REVIEW ARTICLE

MEDICAL PROGRESS

Strategies for Safer Liver Surgery and Partial Liver Transplantation

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THE LIVER POSSESSES THE UNIQUE ABILITY TO REGENERATE WITHIN A short period.[1-3] This feature has led to the development of innovative strategies in liver surgery and transplantation. The anatomy of the liver is paramount in considering advances in hepatic surgery. The liver is divided into eight segments (Fig. 1). In healthy adults, the liver weighs about 1.5 kg (3.3 lb).[4] The blood supply of the liver is carried through two major vessels, the hepatic artery and the portal vein. The portal vein carries a large volume of venous blood to the liver from the gut, pancreas, and spleen, permitting hepatic processing of ingested and absorbed nutrients, among many other functions of the liver. The hepatic veins empty into the inferior vena cava.

LIVER RESECTION AND LIVER TRANSPLANTATION

Resection of hepatic tumors is being performed with increasing frequency worldwide, because it is now possible to select patients with a tumor load restricted to the liver, or with limited extrahepatic disease, thanks to the availability of imaging techniques such as the combination of positron-emission tomography and computed tomography (CT)[5-7] and improved intraoperative and postoperative management.[8-10] This ability to resect hepatic tumors currently offers the only curative option for many patients with primary or secondary liver tumors.[8-10] Liver resection is limited, however, by the need to preserve a sufficient amount of functional liver, because excessive resection leads to liver failure and death within a few days after surgery. Strategies have been developed to increase the volume and function of the potential liver remnant before resection of the diseased part, with the intention of making surgery safer and expanding indications for liver resection.

Liver transplantation has also progressed during the past decade. One of the landmark advances in liver transplantation is the ability to use partial liver grafts obtained from either a deceased donor (a single liver thus obtained can be split and used for two recipients, usually an adult and a child) or a living donor. The minimal amount of functional liver necessary for successful transplantation has been a major concern. For reasons that are unclear, a larger allograft volume is needed for transplantation than might be expected on the basis of experience with liver resection.[11] The possibility of using a small amount of liver tissue (e.g., segments II and III, which are used in transplantation in children with a body weight of ≤15 kg [33 lb][12]) might solve the worldwide problem of a shortage of liver grafts: two adults could benefit from one graft from a single deceased donor, and living donation might gain wider acceptance than is now the case, because a bisegmentectomy (segments II and III) in a healthy donor is associated with a lower relative risk — similar to that of kidney donation — than is a right hemihepatectomy (segments V through

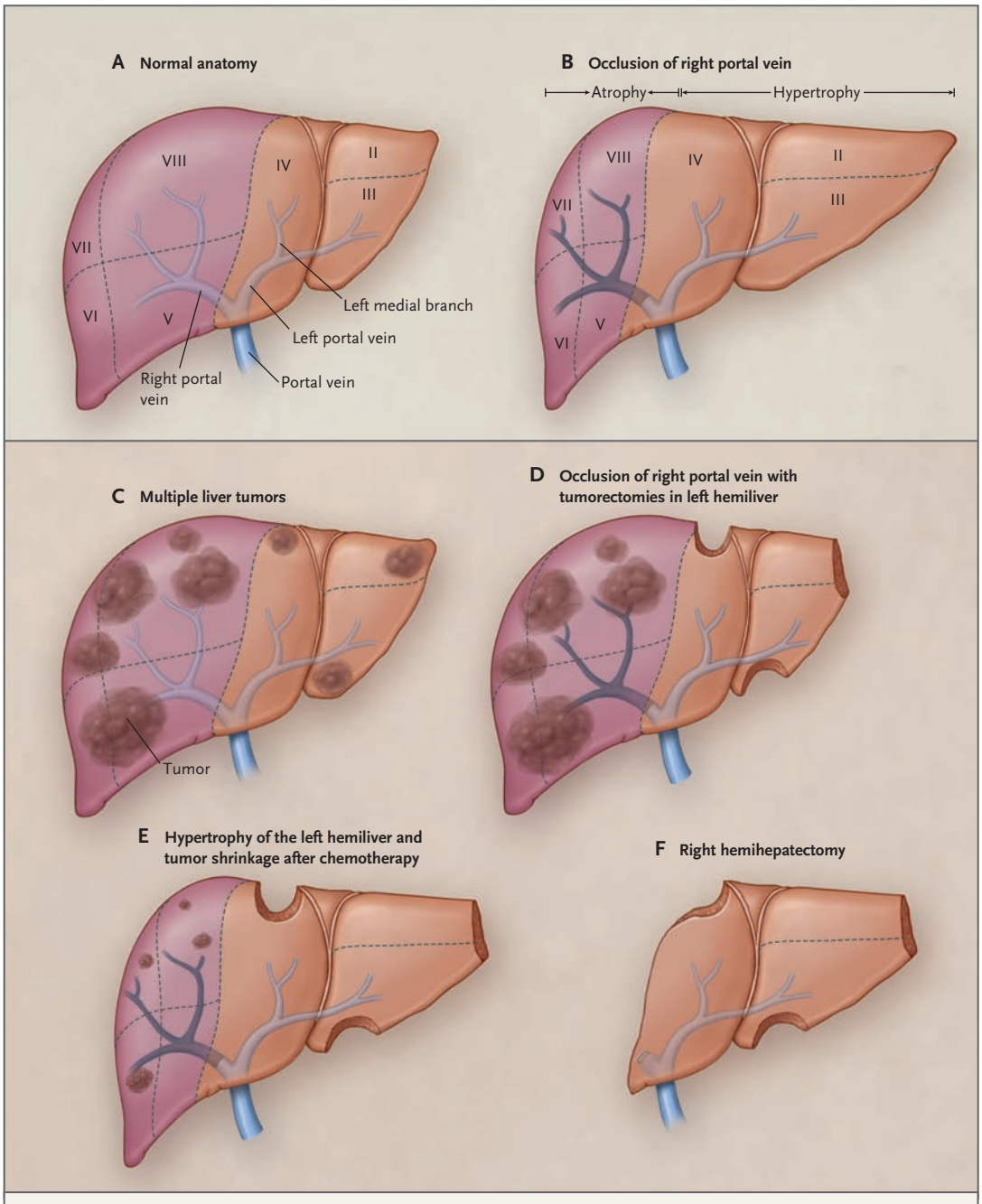


Figure 1. Normal Liver Anatomy and the Principle of Portal-Vein Occlusion with and without Concomitant Chemotherapy.

