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Cirrhosis is Present in Most Patients with Hepatitis B and Hepatocellular Carcinoma

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Abstract

Background& Aims—There is not much data available about the prevalence or effects of cirrhosis in patients with hepatocellular carcinoma (HCC) from viral hepatitis. We compared patients with HCC and hepatitis B virus (HBV) or hepatitis C virus (HCV) infections to determine the proportions of cirrhosis in each group, virologic and tumor characteristics, and overall survival.

Methods—This analysis includes patients with HBV (n=64) or HCV (n=118) infection who were diagnosed with HCC at the Mayo Clinic in Rochester MN from 1994 to 2008; groups were matched for age and sex. The diagnosis of cirrhosis was based on histology and, if histologic information was insufficient or unavailable, clinical indicators that included ascites or varices, thrombocytopenia or splenomegaly, and radiographic configuration of cirrhosis. Virologic characteristics, tumor stage, and patient survival were also assessed.

Results—The prevalence of histologic cirrhosis was 88% among patients with HBV infection and 93% among those with HCV infection ($P=0.46$). When the most inclusive criteria for cirrhosis were applied, cirrhosis was present in 94% of patients with HBV and 97% with HCV ($P=0.24$). Among HCV patients, 5.2% were negative for HCV RNA following antiviral treatment; 63.4% of HBV patients had HBV DNA < 2000 u/ml with or without treatment. Patients with HBV tended to

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Contribution

Ju Dong Yang contributed to study design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript; W. Ray Kim contributed to study concept and design, study supervision, obtaining funding, and critical revision of the manuscript; Ritika Coelho contributed to acquisition of data, critical revision of the manuscript for important intellectual content; Teresa A. Mettler contributed to acquisition and interpretation of data; Joanne T. Benson contributed to analysis and interpretation of data; Terry M. Therneau contributed to analysis and interpretation of data, critical revision of the manuscript for important intellectual content; Bohyun Kim, Lewis R. Roberts, and Schuyler O. Sanderson contributed to study concept and design, interpretation of data, and critical revision of the manuscript.

have less surveillance and more advanced stages of HCC, without differences in survival from those with HCV infection ($P=0.75$).

Conclusion—Most patients with HCC and chronic viral hepatitis had evidence of cirrhosis, including those with HBV infection and those without active viral replication.

Keywords

Liver cancer; liver disease; virology; survival

Introduction

Hepatocellular carcinoma (HCC) is the seventh most common cancer and third leading cause of cancer-related death in the world according to the GloboCan 2008 report¹. Overall, 78% of all HCCs are attributed to either HBV or HCV infection². Most HCCs develop in patients with underlying liver disease - cirrhosis is an independent and significant risk factor for HCC among patients with viral hepatitis. Approximately 3 percent of patients with compensated cirrhosis with HBV or HCV develop HCC per year³. The current American Association for the Study of Liver disease (AASLD) guideline recommends surveillance for HCC in cirrhotic patients whose annual risk is greater than 1.5 %. Thus, the guideline is unequivocal that cirrhotic patients with viral hepatitis need to undergo regular surveillance for HCC⁴. Not all patients with HCC, however, have underlying liver cirrhosis. This is especially well known for patients with chronic HBV infection. On the other hand, it has been widely held that cirrhosis is a prerequisite for the development of HCC among patients with HCV.

In addition to being a risk factor for HCC, cirrhosis with or without hepatic decompensation carries a substantial prognostic implication in patients with HCC. Most prognostic models for HCC incorporate some measure of liver dysfunction as an important component⁵⁻⁷. Thus, assessment of fibrosis and cirrhosis is a critical aspect of clinical evaluation in HCC patients with viral hepatitis.

The aims in this study included (1) to compare the prevalence of cirrhosis; (2) to describe virologic characteristics; and (3) to compare the extent of the tumor and survival subsequent to diagnosis in HCC patients with chronic HBV and HCV infection.

