Commentary (Czito et al): Combined-Modality Treatment for Operable Pancreatic Adenocarcinoma

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Drs. Pisters, Wolff, Crane, and Evans have provided an excellent overview of contemporary approaches to staging, surgical management, and treatment of patients with potentially resectable pancreatic cancer. Given the impressive advances in our understanding of the biology and genetics of pancreatic cancer, we would agree that current opportunities for progress against this malignancy are encouraging. The reality, however, is that mortality rates still exceed 95%. While the article addresses the clinical management of patients with operable pancreatic cancer, this subset of patients constitutes only 10% to 15% of all patients with the disease. This group as well as patients with locally advanced and metastatic disease are in need of new and innovative treatment strategies. In this review, we will highlight several of the points made by the authors.

Pretreatment Staging

Over the past decade, several advances in the imaging and staging of pancreatic cancer have been achieved. Currently, the principal diagnostic tools are helical computed tomography (CT) scans, endoscopic ultrasound (EUS), and laparoscopy. These tools have facilitated the characterization of the primary tumor (resectable vs unresectable) and the identification of metastatic disease. Importantly, patients can be appropriately and reliably triaged to operative and nonoperative therapies. For example, patients who have a low likelihood of complete resection are spared the potential morbidity of laparotomy. Similarly, radiation therapy would generally not be indicated in patients with metastatic disease. High-quality helical, multidetector CT remains the primary modality used in determining stage. To date, the role of positron-emission tomography (PET) scanning in pancreatic cancer remains ill defined. At our institution, PET alone did not predict for vascular involvement in patients with localized disease, lacking the anatomic detail to define direct tumor extension.[1] The role of the combination PET/CT scan in defining resectability remains an active area of investigation. Endoscopic ultrasound is another valuable tool in staging. In experienced hands, EUS allows for accurate preoperative imaging of the pancreas and surrounding vessels, with a high degree of accuracy in defining tumor involvement of adjacent vasculature (superior mesenteric vein, superior mesenteric artery, etc). This aids the surgeon in appropriate selection of patients for resection. In addition, EUS is particularly useful in characterizing smaller tumors that may not be well visualized on CT and providing complementary information on feasibility of resection when employed with CT. EUS-guided fine-needle aspiration biopsy is more than 90% sensitive and 100% specific in diagnosing pancreatic cancer, permitting pretherapy diagnosis without exposing the peritoneal cavity to seeding. This is particularly helpful when neoadjuvant strategies are employed.

Surgery

As pointed out by Pisters et al, institutional variations in outcomes are seen with the treatment of resectable pancreatic cancer. A growing body of literature suggests that high-volume centers have superior perioperative and long-term outcomes compared to institutions performing fewer procedures. This may be due to improved staging, surgical technique, perioperative management, and utilization of adjuvant therapies. Birkmeyer et al performed a retrospective analysis of over 7,000 patients 65 years and older who underwent pancreaticoduodenectomy in the United States from 1992 to 1995. Three-year survival rates were 37% in high-volume centers vs 25% in low-volume hospitals.[2] Based on these and other data, centralization of patients with pancreatic
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of morbidity and mortality and improved long-term survival rates compared to less experienced centralization of patient care to high-volume institutions. Experienced centers have decreased rates of metastases-is mandatory. Systemic treatment of this disease- where the majority of even "localized" patients harbor subclinical metastases.

Fur-ther clarified by randomized trials in the United States and Europe. Clearly, improvement in the role of adjuvant chemoradiation in patients undergoing surgery alone vs 51% for patients receiving adjuvant therapy (P = .099).

