



Three Katsina dolls: *Tawa Katsina* (left) and *Qaa'otorikiwtaqa* (middle) by White Bear Fredericks. *Tawa Katsina* (right) by Jimmy Kewanwytewa. Courtesy of the Heard Museum, Phoenix, Arizona.

*The diagnosis and staging of pancreatic cancer continue to improve, although most treatment approaches are still directed to palliative care.*

## Treatment of Resectable and Locally Advanced Pancreatic Cancer

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**Background:** Pancreatic cancer is the fifth leading cause of cancer death in the United States, with an overall 5-year survival rate of less than 5%. A minority of patients are candidates for surgical resection, but most treatment strategies focus on palliative care.

**Methods:** We discuss strategies in the diagnosis and treatment of resectable and locally advanced pancreatic cancer by reviewing available phase II and phase III trials, as well as large retrospective studies.

**Results:** Surgical resection for pancreatic cancer is done today with an operative mortality rate below 5% and a 5-year survival rate of approximately 25%. There is evidence that chemoradiation may improve survival and quality of life in both the adjuvant setting and for locally advanced disease. Operative, minimally invasive, and endoscopic techniques are successful in palliating pain and jaundice.

**Conclusions:** The diagnosis and treatment of pancreatic cancer continue to improve although most patients will succumb to their disease. Novel methods of earlier detection and more effective systemic therapies are needed to significantly improve outcomes.

### Introduction

The majority of patients with pancreatic adenocarcinoma present at an advanced stage at the time of diagnosis. The prognosis for these patients is poor, with a 1-year survival rate of 20% and a 5-year survival rate of less than 5%. While complete surgical resection may lead to long-term survival in approximately 25% of patients, only 15% are actually resectable. Consequently, most treatment approaches focus on palliative care. This review highlights current strategies in the evaluation and treatment of patients with potentially resectable and locally advanced pancreatic cancer.

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## Clinical Presentation

The most common presenting symptom of patients with pancreatic adenocarcinoma of the pancreatic head is jaundice, which occurs in approximately 70%-80% of these patients. They appear to have higher resectability rates than do patients not presenting with jaundice. Abdominal pain, another common symptom, radiates to the back in approximately 25% of patients. Kelsen et al<sup>1</sup> found that the presence of pain before surgery adversely predicted survival. Median survival for patients with pain was 5.7 months compared with 15 months for those without pain. Other common symptoms include weight loss, recent onset of diabetes, and anorexia. Symptoms typically occur at an average of 4 months prior to the diagnosis of pancreatic cancer.

## Diagnostic Strategies

Patients suspected of harboring a pancreatic malignancy should undergo dual-phase spiral (helical) computed tomography (CT) with 5-mm sections through both the liver and the pancreas. Dual-phase spiral CT (Fig 1) suggests the diagnosis of pancreatic cancer in more than 95% of cases, usually by the presence of a hypovascular mass or pancreatic ductal dilatation. Tumors in the head of the pancreas will typically show evidence of biliary obstruction, including both intrahepatic and extrahepatic ductal dilatation (Fig 2). Patients may present for surgical evaluation with only a conventional CT scan, which is often inadequate for assessing resectability.

The small proportion of patients who present with jaundice and no mass require a more aggressive diagnostic evaluation. For this population, endoscopic

retrograde cholangiopancreatography (ERCP) is necessary to exclude choledocholithiasis and to identify periampullary tumors. In the case of pancreatic cancer, ERCP typically demonstrates obstruction of the common bile duct as well as a long, irregular stricture in the pancreatic duct. Obstruction of both the bile duct and pancreatic duct results in dilatation of both, commonly referred to as the "double duct" sign. Cytologic assessment of pancreatic duct brushings may provide a definitive diagnosis, with sensitivity rates of 33%-62% and specificity rates approaching 100%. Unfortunately, brushings may be normal in more than one third of patients with documented pancreatic cancer.<sup>2</sup> ERCP is also useful in placing an endobiliary stent for patients who have locally advanced or metastatic disease. It is important to note that for patients with a resectable pancreatic mass on CT scan, ERCP increases cost and morbidity but does not alter management. In addition, preoperative biliary drainage appears to increase infectious morbidity and mortality following pancreatic resection.<sup>3</sup>

