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Preoperative Galactose Elimination Capacity Predicts Complications and Survival After Hepatic Resection

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Objective

To analyze a single center's 6-year experience with 258 consecutive patients undergoing major hepatic resection for primary or secondary malignancy of the liver, and to examine the predictive value of preoperative liver function assessment.

Summary Background Data

Despite the substantial improvements in diagnostic and surgical techniques that have made liver surgery a safer procedure, careful patient selection remains mandatory to achieve good results in patients with hepatic tumors.

Methods

In this prospective study, 258 patients undergoing hepatic resection were enrolled: 111 for metastases, 78 for hepatocellular carcinoma (HCC), 21 for cholangiocellular carcinoma, and 48 for other primary hepatic tumors. One hundred fifty-eight patients underwent segment-oriented liver resection, including hemihepatectomies, and 100 had subsegmental resections. Thirty-two clinical and biochemical parameters were analyzed, including liver function assessment by the galactose elimination capacity (GEC) test, a measure of hepatic functional reserve, to predict postoperative (60-day) rates of death and complications and long-term survival. All variables were determined within 5 days before surgery. Data were subjected to univariate and multivariate analysis for two patient subgroups (HCC and non-HCC). The cutoffs for GEC in both groups were predefined. Long-term survival (>60 days) was subjected to Kaplan-Meier analysis and the Cox proportional hazard model.

Results

In the entire group of 258 patients, a GEC less than 6 mg/min/kg was the only preoperative biochemical parameter that predicted postoperative complications and death by univariate and stepwise regression analysis. A GEC of more than 6 mg/min/kg was also significantly associated with longer survival. This predictive value could also be shown in the subgroup of 180 patients with tumors other than HCC. In the subgroup of 78 patients with HCC, a GEC less than 4 mg/min/kg predicted postoperative complications and death by univariate and stepwise regression analysis. Further, a GEC of more than 4 mg/min/kg was also associated with longer survival.

Conclusions

This prospective study establishes the preoperative determination of the hepatic reserve by GEC as a strong independent and valuable predictor for short- and long-term outcome in patients with primary and secondary hepatic tumors undergoing resection.

The incidence of primary hepatic tumors, in particular hepatocellular carcinoma (HCC), is increasing.[1] Hepatic resection or liver transplantation is the only potentially curative option for these patients.[2–4] In addition, liver metastasis, in particular from colorectal cancer, is a common clinical situation, and surgical resection of these metastasis improves survival.[5]

Because of considerable improvements in perioperative intensive care and refinements in surgical technique, rates of death and complications after major liver resection have significantly decreased during the past 20 years.[6–9] Because many patients also have liver cirrhosis or other chronic liver

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disease, death and complications after liver resection may occur, liver failure being one of the most dreaded complications. Different scores[10,11] and quantitative liver function tests[12] have been inaugurated to identify patients at risk for postoperative liver failure and other complications.

We evaluated the predictive value of determination of galactose elimination capacity (GEC) along with 31 other clinical and biochemical parameters in a prospective study. Galactose elimination capacity has been shown to have a predictive value for fulminant hepatic failure,[13] primary biliary cirrhosis,[14] and chronic active hepatitis.[15] Further, it provides additional prognostic information in cirrhotic patients when compared with the Child-Pugh classification.[16] However, its value has never been investigated in the setting of liver resection. This analysis in 258 consecutive patients at a single institution shows that preoperative assessment of functional liver parenchyma by determination of GEC has a predictive value not only for postoperative death and complications but also long-term survival.

METHODS

Between January 1994 and January 2000, data from 307 consecutive patients with liver tumors were entered in a prospective statistical database collection. Patients with extrahepatic tumor dissemination or recurrence of the extrahepatic malignancy at the primary site were not considered. Data from 49 patients with unresectable bilateral tumors were also excluded. The remaining 258 patients underwent liver resections for neoplasms and were further evaluated. Long-term data after surgery were obtained periodically by visits in our outpatient clinic or from the patient's physician records.

