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Recurrence Patterns and Prognostic Factors in Patients with Hepatocellular Carcinoma in Noncirrhotic Liver: A Multi-Institutional Analysis

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Abstract

Background—Hepatocellular carcinoma (HCC) primarily affects patients with a cirrhotic liver. Reports on the characteristics of patients with HCC in noncirrhotic liver, as well as predictors of recurrence and survival, are scarce.

Methods—Between 1992 and 2011, 334 patients treated for HCC in noncirrhotic liver were identified from three major hepatobiliary centers. Clinicopathological characteristics were analyzed and independent predictors of recurrence and overall survival were identified using Cox proportional hazards models.

Results—Median patient age was 58 years and 77 % were male. Most patients had a solitary (81 %) and poorly or undifferentiated tumor (56 %); median size was 6.5 cm. The majority of patients (96 %) underwent liver resection (microscopically negative margins in 94 %), whereas a few had transarterial chemoembolization or transplantation (4 %). Median recurrence-free survival (RFS) was 2.5 years, and 1- and 5-year RFS was 71.1, and 35 %, respectively. Elevated alkaline phosphatase levels [hazards ratio (HR) = 1.82], poor tumor differentiation (HR = 1.4), macrovascular invasion (HR = 2.18), and the presence of satellite lesions (HR = 1.9), or intrahepatic metastases (HR = 2.59) were independently associated with shorter RFS; in contrast, an intact tumor capsule independently prolonged RFS (HR = 0.46). Median overall survival was 5.9 years, and 1- and 5-year overall survival was 86.9, and 54.5 %, respectively. Tumor size ≥5 cm (HR = 2.27), macrovascular (HR = 2.72) or adjacent organ invasion (HR = 3.34), and satellite lesions (HR = 2.18) were independently associated with shorter overall survival, whereas an intact tumor capsule showed a protective effect (HR = 0.51).

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Conclusions—Following resection of HCC in the setting of no cirrhosis, more than one-half of patients were alive after 5 years. However, even among patients with no cirrhosis, recurrence was common. Factors associated with RFS and overall survival included tumor characteristics, such as tumor capsule, satellite lesions, and vascular invasion.

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third-leading cause of cancer-related death in the world.[1] The yearly incidence nearly matches the number of HCC-related deaths per year demonstrating the poor prognosis.[1] The majority of cases (~80 %) are due to liver cirrhosis associated with chronic hepatitis B and C infection. Other, nonviral etiologies of cirrhosis, including chronic alcohol consumption, nonalcoholic steatohepatitis, hemochromatosis, and α1-antitrypsin deficiency, also are risk factors for hepatoma formation. Therefore, HCC is most common in regions of the world (China, Japan, Taiwan, sub-Saharan Africa) where viral hepatitis exposure is prevalent.[2] Despite being low-incidence regions, the United States and Central Europe have increasing rates of HCC likely due to an increase in hepatitis C infection rates during the past 30 years.[3]

Although relatively rare, HCC can develop in the noncirrhotic liver. In fact, the development of HCC in the noncirrhotic liver may be increasing worldwide due to unclear reasons. HCC diagnosis among noncirrhotic patients may be delayed due to lack of screening in this population of patients who do not typically meet criteria for routine HCC surveillance, because these patients do not suffer from chronic liver disease.[4] In turn, patients with HCC arising in a noncirrhotic liver may present with more advanced disease and have a worse prognosis and fewer therapeutic options.[5]

In general, reports on the characteristics of patients with HCC in noncirrhotic liver, as well as predictors of recurrence and survival, are relatively scarce.[6,7] Most previous studies have been from a single institution and have included only a small number of patients. Therefore, the purpose of the current study was to elucidate the clinical presentation and surgical management of patients with HCC in the noncirrhotic liver using a large multicenter, international cohort of patients. Furthermore, we sought to define the prognosis of patients with HCC in the noncirrhotic liver following surgical resection, as well as identify predictors of recurrence and survival.

METHODS

Patient Population

Using a multi-institutional database, 334 patients with HCC in the noncirrhotic liver who were treated between 1992 and 2011 in one of three major hepatobiliary centers in North America, Europe, and Asia were identified (Johns Hopkins Hospital, Baltimore, MD, USA; Institute for Digestive Diseases and Liver Transplantation Fundemi, Bucharest, Romania; Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China). All patients had been diagnosed with HCC in the setting of a liver without cirrhosis, as assessed by pathological examination. The study protocol was approved by the institutional review board of each participating institution.

