Localized Adenocarcinoma of the Pancreas: The Rationale for Preoperative Chemoradiation

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Learning Objectives
After completing this course, the reader should be able to:
1. Define the radiologic (CT) criteria that determine whether a pancreatic neoplasm is surgically resectable, locally advanced, or metastatic.
2. Explain why it is difficult to conduct clinical trials of adjuvant or neoadjuvant therapy in resectable pancreatic cancer.
3. Review the advantages and disadvantages of preoperative versus postoperative adjuvant therapy for patients with pancreatic adenocarcinoma.

Abstract
Pancreatic adenocarcinoma is the fifth leading cause of cancer-related death in the U.S. In spite of advancements in surgical treatment, nearly 80% of patients thought to have localized pancreatic cancer die of recurrent or metastatic disease when treated with surgery alone. Therefore, efforts to alter the patterns of recurrence and improve survival for patients with pancreatic cancer currently focus on the delivery of systemic therapy and irradiation before or after surgery. Postoperative adjuvant therapy appears to improve median survival. However, more than one-fourth of patients do not complete planned adjuvant therapy due to surgical complications or a delay in postoperative recovery of performance status. Utilizing a preoperative (neoadjuvant) approach, overall treatment time is reduced, a greater proportion of patients receive all components of therapy, and patients with rapidly progressive disease are spared the side effects of surgery as metastatic disease may be found at restaging following chemoradiation (prior to surgery).

This paper examines the factors pertinent to clinical trial design for resectable pancreatic cancer, and carefully reviews the existing data supporting adjuvant and neoadjuvant therapy for potentially resectable disease. The Oncologist 2002;7:34-45

Introduction
In 2002, adenocarcinoma of the exocrine pancreas will account for approximately 28,900 deaths in the U.S.—the fifth leading cause of cancer-related death for both men and women this year (following lung, colon, breast, and prostate cancer) [1]. Exocrine pancreatic cancer characteristically spreads by infiltration of surrounding blood vessels and perineural tissues, invasion into regional lymph nodes, and early vascular dissemination. Subclinical metastases are present in most patients at the time of diagnosis, even when imaging studies are normal. Therefore, disease recurrence following a potentially curative pancreaticoduodenectomy remains common, and long-term survival is realized by only 10%-20% of patients who undergo potentially curative surgery [2]. Among patients treated with surgery alone, local recurrence occurs in up to 50%-80%, peritoneal recurrence in 25%, and liver metastases in 50% [2]. When surgery and chemoradiation are used to maxi-
mize local-regional tumor control, liver metastases become the dominant form of tumor recurrence [3].

Recent prospective and retrospective data suggest that the combination of pancreaticoduodenectomy with postoperative adjuvant fluorouracil (5-FU) and external-beam radiation therapy (EBRT) improves survival duration compared with surgery alone [4–6]. However, complications and prolonged recovery time after pancreaticoduodenectomy can prevent the timely delivery of postoperative chemoradiation in at least 25%–30% of eligible patients [5, 7]. This risk, that postoperative adjuvant chemoradiation will be delayed, combined with the awareness that a minimum of 80% of all patients with presumed localized pancreatic cancer actually have extrahepatic metastatic disease at the time of diagnosis, has stimulated interest in the administration of chemotherapy and/or chemoradiation before pancreaticoduodenectomy [3]. Several other factors support the preoperative use of chemoradiation [7]: A) positive gross or microscopic margins of resection along the right lateral border of the superior mesenteric artery (SMA) are common following pancreaticoduodenectomy, suggesting that surgery alone may be an inadequate strategy for local tumor control [8]; B) postoperative recovery does not affect the delivery of multimodality therapy since chemoradiation is given before surgery, and C) patients with disseminated disease evident on restaging studies after chemoradiation are spared a nontherapeutic laparotomy.

Inconsistent definitions of resectability, variations in surgical technique, 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 pancreatic cancer difficult to interpret. Thus, standardized approaches to patient selection (pretreatment staging), operative technique, and pathologic evaluation of surgical specimens have been utilized at our institution for the past decade. Such standardized approaches are essential elements of proper clinical trial design.

