

## Preoperative Gemcitabine and Cisplatin Followed by Gemcitabine-Based Chemoradiation for Resectable Adenocarcinoma of the Pancreatic Head

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### ABSTRACT

#### Purpose

We conducted a phase II trial of preoperative gemcitabine and cisplatin chemotherapy in addition to chemoradiation (Gem-Cis-XRT) and pancreaticoduodenectomy (PD) for patients with stage I/II pancreatic adenocarcinoma.

#### Patients and Methods

Chemotherapy consisted of gemcitabine (750 mg/m<sup>2</sup>) and cisplatin (30 mg/m<sup>2</sup>) given every 2 weeks for four doses. Chemoradiation consisted of four weekly infusions of gemcitabine (400 mg/m<sup>2</sup>) combined with radiation therapy (30 Gy in 10 fractions administered over 2 weeks) delivered 5 days per week. 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 90 patients; 79 patients (88%) completed chemo-chemoradiation. Sixty-two (78%) of 79 patients were taken to surgery and 52 (66%) of 79 underwent PD. The median overall survival of all 90 patients was 17.4 months. Median survival for the 79 patients who completed chemo-chemoradiation was 18.7 months, with a median survival of 31 months for the 52 patients who underwent PD and 10.5 months for the 27 patients who did not undergo surgical resection of their primary tumor ( $P < .001$ ).

#### Conclusion

Preoperative Gem-Cis-XRT did not improve survival beyond that achieved with preoperative gemcitabine-based chemoradiation (Gem-XRT) alone. The longer preoperative interval required more durable biliary decompression (metal stents) but was not associated with local tumor progression. The gemcitabine-based chemoradiation platform is a reasonable foundation on which to build future phase II multimodality trials for stage I/II pancreatic cancer incorporating emerging systemic therapies.

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### INTRODUCTION

Preoperative (neoadjuvant) treatment of localized pancreatic cancer is a logical strategy for a disease that is systemic at diagnosis in most patients. Our group has previously completed three prospective trials exploring the potential value of neoadjuvant therapy using fluorouracil (FU)- or paclitaxel-based chemoradiation followed by surgery.<sup>1-3</sup> Given the superiority of gemcitabine to bolus FU as systemic therapy in advanced pancreatic cancer and its potent radiosensitizing properties, we subsequently performed a phase II trial of preoperative gemcitabine-based chemoradiation

(Gem-XRT; see Evans et al<sup>4</sup> in this issue of *Journal of Clinical Oncology*) in patients with potentially resectable disease.<sup>5,6</sup> A total of 86 patients were enrolled onto the Gem-XRT trial, and 64 patients (74%) underwent pancreaticoduodenectomy (PD). Of these 64 patients, 21 patients (33%) remain alive without evidence of disease recurrence at a minimum follow-up of 5 years. After surgical resection, local recurrences were rare (11%; isolated local recurrence in 3%), and the dominant site of failure was distant metastases. The current trial was designed in response to this pattern of recurrence by delivering more systemic therapy using gemcitabine plus cisplatin, because at the time, a gemcitabine plus

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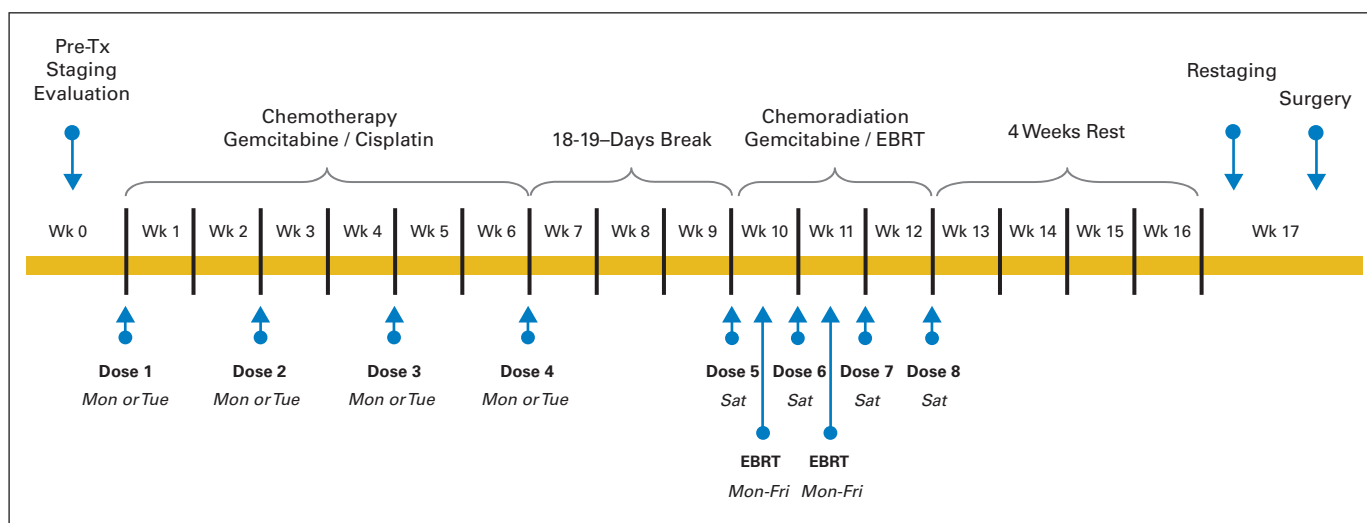
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**Fig 1.** Treatment schema, preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation followed by surgery. Pre-Tx, pretreatment; EBRT, external-beam radiation therapy.

