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NATURAL HISTORY OF T1N0M0 HEPATOCELLULAR CARCINOMA: LARGE SCALE STUDY IN THE UNITED STATES

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Abstract

Background—Hepatocellular carcinoma (HCC) Prognosis is depending on clinicopathological features in addition to treatment provided. We aimed to assess the natural history of TNM stage I HCC tumors which received different treatment over a period of twenty years.

Methods—Between 1992 till 2011 a total of 397 stage I HCC patients were included. Detailed information were retrieved from MD Anderson Cancer Center patients' medical records. Kaplan-Meier method was used to calculate Patients' overall survival (OS). Cox regression analysis was used to calculate the estimate hazard ratio (HR) and 95% confidence interval (CI) of different prognostic factors.

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Results—Out of 397 patients, we have 67.5% males, 42.8% hepatitis related HCC, and 59.7% have underlying cirrhosis. After adjustment for confounding factors we found that all therapeutic modalities associated with significant mortality rate reduction with overall survival of 63, 42.03, 34.3, 22.1 months among patients treated with surgery, ablation, local, and systemic therapy respectively. Restricted analysis among cirrhotic and non-cirrhotic patients showed that ablative and local therapy significantly associated with longer OS compared to systemic therapy.

Conclusion—TNM Stage I HCC patients have favorable prognosis regardless of the type of treatment. Notably, ablative and local therapy significantly improved OS compared to systemic therapy.

Keywords

TNM; Stage I; hepatocellular carcinoma

INTRODUCTION

Hepatocellular carcinoma (HCC) represents 90% of the primary liver cancers. initially, it was considered to be one of the commonest cancer in the developing countries, however, over the last few decades there is a significant increase in the incidence and mortality of HCC in Europe and United States as well.^[1] Nowadays, liver cancer is the fifth most common cancer among males, the ninth in females, and the second most common cause of cancer related mortality worldwide.[1] Furthermore, 31% and 54% of HCC cases can be attributed to hepatitis C virus (HCV) and hepatitis B virus (HBV) infections respectively.^[2] While increasing HCC incidence in the United States has been attributed to dramatic increase in the prevalence of HCV infections in the mid of the last century and HBV infections among the immigrants from endemic countries, in addition to rising the incidence of metabolic syndrome and non-alcoholic steatohepatitis (NASH).[3] In the developing countries, the incidence of HCC is parallels to that of the viral hepatitis.[4] Notably, cirrhosis is the most common predisposing factor for HCC development in western world with a higher risk if cirrhosis is induced by viral hepatitis as compared to other causes of cirrhosis.[2, 4, 5] Presence or absence of cirrhosis along with the tumor characteristics including vascular invasion and portal vein thrombosis, tumor size, and alfa fetoprotein (AFP) are important prognostic indicators in HCC patients that affect the treatment decision and outcome.[1, 6–8]

From 1994 to 2004, there has been a 40% increase in the mortality rate due to HCC in the united states compared to 18% reduction in other cancers related mortality rate.^[1] As HCC prognosis is poor, it is vital to diagnose and treat HCC at an early curable stage.[9–11] According to Barcelona clinic liver cancer (BCLC) guidelines, resection is the only curable treatment modality approach for patients with well-preserved liver function (normal bilirubin levels along with either hepatic venous pressure gradient ≤ 10 mmHg or platelet count $\geq 100,000$) and have a solitary lesion with no vascular invasion or extrahepatic metastasis that is defined according to the American Joint Committee on Cancer (AJCC) 6th edition as TNM stage I [T1N0M0].^[1, 12] While, surgical resection or transplantation is the treatment of choice for appropriate candidates, different Local therapy modalities are considered to be the next logic treatment if patients were medically not candidate for

surgery. Furthermore, systemic therapy is given for these group of patients if they have an European Cooperative Oncology Group (ECOG) performance status 1–2 or they are not candidate for local therapy either due to tumor size or location.[13]

In this study we aimed to identify the key prognostic factors among TNM stage I HCC patients and assess the influence of treatment provided on patients' overall survival (OS).