Methods

Patients

A prospective database tracking all HCC cases at Mayo Clinic Rochester were queried to identify all HCC patients diagnosed between January 1994 to December 2008 with a possible diagnosis of HBV and/or HCV. HBV infection was ascertained by positive serum HBsAg, whereas HCV infection was defined by 1) detectable HCV RNA or 2) anti-HCV positive with a documented history of chronic liver disease. As there were a much larger number of HCV patients, we first identified HBV patients who met the eligibility criteria as described below. Then, for each HBV patient, two HCV patients were selected by matching based on age (within 5 years) and sex. Of the HCV subjects thus selected, those that met the eligibility criteria were included in the final analysis.

In order for a patient to be included in the study, the HCC diagnosis had to be consistent with the AASLD guideline⁴. Namely, the diagnosis was ascertained by histology (n=134) and/or by clinical features (n=36). Additionally, patients with characteristic cross-sectional

and angiographic lesions treated with transarterial chemoembolization (TACE) or transarterial radioembolization (TARE) were also included (n=12).

Exclusion criteria for the study included insufficient histologic or radiographic information to assess cirrhosis, dual infection with HBV and HCV, co-infection with HIV or co-existence of known liver disease other than alcoholic liver disease. This study was approved by the Institutional Review Board of Mayo Foundation.

Histological and Clinical Data

All available pathologic data were obtained to document cirrhosis. The stage of fibrosis was described by the Batts-Ludwig staging system. Stage 0 represents no fibrosis, 1 portal fibrosis, 2 periportal fibrosis, 3 septal fibrosis and 4 cirrhosis. All pathology reports obtained within 6 months from HCC diagnosis were used in the analysis except stage 4 fibrosis which could be anytime prior to the diagnosis of HCC. In addition to the histologic assessment of fibrosis, clinical indicators of cirrhosis were obtained at HCC diagnosis including thrombocytopenia (<150K), splenomegaly (by physical examination or cross-sectional images), ascites (by physical exam, cross-sectional images, or the use of diuretics for control of ascites), varices (by upper endoscopy, cross-sectional images, or history of variceal bleeding) and cirrhotic configuration of the liver in cross-sectional imaging studies (nodular liver surface or caudate lobe hypertrophy).

Other clinical details were obtained from laboratory databases and medical records. Tumor characteristics were assessed by cross-sectional imaging and information about the tumor detection by surveillance, primary treatment modality and survival status at the last follow up was also obtained. A patient was considered to be under HCC surveillance if at least one abdominal ultrasound, CT, or MRI imaging had been obtained within 1 year prior to the diagnosis of HCC.

Statistical analysis

JMP and SAS (SAS Institute, Cary, NC) were used for statistical analyses. The student's t- or Wilcoxon rank sum tests were used to assess the difference of continuous variables and the Chi-square or Fisher's exact tests for comparison of proportions.

Patient survival was assessed from the time of HCC diagnosis to the last known follow-up or death. To ascertain complete capture of all decedents, a proprietary information source (Accurant®) was used to supplement death records in the medical records or the institutional registration file. Based on these sources, vital status of study subjects was assessed as of October 1, 2009. Survival of HBV and HCV patients was estimated using the Kaplan-Meier method and compared by the log rank test.

Results

Patient characteristics

A total of 130 patients with HBV and 512 with HCV were present in the database. After matching HBV and HCV, and excluding ineligible patients, 182 patients were included in the analysis, consisting of 64 with HBV and 118 with HCV (supplementary Figure 1). Patient characteristics are summarized in Table 1. By design, the age and gender distribution in the two groups was similar. As expected, there was over-representation of Asians in the HBV group. Significant alcohol history was more common in the HCV group. The distribution of body mass index (BMI) was similar in the two groups. However, given the higher proportion of Asians for whom a BMI cut-off of 23 is used to define lean BMI, the proportion of overweight BMI was significantly higher among the HBV patients.

Liver biochemical parameters were largely comparable between the two groups. However, serum albumin levels and platelet count were higher among HBV patients.

