

Correlates of Refusal of Surgery in the Treatment of Non-metastatic Pancreatic Adenocarcinoma

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ABSTRACT

Background. Surgical resection is the most important therapeutic intervention for eligible patients with pancreatic cancer; however, a majority of patients never receive surgery for a variety of reasons, including patient refusal. Utilizing the National Cancer Database, we investigated the associated sociodemographic and clinical factors for those patients who refused surgery, and the impact of this decision on overall survival (OS).

Methods and Materials. We analyzed adult patients with non-metastatic adenocarcinoma of the pancreas diagnosed from 2004 to 2013. Univariate and multivariate logistic regression modeling was used to identify factors predictive of refusing surgery, and Kaplan–Meier and log-rank analysis was performed to investigate the effect on OS.

Results. A total of 48,902 patients were identified: 47,107 received surgery (96.3%) and 1795 were offered surgery but refused (3.7%). Factors associated with refusing surgery include both sociodemographic factors [age > 50 years, female sex, Black race, non-private insurance, treatment at a non-academic institution or non-metro facility, Carlson Comorbidity Index of 2 + ($p \leq 0.01$)], and clinical factors [advanced clinical T (tumor) category and tumor size > 20 cm ($p \leq 0.01$)]. Patients who refused surgery and received no treatment at all experienced a median survival of 5.1 months, while those

who refused surgery but received chemoradiotherapy experienced a median survival of 11.2 months. As an index for comparison, those who received surgery had a median survival of 20.5 months.

Conclusion. Refusing surgery is an understudied phenomenon associated with several sociodemographic and clinical factors. The expected prognosis for patients who refuse surgery is presented.

Pancreatic cancer is the fourth leading cause of cancer-related death among both men and women in the US.¹ In the < 20% of patients eligible for surgery,² successful surgical resection is the most important determinant of survival. However, the prognosis is poor, even for those patients with a potentially resectable tumor. Multiple randomized clinical trials have illustrated a median overall survival (OS) of < 23 months following surgical resection and adjuvant therapy for pancreatic cancer,^{3–5} although newer trials have shown some improvement.⁶ Long-term mortality rates have remained largely unchanged.⁷

Because of these statistics, the diagnosis of pancreatic cancer is a devastating event, which may discourage both patients and healthcare providers. These attitudes may lead to perceived futility of treatment. A National Cancer Database (NCDB) study by Bilimoria et al. revealed that 38.2% of patients with stage I pancreatic cancer were not even offered surgery for the treatment of their cancer. The authors hypothesized these results are likely secondary to the pessimism surrounding this disease, even though 96.1% of patients with stage I disease who underwent surgery in this study experienced a complete surgical resection.⁸ Others may be deterred by the extent of surgery required in a pancreaticoduodenectomy, while, in practice, the mortality and severe morbidity rates for this surgery are considered acceptable at large-volume treatment centers.^{9–12}

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The factors associated with refusing surgery for pancreatic cancer are poorly understood and the survival of patients who refuse surgery is not known. We conducted a retrospective review using the NCDB to determine factors associated with refusal of surgery for patients with non-metastatic pancreatic adenocarcinoma, and the subsequent effect of this decision on OS.

METHODS AND MATERIALS

Our database investigation began with 309,709 patients in the NCDB with pathology-proven pancreatic cancer diagnosed between 2004 and 2014. Patients were initially excluded from the analysis if they were diagnosed as clinical stage IV or if histology was anything other than adenocarcinoma. We further excluded those patients in which surgery was not part of the planned treatment course, surgery was not recommended, the patient died before they underwent surgery, or it was unknown if the patient received surgery. Patients who received radiotherapy only were also excluded as this was likely a palliative measure. Finally, patients were excluded if survival data were unknown. A flowchart of the patient inclusion criteria is shown in Electronic Supplementary Figure 1. Patient demographic information analyzed as covariates included patient age, sex, race, insurance status, facility type, geographic region, regional median income, education level, distance to treatment facility, urbanization, and Charlson Comorbidity Index (CCI). The clinical variables included as covariates were clinical T category, nodal status at diagnosis, tumor location, tumor size, and treatment with chemotherapy and radiotherapy. Missing values for all of the variables were treated as missing values and no imputation was performed, nor were they included as a separate group.

