Role of Radiation Therapy in Patients With Resectable Pancreatic Cancer


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In this article, we review the data surrounding the use of chemotherapy (CT) and chemoradiotherapy (CRT) in patients with resectable pancreatic cancer.

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States and accounts for roughly 40,000 deaths each year.[1] Patients generally present with locally advanced or metastatic disease that precludes cure, since symptoms frequently prompt the diagnosis in the absence of effective screening strategies. Even among patients who present with localized disease, the 5-year overall survival (OS) is approximately 20%, but potentially higher in patients with complete surgical resection (R0) and uninvolved lymph nodes.[2,3] Local and/or distant recurrence is common following resection, highlighting the importance of adjuvant therapy.[4,5] Despite the use of neoadjuvant and adjuvant therapies, little progress has been made in the last three decades, and the search for more efficacious treatment continues.[6] In this article, we review the data surrounding the use of chemotherapy (CT) and chemoradiotherapy (CRT) in patients with resectable pancreatic cancer.

Early Adjuvant Therapy Trials

The 1985 GITSG trial

Randomized Trials of Adjuvant Therapy in Patients With Resected Pancreatic Cancer

An early randomized controlled trial for resectable pancreatic cancer, designed by the Gastrointestinal Tumor Study Group (GITSG), laid the foundation for the adoption of CRT in the United States (Table 1). Forty-three patients were enrolled in this clinical trial comparing outcomes of surgery alone to CRT. All patients underwent curative resection of pancreatic adenocarcinoma without evidence of intraperitoneal disease. Split-course radiotherapy (RT) was administered to a total dose of 40 Gy, with a 2-week treatment break. CT consisted of fluorouracil (5-FU) delivered as a bolus infusion (500 mg/m²) during the first 3 days of each RT course and weekly thereafter for a planned course of 2 years. Improvements in median disease-free survival (DFS) and OS with CRT were observed: 11 months vs 9 months, and 20 months vs 11 months, respectively. Two-year OS was 42% in the CRT group vs 15% in the surgery-alone arm.[7] The GITSG trial closed prematurely following enrollment of 43 of an intended 100 patients, due to slow accrual over the 8-year enrollment period. The RT approach in this trial was considered low-dose and antiquated by contemporary standards due to the use of a split-course technique and the use of large treatment fields, which encompassed the entire pancreas/pancreatic bed and the celiac, pancreaticosplenic, peripancreatic, and retroperitoneal regional lymph nodes.[7] Additionally, the inclusion of both CRT and adjuvant CT after surgery evaluated two treatment variables, making it difficult to discern the true effect of either treatment alone. In the CRT arm, there were issues of compliance, with 32% of patients assigned to CRT receiving inappropriate radiation and 25% of...
patients failing to initiate treatment within 10 weeks post surgery, the protocol-specified time limit. Despite these limitations and failure to reach the desired patient accrual, the GITSG trial demonstrated a benefit for CRT, which became standard adjuvant therapy, particularly in the United States.

**European trials**

In Europe, the use of adjuvant CRT underwent further assessment by the European Organization for Research and Treatment of Cancer (EORTC), who designed a trial comparing the use of surgery and adjuvant CRT to surgery alone in 218 patients with resected pancreatic head (n = 114) or periampullary (n = 104) carcinomas. RT, as in the GITSG trial, was delivered in a split course to 40 Gy, with a 2-week treatment break. CT was delivered by continuous infusion (25 mg/kg) but only during RT (for the first 5 days of each RT course).[8] Long-term follow-up of the EORTC trial demonstrated no difference in 5-year OS with CRT use: 25% (CRT) vs 22% (surgery alone). Post-hoc analysis of pancreatic head lesions failed to demonstrate a benefit with CRT, with a median OS of 1.3 years for CRT vs 1 year for surgery alone.[9]

This trial has been criticized for its heterogeneous patient population, which included patients with both pancreatic and periampullary primary tumors. Periampullary carcinomas have been associated with a significantly better prognosis compared with pancreatic cancer; the two entities thus represent truly different diseases and potentially dilute any evidence of benefit from adjuvant CRT.[10] Similar to the GITSG trial, older RT techniques—split course and low total dose—were used. Also, more than 20% of patients in the CRT arm did not receive the intended treatment due to postoperative complications and/or patient refusal. Finally, although a small subset, patients undergoing non-curative resection were still eligible for enrollment. The discordant results of the EORTC and GITSG trials have led some investigators to attribute the OS benefit seen in the GITSG trial to adjuvant CT administration rather than to RT.

