Blackstock and colleagues present a well-written, comprehensive review of the current state of management of both resectable and unresectable pancreatic carcinoma, as well as ongoing research and future strategies. Unfortunately, in the majority of patients, the disease is locally advanced at diagnosis, with or without regional and distant metastases. Unlike recent advances in screening for both prostate and breast cancer, no reliable and/or cost-effective method for identifying patients at risk for pancreatic cancer is available. Also, there is currently no reliable hematologic marker that can identify patients whose cancers are in the earliest developmental stage. Blackstock et al do emphasize that recent advances in laparoscopic techniques have led to better selection of patients for subsequent exploration and surgical resection. Given the reduction in operative mortality during the last 10 years, survival rates have improved.

Benefits of Combined-Modality Therapy Still Debated

Despite the positive, albeit modest, results of the Gastrointestinal Tumor Study Group (GITSG) trials [1,2] and recent data from Johns Hopkins [3], the benefits of combined-modality therapy (radiation therapy plus 5-fluorouracil[5-FU]-based chemotherapy), either in the adjuvant setting or as primary treatment for locally unresectable disease, continue to be debated. The European Organization for Research and Treatment of Cancer (EORTC) is currently conducting a randomized trial in patients who have undergone a resection to address the role of adjuvant combined-modality therapy. Patients are being randomized to observation vs 5-FU chemotherapy given concurrently with 40 Gy of radiation. Preliminary results are not yet available.

More innovative ways of delivering systemic chemotherapy and/or intraperitoneal chemotherapy, combined with altered fractionated radiation schemes, three-dimensional conformal treatment planning, and/or intraoperative radiation, have had variable results. Franklin et al recently reported excellent response rates in a small cohort of patients with unresectable pancreatic cancer treated with a combination of concurrent continuous-infusion 5-FU, cisplatin (Platinol), and hyperfractionated radiation to a dose of 59.4 Gy. Complete and partial responses at the primary site, as judged radiographically, were observed in 88% of patients, with complete responses occurring in 44% by 3 months. Patients were treated solely on an outpatient basis with acceptable morbidity. These impressive response rates raise interesting possibilities for a neoadjuvant approach in patients with locally advanced unresectable disease [4].

Neoadjuvant therapy in patients with resectable disease was recently tested in a phase II trial by the Eastern Cooperative Oncology Group (ECOG). Fifty-three patients with potentially resectable disease received 5-FU and mitomycin (Mutamycin) delivered concurrently with radiation therapy to a dose of 50.4 Gy. Of these, 41 patients underwent surgical exploration and 23 (44%) had resection, which is approximately twice the historical resection rate. Median survival was 16.6 months, and the 2-year survival rate was 30% [5]. Although this approach improved the resectability rate, survival in resected patients was similar to that in other series using either adjuvant combined-modality
therapy or even observation alone after surgery. The issue of maintenance chemotherapy is also unresolved. In the GITSG trials, patients received maintenance 5-FU following the completion of combined-modality therapy. Many retrospective studies from single institutions do not report the percentage of patients who receive maintenance chemotherapy and whether it ultimately has an impact on survival.

**Novel Treatment Strategies**

We agree with Dr. Blackstock and colleagues that, in general, adjuvant combined-modality therapy most likely decreases the risk of local recurrence. However, the rate of regional and distant metastases is high, and thus limits the success of local/regional modalities. This underscores the obvious need to explore novel strategies to improve the poor outcome of this disease. The authors provide an excellent review of currently available preclinical and clinical developments in the fields of radiopharmaceuticals, molecular-based gene therapy, and immunotherapy. Their discussion will help the practicing physician better understand the rationale and motivation behind these trials.

In general, our understanding of the immune system and its interaction and intervention is still limited. Immunotherapy and monoclonal gene therapies that have shown promising results in preclinical studies have frequently proved disappointing when tested in clinical trials. Lymphokine-activated killer cell (LAK) modulation through interleukin-2 (IL-2) stimulation has shown efficacy in recent preclinical and clinical trials in the treatment of mesothelioma and melanoma [6-8]. However, despite encouraging preclinical data in pancreatic cancer, the authors emphasize that no apparent benefit has been seen in clinical trials [9].

In contrast, production of viral-mediated anti-human carcinoembryonic antigen (CEA) vaccine, as well as viral gene/CEA coupling and insertion into pancreatic tumors demonstrated in recent animal studies, appear to be promising [10,11]. As the authors discuss, little is understood about the immunologic mechanisms of these approaches, and no human clinical trials have been reported to date. Further research in this area should continue, especially in light of the disappointing preliminary results with newer chemotherapeutic agents, such as paclitaxel (Taxol), dihydroxyanthracinedione (DHAD), and pirarubicin, in pancreatic cancer.

Blackstock and colleagues also present exciting new data regarding efforts to interfere with K-ras function through the introduction of antisense K-ras expression plasmids into pancreatic tumor cell lines. This approach appears to address the need to simultaneously treat both the peritoneum and primary tumor. We agree with the authors that efforts should be directed toward translating this in vitro approach to clinical trials.

**Impact of Therapies on Quality of Life**

A secondary end point in pancreatic cancer clinical trials is quality of life. A recent multicenter, randomized trial compared gemcitabine (Gemzar) vs 5-FU in patients with advanced disease. Although gemcitabine showed a response rate of 23% vs 5% for 5-FU, this did not translate into a significant survival benefit [12]. However, gemcitabine did improve patients' quality of life. It must be emphasized that similar palliative benefits, such as pain relief, can be obtained with radiation therapy [13].

**Summary**

In summary, the standard therapy, either in the adjuvant setting or for primary locally unresectable adenocarcinoma of the pancreas, is radiation therapy plus 5-FU-based chemotherapy. Although this therapy significantly improves survival, the gains are modest. Further improvements in the treatment of pancreatic cancer will not be seen until we acquire a greater understanding of the mechanisms responsible for the evolution of pancreatic cancer at the molecular level and we are able to translate promising preclinical data on novel approaches, such as immunotherapy and monoclonal gene-based therapy, into successful clinical trials. These approaches need to be strongly supported.

**References:**


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