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Editor in Chief: Lewis Flint, MD, FACS
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CME Pretest | LIVER, PART I
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To earn CME credit, completing the pretest is a mandatory requirement. The pretest should be completed BEFORE reading the overview and taking the posttest. Both tests must be completed online at www.facs.org/publications/srgs/cme.

1. Each of the following contribute to thrombocytopenia and disordered platelet function in patients with liver disease except which one?
   a) Sequestration of platelets in the spleen
   b) Depressed thrombopoietin levels
   c) Folic acid deficiency
   d) Sequestration of platelets in the lung
   e) Platelet autoantibodies

2. Kupffer cells mediate an important step in the development of hepatic fibrosis when these cells stimulate the transformation of hepatic stellate cells to what cell type?
   a) Macrophage
   b) Biliary ductal cell
   c) Endothelial cell
   d) Myofibroblast
   e) Hepatic stem cell

3. Each of the following coagulation factors is synthesized in the liver except which one?
   a) Factor VII
   b) Factor II
   c) Factor IX
   d) Factor IV
   e) Factor VIII

4. Correction of prothrombin time with fresh frozen plasma infusion is indicated for patients with liver disease and abnormal prothrombin time prior to which of the following procedures?
   a) PICC line placement
   b) Bone marrow biopsy
   c) Placement of an intracranial pressure monitor in a patient with fulminant liver failure and intracranial hypertension
   d) Internal jugular catheter placement
   e) Paracentesis

5. Alcohol intake increases fat deposition in the liver by all of the following mechanisms except which one?
   a) Increased fatty acid synthesis
   b) Depressed fatty acid breakdown
   c) Increased fatty acid absorption from the intestine
   d) Vitamin C deficiency
   e) Fat deposition due to hepatic inflammation

6. All of the following factors contribute to cardiovascular status in patients with liver disease except which one?
   a) Increased blood volume
   b) Vasodilation
   c) Excess secretion of myocardial depressant factor
   d) Tachycardia
   e) Systolic and diastolic cardiac dysfunction
7. Which of the following is a subjective scoring factor for calculation of the Child-Turcotte-Pugh class of liver disease?
   a) Bilirubin level
   b) Degree of ascites
   c) Alanine aminotransferase level
   d) Albumin level
   e) History of recent weight loss

8. A 54-year-old patient with cirrhosis due to hepatitis C complains of frequent episodes of right upper quadrant pain. Abdominal ultrasound discloses cholelithiasis. The calculated Child-Turcotte-Pugh class is B. Which of the following is indicated?
   a) Percutaneous gallbladder drainage
   b) Shock-wave lithotripsy
   c) Open cholecystectomy
   d) ERCP with stenting
   e) Laparoscopic cholecystectomy

9. Which of the following MELD scores indicates an excess mortality risk for elective abdominal operation?
   a) 10
   b) 17
   c) 8
   d) 11
   e) 5

10. In addition to MELD score and Child-Turcotte-Pugh class, which of the following has been shown to be important in assessing mortality risk for operation?
    a) BMI
    b) Glomerular filtration rate
    c) Resting electrocardiogram
    d) ASA score
    e) Cardiac ultrasonography

11. Which of the following agents used to treat coagulopathy in patients with liver disease works by suppressing hyperfibrinolysis?
    a) Fresh frozen plasma
    b) Recombinant factor VIIa
    c) Albumin infusion
    d) Tranexamic acid
    e) Fresh whole blood

12. Each of the following comorbid conditions is commonly present in patients with nonalcoholic fatty liver disease (NAFLD) except which one?
    a) Hypertension
    b) Type 2 diabetes
    c) Obesity
    d) Dyslipidemia
    e) Glomerulonephritis

13. Alcohol-related hepatic steatosis progresses to cirrhosis in what percentage of patients who continue to drink alcohol?
    a) 5%
    b) 75%
    c) 20%
    d) 100%
    e) 45%

14. Each of the following physical findings is suggestive of cirrhosis except which one?
    a) Hyperreflexia
    b) Palmer erythema
    c) Spider angiomata
    d) Asterixis
    e) Muscle wasting

15. Abnormal serum levels of aspartate aminotransferase and alanine aminotransferase are present in which percentage of North American patients?
    a) 25%
    b) 60%
    c) 15%
    d) 4%
    e) 30%
16. Which of the following imaging modalities has the highest sensitivity for the detection of hepatic fibrosis?
   a) Radioscintigraphy
   b) Positron emission tomography
   c) Multislice computerized tomography
   d) Doppler ultrasound
   e) Magnetic resonance imaging

17. All of the following factors contribute to the formation of ascites except which one?
   a) Failure of hepatic lymphatic transport to the circulation
   b) Left ventricular dysfunction
   c) Activation of the renin-angiotensin system
   d) Portal hypertension
   e) Mesenteric vasodilation

18. Which of the following marks the division between the left and right halves of the liver?
   a) The right scissura
   b) The umbilical fissure
   c) The left scissura
   d) Cantlie’s line
   e) The caudate lobe

19. Portal vein embolization regularly produces what increase in remnant liver volume at one month after embolization?
   a) 40%
   b) 64%
   c) 11%
   d) 3%
   e) 76%

20. Which of the following is the most common serious postoperative complication following laparoscopic liver resection?
   a) Bile leak
   b) Bleeding
   c) Air embolism
   d) Intestinal perforation
   e) Jaundice

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With this issue, we begin our three-part series focusing on the surgical management of patients with liver disease and liver injuries. We will retain pertinent information contained in the prior issue dealing with this topic (Volume 38, No. 3) and update content in the areas where valuable new information has been published.

This issue will open with a summary of the global health burden caused by liver disease. Following this, current knowledge of the mechanisms of liver cell damage and mechanisms of progression to cirrhosis will be reviewed; processes of liver cell damage that are specific to common liver conditions such as nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease, and viral hepatitis will be covered in these sections.

Advances in imaging, including magnetic resonance imaging (MRI) and intraoperative ultrasound (IOUS), have made precise anatomic localization of resectable liver lesions possible, as well as the ability to determine the relationships between these lesions and hepatic vascular structures and bile ducts. In consideration of this, articles dealing with the fundamental aspects of liver disease diagnoses using history, physical examination, laboratory studies, and imaging will also be presented.

It is important to understand the basics of surgical risk assessment in patients with liver disease; this knowledge makes it possible to have informed discussions about treatment strategies with patients, families, and nonsurgical specialists who are involved in the care of end-stage liver disease (ESLD) patients. Risk assessments and scoring systems that classify risk and aid in establishing a prognosis are statistical techniques; as such, these systems apply to groups of patients, not individual patients. Nonetheless, honest discussions of potential outcomes with patients will, of necessity, include such statistical information. Because surgeons are frequently called upon to deal with elective and emergency surgical problems in patients with ESLD, we will include important details on managing ESLD complications, as well as useful aspects of preparing these patients for surgery, including liver operations and extrahepatic procedures.

The concluding sections of this issue will discuss fundamentals of the surgical anatomy of the liver and techniques in open and laparoscopic liver resection.

Assistance with article selection and content development for this liver series was generously provided by Stuart Knechtle, MD, FACS, and Sabino Zani Jr., MD, of the Department of Surgery at Duke University School of Medicine. I am grateful for their work on behalf of SRGS.
The Health Burden of Liver Disease

Global trends in cirrhosis-related mortality from 1980 to 2010 was the focus of an article by Mokdad and co-authors\(^1\) in *BMC-Medicine*, 2014. This article emphasized the importance of accurate mortality rate estimates for cirrhosis in various countries as well as trends in global mortality rates, since cirrhosis is a preventable disease, and the overall health burden could be reduced through public health interventions. The authors estimated that global cirrhosis deaths increased from 676,000 in 1980 to more than one million in 2010. Of interest is that age-standardized death rates decreased by 22% over the same interval; this was largely driven by decreases in cirrhosis-related mortalities in China, the United States, and in Western Europe. The lowest mortality rate was recorded in Iceland. Decreased mortality rates are most likely due to reductions in alcohol consumption and more widespread hepatitis vaccinations. It is also likely that improved treatment modalities, such as liver transplantation, have had only a minor influence on mortality rates. The authors noted that cirrhosis-related mortality increased in the United Kingdom over the study interval, and data cited in the article suggest that increases in binge drinking contributed to this.

In an editorial that accompanied the article, Byass\(^2\) stressed that the analysis was hampered by the lack of data on large geographical regions such as sub-Saharan Africa. Also, the determination of cirrhosis-related death was made using “verbal autopsy” reports (reports from family members obtained by physicians) and this factor could have caused a significant underestimation of the health burden of cirrhosis.

Rehm and Shield\(^3\) presented additional perspective on the global health burden of alcohol-related liver disease in *Alcohol Research*, 2013. The authors used study data on per capita alcohol consumption, drinking patterns, risk relationships, and mortality to estimate mortality risks for alcohol-attributable cancers, alcohol-related injury, and liver cirrhosis for the years 1990 and 2010. They estimated that 1.5 million deaths occurred from alcohol-related causes in 2010 (accounting for 2.8% of all deaths). Analysis of trends showed that alcohol-related deaths increased for all patient groups. The only decrease in mortality risk occurred for cirrhosis-related deaths in women. The authors concluded that their data confirmed that alcohol-related diseases are a significant global health problem.

Pathophysiology & Mechanisms of Liver Damage in Liver Diseases

The liver has the impressive ability to replace cellular capacity and function after hepatectomy or toxic insult. This capability to heal allows surgeons to perform extended resection in order to cure malignant liver lesions. Moreover, living-donor liver transplantation relies on the ability of both a) the donated liver and b) the liver remnant remaining in the donor to repopulate lost cells and regain function after donation and transplantation. Replacing cells through hyperplasia and hypertrophy of hepatocytes plays an important role in the development of cirrhosis, wherein identification of regenerating nodules is a significant part of the gross and microscopic anatomy of this disease process. In its position as the first organ to receive portal blood draining from the intestine, the liver is a major participant in the response to bacteria and bacterial products (endotoxin) that originate in the intestinal lumen. Damage to hepatocytes resulting in varying degrees of hepatic insufficiency is a critical component of the response to sepsis. Endotoxin delivered to the liver in the portal blood is also an important mediator of the liver cell damage observed in alcoholic liver disease.

Because surgeons frequently are called upon to care for patients with complications of liver disease, and because patients with liver disease require surgical care for nonliver related conditions, a basic understanding of these disease processes is important. In addition, the immune response of the liver to hepatitis virus infection is im-
important to understand because of the insight it provides regarding the development of chronic hepatitis, hepatitis-induced cirrhosis, and hepatocellular cancer. Damage to liver cells may result from processes specific to the type of viral infection, as well as from processes related to immune and inflammatory responses.

**Viral Hepatitis**

Hepatitis due to the hepatitis B and hepatitis C viruses (HBV and HCV, respectively) poses a major global public health problem; several billion people are actively infected. Acute hepatitis can be caused by viral hepatitis infection and alcoholic liver disease; these two conditions can also cause chronic liver disease resulting in steatosis, hepatic fibrosis, and cirrhosis. Hepatitis B is the most common disease leading to hepatocellular carcinoma worldwide. Cirrhosis due to HBV infection remains a problem in developing countries of Asia and Africa. Hepatitis C is a common disease treated by liver transplantation in North America. Chronic hepatitis C with cirrhosis and increased malignancy risk is common in Western countries; patients with alcoholic liver disease and chronic hepatitis due to viral hepatitis infection who develop cirrhosis have an increased risk of hepatocellular cancer. In contrast to HBV, HCV is capable of evading innate and adaptive immune responses. In addition, the virus does not have biologic characteristics that render it vulnerable to vaccines; therefore, in 80% of infected individuals, chronic hepatitis C is a common occurrence after acute hepatitis. \(^4\) \(^5\) Hepatitis C continues to be an important occupational hazard for surgeons, but hepatitis B vaccination has nearly eliminated occupational infection among medical personnel in North America.

Because of the role of hepatitis virus infection in the pathogenesis of chronic liver disease, it is important for surgeons to have a working knowledge of the basic biology of these infections. Yamane and coauthors\(^8\) provided perspective on the mechanisms of liver damage in patients with chronic hepatitis C in *Current Topics in Microbiology and Immunology*, 2013. This article is supplied as a full-text reprint accompanying some formats of SRGS. The authors noted that the pathogenesis of liver injuries in patients with HCV results from an unresolved healing process. Chronic inflammatory changes and ongoing scarring produces fibrotic changes in the liver that may ultimately progress to cirrhosis. The hepatic stellate cell plays a central role in the ongoing inflammatory process. Activation of these cells is mediated by specific viral proteins; cellular activation results in the cells transforming into macrophages that accelerate and intensify the inflammatory process. In addition, virus-specific proteins stimulate TGF-beta production, and this substance participates in the fibrotic process.

Additional data cited in Yamane and coauthors’ review confirmed that hepatic steatosis is more common in patients with chronic hepatitis C. Available studies strongly suggest that steatosis is produced by specific products from the virus itself—data also confirmed that substances produced by HCV can produce insulin resistance and type 2 diabetes mellitus, which are commonly associated with chronic hepatitis C. Core proteins and some non-structural proteins produced by HCV are potent inducers of oxidative stress that is known to produce hepatic cellular damage. Yamane and coauthors concluded that there is evidence that virus-specific substances contribute to both the progression of hepatitis C to hepatocellular carcinoma and to the increased risk of lymphoproliferative disorders that have also been observed in patients with hepatitis C. Discovery of potential therapeutic targets and complete understanding of the virus-specific factors that produce liver damage have been hindered by the lack of a small animal model of hepatitis C. Virus-specific proteins are also mediators of liver damage associated with hepatitis B.

A review article by Suhail and coauthors\(^9\) in the *World Journal of Gastroenterology*, 2014, presented data indicating that virus-specific proteins are produced in different patterns by different HBV genotypes. This observation helps explain why certain complications of hepatitis B, such as early onset hepatocellular carcinoma (with genotype B and C) and fulminant hepatitis (genotype F), are observed more often in specific patient groups.

Current and future treatment strategies for hepatitis C were discussed in an article by Sakamoto and Watanabe\(^10\) in the *Journal of Gastroenterology*, 2009. The authors explained that available therapies include polymerase inhibitors, interferon-based drugs, and protease inhibitors. Clinical responses have been achieved in nearly
two out of three of patients treated with combination therapy approaches for 24-week intervals, but relapse and the development of resistant viral strains are common occurrences. Newer therapies becoming available include Toll-like receptor (TLR) agonists and nonimmune suppressing forms of cyclosporin. Treatment with TLR agonists was associated with excellent antiviral immune response in a single phase-one trial; phase-two trials are now underway. For the present, however, hepatitis C will continue to be an important cause of chronic liver disease and hepatocellular cancer.

Nonalcoholic Fatty Liver Disease

The obesity epidemic in the United States has given rise to an insidious form of chronic liver damage. Fat deposition in the livers of obese patients, especially patients with metabolic syndrome (central obesity, hypertension, and type 2 diabetes), is termed “nonalcoholic fatty liver disease” or NAFLD. NAFLD is an increasingly common diagnosis, and can progress to nonalcoholic steatohepatitis (NASH). In turn, NASH can lead to fibrosis of the liver, cirrhosis, and hepatocellular cancer (although these complications occur in a minority of patients). The progression of NASH to cirrhosis, liver failure, and ESLD has become the most common indication for liver transplantation in the United States.

