HISTORICAL PERSPECTIVE

The surface anatomy of the liver was described as early as 2000 BC by the ancient Babylonians. Even Hippocrates understood and described the seriousness of liver injury. In 1654, Francis Glisson was the first physician to describe the essential anatomy of the blood vessels of the liver accurately. The beginnings of liver surgery are described as rudimentary excisions of eviscerated liver from penetrating trauma. The first documented case of a partial hepatectomy is credited to Berta, who amputated a portion of protruding liver in a patient with a self-inflicted stab wound in 1716.

In the late 1800s, the first gastrectomies and cholecystectomies were being performed in Europe. At that time, surgery on the liver was regarded as dangerous, if not impossible. In 1897, Elliot, in his report on liver surgery for trauma, said that the liver was so “friable, so full of gaping vessels and so evidently incapable of being sutured that it had always seemed impossible to successfully manage large wounds of its substance.” European surgeons began to experiment with techniques of elective liver surgery on animals in the late 1800s. The credit for the first elective liver resection is a matter of debate and many surgeons have been given credit, but it certainly occurred during this period.

The early 1900s saw some small but significant advances in liver surgery. Techniques for suturing major hepatic vessels and the use of cautery for small vessels were applied and reported. The most significant advance of that time was probably that of J. Hogarth Pringle. In 1908, he described digital compression of the hilar vessels to control hepatic bleeding from traumatic injuries. The modern era of hepatic surgery was ushered in by the development of a better understanding of liver anatomy and formal anatomic liver resection. Credit for the first anatomic liver resection is usually given to Lortat-Jacob, who performed a right hepatectomy in 1952 in France. Pack from New York and Quattelbaum from Georgia performed similar operations within the next year and were unlikely to have had any knowledge of Lortat-Jacob’s report. Descriptions of the segmental nature of liver anatomy by Couinaud, Goldsmith, and Woodburne in 1957 opened the door even wider and introduced the modern era of liver surgery.

Despite these improvements, hepatic surgery was plagued by tremendous operative morbidity and mortality from the 1950s into the 1980s. Operative mortality rates in excess of 20% were common and usually related to massive hemorrhage. Many surgeons were reluctant to perform hepatic surgery because of these results, and understandably, many physicians were reluctant to refer patients for hepatectomy. With the courage of patients and their families as well as the persistence of surgeons, safe hepatic surgery has now been realized. A complete list is not possible here, but courageous hepatic surgeons such as Blumgart, Bismuth, Longmire, Fortner, Schwartz, Starzl, and Ton deserve mention.

Advances in anesthesia, intensive care, antibiotics, and interventional radiologic techniques have also contributed tremendously...
to the safety of major hepatic surgery. Total hepatectomy with liver transplantation and live donor partial hepatectomy for transplantation are now performed routinely in specialized transplantation centers. Partial hepatectomy for a large number of indications is now performed throughout the world in specialized centers, with mortality rates of 5% or less. Partial hepatectomy on normal livers is now consistently performed, with mortality rates of 1% to 2%.

Safely performed open hepatic surgery with its liberal use in the management of a wide variety of diseases is now a reality. Moreover, minimally invasive approaches to liver surgery have been developed and are now being used in significant numbers. However, the learning curve remains steep, and the indications for this technique are still being carefully defined. Use of robotics in liver surgery may help in addressing the issues with learning curve with laparoscopy. The addition of robotics offers advanced suturing and articulation that closely approximate the open surgery. This allows a greater proportion of cases to be performed in total minimally invasive fashion. The role of robotics in liver surgery is rapidly evolving. Thermal ablative techniques to treat hepatic tumors, including radiofrequency and microwave ablation, have exploded in popularity. Finally, techniques to improve the safety of liver resection further, such as portal vein embolization to induce preoperative hypertrophy of the future liver remnant (FLR), have been developed and are now being used.

**ANATOMY AND PHYSIOLOGY**

**Anatomy**

**Gross Anatomy**

A precise knowledge of the anatomy of the liver is an absolute prerequisite to performing surgery on the liver or biliary tree. During the last several decades, a greater appreciation for the complex anatomy beyond the misleading minimal external markings has been realized. The anatomic contributions of Couinaud (see later) and the description of the segmental nature of the liver should be embraced and studied by students of hepatic surgery.

**General description and topography.** The liver is a solid gastrointestinal organ whose mass (1.2–1.6 kg) largely occupies the right upper quadrant of the abdomen. The costal margin coincides with the lower margin of the liver, and the diaphragm drapes over the superior surface of the liver. The large majority of the right liver and most of the left liver are covered by the thoracic cage. The posterior surface straddles the inferior vena cava (IVC). A wedge of liver extends to the left side of the abdomen. The liver is invested in peritoneum except for the gallbladder fossa, porta hepatis, and posterior aspect of the liver on either side of the IVC in two wedge-shaped areas. This region of liver to the right of the IVC, which is devoid of peritoneal coverage, is called the bare area of the liver. The peritoneal duplications on the liver surface are referred to as ligaments. The diaphragmatic peritoneal duplications are referred to as the coronary ligaments, whose lateral margins on either side are the right and left triangular ligaments. From the center of the coronary ligament emerges the falciform ligament, which extends anteriorly as a thin membrane connecting the liver surface to the diaphragm, abdominal wall, and umbilicus.

The ligamentum teres (the obliterated umbilical vein) runs along the inferior edge of the falciform ligament from the umbilicus to the umbilical fissure. The umbilical fissure is on the inferior surface to the diaphragm, abdominal wall, and umbilicus. The ligamentum teres (the obliterated umbilical vein) runs along the inferior edge of the falciform ligament from the umbilicus to the umbilical fissure. The umbilical fissure is on the inferior surface to the diaphragm, abdominal wall, and umbilicus.

FIG. 54.1 (A) Historically, the liver was divided into right and left lobes by the external marking of the falciform ligament. On the inferior surface of the falciform ligament, the ligamentum teres can be seen entering the umbilical fissure. (B) The posterior and inferior surface of the liver is shown. The liver embraces the inferior vena cava (IVC) posteriorly in a groove. The lumens of the three major hepatic veins and right adrenal vein can be seen directly entering the IVC. The bare area, bounded by the right and left triangular ligaments, is illustrated. To the left of the IVC is the caudate lobe, which is bounded on its left side by a fissure containing the ligamentum venosum. The lesser omentum terminates along the edge of the ligamentum venosum, and thus the caudate lobe lies within the lesser sac and the rest of the liver lies in the supracolic compartment. A layer of fibrous tissue can be seen bridging the right lobe to the caudate lobe posterior to the IVC, thus encircling it. This ligament of tissue must be divided on the right side in mobilizing the right liver off the IVC. (From Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver and biliary tract. In: Blumgart LH, Fong Y, eds. Surgery of the Liver and Biliary Tract. London: WB Saunders; 2000:3–34.)
hepatic hilum. Venous drainage is through the right, middle, and left hepatic veins that empty directly into the suprahepatic IVC.

**Normal development and embryology.** The developing liver shares a common progenitor with the biliary tree and pancreas. During embryogenesis, signals are transmitted from the cardiac mesenchyme and septum transversum. The molecules regulating this (e.g., fibroblast growth factor, bone morphogenetic protein, Wnt, tissue growth factor beta [TGF-β]) have begun to be elucidated. The liver primordium begins to form in the third week of development as an outgrowth of endodermal epithelium, known as the hepatic diverticulum or liver bud. The connection between the hepatic diverticulum and the future duodenum narrows to form the bile duct, and an outpouching of the bile duct forms into the gallbladder and cystic duct. Hepatic cells develop cords and intermingle with the vitelline and umbilical veins to form hepatic sinusoids. Simultaneously, hematopoietic cells, Kupffer cells, and connective tissue form from the mesoderm of the septum transversum. The mesoderm of the septum transversum connects the liver to the ventral abdominal wall and foregut. As the liver protrudes into the abdominal cavity, these structures are stretched into thin membranes, ultimately forming the falciform ligament and lesser omentum. The mesoderm on the surface of the developing liver differentiates into visceral peritoneum, except superiorly, where contact between the liver and mesoderm (future diaphragm) is maintained, forming a bare area devoid of visceral peritoneum (Fig. 54.2).

The primitive liver plays a central role in the fetal circulation. The vitelline veins carry blood from the yolk sac to the sinus venosus and ultimately form a network of veins around the foregut (future duodenum) that drain into the developing hepatic sinusoids. These vitelline veins eventually fuse to form the portal, superior mesenteric, and splenic veins. The sinus venosus, which empties into the fetal heart, becomes the hepatocardiac channel and then the hepatic veins and retrohepatic IVC. The umbilical veins, which are paired early on, carry oxygenated blood to the fetus. Initially, the umbilical veins drain into the sinus venosus, but at week 5 of development, they begin to drain into the hepatic sinusoids. The right umbilical vein ultimately disappears, and the left umbilical vein later drains directly into the hepatocardiac channel, bypassing the hepatic sinusoids through the ductus venosus. In the adult liver, the remnant of the left umbilical vein becomes the ligamentum teres, which runs in the falciform ligament into the umbilical fissure, and the remnant of the ductus venosus becomes the ligamentum venosum at the termination of the lesser omentum under the left liver (Fig. 54.3).

The adult liver is a complex system of numerous cell types, including hepatocytes, cholangiocytes, neuroendocrine cells, hepatic progenitors (known as oval cells), myofibroblastic mesenchymal cells (known as hepatic stellate cells and portal myofibroblasts), resident macrophages (known as Kupffer cells), and vascular endothelial cells.

**Functional Anatomy**

Historically, the liver was divided into left and right lobes by the obvious external landmark of the falciform ligament. Not only was this description oversimplified, but it was also anatomically incorrect in relation to the blood supply to the liver. Our understanding of functional liver anatomy has become more sophisticated.

The functional anatomy of the liver (Figs. 54.4 and 54.5) is composed of eight segments, each supplied by a single portal triad (also called a pedicle) composed of a portal vein, hepatic artery, and bile duct. These segments are further organized into four sectors, separated by scissurae containing the three main hepatic veins. The four sectors are even further organized into the right and left liver. The terms right liver and left liver are preferable to the terms right lobe and left lobe because there is no external mark that allows the identification of the right and left liver. This system was originally described in 1957 by Goldsmith and Woodburne and by Couinaud. It defines hepatic anatomy because it is most relevant to surgery of the liver. The functional anatomy is more often seen as cross-sectional imaging (Fig. 54.6).

The main scissura contains the middle hepatic vein, which runs in an anteroposterior direction from the gallbladder fossa to the left side of the vena cava. It divides the liver into right and left hemilivers. The line of the main scissura is also known as Cantlie line. The right liver is divided into anterior (segments V and VIII) and posterior (segments VI and VII) sectors by the right scissura, which contains the right hepatic vein. The right portal pedicle is composed of the right hepatic artery, portal vein, and bile duct. It splits into right anterior and right posterior pedicles, which supply the segments of the anterior and posterior sectors.

The left liver has a visible fissure along its inferior surface called the umbilical fissure. The ligamentum teres, containing the remnant of the umbilical vein, runs into this fissure. The falciform ligament is contiguous with the umbilical fissure and ligamentum teres. The umbilical fissure is not a scissura and does not contain a hepatic vein; it contains the left portal pedicle, which contains the left portal vein, hepatic artery, and bile duct. This pedicle runs in this fissure and branches to feed the left liver. The left liver is split into anterior (segments III and IV) and posterior (segment II, the only sector composed of a single segment) sectors by the left scissura. The left scissura runs posterior to the ligamentum teres and contains the left hepatic vein.

At the hilum of the liver, the right portal triad has a short extrahepatic course of approximately 1 to 1.5 cm before entering the substance of the liver and branching into anterior and posterior sectoral branches. The left portal triad, however, has a long extrahepatic course of up to 3 to 4 cm and runs transversely along the

![FIG. 54.2](image-url)
base of segment IV in a peritoneal sheath, which is the upper end of the lesser omentum. This connective tissue is known as the hilar plate (Fig. 54.7). The continuation of the left portal triad runs anteriorly and caudally in the umbilical fissure and gives branches to segments II and III on the left and recurrent branches to segment IV on the right side.

The caudate lobe (segment I) is the dorsal portion of the liver. It embraces the IVC on its ventral surface and lies posterior to the left portal triad inferiorly and the left and middle hepatic veins superiorly. The main bulk of the caudate lobe is to the left of the IVC, but inferiorly, it traverses between the IVC and left portal triad, where it fuses to the right liver (segments VI and VII). This part of the caudate lobe is known as the right portion or the caudate process. The left portion of the caudate lobe lies in the lesser omental bursa and is covered posteriorly by the gastrohepatic ligament (lesser omentum) that separates it from segments II and III anteriorly. The gastrohepatic ligament attaches to the ligamentum venosum (sinus venosus remnant) along the left side of the left portal triad (Fig. 54.8).

The vascular inflow and biliary drainage to the caudate lobe come from both the right and left pedicles. The right side of the caudate, the caudate process, largely derives its portal venous supply from the right portal vein or the bifurcation of the main portal vein. The left portion of the caudate derives its portal venous inflow from the left main portal vein. The arterial supply and biliary drainage are generally through the right posterior pedicle system for the right portion and through the left main pedicle for the left portion. The hepatic venous drainage of the caudate is unique because a number of posterior small veins drain directly into the IVC.

The posterior edge of the left side of the caudate terminates as a fibrous component that attaches to the crura of the diaphragm and also runs posteriorly, wrapping behind the IVC and attaching to segment VII of the right liver. In up to 50% of people, this fibrous component is composed partially or completely of liver parenchyma. Thus, liver tissue may completely encircle the IVC. This structure is known as the caval ligament and is important to recognize in mobilizing the right liver or the caudate lobe off the vena cava.

Anomalous development of the liver is uncommonly encountered. Complete absence of the left liver has been reported. A tongue of tissue extending inferiorly off the right liver has been described (Riedel lobe). Rare cases of supradiaphragmatic liver in the absence of a hernia sac have been noted.

Portal vein. The portal vein provides approximately 75% of the hepatic blood inflow. Despite being postcapillary and largely deoxygenated, its high flow rate provides 50% to 70% of the liver’s oxygen requirement. The lack of valves in the portal venous system provides a system that can accommodate high flow at low pressure. This also allows the measurement of portal venous pressure at any point along the system.

![Diagram of liver development](image-url)

**FIG. 54.3** (A) Umbilical and vitelline vein development of a 5-week-old embryo. The hepatic sinusoids have developed, and, although there are channels that bypass these sinusoids, the vitelline and umbilical veins are beginning to drain into them. (B) In the second month, the vitelline veins drain directly into the hepatic sinusoids. The ductus venosus has formed and accepts oxygenated blood from the left umbilical vein, bypasses the hepatic sinusoids, and directly enters the hepatocardiac channel. (C) By the third month, the vitelline veins have formed into the portal system (splenic, superior mesenteric, and portal veins). The right umbilical vein has disappeared, and the left umbilical vein (future ligamentum teres) drains into the sinus venosus, bypassing the hepatic sinusoids. Note the development of the inferior vena cava and hepatic veins. (From Sadler TW. Langman’s Medical Embryology. 5th ed. Baltimore: Williams & Wilkins; 1985.)
The portal vein forms behind the neck of the pancreas at the confluence of the superior mesenteric vein and the splenic vein. The length of the main portal vein ranges from 5.5 to 8 cm, and its diameter is usually approximately 1 cm. Cephalad to its formation behind the neck of the pancreas, the portal vein runs behind the first portion of the duodenum and into the hepatoduodenal ligament, where it runs along the right border of the lesser omentum, usually posterior to the common bile duct and proper hepatic artery. The left gastric or coronary vein can variably drain into the portal vein, splenic vein, or the junction of the two.

The portal vein divides into main right and left branches at the hilum of the liver. The portal vein is the only vein with both tributaries and branches. The left branch of the portal vein runs transversely along the base of segment IV and into the umbilical fissure, where it gives off branches to segments II and III and feedback branches to segment IV. The left portal vein also gives off posterior branches to the left side of the caudate lobe. The right portal vein has a short extrahepatic course; it usually enters the substance of the liver, where it splits into anterior and posterior sectoral branches. These sectoral branches can occasionally be seen extrahepatically and can come off the main portal vein before its bifurcation. There is usually a small caudate process branch off the main right portal vein or at the right portal vein bifurcation that comes off posteriorly to supply this portion of liver (Fig. 54.9).

There are a number of connections between the portal and systemic venous systems. Under conditions of high portal venous pressure, these portosystemic connections may enlarge secondarily to collateral flow. This concept is reviewed in more detail later in the chapter, but the most significant portosystemic collateral locations are the following: the submucosal veins of the proximal stomach and distal esophagus receive portal flow from the short gastric veins and the left gastric vein and can result in varices, with the potential for hemorrhage; the umbilical and abdominal wall veins recanalize from flow through the umbilical vein in the ligamentum teres, resulting in caput medusae; the superior hemorrhoidal plexus receives portal flow from inferior mesenteric vein tributaries and can form large hemorrhoids; and other retroperitoneal communications yield collaterals that can make abdominal surgery hazardous.

The anatomy of the portal vein and its branches is relatively constant and has much less variation than the biliary ductal and hepatic arterial systems. The standard configuration, where main portal vein divides into the left and right branches and the right portal vein then divides into right anterior and right posterior portal vein, is found in up to 70% of individuals. The most common variant from this configuration is the so-called “portal vein trifurcation,” where the main portal vein divides into three branches: the left portal vein, the right anterior portal vein, and the right posterior portal vein. The second most common variant is the right posterior portal vein originating as the first branch of portal vein. This can also be envisioned as the right anterior portal vein arising from the left portal vein. These two variations account for the majority of the variations from the so-called normal anatomy. The portal vein is rarely found anterior to the neck of the pancreas and duodenum. Entrance of the portal vein directly into the vena

![FIG. 54.4](image.png) Schematic depiction of the segmental anatomy of the liver. Each segment receives its own portal pedicle (triad of portal vein, hepatic artery, and bile duct). The eight segments are illustrated, and the four sectors, divided by the three main hepatic veins running in scissurae, are shown. The umbilical fissure (not a scissural) is shown to contain the left portal pedicle. (From Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver and biliary tract. In: Blumgart LH, Fong Y, eds. Surgery of the Liver and Biliary Tract. London: WB Saunders; 2000:3–34.)

![FIG. 54.5](image.png) Segmental anatomy of the liver. (A) As seen at laparotomy in the anatomic position. (B) In the ex vivo position. (From Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver and biliary tract. In: Blumgart LH, Fong Y, eds. Surgery of the Liver and Biliary Tract. London: WB Saunders; 2000:3–34.)
cava has also been described. Very rarely, a pulmonary vein may enter the portal vein. Finally, there may be a congenital absence of the left branch of the portal vein. In this situation, the right branch courses through the right liver and curves around peripherally to supply the left liver, or the right anterior sectoral vein can arise from the left portal vein.

Hepatic artery. The hepatic artery, representing high-volume oxygenated systemic arterial flow, provides approximately 25% of the hepatic blood flow and 30% to 50% of its oxygenation. The common description of the arterial supply to the liver and biliary tree is present only approximately 60% of the time (Fig. 54.10). The celiac trunk originates directly off the aorta, just below the aortic diaphragmatic hiatus, and gives off three branches—splenic artery, left gastric artery, and common hepatic artery. The common hepatic artery passes forward and to the right along the superior border of the pancreas and runs along the right side of the lesser omentum, where it ascends toward the hepatic hilum, lying anterior to the portal vein and to the left of the bile duct. At the point where the common hepatic artery begins to head superiorly toward the hepatic hilum, it gives off the gastroduodenal artery, followed by the supraduodenal artery and right gastric artery. The common hepatic artery beyond the takeoff of the gastroduodenal artery is called the proper hepatic artery; it divides into right and left hepatic arteries at the hilum. The left hepatic artery heads vertically toward the umbilical fissure to supply segments II, III, and IV. The left hepatic artery usually also gives off a middle hepatic artery branch that heads toward the right side of the umbilical fissure and supplies segment IV. The right hepatic artery usually runs posterior to the common hepatic bile duct and enters Calot triangle, bordered by the cystic duct, common hepatic duct, and liver edge, where it gives off the cystic artery to supply the gallbladder and then continues into the substance of the right liver.

Unlike portal vein anatomy, hepatic arterial anatomy is extraordinarily variable (Fig. 54.11). An accessory vessel is described as an aberrant origin of a branch that is in addition to the normal
branching pattern. A replaced vessel is described as an aberrant origin of a branch that substitutes for the lack of the normal branch. The hepatic artery usually originates off the celiac trunk. However, branches or the entire hepatic arterial system can originate off the superior mesenteric artery. The right and left hepatic arteries can also arise separately off the celiac axis. Replaced or accessory right hepatic arteries come off the superior mesenteric artery and are present approximately 11% to 21% of the time. Hepatic vessels replaced to the superior mesenteric artery run behind the head of the pancreas, posterior to the portal vein in the portacaval space. This is evident on cross-sectional imaging as well as during operative exploration by feeling hepatic artery pulsation in the
lateral border of the hepatoduodenal ligament behind the portal vein and bile duct. The right hepatic artery, in its usual branching pattern, can also course anterior to the common hepatic duct. A replaced or accessory left hepatic artery is present approximately 3.8% to 10% of the time, originates from the left gastric artery, and courses within the lesser omentum, heading toward the umbilical fissure. Other important variations include the origin of the cystic artery usually comes off the right hepatic artery within the triangle of Calot. (From Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver and biliary tract. In: Blumgart LH, Fong Y, eds. Surgery of the Liver and Biliary Tract. London: WB Saunders; 2000:3–34.)

**FIG. 54.9** Anatomy of the portal vein. The superior mesenteric vein (SMV) joins the splenic vein (SV) posterior to the neck of the pancreas (shaded area) to form the portal vein. Note the entrance of the inferior mesenteric vein (IMV) into the splenic vein, the most common anatomic arrangement. In its course superiority in the edge of the lesser omentum posterior to the common bile duct and hepatic artery, the portal vein receives venous effluent from the coronary vein (CV). At the hepatic hilum, the portal vein bifurcates into a larger right portal vein (RPV) and a smaller left portal vein (LPV). The LPV runs transversely at the base of segment IV and enters the umbilical fissure to supply the segments of the left liver. Just before the umbilical fissure, the LPV usually gives off a sizable branch to the caudate lobe. The RPV enters the substance of the liver and splits into right anterior sectoral (RAS) and right posterior sectoral (RPS) branches. It also gives off a posterior branch to the right side of the caudate lobe—caudate process. (From Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver and biliary tract. In: Blumgart LH, Fong Y, eds. Surgery of the Liver and Biliary Tract. London: WB Saunders; 2000:3–34.)

**Hepatic veins.** The three major hepatic veins drain from the superior-posterior surface of the liver directly into the IVC (see Figs. 54.4 to 54.6). The right hepatic vein runs in the right scissura between the anterior and posterior sectors of the right liver and drains most of the right liver after a short (1-cm) extrhepatic course into the right side of the IVC. The left and middle hepatic veins usually join intrahepatically and enter the left side of the IVC as a single vessel, although they may drain separately. The left hepatic vein runs in the left scissura between segments II and III and drains segments II and III; the middle hepatic vein runs in the portal scissura between segment IV and the anterior sector of the right liver, composed of segments V and VIII, and drains segment IV and some of the anterior sector of the right liver. The umbilical vein is an additional vein that runs under the falciform ligament, between the left and middle veins, and usually empties into the left hepatic vein. A number of small posterior venous branches from the right posterior sector and caudate lobe drain directly into the IVC. A substantial inferiorly located accessory right hepatic vein is commonly encountered. There is also often a venous tributary from the caudate lobe that drains superiorly into the left hepatic vein.

**Biliary system.** The intrahepatic bile ducts are the terminal branches of the right and left hepatic ductal branches that invaginate Glisson capsule at the hilum, along with their corresponding portal vein and hepatic artery branches, forming the peritoneal covered portal triads also known as portal pedicles. Along these intrahepatic portal pedicles, the bile duct branches are usually superior to the portal vein, whereas the hepatic artery branches run inferiorly. The left hepatic bile duct drains segments II, III, and IV, which constitute the left liver. The intrahepatic ductal branches of the left liver join to form the main left duct at the base of the umbilical fissure, where the left hepatic duct courses transversely.
across the base of segment IV to join the right hepatic duct at the hilum. In its transverse portion, the left hepatic duct drains one to three small branches from segment IV. The right hepatic duct drains the right liver and is formed by the joining of the anterior sectoral duct (draining segments V and VIII) and the posterior sectoral duct (draining segments VI and VII). The posterior sectoral duct runs in a horizontal and posterior direction; the anterior sectoral duct runs vertically. The main right hepatic duct bifurcates just above the right portal vein. The short right hepatic duct meets the longer left hepatic duct to form the confluence anterior
The filling of the gallbladder; (2) the pancreatic sphincter, present
muscular complex known as the sphincter of Oddi regulates bile flow and prevents reflux of duodenal contents into the biliary tree. There are three major parts to this sphincter: (1) the sphincter choledochus, which is a circular muscle that regulates bile flow and the filling of the gallbladder; (2) the pancreatic sphincter, present

to variable degrees, which surrounds the intraduodenal pancreatic duct; and (3) the sphincter ampullae, made up of longitudinal muscle, which prevents duodenal reflux.

The gallbladder is a biliary reservoir that lies against the inferior surface of segments IV and V of the liver, usually making an impression against the liver. A peritoneal layer covers most of the gallbladder, except for the portion adherent to the liver. Here, the gallbladder adheres to the liver by a layer of fibroconnective tissue known as the cystic plate, an extension of the hilar plate (see Fig. 54.7). Variable in size but usually about 10 cm long and 3 to 5 cm wide, the gallbladder is composed of a fundus, body, infundibulum, and neck, which ultimately empty into the cystic duct. The fundus usually projects just slightly beyond the liver edge anteriorly; when it is folded on itself, it is described as a phrygian cap. Continuing toward the bile duct, the body of the gallbladder is usually close to the second portion of the duodenum and transverse colon. The infundibulum (or Hartmann pouch) hangs forward along the free edge of the lesser omentum and can fold in front of the cystic duct. The portion of gallbladder between the infundibulum and cystic duct is referred to as the neck. The cystic duct is variable in its length, course, and insertion into the main biliary tree. The first portion of the cystic duct is usually tortuous and contains mucosal duplications referred to as the folds of Heister, which regulate the filling and emptying of the gallbladder. The cystic duct usually joins the common hepatic duct to form the common bile duct.

Knowledge of the multiple and frequent variations in the anatomy of the biliary tree is absolutely essential for performing hepatobiliary procedures. Anomalies of the hepatic ductal confluence are common and are present approximately one third of the time. The most common anomalies of the biliary confluence involve variations in the insertion of the right sectoral ducts. Usually, this is the posterior sectoral duct. The confluence can be a trifurcation of the right anterior sectoral, right posterior sectoral, and left hepatic ducts. Either of the right sectoral ducts can drain into the left hepatic duct, the common hepatic duct, the cystic duct, or, rarely, the gallbladder (Fig. 54.13).

Anomalies of the gallbladder itself are rare. Agensis of the gallbladder, bilobar gallbladder with two ducts or a single duct, septations, and congenital diverticulum of the gallbladder have been described. Anomalies of the position of the gallbladder are more common; these include an intrahepatic position and, rarely, location on the left side of the liver. The gallbladder can also have a long mesentery, which can predispose it to torsion.

The position and entry of the cystic duct into the main ductal system are also variable. Double cystic ducts draining a unilobar gallbladder and drainage into hepatic duct branches have been reported. The cystic duct usually joins the common hepatic duct at an angle; but it can run parallel and enter it more distally, and in this situation, the cystic duct can be fused to the hepatic duct along its parallel course by connective tissue. The cystic duct can also run a spiral course anteriorly or posteriorly and enter the left side of the common hepatic duct. Finally, the cystic duct can be very short or even absent (Fig. 54.14).

The supraduodenal and infr hilar bile ducts are predominantly supplied by two axial vessels that run at 3- and 9-o’clock positions. These vessels are derived from the superior pancreatocoduodenal, right hepatic, cystic, gastroduodenal, and retroduodenal arteries. It has been estimated that only 2% of the arterial supply to this portion of the bile duct is segmental, arising directly off the proper hepatic artery. The bile duct and its bifurcation in the hilum derive their arterial blood supply from a rich network of multiple small

**FIG. 54.12** Variations in the anatomy of the cystic artery. (A) Most common anatomy. (B) Double cystic artery, one off the proper hepatic artery. (C) Origin off the proper hepatic artery and coursing anterior to the bile duct. (D) Originating off the right hepatic artery and coursing anterior to the bile duct. (E) Originating from the left hepatic artery and coursing anterior to the bile duct. (F) Originating off the gastroduodenal artery. (G) Originating off the celiac axis. (H) Originating from a replaced right hepatic artery. (From Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver and biliary tract. In: Blumgart LH, Fong Y, eds. Surgery of the Liver and Biliary Tract. London: WB Saunders; 2000:3–34.)
branches from surrounding vessels. Similarly, the retropancreatic bile duct derives its arterial supply from the retroduodenal artery, which provides a rich network of multiple small branches (Fig. 54.15). Venous drainage of the bile duct parallels the arterial supply and drains into the portal venous system. The venous drainage of the gallbladder empties into the veins that drain the bile duct and does not flow directly into the portal vein.

**Nerves.** The innervation of the liver and biliary tract is through sympathetic fibers originating from T7 through T10 as well as parasympathetic fibers from both vagal nerves. The sympathetic fibers pass through celiac ganglia before giving off postganglionic fibers to the liver and bile ducts. The right-sided celiac ganglia and right vagal nerve form an anterior hepatic plexus of nerves that runs along the hepatic artery. The left-sided celiac ganglia and left vagal nerve form a posterior hepatic plexus that runs posterior to the bile duct and portal vein. The hepatic arteries are supplied by sympathetic fibers, whereas the gallbladder and extrahepatic bile ducts receive innervation from sympathetic and parasympathetic fibers. The clinical significance of these nerves is still not well understood. Acute distention of the liver, and thus the liver capsule, can result in right upper quadrant pain, which may be referred to the right shoulder through phrenic nerve innervation of the diaphragmatic peritoneum.

**Lymphatics.** Most lymph node drainage from the liver is to the hepatoduodenal ligament. From here, lymphatic drainage usually continues along the hepatic artery to the celiac lymph nodes and then to the cisterna chyli. Lymphatic drainage can also follow the hepatic veins to lymph nodes in the area of the suprahepatic IVC and through the diaphragmatic hiatus. The lymphatic drainage of the gallbladder and most of the extrahepatic biliary tract is generally into the lymph nodes of the hepatoduodenal ligament. This drainage may follow along the hepatic artery to the celiac lymph nodes, but it can also flow into lymph nodes behind the head of the pancreas or within the aortocaval groove.

**Microscopic Anatomy**

**Functional unit of the liver.** The organization of hepatic parenchyma into microscopic functional units has been described in a number of ways, referred to as an acinus or a lobule (Fig. 54.16). This was originally described by Rappaport and then modified by Matsumoto and Kawakami. A lobule is made up of
a central terminal hepatic venule surrounded by four to six terminal portal triads that form a polygonal unit. This unit is lined on its periphery between each terminal portal triad by terminal portal triad branches. In between the terminal portal triads and the central hepatic venule, hepatocytes are arranged in one-cell-thick plates, surrounded on each side by endothelium-lined and blood-filled sinusoids. Blood flows from the terminal portal triad through the sinusoids into the terminal hepatic venule. Bile is formed within the hepatocytes and empties into terminal canaliculi, which form on the lateral walls of the intercellular hepatocyte. These ultimately coalesce into bile ducts and flow toward the portal triads. This functional hepatic unit provides a structural basis for the many metabolic and secretory functions of the liver.

Between the terminal portal triad and central hepatic venule are three zones that differ in their enzymatic makeup as well as exposure to nutrients and oxygenated blood. There is debate about the shape of these zones and their relationship to the basic lobular unit, but in general, zones 1 through 3 splay out from the terminal portal triad toward the central hepatic venule. Zone 1 (periportal zone) is an environment rich in nutrients and oxygen. Zone 2 (intermediate zone) and zone 3 (perivenular zone) are exposed to environments that are poorer in oxygen and nutrients. The cells of the different zones differ enzymatically and respond differently to toxin exposure and hypoxia. This anatomic arrangement also explains the phenomenon of centrilobular necrosis from hypotension because zone 3 is the most susceptible to decreases in oxygen delivery.

**Hepatic microcirculation.** Terminal portal venous and hepatic arterial branches directly supply the hepatic sinusoids with blood. The portal branches provide a constant but minimal flow into this low-volume system; the arterial branches provide the sinusoids with pulsatile but low-volume flow that enhances flow in the sinusoids. Hepatic arterial branches terminate in a plexus around the terminal bile ductules and provide nutrients. Arterial and portal vein flow varies inversely in the sinusoids and can be compensatory. Local control of blood flow in the sinusoids likely depends on arteriolar sphincters and contraction of the sinusoidal lining by endothelial cells and hepatic stellate cells or portal myofibroblasts. Blood within the sinusoids empties directly into terminal hepatic venules at the center of a functional lobule. This process results in the unidirectional flow of blood in the liver from zone 1 to zone 3.

