Assessing the Role of Chronic Hepatocellular Inflammation in Transformation to Cancer among Hepatic Resection Recipients with HBV-Associated HCC

Spiros P. Hiotis, MD[1], PhD; Fotini Manizate, MD[1];
Sasan Roayaie, MD[1]; Daniel M. Labow, MD[1]; M. Isabel Fiel, MD[2];
Swan N. Thung, MD[2]; and Myron E. Schwartz[1], MD

Departments of Surgical Oncology and Pathology, Mount Sinai School of Medicine, New York, NY

MOUNT SINAI SCHOOL OF MEDICINE

MOUNT SINAI SCHOOL OF MEDICINE

Introduction

- Patients with chronic viral hepatitis B (HBV) are subject to an elevated lifetime risk for hepatocellular carcinoma (HCC).
- Although the risk of cancer is highest among those with severe chronic inflammatory liver damage and cirrhosis, the occurrence of HBV-associated HCC in non-cirrhotic patients is also well established.
- The purpose of this study is to quantify the incidence of independence to chronic inflammation in patients with HBV-HCC, and to characterize the clinical features associated with inflammation-independent cancers.

Hypothesis

- Chronic HBV infection is associated with two independent pathways to hepatocarcinogenesis:

  Inflammation-Associated HBV-HCC

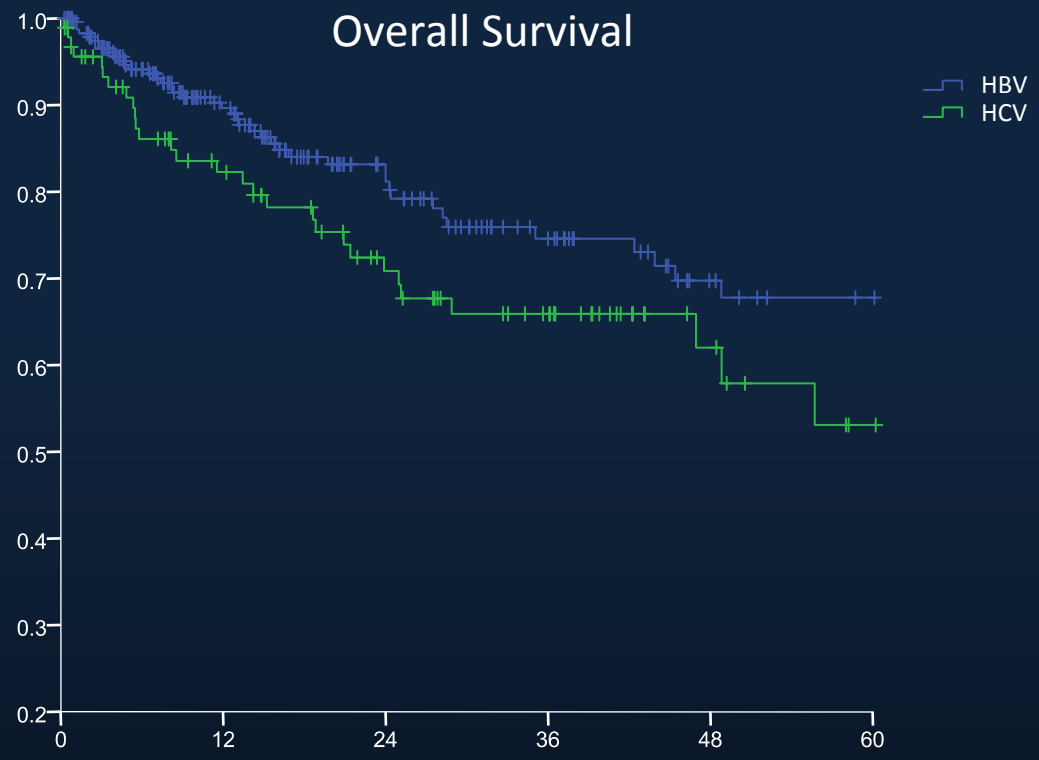
  Inflammation-Independent HBV-HCC

- Inflammation-Associated HBV-HCC arises in patients with severe fibrosis and cirrhosis, occurring as a result of chronic hepatocellular damage analogous to that seen with other inflammation-associated risk factors for HCC (e.g. HCV).

- Inflammation-Independent HCC arises in patients without chronic hepatocellular damage or severe fibrosis, occuring via an independent but parallel pathway to HBV-HCC.

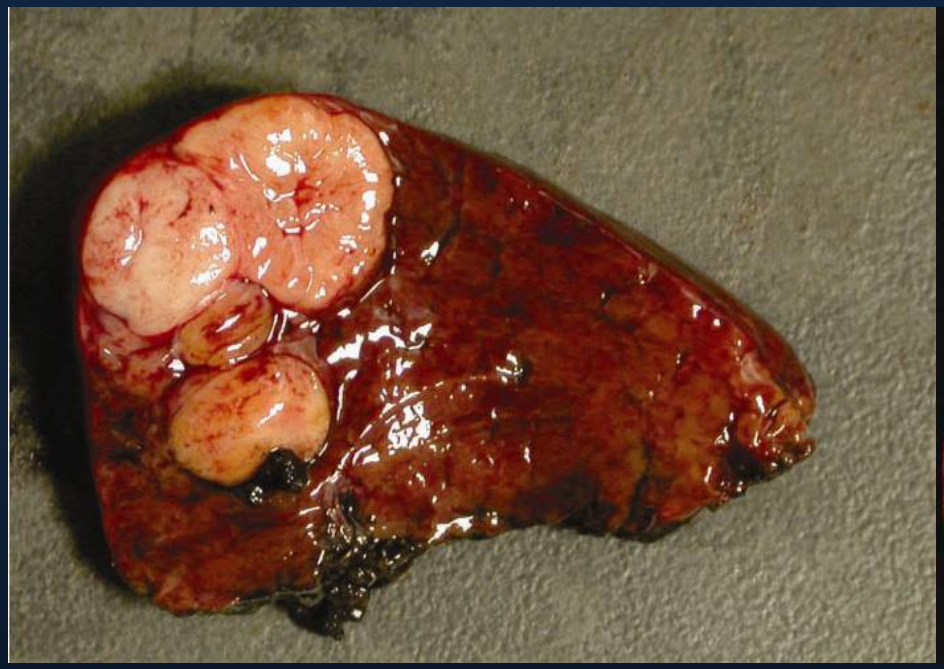
- The incidence and biologic behavior of cancers occurring as a result of the inflammation-independent pathway is a unique characteristic of HBV-HCC.

