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Potentially curative treatment in patients with hepatocellular cancer—results from the liver cancer research network

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SUMMARY

Background
The extent to which potentially curative therapies are used in patients with hepatocellular cancer (HCC) and their related outcomes are unknown in the US.

Aim
To determine the rate and outcomes of potentially curative treatment in patients with HCC.

Methods
Eleven US centers followed patients with HCC between 2001 and 2007. We determined rates of liver transplantation, surgical resection, or tumour ablation during follow-up, examined differences in adjusted survival of patients receiving these treatments, and determined the factors associated with receipt of potentially curative treatment.

Results
Of the 267 patients, 76 (28%) patients had early HCC, defined as Child A or B cirrhosis, with a solitary HCC or ≤3 nodules, each ≤3 cm. Of these, 53 (69.7%) received curative treatment. Thirty six percent of patients with non-early HCC received curative treatment. Compared to patients with non-early HCC who did not receive curative treatment, patients with early HCC and curative treatment had the best survival [hazard ratio, HR = 0.19 (95% CI, 0.08–0.42)] followed by patients with advanced HCC who received curative treatment [HR = 0.37 (95% CI, 0.22–0.64)]. Baseline performance status was significantly associated with receipt of curative treatment as well as survival after adjusting for demographics, clinical characteristics, and HCC stage.

Conclusions
In this multicenter database, most of the patients with early HCC received potentially curative treatment. However, only 28% of patients had early HCC. One-third of patients with non-early HCC also underwent curative therapy. Potentially curative treatment improved survival and this effect was seen in patients with early as well as non-early HCC.

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INTRODUCTION

The incidence of hepatocellular cancer (HCC) has increased by more than two-fold over the past two decades.[1, 2] Most of this increase is attributed to hepatitis C virus (HCV) infection acquired 2–3 decades earlier.[1] A large number of HCV-related HCCs are expected in the next decade given that approximately 3.0 million individuals are HCV infected in the United States.[3]

The prognosis of advanced HCC is poor.[4–6] However several potentially curative treatment modalities are available for patients with early stage HCC. These include surgical resection, liver transplantation, and local ablation. Surgical resection is the primary therapeutic option for patients without advanced cirrhosis and with well-preserved liver function and normal portal pressure. Among candidates who receive resection, 5-year survival can exceed 50%.[4, 7–11] Liver transplantation is the treatment of choice for HCC patients with decompensated cirrhosis, with 5-year recurrence free survival close to 70%.[12] Potential contraindications to liver transplantation include presence of systemic co-morbidities, and current drug and/or alcohol use. For patients who are not candidates for surgical treatment, local tumour ablation treatments can be used to destroy the tumour without damaging the surrounding liver tissue. These tumour ablation therapies include injection of the tumour with absolute ethanol or radiofrequency ablation. The 5-year survival among patients with compensated cirrhosis and HCC smaller than 5 cm who were treated with local ablation may be as high as 50%.[7, 13, 14]

There is a paucity of data evaluating the extent, patterns, and outcomes of potentially curative treatment in patients with HCC in the United States. This information is important not only for understanding the diffusion of this practice but also in determining potential effectiveness of HCC surveillance programs—programs that rely heavily on availability and timely application of curative treatments in patients with early HCC.

Using data from a prospective cohort of patients with HCC, we sought to measure the extent to which patients with HCC received potentially curative treatment and investigated whether use of such treatment improved survival. We also determined the factors associated with receipt of potentially curative treatment among patients with HCC.

MATERIALS AND METHODS

Data Source

We used prospectively collected data from the Liver Cancer Research Network (LCRN), a group of 11 medical centers throughout the United States experienced in the care of patients with liver disease. The 11 centers participating in the LCRN were Beth Israel Deaconess Medical Center, Loyola University Medical Center, Mayo Clinic in Rochester, Oregon Health & Science University, Saint Louis University, University of Michigan, University of Chicago, University of Southern California, University of California in San Diego, Long Beach Veteran Affairs Medical Center, and Vanderbilt University Medical Center.

Patients with HCC were enrolled if they were seen at any of the participating centers between 20 January 2001 and 14 September 2007. The diagnosis of HCC was based on histopathology, and if histopathology was not available, by a mass lesion on imaging with AFP levels >1000 ng/mL, a mass lesion with characteristics of HCC (hypervascularity, arterial to portal vein shunts, portal vein thrombosis near the defect, or tumour in the portal vein) on two liver imaging studies, or 1 additional imaging study showing a mass lesion with characteristics of HCC that either increased in size over time or was accompanied by AFP level >200 ng/mL and more than tripling of baseline value.

