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Title

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Permalink

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Journal

Journal of the American College of Surgeons, 229(1)

ISSN

1072-7515

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Publication Date

2019-07-01

DOI

10.1016/j.jamcollsurg.2019.01.016

Peer reviewed



Published in final edited form as:

J Am Coll Surg. 2019 July ; 229(1): 19–27.e1. doi:10.1016/j.jamcollsurg.2019.01.016.

Impact of Immunotherapy after Resection of Pancreatic Cancer

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Abstract

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 is to determine the impact of adjuvant chemotherapy and immunotherapy (CTx-IT) compared to CTx alone on patient survival following resection of PDAC.

Study Design: Patients who underwent resection of PDAC from 2004 to 2015 were identified from the National Cancer Database (NCDB). Univariate and multivariate Cox proportional hazards models were utilized to determine predictors of overall survival (OS) based on the type of adjuvant therapy received. Patients who received adjuvant immunotherapy were compared to 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 patients (1.3%) 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 with improved overall survival (HR 0.74, $P=0.007$).

Conclusion: The addition of adjuvant immunotherapy to chemotherapy is associated with improved survival compared to 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.

PRÉCIS:

Patients who underwent curative-intent resection of pancreatic adenocarcinoma experienced improved overall survival after receipt of adjuvant immunochemotherapy compared to chemotherapy alone. Receipt of immunotherapy was associated with a survival advantage even in

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Disclosure Information: Nothing to disclose.

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

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patients with adverse risk factors including R1 margins, node positive, and poorly differentiated disease.

Keywords

Immunotherapy; Pancreatic adenocarcinoma; chemotherapy; Pancreatic cancer

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy and is the fourth leading cause of cancer-related mortality in the United States. The incidence and mortality rates are nearly equal, with 55,440 diagnoses and 44,330 cancer-associated deaths projected in 2018.(1) 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 less than 25% even after complete resection with microscopically negative (R0) margins. What is most concerning for the future is that while 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 micro-metastatic 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. CONKO-001 established the role of adjuvant gemcitabine in improving overall survival compared to the observation,(8) and more recent trials have built on this backbone demonstrating further improvements in survival outcomes with multi-drug 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 the metastatic and adjuvant setting, therefore there is great excitement for utilization after pancreatic resection for adenocarcinoma.(13-19) Further, there has been increasing evidence that certain chemotherapies may enhance anti-tumor immune responses. As a result, the premise that combination chemo-immunotherapy may enhance outcomes in PDAC is well-formulated. Given the paucity of data and small single institution studies on combination chemo-immunotherapy in patients with PDAC, the objective of this study was to evaluate outcomes of adjuvant chemotherapy and immunotherapy compared to chemotherapy alone using a large population-based database in a propensity score matched study following resection of PDAC.

METHODS

Patient population and study design

The National Cancer Database (NCDB) was utilized 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 (COC) and the American Cancer Society consisting of approximately 70% of all newly diagnosed malignancies in the United States.(20, 21) The database captures clinicopathologic characteristics from more than 1,500 COC-accredited hospitals in the United States. 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 (ICD-O-3) 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). 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 (BRM) or immunotherapy for pancreatic cancer in the SEER-Rx database.

Statistical Analysis

Continuous variables were presented as medians with interquartile range (IQR) and compared using Mann-Whitney U test. Categorical variables were presented as frequency and percentages and compared using Pearson 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 ratios (HR) with 95% confidence intervals (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, Chicago, IL) and STATA 13.0 statistical software package (STATA Corp, College Station, TX). Significance was set at a P value of <0.05 (two-tailed).

RESULTS

Baseline Characteristics of the adjuvant CTx and CTx-IT Groups

Between 2004 to 2015, 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 patients (1.3%) 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 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 surgery to receipt of adjuvant therapy was 55 days. The 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 to CTx alone (30.3% vs. 20.6%, $P=0.003$, Figure 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%, $P=0.0045$; Figure 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%; $P=0.046$) (Figure 2). When stratified by stage, the 5-year OS after adjuvant CTx-IT was improved in 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 0.643-0.885, $P=0.001$) while 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 1.18-3.05; $P=0.008$) and receipt of immunotherapy were associated with improved survival (HR 0.74, 95% CI 0.59-0.92; $P=0.007$) (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 to CTx-alone among patients with adverse risk factors such as positive margins, node positive disease, and poorly differentiated histology.

