Pierre-Auguste Renoir. *Reading*, 1890.

When applied appropriately, surgical treatment of pancreatic cancer can improve survival and relieve disease-related symptoms.

Surgical Management of Early-Stage Pancreatic Cancer

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Background: *Pancreatic cancer remains a difficult disease to treat. Diagnosis at an early stage may allow curative treatment with resection. In the past, the mortality associated with surgical treatment of pancreatic carcinoma was prohibitive but mortality associated with resection is now commensurate with all other major oncologic resections. Thus, the focus of surgical management has shifted to address several issues: the diagnosis and evaluation of patients with suspected pancreatic cancer, the role of preoperative endobiliary stenting, the role of laparoscopy, the extent of resection, the role of adjuvant and neoadjuvant treatment, and the role of specialized centers in treating the disease.*

Methods: *The current literature is reviewed to address these issues and help guide physicians who first encounter patients with suspected pancreatic cancer as well as surgeons who ultimately resect them. Practical evidence-based information to guide the decision-making process is provided.*

Results: *Surgical morbidity and mortality have achieved parity with other types of major oncologic resection, and a distinct survival advantage is possible when such therapy is applied early in the disease stage. Issues regarding the use of stents, extent of resection, and pre- vs post-operative chemoradiation therapy are becoming clearer as our collective experience broadens.*

Conclusions: *Surgical treatment of pancreatic cancer should be aggressively pursued given the clearly established survival advantage and relief of symptoms achieved when it is applied appropriately.*

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Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the United States. In 2003, an estimated 30,700 patients were diagnosed with pancreatic cancer, the majority of whom presented with locally advanced or metastatic disease that precludes potentially curative surgical therapy.[1] Approximately 4,000 patients will have resectable disease at presentation, and these patients comprise a select

Table 1. — Results From Large Series of Patients Undergoing Pancreaticoduodenectomy for Pancreatic Carcinoma

Author	No. of Patients	Morbidity Rate (%)	Mortality Rate (%)	5-Year Survival Rate (%)	Median Survival (mos)
Fong et al[7] (1995) *	138	45	6	21	NA
Nitecki et al[8] (1995)	201	NA	3	6.8	17.5
Sperti et al[9] (1996)	113	NA	15	12	NA
Neoptolemos et al[10] (1997)	1,026	6	6	NA	NA
Richter et al[11] (1998)	194	29.9	3.09	25.4	NA
Millikan et al[12] (1999)	75	NA	1.3	17	13
Sohn et al[13] (2000)	564	31	2.3	17	17
Conlon et al[14] (2001)	409	54	3	NA	17.2
Balcom et al[15] (2001)	489	51	1	NA	NA
Billingsley et al[16] (2003)**	462	45.9	9.3	NA	NA

NA = not available
* All resections undertaken in patients 70 years or older.
** Veterans Affairs National Surgical Quality Improvement Program.

group that can achieve a 20% to 40% 5-year survival depending on their age, size of tumor, grade, stage, and differentiation.[2-5] In most recent large series of patients undergoing resection for pancreatic cancer, perioperative mortality is now less than 5% and median survival between 12 and 20 months. Five-year survival remains dismal, however, when all patients (including those with positive resection margins) are considered in the survival analysis. Despite these discouraging statistics, they remain in direct contrast to median survival of 4 to 8 months for patients who present with locally advanced disease and 3 to 5 months for patients who present with metastatic disease.[6] Morbidity remains between 20% to 50%, but current focus of surgical management is not whether to undertake the resection but how to minimize morbidity and maximize potential survival benefit. A review of recent large series of patients undergoing pancreaticoduodenectomy for carcinoma is presented in Table 1.[7-16]

Current issues regarding the surgical management of pancreatic cancer can be separated into three categories: preoperative, intraoperative, and postoperative. Preoperative issues include how to best diagnose, evaluate, and palliate candidates for potential resection and where, and by whom, these resections should be undertaken. The use of neoadjuvant therapy is also becoming an important preoperative issue as promising data regarding its thoughtful application are now becoming available. Intraoperative issues include the appropriate use of laparoscopy and the extent of resection that should be undertaken to provide a reasonable hope of survival benefit or palliation when tempered with potential morbidity. Postoperative issues include the role of adjuvant therapy and how to best follow the patient undergoing resection for pancreatic cancer. These issues in the surgical management of pancreatic cancer are delineated in Table 2 and serve as an outline for the remainder of this manuscript.

