ORIGINAL ARTICLE

Hepatectomy for Stage B and Stage C Hepatocellular Carcinoma in the Barcelona Clinic Liver Cancer Classification

Results of a Prospective Analysis

Guido Torzilli, MD, PhD; Matteo Donadon, MD; Matteo Marconi, MD; Angela Palmisano, MD; Daniele Del Fabbro, MD; Antonino Spinelli, MD; Florin Botea, MD; Marco Montorsi, MD

Hypothesis: Using an algorithm for selection of patients with hepatocellular carcinoma (HCC) for surgery, Barcelona Clinic Liver Cancer (BCLC) classification stage B and stage C disease is not a contraindication.

Design: Prospective cohort study.

Setting: University tertiary care hospital.

Patients: Among 163 consecutive patients with HCC, 120 (73.6%) underwent surgery; 113 of 120 (94.2%) underwent resection. Of 113 patients, 61 (54.0%) had BCLC stage 0 or A disease, 24 (21.2%) had stage B disease, and 28 (24.8%) had stage C disease.

Interventions: Surgical strategy was based on the relationship of the tumor to the intrahepatic vascular structures on intraoperative ultrasonography.

Main Outcome Measures: Mortality, morbidity, rate of cut edge local recurrences, and long-term outcome were evaluated. $P < .05$ was considered statistically significant.

Results: Hospital mortality was 0.9%. The overall morbidity was 27.4%, and major morbidity was 3.5%. After a median follow-up of 24 months (range, 1-65 months), there was no cut edge recurrence. For patients with BCLC stages 0 or A, B, and C disease, the 3-year overall survival rates were 81%, 67%, and 74%, respectively (P=.24); the 3-year disease-free survival rates were 30%, 35%, and 15%, respectively (P=.85); and the 3-year hepatic disease-free survival rates were 39%, 44%, and 17%, respectively (P=.79).

Conclusions: Patients with BCLC stage B and stage C HCC can tolerate hepatic resection with low mortality, acceptable morbidity, and survival benefits if resection is performed under strict intraoperative ultrasonographic guidance. These results should prompt revision of the BCLC recommendations.

Arch Surg. 2008;143(11):1082-1090

Author Affiliations: Third Department of Surgery, University of Milan School of Medicine, Istituto Clinico Humanitas Istituto Di Ricovero e Cura a Carattere Scientifico, Rozzano, Milan, Italy.

HEPATOCELLULAR CARCINOMA (HCC) is usually associated with liver cirrhosis and is the principal cause of death among patients with cirrhosis.[1] Apart from liver transplantation that may cure both conditions, treatment of HCC and cirrhosis is complex because of the need to be oncologically radical but simultaneously conservative. In this sense, hepatectomy is considered an invasive approach and has a marginal role in the treatment of HCC.[2,3] According to the Barcelona Clinic Liver Cancer (BCLC) classification,[4] hepatic resection should be performed only in patients with small single tumors without signs of portal hypertension or hyperbilirubinemia. Patients with multiple, large, or vascular invasive HCC should receive palliation or no treatment. However, surgical morbidity and mortality may approach 0% in expert hands,[5-7] and liver resection could offer effective treatment to patients with multiple, large, or vascular invasive HCC.[8-11]

We evaluated the role of surgery in patients with BCLC stage B and stage C HCC. We conducted a prospective study among a consecutive cohort of patients selected for surgery for which BCLC stage B and stage C disease was not a contraindication based on our algorithm.

METHODS

DEFINITIONS

The terminology for liver anatomy and resections is based on the classification by Couinaud.[12] Resections were considered major if at least 3

