Neoadjuvant Strategies for Pancreatic Cancer

Recent prospective and retrospective data suggest that the use of multimodality therapy combining pancreaticoduodenectomy with postoperative adjuvant chemotherapy (fluorouracil) and external-beam radiation improves survival and locoregional tumor control.

Introduction

Pancreatic cancer is the fifth leading cause of cancer-related death for both US men and women and is responsible for 5% of all cancer-related deaths. In 2001, adenocarcinoma of the exocrine pancreas will account for approximately 28,900 deaths in the United States. Because it is usually difficult to diagnose pancreatic cancer while it is still localized and surgically resectable, incidence rates are virtually equal to mortality rates.

Exocrine pancreatic cancer is characterized by infiltration of surrounding blood vessels and perineural tissues, spread to regional lymph nodes, and early vascular dissemination. Most patients present with subclinical liver metastases at the time of diagnosis, even when findings from imaging studies are normal. Thus, disease recurrence following a potentially curative pancreaticoduodenectomy remains common.

Among patients treated with surgery alone, local recurrence develops in up to 80%, peritoneal recurrence in 25%, and liver metastases in 50% of patients. When surgery and chemoradiation are used to maximize locoregional tumor control, liver metastases become the predominant form of tumor recurrence.

Advantages of Multimodality Therapy

Recent prospective and retrospective data suggest that compared with surgery alone, the combination of pancreaticoduodenectomy with postoperative adjuvant fluorouracil (5-FU) and external-beam radiation therapy (EBRT) improves survival and locoregional tumor control. However, the morbidity and often prolonged recovery time associated with pancreaticoduodenectomy prevent the timely delivery of postoperative chemoradiation (chemotherapy and EBRT) in at least 25% to 30% of eligible patients. This risk of delaying postoperative adjuvant chemoradiation prompted investigators to assess the efficacy of administering chemoradiation before pancreaticoduodenectomy in patients with potentially resectable adenocarcinoma of the pancreas.

Several considerations support the preoperative use of chemoradiation. First, positive gross or microscopic margins of resection along the right lateral border of the superior mesenteric artery are common following pancreaticoduodenectomy, suggesting that surgery alone may be an inadequate strategy for local tumor control. Second, because chemoradiation is administered before surgery, delayed postoperative recovery does not affect the delivery of multimodality therapy. Third, patients with disseminated disease evident on restaging studies after chemoradiation are not subjected to an unnecessary laparotomy, since surgery would not benefit these individuals. Fourth, recent data suggest that preoperative chemoradiation may decrease the incidence of pancreaticojejunal anastomotic fistula, the most common complication following pancreaticoduodenectomy.

Inconsistent definitions of resectability, variations in surgical technique (often resulting in positive retroperitoneal margins), and the absence of a uniform system for gross and microscopic evaluation of pancreaticoduodenectomy specimens have made much of the available data on the use of multimodality therapy for localized pancreatic cancer impossible to interpret. Thus, standardized approaches to patient selection (pretreatment staging), operative technique, and pathologic...
evaluation of surgical specimens must be incorporated into clinical trials that are evaluating preoperative or postoperative adjuvant therapy.

This article briefly outlines our system for standardizing these important variables, which are critical to ensuring accurate data in clinical trials, and reviews current and future neoadjuvant chemoradiation strategies for patients with localized adenocarcinoma of the pancreas.

Pretreatment Radiographic Staging

At our institution, high-quality contrast-enhanced helical computed tomography (CT) scanning can accurately assess the relationship of the tumor to the superior mesenteric vessels and the celiac axis. To identify potentially resectable disease (Figure 1), we use the following CT criteria[11]: (1) the absence of extrapancreatic disease; (2) no evidence of direct tumor extension to the superior mesenteric artery or celiac axis, as defined by the presence of a fat plane between the low-density tumor and these arterial structures; and (3) a patent superior mesenteric-portal vein confluence.

The third criterion is based on the assumption that resection and reconstruction of the superior mesenteric vein or superior mesenteric-portal vein confluence are possible. In the absence of extrapancreatic disease, the main goal of preoperative imaging studies is to determine the relationship of the low-density tumor mass to the superior mesenteric artery and celiac axis. This information enables accurate prediction of the likelihood of obtaining a negative retroperitoneal margin of resection. The retroperitoneal margin, also termed the mesenteric margin, corresponds to the tissue along the proximal 3 to 4 cm of the superior mesenteric artery wall (Figure 2).

