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Margin negative resection and pathologic downstaging with multiagent chemotherapy with or without radiotherapy in patients with localized pancreas cancer: A national cancer database analysis

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ABSTRACT

Purpose: Margin-negative (R0) resection is the only potentially curative treatment for patients with pancreatic ductal adenocarcinoma (PDAC). Pre-operative multi-agent chemotherapy alone (MAC) or MAC followed by pre-operative radiotherapy (MAC + RT) may be used to improve resectability and potentially survival. However, the optimal pre-operative regimen is unknown.

Methods: Patients with non-metastatic PDAC from 2006 to 2016 who received pre-operative MAC or MAC + RT before oncologic resection were identified in the National Cancer Database. Univariable and multivariable (MVA) associates with R0 resection were identified with logistic regression, and survival was analyzed secondarily with the Kaplan Meier method and Cox regression analysis.

Results: 4,599 patients were identified (MAC: 3,109, MAC + RT: 1,490). Compared to those receiving MAC, patients receiving MAC + RT were more likely to have cT3-4 disease (76% vs 64%, $p < 0.001$) and cN + disease (33% vs 29%, $p = 0.010$), but were less likely to have ypT3-4 disease (59% vs 74%, $p < 0.001$) and ypN + disease (32% vs 55%, $p < 0.001$) and more likely to have a pathologic complete response (5% vs 2%, $p < 0.001$) and R0 resection (86% vs 80%, $p < 0.001$). On MVA, MAC + RT (OR 1.58, 95% CI 1.33–1.89, $p < 0.001$), evaluation at an academic center (OR 1.33, 95% CI 1.14–1.56, $p < 0.001$), and female sex (OR 1.43, 95% CI 1.23–1.67, $p < 0.001$) were associated with higher odds of R0 resection, while cT3-4 disease (OR 0.81, 95% CI 0.68–0.96, $p = 0.013$) was associated with lower odds of R0 resection.

Conclusion: For patients with localized PDAC who receive pre-operative MAC, the addition of pre-operative RT was associated with improved rates of R0 resection and pathologic response.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death in men and women [1]. At diagnosis, approximately 40–60% of patients will have localized disease [2,3]. Although margin-negative (R0) resection is the only known curative treatment, only 15–20% are initially deemed to have potentially resectable disease per National Comprehensive Cancer Network (NCCN) guidelines criteria [4–6]. Furthermore, for the

Abbreviations: R0, margin negative; PDAC, pancreatic ductal adenocarcinoma; MAC, multiagent chemotherapy; RT, radiotherapy; UVA, univariable analysis; MVA, multivariable analysis; LR, logistic regression; OS, overall survival; IQR, interquartile range; NCDB, National Cancer Database; AJCC, American Joint Committee on Cancer; LVI, lymphovascular invasion; pCR, pathologic complete response.

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select subgroup of patients initially deemed as having potentially resectable disease who proceed directly to surgery, 40–60% will undergo a margin-positive (R1) resection with subsequently poor prognosis [7,8].

Pre-operative treatment strategies are increasingly being explored for patients with potentially resectable [9–14] and borderline resectable [14–20] disease in order to improve the R0 resection rate and potentially survival. Additionally, pre-operative therapy may offer an opportunity to convert patients with locally advanced unresectable disease to operative candidates [15,21–23]. A wide variety of pre-operative regimens have been evaluated, including chemoradiation (CRT) [10,14,17], multiagent chemotherapy (MAC) [9,13,21], or MAC followed by radiotherapy (RT), either as conventionally fractionated CRT [12,15,18,19,22] or stereotactic body radiation therapy (SBRT) [23,24] with data suggesting R0 resection rates ranging from 63 to 89%, 71–93%, and 75–96%, respectively. Prospective randomized trials are needed to better establish the optimal pre-operative regimen for this heterogeneous patient cohort.

In the absence of randomized data, we sought to compare the effectiveness of pre-operative MAC vs. MAC + RT followed by potentially curative oncologic resection for patients with localized PDAC within the National Cancer Database (NCDB).

2. Methods

2.1. Data source

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society, which consists of de-identified information regarding patient demographics, tumor characteristics, first-course treatment for the corresponding diagnosis, and survival for approximately 70% of patients diagnosed with cancer within the United States [25]. The data used in this study were derived from a de-identified file and thus was exempt from institutional review.

2.2. Study cohort

The CONSORT diagram is shown in Fig. 1. Inclusion criteria were patients with non-metastatic PDAC (histology codes 8140, 8141, 8255, 8260, 8261, 8310, 8323, 8440, 8480, 8500, and 8521) who received MAC at least 30 days prior to a potentially curative oncologic surgical resection (surgery of the primary site codes 30–80). In the MAC + RT cohort, we broadly included patients who received non-palliative external beam RT targeting the pancreas or abdomen to a total dose of 20–70 Gy in 3–35 fractions as part of the pre-operative curative-intent therapy. Patients were excluded if they had missing data regarding the sequence of MAC, RT, and surgery or if they had missing clinical T-stage, clinical N-stage, or surgical margin status. To isolate a patient population who received MAC prior to RT, we excluded patients receiving RT prior to MAC and patients who started RT within 30 days of starting MAC.