Thirty-two parameters were analyzed for each patient (Table 1). The GEC was determined by serial measurements of the serum concentration of galactose after a single intravenous bolus dose of 0.5 mg/kg galactose according to Tygstrup,[17] with some modifications, as previously described in detail.[18] The cutoffs of GEC for the two groups were defined before the statistical analysis. The GEC cutoff in patients without HCC was set at 6 mg/min/kg because this is the lower limit of the normal range. The GEC cutoff in patients with HCC was set at 4 mg/min/kg because this represents a 50% reduction of the hepatic contribution to the total GEC.[19] Complications or death occurring either within 60 days from the date of surgery or before hospital discharge were considered postoperative. Major complications were defined as reoperation or massive postoperative bleeding (>300 mL/hour), hemodialysis resulting from renal insufficiency, prolonged antibiotic therapy (>7 days), bile drainage, myocardial infarction, encephalopathy, pulmonary distress with prolonged mechanical ventilation (>24 hours), or sepsis. Complications were defined as minor if discharge or treatment was not delayed and they could be resolved with simple medication.

All patients had combined epidural and general anesthesia with standardized macrocirculatory and respiratory monitoring. An epidural catheter was introduced at level T5–T7 before introduction of general anesthesia, and an epidural solution containing bupivacaine, fentanyl, and epinephrine was infused. General anesthesia was induced with sodium thiopentone, fentanyl, and pancuronium and maintained with 0% to 70% N_2O in O_2 and isoflurane as well as repeated intermittent bolus doses of fentanyl and pancuronium. Blood pressure was monitored continuously through a radial arterial line and maintained at a mean arterial pressure of 70 to 90 mm Hg by adjusting anesthetics or

Table 1. PARAMETERS

Parameter	Criteria	Coding
Gender		male, female
Age		<70, ≥70
Diagnosis of tumor	histology	
ASA score		≤2, >2
Size of tumor	diameter	≤4 cm, >4 cm
Child/Pugh score		<6, ≥6
Ascites		presence, absence
Portal hypertension		presence, absence
Cirrhosis	histologically verified	presence, absence
Jaundice	bilirubin > 50 μmol/L	presence, absence
Viral hepatitis		presence, absence
Diabetes mellitus		presence, absence
Hypertension	varices, or/and hypersplenism, or/and hepatofugal portal flow	presence, absence
Renal dysfunction	creatinine > 150 μmol/L	presence, absence
COPD		presence, absence
Cardiac history	previous myocardial infarct previous bypass or stenting angina or arrhythmia	presence, absence
Platelets	0^9	normal, abnormal
Hemoglobin	g/L	normal, abnormal
INR	≤1.2, >1.2	normal, abnormal
Alkaline phosphatase	U/L	normal, abnormal
Serum ammonium	mmol/L	normal, abnormal
GEC	mg/min/kg	<6, ≥6 if no HCC <4, ≥4 if HCC
Duration of operation	hours	≤4, >4
Extent of resection		major/formal, minor/atypical
Pringle maneuver		performed, not performed
Intraop. units given		≤4, >4
Intraop. blood loss	mL	≤2,500 mL, >2,500 mL
Periop. ventilation	hours	
Length of ICU stay	days	
Bile leakage		presence, absence
Bleeding	reoperation needed	presence, absence
Sepsis		presence, absence

ASA, American Society of Anesthesiology; COPD, chronic obstructive pulmonary disease; GEC, galactose elimination capacity; HCC, hepatocellular cancer; INR, International Normalized Ratio.

infusing colloids and crystalloids. Arterial blood oxygen saturation was measured continuously by pulse oximetry and maintained at more than 90%. The individual surgical approach was determined during surgery according to the size, location, and extent of the liver tumor as well as the results of the preoperative liver function tests. A clear resection margin of at least 1 cm was a standard requirement for resection and was not influenced or determined by other factors. The tumor tissue was completely resected macroscopically in all patients. Nonanatomic or atypical resections were defined as resections of a lesion without regard to segmental or lobar anatomy, including the classically defined wedge resection. Hemihepatectomies or segment-based resections (formal resections) followed the anatomic definitions into segments and lobes according to Couinaud[20] and were performed along the modified resection lines for extended liver resection proposed by Blumgart.[21] Patients routinely underwent intraoperative ultrasonography to determine tumor localization and extent and to exclude the presence of additional lesions in the residual liver. To minimize blood loss, parenchymal dissections were performed using the Cavitron Ultrasonic Surgical Aspirator (Valley Lab, Inc. Stamford, CT). Hemostasis was achieved by argon beam coagulation (Deltamed-Erbe, Winterthur, Switzerland) and by ligation of individual blood vessels and bile ducts. One or two silicon drains were positioned to detect postoperative bleeding or bile leakage.

