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Review

How much liver resection is too much?

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Abstract

Background: Hepatic failure occurring after liver resection carries a poor prognosis and is a complication dreaded by surgeons. Inadequate reserve in the remaining parenchyma leads to a steady decrease in liver function, inability to regenerate, and progression to liver failure. For this reason, many methods to quantify functional hepatic reserve have been developed.

Methods: This article reviews the main methods used in the assessment of hepatic reserve in patients undergoing hepatectomy and their use in operative decision making.

Results: A range of methods to categorically quantify the functional reserve of the liver have been developed, ranging from scoring systems (such as the Child-Pugh classification) to tests assessing complex hepatic metabolic pathways to radiological methods to assess functional reserve. However, no one method has or is ever likely to emerge as a single measure with which to dictate safe limits of resectability.

Conclusions: In the future, the role of residual liver function assessment may be of most benefit in the routine stratification of risk, thus enabling both patient consent to be obtained and surgical procedure to be performed, with full information and facts regarding operative risks. However, there is no one single test that remains conclusively superior.

Keywords: Functional reserve; Hepatic resection; Liver failure

Hepatic failure occurring after liver resection carries a poor prognosis and is a complication dreaded by surgeons. Inadequate reserve in the remaining parenchyma leads to a steady decrease in liver function, inability to regenerate, and progression to liver failure. As always, the use of a precise and uniform definition of hepatic failure across different studies remains a problem. However a useful definition by Jarnagin et al characterizes postoperative hepatic insufficiency and failure as "prolonged hyperbilirubinemia unrelated to biliary obstruction or leak, clinically apparent ascites, prolonged coagulopathy requiring frozen fresh plasma, and/or hepatic encephalopathy" [1].

The aim of surgical resection for primary or secondary liver tumours is the removal of all malignant tissue with a microscopically clear margin, preferably >1 cm. For this reason, the hepatic surgeon must balance the need for optimal clearance from an oncologic perspective while ensuring that sufficient functioning liver remains to sustain life.

Currently, there is no definitive answer to the question "how much liver resection is too much?" A small minority of patients undergoing apparently safe resections still inexplicably develop postoperative hepatic failure despite seemingly sufficient liver remaining at the time of surgery. The search for a method with which to categorically quantify the functional reserve of the liver and tailor surgical intervention has resulted in the development of a range of methods. These methods range from clinical scores such as the Child-Pugh (CP) classification to tests assessing complex hepatic metabolic pathways to radiological methods to assess functional reserve.

Those patients especially at risk are those undergoing larger resections [2] and patients with ≥1 comorbid medical conditions [1]. The presence of clinically significant portal hypertension in cirrhotic patients is also associated with poor post hepatectomy outcome, and the Barcelona Liver Group has recommended avoiding liver resection in such patients [3]. The presence of diabetes has also been associated with increased posthepatectomy mortality [4–6]; however, this view is not universally shared [7].

Some investigators have found preoperative standard liver function tests such as bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase and alanine aminotransferase to be significantly different in patients who die from postresection liver failure compared with those who do not [8]. Some investigators have proposed high alkaline phos-

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phatase in the presence of normal bilirubin with large tumors to be prognostic of postoperative liver failure [9]. However, an increased transaminase level may also indicate ongoing active hepatitis, which is also associated with a poor outcome [10]. This is by no means a unanimous view; many investigators finding no predictive value in standard liver function tests [11,12].

Measurement of serum hyaluronic acid has been found to correlate both with conventional liver function tests, indocyanine green (ICG) R-15, and technetium-99m-guanidinosuccinic acid (GSA) levels. Hyaluronic acid concentration is thought to reflect the degree of hepatic fibrosis and sinusoidal endothelial damage [13]. However, although some tests of hepatic functional reserve are comparable with CP scoring, they are not clearly superior in prognostic ability [14].

Proposed perioperative indicators for the development of postoperative complications and hepatic failure include ongoing hepatitis [12], perioperative blood loss >2000 mL, cirrhosis, concomitant development of postoperative complications, the need for reoperation [12], >4 U transfusion, American Society of Anesthesiologists (ASA) grade [15], bilirubin [16], Child-Turcott class B and C [17], age, extent of resection [18], and preoperative chemotherapy [9].