Table 2. — Current Issues in the Surgical Management of Pancreatic Carcinoma

Preoperative	Intraoperative	Postoperative
Best means to determine resectability	Role of laparoscopy	Role of adjuvant therapy
Role of endobiliary stents	Extent of resection	Appropriate follow-up
Role of neoadjuvant therapy	Role of palliative bypass	

Preoperative Management of the Patient With Suspected Pancreatic Cancer

Most patients with pancreatic cancer present to their primary care physicians with pain or jaundice. This presentation usually leads to either abdominal ultrasound or computed tomography (CT) scan to determine the source of the symptoms. In patients with suspected pancreatic cancer, these "screening" studies may diagnose the source of pain or jaundice but will not answer the most important question: Is this cancer treatable with surgical therapy? At this point, patients with low-density lesions in the pancreas can be separated into one of three categories: resectable, unable to assess resectability based on current imaging, and clearly unresectable. Unresectability can be a result of locally advanced disease or obvious metastatic disease. Patients in the third category should be referred to medical oncology for definitive diagnosis and management. Those in the first two categories are best served by referral to an experienced general surgeon or surgical oncologist who can then determine the appropriate application of resectional or palliative surgical care.

Table 3. — In-Hospital Mortality, Length of Stay, and Charges Following Pancreaticoduodenectomy (PD) in Florida Over 33 Months Stratified by Number of Procedures Per Surgeon

No. of PDs Per Surgeon Over 33 Months	Average Length of Hospital Stay (days)	Mean Hospital Charges ($)	In-Hospital Mortality (%)
1	27.0	91,975	6.6
2	19.4	71,744	5.4
3	19.7	81,844	3.4
4 to 6	19.7	69,768	10.2
7 to 9	19.6	73,198	8.7
10 to 16	17.6	67,193	0.0
>16	16.8	48,419	2.6

Data from Rosemurgy et al.[18]

What Comprises an "Experienced" Surgeon or Surgical Oncologist?

A large body of data suggests that institutional or individual surgeon experience with managing cancer of the pancreas significantly affects outcomes following surgical therapy. In the recent study published by Birkmeyer et al,[17] the impact of institutional experience with several routine and complex surgical procedures on outcome was evaluated. Institutions were categorized according to the number of a given procedure performed per year: fewer than 1, 1 or 2, 3 to 5, 6 to 16, or more than 16. Mortality for each procedure was based on institutional volume. Of all the procedures evaluated, the mortality associated with surgical therapy for pancreatic cancer demonstrated the greatest dependence on institutional experience. Institutions with nominal experience in this illness (1 to 5 resections per year) recorded the highest mortality rates (11% to 16%), while those with the greatest experience showed the lowest (3.8%). Rosemurgy et al[18] evaluated the impact of surgeon experience (rather than institution experience) on length of hospitalization, cost of care, and in-hospital mortality in the state of Florida and further documented the positive impact of an individual surgeon's experience on each of these endpoints (Table 3). These studies recognize the importance of both institutional and individual experience in outcomes following pancreaticoduodenectomy.

While the basis of these findings seems intuitive, their implications are more difficult to interpret. Although many general surgeons are capable of successfully undertaking this operation, the relative infrequency of patients who are candidates for resection concentrates most patients in centers with defined expertise in this disease. This phenomenon perpetuates further refinement within these centers of excellence and fosters mediocrity, if not worse, outside of them.

