The Addition of Chemoradiation to Adjuvant Chemotherapy is Associated With Improved Survival Following Upfront Surgical Resection for Pancreatic Cancer With Nodal Metastases

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Abstract

Background: It is unclear whether the addition of chemoradiation (CRT) to adjuvant chemotherapy (CT) following upfront resection of pancreatic ductal adenocarcinoma (PDAC) provides any benefit. While some studies have suggested a benefit to combined modality therapy (CMT) (adjuvant CT plus CRT), it is not clear if this benefit was related to increased CT usage in patients who received CMT. We sought to clarify the use of CMT in patients who underwent upfront resection of PDAC.

Methods: Patients with non-metastatic PDAC were retrospectively identified from the linked SEER-Medicare database. Those who underwent upfront resection were identified and divided into two cohorts – patients who received adjuvant CT and patients who received adjuvant CMT. Cohorts were compared. Univariate analysis described patient characteristics. Kaplan-Meier and multivariable Cox proportional hazards modeling were used to estimate overall survival (OS).

Results: 3555 patients were identified; 856 (24%) received CT and 573 (16%) received CMT. The median number of CT doses was 11 for both groups. Patients who received CMT were younger, diagnosed in the earlier time frame, and had fewer comorbidities. The median OS was 21 months and 18 months for those treated with CMT and CT ($P < .0001$), respectively, but when stratified by nodal status, the association with improved OS in the CMT cohort was only observed in node-positive patients. On multivariable analysis, receipt of CMT and removal of $>15$ lymph nodes decreased the risk of death ($P < .05$).

Discussion: Receipt of CMT following upfront resection for PDAC was associated with improved survival, which was confined to node-positive patients. The role of adjuvant CMT in PDAC with nodal metastases warrants further study.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC), the fourth leading cause of cancer-related mortality in the United States, is a very aggressive disease with an estimated an estimated 49,830 deaths in 2022\(^1\), and a 5-year overall survival (OS) of only 11.5%.\(^2\) While surgical resection offers the only potentially curative treatment, even amongst patients who are eligible for resection, survival is poor. Distant recurrence following upfront surgical resection remains the most common cause of death, but autopsy series demonstrate that a significant proportion of patients die with or from local recurrence.\(^3\) Since surgical resection alone does not provide adequate distant or locoregional control for pancreatic cancer – multimodality therapy is needed.

Multiple randomized controlled trials (RCT) have investigated the role of adjuvant chemotherapy (CT) and/or chemoradiation (CRT) to determine the optimal treatment strategy in resected PDAC, some which have reported conflicting results,\(^4,5\) as is evidenced by the fact that the current NCCN guidelines recommend adjuvant CT or CRT for resected PDAC.\(^6,7\) The Gastrointestinal Study Group (GITSG) was the first study to evaluate adjuvant CRT for PDAC and found that adjuvant CRT improved OS compared to observation alone.\(^8\) The European Study Group of Pancreatic Cancer (ESPAC)-1 trial demonstrated a survival benefit with adjuvant CT alone, but actually found a negative impact on survival for adjuvant CRT.\(^9,10\) A Radiation Therapy Oncology Group (RTOG) trial later suggested possible efficacy of CRT.\(^11\) Several subsequent adjuvant CT RCTs have further supported the efficacy of adjuvant CT following upfront surgical resection.\(^12,13\) It is unlikely that adjuvant CRT will ever replace adjuvant CT,\(^14\) yet, a clinically relevant questions remains: does the addition of CRT to adjuvant CT – combined modality therapy (CMT) – impact survival for patients with surgically resected PDAC?

To clarify the impact of CMT vs CT on the survival of patients with surgically resected PDAC, we performed a retrospective review of the National Cancer Institute’s (NCI) Surveillance Epidemiology and End Results (SEER)-Medicare linked database. This database was chosen because it contains claims codes which detail the type and quantity of adjuvant CT received. This allowed us to control for specific details of CT as a potential confounder in survival analysis, when examining the benefit of adjuvant CMT. We hypothesized that patients who received CMT would receive a higher number of CT doses, or would receive CT for a longer duration, than those who received CT alone. We hypothesized that this extended use of CT could be associated with improved survival in patients with more substantial locoregional disease burden (i.e. node-positive).

