PERIAMPULLARY AND PANCREATIC ADENOCARCINOMA

Clifford S. Cho, MD, FACS

Appropriate surgical management of periampullary adenocarcinoma (ampullary adenocarcinoma, duodenal adenocarcinoma, and distal cholangiocarcinoma) and pancreas adenocarcinoma requires a familiarity with both anatomy and cancer biology. This chapter describes the clinical behavior of the various subtypes of periampullary adenocarcinoma, the appropriate diagnostic evaluation of the patient afflicted with these malignancies, the surgical anatomy of the pancreas and peripancreatic region, and the nature and outcome of contemporary therapeutic interventions.

Periampullary Adenocarcinoma: Subtypes and Specific Clinical Considerations

Because the ampulla of Vater lies at the anatomic intersection of the pancreas, biliary system, and duodenum, periampullary adenocarcinoma is a conglomerative term that includes the more specific diagnoses of pancreatic adenocarcinoma, distal cholangiocarcinoma, ampullary adenocarcinoma, and duodenal adenocarcinoma. The utility of this term is particularly evident during preoperative evaluation, when precise differentiation between these four diagnostic entities can be difficult. All four of these malignant processes can present with very similar clinical symptoms and diagnostic signs, and the operative management of all four is identical (pancreatoduodenectomy). However, the four diagnoses vary with regard to their biologic behavior and responsiveness to chemotherapy, and appropriate management should be informed by an understanding of their subtle but significant differences.

Importantly, the long-term prognosis is generally poor for patients with pancreatic adenocarcinoma and distal cholangiocarcinoma and is comparatively favorable for patients with duodenal adenocarcinoma; the outlook for patients with ampullary adenocarcinoma is somewhat intermediate.1 Adenocarcinoma arising from the ampulla can be divided into two subtypes: intestinal type, which exhibits a biologic behavior and prognosis similar to that of duodenal adenocarcinoma, and pancreaticobiliary type, which behaves like pancreatic adenocarcinoma and distal cholangiocarcinoma.2 For the purposes of this chapter, we outline the four traditional categories of periampullary adenocarcinoma in terms of their incidence, pathology, prognosis/staging, and therapy.

Pancreatic Adenocarcinoma

Incidence

Pancreatic ductal adenocarcinoma represents the largest subset of periampullary adenocarcinoma. It is the second most common gastrointestinal tract malignancy and the fourth leading cause of cancer-related mortality in the United States. Risk factors for pancreatic adenocarcinoma in this country include family history, increasing age, male gender, African-American race, tobacco use, and chronic pancreatitis. Genetic syndromes that appear to predispose individuals toward pancreatic adenocarcinoma include Peutz-Jeghers syndrome, hereditary pancreatitis, hereditary nonpolyposis colon cancer (Lynch syndrome), familial breast cancer associated with the BRCA2 mutation, and familial atypical multiple mole melanoma (FAMMM) syndrome.

Pathology

The histologic appearance of pancreatic adenocarcinoma is characterized by neoplastic epithelial tumor cells and a densely fibrotic stroma. The marked nuclear atypia and easy infiltration of tumor cells into lymphovascular and perineural tissues reflect its biologic aggressiveness. It has also become apparent that the desmoplastic stroma interacts actively with tumor cells to promote their growth and invasion while impairing the delivery and efficacy of chemotherapy. It is now evident that pancreas adenocarcinoma may arise from precursor lesions known as pancreatic intraepithelial neoplasms (PanINs) that progress from benign toward malignant phenotypes as they accumulate critical gene mutations.3 Histologically, this progression can be measured by the presence of PanIN-1, PanIN-2, and PanIN-3 lesions, which exhibit sequentially increasing levels of cellular and architectural abnormality.

A well-known and defining characteristic of pancreatic adenocarcinoma is its aggressiveness. Based on the remarkably high prevalence of patients who present with metastatic disease at the time of diagnosis, it is evident that this cancer is capable of early systemic dissemination. Indeed, based on the remarkably high prevalence of patients who develop metastatic disease very shortly after undergoing potentially curative resection, it is likely that the majority of pancreatic adenocarcinoma cases have developed systemic dissemination by the time the diagnosis is made.

Prognosis and Staging

As with all of the other subtypes of periampullary adenocarcinoma, the American Joint Committee on Cancer (AJCC) staging system for pancreatic adenocarcinoma is based on the tumor-node-metastasis (TNM) scheme.4 The staging system for pancreatic adenocarcinoma takes into consideration the prognostic relevance of such variables as tumor size and the presence of nodal and distant metastases [see Table 1]. In addition, it accounts for the prognostic difference between resectable and unresectable tumors, which is determined by tumoral invasion into local vascular structures that cannot be resected and reconstructed. As such, an important distinction exists between T3 tumors, which extend beyond the pancreas but not into the celiac axis or superior mesenteric artery (and are likely to be resectable), and T4 tumors, which involve the celiac axis and superior mesenteric artery (and are unresectable). Stage III disease, which is defined by the
presence of a T4 tumor, implies locally advanced disease. Other pathologic features that have been shown to portend a worse prognosis in pancreatic adenocarcinoma are poor differentiated histology, perineural invasion, and lymphovascular invasion.

In addition to the traditional TNM staging convention, patients with pancreatic adenocarcinoma are also classified into the more functional categories of potentially resectable, borderline resectable, locally advanced, and metastatic disease [see Table 2]. This classification system provides information about both the extent of disease and the options for therapeutic intervention. Unfortunately, the anatomic criteria of tumor resectability have been subject to variability, and efforts to develop consensus guidelines distinguishing potentially resectable, borderline resectable, and locally advanced disease have only recently been under way.

Patients with potentially resectable disease are those whose radiographic studies identify primary tumors with no local vascular involvement and no evidence of distant metastatic disease; from an anatomic standpoint, these patients are likely to be candidates for complete operative resection of their pancreatic tumors [see Figure 1]. In reality, only 80 to 90% of patients with potentially resectable disease are able to undergo resection as evidence of distant metastasis or technically unresectable disease is found in 10 to 20% of cases at the time of operative exploration. When managed with surgical resection, the median survival of patients with resectable disease is generally in the range of 18 to 24 months.

Patients with borderline resectable disease harbor radiographic evidence of venous involvement that is amenable to reconstruction and/or minimal arterial involvement with no evidence of distant metastatic disease [see Figure 2]. Anatomically, these patients may be candidates for surgical resection but are at higher risk for having evidence of unresectable disease at the time of operative exploration or undergoing margin-positive resection. For this reason, patients with borderline resectable disease are typically treated with preoperative chemotherapy with or without radiation therapy, with the intention of attempting resection as long as posttreatment imaging does not show evidence of disease progression to locally advanced or metastatic disease. Unlike locally advanced disease, the absence of radiographic regression in patients with borderline resectable disease does not imply that resection should not be attempted. Recent studies suggest that approximately 50 to 70% of patients with borderline resectable disease are ultimately able to undergo resection after preoperative therapy.

When resection is possible, patients with borderline resectable disease are more likely to require venous resection and reconstruction than patients with potentially resectable disease. The median survival for all patients with borderline resectable disease is approximately 14 months; however, accumulating experience with multimodality management suggests that the median survival of patients with borderline resectable disease who ultimately undergo surgical resection is approximately 20 months, which is comparable to that of patients with potentially resectable disease.

Locally advanced disease is defined by the presence of local vascular involvement that cannot be overcome by vascular resection and reconstruction, with no evidence of distant metastatic disease [see Figure 3]. Locally advanced disease is, by definition, not amenable to operative resection.
and is typically managed with chemotherapy with or without radiation therapy. Unfortunately, these regimens are usually not successful in inducing sufficient disease regression to permit operative resection. In rare circumstances where resection does become possible, expected survival may approximate that seen among patients with potentially resectable disease. The median survival of patients with locally advanced disease is approximately 6 to 12 months.

At present, patients with metastatic disease are only eligible for systemic chemotherapy, and their median survival is generally 3 to 9 months [see Figure 4]. As is the case with patients with locally advanced disease, operative intervention is typically reserved for palliation (e.g., gastrojejunostomy for duodenal obstruction and hepaticojejunostomy for biliary obstruction). However, most of these tumor-related complications can be managed using endoscopic and percutaneous interventional radiologic approaches (e.g., endoluminal duodenal stents for duodenal obstruction and biliary stents for biliary obstruction) that offer comparable efficacy with lower procedure-related morbidity.