Data Collection

Standard demographical data were collected. We also recorded specific data on the liver disease, including presenting symptoms, preoperative laboratory values, tumor clinicopathological characteristics, and extent of liver fibrosis and steatosis. Satellite lesions were defined as lesions in the same Couinaud liver segment or within 1 cm of primary tumor; in contrast, lesions in another Couinaud segment or >1 cm of primary tumor were defined as intrahepatic metastases. Tumor encapsulation was assessed by cross-sectional imaging as the presence of intact capsule, disrupted capsule, or absence of capsule. The American Joint Committee on Cancer (AJCC), 7th edition TNM criteria were used for the staging of the tumors. Data on treatment also were collected, including details of surgical resection and information on the postoperative course, such as length of hospital stay and postoperative complications. A major hepatectomy was defined as a resection of at least three liver segments, whereas a minor included two segments or less. Perioperative mortality was calculated based on the number of patients who expired within 90 days of the operation.[8] The postoperative complications were assessed until 30 days after the operation and were graded for severity using the Clavien–Dindo classification (a major complication was defined as one of grade III or higher).[9] Long-term clinical outcomes also were recorded, including data on recurrence and overall survival at last follow-up.

Statistical Analysis

Continuous variables were presented as median values with range unless otherwise indicated. Discrete variables were presented as totals and percentages. Comparison of categorical variables was performed using Chi-square tests, and continuous variables were compared among groups using the Student's *t* test or Mann–Whitney test, as appropriate. The recurrence-free and overall survival (RFS and OS, respectively) were calculated using the Kaplan–Meier method and survival curves were compared using the log-rank test. Cox's proportional hazards regression models were used for multivariate modeling of RFS and OS for patients undergoing liver resection with curative intent. Variable selection for the multivariate models was performed in a backwards stepwise fashion and started with all variables potentially associated with RFS and OS in univariate analysis ($p < 0.2$). Statistical significance was set at $p < 0.05$. All analyses were performed using the STATA 11.2 (Stata Corp., College Station, TX) statistical software package.

RESULTS

Patient and Disease Characteristics

Patient characteristics are presented in Table 1. The median age at diagnosis was 58 years (range 9–85). Patients were predominantly male (258, 77 %); 170 (52 %) were Caucasian, 136 (41 %) Asian, and 24 (7 %) African-American. Almost half of the patients (163, 49 %) did not have chronic viral hepatitis, whereas 129 (39 %) and 45 (13 %) were infected with hepatitis B and C virus, respectively; three patients (1 %) had both hepatitis B and C. Most patients initially presented with abdominal pain ($n = 177$, 53 %), whereas others complained of early satiety ($n = 50$, 15 %), weight loss ($n = 41$, 12 %), or an abdominal mass ($n = 21$, 6 %). In most patients, hepatic enzymes were elevated preoperatively [aspartate aminotransferase in 229 (71 %), alanine aminotransferase in 206 (64 %), alkaline

phosphatase in 96 (31 %)]. The serum alpha-fetoprotein (AFP) was elevated in 214 (73 %) patients; median AFP value was 367.5 ng/mL (range 1–742,126).

Liver disease characteristics are presented in Table 1. Most of the patients had a single (*n* = 269, 81 %) and large (≥5 cm; *n* = 230, 70 %) tumor; median tumor size was 6.5 cm (range 1.1–40.2). More than half of the patients had poorly differentiated (*n* = 176, 54 %) or undifferentiated (*n* = 6, 2 %) tumors. There was macrovascular invasion in 57 (18 %) patients, portal vein invasion in 22 (7 %), and microvascular invasion in 63 (20 %). The tumor was encapsulated with intact capsule in 122 patients (48 %) and disrupted capsule in 57 (22 %); no encapsulation was observed in 75 (30 %) patients. Presence of an intact capsule was not associated with presence of satellite lesions (*p* = 0.966), intrahepatic metastases (*p* = 0.224), or vascular invasion (*p* = 0.534). Extrahepatic disease was detected in 18 patients (9 %), usually in the diaphragm (*n* = 5), peritoneum (*n* = 4), lungs (*n* = 3), or other sites (*n* = 5). Few patients satisfied the Milan criteria (*n* = 29, 15 %), although many had relatively early-stage disease according to the AJCC (7th edition) TNM criteria [stage I in 102 (53 %), stage II in 16 (8 %), stage III in 55 (28 %), stage IV in 21 (11 %) patients]. Most of the patients had no hepatic fibrosis [grade 1 in 28 (14 %), grade 2 or 3 in 6 (3 %)] or steatosis [mild in 24 (12 %), moderate in 10 (5 %), severe in 4 (2 %)].