HCC Overall Survival Following Liver Resection According to Underlying Liver Disease



p<.05

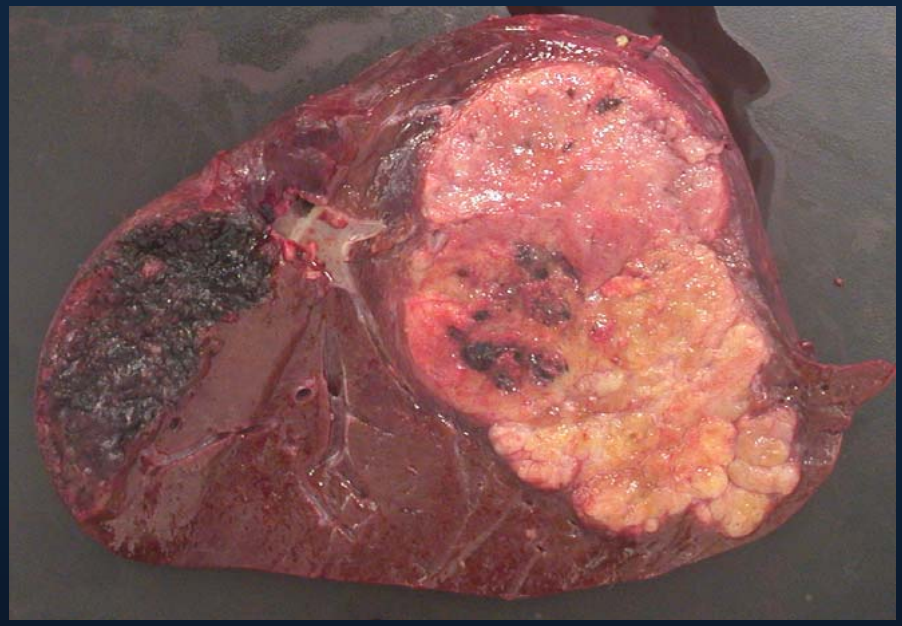
HBV-HCC vs. HCV-HCC:
Mild vs. Severe Parenchymal Fibrosis



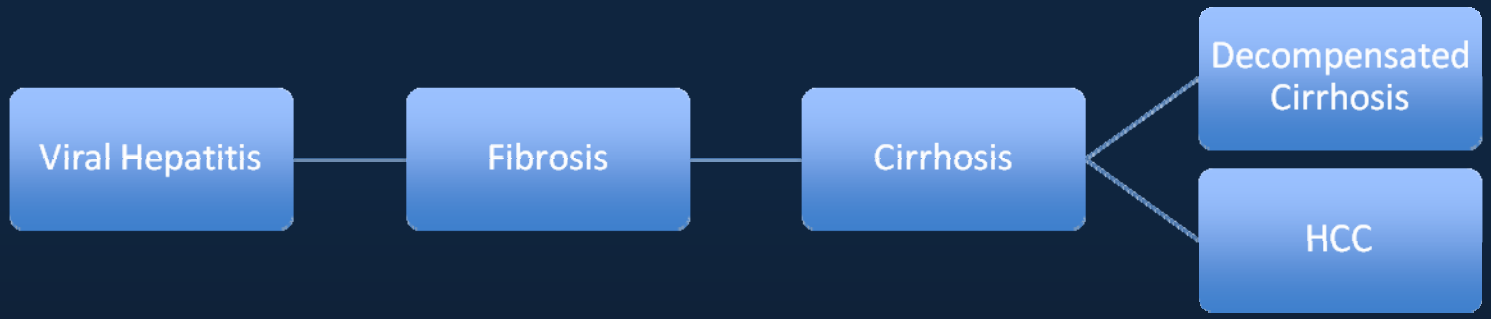
HBV-HCC With Stage 2 Fibrosis in Non-Neoplastic Liver