cisplatin doublet was showing promising activity in advanced disease.<sup>7</sup> We report the results of a phase II trial of preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation (Gem-Cis-XRT) in stage I/II adenocarcinoma of the pancreatic head.

## PATIENTS AND METHODS

### Patients

The institutional review board approved the study protocol, and all patients gave written informed consent. Initial pretreatment evaluation and protocol eligibility were identical to that reported for Gem-XRT.<sup>4</sup> Four to 6 weeks after the completion of Gem-Cis-XRT, patients underwent complete restaging as reported for Gem-XRT, and surgery was considered delayed if it was performed more than 8 weeks after the completion of chemoradiation.

### Chemo-Chemoradiation

The treatment schema is shown in Fig 1. In the chemotherapy phase, gemcitabine (750 mg/m<sup>2</sup>) and cisplatin (30 mg/m<sup>2</sup>) were given every 2 weeks for four doses followed by a 3-week rest. This was followed by the chemoradiation phase of four weekly infusions of gemcitabine (400 mg/m<sup>2</sup>) combined with external-beam radiation therapy (EBRT) to a total dose of 30 Gy (3 Gy per fraction, administered Monday through Friday over 2 weeks). EBRT was delivered 5 days per week (Monday through Friday, beginning 48 to 72 hours after the first dose of gemcitabine). The primary tumor and gross adenopathy were treated with a 3-cm block margin cranially and caudally and a 2-cm block margin radially.

Evaluation during preoperative therapy and treatment dose modifications were identical to that reported for Gem-XRT.<sup>4</sup> Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 3 toxicity criteria. We used the M.D. Anderson Cancer Center grading system for biliary stent toxicity.<sup>4</sup>

### Surgery and Assessment of Response

PD was performed using a standard technique, and major surgical complications were defined as previously described.<sup>8-10</sup> Standardized histologic evaluation of the PD specimen was performed as described by the American Joint Committee on Cancer.<sup>11</sup> Histologic response to preoperative chemoradiation was graded using a previously published grading scheme.<sup>1</sup>

### Follow-Up and Statistical Analysis

Follow-up and statistical analysis were identical to that reported for Gem-XRT.<sup>4</sup> Importantly, recurrent disease was diagnosed by imaging studies as previously defined; tissue confirmation was not required.<sup>4</sup>

## RESULTS

### Treatment

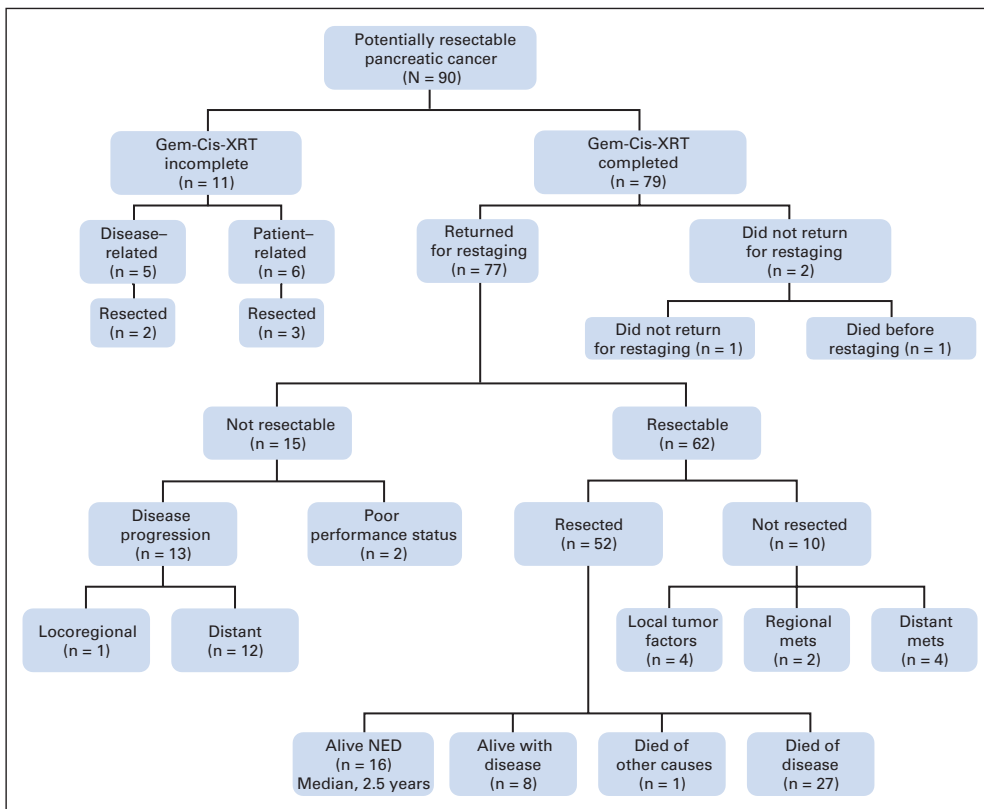
From October 2002 through February 2006, 90 patients were enrolled (Table 1). The flow of all 90 patients through the treatment protocol is illustrated in Fig 2. Seventy-nine patients (88%) completed chemoradiation, and 11 patients (12%) withdrew from treatment during chemotherapy or chemoradiation because of disease-related

