



# Completion of Adjuvant Chemotherapy After Upfront Surgical Resection for Pancreatic Cancer Is Uncommon Yet Associated With Improved Survival

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## ABSTRACT

**Background.** Multiple trials have demonstrated a survival benefit for adjuvant chemotherapy after resection of pancreatic adenocarcinoma. This study aimed to identify the rate for completion of adjuvant chemotherapy, factors associated with completion, and its impact on survival after surgical resection.

**Methods.** The Surveillance Epidemiology and End Results Medicare-linked data was used to identify patients who underwent upfront resection for pancreatic adenocarcinoma from 2004 to 2013. Billing codes were used to quantify receipt and completion of chemotherapy. Factors associated with completion of chemotherapy were identified using multivariable regression. Kaplan–Meier and Cox proportional-hazards modeling were used to examine survival.

**Results.** The inclusion criteria were met by 2440 patients. Of these patients, 65% received no adjuvant chemotherapy, 28% received incomplete therapy, and 7% completed

chemotherapy. The factors associated with chemotherapy completion were nodal metastases and treatment at a National Cancer Institute-designated cancer center ( $p \leq 0.05$ ). Comorbidities decreased the odds of completion ( $p \leq 0.05$ ). The median overall survival (OS) was 14 months for the patients who received no adjuvant chemotherapy, 17 months for those who received incomplete adjuvant chemotherapy, and 22 months for those who completed adjuvant chemotherapy ( $p \leq 0.05$ ). More recent diagnosis, comorbidities, T stage, nodal metastases, and no adjuvant chemotherapy were associated with an increased hazard ratio for death ( $p \leq 0.05$ ). Evaluation of 15 or more nodes and completion of chemotherapy decreased the hazard ratio for death ( $p \leq 0.05$ ).

**Conclusions.** Only 7% of the Medicare patients who underwent upfront resection for pancreatic cancer completed adjuvant chemotherapy, yet completion of adjuvant chemotherapy was associated with improved OS. Completion of adjuvant chemotherapy should be the goal after upfront resection, but neoadjuvant chemotherapy may ensure that patients receive systemic chemotherapy.

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Despite advances in multidisciplinary management, pancreatic adenocarcinoma remains the fourth leading cause of cancer-related death in the United States, accounting for an estimated 44,330 deaths in 2018.<sup>1</sup> Surgical resection is the mainstay of therapy with curative intent, but the 5-year overall survival (OS) rate after pancreatectomy alone is merely 10–20%.<sup>2–4</sup>

Several randomized controlled trials (RCTs) have demonstrated improved OS and disease-free survival (DFS) with completion of adjuvant chemotherapy.<sup>2,3,5-7</sup> As such, the National Comprehensive Cancer Network (NCCN) guidelines recommend resection followed by chemotherapy for resectable pancreatic cancer.<sup>8</sup> Despite this recommendation, receipt of chemotherapy is not universal. In RCTs with highly selected patients who have completely recovered from surgery, the rates for completion of chemotherapy range from 54 to 79%.<sup>5,9-12</sup> Single-institution series and cohort studies report even lower rates of 40–60%.<sup>13,14</sup>

A variety of factors may contribute to why a significant proportion of patients do not receive or complete chemotherapy after resection. Patients often present with poor performance statuses and disease-related comorbidities at the time of diagnosis.<sup>15</sup> Surgical resection itself carries high morbidity. Up to 50% of patients experience a major postoperative complication.<sup>13,16-18</sup> Postoperative complications can result in delayed administration of chemotherapy and decreased likelihood of its administration.<sup>16,17</sup> Furthermore, early disease progression after resection occurs in up to 34% of patients, precluding them from receiving adjuvant chemotherapy.<sup>13,14</sup> The combination of these factors likely results in low rates of initiation and completion of adjuvant chemotherapy.

Although RCTs have demonstrated that adjuvant chemotherapy improves survival after resection, patients may not initiate or complete adjuvant chemotherapy for a myriad of reasons. The rates of initiation and completion of adjuvant chemotherapy have not been well established outside RCTs or single-institution series. Therefore, this study sought to determine the rates of receipt and completion of adjuvant chemotherapy on a population level, factors associated with completion of chemotherapy, and its potential impact on survival of patients with pancreatic adenocarcinoma in the United States.