Treatment and Clinical Outcomes

Treatment characteristics are displayed in Table 2. Almost all patients (*n* = 319, 95 %) received a liver resection [minor and major hepatectomy in 229 (72 %) and 90 (28 %) patients, respectively; concomitant lesion ablation in 7 patients], whereas 12 (4 %) were treated with transarterial chemoembolization (TACE) and 3 (1 %) underwent a liver transplantation. In addition, 28 patients (8 %) received preoperative treatment; TACE, systemic cytotoxic chemotherapy, and biologic agents were administered to 20 (6 %), 6 (2 %), and 6 (2 %) patients respectively. Of the surgically treated patients, 303 (94 %) had R0 (microscopically negative), 11 (3 %) R1 (microscopically positive), and 8 (2 %) R2 (macroscopically positive) surgical margins.

Four patients were lost to follow-up. After a median follow-up of 2.2 years (range 0.1–12.8), half of the patients receiving a curative-intent resection (*n* = 150, 50 %) developed a recurrence. Overall, including the patients receiving TACE, recurrence was confined within the liver in most cases (*n* = 106, 76 %) and less commonly spread to the lungs (*n* = 26, 19 %), peritoneum (*n* = 7, 5 %), bone (*n* = 5, 4 %), or other sites (*n* = 4, 3 %). Treatment of recurrences most commonly consisted of TACE (*n* = 71, 61 %); few patients underwent repeat resection (*n* = 29, 25 %), systemic chemotherapy (*n* = 27, 23 %), or other treatment (*n* = 4, 3 %). A total of 14 patients (5 treated with palliative intent) expired within 90 days of liver-directed treatment (liver resection in 11, TACE in 3) for a periprocedural mortality of 4 %.

Almost a third of the patients (*n* = 112, 35 %) experienced a complication within 30 days postoperatively, most of which were hepatobiliary in nature (*n* = 67, 21 %). Specifically, 30 patients (9 %) developed ascites, 21 (7 %) a perihepatic abscess or fluid collection, 12 biliary fistula (4 %), and 1 cholangitis; 3 patients (1 %) developed progressive liver failure. Few patients developed wound complications (*n* = 12, 4 %), such as surgical site infection (*n*

= 9, 3 %), whereas others had gastrointestinal (*n* = 5, 2 %; i.e., ileus) or other complications (*n* = 28, 9 %). Data on the severity of the complication were available for 74 patients; most of them (*n* = 59, 80 %) had a mild complication.

Predictors of Recurrence and Overall Survival

The median RFS of resected patients was 2.5 years (95 % confidence interval (CI) 2.2–3.4); 1-year, 3-year, and 5-year RFS was 71.1, 45, and 35.0 %, respectively (Fig. 1). The results of the univariate and multivariate analyses for RFS are presented in Table 3. The variables independently associated with an earlier recurrence were preoperative alkaline phosphatase levels ≥120 IU/L [HR = 1.82 (95 % CI 1.19–2.77); median RFS 1.9 vs. 2.5 years for those with lower alkaline phosphatase levels], poor tumor differentiation [hazards ratio (HR) = 1.4 (1.01–1.95); median RFS 2 vs. 4.1 years for those with well or moderately differentiated tumors], macrovascular invasion [HR = 2.18 (1.31–3.61); median RFS 0.9 vs. 2.6 years for those without macrovascular invasion], and the presence of satellite lesions [HR = 1.9 (1.85–4.54); median RFS 1.2 vs. 2.6 years for those without] or intrahepatic metastases [HR = 2.59 (1.28–5.23); median RFS 0.8 vs. 2.5 years for those without]. In contrast, the presence of an intact tumor capsule (as opposed to a disrupted capsule or absence of capsule) was independently associated with longer RFS [HR = 0.46 (0.29–0.73); median RFS 4.1 vs. 2.2 years (Fig. 2a)].