In patients with normal livers, bilirubin levels generally return to normal within 2 to 3 weeks after liver resection, but recovery is prolonged and rates of regeneration decreased in patients with cirrhosis or chronic hepatitis, [19]. The majority of patients undergoing liver resection for metastatic disease will be free from chronic liver disease, whereas a large proportion with hepatocellular carcinoma (HCC) has underlying chronic hepatitis or cirrhosis. Although the latter group is at most risk of developing liver failure after liver resection, those with seemingly normal livers undergoing removal of metastases can and do develop postoperative liver failure after standard hepatectomies.

The presence of significant degrees of fatty infiltration in cadaveric donor livers is known to correlate with higher levels of graft primary nonfunction [20], whereas increased levels of macrovascular steatosis increase the severity of ischemia–reperfusion injuries [21]. In rat models of hepatic steatosis, the mode of cell death after an ischemic reperfusion injury is one of cell necrosis rather than apoptosis [22]. The presence of steatosis has also been reported to increase perioperative morbidity and mortality after liver resection. Behrns et al demonstrated that patients with >30% steatosis as seen on the resected specimen had a mortality rate of 14% compared with patients with no or <30% steatosis, who had mortality rates of 3% and 7%, respectively. This study was relatively small with only 7 out of 135 patients graded as having severe steatosis. There was only 1 mortality in this group, yielding the 14% mortality rate and making conclusions and statistical interpretation difficult. Patients graded as having mild or moderate to severe steatosis, however, also had significantly increased postoperative liver function test results with increased rates of transfusion and longer operating times, which may reflect the greater technical difficulty operating on steatotic livers compared with those having no steatosis [23]. However, studies examining live donor transplantation have not shown any increased complications or mortality of donors with up to 50% of patients with steatosis undergoing mainly left lobectomies [21]. In an analysis by Jarnagin et al of 1,803 patients undergoing hepatic resection, approximately 45% had histologic abnormalities consisting of steatosis, cholestasis, inflammation, cirrhosis, or fibrosis. The investigators did not find the presence of cirrhosis or steatosis to be independent predictors of a worse outcome [1], although the severity of steatosis and Childs classification were not quantified.

Conventionally, liver resections of up to 75%, or 6 liver segments, may be safely performed in patients with normal liver parenchyma, beyond which there are increasing problems with hepatic dysfunction. In those with cirrhosis or chronic hepatitis, the functionality of the residual liver is often uncertain, and these patients are more likely to develop postoperative hepatic dysfunction with similar resection volumes compared with those having normal residual parenchyma.

Operative mortality after hepatic resection in noncirrhotic patients ranges from 3% to 8% [1,24], but for cirrhotic patients it can range from 5% to 25% [11,25–27]. However, Imamura et al, in a series of 1056 hepatectomies, stated a 0% mortality rate. This series included 213 resections for metastatic colon cancer and 532 resections for HCC, and most patients had some degree of underlying cirrhosis [28]. For patients with HCC, postoperative liver failure rates may be as high as 20% in some studies, with subsequent mortality in those developing liver failure approximately 40% to 50% [29,30]. Postoperative hepatic insufficiency in 1 large study by Jarnagin et al occurred in approximately 5% of all patients undergoing resection but resulted in mortality of only 1% of all patients [1]. Significantly, hepatic failure was the sole cause of death in only one third of these patients; in the remainder it developed in conjunction with systemic sepsis, multiorgan failure, or major gastrointestinal haemorrhage, suggesting that the development of postoperative complications may be crucial in those with borderline liver reserves. To confirm or refute the presence of chronic liver disease, it has been suggested that in the case of HCC, preoperative biopsies of nontumorous parenchyma is indicated to confirm or exclude concomitant cirrhosis so that preoperative risk assessment is improved [31].

Methods for Predicting Postoperative Residual Liver Function

ICG clearance rate

ICG is an organic dye and is extracted from the liver by way of a carrier-mediated mechanism and excreted into the bile. It has a rapid uptake and it is eliminated virtually

unchanged because it is not reabsorbed in the intestine, therefore avoiding enterohepatic recirculation. It can be used to measure both hepatic blood flow and hepatocyte function. Biliary ICG excretion correlates with decreased hepatic adenosine triphosphate (ATP) concentration [32], and this decrease in hepatic energy status may reflect a decreased ability for regeneration after surgery.

