Clinical and Translational Radiation Oncology 24 (2020) 34–40

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Original Research Article

The impact of immunotherapy on the survival of pancreatic adenocarcinoma patients who do not receive definitive surgery of the tumor

Saber Amin [a], Michael Baine [a], Jane Meza [b], Morshed Alam [b], Chi Lin [a,*]

[a] Department of Radiation Oncology, University of Nebraska Medical Center, USA
[b] Department of Biostatistics, College of Public Health, University of Nebraska Medical Center, USA

ARTICLE INFO

Article history:
Received 25 March 2020
Revised 26 May 2020
Accepted 1 June 2020
Available online 7 June 2020

Keywords:
Immunotherapy
Chemoradiation and immunotherapy
Chemotherapy plus immunotherapy
Overall survival
Pancreatic ductal adenocarcinoma

ABSTRACT

Background and Purpose: Immunotherapy has shown great efficacy in many cancers, but its role in pancreatic ductal adenocarcinoma (PDAC) remains unclear. The objective of this study was to investigate the impact of immunotherapy on the overall survival of PDAC patients who did not receive definitive surgery of the pancreatic primary tumor site using the National Cancer Database (NCDB).

Materials and Methods: Patients with pancreatic adenocarcinoma who did not receive surgery were identified from NCDB. Cox proportional hazard models were employed to assess the impact of immunotherapy on survival after adjusting for age at diagnosis, race, sex, place of living, income, education, treatment facility type, insurance status, year of diagnosis, and treatment types such as chemotherapy and radiation therapy.

Results: Of 263,886 patients who were analyzed, 911 (0.35%) received immunotherapy. Among patients who received chemotherapy (101,546), and chemoradiation (30,226) therapy, 555/101,546 (0.55%) received chemotherapy plus immunotherapy, and 299/3,022 (9.9%) received chemoradiation plus immunotherapy. In a multivariable analysis adjusted for the factors mentioned above, immunotherapy was associated with significantly improved OS (HR: 0.866 (0.800–0.937); $P < 0.001$) compared to no immunotherapy. Chemotherapy plus immunotherapy was significantly associated with improved OS (HR: 0.848 (0.766–0.938); $P < 0.001$) compared to chemotherapy without immunotherapy. Further, chemoradiation plus immunotherapy was associated with significantly improved OS (HR: 0.813 (0.707–0.936); $P < 0.001$) compared to chemoradiation alone.

Conclusion: In this study, the addition of immunotherapy to chemotherapy and chemoradiation therapy was associated with significantly improved OS in PDAC patients without definitive surgery. The study warrants future clinical trials of immunotherapy in PDAC.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) represents 3.2% of all cancer cases, but it is responsible for 7.2% of all cancer deaths in the United States [1]. Each year, more than 53,000 people in the U.S. are diagnosed with PDAC, while more than 34,000 people die from it [1]. It is predicted that by 2030, PDAC will become the second leading cause of cancer death [2]. Due to the lack of early detection methods, lack of early signs and symptoms, late presentation, disease heterogeneity, and treatment resistance, PDAC is challenging to treat [3]. More than 80% of the patients present with locally advanced (non-resectable) or metastatic disease, while only 20% present with resectable cancer [4]. The five-year survival is 8.1% and 22% in non-resectable and resectable PDAC patients [5,6]. Surgery is the only curative treatment and is associated with a median OS of 28 months when used with adjuvant gemcitabine plus capecitabine [7]. Most recently, the median survival time of up to 54 months has been reported with adjuvant modified FOLFIRINOX in resected pancreatic cancer patients [8]. A median OS of 15.2 months has been reported for locally advanced pancreatic

Abbreviations: NCDB, National Cancer Database; PDAC, Pancreatic adenocarcinoma; MDSC, Myeloid-derived suppressor cells; TME, Tumor microenvironment.

* Corresponding author at: Department of Radiation Oncology, University of Nebraska Medical Center, 986861 Nebraska Medical Center, Omaha, NE, 68198-6861, USA.
E-mail address: clin@unmc.edu (C. Lin).

https://doi.org/10.1016/j.ctro.2020.06.003
2405-6308/Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology.

cancer patients who received capecitabine-based chemoradiation therapy [9]. The median OS of metastatic PC is 11 months in patients who receive FOLFIRINOX [10].

Due to the minimal effectiveness of the current treatments especially for unresectable PDAC, novel treatment strategies such as immunotherapeutics have been proposed and occasionally used in an off-label setting in PDAC, mostly extrapolating the utility in various other malignancies. Immunotherapy has shown efficacy in pancreatic cancer patients who were mismatch repair deficient [11]. The FDA has approved pembrolizumab for the treatment of patients with unresectable or metastatic, microsatellite instability–high (MSI-H) or mis-match-repair–deficient (dMMR) solid tumors, including pancreatic cancer [11]. The approval was based on data from five clinical trials which included six patients with pancreatic cancer, in whom a response rate of 83% (5/6) was reported [11,12]. Many current clinical trials are looking into the efficacy of immunotherapy in PDAC [13–15], but no survival data is available to guide clinicians. Despite the lack of data indicating the survival benefit of immunotherapy in PDAC [16–19], by analyzing the NCDB database; we found that more patients have received immunotherapy in 2014–2016 when compared to previous years. The lack of response of PDAC to mono immunotherapy in the initial trials is partly attributed to the unique immunosuppressive tumor microenvironment, which consists of a dense fibrotic stroma and a scarcity of T cell infiltration [15,20]. It is also possible that the negative results were due to the small sample size and inclusion of heavily pretreated advanced PDAC patients. There is a strong counterargument that combining immunotherapy with other standard treatments has the potential to amplify the efficacy of immunotherapy in PDAC.