We currently utilize a computed tomography (CT)-based preoperative staging system, which defines resectability based on the relationship of the tumor to the celiac axis and the superior mesenteric vessels. Disease is considered to be potentially resectable when CT images show: A) no evidence of extrahepatic disease; B) no evidence of direct tumor extension to the SMA and celiac axis, as defined by the presence of a fat plane between the low-density tumor and these arterial structures, and C) a patent superior mesenteric-portal vein (SMPV) confluence [9]. The third criterion is based on the assumption that resection and reconstruction of the superior mesenteric vein (SMV) or SMPV confluence are possible (Fig. 1) [10, 11]. In the absence of extrahepatic disease, the main goal of preoperative imaging studies is to determine the relationship of the low-density tumor mass to the mesenteric vessels and celiac axis.

**Surgical Considerations**

The current perioperative mortality for pancreaticoduodenectomy at The University of Texas M. D. Anderson Cancer Center (MDACC) is 1% [12]. Recently reported mortality rates from other institutions, including university centers and the Department of Veterans Affairs Hospitals, range from 7.8% to more than 10% [13–16]. Data from Maryland, New York, and Ontario, Canada, have demonstrated that higher patient volume is associated with lower surgery-related mortality [17–20]. The most compelling data regarding the relationship of hospital volume to perioperative mortality and long-term survival after pancreaticoduodenectomy come from Dartmouth Medical School [21, 22]. Birkmeyer and colleagues studied 7,229 Medicare patients older than 65 years who underwent pancreaticoduodenectomy at 1,772 hospitals from 1992 to 1995 [21]. The study population was divided into quartiles according to hospital volume; high-volume centers were defined as those that performed five pancreaticoduodenectomies per year. Forty high-volume hospitals (2%) performed 1,541 (21%) of the pancreaticoduodenectomies. The in-hospital mortality rate was 11% overall, 4% in high-volume hospitals, and 10%–16% in medium-volume (2–5 pancreaticoduodenectomies/year) and very-low-volume (<1 pancreaticoduodenectomy/year).

![Figure 1. Contrast-enhanced CT scan demonstrating a resectable adenocarcinoma of the pancreatic head, with probable focal tumor extension to the lateral wall of the superior mesenteric vein (large arrow). Note the area of low density extending to the superior mesenteric vein just inferior to the tip of the large arrow. This patient may require venous resection and reconstruction at the time of pancreaticoduodenectomy. There is a normal fat plane between the low-density tumor and the superior mesenteric artery (small arrow). The intrapancreatic portion of the common bile duct contains an endoscopic stent placed for biliary drainage.](http://theoncologist.alphamedpress.org/)
hospitals. These data suggest a linear relationship between surgical volume and outcome. Birkmeyer and colleagues suggested that the referral of pancreatic cancer patients to high-volume hospitals could potentially prevent more than 100 deaths per year. Furthermore, in an analysis of survival duration, Birkmeyer and colleagues found that patients who underwent surgery at high-volume hospitals were less likely to experience late mortality [22].

We previously reported the six-step operative technique of pancreaticoduodenectomy currently performed at our institution [23]. The most oncologically important and difficult part of the operation is step six, during which the pancreas is divided and the specimen is removed from the mesenteric vessels. Only after full medial mobilization of the SMV is it possible to identify the SMA (medial to the SMV). The pancreatic head and all soft tissue to the right of the SMA are then removed (Fig. 2). Failure to mobilize the SMPV confluence may result in a positive resection margin (Fig. 3) due to incomplete removal of the uncinate process and the mesenteric soft tissue adjacent to the SMA.

Segmental resection of the SMPV confluence is necessary when the tumor is inseparable from the lateral wall of the SMV or portal vein [11]. However, such isolated venous resection should be performed only in carefully selected patients who have tumor adherence to the SMV or SMPV confluence but have no evidence of tumor extension to the SMA or celiac axis. Invasion of the SMV or portal vein is not associated with histopathologic variables (margin and lymph node positivity) that suggest a poor prognosis, and patient survival after pancreaticoduodenectomy is not affected by the need for venous resection [10]. Because the need for venous resection is unexpected in many patients and is discovered only after gastric and pancreatic transection when nonresectional procedures are no longer an option, surgeons who perform pancreaticoduodenectomies should be familiar with standard techniques for vascular resection and reconstruction of the SMPV confluence (Fig. 4).

