Chemotherapy for Resectable and Advanced Pancreatic Cancer

This article will review the pertinent data on the use of chemotherapy for all stages of pancreatic cancer. For patients with metastatic disease, fluorouracil (5-FU) was the standard of care for several decades until a single agent.

Pancreatic carcinoma is the fourth leading cause of cancer death in the United States. Among the approximately 28,000 cases diagnosed each year, fewer than 5% live 5 years or longer. The American Joint Commission on Cancer (AJCC) has divided the progression of pancreatic cancer into four stages, but clinical decision-making is based on three levels of disease: local and resectable, locally advanced and unresectable, and metastatic disease. This article will discuss the role of chemotherapy at each stage of pancreatic cancer.

Metastatic Disease

Although a number of agents have been evaluated as treatment for pancreatic cancer, efficacy has been limited. Agents such as mitomycin (Mutamycin), doxorubicin, and epirubicin (Ellence) have produced some of the highest response rates, ranging from 13% to 27%. A comparison of phase II trials is limited in that most have been small, with varying proportions of patients with locally advanced (stages II and III) and metastatic (stage IV) disease. In addition, the use of various approaches to radiologic assessment and response criteria have resulted in widely disparate response rates, often for the same therapies.

Fluorouracil

The antimetabolite fluorouracil (5-FU) was among the earliest chemotherapy agents studied for the treatment of this disease. Until recently, it represented the standard against which other agents or combination chemotherapy regimens were tested. Early trials reported response rates > 20% for single-agent 5-FU. However, trials in the early 1990s reported response rates < 15%. In fact, a recent randomized trial showed no response in 57 patients with measurable disease treated with single-agent 5-FU. This decline in the response rate may have been caused by a number of factors. Changes in radiographic technology, which, in turn, led to an improvement in the ability to accurately measure disease, may be the largest contributing factor to this change.

Coadministration of other agents appears to modulate the intracellular effects or metabolism of 5-FU. Modulation of 5-FU with agents such as interferon-alpha, N-phosphonacetyl-l-aspartate (PALA), and leucovorin does not appear to have improved the efficacy of 5-FU. Altering the mode of 5-FU administration from bolus to infusion clearly changes the side-effect profile of 5-FU but does not affect efficacy. Phase II trials of infusional 5-FU have produced results similar to those obtained in trials of bolus 5-FU. Infusional 5-FU given to 24 patients in conjunction with interferon-alpha resulted in an 8% response rate and a median survival of only 4.6 months. Among 35 patients treated with infusional 5-FU in conjunction with PALA, the response rate was 14%, and the median survival was 5.1 months.

More recently, oral formulations of 5-FU have been developed that mimic infusional 5-FU pharmacokinetically without the inconvenience of an infusion port. One such agent is capecitabine (Xeloda), a prodrug converted intracellularly to 5-FU. Another agent (UFT) combines a prodrug, tegafur, with uracil; this compound competes with 5-FU for catabolism by dihydropyrimidine dehydrogenase and thereby reduces 5-FU breakdown. UFT and capecitabine have both been investigated for the treatment of pancreatic cancer and have produced response rates of 0% and 7.3%, respectively, and median survivals of 3.5 and 6 months.

Investigators have tried to improve the efficacy of single-agent 5-FU through the use of combination regimens. Table 1 lists a sampling of randomized chemotherapy trials in pancreatic cancer. Although combinations of 5-FU with doxorubicin (Adriamycin) and mitomycin (FAM), and 5-FU with a platinum, have demonstrated promising results in phase II trials, neither has proved superior to single-agent 5-FU.
Other regimens have met similar fates. The 10.2-month median survival reported in a small, early trial of an intensive multiagent schedule entitled the Mallinson regimen could not be duplicated in a larger randomized trial, which showed the strategy to be no more effective than 5-FU.[9] Finally, although combination regimens have not improved upon the efficacy of single-agent 5-FU, multiagent regimens such as FAM and ELF (etoposide, leucovorin, 5-FU) have produced longer survivals than best supportive care in small randomized trials (Table 1).[2,7-11] Nevertheless, single-agent 5-FU remained the standard of care for patients with advanced pancreatic carcinoma until recently.