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 07/28/2016

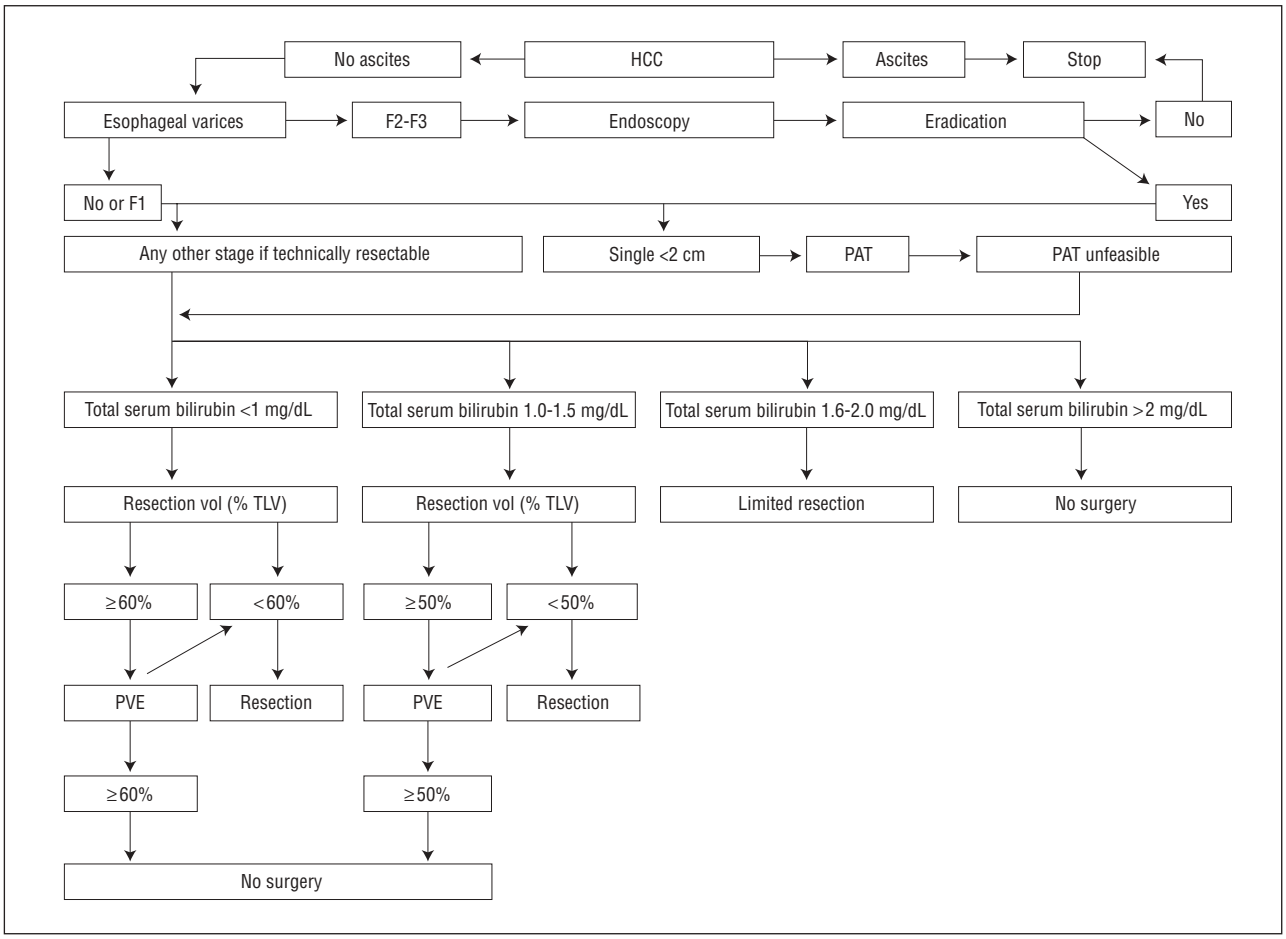

Figure 1. Flowchart for patient selection for surgery and for choice of surgical approach. HCC indicates hepatocellular carcinoma; PAT, percutaneous ablation therapy; PVE, portal vein embolization; TLV, total liver volume; and vol, volume. To convert bilirubin level to micromoles per liter, multiply by 17.104.

adjacent segments were removed. Postoperative death was analyzed at 30 and 90 days. Major postoperative morbidity was considered any complication that required additional surgery or any invasive procedure. Liver failure was considered mild if the serum total bilirubin level ranged from 2 to 5 mg/dL for more than 3 days after surgery, medium if it ranged from more than 5 to 10 mg/dL, and severe if it exceeded 10 mg/dL (to convert bilirubin level to micromoles per liter, multiply by 17.104).

PREOPERATIVE MANAGEMENT

The preoperative imaging workup included abdominal ultrasonography and spiral computed tomography for all patients, as well as magnetic resonance imaging for patients with doubtful lesions on ultrasonography and computed tomography. Chest radiographs were also routinely obtained.

Figure 1 shows our selection flowchart. Patients were selected for surgery based on the presence or absence of ascites, their total serum bilirubin level, and the technical feasibility of success. Technical feasibility was established if residual liver volume with optimal blood inflow, blood outflow, and biliary drainage was expected to be sufficient. Liver volumes were calculated based on computed tomographic images.

Patients with HCC meeting the Milan criteria[13] and younger than 60 years were referred for liver transplantation. Other surgery was considered only if the patient refused liver transplantation. Patients with unresectable HCC were referred for palliation.

The presence of esophageal varices on routinely performed upper gastrointestinal tract endoscopy[14] was not considered an exclusion criterion. Furthermore, we did not exclude patients whose platelet counts were less than $100\times10^3/\mu L$ (to convert platelet count to $\times10^9/L$, multiply by 1.0).

INTRAOPERATIVE ULTRASONOGRAPHIC GUIDANCE

Intraoperative ultrasonography was routinely performed for staging and for resection guidance. Contrast-enhanced intraoperative ultrasonography was used for any new lesion detected on intraoperative ultrasonography.[15]

For tumors associated with major intrahepatic vascular structures (first- and second-order portal vein branches and main hepatic veins), residual liver volume was maximized using intraoperative ultrasonography.[16,17] For capsulated HCC in contact with a vein without discontinuation of its wall, the vessel was spared. Inversely, the vessel was not spared for capsulated HCC in contact with a portal branch with bile duct dilation.

Hepatectomy was extended to include the parenchyma fed by portal branches to be resected. For hepatic vein resection, the tumor-vein relationship, the presence or absence of accessory hepatic veins, and the flow direction on color Doppler imaging of the portal branches were noted. The hepatic vein to be resected was clamped (if not already occluded). Intraoperative ultrasonographic findings were used to maximize sparing of the liver parenchyma.[17]

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 07/28/2016

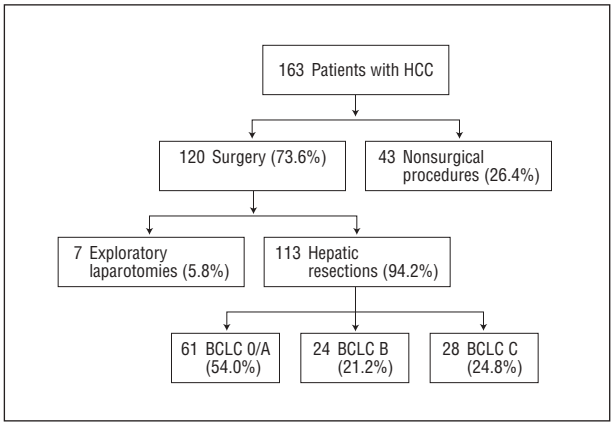

Figure 2. Therapeutic output of patients with hepatocellular carcinoma (HCC) referred to our outpatient clinic. BCLC indicates Barcelona Clinic Liver Cancer.

Table 1. Classification of Patients With Barcelona Clinic Liver Cancer (BCLC) Stage 0 and A and Stage B Hepatocellular Carcinoma

BCLC Stage	No. (%)
0/A (n = 61)	
Single tumor	
≤2 cm	5 (8.2)
≤5 cm	43 (70.5)
≤3 Tumors, none >3 cm	13 (21.3)
B (n = 24)	
Single tumor >5 cm	9 (37.5)
2-3 Tumors, any >3 cm	10 (41.7)
>3 Tumors	5 (20.8)

Table 2. Classification of Macrovascular Invasion Among Patients With Barcelona Clinic Liver Cancer Stage C Hepatocellular Carcinoma

Variable	With Thrombosis	Without Thrombosis	Total
HV or IVC invasion	**1**	**4**	**5**
PV invasion	**7**	**11**	**18**
First-order branch	4	4	
Second-order branch	3	3	
Third-order branch	0	4	
PV plus HV or IVC invasion	**1**	**4**	**5**
First-order PV branch	0	0	
Second-order PV branch	1	2	
Third-order PV branch	0	2	
Total	**9**	**19**	**28**

Abbreviations: HV, hepatic vein; IVC, inferior vena cava; PV, portal vein.