Data from our institution have confirmed the reliability of these CT criteria in a consecutive series of patients with adenocarcinoma of the pancreatic head or uncinate process who underwent laparotomy for planned pancreaticoduodenectomy.[8] We reported a resectability rate of 80% (94 of 118 patients) and a low (17%) rate of positive microscopic retroperitoneal margins. The accuracy of such CT criteria for predicting unresectability is well established.[2]

Surgical Technique

We have previously reported the six-step operative technique of pancreaticoduodenectomy currently performed at our institution.[12] The most important and difficult part of this operation is step 6, during which the pancreas is divided and the specimen is removed from the superior mesenteric-portal vein confluence and the right lateral border of the superior mesenteric artery. Only after full medial mobilization of the superior mesenteric-portal vein is it possible to identify the superior mesenteric artery (lateral to the venous structure). The pancreatic head and all soft tissue to the right of the superior mesenteric artery are then removed by direct ligation of the inferior pancreaticoduodenal artery or arteries. Failure to mobilize the superior mesenteric-portal vein may result in a positive resection margin due to incomplete removal of the uncinate process and the mesenteric soft tissue adjacent to the superior mesenteric artery.

Pathologic Assessment of Surgical Specimens

Both the evaluation of innovative preoperative treatment strategies and the development of reproducible prognostic predictors of patient survival and treatment failure depend on accurate pathologic assessment of surgical specimens. Retrospective pathologic analysis of archival material does not allow accurate assessment of the margins of resection or the number of lymph nodes retrieved. Pathologic evaluation of the pancreaticoduodenectomy specimen includes frozen-section evaluation of the common bile duct transection margin and the pancreatic transection margin.[13] Either transection margin, if positive, is treated with re-resection.

The retroperitoneal or mesenteric margin is defined as the soft tissue directly adjacent to the proximal 3 to 4 cm of the superior mesenteric artery wall. This margin is evaluated by permanent-section microscopic examination and is identified and inked by the surgeon and pathologist (Figure 3). Re-resection to treat a microscopically positive margin is not possible in the
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retroperitoneum, where the aorta and superior mesenteric artery origin limit the extent of surgical resection; therefore, frozen-section evaluation of this margin is not performed. Importantly, this margin cannot be evaluated retrospectively after gross evaluation of the specimen has been completed. Samples of multiple areas of each tumor, including the interface between the tumor and the adjacent uninvolved tissue, are submitted for paraffin-embedded histologic examination (5 to 10 blocks).

The final pathologic evaluation of permanent sections includes a description of tumor histology and differentiation, gross and microscopic evaluation of the tissue of origin (pancreas, bile duct, ampulla of Vater, or duodenum), an assessment of maximal transverse tumor diameter, and a report of lymph node status. Metastatic disease in regional lymph nodes, poorly differentiated histology, and increased size of the primary tumor have been identified as prognostic indicators for poor survival.[14-16] In patients who receive preoperative chemoradiation, the grade of treatment effect is assessed on permanent sections (Table 2).[17]

The continued success of translational research programs requires that an active pancreatic tumor banking program be maintained. Pathologists should routinely bank tumors for collaborative research efforts. Only through the coordinated efforts of such interdisciplinary programs will new treatments advance from the laboratory to clinical practice. At our institution, small sections of normal pancreas (when possible) and tumor are collected immediately for RNA extraction and additional samples are snap-frozen in liquid nitrogen and stored at 80°C. A representative section of tumor and normal tissue is routinely preserved in 70% ethyl alcohol for paraffin block processing, and a hematoxylin-eosin-stained slide is made.

**Issues Unique to the Delivery of Preoperative Chemoradiation for Pancreatic Cancer**

**Pretreatment Biopsy of the Primary Tumor**

Prior to initiating treatment with systemic therapy or EBRT, confirmation of malignancy is required for all patients with metastatic disease. Tissue confirmation of adenocarcinoma can usually be easily obtained in such patients by biopsy of metastatic sites (ultrasound-guided liver biopsy, paracentesis, etc). In patients thought to have localized, unresectable pancreatic cancer (as assessed by CT images), a CT-guided fine-needle aspiration (FNA) biopsy is commonly performed. In patients thought to have potentially resectable pancreatic or periampullary cancer, a preoperative biopsy is not required if a pancreaticoduodenectomy (and postoperative adjuvant therapy) is planned.