Standard measurement involves an overnight fast followed by an injection of .5 mg/kg ICG. Venous blood samples are taken at 0, 5, 10, 15, and 20 minutes after injection. Results can be measured as the percentage of ICG retained after 15 minutes (ICGR-15), and levels are measured on centrifuged samples using a spectrophotometer. Normal values range from 3.5% to 10.6% retention at 15 minutes [8]. It has been shown to be of prognostic significance after hepatic resection in patients with cirrhosis [33,34]. In patients undergoing resection for HCC, it may be of more prognostic significance of in-hospital death compared with the amino acid clearance test or aminopyrine breath test [8]. Fan et al found no difference in hospital mortality between patients with and without cirrhosis despite worse preoperative tests and greater intraoperative blood loss. In their study, most patients with cirrhosis were CP grade A with a postoperative mortality of 12%; however, those with CP grade B had a 50% postoperative mortality rate, suggesting that resection should not be offered to those with CP grade B and above. However, because only 2 patients had CP grade B, the 50% mortality in this group in this study may not be representative. Wide variations of ICGR-15 rates among patients with CP grade A are seen. This may indicate the limitations of using this grading system alone because postoperative mortality occurs even in those with CP grade A. Fan et al proposed that patients with an ICG retention >14% at 15 minutes have greater postoperative risk [33], and this should be taken into account before surgery and the extent of resection adjusted accordingly. However, subsequent work looking further at a preoperative ICGR-15 >14% in patients undergoing hepatectomy for HCC demonstrated no difference in outcome. This study carefully selected patients with high ICGR-15 so that the volume of nontumorous parenchyma was small (i.e., larger diameter tumours), and no difference in blood loss, morbidity, or mortality after resection, including major lobectomy, was noted [35]. The investigators credit the importance of meticulous operative technique and postoperative intensive care with specific measures to prevent hypoxia and hypotension—including postoperative ventilation, albumin infusions, and diuretics—with helping to prevent ischemia of the liver remnant.

Some investigators have proposed a graduated surgical approach, depending on ICGR-15, ranging from simple enucleation to major resection, an approach that results in excellent postoperative mortality, even in patients with cirrhosis [36,37]. Other investigators have also used this approach in selecting technique of resection for cirrhotic patients [38] and determining operability for repeat hepatic resections for HCC [39]. Performance of a safe right hepatectomy has been proposed only in those cirrhotic patients with an ICG-R15 <20% or 22% [40,41]. An ICGR-15 <14% has been shown to be significant for improved mortality for patients with HCC undergoing major hepatectomy (defined as resection of ≥2 segments). If the ICGR-15 was >23%, resection of a single segment only was indicated, although the number of patients with such a high ICGR-15 in this study was small. For patients undergoing major hepatectomy with an ICGR-15 >14%, the relative risk for death was 3% [8]. In a large series by Imamura et al [28], this graduated ICGR-15 method was also employed. Decision regarding operability in patients with HCC and cirrhosis was based on the presence or absence of ascites, total bilirubin, and ICGR-15. By using these criteria, the investigators achieved 0% mortality in 1056 hepatic resections.

When using ICG to calculate the maximal removal, a level >.4 mg/kg/min before hepatectomy resulted in improved mortality and morbidity in a study of 76 patients [42]. Because ICG is excreted in bile, measurement may be affected in those with jaundice; however, the rate of excretion can be measured by way of percutaneous transhepatic biliary drainage in patients with complete biliary obstruction. This measure of ICG content in bile has been proposed to be more representative of hepatic ATP stores than serum ICGR-15 [32]. Uptake of ICG into hepatocytes occurs by way of ATP-independent transporters located on the basolateral membrane of the liver, whereas the excretion of bile into the canalicular space is by way of an ATP-dependent mechanism. Decreased hepatic ATP level has been proposed as an important factor in liver regeneration, liver failure, and postoperative death [43]; however, Fan et al did not find a correlation between preoperative ICG and outcome after operative relief of malignant biliary obstruction [44].

More recently, noninvasive methods of measuring ICG have been developed using pulse spectrophotometry by way of finger probes. This method has been used to measure the elimination rate constant of ICG (ICG-K) after hepatic resection [45]. ICG-K decreases significantly after surgery depending on the volume resected and remains low for 7 days, an effect that is more marked in patients with cirrhosis. This group found good correlation with a preoperative estimation of postoperative ICG-K. This was calculated using the preoperative ICG-K value as a function of the ratio between the remaining liver volume and whole-liver volume as assesses by computerized axial tomography (CAT) volumetric scanning.