The median OS of resected patients was 5.9 years (95 % CI 4.7–7.7); 1-year, 3-year, and 5-year OS was 86.9, 68.9, and 54.5 %, respectively (Fig. 2). The results of the univariate and multivariate analyses for OS are presented in Table 3. The variables independently associated with shorter overall survival were tumor size ≥5 cm [HR = 2.27 (1.27–4.07); median OS 4.9 vs. 5.5 years for those with smaller tumors], macrovascular [HR = 2.72 (1.62–4.56); median OS of 2 vs. 6.6 years for those without] or adjacent organ invasion [HR = 3.34 (1.18–9.51); median OS 1.6 vs. 6.6 years of those without], and the presence of satellite lesions [HR = 2.13 (1.28–3.54); median OS 3.3 vs. 7.7 years of those without]. Presence of an intact tumor capsule exerted a protective effect in OS [HR = 0.51 (0.32–0.82); median OS 6.6 vs. 5.8 years of those with disrupted or without capsule] (Fig. 2b).

DISCUSSION

Although there has been much research dedicated to the study of the etiology and management of HCC in the setting of the cirrhotic liver, data have been limited on the natural history of HCC in noncirrhotic patients. Furthermore, data on the long-term outcomes of patents with HCC in noncirrhotic patients following surgery remain poorly defined. While OS data have been reported, information on overall recurrence and patterns of recurrence are scarce. The current study is important because we examined a large, multi-institutional cohort of patients with HCC in a noncirrhotic liver and identified specific clinicopathological factors that influenced recurrence and OS. Specifically, we noted that OS was 54.5 %. Perhaps more interestingly, we found that recurrence following surgical resection of HCC—even among patients without cirrhosis—was quite high. In fact, at the time of last follow-up 154 patients had experienced a recurrence and the estimated 5-year, RFS was only 35 %. Factors that were associated with recurrence and survival were largely

tumor-related, such as tumor size and the presence of vascular invasion, satellite lesions, or the absence of an intact tumor capsule.

Several investigators have argued that HCC in cirrhotic versus noncirrhotic livers should be regarded as distinct disease processes.[7,10,11] The pathogenesis of HCC in patients with cirrhosis often is related to the sequential progression of regenerative nodules to dysplastic nodules to well-differentiated HCC.[12] On a molecular level, the development of HCC in a cirrhotic liver is related to alterations of p53 expression through several pathways, as well as the activation of the Wnt/beta-catenin pathway.[10,11] In contrast, the development of HCC in the noncirrhotic liver has been noted to be more associated with disruption of the cell cycle due to higher prevalence of beta-catenin mutations, p21 expression, p14 inactivation, and global gene methylation.[10,11] On the clinical level, patients with HCC and no liver disease can present differently and have unique prognostic features compared with patients who have cirrhosis. Because patients with no cirrhosis are not followed with routine surveillance imaging, patients may present later in their clinical course with larger hepatomas. In addition, the lesions may more often be solitary. In fact, this is what we noted in the current study as the vast majority of patients had a single, large tumor. Resection of these lesions may be facilitated by the fact that the nontumorous liver is not cirrhotic, thereby making operative intervention safer. In the current study, the 30-day complication rate was 35 % and most complications were minor. In addition, the 90-day mortality rate was 4 %, which was similar to previous reports of perioperative mortality for hepatic resection.[13]