METHODS

Study design and patients' characteristics

From January 1992 till December 2011, we identified 397 pathologically or radiologically diagnosed HCC patients with TNM stage I that had been referred to MD Anderson Cancer Centre. Detailed epidemiological data, HCC risk factors, and clinicopathologic characteristics were retrieved from patients' medical records including age at diagnosis, gender, Ethnicity, viral hepatitis, alcohol consumption, cigarette smoking, diabetes mellitus, family history of liver cancer or other cancers, personal history of other cancers, tumor differentiation, presence of underlying liver cirrhosis, performance status, serum alpha-fetoprotein (AFP) levels measured in ng/ml, volume of liver occupied by the tumor, degree of liver dysfunction assessed by Child-Turcotte Pugh class (CTP), Different staging systems including BCLC, and Cancer of Liver Italian Program (CLIP) scoring system. Also, we retrieved the initial treatment that patients received and classified it into 5 groups: 1) surgery either liver resection or transplant, 2) ablative therapy including radiofrequency (RFA), ethanol injection, and cryoablation, 3) local therapy including transarterial chemoembolization (TACE), hepatic arterial infusion (HAI), and local radiotherapy (RT), 4) Systemic therapy either chemotherapy or targeted therapy, and 5) Supportive care or hospice. (Table 1) All patients had received treatment based on a multidisciplinary team recommendation. The study was approved by the Institutional review board at MD Anderson Cancer Center.

Statistical analysis

To analyze our data set we used both IBM SPSS Statistics for Windows, version 21.0 (IBM, Armonk, NY) and Stata software (version 7.0; Stata Corporation, College station, Tex). Univariate analysis was done using the χ^2 or Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables. We used Kaplan-Meier analysis to measure the OS defined by the time between the date of diagnosis till the death date or the last follow up date. Median OS and 95% confidence interval (CI) among different epidemiological, risk factors, and clinicopathological characteristics were analyzed by using the log-rank test. The adjusted hazard ratio (HR) with the 95% CI was calculated by cox regression analysis to identify the independent prognostic factors among TNM stage I HCC patients after adjustment for several confounding factors. We repeated the same analysis after classifying patients into two group based on the presence or absence of underlying cirrhosis to identify different in the influence of treatment in the presence of cirrhosis. *P* value <0.05 indicated statistically significant difference.

RESULTS

Among 397 TNM stage I HCC patients, the mean age was 65.04 year with a standard deviation (SD) of 12.5 and the majority of patients were above 60 years of age. 268 (67.5%) of patients were males and 129 (32.5%) were females, with a male and female ratio of 3:1. Additionally, 260 (65.5%) of our patients were Whites and 170 (42.8%) were viral related HCC. 56.4% had a history of alcohol consumption, 59.4% were cigarette smokers, and family history of other cancers was reported in 58.2%. All patients had a solitary nodule with the mean tumor size $\pm$ SD of 6.76 ± 4.58 cm. 72.8% of patients had well to moderate tumor differentiation, 59.7% had underlying liver cirrhosis, ECOG 0–2 (90.5%), AFP <400 ng/ml (74.6%), less than 50% of the liver occupied by the tumor (79.1%), and CTP score A was reported in 78.6% of patients. While, the majority of patients had CLIP score 0–2 (83.1%), based on BCLC staging system 52.2% of patients considered to have an advanced stage (BCLC stage C-D). Finally, approximately 30% of our patients treated with different ablative and local therapy approaches followed by 25.7% treated with surgery either resection or transplantation with the majority of our patients treated with both systemic therapy (20.4%) and hospice (22.4%) (Table 2). As the majority of patients were treated before the FDA approval of sorafenib so we have only 12 patients treated with sorafenib among patients treated with systemic therapy.

Kaplan-Meier curve illustrated that median OS of all TNM stage I patients was 27 months (95% CI; 22.3 – 31.7) (Fig.1). Table 2 shows that there was a significantly shorter OS among patients who have a poorer ECOG performance status, higher AFP, >50% of liver occupied by the tumor, higher CTP score, higher CLIP score, and more advanced BCLC stage. Furthermore, the median OS among surgically treated case was 63 months and 95% CI (43 – 83) compared 42.03 months (35.2 – 48.9) for ablative therapy treated group, 34.3 months (28.3 – 40.3) for local therapy treated patients, 22.1 months (17.1 – 27.1) for systemic therapy treated group, and 8.1 months (5.1 – 11.1) for patients who received only supportive treatment ($P < .0001$). Within systemic therapy treated group median OS of sorafenib treated patients was compared to chemotherapy treated patients (Fig 2). Although there was no significant difference which could be due to small sample size in the sorafenib group there is a trend for longer overall survival among Sorafenib treated patients.