A decrease in ICG clearance has also been demonstrated during episodes of acute rejection after liver transplantation that subsequently improves after an increase in immunosuppressive therapy [46]. Other investigators have looked at potential transplant candidates and found that ICG and the monoethylglycinexylidide test (MEGX) were superior at predicting short-term prognosis compared with standard

liver function tests and CP scores [47]. However, ICG used alone has limitations because mortality is still seen in patients with a "normal" ICGR-15, and survival in those whose increased preoperative ICGR-15 would predict a poor outcome still occurs [33]. In addition, it is a flow-dependent measurement and is therefore affected by wide variations in hepatic blood flow.

Hippurate ratio

This test uses assessment of glycine conjugation of para-aminobenzoic acid (PABA) by the liver. PABA is absorbed from the intestine and extensively metabolized by the liver by phase II conjugation mechanisms that are independent of the cytochrome p450 system. PABA and its acetylated product para-acetamidobenzoic acid are converted to the hippurated compounds, para-aminohippuric acid (PAHA) and para-acetamidohippuric acid, by conjugation with glycine. The hippurate ratio is calculated by comparing levels of PABA and the hippurated metabolites 30 minutes after ingestion of 5 mg/kg oral PABA against baseline levels. It reflects the total amount of glycine conjugates of PABA and is correlated with severity of liver disease. The hippurate ratio at 30 minutes for healthy controls is 59% ± 10.5%, for those with Child's C chronic hepatic failure is 1.9% ± 5%; and for those with acute liver failure is 9.5% ± 16.5% [48]. Although differences are seen between controls and those with chronic liver failure across all Child's classes, there is some overlap (especially Child's A) which may reflect heterogeneity of the underlying liver function in those in the Child's A classification. Generally, patients without liver disease have a hippurate ratio >35%; those with mild disease have a normal or slightly decreased (20% to 60%) to moderately decreased hippurate ratio (5% to 10%); and those with severe liver disease have a very low hippurate ratio (<5%) [48]. The absolute levels of PAHA itself may be a useful prognostic indicator in acute liver failure. In 1 small study of 11 patients with acute liver failure, 6 patients with a zero concentration 30 minutes after ingestion of PABA either died or underwent transplantation, whereas 5 patients with levels greater than zero survived without need for transplantation [48]. Measurement of PAHA in children with fulminant hepatic failure has been proposed as having greater sensitivity for poor outcome compared with King's College criteria [49].

The hippurate ratio has been shown to be decreased in patients with HCC who develop postoperative hepatic failure who had preoperatively or operatively been deemed to have adequate functional reserve by ICG R-15 [30]. It correlates well with the MEGX test in those with chronic liver disease but has the advantages of being orally administered and independent of cytochrome p450 and having fewer adverse effects compared with the MEGX test [50].

Amino acid clearance test

The amino acid clearance test measures the uptake and utilization of amino acids by the liver in protein synthesis. It is a fairly invasive and involved test requiring an overnight fast followed by an infusion of amino acids during 18 hours. Samples are taken from the femoral vein and artery after the infusion and processed for amino acid clearance [51]. It has been used to monitor progress of chronic liver diseases. One study by Clowes et al of cirrhotic patients [52] found a significant difference in the amino acid clearance between survivors and nonsurvivors after portocaval shunting. Lau et al [51] did not find a significant difference in the amino acid clearance in those dying after hepatectomy and attributed this to the relatively early grade (CP A and a few B) of cirrhosis in their group.

Aminopyrine breath test

The aminopyrine breath test measures the demethylation and metabolism of intravenously administered radioactive carbon-labelled aminopyrine. Aminopyrine undergoes N-demethylation in liver microsomes to form amino-antipyrine and formaldehyde. Formaldehyde is oxidized to bicarbonate, which is then either exhaled as carbon dioxide or equilibrated within the body [53]. The exhaled radioactive carbon dioxide allows quantitative measurement of microsomal function of the liver by way of cytochrome P450–dependent pathways. It is decreased in those with chronic liver disease compared with controls [54], and in patients with chronic hepatitis B or C it correlates with CP score and degree of fibrosis [55]. However, it does not have a superior advantage in assessing prognosis compared with CP classification alone [56]. Decreased aminopyrine breath test results have been found to be a significant predictor of mortality after a range of nonhepatic operative interventions in patients with chronic liver disease [57]. Decreased levels are also associated with mortality at 1 year after portocaval shunt [58]. However, Lau et al did not find a correlation between the aminopyrine breath test and mortality in those undergoing hepatectomy for HCC [8], and others have found it inferior to ICG in predicting postoperative mortality [33]. The aminopyrine breath test has also been found to be impaired in patients with biliary obstruction secondary to cholangiocarcinoma, but the degree has not been shown to correlate with an increased risk of morbidity after operative relief of obstruction [44]. The metabolic pathways in aminopyrine excretion are complex and affected by numerous factors including cytochrome-inducing or -inhibiting drugs, smoking, fever, and chronic disease [53]. Other substrates used in breath tests to evaluate microsomal liver function include caffeine, as described later, and diazepam and erythromycin, although there a few data on the latter two drugs' use after hepatic resection [53].

