Treatment Patterns and Outcomes in Patients With Hepatocellular Carcinoma Stratified by Stage-Guided Treatment Categories

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Abstract

Purpose: The purpose of this study was to assess the survival and treatment patterns of hepatocellular carcinoma (HCC) stratified by the NCCN stage-guided treatment categories in the absence of a universally accepted staging system for HCC. **Methods:** Patients with HCC were identified using ICD-9 codes and inclusion in the Huntsman Cancer Institute tumor registry. Patients were stratified by the NCCN groupings around the time of diagnosis as potentially resectable or operable (RESECT), potentially transplantable (TRANSP), unresectable (UNRESECT), inoperable due to performance status (INOPER), or having metastatic (METAST) disease. Survival and treatment patterns were assessed by NCCN stage-guided treatment categories. **Results:** A total of 221 patients (72.9% men) with HCC were identified. At the time of diagnosis, patients were categorized as RESECT (n=28, 12.7%), TRANSP (n=33, 14.9%), UNRESECT (n=77, 34.8%), INOPER (n=40, 18.1%), and METAST (n=38, 17.2%). Staging information was not specified for 5 patients (2.3%) even after chart review. Kaplan-Meier analysis demonstrated significant differences in survival between RESECT and UNRESECT categories, and between UNRESECT and METAST categories. The median survivals in RESECT, TRANSP, UNRESECT, INOPER, and METAST categories were 594, 562, 247, 167, and 44 days, respectively. Patients considered RESECT most frequently underwent resection (61%, n=17) and patients considered TRANSP had the highest use of liver transplants (33.3%, n=11). Use of any treatment was low in the METAST (31.6%, n=12) and INOPER (60.0%, n=24) groups. **Conclusions:** Treatment patterns in the NCCN groupings correlated with recommended treatment strategies. Overall, the NCCN groupings have a linear relationship in overall survival. (J Natl Compr Canc Netw 2015;13:987–994)

Background

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver. The American Cancer Society estimates that 33,190 new cases for primary liver cancer and intrahepatic bile duct cancer were diagnosed in 2014 in the United States.¹ Moreover, Tanaka et al² reported that the incidence of HCC is expected to increase over the next 2 decades.² Cirrhosis is the most common risk factor, which is also a consequence of hepatitis C virus (HCV) or hepatitis B virus (HBV) infections.³ Other risk factors for HCC include heavy alcohol use, Asian race, male sex with confirmed heritable metabolic diseases (Wilson disease, porphyria cutanea tarda, alpha-1

antitrypsin deficiency, tyrosinemia, and glycogen storage diseases), obesity, and diabetes.⁴

A defined tumor or cancer staging system is important to define survival estimates and to guide treatment options.⁵ HCC causes 2 pathologic changes: tumorous changes in the hepatocytes, and cirrhosis, chronic inflammation, and fibrotic changes or liver parenchyma.⁶ These changes have led to several different staging practices for HCC. For example, the AJCC/TNM system evaluates tumor extension and does not take into account the residual liver function,⁷ which may lead to inadequate staging.⁸ Each staging system may not apply to all patients with HCC because of differing tumor

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morphology, and the incidence of comorbidities may vary from region to region. Additionally, the Okuda staging system is inapplicable to early HCC, because it was derived from advanced HCC cases.⁹ The Barcelona Clinic Liver Cancer (BCLC) system is endorsed by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD)^{10,11}; however, the BCLC system's acceptance is not universal.¹² Consequently, geographic-based differences in HCC staging and description still exist, and validation is still an open issue for both Western and Asian-Pacific patients.

Given the absence of a universally accepted staging or descriptive standard for HCC, the 2015 version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Hepatobiliary Cancers classifies the severity of HCC by treatment groups as (1) potentially resectable (RESECT) or transplantable (TRANSP), (2) unresectable (UNRESECT), (3) inoperable based on performance status or comorbidity, with local disease only (INOPER), and (4) metastatic disease (METAST).¹³ Our research used these NCCN groups to assess treatment patterns and survival.