## METHODS

Using the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) linkage with Medicare, patients who received a diagnosis of pancreatic adenocarcinoma from 2004 to 2013 were identified. The SEER registries provide cancer surveillance for 18 geographic areas, representing 34.6% of the U.S. population.<sup>19,20</sup> The registry collects patient, tumor, and treatment characteristics, as well as vital status. The SEER-Medicare database links patients in the SEER program to corresponding Medicare claims.<sup>19</sup>

Patients 66 years old or older with a diagnosis of pancreatic adenocarcinoma were included in the study. Patients who had metastatic disease at diagnosis, a history of another primary malignancy, reception of any preoperative therapy, or treatment with postoperative chemoradiation were excluded from the study.

Tumor stage was determined by the SEER-derived American Joint Committee on Cancer (AJCC) stage group variable, which is a combination of AJCC 6th- and 7th-edition staging. The study was approved by the University of Minnesota's Institutional Review Board.

Receipt of adjuvant chemotherapy was identified using Medicare claims. Initiation of adjuvant chemotherapy was defined as the receipt of a unique billing code for intravenous chemotherapy or a specific J code corresponding to fluorouracil, gemcitabine, or folinic acid within 12 weeks from the date of surgery. The 12-week cutoff for initiation of chemotherapy was based on the European Study Group for Pancreatic Cancer (ESPAC)-3 data showing no difference in OS with initiation of adjuvant chemotherapy up to 12 weeks postoperatively.<sup>11</sup>

During the period of this study, the two most common adjuvant chemotherapeutic agents used for pancreatic cancer were gemcitabine and fluorouracil. In a fluorouracil-based regimen, folinic acid typically is administered intravenously followed by fluorouracil for 5 consecutive days, and repeated every 28 days for six cycles.<sup>21,22</sup> In a gemcitabine-based approach, gemcitabine is administered by intravenous infusion once a week for 3 of 4 weeks, and repeated six times.<sup>10,21</sup> We defined one cycle of chemotherapy using a typical gemcitabine cycle that involves receipt of a unique Medicare claim for chemotherapy on 3 separate days during a month. Not only are gemcitabine regimens more common, but this approach also allows for the most inclusive definition of a chemotherapy cycle.

Completion of adjuvant chemotherapy was defined as completion of six cycles within 10 months after the date of surgery. This extended time frame allowed for prolonged recovery from surgery and possible delays or adjustments in treatment schedules, including missed doses or missed claims. Chemotherapy administered after 10 months likely does not reflect adjuvant chemotherapy and was not included in the analysis.

The patients who met the inclusion criteria were classified into three cohorts (no chemotherapy, incomplete chemotherapy, and complete chemotherapy) based on the number of adjuvant chemotherapy cycles received. Multivariable logistic regression analyses were performed to evaluate factors associated with completion of adjuvant chemotherapy. All models included date of diagnosis, patient age, gender, race, Charlson Comorbidity Index (CCI), T stage, nodal status, number of lymph nodes

evaluated, hospital designation (NCI-designated cancer center), type of surgical resection, and receipt of adjuvant chemotherapy.

Trends over time were analyzed using the Cochran-Armitage test for trend. Survival was analyzed using Kaplan-Meier and Cox proportional-hazard modeling. For all models, sensitivity analyses were performed to ensure that the observed effects were not a product of coding classifications. Results were considered statistically significant for a two-tailed  $p$  value of 0.05 or lower. For all statistical analyses, SAS statistical software, version 9.3 (SAS Institute, Cary, NC, USA) was used.

## RESULTS

### *Patient Population*

The inclusion criteria were met by 2440 patients. The patient characteristics for the entire cohort that underwent upfront surgical resection are presented in Table S1. The median age of all the patients was 74 years. The majority of the patients (81%) were non-Hispanic white, and 46% were male. Half of the cohort had a CCI of 0. Most of the tumors were T stage 3, larger than 2 cm, and node-positive. A Whipple procedure was performed for 70% of the patients.

After upfront surgical resection, 65% of the patients received no adjuvant chemotherapy, 28% received incomplete adjuvant chemotherapy and 7% completed six cycles of adjuvant chemotherapy. An audit of the Medicare claims data was performed to determine the specific chemotherapy regimens used. Of the patients who completed chemotherapy, 97% had at least one specific J code for gemcitabine, and 8% had at least one specific J code for fluorouracil. The patient characteristics based on receipt of adjuvant chemotherapy (no chemotherapy, incomplete chemotherapy, or complete chemotherapy) are presented in Table 1.