Caffeine-clearance tests

Carbon-13-caffeine has been used widely in the assessment of hepatic function. It has a high bioavailability and is principally metabolized in the liver by cytochrome p450 1A2 to its metabolites (theophylline, paraxanthine, and theobromine) [59] with release of radiolabeled carbon dioxide. Its metabolites can be measured by way of blood, saliva, and breath tests [60]. The clearance of caffeine is decreased in breath tests in patients with cirrhosis compared with those having normal or inflamed livers. However, caffeine clearance is increased in smokers across all groups [60]. However, other studies have not demonstrated a difference in caffeine clearance between patients with compensated cirrhosis and those with normal livers [61]. It may serve as a prognostic indicator in those with cirrhosis [62]. The use of caffeine is of interest because it is relatively nontoxic; however, few data exist on its use in the assessment of preoperative functional reserve in the field of hepatic resection.

Galactose-elimination capacity

Galactose-elimination capacity (GEC) determines the microsomal cytosolic capacity of the liver and is prognostic in chronic liver disease such as chronic active hepatitis, cirrhosis, and primary biliary cirrhosis [63]. Injection of .5 g/kg 45% galactose is given as a bolus that saturates the catabolic enzyme system. The rate of galactose elimination depends on the phosphorylation by galactokinase within the hepatic cytoplasm. Normal elimination is >6 mg/kg/min, and it has been demonstrated that, for all patients, a GEC less than this value, when in combination with an ASA score >2, the risk increases of mortality after hepatic resection. For HCC groups alone, predictive factors include GEC <4 mg/kg/min, ASA score >2, and postoperative sepsis. However, this study did not separate those with and without cirrhosis [15]. GEC is also useful in predicting death in patients with advanced cirrhosis and has been used to monitor need for transplantation [64]. For patients with CP grade A, metabolic tests such as the aminopyrine breath test and galactose elimination capacity may be decreased at an earlier stage than tests measuring perfusion [55]. In patients with normal livers, GEC has been shown to decrease with age, which may reflect a decrease in hepatic reserve in older patients [65].

Arterial ketone body ratio

The arterial ketone body ratio (AKBR) is a measure of the ratio of ketone bodies, acetoacetic acid and beta-hydroxybutyric acid, after a period of fasting and reflects the mitochondrial oxidized nicotinamide adenine dinucleotide–to–reduced nicotinamide adenine dinucleotide ratio. Because ketosis and deteriorating liver function develop ketones, beta-hydroxybutyric especially increases with a subsequent decrease in ratio. A primary decrease in the ketone ratio after surgery has been associated with increased mortality. Patients whose ratio decreases to <.4 at the end of surgery have a poor prognosis with mortality ranging from 50% [66] to 100% [67]. Measurement in the early postoperative period has also been used to predict graft survival after transplantation [68]. However, the usefulness has been cast into some doubt because some investigators have not found the AKBR to be an accurate parameter with which to represent the redox state in liver mitochondria. Others have not found a correlation with changes in the AKBR and posthepatectomy complications [69], and the results may be affected by supplemental oxygen therapy [70]. It can be adapted to the hepatic mitochondrial redox tolerance test by the administration of a 75-g oral glucose load to give a redox tolerance indicator (a ratio of the AKBR to glucose). This may better reflect hepatocyte mitochondrial energy production [71]. This ratio is significantly different between patients with cirrhosis and those with normal livers, and a ratio <.5 is associated with a higher rate of postoperative mortality and morbidity [72].