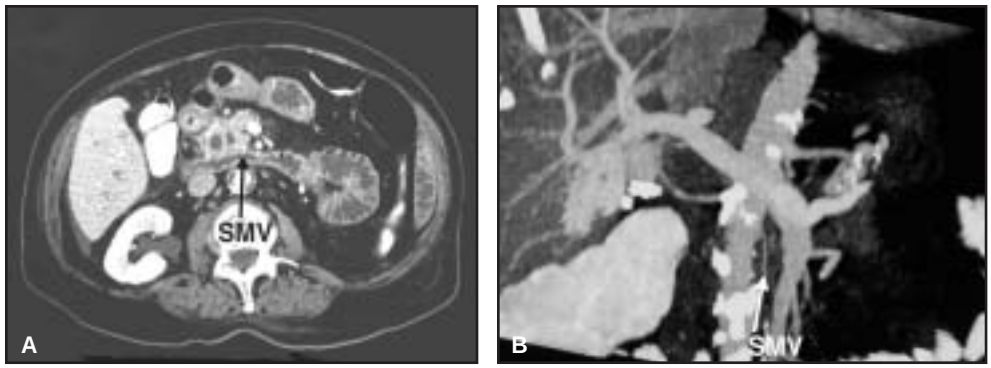
A final argument supporting the referral of patients with pancreatic cancer to high volume centers has to do with determination of resectability. Patients with pancreatic cancer are most adversely affected not when they suffer sometimes unavoidable perioperative morbidity or mortality, but when potentially curative resection is denied to them due to perceived locally advanced disease that may or may not exist. This determination is most accurately made by individuals who encounter such patients on a weekly or daily basis.

Determining Resectability in Pancreatic Cancer

In the majority of cases, a high-quality, double (arterial with delayed venous phase) contrast, helical CT scan of the abdomen and pelvis with 1.5 to 3-mm sections through the pancreas at 5-mm intervals is sufficient to determine resectability in pancreatic cancer. This scanning protocol has been shown to be greater than 80% sensitive in detecting resectable disease and nearly 100% specific.[19,20] Three points must be addressed in the radiologic interpretation of the scan to achieve this level of accuracy: (1) the absence of extra pancreatic or metastatic disease, (2) patency of the portal vein/superior mesenteric vein confluence, and (3) absence of extension of the pancreatic lesion into the superior mesenteric artery. In patients in whom vascular invasion in questionable on CT scan, vascular involvement can be further defined using CT angiogram, magnetic resonance angiography, or endoscopic ultrasound with minimal morbidity. In some cases, venous invasion can never be fully excluded prior to exploration. In these patients, radiologically occult venous involvement is discovered only after the pancreas is divided and the specimen is being lifted to the patient's right side, away from the vein. This finding is almost always manageable with minor venous resection, and given today's imaging options, the surgeon is rarely faced with an unplanned major vascular resection or suboptimal resection. Figs 1A and 1B show an axial CT and corresponding CT angiogram in a patient with resectable disease. Figs 2A and 2B demonstrate similar windows in a patient with clearly unresectable disease.

Is a Tissue Diagnosis Necessary Prior to Surgery for Pancreatic Cancer?

Prior to the advent of endoscopic ultrasound-guided biopsy of pancreatic lesions, percutaneous fine-needle



Figs 1A-B. — Images of (A) representative axial and (B) 3-D angiographic reconstruction in a patient with a resectable pancreatic tumor abutting, but not invading, the superior mesenteric vein the superior mesenteric vein (SMV).

aspiration was considered anathema in patients with potentially resectable pancreatic cancer due to a perceived risk of needle tract seeding. Now, with more institutions implementing neoadjuvant protocols for pancreatic cancer and with the medical empowerment of patients by the Internet, preoperative tissue diagnosis by endoscopic biopsy is becoming a more common occurrence. Endoscopic ultrasound-guided biopsy of pancreatic lesions in 2003 is more than 90% sensitive and 100% specific in diagnosing pancreatic cancer and is equally efficacious in determining local invasion.[21] Its only shortcoming is that it is not yet available in all institutions that offer conventional endoscopic services. In the absence of a neoadjuvant protocol, however, tissue confirmation of a clinically suspicious pancreatic lesion is unnecessary. It may be helpful in patients with an atypical presentation (absence of jaundice) or in patients who are amenable to chemotherapy due to prohibitive operative risk or locally advanced/metastatic disease documented by preoperative imaging.

