TUMORS OF THE PANCREAS, BILIARY TRACT, AND LIVER

Steven M. Strasberg, M.D., F.A.C.S., and David C. Linehan, M.D., F.A.C.S.

Numerous types of tumors affect the pancreas, the biliary tree, and the liver. Each year, hundreds of papers are published on the topics of pancreatic, biliary, and hepatic cancers. Accordingly, in this chapter, we concentrate on essential principles rather than details. In particular, we focus on common malignant tumors, addressing benign tumors and uncommon tumors only insofar as they are important in differential diagnosis.

When a patient presents with an apparent cancer of the pancreas, the biliary tree, or the liver, the surgeon must attempt to answer the following three important questions:

1. What is the diagnosis?
2. What is the surgical stage of the disease—that is, is the tumor resectable?
3. What is the operative rationale that will encompass the disease and produce a margin-free resection (and, for pancreatobiliary cancers, an N1 resection)?

These questions form the underpinning for the process of investigation and management. In what follows, we describe our approach to each of the cancers in these terms.

Pancreatic Cancer

DUCTAL ADENOCARCINOMA

Adenocarcinoma of the Head of Pancreas

Adenocarcinoma of the pancreatic head is common (with 30,000 new cases occurring annually in the United States) but remains one of the hardest GI cancers to cure. In the past 25 years, the efficacy of surgical treatment has improved dramatically, but 5-year actual survival rates in patients who have undergone resection are still low (about 15%).

Cancer of the head of the pancreas is the prototypical tumor that causes painless jaundice; however, other cancers that obstruct bile ducts also cause jaundice, including extrahepatic bile duct cancers, gallbladder cancers, ampullary malignancies, and some duodenal cancers. Some of the following discussion is generalized with an eye to determining the diagnosis in patients presenting with obstructive jaundice [see 5.3 Jaundice].

Clinical evaluation History. The classic presentation of cancer of the head of the pancreas is unremitting jaundice, usually accompanied by dark urine, light stool, and pruritus. Darkening of the urine or pruritus is often the first symptom, and scleral icterus frequently is first noted by family members or coworkers. The pruritus is often severe. The jaundice sometimes is painless but more frequently is associated with epigastric pain. This pain usually is not severe; severe, acute pain is more often associated with other conditions that may cause jaundice (e.g., cholelithiasis and pancreatitis). Back pain suggests that the tumor has invaded tissues outside the pancreas and is unresectable.

Significant weight loss (≥ 10% of body weight) is common even when the pancreatic cancer is resectable.

In some patients, steatorrhea or diarrhea from obstruction of the pancreatic duct, weight loss, pain, or a combination of these is the presenting symptom, rather than jaundice. A presentation with steatorrhea or diarrhea is usually the result of a tumor in the uncinate process that obstructs the pancreatic duct but not the bile duct. Often, these symptoms are overlooked until the tumor extends and causes jaundice. About 5% of patients have a history of diabetes of recent onset. Migratory thrombophlebitis (the Trousseau sign) is uncommon and usually signifies metastatic disease. Pancreatobiliary malignancies cause biliary obstruction, but such obstruction is not commonly associated with biliary tract infection before instruments have been employed in the biliary tree. Therefore, in patients presenting with cholangitis who have not undergone biliary tract instrumentation, other diagnoses should be suspected. Patients with pancreatic cancer may also present with acute pancreatitis as the first manifestation. Vomiting and GI bleeding are uncommon presenting symptoms and suggest the presence of advanced tumors that are obstructing or eroding the duodenum.

Laboratory tests. Serum concentrations of the tumor marker CA 19-9 are often elevated in patients with pancreatic or biliary adenocarcinomas.

Investigative studies Laboratory tests. Liver function tests (LFTs) are of limited value in diagnosis. The serum bilirubin level is elevated in jaundiced patients, with the direct fraction exceeding 50%. The serum alkaline phosphatase level is almost always elevated when the bile duct is obstructed, and levels three to five times normal are common. Aminotransferase levels usually are moderately elevated as well. Very high aminotransferase levels suggest a hepatocellular cause of jaundice, usually viral, though impaction of a stone in the bile duct can cause transient rises in serum aspartate aminotransferase (AST) to levels higher than 1,000 IU/ml. By themselves, LFTs cannot effectively distinguish among jaundice arising from a hepatocellular cause (e.g., viral hepatitis or drug-induced cholestasis), jaundice resulting from a disease of microscopic bile ducts (e.g., primary biliary cirrhosis), and jaundice caused by any of the malignancies that obstruct the major bile ducts. To make this distinction, radiologic imaging tests are required [see Imaging, below].

Serum concentrations of the tumor marker CA 19-9 are often elevated in patients with pancreatic or biliary adenocarcinomas. The upper limit of the normal range is 37 U/ml. Concentrations higher than 100 U/ml are highly suggestive of malignancy, but elevations between 37 and 100 U/ml are less specific. Serum levels generally reflect the extent of the tumor: small tumors (< 1 cm in diameter) are rarely associated with levels higher than 100 U/ml,
fluence, as evidenced by the “beaking” of the vein at that point.

The tumor is invading the right side of the portosplenic confluence, as evidenced by the “beaking” of the vein at that point.

**Figure 1** Shown is a typical hypoattenuating cancer of the pancreatic head. The tumor is invading the right side of the portosplenic confluence.

**Figure 2** In the same patient as in Figure 1, pancreatic duct dilation is apparent in the body of the pancreas, with atrophy of the parenchyma.

whereas very high levels (> 1,000 U/ml) suggest metastatic disease. High levels may also accompany cholangitis. Measurement of CA 19-9 concentrations may be employed to detect recurrences in patients who have elevated CA 19-9 levels that return to normal after tumor resection; a second rise in the CA 19-9 level in the follow-up period is indicative of recurrence in most cases.

**Imaging.** Several different imaging tests may be used for diagnostic purposes in jaundiced patients, including computed tomography, magnetic resonance imaging, endoscopic retrograde choledochopancreatography (ERCP), endoscopic ultrasonography (EUS), and transabdominal ultrasonography. The technical advances in imaging achieved over the past few years are remarkable. CT and MRI, which only a few years ago were limited to axial images, on one hand, and fuzzy MRI cholangiopancreatography (MRCP), on the other, can now provide high-quality images of blood vessels and ducts and their anatomic relation to tumors. These images can even be projected in three dimensions if desired.

Selection of appropriate imaging tests in a jaundiced patient is influenced by patient characteristics and by the symptoms observed. For instance, the type and order of investigations appropriate for an older patient presenting with obstructive jaundice, who is likely to have a malignancy, differ from those appropriate for a young woman with severe pain, who is more likely to have choledocholithiasis. The best initial imaging test in a patient in whom malignancy is suspected is either a fine-cut (3 mm between slices) three-phase (no-contrast phase, arterial phase, and venous phase) helical (spiral) CT scan or a high-quality MRI scan. Although MRI has the advantage of being able to provide a choangiogram (i.e., with MRCP), small and medium-sized radiologic facilities currently tend to be more skilled at CT than at MRI; this difference should be taken into account when the first test is ordered. High-quality MRI scanners and the very latest generation of CT scanners are capable of providing choangiograms and angiograms, as well as axial images.

The typical pancreatic cancer appears as a lucent zone in the pancreatic head [see Figure 1], associated with upstream dilatation of the bile ducts and the gallbladder. Often, the pancreatic duct is also obstructed. As a result, the pancreatic duct may be dilated in the tail, body, and neck of the pancreas, with dilatation terminating sharply at the edge of the tumor. Pancreatic duct dilatation is often accompanied by atrophy of the body and the tail of the pancreas [see Figure 2].

When a jaundiced patient is discovered to have a typical-appearing localized cancer of the pancreatic head on CT scanning, no further diagnostic tests are needed, and operative management should be the next step. Tissue diagnosis is unnecessary. Negative biopsy results rarely change the therapeutic approach, and in that they are sometimes falsely negative, they are potentially misleading. Furthermore, omitting biopsy eliminates the small risk of tumor implantation in the needle tract. Selection of axial imaging as the first test often renders diagnostic ERCP, which is a more invasive test, unnecessary as well. Cholangiography also is not required for staging pancreatic head tumors [see Surgical Staging, below]. The advantages of starting with axial imaging in jaundiced patients with suspected cancer are discussed in greater detail elsewhere [see Biliary Tract Cancer, Extrahepatic Cholangiocarcinoma, Upper-Duct Cholangiocarcinoma, Investigative Studies, below].

**Additional diagnostic imaging for atypical CT or MRI findings.** In many patients with adenocarcinoma of the pancreatic head, the typical CT findings are absent and additional diagnostic imaging is required. Such patients may be categorized into two groups: those with an atypical mass and those with no mass on axial imaging. In either case, before ordering additional tests, it is appropriate to determine whether the CT scan is of adequate quality. For example, the scan may have been performed without contrast, the arterial and venous phases may not have been captured appropriately, or the slice thickness may have been too great for precise visualization of the head of the pancreas. Small adenocarcinomas may be missed when the venous phase is timed poorly, especially if slice thickness is 5 mm or greater, and masses that appear atypical initially may exhibit a typical appearance when the CT scan is optimized. Neuroendocrine cancers commonly display atypical arterial-phase enhancement, which will be missed if the scan is mis timed. In our experience, about 40% of referred patients who underwent
CT scanning before arrival require a so-called pancreas protocol CT scan (i.e., a fine-cut three-phase helical scan) when they are first seen; in many of these cases, the second CT scan yields important diagnostic findings.

