Several different types of tumors affect the pancreas, the biliary tree, and the liver. Each year, hundreds of articles are published regarding pancreatic, biliary, and hepatic cancers. Accordingly, this chapter concentrates on essential principles. In particular, it focuses on common malignant tumors, addressing benign tumors and uncommon tumors only if far 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 pancreaticobiliary 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**

*Ductal Adenocarcinoma of the Head of the Pancreas*

Adenocarcinoma of the pancreatic head is one of the most common gastrointestinal malignancies and, because of its aggressive nature, one of the hardest cancers to cure. The safety of surgical procedures for cancers of the pancreas has improved dramatically, but 5-year actual survival rates of patients who have undergone resection are still low (about 15%). \(^1\) Cancer of the head of the pancreas is the prototypical tumor that causes painless jaundice; however, other cancers that obstruct the bile ducts also cause jaundice, including extrahepatic bile duct cancer, ampullary malignancy, duodenal cancer, and gallbladder cancer. Some of the following discussion is generalized 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, which is often mild. Severe acute pain is more often associated with other conditions that may cause jaundice (e.g., choleodocholithiasis 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, the presenting symptom is steatorrhea or diarrhea from obstruction of the pancreatic duct, weight loss, pain, or a combination of these rather than jaundice. Steatorrhea or diarrhea in the absence of jaundice 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 (Trousseau sign) is uncommon and usually signifies metastatic disease. Pancreaticobiliary malignancies cause biliary obstruction, but such obstruction is not commonly associated with biliary tract infection unless instruments have been employed in the biliary tree. Therefore, other diagnoses should be suspected in patients presenting with cholangitis who have not undergone biliary tract instrumentation. Patients with pancreatic cancer may also present with acute pancreatitis as the first manifestation. Vomiting and gastrointestinal (GI) bleeding are uncommon presenting symptoms and suggest the presence of advanced tumors that are obstructing or eroding the duodenum.

*Physical examination* Examination reveals scleral icterus. In some cases, the distended gallbladder may be palpable. In advanced cases, signs of metastatic disease (e.g., hepatomegaly and ascites) may be detected.

**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, although impaction of a stone in the bile duct can cause transient rises in serum aspartate aminotransferase 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), or 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, whereas very high concentrations (> 1,000 U/mL) suggest metastatic disease. High levels may also accompany cholangitis, but these levels should subside to normal with relief of obstruction or infection, when malignancy is absent. 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.

Imaging  Several different diagnostic imaging tests may be used in jaundiced patients, including computed tomography (CT), magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography (EUS), and transabdominal ultrasonography. The technical advances in imaging achieved over the past few years are remarkable. CT and MRI 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, although, to date, no high level studies have shown an advantage for this type of display.

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 cholangiogram (i.e., magnetic resonance cholangiopancreatography [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 cholangiograms and angiograms, as well as axial images.

The typical pancreatic cancer appears as an area of reduced attenuation (darker zone) in the pancreatic head [see Figure 1], associated with upstream dilatation of 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 may be 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 described above 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. 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 poorly timed, especially if slice thickness is 5 mm or greater, and masses that initially appear atypical may exhibit a typical appearance when the CT scan is optimized. Neuroendocrine cancers commonly display arterial-phase enhancement, which will be missed if the scan is mistimed. 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 intrapancreatic 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, the second CT scan yields important diagnostic findings.

ERCP provides an endoscopic view of the duodenum that allows identification and biopsy of ampullary and duodenal tumors, which 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 intrapancreatic 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, although such support may be reassuring when the CA 19-9 concentration is lower 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 and a presentation in keeping with the diagnosis of cancer, 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 in the remainder of the gland 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 be found to have benign disease; 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. 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. However, in these patients, the serum IgG4 level is characteristically elevated.

EUS is becoming increasingly important in the management of patients with atypical pancreatic head masses. When jaundice is present, EUS with or without ERCP is our usual approach; when it is absent, EUS alone is performed. 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. 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 resection in patients with benign disease, who in most cases are better served by biliary bypass. Fortunately, today, because of improved axial imaging and EUS, a definitive preoperative diagnosis is usually available.

**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 27% of resections done for pancreatic cancer involved resection of these veins. Recently, the term “borderline” has been introduced to describe tumors that are unresectable by standard criteria but that can be encompassed by extending the zone of resection. Usually, such tumors are first treated with chemoradiation. Attempts are also being made to downsize more advanced pancreatic tumors to a resectable state by chemohyperthermia and radiation.

To date, no long-term studies have evaluated either approach. However, given the aggressive nature of this tumor, it is likely that chemotherapy and radiation will effectively downsize tumors in only a small number of patients, at least until much more effective chemotherapeutic agents are available.

