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ORIGINAL RESEARCH

Outcomes Following Resection of Hepatocellular Carcinoma in the Absence of Cirrhosis

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Abstract

Background Hepatocellular carcinoma (HCC) occasionally occurs in non-cirrhotic patients; however, outcomes for these patients are not extensively documented.

Methods We performed an institutional review of patients without cirrhosis who underwent resection for HCC. Clinical data were evaluated to identify factors impacting recurrence-free survival (RFS) and overall survival (OS).

Results Forty-two patients underwent hepatectomy for HCC in the absence of cirrhosis over a 10-year period. Median follow-up was 22 months. For the entire cohort, 1-, 3-, and 5-year RFS was 62%, 42%, and 38% and 1-, 3-, and 5-year OS was 78%, 60%, and 49%, respectively. On univariate analysis, RFS was significantly worse for patients with a disrupted/absent tumor capsule ($p = 0.027$), vascular invasion ($p = 0.030$), elevated alkaline phosphatase ($p = 0.004$), and tumor size > 10 cm ($p = 0.016$). OS was significantly worse for patients with a disrupted/absent tumor capsule ($p = 0.044$), obesity ($p = 0.036$), and elevated alkaline phosphatase ($p = 0.007$) with a trend towards decreased OS for tumor size > 10 cm ($p = 0.07$).

Conclusions Patients undergoing resection for HCC in the absence of cirrhosis have fairly high recurrence and modest survival rates. Pre-operative alkaline phosphatase, tumor size, tumor encapsulation, and vascular invasion are important prognostic factors.

Keywords Hepatocellular carcinoma · Non-cirrhotic · Surgery

Background

Hepatocellular carcinoma (HCC) represents the most common primary hepatic malignancy and is a leading cause of cancer-related death worldwide [1]. HCC most commonly occurs in the setting of cirrhosis related to viral hepatitis, alcohol, non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH), long-standing biliary obstruction, or rare conditions such as hemochromatosis or alpha-1 antitrypsin deficiency. For appropriately selected patients with HCC and cirrhosis, liver transplantation (LT) offers 5-year survival rates as high as 60–75% [2–4].

HCC occasionally occurs in the absence of cirrhosis; however, outcomes for these patients are not extensively documented, particularly in the USA. Unlike patients with cirrhosis involved in a regular screening program for early detection of HCC, patients without cirrhosis are at risk for presenting at a more advanced stage. As these patients have otherwise well-preserved liver function, hepatectomy is the standard treatment provided lack of extrahepatic disease, appropriate performance status, and an adequate future liver remnant. However, unlike well-defined criteria and outcomes for LT in cirrhotic HCC, selection of patients most likely to achieve long-term survival following hepatectomy for HCC in the absence of cirrhosis is not established. The purpose of the

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current investigation was to examine outcomes and predictors of recurrence and survival following hepatic resection for HCC in patients without cirrhosis.

Methods

We performed a retrospective review of patients with a diagnosis of HCC at University of Tennessee Health Science Center-Memphis-affiliated hospitals. Institutional review board approval was obtained prior to data retrieval and analysis. Patients with fibrolamellar tumors and a hepatic fibrosis score > 3 were excluded. Demographic, laboratory, operative, pathology, and follow-up data were collected. Major hepatectomy was defined as resections including ≥ 3 segments. Complications were graded using the Clavien-Dindo classification system [5].

Pathology specimens were reviewed to confirm the diagnosis and evaluate histopathology features including tumor grade, vascular invasion, tumor capsule (presence, absence, and integrity), margin status, and the presence and extent of fibrosis and steatosis of the non-tumor-bearing liver. Tumor (T) and node (N) classification was determined according to the 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual [6].

Statistical analyses were performed using chi-square or Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables. Survival probabilities were estimated using the Kaplan-Meier product-limit method for recurrence-free survival (RFS) and overall survival (OS). These were compared between groups with a log-rank test. All statistical analyses were performed using SPSS Version 23 (Chicago, IL). A p value of less than 0.05 was considered significant.

