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Therapeutic Delays Lead to Worse Survival Among Patients With Hepatocellular Carcinoma

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Abstract

Although prior studies have shown underuse of appropriate therapy in patients with hepatocellular carcinoma (HCC), no studies to date have assessed the prevalence and clinical impact of therapeutic delays among patients with HCC. The goal of this study was to characterize and identify factors associated with underuse and delays in treatment of these patients. A retrospective cohort study was conducted of patients with cirrhosis diagnosed with HCC at a large urban safety net hospital between January 2005 and June 2012. Dates for HCC diagnosis and any treatments were recorded. Univariate and multivariate analysis was used to determine factors associated with treatment underuse and delayed treatment, which was defined as time from diagnosis to treatment exceeding 3 months. The authors identified 267 treatment-eligible patients with HCC, of whom only 62% received HCC therapy. On multivariate analysis, tumor stage (odds ratio [OR], 0.48; 95% CI, 0.36–0.65), Child-Pugh class (OR, 0.49; 95% CI, 0.28–0.84), and black race (OR, 0.55; 95% CI, 0.31–0.99) were associated with lower rates of treatment use. The median time to treatment was 1.7 months, with 31% of patients experiencing delayed treatment. Delayed treatment was associated with the presence of ascites (hazard ratio [HR], 2.8; 95% CI, 1.3–6.1) and current treatment with transarterial chemoembolization (HR, 4.8; 95% CI, 1.8–12.5). After adjusting for tumor stage and Child-Pugh class, treatment underuse (HR, 0.33; 95% CI, 0.24–0.46) and delayed treatment (HR, 0.50; 95% CI, 0.30–0.84) were both associated with significantly worse survival. Results showed that, in addition to one-third of patients not receiving HCC-

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directed therapy, another 30% experienced significant therapeutic delays, leading to worse survival.

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and has an increasing incidence in the United States.¹ Prognosis for patients with HCC largely depends on tumor stage at diagnosis, with curative options only available for patients diagnosed at an early stage.² Surveillance at 6-month intervals is recommended in patients with cirrhosis to detect HCC at an early stage.³ Despite the availability of efficacious surveillance tests, only 40% of patients with HCC are diagnosed at an early stage nationally.^{4, 5} Tumor stage at diagnosis can be influenced by several factors in clinical practice, including low screening rates and delays in follow-up of abnormal screening tests.^{6–10}

Underuse and/or delays in treatment have also been described as a potential cause of poor cancer outcomes.^{11–16} The transition from diagnosis to treatment is a complex process in clinical practice, with several steps that are prone to delays and/or failure. Providers must determine the optimal treatment and refer patients to the appropriate provider, the health care system must schedule these appointments, and patients must adhere to these recommendations. This process may be particularly difficult in patients with HCC given primary care providers' lack of familiarity with the wide array of potential treatment options, each delivered by different providers. For patients diagnosed with HCC, delays as little as 3 months in therapeutic follow-up can allow for significant tumor growth and potentially lead to decreased options for effective treatment.¹⁷

Although prior studies have shown underuse of appropriate treatment among patients with HCC, no studies have provided an in-depth analysis of the prevalence and clinical impact of therapeutic delays.^{18, 19} The primary goals of this study were to characterize and identify factors associated with underuse and delays in treatment among a cohort of patients with HCC.

Methods

Study Population

A retrospective cohort study was conducted on consecutive patients with cirrhosis diagnosed with HCC at Parkland Health & Hospital System, the safety net system for Dallas County, between January 2005 and June 2012. Patients were identified through a combination of ICD-9 codes for HCC (155.0 or 155.2), a prospectively maintained list of patients seen in a multidisciplinary liver tumor clinic, and tumor conference presentation lists. Two authors (Amit Singal, MD, MS, and Adam Yopp, MD) adjudicated all HCC cases to confirm they met diagnostic criteria, based on American Association for the Study of Liver Diseases (AASLD) guidelines.²⁰

Patients with poor performance status (ECOG performance status 3–4) or Child-Pugh C cirrhosis, unless eligible for liver transplant, were excluded because of the lack of therapeutic options associated with a survival benefit. Similarly, patients with locally advanced (ie, tumor thrombus) or metastatic disease before 2008 were excluded given the

lack of proven therapeutic options before the introduction of sorafenib. This study was approved by the Institutional Review Board of University of Texas South-western Medical Center.