Because a negative biopsy in the appropriate clinical setting is usually due to sampling error, most experienced pancreatic surgeons believe that a preoperative or intraoperative pancreatic biopsy is unnecessary and should not influence the decision to proceed with pancreaticoduodenectomy.[18-19] However, in at least 5% to 10% of patients who undergo pancreaticoduodenectomy (without a preoperative pathologic diagnosis) for a presumed pancreatic or periampullary adenocarcinoma, final pathologic review of the resected specimen reveals benign disease (focal pancreatitis) or another histologic diagnosis.[20,21] Therefore, it is generally accepted that preoperative chemoradiation (prior to planned pancreaticoduodenectomy) should only be administered upon cytologic confirmation of malignancy.

Although the risk of a life-threatening toxic event secondary to chemoradiation is low, care should be taken to avoid subjecting patients unnecessarily to the toxicity of induction chemoradiation. Further, as our chemoradiation programs become more effective, the possibility of more frequent complete histologic response to induction therapy would make pretreatment biopsy essential. The growing popularity of neoadjuvant therapy is due in part to the ability to safely obtain a tissue diagnosis of cancer in patients with small resectable tumors.

Endoscopic ultrasound-guided FNA is currently the preferred method at most centers for obtaining a cytologic diagnosis of malignancy. Recent reports of endoscopic ultrasound-guided FNA of the pancreas have demonstrated the accuracy and safety of the procedure.[22,23] When FNA specimens are interpreted by an experienced cytopathologist, false-positive results should not occur, and false-negative results are becoming less frequent as physician experience increases.
**Biliary Obstruction During Preoperative Chemoradiation**

The majority of patients with adenocarcinoma of the pancreatic head have obstruction of the intrapancreatic portion of the common bile duct (biliary obstruction) at the time of diagnosis. The delivery of chemoradiation before pancreaticoduodenectomy delays the surgery and, therefore, requires that patients with biliary obstruction receive some form of nonoperative biliary decompression. This is usually achieved with an endoscopically placed polyethylene stent. Previous investigators have suggested that prosthetic biliary drains may increase the risk of chemoradiation-related morbidity and subsequent operative morbidity and mortality.[24,25]

**Stent-Related Complications:** In a recently published study by the Eastern Cooperative Oncology Group (ECOG), stent-related recurrent biliary obstruction with cholangitis was believed to be the cause of 38% of the hospital admissions for treatment-related complications prior to pancreaticoduodenectomy.[24] This experience prompted a review of the risk of stent-related morbidity at our institution in a cohort of 154 patients treated with preoperative chemotherapy and concurrent EBRT (30 or 50.4 Gy).[26] Nonoperative biliary decompression was performed in 101 patients (66%): endobiliary stent placement in 77 and percutaneous transhepatic catheter placement in 24.

Stent-related complications (occlusion or migration) developed in 15 patients. Of these 15 patients, 7 required hospitalization for administration of antibiotics and for stent exchange (median hospital stay: 3 days). No patient experienced uncontrolled biliary sepsis, hepatic abscess, or stent-related death. The overall risk for biliary stent occlusion (with or without cholangitis) among patients receiving chemoradiation was approximately 15%.[26]

We concluded that preoperative chemoradiation for pancreatic cancer is associated with low rates of hepatic toxicity and biliary stent-related complications, and that the need for biliary decompression should not be viewed as a contraindication to preoperative chemoradiation. However, morbidity may be minimized by treatment at a regional center that employs a multispecialty team approach, by the placement of larger-caliber biliary stents, and by early recognition of stent occlusion.

