Sociodemographic Disparities in the Receipt of Adjuvant Chemotherapy Among Patients With Resected Stage I–III Pancreatic Adenocarcinoma

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ABSTRACT

Background: Adjuvant therapy for resected pancreatic adenocarcinoma was given a category 1 NCCN recommendation in 2000, yet many patients do not receive chemotherapy after definitive surgery. Whether sociodemographic disparities exist for receipt of adjuvant chemotherapy is poorly understood. **Methods:** The National Cancer Database was used to identify patients diagnosed with nonmetastatic pancreatic adenocarcinoma who underwent definitive surgery from 2004 through 2015. Multivariable logistic regression defined the adjusted odds ratio (aOR) and associated 95% CI of receipt of adjuvant chemotherapy. Among patients receiving chemotherapy, multivariable logistic regression assessed the odds of treatment with multiagent chemotherapy. **Results:** Among 18,463 patients, 11,288 (61.1%) received any adjuvant chemotherapy. Sociodemographic factors inversely associated with receipt of any adjuvant chemotherapy included uninsured status (aOR, 0.61; 95% CI, 0.50–0.74), Medicaid insurance (aOR, 0.66; 95% CI, 0.57–0.77), and lower income ($P<.001$ for all income levels compared with ≥$46,000). Black race (aOR, 0.72; 95% CI, 0.57–0.90) and female sex (aOR, 0.75; 95% CI, 0.65–0.86) were associated with lower odds of receiving multiagent chemotherapy. There was a statistically significant interaction term between black race and age/comorbidity status ($P=.03$), such that 26.4% of black versus 35.8% of nonblack young (aged ≤65 years) and healthy (Charlson-Deyo comorbidity score 0) patients received multiagent adjuvant chemotherapy ($P=.006$), whereas multiagent adjuvant chemotherapy rates were similar among patients who were not young and healthy ($P=.15$). **Conclusions:** In this nationally representative study, receipt of adjuvant chemotherapy appeared to be associated with sociodemographic characteristics, independent of clinical factors. Sociodemographic differences in receipt of adjuvant chemotherapy may represent a missed opportunity for improving outcomes and a driver of oncologic disparities.

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Background

Multiple randomized trials have shown improved survival with the addition of adjuvant chemotherapy after surgical resection for patients with pancreatic adenocarcinoma.[1–5] In 2000, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pancreatic Adenocarcinoma recommended 5-FU–based chemoradiation for all resected tumors based on data from a study performed by the Gastrointestinal Tumor Study Group,[6,7] and after publication of results from the CONKO-001 trial in 2007, gemcitabine monotherapy became a standard adjuvant treatment for resected pancreatic cancer.[5,8] More recent trials, including ESPAC-4[3] and PRODIGE 24,[1] which compared adjuvant gemcitabine versus modified FOLFIRINOX (mFOLFIRINOX; fluorouracil/leucovorin/irinotecan/oxaliplatin), have shown a survival benefit with multiagent versus single-agent chemotherapy. According to current NCCN Guidelines, gemcitabine + capecitabine, mFOLFIRINOX, gemcitabine monotherapy, and 5-FU/leucovorin are all category 1 recommendations for adjuvant therapy.[9]

Despite these consensus recommendations, studies have shown that, outside of the clinical trial setting, many patients do not go on to receive adjuvant chemotherapy.[10–13] Variables shown to affect the delivery of postoperative chemotherapy include clinical factors, such as patient age, extent of postoperative complications, and presence of lymph node metastases.[10–13] In contrast, sociodemographic characteristics influencing receipt of adjuvant chemotherapy remain undefined, and the extent of these disparities in routine practice is unknown.

Given the increasingly apparent benefit of chemotherapy in resected pancreatic cancer, we sought to examine the patterns of adjuvant chemotherapy by sociodemographic characteristics in a comprehensive

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national database including patients with stage I–III pancreatic adenocarcinoma undergoing definitive surgical resection.

Methods

Study Cohort

The National Cancer Database (NCDB) captures 70% of incident cancers in the United States treated at American College of Surgeons' Commission on Cancer–accredited programs and was used to identify patients diagnosed with pathologic stage I–III pancreatic adenocarcinoma who underwent definitive surgery, defined as partial or total pancreatectomy, from 2004 through 2015. Patients who underwent local tumor excision only, had no surgery, or had an unknown surgery type were excluded. Only patients receiving all of the first course of treatment or for whom a decision was made not to treat at the reporting facility were included. Patients whose first cancer diagnosis was not pancreatic adenocarcinoma were excluded. In addition, patients surviving <60 days after surgery and those with unknown insurance status, race, cancer stage, income level, or treating facility type were also excluded.

