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A Prediction Scoring System to Select the Surgical Treatment of Liver Cancer

Further Refinement Based on 10 Years of Use

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Objective

This study reports further refinement of a prediction scoring system, which was established in 1980 as a guide to determine a safe limit for hepatectomy, based on 10 years of use.

Summary Background Data

In the past, whether major resection was safe was judged empiricially from the net resection volume or the residual hepatic volume combined with the patient's liver function. However, such judgment was not based on objectively defined criteria.

Methods

Patients with hepatocellular carcinoma (HCC; n=376) and metastatic cancer (n=58) who had hepatectomy at some time from 1981 through 1990 were entered into this study. A prediction score (PS) was computed using a multiple regression equation that consists of computed tomographic scan-estimated resection rate, indocyanine green retention rate, and the patient's age. A PS greater than 55 was classified as a risky zone, a PS of 45 to 55 was considered borderline. and a PS less than 45 was a safe zone.

Results

With HCC and chronic liver disease, all patients in the risky zone died, whereas 33% in the borderline zone died and 7.3% died who were in the safe zone. With metastatic cancer with normal liver, all patients in the risky zone died, whereas no patient in either the borderline or safe zones died. The major cause of death in the risky zone was liver failure due to excessive resection. In the borderline and safe zones, liver failure developed primarily after abdominal sepsis or pulmonary infection, particularly for those with adverse prognostic factors such as disturbed glucose tolerance, lower platelet count, and higher indocyanine green retention rate.

Conclusion

Prediction scores can eliminate deaths related to excessive resection for patients with normal or injured livers. When patients have adverse prognostic factors, careful surgery and postoperative management is mandatory to avoid liver failure triggered by intra- or extra-abdominal sepsis, even if the score remains in a borderline or safe zone.

Two factors that adversely affect the prognosis of patients with hepatocellular carcinoma (HCC) include the frequent presence of liver cirrhosis (70% to 80% of patients),[1] which limits the extent of safe resection, and early intrahepatic portal invasion, which requires a wider resection for cure. Hepatic surgeons therefore must determine what is the maximal extent of resection that can be achieved to minimize the number of surgical deaths and enhance the probability of cure.

At the end of 1980 we used multiple regression analysis[2] to determine which preoperative parameters were important in predicting liver failure after major hepatectomy. These predictors, selected using stepwise regression, were parenchymal hepatic resection rate (PHRR %),[3] indocyanine green dye retention rate 15 minutes after injection of 0.5 mg/kg (ICG R15[%]),[4] and patient age. A prediction score (PS), computed by entering each predictor value into the regression equation, revealed in the retrospective study that all patients with a PS exceeding 50 points died from liver failure, whereas all those who scored less than 50 points survived.

Since the formulation of the regression equation, we adopted this PS-guided treatment strategy for liver cancer. This study reports a further re-evaluation of this PS-guided selection after 10 years of use, from January 1981 through December 1990.

PATIENTS AND METHODS

We included 434 patients in this study, 376 with HCC and 58 with metastatic liver cancer, who had hepatectomy at some time from January 1981 through December 1990. Those who required rehepatectomy for recurrence were excluded. Of the HCC patients, 76% had liver cirrhosis, 12% had chronic hepatitis, and 5% had fibrosis. Coexisting liver disease was found in one of the patients with metastatic cancer. In all of these 434 patients, the PHRR for the tumor-bearing lobe or segment of the liver was measured from the computed tomographic slices. This measurement was based on the formula[3] using a computer-linked electroplanimeter. The ICG R15(%) value and the patient's age were used to compute the Y value (PS), which was derived from the multiple regression equation, $Y = -84.6 + 0.933\ PHRR + 1.11\ ICG\ R15 + 0.999\ age$. Because a previous study indicated that a PS of 50 points was the cutoff value between survivors and nonsurvivors, a PS value greater than 55 was regarded as risky, a PS of 45 to 55 was classified as borderline, and a PS less than 45 was considered safe. The surgical procedures for each group of patients are shown in Table 1. All of the risky or borderline zone patients were those who had hepatic lobectomies without limiting the range of resection. On the other hand, 31% (109 of 357) of those with HCC and a safe PS value had hepatic lobectomy. For the remaining 69% of HCC patients in the safe zone, the resection range was reduced to a segment or less because the PS for a lobectomy exceeded 45 points.