The endothelium-lined sinusoids of the hepatic lobule represent the functional unit of the liver, where afferent blood flow is exposed to functional hepatic parenchyma before being drained into hepatic venules (Fig. 54.17). The hepatic sinusoids are 7 to 15 μm wide but can increase in size by up to ten-fold. This yields a low-resistance and low-pressure (generally 2–3 mm Hg) system. The sinusoidal endothelial cells account for 15% to 20% of the total hepatic cell mass.

Sinusoidal endothelial cells are separated from hepatocytes by the space of Disse (perisinusoidal space). This is an extravascular fluid compartment into which hepatocytes project microvilli, which allows proteins and other plasma components from the sinusoids to be taken up by the hepatocytes. Within this space, the endothelial cells are specialized in that they lack intercellular junctions and a basement membrane but contain multiple large fenestrations. This arrangement provides for the maximal contact of hepatocyte membranes with this extravascular fluid compartment and blood in the sinusoidal space. Thus, this system permits bidirectional movement of solutes (high- and low-molecular-weight substances) into and out of hepatocytes, providing tremendous filtration potential. On the other hand, the fenestrations of the endothelial cells restrict movement of molecules between the sinusoids and hepatocytes and vary in response to exogenous and endogenous mediators.

Other cell types are found along the sinusoidal lining. Kupffer cells, derived from the macrophage-monocyte system, are irregularly shaped cells that also line the sinusoids insinuating between endothelial cells. Kupffer cells are phagocytic, can migrate along sinusoids to areas of injury, and play a major role in the trapping of foreign substances and initiating inflammatory responses. Major histocompatibility complex II antigens are expressed on Kupffer cells but do not confer efficient antigen presentation compared with macrophages elsewhere in the body. Other lymphoid cells also exist in hepatic parenchyma, such as natural killer, natural killer T, CD4 T, and CD8 T cells. These provide the liver with an innate immune system. Hepatic stellate cells, previously known as Ito cells, are cells high in retinoid content (accounting for their phenotypic identification) found in the space of Disse. They have dendritic processes that contact hepatocyte microvilli and also wrap around endothelial cells. The major functions of these stellate cells include vitamin A storage and the synthesis of extracellular collagen and other extracellular matrix proteins. In acute and chronic hepatic liver injuries, hepatic stellate cells are activated to a myofibroblastic state associated with morphologic changes, cellular contractility, decreases in intracellular vitamin A, and production of extracellular matrix. Ultimately, stellate cells play a central role in the development and progression of hepatic

**FIG. 54.15** Blood supply to the common bile duct and common hepatic duct: right hepatic artery (a); 9:00 artery (b); retroduodenal artery (c); left hepatic artery (d); proper hepatic artery (e); 3:00 artery (f); common hepatic artery (g); gastroduodenal artery (h). (From Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver and biliary tract. In: Blumgart LH, Fong Y, eds. Surgery of the Liver and Biliary Tract. London: WB Saunders; 2000:3–34.)
fibrosis to cirrhosis and are the target for the development of antifibrotic treatments.

**Hepatocytes.** Hepatocytes are complex multifunctional cells that make up 60% of the hepatic cellular mass and 80% of the cytoplasmic mass of the liver (Fig. 54.17). The hepatocyte is a polyhedral cell with a central spherical nucleus. As noted, hepatocytes are arranged in single-cell-layer plates lined on either side by blood-filled sinusoids. Every hepatocyte has contact with adjacent hepatocytes, the biliary space (bile canaliculus), and the perisinusoidal space, enabling these cells to perform their broad range of functions. Among the many essential functions of the hepatocyte are the following: uptake, storage, and release of nutrients; synthesis of glucose, fatty acids, lipids, and numerous plasma proteins (including C-reactive protein and albumin); production and secretion of bile for digestion of dietary fats; and degradation and detoxification of toxins.

To carry out these functions, the plasma membrane of the hepatocyte is organized in a specific manner into three specific domains. The sinusoidal membrane is exposed to the space of Disse and has multiple microvilli that provide a surface specialized in the active transport of substances between the blood and hepatocytes. The lateral domain exists between neighboring hepatocytes and contains gap junctions that provide for intercellular communication. The canalicular membrane is a tube containing microvilli formed by two apposed hepatocytes. These bile canaliculi are sealed by zonula occludens (tight junctions), which prevent the escape of bile. The bile canaliculi form a ring around the hepatocyte that drains into small bile ducts known as canals of Hering, which empty into a bile duct at a portal triad. The canalicular membrane contains adenosine triphosphate (ATP)–dependent active transport systems that enable solutes to be secreted into the canalicular membrane against large concentration gradients.

The hepatocyte is one of the most diverse and metabolically active cells in the body, as reflected by its abundance of organelles. There are 1000 mitochondria/hepatocytes occupying approximately 20% of the cell volume. Mitochondria generate energy (ATP) through oxidative phosphorylation and provide the energy for the metabolic demands of the hepatocyte. The hepatocyte mitochondria are also essential for fatty acid oxidation. The monoclonal antibody HepPar1 (hepatocyte paraffin 1) identifies a unique antigen on hepatocyte mitochondria and is widely used to identify hepatocytes or hepatocellular neoplasms on immunohistochemical examination.

An extensive system of interconnected membrane complexes made up of smooth and rough endoplasmic reticulum and the Golgi apparatus compose what is known as the hepatocyte microsomal fraction. These complexes have a diverse range of functions, including the following: synthesis of structural and secreted proteins; metabolism of lipids and glucose; production and metabolism of cholesterol; glycosylation of secretory proteins; bile formation and secretion; and drug metabolism. Finally, hepatocytes also contain lysosomes, which are intracellular single-membrane vesicles that contain a number of enzymes. These vesicles store and degrade exogenous and endogenous substances. Coordination of these numerous organelles in the hepatocyte allows these cells to accomplish a large variety of functions.
Functions

The unique anatomic arrangement of the liver provides a remarkable landscape on which the multiple central and critical functions of this organ can be carried out. The liver is the center of metabolic homeostasis; it serves as the regulatory site for energy metabolism by coordinating the uptake, processing, and distribution of nutrients and their subsequent energy products. The liver also synthesizes a large number of proteins, enzymes, and vitamins that participate in a tremendously broad range of body functions. Finally, the liver detoxifies and eliminates many exogenous and endogenous substances, serving as the major filter of the human body. The following sections summarize this broad range of functions.

Energy

The liver is the critical intermediary between dietary sources of energy and the extrahepatic tissues that require this energy. The liver receives dietary byproducts through the portal circulation and sorts, metabolizes, and distributes them into the systemic circulation. The liver also plays a major role in regulating endogenous sources of energy, such as fatty acids and glycerol from adipose tissues and lactate, pyruvate, and certain amino acids from skeletal muscle. The two major sources of energy that the liver releases into the extrahepatic circulation are glucose and acetoacetate. Glucose is derived from the glycogenolysis of stored glycogen and from gluconeogenesis from lactate, pyruvate, glycerol, propionate, and alanine. Acetoacetate is derived from the β-oxidation of fatty acids. Also, storage lipids such as triacylglycerols and phospholipids are synthesized and stored as lipoproteins by the liver. These can be circulated systemically for uptake by peripheral tissues. These complex and essential functions are regulated by hormones, overall nutritional state of the organism, and requirements of obligate glucose-requiring tissues.

Functional Heterogeneity

To add to the metabolic complexity of the liver, hepatocytes vary in their function, depending on their location within the lobule. This functional heterogeneity of hepatocytes is anatomically related to their location in the three zones of the lobule and is specifically related to the distance from the incoming portal triad. For example, cells located in the periportal zone (zone 1) are exposed to a high concentration of substrates. Thus, uptake of oxygen and solutes is greater here. A critically important function of hepatocytes, however, is their ability to change their metabolic functionality and to be recruited to perform specific functions under varying physiologic conditions, regardless of anatomic location. Sinusoids in the periportal zone are narrower and more tortuous, facilitating increased uptake of substrate by the hepatocytes in this area. In contrast, sinusoids in zone 3 (perivenous) have larger fenestrations, allowing uptake of larger molecules. Thus, sinusoids are also variable in form and function.

Enzymatic makeup, plasma membrane proteins, and ultrastructure are also heterogeneous among the hepatocyte population. This cellular protein variability can also be distinguished on the basis of the hepatocyte location within the lobule. Glucose uptake and release, bile formation, and synthesis of albumin and fibrinogen take place in the periportal zone, whereas glucose catabolism, xenobiotic metabolism, and synthesis of α1-antitrypsin and α-fetoprotein (AFP) occur in the perivenous zone. Another example of enzymatic heterogeneity according to lobular zones is the location of the urea cycle enzymes in zone 3, adjacent to the terminal hepatic veins. The functional hepatocyte heterogeneity...
and its anatomic relationship to the lobular unit account for patterns of damage from metabolic or physiologic insults to the liver.

**Blood Flow**

There is a dual blood supply to the liver that comes from the portal vein and hepatic artery. The portal vein provides approximately 75% of the blood flow to the liver, which is oxygen poor but rich in nutrients. The hepatic artery provides the other 25% of the blood flow, which is oxygen rich and represents systemic arterial blood flow. The large flow rate of the portal vein is still able to provide 50% to 70% of the afferent oxygenation to the liver. Overall, hepatic blood flow represents about 25% of the cardiac output, demonstrating its central role in whole body metabolism. Hepatic blood flow is decreased during exercise and increased after ingestion of food. Carbohydrates have the most profound effect on hepatic blood flow. Hepatic arterial pressure is representative of systemic arterial pressure. Portal pressure is generally 6 to 10 mm Hg, and sinusoidal pressure is usually 2 to 4 mm Hg.

Hepatic blood flow is regulated by various factors. Differences in afferent and efferent vessel pressures as well as muscular sphincters located at the inlet and outlet of the sinusoids play a major role. Muscular sphincter tone is regulated by the autonomic nervous system, circulating hormones, bile salts, and metabolites. Specific endogenous factors known to affect hepatic blood flow include glucagon, histamine, bradykinin, prostaglandins, nitric oxide, and many gut hormones, including gastrin, secretin, and cholecystokinin. The sinusoids are also the primary regulators of hepatic blood flow through contraction and expansion of their endothelial cells, Kupffer cells, and hepatic stellate cells.

A one-way reciprocal relationship between hepatic artery and portal vein flow has been demonstrated. Increases in hepatic arterial flow accompany decreases in portal vein flow, but the opposite does not occur. Hepatic arterial compensation, however, cannot provide complete compensation to support hepatic parenchyma in total portal vein occlusion, which is likely the cause of ipsilateral atrophy in this case. Experimental evidence has suggested that the buildup of adenosine in the liver plays an important role in this hepatic arterial compensatory response.

**Bile Formation**

One of the major functions of the liver is bile production and secretion. The physiologic role of bile is twofold. The first is to dispose of substances secreted into bile; the second is to provide enteric bile salts to aid in the digestion of fats. Bile is a substance containing organic and inorganic solutes produced by an active process of secretion and subsequent concentration of these solutes. The concentration of inorganic solutes in bile in the main biliary tree resembles that of plasma (Table 54.1). In the case of bile loss (e.g., from an external biliary fistula), the high concentrations of protein and electrolytes must be considered in replacing the losses. The osmolality of bile is approximately 300 mOsmol/kg and is accounted for by the inorganic solutes. The major organic solutes in bile are bile acids, bile pigments, cholesterol, and phospholipids.

The contents of bile are generally absorbed from the bloodstream through sinusoids into the hepatocyte through the sinusoidal membrane. Bile is initially secreted by hepatocytes into the canaliculi through specialized microvilli containing lateral membranes of the hepatocytes that form the canaliculi. Tight junctions along the canalicular membranes prevent leakage of bile in the normal state. This also provides a route for paracellular secretion of solutes and water into bile. The canaliculi coalesce into larger bile ductules containing biliary epithelium, which then form the intrahepatic and extrahepatic biliary tree. Thus, the liver, in part, serves as an epithelial structure that moves solutes from the blood to the bile and provides a route of secretion for bile into the intestines.

Approximately 1500 mL of bile is secreted daily, and much of this (~80%) is secreted by hepatocytes into canaliculi. Such canicular bile flow is largely the result of water flow in response to active solute transport. Bile acids are transported from the sinusoidal blood into the hepatocyte by ATP-requiring active transport. Intracellular transport to the canalicular membrane is through bile acid–binding proteins that are transported by a vesicular system derived from the Golgi apparatus. The bile acids are then actively pumped into the canaliculus through an ATP-requiring active transport system. It is well recognized that bile flow has a linear association with bile acid secretion, known as bile acid–dependent flow. Because bile acids form micelles in the bile and do not provide osmotic potential, it is likely that flow related to bile acid secretion is secondary to ions that accompany the bile acids (counterions). Bile flow can also occur in the near-absence of bile acid secretion, known as bile acid–independent flow. Experimental evidence has suggested that bile acid–independent flow is at least partially the result of biliary glutathione secretion.

Once bile has passed from the canaliculi to the biliary ductules and then to main bile ducts, bile undergoes further reabsorption and secretion. The epithelial cells of the biliary tract actively reabsorb and secrete water and electrolytes. Secretion is generally through a chloride channel activated by secretin, its most powerful activator, and its subsequent activation of cyclic adenosine monophosphate production. There is usually a net secretion of water and electrolytes, accounting for the other 20% of biliary secretion. Ultimately, bile becomes highly enriched in bicarbonate ions. Many organic substances, such as glutathione, are degraded in the biliary tree. Many drugs can be secreted into the biliary tree in a highly concentrated form (e.g., ceftriaxone). The gallbladder acts as the reservoir of the biliary tree; its function is to store bile in the fasting state. The gallbladder reabsorbs water, concentrating stored bile, and secretes mucin. Contraction of the gallbladder is mediated hormonally, largely through cholecystokinin, in response to a meal, with the simultaneous relaxation of the sphincter of Oddi and release of bile into the duodenum.

**Enterohepatic Circulation**

Bile salts are primarily produced in the liver and secreted to be used in the biliary tree and intestine. The primary bile salts cholic acid and chenodeoxycholic acid are produced in the liver from

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### TABLE 54.1 Solute concentrations of hepatic bile.

<table>
<thead>
<tr>
<th>SOLUTE</th>
<th>CONCENTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>132–165 mEq/L</td>
</tr>
<tr>
<td>K⁺</td>
<td>4.2–5.6 mEq/L</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>1.2–4.8 mEq/L</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>1.4–3.0 mEq/L</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>96–126 mEq/L</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>17–55 mEq/L</td>
</tr>
<tr>
<td>Bile acids</td>
<td>3–45 mM</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>25–810 mg/dL</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>60–320 mg/dL</td>
</tr>
<tr>
<td>Protein</td>
<td>300–3000 mg/L</td>
</tr>
</tbody>
</table>
cholesterol and subsequently conjugated with glycine or taurine in the hepatocyte. Once secreted in the gut, the primary bile acids are modified by intestinal bacteria to form the secondary bile acids deoxycholic acid and lithocholic acid. Bile acids are reabsorbed passively into the jejunal and actively into the ileum. Thus, the bile acids reenter the portal venous system, and up to 90% of the bile acids are extracted by hepatocytes. Only a small fraction spills over into the systemic circulation because of efficient hepatic extraction, which accounts for low levels of plasma bile acids. After hepatic extraction, bile acids are recirculated into the canaliculi and back into the biliary tree, completing the circuit. A small amount of intestinal bile acids is not absorbed by the portal system and is excreted in the stool. Thus, the active secretion of bile salts from hepatocytes into bile and from ileal enterocytes into the portal vein is the engine behind the enterohepatic circulation.

The enterohepatic circulation is more than a unique mechanism for reusing physiologically valuable bile acids. This circulation of bile constitutes the major mechanism for eliminating excess cholesterol because cholesterol is consumed during the production of bile salts and is excreted in the feces by mixed micelles formed by organic biliary solutes. Bile salts also play a critical role in the absorption of dietary fats, fat-soluble vitamins (i.e., vitamins A, D, E, and K), and lipophilic drugs. Water movement from hepatocytes into bile and water absorption through the small bowel are also regulated by bile salts. The enterohepatic circulation is therefore central to a number of solubilization, transport, and regulatory functions.

**Bilirubin Metabolism**

Bilirubin is the result of heme breakdown. An early phase of heme breakdown, accounting for 20% of bilirubin, is from hemoproteins (heme-containing enzymes) and occurs within 3 days of labeling with radioactive heme. A late phase of heme breakdown, accounting for 80% of bilirubin, is from senescent red blood cells. This occurs approximately 110 days after administration of radioactive labeled heme and is consistent with the life span of red blood cells. Heme is initially broken down into a green biliverdin by heme oxygenase, which is then broken down into the orange bilirubin by biliverdin reductase.

Circulating bilirubin is bound to albumin, which protects many organs from the potentially toxic effects of this compound. The bilirubin-albumin complex enters hepatic sinusoidal blood, where it enters the space of Disse through the large sinusoidal fenestrations. The bilirubin-albumin complex is disassociated in this space. Free bilirubin is internalized into the hepatocyte, where it is conjugated to glucuronic acid. Conjugated bilirubin is then secreted in an energy-dependent fashion into canalicular bile against a large concentration gradient. Bilirubin is secreted with bile into the gastrointestinal tract. Within the gastrointestinal tract, bilirubin is deconjugated by intestinal bacteria to a group of compounds known as urobilinogens. These urobilinogens are further oxidized and reabsorbed into the enterohepatic circulation and secreted into bile. A small percentage of the reabsorbed urobilinogens is excreted into urine. These oxidized urobilinogens account for the colored compounds that contribute to the yellow color of urine and the brown color of stool.

Bilirubin has long been known to be a toxic compound and is the agent responsible for neonatal encephalopathy and cochlear damage secondary to severe unconjugated hyperbilirubinemia (kernicterus). The binding of serum bilirubin to albumin protects the tissues from exposure to bilirubin. However, binding sites can be overwhelmed by increasing amounts of bilirubin or displaced by other binding agents (e.g., various drugs). The mechanism of bilirubin toxicity appears to be related to a number of its effects. Free bilirubin can uncouple oxidative phosphorylation, inhibit ATPases, decrease glucose metabolism, and inhibit a broad spectrum of protein kinase activities.

Portosystemic shunts, such as those seen with cirrhosis and portal hypertension, decrease the first-pass hepatic clearance of bilirubin, resulting in a mildly increased serum unconjugated hyperbilirubinemia. A number of disorders can result in an unconjugated serum hyperbilirubinemia, including neonatal hyperbilirubinemia, an increased bilirubin load caused by hemolytic syndromes, and inherited enzymatic deficiencies such as Crigler-Najjar and Gilbert syndromes. Disorders presenting with serum conjugated hyperbilirubinemia include cholestasis, Dubin-Johnson, andRotor syndromes.

**Carbohydrate Metabolism**

The liver is the center of carbohydrate metabolism because it is the major regulator of storage and distribution of glucose to the peripheral tissues and, in particular, to glucose-dependent tissues such as the brain and erythrocytes. Both liver and muscle are capable of storing glucose in the form of glycogen, but only the liver can break down glycogen to provide glucose for systemic circulation. Glycogen that is broken down can be used only in muscle and is therefore not a source of systemically circulated glucose.

In the fed state, carbohydrate absorbed through the intestines (mostly glucose) is circulated systemically. Carbohydrates reaching the liver are rapidly converted to glycogen for storage. The liver contains up to 65 g of glycogen per kilogram of liver tissue. Excess carbohydrate is mostly converted to fatty acids and stored in adipose tissue. In the postabsorptive state (between meals, non-fasting), there is no further systemic glucose coming directly from the gut, and the liver becomes the primary source of circulating glucose by the breakdown of glycogen. This is crucial for the brain and erythrocytes, which rely on glucose for their metabolism. In the postabsorptive state, most other tissues begin to rely on fatty acids derived from adipose tissue as their primary fuel. Highly active muscle may deplete its own glycogen and depend on liver-derived glucose for its substrate in the postabsorptive state. After 48 hours of fasting, hepatic glycogen is depleted and the liver shifts from glycogenolysis to gluconeogenesis. The substrate for hepatic gluconeogenesis is mostly from amino acids (mainly alanine) derived from muscle breakdown, but they also come from glyceral derived from adipose breakdown. During a prolonged fast, fatty acids from adipose breakdown are β-oxidized in the liver, which releases ketone bodies that then become the primary fuel for the brain.

Transition in and out of these various metabolic states and regulation of carbohydrate metabolism are mostly influenced by glucose concentration in sinusoidal blood and hormonal influences (e.g., insulin, catecholamines, glucagon). In the fasting state, during anaerobic metabolism, lactate is produced, largely from muscle. The liver uses this lactate, which is converted to pyruvate that enters into the gluconeogenic pathways, to produce glucose. This cycle is known as the Cori cycle.

Derangements of carbohydrate metabolism are common in liver disease. Cirrhotics often demonstrate abnormal glucose tolerance. Its mechanism is not completely clear but is probably related to associated insulin resistance. This phenomenon is not caused by shunting of glucose-containing blood away from the liver. Hypoglycemia is a distinctly uncommon entity in chronic liver disease because of the remarkable resilience of the liver and its metabolic
function. Only with massive hepatocyte loss in fulminant hepatic failure does gluconeogenesis fail and hypoglycemia ensue.

**Lipid Metabolism**

Fatty acids are synthesized in the liver during states of glucose excess, when the liver’s ability to store glycogen has been exceeded. Adipocytes have a limited ability to synthesize fatty acids. Therefore, the liver is the predominant source of synthesized fatty acids, although they are largely stored in adipose tissue. During lipolysis, free fatty acids are transported to the liver, where they are metabolized. Fatty acids in the liver undergo esterification with glycerol to form triglycerides for storage or transportation, or they undergo β-oxidation, yielding energy in the form of ATP and ketone bodies. In general, this process is regulated by the nutritional state; starvation favors oxidation, and the fed state favors esterification.

There is a constant cycling of fatty acids between the liver and adipose tissue that is under a delicate balance, which can easily be offset, resulting in fatty infiltration of the liver. A few factors influence this balance; for example, hepatic uptake of fatty acids is a function of plasma concentrations. Although there is no limit to the liver’s ability to esterify fatty acids, its ability to dispose of or to break down fatty acids is limited, as is its ability to secrete triglycerides in the form of lipoproteins. Therefore, conditions of increased circulating fatty acids can easily override the liver’s ability to handle them, resulting in fatty accumulation in the liver. This is known as steatosis or, when it is associated with chronic inflammation in more advanced cases, steatohepatitis. A number of conditions have been associated with hepatic steatosis, such as diabetes, steroid use, starvation, obesity, and extensive administration of cytotoxic chemotherapeutic agents. Fatty liver associated with alcohol intake has a number of causes; it is related to increased lipolysis, reduced oxygenation, and augmented esterification of hepatic fatty acids and may also be related to relative starvation in the chronic alcoholic.

**Protein Metabolism**

The liver is also a central site for the metabolism of proteins and is involved in the synthesis of protein, catabolism of proteins into energy or other storable energy forms such as glucose and fats, no

Vitamin Metabolism

Along with the intestine, the liver is responsible for the metabolism of the fat-soluble vitamins A, D, E, and K. These vitamins are obtained exogenously and absorbed in the intestine. Their adequate intestinal absorption is critically dependent on adequate fatty acid micellization, which requires bile acids.

Vitamin A is from the retinoid family and is involved in normal vision, embryonic development, and adult gene regulation. Storage of vitamin A is solely in the liver and occurs in the hepatic stellate cells. Overingestion of vitamin A can result in hepatic toxicity. Vitamin D is involved in calcium and phosphorus homeostasis. One of vitamin D’s activation steps (25-hydroxylation) occurs in the liver. Vitamin E is a potent antioxidant and protects membranes from lipid peroxidation and free radical formation. Finally, vitamin K is a critical cofactor in the posttranslational γ-carboxylation of the heptatically synthesized coagulation factors II, VII, IX, and X, as well as of protein C and protein S, the so-called vitamin K–dependent cofactors. Cholestasis syndromes can result in the inadequate absorption of these vitamins secondary to poor micellization in the intestine. The associated vitamin deficiency syndromes, such as metabolic bone disease (vitamin D deficiency), neurologic disorders (vitamin E deficiency), and coagulopathy (vitamin K deficiency), can subsequently occur.

The liver is also involved in the uptake, storage, and metabolism of a number of water-soluble vitamins, including thiamine, riboflavin, vitamin B₆, vitamin B₁₂, folate, biotin, and pantothenic acid. The liver is responsible for converting some of these water-soluble vitamins to active coenzymes, transforming some to storage metabolites and using some for enterohepatic circulation (e.g., vitamin B₁₂).

Coagulation

The liver is responsible for synthesizing almost all the identified coagulation factors as well as many of the fibrinolytic system components and several plasma regulatory proteins of coagulation and fibrinolysis. As noted, the liver is critical for the absorption of vitamin K, synthesizes the vitamin K–dependent coagulation factors, and contains the enzyme that activates these factors. Also, the reticuloendothelial system of the liver clears activated clotting factors, activated complexes of the coagulation and fibrinolytic systems, and end products of fibrin degradation. Diseases of the liver are often associated with thrombocytopenia, qualitative platelet abnormalities, vitamin K deficiency with impaired modulation of...
vitamin K–dependent coagulation factors, and disseminated intravascular coagulation. It is no surprise that liver disease is firmly associated with coagulation disorders that are often challenging to deal with.

Warfarin, one of the most commonly dispensed anticoagulants, acts in the liver by blocking vitamin K–dependent activation of factors II, VII, IX, and X. Factor VII has the shortest half-life of the coagulation factors; its deficiency is manifested clinically as abnormalities of the measured prothrombin time (PT) or international normalized ratio (INR). Patients with hepatic synthetic dysfunction similarly have an abnormal PT.

**Metabolism of Drugs and Toxins (Xenobiotics)**
The human body is exposed to an inordinate amount of foreign chemicals during a lifetime. This poses a challenge to our ability to detoxify and to eliminate these potentially harmful chemicals. Many of these chemicals are not incorporated into cellular metabolism and are referred to as xenobiotics. The liver plays a central role in handling them through an enormously complex and numerous set of enzymes and reaction pathways, which are increasingly recognized as new chemicals are discovered.

Hepatic-based reactions to xenobiotics are broadly classified into phase I and phase II reactions. Phase I reactions, through oxidation, reduction, and hydrolysis, increase the polarity and, thus, water solubility of compounds. This in turn allows easier excretion. Phase I reactions do not necessarily detoxify chemicals and may, in fact, create toxic metabolites. Phase I reactions occur in the cytochrome P450 system. Phase II reactions generally act to create a less toxic or less active byproduct. This is generally accomplished through transferase reactions in which a compound is usually coupled to a conjugate, rendering the xenobiotic more innocuous.

**Regeneration**
The liver possesses the unique quality of adjusting its volume to the needs of the body. This is observed clinically in its regeneration after partial hepatectomy or after toxic liver injury. It is also seen in liver transplantation in that donor liver size mismatches adjust to the new host. This quality is highly conserved evolutionarily because of the critical functions of the liver and the fact that the liver is the first line of exposure to ingested toxic agents.

Liver regeneration is a hyperplastic response of all cell types of the liver, in which the microscopic anatomy of the functional liver is maintained. Much information that we have about the regenerative response of the liver is based on experimental evidence in rodents. Normally, quiescent hepatocytes rapidly enter the cell cycle after partial hepatectomy. Maximal hepatocyte DNA synthesis occurs 24 to 36 hours after partial hepatectomy, and maximal DNA synthesis occurs in the other cell types by 48 to 72 hours later. Most of the increase in hepatic mass in rodents is seen by 3 days after partial hepatectomy, and it is usually almost complete after 7 days.

In the late 1960s, it was recognized that circulating factors were responsible, in part, for the regenerative response, and much research has focused on the humoral and genetic control of hepatic regeneration. The major circulating factors that have been identified, largely from rodent studies, are hepatocyte growth factor, epidermal growth factor, transforming growth factors, insulin, and glucagon and the cytokines tumor necrosis factor-α, IL-1, and IL-6. These factors, when infused into a normal host, do not result in hepatic growth, indicating that hepatocytes must be primed in some way before responding to these growth factors. Remarkable progress in the understanding of liver regeneration has been made because of the development of improved genetic and molecular biologic techniques. Hundreds of genes involved at all stages of regeneration have been identified by RNA microarray techniques. Also, numerous cytokine-dependent and growth factor–independent pathways have been further defined. A complete description is beyond the scope of this chapter, however, and many questions still remain.

**Future Developments**
The study of the liver and its physiology continues to be a remarkable and exciting field. As the fields of molecular biology and genetic manipulation have exploded, so has the field of hepatology. Given the lack of alternative options to transplantation for patients with end-stage liver failure, tissue engineering and attempts to provide exogenous hepatic functional support continue to be studied. Liver repopulation with transplanted cells—hepatocytes or hepatic progenitor and stem cells—may also provide future options for patients with liver failure. Although the identification of specific and reliable markers for hepatic stem cells has been elusive, the concepts of liver progenitors and stem cells and their potential usefulness for hepatic repopulation have gained acceptance, making this an exciting area of research. Ongoing genetic comparisons of normal and diseased liver using new molecular biology and cell biology techniques will provide clues about the genetic regulation of liver diseases. Great strides have been made in the effectiveness of gene therapy, and many groups continue to study liver-directed gene therapy strategies to treat acquired and inherited disorders. Ongoing molecular biology studies are researching hepatic cell cycle regulation, with implications for hepatocarcinogenesis. Research studies about the pathogenesis of hepatic fibrosis and, perhaps more exciting, reversal of this process are ongoing and likely to result in significant advances in the future.

**Assessment of Liver Function**
A wide variety of tests are available to evaluate hepatic diseases. Screening for hepatic disease, assessing hepatic function, diagnosing specific disorders, and prognosticating are critical in the management of hepatic disease. For the surgeon, assessment of hepatic function and estimation of the ability of a hepatic remnant to be sufficient after liver resection are also of obvious importance.

Unfortunately, most measures of hepatic disease are gross indicators and lack sensitivity, specificity, and accuracy. We have divided these hepatic function tests into three categories—routine screening, specific diagnostic, and quantitative tests.

**Routine Screening Tests**
Screening blood tests are often used to determine whether there is disease in the hepatobiliary system. Standard liver function tests (LFTs) are generally not tests of function and are not always specific to hepatic disease. Nonetheless, they are valuable as a general screening tool that can provide basic indications to recognize the presence of hepatic disease and to yield clues about the cause of that disease. Total bilirubin, direct bilirubin (conjugated), and indirect bilirubin (unconjugated) levels can be affected by a number of processes related to bilirubin metabolism. Unconjugated hyperbilirubinemia can be a reflection of increased bilirubin production (e.g., hemolysis), drug effects, inherited enzymatic disorders, or physiologic jaundice of the newborn. Conjugated hyperbilirubinemia is generally a result of cholestasis or mechanical biliary obstruction but can also be seen in some inherited disorders or hepatocellular disease.
The transaminases alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the most common serum markers of hepatocellular necrosis, with subsequent leak of these intracellular enzymes into the circulation. AST is found in other organs, such as the heart, muscle, and kidney, but ALT is liver specific. However, the degree of elevation of these enzyme levels has never been shown to be of prognostic value. Alkaline phosphatase (ALP) is expressed in liver, bile ducts, bone, intestine, placenta, kidney, and leukocytes. Isoenzyme determinations can sometimes be helpful for distinguishing the source of an elevated ALP level. Elevations of ALP levels in hepatobiliary diseases are generally secondary to cholestasis or biliary obstruction. Such elevations are caused by increased production of this enzyme. The ALP level can also be increased in malignant disease of the liver. Gamma-glutamyl transpeptidase (GGT) is an enzyme in many organs in addition to the liver, such as the kidneys, seminal vesicles, spleen, pancreas, heart, and brain. Its level can be elevated in diseases affecting any of these tissues. It is also induced by alcohol intake and is elevated in biliary obstruction. Thus, it is also a nonspecific marker of liver disease but can be helpful in determining whether an elevated ALP level is from hepatic disease. 5′-Nucleotidase is also found in a wide variety of organs in addition to the liver, but increased levels are fairly specific to hepatic disease. Like GGT, it can be helpful in determining whether an elevated ALP level is secondary to hepatic disease.

Albumin is synthesized exclusively in the liver and can be used as a general measure of hepatic synthetic function. Because chronic malnutrition and acute injury, infection, and/or inflammation can decrease albumin synthesis, these factors must be taken into account in evaluating a low serum albumin level. Because of the remarkable protein synthetic capacity of the liver, hypoalbuminemia is a marker of severe liver disease. However, it lacks sensitivity and large decreases in hepatic function are required to be reflected in albumin levels. In general, it is most helpful in chronic liver disease.