Assessment of liver cirrhosis

Table 2 represents histological and clinical evaluation of liver cirrhosis. Reliable histologic information to determine the stage of fibrosis was available in 32 of HBV (50%) and 69 of HCV (58%) patients. Of those, the proportion of patients with cirrhosis was non-significantly higher among HCV patients. Clinical evidence of cirrhosis was more prevalent among HCV patients. The proportion of HCV patients with splenomegaly, cirrhotic appearance of the liver and thrombocytopenia (platelets <150K) were statistically significantly higher among HCV patients than those with HBV.

Figure 1 compares the proportion of patients with cirrhosis between HCV and HBV patients. When only histologic evidence was used, the proportion of patients with cirrhosis was 55.1% for HCV and 43.8% for HBV patients. In those without histological evidence of cirrhosis, three clinical indicators, namely (1) ascites or varices, (2) thrombocytopenia or splenomegaly, and (3) cirrhotic configuration of the liver by radiography, were utilized to define cirrhosis. When the most stringent clinical criteria (histological cirrhosis or all three indicators present) were used, 94 of HCV (79.7%) and 47 of HBV (73.4%) patients had cirrhosis ($p=0.34$). If the most inclusive criteria (histological cirrhosis or at least one cirrhosis indicator present) were used, 115 of HCV (97.4%) and 60 of HBV (93.8%) patients had cirrhosis ($p=0.24$). Based on these last criteria (histology or at least one clinical indicator), three (2.6%) HCV and four (6.2%) HBV patients did not have cirrhosis. Detail clinical information on these patients is provided in supplementary Table 1.

Table 3 compares the prevalence of cirrhosis in Asian and Caucasian subjects. Among HBV patients, all Caucasian subjects had evidence of cirrhosis, whereas 62-90% of Asians had evidence of cirrhosis, depending on the criteria used. Data are less clear about HCV, as there were only 8 Asian patients with HCC. We also considered the possibility that portal vein thrombosis may result in portal hypertension without liver cirrhosis and conducted a subgroup analysis after excluding patients with portal vein thrombosis. This did not change the results materially (data not shown).

Virologic characteristics

While all HCV patients were anti-HCV positive, five (5.2%) were not viremic at HCC diagnosis as a result of successful prior antiviral treatment. HCV genotype was available in 46% of HCV patients: Genotypes 1a (30.4%) and 1b (30.4%) were most common, followed by 3a (16.1%), 2b (7.1%), 2c (7.1%), and 4a (5.4%). There was one patient each for genotype 2a (1.8%) and 4c (1.8%). Interestingly, 26 (26%) HCV patients had evidence of previous HBV infection (HBsAg-/anti-HBc+), 10 of whom were anti-HBs-negative.

The vast majority (87%) were HBeAg-negative. There were 19 patients who were receiving antiviral therapy at the time of HCC diagnosis. Excluding those patients, 5 (20.8%) HBeAg-negative patients had normal ALT and low or undetectable levels of HBV DNA (<2,000 IU/mL), meeting the usual criteria for an inactive carrier. Of the 19 patients who were on antiviral therapy, 85.7% had suppressed HBV (HBV DNA < 20,000 IU/mL) and 14.3% did not. Altogether, 26/41 (63.4%) of HBV patients had HBV DNA < 2,000 IU/mL. Additional information on the virologic characteristics is included in supplementary Table 2.

Assessment of tumor characteristics and survival

Table 4 compares tumor characteristics and treatment patterns between HBV and HCV patients. The median tumor size was larger in HBV than HCV patients by 0.8 cm ($p=0.04$).

TNM stage 1 was most common in HCV patients whereas stage 3 was most common in HBV patients, although the difference was not statistically significant ($p=0.45$). HCCs were detected by surveillance in more than half of HCV patients while only a third of HCCs were detected by surveillance in HBV patients. About 60% of patients had treatment with curative intent for HCC. Liver transplantation and surgical resection were the most common treatment modalities used in HCV and HBV patients respectively. Figure 2 demonstrates survival of HBV and HCV patients, which showed no difference ($P=0.75$).