Pre-clinical and clinical studies have indicated that chemotherapy and RT induce immunogenic cell death, increase tumor-specific T cell infiltration, decrease Treg cells and suppress Myeloid-derived suppressor cells (MDSC), which immunotherapy can utilize to improve immune response [20–22]. In pre-clinical studies of PDAC, immunotherapy has elicited tumor regression and improved survival when used in combination with chemotherapy [23–25]. Pre-clinical studies have also found that the combination of RT and targeted Programmed cell death receptor 1, and programmed cell death receptor ligand 1 therapy activates cytotoxic T-cells, reduces MDSC, and induces an abscopal response [25–27]. A pre-clinical study demonstrated that RT is synergistic with anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4) antibody and induces systemic anti-tumor responses in a poorly immunogenic carcinoma compared to anti-CTLA-4 monotherapy [28]. Another preclinical study of PDAC, showed that the use of anti-PD-L1 strongly enhanced tumor response to high dose RT [29]. A trend toward tumor response was also noticed for low dose RT [29]. In the study, RT and gemcitabine both induced the expression of PD-L1 in PDAC [29]. The findings illustrate that immunotherapy could be combined with chemotherapy, RT, or both to enhance the anti-tumor response of these treatments.

The results of these pre-clinical studies in various cancers have led to the design of some of the current clinical trials of immunotherapy combined with chemotherapy and RT [13–15]. Early phase trials of combining immunotherapy, especially checkpoint inhibitors with chemotherapy in pancreatic cancer, have reported some encouraging findings [30–34]. These trials have reported improved median OS for patients who received checkpoint inhibitors with chemotherapy compared to historical data [30–34].

The objective of this study was to investigate the impact of immunotherapy on the overall survival of PDAC patients who did not receive definitive surgery of the pancreas using the National Cancer Database (NCDB). This manuscript only includes patients who did not receive definitive surgery of the pancreatic tumor because patients who do or do not receive definitive surgery are two different populations of patients. Patients who receive surgery do significantly better than those who do not receive surgery. The median survival is 17–23 months in resectable and 4–6 months in nonresectable PDAC [35,36].

2. Methods and materials

2.1. Data source

The data were extracted from the National Cancer Database (NCDB), which is a joint program of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. It captures 70% or more of newly diagnosed malignancies in the United States annually. Since all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

2.2. Study population

Patients age 18 or older, diagnosed with PDAC between 2004 and 2016, were included in the study. Patients who received definitive surgery of the tumor, and those who had missing information on RT, chemotherapy, and immunotherapy were excluded. Patients with unknown or missing information about other covariates were not included in the adjusted multivariable analysis. The surgical site-specific code was used to identify patients with definitive surgery of the tumor and exclude them. There was not enough sample size for immunotherapy plus RT vs. RT alone, and therefore the analysis for this group was not performed. The ICD-O-3 histology codes of 8000, 8010, 8020–8022, 8140, 8141, 8211, 8230, 8500, 8521, 8050, 8260, 8441, 8450, 8453, 8470–8473, 8480, 8481, 8503,8250,8440, 8560 were used for defining PDAC.

2.3. End points

The primary outcome was overall survival (OS) calculated from the date of diagnosis to the date of death from any cause. Those alive or lost to follow up were censored at the date of the last contact.

3. Predictors or explanatory variables

The main predictors of this study were immunotherapy, immunotherapy combined with chemotherapy, and immunotherapy combined with chemoradiation. Age at diagnosis, gender, race, urban and rural living status, income, education, treatment facility type, comorbidity score, insurance status, year of diagnosis, and receipt of chemotherapy, radiation therapy, and immunotherapy were other explanatory variables included in the study.

4. Statistical analyses

Descriptive statistics for categorical and continuous variables were reported. Multivariable logistic analysis was performed to identify predictors of receiving immunotherapy, and the odds ratio was reported as the measure of association with the probability of using immunotherapy. Kaplan-Meier curves and log-rank tests were utilized to report the difference in median OS between groups. Multivariable Cox proportional hazards regression analysis was conducted to assess the association between treatment and OS. Variables with a p-value of < 0.2 in the univariate analysis were included in the multivariable analysis. A p-value of 0.10 was selected as a cut-off point for a variable to stay in the final model in the multivariable analysis. A P-value of 0.05 was used for a sig-

nificant level, which was based on two-sided tests. Separate multivariable Cox proportional hazard regression models were developed for the hazard ratio of immunotherapy combined with chemotherapy and chemoradiation as these combinations are mutually explosive variables. The SAS 9.4 software was used for the analysis.