### *Factors Associated With Completion of Adjuvant Chemotherapy*

Multivariable logistic regression was used to evaluate factors associated with completion of adjuvant chemotherapy (Table 2). A greater severity of comorbidities (CCI  $\geq 2$ ) was associated with significantly decreased odds for completion of chemotherapy (odds ratio [OR], 0.57; 95% confidence interval [CI], 0.36–0.91). Positive nodal status (OR, 1.67; 95% CI, 1.14–2.46) and treatment at an NCI-designated cancer center (OR, 4.25; 95% CI, 2.68–6.76) were associated with significantly increased odds for completion of chemotherapy. Date of diagnosis

was not a significant factor for completion of chemotherapy.

Further evaluation of receipt and completion of chemotherapy over time was performed. Annual rates of initiation and completion of chemotherapy are shown in Fig. 1. No significant trend by year was observed ( $p = 0.49$ ). However, evaluation by period showed a significant decrease in initiation of chemotherapy in the more recent period (2009–2014) compared with the earlier period (2004–2008). During 2009–2014, 25% of the patients initiated chemotherapy, and 7% completed it compared with 31% and 7%, respectively, in the 2004–2008 period (Table 1;  $p = 0.002$ ).

### *Adjuvant Chemotherapy and OS*

The median OS was 14 months for the patients who received no adjuvant chemotherapy, 17 months for those who received incomplete adjuvant chemotherapy, and 22 months for those who completed adjuvant chemotherapy (Fig. 2,  $p \leq 0.05$ ). A Cox proportional-hazards model evaluated factors associated with OS (Table 3). More recent year of diagnosis (2009–2013 vs 2004–2008), higher level of comorbidities (CCI  $\geq 2$  vs 0), higher T stage (T stage 3 and 4 vs T stage 1 and 2), nodal positivity (vs negativity), and receipt of no adjuvant chemotherapy (vs incomplete chemotherapy) all were associated with a significant increase in the hazard ratio for death ( $p < 0.05$ ). Extent of lymphadenectomy ( $\geq 15$  nodes examined) and completion of adjuvant chemotherapy (vs incomplete chemotherapy) were associated with a significantly decreased hazard ratio for death ( $p < 0.05$ ).

## DISCUSSION

This study used a large national database to evaluate rates for initiation and completion of adjuvant chemotherapy after upfront resection for pancreatic adenocarcinoma in the Medicare population. Approximately one-third of the patients initiated adjuvant chemotherapy, but only 7% of the population completed adjuvant chemotherapy after upfront resection.

Receipt of adjuvant chemotherapy was associated with improved survival. Furthermore, this study uniquely demonstrated a significant difference in survival between the patients who received no adjuvant chemotherapy (median OS, 14 months), those who received incomplete adjuvant chemotherapy (median OS, 17 months), and those who completed chemotherapy (median OS, 22 months) ( $p < 0.05$ ). Even after control was used for other relevant variables, completion of adjuvant chemotherapy was

**TABLE 1** Characteristics of the patients with a diagnosis of pancreatic adenocarcinoma from 2004 to 2013 in the SEER-Medicare-linked data stratified by receipt of adjuvant chemotherapy (*n* = 2440)

	None ( <i>n</i> = 1596)		Incomplete ( <i>n</i> = 671)		Complete ( <i>n</i> = 173)		<i>p</i> Value
	<i>N</i>	%	<i>n</i>	%	<i>n</i>	%	
Diagnosis period							0.002
2004–2008	615	62	312	31	72	7	
2009–2013	981	68	359	25	101	7	
Age categories (years)							0.003
66–69	380	63	180	30	45	7	
70–74	402	62	184	29	58	9	
75–79	424	65	186	28	45	7	
≥ 80	390	73	121	23	25	5	
Gender							0.25
Male	747	66	293	26	86	8	
Female	849	65	378	28	87	7	
Race							< 0.0001
Non-Hispanic white	1236	63	582	30	150	8	
Black, other, or unknown	360	76	89	19	23	5	
T stage							0.30
1 & 2	385	68	143	25	37	7	
3 and 4	1211	64	528	25	136	6	
Tumor size (cm)							0.11
< 2	230	70	84	25	16	5	
≥ 2	1366	65	587	28	157	7	
Nodal metastases							0.001
No and missing	706	69	270	26	53	5	
Yes	890	63	401	28	120	9	
Lymph nodes evaluated							0.44
Missing/unknown and ≤ 4	220	71	73	23	19	6	
5–9	325	64	151	30	32	6	
10–14	346	65	142	27	41	8	
15+	705	65	305	28	81	7	
Surgical procedure							0.13
Whipple	1100	65	480	28	120	7	
Total pancreatectomy	230	70	72	22	28	8	
Other	266	65	119	29	25	6	
NCI-designated cancer center							< 0.0001
No	1596	69	576	25	144	6	
Yes	–	–	95	77	29	23	
CCI							0.001
0	814	67	304	25	100	8	
1	435	61	229	32	49	7	
≥ 2	347	68	138	27	24	5	