Methods

Data Source

The University of Utah Health Sciences Center enterprise data warehouse (EDW) provided the HCC research data mart for this study; an EDW derivative was based on the list of HCC cases identified in this study. Death certificates were linked via an electronic master subject computerized index link to the Utah Population Database (UPDB), which hosts state death certificates. Cases within the HCC research data mart were linked to the Huntsman Cancer Institute Tumor Registry (HCI-TR) through the same master subject index, and the HCI-TR was used to identify tumor staging and date of HCC diagnosis. The HCI-TR served to confirm 201 HCC cases. The remaining 20 study cases were confirmed via manual inspection of the case in the medical record.

Patients and Study Design

This study was a retrospective observational cohort analysis. The index date was defined as the date of HCC diagnosis in the EDW. Inclusion criteria were as

follows: patients aged 18 years or older at the time of diagnosis between 1995 and 2010; at least 2 International Classification of Diseases, 9th revision (ICD-9) codes for HCC (ie, 155.0), with ICD for Oncology site and histology codes indicative of HCC in the HCI-TR, and at least 2 encounters in the EDW, with 1 encounter at least 30 days from the index date (Figure 1, available online, in this article, at JNCCN.org). Demographic characteristics (age, sex, race, plan type, region) were recorded on index date and clinical characteristics (Charlson Comorbidity Index [CCI], cirrhosis, HBV, HCV, alcohol liver, encephalopathy, nonalcoholic fatty liver disease) were identified by ICD-9 codes and assessed within 30 days of the index date. Comorbidities were assessed by the CCI in the year prior to the index date and modified by excluding the weight for any solid tumor or metastatic solid tumor diagnosis.¹⁴ Treatment patterns were evaluated according to Current Procedure Terminology (CPT) codes within the EDW for ablation, resection, transplant, embolization, and radiation. Chemotherapy use was obtained from linked pharmacy records within the EDW. Date and cause of death were obtained from the UPDB. Survival and treatments were evaluated on the date of diagnosis forward and stratified by NCCN groupings at the time of diagnosis and censored at the date of last follow-up.

Classification of Stage-Guided Treatment Categories

Stage at diagnosis was ascertained by linking the EDW to the HCI-TR, which provided AJCC TNM staging at diagnosis. All patients with stage IIIB and IIIC disease were classified as UNRESECT, and patients with stage IV (M1) disease were classified as METAST. All patients classified as stage I to IIIa were assessed by chart review to determine whether the treating physicians deemed the patient as resectable, transplantable, unresectable, or inoperable due to performance status around the time of diagnosis. To facilitate chart review, a semiautomated keyword search of the electronic notes was conducted with a specially built text search tool using keywords and Boolean constructs. Only physician notes within 45 days of diagnosis were used to determine the stage-guided treatment categories.

Primary Treatment Modality

The primary treatment modality was categorized into mutually exclusive groups based on the treatment ap-

proach most likely to confer a survival benefit. First, patients who received a liver transplantation at any time during survival were identified. Then patients who received a liver resection without transplantation were selected. Of those remaining, any patient who received radiofrequency ablation, other ablation procedures (cryoablation, percutaneous alcohol injection, microwave), or transarterial chemoembolization were assigned to the liver-directed therapy group. Patients who received chemoembolization and ablation were grouped together, because these procedures are broadly considered locoregional therapy; however, results between ablation and chemoembolization are presented separately. Lastly, patients who received only radiation therapy, systemic therapy, or no therapy were identified (Appendix 1 and Figure 1, both available online, in this article, at JNCCN.org).

Statistical Methods

Descriptive statistics were used to describe demographic characteristics, baseline clinical characteristics, and comorbidities. Chi-square test was used to evaluate the differences between the categorical variables. For time to event, median values and Kaplan-Meier survival estimates were reported. Median survival time among different NCCN groups and different treatments were calculated.