The pre- and intraoperative data were compared for survivors and nonsurvivors in each group. The pattern of blood sugar curve after a 75-g oral glucose tolerance test was classified as having either a parabolic or linear pattern. A parabolic pattern refered to a blood sugar curve in which the blood sugar value at 2 hours decreased toward the preloading value; otherwise it was classified as linear.[5]

Statistical significance was evaluated using the Student's t test; a probability value less than 0.05 was considered significant.

RESULTS

Patients in the Risky Zone

Of the 4 HCC and 3 metastatic cancer patients in this group, 6 died from progressive liver failure within 3

Table 1. PREDICTION SCORE AND SURGICAL PROCEDURE

Prediction Score	Disease	Surgical Procedure TriST	RL	LL	CL	ST	SubST	Wedge
≧55	HCC		3		1			
	Meta	2	1					
45–55	HCC	2	11	1	1			
	Meta	1	6					
≦45	HCC	5	46	41	17	119	57	72
	Meta	2	8	12	4	12	4	6
Total (434)		12	75	54	23	131	61	78

HCC = hepatocellular carcinoma; TriST = trisegmentectomy; CL = central lobectomy; RL = right lobectomy; ST = segmentectomy; LL = left lobectomy; SubST = subsegmentectomy.

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Table 2. PREDICTION SCORE AND MORTALITY

Prediction Score	Mortality (%) Hepatocellular Carcinoma	Metastatic Cancers
≧55	3/4 (75)	3/3 (100)
45–55	5/15 (33)	0/6 (0)
<45	26/357 (7.3)	0/49 (0)
Total	34/376 (9.0)	3/58 (5.2)

Table 4. SURGICAL PROCEDURE IN 357 PATIENTS WITHIN SAFETY ZONE—SURVIVORS *VS.* NONSURVIVORS

	Surgical Procedure							
	TriST	RL	LL	CL	ST	SubST	Wedge	Total
Survivors	4	43	38	16	108	57	65	331
Nonsurvivors	1	3	3	1	11	—	7	26
								357

TriST = trisegmentectomy; CC = central lobectomy; RL = right lobectomy; ST = segmentectomy; LL = left lobectomy; SubST = subsegmentectomy.

months after hepatectomy (Table 2). Only 1 patient survived a right lobectomy; he had a ICG clearance disorder, which elevated the PS to a unusually high level despite the fact that he had only minimal chronic hepatitis.

Patients in the Borderline Zone

Five of the 15 patients with HCC (33%) died from liver failure, whereas liver failure developed in none of the 6 patients with metastatic liver cancer, not associated with chronic liver disease (Table 2). We compared the pre- and intraoperative factors for the nonsurvivors and survivors with HCC and found a significant difference in the ICG R15% and oral glucose tolerance test pattern (Table 3). The oral glucose tolerance test pattern was linear in 80% of the nonsurvivors compared with 20% of the survivors. Differences in conventional liver function tests, the amount of intraoperative blood loss, liver volumes excluding tumor, and tumor size were not significant for the two groups.