Recent retrospective studies have also suggested that the placement of biliary drains and subsequent bacterial colonization of the biliary tree may increase the morbidity[25,27,28] and mortality[25] associated with pancreaticoduodenectomy. Povoski et al found that preoperative biliary drainage increased perioperative morbidity and mortality in 240 consecutive patients who underwent a pancreaticoduodenectomy.[25] The operative mortality rate in these patients after biliary drainage was 7.9%, compared with 1.8% in patients who did not undergo preoperative biliary drainage ($P < .037$). Because of this fourfold increase in the operative mortality rate among patients with stents, the authors recommended that preoperative biliary drainage be avoided whenever possible.

In contrast, Sohn et al reported an operative mortality rate of 1.7% in 408 patients who underwent biliary decompression prior to pancreaticoduodenectomy.[27] Multivariate analysis showed that the only complication associated with preoperative biliary decompression was wound infection ($P = .03$).

In a recent series of 300 consecutive patients who underwent pancreaticoduodenectomy at our institution, 172 (57%) required preoperative biliary drainage (stent group), 35 (12%) underwent surgical bypass prior to referral, and the remaining 93 (31%) received no preoperative biliary decompression (no-stent group).[29] The overall operative mortality rate was 1% (4 patients).

Multivariate logistic regression showed no differences between groups in the incidence of all complications, major complications, infectious complications, intra-abdominal abscess, pancreaticojejunal anastomotic leak, or death. Wound infections were more common in the group that received a stent than in the group that did not receive a stent ($P = .029$). Thus, our experience suggests that preoperative biliary decompression may increase the rate of wound infections but does not increase the risk of major postoperative complications or operative mortality.
Chemoradiation Strategies for Localized Pancreatic Cancer

Drawbacks of Postoperative Chemoradiation

A regimen combining EBRT and concomitant 5-FU chemotherapy has been shown to prolong survival in patients with locally advanced adenocarcinoma of the pancreas.[30] On the basis of these data, the Gastrointestinal Tumor Study Group ( GITSG) conducted a prospective, randomized study of adjuvant chemoradiation (5-FU, 500 mg/m$^2$ for 6 days, and 40-Gy irradiation) following pancreaticoduodenectomy. The study demonstrated that multimodality therapy offered a survival advantage, compared with resection alone.[4,5]

However, because of the prolonged recovery time, 5 (24%) of the 21 patients in the adjuvant chemoradiation arm could not begin chemoradiation until more than 10 weeks after undergoing pancreaticoduodenectomy. Thus, despite the obvious selection bias in patient accrual (the patients most likely to be considered for protocol entry were those who recovered rapidly from surgery and had a good performance status), adjuvant therapy could not be delivered to all patients in a timely fashion.

Similar findings were reported recently by the European Organization for Research and Treatment of Cancer (EORTC).[7] Between 1987 and 1995, 218 patients who had undergone pancreaticoduodenectomy for adenocarcinoma of either the pancreas or the periampullary region were randomly assigned to receive either chemoradiation (40 Gy in a split course and 5-FU given as a continuous infusion at a dose of 25 mg/kg/d during EBRT) or no further treatment. Eleven patients were ineligible for analysis due to incomplete resection of extensive local disease. Of the remaining 207 patients, 114 (55%) had pancreatic cancer.

The overall median survival duration was 24.5 months for the group who received adjuvant therapy and 19 months for the group who underwent surgery alone ($P = .2$). Among patients with pancreatic cancer, the median survival was 17.1 months for those who received adjuvant therapy and 12.6 months for those who had surgery alone ($P = .099$). Although these differences were not significant, the wide confidence interval (CI) for the subset of patients with pancreatic cancer (relative risk: 0.7; 95% CI: 0.5-1.1) preserves the possibility that the chemoradiation arm had a clinically meaningful improvement in survival, which was obscured by the small sample size.