5. Results

In total, 263,886 patients diagnosed with PDAC between 2004 and 2016 who did not receive definitive surgery met the inclusion criteria and were included for the analysis. Of the 263,886 patients, 911 (0.35%) received immunotherapy. Among patients who received chemotherapy (101,546), RT (5,111), and chemoradiation (30,226) therapy, 555/101,546 (0.55%) received chemotherapy plus immunotherapy, 9/5,111 (0.18%) received RT plus immunotherapy, and 299/30,226 (0.99%) received chemoradiation plus immunotherapy. The median age was 71.00, with a range of (18.0–90.0) years. The majority of patients were White, insured, living in the urban areas, had Charlson/Deyo Score of zero, had a high school degree, had income >=$35,000, and received chemotherapy. In the multivariable logistic analysis, older age, black race, no insurance, Charlson/Deyo Score of 1 and 2, community hospital, being less educated, diagnosed before 2011, not receiving chemotherapy, and not receiving RT were all less likely to receive immunotherapy compared to their counterparts (Table 1).

Based on results from the Kaplan Meier curves, patients who received immunotherapy had significantly improved median overall survival compared to patients who did not receive immunotherapy (Fig. 1a) with an absolute median OS benefit of 6.33 [10.60 vs. 4.27; p < 0.0001] months. Subset analysis revealed that patients who received chemotherapy plus immunotherapy had significantly improved median OS compared to those who receive chemotherapy alone (Fig. 1b) with an absolute median OS benefit of 2.33 [9.30 VS. 6.97; p < 0.0001] months. Similarly, patients who received chemoradiation plus immunotherapy had significantly improved median OS compared to patients who received only chemoradiation (Fig. 1c) with an absolute median OS benefit of 3.38 [14.42 vs. 11.04; p < 0.0001] months.

In univariate Cox Proportional analysis (Table2), immunotherapy was associated with significantly improved OS with a hazard ratio (HR) of 0.594 (0.552–0.639); P < 0.0001). Significantly improved OS was also noticed in Immunotherapy plus chemotherapy vs. chemotherapy alone (HR: 0.822 (0.746–0.904); P < 0.0001), and immunotherapy plus chemoradiation vs. chemoradiation alone (HR: 0.735 (0.650–0.831); P < 0.0001). In the univariate Cox analysis, older age, low education, low income, treatment at community hospital, Charlson/Deyo Score of 1 and 2, diagnosis before 2011, not receiving RT, and not receiving chemotherapy were all associated with significantly decreased OS, while Black race and non-white non-black race were associated with significantly improved OS.

In the multivariable Cox proportional hazard analysis (Table 2), receipt of immunotherapy, female sex, and non-white non-black race were associated with significantly improved OS, while older age, low income, treatment at community hospital, Charlson/Deyo of one and two, diagnosis before 2011, not receiving chemotherapy, and not receiving RT were associated with significantly decreased OS. In the multivariable analysis adjusted for all the above factors, immunotherapy was associated with significantly improved OS (HR: 0.866 (0.800–0.937); P < 0.0001) compared to no immunotherapy. The results stayed the same when patients with no treatments were excluded from the analysis. Treatment with chemotherapy plus immunotherapy was significantly associ-

Table 1
Multivariable logistic analysis of the factors associated with the receipt of immunotherapy in PDAC patients with no surgery.

Variable		Immunotherapy N (%) 911	No Immunotherapy N (%) 262,975	Total 263,886	Odds Ratio	95% CI	P
Age at diagnosis, Median (range)		64.00 (21–90)	71.00 (18–90)	263,886	0.973	0.967–0.980	0.0001
Sex	Male	497 (54.56)	131,965 (51.18)	132,462 (50.20)	1	Reference	
	Female	414 (45.44)	131,010 (49.82)	131,424 (49.80)		NS	0.331
Race	White	784 (87.21)	217,747 (83.77)	218,531 (83.78)	1	Reference	
	Black	75 (8.34)	33,124 (12.74)	33,199 (12.73)	0.663	0.515–0.854	0.002
	Other	40 (4.45)	9,067 (3.49)	9,107 (3.49)	1.078	0.755–1.541	0.680
	Unknown	12	3,037	3,049			
Education	>=13% HG	317 (35.11)	114,060 (43.55)	114,377 (43.52)	0.773	0.664–0.901	0.001
	<13%	586 (64.89)	147,832 (56.45)	148,418 (56.48)	1	Reference	
	Unknown	8	1,083	1,091			
Income	>=$35,000	593 (65.74)	152,161 (58.13)	152,754 (58.16)	1	Reference	
	<35,000	309 (34.26)	109,590 (41.87)	109,899 (41.84)		NS	0.516
	Unknown	9	1,224	1,233			
Place of Living	Urban	862 (97.95)	251,360 (98.11)	252,222 (98.11)	1	Reference	
	Rural	18 (2.05)	4,843 (1.89)	4,861 (1.89)		NS	0.488
	Unknown	31	5,768	6,803			
Hospital Type	Academic	589 (65.59)	100,414 (38.43)	101,003 (38.52)	1	Reference	
	Community	309 (34.41)	160,897 (61.57)	161,206 (61.48)	0.383	0.331–0.445	0.0001
	Unknown	13	1,664	1,677			
Insurance Status	Insured	847 (98.26)	249,219 (96.94)	250,066 (96.95)	1	Reference	
	Not insured	15 (1.74)	7,856 (3.06)	7,871 (3.05)	0.440	0.274–0.782	0.010
	Unknown	49	59,00	5,949			
Charlson/Deyo Score	0	716 (78.59)	171,219 (65.11)	171,935 (65.16)	1	Reference	
	1	154 (16.90)	63.980 (24.33)	64,134 (24.30	0.779	0.649–0.934	0.007
	>=2	41 (4.50)	27,776 (10.56)	27,817 (10.54)	0.606	0.435–0.842	0.003
M stage	M0	449 (51.14)	116,598 (45.95)	117,047 (45.97)	1	Reference	
	M1	429 (48.86)	137,142 (54.05)	137,571 (54.03)		NS	0.786
Chemotherapy	Yes	854 (93.74)	130,918 (49.78)	131,772 (49.94)	1	Reference	
	No	57 (6.26)	132057(50.22)	132,114 (50.06)	0.107	0.080–0.143	0.0001
Radiation Therapy	Yes	308 (33.81)	35,029 (13.32)	35,337 (13.39)	1	Reference	
	No	603 (66.19)	227,946 (86.68)	228,549 (86.61)	0.611	0.524–0.713	0.0001
Year of Diagnosis	2004–2010	451(49.51)	126,180 (47.98)	126,631 (47.99)		NS	0.650
	2011–2016	460 (50.49)	136,795 (52.02)	137,255 (52.01)	1	Reference	