Statistical Analysis

To determine the risk factors related to postoperative death, complications, and survival, all relevant data were entered into a statistical file. Using a statistical package program (SPSS, Chicago, IL), all variables were analyzed by the Fisher exact test, the chi-square test, and the Mann-Whitney test where appropriate. First, differences in the various factors were examined between patient groups with and without major postoperative complications, and then multivariate analysis using a logistic stepwise regression model was performed to detect comprehensive correlations and risk factors. Stepwise regression and selection were based on the maximal likelihood ratio test. Only variables with $P < .1$ after univariate analysis were retained for the multiple logistic model. Survival analysis was performed by the Kaplan-Meier method; the significance of the difference between different survival curves was assessed using the log-rank test. Only variables with $P < .1$ were included in the multivariate stepwise regression survival analysis using the Cox proportional hazard model. All data are reported as median and standard deviation and range.

In this study, 32 factors were considered, 27 for the complications analysis and 29 for the survival analysis. Testing all the factors in univariate analysis is the first step in an explorative data analysis (i.e., the extensive multiple testing is not controlling the global first error rate). Applying a correction such as Bonferroni or Holm-Bonferroni indicates that only a few of the factors are still significant prognostic parameters. The multivariate analysis is more informative because the univariate analysis can be confounded by other factors. The univariate analyses were used as indicators for the multivariate one. Factors with $P < .05$ were considered statistically significant.

Table 2. DEMOGRAPHICS (n = 258)

	HCC (n = 78)	Non-HCC (n = 180)
Age*	65 (17–79)	56 (18–85)
Gender		
Female	22 (28%)	82 (46%)
Male	56 (72%)	98 (54%)
ASA	2.2 (1–4)	2.0 (1–4)
I, II	27 (35%)	137 (76%)
III, IV	51 (65%)	43 (34%)
INR*	1.0 (1.3–1.0)	1.0 (1.4–1.0)
GEC*	5.3 (3.16–8.1)	6.1 (3.1–8.1)
Jaundice	6 (7%)	18 (10%)
Cirrhosis	69 (89%)	10 (6%)
Portal hypertension	24 (31%)	5 (3%)
Child-Pugh score		
A	39 (49%)	3 (2%)
B	19 (24%)	–
C	2 (3%)	–

ASA, American Society of Anesthesiology; GEC, galactose elimination capacity; HCC, hepatocellular carcinoma; INR, International Normalized Ratio.
* Data are given as median (range).

RESULTS

A total of 258 patients undergoing liver resection for neoplasms were included in the study. Their median age was 59 years (range 17–85) and the median ASA score was 2.0 (range 1–4). Demographic characteristics of the study population are summarized in Table 2. Hepatic metastases of colon carcinoma (81/258 [31%]) or other hepatic metastases from other sites (30/258 [12%]) and primary HCC (78/258 [30%]) were the predominant indications for liver resection, followed by other primary hepatic tumors (48/258 [19%]) and hilar cholangiocarcinoma (21/258 [8%]). Among the patients with HCC, 89% had cirrhosis, compared with 6% in patients with metastatic liver disease (10/180). Six of these 10 patients with metastatic disease and cirrhosis had a preoperative GEC less than 6 mg/min/kg.

Most patients (158/258 [61%]) underwent segmental or sector-oriented hepatic resections. Fifty-one patients had classical and 28 had extended right hepatectomy. In 31 patients a formal left hepatectomy was performed, and 6 patients underwent extended left hepatectomy. Tissue-preserving nonanatomic liver resections, wedge resections, or left lobar subsegmentectomies were performed in 100 patients (39%). The surgical procedure with regard to the

