Surgical Management of Pancreatic Cancer

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Drs. Ahrendt and Pitt should be congratulated on a comprehensive and well-presented review of the surgical management of pancreatic cancer. Unfortunately, pancreatic cancer continues to be a major cause of cancer-related death. The majority (80%) of patients still present with unresectable locally advanced or metastatic disease.

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Preoperative Imaging Modalities and Laparoscopy
In the 1980s, several surgical series reported dismal resectability rates of 25%. Due to poor imaging techniques, most patients were being staged intraoperatively by manual palpation of the plane between the tumor and the mesenteric vessels. Patients found to be unresectable had then undergone a major laparotomy with little benefit, and postoperative recovery delayed their treatment options.

Dual-phase contrast-enhanced spiral computed tomography (CT) has revolutionized both the detection and staging of pancreatic cancer. The accuracy with which spiral CT predicts resectability ranges from 75% to 90%.[1] CT criteria for surgical resectability include (1) the absence of extrapancreatic disease, (2) a patent superior mesenteric vein-portal vein confluence, and (3) no direct tumor extension into the celiac axis or superior mesenteric artery.

Investigators at the Massachusetts General Hospital reported that 24% of patients thought to have resectable pancreatic cancers on CT scan had occult metastatic disease found on diagnostic laparoscopy.[2] Patients found to have occult disease were spared an unnecessary laparotomy. However, with improved state-of-the-art spiral CT, routine use of staging laparoscopy may not be easily justified.[1]

Ultrasound and PET
More recently, endoscopic ultrasound has been shown to be helpful in detecting small pancreatic cancers. In our practice, the technique is used in patients with a clinical suspicion of pancreatic cancer and an equivocal or negative CT scan. Although the procedure is very user-dependent, it offers the additional benefit of image-guided tissue diagnosis. More experience with whole-body positron-emission tomography may help stage patients more accurately and also may be able to differentiate benign from malignant pancreatic tumors.

Surgical Results and Pathologic Analysis
Despite improved resectability rates and decreased perioperative mortality at high-volume surgical centers, long-term survival following pancreaticoduodenectomy remains poor. Median survival in most series ranges from 18 to 20 months, and 5-year actuarial survival rates range from 7% to 25%.

Patterns of failure after curative resection for pancreatic carcinoma involve both local recurrence (60%) and distant hepatic metastases (60%).[3] Even among patients thought to be resectable for cure by preoperative CT and intraoperative exploration, 50% will have either gross or microscopic involvement of the surgical margins.[4] The most commonly involved is the retroperitoneal margin, which corresponds to the tissue along the proximal 3 to 4 cm of the superior mesenteric artery wall. Several studies have demonstrated that patients with grossly or microscopically positive surgical margins have a median survival of only 8 to 10 months, similar to the survival of patients with unresectable locally advanced tumors. From a technical aspect, failure to mobilize the superior mesenteric-portal vein may result in a positive margin due to incomplete removal of the uncinate process and the mesenteric soft tissue adjacent to the superior mesenteric artery. New treatment strategies to maximize margin-negative resections in patients with pancreatic cancer will hopefully be one component of improved locoregional tumor control.

Both the evaluation of future innovative treatment strategies and the development of reproducible
prognostic predictors of treatment failure depend on an accurate standardized pathologic assessment of the surgical specimen.[5] Retrospective pathologic analysis of archival material does not allow for accurate assessment of resection margins or the number of lymph nodes retrieved. A prospective pathologic evaluation must be initiated by the surgeon’s orientation of the specimen with the pathologist, and identifying the bile duct, pancreatic, and retroperitoneal transection margins.

The final pathologic evaluation of permanent sections should include a description of tumor histology and differentiation, a gross and microscopic evaluation of the tissue of origin (pancreas, bile duct, ampulla of Vater, or duodenum), an assessment of the maximal transverse tumor diameter, and a report of lymph node status. A standardized pathologic analysis will allow for an accurate comparison of novel treatments of pancreatic cancer.

**Adjuvant and Neoadjuvant Treatment Strategies**

In 1985, the Gastrointestinal Study Group (GITSG) reported the first clinical trial evaluating the use of adjuvant fluorouracil (5-FU)-based chemoradiation for resectable pancreatic cancer. This study demonstrated an improvement in both median and 2-year overall survival. With recent data showing a survival benefit for gemcitabine (Gemzar) over 5-FU in patients with advanced disease, studies are currently examining the role of gemcitabine in the adjuvant setting.

The phase III Radiation Therapy Oncology Group (RTOG) trial 9704 is comparing postoperative adjuvant infusional 5-FU vs gemcitabine, both followed by 5-FU-based chemoradiation. Unfortunately, the morbidity and often prolonged recovery time associated with pancreaticoduodenectomy prevent the timely delivery of postoperative chemoradiation in at least 25% to 30% of eligible patients.[6]

This risk of delaying postoperative adjuvant chemoradiation has prompted investigators to assess the safety and efficacy of administering preoperative chemoradiation to patients with resectable adenocarcinoma of the pancreas. The use of preoperative chemoradiation is supported by the following considerations:

1. Radiation therapy is more effective on well-oxygenated cells that have not been devascularized by surgery.
2. Peritoneal tumor implantation due to the manipulation of surgery may be prevented by preoperative chemoradiation.
3. The high frequency of margin-positive resections recently reported supports the concern that the retroperitoneal margin of excision, even when negative, may be only a few millimeters wide.
4. Patients with disseminated disease evident on restaging studies after chemoradiation will not be subjected to laparotomy.
5. Because chemoradiation will be administered first, delayed postoperative recovery will have no effect on the delivery of multimodality therapy.

A prospective trial of preoperative 5-FU chemoradiation demonstrated that this treatment was well tolerated, and all patients received treatment.[7] The local recurrence rate decreased dramatically to 11%, compared to 60% in historical controls treated with surgery alone. This improved locoregional tumor control rate was associated with a decrease in the incidence of positive surgical margins (18%).

**Future Directions**

Because preoperative chemoradiation is a locoregional therapy, this strategy is not expected to significantly improve distant metastatic disease rates. Future treatment strategies should incorporate preoperative chemoradiation for locoregional disease control and novel systemic treatment to control possible micrometastatic disease (and to possibly downstage locally advanced tumors). Major improvements in overall survival will await these novel systemic therapies, but the importance of locoregional tumor control should not be underestimated.

At Emory, we have incorporated a preoperative strategy with full-dose induction chemotherapy followed by chemoradiation for improved locoregional disease control. This phase I/II investigation examined the safety of induction 5-FU, cisplatin, and gemcitabine followed by hyperfractionated chemoradiation in 29 patients. Remarkably, we have seen a 40% objective partial and complete response rate with the induction chemotherapy. We are now investigating this treatment strategy in a phase II trial in borderline and resectable patients.
References:


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