

Assessment of hepatic reserve for indication of hepatic resection: how I do it

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Abstract

The perioperative outcome of hepatic resection has improved remarkably in recent years with improved surgical techniques and perioperative care. As a result, the indications of hepatic resection have been extended to include patients with borderline liver function, especially those with associated cirrhosis. For such patients, proper preoperative assessment of liver function reserve is essential to ensure a low incidence of postoperative liver failure and mortality. In our center, routine preoperative assessment of hepatic function reserve in all patients includes clinical assessment, liver biochemistry, coagulation profile, platelet count, and Child-Pugh classification. The indocyanine green clearance test is routinely performed for patients with chronic liver disease. For patients with cirrhosis undergoing major hepatectomy, computed tomography volumetry and laparoscopy are helpful in evaluating whether the remnant liver volume is adequate. In selected patients with small remnant liver, preoperative portal vein embolization can be employed to induce hypertrophy of the remnant liver even in the presence of chronic hepatitis and mild cirrhosis. Careful assessment of comorbid conditions of patients and meticulous surgical techniques to reduce bleeding and hypoxic injury to the remnant liver are complementary to the selection of patients with adequate liver function reserve, to minimize operative mortality.

Key words Cirrhosis · Hepatic resection · Indocyanine green clearance test · Liver function

Introduction

Hepatic resection is the mainstay of treatment for common hepatobiliary malignancies such as hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, colorectal liver metastasis, and hilar cholangiocar-

cinoma. Hepatic resection is also indicated in some benign diseases, such as benign liver tumors and hepatolithiasis. The two main risks of hepatic resection are massive bleeding and postoperative liver failure, which used to cause a high operative mortality, over 10%, after hepatic resection before the 1980s.^{1–3} Throughout the past two decades, substantial improvement in perioperative outcome after hepatic resection has been achieved, and the operative mortality rate is now typically less than 5% in major hepatobiliary centers.^{4–7} Better understanding of the segmental liver anatomy and improved surgical techniques in controlling hemorrhage are considered the two most important factors that have led to reduced mortality.^{4,6,7}

The delineation of segmental liver anatomy has allowed segmental hepatic resection to be performed with maximum preservation of liver parenchyma without jeopardizing the oncological clearance of liver tumors.⁸ However, many patients with hepatobiliary malignancies present with advanced tumors that require major hepatic resection. In patients with normal liver, resection of up to 70% of the liver mass can be tolerated. However, in patients with underlying chronic liver disease such as chronic hepatitis and cirrhosis, which is commonly associated with HCC, major hepatectomy is associated with a risk of liver failure because of impaired liver regeneration.⁹ In patients with cirrhosis undergoing major hepatectomy, careful preoperative assessment of liver function reserve is of paramount importance in ensuring a low operative mortality. In this article, we describe our approach of preoperative assessment of liver function reserve in patients undergoing hepatic resection.

Preoperative liver function tests

Preoperative assessment of liver function reserve starts with a careful history and physical examination for

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symptoms and signs of portal hypertension and chronic liver failure, such as recent variceal bleeding and ascites, followed by liver biochemistry, coagulation profile, and platelet count. Of all the tools for assessing liver function, the Child-Pugh classification is a simple but useful one that provides an initial clue to the extent of hepatic resection that a cirrhotic patient can tolerate.¹⁰ In our center, Child-Pugh class C cirrhosis is considered an absolute contraindication for hepatic resection. For Child-Pugh class B cirrhotic patients, only minor hepatic resection (resection of two or fewer segments) would be considered. For Child-Pugh class A patients, the decision for a major hepatic resection requires additional liver function tests that provide more refined evaluation of liver function reserve. Child-Pugh classification only provides a rather crude evaluation of liver function reserve, and postoperative liver failure leading to operative mortality can occur after major hepatectomy in Child-Pugh class A cirrhotic patients. There are several quantitative liver function tests, such as the indocyanine green (ICG) clearance test,¹¹ lignocaine clearance test,¹² galactose elimination capacity,¹³ and technetium-99m galactosyl human serum albumin scan.¹⁴ In our center, we routinely use the ICG retention at 15 min (ICGR-15) as a guidance for selection of cirrhotic patients for hepatic resection. For patients with normal liver, clinical assessment, together with conventional liver function tests, is adequate for assessing the liver function reserve.

