Impact of Immunotherapy after Resection of Pancreatic Cancer

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BACKGROUND: Adjuvant immunotherapy has improved outcomes in patients with advanced melanoma; however, the potential benefit for patients with pancreatic ductal adenocarcinoma (PDAC) remains unknown. The aim of this study was to determine the impact of adjuvant chemotherapy and immunotherapy (CTx-IT) compared with CTx alone on patient survival after resection of PDAC.

STUDY DESIGN: Patients who underwent resection of PDAC from 2004 to 2015 were identified from the National Cancer Database. Univariate and multivariate Cox proportional hazards models were used to determine predictors of overall survival (OS) based on the type of adjuvant therapy received. Patients who received adjuvant immunotherapy were compared with those who received adjuvant CTx alone by propensity score matching.

RESULTS: Of 21,313 patients who received curative-intent resection for PDAC followed by adjuvant systemic therapy, 269 (1.3%) patients were treated with adjuvant CTx-IT. Propensity score matching resulted in a cohort of 477 patients: (229 CTx only and 248 CTx-IT). The 5-year OS was higher in the CTx-IT group compared with CTx alone (29.2% vs 18.3%; $p = 0.0045$). On multivariate analysis, the addition of adjuvant immunotherapy was associated was improved overall survival (hazard ratio 0.74; $p = 0.007$).

CONCLUSIONS: The addition of adjuvant immunotherapy to chemotherapy is associated with improved survival compared with chemotherapy alone after curative-intent resection of pancreatic adenocarcinoma. Future research is warranted to match specific immunotherapy agents with susceptible patient populations to improve outcomes for this aggressive disease. (J Am Coll Surg 2019;229:19–29.

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy and is the fourth leading cause of cancer-related mortality in the US. The incidence and mortality rates are nearly equal, with 55,440 diagnoses and 44,330 cancer-associated deaths projected in 2018.[1]

Disclosure Information: Nothing to disclose.

Support for this study: Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under award number K08CA190855 (AVM).

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Presented at the Western Surgical Association 126th Scientific Session, San Jose del Cabo, Mexico, November 2018.

Received January 5, 2019; Accepted January 28, 2019.

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Complete surgical resection remains the mainstay of curative-intent treatment; however, only approximately 10% of patients have disease amenable to complete resection.[2-4] Despite aggressive multidisciplinary care, the 5-year survival for PDAC remains <25%, even after complete resection with microscopically negative (R0) margins. What is most concerning for the future is that although patient selection, perioperative care, and operative mortality have improved over time, cancer-related mortality has remained largely unchanged.[5] Locoregional and distant recurrence rates approach 80%, which is likely secondary to the presence of occult micrometastatic disease at the time of resection.[6,7] The high rate of recurrence underscores the need for more effective systemic adjuvant therapies in this disease.

Based on randomized controlled trials, adjuvant systemic chemotherapy after pancreatectomy has been shown to improve survival and is the standard of care in medically fit patients. The CONKO-001 trial established the role of adjuvant gemcitabine in improving overall

https://doi.org/10.1016/j.jamcollsurg.2019.01.016
ISSN 1072-7515/19

Abbreviations and Acronyms

CTx = chemotherapy
HR = hazard ratio
IT = immunotherapy
NCDB = National Cancer Database
OS = overall survival
PDAC = pancreatic adenocarcinoma

survival compared with the observation,[8] and more recent trials have built on this backbone demonstrating improvements in survival outcomes with multidrug chemotherapy regimens.[9-12]

The role of adjuvant immunotherapy in PDAC, however, remains unclear. It has rapidly emerged as a novel effective therapy in multiple malignancies in both metastatic and adjuvant settings, therefore, there is great excitement for use after pancreatic resection for adenocarcinoma.[13-19] In addition, there has been increasing evidence that certain chemotherapies can enhance antitumor immune responses. As a result, the premise that combination chemoimmunotherapy can enhance outcomes in PDAC is well formulated. Given the paucity of data and small single-institution studies on combination chemoimmunotherapy in patients with PDAC, the objective of this study was to evaluate outcomes of adjuvant chemotherapy and immunotherapy compared with chemotherapy alone using a large population-based database in a propensity score-matched study after resection of PDAC.

METHODS

Patient population and study design

The National Cancer Database (NCDB) was used to identify patients who underwent curative intent resection of PDAC. The NCDB is part of a joint program between the American College of Surgeons Commission on Cancer and the American Cancer Society, consisting of approximately 70% of all newly diagnosed malignancies in the US.[20,21] The database captures clinicopathologic characteristics from more than 1,500 Commission on Cancer-accredited hospitals in the US. Patients with primary diagnosis of adenocarcinoma combined with site-specific code for pancreatic tumors (C25.1-C25.4, C25.7-C25.9) were identified using relevant International Classification of Oncology, 3rd edition histology codes. Only patients with pathologically confirmed PDAC who underwent curative-intent resection were included. Patients with R2 resection and distant metastases were excluded. Given previously established Level 1 data on the association between adjuvant chemotherapy and improved survival after resection of PDAC, patients who did not receive adjuvant chemotherapy were excluded from the study.[8,22,23]

Patients were classified according to first-line adjuvant therapy: chemotherapy alone (CTx) or chemotherapy plus immunotherapy (CTx-IT). The NCDB defines and captures immunotherapy as a treatment using a "biological or chemical agent that alter[s] the immune system or change[s] the host's response to tumor cells." eTable 1 includes drugs classified as biologic response modifiers or immunotherapy for pancreatic cancer in the Surveillance, Epidemiology, and End Results-Rx database.