When no mass is present in a jaundiced patient with a periampullary tumor or another focal obstructing process (e.g., pancreatitis), the CT scan usually shows bile duct dilatation extending down to the infrapancreatic portion of the duct. The dilatation may terminate anywhere from the upper border of the pancreas to the duodenum, depending on the site of the tumor and the nature of the process obstructing the bile duct. In these conditions, ERCP is a good choice as the second test.

ERCP provides an endoscopic view of the duodenum that allows identification and biopsy of ampullary and duodenal tumors that may be blocking the bile duct and producing jaundice. It confirms the presence of a bile duct stricture and displays its form, which is helpful in diagnosis. Focal strictures, especially those with shoulders, suggest malignancy. Long, tapering strictures limited to the infrapancreatic portion of the bile duct suggest chronic pancreatitis. Concomitant narrowing of the pancreatic duct in the head of the pancreas (the double-duct sign) suggests the presence of a small pancreatic cancer that is not visible on the CT scan. Longer or multiple pancreatic strictures suggest chronic pancreatitis. A single focal bile duct stricture in the absence of pancreatic duct abnormalities is the hallmark of cancer of the lower bile duct. Infiltrating cancers of the bile duct may cause more than one stricture along the bile duct, but when more than one stricture is present, other diagnoses (e.g., primary sclerosing cholangitis) should be considered. Both pancreatic and bile ducts may be assessed with brush cytology. This test has a 45% to 50% sensitivity for cancer; therefore, only a positive test result is significant.

ERCP findings in a patient with no mass must be evaluated in the light of findings from other investigations. Patients with the classic double-duct sign or single focal shouldered bile duct strictures are likely to have small pancreatic or bile duct tumors. Further diagnostic support is usually not needed before laparotomy, though such support may be reassuring when the CA 19-9 concentration is higher than 100 U/ml. When doubt persists, EUS often helps resolve it. EUS may identify a small mass that was not seen on the CT scan, and biopsies may then be done. Occasionally, EUS reveals enlarged lymph nodes, which may also undergo biopsy. However, negative EUS-guided biopsy results in patients who present with painless jaundice do not exclude malignancy. When such patients have an identifiable mass on EUS, pancreaticoduodenectomy is recommended, even if EUS-guided biopsy yields negative results. If a nonoperative approach is taken, short-term follow-up at 4 to 6 weeks with repeat imaging and biopsy is mandatory. If the findings persist, laparotomy is advisable.

Occasionally, preoperative testing reveals no mass, but a mass is subsequently discovered by intraoperative palpation or intraoperative ultrasonography (IOUS). A mass palpated in the head of a pancreas that is otherwise normal or near normal in texture is highly suggestive of malignancy and constitutes sufficient justification for resection. The same is true of a mass detected by IOUS if the mass has characteristics of malignancy (i.e., is hypoechoic). If the IOUS findings are inconclusive, biopsy with frozen-section examination is a reasonable approach. In many such cases, the whole pancreas is diffusely firm or hard, and IOUS demonstrates a diffuse change in the normal texture of the gland. When the pancreas is diffusely firm and no localized process is seen on IOUS, biopsies should be directed toward the stent in the bile duct at the point where the bile duct narrows (as seen on ultrasonography).

The ultimate diagnostic test is pancreaticoduodenectomy. If there is a strong suspicion of cancer before laparotomy or the findings at laparotomy are strongly suggestive, this procedure should be performed without preliminary biopsy. When this approach is followed, a small number of patients with suspected malignant disease will ultimately turn out to have benign disease when operated on; this possibility should be explained to patients who do not undergo confirmatory tissue diagnosis before operation. Because of the limited negative predictive value of currently available tests, pancreaticoduodenectomy is sometimes still required to make a definitive diagnosis.

The finding of an atypical pancreatic head mass on a CT scan poses an additional challenge. Atypical masses may take different forms. In some cases, they exhibit attenuation that differs only slightly from that of the surrounding pancreas; in others, they have a ground-glass appearance. They may extend into the body and tail of the pancreas, or they may be localized to the head. With atypical masses, the most common problem is how to differentiate focal pancreatitis from adenocarcinoma. This differentiation can be very difficult to achieve. Pancreatitis may be present without antecedent acute attacks; without a history of alcoholism, gallstones, or hyperlipidemia; without diabetes or steatorrhea; and without calcifications in the gland. Cancer appears to be more common in patients who have had chronic pancreatitis, and the diseases may coexist. Therefore, one cannot feel confident that cancer is absent simply because chronic pancreatitis is present. Cancer should be suspected in patients with an established diagnosis of chronic pancreatitis who undergo a rapid change in status (e.g., weight loss). Diabetes is common in patients with chronic pancreatitis, but it may also be the first sign of pancreatic cancer in patients without chronic pancreatitis. Chronic pancreatitis can cause painless jaundice. A rare immune form of chronic pancreatitis, known as lymphoplasmacytic sclerosing pancreatitis, has been recognized that is particularly hard to differentiate from cancer.

EUS is becoming increasingly important in the management of patients with atypical pancreatic head masses. When jaundice is present, ERCP followed by EUS is our usual approach; when it is absent, EUS without ERCP is preferred. EUS-guided biopsy is superior to CT-guided transabdominal biopsy, in that access to the head of the pancreas is easier and the chance of needle tracking is reduced (because the biopsy is taken through the duodenal wall, which is resected if a Whipple procedure is done).

At the conclusion of all of the preceding investigations, it still may not be clear whether a malignancy is present. Clinical judgment must be exercised in deciding whether to operate or to repeat investigative studies after an interval of 2 to 3 months. Operation is favored in patients who are jaundiced, who have less pain, who have elevated CA 19-9 levels, and whose mass is suspicious for cancer. Elevation of the CA 19-9 concentration beyond 100 U/ml should be regarded as a very important finding. When EUS is inconclusive, ultrasound-guided diagnostic laparoscopy may be performed to obtain core tissue biopsies from several areas of the mass. This technique is especially useful when chronic pancreatitis is strongly suspected, in that the multiple long core biopsies obtainable with this procedure provide a greater degree of assurance against false-negative findings for cancer. Even this test, however, is not 100% accurate in this regard. The penultimate diagnostic test is laparotomy with mobilization of the pancreatic head and IOUS-guided transduodenal core biopsies of the mass. The ideal outcome with this approach is to perform pancreaticoduodenectomy in all patients who actually have cancer while reducing to a reasonable minimum resec-
tion in patients with benign disease, who in most cases are better served by biliary bypass.

**Surgical staging** The term staging is currently used to denote the process by which the surgeon determines whether a tumor is resectable. We prefer to use the term surgical staging for this process so as to distinguish it from those staging classifications that define the life history and prognosis of tumors and provide the basis for comparison of results—namely, the TNM classifications developed by the American Joint Committee on Cancer (AJCC). These latter systems are also of great importance to the surgeon dealing with pancreatic tumors.

Surgical staging is started preoperatively and completed intraoperatively. Preoperative staging tests determine operability—that is, whether the tumor appears resectable after preoperative testing. However, the final decision regarding resectability is made only during the operation, on the basis of intraoperative staging. A tumor of the head of the pancreas is deemed unresectable when it is determined to have extended beyond the boundaries of a pancreaticoduodenectomy. Common reasons for unresectability include (1) vascular invasion (i.e., invasion of the superior mesenteric vein, the portal vein, the superior mesenteric artery, or, less commonly, the hepatic artery); (2) lymph node metastases that fall outside the scope of a pancreaticoduodenectomy (e.g., metastases to para-aortic and celiac lymph nodes); (3) hepatic metastases; (4) peritoneal metastases; and (5) extra-abdominal metastases (usually pulmonary). Limited vascular invasion of the superior mesenteric vein and the portal vein may be overcome by resection and reconstruction and thus is only a relative contraindication to resection. This is especially true when the tumor is small and has arisen in the vicinity of the veins. In a series from our institution (Washington University in St. Louis), about 20% of resections done for pancreatic cancer involved resection of these veins.7

The tests used to establish the diagnosis and those used to accomplish surgical staging go hand in hand. Abdominal CT scans, abdominal MRI, thoracic CT scans, and chest radiographs are obtained to detect hepatic metastases, vascular invasion, and pulmonary metastases. To assess vascular invasion, fine-cut three-phase helical CT scans or MRI scans are required. These tests may detect enlarged lymph nodes, but it should be remembered that nodes may be enlarged for reasons other than cancer. Sometimes, ascitic fluid collections or peritoneal or omental nodules are identified; ascitic fluid may be sent for cytologic analysis, and omental nodules may undergo ultrasound-guided biopsy. Invasion of the mesentery, the mesocolon, or retroperitoneal tissues may also be detected by CT scanning. In the view of some surgeons, such invasion may render the tumor unresectable, but in our experience, this is rarely the case in the absence of concomitant vascular invasion: the resection may still be accomplished with clear margins by resecting the portion of the mesocolon or the mesentery that was locally invaded.

