

Endoscopic and Operative Palliation Strategies for Pancreatic Ductal Adenocarcinoma

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Malignant biliary obstruction, duodenal, and gastric outlet obstruction, and tumor-related pain are the complications of unresectable pancreatic adenocarcinoma that most frequently require palliative intervention. Surgery involving biliary bypass with or without gastrojejunostomy was once the mainstay of treatment in these patients. However, advances in non-operative techniques—most notably the widespread availability of endoscopic biliary and duodenal stents—have shifted the paradigm of treatment away from traditional surgical management. Questions regarding the efficacy and durability of endoscopic stents for biliary and gastric outlet obstruction are reviewed and demonstrate high rates of therapeutic success, low rates of morbidity, and decreased cost. Surgery remains an effective treatment modality, and still produces the most durable relief in appropriately selected patients.
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The incidence of pancreatic cancer in the United States is rising, 48,960 46,420 new cases and 40,560 pancreatic cancer-related deaths in 2014.¹ Despite advances in diagnostic imaging, pre-operative diagnosis, surgical management, and the rise of specialized centers in the treatment of pancreatic adenocarcinoma, the prognosis for the majority of these patients remains strikingly poor.² Consequently, the management of these patients is overwhelmingly one of palliation, directed at relieving symptoms and improving quality of life.

Complete R0 surgical resection remains the only chance for cure; however, 80%–90% of patients present with evidence of metastatic or locally advanced disease precluding curative resection.³ The most common complications of advanced pancreatic cancer requiring intervention are malignant biliary obstruction, duodenal or gastric outlet obstruction, and tumor-associated pain—related to direct extension of the tumor into the bile duct, duodenum, and celiac plexus, respectively. Biliary obstruction and gastric outlet obstruction predominantly occur in

patients with lesions of the head of the pancreas, the most common location for pancreatic adenocarcinoma. Indeed, despite typically presenting earlier than lesions in the body or tail of the pancreas, a recent series indicate that lesions of the head of the pancreas make up approximately 70% of unresectable pancreatic adenocarcinomas.⁴

Open surgical bypass for biliary obstruction and open gastric bypass for duodenal or gastric outlet obstruction have historically been the mainstays of surgical palliation for unresectable disease. Simultaneous biliary and gastric bypass, known as “double loop bypass”, has been used as a prophylactic operation. Opioid analgesics have been used for chronic pain. Advances in endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), and percutaneous computed tomography (CT)-guided techniques have provided alternatives to surgery. Recent series confirm that while the number of resections for curative intent has remained stable over time, the number of patients undergoing operative palliation has significantly decreased.⁵ In fact, most centers now preferentially palliate biliary and gastric outlet obstruction with endoscopically placed biliary and duodenal stents. These non-operative techniques have been proven effective and allow the patient to quickly receive or return to treatment with chemotherapy and/or radiotherapy as directed by the medical oncologist.

The most appropriate course of management can be debated in many cases. The durability of non-operative approaches has been a historical concern,

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Conflicts of interest:

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but many clinical trials—retrospective and prospective randomized—have addressed this issue. What's more, despite advances in preoperative staging, up to a third of patients taken to surgery are found to be unresectable at the time of laparotomy. These patients may be symptomatic at the time of laparotomy and in need of palliation for jaundice, pain, and gastric outlet obstruction.⁶ While still in the operating room, is the surgeon justified in performing operative bypass? Should the surgeon perform prophylactic bypass in asymptomatic patients? Or should the surgeon close the abdomen without performing a palliative procedure and defer all initial palliative interventions to the endoscopist? This review will present the historical discussion and current data supporting the approaches to palliation of pancreatic ductal adenocarcinoma.

BILIARY OBSTRUCTION

Biliary obstruction of the intrapancreatic portion of the common bile duct as a result of malignant disease in the head of the pancreas is the most common reason for palliative surgical intervention in patients with unresectable pancreatic adenocarcinoma. Historically, jaundice is seen in approximately 48-57% of patients with unresectable disease. Painless jaundice—one of the few symptoms of pancreatic adenocarcinoma that allows for "early" detection of disease—is uncommon in patients with advanced disease, as these patients are significantly more likely to present with concomitant abdominal pain, back pain, nausea, and vomiting.^{6,7} Newer series indicate that biliary obstruction is the presenting symptom in 51%–72% of unresectable patients, while developing in as many as 81% during the course of disease if not intervened.^{4,5}

The clinical constellation caused by malignant biliary obstruction begins with marked elevation in serum bilirubin. Jaundice ensues and is accompanied by pruritus in some 20% of patients, which is difficult to treat with medical therapy alone. Fat malabsorption occurs as a result of decreased secretion of bile acids, contributing to malnutrition and cachexia. Finally, unrelieved biliary obstruction ultimately leads to high risk of cholangitis, cholestasis, hepatic dysfunction, and liver failure. In one series, up to 38% of patients that did not undergo palliative therapy died of these terminal sequelae.⁷ Indeed, early data suggested that biliary bypass prolonged survival,⁸ although that notion has been repeatedly challenged. Nevertheless, relief of biliary obstruction remains necessary to maintain quality of life and to prevent the rapid deterioration in clinical condition that accompanies eventual liver failure.

Operative biliary bypass has been the historical gold standard for palliation of malignant biliary

obstruction, and has been considered both effective and durable. Therapeutic failure—defined as the rate of recurrent jaundice—is often reported to be as low as 2%–5%.^{5,6,9} This durability has been challenged, with some series finding the rate of recurrent jaundice to be in the range of 11%–15%.^{7,10} Furthermore, major morbidity and mortality have been associated with operative palliation. For these reasons, endoscopic biliary stent placement in many places has become the intervention of choice for palliation of obstructive jaundice.

Surgical Therapy for Biliary Obstruction

Conventional surgical management of the obstructed distal bile duct has been performed as an open operation consisting of a cholecystoenterostomy, choledochoenterostomy, or hepaticojejunostomy—the choice of which is as frequently determined by surgeon preference as by extent of disease. Either the duodenum or the jejunum may be used as the conduit, with the jejunum being the more common site of enteric anastomosis given relative technical ease and theoretical concerns for eventual tumor extension involving the duodenum. Finally, the choledocho-, cholecysto-, or hepaticojejunostomy may be performed either as loop or a Roux-en-Y reconstruction. Loop construction avoids a jejunojunction and is quicker; however, expert opinion maintains that Roux-en-Y is preferred in patients with anticipated long-term survival, as it lowers the subsequent risk of cholangitis.⁷

Regarding the technique of biliary bypass, hepaticojejunostomy is reserved for cases in which either the extent of bile duct involvement precludes choledochojejunostomy, or the cystic duct-common duct confluence is compromised precluding cholecystojejunostomy; in all other cases, the decision to use the bile duct or the gallbladder is to this day controversial. All of the above types of biliary-enteric bypasses have been demonstrated to be efficacious in retrospective series. One of the earliest studies published on this topic included a review of 8,000 patients from 1965–1980, in which the authors concluded that a loop cholecystojejunostomy should be performed in all patients unless the cystic duct-common duct confluence was directly involved.⁸ Data from the UCLA experience through 1990 demonstrated equal efficacy in terms of relief of biliary obstruction between cholecystojejunostomy and choledochojejunostomy; however, use of the bile duct was associated with significantly higher rate of morbidity (38.3% *v* 27%) and mortality (11.7% *v* 5.4%).⁷ Conversely, a contemporaneous series out of France found that cholecystoenteric bypass was associated with a higher post-operative mortality (20% *v* 14%), lower long-term morbidity

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