PDAC is traditionally considered an immuno-resistant disease. Tumors traditionally reflect a lack of tumor infiltrating lymphocytes and a plethora of suppressor T-cells. This may be one of the reasons that immune-based monotherapy has not resulted in the same clinical responses in PDAC compared to other tumor histologies. However, multiple strategies are being pursued to sensitize cells to anti-tumor immune responses. In particular, chemo-immunotherapy may synergize to improve outcomes over chemotherapy alone given increasing evidence that some chemotherapies may 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 cancer death associated modules and immunogenic cell death, while cyclophosphamide has been shown to promote dendritic cell maturation and upregulate HLA molecules on tumor cells.(27, 28) Thus, 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) 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, though adjuvant vaccines have been shown to stimulate anti-tumor T-cell responses and have been employed to a greater degree in the PDAC, clear efficacy in substantial numbers of patients has been elusive(38-40) IL-2, interferon alpha-2b, and IL-10 have also been used as immunostimulatory agents in combination with chemotherapy for PDAC with measurable activity in the adjuvant setting, though 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 with resectable PDAC, and many of these patients may have been enrolled in clinical trials. There have been several small and underpowered studies on the efficacy of chemo-immunotherapy in the

adjuvant setting for PDAC. In a study of 12 patients who underwent resection for PDAC, Aguilar et al. reported that adjuvant gene-mediated cytotoxic immunotherapy resulted in an OS of 9-30 months.(47) In another study consisting of 43 patients, Matsui et al demonstrated that adjuvant adoptive immunotherapy combined with gemcitabine resulted in a disease-free survival of 15.8 months and overall survival of 24.7 months.(48) Furthermore, a Phase II study of 70 patients treated with gemcitabine and plus algenpantucel-L immunotherapy demonstrated a 12 month disease-free survival of 62% and 12-month overall survival 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 chemo-immunotherapy 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 to chemotherapy alone for PDAC. However, there remain several limitations to the present study. While chemo-immunotherapy was associated with improved survival compared to chemotherapy alone, these patients were younger, had a better performance status, and were more likely to be treated at academic cancer centers. These patient and treatment factors were addressed in the propensity score analysis where age and Charleston comorbidity index were matched, nonetheless inherent selection biases may remain. Furthermore, although this is a large, national dataset, 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. While 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 may 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. Thus, it was not possible to compare outcomes from those who received vaccine therapy to those who received monoclonal antibodies or check-point inhibitors 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 in order 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 to improve outcomes in this aggressive disease.

CONCLUSION

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 to chemotherapy alone. Clinical trials on the feasibility, durability, and long-term survival

benefit of chemo-immunotherapy after resection of pancreatic adenocarcinoma are warranted.

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

| Drug name | Alternative names | 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, Pembrolizumab, Lambrolizumab | Monoclonal antibody |

CAP1-6D, carcinoembryonic antigen peptide 1-6D; EGFR, epidermal growth factor receptor; erbB, erythroblastic oncogene B; GVAX, GM-CSF 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.

ABBREVIATIONS

| | |
|-------------|-----------------------------------------|
| ACS | American College of Surgeons |
| BRM | biologic response modifiers |
| COC | Commission on cancer |
| CTx | chemotherapy |
| IT | immunotherapy |
| NCDB | National Cancer Database |
| OS | overall survival |
| PDAC | pancreatic adenocarcinoma |
| SEER | Surveillance, Epidemiology, End Results |