MEGX

MEGX is based on the conversion of lidocaine to monoethylglycinexylidide by the liver. Lidocaine is metabolized by cytochrome p450 pathways through oxidative N-dealkylation, with MEGX resulting as the major metabolite. The test is performed by intravenous injection of 1 mg/kg lidocaine, and venous samples are collected 15 minutes later from the contralateral arm. MEGX levels are assayed by immunofluorescence, and levels >50 ng/mL are considered normal. Ninety-seven percent is metabolized in the liver, and the remaining 3% is excreted by way of the kidneys. One limitation of the MEGX test is that it relies on hepatic flow and is therefore affected by drugs that increase or decrease hepatic flow [73].

Decreased MEGX levels are found in cirrhotic patients and have been linked to an increased incidence of complications after liver resection [74]. For patients within Child's A classification, those with a MEGX level <25 ng/mL were more likely to suffer postoperative liver dysfunction compared with those whose levels were >25 ng/mL [74]. This study suggested that patients whose MEGX level is <25 ng/mL should have careful preoperative evaluation and that surgical intervention be limited to a wedge resection only.

MEGX has been used to determine risks of developing liver failure after transcatheter arterial chemoembolization in patients with HCC [75]. In this study, 13% of patients developed liver failure after transcatheter arterial chemoembolization and decreased MEGX before the procedure was found to be a better predictor compared with standard liver function tests or ICGR-15. However, the pharmacokinetics of this drug are complicated, and there is some overlap between Child's classes [76]. Timing of measurements also varies, with different studies using levels at 15 or 30 min-

utes; however, some investigators have suggested that measurement at 60 minutes may be a more sensitive marker of liver function [76]. MEGX has been used extensively in the field of liver transplantation because those with chronic liver disease and decreased MEGX formation (<10 ng/mL) have been shown to have poor 1-year survival [77] and are therefore prioritized for transplantation. The value of donor liver MEGX values in predicting graft survival is also controversial, with some investigators finding significant correlation between MEGX value and graft survival [78], whereas other investigators have found no such correlation [78,79].

Trimethadione

The anticonvulsant trimethadione (TMO) has been used to assess hepatic oxidizing ability and hence functional reserve. It is N-demethylated in liver microsomes by P450-dependent mechanisms to dimethadione (DMO). The ratio of TMO to DMO as measured 4 hours after oral administration of TMO is related to presence and histologic severity of liver disease [81] and correlates with CP classification [82]. In a study by Ishikawa et al, the DMO-to-TMO ratio of the remnant was calculated in 45 patients with HCC before liver resection. Five patients had ratios <.15. Three died, and the remaining 2 developed severe postoperative complications [83].

Nuclear imaging

Single-photon–emission computerized tomography (SPECT) with technetium-99m-tin colloid has been used to assess preoperative hepatic function. In a study of 47 patients before hepatic resection, SPECT was used in combination with hepatic volume to calculate a predictive index for liver failure. Those with predictive indices >.35 had a low risk of postoperative liver failure; however, 3 patients with values <.35 died from hepatic failure >1 month after surgery [84]. Measurement of technetium-99m–galactosyl human serum albumin (99mTc-GSA) and the hepatic uptake ratio at 15 minutes has been shown to correlate with postoperative complications, hepatic regeneration, and ICGR-15 [85].

Using 99mTc-GSA enables imaging of the liver and the asialoglycoprotein (ASGP) receptor, which is thought to be responsible for serum glycoprotein metabolism [86]. The hepatic receptor density is related to serum ASGP levels and hepatic function [86]. In combination with serum ASGP levels, static SPECT may be of benefit in evaluating regional liver function and estimating residual hepatic function. Low levels of estimated ASGP receptor of the remnant liver as measured before surgery are associated with postoperative liver dysfunction [87].

Technetium-99m–galactosyl human serum albumin binds to ASGP receptors, which are specific to the hepatic membrane. In patients with liver disease, these receptors are found in decreased numbers, and levels of 99mTc-GSA accumulation in the liver can be compared with the results of standard liver function tests such as albumin, prothrombin time, serum cholinesterase, ICG plasma disappearance rate, and Child-Turcott classification score [88,89]. It can be used to show that hepatic functional reserve decreases gradually but then undergoes a *rapid* decrease once the patient develops Child's grade B cirrhosis [90]. After percutaneous transhepatic portal embolization increases in the liver, the uptake density of 99mTc-GSA in the hypertrophied remnant has been shown to correlate with an improved outcome after hepatectomy [91].

