Original Article

The Current Status of Combined Radiotherapy and Chemotherapy for Locally Advanced or Resected Pancreas Cancer

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Key Words

Pancreas cancer, chemotherapy, radiotherapy, locally advanced, adjuvant

Abstract

Pancreas cancer is the fourth most common cause of cancer deaths. Even for the small percentage of patients who can undergo surgical resection of the primary tumor, the risk of recurrence remains unacceptably high. For patients with localized disease that is not amenable to surgical resection, pain related to the primary tumor can significantly impair quality of life. Attempts to improve the duration and quality of life for these patients have included both chemotherapy and radiotherapy. The addition of chemotherapy to radiation may enhance the local effects of radiation or provide treatment of disease outside the radiation field. The results of clinical trials evaluating the appropriate therapy for locally advanced or resected disease have been inconsistent. In some instances, the methods used in these studies became outdated before the results were available. Hopefully, advances in radiation techniques and systemic drug therapy will provide more durable and clinically relevant results. Meanwhile, treatment decisions should be tailored to the clinical situation, including consideration of treatment toxicity and therapy goals. Recognizing which patients are likely to benefit from combination therapy or systemic therapy alone is a subject of future and ongoing clinical trials. (*JNCCN* 2005;3:637–642)

Pancreas cancer is the tenth most common diagnosed cancer in the United Sates and the fourth most common cause of cancer deaths.[1] In 2005, pancreas cancer will be diagnosed in 32,180 patients, of whom 50% will have metastatic disease at presentation, 10% to 15% will be resectable, and the remaining will have locally advanced unresectable disease. The median survival for patients diagnosed with metastatic disease is approximately 6 to 8 months with gemcitabine-based chemotherapy.[2] Concurrent chemotherapy and radiation have been shown to offer a palliative benefit for patients with locally advanced disease and may improve survival to 12 months. Resectable disease has been treated with chemotherapy and radiation as adjuvant therapy after resection and as neoadjuvant therapy before exploration. Recent data support the use of chemotherapy for resected disease.[3,4] The role of radiotherapy is more controversial. The median survival for patients with resected disease approaches 20 months, with a 5-year survival of 15% to 20%.

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Rationale for Chemoradiotherapy

Surgical resection for pancreatic cancer remains the only therapeutic option that offers a chance at long-term survival. However, after surgical resection alone, single institution reviews have shown locoregional recurrence rates of 50% to 85% and hepatic metastasis in approximately 60% of cases.[5–7] Researchers have proposed that the primary route of spread to the liver is via the lymphatics along the hepatoduodenal and gastroduodenal ligaments, and that this pattern of failure is consistent with persistent disease in the upper abdomen in the postoperative setting.[8]

The goal of radiation is to eradicate tumor in the upper abdomen. A typical external beam radiation dose is 50.4 Gy, with possible reductions in field size after 45 to 50 Gy using multiple fields. Treatment volumes include the preoperative tumor bed delineated on preoperative computed tomography (CT) scan and the regional lymphatics. CT-based individualized treatment planning

is recommended to limit normal tissue toxicity and target specific structures with anatomic variability, such as the superior mesenteric and celiac axis lymph nodes.[9] The use of prophylactic hepatic irradiation was investigated by the Radiation Therapy Oncology Group (RTOG) in an effort to reduce hepatic metastases; however, no obvious survival advantage was seen, and failure to control abdominal disease and primary tumor remained the principal concern.[10]

Circumstantial data indicate that DNA is the critical target for the biologic effects of radiation.[11] Cells that are inhibited from repairing DNA damage or that are naturally deficient in DNA repair enzymes show a distinct radiosensitivity. DNA damage probably occurs as a result of indirect effects on the DNA from radiation-induced ionization of surrounding water. The ionization of water creates hydroxyl radicals, peroxide, hydrated electrons, and oxygen radicals. These highly reactive free radicals interact with DNA, causing double strand breaks that result in mitotic death.