Data Collection

Patient demographics, clinical history, laboratory data, and imaging results were obtained through a review of computerized and paper medical records. Two investigators independently extracted information using standardized forms (Amit Singal, MD, MS, and Adam Yopp, MD), with a third investigator (Jasmin Tiro, PhD) available to resolve discrepancies. Age, gender, race/ethnicity, insurance status, and lifetime alcohol and smoking history were recorded, with active alcohol abuse defined as drinking more than 40 g/d. Average annual household income, percent of persons with employment, and percent of persons with a college degree were based on zip code of residence using 2011 US Census Bureau data. Data regarding liver disease included underlying cause and presence of decompensation (ascites or encephalopathy). Patients were classified according to origin of liver disease, including hepatitis C virus (HCV), hepatitis B virus, alcohol-related liver disease, and nonalcoholic fatty liver disease (NAFLD). Laboratory data of interest at time of diagnosis and treatment included platelet count, creatinine, aspartate aminotransferase, alanine aminotransferase, bilirubin, albumin, international normalized ratio, and α -fetoprotein (AFP).

Dates of HCC diagnosis and treatment initiation were abstracted. HCC diagnosis was determined using AASLD criteria at the time of the study duration, with the diagnosis made based on the presence of a lesion with typical vascular pattern on dynamic imaging (arterial enhancement and washout on delayed images), a mass with an AFP level greater than 200 ng/mL, or histologic confirmation for tumors larger than 1 cm.²⁰ Tumor characteristics were determined by imaging studies, which had all been interpreted by radiologists at the authors' institution, and tumor staging was performed using the Barcelona Clinic Liver Cancer (BCLC) staging system.²¹ HCC treatments were categorized as liver transplantation, resection, radiofrequency ablation, transarterial chemoembolization (TACE), systemic chemotherapy, or best supportive care. In patients who received multiple treatments, time of treatment was the date of the first delivered treatment.

Statistical Analysis

Time to treatment was determined for all treatment-eligible patients using Kaplan-Meier analysis. Cox univariate and multivariate regression analysis were used to identify factors associated with time to treatment. Time to treatment was then analyzed as a dichotomous outcome, with delayed treatment defined as time from diagnosis to treatment longer than 3 months (ie, 90 days), based on tumor doubling time. Fisher exact, analysis of variance, and Mann-Whitney rank sum tests were used to identify factors associated with delayed treatment. Patient sociodemographic and clinical characteristics were assessed, including age, gender, race/ethnicity, primary language, alcohol abuse, insurance status, performance status, cause of liver disease, platelet count, bilirubin, Child-Pugh class, inpatient versus outpatient status at diagnosis, number of primary care visits in the month after HCC diagnosis, and receipt of hepatology care as independent variables. Multivariate logistic

regression was then performed using variables with univariate P values less than .10 and variables of a priori clinical importance (Child-Pugh score). The final multivariate model included all predictor variables with P values less than .05. All data analysis was performed using Stata 11 (StataCorp, College Station, TX).

Results

Patient Characteristics

Between January 2005 and June 2012, a total of 457 patients with cirrhosis were diagnosed with HCC. A total of 190 patients were excluded: 38 with locally advanced tumors before sorafenib availability, 82 with Child-Pugh class C cirrhosis, 52 with poor performance status, and 18 with both Child-Pugh class C cirrhosis plus poor performance status. Table 1 shows baseline characteristics of the remaining 267 patients. The median age of patients was 56 years (range, 28–82 years), and more than 80% were men. The population was racially diverse, comprising 34% African Americans, 32% Hispanic Caucasians, and 25% non-Hispanic Caucasians. The most common causes of cirrhosis were HCV (69%), alcohol-induced liver disease (14%), and NAFLD (9%). The median Child-Pugh score at diagnosis was 6 (range, 5–9), with 52% of patients having Child-Pugh class A cirrhosis. The cohort was diverse with respect to tumor stage, with 130 (49%) having BCLC stage A tumors, 41 (15%) stage B tumors, and 96 (36%) stage C tumors. Most patients (52%) had unifocal disease, although 58 (21.7%) had multifocal infiltrative-type disease.