**Table 1.** Patient Demographics

Characteristic	Gis-XRT <sup>4</sup> (n = 86)		Gis-Cis-XRT (n = 90)	
	No. of Patients	%	No. of Patients	%
Sex				
Male	55	64	50	56
Female	31	36	40	44
Race or ethnicity				
White	71	83	78	87
African American	5	6	3	3
Hispanic	7	8	6	7
Asian	3	3	3	3
Age, years				
Median	64		64	
42-50	7	8	9	10
51-60	23	27	25	28
61-70	38	44	37	41
71-80	18	21	19	21
Current or past smoker				
Yes	59	69	56	62
No	26	30	33	37
Unknown	1	1	1	1
Laparotomy before referral*	8	9	5	6

Abbreviations: Gis-XRT, preoperative gemcitabine-based chemoradiation; Gis-Cis-XRT, gemcitabine and cisplatin followed by gemcitabine-based chemoradiation (current study).

\*Unsuccessful attempt at tumor resection.



**Fig 2.** Algorithm illustrating flow of patients through the protocol treatment. Gem-Cis-XRT, preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation; mets, metastases; NED, no evidence of disease.

factors in five patients and patient-related factors in six patients. Of the latter six patients, all had financial and social issues related to their treatment or their relocation away from home. A successful PD was subsequently performed in five of these 11 patients.

Restaging evaluation was completed in 77 of the 79 patients who completed chemoradiation; two patients did not return for restaging, including one patient who experienced a sudden fatal pulmonary embolism and one patient who declined surgery and other further oncologic treatment. Of the 77 patients who were restaged, 15 patients (19%) did not undergo surgery, owing to a decline in performance status precluding consideration of major abdominal surgery ( $n = 2$ ), lung metastases ( $n = 3$ ), liver metastases ( $n = 8$ ; one of whom was thought to also have local disease progression), bone metastases ( $n = 1$ ), and locally unresectable disease ( $n = 1$ ). Careful review of the initial imaging studies of this latter patient showed stable disease with arterial abutment, which was present at study entry; therefore, in retrospect, this patient was inappropriately entered onto the study. This patient died of disease 13 months from the date of diagnosis.

Sixty-two (78%) of 79 patients who completed preoperative therapy were taken to surgery for planned PD. Unresectable disease was found in 10 patients at laparoscopy or laparotomy, including liver metastases ( $n = 4$ ), carcinomatosis ( $n = 2$ ), and local tumor factors that precluded surgery in the opinion of the operating surgeon ( $n = 4$ ). Review of the operative dictations of the latter four patients (D.B.E.) suggested that PD was not performed because of tumor extension into the root of mesentery in two patients, dense inflammatory tissue encasing the infrapancreatic superior mesenteric vessels of unclear etiology in one patient, and

because of a positive intraoperative biopsy of a common hepatic artery lymph node and extensive soft tissue edema in one patient, probably owing to radiation sensitivity.

A successful PD was completed in 52 (66%) of 79 patients. Resection of the superior mesenteric-portal vein confluence was necessary in 19 (36.5%) of these 52 patients, including tangential excision with primary repair ( $n = 4$ ), saphenous vein patch ( $n = 4$ ), and segmental resection with ( $n = 3$ ) or without ( $n = 8$ ) interposition grafting.

### **Toxicities of Chemo-Chemoradiation, Chemoradiation, and Surgery**

Seventy-nine (88%) of 90 patients completed all therapy. During the systemic phase, one or more doses of gemcitabine was reduced or withheld in three patients and one or more doses of cisplatin was reduced or withheld in five patients. During the radiation phase, gemcitabine doses were withheld or reduced in 45 (57%) of the 79 patients. All 79 patients received all planned radiation treatments. The overall grade 3 to 4 toxicity profile and hospitalizations are listed in Table 2 and compared with our previous Gem-XRT trial. Hospital admission was not required in 39 (49%) of the 79 patients. There were no treatment-related deaths.

