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Preoperative chemoradiation strategies for localized adenocarcinoma of the pancreas*

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Abstract: Patients who undergo pancreaticoduodenectomy alone for adenocarcinoma of the pancreatic head or uncinate process have a median survival of 12 months, and a high incidence of local tumor recurrence (50%–80%) due to the common finding of positive margins following pathologic evaluation of pancreaticoduodenectomy specimens. The available prospective and retrospective data suggest improved survival duration and local-regional tumor control when pancreaticoduodenectomy is combined with 5-FU–based chemoradiation. However, the morbidity and prolonged recovery associated with pancreaticoduodenectomy frequently prevent the timely delivery of postoperative chemoradiation. In contrast, chemoradiation delivered prior to pancreaticoduodenectomy is not associated with toxic effects which delay surgery and has not been shown to increase surgical morbidity or mortality. In fact, recent data suggest that pancreaticojejunal anastomotic leaks, the most common major complication following pancreaticoduodenectomy, are decreased in patients who receive preoperative radiation therapy. Current and future multimodality treatment strategies will capitalize on our expanding understanding of tumor growth and metastasis, allowing more effective radiation sensitizing agents to be combined with external-beam irradiation and surgery, followed by the systemic or regional delivery of novel agents that inhibit essential steps in tumor cell growth.

Key words: pancreas cancer, pancreaticoduodenectomy, chemoradiation

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Introduction

Clinical research in pancreatic adenocarcinoma at the University of Texas M.D. Anderson Cancer Center (MDACC) has focused on the use of chemoradiation strategies as a mechanism to improve local-regional tumor control in patients with potentially resectable disease.[1] Critical to the accurate analysis of preoperative or postoperative adjuvant therapy is the incorporation of a standardized approach to patient selection (pretreatment staging), operative technique, and pathologic evaluation of surgical specimens. The inability of institutions to standardize these important variables is largely responsible for the small amount of data which currently exists on the use of multimodality therapy for pancreatic cancer (Table 1).[2–8] Therefore, we will briefly outline the critical aspects of radiographic staging, surgical technique, and pathologic evaluation of the resected specimen that are necessary to conduct multimodality clinical trials. This review will then focus on current and future strategies for the multimodality management of potentially resectable pancreatic cancer.

Preoperative radiographic staging

Accurate clinical staging requires high-quality (helical) computed tomography (CT) to accurately define the relationship of the tumor to the celiac axis and superior mesenteric vessels. Extension of the primary tumor to involve these vessels is the most common intraoperative finding responsible for local tumor unresectability. At MDACC, we generally use helical CT in the evaluation of patients with presumed pancreatic neoplasms. The development of helical or spiral scanning has improved scan speed; the continuous rotation of the X-ray tube around the gantry allows the entire pancreas to be imaged during the bolus phase of contrast enhancement. In addition, scan data can be processed to display im-

Table 1. Recent chemoradiation studies in patients with resectable pancreatic cancer

First author (Year)	No. of patients[a]	EBRT Dose (Gy)	Chemotherapy agent(s)	Median survival (months)
Postoperative (adjuvant)				
Kalser[5] (1985)	21	40	5-FU	20
Surgery alone	22	—	—	11
GITSG[3] (1987)	30	40	5-FU	18
Whittington[7] (1991)	28	45–63	5-FU, Mito-C	16
Foo[2] (1993)	29	35–60	5-FU	23
Yeo[8] (1997)	120	>45	5-FU	20
Surgery alone	53	—	—	14
Preoperative (neoadjuvant)				
Hoffman[4] (1998)	24	50.4	5-FU, Mito-C	16
Staley[6] (1996)	39	30–50.4	5-FU	19

EBRT, external-beam radiation therapy; 5-FU, 5-fluorouracil; Mito-C, mitomycin C
[a] All patients underwent a pancreatectomy with curative intent

ages in three-dimensional and multiplanar formats. Dilute Gastrografin or 2% barium sulfate is used to opacify the stomach and small bowel before scanning. Water can be used as an oral contrast agent when it is necessary to evaluate the gastric wall or duodenum. Precontrast CT of the liver and pancreas is performed at 10-mm slice thickness to localize the pancreas. Nonionic contrast material (300 mg/dl) is then delivered intravenously by an automatic injector at a rate of 2 to 3 ml/s for a total of 150 ml. Helical CT of the pancreas is performed 60 to 70 s after the start of the injection. A dynamic series of scans through the pancreas is completed at 3-mm slice thickness with a pitch factor of 1.5 to 2.0, depending on the anatomic extent of the tumor. The slice thickness can be increased to 5 mm in a large patient. The rest of the abdomen is then scanned at 7-mm slice thickness.