Figure 2. Illustration of step 6 in the performance of pancreaticoduodenectomy. Step 6 has two important parts: complete mobilization of the superior mesenteric (SMV) and portal veins, and separation of the specimen from the right lateral border of the superior mesenteric artery (SMA). A grossly positive retroperitoneal margin should not occur if high-quality preoperative CT is performed. A microscopically positive retroperitoneal margin may occur in up to 10%-20% of cases.

Figure 3. Specimen photograph (A) and illustration (B) of a pancreaticoduodenectomy specimen. The retroperitoneal margin (tissue adjacent to the superior mesenteric artery [large arrow]) is inked for evaluation of margin status. A small probe is in the bile duct and, just inferior to the small probe, a larger probe is seen within the pancreatic duct. A white Q-tip applicator stick lies over the indentation from the superior mesenteric-portal vein confluence. Complete permanent-section analysis of the pancreaticoduodenectomy specimen requires that it be oriented to enable the pathologist to accurately assess the retroperitoneal margin of excision and other standard pathologic variables.
CHEMORADIATION

Postoperative (Adjuvant) Chemoradiation

The largest single-institution experience with postoperative adjuvant chemoradiation has been reported by Sohn and colleagues from Johns Hopkins University [5, 24]. Of 498 evaluable patients who underwent pancreatectomy for adenocarcinoma of the pancreas, 366 (74%) received adjuvant chemoradiation and 132 (26%) declined adjuvant therapy for "various reasons." The very low mortality and morbidity for pancreatic surgery at Johns Hopkins University would suggest that 26% represents the minimum percentage of patients that will not receive adjuvant therapy if a postoperative strategy is used by other less experienced centers. It is noteworthy that in all previously reported and ongoing postoperative adjuvant trials (with the exception of the Hopkins data) patient enrollment occurs following recovery from surgery; the number of patients not referred for trial entry (due to delayed recovery from surgery) is not known. Importantly, Sohn reported that the successful delivery of adjuvant therapy was associated with a statistically significant improvement in survival duration (19 versus 11 months; \( p < 0.0001 \)).

Chakravarthy recently reported an interim analysis of an intensified postoperative adjuvant regimen for periampullary (pancreatic and nonpancreatic) adenocarcinoma utilizing concurrent 5-FU, leucovorin, dipyridamole, and mitomycin-C, combined with split-course EBRT (50 Gy). While all 45 patients enrolled in this phase II study were able to begin adjuvant therapy, the average time to the start of radiation therapy following surgery was 63 days (range, 41-86 days) [25]. Despite this intensified regimen, median survival (16 months) and disease-free survival (12.4 months) were not appreciably improved when compared with similar patients treated on earlier adjuvant therapy protocols at the same institution (median survival 15 months, median disease-free survival 9 months) [26].

Prospective data are available from both the Gastrointestinal Tumor Study Group (GITSG) and the European Organization for Research and Treatment of Cancer (EORTC). In the GITSG randomized study of adjuvant chemoradiation (5-FU 500 mg/m\(^2\) for 6 days and 40 Gy EBRT) following pancreaticoduodenectomy, 24% of the patients in the adjuvant treatment arm could not begin chemoradiation until more than 10 weeks after surgery.
because of a prolonged recovery time [4, 27]. Similar findings were recently reported by the EORTC [6]. Between 1987 and 1995, 218 patients who had undergone pancreaticoduodenectomy for adenocarcinoma of either the pancreas or the periampullary region were randomized to receive either chemoradiation (40 Gy EBRT in a split course and 5-FU given as a continuous infusion at a dose of 25 mg/kg per day during radiotherapy) or no further treatment. Eleven patients were deemed ineligible for analysis due to incomplete resection in the setting of extensive local disease. As in the GITSG trial, patients in the EORTC trial were considered for enrollment after recovery from pancreatoduodenectomy. Despite this selection bias, 21 (20%) of 104 evaluable patients assigned to receive chemoradiation did not receive the intended therapy because of patient refusal, medical comorbidities, or rapid tumor progression. Of the 207 eligible patients, 114 (55%) had pancreatic cancer; the median survival was 17.1 months for those who received adjuvant therapy and 12.6 months for those who did not.