A review of available literature focusing on NAFLD was by Rinella in JAMA, 2015. The author identified 3,396 candidate studies; from these, the author selected 14 randomized trials, 19 high-quality observational studies, seven meta-analyses, one population-based study, and two practice guideline reports. Also included were 43 reports classified as “other types,” including retrospective observational studies. The author noted that NAFLD was first described in 1980 and is divided into three subtypes: isolated steatosis, steatosis with mild inflammation, and nonalcoholic steatohepatitis. Evidence supports the conclusion that disease progression to cirrhosis can occur in both of the inflammatory subtypes. The most important prognostic factor is the degree of hepatic fibrosis discovered on liver biopsy. The data reviewed disclosed that NAFLD is present in 30% of the US population; the disease’s progressive forms, including steatosis with inflammation and nonalcoholic steatohepatitis, affect 5% of the US population.

Data cited by the author support the conclusion that visceral adipose tissue generates multiple signals that affect glucose and lipid metabolism. Changes in glucose and lipid metabolism lead to deposition of fat in the liver and to the production of a proinflammatory environment within the liver; microbial products from altered gut microorganisms contribute to this environment. Oxidative stress augments the inflammatory response, leading to apoptosis and fibrotic scarring in the liver. Progressive fibrosis can lead to cirrhosis and hepatocellular carcinoma in a small proportion of patients with NAFLD. A diagram describing the mechanisms of NAFLD is supplied in the article and is reproduced as Figure 1. The diagnostic assessment of NAFLD will be discussed in a later section of this review.
A potential contributor to the development of steatosis in patients with NAFLD could be disordered vitamin A metabolism. Vitamin A is known to have an important role in regulating lipid metabolism. An investigation reported by Liu and coauthors\textsuperscript{12} in the *American Journal of Clinical Nutrition*, 2015, presented data from a clinical study that assessed levels of serum retinoic acid in normal subjects and in patients with NAFLD. Serum levels of retinoic acid were significantly lower in patients with NAFLD, especially those with steatohepatitis. In liver biopsies, tissue expression of mRNA and protein levels of the retinoic X receptor were significantly depressed in patients with NAFLD and this was more pronounced in patients with progressive disease subtypes. The authors concluded that abnormalities of vitamin A metabolism are potentially valuable therapeutic targets in patients with NAFLD.

**Alcoholic Liver Disease**

Surgeons frequently encounter patients with acute and chronic sequelae of alcohol abuse, and alcoholic cirrhosis is the second most common indication for liver transplantation in North America. Having some basic knowledge of the mechanism and pathogenesis of alcoholic liver disease will be helpful in caring for these patients.

The primary mechanism that mediates alcohol-induced liver damage was discussed in an article by Altamirano and Bataller\textsuperscript{13} in *Nature Reviews Gastroenterology and Hepatology*, 2011. The authors noted that alcoholic liver disease is responsible for more deaths from cirrhosis than hepatitis C; deaths occur from cirrhosis complications (variceal bleeding, ascites, encephalopathy), progressive liver failure, and infection. Over 90% of heavy drinkers (more than three alcoholic drinks per day) will have some degree of fatty change in the liver. This condition is usually asymptomatic and reversible with cessation of alcohol intake. Fatty changes in the liver have been shown to progress to cirrhosis in 20% of patients who abuse alcohol.

Research studies using experimental animals have shed additional light on the mechanisms of alcohol-associated liver damage. These studies have shown that activation of the immune system, induction of the inflammatory cascade, and liberation of endotoxin into the portal circulation from the intestinal lumen are all important mediators of liver damage. The first example of this type of study was presented in an article by Barnes and coauthors\textsuperscript{14} in *Hepatology*, 2013. The authors emphasized that the liver is a complex, dynamic organ that has large populations of immunologically active cells, including Kupffer cells and natural killer T cells. There are also soluble innate immune system factors that contribute to liver damage. Research cited in the article confirmed that animals that were genetically altered so that there were no secretions of tumor necrosis factor were protected against steatosis and fibrosis in the liver when they were given a chronic dosing schedule of ethanol. Additional data cited by the authors confirmed a role for endotoxin-mediated cellular damage in the liver by induction of TLR4-TRIF immune responses in the Kupffer cells.

Evidence has also suggested that chemokines are active in mediating alcohol-related cellular damage in the liver. Barnes and coauthors investigated the activity of one chemokine, macrophage migration inhibitory factor (MIF), as a potential mediator of liver damage. Wild-type mice and mice who were genetically altered so that MIF was absent were fed ethanol-enriched diets. After four days of feeding, liver enzymes were elevated in wild-type mice, but not in MIF-negative mice. Apoptosis and complement activation occurred in both types of mice, but secretion of tumor necrosis factor was observed only in wild-type mice. With long-term feeding, wild-type mice showed increased sensitivity of liver cells to endotoxin, but MIF-negative mice did not. The authors concluded that MIF is an important mediator of cellular damage that is induced in the liver by exposure to ethanol.

Given the role of gut-produced endotoxin in alcohol-induced liver injuries and additional data that has confirmed increased intestinal permeability that permits movement of endotoxin from the gut into the portal circulation, interest in the role of maintaining normal gut microbiota as a potential means of reducing endotoxin-associated liver damage has increased. A research study that examined the role of the gut microbiota in reducing endotoxin-associated liver damage was by Chen and coauthors\textsuperscript{15} in *Alcoholism Clinical and Experimental Research*, 2015. Acute alcohol exposure was produced in germ-free mice and in mice with normal gut microbiota. Germ-free mice showed significantly greater liver damage after alcohol exposure. Of interest was that metabolism of alcohol
within the liver was increased in germ-free mice. This led the authors to hypothesize that loss of normal gut microorganisms during exposure to alcohol might contribute to stimuli that produce binge drinking.

Another study that examined a potential therapeutic pathway to attenuate endotoxin-induced liver damage was by Gong and coauthors16 in the Journal of Surgical Research, 2013. The authors hypothesized that induction of endotoxin tolerance would reduce endotoxin-associated liver damage through attenuation of the glycogen synthase kinase 3 (GSK-3) inhibitor. Two groups of rats were studied; one group had received prior small doses of endotoxin to produce endotoxin tolerance. Both groups then received large doses of endotoxin. The results showed that the endotoxin-tolerant animals had attenuation of the GSK-3 inhibitor and significantly reduced liver damage. The authors concluded that endotoxin is an important mediator of liver damage and that the extent of damage can be reduced by induction of endotoxin tolerance.

Roh and coauthors17 presented data on the role of the innate immune system in alcohol-related liver damage in the American Journal of Physiology-Gastrointestinal and Liver Physiology, 2015. In this research study, the authors examined the effects of a binge-drinking model of ethanol administration in wild-type mice and in mice that were deficient in TLRs of the innate immune system. The results of the experiment confirmed reduced liver injuries in the TLR-deficient mice. In addition, secretions of neutrophil recruitment mediators were reduced in the TLR-deficient mice. Data from the experiment also showed the participation of Kupffer cells and stellate cells of the innate immune system in mediating the liver damage in wild-type mice. The authors concluded that the innate immune system is active in the production of liver damage due to ethanol intake patterns that resemble binge drinking.

Tumurbaatar and coauthors18 reported on the combined effects of hepatitis C and alcohol intake on mediators of liver cell damage in the American Journal of Pathology, 2013. The authors noted that one mechanism of liver cell damage due to hepatitis C combined with alcohol intake is enhanced oxidative stress. The transcription factor FOXO3 functions to reduce oxidative stress and may be protective against liver cell damage. They fed alcohol to mice who were genetically altered to prevent elaboration of the transcription factor. After three weeks, one-third of the animals showed severe liver damage. In cell culture of liver cells, the combination of hepatitis C and alcohol caused loss of transcription factor activity. The authors concluded that the FOXO3 pathway is a potentially useful therapeutic target for treating alcohol and HCV-induced liver damage.

An additional discussion of risk factors for alcoholic liver disease and potential genetic influences was presented in an article by Gao and Bataller19 in Gastroenterology, 2011. The authors noted that female gender, obesity, drinking patterns (daily heavy alcohol intake beginning at a young age), and associated liver disease (viral hepatitis) are factors that increase the risk of liver disease progression. Of interest is that high caffeine intake has a protective effect on the liver. Research into genetic alterations that may be associated with liver disease progression has increased recently, but no specific alterations have been identified. The main therapies for alcoholic liver disease include behavior modification approaches, group therapy, and psychotherapy designed to eliminate alcohol consumption.

**Hepatic Cirrhosis**

Cirrhosis is the condition that leads to clinical evidence of liver decompensation in patients with liver damage due to hepatitis, alcohol, and NAFLD. An article that provided a useful overview of cirrhosis as a disease entity was by Tsochatzis and coauthors20 in The Lancet, 2014. The authors noted that cirrhosis is the 14th most common cause of death worldwide and the fourth most common cause in Europe. They emphasized that the mortality risk due to cirrhosis varies depending on the stage of the disease. Early stage cirrhosis is associated with a 1% one-year mortality risk and the risk rises to 57% in patients with advanced disease. The authors provided a clear description of the pathophysiology of the various clinical presentations of cirrhosis, including esophageal variceal hemorrhage, hepatic encephalopathy, and hepatopulmonary syndrome. They also included a useful flow chart that summarizes the mechanisms of the various clinical presentations. This chart is reproduced as Figure 2.

Abnormalities of platelets and coagulation proteins are commonly observed in patients with cirrhosis. The liver synthesizes clotting factors I, II, V, VII, and IX; reduced synthesis of these factors contributes to disordered
clotting in patients with liver disease. Measurement of prothrombin time and calculation of the International Normalized Ratio (INR) are commonly used to estimate the extent of abnormal hepatic synthetic function of clotting factors. Prothrombin time prolongation is also contributed to by abnormal Vitamin K metabolism associated with cirrhosis. The degree of prothrombin time prolongation is a key feature of hepatic disease severity scoring systems such as the Child-Turcotte-Pugh classification system and the Model for End-Stage Liver Disease (MELD) score. Bleeding from the gastrointestinal tract and from mucous membranes is commonly observed in patients with advanced liver disease. Bleeding may occur from esophageal varices and control of variceal hemorrhage may be challenging in patients with coagulopathy. Spontaneous bleeding from the gums and from mucosal surfaces of the gastrointestinal tract occurs because of hyperfibrinolysis that results from the downregulation of fibrinolytic inhibitors in the cirrhotic liver.

**Diagnosing Liver Disease**

Surgeons are important participants in the diagnostic process for patients with known or suspected liver diseases. For many patients with diffuse or localized liver disease, liver biopsy is the accepted gold standard for diagnosis. For example, for the patient who is discovered to have a liver tumor, distinguishing between a benign and a malignant lesion is important; when choosing whether and/or how to biopsy a suspected liver tumor, possible diagnostic interventions will include considering a laparoscopic biopsy. Likewise, the diagnostic sequence chosen to confirm the presence and severity of liver disease in a patient with a surgical problem involving the liver or other organs will require careful surgical risk assessment. In fact, many patients with clinically significant liver disease are asymptomatic or minimally symptomatic; because of this, liver disease is discovered frequently by screening laboratory and imaging tests that are performed for symptoms not associated with liver disease.
Medical History & Physical Examination

Traditionally, the diagnostic process begins with a careful medical history followed by a physical examination. With increasing frequency, the physical examination is supplemented by an assessment of liver size with a handheld ultrasound device. As sophisticated laboratory tests and imaging have become available, the value of the physical examination as a means of diagnosing liver disease has been questioned. This question was examined in a letter to the editor by Lenci and coauthors24 in Liver International, 2013. The authors compared liver stiffness assessments obtained from physical examinations performed by experienced hepatologists and from liver elastography results in 64 patients with liver disease and 10 healthy volunteers. The data showed that assessments obtained by physical examination were highly correlated with assessments by elastography. The authors concluded that physical examination supplemented, when necessary, by additional laboratory and imaging studies provides useful and dependable information for assessing liver disease.

As noted previously, handheld ultrasound evaluations for determining liver size are used increasingly. An article that focused on the efficiency and value of teaching ultrasound evaluations of liver size to medical students was by Mouratev and coauthors22 in Teaching and Learning in Medicine, 2013. The authors trained 10 second-year medical students to determine liver size using ultrasound and a standard teaching protocol. Six patients volunteered to be examined by experienced physicians (who did not use ultrasound) and by the 10 trained medical students. The data showed that assessments of liver size by medical students using physical examination supplemented by ultrasound evaluation was consistently more accurate than physical examination alone performed by experienced clinicians. The authors concluded that physical examination supplemented by ultrasound evaluation is accurate and easily taught to medical students.

A summary of useful items that can be obtained from medical history and physical examination was provided in an article by Krier and Ahmed23 in Clinics in Liver Disease, 2009. This article is supplied as a full-text reprint accompanying some formats of SRGS. The authors stressed the importance of obtaining a history of both prescription and nonprescription drug use, particularly any history of herbal medicine use. In addition, travel history, sexual history, transfusion history, and history of tattoos are useful in estimating the risk of exposure to hepatitis, schistosomiasis, and malaria. Documentation of past and current alcohol use and exposure to hepatotoxins is also important. During the physical examination, discovery of hepatosplenomegaly, ascites, palmar erythema, spider angiomata, asterixis, bruising, and muscle wasting will add to evidence for a liver disease diagnosis.

In the World Journal of Gastroenterology, 2014, Torruellas and coauthors24 provided a summary of important medical history features when examining patients who may have alcohol-related liver disease. The authors presented useful historical and physical findings pertinent to the various stages of disease progression. Alcoholic fatty liver may present in an asymptomatic patient, in which case laboratory screening studies will be helpful. Patients may also present with anorexia, fever, and jaundice. Patients with compensated cirrhosis may experience weight loss, anorexia, weakness, fatigue, muscle cramps, amenorrhea, or loss of sexual drive; patients in this category may also have upper abdominal pain. Abdominal distention due to ascites may also be present, and a minority of patients will have proximal muscle weakness and confusion due to early encephalopathy. As cirrhosis progresses, jaundice, a history of gastrointestinal bleeding, and pruritus become more common. Clinical evidence of ascites along with lower extremity edema and bruises will often be found on physical examination.

For patients whose livers, biliary tracts, or other organs may require surgical treatment, it is important to know the extent and stage of liver disease. Udell and coauthors25 discussed strategies for detecting cirrhosis and quantifying the severity of liver disease in JAMA, 2012. This report described a systematic review of the literature that included 86 articles involving more than 19,000 patients. The article also discussed the pathogenesis of some of the physical signs of liver disease. Palmar erythema, spider nevi, decreased body hair, testicular atrophy, and gynecomastia are caused by disordered metabolism of androstenedione that is associated with the development and progression of cirrhosis. Abnormal androstenedione metabolism leads to elevated levels of estrogen in patients with liver disease. Bruising is contributed to by the suppression of the synthesis of clotting factors I, II, V, VII, IX, and X in the diseased liver. As noted previously, factors II, V, VII, and IX are also suppressed due to the disordered
metabolism of Vitamin K that is caused by the progression of cirrhosis. Jaundice and edema are caused by the liver’s abnormal processing of bilirubin and a suppressed synthesis of albumin. Esophageal varices, splenomegaly, peripheral edema, and ascites are formed and/or made worse by portal hypertension.

**Laboratory Testing**

Again, because many forms of liver disease are asymptomatic or minimally symptomatic, suspicion of disease is frequently raised by the discovery of abnormalities in various blood tests obtained when screening blood chemistries during routine examinations or preoperative preparations. Torruellas and coauthors\(^2\) recommended that patients being considered for an alcohol-related liver disease diagnosis have a complete blood count and their liver enzyme levels assessed; abnormalities of liver enzymes indicate that hepatitis B and C tests should be performed. In select patients, autoimmune hepatitis and hemochromatosis tests should also be considered.