**Gemcitabine**

Gemcitabine (Gemzar) has become the drug of choice for first-line treatment of pancreatic cancer. A pyrimidine nucleoside analog, the agent is activated to its triphosphate form by a series of enzymatic steps, starting with the actions of a rate-limiting enzyme, deoxycytidine kinase. The antitumor activity of gemcitabine correlates with DNA incorporation of gemcitabine triphosphate, and may be caused partially by its inhibition of ribonucleotide reductase (a key enzyme in the production of deoxynucleotides), leading to the depletion of normal deoxynucleotide pools.

*Phase II Trials*—Phase II trials of gemcitabine in pancreatic cancer have resulted in only 11% and 6.3% response rates.[12,13] Despite these low response rates, gemcitabine produced median survivals of 5.6 and 6.3 months, and investigators noted that some patients who did not achieve objective tumor responses did experience relief of tumor-related symptoms. To better study this observation, subsequent trials were designed to assess the effects of gemcitabine on specific disease-related symptoms, using a new measure “clinical benefit response.” Clinical benefit response encompasses an evaluation of pain, Karnofsky performance status (KPS), and weight loss and was first reported in a phase II trial in patients with pancreatic cancer refractory to 5-FU.[14] Although only 10.5% of patients with measurable disease had objective partial responses, 27% demonstrated clinical benefit responses.

*Phase III Trial*—A phase III trial comparing single-agent gemcitabine to 5-FU as first-line therapy was also conducted with a primary end point of clinical benefit response.[2] Survival was the secondary end point. Of 160 patients enrolled, 34 were not randomized, mostly due to rapid clinical deterioration. For the remaining 126 patients, clinical benefit response in the gemcitabine arm was significantly better than in the 5-FU arm (23.8% vs 4.8%, respectively, \( P = .0022 \)). Survival analysis also favored the gemcitabine arm with a median and 1-year survival of 5.65 months and 18%, respectively, compared to 4.41 months and 2%, respectively, for the 5-FU arm.

The treatment IND (investigational new drug application) supported the randomized trial data with a similar median survival of 5.1 months for chemonaive patients treated with gemcitabine.[15] Food and Drug Administration approval of gemcitabine was based on the randomized data. Gemcitabine was replaced by 5-FU as the control arm and current standard in more recent randomized trials. Significant effort has been focused on improving results with gemcitabine. First, laboratory data suggested that an alternative gemcitabine administration schedule might be advantageous.[16] The rate-limiting step in activating gemcitabine to its triphosphate form is deoxycytidine kinase. At an infusion rate higher than 10 mg/m²/min, deoxycytidine kinase is saturated. Thus, the standard schedule of 1,000 mg/m² over 30 minutes may not allow full conversion and activation of gemcitabine to gemcitabine triphosphate.

After a phase I study established 1,500 mg/m² administered at a fixed-rate infusion over 150 minutes as the recommended phase II dose, that dose was evaluated against 2,200 mg/m² over 30 minutes in a randomized phase II trial in patients with advanced pancreatic cancer.[16,17] As postulated, the 10 mg/m² infusion rate produced significantly higher intracellular levels of gemcitabine triphosphate in peripheral blood mononuclear cells. Patients treated with the longer infusion schedule also showed a trend toward improved survival, but patient numbers were small. These results justify further testing of the fixed-rate infusion in phase III trials.

**Gemcitabine-Based Combinations**—Another important development was the evaluation of gemcitabine-based combinations. One logical partner was 5-FU. Laboratory studies demonstrated additive effects against HT-29 cells when gemcitabine was administered either prior to or following 5-FU.[18,19] Examples of combination schedules that have been investigated are listed in Table 2. [20-24] As noted earlier, phase II trials have enrolled varying percentages of patients with locally advanced disease and other characteristics that may have had an effect on survival.

