Adjuvant Therapy in Pancreas Cancer: Does It Influence Patterns of Recurrence?

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BACKGROUND: Level 1 data demonstrate that adjuvant chemotherapy (ACT) improves survival after surgical resection of pancreatic ductal adenocarcinoma (PDAC), (adjuvant gemcitabine, CONKO-001 study; adjuvant 5-FU, ESPAC3 study). The role of adjuvant chemoradiation therapy (ACRT) remains controversial. What is less clear is whether adjuvant therapy influences patterns of recurrence. The purpose of this study was to perform the first multicenter study analyzing patterns of recurrence after adjuvant therapy for PDAC.

STUDY DESIGN: Patients undergoing resection for PDAC from 8 medical centers over a 10-year period were analyzed. Demographics, tumor characteristics, operative treatment, type of adjuvant therapy, recurrence pattern, and survival were reviewed. Using Cox-proportional hazards multivariate (MV) regression, the impact of ACT and ACRT on overall survival (OS), local recurrence (LR), and distant recurrence (DR) was investigated.

RESULTS: There were 1,130 patients who were divided into those having surgery alone (n = 392), ACT (n = 291), or ACRT (n = 447). Median follow-up was 18 months. Compared with patients undergoing surgery alone, ACT, but not ACRT, demonstrated a significant OS advantage on MV analysis. Patients receiving ACT had significantly fewer recurrences (LR and DR); those receiving ACRT had significantly less LR but not DR. On subset MV analysis, ACT and ACRT resulted in less LR in patients with lymph node (LN) positive and margin negative disease. No improvements in LR, DR, or OS were seen in margin positive patients with either ACT or ACRT.

CONCLUSIONS: This is the first analysis demonstrating differences in recurrence patterns in PDAC patients based on type of adjuvant therapy. Adjuvant chemotherapy provided an OS advantage likely related to its effect on reducing both LR and DR. Adjuvant chemoradiation therapy appears to decrease LR, but not DR, and therefore has less impact on OS. Future investigations and treatment protocols should consider additional ACT rather than ACRT in the treatment of PDAC. (J Am Coll Surg 2016;222:448–456. © 2016 Published by Elsevier Inc. on behalf of the American College of Surgeons.)

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With an estimated 48,960 new cases in 2015, pancreatic adenocarcinoma (PDAC) represents 3% of all cancers in the United States. Currently, PDAC represents 7% of all cancer deaths, making it the fourth most common cause of cancer death in the US.[1] Based on demographic shifts in the US population, and with the continued increase in the incidence of PDAC, cancer-related deaths due to pancreas cancer are projected to increase dramatically to become the second leading cause of cancer-related deaths before 2030.[2] Although surgical resection offers a potential cure, most patients present with locally advanced or

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Abbreviations and Acronyms

ACRT = adjuvant chemoradiation
ACT = adjuvant chemotherapy
CONKO = Charité Onkologie
DRFS = distant recurrence-free survival
ESPAC = European Study Group for Pancreatic Cancer
HR = hazard ratio
LN = lymph node
IQR = interquartile range
LRFS = local recurrence-free survival
OS = overall survival
PDAC = pancreatic ductal adenocarcinoma

metastatic disease, and only 10% to 15% of patients are candidates for potentially curative resection. Even in patients who have had successful resection, recurrence is common and occurs in up to 50% to 90% of patients.[3,4] These recurrences can occur loco-regionally around the resection bed and adjacent lymphatic tissue and at distant sites including in the liver, peritoneum, lungs, and extra-regional lymph nodes. Unlike more indolent cancers, most patients who have recurrence will ultimately die of their disease.[4,5] The rationale for adjuvant therapy is based on the high incidence of tumor recurrence both locally and at distant sites, presumably because of the presence of micrometastatic disease after surgical resection.

Adjuvant strategies include the use of systemic chemotherapy alone or in conjunction with chemoradiation therapy. The role of adjuvant chemotherapy (ACT) has been well established by several large randomized trials including the Charité Onkologie (CONKO-001),[6] the Japanese Study Group of Adjuvant Therapy for Pancreas Cancer (JSAP-2),[7] and the European Study Group for Pancreatic Cancer (ESPAC) 1 and 3 trials,[8] which all showed a significant survival advantage with ACT for resected PDAC. However, no randomized trial has been able to convincingly support the role of adjuvant chemoradiation therapy (ACRT) for overall survival (OS), and its benefit remains controversial.[6,9-11] Large single-institution studies and other retrospective studies, including our earlier report from the Central Pancreatic Consortium,[12-14] have suggested a possible benefit with the use of ACRT in specific high-risk patients, such as those with lymph node (LN) positive or margin positive disease.

The rationale for the use of ACT is its ability to treat occult metastatic disease, thereby preventing distant recurrence.[15-19] Meanwhile, ACRT is directed toward the loco-regional area and therefore would be more efficacious in treating loco-regional recurrences rather than distant disease.[18,19] Because most patients ultimately die of distant recurrence, this may explain some of the differences in survival benefit between the 2 adjuvant strategies. To date, however, the influence of adjuvant therapies on the patterns of recurrence after surgical resection for PDAC has been poorly studied.

The primary aim of this study was to understand the association of ACT and ACRT with patterns of recurrence and to determine factors influencing loco-regional and distant recurrences and their impact on OS after resection for PDAC. We sought to determine if ACT and ACRT lead to differences in recurrence patterns and thereby influence OS.

METHODS

Data source and patient acquisition

This study is an institutional review board-approved, multi-institutional retrospective review of prospectively maintained databases from 8 academic medical centers comprising the Central Pancreatic Consortium. The goal of the Central Pancreatic Consortium is to study important biologic and clinical questions in regard to pancreatic neoplasms and pancreatic surgery. As such, all institutions are high volume centers with expertise in the multi-disciplinary management of pancreatic cancer.

The study cohort consisted of all patients diagnosed with PDAC who underwent successful surgical resection between January 2000 and December 2010. Patients were excluded from the analysis if they were found to have M1 disease or R2 (grossly positive margin) resections at the time of surgery, if they had a pathologic diagnosis other than PDAC, if they died within 90 days of resection, if they received neoadjuvant therapy, or if their adjuvant therapy status or pattern of recurrence was unknown.

Demographic, clinical characteristics, and definitions

Clinical variables collected included demographic data including age at resection; sex; tumor characteristics including size, grade, stage, lymph nodes removed, margin status; and lymph node status and treatment parameters including the use of preoperative biliary stenting, type of operation, need for blood transfusion, vein resection, and the use of ACT alone, ACRT, or surgery alone. The use of adjuvant therapy was defined as initiation of treatment within 90 days of resection and before any signs of recurrence. The majority of patients who received ACRT also received ACT as part of their regimen. Because the Central Pancreatic Consortium consists of major tertiary referral centers, many of these patients received adjuvant therapy at outside institutions, so details about specific treatment regimens were not available. However, the majority of patients receiving ACT received