

## Preoperative Gemcitabine-Based Chemoradiation for Patients With Resectable Adenocarcinoma of the Pancreatic Head

Douglas B. Evans, Gauri R. Varadhachary, Christopher H. Crane, Charlotte C. Sun, Jeffrey E. Lee, Peter W.T. Pisters, Jean-Nicolas Vauthey, Huamin Wang, Karen R. Cleary, Gregg A. Staerke, Chusilp Charnsangavej, Elizabeth A. Lano, Linus Ho, Renato Lenzi, James L. Abbruzzese, and Robert A. Wolff

### ABSTRACT

#### Purpose

We conducted a phase II trial to assess the outcomes of patients who received preoperative gemcitabine-based chemoradiation and pancreaticoduodenectomy (PD) for stage I/II pancreatic adenocarcinoma.

#### Patients and Methods

Eligible patients with pancreatic head/uncinate process adenocarcinoma and radiographically defined potentially resectable disease received chemoradiation with 7 weekly intravenous (IV) infusions of gemcitabine (400 mg/m<sup>2</sup> IV over 30 minutes) plus radiation therapy (30 Gy in 10 fractions over 2 weeks). Patients underwent restaging 4 to 6 weeks after completion of chemoradiation and, in the absence of disease progression, were taken to surgery.

#### Results

The study enrolled 86 patients. At the time of restaging, disease progression or a decline in performance status precluded 13 patients from surgery. Seventy-three (85%) of 86 patients were taken to surgery, extrapancreatic disease was found in nine, and 64 (74%) of 86 underwent a successful PD. Median overall survival (86 patients) was 22.7 months with a 27% 5-year survival. Median survival was 34 months for the 64 patients who underwent PD and 7 months for the 22 unresected patients ( $P < .001$ ). The 5-year survival for those who did and did not undergo PD was 36% and 0%, respectively.

#### Conclusion

Preoperative gemcitabine-based chemoradiation followed by restaging and evaluation for surgery separated the study population into two different subsets: patients likely to benefit from PD ( $n = 64$ ) and those in whom surgery would be unlikely to provide clinical benefit ( $n = 22$ ). Furthermore, the encouraging overall survival observed in this large trial supports the continued investigation of gemcitabine-based preoperative therapy in resectable pancreatic cancer.

*J Clin Oncol* 26:3496-3502. © 2008 by American Society of Clinical Oncology

### INTRODUCTION

The multimodality treatment of localized pancreatic cancer is an area of active investigation because of the minimal survival benefit afforded by surgery alone. Moreover, in the last 2 decades, no significant improvements in patient survival have been observed in large trials of adjuvant therapy, which rely on a surgery-first approach to resectable disease.<sup>1-3</sup> In contrast, the delivery of chemotherapy and radiation before surgery provides for early treatment of micrometastatic disease, which is present in the majority of patients, allows for the identification of those patients with rapidly progressive metastatic disease at the time of post-treatment/preoperative

restaging (surgery is thereby avoided in these patients), and may increase the R0 resection rate and reduce the risk of local tumor recurrence.<sup>4-5</sup>

Sequential preoperative chemoradiation trials have been performed at our institution using infusional fluorouracil (FU) in combination with standard-fractionation external-beam radiation therapy (EBRT; 50.4 Gy),<sup>6</sup> rapid-fractionation EBRT (30 Gy),<sup>7</sup> and paclitaxel-based chemoradiation.<sup>8</sup> Paclitaxel did not provide an advantage over FU-based chemoradiation programs in terms of resection rate, treatment effect as assessed in the resected specimen, or overall survival.<sup>8</sup> Because gemcitabine is superior to bolus FU for the treatment of advanced pancreatic cancer, its integration

From the Departments of Surgical Oncology, Gastrointestinal Medical Oncology, Radiation Oncology, Gynecologic Oncology, Pathology, and Diagnostic Imaging, The University of Texas M.D. Anderson Cancer Center, Houston, TX.

Submitted December 21, 2007; accepted March 6, 2008.

Supported by the Various Donor Fund, the Lockton Fund for Pancreatic Cancer Research at The University of Texas M.D. Anderson Cancer Center, and Eli Lilly & Co.

Presented in part at the 38th Annual Meeting of the American Society of Clinical Oncology, May 18-21, 2002, Orlando, FL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Douglas B. Evans, MD, Department of Surgical Oncology, Unit 444, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030; e-mail: devans@mdanderson.org.

© 2008 by American Society of Clinical Oncology

0732-183X/08/2621-3496/\$20.00

DOI: 10.1200/JCO.2007.15.8634

into neoadjuvant and adjuvant trials for resected disease was a logical next step.<sup>9</sup> We performed a phase I study of gemcitabine in combination with EBRT in patients with locally advanced disease.<sup>10</sup> The results of this phase I study were sufficiently encouraging to proceed with the trial reported herein.

