Surgical Treatment of Pancreatic Cancer

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INTRODUCTION

Pancreatic cancer continues to be one of the deadliest malignancies encountered with the estimated deaths for 2010 (36,800) nearly equal to the estimated number of new cases (43,140). The number of deaths each year from pancreatic cancer is close to the number from breast cancer (40,230), even though nearly five times as many patients are diagnosed with breast cancer (209,060). Despite this, a pessimistic view of this disease is not justified and needs to be replaced with optimism. A group of patients, selected by a dedicated multidisciplinary pancreatic cancer team, and treated in a high volume pancreatic surgery center, can experience long-term survival after surgical resection of their disease. Most commonly, this situation applies to those with resectable disease in the head of the pancreas, which will be the focus of the current review.

PATIENT SELECTION

The initial evaluation of a patient with known or suspected pancreatic cancer focuses on deciding if surgical resection is an option. Median survival of unresected (locally advanced or metastatic) pancreatic cancer is a dismal six months. Determining if the patient can move from this unfavorable group to the resectable group where median survival is generally >20 months is paramount. This decision is based primarily on radiographic imaging including high resolution multidetector computed tomography (CT) scanning and endoscopic ultrasound (EUS). At a minimum, treating physicians should obtain a CT of the abdomen with thin cuts through the pancreas, dictated by a specific pancreas protocol, and a chest CT. The sensitivity and positive predictive value of dual phase CT scanning for the detection of pancreatic tumors are >90%. Although surgical decisions can be made with CT images alone, EUS allows sampling of the tumor with fine needle aspiration, absolutely vital when considering neoadjuvant therapy, which will be discussed later.

Currently, positron emission tomography (PET) scanning is not a standard preoperative test. Although further information on the primary tumor is not often gained, it appears from early reports that PET technology may be superior to CT in diagnosing metastatic disease. Farma et al recently reported their experience with fusion PET/CT scanning in 82 patients with pancreatic lesions. Importantly, seven patients (11%) were found to have metastatic disease unrecognized by standard imaging, confirmed histologically, and were spared operation. Similar findings were noted by Heinrich et al, who reported an alteration in the treatment plan after PET/CT of 16%, which was found to be cost effective. With further experience and insurance company cooperation, PET/CT may become a standard modality for preoperative staging.

As CT scanning technology has significantly improved, staging laparoscopy has been used less commonly in recent years. Current indications include large pancreatic head masses (>3cm), tumors of the body and tail, suspicious CT findings such as ascites, and significantly elevated CA19-9 (>100 U/mL) without biliary obstruction. Maithel et al noted findings of unresectable disease during diagnostic laparoscopy on patients considered preoperatively to have resectable disease in 26% of the cases when the CA19-9 was >130 U/mL. In contrast, the rate was only 11% in patients with a CA19-9 <130 U/mL.

If a patient is found to have metastatic disease on radiographic imaging, most commonly hepatic lesions, or is medically unfit for operation, non-surgical options are standard. In fit patients without distant tumor spread, surgery is considered, and determining the local extent of disease becomes vital. A recent consensus conference has provided much needed definitions regarding the local tumor relationship with the mesenteric vasculature. These relationships were shown to predict resectional success by Lu et al. In their report, patients with adenocarcinoma of the pancreatic head were graded according to the extent of vessel involvement, ranging from 0 (no involvement) to 4 (encasement). Patients with grade 0 or 1 were uniformly
resectable, while higher grades were less often resectable including a 0% resection rate in the grade 4 patients. Using this data, these guidelines were formulated and will allow us to preoperatively predict surgical success and appropriately stratify patients for clinical trials (Table).

Most importantly, this classification scheme groups patients with technically resectable disease into two subsets: resectable and borderline resectable. Patients labeled, “resectable,” are those in whom surgery should easily result in a microscopically margin negative resection (R0). Patients with, “borderline resectable,” lesions require more technically demanding surgery, are at greater risk for early metastatic disease, and are more likely to have a margin positive resection (R1: microscopically positive, R-2: grossly positive). Margin status is a powerful predictive variable, and every effort should be made to ensure an R0 resection, including a preoperative assessment of likelihood. In the European Study Group for Pancreatic Cancer trial, out of 541 patients, 101 had an R1 resection. This group had a median survival of 10.9 months compared to 19.9 months in patients receiving a margin-negative resection. In a review of over 1,400 Whipple pancreaticoduodenectomy (PD) procedures, Winter et al confirmed the importance of resection margins, finding it to be an independent predictor of survival with a hazard ratio of 1.6 in multivariate analysis.