In the absence of extrapancreatic disease, the relationship of the low-density tumor mass to the superior mesenteric artery (SMA) and celiac axis is the main focus of preoperative imaging studies. The goal of both the pancreatic surgeon and the radiologist in assessing resectability is the accurate prediction of the likelihood of obtaining a negative retroperitoneal margin of resection. Local tumor resectability is most accurately assessed preoperatively; there is no role for exploratory surgery in patients with adenocarcinoma of the pancreas.[9] We utilize objective, reproducible radiologic (CT) criteria to define potentially resectable disease as: 1) the absence of extrapancreatic disease, 2) the absence of direct tumor extension to the SMA 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 (SMPV) confluence.

The accuracy of this form of radiographic staging has been demonstrated in two recent studies from MDACC.[10,11] Spitz and colleagues reported 142 patients with localized adenocarcinoma of the pancreatic head deemed resectable on the basis of radiographic images (criteria as stated above), 118 of whom were taken to surgery for planned pancreaticoduodenectomy. Ninety-four (80%) of the 118 patients underwent successful tumor resection; no patient had a grossly positive margin of resection, and the retroperitoneal margin was microscopically positive in only 17% of resected specimens.[11] The accuracy of CT in predicting unresectability[12,13] and the inaccuracy of intraoperative assessment of resectability[9] are both well established. Pretreatment staging to exclude patients with locally advanced disease is critical to allow accurate interpretation of results from studies examining the value of multimodality therapy in patients with pancreatic cancer.

Surgical technique: pancreaticoduodenectomy

Surgical resection incorporates a six-step technique for pancreaticoduodenectomy with specific attention to the retroperitoneal dissection along the right lateral border of the SMA.[14] This is because a survival benefit from surgical resection of the primary tumor is realized only in patients who undergo a negative-margin pancreaticoduodenectomy. The median survival of 8 to 12 months in patients who undergo pancreaticoduodenectomy and are found to have a positive margin of resection (Table 2)[7,15–20] is no different than the median survival reported in patients with locally advanced disease treated with palliative chemoradiation without surgical resection of the pancreas.[21] While most studies have not precisely defined the retroperitoneal margin, it is reasonable to assume that the margin most frequently reported as positive in patients who undergo pancreaticoduodenectomy is along the superior mesenteric vein (SMV) or proximal SMA.[20] Therefore, we do

Table 2. Median survival for patients who underwent surgical resection for adenocarcinoma of the pancreas and were found to have a positive margin of resection

Reference (year)	*n*	Margin	Median survival (months)
Tepper[15] (1976)	17[a]	G/M	8
Trede[16] (1990)	54	G/M	10
Whittington[7] (1991)	19	G	[b]
Willett[17] (1993)	37	G/M	11
Nitecki[18] (1995)	28	G	9
Yeo[19] (1995)	58	G/M	10
Lillemoe[20] (1996)	64	G/M	12

G, grossly positive margin; M, microscopically positive margin
[a] All patients also had positive regional lymph nodes
[b] Two patients alive at 18 months of follow-up

Table 3. Pathologic evaluation of the pancreaticoduodenectomy specimen

A. Frozen-section analysis
   1. Bile duct transection margin
   2. Pancreatic transection margin
B. Permanent-section analysis
   1. Retroperitoneal margin
   2. Tumor histopathologic type
   3. Degree of differentiation (tumor histopathologic grade)
   4. Tissue of origin (pancreas, distal bile duct, ampulla of Vater, duodenum)
   5. Maximal transverse tumor diameter
   6. Histologic evidence of invasion:
      Vascular
      Lymphatic
      Perineural
      Adjacent tissues (bile duct, duodenum, ampulla of Vater, stomach, peripancreatic tissues[a])
      Superior mesenteric or portal vein (when applicable)
   6. Standard pathologic evaluation of lymph node status (anatomic dissection board)
   7. Grade of chemoradiation effect (when applicable)

[a] Indicates tumor extension through the anterior capsule of the pancreas

not feel that current data justify operation in patients with evidence of arterial encasement on pretreatment imaging studies as it is impossible to perform a margin negative pancreaticoduodenectomy with tumor involvement of the SMA.