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 also detect enlarged lymph nodes, but it should be remembered that nodes may be enlarged for reasons other than cancer. Sometimes intraperitoneal fluid collections or peritoneal or omental nodules are identified; 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 is 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 in this regard; moreover, it is more operator dependent than CT. 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 at laparoscopy. Staging is completed intraoperatively by carefully inspecting the intra-abdominal...
contents, including 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 Table 1 and Table 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 preoperatively whether small liver metastases or celiac node metastases are present if laparotomy is to be undertaken anyway. Trials examining whether better palliation is offered by surgical bypass or endoscopic stenting report conflicting results; on balance, surgical bypass is still a very good treatment for localized unresectable tumors in younger patients without serious comorbidities. We no longer perform staging laparoscopy in patients with adenocarcinoma of the pancreas except in patients who are suspected to have liver or peritoneal metastases on axial imaging. Finally, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful in staging pancreatic cancer. 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.10

Rationale for pancreaticoduodenectomy The technical details of pancreaticoduodenectomy are discussed more fully elsewhere [see 5:24 Procedures for Benign and Malignant 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. Attempts have been made to improve results by extending the operation, either through more extensive lymph node dissections11 or through resections of superior mesenteric, hepatic, or celiac arteries.12 Four randomized trials have now shown no advantage for extended lymph node dissection. Resection of celiac or superior mesenteric arteries has also not been successful in improving overall survival. The lesson seems to be that invasion of additional lymph node regions (N2) or the superior mesenteric or celiac arteries 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 and perhaps short segments of the hepatic artery to address invasion of these structures by otherwise favorable tumors, extended resections are generally unsuccessful. Even these recommended vascular resections are probably best restricted to tumors that have arisen close to the particular vessels 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. These comments do not apply to tumors that initially might have required resection of the celiac or superior mesenteric arteries but that have been downsized by chemotherapy of chemoradiation so that they can be resected without such vascular resections.

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 may be associated with slightly less postoperative GI dysfunction.13 We employ pylorus preservation selectively in older, thinner patients, with the aim of minimizing disruption of GI function.

Adjuvant therapy is often given in resected patients; however, there is controversy regarding the role of chemotherapy

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<th>Table 1</th>
<th>American Joint Committee on Cancer TNM Clinical Classification of Pancreatic Cancer</th>
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| Primary tumor (T) | TX Primary tumor cannot be assessed  
T0 No evidence of primary tumor  
Tis Carcinoma in situ  
T1 Tumor limited to pancreas, ≤ 2 cm in greatest dimension  
T2 Tumor limited to pancreas, > 2 cm in greatest dimension  
T3 Tumor extends beyond pancreas but without involvement of celiac axis or SMA  
T4 Tumor involves celiac axis or SMA |
| Regional lymph nodes (N) | NX Regional lymph nodes cannot be assessed  
N0 No regional lymph node metastasis  
N1 Regional lymph node metastasis |
| Distant metastasis (M) | MX Distant metastasis cannot be assessed  
M0 No distant metastasis  
M1 No distant metastasis |

SMA = superior mesenteric artery.

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<th>American Joint Committee on Cancer Staging System for Pancreatic Cancer</th>
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versus chemoradiation. Randomized trials have shown that chemotherapy is beneficial and have questioned the role of radiotherapy. The latter may be helpful when an R1 resection has been performed.

**Adenocarcinoma of Body and Tail of the 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.

**Investigative studies** The CA 19-9 concentration may be elevated. CT usually shows a lucent (hypoattenuating) mass [see Figure 3], often with extension outside the pancreas and dilatation of the distal pancreatic duct, when the tumor is proximal to the tail of the gland. EUS is very useful for assessing indeterminate lesions.

**Surgical staging** Surgical staging of cancers of the body and the tail is similar to that of cancers of the pancreatic head and is based primarily on CT scanning of the abdomen and the thorax. Unresectability by reason of local invasion is usually attributable to the involvement of the superior mesenteric artery, hepatic artery, or the celiac artery and less commonly to the involvement of the portal vein, the superior mesenteric vein, or the aorta. Another indicator of unresectability is enlarged para-aortic nodes. Invasion of the spleen, the stomach, the left adrenal gland, the mesocolon, the colon, the retroperitoneum, or even the left kidney is not a contraindication to resection provided that clear margins may be expected. Staging laparoscopy is of great value: between 20 and 50% of patients with these tumors are found to have unresectable tumors with this modality, usually due to small liver or peritoneal implants. Cancer of the body and the tail differs from cancer of the head in that there is no effective palliation and therefore no rationale for laparotomy if the lesion is unresectable. Celiac nerve block, which is very helpful in reducing the use of narcotics for pain control, may also be performed laparoscopically or endoscopically.