In Figure 1, the tumor is clearly free from the superior mesenteric and celiac vessels and would be deemed resectable. This patient is generally offered immediate surgery although the option of a clinical trial involving preoperative chemotherapy can be entertained. In Figure 2, there is short segment involvement of the superior mesenteric vein (SMV) without arterial involvement. In the consensus definitions, this would be considered borderline resectable, and a practice of neoadjuvant therapy in this population is often recommended. It is not unreasonable, however, to offer immediate surgery, and, in fact, the National Comprehensive Cancer Network guidelines of resectability do not include short segment venous involvement in their definition of borderline resectability. Major impingement or short segment venous occlusion, however, is always considered borderline resectable. Involvement of the nearby visceral arteries has not been associated with favorable outcomes, and is routinely placed in the borderline or locally advanced categories. Abutment (<180°) or encasement (>180°) of the superior mesenteric artery (SMA) or hepatic artery (HA) often indicates peri-vessel neural infiltration, a high likelihood of early metastatic disease, and increased risk for a margin positive resection. These patients often present with unrelenting back pain, indicative of peri-neural invasion. Certain situations of arterial involvement do not, however, immediately move the patient to a locally advanced, unresectable category. This includes short segment encasement of the HA or short segment SMA abutment. These cases are categorized as borderline resectable disease and an attempt to provide these patients with an opportunity for surgical extirpation should be considered (Table). Clearly this is a more challenging operation, at times requiring arterial reconstruction. In this situation, and when more extensive venous involvement is noted, such as encasement or occlusion, a strategy of preoperative therapy, including chemotherapy and often external beam radiation, is routinely recommended. This may increase the likelihood of a margin negative resection, and will allow time to assess disease biology to avoid operation in patients with early metastatic disease. When the SMA or Celiac trunk is encased, the patient is generally considered to have locally advanced, unresectable disease (Figure 3).
VASCULAR RESECTION

In patients with borderline resectable tumors, including minimal SMV/portal vein (PV) involvement, it is likely that venous resection will be needed. A sizeable amount of data now indicates comparable survival and a lack of increased morbidity when routinely resecting the involved SMV/PV if done in a high volume center with technical expertise. Tseng et al reviewed an experience with 126 PDs requiring venous resections and noted acceptable morbidity and mortality of 21 and 2.1%, respectively. In that study, median survival was 23.4 months in the vascular resection group, not different from a comparable group receiving PD without vascular resection. Although trials looking at extended resections have not shown an improvement in survival, venous resection does not fall within this category of regional pancreatectomy. Short-segment SMV involvement generally does not portend more advanced disease as is the case with arterial involvement and can be considered as a reasonable component of PD. It may even increase the likelihood of obtaining a microscopically negative margin when utilized instead of cutting through the tumor to avoid venous resection.

SURGICAL OUTCOMES

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SURGICAL OUTCOMES

Guidelines formulated to preoperatively predict surgical success and appropriately stratify patients for clinical trials.

<table>
<thead>
<tr>
<th>Resectable</th>
<th>No distant metastases.</th>
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<tr>
<td></td>
<td>No radiographic evidence of superior mesenteric vein (SMV) and portal vein abutment, distortion, tumor thrombus, or venous encasement.</td>
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<tr>
<td></td>
<td>Clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery (SMA).</td>
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<tr>
<td>Borderline resectable</td>
<td>Venous involvement of the SMV/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement, but with suitable vessel proximal and distal to the area of involvement, allowing for safe resection and reconstruction.</td>
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<td></td>
<td>Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.</td>
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<td>Tumor abutment of the SMA not to exceed &gt;180° of the circumference of the vessel wall.</td>
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In the not too distant past, surgical resection of pancreatic head tumors was fraught with unacceptably high morbidity and mortality rates. In the 1960s and 1970s some surgeons even suggested the Whipple (PD) operation be abandoned. Fortunately, in the current era, resection of the pancreatic head can be done safely with acceptable outcomes.

In one of the largest series of PD for pancreatic cancer, Winter et al note a reduction in mortality from 30% in the 1970s to 2% and 1% in the 1990s and 2000s, respectively. The perioperative morbidity rate remained essentially stable, with an overall rate of 38% over the study period. The most common complications were delayed gastric emptying (15%), wound infection (8%), pancreatic fistula (5%), cardiac event (4%), and intra-abdominal abscess (4%). Similar results have been noted by others, including a report from Grobmyer et al that noted a 1% mortality and a 47% morbidity rate when a comprehensive review of every possible complication was undertaken, with most of them being relatively minor grade 2 morbidities.