Diagnosing and staging pancreatic cancer have improved with the advent of several new technologies. Endoscopic ultrasound has an accuracy of 75%-92% in identifying pancreatic neoplasms and can guide the use of fine-needle aspiration biopsy. Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive alternative to ERCP. In a recent study by Magnuson et al<sup>4</sup> involving 25 patients with peripancreatic cancer, MRCP identified the level of biliary obstruction in 96% and correctly predicted malignancy in 84%. The tumor marker CA 19-9 is also helpful in the diagnosis and follow-up of patients with pancreatic cancer. CA 19-9 levels above the upper normal limit of 37 U/mL have an 80% accuracy in identifying patients with pancreatic cancer. The accuracy improves up to 95% when the cutoff value is increased to 200 U/mL.<sup>5</sup>

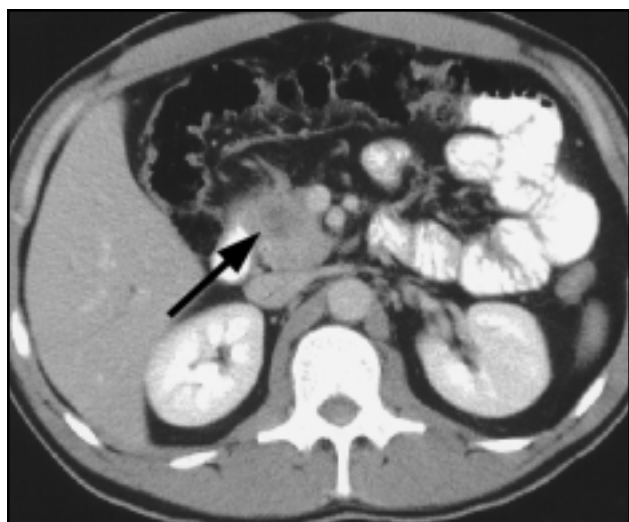


Fig 1. — Biphasic spiral CT scan showing a resectable lesion (arrow) in the head of the pancreas.



Fig 2. — Locally advanced pancreatic cancer with encasement of the mesenteric vessels (arrow).

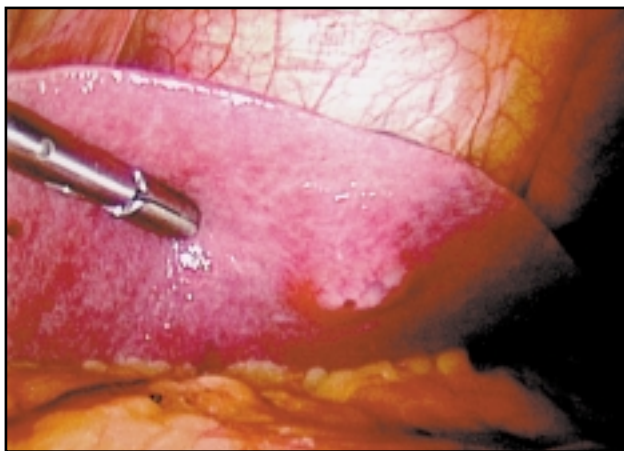


Fig 3. — Identification of a small liver metastasis by laparoscopy not clearly evident on CT scan.

Patients who are Lewis blood group negative — approximately 10% of the US population — do not express the CA 19-9 antigen.

## Pathologic Assessment

Obtaining a histologic diagnosis of pancreatic cancer is important for patients interested in neoadjuvant chemoradiotherapy and for those with locally unresectable or metastatic disease. Patients with a pancreatic mass and evidence of metastatic disease are best served by obtaining a biopsy on the metastatic lesion; this both confirms the histologic diagnosis and accurately defines the stage of disease. Percutaneous biopsy for patients with resectable lesions or those who require palliative surgery is not necessary since it will not alter the treatment plan.