Chemotherapy

Patients were categorized as receiving no chemotherapy, any adjuvant chemotherapy (including both single-agent and multiagent chemotherapy), or multiagent chemotherapy. Those who received any chemotherapy before surgery, those with chemotherapy status unknown, those with chemotherapy and surgery sequence unknown, and those who did not receive chemotherapy because they were diagnosed at autopsy or had died before receipt of recommended therapy were excluded. Adjuvant chemotherapy was defined as chemotherapy delivered within 12 weeks after surgery, as per NCCN Guidelines.[9] Among patients who did not receive adjuvant chemotherapy, whether they refused treatment was recorded. This outcome is described in the NCDB data dictionary as, "Chemotherapy was not administered. It was recommended by the patient's physician, but this treatment was refused by the patient, a patient's family member, or the patient's guardian. The refusal was noted in patient record."[14]

Statistical Analysis

Receipt of Any Adjuvant Chemotherapy

The primary endpoint of interest was receipt of any adjuvant chemotherapy (single-agent or multiagent). Multivariable logistic regression defined the adjusted odds ratio (aOR) of receipt of adjuvant chemotherapy (yes vs no) by race (white [ref], black, Asian, other/unknown), age (continuous), sex (male [ref], female), pathologic cancer stage (I [ref], II, III), Charlson-Deyo comorbidity score (0 [ref], 1, 2, 3), facility type (academic/research center [ref], community cancer program, comprehensive community cancer program, integrated network cancer program), insurance type (private insurance/managed care [ref], uninsured, Medicaid, Medicare, other government), median annual household income (≥$46,000 [ref], $35,000–$45,999, $30,000–$34,999, <$30,000), readmission within 30 days of surgery (no [ref], yes), and treatment era (2004–2006 [ref], 2007–2009, 2010–2012, 2013–2015). The Charlson-Deyo comorbidity index is the most widely used measure of comorbidity and was developed to predict 1-year mortality based on 22 conditions, such as heart disease, AIDS, and diabetes. Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. Scores are summed to provide a total score to predict mortality.[15] Given that major cancer organizations have sought to reduce disparities by increasing access to academic centers,[16–18] among other strategies, the multivariable model was repeated, restricted to patients treated at academic/research centers, to assess whether similar disparities existed among this subgroup. Fisher exact test was used to compare the proportion of patients receiving adjuvant chemotherapy by patient characteristic.

Receipt of Multiagent Versus Single-Agent Adjuvant Chemotherapy

Among patients receiving adjuvant chemotherapy, multivariable logistic regression defined the aOR of receipt of multiagent versus single-agent chemotherapy using the same variables as earlier. Similarly, the multivariable model was repeated, restricted to patients treated at academic/research centers.

Furthermore, a separate model including an interaction term between race (black vs nonblack) and comorbidity status (young and healthy vs not young and healthy) was assessed to determine whether disparities in receipt of multiagent chemotherapy by race varied according to age and overall health status. For this model, young and healthy patients included those aged ≤65 years with a Charlson-Deyo comorbidity score of 0; patients aged ≤65 years and with a Charlson-Deyo comorbidity score of 1 to 3 and those aged >65 years old, regardless of comorbidity score, were categorized as not young and healthy. Fisher exact test was used to compare the proportion of patients receiving multiagent adjuvant chemotherapy by patient characteristic. Notably, multiagent chemotherapy was not an NCCN category 1 treatment recommendation until results of the ESPAC-4 trial were published in 2017; however, based on randomized data published in 2011 showing a

survival advantage associated with FOLFIRINOX versus single-agent gemcitabine in the treatment of metastatic disease,[19] many centers also began adopting multiagent chemotherapy in the definitive postoperative setting.[20] Therefore, analyses for multiagent chemotherapy were restricted to patients treated from 2011 through 2015.

Refusal of Chemotherapy

Among patients who did not receive any adjuvant chemotherapy, the proportion who refused treatment was assessed. Multivariable logistic regression defined the aOR of refusing chemotherapy using the same variables as earlier.

For each model, predicted margins were calculated to show prevalence standardized to distribution of the model covariates. Statistical testing was 2-sided, with $\alpha=0.05$. Data were analyzed using STATA, version 15.1 (StataCorp). The study was deemed exempt from review by the University of Texas Southwestern Medical Center Institutional Review Board.

Results

Baseline Characteristics

A total of 18,463 patients met study inclusion criteria (Figure 1). Median age of the cohort was 66 years; 85.7% were white; 65.5% had a comorbidity score of 0; 84.0% had stage II disease; 57.3% were treated at academic/research centers; and most had private insurance (39.3%) or were covered by Medicaid (52.0%) (Table 1).

Receipt of Any Adjuvant Chemotherapy

A total of 11,288 patients (61.1%) received any adjuvant chemotherapy. Sociodemographic factors inversely associated with receipt of any adjuvant chemotherapy included treatment at an integrated network cancer program (aOR, 0.83 vs academic/research center; 95% CI, 0.75–0.91), uninsured status (aOR, 0.61 vs private insurance/managed care; 95% CI, 0.50–0.74), Medicaid insurance coverage (aOR, 0.66 vs private insurance/managed care; 95% CI, 0.57–0.77), and lower income ($P<.001$ for all income levels vs ≥$46,000) (Table 2). For example, 51.4% of uninsured patients received chemotherapy compared with 62.3% of those with private insurance/managed care ($P<.001$), and 65.5% of patients in the highest income quartile (≥$46,000) received any adjuvant chemotherapy compared with 54.4% in the lowest income quartile (<$30,000; $P<.001$). Clinical factors positively associated with receipt of adjuvant chemotherapy included advanced stage; in contrast, older age, higher Charlson-Deyo comorbidity score, and readmission within 30 days of surgery were inversely associated with receipt of any adjuvant chemotherapy ($P<.001$ for all). Among patients treated at academic centers, uninsured status ($P<.001$), Medicaid insurance ($P=.001$), and lower income ($P<.001$) remained negatively associated with receipt of any adjuvant chemotherapy