**Therapy**

Treatment strategies for patients with pancreatic adenocarcinoma are tailored to their extent of disease as outlined above. The surgical resection techniques outlined in this chapter are applied to patients with potentially resectable and borderline resectable disease and the rare patients with locally advanced disease who demonstrate significant disease regression following preoperative therapy. Systemic chemotherapy is offered to all categories of disease presentation, either as neoadjuvant or adjuvant therapy (or both) for patients with resectable and borderline resectable disease or as definitive palliative therapy for patients with locally advanced and metastatic disease. Radiation therapy can be offered either as neoadjuvant or adjuvant therapy for patients with resectable and borderline resectable disease as a means of maximizing local control of disease or as palliative therapy for patients with locally advanced and metastatic disease presenting with symptoms referable to their primary tumor (e.g., pain).

A significant challenge in the care for patients with pancreatic adenocarcinoma has been its extreme resistance to systemic chemotherapy. Because of this therapeutic limitation and because of the very high incidence of systemic dissemination, the prognosis for most patients with pancreatic adenocarcinoma remains very poor. Great investigative effort has been expended to identify novel systemic treatment options, but chemotherapeutic options remain limited in number and efficacy. Randomized clinical trials have shown that the nucleotide analogue gemcitabine improves quality of life when used as definitive therapy for patients with advanced pancreatic adenocarcinoma and prolongs disease-free survival when used as adjuvant therapy following operative resection. These studies have led to the acceptance of gemcitabine as a mainstay of chemotherapy for pancreatic adenocarcinoma. More recently, the combination of leucovorin, 5-fluorouracil (5-FU), irinotecan, and oxaliplatin (FOLFIRINOX) has been shown to promote modest prolongation of overall survival in comparison with gemcitabine for patients with metastatic pancreatic adenocarcinoma. Based on these findings, FOLFIRINOX is currently being used and investigated in both the neoadjuvant
and adjuvant settings for patients with potentially resectable, borderline resectable, and locally advanced pancreatic adenocarcinoma. However, because of its higher potential for treatment-related toxicity, FOLFIRINOX is generally reserved for patients with excellent performance status. Very recent data suggest that the novel combination of gemcitabine with nanoparticle albumin-bound paclitaxel may offer better outcomes than gemcitabine alone for patients with advanced pancreas cancer; if verified, this combination may eventually represent a better tolerated (but costly) alternative to FOLFIRINOX.

Although adjuvant chemotherapy appears to be associated with a modest improvement in survival, it has become evident that about 30% of patients do not go on to receive adjuvant therapy following pancreatic resection. This observation and the success of preoperative therapy for patients with borderline resectable disease have prompted some centers to adopt a neoadjuvant approach for patients with potentially resectable disease. Another potential advantage to the neoadjuvant approach is improved patient selection. The interval of 2 to 3 months needed to complete preoperative chemotherapy and radiation therapy may provide a window of time during which previously occult metastatic disease may become clinically evident; repeat imaging following completion of preoperative therapy may therefore be used to identify a subset of patients for whom nontherapeutic operative resection can be avoided.

The role of radiation as a routine component of adjuvant therapy remains controversial; postoperative radiation therapy is most commonly used for patients with close or positive resection margins in an effort to minimize the likelihood of local tumor recurrence. Preoperatively, radiation therapy is used as a means to improve the chances of achieving negative resection margins for patients with resectable and borderline resectable disease. For patients with locally advanced or metastatic disease, radiation therapy may offer palliative benefit by ameliorating symptoms referable to local tumoral infiltration.

**DISTAL CHOLANGIOCARCINOMA**

**Incidence**

Cholangiocarcinoma is adenocarcinoma of the biliary tree and can involve any portion of the intrahepatic or extrahepatic biliary system. Distal cholangiocarcinoma, involving the distal intrapancreatic portion of the common bile duct, comprises approximately 20 to 30% of all cholangiocarcinoma cases and about 10 to 20% of all periampullary adenocarcinoma cases.

**Pathology**

Distal cholangiocarcinoma has been subdivided into three macroscopic subtypes: sclerosing tumors are characterized by circumferential ductal thickening with extensive peri ductal fibrosis and inflammation; nodular tumors appear as firm mass lesions growing into the duct lumen; and papillary tumors typically present as soft, friable, pedunculated masses that project into the duct lumen. The important distinction is that papillary tumors are likely to be resectable and exhibit a more favorable prognosis. Histologically, the innermost layer of the bile duct is the inner mucosa. The mucosa is enveloped by subepithelial connective tissue, which is in turn surrounded by a muscular layer that is most prominent along the distal intrapancreatic portion. A layer of adipose tissue covers the wall of the bile duct. The AJCC staging system for distal cholangiocarcinoma uses a tumor (T) system that is defined by the depth of tumor invasion; invasion of adenocarcinoma into the perimuscular adipose tissue is considered to be invasion beyond the wall of the bile duct. One important pathologic feature of cholangiocarcinoma is its insidious propensity for longitudinal spread along the bile duct. One important pathologic feature of cholangiocarcinoma is its insidious propensity for longitudinal spread along the bile duct. Tumor cells often extend well proximal and distal to the dominant mass beneath normal-appearing ductal mucosa. For this reason, great care must be taken to assess the proximal hepatic duct margin for malignant cells using frozen-section pathologic analysis at the time of surgical resection. Another important pathologic characteristic of cholangiocarcinoma is the strong desmoplastic reaction that...
often surrounds these tumors. The difficulty of identifying nests of malignant cells within this dense stroma often makes preoperative cytopathologic diagnosis very challenging.

**Staging and Prognosis**

Unlike pancreatic adenocarcinoma but like ampullary and duodenal adenocarcinoma, the current AJCC staging system for distal cholangiocarcinoma bases its tumor (T) staging on tumor depth, not tumor size [see Table 3].

Similar to staging for pancreatic adenocarcinoma, T4 status is defined by the presence of celiac axis or superior mesenteric artery involvement, which precludes operative resectability. Stages I through IV are defined in the same way as pancreatic adenocarcinoma. As with the other categories of periampullary adenocarcinoma, the major prognostic variables for distal cholangiocarcinoma are tumor depth, nodal status, distant metastases, histologic differentiation, perineural invasion, and lymphovascular invasion.

**Therapy**

For patients with resectable disease, operative therapy consists of pancreaticoduodenectomy. The prevalence of radiologically occult peritoneal metastases and the resulting yield of staging laparoscopy are lower than with pancreatic adenocarcinoma. However, staging laparoscopy may be performed when these two diagnoses cannot be distinguished preoperatively. Because of the propensity of cholangiocarcinoma to spread along the biliary tree, particular attention is paid to the hepatic duct margin at the time of operation, and resection of an additional segment of hepatic duct is undertaken for cases of margin positivity. Guidelines for the use of chemotherapy are less well defined than for pancreatic adenocarcinoma, but gemcitabine-based chemotherapy is typically offered as adjuvant therapy or for patients with node-positive disease or as definitive therapy for patients with unresectable or metastatic disease. As with pancreatic adenocarcinoma, radiation therapy is typically reserved for adjuvant therapy following resection with close or positive resection margins or for palliation of tumor-related symptoms in cases of unresectable disease.

**AMPULLARY ADENOCARCINOMA**

**Incidence**

Adenocarcinoma arising from the ampulla of Vater is relatively rare, representing less than 1% of all gastrointestinal cancers and 10 to 20% of periampullary adenocarcinoma cases. Patients with familial adenomatous polyposis are known to be at higher risk for the development of ampullary adenocarcinoma.