Statistical analysis

Continuous variables were presented as medians with interquartile range and compared using Mann-Whitney U test. Categorical variables were presented as frequency and percentages and compared using Pearson's chi-square or Fisher's exact test, where appropriate. Overall survival (OS) was calculated using Kaplan-Meier method and compared using log-rank test. Univariate and multivariate survival analyses were performed using Cox proportional hazard models and expressed as hazard ratio (HR) with 95% CI.

Propensity score matching was performed using the nearest-neighbor algorithm with a caliper of 0.01 to estimate a propensity score and to create a comparable matched cohort. Patients who underwent adjuvant CTx-IT were matched to those who received adjuvant CTx only. The propensity score was estimated using a multivariate logistic regression model with adjuvant CTx-IT as the treatment of interest. Standardized difference was calculated to evaluate balance in the covariates after matching.

All statistical analyses were performed using SPSS, version 24.0 (IBM Corp) and STATA, version 13.0 (Stata Corp). Significance was set at $p < 0.05$ (2-tailed).

RESULTS

Baseline characteristics of the adjuvant chemotherapy alone and chemotherapy plus immunotherapy groups

Between 2004 and 2015, a total of 21,313 patients received curative-intent resection for PDAC followed by adjuvant systemic therapy. Of these patients, 21,044 received adjuvant CTx only and 269 (1.3%) patients received first-line adjuvant CTx-IT. Table 1 details clinicopathologic characteristics of these patients. Compared with those who received adjuvant CTx alone, patients who received CTx-IT tended to be younger (median 65 vs 62 years; $p < 0.001$) and have a Charlson Deyo Score of 0 (80.3% vs 68.9%; $p < 0.001$). The majority of

Table 1. Clinicopathologic Characteristics of Chemotherapy Alone, and Chemotherapy and Immunotherapy in the Entire Cohort and Propensity Score-Matched Cohort

	Entire cohort			Matched cohort		
Characteristic	**CTx (n = 21,044)**	**CTx+IT (n = 269)**	**p Value**	**CTx (n = 229)**	**CTx+IT (n = 248)**	**p Value**
Female sex, n (%)	10,182 (48.4)	122 (45.4)	0.237	102 (44.5)	112 (45.2)	0.992
Age, y, median (IQR)	65 (5–72)	65 (55–68)	<0.001	61 (54–68)	62 (55–68)	0.715
Race, n (%)			0.006			0.490
White	18,216 (86.6)	240 (89.2)		206 (89.9)	220 (88.7)	
Black	1,986 (9.4)	12 (4.5)		14 (6.1)	12 (4.8)	
Asian	368 (1.8)	8 (2.9)		3 (1.3)	8 (3.2)	
Other	474 (2.3)	9 (3.4)		6 (2.6)	8 (3.2)	
Facility, n (%)			<0.001			<0.001
Academic	10,204 (48.9)	206 (78.0)		108 (51.9)	195 (79.9)	
Community	1,112 (5.3)	1 (0.4)		9 (4.3)	1 (0.4)	
Comprehensive	6,954 (33.4)	47 (17.8)		65 (31.3)	39 (16)	
Integrated network	2,580 (12.4)	10 (3.8)		26 (12.5)	9 (3.7)	
Insurance status, n (%)			<0.001			0.036
None	507 (2.5)	3 (1.1)		10 (4.7)	3 (1.2)	
Private	8,666 (41.9)	157 (58.4)		110 (51.2)	145 (58.5)	
Government	11,140 (53.9)	98 (36.4)		92 (42.8)	92 (37.1)	
Unknown	373 (1.8)	11 (4.1)		3 (1.4)	8 (3.2)	
Charlson Comorbidity Index, n (%)			0.001			0.979
0	14,245 (68.9)	216 (80.3)		183 (79.9)	200 (80.6)	
1	5,113 (24.7)	44 (16.4)		37 (16.2)	40 (16.2)	
2	1,016 (4.9)	7 (2.6)		7 (3.1)	6 (2.4)	
3	213 (15)	2 (0.7)		2 (0.9)	2 (0.8)	
Tumor size, mm, median (IQR)	31 (25–40)	30 (23–40)	0.774	31 (23–40)	30 (23–40)	0.857
Lymphovascular invasion (n = 5,024), n (%)	5,024 (48.9)	44 (47.3)	0.835	55 (56.1)	43 (47.3)	0.223
Grade, n (%)			0.056			0.591
Well	1,602 (7.6)	26 (9.67)		14 (16.1)	23 (9.3)	
Moderate	9,166 (43.6)	97 (36.06)		90 (39.3)	95 (38.3)	
Poor	6,812 (32.4)	54 (34.20)		79 (34.5)	86 (34.7)	
Unknown	3,464 (16.5)	54 (20.07)		46 (20.1)	44 (17.7)	
Total lymph nodes retrieved, median (IQR)	14 (8–20)	15 (9–21)	0.079	14 (9–21)	15 (10–22)	0.156
Margin, n (%)			0.648			0.697
R0	15,695 (78.45)	200 (77.22)		171 (74.7)	189 (76.2)	
R1	4,312 (21.55)	59 (22.78)		58 (25.3)	59 (23.8)	
T stage, n (%)			0.995			0.826
T1	1,294 (6.7)	14 (6.2)		13 (6.4)	13 (6.0)	
T2	2,663 (13.8)	33 (14.6)		23 (11.3)	31 (14.3)	
T3	14,512 (75.4)	171 (75.7)		161 (78.9)	165 (76.0)	
N stage, n (%)			0.105			0.396
N0	6,586 (34.4)	66 (29.2)		68 (33.3)	64 (49.5)	
N1	12,547 (65.6)	160 (70.8)		136 (66.7)	153 (70.5)	
Stage, n (%)			0.289			0.856
I	2,492 (12.2)	25 (9.7)		19 (8.3)	24 (9.7)	
II	16,858 (82.7)	215 (83.7)		195 (85.2)	209 (84.3)	