**Management**

**Rationale for radical antegrade modular pancreatosplenectomy** Logically, the goal of resection of tumors of the body and tail should be the same as that of resection of tumors of the head—namely, excision of the tumor with clear margins, along with the N1 lymph nodes. In practice, this goal generally is not achieved by the traditional retrograde distal pancreatectomy, in which the spleen is taken first and which is not based on the lymph node drainage of the pancreas. Lymph node counts have been low with the traditional procedure, and positive posterior margin rates have been high. As an alternative, we have developed a technique referred to as radical antegrade modular pancreatosplenectomy (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]. Negative tangential margin rates of 90% have been achieved with this approach. 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 of premalignant lesions are mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN) (also referred to as intraductal papillary mucinous tumor). 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.

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

**Clinical evaluation and investigative studies** Patients with MCNs typically present with left-sided abdominal pain, often in the flank and the back. 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,

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**Figure 3** Shown is a typical hypoattenuating cancer of the tail of the pancreas with invasion of the hilum of the spleen and the splenic flexure of the colon. Peritumoral stranding suggests inflammation or invasion of peripancreatic fat.
a thick-walled, uncalcified cyst with associated radiologic signs of pancreatitis and often cholelithiasis, as well as cyst fluid containing 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, 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 individual cysts are tiny (honeycomb pattern), there are many cyst walls within the lesion, and then SCAs may be mistaken for solid tumors. Unlike pseudocysts and IPMNs, neither MCNs nor SCAs communicate with the pancreatic duct, although 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. The cyst fluid obtained from MCNs is often mucinous, and cyologic 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 investigations suggest that MCNs are malignant. 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 cystadenocarcinoma, and it should be evaluated and treated from the outset in the same manner as other adenocarcinomas 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 4 cm in diameter should be excised because of the possibility of malignant degeneration. MCNs associated with internal excrescences or associated with a local solid mass should be removed independent of the size of the cyst. The standard procedure has been open distal pancreatectomy with splenectomy, although lesser procedures, such as spleen-sparing distal pancreatectomy, central pancreatectomy, and enucleation, have all been used as well. Recently, laparoscopic distal pancreatectomy with or without sparing of the spleen has emerged as the procedure of choice because of the advantages of reduced postoperative pain and shortened length of stay. 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). In these cases, a more formal resection that obeys oncologic goals such as a RAMPS procedure should be employed. 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 4 cm cutoff for surgical treatment of MCNs in asymptomatic patients without other signs associated with malignant degeneration is reasonable, but recommendations could change based on additional studies of natural history. Furthermore, it is still possible that malignant degeneration could occur in smaller cysts, although the probability is low. Many cysts smaller than 2 cm 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. Occasionally, MCNs or symptomatic SCAs are located in the head of the pancreas and require pancreactoduodenectomy. Some authorities feel that very large asymptomatic SCAs should also be excised because of rare instances of malignant degeneration.

**Intraductal papillary mucinous neoplasm** IPMN begins as a metaplastic change in the cells lining the pancreatic ducts altering from a low cuboidal serous type of cell to a mucin-producing type. These cells are prone to progress to dysplasia and eventual malignant transformation. Overall, IPMNs appear to undergo malignant transformation more frequently than MCNs. There are two recognized types of IPMN, which may occur either separately or together. Intraductal papillary mucinous neoplasm (IPMN) begins as a metaplastic change in the cells lining the pancreatic ducts altering from a low cuboidal serous type of cell to a mucin-producing type. These cells are prone to progress to dysplasia and eventual malignant transformation. Overall, IPMNs appear to undergo malignant transformation more frequently than MCNs. 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] and is called “main duct IPMN.” In this type, the main pancreatic duct becomes dilated and filled with mucin. As the disease progresses toward malignancy, papillary processes may project into the lumen. The less common type, 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, although 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 sixties. Pain (usually attributable to pancreatitis arising as a result of mucous 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. The characteristic ERCP findings are a dilated papillary orifice (“fish mouth”) with mucus bulging from the orifice and a dilated pancreatic duct when contrast is injected. Sometimes, mucus prevents complete filling of the duct with dye. 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 projecting from the wall of the duct into the lumen. These signal progression of the disease toward neoplasia. In side-branch IPMN, ERCP (and often MRCP) 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** Knowledge of this entity is evolving, and recommendations are the current ones. Large duct IPMN As this entity is highly premalignant, resection is indicated once the diagnosis is made. Pancreactoduodenectomy is usually required as the disease affects the duct in the head of the pancreas in most cases. Although the duct in the body and tail of the gland may be dilated, this does not mean that it is involved in dysplastic changes as dilation may be secondary to obstruction caused by the viscous mucus in the proximal duct. Therefore, the decision of whether to perform a complete pancreatectomy is made at the time of pancreatectoduodenectomy, based on frozen section of the transected pancreatic neck. In most cases, the frozen section will show normal ductal epithelium or only mild or moderate dysplasia. Such patients do not require more pancreas to be resected. Occasionally, carcinoma, carcinoma in situ, or severe dysplasia is found, necessitating the resection of part or all of the remaining pancreas.