HCV-HCC With Stage 4 Fibrosis in Non-Neoplastic Liver

HBV-HCC with Normal Non-Neoplastic Liver Parenchyma



Model:
Viral Hepatitis-Associated Hepatocarcinogenesis



Methods

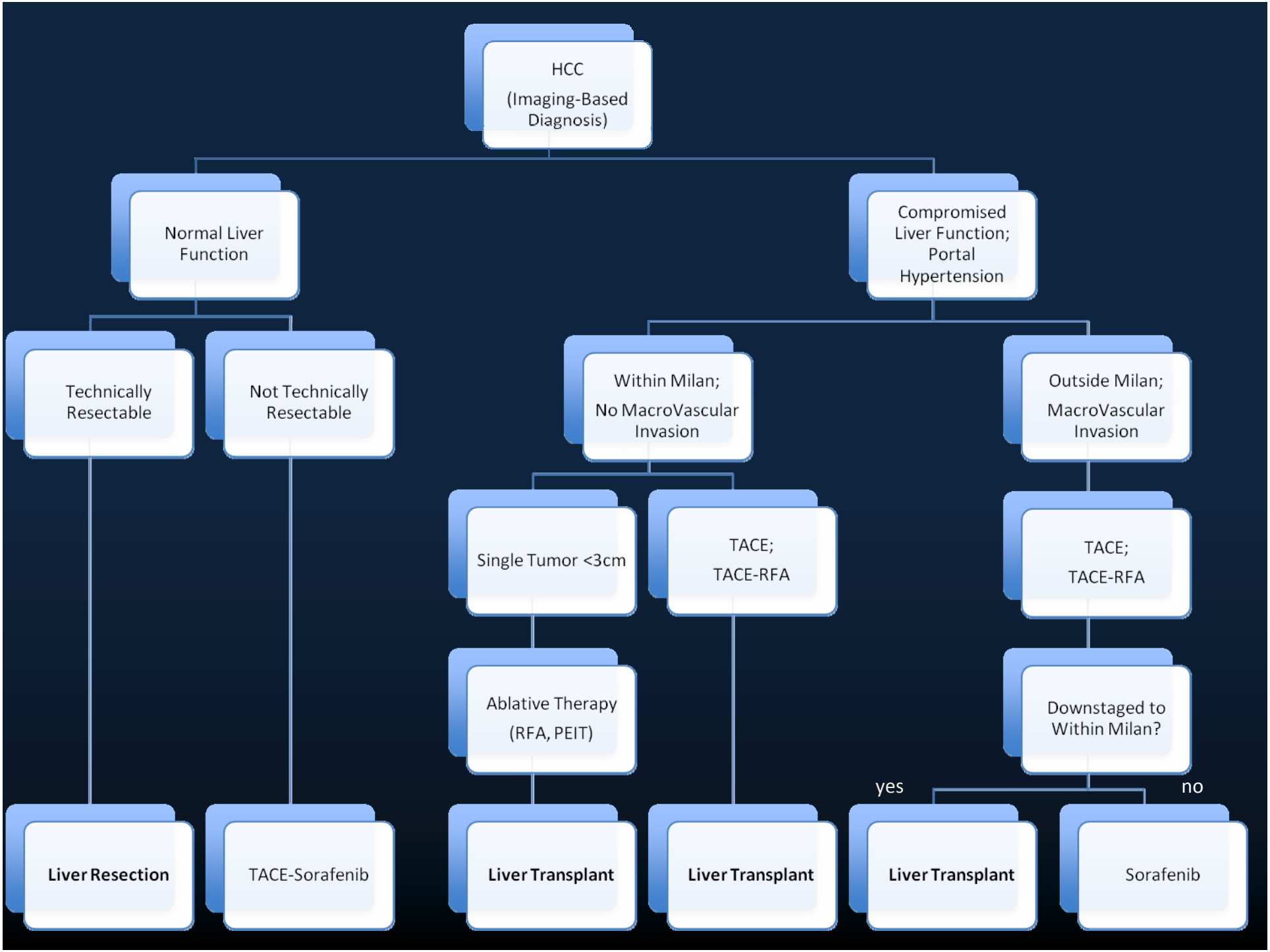
- Data were extracted from a prospective database of patients with HCC treated at Mount Sinai Hospital (New York City) between 1988 and 2008.
- A detailed analysis was performed on non-cirrhotic patients treated with hepatic resection for HBV-HCC.
- Intraoperative assessment of the non-neoplastic liver, histopathology, imaging, and biochemical markers were combined in an attempt to characterize inflammation-independent cancers, vs. those occurring in a setting of chronic inflammation.

Demographics:
HCC According to Underlying Liver Disease

	Patients
Hepatitis C Virus	1,415 (50%)
Hepatitis B Virus	708 (25%)
Alcoholic Liver Disease	226 (8%)
NASH	170 (6%)
Other	85 (3%)
None	226 (8%)
Total	**2,830**

Demographics:
HBV-HCC Treatments Performed

	HBV-HCC
Liver Resection	241 (35%)
Liver Transplant	86 (13%)
Resection + Transplant	10 (1%)
All Others	347 (51%)
Total	684


HCC
(Imaging-Based Diagnosis)
Normal Liver Function
Compromised Liver Function; Portal Hypertension
Technically Resectable
Not Technically Resectable
Within Milan; No MacroVascular Invasion
Outside Milan; MacroVascular Invasion
Single Tumor <3cm
TACE; TACE-RFA
TACE; TACE-RFA
Ablative Therapy (RFA, PEIT)
Downstaged to Within Milan?
yes
no
Liver Resection
TACE-Sorafenib
Liver Transplant
Liver Transplant
Liver Transplant
Sorafenib

Liver Resection Inclusion Criteria

- Patients with HBV-HCC who were treated with liver resection were included in the current detailed analysis.

- Criteria for Liver Resection:
  - HCC
  - Childs A
  - No evidence of portal hypertension (platelet count >100k, wedged hepatic venous pressure gradient ≤10mmHg).
  - No evidence of extrahepatic disease.

  - Relative criteria:
    - Single tumor
    - Tumor confined to a single anatomic lobe

Demographics:
HBV-HCC Liver Resection Patients

	n=241
Age	
median	56
range	22-83
Sex	
male	203 (84%)
female	38 (16%)
Race	
Asian	169 (71%)
Caucasian	23 (9%)
African American	15 (6%)
Hispanic	5 (2%)
other/unknown	29 (12%)
Tumor Size	
mean	6.2cm
standard deviation	4.4