Table 3. PREOPERATIVE DATA IN 15 PATIENTS WITH BORDER ZONE SCORES—SURVIVORS *VS.* NONSURVIVORS

	Survivors (n = 10)	Nonsurvivors (n = 5)	p Value
PHRR (%)	58 ± 24	60 ± 7.8	NS
Age	62 ± 11	65 ± 10	NS
ICG R15	16 ± 4.0	22 ± 4.6	$p < 0.05$
Albumin (g/dL)	3.8 ± 0.4	3.3 ± 0.4	NS
Bilirubin (mg/dL)	0.8 ± 0.4	0.6 ± 0.1	NS
Prothrombin time (%)	91 ± 24	74 ± 12	NS
Platelet (10^3/uL)	11 ± 4.1	19 ± 7.1	NS
OGTT (% linear pattern)	20	80	$p < 0.05$
Liver volume (cm^3)	1299 ± 425	1085 ± 360	NS
Tumor size (cm)	9.2 ± 6.4	6.5 ± 7.0	NS
Blood loss (mL)	2667 ± 1980	2575 ± 1910	NS

OGTT = oral glucose tolerance test; PHRR = parenchymal hepatic resection rate.

Patients in the Safe Zone

The rate of in-hospital death was 7.3% in the patients with HCC compared with 0% in those with metastatic liver cancer (Table 2). Twenty-seven per cent (7 of 26) of the nonsurvivors and 37% (122 of 331) of the survivors had resections reduced from lobectomy to subsegmentectomy or wedge resection because the PS for an entire hepatic lobe resection exceeded 45 (Table 4). The major causes of death were secondary liver failure as a result of intra-abdominal infection due to bile leak or pulmonary infections, and liver failure without any known cause (Table 5).

The pre- and intraoperative data in the 16 nonsurvivors were compared with the data of the 331 survivors and the following features were reported: Those who died had a higher ICG retention rate, a higher frequency of linear oral glucose tolerance test pattern, a lower platelet count, and smaller resection (Table 6). The amount of intraoperative blood loss did not differ for the two groups.

DISCUSSION

The liver has a substantial regenerative ability and an immense reserve capacity. Seventy-five per cent of a

Table 5. CAUSE OF 26 IN-HOSPITAL DEATHS WITH SAFETY ZONE SCORES

Intra-abdominal abscess—liver failure	7
Liver failure without precipitating factors	5
Pulmonary complication—liver failure	4
Posttransfusion hepatitis	3
Postoperative bleeding—DIC	3
Rupture of varices	2
Others	2
	26

DIC = disseminated intravascular coagulation.

Table 6. PREOPERATIVE DATA IN PATIENTS WITH PS IN THE SAFETY ZONE—SURVIVORS *VS.* NONSURVIVORS

	Survivors (n = 331)	Nonsurvivors (n = 16)	p Value
Age	57 ± 8.4	59 ± 6.0	NS
ICG R15	17 ± 8.5	23 ± 7.2	<0.01
Albumin (g/dL)	3.6 ± 0.4	3.2 ± 0.5	<0.01
Bilirubin (mg/dL)	0.7 ± 0.4	0.9 ± 0.3	NS
Prothrombin time (%)	84 ± 17	75 ± 12	NS
WBC (10^3/uL)	5370 ± 1370	5330 ± 2380	NS
Platelet count (10^3/uL)	15 ± 8.6	9.2 ± 3.7	<0.01
OGTT (% linear pattern)	25	64	<0.01
Liver volume (cm^3)	1250 ± 551	1156 ± 2264	NS
Tumor size (cm)	7.2 ± 3.0	4.3 ± 2.4	NS
Weight of resected mass (g)	405 ± 464	200 ± 171	<0.01
Blood loss (mL)	2148 ± 2193	2071 ± 1698	NS

PS = prediction score; OGTT = oral glucose tolerance test.

healthy liver can be resected safely. However, hepatocellular carcinoma is the most common indication for hepatectomy in Japan and usually is associated with chronic liver disease. Therefore an objective method to determine the safe limit of hepatic resection based on the severity of hepatic injury would be valuable.[6]

Whether a major resection is safe has been judged empiricially from the patient's hepatic function or the severity of liver cirrhosis.[7-9] However, such judgments have not been based on objectively defined diagnostic criteria. Therefore we established a prediction score at the end of 1980 to determine the extent of hepatic resection.[2] The extent of resection of the liver parenchyma, excluding the tumor mass, was the most important predictor. Researchers recognized that the net resection rate[7,10] or the residual hepatic volume and function,[11-15] rather than the anatomical range of the resection, is a more reliable guide to determine the appropriate extent of resection. The clinical importance of this factor in determining an early prognosis was substantiated by our previous study.