Methods

Data

The NCI’s SEER-Medicare linked database was used to identify patients diagnosed with PDAC from 2004-2013. The linkage between the SEER Database and Medicare was performed on a person-level. This allowed for analysis of the 1.6 million patients with cancer in the SEER database who are ≥65 years of age and enrolled in Medicare. The SEER database contains patient demographics, tumor characteristics, and vital status for 28% of the US population. The Medicare Provider Analysis and Review and the National Claims History files contain claims for hospitalizations and inpatient procedures. Office visits are captured using a combination of provider charges from the National Claims History files and facility charges from the outpatient Standard Analytical Files.\(^15\) Using claims data, we calculated Charlson Comorbidity Index (CCI), considering the International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes, ICD-9 procedure codes, and Healthcare Common Procedure Coding System procedure codes on the claims.\(^16\) Because cancer was the disease of interest, it was not included in the Charlson Comorbidity Index (CCI).

Patient Population

Patients ≥65 years of age, who were diagnosed with PDAC and underwent upfront surgical resection followed by adjuvant therapy were included. Patients who had metastatic disease at the time of diagnosis, or who had history of another primary malignancy were excluded. Patients who had received any neoadjuvant therapy were also excluded. Although neoadjuvant therapy is entering mainstream practice for patients with borderline resectable and locally advanced PDAC, it is not yet standard of care for resectable PDAC.\(^7,17,18,19\) We therefore excluded these patients in an attempt to more clearly isolate the effect of adjuvant CMT on OS.

All multivariable models included patient age, sex, race, NCI-status of the treatment facility, patient CCI, tumor size, T stage of disease, lymph node status, lymph node number evaluated, and treatment. Age was defined as a categorical variable. The designation of the treating facility as an NCI designated cancer center was derived from the Hospital File and linked via hospital ID. T stage of disease was derived from the American Joint Committee on Cancer (AJCC), Cancer Staging Manual, editions

Keywords

pancreatic ductal adenocarcinoma, surgery, combined modality therapy, chemoradiation, lymph nodes, surveillance epidemiology and end results, medicare
Table 1. Characteristics of all Patients Diagnosed with PDAC\(^a\) who Underwent Upfront Surgical Resection, from Surveillance Epidemiology and End Results-Medicare 2004-2013, N = 3555.

| Characteristics                                    | N   | %  |
|----------------------------------------------------|-----|----|
| Year of diagnosis                                  |     |    |
| 2004-2008                                          | 1531| 43 |
| 2009-2013                                          | 2024| 57 |
| Age at diagnosis                                   |     |    |
| 65-69                                              | 999 | 28 |
| 70-74                                              | 1009| 28 |
| 75-79                                              | 900 | 25 |
| 80-84                                              | 489 | 14 |
| ≥85                                                | 158 | 4  |
| Gender                                             |     |    |
| Male                                               | 1681| 47 |
| Female                                             | 1874| 53 |
| Race                                               |     |    |
| Non-Hispanic white                                 | 2880| 81 |
| Black                                              | 240 | 7  |
| Other or unknown                                   | 435 | 12 |
| Charlson comorbidity index                         |     |    |
| 0                                                  | 1849| 52 |
| 1                                                  | 1012| 28 |
| ≥2                                                 | 694 | 20 |
| Treated at NCI\(^a\)-designated cancer center      |     |    |
| No                                                 | 3267| 94 |
| Yes                                                | 202 | 6  |
| T Stage                                            |     |    |
| 1 and 2                                            | 747 | 21 |
| 3                                                  | 2730| 77 |
| 4                                                  | 78  | 2  |
| Tumor size                                         |     |    |
| < 2 cm                                             | 438 | 12 |
| ≥2 cm                                              | 3058| 86 |
| Unknown                                            | 59  | 2  |
| Lymph nodes evaluated                              |     |    |
| None or unknown                                    | 126 | 4  |
| ≤15                                                | 1789| 50 |
| >15                                                | 1640| 46 |
| Lymph node status                                  |     |    |
| Negative                                           | 1283| 36 |
| Positive                                           | 2146| 60 |
| Missing                                            | 126 | 4  |
| Surgical procedure                                 |     |    |
| Whipple                                            | 2495| 70 |
| Total pancreatectomy                               | 473 | 13 |
| Other                                              | 587 | 17 |
| Adjuvant treatment                                 |     |    |
| No CT\(^a\)                                        | 2126| 60 |
| CT                                                  | 856 | 24 |
| CMT\(^a\)                                          | 573 | 16 |