OPERATIVE PROCEDURES

J-shaped or inverted T-shaped laparotomies were routinely performed. For patients with tumors involving segments 1, 4, 7, and 8 and the cranial segment close to the confluence of the hepatic vein into the inferior vena cava, J-shaped thoracophrenolaparotomy was considered.

Liver dissection was accomplished under intermittent clamping by the Pringle maneuver[18] using crush clamping with Rochester-Péan forceps. Careful examination was made to rule out bile leakage, but cholangiography was not performed for this purpose.[19] Closed 19F suction drains were inserted.

BCLC CLASSIFICATION

Patient disease was stratified according to the BCLC staging classification. The following categories were used.

Stages 0/A

Stage 0 includes single tumors smaller than 2 cm in diameter. Stage A includes single tumors smaller than 5 cm in diameter or up to 3 tumors all smaller than 3 cm in diameter.

Stage B

Stage B includes up to 3 tumors (≥1 of which is >3 cm in diameter) or more than 3 tumors of any size. Single tumors exceeding 5 cm in diameter are included in this stage based on the article by Bruix and Llovet.[2]

Stage C

Stage C includes macrovascular invasion (major portal or hepatic veins). Alternatively, stage C involves lymph node metastases or distant metastases.

PATIENT FOLLOW-UP

Patients were followed up at our institution by an expert hepatobiliary team (G.T., A.P., and D.D.F.) every 3 months. Physical examination, liver function tests, serum α-fetoprotein level, ultrasonography (twice a year), and computed tomography (twice a year) were included.

END POINTS

The study end points were as follows: (1) postoperative morbidity and mortality, (2) rate of blood transfusions, (3) histologic review of surgical margins, (4) rate of cut edge recurrence, (5) long-term survival according to the BCLC classification, (6) disease-free survival according to the BCLC classification, and (7) hepatic disease–free survival according to the BCLC classification.

PATIENTS

From June 30, 2001, to November 1, 2006, a total of 163 patients with HCC were referred to our outpatient clinic. One hundred twenty (73.6%) were selected for surgery; 43 (26.4%) were excluded for advanced disease (n=18) or impaired functional reserve (n=18) or were referred for percutaneous ablation therapy (PAT) (n=7) of single HCC tumors smaller than 2 cm in diameter. Among 18 patients excluded for advanced HCC, 12 had BCLC stage C disease with tumor thrombus in the main portal trunk, 3 had BCLC stage C disease with distant metastasis, and 3 had BCLC stage B disease. Among 120 patients who underwent surgery, 113 (94.2%) underwent resection, and 7 (6%) underwent exploratory laparotomy. **Figure 2** shows the therapeutic output. There were 90 men and 23 women, and the median age was 67 years (age range, 36-87 years). **Table 1** and **Table 2** summarize the criteria for patient inclusion at each BCLC stage, and **Table 3** lists features of the staging groups according to the BCLC classification.

Among patients with BCLC stage 0 or A HCC or with BCLC stage B HCC according to the Milan criteria,[13] 3 patients were

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 07/28/2016

Table 3. Demographic, Clinical, and Pathologic Characteristics of Patients Having Hepatocellular Carcinoma Treated With Curative Resection Stratified According to the Barcelona Clinic Liver Cancer (BCLC) Classification

Characteristic	BCLC Stage[a] 0/A (n=61)	B (n=24)	C (n=28)	*P* Value[b]
Age, median (range), y	68 (57-78)	66 (36-87)	69 (52-79)	.76
Sex, No. (%)				.19
Male	48 (78.7)	22 (91.7)	20 (71.4)	
Female	13 (21.3)	2 (8.3)	8 (28.6)	
Underlying hepatitis, No. (%)				
None	6 (9.8)	5 (20.8)	3 (10.7)	
Hepatitis B	11 (18.0)	4 (16.7)	3 (10.7)	
Hepatitis C	36 (59.0)	15 (62.5)	17 (60.7)	.12
Hepatitis B and C	1 (1.6)	0	0	
Alcohol related	7 (11.5)	0	5 (17.9)	
α-Fetoprotein level, median (range), ng/mL[c]	15 (2-2230)	13 (2-62 184)	18 (2-7175)	.56
No. of tumors, median (range)	1 (1-3)	2 (1-6)	1 (1-6)	.005
Tumor size, median (range), cm	3 (1-5)	5 (2-28)	5 (2-20)	.001
Tumor grade, Edmondson-Steiner,[20] No. (%)[d]				
1	12 (19.7)	4 (16.7)	6 (21.4)	
2	36 (59.0)	11 (45.8)	13 (46.4)	.16
3	4 (6.6)	4 (16.7)	7 (25.0)	
4	1 (1.6)	0	0	
Vascular invasion, No. (%)	0	0	28 (100.0)	.001
Underlying liver disease, No. (%)				
Chronic hepatitis	10 (16.4)	4 (16.7)	8 (28.6)	.37
Cirrhosis	51 (83.6)	20 (83.3)	20 (71.4)	
Esophageal varices, No. (%)				
Negative	50 (82.0)	22 (91.7)	24 (85.7)	
F1	7 (11.5)	2 (8.3)	2 (7.1)	.54
F2	3 (4.9)	0	2 (7.1)	
F3	1 (1.6)	0	0	
PVE, No. (%)	0	0	1 (3.6)	.11
Previous TACE, No. (%)	2 (3.3)	2 (8.3)	2 (7.1)	.57
Previous PAT, No. (%)	2 (3.3)	1 (4.2)	3 (10.7)	.31

Abbreviations: PAT, percutaneous ablation therapy; PVE, portal vein embolization; TACE, transarterial chemoembolization.
SI conversion factor: To convert α-fetoprotein level to micrograms per liter, multiply by 1.0.
[a] See Table 1 and the "Stage C" subsection of the "BCLC Classification" subsection in the "Methods" section for an explanation of the Barcelona Clinic Liver Cancer stages.
[b] χ^2 Test and Kruskal-Wallis test where appropriate.
[c] Unavailable in 14 patients.
[d] Unavailable in 15 patients.

younger than 60 years and were referred for liver transplantation. They refused transplantation and subsequently underwent hepatectomy. All 28 patients with BCLC stage C HCC had concomitant macrovascular invasion evident on imaging, and none had involved lymph nodes or distant metastasis.