Multivariate Cox regression analysis after adjustment for several confounding factors including age, sex, race, hepatitis status, alcohol consumption, diabetes mellitus, pathology differentiation, underlying cirrhosis, ECOG, AFP, Tumor volume, CLIP and BCLC staging systems, we found that treatment received is the only independent predictor for patients OS. Surgical intervention and local therapy associated with 72% and 64% reduction in the mortality rate compared to non-treated patients respectively ($P < .0001$). Additionally, both systemic and ablation therapy associated with 62% reduction in mortality compared to non-treated group with P value $< .0001$ and $.002$ respectively.

Restricted analysis based on the underlying cirrhosis shows that there is a statistically significant difference in median OS among either cirrhotic and non-cirrhotic stage I HCC patients based on the received treatment. Among cirrhotic group, median OS was of surgically treated patients were 46.5 months (95% CI 24.7 – 68.2) with 70% mortality rate

reduction compared to no treatment after adjustment for several confounding factors. Additionally, the median OS for both ablative and local therapy was 41.8 months and 35.7 months respectively. While, there was no significant difference in the HR of ablative therapy (0.54) (95% CI 0.26 – 1.1) ($P = 0.09$) compared to no treatment, there was a significant difference between local therapy and no treatment group (HR 0.41, 95% CI 0.23 – 0.71, $P = .002$). However, systemic therapy associated with the shortest OS compared to other active treatment approaches (21.8 months), it is associated with 61% mortality rate reduction compared to no treatment ($P = .002$). (Table 3)

Additionally, among non-cirrhotic stage I HCC patients, surgery still associated with the longest OS (91.3 months) compared to ablative therapy (42.03 months), local therapy (33.6 months), systemic therapy (20.8 months) and hospice (11.4 months) ($P < .0001$). Surgical intervention significantly associated with the highest mortality rate reduction (91%) ($P < .0001$) followed by ablative therapy (83%) ($P = .007$), local therapy (79%) ($P < .0001$), and systemic therapy (60%) ($P = .03$). (Table 4)

Table 5 shows that there was no significant difference in the HR of ablative therapy 0.73 (95% CI 0.47 – 1.15) and local therapy 0.75 (0.54 – 1.04) as compared to systemic therapy among whole TNM stage I patients ($P = 0.2$ and 0.08) respectively. We achieve the same results when we classified patients based on the underlying cirrhosis except for patients without cirrhosis local therapy shows a significant tendency ($P = .05$)

DISCUSSION

Our study shows that treatment approaches is an independent survival predictor among TNM stage I HCC patients [T1N0M0] defined as solitary HCC lesion with no vascular invasion or extrahepatic metastasis.

Variable prognostic outcomes have been reported in patients with HCC, either depending upon the involvement of bile duct, tumor thrombus, cirrhosis, poor liver function, large tumor size, vascular invasion, satellite lesions etc. Survival rates at 1-, 3-, and 5 years after hepatic resection among patients with and without bile duct tumor thrombus have been reported to be 92%, 77%, and 48% and 88%, 67% and 52% respectively.^[14] Lang et al has observed 3- and 5-year survival rates of 54% and 39% respectively after R0 resection among patients of HCC without cirrhosis.^[15] Morris-Stiff et al have reported median 1-, 3-, and 5-year OS rates as 80.1%, 55% and 37.1% among patients who underwent resection.^[16] However, in these studies they included HCC patients with variable TNM stages.

Notably, HCC may develop on underlying cirrhotic or non-cirrhotic liver. However, presence of cirrhosis associated with worse HCC prognosis and shorter survival. Many of previous studies addressed the prognostic factors in HCC did not classify patients based on the presence or absence of cirrhosis and the stage of the disease that led to including a heterogeneous group of patients.^[8]

In our current study we focused on TNM stage I HCC patients and we assessed the prognostic factors among whole study population and reclassified based the underlying cirrhosis and we found that tumor resection led to longest overall survival among our whole

population, this is held true even when we sub-classified the study population based on the underlying cirrhosis as compared to the other treatment modalities.

Surgical treatment is considered to be a safe and effective treatment option for elderly HCC patients, especially those without peri-operative co-morbidities or with controlled co-morbidities.^[17] In our population, the Majority of our patients were above 60 years of age showing preponderance among the elderly and 25.7% of patients treated with surgery either resection or orthotopic liver transplantation.