## PATIENTS AND METHODS

### Patients

The University of Texas M.D. Anderson Cancer Center (MDACC) Institutional Review Board (Houston, TX) approved the study protocol, and all patients gave written informed consent. All patients underwent pretreatment multidetector contrast-enhanced computed tomography (CT) of the abdomen. The protocol required that a mass be visible in the pancreatic head on CT or endoscopic ultrasound (EUS), and pathologic confirmation of adenocarcinoma.<sup>11</sup> All eligible patients were required to have potentially resectable disease on the basis of physical examination and the following objective CT criteria: (1) no evidence of extrapancreatic disease; (2) no evidence of tumor extension to the superior mesenteric artery (SMA) or celiac axis; and (3) no evidence of occlusion of the superior mesenteric vein (SMV) or SMV–portal vein (PV) confluence.<sup>12</sup> Tumor abutment and encasement of the SMV, in the absence of vessel occlusion or extension to the SMA was considered resectable.

Patients were also required to have a Karnofsky performance status of at least 70, an absolute neutrophil count (ANC) more than 1,500 cells/mm<sup>3</sup>, a platelet count of at least 100,000 cells/mm<sup>3</sup>, a serum creatinine level less than 1.6 mg/dL, and a serum bilirubin level less than 5 mg/dL. When necessary, biliary decompression was accomplished endoscopically by placement of a biliary stent. Patients were excluded if they had evidence of fever, active infection, hepatic transaminases (ALT and AST) greater than 5× the upper limits of normal or significant medical comorbidity precluding consideration of major pancreatic surgery.

Patients underwent restaging evaluation 4 to 6 weeks after the completion of chemoradiation (including CT). Surgery was considered delayed if it was performed 8 or more weeks after the completion of chemoradiation.

### Chemoradiation

The chemoradiation schema is shown in Figure 1. Intravenous (IV) gemcitabine (400 mg/m<sup>2</sup>) was administered over 30 minutes once a week for a total of 7 doses. EBRT was delivered 5 days per week (Monday–Friday, beginning 48–72 hours after the first dose of gemcitabine) to a total dose of 30 Gy in

10 fractions over 2 weeks (3 Gy/d). Radiation volumes were based on three-dimensional conformal CT and included the primary tumor. Pancreaticoduodenal, portahepatic, superior mesenteric, and celiac axis lymph nodes were included in the treatment field with a 2-cm block margin. Weekly evaluations during chemoradiation included assessment of toxicities. Chemotherapy was reduced by 25% if the patient's ANC was less than 1,000 cells/mm<sup>3</sup> or if the platelets were less than 100,000 cells/mm<sup>3</sup>. Chemotherapy was reduced by 50% for any grade 3 nonhematologic toxicities, except for nausea and/or vomiting. Chemotherapy was held if the patient's ANC was less than 500 cells/mm<sup>3</sup> or if the platelets were less than 50,000 cells/mm<sup>3</sup>. Doses that were missed or held because of toxicity were not administered at a later time.

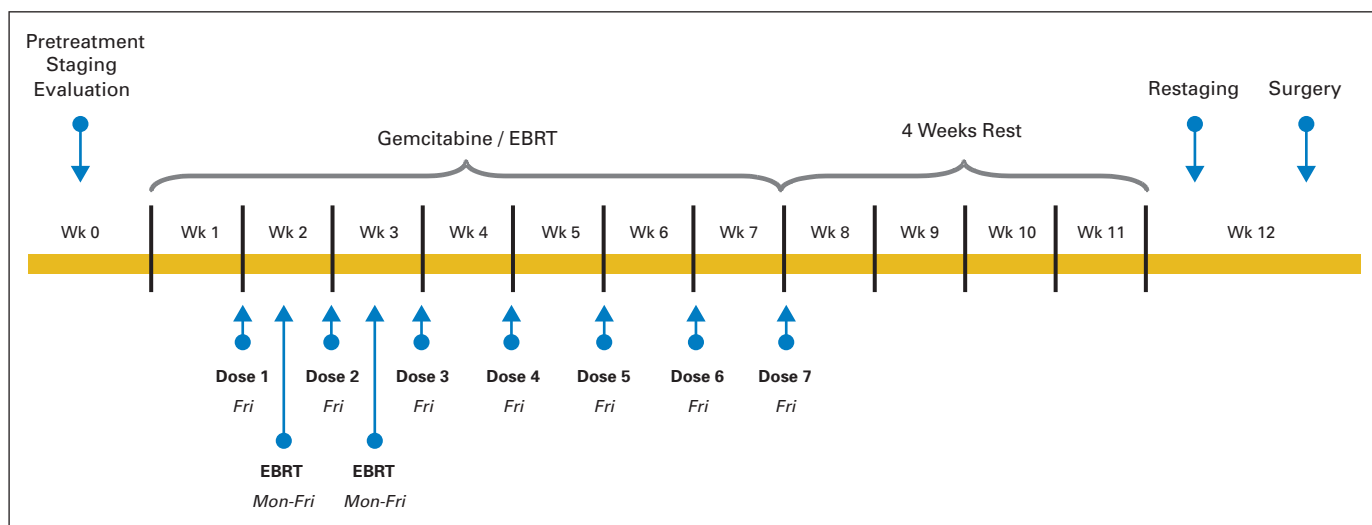
Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 2. We created a grading system to describe the toxicity of biliary stent occlusion which resulted in hyperbilirubinemia and/or transaminitis requiring stent exchange: MDACC grade 1, an elective stent exchange with no evidence of infection and a serum bilirubin no more than 1.5 mg/dL; MDACC grade 2, a therapeutic, outpatient stent exchange with a serum bilirubin more than 1.5 mg/dL and no evidence of cholangitis; MDACC grade 3, a therapeutic stent exchange that required hospitalization and/or was associated with clinical evidence of cholangitis; and MDACC grade 4, a therapeutic stent exchange associated with life-threatening infection.