Table 3. TYPE OF OPERATION PERFORMED ACCORDING TO TYPE OF TUMOR

	HCC (n = 78)	CRC (n = 81)	CCC (n = 21)	Other Metastases (n = 30)	Miscellaneous (n = 48)	Total (n = 258)
Segment-oriented liver resections	45 (58%)	71 (88%)	19 (90%)	12 (40%)	11 (23%)	158 (61%)
Extended right hepatectomy	6 (8%)	15 (19%)	7 (33%)	0	0	28
Right hepatectomy	13 (17%)	22 (27%)	4 (19%)	7 (23%)	5 (10%)	51
Extended left hepatectomy	0	5 (6%)	1 (5%)	0	0	6
Left hepatectomy	10 (13%)	11 (14%)	7 (33%)	0	3 (6%)	31
Segmentectomy	16 (20%)	18 (22%)	0	5 (17%)	3 (6%)	42
Atypical liver resections	33 (42%)	10 (12%)	2 (10%)	18 (60%)	37 (77%)	100 (39%)
Atypical hepatectomy	24 (31%)	10 (12%)	2 (10%)	14 (47%)	3 (6%)	53
Wedge resection	4 (5%)	0	0	4 (13%)	20 (42%)	28
Enucleation	5 (6%)	0	0	0	14 (29%)	19

CCC, cholangiocarcinoma; CRC, colorectal metastases; HCC, hepatocellular cancer.

underlying diagnosis is detailed in Table 3. The surgical time averaged 4.1 ± 1.8 hours, and perioperative blood loss was 2.3 ± 1.9 L. Intermittent portal triad clamping was used in 39 of the 258 patients (15%) and continuous pedicular clamping (Pringle maneuver) in 21 of the 258 (8%).

Postoperative Death and Complications

Six patients (2%) died within 60 days after surgery; all postoperative deaths occurred after extended hepatic resections. Two patients were older than 70 years of age and died of acute myocardial infarction after uneventful surgery. Neither of these two patients had a history of cardiac disease. The other four hospital deaths occurred in patients younger than 60 years of age: one patient died of acute respiratory distress syndrome after multiorgan failure, acute liver failure developed in two patients after extended right hepatectomy, and one patient died of uncontrollable sepsis with consecutive multiorgan failure.

Univariate analysis of the 67 patients (26%) who had major postoperative complications identified 6 of 27 parameters to be significant risk factors for major complications for both groups of patients: concomitant cardiovascular risks; pathologic GEC; ASA score more than 2; duration of surgery more than 4 hours; intraoperative blood loss more than 2.5 L; and red blood cell transfusion more than 4 units (Table 4). In patients with HCC, five more factors were determined to be significantly predictors for complications: age older than 70 years; presence of cirrhosis with Child-Pugh classification B or C; portal hypertension; jaundice; and the extent of resection. Concomitant chronic obstructive pulmonary disease and insulin-dependent diabetes mellitus significantly increased the risk of complications in non-HCC patients.

The multivariate analysis by a stepwise logistic regression model identified two independent significant variables for postoperative complications in both groups: pathologic GEC and concomitant cardiovascular disease. Intraoperative blood loss more than 2.5 L was a strong predictor for patients undergoing liver resection for HCC. An extended hepatic resection was predictive for non-HCC patients (Table 5). The multivariate analysis revealed pathologic liver

Table 4. UNIVARIATE ANALYSIS OF PREDICTING FACTORS FOR POSTOPERATIVE COMPLICATIONS

Variable	*P* Value HCC (n = 78)	Non-HCC (n = 180)
Gender	.624	.291
Age	**.021**	.252
Histology of tumor	.706	.845
Size of tumor	.534	.652
ASA score	**.013**	**.045**
Child-Pugh score	**.032**	—
Cirrhosis	**.015**	.616
Portal hypertension	**.009**	.536
Jaundice	**.048**	.101
Viral hepatitis	.722	.916
Ascites	.622	.101
Diabetes mellitus	.097	**.006**
Renal dysfunction	.179	.061
Arterial hypertension	.522	.156
Cardiac history	**.047**	**.0001**
COPD	.052	**.009**
GEC	**.046**	**.0001**
Hemoglobin	.326	.010
INR	.603	.231
Thrombocytopenia (platelets)	.244	.063
Serum ammonium	.731	.272
Alkaline phosphatase	.078	.552
Operation time	**.041**	**.012**
Extent of resection	**.022**	.078
Intraop. blood unit given	**.031**	**.009**
Intraop. blood loss	**.001**	**.023**
Pringle maneuver	.079	.096

ASA, American Society of Anesthesiology; COPD, chronic obstructive pulmonary disease; GEC, galactose elimination capacity; HCC, hepatocellular cancer; INR, International Normalized Ratio.

