




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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Ariella M. Altman, MD^{1,2}, McKenzie J. White, MD¹ , Schelomo Marmor, PhD, MPH^{1,3,4}, Dip Shukla, MD^{1,5}, Katherine Chang, MD⁶, Emil Lou, MD⁶, Christopher J. LaRocca, MD^{3,7}, Jane Y.C. Hui, MD, MS^{3,7} , Todd M. Tuttle, MD, MS^{3,7}, Eric H. Jensen, MD^{3,7}, and Jason W. Denbo, MD^{3,8}

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.

¹Department of Surgery, University of Minnesota Medical School, Minneapolis, MN, USA

²Division of Surgical Oncology, Department of Surgery, Fox Chase Cancer Center, Philadelphia, PA, USA

³Office of Academic Clinical Affairs, Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA

⁴Center for Clinical Quality & Outcomes Discovery & Evaluation (C-QODE), University of Minnesota, Minneapolis, MN, USA

⁵Department of Anesthesiology, University of Minnesota Medical School, Minneapolis, MN, USA

⁶Division of Hematology, Department of Medicine, University of Minnesota Medical School, Oncology and Transplantation, University of Minnesota, Minneapolis, MN, USA

⁷Division of Surgical Oncology, Department of Surgery, University of Minnesota Medical School, Minneapolis, MN, USA

⁸Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, USA

Corresponding Author:

McKenzie J. White, MD, Department of Surgery, University of Minnesota Medical School, 420 Delaware St SE., MMC 195, Minneapolis, MN 55455, USA.
Email: akers080@umn.edu



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Keywords

pancreatic ductal adenocarcinoma, surgery, combined modality therapy, chemoradiation, lymph nodes, surveillance epidemiology and end results, medicare

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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 49,830 deaths in 2022¹, 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 question 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

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.

	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,

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

	CT only n = 856		CMT n = 573		P-value
	n	%	n	%	
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.

^bP-value not applicable since median number of CT doses equivalent between cohorts.

since there may be underreporting by Medicare sources if patients receive care outside of the Medicare system.²⁰ Surgical procedures performed were categorized as