STATISTICAL ANALYSIS

Continuous variables are presented as median (range), and discrete variables are given as number (percentage). Survival time started from the date of hepatic resection until death; disease-free and hepatic disease–free survival started from the date of hepatic resection until the diagnosis of recurrence. Survival rates were obtained by the Kaplan-Meier method and were compared using the log-rank test. All significance tests were 2-tailed. Univariate analysis was performed for the following variables: age, sex, tumor number, tumor size, macrovascular invasion, tumor grade, cirrhosis, esophageal varices, clinical portal hypertension, serum α-fetoprotein level, extent of hepatectomy, and BCLC classification. All variables significant on univariate analysis were submitted to multivariate analysis using the Cox proportional hazards model. $P<.05$ was considered statistically significant.

RESULTS

SURGICAL PROCEDURE

Preoperative endoscopic banding of F2 and F3 esophageal varices was performed in 6 patients. In 14 patients (12.4%), J-shaped thoracophrenolaparotomy was performed.

Table 4 lists the types of surgical procedures. Full right-sided hepatectomy was performed in 7 patients (6.2%) who met the criteria of a normal serum bilirubin level and a residual liver volume of at least 40%. Closed-suction drains were removed on the seventh postoperative day as previously reported.[21]

POSTOPERATIVE OUTCOMES

Thirty-day hospital mortality occurred in 1 patient. This represented a mortality rate of 0.9%.

The overall morbidity rate was 27.4% (31 of 113 patients). Major morbidity occurred in 4 patients (3.5%), including 3 pleural effusions that required thoracente-

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 07/28/2016

Table 4. Surgical Procedures of Patients Having Hepatocellular Carcinoma Treated With Curative Resection Stratified According to the Barcelona Clinic Liver Cancer (BCLC) Classification

Variable	BCLC Stage[a] 0/A (n=61)	B (n=24)	C (n=28)	*P* Value[b]
Surgery, No. (%)				
Thoracotomy	6 (9.8)	2 (8.3)	6 (21.4)	.24
Minor resection	**58** (95.1)	**20** (83.3)	**10** (35.7)	.001
<1 Segment	36	13	4	
1-2 Segments	22	7	6	
Major resection	**2** (3.3)	**4** (16.7)	**18** (64.3)	.001
3 Segments	2	2	5	
>3 Segments	0	2	13	
Duration of operation, median (range), min	306 (180-620)	390 (240-660)	435 (220-820)	.38
Duration of Pringle maneuver, median (range), min	45 (15-198)	75 (30-165)	73 (30-138)	.22
Blood loss, median (range), mL	200 (10-1500)	200 (80-1200)	400 (100-3000)	.39
Blood transfusions, No. (%)	6 (9.8)	3 (12.5)	7 (25.0)	.16
Drains, median (range)	2 (1-3)	2 (1-3)	1 (1-3)	.36

[a] See Table 1 and the "Stage C" subsection of the "BCLC Classification" subsection in the "Methods" section for an explanation of the Barcelona Clinic Liver Cancer stages.
[b] χ^2 Test and Kruskal-Wallis test where appropriate.

Table 5. Morbidity, Mortality, and Short-term Outcomes of Patients Having Hepatocellular Carcinoma Treated With Curative Resection Stratified According to the Barcelona Clinic Liver Cancer (BCLC) Classification

Variable	BCLC Stage[a] 0/A (n=61)	B (n=24)	C (n=28)	*P* Value[b]
Overall morbidity, No. (%)	**13** (21.3)	**7** (29.2)	**11** (39.3)	.21
Complications, No. (%)				
Major	2 (3.3)	1 (4.2)	2 (7.1)	.97
Minor	11 (18.0)	6 (25.0)	9 (32.1)	.33
Mortality, No. (%)				
30 d	0	0	1 (3.6)	.22
90 d	0	0	0	
Length of stay, median (range), d	9 (8-26)	10 (8-17)	10 (7-20)	.37

[a] See Table 1 and the "Stage C" subsection of the "BCLC Classification" subsection in the "Methods" section for an explanation of the Barcelona Clinic Liver Cancer stages.
[b] χ^2 Test and Kruskal-Wallis test where appropriate.

sis and 1 pneumothorax that required chest tube insertion. No reoperations were needed. Minor morbidity consisted of transient ascites in 12 patients, superficial wound dehiscence in 7 patients, pleural effusion in 3 patients, transient fever in 3 patients, and mild liver failure in 2 patients. Mild liver failure occurred after limited resections in 2 patients with preoperative bilirubin levels ranging from 1.5 to 2 mg/dL. **Table 5** summarizes the complications and short-term outcomes.

The median hospital stay was 9 days. The range was 7 to 20 days.

PATHOLOGIC FINDINGS

The overall median tumor-free margin was 2 mm (range, 0-10 mm). Zero-millimeter margins were obtained in 28 patients with capsulated HCC in contact with hepatic veins or with first- or second-order portal branches. Twenty-eight patients (24.8%) had macrovascular invasion that was established before surgery by imaging and confirmed after surgery by histologic examination (Tables 2 and 3).

LONG-TERM FOLLOW-UP

Among 113 patients, 45 (39.8%) developed recurrences, including 22 with BCLC stage 0 or A disease, 10 with stage B disease, and 13 with stage C disease. Thirty-four patients (30.1%) (19 with stage A disease, 6 with stage B disease, and 9 with stage C disease) had intrahepatic recurrence only, 8 patients (7.1%) (2 with stage A disease, 3 with stage B disease, and 3 with stage C disease) had extrahepatic recurrence only, and 3 patients (2.7%) (1 with stage A disease, 1 with stage B disease, and 1 with stage C disease) had intrahepatic and extrahepatic recurrence. Recurrences were treated in 29 of 45 patients (64.4%), including 16 with BCLC stage 0 or A disease, 7 with stage B disease, and 6 with stage C disease. Intrahepatic recurrence neces-

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 07/28/2016

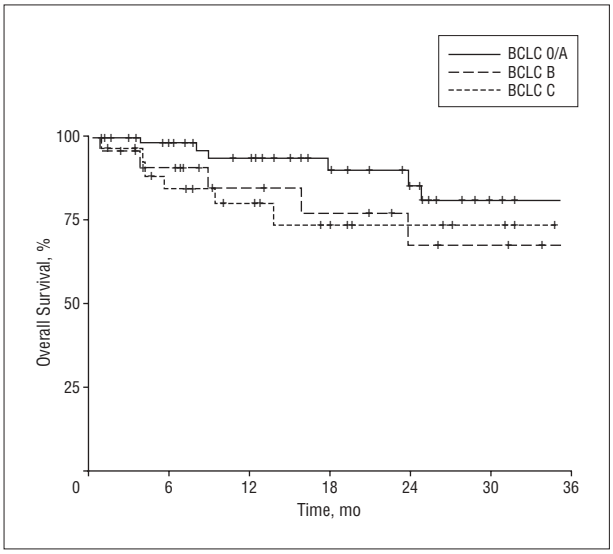

Figure 3. Overall survival curves of patients treated with curative hepatic resection for hepatocellular carcinoma according to the Barcelona Clinic Liver Cancer (BCLC) classification.