EUS may be used to guide biopsy of suspicious lymph nodes when these lie outside the planned resection zone. It has also been employed to assess vascular invasion, but in our experience, it has no advantage over CT scanning in this regard; what is more, it is highly operator dependent. Staging laparoscopy is particularly effective at finding small hepatic and peritoneal nodules. About 20% of patients thought to have resectable pancreatic adenocarcinoma of the head of the pancreas before staging laparoscopy are found to have liver or peritoneal metastases upon laparoscopy.8 Staging is completed intraoperatively by carefully inspecting the intra-abdominal contents, opening the lesser sac, mobilizing the head of the pancreas, performing biopsies of suspicious nodules or nodes outside the planned resection zone, and attempting dissection of the superior mesenteric vein or the portal vein. Formal clinicopathologic staging according to the AJCC’s TNM system is useful for establishing the prognosis and planning additional treatment [see Tables 1 and 2].

All authorities agree that axial imaging of the abdomen and chest (or roentgenography of the chest) is standard practice for staging pancreatic cancer; however, not all agree on the value of other staging tests. Many authorities advocate omission of staging laparoscopy or EUS-guided biopsy of nodes, on the grounds that patients are better served by palliative surgery than by endoscopic stenting of the bile duct. There is no advantage in knowing whether small liver metastases or celiac node metastases are present if laparotomy is to be undertaken anyway. The literature on this issue is unclear regarding what constitutes best practice. The two randomized trials published to date reported differing outcomes, with one favoring surgical bypass9 and the other endoscopic stenting. We continue to recommend staging laparoscopy in patients with adenocarcinoma of the pancreas. In those considered likely to have a short life expectancy because of peritoneal or hepatic metastases discovered upon laparoscopy, the procedure is discontinued, and endoscopic stenting with metal stents is performed. We no longer advocate using staging laparoscopy with ultrasonography to determine if the tumor is unresectable solely because of local vascular invasion; these patients are likely to have a longer life.

### Table 1. American Joint Committee on Cancer TNM Clinical Classification of Pancreatic Cancer

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Regional lymph nodes (N)</th>
<th>Distant metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>NX</td>
<td>MX</td>
</tr>
<tr>
<td>T0</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>T5</td>
<td>Any T</td>
<td>M1</td>
</tr>
</tbody>
</table>

SMA—superior mesenteric artery

### Table 2. American Joint Committee on Cancer Staging System for Pancreatic Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
<td>B0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T1, T2, T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Stage I tumors are Stage I A or B tumors. Stage II tumors are Stage II A or B tumors. Stage III tumors are Stage III A or B tumors. Stage IV tumors are Stage IV A or B tumors.
expectancy and are treated with a double-bypass procedure. Finally, \(^{18}\text{F}\)-fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful in staging pancreatic cancer, but at present, its role is unclear. Given that inflammation is frequently confused with cancer, the major role of this modality will probably be in the detection of distant metastases.

Management Preoperative preparation. All jaundiced patients should receive vitamin K, a fat-soluble vitamin whose absorption is reduced by biliary or pancreatic duct obstruction. Routine preoperative bile duct decompression is unnecessary, except when jaundice has been prolonged or operative treatment will be delayed (e.g., for correction of cardiac or other comorbid conditions). Several studies have shown that surgical outcome is not improved by routine preoperative decompression in jaundiced patients. In fact, stent placement may increase the incidence of postoperative infection.

Rationale for pancreaticoduodenectomy. The technical details of pancreaticoduodenectomy are discussed more fully elsewhere [see Pancreatic Disease]. Therapeutic decision-making necessarily includes consideration of the extent of the procedure. The operative goal is to remove the tumor with clear margins, as well as the N1 regional lymph nodes. Numerous attempts have been made to improve results by extending the operation, either through more extensive lymph node dissections or through resection of the superior mesenteric artery. None of these attempts have been successful in improving overall survival. The lesson is that invasion of additional lymph node regions or the superior mesenteric artery signals an aggressive tumor biology that is unlikely to be overcome by wider resections. Except for resection of the portal vein or the superior mesenteric vein to address invasion of these structures by otherwise favorable tumors, extended resections are no longer recommended. Even these recommended venous resections are probably best restricted to tumors that have arisen close to the veins and involved them while still small; resections of large adenocarcinomas that have grown over time to involve long stretches of the veins are best avoided.

There is also continuing controversy regarding the respective merits of the standard version of the operation and its pylorus-preserving variant. There is no evidence that the two procedures differ with respect to overall survival. Pylorus preservation is associated with gastric-emptying problems in the postoperative period, but overall, it seems to be associated with less postoperative GI dysfunction. We employ pylorus preservation selectively in older, thinner patients, with the aim of minimizing disruption of GI function.

Adenocarcinoma of Body and Tail of Pancreas

Adenocarcinoma of the body and tail of the pancreas is less common than adenocarcinoma of the head. Because it does not produce jaundice, it tends to be recognized relatively late. Accordingly, patients are often in an advanced stage of disease at presentation. Tumors of the midbody tend to invade posteriorly to involve the superior mesenteric artery or the celiac axis, even when these lesions are only 2 to 3 cm in diameter. As a result, tumors of the tail are more likely to be resectable than tumors of the midbody when they are discovered. Many resectable tumors are discovered incidentally; by the time the tumors give rise to symptoms, they are frequently unresectable.

Clinical evaluation Symptoms are nonspecific, consisting of abdominal and back pain (which is usually relieved by sitting up and leaning forward), weight loss, and diabetes of recent onset.
Intraductal papillary mucinous tumor (IPMT). A complete distal papillary mucinous neoplasm (IPMN) (also referred to as main types are mucinous cystic neoplasm (MCN) and intraductal papillary mucinous tumor (IPMT)). A complete discussion of pancreatic cyst disease is beyond the scope of this chapter. Accordingly, we briefly address such disease as it relates to malignant degeneration. The standard procedure has been open distal pancreatectomy with splenectomy, though lesser procedures, such as spleen-sparing distal pancreatectomy, have all been used as well. These procedures appear to be reasonable choices, provided that there is no suggestion of invasive malignancy on imaging (i.e., that there are no excrescences on the inner lining and that the surrounding pancreas appears normal). Enucleation may be associated with a higher incidence of postoperative fistula. If invasive cancer is not detected in the resected specimen, the chances that the malignancy will recur are small; in fact, we have never seen such a recurrence.

The 2 cm cutoff for treatment of MCNs in asymptomatic patients is arbitrary. It is still possible that malignant degeneration could occur in a cyst smaller than 2 cm, but many cysts of this size (RAMPS), which accomplishes the desired goals by performing the resection in an antegrade manner from right to left and which is based on the established lymph node drainage of the gland [see Figure 4]. RAMPS also allows early control of the vasculature.

Mucinous Adenocarcinoma

Mucin-producing cancers are special variants of adenocarcinoma of the pancreas that often arise in preexisting lesions. The two main types are mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN) (also referred to as intraductal papillary mucinous tumor [IPMT]). A complete discussion of pancreatic cyst disease is beyond the scope of this chapter. Accordingly, we briefly address such disease as it relates to cancer of the pancreas, omitting discussion of less common cystic malignancies of the pancreas.

**MCN**

MCN occurs most often in middle-aged women, typically in the body and tail of the pancreas. MCNs are unilocular or septated cysts whose diameters range from subcentimeter size to 15 cm or larger. Occasionally, calcium is present in the wall. Excrucences may be present on the inner wall; if so, malignancy is likely. Most symptomatic MCNs are between 4 and 7 cm in diameter.

**Clinical evaluation and investigative studies.** Patients with MCNs typically present with left-side pain, often in the flank and the back, though these lesions also are frequently discovered incidentally. Pancreatitis is rare and jaundice is uncommon, even when the lesions are situated in the head of the pancreas. MCNs must be differentiated from pseudocysts and from serous cystadenomas (SCAs), which are benign cysts. Differentiation between MCNs and pseudocysts is based on the history, imaging studies, and cyst fluid analysis. The diagnosis of pseudocyst is supported by a history of pancreatitis; a thick-walled, uncalcified cyst with associated radiologic signs of pancreatitis; and cyst fluid with high levels of amylase and lipase and a relatively low level of carcinoembryonic antigen (CEA) (< 500 ng/ml).

SCAs have the same clinical presentation as MCNs. SCAs are more frequently polycystic than MCNs are, but this difference is not a certain means of discriminating between the two. In a minority (25%) of cases, SCAs have a pathognomonic central calcification with radiating arms ringed by multiple grape-sized cysts. When the cysts are tiny (honeycomb pattern), SCAs may also appear to be solid tumors. Unlike pseudocysts and IPMNs, neither MCNs nor SCAs communicate with the pancreatic duct, though they may compress it. Measurement of the CEA level in cyst fluid is a good means of distinguishing MCN from SCA. SCAs have very low levels of CEA, with the cutoff being 5 ng/ml. In MCNs, the cyst fluid is often mucinous, and cytologic assessment may show mucin-producing cells; typically, the fluid is high in CEA. The CA 19-9 concentration may also be used to distinguish MCNs from SCAs, but it is not as reliable as the CEA concentration for this purpose.

**Surgical staging.** Surgical staging is required when MCNs are malignant, and essentially the same methods are used as for any pancreatic adenocarcinoma (see above). Malignancy is suggested by a solid intracystic or extramural component. Sometimes, a mucinous tumor is frankly malignant with a large or dominant solid component. Such a tumor is better termed a mucinous adenocarcinoma, and it should be evaluated and treated from the outset in the same manner as any other adenocarcinoma of the pancreas.