Panel A shows normal liver anatomy, with segments II through VIII shown. Segment I, which lies posteriorly, next to the vena cava, is not shown. The portal vein is shown, with the right portal vein, the left portal vein, and the left medial branch to segment IV. Panel B shows occlusion of the right portal vein, which results in ipsilateral atrophy of the right hemiliver (segments V through VIII) and contralateral compensatory hypertrophy of the left hemiliver segments I through IV. Panel C shows metastases throughout the liver. Panels D, E, and F show a two-stage procedure. In the first stage, small tumorectomies in the potential left remnant hemiliver and occlusion of the right portal vein by means of portal-vein embolization or ligation are performed (Panel D) with concomitant local intraarterial or systemic chemotherapy, resulting in the shrinkage of residual tumors and the right hemiliver, with compensatory hypertrophy of the contralateral hemiliver (Panel E). In the second stage, a curative liver resection (right hemihepatectomy, segments V through VIII, or extended right hemihepatectomy, including segment IV) is performed (Panel F).

VIII) (Fig. 1). The current mortality rate for a right hemihepatectomy in a living donor, which is the resection used for transplantation in an adult recipient, is about 0.2 to 0.5%, with a rate of complications of 15 to 30%.[11,13,14]

This review presents both established and new methods for manipulating liver volume to improve liver surgery and transplantation. We first discuss the process of liver regeneration, then assessment of the minimal liver volume necessary for a given patient and prediction of hepatic function after surgery. Current practice is discussed, along with promising strategies to maximize liver regeneration.

LIVER REGENERATION

RESPONSE TO MAJOR TISSUE LOSS

The human body responds to partial hepatectomy not by regenerating lost segments but by inducing hyperplasia in the liver remnant.[1-3] The anatomical structures of a liver that has undergone partial hepatectomy are therefore distinctly different from those of the original liver.

The process of restoration of liver volume in humans is initiated by the replication of various types of intrahepatic cells, followed by an increase in cell size. The onset and peak of hepatocyte replication vary among species. In humans, replication of hepatocytes generally starts within 1 day after a major resection. Nonparenchymal cells, such as endothelial cells, Kupffer cells (macrophages resident in the liver), and biliary-duct cells, replicate in a delayed fashion. After replication has been completed, growth consisting of an increase in cell size occurs over several additional days.

The initiation and synchronization of replication in different types of hepatic cells depend on the extent of the resection, tissue damage, or both. Low-grade tissue damage (e.g., toxic or ischemic injury) or a relatively small resection (removal of less than 30% of the liver) substantially reduces the replication rate, which also appears to be less synchronized than after a large resection (removal of 70% of the liver).[1,3,15] After a massive resection, up to 90% of the hepatocytes appear to replicate.[1]

MOLECULAR BASIS OF LIVER REGENERATION

Liver regeneration has been studied in rodent models, an approach that permits the determination of cellular events and the analysis of the molecular triggers governing regeneration.[1-3] Briefly, the process of liver regeneration involves mediators similar to those found in acute inflammation. Normally, hepatocytes are in the quiescent G_0 phase. After resection, the remaining hepatocytes enter the G_1 phase. Cytokines derived predominantly from Kupffer cells prime hepatocytes; tumor necrosis factor α (TNF-α) and, subsequently, interleukin-6 are released, contributing to the initiation of the cell cycle (Fig. 2).[16,17] Mitogenic factors are required for the regenerative process to enter the S phase, primarily growth factors such as epidermal growth factor, hepatocyte growth factor, and transforming growth factor α (TGF-α).[18,19] Integration of these signals induces full and synchronized regeneration. Failure to activate this signal cascade can result in a delay in the onset of regeneration, inadequate recovery of liver volume, and eventually clinical signs of liver failure.[20] Termination of the regenerative process appears to be controlled by the action of transforming growth factor β (TGF-β) and other members of the activin family.[21]

Two recent reports shed further light on the mechanisms of regeneration. In one report from our group, platelets (thrombocytes) were shown to be critically involved in regeneration.[22] Serotonin, a neurotransmitter transported within the peripheral circulation by platelets, appears to be a co-mitogen that is essential for hepatic regeneration. Mice deficient in tryptophan hydroxylase 1, which lack peripheral serotonin, have diminished hepatocyte proliferation after partial hepatectomy.[22]

According to another recent report, bile acids also appear to influence regeneration.[23] In experiments in animals in which bile-acid pools were high, regeneration was complete, whereas low bile flow was associated with reduced hepatocyte replication. The signal responsible for this feedback mechanism of regeneration is a nuclear bile receptor, the farnesoid X receptor. This mechanism may be important in integrating the metabolic load of the liver and may have a direct effect on regeneration.[23] The integration of all these signals is necessary for full and synchronized regeneration.

