

Neoadjuvant Therapy Is Associated With Improved Survival in Resectable Pancreatic Adenocarcinoma

Avo Artinyan, MD, MS¹; Daniel A. Anaya, MD¹; Shaun McKenzie, MD²; Joshua D. I. Ellenhorn, MD³; and Joseph Kim, MD³

BACKGROUND: Neoadjuvant therapy has been used to improve survival in operable pancreatic cancer. The authors' objective was to compare long-term outcomes in patients receiving neoadjuvant versus adjuvant therapy for resectable pancreatic adenocarcinoma. **METHODS:** The California Cancer Surveillance Program for Los Angeles County retrospectively identified 458 patients with nonmetastatic pancreatic adenocarcinoma who underwent definitive pancreatic resection and received systemic chemotherapy between 1987 and 2006. The cohort was grouped by timing of systemic therapy—neoadjuvant or adjuvant. Clinicopathologic characteristics and overall survival were compared. Multivariate Cox regression analysis was used to determine the benefit of neoadjuvant therapy, independent of other significant factors. **RESULTS:** Of the 458 patients, 39 (8.5%) received neoadjuvant therapy, and 419 (91.5%) received adjuvant therapy. There was a significantly lower rate of lymph node positivity in the neoadjuvant group (45% vs 65%; $P=.011$) despite a higher rate of extrapancreatic tumor extension. On Kaplan-Meier analysis, the neoadjuvant group had significantly better overall survival compared with the adjuvant group (median survival, 34 vs 19 months; $P=.003$). Overall survival was also improved in the neoadjuvant therapy patients with extrapancreatic disease (median survival, 31 vs 19 months; $P=.018$). On multivariate Cox regression analysis, neoadjuvant therapy was an independent predictor of improved survival (hazard ratio, 0.57; 95% confidence interval, 0.37-0.89; $P=.013$). **CONCLUSIONS:** This is the first population-based study to compare neoadjuvant versus adjuvant treatment strategies in resectable pancreatic cancer. Neoadjuvant therapy is associated with a lower rate of lymph node positivity and improved overall survival and should be considered an acceptable alternative to the surgery-first paradigm in operable pancreatic cancer. *Cancer* 2011;117:2044-9. © 2010 American Cancer Society

KEYWORDS: pancreatic cancer, surgery, chemotherapy, neoadjuvant therapy.

Pancreatic ductal adenocarcinoma remains an important public health concern, largely because of its lethality and the futility of current treatment approaches. Despite advances in screening, diagnosis, and multimodality therapy, the prognosis for pancreatic cancer has improved very little in the past 2 decades, with median survival among all patients on the order of 6 months.¹⁻³ Because of the insidious onset of pancreatic ductal adenocarcinoma, presentation tends to occur late in the disease process. As a result, only a minority of patients are candidates for surgery, with even fewer undergoing complete, margin-negative resection. Even after complete resection, recurrences are common, occurring both locally and systemically, and long-term survival is exceedingly rare.¹⁻⁸

Several multimodal treatment strategies have been used in an effort to improve outcomes from pancreatic ductal adenocarcinoma, including more radical surgery (eg, extended lymphadenectomy)^{9,10} and both adjuvant and neoadjuvant chemotherapy and radiation.^{4,8} Because the primary curative treatment for pancreatic ductal adenocarcinoma is surgical resection, the recommended practice for localized disease outside the clinical trial setting is upfront surgery followed by adjuvant chemotherapy with or without chemoradiation.¹¹ This approach, however, has not led to considerable improvements in locoregional control and survival.