Predictors of Treatment Use

Of the 267 treatment-eligible patients, 165 (62%) received HCC-directed therapy and 102 (38%) did not receive any HCC treatment. Adjusting for BCLC tumor stage and Child-Pugh class, treatment use was associated with significantly improved survival after HCC diagnosis (hazard ratio [HR], 0.33; 95% CI, 0.24–0.46; Figure 1). The median survival of those who received HCC treatment was 25.8 months, compared with only 3.4 months among treatment-eligible patients who did not receive therapy. The 1- and 2-year survival rates among patients who underwent treatment were 71.5% and 53.7%, respectively, compared with 26.2% and 11.8% in those who did not receive HCC-directed treatment.

Predictors of lower treatment use on univariate analysis included black race ($P=.06$), insurance status ($P<.001$), higher Child-Pugh class ($P=.001$), the presence of ascites ($P=.04$), lower albumin at diagnosis ($P<.001$), bilirubin at diagnosis ($P<.001$), and higher BCLC tumor stage ($P<.001$). Albumin and bilirubin levels and the presence of ascites were not entered into multivariate analysis because they are components and collinear with Child-Pugh class. On multivariate analysis, BCLC tumor stage (odds ratio [OR], 0.48; 95% CI, 0.36–0.65), Child-Pugh class (OR, 0.49; 95% CI, 0.28–0.84), and black race (OR, 0.55; 95% CI, 0.31–0.99) were associated with lower rates of treatment use (Table 2). HCC-directed treatment was observed in 101 patients (78%) in BCLC stage A and 25 patients (61%) in BCLC stage B HCC, but only 39 patients (41%) in stage C. Patients with Child-Pugh class A cirrhosis were significantly more likely to undergo HCC treatment than those with Child-Pugh class B cirrhosis (71% vs 52%). Finally, treatment was delivered in 65% of nonblack patients compared with 54% of black patients.

Predictors for Delays in Treatment

Of the 165 patients who received HCC treatment, the median time from diagnosis to treatment was 1.7 months (range, 0.1–42.5 months), with 50 patients (30%) treated at more than 3 months after diagnosis. Table 3 shows the patient characteristics, stratified by the presence or absence of delayed treatment (defined as time to treatment >3 months).

Adjusting for BCLC tumor stage and Child-Pugh class, treatment delays were associated with significantly worse survival (HR, 0.50; 95% CI, 0.30–0.84) after HCC diagnosis (Figure 2). Patients with delayed treatment had 1- and 2-year survival rates of 63.7% and 50.1%, respectively, compared with 89.8% and 64.5% in those without delayed treatment.

Predictors of delayed treatment on univariate analysis included the presence of ascites ($P=.007$), creatinine at diagnosis ($P=.07$), BCLC tumor stage ($P=.09$), and undergoing TACE ($P<.001$). Rates of delayed treatment did not differ according to patient demographics, including age, gender, race, or insurance status. Zip code-level variables, including median household income, percent of persons with college education, and percent of persons with employment, were also not associated with delayed treatment. On multivariate analysis, presence of ascites (HR, 2.8; 95% CI, 1.3–6.1) and current treatment TACE (HR, 4.8; 95% CI, 1.8–12.5) were significantly associated with delayed treatment (Table 4). The median time to treatment for patients undergoing TACE was 2.0 months (interquartile range [IQR], 1.1–4.3 months) compared with 1.3 months (IQR, 0.9–2.1 months) for those undergoing other therapies. Delayed treatment occurred in 41% of patients undergoing TACE but in only 12% of patients undergoing other therapies. The median time to treatment among patients with ascites was 2.8 months (IQR, 1.3–5.5 months) compared with 1.5 months (IQR, 1.0–2.8 months) in those without ascites. Treatment was delayed in 48% of patients with ascites compared with only 24% of those without ascites.