Results

Between March 2005 and August 2016, 640 patients were identified with a diagnosis of HCC. Among these, 42 (15%) underwent hepatectomy for HCC in the absence of cirrhosis. Demographic data, operative/peri-operative details, and pathology findings are listed in Table 1. Median age at diagnosis was 62 years (range, 21–83); 28 patients (67%) were male and the majority Caucasian (71%). Median BMI was 26.9 kg/m^2 (range, 18–38). HBV and HCV were present in 2 and 8 patients, respectively, and 1 patient had co-infection. Preoperative serum alpha-fetoprotein (AFP) was available in 26 patients and elevated (> 9 ng/dl) in 20 (77%), with a median AFP level of 25 ng/dl (range, 0.7–15,677). Only 2 patients presented with clinical jaundice (with bilirubin levels of 11.2 and 13.6 mg/dl, respectively) and at operation, each had biliary obstruction resulting from an intraductal tumor thrombus.

Table 1 Demographic, operative, and pathology characteristics (N = 42)

Demographics	
Median age (years)	62 (21–83)
Sex	
Male	28 (67%)
Female	14 (33%)
Race	
Caucasian	30 (71%)
African-American	9 (22%)
Asian	3 (7%)
Median BMI (kg/m^2)	
Pre-operative clinical data	
No viral hepatitis	31 (74%)
HBV	2 (4%)
HCV	8 (19%)
HBV and HCV	1 (2%)
Alpha-fetoprotein (0–9 ng/ml)	
Normal	6 (14%)
Elevated	20 (48%)
Unknown	16 (38%)
Albumin < 3.4	12 (29%)
Bilirubin > 1.0 mg/dl	9 (21%)
Alk Phos >117 units/ml	17 (40%)
AST > 37 units/ml	26 (62%)
ALT > 56 units/ml	17 (40%)
INR > 1.0	18 (43%)
Pre-operative therapy	3 (7%)
Operative/peri-operative data	
Major hepatectomy	26 (62%)
Minor hepatectomy	16 (38%)
Ablation (in conjunction with resection)	3 (7%)
EBL (cm^3)	550 (100–4000)
PRBC transfusion	11 (25%)
LOS (nights)	7 (2–52)
30-day complication	
None	27 (64%)
Grade I/II	4 (10%)
Grade III/IV	10 (24%)
Grade V	1 (2%)
90-day mortality	4 (10%)
Pathology data	
Solitary tumor	23 (54%)
Median tumor size (cm)	8.1 (1–21)
< 5	10 (24%)
5–10	16 (38%)
> 10	16 (38%)
R0 resection	34 (81%)
Satellite lesions present	17 (40%)
Intrahepatic metastases present	5 (12%)
Tumor capsule	

Table 1 (continued)

Present and intact	10 (24%)
Present with disruption	13 (31%)
Absent	17 (40%)
Unknown	2 (5%)
Portal vein invasion	4 (14%)
Microvascular invasion	19 (44%)
Edmondson and Steiner grade	
1	13 (31%)
2	15 (36%)
3	11 (26%)
4	2 (5%)
Unknown	1 (2%)
Hepatic fibrosis grade	
F0	19 (45%)
F1	13 (31%)
F2	7 (17%)
F3	3 (7%)
Hepatic steatosis	
None	9 (21%)
Minimal	31 (74%)
Moderate	2 (5%)
Adjacent organ invasion	3 (7%)
AJCC T classification	
T1	14 (33%)
T2	14 (33%)
T3	10 (24%)
T4	4 (10%)
AJCC N classification	
N0	17 (40%)
N1	1 (2%)
NX	24 (58%)
AJCC stage	
I	14 (33%)
II	15 (36%)
III	12 (29%)
IV	1 (2%)

HBV, hepatitis B virus; *HCV*, hepatitis C virus; *Alk Phos*, alkaline phosphatase; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *INR*, international normalized ratio; *EBL*, estimated blood loss; *PRBC*, packed red blood cell; *AJCC*, American Joint Committee on Cancer

A solitary tumor was present in 23 (54%) patients with the majority (75%) having a tumor size > 5 cm. Major hepatectomy (≥ 3 contiguous segments) was performed in 26 patients (62%). Post-operative 30-day complication rate was 36% and 90-day mortality was 9.5%. The majority of patients demonstrated no (F0) or minimal (F1) fibrosis and had no or minimal steatosis in non-tumor-bearing liver.

Median follow-up (including 4 patients with 90-day mortality) was 22 months (range, 0–125). Twenty-two patients (52%) had developed disease relapse with a median time to recurrence of 9 months (range, 2–78). Sites of initial recurrence included liver only in 11 (50%), liver with an extrahepatic site (peritoneum, lungs, bone, or brain) in 7 (32%), and extrahepatic sites only in 4 (18%) patients. Fifteen (68%) patients with recurrent disease had died of disease progression, 6 (27%) were alive with disease, and 1 remains without evidence of disease following resection of an isolated intrahepatic recurrence. Management strategies for recurrent disease were varied and are shown in Table 2. There were 16 patients who remained alive without recurrent disease with a median follow-up of 74 months (4–119).