(Continued)

Table 1. Continued

Characteristic	Entire cohort			Matched cohort		
	CTx (n = 21,044)	CTx+IT (n = 269)	p Value	CTx (n = 229)	CTx+IT (n = 248)	p Value
III	1,048 (5.1)	17 (6.6)		15 (6.6)	15 (6.0)	
Type of operation, n (%)			0.665			0.468
Distal pancreatectomy	2,572 (12.22)	28 (10.41)		23 (10.0)	27 (10.9)	
Pancreaticoduodenectomy	14,884 (70.73)	191 (71)		—	—	
Total pancreatectomy	2,785 (13.23)	41 (15.24)		26 (11.4)	40 (16.1)	
Pancreatectomy not otherwise specified	803 (3.82)	9 (3.35)		4 (1.8)	4 (1.6)	
Radiotherapy, n (%)			<0.001			0.967
No	9,468 (45.2)	64 (23.8)		53 (23.1)	57 (22.98)	
Yes	11,497 (54.8)	205 (76.2)		176 (76.9)	191 (77.0)	

CTx, chemotherapy; IQR, interquartile range; IT, immunotherapy.

patients treated with CTx-IT were at academic centers (78% vs 48.9%; $p < 0.001$) and had private insurance (58.4 vs 41.9%; $p < 0.001$). There were no significant differences in tumor size, lymphovascular invasion, grade, number of lymph nodes retrieved, margin status, stage, or type of operation performed.

Survival analysis

Median time from operation to receipt of adjuvant therapy was 55 days. Median follow-up time was 21.8 months. Survival analysis of the entire cohort demonstrated that the 5-year OS was significantly higher in patients treated with adjuvant CTx-IT compared with CTx alone (30.3% vs 20.6%; $p = 0.003$, Fig. 1A). When stratified by stage, the 5-year OS after adjuvant CTx-IT was similar in stage I (38.5% vs 38.4%; $p = 0.534$) and stage III disease (41% vs 12%; $p = 0.0824$), but was associated with improved survival in stage II patients (27.6% vs 18.6%; $p = 0.0011$).

Propensity score matching based on age, sex, race, tumor characteristics, comorbidity index, and treatment resulted in a cohort of 477 patients: 229 CTx only and 248 CTx-IT (Table 1). The median follow-up was 23.3 months in the matched cohort (22.7 months for CTx only group and 24.6 months for CTx-IT). The 5-year OS remained higher in the CTx-IT group compared with CTx alone (29.2% vs 18.2%; $p = 0.0045$; Fig. 1B). Subgroup survival analyses demonstrated improvement in 5-year OS in the CTx-IT group, even among those with positive margins (26.3% vs 13.6%; $p = 0.021$), node-positive disease (24% vs 12.5%; $p = 0.006$), and poorly differentiated histology (26.5% vs 12.8%; $p = 0.046$) (Fig. 2). When stratified by stage, the 5-year OS after adjuvant CTx-IT was improved in

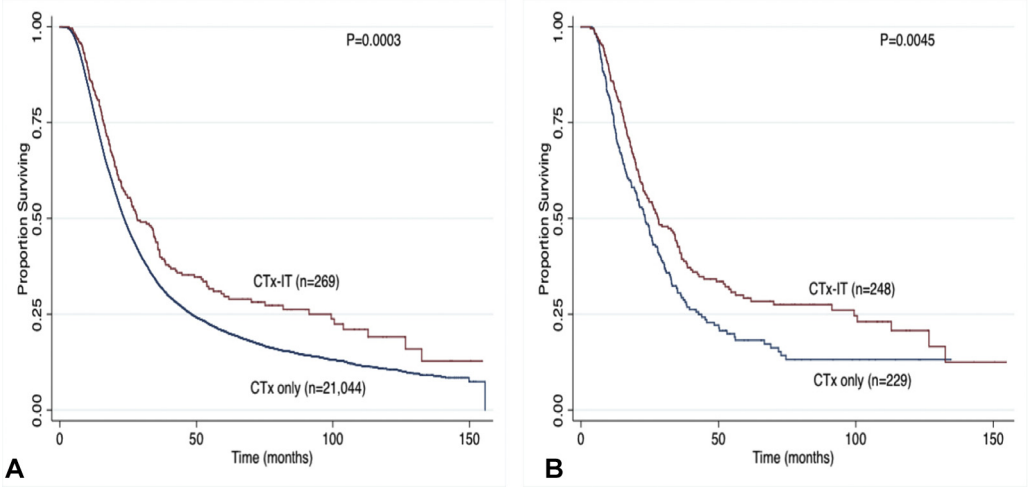

Figure 1. Kaplan-Meier survival curve stratified by type of adjuvant therapy: (A) unmatched cohort and (B) matched cohort. CTx, chemotherapy; IT, immunotherapy.