Three trials using identical regimens of gemcitabine, 1,000 mg/m² IV over 30 minutes, followed by a weekly bolus of 5-FU at 600 mg/m² for 3 of 4 weeks, illustrated the potential effects on survival in locally advanced patients.[20-22] The Eastern Cooperative Oncology Group (ECOG) trial only enrolled patients with metastatic disease and found a median survival of 4.4 months.[20] A larger
study from the Italian Group for the Study of Digestive Tract Cancer (GISCAD) enrolled 54 patients, 46% of whom had locally advanced disease, and reported a median survival of 7 months.[21] The Gruppo de Tumores Gastrointestinales (GETG) study, with 61% of patients having locally advanced disease, showed an 11-month median survival.[22] However, patients in the latter two studies also received leucovorin, 25 mg/m².[21,22] Because leucovorin and other factors may have contributed to the variability in survival rates, interpretation of these comparisons is limited. Other institutions have approached the combination strategy using infusional 5-FU schedules.[23,24] One of these trials, in which 34% of patients had locally advanced disease, reported a promising median survival > 10 months.[24] The ECOG has completed accrual of over 320 patients with locally advanced and metastatic pancreatic cancer to a phase III trial comparing gemcitabine plus bolus 5-FU with gemcitabine alone. Survival was the primary end point. Results were presented at the 2001 annual meeting of the American Society of Clinical Oncology (ASCO). Although the gemcitabine plus 5-FU arm had a survival of 6.7 months compared to 5.4 months for gemcitabine alone, this did not achieve significance (P = .09). Both arms of the trial had low response rates and similar toxicity profiles.[24a]  

Gemcitabine Plus Cisplatin[]Another agent demonstrating evidence of synergy in the laboratory when administered with gemcitabine is cisplatin (Platinol). Limited trials of cisplatin have been conducted in pancreatic cancer. While these have yielded mixed responses, early results from combination trials of cisplatin with gemcitabine have reported response rates ranging from 11.5% to 36.4%. The preliminary results of a randomized trial of cisplatin plus gemcitabine vs single-agent gemcitabine in 63 evaluable patients reported a higher response rate in the combination arm vs the gemcitabine arm (31% vs 10%, respectively).[27] However, this trial also measured clinical benefit response, which was fairly similar for the combination and gemcitabine arms (38% and 45%, respectively). Other platinum agents, such as carboplatin (Paraplatin) and oxaliplatin, are currently under investigation.  

Taxanes  

The taxanes are inhibitors of microtubule depolymerization, which leads to disruption of mitosis, motility, and cellular transport. Of the two currently available taxane analogs, docetaxel (Taxotere) demonstrated anticancer activity, with some studies reporting response rates of 20% or more in pancreatic cancer patients.[28-29] Table 3 lists a few of the published clinical trials involving docetaxel in pancreatic cancer.[28-31] Results have been variable, with some studies reporting median survivals in excess of 6 months. Combination trials of docetaxel and gemcitabine have also produced mixed results, with response rates as high as 33.3%, but the reports have been early and based on limited numbers of patients.[30,31]  

Camptothecins  

The camptothecin analogs (derived from the camptotheca acuminata tree) target topoisomerase I, a nuclear enzyme that normally unwinds, cleaves, and reattaches DNA for transcription and translation. The camptothecin analogs bind topoisomerase I, preventing resealing of the parent strand of DNA so that passage of the replication fork creates double-stranded DNA breaks. Thus, the camptothecins turn topoisomerase I into a cellular poison. Of the camptothecin analogs evaluated thus far for the treatment of advanced pancreatic cancer, irinotecan (CPT-11, Camptosar) and rubitecan (9-nitrocamptothecin, or 9NC) have shown some activity in phase II trials.  

Rubitecan[]The camptothecin analog rubitecan is an oral product that actually converts to 9-aminocamptothecin in the body, without producing the unpredictable side effects associated with camptothecin. The first trial of rubitecan performed in this setting was somewhat difficult to interpret.[32] The 31.7% reported response rate did not take into account 47 patients who were treated on protocol, and response was based on criteria that were not standard, such as changes in symptomatology. The trial reported a median survival of 6.7 months, including some patients with gemcitabine-refractory disease. A subsequent trial in gemcitabine-refractory pancreatic cancer patients demonstrated a response rate of 2.5%, although 27.5% of patients achieved stable disease.[33]  

An ongoing randomized trial is evaluating first-line therapy with rubitecan vs gemcitabine. Two trials of second-line therapy for gemcitabine-refractory pancreatic cancer are also enrolling patients; one will compare rubitecan to 5-FU and the other, rubitecan to "best treatment" as chosen by the individual oncologist. A single-agent phase II trial of irinotecan in 34 pancreatic cancer patients resulted in a response rate of 9%. Median survival was 5.2 months.  