Percutaneous CT or ultrasound-guided fine-needle aspiration (FNA) biopsies are commonly used, although endoscopic ultrasound-guided FNA is becoming more widely available. FNA has an accuracy rate of 60%-100%, but the technique demands the expertise of a cytopathologist and is often limited by the scant material obtained. The key problem with FNA is that a negative result does not preclude the diagnosis of cancer. In one study, more than 50% of patients with atypical or negative cytology were confirmed to have a pancreatic malignancy.<sup>2</sup> As a result, image-guided pancreatic core biopsy has gained popularity. Elvin et al<sup>6</sup> described 47 patients who underwent core biopsy of the pancreas with the correct diagnosis made in 94%.

## Assessing Resectability

Since the only chance of cure for adenocarcinoma of the pancreas is surgical resection, accurately assess-

ing resectability is of paramount importance. Presence of metastatic disease, involvement of the mesenteric or hepatic artery, and obstruction of the portal or superior mesenteric vein are all indicators of unresectable disease. Thin-cut, spiral CT scan predicts resectability in about 70%-80% of patients with carcinoma of the head of the pancreas. Modern CT scanning is useful in determining major vascular involvement but is limited in the ability to identify subcentimeter hepatic lesions and peritoneal implants. The ability of the dual-phase CT scan to identify vascular involvement has eliminated the need for conventional angiography. CT angiography has been advocated by some, although most studies suggest this adds little to a quality spiral CT scan.

The routine use of laparoscopy and laparoscopic ultrasound for staging localized pancreatic cancer is controversial. Few would argue the use of laparoscopy with cancers of the body and tail, where nearly 50% of peritoneal metastases occur. Patients with lesions of the pancreatic head, however, have unsuspected metastases less often (Fig 3). In a recent study, Rivera et al<sup>7</sup> identified intra-abdominal metastases in 24% of patients with pancreatic cancer and negative imaging studies. Laparoscopy appears to improve resectability rates, but the magnitude and relevance of this improvement remain controversial. Laparoscopic ultrasound can provide a more sensitive evaluation of the liver and can help identify major vascular involvement (Fig 4). Minnard et al<sup>8</sup> found that laparoscopic ultrasound was helpful in equivocal cases where laparoscopy could not clearly define resectability. In general, for patients with small, resectable tumors or for those needing palliative surgical bypass, laparoscopy is probably not necessary. In patients being evaluated for neoadjuvant therapy, those with large tumors or tumors that are suspicious of metastatic disease, laparoscopy may help to avoid unnecessary laparotomy.

At the time of laparoscopy, peritoneal washings can be obtained for cytologic assessment.

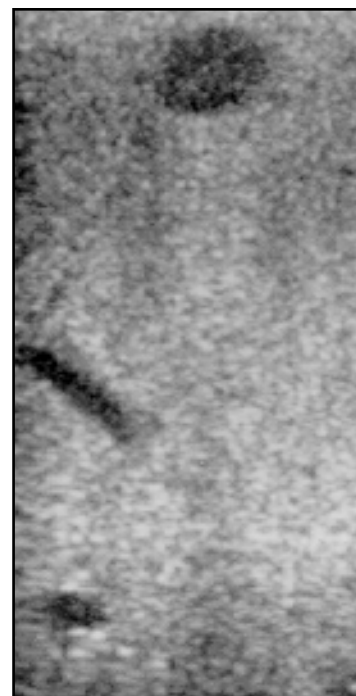


Fig 4. — Identification of a small intrahepatic metastasis by laparoscopic ultrasound.

Makary et al<sup>9</sup> reported that 20%-30% of peritoneal washings were positive for malignant cells at the time of laparoscopy for known pancreatic cancer. Patients with positive washings had a median survival of 8.6 months compared with 13.5 months for patients with negative cytology. Visible recurrence was demonstrated at a median of 2.9 months after obtaining positive peritoneal washings. Merchant et al<sup>10</sup> showed that positive peritoneal cytology predicted unresectability in 94% of patients, with a survival advantage in patients with negative peritoneal cytology. Peritoneal cytology is not routinely performed at all centers but should be considered in patients who are marginally resectable or who are a poor operative risk.