*aAbbreviations: PDAC, pancreatic ductal adenocarcinoma; NCI, National Cancer Institute; CT, chemotherapy; CMT, combined modality therapy.

6 and 7. Radiation treatment receipt was derived from the SEER Patient Entitlement and Diagnosis Summary File (PEDSF) file, since there may be underreporting by Medicare sources if patients receive care outside of the Medicare system.\(^{20}\) Surgical procedures performed were categorized as

Table 2. Characteristics of Patients Who Underwent Upfront Surgical Resection and Received CT\(^a\) or CMT\(^a\) for PDAC\(^b\), from Surveillance Epidemiology and End Results-Medicare 2004-2013, N = 1429.

| Characteristics                                    | CT only (n = 856) | CMT (n = 573) | P-value |
|----------------------------------------------------|-------------------|---------------|---------|
| Year of diagnosis                                  |                   |               |         |
| 2004-2008                                          | 391 46            | 318 56        | .0003   |
| 2009-2013                                          | 465 54            | 255 45        |         |
| Age                                                |                   |               |         |
| 65-69                                              | 229 27            | 197 34        | <.0001  |
| 70-74                                              | 245 29            | 187 33        |         |
| 75-79                                              | 234 27            | 133 23        |         |
| 80-84                                              | 119 14            | 51 9          |         |
| ≥85                                                | 29 3              | 5 1           |         |
| Gender                                             |                   |               |         |
| Male                                               | 385 45            | 275 48        | .28     |
| Female                                             | 471 55            | 298 52        |         |
| Race                                               |                   |               |         |
| Non-Hispanic white                                 | 744 87            | 496 87        | .84     |
| Black                                              | 35 4              | 27 5          |         |
| Other or unknown                                   | 77 9              | 50 9          |         |
| Charlson comorbidity index                         |                   |               |         |
| 0                                                  | 409 48            | 316 55        | .02     |
| 1                                                  | 284 33            | 161 28        |         |
| ≥2                                                 | 163 19            | 96 17         |         |
| Treated at NCI\(^a\)-designated cancer center      |                   |               |         |
| No                                                 | 729 85            | 498 87        | .35     |
| Yes                                                | 127 15            | 75 13         |         |
| T Stage                                            |                   |               |         |
| 1 and 2                                            | 180 21            | 113 20        | .49     |
| 3                                                  | 662 77            | 446 78        |         |
| 4                                                  | 14 2              | 14 2          |         |
| Lymph node evaluation                              |                   |               |         |
| ≤15                                                | 467 55            | 288 50        | .11     |
| >15                                                | 389 45            | 285 50        |         |
| Lymph node status                                  |                   |               |         |
| Negative                                           | 295 34            | 194 34        | .12     |
| Positive                                           | 529 62            | 368 64        |         |
| Missing                                            | 32 4              | 11 2          |         |
| Surgical procedure                                 |                   |               |         |
| Whipple                                            | 609 71            | 395 69        | .37     |
| Total pancreatectomy                               | 101 12            | 82 14         |         |
| Other                                              | 146 17            | 96 17         |         |
| Median number of CT doses                           | 11                | 11            | N/A\(^b\) |

*aAbbreviations: PDAC, pancreatic ductal adenocarcinoma; CT, chemotherapy; CMT, combined modality therapy; NCI, National Cancer Institute.