### Surgery and Assessment of Response

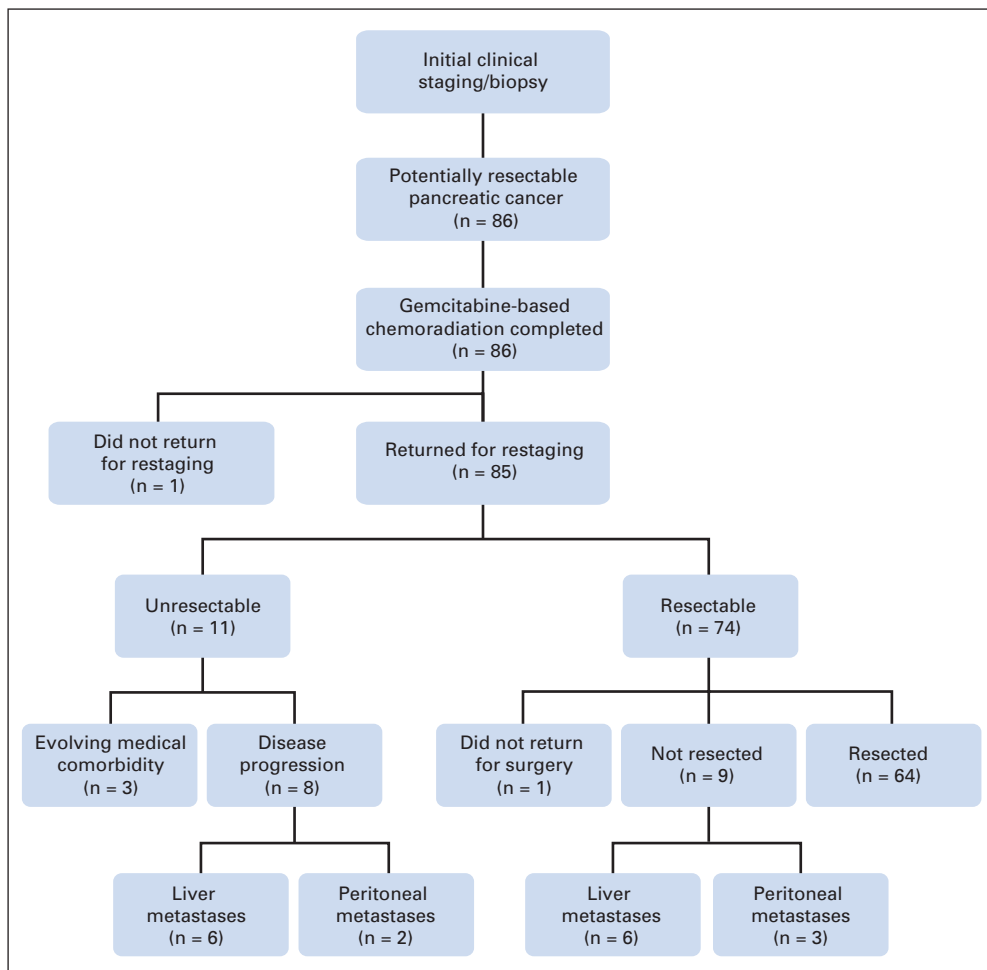
PD was performed using a standard technique, as previously described.<sup>12–14</sup> Operative time and blood loss (in mL) were recorded from the anesthesia record. Major postoperative complications were defined as previously described.<sup>15</sup> Standardized histologic evaluation of the PD specimen was performed as previously described with prospective evaluation of the SMA margin.<sup>16–18</sup> Final margins were recorded as negative (R0) or positive (R1) for tumor. A margin was designated positive if tumor cells were present at the inked SMA margin, the common bile/hepatic duct or the pancreatic transection margins. Histologic response to preoperative chemoradiation was scored in all resected surgical specimens by a GI pathologist using a previously published scoring scheme.<sup>6</sup>

### Follow-Up and Statistical Analysis

After surgery, patients were evaluated every 3 to 4 months by physical examination, chest radiography, and abdominal CT. For those without evidence of disease at 2 years, follow-up was at 6-month intervals. Recurrent disease was defined on follow-up CT imaging; biopsy confirmation was not required. Overall survival was calculated from the time of tissue diagnosis (the median time from tissue diagnosis to protocol entry was 15 days [range 1 to 71



**Fig 1.** Treatment schema for the combination of gemcitabine and radiation therapy. Patients received their first dose of gemcitabine on Friday or Saturday and radiation therapy started the following Monday. Restaging studies were performed 4 to 6 weeks following the last dose of gemcitabine and in the absence of disease progression patients were then brought to surgery for pancreaticoduodenectomy. EBRT, external-beam radiation therapy; wk, week.