Clotting factors are largely synthesized in the liver; abnormalities of coagulation can be a marker of hepatic synthetic dysfunction. Measurement of specific clotting factors, such as factors V and VII, has been used to evaluate hepatic function in the transplantation population. PT or INR is the best test to measure the effects of hepatic disease on clotting, and prolonged PT or elevated INR is usually a marker of advanced chronic liver disease. Hepatic disease can also affect clotting through intravascular coagulation and vitamin K malabsorption. Patients with liver disease have thrombocytopenia. While platelets are not incorporated in any measure of liver function and thrombocytopenia may be multifactorial, platelet levels provide insight into severity of portal hypertension in patients with liver disease.

**Specific Diagnostic Tests**

Once screening tests, along with clinical findings, have suggested liver disease, specific tests can be used to help elucidate the cause and to guide treatment, if necessary. Hepatitis serologies are important to determine the presence of viral hepatitis. Autoimmune antibodies are used to diagnose primary biliary cirrhosis (e.g., antimitochondrial), primary sclerosing cholangitis (e.g., antineutrophil), and autoimmune hepatitis. α1-Antitrypsin and ceruloplasmin levels assist in the diagnosis of α1-antitrypsin deficiency and Wilson disease, respectively. Tumor markers such as AFP and carcinoembryonic antigen (CEA) can be helpful in the diagnosis and management of primary and metastatic tumors of the liver.

In general, the LFTs discussed in this section are gross, nonspecific, and of little if any prognostic value. Many attempts have been made to formulate dynamic and quantitative tests of hepatic function based on the liver’s ability to clear various exogenously administered substances. Despite many years of research, it still remains unclear whether these tests of hepatic function are any better than scoring systems derived from simple blood tests and clinical observations. For example, the aminopyrine breath test is based on cytochrome P450 clearance of radiolabeled aminopyrine. A breath test measuring radiolabeled CO2 as a breakdown product of aminopyrine is performed after administration at a specified time. The results largely depend on the functional hepatic mass, which is generally not depleted until end-stage liver disease has developed. There are varying results of studies comparing the aminopyrine breath test with standard LFTs and scoring systems; its main value appears to be prognosis in chronic liver disease, but it is clearly not an effective test to detect subclinical hepatic dysfunction.

Substances such as antipyrine and caffeine can evaluate liver function in a similar way, with similar results. The lidocaine clearance test yields similar information to the aminopyrine test because it is based on its clearance by the hepatic cytochrome P450 test. Lidocaine clearance is dependent on blood flow and a complex distribution process, but measurement of one of its metabolites, monoethylglycinexylidide, has greatly simplified the test. It has been shown to have some prognostic value in the transplantation population. The galactose elimination test is based on the liver’s role in phosphorylating galactose and converting it to glucose. The rate at which galactose is eliminated from the bloodstream can be used as a measure of hepatic function. Problems related to this test are that the enzymes involved are genetically heterogeneous, and considerable extrahepatic metabolism occurs. Also, multiple blood draws are necessary, which makes the test cumbersome. The value of this test is probably in assessing the prognosis of patients with chronic liver disease rather than in screening. Indocyanine green is a dye removed by the liver by a carrier-mediated process and excreted into bile. This dye is rapidly cleared from the bloodstream and is not metabolized. This is the only test that has been shown to have some prognostic ability in cirrhotic patients undergoing liver resection, although this is not universally demonstrated in studies, nor is it universally accepted.

Nuclear imaging studies overcome some of the limitations of the lidocaine and indocyanine green tests described above and have the advantage of providing simultaneous morphologic (visual) and physiologic (quantitative functional) information about the liver. This not only helps quantitate the liver function but also helps in determining the distribution of that function. Thus, regional (segmental) differentiation allows specific functional assessment of the future remnant liver. Technetium-99m (Tc 99m)-galactosyl human serum albumin scintigraphy and Tc 99m-mebrofenin hepatobiliary scintigraphy potentially identify patients at risk for postresectional liver failure who might benefit from liver-augmenting techniques.

**Quantitative Tests**

A large number of scoring systems based on clinical observation and standard blood tests have been proposed. The most commonly used system is Pugh modification of the Child score (Table 54.2). Although all these systems are less than perfect and not universally accepted, the Child-Pugh score is commonly used for cirrhotic patients who require liver surgery. Mortality and survival rates after hepatectomy have been shown to correlate with this
PORTAL HYPERTENSION

Cirrhosis is the end result of a healing response initiated by chronic liver injury. Cirrhosis is characterized by the development of fibrous septa surrounding regenerating hepatocellular nodules. Besides development of synthetic deficiencies, cirrhosis is associated with development of portal hypertension. At present, effective treatments for cirrhosis are nonexistent. As a result, its treatment has largely been focused on the treatment of resultant portal hypertension and its complications. The major challenge for the hepatologist or surgeon who is treating patients with cirrhosis and end-stage liver disease is determining when definitive treatment (e.g., liver transplantation) rather than palliative treatment (e.g., interventions to prevent recurrent variceal hemorrhage) should be applied. Cirrhosis can be classified as compensated or decompensated based on the absence or presence of clinically evident decompensating events (variceal hemorrhage, encephalopathy, ascites). This classification provides important prognostic information, as patients with compensated cirrhosis have median survival exceeding 12 years whereas patients with decompensated cirrhosis have median survival of only 1.8 years.

Definition

Portal hypertension is defined by a portal pressure gradient (the difference in pressure between the portal vein and the hepatic veins) greater than 5 mm Hg. The best method to estimate this gradient is by transendoscopic-hepatic vein catheterization with a balloon tip catheter. However, higher pressures (8–10 mm Hg) are typically required to begin stimulating the development of portosystemic collaterals. Collateral vessels usually develop where the portal and systemic venous circulations are in close apposition (Fig. 54.18). The collateral network through the coronary and short gastric veins to the azygos vein is clinically the most important because it results in the formation of esophagogastric varices. However, other sites include a recanalized umbilical vein from the left portal vein to the epigastric venous system (caput medusae), retroperitoneal collateral vessels, and the hemorrhoidal venous plexus. In addition to extrahepatic collateral vessels, a significant fraction of portal venous flow passes through anatomic and physiologic (e.g., capillarization of hepatic sinusoids) intrahepatic shunts. As hepatic portal perfusion decreases, hepatic arterial flow generally increases (buffer response).

Pathophysiology

Portal hypertension usually occurs because of increased portal venous resistance that is prehepatic, intrahepatic, or posthepatic in location. Several factors may contribute to this, including the following: increased passive resistance secondary to fibrosis and regenerative nodules; increased hepatic vascular resistance caused by active vasoconstriction by norepinephrine, endothelin, and other humoral vasoconstrictors; and increased portal venous inflow secondary to a hyperdynamic systemic circulation and splanchnic hyperemia. The last one is a major contributor to the maintenance of portal hypertension as portal systemic collaterals develop. Unfortunately, the exact causes remain unknown, but splanchic hormones, decreased sensitivity of the splanchic vasculature to catecholamines, and increased production of nitrous oxide and prostacyclin may be involved. Understanding the pathophysiology of portal hypertension may have therapeutic implications because these factors may represent targets for treatment.

The most common cause of prehepatic portal hypertension is portal vein thrombosis. This accounts for approximately 50% of cases of portal hypertension in children. When the portal vein is thrombosed in the absence of liver disease, hepatopetal (to the liver) portal collateral vessels develop to restore portal perfusion. This combination is termed cavernomatous transformation of the portal vein. Isolated splenic vein thrombosis (left-sided portal hypertension) is usually secondary to pancreatic inflammation or neoplasm. The result is gastroplenic venous hypertension, with superior mesenteric and portal venous pressures remaining

### TABLE 54.2 Child-Pugh classification.

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>NO. OF POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>Prothrombin time (increased seconds)</td>
<td>1–3</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
</tbody>
</table>

Class A, 5–6 points; class B, 7–9 points; class C, 10–15 points.
normal. The left gastroepiploic vein becomes a major collateral vessel, and gastric rather than esophageal varices develop. This variant of portal hypertension is important to recognize because it is easily reversed by splenectomy alone.

The site of increased resistance in intrahepatic portal hypertension may be at the presinusoidal, sinusoidal, or postsinusoidal level. Frequently, more than one level may be involved. The most common cause of intrahepatic presinusoidal hypertension is schistosomiasis. In addition, many causes of nonalcoholic cirrhosis result in presinusoidal portal hypertension. In contrast, alcoholic cirrhosis, the most common cause of portal hypertension in the United States, usually causes increased resistance to portal flow at the sinusoidal (secondary to deposition of collagen in the space of Disse) and postsinusoidal (secondary to regenerating nodules distorting small hepatic veins) levels.

Posthepatic or postsinusoidal causes of portal hypertension are rare; they include Budd-Chiari syndrome (hepatic vein thrombosis), constrictive pericarditis, and heart failure. Rarely, increased portal venous flow alone, secondary to massive splenomegaly (e.g., idiopathic portal hypertension) or a splanchnic arteriovenous fistula, causes portal hypertension.

**Assessment of Chronic Liver Disease and Portal Hypertension**

The key aspects of assessing a patient with suspected chronic liver disease or complications of portal hypertension are the following: diagnosis of the underlying liver disease; estimation of functional hepatic reserve; definition of portal venous anatomy and hepatic hemodynamic evaluation; and identification of the site of upper gastrointestinal hemorrhage, if present. These diagnostic categories take on varying degrees of importance, depending on the clinical situation. For example, estimation of functional hepatic reserve is useful in determining the risk associated with therapeutic intervention and whether definitive (e.g., hepatic transplantation) or palliative (e.g., endoscopic variceal ligation or a shunt procedure) treatment is indicated.

**Variceal Hemorrhage**

Bleeding from esophagogastric varices is the single most life-threatening complication of portal hypertension. It is responsible for approximately one third of all deaths in patients with cirrhosis. Approximately 50% of these deaths are caused by uncontrolled bleeding. The risk for death from bleeding is mainly related to the underlying hepatic functional reserve. Patients with extrahepatic portal venous obstruction and normal hepatic function rarely die of bleeding varices, whereas those with decompensated cirrhosis (e.g., Child-Pugh class C) may face a mortality rate in excess of 50%. Once bleeding is controlled, the greatest risk for rebleeding from varices is within the first few days after the onset of hemorrhage; the risk declines rapidly between that point and 6 weeks. Subsequently, the risk returns to the prehemorrhage rate.

**Treatment**

In a patient with upper gastrointestinal bleeding, general measures are instituted; these include securing the airway (especially in an encephalopathic patient), ensuring adequate access (two large-bore intravenous [IV] lines), fluid infusion, type and crossmatch of blood, and judicious blood and products transfusion. A randomized controlled trial comparing liberal transfusion (transfusion when the hemoglobin fell below 9 g/dL) to restrictive transfusion (transfusion when the hemoglobin levels fell below 7 g/dL) demonstrated that the restrictive strategy led to better survival at 6 weeks and reduced risk of rebleeding. Therapy for portal hypertension and variceal bleeding has evolved over time and now encompasses a spectrum of treatment modalities, in which sequential therapies are often necessary. For acutely bleeding patients with portal hypertension, nonoperative treatments are generally used as a first-line approach as these patients are high operative risks because of decompensated hepatic function. Endoscopic treatment (e.g., sclerosis or ligation) has become the mainstay of nonoperative treatment of acute hemorrhage because bleeding can be controlled in more than 85% of patients. This allows an interval of medical management for improvement of hepatic function, resolution of ascites and encephalopathy, and enhancement of nutrition before definitive treatment for prevention of recurrent bleeding is instituted. Pharmacotherapy can also be initiated, and trials have suggested that it may be as effective as endoscopic treatment. Balloon tamponade, which is infrequently used, can be lifesaving in patients with exsanguinating hemorrhage when other nonoperative methods are not successful. A transjugular intrahepatic portosystemic shunt (TIPS) is another treatment option whereby a percutaneous connection is created within the liver, between the portal and systemic circulations, to reduce portal pressure in patients with complications related to portal hypertension. TIPS has replaced operative shunts for managing acute variceal bleeding when pharmacotherapy and endoscopic treatment fail to control bleeding. As a result, emergency surgical intervention in most centers is reserved for select patients who are not TIPS candidates.

**Endoscopy.** About 80% to 90% of acute variceal bleeding episodes are successfully controlled by endoscopic measures. Sclerotherapy and band ligation of varices are the two main options available for control of acute variceal bleeding. Data suggest that band ligation is better than sclerotherapy in the initial control of bleeding and is associated with fewer complications. The literature also suggests that sclerotherapy, but not band ligation, may increase portal pressures. Thus, at this time, band ligation is the modality of choice for initial control of variceal bleeding. Endoscopic sclerotherapy may be used if technology for band ligation is not available. Early endoscopy, preferably within 12 hours of admission, with an attempt at control of bleeding is recommended. Patients should be started on vasoactive drugs early, and endoscopy with band ligation is performed after initial resuscitation.

**Pharmacotherapy.** Pharmacotherapy works by reducing variceal blood flow, which in turn reduces variceal pressure. Medical therapy should be initiated at the onset of variceal bleeding. Because infections are common in patients with variceal bleeding, antibiotic prophylaxis should be initiated. This has been shown to decrease the infection rate by more than 50%, to decrease rebleeding, and to improve survival. Randomized trials have also shown that somatostatin and its longer-acting analogue octreotide are as efficacious as endoscopic treatment for control of acute variceal bleeding. Because of the minimal adverse effects and ease of administration, octreotide is now commonly used as an adjunct to endoscopic therapy. In fact, the combination of octreotide and endoscopic therapy is more effective than octreotide alone in controlling bleeding and is the preferred treatment for most patients. In severe cases of hemorrhage, vasopressin can be used to diminish splanchnic blood flow. However, because of the adverse systemic effects of vasopressin, nitroglycerin should be simultaneously infused and then titrated to achieve blood pressure control.

**Variceal tamponade.** Controlled trials have demonstrated that balloon tamponade is as effective as pharmacotherapy and
endoscopic therapy in controlling acute variceal bleeding. The major advantages of variceal tamponade using the Sengstaken-Blakemore tube are immediate cessation of bleeding in more than 85% of patients and the widespread availability of this device (Fig. 54.19). However, there are also significant disadvantages of balloon tamponade, including frequent recurrent hemorrhage in up to 50% of patients after balloon deflation, considerable discomfort for the patient, and a high incidence of serious complications when it is used incorrectly by an inexperienced healthcare provider.

Interventional approaches. In most institutions, TIPS has become the preferred treatment for acute variceal bleeding when pharmacotherapy and endoscopic treatment fail. With TIPS, a functional portacaval side-to-side shunt is established. TIPS is able to control bleeding in almost all patients. However, TIPS is associated with risk of encephalopathy. Furthermore, in the case of shunt dysfunction, there is risk of recurrent bleeding. Use of polytetrafluoroethylene (PTFE)-covered stents has been a major step forward. PTFE stents have higher patency rates over time and reduced mortality rates. Use of TIPS in patients with multigorgan failure or in patients with decompensated liver disease is associated with high 30-day mortality. In such patients, early use of TIPS, rather than after failure of other therapies, may be associated with better outcomes.

Operative approaches. Operative procedures are typically reserved for those situations in which TIPS is not indicated or is not available. Selection of the appropriate emergency operation should mainly be guided by the experience of the surgeon. Although nonoperative therapies are effective in most patients with acute variceal bleeding, an emergency operation should be promptly carried out when less invasive measures fail to control hemorrhage or are not indicated. The most common situations requiring urgent or emergency surgery are failure of acute endoscopic treatment, failure of long-term endoscopic therapy, hemorrhage from gastric varices or portal hypertensive gastropathy, and failure of TIPS placement.

Esophageal transection with a stapling device is rapid and relatively simple, but rebleeding rates after this procedure are high. Moreover, there is little evidence that operative mortality rates are lower than after surgical portal decompression.

A commonly performed shunt operation in the emergency setting is the portacaval shunt because it rapidly and effectively decompresses the portal venous circulation. Impressive results have been achieved by Orloff and colleagues, but not by others, when an emergency portacaval shunt is used as routine therapy for acute variceal bleeding. In patients who are not actively bleeding at the time of surgery and in those in whom bleeding is temporarily controlled by pharmacotherapy or balloon tamponade, a more complex operation, such as the distal splenorenal shunt, may be appropriate. The major disadvantage of emergency surgery is that operative mortality rates exceed 25% in most reported series. Early postoperative mortality is usually related to the status of hepatic functional reserve rather than to the type of emergency operation selected.

Prevention of Recurrent Variceal Hemorrhage

After a patient has bled from varices, the likelihood of a repeated episode exceeds 70%. Because most patients with variceal hemorrhage have chronic liver disease, the challenge of long-term management is prevention of recurrent bleeding and maintenance of satisfactory hepatic function. Options available for definitive treatment include pharmacotherapy, chronic endoscopic treatment, TIPS, shunt operations (e.g., nonselective, selective, partial), various nonshunt procedures, and liver transplantation. The most effective treatment regimen usually requires two or more of these therapies in sequence. In most centers, initial treatment consists of pharmacotherapy or endoscopic therapy, with portal decompression by means of TIPS or an operative shunt reserved for failures of first-line treatment. Hepatic transplantation is used for patients with end-stage liver disease.

Pharmacotherapy. A metaanalysis of controlled trials of nonselective β-adrenergic blockade has shown that this treatment significantly decreases the likelihood of recurrent hemorrhage and demonstrates a trend toward decreased mortality. The combination of a beta blocker and long-acting nitrate (e.g., isosorbide 5-mononitrate) has been shown to be more effective than variceal ligation. Combination therapy is also more effective than beta blockade alone. Long-term pharmacotherapy should be used only in compliant patients who are observed closely by their physician.

Endoscopic therapy. Several controlled trials and a metaanalysis comparing endoscopic sclerotherapy with variceal ligation have shown a significant advantage to variceal ligation. Complications are less frequent after variceal ligation, and fewer treatment sessions are required to eradicate varices (Fig. 54.20). Rebleeding and mortality rates also appear to be lower after variceal ligation. The combination of variceal ligation and pharmacotherapy with nonselective beta blockade is more effective than variceal ligation alone. This result has been confirmed in a metaanalysis that included the data from 17 randomized controlled trials. In this trial, combination of beta blocker and endoscopic treatment...
significantly reduced rebleeding rates at 6, 12, and 24 months. Furthermore, mortality at 24 months was significantly lower for the combined treatment group. Thus, at this time, combination therapy should be recommended as the first line of treatment for secondary prophylaxis of variceal bleeding.

Several controlled trials comparing chronic endoscopic therapy with conventional medical management have been completed. Although fewer patients receiving endoscopic treatment than medical treatment experienced rebleeding in all the investigations, recurrent bleeding still occurred in approximately 50% of endoscopic therapy patients. Rebleeding is most frequent during the initial year. Rebleeding rate decreases by about 15% annually thereafter. Although a single episode of recurrent hemorrhage does not signify failure of therapy, uncontrolled hemorrhage, multiple major episodes of rebleeding, and hemorrhage from gastric varices and hypertensive gastropathy all require that endoscopic therapy be abandoned, and another treatment modality substituted. Endoscopic treatment failure secondary to rebleeding occurs in as many as one third of patients. Thus, chronic endoscopic therapy is a rational initial treatment for many patients who bleed from esophageal varices, but subsequent treatment with TIPS, a shunt procedure, a nonshunt operation, or liver transplantation should be anticipated for a significant percentage of patients. Because of its relatively high failure rate, a course of chronic endoscopic therapy should not be undertaken for noncompliant patients and those living a long distance from advanced medical care.

**Interventional therapy.** TIPS is being increasingly used for definitive treatment of patients who bleed from portal hypertension (Fig. 54.21). A major limitation of TIPS, however, is a high incidence (up to 50%) of shunt stenosis or shunt thrombosis within the first year. Shunt stenosis, which is usually secondary to neointimal hyperplasia, is more common than thrombosis and can often be resolved by balloon dilation of the TIPS or, in some cases, by placement of a second shunt. Total shunt occlusion occurs in 10% to 15% of patients. Shunt stenosis and shunt thrombosis are often followed by recurrent portal hypertensive bleeding. TIPS stenosis and occlusion have become less frequent with the use of PTFE-covered stents.

TIPS has been compared with chronic endoscopic therapy in 11 randomized controlled trials. Fewer patients rebled after TIPS (19%) than after endoscopic treatment (47%), but encephalopathy was significantly more common in TIPS patients (34%). TIPS dysfunction developed in 50% of patients. The major advantage of TIPS is that it is a nonoperative approach. Thus, it would appear to be the ideal therapy when only short-term portal decompression is required. Liver transplantation candidates who fail to respond to endoscopic therapy or pharmacotherapy are therefore well suited for TIPS followed by transplantation when a donor organ becomes available. As a result, the patient is protected from bleeding in the interim, and the transplantation procedure may

![Endoscopic ligation of esophageal varices.](image1)


![Transjugular intrahepatic portosystemic shunt placement](image2)

**FIG. 54.21** Transjugular intrahepatic portosystemic shunt placement. The inferior vena cava is accessed through right internal jugular vein. If the right internal jugular vein is unsuitable, the left internal jugular vein may also be used. Through this access, a 5F catheter is placed into the right hepatic vein and wedged into a peripheral branch. Wedged hepatic venography is then performed with CO\(_2\) gas to opacify the portal venous system. Using the wedged hepatic venogram image as a guide, a needle is advanced through the wall of the right hepatic vein and directed in an anteroinferior direction to access the right portal vein. Once the portal vein is cannulated, CO\(_2\) is injected into the parenchymal tract to exclude transgression of the bile duct or hepatic artery. Once proper placement is confirmed, TIPS endoprosthesis is deployed, which creates a shunt between the portal vein and the hepatic vein, thus decreasing resistance and decompressing varices.
be facilitated by the lower portal pressure. Another group of patients in whom TIPS may be advantageous includes those with advanced hepatic functional decompensation who are unlikely to survive long enough for the TIPS to malfunction. Because it functions as a side-to-side portosystemic shunt, TIPS is also effective for the treatment of medically intractable ascites.

**Surgical therapy.** Portosystemic shunts are clearly the most effective means of preventing recurrent hemorrhage in patients with portal hypertension. These procedures are effective because they all decompress the portal venous system to varying degrees by shunting portal flow into the lower pressure systemic venous system. However, diversion of portal blood, which contains hepatotropic hormones, nutrients, and cerebral toxins, is also responsible for the adverse consequences of shunt operations, namely, portosystemic encephalopathy and accelerated hepatic failure. Depending on whether they completely decompress, compartmentalize, or partially decompress the portal venous circulation, portosystemic shunts can be classified as nonselective, selective, or partial. In addition to variceal decompression, selective and partial portosystemic shunts also aim to preserve hepatic portal perfusion and therefore to prevent or to minimize the adverse consequences of these procedures.

**Nonselective shunts.** Commonly used nonselective shunts, all of which completely divert portal flow, include the end-to-side portacaval shunt (Eck fistula), side-to-side portacaval shunt, large-diameter interposition shunts, and conventional splenorenal shunt (Fig. 54.22). The end-to-side portacaval shunt is the prototype of nonselective shunts and is the only shunt procedure that has been compared with conventional medical treatment in randomized controlled trials. Fig. 54.23 combines survival data from four controlled investigations of the therapeutic portacaval shunt, performed in patients with prior variceal hemorrhage. The most common causes of death in medically treated and shunted patients were rebleeding and accelerated hepatic failure, respectively. Although no survival advantage could be demonstrated for shunt patients, all these studies had a crossover bias in favor of medically treated patients, several of whom received a shunt when they developed intractable recurrent variceal hemorrhage. In addition, almost all the trial patients had alcoholic cirrhosis; therefore, these results do not necessarily apply to other causes of portal hypertension. Other important findings of these randomized trials included reliable control of bleeding in shunted patients, variceal rebleeding in more than 70% of medically treated patients, and spontaneous, often severe, encephalopathy in 20% to 40% of shunted patients.

All the other nonselective shunts in Fig. 54.22 maintain continuity of the portal vein, thereby connecting the portal and systemic venous systems in a side-to-side fashion. Therefore, these procedures decompress the splanchnic venous circulation and intrahepatic sinusoidal network. Because the liver and intestines are both important contributors to ascites formation, side-to-side portosystemic shunts are the most effective shunt procedures for relieving ascites as well as for preventing recurrent variceal bleeding. Because they completely divert portal flow, like the end-to-side portacaval shunt, however, side-to-side shunts also accelerate hepatic failure and lead to frequent postshunt encephalopathy.
The conventional splenorenal shunt consists of anastomosis of the proximal splenic vein to the renal vein. Splenectomy is also performed. Because the smaller proximal rather than the larger distal end of the splenic vein is used, shunt thrombosis is more common after this procedure than after the distal splenorenal shunt. Although early series noted that postshunt encephalopathy was less common after the conventional splenorenal shunt than after the portacaval shunt, subsequent analyses have suggested that this low frequency of encephalopathy was probably a result of restoration of hepatic portal perfusion after shunt thrombosis developed in many patients. A conventional splenorenal shunt that is of sufficient caliber to remain patent gradually dilates and eventually causes complete portal decompression and portal flow diversion. A purported advantage of the procedure is that hypersplenism is eliminated by splenectomy. The thrombocytopenia and leukopenia that accompany portal hypertension, however, are rarely of clinical significance, making splenectomy an unnecessary procedure in most patients.

In summary, nonselective shunts effectively decompress varices. Because of complete portal flow diversion, however, they are complicated by frequent postoperative encephalopathy and accelerated hepatic failure. Side-to-side nonselective shunts effectively relieve ascites and prevent variceal hemorrhage. Presently, nonselective shunts are only rarely indicated. TIPS, also a nonselective shunt, is the preferred therapy for most situations in which nonselective shunts were previously used (e.g., patients with both variceal bleeding and medically intractable ascites). In general, a nonselective shunt is constructed only when a TIPS cannot be performed or when a TIPS fails.

**Selective shunts.** The hemodynamic and clinical shortcomings of nonselective shunts stimulated development of the concept of selective variceal decompression. In 1967, Warren and colleagues introduced the distal splenorenal shunt. In the following year, Inokuchi and associates reported their initial results with the left gastric–vena cava shunt, which consists of interposition of a vein graft between the left gastric (coronary) vein and IVC. Therefore, it directly and selectively decompresses esophagogastric varices. However, only a minority of patients with portal hypertension have appropriate anatomy for this operation; experience with it has been limited to Japan, and no controlled trials have been conducted.

The distal splenorenal shunt consists of anastomosis of the distal end of the splenic vein to the left renal vein and interruption of all collateral vessels (e.g., coronary vein and gastroepiploic veins) that connect the superior mesenteric vein and gastroepiploic components of the splanchnic venous circulation (Fig. 54.24). This results in separation of the portal venous circulation into a decompressed gastroepiploic venous circuit and high-pressure superior mesenteric venous system that continues to perfuse the liver. Although the procedure is technically demanding, it can be mastered by most well-trained surgeons who are knowledgeable in the principles of vascular surgery.

Not all patients are candidates for the distal splenorenal shunt. Because sinusoidal and mesenteric hypertension is maintained and important lymphatic pathways are transected during dissection of the left renal vein, the distal splenorenal shunt tends to aggravate rather than to relieve ascites. Thus, patients with medically intractable ascites should not undergo this procedure. However, the larger population of patients who develop transient ascites after resuscitation from a variceal hemorrhage are candidates for a selective shunt. Another contraindication to a distal splenorenal shunt is prior splenectomy. A splenic vein diameter less than 7 mm is a relative contraindication to the procedure because the incidence of shunt thrombosis is high when a small-diameter vein is used. Although selective variceal decompression is a sound physiologic concept, the distal splenorenal shunt remains controversial after an extensive clinical experience spanning almost 40 years.

Although the distal splenorenal shunt results in portal flow preservation in more than 85% of patients during the early postoperative interval, the high-pressure mesenteric venous system gradually collateralizes to the low-pressure shunt, resulting in loss of portal flow in approximately 50% of patients by 1 year. The
degree and duration of portal flow preservation depend on the cause of portal hypertension and the technical details of the operation (the extent to which mesenteric and gastrospenic venous circulations are separated). Although portal flow is maintained in most patients with nonalcoholic cirrhosis and noncirrhotic portal hypertension (e.g., portal vein thrombosis), portal flow rapidly collateralizes to the shunt in patients with alcoholic cirrhosis.

Modification of the distal splenorenal shunt by purposeful or inadvertent omission of coronary vein ligation results in early loss of portal flow. Even when all major collateral vessels are interrupted, portal flow may be gradually diverted through a pancreatic collateral network (pancreatic siphon). This pathway can be discouraged by dissecting the full length of the splenic vein from the pancreas, splenopancreatic disconnection, which results in better preservation of hepatic portal perfusion, especially in patients with alcoholic cirrhosis. However, this extension of the procedure makes it technically more challenging and a significant disadvantage in an era when fewer shunts are being placed because of increased use of endoscopic therapy, TIPS, and liver transplantation.

Six of the seven controlled comparisons of the distal splenorenal shunt and nonselective shunts have included predominantly alcoholic cirrhotic patients. None of these trials has demonstrated an advantage to either procedure with respect to long-term survival. Three of the studies found a lower frequency of encephalopathy after the distal splenorenal shunt, whereas the other trials showed no difference in the incidence of this postoperative complication. In contrast to survival, encephalopathy is a subjective end point that was assessed with various methods in the trials. Another important end point in comparing treatments for variceal hemorrhage was the effectiveness with which recurrent bleeding was prevented. In almost all uncontrolled and controlled series of the distal splenorenal shunt, this procedure was equivalent to nonselective shunts in preventing recurrent hemorrhage. Mainly because of these inconsistent results of the controlled trials, there is no consensus as to which shunting procedure is superior in patients with alcoholic cirrhosis. Because the quality of life (e.g., lower encephalopathy rate) was significantly better in the distal splenorenal shunt group in three of the trials, there appears to be an advantage to selective variceal decompression, even in this population.

Considerably fewer data are available regarding selective shunting in nonalcoholic cirrhosis and noncirrhotic portal hypertension. Because hepatic portal perfusion after the distal splenorenal shunt is better preserved in these disease categories, one might expect improved results. A single controlled trial in patients with schistosomiasis (presinusoidal portal hypertension) has demonstrated a lower frequency of encephalopathy after the distal splenorenal shunt than after a conventional splenorenal shunt (nonselective). Another large series from Emory University has shown that distal splenorenal shunt is associated with better survival in patients with nonalcoholic cirrhosis than in those with alcoholic cirrhosis. However, this has not been a consistent finding in all centers in which the distal splenorenal shunts have been performed.

Several controlled trials have also compared the distal splenorenal shunt with chronic endoscopic therapy. In these investigations, recurrent hemorrhage was more effectively prevented by selective shunting than by sclerotherapy. However, hepatic portal perfusion was maintained in a significantly higher fraction of patients undergoing sclerotherapy. Despite this hemodynamic advantage, encephalopathy rates were similar after both therapies.

The two North American trials were dissimilar with respect to the effect of these treatments on long-term survival. Sclerotherapy with surgical rescue for the one third of sclerotherapy failures resulted in significantly better survival than selective shunt alone, whereas 85% of sclerotherapy failures could be salvaged by surgery. In contrast, a similar investigation conducted in a sparsely populated area (Intermountain West and Plains) showed superior survival after the distal splenorenal shunt. Only 31% of sclerotherapy failures could be salvaged by surgery in this trial. The survival results of these two studies suggest that endoscopic therapy is a rational initial treatment for patients who bleed from varices if sclerotherapy failure is recognized and these patients promptly undergo surgery or TIPS. However, patients living in remote areas are less likely to be salvaged by shunt surgery when endoscopic treatment fails, and therefore, a selective shunt may be preferable initial treatment for such patients.

In one nonrandomized comparison to TIPS, the distal splenorenal shunt had lower rates of recurrent bleeding, encephalopathy, and shunt thrombosis. Ascites was less prevalent after TIPS. A multicenter randomized trial comparing TIPS and the distal splenorenal shunt for the elective treatment of variceal bleeding in good-risk cirrhotic patients has shown generally equivalent results for these two procedures. Rebleeding rates were not significantly different between the distal splenorenal shunt (6%) and TIPS (11%), but this represents the lowest reported rate of rebleeding after TIPS. This was likely secondary to meticulous surveillance of TIPS patency by duplex ultrasound and angiography. Frequent reintervention in TIPS patients (82% compared with 11% for distal splenorenal shunt patients) was necessary to achieve these results. In this trial, postshunt encephalopathy and survival were similar after the two procedures.

Partial shunts. The objectives of partial and selective shunts are the same: effective decompression of varices, preservation of hepatic portal perfusion, and maintenance of some residual portal hypertension. Initial attempts at partial shunting consisted of small-diameter vein-to-vein anastomoses. In general, these thrombosed or dilated with time and thereby became nonselective shunts.

More recently, a small-diameter interposition portacaval shunt using a PTFE graft, combined with ligation of the coronary vein and other collateral vessels, was described (Fig. 54.25). When the prosthetic graft is 10 mm or less in diameter, hepatic portal perfusion is preserved in most patients, at least during the early postoperative interval. Early experience with this small-diameter prosthetic shunt is that less than 15% of shunts have thrombosed, and most of these have been successfully opened by interventional radiologic techniques. A small prospective randomized trial of partial (8 mm in diameter) and nonselective (16 mm in diameter) interposition portacaval shunts has shown a lower frequency of encephalopathy after the partial shunt but similar survival after both types of shunts. In another controlled trial, the small-diameter interposition shunt was discovered to have a lower overall failure rate than TIPS.