\(^b\)P-value not applicable since median number of CT doses equivalent between cohorts.
pancreaticoduodenectomy (Whipple), total pancreatectomy, or other (including distal pancreatectomy). Receipt of adjuvant CT and adjuvant CRT was characterized using Medicare claims codes and the SEER database. Specifically, Medicare claims codes were used to quantify the number of doses of adjuvant CT administered to each patient and to provide insight into which chemotherapeutic agents were prescribed.

### Statistical Analysis

Patients who met inclusion criteria were grouped into two cohorts – those who received adjuvant CT alone, and those who received CMT. Demographics, tumor characteristics, and treatment received were evaluated and compared between cohorts using the chi-squared test. Median OS was analyzed using the Kaplan-Meier method and multivariable Cox proportional hazard modeling. Results were considered statistically significant for a two-tailed $P$-value ≤ .05 and a 95% confidence interval (CI). SAS statistical software, version 9.3 (SAS Institute, Cary, NC) was used for all statistical analyses.

Sensitivity analysis was performed on untreated patients, excluding those who died within two months of diagnosis. These were excluded to reduce confounding by early mortality, based on the assumption that these patients may have had undiagnosed distant metastases, or were too ill to receive a full course of treatment. These alternative analyses had no meaningful effect on our conclusions and are therefore not presented in the following results.

The study was approved by the Institutional Review Board at the University of Minnesota, reference number STUDY00004830. All procedures in this study were conducted in accordance with the University of Minnesota IRB’s approved protocols. A waiver of the
consent process was granted by the above-named IRB because the study involved no more than minimal risk. Supplemental information such as programming code available upon reasonable request to the corresponding author.

### Results

From 2004-2013, 3555 patients were diagnosed with PDAC and met inclusion criteria (Table 1). The median age of the cohort was 73 years, 53% of patients were female, 81% of patients were non-Hispanic white. Most patients had T-stage 3 tumors (77%) and positive lymph nodes (60%). Of the 3555 patients who underwent upfront surgical resection, 40% of patients (1,422) received adjuvant therapy. The characteristics of those who received CT alone and CMT are included in Table 2. Compared to patients who received CT, patients who received CMT were more frequently younger, diagnosed in the earlier time period (2004-2008 vs 2009-2013), and tended to have fewer comorbidities (55% vs 48% CCI 0). The median number of CT doses did not differ between groups (CT – 11 doses, SD 5.9; CMT – 11 doses, SD 6.2). Approximately 90% of patients received single agent gemcitabine.

The median OS for patients who received adjuvant treatment after upfront surgical resection is shown in Figure 1A. The median OS for those who received adjuvant CT was 18 months, while the median OS for those who received CMT was 21 months (P < .0001). Survival of the cohort was also stratified by nodal status (Figure 1B and 1C). In the node-positive cohort, the median OS for those who received adjuvant CT was 17 months while the median OS for those who received CMT was 20 months (P < .0001). Conversely, in the node-negative cohort, the median OS for those who received adjuvant CT was 23 months while the median OS for those who received CMT was 25 months (P-value .09). To adjust for competing risks, survival was further described using a Cox proportional hazards model multivariable analysis (Table 3). Receipt of CMT was significantly associated with decreased risk of death (Hazard Ratio [HR] .80, 95% confidence interval [CI] .71-.91, P = .001). The only other factor found to significantly decrease risk of death was evaluation of greater than 15 lymph nodes (HR .88, CI 0.78-.99 P = .04). On the other hand, more recent diagnosis (HR 1.37 CI 1.22-1.55, 2009-2013 vs 2004-2008), T stage 4 (HR 1.53 CI 1.01-2.31), and node-positive disease (HR 1.46 CI 1.28-1.67) significantly increased the risk of death.

### Discussion

The role of adjuvant CMT after surgical resection for pancreatic cancer has remained uncertain given discrepant results of clinical trials. The present evaluation of patients who received adjuvant therapy for PDAC in the SEER-Medicare linked database found that CT and CMT patients received a similar number of doses of systemic chemotherapy (median, 11 doses) and that CMT was associated with improved median OS, which appeared to be confined to patients with node-positive disease. Notably, patients who received CMT tended to be younger, diagnosed in the earlier time period, and had fewer comorbidities.