Characteristics of patients who received surgical resection versus those who refused surgery were queried. Chi square analysis was used to compare demographic and clinical variables between these two cohorts. Univariate and multivariate logistic regression modeling was used to identify factors predictive of receiving surgery versus refusing surgery. Variables were included in the multivariate analysis if the p value on univariate analysis was < 0.20 , or if the inclusion of the variable resulted in a 10% or greater change in the outcome.^{13,14} The year of diagnosis was analyzed using univariate and multivariate logistic regression as a continuous variable to determine if refusal of surgery changed over time.

Univariate and multivariate Cox proportional hazards modeling was used to analyze the association between receipt of surgery and risk of death, and also to identify which sociodemographic factors and clinical variables

were associated with OS. Variable selection for our multivariate model was completed as mentioned previously, and a propensity score analysis was completed to minimize the confounding variables. A surgery cohort and a refusal cohort were created using propensity score matching, such that there would be no differences between the two groups in the explanatory covariates. Survival curves were calculated using the Kaplan–Meier method and log-rank test. Resectability was determined by the treating institutions and taken as coded in the NCDB. However, as a sensitivity analysis, we eliminated all but T1 and T2 tumors that were < 10 cm, and reported the survival of patients who refused or received surgery. All analyses were performed using the STATA 14.0 statistical package (StataCorp. LLC, College Station, TX, USA).

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. This nationwide, facility-based, comprehensive clinical surveillance resource oncology data set currently captures 70% of all newly diagnosed malignancies in the US annually. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.¹⁵ This study was exempt from Institutional Review Committee approval as there is no identifiable patient information in the NCDB.

RESULTS

A total of 48,902 patients met the study criteria and were included in the analysis: 47,107 (96.3%) received surgical resection, and 1795 (3.7%) refused surgery. The median age of this cohort was 66.3 years, with a median follow-up time of 25.5 months. There were significant differences between these two cohorts (Table 1). Furthermore, there was no time trend in refusal of surgery, even when analyzed with Black patients only. Among the 1795 patients who refused surgery, 771 (42.9%) also refused chemotherapy.

Factors predictive of refusing surgery on multivariate analysis included age between 50 and 69 years (compared with age < 50 years) and age ≥ 70 years ($p < 0.01$); female sex ($p < 0.01$); Black race compared with Caucasian ($p < 0.01$); patients with either no insurance, or Medicaid or Medicare insurance compared with private insurance ($p \leq 0.01$); treatment at a non-academic institution ($p < 0.01$); treatment at an urban ($p = 0.02$) or rural facility ($p < 0.01$) compared with a metro facility; CCI of 2 + compared with a CCI of 0 ($p = 0.03$); clinical T2, T3,

TABLE 1 Baseline characteristics

	Surgical resection (<i>n</i> = 47,107)		Patient refused surgery (<i>n</i> = 1795)		<i>p</i> value
	<i>N</i>	%	<i>N</i>	%	
Age group (years)					
18–49	3497	7	14	1	< 0.001
50–69	24,643	52	324	18	
70+	18,967	40	1457	81	
Sex					
Male	23,890	51	710	40	< 0.001
Female	23,217	49	1085	60	
Race					
White	38,627	83	1441	81	0.002
Black	4414	9	216	12	
Hispanic	2134	5	73	4	
Other	1457	3	49	3	
Insurance					
Private	18,032	39	255	15	< 0.001
No insurance	1207	3	39	2	
Medicaid	2524	5	76	4	
Medicare	24,425	53	1377	79	
Facility type					
Academic	25,761	55	783	44	< 0.001
Other	20,711	45	1010	56	
Geographic region					
Northeast	10,338	22	472	26	< 0.001
South	17,104	37	494	28	
Midwest	11,893	26	557	31	
West	7137	15	270	15	
Income (US\$)					
< 30,000	5475	12	252	15	< 0.001
30,000–34,999	7823	17	359	21	
35,000–45,999	12,284	27	498	29	
46,000+	19,342	43	624	36	
Percentage of residents without a HS degree					
29+	6782	15	286	17	0.036
20–28.9	10,123	23	414	24	
14–19	10,761	24	425	25	
< 14	17,253	38	608	35	
Distance from treatment facility (miles)					
< 50	35,728	78	1527	87	< 0.001
50–200	8288	18	202	11	
> 200	2021	4	33	2	
Urbanization					
Metro	36,862	82	1386	80	0.159
Urban	5587	12	220	13	
Rural	2590	6	117	7	
Charlson Comorbidity Index					
0	31,568	67	1135	63	< 0.001
1	12,293	26	468	26	
2+	3246	7	192	11	