Before initiating therapy, endobiliary stents were placed in 64 (81%) of the 79 patients. Using the M.D. Anderson Cancer Center grading system for biliary stent-related toxicity, there were 24 patients with grade 3 stent occlusions. At least one stent exchange was necessary in 46 (75%) of the 61 patients who entered the protocol with a plastic biliary stent. The increased risk for occlusion of plastic stents owing to the duration of preoperative therapy became clinically apparent after treating approximately 35

**Table 2.** Overall Patient Toxicity Profile (grade 3 and 4) of Gem-Cis-XRT Trial (01-341) in Comparison With Gem-XRT Trial (98-020)

Toxicity	Gem-XRT (n = 86)		Gem-Cis-XRT (n = 79)	
	No. of Patients With Grade 3 to 4 Toxicity	No. of Patients Requiring Hospitalization	No. of Patients With Grade 3 to 4 Toxicity	No. of Patients Requiring Hospitalization
Hematologic	37	3	24	2
Anemia	0	0	2	0
Leukopenia	33	1	19	1
Granulocytopenia	25	0	18	0
Thrombocytopenia	1	0	3	0
Neutropenic fever	2	2	2	2
Constitutional	32	3	30	5
Fatigue	27	0	18	1
Anorexia	11	1	17	4
Pain	3	0	6	1
Failure to thrive	3	2	0	0
Gastrointestinal	30	12	20	7
Nausea	10	1	8	2
Emesis	14	3	7	2
Diarrhea/enteritis	3	2	2	0
Dehydration	9	7	11	3
Constipation	3	2	3	0
Abdominal pain	9	2	8	2
Liver and biliary	24	18	29	24
Elevated total bilirubin	15	11	13	11
Elevated AST	4	3	5	4
Elevated ALT	6	4	5	4
Elevated alkaline phosphatase	2	2	1	0
Stent occlusion	18	18	24	24
Cardiovascular	4	2	7	3
Deep venous thrombosis	2	0	1	0
Pulmonary embolism	2	2	2	1
Pulmonary edema/congestive heart failure	0	0	3	3
Myocardial infarction	0	0	2	2
Other toxicities	18	9	19	7

Abbreviations: Gem-XRT, preoperative gemcitabine-based chemoradiation; Gem-Cis-XRT, gemcitabine and cisplatin followed by gemcitabine-based chemoradiation (current study).

patients. This clinical observation caused us to begin using self-expandable metal stents, which ultimately were placed in 36 (46%) of 79 patients.<sup>12</sup>

The median time from completion of chemoradiation to surgery in the 62 patients who went to surgery for planned PD was 5.6 weeks. Of the 52 patients who underwent successful PD, eight patients (15%) experienced a delay in surgery of more than 8 weeks from the completion of chemoradiation. There were no perioperative deaths, median perioperative blood loss was 675 mL, median operative time was 6.5 hours, and median length of hospital stay was 10 days. Major complications occurred in five (9.6%) of 52 patients, including intraoperative cardiac arrest with a successful resuscitation (n = 1), re-operation on postoperative day 9 because of a wound hematoma (n = 1), aspiration pneumonia (n = 1), and sepsis (n = 2; secondary to a central venous catheter infection and a biliary anastomotic leak). There were no clinically significant pancreatic anastomotic leaks that required percutaneous drainage or re-operation (pancreatic drains were rarely placed at the time of surgery, and therefore subclinical leaks were not detected).

### Histopathology

Pancreatic ductal adenocarcinoma was confirmed in 50 of the 52 patients who underwent PD. In one patient, pathologic analysis

of the resected specimen suggested that the ampulla of Vater may have been the site of origin, and in another, the surgical specimen favored intraductal pancreatic mucinous neoplasm. The diagnosis of intraductal pancreatic mucinous neoplasm was not apparent on preoperative imaging, and pretreatment fine-needle aspiration biopsy demonstrated adenocarcinoma. The pathologic findings for the 52 patients who underwent PD are listed in Table 3 along with comparison to our prior experience with Gem-XRT.

Surgical margins were grossly negative in all patients who underwent PD. A microscopically positive SMA margin was found in one of 52 patients, and a positive final pancreatic parenchymal transection margin was found in one patient (R1 resection rate = 4%). Metastatic disease was found in regional lymph nodes in 30 (58%) of the 52 patients. The median number of nodes resected in all 52 patients was 21.5 nodes. Of the 30 patients with positive nodes, the median number of nodes positive was two (mean, 3.6 nodes).

