

# Preoperative assessment of liver function

Philip D. Schneider, MD, PhD

*Division of Surgical Oncology, Department of Surgery, Cancer Center, School of Medicine,  
University of California, Davis, 4501 X Street, Room 3010, Sacramento, CA 95617, USA*

Assessment of liver function is a critically important tool for selecting patients for hepatic surgery. Not only is it important in the assessment of a patient's ability to withstand resection, it also has clearly played a role in the selection process that surgeons apply to individual patients in tailoring the appropriate extent of resection. These decisions are based on the requirement for adequate margins of resection, balanced against any underlying hepatic functional impairment that tends to limit the safe extent of resection.

In recent years, the assessment of liver function has had an increasingly important role, as surgeons attempt to overcome the limits of anatomic constraints and the volume of tumor to increase resection rates. For it must not be forgotten that surgical resection remains the mainstay of cure for patients with hepatic malignancies, and no effort to achieve resection should go unexplored. The importance of assessing liver function has been further increased because the goal of several aggressive preoperative therapies designed to improve the liver functional reserve before resection requires some means of assessing whether, in fact, functional reserve has been improved.

This article, therefore, reviews those tools available to assess hepatic function and hepatic reserve. It discusses the clinical stratification schemes and recent modifications designed to improve the recognition and assessment of early stage cirrhosis. Two imaging and function tests—indocyanine green retention and 99m-Tc-galactosyl serum albumin scintigraphy—that have been purported to help with the detailed assessment of liver reserve and to augment clinical classification systems are briefly reviewed.

Successful liver resection for primary or metastatic liver tumors involves the surgeon's recognition that hepatic regeneration will occur, and that this metabolic demand is superimposed on the necessary homeostatic functions of the liver. Postoperative tolerance of resection and the ability to regenerate

---

*E-mail address:* [pschneider@ucdavis.edu](mailto:pschneider@ucdavis.edu) (P.D. Schneider).

the missing parenchyma are markedly different among patients. The generally acknowledged equivalency of limited versus major lobar and extended resections has, in a sense, been an implied recognition of the limitations on resection imposed by such conditions as cirrhosis. Four recent series with superior outcomes are reviewed, and the means by which these investigators selected their patients to achieve their results are discussed.

### What is hepatic reserve?

Reserve is defined in Webster's Third Collegiate Dictionary as "a store; a stock; an extra supply; or that part of the assets of a bank which is kept in more or less liquid form as a reasonable provision for meeting all demands which may be made upon it; or portion of corporate earnings set aside to meet future losses or contingent liabilities."

The financial definition of reserve comes closest to the surgeon's concept of what is expected of the liver after complicated injury, invasive procedures, or surgical resection. The financial comparison elucidates the notion that further demands of regeneration or wound healing will be superimposed upon functional obligations of an organ that are essential for aerobic and anaerobic metabolism, protein synthesis and degradation, and various detoxification processes.

Over the years, experienced hepatobiliary surgeons have developed selection criteria that allow them to avoid or to limit liver resection in patients whose ability to tolerate resection appears impaired. In part, this decision process has been aided by clinical classification systems such as the Child classification scheme and various liver-function tests. Despite these tools, it is surprising to some clinicians that liver failure remains a significant contributor to postoperative morbidity and mortality. By the same token, experienced hepatic surgeons have a remarkable ability to match patients to an appropriate operation, thus achieving maximal benefit with low risk.

In Table 1, several series are reviewed in which the overall liver failure rate leading to death ranges from 2% to 65% following hepatic resection for

Table 1  
Liver Failure after hepatic resection: hepatocellular carcinoma

	No. Patients	Deaths	Deaths due to liver failure (%)
Kanematsu et al [38]	50	4 (limited) 2 (lobar)	1 (25%) 1 (50%)
Lee et al [39]	109	6	3 (50%)
Nagasue et al [7]	118	9	5 (55%)
Nagao et al [6]	99	19	8 (42%)
Tsao et al [40]	322	48	32 (65%)
Arii et al [41]	3395	2-25%	
Nonami et al [42]	262	27	27 (100%)

hepatocellular carcinoma (HCC). Patients who have HCC often have underlying cirrhosis as an etiologic factor for their tumors; thus liver failure as a cause of postoperative mortality is not surprising in this group. What is often more surprising, however, is that liver failure is a substantial component of mortality after liver resection for colorectal cancer. Table 2 indicates that mortality rates after resection for colorectal cancer have a wide range, with up to 50% of deaths stemming from liver failure. Prolonged recovery and even late deaths can also occur for this same reason, further indicating the importance of liver reserve in recovery from hepatic surgery.

What then is hepatic reserve? Moving beyond the financial analogy, hepatic reserve is the combined functions of the liver as determined by hepatic parenchyma, the reticuloendothelial system, unique cells in the liver (ie, Ito cells), and hepatic blood flow, including major arterial, portal venous, hepatic venous; and microvascular blood flow in the spaces of Disse. Preservation of parenchymal volume appears to be under the complex control of a number of factors derived from the portal venous circulation, including insulin and hepatocyte growth factors among others. The functions of the liver are varied and some are quite complex. A simplistic summary of liver function includes the synthesis and degradation of glucose and glycogen, fatty acid metabolism, and the synthesis of a variety of proteins, as well as detoxification of lipid soluble toxins, degradation of bilirubin, and the general degradation of serum proteins targeted for routine turnover.

The clinical assessment of hepatic function has evolved from the Child system, developed to understand the significance of cirrhotic liver injury and portal hypertension as they related to patient survival and surgical outcomes for portal-systemic shunt surgery [1]. This system has also been applied to determine mortality estimates for elective operations, and as a means to follow the clinical course of patients with liver disease, in an effort to recognize changes that require alterations in therapeutic strategy.