The value of the ICG clearance test in the preoperative assessment of liver function has been well-documented in several studies.^{11,15,16} In a study that evaluated the value of the ICG clearance test together

with other tests of liver function, including the amino-acid clearance test and the aminopyrine breath test, the ICG clearance test was found to be the most powerful predictor of hospital mortality after hepatectomy, by discriminant analysis.¹¹ Based on our experience of hepatectomy of HCC in the early 1990s, an ICGR-15 of less than 14% was identified as the safety limit for major hepatic resection in cirrhotic patients in a previous study.¹⁷ However, with improved surgical techniques and perioperative care, we found that the limit could be extended. In a more recent study, we observed that the perioperative outcomes after major hepatectomy in 25 patients with an ICGR-15 higher than 14% were comparable to those of 92 patients with an ICGR-15 below 14%, with the median ICGR-15 value in the former group of patients being 17.4%.¹⁸ Currently, we have shifted the upper limit of the ICGR-15 to 20% for major hepatectomy (Fig. 1). A recent study from our group has demonstrated that extended right or left hepatectomy is safe in selected patients with Child-Pugh class A cirrhosis with an ICGR-15 of up to 20%.¹⁹ However, for patients with borderline ICGR-15 values of 14% to 20% undergoing major hepatectomy, attention to the size of the liver remnant and severity of the cirrhosis is important to avoid postoperative liver failure. For patients with Child-Pugh class A cirrhosis being considered for a minor hepatic resection, the decision can usually be made based on liver biochemistry, coagulation profile, and platelet count alone. A cutoff value of the ICGR-15 for predicting mortality after minor hepatic resection in cirrhotic patients has not been established. However, we think that it is prudent to perform the ICG clearance test even in cirrhotic patients being

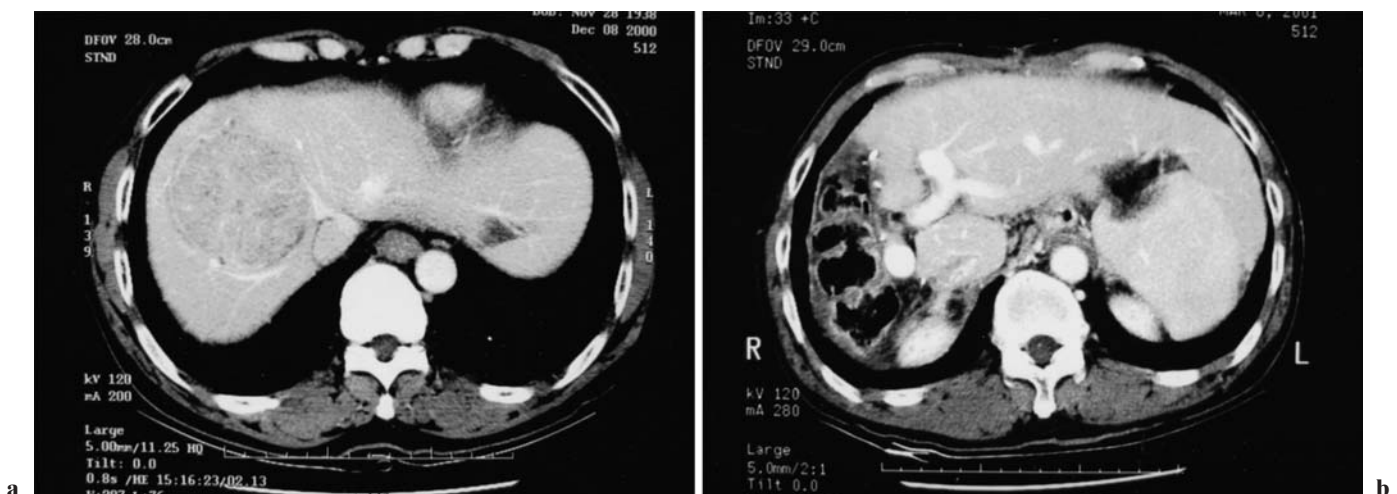


Fig. 1. a,b Computed tomography (CT) scan of a patient with a hepatocellular carcinoma 9 cm in diameter closely related to the middle hepatic vein. There was associated cirrhosis and the preoperative indocyanine green retention at 15 min was

20%. Extended right hepatectomy was performed without operative morbidity or mortality. **b** CT scan 1 month after hepatectomy demonstrated satisfactory hypertrophy of the remnant liver

considered for minor hepatic resection, to provide additional information on the liver function reserve, especially if there is a chance that the operation may be changed to a major hepatic resection after intraoperative assessment of the tumor status.