Hepatic transplantation. Liver transplantation is not a treatment for variceal bleeding but rather needs to be considered for all patients who present with end-stage hepatic failure, whether or not it is accompanied by bleeding. Transplantation in patients who have bled secondary to portal hypertension is the only therapy that addresses the underlying liver disease in addition to providing reliable portal decompression. Because of economic factors and a limited supply of donor organs, liver transplantation is not available to all patients. Also, transplantation is not indicated for some of the more common causes of variceal bleeding, such as schistosomiasis (normal liver function) and active alcoholism (noncompliance).
Patients are first grouped according to their transplantation candidacy. This decision is based on a number of factors, including cause of portal hypertension, abstinence for alcoholic cirrhotic patients, presence or absence of other diseases, and physiologic rather than chronologic age. Transplantation candidates with decompensated hepatic function or a poor quality of life secondary to their liver disease should undergo transplantation as soon as possible.

Most future transplantation and nontransplantation candidates should undergo initial endoscopic treatment or pharmacotherapy unless they bleed from gastric varices or portal hypertensive gastropathy or live in a remote geographic location and have limited access to emergency tertiary care. Patients who live in remote locations and those who fail to respond to endoscopic and drug therapy should receive a selective shunt or TIPS. A controlled trial has shown that if careful surveillance of TIPS patency and frequent TIPS reinterventions are done, these procedures are equally efficacious.

Until improvements in TIPS technology are fully realized, the distal splenorenal shunt is likely to remain a more durable long-term solution and a reasonable alternative for TIPS failure. However, a TIPS is more commonly done, and few surgeons who are experienced in shunt surgery remain. Therefore, it is likely that operative shunts will play an even smaller role in the management of variceal bleeding in the future than they do now. Patients with medically intractable ascites in addition to variceal bleeding are best treated with TIPS when less invasive measures fail to control bleeding. If the TIPS eventually fails, an open side-to-side shunt can then be constructed if the patient has reasonable hepatic function and is not a transplantation candidate. On the other hand, TIPS is clearly indicated for patients with endoscopic treatment failure who may require transplantation in the near future and for nontransplantation candidates with advanced hepatic functional deterioration. Future transplantation candidates should be carefully monitored so that they undergo transplantation at the appropriate time before they become poor operative risks.

The treatment algorithm for variceal bleeding has changed considerably since the 1970s, during which time endoscopic therapy, liver transplantation, and TIPS have become available to these patients. Nontransplantation operations are now less frequently necessary, the survival results are better because patients at high operative risk are managed by other means, and emergency surgery has almost been eliminated.

**INFECTIOUS DISEASES**

**Pyogenic Abscess**

**Epidemiology**

Ochsner and DeBakey, in their classic paper on pyogenic liver abscess in 1938, described 47 cases and reviewed the world literature. This was the largest experience at that time and the first serious attempt to study this disease. In that era, pyogenic liver abscess was largely a disease of people in their 20s and 30s, mostly the result of acute appendicitis. With the marked changes in medical care since then, notably effective antibiotics and prompt effective treatments for acute inflammatory disorders, and an aging population, the spectrum of this disease has changed. Pyogenic liver abscess is now mostly seen in patients in their 50s or 60s and is more often related to biliary tract disease or is cryptogenic in nature.

However, the incidence of pyogenic liver abscess has remained similar. In 1938, Ochsner and DeBakey reported an incidence of 8/100,000 hospital admissions, whereas in 1975, Pitt and
Zuidema reported 13/100,000 hospital admissions. Two large autopsy studies, one from 1901 and another from 1960, have reported similar incidences of pyogenic liver abscess, 0.45% and 0.59%, respectively. More recent studies from the 1980s through the 2000s have suggested small but significant increases in the incidence of pyogenic liver abscess as high as 22/100,000 hospital admissions. These figures may be declining on the basis of more recent data. This may reflect better, more available, and more frequently used high-quality imaging techniques. Hospital admission practices also affect these numbers. A recent population-based study from North America calculated an annual incidence of 3.6 cases/100,000 population. There is no significant gender, ethnic, or geographic differences in disease frequency; the male-to-female ratio is approximately 1.5:1. Comorbid conditions associated with pyogenic abscess are cirrhosis, diabetes, chronic renal failure, and a history of malignant disease.
**TABLE 54.3** Pyogenic abscesses attributable to specific cause.

<table>
<thead>
<tr>
<th>YEAR OF REPORT</th>
<th>NO. OF PATIENTS</th>
<th>PORTAL VEIN</th>
<th>HEPATIC ARTERY</th>
<th>BILIARY TREE</th>
<th>DIRECT EXTENSION</th>
<th>TRAUMA</th>
<th>CRYPTOGENIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1927–1938 (one study*)</td>
<td>622</td>
<td>42</td>
<td>—</td>
<td>—</td>
<td>17</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>1945–1982 (eight studies)</td>
<td>521</td>
<td>17</td>
<td>9</td>
<td>38</td>
<td>10</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>1970–1999 (eight studies)</td>
<td>1264</td>
<td>5</td>
<td>3</td>
<td>38</td>
<td>1</td>
<td>2</td>
<td>43</td>
</tr>
</tbody>
</table>

*Ochsner A, DeBakey M, Murray S. Pyogenic abscess of the liver. *Am J Surg.* 1938;40:292–319. This is the classic study of Ochsner and DeBakey that reviewed 286 previously reported cases and 47 new cases.

**Pathogenesis**

The liver is probably exposed to portal venous bacterial loads on a regular basis and usually clears this bacterial load without problems. The development of a hepatic abscess occurs when an inoculum of bacteria, regardless of the route of exposure, exceeds the liver’s ability to clear it. This results in tissue invasion, neutrophil infiltration, and formation of an organized abscess. The potential routes of hepatic exposure to bacteria are the biliary tree, portal vein, hepatic artery, direct extension of a nearby nidus of infection, and trauma. The relative contribution of these routes to the formation of hepatic abscess is summarized in Table 54.3.

Along with cryptogenic infections, infections from the biliary tree are the most common identifiable cause of hepatic abscess. Biliary obstruction results in bile stasis with the potential for subsequent bacterial colonization, infection, and ascension into the liver. This process is known as ascending suppurative cholangitis. The nature of biliary obstruction is mostly related to stone disease or malignant disease. In Asia, intrahepatic stones and cholangitis (recurrent pyogenic cholangitis [RPC]; see later) are common causes, whereas in the West, malignant obstruction has become a more predominant cause. Other factors associated with increased risk include Caroli disease, biliary ascariasis, and biliary tract surgery. The common link between all causes of hepatic abscesses from the biliary tree is obstruction and bacteria in the biliary tract. Prior biliary-enteric anastomosis has also been associated with hepatic abscess formation, likely because of unimpeded exposure of the biliary tree to enteric organisms.

The portal venous system drains the gastrointestinal tract; therefore, any infectious disorder of the gastrointestinal tract can result in an ascending portal vein infection (pyelophlebitis), with exposure of the liver to large amounts of bacteria. Historically, untreated appendicitis was considered the most common cause of hepatic abscess, but with the advent of antibiotics and the development of prompt and effective treatment of acute intra-abdominal infections, portal venous infections of the liver have become less frequent. The most common causes of pyelophlebitis are diverticulitis, appendicitis, pancreatitis, inflammatory bowel disease, pelvic inflammatory disease, perforated viscus, and omphalitis in the newborn. Hepatic abscess has also been associated with colorectal malignant disease. In a case-control study from Taiwan, the incidence of gastrointestinal cancers was increased fourfold among patients with pyogenic liver abscess compared with controls.6

Any systemic infection (e.g., endocarditis, pneumonia, osteomyelitis) can result in bacteremia and infection of the liver through the hepatic artery. Microabscess formation is a relatively common finding at autopsy in patients dying of sepsis, but these patients are generally not included in analyses of pyogenic liver abscess. Hepatic abscess from systemic infections may also reflect an altered immune response, such as in patients with malignant disease, acquired immunodeficiency syndrome (AIDS), or disorders of granulocyte function. Children with chronic granulomatous disease are particularly susceptible.

Hepatic abscess can be the result of direct extension of an infectious process. Common examples include supplicative cholecystitis, subphrenic abscess, perinephric abscess, and even perforation of the bowel directly into the liver.

Penetrating and blunt trauma can also result in an intrahepatic hematoma or an area of necrotic liver, which can subsequently develop into an abscess. Bacteria may have been introduced from the trauma, or the affected area may be seeded from systemic bacteremia. Hepatic abscesses associated with trauma can be manifested in a delayed fashion up to several weeks after injury. Other mechanisms of iatrogenic hepatic necrosis, such as hepatic artery embolization or, more recently, thermal ablative procedures, can be complicated by abscess. This is an uncommon complication of these procedures but is seen more often when there has been a previous biliary-enteric anastomosis.

Usually, no cause for a hepatic abscess is found. Cryptogenic abscesses predominate in many series and are more common in some case reports. Possible explanations for cryptogenic hepatic abscess are undiagnosed abdominal disease, resolved infectious process at the time of presentation, and host factors such as diabetes or malignant disease rendering the liver more susceptible to transient hepatic artery or portal vein bacteremia. In patients with cryptogenic hepatic abscess who have undergone computed tomography (CT) and ultrasonography, it has been argued whether a diligent search for a cause should ensue. In series evaluating colonoscopy and endoscopic retrograde cholangiopancreatography (ERCP) in patients with cryptogenic abscess, the yield has been low and often is only fruitful in patients with some objective finding that might have suggested a subclinical abnormality (e.g., mildly elevated bilirubin level). In general, these patients should undergo a thorough history, physical examination, and laboratory workup in search of abnormalities in the intestinal tract or biliary tree. Further invasive procedures or imaging studies should be based on clinical suspicions raised by this workup.

**Pathology and Microbiology**

Most hepatic abscesses involve the right hemiliver, accounting for about 75% of cases. The explanation for this is not known, but preferential laminar blood flow to the right side has been postulated. The left liver is involved in approximately 20% of the cases; the caudate lobe is rarely involved (5%). Bilobar involvement with
multiple abscesses is uncommon. Approximately 50% of hepatic abscesses are solitary. Hepatic abscesses can vary in size from less than 1 mm to 3 or 4 cm in diameter and can be multiloculated or a single cavity. At abdominal exploration, hepatic abscesses appear tan and are fluctuant to palpation, although deeper abscesses may not be visible and can be difficult to palpate. Surrounding inflammation can cause adhesions to local structures.

Studies of the microbiology of hepatic abscesses have had variable results for a number of reasons. In early series, sterile abscesses were commonly reported but probably reflected inadequate culture techniques, whereas in modern series, few abscesses are sampled before the administration of antibiotics. Also, the heterogeneity of the routes of infection makes the microbiology variable. Abscesses from pyelophlebitis or cholangitis tend to be polymicrobial with a high preponderance of gram-negative bacilli. Systemic infections, on the other hand, usually cause infection with a single organism.

Although the rate of sterility reported by Ochsner’s review in 1938 was approximately 50%, series in the 1990s reported sterile abscess rates in approximately 10% to 20% of cases. Many hepatic abscesses are polymicrobial in nature and account for approximately 40% of cases. Some have suggested that solitary abscesses are more likely to be polymicrobial. Anaerobic organisms are involved approximately 40% to 60% of the time. The most common organisms cultured were Escherichia coli and Klebsiella pneumoniae. Other commonly encountered organisms are Staphylococcus aureus, Enterococcus sp., viridans streptococci, and Bacteroides spp. Klebsiella is frequently associated with gas-forming abscesses. Enterococci and viridans streptococci are generally found in polymicrobial abscesses, whereas staphylococcal infections are typically caused by a single organism. Uncommonly encountered organisms (<10% of cultures) include species of Pseudomonas, Proteus, Enterobacter, Citrobacter, Serratia, beta-hemolytic streptococci, microaerophilic streptococci, Fusobacterium, Clostridium, and other rare anaerobes. Blood cultures are positive in approximately 50% to 60% of cases. Of note, highly resistant organisms in patients with indwelling biliary catheters, multiple episodes of cholangitis, and repeated use of antibiotics are being encountered as the use of these catheters becomes more common. Fungal and mycobacterial hepatic abscesses are rare and are almost always associated with immunosuppression, usually from chemotherapy.

Clinical Features

The classic description of the presenting symptoms of hepatic abscess is fever, jaundice, and right upper quadrant pain, with tenderness to palpation. Unfortunately, this presentation is present in only 10% of cases. Fever, chills, and abdominal pain are the most common presenting symptoms, but a broad array of nonspecific symptoms can be present (Table 54.4). A study from Taiwan of 133 patients found fever in 96% of patients, chills in 80%, abdominal pain in 53%, and jaundice in 20%. Many of the symptoms, such as malaise and vomiting, were constitutional in nature. Involvement of the diaphragm may result in symptoms of cough or dyspnea. Rarely, patients can present with peritonitis secondary to rupture. Cases of rupture into the pleural space or pericardium have been reported but are distinctly uncommon. The duration of symptoms is variable, ranging from an acute presentation to a chronic illness lasting months. It has been suggested that acute presentation is associated with identifiable abdominal disease, whereas a chronic presentation is often associated with a cryptogenic abscess. A rare complication specific to Klebsiella hepatic abscesses is endogenous endophthalmitis, occurring in approximately 3% of cases. This serious complication is more common in diabetics. The best chance to preserve visual function is with early diagnosis and treatment.

On physical examination, fever and right upper quadrant tenderness are the most common findings. Tenderness is present in 40% to 70% of patients. Jaundice is also found in approximately 25% of cases and is often secondary to underlying biliary disease. Chest findings are often found in approximately 25% of patients, and hepatomegaly is also commonly noted in approximately 50%. Ascites, splenomegaly, and severe sepsis are uncommon signs of hepatic abscesses.

Nonspecific abnormalities of blood tests are common in pyogenic abscesses. Leukocytosis is present in 70% to 90% of patients, and anemia is commonly encountered. Abnormalities of LFT results are generally present. The ALP level is mildly elevated in 80% of patients, whereas total bilirubin concentration is elevated 20% to 50% of the time. Transaminases are mildly elevated in approximately 60% of patients. Severe abnormalities of liver function are almost always associated with underlying biliary disease. Hypoalbuminemia or mild elevations of the PT and INR can be present and reflect a degree of chronicity. None of these blood tests specifically help diagnose a hepatic abscess. However, together they may suggest a liver abnormality that often leads to imaging studies.

The most essential element to establishing the diagnosis of hepatic abscess is radiographic imaging. Chest radiographs are abnormal approximately 50% of the time, and findings generally reflect subdiaphragmatic disease, such as an elevated right

Table 54.4 Pyogenic abscesses with noted symptoms.

<table>
<thead>
<tr>
<th>YEAR OF REPORT</th>
<th>NO. OF PATIENTS</th>
<th>FEVER, CHILLS</th>
<th>NIGHT SWEATS</th>
<th>MALAISE</th>
<th>ANOREXIA, WEIGHT LOSS</th>
<th>NAUSEA, VOMITING</th>
<th>DIARRHEA</th>
<th>ABDOMINAL PAIN</th>
<th>CHEST PAIN</th>
<th>COUGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1927–1938</td>
<td>333</td>
<td>94</td>
<td>—</td>
<td>—</td>
<td>33</td>
<td>—</td>
<td>92</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(one study*)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1945–1982</td>
<td>494</td>
<td>88</td>
<td>8</td>
<td>58</td>
<td>62</td>
<td>40</td>
<td>17</td>
<td>66</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>(eight studies)</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ten studies)</td>
<td></td>
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</tbody>
</table>

*Ochsner A, DeBakey M, Murray S. Pyogenic abscess of the liver. Am J Surg. 1938;40:292–319. This is the classic study of Ochsner and DeBakey that reviewed 286 previously reported cases and 47 new cases.
hemidiaphragm, right pleural effusion, or atelectasis. On occasion, these can be left-sided findings in the case of an abscess involving the left liver. Plain abdominal radiographs, in rare cases, can be helpful. They can show air-fluid levels or portal venous gas (Fig. 54.27).

Ultrasound and CT are the mainstays of diagnostic modalities for hepatic abscess. Ultrasound usually demonstrates a round or oval area that is less echogenic than the surrounding liver. Ultrasound can reliably distinguish solid from cystic lesions. The limitations of ultrasound are in its ability to visualize lesions high up in the dome of the liver and that it is a user-dependent modality. The sensitivity of ultrasound in diagnosing hepatic abscess is 80% to 95%. CT demonstrates similar findings to ultrasound, and lesions are of lower attenuation than surrounding hepatic parenchyma. High-quality CT scans can demonstrate very small abscesses and can more easily identify multiple small abscesses. The abscess wall usually has an intense enhancement on contrast-enhanced CT. The sensitivity of CT in diagnosing hepatic abscess is 95% to 100%. Both CT and ultrasound are useful in diagnosing other intraabdominal pathologic processes, such as biliary disease (ultrasound) and inflammatory disorders such as appendicitis and diverticulitis (CT). Magnetic resonance imaging (MRI) can be helpful in distinguishing the cause of many hepatic masses and evaluating the biliary tree for pathologic changes, but it does not appear to have any distinct advantage over CT in diagnosing hepatic abscess.

**Differential Diagnosis**

Differentiating pyogenic abscess from other cystic infective diseases of the liver, such as amebic abscess or echinococcal cyst, is important because of differences in treatment. Pyogenic abscess (see later) is largely treated by antibiotics and drainage. Amebic abscess is mainly treated by antibiotics, whereas echinococcal cysts often require surgical management. Fortunately, echinococcal cysts can usually be diagnosed by history and characteristic radiologic findings (see later). The presentations of amebic and pyogenic abscesses, however, are more similar, with some notable exceptions that are critical in distinguishing the two (Table 54.5). Amebic abscesses generally occur in young Hispanic men, whereas pyogenic abscess tends to occur in patients 50 to 60 years of age, with no preponderant gender or race. Fever is common in both, but chills and symptoms of a severe acute bacteremia are more common in pyogenic abscess. On serologic testing, *Entamoeba histolytica* antibodies are almost always present in amebic abscesses but are uncommon in patients with pyogenic abscess. A study comparing 471 patients with amebic abscess to 106 patients with pyogenic abscess found age older than 50 years, pulmonary findings on physical examination, multiple abscesses, and low amebic serology titers to be independently predictive of pyogenic abscess. On occasion, differentiating the two is not possible, and diagnostic aspiration or a trial of antiamebic antibiotics may be necessary. Unfortunately, aspiration is diagnostic in amebic abscess only approximately 10% to 20% of the time.

**Treatment**

Before the availability of antibiotics and the routine use of drainage procedures, untreated hepatic pyogenic abscess was almost uniformly fatal. It was not until the classic review by Ochsner and DeBakey in 1938 (see earlier) that routine surgical drainage was used and dramatic reductions in mortality were noted. Open surgical drainage of pyogenic abscesses was the sole treatment (with the addition of antibiotics eventually) for hepatic abscess until the 1980s. Since then, less invasive percutaneous drainage techniques and IV antibiotics have been used. Laparotomy is generally reserved for failures of percutaneous drainage.

Once the diagnosis of pyogenic hepatic abscess is suspected, broad-spectrum IV antibiotics should be started immediately to control ongoing bacteremia and its associated complications. Blood samples and specimens of the abscess from aspiration should be sent for aerobic and anaerobic cultures. In immunosuppressed patients, mycobacterial and fungal cultures of the aspirate should be considered. Patients who are at risk for amebic infections should have blood samples drawn for amebic serology. Until cultures have specifically identified the offending organisms, broad-spectrum antibiotics covering gram-negative, gram-positive, and anaerobic organisms should be used. Combinations such as ampicillin, an aminoglycoside, and metronidazole or a third-generation cephalosporin with metronidazole are appropriate. The optimal duration of antibiotic treatment is not well defined and

**TABLE 54.5** Features of amebic versus pyogenic liver abscess.

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Amebic Abscess</th>
<th>Pyogenic Abscess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20–40 years</td>
<td>&gt;50 years</td>
</tr>
<tr>
<td>Male-to-female ratio</td>
<td>≥10:1</td>
<td>1.5:1</td>
</tr>
<tr>
<td>Solitary versus multiple</td>
<td>Solitary 80%*</td>
<td>Solitary 50%</td>
</tr>
<tr>
<td>Location</td>
<td>Usually right liver</td>
<td>Usually right liver</td>
</tr>
<tr>
<td>Travel in endemic area</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Uncommon (~2%)</td>
<td>More common (~27%)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Elevated bilirubin</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Elevated alkaline phosphatase</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>No</td>
<td>Common</td>
</tr>
<tr>
<td>Positive amebic serology</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*In acute amebic abscess, 50% are solitary.
must be individualized, depending on the success of the drainage procedure. Antibiotics should certainly be continued while there is evidence of ongoing infection, such as fever, chills, or leukocytosis. Beyond this, it is unclear how long to continue antibiotics, but recommendations are usually for 2 weeks or more.

Percutaneous drainage for pyogenic hepatic abscesses was first reported in 1953 but did not gain widespread acceptance until the 1980s with the development of high-quality imaging and expertise in interventional radiologic techniques. During the last 25 years, percutaneous catheter drainage has become the treatment of choice for most patients (Fig. 54.28). Success rates range from 66% to 90%. The obvious advantages are the simplicity of treatment (usually at the time of radiologic diagnosis) and avoidance of general anesthesia and a laparotomy. Relative contraindications to percutaneous catheter drainage include the presence of ascites, coagulopathy, and proximity to vital structures. Percutaneous drainage of multiple abscesses is usually met with a higher failure rate, but reports have demonstrated a high enough success rate that percutaneous approaches should be made first, reserving surgery for failures. A retrospective study comparing surgical with percutaneous techniques for large abscesses (>5 cm) has shown a better success rate with surgical drainage. Despite this, two thirds of percutaneous treatments were successful, and the overall morbidity and mortality rates were similar. There has never been a randomized prospective comparison between percutaneous and surgical therapy for hepatic abscess. However, case series have suggested that for most cases, there are similar success and mortality rates. Modern series attempting to compare these two techniques retrospectively must be read with caution because most patients treated surgically have failed to respond to other less invasive techniques. In general, surgery should be reserved for patients who require surgical treatment of the primary pathologic process (e.g., appendicitis) or for those who have failed to respond to percutaneous techniques. Laparoscopic drainage procedures have been reported with some success, and this can be considered a reasonable option to pursue in select cases.4

Percutaneous aspiration without the placement of an indwelling drain has been investigated by a number of groups. Success rates are generally 60% to 90% and are somewhat similar to those for percutaneous catheter drainage.7 Most patients, however, require more than one aspiration, and 25% of patients require three or more aspirations. One randomized trial has evaluated
percutaneous aspiration versus percutaneous catheter drainage. Success rates were 60% in the aspiration group and 100% in the catheter group. All but one patient in the aspiration group had a single aspiration. Another randomized trial of 64 patients has compared aspiration alone with catheter drainage. There were similar outcomes in terms of treatment success rate, hospital stay, antibiotic duration, and mortality. In the aspiration-only group, 40% required two aspirations and 20% required three aspirations. In general, catheter drainage remains the treatment of choice, although a trial of a single aspiration is reasonable to consider.

Some investigators have reported success with antibiotics alone. Most of these patients, however, have had a diagnostic aspiration and thus at least a partial drainage. Also, other series have reported that antibiotic treatment without drainage carries a prohibitively high mortality (59%–100%). In patients who are not surgical candidates or who refuse any invasive procedure, an attempt at antibiotic treatment is reasonable. However, this is not recommended in other situations.

Liver resection is occasionally required for hepatic abscess. This may be required for an infected hepatic malignant neoplasm, hepatothiitis, or intrahepatic biliary strictures. If hepatic destruction from infection is severe, some patients may benefit from resection.

Outcomes
Mortality from pyogenic hepatic abscess has dramatically improved during the last 70 years. Before the routine use of surgical drainage, pyogenic abscess was uniformly fatal. With the routine use of surgical drainage and the use of IV antibiotics, mortality was reduced to approximately 50%, a figure that stayed relatively constant from 1945 until the early 1980s. Since then, the mortality has been reported from 10% to 20%, and series from the 1990s have demonstrated a mortality rate below 10%. The most recent series from Memorial Sloan-Kettering Cancer Center (MSKCC) has reported a 3% mortality. A number of studies have analyzed factors predictive of a poor outcome in patients with hepatic pyogenic abscess. The presence of malignant disease, factors associated with malignant disease (e.g., jaundice, markedly elevated LFT results), and signs of sepsis appear to be consistent markers of poor prognosis. Signs of chronic disease, such as hyperalbuminemia, are also often associated with a poor outcome. Finally, signs of severe infection, such as marked leukocytosis, acute physiology and chronic health evaluation II (APACHE II) scores, abscess rupture, bacteraemia, and shock, are also associated with mortality.

Amebic Abscess
Epidemiology
Amebiasis is largely a disease of tropical and developing countries but is also a significant problem in developed countries because of immigration and travel between countries. *E. histolytica* is endemic in Mexico, India, Africa, and parts of Central and South America. In 1995, the World Health Organization estimated that 40 to 50 million people suffer from amebic colitis or amebic liver abscess worldwide, resulting in 40,000 to 100,000 deaths each year. Before this, estimates of amebiasis were unreliable because *E. histolytica* (the pathogenic form) was not differentiated from *Entamoeba dispar* (the nonpathogenic form). Male homosexuals with diarrhea, previously thought to harbor *E. histolytica*, were actually found to be infected with *E. dispar*, which requires no treatment. Epidemiologic studies specifically addressing *E. histolytica* infections have estimated that as many as 55% of those in endemic regions are infected, although less than 50% are symptomatic.

In contrast to pyogenic hepatic abscesses, patients with amebic liver abscesses tend to be Hispanic men, 20 to 40 years of age, with a history of travel to (or origination from) an endemic area. Poverty and cramped living conditions are associated with higher rates of infection. A male preponderance of more than 10:1 has been reported in almost all studies. For unclear reasons, menstruating women have a low incidence of invasive amebiasis, and pregnancy appears to abrogate this resistance. Heavy alcohol consumption is commonly reported and may render the liver more susceptible to amebic infection. Patients with impaired host immunity also appear to be at higher risk of infection and have higher mortality rates. Patients with amebic liver abscess without a history of travel to an endemic area often have associated immunosuppression, such as human immunodeficiency virus (HIV) infection, malnutrition, chronic infection, or chronic steroid use.

Pathogenesis
*E. histolytica* is a protozoan and exists as a trophozoite or a cyst. All other species in the genus *Entamoeba* are considered nonpathogenic, and not all strains of *E. histolytica* are considered virulent. Ingestion of *E. histolytica* cysts through a fecal-oral route is the cause of amebiasis. Humans are the principal host, and the main source of infection is human contact with a cyst-passing carrier. Contaminated water and vegetables are also routes of human infection. Once ingested, the cysts are not degraded in the stomach and pass to the intestines, where the trophozoite is released and passed on to the colon. In the colon, the trophozoite can invade mucosa, resulting in disease.

It is thought that the trophozoites reach the liver through the portal venous system. There is no evidence for trophozoites passing through lymphatics. As implied by its name, *E. histolytica* trophozoites can lyse tissues through a complex set of events, including cell adherence, cell activation, and subsequent release of enzymes, resulting in necrosis. The principal mechanism is probably enzymatic cellular hydrolysis. Amebic liver abscesses are formed by progressing, localized hepatic necrosis producing a cavity containing cellular proteinaceous debris surrounded by a rim of invasive amebic trophozoites. Early development of an amebic liver abscess is associated with an accumulation of polymorphonuclear leukocytes, which are then lysed by the trophozoites.

Antiamebic antibodies develop rapidly in patients with invasive disease or an amebic hepatic abscess. Secretory immunoglobulin A (IgA) antibodies have been shown to inhibit adherence to colonic epithelium in vitro. However, the development of these antibodies does not halt the progression of disease. Interestingly, children who lack antiamebic IgG have innate resistance to invasive infection, suggesting an alternative immune-mediated response. There is now evidence that a cell-mediated helper T-cell response is probably the major mechanism of resistance.

Pathology
Hepatic amebic abscess is essentially the result of liquefaction necrosis of the liver producing a cavity full of blood and liquefied liver tissue. The appearance of this fluid is typically described as resembling anchovy sauce; the fluid is odorless unless secondary bacterial infection has taken place. The progressive hepatic necrosis continues until Glisson capsule is reached because the capsule is resistant to hydrolysis by the amebae. Thus, amebic abscesses tend to abut the liver capsule. Because of the resistance of Glisson capsule, the cavity is typically crisscrossed by portal triads protected by this peritoneal sheath. Early on, the formed cavity is ill-defined, with no real fibrous response around the edges. However,
a chronic abscess can ultimately develop a fibrous capsule and may even calcify. Like pyogenic abscesses, amebic abscesses tend to occur mainly in the right liver.

**Clinical Features**

Approximately 80% of patients with amebic liver abscess present with symptoms lasting from a few days to 4 weeks. The duration of symptoms has been found to be typically less than 10 days. The presenting clinical signs and symptoms are summarized in Table 54.6. The typical clinical picture is a patient 20 to 40 years of age who has recently traveled to an endemic area, with fever, chills, anorexia, right upper quadrant pain and tenderness, and hepatomegaly. The abdominal pain is typically constant, dull, and localized to the right upper quadrant. Although some studies report higher numbers, approximately 25% of patients have diarrhea despite an obligatory colonic infection. Synchronous hepatic abscess is found in one third of patients with active amebic colitis. Jaundice, as a result of a large abscess compressing the biliary tree, is not as rare as was once thought, with an average 22% of patients presenting with this feature worldwide. Weight loss and maligias may occur when symptoms have been present for weeks. Pleuritic or right shoulder pain can occur if there is irritation of the right hemidiaphragm. Symptoms and tenderness may be epigastric or left sided if the abscess is located in the left liver. Rupture into the peritoneum with peritonitis occurs infrequently; when it does occur, it is more often with left-sided abscesses. Rare cases of rupture into the pleural space, pericardium, and other intra-abdominal organs have also been reported.

Patients presenting acutely (symptoms < 10 days) versus those with a chronic presentation (>2 weeks) differ clinically. Acute presentations are typically more dramatic, with high fevers, chills, and significant abdominal tenderness. In the acute presentation, 50% of patients have multiple lesions, whereas with the chronic presentation, more than 80% of patients have a single right-sided lesion. A more complicated course tends to ensue in the acute presentation, but response to therapy is similar in both groups.

Laboratory abnormalities are common in amebic abscess (Table 54.6). Patients typically have a mild to moderate leukocytosis, without eosinophilia. Anemia is common. Mild abnormalities of LFT results, including albumin, PT-INR, ALP, AST, and bilirubin levels, are typical. The most common LFT abnormality is an elevated PT-INR. Because more than 70% of patients with amebic liver abscess do not have detectable amebae in their stool, the most useful laboratory evaluation is the measurement of circulating antiamoebic antibodies, which are present in 90% to 95% of patients. A number of serologic tests have been devised over the years. An indirect hemagglutinin test was used extensively in the past and has a sensitivity of 90%. This test has largely been replaced by enzyme immunoassays, which detect the presence of antibodies against the parasite and are simple, rapidly performed, and inexpensive. An enzyme immunoassay has a reported sensitivity of 99% and specificity higher than 90% in patients with hepatic abscess. Unfortunately, the presence of antibodies may reflect prior infection, and interpretation can be difficult in endemic areas. Ongoing studies are focusing on identifying specific *E. histolytica* antigens in an attempt to identify acute infection. Antigen detection kits have been evaluated in endemic areas. These kits can detect the *E. histolytica* lectin antigen in the serum and liver abscess pus and in small studies have been shown to have high sensitivity. However, the sensitivity may decrease if the test is performed after treatment with metronidazole.