TABLE 1 continued

	Surgical resection (<i>n</i> = 47,107)		Patient refused surgery (<i>n</i> = 1795)		<i>p</i> value
	<i>N</i>	%	<i>N</i>	%	
Clinical T category					
T1	4081	9	173	10	< 0.001
T2	9959	22	536	30	
T3	13,003	28	602	34	
T4	1574	3	115	7	
TX	17,529	38	335	19	
Nodal status at diagnosis					
Negative	21,435	46	1167	66	< 0.001
Positive	8732	19	237	13	
Unknown/not accessed	16,101	35	355	20	
Tumor location					
Head	33,231	71	1306	73	< 0.001
Body	3105	7	117	7	
Tail	4849	10	78	4	
Pancreatic duct	492	1	13	1	
Other	5430	12	281	16	
Tumor size (cm)					
< 2	7808	17	278	15	< 0.001
2.1–5	31,394	67	1071	60	
5–20	5198	11	110	6	
> 20	2707	6	336	19	
Chemotherapy and radiotherapy					
No chemotherapy or radiotherapy	15,021	35	1323	75	< 0.001
Single-agent chemotherapy alone	8067	19	118	7	
Multi-agent chemotherapy alone	3290	8	52	3	
Chemotherapy and radiotherapy	16,610	39	265	15	

The total numbers for each variable may not add to the total *n* values listed at the top of the table due to missing values being treated as missing values and therefore no imputation was performed

HS high school, T tumor

and T4 categories compared with clinical T1 disease ($p < 0.01$); and tumor size > 20 cm ($p < 0.01$). Conversely, factors predictive of surgical resection included South and West geographic regions compared with the Northeast ($p < 0.01$); regional median income greater than \$46,000 ($p < 0.01$); distance > 50 miles from a treatment facility ($p < 0.01$); positive nodal status compared with negative nodal status at diagnosis ($p < 0.01$); tumor location in the tail compared with the head ($p < 0.01$); tumor size of 5–20 cm compared with a tumor size < 2 cm ($p < 0.01$); and single-agent and multiagent chemotherapy, and chemoradiotherapy, compared with no chemotherapy and radiotherapy ($p < 0.01$) (Table 2).

OS was lower for patients who refused surgery as part of the treatment for their pancreatic cancer regardless of clinical T category. Median survival for patients receiving surgery versus those who refused was as follows: cT1

disease [27.9 vs. 9.9 months; hazard ratio (HR) 3.49, 95% confidence interval (CI) 2.99–4.06, $p < 0.01$]; cT2 disease (21.7 vs. 7.3 months; HR 3.67, 95% CI 3.35–4.01, $p < 0.01$); cT3 disease (19.4 vs. 6.7 months; HR 3.34, 95% CI 3.08–3.64, $p < 0.01$); and cT4 disease (18.8 vs. 6.2 months; HR 3.74, 95% CI 3.14–4.46, $p < 0.01$) (Fig. 1).

Median OS in patients who received surgery was 20.5 months. Compared with patients who received surgery, those who refused surgery but received chemoradiotherapy had a median OS of 11.2 months (HR 2.28, 95% CI 2.07–2.52, $p < 0.01$), while those who refused surgery and received no treatment at all had a median OS of 5.1 months (HR 4.02, 95% CI 3.79–4.26, $p < 0.01$). Compared with patients who refused surgery and received no treatment at all, those patients who refused surgery but received chemoradiotherapy experienced an

