Published in final edited form as:

J Clin Oncol. 2008 July 20; 26(21): 3503–3510. doi:10.1200/JCO.2007.15.8469.

Analysis of Fluorouracil-Based Adjuvant Chemotherapy and Radiation After Pancreaticoduodenectomy for Ductal Adenocarcinoma of the Pancreas: Results of a Large, Prospectively Collected Database at the Johns Hopkins Hospital

Joseph M. Herman, Michael J. Swartz, Charles C. Hsu, Jordan Winter, Timothy M. Pawlik, Elizabeth Sugar, Ray Robinson, Daniel A. Laheru, Elizabeth Jaffee, Ralph H. Hruban, Kurtis A. Campbell, Christopher L. Wolfgang, Fariba Asrari, Ross Donehower, Manuel Hidalgo, Luis A. Diaz Jr, Charles Yeo, John L. Cameron, Richard D. Schulick, and Ross Abrams
Departments of Radiation Oncology & Molecular Radiation Sciences, Surgery, Pathology, and Medical Oncology, the Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins Hospital; and the Departments of Epidemiology and Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD.

Abstract

Purpose—To examine the efficacy of adjuvant chemoradiotherapy after pancreaticoduodenectomy (PD) for pancreatic adenocarcinoma (PC) in patients undergoing resection at Johns Hopkins Hospital (JHH; Baltimore, MD).

Patients and Methods—Between August 30, 1993, and February 28, 2005, a total of 908 patients underwent PD for PC at JHH. A prospective database was reviewed to determine which patients received fluorouracil (FU) -based CRT. Excluded patients had metastatic disease, died 60 or fewer days after PD, received preoperative therapy, an experimental vaccine, adjuvant chemotherapy or radiation alone. The final cohort includes 616 patients.

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Corresponding author: Joseph M. Herman, MD, Department of Radiation Oncology & Molecular Radiation Sciences, 401 North Broadway, Suite 1440, Baltimore, MD 21231-2410; jherma15@jhmi.edu..

Presented at the 48th Annual Meeting of the American Society for Therapeutic Radiology and Oncology, November 5-9, 2006, Philadelphia, PA.

AUTHOR CONTRIBUTIONS

Conception and design: Joseph M. Herman, Michael J. Swartz, Charles C. Hsu, Jordan Winter, Timothy M. Pawlik, Elizabeth Sugar, Ray Robinson, Daniel A. Laheru, Elizabeth Jaffee, Luis A. Diaz Jr, Charles Yeo, John L. Cameron, Richard D. Schulick

Administrative support: Joseph M. Herman

Provision of study materials or patients: Jordan Winter, Elizabeth Jaffee, Ralph H. Hruban, Charles Yeo, John L. Cameron, Ross Abrams

Collection and assembly of data: Joseph M. Herman, Jordan Winter, Elizabeth Sugar, Ray Robinson

Data analysis and interpretation: Joseph M. Herman, Michael J. Swartz, Charles C. Hsu, Jordan Winter, Timothy M. Pawlik, Luis A. Diaz Jr, Richard D. Schulick

Manuscript writing: Joseph M. Herman, Michael J. Swartz, Charles C. Hsu, Timothy M. Pawlik, Elizabeth Sugar, Daniel A. Laheru, Elizabeth Jaffee, Ralph H. Hruban, Kurtis A. Campbell, Christopher L. Wolfgang, Fariba Asrari, Ross Donehower, Manuel Hidalgo, Luis A. Diaz Jr, Richard D. Schulick, Ross Abrams

Final approval of manuscript: Joseph M. Herman, Michael J. Swartz, Charles C. Hsu, Jordan Winter, Timothy M. Pawlik, Elizabeth Sugar, Ray Robinson, Daniel A. Laheru, Elizabeth Jaffee, Ralph H. Hruban, Kurtis A. Campbell, Christopher L. Wolfgang, Fariba Asrari, Ross Donehower, Manuel Hidalgo, Luis A. Diaz Jr, Charles Yeo, John L. Cameron, Richard D. Schulick, Ross Abrams

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

Results—The median follow-up was 17.8 months (interquartile range, 9.7 to 33.5 months). Overall median survival was 17.9 months (95% CI, 16.3 to 19.5 months). Groups were similar with respect to tumor size, nodal status, and margin status, but the CRT group was younger ($P < .001$), and less likely to present with a severe comorbid disease ($P = .001$). Patients with carcinomas larger than 3 cm ($P = .001$), grade 3 and 4 ($P < .001$), margin-positive resection ($P = .001$), and complications after surgery ($P = .017$) had poor long-term survival. Patients receiving CRT experienced an improved median (21.2 v 14.4 months; $P < .001$), 2-year (43.9% v 31.9%), and 5-year (20.1% v 15.4%) survival compared with no CRT. After controlling for high-risk features, CRT was still associated with improved survival (relative risk = 0.74; 95% CI, 0.62 to 0.89).