The original Child system assessed the degree of ascites, the presence and severity of encephalopathy, and the levels of bilirubin and albumin (Table 3) [2]. Recent modifications of the Child assessment have included the Pugh modification, which includes the prothrombin time (or international

Table 2  
Liver failure after hepatic resection: colorectal cancer metastases

	No. Patients	Deaths	Deaths due to liver failure (%)
Fortner [48]	65	6	3 (50%)
Iwatsuki [49]	48	1	0
Ekberg et al [43]	81	4	2 (50%)
Nordlinger et al [44]	80	4	2 (50%)
Doci et al [45]	100	5	0
Doci et al [46]	208	5	2 (40%)
Nordlinger et al [47]	1568	36 (2.3%)	6 (16%)

Table 3  
Hepatic function assessment using the Child system and its modifications

Variable	Child	Pugh	Campbell
Ascites	X	X	X
Nutrition			X
Encephalopathy	X	X	X
Bilirubin	X	X	X
Albumin	X	X	X
Protome/international normalized ratio (INR)		X	

normalized ratio (INR)) and does not look at nutritional status, except indirectly via plasma albumin levels [3]. In another modification, the Child-Campbell system, a scoring system similar to that of Child-Pugh (CP) is used—presence and degree of ascites, encephalopathy, bilirubin, and albumin, and nutritional status are considered. By replacing the evaluation of prothrombin time or INR with nutrition assessment, the Child-Campbell score can be obtained in locales without the ability to obtain those coagulation tests [4]. Less widely applied alternatives to the CP and Child-Campbell scores include the Apache III scoring system, and ANS, or ascites/nutritional score. The CP score has widest use among surgeons. This has been facilitated by its simple scoring system (Table 4) [3,4].

How useful are these clinical systems? How is general survival equated with the A, B, and C stratification resulting from the Child classification and its refinements? What has been the predictive value of these systems? And, particularly, how well do these classification schemes predict outcomes in liver resection? Are they useful for defining the limits of resection; that is, the limits of hepatic reserve?

In the CP system, a score of 5 to 6 garners a Child A classification. Patients in this stratum generally would be presumed to have virtually no risk for mortality from liver-related causes during the subsequent year. With increasing debility, scores of 7 to 9 merit a classification of B, and these cirrhotic patients carry a 20% risk of 1-year mortality from liver-related complications of cirrhosis such as variceal bleeding and hepatic failure.

Table 4  
Child-Pugh scoring system<sup>a</sup>

Points	1	2	3
Ascites	None	Small or diuretic controlled	Tense
Encephalopathy	Absent	State I–II	State III–IV
Albumin (g/L)	> 3.5	2.8–3.5	<2.8,
Bilirubin (mg/dL)	<2	2–3	> 3
PT(sec above control), or	<4	4–6	> 6
INR	<1.7	1.7–2.3	> 2.3

<sup>a</sup> Child-Pugh Class A, 5–6 total points; Child-Pugh Class B, 7–9 total points; Child-Pugh Class C, 10–15 total points.

A CP score of 10 to 15 out of a total score possible score of 15 merits a C classification. Such patients bear a 55% 1-year mortality risk, again stemming from complications of cirrhosis such as gastrointestinal bleeding and hepatic encephalopathy. Patients classified as B or C become eligible for liver transplant evaluation.

In the Campbell system (substituting nutritional status for prothrombin time), cooperative group data from the Euricterus database demonstrated that only 5% of 1015 cirrhotics would merit classification by Child's criteria [4]. With the Campbell modification, 19% could be classified as Child Class A, and 46% could be classified as Child Class B. Their data also demonstrated that the Pugh's modified Child score, and even the ANS system, also refine the risk estimates for early stage cirrhosis, and therefore may be presumed to provide a better prediction of complications or death from hepatic failure. One would assume that this would apply to surgical risk, as well.

Unfortunately, the predictive value of the Child score for liver resections has been shown to be quite variable. Franco et al [5], for example, demonstrated that the mortality for a Child Class A patient undergoing liver resection was 3.7%, versus 16.7% for both Child Class B and C patients, despite the fact that limited resections were employed. Nagao et al and Nagasue et al demonstrated no differences in mortality based on Child's stratification [6,7]. Bismuth et al, attempting to use a modified stratification system to predict the limits of resection by stage, reported some success, yet noted five deaths in his series, including those of three early-stage cirrhotic patients who had marginal amounts of liver resected and who by preoperative prediction should have survived [8].

Most hepatic surgeons have discovered that the CP scoring system provides refined predictions of risk compared with the Child scheme; however, there is a persisting unreliability of even the CP score with regard to the Child Class A patients (CP score 5–6). For this reason, hepatic surgeons have pursued laboratory and imaging measures to bolster their clinical assessments and to provide objective data to bolster clinical judgments of patient risk from impaired hepatic reserve. In essence, there is a need to identify “good risk” Child-Pugh A patients and “poor risk” Child-Pugh A patients.

### **Laboratory and Imaging studies to augment Child-Pugh assessment**

To overcome the limitations of the CP score for predicting risk of liver failure in patients who are to undergo hepatic surgery, various biochemical tests and imaging studies designed to assess some specific aspect of liver function have been employed to assist in the assessment. These include a variety of single laboratory tests, clearance and tolerance tests, functional imaging, and volumetric tests based on radiological imaging, some of which are listed in **Box 1**.

The ideal function test has yet to be invented. The complexity of liver function is such that this is no surprise; however, a successful liver function

**Box 1. Various tests of liver function used to assess hepatic reserve***Clearance/tolerance tests*

- Aminopyrine breath test
- Indocyanine green (ICG) retention (clearance)
- Bromosulphthalein (BSP) retention
- Galactose tolerance
- Bile acid tolerance
- Beta-hydroxy butyrate/acetoacetate

*Functional imaging and blood flow: uptake/clearance*

- Reticuloendothelium
- Gold
- Sulfur colloid
- Biliary excretion
- Rose Bengal
- Hepatic diacetic acid (HIDA)
- Receptor targeting
- Neogalactosyl albumin (NGA)
- Galactosyl serum albumin (GSA)

test, to assist with preoperative assessment of liver function should be safe, reproducible, and easily performed in an outpatient setting. From the busy surgeon's standpoint, the best test is one that can be performed by colleagues or ancillary staff with the time and facilities to achieve these characteristics. Unfortunately, ease of performance is often linked to analyses intended to simplify the complex results for ease of interpretation. The resulting oversimplification of the analysis may reduce the utility of the tests.

How useful have these tests been in predicting surgical outcome? Clearly the tests employed have been employed because of their ease of application. No single test appears to account for the variability of clinical resection results, and, as will be demonstrated, at this point in time no existing test has proven better than the CP system for assessing hepatic functional reserve.

There is no single laboratory test capable of providing this information. Clearance and tolerance tests, however, offer seemingly attractive means to augment the CP assessment (see Box 1). Of these, the most widely used is indocyanine green (ICG) retention. ICG retention is worth focusing on because of its clear selection as the most popular augmentative test used to select patients for resection following CP scoring.