For the entire cohort, 1-, 3-, and 5-year RFS was 62%, 42%, and 38% and 1-, 3-, and 5-year OS was 78%, 60%, and 49%, respectively. For AJCC stage I, II, and III patients, 5-year RFS and OS were 67%, 49%, and 9% ($p = 0.095$) and 74%, 62%, and 11% ($p = < 0.001$), respectively. Analysis of potential prognostic factors for RFS and OS is shown in Table 3. Increasing tumor size ($p = 0.016$), disruption or absence of a tumor capsule ($p = 0.027$), portal vein invasion ($p = 0.029$), microvascular invasion ($p = 0.009$), and elevated pre-operative alkaline phosphatase (0.004) were each significantly associated with decreased RFS. There was a trend towards decreased RFS for patients with elevated pre-operative AST levels ($p = 0.070$) and BMI ≥ 30 kg/m^2 ($p = 0.100$). Among those with tumor relapse, 16 (72%) developed recurrence ≤ 1 year from the time of resection. The median OS for these patients was 19 months (range, 4–37). Of the 4 patients with portal vein invasion, all had documented recurrence at 3, 6, 8, and 29 months, respectively. Three of these patients had died and 1 is alive and receiving palliative therapy.

OS was significantly lower for patients with BMI ≥ 30 kg/m^2 (0.036), disruption or absence of a tumor capsule ($p = 0.044$), and elevated pre-operative alkaline phosphatase ($p = 0.007$) and AST levels (0.048). There was a trend towards decreased OS for patients with increasing tumor size ($p = 0.070$) and portal vein and microvascular invasion ($p = 0.092$). Five-year RFS and OS were lower for patients requiring intraoperative PRBC transfusion (13% vs 48%; 38% vs 53%) and with intrahepatic metastases (25% vs 40%; 20% vs 54%); however, these did not reach statistical significance.

Discussion

Although HCC most often occurs in the setting of cirrhosis, 10–20% of cases arise in non-cirrhotic livers [7]. Unlike

Table 2 Management of recurrent disease ($N = 22$)

Liver-only recurrence	11 (50%)
TACE or TARE ± sorafenib	4
Chemotherapy ± sorafenib	3
Resection	1
SBRT	1
Hospice	1
Distant ± liver recurrence	11 (50%)
Chemotherapy ± sorafenib	8
SBRT to isolated extrahepatic site	1
Resection of isolated extrahepatic site	1
Hospice	1

TACE, transarterial chemoembolization; *TARE*, transarterial radioembolization; *SBRT*, stereotactic body radiation therapy

patients with cirrhosis, major hepatectomy remains an option for these patients because of otherwise preserved liver function. We identified a subset of patients, 15% within our tumor registry, with HCC without cirrhosis that underwent curative-intent hepatectomy.

While the etiology of HCC in non-cirrhotic livers is not entirely clear, risks include anabolic steroid use, hereditary metabolic disorders, exposure to industrial chemicals, NAFLD, and prior adenoma [8]. In the current series, 5-year OS was 49% and tumor recurrence within 1 year of resection was 38%, demonstrating that even in the absence of advanced liver disease patients with HCC have a relatively poor outcome. Interestingly, these findings are within the range of survival of reported series of hepatic resection for patients with HCC and cirrhosis [9–11].

Factors associated with recurrence and survival in non-cirrhotic HCC patients vary between studies and have included tumor size, multifocality, patient age, extent of resection, elevated AFP, elevated liver function tests, vascular invasion, satellite lesions, poor tumor differentiation, and disruption or absence of a tumor capsule [7, 12–19]. Consistent with this, we found that increasing tumor size, disruption or absence of a tumor capsule, vascular invasion, elevated alkaline phosphatase, elevated transaminases, and obesity had an impact on recurrence and/or survival.