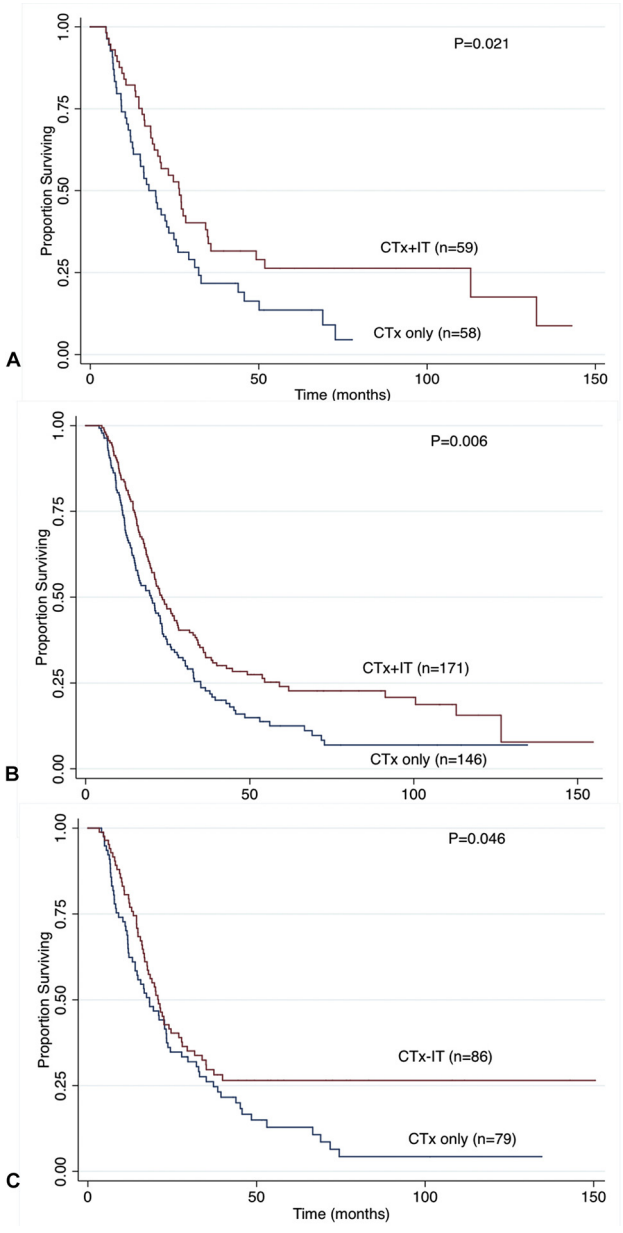

Figure 2. Subgroup analysis on overall survival comparing chemotherapy (CTx) only vs CTx+immunotherapy (IT) in the propensity-matched cohort factors with high-risk factors: (A) R1 margin status, (B) positive lymph node, and (C) poorly differentiated disease.

stage II (5-year OS 27.1% vs 17.6%; p = 0.020), but not stage I (40.0% vs 24%; p = 0.327) or stage III (50% vs 20%; p = 0.222).

After adjusting for patient, pathologic, and treatment characteristics; multivariate survival analysis of the entire unmatched cohort revealed that adjuvant CTx-IT was an independent predictor of improved OS (HR 0.75; 95% CI 0.643 to 0.885; p = 0.001), and older age, R1 margins, advancing stage, and high-grade histology were poor prognostic factors (Table 2). Multivariable analysis of the propensity-matched cohort demonstrated that only non-poorly differentiated histology (HR 1.90; 95% CI 1.18 to 3.05; p = 0.008) and receipt of immunotherapy were associated with improved survival (HR 0.74; 95% CI 0.59 to 0.92; p = 0.007) (Table 3).

DISCUSSION

The current study examined the impact of adjuvant immunotherapy on survival after curative-intent resection for PDAC. Receipt of adjuvant CTx-IT was associated with improved survival and this association persisted when controlled for age, sex, pathology, and treatment in a propensity-matched analysis. Adjuvant CTx-IT was also associated with prolonged survival compared with CTx alone among patients with adverse risk factors, such as positive margins, node-positive disease, and poorly differentiated histology.

Pancreatic ductal adenocarcinoma is traditionally considered an immunoresistant disease. Tumors traditionally reflect a lack of tumor-infiltrating lymphocytes and a plethora of suppressor T cells. This might be one of the reasons that immune-based monotherapy has not resulted in the same clinical responses in PDAC as in other tumor histologies. However, multiple strategies are being pursued to sensitize cells to anti-tumor immune responses. In particular, chemoimmunotherapy can synergize to improve outcomes compared with chemotherapy alone, given increasing evidence that some chemotherapies can enhance anti-tumor immune responses. Gemcitabine has been shown to improve host immune recognition of malignant cells by stimulating dendritic cell maturation, increasing epitope presentation on tumor cells, and decreasing tumor-infiltrating myeloid-deprived suppressor cells.[24-26] Oxaliplatin has been shown to upregulate damage-associated molecular patterns and immunogenic cell death, and cyclophosphamide has been shown to promote dendritic cell maturation and upregulate HLA molecules on tumor cells.[27,28] The combination of immunotherapies with chemotherapy represents a promising strategy to stimulate immunogenicity, inhibit tumor-mediated immunosuppression, and improve survival.