Early trials that evaluated the role of adjuvant CRT included the Gastrointestinal Study Group (GITSG), the European

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**Table 3. Multivariable Cox Proportional Hazard Model. Hazard of Death for Patients Who Received Adjuvant Therapy After Upfront Surgical Resection for PDAC in Surveillance Epidemiology and End Results-Medicare from 2004-2013, N = 1429.**

| Hazard Ratio | 95% Confidence Interval | P-value |
|-------------|-------------------------|---------|
| Year of diagnosis | | |
| 2004-2008 REF | | |
| 2009-2013 1.37 | 1.22 1.55 | <.0001 |
| Age | | |
| 65-69 REF | | |
| 70-74 1.15 | .99 1.33 | .07 |
| 75-79 1.12 | .95 1.31 | .17 |
| 80-84 1.21 | .99 1.49 | .06 |
| ≥85 .91 | .60 1.36 | .63 |
| Gender | | |
| Male REF | | |
| Female .93 | .82 1.04 | .19 |
| Race | | |
| Non-Hispanic white REF | | |
| Black 1.21 | .91 1.63 | .20 |
| Other or unknown 1.19 | | |
| Charlson comorbidity index | | |
| 0 REF | | |
| 1 1.04 | .91 1.20 | .53 |
| ≥2 1.04 | .89 1.22 | .62 |
| Treated at NCI-designated cancer center | | |
| Yes REF | | |
| No .91 | .76 1.37 | 1.08 |
| T Stage | | |
| 1 and 2 REF | | |
| 3 1.14 | .98 1.33 | .10 |
| 4 1.53 | 1.01 2.31 | .04 |
| Lymph node evaluation | | |
| ≤15 REF | | |
| >15 .88 | .78 .99 | .04 |
| Lymph node status | | |
| Negative REF | | |
| Positive 1.46 | 1.28 1.67 | <.0001 |
| Missing 1.26 | .88 1.80 | .22 |
| Surgical procedure | | |
| Whipple REF | | |
| Total pancreatectomy 1.08 | .91 1.29 | .63 |
| Other 1.00 | .85 1.17 | .99 |
| Adjuvant treatment | | |
| CT only REF | | |
| CMT .80 | .71 .91 | .001 |

*Abbreviations: PDAC, pancreatic ductal adenocarcinoma; REF, Reference (Hazard Ratio = 1.00); NCI, National Cancer Institute; CT, chemotherapy; CMT, combined modality therapy.*
The rationale for adding radiation to CT in pancreatic cancer is in part due to observed patterns of disease recurrence following resection. In autopsy series of patients who underwent pancreatic resection for PDAC, 8-30% of patients died with only locoregional recurrence of disease. Specifically, in one study of 76 patients, 30% of patients died with local-only recurrence, while the remaining 70% died with evidence of metastases. CRT, it is thought, may improve local control of disease. In a phase II study designed to evaluate the feasibility and tolerability of a gemcitabine-based CRT protocol in patients who underwent R0 resection for PDAC, the rate of first recurrence as local-only recurrence was lower in those treated with CRT vs CT (11% vs 24%). Furthermore, Parikh et al studied 1130 patients who underwent resection for PDAC and either received no adjuvant therapy, adjuvant CT or adjuvant CRT. With a median follow-up of 18 months, patients who underwent adjuvant CT demonstrated a significant OS benefit on multivariable analysis; however, the patterns of recurrence were different amongst the groups. Receipt of adjuvant CT or adjuvant CRT resulted in less local recurrence in patients with node-positive and margin-negative disease. Further, some meta-analyses have supported the use of CRT in patients with positive resection margins. These potential benefits to adjuvant CRT, as well as mixed results of previous trials, make it a potentially desirable addition to adjuvant systemic CT that warrants further study.