Corresponding author: Joseph Kim, MD, Assistant Professor of Surgery, City of Hope, 1500 East Duarte Road, Duarte, CA 91010; Fax: (626) 301-8865; jokim@coh.org

¹Michael E. DeBakey Department of Surgery and Houston Health Services & Research Center of Excellence, Michael E. DeBakey Veterans Affairs Medical Center, Baylor College of Medicine, Houston, Texas; ²Department of Surgery, University of Kentucky School of Medicine, Lexington, Kentucky; ³Department of Oncologic Surgery, City of Hope Comprehensive Cancer Center, Duarte, California

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Neoadjuvant therapy has been used as an alternative approach primarily at large specialty centers, but consensus regarding the specific role and type of neoadjuvant therapy for resectable pancreatic ductal adenocarcinoma is lacking.^{2,12,13} As a consequence, neoadjuvant therapy has not gained broad acceptance. In addition, there are no randomized, prospective trials comparing neoadjuvant with adjuvant strategies for resectable pancreatic ductal adenocarcinoma. Much of the existing evidence is in the form of single-institution experiences.^{12,14} These data demonstrate decreased margin positivity and local failure and increased survival in the subset of patients who eventually undergo resection.¹²⁻¹⁵

Given this gap in the existing data, we conducted a population-based study to compare survival in patients treated with neoadjuvant chemotherapy followed by pancreatic resection with patients who underwent pancreatic resection followed by adjuvant chemotherapy, which is the current standard of care.¹¹ The purpose of this analysis was to determine whether the results previously observed from single institutions were evident in a broader population and to add to the existing literature regarding the benefit of the neoadjuvant approach. We hypothesized that these patients would demonstrate improved survival compared with patients undergoing a surgery-first approach.

MATERIALS AND METHODS

Patient Population

The Los Angeles County Cancer Surveillance Program database was used in this study. The details of the registry and the nature of data collection and maintenance have been previously described.¹⁶ The Cancer Surveillance Program has served as region 9 of the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute since 1987 and uses the same coding. The primary advantage of this database over larger administrative databases such as those maintained by SEER is its greater level of detail, particularly with respect to details of systemic therapy. Institutional review board approval was obtained for this analysis from City of Hope and the State of California.

All patients with histologically confirmed nonmetastatic pancreatic adenocarcinoma, who underwent definitive pancreatic resection and received systemic chemotherapy with or without radiation between the years 1987 and 2006 were identified. The specific International Classification of Diseases, 3rd edition histology codes used to define adenocarcinoma included 8140-45,

8211, 8260-63, 8290, 8310, 8480-81, 8500-03, 8521-23, and 8570-8576. Definitive resection was identified as partial or complete pancreatectomy corresponding to FORDS (Facility Oncology Registry Data Standards) surgery codes 30-80. Local excisions (FORDS code 25) and pancreatectomy not otherwise specified (FORDS code 90) were excluded.

Definition of Variables and Statistical Analysis

The outcome variable of interest was overall survival, with time of survival defined as the time period between diagnosis and death. Patients who were still alive at the time of analysis were censored at the time they were last known to be alive. The primary factor of interest was the timing of systemic chemotherapy (with or without radiation), which was determined by comparing the date of initiation of chemotherapy treatment to the surgery date. Patients were categorized into 2 groups based on the timing of chemotherapy relative to definitive surgical resection: preoperative/neoadjuvant therapy and postoperative/adjuvant therapy. Other variables of interest included demographic factors, tumor extension, nodal status, and era of treatment. Era of treatment was defined as early (1987-1996) and late (1997-2006), and was included primarily to control for changes in chemotherapy and practice patterns during the study period.

The Kaplan-Meier method was used to estimate overall survival. Differences in survival by timing of chemotherapy were determined using the log-rank test. Multivariate Cox regression analysis was then used to determine the prognostic significance of timing of chemotherapy, adjusting for other significant clinicopathologic factors. Continuous variables were compared using independent-sample Student *t* tests with results reported as means $\pm$ standard errors. Categorical variables were compared using chi-square tests. The results of Cox regression analyses were presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and *P* values for the appropriate statistical tests of significance. In all cases, a *P* value of $\leq .05$ was considered statistically significant. The statistical analysis was performed using SPSS 17.0 (SPSS, Inc., Chicago, Ill).