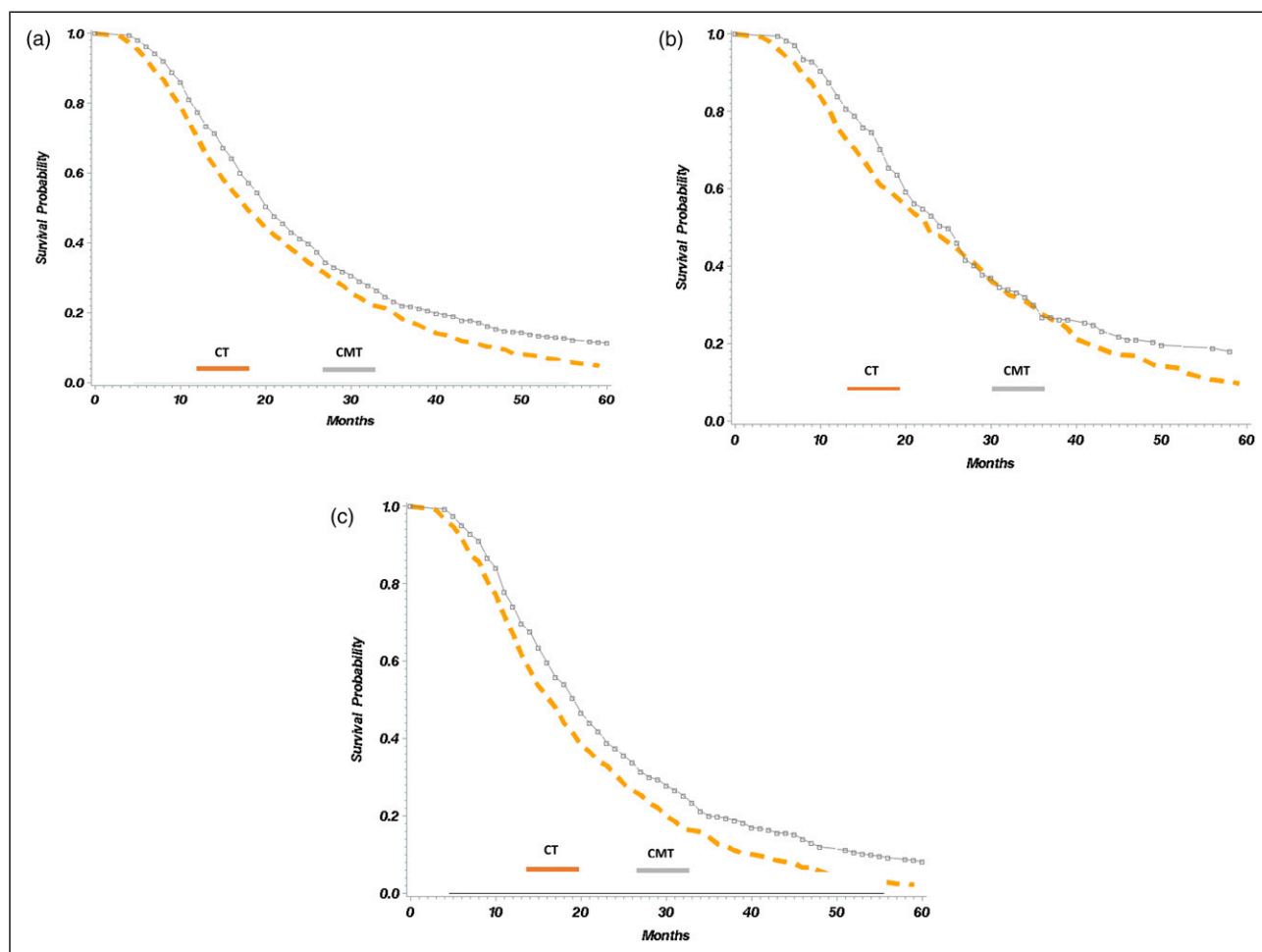


Figure 1. (a) Survival curve, patients who underwent upfront surgical resection for PDAC and received adjuvant CT vs adjuvant CMT in SEER-Medicare, 2004-2013. Median OS 18 months CT, 21 months CMT ($P < .05$). (b) Survival curve, node-negative patients who underwent upfront surgical resection for PDAC and received adjuvant CT vs adjuvant CMT in SEER-Medicare, 2004-2013. Median OS 23 months CT, 25 months CMT ($P = .09$). (c) Survival curve, node-positive patients who underwent upfront surgical resection for PDAC and received adjuvant CT vs adjuvant CMT in SEER-Medicare, 2004-2013. Median OS 17 months CT, 20 months CMT ($P < .05$). Abbreviations: PDAC, pancreatic ductal adenocarcinoma; CT, chemotherapy; CMT, combined modality therapy; OS, overall survival.

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.²¹ 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 $\leq .05$ 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 (STUDY00004830) approved protocols. A waiver of the

Table 3. Multivariable Cox Proportional Hazard Model. Hazard of Death for Patients Who Received Adjuvant Therapy After Upfront Surgical Resection for PDAC^a 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 ^a			
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	.97	1.47	.09
Charlson comorbidity index				
0	REF			
1	1.04	.91	1.20	.53
≥2	1.04	.89	1.22	.62
Treated at NCI^a-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 ^a only	REF			
CMT ^a	.80	.71	.91	.001

^aAbbreviations: PDAC, pancreatic ductal adenocarcinoma; REF, Reference (Hazard Ratio = 1.00); NCI, National Cancer Institute; CT, chemotherapy; CMT, combined modality therapy.

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),⁸ the European

Organisation for the Research and Treatment of Cancer (EORTC)¹⁰ and the European Study Group for Pancreatic Cancer-1 study (ESPAC-1).^{9,10} The GITSG trial first evaluated adjuvant CRT and found an improvement in OS from 11 months to 20 months when compared to observation alone; however, the trial ended prematurely due to low accrual of patients.⁸ The EORTC trial attempted to replicate these results in 218 patients, however found no survival benefit to adjuvant CRT.¹⁰ The subsequent ESPAC-1 trial used a 2×2 factorial design to evaluate CT and CRT vs observation, and found a survival detriment with CRT (14 months vs 17 months) and a survival benefit with adjuvant CT (20 months vs 16 months).⁹ However, interpretation and application of the results of these early trials is difficult in the modern era due to issues with trial design, the use of split course CRT, heterogeneous patient populations, and concerns for selection bias.

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 pancreatectomy for PDAC, 8-30% of patients died with only locoregional recurrence of disease.^{3,22,23} Specifically, in one study of 76 patients, 30% of patients died with local-only recurrence, while the remaining 70% died with evidence of metastases.²² 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%).²⁴ Furthermore, Parikh et al studied 1130 patients who underwent resection for PDAC and either received no adjuvant therapy, adjuvant CT or adjuvant CRT.²⁵ 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.²⁵ Receipt of adjuvant CT or adjuvant CRT resulted in less local recurrence in patients with node-positive and margin-negative disease.²⁵ Further, some meta-analyses have supported the use of CRT in patients with positive resection margins.^{4,26} 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.^{27,28,29,30,31,32,33} 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.²⁸ 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.²⁸ A prior review of the SEER-Medicare linked database evaluated prognostic factors after surgical resection.³² 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 CRT, as in the present study.³² 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 CRT 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 CRT 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.² 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.^{34,35} 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 CRT 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

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

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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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.

ORCID iDs

McKenzie J. White  <https://orcid.org/0000-0002-5328-4938>
Jane Y.C. Hui  <https://orcid.org/0000-0002-2628-0720>

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