Small duct IPMN This entity is less likely to degenerate into malignancy, and the probability of malignant degeneration is related to size. Current indications for resection are cysts exceeding 3 cm in diameter or smaller cysts that are...
associated with symptoms, internal ex crescences, pericyst solid tumor, or pancreatic duct obstruction manifested as a dilation of the duct distal to the cyst.

With either type of IPMN, lifelong follow-up with axial imaging is needed. This problem should be thought of as a field defect in the pancreas. Large duct and small duct IPMNs may coexist, and pancreatic intraepithelial neoplasia (PanIN) lesions (dyslastic lesions of the duct) may coexist with IPMN.

Most patients who require total pancreatectomy tolerate the procedure well when they are enrolled in a program keyed to this operation. 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. The mucinous cancers associated with IPMN have a better prognosis than ductal adenocarcinomas do.21,23

NEUROENDOCRINE CANCERS

Neuroendocrine cancers account for fewer than 5% of surgically treated pancreatic malignancies. Some of these cancers are functional tumors, which produce hormones that lead to paraneoplastic syndromes. Examples include insulinoma, gastrinoma, 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.

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 mass effect and must be differentiated from ductal adenocarcinomas. Nonfunctional neuroendocrine cancers are relatively 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 pancreatectoduodenectomy or distal pancreatectomy [see 5:24 Procedures for Benign and Malignant Pancreatic Disease] is indicated. Given the slow growth rate of neuroendocrine cancers and their relatively favorable prognosis (a 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

Cancers of the biliary tract (cholangiocarcinomas) may arise at any level of the biliary tree from the smallest, most peripheral intrahepatic bile duct to the termination of the common bile duct. The lesions may be subdivided into intrahepatic and extrahepatic cholangiocarcinomas. The former are described below under “Liver Tumors.” Cholangiocarcinomas may grow in one of three phenotypic forms, a mass, a stricture, or an intraluminal polyp or excrescence, although combinations of these forms in different parts of the tumor may be present. The formal designations are “mass forming” (MF), periductal infiltrating (PI), and intraductal growth (IG). The type of growth pattern may affect the clinical presentation.

EXTRAHEPATIC 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 usual insertion point of the cystic duct 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 Table 3 and Table 4].

| Table 3 Am erican Joint Committee on Cancer TNM Clinical Classification of Extrahepatic Bile Duct Cancer |
|-------------------------------------------------|-------------------------------------|
| Primary tumor (T)                               | TX       | Primary tumor cannot be assessed   |
|                                                | T0       | No evidence of primary tumor       |
|                                                | Tis      | Carcinoma in situ                 |
|                                                | T1       | Tumor confined to bile duct histologically |
|                                                | T2       | Tumor invades beyond wall of bile duct |
|                                                | T3       | Tumor invades liver, gallbladder, pancreas, or unilateral branches of portal vein or hepatic artery |
|                                                | T4       | Tumor invades any of the following: main portal vein or branches bilaterally, common hepatic artery, or other adjacent structures (e.g., colon, stomach, duodenum, or abdominal wall) |
| Regional lymph nodes (N)                       | NX       | Regional lymph nodes cannot be assessed |
|                                                | N0       | No regional lymph node metastasis  |
|                                                | N1       | Regional lymph node metastasis    |
| Distant metastasis (M)                         | MX       | Distant metastases cannot be assessed |
|                                                | M0       | No distant metastasis             |
|                                                | M1       | Distant metastasis                |

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5 GASTROINTESTINAL TRACT AND ABDOMEN
9 TUMORS OF THE PANCREAS, BILIARY TRACT, AND LIVER — 9

02/09
Adenocarcinoma of the Head of the Pancreas, has already been addressed elsewhere. Lower duct CCA should be strongly suspected. Mass-forming bile duct cancers may also arise in the lower bile duct, but, for obvious reasons, they are difficult to differentiate from pancreatic adenocarcinomas. Perhaps in the future genetic profiling will permit this to be done. The surgical workup and management are identical.