In a previous study on the ICG clearance test in patients undergoing hepatectomy, we found that the ICGR-15 values were scattered over a wide range among patients who died from hepatectomy, suggesting that this is not the only factor in predicting postoperative mortality or liver failure.¹¹ While the ICGR-15 provides a more refined criterion in selecting patients for major hepatectomy, it should be interpreted by taking into account other parameters of liver function. Patients with active viral hepatitis are associated with a higher risk of postoperative liver failure and mortality.²⁰ A previous study has demonstrated that a serum alanine aminotransferase level greater than four times the normal level was associated with a hospital mortality rate of 37.5%, compared with a hospital mortality rate of 3.9% among patients with serum alanine aminotransferase levels below two times the normal level.²¹ Some authors have advised to perform preoperative liver biopsy to evaluate the severity of hepatitis activity and fibrosis in patients with high serum transaminase levels.²² However, we do not practice preoperative liver biopsy because of the associated risk of bleeding. The levels of serum transaminases provide a reasonable reflection of hepatitis activity. In those patients with markedly elevated serum transaminase levels, hepatectomy should be avoided or deferred until the active hepatitis is under control, with lamivudine for hepatitis B-related hepatitis or interferon for hepatitis C-related hepatitis.

Platelet count is another important parameter that has to be considered. It has been demonstrated that cirrhotic patients with increased portal pressure are at high risk of liver failure after hepatic resection; thus, it has been suggested that hepatic resection should be restricted to patients without hypertension.²³ We do not consider a mild degree of portal hypertension a contraindication for hepatic resection, but major hepatectomy is certainly contraindicated in patients with clinically significant portal hypertension, such as those with a recent history of variceal bleeding or those with grossly detectable ascites. In our opinion, routine preoperative measurement of portal pressure for the selection of cirrhotic patients for hepatectomy is not justified, because of the invasiveness of the procedure. Platelet count can reflect the degree of portal hypertension to a certain extent, which, together with imaging findings, should provide reasonable guidance as to the degree of portal hypertension. An analysis of 1222 patients who underwent hepatectomy in our institution has demonstrated that thrombocytopenia was a significant risk factor of both postoperative morbidity and

hospital mortality.²⁴ In general, cirrhotic patients with a platelet count of less than $100 \times 10^9/l$ should not be considered for major hepatectomy.

Role of preoperative imagings and laparoscopy

Careful preoperative evaluation of tumor status is essential for the selection of appropriate patients with hepatobiliary malignancies for hepatic resection. The extent of the tumor determines the extent of liver resection required, and thereby the volume of remnant liver to be left. Evaluation of the liver remnant volume is important when a major hepatectomy is contemplated, because most of the currently used liver function tests, such as the ICG clearance test, reflect the function of the whole liver rather than the differential function reserve of the remnant liver, and it is the functional reserve of the remnant liver that determines whether a patient will develop postoperative liver failure.

In our center, we mainly rely on helical contrast computed tomography (CT) scans for preoperative assessment of all patients with potentially resectable intrahepatic malignancies. With the helical CT scan, the relationship of the tumor to the major intrahepatic vessels, any satellite tumor nodules, and any tumor invasion of the portal vein or hepatic vein branches can be clearly demonstrated in most cases. These findings are important in determining the extent of hepatectomy required. With the modern three-phase CT scan imaging, preoperative arteriography is seldom necessary in the assessment of patients with hepatobiliary malignancies, except in patients with hilar cholangiocarcinoma, when it is important to be aware of any involvement of the extrahepatic portal vein or hepatic artery. In a patient with a large right lobe liver tumor, it is particularly important to note the relationship between the liver tumor and the middle hepatic vein, because an extended right hepatectomy may be required for an adequate margin if the middle hepatic vein is closely related to the tumor (Fig. 1). Sometimes a small tumor situated at a critical position in the junction between the hepatic veins and the inferior vena cava may also require extended hepatectomy (Fig. 2). In such a situation, the risk of postoperative liver failure is higher than that of extended hepatectomy for a large right lobe tumor, because a large amount of nontumorous liver is removed. Measurement of the volume of the liver remnant by CT volumetry helps to decide the safety of hepatectomy in such cases. The appearance and overall size of the liver can provide the surgeon with some idea of the severity of the underlying cirrhosis. By assessing the size of the spleen and the presence of any varices, the CT scan also provides some information regarding the severity of portal hypertension.