**Management.** In symptomatic patients, preoperative differentiation between MCNs and SCAs is unnecessary, because resection is the treatment for both. In asymptomatic patients, MCNs more than 2 cm in diameter should be excised because of the possibility of malignant degeneration. The standard procedure has been open distal pancreatectomy with splenectomy, though lesser procedures, such as spleen-sparing distal pancreatectomy, laparoscopic distal pancreatectomy, central pancreatectomy, and enucleation, have all been used as well. These procedures appear to be reasonable choices, provided that there is no suggestion of invasive malignancy on imaging (i.e., that there are no excrescences on the inner lining and that the surrounding pancreas appears normal). Enucleation may be associated with a higher incidence of postoperative fistula. If invasive cancer is not detected in the resected specimen, the chances that the malignancy will recur are small; in fact, we have never seen such a recurrence.

The 2 cm cutoff for treatment of MCNs in asymptomatic patients is arbitrary. It is still possible that malignant degeneration could occur in a cyst smaller than 2 cm, but many cysts of this size...
are found in the course of axial imaging performed for other reasons. Such cysts are difficult to diagnose because of the small volume of cyst fluid present, and the benefit to be gained from performing a large number of pancreatectomies for these small cysts is questionable, even when they are diagnosable as MCNs. Some authorities feel that large SCAs should also be excised because of rare instances of malignant degeneration. Occasionally, MCNs or symptomatic SCAs are located in the head of the pancreas and must be treated with pancreatecoduodenectomy.

**IPMN** IPMN begins as the cells lining the pancreatic ducts undergo a metaplastic alteration from a low cuboidal serous type of cell to a mucin-producing type. These cells are prone to dysplasia and eventual malignant transformation. Overall, IPMNs appear to undergo malignant transformation much more regularly than MCNs do. There are two recognized types of IPMN, which may occur either separately or together. The more common type affects the main pancreatic duct [see Figure 5], which becomes dilated and filled with mucin. As the disease progresses toward malignancy, papillary processes may project into the lumen. The less common type, so-called side-branch IPMN, affects the smaller ducts and presents as multiple (usually small) pancreatic cysts. In either type of IPMN, the disease may be either diffuse or focal; when it is focal, the head of the pancreas is the site of disease in the majority (60%) of cases. About 20% of IPMN patients have a malignancy at the time of diagnosis, though the cancer may not be evident until the specimen is examined pathologically.

Clinical evaluation and investigative studies. IPMN occurs predominantly in males and usually affects patients in their 60s. Pain (usually attributable to pancreatitis arising from mucus obstruction of the pancreatic duct) is a common presenting symptom. Another common presentation is pancreatic insufficiency with diabetes or steatorrhea. Accordingly, it is not surprising that formerly, many IPMN patients were diagnosed as having chronic pancreatitis. IPMN may also be discovered incidentally or may present as a cancer with signs and symptoms similar to those of other pancreatic cancers, depending on the part of the gland in which they arise. On rare occasions, cholangitis from obstruction of the common channel by mucus is the presenting problem.

The diagnosis is made on the basis of the presentation and the findings from axial imaging and ERCP. ERCP sometimes shows mucus bulging from the mouth of the pancreatic duct when the duodenum is inspected. In main duct disease, the pancreatic duct is dilated, but sometimes, the mucus prevents complete filling. In this situation, CT scans or MRI with MRCP may be quite useful for detecting ductal dilatation and atrophy of the pancreas. MRCP is best at detecting excrescences emanating from the surface of the duct, which signal progression of the disease toward neoplasia. In side-branch IPMN, ERCP typically demonstrates communication between the cysts and the main duct, which is often normal in size; this finding is not present in MCN or SCA and is very useful for distinguishing side-branch IPMN from these other types of cysts.

Management. IPMN is treated by resecting the involved portion of the gland. In about 50% of patients, the resection margin is involved with atypia or cancer, and the planned resection may have to be extended. In some cases (about 20%), total pancreatectomy is required; in others, partial pancreatectomy and close follow-up of the pancreatic remnant with MRCP and serum CA 19-9 measurement are indicated. Most patients who require total pancreatectomy tolerate the procedure well when they are enrolled in a program keyed to this operation. The mucinous cancers associated with IPMN have a better prognosis than ductal adenocarcinomas do. Frank mucinous cancers may appear in patients with IPMN as well; they should be managed in much the same fashion as other adenocarcinomas, with the additional requirement that the resection should encompass the entire IPMN-bearing portion of the pancreas.

**NEUROENDOCRINE CANCERS**

In most large centers, neuroendocrine cancers account for fewer than 5% of surgically treated pancreatic malignancies. Some of these cancers are functional tumors, which produce hormones leading to paraneoplastic syndromes. Examples include gastrinoma, insulinoma, glucagonoma and vasoactive intestinal polypeptide–secreting tumor (VIPoma), all of which are associated with characteristic clinical syndromes. These syndromes are often produced while the tumors are still small. A detailed discussion of functional neuroendocrine tumors is beyond the scope of this chapter.

---

**Figure 5** (a) CT scan of a patient with main duct IPMN involving the entire length of the pancreatic duct reveals substantial distention of the duct. (b) Shown is a cross-section through the resected specimen.
Other neuroendocrine tumors are nonfunctional and, as a result, reach a larger size before giving rise to symptoms. These lesions present with symptoms caused by the mass effect and must be differentiated from ductal adenocarcinomas. Nonfunctional neuroendocrine cancers are slow-growing tumors that tend to push rather than invade structures but are capable of metastasizing to lymph nodes, as well as to the liver and other organs. Pain is the most common presenting symptom. Jaundice, pancreatitis, and systemic symptoms (e.g., weight loss) are less common with these tumors than with adenocarcinoma of the pancreas. Because of the propensity of neuroendocrine tumors to deflect rather than invade the bile duct, jaundice may be absent even when tumors are located in the head of the gland.

Diagnosis, surgical staging, and treatment rationale are essentially the same for neuroendocrine cancers as for ductal adenocarcinomas. On CT scans, these lesions characteristically show enhancement in the arterial phase and are seen to push on bile ducts and vascular structures rather than encase them. Complete resection by means of pancreatoduodenectomy or distal pancreatectomy [see 5:24 Pancreatic Divisal] is indicated. Given the slow growth rate of neuroendocrine cancers and their relatively favorable prognosis (50% to 60% 5-year survival rate), removal of the primary lesion and any hepatic secondary lesions is justified if all tumor tissue can be removed with clear margins.

Biliary Tract Cancer

EXTRAEPHATIC CHOLANGIOCARCINOMA

Extrahepatic cholangiocarcinoma (CCA) may be subdivided into lower-duct CCA and upper-duct CCA, with the former arising in the intrapancreatic or retroduodenal portion of the bile duct and the latter arising above it. In practice, most upper-duct CCAs (also referred to as hilar CCAs or Klatskin tumors) arise just below the union of the right and left hepatic ducts, at the union of the ducts, or in the main right or left hepatic ducts. Cancer of the midportion of the bile duct at the cystic duct’s usual insertion point is more likely to be an extension of a gallbladder cancer than a primary CCA. AJCC staging criteria for these tumors are useful for establishing the prognosis and planning further treatment [see Tables 3 and 4].

Lower-Duct Cholangiocarcinoma

Clinical evaluation and investigative studies Much of what the surgeon needs to know about lower-duct CCA has already been addressed elsewhere [see Pancreatic Cancer, Adenocarcinoma of Head of Pancreas, above]. By far the most common presentation is painless jaundice with its constellation of associated symptoms (especially pruritus). Laboratory tests reveal the characteristic pattern of obstructive jaundice. A serum CA 19–9 concentration higher than 100 U/ml facilitates the diagnosis. Axial imaging reveals dilation of the intrahepatic bile ducts, the gallbladder (in most cases), and the extrapancreatic bile ducts down to the level of the pancreatic head, where the dilatation terminates abruptly. Usually, no mass is visible. ERCP or MRCP shows a focal stricture, and ERCP brushings are positive in about 50% of cases. EUS may be helpful, in that it is more sensitive for small tumors than CT scanning is. Needle biopsy is directed toward the mass or, if no mass is visible, toward the narrowest segment of the bile duct. A negative biopsy result does not rule out a small bile duct cancer.

The differential diagnosis includes other potential causes of focal strictures of the bile duct. The most common cause of a benign stricture of the intrapancreatic bile duct is pancreatitis, which may be diffuse or focal. Other causes of benign stricture include iatrogenic injury, choledocholithiasis, sclerosing cholangitis, and benign inflammatory pseudotumors [see Upper-Duct Cholangiocarcinoma, Investigative Studies, Imaging, below]. Iatrogenic injuries rarely involve the intrapancreatic portion of the bile duct, though such injuries can occur in this area as a consequence of forceful instrumentation. Sclerosing cholangitis may affect this section of the bile duct but usually affects other areas of the biliary tree as well. The diagnostic steps for differentiating benign neoplasms from malignant tumors are essentially the same for lower-duct CCA as for pancreatic cancer. As noted, resection may be required to make the diagnosis. In any patient presenting with jaundice and a focal stricture of the bile duct, lower-duct CCA should be strongly suspected.

Surgical staging Surgical staging of lower-duct CCAs is usually straightforward. These tumors are usually remote from major vascular structures and thus are not subject to the same local staging considerations as adenocarcinomas of the pancreatic head are. The exception is a tumor that extends to the top of the retroduodenal portion of the bile duct. At this point, the bile duct is apposed to the portal vein and the hepatic artery, and these structures may be invaded by bile duct tumors in this location.