2.3. Covariates

Covariates included patient age, sex, race (White vs. Black vs. Asian vs. other), clinical T-stage (cT1-2 vs. cT3-4), clinical N-stage (cN0 vs. cN1), location within the pancreas (head vs. body vs. tail vs. overlapping/unknown), Charleson Deyo Score (CDS)[26] (0 vs. $\geq$ 1), pretreatment CA 19–9 ($\leq$37.0 vs. 37.1–89.9 vs. $\geq$ 90.0 U/mL vs. unknown) [27], and type of treatment center (non-academic center vs. academic facility vs. unknown). Year of diagnosis was also included as a categorical variable (2006–2011 vs. 2012–2016) given the 2011 publication by Conroy et al. which led to the utilization of 5-fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) for patients with metastatic disease [28] and the subsequent extrapolation to the treatment of localized disease. The interval from start of MAC to surgery was included as a surrogate for MAC duration in patients receiving only MAC and was calculated as the difference between the interval from diagnosis to surgery and the interval from diagnosis to start of MAC. The interval from start of MAC to RT was included as a surrogate for MAC duration in patients receiving MAC + RT and was calculated as the difference between the interval from diagnosis to the start of RT and the interval from diagnosis to the start of MAC.

Outcome variables included pathologic T-stage (ypT0-T2 vs. ypT3-T4 vs. unknown), pathologic N-stage (ypN0 vs. ypN1 vs. unknown), surgical margin status (R0 vs. R1 or R2), histologic grade (well differentiated vs. moderately differentiated vs. poorly differentiated vs. unknown), lymphovascular invasion (LVI present vs. LVI absent vs. unknown), and pathologic complete response (pCR vs. no pCR vs. unknown). Staging was based on the AJCC 6th edition for cases diagnosed before 2010 and the AJCC 7th edition for cases diagnosed from 2010 to 2016. Total radiation dose was calculated as the sum of regional dose and boost dose.

2.4. Objectives

The primary objective of this study was to compare the R0 resection rate between patients who received either MAC or MAC followed by RT prior to a potentially curative surgical resection. Secondary objectives included an evaluation of pathologic response, clinical to pathologic tumor or lymph node (LN) downstaging, and a comparison of overall survival (OS) between patients treated with MAC vs. MAC + RT. We further investigated clinical variables associated with R0 resection and OS.

2.5. Statistical analysis

Baseline characteristics were compared between treatment cohorts (MAC vs. MAC + RT). The χ^2 or the Wilcoxon rank-sum test were used to evaluate for any differences in the cohorts for categorical and continuous variables, respectively. The χ^2 was also used to evaluate for differences in surgical outcomes between all patients receiving MAC vs. MAC + RT, and additionally in the subgroup of patients with cT3-T4 disease. Univariable (UVA) and multivariable (MVA) logistic regression (LR) was used to evaluate for pre-operative clinical and demographic characteristics associated with R0 resection. The surgical outcomes of MAC vs. MAC + RT cohorts were reanalyzed following a propensity score match (PSM) (using bootstrapping with 1-to-1 nearest-neighbor matching without replacement, caliper distance of 20% of the standard deviation of the pooled propensity scores) using covariates associated with receipt of MAC + RT on UVA LR [29–31]. Time from MAC to surgery was evaluated for association with R0 resection in the MAC and MAC + RT cohorts. The time from MAC to RT was evaluated for association with R0 resection in the MAC + RT cohorts.

OS was defined from time of diagnosis and was estimated with the Kaplan-Meier method and compared between the MAC vs. MAC + RT cohorts using the log-rank test. Because follow-up and vital status information was only available on patients diagnosed from 2006 to 2015, the survival analysis was limited to 3,357 (out of 4,599 total) patients. UVA and MVA Cox analysis was used to evaluate for pre-operative clinical and demographic characteristics associated with OS. Variables with $P < 0.1$ on UVA and LR Cox analysis were included in the MVA analyses and added in a forward stepwise fashion. All statistical tests were two-sided, with a threshold of $P < 0.05$ for statistical significance. All analyses were performed using STATA (version 13, College Station, TX).