The disappointing recurrence and survival rates observed in our study are similar to outcomes reported in other series [7, 12–19]. This is likely related, in part, to presentation with more advanced tumors. As these patients would not typically be involved in a routine surveillance program for early tumor detection, it was not surprising to find a median tumor size of 8 cm and that nearly 40% had a tumor > 10 cm. Tumor size was a significant predictor of recurrence (Table 3, Fig. 1b), consistent with other reported series of HCC in non-cirrhotic patients [12, 19, 20]. Although increased tumor size is associated with poorer outcomes, select patients with large tumors may still achieve long-term benefit. Truant et al. evaluated non-cirrhotic HCC patients relative to tumor size and found similar 5-year RFS rates between those with tumors > 8 cm (82%) and < 8 cm (89%) ($p = 0.73$) when no vascular invasion or hepatic fibrosis was present. Furthermore, Yang et al. described a subset of solitary large HCC (> 5 cm) for which patients demonstrated relatively favorable 5-year RFS and OS rates [21]. In previous work, these authors demonstrated a different gene expression profile between this subset of solitary large tumors and nodular HCC, the latter having significant upregulation of several genes involved in invasion and metastases [22].

In our study, disruption or absence of a tumor capsule was a significant predictor of decreased RFS and OS (Table 3, Fig. 1d, h). Of the 10 patients with an intact tumor capsule, median follow-up was 62 months (range, 4–119), and only 2 had developed recurrent disease. Tumor capsule formation may occur as compression and necrosis of surrounding parenchyma stimulate an inflammatory reaction resulting in deposition of a peri-tumoral collagen-rich fibrous layer [23, 24]. In a study by Wu et al., the presence of a tumor capsule resulted in more favorable outcomes for patients with HCC > 5 cm [23]. Furthermore, in a multi-institutional study from centers in the USA, Europe, and China, absence or disruption of a tumor capsule was associated with a marked decrease in RFS and OS [9]. Others have shown tumor encapsulation protects against vascular invasion [24]. Collectively, these data suggest that presence of an intact tumor capsule is a favorable prognostic factor in patients with HCC.

In the current study, elevated pre-operative alkaline phosphatase (> 117 units/ml) was significantly associated with worse RFS and OS (Table 3, Fig. 1a, e). Others have also identified elevated alkaline phosphatase to be associated with worse outcomes in both cirrhotic and non-cirrhotic patients [12, 15]. It may be that this is reflective of compression of small intrahepatic ducts and that the finding of elevated alkaline phosphatase serves as a marker of tumors with less favorable biology.

We did include 11 patients with documented HBV and/or HCV. Admittedly, this resulted in a more heterogeneous cohort. HCC in patients with viral hepatitis generally arises in advanced fibrosis or cirrhosis and results from the sequential progression of regenerative to dysplastic to neoplastic nodules. The molecular mechanisms driving HCC development in this setting are well described [25]. However, it has also been demonstrated that HBV and HCV may be carcinogenic independent of the development of cirrhosis [26–28]. Although none of the patients with viral hepatitis in our study had developed cirrhosis, they did have histologic evidence of chronic hepatitis and fibrosis scores ranging from 1 to 3 in non-tumor-bearing liver. In our series, estimated 5-year RFS and OS rates for patients with viral hepatitis were 33% and 55%, respectively, not significantly different than non-infected patients. Similar to non-infected patients, the majority of these presented with large tumors.

We identified that obese patients (BMI ≥ 30 kg/m^2) had worse OS than non-obese patients. Although patients with NASH, a subset of NAFLD, may progress to cirrhosis and HCC, the majority of patients in the current study had no to minimal hepatic steatosis and none had evidence of NASH. It has been reported that steatosis without steatohepatitis may be carcinogenic [29]. Of note, a number of obese patients also had associated diabetes, hyperlipidemia, and hypertension, features associated with the increasingly prevalent metabolic syndrome. Others have also noted this occurrence and suggested that the chronic pro-inflammatory state associated with these co-morbid conditions likely drives the pathogenesis of HCC and other malignancies observed in these patients [30–32].

Table 3 Univariate analysis of prognostic factors for 5-year RFS and OS ($N = 42$)