Neoadjuvant Therapy in Pancreatic Cancer

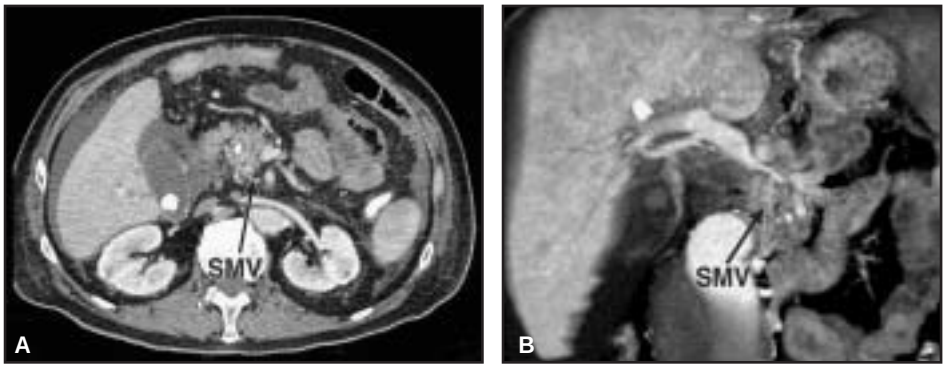
The use of radiation and chemotherapy prior to resection is becoming more common as investigators are beginning to apply these proven concepts in rectal and possibly esophageal cancer to the pancreas. Current protocols and results are discussed in the final section of this manuscript.

Laparoscopy in Determining Stage and Extent of Disease

Some centers have now employed the routine use of laparoscopy in patients with potentially resectable pancreatic cancer. The rationale for this approach is based on the high incidence (15% to 25%) of radiologically occult metastatic disease.[22-24] These centers schedule such evaluations as a separate procedure to avoid disrupting the surgeon's or operating room's schedule in the instance where a patient scheduled for resection is unexpectedly determined to be unresectable. Institutions that rely heavily on high-quality, enhanced helical scanning argue that use of laparoscopy in the presence of a CT scan suggesting resectable disease does not justify its routine application in the few patients whose care will be changed by it. Resection rates approach 75% at institutions that choose to utilize high-quality CT scanning. This is commensurate with resection rates reported by advocates of laparoscopy, thus making the issue one of preference and/or convenience rather than the proven superiority of one method over the other. Finally, some argue that selective use of laparoscopy should be applied in patients whose clinical characteristics predict a higher than average likelihood of radiologically occult metastatic disease. These characteristics include tumors greater than 5 cm, preoperative CA19-9 levels in excess of 700 mg/dL, ascites or tumors in the body or tail of the pancreas.[25,26] The presence of all or any of these factors predicts a high likelihood of metastatic disease despite its absence on preoperative imaging studies.

Preoperative Endobiliary Stenting

Endobiliary stents have been responsible for some of the greatest advances in the management of unresectable pancreatic cancer over the past 15 years, but their use in surgically resectable disease is controversial. Upon presentation to the center of definitive therapy, most patients, regardless of tumor stage, arrive with some type of biliary decompression already in place. This phenomenon has led most centers with a large experience in the surgical management of pancreatic cancer to question the utility



Figs 2A-B. — Images of (A) axial and (B) 3-D reconstruction angiogram in a patient with clear invasion of the superior mesenteric vein (SMV).

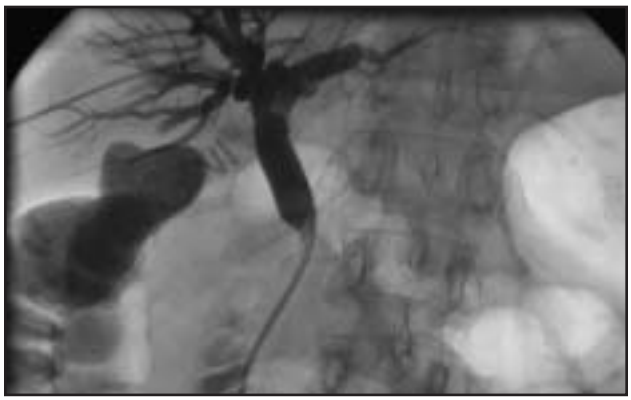


Fig 3. — Typical appearance of biliary ductal obstruction in a patient with pancreatic cancer.

of preoperative stenting in resectable disease. Fig 3 depicts the typical appearance of endoscopic retrograde cholangiopancreatography in a patient with pancreatic cancer and obstructive jaundice that leads many initial caregivers to expedite endobiliary decompression before surgical evaluation.