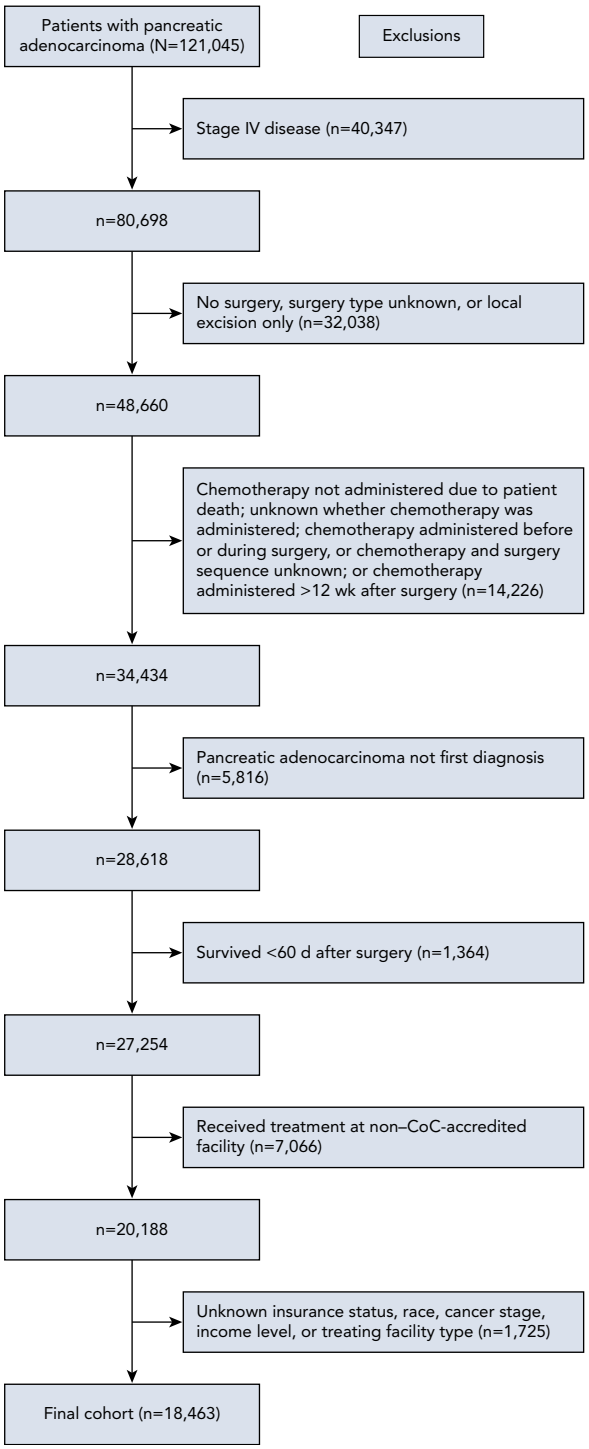

Figure 1. Patient selection process.
Abbreviation: CoC, American College of Surgeons' Commission on Cancer.

(supplemental eTable 1, available with this article at JNCCN.org).

Receipt of Multiagent Versus Single-Agent Adjuvant Chemotherapy

Among 10,600 patients receiving chemotherapy for whom the number of agents was recorded, 3,316 (31.3%) were treated with multiagent chemotherapy. Among patients receiving adjuvant chemotherapy, sociodemographic factors inversely associated with receipt of multiagent chemotherapy included black race (aOR, 0.72 vs white race; 95% CI, 0.57–0.90), female sex (aOR, 0.75 vs male sex; 95% CI, 0.65–0.86), and uninsured status (aOR, 0.61 vs having private insurance/manged care; 95% CI, 0.40–0.95) (Table 2). For example, 23.7% of black patients received multiagent chemotherapy compared with 30.1% of white patients ($P<.001$), and 26.3% of women received multiagent chemotherapy compared with 32.0% of men ($P<.001$). Clinical factors positively associated with receipt of multiagent chemotherapy included advanced cancer stage; in contrast, female sex, older age, and higher Charlson-Deyo comorbidity score were negatively associated with receipt of multiagent chemotherapy ($P<.001$ for all).

Furthermore, there was a statistically significant interaction term between black race and age/comorbidity status ($P=.03$), such that the association between black race and receipt of multiagent adjuvant chemotherapy was observed only for young and healthy patients (aOR, 0.67; 95% CI, 0.52–0.86) and not for black patients who were not young and healthy (aOR, 0.88; 95% CI, 0.73–1.07). Among young and healthy patients, the percentage of black versus nonblack patients receiving multiagent adjuvant chemotherapy was 26.4% versus 35.8%, respectively ($P=.006$). Among patients who were not young and healthy, the percentage of black versus nonblack patients receiving multiagent adjuvant chemotherapy was similar (22.3% vs 26.2%, respectively; $P=.15$). Among patients treated at academic facilities, black race ($P=.046$), female sex ($P=.002$), and uninsured status ($P=.008$) remained negatively associated with receipt of multiagent chemotherapy (supplemental eTable 1).