Characteristic	*N*	5-year RFS (%)	*p* value	5-year OS (%)	*p* value
Age					
< 62	23	33	0.360	35	0.55
≥ 62	19	47		67	
Gender					
Male	27	29	0.550	39	0.175
Female	15	51		69	
Obese (BMI ≥ 30 kg/m^2)					
Yes	14	20	0.100	17	0.036
No	28	46		62	
HBV or HCV					
Yes	11	33	0.722	55	0.824
No	31	37		46	
Elevated AFP (> 9 ng/ml)*					
Yes	22	38	0.776	51	0.934
No	6	20		44	
AFP > 200 ng/ml*					
Yes	8	24	0.691	38	0.460
No	20	34		53	
Bilirubin > 1.0 mg/dl					
Yes	9	33	0.511	33	0.158
No	33	39		53	
Alk Phos > 117 units/ml					
Yes	17	21	0.004	26	0.007
No	25	48		64	
AST > 37 units/ml					
Yes	26	30	0.070	32	0.048
No	16	51		78	
ALT > 56 units/ml					
Yes	17	25	0.387	21	0.028
No	25	43		67	
INR > 1.0					
Yes	18	50	0.171	45	0.798
No	24	29		51	
Major hepatectomy					
Yes	28	37	0.682	54	0.988
No	14	39		40	
PRBC transfusion					
Yes	14	13	0.165	38	0.186
No	28	48		53	
30-day complication					
Yes	15	13	0.394	35	0.028
No	27	48		57	
Tumor size (cm)					
0–4.99	10	65	0.016	75	0.070
5–9.99	16	43		51	
≥ 10	16	13		15	
Satellite lesions					
Yes	17	31	0.479	51	0.872
No	25	45		46	

Table 3 (continued)

Characteristic	*N*	5-year RFS (%)	*p* value	5-year OS (%)	*p* value
Intrahepatic metastases					
Yes	5	25	0.734	20	0.208
No	37	40		54	
Portal vein invasion					
Yes	4	0	0.029	0	0.092
No	38	39		49	
Microvascular invasion					
Yes	19	17	0.009	29	0.092
No	23	55		61	
Edmondson and Steiner grade*					
1/2	28	38	0.621	53	0.423
3/4	13	43		45	
Tumor capsule**					
Intact	10	75	0.027	75	0.044
Disrupted or absent	30	24		38	
Resection margin					
R0	34	36	0.795	49	0.924
R1	8	43		47	
Hepatic fibrosis score					
0/1	32	37	0.863	46	0.696
2/3	10	45		54	
Hepatic steatosis					
Yes	33	36	1.00	44	0.351
No	9	48		76	
AJCC stage (7th ed)					
I	14	67	0.095	74	< 0.001
II	15	49		62	
III	12	9		11	
IV	1	0		0	

*Data missing for 1 patient, **data missing for 2 patients. *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *AFP*, alpha-fetoprotein; *Alk Phos*, alkaline phosphatase; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *INR*, international normalized ratio; *PRBC*, packed red blood cell; *AJCC*, American Joint Committee on Cancer

Although absence of cirrhosis permits an aggressive surgical approach, early recurrences and modest overall survival rates warrant investigation into adjunct or alternative therapies. Truant et al. reported a benefit in RFS and OS in patients at high risk for relapse who were administered adjuvant transarterial chemoembolization (TACE) [20]. This strategy is supported by additional studies demonstrating reduced recurrence and improved survival for patients receiving postoperative TACE following curative-intent resection for tumors > 5 cm or other poor prognostic features [33]. No patient in our series received adjuvant therapy and TACE was reserved as a salvage treatment for unresectable intrahepatic recurrences. However, the findings reported by the previously mentioned studies seem to merit consideration of adjuvant TACE for patients at high risk for recurrence.

The role of LT in non-cirrhotic HCC patients is controversial. Given limitations of organ availability, costs, and issues related to chronic immunosuppression, LT is not considered first-line therapy for patients with resectable HCC in a non-cirrhotic liver. Mergental et al. reported on outcomes of LT as primary or rescue therapy for unresectable HCC in non-cirrhotic patients and found a 5-year OS rate of 59% in patients without macrovascular invasion or lymph node involvement, regardless of tumor size [34]. Moreover, in cases where LT was used to treat recurrent disease, 5-year OS was 83% in patients without macrovascular invasion or lymph node involvement when tumor relapse was > 12 months from initial hepatectomy. Notably, these authors point out that partial hepatectomy is the first choice for treatment in patients with otherwise normal livers. Although we have a robust program at