The log rank test was used to test for statistical differences in survival between groups. The variables tested included age, sex, CCI, NCCN groups, the presence or absence of cirrhosis, alcoholic cirrhosis, serologic evidence of HBV or HCV infection, encephalopathy, and nonalcoholic fatty liver disease. Multivariate Cox proportional hazards regression was used to test the relationship between various prognostic factors and survival in all patients. Variables in the COX analysis were included if they had a *P* value of less than .25 in the univariate analysis. All statistical tests were performed at an a priori significance level of 0.05 using Stata/SE version 10.0 (StataCorp LP, College Station, TX). The protocol for this study was approved by University of Utah Institutional Review Board and the Resource for Genetic and Epidemiologic Research at the University of Utah on November 3, 2010.

Results

Patient Characteristics

The EDW database contained approximately 1.2 million unique patients between 1995 and 2010 (Figure 1, both available online, in this article, at JNCCN.org). A total of 917 adult patients with ICD9 diagnosis codes for HCC were eligible for inclusion and were matched to the HCI-TR (*n*=221). A total of 216 patients were confirmed to have HCC stage information between 1995 and 2010, and the median follow-up time in this cohort was 258 days. The cohort was stratified into the following NCCN staging groups: 13.0% (*n*=28) RESECT; 15.3% (*n*=33) TRANSP; 35.6% (*n*=77) UNRESECT; 18.5% (*n*=40) INOPER; and 17.6% (*n*=38) METAST (Figure 1, available online, in this article, at JNCCN.org). The mean age of the cohort was 59.7 years (SD=12.1). Most subjects were male (73.2%), Caucasian (54.6%), and insured commercially (31.0%), and lived in the state of Utah (73.2%), and the mean modified CCI score was 5.4 ± 2.4 . Cirrhosis was present in 66.2% of patients at diagnosis, and 27.8% patients presented with encephalopathy. Patients in the transplantable group had the highest CCI score, youngest age, and highest proportion of cirrhosis (100%), HCV (70%), encephalopathy (61%), alcoholic cirrhosis (52%), and nonalcoholic fatty liver disease (42%). The distributions of gender (*P*=.001), race (*P*=.008), CCI score (*P*=.011), presence of cirrhosis (*P*<.001), HCV (*P*<.001), alcoholic cirrhosis (*P*=.001), nonalcoholic fatty liver disease (*P*<.001), and encephalopathy (*P*<.001) were significantly different among the NCCN groups (Table 1, available at the end of this article).

Treatment Patterns

Patients classified with RESECT disease had the highest proportion (96.4%) receiving any treatment, followed by TRANSP (81.8%), UNRESECT (80.5%), INOPER (60.0%), and METAST (31.6%) groups. The treatments received generally followed the NCCN Guidelines.^{5,13} The highest use of surgical resection was observed in the RESECT group and more liver transplants were performed in the TRANSP group. Reasons for not receiving a transplant in those classified as transplantable at diagnosis (*n*=22) included still waiting for transplant at last follow-up (*n*=8), size of lesions or disease progression before transplantation (*n*=7), poor performance status or comorbidity (*n*=5), and alcohol/drug abuse

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Table 3 Primary Treatment Modality Received Stratified by Stage at Diagnosis

Treatment	RESECT N=28 n (%)	TRANSP N=33 n (%)	UNRESECT N=77 n (%)	INOPER N=40 n (%)	METAST N=38 n (%)	All N=216 n (%)
Resection	16 (57%)	1 (3%)	5 (6%)	1 (3%)	2 (5%)	25 (12%)
Liver transplant	3 (11%)	11 (33%)	1 (1%)	2 (5%)	—	17 (8%)
Liver-directed therapy	4 (14%)	13 (39%)	40 (52%)	16 (40%)	3 (8%)	76 (35%)
Radiation therapy	3 (11%)	0 (0%)	2 (3%)	1 (3%)	3 (8%)	9 (4%)
Systemic therapy	1 (4%)	1 (3%)	11 (14%)	4 (10%)	4 (11%)	21 (10%)
No treatment	1 (4%)	7 (21%)	18 (23%)	16 (40%)	26 (68%)	68 (31%)

Abbreviations: METAST, metastatic disease; INOPER, inoperable due to performance status; RESECT, potentially resectable or operable; TRANSP, potentially transplantable; UNRESECT, unresectable.