**Fig 2.** Algorithm illustrating flow of patients through the treatment protocol.

days]) and was estimated by the Kaplan-Meier method. The log-rank test was used to compare survival curves. Cox proportional hazards regression was used to assess the association between clinical and pathologic variables of interest and survival. Parameters with  $P \leq .25$  on univariate analysis were included in the multivariate analysis. All statistical tests were two tailed, and  $P < .05$  was considered to be statistically significant.

## RESULTS

### Treatment

From July 1998 through October 2001, 86 patients were enrolled (Appendix Table A1, online only). The flow of all 86 patients through the treatment protocol is illustrated in Figure 2. All patients completed the radiation component, and 85 of 86 patients underwent restaging evaluation. One patient did not return for restaging because of a decline in performance status related to disease progression, and died less than 6 months from the date of diagnosis. Surgery was not performed in 12 (14%) of the 86 patients who completed chemoradiation because of patient refusal ( $n = 1$ ), disease progression ( $n = 8$ ), or medical comorbidities ( $n = 3$ ). The sites of metastases found in the eight patients with metastatic disease at restaging included liver in six and peritoneum in two patients. Medical comorbidities, not apparent at study entry, precluded surgery in 3 patients. These 3 patients experienced rapid disease progression and died 10, 11, and 13 months from

the date of diagnosis. Of note, at the time of restaging CT evaluation, no patient was judged to have locally unresectable disease.

Seventy-three (85%) of 86 patients were taken to surgery for planned PD. Unresectable disease was found in nine patients at laparoscopy ( $n = 1$ ) or laparotomy ( $n = 8$ ) owing to CT-occult liver metastases ( $n = 6$ ) or peritoneal implants ( $n = 3$ ). No patient was found at surgery to have unresectable disease based on local tumor extension. PD was performed successfully in 64 (74%) of 86 patients. Resection of the SMV-PV confluence was necessary in 13 (20%) of these 64 patients (tangential excision with saphenous vein patch [ $n = 4$ ] or segmental resection with [ $n = 4$ ] or without [ $n = 5$ ] interposition grafting), and one patient required tangential resection of the inferior vena cava.

### Toxicities of Chemoradiation and Surgery

All 86 patients completed the radiation component and are included in the toxicity analysis. Gemcitabine doses were withheld or reduced in 46 (53%) of 86 patients because of toxic events; GI (34%), hematologic (53%), endobiliary stent related (12%), or nonstent infectious complications (1%). Table 1 outlines the overall toxicity profile for gemcitabine-based chemoradiation, including hospitalizations. Hospital admission was not required in 48 (56%) of the 86 patients. There were no chemoradiation-associated deaths. Patients who experienced grade 3/4

**Table 1.** Toxicity Profile (grade 3 and 4) of Gemcitabine-Based Chemoradiation in All 86 Patients

Toxicity	No. Patients		No. of Toxic Events	
	Total	Required Hospitalization	Grade 3	Grade 4
<b>Hematologic</b>	37	3	—	—
Anemia	0	0	0	0
Leukopenia	33	1	38	4
Granulocytopenia	25	0	28	2
Thrombocytopenia	1	0	1	0
Neutropenic fever	2	2	2	0
<b>Constitutional</b>	32	3	—	—
Fatigue	27	0	31	0
Anorexia	11	1	11	0
Pain	3	0	3	0
Failure to thrive	3	2	3	0
<b>GI</b>	30	12	—	—
Nausea	10	1	13	0
Emesis	14	3	18	0
Diarrhea/enteritis	3	2	4	0
Dehydration	9	7	12	0
Constipation	3	2	3	0
Abdominal pain	9	2	9	0
<b>Liver and biliary</b>	24	18	—	—
Elevated total bilirubin	15	11	16	0
Elevated AST	4	3	4	0
Elevated ALT	6	4	6	0
Elevated alkaline phosphatase	2	2	2	0
Stent occlusion	18	18	18	1
<b>Cardiovascular</b>	4	2	—	—
Deep venous thrombosis	2	0	2	0
<b>Pulmonary embolism</b>	2	2	2	0
<b>Other toxicities</b>	18	9	18	0

toxicity were less likely to undergo PD, although this was not statistically significant (odds ratio = 0.29;  $P = .26$ ).

Endobiliary stents were placed in 67 (78%) of the 86 patients before treatment began. Of the 67 patients with plastic biliary stents, 23 (34%) underwent a total of 27 stent exchanges. Endobiliary self-expandable metal stents were placed at the time of stent exchange in 2 patients.<sup>19</sup>

The median time from completion of preoperative therapy to surgery in the 73 patients who went to surgery was 5.6 weeks. Of the 64 patients who underwent successful PD, 10 (16%) experienced a delay in surgery of more than 8 weeks from the completion of chemoradiation. Major complications occurred in six patients (9%) including perioperative death ( $n = 1$ ), chylous ascites ( $n = 1$ ), transient bilious drainage from an abdominal drain ( $n = 1$ ), percutaneous drainage of intra-abdominal (sterile) fluid collections ( $n = 2$ ), and postoperative GI hemorrhage, which was managed conservatively ( $n = 1$ ). The perioperative death was the result of multisystem organ failure after reoperation for sepsis secondary to a pancreatic anastomotic leak.