In contrast to tumor extension to the SMA, isolated involvement of the SMV or SMPV confluence is treated with venous resection and reconstruction. Traditionally, tumor involvement of the SMV or SMPV confluence has been considered a contraindication to pancreaticoduodenectomy. However, reports of venous resection at the time of pancreaticoduodenectomy often involved patients with retroperitoneal tumor extension involving the SMA or celiac axis resulting in incomplete tumor resection.[22,23] In contrast, isolated involvement of the SMPV confluence without radiographically evident involvement of the SMA can be managed intraoperatively with resection of the involved segment of vein and vascular reconstruction.[24] Data from MDACC demonstrate that resection of the SMV at the time of pancreaticoduodenectomy can be done safely and is not associated with retroperitoneal margin positivity (when high-quality preoperative imaging excludes patients with tumor extension to the SMA). Detailed evaluation of patients who required venous resection and reconstruction reveals a long-term outcome that is comparable to that of similarly staged patients not requiring vascular resection.[25,26] The fundamental distinction between tumor involvement of the SMV or SMPV confluence and tumor involvement of the SMA is critical to the accurate interpretation of any study reporting results of extended pancreaticoduodenectomy to include vascular resection and reconstruction.

Pathologic staging

Accurate pathologic assessment of surgical specimens is critical for both the evaluation of innovative preoperative treatment strategies and the development of reproducible predictors of patient survival and treatment failure. Retrospective pathologic analysis of archival material does not allow accurate assessment of margins of resection or number of lymph nodes retrieved. The standard pathologic evaluation of the pancreaticoduodenectomy specimen developed at MDACC[27] (Table 3) begins by first performing frozen-section evaluations of the common bile duct transection margin and the pancreatic transection margin. A positive bile duct or pancreatic transection margin is treated with re-resection. The retroperitoneal transection margin is defined as the soft-tissue margin directly adjacent to the proximal 3 to 4 cm of the SMA. This margin is evaluated by permanent-section microscopic examination of a 2- to 3-mm full-face (en-face) section of the margin. Re-resection (for a microscopically positive margin) is not possible in the retroperitoneum where the aorta and SMA origin limit the extent of surgical resection. Samples of multiple areas of each tumor, including the interface between tumor and adjacent uninvolved tissue, are submitted for paraffin-embedded histologic examination (5 to 10 blocks). Four-micron-thick sections are cut and stained with hematoxylin and eosin. 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), and assessments of maximal transverse tumor diameter, the presence or absence of

Table 4. Grading system for chemoradiation treatment effect

Grade	Histologic appearance
I	Characteristic cytologic changes of malignancy are present, but little (<10%) or no tumor cell destruction is evident
II	In addition to characteristic cytologic changes of malignancy, 10%–90% of tumor cells are destroyed
IIA	Destruction of 10%–50% of tumor cells
IIB	Destruction of 51%–90% of tumor cells
III	Few (<10%) viable-appearing tumor cells are present
IIIM	Sizable pools of mucin are present
IV	No viable tumor cells are present
IVM	Acellular pools of mucin are present

From ref. 29

perineural, lymphatic, and vascular invasion, and lymph node status and location (as outlined on the anatomical pathology dissection board). When segmental resection of the SMV is required, the area of presumed tumor invasion of the vein wall is serially sectioned and examined in an attempt to discriminate benign fibrous attachment from direct tumor invasion. In patients who receive preoperative chemoradiation, the grade of treatment effect is assessed on permanent sections (Table 4).[26]

As the use of multimodality treatment strategies for patients with pancreatic cancer becomes more common, it will be important to standardize pathologic assessment of tumor specimens. Our systematic approach should serve as a model for others engaged in protocol-based clinical research involving the surgical management of patients with pancreatic cancers.

