIOT and OS in patients with poorly differentiated PDAC. Future studies should aim at identifying factors associated with RIOT within the optimal time-frame from surgical resection in patients with poorly differentiated PDAC to understand the generalizability of these findings.

The limitations of our study include its retrospective nature and the associated selection bias, which may have influenced RIOT rates and the timing of RIOT. Since the NCDB is a hospital-based database, it includes only patients treated at Commission on Cancer-accredited facilities and is not representative of the entire U.S. population. This may limit the generalizability of our findings. We did not evaluate postoperative complications, as NCDB does not record specific postoperative

complication data, which may be a critical factor in timely administration of RIOT. We acknowledge the lack of details in the NCDB related to disease-free survival as well as adjuvant therapy, such as the name, dose, duration, frequency and toxicity / adverse events. Due to this limitation, we were unable to determine which patients actually completed the intended adjuvant therapy. Our survival analysis may also be confounded by unobservable differences in surgeon expertise, experience and the lack of details regarding annual surgical volume. Limiting our analysis to patients who received upfront resection may reduce the generalizability of our findings as many patients now receive neoadjuvant chemotherapy. Despite these limitations, our study investigates the impact of receipt and timing of RIOT on OS and identifies factors associated with RIOT within 9 weeks in patients with poorly differentiated PDAC.

In conclusion, patients with poorly differentiated pancreatic ductal adenocarcinoma who return to intended oncologic therapy within 9 weeks demonstrate an association with improved overall survival compared to patients who return to intended oncologic therapy after 9 weeks. Treatment at non-academic facility is associated with timely return to intended oncologic therapy within 9 weeks; the reason for this finding may be interesting to evaluate in future studies. Additional studies should aim at exploring other factors that may influence the timing of return to intended oncologic therapy to optimize the delivery of multimodal treatment and improve overall survival, especially for patients with poorly differentiated pancreatic ductal adenocarcinoma.

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6. Figures

Figure 1. Stages of Pancreatic Ductal Adenocarcinoma (A) Resectable (B) Borderline-resectable (C) Locally advanced (D) Oligometastatic (E) Metastatic (adapted with permission from Springfield et al.).[33]