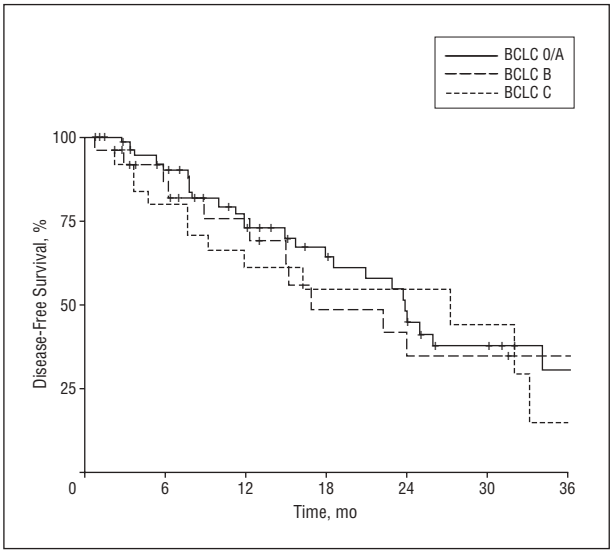

Figure 4. Disease-free survival curves of patients treated with curative hepatic resection for hepatocellular carcinoma according to the Barcelona Clinic Liver Cancer (BCLC) classification.

sitated treatment in 23 of 34 patients (67.6%) as follows: transarterial chemoembolization (TACE) in 13 patients (9 with stage A disease, 2 with stage B disease, and 2 with stage C disease), reresection in 5 patients (4 with stage A disease and 1 with stage B disease), PAT in 3 patients (2 with stage A disease and 1 with stage B disease), PAT and surgery in 1 patient (with stage C disease), and PAT and TACE in 1 patient (with stage C disease). Extrahepatic recurrences required treatment in 3 of 8 patients (37.5%), including 2 patients (with stage B disease) who underwent surgery for pelvic metastasis and for adrenal metastasis and 1 patient (with stage C disease) who received chemotherapy. All 3 patients with intrahepatic and extrahepatic recurrence (1 with stage A disease, 1 with stage B disease, and 1 with stage C disease) received TACE. The median follow-up for the entire series was 24 months (range, 1-65 months).

For patients with BCLC stage 0 or A, stage B, and stage C disease, the 1-year and 3-year overall survival rates were 93% and 81%, 85% and 67%, and 80% and 74%, respectively (P=.24) (**Figure 3**). The median follow-up periods were 24 months (range, 1-61 months) for patients with stage 0 or A disease, 22 months (range, 7-65 months) for patients with stage B disease, and 20 months (range, 7-44 months) for patients with stage C disease. Combining 52 patients with BCLC stage B or stage C HCC, the 1-year and 3-year overall survival rates were 82% and 70%, respectively (P=.09). The median follow-up was 20 months (range, 7-65 months).

For patients with BCLC stage 0 or A, stage B, and stage C disease, the 1-year and 3-year disease-free survival rates were 77% and 30%, 75% and 35%, and 66% and 15%, respectively (P=.85) (**Figure 4**). Combining 52 patients with BCLC stage B or stage C HCC, the 1-year and 3-year disease-free survival rates were 70% and 28%, respectively (P=.76).

For patients with BCLC stage 0 or A, stage B, and stage C disease, the 1-year and 3-year hepatic disease-free survival rates were 81% and 39%, 85% and 44%, and 77% and 17%, respectively (P=.79) (**Figure 5**). Grouping 52 patients with BCLC stage B or stage C HCC, the 1-year and 3-year hepatic disease–free survival rates were 81% and 34%, respectively (P=.90).

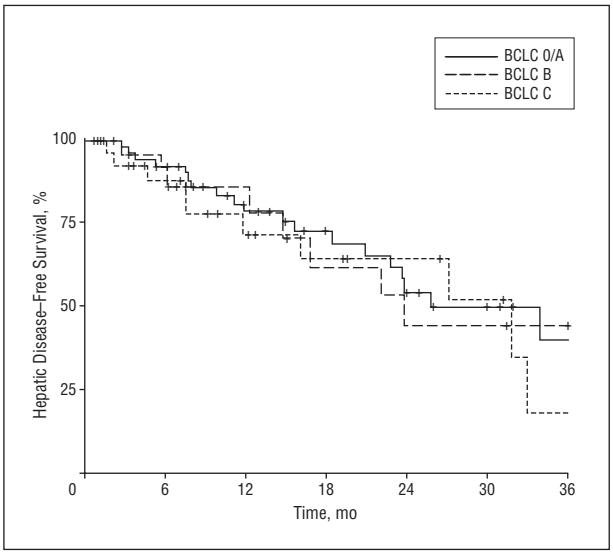

Figure 5. Hepatic disease–free survival curves of patients treated with curative hepatic resection for hepatocellular carcinoma according to the Barcelona Clinic Liver Cancer (BCLC) classification.

UNIVARIATE AND MULTIVARIATE ANALYSES

The univariate analysis of outcome was performed on 13 variables. Tumor size (P=.02) and tumor grade (P=.001) were statistically correlated with overall survival (**Table 6**). Both remained statistically significant on multivariate analysis (hazard ratio, 1.487; 95% confidence interval, 1.134-1.949 [P=.004] for tumor size; and hazard ratio, 1.388; 95% confidence interval, 1.083-1.777 [P=.009] for tumor grade).