CCI were 2.14 times as likely to die as those with a lower CCI (95% CI, 1.30–3.52; $P=.003$). Conversely, patients who were older had a 0.03% reduction in the risk of death compared with those who were younger (95% CI, 0.96–0.99; $P=.005$) (Table 5).

Discussion

To our knowledge, this is the first study stratifying survival in HCC by the NCCN stage-guided treatment categories specified in the NCCN Guidelines. Our study demonstrates distinct overall survival and treatments based on these categories. Our results showed no statistically significant difference in survival between the RESECT and TRANSP groups ($P=.94$) and the UNRESECT and INOPER ($P=.79$) groups, but the treatment decisions were different between these groups. Survival outcomes between the RESECT and TRANSP groups were similar, partly

because only 33% of the TRANSP group received a transplant, because many were still waiting for transplant at last follow-up. Survival outcomes were improved in patients receiving a liver transplant compared with those undergoing a surgical resection alone; however, this did not meet significance, presumably because of sample size considerations. In general, the NCCN stage-guided treatment categories predicted overall survival.

Similar to our studies,^{15,16} resected patients or those who received liver-directed therapies had improved median overall survival (21.6 and 14.1 months, respectively). Our study also demonstrates that liver-directed therapies improve survival compared with no treatment, which is similar to recent systemic reviews and cohort studies.^{16–18}

Our results suggest that patients who are older had a 0.03% reduction in the risk of the death compared with those who were younger (95% CI, 0.96–0.99; $P=.005$); however, patients older than 65 years in our cohort were less cirrhotic (68% vs 76%) and

Figure 2 Primary treatment modality received stratified by year.

Figure 3 Kaplan-Meier curve among different NCCN groups. Abbreviations: METAST, metastatic disease; INOPER, inoperable due to performance status; RESECT, potentially resectable or operable; TRANSP, potentially transplantable; UNRESECT, unresectable.

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Table 4 Overall Survival Outcomes

	N	Median Survival (IQR), mo	P Value
Median overall survival	216	11.4 (3.5–30.8)	–
NCCN Grouping			
RESECT	28	29 (11.2–60.9)	Ref
TRANSP	33	29.3 (12.2–43.5)	.759
UNRESECT	77	11.1 (4.8–28.1)	.027
INOPER	40	9.5 (4.1–32.9)	.032
METAST	38	1.4 (0.7–5.2)	<.001
Primary treatment modality			
Resection	25	21.6 (9.6–43.5)	Ref
Liver transplantation	17	30.8 (18.8–60.9)	.211
Liver-directed therapy	76	14.1 (7.6–33.4)	.520
Ablation	22	28.1 (17.0–34.5)	.714
Embolization	54	12.1 (5.1–33.4)	.222
Radiation therapy	9	9.5 (5.2–11.4)	.159
Systemic therapy	21	7.1 (2.8–11.4)	.003
No therapy	68	2.9 (0.7–11.1)	≤.001

Abbreviations: IQR, interquartile range; METAST, metastatic disease; INOPER, inoperable due to performance status; Ref, reference; RESECT, potentially resectable or operable; TRANSP, potentially transplantable; UNRESECT, unresectable.

had a reduced incidence of HBV or HCV (35.8% vs 62.4%) compared with younger patients. Kim et al¹⁹ reported no statistical significant difference among 5-year disease-specific survival rates between those aged 35 to 49 years, 50 to 64 years, and older than 65 years (87% vs 86% vs 85%; $P=.858$) after orthotopic liver transplant. Moreover, Hanazaki et al²⁰ found that the overall and disease-free survival rates after hepatic resections were also similar between older and younger patients ($P=.95$). Because of the small

sample size of the study, the finding of increasing survival with increasing age should be interpreted with caution. Even though sex is not a significant factor for HCC survival in the current study ($P=.407$), Yang et al²¹ found that the hazard ratio for overall survival of women versus men was 0.83 (95% CI, 0.77–0.88).