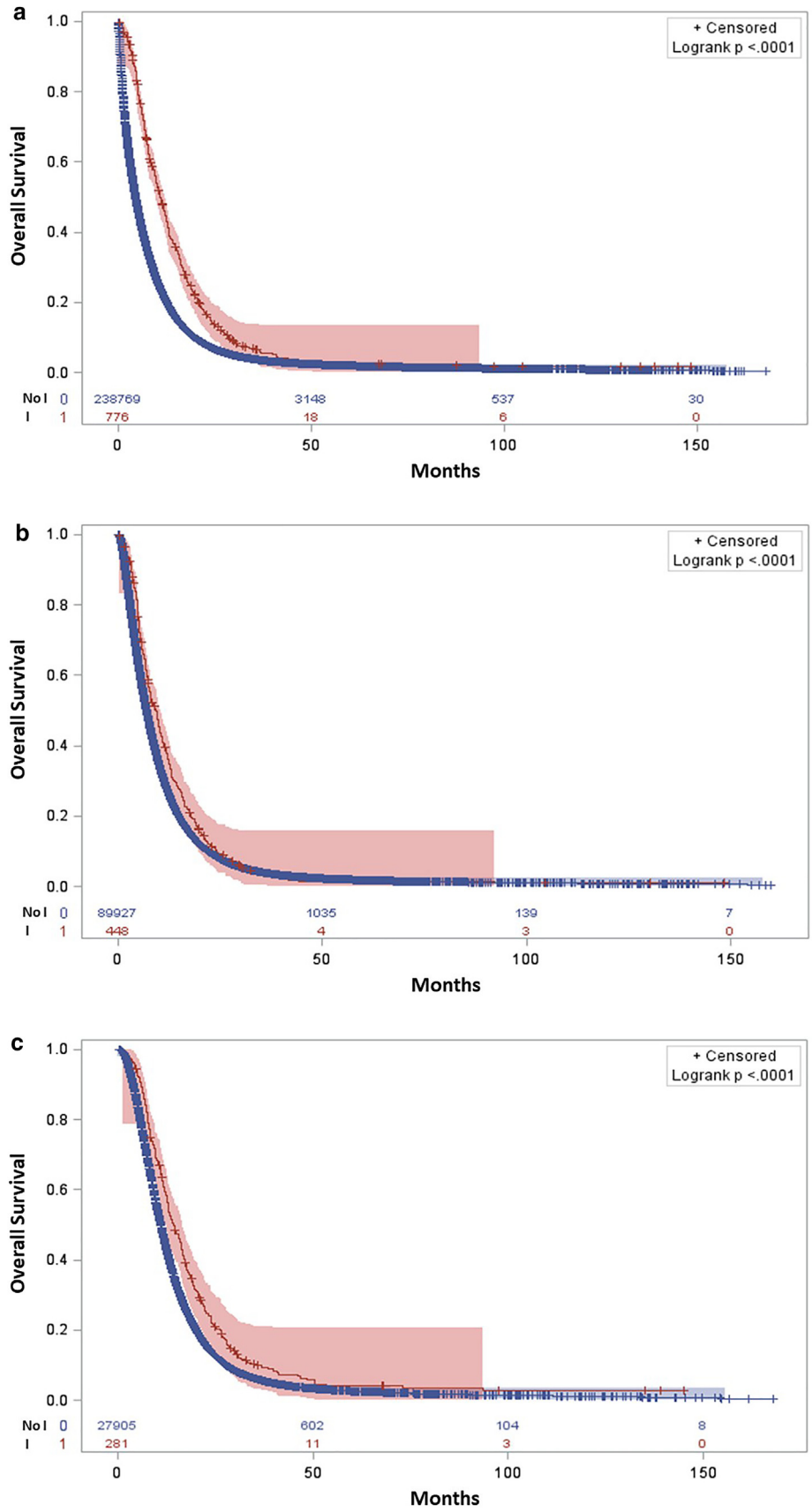

Fig. 1. Overall survival with (red) or without (blue) immunotherapy for (A) all patients; (B) patients who received chemotherapy; (C) patients who received chemoradiation therapy.