Checkpoint blockade immunotherapy has resulted in impressive responses in the metastatic setting of various tumor histologies and, more recently, has been tested in the adjuvant setting. Specifically, FDA approval has already been granted for the use of either adjuvant nivolumab or pembrolizumab in advanced melanoma,[29,30] cervical cancer,[31] bladder cancer,[19,32] and renal cancer,[33]

Table 2. Multivariate Analysis of Factors Associated with Overall Survival after Resection of Pancreatic Adenocarcinoma in Entire Cohort (n = 17,496)

Characteristic	Hazard ratio	95% CI	p Value
Age, y	1.007	1.005–1.009	<0.001
Sex			
Male	ref	—	—
Female	0.970	0.935–1.002	0.069
Race			
White	ref	—	—
Black	1.045	0.984–1.110	0.149
Asian	0.912	0.795–1.045	0.186
Other	0.785	0.694–0.889	<0.001
Charlson Comorbidity Index			
0	ref	—	—
1	1.258	1.172–1.30	<0.001
2	1.601	1.490–1.719	<0.001
3	1.227	1.131–1.331	<0.001
Grade			
Well	ref	—	—
Moderate	1.265	1.179–1.358	<0.001
Poor	1.613	1.501–1.733	<0.001
Unknown	1.259	1.160–1.367	<0.001
Margin status			
R0			
R1	1.550	1.487–1.614	<0.001
Adjuvant therapy			
CTx	ref	—	—
CTx+IT	0.766	0.653–0.897	0.001
Stage			
I	ref	—	—
II	1.590	1.500–1.686	<0.001
III	2.002	1.821–2.200	<0.001
Radiotherapy	0.924	0.892–0.958	<0.001
Type of operation			
Distal pancreatectomy	ref	—	—
Pancreaticoduodenectomy	1.029	0.974–1.087	0.309
Total pancreatectomy	1.027	0.959–1.100	0.441
Pancreatectomy not otherwise specified	1.284	0.145–1.440	<0.001

CTx, chemotherapy; IT, immunotherapy.

based on the results of recent clinical trials. In addition to checkpoint blockade, tumor vaccines, monoclonal antibodies, adoptive cell transfer, and immune modulators have shown impressive efficacy when delivered systemically or, in some cases, intratumoral.[15,17-19,34-36] Checkpoint blockade, either alone or in combination with chemotherapy, has been studied in early-stage PDAC trials, but to date have not led to FDA approval in metastatic pancreas cancer, and use has been limited in the adjuvant setting.[37] Similarly, although adjuvant vaccines have been shown to stimulate anti-tumor T-cell responses and have been used to a greater degree in PDAC, clear efficacy in substantial numbers of patients has been elusive.[38-40] Interleukin-2, interferon α2b, and interleukin-10 have also been used as immunostimulatory agents in combination with chemotherapy for PDAC with measurable activity in the adjuvant setting, although larger numbers of patients will need to be treated to determine efficacy.[41-46]

The immunotherapy group represents only 1.3% of patients who received adjuvant therapy for PDAC, indicating that this is a very highly select group of patients

Table 3. Multivariate Cox Regression Survival Analysis of Factors Associated with Overall Survival after Resection of Pancreatic Adenocarcinoma in Matched Cohort (n = 447)

Characteristic	Hazard ratio	95% CI	p Value
Grade			
Well	ref	—	—
Moderate	1.556	0.969–2.499	0.067
Poor	1.901	1.184–3.050	0.008
Unknown	1.082	0.634–1.848	0.773
Margin status			
R0	ref	—	—
R1	1.240	0.966–1.593	0.092
Adjuvant therapy			
CTx	ref	—	—
CTx+IT	0.737	0.590–0.919	0.007
Stage			
I	ref	—	—
II	1.492	0.944–2.360	0.086
III	1.686	0.879–3.231	0.115

CTx, chemotherapy; IT, immunotherapy.

with resectable PDAC, and many of these patients might have been enrolled in clinical trials. There have been several small and underpowered studies on the efficacy of chemoimmunotherapy in the adjuvant setting for PDAC. In a study of 12 patients who underwent resection for PDAC, Aguilar and colleagues[47] reported that adjuvant gene-mediated cytotoxic immunotherapy resulted in an OS of 9 to 30 months. In another study consisting of 43 patients, Matsui and colleagues[48] demonstrated that adjuvant adoptive immunotherapy combined with gemcitabine resulted in disease-free survival of 15.8 months and OS of 24.7 months.[48] In addition, a phase II study of 70 patients treated with gemcitabine plus algenpantucel-L immunotherapy demonstrated a 12-month disease-free survival rate of 62% and 12-month overall survival rate of 86%.[49] This led to a multicenter phase III randomized controlled trial (IMPRESS trial, NCT01072981) evaluating the impact of algenpantucel-L immunotherapy with gemcitabine in patients with surgically resected PDAC. Other ongoing trials using chemoimmunotherapy remain under investigation, including combining gemcitabine with nab-paclitaxel, nivolumab, and a CD40 agonistic monoclonal antibody.