LIVER VOLUME

MINIMAL VOLUME FOR THE SURGICALLY CREATED LIVER REMNANT OR ALLOGRAFT

Below a certain threshold volume, a liver remnant cannot sustain metabolic, synthetic, and

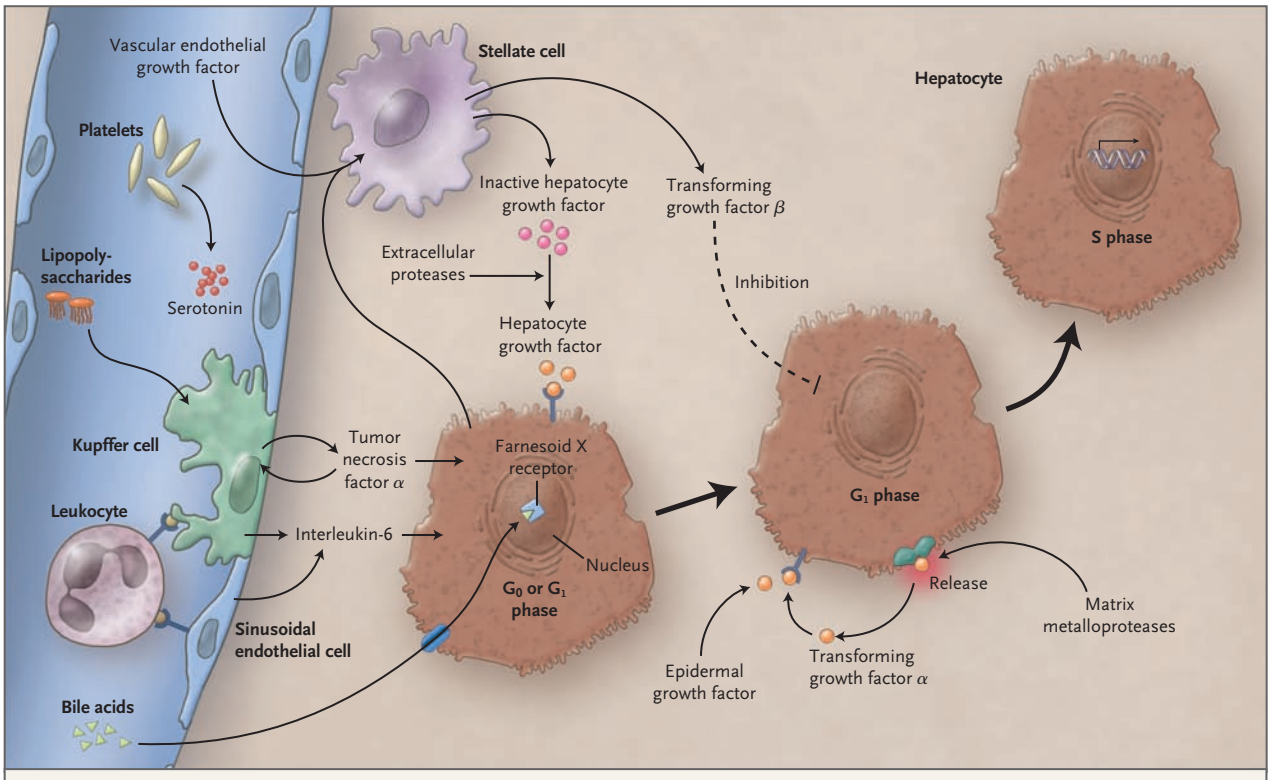


Figure 2. Pathways of Liver Regeneration Initiated by Major Hepatectomy.

After hepatectomy, nonparenchymal cells, such as stellate cells, Kupffer cells, leukocytes, and platelets, are activated by soluble factors, such as vascular endothelial growth factor and lipopolysaccharide. Interaction between activated vascular components, including platelets, leukocytes, sinusoidal endothelial cells, and Kupffer cells, results in the release of tumor necrosis factor α, interleukin-6, and serotonin. The cytokines cause a priming of the remnant hepatocytes, and concurrently, extracellular proteases such as urokinase-type plasminogen activator convert inactive hepatocyte growth factor to its active form. Inactive hepatocyte growth factor, which is secreted by stellate cells, is a mitogen that induces hepatocyte proliferation. Matrix metalloproteases convert membrane-bound transforming growth factor α into the soluble form. In an autocrine loop, transforming growth factor α, along with endothelial growth factor, signals through the endothelial growth factor receptor. The cytokines and the growth factors act in concert to initiate the reentry of quiescent hepatocytes (in the G_0 phase) into the cell cycle from the G_1 phase to the S phase, resulting in DNA synthesis and hepatocyte proliferation. To signal the end of proliferation, transforming growth factor β blocks further replication. The metabolic load resulting from the loss of hepatocytes is indicated by the accumulation of bile acids in the blood. The bile acids enter the hepatocytes and drive bile acid receptors such as the farnesoid X receptor, resulting in increased protein and DNA synthesis.

detoxifying functions. In this situation, the postoperative course evolves with signs of liver failure, primarily jaundice, coagulopathy, encephalopathy, and ascites, as well as renal and pulmonary failure, all of which may become apparent only 3 to 5 days after surgery. Together, these signs have been termed the "small-for-size syndrome."[24,25] Studies in mice suggest that the failure of a partial liver to regenerate is the most important contributing factor in the small-for-size-syndrome.[20]

Although the removal of up to 75% of the total liver volume is feasible in a young patient (≤40 years of age) with normal hepatic parenchyma, resection must be more conservative in the presence of underlying liver diseases or in elderly patients (e.g., ≥70 years of age) (Table 1).

CIRRHOSIS

The best-studied underlying liver disease in persons undergoing resection is cirrhosis, which is associated with the development of hepatocellular carcinoma. The cirrhotic liver tolerates acute tissue loss poorly, given its impaired function and decreased ability to regenerate.[26] In addition, portal hypertension, if present, is associated with a poor outcome because of compromised portal flow and the risk of postoperative upper gastrointestinal bleeding.[27] These features are critical in selecting patients with cirrhosis for surgery.[27] For example, a right hemihepatectomy is associated with a low risk of liver failure or death in patients with cirrhosis who have normal serum bilirubin levels and prothrombin times and do not have

any signs of portal hypertension. In contrast, even a limited wedge (localized) resection may result in liver failure and death in patients with poor liver function and portal hypertension.