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 07/28/2016

Table 6. Univariate Analysis of Outcomes in Patients Treated With Curative Resection for Hepatocellular Carcinoma

Variable	Patients	3-y Survival, %	*P* Value[a]
Overall	113	76	
Age, y			
≤65	41	74	.79
>65	72	78	
Sex			
Male	89	77	.23
Female	24	72	
Quantity of tumors			
Single	71	81	.29
Multiple	42	65	
No. of tumors			
≤3	105	77	.30
>3	8	67	
Tumor size, cm			
≤5	85	83	.02
>5	28	56	
Macrovascular invasion			
No	85	77	.25
Yes	28	74	
Tumor grade, Edmondson-Steiner,[20][b]			
1-2	81	88	.001
3-4	16	39	
Cirrhosis			
No	22	90	.18
Yes	91	73	
Esophageal varices			
Absent	96	78	.12
Present	17	72	
Clinical portal hypertension[c]			
No	85	77	.39
Yes	28	78	
α-Fetoprotein level, ng/mL[d]			
≤400	86	76	.38
>400	10	77	
Extent of resection			
Minor	89	75	.58
Major	24	67	
Barcelona Clinic Liver Cancer classification[e]			
0/A	61	90	.09
B and C	52	70	

SI conversion factors: To convert α-fetoprotein level to micrograms per liter, multiply by 1.0; to convert platelet count to $\times 10^9$/L, multiply by 1.0.

[a] Log-rank test.

[b] Unavailable in 16 patients.

[c] Patients with esophageal varices or with a platelet count of less than 100×10^3/μL.

[d] Unavailable in 17 patients.

[e] See Table 1 and the "Stage C" subsection of the "BCLC Classification" subsection in the "Methods" section for an explanation of the Barcelona Clinic Liver Cancer stages.

COMMENT

The BCLC classification is considered one of the most reliable staging systems for HCC because it considers tumor stage, liver function, and physical status.[4,22] Based on this staging system, surgical treatment should be reserved for patients with single lesions not exceeding 5 cm and without portal hypertension or hyperbilirubinemia.[2,23] The estimated 3-year survival for patients with untreated stage B or C HCC ranges from 8% to 50%; for these patients, the BCLC classification recommends palliation using TACE or new therapeutic agents.[2] The rationale for this policy is based on the fact that a more aggressive approach would be too risky and that surgical treatment of HCC is associated in many medical centers with mortality and morbidity.[24] However, the definition of resectability is equivocal: similar patients are submitted to resection by some authors[8-11] and by other authors[25] are considered unresectable and are treated during surgery with thermal ablation. Because the surgical indications are confusing, it is understandable that the nonsurgical scientific community does not officially recommend surgery (in any guideline) for advanced HCC.[23] However, physicians often refer patients who would not normally be considered for surgery. Indeed, large numbers of patients with BCLC stage B and stage C HCC are described herein, despite referral primarily by oncologists, hepatologists, and interventional radiologists. In fact, some recent studies[22,26] supporting the BCLC classification did not follow its therapeutic recommendations.

The truth is that safe and effective surgical intervention in patients having HCC is possible even in those with concomitant cirrhosis.[5-7] Surgical policy is key, as many series with greater mortality had higher rates of major resections. For patients with cirrhosis, the extent of parenchymal removal should be considered. A similar dilemma occurred with TACE, which is now selectively recommended[27]; this was not the case in the past, when the mortality and morbidity of TACE were thought to be more extensive.[28,29] Surgery achieves an even higher standard of safety than TACE when selectively and conservatively performed.[16,17]

The present series involves a prospectively enrolled cohort of patients who were candidates for hepatic resection. Curiously, half of the patients had disease classified as BCLC stage B or stage C, but the resectability rate among the outpatient referred population was 73.6% (69.3% after excluding 7 patients who underwent exploratory laparotomies). Our conservative approach, which resulted in the removal of more than 3 liver segments in only 13.3% of patients, and our algorithm for patient selection (Figure 1) allowed us to achieve this high rate of resectability, with 0.9% perioperative mortality and minimal major morbidity.

Some surgeons rely on the Child classification alone in selecting patients for surgery.[30] This classification assists in ruling out patients for surgery who have Child class B and C disease rather, as opposed to selecting an operation for patients having Child class A disease.[7,31,32] Indocyanine green retention rate at 15 minutes (ICGR-15), galactose elimination capacity, and the Model of End-stage Liver Disease score are also used to predict the risk of postoperative liver failure.[6,32-35] However, no consensus exists,[36] and mortality continues to be unacceptable, despite proposed methods.[32] Our selection flowchart is a modified version of an algorithm based on serum bilirubin level and ICGR-15[6,33]; we used residual liver volume estimation instead of ICGR-15. The results herein demonstrate that our algorithm predicts a safe outcome; indeed, the 2 patients with mild postoperative liver

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 07/28/2016

failure would have received the same treatment if they had been selected using ICGR-15.

The 14.2% of patients who received blood transfusion is below the rates reported in the literature (range, 23%-49%).[37-40] Although this is in part due to a policy restricting blood administration,[41,42] it is also a result of the conservativeness of our surgical approach.

Fifteen percent of patients in our series had esophageal varices, and almost one-third of them had endoscopic banding before surgery (Table 3). Two-thirds of these patients had BCLC stage 0 or A disease, and according to the BCLC classification they should not have been submitted for surgery. Capussotti et al[43] reported in 2006 that treatment of esophageal varices did not significantly affect outcomes, and our data confirm this (Table 6). In our series, portal hypertension was not estimated using the hepatic vein pressure gradient,[44] which is an invasive procedure for which the findings are not always useful.[45,46] More important, adopting esophageal varices as the criterion for portal hypertension might simply have underestimated its degree.

In the present series, the high 3-year survival rates of patients with BCLC stage B and stage C HCC demonstrate that surgery provides prognostic benefits compared with PAT, TACE, or new therapeutic agents. The safety and radicality of PAT and TACE independently or in combination are incomparable with those reported herein. Indeed, patients undergoing these procedures (mostly patients with single tumors and without vascular invasion) experience mortality ranging from 2% to 4% and complete tumor ablation ranging from 9% to 57%.[47,48]

The present study reestablishes the fundamental role of oncologic surgery for survival of these patients during the midterm, despite disease progression. This was particularly evident for patients with BCLC stage B and stage C HCC. The results herein may suggest new therapeutic scenarios for these patients considering the ongoing improvements in medical treatment of HCC.[49,50] Patients with BCLC stage C HCC had 74% survival at 3 years (Figure 3). The 15% disease-free survival (Figure 4) and 17% hepatic disease–free survival (Figure 5) may seem inadequate. However, the poor life expectancy of these patients if untreated should be considered,[3] as well as the finding herein that 64.4% of them had treatable recurrences.