After patient consent, standardized data collection forms were used to collect sociodemographic, risk factor, liver disease, tumour, and treatment characteristics-related information. Patients were followed longitudinally at 6 months intervals. Tumour and treatment parameters were recorded during each follow up visit.

Study sample

Our study sample comprised of patients diagnosed with HCC with at-least one follow up visit during the study period. We categorized patients on the basis of Barcelona Center Liver Cancer (BCLC) staging.[5] We defined early stage HCC as Child Class A or B, with a solitary HCC that was <5 cm in size, or up to 3 nodules, each <3 cm in size. We excluded patients if they did not have data to allow estimation of the BCLC stage. The BCLC staging system incorporates information regarding performance status in classifying the stage of HCC. We removed performance status criterion in ascertaining stage of HCC because we wanted to examine the independent effect of this variable on the receipt of curative treatment as well as patients' long term outcomes. However, as a sensitivity analysis, we strictly followed the BCLC system and classified patients with limited performance status as non-early HCC. In another analysis, we re-classified patients as eligible for potentially curative therapy if they met the University of California, San

Francisco (UCSF) expanded criteria defined as evidence of single lesion $\leq$6.5 cm or up to 3 lesions, none larger than 4 cm, with a maximum combined tumour bulk of $\leq$8 cm.[15] Patients with any evidence of extra-hepatic spread or vessel involvement were excluded from early stage group regardless of their local tumour burden.

Study outcomes

We defined a patient as having received potentially curative treatment if s/he received liver transplantation, surgical resection (wedge resection, segmental resection, lobectomy), or tumour ablation (alcohol injection ablation and radiofrequency ablation) during follow up. We defined patients' index date as the date of first diagnosis of HCC. We followed all participants longitudinally and terminated the follow-up at either the time of the patient's death or 14 September 2007, whichever occurred first.

Statistical analysis

We analyzed patient data using SAS, version 9.2 (SAS Inc., Cary, NC, USA). All *P*-values were two-sided using an alpha of 0.05. We used ANOVA to compare means between groups and used chi-square or Fisher's Exact tests to compare proportions. We expected to see a strong association between the stage of HCC and survival. Therefore, to examine the relationship between curative treatment and survival, we used an interaction term for this variable (receipt vs. non-receipt of potentially curative treatment) and a binary variable indicating early vs. non-early HCC using bivariate Cox proportional-hazards model. We next measured the independent relationship between curative treatment and survival while adjusting for the following predictors at baseline: age, gender, race, liver disease severity (as measured by presence of ascites and baseline values of bilirubin and albumin), presence of medical comorbidity, performance status, and HCC volume of the treating center. Based on centers' self-reported data regarding the annual number of unique HCC patients seen, we categorized each center as high (>100 patients) vs. medium-low volume (<100 patients) center. Table 1 specifies the definitions and categorization of other variables. We did not include MELD score in our analysis because it was missing in 60% of our patients (data collection for the study preceded introduction of MELD score as a prognostic marker for liver transplant allocation in the US). We computed the adjusted hazard ratios (HR) and 95% CI to estimate the strength of association of each predictor with time to death. Using multivariate logistic regression analysis, we determined whether and to what extent patient demographic (age, sex, race), liver disease characteristics (liver disease severity), medical co-morbidity, performance status, and treating facility characteristics (medical center volume) were associated with receipt of potentially curative treatment among patients with HCC, while adjusting for stage of cancer. To determine if the pre-specified covariates had differential impact on treatment decisions in patients with early vs. non-early HCC, we stratified the sample based on the stage of HCC and conducted a regression analysis in each group separately. We entered number and size of HCC tumours as additional variables in these sensitivity analyses. Last, we considered the possibility that we might have classified some patients who died while awaiting liver transplantation as untreated, where in fact these patients received the recommended treatment related care (i.e. referral for transplantation). In order to address this, we re-classified patients who were considered eligible for (but did not receive) transplantation during the study follow-up as having received the recommended treatment related care for their HCC. We then repeated the Cox proportional-hazards model to examine the relationship between treatment and survival using this new variable.