Table 5. RISK FACTORS SIGNIFICANTLY INFLUENCING POSTOPERATIVE DEATH AND COMPLICATIONS USING STEPWISE LOGISTIC REGRESSION ANALYSIS

Variable	Beta Coeff.	Standard Error	Odds Ratio	95% Conf. Interval	*P* Value
Complications					
HCC (n = 78)					
GEC (mg/min/kg ≤ 4.0)	0.749	0.014	**2.215**	2.058–2.174	**0.012**
Cardiovascular disease*	0.281	0.011	**1.324**	1.296–1.353	**0.043**
Blood loss > 2,500 mL	0.290	0.149	**1.336**	0.998–1.790	**0.046**
Non-HCC (n = 180)					
GEC (mg/min/kg ≤ 6.0)	0.717	0.011	**2.048**	2.005–2.093	**0.001**
Cardiovascular disease*	0.229	0.028	**1.257**	1.190–1.328	**0.009**
Extent of resection	0.165	0.018	**1.179**	1.139–1.222	**0.49**
Death					
HCC (n = 78)					
GEC (mg/min/kg ≤ 4.0)	−0.296	0.025	**0.744**	0.708–0.781	**0.011**
Jaundice†	0.934	0.127	**2.545**	1.984–3.264	**0.001**
Operation time > 4 hours	−0.430	0.106	**0.651**	0.528–0.801	**0.046**
Non-HCC (n = 180)					
GEC (mg/min/kg ≤ 6.0)	−0.212	0.018	**0.809**	0.781–0.838	**0.019**
Jaundice†	0.269	0.061	**1.309**	1.161–1.475	**0.003**

GEC, galactose elimination capacity; HCC, hepatocellular cancer.
* Positive cardiac history: previous myocardial infarct, previous coronary bypass or stenting, angina, arrhythmia.
† Bilirubin serum level > 50 mg/L.

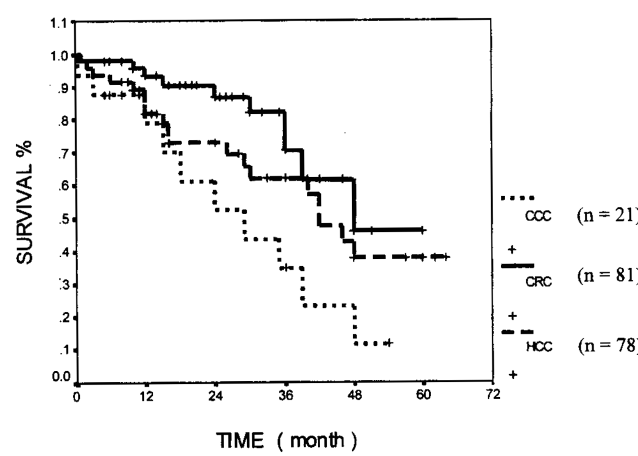
function (low GEC), preoperative jaundice, and prolonged duration of surgery (>4 hours) were independent risk factors for death.

With the predefined cutoff of 4.0 mg/min/kg, the GEC had a sensitivity of 51.9% and a specificity of 100% in the HCC group. In the non-HCC group (with a cutoff of 6.0 mg/min/kg), GEC showed a sensitivity of 92.5% and a specificity of 64.5%. The positive and negative predictive values were 100% and 79.7%, respectively, for the HCC group (with a cutoff of 4.0) and 43.0% and 96.7%, respectively, for the non-HCC group (with a cutoff of 6.0).

Survival

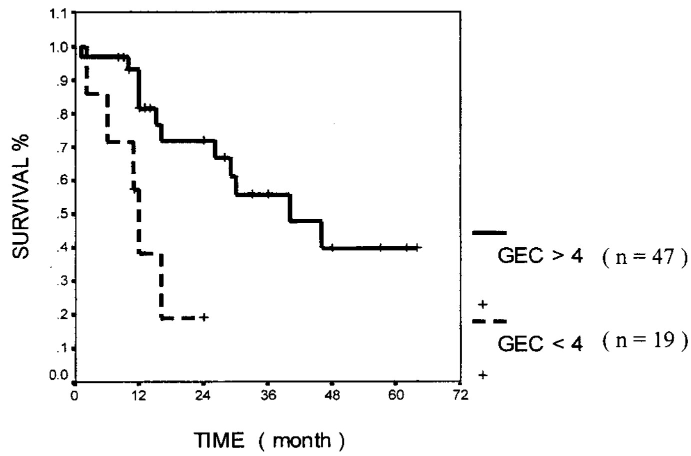
The median follow-up period was 36 months (range 1–67). Overall 1-year, 3-year, and 5-year survival rates were 89%, 62%, and 39% (median 42 months) in patients with HCC, 96%, 70%, and 48% (median 48 months) for patients with resected colorectal metastases, and 78%, 35%, and 11% (median 18 months) in patients with hilar cholangiocarcinoma (Fig. 1).

