Survival Differences by Race/Ethnicity and Treatment for Localized Hepatocellular Carcinoma Within the United States

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Abstract Racial differences among hepatocellular carcinoma survival have been reported, but the etiology behind these disparities remains unclear. Using multi-variable logistic regression analysis, our retrospective cohort study investigated the demographic disparities in survival among localized hepatocellular carcinoma in the United States. From 1998 to 2001, 2,776 cases of localized hepatocellular carcinoma were identified. Significant racial/ethnic disparities in overall survival and utilization of therapies were identified. Compared with non-Hispanic white males, black females were 56% less likely to survive 3 years (OR 0.44; 95% CI 0.21–0.93). Treatment-specific models also demonstrated disparities, e.g., compared with non-Hispanic whites, Asians receiving transplantation were 77% more likely to survive 3 years (OR, 1.77; 95% CI 1.28–2.44). There are significant racial/ethnic disparities in 3-year survival among patients with localized hepatocellular carcinoma. These differences are partially explained by demographic differences in utilization of therapy and in stage-specific survival for each therapy.

Keywords Racial disparities · Cancer epidemiology · Survival differences · Primary liver cancer
National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) cancer registry has incorporated more detailed information on therapeutic interventions; these data now permit a population-based assessment for treatment disparities, treatment responses, and survival for different demographic groups.

We performed a study utilizing high-quality data from the SEER cancer registry to evaluate whether race and ethnicity were associated with survival after the diagnosis of localized stage hepatocellular carcinoma, adjusted for sex, age, year of diagnosis, and treatment type. We then evaluated whether survival differences were explained by geographic or demographic disparities in treatment administered or demographic differences in the response to treatment.

Methods

Data Sources

We analyzed data from the SEER registry, a population-based cancer registry covering approximately 26% of the US population, for the years 1998–2004 (the most recent year of data). The SEER population is comparable to the general US population with regards to measures of poverty and education [27]. Prior to 1998, the SEER program compiled only basic information for cancer-directed surgical therapies. Starting in 1998, SEER registries added detailed therapeutic interventions such as ablation, transplantation, etc. The 1998–2004 data set includes data from registries in 17 geographic regions: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, California (San Francisco–Oakland, Los Angeles, San Jose–Monterey, and Greater California, which includes Central California, Sacramento, Tri-County, Desert Sierra, Northern California, San Diego/Imperial County, Orange County), Seattle–Puget Sound, Utah, Rural Georgia, the Alaska Native Tumor Registry, Kentucky, Louisiana, and New Jersey [27, 28].

Case Definitions

Cases of hepatocellular carcinoma were identified using anatomic site (liver: C22.0) and histology codes (hepatocellular carcinoma: 8170–8175) from the International Classification of Disease for Oncology, 3rd ed. [29]. Hepatocellular carcinoma, NOS (8170), accounted for 98.9% of our cases. Localized cancers were classified using SEER staging criteria [30]; a “localized” SEER stage included cancers confined to one lobe of the liver (with or without vascular invasion), and without evidence of nodal or extrahepatic involvement.

Race/Ethnicity Definitions

Our analyses utilized the following SEER race and ethnicity categories: non-Hispanic whites, blacks, Asian/Pacific Islanders (Asian/PI), and Hispanic whites (Hispanics). The small number of cancer cases among other groups (American Indian/Alaskan, black Hispanics, Asian/PI Hispanics) precluded the calculation of precise estimates for these populations.

Treatment Definitions

The SEER database includes information regarding the type of therapy received by each patient. Among patients receiving multiple treatments (e.g., radiation prior to resection), only the first treatment is recorded. We grouped therapeutic interventions into five categories: no invasive therapy, local tumor destruction (including photodynamic therapy, electrocautery, cryosurgery, laser, percutaneous ethanol injection, and local tumor destruction not otherwise specified [NOS]), radio frequency ablation, resection (wedge, segmental, or lobectomy), and liver transplantation [30].

Outcome Definitions

The main outcome was the proportion of persons surviving 3 years after a localized hepatocellular carcinoma diagnosis. This outcome (rather than shorter intervals) was chosen given the overall 3-year survival for localized hepatocellular carcinoma in our data set was <30% and the 3-year interval decreased the impact of lead time bias from detection for any demographic group. Detailed treatment data and follow-up was available for the years 1998–2004; thus, a case diagnosed in 2001 had 3 years of follow-up available. Longer intervals (e.g., 5 years) provided relatively few cases for analysis.