Refusal of Chemotherapy

Among 7,175 patients who did not receive chemotherapy, 880 (12.3%) patients were recorded as refusing chemotherapy. Female sex (aOR, 1.19; 95% CI, 1.03–1.39) and more recent treatment era ($P<.001$) were associated with increased odds of refusing chemotherapy (Table 3). Notably, race, insurance type, and income level were not associated with treatment refusal. Clinical factors associated with greater odds of refusal were increasing age

Table 1. Baseline Patient Characteristics

Characteristic	n (%)
Total, N	18,463
Age, median (IQR), y	66 (58–74)
Race	
White	15,821 (85.7)
Black	2,044 (11.1)
Asian	437 (2.4)
Other	161 (0.9)
Sex	
Male	9,332 (50.4)
Female	9,131 (49.5)
Charlson-Deyo comorbidity score	
0	12,092 (65.5)
1	4,973 (26.9)
2	1,041 (5.6)
3	357 (1.9)
Cancer stage	
I	2,367 (12.8)
II	15,514 (84.0)
III	582 (3.2)
Readmission within 30 d of surgery	
No	17,066 (92.4)
Yes	1,397 (7.6)
Insurance type	
Private insurance/managed care	7,256 (39.3)
Uninsured	529 (2.9)
Medicaid	877 (4.8)
Medicare	9,610 (52.0)
Other government	191 (1.0)
Income level	
≥$46,000	7,773 (42.1)
$35,000–$45,999	5,069 (27.5)
$30,000–$34,999	3,250 (17.6)
<$30,000	2,371 (12.8)
Facility type	
Academic/Research center	10,586 (57.3)
Community cancer program	566 (3.1)
Comprehensive community cancer program	5,033 (27.3)
Integrated network cancer program	2,278 (12.3)
Treatment era	
2004–2006	4,663 (25.3)
2007–2009	5,336 (28.9)
2010–2012	4,137 (22.4)
2013–2015	4,327 (23.4)

Abbreviation: IQR, interquartile range.

Table 2. Multivariable Logistic Regression of Receiving Any or Multiagent Chemotherapy

	Any Chemotherapy (N=18,463)			Multiagent Chemotherapy[a] (N=10,600)		
Characteristic	**aOR (95% CI)**	***P* Value**	**% (95% CI)**	**aOR (95% CI)**	***P* Value**	**% (95% CI)**
Age (per y)	0.95 (0.94–0.95)	<.001	N/A	0.97 (0.96–0.98)	<.001	N/A
Race						
White	Ref		61.2 (60.4–61.9)	Ref		30.1 (28.6–31.6)
Black	1.01 (0.91–1.12)	.85	61.4 (59.3–64.5)	0.72 (0.57–0.90)	.003	23.7 (20.1–27.4)
Asian	0.96 (0.78–1.18)	.68	60.2 (55.8–64.6)	1.03 (0.69–1.53)	.89	30.7 (22.6–38.7)
Other	0.81 (0.58–1.13)	.21	56.5 (49.2–63.9)	0.93 (0.47–1.86)	.84	28.7 (15.5–42.3)
Sex						
Male	Ref		61.6 (60.6–62.5)	Ref		32.0 (30.0–33.9)
Female	0.96 (0.9–1.02)	.20	60.7 (59.7–61.7)	0.75 (0.65–0.86)	<.001	26.3 (24.3–28.2)
Charlson-Deyo comorbidity score						
0	Ref		61.8 (61.0–62.6)	Ref		31.0 (29.3–32.8)
1	0.96 (0.89–1.00)	.23	60.8 (59.6–62.1)	0.80 (0.68–0.94)	.005	26.5 (24.0–29.1)
2	0.87 (0.76–0.99)	.04	58.7 (55.9–61.5)	0.82 (0.61–1.11)	.21	27.2 (21.6–32.7)
3	0.62 (0.50–0.78)	<.001	51.3 (46.4–56.1)	0.36 (0.19–0.69)	.002	14.2 (6.5–21.9)
Cancer stage						
I	Ref		47.6 (45.7–50.0)	Ref		21.2 (16.6–25.9)
II	2.01 (1.83–2.20)	<.001	63.2 (62.5–64.0)	1.58 (1.18–2.12)	.002	29.7 (28.2–31.1)
III	1.78 (1.47–2.16)	<.001	60.6 (56.8–64.5)	2.48 (1.46–4.19)	.001	39.4 (29.1–49.7)
Readmission within 30 d of surgery						
No	Ref		62.1 (61.3–62.7)	Ref		29.3 (27.9–30.7)
Yes	0.57 (0.51–0.64)	<.001	50.0 (47.1–52.0)	0.99 (0.74–1.31)	.92	29.0 (23.5–34.5)
Insurance type						
Private insurance/managed care	Ref		62.3 (61.1–63.6)	Ref		29.1 (26.9–31.4)
Uninsured	0.61 (0.50–0.74)	<.001	51.4 (47.2–55.5)	0.61 (0.40–0.95)	.02	20.4 (13.7–27.2)
Medicaid	0.66 (0.57–0.77)	<.001	53.3 (49.9–56.6)	0.81 (0.60–1.09)	.16	25.0 (19.8–30.2)
Medicare	0.96 (0.89–1.05)	.39	61.5 (60.5–62.5)	1.07 (0.89–1.28)	.49	30.4 (28.0–32.9)
Other government	1.02 (0.74–1.40)	.91	62.7 (59.5–62.0)	1.11 (0.59–2.11)	.74	31.3 (18.2–44.5)
Income level						
≥$46,000	Ref		65.5 (64.5–66.6)	Ref		30.4 (26.1–34.7)
$35,000–$45,999	0.80 (0.74–0.86)	<.001	60.8 (59.5–62.0)	0.96 (0.76–1.22)	.73	30.0 (27.5–31.6)
$30,000–$34,999	0.65 (0.59–0.71)	<.001	56.2 (54.6–57.8)	0.89 (0.70–1.15)	.37	28.1 (25.5–30.7)
<$30,000	0.60 (0.54–0.66)	<.001	54.4 (52.4–56.3)	0.96 (0.73–1.26)	.77	29.6 (26.1–33.1)
Facility type						
Academic/Research center	Ref		61.1 (60.2–62.0)	Ref		29.4 (27.7–31.0)
Community cancer program	1.13 (0.94–1.36)	.21	63.7 (59.9–67.5)	0.55 (0.29–1.04)	.07	18.8 (9.3–28.2)
Comprehensive community cancer program	1.08 (1.00–1.16)	.05	62.7 (61.4–64.0)	0.96 (0.81–1.14)	.67	29.3 (27.7–31.0)
Integrated network cancer program	0.83 (0.75–0.91)	<.001	57.0 (55.1–59.0)	1.12 (0.89–1.41)	.33	31.7 (27.2–36.2)
Treatment era						
2004–2006	Ref		59.5 (58.1–60.9)	N/A		N/A
2007–2009	1.19 (1.09–1.29)	<.001	63.2 (62.0–64.5)	N/A		N/A
2011–2012	1.08 (0.99–1.19)	.08	61.3 (60.0–62.7)	Ref		29.3 (27.1–31.5)
2013–2015	1.03 (0.95–1.13)	.46	60.2 (58.9–61.6)	1.00 (0.87–1.15)	.98	29.2 (27.5–31.0)

