Disparities in the Use of Neoadjuvant Therapy for Resectable Pancreatic Ductal Adenocarcinoma

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ABSTRACT

Background: Current guidelines support either immediate surgical resection or neoadjuvant therapy (NT) for patients with resectable pancreatic ductal adenocarcinoma (PDAC). However, which patients are selected for NT and whether disparities exist in the use of NT for PDAC are not well understood. **Methods:** Using the National Cancer Database from 2004 through 2016, the clinical, demographic, socioeconomic, and hospital-related characteristics of patients with stage I/II PDAC who underwent immediate surgery versus NT followed by surgery were compared. **Results:** Among 58,124 patients who underwent pancreatectomy, 8,124 (14.0%) received NT whereas 50,000 (86.0%) did not. Use of NT increased significantly throughout the study period (from 3.5% in 2004 to 26.4% in 2016). Multivariable logistic regression analysis showed that travel distance, education level, hospital facility type, clinical T stage, tumor size, and year of diagnosis were associated with increased use of NT, whereas comorbidities, uninsured/Medicaid status, South/West geography, left-sided tumor location, and increasing age were associated with immediate surgery (all $P < .001$). Based on logistic regression–derived interaction factors, the association between NT use and median income, education level, Midwest location, clinical T stage, and clinical N stage significantly increased over time (all $P < .01$). **Conclusions:** In addition to traditional clinicopathologic factors, several demographic, socioeconomic, and hospital-related factors are associated with use of NT for PDAC. Because NT is used increasingly for PDAC, efforts to reduce disparities will be critical in improving outcomes for all patients with pancreatic cancer.

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Background

Pancreatic ductal adenocarcinoma (PDAC) is the third most common cause of cancer-related death in the United States and long-term outcomes remain dismal, with a 5-year overall survival rate of 9%.¹ The incidence of PDAC is increasing, and it is expected to become the second most common cause of cancer-related mortality over the next few decades. Although surgical resection of localized pancreatic cancers is necessary for curative-intent treatment, most patients will develop recurrent disease. Although adjuvant chemotherapy improves survival for all patients with resected PDAC,^{2,3} up to 50% of patients will not initiate postoperative chemotherapy, typically because of poor performance status after major surgery.^{4–6} A greater number of patients will be unable to complete the intended course of adjuvant therapy for similar reasons.^{7,8}

The administration of chemotherapy with or without radiation therapy (RT) before surgical resection is an alternative strategy that ensures its early and near universal delivery. Neoadjuvant therapy (NT) offers several other theoretical benefits including improved margin-negative resection rates, decreased lymph node positivity, early treatment of presumed micrometastatic disease, and the ability to measure in vivo response to therapy histologically after resection.^{9–14} In addition, evidence of improved survival with this approach has been supported by results from large cancer databases,¹² meta-analyses of nonrandomized trials,^{15–17} Markov decision analysis models,^{18,19} and randomized controlled trials.^{20,21}

Based on this evidence, recent practice guidelines have recognized use of NT as the preferred treatment strategy for patients with borderline resectable cancer and as an acceptable treatment option for patients with potentially resectable cancer.^{22,23} Nevertheless, although NT has become the preferred treatment strategy at some high-volume referral centers in the United States, its

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overall use for patients with PDAC is low. Indeed, which patients are selected for NT and whether disparities exist in the use of NT for PDAC are not well understood. Therefore, the objective of this study was to examine trends in the indications for NT among patients with resectable PDAC using a population-based approach.

Methods

We performed a retrospective review of adult patients from the National Cancer Database (NCDB) from 2004 through 2016. The NCDB is a national cancer registry that includes data from more than 1,500 Commission on Cancer-accredited facilities. Jointly sponsored by the American College of Surgeons and American Cancer Society, it currently captures more than 70% of newly diagnosed cancers within the United States. Relevant patient characteristics, tumor staging, type of initial treatment provided, and long-term survival outcomes are recorded by trained registrars according to nationally standardized coding definitions.^{24,25} For the purposes of this study, the most currently available participant use file containing data from 2004 through 2016 was used. All patients with stage I–II PDAC who underwent pancreatectomy were included. Patients with clinical T4 lesions and those with unknown treatment sequencing status were excluded. NT was defined as receipt of chemotherapy or RT before curative-intent surgical resection.