### Table 3 American Joint Committee on Cancer TNM Clinical Classification of Extrahepatic Bile Duct Cancer

<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, T2, 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>

### Table 4 American Joint Committee on Cancer Staging System for Extrahepatic Bile Duct Cancer

<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, T2, 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>
Management  The treatment for resectable lesions is pancreaticoduodenectomy.

Upper-Duct Cholangiocarcinoma

Upper-duct (or hilar) CCA is a sporadically occurring tumor that may also be seen in patients with primary sclerosing cholangitis, ulcerative colitis, or parasitic infestation. It is characteristically slow growing and locally invasive, and it metastasizes more readily to lymph nodes than systemically, though intrahepatic and peritoneal metastases are not uncommon. Most hilar CCAs are cicatrizing diffusely infiltrating cancers, but some are nodular, and others present as papillary ingrowths. These tumors are divided into four types according to the Bismuth classification, which is based on the upper extent of the tumor [see Figure 6].25

When the CCA originates in one of the hepatic ducts, that duct may be obstructed for a considerable period before the tumor causes jaundice by growing into the other hepatic duct or the common bile duct. Such prolonged unilateral obstruction before the onset of the presenting symptom of jaundice may result in atrophy of the obstructed side of the liver, which may affect subsequent management. For example, because the disease is more advanced on the obstructed side, it is the atrophied half of the liver that will be removed in almost all cases where resection is indicated. In addition, when one side of the liver undergoes atrophy, the other side undergoes hypertrophy. These changes lead to rotation of the liver, which in turn may cause the structures in the hepatoduodenal ligament to be rotated out of their normal anatomic location. For instance, if hypertrophy of the left hemiliver develops, the hepatic artery may come to lie directly in front of the bile duct.

Clinical evaluation  The usual presentation of hilar CCA consists of painless jaundice with its accompanying symptoms (especially pruritus), though some pain may be present. Cholangitis before instrumentation of the bile duct is uncommon. In patients who present in the late stages of the disease, general manifestations of cancer (e.g., malaise, weight loss, or ascites) may be noted.

Investigative studies  Laboratory tests. Laboratory testing follows the pattern previously described for obstructive jaundice [see Pancreatic Cancer, above]. Again, the most helpful diagnostic laboratory test is the serum CA 19-9 concentration: levels higher than 100 U/ml are strongly suggestive of cancer. In patients with primary sclerosing cholangitis, the presence of CCA is often suggested by a rapid deterioration in condition. It is not unusual for patients with hilar CCA to have undergone a cholecystectomy in the recent past; the symptoms of pain and jaundice may be mistaken for symptoms of gallbladder disease in patients who happen also to have gallstones.

Imaging. Earlier [see Pancreatic Cancer, Ductal Adenocarcinoma, Adenocarcinoma of Head of Pancreas, above], the point was made that it is preferable to employ axial imaging rather than ERCP as the first imaging test in the jaundiced patient because doing so will often render ERCP, an invasive test, unnecessary. This point carries even more force in the setting of hilar CCA. Injection of dye

Figure 6  Depicted is the Bismuth classification of hilar CCA (a through e).
Axial imaging usually shows thickening of the gallbladder wall or the presence of a mass involving the infundibulum. Mirizzi syndrome is another cause of a focal stricture of the middle or upper bile duct. This syndrome results from compression of the bile duct by a large gallstone in the infundibulum and is usually associated with severe inflammation of the gallbladder and the characteristic signs and symptoms of acute cholecystitis. The duct is typically bowed to the left rather than focally narrowed, as in cancer. Iatrogenic causes should be considered if the patient has had a cholecystectomy. On occasion, a stricture appears years after the operation. In these cases, the probable cause of the stricture is ischemic injury to the bile duct. The presence of clips close to or indenting the duct is a clue that such injury is a possibility. Choledocholithiasis may also cause strictures, especially if cholangitis has occurred. Strictures are also frequent with recurrent pyogenic (oriental) cholangitis. Other rare tumors of the bile duct (e.g., neuroendocrine tumors) may mimic cholangiocarcinoma.

**Surgical staging** Often, the first axial imaging test reveals only the presence of intrahepatic bile duct dilatation, which stops abruptly as the ducts merge in the hepatic hilum. This finding, however, leads to MRI or CT aimed at providing high-quality cholangiograms and angiograms of the hepatic arteries and the portal veins. Surgical staging of hilar CCA, unlike that of lower-duct CCA, requires exact knowledge of the macroscopic upper extent of the tumor in the bile duct. Furthermore, invasion of hepatic arteries and portal veins is common and frequently affects resectability. Thus, surgical staging also requires accurate determination of the extent of hepatic arterial or portal venous invasion and assessment of the degree of atrophy.

Bismuth type IV tumors are not resectable, except by liver transplantation. Type I through III tumors are resectable, provided that the main portal vein and the proper hepatic artery, as well as the portal vein and the hepatic artery to the side of the liver to be retained, are not invaded by tumor and that the side to be retained is not atrophic. Involvement of the main portal vein or the hepatic artery is a relative rather than an absolute contraindication; lesser degrees of involvement can be handled by means of vascular resection and reconstruction in specialized centers. Unusual combinations of events may prelude resection (e.g., atrophy on one side of the liver and invasion of the hepatic artery supplying the other side, or invasion of the portal vein to one side and the bile duct on the other side to the level of the secondary biliary branches).

MRI (with MRCP and magnetic resonance angiography [MRA]) or CT with the latest generation of scanners can provide complete information regarding the extent of bile duct involvement and the degree of vascular invasion. Doppler ultrasonography is also excellent for evaluating vascular invasion. ERCP may be used for additional assessment of the extent of the tumor on the side to be retained if a stent on that side is deemed necessary. The use of percutaneous cholangiography is controversial, the main concern being the risk of tumor seeding along the tube, into the peritoneal cavity, and onto the surface of the liver or the abdominal wall. Nevertheless, this procedure is used extensively in Japan, where surgeons have considerable experience with selective decompression of parts of the liver as a preoperative strategy.

Assessment of distant metastases is achieved by means of axial imaging of the chest and the abdomen. Staging laparoscopy identifies 10% to 15% of cancers that are unresectable because of peritoneal or liver metastases. FDG-PET identifies about 15% of patients with distant metastases. At present, neither of these tests is routinely employed in this setting.
Malignant Biliary Tract Disease

Intrahepatic metastases (and if the tumor can be removed in its entirety by means of bile duct resection [see 5:22 Procedures for Benign and Malignant Biliary Tract Disease] combined with liver resection [see 5:23 Hepatic Resection]. The goal of resection of the tumor, the portal and celiac lymph nodes, the side of the ductal involvement is greater (via hemihepatectomy or trisectionectomy), and the caudate lobe is resected because cholangiocarcinomas tend to invade along the short caudate bile ducts, which enter the posterior surfaces of the main right and left bile ducts at the bifurcation of the common hepatic duct.)

Liver transplantation has been used successfully to manage Bismuth type IV tumors and is usually performed after neoadjuvant chemoradiation therapy and staging laparotomy in highly selected patients.29

GALLBLADDER CANCER

The incidence of gallbladder cancer in the United States is about 9,000 cases a year. This cancer almost always arises in patients with preexisting gallstones and is most often seen in elderly patients. Like ductal adenocarcinoma of the pancreas, it is highly malignant, and it tends to spread at an early stage to lymph nodes, to peritoneal surfaces, and through the bloodstream. AJCC staging criteria are helpful for planning management of this cancer [see Tables 5 and 6].

Clinical Evaluation

Gallbladder cancer is discovered incidentally either during performance of cholecystectomy for symptomatic cholelithiasis or when the tumor causes symptoms related to invasion of the bile duct or metastatic disease. In stage I and II disease, which is confined to the wall of the gallbladder, the symptoms are usually those of the associated stones—that is, the patient has biliary colic, and the cancer is silent. In later stages of disease, jaundice, weight loss, a palpable right upper quadrant mass, hepatomegaly, and the cancer is silent. In later stages of disease, jaundice, weight loss, a palpable right upper quadrant mass, hepatomegaly, and ascites may develop. Jaundice occurs in about 50% of patients. It is a poor prognostic sign because it signifies extension of the tumor beyond the gallbladder and obstruction of the extrahepatic bile ducts. Consequently, most gallbladder cancer patients with jaundice have unresectable tumors. Because the signs and symptoms of gallbladder cancer are nonspecific, delays in diagnosis are common. As a result, most gallbladder cancers are not diagnosed until they have reached stage III or IV; thus, most of these aggressive tumors are unresectable at presentation, even when the patient is not jaundiced.

Investigative Studies

Laboratory tests

In stages I and II, LFTs usually yield normal results. In later stages, laboratory test abnormalities may be noted that are not diagnostic but are consistent with bile duct obstruction. Elevated alkaline phosphatase and bilirubin levels are most helpful diagnostic indicator.