Farinati et al¹⁵ stated the purpose of a staging system is to (1) provide prognostic information, (2) distinguish the treatments results, and (3) recommend the treatment in a given stage. Sirivatanauksorn and Tovikkai⁶ compared 6 HCC prognostic staging systems: Okuda,⁹ TNM,⁸ CLIP,²² BCLC,¹⁰ CUPI,²³ and JIS²⁴ using the patients in Thailand from 2001 to 2007, and they concluded that TNM and Child-Pugh are the representative systems in patients with HCC who undergo surgical resection. Marrero et al¹² compared 7 HCC prognostic staging systems, including the above staging systems and GRETCH,²⁵ using the patients in University of Michigan from 2000 to 2003, and concluded that the BCLC staging system provided the best prognostic stratification for patients who have both cirrhosis and HCC, because it includes performance status, tumor extent, liver function, and treatment.²⁶ Each system includes different characteristics and has its own advantages and disadvantages (Table 6).^{12,24,26,27} Based on our study, the NCCN stage-guided treatment categories provide prognostic information and distinguish treatment pathways. Therefore, NCCN stage-guided pathways can provide a reliable stratification system in HCC.

This study had some limitations. First, we cannot confirm the data accuracy in the EDW; documentation errors may be present in the electronic chart. Even though stage at diagnosis was validated through chart review, documentation errors may still exist. The major limitation of a retrospective study is the precise identification of the supposed phenotype, although this is negligible in this registry-verified study. Another problem is that, although we can assume registry cases are nearly perfect as to phenotype (stage at diagnosis), we cannot assume the same ascertainment through manual identification by the research team for the stage-guided treatment category. Second, medication and procedure data may be incomplete, because some patients may receive treatment outside the institution, which is not captured in the EDW. Also, our limited cohort size was not able to predict some of the outcomes, presumably because of low power to detect differences in smaller subgroups. In addition, a time

Figure 4 Kaplan-Meier curve among different treatment groups.

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Table 5 Predictors of Survival: Cox Regression Multivariate Analysis (Excluding Patients With Metastatic Disease)

Variable	n	Univariate Overall Survival		Multivariate Overall Survival	
		HR (95% CI)	P Value	HR (95% CI)	P Value
Cirrhosis (Ref: no cirrhosis)	178	1.03 (0.68–1.55)	.905	–	–
Alcoholic cirrhosis (Ref: no alcoholic cirrhosis)	178	0.89 (0.59–1.34)	.581	–	–
HBV (Ref: no HBV)	178	1.31 (0.79–2.18)	.290	–	–
HCV (Ref: no HCV)	178	0.95 (0.65–1.39)	.794	–	–
Sex (female vs male) (Ref: female)	178	1.19 (0.79–1.80)	.407	–	–
Encephalopathy (Ref: no encephalopathy)	178	1.09 (0.74–1.62)	.661	–	–
Age (continuous)	178	0.99 (0.97–1.00)	.126	0.97 (0.96–0.99)	.004
State (others vs Utah) (Ref: others)	178	1.02 (0.99–1.06)	.123	1.02 (0.99–1.05)	.190
Nonalcoholic fatty liver disease (Ref: nonalcoholic fatty liver disease)	178	0.71 (0.46–1.12)	.143	0.79 (0.49–1.28)	.340
NCCN Category	178				
RESECT			Ref		Ref
TRANSP		0.93 (0.47–1.84)	.827	0.79 (0.38–1.64)	.530
UNRESECT		1.97 (1.13–3.42)	.016	2.02 (1.15–3.55)	.010
INOPER		2.05 (1.11–3.77)	.021	1.94 (1.04–3.62)	.040
CCI	178				
0–4			Ref		Ref
5–6		1.03 (0.65–1.63)	.890	1.09 (0.68–1.75)	.710
7–13		1.48 (0.94–2.33)	.095	2.14 (1.30–3.52)	.003