Of the 207 eligible patients, 114 (55%) had pancreatic cancer; the median survival was 17.1 months for those who received adjuvant therapy and 12.6 months for those who received surgery alone ($p = 0.099$). Although these differences were not statistically 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 that was obscured by the small sample size.

The recently reported interim results of the European Study Group of Pancreatic Cancer (ESPAC)-1 study suggest that chemotherapy, rather than chemoradiation, is the essential component of adjuvant therapy [28, 29]. The ESPAC-1 trial was a four-arm study with a 2 × 2 factorial design that compared the effects of adjuvant chemoradiation (5-FU and 40 Gy in a split course), adjuvant chemotherapy (5-FU and folinic acid), chemoradiation followed by chemotherapy, and observation alone following pancreatoduodenectomy for pancreatic or periampullary adenocarcinomas. Accrual for this study began in 1994, and medical centers in 11 countries randomized 541 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 only chemoradiation or no chemoradiation. In the latter two nonfactorial groups, patients could receive nonstandardized therapy at the discretion of their treating physicians. For example, patients who were randomized in the nonfactorial design to chemotherapy or no chemotherapy could receive EBRT. Importantly, nonrandomized treatments were not standardized. The preliminary analysis of the ESPAC-1 trial concluded that adjuvant chemoradiation provides no survival benefit, and adjuvant systemic chemotherapy consisting of 5-FU and leucovorin (which is largely ineffective in patients with measurable metastatic disease) increased survival duration [28]. However, in the subset of 285 patients randomized by the 2 × 2 factorial design, there was no benefit to chemotherapy.

An additional recently reported adjuvant treatment strategy combines 45-54 Gy of EBRT with 5-FU, cisplatin, and interferon-α (IFN-α) [30]. Use of IFN-α in pancreatic cancer is based on the known ability of IFN-α to function as a radiosensitizer and its use in other gastrointestinal malignancies [31, 32]. Nukui et al. reported on 33 patients who underwent pancreatoduodenectomy and were then assigned in a nonrandomized fashion to receive either 45-54 Gy EBRT with concomitant 5-FU, or IFN-α-based chemoradiation (45-54 Gy, with concomitant continuous infusion 5-FU [200 mg/m²/day], bolus cisplatin [30 mg/m²/week], and subcutaneous IFN-α [3 × 10⁶ u/day, every other day]) [30]. While the sample size was small, the 17 patients treated with the IFN-α regimen had a significantly greater actuarial 2-year survival compared with those receiving EBRT and 5-FU alone (84% versus 54%, $p = 0.04$). The 2-year survival in the “control” arm compares favorably with other recently published series of adjuvant 5-FU and EBRT, which have generally been in the range of 40% [4, 7, 24]. The strategy of combination chemoradiation utilizing IFN-α provides yet another treatment schema which may prove beneficial in the adjuvant or neoadjuvant setting. In fact, the American College of Surgeons Oncology Group plans a phase III trial incorporating IFN-α.

Preoperative (Neoadjuvant) Chemoradiation

A standard-fractionation treatment schema was used in the first studies of preoperative chemoradiation and pancreatoduodenectomy at our institution [33, 34]. Radiation therapy was delivered 5 days/week over 5.5 weeks using a four-field technique. Patients received a total dose of 50.4 Gy of EBRT in 28 fractions, 1.8 Gy/fraction, combined with 300 mg/m² per day of 5-FU given Monday-Friday by continuous infusion [34]. The liver was the most frequent site of tumor recurrence, and liver metastases were a component of treatment failure in 53% of all patients who had recurrences. Isolated local or peritoneal recurrences were documented in only 11% of patients. In contrast, previous reports of pancreaticoduodenectomy alone for adenocarcinoma of the pancreas documented local recurrence in 50%-80% of patients [8, 35, 36]. However, this 5.5-week standard-fractionation chemoradiation program was associated with gastrointestinal toxicity (nausea, vomiting, and dehydration) that required hospital admission of one-third of patients [33]. Similarly, the multicenter Eastern Cooperative Oncology Group trial documented the need for hospital admission of 51% of patients.
during or within 4 weeks after completing preoperative chemoradiation [37].