Discussion

This study is the first to provide an in-depth analysis of the prevalence and clinical impact of therapeutic delays among patients with HCC. In addition to treatment underuse, findings showed that therapeutic delays are common, with nearly 1 in 3 patients experiencing delays exceeding 3 months. Therapeutic delays potentially allow for interval tumor growth and are associated with worse survival, after adjusting for tumor stage and Child-Pugh class. Interventions for improving timely delivery of treatment to patients with HCC are clearly needed.

The transition from diagnosis to treatment is a complex process, involving several steps and interfaces with multiple new providers.²² Providers must be aware of the cancer diagnosis, complete the staging workup, determine the optimal treatment, and finally refer patients to the appropriate consultants. Patients may be asked to make multiple transitions between several providers as various treatment options are considered. A breakdown at any step results in delayed or underuse of treatment. This process may be particularly challenging for safety net institutions, because they can be overwhelmed with the large number of patients relative to limited clinic appointment availability. Further studies are necessary to characterize determinants of therapeutic delays and help identify potential intervention targets.

The complex array of potential treatment options, each delivered by a different type of provider, may make this process even more difficult for patients with HCC. The authors found that undergoing locoregional therapy with TACE was significantly associated with therapeutic delays, which highlights the potential for delays during transitions between providers. For locoregional therapy to be delivered, patients may be transitioned among several providers, including primary care providers, hepatologists, oncologists, and interventional radiologists. A recent study found that HCC diagnosis at a transplant facility, where several of these specialists are likely present, was associated with an increased likelihood of receiving HCC treatment.²³ The institution of multidisciplinary liver tumor conferences and clinics are one possible mechanism to facilitate timely, appropriate care and better communication among providers.

Several studies have reported racial disparities in HCC surveillance⁹ and treatment use,^{24–27} although some report difficulty in distinguishing racial and socioeconomic disparities, because these can be highly correlated. In the present study, socioeconomic factors such as insurance status, median household income (by zip code), and percent of persons with employment (by zip code) were not associated with treatment underuse. However, black patients were significantly less likely to receive HCC treatment after adjusting for several medical and socioeconomic factors, including liver function, tumor stage, and insurance status. This finding is particularly concerning given that these patients were eligible for treatments associated with a survival benefit. However, mediators of these racial disparities in treatment use could not be determined. Further studies are needed to determine whether racial disparities in HCC treatment are driven by provider-level or patient-level attitudes and behaviors.

Although not the primary focus of this study, some overuse of HCC treatment was surprisingly observed. Of the 190 patients who were excluded from the study population, 15 (7.9%) received HCC treatment: 11 underwent TACE, 2 underwent radiofrequency ablation, and 2 patients received sorafenib. All 15 patients had Child-Pugh C cirrhosis and therefore had BCLC stage D tumors. Guidelines from the AASLD clearly state that survival among these patients is driven by liver function and that they do not benefit from HCC treatment. HCC-directed treatment should be avoided to preclude treatment-related side effects in the absence of any benefit. Treatment overuse is particularly concerning for resource-strapped safety net institutions. This study is the first to suggest potential overuse of HCC treatment, and further studies are needed to determine its prevalence nationally.

This study has several limitations. The conclusions reflect a retrospective analysis of patients with HCC seen at a large urban safety net hospital, and therefore may not be generalized to other practice settings. Further studies, with larger sample sizes, are necessary to identify other potential predictors of therapeutic delays and determine if these results are generalizable. Given its retrospective nature, this study was also limited by possible unmeasured confounders and missing data. Although some patients may have received HCC-directed therapy at outside institutions, the authors believe this is unlikely given that Parkland, as the safety net health system for Dallas County, is the only option for most indigent patients. The retrospective nature of this study could have also led to measurement bias, including inaccurate estimates of alcohol intake. Overall, the authors believe the

study's limitations are outweighed by its strengths, including its well-characterized cohort and its racially and socioeconomically diverse population. Most importantly, this study is the first to characterize the prevalence and clinical impact of therapeutic delays in patients with HCC.