TABLE 2 Predictors of receiving surgery versus refusing surgery

	Univariate analysis		<i>p</i> value	Multivariate Analysis		<i>p</i> value
	OR	95% CI		OR	95% CI	
Age group (years)						
18–49	1	Reference		1	Reference	
50–69	3.28	1.92–5.61	< 0.01	3.88	1.90–7.91	< 0.01
70+	19.19	11.32–32.52	< 0.01	14.86	7.27–30.38	< 0.01
Sex						
Male	1	Reference		1	Reference	
Female	1.57	1.43–1.73	< 0.01	1.38	1.23–1.54	< 0.01
Race						
White	1	Reference		1	Reference	
Black	1.31	1.13–1.52	< 0.01	1.56	1.30–1.88	< 0.01
Hispanic	0.92	0.72–1.16	0.48	1.00	0.75–1.33	0.99
Other	0.90	0.67–1.20	0.48	0.94	0.67–1.31	0.70
Insurance						
Private	1	Reference		1	Reference	
No insurance	2.28	1.62–3.22	< 0.01	2.46	1.65–3.67	< 0.01
Medicaid	2.13	1.64–2.76	< 0.01	1.89	1.40–2.55	< 0.01
Medicare	3.99	3.48–4.56	< 0.01	1.47	1.24–1.74	< 0.01
Facility type						
Academic	1	Reference		1	Reference	
Other	1.60	1.46–1.76	< 0.01	1.52	1.35–1.70	< 0.01
Geographic region						
Northeast	1	Reference		1	Reference	
South	0.63	0.56–0.72	< 0.01	0.52	0.45–0.61	< 0.01
Midwest	1.03	0.90–1.16	0.69	1.03	0.89–1.20	0.69
West	0.83	0.71–0.97	0.02	0.75	0.62–0.90	< 0.01
Income (US\$)						
< 30,000	1	Reference		1	Reference	
30,000–34,999	1.00	0.85–1.18	0.97	1.04	0.85–1.27	0.70
35,000–45,999	0.88	0.75–1.03	0.11	0.87	0.71–1.08	0.21
46,000+	0.70	0.60–0.81	< 0.01	0.65	0.52–0.83	< 0.01
Percentage of residents without a HS degree						
29+	1	Reference		1	Reference	
20–28.9	0.97	0.83–1.13	0.70	0.97	0.80–1.17	0.75
14–19	0.94	0.80–1.09	0.40	1.03	0.83–1.27	0.80
< 14	0.84	0.72–0.96	0.01	1.09	0.87–1.37	0.46
Distance from treatment facility (miles)						
< 50	1	Reference		1	Reference	
50–200	0.57	0.49–0.66	< 0.01	0.46	0.38–0.56	< 0.01
> 200	0.38	0.27–0.54	< 0.01	0.35	0.23–0.54	< 0.01
Urbanization						
Metro	1	Reference		1	Reference	
Urban	1.05	0.91–1.21	0.53	1.23	1.03–1.47	0.02
Rural	1.20	0.99–1.46	0.06	1.65	1.28–2.13	< 0.01
Charlson Comorbidity Index						
0	1	Reference		1	Reference	
1	1.06	0.95–1.18	0.31	0.90	0.80–1.02	0.11
2+	1.65	1.41–1.93	< 0.01	1.22	1.02–1.46	0.03

TABLE 2 continued

	Univariate analysis		<i>p</i> value	Multivariate Analysis		<i>p</i> value
	OR	95% CI		OR	95% CI	
Clinical T category						
T1	1	Reference		1	Reference	
T2	1.27	1.07–1.51	0.01	1.71	1.39–2.12	< 0.01
T3	1.09	0.92–1.30	0.32	1.74	1.41–2.15	< 0.01
T4	1.72	1.35–2.20	< 0.01	2.67	1.98–3.60	< 0.01
TX	0.45	0.37–0.54	< 0.01	0.39	0.30–0.52	< 0.01
Nodal status at diagnosis						
Negative	1	Reference		1	Reference	
Positive	0.50	0.43–0.57	< 0.01	0.52	0.44–0.61	< 0.01
Unknown/not accessed	0.40	0.36–0.46	< 0.01	0.90	0.73–1.10	0.30
Tumor location						
Head	1	Reference		1	Reference	
Body	0.96	0.79–1.16	0.67	0.90	0.72–1.12	0.33
Tail	0.41	0.33–0.52	< 0.01	0.38	0.29–0.49	< 0.01
Pancreatic duct	0.67	0.39–1.17	0.16	0.58	0.31–1.08	0.09
Other	1.32	1.15–1.50	< 0.01	1.06	0.90–1.24	0.50
Tumor size (cm)						
2	1	Reference		1	Reference	
2.1–5	0.96	0.84–1.10	0.53	0.88	0.75–1.04	0.14
5–20	0.59	0.48–0.74	< 0.01	0.62	0.48–0.80	< 0.01
> 20	3.49	2.96–4.11	< 0.01	3.81	3.10–4.69	< 0.01
Chemotherapy and radiotherapy						
No chemotherapy or radiotherapy	1	Reference		1	Reference	
Single-agent chemotherapy alone	0.17	0.14–0.20	< 0.01	0.17	0.14–0.21	< 0.01
Multi-agent chemotherapy alone	0.18	0.14–0.24	< 0.01	0.22	0.16–0.30	< 0.01
Chemotherapy and radiotherapy	0.18	0.16–0.21	< 0.01	0.21	0.18–0.25	< 0.01

