

Surgery for Pancreatic Cancer: Recent Controversies and Current Practice

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Pancreatic duct carcinoma remains a common disease with a poor prognosis. More than 30,000 Americans will die of the disease in 2004, making it the fourth leading cause of cancer death. Despite significant advances in the treatment of many other human tumors, the 5-year survival rate for persons diagnosed with pancreatic cancer has not changed in decades and remains <5%. This is due both to the inherently aggressive biology of the disease and to its late diagnosis in most cases. Surgical resection of localized disease remains the only hope for cure of pancreatic cancer. Over the past 2 decades, significant advances in diagnostic imaging, staging, surgical technique, and perioperative care have led to marked improvement in the surgical management of pancreatic cancer patients. Operative mortality rates for pancreaticoduodenectomy are now <5% at major centers, and the average length of hospital stay has been reduced to <2 weeks. Improvements in patient outcome after pancreatic cancer surgery have made possible, for the first time, the design and conduct of large adjuvant therapy studies in pancreatic cancer. Such clinical trials are critical for improving outcomes for pancreatic cancer patients.

Pancreatic cancer remains a common disease with a poor prognosis. In 2005, the American Cancer Society estimates that there will be approximately 32,180 new cases of pancreatic cancer in the United States, with 31,800 deaths, making it the fourth most common cause of cancer death.¹ The nearly equal rates of incidence and mortality show the virulent nature of this malignancy. Despite these sobering statistics, surgery does have the potential to cure pancreatic cancer. Unfortunately, although pancreatic cancer is biologically aggressive from the outset, it is most often clinically quiescent and remains so until its later stages. Thus, only 15%–20% of patients are candidates for surgery upon diagnosis. Of those who do undergo potentially curative surgery, most patients eventually relapse and die of their disease. Advances in surgical technique, anesthesia, and perioperative care during the last 2 decades have significantly improved outcomes for patients undergoing pancreatic cancer surgery. Abundant literature has been devoted to

examining the technical aspects of pancreaticoduodenectomy, the most common operation for pancreatic cancer. In recent years, surgical investigators have explored more locally aggressive operations, including vascular resection and extended lymphadenectomy, to improve patient outcome. Adjuvant therapy for pancreatic cancer remains an active area of investigation, because it is clear that only through the use of multimodality therapy will significant strides be made toward improving patient survival. In this review, we discuss the current status of surgery for pancreatic cancer, highlighting important controversies and areas of active investigation.

Presentation

Most patients with pancreatic cancer present late in the course of their disease. The most common presenting symptoms include epigastric abdominal pain (often radiating to the back), weight loss, fatigue, and anorexia. Such symptoms generally reflect the presence of locally advanced and/or metastatic disease; thus, once patients develop symptomatic disease, they are rarely candidates for surgical resection. The classic presentation of painless jaundice is associated with cancers of the pancreatic head and is present in 50%–60% of patients at diagnosis. The presence of jaundice is generally indicative of less advanced disease and a higher likelihood of resectability. Biliary and pancreatic duct obstruction often results in steatorrhea and malabsorption. The recent onset of diabetes is another common finding in newly diagnosed pancreatic cancer patients such that pancreatic cancer should be considered in patients who develop diabetes late in life. Apart from jaundice, physical find-

Abbreviations used in this paper: CRT, chemoradiation; CT, computerized tomography; DGE, delayed gastric emptying; ERCP, endoscopic retrograde cholangiopancreatography; ESPAC, European Study Group of Pancreatic Cancer; EUS, endoscopic ultrasonography; 5-FU, 5-fluorouracil; GITSG, Gastrointestinal Study Group; MRI, magnetic resonance imaging; PET, positron emission tomography; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

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ings of pancreatic cancer are rare but can include ascites, a palpable mass secondary to peritoneal metastases, and left-sided supraclavicular adenopathy, each of which indicates advanced disease. Perhaps the most critical assessment to be made on clinical examination is an assessment of the patient's performance status, because this will dictate his or her suitability for surgical and non-surgical therapy.

Clinical and Pathologic Staging

Pancreatic cancer staging is problematic in that accurate pathologic staging is possible only for patients who undergo surgical resection. For all other patients, clinical staging is based on diagnostic imaging. The American Joint Committee on Cancer (in cooperation with the TNM committee of the International Union Against Cancer) staging system is depicted in Table 1. Although this system is prognostic for overall survival, it is not particularly useful in guiding treatment, because some patients with advanced-stage disease (ie, stage IVA) may be candidates for surgical resection, whereas others are not. For this reason, pancreatic cancer patients are generally grouped by clinicians as having resectable, locally advanced, or metastatic disease. Diagnostic imaging is used to most accurately determine the appropriate grouping for each patient, and this guides the selection of therapy.

Diagnosis and Assessment for Surgical Resection

Staging is a critical part of pancreatic cancer management, as it is for all solid tumors. For pancreatic cancer patients, however, the principal goal of staging is the determination of resectability. Even with the most effective standard therapies, patients with locally advanced and metastatic pancreatic cancer have a median survival of approximately 10–12 months and 4–6 months, respectively. Given the significant morbidity and quality of life lost after nontherapeutic laparotomy, it is incumbent on the pancreatic cancer surgeon to minimize its occurrence. Furthermore, for patients who undergo resection, it is critical that every effort be expended to achieve microscopically negative surgical margins. Numerous studies have shown that patients with residual disease in the form of positive macroscopic or microscopic margins have survival rates similar to those treated nonoperatively²⁻⁵ (Table 2). Accurately defining the anatomy of the primary tumor relative to the surrounding normal structures and the presence of metastatic disease is therefore critical to determining the likelihood of potentially curative surgery.

The current standard for pancreatic cancer staging remains the use of high-quality thin-section computerized tomography (CT) scans. Today, with modern, multidetector CT machines, excellent spatial resolution can be achieved with a marked decrease in acquisition time

Table 1. TNM Classification and AJCC Staging of Pancreatic Cancer

Definition of tumor	Regional lymph nodes	Distant metastasis	AJCC stage
TX: primary tumor cannot be assessed	NX: regional lymph nodes cannot be assessed	MX: distant metastasis cannot be assessed	IA: T1, N0, M0
T0: no evidence of primary tumor	N0: no regional lymph node metastasis N1: regional lymph node metastasis pN1a: metastasis in a single regional lymph node	M0: no distant metastasis	IB: T2, N0, M0
Tis: in situ carcinoma	pN1b: metastasis in multiple regional lymph nodes	M1: distant metastasis	II: T3, N0, M0
T1: tumor limited to the pancreas, ≤2 cm in greatest dimension			III: T1, N1, M0; T2, N1, M0; T3, N1, M0
T2: tumor limited to the pancreas, >2 cm in greatest dimension			IVA: T4, any N, M0
T3: tumor extends directly into duodenum, bile duct, or peripancreatic tissues			IVB: any T, any N, M1
T4: tumor extends directly into stomach, spleen, colon, or celiac axis vessels			

AJCC, American Joint Committee on Cancer.