**Pathology**

The ampulla of Vater consists of the ductal lining of the distal common bile duct and pancreatic duct and the intestinal epithelium that overlies this duct. Recent studies suggest that ampullary adenocarcinoma consists of two histologic subtypes. Intestinal-type ampullary adenocarcinoma appears to originate from the intestinal epithelium of the ampulla and is likely to arise from the adenoma to adenocarcinoma sequence of mutational genesis that characterizes other intestinal adenocarcinoma tumors. In contrast, pancreaticobiliary-type ampullary adenocarcinoma is likely to originate from the endothelial lining of the ductal component and may develop from dysplastic precursor intraepithelial neoplasms that progress toward adenocarcinoma, as is seen with pancreatic adenocarcinoma. In cases of larger tumors, where the epicenter of origin may be difficult to discern, it may become difficult to distinguish between intestinal-type ampullary adenocarcinoma and duodenal adenocarcinoma or between pancreaticobiliary-type ampullary adenocarcinoma and distal cholangiocarcinoma or pancreatic adenocarcinoma. However, these distinctions may be of little clinical consequence as the prognosis and treatment of these alternative diagnoses are very similar; indeed, it has been argued that all cases of periampullary adenocarcinoma may be more appropriately divided into two broad categories of intestinal versus pancreaticobiliary adenocarcinoma. Most cases of ampullary adenocarcinoma are well differentiated in their histologic appearance.

**Staging and Prognosis**

Because of their location, ampullary adenocarcinoma commonly presents at an earlier stage than pancreatic adenocarcinoma as even small tumors are capable of causing symptoms of obstructive jaundice. Accordingly, ampullary adenocarcinoma is more commonly resectable at the time of diagnosis than pancreatic adenocarcinoma. The current AJCC staging system for ampullary adenocarcinoma incorporates tumor depth and nodal and distant metastases;

<table>
<thead>
<tr>
<th>Table 3</th>
<th>AJCC Staging System for Distal Cholangiocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor (T)</td>
<td>Tx: Primary tumor cannot be assessed</td>
</tr>
<tr>
<td></td>
<td>T0: No evidence of primary tumor</td>
</tr>
<tr>
<td></td>
<td>Tis: Carcinoma in situ</td>
</tr>
<tr>
<td></td>
<td>T1: Tumor confined to the bile duct histologically</td>
</tr>
<tr>
<td></td>
<td>T2: Tumor invades beyond the wall of the bile duct</td>
</tr>
<tr>
<td></td>
<td>T3: Tumor invades the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis or the superior mesenteric artery</td>
</tr>
<tr>
<td></td>
<td>T4: Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)</td>
</tr>
<tr>
<td>Regional lymph nodes (N)</td>
<td>Nx: Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td></td>
<td>N0: No regional lymph node metastases</td>
</tr>
<tr>
<td></td>
<td>N1: Regional lymph node metastasis</td>
</tr>
<tr>
<td>Distant metastasis (M)</td>
<td>M0: No distant metastasis</td>
</tr>
<tr>
<td></td>
<td>M1: Distant metastasis</td>
</tr>
</tbody>
</table>

Stage 0: Tis N0 M0
Stage IA: T1 N0 M0
Stage IB: T2 N0 M0
Stage IIA: T3 N0 M0
Stage IIB: T1 N1 M0, T2 N1 M0
Stage III: T3 N1 M0
Stage IV: T4 Any N M0
Stage IV: Any T Any N M1

AJCC = American Joint Committee on Cancer.
unlike pancreatic adenocarcinoma but like distal cholangiocarcinoma and duodenal adenocarcinoma, tumor (T) staging is defined by depth of invasion (confined within the ampulla or invasion into the duodenum or pancreas or beyond) rather than tumor size [see Table 4]. Stages I through IV are defined in the same way as pancreatic adenocarcinoma and distal cholangiocarcinoma. Like the other categories of periampullary adenocarcinoma, pathologic variables that have been shown to have prognostic significance for ampullary adenocarcinoma include depth of invasion, nodal status, histologic differentiation, perineural invasion, and lymphovascular invasion. The histologic distinction of intestinal versus pancreaticobiliary type has also been shown to be of central prognostic importance as survival outcomes following pancreaticoduodenectomy have been shown to be favorable among patients with intestinal-type ampullary adenocarcinoma.2

**Table 4** AJCC Staging System for Ampullary Adenocarcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

AJCC = American Joint Committee on Cancer.

**Therapy**

For patients with resectable disease, operative conduct involves pancreaticoduodenectomy. The prevalence of radiologically occult peritoneal metastases is low enough to avoid the need for routine staging laparoscopy in cases where a definitive diagnosis of ampullary adenocarcinoma is made preoperatively. Ampullectomy, in which the ampulla of Vater is resected and the pancreatic and bile ducts are reapproximated through a transduodenal approach, is used for resection of adenomatous polyps with no evidence of invasive disease. This less radical approach obviously does not permit resection and analysis of lymph nodes. Unfortunately, even early stages of invasion (e.g., T1 ampullary adenocarcinoma) are associated with a real risk of nodal metastasis; therefore, ampullectomy is not recommended for even early cases of ampullary adenocarcinoma due to the risk of understaging and the risk of margin-positive resection. Guidelines for the use of chemotherapy are not rigorously defined for ampullary adenocarcinoma. 5-FU-based chemotherapeutic regimens such as FOLFOX (5-fluorouracil, leucovorin, oxaliplatin) that are effective elsewhere in the gastrointestinal alimentary tract are generally employed for intestinal-type ampullary adenocarcinoma (either as adjuvant therapy for node-positive disease or as systemic therapy for unresectable disease). In contrast, gemcitabine-based regimens are generally employed for pancreaticobiliary-type ampullary adenocarcinoma.

**DUODENAL ADENOCARCINOMA**

**Incidence**

Although duodenal adenocarcinoma represents less than 1% of all alimentary tract malignancies, the duodenum is the location of approximately 50% of all small intestinal adenocarcinoma. The majority of duodenal adenocarcinoma cases are sporadic, but conditions such as familial adenomatous polyposis, hereditary nonpolyposis colon cancer syndrome (Lynch syndrome), Crohn disease, Peutz-Jeghers syndrome, and neurofibromatosis type 1 (von Recklinghausen disease) are associated with an increased risk of duodenal adenocarcinoma.

**Pathology**

Like other forms of alimentary tract adenocarcinoma, duodenal adenocarcinoma likely develops from antecedent adenomas through sequential genetic mutations. An obvious anatomic feature that distinguishes the pathologic behavior of duodenal adenocarcinoma is the close apposition of the proximal duodenum to the ampulla, distal bile duct, and pancreas; unlike other regions of the small intestine, where resection of associated lymph nodes involves simple mesenteric resection, resection of lymph nodes associated with the duodenum often requires pancreaticoduodenectomy.

**Staging and Prognosis**

The current AJCC staging system for duodenal adenocarcinoma is identical to that of other forms of small intestinal adenocarcinoma [see Table 5]. The tumor (T) staging system is based on tumor depth. T4 status is defined by the presence of invasion into adjacent organs and structures (such as the bile duct or pancreas); unlike pancreatic adenocarcinoma or distal cholangiocarcinoma, T4 status does not necessarily imply the presence of unresectable disease. Unlike the other categories of periampullary adenocarcinoma, the nodal (N) staging system accounts for the number of involved lymph nodes, with N1 disease signifying the presence of one to three nodal metastases and N2 disease signifying metastasis to four or more regional lymph nodes. Stage I implies a superficial tumor with no nodal metastases, stage II implies a deep tumor with no nodal metastases, and stage III implies the presence of nodal metastases.
**Table 5  AJCC Staging System for Duodenal Adenocarcinoma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Depth</th>
<th>Lymph Node Metastasis</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0 M0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1 T2 T3</td>
<td>N0 M0</td>
<td>M0</td>
</tr>
<tr>
<td>II A</td>
<td>T4</td>
<td>N0 M0</td>
<td>M0</td>
</tr>
<tr>
<td>II B</td>
<td>Any T</td>
<td>N1 M0</td>
<td>M0</td>
</tr>
<tr>
<td>III A</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

AJCC = American Joint Committee on Cancer.