OR odds ratio, CI confidence interval, HS high school, T tumor

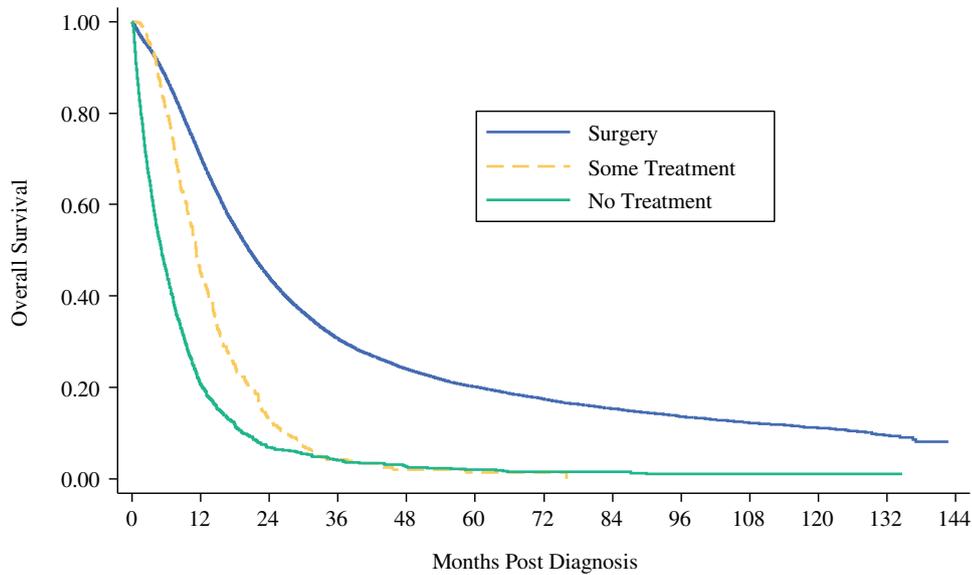
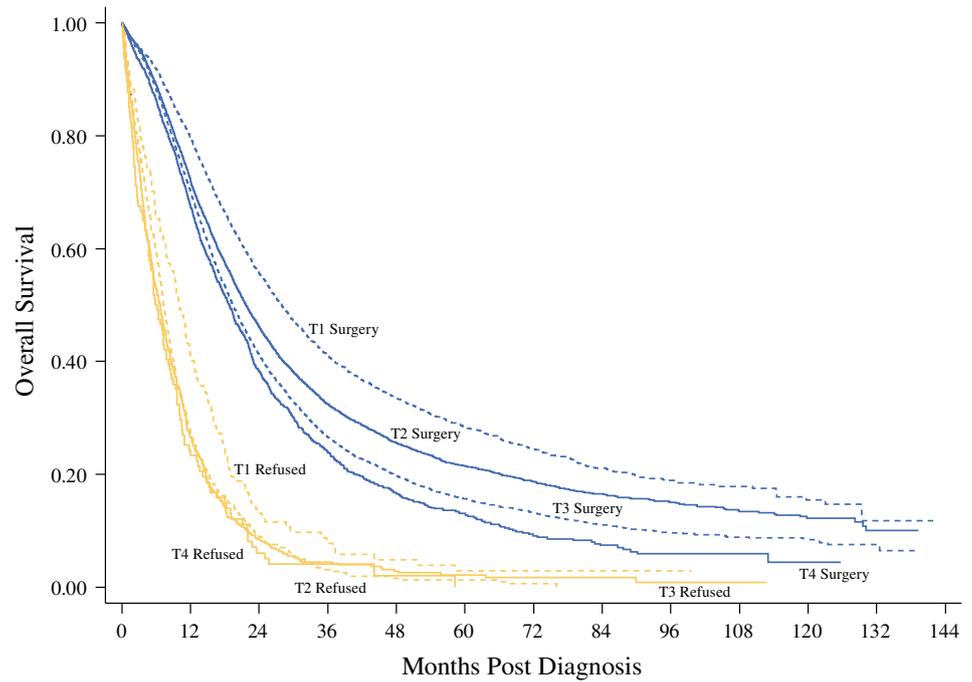
OS advantage (HR 0.57, 95% CI 0.51–0.63, $p < 0.01$) (Fig. 2). Patients who received single-agent chemotherapy alone had a median survival of 9.1 months, whereas patients who received multiagent chemotherapy alone had a median survival of 10.2 months. In our sensitivity analysis of patients who would be more likely to be objectively resectable (T1 and T2 tumors < 10 cm, $N = 15,082$), patients had a median survival of 23.3 months if they received surgery, and 7.8 months if they refused surgery ($p < 0.01$). Factors associated with OS were only observed in those patients who refused surgery. Patients experienced a survival detriment if they were treated at a non-academic institution ($p = 0.01$), had a CCI of 2 + compared with a CCI of 0 ($p < 0.01$), if nodal status was unknown or not accessed at diagnosis compared with those with negative nodes ($p < 0.01$), and if tumor size was > 20 cm ($p < 0.01$) (Table 3). On propensity score analysis, results