Discussion

Chronic viral hepatitis promotes release of inflammatory cytokines, leading to generation of genotoxic reactive oxygen species and cell proliferation as well as activation of the liver fibrosis cascade⁸. These lead to acceleration of hepatocyte cell cycles and an increased risk of genetic alterations, which may culminate in malignant transformation of hepatocytes. In addition to these events common to both viruses, several features of HBV suggest a direct carcinogenic role of HBV that may foster HCC development in the absence of cirrhosis. HBV DNA can integrate into the host genome, generating genetic instability and affecting the expression of tumor suppressors and oncogenes^{9, 10}. In addition, the HBx protein is capable of transactivating cellular promoters in oncogenic pathways^{11, 12}. In contrast, carcinogenesis in chronic HCV infection has been believed to be by fibrogenesis and cirrhosis. However, emerging evidence suggests that HCV may have a direct role in hepatocarcinogenesis as well and several studies have documented HCC developing in HCV patients without cirrhosis.¹³⁻¹⁵

These previous data put the results of this analysis in perspective. In the comparison between HCC patients with HBV and HCV, although the prevalence of cirrhosis was consistently higher in patients with HCV than those with HBV, advanced fibrosis or cirrhosis was present in the great majority in both groups. A common misconception with regard to HCC occurring in non-cirrhotic HBV patients is that their liver is not only non-cirrhotic but also non-fibrotic. Our data show that only 6.2% of HBV and 2.6% of HCV patients had no evidence of cirrhosis. This overall result does not change even when we take the three patients with HBV back into account (footnote, Table 1), who failed to match with a patient with HCV because of their young age. Only one of the three had no evidence of fibrosis.

The proportion of HBV patients with cirrhosis at HCC diagnosis in this analysis was higher than that in previous studies in Asia^{16, 17}. Our comparison between Caucasian and Asian patients with HBV reveals an interesting insight. While all Caucasian patients with HBV had liver cirrhosis, smaller proportions of Asian patients had evidence of cirrhosis. This observation, however, should not necessarily be construed to indicate genetic differences in susceptibility to non-cirrhotic HCC among Asians. Other factors in Asian patients that may have contributed to this observation include longer duration of infection allowing viral genomic integration, higher prevalence of HBV genotype C which has been associated with development of HCC at a younger age and other environmental factors that may augment the direct oncogenic potential of HBV. A parallel comparison among HCV patients may have been useful, yet the small number of Asian HCC patients with HCV infection is a limitation of this study. Nonetheless, the main finding of this work remains true that among Asian patients with HBV, the majority of HCC still occur in the setting of cirrhosis.

Our analysis of virologic characteristics highlights that HCC may still occur in HBV patients without active replication or in sustained virologic responders to HCV therapy. Large prospective cohort studies have shown that HBV patients with high levels of DNA regardless of their HBeAg status are at increased risk of HCC¹⁸. Conversely, antiviral-

induced suppression of viral replication may decrease the risk of HCC¹⁹⁻²². In this study in which more than 80% of untreated HBV patients were HBeAg-negative, 21% of such patients were inactive carriers at HCC diagnosis. Similarly a recent cohort study showed that even inactive HBV carriers have 4.6 times high risk for HCC than individuals without HCV or HBV²³. The predominance of HBeAg-negative patients in our data is also in line with previous studies^{24, 25}, which reflects the tendency that by the time HCC develops in their 50s, most patients have already experienced HBeAg seroconversion. More importantly, the recent emphasis in the correlation between HBV DNA and HCC risk should not detract the clinician from looking for subtle signs of cirrhosis even in apparent inactive carriers. Cirrhosis remains by far the strongest risk factor of HCC compared to any level of HBV DNA. A similar recommendation may be made about HCV patients. Several reports indicate that sustained virologic response to anti-HCV therapy decreases the risk of HCC although some degree of risk persists in patients with cirrhosis²⁶⁻²⁸. All in all, our data underline the need for continued vigilance for HCC in cirrhotic patients with current or past history of chronic HCV infection.