**Surgical Anatomy**

**Pancreatic Head**

**Anatomic Considerations**

The head of the pancreas rests within the first, second, and third portions of the duodenum. It is surrounded superiorly by the porta hepatitis, posteriorly by the left renal vein and aortocaval space, and anteriorly and inferiorly by the transverse mesocolon. Operative exposure of the pancreatic head therefore begins by dissecting along the avascular plane between the transverse mesocolon and duodenum and pancreas, reflecting the transverse colon caudally. Dissection along this plane permits exposure of the second and third portions of the duodenum and the superior mesenteric vein below the level of the pancreas. The retroperitoneum along the lateral border of the duodenal sweep and porta hepatitis is then incised, and the pancreatic head is elevated by dividing its posterior avascular plane (the Kocher maneuver). This mobilization can be taken all the way to the neck of the pancreas and distal duodenum. Within the parenchyma of the pancreatic head, the bile duct and pancreatic duct most commonly join to form a common channel that empties into the ampulla of Vater at a point between the superior two thirds and inferior one third of the second portion of the duodenum. Operative exposure of the ampulla therefore typically requires a longitudinally oriented lateral incision along the distal half of the second duodenal portion.

**Clinical Considerations**

Because of the proximity of the pancreatic and bile ducts, tumors of the periampullary region and pancreatic head often present with clinical and radiographic evidence of ductal obstruction. Clinical symptoms and signs of bile duct obstruction typically precede those of pancreatic ductal obstruction. As a result, the initial manifestation of periampullary and pancreatic head malignancies is often jaundice without cholangitic fevers or pain. Radiographic evidence of intrahepatic and extrahepatic biliary dilatation and pancreatic ductal dilatation is common and diagnostic of mechanical obstruction. Because of the anatomic intimacy of the distal biliary system, pancreatic head, and duodenum, oncologic resection of even early periampullary malignancies usually requires pancreaticoduodenectomy. Consideration can be given to a more limited resection in cases of premalignant adenomatous tumors of the duodenum or ampulla of Vater, where margin clearance and nodal status are not of paramount clinical concern.

**Porta Hepatis**

**Anatomic Considerations**

Enveloped in a peritoneal sheath, the porta hepatitis resides at the right lateral aspect of the hepato-duodenal ligament and houses a triad of structures: the common hepatic/bile duct, hepatic artery, and portal vein. Along its inferior aspect, the common bile duct is found in the right anterior aspect of the porta hepatitis before it traverses behind and then into the pancreatic head. A portion of the intrapancreatic distal common bile duct can be dissected out of the
Figure 5  
(a) General morphology of the pancreas. (b) The relationship of the pancreas to other organs. (c) The relationship of the pancreas to other organs shown sagitally. (d) The uncinate process, which can vary in medial extent to the superior mesenteric vein (SMV) (a), under the SMV (b), or behind the superior mesenteric artery (c). BL = bladder; C = colon; D = duodenum; LV = liver; P = pancreas; R = rectum; SI = small intestine; ST = stomach.

Scientific American Surgery

12/13
pancreas, but care must be taken to avoid injury to the pancreatic duct at their point of confluence. The proper hepatic artery is located at the left anterior aspect of the porta hepatis, where the common hepatic artery, proper hepatic artery, and gastroduodenal artery can be dissected. The common hepatic artery can be dissected back to its origin at the celiac axis. The portal vein runs posteriorly in the porta hepatis. The portal vein can be exposed from its anterior aspect between the common bile duct and the proper hepatic artery; this exposure is facilitated by dividing the overlying gastroduodenal artery. Alternatively, the portal vein can also be exposed by incising the peritoneal sheath over the right posterolateral porta hepatis between the common bile duct and the portal vein and elevating the common bile duct anteriorly. The common hepatic artery and portocaval lymph nodes are often large, even in the absence of metastatic involvement. Blunt dissection can be undertaken along the avascular plane between the anterior aspect of the portal vein and the posterior aspect of the pancreatic neck; obliteration of this avascular tissue plane in the setting of cancer typically indicates the presence of tumor invasion into the portal vein or superior mesenteric vein.

Clinical Considerations

Because of the prevalence of obstructive jaundice in patients with periampullary and pancreatic head malignancies, biliary decompression using endobiliary stents is often performed prior to operative resection. Stent insertion or subclinical bouts of cholangitis resulting from biliary instrumentation can promote inflammatory changes that can make operative dissection of the porta hepatis more challenging. Inflammation may also lead to enlarged portal lymph nodes in the absence of metastatic disease. During pancreaticoduodenectomy, the inflow into the pancreas and duodenum through the gastroduodenal artery must be divided; care must be taken to ensure proper delineation of the trifurcation of the common hepatic artery, proper hepatic artery, and gastroduodenal artery as inadvertent division of the proper hepatic artery will result in arterial ischemia to the liver.

Pancreatic Neck and Uncinate Process

Anatomic Considerations

The neck of the pancreas is the portion of the pancreas that is anterior to the portal vein, superior mesenteric vein, and superior mesenteric artery [see Figure 5a]. The portal vein passes behind the pancreatic neck at its superior aspect, and the superior mesenteric artery and vein emerge from behind the pancreatic neck at its inferior aspect. The uncinate process of the pancreas resides posterior and medial to the superior mesenteric vein and artery [see Figure 5d]. The superior aspect of the pancreatic neck can be exposed by dissecting along the portal vein as described above. Access to the inferior aspect of the pancreatic neck is facilitated by retracting the head of the pancreas to the right and dissecting the uncinate process off the right lateral border of the superior mesenteric vein. The right gastroepiploic vein and middle colic vein typically converge onto a common trunk entering the superior mesenteric vein just below the pancreatic neck. The superior mesenteric artery is posterior and to the left of the superior mesenteric vein; as a result, it can be accessed following a Kocher maneuver by rotating the pancreatic neck and superior mesenteric vein anteriorly; this maneuver effectively pulls the superior mesenteric artery toward the right, exposing it to the surgeon’s view. The insertion of the splenic vein onto the superior mesenteric vein and the origin of the splenic artery from the celiac axis are both posterior to the pancreatic neck. As a result, full exposure of these structures usually requires transection of the pancreatic neck.

Clinical Considerations

Because of the location of the celiac axis and superior mesenteric vessels, tumors arising from the pancreatic neck are often the most challenging in terms of resectability. The proximity of the superior mesenteric vein means that tumors arising from the uncinate process often require concomitant venous resection and reconstruction.

Pancreatic Body and Tail

Anatomic Considerations

The body of the pancreas is found posterior to the stomach, and the tail of the pancreas rests against the splenic hilum [see Figure 5a]. The splenic vein courses along the body of the pancreas and is typically adherent to its posterior aspect. In contrast, the splenic artery usually follows a more tortuous and extrapancreatic course and can often be found above the superior aspect of the pancreatic body. Because of its location within the lesser sac, the pancreatic body and tail are best approached either through the gastrocolic ligament or through the gastrohepatic ligament. Full exposure of the pancreatic tail is facilitated by dividing the short gastric vessels. The pancreatic body and tail are mobilized by incising the retroperitoneum along the superior and inferior aspects of the pancreatic body and dissecting along the avascular plane between the pancreas and deeper retroperitoneal structures such as the aorta and left adrenal gland. Mobilization of the pancreatic tail can be facilitated by dividing the peritoneal and diaphragmatic attachments of the spleen, elevating the spleen anteriorly, and dissecting along the avascular plane behind the splenic hilus and pancreatic tail from the left.

Clinical Considerations

Unlike right-sided pancreatic tumors, tumors arising from the pancreatic body and tail are unlikely to cause obstructive jaundice. Although left-sided pancreatic tumors may obstruct the pancreatic duct, clinical manifestations of pancreatic ductal obstruction are more insidious and less noticeable than those of biliary obstruction. As a result, left-sided tumors are typically more advanced in terms of size and metastatic dissemination than right-sided tumors. One ominous sign of left-sided pancreatic tumors is intractable midback pain as this can be a result of tumoral infiltration into the para-aortic neural tissues behind the body of the pancreas. Long-standing malignant obstruction of the pancreatic duct can cause clinical symptoms of malabsorptive steatorrhea resulting from impaired pancreatic exocrine function and radiographic findings of pancreatic ductal dilatation and parenchymal atrophy of the obstructed portion of
the pancreas. On the other hand, unlike the pancreatic head, neck, and uncinate process, much of the pancreatic body is free from critical vascular structures. Moreover, unlike the portal vein, superior mesenteric vein, or superior mesenteric artery, the splenic artery and vein can be resected with impunity. Consequently, resection of left-sided tumors can often be performed without the need for vascular reconstruction. To remove the lymph nodes along the splenic artery and vein, splenic hilum, and spleen, a concomitant en bloc splenectomy is typically incorporated into a left pancreatectomy when resection is performed for malignancy; in contrast, consideration can be given to a spleen-preserving left pancreatectomy when it is performed for premalignant tumors (e.g., cystic lesions) or tumors with a low potential for lymphatic dissemination (e.g., metastases to the pancreas).