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

<table>
<thead>
<tr>
<th>Stage</th>
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</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
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</table>

### 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 the Head of the 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 extrahepatic 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. 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. “Spyglass” cholangioscopy, in which a small endoscope is directed into the biliary tree along a catheter placed by duodenoscopy, facilitates direct biopsy of the bile duct wall and lesions that project into the lumen.

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, although 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. Mass-forming bile duct cancers may also arise in the lower bile duct, but, for obvious reasons, they are difficult to differentiate from pancreatic adenocarcinomas. Perhaps in the future genetic profiling will permit this to be done. The surgical workup and management are identical.

### 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.

**Management** The treatment for resectable lesions is pancreaticoduodenectomy, and the rationale for the extent of the resection is the same as for adenocarcinoma of the head of the pancreas.

### 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 characterized by slow growing and locally invasive, and it metastasizes more readily to lymph nodes than systemically, although intrapancreatic and peritoneal metastases are not uncommon. Most hilar CCAs are cicatrizing diffusely infiltrating cancers (PI tumors), but some form masses (MF type), and others present as papillary ingrowths (IG type). These tumors are also subdivided by the upper level of the tumor in the biliary tree according to the Bismuth classification [see Figure 6].

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, the atrophied half of the liver will be removed in almost all cases in which resection is indicated. In addition, when one side of the liver undergoes atrophy, the other side undergoes hypertrophy. These changes may 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), although 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. In patients with primary sclerosing cholangitis, the presence of CCA is often suggested by a rapid deterioration in the patient’s general 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.

**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.
Imaging Earlier [see Pancreatic Cancer, Ductal Adenocarcinoma, Adenocarcinoma of the Head of the 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 above the malignant stricture is an integral part of ERCP. Once the dye has been injected, stents must be placed to prevent post-ERCP cholangitis. This process may involve insertion of bilateral stents, including a stent in the atrophic hemiliver. Bilateral stenting is disadvantageous because the aim is to encourage atrophy of the hemiliver to be resected and hypertrophy of the hemiliver to be retained, and insertion of a stent in the atrophic side negates that aim. Starting with CT or MRI rather than with ERCP allows detection of any hilar CCA present simultaneously with detection of atrophy. At this point, the patient can be evaluated by a multidisciplinary team with expertise in this disease, and a decision can be made regarding which side of the biliary tree to decompress (if either). Whether stents should be employed in treating hilar CCA is debatable, but if a stent is inserted, only the side to be retained should be intubated. MRCP now provides resolution that is close to that obtained with direct cholangiography [see Figure 7].

ERCP does have one significant advantage in that it allows brushings to be obtained. Standard brushing techniques at this high level in the biliary tree are even less sensitive than those at lower levels, but spyglass technology (see above) has opened this area of the biliary tree to direct biopsy on a routine basis. EUS has been employed to obtain diagnostic tissue, with some degree of success; however, because the biopsy needle passes through the peritoneal cavity, concerns have been expressed regarding possible tumor seeding. Such seeding has not been an issue with lower duct cancers, because the biopsy tract is entirely within the future resection specimen. In many cases, a tissue diagnosis cannot be obtained preoperatively, and the diagnosis is based on the presence of a focal hilar stricture that causes jaundice.

Focal strictures of the upper bile ducts are strongly suggestive of cancer, but CCAs must also be differentiated from benign inflammatory tumors (also referred to as hepatic inflammatory pseudotumors and benign fibrosing disease).26 These inflammatory masses mimic upper duct CCAs but...
Figure 7 Shown is Bismuth type II cholangiocarcinoma. The right and left hepatic ducts are dilated (upper arrows), whereas the common hepatic duct is normal sized.

consist of chronic inflammatory cells and fibrous material. One distinguishing characteristic is that they do not involve blood vessels. Even today, they are very difficult to distinguish from cancers before pathologic examination of a resected specimen. Benign inflammatory tumors appear to occur most frequently in intrahepatic upper ducts, but they also occur intrahepatically and, less commonly, in lower ducts.

Gallbladder cancer may invade the porta hepatitis and appear as a CCA, especially on ERCP. Gallstones are usually present. 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. Cholecdocholithiasis 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 preclude 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. In our experience, the combination of these two investigations usually provides more useful staging information than either individually. Both are dependent on highly experienced radiologists. 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. Staging laparoscopy has provided a good yield of unresectable cases in some studies but not in others.

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.