Conclusion—These data suggest that adjuvant concurrent FU-based CRT significantly improves survival after PD for PC when compared with patients not receiving CRT. These data support the use of combined adjuvant CRT for PC.

INTRODUCTION

The majority of patients diagnosed with pancreatic adenocarcinoma (PC) present at an advanced stage that precludes cure. In patients with localized disease, surgical resection is the only potentially curative therapy.¹ Both local and systemic recurrences are common after a pancreaticoduodenectomy (PD) or total pancreatectomy.² This pattern of failure suggests that both systemic and local adjuvant therapy may have a positive impact on survival. In an attempt to improve outcomes, the efficacy of adjuvant chemoradiotherapy (CRT) and chemotherapy has been evaluated in several trials.

A landmark randomized trial conducted under the auspices of the GI Tumor Study Group (GITSG) demonstrated improved overall survival (OS) with the use of adjuvant CRT after definitive surgery.^{3,4} These findings were supported by a trial from Johns Hopkins Hospital (JHH; Baltimore, MD) that evaluated adjuvant CRT ($n = 99$) versus surgical resection alone ($n = 53$).⁵ Patients receiving postoperative CRT had an improvement in median survival (20 v 14 months) and 2-year survival (40% v 31%) when compared with observation ($P = .003$). In contrast, trials in Europe have not confirmed a statistically significant survival benefit with CRT,⁶ and in fact, some European studies suggest a detrimental effect on survival with CRT compared with chemotherapy or surgery alone.^{7,8} The inconsistencies of these trials complicate decision making about which patients should receive adjuvant CRT or chemotherapy alone.⁹

Studies demonstrating a benefit in CRT have been criticized because of small sample sizes and patient-selection bias.^{10,11} To address these limitations, we performed a retrospective analysis of a large prospectively collected cohort of patients ($N = 616$) undergoing resection of proximal PC at JHH. The purpose of this study is to evaluate whether adjuvant fluorouracil (FU) -based CRT improves survival compared with surgery alone in this large cohort.

PATIENTS AND METHODS

Between August 30, 1993, and February 28, 2005, data were prospectively collected on all patients undergoing elective PD or total pancreatectomy at JHH. Distal pancreatectomy alone and other periampullary tumors were excluded. All pathology specimens were reviewed by a single pathologist (R.H.H.) to ensure consistent interpretation of ductal adenocarcinoma histology, tumor margin, and nodal status.¹²

Patients underwent a pylorus preserving, classic, or total PD. The standard surgical approaches at JHH are as follows: A pylorus-preserving PD included resection of the head

and uncinate process of the pancreas, distal bile duct, all but the most proximal duodenum, and gall bladder when present. A classic PD also included the antrum of the stomach. A total PD included the entire pancreas with the spleen. Lymph nodes were considered positive if any lymph node in the resection specimen contained metastatic carcinoma, whether it was involved by direct extension or was contiguous with the primary tumor. Resection margins were considered positive if the carcinoma was close (within 1 mm) or present at the final pancreatic neck, uncinate process, bile duct, or duodenal or retroperitoneal soft tissue margin. Perineural and perivascular invasion were not recorded routinely until early 2004, and therefore were not included in the final analysis.

Johns Hopkins University institutional review board permission was granted before chart review. A total of 908 patients underwent surgical resection for ductal adenocarcinoma at JHH during the period of the study. Patients were excluded if they were found to have T4 or M1 disease at the time of surgery (n=16) or death occurred 60 or fewer days after PD (n = 43). Patients were excluded if they received preoperative therapy (n= 19), if metastatic disease was identified before the initiation of CRT (n = 17), if it was unknown whether they received CRT (n = 44), or if they received adjuvant chemotherapy alone or radiation alone (n = 73). Sixty-seven patients were excluded because they received non-FU-based therapy or an experimental vaccine. The final study cohort includes 616 patients. Among them, 345 (56%) received no adjuvant CRT, 134 (21.8%) received FU-based CRT at JHH, and 137 (22.2%) received FU-based CRT at another facility. Patient follow-up information was obtained from hard-copy and electronic hospital charts. Survival was determined and cross checked by review of clinical follow-up information, cancer center abstracting services, and the Social Security Death Index.