The most persuasive study against preoperative stenting involved 126 patients undergoing resection at Memorial Sloan-Kettering Cancer Center.[27] All patients underwent preoperative biliary drainage by means of endoscopic stents, percutaneous stents, or surgical drainage. Preoperative biliary drainage was noted to be the only statistically significant variable associated with complications in general, infectious complications, intra-abdominal abscess, and postoperative death. Subsequent recent studies at several other high-volume institutions have failed to confirm these findings, only demonstrating significant increases in wound complications, operative time, or transfusion requirement in patients undergoing preoperative stents.[28-32] Unfortunately, all of these studies are retrospective reviews and none are prospective. As such, it is difficult to draw any meaningful conclusions regarding the appropriateness of preoperative stenting in patients with resectable disease. However, the preponderance of data suggests that in asymptomatic patients with clearly resectable disease in whom delay in surgical therapy is not anticipated (ie, neoadjuvant therapy protocols), preoperative decompression may offer little benefit while potentially increasing complications. Each author advocates the selective application of stents in patients who are expected to undergo pancreaticoduodenectomy. Table 4 summarizes the largest recent comparative trials of stenting in patients undergoing pancreaticoduodenectomy.

Intraoperative Management of Pancreatic Cancer

Extent of Radical Resection

There are two issues regarding the extent of resection in pancreatic cancer: the role of major vascular resection and the extent of lymphadenectomy. In the setting of the need for potential venous resection, the issue has less to do with whether venous resection should be pursued, but rather what are the survival implications of leaving a positive microscopic (R1 resection) or macroscopic margin (R2 resection). The implications of any positive margin in pancreatic cancer are well established. Leaving patients with positive margins, either microscopic or macroscopic, results in survival that is tantamount to palliative chemoradiotherapy without surgery. These data are extrapolated from several large series evaluating survival in patients with R1 or R2 resection compared to those with negative (R0) margins and are summarized in Table 5.[3,8,9,12,13,33-39] In patients who undergo venous resection in whom an R0 resection can be achieved, there is no difference in either survival or complications compared with those undergoing standard pancreaticoduodenectomy. Therefore, major vascular resection should be pursued when the opportunity to obtain negative microscopic margins is possible. Several studies document that mesenteric portal venous resection can be done safely and with favorable survival benefit.[40-42] These studies include patients in whom venous

Table 4. — Recent Comparative Trials Evaluating the Implications of Preoperative Biliary Stenting in Patients Undergoing Pancreaticoduodenectomy

Author	No. of Patients		Major Morbidity		Mortality		Significant Findings in Stent Group
	Stent	No Stent	Stent	No Stent	Stent	No Stent	
Povoski et al[27] (1999)	126	116	55%	39%	7.9%	1.8%	Increase in infectious complications, abscess, and death
Sohn et al[28] (1999)	408	159	35%	30%	1.7%	2.5%	Increase in hemobilia, pancreatic fistula, and wound infection
Martignoni et al[29] (1999)	99	158	49%	71%	3%	1.9%	Biliary drainage does not affect early or late outcome in patients undergoing pancreaticoduodenectomy
Pisters et al[30] (2003)	172	93	22%	31%	1%	1%	Increased wound infection
Hodul et al[31] (2003)	154	58	32%	28%	1.9%	1%	Increased operative time, blood transfusions and wound infections

infiltration is detected on preoperative imaging studies and those in whom infiltration is discovered intraoperatively. In general, these authors will pursue resection if preoperative imaging documents less than 180° circumferential *venous* involvement. It is important to distinguish venous infiltration from arterial infiltration; the latter (or even extension of the tumor mass to the left of the mesenteric vessels) virtually guarantees an inability to achieve R0 margins and, as a result, potentially curative resection.

The question as to whether extensive lymphadenectomy is of benefit is driven by data from Italy suggesting that this results in improved survival. This study randomized 81 patients to standard pancreaticoduodenectomy vs radical lymphadenectomy.[43] In a post hoc subgroup analysis of all patients with positive nodal disease, a significant survival advantage was noted in patients undergoing radical lymphadenectomy. This question has been addressed in the American experience in a prospective randomized trial by the group at Johns Hopkins Medical Institutions.[44-46] In this study, 294 patients were prospectively randomized to standard or extended pancreaticoduodenectomy. The extended resection included a retroperitoneal lymphadenectomy extending from the celiac axis superiorly, the origin of the inferior mesenteric artery inferiorly, the right kidney laterally, and the aorta medially. A group of 146 patients were randomized to the standard resection, and the other 148 patients were randomized to the extended resection group. The groups were similar in terms of demographics, stage of disease, and comorbidities. The study found a significantly higher number of complications in the extended resection group but, more importantly, no statistical improvement in overall survival. This study confirmed the bias of the American surgical community against extended lymphadenectomy in oncologic resections in general (especially in upper gastrointestinal cancers) and specifically in pancreatic cancer.