An additional European trial conducted by the European Study Group for Pancreatic Cancer (ESPAC) aimed to further explore the question of appropriate adjuvant therapy for "macroscopically" resected pancreatic cancers. In this ESPAC-1 study, 541 patients with pancreatic adenocarcinoma underwent surgery and received CRT, CT, CRT followed by CT, or no further treatment. Although planned as a 2×2 randomization design, only 285 patients were randomized to one of the above treatment arms. The remainder were, per patient or physician preference, randomized only for CRT (vs no CRT) or CT (vs no CT) in an attempt to enhance patient accrual. RT was delivered in a manner similar to that used in the GITSG and EORTC trials, and bolus 5-FU (425 mg/m²) chemotherapy was administered along with leucovorin (LV) (20 mg/m²). On initial analysis, outcomes from all three cohorts (2×2 factorial, CT vs no CT, and CRT vs no CRT) were analyzed collectively, specifically evaluating patients who received CRT or no CRT and CT or no CT. No difference in survival was seen in patients who received CRT compared with patients who did not receive CRT. In the CT arm, however, a 35% reduction in death was seen in the group who received CT compared with those who received no CT, with a difference in median survival of 19.7 months vs 14 months.[11] Long-term results of the patients randomized in the 2×2 schema were subsequently reported. This analysis suggested a survival detriment in patients receiving CRT, who had a 5-year OS of 10%, compared with 20% in those who did not receive CRT. However, in patients receiving CT, an improvement in OS continued to be seen at 5 years: 21% (CT) vs 8% (no CT).[12]

A number of problems are associated with the interpretation of these data. First, the complex trial design has the potential for bias, since patients and/or physicians could select randomization for one treatment variable. Also, as in the aforementioned trials, the RT technique used was, by contemporary standards, considered outdated, employing split course and low total dose. No details of RT delivery or central quality assurance for RT, surgery, or pathology were available. In addition, many treatment violations occurred, as only 62% of patients received full CRT treatment and only 42% of patients in the CT arms completed the predefined regimen. Although many have attempted to draw conclusions from the updated publication, the 2×2 cohort of the study was not powered to detect OS differences. Patients receiving CRT in the ESPAC trial experienced poorer survival outcomes compared with those in other reported CRT series, and patients who had received prior chemotherapy and/or radiation therapy were still eligible for enrollment. Despite these critiques, some have speculated that the detriment seen in the CRT group may have resulted from delayed administration of systemic therapy.

Another common critique of all of the early trials of adjuvant therapy is their lack of restaging after surgical resection and prior to the initiation of adjuvant therapy to evaluate the presence of persistent or metastatic disease. The time between initial staging and the commencement of
adjuvant treatment can be as long as 3 to 4 months, during which a significant minority of patients would be expected to develop radiographically apparent metastases. Without interval restaging, these patients might inappropriately receive CRT. Although these 3 trials formed the foundation for adjuvant treatment approaches to resectable pancreatic cancer, perhaps because each trial was fraught with flaws, there continues to be little consensus regarding "most appropriate" treatment. A relative dichotomy in adjuvant treatment approaches for resectable pancreatic cancer has emerged between the United States and parts of Europe, with adjuvant CRT frequently implemented in the United States and adjuvant chemotherapy alone used in parts of Europe.

**Trials of Adjuvant Gemcitabine-Based Chemotherapy**

In parts of Europe, the EORTC and ESPAC-1 trials were felt to provide sufficient evidence to exclude the routine use of adjuvant CRT in favor of adjuvant CT alone. The Charite Onkologie (CONKO) trial from Germany randomly assigned 368 patients with R0 or R1 resection either to treatment with six cycles of adjuvant gemcitabine (Gemzar) (three weekly infusions of 1000 mg/m²) or to observation. Patients with a carbohydrate antigen 19-9 (CA 19-9) or carcinoembryonic antigen (CEA) level greater than 2.5 times the upper limit of normal were excluded. Low rates of grade 3-4 toxicities were seen in the gemcitabine arm, with the majority of these being hematologic toxicities. The primary study endpoint of DFS was significantly improved to 13.4 months with gemcitabine, compared with 6.9 months for surgery alone. This improvement was seen in both the R0 and R1 subgroups.[13] At initial publication there was no difference in OS; however, with longer follow-up, median and 5-year OS were both improved in patients receiving gemcitabine (23 months vs 20 months, and 21% vs 9%, respectively).[14] These findings were supported by a smaller randomized study from Japan, which again demonstrated a DFS benefit for adjuvant gemcitabine compared to surgery alone.[15] This well-conceived and implemented trial established gemcitabine as the adjuvant chemotherapy of choice.