Preoperative information was collected prospectively. Severe comorbid conditions included coronary artery disease, chronic obstructive pulmonary disease, and cerebrovascular accidents. Patients were identified with diabetes mellitus (DM) if they were diagnosed before surgical resection. Data describing postoperative complications were collected and described elsewhere.⁵ Intraoperative estimated blood loss during surgery and length of hospital stay were evaluated.

Postoperatively, most patients were seen by a medical and radiation oncologist and offered JHH standard therapy, which consisted of continuous infusion FU with radiation therapy followed by maintenance FU for an additional 2 to 6 months. Patients with a satisfactory recovery from PD were encouraged to accept either standard or protocol therapy. Patients treated elsewhere were given the same recommendations before discharge as those patients treated at JHH. These recommendations were often communicated to outside physicians in a dictated consultation. Patients who elected to receive no therapy did so after being informed fully about the potential risks and benefits of such therapy.

For those patients treated at JHH, the clinical treatment volume was defined as follows: the hepatojejunostomy, pancreaticojejunostomy, and the proximal celiac and superior mesenteric arteries. These structures, plus the retroperitoneal lymph nodes, were expanded by 1.5 cm for the final planning treatment volume. The median daily fraction size and total dose was 1.8 Gy and 50 Gy, respectively. The majority (79%) of patients treated at JHH received a continuous course of radiation therapy without a planned break. The details of therapy could not be fully assessed for patients treated elsewhere.

Statistical Analysis

Statistical analyses were performed using STATA software, version 9 (StataCorp, College Station, TX). Summary statistics for continuous and dichotomous variables are provided. Tests of differences were performed using *t* tests and χ^2 tests. For characteristics with

individuals missing data, χ^2 tests were performed including only those with known status, as indicated. The primary outcome variable was OS, defined as the time from surgical resection for PC to death. Individuals were censored at March 29, 2007. Survival curves were estimated using Kaplan-Meier techniques.¹³ Comparisons of OS between groups were made using the log-rank test. Median OS (in months) with 95% CIs was estimated within each risk group and by adjuvant treatment. The proportion of individuals surviving up to 2 and 5 years was calculated using life tables, with comparison by adjuvant treatment performed using the log-rank test with survival time censored at 2 and 5 years, respectively.

We used proportional hazards models to examine the association of adjuvant treatment and other patient characteristics with mortality.¹⁴ Univariate analyses were used to examine individual risk factors and associations with mortality (N = 616). To examine the independent association of adjuvant therapy and OS after surgical resection, multivariate analyses were performed adjusting for confounders. Multivariate models did not include individuals missing information on comorbid conditions or surgical complications (n = 21). Univariate models were comparable when including (N = 616) and excluding (n = 595) those missing data on comorbid disease or surgical complications. Multivariate modeling was used to explore the interactions between adjuvant CRT and individual variables.

RESULTS

The median follow-up for the entire cohort was 17.8 months (interquartile range [IQR], 9.7 to 33.5 months). Overall median survival was 17.9 months (95% CI, 16.3 to 19.5 months). The median age at the time of surgery was 68 years (range, 34 to 92 years). Sixty-one percent of patients were at least 65 years of age, 52% were male, and the majority (90%) of patients were white. Severe comorbid disease, history of DM, and weight loss at presentation were reported in 22%, 25%, and 52% of patients, respectively.

The majority (93.7%) of patients underwent PD and the remainder (6.3%) underwent a total pancreatectomy. Intraoperative blood loss less than 700 mL occurred in 59.0% of patients. Complications after surgery were experienced by 36% of patients. Tumor size was more than 3 cm in 38% of patients. Positive margins were identified in 44.6% of the tumor specimens, while 80.2% had involved lymph nodes. Because the American Joint Committee on Cancer (AJCC) staging manual was updated in 2002, staging was inconsistent through the period of study and therefore was not evaluated. Because patient characteristics and survival did not differ significantly for those who received adjuvant CRT at JHH (n = 137; median OS, 21.0 months) and at other institutions after resection at JHH (n = 134; median OS, 21.2 months), these groups were combined for further analyses (n = 271).

