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, Michael Baine, Jane Meza, Morshed Alam, Chi Lin

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

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.

Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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...
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 tumorspecific 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, 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-
Multivariable logistic analysis of the factors associated with the receipt of immunotherapy in PDAC patients with no surgery.

The analysis was conducted using mutually exclusive variables. The SAS 9.4 software was used for the analysis. 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 results were based on two-sided tests. Separate multivariable Cox proportional hazard analysis (Table 2) was used to identify significant factors associated with the receipt of immunotherapy.

### 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 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 (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 score 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 (%) | No Immunotherapy N (%) | 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                | Female                 |               | 1          | Reference  |        |
|                                 | 497 (54.56)         | 414 (45.44)            |               |            |            |        |
| Race                            | White               | Black                  |               | 1          | Reference  |        |
|                                 | 784 (87.21)         | 75 (8.34)              |               |            |            |        |
| Other                           | 40 (4.45)           | 9 (1.02)               |               |            |            |        |
| Education                       |                     |                        |               |            |            |        |
|                               | >=13% HG            |                        |               |            |            |        |
|                                 | 317 (35.11)         | 309 (34.26)            |               |            |            |        |
| Education                       | <13%                |                        |               |            |            |        |
|                                 | 586 (64.89)         | 105 (11.87)            |               |            |            |        |
| Income                          |                     |                        |               |            |            |        |
|                               | >=$35,000           |                        |               |            |            |        |
|                                 | 593 (65.74)         | 152 (15.81)            |               |            |            |        |
|                                | <35,000             |                        |               |            |            |        |
|                                 | 309 (34.26)         | 105 (11.87)            |               |            |            |        |
| Place of Living                 |                     |                        |               |            |            |        |
|                               | Urban               |                        |               |            |            |        |
|                                 | 862 (97.95)         | 251,360 (98.11)        |               |            |            |        |
|                                | Rural               |                        |               |            |            |        |
|                                 | 18 (2.05)           | 4,843 (1.89)           |               |            |            |        |
| Hospital Type                   |                     |                        |               |            |            |        |
|                               | Academic            |                        |               |            |            |        |
|                                 | 589 (65.59)         | 100,414 (38.43)        |               |            |            |        |
|                                | Community           |                        |               |            |            |        |
|                                 | 309 (34.41)         | 160,897 (61.57)        |               |            |            |        |
|                                | Unknown             |                        |               |            |            |        |
|                                 | 13                  | 1,664                  |               |            |            |        |
| Insurance Status                |                     |                        |               |            |            |        |
|                               | Insured             |                        |               |            |            |        |
|                                 | 847 (98.26)         | 249,219 (96.94)        |               |            |            |        |
|                                | Not insured         |                        |               |            |            |        |
|                                 | 15 (1.74)           | 7,856 (3.06)           |               |            |            |        |
|                             | Unknown             |                        |               |            |            |        |
|                                 | 49                  | 59.00                  |               |            |            |        |
| Charlson/Deyo Score            |                     |                        |               |            |            |        |
|                               | 0                   |                        |               |            |            |        |
|                                 | 716 (78.59)         | 171,219 (65.11)        |               |            |            |        |
|                                | 1                   |                        |               |            |            |        |
|                                 | 154 (16.90)         | 63,980 (24.33)         |               |            |            |        |
|                                | >=2                 |                        |               |            |            |        |
|                                 | 41 (4.50)           | 27,776 (10.56)         |               |            |            |        |
| M stage                         |                     |                        |               |            |            |        |
|                               | M0                  |                        |               |            |            |        |
|                                 | 449 (51.14)         | 116,598 (45.95)        |               |            |            |        |
|                                | M1                  |                        |               |            |            |        |
|                                 | 428 (48.86)         | 137,142 (54.05)        |               |            |            |        |
| Chemotherapy                    |                     |                        |               |            |            |        |
|                               | Yes                 |                        |               |            |            |        |
|                                 | 854 (93.74)         | 130,918 (49.78)        |               |            |            |        |
|                                | No                  |                        |               |            |            |        |
|                                 | 57 (6.26)           | 132,057 (46.22)        |               |            |            |        |
| Radiation Therapy              |                     |                        |               |            |            |        |
|                               | Yes                 |                        |               |            |            |        |
|                                 | 308 (33.81)         | 35,029 (13.32)         |               |            |            |        |
|                                | No                  |                        |               |            |            |        |
|                                 | 603 (66.19)         | 227,945 (86.68)        |               |            |            |        |
| Year of Diagnosis               |                     |                        |               |            |            |        |
|                               | 2004–2010           |                        |               |            |            |        |
|                                 | 460 (50.49)         | 136,795 (52.02)        |               |            |            |        |
|                               | 2011–2016           |                        |               |            |            |        |
|                                 | 460 (50.49)         | 136,795 (52.02)        |               |            |            |        |
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.
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: 0.813 (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.

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 signifi-

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

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   |       | Reference            |           | Reference                     |           |
| 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     |       | Reference            |           | Reference                     |           |
| 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.
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 capcitabine [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 synergistic 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 criocticulin, 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 chemoradia tion 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(1):17–21.

[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] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.

[5] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67(1):7–30.

[6] 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.

[7] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.

[8] 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.

[9] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.

[10] 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.

[11] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.

[12] 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.

[13] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.

[14] 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.

[15] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.

[16] 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.

[17] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.

[18] 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.

[19] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.

[20] 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.

[21] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.

[22] 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.

[23] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.

[24] 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.

[25] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.

[26] 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.

[27] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.

[28] 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.

[29] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.

[30] 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.

[31] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.

[32] 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.

[33] Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer therapy with immune checkpoint antibodies: A systematic review. Oncotarget 2017;8(22):6286–95.