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 35% 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 hilar CCA 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. (The caudate lobe is resected because cholangiocarcinoma tends to invade along the short caudate bile ducts, which are sometimes involved by microscopic tumor.28 This provides a wide resection zone and removes an area that is frequently involved by microscopic tumor.29)

Liver transplantation has been used successfully to manage Bismuth type IV tumors and is usually performed after neo-adjuvant chemoradiation therapy and staging laparotomy in highly selected patients.29 Liver transplantation for Bismuth tumors of lesser Bismuth grades is highly controversial.

### 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 tends to spread at an early stage to lymph nodes, to peritoneal surfaces, and to areas of the liver distant from the gallbladder fossa. AJCC staging criteria are helpful for planning management of this cancer [see Table 5 and Table 6].

#### Clinical Evaluation

Gallbladder cancer is discovered either incidentally during performance of cholecystectomy for symptomatic cholelithiasis or when the tumor causes symptoms related to invasion of the bile duct or to the effects of metastatic disease. In early stages of the disease in which the tumor 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, or 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.

**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 common. An elevation in the serum CA 19-9 concentration is the most helpful diagnostic indicator.

<table>
<thead>
<tr>
<th><strong>Table 5</strong></th>
<th>American Joint Committee on Cancer TNM Clinical Classification of Gallbladder Cancer</th>
</tr>
</thead>
</table>
| **Primary tumor (T)** | TX Primary tumor cannot be assessed  
T0 No evidence of primary tumor  
Tis Carcinoma in situ  
T1 Tumor invades lamina propria or muscle layer  
T1a Tumor invades lamina propria  
T1b Tumor invades muscle layer  
T2 Tumor invades perimuscular connective tissue; no extension beyond serosa into liver  
T3 Tumor perforates serosa (visceral peritoneum) and/or directly invades one adjacent organ or structure such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts  
T4 Tumor extends > 2 cm into liver or invades two or more adjacent organs (e.g., duodenum, colon, pancreas, omentum, or extrahepatic bile ducts) |
| **Regional lymph nodes (N)** | NX Regional lymph nodes cannot be assessed  
N0 No regional lymph node metastasis  
N1 Regional lymph node metastasis |
| **Distant metastasis (M)** | MX Distant metastasis cannot be assessed  
M0 No distant metastasis  
M1 Distant metastasis |

<table>
<thead>
<tr>
<th><strong>Table 6</strong></th>
<th>American Joint Committee on Cancer Staging System for Gallbladder Cancer</th>
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<td><strong>Stage</strong></td>
<td>T</td>
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 Imaging  Because gallbladder cancer is most curable in its early stages and because the symptoms in those stages are those of cholelithiasis, it is important for surgeons to be aware of subtle signs of gallbladder cancer that are occasionally present on sonograms. These signs include asymmetrical thickening of the gallbladder wall, thickening of the wall in a patient without a history of biliary colic, 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, although 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. 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 of 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 on staging laparoscopy, and as with carcinoma of the body of the pancreas, no useful palliative measures can be undertaken at laparotomy.

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 extraroserol 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 extraroserol 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 the portal and hepatic lymph nodes are recommended. Resection of the extrahepatic bile duct and hepaticojunostomy may be needed in some cases to obtain a complete node clearance, but this is being done less frequently as experience with portal node clearance has been obtained. 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 is the result of contact between the malignancy and the tissues surrounding the port site at the time of gallbladder extraction. Therefore, 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) a lack of experience with the procedure for T2 tumors. Not infrequently, patients are referred to hepatic-pancreatic-biliary 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. \(^{32}\)

**Gallbladder polyps** Benign gallbladder polyps may be adenomas or more commonly a focal form of cholesterolosis. Multiple polyps are most often due to cholesterolosis. 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 asymptomatic polyps in this size range should be followed because they are more likely to be due to cholesterolosis. 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. \(^{33}\) Gallbladder sludge and stones may be mistaken for polyps. They are differentiated by using Doppler ultrasonography to determine if the lesion has internal blood flow. If internal blood flow is absent, the lesion is unlikely to be a polyp.

**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...

*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).
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 is unusual as a result of the need in the fetus that the umbilical portion of the portal vein acts as a conduit carrying blood in the reverse direction to that postnatally.

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.”

### Table 7 Brisbane 2000 Terminology for Hepatic Anatomy and Resections of the 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 hemipatectomy (stipulate ± caudate lobe)</td>
<td>The border or watershed separating the two hemilivers is a plane that intersects the gallbladder fossa and the IVC 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 hemipatectomy (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>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>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 trisectionectomy (preferred) or Extended right hepatectomy or Extended right hemipatectomy (stipulate ± caudate lobe)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>Sg 2, 3, 4, 5, 8 (± caudate lobe)</td>
<td>Left trisectionectomy (preferred) or Extended left hepatectomy or Extended left hemipatectomy (stipulate ± caudate lobe)</td>
<td></td>
</tr>
<tr>
<td>Third order (segment)</td>
<td>Segments 1–8</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>

IHPBA = International Hepato-Pancreato-Biliary Association; IVC = inferior vena cava.