RESULTS

Patient Cohort

Four hundred sixty-four patients with nonmetastatic pancreatic adenocarcinoma who underwent pancreatic resection and received systemic therapy were identified. The

Table 1. Characteristics of the Sample Population (N = 458)

Factors	No. (%)
Age, y ^a	61.8 ± 10.6
Sex	
Male	215 (46.9%)
Female	243 (53.1%)
Tumor size, mm ^a	37.3 ± 17.8
Extent of primary tumor	
Localized	91 (21.5%)
Extrapancreatic	332 (78.5%)
Lymph node status	
Negative	152 (36.5%)
Positive	271 (63.5%)
Timing of chemotherapy	
Neoadjuvant	39 (8.5%)
Adjuvant	419 (91.5%)
Radiation	
No	167 (35.9%)
Yes ^b	291 (64.1%)
Time period	
1987-1996	133 (29.0%)
1997-2006	325 (71.0%)

^aData are expressed as mean ± standard deviation.^bIncludes intraoperative radiation and/or unknown treatment sequence.

timing of therapy was known for 458 patients, and this cohort constituted the study group. The characteristics of the study population are presented in Table 1. The mean age of the cohort was 62 years, and most patients were female (53%). The large majority of pancreatic tumors had extrapancreatic extension (ie, T3 or T4 disease) (79%) with evidence of nodal metastasis (64%).

With respect to timing of treatment, only a small minority (8.5%) of patients received neoadjuvant therapy, whereas the majority (91.5%) received adjuvant therapy. Most patients (64.1%) also received radiation at some point during their treatment; however, the overwhelming majority (94%) received adjuvant radiation. Of the 14 patients who received preoperative radiation, 12 of these patients also received neoadjuvant chemotherapy.

Comparison of Patient Characteristics

Table 2 presents a univariate comparison of patient characteristics according to timing of systemic therapy. There was no significant difference in age, sex, or tumor size between the 2 treatment groups. However, the neoadjuvant therapy group had a lower rate of lymph node-positive tumors (44% vs 65%) despite having a tendency toward a higher proportion of extrapancreatic lesions (86% vs 77%). The neoadjuvant therapy group was also

less likely to receive radiation at any point during treatment (46% vs 65%, $P = .018$); when they did receive radiation, it was more often administered in the neoadjuvant setting (66% vs 1%, $P < .001$). There was no association between timing of chemotherapy and time period, demonstrating an equally low likelihood of neoadjuvant treatment in both time periods ($P = .63$).

Survival Analysis

The observed median survival for the entire group of resected pancreatic cancer patients was 19.5 months, with an estimated 5-year overall survival of 16%. Figure 1 presents a comparison of survival by timing of chemotherapy. The neoadjuvant therapy group had significantly better overall survival compared with the adjuvant therapy group (median survival, 33.8 vs 19.0 months, respectively; $P = .003$). Figure 2 presents the results of survival analysis in patients with extrapancreatic disease. In this population, which may include patients with borderline-resectable disease, the neoadjuvant therapy group also had significantly better overall survival compared with the adjuvant therapy group (median survival, 31.1 vs 19.0 months; $P = .018$).

The results of multivariate Cox regression analysis are presented in Table 3. Neoadjuvant chemotherapy was associated with significantly improved outcome after controlling for extent of disease (lymph node status and tumor extension) and radiation therapy, with a 43% decreased risk of death compared with the adjuvant therapy group (HR, 0.57; 95% CI, 0.37-0.89; $P = .013$).

DISCUSSION

Surgical resection currently remains the only means of cure for operable pancreatic cancer. Therefore, a surgery-first approach with the administration of various adjuvant therapies has generally been favored and is the current standard of care.^{4,8,17} Phase 3 trials of adjuvant therapy have demonstrated improvements in both disease-free and overall survival, although the absolute increases have been relatively small.^{5,7,17} Furthermore, the adjuvant therapy approach has been associated with several shortcomings, including high rates of both local and distant failure and persistently poor long-term survival.^{2,4-8,17-20} Moreover, a significant proportion of patients fail to complete planned adjuvant therapy because of treatment-related morbidities, progression of disease, and poor functional status after surgical resection.^{5-7,21,22}