In order to keep pancreatic cancer surgery as safe as possible, it is clear that it should be done in a medical center where these highly complex operations are performed routinely. There is no question that surgeons are best at what they do often, and the literature clearly indicates a reduction in morbidity and mortality when this operation is done in a high volume center (>15-20 PD/year). There may even be a benefit from being performed in a teaching institution. Tseng et al showed this benefit of experience in a paper noting a significant reduction in blood loss and operative time after a surgeon had completed 60 PDs.
Importantly, surgical experience likely increases the rate of complete resections with no microscopic residual tumors (R0). Pathologists have recently taught us that assessment of the, “retroperitoneal,” “uncinate,” or, “SMA,” margin is extremely important and, until recently, often ignored. When a PD margin is positive, it is most often the left edge of the uncinate process where it abuts the SMA. Esposito et al reviewed a group of specimens that had previously been labeled R0 with a standardized approach to the SMA margin. They found that nearly 75% of these resections were actually margin positive. In order to increase the chances of obtaining a negative retroperitoneal margin, it is absolutely essential to skeletonize the SMA on its right lateral border (Figure 4). This is the most technically challenging aspect of the PD where experience and expertise is paramount. With extensive experience, adopting the “SMA first,” technique, and becoming facile with portal venous resection and reconstruction, these difficulties can be overcome. This likely increases the rate of margin negative resections, the surgeon’s main contribution to patient survival.

Although the surgeon volume is important, it really is the entire perioperative team that is necessary to obtain excellent outcomes. This includes appropriate preoperative optimization through cardiology and pulmonary support, intra-operative management by skilled anesthesiologists, and aggressive post-operative monitoring to ensure complications are noted early in their course when alterations in care can limit their negative effects. Nurses with experience caring for pancreatectomy patients are likely as important as anybody on the team. Access to skilled interventional radiologists, endocrinology for commonly seen hyperglycemia, nutritionists, 24/7 resident coverage, and other support services all combine to create a team that can minimize morbidity and mortality.

**SURVIVAL**

While we have improved significantly on the safety of surgical therapy for pancreatic cancer in recent years, the ultimate test is patient survival, and there are now large series demonstrating long-term survivors in this patient population. Winter et al in their large series report a median survival of 19 months and a five year survival of 20% in the most recent decade. A recent update of the large, randomized prospective Charité Onkologie (CONKO) trial noted a median survival in the experimental arm (surgically resected plus gemcitabine) of 22.8 months. Looking at recent data from our center’s cancer database, maintained in accordance with the American College of Surgeons’s Commission on Cancer database requirements, on over 250 patients undergoing PD for pancreatic cancer had an overall five year survival of 21%.

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**Figure 4.** In this intra-operative photo, the right lateral border of the superior mesenteric artery has been skeletonized (arrow). This careful dissection maximally increases the chances for a margin-negative resection of the tumor. (PV, portal vein; asterisk, cut edge of pancreas; IVC, inferior vena cava)

**Figure 5.** In a recent review of data, maintained in accordance with the American College of Surgeons’s Commission on Cancer database requirements, on over 250 patients undergoing surgery for pancreatic cancer at Ochsner, five year survival was 21%. Neoadjuvant therapy was not aggressively recommended during this time period.
rate of 21% (Figure 5). Patients with tumor confined within the pancreatic head, had a much better long-term survival rate of 32%. Although these numbers are not nearly good enough, it is clear a group of patients with pancreatic cancer can obtain long-term survival with surgical resection.

