

# Racial/Ethnic Disparities in Access to Care and Survival for Patients With Early-Stage Hepatocellular Carcinoma

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**Objective:** To determine whether controlling for differences in the use of invasive therapy affects racial/ethnic differences in survival of early-stage hepatocellular carcinoma (HCC).

**Design:** A retrospective cohort study using Surveillance, Epidemiology, and End Results (SEER) HCC data. Invasive therapy was defined as tumor ablation, hepatectomy, or liver transplant. Race/ethnicity was defined as white, black, Asian, Hispanic, or other. Racial/ethnic differences in overall and treatment-adjusted survival were assessed using the Kaplan-Meier method and base- and treatment-stratified multivariable Cox proportional hazards models.

**Patients:** All patients diagnosed as having stage I or II HCC from January 1, 1995, through December 31, 2006 (N=13 244).

**Setting:** Data were obtained from the National Cancer Institute's SEER registry.

**Main Outcome Measures:** Differences in survival by race/ethnicity accounting for the use of invasive therapy and treatment benefit.

**Results:** Overall, 32.8% of patients received invasive therapy. We found higher mortality rates in the base survival model for black (hazard ratio [HR], 1.24; 95% confidence interval [CI], 1.15-1.33) and Hispanic (1.08; 1.01-1.15) patients and lower mortality rates in Asian patients (0.87; 0.82-0.93) compared with whites. After treatment stratification, compared with white patients, blacks had a 12% higher mortality rate (HR, 1.11; 95% CI, 1.03-1.20), Hispanics had a similar mortality rate (0.97; 0.91-1.04), and Asians had a 16% lower mortality rate (0.84; 0.79-0.89).

**Conclusions:** For early-stage HCC, racial/ethnic disparities in survival between minority and white patients are notable. After accounting for differences in stage, use of invasive therapy, and treatment benefit, no racial/ethnic survival disparity is evident between Hispanics and whites, but blacks have persistently poor survival.

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**H**EPATOCELLULAR CARCINOMA (HCC) is the fifth leading cause of death from cancer worldwide and has a markedly increasing incidence in the United States.<sup>1</sup> Survival among patients with advanced HCC is dismal, with an overall 5-year rate of 5%.<sup>2</sup> Patients diagnosed as having an early stage stand the best chance of cure. The available treatment strategies, including tumor ablation, hepatic resection, liver transplant, or combined modalities, require highly complex care only available in tertiary referral centers. To obtain care in these centers, patients need to overcome several barriers that may precipitate health care disparities along racial/ethnic lines and may have downstream effects on survival.

Recent data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program suggest that significant racial/ethnic disparities exist in the use of surgical therapy for HCC.<sup>3-5</sup> Black patients with HCC receive surgical

## See Invited Critique at end of article

therapy less often than white patients. It remains unclear whether racial/ethnic differences in survival are linked to these differences in the receipt of invasive therapy.

In this study, we report on the survival of 13 244 patients with early-stage HCC from the SEER registry. We aimed to determine whether racial/ethnic differences in survival could be explained by differences in the use of invasive therapy. We hy-

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pothesized that survival differences between racial/ethnic groups would be minimal after accounting for variation in receipt of invasive therapy and its specific effects on survival.

## METHODS

### STUDY POPULATION

The SEER registry (<http://www.seer.cancer.gov>) is a comprehensive cancer surveillance program based on local and regional cancer registries that samples 26% of the US population. It is maintained by the Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch of the National Cancer Institute. We used the deidentified SEER limited-use data set (1973-2006) to create the retrospective cohort, acquired in accordance with the SEER data use agreement. Patients with HCC were identified on the basis of being assigned SEER diagnosis code 220. Those with early-stage (stage I or II) disease were identified according to SEER modified stage criteria for patients from 1995 through 2003 or the American Joint Committee on Cancer TNM guidelines for patients from 2004 through 2006. **Table 1** displays the SEER staging criteria used to define stages I and II disease.