## Pancreatic Resection

For tumors of the pancreatic head, neck, or uncinate process, pancreaticoduodenectomy (Whipple procedure) remains the only potentially curative modality. Patients with localized disease by preoperative evaluation should be offered the opportunity for surgical resection. There is little role for "exploratory laparotomy" for presumed pancreatic cancer; the intent should be curative resection. Careful preoperative or minimally invasive evaluation may spare patients with advanced disease from undergoing unnecessary laparotomy.

At operation, patients are assessed for resectability by thorough evaluation of the liver, peritoneal surfaces, and celiac lymph nodes. If the pancreatic mass appears resectable, then a biopsy is unnecessary since this will not alter operative decision making. Pancreaticoduodenectomy is performed in a standard stepwise fashion beginning with an extended Kocher maneuver, which allows palpable assessment of the pancreatic head and the relationship of the mass to the mesenteric vessels. The dissection moves to the porta hepatis where the gallbladder is mobilized down to its junction with the common hepatic duct. The common hepatic duct is then transected, allowing better visualization of the portal vein. If the "tunnel" under the pancreatic neck overlying the portal vein is free and there is no involvement of the superior mesenteric artery, the tumor is considered resectable. At this point, formal resection begins and the stomach is transected (or duodenum transected for pylorus-preserving resection). The proximal jejunum is also transected approximately 10 cm distal to the ligament of Treitz, and the mesentery is divided. The pancreas is transected at the neck to allow dissection of the uncinate process off the portal and superior mesenteric veins and the superior mesenteric artery. Tumors involving the portal or superior mesenteric vein are resected en bloc followed by primary anastomosis or vein graft. Two recent reports<sup>11,12</sup>

demonstrated that patients who required portal vein resection had similar morbidity and long-term survival compared with patients who did not require portal vein resection.

Reconstruction is performed in a counterclockwise direction and typically includes pancreaticojejunostomy, hepaticojejunostomy, and gastrojejunostomy. Numerous pancreaticojejunostomy techniques have been described in an attempt to minimize the likelihood of a pancreatic leak, a serious complication following pancreaticoduodenectomy. One common method is a two-layer, end-to-side pancreaticojejunostomy over a small silastic stent. An end-to-end invaginating anastomosis is useful for a small, nonfibrotic gland with a nondilated pancreatic duct. With careful attention to detail, clinically relevant leak rates can be kept to less than 10%. Perioperative use of octreotide may reduce this even further. A single-layer, end-to-side hepaticojejunostomy is then constructed at approximately 8-10 cm proximal to the pancreatic anastomosis. Finally, the gastrojejunostomy (or a duodenojejunostomy in a pylorus-preserving resection) is performed. Drains are typically placed in the region of the pancreatic and biliary anastomoses. However, a recent study by Heslin et al<sup>13</sup> showed no difference in the risk of fistula, abscess, or reoperation between patients who had no intra-abdominal drains and those who had drains placed following pancreaticoduodenectomy.

Modifications of the classic Whipple procedure have emerged over the years. The pylorus-preserving Whipple procedure avoids partial gastrectomy and is believed by its proponents to provide better long-term function with fewer marginal ulcers. Critics express concerns regarding adequacy of the cancer operation, problems with postoperative delayed gastric emptying, and longer hospital stays. Since no prospective, randomized data are available that compare the two techniques, either is considered appropriate. On the other end of the spectrum is extended pancreaticoduodenectomy, which involves extensive retroperitoneal lymph node and soft-tissue resection. In the United States, extended resection is generally not advocated out of concern for increased morbidity and the lack of randomized data showing a survival benefit.