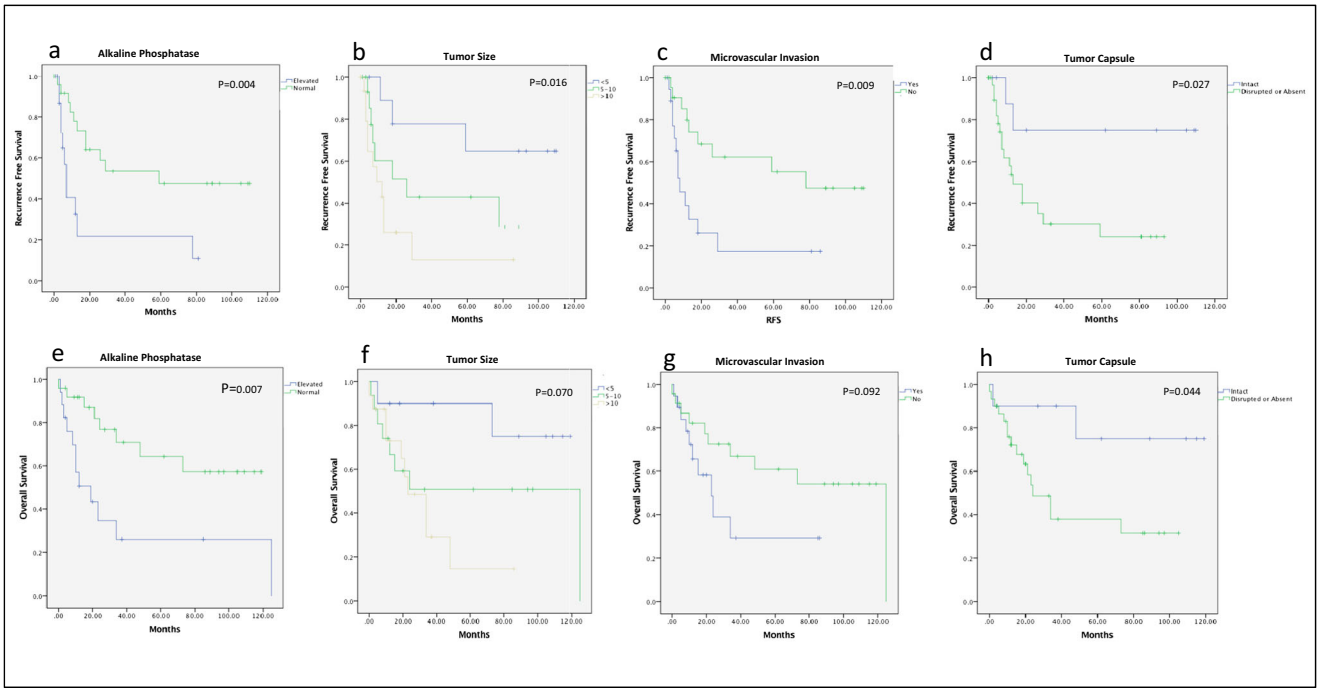

Fig. 1 Kaplan-Meier curves for recurrence-free and overall survival relative to pre-operative alkaline phosphatase (**a**, **e**), tumor size (**b**, **f**), microvascular invasion (**c**, **g**), and tumor capsule (**d**, **h**)

our institution, LT has not been incorporated as salvage therapy for non-cirrhotic patients with recurrent disease.

The current study is limited in that it is a retrospective study of a relatively small number of patients, which precluded meaningful multivariate analysis. We also included patients with known risk factors for HCC including viral hepatitis, fibrosis, and steatosis. However, none of these patients had cirrhosis at the time of diagnosis, and to our knowledge, none had since progressed to cirrhosis. We were surprised to find that tumor differentiation, satellite lesions, and intrahepatic metastases did not significantly impact recurrence or survival; however, this may be related to having a small cohort. Despite these limitations, there are very few reports on outcomes for these patients from the USA, and the current study highlights that even patients with preserved liver function demonstrate high recurrence rates and modest survival outcomes.

Conclusion

HCC most commonly arises in the setting of cirrhosis; however, approximately 10–20% of cases will occur in non-cirrhotic livers. Although these patients have otherwise well-preserved liver function and may safely undergo major hepatectomy, recurrence and survival outcomes remain disappointing. Elevated pre-operative alkaline phosphatase was associated with decreased RFS and/or OS, and it may be that this serves as surrogate marker of tumors with less favorable biology. Important tumor-related factors associated with decreased RFS and OS included increasing tumor size, disruption or absence of a tumor capsule, and vascular invasion. Future analysis of a larger cohort is likely to better define prognostic factors and help select patients most likely to achieve long-term benefit from resection.

Compliance with Ethical Standards

This study did not receive any funding. No author has any financial conflict of interest. This article represents a retrospective review of an institutional experience and does not contain any studies with human participants performed by any of the authors.

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