To our knowledge, the current study represents the largest retrospective study on adjuvant immunotherapy with chemotherapy compared with chemotherapy alone for PDAC. However, there remain several limitations. Although chemoimmunotherapy was associated with improved survival compared with chemotherapy alone, these patients were younger, had a better performance status, and were more likely to be treated at academic cancer centers. Though patient and treatment factors were addressed in the propensity score analysis where age and Charleston Comorbidity Index were matched, inherent selection biases can remain. In addition, although this is a large, national data set, the immunotherapy group still represents a highly selective group likely enrolled in clinical trials, as biases could not be controlled given the retrospective nature of the database. Although we attempted to reduce bias and created a balanced cohort by accounting for covariates that predict receipt of treatment by propensity score matching based on patient and tumor characteristics, unknown confounders not captured in the database might result in biases not accounted for in the propensity score-matched cohort, as any hidden or latent biases might remain even after matching and multivariable analysis. In addition, the NCDB does not provide granular data on the specific type of chemotherapy or immunotherapy used, or on microsatellite-instability status for PDAC patients. It was not possible to compare outcomes from those who received vaccine therapy with those who received monoclonal antibodies or checkpoint inhibitors, for example, that would allow subgroup survival analyses based on type of immunotherapy used or microsatellite-instability status. Nevertheless, using this large national database provided sufficient patient numbers as a whole to identify patterns of response to chemoimmunotherapy that have been difficult to quantify from small retrospective series or single-arm, early-stage prospective trials. Clearly, the next steps will be to match specific immunotherapy and chemotherapy agents with susceptible patient populations to identify the optimal chemoimmunotherapy strategies that may improve outcomes in this aggressive disease.

CONCLUSIONS

Although primary surgical resection followed by systemic chemotherapy remains the standard of care for localized pancreatic adenocarcinoma, the combination of adjuvant chemotherapy and immunotherapy was associated with improved survival compared with chemotherapy alone. Clinical trials on the feasibility, durability, and long-term survival benefit of chemoimmunotherapy after resection of pancreatic adenocarcinoma are warranted.

Author Contributions

Study conception and design: Tran, AV Maker
Acquisition of data: Tran, VK Maker, AV Maker
Analysis and interpretation of data: Tran, AV Maker
Drafting of manuscript: Tran, AV Maker
Critical revision: Tran, VK Maker, AV Maker

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
2. Kooby DA, Gillespie TW, Liu Y, et al. Impact of adjuvant radiotherapy on survival after pancreatic cancer resection: an appraisal of data from the national cancer data base. Ann Surg Oncol 2013;20:3634–3642.
3. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. Lancet 2004;363[9414]:1049–1057.
4. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas 201 patients. Ann Surg 1995;221:721–731; discussion 731–733.
5. Winter JM, Brennan MF, Tang LH, et al. Survival after resection of pancreatic adenocarcinoma: results from a single institution over three decades. Ann Surg Oncol 2012;19:169–175.
6. Smeenk HG, Tran TC, Erdmann J, et al. Survival after surgical management of pancreatic adenocarcinoma: does curative and radical surgery truly exist? Langenbecks Arch Surg 2005;390:94–103.
7. Wolfgang CL, Herman JM, Laheru DA, et al. Recent progress in pancreatic cancer. CA Cancer J Clin 2013;63:318–348.
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. de WMR, Talamonti MS, Baker MS, et al. Primary systemic therapy in resectable pancreatic ductal adenocarcinoma using mFOLFIRINOX: a pilot study. J Surg Oncol 2018;117:354–362.
10. Sinn M, Bahra M, Liersch T, et al. CONKO-005: Adjuvant Chemotherapy With Gemcitabine Plus Erlotinib Versus Gemcitabine Alone in Patients After R0 Resection of Pancreatic Cancer: a multicenter randomized phase III trial. J Clin Oncol 2017;35:3330–3337.
11. 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[10073]:1011–1024.
12. 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.
13. Elkord E, Dangoor A, Drury NL, et al. An MVA-based vaccine targeting the oncofetal antigen 5T4 in patients undergoing surgical resection of colorectal cancer liver metastases. J Immunother 2008;31:820–829.
14. Geevarghese SK, Geller DA, de Haan HA, et al. Phase I/II study of oncolytic herpes simplex virus NV1020 in patients with extensively pretreated refractory colorectal cancer metastatic to the liver. Hum Gene Ther 2010;21:1119–1128.
15. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med 2013;369:134–144.
16. Harrop R, Connolly N, Redchenko I, et al. Vaccination of colorectal cancer patients with modified vaccinia Ankara delivering the tumor antigen 5T4 (TroVax) induces immune responses which correlate with disease control: a phase I/II trial. Clin Cancer Res 2006;12[Pt 1]:3416–3424.
17. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182–1191.
18. Perez MC, Miura JT, Naqvi SMH, et al. Talimogene laherparepvec (TVEC) for the treatment of advanced melanoma: a single-institution experience. Ann Surg Oncol 2018;25:3960–3965.
19. Powles T, Eder JP, Fine GD, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014;515[7528]:558–562.
20. Menck HR, Cunningham MP, Jessup JM, et al. The growth and maturation of the National Cancer Data Base. Cancer 1997;80:2296–2304.
21. Partridge EE. The National Cancer Data Base: ten years of growth and commitment. CA Cancer J Clin 1998;48:131–133.
22. Neoptolemos JP, Stocken DD, Tudur Smith C, et al. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. Br J Cancer 2009;100:246–250.
23. Ueno H, Kosuge T, Matsuyama Y, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. Br J Cancer 2009;101:908–915.
24. Ghansah T, Vohra N, Kinney K, et al. Dendritic cell immunotherapy combined with gemcitabine chemotherapy enhances survival in a murine model of pancreatic carcinoma. Cancer Immunol Immunother 2013;62:1083–1091.
25. Jackaman C, Majewski D, Fox SA, et al. Chemotherapy broadens the range of tumor antigens seen by cytotoxic CD8(+) T cells in vivo. Cancer Immunol Immunother 2012;61:2343–2356.
26. Liu WM, Fowler DW, Smith P, Dalgleish AG. Pre-treatment with chemotherapy can enhance the antigenicity and immunogenicity of tumours by promoting adaptive immune responses. Br J Cancer 2010;102:115–123.
27. Tesniere A, Schlemmer F, Boige V, et al. Immunogenic death of colon cancer cells treated with oxaliplatin. Oncogene 2010;29:482–491.
28. Schiavoni G, Sistigu A, Valentini M, et al. Cyclophosphamide synergizes with type I interferons through systemic dendritic cell reactivation and induction of immunogenic tumor apoptosis. Cancer Res 2011;71:768–778.
29. Eggermont AMM, Robert C, Suciu S. Adjuvant pembrolizumab in resected stage III melanoma. N Engl J Med 2018;379:593–595.
30. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017;377:1824–1835.
31. Saglam O, Conejo-Garcia J. PD-1/PD-L1 immune checkpoint inhibitors in advanced cervical cancer. Integr Cancer Sci Ther 2018;5[2].
32. Hakenberg OW. Nivolumab for the treatment of bladder cancer. Expert Opin Biol Ther 2017;17:1309–1315.
33. Atkins MB, Plimack ER, Puzanov I, et al. Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. Lancet Oncol 2018;19:405–415.
34. Kemeny N, Brown K, Covey A, et al. Phase I, open-label, dose-escalating study of a genetically engineered herpes simplex virus, NV1020, in subjects with metastatic