These findings prompted a change in the delivery of preoperative chemoradiation at our institution in favor of rapid-fractionation or short-course EBRT. We recently completed a prospective trial of rapid-fractionation chemoradiation delivered over 2 weeks to a total dose of 30 Gy (10 fractions, 3.0 Gy/fraction, 5 days/week) combined with 300 mg/m² per day 5-FU given by continuous infusion, 5 days/week in patients with potentially resectable pancreatic cancer [38]. This chemoradiation program was designed to avoid the gastrointestinal toxicity seen with standard-fractionation chemoradiation while attempting to maintain the excellent local control achieved with multimodality therapy. Rates of local tumor control and patient survival times achieved were equal to the results obtained with standard-fractionation (5.5 week) chemoradiation: local-regional recurrence developed in only 10% of patients who underwent resection; and the median survival for patients who received preoperative chemoradiation and pancreaticoduodenectomy was 25 months. These very encouraging results are likely secondary to accurate patient staging, a standardized surgical technique emphasizing margin-negative resection, and the use of preoperative chemoradiation. The importance of all three components of therapy cannot be overemphasized; similar results have been reported for carefully staged patients with rectal cancer treated with preoperative radiation therapy and total mesorectal excision with sharp pelvic dissection [39].

The most recent data from our institution also support the use of rapid-fractionation chemoradiation [40]. Preoperative chemoradiation and pancreaticoduodenectomy were delivered to 132 consecutive patients with adenocarcinoma of the pancreas: 44 patients received standard-fractionation EBRT (45-50 Gy, 1.8 Gy/fraction per day), and 88 patients received rapid-fractionation EBRT (30 Gy, 3.0 Gy/fraction per day). Intraoperative radiation therapy (IORT) was delivered to 74 patients at the discretion of the operating surgeon. The overall median survival from the time of tissue diagnosis was 21 months, and the 5-year survival was 23% (range 15%-35%, 95% CI). Survival duration was not influenced by the dose of preoperative EBRT, the chemotherapy agent used, or the delivery of IORT. Only eight patients (10%) developed local (tumor bed) recurrence. The survival duration of these 132 patients compares favorably with recently reported series of patients treated by pancreaticoduodenectomy alone, and to those treated with combined postoperative adjuvant 5-FU-based chemoradiation (median survival 11-20 months) [4, 6, 24, 27] despite the fact that 36 patients (27%) had undergone an unsuccessful attempt at tumor resection prior to referral, and 57 patients (43%) required vascular resection and reconstruction at the time of pancreaticoduodenectomy. These data suggest that short-course chemoradiation (30 Gy over 2 weeks) combined with pancreaticoduodenectomy performed on accurately staged patients may be equivalent to standard-fractionation chemoradiation (45-50 Gy over 5-6 weeks).

Despite surgeons’ ability to perform pancreaticoduodenectomy safely, the procedure is too extensive and complex to enable the consistent postoperative delivery of standard-fractionation adjuvant chemoradiation [5, 6]. In the absence of compelling data demonstrating superior survival results with either a preoperative or postoperative treatment approach, 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. Further, preoperative chemoradiation treatment strategies will spare many patients the morbidity and mortality associated with laparotomy, as up to one-fourth of patients will show evidence of metastatic disease at the time of preoperative restaging following chemoradiation, and thus would not benefit from surgery (Fig. 5).

Factors That Complicate the Delivery of Preoperative Chemotherapy or Chemoradiation

In order to deliver systemic therapy or chemoradiation prior to surgery in patients with suspected pancreatic cancer, such patients require tissue confirmation of malignancy and a durable means of biliary decompression if biliary obstruction is present. Pancreatic biopsy and biliary decompression would not be necessary if surgery were to occur immediately following diagnosis.