The primary outcome of interest was patient survival. Mortality data in the SEER registry were obtained via linkages with the National Center for Health Statistics. Vital status was recorded, and the date of latest follow-up for the study cohort was December 21, 2006. Invasive therapy was defined as tumor ablation or local tumor destruction (labeled as ablation in this study), hepatic resection, or liver transplant. The primary exposure of interest was race/ethnicity. Race and ethnicity were considered together because they represent social constructs that create a context through which patients access the health care system. Race/ethnicity was classified by the SEER coding scheme and defined as non-Hispanic white (white), black, Hispanic, Asian, or other. The last category consisted of Native Americans and Alaskans, Native Hawaiians, and those of unknown or mixed race/ethnicity. Those of nonwhite Hispanic ethnicity were placed in the other category.

Clinical and socioeconomic factors that could potentially affect access to invasive therapy or patient survival were also included in the analysis. Clinical variables included patient age at diagnosis, date of diagnosis, and tumor size. The SEER registry provides socioeconomic covariates based on county-level variables obtained from the US Census Bureau matched to the patient's place of residence. For this analysis, we selected the following variables to reflect educational, economic, and social status in the county: percentage of individuals with a high school diploma, median annual household income, percentage of individuals living below the federal poverty line, percentage of individuals with white-collar jobs, and percentage of households self-identified as being isolated by language.

### STATISTICAL ANALYSIS

The analytic approach included a multivariable patient-level model of the effects of race/ethnicity on patient survival and treatment-adjusted patient survival. We compared clinical, demographic, and socioeconomic variables by racial/ethnic designation and used these in covariate adjustment. Univariate analyses were completed using the  $\chi^2$  method, the 2-sample *t* test, or analysis of variance where appropriate.

For the overall and treatment-adjusted survival analysis, we used the Kaplan-Meier method to calculate time-to-death estimates from the time of diagnosis. Differences in these esti-

**Table 1. Clinical Staging of Hepatocellular Carcinoma in the SEER Registry in the Study Cohort**

Stage/Clinical Description	TNM Classification <sup>a</sup>	SEER Modified Criteria
<b>I</b>		
Single lesion (1 lobe) without vascular invasion	T1	Localized
>1 Lobe involved by contiguous growth (single lesion) without vascular invasion	T1	Regional by direct extension
Extension of single lesion to gallbladder (single lobe or >1 lobe by contiguous growth) without vascular invasion	T1	Regional by direct extension
<b>II</b>		
Single lesion (1 lobe) with intrahepatic vascular invasion	T2	Localized
>1 Lobe involved (single lesion) with vascular invasion	T2	Regional by direct extension
Multiple tumors all <5 cm	T2	Regional by direct extension
Extension of single lesion to gallbladder (single lobe or >1 lobe by contiguous growth) with vascular invasion	T2	Regional by direct extension
Tumor involvement in extrahepatic bile ducts	T2	Regional by direct extension

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

<sup>a</sup>Based on American Joint Committee on Cancer staging.<sup>6</sup>

mates stratified on race/ethnicity or therapy type were calculated using the log-rank test. Patient survival was censored at death or at the end of follow-up.

Multivariable Cox proportional hazards regression was used to assess the independent effects of race/ethnicity on mortality risk. To explore the relationships among race/ethnicity, socioeconomic factors, and mortality related to HCC, 2 separate models were constructed: a base model of risk-adjusted survival and a second risk-adjusted survival model that included treatment effects. The base model estimated time to death using race/ethnicity as the primary exposure variable, risk-adjusted for stage and clinical, demographic, socioeconomic, and geographic factors (hospital service area) that were associated with mortality. The second model applied a treatment effect to the base model. The effect of treatment was applied by stratifying the time-to-death analysis by the invasive treatment received, defined as tumor ablation, hepatic resection, liver transplant, or no therapy. Stratified models assume varying hazard functions for death within each stratum, and each treatment represented an individual stratum. We assumed that patients who received tumor ablation, hepatic resection, liver transplant, or no therapy had intrinsic differences that affected which therapy was selected for them and, therefore, their survival over time. For example, patients who undergo hepatectomy for early HCC have an inherently different mortality risk than those who undergo liver transplant, possibly because of the presence of cirrhosis, the need of posttransplant immunosuppression, differences in tumor anatomy that determine whether resection will be technically feasible, or comorbidities that affect surgical risk. The varying survival assumption was assessed graphically. The covariates in the base model were tested within each stratum, and their effects on the hazard of death were summarized in a single hazard ratio.