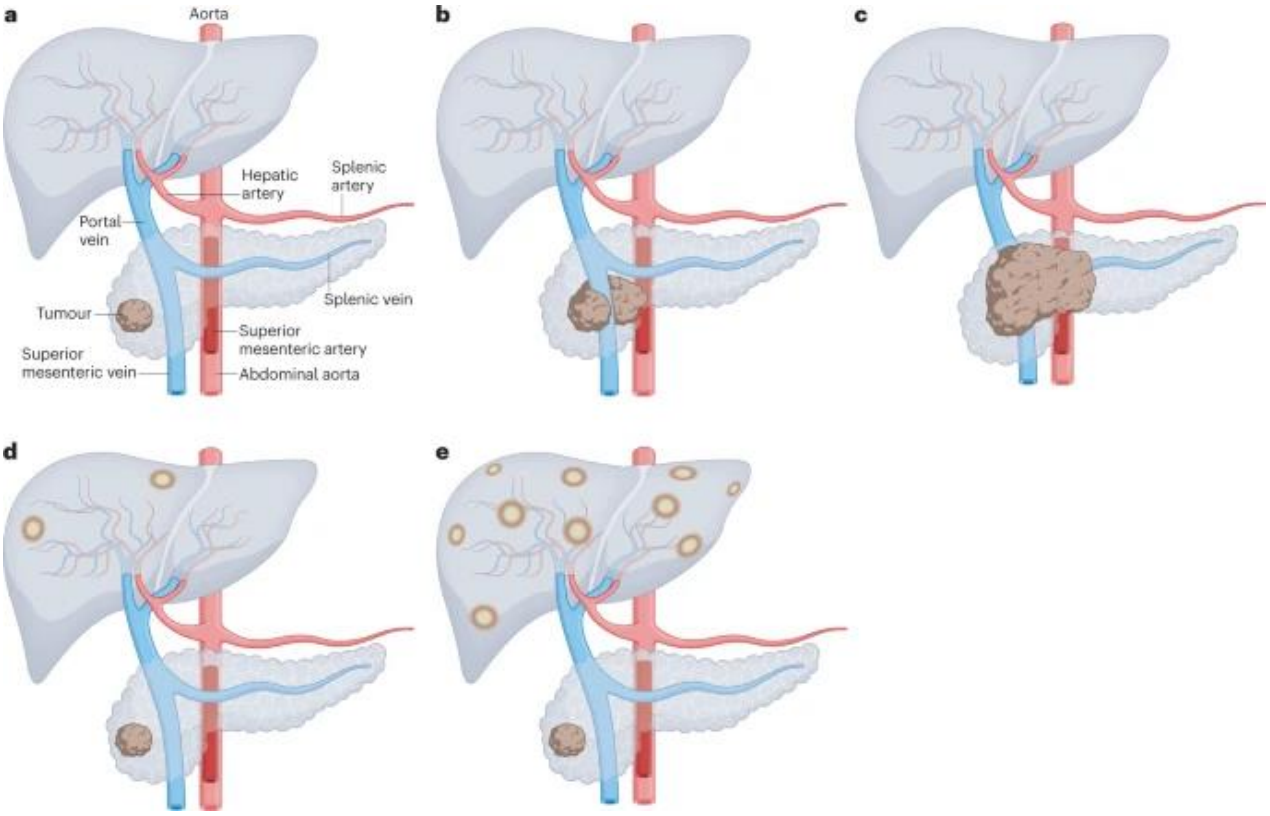
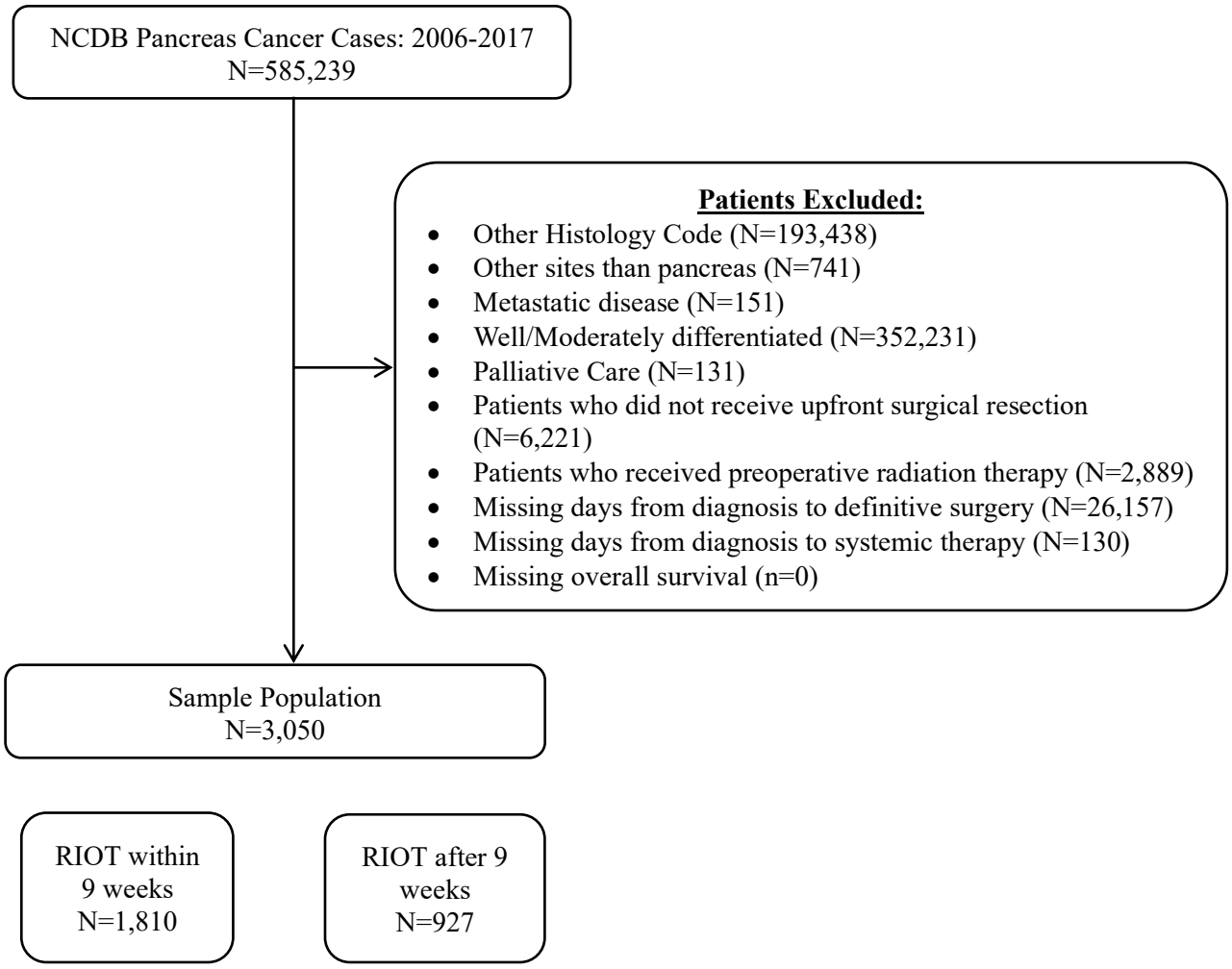