Demographic, socioeconomic, treatment facility, clinical, and treatment-related variables were abstracted from the NCDB. The Charlson-Deyo score was used to categorize comorbidities. Travel distance, median income, and percentage of individuals without a high school degree were recorded based on the county of residence and reported as quartiles. Region was defined as metropolitan, urban, or rural, whereas geography was defined as East, West, South, or Midwest. Tumor, including clinical and pathologic TNM stages as defined by the AJCC, and treatment-related factors were also abstracted.

Demographic, socioeconomic, clinical, and histopathologic factors of patients who underwent immediate surgery were compared with those of patients who received NT before surgery. Continuous variables were compared using *t* test, whereas categorical variables were compared using the chi-square test. Univariable logistic regressions were performed to assess for factors independently associated with NT. Multivariable logistic regression was performed using clinically relevant factors and those significantly related to NT on the univariate regressions. Finally, changes in the impact of predictive clinicopathologic factors and receipt of NT over time were measured. Candidate variables were assessed by measuring interaction factors with time using logistic regression. The changing relationship with NT use over

time among the variables with statistically significant interaction factors was then further investigated by measuring the odds ratio (OR) and confidence interval at each time point during the study period. Statistical significance was set at 2-sided $\alpha < 0.05$. All statistical analyses were performed using STATA, version 15.1 (StataCorp LLC)

Results

Among 58,124 patients who underwent pancreatectomy in the NCDB from 2004 through 2016, 8,124 (14.0%) received NT and 50,000 (86.0%) did not. NT consisted of chemotherapy alone (51.3%), chemotherapy and RT (46.7%), or RT alone (2.1%). Use of NT increased significantly throughout the study period (from 3.5% in 2004 to 26.4% in 2016), primarily related to increases in the percentage of patients who received chemotherapy alone (from 0.6% in 2004 to 17.9% in 2016) (Figure 1).

Characteristics of patients undergoing immediate surgery versus NT followed by surgery are reported in Table 1. Statistically significant differences were observed in most variables, partly due to the large sample size. In general, patients who received NT were younger (mean age, 64.08 ± 9.70 vs 66.68 ± 10.55 years), had greater travel distance (>38.8 miles: 34.0% vs 26.8%), were more likely to have private insurance (44.4% vs 35.6%), and had received care at an academic/research facility (65.6% vs 54.1%). They were also more likely to have more advanced clinical stage disease (cT3: 55.8% vs 27.6%; cN1: 27.5% vs 17.4%) and larger tumors (mean 2.6 ± 4.1 vs 1.5 ± 3.1 cm) but less likely to have left-sided tumors requiring distal pancreatectomy (9.7% vs 15.1%).

Table 2 reports the results of multivariable logistic regression of factors independently associated with NT use. Increasing travel distance, higher education level, hospital facility type (ie, academic/research facility or an integrated network cancer program compared with a community cancer program), higher clinical T stage, larger tumor size, and more recent year of diagnosis were

Figure 1. Trends in the percentage of patients with stage I–II resected pancreatic cancer who received NT before surgery. Abbreviations: NT, neoadjuvant therapy; RT, radiation therapy.

Table 1. Characteristics of Patients Undergoing Immediate Surgery Versus NT and Surgery

	Immediate Surgery n (%)	NT n (%)	P Value
Total, n	50,000	8,124	
Age, mean (SD), y	66.68 (10.55)	64.08 (9.70)	<.001
Sex			.31
Male	25,447 (50.9%)	4,184 (51.5%)	
Female	24,553 (49.1%)	3,940 (48.5%)	
Race			<.001
White	42,881 (85.8%)	7,087 (87.2%)	
Black	4,845 (9.7%)	738 (9.1%)	
Other ^a	2,274 (4.5%)	299 (3.7%)	
Charlson-Deyo score			<.001
0	32,457 (64.9%)	5,454 (67.1%)	
1	13,147 (26.3%)	2,051 (25.2%)	
2	3,142 (6.3%)	444 (5.5%)	
≥3	1,254 (2.5%)	175 (2.2%)	
Travel distance, miles			≤.001
≤5.5	11,212 (22.5%)	1,321 (16.3%)	
>5.5–13.6	12,136 (24.3%)	1,782 (22.0%)	
>13.6–38.8	13,153 (26.4%)	2,242 (27.7%)	
>38.8	13,339 (26.8%)	2,755 (34.0%)	
Insurance status			<.001
Not insured	1,200 (2.4%)	124 (1.5%)	
Private	17,787 (35.6%)	3,603 (44.4%)	
Medicaid	2,240 (4.5%)	346 (4.3%)	
Medicare	27,428 (54.9%)	3,727 (45.9%)	
Other government	570 (1.1%)	114 (1.4%)	
Unknown	775 (1.6%)	210 (2.6%)	
Median income, \$USD			<.001
<\$38,000	8,089 (16.2%)	1,138 (14.1%)	
\$38,000–\$47,999	11,219 (22.5%)	1,896 (23.4%)	
\$48,000–\$62,999	13,201 (26.5%)	2,268 (28.0%)	
≥\$63,000	17,281 (34.7%)	2,790 (34.5%)	
% No high school degree			<.001
≥21.0%	7,627 (15.3%)	980 (12.1%)	
13.0%–20.9%	12,789 (25.7%)	1,909 (23.6%)	
7.0%–12.9%	16,445 (33.0%)	2,884 (35.6%)	
<7.0%	12,950 (26.0%)	2,323 (28.7%)	
Region			.002
Metropolitan	39,908 (82.1%)	6,359 (80.4%)	
Urban	7,691 (15.8%)	1,369 (17.3%)	
Rural	1,021 (2.1%)	179 (2.3%)	
Facility type			<.001
Community cancer program	15,964 (32.2%)	1,822 (22.6%)	
Academic/Research program	26,803 (54.1%)	5,279 (65.6%)	
Integrated network cancer program	6,792 (13.7%)	949 (11.8%)	