were consistent showing considerably different survivals for patients who received or refused surgery (Electronic Supplementary Figure 2).

DISCUSSION

In this analysis, we identify important sociodemographic and clinical attributes associated with refusal of surgery for the treatment of adenocarcinoma of the pancreas, including age > 50 years, female sex, Black race, medical comorbidities, non-private insurance, treatment at a non-academic institution, advanced clinical T category, and large tumor size. The sociodemographic attributes of these patients should inform providers and spur further research about decision making in these groups. While a causative correlation cannot be assumed, we found that refusal of surgery is associated with significantly reduced survival. In our study, median survival for patients who received surgery for pancreatic cancer was 20.5 months, consistent

FIG. 1 Survival curve comparing patients who received surgery versus patients who refused surgery stratified by T category. T classification is derived from preoperative imaging in both groups. T tumor



Number at risk	0	12	24	36	48	60	72	84	96	108	120	132	144
Surgery	47070	32096	18202	10592	6837	4512	3030	1993	1252	687	313	59	0
Some Treatment	441	191	51	11	4	2	2	0	0	0	0	0	0
No Treatment	1317	252	73	36	21	15	11	9	4	3	1	1	0

FIG. 2 Survival curve comparing patients who received surgery versus patients who refused surgery but received some treatment (chemoradiotherapy) versus patients who received no treatment (refused surgery and received no chemotherapy or radiotherapy)

with randomized clinical trials.³⁻⁵ In addition, our survival data for patients who refused surgery is consistent with data for patients who were not offered surgery but were eligible for resection based on staging.⁸

It is important to note that the decision to refuse surgery is complex; it is often the result of long discussions with providers who lend nuance and direction to patients' decisions. The NCDB does not capture the nuances of this process and our goal is simply to provide outcomes data.

TABLE 3 Predictors of overall survival only in patients who refused surgery

	Univariate		<i>p</i> value	Multivariate		<i>p</i> value
	HR	95% CI		HR	95% CI	
Age group (years)						
18–49	1	Reference				
50–69	1.06	0.60–1.89	0.84			
70+	1.19	0.67–2.10	0.55			
Sex						
Male	1	Reference				
Female	1.06	0.96–1.17	0.28			
Race						
White	1	Reference		1	Reference	
Black	0.83	0.71–0.97	0.02	0.83	0.70–0.97	0.02
Hispanic	0.80	0.62–1.05	0.10	0.73	0.55–0.97	0.03
Other	0.80	0.59–1.08	0.14	0.76	0.56–1.05	0.09
Insurance						
Private	1	Reference				
No Insurance	0.84	0.57–1.24	0.38			
Medicaid	1.18	0.89–1.55	0.25			
Medicare	1.06	0.92–1.22	0.44			
Facility type						
Academic	1	Reference		1	Reference	
Other	1.19	1.08–1.32	< 0.01	1.15	1.04–1.28	0.01
Geographic region						
Northeast	1	Reference		1	Reference	
South	1.11	0.97–1.26	0.13	1.09	0.94–1.26	0.26
Midwest	1.13	0.99–1.28	0.06	1.11	0.97–1.28	0.12
West	1.11	0.95–1.29	0.20	1.07	0.90–1.27	0.46
Income (US\$)						
< 30,000	1	Reference				
30,000–34,999	0.96	0.81–1.13	0.60			
35,000–45,999	1.00	0.85–1.17	0.97			
46,000+	0.96	0.83–1.12	0.63			
Percentage of residents without a HS degree						
29+	1	Reference				
20–28.9	1.00	0.86–1.18	0.96			
14–19	1.04	0.89–1.22	0.62			
< 14	0.98	0.85–1.14	0.81			
Distance from treatment facility (miles)						
< 50	1	Reference				
50–200	1.01	0.86–1.18	0.93			
> 200	1.26	0.87–1.80	0.22			
Urbanization						
Metro	1	Reference		1	Reference	
Urban	1.14	0.98–1.32	0.10	1.08	0.93–1.27	0.31
Rural	0.96	0.79–1.17	0.68	0.87	0.71–1.06	0.17
Charlson Comorbidity Index						
0	1	Reference		1	Reference	
1	1.13	1.01–1.27	0.03	1.09	0.96–1.23	0.18
2+	1.31	1.12–1.54	< 0.01	1.29	1.09–1.53	< 0.01