Irinotecan Plus Gemcitabine[]With preclinical data suggesting benefit for the combination of irinotecan and gemcitabine, a phase II trial of irinotecan in combination with gemcitabine was conducted in pancreatic cancer patients.[35] Of the 45 patients enrolled (27% had locally advanced
disease), 9 (20%) responded to therapy, with a median survival of 6 months. A phase III analysis is currently evaluating irinotecan in combination with gemcitabine vs single-agent gemcitabine.

**Matrix Metalloproteinase Inhibitors**

Matrix metalloproteinases, the targets of matrix metalloproteinase inhibitors, are a collection of more than 25 enzymes that exist in a variety of normal and malignant tissues. Matrix metalloproteinases appear to play a role in the degradation of basement membrane and surrounding stroma, tumor angiogenesis, tumor cell invasion, and the establishment and growth of metastases. The matrix metalloproteinase inhibitors are currently being evaluated for the treatment of pancreatic cancer in phase III trials.

Two matrix metalloproteinase inhibitors, marimastat and BAY 12-9566, have completed phase III trials in patients with advanced pancreatic cancer. The randomized trial of marimastat vs gemcitabine showed no benefit with marimastat.[36] In the BAY 12-9566 trial, the median survival of 6.4 months with gemcitabine was significantly better than the 3.2-month survival with the matrix metalloproteinase inhibitor \( (P = .0001) \).[37] There is no definitive explanation for the apparent ineffectiveness of these agents. The simplest answer is that they have no activity against pancreatic cancer, as has been the case for so many classes of agents before.

The failure of the matrix metalloproteinase inhibitors to show any effect may be related to other functions, such as the inhibition of angiostatin. Angiostatin inhibits tumor growth, and although the matrix metalloproteinase inhibitors slow tumor growth by decreasing matrix degradation, they may also increase tumor growth by inhibiting angiostatin. Therefore, it is possible that the matrix metalloproteinase inhibitors selectively target a subpopulation of cells that is not large enough to produce a visible effect. Finding the cause for the lack of clinical activity seen with marimastat and BAY 12-9566 will help in designing future trials of other matrix metalloproteinase inhibitors.

**Conclusions About Metastatic Disease**

Single-agent gemcitabine has become the standard of care for metastatic pancreatic carcinoma. Currently, no single agent has achieved better results than those produced by gemcitabine. Combinations of other agents with gemcitabine are being evaluated in an attempt to improve on the efficacy of gemcitabine alone. The issue of clinical benefit will be important in combination trials, because small gains in survival will need to be accompanied with no loss in quality of life.

Although cytotoxic chemotherapy is the focus of this article, there may be a role for other treatment modalities such as immunotherapies, gene therapies, and possibly even hormonal therapies in the treatment of metastatic pancreatic cancer. Advances in systemic therapy for metastatic disease may be crucial to achieving improvements in the therapy of locally advanced and resectable disease.

**Locally Advanced, Unresectable Disease**

For decades, the treatment of locally advanced, unresectable pancreatic cancer was determined by the results of a few trials conducted by the Gastrointestinal Tumor Study Group (GITSG). The results of one large GITSG trial demonstrated that radiation alone was inferior to chemoradiation.[38] In that study, 227 patients were randomized to 60-Gy irradiation or 5-FU with either high-dose (60 Gy) or low-dose radiation (40 Gy). Although the radiation-alone arm produced only a 5.3-month median survival, the two combined-modality arms produced survivals of 9.3 and 9.7 months, respectively. Other trials explored the role of radiation and whether or not it enhanced the effect of the chemotherapy. The results of studies performed by ECOG and GITSG comparing chemotherapy alone to combined chemoradiation directly contradicted each other.[39,40] The GITSG randomized 43 patients to chemotherapy with SMF (streptozocin [Zanosar], mitomycin, 5-FU) or to 5-FU plus radiation followed by SMF chemotherapy.[39] This trial showed a significant survival benefit for chemoradiation over chemotherapy alone (median survivals of 9.7 and 7.4 months, respectively, \( P < .02 \)). However, the ECOG trial, which randomly assigned 50 pancreatic cancer patients to either 5-FU alone or 5-FU in conjunction with radiation therapy, showed an identical median survival of slightly more than 9 months for the two treatment arms.[40]

Both studies had weaknesses, however, and both were small. The ECOG trial was a stratified randomization that included both pancreatic and stomach cancer patients. Thus, neither study can be accepted as conclusive evidence for or against chemoradiation compared to chemotherapy alone.