As shown in Table 4, HBV patients tended to have more advanced HCCs than those with HCV. Our data suggest that Asian patients with HBV are not subjected to as rigorous HCC surveillance as Caucasian counterparts, leading to discovery of the tumor at a later stage. However, it is still possible that HCCs associated with HBV may display different biological behaviors than those with HCV, as similar observations have been made in Asia^{29, 30}. Despite a tendency for a higher tumor burden in HBV patients, surgical resection was 2.3 times more common, which may be attributed to better preserved liver function. In contrast, liver transplantation and ablative therapy were more commonly performed in HCV patients. These differences notwithstanding, there was no evidence that survival was superior in either group of patients as shown in Figure 2. Others have reported that HCC prognosis was not different between patients with HBV and HCV after surgical resection²⁹⁻³¹. In this study, the equivalence in survival may reflect a balance between better hepatic functional reserve in HBV patients on the one hand and less advanced tumor stage in HCV patients on the other.

This study specifically evaluated the prevalence and potential implications of underlying liver cirrhosis in HCC patients with chronic viral hepatitis. Strengths of our study include the prospective identification of study candidates, careful matching of HBV and HCV patients to highlight differences in the two groups and several sensitivity analyses in terms of patient subgroups as well as clear definitions of clinical criteria for the diagnosis of cirrhosis. On the other hand, limitations related to the lack of histologic assessment of the liver in all patients may not have been completely addressed by the matching and sensitivity analyses. With the study setting being at a referral center, our patients may not be entirely generalizable to HCC patients in general. However, we have no reason to believe that these issues affected HBV or HCV patients differentially.

In conclusion, this analysis clearly showed that cirrhosis was present in the majority of HCC patients with chronic viral hepatitis B and C in the US. Although the proportion of patients with cirrhosis was consistently higher in HCV patients than in HBV, the majority of HBV patients with HCC still had evidence of advanced fibrosis and cirrhosis. We also demonstrated that patients without evidence of active replication of HBV or HCV may still be at increased risk of developing HCC, especially if they already have cirrhosis. Finally, despite their lower prevalence of cirrhosis and better preserved liver function, HBV patients did not have better survival, in part because their HCC was diagnosed at a more advanced stage, presumably from less rigorous surveillance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

HCC	hepatocellular carcinoma
HBV	hepatitis B virus
HCV	hepatitis C virus

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Figure 1.

Comparison of advanced fibrosis/cirrhosis between HBV and HCV at HCC diagnosis. Clinical indicators of cirrhosis include (1) ascites or varices, (2) platelets <150K or splenomegaly, and (3) cirrhotic configuration of the liver by cross-sectional imaging.

^aPresence of cirrhosis on histology or all three clinical cirrhosis indicators.

^bPresence of cirrhosis on histology or at least 2 clinical cirrhosis indicators.

^cPresence of cirrhosis on histology or at least 1 clinical cirrhosis indicator.