Figure 2. Schematic depicting inclusion and exclusion criteria of patients with pancreatic ductal adenocarcinoma

Abbreviations: NCDB, National Cancer Database, RIOT, Return to Intended Oncologic Therapy



7. Tables

Table 1. Descriptive Statistics

Variable	Level	N (%) (N=3050)
Race	White	2657 (87.1)
	Black	270 (8.9)
	Other	123 (4.0)
Age	Median	62 years
	Below Median	1589 (52.1)
	Above Median	1461 (47.9)
Sex	Male	1583 (51.9)
	Female	1467 (48.1)
Year of Diagnosis	2006-2010	926 (30.4)
	2011-2017	2124 (69.6)
Charlson-Deyo Score	0	1995 (65.4)
	1+	1055 (34.6)
Insurance Status	Private	1181 (38.7)
	Medicare/Medicaid/Other Government/Not Insured	1869 (61.3)
Pathologic T	1-2	417 (14.6)
	3-4	2441 (85.4)
	Missing	192
Pathologic N	0	777 (27.4)
	1	2059 (72.6)
	Missing	214
Median Household Income	>=$68,000	922 (37.1)
	$48,000-$67,999	671 (26.9)
	$38,000-$47,999	546 (21.9)
	<$38,000	350 (14.1)
	<7.0%	708 (28.4)
	7.0-12.9%	808 (32.4)

Variable	Level	N (%) (N=3050)
Education (% No High School Degrees Quartile)	13.0-20.9%	622 (24.9)
	>=21%	352 (14.1)
Surgical Margins	Negative	2375 (77.9)
	Positive	604 (19.8)
	Missing	71 (2.4)
RIOT within 9 weeks	Yes	1810 (66.1)
	No	927 (33.9)
	Missing	313
Time from diagnosis to surgery (days)	Mean	21.01
	Median	17.00
	Range	0-409
	Interquartile Range	3-29
Time from surgery to adjuvant therapy	Mean	58.51
	Median	55.00
	Range	0-417
	Interquartile Range	42-70

RIOT, Return to Intended Oncologic Therapy

Table 2. Factors associated with overall survival based on univariate Cox regression analysis

			Overall Survival		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
RIOT within 9 weeks	Yes	1810	0.91 (0.83-0.99)	**0.025**	**0.025**
	No	927	-	**-**	
Age	Above Median	1297	1.14 (1.05-1.23)	**0.002**	**0.002**
	Below Median	1440	-	**-**	
Race	Black	230	1.22 (1.06-1.41)	**0.007**	**0.017**
	Other	113	0.93 (0.75-1.14)	0.480	
	White	2394	-	**-**	
Sex	Female	1320	0.95 (0.87-1.03)	0.187	0.186
	Male	1417	-	**-**	
Facility Type	Academic/Research Program	1361	0.85 (0.78-0.92)	**<.001**	**<.001**
	Non-Academic	1349	-	**-**	
Insurance Status	Private	1072	0.89 (0.82-0.97)	**0.007**	**0.007**
	Medicare/Medicaid/Other Government/Not Insured	1665	-	**-**	
Charlson-Deyo Score	1+	922	1.13 (1.04-1.23)	**0.005**	**0.005**
	0	1815	-	**-**	
Year of Diagnosis	2011-2017	1936	0.84 (0.77-0.92)	**<.001**	**<.001**
	2006-2010	801	-	**-**	
Pathologic T	1-2	396	0.71 (0.63-0.80)	**<.001**	**<.001**
	3-4	2187	-	**-**	
Pathologic N	0	720	0.66 (0.60-0.72)	**<.001**	**<.001**
	1	1841	-	**-**	