**Infusions Prolong Drug Exposure**

Considering the short half-life of 5-FU, bolus injections, as used in the ECOG and GITSG trials listed above, provide very brief therapeutic exposures to the radiosensitizing agent. However, infusional 5-FU prolongs drug exposure during and after irradiation. An ECOG phase I trial determined that a continuous infusion of 5-FU at a dose of 250 mg/m²/d can be administered throughout a radiation
course of 59.4 Gy.[41] The median survival for the entire group of 25 patients with locally advanced
disease was 11.9 months with a 2-year survival rate of 19%. Although these results compared
favorably to those achieved with bolus 5-FU regimens, survival may have been improved by the
inclusion of nine biliary tract cancer patients. No subsequent randomized trials have been performed
to follow-up on these encouraging results.

As in metastatic disease, an alternative to continuous infusion of 5-FU is the use of oral 5-FU agents.
Preliminary results of a study of UFT and radiation therapy show this approach to be feasible.[42]

**Gemcitabine as a Radiosensitizer**

Because gemcitabine is effective in the metastatic setting, several trials have evaluated gemcitabine
as a radiation-sensitizing agent. True to the preclinical models suggesting that gemcitabine is a very
potent radiation sensitizer, the maximum tolerated dose of gemcitabine when given with radiation
has been well below the standard systemic dose. In one clinical trial of gemcitabine administered on
a twice-weekly basis, the recommended phase II dose was only 40 mg/m².[43] The dose-limiting
xicities were hematologic effects and nausea/vomiting.

One intriguing phase I trial conducted by McGinn et al used full-dose gemcitabine from study
initiation and escalated doses of radiation.[44] The rationale for this design was that pancreatic
cancer is a systemic disease, and with this regimen, the systemic therapy dose was not sacrificed for
the local treatment. Radiation was administered for 3 weeks, starting at 1.6 Gy/fraction and
escalating to 1.8 Gy/fraction. At last report, the dose of radiation was 2.0 Gy/fraction (total dose: 30
Gy). Of the five dose-limiting toxicities, four were hematologic and one was duodenal ulcer. A second
duodenal ulcer was not dose-limiting. However, the results of this and most related trials are
preliminary, and the use of the combination of gemcitabine and radiation is not recommended
outside the context of a well-designed clinical trial.

Using the rationale that both 5-FU and gemcitabine show some level of antitumor activity and both
can be radiosensitizers, several phase I trials have studied both drugs in conjunction with radiation.
ECOG attempted to build on the results of the previously discussed phase I trial using a continuous
infusion of 5-FU in conjunction with weekly gemcitabine.[45] Unfortunately, at 200 mg/m²/d of 5-FU,
even very low doses of gemcitabine (50 mg/m²/wk) were not tolerated. A second group using
continuous-infusion 5-FU at 200 mg/m²/d with 100 mg/m²/wk of gemcitabine reported similar initial
results.[46] However, reducing the schedule of infusional 5-FU from 7 to 5 days per week allowed
dose escalation. Nevertheless, systemic doses of chemotherapy are generally compromised when
coadministered with radiation therapy.

**Conclusions About Locally Advanced, Unresectable Disease**

It can be argued that there is no current standard for the therapy of locally advanced, unresectable
pancreatic cancer. Although chemoradiation is a commonly used treatment, the fact that these
patients are frequently enrolled in trials of chemotherapy alone strongly suggests a lack of
confidence in the limited evidence favoring chemoradiation. The newer chemotherapy agents may
prove more effective than 5-FU as radiation sensitizers, but they may be more useful for systemic
control. As evidenced by the high risk of recurrence among patients with resected pancreatic cancer,
this disease is generally systemic at diagnosis, regardless of radiographic appearance. Thus,
advances in systemic therapy are likely to be the source of future advances in the treatment of
locally advanced disease as well as metastatic disease.