Krier and Ahmed\(^3\) explained that the main laboratory tests used to diagnose liver disease are serum bilirubin, albumin, platelet count, prothrombin time (and INR), and the various transferase enzyme levels. They emphasized that the results of these blood tests make it possible to estimate the degree of cholestasis and hepatocellular injury. These authors also noted that most patients present with mixed patterns of abnormal blood tests that cannot be classified entirely into a single injury pattern. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are found to be abnormal in 3–4% of the general population, and evaluating patients with abnormal values for liver disease is a common clinical endeavor. The enzymes are located intracellularly, have both cytoplasmic and mitochondrial forms, and, as their names suggest, catalyze the transfer of alanine and aspartate to the alpha keto group of glutaric acid during the process of gluconeogenesis. Krier and Ahmed emphasized that these enzymes are found in multiple tissues, not just in the liver; therefore, abnormal levels may be due to thyroid disease and muscle disease as well as liver disease. Currently, the most common hepatic cause of mild enzyme elevations is probably NAFLD. High levels of enzymes occur with acute viral hepatitis and ischemic liver injuries. High levels can also be observed in the early stages of biliary obstruction. Very high levels (more than 1,000-fold increase over normal) are typically seen in toxic liver injuries (acetaminophen ingestions) and severe liver ischemia. Krier and Ahmed stressed that transaminase enzyme levels, by themselves, and the extent of liver disease detected by liver biopsy correlate poorly; for example, abnormally low levels of AST and ALT can be observed in the late stages of cirrhosis. Alkaline phosphatase is another enzyme that is present in many tissues other than the liver. It is elevated in the early stages of biliary obstruction. An additional enzyme that can be assayed is Gamma glutamyl transaminase; abnormal levels of this enzyme are not sufficiently specific enough to be helpful in diagnosing or quantifying liver disease. Krier and Ahmed noted that prothrombin time and albumin levels are markers of hepatic synthetic function. Bilirubin occurs in unconjugated (indirect) and conjugated (direct) forms: elevation of unconjugated bilirubin suggests increased hemoglobin production (hemolysis) or suppression of hepatic conjugation function, while elevation of conjugated bilirubin occurs when bile outflow is obstructed.

Carey and Carey\(^4\) discussed laboratory studies that are valuable in the noninvasive diagnosis of liver fibrosis and cirrhosis in the Cleveland Clinic Journal of Medicine, 2010; their article is supplied as a full-text reprint accompanying some formats of SRGS. The authors noted that the development of liver fibrosis that progresses to cirrhosis proceeds in several stages. Initially, fibrosis is restricted to the portal triads. As the disease progresses, fibrosis extends to periportal areas, then cirrhotic nodules begin to connect the portal areas. When frank cirrhosis develops, islands of hepatocytes are completely surrounded by fibrous tissue. “Routine” hepatic blood tests can suggest the presence of fibrosis/cirrhosis, but these findings are nonspecific. The authors provided a valuable website that discusses liver blood tests: www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/hepatology/guide-to-common-liver-tests. Several scoring systems that use transaminase levels, platelet counts, patient age, gamma globulin levels, and prothrombin times are useful for predicting advanced fibrosis and cirrhosis. The scores vary depending on the etiology of the liver disease. Direct blood tests for liver cirrhosis assay for metabolites associated with the scarring process, such as matrix metalloproteinases, procollagen
type three amino terminal peptide, laminin, hyaluronic acid, and collagen types I and IV. The authors noted that added accuracy is provided by imaging studies. This topic will be reviewed in the next section.

Udell and coauthors evaluated the data in supporting literature to determine methods of accurately predicting cirrhosis. The presence of ascites and spider nevi were physical signs suggestive of cirrhosis. Thrombocytopenia was the most dependable laboratory test. Two available scoring systems—the Boncini score (score >7 highly suggestive of cirrhosis) and the Lok index (index <0.2 suggestive of no cirrhosis)—were also dependable in documenting the presence or absence of cirrhosis. These scoring systems (illustrated in Figure 3) use INR, platelet count, and the ratio of AST to ALT.

Liver Imaging

The most commonly employed imaging modalities for detecting liver lesions and diagnosing the presence and extent of chronic liver disease are radioscintigraphy, ultrasonography, computerized tomographic (CT) imaging, and MRI. In selected patients with primary or metastatic malignancy of the liver, positron emission tomography combined with CT imaging (PET-CT) may assist with staging the malignancy by providing an accurate assessment of nodal basins in the abdomen and thorax. Numerous reports attest to the accuracy and overall value of imaging studies. Despite this, there are pitfalls in liver imaging that need to be kept in mind; these are reviewed in an article by Vilgrain and coauthors in *Radiology*, 2016. The authors noted that imaging findings, including a nodular liver surface, atrophy of the right lobe, and hypertrophy of the left lobe, are commonly thought to be diagnostic of cirrhosis. However, portal venous obstruction and biliary obstruction may cause atrophy and hypertrophy of the liver lobes that mimic the findings in cirrhotic patients. Hepatic venous obstruction may also cause lobar atrophy. The authors emphasized that examining the relationships of hepatic neoplastic lesions to hepatic arteries and veins can help determine whether the lesion arises from the liver or is a metastatic lesion. There are also lesions that mimic tumors, but are actually fibrous lesions or inflammatory lesions. In most instances, lesions that appear to be neoplastic on CT imaging can be differentiated using MRI and liver-specific contrast agents.

### Imaging for Fibrosis & Cirrhosis Diagnoses

Carey and Carey noted that specific modifications of ultrasonography instruments and magnetic resonance technology have been developed to quantify the extent of fibrosis and cirrhosis. Both techniques depend on the measurement of stiffness in the liver tissue by assessing the response of the liver to a transmitted pressure wave. Ultrasound elastography is used in many parts of the world, but at the time that Carey and Carey’s article was published, the device was not approved for use in the United States. The device can dependably diagnose the presence of cirrhosis. The sensitivity for diagnosis of lesser degrees of fibrosis...
varies from 70% to 84% according to data cited in the article. Specificities range from 84% to 94%. The device is most helpful in diagnosing and staging liver disease severity in patients with hepatitis C. Ultrasound elastography is of limited value in obese patients and patients with metabolic syndrome.

Additional data on using ultrasound examinations to diagnose hepatic fibrosis are included in an article by Bonekamp and coauthors in the *Journal of Hepatology*, 2009. These authors reported a systematic literature review that examined 125 articles. The data were relevant to Doppler ultrasonography, contrast-enhanced ultrasonography, and ultrasound elastography. All techniques were relatively dependable in diagnosing cirrhosis, with positive and negative predictive values ranging from 78% to 94%, depending on the report. For diagnosing lesser degrees of fibrosis, only ultrasound elastography demonstrated sensitivity and specificity exceeding 70%. This report confirmed the superior performance of ultrasound elastography in patients with hepatitis C and the limitations of the technique in obese patients and in patients with metabolic syndrome. In a review by Schwenzer and coauthors, data was cited that suggest ultrasound assessments of hepatic fibrosis are also limited by inter-operator variability. All of the reports agreed that the main advantages of ultrasound imaging are availability, ease of obtaining repeated examinations, and the immediate availability of real-time results. These characteristics make this modality particularly valuable for determining the presence of severe steatosis in potential liver donors.

Carey and Carey found that MRI has significant potential for accurately diagnosing hepatic fibrosis along the entire continuum of progression. They reviewed data relevant to magnetic resonance elastography that confirmed sensitivity and specificity of 93% and 84%, respectively, for this technique in discriminating mild fibrosis from more severe forms. They noted that the main drawback of this technique is its cost. Data presented by Bonekamp and coauthors and Schwenzer and coauthors also confirmed the accuracy of magnetic resonance elastography in diagnosing hepatic fibrosis.

**Imaging for Hepatic Neoplasm Diagnoses**

The common benign tumors encountered by surgeons include hepatic hemangiomas and adenomas, while the common malignant lesions are metastatic tumors (mostly from colorectal and neuroendocrine primary tumors), cholangiocarcinomas, and hepatocellular cancers. A detailed discussion of the biology and surgical management of benign and malignant tumors of the liver will be presented in SRGS’ second and third issues of its liver series.

Because surgical resection presents the only opportunity to cure most hepatic neoplasms, accurate imaging is necessary to help stage the lesion(s) and to obtain detailed anatomic information to make lesion resection safer. In this section, we will discuss the value of imaging technologies in diagnosing and managing common malignant lesions of the liver.

Sahani and coauthors reviewed imaging approaches for metastatic lesions of the liver from colorectal cancers in *Annals of Surgery*, 2014. This article is supplied as a full-text reprint accompanying some formats of SRGS. According to the authors, colorectal cancer is the third most common cancer among Americans, and liver metastases are present at the time of initial diagnosis in up to 30% of patients. Although ultrasound imaging of the liver is inexpensive and widely available, the sensitivity and specificity of ultrasonography for the characterization of liver metastases is low. Data cited by the authors suggested that adding microbubble intravascular contrast material may increase the accuracy of diagnostic ultrasounds. On the other hand, intraoperative ultrasonography is a valuable adjunct for identifying small lesions and documenting relationships between lesions and hepatic vascular and biliary ductal systems. The authors emphasized that multidetector CT (MDCT) imaging is useful for vascular mapping, detecting extrahepatic lesions, and estimating liver volume. In addition, MDCT is widely available and relatively inexpensive. Limitations of MDCT imaging include its limited ability to detect small lesions and its poor accuracy in patients with steatosis, especially when the steatosis is induced by chemotherapy. Allergy to contrast media and impaired renal function may also limit the utility of MDCT.
Compared with MDCT, contrast-enhanced MRI (CE-MRI) is more sensitive and specific in identifying small metastases. Sensitivities for CE-MRI exceed 80% and specificities approach 97% according to data cited by the authors. MRI is limited because it cannot be used for claustrophobic patients, and CE-MRI cannot be used in patients with impaired renal function. Diffusion-weighted MRI is useful in patients with allergies or impaired renal function since contrast media are not needed. Data cited by the authors confirmed that PET-CT imaging is useful for identifying extrahepatic disease, but is a costly test that does a poor job detecting small lesions after chemotherapy.

Neikel and coauthors \(^3^1\) analyzed the comparative value of various imaging modalities for metastatic liver lesions in *Radiology*, 2010. These authors conducted a systematic review of the literature and found 36 studies that met their quality standards. The data disclosed that MRI is the most dependable first-line means of imaging metastatic lesions; its main advantage is its ability to accurately image lesions less than 10 mm in diameter. Also, as noted in prior discussions, MRI provides superior anatomic information for planning resection procedures.

Gakhal and coauthors \(^3^2\) presented an overview of diagnostic imaging for biliary malignancies in *Surgical Oncology Clinics of North America*, 2009. The authors began by defining the two objectives of imaging hepatic malignancies: to display the lesions clearly and to stage the malignancy accurately. Barriers to curative resection include extensive invasion of biliary ducts in more than one lobe of the liver, and invasion or encasement of hepatic arterial branches and portal venous branches in more than one liver area. Vascular invasion often leads to atrophy of a portion of the liver and documenting this is an important aspect of staging. A table listing the critical information to be obtained from image interpretation is supplied in the article and is reproduced as Figure 4.

Gakhal and colleagues recommended CE-MRI as the most accurate and comprehensive imaging approach for hepatic tumors. The authors also cited steady improvements in MRI quality. To achieve maximum quality, the patient must be able to perform an adequate breath-hold maneuver. If this is not possible, CT imaging is the preferred alternative. The authors cited data confirming accuracies of 90% or more for determining tumor status and delineating bile duct invasion. The data indicated that, compared with cholangiography, MRI determines bile duct invasion more accurately. MRI is also superior to angiography and portal venography for documenting vascular invasion by tumors; cited data confirmed accuracies in the 90% range.

Gakhal and colleagues next reviewed the utility of CT imaging. They noted that the invasion of adjacent tissue is accurately displayed on multi-slice CT images, but documentation of extended biliary ductal involvement by cholangiocarcinoma is not demonstrated with the same accuracy as MRI. Data presented in the article indicated that ultrasound is a valuable first-line study for determining the cause of bile duct obstruction, but that it is not as accurate as CT or MRI for staging and documenting vascular and biliary ductal involvement. Similarly, PET-CT is not accurate enough to provide good staging and invasion information; this type of imaging is better for documenting the characteristics of intrahepatic cholangiocarcinoma, since these lesions are usually larger than extrahepatic cholangiocarcinomas at presentation. The authors added that PET-CT images may provide information on distant metastases that preclude curative resection.
Imaging is valuable in diagnosing, staging, and operative planning for patients with hepatocellular carcinoma. This topic was discussed in an article by Outwater in Cancer Control, 2010. The author reviewed data that confirmed the value of ultrasound as an initial screening modality for patients suspected of having hepatocellular carcinoma. Ultrasound is also valuable for guiding percutaneous biopsy and interventions, as well as documenting important anatomic information during hepatic resection. The main value of CT imaging in patients with hepatocellular cancer is to demonstrate metastatic foci outside of the liver in the abdomen and in the chest. Additionally, CT images are useful for monitoring the progress of lesions treated with chemotherapy and/or radiofrequency ablation. The author provided data confirming MRI’s superiority in determining the precise anatomic characteristics of the tumor and assisting with planning for resection. Additional discussion on the use of imaging in the management of hepatocellular cancer was presented by Ayyappan and Jhaveri in Expert Reviews in Anticancer Therapy, 2010. Interested readers are encouraged to review the content of this article.

**Indications for Liver Biopsy**

Traditionally, liver biopsy has been contemplated for patients with clinical evidence suggesting liver disease or liver neoplasia. However, liver biopsy is expensive (> $1,000.00), carries a risk of complications (bleeding, bile leak), and is subject to sampling error, and these drawbacks have stimulated interest in developing noninvasive means of diagnosing liver disease and quantifying disease severity. A discussion of the contemporary use of needle biopsy of the liver, including an overview of the current status of noninvasive diagnostic methods, is found in the article by Carey and Carey. They indicated that liver biopsy continues to be a valuable adjunct to diagnosis in patients with coexisting disorders (hepatitis C and HIV), overlapping diagnoses (primary biliary cirrhosis and autoimmune hepatitis), and where there is significant diagnostic uncertainty. Liver biopsy is also helpful in quantifying the severity of liver disease, especially in patients with steatosis or who need their liver’s histologic changes to be monitored (e.g., post-liver transplant). The authors then acknowledged various problems with liver biopsy: cited data indicated frequent reports of pain after liver biopsy, serious bleeding, and bile leakage. Sampling error was a significant problem as well—Carey and Carey shared data from a study of laparoscopy-guided liver biopsy in patients with chronic hepatitis C; when both right and left lobes of the liver were biopsied, results were significantly different in nearly 25% of patients.

**Assessing Operative Risk in Patients with Liver Disease**

Surgeons will be asked to advise patients with liver disease and indications for surgical procedures involving the liver or other organs. Fortunately, methods for determining operative risk and predicting the outcome of operative procedures have improved. In this section, we will discuss articles that deal with quantifying operative risk in patients with liver disease. Available scoring systems such as the Child-Pugh score and the MELD score have been used to estimate operative risk in patients with variceal hemorrhage and in patients who are candidates for liver transplantation; data relevant to these scoring systems will be reviewed in a later section.

