

# Preoperative Chemotherapy, Radiotherapy, and Surgical Resection of Locally Advanced Pancreatic Cancer

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**Hypothesis:** Neoadjuvant therapy has the potential to induce regression of high-risk, locally advanced cancers and render them resectable. Preoperative chemoradiotherapy is proposed as a testable treatment concept for locally advanced pancreatic cancer.

**Design:** Fourteen patients (8 men, 6 women) with locally advanced pancreatic cancer were surgically explored to exclude distant spread of disease, to perform bypass of biliary and/or gastric obstruction, and to provide a jejunostomy feeding tube for long-term nutritional support. A course of chemotherapy with fluorouracil and cisplatin plus radiotherapy was then initiated. Reexploration and resection were planned subsequent to neoadjuvant therapy.

**Main Outcome Measures:** Tumor regression and survival.

**Interventions:** Surgically staged patients with locally advanced pancreatic cancer were treated by preoperative chemotherapy with bolus fluorouracil, 400 mg/m<sup>2</sup>, on days 1 through 3 and 28 through 30 accompanied by a 3-day infusion of cisplatin, 25 mg m<sup>2</sup>, on days 1 through 3 and 28 through 30 and concurrent radiotherapy, 45 Gy. Enteral nutritional support was maintained via jejunostomy tube.

**Results:** Of 14 patients who enrolled in the protocol and were initially surgically explored, 3 refused the second operation and 11 were reexplored; 2 showed progressive disease and were unresectable and 9 (81%) had definitive resection. Surgical pathologic stages of the resected patients were: Ib (2 patients), II (2 patients), and III (5 patients). Pancreatic resection included standard

Whipple resection in 1 patient, resection of body and neck in 1 patient, and extended resection in 6 patients (portal vein resection in 6, arterial resection in 4). One patient who was considered too frail for resection had core biopsies of the pancreatic head, node dissection, and an interstitial implant of the tumorous head. Pathologic response: 2 patients had apparent complete pathologic response; 1 patient had no residual cancer in the pancreatotomy specimen, the other patient who had an iridium 192 interstitial implant had normal core biopsies of the pancreatic head. Five patients had minimal residual cancer in the resected pancreas or microscopic foci only with extensive fibrosis, and 2 patients had fully viable residual cancer. Lymph node downstaging occurred in 2 of 4 patients who had positive peripancreatic nodes at the initial surgical staging. There was 1 postoperative death at 10 days. Sepsis, prolonged ileus, and failure to thrive were major complications. In the definitive surgery group the median survival was 19 months after beginning chemoradiotherapy and 16 months after definitive surgery. The absolute 5-year survival was 11% of 9 patients, 1 is surviving 96 months (with no evidence of disease) after chemoradiotherapy and extended pancreatic resection including resection of the superior mesenteric artery and the portal vein for stage III cancer. In the nonresected group the mean survival was 9 months (survival range, 7-12 months) after initiation of chemoradiotherapy.

**Conclusion:** A pilot study of preoperative chemoradiotherapy with infusional cisplatin and radiation induced a high rate of clinical pathologic response in patients with locally advanced pancreatic cancer and merits further study in these high-risk patients.

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**I**N RECENT YEARS there has been a strong emphasis on preoperative chemotherapy and radiotherapy for a variety of gastrointestinal cancers. In cancer of the pancreas, both Fox Chase and M. D. Anderson Cancer Centers' experiences suggest value in this form of therapy.<sup>1-6</sup> Although postoperative radiotherapy in com-

bination with subsequent sensitizing adjuvant fluorouracil was shown to be

*See Invited Critique  
at end of article*

associated with improved survival in a randomized trial by the Gastrointestinal Study

## PATIENTS, MATERIALS, AND METHODS

The pancreatic cancer protocol initiated in 1990 was directed toward enrolling patients with locally advanced pancreatic cancer that was potentially resectable. Patients had initial evaluation by computed tomographic and/or magnetic resonance imaging scans and endoscopic retrograde cholangiopancreatography. Patients considered candidates for the protocol subsequently were scheduled to be explored for staging and tissue diagnosis. At laparotomy, a serious effort was made to obtain histological documentation of pancreatic cancer either from the primary tumor or from adjacent lymph nodes. Also, an assessment was made of the tumor's size and its proximity to other organs and major vascular structures, eg, a portal vein. Dissection of the tumor was avoided to minimize adhesions with potential for increased radiation damage. A Roux-en-Y choledochojejunostomy and gastrojejunostomy were performed with minimal manipulation of the small bowel, and efforts were made to position the bowel loops away from the pancreatic radiation field. It was planned that at reexploration the surgeon would be able to theoretically "lift the pancreatic tumor out its bed" with minimal recon-

struction requirements. Thus, the previously prepared by-passed bile duct site and gastric site could be simply divided with the stapler, obviating the need for gastrointestinal reconstruction except for the pancreatic stump. In some cases, the pancreatic stump was only oversewn, rather than reanastomosed taking advantages of the known reduction of pancreatic secretion due to the effects of radiotherapy.<sup>9</sup> Placement of the jejunostomy tube for feeding and double lumen subcutaneous port and catheter for vascular access to administer chemotherapy were also performed.