Multimodality treatment strategies

External-beam radiation therapy (EBRT) and concomitant 5-fluorouracial (5-FU) chemotherapy (chemoradiation) have been shown to prolong survival in patients with locally advanced adenocarcinoma of the pancreas.[21] Those data were the foundation for a prospective, randomized study by the Gastrointestinal Tumor Study Group (GITSG) of adjuvant chemoradiation (500 mg/m^2/day of 5-FU for 6 days and 40 Gy of radiation) following pancreaticoduodenectomy. That trial demonstrated a survival advantage from multimodality therapy compared with resection alone.[3,5] However, because of a prolonged recovery, 5 (24%) of the 21 patients in the adjuvant chemoradiation arm could not begin chemoradiation until more than 10 weeks after pancreaticoduodenectomy. This, despite the obvious selection bias in patient accrual; the patients likely to be considered for protocol entry were those who recovered rapidly from surgery and had a good performance status. Similar findings have recently been reported from the European Organization for Research and Treatment of Cancer (EORTC). The EORTC initiated a study in 1987 comparing adjuvant 5-FU–based chemoradiation following pancreatectomy with surgery alone.[28] Between 1987 and 1995, 218 patients were randomized to receive either chemoradiation or no further treatment following pancreaticoduodenectomy for adenocarcinoma of the pancreas (55%) or periampullary region (45%). Median survival duration, reported in abstract form, was 23.5 months for those who received adjuvant therapy and 19.1 months for those who received surgery alone; subset analysis for patients with adenocarcinoma of pancreatic origin has not been reported. Importantly, 22% of those randomized to receive chemoradiation did not receive intended therapy due to postoperative complications or patient refusal.

A similar selection bias is likely to be in effect when attempts are made to retrospectively compare patients who received postoperative adjuvant chemoradiation with patients who were treated only with pancreaticoduodenectomy. However, recently reported data from Yeo and colleagues at Johns Hopkins University add further support to the use of multimodality therapy.[8] Those investigators reviewed all patients who underwent pancreaticoduodenectomy for adenocarcinoma of the pancreatic head during a 4-year period. One hundred and twenty patients received adjuvant chemoradiation, and 53 underwent pancreaticoduodenectomy alone. Median survival for those receiving adjuvant therapy was 19.5 months compared with 13.5 months for the group who received surgery alone.

The risk of delaying adjuvant therapy, combined with published experiences of successful pancreatic resection following EBRT, prompted many institutions to initiate studies in which chemoradiation was given preoperatively.[29,30] Results of these and other studies have suggested specific advantages of preoperative versus postoperative chemoradiation including the following:[1] 1) Because chemotherapy and irradiation were given first, delayed postoperative recovery had no effect on the delivery of multimodality therapy;[6,29] 2) Pancreaticojejunal anastomotic leaks, the most common major complication following pancreaticoduodenectomy, were decreased in patients who received preoperative chemoradiation;[31] 3) The high frequency of positive-margin resections recently reported supports the concern that the retroperitoneal margin of excision, even when negative, may be only a few millimeters — surgery alone is inadequate local therapy for most patients;[17] and 4) Patients with disseminated disease, evident on restaging studies after chemoradiation, will not be subjected to laparotomy.[11]

In patients who receive chemoradiation prior to planned pancreaticoduodenectomy, a repeat staging CT scan after chemoradiation reveals liver metastases in approximately 25%.[11] 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 a major surgical procedure only to have liver metastases found soon after surgery. In the MDACC trials, patients who were found to have disease progression at the time of restaging had a median survival of only 7 months.[11] The avoidance of a lengthy recovery period and the potential morbidity of pancreaticoduodenectomy in patients with such a short expected survival duration represents a distinct advantage of preoperative over postoperative chemoradiation. When delivering multimodality therapy for any disease, it is beneficial, when possible, to deliver the most toxic therapy last, thereby avoiding morbidity in patients who experience rapid disease progression not amenable to currently available therapies.