colorectal carcinoma to the liver. Hum Gene Ther 2006;17:1214–1224.
35. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–2520.
36. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443–2454.
37. Rosenberg A, Mahalingam D. Immunotherapy in pancreatic adenocarcinoma-overcoming barriers to response. J Gastrointest Oncol 2018;9:143–159.
38. Disis ML, Bernhard H, Jaffee EM. Use of tumour-responsive T cells as cancer treatment. Lancet 2009;373[9664]:673–683.
39. Kamphorst AO, Araki K, Ahmed R. Beyond adjuvants: immunomodulation strategies to enhance T cell immunity. Vaccine 2015;33[Suppl 2]:B21–B28.
40. Tanyi JL, Bobisse S, Ophir E, et al. Personalized cancer vaccine effectively mobilizes antitumor T cell immunity in ovarian cancer. Sci Transl Med 2018;10[436].
41. Bellone G, Novarino A, Vizio B, et al. Impact of surgery and chemotherapy on cellular immunity in pancreatic carcinoma patients in view of an integration of standard cancer treatment with immunotherapy. Int J Oncol 2009;34:1701–1715.
42. Buzaid AC, Legha SS. Combination of chemotherapy with interleukin-2 and interferon-alfa for the treatment of advanced melanoma. Semin Oncol 1994;21[Suppl 14]:23–28.
43. Davis M, Conlon K, Bohac GC, et al. Effect of pemetrexed on innate immune killer cells and adaptive immune T cells in subjects with adenocarcinoma of the pancreas. J Immunother 2012;35:629–640.
44. Hoffmann K, Mehrle S, Schmidt J, et al. Interferon-alpha restitutes the chemosensitivity in pancreatic cancer. Anticancer Res 2008;28[3A]:1499–1507.
45. Schmidt J, Abel U, Debus J, et al. Open-label, multicenter, randomized phase III trial of adjuvant chemoradiation plus interferon Alfa-2b versus fluorouracil and folinic acid for patients with resected pancreatic adenocarcinoma. J Clin Oncol 2012;30:4077–4083.
46. Schmidt J, Jager D, Hoffmann K, et al. Impact of interferon-alpha in combined chemoradioimmunotherapy for pancreatic adenocarcinoma (CapRI): first data from the immunomonitoring. J Immunother 2007;30:108–115.
47. Aguilar LK, Shirley LA, Chung VM, et al. Gene-mediated cytotoxic immunotherapy as adjuvant to surgery or chemoradiation for pancreatic adenocarcinoma. Cancer Immunol Immunother 2015;64:727–736.
48. Matsui H, Hazama S, Sakamoto K, et al. Postoperative adjuvant therapy for resectable pancreatic cancer with gemcitabine and adoptive immunotherapy. Pancreas 2017;46:994–1002.
49. Hardacre JM, Mulcahy M, Small W, et al. Addition of algenpantucel-L immunotherapy to standard adjuvant therapy for pancreatic cancer: a phase 2 study. J Gastrointest Surg 2013;17:94–100; discussion 101.