Table 5. — Median Survival Following R1 and R2 Resection for Pancreatic Cancer

Author (year)	No. of Patients	Type of Resection	Median Survival (mos)
Neoptolemos et al[3] (2001)*	448	R0	16.9
Breslin et al[33] (2001)	16	R1	25
Sohn et al[13] (2000)	184	R1/R2	12
Millikan et al[12] (1999)	22	R1	8
Hosotani et al[38] (1997)	70	R1/R2	6
Lillemoe et al[34] (1996)	64	R1/R2	12
Sperti et al[9] (1996)	19	R1/R2	7
Nitecki et al[8] (1995)	28	R2	9
Yeo et al[39] (1995)	58	R1/R2	10
Willett et al[35] (1993)	37	R1/R2	12
Trede et al[36] (1990)	54	R1/R2	10
Tepper et al[37] (1976)	17	R1/R2	8

* From ESPAC-1 randomized controlled trial.

A more salient controversy among American surgeons is whether pylorus preservation is of any oncologic or physiologic consequence. Arguments in favor of pylorus preservation include a decreased incidence of postgastrectomy syndromes (bile reflux gastritis/ dumping), a shorter operative time, and a more physiologic reconstruction due to preservation of the hormonal function of the antrum and pylorus. Arguments in favor of the standard Kaush-Whipple procedure, which involves resection of the antrum, include a lower incidence of delayed gastric emptying and, as a result, a shorter hospitalization. Less importantly, some argue that there may be some benefit to resection of more lymphatic-bearing tissue in the standard operation.

Several studies have compared each technique for benign and malignant disease, none of which are sufficiently powered to definitively answer the question as to which is better. A recent trial by Seiler et al[47,48] randomized 77 patients to standard Whipple[43] vs pylorus-preserving duodenectomy.[40] The standard Whipple procedure was associated with longer operative time and greater blood loss, but surgical morbidity, the length of hospitalization, and incidence of delayed gastric emptying were the same in the two groups. At 18 months after surgery, there was no difference in tumor recurrence or overall survival. In the absence of level I data to support either procedure, most surgeons rely on personal preferences or patient-specific circumstances (eg, inflammation or tumor extension into the distal stomach) to determine which type of reconstruction to pursue.

Palliative Bypass

Endobiliary stenting represents one of the greatest advances in the management of pancreatic cancer since Whipple described the operation that bears his name in 1929. Unfortunately, this medical breakthrough is most advantageous to patients who have no chance of being cured than to those who are unresectable. Now, operative biliary bypass in patients with pancreatic cancer is infrequent as both plastic and titanium stents effectively decompress biliary obstruction for the relatively short period of time in which they are necessary. The question then shifts to the role of enteric bypass or duodenal stents to relieve gastric outlet obstruction. The experience with duodenal stents is limited, but in general, is rarely applied in this setting. Gastrojejunostomy relieves gastric outlet obstruction but becomes necessary only in approximately 10% to 20% of patients with unresectable disease. A study from Johns Hopkins explored the utility of enteric bypass in asymptomatic patients with unresectable pancreatic cancer who at the time of exploration were thought not to be at risk for imminent gastric outlet obstruction.[49] The 87 patients were randomized to retrocolic gastrojejunostomy or no bypass at all. There was no significant difference in survival between the two groups. No gastric out-

let obstruction developed in the group receiving bypass, whereas 19% of those randomized to observation developed gastric outlet syndrome and subsequently underwent stenting or gastric bypass. There were no significant differences in length of stay or complications following prophylactic gastrojejunostomy vs observation, leading the authors to conclude that this is a reasonable approach to patients with unresectable pancreatic cancer. Despite these data, most institutions continue to wait until symptoms develop and then offer surgical palliation in patients in whom performance status justifies yet another surgical intervention. An important point to consider is that as new chemotherapeutic regimens that may prolong survival in unresectable patients become available, the number of patients developing symptomatic gastric outlet obstruction may also increase, thereby lowering the threshold for prophylactic gastrojejunostomy.