FATTY LIVER

Liver steatosis is another common condition and is usually related to obesity, the presence of metabolic disorders, or the intake of alcohol or drugs; hepatic steatosis increases the risk of liver resection, according to most large studies.[8,28,29] Experimental data indicate that macrosteatosis (the presence of a single large droplet of fat, displacing the nucleus, in hepatocytes) increases this risk more than does microsteatosis (the presence of small, multiple fat deposits in hepatocytes).[30] How to adjust the extent of liver resection in patients with steatosis is unclear, but most experienced surgeons consider that mild steatosis (up to 30% of hepatocytes containing fat) represents a minimal additional risk or none, whereas patients with severe steatosis (more than 60% of hepatocytes containing fat) should undergo only limited resection (e.g., one or two segments). In patients with moderate steatosis (30 to 60% of hepatocytes containing fat), caution is necessary, particularly if macrosteatosis is present, and conservative resection should be favored over major resection.[29] Steatosis can often be treated successfully within a few weeks if the patient is placed on a strict low-fat, high-protein diet (initially, 1400 calories per day, with a rapid reduction to 1200 and then to 1000 calories).[31] Liver biopsies should be performed in patients with suspected moderate-to-severe steatosis to document improvement with such a diet. The association between inflammation (marked by leukocyte infiltration), hepatocellular ballooning, and steatosis, termed nonalcoholic steatohepatitis, constitutes an additional operative risk.[32-34]

LIVER AFTER CHEMOTHERAPY

An increasing number of patients with tumors undergo extensive chemotherapy with multiple drugs before surgery. Drugs such as irinotecan (Campto, Pfizer) and, to a lesser degree, oxaliplatin (Eloxatin, Sanofi Aventis) have been associated with the development of steatohepatitis,[33,34] and among patients receiving these drugs, the rates of complications and death after major liver resection are likely to be increased, as compared with the rates among patients not receiving these drugs.[33,34] We and others avoid major resection in such patients.[33] In addition, severe hepatic sinusoidal obstruction, occasionally associated with nodular regenerative hyperplasia, has been ascribed to oxaliplatin-based chemotherapy.[35-37] These vascular obstructions result in a bluish appearance of the liver, known as the blue liver syndrome.[36] Patients with this histologic feature are at higher risk for intraoperative blood loss and postoperative complications than are patients without this feature. Bevacizumab (Avastin, Hoffmann–La Roche), a monoclonal antibody targeting vascular endothelial growth factor (VEGF) in combination with cytotoxic chemotherapy, appears to improve survival in patients with metastatic colorectal cancer.[38] Because VEGF influences liver regeneration through its regulation of angiogenesis and the release of growth factors, and because bevacizumab therapy impairs wound healing,[39] the effect of bevacizumab may be deleterious.[40] However, when there is a window of 6 to 8 weeks between the administration of bevacizumab and the surgery, the risk of perioperative complications after liver resection may not be increased.[41] Although most experienced clinicians favor wedge, rather than major, resection in patients exposed to extensive chemotherapy, there is currently no consensus for managing the care of such patients, and the optimal window between the completion of chemotherapy and surgery remains uncertain.

Table 1. Risk Factors for Postoperative Liver Failure.

Older age (e.g., ≥70 yr)
Cirrhosis
Fibrosis
Hepatitis
Intraoperative blood loss
Ischemia
Obstructive cholestasis
Preoperative chemotherapy
Steatosis

REMNANT DONOR LIVER AND PARTIAL GRAFT

Particular caution is indicated when subjecting healthy living donors to the major liver surgery that donation necessitates. Zero mortality and low morbidity are the goals, and surgery should not be considered if the liver remnant of a potential donor would be below 35% of its initial volume.[11,42] Furthermore, although potential donors with up to 15% steatosis are generally accepted

by most transplantation centers, those with higher liver-fat content are usually not accepted or are placed in a weight-loss program.

An important concept in the growing field of partial liver transplantation is that of minimal viable graft volume. An allograft mass that is 35 to 40% of a normal liver, often expressed as a ratio of the graft to the total body weight of the recipient (0.8 to 1%), must be obtained to ensure successful and viable transplantation.[43] On the basis of such a measure, a transplant recipient with a body weight of 75 kg (165 lb) should receive a graft weighing 600 to 750 g (1.3 to 1.7 lb), which is usually obtained only by a right hemihepatectomy. Recipients with more severe disease require a higher graft volume.[42] Also, surgical technique, such as reconstruction of the hepatic veins to make optimal outflow possible, is crucial to ensure early postoperative function and regeneration of the graft.[44]

PREOPERATIVE EVALUATION

CLINICAL AND BIOCHEMICAL TESTS

Assessment of the volume of the potential liver remnant or allograft as well as measurement of preoperative liver function are essential. Routine liver biochemical measurements (i.e., bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels), a coagulation profile, and a platelet count, combined with the proper assessment of the predicted volume of the liver remnant on CT or magnetic resonance imaging (MRI), generally suffice for an assessment of a candidate with normal liver parenchyma for major liver surgery. The situation is more complicated in a candidate with preexisting liver dysfunction. In a patient with cirrhosis, the evaluation most often used relies on the Child–Turcotte–Pugh classification, which is based on a score that includes bilirubin and albumin levels, prothrombin time, and the presence or absence of ascites and encephalopathy (Table 2).[46,47] Many clinicians add upper gastrointestinal endoscopy to rule out esophagogastric varices, a sign of portal hypertension. A low platelet count (<100,000 per cubic millimeter) or the presence of large varices on preoperative imaging (CT or MRI) rules out patients with cirrhosis as candidates for major liver resection.[48] Other practitioners recommend direct measurement of the actual hepatic venous pressure gradient in order to select patients with cirrhosis who might be candidates for liver resection.[27]