Adenocarcinomas of the body and tail of the pancreas are surgically managed with distal pancreatectomy. Patients with lesions in the body and tail present with more advanced disease and have lower respectability rates than do patients with lesions in the pancreatic head. Brennan et al<sup>14</sup> described 34 patients with pancreatic adenocarcinoma of the body and tail and showed only a 10% resectability rate. When completely resected, however, adenocarcinoma of the body

Table 1. — Comparison of Pancreatic Resection Alone vs Resection Followed by External-Beam Radiotherapy and 5-Fluorouracil

Trial	Trial Design	Surgery		Surgery and Postoperative Chemotherapy	
		Number of Patients	Median Survival	Number of Patients	Median Survival
GITSG (1985) <sup>21,22</sup>	Prospective, randomized	22	10.9 mos	21	21.0 mos
University of Pennsylvania (1991) <sup>24</sup>	Retrospective	33	21.0 mos	20	29.0 mos
Johns Hopkins University (1997) <sup>25</sup>	Prospective, nonrandomized	53	13.5 mos	120	19.5 mos
EORTC (1999) <sup>23</sup>	Prospective, randomized	54	12.6 mos	60	17.1 mos

GITSG = Gastrointestinal Tumor Study Group  
 EORTC = European Organization for Research and Treatment of Cancer

and tail of the pancreas has a similar survival to lesions in the pancreatic head. Splenectomy is often required in conjunction with distal pancreatectomy, although routine removal has been questioned. In one retrospective study,<sup>15</sup> patients who underwent splenectomy had a median survival of 12.2 months compared with 18.8 months in patients without splenectomy.

## Outcome After Pancreatic Resection

Considerable improvements in operative results and long-term survival following pancreaticoduodenectomy for pancreatic cancer have evolved over the last three decades. Operative mortality was 25% in the 1970s with rare 5-year survivors. Large, single-institution reviews in the 1990s reported operative mortality rates of 3% or less and 5-year survival rates of approximately 25%.<sup>16,17</sup> Three studies<sup>18-20</sup> reported on the importance of hospital volume on outcomes following pancreatic resection, and all three concluded that pancreatic resections done at high-volume centers were associated with lower operative morbidity and mortality.

A number of prognostic factors following surgical resection for pancreatic cancer have been identified. Patients with aneuploid tumors and those with increased tumor suppressor gene mutations (p53, p16, and DPC4) have shorter survival. Routine pathologic analysis has also been correlated with outcome. In two large pancreaticoduodenectomy series,<sup>16,17</sup> the presence of positive lymph nodes, tumor size greater than 2.5-3 cm, and poor histologic tumor differentiation were predictors of worse survival by multivariate analysis. Positive resection margins in one of these studies<sup>16</sup> was also a strong predictor of poor outcome. Patients with node-negative tumors have a 5-year survival rate of approximately 35%, while survival rates in those with tumors less than 2.5 cm in diameter ranges from 25%-40%. Long-term survivors among patients with larger tumors or positive nodes are rare. Other perioperative

factors such as operative blood loss, operative time, and extended resection are inconsistently associated with survival.

## Adjuvant Therapy Following Resection

The high rate of locoregional failure following surgical resection for adenocarcinoma of the pancreas has prompted investigators to evaluate the role of adjuvant chemoradiation (Table 1). The Gastrointestinal Tumor Study Group (GITSG)<sup>21,22</sup> conducted a phase III randomized trial to evaluate combined radiation therapy (RT) and 5-fluorouracil (5-FU) following surgical resection for adenocarcinoma of the pancreas. The study accrued slowly, taking 7 years to randomize 43 patients either to surgery alone or to surgery followed by split course radiation (40 Gy) and bolus 5-FU. Median survival was significantly improved in the patients receiving the postoperative adjuvant therapy (21 months) compared with those receiving surgery alone (10.9 months).

The European Organization for Research and Treatment of Cancer (EORTC)<sup>23</sup> attempted to confirm the benefit of postoperative adjuvant RT and 5-FU in a phase III randomized trial of 114 patients with pancreatic cancer. While median survival was 17.1 months in patients randomized to the RT/5-FU arm compared with 12.6 months in patients without adjuvant therapy, this was not statistically significant ( $P=0.099$ ). Criticism of this EORTC study has focused on the small sample size, the finding that 20% of patients in the treatment group never received postoperative therapy, and the omission of 5-FU following radiotherapy.