At the same time the CONKO trial was enrolling patients, ESPAC-3, the largest randomized controlled trial in pancreatic cancer to date, enrolled 1088 patients with pancreatic adenocarcinoma who were undergoing R0 or R1 resection. Patients were randomly assigned to six cycles of adjuvant gemcitabine (three weekly infusions of 1000 mg/m²) or six cycles of bolus 5-FU/LV (5-FU, 425 mg/m²; LV, 20 mg/m²). Patients receiving 5-FU/LV experienced significantly higher rates of grade 3-4 gastrointestinal toxicity (stomatitis and diarrhea), whereas patients receiving gemcitabine experienced significantly higher rates of grade 3-4 hematologic toxicity. At a median follow-up of 34.2 months, there was no difference between the two groups in the primary endpoint of OS. Given its favorable toxicity profile, in many parts of Europe gemcitabine alone is considered the standard adjuvant treatment in patients with resectable pancreatic cancer.[16] The focus of future European adjuvant therapies for resectable pancreatic cancer has centered primarily on finding the ideal combination of systemic agents. The ongoing ESPAC-4 trial is accruing patients with resected pancreatic cancer for randomization to gemcitabine alone vs gemcitabine/capecitabine; the trial is expected to close in 2014.

**Adjuvant Chemoradiation Trials Involving Gemcitabine**

Unlike in parts of Europe, where the focus of adjuvant therapy has been chemotherapy, adjuvant chemoradiation continues to be utilized in the United States. The Radiation Therapy Oncology Group (RTOG) 9704 study was a randomized trial comparing adjuvant 5-FU-based chemotherapy to gemcitabine-based chemotherapy, with both regimens implementing CRT. Patients with resected pancreatic adenocarcinoma were randomly assigned to receive either continuous infusion 5-FU (250 mg/m²/day) or gemcitabine (1000 mg/m² weekly) for 3 weeks prior to CRT and for 12 weeks after CRT. CRT in both groups consisted of 50.4 Gy delivered with continuous infusion 5-FU (250 mg/m²/day). Prospective quality assurance of all RT plans was required. This trial was powered to demonstrate a survival benefit for the entire cohort and for the subgroup of patients with pancreatic head lesions. On initial analysis of the pancreatic head subgroup, a non-significant trend toward improved median survival and 3-year OS was seen in the gemcitabine arm: 20.5 months vs 16.9 months, and 31% vs 21%, respectively. However, a higher incidence of ≥ grade 3 hematologic toxicity was also seen in the gemcitabine group, with no significant differences seen in severe nonhematologic toxicities.[17] A recent update of this trial reported median survival and 5-year OS rates in patients with pancreatic head tumors of 20.5 months and 22% in those who received gemcitabine, compared with 17.1 months and 18% in those who received 5-FU. On multivariate analysis, in the subgroup of patients with pancreatic head lesions who received gemcitabine, there
was a nonsignificant trend toward improved OS ($P = .08$).[18]

**Figure**

Trial Schema for the US Intergroup/RTOG 0848/EORTC Trial

A secondary aim of RTOG 9704 was to assess the ability of post-resection CA 19-9 levels to predict survival. When CA 19-9 levels were analyzed in a cohort of 385 patients as a dichotomized variable ($<180$ IU/mL vs $\geq 180$ IU/mL, $\leq 90$ IU/mL vs $> 90$ IU/mL), there was a significant survival difference favoring patients with CA 19-9 levels of less than 180 IU/mL. This corresponded to a 72% reduction in the risk of death.[19] A major strength of the RTOG study was the rigorous, centralized quality control of RT techniques and delivery. A recent analysis demonstrated that patients treated per study guidelines had a significant survival advantage, indicating the importance of centralized review and treatment technique in this disease.[20]

In RTOG 9704, 28% of patients experienced local recurrence as the first site of relapse, which is considerably lower than the rates in previously discussed randomized trials and historical series involving chemotherapy-alone approaches. However, distant failure as first site of relapse remained high at 73%. These high rates of distant failure and the need for more effective systemic therapy, as well as controversy surrounding the role of CRT in resected patients, led to the design of the current, multinational RTOG 0848/EORTC trial discussed below.