With regard to long-term outcome, the 5-year RFS and OS was 35 and 53 %, respectively. It is important to note that the incidence of recurrence among patients with HCC in a noncirrhotic liver was high. At a median follow-up of 2.2 years, half of the patients receiving a resection with curative intent had experienced a recurrence and the Kaplan–Meier estimate of recurrence at 5 years was 65 %. Despite the lack of cirrhosis, the most common location for recurrence was overwhelmingly within the liver (76 %); less common sites included the lung, peritoneum, and bone. These data may have important implications to inform the need for surveillance following resection of HCC in noncirrhotic patients. Our data suggest that clinicians should remain vigilant in postoperative surveillance as recurrence appears to be fairly common even among patients without cirrhosis. Predictors of an earlier recurrence included tumor-specific factors, such as tumor size and poor differentiation, macrovascular invasion, and the presence of satellite lesions or intrahepatic metastases. These findings may represent a more aggressive biology, potentially related to delayed identification of disease.[14,15] As such, recurrence may be more likely due to the formation of local recurrent disease/intrahepatic metastasis as opposed to de novo disease. In contrast, the presence of an intact tumor capsule was associated with a protective effect. Patients with an intact tumor capsule had a roughly 50 % reduction in the hazard of recurrence versus patients with either no capsule or those with a disrupted capsule. The protective effect of an intact tumor capsule had been noted in earlier series of patients with HCC.[16–19] This finding may be related to the capsule functioning as a protective barrier to local and vascular invasion.[20,21] In fact, it has been suggested that the protective effect of an intact tumor capsule may be most pronounced for large tumors; in this regard, 70 % of our patients had tumors ≥5 cm.[16]

Previous series reporting on noncirrhotic patients with HCC reported a 5-year OS ranging from 26 to 40 %, whereas outcomes of more contemporary series have varied.[22,23] In some series the 5-year OS was as low as 42–44 %, whereas other investigators have reported 5-year survival as high as 60–64 %.[24–28] In the current study, we noted a long-term 5-year survival of 54.5 %. Collectively these data suggest that the long-term outcome of noncirrhotic patients with HCC is somewhat better than patients with HCC in the setting of cirrhosis and may be more comparable to the survival seen for patients with fibrolamellar HCC.[29] This is likely due to the fact that the cirrhotic patients have underlying liver disease that lends itself to future hepatic decompensation, as well as an increased risk of de novo HCC formation, particularly those with HCV and HBV cirrhosis. Similar to recurrence, long-term survival was associated with tumor-specific factors, such as tumor size and vascular invasion; both of these factors were predictive of a worse outcome. Other factors associated with an increased risk of long-term mortality included higher serum alkaline phosphatase levels. High serum alkaline phosphatase may predict recurrence and mortality in both cirrhotic and noncirrhotic patients with HCC, potentially as a surrogate of large tumor size or rapid growth compressing the bile ducts.[22,30–32]

The present study had several limitations. First, we did include a small number of patients with mild fibrosis or steatosis, which may have impacted our findings. However, none of these patients had frank cirrhosis and therefore were still appropriate to include in the study cohort of noncirrhotic patients. We also included patients who were afflicted with either HBV or HCV, two known inciting agents of hepatocarcinogenesis in the absence of cirrhosis.[33,34] Furthermore, as all other published studies on this topic, the study was retrospective in nature, which may have resulted in some limitations with regard to data selection, as well as selection bias for receipt of surgery. Lastly, although the multi-institutional study design offered benefits in terms of higher statistical power and international generalizability of the results, collaborating with multiple institutions limited the ability to easily standardize all diagnostic and treatment criteria.

CONCLUSIONS

After resection of HCC in the setting of no cirrhosis, more than one-half of patients were alive after 5 years. However, even among patients with no cirrhosis, recurrence was common. Factors associated with disease-free or OS included tumor characteristics, such as tumor size and grade, capsule, vascular invasion, and presence of satellite lesions. Whereas noncirrhotic patients may lack the classic “field-defect” of a cirrhotic liver, these patients may harbor a molecular field defect that differs from that of a cirrhotic liver. Future studies should be designed to understand the genomic profile of these livers to provide information regarding the underlying reasons that predisposes noncirrhotic livers to form HCC.

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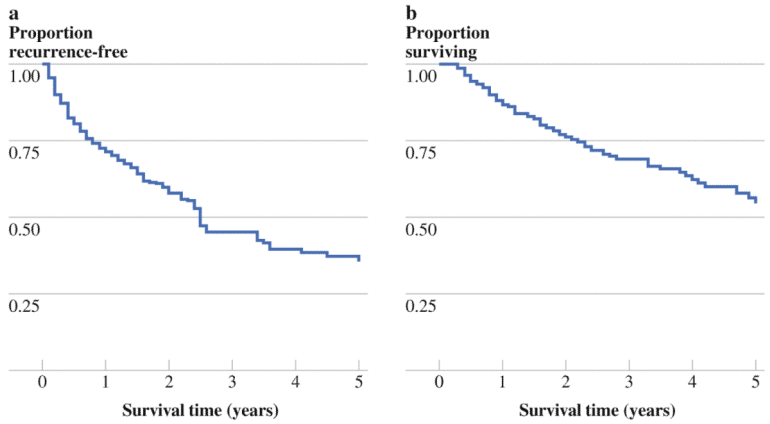