The patients received radiotherapy augmented with sensitizing chemotherapy by bolus fluorouracil, 400 mg/m<sup>2</sup> for 3 days, accompanied by continuous 3-day infusion of cisplatin, 25 mg/m<sup>2</sup> per day, on days 1 through 3 during weeks 1 and 4 of the radiotherapy course which consisted of 45 Gy delivered via 4 fields to the pancreas in 180-Gy daily fractions. Restaging occurred approximately 1 to 2 weeks after the completion of chemoradiotherapy. The patients were scheduled for definitive resection unless there was progression of disease. During the treatment with chemoradiotherapy, patients were given jejunostomy feedings to maintain weight using a variety of commercially available supplements. Because it was anticipated that most patients entering the protocol would have an approximate 10% loss of body weight, an effort was made to retain the patient's weight during chemoradiotherapy.

Group,<sup>7-8</sup> there are many reasons to consider preoperative therapy for localized pancreatic adenocarcinoma. Theoretical advantages include increased vulnerability of cancer cells to therapy because of intact vasculature, better tumor cell oxygenation, and increased probability of sterilizing the cancer cells at the margin of resection prior to surgical manipulation. Conceptually, preoperative therapy is associated with better tissue tolerance to radiation therapy and decreased injury to the small bowel. In contrast, postoperative radiotherapy may increase tissue damage to the manipulated small bowel that becomes fixed in the radiation field due to adhesions. Preoperative therapy also provides an opportunity for short-term observation of the tumor's response to treatment in these very high-risk patients. Metastases can also be excluded that may not have been recognized early in the patient's course, but which may ultimately be manifest at the time of planned restaging prior to surgical resection. Thus, the risk of performing unnecessary radical resection on patients with metastases is reduced, and it is also thought that there are fewer pancreaticojejunostomy leaks due to the effects of postsurgical radiotherapy on the pancreas.<sup>9</sup>

Review of the Massachusetts General Hospital experience by Tepper et al<sup>10</sup> also suggests benefit from preoperative vs postoperative radiotherapy. Pilepich and Miller<sup>11</sup> and Kopelson<sup>12</sup> first reported treatment with preoperative radiotherapy alone in the early 1990s and had three 5-year survivors among 10 patients who underwent Whipple resection during a 9-year period. Ishikawa et al<sup>13</sup> gave preoperative radiation doses of 40 to 50 Gy using a 2-field technique in 2-Gy fractions. In an analysis of 23 patients, they demonstrated a resectability rate of 74% with a lower local recurrence rate in the

group that received preoperative radiotherapy compared with the patients undergoing surgery alone although there was no difference in 5-year survival rates of 22% and 26%, respectively.<sup>13</sup>

Combined chemotherapy and radiotherapy have been systematically used by the groups at Fox Chase Cancer Center, Philadelphia, Pa, and M. D. Anderson Cancer Center, Houston, Tex. The Fox Chase Cancer Center experience began as a pilot study<sup>14</sup> that was expanded into an Eastern Cooperative Oncology Group trial. It used 50.5-Gy irradiation in 1.8-Gy fractions through 3 × 4 fields in addition to chemotherapy with fluorouracil as a 96-hour infusion on days 2 through 5 and 29 through 32 along with mitomycin, 10 mg, on day 2.<sup>2</sup> In the Fox Chase Cancer Center experience, 6 of 26 patients had decreased tumor size in the radiation field, 30 patients had stable measurements, and 14 patients had minimal (25%-50%) reduction in the product of the greatest perpendicular diameters. There were 2 patients who had a partial response (>50% reduction in the product of the 2 diameters). The Fox Chase study showed a 40% 5-year projected survival rate with follow-up of 16 through 72 months in 11 patients after potentially curative resection. The median survival was 45 months. These results seemed to be durable as reviewed 2 years later.<sup>3</sup>

At M. D. Anderson Cancer Center, a total of 51 patients were treated on a protocol using radiotherapy, 45 to 50.4 Gy, and 1.8 Gy per fraction, with additional dosage of intraoperative radiotherapy at a dose of 10 to 20 Gy.<sup>4-6</sup> Continuous infusion fluorouracil, 300 mg/m<sup>2</sup> per day, 5 days a week was given during radiotherapy. Among the 30 patients resected, there was an 18-month median survival rate and only 3 (17%) of 18 recurring patients had local recurrence as the first site of recurrent disease.