The survival advantage for the combination of chemoradiation and surgery compared with surgery alone (Table 1) likely results from improved local-regional tumor control. Because of the poor rates of response to 5-FU–based systemic therapy in patients with measurable metastatic disease, it is unlikely that current chemoradiation regimens significantly impact the development of distant metastatic disease.[1] Recent data from MDACC support this belief.[6,11] Thirty-nine patients with biopsy-proven adenocarcinoma of the pancreatic head received preoperative infusional 5-FU (300 mg/m^2/day, M-F) and EBRT (50.4 Gy) followed by pancreaticoduodenectomy and electron-beam intraoperative radiation therapy (10 Gy). Thirty-eight patients were evaluable for analysis of patterns of treatment failure; there was one perioperative death. Overall, there were 38 recurrences in 29 patients: 8 (21%) recurrences were local-regional (pancreatic bed and/or peritoneal cavity), and 30 (79%) were distant (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). Fourteen patients (37% of all patients; 48% of patients who had recurrences) had liver metastases as their only site of recurrence. Isolated local or peritoneal recurrences were documented in only four patients (11%). In contrast, previous reports of pancreaticoduodenectomy for adenocarcinoma of the pancreas have documented local recurrence in 50%–80% of patients.[1] This improvement in local-regional control was seen despite the fact that 14 of 38 evaluable patients had undergone laparotomy with tumor manipulation and biopsy prior to referral for chemoradiation and reoperation. If these 14 patients were excluded, only two patients (8%) would have experienced local or peritoneal recurrence as any component of treatment failure. However, because of the larger percentage of patients who developed distant metastatic disease, predominantly in the liver, improved local-regional tumor control translated into only a small improvement in median survival compared with that in other recently published studies. Therefore, in the absence of more effective systemic therapy, the goal of chemoradiation (preoperative or postoperative) and pancreatectomy should be to maximize local-regional tumor control while minimizing treatment time, treatment-related toxicity, and cost.

The first report of standard-fractionation chemoradiation (50.4 Gy over 5.5 weeks with concomitant 5-FU) from MDACC documented gastrointestinal toxic effects (nausea, vomiting, and dehydration) that required hospital admission in one third of patients.[29] The recently reported multicenter Eastern Cooperative Oncology Group (ECOG) trial documented the need for hospital admission in 51% of patients during or within four weeks of completing chemoradiation.[4] This finding caused us to change the delivery of EBRT and 5-FU to a rapid-fractionation program of chemoradiation designed to avoid the gastrointestinal toxicity seen with our standard 5.5 week program while attempting to maintain the excellent local tumor con-trol achieved with multimodality therapy.[32] Rapid-fractionation chemoradiation was delivered over 2 weeks with 18-MeV photons using a four-field technique to a total dose of 30 Gy, prescribed to the 95% isodose, at 3 Gy/fraction (10 fractions), 5 days/week. 5-FU was given concurrently by continuous infusion at a dosage of 300 mg/m^2/day, 5 days/week. This program was based on the principle that the total radiation dose required to obtain a given biological effect decreases as the dose per fraction increases. Restaging with chest radiography and abdominal CT was peformed 4 weeks after completion of chemoradiation in preparation for pancreaticoduodenectomy. Thirty-five patients received this treatment, 27 were taken to surgery, and 20 (74%) underwent successful pancreaticoduodenectomy. Local tumor control and patient survival were equal to our results with standard-fractionation (5.5 wks) chemoradiation.[33]

In an effort to compare preoperative and postoperative chemoradiation strategies we recently reported on the multimodality treatment of 142 consecutive patients with localized adenocarcinoma of the pancreatic head deemed resectable on the basis of pretreatment radiographic images.[11] The subset of 41 patients who completed protocol-based preoperative chemoradiation and pancreaticoduodenectomy (27 patients received standard-fractionation chemoradiation [50.4 Gy] and 14 patients received rapid-fractionation chemoradiation