SEER Surveillance epidemiology and end results program, CCI Charlson comorbidity index, NCI National Cancer Institute

associated with improved survival compared with no adjuvant chemotherapy and incomplete adjuvant chemotherapy.

Administration of adjuvant chemotherapy after resection with curative intent has been demonstrated to improve DFS and OS.<sup>2,3,5,7,22,23</sup> In 2001, the initial results of the ESPAC-1 trial were published, demonstrating that adjuvant

**TABLE 2** Odds for completion of adjuvant chemotherapy after upfront surgical resection for pancreatic adenocarcinoma among patients who received at least one dose of adjuvant chemotherapy

	OR	95% CI	
Diagnosis period			
2004–2008	1.00	Reference	
2009–2013	1.05	0.75	1.45
Age categories (years)			
66–69	1.00	Reference	
70–74	1.20	0.79	1.82
75–79	0.97	0.62	1.51
80–84	0.73	0.42	1.26
≥ 85	0.43	0.15	1.22
Gender			
Male	1.00	Reference	
Female	0.84	0.61	1.16
Race			
Non-Hispanic white	1.00	Reference	
Black	0.77	0.36	1.61
Other	0.61	0.35	1.06
Surgical procedure			
Whipple	1.00	Reference	
Total pancreatectomy	1.35	0.87	2.09
Other	0.95	0.60	1.51
Tumor size (cm)			
< 2	1.00	Reference	
≥ 2	1.43	0.82	2.49
T stage			
1 and 2	1.00	Reference	
3	1.12	0.74	1.69
4	0.64	0.15	2.73
CCI			
0	1.00	Reference	
1	0.82	0.57	1.2
≥ 2	<b>0.57</b>	<b>0.36</b>	<b>0.91</b>
Nodal metastases			
None	1.00	Reference	
<b>Yes</b>	<b>1.67</b>	<b>1.14</b>	<b>2.46</b>
No nodes evaluated	1.75	0.78	3.93
Lymph nodes evaluated			
< 15	1.00	Reference	
15+	1.08	0.77	1.51
NCI-designated cancer center			
No	1.00	Reference	
<b>Yes</b>	<b>4.25</b>	<b>2.68</b>	<b>6.76</b>

Bold type designates statistical significance

OR odds ratio, CI confidence interval, CCI Charlson Comorbidity Index, NCI National Cancer Institute

fluorouracil-based chemotherapy improved survival over surgery.<sup>3,22</sup> In 2007, Charite Onkologie (CONKO)-001 further solidified adjuvant chemotherapy as the standard of care by demonstrating a 10% improvement in 5-year OS with gemcitabine compared with observation.<sup>10</sup> The subsequent ESPAC-3v2 and ESPAC-4 trials more clearly defined optimal adjuvant chemotherapy regimens.<sup>3,5,11,21</sup> Recently, a modified FOLFIRINOX regimen was evaluated in the adjuvant setting, demonstrating improved DFS and OS compared with adjuvant gemcitabine, but with an increased rate of serious adverse events.<sup>12</sup>