In patients thought to have potentially resectable pancreatic or periampullary cancer, most experienced pancreatic surgeons believe that preoperative or intraoperative pancreatic biopsy is unnecessary [41, 42]. However, in the absence of tissue confirmation of malignancy, diagnostic uncertainty remains. Further, most pancreatic resections are not performed in regional referral centers or tertiary cancer centers. Indeed, a recent review of 24,926 patients undergoing pancreaticoduodenectomy nationwide revealed that 58% of patients underwent pancreaticoduodenectomy at rural or urban-nonteaching hospitals where the operative mortality rate ranged from 10.6% (urban non-teaching) to 19.0% (rural) [43]. Since the majority of patients undergo pancreaticoduodenectomy with this risk for mortality, many physicians and surgeons are not willing to proceed with surgery in the absence of a tissue diagnosis of malignancy. Despite improvements in radiographic imaging, such diagnostic uncertainty often results in therapeutic indecision. Therapeutic indecision often leads to exploratory surgery at
which time surgeons frequently attempt intraoperative biopsy (leading to unnecessary complications) or incorrectly judge a primary pancreatic tumor to be resectable or unresectable. In contrast to the diagnostic and staging evaluation of all other solid tumors in which the diagnostic phase appears distinct from the treatment phase, with pancreatic and periampullary malignancies, diagnosis and treatment are often a continuum. Patients rapidly transition from excellent health, to painless jaundice, to the operating room; their first chance to seek a second opinion or explore available options for protocol-based therapy is after already having undergone an unsuccessful attempt at surgical resection or when recovering from complications secondary to an ill-advised intraoperative pancreatic biopsy. The advent of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) combined with high-quality CT and endobiliary stent placement allows this disease to be treated like all other solid tumors; the diagnostic phase is separated from the treatment phase. Patients with suspected pancreatic or periampullary cancer can be accurately staged with contemporary CT imaging, biliary obstruction can be relieved with endobiliary decompression, and the diagnosis established endoscopically with EUS-FNA.

Controversy also exists regarding the use of preoperative biliary drainage (which is necessary if surgery is to be delayed due to, for example, the use of preoperative chemoradiation) and the potential for increased pancreaticoduodenectomy-associated morbidity and mortality. Recent reports suggest increased morbidity and mortality after pancreaticoduodenectomy in patients who undergo preoperative biliary drainage [44, 45]. We recently completed a retrospective analysis of 300 consecutive patients who underwent pancreaticoduodenectomy [12]. Multivariate analysis demonstrated no increase in the risk of major postoperative complications or death associated with preoperative stent placement. Others have confirmed this finding [34, 46, 47]. Even the subset of patients who undergo neoadjuvant chemoradiation with stents in place do not suffer clinically significant biliary stent-related complications [12]. Thus, endobiliary decompression as part of an organized staging evaluation does not increase the risk associated with subsequent therapies including chemoradiation and surgery.

**Gemcitabine-Based Chemoradiation**

The survival duration of patients with early-stage pancreatic cancer will only improve with the addition of more effective systemic therapy designed to destroy the occult micrometastatic disease that is present in the majority of
patients at the time of pancreaticoduodenectomy. In addition, systemic agents with improved radiation-sensitizing effects may result in a greater cytotoxic impact on the primary tumor. Gemcitabine (2′,2′-difluorodeoxycytidine, Gemzar®) is a deoxycytidine analogue that inhibits DNA replication and repair. In a randomized trial, gemcitabine was compared with 5-FU in previously untreated patients [48]. Patients treated with gemcitabine had a median survival of 5.7 months compared with 4.4 months ($p = 0.0025$) in those treated with 5-FU. Twenty-four percent of patients treated with gemcitabine were alive at 9 months compared with 6% of patients 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 [49].

We recently reported a phase I study of short-course (rapid-fractionation) EBRT and concomitant weekly gemcitabine in patients with locally advanced adenocarcinoma of the pancreatic head [50]. Patients received seven weekly doses of gemcitabine with 30 Gy of EBRT (3.0 Gy/fraction, 5 days/week) delivered during the first 2 weeks of chemotherapy. Grade 3-4 hematologic toxicity was observed in more than half the patients treated. Nonhematologic toxicities were considerable and included fatigue, anorexia, nausea, vomiting, and dehydration; 44% of patients required admission to the hospital for management of nausea, vomiting, and dehydration. The risk of hospitalization appeared to be dose-related. We concluded that when gemcitabine is given 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$^2$ per week for 7 weeks. This amount is approximately one-third the recommended dose of gemcitabine when administered as a single agent for the treatment of advanced pancreatic cancer. Seventeen patients were evaluated for response, and eight patients (47%) had evidence of a local anticancer effect. Four of these eight patients had a partial response to therapy. The 1-year survival rate for patients who had an objective response to therapy was 66%. The responses observed suggest that gemcitabine is a clinically relevant radiosensitizer in patients with pancreatic adenocarcinoma. However, the toxic effects are considerable and until dose and scheduling issues are resolved, concomitant administration of gemcitabine and radiation therapy should be considered investigational.