Abbreviation: aOR, adjusted odds ratio; N/A, not applicable.
[a]Among patients receiving adjuvant chemotherapy.

Table 3. Multivariable Logistic Regression of Refusing Any Chemotherapy

	Refusal of Chemotherapy (N=7,175)		
Characteristic	**aOR (95% CI)**	***P* Value**	**% (95% CI)**
Age (per y)	1.01 (1.00–1.02)	.005	N/A
Race			
White	Ref		11.3 (10.6–12.1)
Black	0.93 (0.73–1.20)	.58	10.7 (8.5–12.9)
Asian	0.86 (0.52–1.40)	.55	10.0 (5.7–14.2)
Other	0.83 (0.35–1.94)	.66	9.6 (2.4–16.8)
Sex			
Male	Ref		10.3 (9.3–11.3)
Female	1.19 (1.03–1.39)	.02	12.0 (11.0–13.1)
Charlson-Deyo comorbidity score			
0	Ref		10.7 (9.8–11.6)
1	1.20 (1.02–1.42)	.03	12.5 (11.1–13.9)
2	0.78 (0.56–1.09)	.15	8.6 (6.2–11.1)
3	1.60 (1.08–2.38)	.02	15.9 (10.9–20.9)
Cancer stage			
I	Ref		9.5 (7.9–11.1)
II	1.26 (1.01–1.55)	.03	11.6 (10.8–12.4)
III	1.11 (0.68–1.83)	.67	10.4 (6.3–14.6)
Readmission within 30 d of surgery			
No	Ref		11.4 (10.7–12.2)
Yes	0.78 (0.60–1.01)	.06	9.2 (7.1–11.2)
Insurance type			
Private insurance/managed care	Ref		9.8 (8.3–11.2)
Uninsured	1.41 (0.89–2.23)	.14	13.1 (8.2–18.0)
Medicaid	1.22 (0.82–1.80)	.33	11.6 (7.9–15.3)
Medicare	1.24 (1.00–1.52)	.05	11.7 (10.7–12.7)
Other government	0.99 (0.42–2.34)	.85	9.6 (2.4–16.9)
Income level			
≥$46,000	Ref		10.8 (9.7–12.0)
$35,000–$45,999	1.10 (0.92–1.33)	.29	11.7 (10.4–13.2)
$30,000–$34,999	1.08 (0.88–1.33)	.44	11.6 (10.0–13.2)
<$30,000	0.98 (0.77–1.25)	.88	10.6 (8.8–12.5)
Facility type			
Academic/Research center	Ref		10.9 (10.0–11.9)
Community cancer program	1.15 (0.73–1.80)	.56	12.3 (7.7–16.9)
Comprehensive community cancer program	1.18 (0.99–1.39)	.06	12.6 (11.1–14.0)
Integrated network cancer program	0.86 (0.68–1.08)	.20	9.5 (7.8–11.3)
Treatment era			
2004–2006	Ref		7.0 (6.9–8.2)
2007–2009	1.29 (1.02–1.63)	.04	8.9 (7.7–10.1)
2010–2012	1.88 (1.49–2.37)	<.001	12.4 (10.8–14.0)
2013–2015	2.71 (2.18–3.37)	<.001	16.9 (15.2–18.6)

Abbreviation: aOR, adjusted odds ratio.

(P=.005) and higher comorbidity score (P≤.03 for Charlson-Deyo comorbidity scores of 3 and 1 compared with score of 0).