			Overall Survival		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Margins	Negative	2190	0.63 (0.57-0.70)	**<.001**	**<.001**
	Positive	489	-	**-**	
Median Household Income	>=$68,000	922	0.88 (0.77-1.00)	0.059	0.225
	$48,000-$67,999	671	0.88 (0.77-1.02)	0.083	
	$38,000-$47,999	546	0.87 (0.75-1.01)	0.064	
	<$38,000	350	-	-	
Education (% No High School Degrees Quartile)	<7.0%	708	1.01 (0.88-1.16)	0.912	0.100
	7.0-12.9%	808	0.97 (0.84-1.11)	0.615	
	13.0-20.9%	622	1.11 (0.96-1.28)	0.148	
	>=21%	352	-	-	

RIOT, Return to Intended Oncologic Therapy

Table 3. Factors associated with overall survival based on multivariable Cox regression analysis

		Overall Survival		
Covariate	**Level**	**Hazard Ratio (95% CI)**	**HR P-value**	**Overall P-value**
RIOT within 9 weeks	Yes	0.90 (0.82-0.99)	**0.032**	**0.032**
	No	-	-	
Age	Above Median	1.09 (0.98-1.21)	0.113	0.113
	Below Median	-	-	
Race	Black	1.29 (1.10-1.52)	**0.002**	**0.006**
	Other	0.92 (0.72-1.16)	0.473	
	White	-	-	
Facility Type	Academic/Research Program	0.83 (0.76-0.91)	**<.001**	**<.001**
	Non-Academic	-	-	
Insurance Status	Private	0.91 (0.82-1.02)	0.103	0.103
	Medicare/Medicaid/Other Government/Not Insured	-	-	
Charlson-Deyo Score	1+	1.12 (1.02-1.24)	**0.016**	**0.016**
	0	-	-	
Year of Diagnosis	2011-2017	0.84 (0.76-0.93)	**0.001**	**0.001**
	2006-2010	-	-	
Pathologic T	1-2	0.75 (0.66-0.86)	**<.001**	**<.001**
	3-4	-	-	
Pathologic N	0	0.71 (0.64-0.79)	**<.001**	**<.001**
	1	-	-	
Margins	Negative	0.69 (0.62-0.78)	**<.001**	**<.001**
	Positive	-	-	
Education (% No High School Degrees Quartile)	<7.0%	1.05 (0.90-1.22)	0.567	0.096
	7.0-12.9%	0.97 (0.83-1.12)	0.656	
	13.0-20.9%	1.12 (0.96-1.31)	0.140	
	>=21%	-	-	

		Overall Survival		
Covariate	**Level**	**Hazard Ratio (95% CI)**	**HR P-value**	**Overall P-value**

* Number of observations in the original data set = 2737. Number of observations used = 2260.

** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Median Household Income.

Table 4. Factors associated with RIOT within 9 weeks based on univariate logistic regression analysis

Covariate	Level	N	RIOT within 9 weeks		
			Odds Ratio (95% CI)	**OR P-value**	**Overall P-value**
Age	Below Median	1440	1.21 (1.04-1.42)	**0.016**	**0.016**
	Above Median	1297	-	-	
Race	White	2394	1.09 (0.74-1.62)	0.656	0.308
	Black	230	0.88 (0.55-1.41)	0.606	
	Other	113	-	-	
Facility Type	Non-Academic	1349	1.17 (1.00-1.37)	0.057	0.057
	Academic/Research Program	1361	-	-	
Insurance Status	Private	1072	1.25 (1.06-1.47)	**0.008**	**0.008**
	Medicare/Medicaid/Other Government/Not Insured	1665	-	-	
Charlson-Deyo Score	0	1815	1.15 (0.98-1.36)	0.092	0.092
	1+	922	-	-	
Year of Diagnosis	2006-2010	801	0.99 (0.83-1.17)	0.879	0.879
	2011-2017	1936	-	-	
Pathologic T	1-2	396	0.93 (0.74-1.16)	0.522	0.522
	3-4	2187	-	-	
Pathologic N	0	720	0.98 (0.81-1.17)	0.803	0.803
	1	1841	-	-	