Several factors may explain our good results. Conservativeness as opposed to radicality might induce a lower expression of growth factors after surgery, which seem to be associated with liver regeneration and with tumor recurrence.[50] Intraoperative staging based on intraoperative ultrasonography and contrast-enhanced intraoperative ultrasonography may influence the radicality of surgery[51] and may explain our 39% survival at 3 years among patients with high-grade HCC (Table 6).

Extensive use of intraoperative ultrasonographic guidance allowed us to minimize tumor-free resection margins. Several patients had tumor exposed on the cut surface, but we did not observe any cut edge recurrence. Moreover, most authors agree that there is no need for a 1-cm safety margin if tumor clearance is obtained.[52,53] Conversely, Shi et al[54] in 2007 stated that a 2-cm margin should be obtained; however, they reported a 29% rate of local recurrence among patients with narrower resection margins, which is inconsistent with other series.[55]

A strength of this study was the strict postoperative follow-up. Furthermore, we were able to treat 67.6% of patients with intrahepatic recurrence, and the treatment was reresection in 21.7% of them.

In conclusion, the combination of radicality and conservativeness achievable with intraoperative ultrasonographic guidance has transferred to liver surgery the radical but conservative policy that has been successfully applied in the surgical treatment of breast cancer.[56] Applying this concept, our study shows that in lieu of palliation a properly performed hepatic resection may offer increased life expectancies for patients with intermediate and advanced HCC.

Accepted for Publication: June 15, 2007.
Correspondence: Guido Torzilli, MD, PhD, Third Department of Surgery, University of Milan, Istituto Clinico Humanitas Istituto Di Ricovero e Cura a Carattere Scientifico, Via Manzoni 56, 20089, Rozzano, Milan, Italy (guido.torzilli@unimi.it).
Author Contributions: *Study concept and design:* Torzilli. *Acquisition of data:* Torzilli, Donadon, Marconi, Palmisano, Del Fabbro, Spinelli, Botea, and Montorsi. *Analysis and interpretation of data:* Torzilli, Donadon, Marconi, and Palmisano. *Drafting of the manuscript:* Torzilli, Donadon, Marconi, Del Fabbro, Spinelli, and Botea. *Critical revision of the manuscript for important intellectual content:* Torzilli and Montorsi. *Statistical analysis:* Torzilli, Donadon, and Botea. *Administrative, technical, and material support:* Marconi, Palmisano, Del Fabbro, and Spinelli. *Study supervision:* Torzilli and Montorsi.
Financial Disclosure: None reported.
Additional Contributions: Rosalind Roberts provided editorial assistance during the preparation of the manuscript.

REFERENCES

1. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology*. 1997;112(2):463-472.
2. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology*. 2002;35(3):519-524.
3. Llovet JM, Fuster J, Bruix J; Barcelona-Clinic Liver Cancer Group. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. *Liver Transpl*. 2004;10(2)(suppl 1):S115-S120.
4. Marrero JA. Staging systems for hepatocellular carcinoma: should we all use the BCLC system? *J Hepatol*. 2006;44(4):630-632.
5. Imamura H, Seyama Y, Kokudo N, et al. One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg*. 2003;138(11):1198-1206.
6. Torzilli G, Makuuchi M, Inoue K, 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):984-992.
7. Fan ST, Lo CM, Liu CL, et al. Hepatectomy for hepatocellular carcinoma: toward zero hospital deaths. *Ann Surg*. 1999;229(3):322-330.
8. Ng KK, Vauthey JN, Pawlik TM, et al; International Cooperative Study Group on Hepatocellular Carcinoma. Is hepatic resection for large or multinodular hepatocellular carcinoma justified? results from a multi-institutional database. *Ann Surg Oncol*. 2005;12(5):364-373.
9. Minagawa M, Makuuchi M, Takayama T, Ohtomo K. Selection criteria for hepatectomy in patients with hepatocellular carcinoma and portal vein tumor thrombus. *Ann Surg*. 2001;233(3):379-384.
10. Pawlik TM, Poon RT, Abdalla EK, et al. Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. *Surgery*. 2005;137(4):403-410.