Multiple prior studies have evaluated the role of CRT as a component of adjuvant therapy for resected PDAC, but due to lack of granular detail regarding amount of CT received between treatment regimens, it remains unclear if there truly is a survival benefit associated with the combined use of CRT and adjuvant CT. Kooby et al used the National Cancer Database to compare outcomes in patients who received no adjuvant therapy, adjuvant CT alone, and adjuvant CRT. They reported that CRT was associated with improved survival, but adjuvant CT remained a notable confounder as there was no classification, quantification, or comparison of systemic CT use between the groups. A review of the SEER database, including 2532 patients with resected PDAC found an improvement in OS to 20 months among those treated with radiation after surgical resection compared to those not treated with radiation; however CT use was not evaluated. A prior review of the SEER-Medicare linked database evaluated prognostic factors after surgical resection. In this study of 396 patients, the receipt of adjuvant treatment (adjuvant CT and/or adjuvant radiation) significantly improved median OS; however, the study did not specifically compare receipt of adjuvant CT alone to adjuvant CMT, as in the present study. Similarly, a few other national database studies have investigated the role of adjuvant CRT, but none have compared the addition of CRT to adjuvant CT in resected PDAC. Thus, despite prior randomized studies and more recent reviews, the effectiveness of CMT compared to CT alone for pancreatic cancer is still largely unknown. In the present study, contrary to what was hypothesized, there was no difference in the number of systemic chemotherapy doses administered to the CT and CMT groups. Yet, the addition of adjuvant CRT to CT was associated with an improvement in median OS. When stratified by nodal status, the association with improved OS was confined to the node-positive patients, as hypothesized, while the addition of CRT was not associated with improved OS in node-negative patients.

It is important to note some of the limitations of this study. The retrospective design and the use of a large epidemiological and billing database introduce inherent selection and coding biases. The data derived from databases is not collected to answer specific research questions, and may be subject to unmeasured confounding and have incomplete data. The Medicare fee-for-service population is restricted to patients aged ≥65; however, the median age of patients diagnosed with PDAC is 70, and the median age of our population was 73 years. Although augmentation of the SEER database with Medicare claims data allowed description of types and doses of chemotherapy, the finer details of chemotherapeutic dosing, regimen choice, and regimen adherence, as well as the radiotherapeutic modality and dose used are not discernable through the data. We are also not able to comment on the reason for the low numbers of completion of adjuvant therapy, though it is known that many patients do not complete adjuvant therapy following upfront resection of PDAC. Finally, due to the nature of the SEER-Medicare linked data, granular patient- and tumor-related information such as patient functional status, perineural or neurovascular invasion, and resection margin status are not available. Nonetheless, the SEER-Medicare database provided insights into and quantification of adjuvant CT, which has been absent from previous national database investigations into the role of adjuvant CRT in resected PDAC.

Conclusion

Our data suggests that although CMT may not benefit all patients, those with node-positive disease seem to have improved survival. Future rigorous randomized controlled trials using modern adjuvant CT and CRT regimens are needed to further evaluate the utility of adjuvant CRT in resected PDAC.
Appendix

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| CI           | 95% confidence interval |
| CT           | chemotherapy |
| CMT          | combined modality therapy |
| ESPAC-1      | European Study Group of Pancreatic Cancer-1 |
| GITSG        | Gastrointestinal Study Group |
| HR           | hazard ratio |
| IRB          | Institutional Review Board |
| NCCN         | National Comprehensive Cancer Network |
| NCI          | National Cancer Institute |
| OS           | overall survival |
| PDAC         | pancreatic ductal adenocarcinoma |
| RCT          | randomized controlled trials |
| RTOG         | Radiation Therapy Oncology Group |
| SEER         | Surveillance Epidemiology and End Results |

Author Contributions

AA – study conception, design, data interpretation, manuscript preparation. MW – data interpretation, manuscript preparation, manuscript revision. SM – study conception, data collection, data analysis and interpretation, manuscript revision. DS – data interpretation, manuscript preparation. KC – data interpretation, manuscript revision. EL – data interpretation, manuscript revision. CL – study conception, design, data interpretation, manuscript revision. JYCH – data interpretation, manuscript revision. TMT – data interpretation, manuscript revision. EHJ – study conception, design, data interpretation, manuscript revision. JD – study conception, design, data interpretation, manuscript revision, final approval of manuscript.