While, surgery is the main curable treatment modalities in early stage HCC patients, some patients may be not candidate for surgical approaches either due to poor performance status or associated medical co-morbidities. In these situations, patients should be treated either with local therapy, ablative procedures, or systemic therapy. Notably, in our study, the median OS with systemic therapy was significantly shorter than both ablative and local therapy among the whole studied population even when we classified patients based on the underlying cirrhosis. Our study had several strengths, including the large number of patients studied over a period of nineteen years. We also used TNM staging for our analysis as it is considered to be an independent predictor of postoperative overall survival in elderly HCC patients.^[17] Additionally, our results of favorable outcome in patients with single tumors and no vascular invasion or extrahepatic metastasis is consistent with recent reports about the good prognosis among this patient population. Furthermore, our database had all clinicopathologic variables collected in a prospective manner at time of enrollment and patients have all treatment history data available for retrospective retrieval. However, our study has some limitation. First, the retrospective nature of the analysis. Second, among patients treated with systemic therapy, only 12 of them had been treated with sorafenib which was approved by the Food and Drug Administration in 2007 to be the only effective HCC systemic therapy associated with prolongation of OS and now is the standard systemic therapy for unresectable HCC patients with preserved liver function, defined as Child-Pugh A.^[1, 18] Although, we have a limited number of sorafenib treated patients, sorafenib treated patients tend to have a longer OS compared to patients treated with other systemic therapy modalities. Additionally, systemic therapy induced a higher rate of mortality reduction compared to no active treatment. So, larger prospective studies are warranted to assess sorafenib outcome for TNM stage I HCC patients who are not candidates for either surgery or ablative/local approaches in presence and absence of cirrhosis.

DISCUSSION

In conclusion, overall TNM stage I HCC patients have a favorable prognosis. Our results indicate that surgery is the best treatment modalities followed by ablative and local therapy. While, systemic therapy associated with the shortest OS, it is still a suitable treatment option for patients who are not candidate for both surgery and local treatment. Up to our knowledge there is no major studies reported the systemic therapy outcome within THN stage I HCC patients. Further prospective studies are warrantee to understand the impact of sorafenib on early stage HCC patients.

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Figure 1:
Median overall survival (OS) among the whole TNM stage I HCC patients.

Figure 2:
Median overall survival (OS) among patients treated with versus systemic therapy.

Table 1:

Types of local, ablation, and systemic therapy that patients received

Type of Treatment	All TNM stage I patients N=397	TNM stage I with cirrhosis N=237	TNM stage I without cirrhosis N=159
Ablation therapy			
Radiofrequency	24	19	5
Ethanol injection	2	2	0
Cryotherapy	2	1	1
Local therapy			
Trans arterial chemoembolization	84	55	29
Radiation	6	4	2
Y90	3	2	1
Systemic therapy			
Soarfenib	12	5	7
Bevacizumab + Erlotinib	3	1	2
Others *	66	38	29

* Others includes 5 Fluorouracil + Interferon, capecitabine alone, PIAF [cisplatin, human recombinant alpha-interferon-2a, doxorubicin, and 5 Fluorouracil], FLAP [floxuridine, leucovorin, doxorubicin, and Cisplatin], capecitabine with interferon, capecitabine with radiotherapy, doxorubicin alone, 5 Fluorouracil with doxorubicin, erlotinib alone, GAP [Gemcitabine, doxorubicin, Cisplatin], 5 Fluorouracil alone, thalidomide alone, Gemcitabine alone.

Table 2: HCC TNM stage I patients demographics, clinico-pathological characteristics, and median overall survival among each parameter