Two retrospective studies<sup>24,25</sup> also suggest a benefit to adjuvant chemoradiotherapy. Investigators at the University of Pennsylvania<sup>24</sup> reviewed 72 patients with adenocarcinoma of the pancreas treated between 1981 and 1989. A total of 33 patients received surgery alone, 19 underwent postoperative radiation, and 20 had post-

operative radiation plus 5-FU. The survival rate at 3 years in the three arms was 22%, 11%, and 47%, respectively. The incidence of locoregional failure was reduced in the groups receiving postoperative adjuvant therapy. In a larger study, Yeo and colleagues<sup>25</sup> performed pancreaticoduodenectomy on 174 patients for adenocarcinoma of the pancreas and compared patients who had adjuvant RT and 5-FU to those who had surgery alone. The groups were comparable in terms of tumor size, lymph node involvement, resection margin status, race, gender, blood loss, and tumor differentiation. Postoperative chemoradiation was associated with improved median survival (19.5 months) compared with surgery alone (13.5 months).

A large European trial is currently underway that will help clarify whether adjuvant chemoradiation is beneficial. The European Study Group for Pancreatic Cancer trial (ESPAC-1) is a phase III study randomizing patients with resected adenocarcinoma of the pancreas to surgery alone, to surgery plus RT and 5-FU, to surgery plus 5-FU and leucovorin, or to surgery and RT plus 5-FU with adjuvant 5-FU and leucovorin. The Radiation Therapy Oncology Group (RTOG) is attempting to establish the role of additional chemotherapy after combined RT and 5-FU for resected adenocarcinoma of the pancreas. All patients receive protracted infusional 5-FU and postoperative radiation (50.4 Gy) in 28 fractions and are then randomized to multiple cycles of either infusional 5-FU or gemcitabine.

## Preoperative Chemoradiation

Preoperative chemoradiation has been advocated in an effort to improve resectability, to reduce local recurrences, and possibly to improve survival. Hoffman et al<sup>26</sup> treated 34 patients with resectable adenocarcinoma of the pancreas using preoperative radiation (50.4 Gy), infusional 5-FU, and mitomycin C. A significant pathologic response was seen in most patients, and only 1 case demonstrated involved surgical margins. Median survival in the 11 patients undergoing resection was 45 months with an estimated 5-year survival rate of 40%. Evans et al<sup>27</sup> reported a similar experience in 28 patients treated with 50.4 Gy and infusional 5-FU. Six patients progressed locally during treatment, 5 developed metastatic disease, and 17 patients underwent resection for possible cure. Pathologic assessment demonstrated over 50% necrosis in nearly half of the resected patients.

The influence of preoperative chemoradiotherapy in reducing local recurrence was examined in a phase II Eastern Cooperative Oncology Group trial.<sup>28</sup> Preoperative external beam irradiation (50.4 Gy), infusional

5-FU, and mitomycin C was given to 53 patients. Nine patients either had local progression or developed metastatic disease prior to their scheduled surgery. Unresectable or metastatic disease was found in 17 patients (32%) at the time of surgery, and 24 patients (45%) underwent potentially curative resection. The median survival rate in patients undergoing resection was 15.7 months. Local-only failures were not seen, and only 3 of 24 resected patients had a local failure with simultaneous distant metastases.

Preoperative chemoradiation therapy can be delivered safely and may decrease locoregional recurrences. Recent studies have attempted to simplify the preoperative RT component or identify better systemic therapy. Pisters et al<sup>29</sup> described the use of short-course rapid-fractionation RT (30 Gy in 10 fractions) with concurrent 5-FU followed by pancreaticoduodenectomy and intraoperative RT (10-15 Gy) in 35 patients. With a median follow-up of 37 months, the 3-year survival rate in the patients who completed the combined modality therapy was 23%. Several groups are studying the efficacy and safety of gemcitabine, a potent radiosensitizer that has shown clinical benefit in advanced pancreatic cancer, together with RT in the neoadjuvant setting. Data from phase II studies using gemcitabine may lead to future randomized trials.

## Palliative Resection

The role for palliative pancreaticoduodenectomy (resection with microscopic residual disease) is another subject for debate. This subgroup of patients will all recur and ultimately die of their disease. A large, single-institution report<sup>30</sup> reviewed the outcome of 64 patients undergoing pancreaticoduodenectomy for pancreatic cancer with positive resection margins and compared the results to 62 consecutive patients with locally advanced unresectable disease undergoing palliative double bypass. Actual 1-year survival was 62.5% in the resection group compared with 39% in the bypass group. Perioperative morbidity and mortality were similar in the two groups with only a small increase in hospital stay for the resection group. Assuming that pancreaticoduodenectomy can be performed safely, it appears to improve both survival and quality of life compared with bypass alone.