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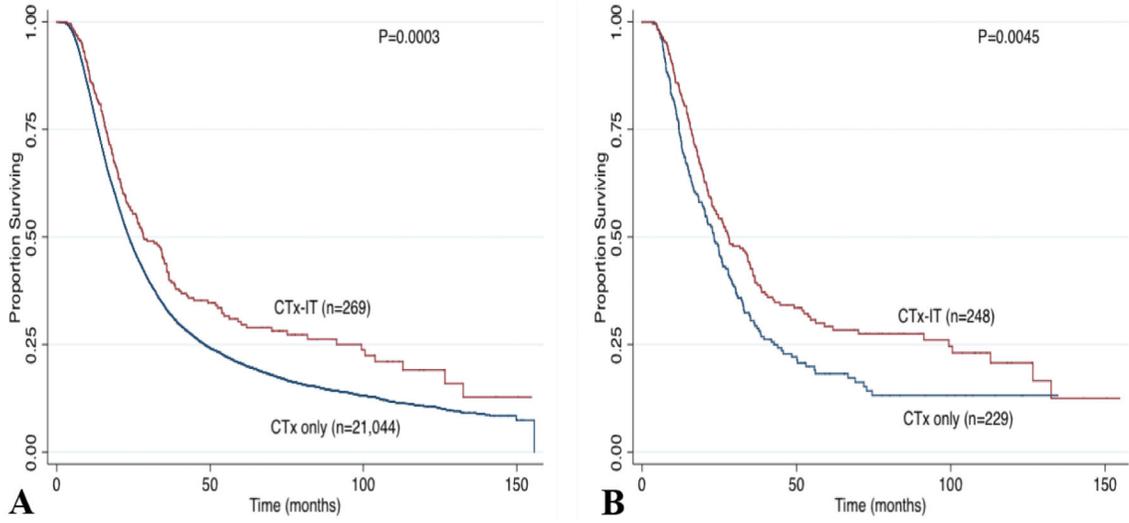


Figure 1. Kaplan Meier survival curve stratified by type of adjuvant therapy: (A) unmatched cohort and (B) matched cohort. CTx, chemotherapy; IT, immunotherapy.

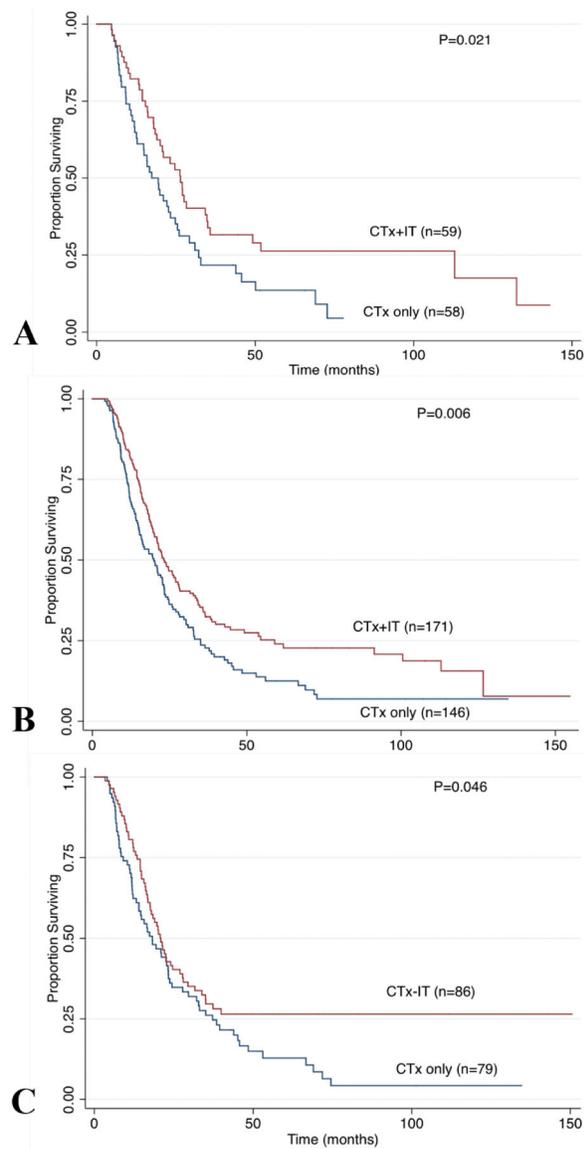


Figure 2. Subgroup analysis on overall survival comparing CTx (chemotherapy) only vs CTx+IT (immunotherapy) in the propensity matched cohort factors with high risk factors: (A) R1 margin status, (B) positive lymph node, and (C) poorly differentiated disease.