Demographics:
HBV-HCC Liver Resection Patients

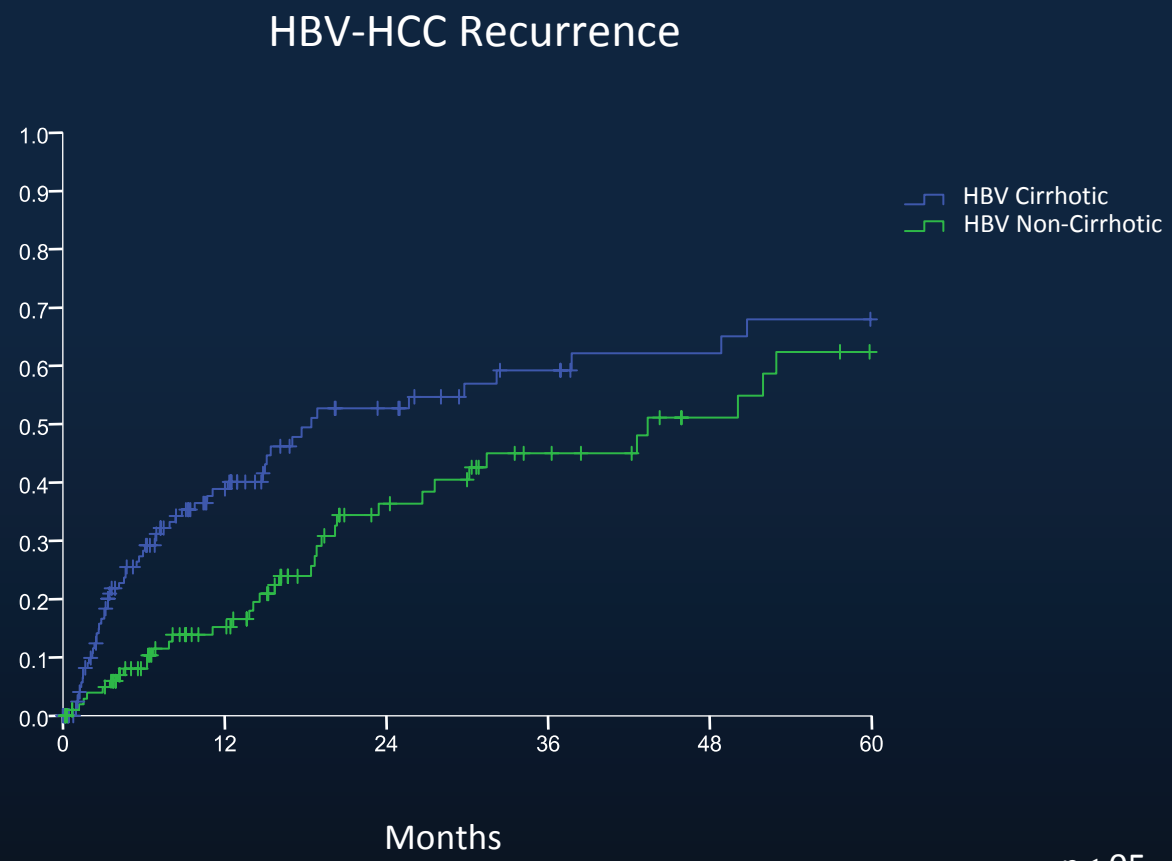
	Non-Cirrhotic n=107	Cirrhotic n=134
Age		
median	55	57
range	22-82	34-83
Sex		
male	84 (79%)	119 (89%)
female	23 (21%)	15 (11%)
Race		
Asian	81 (76%)	88 (66%)
Caucasian	9 (8%)	14 (10%)
African American	4 (4%)	11 (8%)
Hispanic	0 (0%)	5 (4%)
other/unknown	13 (12%)	16 (12%)
Tumor Size		
mean	6.7cm	5.9cm
standard deviation	5.2	3.7

HBV-HCC Tumor-Specific Prognostic Variables

	Non-Cirrhotic	Cirrhotic	
Milan Criteria:			
Within	51 (49%)	64 (48%)	
Outside	54 (51%)	69 (52%)	p=NS
Vascular Invasion:			
None	32 (29%)	40 (31%)	p=NS
Microvascular	61 (55%)	53 (41%)	
Macrovascular	17 (16%)	35 (28%)	p<.05
Number of Tumors:			
1	92 (88%)	107 (80%)	
2-3	12 (11)	21 (16%)	
>3	1 (1%)	5 (4%)	p=NS
Largest Tumor Diameter:			
≤5cm	62 (52%)	66 (50%)	
5-10cm	28 (24%)	46 (35%)	
≥10cm	28 (24%)	20 (15%)	p=NS
Serum AFP:			
<1000ng/ml	77 (75%)	86 (70%)	
≥1000ng/ml	25 (25%)	37 (30%)	p=NS
Differentiation:			
Well	15 (15%)	22 (17%)	
Moderate	67 (66%)	62 (48%)	
Poor	19 (19%)	44 (35%)	p<.05