## Histopathology

The pathologic findings for the 64 patients who underwent PD appear in Table 2 and are compared with results from our previous FU-based and paclitaxel-based preoperative chemoradiation studies. Surgical margins were grossly negative in all patients who underwent PD. A microscopically positive SMA margin was found in the surgical specimens of four (6%) of 64 patients, and a positive final pancreatic parenchymal transection margin was found in 3 (5%) patients. Metastatic disease was found in regional lymph nodes in 24 (38%) of the 64 patients. The median number of nodes examined in all 64 patients was 17.5. Of the 24 patients with positive nodes, the median number of nodes positive was 2.0 (mean, 2.4 nodes).

There were no statistically significant differences in overall survival by treatment effect scores (Table A2). There was no association between the extent of treatment effect and positive lymph nodes or positive surgical margins.

## Survival and Disease Recurrence

At last follow-up, 65 (76%) of 86 patients have died, comprising all 22 who did not undergo PD and 43 (67%) of the 64 patients who completed all intended treatment. The median overall survival of all 86 patients was 22.7 months (95% CI, 15.9 to 29.5; Fig 3); the overall progression-free survival was 15.4 months (95% CI, 7.8 to 23.0). The 5-year survival for all 86 patients was 27%. Median survival was 34.0 months (95% CI, 23.8 to 44.2) for the 64 patients who underwent PD and 7.1 month (95% CI, 6.1 to 8.1) for the 22 patients who did not undergo PD ( $P < .001$ ). The 5-year survival for those who did and did not undergo PD was 36% and 0% respectively.

Among the 64 patients who underwent PD, 37 (58%) have died as a result of recurrent pancreatic cancer and six (9%) of other causes (including the one perioperative death), and 21 patients (33%) are currently alive. The overall progression-free survival for all 64 patients was 28.6 months (95% CI, 22.0 to 35.2). The 37 patients who developed recurrent pancreatic cancer experienced recurrence at a median of 13.2 months (range, 6.3 to 79.9 months) from the date of diagnosis. First sites of recurrence included distant organ in 30 (47%) of 64 patients, peritoneal cavity in eight (13%), and local tumor bed recurrence in seven (11%); in two of these seven patients, this was an isolated site of recurrence. None of the seven patients with local recurrence had a positive SMA margin. The liver was the most common site of tumor recurrence (15 [41%] of 37 patients with recurrence). For the 64 patients who underwent PD, covariates of interest were assessed separately in a univariate fashion (Table A3). On multivariate analysis, the only factors found to influence survival were the number of positive lymph nodes (hazard ratio [HR] = 1.48;  $P < .001$ ; 95% CI, 1.23 to 1.79) and major postoperative complications (HR = 4.46;  $P = .003$ ; 95% CI, 1.67 to 11.87). When major postoperative complications ( $n = 6$ ) were excluded, the influence of positive lymph nodes remained essentially unchanged (HR = 1.41;  $P \leq .001$ ; 95% CI, 1.18 to 1.70). When we considered N stage (and excluded the number of positive lymph nodes) the influence of N stage remained significant (HR = 2.5;  $P = .006$ ; 95% CI, 1.30 to 4.8).

## DISCUSSION

This report adds to the recently published experience with gemcitabine-based chemoradiation delivered in a neoadjuvant setting to patients with

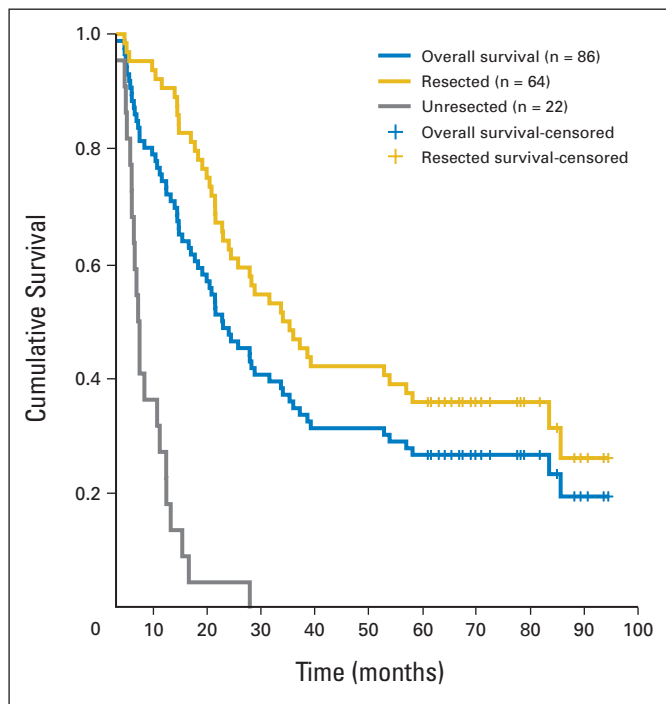
**Table 2.** Pathologic Findings in the Present Report Compared With the Authors' Three Previously Published Trials of Neoadjuvant Therapy and Pancreaticoduodenectomy