A comparison of the demographics of patients treated with surgery and adjuvant CRT or surgery alone is presented in Table 1. Two hundred seventy-one patients (44%) received adjuvant CRT, whereas 345 (56%) did not receive CRT after surgery. The median age of those who received adjuvant CRT was 64.0 years (range, 34 to 84 years; IQR, 57 to 72 years) versus 70.0 years (range, 34 to 92 years; IQR, 63 to 77 years) for the observation group ($P < .001$). Surgery-alone patients were more likely to have a severe comorbid disease (26% v 15%; $P = .001$) than patients treated with adjuvant CRT. Higher rates of postoperative complications were seen in the observation group (39% v 31%; $P = .052$). Patients receiving adjuvant CRT were more likely to have positive margins after resection (48% v 42%) but this was not statistically significant ($P = .141$). The median tumor size, percentage node positive, lymph node ratio more than 50%, intraoperative blood loss of at least 700 mL, and length of stay (median, 9 days), were similar in both groups.

The influence of patient- and treatment-specific factors on survival are presented in Table 2. Age, sex, race, surgery type, intraoperative blood loss, and length of stay did not significantly affect the median, 2-year, and 5-year survival of patients in our analysis. However, having a severe comorbid disease ($P = .018$), DM ($P < .001$), and complications after surgery ($P = .017$) were negatively associated with OS. Also, patients with tumors larger than 3 cm ($P = .001$), histologic grade more than 2 ($P < .001$), and margin-positive resection ($P = .001$) experienced a significantly shorter survival. Positive nodes were also associated with a worse survival (relative risk = 1.22), although it was not statistically significant ($P = .075$).

As demonstrated in Figure 1, patients who received adjuvant CRT had an improved median, 2-year, and 5-year survival compared with surgery alone (21.2 v 14.4 months; 43.9% v 31.9%, and 20.1% v 15.4%, respectively, for adjuvant CRT v no CRT; $P < .001$). Table 3 displays the median and 5-year survival for patients receiving adjuvant CRT versus no CRT by risk categories. Compared with surgery alone, adjuvant CRT resulted in improved survival among all high-risk subgroups, including those at least 65 years of age (median OS, 21.0 v 14.6 months) or those with severe comorbidities (median OS, 19.5 v 11.5 months).

To adjust for competing risk factors, we performed a multivariate analysis to assess whether adjuvant CRT would remain a predictor of OS (Table 4). After adjusting for age, sex, race, surgery type, tumor size, grade, margin and node status, comorbid disease, diabetes, and surgical complications, adjuvant CRT still demonstrated a significant protective effect (relative risk = 0.74; $P < .001$). We examined the effect of adjuvant CRT on survival, stratified by margin status (Table 4). Adjuvant CRT improved survival among both margin-negative ($P = .014$) and margin-positive ($P = .001$) patients (Fig 2). Among margin-negative patients, adjuvant CRT had a significantly protective effect on univariate ($P = .014$; $n = 341$) and multivariate analyses ($P = .035$; $n = 329$). Adjuvant CRT had a similar effect among margin-positive patients (univariate $P = .001$; $n = 275$; multivariate $P = .002$; $n = 266$).

Although the study was not designed to detect interactions between therapy type and risk factors, exploratory analyses were performed. Appendix Figure A1 (online only) shows the OS for the patients in the CRT and no CRT cohorts stratified by nodal status. Node-positive patients who received adjuvant CRT show a benefit over the no-CRT group. The node-negative patients do not show the same benefit. However, the interaction between nodal status and treatment is not significant. There was no significant interaction between tumor margin status, tumor diameter, or tumor grade and treatment. There were significant interactions between adjuvant CRT and the risk factors sex ($P = .020$), diabetes ($P = .035$), and surgical complications ($P = .015$), each interaction term individually examined in a multivariate model adjusting for confounders. In each subset, there was still a survival benefit seen with adjuvant therapy (surgical complications displayed in Appendix Figure A2, online only).

DISCUSSION

This analysis of a prospectively collected database of patients treated with contemporary FU-based CRT versus no CRT supports the following two conclusions: First, the administration of CRT after surgical resection of PC results in a statistically significant improvement in the median, 2-year, and 5-year OS when compared with no CRT. Second, this survival benefit is present regardless of high-risk tumor characteristics and after controlling for age, comorbidities, and surgical complications.