Declaration of Conflicting Interests

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Ethics Statement

This study was approved by the Institutional Review Board at the University of Minnesota (IRB), reference number STUDY00004830. All procedures in this study were conducted in accordance with the University of Minnesota IRB’s (STUDY00004830) approved protocols. A waiver of the consent process was granted by the above-named IRB because the study involved no more than minimal risk.

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References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA A Cancer J Clin. 2022;72(1):7-33. doi:10.3322/caac.21708
2. Cancer Stat Facts: Pancreatic Cancer. NIH National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Published 2022. Accessed April 30, 2022. https://seer.cancer.gov/statfacts/html/pancreas.html
3. Mao C, Domenico DR, Kim K, Hanson DJ, Howard JM. Observations on the developmental patterns and the consequences of pancreatic exocrine adenocarcinoma, findings of 154 autopsies. Arch Surg. 1995;130(2):125-134. doi:10.1001/archsurg.1995.01430020015001
4. Ghanem P, Smith R, Tudor-Smith C, Ranaty M, Neoptolemos JP. Neoadjuvant and adjuvant strategies for pancreatic cancer. Eur J Surg Oncol. 2008;34(3):297-305. doi:10.1016/j.ejso.2007.07.204
5. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med. 2014;371(11):1039-1049. doi:10.1056/NEJMra1404198
6. Tempero MA, Malafa MP, Chiorean EG, et al. Pancreatic adenocarcinoma, version 1.2019 featured updates to the NCCN guidelines. JNCCN J Natl Compr Canc Netw. 2019;17(3):203-210. doi:10.6004/jnccn.2019.0014
7. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma (Version 1.2022). Published 2022. Accessed April 30, 2022. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455
8. The Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Cancer 1987;59(12):2006-2010.
9. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: A randomised controlled trial. Lancet. 2001;358(9293):1576-1585. doi:10.1016/S0140-6736(01)06651-X
10. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350(12):1200-1210. doi:10.1056/nejmoa032295
11. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: A randomized controlled trial. JAMA, J Am Med Assoc. 2008;299(9):1019-1026. doi:10.1001/jama.299.9.1019
12. Oettel H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: The CONKO-001 randomized trial. JAMA, J Am Med Assoc. 2013;310(14):1473-1481. doi:10.1001/jama.2013.279201
13. Edelstein J, Benabdellahi M, Bertaut A, et al. Gemcitabine and oxaliplatin chemotherapy or surveillance in resected biliary tract cancer (Prodige 12-accord 18-Unicancer GI): A randomized phase III study. J Clin Oncol. 2019;37(8):658-667. doi:10.1200/JCO.18.00050
14. Sultana A, Tudor Smith C, Cunningham D, et al. Systematic review, including meta-analyses, on the management of locally advanced...
pancreatic cancer using radiation/combined modality therapy. Br J Cancer. 2007;96(8):1183-1190. doi:10.1038/sj.bjc.6603719

15. Medicare Claims Files. NIH National Cancer Institute, Division of Cancer Control and Population Sciences. Published 2021. Accessed April 30, 2022. https://healthcaredelivery.cancer.gov/seermedicare/medicare/claims.html

16. Comorbidity SAS Macro (2014 Version). NIH National Cancer Institute, Division of Cancer Control and Population Science. Published 2014. Accessed October 31, 2018. https://healthcaredelivery.cancer.gov/seermedicare/considerations/macros-2014.html

17. Oba A, Ho F, Bao QR, Al-Musawi MH, Schulick RD, Chiaro MD. Neoadjuvant treatment in pancreatic cancer. Front Oncol. 2020;10:1-10. doi:10.3389/fonc.2020.00245

18. Chawla A, Ferrone CR. Neoadjuvant therapy for resectable pancreatic cancer: An evolving paradigm shift. Front Oncol. 2019;9(OCT):10-13. doi:10.3389/fonc.2019.01085

19. Springfield C, Neoptolemos JP. The role of neoadjuvant therapy for resectable pancreatic cancer remains uncertain. Nat Rev Clin Oncol. 2022;19:285-286.