Histologic response to preoperative chemoradiation in the resected specimens is listed in Table 3. When the 20 patients with treatment scores I and IIA (minor response) were compared with the 31 patients with treatment scores IIB and III (partial response), there was no association between the extent of treatment effect (minor v partial response) and tumor size, nodal status, or margin

**Table 3.** Pathologic Findings in Patients Who Underwent Pancreaticoduodenectomy

Histologic Findings	Gem-XRT		Gem-Cis-XRT*		P
	No. of Patients	%	No. of Patients	%	
No. of patients who underwent resection/total	64/86	74	52/79	66	.23
Treatment effect score†					.12
I	12	19	2	4	
Ila	15	23	18	35	
Ilb	28	44	24	46	
III	8	13	7	13	
IV	1	1	0	0	
AJCC T stage†					.13
T1	12	19	5	10	
T2	9	14	3	6	
T3	43	67	43	83	
AJCC N stage†					.01
N0	40	63	20	38	
N1	24	37	31	60	
Microscopically positive surgical margin	7	11	2	4	.18
SMA	4	6	1	2	
Pancreatic parenchyma	3	5	1	2	
Bile duct	0	0	0	0	—

Abbreviations: Gem-XRT, preoperative gemcitabine-based chemoradiation; Gem-Cis-XRT, gemcitabine and cisplatin followed by gemcitabine-based chemoradiation; AJCC, American Joint Committee on Cancer; SMA, superior mesenteric artery.  
\*Current study.  
†For 01-341, n = 51, as the patient with a question of intraductal pancreatic mucinous neoplasm was not scored for treatment effect.

status. Table 4 lists the treatment effect score and overall survival for patients in both clinical trials.<sup>4</sup>

### Survival and Disease Recurrence

At last follow-up, 55 (70%) of 79 patients have died, including all 27 patients who did not undergo resection and 28 (54%) of the 52 patients who underwent PD (27 patients died of disease progression, and one patient died of complications after a neurosurgical procedure unrelated to her cancer diagnosis). Twenty-four (46%) of 52 patients are alive, including 16 (31%) of 52 patients without evidence of disease and eight patients with disease at a median follow-up of 29.3 months (range, 11.9 to 56.5 months).

The median overall survival of all 90 patients from the date of diagnosis was 17.4 months (95% CI, 14.53 to 20.34 months; Fig 3), and the overall progression-free survival was 13.2 months (95% CI, 11.9 to 14.4 months). The one patient who was entered inappropriately onto the study did not change the overall or progression-free survival. The median survival of the 79 study patients who completed chemo-chemoradiation was 18.7 months (95% CI, 15.1 to 22.3 months) Median survival was 31.0 months (95% CI, 21.7 to 40.3 months) for the 52 patients who underwent PD and 28.3 months for the 50 patients with ductal adenocarcinoma (95% CI, 18.5 to 38.2 months). Median survival was 10.5 months (95% CI, 9.9 to 11.2 months) for the 27 patients who did not undergo surgical resection of their primary tumor ( $P < .001$ ; Fig 4). Comparison of the appropriate survival curves for Gem-XRT and Gem-Cis-XRT is shown in Figs 5 and 6.

Among the 52 patients who underwent PD, recurrent pancreatic cancer developed in 35 patients (65%) at a median of 8.9 months after surgery; 27 patients have died of recurrent pancreatic cancer, and eight patients are alive with disease. First sites of recurrence included distant organ in 22 patients (42%), peritoneal cavity in 16 patients (31%), and local recurrence in 13 patients (25%). None of the 13 patients with local recurrence had a positive SMA margin, and three of 13 (three [6%] of 52 at-risk patients) had this as an isolated site of recurrence (in one patient who subsequently died of aortic stenosis, the presumed local recurrence was PET positive but not well seen on CT). For the 52 patients who underwent PD, covariates of interest were separately assessed in a univariate fashion using the variables described in the Gem-XRT report.<sup>4</sup> Those that were significant using  $P \leq .25$  were included in the multivariate Cox proportional hazards model. The only variable found to be significantly associated with risk of death on multivariate analysis was hospital length of stay ( $P = .028$ ; hazard ratio = 1.14; 95% CI, 1.02 to 1.28).

Of the 11 patients who withdrew from treatment shortly after enrollment, five patients ultimately underwent PD after completing a short course of off-protocol therapy. Ten of the 11 patients are dead of disease, and one patient (who underwent PD) is alive with lung metastases. The median survival for these 11 patients was 14.6 months (95% CI, 10.6 to 18.5 months).