As in the GITSG trial, patients in the EORTC trial were considered for enrollment after recovering from a pancreaticoduodenectomy. Despite this selection bias, 21 (20%) of 104 evaluable patients assigned to the chemoradiation arm did not receive the intended therapy because of patient refusal, medical comorbidities, or rapid tumor progression. In the recently reported experience from Johns Hopkins University, 26% of patients who underwent pancreaticoduodenectomy did not receive intended adjuvant therapy.[6]

Preoperative Chemoradiation

**M. D. Anderson Studies:** We used a standard-fractionation treatment schema in the first studies of preoperative chemoradiation and pancreaticoduodenectomy at our institution. [17,31] Radiation therapy was delivered 5 days per week over 5.5 weeks with 18-MeV photons. Using a four-field technique, patients received a total dose of 50.4 Gy prescribed to the 95% isodose at 1.8 Gy/fraction (28 fractions). Fluorouracil was administered concurrently by continuous infusion at a dose of 300 mg/m$^2$/d, 5 days per week, through a central venous catheter. One patient died and 38 were evaluable for analysis of patterns of treatment failure.[31]

Tumor recurrence was documented in 29 patients: 8 recurrences (21%) were locoregional (in the pancreatic bed and/or peritoneal cavity), and 30 (79%) were distant (in the lung, liver, and/or bone). The liver was the most frequent site of tumor recurrence, and liver metastases were a component of treatment failure in 53% of patients (69% of all patients who had recurrences). Isolated local or peritoneal recurrences were documented in only four patients (11%). In contrast, previous reports of pancreaticoduodenectomy alone for adenocarcinoma of the pancreas reported local recurrences in 50% to 80% of patients.[9,32,33]
An improvement in locoregional control with preoperative chemoradiation was seen even though 14 of 38 evaluable patients had undergone laparotomy with tumor manipulation and biopsy prior to referral for chemoradiation and reoperation. Excluding these 14 patients, local or peritoneal recurrence led to treatment failure in only 2 patients (8%). However, this 5.5-week chemoradiation program was associated with gastrointestinal toxicity (nausea, vomiting, and dehydration) that required one third of the patients to be hospitalized.[17] In addition, the recently reported multicenter ECOG trial documented a hospital admission rate of 51% of patients during or within 4 weeks after completing chemoradiation.[24]

These findings prompted a change in the delivery of preoperative chemoradiation at our institution in favor of rapid-fractionation or short-course EBRT. In a prospective trial in 35 patients, rapid-fractionation chemoradiation at a total dose of 30 Gy (3 Gy/fraction [10 fractions] 5 days per week) was delivered over 2 weeks. Fluorouracil was administered concurrently by continuous infusion at a dose of 300 mg/m²/d, 5 days per week.[34] This chemoradiation program was designed to avoid the gastrointestinal toxicity seen with standard-fractionation chemoradiation (delivered over 5.5 weeks) while attempting to maintain the excellent local tumor control achieved with multimodality therapy.

As with other neoadjuvant treatment schemas, patients were restaged with chest radiography and abdominal CT 4 weeks after completing chemoradiation in preparation for pancreaticoduodenectomy. Of the 35 patients who completed chemoradiation, 27 were taken to surgery, and 20 (74%) underwent successful pancreaticoduodenectomy.[34] The rates of local tumor control and patient survival achieved were equal to the results obtained with standard-fractionation chemoradiation. A locoregional recurrence developed in only 2 (10%) of the 20 patients who underwent resection, and the median survival for all 20 patients was 25 months (Table 3).

Data from 132 consecutive patients who received preoperative chemoradiation and underwent pancreaticoduodenectomy for adenocarcinoma of the pancreas at our institution also support the use of rapid-fractionation chemoradiation.[35] Standard-fractionation (45 to 50 Gy, 1.8 Gy/fraction per day) EBRT was administered to 44 patients, and 88 received rapid-fractionation EBRT (30 Gy, 3 Gy/fraction per day). Prior to referral, 36 patients (27%) underwent an unsuccessful attempt at tumor resection. In addition, 57 patients (43%) required vascular resection and reconstruction at the time of pancreaticoduodenectomy. Intraoperative radiation therapy was delivered to 74 of the 105 patients. At the discretion of the operating surgeon, intraoperative radiation therapy was not administered to those who underwent long, difficult operations.

The overall median survival from the time of tissue diagnosis was 21 months. Survival duration was not influenced by the dose of preoperative EBRT, the chemotherapy agent used, or the delivery of intraoperative radiation therapy. Univariate and multivariate analyses revealed superior survival times among patients who had no evidence of lymph node metastasis (P = .03). The data suggested that short-course chemoradiation (30 Gy in 2 weeks) combined with a pancreaticoduodenectomy performed in accurately staged patients is equivalent to standard-fractionation chemoradiation (45 to 50 Gy in 5 to 6 weeks).