Fig. 2. **a** A patient with a hepatocellular carcinoma 4cm in diameter situated at the junction of the right and middle hepatic veins with the inferior vena cava (*arrows*). An extended right hepatectomy was required, with the sacrifice of a large volume of nontumorous liver in the right lobe. The left lobe volume was only 21.4% of the estimated standard

liver volume (**b**). Percutaneous portal vein embolization was performed (**c**). Four weeks after portal vein embolization, the left lobe volume had increased to 34.8% of the estimated standard liver volume (**d**). Hepatectomy was performed without complication, and histological examination revealed chronic hepatitis in the nontumorous liver

For patients with hilar cholangiocarcinoma, in addition to the CT scan, cholangiography is important to determine the level of involvement of the right and left hepatic ducts, and hence the extent of hepatic resection required. In our center, we usually perform bilateral percutaneous transhepatic biliary drainage to relieve obstructive jaundice, and cholangiography is performed via the drains to show the extent of intrahepatic bile duct involvement in both sides. However, we do not routinely perform transhepatic cholangioscopy as described by some authors.²⁵

CT volumetry has been shown to be helpful in selecting patients for major hepatic resection.²⁶ One study has demonstrated that a small remnant liver volume was associated with worse postoperative liver function and a higher major complication rate after extended hepatectomy.²⁷ However, the safety limit for the remnant liver volume in patients with normal liver remains controversial, ranging from 25% to 40% of the total nontumorous or functional liver volume as reported in different studies.²⁶⁻²⁸ In a recent study, the incidence of complications after major hepatectomy was found to be similar be-

tween patients with a remnant liver volume of 30% or less of the preoperative functional liver volume compared with those with a remnant liver volume of more than 30% of the preoperative functional liver volume, although the former group had a longer hospital stay.²⁸ In our center, we employed CT volumetry selectively in patients with borderline liver function reserve as indicated by liver function tests, particularly in patients with an ICGR-15 of 14% to 20%. Our radiologists have not been able to provide a routine service of CT volumetry for all patients undergoing major hepatectomy because of the high case load volume in our center. Nevertheless, CT volumetry may not be necessary in patients with a good ICGR-15 when the remnant liver volume grossly appears adequate on examination of the CT scan by an experienced liver surgeon.

In addition to CT volumetry, we found laparoscopy useful for assessing the severity of cirrhosis and the size of the remnant liver. However, the reliability of laparoscopic assessment of the remnant liver depends very much on the experience of the surgeon. The use of laparoscopic ultrasound allows careful examination of the extent of the tumor. New findings, such as bilobar disease or invasion of the main portal vein or the inferior vena cava, which are not present in the preoperative CT scan examination, may obviate an unnecessary laparotomy. In a study of 198 patients with HCC who underwent laparoscopy and laparoscopic ultrasound between June 1994 and December 1998 in our center, unnecessary laparotomy was avoided in 31 patients, and inadequate remnant liver size in the presence of cirrhosis accounted for 28% of the causes of unresectable disease not detected by preoperative assessment.²⁹ However, the study was performed before the use of CT volumetry in our center. With the use of CT volumetry, it is expected that the detection of inadequate liver remnant with laparoscopy may be less frequent, but laparoscopy still has an important role in assessing the tumor status.

Preoperative portal vein embolization

For patients with inadequate remnant liver volume who require major or extended hepatectomy, preoperative portal vein embolization is useful in inducing hypertrophy of the remnant liver.^{26,27} A few recent studies have demonstrated that preoperative portal vein embolization is effective in inducing hypertrophy of the remnant liver, even in patients with mild cirrhosis or chronic hepatitis.^{30–32} In our center, right portal vein embolization is frequently performed in patients with hilar cholangiocarcinoma requiring extended right hepatectomy. We also perform portal vein embolization in selected patients with chronic hepatitis or mild cirrhosis

undergoing major hepatectomy when the remnant liver volume is less than 30%–35% of the estimated standard liver volume, which can be calculated using a formula based on the body surface area.³³ Figure 2 shows the CT scans of a patient with a small remnant liver who had liver hypertrophy induced by portal vein embolization.

Other factors in the selection of patients for hepatectomy

While the above provides an account of our general approach in assessing the liver function reserve before hepatectomy, there are other factors that we will take into consideration when deciding whether a patient is suitable for hepatectomy. The risk of liver failure depends not only on the function reserve of the remnant liver but also on other factors. Major postoperative complications such as severe sepsis often precipitate liver failure in a patient with otherwise adequate liver function reserve. Advanced age and comorbid conditions are factors that may increase the risk of postoperative complications, especially in patients undergoing major hepatectomy. In a previous study of extended hepatectomy for HCC performed in our institution, a comorbid condition was found to be a significant risk factor of hospital mortality.³⁴ In a more recent analysis, we found that elevated serum creatinine level was another risk factor of hospital mortality after hepatectomy. Hence, patients with chronic renal failure should not be considered for major hepatectomy. Although we have previously shown that hepatectomy is safe in elderly patients more than 70 years old, it is noteworthy that this was the result of careful case selection in terms of the patients' comorbid conditions.³⁵