**Periampullary and Pancreatic Adenocarcinoma: General Clinical Considerations**

**DIAGNOSIS AND STAGING**

A common manifestation of periampullary adenocarcinoma is biliary obstruction. Symptoms of biliary obstruction that prompt patients to seek medical attention include acholic stools, dark urine, pruritus, and cutaneous jaundice. Other general symptoms of pancreatic adenocarcinoma not specifically confined to those originating in the right pancreas include anorexia and weight loss. Very often, the only abnormal physical examination finding is that of jaundice; classic findings of cachexia, ascites, left supraclavicular lymphadenopathy (Virchow node), periumbilical peritoneal metastases (Sister Mary Joseph node), or pararectal pelvic drop metastases (Blumer shelf) are generally indicative of advanced disease. Laboratory evidence of a direct bilirubinemia in conjunction with elevated canalicular enzymes (alkaline phosphatase, \( \gamma \)-glutamyltransferase) supports the diagnosis of biliary obstruction. In this setting, radiographic diagnostics are directed toward the confirmation and staging of cancer. Although transabdominal ultrasonography is useful for confirming biliary dilatation, this information typically adds little beyond that which can already be construed from laboratory blood tests; moreover, ultrasonography usually does not image the pancreas clearly enough to permit accurate tumor localization or staging. In contrast, cross-sectional imaging with contrast-enhanced computed tomography (CT) or magnetic resonance (MR) can provide information about tumor localization, resectability as determined by the anatomic relationship of tumor to adjacent vascular structures, and the presence or extent of metastatic dissemination. In cases of resectable disease, imaging studies must be thoroughly studied prior to undertaking resection to anticipate the potential need for variations in operative conduct (e.g., areas of vascular invasion by tumor or aberrant vascular anatomy). Common sites of metastatic spread are the lymph nodes, the liver, and peritoneal surfaces. The presence of enlarged, rounded, or centrally necrotic lymph nodes is suggestive of nodal metastasis. Hepatic metastases typically present as low-attenuation rounded lesions within the liver, and peritoneal metastases often appear as areas of abnormal nodularity along the omentum or peritoneal surfaces or as unexplained free fluid within dependent portions of the abdominopelvic cavity (the perihepatic and hepatorenal spaces and true pelvis). Positron emission tomography (PET) is of limited utility in the staging of periampullary and pancreatic adenocarcinoma because of the potential for false negative studies.

Endoscopic modalities are an important component of the diagnostic algorithm for patients with periampullary adenocarcinoma. Endoscopic retrograde cholangiopancreatography (ERCP) is a means of obtaining cholangiographic imaging of distal biliary obstructive lesions, collecting brushings of the distal biliary obstructive lesion for cytologic analysis, and correcting biliary obstruction with the placement of transpapillary endobiliary stents. Patients presenting with obstructive jaundice may benefit from biliary decompression. In addition to restoring hepatic function and ameliorating the complications of impaired biliary excretion (e.g., coagulopathy resulting from impaired bile-mediated intestinal absorption of vitamin K), correction of obstructive jaundice provides significant palliation of pruritus. For patients with resectable disease, these potential benefits should be weighed against the risk of increased postoperative infectious complications that has been associated with preoperative biliary decompression.\(^{1,3,14}\) Therefore, preoperative stent placement should be used selectively for patients with marked hyperbilirubinemia or physiologic consequences of jaundice (cholangitis, coagulopathy, intractable pruritus). If stenting is necessary in patients who will undergo resection, preference is given to placement of temporary plastic stents. Plastic endobiliary stents are prone to occlusion and require repeat endoscopic exchanges every 2 to 3 months; therefore, patients who are unlikely to undergo operative resection or who will likely require a prolonged course of preoperative therapy should receive self-expanding metallic stents, whose average patency approaches 1 year. In contrast to percutaneous transhepatic approaches to biliary stent insertion (in which stents are inserted transcutaneously into the intrahepatic biliary tree and across the ampulla), ERCP has the advantage of avoiding the discomfort and care associated with external biliary drains.

Endoscopic ultrasonography (EUS) involves the application of a small ultrasonography probe against the pancreas through the adjacent gastric or duodenal wall. EUS permits precise visualization of tumors, surrounding vascular structures, biliary and pancreatic ducts, and peripancreatic lymph nodes. In this way, EUS can establish preoperative tumor (uT) and nodal (uN) staging. This can be especially useful in the evaluation of adenomatous periampullary polyps. Ultrasonographic evidence of tumor infiltration beyond the mucosa of the duodenum or ampulla can be indicative of invasive disease. In addition, EUS enables safe and accurate image-guided fine-needle aspiration or core-needle biopsy of pancreatic tumors. Although the large majority of patients presenting with a pancreas mass and painless jaundice will ultimately be found to have pancreatic adenocarcinoma, histologic verification of this diagnosis may be necessary for patients who require preoperative or definitive chemotherpay and/or chemoradiation therapy.

Another procedure used for diagnostic staging is laparoscopic exploration. An outpatient staging laparoscopy may be useful in cases of periampullary or pancreatic adenocarcinoma where there is a high suspicion for subradiologic...
intraperitoneal metastases (as suggested by findings such as nonphysiologic intraperitoneal free fluid or markedly elevated CA19-9 levels in the absence of jaundice). Staging laparoscopy is also useful in cases of borderline resectable or locally advanced pancreas adenocarcinoma as identification of metastatic disease may obviate the role of local radiation therapy. In these circumstances, laparoscopic exploration begins with a close examination of the retroperitoneal cavity for ascites fluid, hepatic lesions, omental lesions, and peritoneal lesions. Following placement of a camera port, a second port is inserted, through which an instrument may be used to assist in visualization of the undersurfaces of the liver and peritoneal surfaces. If ascites fluid is identified, samples are aspirated and submitted for cytologic analysis. If ascites fluid is not seen, the peritoneal surfaces are irrigated with saline solution, and the effluent is collected and submitted for cytologic analysis. The presence of even microscopic quantities of metastatic adenocarcinoma cells from peritoneal washings has been shown to carry as much prognostic significance as visible foci of metastatic disease. Metastatic deposits most commonly appear as firm, white nodular masses, and any suspicious lesions are biopsied. Peritoneal washings are obtained prior to obtaining biopsies so as to avoid potential cytologic contamination with blood cells resulting from bleeding at biopsy sites.

THERAPY

Traditional treatment modalities for patients with periampullary adenocarcinoma are surgical resection, chemotherapy, and radiation therapy. The types of modalities employed and the sequence in which they are used are selected based on stage and local extent of disease, patient comorbidity, and institutional preferences. The intent of each treatment modality can be simplistically outlined as follows: surgical resection is used for removal of primary tumors and regional lymph nodes in circumstances where distant metastatic disease is not demonstrable; chemotherapy is used to treat suspected or demonstrable metastatic disease; and radiation therapy is used when cytoreduction of local tumors is desirable for purposes of either increasing the likelihood of a margin-negative resection or palliating tumor mass-related symptoms. As outlined below, the propensity for systemic dissemination of pancreatic and periampullary adenocarcinoma usually requires the use of multimodality therapy that combines local therapies such as surgical resection and radiation therapy with systemic chemotherapy. Specific operative procedures for pancreatic adenocarcinoma and periampullary adenocarcinoma are outlined below; specific strategies for the implementation of surgical resection, chemotherapy, and radiation therapy are outlined for each subtype of periampullary adenocarcinoma.