**Table 1. Preoperative Chemoradiation for Carcinoma of the Pancreas: A Phase II Study\***

	No. of Patients
Definitive resection	9
Stage	
Ia T1N0M0	1
Ib T2N0M0	1
II T3N0M0	2
III T2N1M0	2
T3N1M0	3
Not resected	5†
Explored surgically (disease progressed)	2
Refused surgery	3

\*A total of 14 patients were enrolled in the protocol (8 men; 6 women) with an average age of 62 years (age range, 42-76 years).  
†Two patients were stage II; 3, stage III.

**Table 2. Extent of Pancreatic Resection**

Procedure	No. of Patients
Standard Whipple resection only	1
Subtotal pancreatectomy	1
Interstitial implant*	1
Extended Whipple resection	6
Vascular resection	6
Portal vein resection	6
Major arterial resection†	4
Other organ resection (colon)	2

\*Consisted of an iridium 192 interstitial implant in the head of the pancreas only plus lymph node dissection.

†Consisted of 1 superior mesenteric artery reconstructed by saphenous vein graft to the iliac artery, 1 common hepatic artery reconstructed by saphenous vein graft, 1 resection of a portion of the celiac axis including the origin of the left hepatic artery, and 1 resection of a portion of the celiac artery axis including the splenic artery.

This is in contrast with postoperative therapy results published by the Gastrointestinal Tumor Study Group in which the local recurrence rate was 43%.<sup>7,8</sup> A more recent update of the M. D. Anderson Cancer Center experience compared outcomes in patients treated by preoperative chemoradiotherapy vs postoperative therapy.<sup>15</sup> No difference was noted in the overall survival, but there were differences by the pattern of recurrence between 41 patients given preoperative chemoradiotherapy (local/regional recurrence, 10%) vs 19 patients given postoperative chemoradiotherapy (local/regional recurrence, 21%).

In early 1990, we initiated a preoperative treatment protocol for patients with locally advanced pancreatic cancer. This consisted of preoperative radiotherapy, 45 Gy, combined with bolus injections of fluorouracil, 400 mg/m<sup>2</sup>, for days 1 through 3 and 28 through 30, accompanied by a 3-day infusion of cisplatin, 25 mg/m<sup>2</sup>, on days 1 through 3 and 28 through 30.<sup>16</sup> Patients were all surgically explored prior to initiation of preoperative therapy to stage the disease. Gastrointestinal and biliary bypass were performed along with placement of a jejunostomy feeding tube to permit adequate nutrition during the period of chemoradiotherapy. Patients were restaged 1 to 2 weeks after completion of therapy with plans to reexplore and resect.

## RESULTS

### PATIENT CLINICAL MATERIAL

Fourteen patients (8 men and 6 women) were enrolled in the protocol between March 1990 and February 1992 (**Table 1**). Their average age was 62 years (age range, 42-76 years). Of 11 patients who completed the preoperative therapy and were surgically explored, 9 (81%) had definitive surgery. Three of the patients who completed the chemoradiotherapy protocol refused the second surgical exploration. Of the patients who initiated the protocol, but did not have definitive surgery, 3 were considered to have locally advanced disease (stage III) with tumor abutting a portal vein and 2 had bulky stage II disease. **Table 2** gives the extent of pancreatic resection

for the 9 patients who completed the protocol and were subjected to surgical treatment.

Of the 6 patients who underwent extended Whipple resection plus regional node dissection, portal vein resection was performed in all of them and major arterial resection was done in 4 (**Table 2**). All 9 patients had an extended lymph node dissection of portahepatis nodes, as well as the peripancreatic and paraduodenal nodes, and dissection of the uncinate process and complete clean out of the aortocaval nodes behind the pancreas. The lymph node dissection included the celiac axis nodes, those along the hepatic artery and the splenic artery with dissection of the takeoff of the right gastric artery. The portal vein was reconstructed by reapproximating the cut-ends of the portal vein in 3 patients and replacement grafts with the larger portion of the saphenous vein in 3 patients. The resected superior mesenteric artery was reconstructed using a saphenous vein graft to the iliac artery and a resected common hepatic artery was also reconstructed using the saphenous vein.