Table 1.

Clinicopathologic Characteristics of Chemotherapy Alone, and Chemotherapy and Immunotherapy in the Entire Cohort and Propensity Score Matched Cohort

| Characteristic | Entire cohort | | | Matched cohort | | |
|-------------------------------------------|-------------------|-------------------|------------|----------------|-------------------|------------|
| | 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 (%) | | | | | | |
| White | 18,216 (86.6) | 240 (89.2) | 0.006 | 206 (89.9) | 220 (88.7) | 0.490 |
| 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 (%) | | | | | | |
| Academic | 10,204 (48.9) | 206 (78.0) | <0.001 | 108 (51.9) | 195 (79.9) | <0.001 |
| 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 (%) | | | | | | |
| None | 507 (2.5) | 3 (1.1) | <0.001 | 10 (4.7) | 3 (1.2) | 0.036 |
| 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 | 14,245 (68.9) | 216 (80.3) | 0.001 | 183 (79.9) | 200 (80.6) | 0.979 |
| 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 (1.0) | 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) | 5,024 (48.9) | 44 (47.3) | 0.835 | 55 (56.1) | 43 (47.3) | 0.223 |
| Grade, n (%) | | | | | | |
| Well | 1,602 (7.6) | 26 (9.67) | 0.056 | 14 (16.1) | 23 (9.3) | 0.591 |
| 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 (%) | | | | | | |
| R0 | 15,695 (78.45) | 200 (77.22) | 0.648 | 171 (74.7) | 189 (76.2) | 0.697 |
| R1 | 4,312 (21.55) | 59 (22.78) | | 58 (25.3) | 59 (23.8) | |
| T stage, n (%) | | | | | | |

| Characteristic | Entire cohort | | | Matched cohort | | |
|--------------------------|-------------------|-------------------|------------|----------------|-------------------|------------|
| | CTx (n=21,044) | CTx+IT (n=269) | p Value | CTx (n=229) | CTx+IT (n=248) | p Value |
| T1 | 1,294 (6.7) | 14 (6.2) | 0.995 | 13 (6.4) | 13 (6.0) | 0.826 |
| 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 (%) | | | | | | |
| N0 | 6,586 (34.4) | 66 (29.2) | 0.105 | 68 (33.3) | 64 (49.5) | 0.396 |
| N1 | 12,547 (65.6) | 160 (70.8) | | 136 (66.7) | 153 (70.5) | |
| Stage, n (%) | | | | | | |
| I | 2,492 (12.2) | 25 (9.7) | 0.289 | 19 (8.3) | 24 (9.7) | 0.856 |
| II | 16,858 (82.7) | 215 (83.7) | | 195 (85.2) | 209 (84.3) | |
| III | 1,048 (5.1) | 17 (6.6) | | 15 (6.6) | 15 (6.0) | |
| Type of operation, n (%) | | | | | | |
| Distal pancreatectomy | 2,572 (12.22) | 28 (10.41) | 0.665 | 23 (10.0) | 27 (10.9) | 0.468 |
| Pancreaticoduodenectomy | 14,884 (70.73) | 191 (71) | | | | |
| Total pancreatectomy | 2,785 (13.23) | 41 (15.24) | | 26 (11.4) | 40 (16.1) | |
| Pancreatectomy NOS | 803 (3.82) | 9 (3.35) | | 4 (1.8) | 4 (1.6) | |
| Radiotherapy, n (%) | | | | | | |
| No | 9,468 (45.2) | 64 (23.8) | <0.001 | 53 (23.1) | 57 (22.98) | 0.967 |
| Yes | 11,497 (54.8) | 205 (76.2) | | 176 (76.9) | 191 (77.0) | |

CTx, chemotherapy; IQR, interquartile range; IT, immunotherapy; NOS, not otherwise specified.

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 NOS | 1.284 | 0.145-1.440 | <0.001 |

CTx, chemotherapy; IT, immunotherapy; NOS, not otherwise specified.

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.