Statistical Analysis

Analyses were performed using the SEER*Stat 6.5.3 (National Cancer Institute, Maryland) and Stata statistical packages (release ten, Stata Corporation, Texas). Odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression models, with an outcome variable of 3-year survival; we did not use hazard ratios to decrease lead or length time biases incorporated into time-to-event analyses. Multivariable logistic regression models were adjusted for sex, age, year of diagnosis, race/ethnicity, and therapeutic intervention. Geography (via SEER registry location) was also evaluated as a potential confounder. Our study focused on the five geographic regions with >450 total hepatocellular carcinoma cases (San Francisco–Oakland, Los Angeles, San Jose–Monterey, and Greater California, which includes Central California, Sacramento, Tri-County, Desert Sierra, Northern California, San Diego/Imperial County, Orange County), Seattle–Puget Sound, Utah, Rural Georgia, the Alaska Native Tumor Registry, Kentucky, Louisiana, and New Jersey [27, 28].
Francisco-Oakland, Detroit, Los Angeles, Greater California, and New Jersey) to ensure enough statistical power to assess differences among treatment distribution between ethnic subgroups.

**Results**

**Overview**

The mean proportion of persons surviving three years after a localized hepatocellular carcinoma diagnosis during the period 1973–1997 was 18.1% (95% CI 15.9–20.3), with the lowest proportion among blacks (10.0%; 95% CI 6.5–13.5) and the highest among Asian/PI (23.0%; 95% CI 19.9–26.1). For the 1998–2001 time interval, the 3-year survival proportions for cases diagnosed were higher for the group as a whole (28.1%; 95% CI 26.3–29.9) and for each race/ethnicity group compared with cancers diagnosed between 1973 and 1997 (Table 1).

**Distribution of Therapy by Type and Geographic Region**

We investigated whether differences in survival by race/ethnicity were explained by variations in therapy received. The administration of any invasive intervention was highest among Asian/PI (38.9%; 95% CI 35.0–42.1) and lowest among Hispanics (25.5%; 95% CI 21.7–29.3) (Table 2). For specific treatments, Asian/PI were the most likely to receive hepatic resection (24.5%; 95% CI 21.6–27.9) and Hispanics were the least likely (9.4%; 95% CI 7.1–12.3). Non-Hispanic whites were the most likely to receive liver transplantation (9.4%; 95% CI 8.0–11.0) and blacks were the least likely (4.8%; 95% CI 2.7–7.9). The proportions receiving local tumor destruction therapy and radiofrequency ablation were similar among all racial/ethnic groups.

We evaluated whether the differences in treatment received were due to geographic differences. If a given region, for example, was more likely to provide hepatic resection as a treatment and that region had a higher proportion of Asian/PI, geography may confound the association between hepatic resection and Asians/PI. Geography, however, did not explain the treatment differences seen. The use of specific therapies differed markedly by geographic region between the five SEER regions that reported at least 450 cases, but the general patterns of treatment differences by race/ethnicity were similar within each region (Table 3). Similar to the pooled data from all registries, within each region Asian/PI were generally more likely to receive resection, non-Hispanic whites and Hispanics were more likely to receive transplantation, and

| **Table 1** Three-year survival in patients diagnosed with localized hepatocellular carcinoma, stratified by race/ethnicity |
| --- | --- | --- | --- |
| Cases diagnosed from 1973 to 1997 | Cases diagnosed from 1998 to 2001 |
| **Male and female** | **3 year survival (%)** | **95% CI** | **Total cases** | **3 year survival (%)** | **95% CI** | **Total cases** |
| Non-Hispanic white | 18.1 | 15.9–20.3 | 1,556 | 28.3 | 25.8–30.8% | 1,328 |
| Black | 10.0 | 6.5–13.5 | 324 | 18.8 | 13.9–23.7% | 275 |
| Asian/PI | 23.0 | 19.9–26.1 | 770 | 32.6 | 28.9–36.3% | 697 |
| Hispanic white | 15.4 | 11.5–19.3 | 364 | 26.1 | 22.0–30.2% | 476 |

SEER dataset time periods, 1973–1997 versus 1998–2001 (with subsequent 3-year survival data through 2004)