Complications are listed in **Table 3**. Sepsis was a frequent problem after resection. One patient who had splenic artery resection developed splenic infarct requiring splenectomy and subsequently developed sepsis. Two other patients also had postoperative sepsis. One patient developed a small-bowel infarct requiring surgical exploration and resection of the small bowel. One patient required reoperation for prolonged ileus and had a markedly dilated bowel that poorly tolerated tube feedings, thus resulting in poor maintenance of nutrition that required additional support with total parenteral nutrition. One patient required reoperation for gastric outlet obstruction. The mean stay in the intensive care unit was 6.8 days (range, 1-18 days). The mean length of stay in the hospital was 20 days (range, 14-40 days).

There was 1 postoperative death on day 10 that occurred in a relatively healthy 49-year-old man. This patient had been initially surgically explored in a nearby hospital and was found to have tumor that encased the pancreas and the portal vein as well as biopsy-proven peripancreatic nodal metastases. He was subsequently reexplored after chemoradiotherapy and had an extended total pancreatectomy. The hepatic artery was narrowed and

**Table 3. Surgical Complications in Resected Patients**

Complication*	No. of Patients
Gastrointestinal	
Prolonged ileus	5
Gastric outlet obstruction (required exploration)	1
Small-bowel	
Obstruction (surgically explored)	2
Perforation (resected)	1
Splenic infarct	1
Pseudocyst formation	1
Infections	
Sepsis (bacteremia)	5
Intra-abdominal abscess/collection (required drainage)	4
Diarrhea ( <i>Clostridium difficile</i> )	4
Renal	
Renal insufficiency (temporary)	3
Hepatic insufficiency and hyperbilirubinemia	3
Pulmonary	
Insufficiency (pneumonia, ARDS)	4
Prolonged intubation >3 d or required reintubation	6
Death	
Postoperative death due to multisystem failure after extended resection of portal vein/common hepatic artery	1
Hospitalization	
ICU, d, mean (range)	6.8 (1-18)
Length of stay, d, mean (range)	20 (14-40)

\*ARDS indicates acute respiratory distress syndrome; ICU, intensive care unit.

encased by the pancreatic mass. Because of the artery's small size, its contribution to the liver was underappreciated and its reconstruction was delayed until the end of the procedure. The initial reconstruction was complicated by thrombosis of the hepatic artery. This was recognized by subsequent acidosis requiring reexploration and reconstruction of the hepatic artery. Postoperatively, the patient developed signs of liver failure and then progressed to develop multisystem failure and death. Autopsy showed multiple sites of necrosis of the liver as a major cause of death. There were only microscopic foci of residual cancer in the resected specimen, and all the nodes removed at surgery (and at autopsy) were negative despite demonstration of biopsy-proven peripancreatic nodal metastases at the first operation.

#### CLINICAL PATHOLOGIC RESPONSE TO PREOPERATIVE THERAPY

Clinical pathologic findings are given in **Table 4** and **Table 5**. Our pathological review attempted to determine the extent of residual cancer in the specimen and to categorize these as moderate to extensive disease (essentially no change) vs minimal disease, either microscopic foci or minimal scattered foci of pancreatic cancer, or no demonstrable pancreatic cancer. All primary margins, including the margin at the vascular resected sites and in the uncinate process area, were examined. The presence of nodes in the specimen were noted and an effort was made to determine the extent of fibrosis, atrophy, or necrosis in remaining pancreatic (or tumor) tissue.

Two patients had persistence of viable tumor in the pancreatic specimen apparently unchanged by the therapy (Table 4). There were 5 patients who had minimal disease, ie, either microscopic foci or minimal scattering of residual cancer cells, with some cases associated with dead cells or fibrous tissue. One pathology specimen was considered unevaluable. Two patients had no residual cancer in the examined specimen. One of these was a 62-year-old, 36.6-kg woman who had extensive weight loss and initially refused surgery. She had a large pancreatic mass (5 x 6 cm), but at reexploration it was reduced to a clearly defined 3- or 4-cm fibrotic mass in the head of the pancreas. Because of her small size (36.6 kg) and nutritional impairment, we elected to do 3 core biopsies of the fibrotic mass, lymph node dissection, and an iridium 192 interstitial implant (rather than resection). All 3 core biopsy specimens showed fibrosis only and no cancer cells. Radiation implant catheters were placed into the pancreas and she was treated postoperatively with iridium 192 using an afterloading technique. This patient tolerated the procedure well, surviving some 19 months after her chemoradiotherapy and 15 months after the surgery, finally dying of metastases. The other patient without residual disease had an extended Whipple resection with portal vein resection, and had dense fibrosis with no residual cancer in the specimen. He subsequently developed metastases and died 16 months later.