Table 2
Univariable and multivariable Cox proportional regression analysis of factors associated with OS of PC.

Variable		Univariable analysis		Multivariable analysis	
		Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Age at diagnosis (continuous)		1.018 (1.018–1.018)	<0.0001	1.012 (1.011–1.012)	<0.0001
Sex	Male	Reference		Reference	
	Female	0.994 (0.986–1.003)	<0.179	0.944 (0.935–0.952)	<0.0001
Race	White	Reference		Reference	
	Black	0.972 (0.960–0.984)	<0.0001	0.991 (0.978–1.005)	<0.210
	non-white non-black	0.866 (0.846–0.887)	<0.0001	0.885 (0.863–0.908)	<0.0001
Education	>=13% HG	1.049 (1.041–1.058)	<0.0001	0.988 (0.977–0.998)	0.021
	<13% HG	Reference		Reference	
Income	>=$35,000	Reference		Reference	
	<$35,000	1.091 (1.081–1.100)	<0.0001	1.069 (1.057–1.080)	<0.0001
Place of Living	Urban	Reference		Reference	
	Rural	1.078 (1.046–1.112)	<0.0001	1.045 (1.012–1.079	0.008
Hospital Type	Academic	Reference		Reference	
	Community	1.279 (1.268–1.290)	<0.0001	1.176 (1.165–1.186)	<0.0001
Insurance Status	Insured	Reference		Reference	
	Not insured	0.977 (0.953–1.002)	0.066	1.065 (1.039–1.093)	<0.0001
Charlson/Deyo Score	0	Reference		Reference	
	1	1.171 (1.160–1.183)	<0.0001	1.116 (1.105–1.128)	<0.0001
	>=2	1.520 (1.499–1.541)	<0.0001	1.351 (1.331–1.371)	<0.0001
Year of Diagnosis	2004–2010	1.181 (1.171–1.191)	0.0001	1.181 (1.170–1.191)	0.0001
	2011–2016	Reference		Reference	
M stage	M0	0.656 (0.651–0.662)	0.0001	0.563 (0.558–0.569)	0.0001
	M1	Reference			
Chemotherapy	Yes	Reference		Reference	
	No	2.146 (2.128–2.165)	<0.0001	2.096 (2.075–2.116)	<0.0001
Radiation Therapy	Yes	Reference		Reference	
	No	1.755 (1.734–1.776)	<0.0001	1.107 (1.092–1.123)	<0.0001
Immunotherapy	Yes	0.594 (0.552–0.639)		0.866 (0.800–0.937)	
	No	reference	<0.0001	reference	<0.0004

ated with improved OS (HR: 0.848 (0.766–0.938); P < 0.001) compared to chemotherapy without immunotherapy. Further, chemoradiation plus immunotherapy was associated with significantly improved OS (HR: 00.813 (0.707–0.936); P < 0.004) compared to chemoradiation alone. Both models were adjusted for the same factors mentioned previously. The one- and two-year survival rate was 60% (CI: 54%–66%) and 23% (CI: 18%–28%) for chemoradiation plus immunotherapy, 37% (CI: 33%–42%) and 11% (CI: 8%–13%) for chemotherapy plus immunotherapy, 45% (CI: 45%–46%) and 14% (CI: 13%–14%) for chemoradiation alone, and 28% (CI: 27%–28%) and 9% (CI: 8%–9%) for chemotherapy alone. Table 3 has the results of the univariable and multivariable analysis.

This analysis includes immunotherapy delivered both concomitantly and sequentially with chemotherapy or chemoradiation therapy. It should be noticed that the sample size of patients who received immunotherapy and chemotherapy (96/555, 17%) or immunotherapy and chemoradiation therapy (23/299, 7.7%) outside of 30 days window of each other was very small. The analysis excluding these patients did not affect the final results.

We also compared the OS of chemotherapy plus immunotherapy to chemotherapy alone and chemoradiation plus immunotherapy to chemoradiation alone stratified by M stage. We found that chemotherapy plus immunotherapy is associated with a lower risk of death when compared to chemotherapy alone in M1 patients but not M0 patients (Table 4). On the other hand, chemoradiation therapy plus immunotherapy is associated with a lower risk of death when compared to chemoradiation therapy alone in M0 patients but not M1 patients (Table 4). We did not analyze Patients who received immunotherapy only since the sample size for this cohort is very small (22 for M0 and 26 for M1).

6. Discussion

The current analysis demonstrated that adding immunotherapy to either chemotherapy or chemoradiation therapy leads to a significant OS benefit in both univariable and multivariable Cox regression analysis. What is unique about our study is that chemoradiation plus immunotherapy was associated with a signif-

Table 3
Univariate and multivariate analysis of Combining Immunotherapy with Chemotherapy and Radiation therapy.

Variable		N (%)	Univariable analysis		Multivariable analysis	
			Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Chemo and immunotherapy combination	Chemotherapy Only	100,991 (99.45%)	Reference		Reference	
	Chemo plus Immunotherapy	555 (0.55%)	0.822 (0.746–0.904)	<0.0001	0.848 (0.766–0.938)	0.001
Chemoradiation plus immunotherapy combination	Chemoradiation Only	29,927 (99.01%)	Reference		Reference	
	Chemoradiation plus Immunotherapy	299 (0.99%)	0.735 (0.650–0.831)	<0.0001	0.813 (0.707–0.936)	0.004

Two different models were developed for the multivariable analysis of Table 3 because the treatment combination variables were mutually exclusive.