**Liver Failure in Noncirrhotic Patients**

In the Journal of the American College of Surgeons, 2007, Mullen and coauthors reviewed patient data in order to develop a method for predicting liver failure in noncirrhotic patients undergoing major hepatectomy. This article is supplied as a full-text reprint accompanying some formats of SRGS. The authors reviewed outcomes on 1,059 patients who underwent major hepatic resection (3–4 liver segments). The patients were cared for in three tertiary centers over a 10-year interval. Complications occurred in 43% of patients. Mortality at 90 days was 4.7%. The authors stressed that this mortality rate was 47% higher than the 30-day mortality rate; this finding serves to place necessary emphasis on using mortality rates out to at least 90 days to better provide patient’s with...
accurate prognostic information. Postoperative mortality was due to liver-related causes in 2.8% of patients, and due to nonliver-related causes in 1.9% of patients. The authors reviewed several postoperative test results and used areas under the receiver-operator curve to determine which results were most predictive of liver-related death. The data analysis showed that peak bilirubin levels of 7.0 mg/dl were the most accurate predictors of liver failure that led to mortality. Other factors that were associated with an increased risk of postoperative complications and patient death were older age, performance of additional procedures at the time of hepatectomy, and perioperative transfusion. Mullen and coauthors concluded that peak postoperative bilirubin levels could be used to predict liver failure and death in noncirrhotic patients undergoing major hepatectomies.

**Risk Factors for Perioperative Mortality**

In patients undergoing hepatectomy, it is also important to consider patient characteristics that have been identified as risk factors for perioperative mortality and morbidity, such as obesity and preoperative malnutrition. Langella and coauthors\(^3^6\) analyzed outcomes data on obese patients who underwent liver resection procedures in *Surgery*, 2015. The authors reviewed outcomes data on 1,021 patients who underwent liver resection in a single institution over a 15-year interval. Using a standard definition of obesity (BMI ≥30), the authors identified 140 patients for outcomes analysis. The data analysis showed that obese patients were more likely to be male (78%) and were significantly more likely to have associated hypertension, diabetes, and ischemic heart disease compared with nonobese patients. In addition, operative time was longer for obese patients and the risk of perioperative transfusion was significantly higher compared with nonobese patients. The frequency of additional procedures was equivalent in obese and nonobese patients. Mortality rates were not different in the two groups, but postoperative morbidity was higher in obese patients, mainly due to increased frequency of pulmonary complications. Older age was an independent predictor of severe complications in obese patients. As in other reports, age, increased blood loss, and additional procedures were predictive of morbidity in both obese and nonobese patients. The authors concluded that preoperative interventions to improve pulmonary function can possibly help reduce operative complications in obese patients.

Preoperative malnutrition has also been associated with increased operative risks in a variety of surgical settings. In the *British Journal of Surgery*, 2015, Levolger and coauthors\(^3^7\) reviewed outcomes data on patients with preoperative evidence of malnutrition who underwent hepatic, pancreatic, and biliary operations. This article is supplied as a full-text reprint accompanying some formats of *SRGS*. The authors performed a systematic review of available literature using standard analytic approaches. The review process identified 13 observational studies of sufficient quality for inclusion. Malnutrition was identified when patients had evidence of muscle mass loss (presence of sarcopenia identified on CT imaging). Frequency of malnutrition varied widely in the included articles (17%–79%); this variation was likely due to the focus of the individual study. Malnutrition tripled the operative mortality risk for liver procedures. In patients operated on to cure their cancer, malnutrition decreased overall survival and was associated with increased tumor recurrence rates. The authors concluded that using CT imaging to identify sarcopenia will help estimate operative risk increases due to malnutrition. Additional research is needed to confirm whether or not preoperative nutritional support could improve operative risk.

Another article focusing on operative risk in patients with liver disease was by Frye and Perri\(^3^8\) in *Expert Review in Gastroenterology and Hepatology*, 2009. The authors opened their discussion by presenting data estimating the frequency of abnormal transaminase levels in the general population; they noted that some estimates of this frequency have approached 10%. Additional data was cited that suggested patients with modest (less than twice normal levels) elevations of liver enzymes in the absence of evidence of acute hepatitis, ascites, encephalopathy, jaundice, and abnormal liver synthetic function are not at an increased risk of mortality and morbidity for elective operations.

Operative risk is also high in patients with advanced liver disease, especially with clinical evidence of acute hepatitis. Frye and Perri cited data from a 1963 study of patients who underwent exploratory laparotomy for the evaluation of jaundice and were found to have acute viral
hepatitis. Mortality was 9.5% in this group of patients and major complications were recorded in more than 11% of patients. Data from a group of patients who underwent abdominal operations during episodes of alcoholic hepatitis recorded a mortality rate of more than 30% and all deaths were due to liver failure. Of interest is that patients who underwent portal-caval shunt operations for bleeding esophageal varices during episodes of acute alcoholic hepatitis did not have a mortality risk significantly higher than patients with cirrhosis (but without alcoholic hepatitis) who underwent portal-caval shunt operations. This observation is possibly due to the fact that surgical shunts (but not transjugular intrahepatic shunts) for portal hypertension may increase hepatic nutrient blood flow (according to a recently published article).

**Surgical Risks in Cirrhotic Patients**

Frye and Perri discussed potential causes of increased surgical risk in patients with cirrhosis. They listed common surgical complications encountered in this patient group: excess bleeding, cardiac dysfunction, hepatic encephalopathy, infection, poor wound healing, development of ascites, and renal dysfunction. Excess bleeding may be due to thrombocytopenia, deficiencies of clotting factors synthesized by the liver, and/or injury to thin-walled veins that are enlarged due to portal hypertension. Frye and Perri cited data supporting the presence of increased circulating blood volume and vasodilation in patients with cirrhosis; this condition worsens as severity of liver function progresses. While there is hyperdynamic cardiac function in cirrhotic patients, detailed studies have disclosed systolic and diastolic dysfunction that worsens with the progression of cirrhosis. Cirrhotic patients are, therefore, at an increased risk for cardiac dysrhythmia and congestive cardiac failure in the perioperative period. Hepatic encephalopathy can be precipitated or worsened by the effects of anesthetic drugs, analgesics, and sedatives administered perioperatively. The authors cited data indicating that postoperative infection risk increased more than 11-fold compared to surgical patients without cirrhosis. Hypoalbuminemia and susceptibility to infection contributes to poor wound healing, and the development or worsening of ascites can increase the risk of abdominal wound dehiscence. Postoperative renal dysfunction usually presents as prerenal azotemia or renal failure associated with antibiotic therapy or sepsis. The authors recommended careful monitoring of fluid volume status and renal function in the perioperative period.

Frye and Perri went on to discuss methods of predicting mortality and morbidity for patients with cirrhosis who require surgical intervention. The type of operation needed is a main driver of risk. For example, data are available that disclose a very low mortality risk for elective repair of umbilical hernia in cirrhotic patients. Also, laparoscopic cholecystectomy is a safe intervention for symptomatic cholelithiasis in patients with cirrhosis. Cardiac surgery, on the other hand, is associated with a significantly increased mortality risk in patients with cirrhosis.

**Predictive Scoring Systems**

As mentioned earlier, predictive scoring systems for patients with cirrhosis include the Child-Turcotte-Pugh and the MELD scoring systems. Frye and Perri noted that the Child-Turcotte-Pugh score was introduced in 1973 as a means to predict outcomes of esophageal transection for the treatment of bleeding esophageal varices; this score is illustrated in Figure 5. The score awards points based on severity assessments of encephalopathy and ascites and objective abnormalities of hepatic function tests. Cumulative scores then place patients in groups of increasing liver disease severity (A, B, and C). Critics of
the Child-Turcotte-Pugh system have targeted the first two components because they require a clinician’s subjective judgment.

The MELD score is illustrated as Figure 6. The MELD scoring system is calculated from a formula based on the serum creatinine, serum bilirubin, and the INR. This scoring system is currently used to determine placement on the UNOS waiting list for liver transplantation, and has the advantage of being completely objective.

Assessments of hepatic blood flow and hepatic clearance function are popular in European liver surgery centers. The most common test performed is the indocyanine green clearance test. The available tests are reviewed in an article by Morris-Stiff and coauthors40 in the Journal of Gastrointestinal Surgery, 2009. They noted that the normal retention of indocyanine green at 15 minutes after injection is 3%–10% (clearance of 90%–97%). Data from several reports investigating the predictive value of the test in assessing hepatic resection risks indicated that retention at 15 minutes of less than 20% was associated with acceptable mortality risk for major hepatic resection. Retention of less than 40% indicated that enucleation of a liver lesion could be safely undertaken, but that mortality risk for major hepatic resection would be excessive. Frye and Perri38 noted that the main barrier to using indocyanine green clearance testing in the United States is the lack of the test’s availability.

The article by Frye and Perri presented data from several studies on outcomes of operations in patients with cirrhosis. Outcomes were predicted with equal accuracy for the Child-Turcotte-Pugh and MELD scoring systems. Child-Turcotte-Pugh classification C and a MELD score of 17 or more predicted excessive mortality risks that would consistently discourage an operation. Low mortality was predicted by Child-Turcotte-Pugh class A and a MELD score of eight or less. Elective and most emergency operations can be safely undertaken in the low-risk patient group, with anticipated mortality risk equivalent to patient groups without cirrhosis. Most cited reports support the conclusion that Child-Turcotte-Pugh classification B patients with a MELD score of 9–18 will have an acceptable mortality risk for elective operations of low physiologic impact (laparoscopic cholecystectomy, elective hernia repair) and an increased mortality risk for elective higher impact operations (cardiac and vascular procedures, hepatic resection) and for most emergency procedures. Additional data cited by Frye and Perri confirmed the importance of patient age and overall operative risk assessment using scores such as the ASA score for predicting outcomes of surgical procedures in liver disease patients. Studies comparing the predictive accuracy of the Child-Turcotte-Pugh class and MELD score systems have not demonstrated the superiority of one score over the other.

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Additional discussion of the preoperative evaluation of patients with liver disease was by Martin41 in the Cleveland Clinic Journal of Medicine Supplement 4, 2009. This article is supplied as a full-text reprint accompanying some formats of SRGS. The discussion in this article presented clear descriptions of the clinical progression of liver disease and the meaning of various degrees of liver decompensation for prediction of operative outcomes. Effects of various anesthetic agents on liver blood flow and metabolism were also discussed, and Martin presented data that supported assessing multiple risk factors, including the Child-Turcotte-Pugh class and MELD score; he included a table that is reproduced as Figure 7. A multivariate analysis of various risk factors’ impacts on surgical complications associated the presence of one risk factor with a risk of less than 10%. Risk of complications rises to more than 30% with three risk factors and approaches 100% with seven or eight risk factors.
Surgical Complications of End-Stage Liver Disease

Complications of advanced liver disease commonly encountered by surgeons include bleeding esophageal varices (to be discussed in a subsequent issue of SRGS), gallstone disease, ascites, and complicated umbilical hernia in patients with ascites.

Diagnosing & Managing Ascites

The onset of ascites that is detectable on physical examination is an important sign that cirrhosis has progressed to an advanced stage. Surgeons will be asked to assist in managing patients with complications of ascites, including complicated umbilical hernia. Patients with ascites are also vulnerable to spontaneous bacterial peritonitis. When this diagnosis is considered, other causes of peritonitis will need to be excluded and surgeons will be involved in this process.

Hou and Sanyal\(^{12}\) provided a helpful review of the pathophysiology of ascites in the Medical Clinics of North America, 2009. They emphasized that the primary cause of ascites is resistance to portal flow in the liver due to cirrhosis. Splanchnic vasodilation occurs because of multiple factors, including the local elaboration of nitric oxide and other vasodilator substances. Bacterial translocation occurs from the intestine to mesenteric lymph nodes, and this process stimulates release of vasodilating cytokines. Splanchnic vasodilation results in increased lymph production in the mesentery and liver. When this production overcomes the ability to release the lymph into the circulation, ascites is aggravated. Finally, splanchnic vasodilation causes reduced central blood volume, and this factor causes activation of the renin-angiotensin system, resulting in reduced urine production and additional fluid retention that also contributes to ascites formation.

When physical examination findings suggest the presence of ascites, other stigmata of liver disease should be sought. Mild forms of ascites are detectable by abdominal ultrasound. A clinical grading system of ascites promulgated by the International Ascites Club was presented in the review by Hou and Sanyal and is reproduced as Figure 8. Paracentesis with examination of the ascitic fluid is a useful procedure (in patients without coagulopathy) to exclude bacterial peritonitis and to help determine the cause of ascites.

When medical management and large volume paracentesis fail to control ascites, options include using surgical shunts to eliminate portal hypertension. Less invasive approaches include peritoneal-venous shunts. The complications of peritoneal-venous shunts, such as disseminated intravascular coagulation, infection, and subclavian vein occlusion, have greatly limited the value of this intervention.

In the review article by Tsochatzis and coauthors,\(^{20}\) the authors provided an overview of the pathophysiology of ascites, along with recommendations for preventing and managing the complications of this condition. The illustration they included that summarizes essential steps in managing ascites is reproduced as Figure 9.

<table>
<thead>
<tr>
<th>Factors independently predictive of complications and mortality in cirrhotic patients undergoing surgery*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictors of complications</td>
</tr>
<tr>
<td>Child-Pugh class B or C</td>
</tr>
<tr>
<td>Asites</td>
</tr>
<tr>
<td>Etiology of cirrhosis other than primary biliary cirrhosis</td>
</tr>
<tr>
<td>Elevated creatinine</td>
</tr>
<tr>
<td>Preoperative infection</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Preoperative upper GI bleeding</td>
</tr>
<tr>
<td>Invasiveness of surgical procedure</td>
</tr>
<tr>
<td>Intraoperative hypotension</td>
</tr>
</tbody>
</table>

*According to multivariate analysis in a retrospective study of 733 patients.\(^{1}\) COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; ASA = American Society of Anesthesiologists.
Complicated Umbilical Hernia in Patients with Ascites

As noted above, surgeons will be faced with the challenge of dealing with complicated umbilical hernias in patients with tense ascites. In SRGS Vol. 41 No. 7, a detailed discussion of the management of common hernias was presented, and readers are encouraged to review that information. It is evident from the data available that outcomes for elective mesh repair of umbilical hernias in patients with ascites have improved and rates of mortality and morbidity approach those obtained in patients without liver disease. Transjugular intrahepatic portosystemic shunt (TIPS) is a useful method for managing ascites in patients when medical therapy fails to control it, though there is an inevitable delay in resolution of ascites after TIPS. When hernia complications occur, such as ascitic leakage and skin necrosis, these problems can be managed with local wound care until control of ascites with TIPS and elective hernia repair can take place. Ideally, TIPS should precede hernia repair. In umbilical hernias with severe complications, such as incarceration with necrotic bowel or extensive skin necrosis, emergency debridement and repair may be necessary, followed by postoperative TIPS.

Surgical Anatomy of the Liver

Successful surgical management of liver trauma, neoplasms of the liver, and liver transplant procedures requires a clear understanding of the anatomy of the liver, associated vascular structures, the biliary tract, and the ligamentous attachments. In this section, we will discuss two current review articles that focused on the surgical anatomy of the liver.