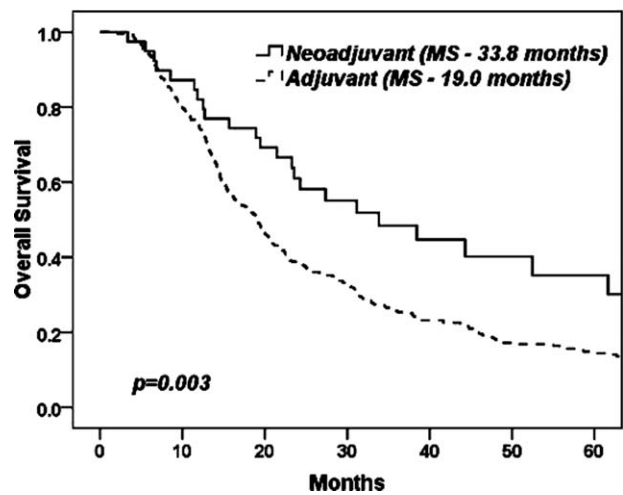
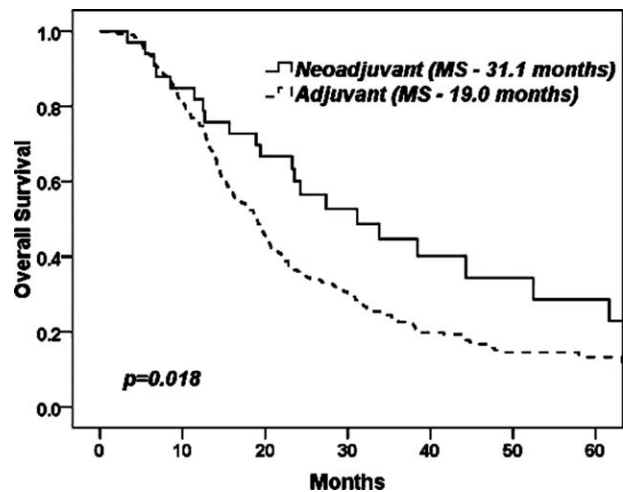
Table 2. Comparison of Characteristics by Timing of Systemic Therapy

Factors	Timing of Chemotherapy		P
	Neoadjuvant, n = 39	Adjuvant, n = 419	
Age, y ^a	61.7 ± 1.62	61.8 ± 0.52	.93
Sex			.57
Male	20 (51.3%)	195 (46.5%)	
Female	16 (44.4%)	224 (53.5%)	
Tumor size, mm	40.8 ± 2.7	37.0 ± 0.92	.24
Lymph node status			.010
Negative	20 (55.6%)	132 (34.1%)	
Positive	16 (44.4%)	255 (65.9%)	
Extent of primary tumor			.19
Localized	5 (13.2%)	86 (22.3%)	
Extrapancreatic	33 (86.8%)	299 (77.7%)	
Radiation			.018
No	21 (53.8%)	146 (34.8%)	
Yes	18 (46.2%)	273 (65.2%)	
Timing of radiation			<.001
Preoperative	12 (66.7%)	2 (0.7%)	
Postoperative/other	6 (33.3%)	271 (99.3%)	
Time period			.63
1987-1996	10 (25.6%)	123 (29.4%)	
1997-2006	29 (74.4%)	296 (70.6%)	

^aData are expressed as mean ± standard deviation.

Although the role of neoadjuvant therapy for operable pancreatic cancer remains unclear and is continuing to evolve, neoadjuvant therapy for resectable pancreatic cancer has been suggested as a means of addressing these shortcomings. The potential benefits of the neoadjuvant paradigm include the early treatment of micrometastatic disease, delivery of therapy to a well-vascularized primary tumor, and a significantly greater likelihood of completing a full course of therapy.^{2,12-15} Neoadjuvant therapy also serves as a means to identify patients unlikely to benefit from radical surgery. This may include the 13% to 20% of initially resectable patients who develop distant disease during neoadjuvant therapy, have poor functional reserve, and are therefore unable to tolerate the physiologic demands of treatment.^{2,14,15,21} The remaining subset of patients who are eligible for surgery can expect to undergo successful pancreatotomy with lower positive margin rates, decreased nodal positivity, and reduced local recurrence, and with improved overall survival compared with historical data.^{12,13,20}