Table 4
Multivariable Cox regression analysis of treatments combinations stratified by M stage.

Treatments		M0 at diagnosis		M1 at diagnosis	
		N	HR (95Cl)	N	HR (95Cl)
Chemotherapy	Plus Immunotherapy	179	0.912 (0.768–1.084)	361	**0.822(0.725–0.932)**
	No immunotherapy	31,885	Ref	66,444	Ref
Chemoradiation	Plus immunotherapy	241	**0.820(0.705–0.955)**	40	0.778 (0.542–1.115)
	No immunotherapy	24,302	Ref	4,905	Ref

HR is from MVA. Factors included in MVA were the age of diagnosis, gender, race, income, education, place of living, hospital type, insurance status, Charlson/Deyo score, and year of diagnosis.

icantly improved OS, which to our knowledge, has not been investigated yet.

The resistance of PDAC to the standard-of-care treatments is multifactorial [37]. Local therapies such as surgery and RT failed to show significant success because PDAC metastasizes microscopically early in the disease course, which limits the effectiveness of these treatments [38,39]. The presence of a strong desmoplastic stroma and the ability of the PDAC cells to go through a profound oncogenic alteration contribute to the failure of systemic therapies in PDAC [37,40,41]. However, OS has improved significantly in resectable, locally advanced, and metastatic PDAC with the use of modern chemotherapeutic agents such as FOLFIRINOX or capecitabine [7–10].

The tumor microenvironment (TME) of PDAC evades immune response by up-regulating programmed-death ligand 1, up-regulating CTLA4, recruitment of MDSC, and tumor-associated macrophages [42–47]. Based on these characteristics of the tumor, a multidisciplinary treatment approach of combining various systemic therapies such as immunotherapy and chemotherapy with each other or with local therapies such as RT may deliver better results. Immunotherapy may produce synergetic interaction with chemotherapy and radiation therapy as they increase tumor-specific T cell infiltration, decrease Treg cells, and suppress MDSC [20–22,48]. Various combination treatment strategies have been proposed to overcome the resistance of PDAC to immunotherapy. The combination of immunotherapies with chemotherapy and chemoradiation in PDAC represents a promising strategy to stimulate immunogenicity, improve antigen recognition, increase the presentation of neoantigen, utilize abscopal effect, inhibit tumor-mediated immunosuppression, and improve survival [20,49,50].

The improved OS with the addition of immunotherapy to standard treatments reported in our study may be synergistic. Chemotherapy can recruit and activate dendritic cells, trigger the release of tumor-specific antigens, and reduce Treg cells [20]. Chemotherapy, especially gemcitabine, has been associated with an increase in tumor-specific T cell infiltration, a decrease in Treg cells, and the suppression of MDSC in pre-clinical and clinical studies [21,48,51]. Radiation therapy promotes the translocation of calreticulin, which enables T cells to clear tumor cells [51]. More importantly, through the abscopal effect, RT causes the release of tumor-associated antigens [52], which stimulates a tumor-specific immune response, allowing the immune cells (T-cells) to recognize and attack both the primary tumor and metastatic disease in a sort of auto-vaccination [53–58]. Chemotherapy and RT also cause the release of neoantigens and upregulation of inflammatory cytokines, which promote the presentation of the neoantigens in the TME and thereby increase the immunogenicity of the tumor cells, making them better targets for immunotherapy [57–62].

Our results are consistent with the preliminary findings of the ongoing phase 1 trials of immunotherapy and chemotherapy [30–34]. The median OS reported in these trials is similar to the median OS reported in our study. In phase I trial of 34 patients with metastatic PC, patients who received anti-CTLA4 with gemcitabine had a median OS of 7.4 months, much longer than the historical data from chemotherapy alone [30]. Another trial which included 16 patients with advanced PC and investigated the combination of gemcitabine with anti-CTLA4 reported a median OS of 8.4 months [31]. An early-phase trial with 50 patients investigated anti-PD-1, nivolumab in combination with *nab*-paclitaxel (*nab*-P) ± gemcitabine in advanced PDAC, reported a median OS of 9.9 months with a 6-months OS rate of 73% [32]. A dose-escalation phase 1 trial of CD40 agonist combined with gemcitabine of advanced PDAC which include 22 patients reported a median OS of 7.4 months for patients who received CD40 with gemcitabine compared to 5.7 months for gemcitabine alone [33]. A study of PF-04136309, a human chemokine receptor 2 (CCR2) in combination with chemotherapy in patients with borderline resectable or advanced PDAC that included 49 patients reported 49% overall response rate and 97% stable disease in the combined arm, while in the chemotherapy alone arm, there was no overall response reported, but 80% achieved stable disease [34].

The strength of the current study is the large sample size. A large sample size allowed us to adjust for the important patient and tumor characteristics in the multivariable analysis. More importantly, we were able to stratify patients by definitive surgery. However, our research is not without limitations, and those limitations are inherent to NCDB which include incomplete data and ascertainment bias, lack of data about the cause of death, lack of detailed information on the use of multi-agent chemotherapy regimens, and lack of information on the type of immunotherapy and if a single or combined immunotherapy was used. Also, the NCDB does not provide data on the microsatellite-instability status for PDAC patients who are more likely to respond to immunotherapy. Due to the small sample size, the analysis of comparing the impact of RT plus immunotherapy vs. RT alone was not performed.