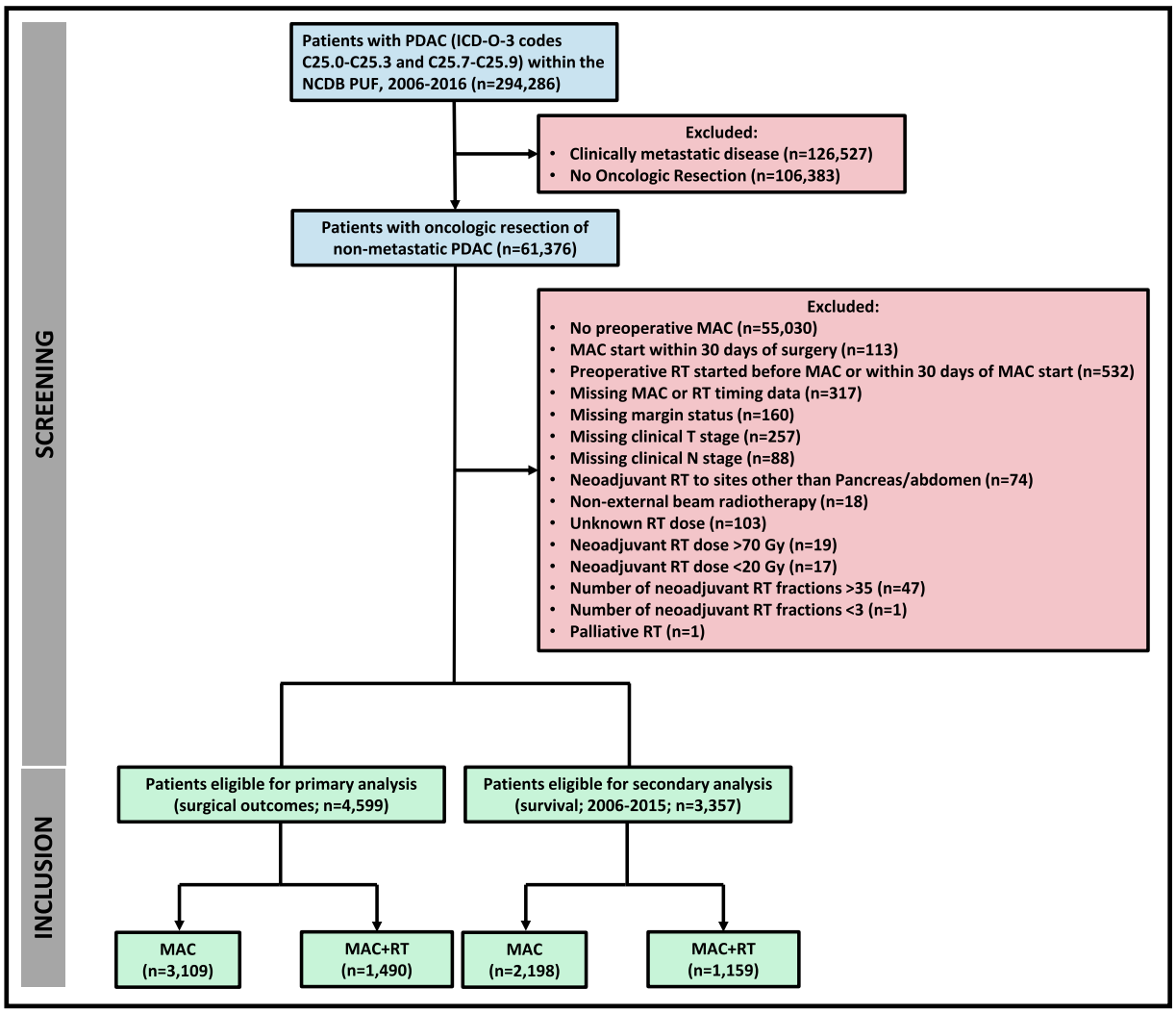

Fig. 1. CONSORT diagram delineating cohort selection. PDAC: Pancreatic ductal adenocarcinoma. NCDB: National Cancer Database. PUF: Participant use file. MAC: Multi-agent chemotherapy. RT: Radiotherapy.

3. Results

Baseline cohort characteristics are shown in Table 1. A total of 4,599 patients who received pre-operative MAC were included in the primary analysis and 1,490 (32%) of these patients received pre-operative RT. Patients who received MAC + RT, compared to MAC, had a higher clinical disease burden, with higher rates of cT3-T4 disease (76% vs. 64%, $P < 0.001$) and cN1 disease (33% vs. 29%, $P = 0.008$). Although the median age of each cohort was 64 years old, MAC + RT patients were younger compared to MAC patients ($P = 0.002$). The median interval between start of MAC to surgery was 3.7 months (IQR 2.8–4.9) for patients in the MAC cohort. The median interval between start of MAC to RT and start of MAC to surgery was 3.0 months (IQR 2.4–4.3) and 5.8 months (IQR 4.8–7.2) for patients receiving MAC + RT, respectively.

The median pre-operative dose of RT was 50.4 Gy (IQR 36–50.4) and median number of fractions was 27 (IQR 5–28). The most common RT regimens were 50.4 Gy in 28 fractions (40%), 33 Gy in 5 fractions (7%), and 50 Gy in 25 fractions (6%). The median number of dissected LNs was 18 (IQR 12–25) for the entire cohort, 19 (IQR 13–26) for patients receiving MAC, and 16 (IQR 10–22) for patients receiving MAC + RT ($P < 0.001$). Among patients receiving MAC, 643 (21%) received postoperative radiotherapy.

The surgical outcomes are shown in Table 2. Patients in the MAC + RT cohort, compared to MAC, had lower rates of ypT3-T4 disease (59% vs. 74%, $P < 0.001$) and ypN1 disease (32% vs. 55%, $P < 0.001$). Additionally, patients receiving MAC + RT, compared to MAC, had higher rates of pCR (5% vs. 2%, $P < 0.001$) and R0 resection (86% vs. 80%, $P < 0.001$) and lower rates of LVI (19% vs. 33%, $P < 0.001$). On post hoc subgroup analysis, MAC + RT vs. MAC was associated with a significant improvement in R0 resection rate for patients with cT3-T4 disease (87% vs. 78%, $P < 0.001$) but not for patients with cT1-T2 disease (86% vs. 83%, $P = 0.267$).