**Indocyanine green retention**

ICG is a tricarboyanine dye that binds to albumin and alpha-1 lipoproteins. Its active transfer into the liver parenchymal cells leads to

a rapid disappearance from the plasma, and it appears to be solely removed by the liver [9]. From the parenchymal cell, it is secreted into the bile in much the same way as an earlier function test dye, bromsulphthalein [10]. The surgical community has generally opted for the retention time at 15 minutes as a single test—ICG 15 (Fig. 1). This can be determined by serum sampling, or, as described recently, the percent retention can be determined by pulsed spectrophotometry, using an optical sensor placed on the finger in a similar fashion to an oxygen saturation monitor [11].

In more detailed investigations, several serum values are used to obtain a number of time points to generate a rate-constant, indicating the rate at which the dye disappears from the serum. In this fashion, it has been determined that, rather than being a true index of parenchymal function, there is a substantial influence of hepatic blood flow—both total hepatic blood flow and unit-by-unit flow within the hepatic parenchyma—on the retention of the dye [10]. Hepatic artery vasodilatation may markedly influence the value in the same patient, even on the same day. There is general agreement on the retention values that support major liver resection. Clearance is considered to be impaired when 15% or more of the dye remains within the plasma 15 minutes following the injection of 0.5 mg/kg ICG. Thus, patients with CP scores of 5 or 6 (Child A) and ICG 15 of greater than 14% are the “bad risk” CP A patients whose functional reserve is limited. ICG 15 correlates strongly with CP scores. It also correlates strongly with the rate of disappearance of tagged asialoglycoproteins [12].

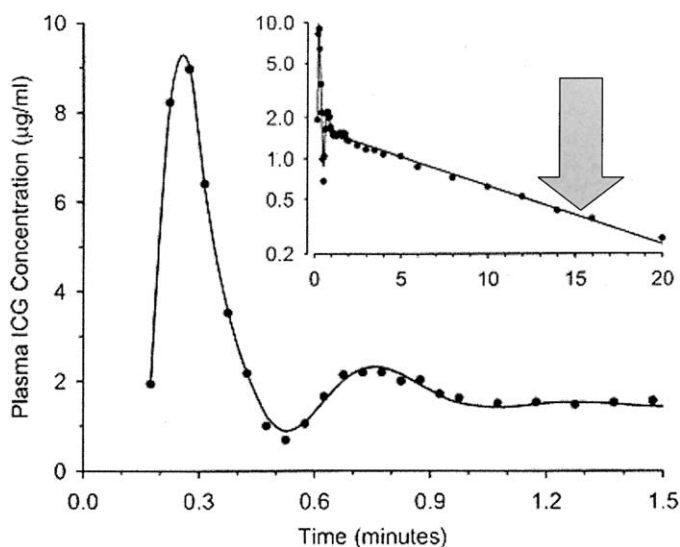


Fig. 1. A typical ICG clearance curve, which can be obtained by serial plasma sampling or optical pulse spectrophotometry. The arrow marks the ICG 15-minute retention value that is most frequently used to judge the adequacy of liver function.

In two important papers assessing the technique of portal vein embolization-improving hepatic functional reserve, Wakabayashi et al and Nakano et al correlated ICG values with hepatic hypertrophy of the contralateral lobe after portal vein embolization [13,14]. The ICG disappearance rate generally worsened (in 16 of 19 patients) at 2 weeks following treatment. Wakabayashi et al noted that ICG retention was prolonged in a number of patients who subsequently died, but that numerous patients underwent resection without mortality, even in the face of elevated or prolonged ICG clearance. Interestingly, the ICG retention rate worsened in virtually all patients following portal vein embolization at 2 weeks, increasing from a mean of  $15.9 \pm 6.27\%$  to  $20.8 \pm 5.6\%$  at 2 weeks. Either 2 weeks is too early to see improved ICG return to baseline clearance, or the altered blood flow due to portal vein embolization results in ICG 15 retention values that do not permit an estimate of hepatocyte function. There is only weak evidence that this test can be useful in assessing the successful accomplishment of liver resection, and lack of correlation is well described [13,15]. Furthermore, the variability of the results depending on total hepatic blood flow, and regional variations can markedly alter the retention value. This reconfirms the information, available as early as 1989, that no quantitative liver function test provided a clear advantage beyond the CP score for predicting outcome in cirrhosis [16]. There have always been strong correlations of the tests with the CP score, but none, including ICG retention, has been directly correlated with outcome.

### **99m-Tc-galactosyl-human serum albumin scintigraphy**

Nuclear imaging with a variety of agents has existed for years, including sulfur and gold colloid scans, and uptake and excretion of Rose Bengal and HIDA. These scanning agents assessed the reticuloendothelial uptake of colloid and the biliary excretion of HIDA. A more recent functional imaging technique with great promise involves receptor targeting with radiolabeled synthetic asialoglycoproteins. In 1966, an active transport process involving the endocytotic removal of senescent serum glycoproteins, which were desialated to allow them to be identified and removed from the circulation by the hepatic parenchyma, was described by Ashwell [17]. Taking advantage of the role of the liver in metabolizing senescent proteins through an active transport process facilitated by hepatocyte membrane receptors, the potential for using this as a liver scanning agent was proposed by Eckelman et al [18], and a synthetic asialoglycoprotein, galactosyl-neoglycoalbumin (NGA), was complexed to 99m-Tc to study hepatocyte binding via the asialoglycoprotein receptor [19–21]. In addition, imaging provided volumetric/anatomic information, as well as a functional assessment of the ability of the liver to clear the synthetic asialoglycoproteins. Kudo et al, in 1991, reported the development of a similar synthetic

asialoglycoprotein, galactosyl human serum albumin (GSA) [22]. This has subsequently been approved for use as a liver-scanning agent in Japan (Nihon Mediphysics, Nishinomiya, Japan), although its use in the United States remains investigational.

Patients undergoing a GSA study receive a bolus injection of 185 MBq  $^{99m}\text{Tc}$ -GSA. A dynamic scintigraph is obtained with gamma cameras located over the heart and liver (Fig. 2). The data can then be acquired as planar or single photon emission computed tomography (SPECT) images (Fig. 3). Typical time-activity curves are generated, as shown in Fig. 2. Abnormal values generate curves such as shown in Fig. 4.