| **Table 2** Distribution of invasive therapies administered, stratified by race/ethnicity, among patients with localized hepatocellular carcinoma (years 1998–2004) |
| --- |
| **Therapy** | **Count** | **Percent (%)** | **95% CI** |
| **Non-Hispanic white** | | | |
| No invasive therapy | 1,033 | 67.8 | 65.4–70.2 |
| Radio frequency ablation | 28 | 1.8 | 1.2–2.6 |
| Local tumor destruction | 73 | 4.8 | 3.8–6.0 |
| Resection | 246 | 16.1 | 14.3–18.1 |
| Transplant | 143 | 9.4 | 8.0–11.0 |
| **Black** | | | |
| No invasive therapy | 228 | 73.6 | 68.3–78.4 |
| Radio frequency ablation | 6 | 1.9 | 0.7–4.2 |
| Local tumor destruction | 15 | 4.8 | 2.7–7.9 |
| Resection | 46 | 14.8 | 11.1–19.3 |
| Transplant | 15 | 4.8 | 2.7–7.9 |
| **Asian/PI** | | | |
| No invasive therapy | 457 | 61.1 | 57.9–65.0 |
| Radio frequency ablation | 12 | 1.6 | 0.8–2.8 |
| Local tumor destruction | 47 | 6.3 | 4.7–8.3 |
| Resection | 183 | 24.5 | 21.6–27.9 |
| Transplant | 44 | 5.9 | 4.3–7.9 |
| **Hispanic white** | | | |
| No invasive therapy | 395 | 74.5 | 70.7–78.3 |
| Radio frequency ablation | 12 | 2.3 | 1.2–3.9 |
| Local tumor destruction | 29 | 5.5 | 3.7–7.8 |
| Resection | 50 | 9.4 | 7.1–12.3 |
| Transplant | 43 | 8.1 | 5.9–10.8 |
blacks were less likely to receive any treatment. For example, in Detroit only 5.2% of blacks received transplantation compared with 12.8% of non-Hispanic whites ($P < 0.02$). Even among Asian/PI, who generally were more likely to receive some treatment, significant differences in transplantation were identified (6.2% in Asians/PI vs. 12.5% in non-Hispanic whites; Los Angeles, $P < 0.01$) (Table 3). Age and gender adjusted analyses for the comparisons presented above were all statistically significant ($P < 0.05$).

Adjusted Survival Analyses

Race/ethnic differences in the proportion surviving 3 years still persisted after adjustment for therapy type, age, and year of diagnosis. For example, compared to non-Hispanic white males (the largest group), black females were 56% less likely to survive at least 3 years (OR 0.44; 95% CI 0.21–0.93) and Asian/PI males were 31% more likely to survive at least 3 years (OR 1.31; 95% CI 1.00–1.72) (Table 4).

Treatment Response

We evaluated whether the survival disparities were explained by demographic differences in the response to each treatment modality, given adjustment for treatment type alone did not eliminate the survival differences for localized disease. We compared survival for each treatment regimen vs. no treatment, stratified by sex or race/ethnicity, and adjusted for age and year of diagnosis.

The response to local tumor destruction was lower in females than in males (females: 19.5% 3-year survival, OR 2.00, 95% CI 0.91–4.39; males: 46.3% survival, OR 7.57, 95% CI 5.06–11.33). In contrast, 3-year survival rates were comparable between males and females for surgical resection, transplantation, and radio frequency ablation. For both males and females, patients receiving transplantation were the most likely to survive 3 years (males: 80.2% survival, OR 26.94, 95% CI 18.07–40.18; females: 80.4% survival, OR 19.76, 95% CI 10.04–38.90) (Table 5).

The response to therapy for local stage disease varied by race/ethnicity, even after adjustment for sex, age, and year.
of diagnosis (Table 6). For any given treatment, compared with non-Hispanic whites, Asian/PI had trends for the greatest overall survival after treatment, whereas blacks had the least benefit, although some confidence intervals overlapped 1.00. For example, Asian/PI who received transplants for limited stage disease were 77% more likely to be alive 3-years postdiagnosis than similar non-Hispanic whites matched for age, sex, and year of diagnosis (OR 1.77, 95% CI 1.28–2.44). In contrast, there was a strong trend for blacks to be less likely to survive 3 years after resection, compared with non-Hispanic whites (OR 0.65, 95% CI 0.42–1.01). These general trends were similar for all treatment modalities including local tumor destruction, radio frequency ablation, resection, and transplantation.

**Discussion**

Among patients with localized hepatocellular carcinoma, our study identified substantial and significant differences

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### Table 4 Multivariable logistic regression analysis of 3-year survival by sex and race/ethnicity

| Predictor variable              | 3-year survival % | Cases | OR 95% CI          | OR 95% CI          |
|---------------------------------|-------------------|-------|--------------------|--------------------|
|                                 | 3-year survival   | Age and date adjusted | Age, date, and treatment adjusted |
| Non-Hispanic white male         | 27.8              | 998   | 1.00               | Reference          |
| Non-Hispanic white female       | 29.7              | 330   | 1.48               | 1.12–1.94          |
| Black male                      | 21.7              | 193   | 0.65               | 0.45–0.95          |
| Black female                    | 12.0              | 82    | 0.40               | 0.20–0.80          |
| Asian/PI male                   | 33.2              | 497   | 1.39               | 1.10–1.76          |
| Asian/PI female                 | 31.2              | 200   | 1.47               | 1.06–2.05          |
| Hispanic white male             | 24.8              | 338   | 0.81               | 0.61–1.08          |
| Hispanic white female           | 29.3              | 138   | 1.19               | 0.79–1.79          |

Cases include localized hepatocellular carcinoma diagnosed from 1998 to 2001 (with 3-year follow-up through 2004). The 3-year survival is a crude (unadjusted) value.