Postoperative Management of Pancreatic Cancer

Adjuvant Chemotherapy

The low cure rate associated with complete surgical resection of pancreatic tumors has prompted the oncology community to investigate a myriad of adjuvant treatment regimens in patients with pancreatic cancer. A high incidence of liver metastases following pancreaticoduodenectomy has forced the issue of adjuvant chemotherapy, while the high incidence of local recurrence has forced the issue of adjuvant radiation treatment. Ultimately, those adjuvant strategies addressing both issues have gained the most attention among medical oncologists but with little objective data to support their universal application. The Gastrointestinal Tumor Study Group (GITSG) devised a protocol in the early 1980s to prospectively study the efficacy of adjuvant chemoradiotherapy in resected pancreatic cancer.[4] Twenty-two patients were randomized to receive no treatment and 21 patients received bolus 5-fluorouracil (5-FU) at 500 mg/m^2 for the first 3 days of two 2-week courses of radiotherapy (40 Gy) followed by weekly bolus 5-FU for 2 years. In this small trial, a survival advantage of 9 months (20 vs 11 months) was observed for the group receiving therapy. This study provided the *evidence* on which adjuvant treatment decisions are made in almost all patients undergoing pancreaticoduodenectomy in the United States today. Criticisms include the low number of patients enrolled and the relatively low dose of radiation therapy that was given. Finally, since this study was completed, gemcitabine has replaced 5-FU as standard therapy in pancreatic cancer and thus the results are dated at best. Although a potent radiosensitizer, gemcitabine is thought too toxic when given with radiotherapy for wholesale substitution with 5-FU.

More recently, the universal application of radiation therapy as an adjuvant has come into question. This issue was addressed in a large prospective randomized trial known as the European Study of Pancreatic Cancer (ESPAC)-1 trial. A total of 541 patients were randomized in a 2 × 2 factorial design to receive either chemoradiotherapy alone or observation, or chemotherapy alone (intravenous bolus folinic acid [20 mg/m^2] followed by intravenous 5-FU [425 mg/m^2]) or observation. In 175 patients who received chemoradiotherapy vs 178 patients who received no treatment, median survival was not statistically different at 15.5 and 16.1 months, respectively. In 238 patients receiving chemotherapy alone vs 235 who were observed, median survival was statistically improved by more than 6 months (19.7 vs 14 months). The results of this study are in direct contrast with those of the GITSG trial in that the addition of radiation seemed to add no survival advantage, while the adjunctive use of chemotherapy seemed to extend survival by more than 6 months.[2]

Finally, interferon-based adjuvant chemoradiation has recently shown some promise in pancreatic cancer. In a recent study published by Picozzi et al,[50] 43 patients undergoing pancreaticoduodenectomy at Virginia Mason Medical Center in Seattle received an investigational protocol consisting of external-beam radiation (45–54 Gy in 25 fractions) and three-drug chemotherapy: continuous infusion 5-FU (200 mg/m^2 daily, days 1 to 35), weekly intravenous bolus cisplatin (30 mg/m^2 daily, days 1, 8, 15, 22, and 29), and subcutaneous alpha interferon (3 × 10^6 units days 1–35) followed by continuous infusion 5-FU (200 mg/m^2 daily, weeks 9–14 and 17–22). All patients completed radiation therapy, but 42% were hospitalized due to gastrointestinal toxicity. At a mean follow-up of 32 months, two thirds of patients were still alive and, consequently, median survivorship had not been reached. Actual overall survival rates at 1, 2, and 5 years were 95%, 64%, and 55%, respectively. These findings lie in stark contrast to traditional survivorship data with standard adjuvant protocols (despite the above average toxicity profile requiring hospitalization) and have withstood an independent audit by experts in the field. As such, a multi-institution trial sponsored by the American College of Surgeons Oncology Group is now being undertaken to further validate these exciting results.