In an effort to simplify interpretation of the data, particularly with regard to proposed surgical use, most investigators have chosen to use the L15 value as an overall estimate of hepatocyte asialoglycoprotein receptor number (Fig. 2). Thus the data can be acquired to indicate both the rate of uptake into the liver (or disappearance from the blood pool) and the total number of receptors available. For estimates of postoperative receptor volume, either SPECT images from the GSA scintigraph or CT estimates of the estimated remaining volume of a resection could be used to predict the total number of receptors remaining. The first summary of the US clinical experience with the asialoglycoprotein analog, NGA, demonstrated the correlation of NGA with the CP score, the aminopyrine breath test, and ICG retention [20]. Whether the test provided specific, unique, adjunctive information was not certain. Verification of these data followed with the Japanese analog, GSA, correlating this not only with the ICG retention at

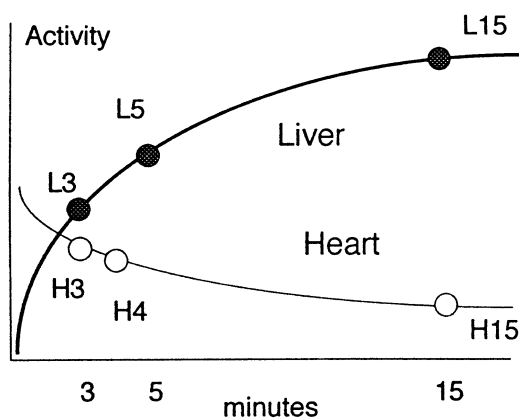


Fig. 2. GSA time-activity curves for the heart and liver. The L15 value has been widely used in the surgical literature to connote functioning receptor number and thus, liver functional volume. (From Nakajima K KK, Mizutani Y, Hwang E-U, Michigishi T, Tonami N, Kobayashi K. Simple scintigraphic parameters with Tc-99m galactosyl human serum albumin for clinical staging of chronic hepatocellular dysfunction. *Ann Nucl Med* 1999;13(1):5–11; p. 6; with permission.)

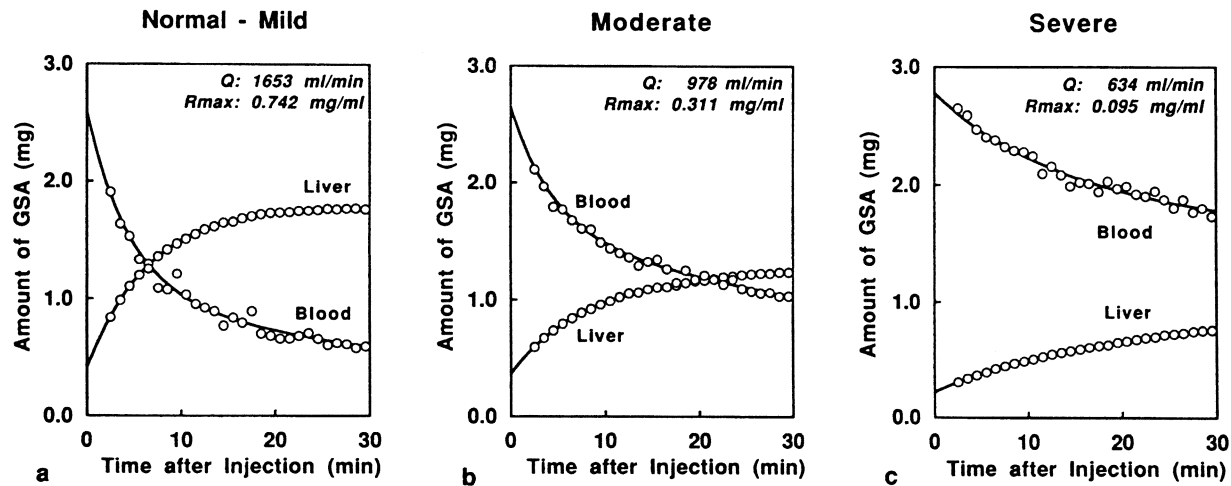


Fig. 3. Sample GSA curves for normal or mildly impaired liver function, moderately impaired liver function, and severely impaired liver function. (From Ha-Kawa SK, Tanaka Y, Hasebe S, Kuniyasu Y, Koizumi K, Ishii Y, et al. Compartmental analysis of asialoglycoprotein receptor scintigraphy for quantitative measurement of liver function: a multicentre study. Eur J Nucl Med, 1997;24:130-7; p. 116; with permission.)

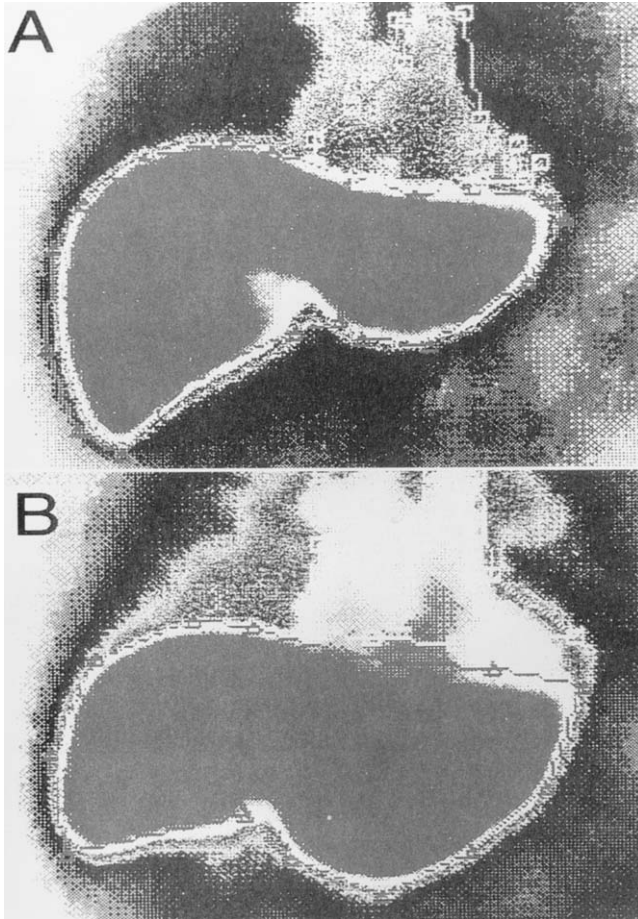


Fig. 4. GSA planar image before and after right portal vein embolization demonstrating both the increased left lobes size and asialoglycoprotein receptor number. SPECT images are also obtainable. (From Kubo S, Shiomi S, Tanaka H, Shuto T, Takemura S, Mikami S, Uenishi T, et al. Evaluation of the effect of portal vein embolization on liver function by  $^{99m}\text{Tc}$ -galactosyl human serum albumin scintigraphy. *J Surg Res* 2002;107:113–8; p. 132; with permission.)