Operative Procedures

The intent of surgical resection for pancreatic and periampullary adenocarcinoma is to achieve maximal therapeutic and diagnostic benefit through complete, margin-negative tumor extirpation and thorough sampling of local lymph nodes. As a result, limited and local forms of tumor resection such as ampullectomy, segmental pancreactectomy, or tumor enucleation have no general role in the management of pancreatic and periampullary adenocarcinoma. Rather, primary options for operative resection are pancreaticoduodenectomy and distal (left) pancreatectomy. Prior to undertaking operative resection, preoperative imaging studies must be comprehensively reviewed; evidence of vascular invasion by tumor or variations in vascular and/or/biliary anatomy may predict the need for subtle but important changes in operative strategy and conduct.

Pancreaticoduodenectomy

Pancreaticoduodenectomy is the operative procedure of choice for resectable cases of periampullary adenocarcinoma or pancreatic adenocarcinoma localized to the pancreatic head or uncinate process. Because of the intimate anatomic interrelationship between the pancreatic head, duodenum, and distal biliary system, all three structures must be removed together, and operative reconstruction is necessary to restore intestinal, biliary-enteric, and pancreatic-enteric continuity.

Operative Conduct

Open pancreaticoduodenectomy can be performed through a vertically oriented upper midline or transversely oriented epigastric or bilateral subcostal incision. The specific sequence of steps used in the conduct of this operation can be variable, but the first step should always be a thorough exploration of the abdominopelvic contents; identification of previously undetected metastatic disease is a contraindication to proceeding with resection. In cases of primary tumors arising in the head of the pancreas, 15 to 20% of patients have metastatic disease that is not identified on preoperative cross-sectional imaging. Therefore, initial exploration can be performed laparoscopically so as to avoid the potential morbidity of a laparotomy incision if metastatic disease is detected and resection is not indicated. If no evidence of distant metastasis is found, focused exploration is undertaken to look for regional spread that might also alter the decision to undertake tumor resection. The celiac axis is palpated and inspected for evidence of nodal metastases, and suspiciously enlarged and firm lymph nodes may be removed for frozen pathologic analysis. Positive lymph nodes in the field of resection are not a contraindication to resection; however, nodal metastases around the celiac axis, ligament of Treitz, and other distant areas carry nearly the same negative prognostic weight as more distant foci of metastatic disease. In addition, the transverse colon is elevated, and the root of the small bowel mesentery is inspected; evidence of tumoral extension across the transverse mesocolon at this location may indicate the presence of locally advanced disease.

If no contraindication to resection is identified, the hepatic flexure is mobilized and the transverse colon is separated from the pancreas and duodenum, exposing the first, second, and third portions of the duodenum. With the transverse colon reflected caudally, a generous Kocher maneuver is executed, detaching the duodenum and pancreatic head from the retroperitoneum. This dissection continues along the right lateral aspect of the porta hepatitis, and the inferior vena and left renal vein are exposed [see Figure 6]. Mobilization of the retroperitoneal attachments of the duodenum
Kocher maneuver. Once the duodenum is exposed by dissecting the transverse mesocolon off the duodenum and stomach, the lateral peritoneal attachments of the duodenum and portal hepatitis are incised. The duodenum and head of pancreas are dissected off the inferior vena cava and aorta along the avascular retro-duodenal plane. This dissection can be taken all the way to the ligament of Treitz. Palpation of the posterior aspect of the pancreatic head permits evaluation of the anatomic relationship between a periampullary tumor and the superior mesenteric vein and superior mesenteric artery.

in this manner can usually be completed all the way to the ligament of Treitz. By dissecting along the avascular plane between the transverse mesocolon and duodenum and pancreas, the superior mesenteric vein is identified below the level of the pancreatic head, and the uncinate process is dissected off the right lateral aspect of the superior mesenteric vein. The pancreatic head is palpated for evidence of tumoral invasion into the superior mesenteric vein and artery.

The peritoneum overlying the porta hepatitis is incised to identify the common bile duct and the junction of the common hepatic artery and proper hepatic artery. If present, the endobiliary stent can be palpated within the lumen of the typically dilated common bile duct. The right gastric artery is divided, and the common hepatic artery, proper hepatic artery, and gastroduodenal artery are exposed. The gastroduodenal artery should be dissected distally over the anterior aspect of the pancreatic neck. Transient occlusion of the gastroduodenal artery should result in no impedance of flow through the proper hepatic artery; interruption of flow may indicate that the anatomy has not been properly delineated (e.g., one may have misinterpreted the proper hepatic artery to be the gastroduodenal artery) or that chronic occlusion of the celiac artery has caused the hepatic arterial inflow to rely on reversed flow from the superior mesenteric artery via the gastroduodenal artery. If no impedance of flow is noted, the gastroduodenal artery should be securely ligated and divided as far from the common and proper hepatic arteries as possible. An unusual but potentially devastating complication of pancreaticoduodenectomy is hemorrhage from the ligated gastroduodenal artery; preserving a stump of the gastroduodenal artery may permit interventional radiologic placement of embolization particles into this vessel without interrupting flow through the proper hepatic artery. Further dissection is undertaken to identify the portal vein, and blunt dissection is undertaken along the anterior aspect of the portal vein behind the neck of the pancreas; obstruction encountered during this dissection may indicate the presence of tumoral abutment or invasion of the portal vein. The plane between the common hepatic duct and portal vein is developed. A cholecystectomy may also be performed at this time, and the common hepatic duct is circumferentially dissected above the level of the cystic duct insertion. The common hepatic duct may be sharply divided at this time, after which a circumferential margin of common hepatic duct should be excised for frozen-section pathologic analysis; if carcinoma is present, an additional segment of proximal common hepatic duct is
taken. This is especially important if a distal cholangiocarcinoma is suspected. If present, the endobiliary stent can be removed. The distal common hepatic duct is ligated with a marking stitch for pathologic orientation, and the proximal common hepatic duct is temporarily occluded with a small clamp so as to avoid bile spillage. The distal common hepatic duct is mobilized off the portal vein, with care taken to incorporate the portocaval lymph node with the planned resection specimen. Even if a replaced or accessory right hepatic artery was not visualized by preoperative imaging, the existence of this aberrant vessel should be excluded by palpating the right posterolateral aspect of the portal vein and common bile duct for arterial pulsation. If present, care must be taken to identify and avoid injury to this important structure.

Blunt dissection of the retropancreatic tunnel over the portal vein and superior mesenteric vein is completed by exposing the superior mesenteric vein below the level of the pancreatic neck [see Figure 7]. To facilitate this exposure, the gastrocolic ligament is incised and separated from the transverse mesocolon. Access to the superior mesenteric vein is improved by dividing the left gastroepiploic vein just proximal to its point of insertion on the superior mesenteric vein. Of note, the left gastroepiploic vein often forms a short common channel with the middle colic vein before draining into the superior mesenteric vein, and care is taken to avoid division of the middle colic vein. Blunt dissection is then undertaken over the anterior aspect of the superior mesenteric vein from below the neck of the pancreas, after which a vessel loop may be placed around the pancreatic neck. Access to the pancreatic neck is facilitated by dividing the distal stomach (the so-called classic pancreaticoduodenectomy) or by dividing the proximal duodenum distal to the pyloric musculature (the pylorus-preserving pancreaticoduodenectomy). Stay sutures can be placed along the superior and inferior aspects of the pancreatic neck on either side of the planned transection plane to facilitate its elevation off the underlying portal vein and superior mesenteric vein.

The ligament of Treitz is then identified below the level of the transverse mesocolon, and the proximal jejunum is divided 10 to 20 cm distal to the ligament of Treitz. The mesentery of the proximal jejunum is divided, and division of the ligament of Treitz is completed, after which the proximal jejunum and distal duodenum may be passed.
behind and to the right of the superior mesenteric vessels. By reflecting the duodenum to the right, the uncinate process can be dissected off superior mesenteric vein, with care taken to divide the inferior pancreaticoduodenal vein, which enters into the pancreas, and to preserve the first jejunal vein, which typically courses underneath the uncinate process and around the superior mesenteric artery.