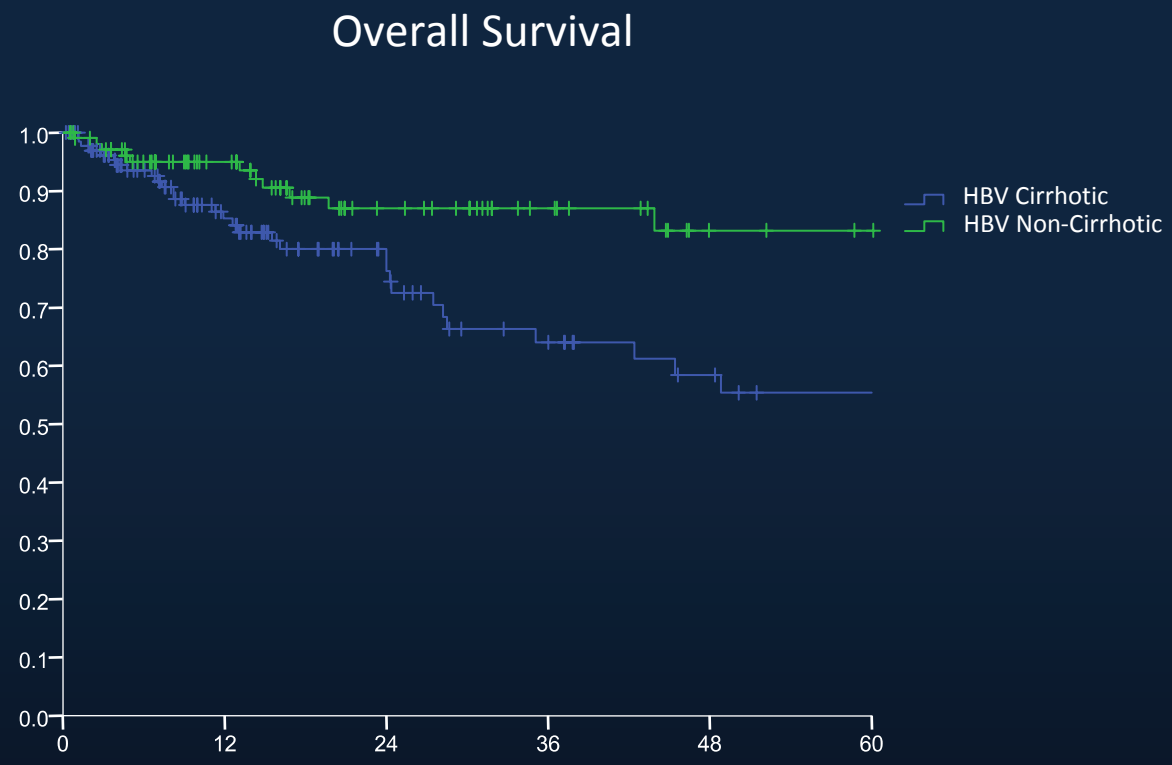
Chi Square

HBV-HCC Tumor Recurrence According to the Presence or Absence of Cirrhosis



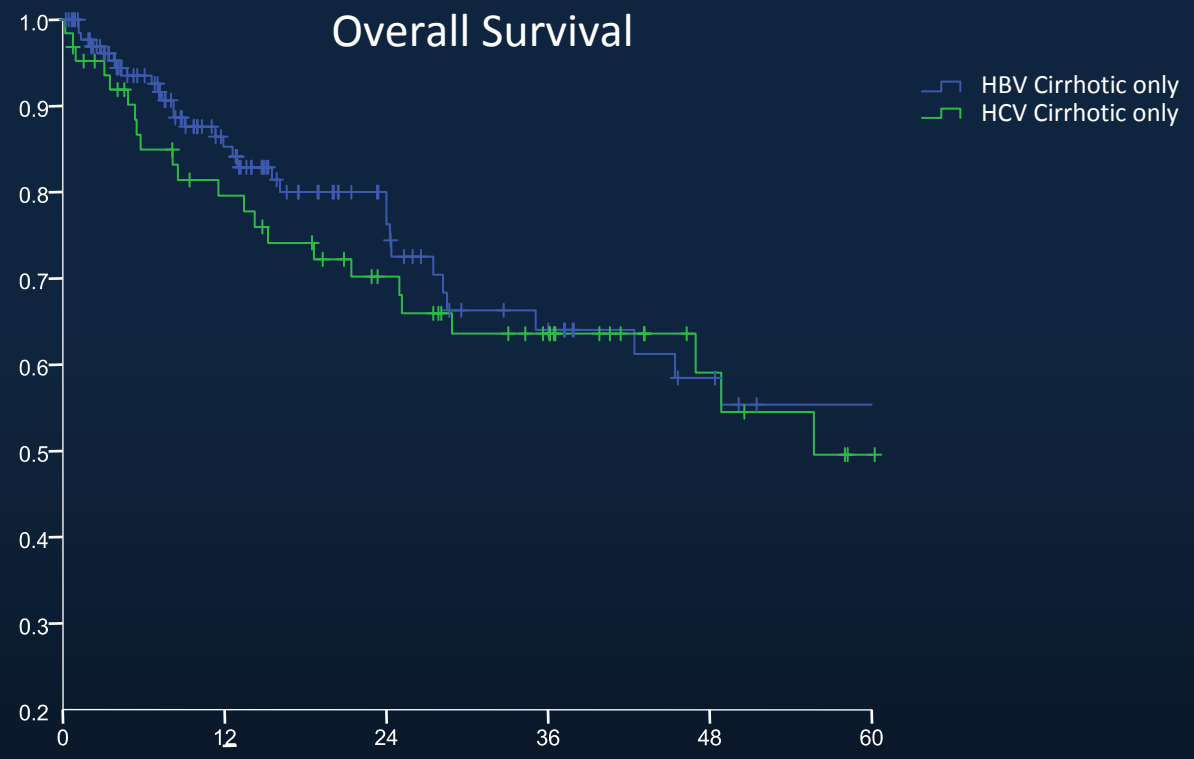
p<.05

HBV-HCC Overall Survival According to the Presence or Absence of Cirrhosis



p<.05

HCC Overall Survival Following Liver Resection
HBV vs. HCV (Cirrhotics Only)



p=NS

HBV-HCC Association to Severity of Parenchymal Inflammation

	Normal Liver n=36	Fibrotic Liver n=71	Cirrhotic Liver n=134	Total
Low-Normal ALT*	13 (36%)	18 (25%)	26 (19%)	57
Normal-Range ALT**	15 (42%)	36 (51%)	65 (49%)	116
High ALT^{+}	6 (17%)	17 (24%)	39 (29%)	62
Indeterminate Preoperative ALT	2 (5%)	0	4 (3%)	6
Total	36/241 (15%)	71/241 (29%)	134/241 (56%)	241