15 minutes, but also with the index of cirrhosis scores, whereas the ICG retention had no correlation with the histologic scores indicating extent of necrosis and fibrosis in patients with chronic active hepatitis [23].

A follow-up article by Kwon et al used technetium GSA to correlate ICG retention and GSA functional imaging [22,24]. This suggested that there is an absolute receptor number below which extended liver resection could not be performed. In their series of 90 patients, however, there were only two operative deaths, one in a low-risk group, and one a patient with marked discrepancy between the GSA and the ICG. In a patient with chronic

hepatitis such a discrepancy may be important, as patients who have the ability to regenerate may also have active, aggressive cirrhosis that may compromise the results.

Ha-Kawa et al provided further studies to define the spectrum of typical time-activity curves for cirrhosis [25]. Their multicenter study indicated that this technology was reproducible in a number of settings. Using SPECT images, Hwang et al demonstrated that GSA could be used to predict the remainder of functional receptors, based on the likely size of the resection and extent of receptor populations remaining [26].

In a natural history study of hilar cholangiocarcinoma, Akaki et al recognized that occlusion of the portal vein resulted in decreased receptor numbers in the occluded segment [1]. Of more relevance to surgeons is whether this resulted in an increase of receptors in the contralateral lobe. This was more directly addressed by Nakano et al, identifying patients for transarterial chemoembolization on the basis of receptor numbers. They discovered that patients, who on the basis of their low receptor numbers at the L15 point of the GSA kinetic scan, received portal vein embolization [14] that activity was found to increase, suggesting increased receptor numbers for the entire liver after the resection. This information is confusing, because one would anticipate an ultimate homeostatic redistribution of receptors. Their data also disclosed that a number of patients who were felt to be clearly resection candidates, and who then underwent transarterial chemoembolization, had decreases in the receptor number [14]. The trend of ICG retention and GSA scanning suggested an increase in receptor numbers when in fact we expect homeostasis at best, but on an uncertain timetable. One simple conclusion is that blood flow may alter GSA results, much as ICG retention test values are altered by changes in hepatic blood flow such as occurs in this acute situation following portal vein occlusion. A more complex analysis raises the question as to whether the mathematical model yielding receptor numbers is related to hepatocyte mass. If so, receptor expression might still vary, for reasons independent of the known hyperplasia occurring after portal vein embolization [27]. Similar derangements in GSA uptake also occur postoperatively. How this affects the time-activity curves results for GSA has been demonstrated by Tanaka et al [28]. But beyond the fact that changes occur, data regarding the specific changes resulting from specific surgical procedures are being acquired.

Kokudo et al helped elaborate on this point by demonstrating that receptor recovery after hepatic resection occurred over a number of days, and that by 21 days after resection most patients still demonstrated marked reduction in receptor concentrations [29]. Followed over time, receptor numbers appear to increase, even after 150 days postresection. Thus estimation of reserve must take into account the fact that there will be a temporary dysfunction in asialoglycoprotein endocytosis (and hepatic blood flow) that may improve with time, as long as regeneration occurs without progressive fibrosis or complicating necrosis. Changes in blood flow

as estimated by dynamic curves or alternative tests have not been done in the postoperative state.

Fujioka et al, attempting to estimate functional reserve and correlate this with CT images and ICG retention, used the L15 receptor number to identify those patients with likely complications. Only 1 patient in their group of 35 patients died from liver failure [30]. Thus the predictive value to the test is limited by concomitant careful selection.

Uetake et al studied 13 patients and found that the 15-minute receptor volume correlated with an estimate of the resection volume [31]. This led to an accurate assessment of the postoperative receptor numbers, and they predicted the potential utility of GSA in the selection of patients for specific surgical procedures, based on estimates of functional remnant receptor volume [31]. Elaborating on this finding, Wakabayashi et al demonstrated that the receptor numbers could be estimated and correlated with CT volumetry [32]. And they demonstrated that, as with ICG, blood flow appeared to markedly change these values, raising the question whether simple receptor assay at 15 minutes (the L15) adequately conveys the extent of liver disease or recovery. In the most encouraging study to date, Kubo et al, employing portal vein embolization to increase hepatic reserve, demonstrated a shift in receptor numbers from right to left lobe as the liver became hyperplastic on the left [33]. This is one of the truly encouraging findings from the early literature regarding GSA.

Overall, use of GSA clinically is in its infancy. That GSA results correlate with ICG, CP, and other indices of liver function is not disputed. Whether it supplies additional information is a more complicated question to answer. It is clear from the foregoing discussion that GSA may suffer from some of the same drawbacks as ICG with regard to blood flow influences on the uptake of the agent. Virtually all of the studies discussed above correlate the GSA with another function test or the CP score. Not only are the results not correlated with outcomes, but also, the surgical results are uniformly excellent, and the small number of deaths does not provide an opportunity to correlate the test with the spectrum of postoperative liver dysfunction and failure. In addition, the simplified analyses using L15 alone may be an even greater problem for GSA analysis than for ICG, having to take into account not only functional hepatocyte mass but blood flow—always impaired in cirrhosis—as well.

The search for a simple number such as the L15 from the GSA scan, or the 15-minute ICG retention, ignores much important information acquired with these tests, and may do an unjust disservice to both of these methods. A simple means to summarize the acquired information and yet reflect the extent of the data acquired would be invaluable.

One of the most intriguing aspects of portal vein embolization to improve hepatic resection options in cirrhosis has gone beyond the demonstration of a volumetric change in the contralateral lobe after portal vein embolization, with and without combined hepatic artery embolization; in a limited study,

improved ICG clearance has also been demonstrated [13]. It is exciting that predictable volume increases due to hyperplasia of contralateral unembolized liver parenchyma have now been followed by data convincingly demonstrating a degree of improved function—even in cirrhotics. Kubo et al's data are the most convincing evidence to date that functional improvement, not just hyperplasia, may result from portal vein embolization, and that Tc-GSA can detect this (Fig. 4) [33].