## Palliation of Unresectable Pancreatic Cancer

The main objectives of palliation are relief of obstructive jaundice, prevention or relief of gastrointestinal obstruction, and management of pain. There

Table 2. — Comparative Results With Surgical Bypass, Percutaneous Stent Placement, or Endoscopic Stent Placement in Patients With Malignant Obstruction of the Common Bile Duct

Result	Surgical Bypass (n = 1,807)		Percutaneous Stent (n = 490)		Endoscopic Stent (n = 689)	
	Range	Mean	Range	Mean	Range	Mean
30-day mortality (%)	0-31	12	6-33	9	0-20	14
Hospital stay (days)	9-30	17	13-18	14	3-26	7
Success rate (%)	75-100	93	4-67	92	82-100	90
Early complications (%)	6-56	31	4-67	16	8-34	21
Late complications (%)	5-47	16	7-38	28	13-45	28

n = number of patients  
 From Watanapa P, Williamson RC. Surgical palliation for pancreatic cancer: developments during the past two decades. *Br J Surg.* 1992;79:8-20. Reproduced with permission.  
<http://www.blackwell-science.com/bis>

are a number of palliative options for obstructive jaundice, including placement of either an endoscopic biliary stent or an operative biliary bypass. When patients undergo laparotomy for possible resection and are found to be unresectable, a biliary enteric bypass should be performed at that time.

Determining which type of bypass is best has remained controversial. Choledochoduodenostomy is associated with recurrent jaundice in approximately one third of patients and is not recommended. Cholecystojejunostomy is still commonly used, but in a large meta-analysis,<sup>31</sup> it was associated with 84% long-term patency compared with 97% long-term patency with choledochojejunostomy. When the gallbladder is used for bypass, the risk of cholangitis together with recurrent jaundice increases. Cholecystojejunostomy may be an appropriate alternative when life expectancy is limited. An example is the finding of metastatic disease at laparoscopy, where a cholecystojejunostomy could be performed using minimally invasive techniques.

In patients found to be unresectable based on preoperative assessment, there is continuing debate about whether they should undergo endoscopic stent placement or operative bypass. A large review by Watanapa et al<sup>31</sup> showed that endoscopic stents and surgical bypass produced comparable mortality and short-term success rates, but endoscopic stents were associated with shorter hospital stays. Early complications occurred in 21% of patients with endoscopic stents and in 31% of patients treated with surgical bypass. Late complications, however, were noted in 16% of the operative group compared with 28% in the endoscopic stent group, including the need to replace stents at periodic intervals (Table 2). In a study by van den Bosch et al,<sup>32</sup> endoscopic drainage was compared with surgical bypass and stratified for survival at less

than or greater than 6 months. In both groups, early postprocedure morbidity was higher with surgery. The late morbidity in patients who lived longer than 6 months was 60% in the endoprosthesis group but only 5% in the surgery group. They concluded that endoscopic prosthesis is favored for patients with advanced disease and with an anticipated survival less than 6 months.

The use of prophylactic gastrojejunostomy for patients with locally advanced pancreatic cancer is also a controversial issue. A prospective, randomized trial<sup>33</sup> compared two groups of patients with unresectable periampullary cancer managed operatively. Late gastric outlet obstruction developed in 19% of patients who did not have a prophylactic gastrojejunostomy, but obstruction did not develop in those who underwent gastrojejunostomy. Other retrospective analyses have generally shown similar findings, with 15%-20% of patients developing late gastric outlet obstruction requiring therapeutic intervention. Gastrojejunostomy should be considered at the time of open surgery since it can be done with minimal additional morbidity and mortality. Patients who are found at laparoscopy to have metastatic disease and already have an endoprosthesis in place probably do not warrant the additional morbidity of a gastrojejunostomy.