Discussion

In this study, the largest US cancer registry was used to assess trends in management of potentially curable pancreatic cancer. We observed significant disparities in the receipt of timely adjuvant chemotherapy among patients with resected stage I–III pancreatic cancer over an 11-year period. Specifically, receipt of any adjuvant chemotherapy was associated with economic factors, such as insurance type and income, whereas receipt of multiagent chemotherapy appeared to be associated with demographic variables, including sex and race. These associations persisted when analyses were restricted to patients treated at academic centers. Furthermore, given the positive interaction term between black race and age/comorbidity status, the disparity in treatment with multiagent chemotherapy was particularly relevant for the younger, healthier cohort, which may benefit the most from aggressive chemotherapy.

Given the well-established increased survival associated with receipt of adjuvant chemotherapy,[2–5] our findings have several important implications. First, in contrast to prior studies that have shown development of postoperative complications, readmission rates, age, and comorbidity to be associated with receipt of adjuvant chemotherapy,[10–13] our study suggests that sociodemographic variables are also strongly predictive of whether patients receive chemotherapy for resected pancreatic cancer, independent of clinicopathologic characteristics. Therefore, given that differences in quality of care may contribute to disparities in cancer survival, our findings suggest that outcomes for certain subgroups of patients could be improved by increasing the proportion receiving guideline-concordant adjuvant chemotherapy. In particular, black patients who were young and healthy were significantly less likely than their nonblack counterparts to receive multiagent chemotherapy, and the difference between these groups was 9.4%. We cannot be sure of the drivers of this interaction; however, we hypothesize that it could be due to overall lower rates of recommending aggressive chemotherapy in older and less healthy patients, such that disparities between racial groups were not apparent among those subgroups. This finding suggests that the subgroup of black patients who may be optimal chemotherapy candidates with the highest potential for improved outcomes could be missing the opportunity to benefit from aggressive postoperative therapy. Notably, this racial disparity was only observed for receipt of multiagent chemotherapy, which was not an NCCN category 1 recommendation during our study interval. Given the recent publication of the PRODIGE 24 study findings, showing a significant disease-free and overall survival benefit associated with adjuvant mFOLFIRINOX versus gemcitabine alone,[1] our results should prompt further investigations regarding whether racial disparities remain among patients currently undergoing treatment.

We were not surprised to observe that different variables were associated with receipt of any versus multiagent adjuvant chemotherapy. We hypothesize that the ability to receive any cancer treatment, including chemotherapy, for a specific diagnosis may be affected by patients' financial status, particularly in the era of bundled payments. Therefore, economic factors such as insurance type and income level were associated with receipt of any adjuvant chemotherapy. In contrast, once a patient is able to receive adjuvant chemotherapy, the decision to treat with multiple versus single agents is less likely to be influenced by cost issues and thus may be more likely affected by patient or provider biases. Accordingly, receipt of multiagent chemotherapy appeared to be associated with demographic variables, including sex and race.

The persistent disparities in receipt of adjuvant chemotherapy, including multiagent chemotherapy, observed at academic cancer centers in this study are concerning. Several major cancer organizations have sought to reduce disparities in outcomes of high-risk cancers by improving access to research-focused cancer centers, among other initiatives.[16–18] However, even among academic medical centers, receipt of any adjuvant chemotherapy appeared to be determined in part by income level and insurance type, despite the general notion that academic facilities accept a greater number of insurance plans, including government-sponsored insurance, and have resources to provide care for disadvantaged individuals. Similarly, black patients at academic centers were less likely to receive multiagent chemotherapy. We hypothesize several reasons for this persistent disparity. It is possible that cancer care systems, such as those of large academic centers, are complex to navigate and that at-risk groups experience greater difficulty in obtaining proper treatment as a result. Alternatively, differences in treatment received could be attributed to patient preferences or physician bias. Our results suggest that mitigating disparities in quality of care for pancreatic cancer will require more than simply increasing access to treatment at academic cancer centers; specifically, policies and guidelines should be established to regularly track receipt of guideline-concordant care by relevant sociodemographic characteristics. The availability of patient care navigators could also help mitigate disparities in treatment by providing assistance to individuals at greatest risk for not receiving care due to the increasing complexity of the healthcare system.

The analysis of factors associated with documented refusal of chemotherapy merits further discussion. Prior studies have also shown that women are less likely than men to receive aggressive cancer treatments[21]; however, this sex disparity has not previously been shown to be related to refusal of treatment. Interestingly, despite increasing evidence of a significant benefit from adjuvant chemotherapy over the past 2 decades, more recent treatment era was associated with higher odds of chemotherapy refusal. This may reflect increased patient involvement in treatment decision-making, which is generally considered a progressive and positive feature of the healthcare system; that said, such a trend could be problematic if it facilitates poorer adherence with established guidelines for cancer care, especially now that such impressive survival results with more-intensive adjuvant therapy have been shown. Notably, there was no association of black race, income level, and insurance type with refusal of chemotherapy, although these variables were associated with lower odds of receiving any chemotherapy or multiagent chemotherapy. This finding is in contrast to prior studies that have shown higher rates of refusal of definitive cancer treatment among black patients.[22–25] In addition to citing physician mistrust and medical suspicion as personal factors that may be driving the higher refusal rates,[22] these studies suggest that insurance type and access to care are also likely, if not dominant, contributors.[26,27] Given that race, insurance type, and income were not found to be associated with chemotherapy refusal in our cohort, these findings should serve as an impetus for further research regarding potential biases among providers or systems-level issues that may be interfering with treatment among these subgroups.