The appropriate choice of adjuvant therapy for patients with resectable PC is controversial. In the United States, the standard recommendation has been to offer CRT based on the

findings of the GITSG study, which has been criticized for slow accrual, small sample size, and outdated split-course radiation therapy. Nevertheless, it remained the primary trial supporting adjuvant CRT for many years.³ In 1997, Yeo et al⁵ published a prospective single-institution series of 99 patients treated with split-course CRT. The findings confirmed the GITSG results, thus further supporting the use of adjuvant CRT.

The European Organisation for Research and Treatment of Cancer published a phase III randomized trial comparing observation with postoperative CRT.⁶ Compared with those under observation (n = 54), patients receiving adjuvant CRT (n = 60) had a borderline significant improvement in median survival (17.1 v 12.6 months). Patients in the adjuvant-CRT arm did not receive maintenance chemotherapy, a major change from the GITSG trial. Subsequently, two European Study Group for Pancreatic Cancer studies reported a reduction in OS with the use of adjuvant CRT using the GITSG split-course regimen. Although these trials have been criticized for poor quality assurance and selection bias, they clearly questioned the safety and efficacy of combined chemoradiotherapy.^{7,8}

Improved radiation techniques allows for multiple beams of radiation to be delivered to the tumor bed and adjacent lymph nodes while sparing normal adjacent structures.¹⁵ These improvements allow for uninterrupted delivery of CRT, thus eliminating the need for a planned treatment break. Small, single-institution studies have suggested that modern CRT can be delivered safely and result in favorable outcomes.^{10,11,16} Here, we report one of the largest (N = 616) prospectively collected single-institution series in an era when most patients were treated with continuous FU-based CRT.

Although not randomized, this study demonstrates a clear benefit in the median, 2-year, and 5-year survival for patients treated with adjuvant CRT compared with surgical resection alone. This is consistent with previous US trials and questions the assertion that CRT results in decreased survival compared with surgery alone. The median and 5-year survival (21 months and 20%, respectively) for adjuvant CRT in the current study is similar to that reported in the GITSG study (20 months), despite the fact that a higher proportion of patients in the current cohort had positive margins (45% v 0%) and node-positive disease (80% v 30%). The median and 5-year survival reported here also compare favorably with other published studies (Appendix Table A1, online only).

Our results are supported by the Radiation Therapy Oncology Group 97-04 trial.¹⁷ All patients were treated with continuous infusion-FU and conformal RT. In a preplanned analysis of patients with tumors of the head of the pancreas (n = 380), the median survival was 18.8 months if gemcitabine was administered before and after FU-based CRT. This was significantly superior to the median survival seen in the CRT arm without gemcitabine: 16.7 months ($P = .047$; hazard ratio = 0.79; 95% CI, 0.63 to 0.99). This study demonstrates that modern CRT appears efficacious, and survival can be improved by adding gemcitabine to CRT.

Recently, a phase III randomized trial (N = 368) compared adjuvant gemcitabine (6 months) with observation (Charité Onkologie [CONKO]-001).¹⁸ This study demonstrates that adjuvant gemcitabine alone is efficacious in patients with resected pancreatic cancer. In the CONKO study, 70% of patients had node-positive disease and 19% margin-positive resections. The median survival in our study (21.2 months) is similar to that in the CONKO trial (22.1 months), despite having a greater proportion of patients with node-positive (82%) and margin-positive (48%) resections. The CONKO and the Radiation Therapy Oncology Group 97-04 studies demonstrate improved survival with the addition of gemcitabine. Integration of gemcitabine during modern continuous-course radiation in the adjuvant setting may result in further improvements in survival.

In our analysis, patients with node- or margin-positive disease clearly benefited from adjuvant CRT. Patients with large (> 3 cm) and high-grade (3-4) tumors also had improved survival with the addition of adjuvant CRT. Examining adjuvant CRT in a nonrandomized setting is somewhat controversial because the argument can be made that patients who receive adjuvant CRT are inherently “healthier” and have risk factor profiles that lend themselves to better survival. Therefore, interactions between adjuvant CRT and individual variables were examined using a multivariate model. In each stratum, those patients who did not receive adjuvant CRT had a worse median OS.

There are several limitations of the current study. First, this is a retrospective study of CRT treatment, even though all patients were identified from a prospectively collected database of patients undergoing definitive surgical resection at a single institution. As with most retrospective studies, some patients were lost to follow-up. However, every effort was made to identify those patients who died by reviewing the electronic medical record, the cancer registry, or the Social Security Death Index. Patients who received no adjuvant therapy were older and more likely to have medical comorbidities. This could suggest potential selection bias. However, after controlling for these and other potential confounding variables in multivariate analyses, adjuvant CRT still had a protective effect compared with observation alone.