Comparison of prediction scores and the early postoperative course reconfirmed, in a consecutive large series since the PS system was established, that the mortality rate secondary to liver failure was nearly 100% in patients with a PS exceeding 55, regardless of the presence of concomitant liver disease. This indicates that the extent of resection does not correlate with hepatic reserve in patients with scores in the risky zone. Clearly resection should be limited or rejected in favor of medical therapy, such as transarterial embolization[16] or percutaneous ethanol injection,[17] depending on the size and number of nodules.

In patients with borderline PS scores between 45 and 55, resection is safe as long as coexisting liver disease is absent. On the other hand, HCC patients with chronic liver disease have a high risk of death from liver failure. Our study showed that operative risk increases in patients with a linear glucose tolerance curve. This result corroborates previously reported findings that showed that complications after hepatectomy were high in patients with a linear pattern,[5] which correlated well with hepatic mitochondrial dysfunction.[18] Therefore treatment of patients with borderline scores can be based on this guideline: Resection may be safe only when the liver is normal or the glucose tolerance curve is parabolic. Otherwise, resection should be regarded as risky and the patient should be treated accordingly.

As for scores in the safe zone, all patients with metastatic liver cancer, not accompanied by chronic liver disease, had uncomplicated postoperative courses, as expected. In contrast, the patients with HCC had an unexpected mortality rate of 7.3%, although this was considerably lower than that seen in those with borderline scores. Approximately 70% of these deaths occurred in patients who had a significant reduction in the resection volume from a hepatic lobe or segment to a lesser range, in order to lower the PS to less than 45. The major cause of death was liver failure, often accompanied by a precipitating factor such as intra-abdominal or pulmonary sepsis. Intraoperative bleeding, often related to the surgery and location or extent of the tumor, is a precipitating factor for liver failure or multiple-organ failure.[19,20] This was, however, only a marginal adverse factor in our series.

The patients who have a higher ICG retention rate, a disturbed glucose tolerance pattern, and a lower platelet count were susceptible to prolongation of local sepsis even if the resection range was small and the PS was in a safe zone. These results suggest that prolonged infections can be an important predisposing factor of liver failure caused perhaps by the release of cytokines from activated Küppfer cells[21,22] and spill-over of endotoxin due to depressed reticuloendothelial function after hepatectomy.

Routine use of the bile leak test and closed continuous drainage and frequent use of thoracoabdominal exposure for tumors located in the posterior segment or dome in the right lobe has eliminated intra-abdominal abscesses without increasing the mortality and morbidity rates in the past 5 years (unpublished data). This is inconsistent with another study[23] that reported that the thoracoabdominal approach resulted in high rates of morbidity and mortality.

When planning a treatment regimen for hepatic cancer, a safe limit for hepatectomy based on the patient's hepatic reserve should be the primary consideration. In addition, when the PS is borderline or safe, planned hepatectomy should be re-evaluated based on other factors, such as the liver pathology, glucose tolerance, ICG retention rate, and platelet count. Factors contributing to liver failure, such as infection and perioperative bleeding, should be eliminated, especially in patients with a minimal safe margin (that is, those with a higher ICG retention, a disturbed glucose tolerance pattern, and a lower platelet count). Finally, we should not perform a risky surgical therapy for HCC patients who have risk factors because other options, such as selective embolization or ethanol injection, offer an acceptable level of tumor necrosis and good quality of life.

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