FIG. 1.

a Recurrence-free survival of noncirrhotic patients with hepatocellular carcinoma. **b** Overall survival of noncirrhotic patients with hepatocellular carcinoma

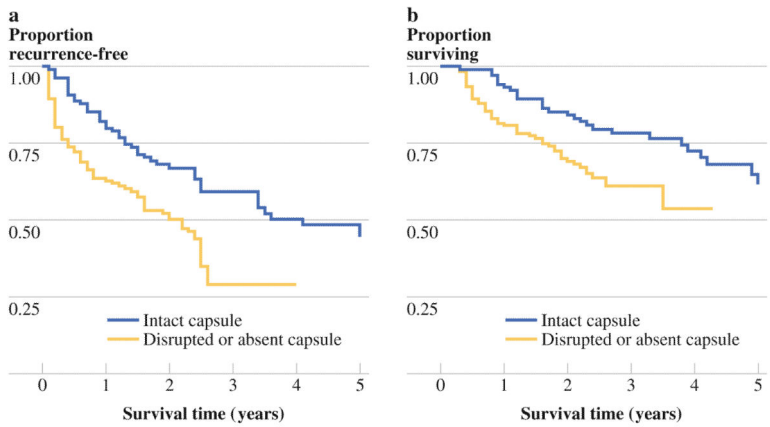

FIG. 2.

a Recurrence-free survival of noncirrhotic HCC patients with intact versus disrupted or completely absent tumor capsule undergoing hepatectomy with curative treatment intent ($p < 0.001$, log-rank test). **b** Overall survival of noncirrhotic HCC patients with intact versus disrupted or completely absent tumor capsule undergoing hepatectomy with curative treatment intent ($p = 0.016$, log-rank test)

TABLE 1

Patient and disease characteristics (n = 334)

Characteristic	No.	%
Age at diagnosis, yr; median (range)	58 (9–85)	
Male gender	258	77.2
Race		
Caucasian	170	51.5
African-American	24	7.3
Asian	136	41.2
Comorbidity (n = 201)		
Hypertension	109	54.2
Hyperlipidemia	47	23.4
Ischemic heart disease	43	21.4
Noninsulin-dependent diabetes mellitus	39	19.4
Insulin-dependent diabetes mellitus	12	6
Hemochromatosis	4	2
Other	43	21.4
Hepatitis status		
No chronic viral hepatitis	163	48.8
Hepatitis B	129	38.6
Hepatitis C	45	13.5
Both hepatitis B and C	3	0.9
Significant tobacco smoking history (≥10 pack × years)	94	31.4
History of alcohol abuse	42	12.6
Solitary tumor	269	80.5
Tumor size, cm; median (range)	6.5 (1.1 – 40.2)	
Bilobar tumor distribution	64	19.2
Portal vein invasion	22	6.6
Macrovascular invasion	57	17.6
Microvascular invasion	63	19.5
Adjacent organ invasion	9	2.8
Presence of satellite lesions	67	20.9
Presence of intrahepatic metastases	30	9.3
Presence of extrahepatic disease (n = 202)	18	8.9
Regional lymph node metastasis (n = 322)	5	1.6
Distant metastasis (n = 202)	18	8.9
Edmonson grade		
Well differentiated	59	18.2
Moderately differentiated	84	25.8
Poorly differentiated	176	54.2
Undifferentiated	6	1.8
Tumor capsule (n = 254)		

Characteristic	No.	%
Intact	122	48
Disrupted	57	22.4
Absent	75	29.5
TNM stage (*n* = 194)		
I	102	52.6
II	16	8.2
III	55	28.4
IV	21	10.8
Tumor within Milan criteria (*n* = 189)	29	15.3
Metavir fibrosis grade		
0 (no scarring)	160	82.5
1 (minimal portal fibrosis without septa)	28	14.4
2 (portal fibrosis with few septa)	4	2.1
3 (numerous septa without cirrhosis)	2	1
Steatosis		
Absent	158	80.6
Mild	24	12.2
Moderate	10	5.1
Severe	4	2