We used commercially available software (STATA, version 10.0; StataCorp, College Station, Texas) to complete statistical analyses. Statistical significance was defined at a *P* value of .05.

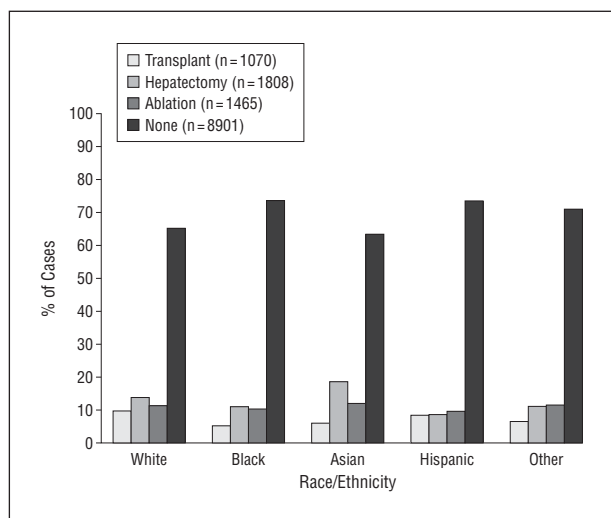
**Table 2. Clinical, Demographic, and Socioeconomic Attributes of Patients Diagnosed as Having Early-Stage Hepatocellular Carcinoma by Race<sup>a</sup>**

	Race/Ethnicity, %					P Value
	White (n=6316)	Black (n=1397)	Hispanic (n=2230)	Asian (n=3022)	Other (n=279)	
Age at diagnosis, mean (SD), y	65.1 (12.7)	60.4 (12.0)	61.9 (12.0)	63.1 (12.7)	61.3 (11.8)	.001
Male sex	74.7	73.5	73.5	71.2	71.7	.12
Tumor size, mean, cm <sup>b</sup>	5.00	5.00	4.75	5.32	5.32	.001
Married at diagnosis	70.7	49.2	66.9	83.7	59.5	.001
Median annual household income in county, \$	48 197	45 363	45 685	52 415	46 821	.001
High school graduates only <sup>c</sup>	19.3	21.5	24.3	20.3	19.0	.001
Persons living in poverty <sup>c</sup>	11.9	14.6	15.1	12.2	13.4	.001
White-collar employment <sup>c</sup>	36.6	36.2	36.1	39.2	35.7	.001
Language-isolated households <sup>c</sup>	6.0	6.2	9.8	10.1	7.0	.001
Receipt of invasive therapy	34.8	26.4	26.5	36.6	29.0	.001

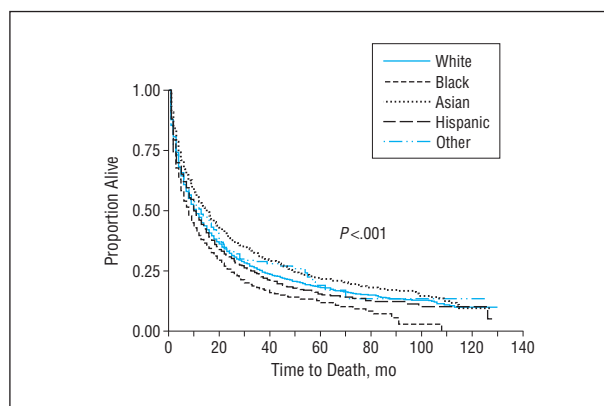
<sup>a</sup>Unless otherwise indicated, data are expressed as percentage of patients per race/ethnicity group. Groups are described in the "Study Population" subsection of the "Methods" section.