Using 99mTc-GSA may more accurately reflect actual hepatocyte volume because the receptors are absent on fibrous and stromal tissues. This hepatocyte volume may give a better indication of hepatic reserve and regenerative ability than total liver-volume measurements [92]. Technetium-99m–galactosyl human serum albumin SPECT has been used to calculate a predictive residual index by combining volumetric measurements of functional liver volume and total liver volume with a radiotracer. When applied to 57 patients with underlying hepatic disease undergoing resection, no patient with a predictive residual index >.38 developed hepatic failure. Five patients developed postoperative complications, and all had a predictive residual index <.37 [93].

Volumetric analysis

Rather than the total volume resected (because diseased livers are frequently enlarged), it has been suggested that the important determinant is the volume of functioning parenchyma remaining. Various methods have been adopted to assess the volume of the hepatic remnant before surgery. Most studies assess the remaining liver volume, excluding the volume of the lesion to be excised from the calculations, thereby assessing only nonmalignant hepatocytes. However, care should be taken with large tumours replacing large volumes of the liver because these may artificially increase the percentage of liver remaining after resection due to compression and destruction of normal tissue.

Preoperative estimation of residual liver volume using CAT volumetric scanning has been shown to correlate well with the actual volume resected at surgery [36]. Kubota et al proposed that resection ≤60% of nontumorous parenchyma was acceptable in patients with normal livers and that resections ≤50% of nontumorous parenchyma was acceptable in patients with an ICG-R15 between 10% and 20%. They recommended that when the volume of nontumorous parenchyma to be resected in noncirrhotic patients is >60% with a concomitant ICGR-15 of 10% to 20%, preoperative portal vein embolization (PVE) is indicated to increase the volume of residual liver [36].

In hepatitis B– or C–positive patients who undergo right hepatectomy, postoperative liver volume <250 mL/m^2 is predictive of postoperative liver failure [94]. Thirty-five

percent of patients who underwent a right hepatectomy and who had a residual volume <250 mL/m^2 developed postoperative liver failure. This study found no statistical difference in mortality between patients with or without cirrhosis and ICGR-15 test or perioperative blood loss, but a statistically higher proportion of patients with diabetes developed liver failure.

Yigitler et al examined patients with normal livers undergoing resection and correlated a ratio of residual to functional liver volume. Although they found no correlation between remnant liver volume and liver failure, those patients with smaller remnants had more complications and a prolonged Intensive Care Unit stay. They therefore recommended consideration of preoperative PVE in patients with normal livers with an anticipated residual liver volume–to–functional liver volume ratio <30% [95].

Shoup et al examined patients with non-cirrhotic livers undergoing hepatectomy for colorectal metastases. Using semiautomated contouring and volumetric analysis of preoperative scans, the estimated volume of residual liver—excluding tumour volume—was calculated. For patients undergoing trisegmentectomy and with ≤25% of liver remaining, 90% developed hepatic dysfunction as defined by increased bilirubin or prolonged prothrombin time compared with patients with >25% of liver remaining after trisegmentectomy ($P < .0001$). Those with hepatic dysfunction also had an increased complication rate and a longer hospital stay [96]. However, the sensitivity of this method was low; some patients with >25% and even >40% remaining liver developed hepatic dysfunction. Volumetric analysis in this study was not correlated with functional assessments of liver reserve.

In those patients with underlying liver disease, Azoulay et al limited resection of >2 segments to those patients who were <70 years of age with ICGR-15 <10%, albumin >30 g/L, bilirubin <20 mmol/L, prothrombin time >80% of normal, and an estimated rate of remnant functional liver parenchyma >40% as measured by CAT [97]. In those with a remnant <40%, PVE was performed. In a group of 9 patients undergoing PVE, no patients developed postoperative liver failure compared with 3 of 19 who did not undergo PVE before their resections. Hemming et al examined the role of PVE in patients undergoing extended hepatectomies [98]. Patients were selected for PVE if the remnant liver volume was <25% in those with normal liver or <40% in those with underlying liver disease. There was no difference in postoperative mortality, but those who underwent preoperative embolization had significant decreases in postoperative liver function parameters, fresh frozen plasma utilization, and incidence of liver failure.

Correlating Methods Into Scoring Systems

The most widely used scoring system in assessment of suitability for hepatic resection is the CP classification of patients with cirrhosis, against which a test of residual function should be compared. Operative mortality and morbidity after hepatic resection is increased in those with class B and C cirrhosis compared with those having class A disease [99], although some have not shown a difference in survival between those with grade A and grade B disease [100,101]. Naturally, one of the main difficulties in assessing mortality among CP grades is the inevitable paucity of patients with grade C disease.