Table 2. Published Survival After Pancreaticoduodenectomy

Study	n	Margin status	Survival
Neoptolemos ⁸⁰	101	R1	11 mo median
Sohn ¹⁰³	184	R1/R2	12 mo median
Nishimura ¹⁰⁴	70	R1/R2	6 mo median
Yeo ¹⁰⁵	58	R1/R2	10 mo median
Nitecki ²	28	R2	Overall actuarial 5-y survival 6.8%
Willett ⁴	37	R1/R2	For R1 patients, median survival 12 mo. There were no survivors past 41 mo

R0, microscopically complete resection; R1, positive margins by microscopy; R2, macroscopic tumor at surgical margins.

compared with older-generation scanners.⁶ The advent of 16- and 32-slice CT machines shortens volume acquisitions, and quicker scan times permit better enhancement of mesenteric and celiac vessels. The accuracy of even older-generation scanners to predict resectability exceeded 80% in many studies.^{7,8}

CT is particularly accurate in defining the relationship of the primary tumor to the superior mesenteric vein (SMV)/portal vein (PV) confluence, superior mesenteric artery (SMA), and celiac axis. It is the relationship of the pancreatic head cancer to the retroperitoneal soft tissues that is critical to predicting the likelihood of achieving a margin-negative resection. The other surgical margins (pancreas and bile duct) can be re-resected at the time of operation in the event of microscopic involvement by tumor. The retroperitoneal soft tissue margin, in contrast, is limited by the SMA and aorta. When evaluating a patient for operation, we use the following criteria to determine potential resectability: (1) no evidence of extrapancreatic or distant metastatic disease, (2) patency of the PV and SMV confluence, and (3) no involvement of the celiac axis or SMA.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has been used with increasing frequency in the diagnosis of pancreatic masses; this may be due to its increased availability. MRI is capable of providing staging information similar to that from a CT scan and can be performed in patients with allergies to CT contrast. It is more expensive, and the procedure takes longer. Although previously the ability of MRI to provide images in multiple planes was a clear advantage over CT, the introduction of multidetector CT and sophisticated imaging software has largely negated this.⁹ Considering the rapidly evolving nature of imaging technology, it has been difficult to study CT vs MRI. Recently, an innovative report described MRI with manganese-DPDP (mangafodipir) of focal solid pancre-

atic lesions.¹⁰ Thirty-four patients with suspected solid pancreatic lesions underwent MRI before and after infusion of 5 μ mol/kg manganese-DPDP (Nycomed Amer-sham Health, Oslo, Norway). The definitive diagnosis was pancreatic malignancy in 18 patients, focal pancreatitis in 5, and neuroendocrine tumors in 3. Four patients with suspected lesions at ultrasound, CT, or both were free of focal pancreatic disease. Manganese-DPDP MRI identified 17 of 18 malignancies, 2 of 3 endocrine neoplasms, and 5 of 5 cases of focal pancreatitis; 4 patients without pancreatic lesions were correctly identified. The manganese-DPDP MRI accuracy in detecting focal pancreatic solid lesions was 93%. MRI missed 1 small adenocarcinoma (the only pT1 in the group) and 1 insulinoma (with manganese uptake similar to that of the surrounding parenchyma). Mangafodipir was also useful for excluding the presence of pancreatic lesions suspected at ultrasound or CT. The characterization of lesions by newer MRI techniques remains challenging and requires additional study. At present, MRI for pancreatic cancer staging is generally limited to instances in which patients cannot receive CT contrast, because it offers no other major advantages over CT and is a more expensive imaging modality.

Endoscopic Ultrasonography

When tumors are small or poorly visualized on CT scan, endoscopic ultrasonography (EUS) provides a minimally invasive, accurate method of defining the extent of the primary tumor/vessel relationships and evaluating surrounding lymph nodes. EUS is currently the method of choice for obtaining a pathologic diagnosis of malignancy. Numerous reports have documented the safety and accuracy of EUS-guided biopsy in the evaluation of pancreatic cancer.¹¹⁻¹⁴ Pretreatment confirmation of malignancy is critical for patients with locally advanced or metastatic disease who will be treated non-operatively. It is also mandatory for patients who are to receive neoadjuvant therapy to document the presence of malignancy and adenocarcinoma histology. For patients presenting with a low-density solid mass in the pancreas and who have resectable disease by CT criteria, a histological diagnosis of malignancy is unnecessary.

Endoscopic Retrograde Cholangiopancreatography

The role of endoscopic retrograde cholangiopancreatography (ERCP) in the evaluation of pancreatic cancer is confined to palliation of obstructive jaundice, particularly in patients who are not candidates for surgery. ERCP has no role in staging pancreatic cancer

except as a means to rule out alternative causes of biliary obstruction such as choledocholithiasis and benign stricture. A recent National Institutes of Health consensus conference concluded that ERCP and stent placement should not be routinely performed before pancreaticoduodenectomy in the presence of a clear low-density mass on CT scan.¹⁵

Diagnostic Laparoscopy

The limits of CT remain its poor sensitivity in detecting small-volume peritoneal surface metastases and hepatic metastases <1 cm. This lack of sensitivity led surgeons to investigate additional means to clinically stage patients, and this coincided with the exponential growth of laparoscopic surgery in the early 1990s. Laparoscopy is now considered a fundamental part of the armamentarium of the pancreatic cancer surgeon. In the early 1990s, intracorporeal ultrasound was used in conjunction with laparoscopy, and this new modality extended the range of minimally invasive pancreatic cancer staging. Staging laparoscopy with or without laparoscopic ultrasound can provide tissue diagnosis of both metastatic surfaces and intraparenchymal lesions. Several recent prospective studies have shown the utility of this diagnostic modality.

The singular controversy with respect to laparoscopy for pancreatic cancer is whether it should be used in all patients or applied selectively. Because most patients with newly diagnosed pancreatic cancer are unresectable because of the presence of metastatic disease, not surprisingly, performing laparoscopy early in the staging algorithm has a high yield. This was well shown in early studies of laparoscopy by Warshaw et al¹⁶ and Cuschieri et al¹⁷. In a large study by Rumstadt et al,¹⁸ 398 patients with pancreatic and periampullary cancers were staged with CT scan. Of these, 194 cases were considered potentially resectable, and 172 (89%) patients underwent pancreaticoduodenectomy. Only 9 patients (5%) were found to have occult metastatic disease and thus would have benefited from laparoscopy. Thus, with the use of high-quality CT scan, the likelihood of detecting metastatic disease at laparoscopy declines considerably. The use of laparoscopy as a staging tool should therefore be confined to patients who seem resectable by high-quality CT scan. Even within this group, however, the routine use of laparoscopy may not be cost-effective. What can be gleaned from the existing studies of laparoscopy in pancreatic cancer is that the pretest probability of metastatic disease will determine the incidence of positive findings and, therefore, its utility.^{19–23} At the University of Cincinnati, laparoscopy is used selectively in patients under-

going pancreatic cancer surgery. Our indications for laparoscopy include (1) primary tumor >3 cm, (2) preoperative CA 19-9 level >1000 U/mL, or (3) equivocal findings of locally advanced or metastatic disease on CT scan. We have found these factors to be associated with an increased risk of occult metastatic disease. In the absence of these findings, the incidence of laparoscopic findings altering management is <10%.