The pancreatic neck is divided as the stay sutures along the pancreatic neck are elevated so as to avoid injury to the portal vein and superior mesenteric vein. If tumoral invasion into these venous structures is present, exposure of the area of venous involvement usually requires partial division of the pancreatic neck. In these circumstances, great care is taken during division of the pancreatic neck to avoid injury to the portal vein or superior mesenteric vein. The region of the pancreatic duct is divided sharply to avoid thermal injury to this structure. Bleeding points along the pancreatic parenchyma can be controlled with diathermy or suture ligation. After the pancreatic neck is divided, a margin of pancreatic neck is sharply excised and submitted for frozen-section pathologic analysis; if carcinoma is present, an additional segment of pancreas is taken. The right lateral aspect of the portal vein and superior mesenteric vein is then dissected off the pancreas. The final plane of dissection is the retroperitoneal margin. To maximize the chances of a margin-negative resection, this dissection is undertaken along the right lateral aspect of the superior mesenteric artery. By reflecting the planned resection specimen to the right, the superior mesenteric artery is effectively pulled to the right of the superior mesenteric vein, permitting clear visualization of this final resection margin [see Figure 8]. All lymphovascular structures are divided between clips or ligatures, with care taken to avoid injury to the superior mesenteric artery. If present, the replaced or accessory right hepatic artery must be carefully preserved during this retroperitoneal dissection.

In cases of portal vein or superior mesenteric vein invasion, the area of venous involvement is fully exposed. Vessel loops and vascular clamps are used to obtain control of all venous inflow and outflow after systemic heparinization; this typically requires control of all trunks of the superior mesenteric vein, splenic vein, portal vein, and possibly the left gastric vein and inferior mesenteric vein. The area of venous involvement is sharply excised, after which venous reconstruction is completed. Depending on the extent of venous resection needed, reconstruction can be performed using primary closure, a bovine pericardial patch, or autologous saphenous vein or left renal vein or internal jugular vein graft. It is important to orient the resected specimen carefully for pathologic assessment, using sutures or colored ink to mark the common hepatic duct, portal vein/superior mesenteric vein margin, superior mesenteric artery margin, posterior margin, and pancreatic neck margin for the pathologist.

After ensuring hemostasis, reconstruction is initiated by passing the distal jejunal stump through a defect fashioned in an avascular portion of the transverse mesocolon. The jejunum is positioned to reach the transected common hepatic duct and pancreatic neck without tension. The hepaticojejunostomy is typically constructed in an end-to-side manner using a running or interrupted absorbable suture. The pancreaticojejunostomy is constructed either in an end-to-side fashion (by creating a duct-to-mucosa anastomosis between the pancreatic duct and a small jejunotomy followed by a series of reinforcing sutures between the pancreatic parenchyma and the jejunal serosa) or in an end-to-end fashion (by inverting the stump of the pancreas into the cut end of the jejunum) [see Figure 9]. The final anastomosis is the gastrojejunostomy (for classic pancreaticoduodenectomy) or duodenojejunostomy (for pylorus-preserving pancreaticoduodenectomy), which can be performed in an antecolic or retrocolic fashion. Although there is mixed evidence in support of routine intraoperative drain placement, most surgeons place drains adjacent to the hepaticojejunostomy and pancreaticojejunostomy anastomoses to monitor for and potential control of anastomotic fistulae and a nasogastric tube that can typically be removed very early in the postoperative course.15,16

**Outcomes**

Despite numerous improvements that have been made in perioperative management in recent decades, pancreaticoduodenectomy is still associated with significant risks of postoperative mortality and morbidity. Nationally, the risk of operative mortality following pancreaticoduodenectomy is as high as 6 to 7%. However, there appears to be an inverse relationship between hospital volume and operative mortality, with high-volume centers demonstrating operative mortality of 1 to 3%.17,18 Operative morbidity rates remain high; when operative complications are strictly defined and recorded, the risk of major postoperative complications is still on the order of 30%.19 Two complications that are specifically associated with pancreaticoduodenectomy are pancreatic fistula and delayed gastric emptying.

Pancreatic fistula is defined as leakage of pancreatic fluid (generally defined by an amylase level greater than three times that of serum on or after postoperative day 3) from either the pancreatic-enteric anastomosis or the cut surface of the pancreas. Risk factors that have been consistently identified for pancreatic fistula are the presence of a small pancreatic duct size and a soft pancreatic parenchymal texture. However, there is no consistent evidence that the technique of anastomosis (e.g., invaginated pancreaticojejunostomy versus duct-to-mucosa pancreaticojejunostomy or pancreaticojejunostomy versus pancreaticogastrostomy) meaningfully alters the likelihood of pancreatic fistula. Management of pancreatic fistulae centers on the ability to adequately control the fistula so as to avoid the accumulation of undrained fluid. This may require the retention and/or placement of drains around the region of the pancreatic-enteric anastomosis; in rare circumstances, reoperative exploration may be needed to adequately drain a large and uncontrolled pancreatic fistula. Undrained collections of pancreatic fluid can result in pain, fevers, and sepsis. A particularly dreaded complication of pancreaticoduodenectomy is gastroduodenal artery hemorrhage; undrained amylase-rich fluid from the pancreatic-enteric anastomosis can occasionally erode the ligated gastroduodenal artery stump, resulting in significant and potentially life-threatening hemorrhage requiring interventional radiologic embolization or stenting or reoperation. The International Study Group of Pancreatic Surgery recently developed a pancreatic fistulae...
Figure 8  Pancreatoduodenectomy. (a) The planned resection specimen is reflected to the right as the superior mesenteric vein is reflected to the left. This maneuver exposes the retroperitoneal attachments of the pancreas, which are divided along the right lateral aspect of the superior mesenteric artery. (b) Intraoperative photograph of anatomy depicted in (a) following pancreatic neck transection. (c) Intraoperative photograph of anatomy depicted in (a) immediately following specimen removal.

Figure 9  Pancreatoduodenectomy. The two options for pancreaticojejunostomy construction are (a) the end-to-side duct-to-mucosa anastomosis and the (b) end-to-end invaginated anastomosis.

Scientific American Surgery
Although it is generally assumed that delayed gastric emptying is caused by mechanical obstruction, the pathogenesis of delayed gastric emptying remains unclear, but it results in slow resumption of oral intake. Management often requires prolonged nasogastric decompression, intravenous hydration, parenteral, nasojejunal, or jejunal tube-based nutritional support; and liberal use of prokinetic agents such as metoclopramide or erythromycin. The onset of pancreatic fistula appears to be a risk factor for delayed gastric emptying. Numerous strategies involving alterations of the intestinal anastomosis and prophylactic prokinetic agents have been devised to minimize the likelihood of delayed gastric emptying, but none has consistently shown efficacy. As with pancreatic fistula, the International Study Group of Pancreatic Surgery has developed a grading system to describe the severity of delayed gastric emptying [see Table 6]. When classified in this manner, the incidence of grade A, B, and C pancreatic fistulae after pancreaticoduodenectomy is generally reported to be in the range of 15%, 10%, and less than 5%, respectively.

Table 6 International Study Group of Pancreatic Surgery Definition of Postoperative Pancreatic Fistula after Pancreatic Surgery

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Reappearance</th>
<th>Need for TPN, TF, Antibiotics, IR Drainage</th>
<th>Fluid Collection on US/CT (if obtained)</th>
<th>Persistent Drainage &gt; 3 wk</th>
<th>Reoperation</th>
<th>Death Related to POPF</th>
<th>Signs of Infection</th>
<th>Sepsis</th>
<th>Readmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Well</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>B</td>
<td>Often well</td>
<td>Yes/no</td>
<td>Usually yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes/no</td>
<td>Yes/no</td>
</tr>
<tr>
<td>C</td>
<td>Ill</td>
<td>Yes/yes</td>
<td>Yes/yes</td>
<td>Yes/yes</td>
<td>Yes/no</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes/no</td>
</tr>
</tbody>
</table>

CT = computed tomography; IR = interventional radiology; POPF = postoperative pancreatic fistula; TF = tube feedings; TPN = total parenteral nutrition; US = ultrasonography.

Table 7 International Study Group of Pancreatic Surgery Definition of Delayed Gastric Emptying after Pancreatic Surgery

<table>
<thead>
<tr>
<th>DGE Grade</th>
<th>Nasogastric Tube Required</th>
<th>Unable to Tolerate Solid Oral Intake by POD</th>
<th>Vomiting/Use of Distention</th>
<th>Prokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4–7 days or reinsertion &lt; POD</td>
<td>7</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>B</td>
<td>8–14 days or reinsertion &gt; POD</td>
<td>14</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>C</td>
<td>&gt; 14 days or reinsertion &gt; POD 14</td>
<td>21</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

DGE = delayed gastric emptying; POD = postoperative day.
analyses, pylorus preservation has been associated with a slight increase in the incidence of early postoperative delayed gastric emptying.  