The first article was by Abdel-Misih and Bloomston in the Surgical Clinics of North America, 2010. This article is supplied as a full-text reprint accompanying some for-
mats of SRGS. The authors opened their discussion with the importance of the contributions of Couinaud to the understanding of the lobar and sub-lobar anatomy of the liver, as well as the classic contributions of Bismuth that have provided the anatomic foundations of current approaches to liver resection. The Bismuth article in the World Journal of Surgery, 1982, was a classic review of the foundations of modern hepatic surgery based on the functional anatomy of the liver. Bismuth credited Cantlie; McIndoe and Counseller; Ton That Tung; Couinaud; and the work of Goldsmith and Woodburne for contributing to the success of modern hepatic surgery. Bismuth chose to utilize, mainly, the work of Couinaud as a basis for the anatomic knowledge that leads to successful hepatectomy. Bismuth observed that the liver is divided into right and left hemi-livers by the main scissura or Cantlie’s line. Cantlie’s line runs from the gallbladder bed to the left side of the inferior vena cava; this line is at an angle of 75° with the horizontal. The right scissura, which contains the right hepatic vein, courses from the anterior surface of the liver to the right side of the inferior vena cava and describes an angle of 40° with the horizontal; both of these angles open to the left. The middle hepatic vein lies in the main scissura. Bismuth pointed out that the right hepatic vein runs into the right scissura, which lies along a line midway between the right margin or the liver and the right side of the gallbladder bed (according to Couinaud), and is three fingerbreadths anterior to a line describing the right margin of the liver (according to Ton That Tung). Abdel-Misih and Bloomston emphasized that IOUS has made locating the hepatic veins within these scissures easier and more precise for hepatic surgeons. Their review article contains helpful anatomic drawings that demonstrate the vascular, biliary, and ligamentous structures of the liver and their courses within the hepatic lobes. Readers are encouraged to review this information. Bismuth explained that the left hepatic vein courses within the left scissura and that this area is distinct from the umbilical fissure. He also noted that the umbilical fissure contains a portal pedicle and the left hepatic vein courses dorsal to the umbilical fissure behind segment 4 and between segments 2 and 3.

Using these anatomical definitions, right and left hemihepatectomy resections of the liver are done along Cantlie’s line that extends from the right border of the gallbladder fossa to the inferior vena cava. This anatomy is illustrated in the article. Bismuth expressed his belief that the terms “left lobectomy” and “right lobectomy” lead to confusion since, in terms of the morphologic anatomy of the liver, the right and left lobes are demarcated by the umbilical fissure and not by Cantlie’s line. Bismuth stated his preference of the terms right and left hepatectomy for the sake of precision.

Abdel-Misih and Bloomston provided a concise description of the relationships of the hepatic vasculature and the biliary tract within the porta hepatii. Control of the hepatic hilar structures is accomplished by taking advantage of the anatomic connection of the main and lesser peritoneal sacs represented by the foramen of Winslow. Blunt dissection of this opening permits, and the gastrohepatic ligament facilitate, encircling of the porta hepatii structures with a tourniquet so that occlusion can occur if necessary. After division of the right and left triangular ligaments, the bare area of the liver is exposed and control of the inferior vena cava just caudal to the diaphragm can be obtained with a tourniquet tape. Dissection dorsal to the porta hepatii exposes the inferior vena cava below the liver. After control of these primary vascular structures, dissection of the arteries, portal veins, and hepatic veins relevant to the portion of the liver to be resected can be accomplished. Control of the vasculature prior to parenchymal transection helps to minimize bleeding during transection. An additional positive feature of pretransection vascular control and division is that discoloration of the liver provides a guide for the surgeon to perform accurate parenchymal transection. Bismuth warned that erroneous ligation of a variant hepatic artery may lead to loss of liver tissue and that dissection of the hepatic veins may lead to bleeding. The most common variants of hepatic arteries are clearly illustrated in the review by Abdel-Misih and Bloomston.

Bismuth noted that Ton That Tung proposed an alternate technique (the anterior approach), in which parenchymal transection precedes ligation of the vessels; this technique allows resection of only the liver tissue needing to be resected, but this advantage comes at the cost of more bleeding during transection. The fundamental maneuvers of the two techniques were illustrated in Bismuth’s paper. Bismuth proposed a hybrid of the two techniques, in which hepatic hilar dissection is done to identify the main hepatic artery, while portal vein branch
is done to the area to be resected, so that these may be intermittently clamped during the dissection. The liver is completely mobilized and the vena cava dissected. Parenchymal transection along Cantlie’s line is carried out (for conventional right or left hepatectomy) and ligation of the portal vein and hepatic artery branches is done within the parenchyma of the liver above the area where the intermittent occluding clamp is applied. Hepatic vein ligation can be done under direct vision at the end of the parenchymal transection. Abdell-Misih and Bloomston\(^43\) emphasized the usefulness of IOUS for mapping of portal venous anatomy and the hepatic veins. They stressed the importance of surgeon awareness of small hepatic veins that mostly drain the right lobe of the liver and enter the inferior vena cava to the left of the midline. Also, an accessory right hepatic vein may be occasionally encountered.

For large lesions, Bismuth\(^44\) suggested full control of the hepatic hilar structures and the inferior vena cava. He found that some have suggested that the aorta be controlled as well, but he stated that this is unnecessary in elective liver surgery. The next section of this review will provide additional discussion of the technical aspects of liver resection.

The final paper to be discussed in this section dealt with the important anatomic information necessary for successful vascular isolation of the liver. This paper was by MacKenzie and coauthors\(^45\) in the Journal of Gastrointestinal Surgery, 2005. The authors described their techniques for obtaining anatomic information about the areas where the hepatic veins enter the inferior vena cava in 20 fresh cadavers. They then discussed their surgical technique for isolating the same areas and they presented results in 45 consecutive patients who had resection of at least two liver segments. The authors acknowledged that their operative techniques changed during the four-year interval when the clinical experience was recorded. Important changes included the adoption of a low venous pressure protocol, the use of the ultrasonic dissector, and most recently, the adoption of the harmonic scalpel for parenchymal transection. The results of the cadaveric dissections showed that the right hepatic vein-inferior vena cava junction was oriented vertically, while the left/middle hepatic vein-inferior vena cava junction was oriented transversely. They found a common trunk for the left and middle hepatic veins in 95% of instances. The junction of the right hepatic vein with the IVC was caudal to the junction of the middle/left hepatic veins with the IVC. The left hepatic vein crossed the left edge of the IVC in all their specimens and the middle hepatic vein trunk extended caudally anterior to the IVC in all specimens. The authors described the hepatic-caval ligament as being fibrous or composed of liver tissue and extending from the caudate lobe of the liver across the inferior vena cava to the dorsal surface of the right hepatic lobe. Mobilization of the liver and dissection of the hepatic vein-inferior vena cava junctions universally “kinked” the IVC and reduced cross-sectional area of the IVC, giving rise to concern that this might produce adverse hemodynamic changes. The authors emphasized that regardless of the specific technique that is utilized to achieve vascular control, the goal is to minimize blood loss and reduce the time that the liver is rendered ischemic. They believed that their technique of hepatic vein dissection and intermittent hilar clamping achieves these goals. MacKenzie and coauthors’ data, however, are not consistent with their recommendations. They indicated that their average blood loss was around 1,000 ml per patient, and that four of the 45 patients had blood loss in excess of 2,000 ml; this high average of blood loss was attributed to not routinely dividing the large vein draining the caudate lobe that they identified in many of their patients. From reading their report, it is clear that dissecting the junctions of the hepatic veins and the inferior vena cava is tedious and does not necessarily result in less blood loss than other techniques.

Techniques for Optimizing Liver Resection Outcomes

A number of preoperative, intraoperative, and postoperative approaches are known to improve outcomes of hepatic resection. The articles selected for this section provide a detailed evaluation of the strength of the supporting evidence for these various technical maneuvers and allow readers to judge each method’s contribution to improvements in hepatic resection outcomes.

Techniques for Optimizing Liver Resection Outcomes | LIVER, PART I
The first article reviewed was by Clavien and coauthors in the *New England Journal of Medicine*, 2007. The authors began by noting that recovery of hepatic function following hepatic resection for living donor liver transplantation or for liver tumors depends on hyperplasia of cells in the remaining liver remnant (liver regeneration was discussed in a previous section of this review). They observed that hepatocytes begin to recover within one day of liver resection, while Kupffer cells and ductal cells recover later; numerous growth factors are involved in the recovery process. The authors stressed that recent data generated by their group has documented the importance of platelets, neurotransmitters (serotonin), and bile acids in the recovery process.

Total occlusion of the hepatic hilar vessels (Pringle maneuver) can be useful in reducing bleeding, but occlusion may produce ischemic damage to the liver that will remain after resection. The authors found that intermittent occlusion of the vessels can be a safer approach to control bleeding. By reducing ischemic damage to the remaining liver, intermittent occlusion may decrease the risk of postoperative liver failure. Another approach to reducing ischemic damage to the remnant liver is “ischemic preconditioning.” This approach uses a short interval (10 minutes) of total vascular occlusion followed by 10 minutes of unrestricted inflow prior to clamping vessels during the liver resection process. In theory, this maneuver should facilitate the generation of vasodilator substances such as nitric oxide within the liver. A Cochrane review of this technique was by Gurusamy and coauthors in the *Cochrane Database Systematic Reviews*, 2009. After analyzing the results of the included studies, there was no evidence that ischemic preconditioning provided any benefit in terms of decreased risk of mortality or complications following liver resection.

In addition to occlusion of inflow vessels, bleeding from the liver may be controlled by using manual compression of the remnant liver edge, cautery, and applying materials to assist the clotting process. Figueras and coauthors discussed using fibrin sealant to control bleeding from the liver edge in *Annals of Surgery*, 2007. The authors conducted a randomized prospective study involving 300 patients who underwent liver resection for various liver diseases. The experimental groups had aerosolized fibrin glue sealant (5mL) applied to the raw surface of the remnant liver. The control group did not receive fibrin glue sealant. The data disclosed no differences in measured blood loss, number of transfusions, mortality, or complication rates when the groups were compared.

Clavien and colleagues next discussed the minimum liver volume needed to sustain hepatic function. They stated that postoperative liver failure is caused by removal of liver substance and/or destruction of function in the remnant liver to an extent that hepatic synthetic and detoxifying functions cannot be maintained. This condition clinically manifests as postoperative liver failure, characterized by jaundice, coagulopathy, encephalopathy, ascites, and associated renal and pulmonary failure. It is possible to remove up to 75% of the liver in a young person with normal liver function. In patients 65 years and older, and in the presence of associated liver diseases such as cirrhosis, hepatitis, and steatosis, smaller volumes of liver can be removed with satisfactory maintenance of function. Other factors that influence the amount of liver that can be successfully removed include obstructive cholestasis, preresection chemotherapy, and intraoperative liver damage from ischemia or blood loss. The severity of associated liver disease is also important. Right or left hepatectomy is well tolerated by patients with cirrhosis, as long as the bilirubin is normal and there is no reduction in hepatic synthetic function (normal prothrombin time). In patients with clinically obvious portal hypertension and coagulopathy, postoperative liver failure can occur after even a small wedge resection. Similarly, the extent of steatosis influences the risk of postoperative liver failure. When 30% or fewer hepatocytes contain fat on histologic examination, little or no additional risk is present. When more than 60% of liver cells show fatty change, major liver resection is contraindicated. With moderate steatosis (30%–60% of hepatocytes showing fatty change), most liver surgeons opt for conservative resection, although strict guidelines are not available. According to the authors, liver resection is usually safe after chemotherapy, as long as an interval of 6–8 weeks is allowed after completing chemotherapy. Chemotherapy-induced liver damage can, if extensive, cause a blue discoloration of the liver; this change is associated with increased risk of intraoperative blood loss and postoperative liver insufficiency.
Postoperative Liver Failure: Pathophysiology, Prevention & Management

An article by Garcea and Maddern that focused on postoperative liver failure was developed during an extensive analysis of existing literature and published in the *Journal of Hepatic Pancreatic and Biliary Surgery*, 2009. The authors noted that liver resection is the only potentially curative procedure for hepatic malignancy. Even so, they emphasized that only 20%–30% of patients will have the type of tumors whose anatomies and extent of involvement of the liver allow for the complete removal of the lesion(s). According to the authors, safe remnant liver volume for patients without underlying diffuse liver disease is 20%–25% of the volume of the normal liver. For patients with steatosis or a history of prior chemotherapy, the remnant volumes increase to 30%–60% of the initial liver volume. For patients with cirrhosis, the safe liver remnant may need to be even larger. Garcea and Maddern observed that mild derangement of liver function is common after a major hepatic resection and is characterized by abnormal bilirubin; this usually resolves in 6–7 days postoperatively. Failure of resolution may herald the onset of progressive liver failure.

Liver failure is the most common cause of postoperative mortality after liver resection. Progressive liver failure may present as cholestasis with regeneration of liver cells and fibrosis or with non-regeneration of liver cells and extensive apoptosis of remaining hepatocytes. The main etiologies contributing to postoperative liver failure are small liver remnant, failure of hepatocyte energy metabolism, and liver damage due to infection. Failure of hepatocyte energy metabolism is contributed to by intraoperative ischemia due to blood loss and prolonged clamping of inflow vessels. Aggressive efforts to minimize intraoperative blood loss using multiple parenchymal transection instruments have helped reduce intraoperative hemorrhaging. Accurate definitions of liver anatomy using preoperative imaging and IOUS have also played a part in reducing intraoperative blood loss. Portal hypertension may contribute to loss of nutrient hepatic flow, but portal decompression has accelerated hepatocyte apoptosis and has not led to improved outcomes.

Infection is an important contributor to liver failure. Liver resection reduces Kupffer cell numbers and, therefore, clearance of bacteria from portal blood is impaired. Sepsis further impairs liver function because of elaboration of multiple inflammatory cytokines. Jaundice from biliary obstruction and reduction of enteral bile salt levels increase the risk of liver failure as well. Bile drainage with restoration of enteral bile salts helps to prevent liver failure.

Additional information relating to the prevention and management of liver failure is found in an extensive review of the available literature by Hammond and coauthors in the *British Journal of Surgery*, 2011. This article is supplied as a full-text reprint accompanying some formats of *SRGS*. From the analysis of available literature, the authors produced an informative algorithm describing the factors that contribute to postoperative liver failure. This algorithm is reproduced as Figure 10. In addition, the authors developed a step-by-step strategy for managing postoperative liver failure, and this is illustrated as Figure 11.
Strategies for Assessing & Increasing Remnant Liver Volume

Clavien and coauthors\(^6\) emphasized the importance of determining the safe amount of remnant liver that can remain after resection. Tumor involvement of portal vein branches may reduce nutrient flow to the liver involved with the tumor. This phenomenon is known to induce liver hypertrophy in the remaining liver remnant. Induction of liver hypertrophy can be produced in the remnant liver by embolizing the portal vein branch to the portion of the liver that is to be resected. When the liver is involved with a malignant tumor, portal vein embolization can be done with material containing chemotherapy drugs. Biliary obstruction reduces the capacity of the liver to hypertrophy. In liver resection candidates with obstructive jaundice, bile drainage can be used to augment efforts to induce hypertrophy in the liver remnant.