RESULTS

Sample Characteristics

The LCRN database included information on 512 patients with HCC. Of these, 302 completed at-least one follow up and 267 had complete data to allow staging on the basis of BCLC criteria. These 267 patients constituted the cohort for this analysis. The mean age ±standard deviation (SD) of eligible patients was 59 ± 10 years, and 76% were male. Seventy seven percent were White, 10% African American, and 10% belonged to other racial groups (Table 1). The most common etiologies for liver disease included viral hepatitis (62.6%), alcohol-related liver disease (11.9%), and metabolic or cryptogenic liver diseases (8.2%). At baseline, 36% had moderate-to-severe ascites, 8.6% had at-least one medical comorbidity, 21.4% was smokers, and approximately 67% used alcohol. Fifty one percent of patients had normal performance status (defined as Eastern Cooperative Performance Status[16] grade 0) and approximately 37% were seen in high volume centers.

Seventy six (28%) patients had early stage HCC on the basis of BCLC criteria. Patients with early HCC were less likely to have ascites (28.9% vs. 38.7%) and

Table 1 | Baseline demographic and clinical characteristics of 276 patients with early and advanced hepatocellular cancer (HCC) who had at-least one follow up visit

	Total (N = 267)	Early HCC (N = 76)	Not early HCC (N = 191)	P-value
Demographic characteristics				
Age, %				0.07
<60	148 (55.4)	49 (64.5)	99 (51.8)	
60–70	67 (25.1)	17 (22.4)	50 (26.2)	
>70	48 (18.0)	8 (10.5)	40 (20.9)	
Missing	4 (1.5)	2 (2.6)	2 (1.1)	
Gender, %				0.94
Male	203 (76.0)	58 (76.3)	145 (75.9)	
Race, %				0.88
Caucasian	205 (76.8)	59 (77.6)	146 (76.4)	
African American	27 (10.1)	8 (10.5)	19 (10.0)	
Other*	27 (13.1)	9 (11.9)	26 (13.6)	
Clinical characteristics, %				
Etiology of liver disease				0.28
Viral hepatitis	167 (62.6)	57 (75.0)	110 (57.6)	
Non-viral hepatitis	57 (21.3)	15 (19.7)	42 (22.0)	
Missing	43 (16.1)	4 (5.3)	39 (20.4)	
Liver disease severity				
Ascites (Yes)	96 (36.0)	22 (28.9)	74 (38.7)	**0.057**
Ascites (No)	158 (59.1)	54 (71.1)	104 (54.5)	
Missing	13 (4.9)	0	13 (6.8)	
Bilirubin, mg/dL				**0.002**
≤3.0	230 (86.1)	74 (97.4)	156 (81.7)	
>3.0	30 (11.3)	2 (2.6)	28 (14.7)	
Missing	7 (2.6)	0	7 (3.6)	
Albumin, mg/dL				0.89
≤3.0	77 (28.8)	22 (28.9)	55 (28.8)	
>3.0	184 (68.9)	54 (71.1)	130 (68.1)	
Missing	6 (2.3)	0	6 (3.1)	
Medical comorbidity	23 (8.6)	9 (11.8)	14 (7.3)	0.23
Smoker	57 (21.4)	16 (21.1)	41 (21.5)	0.94
Alcohol use				0.07
None	78 (29.2)	14 (18.4)	64 (33.5)	
0–40 g/day	77 (28.9)	24 (31.6)	53 (27.7)	
>40 g/day	101 (37.8)	33 (43.4))	68 (35.6)	
Missing	11 (4.1)	5 (6.6)	6 (3.2)	
Performance status,† %				0.07
Normal	137 (51.3)	46 (60.5)	91 (47.6)	
Limited	126 (47.2)	30 (39.5)	96 (50.3)	
Missing	4 (1.5)	0	4 (2.1)	
Site volume, %				**0.02**
High	99 (37.1)	36 (47.4)	63 (32.9)	
Medium or low	168 (62.9)	40 (52.6)	128 (67.1)	

P-values are comparisons of patients with early HCC vs. non-early HCC. Bold face P-values indicate significance at alpha of 0.05.

* Other race includes Hispanic, Asian, Indian (subcontinent), African, Pacific Islander, Native American, Alaskan Native/Aleut or unknown.