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 07/28/2016

11. Ikai I, Yamamoto Y, Yamamoto N, et al. Results of hepatic resection for hepatocellular carcinoma invading major portal and/or hepatic veins. *Surg Oncol Clin N Am*. 2003;12(1):65-75.
12. Couinaud C. *Le Foie: Etude Anatomiques et Chirurgicales*. Paris, France: Masson Publishers; 1957.
13. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996; 334(11):693-699.
14. Japanese Research Society for Portal Hypertension. The general rules for recording endoscopic findings on esophageal varices. *Jpn J Surg*. 1980;10(1):84-87.
15. Torzilli G, Del Fabbro D, Olivari N, Callida F, Montorsi M, Makuuchi M. Contrast-enhanced ultrasonography during liver surgery. *Br J Surg*. 2004;91(9):1165-1167.
16. Torzilli G, Montorsi M, Donadon M, et al. "Radical but conservative" is the main goal for ultrasonography-guided liver resection: prospective validation of this approach. *J Am Coll Surg*. 2005;201(4):517-528.
17. Torzilli G, Montorsi M, Del Fabbro D, Palmisano A, Donadon M, Makuuchi M. Ultrasonographically guided surgical approach to liver tumours involving the hepatic veins close to the caval confluence. *Br J Surg*. 2006;93(10):1238-1246.
18. Pringle JH. Notes on the arrest of hepatic hemorrhage due to trauma. *Ann Surg*. 1908;48(4):541-549.
19. Ijichi M, Takayama T, Toyoda H, Sano K, Kubota K, Makuuchi M. Randomized trial of the usefulness of a bile leakage test during hepatic resection. *Arch Surg*. 2000;135(12):1395-1400.
20. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48900 necropsies. *Cancer*. 1954;7(3):462-503.
21. Torzilli G, Olivari N, Del Fabbro D, et al. Bilirubin level fluctuation in drain discharge after hepatectomies justifies long-term drain maintenance. *Hepatogastroenterology*. 2005;52(64):1206-1210.
22. Cillo U, Vitale A, Grigoletto F, et al. Prospective validation of the Barcelona Clinic Liver Cancer staging system. *J Hepatol*. 2006;44(4):723-731.
23. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology*. 2005;42(5):1208-1236.
24. Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. *Ann Surg*. 2006; 243(3):373-379.
25. Raut CP, Izzo F, Marra P, et al. Significant long-term survival after radiofrequency ablation of unresectable hepatocellular carcinoma in patients with cirrhosis. *Ann Surg Oncol*. 2005;12(8):616-628.
26. Mazzaferro V, Romito R, Schiavo M, et al. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. *Hepatology*. 2006;44(6):1543-1554.
27. Takayasu K, Arii S, Ikai I, et al; Liver Cancer Study Group of Japan. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology*. 2006;131(2):461-469.
28. Vetter D, Wenger JJ, Bergier JM, Doffoel M, Bockel R. Transcatheter oily chemoembolization in the management of advanced hepatocellular carcinoma in cirrhosis: results of a Western comparative study in 60 patients. *Hepatology*. 1991; 13(3):427-433.
29. Bronowicki JP, Vetter D, Dumas F, et al. Transcatheter oily chemoembolization for hepatocellular carcinoma: a 4-year study of 127 French patients. *Cancer*. 1994; 74(1):16-24.
30. Fong Y, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a Western center. *Ann Surg*. 1999;229(6):790-799.
31. Belghiti J, Regimbeau JM, Durand F, et al. Resection of hepatocellular carcinoma: a European experience on 328 cases. *Hepatogastroenterology*. 2002; 49(43):41-46.
32. Teh SH, Christein J, Donohue J, et al. Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: Model of End-stage Liver Disease (MELD) score predicts perioperative mortality. *J Gastrointest Surg*. 2005;9(9):1207-1215.
33. Miyagawa S, Makuuchi M, Kawasaki S, Kakazu T. Criteria for safe hepatic resection. *Am J Surg*. 1995;169(6):589-594.
34. Lau H, Man K, Fan ST, Yu WC, Lo CM, Wong J. Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. *Br J Surg*. 1997;84(9):1255-1259.
35. Redaelli CA, Dufour JF, Wagner M, et al. Preoperative galactose elimination capacity predicts complications and survival after hepatic resection. *Ann Surg*. 2002; 235(1):77-85.
36. Poon RT, Fan ST. Hepatectomy for hepatocellular carcinoma: patient selection and postoperative outcome. *Liver Transpl*. 2004;10(2)(suppl 1):S39-S45.
37. Di Stefano DR, de Baere T, Denys A, et al. Preoperative percutaneous portal vein embolization: evaluation of adverse events in 188 patients. *Radiology*. 2005; 234(2):625-630.
38. Azoulay D, Castaing D, Smail A, et al. Resection of nonresectable liver metastases from colorectal cancer after percutaneous portal vein embolization. *Ann Surg*. 2000;231(4):480-486.
39. Elias D, Ouellet JF, De Baere T, Lasser P, Roche A. Preoperative selective portal vein embolization before hepatectomy for liver metastases: long-term results and impact on survival. *Surgery*. 2002;131(3):294-299.
40. Grazi GL, Ercolani G, Pierangeli F, et al. Improved results of liver resection for hepatocellular carcinoma on cirrhosis give the procedure added value. *Ann Surg*. 2001;234(1):71-78.
41. Makuuchi M, Takayama T, Gunven P, Kosuge T, Yamazaki S, Hasegawa H. Restrictive versus liberal blood transfusion policy for hepatectomies in cirrhotic patients. *World J Surg*. 1989;13(5):644-648.
42. Torzilli G, Gambetti A, Del Fabbro D, et al. Techniques for hepatectomies without blood transfusion focusing on interpretation of postoperative anemia. *Arch Surg*. 2004;139(10):1061-1065.
43. Capussotti L, Ferrero A, Vigano L, Muratore A, Polastri R, Bouzari H. Portal hypertension: contraindication to liver surgery? *World J Surg*. 2006;30(6):992-999.
44. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology*. 1999; 30(6):1434-1440.
45. Keiding S, Vilstrup H. Intrahepatic heterogeneity of hepatic venous pressure gradient in human cirrhosis. *Scand J Gastroenterol*. 2002;37(8):960-964.
46. Wadhawan M, Dubey S, Sharma BC, Sarin SK, Sarin SK. Hepatic venous pressure gradient in cirrhosis: correlation with the size of varices, bleeding, ascites, and Child's status. *Dig Dis Sci*. 2006;51(12):2264-2269.
47. Veltri A, Moretto P, Doriguzzi A, Pagano E, Carrara G, Gandini G. Radiofrequency thermal ablation (RFA) after transarterial chemoembolization (TACE) as a combined therapy for unresectable non-early hepatocellular carcinoma (HCC). *Eur Radiol*. 2006;16(3):661-669.
48. Molinari M, Kachura JR, Dixon E, et al. Transarterial chemoembolisation for advanced hepatocellular carcinoma: results from a North American cancer centre. *R Coll Radio Clin Oncol*. 2006;18(9):684-692.
49. Gollob JA, Wilhelm S, Carter C, Kelley SL. Role of Raf kinase in cancer: therapeutic potential of targeting the Raf/MEK/ERK signal transduction pathway. *Semin Oncol*. 2006;33(4):392-406.
50. Yoon SS, Kim SH, Gonen M, et al. Profile of plasma angiogenic factors before and after hepatectomy for colorectal cancer liver metastases. *Ann Surg Oncol*. 2006;13(3):353-362.
51. Torzilli G, Palmisano A, Del Fabbro D, et al. Contrast-enhanced intraoperative ultrasonography during surgery for hepatocellular carcinoma in liver cirrhosis: is it useful or useless? a prospective cohort study of our experience. *Ann Surg Oncol*. 2007;14(4):1347-1355.
52. Poon RT, Fan ST, Ng IO, Wong J. Significance of resection margin in hepatectomy for hepatocellular carcinoma: a critical reappraisal. *Ann Surg*. 2000;231 (4):544-551.
53. Ochiai T, Takayama T, Inoue K, et al. Hepatic resection with and without surgical margins for hepatocellular carcinoma in patients with impaired liver function. *Hepatogastroenterology*. 1999;46(27):1885-1889.
54. Shi M, Guo RP, Lin XJ, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. *Ann Surg*. 2007;245(1):36-43.
55. Matsui Y, Terakawa N, Satoi S, et al. Postoperative outcomes in patients with hepatocellular carcinomas resected with exposure of the tumor surface: clinical role of the no-margin resection. *Arch Surg*. 2007;142(7):596-602.
56. Veronesi U, Saccozzi R, Del Vecchio M, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N Engl J Med*. 1981;305(1):6-11.

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 07/28/2016