Figure 2.
Comparison of survival between HBV and HCV patients

Table 1

Patient characteristics

	All patients			p value
	HCV (N=118)	HBV ^c (N=64)	Total (N=182)	
Age mean (SD)	57.1 (10.6)	57.4 (10.5)	57.2 (10.5)	
Male gender	102 (86.4%)	58 (90.6%)	160 (87.9%)	0.41
Race/Ethnicity				<0.01
Missing	3	0	3	
Caucasian	94 (81.7%)	18 (28.1%)	112 (62.6%)	
African American	12 (10.4%)	6 (9.4%)	18 (10.1%)	
Asian	8 (7.0%)	39 (60.9%)	47 (26.3%)	
Others	1 (0.9%)	1 (1.6%)	2 (1.1%)	
Alcohol^a	32 (28.6%)	2 (3.8%)	34 (20.5%)	<0.01
Diabetes	27 (23.3%)	10 (15.6%)	37 (20.6%)	0.22
BMI	26.9 (4.9)	26.7 (3.8)	26.8 (4.6)	0.80
Overweight^b	64 (62.8%)	46 (80.7%)	110 (69.2%)	0.02
AST IU/L mean (SD)	138.3 (136.9)	175.9 (257.0)	150.7 (185.3)	0.31
ALT IU/L mean (SD)	109.9 (122.1)	88.4 (64.1)	103.1 (107.6)	0.14
ALP IU/L mean (SD)	272.5 (219.1)	237.5 (139.8)	261.0 (196.8)	0.21
Bilirubin mg/dL (SD)	2.3 (3.5)	2.6 (3.8)	2.4 (3.6)	0.68
INR	1.3 (0.6)	1.2 (0.4)	1.3 (0.6)	0.45
MELD	12.1 (6.2)	11.6 (6.1)	11.9 (6.1)	0.66
Albumin g/dL (SD)	3.3 (0.7)	3.5 (0.8)	3.4 (0.7)	0.05
Platelets *10 ⁹ /L (SD)	122.4 (93.3)	157.3 (73.5)	134.0 (88.6)	0.01

HCV, hepatitis C virus; SD, Standard deviation; HBV, hepatitis B virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; MELD, Model for end stage liver disease.

^a Patient with significant alcohol intake and concomitant alcoholic liver disease recorded in medical chart by clinical judgement.

^b BMI of 23 or over were defined as overweight in Asian and 25 or over in races other than Asian

^c Three HBV patients with age<35 years and one HBV patient with age >90 years, were excluded from the study as there were no suitable matches among the HCV patients.

Table 2

Histologic and clinical assessment of cirrhosis

	All patients				p value
	HCV (N=118)	HBV (N=64)	Total (N=182)		
Fibrosis stage^a					0.91
Missing	49	32	81		
0	1 (1.4%)	1 (3.1%)	2 (2.0%)		
1	2 (2.9%)	1 (3.1%)	3 (3.0%)		
2	1 (1.4%)	2 (6.3%)	3 (3.0%)		
3	1 (1.4%)	0 (0%)	1 (1.0%)		
4	64 (92.8%)	28 (87.5%)	92 (91.0%)		
Clinical Indicators					
Ascites	63 (53.4%)	26 (41.9%)	89 (49.4%)		0.14
Splenomegaly	89 (78.8%)	32 (54.2%)	121 (70.3%)		<0.01
Cirrhotic configuration	103 (91.2%)	46 (74.2%)	149 (85.1%)		<0.01
Platelet count <150K	90 (77.6%)	31 (53.5%)	121 (69.5%)		<0.01
Varices	75 (81.5%)	34 (73.9%)	109 (79.0%)		0.30

^a Batts-Ludwig staging system: 0, no fibrosis; 1, portal fibrosis; 2, periportal fibrosis; 3, septal fibrosis; 4, cirrhosis.

Table 3
Comparison of cirrhosis proportion between HBV and HCV at HCC diagnosis among Caucasian and Asian patients