TABLE 3 continued

	Univariate		<i>p</i> value	Multivariate		<i>p</i> value
	HR	95% CI		HR	95% CI	
Clinical T category						
T1	1	Reference		1	Reference	
T2	1.32	1.10–1.59	< 0.01	1.20	0.94–1.53	0.14
T3	1.38	1.15–1.65	< 0.01	1.21	0.97–1.53	0.10
T4	1.49	1.17–1.91	< 0.01	1.27	0.94–1.70	0.12
TX	1.63	1.34–1.98	< 0.01	0.96	0.72–1.28	0.81
Nodal status at diagnosis						
Negative	1	Reference		1	Reference	
Positive	1.13	0.98–1.31	0.10	1.06	0.91–1.24	0.46
Unknown/not accessed	1.44	1.27–1.63	< 0.01	1.44	1.19–1.74	< 0.01
Tumor location						
Head	1	Reference		1	Reference	
Body	0.88	0.72–1.08	0.21	0.89	0.72–1.11	0.32
Tail	1.13	0.90–1.43	0.30	0.98	0.76–1.26	0.86
Pancreatic duct	0.55	0.31–0.97	0.04	0.42	0.23–0.80	0.01
Other	1.01	0.88–1.16	0.85	0.87	0.75–1.01	0.06
Tumor size (cm)						
< 2	1	Reference		1	Reference	
2.1–5	1.30	1.13–1.50	< 0.01	1.25	1.03–1.51	0.02
5–20	1.64	1.30–2.07	< 0.01	1.41	1.07–1.86	0.01
> 20	1.48	1.25–1.75	< 0.01	1.40	1.14–1.73	< 0.01
Chemotherapy and radiotherapy						
No chemotherapy or radiotherapy	1	Reference		1	Reference	
Single-agent chemotherapy alone	0.72	0.60–0.88	< 0.01	0.69	0.56–0.84	< 0.01
Multi-agent chemotherapy alone	0.59	0.44–0.79	< 0.01	0.56	0.41–0.76	< 0.01
Chemotherapy and radiotherapy	0.53	0.46–0.61	< 0.01	0.50	0.43–0.58	< 0.01

HR hazard ratio, CI confidence interval, HS high school, T tumor

Our finding that patients who refuse surgery have poor survival is not evidence surgery would have benefited them.

In the refusal cohort, a majority of patients were older, fewer had private insurance, and fewer received no treatment at all. In general, these factors are associated with worse OS. In contrast, in the refusal cohort, more patients were female and more had a negative nodal status at diagnosis. In general, these factors are favorable in terms of OS. A propensity score analysis confirmed the survival findings while minimizing the confounding variables.