## DISCUSSION

Over more than 15 years, our group has standardized the pretreatment staging, surgery and pathologic assessment of resection margins,

**Table 4.** Treatment Effect Score and Overall Survival for Patients in Both Clinical Trials Who Underwent Pancreaticoduodenectomy and Comparison With Gem-XRT Trial

Treatment Score	Gem-XRT <sup>4</sup> (n = 64)			Gem-Cis-XRT* (n = 51)†		
	No. of Patients	Median Survival (months)	95% CI	No. of Patients	Median Survival (months)	95% CI
I	12	25.7	4.7 to 46.6	2	10.4	—
Ila	15	34.0	0.0 to 75.6	18	26.4	20.8 to 32.0
Ilb	28	31.5	17.2 to 45.8	24	36.2	16.1 to 56.3
III	8	27.8	0.0 to 89.3	7	Not reached	—
IV	1	38.5	—	0	—	—

Abbreviation: Gem-XRT, preoperative gemcitabine-based chemoradiation; Gem-Cis-XRT, gemcitabine and cisplatin followed by gemcitabine-based chemoradiation.  
\*Current report.  
†One patient with a question of intraductal pancreatic mucinous neoplasm was not included.

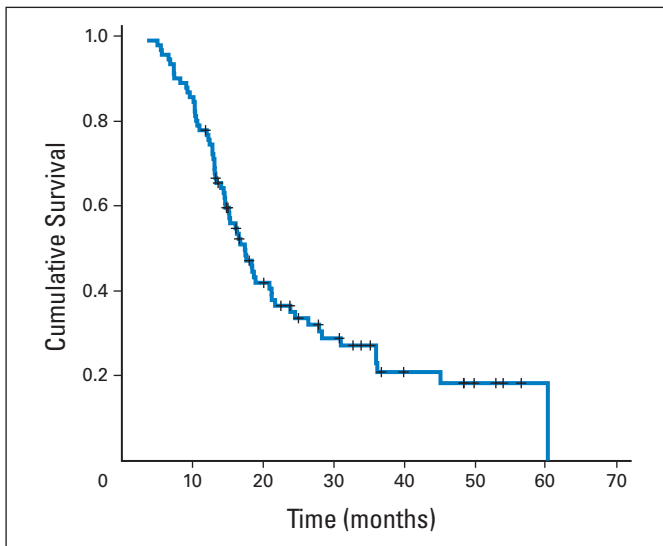


Fig 3. Kaplan-Meier survival curve for all 90 patients.

and grade of treatment effect used to design and conduct neoadjuvant trials for stage I/II pancreatic cancer.<sup>1-4,13</sup> This has allowed us to internally compare our results over time using varied preoperative chemoradiation regimens. This study of preoperative Gem-Cis-XRT was performed based on the early results from our recently completed phase II trial of Gem-XRT.<sup>4</sup> Considering both sequentially performed trials, a total of 176 patients have been treated, representing the largest protocol-based experience to date of preoperative gemcitabine-based chemoradiation in patients with stage I/II pancreatic cancer. The analyses of these trials suggest the following conclusions and raise additional questions for further study.

The results observed with Gem-Cis-XRT were not superior to those observed with Gem-XRT (Table 5). The median survival for the 52 patients who underwent PD after Gem-Cis-XRT was 31 months, which is less, although not statistically different, than the 34-month

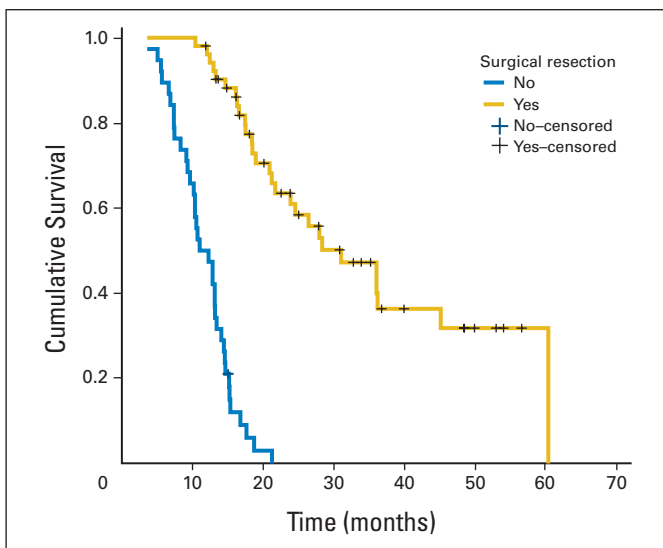


Fig 4. Kaplan-Meier survival curve for those who did (n = 52) and did not (n = 38) undergo surgical resection of the primary tumor.