Overall, when comparing cT stage with ypT stage, 28% of patients had conversion to lower ypT stage, 43% of patients had stable ypT-stage, and 23% had a higher ypT stage. Patients receiving MAC + RT vs. MAC had improved conversion rates to lower ypT-stage when evaluating all patients (39% vs. 23%, $P < 0.001$) and when evaluating only the subgroup of patients diagnosed with cT3-T4 disease (46% vs. 31%, $P < 0.001$). Although only 30% of patients had clinical evidence of LN involvement (cN1), 48% of patients had pathologically involved LNs at the time of surgery. When evaluating only patients diagnosed with cN1 disease, there was a higher rate of LN clearance (i.e. cN1 to ypN0) when comparing MAC + RT vs. MAC cohorts (51% vs. 27%, $P < 0.001$).

The PSM was performed using age, diagnosis year, location within the pancreas, treatment facility type, cT stage, and cN stage.

Table 1
Cohort Characteristics.

Variable	Total n = 4,599 (percentage)	MAC n = 3,109 (percentage)	MAC + RT n = 1,490 (percentage)	χ^2 P-value
Median Age	64 (IQR 57–70)	64 (IQR 57 – 71)	64 (IQR 57 – 69)	**0.002***
Gender				0.114
Male	2,343 (51)	1,609 (52)	734 (49)	
Female	2,256 (49)	1,500 (48)	756 (51)	
Race				
White	4,040 (88)	2,732 (88)	1,308 (88)	0.173
Black	379 (8)	251 (8)	128 (8)	
Asian	98 (2)	75 (3)	23 (2)	
Other	82 (2)	51 (2)	31 (2)	
Year of Diagnosis			NA	**<0.001**
2006–2011	610 (13)	358 (12)	252 (17)	
2012–2016	3,989 (87)	2,751 (88)	1,238 (83)	
Charleson Deyo Score				0.889
CDS 0	3,093 (67)	2,093 (67)	1,000 (67)	
CDS > 0	1,506 (33)	1,016 (33)	490 (33)	
Clinical T-stage				**<0.001**
cT1-2	1,484 (32)	1,130 (36)	354 (24)	
cT3-4	3,115 (68)	1,979 (64)	1,136 (76)	
Clinical N-stage				**0.010**
cN0	3,218 (70)	2,213 (71)	1,005 (67)	
cN1	1,381 (30)	896 (29)	485 (33)	
Pretreatment CA 19–9				0.668
Within normal limits (≤37 U/mL)	922 (20)	628 (20)	294 (20)	
37.1–89.9 U/mL	386 (8)	255 (8)	131 (9)	
≥90.0 U/mL	1,930 (42)	1,292 (42)	638 (43)	
unknown	1,361 (30)	934 (30)	427 (29)	
Tumor Location within the Pancreas				**<0.001**
Head	3,498 (76)	2,400 (77)	1,098 (74)	
Body	514 (11)	305 (10)	209 (14)	
Tail	247 (5)	182 (6)	65 (4)	
Overlapping/unknown	340 (7)	222 (7)	118 (8)	
Preoperative Radiation Dose and Fractionation				NA
50.4 Gy in 28 fractions	NA	NA	603 (40)	
33 Gy in 5 fractions	NA	NA	110 (7)	
50 Gy in 25 fraction	NA	NA	96 (6)	
Other regimen	NA	NA	681 (46)	
Type of Surgery				0.697
Pancreaticoduodenectomy	3,075 (67)	2,093 (67)	982 (66)	
Partial pancreatectomy +/- duodenectomy	900 (19)	602 (19)	298 (20)	
Total pancreatectomy +/- subtotal gastrectomy or duodenectomy	588 (13)	392 (13)	196 (13)	
Pancreatectomy not otherwise specified	36 (1)	22 (1)	14 (1)	
Treatment Facility				**0.001**
Non-academic Center	1,494 (32)	1,067 (34)	427 (29)	
Academic Center	3,067 (67)	2,016 (65)	1,051 (71)	
Unknown	38 (1)	26 (1)	12 (1)	
Time from starting MAC to Surgery (months)	4.4 (IQR 3.2 – 5.9)	3.7 (IQR 2.8 – 4.9)	5.8 (IQR 4.8 – 7.2)	**<0.001***

* P-value determined via Wilcoxon ranksum test.

1,150 matched pairs were created with no significant difference in the matched covariates between MAC and MAC + RT (Table A1). The surgical outcome differences between MAC and MAC + RT persisted between the PSM cohorts, with significantly improved R0 resection rate, lower ypT and ypN stage, and higher rates of pCR in the matched MAC + RT cohort (Table A2).

Table 3 shows the LR evaluating the association between pre-operative clinical variables and R0 resection. On MVA, receipt of MAC + RT (OR 1.58, 95% CI 1.33–1.89, $P < 0.001$) and evaluation at an academic center (OR 1.33, 95% CI 1.14–1.56, $P < 0.001$) were significantly associated with improved R0 resection and cT3-4 disease was significantly associated with lower odds of R0 resection (OR 0.81, 95% CI 0.68–0.96, $P = 0.013$). The time from the start of MAC to surgery was not associated with improved R0 resection for the MAC cohort or the MAC + RT cohort when analyzed as a continuous variable or stratified by median value (both $P > 0.1$). Additionally, the time from start of MAC to RT was not associated with R0 resection in patients receiving MAC + RT ($P > 0.1$).