<sup>b</sup>Recorded only in the late era (2674 total observations).

<sup>c</sup>Indicates summative estimates of county-level attributes for each patient.



**Figure 1.** Distribution of surgical therapy for patients with early-stage hepatocellular carcinoma by race/ethnicity. Black and Hispanic patients had the highest proportions of untreated patients. Tumor ablation was used in approximately 10% to 12% of cases, regardless of race/ethnicity. Asian patients were significantly more likely to undergo hepatic resection than other groups ( $P < .001$ ). Liver transplant was more common among white than black, Hispanic, Asian, or other patients.



**Figure 2.** Racial/ethnic disparity in overall survival after diagnosis with early-stage hepatocellular carcinoma. Overall survival differences regardless of treatment status were statistically significant between racial/ethnic groups, and black patients had the poorest survival.

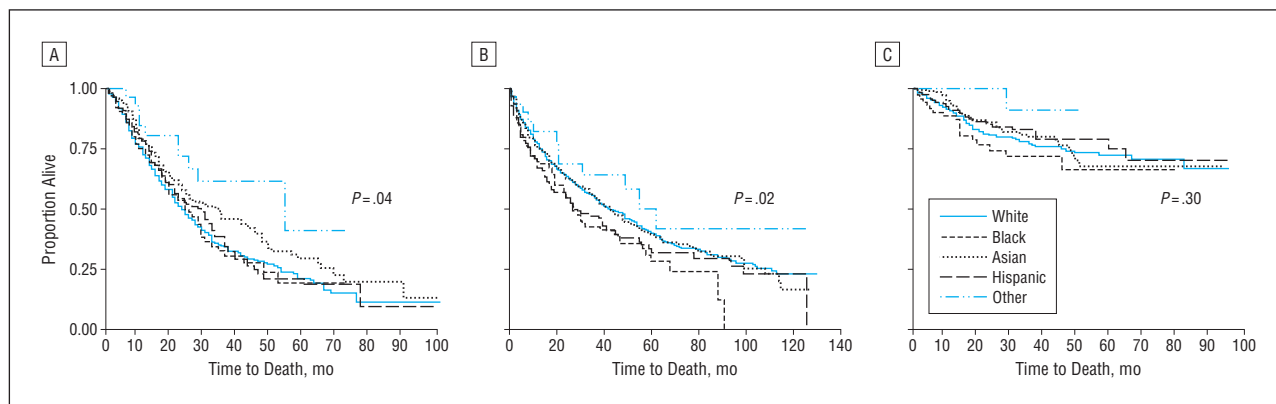
## RESULTS

We included 13 244 patients with early-stage HCC diagnosed between January 1, 1995, and December 31, 2006. Of these, 6316 (47.7%) were white, 3022 (22.8%) were Asian, 2230 (16.8%) were Hispanic, 1397 (10.5%) were black, and 279 (2.1%) were categorized as other. **Table 2** gives the clinical, demographic, and socioeconomic differences in the cohort by patient race/ethnicity. The mean (SD) age was 63.6 (12.6) years. White patients were older at diagnosis; 73.5% of patients were male, which was similar across races/ethnicities. Asian and other patients had larger tumors than those in the other 3 groups. Black patients had a significantly lower percentage of married patients than the other groups. When considering education, employ-

ment, and financial conditions, Asian patients appeared to reside in areas of higher socioeconomic status compared with white, black, Hispanic, and other patients.

During the study period, only 32.8% of patients received invasive therapy for HCC. **Figure 1** displays the racial/ethnic treatment distribution. Black and Hispanic patients had higher proportions of untreated patients compared with white, Asian, and other patients ( $P < .001$ ). Asian patients had much higher rates of hepatic resection than the other groups. The proportion receiving tumor ablation was fairly uniform for each group, from 9.6% to 12.0%. White patients underwent liver transplant more often than any other racial/ethnic group.