**Adjuvant Therapy**

Unfortunately, few patients with pancreatic cancer present with potentially resectable disease. For
this group of patients (generally stage I), the treatment of choice is surgery. However, retrospective
analyses suggest that median survival, even today, is only 15.5 months, with 21% of patients alive
at 5 years.[47] Therefore, adjuvant chemotherapy and radiation have been studied in an attempt to
improve on the operative results.

**Key Clinical Trials**

There are four reported adjuvant therapy trials of chemotherapy in patients with resected pancreatic
cancer. **GITSG Trial** The frequent use of adjuvant therapy is based on the results of the Gastrointestinal
Tumor Study Group (GITSG) trial,[48] in which 43 patients were randomized to receive adjuvant
therapy (21 patients) or no adjuvant therapy (22 patients). Adjuvant therapy consisted of 4,000 cGy
of radiation administered in two courses of 2,000 cGy each over 2 weeks, with 5-FU, 500 mg/m²,
given on days 1 to 3 of each course. This regimen was followed by 500 mg/m² of 5-FU weekly for 2
years.
The study took 8 years to accrue the few patients enrolled. Nonetheless, there was a significant increase in median (21 vs 11 months, \(P = .05\)) and 2-year survival (43\% vs 18\%, \(P = .05\)) among patients in the chemoradiation arm, compared to the surgery alone arm. Because of the small number of patients randomized, the GITSG performed a phase II trial in which 30 additional patients were treated with the same chemoradiation regimen and achieved similar results, with a median survival of 18 months.[49]

**Norwegian Trial** A second trial, from Norway, randomized 61 patients to either AMF (doxorubicin [Adriamycin], mitomycin, 5-FU) after surgery or surgery alone.[50] AMF produced a prolonged median survival similar to that observed in the GITSG study despite the lack of irradiation, but long-term survival was not affected by adjuvant chemotherapy.

**EORTC Trial** More recently, two European trials reevaluated the utility of adjuvant therapy in the treatment of this disease. The European Organization for Research and Treatment of Cancer (EORTC) trial enrolled 218 patients with periampullary tumors and pancreatic cancer.[51] Patients were stratified by tumor location (periamplillary vs pancreatic), and randomized to either continuous-infusion 5-FU during radiation therapy after surgery or surgery alone. No postradiation chemotherapy was given.

Of the 218 randomized patients, 207 were eligible, and 114 of the eligible patients had pancreatic cancer. When all 207 patients were analyzed, survival in the control group was not significantly different than in the adjuvant therapy group (19 vs 24.5 months, respectively). Among the pancreatic cancer patients, there was a trend toward improved median survival in the adjuvant therapy group (17.1 vs 12.6 months, \(P = .099\)). Given that this was just a trend, the researchers concluded that there was no benefit to the use of adjuvant therapy in pancreatic cancer.

**The ESPAC Trial** The European Study Group for Pancreatic Cancer (ESPAC)-1 trial was designed as a 2 × 2 randomization with one randomization to either chemotherapy or no chemotherapy, and the other to radiation or no radiation in patients with pancreatic cancer after potentially curative resection.[52,53] (While a 2 × 2 design creates four subgroups, it is not designed to find the "best" subgroup among the four.) Even in the radiation alone arm, radiation was administered with radiosensitizing chemotherapy, following the same protocol used in the GITSG study. Chemotherapy, alone or after irradiation, was given as a five-times-daily bolus of 5-FU repeated on a monthly basis for six cycles.

There was no significant difference in survival between the chemoradiation group and the no-chemoradiation group (14 vs 15.7 months, respectively, \(P = .24\)). However, the median survival of patients who received chemotherapy was significantly better than that of those who did not (19.5 vs 13.5 months, respectively, \(P = .003\)). The effect of chemotherapy appeared to be diminished by the addition of radiotherapy.

Critics have suggested that the flaws in this study prevent any definitive conclusions to be drawn about adjuvant therapy for pancreatic cancer. The inclusion of patients with positive margins may have had an impact on local recurrence rates as well as metastatic recurrences, because margins would denote noncurative resection. Also, several sites included in this study did not have access to either chemotherapy or radiation. Those sites participated in one of the two randomizations, but not both. This created three different randomization protocols. It is unclear how inclusion of these sites may have affected the results in a 2 × 2 design. However, based on data derived from this trial, the next (ongoing) ESPAC trial was designed to confirm the results achieved in the chemoradiation arm by evaluating a control arm of surgery alone vs surgery followed by chemotherapy.