Radiologic studies are a critical element in the diagnosis of amebic liver abscess. Plain chest radiographs are abnormal in approximately 50% of cases, usually demonstrating an elevated right diaphragm, pleural effusion, or atelectasis. Abdominal ultrasound has a reported accuracy of approximately 90% when it is combined with a typical history and clinical presentation. Typical findings on abdominal ultrasound are a rounded lesion abutting the liver capsule (see earlier) without significant rim echoes, interpreted as an abscess wall. The contents of the cavity are usually hypoechoic and nonhomogeneous (Fig. 54.29). These findings on ultrasound are found in 40% to 70% of cases. Abdominal CT scanning is probably more sensitive than

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**Table 54.6** Signs, symptoms, and laboratory findings in amebic liver abscess.*

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>AVERAGE</th>
<th>RANGE</th>
<th>NO. OF CASES REVIEWED</th>
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<tbody>
<tr>
<td>Abdominal pain (%)</td>
<td>92</td>
<td>73–100</td>
<td>1701</td>
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<tr>
<td>Fever (%)</td>
<td>90</td>
<td>72–100</td>
<td>2192</td>
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<tr>
<td>Abdominal tenderness (%)</td>
<td>78</td>
<td>40–100</td>
<td>1424</td>
</tr>
<tr>
<td>Hepatomegaly (%)</td>
<td>62</td>
<td>20–100</td>
<td>1539</td>
</tr>
<tr>
<td>Anorexia (%)</td>
<td>47</td>
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<td>499</td>
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<tr>
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<td>11–83</td>
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<tr>
<td>Diarrhea (%)</td>
<td>23</td>
<td>12–40</td>
<td>1426</td>
</tr>
<tr>
<td>Jaundice (%)</td>
<td>22</td>
<td>5–50</td>
<td>1630</td>
</tr>
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<table>
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<tr>
<th>Laboratory Tests</th>
<th></th>
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<th></th>
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<tbody>
<tr>
<td>Stool cysts, trophozoites (%)</td>
<td>12</td>
<td>4–30</td>
<td>4908</td>
</tr>
<tr>
<td>Amebae in cyst aspirate (%)</td>
<td>42</td>
<td>30–76</td>
<td>1402</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.1</td>
<td>10.2–12.8</td>
<td>229</td>
</tr>
<tr>
<td>Alkaline phosphatase (% &gt;120U/L)</td>
<td>76</td>
<td>65–91</td>
<td>589</td>
</tr>
<tr>
<td>Total bilirubin (g/dL)</td>
<td>1.4</td>
<td>0.8–2.4</td>
<td>509</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.8</td>
<td>2.3–3.4</td>
<td>404</td>
</tr>
<tr>
<td>AST (× upper limit normal)</td>
<td>1.7</td>
<td>1.0–2.5</td>
<td>459</td>
</tr>
</tbody>
</table>

*In an extensive literature review.
ultrasound and is helpful in differentiating amebic from pyogenic abscess, with rim enhancement noted in the pyogenic abscess (Fig. 54.30). CT can also be helpful in identifying simple cysts and necrotic tumors. MRI of the liver has no distinct advantages over CT or ultrasound in typical cases but may be helpful in differentiating atypical lesions. Nuclear medicine studies, such as gallium scanning or Tc 99m liver scans, can be helpful in differentiating pyogenic from amebic abscesses because the amebic abscesses typically do not contain leukocytes and therefore do not light up on these scans.

When this workup is still not definitive and diagnostic uncertainty persists, two options should be considered. First, a therapeutic trial of antiamebic drugs can be used. If a rapid improvement occurs, this supports the diagnosis. In situations in which amebic serology is inconclusive and a therapeutic trial of antibiotics is deemed inappropriate or has failed to improve symptoms, the second option, a diagnostic aspiration, should be considered. A pyogenic abscess would have bacteria and leukocytes, whereas an amebic abscess would contain the typical so-called anchovy sauce. Cultures of amebic abscess are usually negative and do not contain leukocytes. In patients for whom neoplasn or hydatid disease is in the differential diagnosis, aspiration should not be performed.

### Differential Diagnosis

The differential diagnosis of an amebic liver abscess can be broad and include diseases such as viral hepatitis, echinococcal disease, cholangitis, cholecystitis, and even other inflammatory abdominal disorders, such as appendicitis. Malignant lesions of the liver can also have similar presentations in atypical situations. On occasion, primary pulmonary disorders must be considered. Usually, the most important distinction to be made is between pyogenic and amebic abscess. The essential elements of this distinction are summarized in Table 54.5 and in the earlier section on pyogenic abscess.

### Treatment

The mainstay of treatment for amebic abscesses is metronidazole (750 mg orally, three times daily for 10 days), which is curative in more than 90% of patients. Clinical improvement is usually seen within 3 days. Other nitroimidazoles (e.g., secnidazole, tinidazole) are also as effective and are commonly used outside the United States. If response to metronidazole is poor or the drug is not tolerated, other agents can be used. Emetine hydrochloride is effective against invasive amebiasis, particularly in the liver, but requires intramuscular injections and has serious cardiac side effects. A more attractive option is chloroquine, but this is a less effective agent. After treatment of the liver abscess, it is recommended that luminal agents such as iodoquinol, paromomycin, and diloxanide furoate be administered to treat the carrier state.

Therapeutic needle aspiration of amebic abscesses has been proposed. However, a Cochrane systematic review did not support any benefit of therapeutic aspiration in addition to metronidazole treatment over metronidazole treatment alone to hasten clinical or radiologic resolution of amebic liver abscesses. In general, aspiration is recommended for diagnostic uncertainty (see earlier), with failure to respond to metronidazole therapy in 3 to 5 days, or in abscesses thought to be at high risk for rupture. Abscesses larger than 5 cm in diameter and in the left liver are thought to carry a higher risk of rupture, and aspiration should be considered.

### Outcomes

Although amebic liver abscesses usually respond rapidly to treatment, there are uncommon complications of which one must be aware. The most frequent complication of amebic abscess is rupture into the peritoneum, pleural cavity, or pericardium. The size of the abscess appears to be the most important risk factor for rupture, and the overall incidence of rupture ranges from 3% to 17%. Most peritoneal ruptures tend to be contained by the diaphragm, abdominal wall, or omentum, but rupture can fistulize into a hollow viscus. A peritoneal rupture usually is manifested as abdominal pain, peritonitis, and a mass or generalized distention. Laparotomy was advocated in the past for this complication, but now many patients are treated successfully with percutaneous drainage. Laparotomy is indicated in cases of doubtful diagnosis, hollow viscus perforation, fistulization resulting in hemorrhage or sepsis, and failure of conservative therapy. Rupture into the pleural space usually results in a large and rapidly accumulated effusion that collapses the involved lung. Treatment consists of thoracentesis, but if secondary bacterial infection ensues, more aggressive surgical approaches may be necessary. Rupture can occur into the bronchi and is usually self-limited with postural drainage and bronchodilators. Rarely, a left-sided abscess may rupture into the pericardium and can be manifested as an asymptomatic pericardial effusion or even tamponade. This must be treated with aspiration or drainage through a pericardial window. Other complications include compression of the biliary tree or IVC from a very large abscess and the development of a brain abscess.

The mortality for all patients with amebic liver abscess is approximately 5% and does not appear to be affected by the addition of aspiration to metronidazole therapy or by chronicity of symptoms. When an abscess ruptures, mortality ranges from 6% to as high as 50%. Factors independently associated with poor outcome are elevated serum bilirubin level (>3.5 mg/dL), encephalopathy, hypoalbuminemia (<2.0 g/dL), multiple abscess cavities, abscess volume larger than 500 mL, anemia, and diabetes. Although clinical improvement after adequate treatment with antiamebic agents is the rule, radiologic resolution of the abscess cavity is usually delayed. The average time to radiologic resolution is 3 to 9 months, and in some patients, it can take years. Studies have shown that more than 90% of the visible lesions disappear radiologically, but a small percentage of patients are left with a clinically irrelevant residual lesion.
Hydatid Cyst

Hydatid disease or echinococcosis is a zoonosis that occurs primarily in sheep-grazing areas of the world but is common worldwide because the dog is a definitive host. Echinococcosis is endemic in Mediterranean countries, the Middle East, Far East, South America, Australia, New Zealand, and east Africa. Humans contract the disease from dogs, but there is no human-to-human transmission.

There are three species that cause hydatid disease. *Echinococcus granulosus* is the most common, and *Echinococcus multilocularis* and *Echinococcus ligartus* account for a small number of cases. Dogs are the definitive host of *E. granulosus*; the adult tapeworm is attached to the villi of the ileum. Up to thousands of ova are passed daily and deposited in the dog’s feces. Sheep are the usual intermediate host, but humans are an accidental intermediate host. Humans are an end stage to the parasite. In the human duodenum, the parasitic embryo releases an oncosphere containing hooklets that penetrate the mucosa, allowing access to the bloodstream. In the blood, the oncosphere reaches the liver (most commonly) or lungs, where the parasite develops its larval stage—the hydatid cyst.

Three weeks after infection, a visible hydatid cyst develops, which then slowly grows in a spherical manner. A pericyst or fibrous capsule derived from host tissues develops around the hydatid cyst. The cyst wall itself has two layers, an outer gelatinous membrane (ectocyst) and an inner germinal membrane (endocyst). Brood capsules are small, intracystic cellular masses in which future worm heads develop into scoleces. In a definitive host, the scoleces develop into an adult tapeworm; but in the intermediate host, they can differentiate only into a new hydatid cyst. Freed brood capsules and scoleces are found in the hydatid fluid and form the so-called hydatid sand. Daughter cysts are true replicas of the mother cyst. Hydatid cysts can die with degeneration of the membranes, development of cystic vacuoles, and calcification of the wall. Calcification of a hydatid cyst, however, does not always imply that the cyst is dead.

Hydatid cysts are diagnosed in equal numbers of men and women at an average age of about 45 years. Approximately 75% of hydatid cysts are located in the right liver and are solitary. The clinical presentation of a hydatid cyst is largely asymptomatic until complications occur. The most common presenting symptoms are abdominal pain, dyspepsia, and vomiting. The most frequent sign is hepatomegaly. Jaundice and fever are each present in approximately 8% of patients. Bacterial superinfection of a hydatid cyst can occur and be manifested like a pyogenic abscess. Rupture of the cyst into the biliary tree or bronchial tree or free rupture into the peritoneal, pleural, or pericardial cavities can occur. Free ruptures can result in disseminated echinococcosis or a potentially fatal anaphylactic reaction. In cases of diagnostic uncertainty, a battery of serologic tests are available to evaluate antibody response, but all are plagued by low sensitivity and specificity.

Ultrasound is most commonly used worldwide for the diagnosis of echinococcosis because of its availability, affordability, and accuracy. A number of findings on ultrasound can be diagnostic but depend on the stage of the cyst at the time of the examination. A simple hydatid cyst is well circumscribed with budding signs on the cyst membrane and may contain free-floating hyperechogenic hydatid sand. A rosette appearance is seen when daughter cysts are present. The cyst can be filled with an amorphous mass, which can be diagnostically misleading. Calcifications in the wall of the cyst are highly suggestive of hydatid disease and can be helpful in the diagnosis (Fig. 54.31). Similar findings are seen on CT or
Although surgery remains the treatment of choice, further prospective trials are clearly indicated to address this interesting and potentially useful technique. Treatment of echinococcosis with albendazole or mebendazole is effective at shrinking cysts in many patients with *E. granulosus* infection, but cyst disappearance occurs in well below 50% of patients. Preoperative treatment may decrease the risk of spillage and is a reasonable and safe practice. Medical therapy without definitive resection or drainage should be considered only for widely disseminated disease or poor surgical candidates.

**Fig. 54.32** (A) Peripheral hydatid cyst of the left liver. (B) Intact specimen after pericystectomy. Note that the entire pericyst has been removed. (From Milicevic MN. Hydatid disease. In: Blumgart LH, Fong Y, eds. *Surgery of the Liver and Biliary Tract*. London: WB Saunders; 2000:1167–1204.)

MRI scans. These cross-sectional imaging studies can also evaluate extrahepatic disease and demonstrate detailed hepatic anatomic relationships to the cyst. In patients with suspected biliary involvement, ERCP or percutaneous transhepatic cholangiography may be necessary.

Although the treatment of hepatic hydatid cysts is primarily surgical, alternative options are in evolution. In general, most cysts should be treated; but in older patients with small, asymptomatic, densely calcified cysts, conservative management is appropriate. In preparation for an operation, preoperative steroids have been recommended but are not universally used. The anesthesiologist should have epinephrine and steroids available in case of an anaphylactic reaction. A number of operations have been used, but in general, the abdomen is completely explored, the liver mobilized, and the cyst exposed. Packing off the abdomen is important because rupture can result in anaphylaxis and diffuse seeding. The cyst is usually then aspirated through a closed suction system and flushed with a scleroidal agent, such as hypertonic saline. The cyst is then unroofed, which can then be followed by a number of possibilities, including excision (or pericystectomy), marsupialization procedures, leaving the cyst open, drainage of the cyst, omentoplasty, and partial hepatectomy to encompass the cyst. Total pericystectomy or formal partial hepatectomy can also be performed without entering the cyst (Fig. 54.32). Both radical (resection) and conservative (drainage and evacuation) surgical approaches appear to be equally effective at controlling disease, although a prospective comparison has never been performed. When bile duct communication is diagnosed preoperatively or at operation, it must be meticulously sought after. Simple suture repair is often sufficient, but major biliary repairs, approaches through the common bile duct, or postoperative ERCP may be necessary. Laparoscopic techniques for drainage and unroofing of cysts have been reported in a number of series, with encouraging results. Recurrence rates after surgical treatment range from 1% to 20% but are generally 5% or less in experienced centers.

In the past, percutaneous aspiration of hydatid cysts was contraindicated because of the risk of rupture and uncontrolled spillage. However, percutaneous aspiration with injection of scleroidal agents has been reported with high success rates in highly selected patients. This technique is known as puncture, aspiration, injection, and reaspiration PAIR and has become more accepted in some centers. Two randomized trials, one comparing PAIR with surgery (*N* = 50) and one comparing PAIR with medical therapy, have shown similar success rates. These trials were small and had significant methodologic problems, limiting the ability to draw firm conclusions. Although surgery remains the treatment of choice, further prospective trials are clearly indicated to address this interesting and potentially useful technique. Treatment of echinococcosis with albendazole or mebendazole is effective at shrinking cysts in many patients with *E. granulosus* infection, but cyst disappearance occurs in well below 50% of patients. Preoperative treatment may decrease the risk of spillage and is a reasonable and safe practice. Medical therapy without definitive resection or drainage should be considered only for widely disseminated disease or poor surgical candidates.

**Recurrent Pyogenic Cholangitis**

RPC is a syndrome of repeated attacks of cholangitis secondary to biliary stones and strictures that involve the extrahepatic and intrahepatic ducts. The condition has many names but is often referred to as Oriental cholangiohepatitis or hepatolithiasis. The disease is almost exclusively found in Asians and Asian medical centers. However, it is also seen in Asian immigrants throughout the world. Men and women are equally affected, and, historically, the disease strikes at an early age (20–40 years) in patients from lower socioeconomic classes.

The cause of RPC is unknown but is related to recurrent infection of biliary radicals with gut bacteria. Ultimately, stones and strictures develop in the biliary tree, but it is not known which occurs first. The stones are bilirubinate stones; in some patients, no stones are found and only biliary sludge is demonstrated. An association between RPC and *Clonorchis sinensis* and *Ascaris lumbricoides* infection has been noted, but a true causal relationship has never been proven.

Strictures can be found anywhere in the biliary tree but usually involve the intrahepatic main hepatic ducts, most often the left hepatic duct. The gallbladder is involved only in approximately 20% of cases. Cirrhosis and liver failure are seen only in longstanding disease, usually after multiple operations. Other complications include choledochocholedochal fistulas and acute pancreatitis from common bile duct stones. An increased incidence of cholangiocarcinoma has been noted, but a causal relationship has never been proven.

The typical patient with RPC is a young Asian of a lower socioeconomic background who presents with repeated bouts of cholangitis. The symptoms and presentation are those of cholangitis. These include fever, right upper quadrant abdominal pain, and jaundice. Biliary obstruction is usually incomplete, and
therefore, marked jaundice and pruritus are not common. There is usually leukocytosis and abnormal LFT results consistent with biliary obstruction. Evaluation of the anatomic distribution of disease is critical to formulation of a sound therapeutic plan. A combination of ultrasound, CT, and direct cholangiography is often necessary to evaluate these patients. Direct cholangiography is performed endoscopically or transhepatically and is considered an important study complementing the cross-sectional imaging. Magnetic resonance cholangiopancreatography can combine cross-sectional imaging and cholangiography in one noninvasive test and may ultimately replace direct cholangiography.

In an acute presentation, most patients improve with conservative management, allowing time for radiologic studies and planning of a definitive operation, which is the treatment of choice. If intervention is necessary during the acute phase, it must focus on adequate decompression of the biliary tree through open common bile duct exploration or endoscopic papillotomy with stenting. Although nonoperative approaches, such as percutaneous transhepatic cholangioscopic lithotomy, have been developed, surgical treatment remains the treatment of choice. Percutaneous transhepatic cholangioscopic lithotomy is generally used for poor-risk surgical patients and those who have failed to respond to surgical treatment. Stone clearance rates are high (>80%) and necessary for a successful long-term outcome. Unfortunately, stone recurrence is common and is mostly related to the presence of biliary strictures.

The goal of operative approaches is to clear the biliary tree of stones and to bypass, resect, or enlarge strictures. Many cases require only exploration of the common bile duct with or without hepaticejunostomy. In complicated cases, providing permanent access to the biliary tree for interventional radiologic procedures by extending the end of the Roux-en-Y hepaticejunostomy to the skin or subcutaneous space has been a successful approach (Fig. 54.33). Other potentially necessary procedures include stricturoplasty and partial hepatectomy. Partial hepatectomy is advocated for patients with intrahepatic strictures, hepatic atrophy, liver abscess, or suspicion of cholangiocarcinoma.

In a large series from Asia, where surgery and hepatectomy are liberally applied, surgical mortality rates are 1%. Moreover, with aggressive treatment, there is almost a 100% stone clearance rate. Long-term outcome is excellent, with a less than 5% stone recurrence rate. Long-term survival is mostly related to the presence of cholangiocarcinoma, which is found in approximately 10% of patients. Particularly complicated cases can have a higher rate of recurrent symptoms.

NEOPLASMS

Solid Benign Neoplasms

It is estimated that benign focal liver masses are present in approximately 10% to 20% of the population in developed countries. With the increasing use of rapidly improving radiologic examinations, these entities have been encountered more frequently. Familiarity with the clinical characteristics, natural history, imaging characteristics, and indications for surgery in these tumors is essential. Many benign lesions can be adequately characterized by modern imaging studies, such as CT, ultrasound, and MRI. In unclear cases, serum tumor markers (e.g., AFP, CEA) and a search for a primary tumor in the case of suspected metastases should be carried out. A resection might be necessary to make a definitive diagnosis. Laparoscopy for assessment, biopsy, or resection has become an important diagnostic technique as well.
Liver Cell Adenoma

Liver cell adenoma (LCA) is a relatively rare benign proliferation of hepatocytes in the context of a normal liver. It is predominantly found in young women (aged 20–40 years) and is often associated with steroid hormone use, such as long-term oral contraceptive pill (OCP) use. Increased prevalence of LCA was observed in the 1970s, following the introduction of oral contraceptives. Male anabolic hormone use can also predispose to development of LCA. The female-to-male ratio is approximately 11:1. Other risk factors for LCA include vascular liver diseases, glycogenosis type 1A, and familial adenomatous polyposis. LCAs are usually singular, but multiple lesions have been reported in 12% to 30% of cases. Liver adenomatosis is defined by the presence of more than 10 LCAs in the liver. Interestingly, cases with multiple adenomas are not associated with OCP use and do not have as dramatic a female preponderance. On histologic evaluation, LCAs are composed of cords of benign hepatocytes containing increased glycogen and fat. Bile ductules are not observed histologically, and the normal architecture of the liver is absent in these lesions. Hemorrhage and necrosis are commonly seen. On the basis of detailed molecular pathology correlation studies, a French collaborative group has recently proposed a molecular-pathologic classification whereby the adenomas are classified as β-catenin mutated adenoma, HNF1A mutated adenoma, inflammatory adenoma, and not otherwise specified adenoma. Molecular studies have also identified genetic signatures associated with a higher risk of malignant transformation. Specifically, highest risk of malignant transformation is observed in LCA with β-catenin activation. With further research, new pathways driving the formation of adenomas are being identified and the “not otherwise specified adenoma” group is becoming smaller. For example, recently, sonic hedgehog activation has been observed in 5% of LCAs. Interestingly, these LCAs with sonic hedgehog activation are associated with obesity and bleeding. Furthermore, LCA with β-catenin mutations can be further classified by the nature of the mutation. For example, those with exon-3 mutation have increased risk of hepatocellular carcinoma (HCC) degeneration, whereas mutation in exon 7/8 leads to only weak activation of β-catenin and no risk of malignant transformation.

Patients with LCA present with symptoms approximately 50% to 75% of the time. Upper abdominal pain is common and may be related to hemorrhage into the tumor or local compressive symptoms. The physical examination is usually unrevealing, and tumor markers are normal. Dramatic presentations with free intraperitoneal rupture and bleeding can occur. Imaging tends to be characteristic and obviates the need for tissue diagnosis most of the time. Because of intratumoral hemorrhage, the necrosis and fat component of LCA tends to be heterogeneous on CT. On contrast-enhanced CT, LCA tends to have peripheral enhancement with centripetal progression. MRI scans of LCA also have specific imaging characteristics, including a well-demarcated heterogeneous mass containing fat or hemorrhage. Despite high-quality imaging, resection may sometimes be necessary to secure a diagnosis in difficult cases. Intriguingly, studies are elucidating a correlation between the molecular subtypes described and imaging characteristics.

The two major risks of LCA are rupture, with potentially life-threatening intraperitoneal hemorrhage, and malignant transformation. Quantifying the risk of rupture is difficult, but it has been estimated to be as high as 30% to 50%, with all instances of spontaneous rupture occurring in lesions 5 cm and larger. Although there are numerous reports of transformation of LCA into HCC, the true risk of transformation is probably low. Hepatic adenomas with β-catenin activation should be considered for early surgical intervention as malignant transformation most commonly occurs in this subtype.

Patients who present with acute hemorrhage need emergent attention. If possible, hepatic artery embolization is a helpful and usually effective temporizing maneuver. Once the patient is stabilized and appropriately resuscitated, a laparotomy and resection of the mass are required. Symptomatic masses should be similarly resected. Patients with asymptomatic LCAs taking OCPs can be watched for regression after stopping of the OCPs, although progression and rupture have been observed in this setting. Behavior of LCAs during pregnancy has been unpredictable, and resection before a planned pregnancy is usually recommended. Overall, the surgeon must compare the risks of expectant management with serial imaging studies and AFP measurements against those of resection. Resection is usually recommended because of low mortality in experienced hands and the risks of observation. Margin status is not important in these resections, and limited resections can be performed. The management of adenomatosis is controversial, but large lesions should probably be resected because of the risk of rupture, whereas the risk of malignancy is low in lesions smaller than 5 cm. On occasion, liver transplantation is necessary for aggressive forms of adenomatosis.

Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) is the second most common benign tumor of the liver after hemangioma and is predominantly discovered in young women. FNH is characterized by a central fibrous scar with radiating septa, although no central scar is seen in approximately 15% of cases. On microscopic examination, FNH contains cords of benign-appearing hepatocytes divided by multiple fibrous septa originating from a central scar. Typical hepatic vascularity is not seen, but atypical biliary epithelium is found scattered throughout the lesion. The central scar often contains a large artery that branches out into multiple smaller arteries in a spoke wheel pattern. The cause of FNH is not known, but the most common theory is that FNH is related to a developmental vascular malformation. Female hormones and OCPs have been implicated in the development and growth of FNH, but the association is weak and difficult to prove.

In most patients, FNH is an incidental finding at laparotomy or, more commonly, on imaging studies. If symptoms are noted, vague abdominal pain is most often present, but a variety of nonspecific symptoms have been described. It is often difficult to ascribe these reported symptoms to the presence of FNH, and therefore, other possible causes must be sought. Physical examination is usually unrevealing, and mild abnormalities of liver function may be found. Serum AFP levels are normal.

With advances in hepatobiliary imaging, most cases of FNH can be diagnosed radiologically with reasonable certainty. Contrast-enhanced CT and MRI have become accurate methods of diagnosing FNH. FNH typically shows strong hypervascularity in the arterial phase of CT or MRI with central nonenhancing scar. The enhancement fades over time, and the lesion becomes isointense to the liver parenchyma in the portal and delayed phases. When no central scar is seen, however, radiologic diagnosis is difficult, and differentiation from LCA or a malignant mass, especially fibrolamellar HCC, can sometimes be impossible. On occasion, histologic confirmation is necessary, and resection is recommended for definitive diagnosis. Fine-needle aspiration for the diagnosis of FNH has been recommended but is often unrevealing.
Hemangiomas are usually asymptomatic and found incidentally on imaging studies. Large compressive masses may cause vague upper abdominal symptoms. Symptoms ascribed to a liver hemangioma, however, mandate a search for other disease because an alternative cause of symptoms will be found in approximately 50% of cases. Rapid expansion or acute thrombosis can occasionally cause symptoms. Spontaneous rupture of liver hemangiomas is exceedingly rare. An associated syndrome of thrombocytopenia and consumptive coagulopathy known as Kasabach-Merritt syndrome is rare but well described.

LFT results and tumor markers are usually normal in liver hemangiomas. Radiologic investigation can make the diagnosis reliably in most cases. CT and MRI are usually sufficient if a typical peripheral nodular enhancement pattern is seen. Isotope-labeled red blood cell scans are an accurate test but are rarely necessary if high-quality CT and MRI are available. Percutaneous biopsy of a suspected hemangioma is potentially dangerous and inaccurate. Therefore, biopsy is not recommended.

The natural history of liver hemangioma is generally benign; it appears that most remain stable for a long time, with a low risk of rupture or hemorrhage. Growth and development of symptoms do occur, however, occasionally requiring resection. There has never been a report of malignant degeneration of a liver hemangioma. An asymptomatic patient with a secure diagnosis can therefore be simply observed. Symptomatic patients should undergo a thorough evaluation looking for alternative explanations for the symptoms but are candidates for resection if no other cause is found. Rupture, significant change in size, and development of the Kasabach-Merritt syndrome are indications for resection. In rare cases of diagnostic uncertainty, resection may be necessary for a definitive diagnosis to be made. Resection of liver hemangiomas should be performed, with minimal morbidity and mortality. The preferred approach to resection is enucleation with arterial inflow control, but anatomic resections may be necessary in some cases. Surgery on large central hemangiomas can be associated with significant morbidity.

Liver hemangiomas in children are common, accounting for approximately 12% of all childhood hepatic tumors. They are usually multifocal and can involve other organs. Large hemangiomas in children can result in congestive heart failure secondary to arteriovenous shunting. Untreated symptomatic childhood hemangiomas are associated with high mortality. On the other hand, almost all small capillary hemangiomas resolve. Symptomatic childhood hemangiomas may be treated with therapeutic embolization; medical therapy should be initiated for congestive heart failure. Radiation and chemotherapeutic agents have been used, but experience has been limited. Resection may be necessary for symptomatic lesions or rupture.

**Other Benign Tumors**

Most benign solid liver tumors are LCAs, FNHs, or hemangiomas, but there are other benign hepatic tumors. However, these are rare and can be difficult to differentiate from malignant neoplasms. Macrogeneic nodules, previously known as adenomatous hyperplasia, are single or multiple, well-circumscribed, bile-stained, bulging surface nodules that occur primarily in cirrhotics.
and result from the hyperplastic response to chronic liver injury. These lesions have malignant potential and can be difficult to distinguish from HCC. Nodular regenerative hyperplasia is a benign diffuse micronodular (usually <2 cm) process associated with lymphoproliferative disorders, collagen vascular diseases, and the use of steroids or chemotherapy. Nodular regenerative hyperplasia has no malignant potential and is not associated with cirrhosis. Biopsy may be necessary to distinguish these focal nodules from malignant neoplasms.

Mesenchymal hamartomas are rare solitary tumors of childhood that account for 5% of pediatric liver tumors. They are usually large cystic masses found in the right liver that present as progressive, painless, abdominal distention. Resection of mesenchymal hamartomas may be necessary in the case of large lesions causing a mass effect.

Fatty tumors of the liver are rarely encountered but can usually be distinguished by typical characteristics on CT or MRI scans. Fatty tumors of the liver include primary lipomas, myelolipomas (which contain hematopoietic tissue), angiolipomas (which contain blood vessels), and angiomylipomas (which contain smooth muscle). Focal fatty change in the liver can be confused with a neoplastic process and is becoming more common with improved imaging and the increasing incidence of hepatic steatosis.

Benign fibrous tumors of the liver can become large and symptomatic, requiring resection. Inflammatory pseudotumors of the liver are localized masses of inflammatory cells that can mimic a neoplasm. The cause of these inflammatory lesions is unknown but may be related to thrombosed vessels or old abscesses. Other extremely rare benign hepatic tumors include leiomyomas, myxomas, schwannomas, lymphangiomas, and teratomas.

Intrahepatic biliary cystadenomas or bile duct adenomas are rare but can cause biliary symptoms. Biliary hamartomas and biliary hyperplasia are common and are often seen as small white surface lesions that can mimic small metastatic tumors at abdominal exploration. Adrenal and pancreatic rests have also been found in the liver.

**Primary Solid Malignant Neoplasms**

**Hepatocellular Carcinoma**

**Epidemiology.** Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally. HCC is the most common primary malignant neoplasm of the liver and one of the most common malignant neoplasms worldwide. The epidemiology of HCC varies around the world, being affected by the varying etiologies in different parts of the world. Hepatitis B is the most common cause of HCC worldwide. Thus, the highest incidence of HCC occurs in geographical areas where hepatitis B is rampant, namely sub-Saharan Africa and southeast Asia (>10–20 cases/100,000). The lowest incidence (1–3 cases/100,000) is found in Australia, North America, and Europe. Epidemiologic evidence strongly suggests that HCC is largely related to environmental factors; the incidence of HCC in immigrants eventually approaches that of the local population after several generations. An exception to this is that whites living in high-prevalence areas tend to have a low incidence of HCC. This is likely related to the continuation of the lifestyle and environment of their home country. It is probable that the variation in incidence rates among immigrants is related to hepatitis B virus (HBV) carrier rates. A significant rise in the incidence of HCC in the United States and other Western countries has been noted during the last 35 years. However, recent data suggest that at least in the United States, the epidemic may have peaked as the incidence rates have stabilized in the last few years. The explanation for the observed increase during the last few decades is not understood, but the emergence of hepatitis C virus (HCV) infection and immigration patterns have been suggested. In the United States, HCC incidence is highest in Asians, Pacific Islanders, and Native Americans and lowest among Caucasians. HCV is the most common cause of HCC, accounting for more than half of all cases in the United States and with HBV only present in up to 20% of cases. A third of HCC cases are not infected by either virus. Risk of HCC is further increased in obese patients and in those with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Given that obesity and its ensuing complications are increasing at epidemic proportion in the Western world, obesity as the cause of HCC is becoming more important. Recent data also suggest that addressing the environmental factors can lead to reduction in incidence of HCC. In Taiwan, treatment of chronic hepatitis B and C under the auspices of a national viral hepatitis therapy program has met with a reduction in incidence and mortality due to HCC.

HCC is two to eight times more common in men than in women in low- and high-incidence areas. Although sex hormones may play a minor role in the development of HCC, the higher incidence in men is probably related to higher rates of associated risk factors, such as HBV infection, cirrhosis, smoking, alcohol abuse, and higher hepatic DNA synthesis in cirrhosis. In general, the incidence of HCC increases with age, but a tendency to development of HCC earlier in high-incidence areas has been noted. For example, in Mozambique, 50% of patients with HCC were found to be younger than 30 years. This may be related to differing ages at infection and the natural histories of hepatitis B and C.

**Causative factors.** A large number of associations between hepatic viral infections, environmental exposure, alcohol use, smoking, genetic metabolic diseases, cirrhosis, and OCP use and the development of HCC have been recognized. Overall, 75% to 80% of HCC cases are related to HBV (50%–55%) or HCV (25%–30%) infections. It is also clear from research that the development of HCC is a complex and multistep process that involves a number of these risk factors.

Many years of research have documented a clear association between persistent HBV infection and the development of HCC. Up to 5% of the world population is chronically infected with HBV. Chronic HBV infection accounts for up to 50% of the world’s cases of HCC and most of the cases of childhood HCC. Studies have estimated relative risks of 5 to 100 for the development of HCC in HBV-infected individuals compared with noninfected individuals. The risk of developing HCC is also affected by the presence of other factors including, age, Asian or African ancestry, family history, viral factors (genotype, duration of infection, coinfection with HCV, HIV or hepatitis D), and environmental factors (exposure to aflatoxin, alcohol, and tobacco). Other evidence includes the following observations: geographic areas high in HBV infection have high rates of HCC; HBV infection precedes the development of HCC; the sequence of HBV infection to cirrhosis to HCC is well documented; and the HBV genome is found in the HCC genome. The HBV has known oncogenes, but insertional mutagenesis into hepatocytes may be a contributing factor to the development of HCC. Another proposed mechanism is related to cirrhosis and chronic hepatic inflammation, which is present in 60% to 90% of patients with HBV infection and HCC. Cirrhosis, however, is not a prerequisite for the development of HBV-related HCC. The risk of HCC is not simply related to HBV exposure but
Ingestion of contaminated foods results in aflatoxin exposure. Peanuts, and food products in tropical and subtropical regions. The development of HCC, but the evidence is not consistent, and shown to be directly carcinogenic in hepatocytes. Thus, alcohol risk of HCC, and there may be a synergistic effect with HBV associated with the development of HCC. Research has demonstrated that cirrhotic livers with higher DNA replication rates are associated with a lower risk of HCC. Factors associated with a more rapid progression include male gender, chronic alcohol use, and older age at the time of infection. Although the natural history of HCV infection is not completely understood, it appears to be one of chronic infection, with a benign early course. However, the ultimate development of cirrhosis with increased risk of HCC may ensue. The rate of HCC among HCV-infected persons ranges from 1% to 3% over 30 years, and in individuals with HCV-related cirrhosis, HCC develops at an annual rate of 1%–4%. Studies on the rates of progression to cirrhosis estimate a median time of 30 years, but differing progression rates yield a range of less than 20 years to more than 50 years. Factors associated with a more rapid progression include male gender, chronic alcohol use, and older age at the time of infection. HCV is an RNA virus that does not integrate into the host genome, and therefore, the pathogenesis of HCV-related HCC may be related more to chronic inflammation and cirrhosis than to direct carcinogenesis. Data from era of interferon-based therapy suggests that the patients who achieved a sustained viral response had up to 75% reduction in their risk of HCC. This is exciting and has immense global health significance, especially now as there are many effective HCV treatments available. However, future studies will determine if these new treatments will change the incidence and course of HCC.