Although these differences were not significant, the wide confidence interval (CI) for the subset of patients with pancreatic cancer (relative risk = 0.7; 95% CI = 0.5-1.1) raised the possibility that the chemoradiation arm had a clinically meaningful improvement in survival, which was obscured by the small sample size. In addition, pancreatic cancer and other periampullary cancers may have different natural histories, and therefore, the favorable outcome of other periampullary cancers may obscure potential benefits for pancreatic cancer patients. The EORTC study was criticized for the radiation techniques used: Radiation was delivered in a split-course manner, and the dose was suboptimal. Moreover, these investigators did not prospectively assess the completeness of the surgical margins, and 20% of patients randomized to treatment never received it.[5] Nevertheless, the trial did show a trend toward benefit of adjuvant therapy despite being underpowered, and some investigators believe it supports the conclusion of the GITSG trial. In the largest randomized study evaluating the role of adjuvant treatment in resected pancreatic cancer, investigators reported study results from the first European Study Group for Pancreatic Cancer (ESPAC) trial. Patients were randomized to one of four treatment groups: observation, radiochemotherapy, chemotherapy alone, and radiochemotherapy followed by chemotherapy. Study results showed that (1) the 5-year survival rate was 21% among patients who received chemotherapy and 8% among patients who did not receive chemotherapy for patients randomized to the 2 * 2 factorial design of this study, and (2) patients receiving chemoradiation had a significant decrease in survival vs patients not receiving chemoradiation.[6] As noted in the review by Pisters et al, interpretation of trial results is complicated by low (and unavailable) compliance rates, as well as lack of quality assurance from both a pathologic and radiologic standpoint. The importance of the latter was recently demonstrated in a US Intergroup gastric trial where greater than one-third of the originally designed fields required prospective modification. As in the GITSG and EORTC trials, antiquated radiation doses, techniques, and chemotherapy administration were used. In addition, 30% of patients did not receive the protocol-prescribed dose. Given these perceived weaknesses, the use of adjuvant chemotherapy alone following pancreatic cancer resection has not been adapted as standard treatment in the United States. Adjuvant Chemotherapy

The effic-acy of chemotherapy in pancreatic cancer is modest. In a recent study by Burris et al, patients with advanced and metastatic pancreatic cancer were randomized to receive either gemcitabine (Gemzar) or fluorouracil (5-FU) given in bolus fashion. Objective response rates were 5.6% and 0%, respectively. A medi-an survival difference of 1.2 months was observed, as was a gain in "clinical benefit." These differences were judged significant enough to change first-line treatment in these patients from 5-FU to gemcitabine.[7] The role of gemcitabine as adjuvant therapy will be further clarified by randomized trials in the United States and Europe. Clearly, improvement in the systemic treatment of this disease- where the majority of even "localized" patients harbor subclinical metastases-is mandatory. Future Directions

Immediate improvement in the outcome of pancreatic cancer patients could likely be achieved by centralization of patient care to high-volume institutions. Experienced centers have decreased rates of morbidity and mortality and improved long-term survival rates compared to less experienced
centers. As discussed, the role of adjuvant chemotherapy and radiation remains controversial, and a further randomized trial may ultimately be required to address the question of efficacy of adjuvant therapy. One possible trial design addressing this question would be a three-arm study stratifying patients undergoing resection to chemotherapy only, combined radiochemotherapy, or radiochemotherapy followed by further chemotherapy. With state-of-the-art quality assurance, such a trial would clarify the role of adjuvant treatment. Despite these controversies, current treatment approaches to resected pancreatic cancer are modestly effective at best. Because of the high propensity for distant metastases in this setting, ultimate treatment success will likely come from improvements in systemic therapy. We are presently conducting a phase I trial evaluating the use of epidermal growth factor receptor inhibitors concurrent with "standard" neoadjuvant radiochemotherapy approaches in nonmetastatic patients. Strategies such as this as well as integration of newer, novel therapies (vascular endothelial growth factor inhibitors, immunotherapy, etc) with existing approaches hold promise in the treatment of this disease. **Conclusions**

Drs. Pisters, Wolff, Crane, and Evans have provided an excellent state-of-the art overview of the current management and controversies that exist in patients with potentially resectable pancreatic cancer. Pancreatic cancer remains one of the most formidable challenges in oncology. Combined-modality treatment has been used in the adjuvant or neoadjuvant setting in attempts to improve outcome. Although an earlier study suggested the benefit of adjuvant chemoradiation in patients undergoing pancreaticoduodenectomy, the definitive benefits of this approach have not been confirmed. Ongoing studies are examining the potential benefits of newer cytotoxic chemotherapeutic agents as well as targeted biologic therapies in the adjuvant or neoadjuvant setting. Further understanding of the mechanism of carcinogenesis in pancreatic cancer coupled with the arrival of biologically targeted agents may provide new avenues of research and progress in this disease.

**Disclosures:**
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