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Recent Advances and Prospects for Multimodality Therapy in Pancreatic Cancer

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The outcomes for treatment of pancreatic cancer have not improved dramatically in many decades. However, the recent promising results with combination chemotherapy regimens for metastatic disease increase optimism for future treatments. With greater control of overt or occult metastatic disease, there will likely be an expanding role for local treatment modalities, especially given that nearly a third of pancreatic cancer patients have locally destructive disease without distant metastatic disease at the time of death. Technical advances have allowed for the safe delivery of dose-escalated radiation therapy, which can then be combined with chemotherapy, targeted agents, immunotherapy, and nanoparticulate drug delivery techniques to produce novel and improved synergistic effects. Here we discuss recent advances and future directions for multimodality therapy in pancreatic cancer.
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Introduction

Pancreatic cancer is the third most common gastrointestinal malignancy in the United States, with 48,960 new cases expected to be diagnosed in 2015.[1] With annual rates of incidence and mortality mirroring one another and projections estimating it to be the second most common cause of cancer-related mortality by 2030, treatment of this aggressive cancer remains as one of the most challenging clinical dilemmas.[2] About half of all patients have distant metastases at the time of diagnosis that makes them ineligible for potentially curative surgical resection.[3] Of the remaining patients, only 10%-15% have resectable disease, whereas the rest comprise a heterogeneous group of unresectable pancreatic cancers without evidence of distant metastases but still ineligible for surgery. Pancreatic ductal adenocarcinoma (PDAC, henceforth referred as pancreatic cancer) is the dominant histology (85%). The 5-year overall survival (OS) rate of these patients is less than 5%, and the conventional treatment options of cytotoxic chemotherapy, chemoradiation therapy (CRT), and surgery have, unfortunately, not been able to alter this rate over the last 2 decades.[4] These dismal outcomes emphasize the need for novel treatment strategies. The current review highlights recent advances in pancreatic cancer treatment and promising combinations of radiation therapy (RT) with novel therapeutics.

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CRT: Where Do We Stand?

Adjuvant Therapy for Resectable Disease

The 5-year OS rate is only 15%-20% in patients with resectable tumors, largely because of the presence of occult metastatic disease at the time of surgery and subclinical residual local disease after surgery. In particular, the technical difficulty associated with dissecting along the retroperitoneal margin (proximal 3-4 cm of the superior mesenteric artery [SMA]), the superior mesenteric venous-portal venous confluence, the celiac trunk, and the lack of tools to pathologically assess margin status intraoperatively contribute to high locoregional failure rates (up to 50%).[5-7] Perioperative factors like margin status, lymph node ratio (number of involved nodes to total number of nodes examined), perineural or perivascular invasion, and tumor size are other important prognostic

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determinants of OS.[8,9] Given the competing risks of locoregional and systemic failure, both chemotherapy and RT have been used in an adjuvant fashion after surgery in attempts to improve disease control.

The use of an adjuvant fluoropyrimidine-based CRT in the United States is based on the results reported by the Gastrointestinal Tumor Study Group (GITSG) study that randomized patients to either observation or adjuvant CRT after surgical resection. The 22 patients who underwent observation had an inferior median OS duration (11 vs 20 months, $p = 0.035$) and 2-year OS rate (15% vs 42%) as compared with the 21 patients who received CRT.[10] Subsequent analysis also showed a similar benefit with CRT in patients who were not randomized (median OS of 18 months and 2-year OS rate of 46%).[11] However, the European Organization for Research and Treatment of Cancer trial did not find a statistically significant OS or local control benefit for patients randomized to observation vs adjuvant CRT (19 vs 24.5 months, $p = 0.21$).[12] Subsequently, in a 2 × 2 factorial study design the European Study Group for Pancreatic Cancer (ESPAC)-1 trial compared observation with adjuvant 5-fluorouracil (5-FU) chemotherapy or CRT. Interestingly, patients who received CRT had a worse OS duration (15.9 vs 17.9 months, $p = 0.05$) and 2-year OS rate (29% vs 40%, $p = 0.05$) compared with observation, whereas those who received adjuvant chemotherapy lived longer than the observation group (OS duration of 20.1 vs 15.5 months, $p = 0.009$).[13,14] This was followed by the Charite Onkologie Clinical (CONKO-001) trial which compared single-agent adjuvant gemcitabine with observation alone and showed a similar benefit in terms of disease-free survival (14.2 vs 7.5 months, $p < 0.001$) in the initial analysis, and OS duration (22.8 vs 20.2 months, $p = 0.01$) in the updated report, regardless of the margin or nodal status.[5] Given the similar level of benefit seen with adjuvant 5-FU and gemcitabine in the ESPAC-1 and CONKO-001 trials, the ESPAC-3 trial was designed to compare adjuvant gemcitabine with bolus 5-FU or leucovorin (LV). This study showed similar OS between the 2 groups but less grade 3-4 toxicity in the gemcitabine arm (7.5% vs 14%, $p < 0.01$).[15] These studies laid the foundation for the use of adjuvant chemotherapy in Europe with gemcitabine as the preferred regimen. However these trials have been criticized for their lack of surgical and pathological quality assurance, chemotherapy schedule, lack of adherence to protocol guidelines in terms of RT, and chemotherapy delivery, as well as suboptimal design in terms of treatment initiation, RT field design and split-course RT schedule.