In summary, we believe that this study strongly supports the continued use of adjuvant FU-based CRT in patients with resected PC. The benefit is consistent across all high-risk groups. This study does not address the controversy as to whether adjuvant CRT is superior to chemotherapy alone. It does, however, call into question the results of the European Study Group for Pancreatic Cancer trial that suggest that adjuvant FU-based CRT may be inferior to surgery alone. Furthermore, the patient survival rates reported here compare favorably with survival data from other adjuvant trials (Appendix Table A1), despite having a large proportion of patients with known adverse prognostic features.

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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Fig 1.
Overall survival after surgical resection for pancreatic adenocarcinoma, by treatment group.

Fig 2.
Overall survival by adjuvant chemoradiotherapy therapy, stratified by tumor margin status.

Table 1

Baseline Characteristics Between Treatment Groups

Characteristic	Observation Only (n = 345)		Adjuvant Chemoradiation Therapy (n = 271)		P
	No.	%	No.	%	
Demographics					
Age at surgery, years					< .001
Mean	68.6		63.9		
Standard deviation	10.9		10.2		
Median	70.0		64.0		
Range	34-92		34-84		
Male sex	171	49.6	147	54.2	.249
Race					
White	314	91.0	242	89.3	.699
Black	22	6.4	19	7.0	
Other	9	2.6	10	3.7	
Comorbid disease and presenting symptoms					
Severe comorbid disease (COPD or CVA/CAD)					
No	247	71.6	221	81.6	.001*
Yes	89	25.8	40	14.8	
Unknown	9	2.6	10	3.7	
Diabetes					
No	243	70.4	205	75.7	.081*
Yes	93	27.0	56	2.7	
Unknown	9	2.6	10	3.7	
Hypertension					
No	180	52.2	160	59.0	.058*
Yes	156	45.2	101	37.3	
Unknown	9	2.6	10	3.7	
Weight loss at presentation					
No	152	44.1	126	46.5	.818*

Characteristic	Observation Only (n = 345)		Adjuvant Chemoradiation Therapy (n = 271)		P
	No.	%	No.	%	
Yes	168	48.7	134	49.5	
Unknown	25	7.3	11	4.0	
Treatment					.683
Surgery type					
Classic PD	98	28.4	70	25.8	
PP PD	224	64.9	185	68.3	
Classic/PP total pancreatectomy	23	6.7	16	5.9	
Surgical complication					.052*
No	208	60.3	182	67.2	
Yes	134	38.8	84	31.0	
Unknown	3	0.9	5	1.9	
Tumor characteristics					.372
Tumor diameter, cm					
Mean	3.2		3.1		
Standard deviation	1.5		1.3		
Median	3.0		3.0		
Range	0.1-14.0		0.5-8.5		
Node status					.341
Negative	73	21.2	49	18.1	
Positive	272	78.8	222	81.9	
Histologic grading					.099
1	8	2.3	12	4.4	
2	177	51.3	154	56.8	
3	158	45.8	105	38.8	
4	2	0.6	0	.0	
Margin					.141
Negative	200	58.0	141	52.0	
Positive	145	42.0	130	48.0	

Abbreviations: COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; CAD, coronary artery disease; PD, pancreaticoduodenectomy; PP, pylorus-preserving.
* χ^2 compares only nonmissing values.

Table 2

Associations of Overall Survival with Patient Tumor and Treatment Characteristics