Variables	T1N0M0 N=397 (%)	Median overall survival Months (95%CI)	P value	Univariate HR (95%CI)	P value	Multivariate adjusted HR (95%CI)	P value
Age (ys)	60	31.8 (22.6–40.9)	.07	Reference		Reference	
	>60	27.4(22.7–32.1)		1.25 (0.98–1.6)		1.13 (0.83–1.53)	
Sex	Females	29.2 (18.8–39.6)	.2	Reference		Reference	.4
	Males	28.5 (23.1–33.9)		1.17 (0.92–1.48)		1.08 (0.77–1.52)	
Race	Non-white	26.3 (21.05–31.6)	.06	Reference		Reference	.7
	White	30.5 (23.5–37.4)		0.8 (0.64–1.01)		1.01 (0.75–1.35)	
	None	30.2 (23.3–37.1)		Reference		Reference	
Hepatitis	None	227 (57.2)	.1	Reference		Reference	.9
	Viral	170 (42.8)		1.18 (0.95–1.48)		1.07 (0.78–1.47)	
Alcohol *	No	172 (43.3)	.6	Reference		Reference	.7
	Yes	224 (56.4)		1.06 (0.85–1.33)		1.08 (0.79–1.47)	
smoking *	No	159 (40.1)	.4	Reference		Reference	.6
	Yes	236 (59.4)		1.09 (0.87–1.37)			
Diabetes mellitus *	No	267 (67.3)	.7	Reference		Reference	.8
	Yes	126 (31.7)		1.04 (0.8–1.3)		1.05 (0.77–1.44)	
FHx liver Ca. *	No	357 (89.9)	.3	Reference		Reference	
	Yes	24(6)		0.76 (0.46–1.23)			
FHx of cancers *	No	150 (37.8)	.2	Reference		Reference	
	Yes	231 (58.2)		0.86 (0.68–1.08)			
Personal history of cancer *	No	325 (81.9)	.4	Reference		Reference	
	Yes	67 (16.9)		0.87 (0.65–1.17)			
Pathology differentiation *	Well	174 (43.8)	.3	Reference		Reference	.8
	Moderate	115(29)		0.82 (0.63–1.07)		0.97 (0.72–1.3)	
	Poorly	43 (10.8)		1.02 (0.7–1.5)		1.09 (0.68–1.73)	
Presence of cirrhosis *	No	159 (40.1)	.2	Reference		Reference	.7
	Yes	237 (59.7)		1.1 (0.92–1.44)		1.05 (0.77–1.44)	
ECOG *	0	188 (47.4)	<.0001	Reference		Reference	

Variables	T1N0M0 N=397 (%)	Median overall survival Months (95%CI)	P value	Univariate HR (95%CI)	P value	Multivariate adjusted HR (95%CI)	P value
AFP (ng/ml)	1–2	21.6 (15.3–27.9)		1.64(1.3–.07)	<.0001	3.83 (0.17–86.47)	0.4
	3–4	34 (8.6)		3.59 (2.44–5.27)	<.0001	0.5 (0.03–8.64)	0.6
	<400	296 (74.6)	<.0001	Reference		Reference	
% of liver tumor involvement *	400	101 (25.4)		1.62 (1.23–2.08)	<.0001	1.15 (0.75–1.74)	0.5
	50%	314(79.1)	.001	Reference		Reference	
	>50%	56 (14.1)		1.69(1.23–2.3)	.001	1.03 (0.58–1.82)	0.9
Child–Pugh Class *	A	312 (78.6)	<.0001	Reference		Reference	
	B	67(16.9)		1.63 (1.23–2.17)	.001	1.2 (0.83–1.74)	0.3
	C	10(2.5)		4.53 (2.32–8.84)	<.0001	0.54 (0.09–3.36)	0.5
CLIP score *	Stage 0–2	330(83.1)	<.0001	Reference		Reference	
	Stage 3	29 (7.3)		3.16 (2.12–4.69)	<.0001	2.14 (0.94–4.86)	0.07
	Stage 4–6	3 (0.8)		9.21(2.9–29.2)	<.0001	ND(ND–ND)	0.9
BCLC stage	Stage 0–A	91(22.9)	<.0001	Reference		Reference	
	Stage B	99 (24.9)		1.28 (0.92–1.78)	.1	1.06 (0.71–1.59)	0.8
	Stage C	167 (42.1)		1.81 (1.35–2.43)	<.0001	0.32 (0.01–7.31)	0.5
	Stage D	40(10.1)		4.38(2.91–6.57)	<.0001	3.41 (0.19–62.23)	0.4
	BSC	89 (22.4)	<.0001	Reference		Reference	
First-line treatment *	Surgery	102 (25.7)		0.16 (0.11–0.23)	<.0001	0.28 (0.18–0.44)	<.0001
	Ablation †	28(7.1)		0.29 (0.19–0.45)	<.0001	0.38(0.21–0.7)	.002
	Local ‡	93 (23.4)		0.29 (0.21–0.41)	<.0001	0.36 (0.23–0.56)	<.0001
	Systemic	81 (20.4)		0.37 (0–27–0.52)	<.0001	0.38 (0.24–0.62)	<.0001

Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; ECOG, European Cooperative Oncology Group; AFP, alpha fetoprotein; CLIP, Cancer of Liver Italian Program; BCLC, Barcelona clinic liver cancer