Neoadjuvant Therapy

The successful application of neoadjuvant protocols in rectal and, to a lesser degree, esophageal cancer has led some investigators to study its applicability in cancer of the pancreas. This, in association with low rates of resectability in the general population of patients with pancreatic cancer and the risk that postoperative chemotherapy or radiation will be delayed or abandoned, offers sound rationale for investigating this therapeutic strategy. As such, the theoretical advantages of neoadjuvant chemoradiotherapy are that virtually all patients who go on to surgical therapy are assured of completing a full and therapeutic regimen of chemotherapy and radiation. Second, it selects patients

with tumors amenable to surgical management by removing those patients with metastatic or locally advanced disease who, at first presentation, may appear resectable. Least importantly, it may offer an opportunity to downstage a patient with locally advanced cancer at presentation, although reports of this phenomenon are anecdotal.[51,52]

Data from the Johns Hopkins Hospital reveal that only 3 in 4 patients undergoing pancreaticoduodenectomy ultimately receive adjuvant therapy; given the low mortality associated with pancreatic resection at that institution, one can assume that *at least* one quarter of patients undergoing the Whipple operation at any center will not receive adjuvant therapy. Successful completion of adjuvant therapy at that institution is associated with a statistically significant improvement in survival (19 vs 11 months). Investigators at M. D. Anderson Cancer Center, the strongest proponents of neoadjuvant therapy, cite these statistics as compelling reasons to pursue neoadjuvant therapy. Their data suggest an overall survival benefit to neoadjuvant therapy, but the question regarding patient selection remains. In a recently published series involving 132 patients receiving either standard fractionation external beam radiation therapy (45 to 50.4 Gy, 1.8 Gy/day, 44 patients) or rapid fractionation (30 Gy, 3.0 Gy/day over 2 weeks, 88 patients), median survival from the time of diagnosis was 21 months and the 5-year survival rate was 23%.[33] Eight patients (10%) of 79 who had recurrences developed local recurrence. The authors of this study further add that this group of patients included 36 who had undergone failed prior resection and 57 who required vascular resection, admittedly an unselected series. These data compare favorably to historical cohorts receiving 5-FU-based chemoradiation or no adjuvant therapy (median survival was 11 to 20 months).

The disadvantages of neoadjuvant therapy include the need for a tissue diagnosis before treatment can begin, which, as stated earlier, can sometimes be challenging, the need for durable biliary decompression, and the potentially preventable progression of disease that may occur while a patient is waiting to receive or receiving neoadjuvant therapy. Finally, most neoadjuvant protocols are rigorous and highly toxic requiring hospital admission in as many as 50% of patients during the course of therapy. They may unwittingly select those patients best suited to successfully undergo pancreaticoduodenectomy and thus provide unrealistic survival expectations compared with standard treatment. Again, no level I data exist to support neoadjuvant over standard adjuvant chemoradiation in pancreatic cancer. Prospective randomized trials investigating this concept are thought to be too difficult to complete due to the high number of patients who fail to complete or receive a full course of either therapy.

Postoperative Care and Follow-Up

With the addition of either preoperative or postoperative chemoradiation, local recurrence following pancreaticoduodenectomy has diminished to less than 10%. As such, surgical intervention for recurrent disease that manifests as hepatic metastases is rarely indicated. Gemcitabine is administered on a weekly basis for at least 6 months so most patients undergo weekly laboratory studies and physical examinations prior to the administration of chemotherapy. CA19-9 levels are followed every 3 months or after a course of chemotherapy is completed. In general, CT scans are ordered when a patient develops new symptoms suggestive of tumor recurrence or an unexplained increase in CA19-9 levels. Because few patients undergo reoperation after initial surgical treatment, surveillance CT scans are rarely utilized, if ever. In the setting of rising tumor markers but no radiologic evidence of recurrent disease, positron emission tomographic (PET) scanning may also be useful to document recurrence and to help determine whether cytotoxic chemotherapy should be changed or discontinued. However, it is difficult to achieve insurance approval for PET scanning in this setting. This should change as second- and third-line therapies become available in the foreseeable future. Surgical therapy for patients with documented disease recurrence is usually reserved for those with symptomatic gastrointestinal obstruction that carry minimal tumor burden, cachexia, and operative risk.

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