DYNAMIC LIVER TESTS

Other quantitative liver-function tests are most often used in Asia, where the majority of patients

Table 2. Child–Turcotte–Pugh Classification.*

Biochemical and Clinical Criteria	Points		
	1	2	3
Albumin (g/dl)	>3.5	2.8–3.5	<2.8
Bilirubin (mg/dl)	>2.0	2.0–3.0	<3.0
Prothrombin time			
Seconds	<4	4–6	>6.0
International normalized ratio	<1.7	1.7–2.3	>2.3
Ascites	None	Moderate (or suppressed with medication)	Tense (or refractory to medication)
Encephalopathy	None	Grades I–II (or suppressed with medication)	Grades III–IV (or refractory to medication)

* Most authors divide the cumulative score of the Child–Turcotte–Pugh classification into grade A (5–6 points, indicating well-compensated disease), grade B (7–9 points, significant functional compromise), and grade C (10–15 points, decompensated disease). Encephalopathy is graded according to the West Haven criteria of altered mental state in hepatic encephalopathy,[45] as follows: grade I, lack of awareness, shortened attention, euphoria, or anxiety; grade II, lethargy or apathy and minimal disorientation; grade III, somnolence to semistupor with gross disorientation; grade IV, coma with unresponsiveness to verbal or noxious stimuli. Asterixis ("flapping tremor") is often observed in patients with grade I altered mental state and is always present in patients with grades II and III. To convert values for bilirubin to micromoles per liter, multiply by 17.1.

undergoing liver surgery have hepatocellular carcinoma related to hepatitis B or C cirrhosis. Metabolic tests (Table 3) target different aspects of hepatic physiology.[49-51] The most commonly used test is intravenous injection of indocyanine green (0.5 mg per kilogram), a dark bluish-green tricarbocyanine dye that rapidly binds to plasma β-lipoprotein and is completely and exclusively removed by hepatocytes. Indocyanine green is excreted into bile in unmodified form and does not enter the enterohepatic recirculation.[52] The rate of retention of indocyanine green determined at 15 minutes after injection must be interpreted in the context of other factors.[50,52] For example, patients with a favorable Child–Turcotte–Pugh score of A (Table 2) and a retention rate of indocyanine green at 15 minutes of less than 14% generally tolerate major hepatectomy well, whereas those with a retention rate greater than 20% should be excluded from major liver resection. Patients with retention rates between 14 and 20% should undergo surgery only after an assessment of liver volume with possible preoperative portal-vein embolization (Fig. 3A).[48,53]

SAFER LIVER RESECTION AND PARTIAL LIVER TRANSPLANTATION

STRATEGIES FOR MANIPULATING LIVER VOLUME

Experiments performed almost a century ago suggested that selective occlusion of the portal branch causes atrophy of the ipsilateral liver lobe and hypertrophy of the contralateral lobe.[54] Induced atrophy of the occluded hemiliver is triggered by increased apoptotic activity, whereas hypertrophy of the nonoccluded lobe appears to be linked to increased cellular proliferation.[55] In the late 1980s, Makuuchi and colleagues first used the selective-occlusion strategy in patients to extend the limits of liver resection (Fig. 1).[56] Selective interruption of the portal flow to a portion of the liver can be achieved by means of portal-vein embolization or ligation. Although portal-vein ligation requires a surgical (open or laparoscopic) approach, portal-vein embolization can be performed percutaneously, usually by means of a transhepatic approach using embolic materials such as gelatin sponge, cyanoacrylate with ethiodized oil, alcohol, fibrin glue, particles, or coils.[57] Both embolization and ligation of the portal vein are usually performed at the right portal vein in preparation for a right hemihepatectomy (removal of segments V through VIII) or an extended right hemihepatectomy (removal also of segment IV) in instances when the potential liver remnant would otherwise be too small.[56,58-61] When an extended right hemihepatectomy is to be performed, the volume of the liver remnant is optimized by the addition of occlusion of the left medial branch (segment IV) (Fig. 1).[62] Portal-vein embolization or ligation has recently been integrated into and is considered essential to a strategy for two-stage hepatectomy

Table 3. Dynamic Tests to Assess Liver Function Preoperatively.

Function Measured	Test	Principle of Test
Microsomal hepatic function	Breath tests (C-labeled aminopyrine, methacetin, caffeine)	Breath tests are used to probe hepatic microsomal P450 enzyme activity and investigate hepatocellular function by assessing liver oxidation. The exhaled labeled CO_2 is measured.
	Clearance tests (antipyrine, caffeine, lidocaine)	Clearance tests probe the hepatic microsomal P450 enzyme activity and measure either the metabolic elimination of the test compound or the appearance of metabolites in the blood that are primarily dependent on the hepatic metabolic capacity.
Cytosolic hepatic function	Elimination capacity test (galactose)	The capacity for elimination of galactose is estimated by serial measurements of serum galactose levels after administration of an intravenous bolus of galactose; galactose is metabolized by the cytosolic enzyme galactokinase.
Liver perfusion and biliary excretion	Clearance test (indocyanine green)	Indocyanine green is distributed in the serum, removed by the liver, and excreted unchanged into bile without entering the enterohepatic circulation.
Liver perfusion	Clearance tests (low-dose galactose, sorbitol)	The high rate of hepatic extraction of low-dose galactose and sorbitol by the sinusoidal membrane of hepatocytes implies a hepatic plasma flow–dependent mechanism.
Hepatocyte mass	Uptake test (technetium-99m–galactosyl human serum albumin labeling)	Technetium-99m–galactosyl human serum albumin accumulates only in the liver by ligand–receptor binding and is visualized on scintigraphy.

for initially unresectable, multiple liver tumors (Fig. 1).[63-65] Currently, portal-vein ligation is used only during an open procedure — for example, insertion of a device for selective intraarterial delivery of chemotherapy or limited hepatectomy for planned two-stage procedures.[65]