Positron Emission Tomography

The use of positron emission tomography (PET) for clinical staging is under active investigation in pancreatic cancer. An initial study by Rose et al²⁴ found that PET had a sensitivity of 92% and a specificity of 85% in diagnosing pancreatic cancer. PET was able to clarify diagnoses that were uncertain and to document metastatic disease where CT findings were equivocal. The principal question surrounding PET for pancreatic cancer remains how it should fit into overall disease management. It is unclear whether PET can detect otherwise occult metastatic disease with sufficient sensitivity and specificity to make it useful in the initial staging evaluation of pancreatic cancer patients. PET has been shown to identify pancreatic cancer and differentiate it from chronic pancreatitis with a sensitivity of 85%–98% and a specificity of 53%–93%, and this wide variation in study results is a source of concern.²⁵ The utility of PET to assess the response to neoadjuvant treatment remains an area of active investigation. At present, the utility of PET staging for pancreatic cancer remains undefined, particularly for patients who seem resectable by CT criteria. Further clinical studies, especially including patients with early tumor stages (small tumor size), are needed before its routine use can be justified.

Percutaneous Biopsy

As previously mentioned, in patients who present with a low-density solid mass in the pancreas and who have resectable disease, a histological diagnosis of malignancy is generally unnecessary. It is necessary to obtain tissue when patients are believed to be inoperable according to preoperative imaging or in the circumstance of planned neoadjuvant therapy. Again, EUS-guided biopsy is clearly the preferred method to obtain tissue in these instances. In the rare case in which EUS-guided biopsy is unsuccessful or if it is unavailable, CT-guided fine-needle aspiration can be performed safely in experienced hands. Much like in other solid malignancies, there has been considerable debate about the possibility of tumor seeding and implantation along the biopsy tract. There have been published reports in the literature

describing pancreatic cancer seeding after percutaneous biopsy. The incidence of seeding in these reports ranges from 1% to 16%.^{26,27} A recent report examined the incidence of peritoneal carcinomatosis in 46 patients who had undergone EUS-guided biopsy vs 43 who had CT-guided pancreatic biopsy. The incidence of carcinomatosis was 2.2% in the EUS biopsy group vs 16.3% in the CT-guided group ($P < .025$).²⁷ Therefore, when tissue is required, we recommend EUS-guided biopsy as the diagnostic method of choice in patients with suspected pancreatic cancer.

Surgery for Pancreatic Cancer

Walter Kausch initially described the technique of pancreaticoduodenectomy in 1912. Two decades later (1935), Allen O. Whipple performed a 2-stage pancreaticoduodenectomy that consisted of biliary diversion and gastrojejunostomy during the initial operation followed by resection of the pancreatic head and duodenum up to 3 weeks later. In 1941, Whipple modified the procedure to a 1-stage pancreaticoduodenectomy with a concomitant pancreaticojejunostomy.²⁸ Although major advances have been made in the surgical management of pancreas cancer since the era of Whipple, the principal goal remains the same: removal of all gross and microscopic disease within the pancreas and draining lymph nodes, a so-called margin-negative or R0 resection.

The anatomic location of the tumor within the pancreas dictates the type of resection. A lesion confined to the pancreatic head or uncinate process requires pancreaticoduodenectomy. Given that 60%–70% of pancreatic cancers arise in the head, pancreaticoduodenectomy is by far the most common operation performed for pancreatic cancer. Because of the late presentation of symptoms, most patients with adenocarcinoma of the pancreatic body and tail present with locally advanced disease and/or distant metastases, thus precluding surgical therapy. However, for patients with clinically localized disease, a distal pancreatectomy is the appropriate surgical resection. Central pancreatic tumors of the neck and body are rarely resectable, again because of either the presence of metastatic disease or extension to the SMA or hepatic artery. When resectable, tumors in this location are approached according to their exact anatomic location. If they are nearer to the head of the gland, an extended pancreaticoduodenectomy may be performed. This has the advantage of sparing the pancreatic parenchyma and lessening the risk of postoperative diabetes. For lesions nearer the tail, a distal subtotal pancreatectomy is performed. Central pancreatectomy, which is now often used to resect premalignant and low-grade

lesions of the neck and mid body, has not been adopted for the treatment of pancreatic adenocarcinoma by most surgeons because of concerns regarding adequate lymph node and retroperitoneal soft tissue clearance.

Technical Aspects of Pancreaticoduodenectomy

The operation may be divided into several well-defined steps, as described by Tyler and Evans²⁹ and others. First, the gastrocolic ligament is opened, the transverse and right colon are mobilized, and the duodenum is exposed. At this point, a segment of infrapancreatic SMV is exposed by dissection down the middle colic and gastroepiploic vessels. In step 2, an extended Kocher maneuver (medial mobilization of the duodenum) is performed to expose the left renal vein and aorta. Some surgeons expose the infrapancreatic SMV during this extended medial mobilization of the duodenum. In step 3, the gallbladder is removed, and the common bile duct and the gastroduodenal artery are divided, thus exposing the suprapancreatic PV. Next, the stomach is divided (the duodenum, in cases of pylorus preservation), followed by division and dissection of the proximal jejunum/distal duodenum. The next step involves division of the pancreatic neck over the SMV/PV confluence. The last and most critical step in the extirpation is dissection of the pancreatic head and uncinate process from their attachments to the SMV and artery. The SMA defines the limits of retroperitoneal dissection. Once the surgeon has reached this point in the operation, he or she has committed to it. Thus, if tumor extends to the SMA or if the surgeon does not extend the dissection to this level, a positive margin will result. As mentioned previously, it is imperative that high-quality thin-section CT scanning be used to accurately define the relation of the tumor to the SMV and SMA to avoid such circumstances. The reconstruction is then completed, beginning with a pancreaticojejunostomy or pancreaticogastrostomy and followed by a choledochojejunostomy and gastrojejunostomy or duodenojejunostomy. We prefer to place a feeding jejunostomy tube in the event that a patient should develop postoperative delayed gastric emptying (DGE) or simply is slow to resume adequate caloric intake. The use of a surgical gastrostomy tube is surgeon dependent. We do not routinely use surgical drains, because they have not been shown to reduce complications or the need for subsequent interventions.^{30,31}

Biliary Drainage

To alleviate jaundice, preoperative biliary stents are often used in patients with benign and malignant

biliary obstruction. In the past, preoperative biliary drainage was performed routinely because of concerns about the morbidity of pancreaticoduodenectomy in the jaundiced patient. These concerns have been shown by randomized trials to be unfounded, and stenting is now used primarily to palliate symptoms of jaundice (such as pruritus) or in the setting of neoadjuvant therapy when resection is to be intentionally delayed. The question of whether preoperative stenting actually contributes to postoperative morbidity has been the subject of controversy in the surgical literature. Povoski et al³² reported the Memorial Sloan-Kettering experience with preoperative biliary drainage in 240 consecutive patients undergoing pancreaticoduodenectomy. In this series, 175 patients underwent preoperative biliary instrumentation (endoscopic, percutaneous, or surgical instrumentation; Table 3). One hundred twenty-six patients (53%) underwent preoperative biliary drainage (endoscopic stents, percutaneous drains/stents, or surgical drainage). The overall postoperative morbidity rate after pancreaticoduodenectomy was 48% (114/240). Infectious complications occurred in 34% (81/240) of patients. Intra-abdominal abscess occurred in 14% (33/240) of patients. The postoperative mortality rate was 5% (12/240). Preoperative biliary drainage was determined to be the only statistically significant variable associated with complications ($P = .025$), infectious complications ($P = .014$), intra-abdominal abscess ($P = .022$), and postoperative death ($P = .037$). The authors concluded that preoperative biliary drainage, but not preoperative biliary instrumentation alone, was associated with increased morbidity and mortality and suggested that preoperative biliary drainage should be avoided whenever possible in

patients with potentially resectable pancreatic and peripancreatic tumors.