The radiosensitivity of cancer cells changes as cells progress through the cell cycle. These differences are probably caused by chromosome susceptibility at different parts of the cell cycle (i.e., increased susceptibility to radiation during early S phase when the DNA is uncoiled) and the efficiency of chromosome repair (i.e., most efficient during late S phase and early G_2, making the cells radiation resistant). Radiosensitizers can manipulate the cell to maximize cell kill by inhibiting DNA repair and arresting cells in susceptible phases of the cell cycle. Apoptosis (programmed cell death) has also been implicated as a means of radiation induced cytotoxicity.

Chemotherapeutic agents have been shown to make cancer cells more susceptible to death by radiation than the surrounding healthy cells. The mechanism that produces cytotoxicity is often not the same mechanism that increases radiation sensitivity.

The radiosensitizing properties of 5-fluorouracil (5-FU) results from increased DNA damage, with a decrease in DNA repair capability and accumulation of cells in the early S phase.[12] Conversely, paclitaxel inhibits microtubule depolymerization, which blocks cell cycle progression, accumulating tumor cells in the G2/M phase.[13] The mitotic arrest forces tumor cells to remain in the most radiosensitive phase of the cell cycle.

Gemcitabine has exhibited radiosensitizing properties in vitro, even at non-cytotoxic doses.[14] The mechanism for gemcitabine-induced radiation enhancement is not dependent on the increased pools of dFdCTP (the metabolite required for cytotoxicity) but does require the cells to be depleted of dATP and arrested in S phase. Additionally, gemcitabine did not affect either radiation-induced DNA damage or repair. Exploiting these properties of chemotherapy have enhanced the efficacy of radiotherapy.

Randomized Studies

Locally Advanced Disease

A series of randomized studies of therapy for locally advanced pancreas cancer were performed in the United States by the Gastrointestinal Tumor Study Group (GITSG). Based on findings from various single-arm studies, 227 subjects were randomized to receive high-dose (60 Gy) radiation, moderate-dose (40 Gy) radiation with 5-FU, or high-dose radiation with 5-FU.[14,15] Radiation was delivered at 2 Gy per day, 5 days each week for 2 weeks followed by a 2-week break period (split-course). 5-FU was given at 500 mg/m^2 daily for 3 days of each 2-week radiation course. After completion of combination therapy, maintenance 5-FU was given at 500 mg/m^2 weekly for 2 years or until tumor progression.

With approximately 25 subjects in each arm, the authors found high-dose radiation without 5-FU clearly inferior to both of the regimens containing 5-FU, and this study arm was discontinued. Median survival times in the arms containing 5-FU was nearly double that of the non-chemotherapy arm (42.2 and 40.3 weeks compared with 22.9 weeks; $P < .01$). The predominate site of first progression in all arms was simultaneous local and distant metastases.

Attempts to improve on the systemic control of localized pancreas cancer led to the randomized trial comparing systemic chemotherapy with combination chemotherapy and radiation.[16] A regimen of 5-FU, mitomycin, and streptozocin (SMF) was compared with radiation (54 Gy) given 5 days each week for 6 weeks, with 5-FU at 350 mg/m^2 for the first 3 days and last 3 days of radiation followed by the SMF regimen. Systemic chemotherapy continued for a total of 2 years or until disease progression. With 43 subjects treated, 12-month survival was clearly higher (41%) with combination therapy than with systemic chemotherapy alone (19%).

Subsequent studies by the GITSG showed no benefit to the use of doxorubicin with moderate-dose radiation delivered on a continuous schedule compared with high-dose radiation with 5-FU delivered on a split-course schedule.[17] Despite a lower total

radiation dose, the doxorubicin-containing regimen had significantly greater toxicity.

Hyperfractioned radiation dosing with chemotherapy was explored in a single-arm study showing excessive toxicity and a median survival of 35 weeks.[18] Phase I and II studies have shown that the use of continuous infusion 5-FU throughout the radiation course is effective, with less toxicity.[19–21] This has been the accepted standard used in subsequent clinical trials.