20. Virnig BA, Warren JL, Cooper GS, Klambunde CN, Schussler N, Freeman J. Studying radiation therapy using SEER-Medicare-linked data. Med Care. 2002;40(8 suppl l):49-54. doi:10.1097/00000658-200208001-00007

21. Procedure Codes for SEER-Medicare Analyses. NIH National Cancer Institute, Division of Cancer Control and Population Sciences. https://healthcaredelivery.cancer.gov/seermedicare/considerations/procedure_codes.html

22. Iacobuzio-Donahue CA, Fu B, Yachida S, Luo M, 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):1806-1813. doi:10.1200/JCO.2008.17.7188

23. Kamisawa T, Isawa T, Koike M, Tsuruta K, Okamoto A. Hematogenous metastases of pancreatic ductal carcinoma. Pancreas. 1995;11(4):345-349. doi:10.1097/0000066676-199511000-00005

24. van Laethem JL, Hammel P, Mornex F, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: A randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. J Clin Oncol. 2010;28(29):4450-4456. doi:10.1200/JCO.2010.30.4346

25. Parikh AA, Maiga A, Bentrem D, et al. Adjuvant therapy in pancreas cancer: Does it influence patterns of recurrence? J Am Coll Surg. 2016;222(4):448-456. doi:10.1016/j.jamcollsurg.2015.12.031

26. Stocken DD, Büchler MW, Dervenis C, et al. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. Br J Cancer. 2005;92(8):1372-1381. doi:10.1038/sj.bjc.6602513

27. McDade TP, Hill JS, Simons JP, et al. A national propensity-adjusted analysis of adjuvant radiotherapy in the treatment of resected pancreatic adenocarcinoma. Cancer. 2010;116(13):3257-3266. doi:10.1002/cncr.25069

28. Koooby DA, Gillespie TW, Liu Y, et al. Impact of adjuvant radiotherapy on survival after pancreatic cancer resection: An appraisal of data from the national cancer data base. Ann Surg Oncol. 2013;20(11):3634-3642. doi:10.1245/s10434-013-3047-x

29. Sugawara A, Kunieda E. Effect of adjuvant radiotherapy on survival in resected pancreatic cancer: A propensity score surveillance, epidemiology, and end results database analysis. J Surg Oncol. 2014;110(8):960-966. doi:10.1002/jso.23752

30. Artinyan A, Hellan M, Mojica-Manosa P, et al. Improved survival with adjuvant external-beam radiation therapy in lymph node-negative pancreatic cancer: A United States population-based assessment. Cancer. 2008;112(1):34-42. doi:10.1002/cncr.23134

31. Hazard L, Tward JD, Szabo A, Shrieve DC. Radiation therapy is associated with improved survival in patients with pancreatic adenocarcinoma: Results of a study from the Surveillance, Epidemiology, and End Results (SEER) registry data. Cancer. 2007;110(10):2191-2201. doi:10.1002/cncr.23047

32. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: A population-based, linked database analysis of 396 patients. Ann Surg 2003; 237(1):74-85. doi:10.1097/00000658-200301000-00011

33. Hsu CC, Herman JM, Corsini MM, et al. Adjuvant chemoradiation for pancreatic adenocarcinoma: The johns hopkins hospital-mayo clinic collaborative study. Ann Surg Oncol. 2010; 17(4):981-990. doi:10.1245/s10434-009-0743-7

34. DePeralta DK, Ogami T, Zhou JM, et al. Completion of adjuvant chemotherapy after upfront surgical resection for pancreatic cancer is uncommon yet associated with improved survival. Ann Surg Oncol. 2019;26(12):4108-4116. doi:10.1245/s10434-019-07602-6

35. Altman AM, Wirth K, Marmor S, et al. Completion of adjuvant chemotherapy after upfront surgical resection for pancreatic cancer is uncommon yet associated with improved survival. Ann Surg Oncol. 2019;26(12):4108-4116. doi:10.1245/s10434-019-07602-6

36. Park HS, Lloyd S, Decker RH, Wilson LD, Yu JB. Overview of the Surveillance, Epidemiology, and End Results Database: Evolution, Data Variables, and Quality Assurance. Current Problems in Cancer. 2012;36(4):183-190. doi:10.1016/j.crrpblncancer.2012.03.007