The risk of liver failure also depends on technical factors. It has been documented that massive bleeding was a risk factor of post-hepatectomy liver failure, independent of liver function reserve.¹⁵ Inappropriate surgical techniques causing intraoperative hypoxic injury to the remnant liver, such as prolonged use of the Pringle maneuver³⁴ and prolonged rotation of the liver with twisting of inflow and outflow vascular pedicles,⁴ may also result in liver failure, even when the preoperative liver function reserve appears adequate. In this regard, centers with less experience in hepatectomy may have to allow for a greater safety margin in terms of liver function reserve when selecting patients for hepatectomy.

Conclusions

Routine preoperative assessment of hepatic function reserve in our center includes clinical assessment, liver

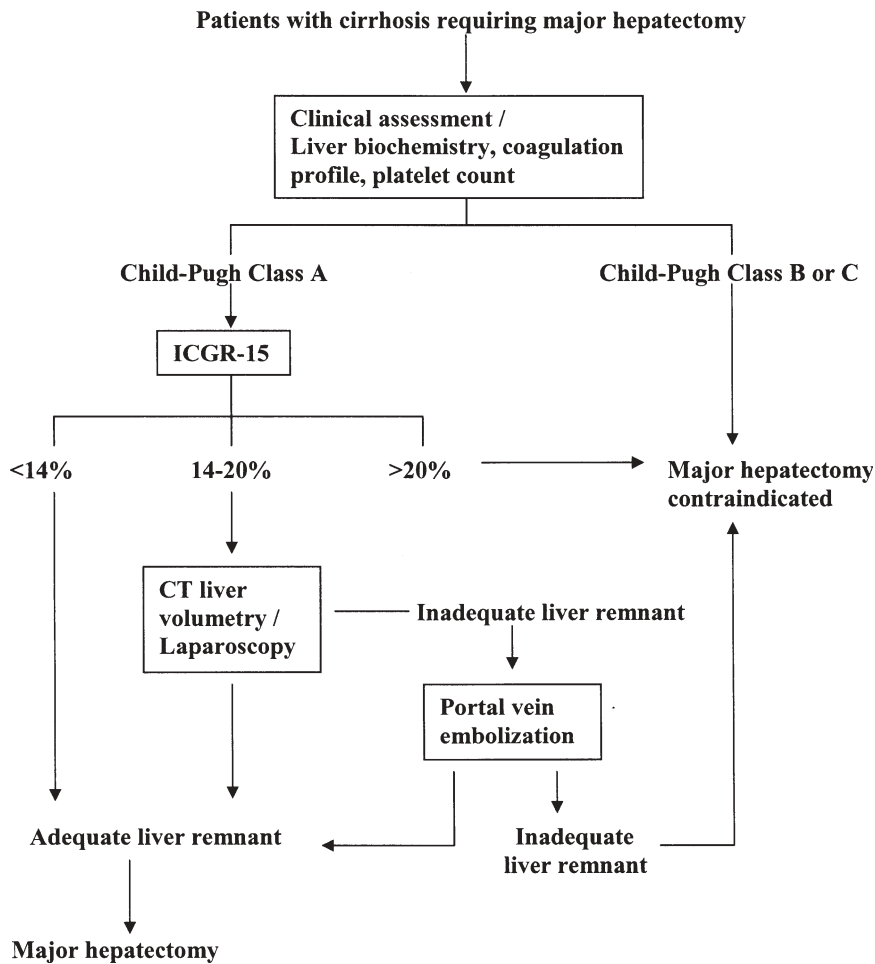


Fig. 3. Flow chart showing approach to preoperative assessment for selecting patients with cirrhosis for major hepatectomy

biochemistry, coagulation profile, platelet count, and Child-Pugh classification, and, in patients with chronic liver disease, the ICG clearance test. The risk of liver failure is highest in patients with cirrhosis undergoing major hepatectomy. For such patients, CT volumetry and laparoscopy are employed to assess the adequacy of the remnant liver volume when the liver function reserve appears borderline based on the ICGR-15 result. In selected patients with a small liver remnant, we perform preoperative portal vein embolization to induce hypertrophy of the remnant liver. Our approach in selecting patients with cirrhosis for major hepatectomy is summarized in Fig. 3. Careful attention to comorbid conditions of the patients and meticulous surgical techniques to avoid massive blood loss and intraoperative hypoxic injury to the remnant liver are of equal importance to ensure safe hepatectomy in patients with limited liver function reserve.

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