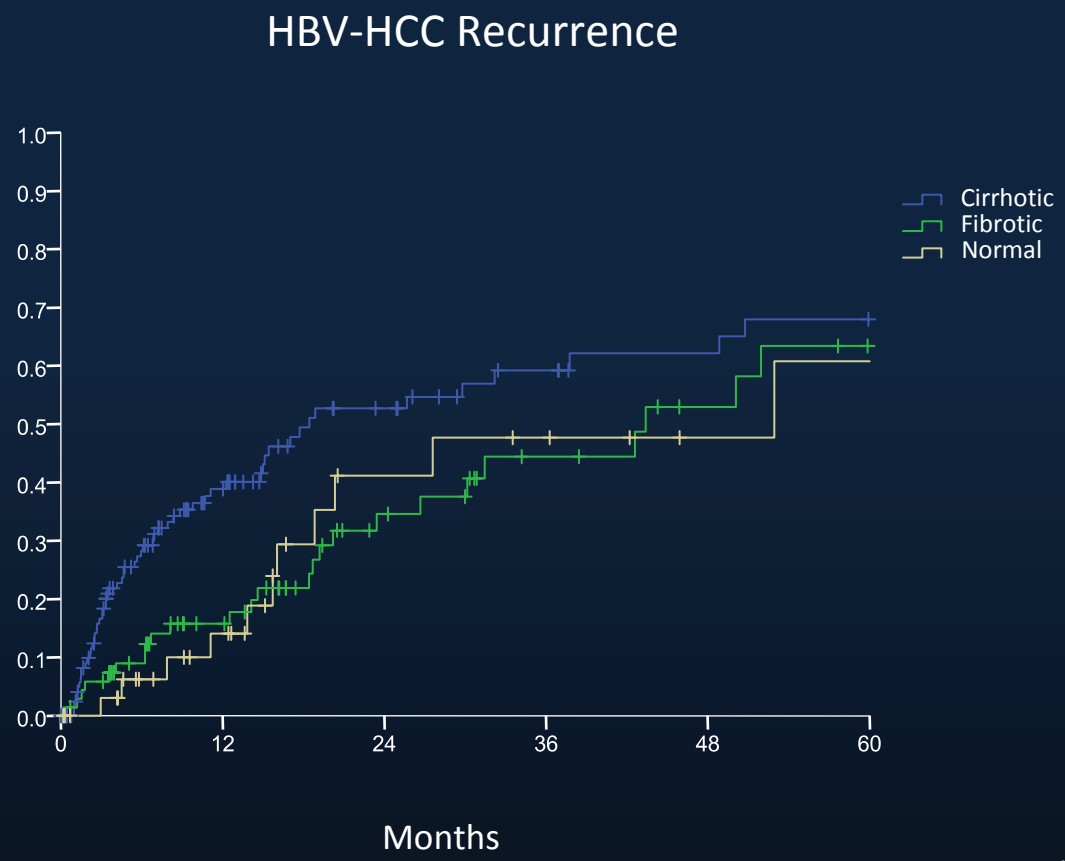
**Low-Normal ALT: <19 i.u./L (females), <30 i.u./L (males)*
***Normal ALT: >Low-Normal ALT, but <53 i.u./L*
$^{+}$High ALT: >53 i.u./L

HBV-HCC Tumor-Specific Prognostic Variables

	Normal Liver	Fibrotic	Cirrhotic	
Milan Criteria:				
Within	12 (33%)	39 (57%)	64 (48%)	
Outside	24 (73%)	30 (43%)	69 (52%)	p=NS
Vascular Invasion:				
None	10 (30%)	22 (32%)	40 (31%)	
Microvascular	17 (52%)	34 (50%)	53 (41%)	
Macrovascular	6 (18%)	12 (18%)	35 (28%)	p=NS
Number of Tumors:				
1	33 (92%)	59 (86%)	107 (80%)	
2-3	3 (8%)	9 (13%)	21 (16%)	
>3	0	1 (1%)	5 (4%)	p=NS
Largest Tumor Diameter:				
≤5cm	20 (41%)	42 (61%)	66 (50%)	
5-10cm	15 (31%)	13 (19%)	46 (35%)	
≥10cm	14 (28%)	14 (20%)	20 (15%)	p=NS
Serum AFP:				
<1000ng/ml	24 (71%)	53 (78%)	86 (70%)	
≥1000ng/ml	10 (29%)	15 (22%)	37 (30%)	p=NS
Differentiation:				
Well	6 (18%)	9 (13%)	22 (17%)	
Moderate	19 (58%)	48 (71%)	62 (48%)	
Poor	8 (24%)	11 (16%)	44 (35%)	p=NS