† Performance status was assessed on the basis of Eastern Cooperative Performance Status (ECOG) classification. ECOG status 0 means that the patient is fully active, able to carry on all activities without restriction.

more likely to have serum bilirubin value ≤ 3 mg/dL (97.4% vs. 81.7%) than those with non-early HCC. High volume centers were more likely to see early HCC than medium-low volume centers (47.4% vs. 32.9%). One hundred and nine (40.8%) patients met the UCSF expanded criteria.

Compared to patients without any follow up, those with at-least one follow up (study cohort) were more likely to be White (76% vs. 60%), less likely to have ascites (35.4% vs. 41.4%), and more likely to have serum bilirubin value greater than 3 mg/dL (84.4% vs. 76.7%) or limited performance status (45.4% vs. 54.8%). There were no significant differences between patients with and without follow-up in regards to age, gender, comorbidity, and stage of HCC (BCLC stage and UCSF status) (data not shown).

Rate of potentially curative treatment

During a mean follow up of 448 ± 501 days, 11 (14.5%), 23 (30.3%), and 30 (39.5%) patients with early stage HCC underwent surgical resection, tumour ablation, and liver transplantation (Table 2). Overall, 53 (69.7%) patients with early HCC received any potentially curative treatment. In contrast, 27 (14.1%), 33 (17.3%), and 22 (11.5%) patients without early stage HCC received surgical resection, tumour ablation, and liver transplantation, respectively.

Association between receipt of potentially curative treatment and survival

One hundred and nineteen (39.4%) patients died during the study follow up. Figure 1 displays the results of the bivariate Cox-proportional hazard models. We divided the patients into four groups: those with (i) early stage HCC with curative treatment; (ii) early stage HCC without curative treatment; (iii) non-early stage HCC with curative treatment, or (iv) non-early stage HCC without curative treatment. Appendix S1 displays the baseline characteristics stratified by these four groups.

Patients with non-early stage HCC who did not receive any potentially curative treatment had the lowest survival rate; 1- and 2-year survival rates for these patients were 44.5% and 28.8%, respectively. Compared with this group, likelihood of survival was substantially higher for patients with early HCC and curative treatment [1- and 2-year survival rates = 88.2% and 81.0%; HR for mortality = 0.14 (95% CI, 0.07–0.30)] and those with non-early HCC who received potentially curative treatment [1- and 2-year survival rates = 70.7% and 59.6%; HR for mortality = 0.37 (95% CI, 0.23–0.59)]. The survival rates of patients with early HCC who did not receive any curative treatment did not significantly differ from those with non-early HCC and no curative treatment [1- and 2-year survival rates = 65.2% and 33.5%; HR for mortality = 0.72 (95% CI, 0.37–1.40)].

The results did not change after adjustment for age, gender, race, medical comorbidity, functional status, and stage of liver disease in the multivariable Cox proportional hazards model (Table 3) nor in the sensitivity analyses that classified patients based on the UCSF criteria (Appendix S2), In addition, there was no change when strictly following BCLC criteria (by including performance status in the estimation of BCLC stage), or using alternative definition for HCC treatment care (by including patients who were considered eligible for, but who did not receive liver transplantation, in the treated groups) (Appendix S3).

Table 2 | Proportion of patients with early or non-early HCC receiving each of the potential curative treatments for hepatocellular cancer

Treatment, %	Total (*N* = 267)	Early HCC (*N* = 76)	Non-early HCC (*N* = 191)	*P*-value
Surgical resection	38 (14.2)	11 (14.5)	27 (14.1)	0.9432
Tumour ablation	56 (21.0)	23 (30.3)	33 (17.3)	0.0187*
Liver transplantation	52 (19.5)	30 (39.5)	22 (11.5)	<0.0001*
Any potentially curative treatment	122 (45.7)	53 (69.7)	69 (36.1)	0.0001*

Surgical resection includes wedge resection, segmental resection, and lobectomy.

Tumour ablation includes alcohol injection ablation and radiofrequency ablation.

Any curative treatment includes any of the above three treatment methods. Of note, some patients received more than one potentially curative treatment. Therefore, the numbers presented in the individual cells do not add up to the total number of patients included in the last cell for each column.

Among 145 patients who did not receive curative therapies (surgical resection, tumour ablation, or liver transplant), 41 (28.3%) were treated with other modalities. Most of these patients received TACE (*n* = 31). Sorafenib was not available for clinical use during the data collection phase of the study.

P-values are comparisons of patients with early HCC vs. non-early HCC.