Pancreatic margins were negative for disease in all 9 patients. Three patients required completion of total pancreatectomy because of concern on examination of the frozen section regarding the adequacy of the pancreatic margin at the distal line of resection. Vascular invasion was demonstrated in the resected portal vein in 2 patients. In 1 patient there was disease within 0.5 mm of the portal vein (at resection it was invading the portal vein). The other patient had clinical extension into the portal vein at surgery and had gross and microscopic invasion of the resected portal vein. One of the 4 patients who underwent arterial resection had demonstrated invasion into the adventitia of the splenic artery near its junction with the celiac artery and 1 patient did have invasion of celiac artery plexus tissue. Lymph node metastases had been demonstrated overall in 4 patients. At the initial operative staging 2 patients had demonstrated nodal metastases by biopsy. At resection 2 patients had lymph nodes involved by metastases and the 2 patients who had demonstrated nodal metastases at initial biopsy were shown to be negative after chemoradiotherapy and resection.

Although radiologic imaging was unsatisfactory in demonstrating the effect of preoperative therapy, the combined surgical pathologic findings were helpful in assessing antitumor effects of chemoradiotherapy (Table 4). Of 11 patients who were reexplored after chemoradiotherapy, 2 had progression and were unresectable. There were 4 patients with very large cancers, apparently invading the portal vein and other vascular structures, which were classically thought to be unresectable. These did respond to therapy and became resectable, albeit requiring extended resection and, generally, portal vein resection. Two other patients with large tumors also had documented peripancreatic macroscopic and microscopic nodal

**Table 4. Clinical Pathologic Review of Resected Patients\***

Cancer Stage	No. of Patient	Residual Cancer in Resected Specimen			Associated Findings		
		Moderate to Extensive Viable Cancer	Minimal Microscopic Foci Only	No Cancer Found	Pancreatic Margin +/-	Vascular Invasion	(LN) +/-
T1N0M0	1		NA		-	NA	(5) -
T2N1M0	2	+			-	-	(8) -†
T3N1M0	3‡			+	-	NA	(3) -
T3N0M0	4			+	-	-	(6) -
T3N1M0	5		+		-	PV	(2/5) +
T2N1M0	6		+		-	-	(3) -
T3N0M0	7		+		+ → -§	PV	(5) -
T3N1M0	8		+		+ → -§	PV	(11) -†
T3N1M0	9	+	+		+ → -§	SA/PV	(4/18) -†
<b>Total</b>	<b>9</b>	<b>2</b>	<b>5</b>	<b>2</b>	<b>9-</b>	<b>4+/3-</b>	<b>2+/7-</b>

\*LN indicates the number of lymph nodes involved; NA, not evaluable; - sign, negative or normal; + sign, positive or abnormal; PV, portal vein; and SA, splenic artery.

†Indicates nodal metastases were demonstrated at the initial staging laparotomy.

‡Patient underwent an iridium 192 interstitial implant in the head of the pancreas only plus lymph node dissection. Three core biopsies were performed on the fibrotic mass.

§Patient required completion of a total pancreatectomy to obtain negative margin.

**Table 5. Clinical Pathologic Response Determined at Reexploration in 11 Patients\***

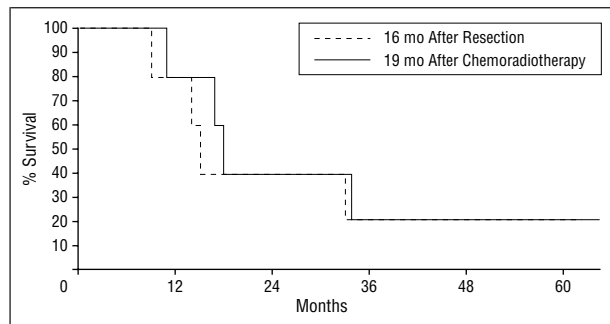
Tumor Extent at Initial Staging Laparotomy Prior to Therapy						
Potentially Resectable by Conventional Whipple Resection						
No. of Patients	Cancer Stage	Tumor Extent (Organ Invasion)	Resectable	Tumor Extent at Second Operation After Chemoradiotherapy or Radiotherapy		
2	T3N?	Large mass (PV)	Unknown	Disease progressed/not resectable		
	T3N?	Large mass (PV)	Unknown			
3	T3N?	Pancreatic head mass	Yes	Clinically resectable/refused 2nd surgery		
	T3N?	Large mass (?PV)	Unknown			
	T3N?	Pancreatic head mass	Yes	Clinically resectable/refused 2nd surgery		
3	T3N?	Pancreatic head	Yes			
	T2N1	Pancreatic head	Yes	Reduced tumor size/resect clear margin		
	T2N?	Body-neck tumor	Yes			
				No evaluable effect/resectable clear margin		
Not Resectable by Conventional Whipple Resection at Initial Laparotomy						
No. of Patients	Cancer Stage	Tumor Extent (Organ Invasion)	Vascular Resection	Pathologic Invasion	Node Status	
Large mass and vascular extension						
4	T3N1	Pancreatic head/neck + celiac, PV	LHA, PV	PV+	2/5+	
	T3N0	Pancreatic head/duodenal + SMA, PV	SMA/PV	SMA- PV+	-	
	T3N0	Pancreatic head + PV	PV	PV-	-	
	T3N1	Pancreatic head + celiac, PV	SA, PV	CA- SA+, PV+	4/18+	
Large mass + vascular extension + LN metastasis						
2	T3N1	Tumor encased PV + LN metastasis	CHA + PV	PV+	LN-	
	T3N1	Tumor 9 × 5-cm celiac node+	PV	PV-	LN-	