Because of encouraging results in patients with locally advanced disease, gemcitabine-based chemoradiation is being studied in patients with potentially resectable pancreatic cancer. 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$^2$) [51]. 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; patients with no evidence of disease progression are then taken to surgery. To date, more than 80 patients have been entered into this treatment program. Although follow-up is incomplete, preventing survival analysis at this time, the histologic responses to induction therapy (in the resected specimen) appear to be superior to those obtained with previous regimens [52].

Additional studies of gemcitabine as a treatment for pancreatic cancer have focused on its dose and schedule of administration, both alone and in combination with other cytotoxic agents. A subsequent randomized phase II trial in patients with metastatic pancreatic cancer suggested that short infusional schedules of gemcitabine (10 mg/m$^2$/minute) might be more effective than the standard 30-minute bolus administration [53]. Preliminary results from this trial demonstrated that compared with 2,300 mg/m$^2$ over 30 minutes, 1,500 mg/m$^2$ delivered over 150 minutes (10 mg/m$^2$/minute) led to a higher objective response rate (16.2% versus 2.7%) and a longer median survival (6.1 versus 4.7 months). Gemcitabine has also been investigated in combination with other cytotoxic agents. Recent data suggest superior activity with gemcitabine doublets (gemcitabine/5-FU, gemcitabine/cisplatin, gemcitabine/irinotecan) compared with single-agent gemcitabine [54]. Phase III trials are currently being conducted to compare gemcitabine alone with these doublets. The next generation phase II study of preoperative chemoradiation for resectable pancreatic cancer at MDACC utilizes infusional gemcitabine in combination with cisplatin.

Emerging Systemic Therapies for Preoperative or Postoperative Delivery

The addition of novel systemic therapies that target specific molecular events involved in pancreatic tumorigenesis may enhance the treatment of distant microscopic metastases. Such systemic agents are designed to inhibit specific signals required for tumor cell growth and metastasis.

The HER2/neu oncoprotein is a receptor tyrosine kinase that transduces growth-promoting signals. Inhibition of the HER2/neu oncoprotein with specific antibodies initiates growth inhibition and promotes apoptosis in tumor cells. Trastuzumab (herceptin) is a humanized monoclonal antibody developed in mice that binds the HER2 receptor.
In preclinical studies, herceptin led to growth inhibition in cell lines overexpressing HER2/neu. Herceptin appears to have synergistic effects when combined with most cytotoxic agents. Clinical trials in patients with metastatic breast cancer whose tumors overexpressed HER2/neu demonstrated that herceptin had activity as a single agent, with objective response rates ranging from 11% to 26% [55, 56]. In a subsequent trial, response rates and survival were improved in women who received both herceptin and paclitaxel compared with paclitaxel alone for metastatic breast cancer (all patients had tumors with overexpression of HER2/neu) [57]. Thirty percent to 40% of human pancreatic tumors overexpress HER2/neu though the role of herceptin has not been defined. Currently, a phase II trial of herceptin and gemcitabine is under way in patients with measurable metastatic pancreatic cancer.

Antibodies to the epidermal growth factor receptor (EGFR) have been shown to inhibit tumor growth and metastasis. Recently, a humanized monoclonal antibody to EGFR (C225) has demonstrated potent competitive binding to the receptor, leading to tumor cell growth inhibition [58]. In vitro studies suggest an additive effect of C225 with cytotoxic agents, and data from our institution suggest a synergistic interaction between gemcitabine and C225 in animal models of metastatic pancreatic cancer [59]. A phase II trial that examines the toxicity and efficacy of gemcitabine combined with C225 has recently been completed in patients with advanced pancreatic cancer.

Since the ras oncogene is mutated and thereby constitutively activated in the majority of pancreatic cancers, inhibition of ras signaling has been proposed as a target for therapy. Ras protein function can be inhibited by interrupting post-translational processing (farnesylation), which is necessary to localize ras proteins to the cytoplasmic side of the plasma membrane. This is possible as a result of the discovery and synthesis of specific small molecules that inhibit the enzyme, protein farnesyl transferase [60, 61]. Preclinical studies of one such agent, R115777, have shown growth inhibition of a variety of human tumor xenografts implanted in nude mice. Specifically, an antiproliferative histologic response was shown when nude mice bearing CAPAN-2 human pancreatic tumors were treated with R115777 [62].