The Johns Hopkins group evaluated 567 patients who underwent pancreatic resection without prior operative biliary bypass.³³ Preoperative biliary stenting was performed in 408 patients (72%), whereas the remaining 159 patients (28%) did not undergo biliary stenting. In the stented group, 64% had stents placed via a percutaneous approach, and 36% had stents placed endoscopically. Those who had stents placed were more likely to have jaundice (67% vs 38%; $P < .001$) and fever (5% vs 1%; $P = .03$) as presenting symptoms. Patients who had stents placed had a perioperative mortality rate of 1.7%, compared with 2.5% in those who did not ($P = .3$). Although the overall complication rates were 35% in those who had stents placed and 30% in those who did not (not significant), patients with stents experienced a significantly increased incidence of pancreatic fistula (10% vs 4%; $P = .02$) and wound infection (10% vs 4%; $P = .02$). The incidence of other postoperative complications was similar between groups. Eight patients (3%) in the percutaneous stent group developed hemobilia after stent placement, whereas none of the patients undergoing endoscopic stent placement developed hemobilia ($P = .03$).

Pisters et al³⁴ reviewed the M. D. Anderson experience in 300 consecutive patients who underwent pancreaticoduodenectomy. In this study, 172 had preoperative biliary stenting, 35 had surgical biliary bypass, and 93 did not receive preoperative stenting. In this study, no increase in the risk of major postoperative complications or death was associated with preoperative stent placement. As shown in other studies, the incidence of wound

Table 3. Studies of Preoperative Biliary Stenting in Pancreatic Cancer

Study	n	% With infectious complications	% With wound infections	% Intra-abdominal abscess
Povoski et al ³²	240			
Stented	126	41	19	
Unstented	114	25	8	
Sohn et al ³³	567			
Stented	408	32	10	4
Unstented	159	22	4	6
Hochwald et al ³⁴	71			
Stented	42	66	29	12
Unstented	29	38	14	14
Heslin et al ³⁵	74			
Stented	39	46		
Unstented	35	11		
Pisters et al ³⁴	265			
Stented	172	37	13	6
Unstented	93	31	4	11
Hodul et al ³⁶	212			
Stented	154	28	8	7
Unstented	58	20	0	5

infection was significantly increased ($P = .022$) in the preoperative stent group (13% vs 4%).

Thus, it seems that stenting may increase the incidence of perioperative infection, likely secondary to bacterial contamination of bile (bactibilia) that results after instrumentation of the biliary tree. Preoperative biliary stenting is safe, but because of the previously mentioned risks, it should probably be limited to patients receiving neoadjuvant therapy and those who are severely symptomatic but who will have some delay before operation.

Standard Pancreaticoduodenectomy Versus Pylorus-Preserving Pancreaticoduodenectomy

In 1944, Watson reported a pancreaticoduodenectomy for ampullary carcinoma, in which the entire stomach and 1 inch of duodenum were preserved. Gastrointestinal continuity was preserved with a duodenojejunostomy.³⁵ He hypothesized that preservation of the stomach would lead to better digestion and improved nutrition and that a duodenojejunostomy would prevent marginal ulceration. The modern pylorus-preserving pancreaticoduodenectomy was popularized by Traverso and Longmire.^{36,37} Since its reintroduction, concerns have been raised regarding the use of pylorus-preserving pancreaticoduodenectomy for pancreatic head cancers because of the question of whether preservation of the pylorus would limit nodal clearance of the suprapyloric and infrapyloric perigastric nodes.

Retrospective series have raised the concern that after pylorus-preserving pancreaticoduodenectomy, the incidence of postoperative DGE is increased. One such randomized controlled trial compared standard pancreaticoduodenectomy ($n = 15$) with pylorus-preserving pancreaticoduodenectomy ($n = 16$) for patients with resectable periampullary carcinoma.³⁸ DGE seemed more frequent in the pylorus-preserving pancreaticoduodenectomy group (6 of 16 patients) than in the standard pancreaticoduodenectomy group (1 in 15; $P = .08$). Seiler et al³⁹ conducted a randomized trial for patients with resectable pancreatic cancer and periampullary tumors who had standard pancreaticoduodenectomy ($n = 40$) and pylorus-preserving pancreaticoduodenectomy ($n = 37$). The standard pancreaticoduodenectomy was associated with a longer operative time; operative blood loss, surgical morbidity (including DGE, bleeding, fistulas, and infections) and mortality, and length of hospitalization were not significantly different between the 2 trial groups. Sixty-one patients (pancreaticoduodenectomy, $n = 33$; pylorus-preserving pancreaticoduodenec-

tomy, $n = 28$) with histology-confirmed pancreatic or periampullary adenocarcinomas were analyzed for long-term follow-up. There were no statistical differences in disease recurrence or overall survival at a mean follow-up of 1.1 years. According to Kaplan–Meier analysis, median survival was 16 months for pancreaticoduodenectomy and 24 months for pylorus-preserving pancreaticoduodenectomy; however, these differences were not statistically significant ($P = .29$). Zerbi et al⁴⁰ found no significant differences between patients who underwent pancreaticoduodenectomy ($n = 35$) vs pylorus-preserving pancreaticoduodenectomy ($n = 37$) for pancreatic cancer, with a median survival of 15 months for pancreaticoduodenectomy and 17 months for pylorus-preserving pancreaticoduodenectomy.

Tran et al⁴¹ recently reported the results of a prospective randomized multicenter trial ($n = 170$ patients) to assess standard pancreaticoduodenectomy vs pylorus-preserving pancreaticoduodenectomy for pancreatic and periampullary tumors. In this study, the groups were well matched for age and sex distribution, tumor location, and stage. The authors found no differences in median blood loss, duration of operation, or postoperative DGE between the 2 techniques. There was a marginal difference in postoperative weight loss (less was seen with standard pancreaticoduodenectomy). Positive margins of resection were found for 12 patients in the pancreaticoduodenectomy group and 19 patients in the pylorus-preserving pancreaticoduodenectomy group ($P < .23$). The median disease-free survival was 14 months in the pancreaticoduodenectomy patients and 15 months in pylorus-preserving pancreaticoduodenectomy patients ($P = .80$). There were no significant statistical differences in overall survival between the 2 groups ($P < .90$). Therefore, the authors concluded that both operations are equally effective for the treatment of pancreatic and periampullary carcinoma.

On the basis of existing retrospective and prospective reports, standard pancreaticoduodenectomy and pylorus-preserving pancreaticoduodenectomy seem to have comparable perioperative morbidity and mortality, and there seem to be no major differences in postoperative DGE or nutritional status. To date, no study has shown a difference in recurrence or survival between pancreaticoduodenectomy and pylorus-preserving pancreaticoduodenectomy. Thus, surgeon preference and experience should dictate the type of pancreatic resection and reconstruction.

