Research Article

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Liver resection for hepatocellular carcinoma in 313 Western patients: Tumor biology and underlying liver rather than tumor size drive prognosis

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Background & Aims: Treatment decisions for hepatocellular carcinoma are mostly guided by tumor size. The aim of this study was to analyze resection outcomes according to tumor size and characterize prognostic factors.

Methods: Patients resected at a Western center between 1989 and 2010 were grouped by largest tumor size: <50 mm, 50–100 mm, and >100 mm. The primary end points were overall- and recurrence-free survival. Univariate associations with primary endpoints were entered into a Cox proportional hazard regression model.

Results: Three hundred thirteen patients underwent resection: 111 (36%) had tumors <50 mm, 113 (36%) had tumors between 50 and 100 mm, and 89 (28%) had tumors >100 mm. Five-year overall and disease-free survival rates for the three groups were 67%, 46%, and 34%, and 32%, 27%, and 27%, respectively. Thirty-five patients, mostly from <50 mm group, underwent transplantation which was associated with a 91% 5 year survival rate. Tumor size was not an independent predictor of overall or recurrence-free survival on multivariate analyses. Independent predictors of decreased overall survival were: intraoperative transfusion (HR = 2.60), cirrhosis (HR = 2.42), poorly differentiated tumor (HR = 2.04), satellite lesions (HR = 1.69), alpha-fetoprotein >200 (HR = 1.53), and microvascular invasion (HR = 1.48). The use of salvage transplantation was an independent predictor of improved survival (HR = 0.21). Recurrence-free survival was predicted by intraoperative transfusion (HR = 2.15), poorly differentiated tumor (HR = 1.87), microvascular invasion (HR = 1.71) and cirrhosis (HR = 1.69).

Conclusion: By studying a large group of patients across a distribution of tumor sizes and background liver diseases, it is demonstrated that size alone is a limited prognostic factor. Tumor biology and condition of the underlying liver are better prognosticators and should be given closer attention. Although hampered by recurrence rates, resection is safe and offers good overall survival. In addition, it may allow for better selection for salvage transplantation after consideration of histopathological risk factors.

Introduction

Surgical resection and liver transplantation remain the gold standard therapies for hepatocellular carcinoma (HCC). Liver transplantation is considered the best curative treatment by treating both the tumor and the underlying liver disease and it is the only surgical option in patients with decompensated cirrhosis [1]. However, it suffers major limitations: most allocation systems limit transplantation to early HCC and, more importantly, it is significantly hampered by severe donor organ shortage. By contrast, liver resection is readily available and not limited by tumor size, its only limitations are determined by functional hepatic reserve and portal hypertension. This recognizes that surgical resection has become increasingly safe, and that new techniques such as laparoscopy have demonstrated reduced morbidity in selected cirrhotic patients [2–13].

The objective of this study was to analyze the prognostic factors of survival after resection for HCC in a large Western series of patients with various causes of liver disease at a tertiary referral center offering all modalities of treatment. Since outcomes for HCC are generally believed to be related to tumor size, patients were stratified according to tumor diameter.

Keywords: Prognosis; Pathology; Cirrhosis; Transplantation; Liver disease.
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Abbreviations: HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein.

Patients and methods

Patients who underwent liver resection for HCC between March 1989 and September 2010 at Hôpital Henri Mondor, Creteil, France were studied. Patients were divided into three groups based on largest tumor size at pathology: <50 mm, 50–100 mm, and >100 mm. These three demarcations were in consideration of the Milan criteria, American Joint Committee on Cancer, Liver Cancer Study Group of Japan, and literature comparing tumors less or greater than 100 mm [10]. These divisions have implications with regard to treatment, underlying parenchyma, and a broad body of outcome research for comparison. Raw data from a prospective database were analyzed.

Evaluation and operative management

All patients with HCC were discussed at a weekly multidisciplinary meeting. Contraindications to surgery included poor functional status, decompensated liver disease and distant metastases. Patients with preoperatively diagnosed main portal vein, main hepatic vein or inferior vena cava tumor thrombus were excluded from this study (n = 20).