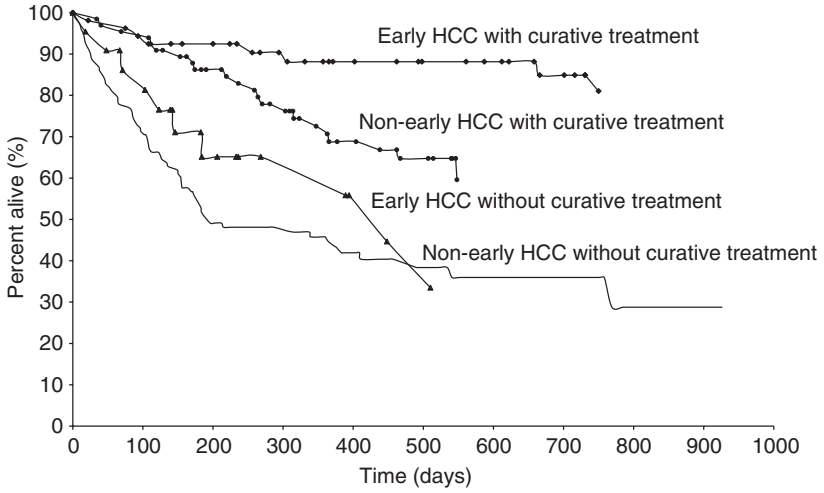

Figure 1 | Results of the Bivariate Cox-proportional Hazard Models. We divided patients into four groups: those with (i) early stage HCC with curative treatment; (ii) early stage HCC without curative treatment; (iii) non-early stage HCC with curative treatment or (iv) non-early stage HCC without curative treatment. Early stage defined as Child Class A or B, with a solitary HCC that was $\leq$5 cm in size, or up to 3 nodules, each $\leq$3 cm in size. The data are truncated at 700 days.

Table 3 | Hazard ratio for variables associated with survival in Cox multivariate proportion hazards model

Variables	Hazard ratio	95% CI	*P*-value
Curative treatment by HCC stage*			
Non-early HCC without curative treatment	Reference		
Early HCC with curative treatment	**0.19**	**0.08–0.42**	**<0.0001**
Early HCC without curative treatment	0.88	0.43–1.77	0.71
Non-early HCC with curative treatment	**0.37**	**0.22–0.64**	**0.0004**
Demographics			
Age in years			
<60	Reference		
60–70	0.76	0.46–1.27	0.29
>70	1.39	0.80–2.42	0.24
Male	0.82	0.49–1.38	0.47
Race			
White	Reference		
Black	0.78	0.36–1.69	0.54
Other race	1.20	0.63–2.24	0.57
Clinical characteristics			
Medical comorbidity	1.62	0.82–3.18	0.15
Presence of ascites	1.23	0.77–1.98	0.37
Bilirubin, ≤3.0 mg/dL	0.69	0.37–1.28	0.24
Albumin, ≤3.0 mg/dL	1.51	0.92–2.47	0.09
Normal performance status (ECOG† = 0)	**0.62**	**0.40–0.98**	**0.04**
High volume site	0.90	0.57–1.43	0.66

Bold face indicate significance at alpha of 0.05.

We excluded patients with missing values on independent variables from the model.

* Early stage defined as Child Class A or B, with a solitary HCC that was $\leq$5 cm in size, or up to 3 nodules, each $\leq$3 cm in size.

† Based on the Eastern Cooperative Performance Status (ECOG).

Patients with normal performance status were 38% less likely to die than those with compromised performance status after adjusting for patient demographics, clinical characteristics, as well as stage and treatment of HCC (Table 3).

Factors associated with receipt of potentially curative treatment in patients with HCC

As expected, the odds of receiving potentially curative treatment were significantly higher in patients with early HCC than those with non-early HCC (OR = 4.44, 95% CI = 2.34–8.42) (Table 4). In addition, patients with normal performance status had a 2-fold higher odds of receiving curative treatment than those with compromised performance status (OR = 2.16, 95% CI = 1.19–3.91).

In the sensitivity analyses, we found a similar (and perhaps stronger) association between performance status and receipt of curative therapy in the sub-group of patients with non-early HCC (OR = 3.08, 95% CI = 1.41–6.70) but not in patients with early HCC (Appendix S4). In addition, the odds of receiving potentially curative treatment decreased as the tumour size increased in both sub-groups (with early and non-early HCC) (Appendix S4). Patients with early HCC seeking care in high volume facilities had an approximately 5-fold higher odds of receiving curative treatment than those seen in medium to low volume facilities (OR = 4.88, 95% CI = 1.11–21.40).