The estimated median OS was 29.0 months (95% CI 28.1–30.2). The median survival for patients in the MAC vs. MAC + RT cohorts was 28.4 months (95% CI 27.3–29.8) vs. 30.7 months (95% CI 28.6–32.6), $P = 0.09$. Fig. 2 shows the unadjusted Kaplan-Meier survival estimates for the MAC vs. MAC + RT cohorts. On Cox MVA (Table 4), variables independently associated with survival included age (HR 1.01, 95% CI 1.00–1.01, $P = 0.006$), cN1 disease (HR 1.16, 95% CI 1.05–1.27, $P = 0.002$), CA 19–9 ≥ 90 U/mL (HR 1.16, 95% CI 1.02–1.31, $P = 0.021$), and evaluation at an academic center (HR 0.81, 95% CI 0.73–0.89, $P < 0.001$). There was no difference in survival from time of surgery between MAC vs. MAC + RT ($P = 0.759$).

4. Discussion

The purpose of this study was to evaluate R0 resection rates in patients receiving MAC vs. MAC + RT prior to oncologic resection for localized PDAC utilizing a nationally representative dataset. Despite presenting with more advanced clinical disease, patients receiving MAC + RT had lower postoperative pathologic stage, more frequent pCR, and improved R0 resection rates compared to patients receiving pre-operative MAC alone. These data serve pri-

Table 2
Surgical Outcomes.

Variable	Total n = 4,599 (percentage)	MAC n = 3,109 (percentage)	MAC + RT n = 1,490 (percentage)	χ^2 P-value
Surgical Margin Status				**<0.001**
Negative	3,776 (82)	2,490 (80)	1,286 (86)	
Positive	823 (18)	619 (20)	204 (14)	
Pathologic T stage				**<0.001**
ypT0-2	1,134 (25)	654 (21)	480 (32)	
ypT3-4	3,179 (69)	2,296 (74)	883 (59)	
Unknown	286 (6)	159 (5)	127 (9)	
Pathologic N stage				**<0.001**
ypN0	2,148 (47)	1,248 (40)	900 (60)	
ypN1	2,185 (48)	1,709 (55)	476 (32)	
Unknown	266 (6)	152 (5)	114 (8)	
Pathologic CR				**<0.001**
No pCR	4,156 (90)	2,877 (93)	1,279 (86)	
pCR	138 (3)	60 (2)	78 (5)	
unknown	305 (7)	172 (6)	133 (9)	
Grade				0.693*
Well differentiated	296 (6)	208 (7)	88 (6)	
Moderately differentiated	1,439 (31)	1,044 (34)	395 (27)	
Poorly differentiated	837 (18)	599 (19)	238 (16)	
Unknown	2,027 (44)	1,258 (40)	769 (52)	
LVI				**<0.001***
LVI absent	1,970 (43)	1,297 (42)	671 (45)	
LVI present	1,322 (29)	1,037 (33)	285 (19)	
Unknown	1,309 (28)	775 (25)	534 (36)	

*P-value calculated after excluding unknowns in this category

Table 3
Logistic Regression for Variables Associated with R0 Resection.

Variable	Univariate Odds Ratio (95% CI)	P-value	Multivariable Odds Ratio (95% CI)	P-value
Age (continuous)	1.01 (1.00 – 1.01)	0.112	NA	
Sex				
Male	Reference		Reference	
Female	1.45 (1.24 – 1.68)	**<0.001**	1.43 (1.23 – 1.67)	**<0.001**
Race			NA	
White	Reference			
Black	1.02 (0.78 – 1.35)	0.868		
Asian	0.91 (0.55–1.52)	0.728		
Other	1.78 (0.89 – 3.58)	0.104		
Year of Diagnosis			NA	
2006–2011	Reference			
2012–2016	0.97 (0.78 – 1.22)	0.806		
Charleson Deyo Score			NA	
CDS 0	Reference			
CDS > 0	0.91 (0.77 – 1.06)	0.235		
Clinical T-stage				
cT1-2	Reference		Reference	
cT3-4	0.85 (0.72 – 1.00)	0.053	0.81 (0.68 – 0.96)	**0.013**
Clinical N-stage				
cN0	Reference		Reference	
cN1	0.83 (0.70 – 0.97)	**0.019**	0.85 (0.72 – 1.00)	0.051
Pretreatment CA 19–9				
Within normal limits (≤37 U/mL)	Reference		Reference	
>37 to < 90 U/mL	0.86 (0.63 – 1.17)	0.332	0.85 (0.62 – 1.16)	0.302
>90 U/mL	0.82 (0.67 – 1.02)	0.072	0.82 (0.67 – 1.02)	0.070
unknown	0.86 (0.69 – 1.08)	0.201	0.87 (0.70 – 1.10)	0.243
Treatment Facility				
Non-academic Center	Reference		Reference	
Academic Center	1.35 (1.16 – 1.59)	**<0.001**	1.33 (1.14 – 1.56)	**<0.001**
Unknown	0.99 (0.45 – 2.19)	0.988	0.98 (0.45 – 2.20)	0.979
Pre-operative Treatment				
MAC	Reference		Reference	
MAC + RT	1.57 (1.32 – 1.86)	**<0.001**	1.58 (1.33 – 1.89)	**<0.001**

marily to guide patient selection and pre-operative treatment strategies for patients being evaluated for potentially curative surgical resection for PDAC.