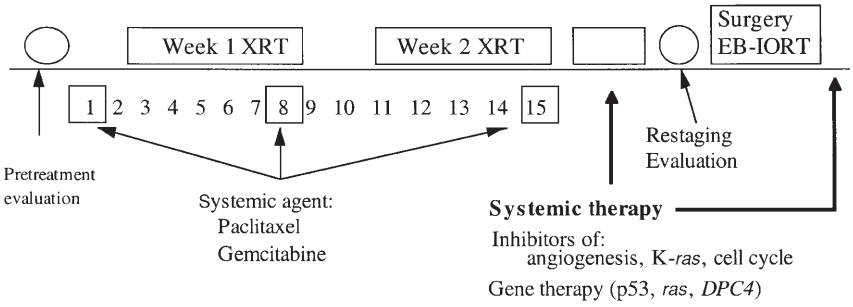

Fig. 1. The future of multimodality therapy for patients with potentially resectable adenocarcinoma of the pancreatic head. Treatment schemas emphasize the importance of minimizing toxicity, and treatment duration, while attempting to improve therapeutic efficacy. Cytotoxicity is enhanced by combining radiation therapy with more potent radiation-sensitizing agents. Systemic therapy is continued after both chemoradiation and surgery with systemic agents of low toxicity directed at specific molecular events involved in pancreatic tumorigenesis (i.e., inhibition of angiogenesis, the use of protease inhibitors [matrix metalloproteinase inhibitors], inhibition of *ras*-dependent signal transduction, or strategies for the use of gene therapy). *EB-IORT*, electron-beam intraoperative radiation therapy

[30 Gy]) were compared to 19 patients who received pancreaticoduodenectomy and postoperative adjuvant chemoradiation. Overall median follow-up for these 60 patients was 19 months. No patient who received preoperative chemoradiation experienced a delay in surgery because of chemoradiation toxicity, but 6 (24%) of 25 eligible patients did not receive intended postoperative chemoradiation because of delayed recovery following pancreaticoduodenectomy. Patients treated with rapid-fractionation preoperative chemoradiation had a significantly ($P < 0.01$) shorter duration of treatment (median, 62.5 days) compared with patients who received postoperative chemoradiation (median, 98.5 days) or standard-fractionation preoperative chemoradiation (median, 91.0 days) (Fig. 1). No patient who received preoperative chemoradiation and pancreaticoduodenectomy experienced a local recurrence; peritoneal (regional) recurrence occurred in 10% of these patients. Local or regional recurrence occurred in 21% of patients who received pancreaticoduodenectomy and postoperative chemoradiation.

New radiation sensitizing agents

Paclitaxel is a plant product isolated from the stem bark of *Taxus brevifolia*, the western yew, a small evergreen indigenous to the Pacific Northwest.[34] Paclitaxel enhances the polymerization of tubulin to stable microtubules, inhibiting spindle cell function during mitosis, thereby preventing normal cell replication. Cells exposed to paclitaxel experience growth arrest in the G2/M phase of the cell cycle — a state during which they are especially sensitive to irradiation. In clinical trials, patients with a variety of solid tumors including ovary, breast, and metastatic pancreatic adenocarcinoma have demonstrated objective responses to taxanes (paclitaxel and docetaxel) despite significant tumor burdens which failed to respond to conventional therapy.[34,35] Recently, Safran and colleagues from the Brown University Oncology Group performed a phase I study using paclitaxel and concurrent EBRT in patients with locally advanced pancreatic and gastric adenocarcinoma.[36] Dose-limiting toxicity was due to abdominal pain, nausea, and anorexia and occurred at 60 mg/m^2/week. Four objective (radiographic) partial responses were observed in 13 patients with pancreatic cancer.

The above data provide the rationale for the recently reported study from Vanderbilt of preoperative paclitaxel (30 to 75 mg/m^2/week) and concurrent standard-fractionation EBRT (45 Gy; 1.8 Gy/fraction) for patients with potentially resectable adenocarcinoma of the pancreatic head.[37] Five patients have been entered and four have undergone successful pancreaticoduodenectomy and are alive with a minimum follow-up of 15 months. At MDACC, paclitaxel (60 mg/m^2/week for 3 wks) has been combined with rapid-fractionation EBRT (30 Gy/2 weeks; 3 Gy/fraction). Preliminary experience with this regimen has demonstrated minimal toxicity and improved histologic response in the resected pancreatic tumor compared to previous studies with 5-FU-based preoperative chemoradiation (Evans, unpublished data).