Although we are not ready to remove EBRT from the study of protocol-based treatment of localized pancreatic cancer, the availability of more potent radiation-sensitizing agents and techniques to ensure complete surgical resection makes the study of shorter-course, less toxic EBRT attractive in contemporary clinical trial design.

**European Study Group of Pancreatic Cancer:** The recently reported interim results of the European Study Group of Pancreatic Cancer (ESPAC)-1 trial also call into question the therapeutic efficacy of EBRT.[36] The ESPAC-1 trial is a four-arm study with a 2 × 2 factorial design that compares the effects of adjuvant chemoradiation (5-FU and 40 Gy in a split course), adjuvant chemotherapy (5-FU and leucovorin), chemoradiation followed by chemotherapy, and observation alone following pancreaticoduodenectomy in patients with pancreatic or periampullary carcinomas. Accrual for this study began in 1994, and medical centers in 11 countries have randomized 530 patients.

Most patients were entered into the randomized 2 × 2 factorial design. However, either because of
lack of access to EBRT or because of specific institutional bias, 188 patients were randomized to receive only chemotherapy or no chemotherapy, and 68 patients were randomized to receive either chemoradiation or no chemoradiation. In the latter two nonfactorial groups, patients could receive nonstandardized therapy at the discretion of their physicians. For example, patients in the nonfactorial design who were randomly assigned to chemotherapy or no chemotherapy could receive EBRT. Importantly, nonrandomized treatments were not standardized. Preliminary results suggest no benefit to postoperative chemoradiation.[36]

Restaging: Repeat staging CT after chemoradiation reveals liver metastases in approximately 25% of patients who receive chemoradiation before planned pancreaticoduodenectomy.[8,34] If these patients had undergone pancreaticoduodenectomy at the time of diagnosis, it is probable that the liver metastases would have been subclinical; these patients would, therefore, have undergone major surgery only to have liver metastases found soon after surgery.

In trials reported from our institution, patients who were found to have disease progression at the time of restaging had a median survival of only 7 months.[3] The avoidance of a lengthy recovery period and the potential morbidity of pancreaticoduodenectomy in patients with such a short duration of expected survival represent a distinct advantage of preoperative over postoperative chemoradiation. When administering multimodality therapy for any disease, it is beneficial, whenever possible, to deliver the most toxic therapy last, thereby avoiding morbidity in patients who experience rapid disease progression that is not amenable to currently available therapies.

Despite a surgeon’s ability to perform pancreaticoduodenectomy safely, the procedure is too extensive and complex to allow the consistent postoperative delivery of standard-fractionation adjuvant chemoradiation.[6,7] Data demonstrating superior survival results for a preoperative vs a postoperative treatment approach are lacking; however, all available data suggest that a greater proportion of patients receive potentially beneficial adjuvant therapy, with a reduced overall treatment time, when chemoradiation is administered in a neoadjuvant setting (Figure 4).

Moreover, preoperative chemoradiation treatment strategies will spare many patients the morbidity and mortality associated with laparotomy. This is due to the fact that as many as one-fourth of patients will present with metastatic disease at the time of preoperative restaging following chemoradiation, and thus, will not benefit from surgery.

Chemoradiation to Downstage Locally Advanced Pancreatic Cancer

5-FU-Based Chemoradiation

In an effort to improve survival, and more recently, to downstage advanced locoregional disease to allow surgical resection, chemoradiation has been administered to patients with locally advanced, unresectable pancreatic cancer. The GITSG randomized patients with locally advanced pancreatic cancer to receive 40 Gy of EBRT plus 5-FU, 60 Gy plus 5-FU, or 60 Gy without chemotherapy.[30] Median survival of patients in the study was 10 months in each of the chemoradiation groups and 6 months for those who received 60 Gy without 5-FU.

All patients had undergone laparotomy and therefore had been surgically staged. Only patients with disease confined to the pancreas and peripancreatic organs, regional lymph nodes, and regional peritoneum were eligible for the study. Thus, although surgical staging resulted in a more uniform study population, it also introduced significant selection bias (only rapidly recovering patients were considered for treatment). Any comparison of these data with the results of future studies must factor in this selection bias.