Characteristic	No.	%	Survival (%)			Survival (months)			Univariate Analysis		
			2 Year	5 Year		Median	95% CI		RR	95% CI	P
Age ≥ 65 years											
No	241	39.1	38.2	21.7		18.8	15.6 to 21.2		1.00		
Yes	375	60.9	36.5	14.7		17.4	15.6 to 19.5		1.19	1.00 to 1.43	.054
Sex											
Female	298	48.4	35.9	15.2		16.8	14.1 to 19.4		1.00		
Male	318	51.6	38.4	19.5		18.5	16.8 to 20.7		0.87	0.73 to 1.04	.119
Race											
White	556	90.3	36.9	17.1		17.5	16.0 to 19.2		1.00		
Black/other	60	9.7	40.0	20.5		20.6	14.3 to 25.9		0.87	0.64 to 1.18	.374
Severe comorbid disease											
No	468	78.4	39.3	18.2		18.6	16.3 to 20.5		1.00		
Yes	129	21.6	28.7*	13.7*		16.8*	12.0 to 18.4		1.29	1.04 to 1.59	.018
Diabetes											
No	448	75.0	40.4	19.8		18.3	16.8 to 20.3		1.00		
Yes	149	25.0	26.9†	9.4‡		15.0‡	12.9 to 19.4		1.42	1.17 to 1.74	<.001
Weight loss at presentation											
No	278	47.9	37.1	18.3		17.6	15.4 to 20.0		1.00		
Yes	302	52.1	36.1	16.5		17.7	15.6 to 19.8		1.07	0.89 to 1.28	.464
Adjuvant treatment											
Observation	345	56.0	31.9	15.4		14.4	12.2 to 16.9		1.00		
Adjuvant CRT	271	44.0	43.9‡	20.1‡		21.2‡	18.9 to 24.3		0.72	0.60 to 0.86	<.001
Surgery type											
Pancreaticoduodenectomy	577	93.7	37.8	17.7		18.3	16.8 to 19.9		1.00		
Total pancreatectomy	39	6.3	28.2	14.1		12.1	9.8 to 15.3		1.36	0.96 to 1.94	.088
Complications											
No	390	64.1	39.2	19.0		18.4	16.8 to 20.6		1.00		
Yes	218	35.9	32.6*			16.0*	12.9 to 18.8		1.25	1.04 to 1.49	.017

Characteristic	No.	%	Survival (%)		Survival (months)		Univariate Analysis		P
			2 Year	5 Year	Median	95% CI	RR	95% CI	
Tumor diameter > 3 cm									
No	380	61.7	41.8	20.1	19.8	17.9 to 22.4	1.00		
Yes	236	38.3	29.7 [‡]	13.1 [‡]	14.6 [‡]	12.9 to 16.8	1.34	1.12 to 1.60	.001
Node status									
Negative	122	19.8	45.1	21.4	20.7	15.9 to 27.0	1.00		
Positive	494	80.2	35.2	16.5	17.3	15.6 to 18.9	1.22	0.98 to 1.53	.075
Histologic grade									
1 to 2	351	57.0	45.3	21.6	21.0	19.3 to 24.6	1.00		
3 to 4	265	43.0	26.4 [‡]	12.0 [‡]	13.3 [‡]	12.3 to 15.8	1.59	1.34 to 1.90	< .001
Margin									
Negative	341	55.4	42.8	20.3	20.0	18.2 to 22.8	1.00		
Positive	275	44.6	30.2 [‡]	13.9 [‡]	15.4 [‡]	13.9 to 17.5	1.34	1.12 to 1.59	.001

Abbreviations: RR, relative risk; CRT, chemoradiotherapy.

^{*} $P < .05$.

[‡] $P < .01$.

[‡] $P < .001$.

Table 3

Survival Between Treatment Groups by Patient, Tumor, and Treatment Characteristics

Characteristic	Patients				Overall Survival			
	Observation		Adjuvant CRT		Observation		Adjuvant CRT	
	No.	%	No.	%	Median (months)	95% CI	Median (months)	95% CI
All patients	345	56.0	271	44.0	14.4	12.2 to 16.9	21.2	18.9 to 24.3
Age, years								
< 65	104	43.2	137	56.9	12.2	11.1 to 19.4	21.2	18.1 to 25.2
65	241	64.3	134	35.7	14.6	12.5 to 17.5	21.0	18.3 to 24.9
Sex								
Female	174	58.4	124	41.6	12.1	10.1 to 15.5	22.7	18.8 to 25.9
Male	171	53.8	147	46.2	16.9	14.3 to 19.9	19.9	17.7 to 22.8
Margin								
Negative	200	58.7	141	41.4	17.0	13.2 to 20.6	24.3	19.9 to 30.4
Positive	145	52.7	130	47.3	11.4	9.6 to 14.4	18.3	16.0 to 22.2
Node								
Negative	73	59.8	49	40.2	15.9	12.0 to 28.3	23.2	18.4 to 31.1
Positive	272	55.1	222	44.9	14.3	11.5 to 16.9	20.6	18.1 to 24.0
Primary tumor								
Tumor 3 cm	211	55.5	169	44.5	17.0	13.2 to 20.0	23.7	19.6 to 27.0
Tumor > 3 cm	134	56.8	102	43.2	11.7	10.1 to 14.6	18.5	15.3 to 22.7
Histology, grade								
1 to 2	185	52.7	166	47.3	18.2	14.6 to 20.7	25.0	21.9 to 32.0
3 to 4	160	60.4	105	39.6	11.4	9.4 to 13.0	16.1	13.9 to 19.6
Severe comorbid disease								
No	247	52.8	221	47.2	14.6	12.2 to 18.1	21.9	19.2 to 24.8
Yes	89	69.0	40	31.0	11.5	8.7 to 17.3	19.5	16.0 to 27.0
Diabetes								
No	243	54.2	205	445.8	16.8	13.0 to 18.6	20.5	18.3 to 24.9
Yes	93	62.4	56	37.6	10.4	9.1 to 14.6	22.4	18.4 to 25.4
Complications								