*It is also permissible to refer to any resection in terms of its third-order components. Thus, a left hemipatectomy may be referred to as a resection Sg 2–4 (or 1–4).
The second-order division divides each of the hemilivers into two parts \[\text{see Figure 8 and Table 7}\], referred to as sections. The right hemiliver comprises the right anterior section and the right 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 \[\text{see Figure 8 and Table 7}\]. The caudate lobe, a unique portion of the liver that is separate from the right and left hemilivers, is also referred to as segment 1. The left lateral section comprises segments 2 and 3; the left medial section comprises segment 4 (which is sometimes further divided into segments 4a and 4b); the right anterior section comprises segments 5 and 8; and the right posterior section comprises segments 6 and 7.

**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 \[\text{see Table 8 and Table 9}\].

**Clinical evaluation** The usual presentation of sporadic HCC consists of pain, mass, and systemic symptoms of cancer, although 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 \(\alpha\)-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 \[\text{see Figure 9}\]. A pseudocapsule is often visualized, which is best seen on portal venous–phase images. MRI has been found to be more sensitive than CT in the detection of HCC. The characteristic findings are those of a hypervascular tumor on the arterial phase with washout of contrast in the venous phase. These findings also help differentiate HCC from cirrhotic...
nodules, which typically do not show washout. Multifocality is also common in HCC, unlike 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-Pugh class A patients with near-normal bilirubin levels (<1.5 mg/dL), a normal or marginally raised prothrombin time, 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 clearance is used in Child-Pugh 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-Pugh class B or C patients with chronic liver disease. The rationale for surgery in Child-Pugh 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-Pugh 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-Pugh 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. 36,37 provided that the patients still meet the 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 resection followed by transplantation if disease recurs. 36,37 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 the introduction of the Model for End-stage Liver Disease (MELD) scoring system, which gives priority to recipients with HCC. It is common in the United States—and even more usual in countries with longer waiting times—to inhibit the growth of the HCC with various bridging-to-transplantation strategies during the waiting period for OLT. Such strategies include systemic chemotherapy, local treatments (e.g., radio-frequency [RF] ablation and alcohol injection), transarterial chemoembolization (TACE), and even resection of the HCC (so-called bridge resection). TACE may also be used to downsize tumors so that they meet transplant criteria.

In patients with nondiseased livers, the extent of resection depends on the size and position of the tumor. As much as 75% of the liver may be safely excised when normal liver function is present. The size of the future hepatic remnant may be determined by means of imaging. PVE of the side of the liver to be resected may be performed preoperatively to increase the size of the future remnant. It may also be used for this purpose in patients with liver disease. In these patients, PVE functions as a test of the liver’s ability to regenerate. Failure to respond to PVE is itself a contraindication to surgery in patients with chronic liver disease.

As a rule, liver resections for HCC should be anatomic [see 5:23 Hepatic Resection]. Recurrence rates are higher with nonanatomic resections because HCCs grow along portal veins and metastasize locally within segments, sections, or hemilivers, depending on how far they reach back along the portal veins. When a nonanatomic resection is performed, the resection margins should be 2 cm or greater. When HCC reaches the main portal vein, resection is generally contraindicated; the results are very poor in this situation.

**Intrahepatic Cholangiocarcinoma**

**Clinical evaluation** Intrahepatic CCAs arise from intrahepatic bile ducts. The three phenotypic types, MF, PI, and IG, are described above. The MF type is by far the most common. Intrahepatic CCA tumor usually occurs in normal livers. The presentation is similar to that of sporadic HCC.

**Investigative studies** The appearance of intrahepatic CCA on CT is suggestive of a secondary tumor [see Figure 10]. Unlike HCC, diagnosis of intrahepatic CCA often requires biopsy, which reveals an adenocarcinoma that is indistinguishable from a hepatic metastasis. 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 helpful method by which an extrahepatic primary tumor may be identified.

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

**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 [see Figure 11] 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 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 scans change management as a result of detecting unsuspected extrahepatic or intrahepatic disease. Sometimes it demonstrates that apparent metastases are actually benign lesions. Second primary tumors 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 intra-abdominal 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, although 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

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**Figure 10** Computed tomographic scan shows a mass-forming intrahepatic cholangiocarcinoma.