INDICATIONS FOR PORTAL-VEIN OCCLUSION

Portal-vein embolization is indicated only if the volume of the potential liver remnant would be below the threshold associated with a high risk of inadequate liver volume after surgery.[66,67] Most surgeons consider a major resection 2 to 4 weeks after portal-vein occlusion, when the maximal changes in volume have been reached.[68] Portal-vein embolization is also increasingly used as a dynamic preoperative test to identify patients in whom liver regeneration will be impaired, who for that reason should not undergo the surgery.[66] This approach is especially relevant for patients with chronic liver diseases, cholestasis, and a history of chemotherapy.[66,69] It is supported by a study in patients with cirrhosis in whom the failure of regeneration after portal-vein embolization predicted a poor outcome after surgery.[67] Although there are no universally accepted guidelines, two algorithms for the treatment of patients with normal livers (Fig. 3A) or cirrhotic livers (Fig. 3B) summarize what we consider a reasonable approach to major resection.

PORTAL-VEIN OCCLUSION WITH CHEMOTHERAPY

New strategies have focused on combining selective portal-vein obstruction with the concomitant administration of systemic[59,64,69,70] or selective intraarterial hepatic[65] chemotherapy before liver resection, with the aim of achieving both a reduction in the tumor size and a change in liver volume (Fig. 1 and Fig. 4). These strategies have been applied mainly in patients with a nonresectable, advanced tumor load and a liver remnant that was predicted to be too small for resection. The regimen and the timing of systemic chemotherapy and portal-vein embolization have been variable, but fluorouracil-based chemotherapy with or without oxaliplatin, irinotecan, or bevacizumab is the regimen most often used.[59,64,70] In a pilot study, continuous delivery of selective intraarterial chemotherapy with floxuridine (FUDR, Hoffmann–La Roche) and right portal-vein ligation in 11 patients with multiple nonresectable metastases of colorectal origin were associated with a significant decrease in tumor volume and a significant increase in the volume of the contralateral left hemiliver (Fig. 4).[65] About one third of the patients receiving this treatment underwent curative liver resection 3 months after the start of treatment. Impairment of the hypertrophy induced by portal-vein obstruction that results from concomitant continuous chemotherapy, although a concern, has not been observed to date.[71] When liver resection is not performed after portal-vein embolization or ligation, the use of further systemic or regional chemotherapy remains possible. The main complication of selective hepatic delivery of floxuridine appears to be the development of intrahepatic and extrahepatic biliary strictures.[72,73]

Figure 3 (facing page). Proposed Decision Tree for Major Hepatectomy in Patients with Normal Liver Parenchyma and Those with Cirrhosis.

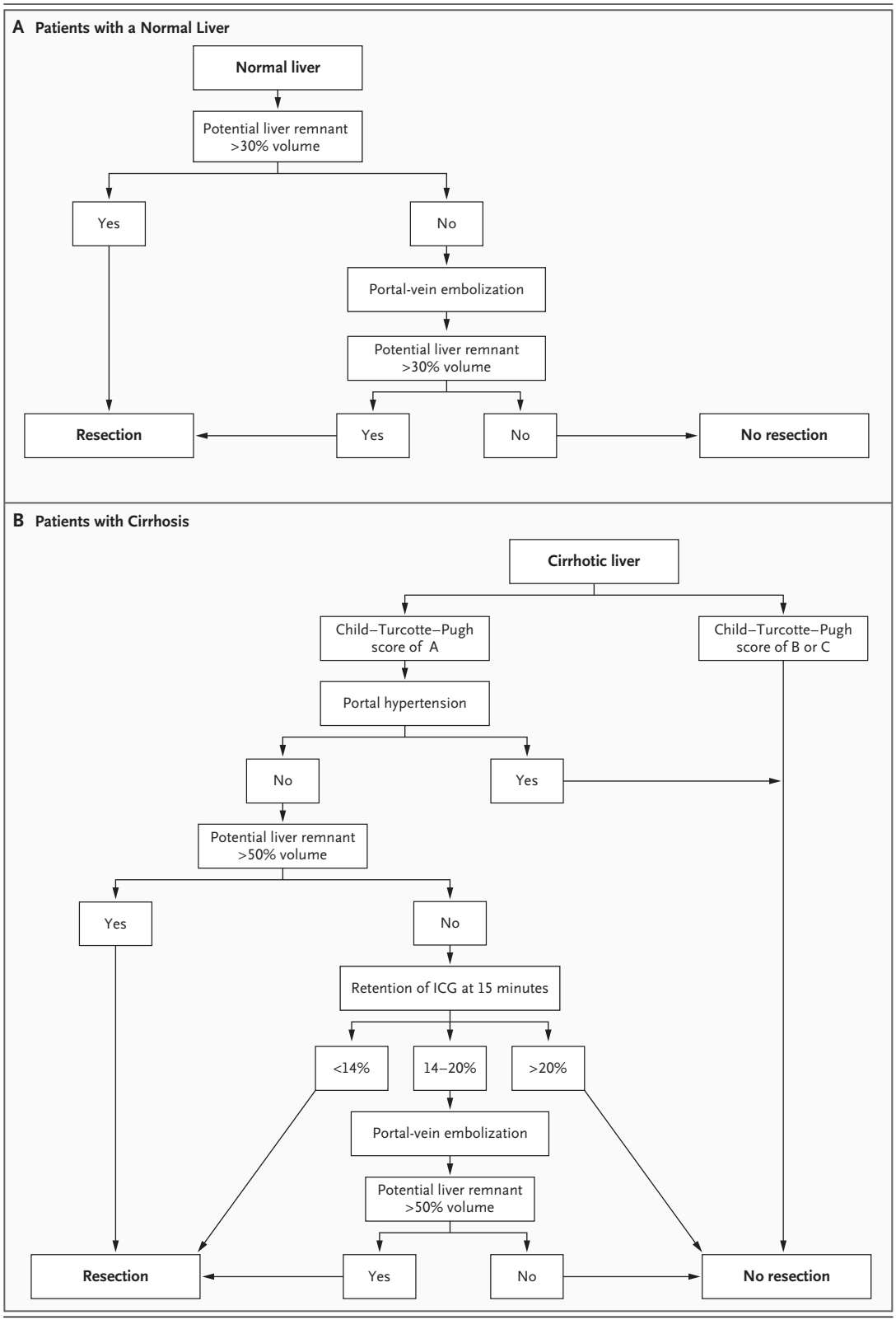
The cutoff points of 30% volume (Panel A) and 50% volume (Panel B) for the potential liver remnant are based on our current practice and available data. For cirrhotic livers with a rate of retention of indocyanine green (ICG) that is less than 14% at 15 minutes (Panel B) and livers with underlying noncirrhotic diseases such as steatosis or fibrosis, we apply the algorithm for normal liver parenchyma with a higher cutoff point (35 to 40%) for the volume of the potential liver remnant.