Characteristic	Patients				Overall Survival				5-Year Survival (%)	
	Observation		Adjuvant CRT		Observation		Adjuvant CRT		Observation	Adjuvant CRT
	No.	%	No.	%	Median (months)	95% CI	Median (months)	95% CI		
No	208	53.3	182	46.7	16.8	13.2 to 19.9	20.3	18.0 to 24.3	19.0	19.1
Yes	134	61.5	84	38.5	11.5	9.3 to 14.9	22.4	18.8 to 29.8	10.2	20.0

Abbreviation: CRT, chemoradiotherapy.

Multivariate Cox Proportional Hazards Survival Analysis of Adjuvant CRT and Overall Survival in All Patients and Stratified By Margin Status

Table 4

Variable	All (n = 595)			Margin Negative (n = 329)			Margin Positive (n = 266)		
	Multivariate Model			Multivariate Model			Multivariate Model		
	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
Adjuvant treatment									
Observation	1.00			1.00			1.00		
Adjuvant CRT	0.74	0.62 to 0.89	<.001	0.76	0.59 to 0.98	.035	0.64	0.48 to 0.84	.002
Age, years									
< 65	1.00			1.00			1.00		
65	1.10	0.90 to 1.33	.357	1.02	0.79 to 1.34	.860	1.22	0.91 to 1.64	.191
Sex									
Female	1.00			1.00			1.00		
Male	0.78	0.65 to 0.94	.010	0.84	0.66 to 1.09	.186	0.72	0.54 to 0.94	.018
Race									
White	1.00			1.00			1.00		
Nonwhite	0.85	0.62 to 1.17	.322	0.71	0.46 to 1.10	.128	1.04	0.63 to 1.73	.867
Margin									
Negative	1.00								
Positive	1.34	1.11 to 1.62	.002						
Node									
Negative	1.00			1.00			1.00		
Positive	1.13	0.89 to 1.42	.321	1.34	1.00 to 1.80	.054	0.89	0.61 to 1.30	.549
Tumor size, cm									
< 3	1.00			1.00			1.00		
3	1.28	1.06 to 1.55	.011	1.40	1.08 to 1.83	.012	1.18	0.89 to 1.55	.245
Histology, grade									
1 to 2	1.00			1.00			1.00		
3 to 4	1.55	1.29 to 1.86	<.001	1.23	0.95 to 1.59	.124	2.21	1.68 to 2.92	<.001
Surgery type									
Classic Whipple	1.00			1.00			1.00		

Variable	All (n = 595)			Margin Negative (n = 329)			Margin Positive (n = 266)		
	Multivariate Model			Multivariate Model			Multivariate Model		
	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
Pylorus-preserving Whipple	1.22	0.99 to 1.51	.058	1.21	0.91 to 1.60	.197	1.20	0.87 to 1.66	.263
Total pancreatectomy	1.41	0.95 to 2.09	.089	2.07	1.22 to 3.48	.007	0.94	0.50 to 1.75	.835
Severe comorbid disease									
No	1.00			1.00			1.00		
Yes	1.17	0.94 to 1.46	.161	1.24	0.92 to 1.68	.161	0.97	0.69 to 1.37	.867
Diabetes									
No	1.00			1.00			1.00		
Yes	1.28	1.04 to 1.58	.020	1.31	0.97 to 1.77	.078	1.36	1.00 to 1.85	.049
Surgical complications									
No	1.00			1.00			1.00		
Yes	1.16	0.97 to 1.40	.111	1.29	1.00 to 1.68	.054	1.17	0.89 to 1.55	.250

Abbreviations: CRT, chemoradiotherapy; RR, relative risk.