* Some of the data were not available in the patients' medical records or the staging couldn't be calculated due to missing parameters including alcohol drinking (n=1), diabetes mellitus (n=4), cigarette smoking (n=2), family history of liver cancer (n=16), family history of other cancers (n=16), personal history of cancer (n=5), pathological differentiation (n=65), presence of cirrhosis (n=1), ECOG (n=4), % of liver tumor Involvement (n=27), CLIP score (n=35), and first-line treatment (n=4)

† Ablation therapy includes radiofrequency (RFA), ethanol injection, and cryoablation

‡ Local therapy includes transarterial chemoembolization (TACE), hepatic arterial infusion (HAI), and local radiotherapy (RT), radiofrequency (RFA)

Table 3:

HCC TNM stage I patients with cirrhosis: demographics, clinico-pathological characteristics, and median overall survival among each parameter

Variables	T1N0M0 N=237	Median overall survival Months (95%CI)	P value	Univariate HR (95%CI)	P value	Multivariate adjusted HR (95%CI)	P value
Age (ys)	60	35.7 (18.2–53.2)	.1	Reference		Reference	
	>60	27.4 (22.03–32.8)		1.26 (0.92–1.73)	.1	1.62 (1.06–2.47)	.03
Sex	Females	32.1 (15.5–48.8)	.7	Reference		Reference	
	Males	27.4 (22.1–32.7)		1.06 (0.77–1.46)	.7	1.11 (0.71–1.73)	.6
Race	Non-white	26.2 (20.9–31.5)	.6	Reference		Reference	
	White	29.5 (20.5–38.4)		0.92 (0.68–1.24)	.6	1.15 (.79–1.68)	.5
	None	27.5 (15.04–40.03)		Reference		Reference	
Hepatitis	Viral	29 (24.6–33.4)	.9	1.02 (0.77–1.36)	.9	1.13 (.76–1.67)	.5
	No	25.3 (16.5–34.01)		Reference		Reference	
Alcohol *	Yes	29.5 (22.7–36.3)	.5	0.9 (0.67–1.2)	.5	0.97 (0.64–1.48)	.9
	No	25.3 (15.8–34.8)		Reference			
smoking *	Yes	30.5 (23.5–37.4)	.7	0.94 (0.7–1.28)	.7		
	No	28.9 (22.9–34.9)		Reference		Reference	
Diabetes mellitus *	Yes	27.5 (15.3–39.8)	.4	1.13 (0.83–1.53)	.4	1.28 (0.84–1.95)	.3
	No	28.8 (22.9–34.6)		Reference			
FHx liver Ca. *	Yes	63 (7.2–118.8)	.07	0.52 (0.26–1.06)	.07		
	No	25.3 (14.3–36.3)		Reference			
FHx of cancers *	Yes	31.3 (23.2–39.3)	.5	0.5 (0.67–1.22)	.5		
	No	27.4 (21.4–33.4)		Reference			
Personal history of cancer *	Yes	32.4 (23.3–41.6)	1	1.002 (0.69–1.47)	1		
	Well	26.6(19.97–33.2)		Reference		Reference	
Pathology differentiation *	Moderate	35.6 (29.3–41.9)	.4	0.85 (0.6–1.19)	.3	0.85 (0.58–1.25)	.4
	Poorly	21.8 (3.1–40.4)		1.16 (0.7–1.94)	.6	1.48 (0.79–2.76)	.2
	0	43.7 (35.8–51.6)		Reference		Reference	
ECOG *	1–2	21.8 (14.5–29.05)	<.0001	1.78 (1.31–2.41)	<.0001	24.99 (1.97–317.66)	.01
	3–4	5.7 (2.8–8.7)		5.46 (3.33–8.95)	<.0001	3.26 (1.38–7.72)	.007

Variables	T1N0M0 N=237	Median overall survival Months (95%CI)	P value	Univariate HR (95%CI)	P value	Multivariate adjusted HR (95%CI)	P value
AFP (ng/ml)	<400	32.4(26.2–38.6)	.001	Reference	.001	Reference	.002
	400	11.9 (4.5–19.4)					
% of liver tumor involvement *	50%	32.4(27.3–37.6)	<.0001	Reference	<.0001	Reference	.5
	>50%	5.8(2.3–9.3)					
Child–Pugh Class *	A	35.2 (28.6–41.8)	<.0001	Reference	<.0001	Reference	.1
	B	12.7 (4.3–21.1)					
	C	2.8 (1.04–4.6)					
CLIP score *	Stage 0–2	34.5 (28.5–40.4)	<.0001	Reference	<.0001	Reference	.009
	Stage 3	4.6 (3.3–5.9)					
	Stage 4–6	1.4(ND–ND)					
BCLC stage	Stage 0–A	47.8 (38.4–57.3)	<.0001	Reference	<.0001	Reference	.1
	Stage B	25.9 (15.9–35.8)					
	Stage C	24.6 (15.8–33.5)					
	Stage D	5.5 (3.6–7.3)					
	BSC	7.8(5.1–10.5)					
First-line treatment *	Surgery	46.5 (24.7–68.2)	<.0001	Reference	<.0001	Reference	<.0001
	Ablation †	41.8 (35.6–47.9)					
	Local ¶	35.7 (23.1–48.3)					
	Systemic	21.8(10.2–33.3)					

Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; ECOG, European Cooperative Oncology Group; AFP, alpha fetoprotein; CLIP, Cancer of Liver Italian Program; ND, not detectable; BCLC, Barcelona clinic liver cancer

* Some of the data were not available in the patients' medical records or the staging couldn't be calculated due to missing parameters including alcohol drinking (n=1), diabetes mellitus (n=4), cigarette smoking (n=2), family history of liver cancer (n=16), family history of other cancers (n=16), personal history of cancer (n=5), pathological differentiation (n=65), presence of cirrhosis (n=1), ECOG (n=4), % of liver tumor Involvement (n=27), CLIP score (n=35), and first-line treatment (n=4)

† Ablation therapy includes radiofrequency (RFA), ethanol injection, and cryoablation

¶ Local therapy includes transarterial chemoembolization (TACE), hepatic arterial infusion (HAI), and local radiotherapy (RT), radiofrequency (RFA)

HCC TNM stage I patients without cirrhosis: demographics, clinico-pathological characteristics, and median overall survival among each parameter

Table 4:

Variables	T1N0M0 N=159	Median overall survival Months (95%CI)	P value	Univariate HR (95%CI)	P value	Multivariate adjusted HR (95%CI)	P value
Age (ys)	60	31.6 (18.1–45.1)	.2	Reference		Reference	
	>60	28 (18.1–37.9)		1.28 (0.86–1.91)	.2	1.44 (0.81–2.58)	.2
Sex	Females	25.4 (11.6–39.2)	.1	Reference		Reference	
	Males	29.9 (21.1–38.8)		1.29 (0.89–1.85)	.1	0.79 (0.42–1.5)	.4
Race	Non-white	28 (18.5–37.4)	.03	Reference		Reference	
	White	32.1 (21.5–42.7)		0.67 (0.46–0.97)	.04	0.87 (0.5–1.5)	.6
	None	32.1 (22.7–41.5)		Reference		Reference	
Hepatitis	Viral	18.5 (1.1–35.9)	.06	Reference		Reference	
	No	28.7 (15.6–41.8)		1.47 (0.99–2.19)	.06	1.36 (0.73–2.5)	.3
Alcohol *	No	28.7 (15.6–41.8)	.2	Reference		Reference	
	Yes	29.9 (19.1–40.8)		1.29 (0.91–1.84)	.2	1.57 (0.92–2.69)	.1
smoking *	No	28.7 (17.8–39.6)	.2	Reference		Reference	
	Yes	29.9 (19.7–40.2)		1.28 (0.89–1.82)	.2	Reference	
Diabetes mellitus *	No	25.1 (17.6–32.5)	.8	Reference		Reference	
	Yes	34.4 (24.7–44.1)		0.94 (0.65–1.37)	0.8	0.93 (0.54–1.61)	.8
FHx liver Ca. *	No	30.2 (21–39.4)	.7	Reference		Reference	
	Yes	32.1 (10.9–53.3)		1.17 (0.59–2.3)	0.7	Reference	
FHx of cancers *	No	29.9 (19.3–40.5)	.2	Reference		Reference	
	Yes	32.1 (20.1–44.1)		0.81 (0.56–1.16)	.2	Reference	
Personal history of cancer *	No	28.7 (19.8–37.6)	.2	Reference		Reference	
	Yes	30.2 (11.7–48.7)		0.75 (0.47–1.18)	.2	Reference	
Pathology differentiation *	Well	29.9 (19.9–40)	.6	Reference		Reference	
	Moderate	31.6 (16.05–47.2)		0.82 (0.54–1.25)	.4	1.24 (0.71–2.17)	.4
	Poorly	24.4 (22.2–26.6)		0.92 (0.51–1.67)	.8	0.96 (0.44–2.09)	.9
ECOG *	0	38.5 (27.9–49.03)	.02	Reference		Reference	
	1–2	21.3 (12.5–30.05)		1.47 (1.01–2.14)	.04	1.19 (0.59–2.39)	.6
	3–4	11.8 (2.04–21.5)		2.13 (1.11–4.05)	.02	1.08 (0.42–2.76)	.9