Contemporaneously, the RT Oncology Group (RTOG) designed the RTOG 9704 trial with a more standard CRT regimen and post hoc radiation quality assurance.[16] In this study, patients with resected pancreatic adenocarcinomas were randomized to receive continuous adjuvant 5-FU-based CRT sandwiched between either 5-FU or gemcitabine chemotherapy courses. The results of this study showed a trend toward improved OS in the gemcitabine arm compared with the 5-FU arm (20.5 vs 17.1 months, $p = 0.08$). The dominant pattern of first failure was distant (73%) whereas only 28% had local-first recurrence.[17] This is fairly low when compared with the CONKO-001 and ESPAC-3 trials which had high rates of local failure (34%-41% and 63%, respectively). Moreover, failure to adhere to the RT protocol dose and volume guidelines for tumor and normal tissues was associated with an inferior OS. The results of the RTOG 9704 trial illustrate that optimal CRT regimens administered adjuvantly in the background of surgical, pathological and radiation quality assurance could potentially translate to survival benefit. The survival results are also supported by retrospective studies conducted by Corsini et al[18] (Mayo experience) and Herman et al[19] (Johns Hopkins experience) which report improved OS with adjuvant CRT compared with observation alone.

RTOG 0848 (NCT01013649) is an ongoing phase III trial evaluating the role of adjuvant radiotherapy for resectable patients. After initially receiving gemcitabine with or without erlotinib, patients without progression are then randomized to chemotherapy or chemotherapy followed by 5-FU-based CRT. ESPAC-4 is evaluating the efficacy of adding capecitabine to gemcitabine postoperatively. Studies are also underway to test the use of highly active chemotherapeutic agents like FOLFIRINOX (PRODIGE trial, NCT01526135) and nab-paclitaxel or gemcitabine (APACT trial, NCT01964430) in the adjuvant setting given the improved survival benefit in the metastatic setting (PRODIGE 4-ACCORD 11 and MPACT trial).[20,21] These studies would help to optimize the adjuvant treatment approach for resectable patients.

Neoadjuvant Therapy for Borderline Resectable Disease

One of the major challenges in the management of pancreatic cancer is to distinguish patients who clearly have resectable tumors from those who would have positive margins and are thus unlikely to benefit from upfront surgery. Until recently, patients with threatened retroperitoneal margins were deemed unresectable. These patients are more aptly categorized today as having borderline resectable pancreatic cancer (BRPC).[22,23] This includes tumors with segmental occlusion of the superior mesenteric venous-portal venous confluence (able to be resected and reconstructed), $<180^{\circ}$ abutment of the SMA and celiac axis, and abutment or short segment encasement of the common hepatic artery. Patients with equivocal evidence of metastasis or marginal performance status are also sometimes included in the definition of BRPC.

The use of CRT in the neoadjuvant setting has gained traction in BRPC patients with the rationale that preoperative therapy increases the chances of an R0 (margin negative) resection.[24] Additional benefits of neoadjuvant CRT include early treatment of micrometastatic or subclinical disease, lower toxicity (better tolerance), enhanced delivery of CRT before surgical modification of vasculature, and lower rates of postoperative complications like pancreaticojejunal anastomotic fistula. This also allows for selection of optimal surgical candidates as those with aggressive metastatic disease or poor performance status are identified during the preoperative treatment period.[24,25]

Multiple reports from single institutions suggest that neoadjuvant CRT is beneficial in this subset of patients. Mehta et al[26] demonstrated an overall resection rate of 60%