Abbreviations: CCI, Charlson Comorbidity Index; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; INOPER, inoperable due to performance status; Ref, reference; RESECT, potentially resectable or operable; TRANSP, potentially transplantable; UNRESECT, unresectable.

lag of 1 year was present in the concurrency of death certificates from the Utah Department of Health and updates to UPDB. Lastly, the clinical characteristics in our study were limited by missing/unknown data, particularly for the extent of cirrhosis and the morbidity associated with liver insufficiency.

Conclusions

Through standard review of medical notes with mitigation of variance, we demonstrate that the NCCN stage-guided treatment categories defined by the NCCN Guidelines predict overall survival and treatment use. Even though this study only used case records around the time of diagnosis for retrospective

case stratification to the NCCN stage-guided groups, the categorization may be biased by the treatments received. Therefore, further validation in a prospective cohort is warranted. Additionally, because of the small sample size of the current study, future studies could be conducted across cancer centers to obtain the necessary sample size and power to fully validate the NCCN stage-guided treatment categories.

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Table 1 Demographics and Clinical Characteristics of Study Subjects

Demographic Variable	RESECT (N=28) n (%)	TRANSP (N=33) n (%)	UNRESECT (N=77) n (%)	INOPER (N=40) n (%)	METAST (N=38) n (%)	All (N=216) n (%)	P Value
Age, y (mean $\pm$ SD)	60.9 $\pm$ 13.7	57.6 $\pm$ 7.5	58.5 $\pm$ 12.0	60.8 $\pm$ 9.6	61.7 $\pm$ 16.3	59.7 $\pm$ 12.1	.21
Sex							.001
Male	12 (43%)	29 (88%)	56 (73%)	32 (80%)	29 (76%)	158 (73%)	
Female	16 (57%)	4 (12%)	21 (27%)	8 (20%)	9 (24%)	58 (27%)	
Race							.008
Black/African American	0 (0%)	1 (3%)	2 (3%)	1 (3%)	2 (5%)	6 (3%)	
Caucasian/White	18 (64%)	22 (67%)	48 (62%)	17 (43%)	13 (34%)	118 (55%)	
Others	5 (18%)	3 (9%)	13 (17%)	9 (23%)	4 (11%)	34 (16%)	
Unknown	5 (18%)	7 (21%)	14 (18%)	13 (33%)	19 (50%)	58 (27%)	
Plan type							.19
Commercial	10 (36%)	10 (30%)	26 (34%)	14 (35%)	7 (18%)	67 (31%)	
Medicare	11 (39%)	12 (36%)	21 (27%)	12 (30%)	7 (18%)	63 (29%)	
Medicaid	4 (14%)	1 (3%)	14 (18%)	2 (5%)	6 (16%)	27 (13%)	
Others	3 (11%)	7 (21%)	12 (16%)	6 (15%)	5 (13%)	23 (11%)	
Missing value	0 (0%)	3 (9%)	4 (5%)	6 (15%)	13 (34%)	26 (12%)	
Region							.711
Utah	18 (64%)	21 (64%)	56 (73%)	33 (83%)	30 (79%)	158 (73%)	
Non-Utah	10 (36%)	12 (36%)	21 (27%)	7 (18%)	8 (21%)	58 (27%)	
Charlson Comorbidity Index scores, mean $\pm$ SD	4.9 $\pm$ 2.7	6.3 $\pm$ 1.9	5.5 $\pm$ 2.3	5.6 $\pm$ 2.1	4.8 $\pm$ 2.8	5.4 $\pm$ 2.4	
0–4	16 (57%)	3 (9%)	24 (31%)	11 (28%)	17 (45%)	71 (33%)	.011
5–6	6 (21%)	16 (48%)	29 (38%)	15 (38%)	9 (24%)	75 (35%)	
7–13	6 (21%)	4 (12%)	24 (31%)	14 (35%)	12 (32%)	70 (32%)	
Cirrhosis	12 (43%)	33 (100%)	58 (75%)	28 (70%)	12 (32%)	143 (66%)	<.001
HBV only	4 (14%)	2 (6%)	12 (16%)	6 (15%)	2 (5%)	26 (12%)	.387
HCV only	3 (11%)	23 (70%)	31 (40%)	16 (40%)	10 (26%)	83 (38%)	<.001
Alcoholic liver	4 (14%)	17 (52%)	26 (34%)	6 (15%)	6 (16%)	59 (27%)	.001
Encephalopathy	5 (18%)	20 (61%)	22 (55%)	11 (28%)	2 (5%)	60 (28%)	<.001
Nonalcoholic fatty liver disease	7 (25%)	14 (42%)	9 (12%)	8 (20%)	0 (0%)	38 (18%)	<.001