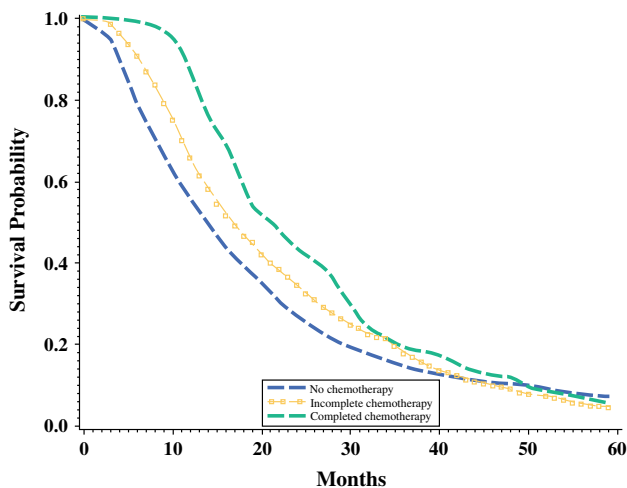
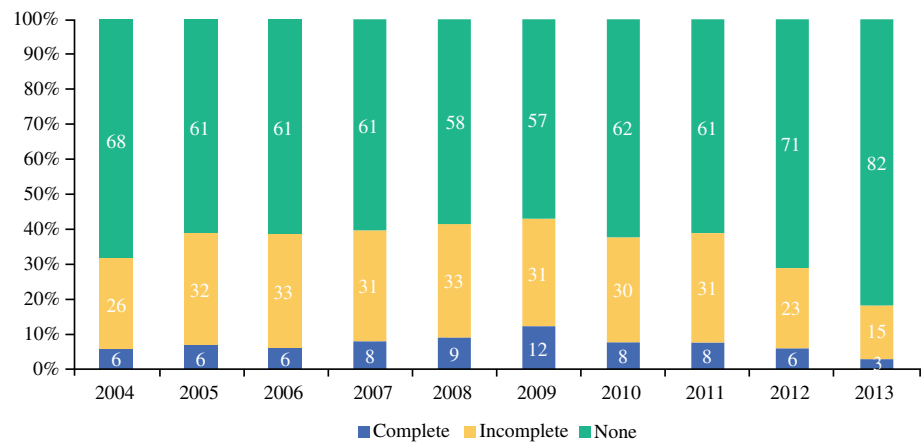
Despite the survival benefits attributed to adjuvant chemotherapy, only 35% of Medicare patients initiated chemotherapy, and only 7% completed the courses. Prior RCTs have demonstrated that at best, 54–79% of patients receive adjuvant chemotherapy per protocol.<sup>5,9,10,12,22</sup> In CONKO-001, 87% of the patients received at least one cycle of treatment, whereas only 62% completed treatment per protocol, and 9.7% received no adjuvant chemotherapy.<sup>10</sup> In retrospective reviews and large institutional series, the rates of chemotherapy administration are significantly less.<sup>13,14,16,24–26</sup> In a population-based study of 203 patients, 41.9% of the patients completed adjuvant chemotherapy, whereas 20.2% received incomplete chemotherapy, and 37.9% received no adjuvant chemotherapy.<sup>13</sup> Another study evaluated NCCN compliance and found that only 35% of the patients received the recommended multi-modality care.<sup>25</sup>

The current study used a population-based data set and further demonstrated low rates of initiation and completion of adjuvant chemotherapy in the Medicare population. The dramatic difference between this study and prior studies in the rates for initiation and completion of adjuvant chemotherapy likely is related to patient selection. An RCT includes only patients who have completely recovered from resection, have a good performance status, and show no evidence of disease. Although this is necessary for conducting a well-designed trial, it does not reflect the reality of patient recovery and treatment after surgery.

The current study represented the full gamut of patients who underwent upfront surgical resection for pancreatic cancer. Furthermore, the SEER-Medicare database also included patients in a variety of health care systems, not just large tertiary referral centers, thus providing a near-complete cross-section of patients and outcomes.

The poor receipt of guideline-compliant care with respect to administration of adjuvant chemotherapy certainly is multifactorial, including both patient and provider variables. Prior studies have shown that up to 50% of patients may experience postoperative complications,<sup>17</sup> with almost one-fourth of the patients experiencing at least

**FIG. 1** Rates for initiation and completion of chemotherapy by year of diagnosis. Numbers represent the percentage of patients with a diagnosis of pancreatic adenocarcinoma who underwent upfront surgical resection and subsequently received complete, incomplete, or no chemotherapy in the adjuvant setting ( $p = 0.49$ )