The RTOG 0848/EORTC trial randomly assigns patients with resected pancreatic head adenocarcinoma (stratified based on CA 19-9 level and nodal and margin status) to receive treatment with either gemcitabine alone or gemcitabine combined with erlotinib (Tarceva) for five cycles. If no progression is seen on restaging studies following the completion of systemic therapy, patients are further randomized to receive an additional cycle of the previously administered chemotherapy (for a total of six cycles) with or without CRT (50.4 Gy) using modern radiation techniques/central RT quality assurance, with concurrent capecitabine (Xeloda) or 5-FU (Figure). This trial seeks to answer two primary questions: 1) what is the role of the small-molecule epidermal growth factor receptor (EGFR) inhibitor, erlotinib, in the adjuvant therapy of pancreatic cancer? and 2) what is the role of CRT in the era of modern chemotherapy, particularly in patients who do not experience early disease progression? This is the only contemporary randomized clinical trial evaluating the role of CRT in the adjuvant setting.

**Nonrandomized Studies**

In addition to the randomized studies above, several large, single-institution series have suggested a benefit for adjuvant CRT. A review of the Mayo Clinic experience reported the outcomes of 472 patients who underwent R0 resection between 1975 and 2005. Despite more adverse prognostic features in patients receiving CRT (higher histological grade and greater lymph node involvement), median survival, 2-year OS, and 5-year OS were significantly improved in the CRT cohort compared with patients who received no adjuvant therapy: 25.2 months vs 19.2 months, 50% vs 39%, and 28% vs 17%, respectively.[21] A similar series from Johns Hopkins compared 908 patients who underwent pancreaticoduodenectomy between 1993 and 2005 and received surgery alone or CRT. Patients receiving CRT experienced a significant improvement in median survival, 2-year OS, and 5-year OS: 21.2 months vs 14.4 months, 43.9% vs 31.9%, and 20.1% vs 15.4%, respectively.[22] Despite the inherent biases of non-randomized, retrospective trials, these data, along with data on the patterns of failure in the above randomized studies, suggest that there are patient subgroups that stand to benefit from the addition of CRT to surgical resection.

**Neoadjuvant Chemoradiotherapy**

In other gastrointestinal malignancies (ie, rectum, esophagus), the use of neoadjuvant CRT has become standard practice. Given the potential for significant delays in the delivery of adjuvant therapy in up to one third of patients following surgical resection and the modest survival gains associated with adjuvant therapy, delivery of neoadjuvant therapy offers a potentially attractive alternative.[23] Potential advantages of preoperative therapy include an undisrupted tumor...
vasculature, which allows for improved delivery of chemotherapy and radiosensitizing oxygenation. Downstaging may occur, potentially allowing the resection of more advanced lesions and sterilization of the operative region, which may reduce the risk of spread during surgical manipulation. Preoperative treatment also avoids delay in adjuvant therapy delivery due to postoperative recovery, and importantly, avoids potentially morbid radical resection in patients with rapidly progressive disease. Finally, neoadjuvant CRT has also been associated with a reduction in the incidence of pancreatic leak, as well as leak-associated morbidity and mortality.[24]

### TABLE 2

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<th>Trials of Neoadjuvant Therapy in Patients With Resectable Pancreatic Cancer</th>
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 Unlike with adjuvant therapy, no phase III randomized trials of neoadjuvant CRT have been performed, and the vast majority of data come from phase II and retrospective studies (Table 2). The evolution of CRT in the neoadjuvant setting appears to parallel advances made with adjuvant therapy, with its transition to gemcitabine-containing regimens. In 2008, two published phase II studies from MD Anderson Cancer Center evaluated the use of gemcitabine as part of a neoadjuvant regimen. One trial enrolled 86 patients with radiographically resectable adenocarcinoma of the pancreatic head/uncinate. Patients received weekly gemcitabine (400 mg/m$^2$) with 30 Gy RT over 2 weeks. After restaging 4 to 6 weeks post-CRT, 73 patients (85%) underwent surgery, with 64 (74%) undergoing successful resection. Median survival in resected vs unresected patients was 34 months vs 7 months, with corresponding 5-year OS rates of 36% and 0%, respectively. In patients undergoing pancreaticoduodenectomy, only 11% experienced local failure, with distant failure accounting for the majority of the mortality.[25]

 Given the high incidence of distant disease development, a simultaneously conducted phase II trial incorporated cisplatin (CDDP) and gemcitabine prior to initiation of CRT with gemcitabine. Induction chemotherapy consisted of CDDP (30 mg/m$^2$) and gemcitabine (750 mg/m$^2$) every 2 weeks for four cycles followed by four weekly infusions of gemcitabine (400 mg/m$^2$) together with 30 Gy RT. Sixty-two patients (78%) underwent surgery, and 52 (66%) had successful resection. The median survival for patients undergoing surgery was 31 months, compared with 10.5 months in the unresected patients.[26]