Histologic Findings	FU/50.4 Gy (Evans et al <sup>6</sup> )		FU/30 Gy (Pisters et al <sup>7</sup> )		Paclitaxel/30 Gy (Pisters et al <sup>8</sup> )		Current Trial	
	No.	%	No.	%	No.	%	No.	%
Total No. of resected patients	17		20		19		64	
Treatment effect score								
I	2	12	11	55	8	42	12	19
IIa	8	47	5	25	7	37	15	23
IIb	3	18	4	20	4	21	28	44
III	4	23	0	0	0	0	8	13
IV	0	0	0	0	0	0	1	1
AJCC T stage								
T1	NA		0	0	1	5	12	19
T2	NA		5	25	8	42	9	14
T3	NA		15	75	10	53	43	67
AJCC N stage								
N0	12	71	7	35	9	47	40	63
N1	5	29	13	65	10	53	24	38
Microscopically positive surgical margin								
SMA	3	18	2	10	6	32	4	6
Pancreatic parenchyma	0	0	0	0	0	0	3	5
Bile duct	0	0	0	0	0	0	0*	0

Abbreviations: FU, fluorouracil; AJCC, American Joint Committee on Cancer; SMA, superior mesenteric artery; NA, not applicable.

\*Margins were not assessed in two patients who underwent reoperative PD due to the dense inflammatory change and the inability to obtain an additional margin for analysis.

potentially resectable pancreatic cancer and represents the largest protocol-based experience to date (Table 3).<sup>20-23</sup> The median survival of the 64 resected patients was 34 months, and 21 (33%) remain alive without evidence of disease recurrence at a minimum follow-up of 5 years.



**Fig 3.** Survival curve for all 86 patients and survival curves for the patients who underwent pancreaticoduodenectomy (PD; n = 64) versus those who did not undergo PD (n = 22).

There are several conclusions to be drawn from the results of this trial. First, the findings reported herein are consistent with our previous observation that neoadjuvant treatment sequencing accurately identifies those patients who are unlikely to achieve a survival benefit from surgery and enriches the population of patients who undergo PD with those most likely to benefit from such a large operation.<sup>7-8</sup> Further, when we examined the outcome of the 64 patients who underwent a potentially curative PD, the prognostic variables that negatively influenced survival included the presence of lymph node metastases, the number of positive lymph nodes, and major postoperative complications. The impact of lymph node metastasis in the surgical specimen has been previously reported and is consistent with published data from our institution.<sup>18</sup> However, the tolerance to preoperative therapy and surgery appears to also reflect the underlying biology of the host-tumor relationship, and our data suggest that patients who struggle through induction therapy or surgery are less likely to do well. This finding lends further support to a neoadjuvant strategy for pancreatic adenocarcinoma.

Second, in comparison with our previously published FU- and paclitaxel-based preoperative regimens, this gemcitabine-based approach has led to better survival for those patients who underwent PD.<sup>6-8</sup> Furthermore, the survival results compare favorably with data reported from modern adjuvant trials for resected pancreatic cancer.<sup>2-3</sup> We believe preoperative gemcitabine-based chemoradiation has two distinct advantages in this regard. Gemcitabine likely provides superior systemic treatment of micrometastases compared with FU or paclitaxel, and although the superiority of gemcitabine over single-agent FU is quite modest in advanced disease, the differences in efficacy may be magnified in a patient population with very low systemic tumor burden. This cannot be assumed for patients who

**Table 3.** Published Experience With Preoperative Gemcitabine-Based Chemoradiation and Surgery for Localized Pancreatic Adenocarcinoma

Variable	Hoffman <sup>20</sup> (1998)	Joensuu <sup>21</sup> (2004)	Talamonti <sup>22</sup> (2006)	Palmer <sup>23</sup> (2007)	Current Report
No. of patients	15	28	20	50	86
Gemcitabine dose, mg/m <sup>2</sup>	300-500 weekly ×6	50 2×/week	1,000 weekly ×9	1,000/week ×7*	400 weekly ×7
Radiation dose, Gy	50.4	50.4	36	None	30
Median survival of all patients, months	NA	25	NA	14	23
No. resected	8	20	17	27	64
Median survival of resected patients, months	NA	NA	26	28	34
Median survival of patients not resected, months	NA	NA	NA	9	7

Abbreviation: NA, not applicable.

\*Radiation therapy was not administered, and 26 of the 50 patients also received cisplatin 25 mg/m<sup>2</sup>.

undergo surgery first, in whom the stress of surgery and delay in the delivery of systemic therapy may alter the host-tumor relationship.