\*Resectable status indicates unknown without dissection; PV, portal vein; RND, regional node dissection; CHA, common hepatic artery; LHA, left hepatic artery; SMA, superior mesenteric artery; SA, splenic artery; CA, celiac artery; and LN, lymph node.

metastases at initial exploration (peripancreatic and celiac nodes, respectively). These are generally considered high-risk signs precluding resection. Both patients responded to chemoradiotherapy and were node negative at resection. Of 2 patients who were considered resectable prior to preoperative therapy, both had substantial regression following preoperative therapy. One patient with a cancer of the body and tail of the pancreas was not considered evaluable for determining a response.

**LONG-TERM OUTCOME**

Of the 5 patients who were not resected, survival ranged from 7 to 12 months (mean survival, 9 months) (Figure). Of the 9 resected patients, the median survival after chemoradiotherapy was 19 months and after resection it was 16 months (Figure). There was 1 long-term survivor (patient 7, Table 4), who is alive without disease 96 months past chemoradiotherapy. He had locally exten-



Disease-specific survival of patients receiving preoperative chemoradiotherapy for carcinoma of the pancreas. Boston University School of Medicine-Roger Williams Hospital study.<sup>25</sup>

sive cancer which invaded the superior mesenteric artery and the portal vein, but had demonstrated a dramatic response to preoperative therapy. He required a near total pancreatectomy with resection of the superior mesenteric artery and portal vein because of adherence of the pancreatic mass. The margins and nodes were negative for disease. Microscopic disease was noted near the portal vein with no direct invasion. In another patient who had survived 36 months after an extended pancreatic resection including a portion of the celiac axis and portal vein, reexploration at 24 months showed intra-abdominal metastases including an omental implant that appeared to be in the radiation field. These were locally resected. The patient was subsequently treated with continuous infusion of fluorouracil, 250 to 300 mg/m<sup>2</sup> per day, and cisplatin, 100 mg/m<sup>2</sup>, every 4 weeks and survived 12 months before dying of metastases 36 months after initiation of chemoradiotherapy and 34 months after undergoing resection.

There were 3 patients dead of other causes, but apparently free of cancer. One patient who was functionally normally after resection of a body of pancreas developed confusion and was readmitted to the hospital with unrecognized sepsis from which she finally died (post-mortem examination showed intra-abdominal sepsis but no residual cancer). Another patient was also readmitted to a medical service because of failure to thrive and was found to have sepsis, but was never reexplored. Post-mortem examination showed intra-abdominal sepsis, but no tumor. One patient, despite an initial favorable postoperative course, developed brittle diabetes, malnutrition, generalized failure to thrive, chronic cholangitis, and unremitting ileus. Having a poor response to enteral nutrition requiring home total parenteral nutrition, the patient was readmitted to the hospital and subsequently died.

#### COMMENT

This small pilot study describes the outcomes of preoperative chemoradiotherapy in 14 surgically staged patients with biopsy-proven, locally advanced cancer of the pancreas, of whom 11 were surgically reexplored, 3 refused further surgery. Two patients showed progression and 9 (82%) of 11 were able to have definitive surgery (resection in 8 and an iridium 192 interstitial implant in 1). Radiologic imaging with computed tomographic and magnetic resonance imaging scans did not clearly show any meaningful tumor responses, nor did it demonstrate intra-

abdominal metastases in the 2 patients who were found to have disease progression at reexploration. Although the initial plan was to be able to do a limited operative procedure (lift the tumor out of the irradiated site), this turned out to be infeasible. In most patients an extended resection was necessary, in part, to define vital structure involvement more safely. A standard Whipple resection was feasible in 1 patient, a total pancreatectomy in 1 patient, and a radiation implant of pancreatic head plus node dissection was done in 1 fragile patient. Six patients required portal vein resection. Four had a major arterial resection included the superior mesenteric artery in 1 patient, the common hepatic artery in 1 patient, a portion of the celiac axis including left hepatic artery in 1 patient, and the splenic artery alone in 1 patient. There was 1 postoperative death of a patient at 10 days after an extended hepatic artery resection that was complicated by thrombosis of the reconstructed hepatic artery, probably secondary to technical difficulties and delay in corrective reconstruction.