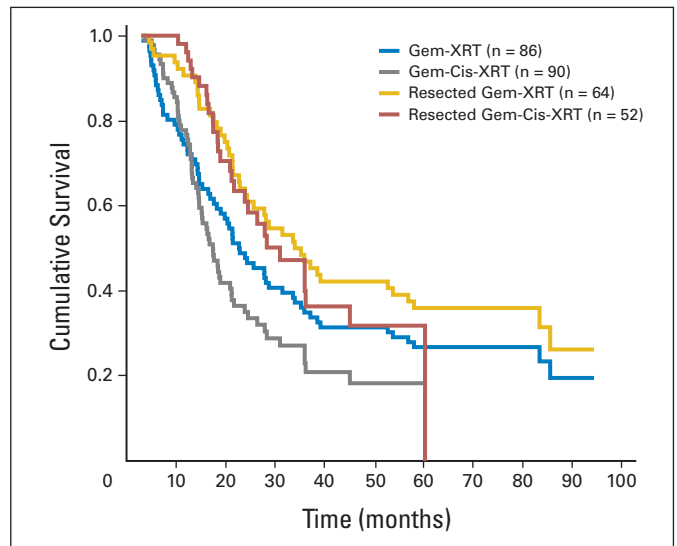


Fig 5. Comparison of survival curves for preoperative gemcitabine-based chemoradiation (Gem-XRT) and gemcitabine and cisplatin chemotherapy in addition to gemcitabine-based chemoradiation (Gem-Cis-XRT; all patients) and comparison of survival curves for Gem-XRT (n = 64) and Gem-Cis-XRT (n = 52) of patients who underwent pancreaticoduodenectomy.

median survival observed for the 64 patients who underwent PD after Gem-XRT ( $P = .41$ ). There was insufficient power to detect differences in survival based on the sizes of the two study populations, and it remains unclear whether there were other confounding variables unique to such complicated treatment sequencing in patients with pancreatic cancer. However, there was a statistically significant increase in the number of patients with N1 disease in this trial compared with Gem-XRT (Table 3; 60% v 38%), which was most likely due to a greater number of node-positive patients at study entry (the treatment effect in the primary tumor was identical in both trials, suggesting a similar downstaging of node-positive disease).

Because the longer duration of preoperative Gem-Cis-XRT in comparison with Gem-XRT did not lead to a superior survival after PD, we did consider whether extending the duration of preoperative therapy may have negatively impacted survival. Of the 90 patients enrolled onto this trial, 62 patients (69%) were taken to surgery for planned PD, compared with 73 (85%) of 86 patients enrolled onto the Gem-XRT trial. The main reason for this difference included a larger number of patients who did not make it to post-treatment, preoperative restaging, one (1%) of 86 patients in Gem-XRT and 13 (14%) of 90 patients in the current trial. The difference between Gem-XRT and Gem-Cis-XRT included the greater complexity of the latter treatment program and the level of individual patient commitment and endurance required to complete the entire course of preoperative therapy. Of note, there was no difference in the resectability rate between trials for those patients who completed all neoadjuvant therapy and were restaged (Gem-XRT, 64 [75%] of 85 patients; Gem-Cis-XRT, 52 [68%] of 77 patients;  $P = .27$ ), suggesting that the increased length of time devoted to preoperative therapy in the current trial did not predispose to an increased incidence of disease progression. There was also no difference in the surgical resectability rate for those patients ultimately taken to surgery (Gem-XRT, 86%; Gem-Cis-XRT, 84%).

In the present report, isolated local tumor progression at the time of preoperative restaging was suggested in only one patient; there were

Preoperative Chemotherapy Followed by RT for Pancreatic Cancer

**Table 5.** Comparison of the Two Neoadjuvant Clinical Trials

Characteristic	Gem-XRT <sup>4</sup>		Gem-Cis-XRT*		P
	No. of Patients	%	No. of Patients	%	
Total No. of patients	86		79†		—
Median age, years	65		65		.85
Smokers	59	69	48	61	.29
Previous laparotomy	8	9	4	5	
With biliary stent	67	78	64	81	.62
With metal stent	2	2	36	46	< .001
Hospitalized with grade 3 to 4 toxicity before restaging	38	44	40	51	.26
Grade 3 or 4 toxicity	74	86	63/79	80	.28
Patients who completed all treatment to include PD	64	74	52	66	.23
N1	24/64	38	31/52	60	.01
T3	43/64	67	43/52	83	.04
Vascular resection	13/64	20	19/52	36	.05
SMA margin positive	4/64	6	1/52	2	.38
Histologic response IIB to IV	37/64	58	31/52	60	.75
Deaths during treatment	1		0		
Median survival of all patients, months	22.7		17.4		.08
Median survival of patients who completed all treatment, months	34.0		31.0		.41
Median survival of patients who did not complete all treatment, months	7.1		10.5		.12
Isolated local failure	2/64	3	3/52	6	.66

Abbreviations: Gem-XRT, preoperative gemcitabine-based chemoradiation; Gem-Cis-XRT, gemcitabine and cisplatin followed by gemcitabine-based chemoradiation; PD, pancreaticoduodenectomy; SMA, superior mesenteric artery.  
\*Current study.  
†Seventy-nine patients in the current report completed preoperative therapy.