Extended Lymphadenectomy

As for nearly all epithelial malignancies, the presence of nodal metastases is a significant prognostic factor

in pancreatic cancer. In a standard pancreaticoduodenectomy, peripancreatic nodes and the subpyloric nodes are generally removed. The high risk of locoregional recurrence after pancreaticoduodenectomy prompted the hypothesis that a more extensive lymphadenectomy may favorably affect recurrence and overall survival. One prospective, randomized multicenter trial compared standard (n = 40) to extended (n = 41) lymphadenectomy during pancreaticoduodenectomy for adenocarcinoma of the pancreatic head.⁴² Overall survival was 12 months for the standard and 15 months for the extended lymphadenectomy groups (Table 4). However, there was no significant difference between the 2 groups in the incidence of positive microscopic resection margins or in the number of resected lymph nodes.

A trial from the Johns Hopkins Hospital randomized patients with resectable periampullary adenocarcinoma to a standard pancreaticoduodenectomy (n = 56) or pancreaticoduodenectomy with extended lymphadenectomy (n = 58).⁴³ In this study, more lymph nodes were resected in the extended resection group (27 vs 16 nodes; *P* < .001). The 1-year survival for patients with pancreatic adenocarcinoma was 71% and 80% for the standard and radical resection arms, respectively. These findings prompted a larger trial, which included 146 patients in the standard pancreaticoduodenectomy group and 148 patients in the extended pancreaticoduodenectomy group.⁴⁴ In this study, extended lymphadenectomy was associated with a longer hospital stay and an increased incidence of pancreatic fistula, DGE, and postoperative complications (*P* < .05). In this report, extended pancreaticoduodenectomy was not associated with a survival benefit (median survival, 28 vs 30 months; 3-year survival, 38% vs 36%). These results suggest that extended pancreaticoduodenectomy is associated with an equivalent mortality but with a higher morbidity rate. Of note, only 1 patient (.6%) had a perigastric lymph node that would not have been resected as part of standard pancreaticoduodenectomy. No patient had a retroperitoneal node as the only evidence of nodal disease spread. In fact,

only 15% of patients undergoing extended resection had positive retroperitoneal nodes.

The only patients who could potentially benefit from extended lymphadenectomy are those with N2 nodal disease (15%), negative surgical margins (91%), and an absence of occult M1 disease (5%–10%). Combining these factors shows that <2% of patients with resectable pancreatic cancer could benefit from more aggressive lymphadenectomy. Clearly, improvements in outcome must come from earlier diagnosis and improved systemic therapies rather than extending the field of lymph node harvest.

Vascular Resection

Traditionally, tumor extension to the SMV/PV, SMA, or branches of the celiac axis has been considered a contraindication to surgical resection. This idea was first challenged by Fortner et al⁴⁵ in the 1970s with the introduction of the regional pancreatectomy. This procedure included a total pancreaticoduodenectomy and resection of the SMV/PV, as well as resection of the SMA in selected cases. The rationale for regional pancreatectomy was the hypothesis that much of pancreatic cancer recurrence was caused by inadequate local therapy and that outcomes could be improved by improving local tumor clearance. Unfortunately, the procedure was associated with extremely high morbidity and no improvement in overall survival. Fortner's work did show that segments of the SMV/PV could be resected safely, thus pioneering more current investigations as to the utility of this technique in pancreatic cancer surgery. Fortner's studies also showed that much of the poor prognosis associated with pancreatic cancer is a reflection of aggressive biology rather than merely inadequate surgery. Despite this, it is now well accepted that positive surgical margins are associated with extremely poor outcomes.

Margin-positive resections are associated with patient survival that is no different from that achieved with chemoradiation therapy (CRT) for locally advanced disease. It remains unclear whether positive surgical margins are more reflective of an aggressive tumor as opposed to inadequate surgery. Several groups have now challenged the notion that tumor extension to the SMV/PV reflects aggressive biology and have hypothesized that involvement of the SMV/PV is a reflection of location and not of tumor biology.

Multiple retrospective studies have evaluated the patterns of recurrence and survival after pancreaticoduodenectomy with venous resection (Table 5). Almost a decade ago, Fuhrman et al⁴⁶ reported the initial M. D. Anderson experience with SMV/PV resection. In this

Table 4. Selected Results of Studies Comparing Standard Pancreaticoduodenectomy (PD) and Pancreaticoduodenectomy With Extended Lymphadenectomy (ExPD)

Study	Patients	Results
Pedrazzoli et al ⁴²	PD (n = 40) ExPD (n = 41)	Mean overall survival 12 mo vs 15 mo (<i>P</i> = .65)
Yeo et al ⁴³	PD (n = 56) ExPD (n = 58)	Median survival 30 mo vs 28 mo (<i>P</i> = .60)
Capussotti et al ⁸⁷	PD (n = 112) ExPD (n = 37)	Trend toward improved survival in first 2 y after ExPD

study, to be eligible for resection, patients were required to fulfill the following CT scan criteria: absence of extrapancreatic disease, no tumor encasement of the SMA or celiac axis, and a patent SMV/PV confluence. Tumor adherence to the SMV or SMV/PV confluence was assessed during surgery, and en bloc venous resection was performed to achieve complete tumor clearance. Fifty-nine patients underwent pancreaticoduodenectomy: 36 without venous resection and 23 with en bloc resection of the SMV/PV confluence. No differences in hospital stay, morbidity, mortality, tumor size, margin positivity, nodal positivity, or tumor DNA content were observed between groups. The authors concluded that segmental resection of the SMV/PV confluence could be performed safely during pancreaticoduodenectomy. Tumors involving the SMV/PV confluence were associated with a pathologic stage and grade similar to those of tumors not involving the SMV/PV. This suggests that there was no inherent biological difference between the 2 groups. Most importantly, if a histological R0 resection was achieved, Kaplan–Meier analysis showed equivalent survival curves in these 2 groups of patients.

Leach et al⁴⁷ updated the M. D. Anderson experience on 31 patients with venous resection and reported a median survival of 22 vs 20 months for patients undergoing pancreaticoduodenectomy without venous resection. Other investigators have reported poorer survival for patients undergoing SMV/PV resection. Roder et al⁴⁸ reported on 31 patients with periampullary malignancy who underwent pancreaticoduodenectomy with resection of the SMV/PV. Of the 29 patients with pancreatic or bile duct cancer, the median survival was only 8 months. The authors concluded that most patients with SMV/PV involvement have a poor prognosis and that few patients benefit from this aggressive approach. This study was

flawed, however, in that only 32% of patients underwent an R0 resection. Because most patients had positive surgical margins, it is not surprising that patient survival was poor.

A study from Memorial Sloan-Kettering identified 58 patients who underwent resection of the SMV/PV for pancreatic cancer.⁴⁹ In this study, the incidence of margin positivity was 27% for patients undergoing vein resection vs 24% for those who did not (not significant). The incidence of positive lymph nodes was also similar, and, most notably, there was no difference in median survival between the 2 groups. At present, the preponderance of data suggest that for patients with isolated involvement of the SMV/PV, pancreaticoduodenectomy and venous resection is associated with a survival no different from that of patients who undergo standard pancreaticoduodenectomy. It should be emphasized that the rationale in adding venous resection to pancreaticoduodenectomy is to achieve a histologically negative margin of resection. The presence of tumor extension to the SMA or celiac axis remains a contraindication to pancreaticoduodenectomy, because these vessels are enveloped in a neural plexus that, once infiltrated with tumor, precludes resection with negative margins.