Gemcitabine (2′,2′-difluorodeoxycytidine, Gemzar) is a deoxycytidine analogue capable of inhibiting DNA replication and repair. Following a phase I study,[38] gemcitabine was evaluated in a multicenter trial of 44 patients with advanced pancreatic cancer.[39] While only five objective responses were documented, the investigators noted frequent subjective symptomatic benefits, often in the absence of an objective tumor response. Toxicity appeared minor and included myelosuppression, particularly thrombocytopenia, as well as a

flu-like syndrome and mild hemolytic-uremic syndrome. Based on these observations, two subsequent trials of gemcitabine in patients with advanced pancreatic cancer have been completed. In one randomized trial, gemcitabine was compared to 5-FU in previously untreated patients.[40] Patients treated with gemcitabine had a median survival of 5.65 months compared to 4.41 months ($P = 0.0025$) in those treated with 5-FU. Twenty-four percent of patients treated with gemcitabine were alive at 9 months compared to 6% of patients treated with 5-FU. In addition, more clinically meaningful effects on disease-related symptoms (pain control, performance status, weight gain) were seen with gemcitabine (23.8% of patients) than with 5-FU (4.8% of patients). Similar systemic effects and demonstrable disease responses were documented in patients who were treated with gemcitabine after experiencing disease progression while receiving 5-FU.[41]

Gemcitabine is also a potent radiation sensitizer of human pancreatic cancer cells in vitro, supporting studies examining its use in vivo. Laboratory studies suggest that the inhibitory effect of gemcitabine on DNA synthesis (when combined with irradiation) is prolonged in tumor compared to normal tissues.[42] This may provide a window of opportunity for the combination of gemcitabine and EBRT when delivered in a fractionated schedule. Such data provide the basis for the recently reported phase I studies of this drug-radiation combination. Blackstock and colleagues treated 8 patients with combined standard-fractionation EBRT (50.4 Gy/5.5 weeks; 1.8 Gy/fraction) and twice weekly, escalating doses of gemcitabine (20 mg/m^2, 40 mg/m^2, 60 mg/m^2); no grade IV toxicites were observed and the MTD has not been reached.[43] McGinn and colleagues reported the treatment of 13 patients in a multiinstitutional setting with standard-fractionation EBRT (50.4 Gy) and an escalating weekly dose of gemcitabine (200 mg/m^2, 300 mg/m^2, 400 mg/m^2).[44] Three patients required hospital admission for nausea and vomiting. Enrollment continues at a gemcitabine dose of 500 mg/m^2/week, and the MTD has not yet been reached. Wolff and colleagues from MDACC have reported a phase I study of rapid-fractionation EBRT (30 Gy/2 weeks; 3 Gy/fraction) and concomitant weekly gemcitabine in patients with locally advanced adenocarcinoma of the pancreatic head.[45] Gemcitabine was given during the first two weeks of irradiation and continued weekly to complete a 7-week course of systemic therapy. At this schedule of administration, 500 mg/m^2/week was judged to be above the MTD for this drug-radiation combination. Five of 10 evaluable patients demonstrated response to treatment with an occasional impressive radiographic response.

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, 500 mg/m^2).[46] Eight of 15 patients were hospitalized after chemoradiation. Pancreaticoduodenectomy was completed in 8 patients, yet 6 of these 8 patients were found to have positive resection margins following pathologic analysis of the resected specimen.

Conclusion

Despite surgeons' ability to perform pancreaticoduodenectomy safely, it remains too extensive and complex a procedure to enable the consistent postoperative delivery of standard-fractionation adjuvant chemoradiation. In the absence of compelling data demonstrating superior survival results with either a preoperative or postoperative treatment approach, data from MDACC suggest that a greater proportion of patients receive potentially beneficial adjuvant therapy when chemoradiation is administered prior to pancreaticoduodenectomy. Moreover, preoperative treatment strategies will spare a significant number of patients the morbidity and mortality associated with laparotomy, as up to one-fourth of patients will evidence metastatic disease at the time of preoperative restaging following chemoradiation. Therefore, in an effort to build upon our experience with 5-FU-based chemoradiation, current (and future) therapies combine improved radiation-sensitizing agents, radiation therapy, and surgery with the systemic or regional delivery of novel agents that inhibit essential steps in tumor cell growth (Fig. 1).

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