**FIG. 2** Kaplan–Meier survival curve for all the patients in the SEER-Medicare-linked data who underwent upfront surgical resection for pancreatic adenocarcinoma from 2004 to 2013 stratified by receipt of adjuvant chemotherapy. The median overall survival was 14 months for the patients who received no adjuvant chemotherapy, 17 months for those who received incomplete adjuvant chemotherapy, and 22 months for those who completed adjuvant chemotherapy ( $p < 0.05$ )

one serious complication.<sup>16</sup> Findings have shown that the presence of a serious complication significantly increases the odds of not receiving adjuvant chemotherapy.<sup>16</sup>

In addition to postoperative complications, other factors reported as barriers to the receipt of optimal therapy include advanced age, poor performance status, early disease progression, and treatment center characteristics.<sup>13–17,25,27</sup> In a large review of the California Cancer Registry, the receipt of guideline-compliant care significantly decreased with increasing age.<sup>25</sup> In the current review of SEER-Medicare data, advanced age and comorbidities were similarly associated with decreased odds of chemotherapy completion. The low rates of chemotherapy administration after upfront resection in the Medicare population, particularly those of

advanced age, is notable because a previous review of SEER-Medicare showed only a very small benefit of surgery over chemotherapy alone for patients 80 years old or older.<sup>28</sup>

The two positive predictors of adjuvant chemotherapy completion were treatment at an NCI-designated cancer center and nodal metastases. Treatment at an NCI-designated cancer center was associated with more than a fourfold increase in the odds of a patient completing chemotherapy, in line with prior studies showing that patients who received care at high-volume centers have improved outcomes after pancreatotomy,<sup>29,30</sup> and are more likely to receive guideline-compliant care.<sup>25,27</sup>

In this analysis of SEER-Medicare data, the presence of nodal disease was independently associated with an increased likelihood of completion of adjuvant chemotherapy. This finding may be in response to the fact that nodal metastases are a negative prognostic factor.<sup>31–35</sup> Providers may be more attuned to the importance of adjuvant chemotherapy in the setting of an NCI-designated cancer center and for patients with nodal metastases.

Importantly, receipt and completion of adjuvant chemotherapy did not increase over time. The two major trials that established adjuvant chemotherapy guidelines (ESPAC-1 and CONKO-001) were published in 2001 and 2007, respectively.<sup>3,10</sup> The current study was designed to compare the early period (2004–2008) with the later period (2009–2013) to account for any change in practice caused by the publication of CONKO-001.<sup>10</sup> However, no significant increase was observed. In the early period (2004–2008), 31% of the patients initiated chemotherapy and 7% completed chemotherapy, whereas the corresponding rates in the late period (2009–2014) were 25% and 7% ( $p = 0.002$ ). The fact that use and completion of adjuvant chemotherapy did not increase after the publication of CONKO-001 suggests that obstacles other than a perceived paucity of high-level data to support adjuvant chemotherapy existed at that time.

**TABLE 3** Cox proportional-hazards model for death of patients treated with upfront surgical resection for pancreatic cancer in the SEER-Medicare data set from 2004 to 2013

	HR	95% CI		<i>p</i> Value
Diagnosis period				
2004–2008	1.00	Reference		
<b>2009–2013</b>	<b>1.29</b>	<b>1.18</b>	<b>1.42</b>	<b>&lt;.0001</b>
Age categories (years)				
66–69	1.00	Reference		
70–74	1.09	0.96	1.23	0.19
75–79	1.06	0.93	1.20	0.39
80–84	1.01	0.87	1.16	0.92
≥ 85	0.97	0.79	1.20	0.80
Gender				
Male	1.00	Reference		
Female	0.93	0.85	1.02	0.10
Race				
Non-Hispanic white	1.00	Reference		
Black	1.10	0.91	1.32	0.33
Other or unknown	1.03	0.90	1.18	0.65
CCI				
0	1.00	Reference		
1	1.04	0.94	1.15	0.49
<b>≥ 2</b>	<b>1.25</b>	<b>1.11</b>	<b>1.40</b>	<b>0.0002</b>
T stage				
1 and 2	1.00	Reference		
<b>3</b>	<b>1.31</b>	<b>1.16</b>	<b>1.47</b>	<b>&lt;0.0001</b>
<b>4</b>	<b>2.20</b>	<b>1.59</b>	<b>3.02</b>	<b>&lt;0.0001</b>
Nodal metastases				
No	1.00	Reference		
<b>Yes</b>	<b>1.48</b>	<b>1.33</b>	<b>1.63</b>	<b>&lt;0.0001</b>
Missing	1.11	0.87	1.42	0.41
Lymph nodes evaluated				
< 15	1.00	Reference		
<b>15+</b>	<b>0.85</b>	<b>0.78</b>	<b>0.94</b>	<b>0.001</b>
NCI-designated cancer center				
Yes	1.00	Reference		
No	0.96	0.78	1.19	0.73
Surgical procedure				
Whipple	1.00	Reference		
Total pancreatectomy	1.03	0.91	1.18	0.63
Other	1.00	0.88	1.13	0.99
Adjuvant chemotherapy				
<b>None</b>	<b>1.35</b>	<b>1.22</b>	<b>1.51</b>	<b>&lt;0.0001</b>
Incomplete	1.00	Reference		
<b>Complete</b>	<b>0.78</b>	<b>0.65</b>	<b>0.95</b>	<b>0.01</b>