In conclusion, therapeutic delays were found to be common and lead to worse outcomes among patients with HCC. Findings showed that in addition to one-third of patients not receiving HCC-directed therapy, another 20% experienced significant therapeutic delays, potentially allowing for interval tumor growth. Both underuse and delays in treatment are independently associated with worse survival, after adjusting for tumor stage and Child-Pugh class. This study highlights that therapeutic delays may be an important issue among patients with HCC, and further studies in large cohorts are necessary. If confirmed, interventions are needed to improve the timely delivery of appropriate treatment to patients with HCC.

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Figure 1.
Overall survival, stratified by treatment use (adjusted for Barcelona Clinic Liver Cancer tumor stage and Child-Pugh class).
Abbreviation: HR, hazard ratio.

Figure 2.
Overall survival, stratified by the presence of treatment delays (adjusted for Barcelona Clinic Liver Cancer tumor stage and Child-Pugh class).
Abbreviation: HR, hazard ratio.

Table 1

Patient Characteristics by Presence or Absence of Treatment Use

Patient Characteristics	Patients Receiving HCC Treatment (n=165)	Patients Not Receiving HCC Treatment (n=102)	P Value
Age, y	56.5 (33.7–81.5)	56 (28.3–82.8)	.38
Gender (% male)	132 (80.0%)	87 (85.3%)	.33
Race			.39
Caucasian	43 (26.2%)	23 (22.6%)	
Black	49 (29.9%)	41 (40.2%)	
Hispanic	56 (34.1%)	29 (28.4%)	
Asian	16 (9.8%)	9 (8.8%)	
Cause			.49
Hepatitis C	111 (67.3%)	73 (71.6%)	
Hepatitis B	16 (9.7%)	6 (5.9%)	
Alcohol	23 (13.9%)	13 (12.7%)	
NAFLD	15 (9.1%)	10 (9.8%)	
Insurance status			<.001
Medicare	26 (15.8%)	18 (17.7%)	
Medicaid	35 (21.2%)	23 (22.5%)	
Private insurance	10 (6.0%)	3 (2.9%)	
Parkland Health Plus ^a	94 (57.0%)	58 (56.9%)	
Alcohol (% active)	43 (26.1%)	33 (32.7%)	.27
HIV status (% positive)	15 (12.7%)	4 (5.2%)	.14
Presence of ascites	44 (26.7%)	40 (39.2%)	.04
Presence of hepatic encephalopathy	8 (4.9%)	6 (5.9%)	.78
Platelet count, ×1000/mm ³	125 (17–842)	130 (30–582)	.10
AST, U/L	97 (17–1089)	98 (22–582)	.32
ALT, U/L	55 (11–601)	47 (12–354)	.12
Bilirubin, mg/dL	1.0 (0.2–5.7)	1.4 (0.2–35.2)	<.001
Albumin, g/dL	3.4 (1.8–4.7)	3.0 (2.1–4.5)	<.001
Creatinine, mg/dL	0.8 (0.4–9.0)	0.8 (0.4–7.5)	.22
INR	1.2 (0.9–2.0)	1.3 (1.0–3.3)	<.001
Child-Pugh score	6 (5–9)	7 (5–9)	<.001
<i>Child-Pugh classification</i>			.002
Child A	98 (59.4%)	40 (39.2%)	
Child B	67 (40.6%)	62 (60.8%)	
<i>Tumor stage</i>			<.001
BCLC A	101 (61.2%)	29 (28.4%)	
BCLC B	25 (15.2%)	16 (15.7%)	
BCLC C	39 (23.6%)	57 (55.9%)	

All data are expressed as median (range) unless otherwise specified.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma;

INR, international normalized ratio; NAFLD, nonalcoholic fatty liver disease.

^aSliding fee scale program, which provides a subsidy for medical care, such as HCC treatment.

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Table 2

Predictors of Treatment Use

Variable ^a	Univariate Analysis		Multivariate Analysis	
	OR	95% CI	OR	95% CI
BCLC tumor stage	0.44	0.33–0.59	0.48	0.36–0.65
Child-Pugh class	0.44	0.27–0.73	0.49	0.28–0.84
Black race	0.63	0.38–1.06	0.55	0.31–0.99
Insurance status	0.82	0.66–1.03	0.82	0.64–1.05

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; OR, odds ratio.