These data may have major clinical implications. In the metastatic and post-operative settings, MAC has demonstrated improved clinical response rates and overall survival when compared to single agent chemotherapy [7,8,28,32]. These data have been extrapolated and routinely incorporated into the pre-operative treatment algorithm for patients with borderline resectable or locally advanced disease as a means of controlling possible occult distant metastatic disease, selecting for favorable tumor biology, and improving opportunities for potentially curative R0 resection [4,33]. We demonstrate that pre-operative MAC offers improved R0 resection rates when compared with historical series

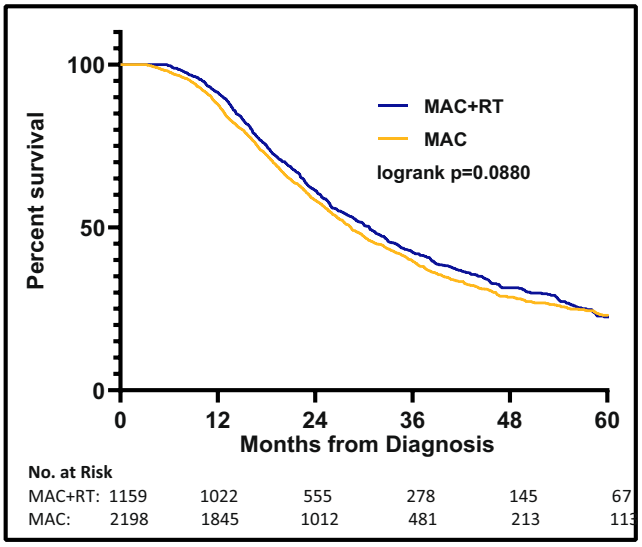

Fig. 2. Kaplan Meier survival estimates stratified by choice of neoadjuvant therapy. MAC: Multiagent chemotherapy. MAC + RT: Multiagent chemotherapy followed by radiotherapy.

[7,8]; however, the addition of RT further improves the R0 resection rate and pathologic down-staging compared to MAC alone [14,16,17]. Our data suggest heterogeneity of treatment effect amongst subgroups, with potential preferential advantages in R0 resection rate for patients with cT3-4 disease treated with MAC + RT. While the NCDB is limited to TNM staging without characterization of surgical resectability status as defined per NCCN criteria, this study's cohort may be reasonably representative of patients with NCCN borderline resectable or locally advanced PDAC as the majority of our cohort had AJCC 6-7th edition cT3 (extrapancreatic extension) and cT4 disease (involvement of local vasculature). Thus, these data suggest the selective utilization of MAC + RT for patients with NCCN borderline resectable and locally advanced disease.

These data compliment prior data evaluating the role of pre-operative CRT or MAC + RT in patients with borderline resectable disease [14,15,17–19,22,23]. A generalized summary is that pre-operative MAC + RT is associated with pathologic tumor down-staging, pathologic LN clearance, pCR rates of 5–15%, and R0 resection rates as high as 93–100% in select series. However, we must acknowledge that 30–60% of patients may not proceed with surgical resection predominately due to interval development of distant metastatic disease. For example, the phase II ALLIANCE A021101 trial investigated a regimen of modified FOLFIRINOX (mFOLFIRINOX) followed by pre-operative conventionally fractionated CRT for a cohort of 22 patients with borderline resectable PDAC. Fifteen patients proceeded to surgery with a high rate of R0 resection (93%) and a 13% pCR rate [18]. These favorable results spurred the randomized phase II ALLIANCE A021501 study which evaluated 8 pre-operative cycles of mFOLFIRINOX vs. 7 cycles of mFOLFIRINOX followed by SBRT. Initial publication is eagerly anticipated, and it should provide further guidance of the optimal pre-operative regimen for patients with borderline resectable PDAC.

Recently, the PREOPANC trial randomized patients with resectable and borderline resectable PDAC to receive either up-front surgery or preoperative gemcitabine-based CRT to a dose of 36 Gy in 15 fractions followed by surgery [14]. The trial found that preoperative CRT was associated with an improved R0 resection rate (71% vs. 40%, $p < 0.001$) and a lower rate of ypN+ (33% vs. 78%, $p < 0.001$). In the predefined subgroup of patients with borderline resectable

Table 4
Cox Regression for Clinical Variables Associated with Overall Survival.

Variable	Univariate Hazard Ratio (95% CI)	P-value	Multivariable Hazard Ratio (95% CI)	P-value
Age (continuous)	1.01 (1.00 – 1.01)	**0.024**	1.01 (1.00 – 1.01)	**0.006**
Sex			NA	
Male	Reference			
Female	0.96 (0.88 – 1.05)	0.333		
Race			NA	
White	Reference			
Black	0.91 (0.77 – 1.08)	0.281		
Asian	0.86 (0.62 – 1.20)	0.380		
Other	0.82 (0.56 – 1.20)	0.310		
Year of Diagnosis			NA	
2006–2011	Reference			
2012–2016	1.06 (0.95 – 1.18)	0.325		
Charleson Deyo Score			NA	
CDS 0	Reference			
CDS > 0	1.04 (0.94 – 1.14)	0.473		
Clinical T-stage				
cT1-2	Reference		Reference	
cT3-4	1.09 (0.99 – 1.20)	0.085	1.10 (0.99 – 1.21)	0.064
Clinical N-stage				
cN0	Reference		Reference	
cN1	1.15 (1.05 – 1.26)	**0.004**	1.16 (1.05 – 1.27)	**0.002**
Pretreatment CA 19–9				
Within normal limits(≤37 U/mL)	Reference		Reference	
>37 to < 90 U/mL	1.13 (0.94 – 1.36)	0.201	1.12 (0.93 – 1.35)	0.215
≥90 U/mL	1.16 (1.02 – 1.31)	**0.022**	1.16 (1.02 – 1.31)	**0.021**
unknown	1.15 (1.01 – 1.31)	**0.040**	1.13 (0.99 – 1.29)	0.062
Treatment Facility				
Non-academic Center	Reference		Reference	
Academic Center	0.81 (0.74 – 0.90)	**<0.001**	0.81 (0.73 – 0.89)	**<0.001**
Unknown	0.96 (0.60 – 1.54)	0.869	1.19 (0.73 – 1.94)	0.484
Pre-operative Treatment			NA	
MAC	Reference		Reference	
MAC + RT	0.92 (0.84 – 1.01)	0.088	0.91 (0.83 – 1.00)	0.061