Assessing Remnant Liver Volume

Volumetric assessment of remnant liver volume is accomplished using CT imaging. Traditionally, the ratio of projected remnant liver volume to baseline liver volume is expressed as a percentage. The expected safe percentage volumes of liver remnants based on estimates of the extent of diffuse liver disease have been referred to in earlier discussions. An article that described an alternative method of expressing safe remnant liver volume was by Truant and coauthors\(^5\) in the Journal of the American College of Surgeons, 2007. The authors began by observing that the expression of remnant liver volume based on baseline total liver volume or calculated normal liver volume are methods prone to error because total liver volume assessments include abnormal (malignant tissue) or nonfunctioning (ischemic) liver tissue. Living donor liver transplantation protocols compare anticipated remnant liver volume to body weight, with a cutoff of 0.5% for a viable and safe liver remnant. The authors prospectively evaluated this method of predicting safe liver remnant volume in a group of 31 patients. The analysis found that there was no difference in patient outcomes when safe liver remnant volume (calculated as a percentage of baseline or total liver volume) was <25%, compared to patients with remnant volumes of >25%. Of interest was that remnant volume to body weight of <0.5% was associated with significantly worse outcomes compared to patients with remnant volumes of >0.5%. The authors noted that the selected patient group had certain important characteristics: the patients all underwent major liver resection (right trisegmentectomy) and none of them had evidence of cirrhosis or steatosis. The authors indicated that interpretation of their study could be limited by the fact that patients in the higher risk remnant volume group were older than patients in the lower risk group. Nonetheless, the authors believe this evidence supports the consideration of remnant liver-to-body weight ratio as a means of assessing safe remnant liver volume.

**Figure 11**

Stepwise management of postoperative liver failure. Reproduced from Hammond and coauthors with permission.

<table>
<thead>
<tr>
<th>Step</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection</td>
<td>Bilirubin &lt; 5.0 mg/dL (85 μmol/L), INR &lt; 1.0, ascites/paracentesis on postoperative day 5</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Hemoglobin, serum albumin, platelet count, PT/INR, BUN, creatinine, LFTs</td>
</tr>
<tr>
<td>Treatment</td>
<td>Intensive care, nutritional support, antibiotics, diuretics, bile salts, EN, dialysis</td>
</tr>
<tr>
<td>Hepatoprotection</td>
<td>None</td>
</tr>
<tr>
<td>Stress ulceration prophylaxis</td>
<td>Prophylactic proton pump inhibitor</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Enteral preferably over total parenteral nutrition</td>
</tr>
<tr>
<td>Steps</td>
<td>Remove dead space, clamp liver, and prime and fire IVC with 300-500 mL of saline</td>
</tr>
<tr>
<td>Multidrug dystrophy</td>
<td>Cardiopulmonary bypass, dopamine, viroprophylaxis, antibiotics, H2-receptor blockers</td>
</tr>
<tr>
<td>Coagulopathy and thrombocytopenia</td>
<td>Acute liver disease, antithrombin III, platelets &lt; 50,000, D-dimer &gt; 0.5</td>
</tr>
<tr>
<td>Vascular inflow/outflow</td>
<td>Doppler ultrasonography, CT/MRI angiography</td>
</tr>
<tr>
<td>Large-volume access</td>
<td>IV lines or transjugular liver access, central venous catheters</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Common bile duct injury, biliary enteric anastomosis</td>
</tr>
</tbody>
</table>

*Although this table is used in many cases, there is no definitive evidence of levels based on postoperative liver failure. TPN, total parenteral nutrition; EN, enteral nutrition; IVC, inferior vena cava; INR, international normalized ratio; CRF, chronic renal failure; MRSA, methicillin-resistant Staphylococcus aureus; TIPS, transjugular intrahepatic portosystemic shunt; BUN, blood urea nitrogen; INR, international normalized ratio; CRF, chronic renal failure; TIPS, transjugular intrahepatic portosystemic shunt; BUN, blood urea nitrogen; INR, international normalized ratio; CRF, chronic renal failure; TIPS, transjugular intrahepatic portosystemic shunt; BUN, blood urea nitrogen; INR, international normalized ratio.
Inducing Remnant Growth with Portal Vein Embolization

Early efforts to increase the volume of planned remnant livers included open ligation of the portal vein branch to the portion of the liver to be removed. Portal vein embolization is a percutaneous technique that does not require an open operation. Furthermore, embolic material can be made from chemotherapeutic drugs so that tumors in the portion of the liver planned for resection can be treated. Portal vein chemoembolization also helps offset the potential disadvantage that tumor-bearing tissue in areas bordering the remnant liver might hypertrophy in response to increased portal flow. In *Annals of Surgery*, 2008, Abulkhir and coauthors reviewed available literature published in English that focused on techniques and outcomes of portal vein embolization. The articles reviewed reported data on nearly 1,100 patients. The analysis disclosed that remnant liver hypertrophy assessed by CT imaging and volumetric calculation ranged from 9%–11.5% at one month following embolization. The planned liver resection could be accomplished in 85% of patients. The most common reasons for failure to undergo the planned resection were unfavorable tumor characteristics (vascular invasion) or spread of the tumor to multiple areas outside the liver. After embolization and subsequent resection, less than 1% of patients developed fatal liver failure. Transient liver failure was observed in 2.5% of patients. The authors compared techniques of portal vein embolization and determined that the preferred technique was percutaneous transhepatic portal vein catheterization and embolization.

A second literature review on this topic was by Liu and Zhu in the *American Journal of Surgery*, 2009. The data reviewed supported the conclusion that portal vein embolization is associated with a reduced rate of complications after liver resection and shorter durations of hospital stay. The authors noted that promising avenues for future approaches to improving remnant liver volume included portal vein embolization with stem cell infusion to hasten and increase remnant liver hypertrophy. Another promising technique is simultaneous portal vein and hepatic artery embolization, which is used to reduce the impact of increased hepatic arterial flow to the planned area of resection (hepatic arterial buffer response) that follows portal vein embolization.

Another article by van Gulik and coauthors in *Digestive Surgery*, 2008, examined controversies surrounding the use of portal vein embolization. The authors found that portal vein embolization using the percutaneous technique is employed in many liver surgery centers; however, there are data, notably from the Memorial Sloan Kettering Cancer Center, that suggest most patients requiring major hepatectomy can be successfully managed without portal vein embolization. Complications of this technique include “spillover” of embolic material into the remnant liver segment and thrombosis of portal vein branches. The authors noted that data that precisely define the risk of these events are scarce. There is abiding concern that portal vein embolization may stimulate liver tumor growth, but this risk can be offset by adhering to a short interval (3–4 weeks) between embolization and resection and by using embolic material that contains chemotherapeutic agents.

The final article reviewed in this section was by van den Esschert and coauthors in the *Journal of Gastrointestinal Surgery*, 2009. These authors conducted a retrospective comparison of postoperative liver regeneration in patients who did (n=10) and did not (n=13) undergo preoperative portal vein embolization. Predicted remnant liver volume was higher in patients who did not undergo embolization. Postoperatively, recovery of liver volume and liver function was satisfactory in both groups. The authors concluded that portal vein embolization is safe and does not adversely influence postresection recovery of the liver.

Perioperative Management of Liver Resection for Improved Outcomes

Enhanced recovery pathways (ERAS) have been shown to be associated with improved outcomes in patients undergoing colorectal operations. A summary of recommendations for ERAS pathways is available from the American College of Surgeons.
College of Surgeons’ Evidence-Based Decisions in Surgery: www.facs.org/education/resources/ebds-guidelines.

Enhanced recovery programs have also been used for patients undergoing liver resection. Dunne and coauthors provided data from a before-and-after comparison of patients treated prior to and after the implementation of an ERAS pathway in the Journal of Surgical Oncology, 2014. This article is supplied as a full-text reprint accompanying some formats of SRGS. A total of 304 patients were included, with 161 patients in the later cohort. Data analysis confirmed a significant decrease in the proportion of patients hospitalized for 10 days or more, although the median length of stay was equivalent in both cohorts. Admissions to critical care units were significantly fewer in the recent cohort; complication rates (38.2%) were equal in the two groups. There was only one perioperative death and that occurred in the early cohort. The authors concluded that their data suggests a benefit in implementing an ERAS pathway.

Components of most ERAS pathways include goal-directed intraoperative fluid administration protocols. Correa-Gallego and coauthors reported the results of a randomized prospective trial of goal-directed fluid therapy using intraoperative assessments of stroke volume variation in the Journal of the American College of Surgeons, 2015. According to the authors, stroke volume variation was measured with a commercially available sensor and the percentage change between the maximal and minimal values during a defined time interval divided by the mean value during the time interval that provides insight on the variation of left ventricular output in response to changes in intrathoracic pressure. All randomized patients had liver resections done using a low central venous pressure protocol. During the study interval (2012–2014), 135 patients were randomized. Rates of overall and severe morbidity were equivalent in the two groups. Patients in the goal-directed therapy group received lower volumes of perioperative intravenous fluids. The authors concluded that goal-directed fluid therapy using stroke volume variation is feasible and safe.

The use of regional anesthesia is also a component of ERAS pathways. An article that reported data comparing outcomes of patients undergoing liver resection for colorectal cancer metastases who received epidural vs. intravenous anesthesia was by Zimmitti and coauthors in Annals of Surgical Oncology, 2016. Prior data had associated epidural anesthesia with a lower recurrence risk of cancer after oncologic surgery. The study compared outcomes in 390 patients who received epidural anesthesia with 120 patients who received intravenous anesthesia. Patients in the epidural anesthesia group had a higher frequency of associated procedures and longer operative times. Data analysis showed that patients in the epidural anesthesia group had higher five-year recurrence-free survival rates, but that overall survival rates were equivalent. The authors also cited data supporting the conclusion that intravenous, opioid-based anesthesia is associated with impairment of immune responses and higher rates of cancer recurrence both in animal and patient studies of various tumor types. Additional data showed that outcomes in patients with colorectal cancers have been mixed, with some studies showing lower recurrence rates mostly in older patients. The authors concluded that the benefits of regional anesthesia include improved pain control and faster recovery rates; higher rates of recurrence-free survival may be an extra benefit.

Technical Features of Safe Liver Resection

Familiarity with the surgical anatomy of the liver permits complete dissection of the vascular and biliary structures of the planned resected segment and accurate parenchymal transection. A full understanding of the anatomy of the hepatic veins and retrohepatic vena cava is also necessary for safe hepatectomy. The lobar anatomy of the liver was discussed previously; a review of techniques for maintaining low central venous pressure and for intermittent occlusion of the hilar vessels is used frequently to reduce volumes of intraoperative bleeding. In this section, we will focus on articles that describe and evaluate technical maneuvers for accurate identification and protection of the hepatic veins. Following this discussion, we will present parenchymal transection techniques. Outcomes of hepatic resection for specific disease processes, such as hepatic adenoma, hepatocellular cancer, and metastatic disease to the liver, will be reviewed in subsequent issues of SRGS.
Parenchymal Sparing Hepatectomy

For patients with multiple liver lesions and for patients with impaired liver function, efforts to preserve hepatic parenchyma are important. An article that presented data on the impact of a parenchymal sparing technique on intraoperative blood loss was by Day and coauthors in Surgery, 2016. This article is included as a full-text reprint accompanying some formats of SRGS. The authors described a technique of liver tissue transection wherein one surgeon divided the tissue with an ultrasonic aspirator, while the second surgeon worked to control parenchymal bleeding with a saline-linked floating ball electrocautery device. The authors conducted a retrospective review of data contained in a prospectively maintained database. A before-and-after model was used that identified patients in an early cohort and in a more recent one. When the two cohorts were compared, the two-surgeon liver-division technique was associated with a significant reduction in blood loss, transfusion rate, and length of hospital stay. This improvement was accomplished in spite of the fact that the more recent patient cohort had higher ASA scores, lower preoperative hemoglobin levels, and lower preoperative platelet counts. The authors acknowledged the possibility that other unidentified factors could have contributed to these outcomes. Nonetheless, the two-surgeon liver-division technique is worthy of consideration.

The Liver Hanging Maneuver

The liver hanging maneuver is a method of suspending the liver for parenchymal transection by developing a plane between the ventral surface of the retrohepatic inferior vena cava and the dorsal surface of the liver. This maneuver assists the surgeon in identifying the plane of parenchymal transection for a left or right hemihepatectomy. Gaujoux and coauthors reviewed the anatomic basis and technique of the liver hanging maneuver in the American Journal of Surgery, 2007. The authors began the review by stressing the potential advantages of the maneuver. By passing a tape along the dissected plane between the retrohepatic inferior vena cava and the dorsal surface of the liver and elevating the liver, the line of transection for a right or left hemihepatectomy is clearly delineated; this maneuver can permit transection of the parenchyma without prior mobilization of the liver, reduce operating time, and, theoretically, reduce tumor dissemination and help avoid ischemic damage resulting from mobilization of the remnant liver. Disadvantages of the maneuver are that the plane of dissection is developed blindly after first visualizing the trunks of the right and combined middle and left hepatic veins at the superior surface of the liver. Injury to the inferior vena cava and/or a hepatic vein branch entering the inferior vena cava could produce bleeding in an area that would be difficult to expose.

The authors next reviewed cadaver and clinical anatomic studies of the avascular plane and the method of dissection. They found that the reported risk of bleeding during dissection ranged from 0% to 6%. Over 85% of reported bleeding episodes resulted from injury to a small (<6 mm diameter) vein draining the dorsal surface of the liver and entering the anterior surface of the retrohepatic inferior vena cava. Data from anatomic and clinical studies cited by the authors indicate that most of the small veins that enter the anterior surface of the inferior vena cava are located caudal to the intended plane of dissection. Bleeding from these small hepatic veins can usually be controlled by gently compressing the anterior surface of the retrohepatic inferior vena cava. Veins that might be encountered are most often located to the left of the midline of the inferior vena cava. If the plane of dissection is placed to the right of the midline of the inferior vena cava, nearly all of these veins will be avoided. An illustration of the placement of the plane of dissection is included in the article and reproduced as Figure 12. According to the authors, larger veins such as those draining the caudate lobe enter the inferior vena cava on the left lateral surface of the inferior vena cava. The vein draining the caudate lobe is identified and ligated at the beginning of the dissection. The authors emphasized that it is necessary to dissect along the ventral surface of the inferior vena cava in both cranial-to-caudal and caudal-to-cranial directions to determine the presence of an inferior and middle right hepatic vein. If encountered, these veins are encircled with a vascular tape, but are not ligated. Data cited by the authors from the literature that they reviewed indicate that the liver hanging maneuver can be successfully performed in more than 95% of patients. The most frequent reason that the maneuver cannot be completed
is tumor invasion of the retrohepatic vena cava. No data were presented confirming the benefits of the liver hanging maneuver for tumor recurrence or function of the remnant liver tissue.

Modifications of maneuvers to obtain vascular control can be used to facilitate liver resections other than right or left hemihepatectomy. An article discussing these modifications was by Liddo and coauthors in*HPB Oxford*, 2009. These authors cited data supporting the benefits of the anterior approach to parenchymal transection without prior liver mobilization. Data were presented from a randomized prospective study of the anterior approach. Patients were randomly assigned to receive the anterior approach or a “conventional” liver mobilization approach. All resections were done for hepatocellular carcinoma. Tumor recurrence rates and postoperative liver failure rates were significantly lower in the patients having the anterior approach. Liddo and colleagues contended that the liver hanging maneuver that is used to facilitate identification of the line of parenchymal transection for the anterior approach can be safely used for most types of liver resection and not only for right or left hemihepatectomy. The authors listed several technical modifications that they believed made the maneuver safer, including the use of IOUS to identify small venous branches entering the hepatic surface of the retrohepatic vena cava. Identification allows these veins to be avoided. Liddo and coauthors began developing the plane by opening the space between the common trunk of the middle and left hepatic veins and the trunk of the right hepatic vein. Gentle blunt dissection of a plane slightly to the right of the midline of the inferior vena cava was developed with ultrasound assistance using a nasogastric tube as a dissector.