TABLE 2

Treatment characteristics (*n* = 334)

Characteristic	No.	%
Preoperative treatment	28	8.4
TACE	20	6
Cytotoxic chemotherapy	6	1.8
Biologic agents	6	1.8
Portal vein embolization	7	2.1
Treatment type		
Resection	312	93.4
Resection & ablation	7	2.1
Transplantation	3	0.9
TACE	12	3.6
Extent of liver resection		
Minor hepatectomy (< 3 segments)	229	71.8
Major hepatectomy (≥ 3 segments)	90	28.2
Surgical margins		
R0 (microscopically negative)	303	94.1
R1 (microscopically positive)	11	3.4
R2 (macroscopically positive)	8	2.5
Lymphadenectomy	37	11.5
Hepatoduodenal ligament	27	75
Celiac/aorto-caval	2	5.6
Hepatoduodenal + celiac/aorto-caval	7	19.4
Treatment intent		
Curative	316	94.6
Palliative	18	5.4
Intraoperative blood loss, mL; median (range) (*n* = 270)	300 (20–4200)	
PRBC transfusion (*n* = 193)	71	36.8
Units; median (range)	3 (0–17)	
Operative time, hr; median (range) (*n* = 98)	3.3 (1.0–13.3)	
Length of hospital stay, days; median (range)	13 (1–72)	
Complication severity (Clavien–Dindo classificatic (*n* = 74)		
Mild (grade I–II)	59	79.7
Severe (grade III–V)	15	20.3
Postoperative treatment	127	38.4
TACE	74	22.4
Chemotherapy	33	10
Doxorubicin-based (*n* = 26)	14	53.8
Sorafenib-based (*n* = 26)	8	30.8
Other (*n* = 26)	7	26.9
Radiotherapy	3	0.9

TACE transarterial chemoembolization, *PRBC* packed red blood cell

TABLE 3

Predictors of recurrence-free and overall survival

Prognostic factor	*n* (%)	Recurrence-free survival (RFS)			Overall survival (OS)		
		Univariate	Multivariate		Univariate	Multivariate	
		p value	HR (95 % CI)	*p* value	*p* value	HR (95 % CI)	*p* value
Hepatitis B or C	171 (51)	0.123	–		0.989	–	
Smoking	94 (31)	0.923	–		0.423	–	
AFP ≥ 200 ng/mL	166 (57)	<0.001	–		0.005	–	
Alkaline phosphatase ≥ 120 IU/L	96 (31)	0.117	1.82 (1.19–2.77)	0.006	<0.001	–	
Multiple lesions	64 (19)	0.008	–		0.193	–	
Tumor size ≥ 5 cm	230 (70)	0.070	–		<0.001	2.27 (1.27–4.07)	0.006
Poor tumor differentiation[a]	182 (56)	<0.001	1.4 (1.01–1.95)	0.046	<0.001	–	
Microvascular invasion	63 (20)	0.208	–		0.094	–	
Macrovascular invasion	57 (18)	<0.001	2.18 (1.31–3.61)	0.003	<0.001	2.72 (1.62–4.56)	<0.001
Adjacent organ invasion	9 (3)	0.213	–		0.002	3.34 (1.18–9.51)	0.024
Intact tumor capsule[b]	122 (48)	<0.001	0.46 (0.29–0.73)	0.001	0.016	0.51 (0.32–0.82)	0.005
Satellite lesions	67 (21)	<0.001	1.90 (1.85–4.54)	<0.001	<0.001	2.13 (1.28–3.54)	0.004
Intrahepatic metastases	30 (9)	<0.001	2.59 (1.28–5.23)	0.008	0.105	–	
Positive surgical margins	19 (6)	0.237	–		0.803	–	
Postoperative complications	112 (35)	0.056	–		0.137	–	

The multivariate models on RFS and OS included 217 and 239 patients, respectively, due to missing data or nonapplicability *HR* hazards ratio, *AFP* alpha fetoprotein

[a] Undifferentiated or poorly differentiated (Edmondson grades 3–4) versus moderately or well-differentiated tumors (Edmondson grades 1–2)

[b] Intact capsule versus disrupted capsule or absence of capsule