Because surgical resection of the primary tumor remains the only potentially curative treatment for pancreatic cancer, preoperative chemoradiation has been studied for its ability to convert locally unresectable pancreatic cancer to resectable disease (Table 4).[37-48] In early studies, EBRT and 5-FU were used for this purpose. In a report from the New England Deaconess Hospital, 16 patients with locally advanced, unresectable pancreatic cancer were treated with 45 Gy of EBRT and infusional 5-FU to enhance resectability.[48] Only 2 (13%) of the patients were able to undergo
resection. Similarly, investigators from Duke University reported that only 2 (8%) of 25 patients with locally advanced pancreatic cancer treated with 45 Gy of EBRT and 5-FU (with or without cisplatin [Platinol] or mitomycin [Mutamycin]) subsequently underwent complete resection that resulted in negative margins.[42]

The available literature suggests that it is unlikely that 5-FU-based chemoradiation schemas can make unresectable lesions resectable and thereby increase the number of patients who can be cured with multimodality therapy.

**Gemcitabine-Based Chemoradiation**

More effective radiation sensitization may result in a greater cytotoxic effect at the local tumor site. Gemcitabine (Gemzar) is a deoxycytidine analog capable of inhibiting DNA replication and repair. In a randomized trial, gemcitabine was compared to 5-FU in previously untreated patients.[49] Patients treated with gemcitabine had a median survival of 5.7 months, compared with 4.4 months ($P = .0025$) for those treated with 5-FU. Of patients treated with gemcitabine, 24% were alive at 9 months compared with 6% of those treated with 5-FU. In addition, more clinically meaningful effects on disease-related symptoms (pain control, performance status, and weight gain) were seen with gemcitabine (23.8% of patients) than with 5-FU (4.8% of patients). Gemcitabine is also a potent radiation sensitizer of human pancreatic cancer cells, and laboratory studies suggest that gemcitabine lowers the threshold for radiation-induced tumor cell apoptosis.[50]

Investigators recently combined EBRT (45 Gy) with gemcitabine (300 mg/m$^2$ on days 1, 15, and 29) and continuous-infusion 5-FU (350 mg/m$^2$) in 10 patients with locally advanced pancreatic cancer (Table 4).[41] Patients also received additional systemic therapy consisting of gemcitabine and cisplatin before and after chemoradiation. A reduction in the size of the primary tumor was seen in seven patients, of whom five underwent surgical resection.

Another recent report evaluated the combination of EBRT (55.8 Gy) and cisplatin with escalating doses of weekly gemcitabine in 24 patients with locally advanced pancreatic cancer.[37] Of these 24 patients, 7 underwent surgical resection of the primary pancreatic tumor. The most recent report from the University of Michigan involved 22 patients thought to have locally advanced pancreatic cancer on the basis of either intraoperative findings or endoscopic ultrasound or CT images.[40] Of the 22 patients, 8 (36%) had radiographic evidence of a partial response following chemoradiation and 5 (23%) underwent pancreaticoduodenectomy.

These studies suggest that the combination of multiple, more effective radiosensitizers with EBRT may result in significant local tumor response. As the definition of locally advanced pancreatic cancer is broadened, however, results will appear more promising. Thus, all studies of novel chemoradiation regimens should adhere to a strict CT-based definition of locally advanced pancreatic cancer that includes arterial involvement (low-density tumor inseparable from the superior mesenteric artery or celiac axis on contrast-enhanced CT) or venous (superior mesenteric vein or superior mesenteric-portal vein confluence) occlusion.

Encouraging data from small pilot studies provided the basis for several ongoing phase I and II studies of gemcitabine in combination with EBRT in patients with locally advanced pancreatic cancer. Gemcitabine is being given in escalating weekly doses as a single agent with EBRT,[39,51] in combination with 5-FU and EBRT,[41,52] in combination with cisplatin and EBRT,[37,53] at a fixed dose with escalating doses of EBRT,[54,55] and as a twice-weekly infusion with either standard-fractionation EBRT[43] or split-course EBRT.[56]