Although the radiological response to preoperative therapy was inconclusive in these patients, the clinical pathologic response was clearly present. No tumor was identified in 2 patients. There were 5 patients in whom only minimal cancer was left, ie, microscopic foci, and there were 2 patients in whom residual cancer with viable cells was still present.

None of the 9 patients had margins of the resected tumor specimen involved by cancer. This would appear to be related to the effect of chemoradiotherapy, but may also be related to the wide field resections adopted (necessitating vascular resection in 6 patients). Three patients required additional resection of the pancreatic stump because of frozen section evidence of margin involvement by tumor. Of these, one patient had a tumor within 0.5 mm of the resected portal vein, and another patient had extensive involvement of the splenic artery at its origin in the celiac artery and the wall of the portal vein, although no intraluminal tumor was described. One patient had a tumor within the plexis of the celiac artery and 1 patient had a tumor near the adventitia of the splenic artery. The remaining patients did not have documentation of vascular invasion into major vascular structures. In addition, 2 of 4 patients with demonstrated nodal metastases at initial staging laparotomy had nodal downstaging and negative nodal pathology at resection.

In the Fox Chase Cancer Center study, 2 pathologists reviewed the specimens after resection. A grading system was established that used 5 perpendicular sections of resected tumor to measure the percentage of malignant cells, fibrosis, necrosis, and other parameters within the area of the tumor as recorded on slides. The percentages were averaged for all slides taken through the tumor. There were 4 of 28 Fox Chase Cancer Center patients who had more than 90% histological reduction of cancer cells, 9 had 75% to 89% reduction, and 7 had 50% to 74% reduction. None had a complete pathologic response. In their cases with the best response, neoplastic cells were present individually, or in small groups, in infiltrating desmoplastic stroma showing severe effects of chemoradiotherapy. In the M. D. Anderson Cancer Center experience similar results were observed including 4 of 17 patients noted to have more than 90% cancer cell

destruction.<sup>5</sup> Ishikawa et al,<sup>17</sup> using a somewhat different grading system, demonstrated histological responses in 10 of 13 specimens examined.

Another study, similar in design, by Jessup et al<sup>18</sup> described 23 patients of whom 4 had resectable tumors, but the true antitumor response is unclear. Although there was 1 long-term survivor of longer than 68 months after resection, the median survival of the group was limited, 18 months after chemoradiotherapy and 13 months after resection. This is much less than that reported by either the Fox Chase or the M. D. Anderson Cancer Center groups. In part, this may reflect differences in patient selection.

A variety of new investigational efforts have been used in advanced cancer of the pancreas.<sup>19</sup> Of 32 trials reviewed using 25 drugs or drug combinations, only 3 treatment programs had an estimated 10% clinical response rate. Combined therapy with fluorouracil and N-phosphonoacetyl-L-aspartic acid produced a response rate of 14% (median survival, 5.1 months).<sup>20</sup> Iproplatin, produced a response rate of 9.4%, but no median survival rate was given.<sup>21</sup> Gemcitabine hydrochloride, an investigational new agent, was associated with a response rate of 11.4% (and a median survival of 5.6 months).<sup>22</sup> In previously untreated patients, gemcitabine proved to be superior to fluorouracil in terms of clinical benefit response rate (23.8% vs 4.8%) and in median survival 5.56 vs 4.4 months, respectively,  $P = .002$ .<sup>23</sup> In a companion study of patients who had developed tumor progression while receiving fluorouracil, 27% showed "clinical benefit" responses while receiving gemcitabine.<sup>24</sup> These 2 studies provided the basis for the Food and Drug Administration, Washington, DC, to approve gemcitabine for the treatment of patients with advanced pancreatic cancer. The use of gemcitabine in the preoperative therapy would appear to be warranted.

In the Brown Oncology Group, Safran et al<sup>25</sup> have demonstrated a high response rate (31%) in patients with advanced cancers of the pancreas and gastric cancer using paclitaxel (Taxol) plus radiotherapy. We have adapted this to a neoadjuvant protocol for locally advanced pancreatic cancer. The next study will emphasize patient selection using rigorous staging with computed tomographic scanning and laparoscopy along with bypass by biliary endoscopic stenting (and with laparoscopic gastrointestinal bypasses, if needed). The chemoradiotherapy includes paclitaxel 50 mg/m<sup>2</sup> per week for 6 weeks, plus 50 Gy of irradiation over 5 weeks. Patients will then be reexplored for resection.