In conclusion, this research study found significantly improved OS in patients receiving standard therapies such as chemotherapy and chemoradiation when combined with immunotherapy. These findings warrant clinical trials looking into the impact of immunotherapy combined with chemotherapy and chemoradiation in PDAC patients.

Declaration of Competing Interest

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

Acknowledgement

There are no acknowledgements.

References

[1] Cancer Institute (NIH). Surveillance, Epidemiology, and End Result Program (SEER). Cancer stat National facts: Pancreatic cancer. https://seer.cancer.gov/statfacts/html/pancreas.html. Updated 2019. Accessed 01/10, 2019.

[2] Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the united states. Cancer Res 2014;74(11):2913–21.
[3] Skelton RA, Javed A, Zheng L, He J. Overcoming the resistance of pancreatic cancer to immune checkpoint inhibitors. J Surg Oncol 2017;116(1):55–62.
[4] Melstrom LG, Salazar MD, Diamond DJ. The pancreatic cancer microenvironment: A true double agent. J Surg Oncol 2017;116(1):7–15.
[5] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67(1):7–30.
[6] Sideras K, Biermann K, Yap K, et al. Tumor cell expression of immune inhibitory molecules and tumor-infiltrating lymphocyte count predict cancer-specific survival in pancreatic and ampullary cancer. Int J Cancer 2017;141(3):572–82.
[7] 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):1011–24.
[8] Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med 2018;379(25):2395–406.
[9] Mukherjee S, Hurt CN, Bridgewater J, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): A multicentre, randomised, phase 2 trial. Lancet Oncol 2013;14(4):317–26.
[10] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19):1817–25.
[11] Lemery S, Keegan P, Pazdur R. First FDA approval agnostic of cancer site - when a biomarker defines the indication. N Engl J Med 2017;377(15):1409–12.
[12] Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357(6349):409–13.
[13] Thind K, Padrnos LJ, Ramanathan RK, Borad MJ. Immunotherapy in pancreatic cancer treatment: A new frontier. Therap Adv Gastroenterol 2017;10(1):168–94.
[14] Kang J, Demaria S, Formenti S. Current clinical trials testing the combination of immunotherapy with radiotherapy. J Immunother Cancer. 2016;4:51-016-0156-7. eCollection 2016
[15] Kabacaoglu D, Ciecielski KJ, Ruess DA, Algul H. Immune checkpoint inhibition for pancreatic ductal adenocarcinoma: Current limitations and future options. Front Immunol 2018;9:1878
[16] Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366(26):2455–65.
[17] Royal RE, Levy C, Turner K, et al. Phase 2 trial of single agent ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother 2010;33(8):828–33.
[18] Patnaik A, Kang SP, Rasco D, et al. Phase I study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. Clin Cancer Res 2015;21(19):4286–93.
[19] Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515(7528):563–7.
[20] Young K, Hughes DJ, Cunningham D, Starling N. Immunotherapy and pancreatic cancer: Unique challenges and potential opportunities. Ther Adv Med Oncol 2018;10:1758835918816281.
[21] Chang JH, Jiang Y, Pillarisetty VG. Role of immune cells in pancreatic cancer from bench to clinical application: An updated review. Medicine (Baltimore) 2016;95(49):e5541.
[22] Torphy RJ, Zhu Y, Schulick RD. Immunotherapy for pancreatic cancer: Barriers and breakthroughs. Ann Gastroenterol Surg 2018;2(4):274–81.
[23] Beatty GL, Chiorean EG, Fishman MP, et al. CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. Science 2011;331(6024):1612–6.
[24] Byrne KT, Vonderheide RH. CD40 stimulation obviates innate sensors and drives T cell immunity in cancer. Cell Rep 2016;15(12):2719–32.
[25] Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res 2014;74(19):5458–68.
[26] Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest 2014;124(2):687–95.
[27] Sharabi AB, Nirschl CJ, Kochel CM, et al. Stereotactic radiation therapy augments antigen-specific PD-1-mediated antitumor immune responses via cross-presentation of tumor antigen. Cancer Immunol Res 2015;3(4):345–55.
[28] Demaria S, Kawashima N, Yang AM, et al. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. Clin Cancer Res 2005;11(2 Pt 1):728–734.
[29] Azad A, Yin Lim S, D'Costa Z, et al. PD-L1 blockade enhances response of pancreatic ductal adenocarcinoma to radiotherapy. EMBO Mol Med 2017;9(2):167–80.
[30] Aglietta M, Barone C, Sawyer MB, et al. A phase I dose escalation trial of tremelimumab (CP-675,206) in combination with gemcitabine in chemotherapy-naive patients with metastatic pancreatic cancer. Ann Oncol 2014;25(9):1750–5.
[31] Kalyan A, Kircher SM, Mohindra NA, et al. Ipilimumab and gemcitabine for advanced pancreas cancer: A phase ib study. JCO 2016;34(15):e15747–e15747.