The true relationship of cirrhosis and HCC is difficult to ascertain, and suggestions of causation remain speculative. Cirrhosis is not required for the development of HCC, and hepatocarcinogenesis is not an inevitable result of cirrhosis. The relationship of cirrhosis and HCC is further complicated by the fact that they share common associations. Furthermore, some associations (e.g., HBV infection, hemochromatosis) are associated with higher risk of HCC, whereas others (e.g., alcohol, primary biliary cirrhosis) are associated with a lower risk of HCC. Research has demonstrated that cirrhotic livers with higher DNA replication rates are associated with the development of HCC.

Chronic alcohol abuse has been associated with an increased risk of HCC, and there may be a synergistic effect with HBV and HCV infection. Alcohol causes cirrhosis but has never been shown to be directly carcinogenic in hepatocytes. Thus, alcohol likely acts as a cocarcinogen. Cigarette smoking has been linked to the development of HCC, but the evidence is not consistent, and the contributing risk independent of viral hepatitis is likely to be small. Aflatoxin, produced by Aspergillus spp., is a powerful hepatotoxin. With chronic exposure, aflatoxin acts as a carcinogen and increases the risk of HCC. The offending fungi grow on grains, peanuts, and food products in tropical and subtropical regions. Ingestion of contaminated foods results in aflatoxin exposure. Levels of aflatoxin in these implicated foods are regulated in the United States.

Other chemicals have also been implicated as carcinogens related to HCC. These include nitrites, hydrocarbons, solvents, pesticide, and vinyl chloride. Thorotrast (colloidal thorium dioxide) is an angiographic medium that was used in the 1930s. It emits high levels of long-lasting radiation and has been associated with hepatic fibrosis, angiosarcoma, cholangiosarcoma, and HCC. Associations with inherited metabolic liver diseases, such as hereditary hemochromatosis, α1-antitrypsin deficiency, and Wilson disease, have also been implicated as risk factors for HCC. Associations with hormonal manipulations, such as the use of OCPs and anabolic steroids, have been suggested but are weak and are probably better linked specifically to adenoma and well-differentiated HCC. Research has been focusing on relationships of HCC with diabetes, obesity, and metabolic syndrome.

**Clinical presentation.** Most commonly, patients presenting with HCC are men 50 to 60 years of age who complain of right upper quadrant abdominal pain and weight loss and have a palpable mass. In countries endemic for HBV, presentation at a younger age is common and probably related to childhood infection. Unfortunately, in unscreened populations, HCC tends to be manifested at a later stage because of the lack of symptoms in early stages. Presentation at an advanced stage is often with vague right upper quadrant abdominal pain that sometimes radiates to the right shoulder. Nonspecific symptoms of advanced malignant disease, such as anorexia, nausea, lethargy, and weight loss, are also common. Another common presentation of HCC is hepatic decompensation in a patient with known mild cirrhosis or even in patients with unrecognized cirrhosis.

HCC can rarely be manifested as a rupture, with the sudden onset of abdominal pain followed by hypovolemic shock secondary to intraperitoneal bleeding. Other rare presentations include hepatic vein occlusion (Budd-Chiari syndrome), obstructive jaundice, hemobilia, and fever of unknown origin. Less than 1% of cases of HCC are manifested with a paraneoplastic syndrome, usually hypercalcemia, hypoglycemia, and erythrocytosis. Small, incidentally noted tumors have become a more common presentation because of the knowledge of specific risk factors, screening programs for diagnosed HBV or HCV infection, and increasing use of high-quality abdominal imaging.

**Diagnosis.** Radiologic investigation is a critical part of the diagnosis of HCC. In the past, liver radioisotope scans and angiography were common methods of diagnosis, but ultrasound, CT, and MRI have replaced these studies. Ultrasound plays a significant role in screening and early detection of HCC, but definitive diagnosis and treatment planning rely on CT or MRI. Contrast-enhanced CT and MRI protocols aimed at diagnosing HCC take advantage of the hypervascularity of these tumors, and arterial-phase images are critical to assess the extent of disease adequately. Unlike many other cancers, the diagnosis of HCC can be established based on imaging findings alone. Typical imaging criteria for HCC include rapid arterial enhancement followed by washout in the delayed phase. An enhancing capsule supports the diagnosis of HCC. CT and MRI also evaluate the extent of disease in terms of peritoneal metastases, nodal metastases, and extent of vascular and biliary involvement. Detection of bland or tumor thrombus in the portal or hepatic venous system is also important and can be diagnosed with any of these modalities (Fig. 54.35).

AFP measurements can be helpful in the diagnosis of HCC. However, AFP measurement is associated with multiple problems. First, AFP measurements have low sensitivity and specificity. The
specificity and positive predictive values of AFP improve with higher cutoff levels (e.g., 400 ng/mL) but at the cost of sensitivity. False-positive elevations of serum AFP levels can be seen in inflammatory disorders of the liver, such as chronic active viral hepatitis. Furthermore, AFP is not specific to HCC and can be elevated with intrahepatic cholangiocarcinoma (IHC) and colorectal metastases. With improvements in imaging technology and the ability to detect smaller tumors, AFP is largely used as an adjunctive test in patients with liver masses. AFP levels are particularly useful in monitoring treated patients for recurrence after normalization of levels.

Since the proposal of guidelines for the diagnosis of HCC by the Barcelona-2000 European Association for the Study of the Liver conference and the American Association for the Study of Liver Disease, new data have accumulated and the recommendations have evolved. AFP used to play a major role in the diagnosis of HCC larger than 2 cm. However, given the excellent performance of contrast-enhanced imaging modalities, AFP does not play a critical role in the diagnosis of HCC anymore. For hepatic nodules 1 to 2 cm on a background of cirrhosis, a contrast-enhanced triple-phase CT and MRI scan is now recommended. If typical features of HCC on imaging (arterially enhancing mass with washout of contrast material in delayed phases) are observed, diagnosis of HCC is presumed. For lesions larger than 2 cm, a single study may suffice. However, for lesions 1 to 2 cm, contrast-enhanced CT and MRI have a sensitivity of 53% to 62%, specificity of approximately 100%, positive predictive value of 95% to 100%, and negative predictive value of 80% to 84%. The performance of both MRI and CT in a sequential fashion can increase the sensitivity and may be required for difficult cases.

Patients with appropriate risk factors and suggestive radiologic features, with or without an elevated AFP level, who are candidates for potentially curative surgical therapy do not require preoperative biopsy unless the diagnosis is in question. Percutaneous fine-needle aspiration of HCC does run a small risk of tumor cell spillage (estimated to be ~1%) and rupture or bleeding, especially in cirrhotic livers and subcapsular tumors. Once the diagnosis of HCC has been made, the disease must be staged to develop an appropriate treatment plan. Most patients with HCC have two diseases, and survival is as much related to the tumor as it is to cirrhosis. Staging includes an extent of disease and extent of cirrhosis workup.

In assessing the extent of disease, the common sites of metastases must be considered. HCC largely metastasizes to the lung, bone, and peritoneum. Preoperative history should focus on symptoms referable to these areas. Extent of disease in the liver, including macrovascular invasion and the presence of multiple liver masses, must also be considered. Cross-sectional abdominal imaging, including arterial-phase images (see earlier), yields information on the extent of disease in the liver as well as peritoneal disease. Preoperative chest CT is mandatory because lung metastases are usually asymptomatic. Routine bone scans are not performed unless there are suggestive symptoms or signs.

Assessment of liver function is absolutely critical in considering treatment options for a patient with HCC. Liver resection is considered the treatment of choice for HCC, and the risk of postoperative liver failure and death must be considered. This risk is related to the degree of cirrhosis, portal hypertension, amount of liver resected (functional liver reserve), and regenerative potential response. Other successful treatments are available for HCC, such as ablative techniques, embolization techniques, and liver transplantation. Therefore, a complete assessment of tumor and liver function must be carried out. A number of tests of liver function are available, generally divided into clinical assessment and functional tests, and there are many clinical assessment schemes (see earlier). However, Child-Pugh status is used most often. Child-Pugh class C patients are not candidates for resectional therapy, whereas Child-Pugh class A patients can usually tolerate some extent of liver resection. Many consider Child-Pugh class B patients to be candidates for operation, but they are generally borderline, and therapy must be individualized.

Outside of scoring systems, it has been demonstrated that significant portal hypertension, regardless of biochemical assessments, is highly predictive of postoperative liver failure and death. Portal hypertension can be assessed directly through hepatic vein wedge pressures, but it is usually obvious on high-quality imaging in the form of splenomegaly, a cirrhotic-appearing liver, and intrabdominal varices. Blood work usually demonstrates marked cytopenias. Most typically, patients have thrombocytopenia. Functional tests of liver function have been well described but are not routinely used in most Western centers because the results of studies evaluating their predictive value have been mixed.

Staging laparoscopy has been used as a staging tool in HCC and spares about one in five patients a nontherapeutic laparotomy. Laparoscopy yields additional information about the extent of disease in the liver, extrahepatic disease, and cirrhosis. The yield of laparoscopy is dictated by the extent of disease and is only selectively used. The presence of clinically apparent cirrhosis, radiologic evidence of vascular invasion, or bilobar tumors increases the yield to 30%, whereas without these factors, the yield is 5%. There are a number of staging systems for HCC, but none have been shown to be particularly superior; they probably depend on the specific population in which the disease is being staged as well as the cause of HCC in that particular population of patients. The tumor, node, metastasis (TNM) staging system is not routinely used for HCC because it does not accurately predict survival; it does not take liver function into account. Moreover, the TNM staging system relies on pathology that is frequently unavailable preoperatively. The Okuda staging system is an older but simple and effective system that takes liver function and tumor-related factors into account. It adds up a single point for the presence of
A variety of prognostic factors predictive of survival after resection have been identified, but none are universally agreed on. The most commonly cited negative prognostic factors are tumor size, tumor involving more than 50% of the liver, presence of ascites, albumin level less than 3 g/dL, and bilirubin level higher than 3 mg/dL. The Okuda staging system reliably distinguishes patients with a prohibitively poor prognosis from those with potential for long-term survival. The most well-validated staging system is the Cancer of the Liver Italian Program, which was rigorously developed and has been prospectively validated (Table 54.7). An example of a scoring system that is probably population specific is the Chinese University Prognostic Index, which takes into account TNM stage, symptoms, and ascites and the levels of AFP, bilirubin, and ALP; it appears to apply mainly to HBV-related HCC in China.

**Pathology.** On histologic evaluation, HCC is graded as well, moderately, or poorly differentiated. The grade of HCC, however, has never been shown to predict outcome accurately. In gross appearance, the growth patterns of HCC have been classified in a number of ways. The most useful scheme divides HCC into three distinct growth patterns that have distinct relationships to outcome. The pushing type of HCC is connected to the liver by a small vascular stalk and is easily resected without sacrifice of a significant amount of adjacent nonneoplastic liver tissue. This type can grow to substantial size without involving much normal liver tissue. The pushing type of HCC is well demarcated and often contains a fibrous capsule. It is characterized by growth that displaces vascular structures rather than invading them. This type is usually resectable. The last type is called the infiltrative type of HCC, which tends to invade vascular structures, even at a small size. Resection of the infiltrative type is often possible, but positive histologic margins are common. Small tumors (<5 cm) usually do not fall into any of these groups and are often discussed as a separate entity.

Finally, HCC can be manifested in a multifocal manner. Most HCC probably starts as a single tumor, but ultimately multiple satellite lesions can develop secondary to portal vein invasion and metastases. Multifocal tumors throughout the liver probably represent the end stage of HCC with multiple metastases and multiple primary tumors.

**Treatment.** There are a large number of treatment options for patients with HCC, reflecting the heterogeneity of this disease and the lack of a proven superior treatment, except complete resection (Box 54.1). Deciding on a treatment regimen for any one patient must take into consideration the stage of malignancy, the condition of the patient and of the liver, and the experience of the treating physician.

**Surgical management**

**Resection.** Complete excision of HCC by partial hepatectomy or by total hepatectomy and liver transplantation is the treatment of choice, when possible, because it has the highest chance of long-term survival. In general, however, only 10% to 20% of patients are considered to have resectable disease. Historically, mortality rates for partial hepatectomy have ranged from 1% to 20%, but if it is performed in healthy patients without advanced cirrhosis, most series have a mortality rate of less than 5%. Advances in surgical technique have also allowed the development of limited segmental resections when appropriate, which preserves liver function and improves early postoperative recovery. Selection of the appropriate patient for resection is critical and must take into account the condition of the liver and extent of disease. Hepatic resection is indicated as a potentially curative option in patients with adequate liver function (Child-Pugh Class A without portal hypertension) and solitary HCC without major vascular invasion. Patients with Child-Pugh class B or C cirrhosis or portal hypertension do not tolerate resection. The volume of the FLR is also an important consideration and is associated with postoperative complications and mortality. Preoperative portal vein embolization is an effective strategy to increase the volume and function of the FLR and should be used liberally in patients with Child-Pugh class A cirrhosis with a small FLR (i.e., <30%–40% of the total liver volume) who are being considered for a major resection. The overall postresection survival rates for HCC are 58% to 100% at 1 year, 28% to 88% at 3 years, 11% to 75% at 5 years, and 19% to 26% at 10 years. These results obviously depend on the stage of the tumor and degree of cirrhosis in each particular series. Together, they give a sense of the possibilities.

**TABLE 54.7 Cancer of the Liver Italian Program score.*

<table>
<thead>
<tr>
<th>CLINICAL PARAMETERS</th>
<th>CUTOFF VALUES</th>
<th>POINTS</th>
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<td></td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>2</td>
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<tr>
<td>Tumor morphology</td>
<td>Uninodular, &lt;50% extension</td>
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<td>Multinodular, &lt;50% extension</td>
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<td></td>
<td>Massive or extension &gt;50%</td>
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<tr>
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<td>0</td>
</tr>
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<td>Yes</td>
<td>1</td>
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</tbody>
</table>

AFP, a-Fetoprotein.

*Score ranges from 0 to 6; a score of 4 to 6 is generally considered advanced disease, whereas a score of 0 to 3 has the potential for long-term survival.

**Box 54.1 Treatment options for hepatocellular carcinoma.**

- **Surgical**
  - Resection
  - Orthotopic liver transplantation

- **Ablative**
  - Ethanol injection
  - Acetic acid injection
  - Thermal ablation (cryotherapy, radiofrequency ablation, microwave)

- **Transarterial**
  - Embolization
  - Chemoembolization

- **Radiotherapy**
  - Combination transarterial and ablative: external beam radiation

- **Systemic**
  - Chemotherapy
  - Hormonal
  - Immunotherapy
cirrhosis, infiltrative growth pattern, vascular invasion, intrahepatic metastases, multifocal tumors, lymph node metastases, margin less than 1 cm, and lack of a capsule. The best outcomes are found in patients with single small tumors, but size alone should not contraindicate resection. Especially for patients with large tumors that are outside the criteria for transplantation, not many therapeutic options are available. In such patients with adequate liver function, adequate functional liver remnant, and resectable tumors, surgical resection may offer the best possible outcomes. Multifocal tumors and major vascular invasion are generally associated with a poor outcome, but some groups advocate resection in highly select patients. A randomized controlled trial corroborated these findings. In this study, patients with multifocal HCC outside Milan criteria were randomized to resection or transarterial chemoembolization. In this study, resection provided better overall survival for patients with multifocal HCC compared with transarterial chemoembolization, suggesting that resection may be an option for these patients. For potentially resectable tumors that have high-risk features, various neoadjuvant strategies may help select patients for resection. For instance, a period of observation and tumor control with intraarterial therapies (e.g., transarterial chemoembolization/radioembolization) may help select patients who will benefit most from resection.

**Transplantation.** Theoretically, orthotopic liver transplantation is the ideal treatment for HCC because it addresses the liver dysfunction and cirrhosis and the HCC. The limitations of transplantation are the need for chronic immunosuppression and the lack of organ donors. There has been growing interest in the use of partial hepatectomy from live donors, which addresses the lack of organ donors but remains a somewhat controversial approach. Early series of transplantation for HCC had high recurrence rates and relatively poor long-term survival, largely attributed to the fact that most of these patients were undergoing transplantation for advanced disease. Refinements in patient selection—namely, patients with single tumors smaller than 5 cm or no more than three tumors 3 cm in size—have resulted in improved outcomes. Long-term survival rates with more stringent selection criteria have ranged from 50% to 85%. Studies have begun to expand the indications for orthotopic liver transplantation without a major effect on long-term survival but likely an increase in overall recurrence rates. While the enlisted patient with HCC and cirrhosis awaits organ availability, the progression of HCC is typically controlled with locoregional therapy including ablation and transarterial therapies. Comparison of results of resection with transplantation is difficult as the patients considered for transplantation have a period of observation during which the patients with aggressive disease progress and dropout from the transplant list. As such, these two strategies should be viewed as complementary rather than competitive. Patients with advanced cirrhosis (Child class B and C) and early-stage HCC should be considered for transplantation, whereas those with Child class A cirrhosis have similar results with transplantation and resection and should probably be resected.

**Locoregional therapies**

**Ablation.** A number of other nonsurgical local ablative therapies are available for the treatment of small tumors. Percutaneous ethanol injection (PEI) is a useful technique for ablating small tumors. The tumor is killed by a combination of cellular dehydration, coagulative necrosis, and vascular thrombosis. Most tumors smaller than 2 cm can be ablated with a single application of PEI, but larger tumors may require multiple injections. Long-term survival after PEI for tumors smaller than 5 cm has been reported to range from 24% to 40%. Percutaneous injection of acetic acid is a technique similar to PEI but has stronger necrotizing abilities, making it more useful in septated tumors.

Thermal ablative techniques that freeze or heat tumors to destroy them have become popular. Cryotherapy uses a specialized cryoprobe to freeze and thaw tumor and surrounding liver tissue, with resulting necrosis. Cryotherapy is usually performed at laparotomy or laparoscopically, but it has been performed with percutaneous techniques. One advantage is that the ice ball formed is easily monitored with ultrasound. Disadvantages include a heat sink effect, limiting the usefulness of freezing near major blood vessels and a relatively high complication rate of 8% to 41%. Reported 2-year survival rates for cryoablation of HCC range from 30% to 60%, but no comparative studies to resection have been carried out. Radiofrequency ablation (RFA) uses high-frequency alternating current to create heat around an inserted probe, resulting in temperatures higher than 60°C (140°F) and immediate cell death. Although initially limited to smaller tumors, improvements in technology have created RFA probes reportedly able to ablate tumors as large as 7 cm. Nonetheless, the efficacy of RFA for HCCs larger than 3 cm is limited because of increased local recurrence rates. RFA is also limited by the protective effect of blood vessels and does not ablate well in these areas. The procedure can easily be performed percutaneously, with low complication rates, and optimal guidance systems are being developed. Recent data suggest that resection may be superior to RFA for small HCCs in terms of both disease-free and overall survival. Microwave ablation has emerged as an alternative thermoablative procedure.

**Arterially directed therapies.** Transarterial therapy for HCC is based on the fact that most of the tumor's blood supply is from the hepatic artery. Today, the transarterial therapy is applied in a percutaneous fashion, thus avoiding morbidity and mortality of laparotomy. Percutaneous transarterial embolization can induce ischemic necrosis in HCC, resulting in morbidity and mortality of laparotomy. Percutaneous transarterial embolization can induce ischemic necrosis in HCC, resulting in morbidity and mortality of laparotomy. Percutaneous transarterial embolization can induce ischemic necrosis in HCC, resulting in morbidity and mortality of laparotomy. Percutaneous transarterial embolization can induce ischemic necrosis in HCC, resulting in morbidity and mortality of laparotomy.

Attempts to improve the efficacy of arterial embolization have included adding chemotherapeutic agents (chemoembolization) to the bland embolization particles and oils, such as ethiodized oil (Ethiodol), that are selectively taken up by HCCs. Although chemoembolization has not been shown to be superior to bland embolization with regard to survival, a trial suggested an improvement in local control with chemoembolization. Seven randomized trials have compared embolization or chemoembolization with conservative management. Two of these trials and a metaanalysis have confirmed an overall survival advantage from the embolization strategies. The selection of appropriate candidates for embolization is important, and treatment should generally be limited to patients with preserved liver...
function and asymptomatic multinodular tumors without vascular invasion. Poor selection will result in a higher incidence of treatment-induced liver failure, offsetting the potential benefits. Intraarterial injections of iodine-131 with Ethiodol or yttrium-90 in glass microspheres have also been used to deliver localized radiation to HCCs, with reports of dramatic response rates. Transarterial radiotherapy is a potentially promising therapy for HCC as a primary or adjuvant therapy.

Radiation. External beam radiation therapy (EBRT) has a limited role in the treatment of HCC, although occasional dramatic responses are seen. EBRT is limited by damage to normal liver parenchyma and to surrounding organs, but newer methods of conformal radiotherapy and breath-gated techniques are improving the usefulness of this treatment modality.

Systemic therapies

Chemotherapy. Systemic chemotherapy with a variety of agents (e.g., cisplatin, doxorubicin, etoposide, 5-fluouracil [5-FU], mitomycin C, amsacrine, mitoxantrone, picibanil, tamoxifen, uracil, VM-26) has been ineffective and has had a minimal role in the treatment of HCC. Response rates are generally below 20% and of short duration. Hormonal therapy has been used in small numbers of patients with HCC, with some early promising results, but have not yet demonstrated superiority to standard regimens.

Most recently, sorafenib, a molecular targeted therapy that inhibits the serine-threonine kinases Raf-1 and B-Raf and the receptor tyrosine kinase activity of vascular endothelial growth factor receptors 1, 2, and 3 and platelet-derived growth factor β, was evaluated. Llovet and colleagues randomized 599 patients with advanced-stage HCC and Child-Pugh level A cirrhosis to oral sorafenib or placebo. The median overall survival was 10.7 months in the sorafenib group and 7.9 months in the placebo group (P < 0.001), a difference of 2.8 months. The median time to radiologic progression was 5.5 months in the sorafenib group and 2.8 months in the placebo group (P < 0.001), a difference of 2.7 months. Neither group demonstrated any complete responses by radiologic criteria. Although the adverse event profile of sorafenib was similar to the placebo group, this and earlier studies have shown that sorafenib is best tolerated in patients with Child-Pugh class A cirrhosis. With better understanding of the molecular pathogenesis, there is hope that novel therapeutics will be increasingly evaluated in this disease.

Immunotherapy. Immunotherapy has shown some success against HCC. In a nonrandomized phase I/II multi-institution trial evaluating anti-program cell death protein-1 (anti-PD-1) antibody nivolumab objective response rate of ~20% was observed. A randomized controlled trial comparing efficacy of sorafenib to nivolumab as definitive treatment of advanced HCC is currently in process.

In summary, a plethora of treatment options are available for treatment of HCC. Selection of the appropriate treatment modality is based on disease extent, presence or absence of portal hypertension, and liver reserve. Patients with resectable disease with maintained liver reserve and absence of portal hypertension are best treated with resection. Patients with advanced underlying liver disease and with portal hypertension are best treated with liver transplantation. Liver transplantation is applicable only if the tumor is 5 cm or smaller or there are two or three tumors, the largest of which is 3 cm or smaller. Expanded criteria for transplantation are being increasingly used. In patients with very small tumors and with multiple comorbidities, percutaneous ablative techniques may be applied. The efficacy of ablation decreases with increasing size of the tumor. For multifocal disease in the absence of macrovascular invasion and extrahepatic disease, neither resection nor transplantation is applicable, and transarterial therapies offer the best results. For symptomatic patients with advanced disease, with macrovascular involvement, and in the presence of extrahepatic disease, sorafenib is an option. For patients with extensive disease who are symptomatic with deterioration of their performance status and who have severe deterioration of their liver function, any treatment modality is unlikely to provide significant benefit, and these patients should be offered supportive treatment only.

Postoperative adjuvant treatment. Currently, there is no recommended adjuvant treatment after HCC resection. This is largely due to lack of effective chemotherapy for HCC. In a phase III double-blind placebo-controlled study evaluating the efficacy of sorafenib in decreasing recurrence of HCC in patients who underwent complete radiologic response after resection or ablation, sorafenib treatment was not able to decrease recurrence. However, antiviral treatment in patients with HBV infection has been shown to decrease the risk of HCC recurrence and HCC-related deaths. With availability of newer and effective antivirals for treatment of HCV, similar results are hoped for in patients infected with this virus. While lower level of evidence does suggest that sustained viral response is associated with improved OS and better recurrence-free survival following resection or locoregional therapy for HCV related HCC, this needs to be confirmed in better-designed trials.

Distinct variants of HCC. Fibrolamellar HCC is a variant of HCC with remarkably different clinical features, summarized in Table 54.8. This tumor generally occurs in younger patients without a history of cirrhosis. The tumor is usually well demarcated and encapsulated and may have a central fibrotic area. The central scar can make distinguishing this tumor from FNH difficult. On histologic evaluation, fibrolamellar HCC is composed of large polygonal tumor cells embedded in a fibrous stroma, forming lamellar structures (Fig. 54.37). Fibrolamellar HCC does not produce AFP but is associated with elevated neurotensin levels. In general, fibrolamellar HCC has a better prognosis than HCC, probably related to high resectability rates, lack of chronic liver disease, and a more indolent course. Long-term survival can be expected in approximately 50% to 75% of patients after complete resection, but recurrence is common and occurs in at least 80% of patients. The presence of lymph node metastases predicts a worse outcome. Resection of lymph node metastases and recurrent disease has been advocated because of a lack of alternative therapy and the possibility of long-term survival. A study identified a chimeric transcript that is expressed in fibrolamellar HCC but not in the adjacent normal liver. The study also suggested that this transcript codes

### Table 54.8 Comparison of standard HCC and fibrolamellar HCC.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>HCC</th>
<th>FIBROLAMELLAR HCC</th>
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</thead>
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<tr>
<td>Male-to-female ratio</td>
<td>2:1–8:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Median age</td>
<td>55 years</td>
<td>25 years</td>
</tr>
<tr>
<td>Tumor</td>
<td>Invasive</td>
<td>Well circumscribed</td>
</tr>
<tr>
<td>Resectability</td>
<td>&lt;25%</td>
<td>50%–75%</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>90%</td>
<td>5%</td>
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<tr>
<td>AFP positive</td>
<td>80%</td>
<td>5%</td>
</tr>
<tr>
<td>Hepatitis B positive</td>
<td>65%</td>
<td>5%</td>
</tr>
</tbody>
</table>

AFP, α-Fetoprotein; HCC, hepatocellular carcinoma.
HCC, complete resection is the only potentially curative treatment. There is a high incidence of multifocality, vascular invasion, and extrahepatic metastases, resulting in relatively poor long-term survival rates of 10% to 20%.

Intrahepatic Cholangiocarcinoma

Cholangiocarcinoma is an uncommon neoplasm, with an incidence of 1 to 2/100,000 in the United States, and can develop anywhere along the biliary tree from the ampulla of Vater to the peripheral intrahepatic bile ducts. Most of these tumors (40% to 60%) involve the biliary confluence (Klatskin tumor), but approximately 10% emanate from intrahepatic ducts and are known as IHC. IHC is the second most common primary hepatic neoplasm. Studies on the incidence and natural history of IHC have been confused by the fact that, in the past, many of these tumors were mistaken for metastatic adenocarcinoma because biopsy is unable to differentiate the two.

IHC is associated with diseases that cause biliary inflammation and fibrosis. Historically, the most common risk factors for the development of cholangiocarcinoma (all types) were primary sclerosing cholangitis, choledochal cyst disease, hepatolithiasis, and RPC. Recent epidemiologic evidence has now linked IHC to HBV infection, HCV infection, cirrhosis, nonalcoholic steatohepatitis, and diabetes. Increases in the diagnosis of IHC in the United States are likely related to better recognition of the disease, changed classification, and perhaps the rise in HCV infections in the 1960s and 1970s.

The clinical presentation of IHC is similar to that of HCC. These tumors are asymptomatic in early stages. When present, the most common symptoms are right upper abdominal pain and weight loss. Jaundice occurs less commonly as these tumors tend to arise in the periphery of the liver. More commonly, patients present with incidentally found liver masses on cross-sectional imaging. Unlike in HCC, the AFP levels are normal, although CEA or CA 19-9 levels can be elevated in some cases. Because metastatic adenocarcinoma to liver is more common, IHC is a diagnosis of exclusion, and a search for a primary tumor with upper and lower gastrointestinal endoscopy and cross-sectional imaging of the chest, abdomen, and pelvis should be carried out. If a biopsy has been performed, it is often read as adenocarcinoma. Although special stains may suggest diagnosis of IHC, they are not conclusive. On CT and MRI, IHC is seen as a focal hepatic mass that may be associated with peripheral biliary dilation. The mass typically has peripheral or central enhancement on contrast-enhanced scans. Furthermore, unlike HCC there is persistent enhancement on delayed phases due to the fibrotic nature of cholangiocarcinoma, in contrast with the vascular nature of HCC. Hepatic capsular retraction is also frequently observed. Intrahepatic metastases, lymph node metastases, and growth along the biliary tree are often encountered.

Complete resection is the treatment of choice for IHC. The concept of optimal surgical margins in the treatment of IHC is evolving. However, surgeons should strive for R0 margins. Due to large tumor size and invasion into the surrounding structures, major hepatectomies with or without resection of surrounding organs may be required for achieving a margin negative resection. Resectability rates generally range up to 60%, and long-term survival in unresected patients is rare. If it is completely resected, 3-year survival rates range from 16% to 61%, and 5-year survival rates range from 24% to 44%. Factors associated with a poor outcome include multifocality, lymph node metastases, vascular invasion, and positive margins. These factors have now been included in the
American Joint Committee on Cancer (AJCC) staging system. A review of prospectively evaluated patients with IHC who underwent resection suggested that while patients with R0 resection did better when compared with R1 resection, width of margin did not influence outcomes. Because of the rarity of IHC, little is known about the effectiveness of radiation therapy and chemotherapy for IHC in the adjuvant setting. Thus, their application is not routine. Use of chemotherapy as an adjuvant strategy is controversial. Due to the overall low incidence of biliary cancers, studies of adjuvant therapy have typically clubbed various disease sites to include both intrahepatic and extrahepatic cholangiocarcinoma as well as gallbladder cancer. In a recently reported clinical trial from the United Kingdom (phase III BILCAP study), patients with completely resected gallbladder and cholangiocarcinoma were randomized to receive adjuvant capecitabine or observation. Although on intention-to-treat analysis, adjuvant capecitabine did not improve survival, when comparing patients who received adjuvant therapy per-protocol, adjuvant capecitabine was associated with 25% reduced risk of death. Retrospective studies have provided conflicting evidence regarding the benefits of adjuvant therapy. Regional hepatic artery chemotherapy is currently under study and may be a promising approach.

**Other Primary Malignant Neoplasms**

Hepatoblastoma is the most common primary hepatic tumor of childhood. There are approximately 50 to 70 new cases per year in the United States. Rare cases of adult hepatoblastoma have been reported, but overall, the median age at presentation is 18 months, and almost all cases occur before the age of 3 years. Hepatoblastoma has been associated with the familial polyposis syndrome. There are a number of histologic subtypes, but in general, the tumor is derived from fetal or embryonic hepatocytic progenitors, and mesenchymal elements are often present. This tumor generally is manifested as an asymptomatic mass. Mild anemia and thrombocytosis are commonly found at presentation. Serum AFP levels are elevated in 85% to 90% of patients and can serve as a useful marker for therapeutic response. Most studies have supported the use of chemotherapy followed by resection, and survival appears to be dependent on complete resection. Chemotherapy can serve to downstage tumors, which facilitates resection. In patients without metastatic disease or the anaplastic variant, long-term survival rates of 60% to 70% can be expected with complete resection. Interestingly, 50% of patients with pulmonary metastases can be cured with resection of the hepatic tumor and chemotherapy or resection of the pulmonary metastases.

A variety of sarcomas can rarely be manifested as primary liver tumors, but they must always be considered metastatic lesions until proven otherwise. Angiosarcoma is probably the best-described primary hepatic sarcoma because of its well-known association with vinyl chloride or Thorotrast exposure. Angiosarcoma typically is manifested as multiple hepatic masses and can appear in childhood. Long-term survival is uncommon with primary hepatic angiosarcoma. Other sarcomas, including leiomyosarcoma, malignant fibrous histiocytoma, embryonic sarcoma, and primary hepatic rhabdoid tumors, have been described but are rare. The last two lesions are typically seen in the pediatric population.