Adjuvant Therapy

The benefit shown with combination chemotherapy and radiation in locally advanced disease led to evaluation of these regimens as adjuvant therapy after surgical resection. Forty-three subjects with all disease resected were randomized to undergo observation alone or combination chemotherapy with 5-FU and split-course moderate dose radiation as used in the original GITSG study.[22] The treatment group showed a survival benefit compared with the observation group with a median survival of 20 months compared with 11 months, respectively, and a 2-year survival of 43% compared with 18%, respectively ($P < .03$). An additional 30 subjects were treated with the adjuvant therapy to confirm these findings.[23] In the confirmatory study, a median survival of 18 months was seen, with a 2-year survival rate of 46%, which is consistent with the patients in the treatment group of the randomized study. Based on these studies, the combined use of radiation therapy and 5-FU was recommended after surgical resection.

The European Organization for Research and Treatment of Cancer (EORTC) conducted an analogous study of combination therapy compared with observation for 218 patients with resected disease.[24] Subjects were treated with radiation to a total dose of 40 Gy using the split-course radiation schedule, with 5-FU at a dose of 25 mg/kg as a continuous infusion over 24 hours during radiation only. Systemic chemotherapy was not continued after completion of combination therapy. The toxicity profile seen for the treated patients was favorable, with no significant hematologic toxicity, no dose reductions of 5-FU needed, and only one major toxicity. However, therapy showed no demonstrable benefit, with progression free survival rates of 16 and 17.4 months in the observation and treatment groups, respectively; and 2-year progression free survival of 38% and 37%, respectively. The site of first progression (locoregional compared with distant) and location of distant progression (liver, lung, or other) were identical for both arms.

Why the results of this study differed from those in the U.S. study is unclear. The EORTC study did not include systemic 5-FU chemotherapy after completion of combination therapy; however, 5-FU alone has never been shown to have a significant impact on patient survival in pancreatic cancer. What may be more important is the inclusion of patients with ampullary cancer (~44%) in the EORTC study but not in the GITSG study. Ampullary cancer is associated with a better prognosis independent of stage and patients may not benefit to the same degree from adjuvant therapy as those with pancreatic cancer. Regardless, this divergence has led to ongoing debate and differences in opinion concerning the appropriate therapy for resected pancreas cancer.

The European Study Group for Pancreatic Cancer (ESPAC) pursued a multicenter trial to further assess the benefit of 5-FU-based chemoradiotherapy and maintenance chemotherapy.[3] The study was designed as a 2×2 factorial randomization in which 289 subjects were randomized to receive chemoradiotherapy, chemotherapy, chemoradiotherapy followed by chemotherapy, or observation. The results were to be analyzed for chemoradiotherapy compared with no chemoradiotherapy and chemotherapy compared with no chemotherapy. However, because of poor compliance with the assigned treatment arm, two further random assignment options were introduced, comparing chemoradiotherapy with observation and chemotherapy with observation.

Subjects were stratified according to the treatment center and resection margin status (positive or negative). The radiotherapy was split-course to a total dose of 40 Gy similar to the GITSG trial, with bolus 5-FU 500 mg/m^2 given on the first 3 days of each radiotherapy course. The chemotherapy was given as a bolus injection of 5-FU 425 mg/m^2 and leucovorin 20 mg/m^2 for 5 days every 28 days for 6 cycles. The investigators found a worse median survival with chemoradiotherapy compared with no chemoradiotherapy (15.9 vs. 17.9 months; $P = .05$), and an improved median survival with chemotherapy compared with no chemotherapy (20.1 vs. 15.5 months; $P = .009$). The median survival in the observation alone arm was 16.9 months. The study was not powered to perform comparisons across the 4 treatment groups. Although data for complete recurrence were not reported, of all recurrences, local recurrences were a component in 62% of cases.