**Figure 2** displays racial/ethnic differences in unadjusted survival. All groups reached median survival in less than 16 months. Overall 5-year survival was 17.9% for all patients with early-stage HCC and by race/ethnicity was 18.2% for whites, 12.2% for blacks, 15.2% for Hispanics, 22.0% for Asians, and 17.1% for other patients ( $P < .001$ ). Median survival was 5 months longer for Asians (15 months) than for whites and Hispanics (10 months each) and 7 months longer than for blacks (8 months). Patients in the other race/ethnicity



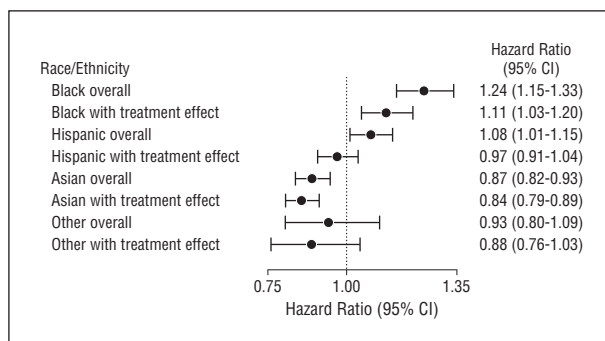
**Figure 3.** Survival differences by race/ethnicity after tumor ablation (A), hepatectomy (B), and liver transplant (C) for early-stage hepatocellular carcinoma. After tumor ablation and hepatic resection, black and Hispanic patients had the worst survival. Asian patients had better survival than white patients after ablation and similar survival after hepatectomy. After liver transplant, there were no significant differences in survival by race/ethnicity.

group had a median survival of 1 year. Among patients with stage I disease, median survival by race was longest among Asians (18 months), followed by other (17 months), whites (14 months), Hispanics (12 months), and blacks (9 months) ( $P < .001$ ). Asian patients with stage II disease had superior survival (8 months) compared with whites (6 months), blacks (5 months), Hispanics (7 months), and other patients (6 months) ( $P < .001$ ) (data not shown).

Survival conditional on receiving therapy also differed by race/ethnicity ( $P = .004$ ). When we included for evaluation those who received therapy, median survival improved to 29 months for black, 43 months for white, 40 months for Hispanic, 45 months for Asian, and 59 months for other patients (data not shown). Among those who did not receive any invasive therapy, median survival was 4 to 6 months for all groups.

Each therapy type also demonstrated unique racial/ethnic survival differences (**Figure 3**). After tumor ablation, Asian patients demonstrated the best long-term survival with a 5-year survival rate of greater than 30% compared with the white, black, and Hispanic patients, who all had a 5-year survival rate of less than 20% ( $P = .004$ ). Among patients who underwent hepatic resection, less than 30% of the black and Hispanic patients were alive at 5 years, whereas Asian and white patients had similar 5-year survival rates of approximately 40% ( $P = .02$ ). For patients who underwent liver transplant, there were no significant differences in survival noted by race/ethnicity.

Even after adjusting for stage and clinical and socioeconomic factors, racial/ethnic disparities in survival were evident (**Figure 4**). The forest plot shows mortality risk for each minority group relative to white patients in the base model and after accounting for differences in treatment. In the base model, mortality rates for black and Hispanic patients were significantly higher than that for white patients, by 24% and 8%, respectively, whereas Asian patients displayed a 13% lower mortality rate. After accounting for treatment effect, compared with white patients, black patients had a persistent disparity in mortality but of lower magnitude. The relative risk difference decreased from 24% to 11% (hazard ratio, 1.11; 95% confidence interval, 1.03-1.20). Hispanic patients had no significant mortality difference from white patients. For Asian patients, the mortality difference increased, with



**Figure 4.** Racial/ethnic differences in relative mortality risk for patients with early-stage hepatocellular carcinoma overall and with treatment effects. In each model, white race is the reference group. Black race was a significant predictor of poor survival in the overall base survival model. Accounting for treatment effects attenuated the apparent disparity in survival compared with white patients, but the difference remained statistically significant. Hispanic patients had worse survival at baseline compared with white patients, but the disparity was negligible after adjusting for treatment effects. Asian patients had better survival compared with white patients in the overall model and the treatment effects model. CI indicates confidence interval.

a 16% better survival rate (HR, 0.84; 95% CI, 0.79-0.89) vs white patients. Patients with other race/ethnicity did not have significant differences in mortality risk compared with white patients in either model.