Several modifications have focused on the pancreatic-enteric anastomosis. As stated earlier, two common methods for performing the pancreaticojunostomy anastomosis are the duct-to-mucosa anastomosis and the invaginated anastomosis [see Figure 9]. In the former, a small jejunalostomy is made just opposite from the pancreatic duct, and fine absorbable sutures are used to create an end-to-side (pancreas-to-jejunum) anastomosis; additional sutures are used to imbricate the pancreatic neck to the jejunum. In the latter, an end-to-end anastomosis is fashioned by placing one row of sutures between the cut end of the pancreatic neck and the lumen of the jejunum and a second row of sutures between the pancreatic body and the cut end of the jejunum; in this way, the cut end of the pancreas is invaginated into the cut end of the jejunum. Comparative analyses of these two anastomotic techniques have not consistently proven one to be better than the other in terms of the likelihood of postoperative pancreatic fistula. Yet another modification has been construction of a pancreaticogastrostomy instead of a pancreaticojunostomy; in this technique, the pancreatic neck is mobilized so as to permit an anastomosis between the pancreas and the posterior aspect of the stomach. Although data are mixed, the pancreaticogastrostomy has not yet been definitively shown to be preferable to the pancreaticojunostomy.  

As outlined above, the gastrojejunalostomy or duodenojejunostomy can be performed in an antecolic or retrocolic fashion. Several studies have suggested that the antecolic reconstruction is associated with a lower incidence of delayed gastric emptying; however, this conclusion has not been reached in all analyses of this subject.  

Recent modifications have focused on the development of minimally invasive approaches to pancreatidudenedectomy. Laparoscopic-assisted, robotic-assisted laparoscopic, and total laparoscopic pancreatidudenedectomy have all been shown to be possible and, when performed in well-selected cases by surgeons experienced in both pancreatic and laparoscopic surgery, associated with comparable outcomes. The actual conduct of the operation is similar to that of the open approach, with a heavier reliance on energy devices and clips for tissue sealing and division.  

**DISTAL (LEFT) PANCREATECTOMY**  

Distal (left) pancreatectomy is performed for resection of tumors in the pancreatic neck, body, or tail. When performed for adenocarcinoma, concomitant en bloc splenectomy is routinely performed.  

**Operative Conduct**  

Open distal pancreatectomy can be performed through a vertically oriented upper midline or transversely oriented epigastric or left subcostal incision. When performed for pancreatic adenocarcinoma, an initial staging laparoscopy is often performed to exclude the possibility of small peritoneal metastases that may have eluded preoperative diagnostics. If no evidence of metastatic disease is identified, the pancreas is exposed by entering the lesser sac through the gastrocolic and hepatogastric ligaments. The gastrocolic ligament is divided all the way to the fundus of the stomach, during which the short gastric vessels are divided. The lienocolic ligament is divided, permitting downward retraction of the left hemocolon and exposure of the splenic hilus.  

Avascular adhesions between the posterior aspect of the stomach and the anterior aspect of the pancreas are divided. The tumor is localized by palpation or, in the case of small tumors, intraoperative ultrasonography. Dissection begins at a point well to the right of the tumor, where the retroperitoneum is incised along the superior and inferior aspects of the pancreas. Blunt dissection is undertaken to encircle the pancreas along the point of planned parenchymal transection. For tumors in the pancreatic neck or body, this may require retropancreatic dissection along the anterior aspect of the portal vein and superior mesenteric vein in a manner similar to that performed during pancreaticoduodenectomy. Prior to dividing the pancreas, it is preferable to control the splenic artery and vein. Exposure of the splenic artery is usually easier as it is typically separate from the superior aspect of the pancreatic neck. Once divided, the spleen may be compressed so as to “autotransfuse” blood out of the spleen and back through the splenic vein. Exposure of the splenic vein usually requires careful dissection as it is typically adherent against the superoposterior aspect of the pancreas. Numerous venous tributaries are found along the course of the splenic vein. The pancreas can then be transected using a stapler, sharp transection, or energy-based devices. There is preliminary evidence to suggest that reinforcement of staple lines with mesh may decrease the incidence of fistula following stapled transection.  

Frozen-section analysis of the pancreatic transection margin is performed at this point; if evidence of margin positivity is encountered, an additional segment of pancreas is mobilized and divided. When nonstapled transection is performed, the cut end of the remnant pancreas is sutured so as to minimize the risk of pancreatic fistula. When the line of pancreatic parenchymal transection is at the neck of the pancreas, it is generally easier to divide the pancreas first, after which the origin of the splenic artery and the insertion of the splenic vein into the superior mesenteric vein may be exposed and divided.  

Dissection then proceeds from right to left toward the splenic hilus by incising the retroperitoneum along the superior and inferior aspects of the pancreas. Depending on the site of parenchymal transection and the venous anatomy, the inferior mesenteric vein may require division if it drains into the splenic vein and is encountered during this dissection. Along the inferior aspect of the pancreas, care is taken to avoid injury to the adjacent duodenum. Posteriorly, the optimal plane of dissection follows the anterior aspect of the left adrenal gland and kidney. As dissection proceeds to the spleen, the avascular diaphragmatic attachments of the spleen are divided, after which elevation of the spleen will expose the splenic hilus. Following removal, the specimen is passed off the operative field and the splenic bed, retroperitoneum, and splenic vessels are inspected for hemostasis. Most surgeons place a drain near the cut end of the remnant pancreas, but nasogastric tubes are usually not necessary.
Outcomes

In comparison with pancreaticoduodenectomy, published rates of operative mortality following distal pancreatectomy are generally in the range of 1%.\(^2\) However, as with pancreaticoduodenectomy, the potential for postoperative morbidity remains significant. A relatively common complication following distal pancreatectomy is postoperative pancreatic fistula. Unlike pancreaticoduodenectomy, pancreatic fistula is due to failure of complete occlusion of the cut surface of the pancreas. Most series describe an incidence of clinically significant pancreatic fistula of 10 to 20% following distal pancreatectomy.\(^2\)

Operative Modifications

A number of studies have sought to evaluate the optimal method of pancreatic transection. Some studies have identified lower rates of pancreatic fistula with the use of stapling devices, but this finding has not been universally consistent. Some surgeons perform the dissection from left to right, beginning with splenic mobilization. A potential advantage of performing the dissection from right to left is the opportunity for early vascular control and more accurate access to the proper posterior plane of dissection along the anterior aspects of the left adrenal gland and left kidney. Although several methods of splenic preservation are available to the surgeon undertaking resection of the left pancreas, these techniques are not recommended for the treatment of pancreatic adenocarcinoma as these approaches increase the likelihood of margin positivity and decrease the likelihood of satisfactory nodal staging.

There has been a greater maturity of experience with laparoscopic distal pancreatectomy than with laparoscopic pancreaticoduodenectomy. Indeed, minimally invasive approaches to distal pancreatectomy have matured to the point where numerous comparative analyses have established laparoscopic techniques as a very reasonable and standard alternative to traditional open pancreatectomy.\(^2\) Retrospective series indicate that laparoscopic distal pancreatectomy may be associated with favorable outcomes in terms of intraoperative bleeding and postoperative complications compared with open distal pancreatectomy, with no measurable oncologic disadvantage in terms of margin clearance or lymph node yield. A number of technical variants, including laparoscopic-assisted, robotic-assisted laparoscopic, and total laparoscopic distal pancreatectomy, have been well described. Unlike pancreaticoduodenectomy, distal pancreatectomy does not usually require anastomotic construction; as such, the emphasis on robotic assistance has been less pronounced.

Financial Disclosures: Clifford S. Cho, MD, FACS, has no relevant financial relationships to disclose.

References


Acknowledgments

Figure 5 Christine Kenney
Figure 6 Susan Brust, CMI. Revised and updated by Christine Kenney.
Figure 7a Tom Moore
Figures 8a and 9 Tom Moore. Adapted from originals by Corinne Sandone.