Abnormal GEC, sepsis after surgery, and a high ASA score (>2) significantly predicted decreased survival in all patients undergoing liver surgery. In patients with colorectal metastases and other secondary liver malignancies, age older than 70 years and coexistent jaundice before surgery were additional predictors for poor long-term outcome. In patients with HCC, a duration of surgery of more than 4 hours and postoperative sepsis were significantly associated with shortened survival (Table 6). In addition, patients undergoing liver resection for HCC had significantly poorer survival if their preoperative GEC was decreased (<4 mg/min/kg, $P = .003$ by log-rank test) (Fig. 2). Patients with tumors other than HCC had a better survival if their preoperative GEC exceeded 6 mg/min/kg (Fig. 3; $P < .03$ by log-rank test). Twenty-eight non-HCC patients had a GEC less than 6 mg/min/kg, but none was below 5.6. Six of these 28 patients had liver cirrhosis.



HCC n=	67	53	46	27	25
CRC n=	75	70	55	37	33
CCC n=	18	11	7	2	0

Figure 1. Comparison of survival rates (Kaplan-Meier) between different diagnoses in patients undergoing hepatic resection for malignancies. Median survival for cholangiocarcinoma (CCC) was significantly worse (18 months) than that for colorectal carcinoma (CRC, 48 months) and that for hepatocellular carcinoma (HCC, 41 months). Log-rank test, $P = .0173$.



GEC>4:	n=39	34	27	19	15	
GEC<4:	n= 7	3	end of follow-up			

Figure 2. Cumulative survival for patients with hepatocellular carcinoma in terms of preoperative liver function (galactose elimination capacity [GEC], mg/min/kg). Log-rank test, *P* = .003.

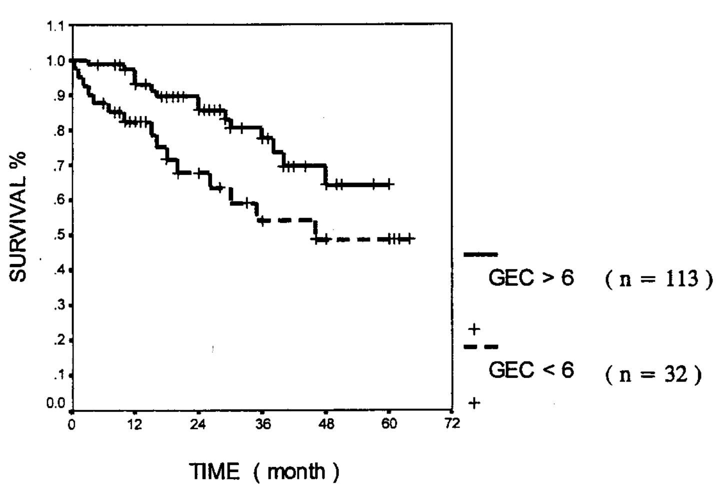
The multivariate Cox regression analysis assessing the significant prognostic factors of univariate analysis revealed a GEC less than 6 mg/min/kg and an ASA score greater than 2 as independent factors for shorter survival in patients regardless of tumor etiology. In non-HCC patients the same factors were identified, plus age older than 70 years. In patients with HCC, predictive factors were GEC less than 4 mg/min/kg, ASA score greater than 2, and postoperative sepsis (Table 7).

DISCUSSION

In this prospective study, we analyzed a variety of parameters with respect to their ability to predict postoperative death and complications after hepatic resection for primary or secondary hepatic malignancy. We showed that GEC is consistently better than other parameters, including the Child-Pugh classification, to predict not only postoperative complications but also long-term survival. This was true for patients undergoing hepatic resection for metastasis of colorectal cancer as well as for those undergoing hepatic resection for HCC.