As discussed above, function studies so far have been linked to CP scores, whereas the tests should more appropriately be linked to outcomes. The potential role of these agents in evaluating resection must demonstrate that they are improvements over CP stratification, or at least additive, and do not simply duplicate predictive data acquired from the CP score.

### **Patient selection and resection outcomes: lessons learned from four recent series**

Torzilli et al, in 1999, reported that “no mortality” liver resection for hepatocellular carcinoma was possible [34]. For preoperative selection, the three parameters that they chose to employ were: (1) the presence of ascites, (2) the serum bilirubin level, and (3) the ICG 15. The projected remaining liver volume was analyzed by computer tomographic volume averaging. For patients with projected remnant volumes under 40% or ICG 15 values of 10% to 20%, portal venous embolization was performed to increase the projected remnant volume preoperatively. One hundred seven patients underwent resection of hepatocellular carcinoma without mortality. The authors outlined a method of combining bilirubin and ascites to select patients for ICG retention studies and to suggest which patients were appropriate candidates for limited resections or for extended resections.

Analysis of their selection criteria indicate that only CP score 5 or 6 (CP Class A) patients underwent surgery. ICG 15 was used to select the very best patients (ICG 15 <10%) for extended resection (four or greater segments). All other CP Class A stratum patients underwent lesser resections as guided by the ICG 15 value. This is a notable series, with a remarkable reliance on ICG 15 for guidance and an aggressive use of portal vein embolization to attempt to increase functional reserve.

Poon et al, reporting their experience with 45 extended resections for HCC, selected CP Class A patients, who then underwent ICG 15 evaluation [35]. A combination of detailed imaging to assess remnant volume and laparoscopy with laparoscopic ultrasound, in order to detect moderate to severe cirrhosis at the time of planned resection, was employed to further select patients who might then undergo extended resection. Their group of 45 extended resection patients (greater than four segments) were compared with a group of 161 patients with four or fewer segment resections. In each group, a single death (out of three and six total in each group, respectively)

occurred that could be attributed to liver failure. Two of the deaths occurred in Child-Pugh Class A patients and one occurred among 3 Child Class B patients. The authors concluded that extended resection was not indicated in Childs Class B patients. For CP Class A patients, a combination of the 15-minute ICG retention <14% for any patient, or a value between 14% and 20%, for a patient with a predicted large liver remnant volume, satisfactory results could be anticipated.

Jarnagin et al reported their experience (1991–2001) with 1803 liver resection cases for primary and metastatic disease [36]. Preoperative selection of CP Class A patients was coupled with a detailed radiologic workup. A meticulous intraoperative assessment led to a mortality of 3.1%, with only 6 of 55 deaths being linked directly to hepatic failure. The authors relied heavily on parenchyma-sparing, segmental resection. That the number of patients in the series developing liver failure was 5% (99 patients) is a testimony to the aggressiveness of the therapy. Other than the projected number of hepatic segments involved and the perioperative blood loss, no other factors reliably predicted mortality.

Redaelli et al used galactose elimination capacity with the aminopyrine breath test, in an analogous manner to the use of ICG reported above, to select 167 patients who underwent curative resection; 6 patients of 167 or 3.6% died [37]. Only 2 died of acute liver failure, and these died despite undergoing tissue-preserving resections.

The overwhelming message is that there is a considerable amount of experience-based selection in each of these series. The avoidance of greater than four-segment resections in “bad-risk” Child-Pugh Class A patients is a clear-cut goal, unless the option of portal vein occlusion is to be pursued. The estimated remnant volume—determined by preoperative imaging or by direct intraoperative assessment—and the severity of the cirrhosis determined at surgery, which is difficult to precisely quantify, appear to be of critical importance in patient selection. One question that arises from these papers is whether there is a test that provides a substantial benefit in the selection of patients for resection beyond clinical experience and the CP score. The Memorial-Sloan Kettering data reported by Jarnagin suggest that experience may play a critical, positive role in patient selection if ICG retention is not used.

## **Summary**

At the present time, the decision to resect and the choice of the extent of a hepatic resection are largely based on surgical judgment. The CP score is the best assessment tool we can now employ. There is uniform agreement that even segmental resections are not possible in the vast majority of Child Class B patients, CP score 7 to 9. The CP score can be augmented by radiographic testing, ICG retention testing, and by assessing tumor extent and the severity of the patient’s cirrhosis at surgery.

Surgeons need a simple means to assist with liver function evaluation—a test to augment the CP score. Although determining ICG retention is simple, it is questionable whether it adds to one's ability to define the poor-risk patient with better accuracy than the CP score. Abundant data exist to dispute the accuracy and reproducibility of ICG retention. That surgeons use it says more about the fervent desire to find a test that supports clinical judgment in these difficult patients than the scientific validity of the test.

Whether a series of tests would better define the Child-Pugh Class A patient who is also a relatively poor risk is not clear at present. Many investigations demonstrate the correlation of various assessment tools with each other, yet nothing distinguishes them in predicting risk beyond what is learned from the CP score.

In a group of CP Class A patients, the extent of the disease, the nature of underlying cirrhosis, and the extent of resection provide the clinical backdrop against which a decision for resection must be made. It may well be that one test may not do it, or that one single assessment of the ICG or the 15-minute receptor volume of GSA may be inadequate to project the nuances of liver function. Thus, 99m-Tc GSA scintigraphy will provide volumetric receptor data, as well as kinetic distribution curves, and may prove a useful test in the future. Whether GSA is ultimately to be proven useful requires a correlation of the test with actual clinical outcomes, rather than correlation with other tests or with the CP score. Discovering which patients are the poor risk Child Class A patients is the desired goal. To have value, the GSA scan must augment, not mimic, the CP score. In view of the fact that experienced surgeons appear to be astute in their ability to select patients for hepatic resection, finding a more refined test will require large numbers of patients at several centers to correlate the test results and the outcomes against the spectrum of postoperative liver failure, including death.