^a Albumin and bilirubin levels and presence of ascites were also significant on univariate analysis but removed from the multivariate model given their collinearity with Child-Pugh class.

Table 3 Patient Characteristics by Presence or Absence of Delayed Treatment^a

Patient Characteristics	Patients Receiving Delayed Treatment (n=115)	Patients Not Receiving Delayed Treatment (n=50)	P Value
Age, y	56.5 (33.7–81.5)	56.5 (41.5–75.8)	.85
Gender (% male)	93 (81.6%)	38 (76.0%)	.41
Race			.77
Caucasian	30 (26.5%)	12 (24.0%)	
Black	36 (31.9%)	13 (26.0%)	
Hispanic	36 (31.9%)	20 (40.0%)	
Asian	11 (9.7%)	5 (10.0%)	
Cause			.89
Hepatitis C	75 (65.8%)	35 (70.0%)	
Hepatitis B	12 (10.5%)	4 (8.0%)	
Alcohol	16 (14.0%)	7 (14.0%)	
NAFLD	11 (9.7%)	4 (8.0%)	
Insurance status			.29
Medicare	17 (14.9%)	9 (18.0%)	
Medicaid	26 (22.8%)	9 (18.0%)	
Private insurance	5 (4.4%)	5 (10.0%)	
Uninsured	66 (57.9%)	27 (54.0%)	
Alcohol (% active)	31 (27.2%)	11 (22.0%)	.56
HIV status (% positive)	10 (13.0%)	5 (10.0%)	1.00
Presence of ascites	23 (20.2%)	21 (42.0%)	.007
Presence of hepatic encephalopathy	4 (3.5%)	4 (8.0%)	.25
Platelet count, ×1000/mm ³	130 (17–842)	120 (35–387)	.23
AST, U/L	96 (17–1089)	102 (17–387)	.89
ALT, U/L	57 (12–601)	52 (11–245)	.71
Bilirubin, mg/dL	1.0 (0.2–5.7)	1.1 (0.3–2.8)	.81
Albumin, g/dL	3.5 (2.1–4.7)	3.4 (1.8–4.6)	.43
Creatinine, mg/dL	0.8 (0.4–3.3)	0.9 (0.5–9.0)	.07
INR	1.2 (0.9–2.0)	1.2 (0.9–1.8)	.95
Child-Pugh score	6 (5–9)	7 (5–9)	.04
Child-Pugh classification			.12
Child A	72 (63.2%)	25 (50.0%)	
Child B	42 (36.8%)	25 (50.0%)	
Tumor stage			.09
BCLC A	64 (56.1%)	37 (74.0%)	
BCLC B	19 (16.7%)	6 (12.0%)	
BCLC C	31 (27.2%)	7 (14.0%)	
Primary HCC treatment			
Liver transplantation	1 (0.9%)	5 (10.0%)	

Patient Characteristics	Patients Receiving Delayed Treatment (n=115)	Patients Not Receiving Delayed Treatment (n=50)	P Value
Resection	23 (20.0%)	4 (8.0%)	
RFA	12 (10.4%)	4 (8.0%)	
TACE	53 (46.1%)	34 (68.0%)	
Systemic therapy	26 (22.6%)	3 (6.0%)	

All data are expressed as median (range) unless otherwise specified

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; INR, international normalized ratio; NAFLD, nonalcoholic fatty liver disease; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

^aDelayed treatment was defined as time from diagnosis to treatment exceeding 90 days.

Table 4

Predictors of Therapeutic Delays

Variable	Univariate Analysis		Multivariate Analysis	
	OR	95% CI	OR	95% CI
Presence of ascites	2.87	1.39–5.91	2.76	1.25–6.08
Undergoing TACE	4.97	2.06–12.0	4.78	1.83–12.5
BCLC tumor stage	0.61	0.39–0.96	0.71	0.43–1.17
Creatinine (continuous)	1.76	0.76–4.07	1.73	0.74–4.01

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; OR, Odds ratio; TACE, transarterial chemoembolization.