## COMMENT

Racial/ethnic disparities in health care access and outcomes were notable in our study. For patients with early-stage HCC, racial/ethnic differences in demographics and socioeconomic status were significant, as were differences in the use of tumor ablation, hepatectomy, and liver transplant. Black and Hispanic patients received significantly less invasive therapy than did white or Asian patients. After adjusting for the receipt of various treatments and their respective effects on mortality risk, we found that racial/ethnic disparities in survival for black compared with white patients were persistent, although diminished. Hispanic and white patients had similar mortality rates after adjusting for treatment effects. Asian patients had better survival than white patients at baseline and with treatment effects.

With only 32.8% of the cohort receiving surgical therapy, our analysis indicates a significant underuse of appropriate interventions for the most treatable stages of HCC, particularly among black and Hispanic patients. This is particularly concerning given the increasing proportion of these racial/ethnic groups in the US population.<sup>7</sup> Several SEER-based reports have evaluated racial/ethnic disparities in access to care for HCC,<sup>3-5</sup> and our study supports these findings. We also identified racial/ethnic variation in the use of specific treatments; for example, the rate of hepatectomy was much higher in Asian patients than any other group, and there was nearly a 2-fold-lower rate of liver transplant in black compared with white patients. This phenomenon is clearly contingent on access to care because a recent study of wait-listed transplant candidates demonstrated no differences between black and white patients with regard to transplant rates for HCC.<sup>8</sup> Racial/ethnic equity in treatment rates is clearly possible if patients have the resources to overcome prohibitive barriers in access to care. It is unclear and alarming why so few patients with treatable HCC were registered with SEER but did not receive any curative therapy. Our study speaks to a potentially larger public health problem of poor access to complex cancer care for patients of all racial/ethnic groups.

Beyond access, few reports have addressed racial/ethnic differences in survival for patients with HCC. Sloane et al<sup>3</sup> examined all SEER HCC cases in black and white patients during a 10-year period from 1992 through 2001 and found that black patients were 4% to 20% more likely to die of localized HCC after adjusting for age, sex, and treatment status. Davila and El-Serag<sup>9</sup> used a 1987-2001 SEER cohort and found that black-white survival was equitable and that Hispanic patients had poorer survival compared with white patients after adjusting for treatment. Wong and Corley<sup>10</sup> evaluated nearly 2800 localized HCC cases and found that black women had nearly 60% lower 3-year survival compared with non-Hispanic white men. These studies support our hypothesis but have some limitations that were improved on in our analysis. We report on a much larger cohort than these studies, with more than 13 000 patients, and focused our analysis on patients with early-stage disease most likely to be treated invasively. Previous studies attempted to evaluate the implications of treatment effects on racial/ethnic disparities in survival, but these efforts were compromised by including patients who were otherwise ineligible for the treatments considered. Our statistical approach, which used stratified Cox proportional hazards models, provided more precise estimates of relative mortality risk for a given racial/ethnic group by not censoring data and by accounting for varying mortality hazards associated with multiple therapies. The previous studies assumed a uniform baseline hazard of mortality, although patients with HCC may have numerous unmeasured clinical factors that affect their mortality risk in different ways, such as the presence of cirrhosis. These factors also likely influence the choice of therapy. This level of methodological rigor allowed for more accurate between-race/ethnicity comparisons on survival, given the varying effects of the treatments received or not received.