PORTAL-VEIN EMBOLIZATION WITH CHEMOEMBOLIZATION

Another strategy in patients with hepatocellular carcinoma is the sequential use of transarterial chemoembolization, portal-vein embolization, and then major liver resection.[67,74] Transarterial chemoembolization is directed both to the tumor treatment and to embolization of arterioportal shunts, which are frequently present in cirrhosis. Transarterial chemoembolization may prevent tumor progression during the period of portal-vein embolization and the planned surgery.[75] This approach, as compared with portal-vein embolization alone, has been associated with more efficient hypertrophy and improved tumor control before major hepatectomy.[67]

PORTAL-VEIN EMBOLIZATION WITH BILIARY DRAINAGE

Patients with hilar cholangiocarcinomas often require complex liver resection. Since segment I is also removed during such resection because of a high incidence of recurrence at this location, the



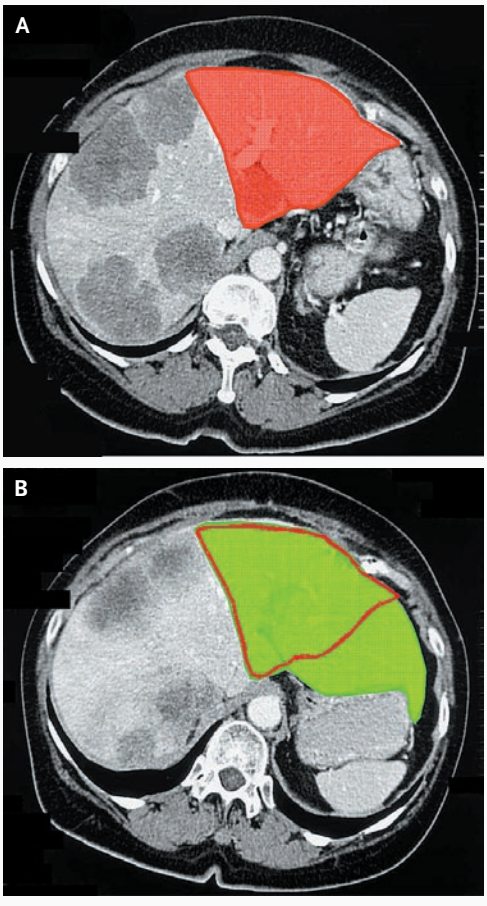


Figure 4. CT Images of the Effects of Portal-Vein Ligation and Selective Administration of Intraarterial Chemotherapy.

A 58-year-old patient with multifocal colorectal liver metastases underwent ligation of the right portal vein (segments V through VIII) and the medial portal vein (segment IV) to induce compensatory hypertrophy of segments II and III (red, before ligation) and the implantation of a pump to selectively deliver chemotherapy in the gastroduodenal artery (Panel A). After administration of continuous intraarterial chemotherapy with floxuridin, the colorectal liver metastases were significantly reduced (by about 60%), and significant hypertrophy (100%) (green, after ligation) developed in the left liver 3 months later (Panel B). Adapted from Selzner et al.,[65] with the permission of the publisher.

liver remnant typically consists only of segments II and III and the upper part of segment IV.[76,77] These patients frequently present with severe cholestasis and impaired liver function due to obstruction of the bile duct. A preoperative strategy of biliary drainage of the potential liver remnant followed by portal-vein embolization of the area of the planned resection has been reported to reverse cholestasis and increase the size of the potential liver remnant before surgery.[77-79] Although the optimal timing of these interventions has not been determined, we, and others,[80] now perform portal-vein embolization within 1 to 3 weeks after biliary drainage and consider surgery after the cholestasis resolves (usually when the bilirubin level is less than 50 μmol per liter [2.9 mg per deciliter]) and there is an adequate regenerative response (Fig. 3). With the use of this strategy, several studies of extensive liver resections for hilar cholangiocarcinomas without perioperative deaths have been reported.[61,77,78]

EFFECT ON TUMOR GROWTH

A legitimate concern is whether the stimulus for liver regeneration induced by portal-vein occlusion might enhance tumor growth. Although there have been few reports of an influence of portal-vein occlusion on tumor growth,[70,81-83] most other studies of colorectal liver metastases have failed to show any negative effect of portal-vein occlusion on tumor growth or reduced patient survival after surgery.[59,65,84,85] One study reported a lower rate of recurrence of hepatic cancer after portal-vein embolization that was followed by surgery, as compared with resection alone.[85] However, the intuitive concern that metastases in the nonembolized hemiliver might grow more rapidly after right portal-vein embolization has led to the proposal of a two-stage procedure. In the first stage, all visible metastases in the left hemiliver are cleared in association with right portal-vein embolization[64] or ligation,[65] and in the second stage, about 4 weeks later, a right or extended right hemihepatectomy is performed. When concomitant chemotherapy is used, definitive liver resection is usually performed 3 or more months after the start of treatment (Fig. 1).