Our findings must be viewed within the limitations of the NCDB. The cohort was limited to patients treated at American College of Surgeons' Commission on Cancer–accredited cancer programs, and thus our results may not reflect patterns of care at other cancer centers. However, the NCDB is the largest US cancer registry, capturing 70% of incident cancers, and it also includes comprehensive treatment information, including details regarding chemotherapy administration, and is therefore one of the most robust databases for analyzing disparities in patterns of care. Second, multiagent chemotherapy was not included in NCCN Guidelines as a category 1 recommendation until 2017; currently the NCDB includes patients treated up to 2015. However, changes in physician practice patterns often precede the establishment of definitive guidelines, and the disparities observed in our study suggesting that black patients were less likely to receive more aggressive postoperative chemotherapy are noteworthy because multiagent chemotherapy was eventually shown to be associated with improved survival. Future studies are needed to assess patterns in receipt of multiagent chemotherapy after publication of results from the ESPAC-4 and PRODIGE 24 trials.[1,3] Third, refusal of chemotherapy was recorded only for patients who refused any chemotherapy; therefore, we cannot determine whether certain patients were more likely to refuse multiagent chemotherapy (and choose single-agent chemotherapy) and therefore assess whether this could have contributed to their lower odds of receiving multiagent chemotherapy. In addition, refusal was physician-recorded in the NCDB without further elaboration on the specifics; thus, it is possible that patients were incorrectly categorized as refusing chemotherapy, and we do not have further information on the reasons.

Conclusions

Our study shows sociodemographic disparities in the receipt of adjuvant chemotherapy for pancreatic cancer. Further research is needed to identify the processes leading to the lower likelihood of certain patient subgroups receiving postoperative adjuvant chemotherapy, including multiagent chemotherapy. Once these issues are identified, interventions should be undertaken to mitigate these disparities, with the goal of improving treatment outcomes for all patients with pancreatic cancer.

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References

1. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med 2018;379:2395–2406.
2. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet 2001;358:1576–1585.
3. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a

multicentre, open-label, randomised, phase 3 trial. Lancet 2017; 389:1011–1024.
4. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200–1210.
5. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 2007;297:267–277.
6. Tempero MT, Abbruzzese JL, Benson AB III, et al. NCCN Practice Guidelines for Pancreatic Cancer. Version 2000. To view the most recent version, visit NCCN.org.
7. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection [erratum in Arch Surg 1986;121:1045]. Arch Surg 1985;120:899–903.
8. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA 2013;310: 1473–1481.
9. Tempero MA, Malafa MP, Chiorean EG, et al. NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 1.2019. Accessed November 1, 2018. To view the most recent version, visit NCCN.org.
10. Åkerberg D, Björnsson B, Ansari D. Factors influencing receipt of adjuvant chemotherapy after surgery for pancreatic cancer: a two-center retrospective cohort study. Scand J Gastroenterol 2017;52:56–60.
11. Bilimoria KY, Bentrem DJ, Lillemoe KD, et al. Assessment of pancreatic cancer care in the United States based on formally developed quality indicators. J Natl Cancer Inst 2009;101:848–859.
12. Jaap K, Fluck M, Hunsinger M, et al. Analyzing the impact of compliance with national guidelines for pancreatic cancer care using the National Cancer Database. J Gastrointest Surg 2018;22:1358–1364.
13. Krishnan M, Ahmed A, Walters RW, et al. Factors affecting adjuvant therapy in stage III pancreatic cancer—analysis of the National Cancer Database. Clin Med Insights Oncol 2017;11:1179554917728040.
14. American College of Surgeons. National Cancer Database - Data Dictionary PUF 2016. Available at: http://ncdbpuf.facs.org/node/259?q=print-pdf-all. Accessed September 18, 2019.
15. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383.
16. Byers T, Mouchawar J, Marks J, et al. The American Cancer Society challenge goals: how far can cancer rates decline in the U.S. by the year 2015? Cancer 1999;86:715–727.
17. Mahal BA, Chen YW, Muralidhar V, et al. National sociodemographic disparities in the treatment of high-risk prostate cancer: do academic cancer centers perform better than community cancer centers? Cancer 2016;122:3371–3377.
18. Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. CA Cancer J Clin 2004;54:78–93.
19. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–1825.
20. Tong H, Fan Z, Liu B, et al. The benefits of modified FOLFIRINOX for advanced pancreatic cancer and its induced adverse events: a systematic review and meta-analysis. Sci Rep 2018;8:8666.
21. Ward MM, Ullrich F, Matthews K, et al. Who does not receive treatment for cancer? J Oncol Pract 2013;9:20–26.
22. Lin JJ, Mhango G, Wall MM, et al. Cultural factors associated with racial disparities in lung cancer care. Ann Am Thorac Soc 2014;11:489–495.
23. Shavers VL, Brown ML. Racial and ethnic disparities in the receipt of cancer treatment. J Natl Cancer Inst 2002;94:334–357.
24. Howell EA, Chen YT, Concato J. Differences in cervical cancer mortality among black and white women. Obstet Gynecol 1999;94:509–515.
25. Merrill RM, Merrill AV, Mayer LS. Factors associated with no surgery or radiation therapy for invasive cervical cancer in black and white women. Ethn Dis 2000;10:248–256.
26. Breen N, Wesley MN, Merrill RM, et al. The relationship of socio-economic status and access to minimum expected therapy among female breast cancer patients in the National Cancer Institute Black-White Cancer Survival Study. Ethn Dis 1999;9:111–125.
27. Michalski TA, Nattinger AB. The influence of black race and socioeconomic status on the use of breast-conserving surgery for Medicare beneficiaries. Cancer 1997;79:314–319.