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; METAST, metastatic disease; INOPER, inoperable due to performance status; RESECT, potentially resectable or operable; TRANSP, potentially transplantable; UNRESECT, unresectable.

Table 6 Comparison of Staging Systems for Hepatocellular Carcinoma

Staging Classification	Tumor Staging	Liver Function	Performance Status	Serum Tumor Markers	Validation
Okuda ⁹	Tumor size (</> 50% of liver)	Ascites, albumin, bilirubin	No	No	NA
TNM ⁸	Number of nodules, tumor size, presence of portal vein thrombosis, and presence of metastasis	No	No	No	NA
CLIP ²²	Number of nodules, Tumor size (</> 50% of liver), and presence of portal vein thrombosis	MELD	No	AFP	Canada; Italy; Japan
BCLC ¹⁰	Number of nodules, tumor size, presence of portal vein thrombosis	Child-Pugh, bilirubin, portal hypertension	Yes	No	Italy; USA
CUPI ²³	TNM	Ascites, bilirubin, alkaline phosphatase	Presence of symptoms	AFP	NA
JIS ²⁴	TNM	MELD	No	No	Japan
GRETCH ²⁵	Presence of portal vein thrombosis	Bilirubin, alkaline phosphatase	Karnofsky score	AFP	NA
NCCN ¹³	Tumor size	Child-Pugh, bilirubin, albumin, alkaline phosphatase, portal hypertension	Yes	AFP	NA

Abbreviations: AFP, α -fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; GRETCH, Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire; JIS, Japan Integrated Staging; MELD, Model For End-Stage Liver Disease; NA, not available.

Stage-Guided Treatment for Hepatocellular Carcinoma

Figure 1 Flowchart of study cohort.

Abbreviations: Dx, diagnosis; EDW, University of Utah Health Sciences Center enterprise data warehouse; HCC, hepatocellular carcinoma; ICD-9, International Classification of Diseases, 9th revision; METAST, metastatic disease; INOPER, inoperable due to performance status; RESECT, potentially resectable or operable; TRANSP, potentially transplantable; UNRESECT, unresectable.

Appendix 1 Algorithm for the primary treatment modality. Group based on procedures most likely to have a meaningful benefit and received at any time.

All patients who had a transplant	• Liver transplantation
If not a transplant, then resection	• Resection
If no transplant or resection, then embolization	• Liver-directed therapy
If none of the above, chemotherapy	• Systemic therapy
If none of the above, radiation	• Radiation therapy
No treatments	• No therapy