Discussion

DR GEORGE B KAZANTSEV (Oakland, CA): This study focuses on long-term survival after curative resection for pancreatic adenocarcinoma. The goal of this study was to explore the role of immunotherapy given in adjuvant settings in combination with chemotherapy, as compared with chemotherapy alone. Using the National Cancer Database (NCDB), the authors identified 21,313 patients who received adjuvant therapy after curative resection for pancreatic cancer between 2004 and 2015. Propensity score matching was used to develop 2 comparable cohorts of patients who received a combination of chemotherapy and immunotherapy and those who got chemotherapy alone. Statistical analysis demonstrated significantly improved overall survival in patients receiving combination treatments. The difference remained significant when patients were stratified by stage, as well as by tumor, characteristics such as margin status, lymph node positivity, and degree of tumor differentiation. The addition of chemotherapy was found to be an independent predictor of improved overall survival.

The group of patients who received immunotherapy represents only 1.3% of the study population. As you acknowledge in your manuscript, those patients tended to be younger, have private insurance, and were treated in academic centers. This looks like a highly select group of patients who might have been healthier or might have received more aggressive chemotherapy, which is a common practice in academic centers. Do you think that this possible selection bias could have accounted for some survival benefit?

Appendix 1 in your manuscript lists 25 different treatments meeting the definition of immunotherapy under NCDB guidelines. Many of those treatments, including monoclonal antibodies and cancer vaccines, produced some disappointing results in clinical trials and/or failed to advance into clinical practice. How would you reconcile those observations with the results of your study? Would you be able to separate the therapies that hold future promise from those that do not?

Finally, your survival analysis noted 30% 5-year overall survival in the chemotherapy plus immunotherapy group. Recent advances in pancreatic cancer treatments, such as the use of multiagent chemotherapy regimens shift toward neoadjuvant approach, and advanced radiation techniques have produced comparable or superior results with 5-year survival reported in excess of 30%. Do you see the introduction of chemotherapy in adjuvant settings in the clinical practice in the near future?

DR AJAY V MAKER (Chicago, IL): Your first question was about matching of the groups of patients. Very few patients did receive chemoimmunotherapy—269 in total. That was 1.3% of the total population of more than 20,000 patients. One of the limitations in evaluating the individual trials using immunotherapy for pancreatic cancer to date has been that they enrolled a very small number of patients. What the current analysis allowed was a slightly better ability to power this analysis for survival. I do not think that is a limitation that can be completely resolved from a database such as the NCDB because it includes multiple treatment strategies. This problem will be solved only with prospective clinical trials. You mentioned, of course, that those patients were mostly treated in academic centers and they had private insurance; that is true. To attempt to address some of the selection biases inherent to this retrospective analysis, we performed propensity score matching using the nearest-neighbor algorithm that included these variables and the Charlson Comorbidity Index. That was the best we could control for in a matched cohort. As far as the question as to whether

eTable 1. Immunotherapy Drugs Used in Pancreatic Cancer in Surveillance, Epidemiology, and End Results-Rx Database

Drug name	Alternative name	Category
Pancreatic tumor cell vaccine	—	Vaccine
CEA (CAP1-6D) peptide	—	Vaccine
Antibody ganitumab (AMG-479)	—	Monoclonal antibody inhibitor of IGF-IR
Dalotuzumab	MK-0646	Humanized monoclonal antibody
Avicine	—	Vaccine
GVAX vaccine	CG 8123	Vaccine
RAS 5-17 peptide vaccine	—	Vaccine
Oncophage	Heat shock protein-peptide complex (HSPPC-96)	Vaccine
RC-3095	—	Bombesin/gastrin-releasing peptide antagonist
Cetuximab	Erbitux, C-225/IMC-C225	Monoclonal antibody, anti-EGFR antibody
TNFerade	—	Gene therapy
Gastrimmune	—	Vaccine
P53 and RAS vaccine	—	Vaccine
CEA-Vac	—	Vaccine
BrevaRex	—	Passive monoclonal antibody
O-Vax	—	Vaccine
Recombinant soluble PSMA vaccine	—	Vaccine
Telomerase cancer vaccine	—	Vaccine
Anti-gastrin therapeutic vaccine	—	Vaccine
Virulizin	—	Macrophage activator
Vaccinia-MUC-1 vaccine	—	Vaccine
PanVac	—	Vaccine
P16 program	—	Gene therapy
CEA-cide	—	Anti-CEA monoclonal antibody
Peripheral blood lymphocytes transduced with a gene encoded chimeric T-cell receptor	—	Gene therapy
Trastuzumab	Anti-erbB2 monoclonal antibody, Anti-HER2/c-erbB2 monoclonal antibody	Targeted therapy: epidermal growth factor receptor
Keytruda	MK-3475, SCH-900475, lambrolizumab, pembrolizumab	Monoclonal antibody

CAP1-6D, carcinoembryonic antigen peptide 1-6D; EGFR, epidermal growth factor receptor; erbB, erythroblastic oncogene B; GVAX, granulocyte-macrophage colony-stimulating factor gene transduced autologous pancreatic cancer vaccine; IGF-IR, insulin-like growth factor receptor; MUC-1, mucin 1; PSMA, prostate specific cancer antigen human recombinant; TNF, tumor necrosis factor.