Table 4 | Factors associated with receipt of curative treatment in patients with hepatocellular cancer (*N* = 267). Results are derived from multivariate logistic regression analyses

Variables	Odds ratio	95% CI	*P*-value
Demographics			
Age in years			
<60	Reference		
60–70	1.08	0.56–2.11	0.65
>70	0.87	0.38–1.97	0.65
Male	0.82	0.41–1.61	0.56
Race			
White	Reference		
Black	0.68	0.26–1.77	0.67
Other race	0.71	0.28–1.83	0.78
Clinical Characteristics			
Medical comorbidity	1.24	0.44–3.51	0.68
Presence of ascites	0.74	0.38–1.45	0.38
Bilirubin, ≤3.0 mg/dL	0.51	0.20–1.30	0.16
Albumin, ≤3.0 mg/dL	1.05	0.52–2.14	0.87
Normal performance status (ECOG* = 0)	**2.16**	**1.19–3.91**	**0.01**
Early stage HCC†	**4.44**	**2.34–8.42**	**<0.0001**
High volume site	1.57	0.86–2.87	0.14

* Based on the Eastern Cooperative Performance Status (ECOG).

† Early stage defined as Child Class A or B, with a solitary HCC that was ≤5 cm in size, or up to 3 nodules, each ≤3 cm in size.

Bold face indicate significance at alpha of 0.05.

DISCUSSION

In this large multicenter observational study, less than one-third of patients with HCC were diagnosed at an early stage. Consistent with other studies, patients with early HCC who underwent potentially curative treatment had excellent survival.[4, 7, 9–11, 13, 14] However, only 70% of patients with early disease received potentially curative treatment. Although we could not ascertain whether and to what extent patients in our study received surveillance for HCC prior to their diagnosis, given that the data represent patients seen in centers with specialized expertise in management of HCC patients, these estimates likely represent the maximum benefit that can be expected from the current practice of HCC surveillance and treatment. Indeed, an analysis of Surveillance, Epidemiology, and End Results registry showed that 21% of patients with small, non-metastatic HCC received liver transplantation.[17] Another study limited to 65 years and older Medicare population found that 34% of patients with early HCC (defined as patients with single lesions or those with lesions <3 cm) received any potentially curative treatment.[18] Our data show that, in the best case scenario, these rates can be twice as high as reported in these population based studies, and thus provide the upper boundary of the potential effect of HCC surveillance and treatment—data that are relevant in counseling patients regarding chances of treatment receipt and outcomes, in conducting cost-effectiveness analyses, and in guiding policies regarding HCC surveillance in the vulnerable cohort of patients at risk for HCC.

We also found that 36% of patients who were not candidates for curative treatment based in the staging system received curative treatment and that these patients had significantly improved survival compared to patients without such treatment. Although there is no one universally accepted HCC staging system, many have adopted the BCLC system, and we used this system to stratify our patients for this study. The goal of BCLC (and other staging systems) is to predict patients' outcomes and to tailor therapy in order to maximize overall effectiveness of treatment. In our study, stage of HCC was the strongest driver of treatment decisions—and hence the prognosis of

patients. Nonetheless, we found that physicians frequently crossed these stage-specific boundaries to extend curative treatment to patients with more advanced HCC. Our results suggest that this decision, at least in part, is guided by the general health of the patient. Specifically, we found that patients with advanced HCC but with well-preserved performance status were 4-fold more likely to receive curative treatment compared to those with compromised performance status. These patients with non-early HCC, when treated, had modest improvement in their survival. Collectively these data suggest that physicians might be using the correct heuristic in identifying candidates for curative treatment and that this heuristic might tap into aspects of underlying risk or disease severity that are not fully captured by staging alone. We found that performance status provides important prognostic information in patients with HCC that goes beyond the information furnished by clinical and tumour burden variables used in routine practice. Our data, therefore, provide a compelling rationale for incorporating formal evaluation of patients' performance status into clinical decision-making in patients with HCC.

We also found that individual centers might vary in how they manage patients with early HCC. Patients with early HCC who were seen in high volume centers were significantly more likely to receive a potentially curative treatment than those seen in low-medium volume centers after controlling for patient-related variables. However, due to the limited sample size in this sub-group, our estimates may not be optimally reliable and thus should be interpreted with caution. Despite this, our data provide preliminary insight into the likely importance of center effect in explaining the variation in treatment rates among patients with early HCC.