Non-Hodgkin lymphoma can be manifested primarily in the liver, with or without extrahepatic disease. Primary hepatic lymphoma should be treated in the same manner as lymphoma elsewhere in the body if the diagnosis can be made before a liver resection.

Primary hepatic neuroendocrine tumors or carcinoid tumors have been described but are probably extremely rare. Distinguishing the rare primary hepatic neuroendocrine tumor from a metastatic lesion can be difficult because the extrahepatic primary tumor can be radiologically occult for many years, and the liver is the most common site of metastases.

Malignant germ cell tumors of the liver including teratomas, choriocarcinomas, and yolk sac tumors are very rare and are principally described in the pediatric population.

Epithelioid hemangioendothelioma of the liver is a rare malignant vascular tumor that is manifested with multiple bilateral hepatic masses. Extrahepatic metastases occur in approximately 25% of patients and clinical behavior is unpredictable, with some patients having a prolonged indolent course. Most patients ultimately die of liver failure, but cases of successful transplantation have been reported.

**Metastatic Tumors**

The most common malignant tumors of the liver are metastatic lesions. The liver is a common site of metastases from gastrointestinal tumors, presumably because of dissemination through the portal venous system. The most relevant metastatic tumor of the liver to the surgeon is colorectal cancer because of the well-documented potential for long-term survival after complete resection. However, a large number of other tumors commonly metastasize to the liver, including cancers of the upper gastrointestinal system (stomach, pancreas, biliary), genitourinary system (renal, prostate), neuroendocrine system, breast, eye (melanoma), skin (melanoma), soft tissue (retroperitoneal sarcoma), and gynecologic system (ovarian, endometrial, cervical). The large majority of metastatic liver tumors that present with concomitant extrahepatic disease will have unresectable liver disease or are not curable with resection, limiting the role of the surgeon to highly select cases. Metastatic adenocarcinoma to the liver of unknown primary is often a primary IHC, and this diagnosis must always be kept in mind.

Traditionally, cancer spread to a distant site was considered a systemic disease in which locoregional therapies (i.e., surgery) were not effective. Some metastatic tumors to the liver, in particular, metastatic colorectal cancer, have been shown to be an exception to this rule. More than 35 years of clinical research has documented that metastatic colorectal cancer isolated in the liver can be resected with the potential for long-term survival and cure. Advances in systemic and regional chemotherapy have also broadened the number of patients eligible for surgical therapy and probably have improved long-term survival after resection. Selection of patients is the most important aspect of surgical therapy for metastatic disease in the liver, and clinical follow-up of resected patients has identified those most and least likely to benefit. Although long-term survival is common and occurs in up to 50% to 60% of patients in current series, recurrence and chronic multimodal therapy are common, occurring in approximately 75% of patients. Therefore, an important aspect of treatment is realistic expectations and honest patient education. Tumors other than colorectal cancer manifested as isolated or limited hepatic metastases can also be resected for potential long-term survival, but data on these other tumors are sparse and less compelling than for colorectal cancer.

**Colorectal Metastases**

Every year, there are more than 140,000 new cases of colorectal cancer in the United States. Up to 60% of these patients will
develop metastases during the course of their disease. A large proportion of these patients will have metastases to the liver, which can be the only site of metastatic disease for some. In this regard, liver metastases can present synchronously (i.e., at the time of diagnosis of primary disease) or metachronously (arbitrarily defined as >1 year after the diagnosis of primary disease). Literature suggests that synchronous liver metastases portend to a worse prognosis than metachronous disease.\(^{30}\) Most of these cases of liver metastases are associated with widespread metastatic disease or unresectable hepatic metastases. It is estimated that approximately 5% to 10% of these patients are candidates for a potentially curative liver resection. With improved response rates to modern chemotherapy and advances in hepatic surgery; however, more patients are now candidates for hepatectomy than in the past; at present, up to 20% of patients may be candidates.

**Presentation.** In the distant past, patients with hepatic colorectal metastases generally presented with symptoms and signs of advanced malignant disease, such as pain, ascites, jaundice, weight loss, and a palpable mass. Presentation with these symptoms is a poor prognostic sign; few of these patients are candidates for therapy aside from chemotherapy or supportive care. This has led most physicians to observe patients with resected primary colorectal cancer carefully who are potential candidates for aggressive therapy with serial physical examinations, cross-sectional imaging studies, LFTs, and determination of CEA levels. Although not supported by randomized trials, clinical observations have indicated that patients who are carefully observed with serial physical examinations, cross-sectional imaging studies, LFTs, and determination of CEA levels are those often found to have resectable metachronous disease and the greatest potential for long-term survival. In addition to these patients, some are found to have synchronous metastatic disease at the time of diagnosis of the primary colorectal cancer on preoperative imaging or at laparotomy.

Although an elevated CEA level is not specific for recurrent colorectal cancer, a rising CEA level on serial examinations and a new solid mass on imaging studies are diagnostic of metastatic disease. Mild elevations in LFT results are common in metastatic colorectal cancer to the liver but are not effective as a screening tool. The levels most commonly elevated are those of ALP, GGT, and lactate dehydrogenase. Imaging of hepatic metastases with high-quality CT or MRI is important for determining resectability and operative planning. Most physicians use thin-cut (5 mm), high-resolution, dynamic, contrast-enhanced helical scanning techniques. Timing with IV administration of a contrast agent should correspond to the portal venous phase to maximize hepatic parenchymal enhancement, which improves the disparity between parenchyma and tumor.

**Workup.** Once a patient with colorectal liver metastases is considered a candidate for surgical therapy, a complete extent of disease workup must be performed. Colonoscopy should be performed if it has been longer than 1 year since the last examination to rule out local recurrence or metachronous colorectal lesions. Complete abdominal and pelvic cross-sectional imaging must also be performed to rule out extrhepatic disease and aid with operative planning by identifying the number, location, and relationship of liver metastases to the hepatic vasculature. Chest CT is often performed but is of low yield. Many studies have evaluated the added benefit of positron emission tomography (PET) scans to detect occult extrhepatic disease. Approximately 25% of patients have a change in management based on PET scan findings, but this is highly variable, depending on the quality of cross-sectional imaging, radiologic interpretation, and patient selection (Fig. 54.38). A randomized trial of PET/CT versus CT in patients with potentially resectable colorectal liver metastases has been published.\(^{31}\) In this trial, the use of PET/CT did not result in significant changes in surgical management, and there was no difference in resectability or long-term outcomes between the two groups. This trial provides definitive evidence that routine use of PET does not significantly affect outcomes among patients with potentially resectable colorectal cancer liver metastasis. With use of staging laparoscopy, 10% of patients are spared a nontherapeutic laparotomy, and the yield of laparoscopy correlates with the number of poor prognostic factors present, allowing it to be used on a selective basis.

**Management**

**Surgical approach.** To date, a prospective trial comparing surgery with no treatment or chemotherapy alone has not been performed, nor is this likely ever to be done. Therefore, the rationale for liver resection comes from retrospective comparisons of these treatment strategies. The surgeon must understand the natural history of colorectal liver metastases left untreated or treated with systemic chemotherapy to interpret survival data associated with
hepatic metastases, close margins, and inability to resect all disease because of hepatic toxicity (steatohepatitis and sinusoidal obstructive syndrome) and higher rates of postoperative liver failure.

From these large series, we have learned much about prognostic factors as well as which patients are most likely to benefit from a liver resection for hepatic colorectal metastases. Although not all studies agree, it has been found that poor prognostic factors include extrahepatic metastases, involved lymph nodes with the primary colorectal tumor, synchronous presentation (or shorter disease-free interval), larger number of tumors, bilobar involvement, CEA level elevation more than 200 ng/mL, size of largest hepatic tumor more than 5 cm, and involved histologic margins. In a series of 1001 liver resections from MSKCC, a multivariate analysis identified five preoperative factors as the most influential on outcome: size larger than 5 cm, disease-free interval less than 1 year, more than one tumor, lymph node–positive primary, and CEA level higher than 200 ng/mL. Using these five factors, we have developed a risk score predictive of recurrence after liver resection (Table 54.10).

Traditionally, the presence of extrahepatic disease, four or more hepatic metastases, close margins, and inability to resect all disease in the liver have been considered contraindications to hepatectomy. The only one of these historical contraindications that holds true today is the inability to resect all disease. Recent reports have shown that hepatectomy for four or more metastases is associated with an approximate 5-year survival of 33%, despite a high recurrence rate. Although the width of the closest margin has been shown to be associated with outcome, it is often confounded by its relationship to an overall poor prognostic tumor (i.e., multiple synchronous tumors). However, close or involved margins do not appear to preclude the possibility of long-term survival, but patients with positive margins tend to fare poorly. Nonetheless, attempts at wide margins more than 1 cm are appropriate, when possible. Resection of extrahepatic metastases that present simultaneously with liver metastases has been shown to be associated with long-term survival in highly select cases. The sites that appear to be associated with the best outcomes in this situation are limited lung metastases, locoregional recurrences of the primary tumor, and portal lymph nodes. These results have been further confirmed in a metaanalysis of 50 studies including 3481 patients with colorectal liver metastases with extrapleural disease. With availability of more effective chemotherapy, selected patients with extrahepatic disease should be considered for resectional therapy. Selection of patients is critical for this aggressive approach and generally requires preoperative chemotherapy to exclude progression and consideration of the overall bulk of metastatic disease.

Although long-term survival after liver resection for hepatic colorectal metastases is clearly possible, recurrence of disease is common. Overall, approximately 75% of patients have recurrence, but in high-risk situations (e.g., four or more tumors, extrahepatic disease), recurrence rates approach 100%. Approximately 50% of recurrences are isolated to the liver, and a small number of these patients (~5% of all patients undergoing liver resection) are candidates for a second liver resection. These highly select patients who undergo a second liver resection with complete removal of all disease can expect further 5-year survival rates of 30% to 40%. Limited and isolated lung recurrences can also be resected with the potential for further long-term survival. Furthermore, multiple lines of effective chemotherapy are now available, associated with prolongation of survival. Because of the potential for further effective therapeutic interventions after liver resection, patients eligible for such treatment should be observed with serial CEA level determinations and imaging studies to detect recurrences at an early, potentially treatable phase.

Adjuvant therapy. Adjuvant chemotherapy has been used in an attempt to reduce recurrence and to improve long-term survival. Prospective randomized clinical trials have shown a benefit to adjuvant hepatic intraarterial chemotherapy. However, results of randomized controlled trials on the benefit of adjuvant systemic chemotherapy after resection of hepatic metastases have been mixed. In a multicenter randomized trial, Portier and associates randomized 173 patients to hepatic resection alone (87 patients) or to hepatic resection plus adjuvant chemotherapy (5-FU–folinic acid) for 6 months (86 patients). Even though this chemotherapy regimen is no longer standard, the 5-year disease-free survival rate was 26.7% for patients who had surgery alone and 33.5% for patients who had surgery plus chemotherapy (P = 0.028). A nonsignificant trend toward improved overall survival was also observed in the chemotherapy arm. The results of this trial were pooled with another phase 3 trial that failed to accrue. This pooled analysis failed to show a statistically significant improvement in progression-free survival or overall survival. In this analysis, there were 278 patients (138 in the surgery with chemotherapy arm and 140 in the surgery plus chemotherapy arm).
## TABLE 54.9 Results of hepatic resection for hepatic colorectal metastases.

<table>
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<tr>
<th>STUDY</th>
<th>NO. OF PATIENTS</th>
<th>OPERATIVE MORTALITY RATE (%)</th>
<th>1 YEAR</th>
<th>5 YEARS</th>
<th>10 YEARS</th>
<th>MEDIAN SURVIVAL (MONTHS)</th>
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<td>82</td>
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<td>Major hepatectomy (MH) vs. parenchyma sparing hepatectomy (PSH)</td>
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<td>Van Amerongen, 2016</td>
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<td>0.8</td>
<td>92</td>
<td>35</td>
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<tr>
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<td>1.3</td>
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<tr>
<td>CG</td>
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<td>1</td>
<td>42</td>
<td>—</td>
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*In selected series with more than 100 patients.
†The 5-year survival rate in the patients operated on in the most current time period in this study was 58%.
‡Long-term results of two-stage hepatectomy versus one-stage hepatectomy used in combination with ablation approaches.
§Combined data from two hepatobiliary centers, data analyzed with respect to receipt of preoperative chemotherapy or not.
‖Number of tumors higher in the preoperative chemotherapy group (2.8 ± 2.2) compared with those with no preoperative therapy (1.8 ± 1.6).

Arm and 140 in the surgery-alone arm). Median progression-free survival was 27.9 months in the chemotherapy arm compared with 18.8 months in the surgery arm (hazard ratio, 1.32; 95% CI, 1.00–1.76; P = 0.058). Median overall survival was 62.2 months in the chemotherapy arm compared with 47.3 months in the surgery arm (hazard ratio, 1.32; 95% CI, 0.95–1.82; P = 0.095). Adjuvant chemotherapy was independently associated with both progression-free survival and overall survival in multivariable analysis.

In another multi-institutional randomized controlled trial (European Organization for Research and Treatment and Cancer, EORTC 40983 trial), Nordlinger and colleagues randomized
364 patients into two groups; 182 patients were treated with surgery alone, and 182 patients had surgery plus systemic chemotherapy. Three cycles of systemic 5-FU–folinic acid plus oxaliplatin (FOLFOX4) were administered preoperatively and postoperatively in the chemotherapy group. Among eligible patients after randomization, the progression-free survival of patients at 3 years was 28.1% in the group with surgery alone and 36.2% in the group with surgery plus chemotherapy ($P = 0.041$). When analyzed by all patients, there was no significant difference in outcome. Long-term results of this trial have been released, and no difference in overall survival was observed with addition of chemotherapy. Although this trial provides evidence that perioperative systemic chemotherapy can delay recurrence of disease, there is little difference in the recurrences at later time points. Also, the benefit of adjuvant chemotherapy may be related to better selection of patients. The role of adjuvant therapy in the treatment of colorectal liver metastases is further supported by a metaanalysis of 10 studies including 1896 patients. In this metaanalysis, use of perioperative therapy significantly improved disease-free survival but did not affect the overall survival. In summary, there is level 1 clinical evidence that adjuvant systemic chemotherapy, when combined with liver resection, modestly improves progression-free survival in patients with colorectal liver metastases. At this time, the general consensus is that patients with liver metastases benefit from 6 months of perioperative adjuvant therapy.

Neoadjuvant chemotherapy for resectable metastases is also a common strategy to treat occult systemic disease and can be helpful in selecting the small group of patients ($<10\%$) who progress while receiving chemotherapy and have a poor outcome after hepatectomy. A prospective randomized study by the National Surgical Adjuvant Breast and Bowel Project has begun accruing patients to study the role of adjuvant chemotherapy in these patients.

A convincing argument for adjuvant therapy with the use of hepatic arterial infusion (HAI) chemotherapy can be made. The rationale for adjuvant hepatic artery chemotherapy is based on the fact that liver metastases derive most of their blood supply from the hepatic artery. Regional infusion of chemotherapeutic agents such as fluorodeoxyuridine has hepatic extraction rates of 90%, providing high local concentrations with minimal systemic toxicity. Furthermore, approximately 50% of all recurrences after hepatectomy involve the liver, so controlling the liver is likely to affect long-term outcome. There is clearly a higher response rate for liver tumors with HAI therapy compared with systemic therapy. A trial from MSKCC comparing HAI therapy with systemic chemotherapy to systemic chemotherapy alone has demonstrated significantly lower recurrence rates (9% and 36%) and a survival advantage at 2 years (86% vs. 72%). Other trials have shown HAI therapy with fluorodeoxyuridine to be more effective than hepatectomy alone, with significantly improved disease-free survival. HAI has not been widely adopted due to the requirement of specific technical expertise and availability of effective systemic therapy. However, HAI is a useful strategy benefiting patients with liver-only colorectal metastases when applied in carefully selected patients.

**Unresectable liver-only metastatic disease.** For patients with unresectable liver-only metastatic disease, preoperative systemic and HAI chemotherapy has been shown to convert some patients to resection candidates. A critical observation in these patients is that outcome after complete resection appears to be as good as in those who were resectable at initial presentation. Strategies to extend the limits of liver resection have used parenchyma-preserving segmental resections, two-stage operations, and thermal ablative techniques, such as cryoablation or RFA. Most recently, microwave ablation is being studied as a treatment for these patients, and long-term results suggest that recurrence rates increase with the size of the tumor and when ablation is performed for the tumor close to the vessels. Recent results suggest that microwave ablation either alone or in combination with liver resection can provide good long-term results. Thus, multiple bilobar tumors can be extirpated by a combination of resection and ablation with preservation of sufficient hepatic parenchyma.

In summary, the treatment of hepatic colorectal metastases is evolving at a rapid pace, and improvements in hepatic surgery and chemotherapy have greatly improved prospects for patients. Chemotherapy has improved, but long-term survival with this modality alone is rare. Combinations of chemotherapy and complete resection of hepatic metastases are associated with long-term survival in up to 50% to 60% of patients. Long-term survival also appears to be possible in patients undergoing resection of extensive hepatic metastases and limited extrahepatic disease. Complete resection of hepatic metastases appears to be a critically important treatment modality that is necessary for long-term survival.

**Neuroendocrine Metastases**

Liver metastases from neuroendocrine tumors are common but vary according to the primary tumor type. Examples of primary tumors that commonly metastasize to the liver are gastrinomas, glucagonomas, somatostatinomas, and nonfunctional neuroendocrine tumors. Insulinomas and carcinoid tumors metastasize to the liver less commonly.

There are two issues to consider in determining the appropriate therapy for metastatic neuroendocrine tumors. First, these are slow-growing, indolent tumors in which long-term survival is possible even in the absence of treatment. Thus, assessing the effects of any treatment is difficult. Second, these tumors often secrete functional neuropeptides that can create debilitating syndromes of hormonal excess, so the goal of treatment is focused more often on quality of life rather than on prolongation of life.

A number of effective nonsurgical therapies exist for neuroendocrine liver metastases. Long-acting somatostatin analogues are useful for alleviating hormonal symptoms and may have a cytostatic role as well. Liver tumors can also be treated by hepatic

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**TABLE 54.10 Clinical risk score and survival in 1001 patients undergoing liver resection for metastatic colorectal cancer.**

<table>
<thead>
<tr>
<th>SCORE</th>
<th>1 YEAR</th>
<th>3 YEARS</th>
<th>5 YEARS</th>
<th>MEDIAN SURVIVAL (MONTHS)</th>
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<tr>
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<tr>
<td>5</td>
<td>71</td>
<td>27</td>
<td>14</td>
<td>22</td>
</tr>
</tbody>
</table>


*Each of the following five risk factors equals 1 point: node-positive primary, disease-free interval <12 months, >1 tumor, size >5 cm, carcinoembryonic antigen level >200 ng/mL. Score is total number of points in an individual patient.
arterial embolization or thermoablative approaches. Combinations of these therapies can be effective in cytoreducing tumor loads and alleviating symptoms of hormonal excess.

Liver resection can play a role in patients whose tumor can be completely encompassed. High-quality CT of the chest, abdomen, and pelvis with liver protocol should be obtained in all patients to define the extent of disease. Most well-differentiated neuroendocrine tumors express somatostatin receptors, and this has been leveraged previously by the 111In-octreotide scan to diagnose and define the extent of disease. Now, where available, octreotide scan has been superseded by PET combined with CT (PET/CT) using 68Ga-DOTA peptides. 68Ga-DOTA PET/CT provides higher resolution than octreotide scan, thus allowing better localization and greater sensitivity (82%–100%) and specificity (67%–100%) for neuroendocrine metastases. Due to this increased sensitivity, preoperative use of 68Ga-DOTA has been shown to influence the therapeutic strategy and/or extent of surgery for up to 60% of patients with neuroendocrine tumors. Whether that applies to patients with neuroendocrine liver metastases preparing for surgery remains to be seen.

Because these tumors are indolent, any therapy must be delivered with minimal morbidity. This has been the case in experienced hepatobiliary units. Five-year survival rates in excess of 50% to 75% can be expected if a complete resection is accomplished. Retrospective comparisons have suggested that this survival is better than that in untreated patients, but selection bias accounts for at least some of this difference. Because of the rarity of this diagnosis, no prospective data exist. The other role of surgery is for those patients who have failed to respond to medical therapy and have refractory symptoms of hormonal excess. If preoperative staging suggests that at least 90% of tumor can be removed without prohibitive operative risk, surgical cytoreduction is reasonable. Symptom improvement can be expected in most patients if adequate cytoresection is achieved. Formal resections with wide margins are not necessary for neuroendocrine tumors, and techniques such as enucleation and wedge resection are reasonable options. Thermoablative approaches, such as cryoablation and RFA, are also attractive alternatives in this type of cytoreductive surgery. Laparoscopic RFA has recently been used, although long-term follow-up is not available.

Noncolorectal, Nonneuroendocrine Metastases

Other tumors can be manifested as isolated liver metastases, but these are uncommon situations and therefore data for these situations are sparse.42 There are many tumors that can be manifested in this way, including breast, lung, melanoma, soft tissue sarcoma, Wilms tumor, ocular melanoma, upper gastrointestinal (gastric, pancreas, esophagus, gallbladder), adrenocortical, urologic (bladder, renal cell, prostate, testicular), and gynecologic (uterine, cervical, ovarian) tumors. General principles that should be considered in dealing with these tumors as isolated liver metastases are similar to those for metastatic colorectal cancer. Prognosis tends to be dismal if there is extrahepatic disease, multiple tumors, large tumors, or a short disease-free interval, and patients should be carefully selected for surgery on the basis of these factors. Patients with liver-only metastatic disease should be treated with systemic chemotherapy before being considered for liver resection. This helps not only control the disease but also selects outpatients who have rapidly progressive disease and who will not benefit from liver resection.

Although there have been rare reports of long-term survival after resection of isolated liver metastases from upper gastrointestinal tumor, in general, these patients have a dismal prognosis and liver resection is not recommended. In most series, liver resection for genital tumors has the best prognosis, and in well-selected patients, liver resection should be considered. Breast tumor, melanoma, and sarcoma patients rarely present with isolated liver metastases, and with a long disease-free interval or long-term stability on chemotherapy, liver resection should be considered. In general, liver resection for metastatic noncolorectal, nonneuroendocrine tumors has to be considered cytoreductive and should be used only in the most favorable situations (see earlier). Liver resection can also be an effective therapy for symptomatic tumors in patients who have a reasonable life expectancy and no other effective therapy.

Cystic Neoplasms

Simple Cyst

Simple cysts of the liver contain serous fluid, do not communicate with the biliary tree, and do not have septations. They are generally spherical or ovoid and can be as large as 20 cm. Large cysts can compress normal liver, inducing regional atrophy and sometimes compensatory contralateral hypertrophy. In 50% of cases, the cysts are singular. On histologic evaluation, a single layer of cuboidal or columnar cells without atypia lines these cysts. Simple cysts are generally regarded as congenital malformations.

Simple cysts are a relatively common finding in adults and are mostly asymptomatic incidental radiologic findings. On occasion, a large cyst will cause symptoms. Although CT demonstrates anatomic relationships, ultrasound is a helpful test of choice to confirm a single, thin-walled simple cyst. Hydatid disease, cystadenoma, and metastatic neuroendocrine tumor are the most important differential diagnoses to consider. A thick or nodular wall raises the suspicion of a cystadenoma but can also represent hemorrhage within the cyst. The most common complication is intracystic bleeding, but overall, complications are rare. The treatment of simple hepatic cysts is indicated only if they are symptomatic or there is diagnostic uncertainty. Because most cysts are asymptomatic, a thorough evaluation of the cause of the symptoms must be carried out before attributing them to the cyst. Nonsurgical treatment consists of aspiration and injection of a sclerosing agent. Few studies have documented long-term follow-up of sclerotherapy for hepatic cysts. Surgical therapy is achieved by fenestration or unroofing of the portion of the cyst that is extrahepatic. This can be performed at laparotomy with good long-term results or through laparoscopic approaches. The laparoscopic approach is favored, but long-term efficacy has not been well documented.43 A metaanalysis including nine retrospective case-control studies involving 657 patients comparing laparoscopic fenestration with the open approach demonstrated that the laparoscopic approach was associated with shorter operative time, shorter hospital stay, and less operative blood loss with no difference in cyst recurrence rates.44

Cystadenoma and Cystadenocarcinoma

Cystadenoma of the liver is a rare neoplasm that generally is manifested as a large cystic mass, usually 10 to 20 cm. The cyst has a globular external surface with multiple protruding cysts and lobules of various sizes. The fluid contained in these cysts is usually mucinous. On microscopic examination, atypical cuboidal or columnar cells resting on a basement membrane, with ovarian-like stroma, line the cysts. The epithelium often forms polypoid or papillary projections.
trahepatic lesions of type IV bile duct cysts and Caroli disease are of the extrahepatic bile duct and intrahepatic ducts. In contrast, intrahepatic biliary tree, but in type IV cysts, there is involvement of biliary-enteric continuity. Most bile duct cysts involve the extrahepatic biliary tree that are usually diagnosed in childhood but can eventually progress to their malignant counterpart, cystadenocarcinomas. Cystadenocarcinoma is an extremely rare malignant neoplasm with little documentation of its natural history and outcome after resection. Malignant degeneration is typically suggested on imaging, with large projections and a markedly thickened wall. The treatment of cystadenoma or cystadenocarcinoma is complete excision, which can be done with an enucleation if there is no evidence of invasive malignant disease. Incomplete resection risks recurrence or the development of cystadenocarcinoma.

**Polycystic Liver Disease**

Liver cysts are commonly seen in patients with the autosomal dominant inherited adult polycystic kidney disease. The cysts are histologically similar to simple cysts (see earlier). The main difference between the two entities is the number of cysts. When liver cysts are present in patients with adult polycystic kidney disease, they are always multiple in number. Also, there are usually numerous microscopic hepatic cysts as well as the grossly visible macrocysts. Despite the large number of liver cysts, hepatic parenchyma and function are usually preserved. Liver cysts are always preceded by kidney cysts, and their prevalence in adult polycystic kidney disease increases with age. In those younger than 20 years, the prevalence of liver cysts is 0%, whereas in those older than 60 years, it is 80%.

Liver cysts in patients with adult polycystic kidney disease are generally asymptomatic, but in a few patients, numerous large cysts may cause abdominal pain and distention. LFT results are almost always normal. Rare complications can occur; these include infection and intracystic bleeding. Ultrasound and CT reveal multiple simple cysts throughout the liver and kidneys. Treatment of polycystic liver disease is reserved for severe symptoms related to large cysts and complications. Treatment includes percutaneous aspiration with or without sclerotherapy, cyst fenestration (by laparotomy or laparoscopy), hepatic resection, and orthotopic liver transplantation. Liver transplantation is used only with progressive disease after fenestration or resection with liver or renal dysfunction. In the context of renal failure, a combined kidney and liver transplantation may be appropriate.

**Bile Duct Cysts**

Bile duct cysts or choledochal cysts are congenital dilations of the biliary tree that are usually diagnosed in childhood but can present in adulthood. Because of the risk of malignancy and recurrent cholangitis, treatment is excision with reestablishment of biliary-enteric continuity. Most bile duct cysts involve the extrahepatic biliary tree, but in type IV cysts, there is involvement of the extrahepatic bile duct and intrahepatic ducts. In contrast, Caroli disease (type V) is characterized by multiple intrahepatic cysts. Thus, bile duct cysts must be considered in the differential diagnosis of a patient with multiple hepatic cystic lesions. The intrahepatic lesions of type IV bile duct cysts and Caroli disease are multifocal dilations of the segmental bile ducts separated by portions of normal-caliber bile ducts. Approximately 50% of cases of Caroli disease are associated with congenital hepatic fibrosis; the cysts are diffusely located throughout the liver. In the other 50% of cases, the dilations may be confined to a portion of the liver, usually the left hemiliver. Recurrent bacterial cholangitis usually dominates the clinical course of these diseases, and death generally ensues within 5 to 10 years without adequate treatment. When intrahepatic bile duct cysts are localized, hepatic resection, with or without biliary reconstruction, is the treatment of choice. Treatment of diffuse hepatic involvement is poor; in complicated cases, the only probably effective treatment is transplantation.

**Principles of Hepatic Resection**

Although liver resections were performed in the late 1800s, it was not until 1952 that Lortat-Jacob was given credit for the first true anatomic right hepatectomy. This event ushered in the modern era of hepatic surgery. However, early series were plagued by high morbidity and mortality, which were largely related to massive intraoperative blood loss. Series from the 1970s and 1980s often reported mortality rates in excess of 10%, often as high as 20%, especially for major resections. This high mortality limited the use of liver resection, and there was reluctance to refer patients for such operations. During the last three decades, a number of advances have improved perioperative outcomes dramatically for patients undergoing major hepatic surgery. The understanding that most blood loss during a liver resection comes from the hepatic veins has prompted surgeons to perform these operations with a low central venous pressure. We perform partial hepectomy with a central line in place, the patient in a mild Trendelenburg position, and fluid restriction and venodilators if necessary to maintain a central venous pressure lower than 5 mm Hg. The other major advance has been an improved understanding of the segmental anatomy of the liver, making intrahepatic dissection safer and more precise. There are numerous techniques to transect liver tissue and many methods to coagulate and to control vessels. The most important concept, however, is that dividing liver tissue is a dissection done by a surgeon with complete understanding of the liver’s vascular anatomy.

In experienced centers, perioperative mortality is routinely 5% or less and depends on a number of factors. The three most critical factors related to perioperative morbidity are blood loss, the amount of normal liver resected, and the condition of the liver itself (e.g., cirrhosis). A partial hepectomy must be performed with these factors in mind to minimize morbidity. In a review of more than 1800 liver resections during a 10-year period from MSKCC, the operative mortality was 3.1%. The median blood loss was 600 mL, and two thirds of patients did not require a red blood cell transfusion. Overall, postoperative morbidity was 45%, but the median hospital stay was 8 days. Morbidity was mostly related to blood loss and the extent of resection. Minor resections were associated with a mortality of 1%. Most complications and deaths were seen in complex biliary tumors, cirrhosis with HCC, and extensive resections. Improving outcomes after partial hepectomy continue, and experienced hepatobiliary centers have reported mortality rates that approach 1% to 2%, with fewer patients now requiring perioperative blood transfusions. As a result of the increasing safety of hepatic surgery, liver resection has become the treatment of choice for many malignant and benign hepatic conditions.

Bile leaks are a problem in cases requiring complex biliary reconstruction but can also occur in approximately 10% to 20%...
of hepatectomies without biliary reconstruction. Careful ligation of biliary radicals is of obvious importance in minimizing this complication. Because of the regenerative capacity of the liver, resections of up to 80% of normal noncirrhotic livers can be performed, with functional compensation within a few weeks. Because many resections encompass tumors and normal liver, the concepts of functional liver parenchyma and FLR volume are important because there is often compensatory hypertrophy of normal liver when tumors occupy a significant amount of the liver volume. The risk of hepatic dysfunction is minimal if the reduction of functional liver parenchyma is less than 50% but begins to rise when this figure approaches 20% to 25%. Patients with cirrhosis have much higher rates of postoperative liver dysfunction because of impaired regenerative capacity and impaired primary liver function. Liver failure, extrahepatic multigang failure, and death are serious hazards to performance of major liver resections in cirrhotics. In general, patients with Child class B or C cirrhosis or portal hypertension do not tolerate liver resections, and selection of patients is therefore critical. Ascites and infectious complications are also common problems after major liver resection. One strategy to minimize postoperative liver dysfunction and morbidity after major hepatectomy is to embolize the portal vein percutaneously on the side of the liver to be resected. In approximately 4 weeks, this induces atrophy of the liver parenchyma to be resected and hypertrophy of the FLR. In turn, this increases the relative volume of the FLR.

Techniques of liver resection differ according to the disease being treated. In benign hepatic diseases requiring resection, the indications for operation are usually symptoms or infection. Removal of normal liver should be kept to a minimum in these cases, and techniques such as enucleation are appropriate, although a major resection is occasionally necessary. For malignant disease, a margin of normal tissue is important, and formal anatomic resections yield the best results. Techniques such as wedge resection often result in higher rates of margin involvement and disease recurrence and should therefore be used carefully and sparingly. It must be noted that for colorectal liver metastases, parenchymal sparing nonanatomic resection provides comparable oncologic outcomes with marked reduction in complications when compared to major hepatic resections.67–69

Detailed knowledge of liver anatomy is essential to the practice of safe hepatic surgery (see earlier). Unfortunately, detailed and complicated descriptions of liver anatomy and common liver resections can be confusing to the student. A 2000 consensus conference conducted in Brisbane, Australia, with the assistance of the Americas Hepato-Pancreato-Biliary Association has published guidelines for this terminology (Table 54.11 and Fig. 54.39). In general, the term lobectomy is not preferred because there are no external markings on the liver denoting a lobe. When in doubt, one should always revert to the numeric segments of the liver if there is any confusion about the description of a liver resection. Recall that the right liver is composed of segments V through VIII, and right hepatectomy and right hemihepatectomy are appropriate terms for resection of these segments. Segments II through IV compose the left liver, and left hepatectomy and left hemihepatectomy are appropriate terms for resection of these segments. A right hepatectomy can be extended farther to the left to include segment IV, and a left hepatectomy can be extended farther to the right to include segments V and VIII. Terms such as extended right-left hepatectomy, right-left trisegmentectomy, and trisegmentectomy are appropriate to describe these resections. Resection of segments II and III is a commonly performed sublobar resection and is often referred to as a left lateral segmentectomy or left lateral sectionectomy. Other common sublobar resections, such as that of the right posterior sector (segments VI and VII) or the right anterior sector (segments V and VIII), are referred to as a right posterior sectorectomy-sectionectomy and right anterior sectorectomy-sectionectomy, respectively. Single or bisegmental resections can always be simply referred to by a numeric description of the segments to be resected.