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Table 1. Characteristics of Patients Undergoing Immediate Surgery Versus NT and Surgery (cont.)

	Immediate Surgery n (%)	NT n (%)	P Value
Geography			<.001
East	11,017 (22.2%)	2,004 (24.9%)	
South	18,645 (37.6%)	2,781 (34.5%)	
Midwest	12,604 (25.4%)	2,273 (28.2%)	
West	7,293 (14.7%)	992 (12.3%)	
AJCC clinical T stage			<.001
cT1	5,500 (11.4%)	545 (6.8%)	
cT2	12,667 (26.2%)	2,390 (29.8%)	
cT3	13,356 (27.6%)	4,477 (55.8%)	
cTx	16,794 (34.7%)	608 (7.6%)	
AJCC clinical N stage			<.001
cN0	26,182 (54.0%)	5,235 (65.3%)	
cN1	8,442 (17.4%)	2,208 (27.5%)	
cNx	13,869 (28.6%)	577 (7.2%)	
Size of tumor, mean (SD), cm	1.5 (3.1)	2.6 (4.1)	<.001
Lymphovascular invasion			<.001
Not present	13,105 (43.1%)	3,087 (45.7%)	
Present	13,638 (44.8%)	1,945 (28.8%)	
Unknown	3,690 (12.1%)	1,717 (25.4%)	
Grade			<.001
Well-differentiated	4,910 (10.6%)	572 (11.4%)	
Moderately differentiated	24,111 (52.1%)	2,733 (54.5%)	
Poorly differentiated	17,295 (37.3%)	1,711 (34.1%)	
Surgery			<.001
Pancreatoduodenectomy	34,864 (69.7%)	5,957 (73.3%)	
Distal pancreatectomy	7,547 (15.1%)	784 (9.7%)	
Total pancreatectomy	6,200 (12.4%)	1,070 (13.2%)	
Other/Unknown	1,389 (2.8%)	313 (3.9%)	
Surgical approach			<.001
Unknown	5,083 (16.7%)	1,243 (18.4%)	
Minimally invasive	5,519 (18.1%)	1,096 (16.2%)	
Open	19,835 (65.2%)	4,410 (65.3%)	

Abbreviation: NT, neoadjuvant therapy.

^aIncluding nonwhite/black.

all associated with an increased use of NT (all $P<.001$). In addition, higher comorbidities, uninsured/Medicaid status, South/West geography (vs East), left-sided tumor location, and increasing age were inversely associated with NT.

Changes in association with NT use over time were assessed via logistic regression interaction factors (supplemental eFigure 1, available with this article at JNCCN.org). The association between NT use and yearly median income ($\geq \$63,000$: OR, 1.03; 95% CI, 1.01–1.06; $P<.01$), education level ($<7\%$ without high school degree: OR,

1.04; 95% CI, 1.02–1.07; $P<.01$), Midwest location (OR, 1.04; 95% CI, 1.02–1.07; $P<.01$), clinical T stage (cT3: OR, 1.05; 95% CI, 1.02–1.09; $P<.01$), and clinical N stage (cN1: OR, 1.06; 95% CI, 1.04–1.08; $P<.01$) significantly increased over time, whereas tumor size (OR, 0.99; 95% CI, 0.99–0.99; $P<.001$) decreased. The changing ORs of these factors over time are displayed in Figure 2.