Pancreatic Anastomotic Leak and the Use of Octreotide

A wealth of surgical literature has been devoted to various technical aspects of pancreaticoduodenectomy. Before the 1980s, mortality rates of >20% were common, and morbidity rates were even higher.⁵⁰ The most frequent source of major morbidity after pancreaticoduodenectomy is leakage at the site of pancreatic anastomosis: this most often results in peripancreatic fluid collection, abscess, or the development of pancreatic fistula. Countless methods have been described to reduce leak rates, including descriptions of various anastomotic techniques, the use of pancreatic duct internal and internal/external stents, and fibrin glue.^{51–54} What is clear from the literature is that numerous techniques may be associated with low rates of leak and that the occurrence of leak reliably relates to several predominant factors. The texture of the pancreas and size of the pancreatic duct seem to be major risk factors for leak. A small pancreatic duct and soft pancreatic texture are consistently associated with higher leak rates, presumably because smaller ducts make the anastomosis inherently more technically challenging and because a soft, more “normal” pancreas cannot hold sutures as well. It is also likely that a more normal pancreas has a higher output of pancreatic enzymes. There have been conflicting reports regarding the

Table 5. Selected Studies of Portal Vein/Superior Mesenteric Vein Resection (VR)

Study	No. patients	Results
Fuhrman et al ⁴⁶	VR (23) Standard PD (36)	No differences in morbidity or mortality
Leach et al ⁴⁷	VR (31) Standard PD (44)	Median survival 22 mo vs 20 mo ($P = .25$)
Bachelier et al ⁸⁸	VR (31) Standard PD (119)	Equivalent 2-y survival rates
Nakagohri et al ⁸⁹	VR (33) Standard PD (48)	Median survival 15 mo vs 10 mo ($P = .44$)
Howard et al ⁹⁰	VR (13) Standard PD (23)	Median survival 13 mo vs 12 mo ($P = NS$)
Nakano et al ⁹¹	VR (146) Standard PD (54)	Equivalent survival rates between groups
Tseng et al ⁹²	VR (110) Standard PD (181)	Median survival 23.4 mo vs 26.5 mo ($P = .17$)

PD, pancreaticoduodenectomy; NS, not significant.

perioperative use of the somatostatin analogue octreotide as a means of decreasing pancreatic exocrine secretion and leak after pancreaticoduodenectomy.

Nine prospective randomized trials have now examined the use of somatostatin analogues to prevent pancreatic leak after pancreatectomy. Several studies from Europe showed decreased pancreatic fistula rates associated with the use of octreotide. These studies varied somewhat in that some found a decreased incidence of fistula in all patients, whereas others found an effect only in patients with benign disease or only in those undergoing distal pancreatectomy.⁵⁵⁻⁵⁹ Two randomized trials from the United States examined the role of octreotide in decreasing the pancreatic fistula rate after pancreaticoduodenectomy. A study from Lowy et al⁶⁰ found no decrease in pancreatic leak rates among patients who received octreotide after pancreaticoduodenectomy for malignancy. Yeo and colleagues^{61,62} from Johns Hopkins, similarly, found no benefit to the use of octreotide given after pancreaticoduodenectomy. Another recent study from Sarr⁶³ examined the use of vapreotide, a long-acting somatostatin analogue, in the setting of pancreatectomy. The authors found no benefit to vapreotide in reducing pancreas-related leaks or other complications. The most recent study by Suc et al⁶⁴ examined the use of octreotide to prevent intra-abdominal complications after pancreatectomy. The authors found that overall octreotide did not reduce the risk of complications. Of the studies that have examined the use of somatostatin analogues for prevention of pancreatic-associated complications in the setting of surgery for pancreatic neoplasms, none has shown a benefit. Each of the European studies that did show some benefit with octreotide included patients undergoing surgery for chronic pancreatitis. Thus, on the basis of available data, the routine use of octreotide after pancreatectomy for pancreatic cancer cannot be recommended.

Operative Mortality and Regionalization

As discussed previously, even at major academic centers, operative mortality rates after pancreaticoduodenectomy routinely approached and often exceeded 20% until the 1980s. Since then, advances in operative techniques, anesthesia, and perioperative care have resulted in significant improvements in mortality, morbidity, and length of hospital stay. Mortality rates at most high-volume centers are <5%, and numerous centers have reported rates <2%. Centers with less experience continue to report mortality rates in the range of 7%–15%, and this has prompted studies of the effects of regional-

ization of the procedure to major centers. Birkmeyer et al⁶⁵ examined data from the Medicare claims database and found that the overall 3-year survival was higher for patients treated at high-volume centers (37%) than at medium-volume (29%) and low-volume (26%) centers. Even after adjusting for perioperative deaths and case mix, patients treated at high-volume centers were less likely to experience late mortality. Similar improvements in outcome were shown by analyses of state databases from Maryland and New York, as well as in studies from Europe.⁶⁶⁻⁷⁰ Rosemurgy et al⁷¹ showed that among surgeons in Florida, the more frequently surgeons performed pancreaticoduodenectomy, the lower the in-hospital mortality rate, length of stay, and hospital charges. Thus, it seems that patient care is optimized and costs are minimized when patients are referred to centers with active treatment programs for pancreatic cancer.

Palliative Surgery

A critical tenet of pancreatic cancer surgery is that, in general, operations should be performed with curative intent only. The use of laparotomy and gastric and biliary bypass as routine palliative measures is no longer justified in most pancreatic cancer patients. The ability to palliate disease with endoscopic stenting combined with the extremely limited survival of patients with advanced pancreatic cancer has made most palliative surgery obsolete and not in the patient's best interests. Laparotomy for palliation carries a mortality rate of 2%–5%, a morbidity rate of 20%–30%, and a median hospital stay of >10 days in most series.^{72,73} Combined with recovery time from surgery, patients spend a significant proportion of their remaining life getting over the effects of a palliative procedure. It can be argued that patients with a good performance status and limited locally advanced disease whose life expectancy may exceed 1 year are good candidates for palliative operation. Unfortunately, predicting life expectancy is difficult at best. At the University of Cincinnati, our practice is to perform endoscopic stenting in patients who are not candidates for curative surgery. If patients cannot be stented internally or if they develop stent-related complications that limit treatment, they are referred for operative bypass. A prospective randomized study by Lillemoe et al⁷⁴ showed that 20% of patients undergoing palliative biliary bypass will later require gastric decompression. On the basis of these data and the fact that gastrojejunostomy adds little in the way of morbidity, it is our policy to perform routine gastrojejunostomy along with a Roux-en-Y choledochojejunostomy as our preferred palliative operation for pancreatic cancer patients.