It appears that one lesson learned from portal vein embolization is that functional liver volume can be preserved. The compensatory hyperplasia that occurs in the contralateral hepatic lobe demonstrates two important features: (1) function of the opposite lobe has been transferred when evaluated by 99m-Tc-GSA, and (2) one considerable metabolic drain on the postoperative recovery from hepatic resection (ie, liver regeneration) can be attended to before the surgery. Cirrhotic livers do regenerate, but more slowly. Thus, pregrowing the remnant section of liver eliminates one stress on liver reserves following liver resection. For hepatocellular carcinoma or metastasis in cirrhotic patients, portal vein occlusion may be the best way to improve hepatic functional reserve. ICG retention may not corroborate return-to-baseline hepatic function within 2 weeks of portal vein occlusion, but may demonstrate a return to baseline when studied 6 to 8 weeks following the procedure. 99m-Tc-GSA is presently the best means to document compensatory hyperplasia and, possibly, a shift of functional reserve to the planned remnant of a more than four-segment hepatic

resection. Whether this will predict the safe outcome of resection remains to be seen.

## References

- [1] Akaki S, Mitsumori A, Kanazawa S, Togami I, Takeda Y. Lobar decrease in 99m-Tc-GSA accumulation in hilar cholangiocarcinoma. *J Nucl Med* 1999;40(3):394–8.
- [2] Child CG, Turcotte JG. Surgery and portal hypertension. *Major Probl Clin Surg* 1964;1: 1–85.
- [3] Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646–9.
- [4] Reisman Y, Gip CH, Lavelle SM. Assessment of liver cirrhosis severity in 1015 patients of the Euricterus database with Campbell-Child, Pugh-Child and with ascites and ascites-nutritional state (ANS) related classifications. Euricterus Project Management Group. *Hepatogastroenterology* 1997;44(17):1376–84.
- [5] Franco D, Capussotti L, Smadja C, Bouzari H, Meakins J, Kemeny F, et al. Resection of hepatocellular carcinomas. Results in 72 European patients with cirrhosis. *Gastroenterology* 1990;98(3):733–8.
- [6] Nagao T, Inoue S, Goto S, Mizuta T, Omori Y, Kawano N, et al. Hepatic resection for hepatocellular carcinoma. Clinical features and long-term prognosis. *Ann Surg* 1987; 205(1):33–40.
- [7] Nagasue N, Yukaya H, Ogawa Y, Sasaki Y, Chang YC, Niimi K. Clinical experience with 118 hepatic resections for hepatocellular carcinoma. *Surgery* 1986;99(6):694–701.
- [8] Bismuth H, Houssin D, Ornowski J, Meriggi F. Liver resections in cirrhotic patients: a Western experience. *World J Surg* 1986;10(2):311–7.
- [9] Wheeler HO, Cranston WI, Meltzer JJ. Hepatic uptake and biliary excretion of indocyanine green in the dog. *Proc Soc Exp Biol Med* 1958;99:236.
- [10] Cherrick GR, Stein SW, Leevy CM, Davidson CS. Indocyanine green: observations on its physical properties, plasma decay, and hepatic extraction. *J Clin Invest* 1960;39:592.
- [11] Okuchi O, Kaneko T, Sugimoto H, Inoue S, Takeda S, Nakao A. ICG pulse spectrophotometry for perioperative liver function in hepatectomy. *J Surg Res* 2002;103:109–13.
- [12] Nakajima K, Kinuya T, Mizutani Y, Hwang E-U, Michigishi T, Tonami N, Kobayashi K. Simple scintigraphic parameters with Tc-99m galactosyl human serum albumin for clinical staging of chronic hepatocellular dysfunction. *Ann Nucl Med* 1999;13(1):5–11.
- [13] Wakabayashi H, Okada S, Maeba T, Maeta H. Effect of preoperative portal vein embolization on major hepatectomy for advanced-stage hepatocellular carcinomas in injured livers: a preliminary report. *Jpn J Surg* 1997;27:403–10.
- [14] Nakano H, Yoshida K, Takeuchi S, Kumada K, Yamaguchi M, Jaeck D. Liver scintigraphy is useful for selecting candidates for preoperative transarterial chemo-embolization among patients with hepatocellular carcinoma and chronic liver disease. *Am J Surg* 1999;178(11):385–9.
- [15] Lam CM, Fan ST, Lo CM, Wong J. Major hepatectomy for hepatocellular carcinoma in patients with an unsatisfactory indocyanine green clearance test. *Br J Surg* 1999;86(8): 1012–7.
- [16] Albers I, Hartmann H, Bircher J, Creutzfeldt W. Superiority of the Child-Pugh classification to quantitative liver function tests for assessing prognosis of liver cirrhosis. *Scand J Gastroenterol* 1989;24(3):269–76.
- [17] Ashwell G, SC. Hepatic recognition and catabolism of serum glycoprotein. *JAMA* 1981; 246:2358–64.
- [18] Eckelman WC, Reba RC, Gibson RE, Rzeszotarski WJ, Vieras F, Mazaitis JK, et al. Receptor-binding radiotracers: a class of potential radiopharmaceuticals. *J Nucl Med* 1979;20(4):350–7.