**Trial Considerations** Why have the trials been unable to establish a definitive benefit for adjuvant therapy? It is possible that the flaws in study design noted by critics have prevented the benefits from being realized. It is also possible that the agents used were ineffective. Radiation may not confer a clear benefit and in ESPAC-1 there was even suggestion of detriment because pancreatic cancer is a systemic illness. Ultimately, more studies need to be conducted.

The cooperative groups in the United States have also initiated an adjuvant trial evaluating gemcitabine as systemic therapy vs 5-FU (systemic therapy being given 2 months prior to and 2 months after the chemoradiation). Both arms of the intergroup trial will receive the same chemoradiation regimen. Thus, with no arm limited to surgery alone, the intergroup trial will answer questions about systemic therapy but will not contain an established control arm.

**The Neoadjuvant Approach** What might the next step in adjuvant therapy be? There are concerns that up to one-fourth of patients undergoing resection do not recover quickly enough to receive adjuvant therapy.[54] To avoid this problem, some investigators have studied the neoadjuvant approach. Several phase II trials of this approach are listed in Table 4.[55-58] However, the potential benefits of a neoadjuvant...
approach remain theoretical. In two retrospective analyses, survival was no better for patients treated with the neoadjuvant approach than for those treated postoperatively. [54,59] At present, use of neoadjuvant therapy in pancreatic cancer should remain limited to clinical trials.

Conclusions About Resectable Pancreas Cancer
The standard for treatment of early stage disease is resection. However, surgery alone does not cure the majority of patients with pancreatic cancer. Thus, a multidisciplinary approach appears necessary to improve on the current results. To that end, when carefully analyzed, adjuvant therapy trials have suggested a benefit for chemoradiation, although some argue that chemotherapy alone might suffice. As mentioned previously, advances in systemic therapy will be the source of improvements in the adjuvant therapy of this disease.

Future Considerations
Due to the systemic nature of pancreatic cancer, refining the radiation and surgical therapies of this disease is likely to have a modest impact on survival. Future improvements in the prognosis of patients with pancreatic cancer will stem from new systemic therapies and multimodality approaches. Although cytotoxic agents in various phases of development have shown promising activity, other targets for therapy need to be evaluated. As mentioned, hormonal therapies may have a role in the systemic treatment of this disease; however, results, thus far, have been mixed. Immunotherapy and gene therapy approaches have entered initial trials. Advocates of immune therapy have suggested that this modality may prove most effective in minimal disease settings such as adjuvant therapy after surgical resection.

Agents With Novel Targets
Growing knowledge of the molecular biology of cancer has led to a proliferation of new anticancer agents with novel targets. Several classes of these agents are now entering trials. Matrix metalloproteinase inhibitors were among the first of several classes tested that target the matrix within which cancer grows. Agents that target the process of new blood vessel formation have also entered clinical trials. The farnesyl transferase inhibitors were designed to block the activation of the Ras protein. This protein, of which the kirsten-Ras (k-Ras) isoform is mutated in the majority of pancreatic cancer patients, activates a kinase cascade that results in cellular growth. The mutated form remains activated longer than the wild-type, leading to uncontrolled growth. The farnesyl transferase inhibitors are currently in phase II and III trials, but whether their true mechanism of action is preventing the activation of k-Ras is in question. Inhibitors of growth factors in the HER family may also play a role in pancreatic cancer. Trastuzumab (Herceptin), which inhibits HER2/neu, is undergoing evaluation in patients who overexpress HER2/neu. The inhibitors of another member of the HER family, the epidermal growth factor receptor (EGFR), have entered clinical trials as well. While some of the EGFR inhibitors are chemicals and may be considered chemotherapies, others are antibodies, and still others are antisense oligonucleotides. Newer classes of agents are just entering clinical trials, and whether effective alone or in combination with standard cytotoxic therapy, the hope is that they will significantly alter the future of patients with pancreatic cancer.

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