Adjuvant Therapy

The current practice of using adjuvant 5-fluorouracil (5-FU)-based CRT in the United States is based primarily on the results of a small prospective randomized trial from the Gastrointestinal Study Group (GITSG).⁷⁵ In this study, patients received adjuvant CRT (500 mg/m² per day of 5-FU for 6 days and 4000 cGy of external beam radiation) vs observation alone after pancreaticoduodenectomy. The GITSG trial showed a survival advantage for multimodality therapy over surgical resection alone (20 vs 11 months; Table 6). Retrospective studies from the Johns Hopkins Hospital and the Mayo Clinic confirmed the GITSG results.^{76,77} A prospective case control study from Johns Hopkins also showed a benefit to CRT.⁷⁸ In this report, patients with resected adenocarcinoma of pancreas were offered 3 options for postoperative treatment after pancreaticoduodenectomy: (1) standard therapy—external beam radiation therapy to the pancreatic bed (4000–4500 cGy) given with two 3-day 5-FU courses and followed by weekly bolus 5-FU (500 mg/m² per day) for 4 months; (2) intensive therapy—external beam radiation therapy to the pancreatic bed (5040–5760 cGy) with prophylactic hepatic irradiation (2340–2700 cGy) given with and followed by infusional 5-FU (200 mg/m² per day) plus leucovorin (5 mg/m² per day) for 5 of 7 days for 4 months; or (3) no therapy—no postoperative CRT. Pancreaticoduodenectomy was performed in 174 patients, 99 patients elected standard therapy, 21 elected intensive therapy, and 53 patients declined adjuvant therapy. Postoperative adjuvant CRT improved median survival (19.5

vs 13.5 months without therapy; $P = .003$). The intensive therapy group had no survival advantage compared with the standard therapy group (17.5 vs 21 months; not significant).

On the basis of the initial GITSG report, the European Organization for Research and Treatment of Cancer conducted a trial involving 207 patients randomized to receive either CRT (4000 cGy in a split course and 5-FU given as a continuous infusion at 25 mg/kg per day during external beam radiation) or no further treatment after pancreaticoduodenectomy for adenocarcinoma of the pancreas or periampullary region.⁷⁹ Unfortunately, only 55% of patients in this study had pancreatic adenocarcinoma, whereas the remaining 45% had a periampullary malignancy of bile duct or ampullary origin. The median survival was 24.5 months for the group that received adjuvant therapy and 19 months for the group that received surgery alone ($P = .2$); for pancreatic cancer patients, the median survival was 17.1 months for the adjuvant therapy group and 12.6 months for the surgery-alone group ($P = .099$). This trended toward significance in favor of adjuvant therapy, and some argued that the study was flawed because it was not sufficiently powered to detect such a difference among the sample size of pancreatic cancer patients enrolled.

The European Study Group of Pancreatic Cancer (ESPAC) recently completed a larger prospective randomized trial that evaluated the value of postoperative adjuvant therapy with 5-FU/folinic acid with and without radiation.⁸⁰ After resection, patients were randomly assigned to adjuvant CRT (2000 cGy in 10 daily fractions

Table 6. Recent Studies of Preoperative CRT in Pancreatic Cancer

Study	No./type of patients	No. Resected	EBRT (Gy)	Chemotherapy	CR	Margins of resection positive (%)	Median survival (mo)
Calvo ⁹⁴	15 PR	9	45–50	Tegafur	3	2	28 mo for R0 resection
Sasson ⁹⁵	116 PR	61	50.4	n = 35 5-FU, mito-C; n = 26 gemcitabine	—	—	Neoadjuvant 23 mo vs no preoperative CRT 16 mo ($P = .03$)
Wolff ⁸³	86 PR	18	30	Gemcitabine	—	—	37
Cooperman ⁹⁶	68 LA	20	54	Streptozocin, cisplatin, 5-FU	5	1	42
White ⁹⁷	111/53 PR 58 LA	28 PR 11 LA	45	5-FU, mito-C, cisplatin	2	11	—
Breslin ⁹⁸	132 PR	132	30–50.4	5-FU, paclitaxel, gemcitabine	—	16	21
Mehta ⁹⁹	15 PR	9	50.4–56	5-FU	2	0	30
Snady ¹⁰⁰	68 UR	20	54	Streptozocin, cisplatin, 5-FU	6	—	24
Hoffman ¹⁰¹	53 PR	24	50.4	5-FU, mito-C	0	7	16
Evans ¹⁰²	28 PR	17	50.4	5-FU	0	3	—

CR, complete response; PR, potentially resectable; LA, locally advanced; UR, unresectable; 5-FU, 5-fluorouracil; mito-C, mitomycin C; CRT, chemoradiotherapy; EBRT, external beam radiation.

over 2 weeks with 500 mg/m² 5-FU intravenously on days 1–3, repeated after 2 weeks) or chemotherapy (intravenous 5-FU 425 mg/m² and folinic acid 20 mg/m² daily for 5 days, monthly for 6 months). Clinicians could randomize patients into a 2 × 2 factorial design (observation, CRT alone, chemotherapy alone, or both) or into one of the main treatment comparisons (CRT vs no CRT or chemotherapy vs no chemotherapy). In this trial, 541 eligible patients with pancreatic cancer were randomized: 285 in the 2 × 2 factorial design (70 CRT, 74 chemotherapy, 72 both, and 69 observation); a further 68 patients were randomly assigned to CRT or no CRT and 188 to chemotherapy or no chemotherapy. In the initial report, the median follow-up of the 227 patients still alive (42% of the initial cohort) was 10 months (range, 0–62 months). There was no survival benefit for adjuvant CRT (15.5 months in 175 patients with CRT vs 16.1 months in 178 patients without; *P* = .24). There was evidence of a survival benefit for adjuvant chemotherapy (19.7 months in 238 patients with chemotherapy vs 14.0 months in 235 patients without; *P* = .0005).

Recently, ESPAC reported additional survival data at a median follow-up of 47 months for the surviving patients.⁸¹ The estimated 5-year survival rate was 10% among patients assigned to receive CRT and 20% among patients who did not receive CRT (*P* = .05). The 5-year survival rate was 21% among patients who received chemotherapy and 8% among patients who did not receive chemotherapy (*P* = .009). The authors concluded that adjuvant chemotherapy confers a significant survival benefit to patients with resected pancreatic cancer, whereas adjuvant CRT has a deleterious effect on survival.

Numerous criticisms of the ESPAC-1 trial have been raised, many regarding the complicated randomization scheme. Especially troubling is the fact that 62% of patients experienced local recurrence as a component of first failure. Of these, 35% experienced local recurrence as the only site of initial failure. These high rates of local relapse, along with a lack of quality assurance for radiation therapy planning, imaging, or pathology, raise serious questions about the quality of the radiation therapy that patients received and about the standardization of pathologic margin assessment. Because of these issues, the results of ESPAC-1 have not affected the standard of care in the United States. ESPAC is currently conducting a follow-up study comparing the efficacy of adjuvant 5-FU/folinic acid with that of adjuvant gemcitabine.