Gemcitabine also has potent radiosensitizing properties, and this is critical in a disease with a propensity for positive surgical margins and local recurrence.<sup>24</sup> Pancreatic cancer is somewhat unique in its ability to spread along perineural sheaths and particularly along the autonomic ganglia surrounding the SMA. This allows tumor access, at a microscopic level, to the SMA and celiac ganglia, thereby predisposing patients to local recurrence even when all gross tumor has been removed. It is precisely this microscopic disease, which infiltrates perineural tissue at the periphery of the tumor, that is the target of adjuvant chemoradiation administered pre- or postoperatively. Our data on histologic assessment of treatment effect (Table 2) suggests that greater tumor cell killing was generated using gemcitabine as the radiosensitizer compared with FU or paclitaxel. Moreover, the low rate of local recurrence reported in this trial (11% as any component of failure and 3% as isolated local recurrence) is likely caused, in part, by preoperative chemoradiation. Other variables, in addition to the use of multimodality therapy, including T stage, tumor size and location (with respect to the SMA), lymph node status, and the quality of the surgical dissection also influence the rate of local recurrence.

Although treatment was associated with both hematologic and nonhematologic toxicity, there were no chemoradiation-associated deaths, and all patients completed the radiation component of therapy. Of the 67 patients with plastic biliary stents, 23 (34%) required a total of 27 stent exchanges before surgery and 18 (8%) of 23 were admitted to the hospital. Our current practice of placing metal stents in patients with potentially resectable disease will likely contribute to a major reduction in stent-related morbidity in the future.<sup>19</sup> In contrast to the preoperative period, there were no surgery-related complications that could be attributed to the preoperative therapy. In fact, as noted by us and other investigators, pancreatic anastomotic leak was less common when chemoradiation was delivered before PD.<sup>25</sup> The overall low rate of surgical complications likely reflects the small number of participating surgeons and the high level of experience of both the surgeons and the institution with pancreatic surgery.

Of note, the feasibility of this study was based on the ability to obtain a cytologic diagnosis of adenocarcinoma via EUS-guided fine-needle aspiration biopsy and the ability to endoscopically decompress the biliary tree in those patients with obstructive jaundice.<sup>11,18,26</sup> When the diagnosis of adenocarcinoma can be confirmed safely, utilizing a minimally invasive technique such as EUS-guided fine-needle aspiration, and durable biliary decom-

pression can be achieved, localized pancreatic cancer can then be treated similarly to other GI solid tumors. Namely, the diagnostic phase can be separated from the treatment phase, stage-specific protocol-based therapy can be used, and exploratory surgery on an urgent basis is no longer needed.

Lastly, the predominant pattern of failure seen among the patients who underwent PD was systemic; therefore, in an attempt to build on the encouraging results from this trial, we have conducted a phase II trial of preoperative gemcitabine-based chemoradiation that incorporates combination chemotherapy. The results, which can be viewed in the companion article,<sup>27</sup> suggest that the addition of currently available cytotoxic therapy to chemoradiation does not further improve patient outcomes. Nevertheless, as we develop more effective systemic therapies for this disease, the support for treatment schemas that place surgery after a period of induction therapy will be even more compelling. Importantly, locoregional disease control will become increasingly appreciated as necessary for long-term survival. Thus, our ongoing investigations of multimodality therapy for stage I/II pancreatic cancer continue to explore novel therapies in addition to a gemcitabine-based chemoradiation platform.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Employment or Leadership Position:** None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** None **Research Funding:** Douglas B. Evans, Eli Lilly and Co **Expert Testimony:** None **Other Remuneration:** None

#### AUTHOR CONTRIBUTIONS

**Conception and design:** Douglas B. Evans, Christopher H. Crane, James L. Abbruzzese, Robert A. Wolff

**Administrative support:** Douglas B. Evans, James L. Abbruzzese

**Provision of study materials or patients:** Douglas B. Evans, Gauri R. Varadhachary, Christopher H. Crane, Jeffrey E. Lee, Peter W.T. Pisters,

Jean-Nicolas Vauthey, Huamin Wang, Karen R. Cleary, Gregg A. Staerckel, Chusilp Charnsangavej, Elizabeth A. Lano, Linus Ho, Renato Lenzi, James L. Abbruzzese, Robert A. Wolff

**Collection and assembly of data:** Douglas B. Evans, Gauri R. Varadhachary, Charlotte C. Sun

**Data analysis and interpretation:** Douglas B. Evans, Gauri R. Varadhachary, Charlotte C. Sun, Robert A. Wolff

**Manuscript writing:** Douglas B. Evans, Gauri R. Varadhachary, Christopher H. Crane, Charlotte C. Sun, Robert A. Wolff

**Final approval of manuscript:** Douglas B. Evans, Gauri R. Varadhachary, Christopher H. Crane, Charlotte C. Sun, Jeffrey E. Lee, Peter W.T. Pisters, Jean-Nicolas Vauthey, Huamin Wang, Karen R. Cleary, Gregg A. Staerckel, Chusilp Charnsangavej, Elizabeth A. Lano, Linus Ho, Renato Lenzi, James L. Abbruzzese, Robert A. Wolff