no such patients in the Gem-XRT trial. Therefore, the rate of local tumor progression precluding surgery was 0.6% (one of 176 patients), which does not support the concern that a neoadjuvant treatment schema may result in loss of a surgical window of opportunity for resection of the primary tumor. It is not clear whether a lengthy preoperative treatment schema that does not include EBRT would result in a similar outcome. The higher incidence of local recurrence

after surgery in this trial compared with Gem-XRT (Table 6) may be due to the greater proportion of patients with T3 and/or N1 disease in this report, the location of the primary tumor in relation to the SMA, and the unknown potential for chemotherapy given before chemoradiation to enhance radiation resistance. Our recent experience with borderline resectable disease (tumor-artery abutment) suggests that standard fractionation (50.4 Gy; 1.8 Gy/fraction) chemoradiation

**Table 6.** Comparison of the Past and Present Neoadjuvant Clinical Trials at The University of Texas M.D. Anderson Cancer Center

Characteristic	FU + 50.4 Gy		FU + 30 Gy		Paclitaxel + 30 Gy		Gem-XRT <sup>4</sup>		Gem-Cis-XRT*	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Reference No.	1		2		3		4			
No. of patients	28		35		37		86		90	
Overall survival, months	NA		NA		12		23		17	
Hospitalized before restaging	9	32	1	1	6/35	17	36	42	40†	51
Completed all treatment including PD	17	60	20	57	20	54	64	74	52	66
Histologic response IIB to IV/total undergoing resection	7	41	4	20	4/19	21	37	58	31†	60
SMA margin positive	3	18	2	10	6/19	32	4	6	1	2
Deaths during treatment	1	4	0		0		1	1	1‡	1
Median survival of patients who completed all treatment, months	NA		25		19		34		31	
Median survival of patients who did not complete all treatment, months	NA		7		10		7.1		10.5	
Local recurrence	NA		1	5	0		7	11	13	25
Isolated local recurrence	NA		1	5	0		2	3	3	6

Abbreviations: FU, fluorouracil; Gem-XRT, preoperative gemcitabine-based chemoradiation; Gem-Cis-XRT, gemcitabine and cisplatin followed by gemcitabine-based chemoradiation; NA, not applicable; PD, pancreaticoduodenectomy; SMA, superior mesenteric artery.  
\*Current report.  
†Of the 79 patients who completed preoperative therapy.  
‡This patient was one of the 11 patients who withdrew from treatment before restaging.

may be preferred in cases where the tumor is close to or involving the arterial margin on pretreatment imaging.<sup>14</sup> Further, the ability of 30 Gy of EBRT to prevent local recurrence will also be influenced by the quality of the surgery, especially at the SMA margin. As the quality of the surgery declines, a higher dose of radiation (50.4 Gy) may be necessary to achieve a similar rate of local control. Importantly, we used high-quality computed tomography imaging to detect intra-abdominal recurrence, and therefore our sensitivity for the detection of local recurrence was high; virtually all patients were asymptomatic at the time of disease recurrence.

The two gemcitabine-based preoperative chemoradiation regimens lead to better survival when compared with our earlier trials, which delivered FU or paclitaxel as radiosensitizers (Table 6). Given the standardization we have used in the conduct of our preoperative trials, this seems likely related to the use of gemcitabine, which is a superior systemic treatment than FU and is also a potent radiosensitizer.<sup>5,6</sup> In addition, although caution is required when making external comparisons, the survival duration for patients who underwent resection in this trial (31 months) and our previous Gem-XRT trial (34 months) is encouraging when viewed in the context of the survival durations reported in trials of postoperative adjuvant therapy (20 to 22 months).<sup>15,16</sup> Of note, the median survival of all 176 patients entered onto both trials (Gem-XRT, 22.7 months; Gem-Cis-XRT, 17.4 months) was longer than some may have anticipated; a comparison group in the literature to consist of all patients who underwent surgery first with anticipation of receiving postoperative adjuvant therapy (including those who did and did not receive intended therapy) is not available.

In conclusion, although preoperative chemoradiation as delivered in Gem-XRT resulted in a favorable survival duration, especially for patients who underwent PD, the addition of systemic therapy with gemcitabine and cisplatin delivered before gemcitabine-based chemoradiation did not result in a further improvement in survival. Nevertheless, the results from our preoperative gemcitabine-based chemoradiation trials are sufficiently compelling to justify broader investigation of neoadjuvant treatment for localized stage I/II pancreatic cancer. The current and future direction of our clinical trials includes incorporation of molecular targeted therapies in addition to chemotherapy and EBRT in the preoperative setting. Furthermore, recent data from our group suggest that these strategies may also be

applicable to patients defined as having borderline resectable pancreatic cancer.<sup>14</sup>

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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