	HBV			HCV		
	Asian (N=39)	Caucasian (N=18)	p value	Asian (N=8)	Caucasian (N=94)	p value
Histologic cirrhosis	13/17 (76.5%)	13/13 (100%)	0.11	4/4 (100%)	54/57 (94.7%)	1
Ascites	12/37 (32.4%)	10/18 (55.6%)	0.10	6/8 (75.0%)	50/94 (53.2%)	0.29
Splenomegaly	14/34 (41.2%)	15/18 (83.3%)	0.01	5/7 (71.4%)	75/91 (82.4%)	0.61
Cirrhotic configuration	26/37 (70.3%)	14/18 (77.8%)	0.75	7/8 (87.5%)	83/90 (92.2%)	0.51
Platelet count <150K	15/35 (42.9%)	12/16 (75.0%)	0.04	7/8 (87.5%)	75/93 (80.7%)	1
Varices	17/25 (68.0%)	13/16 (81.3%)	0.48	4/5 (80.0%)	62/74 (83.8%)	1
Histology $\pm$ 3 of 3 criteria ^a	24/39 (61.5%)	18/18 (100%)	<0.01	6/8 (75.0%)	78/94 (83.0%)	0.63
Histology $\pm$ 2 of 3 criteria ^b	28/39 (71.8%)	18/18 (100%)	0.01	8/8 (100%)	87/94 (92.6%)	1
Histology $\pm$ 1 of 3 criteria ^c	35/39 (89.7%)	18/18 (100%)	0.30	8/8 (100%)	91/94 (96.8%)	1

Clinical indicators of cirrhosis include (1) ascites or varices, (2) platelets <150K or splenomegaly, and (3) cirrhotic configuration of the liver by cross-sectional imaging.

^a Presence of cirrhosis on histology or all three clinical cirrhosis indicators.

^b Presence of cirrhosis on histology or at least two clinical cirrhosis indicators.

^c Presence of cirrhosis on histology or at least one clinical cirrhosis indicator.

Table 4

Comparison of tumor characteristics at HCC diagnosis and treatment approach

All patients				
	HCV (N=118)	HBV (N=64)	Total (N=182)	p value
Tumor size cm [IQR]	3.6 [2.5-6]	4.4 [2.6-8]	4 [2.5-6.5]	0.04
Tumor number [IQR]	1 [1-3]	2 [1-4]	1 [1-4]	0.14
Portal vein invasion	32(27.1%)	18(28.5%)	50(27.6%)	0.84
TNM Classification				
T				0.27
1	54 (45.8 %)	22 (35.5 %)	76 (42.2%)	
2	24 (20.3%)	12 (19.4%)	36 (20.0%)	
3	40 (33.9%)	27 (43.5%)	67 (37.2%)	
4	0 (0%)	1 (1.6%)	1 (0.6%)	
N				0.72
1	6 (5.2%)	4 (6.5%)	10 (5.6%)	
M				0.72
1	6(5.1%)	4(6.4%)	9 (5.5%)	
TNM Stage				0.45
1(T1 N0 M0)	52 (44.4%)	21 (33.3%)	73 (40.6%)	
2(T2 N0 M0)	23 (19.7%)	12 (19.0%)	35 (19.4%)	
3(T3,4, Any N, M0)	36 (30.8%)	26 (41.3%)	62 (34.4%)	
4(Any T, Any N, M1)	6 (5.1%)	4 (6.4%)	10 (5.6%)	
AFP (ng/dL) [IQR]	34.2 [5.9-363]	79 [6.4-2990]	47 [5.9-703]	0.11
Surveillance	62 (53.0%)	22 (36.7%)	84 (47.5)	0.04
Treatment				0.03
Resection	15 (14.7%)	15 (33.3%)	30 (20.4%)	
Liver transplant	39(38.2 %)	13 (28.9%)	52 (35.4 %)	
Local ablation	8 (7.8%)	0 (0%)	8 (5.4%)	
TACE/TARE	24 (23.5%)	10 (22.2%)	34 (23.1 %)	
Systemic Tx ^a	5 (4.9%)	0 (0%)	5 (3.4%)	
Comfort care	11 (10.8%)	7 (15.6%)	18 (12.2%)	

[IQR]: Inter quartile range

T1: Solitary tumor without vascular invasion

T2: Solitary tumor with vascular invasion, or multiple tumors none more than 5 cm

T3: Multiple tumors more than 5 cm or tumor involving a major branch of the portal or hepatic vein(s)

T4: Tumors with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum

N0: No regional lymph node metastasis; N1: Regional lymph node metastasis

M0: No distant metastasis; M1: Distant metastasis

TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization

^a Systemic chemotherapy/targeted treatments