**M. D. Anderson Study:** Researchers from our institution have reported a phase I study of rapid-fractionation EBRT and concomitant weekly gemcitabine in patients with locally advanced adenocarcinoma of the pancreatic head.[51] The study enrolled 18 patients with pathologically proven, locally advanced disease. Patients received seven weekly doses of gemcitabine with 30 Gy of EBRT (3 Gy/fraction, 5 days per week) delivered during the first 2 weeks of therapy. Six patients received gemcitabine at 350 mg/m$^2$/wk, 9 patients at 400 mg/m$^2$/wk, and 3 patients at 500 mg/m$^2$/wk.
Grade 3/4 hematologic toxicity was observed in more than half the patients treated. Nonhematologic side effects were significant and included fatigue, anorexia, nausea, vomiting, and dehydration. Management of nausea/vomiting and dehydration required hospitalization in 44% of patients. The risk of hospitalization appeared to be dose related; all three patients treated with 500 mg/m$^2$/wk were admitted to the hospital during treatment. Interestingly, patients who received the highest dose of gemcitabine (500 mg/m$^2$/wk) had a lower incidence of grade 3/4 hematologic toxicity, but all had grade 3/4 gastrointestinal side effects. Conversely, patients treated at either 350 mg/m$^2$/wk or 400 mg/m$^2$/wk were more likely to develop grade 3 myelosuppression.

We postulate that the dose of 500 mg/m$^2$/wk led to severe mucosal injury that precluded continued therapy on schedule. Patients assigned to receive either 350 or 400 mg/m$^2$/wk were more likely to receive the full weekly dose of gemcitabine, and therefore, were more prone to develop hematologic toxicity. Although gastrointestinal toxicity was also common in this group, myelosuppression was most likely related to the higher cumulative dose of gemcitabine. These results suggest that when gemcitabine is administered weekly with concomitant radiation therapy delivered at a dose of 30 Gy in 10 fractions, the maximum tolerated dose of gemcitabine is between 350 and 400 mg/m$^2$/wk for 7 weeks (approximately one third the recommended dose of gemcitabine when administered as a single agent for the treatment of advanced pancreatic cancer).

A total of 17 patients were evaluated for response, and 8 (47%) had evidence of a local anticancer effect. Of these eight patients, four (24%) had a partial response to therapy. The median survival for the entire group was 6 months. The 1-year survival of patients who had an objective response to therapy was 66%. The responses observed in this group suggest gemcitabine is a clinically relevant radiosensitizer in patients with pancreatic adenocarcinoma. However, the toxic effects are significant, suggesting that until dose and scheduling issues are resolved, concomitant administration of gemcitabine and radiation therapy should be considered investigational.

Preoperative Gemcitabine-Based Chemoradiation: Because of the encouraging results achieved in patients with locally advanced disease, gemcitabine-based chemoradiation is being studied in patients with potentially resectable pancreatic cancer (as defined by CT). Hoffman and colleagues have reported a phase I study of preoperative standard-fractionation EBRT (50.4 Gy) and escalating weekly doses of gemcitabine (300 mg/m$^2$, 400 mg/m$^2$, and 500 mg/m$^2$).[57] Pancreaticoduodenectomy was performed in eight patients.

The current phase II protocol available at our institution for patients with potentially resectable pancreatic cancer is based on the results of the phase I study reported by Wolff et al (discussed above).[50] Patients receive gemcitabine-based chemoradiation followed by a complete restaging evaluation. Those with no evidence of disease progression then undergo pancreaticoduodenectomy. To date, more than 70 patients have been entered into this protocol. Although follow-up is incomplete, preventing survival analysis at this time, histologic responses to induction therapy (in the resected specimen) appear to be superior to those obtained with previous regimens.[58]

Future Directions

Our institution currently emphasizes the use of new, more potent radiation-sensitizing agents and the preoperative delivery of systemic therapy for treatment of patients with potentially resectable adenocarcinoma of the pancreas (Figure 4). In the future, the addition of novel systemic therapies directed at specific molecular events involved in pancreatic tumorigenesis (ie, inhibition of ras-dependent signal transduction, the use of protease inhibitors such as matrix metalloproteinase inhibitors, or the inhibition of angiogenesis) can be used to enhance the treatment of distant microscopic metastases present in most patients with pancreatic cancer. Such agents should be minimally toxic to allow for administration during both the preoperative and the postoperative periods.

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