As experience with the liver hanging maneuver has increased, complications have decreased. The authors found that the most common cause of bleeding during the dissection in current practice is entry into the liver substance resulting from incomplete opening of the fibrous tissue separating the liver substance from the ventral wall of the inferior vena cava. They emphasized that increasing resistance to passage of the dissecting instrument suggests entry into the liver substance. Injury to a short hepatic vein is usually the result of placing the plane of dissection too far to the left on the surface of the inferior vena cava. Bleeding can be controlled by inserting gauze into the dissected space and by allowing the weight of the liver to compress the surface of the vena cava. The authors emphasized that the only specific contraindications to the liver hanging maneuver are scarring and tumor infiltration that obliterate the plane of dissection. They also observed that suspicion of tumor infiltration on preoperative imaging is frequently not confirmed at the time of operation and that an attempt to complete the maneuver is warranted in such patients. The article closed with illustrations of several modifications of the maneuver that permit application to liver resections other than right or left hemihepatectomy. Readers are encouraged to review these illustrations.

A case series that reviewed clinical experience with the liver hanging maneuver was by Ogata and coauthors in*Annals of Surgery*, 2007. This clinical series described the experience from the center that pioneered the liver hanging maneuver. The series comprised 242 patients seen over the interval from 2001 to 2005. The authors found
that successful completion of the maneuver was achieved in 74% of patients during their early experience. Over the most recent three-year interval, from 2003 to 2005, the success rate of the maneuver has been 94%. As noted in prior discussions, the only consistent contraindication to the maneuver is obliteration of the plane of dissection. Bleeding was encountered in 2% of patients, but was judged to be “major” (defined by volume of blood loss of 100–200 mL) in only two patients.

**Techniques for Parenchymal Transection**

Multiple devices are used for parenchymal transection during liver resection. The traditional approach is the “clamp-crush” technique. The line of parenchymal transection is marked with electrocautery applied to the liver capsule. Small segments of parenchyma can be crushed by closing a Kelly or Pean clamp across the selected segment of parenchyma. Bile ducts and hepatic vessels are not transected using this method and these can be identified and clipped/ligated. The other devices that are used include the ultrasonic aspirator, the LigaSure™ device, the cutting stapler, and the argon beam coagulator. Each of these is chosen because of the perception that using one or more of these instruments is associated with lower blood loss than the traditional “clamp-crush” method.

Ikeda and coauthors\(^6\) presented a prospective randomized trial of a vessel-sealing device (LigaSure™) vs. the clamp-crush technique in *Annals of Surgery*, 2009. The authors reported a trial that included 120 patients. Patients were randomly assigned to have parenchymal transection with the vessel-sealing device or with the clamp-crush technique. Blood loss, transfusion volumes, mortality, and complication rates were compared. Data analysis revealed no advantage gained by using the vessel-sealing device, although both techniques appeared to be safe.

Schemmer and coauthors\(^7\) offered an anecdotal report of clinical experience using the cutting stapler for parenchymal resection in *HPB Oxford*, 2008. These authors described their approach to using the stapler and asserted that operative times, transfusion need, blood loss, and overall costs of liver resection have decreased since they adopted the stapler approach to parenchymal transection.

Dokleastic and coauthors\(^8\) presented a prospective randomized trial comparing the clamp-crush technique to the vessel sealing device and the Cavitron ultrasonic aspirator for liver parenchymal transection in *Hepatogastroenterology*, 2011. This trial involved three groups of 20 patients each. When the data were analyzed, there was no clear advantage for any technique, though the clamp-crush method was associated with a shorter duration of transection time and a slightly lower blood-loss volume.

Balaa and colleagues\(^9\) reported on using the cutting stapler for vascular control and parenchymal transection in the *Journal of Gastrointestinal Surgery*, 2008. The authors reported short warm ischemia times (averaging less than 10 minutes) and a low transfusion rate (10% of patients receiving transfusion). They also noted that the time required for parenchymal transection was 10 minutes, on average.

Radio frequency ablation of liver lesions has been utilized as a means of treating patients with liver cancers that are not amenable to resection. Percutaneous radio frequency ablation as a means of managing malignant liver lesions will be discussed in a subsequent issue of *SRGS*. The application of radio frequency energy, delivered through needle probes placed in the parenchyma of the liver along the line of resection, to produce a controlled region of coagulation necrosis and hemostasis (after identifying a satisfactory margin of resection using IOUS) was a technique described by Ayav and coauthors\(^10\) in *Digestive Surgery*, 2007. This report provided data from a clinical case series of 236 patients, 41 of whom underwent major hepatectomies. Radio frequency probes were used to create a zone of coagulation necrosis along the parenchymal transection line. The authors pointed out that the probe is positioned at the deepest point of the liver substance and sections of the liver 3 cm in thickness are progressively coagulated. The technique can be completed with minimal blood loss and inflow occlusion is not required according to these authors. Intraoperative blood loss averaged 157 ml and only 10 patients required transfusion. Mortality was 2.4% and 50 patients developed complications, including five patients who developed bile leaks. Mean postoperative stay was somewhat prolonged at 11 days. This length of stay raises suspicion that recovery might be somewhat prolonged by producing a portion of necrotic liver that is left after resection is concluded.
Lupo and colleagues\textsuperscript{68} published an article that carefully examined the complication rate following the application of radiofrequency energy via needle probes for parenchymal transection in the \textit{British Journal of Surgery}, 2007. Fifty patients were randomized to have parenchymal transection by the application of radio frequency energy (24 patients) or by the traditional clamp-crush technique (26 patients). The groups were satisfactorily matched and randomization was done in the operating room using random numbers. There were no deaths. More patients in the clamp-crush group required transfusion compared to the radio frequency group (13/26 vs. 8/24), but this was not statistically significant. Eight of the 24 patients in the radio frequency ablation group developed complications including abscess, biliary fistula, and bile duct stenosis. No complications were recorded in the clamp-crush group and there were no deaths in either group. The authors concluded that radiofrequency application can facilitate parenchymal transection, but at the cost of a higher complication rate.

Delis and coauthors\textsuperscript{69} compared the clamp-crush technique of liver transection to radiofrequency ablation for parenchymal transection in \textit{HPB Oxford}, 2009. The authors reported a single-center case series of 196 patients. The clamp-crush technique or radiofrequency ablation was used for parenchymal transection according to the preference of the operating surgeon. When the groups were analyzed, no differences in any meaningful outcome was noted except for patients with MELD scores of >9; in this group, 10 patients were treated with the clamp-crush technique and 12 patients had radiofrequency ablation. Blood loss and operating time were lower with radiofrequency ablation. This small clinical experience suggests a benefit for a highly select patient group. Additional data would be helpful to guide clinical decisions.

\section*{IOUS: Valuable Assistance for Hepatic Resection}

Surgeons planning to perform hepatic resection to treat primary and metastatic lesions in the liver are increasingly using IOUS for real-time assessments of the relationships of the lesions to the hepatic blood vessels and to detect additional lesions not displayed on preoperative imaging. As sophisticated MRI has supplanted CT imaging as the main means of staging hepatic tumors, the number of unsuspected lesions detected on intraoperative imaging has declined significantly. Sietses and coauthors\textsuperscript{70} documented the value of intraoperative ultrasonography in \textit{Surgical Endoscopy}, 2010. This article is supplied as a full-text reprint accompanying some formats of \textit{SRGS}. The authors reviewed findings from preoperative CT imaging and IOUS findings in 100 patients undergoing open hepatic operation for treatment of liver metastases, and discovered that IOUS findings differed from preoperative imaging in 38\% of patients. Usually, the IOUS found additional small lesions not seen on preoperative imaging, and because of IOUS imaging, the operative strategy was changed in 35 out of 117 procedures. The authors acknowledged that preoperative imaging with CT alone is not as accurate in the discovery of all lesions as preoperative MRI combined with PET-CT.

Data reviewed above have emphasized the contribution of IOUS to the success of laparoscopic liver resection. Santambrogio and coauthors\textsuperscript{71} concentrated on IOUS as an adjunct to laparoscopic liver procedures in \textit{Surgical Endoscopy}, 2007. Beginning in 1996, the authors performed laparoscopic liver resection with ultrasound guidance in 17 patients. They observed that ultrasound examination discovered unsuspected additional lesions in 17\% of patients. There were no operative mortalities, but complications occurred in three cirrhotic patients. Conversion to open hepatectomy was necessary in two patients. The authors concluded that their experience suggested that laparoscopic resection is best suited for patients with lesions in the left lobe of the liver and they stressed that ultrasound imaging enables the surgeon to determine the precise anatomic location of the tumor, along with complete delineation of the anatomic relationships of the tumor with hepatic vessels that is necessary for satisfactory surgical and oncologic outcomes.

\section*{Laparoscopic Liver Procedures}

The successful application of laparoscopic techniques to currently accepted approaches to hepatic diseases could offer a safe alternative to open hepatic resection, especially for patients with compromised liver function due to cirrhosis. Noted previously in this review is the relationship between chronic liver disease and both mortality and mor-
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bidity of liver resection. Offering a less invasive alternative to open hepatectomy would be a positive addition to the surgical armamentarium, so long as the procedures were safe and, for malignant lesions, oncologic outcomes were acceptable. In addition, reoperation rates for bleeding or bile leakage would need to be low. Encouraging reports of techniques for laparoscopic hepatectomy have appeared and these updates will be discussed in this section. Articles reporting experience with laparoscopic liver resection for specific lesions will be discussed in the sections of the review dealing with those conditions.

Recommendations for use of laparoscopic liver resection were presented in an article by Wakabayashi and coauthors in Annals of Surgery, 2015. This article is supplied as a full-text reprint accompanying some formats of SRGS. The article presented the recommendations of a panel group of experts in minimally invasive hepatic surgery at a consensus conference held in October 2014. The panel considered seventeen questions; the available evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, and recommendations were termed strong, moderate, or weak based on the expert group consensus. The first group of recommendations had to do with reporting laparoscopic liver resection outcomes: the panel recommended that both 30-day and 90-day mortality rates be reported so that all significant adverse events could be captured. This was rated a strong recommendation. The expert group suggested that large registry studies were most likely to be good resources for 90-day outcomes data. The panel next recommended that 30-day and 90-day morbidity rates be reported, and that high-quality studies (which include patients with lesions that are near vascular and biliary ductal structures) were needed to confirm whether rates of margin negativity were adequate.

The panel next recommended that hospital lengths of stay be reported in studies of the effectiveness of laparoscopic liver resection. The panel recommended similar reporting requirements for major liver resection and emphasized that registry studies would be of particular value in determining outcomes for major liver resections done laparoscopically, since the frequency of laparoscopic major liver resections and postoperative mortality are both low. Because of the low event rates, noninferiority is difficult to confirm unless larger sample sizes can be obtained.

Additional recommendations included use of pneumoperitoneum pressure of 10–14 mm Hg and low central venous pressure to assist with bleeding control. Transection of the liver parenchyma using an energy device for the superficial layers followed by meticulous dissection of deeper structures using an ultrasonic aspirator device or a clamp-crush technique was also recommended, as well as dissection of hilar structure using dissection of individual structures.

Interestingly, the panel determined that the evidence supporting their recommendations was weak and they emphasized the need for additional high-quality studies. Interested readers are encouraged to review this entire article.

Cauchy and coauthors focused on risk factors and consequences of conversion from a laparoscopic liver resection to an open procedure in the British Journal of Surgery, 2015. The article was a retrospective case series analysis of 223 patients seen at two tertiary referral hospitals over a 13-year interval. Laparoscopic major hepatic resection was the initial approach in all patients. Conversion to an open procedure was necessary in 13.5% of patients. Bleeding and failure of resection progression were the main causes of conversion. Risk factors for conversion included age >75 years, BMI >28, diabetes, tumor diameter >10 cm, and need for biliary reconstruction. Morbidity was significantly higher in patients who required conversion. Propensity score techniques were used to provide matched comparisons of patients who required conversion with patients who had open hepatic resections. This analysis showed that morbidity was not significantly higher in patients who had conversion from a laparoscopic major liver resection compared to patients undergoing open major hepatectomy.

Available data support the conclusion that bleeding is one of the major concerns in laparoscopic liver resection. Results presented in the clinical series reviewed previously indicated that the frequency of intraoperative transfusion (an admittedly coarse method of judging bleeding risk) ranges from 2% to 20%. Abu Hilal and coauthors focused on the problem of intraoperative bleeding and approaches to hemorrhage control in Surgical Endoscopy, 2010. The authors noted that intraoperative maneuvers to lessen the risk of bleeding in open liver operations include maintaining venous pressure in the 0–5 cmH₂O
range; however, they added that this level of central vascular pressure is too low for laparoscopic liver resection because of the danger of venous air embolism due to the pneumoperitoneum needed for laparoscopic procedures. The experience of these authors indicated that several types of available laparoscopic clips are useful for controlling vessels. The authors emphasized the importance of accurate visualization of the full circumference of the vessel prior to clipping. Vascular staplers are useful for parenchymal transection and control of hepatic veins. Abu Hilal and coauthors said that they used several instruments to control parenchymal bleeding, including radiofrequency ablation instruments, harmonic scalpel, and the ultrasonic surgical aspirator. They underscored the value of compressing the bleeding surface, and that conversion to a hand-assisted method may facilitate compression of the liver. The authors’ experience indicated that bleeding risk is higher for right-side resections than for left-side resections.

Results of the 2008 consensus conference on laparoscopic hepatectomy were presented in an article by Buell and coauthors in *Annals of Surgery*, 2009. Forty-five hepatic surgery experts gathered to develop a series of statements describing the current status of laparoscopic liver resection and to offer guidance for terminology and best practices. The participants agreed that laparoscopic liver procedures should be termed “pure laparoscopy,” “hand-assisted,” and “hybrid technique” when describing procedures done entirely laparoscopically, done using hand assistance, and performed using both techniques. Conference participants recognized that major hepatic resections (hemihepatectomies) have been performed laparoscopically. The participants urged caution in rapidly expanding the use of laparoscopic hemihepatectomy because of concerns that standardized training programs to prepare surgeons for safe conduct of these procedures were not yet available. There was agreement that the best candidates for laparoscopic hepatic resection were patients with solitary lesions <5 cm in diameter located in segments 2–6 of the liver. They further agreed that left lateral sectionectomy performed laparoscopically was standard care.

The conference participants acknowledged that laparoscopic liver resection has not been subjected to rigorous randomized controlled clinical trials. Given the increasing use of these techniques worldwide, large organized randomized trials are probably not feasible. The consensus parameters for laparoscopic surgery are reflected in large clinical experiences that have been published. A single institution experience was presented in an article by Bryant and coauthors in *Annals of Surgery*, 2009. The report presented a retrospective analysis of data from a prospectively maintained patient registry; over the course of 11 years, 166 laparoscopic resections were performed. The lesions resected were nearly evenly split between malignant and benign tumors. In agreement with the consensus recommendations, 146 of the 166 patients had lesions located in segments 2–6. Of the 166 patients, 148 had single lesions and only 13 patients had lesions larger than 8 cm. The median lesion diameter was 3.5 cm. The operative technique for laparoscopic liver resection, as practiced by Bryant and coauthors, was described in detail, which adds value to their report. The authors revealed that resections for malignant disease increased as their experience grew. Most of the malignant lesions resected were hepatocellular carcinoma. Participants in the consensus conference that is described in the article by Buell and coauthors acknowledged the continuing controversy regarding the best approach to single small hepatocellular carcinoma lesions. Data from reports of clinical experience with percutaneous radiofrequency ablation suggest that this approach has equivalent results compared to open or laparoscopic liver resection. Bryant and colleagues data supported the conclusion that laparoscopic liver resection for malignant lesions has equivalent outcomes to open procedures. Similar results were reported in a second single-center experience by Kazaryan and coauthors in *Archives of Surgery*, 2010.