Palliation of pain should be considered in patients undergoing open surgery who are found to be unresectable. A prospective, randomized trial<sup>34</sup> comparing intraoperative chemical splanchnicectomy with 50% alcohol vs a placebo injection reported a reduction of the mean pain score in the alcohol group vs the saline placebo group. The patients who had marked pain preoperatively and received celiac alcohol ablation actually had an improvement in survival. In patients not undergoing laparotomy, a percutaneous celiac nerve

block should be considered when long-acting narcotics are ineffective. Pain relief is described in 80%-90% of patients using this technique. Despite these favorable results, chemical splanchnicectomy for unresectable pancreatic cancer remains underutilized.

## Chemoradiation for Locally Advanced Pancreatic Cancer

A number of groups have studied the efficacy of chemoradiation for locally advanced pancreatic cancer. The GITSG<sup>35</sup> conducted a phase III trial with 194 patients randomized into three groups: high-dose radiation (60 Gy), moderate-dose radiation (40 Gy) plus bolus 5-FU, or high-dose radiation (60 Gy) plus bolus 5-FU. Median survival improved in the combined-modality arms (40 weeks) compared with the radiation-alone arm (22.9 weeks). The 1-year survival rate was 40% in the combined-modality arms and 10% in the radiation-alone arm. In another ECOG randomized trial, RT plus 5-FU was compared to 5-FU alone in patients with locally advanced pancreatic adenocarcinoma.<sup>36</sup> The median survival was 8 months in both groups. A subsequent GITSG trial<sup>37</sup> for patients with locally advanced disease randomized 48 patients to streptozocin, mitomycin C, and 5-FU (SMF) chemotherapy or combined chemoradiation therapy with 54 Gy and 5-FU followed by SMF chemotherapy. Median survival improved from 32 weeks to 42 weeks in patients receiving the combined therapy.

Based on these studies, it appears that multimodality therapy with RT plus 5-FU prolongs survival in patients with locally advanced, unresectable pancreatic cancer. Several ongoing studies are attempting to improve on these modest benefits. RTOG 98-12 is a phase II study in which patients with unresectable adenocarcinoma of the pancreas are treated with radiation (50.4 Gy) and concurrent weekly paclitaxel (50 mg/m<sup>2</sup>). Another phase II study, Cancer and Leukemia Group B (CALGB) 89805, is combining twice-weekly gemcitabine with RT. Responding and stable patients then receive additional gemcitabine for a total of 16 weeks.

Newer techniques in radiation delivery, such as 3-dimensional (3-D) conformal radiotherapy, are also being investigated. Munzone et al<sup>38</sup> have reported preliminary data using epirubicin (50 mg/m<sup>2</sup>) and cisplatin (60 mg/m<sup>2</sup>) every 3 weeks, and continuous infusion 5-FU (200 mg/m<sup>2</sup> per day) with concurrent 3-D conformal radiotherapy to a dose of 63 Gy for locally advanced adenocarcinoma of the pancreas. The therapy was well tolerated with a median survival of 11 months and with 47% of patients alive at 1 year.

## Conclusions

Although the majority of patients with pancreatic cancer will die of their disease, the diagnosis and management of patients with resectable disease continue to improve. Pancreaticoduodenectomy is now performed in tertiary centers with mortality rates at consistently less than 5%. Patients with smaller node-negative tumors may have 5-year survival rates approaching 30%-40%. Patients without obvious metastatic disease should be evaluated by experienced surgeons so the patients will not be denied potential curative resection or effective surgical palliation. Both endoscopic drainage and operative biliary drainage are associated with high success rates and acceptable morbidity and mortality. Patients with advanced disease and limited life expectancy may be better served with endobiliary stents, while surgical bypass should be considered for those with longer life expectancy. In the adjuvant setting, RT and chemotherapy with resection appear to modestly prolong survival, while in patients with locally advanced disease, RT and chemotherapy may be used as definitive therapy. More significant improvements in long-term outcome await novel methods for earlier detection, better assessment of high-risk groups, and the development of more effective systemic treatments such as hormone therapy or gene-based immunotherapy.

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