The most notable finding in our study was that racial/ethnic variation in HCC outcome is related to access and variable treatment effect from specific therapies. After ad-

justing for treatment effects, the racial/ethnic disparity in survival between black and white patients decreased but persisted. This finding is linked to 2 major issues that contribute to health-related disparities in minority populations: black patients have poor access to treatment, and, even after obtaining treatment, they have relatively poor outcomes compared with white patients. This is particularly concerning given that the incidence of HCC is reportedly increasing in the black population faster than in other racial/ethnic groups.<sup>11</sup> Despite low rates of receiving invasive therapy among Hispanic patients, the relative treatment effect among those who had access to care was profound. After accounting for the effect in treatment, the disparity in survival between Hispanic and white patients with HCC disappeared. Differences in survival between Asian and white patients widened after adjustment for their high rate of invasive therapy use and the effectiveness of treatment. This may be explained by Asian patients tending to present with HCC resulting from chronic hepatitis B virus infection with compensated liver function and by greater awareness of HCC owing to screening programs that target this population.<sup>12,13</sup>

Our work has some notable limitations. One particular concern is with regard to staging classification. Although SEER is rigorous in its data collection, survival in our study was dismal and potentially could result from the undercoding of stage. Furthermore, if minority patients presented with more advanced early-stage disease but were inappropriately designated as having stage I or II HCC, this could potentially explain racial/ethnic differences in survival. In addition, the level of clinical detail on HCC in the registry does not capture significant factors that may affect the use of surgical therapy or survival, such as tumor characteristics, medical comorbidities, presence of chronic liver disease, and information on the details of all treatments received. The county-level socioeconomic data may not fully capture the economic, educational, and social factors for individual patients and could confound estimates of mortality risk. The use of overall survival as the primary outcome does not account for noncancer factors that affect mortality risk, and data on recurrence were also unavailable. In the context of these limitations, our analysis represents, to our knowledge, the most comprehensive study on racial/ethnic differences in survival for early stage HCC.

This study has important implications for health policy. The issue of health-related racial/ethnic disparities is complicated. Improving access to care is one step, but further research regarding the heterogeneity of treatment effects is needed. Some evidence that suggests racial/ethnic disparities in access to specialized care may be linked to the providers and facilities that serve minority patients.<sup>14</sup> Further provider education on the importance of HCC screening in at-risk groups may be helpful in alleviating these disparities. Cultural competence training in health care organizations may improve provider bias that could affect medical decision making. Minority patients may fear and mistrust the health care system, which may affect their use of health services. These issues require culturally sensitive policy interventions, potentially increasing the number of minority cancer care providers and partnering with community groups for cancer care initiatives.<sup>15</sup> Persistent racial/ethnic disparities in survival even after adjust-

ing for the effects of treatment are of particular concern and may be related to the quality of health care delivered.<sup>14</sup> This variation may require a comprehensive evaluation of centers where minorities receive care to standardize and improve the structure and process of cancer care delivery. As emerging therapies for complex cancers such as HCC evolve and disseminate, racial/ethnic equity in access to care and outcomes should remain at the forefront of health policy goals.

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## INVITED CRITIQUE

# Undertreatment of Patients With Early-Stage Hepatocellular Carcinoma

In this article, the authors study how race and ethnicity affect use of surgical therapy and survival for patients with HCC while controlling for stage of disease and differences in use of invasive therapy. They performed their study using SEER data, analyzing information from 13 244 patients diagnosed as having stage I or II HCC during the period from 1995 to 2006. The authors initially hypothesized that survival differences between racial and ethnic groups would be minimal after accounting for variation in the use of invasive therapy and the specific effects of treatment on survival.

Perhaps one of the most surprising results was that only 32.8% of all patients received invasive therapy for

early-stage disease. This is alarming because stage I and II disease is typically treated with good outcomes. In the base model without treatment stratification, black and Hispanic patients had higher mortality rates compared with whites, and Asians had lower mortality rates. After treatment stratification, Hispanics had a mortality rate similar to that of white patients, whereas blacks and Asians had lower and higher mortality rates, respectively, than before stratification.

The authors assumed that patients who received tumor ablation, hepatic resection, liver transplantation, or no therapy had intrinsic differences that affected which therapy was selected for them. This assumption may not be as valid as the authors think because sometimes pa-