Nguyen and coauthors presented additional clinical outcomes data for laparoscopic liver resection in *Annals of Surgery*, 2009. The authors reported a systematic review of the literature. Their analysis identified 127 pertinent articles that described experience with more than 2,800 patients, and they disclosed that 50% of laparoscopic resections were done for malignant lesions, although the proportion of procedures done for malignant disease increased over time. Overall and disease-free survival at three and five years for hepatocellular carcinoma and for colorectal metastatic lesions was equivalent to the results of open operations. The authors stressed, however, that the lesions resected laparoscopically were, for the most part,
small, peripherally located lesions, and that this selection bias could be important. One interpretation is that results for this select group of patients should be better than for patients resected using open operations. Overall mortality reported from these two large collections of clinical data was less than 0.5%. There were no intraoperative deaths reported and most postoperative deaths were due to liver failure. Overall morbidity was 10%–11%, with bile leak being the most troublesome complication.

Buell and coauthors\textsuperscript{75} stated that conference participants discussed conversion to an open procedure from a laparoscopic approach, and that the panel agreed that conversion was prudent if complications were encountered or if the procedure’s progress was stalled; however, they stressed that rates of conversion should not be used as an index of quality for laparoscopic surgery. The participants asserted that the discovery of benign asymptomatic liver lesions using imaging has increased, and they agreed that indications for laparoscopic liver resection should not be widened to include such lesions and that unroofing of benign liver cysts should not be considered equivalent to laparoscopic hepatic resection. A consensus was reached that open or laparoscopic liver resection is the desired approach for metastatic lesions of the liver from colorectal cancers. There was concern that detection of small associated metastatic lesions during laparoscopic approaches was not optimal and that additional studies of oncologic effectiveness of laparoscopic liver resection were needed.

Articles comparing outcomes for laparoscopic procedures to outcomes of open abdominal procedures have documented decreased hospital lengths of stay, reduced pain, and earlier return to normal activities. Data pertinent to laparoscopic liver resection outcomes compared to open procedures were presented in both a prospective single-center experience described by Aldrighetti and coauthors\textsuperscript{79} in the \textit{Journal of Gastrointestinal Surgery}, 2008, and in a systematic literature review by Nguyen and coauthors\textsuperscript{80} in \textit{Archives of Surgery}, 2011. Both of these reports documented similar benefits in terms of shorter hospitalization, reduced pain, and increased recovery time.

Hepatic Resection Safety & Postoperative Quality of Life

Most available data support the conclusion that hepatic resection can be carried out with a mortality risk of 5% or less and a complication risk in the 15%–35% range. From these data, one can agree that hepatic resection is relatively safe and that outcomes are driven by risk factors such as liver disease, age, and patient comorbid conditions (see earlier discussion). Long-term outcomes are usually judged by quality of life assessments, with the understanding that survival over the long term will be driven by the disease process for which the liver resection was done. In this section, we will discuss articles that examine long-term quality of life in patients after liver resection.

Martin and coauthors\textsuperscript{81} presented data on quality of life after recovery from major liver resection in \textit{Surgery}, 2007. The authors emphasized that for surgical oncologists, health-related quality of life assessments and accurate reporting are both equally as important as reports of operative outcomes, five-year survivals, and disease-free survival. The authors went on to review previous work in this area that they and others have contributed. These reports documented a quality of life benefit that accrues from hepatic resection for hepatocellular carcinoma; the authors cited data that revealed a diminished quality of life at six weeks postoperatively for major hepatic resection. Long-term quality of life was similar for major hepatic resection, minor resection, and radio frequency ablation. The authors asserted that there have been no quality of life assessments of the recovery trajectory for major and minor hepatic resection, and that their report is designed to address this issue. The authors divided the patients into groups based on the extent of hepatic resection. Minor hepatectomy was defined as a resection of one or two Couinaud segments, while a major hepatectomy was defined as a resection of three or more segments. Thirty-two patients were fully assessed and reported. Twenty-four patients underwent major resections and eight underwent minor resections. The groups were similar in age and frequency of comorbid conditions. The minor resection patients underwent more concomitant procedures than did the major hepatectomy patients. While there were no perioperative deaths, 11 patients in the major resection group developed complications, and three patients in the minor resection group developed complications. A battery
of questions drawn from multiple quality of life assessment tools was administered by the operating surgeon and/or a research nurse preoperatively, at hospital discharge, at the time of the first postoperative visit (2–3 weeks postoperatively), and at three additional time points (six weeks, three months, and six months). For patients who did not survive for six months, quality-of-life assessments were continued up until the final postoperative visit. The authors observed that a return to baseline quality of life occurred at 3–6 weeks for patients who had undergone minor hepatic resection, but that this baseline return was delayed until 6–12 weeks postoperatively in patients who underwent major hepatectomy. For patients who sustained a major postoperative complication, return to baseline quality of life was delayed until the 6-month evaluation. In the discussion of their paper, the authors stressed that the timing of postoperative chemotherapy or radiation therapy cannot be set arbitrarily, and that these therapeutic decisions should take quality-of-life assessments into account. Based on their data, the authors suggested that additional therapies be delayed until at least 6–12 weeks in patients undergoing major hepatectomy.

Long-term quality of life was analyzed in two articles written by European liver surgery centers. The first was by Kamphues and coauthors in BMC Surgery, 2011. This report presented quality of life data on 146 patients who had liver resection for benign disease. There was no perioperative mortality, although the disease recurred during follow-up in 13% of patients; the most common forms of recurrence were liver cysts. Quality of life was assessed using a standard instrument developed by the European Organization for Research and Treatment of Cancer. At a mean follow-up of 56 months, the authors found that quality of life had returned to a point that was significantly better than the baseline assessment—significant improvement had occurred in seven out of nine symptom domains. The authors concluded that treatment of benign liver lesions with hepatic resection is safe and leads to an improved quality of life.

Banz and coauthors compared long-term quality of life in patients who underwent hepatic resection for benign disease to patients who had resection for malignant disease in the World Journal of Surgery, 2009. This report described the results of objective and subjective quality-of-life scores assessed at more than two years following hepatic resection. Of interest is that the data disclosed similar patient opinions regarding quality of life in both groups. Objective assessments, however, disclosed significantly worse scores for items such as fatigue and weight loss in patients who underwent liver resection for malignant disease. The authors opined that patients with a poor prognosis who have hope for improvement with continued therapy may rate their overall quality of life better than objective assessments because of the quality of hope. It was further asserted that hope is what influences patients to undergo aggressive therapies when there is little statistical chance of improvement in survival. Banz and coauthors concluded with the recommendation that surgeons and oncologists consider these factors when caring for patients with malignant diseases of the liver.
I hope that you have found this first issue of our series on surgical diseases of the liver helpful. In the subsequent issue, we will review liver injuries and the management of metastatic lesions of the liver. In the final issue of the series, we will review material on the biology, diagnosis, and management of primary malignant lesions of the liver.

Thanks for reading SRGS!

Lewis Flint, MD, FACS
Editor in Chief


References


1. According to data cited by Mokdad and coauthors, the lowest cirrhosis-related mortality rates are recorded in which of the following countries?
   a) Norway
   b) Denmark
   c) Belgium
   d) Iceland
   e) France

2. Rehm and Shield presented information on the number of deaths attributable to alcohol-related causes. In 2010, the number was estimated to be which of the following?
   a) 1.5 Million
   b) 250,000
   c) 7.5 million
   d) 100,000
   e) 20 Million

3. Elements that contribute to the development of nonalcoholic fatty liver disease (NAFLD) include all of the following except which one?
   a) Central obesity
   b) Hypertension
   c) Fat deposition in the liver
   d) Type II diabetes
   e) Family history of hepatitis B infection

4. Which of the following cell types is activated by specific hepatitis C virus proteins leading to conversion of the cells to macrophages?
   a) Hepatocyte
   b) Biliary ductal cell
   c) Stellate cell
   d) Endothelial cell
   e) Polymorphonuclear leucocyte

5. Data presented by Suhail and coauthors confirmed that early-onset hepatocellular carcinoma is more common in which of the genotypes of hepatitis B virus?
   a) Genotype A
   b) Genotypes B and C
   c) Genotype D
   d) Genotype F
   e) Risk is the same in all genotypes

6. The most dependable prognostic finding in patients with NAFLD is which of the following?
   a) Degree of steatosis on hepatic MRI
   b) Liver size determined by ultrasound
   c) The patient’s MELD score
   d) Degree of fibrosis on liver biopsy
   e) Serum bilirubin level

7. Data from the study reported by Liu and coauthors suggested that NAFLD might be influenced by disordered metabolism of which of the following vitamins?
   a) Vitamin K
   b) Vitamin B
   c) Vitamin A
   d) Vitamin D
   e) Vitamin C

8. According to information presented in the article by Krier and Ahmed, all of the following are physical findings suggestive of cirrhosis except which one?
   a) Hepatosplenomegaly
   b) Ascites
   c) Palmar erythema
   d) Muscle wasting
   e) Nystagmus
9. Abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are discovered in what proportion of the general population?
   a) 12%
   b) 33%
   c) 50%
   d) 3%–4%
   e) 0.25%

10. According to data cited by Vilgrain and coauthors, imaging findings of nodular liver surface, atrophy of the right lobe of the liver, and hypertrophy of the left lobe, findings thought to be diagnostic of cirrhosis of the liver can also be found in patients with which of the following conditions?
   a) Biliary obstruction
   b) Hepatic metastases from colorectal cancer
   c) Hepatoblastoma
   d) Hepatic artery aneurysms
   e) Hairy cell leukemia

11. Which of the following is a factor limiting the accuracy of multi-detector CT imaging for diagnosis of metastatic lesions of the liver?
   a) Enlarged liver
   b) Presence of more than two lesions
   c) Inability of the patient to hold their breath
   d) Steatosis induced by chemotherapy
   e) Concomitant gallstone disease

12. According to data presented by Mullen and coauthors regarding patients who underwent major hepatic resection, compared with 30-day mortality, 90-day mortality was which of the following?
   a) Unchanged from 30-day mortality
   b) Increased by 3%
   c) Increased by 47%
   d) Increased by 12%
   e) Increased by 22%

13. Complication rates following hepatectomy are higher in obese patients because of which of the following?
   a) An increased incidence of ischemic heart disease
   b) Increased incidence of renal insufficiency
   c) Increased risk of deep vein thrombosis
   d) Increased risk of pulmonary complications
   e) Increased incidence of pressure ulcers

14. The right scissura of the liver courses from the anterior liver surface to the right side of the inferior vena cava and contains which of the following structures?
   a) Right hepatic vein
   b) Main suspensory ligament
   c) Left branch of the main bile duct
   d) The gall bladder
   e) Right hepatic artery

15. According to Clavien and coauthors, the earliest cell type to recover after liver resection is which one?
   a) Kupffer cell
   b) Stellate cell
   c) Biliary ductal cell
   d) Endothelial cells
   e) Hepatocytes

16. Data reported by Dunne and coauthors suggest that introduction of an enhanced recovery pathway is associated with which of the following in patients undergoing hepatectomy?
   a) Reduced mortality
   b) Reduced overall morbidity
   c) Reduced rate of pulmonary complications
   d) Fewer postoperative intensive care admissions
   e) Increased risk for perioperative transfusion
17. According to data presented by Day and coauthors, the use of a two-surgeon hepatic parenchymal dissection technique was associated with which of the following?

a) An increased risk for bile leak
b) Reduced rates of postoperative jaundice
c) Unchanged lengths of hospital stay
d) Reduced risk of postoperative urinary tract infection
e) Reduced rates of transfusion

18. Data reported by Sietses and coauthors showed that results of intraoperative ultrasound differed from results from preoperative CT imaging in what proportion of patients?

a) 2.5%
b) 38%
c) 11%
d) 51%
e) 0.2%

19. The article by Cauchy and coauthors documented a rate of conversion from laparoscopic to open liver resection of which of the following?

a) 1%
b) 35%
c) 50%
d) 13.5%
e) 6%

20. A limitation to the use of low central venous pressure and high pneumoperitoneum pressure as a means of reducing bleeding risk in patients undergoing laparoscopic liver resection is which of the following?

a) Risk of postoperative pneumonia
b) Increased risk of conversion to an open procedure
c) Increased risk of postoperative renal insufficiency
d) Higher overall mortality rates
e) Increased risk of air embolism

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21. This issue met the stated learning objectives.

a) Strongly agree
b) Agree
c) Neutral
d) Disagree
e) Strongly disagree

22. The content was relevant to my educational needs and practice environment.

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b) Agree
c) Neutral
d) Disagree
e) Strongly disagree

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c) Neutral
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e) Strongly disagree

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c) Neutral
d) Disagree
e) Strongly disagree

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1. Liver injury and disease pathogenesis in chronic hepatitis C...45-70
   Yamane D, McGivern DR, Masaki T, Lemon SM.
   The authors consider the virus-specific factors that produce liver damage in patients with hepatitis C.

2. The asymptomatic outpatient with abnormal liver function tests...71-81
   Krier M, Ahmed A.
   Krier and Ahmed provide clear guidance and advice for the evaluation of asymptomatic patients with abnormal liver function test results.

3. Noninvasive tests for liver disease, fibrosis, and cirrhosis: Is liver biopsy obsolete?...82-90
   Carey E, Carey WD.
   Carey and Carey present a thorough review of diagnostic tests for quantifying the extent of liver disease.

4. Current status of imaging and emerging techniques to evaluate liver metastases from colorectal carcinoma...91-102
   Sahani DV, Bajwa MA, Andrabi Y, Bajpai S, Cusack JC.
   The authors present data on the use of imaging to evaluate patients with liver metastases from colorectal cancer.

5. Systematic review of sarcopenia in patients operated on for gastrointestinal and hepatopancreatobiliary malignancies...103-113
   Levolger S, van Vugt JL, de Bruin RW, IJzermans JNM.
   This report suggests that the discovery of sarcopenia on preoperative CT imaging can provide useful prognostic information and guidance for preoperative interventions to improve nutritional status.

6. Perioperative considerations for patients with liver disease...114-118
   Martin P.
   Martin provides a valuable review of the preoperative preparation of patients with liver disease.

7. Liver anatomy...119-129
   Abdel-Misih SR, Bloomston M.
   The authors present a clear and useful review of the surgical anatomy of the liver.

8. Prediction, prevention and management of postresection liver failure...130-142
   Hammond JS, Guha IN, Beckingham IJ, Lobo DN.
   The authors provide useful information on posthepatectomy liver failure.

9. Enhanced recovery in the resection of colorectal liver metastases...143-148
   Dunne DF, Yip VS, Jones RP, et al.
   The authors share insights about the potential value of enhanced recovery pathways for patients undergoing liver procedures.

10. Advances in hepatectomy technique: Toward zero transfusions in the modern era of liver surgery...149-157
    Day RW, Brudvik KW, Vauthey JN, et al.
    The authors provide useful guidance for selection of hemostatic techniques for liver resection.

11. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka...158-168
    The authors review recommendations from a consensus conference that considered the usefulness of laparoscopic liver resection and the appropriate factors that should be included in reports of techniques and outcomes.
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