PDAC, pre-operative CRT was associated with improved OS, disease-free survival, and local failure-free interval. The present study supports the improved R0 resection rate and lymph node clearance with preoperative radiotherapy, though was unable to show a statistically significant improvement in survival. This may be due to differences in the present study including the likely selection biases for MAC vs. MAC + RT, the presence of neoadjuvant MAC in both treatment cohorts, the exclusion of patients who did not undergo curative-intent surgery, and the inability for us to stratify by resectability status due to the lack of coding within the NCDB.

A prior analysis of the NCDB (2004–2013) examined the effect of single-agent or multi-agent chemotherapy and pre-operative CRT on survival and R0 resection rates in patients with resected pancreatic cancer [34]. Contradictory to the present analysis, they were unable to identify a significant difference in R0 resection rates when comparing pre-operative MAC with pre-operative MAC + RT. This alternate outcome may be related to differences in inclusion criteria, since when the present analysis is restricted to overlapping years of diagnosis with the prior study (2006–2013), MAC + RT remains associated with improved R0 resection rates (n = 1,495, R0 rate 87% vs. 80%, P = 0.001). Comparative strengths in the inclusion criteria of the current study include 1) a larger cohort of patients receiving MAC and MAC + RT due to the larger range in years of diagnosis and inclusion of additional histology codes (infiltrating duct carcinoma NOS, infiltrating ductal carcinoma, and mucinous adenocarcinoma), 2) careful selection for receipt of MAC prior to RT utilizing sequencing and timing variables, 3) a refined RT cohort to include only those patients with a clinically reasonable course of pancreas-directed RT, 4) a more contemporary cohort which likely received MAC regimens of mFOLFIRINOX or gemcitabine plus albumin-bound paclitaxel, and 5) exclusion of local excision only, since this would not be classified as a potentially curative oncologic resection.

The present analysis also revealed that female sex and treatment at an academic center were associated with an improved R0 resection rate. Though the literature reveals select studies implicating female sex in the epidemiology of PDAC [35,36], there is no proven association of female sex with disease outcomes, and the result herein should be considered hypothesis-generating. Several prior reports, however, have shown an association of improved outcomes for patients managed with PDAC treated at academic or high volumes centers [37,38] consistent with the present study.

Several limitations should be discussed. First, the NCDB does not record preoperative imaging data or NCCN resectability status, and thus the extent of vessel abutment or encasement and breakdown of resectability status as defined per NCCN criteria is unknown. However, given the advanced clinical T and N stage in the current cohort, it is likely that this study was predominately composed of patients with NCCN borderline resectable and locally advanced PDAC. Second, this analysis only includes patients who were able to eventually undergo curative-intent surgery. It is not possible in the NCDB to determine which patients with localized PDAC who first receive MAC were initially considered for eventual surgery but never underwent it. Therefore, there was an inherent selection bias for patients with more favorable biology and no development of early distant metastasis - a phenomenon known to occur in approximately 15% of patients with resectable disease [10,12,39] and approximately 30–60% of patients with borderline resectable or locally advanced disease [18,40]. Third, the NCDB does record MAC vs single-agent chemotherapy but not the specific chemotherapy agents delivered or the number of cycles administered. The intervals from MAC to surgery and MAC to RT were used as surrogates for chemotherapy duration, though a longer interval may also be related to treatment toxicity and delay. This is important, as there is differential efficacy amongst chemotherapy agents and number of chemotherapy cycles has been associated with outcomes [15]. Fourth, we included a wide range of RT doses and presumably target volumes in an effort to capture all curative intent therapy. Thus, it is unclear which, if any, RT regimen is most beneficial, though this will be a topic of future study. There may be benefit to hypofractionated techniques where there is less delay between MAC and surgery. Fifth, the median number of LN retrieved was less for patients receiving MAC + RT vs. MAC (16 vs. 19, P < 0.001). This may have contributed to the improved ypN0 rate in patients receiving MAC + RT, though it is a known phenomenon that preoperative RT decreases LN yield [41]. Sixth, there was a substantial number of patients who were coded as having unknown grade and LVI status. The reasons for this are unclear, though these numbers were higher in the MAC + RT cohort. When interpreted with the improved tumor downstaging with MAC + RT, it may suggest that response to neoadjuvant therapy may make pathologic determination of grade and LVI more difficult. Finally, comparative effectiveness research performed using large observational registries can be subject to significant bias so these data should be viewed as hypothesis-generating and must be validated in the context of a prospective randomized trial [42].