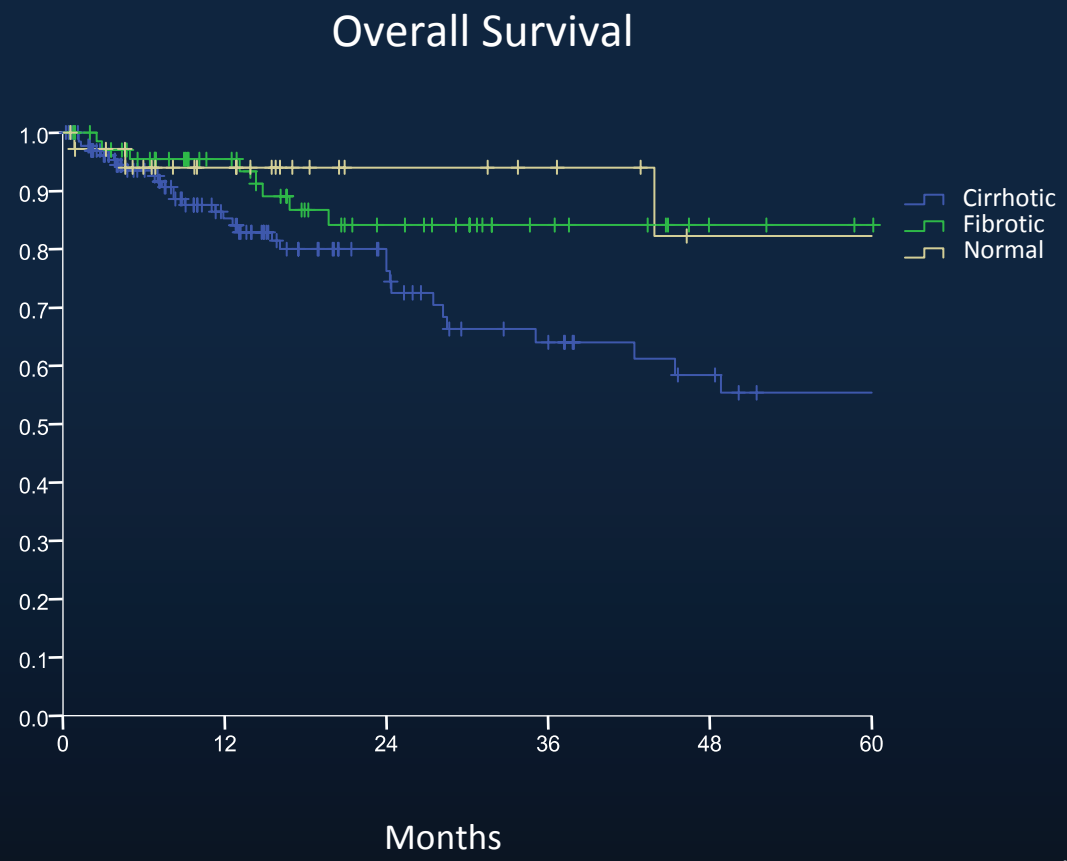
Chi Square

HBV-HCC Tumor Recurrence According to Chronic Histologic Inflammatory Changes



p<.05

HBV-HCC Overall Survival According to Chronic Histologic Inflammatory Changes



p<.05

HBV-HCC: Inflammation Independent Environment

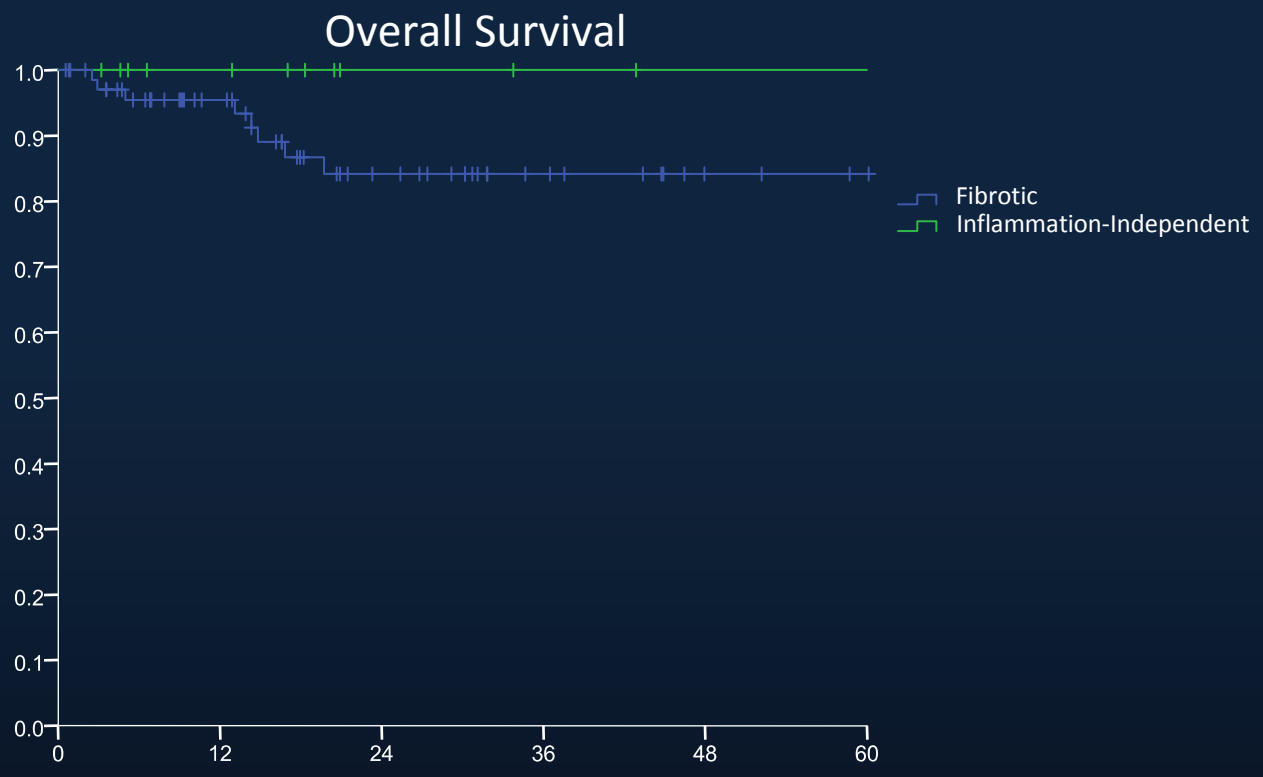
	Normal Liver n=36	Fibrotic Liver n=71	Total
Low-Normal ALT*	13 (36%)	18 (25%)	31
Normal ALT **	15 (42%)	36 (51%)	51
High ALT+	6 (17%)	17 (24%)	23
Indeterminate Pre-operative ALT	2 (5%)	0	2
Total	36/107 (34%)	71/107 (66%)	107

**Low-Normal ALT: <19 i.u./L (females), <30 i.u./L (males)*
***Normal ALT: >Low-Normal ALT, but <53 i.u./L*
+High ALT: >53 i.u./L

HBV-HCC Tumor-Specific Prognostic Variables: Inflammation-Independent vs. Fibrotic