Our figures compare well with the literature.[5–7,22] In the short term, 20% to 50% of cirrhotic patients undergoing hepatic resection for HCC have postoperative complications, hepatic failure being the most frequent and most lethal.[23] The volume of liver that can be safely resected without inducing liver insufficiency is unknown. It is certainly less in patients with cirrhosis, because their liver has not only a diminished preoperative hepatic reserve but also a reduced capacity to regenerate.[24,25]

Numerous factors have been suggested to influence the prognosis of patients undergoing hepatic resection, such as age;[26] presence of cirrhosis;[23] distribution,[27] size,[28] and number[29] of liver metastases; size of the HCC;[22,30] Okuda stage of the HCC;[31] tumor invasion of the portal vein;[32] type of surgery;[33] blood loss during surgery;[34–36] and concomitant diseases, such as diabetes mellitus.[37] We took



GEC>6:	n=	109	99	88	71	35
GEC<6:	n=	27	21	18	15	12

Figure 3. Cumulative survival for patients without hepatocellular carcinoma in terms of preoperative pathologic galactose elimination capacity (GEC) test. Log-rank test, *P* = .0282.

Table 6. RESULTS OF UNIVARIATE ANALYSIS FOR SURVIVAL

	P Value	
Variable	HCC (n = 78)	Non-HCC (n = 180)
Gender	.942	.092
Age	.121	**.001**
Size of tumor	.096	.828
ASA score	**.031**	**.0001**
Cirrhosis	.228	.503
Portal hypertension	.065	.244
Jaundice	.090	**.048**
Viral hepatitis	.446	.189
Ascites	.954	.747
Diabetes mellitus	.112	.211
Renal dysfunction	.264	.893
Arterial hypertension	.093	.512
Cardiac history	.071	.577
COPD	.357	.513
GEC	**.037**	**.026**
Operation time	**.031**	.511
Extent of resection	.058	.622
Intraop. blood unit given	.108	.171
Intraop. blood loss	.067	.425
Pringle maneuver	.123	.113
Length of ICU stay	.065	.089
Periop. ventilation	.082	.091
Serum ammonium	.079	.876
Alkaline phosphatase	.096	.063
INR	.255	.544
Hemoglobin	.821	.857
Reoperation	.424	.095
Bile leakage	.072	.455
Sepsis	**.042**	**.002**

ASA, American Society of Anesthesiology; COPD, chronic obstructive pulmonary disease; GEC, galactose elimination capacity; HCC, hepatocellular cancer.

these parameters into account in our analysis (see Table 1); in addition, we performed preoperative determination of the GEC. This test is safe, inexpensive, and reproducible. In animals, it correlates closely with liver weight[38] and, more relevant for patients with chronic liver disease, with hepatocellular mass in animal models of chronic liver disease.[39] The rate-limiting step in galactose metabolism is phosphorylation of galactose by galactokinase, an enzyme located in the cytosol of hepatocytes;[19,40] therefore, hepatic GEC is considered to depend primarily on the mass of functional hepatocytes.[19] In patients, it has been found to be of prognostic value in chronic active hepatitis,[15] cirrhosis,[16] and primary biliary cirrhosis.[14]

Liver cirrhosis, even when compensated, may complicate hepatic resection as a result of coagulopathy or portal hypertension. Conventional biochemical liver tests have only limited value when it comes to estimating hepatocellular reserve; elevated serum bilirubin or decreased prothrombin time before surgery represent warning signs. Therefore, Hasegawa et al[41] considered a serum bilirubin level of more than 2.0 mg/dL (35 μmol/L) an absolute contraindication for hepatic resection. These two parameters are part of the Child-Pugh classification, originally described to identify patients for portocaval shunting.[10] Indeed, different studies found the Child-Pugh classification to be a good predictor of perioperative death in patients with cirrhosis undergoing abdominal resection, with 10%, 30%, and 76% to 82% death rates in patients with Child class A, B, and C, respectively.[42,43] In contrast, Japanese groups did not find the Child-Pugh classification to be helpful to identify long-term survivors.[44,45] One of these authors reported more recently a correlation between the Child-Pugh classification and long-term survival,[46] but the number of patients with a Child class C was small. This probably reflects the fact that surgeons today exclude Child class C patients from surgery; this is also reflected in our series, where only two patients with Child class C underwent surgery. Thus, the Child classification can be used to exclude patients from surgery, but in those who do undergo surgery, it fails to predict death and complications.