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Sociodemographic Disparities in the Receipt of Adjuvant Chemotherapy Among Patients With Resected Stage I–III Pancreatic Adenocarcinoma

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eTable 1: Multivariable aORs of Receiving Chemotherapy at Academic Centers

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Characteristic	Any Chemotherapy (N=10,586)			Multiagent Chemotherapy (N=6,160)		
	aOR (95% CI)	*P* Value	% (95% CI)	aOR (95% CI)	*P* Value	% (95% CI)
Age (per y)	0.95 (0.94–0.95)	<.001	N/A	0.97 (0.96–0.98)	<.001	N/A
Race						
White	Ref		61.3 (60.4–62.3)	Ref		30.2 (28.3–32.1)
Black	1.03 (0.90–1.18)	.64	61.8 (59.1–64.5)	0.76 (0.57–0.99)	.046	24.8 (20.2–29.4)
Asian	1.20 (0.91–1.57)	.19	64.4 (59.0–69.8)	1.19 (0.77–1.85)	.43	34.0 (24.8–43.3)
Other	0.69 (0.46–1.06)	.09	53.3 (44.1–62.6)	0.80 (0.35–1.83)	.60	26.0 (10.8–41.2)
Sex						
Male	Ref		61.5 (60.2–62.7)	Ref		32.1 (29.7–34.4)
Female	0.99 (0.91–1.08)	.89	61.3 (60.0–62.5)	0.77 (0.65–0.91)	.002	26.7 (24.4–29.2)
Charlson-Deyo comorbidity score						
0	Ref		61.7 (60.7–62.8)	Ref		30.9 (28.8–33.0)
1	0.99 (0.90–1.09)	.89	61.6 (60.0–63.3)	0.84 (0.69–1.02)	.08	27.4 (24.1–30.6)
2	0.90 (0.75–1.08)	.24	59.1 (55.3–62.9)	0.79 (0.53–1.17)	.24	26.3 (19.2–33.4)
3	0.63 (0.47–0.85)	.003	51.8 (45.2–58.5)	0.65 (0.31–1.33)	.23	22.7 (10.6–34.9)
Cancer stage						
I	Ref		47.6 (45.0–50.2)	Ref		20.5 (14.8–26.3)
II	2.03 (1.80–2.30)	<.001	63.4 (62.4–64.3)	1.69 (1.17–2.44)	.006	30.0 (28.3–31.8)
III	2.00 (1.52–2.62)	<.001	63.0 (57.8–68.1)	2.75 (1.42–5.35)	.003	40.7 (27.8–53.7)
Readmission within 30 d of surgery						
No	Ref		62.3 (61.4–63.2)	Ref		29.8 (28.0–31.5)
Yes	0.57 (0.49–0.67)	<.001	50.1 (46.9–53.3)	0.89 (0.63–1.26)	.52	27.5 (21.0–34.0)
Insurance type						
Private insurance/managed care	Ref		63.8 (62.1–65.4)	Ref		29.7 (27.0–32.4)
Uninsured	0.59 (0.46–0.75)	<.001	52.1 (46.7–57.4)	0.45 (0.25–0.81)	.008	16.4 (8.7–24.1)
Medicaid	0.72 (0.59–0.88)	.001	56.7 (52.3–61.0)	0.75 (0.52–1.07)	.11	24.2 (17.9–30.4)
Medicare	0.88 (0.79–0.99)	.03	61.0 (59.6–62.3)	1.08 (0.86–1.35)	.51	31.2 (28.1–34.4)
Other government	1.20 (0.77–1.86)	.43	67.4 (58.7–76.1)	1.03 (0.41–2.56)	.95	30.2 (11.8–48.6)
Income level						
≥$46,000	Ref		67.0 (65.7–68.2)	Ref		30.1 (27.8–32.5)
$35,000–$45,999	0.73 (0.66–0.80)	<.001	60.0 (58.2–61.7)	0.87 (0.70–1.07)	.18	27.3 (24.0–30.6)
$30,000–$34,999	0.56 (0.50–0.63)	<.001	54.2 (52.0–56.4)	1.08 (0.83–1.40)	.58	31.6 (26.8–36.5)
<$30,000	0.55 (0.48–0.62)	<.001	53.7 (51.1–56.3)	1.00 (0.75–1.33)	.99	30.1 (24.8–35.3)
Treatment era						
2004–2006	Ref		57.8 (56.0–59.6)	N/A		N/A
2007–2009	1.13 (1.01–1.27)	.04	60.7 (59.0–62.4)	N/A		N/A
2011–2012	1.26 (1.12–1.42)	<.001	63.1 (61.4–64.9)	Ref		29.0 (26.3–31.7)
2013–2015	1.32 (1.17–1.48)	<.001	63.8 (62.1–65.5)	1.05 (0.88–1.24)	.60	30.0 (27.8–32.1)

Abbreviations: aOR, adjusted odds ratio; N/A, not applicable.