[32] Wainberg ZA, Hochster HS, Kim EJ, et al. Phase I study of nivolumab (nivo) + nab-paclitaxel (nab-P) + gemcitabine (gem) in advanced pancreatic cancer (APC). JCO 2019;37(4):298–9.
[33] Beatty GL, Torigian DA, Chiorean EG, et al. A phase I study of an agonist CD40 monoclonal antibody (CP-870,893) in combination with gemcitabine in patients with advanced pancreatic ductal adenocarcinoma. Clin Cancer Res 2013;19(22):6286–95.
[34] Nywening TM, Wang-Gillam A, Sanford DE, et al. Targeting tumour-associated macrophages with CCR2 inhibition in combination with FOLFIRINOX in patients with borderline resectable and locally advanced pancreatic cancer: A single-centre, open-label, dose-finding, non-randomised, phase 1b trial. Lancet Oncol 2016;17(5):651–62.
[35] Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet 2011;378(9791):607–20.
[36] Gong J, Tuli R, Shinde A, Hendifar AE. Meta-analyses of treatment standards for pancreatic cancer. Mol Clin Oncol 2016;4(3):315–25.
[37] Oberstein PE, Olive KP. Pancreatic cancer: Why is it so hard to treat?. Therap Adv Gastroenterol 2013;6(4):321–37.
[38] Tsai S, Evans DB. Therapeutic advances in localized pancreatic cancer. JAMA Surg 2016;151(9):862–8.
[39] Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. J Clin Oncol 2009;27(11):1806–13.
[40] Konstantinidis IT, Warshaw AL, Allen JN, et al. Pancreatic ductal adenocarcinoma: Is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a "true" R0 resection?. Ann Surg 2013;257(4):731–6.
[41] Koido S, Homma S, Takahara A, et al. Current immunotherapeutic approaches in pancreatic cancer. Clin Dev Immunol 2011;2011:267539.
[42] Chen L. Co-inhibitory molecules of the B7-CD28 family in the control of T-cell immunity. Nat Rev Immunol 2004;4(5):336–47.
[43] Chambers CA, Kuhns MS, Egen JG, Allison JP. CTLA-4-mediated inhibition in regulation of T cell responses: Mechanisms and manipulation in tumor immunotherapy. Annu Rev Immunol 2001;19:565–94.
[44] Flies DB, Chen L. The new B7s: Playing a pivotal role in tumor immunity. J Immunother 2007;30(3):251–60.
[45] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer immunotherapy with antibodies to the PD-1 and PD-L1 pathway. Trends Mol Med 2015;21(1):24–33.
[46] Umansky V, Sevko A. Tumor microenvironment and myeloid-derived suppressor cells. Cancer Microenviron 2013;6(2):169–77.
[47] Chanmee T, Ontong P, Konno K, Itano N. Tumor-associated macrophages as major players in the tumor microenvironment. Cancers (Basel) 2014;6(3):1670–90.
[48] Rosenberg A, Mahalingam D. Immunotherapy in pancreatic adenocarcinoma-overcoming barriers to response. J Gastrointest Oncol 2018;9(1):143–59.
[49] Blair AB, Zheng L. Rational combinations of immunotherapy for pancreatic ductal adenocarcinoma. Chin Clin Oncol 2017;6(3):31.
[50] Kershaw MH, Devaud C, John LB, Westwood JA, Darcy PK. Enhancing immunotherapy using chemotherapy and radiation to modify the tumor microenvironment. Oncoimmunology 2013;2(9):e25962.
[51] Golden EB, Pellicciotta I, Demaria S, Barcellos-Hoff MH, Formenti SC. The convergence of radiation and immunogenic cell death signaling pathways. Front Oncol 2012;2:88.
[52] Demaria S, Ng B, Devitt ML, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. Int J Radiat Oncol Biol Phys 2004;58(3):862–70.
[53] Siva S, MacManus MP, Martin RF, Martin OA. Abscopal effects of radiation therapy: A clinical review for the radiobiologist. Cancer Lett 2015;356(1):82–90.
[54] Barker HE, Paget JT, Khan AA, Harrington KJ. The tumour microenvironment after radiotherapy: Mechanisms of resistance and recurrence. Nat Rev Cancer 2015;15(7):409–25.
[55] Vatner RE, Cooper BT, Vanpouille-Box C, Demaria S, Formenti SC. Combinations of immunotherapy and radiation in cancer therapy. Front Oncol 2014;4:325.
[56] Markowitz GJ, Havel LS, Crowley MJ, et al. Immune reprogramming via PD-1 inhibition enhances early-stage lung cancer survival. JCI Insight 2018;3(13). 10.1172/jci.insight.96836.
[57] Haynes NM, van der Most RG, Lake RA, Smyth MJ. Immunogenic anti-cancer chemotherapy as an emerging concept. Curr Opin Immunol 2008;20(5):545–57.
[58] Ma Y, Conforti R, Aymeric L, et al. How to improve the immunogenicity of chemotherapy and radiotherapy. Cancer Metastasis Rev 2011;30(1):71–82.
[59] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases–elimination, equilibrium and escape. Curr Opin Immunol 2014;27:16–25.
[60] Germano G, Lamba S, Rospo G, et al. Inactivation of DNA repair triggers neoantigen generation and impairs tumour growth. Nature 2017;552(7683):116–20.
[61] Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science 2015;348(6230):69–74.
[62] Demaria S, Formenti SC. Role of T lymphocytes in tumor response to radiotherapy. Front Oncol 2012;2:95.