Patients with HCC and no recognized cirrhosis were directed towards resection. In such patients, operative management was pursued for both solitary and multiple lesions when curative resection was anticipated. In cases with recognized compensated cirrhosis, our practice has been to consider resection for solitary lesions based on best available imaging, and transplantation in patients with multiple lesions within Milan criteria [14]. Occasionally, cirrhotic patients with more than one nodule and a contra-indication to transplantation were considered for resection. Selection criteria for resection in cirrhotic patients included solitary nodule, Child-Pugh A class, no esophageal varices, a platelet count $\geqslant 100 \times 10^9$/L, and an anticipated remnant liver volume >40%. If the resection would require $\leqslant 1$ segment, select patients with Child-Pugh B cirrhosis and/or moderate portal hypertension (platelet count 50–100 $\times 10^9$/L, grade 1 varices) were considered [8]. Since 2002, portal vein embolization was routinely performed before right hepatectomy in the presence of chronic liver disease. More recently, sequential transarterial chemoembolization and portal vein embolization have been used in preparation to right or extended right hepatectomy in selected cases of right sided large HCC. The laparoscopic approach has been implemented for limited resection of peripheral HCC <50 mm located in segments 2–6 since 1998 [6,8,14]. Most resections were intended to be anatomic in order to resect the tumor's portal territory. However, in a few patients with peripheral lesions and suboptimal liver function or portal hypertension, partial resection including the tumor and an intended 1–2 cm margin were performed.

Follow-up included liver function tests, alpha-fetoprotein (AFP) and triple-phase CT or MRI at 3 months post-operatively, and every 3 months for two years. Thereafter, laboratories and imaging were repeated at 6 month intervals through 5 years, and annually thereafter. Patients with tumor recurrence within Milan criteria were considered for salvage transplantation; selection criteria for transplantation, including age less than 65 years, have been previously published [14]. Other treatment options for recurrences included repeat surgery, percutaneous ablation, transarterial treatment, sorafenib or supportive care as indicated.

As this study included patients treated before implementation of the MELD score, INR was not available for all cases. Therefore liver function was defined by normal bilirubin and prothrombin time in non-cirrhotic patients and by the Child-Pugh classification for cirrhotic patients.

Lesion size is reported as longest diameter on cross-sectional imaging and on gross pathology. In the current investigation, multiple lesions were determined by preoperative imaging or at surgery and categorized distinctly from satellite lesions, which were gross pathological findings of small lesions located in the vicinity of the resected tumor and undetected by imaging.

End points and statistical analysis

The primary end points were overall survival and recurrence-free survival. Overall survival was from date of resection to last living visit or loss to follow-up. Recurrence-free survival was measured from date of resection to hepatic recurrence or death. Post-operative deaths were included in all time-to-event analyses. The Clavien classification for surgical complications was used to characterize surgical morbidity and mortality [15].

Continuous variables, reported as median and range, were compared with the Student *t* test or Mann–Whitney–Wilcoxon test for variables with abnormal distribution, and categorical variables with Pearson's χ^2 or Fisher's exact tests where appropriate. Univariate associations between clinical variables and the primary end points were conducted by the Log-rank test and those with $p < 0.1$ were entered into a step-down Cox proportional hazard regression model. Analyses were performed using Stata 11 (StataCorp, College Station, Texas). The Institutional Review Board approved this protocol.

Results

Preoperative details

Three hundred thirteen patients were studied: 111 patients (36%) had tumors <50 mm, 113 (36%) had tumors between 50 and 100 mm, and 89 (28%) had tumors >100 mm (Table 1). An etiology of liver disease was recognized in 82% of the patients, with hepatitis B and C viruses being present in 25% and 24% respectively. Patients with larger tumors were more likely to

Table 1. Clinical characteristics of patients with HCC undergoing resection.

	Group	<50 mm	50-100 mm	>100 mm	*p* value
Number of patients	313	111 (36)	113 (36)	89 (28)	-
Male sex	250 (80)	86 (78)	94 (83)	70 (79)	0.535
Age, yr	59 ± 14	62 ± 9	59 ± 14	55 ± 16	<0.001
Recognized etiology of liver disease					
None	57 (18)	1 (1)	17 (15)	39 (43)	
Hepatitis B virus	77 (25)	25 (23)	27 (24)	25 (28)	
Hepatitis C virus	76 (24)	41 (37)	29 (26)	6 (7)	
Alcohol	61 (20)	26 (23)	24 (21)	11 (12)	
Other liver pathology	42 (13)	18 (16)	16 (14)	8 (9)	<0.001
Normal liver function*§	303 (97)	108 (97)	107 (95)	88 (99)	0.228
Platelet count <100,000/μl	35 (11)	24 (22)	11 (10)	0	<0.001
AFP >200 ng/ml	87 (28)	14 (13)	34 (30)	39 (44)	<0.001
Pre-operative imaging					
Index tumor size, mm	69 ± 44	30 ± 9	65 ± 20	124 ± 35	<0.001
Solitary tumor	238 (77)	86 (78)	88 (78)	64 (72)	0.517

*Defined by normal bilirubin and prothrombin time.
§Includes Child-Pugh A patients with cirrhosis.