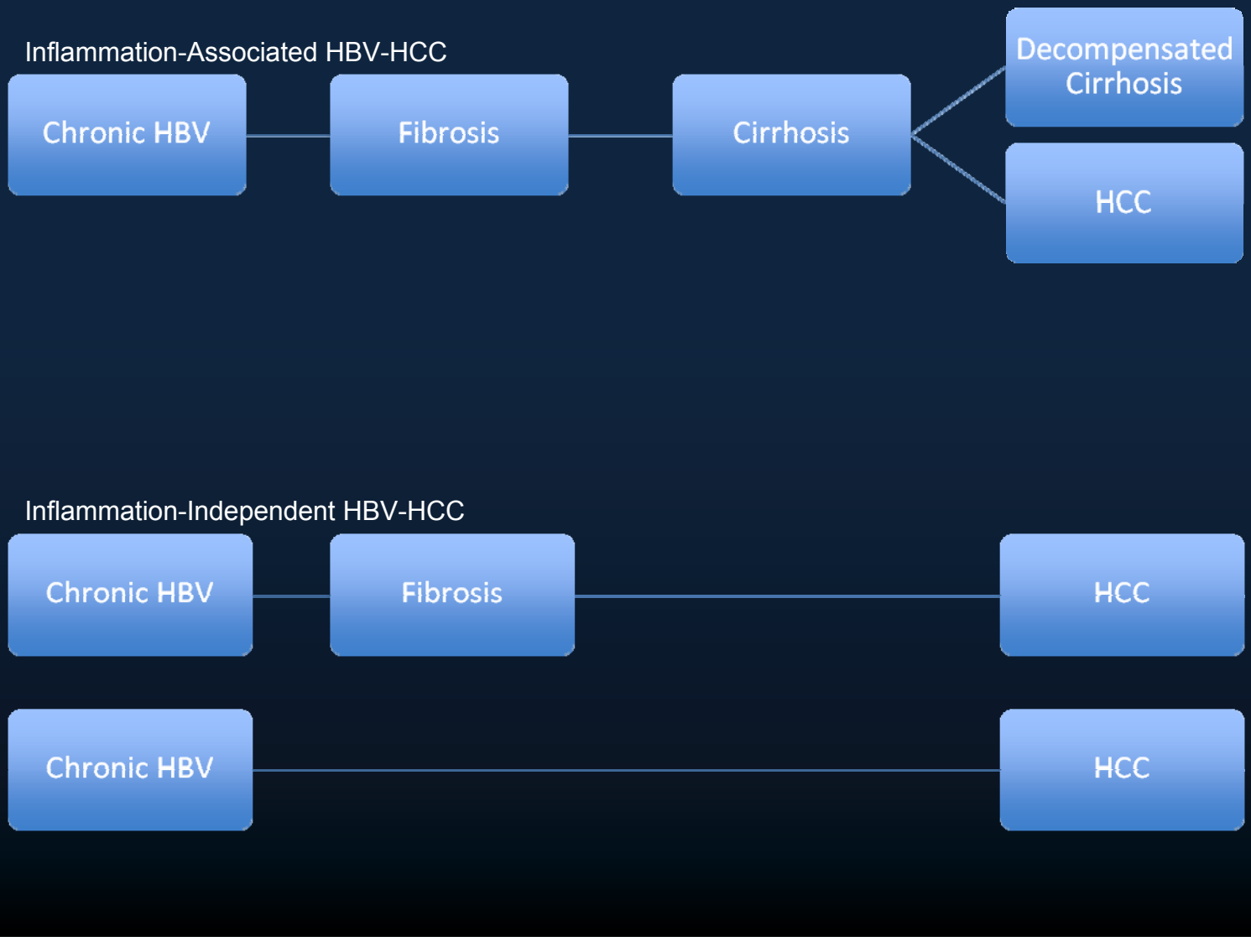
	Inflammation-Independent (Normal Liver, Low-Normal ALT)	Fibrotic	
Milan Criteria:			
Within	6 (46%)	39 (57%)	
Outside	7 (54%)	30 (43%)	p=NS
Vascular Invasion:			
None	3 (25%)	22 (32%)	
Microvascular	8 (67%)	34 (50%)	
Macrovascular	1 (8%)	12 (18%)	p=NS
Number of Tumors:			
1	12 (92%)	59 (86%)	
2-3	1 (8%)	9 (13%)	
>3	0	1 (1%)	p=NS
Largest Tumor Diameter:			
≤5cm	7 (54%)	42 (61%)	
5-10cm	4 (31%)	13 (19%)	
≥10cm	2 (15%)	14 (20%)	p=NS
Serum AFP:			
<1000ng/ml	9 (69%)	53 (78%)	
≥1000ng/ml	4 (31%)	15 (22%)	p=NS
Differentiation:			
Well	2 (17%)	9 (13%)	
Moderate	7 (58%)	48 (71%)	
Poor	3 (25%)	11 (16%)	p=NS

HBV-HCC Overall Survival
Inflammation-Independent Cancers Compared to Fibrotic



p=NS

Model:
HBV-HCC



Conclusions

- 684 total patients with HBV-associated HCC were treated, and 241 liver resections were performed with accurate scoring of the non-neoplastic liver.
  - Cirrhosis was established in 134/241 (56%) cases
  - Among the remaining 107/241 (44%) non-cirrhotic patients:
    - hepatic fibrosis was present in 71/241 (29%) of cases
    - the non-neoplastic liver was normal in 36/241 (15%) cases
- 36/241 (15%) of all patients with HBV-HCC develop cancer in the absence of cirrhosis or hepatic fibrosis.
- A small but definable percentage of non-cirrhotic HBV-HCC patients (13/36 with normal liver, 36%) develop cancer in the absence of any measurable manifestation of chronic hepatic inflammation (normal liver and low-normal ALT).
- HBV-HCC Outcomes in patients with underlying cirrhosis, including cancer recurrence and overall survival, are worse than those observed in patients with lesser degrees of parenchymal inflammatory changes.

Acknowledgments

- *Research Support Provided by Gilead Sciences, Inc.*