A Radiation Therapy Oncology Group–led Intergroup adjuvant study was recently completed. This trial, which exceeded its accrual goal and randomized 568 patients, is the largest trial for patients with resected pancreatic

cancer that has ever been performed. The trial compared the efficacy of systemic 5-FU vs gemcitabine when administered before and after 5-FU–based CRT for resected pancreatic cancer. Patients were stratified by nodal involvement, tumor diameter, and status of surgical margins. Pre-CRT chemotherapy consisted of 3 weeks of continuous 5-FU infusion, 250 mg/m² per day for patients on the first arm of the study, or 3 weeks of gemcitabine, 1000 mg/m² per day as a half-hour bolus once weekly for those on the second arm. The CRT therapy was identical for both arms and began within 1–2 weeks of completion of the previous protocol. Radiation was given as 5040 cGy with continuous infusion 5-FU 250 mg/m². Post-CRT chemotherapy began within 3–5 weeks, and all patients were required to have repeat imaging to eliminate those whose disease had progressed. Arm 1 patients received 3 months of continuous-infusion 5-FU, 4 weeks on, 2 weeks off, for a total of 2 cycles. Arm 2 patients received 3 months of gemcitabine, 3 weeks on, 1 week off, for a total of 3 cycles. Results of this study are due within the year. Table 7 depicts summaries of randomized adjuvant therapy trials in pancreatic cancer.

A recently published trial from the Virginia Mason Medical Center showed encouraging survival data with a novel CRT regimen.⁸² In their study, 43 patients underwent pancreaticoduodenectomy for pancreatic cancer. These patients then received external beam radiation at a dose of 4500–5400 cGy (25 fractions over 5 weeks) and 3-drug chemotherapy: continuous-infusion 5-FU (200 mg/m² daily on days 1 to 35), weekly intravenous bolus cisplatin (30 mg/m² daily on days 1, 8, 15, 22, and 29), and subcutaneous α -interferon (3×10^6 units on days 1 to 35). This CRT was followed by continuous-infusion 5-FU (200 mg/m² daily on weeks 9 to 14 and 17 to 22). CRT was generally initiated between 6 and 8 weeks after surgery. With a mean follow-up time of 31.9 months, 67% of the patients are alive; thus, at the time of publication, median survival had not been reached. Actuarial overall survival for the 1-, 2-, and 5-year periods was 95% (95% confidence interval, 91%–98%), 64% (confidence interval, 56%–72%), and 55% (confidence interval, 46%–65%), respectively. These results were obtained despite a high incidence of lymph node involvement and advanced tumor stage. A major drawback to this CRT regimen was the associated toxicity. Forty-two percent of patients were hospitalized during CRT, virtually all because of gastrointestinal toxicity. From this limited patient series, the actuarial 2- and 5-year overall survival rates suggest a potential for improved long-term survival.

Because the results from the Virginia Mason Medical Center showed a remarkable improvement over accepted

Table 7. Results of Selected Adjuvant Therapy Trials

Study group	n	Survival					
		Median (mo)		2-y (%)		5-y (%)	
		Surgery	S + C ± RT	Surgery	S + C ± RT	Surgery	S + C ± RT
GITSG ⁷⁵	43	11	20 ^a	18	43 ^a	8	18 ^a
NPCT ⁹³	61	11	23 ^a	32	43 ^a	8	4
EORTC ⁷⁹	207						
Pancreatic	114	12.6	17.1	23	37	10	20
Periampullary	93	40.1	39.5	64	70	36	38
ESPAC ⁸⁰	541	15.5	16.1	34	18		
ESPAC ⁸¹	289	17.9	15.9 ^a	41	29	20	10
RTOG (results pending)	568						

GITSG, Gastrointestinal Study Group; NPCT, Norwegian Pancreatic Cancer Trial; EORTC, European Organization for Research and Treatment of Cancer; ESPAC, European Study Group for Pancreatic Cancer Trial-1; RTOG, Radiation Therapy Oncology Group; S + C ± RT, surgery followed by chemotherapy with or without external beam radiation.

^a*P* < .05 vs surgery-alone group.

CRT regimens, the American College of Surgeons carefully audited the study data and reconfirmed its accuracy. The American College of Surgeons Oncology Group has since supported a large multicenter phase II study (Z05031A2) to further evaluate α -interferon-based adjuvant therapy for resected pancreatic cancer (http://www.acosog.org/studies/synopses/Z05031_Synopsis.pancreaticoduodenectomyf).

Neoadjuvant Therapy

The underlying principles of neoadjuvant treatment make it particularly attractive in pancreatic cancer given the morbidity of surgery and the generally poor prognosis for patients with resectable disease. The rationale for neoadjuvant therapy in pancreatic cancer is as follows. (1) The goal of neoadjuvant therapy is downstaging of the tumor and, in combination with an R0 resection, increasing the chances of survival. With effective therapy, a certain percentage of potentially unresectable tumors may be down-staged to enable surgical resection. (2) Radiation therapy is more effective on well-oxygenated cells that have not been devascularized by surgery. (3) Preoperative treatment may prevent implantation and dissemination of tumor cells at laparotomy. (4) Patients with metastatic disease on restaging after neoadjuvant therapy will not be subjected to unnecessary laparotomy. (5) Delayed postoperative recovery will not affect the delivery of neoadjuvant therapy, as it does in approximately 25% of the patients who receive adjuvant CRT therapy. For these reasons, preoperative or neoadjuvant CRT is a logical strategy to evaluate, and numerous phase II trials have been performed showing that this is a feasible paradigm.

Patients eligible for neoadjuvant therapy are those with radiographically resectable, biopsy-proven pancreatic adenocarcinoma. Patients with borderline resectable lesions (ie, those involving more than one third of the circumference of

the SMV with vein compression or encroaching on the SMA or celiac axis branches) have been included sporadically in phase II trials but should best be studied separately.

Several single-institution trials using different CRT regimens are summarized in Table 6. The most encouraging results were recently reported by Wolff et al⁸³ from the M. D. Anderson Cancer Center. In this study, 86 patients were treated with 7 doses of neoadjuvant gemcitabine at 400 mg/m² (days 1, 8, 15, 22, 29, 36, and 43) and 30 Gy of external beam radiation given in 10 fractions on days 4–8 and 11–15. Although 43% of patients required hospitalization, the resectability rate was high, at 74%, and the median survival for resected patients was 37 months. Overall, neoadjuvant chemotherapy trials have reported low rates of local failure, thus emphasizing that when CRT can be successfully delivered, local therapy is effective. Future trials must include more effective systemic treatment as patients continue to relapse within the liver and peritoneal surfaces. Multi-institutional trials through several cooperative groups are currently being developed to better evaluate the viability of neoadjuvant treatment outside the setting of single specialty centers.

Summary

Pancreatic cancer remains a lethal disease with an overall poor outcome after “curative” surgery. Despite this, surgical resection offers the only possibility of long-term cure. The morbidity and mortality associated with pancreatic surgery have declined significantly in the last 2 decades. Advances in diagnostic imaging and laparoscopy have contributed to limiting the number of pancreatic cancer patients who are subjected to nontherapeutic laparotomy. Even resection of the SMV/PV can be performed safely, and a margin-negative resection of the SMV/PV confluence offers a pattern of recurrence and survival equivalent to that

with a standard R0 pancreaticoduodenectomy resection. Although it is controversial, adjuvant CRT after pancreatic resection remains the standard of care in the United States. Neoadjuvant strategies remain of great interest but await testing in multi-institutional trials. Advances in surgical technique and aftercare have made the design and completion of large randomized trials of adjuvant therapy possible in recent years. This is a critical development because it is clear that significant improvements in survival for pancreatic cancer patients await the development and testing of more effective multimodality therapies.

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