Based on these results, the ESPAC investigators concluded that adjuvant chemotherapy should be the standard of care after surgical resection. These conclusions are not generally accepted, however, because the study design and outdated radiation schedule limit the relevance of this study for the adjuvant treatment of resected pancreas cancer.[25]

New Approaches

Since the results of these studies have become available, advances have been made in the delivery of radiation and the development of more active chemotherapeutic agents. Researchers have shown that split-course radiotherapy, as used in the early GITSG studies and the ESPAC study, is suboptimal compared with uninterrupted radiation. This may account for the poor local control seen with the use of chemoradiotherapy in the ESPAC study. Furthermore, clinical trials incorporating radiation critically must adhere to strict quality control and field specifications, which was not done in the ESPAC study. In addition, all of the prior studies were designed and conducted before gemcitabine was recognized as an active chemotherapy agent in pancreatic cancer. Gemcitabine is also known to have potent radiosensitizing properties. Clinical trials incorporating these advances are ongoing.

Preliminary results of a recently reported adjuvant study evaluated chemotherapy with gemcitabine compared with observation after surgical resection. Median disease-free survival was 14.21 months compared with 7.46 months ($P = .001$).[4] The RTOG is evaluating the addition of gemcitabine therapy to chemoradiation (unpublished data). After complete surgical resection, all subjects received uninterrupted radiation to 50 Gy with continuous infusion 5-FU at 250 mg/m^2 daily and were randomized to receive either 5-FU or gemcitabine chemotherapy before and after combined chemoradiation. The results of this study should be available soon and will help to clarify the contribution of chemotherapy in addition to chemoradiotherapy.

Investigators at the Virginia Mason Medical Center evaluated the use of radiotherapy and 3-drug therapy with 5-FU, cisplatin, and alpha interferon (IFNα) in the adjuvant setting.[26] The study involved 43 subjects with resected adenocarcinoma of the pancreatic head; 86% of the subjects had stage III or IVa disease and 84% had lymph node involvement. The patients received between 45 and 54 Gy to the pancreatic bed over 5 weeks, and concurrent with radiotherapy, continuous infusion 5-FU at 200 mg/m^2 (days 1–35), bolus cisplatin 30 mg/m^2 (days 1, 8, 15, 22, 29), and subcutaneous IFNα 3 million units every other day (days 1–35) were administered. After chemoradiation, continuous infusion 5-FU at a dose of 200 mg/m^2 daily (days 64–105 and 120–161) was given. Significant toxicity was encountered, with 42% requiring hospitalization during therapy. Mean follow-up was 31.9 months, and 2-year and 5-year actuarial overall survival rates were 64% and 55%, respectively. Median survivorship had not yet been reached. The American College of Surgeons Oncology Group (ACOSOG) has also pursued a single-arm phase II study using the Virginia Mason regimen. If these impressive results can be duplicated, a phase III study will be initiated.

As mentioned previously, gemcitabine is a potent radiosensitizer and also the most effective systemic therapy for pancreas cancer. In an attempt to maximize the radiosensitizing properties, the Cancer and Leukemia Group B (CALGB) conducted a study of gemcitabine at a dose of 40 mg/m^2 given twice weekly with continuous standard radiation for locally advanced pancreas cancer.[27] The median overall survival for 38 subjects was only 8.2 months. Dose escalation of gemcitabine to achieve effective systemic concentration has proven to be challenging. A dose escalation schema of gemcitabine from 50 to 100 mg/m^2 weekly was attempted in combination with continuous infusion 5-FU and radiation to 59.4 Gy.[28] Excessive toxicity was encountered, requiring dose de-escalation and eventual abandonment of the regimen.

Previous gemcitabine-based combined-modality regimens used standard radiotherapy doses, fractionation, and field size (including prophylactic treatment of celiac and portal lymph nodes). A recent phase I trial investigated the use of standard gemcitabine doses with modified radiotherapy fields and reduced radiotherapy doses.[29] Using a field size consisting of the gross tumor volume with a 1-cm margin and a radiation dose of 2.4 Gy for 15 fractions, the standard dose of gemcitabine (1,000 mg/m^2) was tolerated when given weekly during 3 weeks of radiation. Three-dimensional radiation treatment planning was used in all cases.