Discussion

An increasing body of literature supports the use of NT in the management of localized PDAC given its

Table 2. Multivariable Logistic Regression for Receipt of Neoadjuvant Therapy Before Surgical Resection

	OR	95% CI	P Value
Age	0.97	0.97–0.97	<.001
Sex			
Male	Ref		
Female	1.04	0.98–1.09	.19
Race			
White	Ref		
Black	0.97	0.90–1.08	.77
Other ^a	0.79	0.69–0.91	.001
Charlson-Deyo score			
0	Ref		
1	0.97	0.91–1.03	.29
2	0.89	0.80–1.00	.05
≥3	0.81	0.68–0.96	.02
Travel distance, miles			
≤5.5	Ref		
>5.5–13.6	1.17	1.08–1.27	<.001
>13.6–38.8	1.25	1.15–1.35	<.001
>38.8	1.47	1.35–1.61	<.001
Insurance status			
Private	Ref		
Not insured	0.55	0.44–0.67	<.001
Medicaid	0.73	0.64–0.84	<.001
Medicare	0.94	0.88–1.09	.08
Other government	1.06	0.85–1.33	.61
Unknown	1.71	1.41–2.07	<.001
Median income, \$USD			
<\$38,000	Ref		
\$38,000–\$47,999	1.07	0.98–1.18	.14
\$48,000–\$62,999	1.01	0.91–1.11	.91
≥\$63,000	0.83	0.74–0.93	.001
% No high school degree			
≥21.0%	Ref		
13.0%–20.9%	1.14	1.04–1.25	.01
7.0%–12.9%	1.40	1.27–1.55	<.001
<7.0%	1.60	1.43–1.79	<.001
Region			
Metropolitan	Ref		
Urban	1.00	0.92–1.08	.99
Rural	1.04	0.87–1.25	.68
Facility type			
Community cancer program	Ref		
Academic/Research program	1.51	1.42–1.62	<.001
Integrated network cancer program	1.21	1.11–1.33	<.001

(continued)

Table 2. Multivariable Logistic Regression for Receipt of Neoadjuvant Therapy Before Surgical Resection (cont.)

	OR	95% CI	P Value
Geography			
East	Ref		
South	0.79	0.74–0.85	<.001
Midwest	0.94	0.87–1.01	.08
West	0.77	0.70–0.84	<.001
AJCC clinical T stage			
cT1	Ref		
cT2	2.01	1.82–2.23	<.001
cT3	3.69	3.34–4.09	<.001
cTx	0.55	0.47–0.63	<.001
AJCC clinical N stage			
cN0	Ref		
cN1	0.99	0.93–1.05	.65
cNx	0.98	0.86–1.10	.69
Size of tumor	1.00	1.00–1.00	<.001
Surgery			
Pancreatoduodenectomy	Ref		
Distal pancreatectomy	0.59	0.54–0.64	<.001
Total pancreatectomy	1.07	0.99–1.15	.11
Other/Unknown	1.31	0.13–1.52	<.001
Year of diagnosis	1.16	1.15–1.17	<.001

Abbreviation: OR, odds ratio.

^aIncluding nonwhite/black.

association with improved margin- and lymph node-negative resection rates, the opportunity to ensure near-universal receipt of nonsurgical therapies, and the early prioritization of systemic therapy for a primarily systemic disease. Nevertheless, little research has explored the characteristics of patients who receive NT from a population-based perspective. Results of our study highlight several important findings. First, the proportion of patients receiving NT before surgical resection is increasing rapidly, and is primarily driven by those who receive systemic chemotherapy alone. Second, in addition to traditional clinicopathologic factors, several demographic, socioeconomic, and hospital-related factors are associated with use of NT for PDAC, suggesting the possibility of health-related disparities in receipt of this treatment approach. Third, the strength of the association between NT and time has been increasing among those with higher median incomes and education levels and those with more advanced T and N stage tumors.

Previous population-based analyses investigating trends in the use of NT for PDAC have shown increases,

Figure 2. Trends in the calculated ORs of each factor's association with neoadjuvant therapy over time: (A) median income (baseline, <\$38,000), (B) education level (baseline, ≥21.0% with no high school degree), (C) geographic location (baseline, East), (D) clinical T stage (baseline, cT1), (E) clinical N stage (baseline, cN0), and (F) tumor size (for a 10-cm tumor). Abbreviation: OR, odds ratio.

but its overall use in the United States has remained low (<20%).^{10,26} Our study using the most contemporary data from the NCDB shows that these trends have continued, with approximately 26% of patients with resected PDAC having received NT in 2016. Despite these trends, these low rates remain in stark contrast to the routine use of NT in other cancers to improve overall survival,²⁷ margin-negative resection rates,²⁸ and local recurrence,²⁹ or to facilitate less invasive surgery.³⁰ Although an ongoing

evolution of practice changes will be expected as evidence supporting the efficacy of NT accumulates, further investigation into the reasons for the relatively low use rates of NT observed in PDAC would be indicated.