Our study corroborates the results of the single-institution experiences by demonstrating that patients

**Figure 1.** Kaplan-Meier curves compare overall survival in patients according to timing of systemic therapy. MS indicates median survival.**Figure 2.** Kaplan-Meier curves compare overall survival in patients with extrapancreatic disease (ie, T3 or T4 disease) according to timing of systemic therapy. MS indicates median survival.

who undergo resection after neoadjuvant therapy have a lower rate of nodal positivity and significantly improved survival compared with those treated with surgery followed by adjuvant therapy. This is in contrast to the results from the meta-analysis by Gillen et al, who reported no difference in survival between neoadjuvant therapy and adjuvant therapy in patients with resectable disease.²³ However, our observed median survival of 34 months in this subset of patients is similar to previously published data.¹²⁻¹⁵ Given our results, the findings of multiple single-institution experiences,¹²⁻¹⁴ and the

Table 3. Multivariate Cox Regression Analysis for Overall Survival

Factors	HR (95% CI)	P
Timing of chemotherapy		.013
Adjuvant	1.00	
Neoadjuvant	0.57 (0.37-0.89)	
Lymph node status		.054
Negative	1.00	
Positive	1.25 (1.00-1.57)	
Extent of primary tumor		.032
Localized	1.00	
Extrapancreatic	1.34 (1.03-1.75)	
Radiation		.007
No	1.00	
Yes	0.73 (0.58-0.92)	

HR indicates hazard ratio; CI, confidence interval.

known shortcomings of the adjuvant approach, neoadjuvant therapy in potentially resectable patients is potentially a better approach than upfront surgery.

Although, it was not possible to determine which patients met the criteria for borderline resectability in our current study, 78% of our total population had extrapancreatic disease, with a greater proportion (86% vs 78%) noted in the neoadjuvant therapy group. Even in this subset of patients, who may have been more likely to have had borderline-resectable disease, there was again a clear advantage to the neoadjuvant approach, with the median survival of 31.1 months similar to the previously reported results of a large single-institution review of borderline-resectable patients.¹⁵

The results we have presented should be interpreted in light of several limitations. As with all retrospective studies, there is the risk of selection bias, and this may be particularly true in patients treated by a neoadjuvant approach. We have no data regarding the rates of resectability and dropout for all patients who were treated with or considered for the neoadjuvant therapy approach. This may increase the risk for selection and treatment biases, because our analysis only examined patients who were able to complete neoadjuvant therapy and who subsequently remained eligible for surgical resection. Although patients selected in this manner may have more favorable tumor biology, the primary objective of our study was to examine the timing of therapy in relation to curative-intent surgical resection. Additional drawbacks include specific limitations of the Cancer Surveillance Program database. Notably, the Cancer Surveillance Program does not have information regarding surgical margin status and

local failure rates. In addition, the database does not contain information regarding the specific type of chemotherapeutic agent used. Although we did attempt to control for changes in treatment over time, it does not appear that potential variations in treatment regimens over time impacted our results.

To conclude, we have demonstrated improved overall survival in a population of patients with pancreatic adenocarcinoma who underwent neoadjuvant therapy followed by resection, compared with a similar cohort who underwent resection first followed by adjuvant therapy. Indeed, our study demonstrated that only a small fraction of resected patients (<10%) were treated with the neoadjuvant paradigm. Large centers with multidisciplinary expertise have been more aggressive with neoadjuvant therapy for both localized and borderline resectable pancreatic cancer as part of ongoing clinical trials. In light of the morbidity of pancreatic resection and the generally poor oncologic results observed with a resection-first approach, neoadjuvant therapy should be considered a reasonable alternative to upfront surgery and warrants broader application.

CONFLICT OF INTEREST DISCLOSURES

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