Covariate	Level	N	RIOT within 9 weeks		
			Odds Ratio (95% CI)	OR P-value	Overall P-value
Margins	Negative	2190	1.06 (0.87-1.31)	0.559	0.559
	Positive	489	-	-	
Median Household Income	$48,000-$67,999	671	0.77 (0.62-0.95)	**0.014**	**0.012**
	$38,000-$47,999	546	0.71 (0.57-0.89)	**0.002**	
	<$38,000	350	0.83 (0.64-1.07)	0.150	
	>=$68,000	922	-	-	
Education (% No High School Degrees Quartile)	<7.0%	708	1.29 (0.99-1.68)	0.059	0.242
	7.0-12.9%	808	1.28 (0.99-1.66)	0.065	
	13.0-20.9%	622	1.23 (0.94-1.62)	0.131	
	>=21%	352	-	-	

RIOT, Return to Intended Oncologic Therapy

Table 5. Factors associated with RIOT within 9 weeks based on multivariable logistic regression analysis

Covariate	Level	N	RIOT within 9 weeks	
			Odds Ratio (95% CI)	**OR P-value**
Age	Above Median	1182	0.87 (0.71-1.05)	0.152
	Below Median	1284	-	-
Facility Type	Non-Academic	1226	1.18 (1.01-1.38)	**0.030**
	Academic/Research Program	1240	-	-
Insurance Status	Private	957	1.16 (0.95-1.42)	0.148
	Medicare/Medicaid/Other Government/Not Insured	1509	-	-
Charlson-Deyo Score	1+	829	0.85 (0.71-1.01)	0.063
	0	1637	-	-
Median Household Income	$48,000-$67,999	666	0.72 (0.56-0.91)	**0.007**
	$38,000-$47,999	540	0.66 (0.50-0.86)	**0.003**
	<$38,000	345	0.86 (0.61-1.21)	0.383
	>=$68,000	915	-	-
Education (% No High School Degrees Quartile)	<7.0%	702	1.08 (0.77-1.53)	0.645
	7.0-12.9%	804	1.29 (0.96-1.75)	0.095
	13.0-20.9%	612	1.29 (0.97-1.72)	0.078
	>=21%	348	-	-

* Number of observations in the original data set = 2737. Number of observations used = 2466.

** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Margins, AJCC Pathologic N, AJCC Pathologic T, Year of Diagnosis, and Race.

8. Supplementary Tables

Supplementary Table 1. Topographic descriptions for Pancreatic Neoplasms and ICD-O-3 Codes

ICD-O-3 Code	Description
C250	Malignant neoplasm of head of pancreas
C251	Malignant neoplasm of body of pancreas
C252	Malignant neoplasm of tail of pancreas
C253	Malignant neoplasm of pancreatic duct
C257	Malignant neoplasm of other parts of pancreas
C258	Malignant neoplasm of overlapping sites of pancreas
C259	Malignant neoplasm of pancreas, unspecified

Supplementary Table 2. Cox Proportional Hazard Regression Analyses Exploring OS based on Different Timing of Return to Intended Oncologic Therapy (RIOT)

Multivariable Model No*	Time to RIOT	N	Overall Survival	
			Hazard Ratio (95% CI)**	P-value
1	≤5 weeks	419	1.02 (0.89-1.17)	0.77
	>5 weeks	2631	-	
2	≤6 weeks	782	0.96 (0.87-1.07)	0.45
	>6 weeks	2268	-	
3	≤7 weeks	1225	0.90 (0.82-0.99)	**0.029**
	>7 weeks	1825	-	
4	≤8 weeks	1687	0.89 (0.82-0.98)	**0.015**
	>8 weeks	1363	-	
5	≤9 weeks	2024	0.90 (0.82-0.99)	**0.032**
	>9 weeks	1026	-	
6	≤12 weeks	2655	1.01 (0.88-1.15)	0.93
	>12 weeks	395	-	
7	≤16 weeks	2913	0.86 (0.70-1.05)	0.13
	>16 weeks	137	-	

*Each model was adjusted for age (>62 years vs. ≤62 years), race (White, Black or others), facility type (academic/research program vs. non-academic), insurance status (private or Medicare/Medicaid/other government or not insured), Charleson-Deyo score (0 or 1+), year of diagnosis (2006-2010 or 2011-2017), pathologic T (1-2 or 3-4), pathologic N (0 or 1) and surgical margins (positive or negative).

**Multivariable Cox regression model was used to calculate HR and 95% confidence intervals.