SMALL LIVER GRAFT

In liver transplantation, only a few clinically applicable strategies are available to ensure sufficient function of undersize grafts obtained from living or deceased donors. Prolonged cold ischemia during organ procurement has a negative effect on liver regeneration[86] and the clinical outcome after transplantation.[87] Therefore, efforts should be made to keep the ischemia time as short as possible. Recipients who are in poor general condition and have low hepatic reserve are at increased

risk for complications after partial liver transplantation.[42] Such patients should be considered candidates only for the transplantation of a whole cadaveric organ.

Injury to small grafts is associated with portal hyperperfusion, caused by the combination of a low liver volume and preexisting portal hypertension.[25] Although enhanced liver regeneration might have been anticipated on the basis of increased portal flow, portal hyperperfusion is currently seen by many as the cause of failure in small grafts. One explanation is that changes in portal flow induce reciprocal effects on hepatic arterial flow, implying that post-transplantation portal hyperperfusion results in a compensatory decrease in arterial flow.[88] A reduction in the portal venous flow by means of portal banding, splenic-artery ligation, or a hemiportocaval shunt may prevent postoperative liver failure, resulting in improved survival of the graft and the patient after transplantation of a partial liver graft.[25,89] For split-liver transplantation of a cadaveric graft, only optimal grafts are used, and grafts from older donors (>50 years of age), steatotic organs, and organs with a low ratio of the graft weight to the total body weight of the recipient should be avoided.[90,91]

HEPATOPROTECTIVE STRATEGIES

PHARMACOLOGIC APPROACHES

Efforts to develop pharmacologic means of protecting the liver from damage during regeneration have identified a few molecular targets. Our group has recently shown that pentoxifylline (Trental, Hoechst–Roussel), an inhibitor of TNF-α synthesis in Kupffer cells that has other properties such as vasodilatation and induction of the interleukin-6 pathway, reduces the likelihood of inadequate liver function in the liver remnant in a murine model of partial liver transplantation.[20] Pretreatment of a small graft (30% of the total liver volume) and of the recipient with pentoxifylline prevents lethal outcomes and fully restores regeneration.[16]

Acetylcysteine, a precursor of glutathione, has been widely studied as a protective molecule. Clinical trials of its use in the perioperative treatment of patients undergoing liver transplantation showed reduced levels of circulating selectins[92] and a reduction in the severity of rejection in pediatric patients undergoing liver transplantation,[93] but neither study showed an overt benefit for the patient.

Other molecules, such as cardiotrophin-1, a member of the interleukin-6 cytokine family, have shown a hepatoprotective potential in rescuing regeneration and in animal survival after 90% hepatectomy in rats.[94] Drugs associated with a reduction in portal pressure, such as somatostatin,[95] fingolimod (FTY720, Novartis Pharma),[96] or the low-dose nitric oxide donor FK 409,[97] provided significant protection in rat models of small-graft transplantation. These drugs have additional effects that might contribute to protection, such as down-regulation of endothelin-1, up-regulation of heme oxygenase-1[95,97] or interleukin-10,[97] and activation of Akt signaling, which has been shown to be related to cell survival.[96] An immunosuppressive agent, sirolimus (Rapamune, Wyeth–Ayerst), has also been shown to minimize injury and improve survival — effects that may be related to suppression of the activation of hepatic stellate cells — in a model of partial graft transplantation in cirrhotic rats.[98] Although these strategies have been successful in animal models, their usefulness in humans remains to be demonstrated in clinical trials.

SURGICAL APPROACHES

Occlusion of the portal triad (the Pringle maneuver) and total vascular exclusion (concomitant clamping of the infrahepatic and suprahepatic vena cava and the portal triad) are techniques used to minimize blood loss and the need for blood transfusions during liver surgery.[8,99] Both techniques, however, cause inevitable ischemic injury that may impair liver regeneration after major hepatectomy.[100] Intermittent clamping of the portal triad and ischemic preconditioning (a brief period of ischemia followed by a short interval of reperfusion) are established nonpharmacologic strategies to protect the liver from prolonged ischemic injury.[101-103] The underlying protective principle of ischemic preconditioning is that cells are exposed to a limited stress that triggers natural defense mechanisms against subsequent ischemic injury.[104-106] Intermittent clamping and ischemic preconditioning are highly and equally effective in minimizing postoperative injury to the liver, but intermittent clamping appears to be superior for long periods of ischemia (≥75 minutes).[103,107,108] (For detailed insights into hepatoprotective strategies, see Selzner et al.[109])

CONCLUSIONS

There has been substantial progress in both liver surgery and liver transplantation owing to improved preoperative diagnosis and intraoperative and postoperative care. Factors that limit the achievement of curative tumor resection are the high morbidity and mortality rates associated with insufficient volume of the liver remnant. Many tumors that were previously considered to be unresectable are now amenable to complete resection through innovative strategies that make manipulation of the liver volume possible. Portal-vein embolization or ligation causes atrophy of the ipsilateral hemiliver and hypertrophy of the contralateral side. Portal-vein embolization appears to be particularly valuable in patients who have underlying liver disease. The concomitant administration of chemotherapy may further decrease both the tumor load and postoperative recurrences.

The use of partial liver transplantation is also rapidly increasing, as transplantation surgeons and hepatologists attempt to overcome the worldwide shortage of organs available for transplantation. Unfortunately, there is still a need for a substantial graft volume to support life, which places healthy donors at substantial risk. In the future, the use of new drugs based on innovative experimental models, together with a better understanding of the pathways leading to liver regeneration, may permit a very small liver remnant to regenerate, resulting in safer surgery for living donors and for patients with large tumors.

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