 A recent review of the Surveillance, Epidemiology, and End Results (SEER) database also supports the use of neoadjuvant treatment. This analysis included 3,885 patients treated for resectable pancreatic cancer: 70 patients (2%) received neoadjuvant RT, 1,478 (38%) received adjuvant RT, and 2,337 (60%) were treated with surgery alone. Given that the SEER database does not provide information on administration of CT, this variable could not be assessed. Median OS was 23 months in patients receiving neoadjuvant RT, 17 months in those who received adjuvant RT, and 12 months in the surgery-alone cohort.[27]

 Despite the potential advantages and encouraging results using a neoadjuvant CRT approach, no randomized trial results exist comparing neoadjuvant to adjuvant therapy, and its role continues to be investigated. A multicenter randomized phase II study evaluating neoadjuvant therapy in pancreatic carcinoma is currently recruiting.[28] This multinational study is comparing outcomes of patients with resectable disease treated with neoadjuvant gemcitabine-based CRT followed by surgery to outcomes in patients undergoing upfront surgery. Resection is followed by adjuvant gemcitabine-based chemotherapy in both arms.

### Emerging Radiotherapy Technologies

Intensity-modulated radiotherapy (IMRT) is a technique that breaks up a typical radiation treatment field into smaller "beamlets." It is implemented either as dynamic IMRT (collimating leaves move in and out of the radiation beam path during treatment) or as "step and shoot" IMRT (leaves change field shape while the machine is off). The cumulative effect is that the prescription dose conforms around delineated target volumes, significantly reducing doses to adjacent normal tissues. This technology has increasingly been used in a number of gastrointestinal malignancies, including pancreatic cancer. Early clinical data support both the feasibility of this technique and its potential for reducing acute gastrointestinal toxicity.[29-31] An analysis from the University of Maryland
evaluated 46 patients treated with IMRT and concurrent 5-FU-based chemotherapy. Acute toxicities in these patients were compared with those in a control group enrolled in RTOG 9704 who received conventional 3D treatment. There was a statistically significant reduction in acute grade 3-4 GI toxicity in the patients who received radiotherapy via IMRT compared with those who received 3D conformal radiotherapy.[31] IMRT can also result in a significant reduction of dose to normal structures, including the liver, kidneys, stomach, and small bowel.[30] This may allow alternate novel systemic agents to be administered with radiotherapy.[29]

Another radiation technique being investigated in the treatment of pancreatic cancers is stereotactic body radiotherapy (SBRT). SBRT involves the delivery of high dose-per-fraction radiation treatments over a small number of fractions (generally 1 to 5 treatments), utilizing techniques that permit very highly conformal dose delivery of external beam radiotherapy. The postulated advantage of SBRT is that it can potentially improve local control through the delivery of ablative doses of radiation, while minimizing associated side effects. Few institutions have published experience utilizing this technique, and the data are largely in the setting of locally advanced disease.[32,33] Stanford University has implemented an institutional protocol for the treatment of locally advanced pancreatic cancer utilizing 25 Gy single fraction with systemic therapy. This single, high dose of radiation has been estimated to result in delivery of a higher biologically equivalent dose compared with more standard, protracted course radiation therapy, although there is also a potential for increased risk of injury to normal tissue. A recent report from these investigators described 77 patients treated with SBRT and found that freedom from local progression was 91% at 6 months and 84% at 12 months. No patients experienced grade 3 acute toxicity and 9% had ≥ grade 3 late toxicity.[33] Ultimately the role of IMRT and SBRT in treatment of pancreatic cancer remains to be further defined.
Conclusions

Older trials evaluating outcomes of CRT, CT, and surgery alone in patients with resected pancreatic cancer are fraught with flaws. Despite this, adjuvant CT alone has evolved and remains the standard of care in the adjuvant treatment of resectable pancreatic cancer throughout much of Europe. In the United States, the role of CRT continues to be redefined in the era of modern chemotherapeutics. The currently active RTOG 0848/EORTC study will help not only to further clarify the role of CRT, but also to assess the utility of small-molecule EGFR therapy in the treatment of this disease. The use of neoadjuvant CRT in patients with resectable disease offers potential advantages as well as promising local control and survival results based on institutional data, although randomized trials are lacking. Despite advances in many aspects of oncologic evaluation and management, including preoperative evaluation (endoscopic ultrasound, computed tomography), surgical techniques, perioperative care, systemic therapy, and radiotherapy, the 5-year OS rate for patients with resectable pancreatic cancer remains approximately 20%. Further advances in systemic therapies, study of the optimal sequencing of therapies, earlier detection of disease, and development of new and novel therapeutic options are urgently needed in the treatment of this formidable disease.

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