Few studies have previously investigated which patients are selected to receive NT. Some studies have found that younger patient age is associated with receipt of NT.^{10,26} Our study confirms this association but also notes that patients with a greater number of

comorbidities, without private insurance, who live in counties with lower median incomes and education levels, or are treated at community cancer programs were less likely to receive NT. These findings are similar to those of recent studies highlighting the existence of disparities in receipt of chemotherapy after pancreatectomy based on age, race, insurance coverage, and socioeconomic status.^{4,31–33} The finding that increased travel distance was independently associated with greater use of NT was unexpected, and may reflect that patients who are able and willing to travel long distances to high-volume referral centers are subsequently more likely to be treated with NT.^{34,35} By evaluating the interaction between NT use, time, and covariates, our findings indicate that some disparities in NT use, namely based on socioeconomic status and geographic location, may be worsening over time.

Identifying which factors are associated with the receipt of NT is important for identifying disparities in the multidisciplinary care of patients with PDAC. Highlighting these disparities could lead to interventions that increase NT use rates. For example, early evidence suggests improved oncologic outcomes among hospitals that are high users of NT³⁶; therefore, providing feedback to low-use hospitals could represent an opportunity for quality improvement. Ensuring adequate access for all patients to facilities that provide NT is equally important. Finally, initiatives that educate patients and providers about the potential advantages and disadvantages of NT for PDAC should be emphasized.

Little is known about how treatment decision-making occurs for patients with resectable PDAC and whether specific barriers to the use of NT exist. Further data on patient and physician preferences and the patient experience during NT may highlight opportunities to improve shared decision-making and allocate necessary resources before and during treatment. One potential barrier to the use of NT is concerns regarding treatment toxicities that may preclude the eventual receipt of surgery. Although previous studies have reported the dropout rate during NT due to worsening performance status to be extremely low,^{37,38} these concerns may be amplified at lower-volume hospitals that may not have the necessary resources to manage toxicities associated with NT, instead opting to select patients for immediate surgery. As use of more-intense chemotherapy regimens (eg, mFOLFIRINOX) in NT increases, these disparities could worsen. Additional research is needed into potential barriers and facilitators to ensure that all patients have access to multimodality therapy for PDAC.

Although our study represents one of the first efforts to specifically evaluate the characteristics of patients receiving NT for PDAC using a population-based approach, the findings should be interpreted within the context of its limitations. First, given the retrospective nature of the study and the inclusion of only patients with resected PDACs, we were unable to identify and include patients who received NT with a curative intent but ultimately did not undergo surgery. Although prior studies have suggested this occurs relatively infrequently among patients with resectable cancers,³⁷ this omission may bias the results in unpredictable ways. Second, we included patients with stage I and II cancers as a surrogate for resectable disease because the NCDB does not currently include data on anatomic staging classification systems. Similarly, we chose to exclude patients with stage III cancers to minimize the selection bias of patients with borderline resectable or locally advanced cancers that were treated with NT and successfully resected. Third, although the NCDB contains comprehensive demographic, socioeconomic, clinical, and treatment-related information, some data that could potentially influence the decision to administer NT (eg, CA 19-9 levels) and specific information on NT used (eg, chemotherapy regimen, RT modality) are not available.

Conclusions

In this contemporary population-based cancer registry, the use of NT for localized PDAC is increasing, primarily due to increases in the use of chemotherapy alone without RT before pancreatectomy. In addition to traditional clinicopathologic factors, several demographic, socioeconomic, and hospital-related factors are associated with the use of NT for PDAC, and the strength of some of these associations is increasing over time. Because NT is used increasingly for PDAC, efforts to reduce disparities will be critical to improving the outcomes of all patients with pancreatic cancer.

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Disparities in the Use of Neoadjuvant Therapy for Resectable Pancreatic Ductal Adenocarcinoma

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eFigure 1: Forest Plot of Interaction Factors Demonstrating Weight of Association With Neoadjuvant Therapy Use Over Time

eFigure 1. Forest plot of interaction factors demonstrating weight of association with neoadjuvant therapy use over time.