- [19] Pimstone NR Sr, Vera DR, Hutak DP, Trudeau WL. Evaluation of hepatocellular function by way of receptor-mediated uptake of a technetium-99m-labelled asialoglycoprotein analog. *Hepatology* 1994;20(4):917–23.
- [20] Stadalnik RC, Vera DR, Woodle ES, Trudeau WL, Ward RE, Krohn KA. Technetium-99m-NGA functional hepatic imaging: preliminary clinical experience. *J Nucl Med* 1985; 26:1233–42.
- [21] Vera DR, Stadalnik RC, Krohn KA. (Tc-99m)-galactosyl-neoglycoalbumin: preparation and preclinical studies. *J Nucl Med* 1985;26:1157–67.
- [22] Kudo M, Todo A, Ikekubo K, Hino M, Yonekura Y, Yamamoto K, et al. Functional hepatic imaging with receptor-binding radiopharmaceutical: clinical potential as a measure of functioning hepatocyte mass. *Gastroenterol Jpn* 1991;26(6):734–41.
- [23] Sasaki N, Shiomi S, Iwata Y, Nishiguchi S, Kuroki T, Kawabe J, et al. Clinical usefulness of scintigraphy with 99m-Tc-galactosyl-human serum albumin for prognosis of cirrhosis of the liver. *J Nucl Med* 1999;40(10):1652–6.
- [24] Kwon A-H, Ha-Kawa SK, Uetsuji S, Kamiyama Y, Tanaka Y. Use of technetium 99m diethylenetriamine-pentaacetic acid-galactosyl-human serum albumin liver scintigraphy in the evaluation of preoperative and postoperative hepatic functional reserve for hepatectomy. *Surgery* 1995;117(4):429–34.
- [25] Ha-Kawa SK, Tanaka Y, Hasebe S, Kuniyasu Y, Koizumi K, Ishii Y, et al. Compartmental analysis of asialoglycoprotein receptor scintigraphy for quantitative measurement of liver function: a multicentre study. *Eur J Nucl Med* 1997;24(2):130–7.
- [26] Hwang E-H, Taki J, Shuke N, Nakajima K, Kinuya S, Konishi S, Michigishi T, et al. Preoperative assessment of residual hepatic functional reserve using 99m-Tc-DTPA-galactosyl-human serum albumin dynamic SPECT. *J Nucl Med* 1999;40(10):1644–51.
- [27] Harada H, Imamura H, Miyagawa S, Kawasaki S. Fate of the human liver after hemihepatic portal vein embolization: cell kinetic and morphometric study. *Hepatology* 1997;26(5):1162–9.
- [28] Tanaka A, Shinohara H, Hatono E, Sato S, Kanazawa A, Yamaoka Y, Torizuka T, et al. Perioperative changes in hepatic function as assessed by asialoglycoprotein receptor indices by technetium 99m galactosyl human serum albumin. *Hepatogastroenterology* 1999;46: 369–75.
- [29] Kokudo N, Vera DR, Koizumi M, Seki M, Sato T, Stadalnik RC, Takahashi T. Recovery of hepatic asialoglycoprotein receptors after major hepatic resection. *J Nucl Med* 1998; 40(1):137–41.
- [30] Fujioka H, Kawashita Y, Kamohara Y, Yamashita A, Mizoe A, Yamaguchi J, Azuma T, et al. Utility of technetium-99m0labeled-galactosyl human serum albumin scintigraphy for estimating the hepatic function reserve. *J Clin Gastroenterol* 1999;28(4):329–33.
- [31] Uetake M, Koizumi K, Yagawa A, Nogata H, Tezuka T, Kono H, Ozawa T, et al. Use of Tc-99m DTPA galactosyl human serum albumin to predict postoperative residual liver function. *Clin Nucl Med* 1999;24(6):428–34.
- [32] Wakabayashi H, Nishiyama Y, Ushiyama T, Maeba T, Maeta H. Evaluation of the effect of age on functioning hepatocyte mass and liver blood flow using liver scintigraphy in preoperative estimations for surgical patients: comparison with CT volumetry. *J Surg Res* 2002;106:246–53.
- [33] Kubo S, Shiomi S, Tanaka H, Shuto T, Takemura S, Mikami S, Uenishi T, et al. Evaluation of the effect of portal vein embolization on liver function by 99m-Tc-glactosyl human serum albumin scintigraphy. *J Surg Res* 2002;107:113–8.
- [34] Torzilli G, Makuuchi M, Inoue K, Takayama T, Sakamoto Y, Sugawara Y, et al. No-mortality liver resection for hepatocellular carcinoma in cirrhotic and noncirrhotic patients: is there a way? A prospective analysis of our approach. *Arch Surg* 1999;134(9):984–92.
- [35] Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, et al. Extended hepatic resection for hepatocellular carcinoma in patients with cirrhosis: is it justified? *Ann Surg* 2002; 236(5):602–11.

- [36] Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg* 2002;236(4):397–406 [discussion: 406–7].
- [37] Redaelli CA, Wagner M, Krahenbuhl L, Gloor B, Schilling MK, Dufour J-F, Buchler MW. Liver surgery in the era of tissue-preserving resections: early and late outcome in patients with primary and secondary hepatic tumors. *World J Surg* 2002;26:1126–32.
- [38] Kanematsu T, Takenaka K, Matsumata T, Furuta T, Sugimachi K, Inokuchi K. Limited hepatic resection effective for selected cirrhotic patients with primary liver cancer. *Ann Surg* 1984;199(1):51–6.
- [39] Lee CS, Sung JL, Hwang LY, Sheu JC, Chen DS, Lin TY, et al. Surgical treatment of 109 patients with symptomatic and asymptomatic hepatocellular carcinoma. *Surgery* 1986;99(4):481–90.
- [40] Tsao JI, Asbun HJ, Hughes KS, Abaubara S, August DA, Azurin A, et al. Hepatoma registry of the Western world. Repeat Hepatic Resection Registry. *Cancer Treat Res* 1994;69:21–31.
- [41] Arai S, Okamoto E, Imamura M. Registries in Japan: current status of hepatocellular carcinoma in Japan. Liver Cancer Study Group of Japan. *Semin Surg Oncol* 1996;12(3):204–11.
- [42] Nonami T, Nakao A, Kurokawa T, Inagaki H, Matsushita Y, Sakamoto J, et al. Blood loss and ICG clearance as best prognostic markers of post-hepatectomy liver failure. *Hepatogastroenterology* 1999;46(27):1669–72.
- [43] Ekberg H, Tranberg KG, Andersson R, Lundstedt C, Hagerstrand I, Ranstam J, et al. Determinants of survival in liver resection for colorectal secondaries. *Br J Surg* 1986;73(9):727–31.
- [44] Nordlinger B, Quilichini MA, Parc R, Hannoun L, Delva E, Huguet C. Hepatic resection for colorectal liver metastases. Influence on survival of preoperative factors and surgery for recurrences in 80 patients. *Ann Surg* 1987;205(3):256–63.
- [45] Doci R, Gennari L, Bignami P, Montalto F, Morabito A, Bozzetti F. One hundred patients with hepatic metastases from colorectal cancer treated by resection: analysis of prognostic determinants. *Br J Surg* 1991;78(7):797–801.
- [46] Doci R, Gennari L, Bignami P, Montalto F, Morabito A, Bozzetti F, et al. Morbidity and mortality after hepatic resection of metastases from colorectal cancer. *Br J Surg* 1995;82(3):377–81.
- [47] Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. *Cancer* 1996;77(7):1254–62.
- [48] Fortner JG, Silva JS, Bolbey RB, Cox EB, Maclean BJ. Multivariate analysis of a personal series of 247 consecutive patients with liver metastases from colorectal cancer. I. Treatment by hepatic resection. *Ann Surg* 1984;199:306–16.
- [49] Iwatsuki S, Esquivel CO, Gordon RD, Starzl TE. Liver resection for metastases from colorectal cancer. I. *Surgery* 1984;199:306–16.