**NEOADJUVANT THERAPY**

Several large randomized trials indicate a survival benefit of adjuvant therapy. They have not, however, demonstrated significant advancements in patient survival for nearly two decades. Traditionally, a surgery first followed by chemotherapy design has been utilized. In an effort to improve on the relatively poor outcomes noted, a neoadjuvant (chemotherapy plus external beam radiation prior to surgery) approach has been utilized and offers a number of theoretical advantages. This method affords immediate therapy of early metastatic disease and increases the portion of patients completing treatment as post-operative debilitation often hinders delivery of the full course of chemotherapy. Preoperative therapy also ensures delivery of chemotherapy while the tumor bed is well vascularized, and allows time to assess disease biology. When done as part of a clinical research protocol, tissue harvested at surgery can be analyzed for treatment effect. Development of distant metastases is the primary form of disease progression while on a neoadjuvant protocol. This group of patients is clearly not benefited by surgery and can only be identified by waiting a period of time. If a patient develops liver metastases during preoperative therapy, it is not due to surgical delay, but rather was likely present at initial evaluation and radiographically undetectable due to small size. This indicates aggressive tumor biology, which can not be overcome with surgery. Finally, the rate of margin-negative resections may be increased. Pingpank et al, looking at 100 patients undergoing PD for pancreatic cancer, noted margin positivity in 74.4% of patients undergoing a surgery first approach while 49.1% or patients receiving neoadjuvant chemoradiation had all six margins negative upon careful pathologic assessment (p=0.013). This is especially important for those with borderline resectable disease where obtaining an R0 resection can be quite difficult. This borderline group is also at risk for early metastatic disease, again making the neoadjuvant approach attractive.

Evans et al recently reported on 86 patients with resectable disease, including short segment SMV involvement, receiving preoperative gemcitabine based chemoradiation prior to undergoing PD for pancreatic cancer. Overall median survival for the entire group was 22.7 months, with a 27% five year survival. In the group that went on to PD (64/86), median survival was 34 months with a 36% five year survival. Of those who did not undergo surgery after preoperative treatment, disease progression included hepatic or peritoneal metastases. It is likely that with this form of distant progression there was early microscopic metastatic disease which was too small to show up on initial staging. While survival rates of neoadjuvant trials are clearly benefited by drop-out of patients with early metastatic disease, the above theoretical advantages make it a reasonable approach, especially for those with borderline resectable tumors.

**MULTIDISCIPLINARY TREATMENT PLANNING**

With all of the components of therapy mentioned in mind, it is clear a multidisciplinary team dedicated to the treatment of patients with pancreatic cancer is needed to make appropriate therapeutic decisions. This includes radiologists with an interest in abdominal imaging, gastroenterologists with EUS capabilities, radiation oncologists, GI medical oncologists, a GI pathologist, and surgeons with specific fellowship training and interest in upper GI surgical oncology. Generally this includes presenting each patient at a weekly tumor board meeting to individualize treatment and appropriately select patients for surgery. Pawlik et al noted this strategy to alter therapy in 18.7% of patients based on a more thorough review of radiologic imaging, and 3.4% based on further pathologic evaluation by a dedicated GI pathologist. Furthermore, their group noted a significant increase in the number of patients identified for enrollment in a familial pancreatic cancer registry. Our center has adopted such an approach and believes it is vital. Not only are treatment decisions made by incorporating the perspectives of several disciplines, but possible enrollment in clinic trials and performance reviews can be incorporated to continually ensure optimum care.

**LOOKING TO THE FUTURE**

Although small steps forward are being made, it must be recognized that for the majority of patients with resectable pancreatic cancer we are failing. As noted previously, current large adjuvant trials barely improve on survival from the Gastrointestinal Tumor Study Group trial that was published in 1985. A recent article from the National Cancer Institute outlined goals for future research relating to this terrible disease. In this manuscript, Phillip et al outline important areas for research including targeted agents based on molecular pathways, utilization of preclinical models, future clinical trial design, establishing biorepositories, and the development of biomarkers. Biorepositories will be incredibly important in researching new targeted agents based on molecular pathways, utilization of preclinical models, future clinical trial design, establishing biorepositories, and the development of biomarkers. Biorepositories will be incredibly important in researching new targeted agents based on molecular pathways, utilization of preclinical models, future clinical trial design, establishing biorepositories, and the development of biomarkers.
CONCLUSION

Although pancreatic cancer continues to carry a dismal prognosis, there are glimmers of hope. There is a select group of patients who benefit from surgical resection and have a real chance at long-term survival. These patients are best treated in a high volume center with a multidisciplinary approach to ensure proper patient selection. While we continue to improve surgical outcomes, multi-institutional clinical trials, molecular assessment of banked specimens, and translational biomarker research are needed to advance adjuvant therapy and finally see major improvements in overall patient survival. This will not be an easy task. The surgical therapy needed is difficult to not only perform, but recover from, and the research required to finally create uniformly successful adjuvant therapy is a daunting challenge. We should not give in to pessimism, however, for, as Frederick Douglass noted, without struggle there is no progress. Pancreatic cancer patients deserve our struggle and our optimism.

REFERENCES


Drs. Conway and Bolton are with Surgical Oncology at the Ochsner Medical Center, New Orleans.