## REFERENCES

1. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer: Gastrointestinal Tumor Study Group. *Cancer* 59:2006-2010, 1987
2. Neoptolemos JP, Stocken DD, Friess H, et al: European Study Group for Pancreatic Cancer: A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 350:1200-1210, 2004
3. Oettle H, Post S, Neuhaus P, et al: Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: A randomized controlled trial. *JAMA* 297:267-277, 2007
4. Crane CH, Varadhachary G, Wolff RA, et al: The argument for pre-operative chemoradiation for localized, radiographically resectable pancreatic cancer. *Best Pract Res Clin Gastroenterol* 20:365-382, 2006
5. Spitz FR, Abbruzzese JL, Lee JE, et al: Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. *J Clin Oncol* 15:928-937, 1997
6. Evans DB, Rich TA, Byrd DR, et al: Preoperative chemoradiation and PD for adenocarcinoma of the pancreas. *Arch Surg* 127:1335-1339, 1992
7. Pisters PWT, Abbruzzese JL, Janjan NA, et al: Rapid-fractionation preoperative chemoradiation, PD, and intraoperative radiation therapy for resectable pancreatic adenocarcinoma. *J Clin Oncol* 16:3843-3850, 1998
8. Pisters PWT, Wolff RA, Janjan NA, et al: Preoperative paclitaxel and concurrent rapid-fractionation radiation for resectable pancreatic adenocarcinoma: Toxicities, histologic response rates, and event-free outcome. *J Clin Oncol* 20:2537-2544, 2002
9. Burris HA, Moore MJ, Andersen J, et al: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. *J Clin Oncol* 15:2403-2413, 1997
10. Wolff RA, Evans DB, Gravel DM, et al: Phase I trial of gemcitabine combined with radiation for the treatment of locally advanced pancreatic adenocarcinoma. *Clin Cancer Res* 7:2246-2253, 2001
11. Raut CP, Grau AM, Staerckel GA, et al: Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration in patients with presumed pancreatic cancer. *J Gastrointest Surg* 7:118-128, 2003; discussion 127-128
12. Evans DB, Lee JE, Tamm EP, et al: Pancreaticoduodenectomy (Whipple Operation) and total pancreatectomy for cancer, in Fischer JF (ed): *Mastery of Surgery* (ed 5). Philadelphia, PA, Lippincott Williams & Wilkins, 2007, pp 1299-1317
13. Yen TWF, Abdalla EK, Pisters PWT, et al: Pancreaticoduodenectomy, in VonHoff DD, Evans DB, Hruban RH (eds): *Pancreatic Cancer*. Sudbury, MA, Jones and Bartlett Publishers, 2005, pp 265-285
14. Tseng JF, Raut CP, Lee JE, et al: PD with vascular resection: Margin status and survival duration. *J Gastrointest Surg* 8:935-950, 2004; discussion 949-950
15. Pisters PWT, Hudec WA, Hess KR, et al: Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. *Ann Surg* 234:47-55, 2001
16. Staley CA, Cleary KA, Abbruzzese JA, et al: Need for standardized pathologic staging of PD specimens. *Pancreas* 12:373-380, 1996
17. Exocrine pancreas, in Greene FL, Page DL, Fleming ID, et al (eds): *AJCC Cancer Staging Manual*. Chicago, IL, AJCC, 2002, pp 157-164
18. Raut CP, Tseng JF, Sun CC, et al: Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Ann Surg* 246:52-60, 2007
19. Mullen JT, Lee JH, Gomez HF, et al: PD after placement of endobiliary metal stents. *J Gastrointest Surg* 9:1094-1104, 2005
20. Hoffman JP, McGinn C, Szarka J, et al: A phase I study of preoperative gemcitabine (GEM) with radiation therapy (RT) followed by postoperative GEM for patients with localized, resectable pancreatic adenocarcinoma (PAC). *Proc Am Soc Clin Oncol* 17:283a, 1998 (abstr 1090)
21. Joensuu TK, Kiviluoto T, Karkkainen P, et al: Phase I-II trial of twice-weekly gemcitabine and concomitant irradiation in patients undergoing pancreaticoduodenectomy with extended lymphadenectomy for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 60:444-452, 2004
22. Talamonti MS, Small W Jr, Mulcahy MF, et al: A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. *Ann Surg Oncol* 13:150-158, 2006
23. Palmer DH, Stocken DD, Hewitt H, et al: A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: Gemcitabine alone versus gemcitabine combined with cisplatin. *Ann Surg Oncol* 14:2088-2096, 2007
24. Crane CH, Wolff RA, Abbruzzese JL, et al: Combining gemcitabine with radiation in pancreatic cancer: Understanding important variables influencing the therapeutic index. *Semin Oncol* 28:25-33, 2001
25. Lowy AM, Lee JE, Pisters PWT, et al: Prospective, randomized trial of octreotide to prevent pancreatic fistula following pancreaticoduodenectomy for malignant disease. *Ann Surg* 226:632-641, 1997
26. Chen VK, Arguedas MR, Baron TH: Expandable metal biliary stents before pancreaticoduodenectomy for pancreatic cancer: A Monte-Carlo decision analysis. *Clin Gastroenterol Hepatol* 3:1229-1237, 2005
27. Varadhachary GR, Wolff RA, Crane CH, et al: Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 26:3487-3495, 2008

## Acknowledgment

We thank Aileen San Miguel for research nurse support and Henry Gomez for data management administration.

## Appendix

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