Table 5  American Joint Committee on Cancer TNM Clinical Classification of Gallbladder Cancer

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Regional lymph nodes (N)</th>
<th>Distant metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX Primary tumor cannot be assessed</td>
<td>NX Regional lymph nodes cannot be assessed</td>
<td>MX Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>T0 No evidence of primary tumor</td>
<td>N0 No regional lymph node metastasis</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>Tis Carcinoma in situ</td>
<td>N1 Metastasis in cystic duct, pericholedochal, or hilar lymph nodes (i.e., in hepatoduodenal ligament)</td>
<td>M1 Distant metastasis</td>
</tr>
<tr>
<td>T1 Tumor invades lamina propria or muscle layer</td>
<td>N2 Metastasis in peripancreatic (head only), peripancreatic, perportal, celiac, or mesenteric lymph nodes</td>
<td></td>
</tr>
<tr>
<td>T1a: Tumor invades lamina propria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1b: Tumor invades muscle layer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 Tumor invades perimuscular connective tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 Tumor perforates serosa (visceral peritoneum) or directly invades one adjacent organ (≤ 2 cm into liver)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4 Tumor extends &gt; 2 cm into liver or invades two or more adjacent organs (e.g., duodenum, colon, pancreas, omentum, or extrahepatic bile ducts)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Management

Preoperative preparation. Unlike cancers of the lower bile duct, cancers of the upper bile duct usually necessitate major liver resection [see 5:22 Procedures for Benign and Malignant Biliary Tract Disease]. Consequently, it has been argued that the risk of postoperative hepatic failure may be lowered by preoperative decompression, especially decompression of the side to be retained, which has the dual purpose of allowing that side to recover function and of actually encouraging hypertrophy. On the other hand, stents may introduce bacteria and cause cholangitis. As noted (see above), selective percutaneous decompression is an accepted strategy in Japan; often, multiple stents are inserted.28

A reasonable strategy is to proceed to operation if (1) the patient is relatively young (< 70 years), (2) there are no serious comorbid conditions, (3) the jaundice has been present for less than 4 weeks, (4) the serum bilirubin concentration is lower than 10 mg/dl, (5) the future remnant liver will include more than 30% of the total liver mass, and (6) the patient has not undergone biliary instrumentation (which always contaminates the obstructed biliary tract). In all other cases, we routinely decompress the side of the liver to be retained and wait until the serum bilirubin concentration falls to 3 mg/dl. When the future remnant liver will include less than 30% to 35% of the total liver mass, portal vein embolization (PVE) of the side to be resected may be performed to induce hypertrophy of the remnant. Because resection for hilarCCA is a major procedure in a somewhat compromised liver, it is contraindicated in patients who are in poor general condition or who have major organ dysfunction.

Rationale for surgery.

Patients with upper-duct CCA are candidates for resection if they have no distant metastases (including intrahepatic metastases) and if the tumor can be removed in its entirety by means of bile duct resection [see 5:22 Procedures for Benign and Malignant Biliary Tract Disease] combined with liver resection [see 5:23 Hepatic Resection]. The goal of resection of upper-duct CCA is to achieve clear resection margins by removing the tumor, the portal and celiac lymph nodes, the side of the liver in which the ductal involvement is greater (via hemihepatectomy or trisectionectomy), and the caudate lobe.
Imaging  Because gallbladder cancer is most curable in its early stages and because the symptoms in those stages are those of cholecystitis, it is helpful to be aware of subtle signs of gallbladder cancer that are occasionally present on sonograms. These signs include thickening of the gallbladder wall, a mass projecting into the lumen, multiple masses or a fixed mass in the gallbladder, calcification of the gallbladder wall (so-called porcelain gallbladder), and an extracholecystic mass. Displacement of a stone to one side of the gallbladder should also be viewed with suspicion.

In later stages of disease, CT scans usually show a gallbladder mass with or without invasion of the liver or other adjacent organs. Obstruction of the bile duct produces the usual features associated with obstructive jaundice. Percutaneous CT-guided biopsy is a useful technique for confirming the diagnosis in patients with unresectable tumors. Porcelain gallbladder is a premalignant condition, though there is some evidence that the incidence of cancer depends on the pattern of calcification: selective mucosal calcification apparently carries a significant risk of cancer, whereas diffuse intramural calcification does not.60 It seems reasonable to resect only tumors with the former pattern, but whenever there is a question about the pattern of calcification, one should err on the side of resection.

Surgical Staging

Staging of gallbladder cancer requires knowledge of the extent of direct invasion into the liver and other adjacent organs and tissues (especially the bile duct, the portal veins, and the hepatic arteries). As in hilar CCA, this information may be obtained by means of MRCP and MRA or CT with the latest-generation scanners. Staging laparoscopy is very helpful in managing gallbladder cancer. As many as 50% of patients with this disease are found to have peritoneal or liver metastases upon staging laparoscopy,8 and they are found more often with hilar CCA than with gallbladder cancer.

Management

Rationale for surgery  When early-stage gallbladder cancer is suspected on the basis of diagnostic imaging, open cholecystectomy, rather than laparoscopic cholecystectomy, is probably the procedure of choice [see 5:21 Cholecystectomy and Common Bile Duct Exploration and 5:22 Procedures for Benign and Malignant Biliary Tract Disease]. Intraoperatively, if there is no evidence of spread outside the gallbladder, we recommend performing an extraserosal cholecystectomy, in which the fibrous liver plate is excised along with the gallbladder so that bare liver is exposed. It is possible to perform an extraserosal resection laparoscopically; however, in our opinion, this should not be attempted, because gallbladder perforation and bile spillage are more common with the laparoscopic version of the procedure. The negative consequences of tumor implantation or incomplete excision far outweigh any benefit that a minimally invasive approach might confer.

The excised specimen should be inked and a frozen section obtained. If there is gallbladder cancer in the specimen but the resection margins are clear and the tumor is a T1 lesion (i.e., has not penetrated the muscularis), the procedure is considered complete, in that lymph node metastases are uncommon with T1 tumors (incidence < 10%). However, lymph node metastases are present in 50% of patients with T2 lesions (i.e., tumors that have invaded the muscularis). Therefore, if margins are positive or the tumor is a T2 lesion, resection of segments 4b and 5 of the liver and dissection of portal and celiac lymph nodes, along with resection of the extrahepatic bile duct and hepaticojejunostomy, are recommended. If it is already clear at the commencement of the operation that the tumor is T2, one should proceed directly to liver, lymph node, and bile duct resection.

In more advanced stages of disease (T3 and T4), the aim is still excision with clear margins and resection of portal and celiac lymph nodes. To obtain clear local margins with these tumors, in addition to what is required for T2 tumors, more extensive hepatic resections—up to a trisectionectomy (resection of segments 4 through 8) [see Liver Cancer, Anatomic Considerations, below]—may be necessary, as well as resection of adjacent organs.

Incidentally discovered gallbladder cancer  Gallbladder cancer may be an incidental finding at laparoscopic cholecystectomy, as it has been at open cholecystectomy. The incidence of this finding ranges from 0.3% to 1.0%. A concern that has arisen in the current era, in which the laparoscopic approach to cholecystectomy is dominant, is the risk of port-site implantation of tumor. Port-site implantation may simply be the result of contact between the malignancy and the tissues surrounding the port site at the time of gallbladder extraction; however, positive pressure pneumoperitoneum may also play a causative role. When evidence of gallbladder wall thickening is noted intraoperatively, the gallbladder should be extracted in a sac. The gallbladder should be inspected at the time of extraction, and any questionable areas should undergo biopsy.

If a gallbladder cancer is discovered at the time of operation, it should be treated without delay according to the principles stated earlier (i.e., depending on whether the margins on the excised gallbladder are clear and on the T stage of the tumor). From an oncologic viewpoint, it would seem ideal to resect the tissue around all trocar port sites. From a technical viewpoint, however, it would be very difficult and impractical to excise the full thickness of the abdominal wall circumferentially around four port sites, especially because the tract of the port site often is not at a 90° angle to the abdominal wall. If the gallbladder was extracted through a port site without having been placed into a bag, it is reasonable to attempt excision of that one port site.

Sometimes, cancer is suspected, but frozen-section examination is inconclusive and the definitive diagnosis of cancer is not made until the early postoperative period. More often, cancer is not suspected intraoperatively, and the diagnosis is made only when permanent sections of the gallbladder are examined. In these situations, patients with completely excised T1 lesions require no further therapy, and patients with higher-stage lesions should undergo reoperation in accordance with the principles outlined earlier (see above). Other appropriate reasons for not performing the additional surgery at the time of the cholecystectomy are (1) the desire to discuss the management scheme with the patient and (2) lack of experience with the procedure for T2 tumors. Not infrequently, patients are referred to hepatic-pancreatic-biliary (HPB) centers 10 to 14 days after surgery, which is an inopportune time for reoperation, especially if the first procedure was difficult. Surgery may then be delayed for 3 to 4 weeks. We restage patients with abdominal CT scans when they are referred with this diagnosis, and it is not unusual to find hepatic metastases when this is done. The survival rate is much higher after radical resection than after cholecystectomy, even when cholecystectomy was the first procedure.61

Gallbladder polyps  Gallbladder polyps are discovered incidentally on ultrasonograms or CT scans or are diagnosed when they cause biliary colic. They may be malignant but are rarely so when less than 1 cm in diameter, especially when they are multiple. Most gallbladder polyps are less than 0.5 cm in diameter; these are almost always benign cholesterol polyps and may be followed if they are not giving rise to symptoms. Single polyps
between 0.5 and 1 cm in diameter should probably be removed by means of cholecystectomy; multiple polyps in this size range should be followed. About one quarter of all single gallbladder polyps more than 1 cm in diameter are malignant, and such polyps should be treated as malignant as a matter of policy. Almost all polyps more than 1.8 cm in diameter are malignant.33

Liver Cancer

ANATOMIC CONSIDERATIONS

A long-standing problem in discussing any surgical liver disease, especially liver cancer, has been the confusing terminology applied to liver anatomy and the various hepatic resections. Fortunately, a lucid and cogent terminology has emerged that is sanctioned by both the International Hepato-Pancreato-Biliary Association (IHPBA) and the American Hepato-Pancreato-Biliary Association (AHPBA).31 This terminology has been widely adopted around the world and translated into many languages. It may be briefly summarized as follows.