Attempts have been made to "score" patients using a variety of parameters to predict those at risk of postoperative liver failure with more accuracy and reproducibility. Yamanaka et al proposed a formula based on a multiple regression analysis of 17 preoperative parameters based on 36 patients who underwent varying degrees of hepatic resection. The formula incorporated parenchymal hepatic resection rate as assessed by CAT and ICG retention rate and age and found that those patients dying from postoperative liver failure had scores >50. By implementing these scores before surgery and decreasing the size of resection accordingly, they decreased mortality from 17% to 6% [102]. However, this is a fairly involved calculation (score = −84.6 + .933 PHRR + 1.11 ICGR15 + .999 age) that may make it unfavorable in routine practice. Further work using this scoring system classified patients into different categories based on their predictive score. A score of >55 deemed the patient at risk; 45 to 55, borderline; and <45, safe [103]. Six of seven patients, including 3 undergoing resection for metastatic cancer, undergoing lobectomy in the risky zone died from progressive liver failure. Of the borderline patients, 5 of 15 died, although none of the 6 patients with metastatic cancer died. In this group, the investigators found that 80% of the nonsurvivors had a linear compared with parabolic curve oral glucose test pattern, which was previously shown to be of prognostic significance in patients undergoing hepatectomy [104], and they concluded this may have placed the patients in the at-risk group. Perhaps surprisingly, in those considered to be in the safe zone, 26 of 376 patients (7.3%) undergoing resection for HCC died, the majority due to hepatic failure secondary to bile leak or infective episode despite a proportion of these patients having the size of resection decreased because they had previously been in the borderline or at-risk category. However, none of the 49 patients in the safe group undergoing resection for metastases died. Overall, those with a higher ICGR, disturbed glucose tolerance test, and low platelets were at greater risk of local sepsis after surgery. The investigators concluded that nonsurgical therapy should be considered as a first-line treatment for those patients in the at-risk group. For those in the safe or borderline groups, the planned hepatectomy should take into account liver pathology, glucose tolerance, platelet count, and ICG retention rate because these may further increase the risk of liver failure. However, the addition of the extra factors decreases the usefulness of the scoring system outside those patients in the at-risk category.

Torzilli et al proposed an algorithm to guide decision making for patients with HCC [105]. Using an algorithm based on the presence or absence of ascites, total serum bilirubin, and ICGR-15, they achieved a 0% 30-day mortality with 26% morbidity in a series of 107 patients, 60% of whom had cirrhosis and only 6% of whom had histologically normal livers. The remainder had a combination of fibrosis, hepatitis, primary biliary cirrhosis, and/or fatty liver.

Comments

As with many surgical conundrums, it is unlikely that 1 method to assess residual liver function currently available will emerge as a single measure with which to dictate safe limits of resectability, nor is it likely that 1 test will be adopted to conclusively "rule out" any form of surgical intervention. Rather, the information gathered from such tests should be added to our prognostic and surgical planning armamentarium. As discussed previously, although many parameters are used to indicate a high risk of postoperative liver failure, no test is 100% accurate, and there is a real risk of denying surgical treatment to patients who may benefit. Although many tests exist that can be used to indicate hepatic reserve, to be of use in the clinical situation this information must be translated into a practical guide on how much liver is "safe" to remove while balancing this with the need for an adequate procedure from an oncologic perspective. Tissue-preserving segmentectomies have been demonstrated to show comparable survival results as hemihepatectomy in liver secondaries and may actually have a survival advantage in HCC [106], and this may be an increasing trend for those with poor hepatic reserve.

The role of liver residual liver function assessment may in the future be of most benefit in the routine stratification of risk, thus enabling the surgical procedure and patient consent to be obtained with full information and facts regarding operative risks. The identification of patients at higher risk of postoperative liver failure may enable the increased use of strategies such as PVE to increase the volume of residual liver. However, at present PVE remains controversial, especially in the context of colorectal liver metastases.

In addition, improvements in operative technique and postoperative care should be directed at decreasing the development of postoperative complications, which for vulnerable at-risk patients may herald the inexorable slide into liver failure. It seems likely that future scoring methods using several criteria—including patient demographics, standard liver function tests, volumetric analysis, and tests of hepatic functional reserve [80]—will emerge to more accurately encompass the many factors associated with the development of hepatic failure after liver resection.

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