A detailed discussion of the techniques of liver resection is beyond the scope of this chapter; in general, it requires specialty training, but general principles can be discussed. A liver resection must consider the disease to be treated and the goal of the operation, whether that is a margin-negative resection of a malignant neoplasm or the removal of benign tissue to alleviate symptoms. The most basic steps can be distilled down to inflow control (portal vein, hepatic artery, bile duct), outflow control (hepatic veins), and parenchymal transection, with preservation of a liver remnant of adequate size with intact inflow, biliary drainage, and venous outflow.

The most common approach to an anatomic resection, in the most common order, is mobilization of the liver to be resected, dissection of inflow and outflow structures, division of the inflow, division of the outflow, and parenchymal transection. Mobilization of the liver involves division of the right or left triangular ligaments, freeing up the liver from the diaphragm. Often, the liver must be mobilized completely off the vena cava, which it straddles, and this requires careful dissection and division of multiple retrohepatic caval venous branches. For major resections, the hepatic vein of the resected portion of liver is often encircled before the resection. There are various techniques to dissect, control, and divide inflow vessels. Classic inflow control is obtained by dissection of the liver hilum, with control of the portal vein and

### TABLE 54.11 Nomenclature for most common major anatomic hepatic resections.

<table>
<thead>
<tr>
<th>SEGMENTS†</th>
<th>COUINAUD, 1957</th>
<th>GOLDSMITH AND WOODBURNE, 1957</th>
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<td>V–VIII</td>
<td>Right hepatectomy</td>
<td>Right hepatic lobectomy</td>
<td>Right hemihepatectomy</td>
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<tr>
<td>IV–VIII†</td>
<td>Right lobectomy</td>
<td>Extended right hepatic lobectomy</td>
<td>Right trisegmentectomy</td>
</tr>
<tr>
<td>II–IV</td>
<td>Left hepatectomy</td>
<td>Left hepatic lobectomy</td>
<td>Left hemihepatectomy</td>
</tr>
<tr>
<td>II, III</td>
<td>Left lobectomy</td>
<td>Left lateral segmentectomy</td>
<td>Left lateral sectionectomy</td>
</tr>
<tr>
<td>II, III, IV, V, VIII‡</td>
<td>Extended left hepatectomy</td>
<td>Extended left lobectomy</td>
<td>Left trisegmentectomy</td>
</tr>
</tbody>
</table>

*The original terminology is based on the anatomic descriptions of Couinaud and of Goldsmith and Woodburne.
†See Fig. 54.40A–E
‡Another common name for these operations is right or left trisegmentectomy.
hepatic artery to the hemiliver to be resected. These can be suture ligated or divided with vascular staplers. Unless tumor proximity mandates, we advocate dividing the bile duct within the liver substance to minimize absolutely contralateral biliary injuries related to anatomic anomalies. Inflow control can also be obtained by dissection of the intrahepatic inflow pedicle to the anatomic section of liver to be resected. Recall that the inflow structures invaginate peritoneum at the hepatic hilum and run intrahepatically as an invested pedicle of the three inflow structures. The inflow pedicles can be encircled by making flanking hepatotomies or by splitting parenchyma down to the pedicle of interest. The pedicle can usually be divided with a vascular stapler, but suture ligation is sometimes necessary. Typically, the hepatic vein is divided in its extrahepatic position, which can also usually be done with a vascular stapler.

The hepatic vein can also be divided within the substance of the liver during parenchymal transection. There are a number of methods of parenchymal transection, ranging from complex ultrasonic irrigators to radiofrequency energy coagulators to a simple clamp-crushing technique. In experienced hands, these can all be used effectively to minimize blood loss, and it is important to develop a specific technique that one is comfortable performing. Ultimately, parenchymal transection is about dissecting intrahepatic anatomy, controlling vascular and biliary structures, minimizing blood loss, and avoiding injury to the FLR.

HEMOBILIA

A case of lethal hemobilia secondary to penetrating abdominal trauma was first described by Glisson in 1654. It was not until 1948 that Sandblom coined the term hemobilia in his seminal paper on the subject. Hemobilia is defined as bleeding into the biliary tree from an abnormal communication between a blood vessel and bile duct. It is a rare condition that is often difficult to

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**FIG. 54.39** Commonly performed major hepatic resections are indicated by the shaded areas. (A) Right hepatectomy, right hepatic lobectomy, or right hemihepatectomy (segments V to VIII). (B) Left hepatectomy, left hepatic lobectomy, or left hemihepatectomy (segments II to IV). (C) Right lobectomy, extended right hepatic lobectomy, or right trisectionectomy (trisegmentectomy; segments IV to VIII). (D) Left lobectomy, left lateral segmentectomy, or left lateral sectionectomy (segments II to III). (E) Extended left hepatectomy, extended left lobectomy, or left trisectionectomy (trisegmentectomy; segments II to V, VIII). See Table 54.11. (From Blumgart LH, Jarnagin W, Fong Y. Liver resection for benign disease and for liver and biliary tumors. In: Blumgart LH, Fong Y, eds. Surgery of the Liver and Biliary Tract. London: WB Saunders; 2000:1639–1714.)
distinguish from common causes of gastrointestinal bleeding. The most common causes of hemobilia are iatrogenic trauma, accidental trauma, gallstones, tumors, inflammatory disorders, and vascular disorders. Major hemobilia is relatively uncommon, whereas minor inconsequential hemobilia is a common consequence of gallstone disease or interventional radiologic hepatic procedures.

Causes
The most common cause of hemobilia is iatrogenic trauma to the liver and biliary tree. Before the 1980s, the ratio of hemobilia attributed to accidental trauma compared with iatrogenic trauma was 2:1, but iatrogenic trauma is now regarded as the cause of hemobilia in 40% to 60% of cases. Percutaneous liver biopsy results in hemobilia in less than 1% of cases, but percutaneous transhepatic biliary drainage procedures have an incidence of 2% to 10%. Similarly, surgical exploration of the biliary tree can result in hemobilia from direct injury or arterial pseudoaneurysm. A number of cases of hemobilia after cholecystectomy have been reported. Hemobilia secondary to accidental trauma is more common with blunt than with penetrating abdominal trauma and occurs with a reported incidence of 0.2% to 3%. Risk factors for the development of hemobilia after accidental trauma are central hepatic rupture with a cavity, the use of packs, and inadequate drainage. The gallbladder can be a source of bleeding from trauma, gallstones, or acalculous cholecystitis. Primary vascular diseases, such as aneurysms, angiodyplasia, and hemangiomata, are rare causes of hemobilia. Malignant tumors of the liver, biliary tree, gallbladder, and pancreas as well as parasitic infections, hepatic abscesses, and cholangitis are uncommon causes of hemobilia.

Clinical Presentation
Portal venous bleeding into the biliary tree is rare and often self-limited unless the portal pressure is elevated. Minor hemobilia generally runs an uneventful asymptomatic clinical course. However, arterial hemobilia, the most common source, can be dramatic. Clinical sequelae of hemobilia are related to blood loss and the formation of potentially occlusive blood clots in the biliary tree. The classic triad of symptoms and signs of hemobilia is upper abdominal pain, upper gastrointestinal hemorrhage, and jaundice. In one report, all three were present in 22% of patients. The symptoms and signs of major hemobilia are melena (90% of cases), hematemesis (60% of cases), biliary colic (70% of cases), and jaundice (60% of cases). Upper gastrointestinal bleeding seen in conjunction with biliary symptoms must always raise the suspicion of hemobilia. One interesting aspect of hemobilia is the tendency for delayed presentations, up to weeks after the inciting causal event, as well as recurrent and brisk but limited bleeding during months and even years. Blood clots in the biliary tree can masquerade as stones if hemobilia goes unrecognized. These clots can cause cholangitis, pancreatitis, and cholecystitis.

Diagnostic Workup
Once hemobilia is suspected, the first evaluation should be upper gastrointestinal endoscopy, which rules out other sources of hemorrhage and may visualize bleeding from the ampulla of Vater. However, upper endoscopy is diagnostic of hemobilia in only approximately 10% of cases. If upper endoscopy is diagnostic and conservative management is planned, no further studies are necessary. Ultrasound or CT may be helpful in demonstrating intrahepatic tumor or hematoma. Evidence of active bleeding into the biliary tree may be seen on contrast-enhanced CT in the form of pooling contrast material, intraluminal clots, or biliary dilatation. CT may also show risk factors associated with hemobilia, such as cavating central lesions and aneurysms. Arterial angiography is now recognized as the test of choice when significant hemobilia is suspected and will reveal the source of bleeding in approximately 90% of cases. Cholangiography demonstrates blood clots in the biliary tree that may appear as stringy defects or smaller spherical defects that may be difficult to distinguish from stones.

Treatment and Outcomes
The treatment of hemobilia must be focused on stopping the bleeding and relieving biliary obstruction. Most cases of minor hemobilia can be managed conservatively with correction of coagulopathy, adequate biliary drainage (only if necessary), and close observation. In a review of 171 reported cases from 1996 to 1999, 43% of cases were successfully managed conservatively. The first line of therapy for major hemobilia was transarterial embolization, and success rates of 80% to 100% were reported. Angiography with transarterial embolization is indicated for major hemobilia requiring blood transfusion (Fig. 54.40).

Surgery is indicated when conservative therapy and transarterial embolization have failed. Surgical treatment of hemobilia is rarely necessary, and even in cases in which a laparotomy may be mandated for other reasons, transarterial embolization is still the therapy of choice for hemobilia because of its lower morbidity. Surgical approaches generally involve ligation of bleeding vessels, excision of aneurysms, or nonselective ligation of a main hepatic artery. Hepatic resection may be necessary for failed arterial ligation or for cases of severe trauma or tumor. Hemorrhage from the gallbladder or hemorrhagic cholecystitis mandates cholecystectomy. There have been isolated reports of successful management of hemobilia with endoscopic coagulation, somatostatin, and vasopressin. The management of hemobilia after percutaneous transhepatic biliary drainage usually consists of removal of the catheter or replacement with larger catheters but may require transarterial embolization.

At the time of Sandblom's report from the early 1970s, the mortality for hemobilia was at least 25%. A report from 1987 noted a mortality of 12%. In a review of cases from 1996 through 1999, only four deaths were reported. There has clearly been a reduction in mortality from hemobilia, which is probably related to two factors. First, the incidence of minor self-limited hemobilia has increased secondary to the rising number of percutaneous hepatic procedures. Second, improvements in selective angiography and transarterial embolization have greatly improved the treatment of major hemobilia.

Bilhemia
Bilhemia is an extremely rare condition in which bile flows into the bloodstream through the hepatic veins or portal vein branches. This flow occurs in the context of a high intrabiliary pressure exceeding that of the venous system. The cause can be gallstones eroding into the portal vein or accidental or iatrogenic trauma. The condition can be fatal secondary to embolization of large amounts of bile into the lungs. Usually, however, bile flow is low, and the fistulas close spontaneously. The clinical presentation is that of rapidly increasing jaundice, marked direct hyperbilirubinemia without elevation of hepatocellular enzyme levels (e.g., AST, ALT), and septicemia. This diagnosis is best determined by ERCP. Treatment is directed at lowering intrabiliary pressures through stents or sphincterotomy.
VIRAL HEPATITIS AND THE SURGEON

Epidemics of jaundice were noted in ancient civilizations and recorded by Hippocrates. During World War II, these epidemics were called catarrhal jaundice. More than 28,000 cases were documented at that time. Epidemiologic studies in the 1940s documented the difference between bloodborne hepatitis (hepatitis B) and enteric hepatitis (hepatitis A). The most important discovery was that of the Australia antigen by Blumberg and coworkers in 1965. This antigen proved to be the hepatitis B surface antigen (HBsAg) and provided a means for differentiating the two types of hepatitis and characterizing the epidemiology of this disease. This discovery also led to the development of HBV vaccines based on this antigen with obvious and profound effects worldwide. Further research led to the discovery of the delta virus (hepatitis D) and hepatitis C, explaining cases of non-A, non-B hepatitis. Hepatitis E has been found to be a unique enteral form of infectious hepatitis; the hepatitis G virus, discovered in 1995, is still being defined.

Viral hepatitis is a major health problem and is the most common cause of liver disease worldwide. Although fulminant acute hepatitis is uncommon, there are more than 5 million people who suffer from chronic hepatitis. It is estimated that more than 15,000 patients die each year of viral hepatitis in the United States alone. Viral hepatitis is not a surgical disease, but it has important consequences for surgeons and surgical patients. For any surgeon performing hepatic surgery, the functional state of the liver is extremely important, and patients with chronic viral hepatitis require special attention before any surgical intervention. Also, chronic viral hepatitis is a common cause of HCC. Finally, the risk of transmission from patient to surgeon and vice versa is an issue with which all surgeons should be familiar.

Definition

Viral hepatitis is an infection of the liver by one of six known viruses that have diverse genetic compositions and structures. Hepatitis A virus (HAV), HCV, hepatitis D virus (HDV), hepatitis E virus (HEV), and hepatitis G virus (HGV) have RNA genomes, whereas HBV has a DNA genome that replicates through RNA intermediates. HAV and HEV are both responsible for forms of epidemic hepatitis and are transmitted through the fecal-oral route. HBV is the only one with the potential to integrate into
host genomes, although this is not required for replication. HCV replicates in the cytoplasm of hepatocytes and has complex mechanisms of evading host immunity through hypervariable areas in its genome. HDV requires the presence of HBV coinfection for replication and infectivity and can alter the clinical course of HBV infection. HGV was discovered more recently and has similarities to HCV but has no definitive association with clinical hepatitis.

**Diagnosis**

Table 54.12 summarizes the serologic tests and their implications for HAV, HBV, and HCV. The diagnosis of HAV infection relies on the determination of antibodies to HAV. Both IgM and IgG antibodies are present early in the infection, but only IgG persists long term. HAV antibodies and tests for HAV RNA have been developed but are generally restricted to research laboratories.

HBV infection has been characterized by a number of antigens and antibodies (Fig. 54.41). HBsAg is the hallmark of the diagnosis of HBV infection and appears in the serum 1 to 10 weeks after infection; it usually disappears in 4 to 6 months, but persistence in the serum beyond 6 months implies chronic infection. Anti-hepatitis B surface antigen (anti-HBs) antibodies usually appear during a window period after the disappearance of HBsAg and indicate recovery after HBV infection. Anti-HBs antibodies are also induced by the HBV vaccine. The hepatitis B core antigen (HBcAg) is an intracellular antigen that is not detectable in serum. On the other hand, anti-HBc antibodies are detectable early after infection and persist after recovery and in chronic infections. HBeAg is a secretory protein that is a marker of HBV replication and infectivity. It is usually present early and may persist for years in chronic infection but generally disappears within months in the absence of chronic infection. Seroconversion to anti-HBe antibodies is usually associated with resolution of infection. Determining the presence of HBeAg or anti-HBe antibodies helps decipher the phases of infection described below. It has also been shown that many patients who have seroconverted often have measurable HBV DNA, albeit at low levels. Quantification of HBV DNA in the serum has become the most accurate way of assessing HBV activity. Evidence has shown that many patients thought to have resolved acute HBV infection may have persistent viral infection and may be at risk for ongoing hepatitis or reactivation.

The diagnosis of HCV infection relies on the detection of antibodies to a number of HCV antigens. Current immunoassays are highly specific and sensitive. No specific HCV antigen tests exist, but there are a variety of quantitative and qualitative tests for HCV RNA, which have become important in confirming the diagnosis in unclear cases and assessing responses to therapy.

HDV coinfection of HBV-infected patients is best diagnosed by detection of HDV RNA, which can be measured in serum. The HDV antigen can be detected in liver specimens. HEV infection can be diagnosed by measurement of antibodies in serum or by detection of the virus or its components in feces, serum, or the liver itself.

**Epidemiology and Transmission**

The incidence of hepatitis A has fallen dramatically since the introduction of effective vaccines, but vaccination is not routine in all countries. Hepatitis A is common in third-world countries, with seropositivity rates approaching 100% in some populations. Infection occurs in childhood and is facilitated by poor hygiene and sanitation. Infection rates are much lower in developed countries. In the United States, approximately 10% of children and
35% of adults have been infected with HAV. Despite vaccination availability, 6000 cases were reported in the United States in 2004. The primary route of HAV infection is the fecal-oral route. Most cases of HAV occur because of ingestion of contaminated water or food and person-to-person contact. Parenteral transmission is possible but uncommon. Sexual transmission has been documented in homosexual men.

Hepatitis B is a major worldwide health problem. There are more than 300 million carriers and 250,000 associated deaths annually. The prevalence of HBV infection has considerable geographic variation. Low prevalence areas such as the United States and Western Europe have carrier rates of 0.1% to 2%. In these regions, transmission is generally through sexual intercourse or IV drug abuse. Carrier rates in intermediate-prevalence areas such as Japan and Singapore range from 3% to 5%. In high-prevalence areas such as Southeast Asia and sub-Saharan Africa, carrier rates range from 10% to 20%. Transmission in high-prevalence areas is largely perinatal and horizontal during childhood.

Transfusion-associated HBV infection was common in the 1960s, and the risk has been estimated to be as high as 50% at that time. Currently, screening programs and limitation of blood donation to voluntary donors have decreased the risk of acquiring HBV from a blood transfusion to 1 in 63,000. Percutaneous transmission through the use of any contaminated needle is a major route of HBV infection and is common in IV drug abusers. Sexual transmission is common in low-prevalence countries and is estimated to account for approximately 30% of cases in the United States. There is a particularly high incidence in male homosexuals and heterosexuals with multiple sexual partners. Perinatal HBV infection accounts for less than 10% of cases in the United States but is common in endemic regions, with rates of transmission of 90% in some areas. Horizontal transmission among children is common and is probably related to minor breaks in the skin and mucous membranes. HBV is the most commonly transmitted virus among healthcare personnel, and transmission is usually patient to patient or patient to worker. Needle-stick risk has been related to HBeAg positivity. Rare cases of physician-to-patient transmission have been reported.

Hepatitis C is the most common cause of chronic liver disease in the United States, with an estimated prevalence of 1.8% accounting for 3.9 million infected people. New infections typically occur at a younger age (20–39 years), and the most common risk factor is IV drug abuse. Healthcare workers have higher carrier rates than the general public. Transmission among healthcare workers is usually related to needle-stick incidents, and the risk of transmission is higher than that of HBV and HIV. In the past, blood transfusion was the major cause of HCV infection, accounting for at least 85% of cases. Currently, less than 2% of acute infections are caused by transfusions, and the risk of transfusion-associated transmission is estimated to be about 1 in 10,000. Although HCV has never been documented in semen, it is estimated that approximately 20% of HCV infections are caused by sexual transmission. Risk of sexual transmission appears to be related to the number of partners and presence of other sexually transmitted diseases. Monogamous sexual partners of HCV-infected people occasionally test positive for HCV in the absence of other risk factors, but this appears to be rare. Perinatal transmission has been documented but is also rare. No identifiable risk factors are found in 30% to 40% of HCV cases.

HDV infection occurs worldwide with a variable distribution that parallels that of HBV infection. Approximately 5% of HBsAg-positive patients also harbor HDV infection. Transmission of HDV is parenteral and can occur only in patients previously infected with HBV.

HEV is endemic in Southeast Asia and central Asia and occurs with low frequency in other areas of the world. HEV infection outbreaks are usually large, affecting hundreds to thousands of people at once, and often follow large rains and flooding. There is a particularly high incidence and mortality in pregnant women. Transmission is fecal-oral and usually related to contaminated drinking water or food. Person-to-person transmission and vertical transmission are rare.

### Pathogenesis and Clinical Presentation

The pathogenesis of hepatic injury from these viral infections is not completely understood. For all the viruses discussed in this section, hepatic inflammation appears to be caused by direct cyto-toxicity or immune-related phenomena. A combination of these two mechanisms probably underlies the cause of hepatic damage.

Humans are the only host for HAV, and no reservoir of infection has been identified. After oral intake, HAV can survive the acidic gastric pH, but the mechanism of hepatic uptake is not known. HAV infection results in acute inflammation of the liver and has no associated chronic sequelae. The most recent data suggest that hepatocyte damage is most likely an immunopathologic response rather than direct hepatotoxicity. Most children with HAV infection younger than 2 years are asymptomatic, whereas in pediatric patients older than 3 years, 80% will develop symptoms. Fulminant hepatitis develops in 1% to 5% of cases, and mortality is generally below 1%.

HBV is a member of the Hepadnaviridae family that is characterized by a genome consisting of partially double-stranded, circular DNA. After viral entry into the hepatocyte, the viral genome is delivered into the nucleus, where it is converted into fully double-stranded DNA and then covalently closed circular DNA. This stable form of HBV DNA is responsible for its persistence in infected hepatocytes. HBV also has the ability of integrating into the hepatocyte genome.

Approximately 70% of patients with acute HBV infection have subclinical or anicteric hepatitis; the other 30% have icteric hepatitis. The incubation period for HBV infection ranges from 1 to 4 months. A prodromal serum sickness–like syndrome may develop, followed by a multitude of constitutional symptoms, such as malaise, anorexia, and nausea. The constitutional symptoms last about 10 days and are followed by jaundice in 30% of patients. Clinical symptoms usually disappear within 3 months. Fulminant hepatic failure develops in 0.1% to 0.5% of patients. Almost 80% of patients with fulminant HBV-related hepatitis will die unless liver transplantation is performed.

Risk of chronic HBV infection is related to immunocompetence and age. Immunocompetent adults have a risk of less than 5%, whereas 30% of children and 90% of infants will develop chronic disease. The effect of age on HBV persistence is most likely due to difference in immune maturity between adults and young children. The natural history and disease course of chronic HBV infection are the result of complex interactions between the virus and host immune response. A substantial proportion of patients will develop liver injury, cirrhosis and its complications, and hepatocellular cancer, whereas others will harbor the virus with limited, if any, injury. Different phases of HBV infection, each with unique viral and biochemical profiles, have been described. The first phase, **HBeAg-positive chronic infection** (previously known as immune tolerant phase), is characterized by high serum HBV DNA but normal liver enzymes. There is a high serum level...
of HBeAg, and patients in this phase are highly contagious due to the high level of HBV DNA. However, it must be noted that these phases are not necessarily sequential and can be reversed. The second phase, **HBeAg-positive chronic hepatitis B**, is characterized by all the features of phase I along with elevated ALT, suggesting liver damage. Liver biopsy at this stage will demonstrate moderate or severe liver necroinflammation. The third phase, **HBeAg-negative chronic hepatitis B** (previously termed “inactive carrier” phase), is characterized by absence of HBeAg, presence of serum antibodies to HBeAg, undetectable or low levels of HBV DNA and normal liver enzymes. The fourth phase is termed **HBeAg-negative chronic hepatitis B** and is characterized by the lack of serum HBeAg, detectable anti-HBe levels, persistent moderate to high levels of serum HBV DNA, as well as fluctuating or persistently elevated ALT levels. Most patients with chronic HBV infection are asymptomatic, but some may experience exacerbations of symptoms. Progression to cirrhosis is marked by hepatic synthetic dysfunction and often cytopenias, related to hypersplenism. Extrahepatic manifestations of HBV infection, caused by circulating immune complexes, occur in approximately 10% to 20% of patients; these include polyarteritis nodosa, glomerulonephritis, essential mixed cryoglobulinemia, and papular acrodermatitis. The sequelae of chronic HBV infection range from none to cirrhosis, HCC, hepatic failure, and death. It has been noted that patients thought to have previously cleared the infection can have a reactivation, especially during a period of immunosuppression. In nonendemic areas, the long-term risk appears to be low, but in endemic areas, chronic HBV infection is a significant cause of morbidity and mortality.

HCV is an RNA virus with a single-stranded RNA genome. This genomic RNA encodes a single protein that can be cleaved by a protease enzyme into its components. HCV replicates in the hepatocyte cytoplasm. The components of viral replication are targeted by the recently successful direct-acting antivirals. For instance, protease inhibitors target the protease responsible for cleaving the initial protein into the various viral components. Acute HCV infection generally is manifested with mild elevation of hepatocellular enzyme levels. In general, 80% of cases occur 5 to 12 weeks after infection. Symptoms occur in less than 30% of patients and are usually so mild and nonspecific that they do not affect daily life. Jaundice occurs in less than 20% of patients, and fulminant hepatic failure caused by HCV is extremely uncommon. Chronic HCV infection develops in approximately two thirds of patients; the other third appear to clear the infection. Most patients with chronic HCV infection are asymptomatic without evidence of overt liver disease and present with only mildly elevated hepatocellular enzyme levels. Despite this quiet clinical course, patients with chronic HCV infection are at risk for development of cirrhosis and HCC. Estimates place the risk of cirrhosis at 2% to 20% at a 20- to 30-year interval. The risk for development of HCC from that point has been estimated at 1% to 4%/year. Progression of liver damage can be variable, and several factors appear to affect its rate. Factors associated with a more rapid progression include male gender, older age at infection, immunosuppression (e.g., HIV infection), coinfection with HBV, moderate alcohol intake, and obesity. Extrahepatic manifestations, such as autoimmune disorders and lymphoma, can occur with HCV infection and are likely related to circulating immune complexes.

The clinical presentation of HDV infection is related to a complex relationship between the degree of HBV and HDV infection. Simultaneous coinfection with high expression of HBV and HDV results in higher rates of acute fulminant hepatitis. Superinfection in a previous HBV carrier generally results in more rapidly progressive chronic liver damage. Some milder forms of acute HDV infection are associated with decreased expression of HDV and repression of HBV infection.

Hepatitis E has a histologic picture different from that of the other viral hepatitides in that a cholestatic type of hepatitis is seen in more than 50% of patients. HEV is introduced orally, and it is not known how the virus travels to the liver. The incubation period of HEV infection ranges from 2 to 9 weeks. The most common form of illness is acute icteric hepatitis; most series report jaundice in more than 90% of patients. Asymptomatic forms of the disease occur and are probably more common than the icteric form, but the actual frequency is unknown. The disease is usually self-limited, but fulminant hepatic failure can occur in a small percentage of patients. Overall, the mortality rate is probably significantly less than 1%. Pregnant women tend to have a more severe clinical course; mortality rates range from 5% to 25%.

**Prevention**

HAV infection prophylaxis relies on sanitary measures and administration of serum immunoglobulin. The development of safe and effective HAV vaccines, however, has made the use of preexposure immunoglobulin unnecessary. Serum immunoglobulin is still the therapy of choice for postexposure prophylaxis and may be safely given, along with active immunization. In the United States, the Centers for Disease Control and Prevention (CDC) has recommended universal vaccination of children on the basis of the safety and efficacy of the vaccine in high-risk populations. Public health researchers are investigating vaccination schemes to eradicate HAV infection in high-risk populations throughout the world. However, cost-benefit analyses have not supported universal vaccination worldwide. Similarly, HEV infection prophylaxis has focused on sanitary measures, particularly strategies aimed at drinking water. Unfortunately, HEV immunoglobulin has not been successful in preexposure or postexposure prevention of HEV infection, whereas anti-HEV antibodies appear to be effective at attenuating the clinical syndrome. Vaccines for HEV infection have been developed and evaluated in clinical trials.

Remarkable advances have been made in the prevention of HBV infection. In the past, prevention of HBV infection was limited to passive immunization with immunoglobulin containing high titers of antibody to HBsAg. Currently, immunoglobulin immunization is used only in postexposure prophylaxis. HBsAg-containing vaccines have been developed with good safety and efficacy profiles. These vaccines are used primarily for postexposure prophylaxis but can also be used in a postexposure setting along with immunoglobulin. Currently, CDC recommends a three-dose HBV vaccination for all children, with the first dose being administered preferably within 24 hours after birth followed by two subsequent booster doses. Although no vaccine is available for HDV infection, effective prevention of HBV infection prevents HDV infection.

The only effective preventive strategy for HCV infection relies on public health principles aimed at the major risk factors for transmission. Conventionally prepared anti-HCV immunoglobulin has been evaluated in a number of trials and has not been demonstrated to prevent transfusion-related non-A, non-B hepatitis. Screening of blood donors has rendered this issue irrelevant today. Unfortunately, because of various obstacles, a successful HCV vaccine has not been developed.
Treatment
Treatment of HAV or HEV infection is supportive in nature and is generally aimed at correcting dehydration and providing adequate calorie intake. Although fatigue may mandate significant periods of rest, hospitalization is usually not necessary, except in cases of fulminant liver failure.

The treatment of HBV infection is largely aimed at patients with chronic active disease. Interferon-alfa and the nucleoside analogue lamivudine used to be the only two approved therapies for the treatment of HBV. Now, many nucleoside analogues for the treatment of HBV infection have been developed and probably work through inhibition of DNA synthesis. Interferon-alfa is an immunomodulatory agent with some antiviral properties that can induce a virologic response in 35% to 40% of patients. However, long-term benefit with interferon therapy has not been proven. Oral nucleoside analogues are currently the main form of anti-HBV treatment, which include entecavir and two prodrugs of tenofovir. These three drugs are very effective in inducing virologic suppression in a high proportion of patients with favorable safety and tolerability profiles. Entecavir is not recommended in patients who have been previously treated with lamivudine or telbivudine. On the other hand, tenofovir derivatives are effective in patients with lamivudine and telbivudine resistance. Long-term viral suppression with nucleoside analog therapy leads to significant histologic improvement, including regression of cirrhosis, reduced complications of cirrhosis, and decreased risk of developing HCC. Indication for treatment of HBV infection is based on three parameters: serum HBV DNA, serum ALT levels, and severity of liver disease. All experts agree that patients with cirrhosis, with or without decompensation, should be treated when serum HBV DNA is detectable. Most experts will also suggest treatment with higher levels of HBV DNA with ALT elevations or with moderately elevated levels of HBV DNA with evidence of liver fibrosis.

During the last 20 years, tremendous advances in the treatment of HCV infection have occurred. Interferon-alpha and ribavirin were the recommended treatment for hepatitis C for the longest time. A benefit for interferon-alfa in the treatment of non-A, non-B hepatitis was originally demonstrated in 1986, before the discovery of HCV. With interferon-alpha treatment regimens, complete viral response, defined as sustained loss of serum viral RNA, occurs in 12% to 20% of patients. The addition of ribavirin to interferon-alfa resulted in response rates of 35% to 45%. In the most recent trials, treatment with pegylated interferon-alfa and ribavirin for 48 weeks resulted in viral clearance in 55% of patients. The specific genotype appears to be predictive of response, with some types resulting in response rates of 80% and others of 45%. Relapse can occur, but it usually occurs with monotherapy and shortened courses of therapy. Interferon-alfa regimens had significant side effects. During recent years, the treatment of chronic HCV infection has been revolutionized by the introduction of direct-acting antivirals (e.g., ledipasvir, sofosbuvir, glecaprevir, pibrentasvir, velpatasvir) that target specific nonstructural proteins of HCV and thus disrupt viral replication and infection. Combinations of these medications have now become the first-line treatment and have effectively replaced prior regimens of pegylated interferon-alpha and ribavirin as the standard of care where available. The current all-oral treatments are of shorter duration, have fewer side effects, and have higher cure rates. By tailoring the combination of direct-acting antiviral agents to patient factors and the specific HCV genotype, a sustained virologic response can be achieved in greater than 90% of patients.

This study analyzes factors associated with differences in long-term outcomes after hepatic resection for metastatic colorectal cancer. Despite worse clinical and pathologic features, survival rates after hepatic resection for colorectal metastases have improved, which might be attributable to improvements in patient selection, operative management, and chemotherapy.


Imaging modalities are key in diagnosing and differentiating various focal liver lesions. This monograph covers the critical elements of ultrasonography, computed tomography, and MRI of focal liver lesions.


One of the largest series of hepatic resections that documents the remarkable improvement in perioperative outcomes.


This review article covers the diagnosis and management of cystic disease of the liver including hydatid disease.


This manuscript reviews the place and evolution of robotics in the current era of minimally invasive liver surgery.


This review describes the epidemiology, risk factor, and natural history of hepatitis C infection. It also comprehensively reviews the new developments which have revolutionized the treatment of hepatitis C.


A classic landmark study on pyogenic abscesses of the liver. This was the first serious attempt to study hepatic abscesses and ushered in the modern era of treatment.


This is an excellent, comprehensive, and practical review of the treatment of ascites in patients with cirrhosis.


This excellent article analyzes the reasoning and the evidence underscoring the benefit of metastatectomy for colorectal liver and other metastases.

REFERENCES