A multi-institution phase II trial using a similar regimen for localized pancreas cancer was completed.[30] Twenty subjects enrolled had potentially resectable disease. Gemcitabine was given at a dose of 1,000

mg/m^2 on days 1 and 8 of a 21-day cycle preceding and after a 28-day cycle of gemcitabine (1,000 mg/m^2 on days 1, 8, and 15) and concurrent radiation. Nineteen subjects (95%) completed therapy without interruption, and one experienced grade 3 gastrointestinal toxicity. Of 20 patients, 17 (85%) underwent pancreaticoduodenectomy. Pathology revealed clear margins in 16 of 17 (94%) and uninvolved lymph nodes in 11 of 17 (65%). With a median follow-up of 18 months, 7 (41%) of the 17 patients who had undergone resection are alive with no recurrence, 3 (18%) are alive with distant metastases, and 7 (41%) have died. Not only did this trial show the safety of this preoperative gemcitabine-based combined-modality regimen, but the surgical findings suggest significant tumor response.

Future Studies

Ongoing studies are being conducted to evaluate the appropriate use of chemoradiation in the treatment of locally advanced and resected pancreas cancer. Chemoradiotherapy clearly has a role in palliating symptoms, particularly pain, related to the primary pancreas tumor. Furthermore, all the studies showing a survival benefit for chemoradiation compared with chemotherapy were conducted before gemcitabine was available. Gemcitabine has been shown to improve survival and offer clinical benefits, including pain relief,[2] and the Eastern Cooperative Oncology Group (ECOG) is conducting a randomized phase III study to compare systemic therapy with gemcitabine with combination therapy with gemcitabine and radiation. The primary endpoint is survival, and a secondary endpoint is quality-of-life measures.

Systemic chemotherapy for advanced pancreas cancer is evolving with the addition of cancer-specific targeted therapies. Adding the monoclonal antibody bevacizumab to gemcitabine may have a role in the treatment of advanced disease and is also being explored in locally advanced disease. RTOG is studying bevacizumab added to standard radiation therapy and capecitabine as a radiosensitizing agent. At Northwestern University, the reduced field and dose radiation technique with full dose gemcitabine is being further explored with the addition of bevacizumab. Researchers are performing phase I testing on epidermal growth factor receptor modifiers with radiation and gemcitabine, based on the activity of these agents in metastatic disease.

Radiation techniques are evolving as well. Three-dimensional conformal radiation therapy allows for coverage of the target volume, sparing the non-target tissue. Intensity-modulated radiation therapy allows for nonuniform delivery of radiation, and more precise targeting.

Future studies of adjuvant therapy are needed to elucidate the role of chemotherapy and radiation after surgical resection. The completed studies have used suboptimal radiation schedules, do not include adequate quality control, and have used less efficacious chemotherapy regimens. Planned and ongoing studies should evaluate combination chemoradiation schedules with chemotherapy and molecular targeted agents, and neoadjuvant approaches. Continued participation in clinical trials is imperative to answer these important questions.

Conclusions

The current status of combined radiotherapy and chemotherapy for locally advanced and resected pancreas cancer is a moving target. Combination chemoradiotherapy showed improved survival for locally advanced pancreas cancer when the only systemic therapy for pancreas cancer was 5-FU. Now that gemcitabine has shown a survival advantage and symptom relief compared with 5-FU, the ECOG study comparing gemcitabine and gemcitabine with radiation answers an important clinical question. Meanwhile, advances in radiation therapy may allow for more intensive therapy with less toxicity.

The appropriate adjuvant therapy remains elusive, with the addition of chemoradiation still debated. The plethora of data showing a benefit from combined therapy support this approach. The advanced radiation techniques and better understanding of radiation biology support the use of radiation therapy to eradicate micrometastatic disease from the residual lymphatics and surrounding tissue in the tumor bed. Ultimately, only obliteration of microscopic local and metastatic disease will result in improved survival and cure.

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