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**A** prospective uncontrolled study on preoperative chemoradiotherapy in patients with locally advanced pancreatic cancer is presented. The neoadjuvant therapeutic regimen consisted of fluorouracil, 400 mg/m<sup>2</sup>, and cisplatin, 25 mg/m<sup>2</sup>, along with concurrent radiation of 45 Gy. Patients were surgically staged prior to the neoadjuvant regimen and had biliary along with gastric bypass as well as a feeding jejunostomy tube placed. Of 14 patients, 11 underwent reexploration. Two of these 11 patients had progressive disease that was unresectable; 9 had definitive resections, 6 of whom had either portal vein or major arterial resections. There was 1 hospital death and 1 long-term survivor (>96 months). Median survival was 16 months after definitive surgery.

Although this study represents another valuable effort to improve the prognosis of patients with pancreatic cancer, even after potentially curative resection, a number of concerns remain. It is stated that only patients with locally advanced pancreatic cancer that was potentially resectable were included. Of 14 patients undergoing the neoadjuvant protocol, 3 refused a second surgical procedure. Of the 11 patients who had reexploration, 2 had metastatic disease. One patient did not have resection but only radiation implant. Of the 8 patients undergoing potentially curative resection, only 1 had a standard Whipple procedure, 6 had an extended resection requiring portal vein and/or major arterial resection and reconstruction, and 1 had a subtotal pancreatectomy. The combination of neoadjuvant treatment with aggressive surgery produced an extensive number of complications. Five of the 8 patients who underwent resection developed sepsis or intra-abdominal abscesses. Two patients had small-bowel obstruction, 1 had small-bowel perforation, 1 had splenic infarct, and 1 had pseudocyst formation. Pulmonary insufficiency and acute respiratory distress syndrome occurred in 4 patients, and renal and hepatic insufficiency occurred in 3 patients each. One patient died at day 10, and 3 patients died of other causes than cancer. Two of these 3 patients died from intra-abdominal sepsis. A possible connection to the neoadjuvant therapy and/or the aggressive surgery is very likely. The third patient developed chronic cholangitis and unremitting ileus and died. In context with the previous surgery and preoperative chemoradiotherapy, a causal relationship cannot be excluded. But it must be emphasized that there was no proof of cancer in postmortem examinations. The 16-month median survival after resectional therapy is not better than that of other series without preoperative chemoradiotherapy.

Despite the points of criticism, it seems noteworthy to realize that from 8 resected patients, 6 seem to have responded histologically to the neoadjuvant treatment. This observation clearly needs attention. However, overall this fact does not seem to significantly alter survival and carried the price of extensive morbidity. The benefit of the proposed strategy remains in doubt, but it is a step in the right direction of trials of neoadjuvant therapy in pancreatic cancer.

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## IN OTHER AMA JOURNALS

### ARCHIVES OF INTERNAL MEDICINE

#### Lying for Patients: Physician Deception of Third-Party Payers

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**Background:** Some physicians may resort to deception to secure third-party payer approval for patient procedures. Related physician attitudes, including willingness to use deception, are not well understood.

**Objective:** To determine physician willingness to deceive a third-party payer and physician attitudes toward deception of third-party payers.

**Methods:** A cross-sectional mailed survey was used to evaluate physician willingness to use deception in 6 vignettes of varying clinical severity: coronary bypass surgery, arterial revascularization, intravenous pain medication and nutrition, screening mammography, emergent psychiatric referral, and cosmetic rhinoplasty. We evaluated 169 board-certified internists randomly selected from 4 high- and 4 low-managed care penetration metropolitan markets nationwide for willingness to use deception in each vignette.

**Results:** Physicians were willing to use deception in the coronary bypass surgery (57.7%), arterial revascularization (56.2%), intravenous pain medication and nutrition (47.5%), screening mammography (34.8%), and emergent psychiatric referral (32.1%) vignettes. There was little willingness to use deception for cosmetic rhinoplasty (2.5%). Rates were highest for physicians practicing in predominantly managed care markets, for clinically severe vignettes, and for physicians spending less time in clinical practice. Physician ratings of the justifiability of deception varied by perspective and vignette.

**Conclusions:** Many physicians sanction the use of deception to secure third-party payers' approval of medically indicated care. Such deception may reflect a tension between the traditional ethic of patient advocacy and the new ethic of cost control that restricts patient and physician choice in the use of limited resources. (1999;159:2263-2270)

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