There are several other possible explanations for lack of curative treatment in the 30% of patients with early HCC who did not receive such treatment. It is plausible that despite being in the 'early' HCC group, patients without curative treatment had higher tumour burden (i.e. larger lesions, etc.) compared to those who received curative treatment, and our results support this possibility (Appendix S4). Another explanation may be presence of more advanced liver disease and higher comorbidity—factors that are important drivers of HCC treatment decisions. Indeed, we found that early HCC patients who did not receive curative treatment were older, were more likely to have medical comorbidity, and more severe liver disease than those who received curative treatment, although these estimates were not statistically significant, perhaps because of power limitations. Other possible explanations may include patient preference and insurance related barriers. We lacked reliable variables to determine the role of these factors as part of this study. Larger studies with longer follow up are needed to confirm our observations and to evaluate the impact of center effect as well as other variables.

Our analysis has several strengths. First, we used data from a prospectively enrolled cohort of patients with HCC instead of using administrative databases. The study relied on standardized criteria for HCC diagnosis that in turn were directly derived from the available clinical practice guidelines in HCC. As a result, we minimized any ascertainment bias in classifying patients with HCC. Second, our analysis used data from a demographically diverse group of patients with HCC seen in different regions of the U.S. Third, the Liver Cancer Network database included a broad array of data, allowing us to capture and adjust for the full range of patient-level variables that might affect the receipt and outcomes of treatment among treatment-eligible patients. These included socio-demographic characteristics, tumour-related characteristics, stage of liver disease, and medical comorbidity, among others.

Our analysis also has potential weaknesses. The sample population constituted primarily of patients with access to healthcare system that were seen at tertiary care centers. Thus, as stated earlier, our results are likely biased upwards. However, our data provide the upper limit of potential effect of current process of care in HCC. Second, the observational nature of the study makes it hard to draw firm causal inferences regarding impact of curative treatment on patient survival. However, randomized controlled trials designed to determine the effect of potentially curative treatments are not possible because of cost, feasibility, and ethical considerations. Within the limitations of the study design, the longitudinal nature of the data, finding of a strong association, and the temporality of the cause and effect suggest that the receipt of potentially curative treatment is causally linked to better outcomes in this geographically diverse sample of patients with HCC. Third, due to power limitations, estimates from the sub-group (i.e. sensitivity) analyses may not be optimally reliable. Future research will aim to confirm these findings and to determine the role of patient related factors using larger sample sizes and longer duration of follow-up.

In conclusion, our results suggest that survival in HCC can be improved if it is diagnosed at an early stage and potentially curative therapy is applied in a timely manner. However, only 28% of patients have early stage disease at the time of HCC diagnosis, suggesting that the most important step to make inroads into the problem of suboptimal outcomes in HCC may be to focus on

implementation of routine surveillance in patients who are at risk for HCC so that more patients are diagnosed earlier in the course of their disease. We also found that approximately one-third of patients with non-early stage disease received potentially curative treatment, and that these patients had improved outcomes. Evidence based modifications in HCC staging algorithms and routine incorporation of performance status into clinical decision-making may help achieve the goal of making treatment more effective and cost-effective in patients with HCC.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Baseline demographic and clinical characteristics of 276 patients with hepatocellular cancer (HCC) stratified by stage and treatment of HCC.

Appendix S2. Hazard ratio for variables associated with survival in Cox multivariate proportion hazards models using the University of California San Francisco (UCSF) expanded guidelines to define stage of hepatocellular cancer (HCC).

Appendix S3. Hazard ratio for variables associated with survival in 2 Cox multivariate proportion hazards models conducted as part of sensitivity analyses. Model 1 incorporated performance status information in the estimation of BCLC stage (i.e. strictly following the BCLC staging criteria) and evaluated receipt vs. non-receipt of potentially curative treatment for hepatocellular cancer (HCC). Model 2 employed an alternative definition of HCC treatment care (i.e. included patients who were considered eligible for, but who did not receive liver transplantation, in the treated groups) in addition to strictly following the BCLC staging criteria.

Appendix S4. Factors associated with receipt of curative treatment in patients with early and non-early HCC. Results are derived from 2 separate multivariate logistic regression analyses for each sub group.

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