The fundamental principle is that the anatomic divisions of the liver are based on vascular and biliary anatomy rather than on surface markings [see Figure 8]. This is an important point because surgical resection is a process of isolating specific liver volumes serviced by specific vascular and biliary structures. The anatomic ramifications of the hepatic artery and the bile duct are regular and virtually identical. Liver anatomy is best understood by first following these structures through a series of orderly divisions. The branching of the portal vein on the right side is similar to that of the bile duct and the hepatic artery, but its branching on the left side, because of the fetus’s need to use the umbilical portion of the portal vein as a conduit, is unusual.

The first-order division of the proper hepatic artery and the common hepatic duct into the right and left hepatic arteries and the right and left hepatic ducts, respectively, results in division of the liver into two parts (or volumes), referred to as the right and left hemilivers (or the right and left livers) [see Figure 8 and Table 7]. In this system of terminology, the term lobe is never used to denote a hemiliver, because it bears no relation to the internal vascular anatomy. The right hepatic artery supplies the right hemiliver, and the left hepatic artery supplies the left hemiliver. The right and left hepatic ducts drain the corresponding hemilivers. The plane between these two zones of vascular supply is called a watershed. The border or watershed of the first-order division is a plane that intersects the gallbladder fossa and the fossa for the inferior vena cava and is called the midplane of the liver.

The second-order division divides each of the hemilivers into two parts [see Figure 8 and Table 7], referred to as sections. The right hemiliver comprises the right anterior section and the right posterior section, while the left hemiliver comprises the left anterior section and the left posterior section.

Figure 8 Illustrated are the anatomic divisions of the liver according to IHPBA/AHPBA-sanctioned terminology, including first-order divisions (hemilivers), second-order divisions (sections) and third-order divisions (segments).
posterior section. These sections are supplied by a right anterior sectional hepatic artery and a right posterior sectional hepatic artery and are drained by a right anterior sectional hepatic duct and a right posterior sectional hepatic duct. The left hemiliver comprises the left medial section and the left lateral section. These sections are supplied by a left medial sectional hepatic artery and a left lateral sectional hepatic artery and are drained by a left medial sectional hepatic duct and a left lateral sectional hepatic duct.

The third-order division divides the liver into nine segments, each of which has its own segmental artery and bile duct. The caudate lobe comprises segments 1 and 9. 

**Table 7 Brisbane 2000 Terminology for Hepatic Anatomy and Resections from IHPBA**

<table>
<thead>
<tr>
<th>Level of Division</th>
<th>Preferred Anatomic Term</th>
<th>Corresponding Couinaud Segments (Sg)</th>
<th>Preferred Term for Surgical Resection*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>First order (hemiliver)</td>
<td>Right hemiliver or Right liver</td>
<td>Sg 5–8 (± caudate lobe)</td>
<td>Right hepatectomy or Right hemihepatectomy (stipulate ± caudate lobe)</td>
<td>The border or watershed separating the two hemilivers is a plane that intersects the gallbladder fossa and the inferior vena cava fossa; this plane is referred to as the midplane of the liver</td>
</tr>
<tr>
<td></td>
<td>Left hemiliver or Left liver</td>
<td>Sg 2–4 (± caudate lobe)</td>
<td>Left hepatectomy or Left hemihepatectomy (stipulate ± caudate lobe)</td>
<td></td>
</tr>
<tr>
<td>Second order (section)</td>
<td>Right anterior section</td>
<td>Sg 5, 8</td>
<td>Right anterior sectionectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right posterior section</td>
<td>Sg 6, 7</td>
<td>Right posterior sectionectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left medial section</td>
<td>Sg 4</td>
<td>Left medial sectionectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left lateral section</td>
<td>Sg 2, 3</td>
<td>Left lateral sectionectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>Sg 4–8 (± caudate lobe)</td>
<td>Right trisectectomy (preferred) or Extended right hepatectomy (stipulate ± caudate lobe)</td>
<td>The borders or watersheds separating the sections within the hemilivers are planes referred to as the right intersectional plane (for which there is no surface marking) and the left intersectional plane (which passes through the umbilical fissure and the attachment of the falciform ligament)</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>Sg 2, 3, 4, 5, 8 (± caudate lobe)</td>
<td>Left trisectectomy (preferred) or Extended left hepatectomy (stipulate ± caudate lobe)</td>
<td></td>
</tr>
<tr>
<td>Third order (segment)</td>
<td>Segments 1–9</td>
<td>Any Sg</td>
<td>Segmentectomy (stipulate Sg—e.g., segmentectomy 7)</td>
<td>The borders or watersheds of the segments are planes referred to as the intersegmental planes</td>
</tr>
<tr>
<td></td>
<td>Two contiguous segments</td>
<td>Any two Sg in continuity</td>
<td>Bisegmentectomy (stipulate Sg—e.g., bisegmentectomy 7, 8)</td>
<td></td>
</tr>
</tbody>
</table>

*It is also permissible to refer to any resection in terms of its third-order components. Thus, a left hemihepatectomy may be referred to as a resection Sg 2–4 (or 1–4). |

†The caudate lobe comprises segments 1 and 9. IHPBA—International Hepato-Pancreato-Biliary Association

**PRIMARY CANCERS**

**Hepatocellular Cancer**

Hepatocellular cancer (HCC), or hepatoma, is the fifth most common cancer in the world. About 90% of cases arise in patients with chronic liver disease, especially when the disease has progressed to cirrhosis. Although any condition that produces cirrhosis may lead to HCC, the most common cause is viral hepatitis. In the United States, some 3 million people are infected with hepatitis C virus (HCV), and more than 1 million people have liver disease associated with hepatitis B virus (HBV). HCV infection is much more likely to lead to HCC than HBV infection is. AJCC staging criteria are useful for planning the management of liver cancer (see Tables 8 and 9).

**Clinical evaluation** The usual presentation of sporadic HCC consists of pain, mass, and systemic symptoms of cancer, though the disease may also be discovered incidentally. HCC occurring as a complication of liver disease may present similarly, but it is often manifested first as a deterioration of liver function with the onset of jaundice, ascites, or encephalopathy.

**Investigative studies** Screening programs are employed in high-risk populations. These programs, which use α-fetoprotein (AFP) levels and ultrasonographic examination of the liver to detect early HCC, may detect asymptomatic tumors.
The diagnosis of sporadic HCC is based on elevation of AFP levels (an indicator with 50% to 60% sensitivity) and the presence of a hepatic mass on axial images. HCCs typically demonstrate hypervascularity, which is best seen on arterial-phase images [see Figure 9]. A pseudocapsule is often visualized, which is best seen on portal venous–phase images. Multifocality is also common in HCC, and this finding often serves to differentiate it from other hepatic neoplasms. Routine biopsy is not indicated in patients with a characteristic mass, those who have a mass and an elevated AFP level, or those who are symptomatic and require treatment for pain. HCC may be very well differentiated and difficult to distinguish from hepatic adenoma and focal nodular hyperplasia on biopsy. It may also be hard to distinguish from cirrhotic nodules. Biopsy is associated with a small risk of bleeding or tumor seeding.

### Surgical staging
Staging of sporadic HCC requires axial imaging of the abdomen and imaging of the chest. FDG-PET scanning is only marginally useful: HCCs are typically well differentiated, and as a result, only 50% of the tumors are visualized. Staging laparoscopy is helpful: additional tumors are found in about 15% of patients.34

Staging also requires evaluation of the extent of liver disease. The Child–Pugh classification is used to determine operability: With few exceptions, resection is limited to Child class A patients with normal bilirubin levels (< 1.5 mg/dl), a normal or marginally raised prothrombin time (PT), and no or minimal portal hypertension. The extent of resection must be tailored to the severity of the liver disease. For instance, resection of more than two segments is limited to patients with normal liver function. Too-extensive resection puts the patients at risk for liver failure in the postoperative period. In Japan and China, indocyanine green (ICG) clearance is used in Child class A patients to determine the possible extent of resection.

### Management
Rationale for surgery. The rationale for surgery is clear in patients without liver disease or in Child class B or C patients with chronic liver disease. The rationale for surgery in Child class A patients, however, remains controversial. Partial liver resection [see 5:23 Hepatic Resection] is the procedure of choice for sporadic HCC in patients with normal livers. In Child class B or C patients with chronic liver disease, liver resection can be hazardous, and orthotopic liver transplantation (OLT) is the procedure of choice. To justify the use of donor organs, however, it is necessary to select patients with HCC so that the long-term outcome of OLT for HCC is similar to that of OLT for benign conditions. To achieve this goal, OLT is restricted to patients with a single tumor less than 5 cm in diameter or to patients with as many as three tumors, none of which are more than 3 cm in diameter (the Milan criteria). These criteria have been shown to be associated with OLT outcomes comparable to those for benign conditions.35

In Child class A patients with liver disease, hepatic resection and OLT are options if the Milan criteria are met. The optimal therapeutic approach in this situation has been the subject of considerable debate, with proponents arguing for one of two strategies—namely, (1) primary OLT or (2) resection followed by OLT if HCC recurs, provided that the patients still meet criteria for OLT (so-called salvage OLT). A complete discussion of this controversy is beyond the scope of this chapter. Currently, it would seem that the best strategy in patients who meet the criteria for OLT is to perform primary OLT for HCV-associated disease36 and to perform resection and salvage OLT for HBV-associated disease37 and other HCCs of non-HCV origin. In patients who do not meet the OLT criteria, resection would be performed even if the tumor is of HCV origin. At present, there is a trend toward liberalizing the OLT criteria to include single tumors 6 or 7 cm in diameter, especially if the source of the organ is a living donor.