There are many reasons for patients to refuse surgery for the treatment of pancreatic cancer, including poor overall prognosis with limited improvement in survival, cost of treatment, and morbidity and mortality associated with surgery. Some investigators, such as Chamberlain et al. contest that surgical management of pancreatic cancer is no better or worse than many other advanced or terminal illnesses, and cite the undeniable survival advantages and

often exaggerated rates of morbidity and mortality.¹⁶ Bilimoria et al. showed a median survival of 19.3 months for patients with stage I disease who underwent resection, versus 8.4 months for those who were not offered surgery.⁸ With the addition of our analysis, it appears that whether a patient is not offered surgery or refuses surgery, survival is greatly decreased compared with those who received surgery. It is important to emphasize that mortality and severe morbidity associated with resection is acceptable at large-volume centers,^{9–12} and data have shown that quality of life following surgery is excellent.^{17,18}

The effect of neoadjuvant therapy also bears discussion. Clinical and pathological tumor stages are often discordant, and some patients with borderline resectable¹⁹ and locally advanced²⁰ cancer will be operable after neoadjuvant therapy. However, CT findings do not accurately reflect response to treatment.²¹ Taking these points into account, patients with borderline resectable and locally advanced

tumors must remain engaged and be appropriately counseled about these issues to make an informed decision regarding surgery.

Cancer treatment refusal is an interesting topic that warrants additional research. It is suggested that the decision to refuse treatment is a complex one that is dictated by the patient's personal beliefs and values.²² Many factors affect the decision to refuse conventional oncologic treatment, including poor communication, the emotional impact of diagnosis, fear of side effects, and desire for control over the decision-making process.²³ Psychological disorders such as depression have also been shown to play a role.²⁴ Alternatively, some patients may elect to pursue complementary and alternative medicine. It is possible that improved communication with patients and within the medical community, including referring physicians, could improve outcomes for some patients identified as more likely to refuse surgery.

There were a number of demographic variables associated with our cohort of patients who refused surgery. Older patients were more likely to refuse surgery. The association between advancing age and refusal of cancer treatment in general has been shown in a number of studies.^{25–27} Studies have documented a higher refusal rate for definitive surgery among cancer patients who are Black, for several disease sites. Research has identified several factors coinciding with this, including a more prevalent belief among Black patients that quality of life would be worse after surgery,²⁸ and miscommunication or bias during the patient encounter.²⁹

Non-private insurance was also associated with refusal of surgery. This may represent a surrogate for socioeconomic status or buy-in to the medical system in general. Conversely, patients in the highest regional income category were more likely to receive surgery. This raises the concern that socioeconomic status or the ability to pay is playing a role in the decision to forgo life-prolonging treatment. Similar data have been published with the association of less-affluent groups refusing oncologic surgery.^{25,26,30}

There were significant clinical variables that were also associated with patients who refused surgery. Patients with advanced T categories and tumor size > 20 cm were also more likely to refuse surgery. Tumors > 20 cm were rare and may have been cystic in nature in some cases. The association between advanced disease and refusal of treatment has been previously shown,^{26,27,30} and this phenomenon is likely to be explained by the perceived futility of treatment. Yet, the survival advantage of surgery is similar, even in larger and more locally advanced tumors, as seen above.

There was no time trend in the refusal of surgery over our study period. Shah et al. previously reported that Black patients with pancreatic cancer refused surgery more often than White patients, but this disparity decreased over their study period.³¹ We also analyzed Black patients only, but again did not discover a trend over time. The likely explanation is the difference in study periods, as Shah et al. analyzed patients between 1988 and 2009 and our study period was between 2004 and 2014. It is encouraging that we did not discover a time trend among Black patients, although they are still more likely to refuse surgery.

This study has important limitations, some of which are common among retrospective and population-level analyses. This includes selection bias that is inherent with all retrospective reviews. It is possible that our cohort of patients who refused surgery were less healthy or able to tolerate surgery in ways that could not be captured by the NCDB data, and that the survival difference between surgical patients and those who refused surgery is, in actuality, less than reported in our study. It is also possible that providers could have discouraged those patients who were recognized as poor surgical candidates to not receive surgery, while recording that surgery was technically offered to them. In addition, the registrars recording the data may not have found enough detail or nuance in the medical record to accurately determine which patients were really 'offered' and 'refused' a surgery. More robust counseling and record keeping is needed to ensure patients have received proper counseling and there is proper documentation of treatment options and plan of care.³² Finally, clinical T stage is difficult to determine in patients who do not undergo surgery, and cannot be taken as fully accurate.

CONCLUSIONS

We present the expected survival outcomes for patients who refuse surgery using a large aggregate dataset. Our results revealed several important factors associated with refusal of surgery for pancreatic cancer, including race, sex, insurance type, and treatment facility type. The decision to refuse surgery is complex and often appropriate; however, providers should also keep in mind the socioeconomic factors that may play a role in this decision.

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