Recently, the EORTC reported the first phase I trial of the oral farnesyl transferase inhibitor SCH66336, given twice daily to patients with a variety of advanced solid tumors. Dose-limiting toxicities included myelosuppression, neurocortical toxicity, nausea, vomiting, and anorexia [63]. These investigators reported that a dose of 200 mg twice daily could be given orally for a prolonged period of time, and recommended this dose for further phase II trials.

Matrix metalloproteinase inhibitors (MMPIs), endogenous factors that tightly regulate the activity of proteases in the extracellular milieu, have been synthesized for potential therapeutic use. These include marimastat, prinomastat, and BAY 12-9566. Marimastat is an orally bioavailable agent that has been studied in patients with advanced prostate cancer, colorectal cancer, ovarian cancer, and pancreatic cancer. The dose-limiting toxicity is often musculoskeletal pain including arthralgias and myalgias [64]. One trial that compared oral administration of marimastat (5, 10, or 25 mg bid) with gemcitabine (1,000 mg/m²) in patients with advanced pancreatic cancer found a similar 1-year survival between patients who received 25 mg of marimastat and those who received gemcitabine [65]. However, no clinical efficacy was reported in a number of recently completed phase III trials using marimastat, prinomastat, or BAY 12-9566 alone or in combination with standard chemotherapy [66]. It is postulated that MMPIs may be important in the early aspects of cancer metastasis (local invasion and micrometastasis), and thus would not be expected to be effective in an advanced setting. Whether a role exists for these agents in the treatment of patients with early-stage tumors or very low-volume metastatic disease awaits further study.

Cyclooxygenase (COX) is a key enzyme in the conversion of arachidonic acid to prostaglandins and other eicosanoids. In vitro, animal and epidemiologic studies have shown a positive correlation between the expression of COX (especially COX-2) and colonic cancer growth and resistance to apoptosis [67, 68]. Based on its role in colon carcinogenesis, investigators have studied and confirmed that COX-2 is overexpressed in multiple pancreatic cancer cell lines [69-71]. Molina et al., from our institution, demonstrated cytoplasmic COX-2 expression in 14 of 21 (67%) pancreatic ductal carcinomas obtained at the time of pancreatectomy [69]. COX-2 expression was also found to be elevated in carcinomas relative to histologically normal pancreatic tissue obtained from the same individuals. Further, there was a dose-dependent inhibition of cell proliferation in five different human pancreatic cell lines produced by the nonselective COX inhibitor sulindac sulfide and the COX-2 inhibitor NS398. While the role of COX inhibitors for chemoprevention and possibly for adjuvant treatment of pancreatic cancer is unclear, clinical trials incorporating COX inhibitors are in development.

Tumor angiogenesis is important in the development and growth of metastatic implants, and a variety of endogenous angiogenic factors have been identified. One such peptide is vascular endothelial growth factor (VEGF), which is often overexpressed in pancreatic cancer [72]. This ligand and its receptor tyrosine kinase represent potential targets for inhibition of function and thereby tumor growth and metastasis.
A specific inhibitor of the receptor tyrosine kinase (Flk-1/KDR) for VEGF has been discovered (SU5416) [73]. Clinical trials investigating SU5416 as an anti-angiogenic agent are being designed and conducted, with initial results suggesting some activity. Two other angiogenesis inhibitory molecules that have been isolated from tumor-bearing animals are angiostatin, which is a peptide fragment of plasminogen, and endostatin, a fragment from collagenase XVIII [74]. Both angiostatin and endostatin have shown significant antitumor activity in animal models, and angiostatin has induced tumor dormancy in mice [75, 76]. Endostatin is currently undergoing phase I clinical testing.

In the absence of more effective systemic therapies for pancreatic cancer, the length and quality of life of patients with localized pancreatic cancer will be maximized by accurate preoperative assessment of resectability, standardized techniques of tumor resection, and the routine use of protocol-based adjuvant or neoadjuvant therapy. Pancreatectoduodenectomy should always be performed as part of a multimodality approach involving chemotherapy or chemoradiation. Whenever possible, all patients with pancreatic cancer should be offered protocol-based therapy.

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