Bold text designates statistical significance

SEER surveillance epidemiology and end results program, HR hazard ratio, CI confidence interval, CCI Charlson comorbidity index, NCI National Cancer Institute

Given the low rates of receipt and completion of adjuvant chemotherapy, a neoadjuvant approach to chemotherapy may enable more patients to receive systemic treatment. Some of the theoretical advantages of neoadjuvant chemotherapy are early initiation of systemic therapy to treat micro-metastatic disease, ability to select out favorable tumor biology before potentially morbid operations, and potential to downstage the primary tumor.<sup>36–39</sup> Over time, some centers have begun to adopt a neoadjuvant approach for pancreatic cancer, which was accepted at first only for borderline resectable/locally advanced tumors but has spread to use for resectable cancer. However, a recent National Cancer Database (NCDB) study of 18,332 patients with a diagnosis of stages 1 to 3 pancreatic cancer from 2003 to 2011 who underwent surgical resection found that only 1736 patients (9.5%) received neoadjuvant therapy.<sup>40</sup>

The inherent limitations of this study stemmed from its retrospective nature and its data source. All retrospective studies are subject to reporting and selection bias. In the SEER-Medicare database, information on chemotherapy is claims-based and subject to missing or erroneous claims. However, previous studies have validated this practice.<sup>41–45</sup> Furthermore, augmentation of SEER data with Medicare claims significantly improves the reliability of chemotherapy reporting.<sup>45</sup> Although we were unable to obtain granular information on the regimens for each patient and his or her unique clinical course, the data set did allow evaluation, quantification, and characterization of adjuvant chemotherapy.

Completion of adjuvant chemotherapy in this study was defined by a count of chemotherapy codes/claims for a typical gemcitabine regimen. Therefore, the current study may have overreported the actual completion rate for adjuvant chemotherapy because patients who received 5-fluorouracil (5-FU) require more doses of chemotherapy to complete a cycle. This approach was adopted to avoid introducing bias into the study by underreporting completion of adjuvant chemotherapy and because gemcitabine was the most common chemotherapy used. It was impossible to determine whether adjuvant chemotherapy was recommended to patients and the specific reasons why this may or may not have occurred. Finally, the SEER data set does not contain margin status data from the surgical pathology specimen. Nonetheless, adjuvant chemotherapy is recommended after upfront surgical resection regardless of the margin status.<sup>46</sup>

Despite these limitations, this was the largest and most comprehensive analysis to evaluate adjuvant chemotherapy completion for patients with pancreatic cancer in the United States.

In conclusion, this analysis of the Medicare population demonstrated that initiation and completion of adjuvant chemotherapy after upfront surgical resection of pancreas cancer occur infrequently, only for 35% and 7% of the patients, respectively. Also, this study demonstrated that completion of adjuvant chemotherapy was associated with better survival than experienced by patients who received incomplete or no chemotherapy. The main obstacles to completion of adjuvant chemotherapy appear to be advanced age, comorbidities, recovery after surgical resection, and the health care delivery system. Completion of systemic adjuvant chemotherapy should be the goal after surgical resection for patients with pancreatic cancer because it is associated with improved survival, but this goal remains elusive. A neoadjuvant approach to chemotherapy administration may obviate some of these obstacles and help to ensure that more patients receive and complete systemic chemotherapy for pancreatic cancer.

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