When OLT is to be performed, it is important that the waiting time be short; these tumors progress over a timescale of a few months, and when viewed on an intention-to-treat basis, the results of OLT deteriorate significantly if the waiting time is long.38 In the United States, this concern has been dealt with by...
that is indistinguishable from a hepatic metastasis arising from a primary adenocarcinoma in one of several intra-abdominal or extra-abdominal sites. Special stains may be helpful in differentiating this tumor from a true secondary malignancy, but the differentiation is rarely certain. An elevated CA 19-9 concentration is strongly suggestive of this diagnosis if it is higher than 100 U/ml. To make the diagnosis of intrahepatic CCA, primary tumors in other sites must be excluded by means of axial imaging of the chest, the abdomen, and the pelvis; upper and lower GI endoscopy; and mammography. FDG-PET scanning is another means by which an extrahepatic primary may be identified, but it has not been fully evaluated in this setting.

**Surgical staging** FDG-PET scanning appears to be a promising staging tool for identifying portal lymph node and distant metastases when the primary is actually an intrahepatic CCA. Portal lymph node metastases are a contraindication to resection in patients with MF tumors; the results of resection in this situation are very poor. Left-side tumors may metastasize to lymph nodes at the cardia of the stomach and along the lesser curvature.

**Management** The considerations related to resection for intrahepatic CCA are similar to those for sporadic HCC (see above). Liver transplantation generally is not performed for this tumor, because of the typically poor results.

**SECONDARY CANCERS**

**Colorectal Metastases**

**Clinical evaluation and investigative studies** About 50% of the 150,000 patients who are diagnosed with colorectal cancer annually in the United States either have or will have liver metastases. About 10% of patients with these colorectal metastases (CRMs) are eligible for liver resection. CRMs may be diagnosed either at the time of treatment of the primary colorectal cancer (synchronous tumors) or at a later stage (metachronous tumors).

Synchronous tumors are diagnosed by means of either preoperative CT scanning or intraoperative palpation. LFTs may show elevations (especially of the serum alkaline phosphatase level), but these results are not specific. CEA levels are not helpful as long as the primary tumor is in place. Metachronous tumors are most often diagnosed in the course of a postcolectomy surveillance program, either by imaging the liver with CT scans or FDG-PET scans or by detecting a rise in the CEA level. When synchronous metastases are discovered preoperatively, a FDG-PET scan should be done to complete the staging.

**Surgical staging** In about 25% of patients, FDG-PET scanning changes management by detecting unsuspected extrahepatic or intrahepatic disease. Sometimes, it demonstrates that apparent metastases are actually benign lesions. Second primaries are not uncommon in patients with metachronous lesions; accordingly, such patients should also be staged by means of colonoscopy, if this procedure was not done in the preceding 6 months, as well as FDG-PET scanning. Staging laparoscopy adds little to staging if an FDG-PET scan has been done.

Intraoperative staging consists of careful palpation of intrabdominal structures, including hepatic and portal venous lymph nodes. In patients with metachronous lesions, however, palpation of the entire abdomen may be limited by adhesions from previous operations. IOUS of the liver may also detect unsuspected lesions, though this is less likely if the patient has already been staged by means of FDG-PET.
The main value of FDG–PET in this setting is its ability to discover unsuspected extrahepatic disease. In so doing, it helps eliminate futile hepatic resections. If a patient with extrahepatic disease is treated with hepatic resection, a “recurrence” is inevitable. Elimination of pointless resections has a positive effect on survival: a 2004 study from our institution found that the overall 5-year survival rate after FDG–PET was about 60%, compared with 40% after conventional imaging.\(^{39}\) Furthermore, the study showed that after FDG–PET scanning, the classic prognostic factors of the secondary tumor (e.g., tumor number and tumor size) were no longer significant; rather, the most important prognostic factor was the grade of the primary tumor. FDG–PET–scanned patients with poorly differentiated primary tumors did very poorly in terms of overall survival after hepatic resection.\(^{39}\) Currently, standard PET scanners are rapidly being replaced with CT–PET scanners, which fuse the images and provide superior diagnosis and staging. For planning surgical extirpation, however, the level of detail provided by high-quality contrast-enhanced CT or MRI is also required.

**Management Rationale for surgery.** The criteria that determine eligibility for resection are (1) that the primary tumor has been or can be completely resected, (2) that (with uncommon exceptions) there is no extrahepatic tumor (other than the primary), and (3) that it is possible to resect all tumors in the liver while leaving enough of a hepatic remnant to ensure that hepatic failure does not develop postoperatively. The considerations governing the extent of the resection and the use of PVE are similar to those for sporadic HCC.

Treatment of multiple tumors is much more common with CRMs than with HCC. However, nonanatomic resections are as effective as anatomic resections as long as the resection margin is microscopically clear. The traditional view has been that resection margins of 1 cm are mandatory. Whereas 1 cm margins may still be a reasonable goal, margins as narrow as 1 mm are satisfactory and are probably as effective as traditional margins, provided that they are free of microscopic and gross cancer. When close margins are expected, transection of the liver with a saline-linked RF ablation device may be useful, in that this device leaves a margin of devitalized tissue in the patient, as well as in the specimen.\(^{40}\) When the margin is very close, it may be extended by painting the cut surface of the hepatic remnant with the RF device.

Synchronous resection of the primary tumor and the liver metastases has proved to be safe\(^ {41}\) and is desired by many patients. The decision to proceed with hepatic resection should not be made until resection of the primary tumor has been completed and it has been determined that the margins are clear and the patient is stable. Some patients with a small number of lung lesions in addition to liver lesions have been cured by resection.

**Ablation of colorectal metastases.** In situ destruction of tumors with cryotherapy or RF ablation may expand the surgeon’s ability to eradicate CRMs localized to the liver.\(^ {42}\) RF ablation has largely supplanted cryotherapy in this context as a result of its lower incidence of complications and greater ease of use. Ablation may be used either as an adjunct to operative management or as the sole treatment when there are many metastases (but usually < 10). The efficacy of RF ablation as an adjunct to surgery remains to be determined. It is doubtful, however, that using this modality alone to eradicate multiple lesions will improve overall survival significantly, because the tumor biology in such cases is likely to be that of an aggressive tumor. FDG–PET scans should be performed in all such patients; the likelihood of discovering extrahepatic tumors increases as the number of hepatic tumors increases.\(^ {19}\)

RF ablation is not recommended for treatment of resectable metastases: it is not approved for this purpose, and using it in this way would mean substituting an unproven therapy of unknown efficacy for a proven therapy of known value. If a consenting patient with resectable metastases nevertheless insists on this less invasive therapy, the surgeon should document that the preceding considerations have been explained to him or her. RF ablation may be applied by means of open, laparoscopic, or percutaneous methods. There is good reason to believe that targeting ability is degraded as one moves to less invasive methods. This consideration should also be explained to patients, though undoubtedly there are some patients who, because of comorbid conditions, are candidates only for percutaneous or laparoscopic approaches.

**Neuroendocrine Metastases**

Neuroendocrine metastases are characteristically slow growing. Some are functional, especially if they arise from the ileum; metastatic liver disease from this source may produce carcinoid syndrome.
The differential diagnosis of the benign solid hepatic mass includes hepatic adenoma, focal nodular hyperplasia (FNH), focal fatty infiltration, cavernous hemangioma, and other rare neoplasms (e.g., mesenchymal hamartoma and teratoma)—all of which must be distinguished not only from one another but also from malignant tumors. In the past, several diagnostic tests (e.g., ultrasonography, CT, sulfur colloid scanning, and angiography) were used to differentiate these neoplasms. Currently, our usual practice is to perform MRI with gadolinium contrast enhancement, which generally allows accurate differentiation among benign tumors with a single test. Cavernous hemangiomas are usually easy to distinguish because they have a characteristic appearance on MRI (hypointense on T1-weighted images, very intense on T2-weighted images, and filling in from the periphery with gadolinium injection); if they are asymptomatic, they need not be resected. It is important to distinguish asymptomatic FNHs from hepatic adenomas; whereas resection is recommended for adenomas, because of their potential for hemorrhage or malignant degeneration, asymptomatic FNHs can safely be observed. An FNH is nearly isointense on T1- and T2-weighted images; it shows slightly more enhancement than normal liver parenchyma in the early phase after contrast injection, then becomes isointense. A central scar is often, but not always, seen. Conversely, a hepatic adenoma exhibits strong early-phase enhancement with contrast administration, and it tends to be hyperintense on T1-weighted images.

Given that a symptomatic hepatic mass is usually treated with resection, preoperative biopsy for tissue diagnosis is rarely necessary or desirable. Modern noninvasive radiologic tests, in conjunction with a careful patient history, are often quite accurate in predicting histologic diagnosis. Biopsy of hepatic lesions should not be performed indiscriminately, because there is a small risk of complications or tumor tracking and because biopsy results often do not change management. As a rule, biopsies should be performed when definitive surgical intervention is not planned and when pathologic confirmation is necessary for institution of nonsurgical therapy.

References


Acknowledgment

Figures 4, 6, and 8  Tom Moore.