Different studies have evaluated a variety of quantitative liver function tests to predict postoperative death and complications. In an early study on a limited number of patients (38 patients, mostly with alcoholic liver disease) undergoing a variety of visceral surgical procedures, the aminopyrine breath test, a measure of microsomal function, was found to be superior to the Child-Pugh classification in predicting complications and survival.[47] Indocyanine green retention in combination with radiologic estimation of the liver volume was found to be of value to predict posthepatectomy liver failure.[48,49] Others have reported the indocyanine green clearance test to be a good preoperative predictor of death and complications in patients undergoing liver resection for HCC.[35,50–52]

Quantitative liver function tests, whether indocyanine green retention or GEC, are superior presumably because they are less determined by extrahepatic factors (as is the case with serum bilirubin, serum albumin, or prothrombin time), and that allows a better estimate of hepatic functional reserve than conventional liver tests, whether alone or combined into a score.

Postoperative liver failure in patients with hepatic metastasis and presumably normal functional reserve is much rarer than in patients with HCC, who practically all have underlying structural disease.[53] In noncirrhotic patients having resection for metastases, preoperative serum alkaline phosphatase has been reported to predict postoperative liver insufficiency.[54] In our univariate analysis, we found abnormal alkaline phosphatase to predict short-term survival but not postoperative complications; this prognostic value was not confirmed in multivariate analysis. In contrast, GEC was informative regarding postoperative complications and survival in patients undergoing liver resection for tumors other than HCC, in particular those with metastatic disease. This finding was surprising because liver function is thought to be maintained in patients with metastasis to the liver. In

Table 7. FACTORS SIGNIFICANTLY ASSOCIATED WITH SURVIVAL AFTER MULTIVARIATE ANALYSIS USING COX PROPORTIONAL HAZARD MODEL

Variable	Beta Coeff.	Standard Error	Hazard Ratio	95% Conf. Interval	*P* Value
HCC (n = 78)					
GEC (mg/min/kg < 4.0)	−1.3339	0.5257	**0.263**	0.094–0.738	**.0114**
ASA score III/IV	0.8114	0.3727	**2.251**	1.084–4.673	**.03**
Sepsis	1.1626	0.516	**3.198**	1.164–8.788	**.024**
Non-HCC (n = 180)					
GEC (mg/min/kg < 6.0)	−1.4132	0.574	**0.243**	0.079–0.750	**.047**
ASA score III/IV	0.025	0.0084	**1.025**	1.009–1.042	**<.001**
Age > 70 years	−0.0646	0.0287	**0.937**	0.886–0.992	**.0337**

ASA, American Society of Anesthesiology; GEC, galactose elimination capacity; HCC, hepatocellular cancer.

some patients the GEC was certainly diminished as a result of underlying liver disease, in particular cirrhosis in 10 patients. This cannot explain the discriminant capacity of GEC alone, however.

This raises the question of whether liver function is affected by the presence of hepatic metastasis. In a recent large series on hepatic resections for metastatic disease, mostly tumor burden and time to recurrence determined survival.[11] In line with this concept, antipyrine clearance was maintained regardless of tumor burden.[55,56] However, in the latter study a decrease in conjugation reactions was found, suggesting that liver metastases could affect certain aspects of liver function.[56] Earlier studies found sulfobromophthalein clearance to be impaired in patients with hepatic metastases,[57] suggesting that unrecognized cholestasis could impair liver function. This contention is supported by the fact that even in the absence of metastasis, signs of cholestasis are often found in liver biopsy samples from patients with proven hepatic metastases.[58] Finally, nuclear medicine techniques[59] and duplex sonography[60] can show alterations of hepatic perfusion in the presence of metastases. Whether the diminution of GEC in some patients with metastatic disease is due to cholestasis or alterations of hepatic perfusion cannot be answered from the present investigation.

In conclusion, we found the GEC to be an important preoperative piece of information in assessing the risk of hepatic resection in patients with primary and secondary hepatic focal lesions. This simple, safe, and inexpensive test provides predictive information regarding both the short-term outcome and long-term survival. This analysis validates the use of performing a GEC before hepatic resection to stratify patients and exclude those at high risk.

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