In conclusion, for patients with localized PDAC who receive pre-operative MAC, the addition of RT prior to surgery was associated with improved rates of R0 resection and lower pathologic stage despite this cohort having more advanced clinical disease. These results suggest continued inclusion of RT in the pre-operative regimen for patients with borderline resectable and locally advanced PDAC being considered for potentially curative resection. Prospective evaluation of the optimal pre-operative regimen for patients with PDAC is warranted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix

Table A1
Propensity-Score-Matched Patient Characteristics.

Variable	Total n = 2,300 (percentage)	MAC n = 1,150 (percentage)	MAC + RT n = 1,150 (percentage)	χ^2 P-value
Median Age	64 (IQR 57–69)	64 (IQR 57 – 70)	63 (IQR 57 – 69)	0.305*
Gender				0.802
Male	1,150 (50)	572 (50)	578 (50)	
Female	1,150 (50)	578 (50)	572 (50)	
Race				

(continued on next page)

Table A1 (*continued*)

Variable	Total n = 2,300 (percentage)	MAC n = 1,150 (percentage)	MAC + RT n = 1,150 (percentage)	χ^2 P-value
White	2,021 (88)	1,008 (88)	1,013 (88)	0.342
Black	190 (8)	97 (8)	93 (8)	
Asian	47 (2)	28 (2)	19 (2)	
Other	42 (2)	17 (2)	25 (2)	
Year of Diagnosis				0.511
2006–2011	499 (22)	256 (22)	243 (21)	
2012–2016	1,801 (78)	894 (78)	907 (79)	
Charleson Deyo Score				0.228
CDS 0	1,559 (68)	793 (69)	766 (67)	
CDS > 0	741 (32)	357 (31)	384 (33)	
Clinical T-stage				0.921
cT1-2	526 (23)	264 (23)	262 (23)	
cT3-4	1,774 (77)	88 (77)	888 (77)	
Clinical N-stage				0.567
cN0	1,523 (66)	755 (66)	768 (67)	
cN1	777 (34)	395 (34)	382 (33)	
Pretreatment CA 19–9				0.460
Within normal limits ($\leq$37 U/mL)	448 (19)	225 (20)	223 (19)	
37.1–89.9 U/mL	201 (9)	106 (9)	95 (8)	
$\geq$90.0 U/mL	957 (42)	461 (40)	496 (43)	
unknown	694 (30)	358 (31)	336 (29)	
Tumor Location within the Pancreas				0.925
Head	1,702 (74)	858 (75)	844 (73)	
Body	315 (14)	153 (13)	162 (14)	
Tail	105 (5)	52 (5)	53 (5)	
Overlapping/unknown	178 (8)	87 (8)	91 (8)	
Type of Surgery				0.863
Pancreaticoduodenectomy	1,524 (66)	756 (66)	768 (67)	
Partial pancreatectomy +/- duodenectomy	457 (20)	235 (20)	222 (19)	
Total pancreatectomy +/- subtotal gastrectomy or duodenectomy	303 (13)	150 (13)	153 (13)	
Pancreatectomy not otherwise specified	16 (1)	9 (1)	87(1)	
Treatment Facility				0.864
Non-academic Center	627 (27)	311 (27)	316 (28)	
Academic Center	1,655 (72)	831 (72)	824 (72)	
Unknown	18 (1)	8 (1)	10 (1)	
Time from starting MAC to Surgery (months)	4.9 (IQR 3.5 – 6.4)	3.7 (IQR 2.8 – 5.1)	5.7 (IQR 4.7 – 7.0)	**<0.001**

Table A2
Propensity-Score-Matched Outcomes.

Variable	Total n = 2,300 (percentage)	MAC n = 1,150 (percentage)	MAC + RT n = 1,150 (percentage)	χ^2 p-value
Median Overall Survival (95% CI)	29.9 (28.3 – 31.0)	28.7 (27.4–30.7)	30.7 (28.2 – 32.6)	0.312*
Surgical Margin Status				**<0.001**
Negative	1,900 (83)	905 (79)	996 (87)	
Positive	400 (17)	245 (21)	155 (13)	
Pathologic T stage				**<0.001**
ypT0-2	598 (26)	242 (21)	356 (31)	
ypT3-4	1,518 (66)	832 (72)	686 (60)	
Unknown	184 (8)	76 (7)	108 (9)	
Pathologic N stage				**<0.001**
ypN0	1,139 (50)	451 (39)	688 (60)	
ypN1	979 (43)	618 (54)	361 (31)	
Unknown	182 (8)	81 (7)	101 (9)	
Pathologic CR				**<0.001**
No pCR	2,025 (88)	1,045 (91)	980 (85)	
pCR	78 (3)	22 (2)	56 (5)	
unknown	197 (9)	83 (7)	114 (10)	
Grade				0.848**
Well differentiated	163 (7)	92 (8)	71 (6)	
Moderately differentiated	689 (30)	372 (32)	317 (28)	
Poorly differentiated	440 (19)	241 (21)	199 (17)	
Unknown	1,008 (44)	445 (39)	563 (49)	
LVI				**<0.001****
LVI absent	968 (42)	461 (40)	507 (44)	
LVI present	575 (25)	363 (32)	212 (18)	
Unknown	757 (33)	326 (28)	431 (37)	

*P-value calculated with the Log Rank test
**P-value calculated after excluding unknowns in this category

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