**Figure 11** Colorectal metastasis. (a) Computed tomography shows a single large tumor in right hemiliver; (b) is the resected specimen.
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. Furthermore, after FDG-PET scanning has been done, the most important prognostic factors determining long-term outcome are the grade of the primary colorectal tumor and whether the primary tumor had metastasized to lymph nodes. FDG-PET–scanned patients with poorly differenti ated primary tumors do poorly in terms of overall survival after hepatic resection. In recent years, standard PET scanners have been 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 classic criteria that determined 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 tumor), 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 and lesser margins lead to poorer results. This view has been challenged in several studies that claim that 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. This issue must be considered to still be unsettled, and, certainly, 1 cm margins should be the goal whenever feasible. 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 and in the specimen. 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 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.

The classical criteria for resection have been challenged and extended by new surgical approaches and the advent of much improved chemotherapy, including oxaliplatin and irinotecan, as well as the targeted monoclonal antibodies bevacizumab and cetuximab. These agents have demonstrated the ability to downsize colorectal tumors both in the liver and at extrahepatic sites. Thus, many formerly unresectable patients can now have liver resection after downsizing with chemotherapy. It is generally agreed that the best time for surgery is when the size and the position of tumors are such that liver resection can be done safely. Continuing chemotherapy until maximal effect is undesirable because irinotecan has been associated with the development of steatohepatitis and oxaliplatin with endotheliolitis. These injuries can make liver resection hazardous. Furthermore, continued downsizing may make tumors difficult to locate. This is important because although tumors may show a complete radiologic response on CT and FDG-PET scans, this is infrequently associated with a complete pathologic response. The ability to resect multiple large tumors from the liver has been enhanced by PVE and two-stage hepatectomy. In this approach, one side of the liver is cleared of tumor and the portal vein on the other side is occluded. At a second stage, the atrophied side containing the bulk of the disease (usually the right hemiliver) is excised.

Extrahepatic disease in patients with hepatic metastases Good results have been obtained in patients with recurrent disease in the primary colorectal site and liver metastases, as well as liver and lung metastases. With the advent of the new chemotherapy, it may be warranted to extend this approach to patients with liver and portal lymph node metastases but not with positive lymph nodes in the celiac or para-aortic regions. Peritoneal metastases have been treated successfully by resection combined with hyperthermic intraperitoneal chemotherapy. Whether this approach combined with liver resection would be effective in patients with liver and peritoneal metastases is uncertain. Its application seems warranted in selected well-followed cases.

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. 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. Recent data suggest that the preceding statement is correct. FDG-PET scans should be performed in all such patients; the likelihood of discovering extrahepatic tumors increases as the number of hepatic tumors increases.

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. Again, based on recent publications, it is highly likely that RF ablation results in poorer long-term survival than liver resection. 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. 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, although, 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. \(^{11}\) In-pentetreotide imaging (OctreoScan, Mallinckrodt Inc., Hazelwood, Missouri) provides staging information comparable to that provided by FDG-PET in patients with CRMs.

The aims of surgical treatment are (1) to eradicate the cancer and (2) to reduce hormonal symptoms. The considerations regarding tumor eradication for neuroendocrine metastases are similar to those for CRMs—that is, resection should be performed if all cancer can be removed and no extrahepatic cancer is detectable. In highly symptomatic patients in whom conservative therapy with octreotide has failed, debulking the tumor by means of either chemoembolization or surgery may provide relief. The former is more suitable for patients with multiple small, diffuse metastases, whereas the latter is preferred for patients with large localized tumors. RF ablation may also be employed, either combined with surgical treatment or alone; this is an excellent use of this procedure in that the aim is cytoreduction rather than eradication. Debubling tumors in asymptomatic patients with the intention of extending survival is controversial. It is not recommended when more than 10% of the tumor will remain.

Noncolorectal, Non-neuroendocrine Metastases

Occasionally, liver metastases from other primary sites behave like CRMs in that they are localized to part of the liver in the absence of extrahepatic disease. Such patients can be managed according to the same approach employed for CRMs, although the outcome is somewhat less satisfactory. Tumors that have been treated in this way with acceptable results include breast cancers, renal cell cancers, gastric cancers, acinar cell cancers of the pancreas, and ovarian cancers. Liver resection for more aggressive malignancies (e.g., metastases from gallbladder cancer and pancreatic ductal adenocarcinomas) can be expected to yield very poor results.

Incidentally Discovered Asymptomatic Hepatic Mass

Now that transaxial imaging of the abdomen is commonly performed for a variety of complaints, the problem of the incidentally discovered asymptomatic hepatic mass is being encountered with increased frequency. Generally, cysts are easily distinguished from solid tumors; the main diagnostic issue is differentiation of the various solid lesions.

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 and 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 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.

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References