Variables	T1N0M0 N=159	Median overall survival Months (95%CI)	P value	Univariate HR (95%CI)	P value	Multivariate adjusted HR (95%CI)	P value
AFP (ng/ml)	<400	37.8 (26.7–48.9)	.03	Reference		Reference	
	400	20.8 (11.6–30.03)		1.54 (1.05–2.26)	.03	0.6 (0.28–1.29)	.2
% of liver tumor involvement *	50%	36.7 (25.4–48.1)	.06	Reference		Reference	
	>50%	14.4 (2.2–26.5)		1.51 (0.97–2.35)	.07	1 (0.45–2.2)	1
Child–Pugh Class *	A	32.1 (23.1–41.1)	.7	Reference		Reference	
	B	21.9 (9.01–34.8)		1.26 (0.7–2.3)	.4	1.18 (0.55–2.53)	.7
	C	28 (ND–ND)		1.58 (0.22–11.41)	.6	3.03 (0.31–30.1)	.3
CLIP score *	Stage 0–2	36.7 (25.8–47.7)	.003	Reference		Reference	
	Stage 3	14.4 (9.5–19.2)		2.4 (1.36–4.24)	.003	1.99 (0.56–6.99)	.3
	Stage 4–6	12 (ND–ND)		4.28 (0.58–31.4)	.2	ND (ND–ND)	ND
BCLC stage	Stage 0–A	47.1 (18.8–75.4)	.04	Reference		Reference	
	Stage B	36.4 (22.7–50.2)		1.29 (0.75–2.21)	.4	0.82 (0.41–1.65)	.6
	Stage C	21.3 (12.5–30.05)		1.72 (1.01–2.93)	.05	ND (ND–ND)	ND
	Stage D	17.1 (3.5–30.7)		2.48 (1.2–5.14)	.01	ND (ND–ND)	ND
First-line treatment *	BSC	11.4 (6.9–15.8)	<.0001	Reference		Reference	
	Surgery	91.3 (58.2–124.5)		0.1 (0.06–0.18)	<.0001	0.09 (0.04–0.2)	<.0001
	Ablation †	42.03 (ND–91.1)		0.2 (0.08–0.5)	.001	0.17 (0.05–0.62)	.007
	Local ‡	33.6 (29.2–38.1)		0.24 (0.14–0.41)	<.0001	0.21 (0.09–0.47)	<.0001
	Systemic	20.8 (10.5–31.2)		0.39 (0.23–0.65)	<.0001	0.4 (0.18–0.91)	.03

Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; ECOG, European Cooperative Oncology Group; AFP, alfa fetoprotein; ND, not detectable; CLIP, Cancer of Liver Italian Program; BCLC, Barcelona clinic liver cancer

* Some of the data were not available in the patients' medical records or the staging couldn't be calculated due to missing parameters including alcohol drinking (n=1), diabetes mellitus (n=4), cigarette smoking (n=2), family history of liver cancer (n=16), family history of other cancers (n=16), personal history of cancer (n=5), pathological differentiation (n=65), presence of cirrhosis (n=1), ECOG (n=4), % of liver tumor Involvement (n=27), CLIP score (n=35), and first-line treatment (n=4)

† Ablation therapy includes radiofrequency (RFA), ethanol injection, and cryoablation

‡ Local therapy includes transarterial chemoembolization (TACE), hepatic arterial infusion (HAI), and local radiotherapy (RT), radiofrequency (RFA)

Table 5:

Multivariate cox regression analysis to assess hazard ratio and 95% confidence interval of local and ablative therapy compared to systemic therapy among stage I HCC patients

Treatment	TNM stage I HCC N = 297		TNM stage I HCC with cirrhosis N = 237		TNM stage I HCC without cirrhosis N = 159	
	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P
Systemic						
Ablative	0.73 (0.47–1.15)	.2	0.93 (0.53–1.61)	.8	0.5 (0.21–1.2)	.1
Local	0.75 (0.54–1.04)	.08	0.91 (0.58–1.42)	.7	0.6 (0.36–0.99)	.05