### Table 5 Multivariable logistic regression analysis of 3-year survival by category of invasive therapy received

| Predictor variable              | 3-year survival | Adjusted OR | 95% CI          |
|---------------------------------|-----------------|-------------|----------------|
| **Male**                        |                 |             |                |
| No invasive therapy             | 11.9%           | 1.00        | Reference      |
| Radio frequency ablation        | 44.1%           | 6.11        | 3.15–11.87     |
| Local tumor destruction         | 46.3%           | 7.57        | 5.06–11.33     |
| Resection                       | 53.4%           | 8.98        | 6.86–11.76     |
| Transplant                      | 80.2%           | 26.94       | 18.07–40.18    |
| **Female**                      |                 |             |                |
| No invasive therapy             | 13.0%           | 1.00        | Reference      |
| Radio frequency ablation        | 44.0%           | 2.89        | 0.95–8.84      |
| Local tumor destruction         | 19.5%           | 2.00        | 0.91–4.39      |
| Resection                       | 56.8%           | 8.31        | 5.52–12.50     |
| Transplant                      | 80.4%           | 19.76       | 10.04–38.90    |
by race/ethnicity in overall 3-year survival, type of therapy administered for limited stage disease, and survival after specific therapies. Compared with non-Hispanic whites, blacks were less likely to survive 3 years after diagnosis, less likely to receive any treatment, and, when treated, less likely to survive 3 years for most specific treatment types; the lowest survival times were found in black females. In contrast, Asian/PI had the highest 3-year survival outcomes for each specific treatment type. Although the likelihood of treatment varied somewhat by geographic region, demographic disparities in receipt of therapy existed in most geographic regions and geography did not explain the overall patterns of survival or treatment by race/ethnicity (Table 3). While our study focused on regions where the number of localized hepatocellular carcinoma cases exceed 450 for purposes of statistical analysis, the same discrepancies persisted even among more rural areas of the country that were not included in Table 3. For example, in the Kentucky registry, 12.8% of non-Hispanic whites received liver transplantation compared with 6.3% of blacks. Similarly, among patients with localized hepatocellular carcinoma in Louisiana, 19.2% of non-Hispanic whites received transplantation compared with 11.7% of blacks.

Current estimates of survival outcome among patients diagnosed with hepatocellular carcinoma are concerning. Between 1977 and 1996, 1-year survival improved from 14 to 23%, but overall and longer-term survival remained poor [8]. Patients with localized cancers have the greatest potential for benefit from therapeutic interventions. One study among 4,008 patients diagnosed with hepatocellular carcinoma between 1988 and 1998 reported a 5-year survival of 33% among those with small, unifocal, non-metastatic cancers who underwent surgical intervention compared with a 7% 5-year survival among those who did not receive surgery [11]. The same study noted that 45% of patients with potentially resectable tumors did not receive surgery. Additional studies investigating treatment outcomes have also suggested possible underutilization of potentially curative therapy among patients with localized cancers [10–13].

The current study extends prior reports that evaluated demographic variables and hepatocellular carcinoma [10–26]. A prior study in Medicare patients suggested geographic differences in treatment for hepatocellular carcinoma; however, it is unclear if the results in this population (median age 74 years) can be generalized given older patients may be less likely to receive aggressive interventions such as liver transplantation [10]. Prior studies that utilized the SEER database found racial/ethnic differences in survival overall, but this was prior to the availability of recent detailed data on therapeutic interventions (such as radio frequency ablation, tumor destruction by electrocautery or fulguration, cryosurgery, laser, and percutaneous ethanol injection) that were evaluated in the current study, and there were not detailed analyses of limited stage disease, the stage most responsive to treatment [10, 12, 13, 26]. Furthermore, a survival analysis that includes all stages of cancers may be confounded by variations in treatment availability and utility as more aggressive cancers may not be offered invasive therapies. Thus, the current analysis included all ages, expanded data on therapeutic interventions, and focused specifically on localized cancers, which have the greatest potential to demonstrate a survival benefit and to identify any disparities that may exist.

Our findings suggest that demographic differences in the likelihood of receiving treatment and responses to treatment may at least partially underlie the described differences in survival outcome by race/ethnicity. Racial disparities in receipt of surgical therapy have been suggested by others as well [19, 20, 23, 24]. Demographic differences in the delivery of health care are well documented [31, 32]; for example, blacks and women are less likely to receive aggressive cardiac interventions in the presence of coronary artery disease [33–35]. Potential explanations include unequal access to health care, inappropriate overuse in other groups, physician attitudes towards disease risk in different demographic groups, patient attitudes towards medical care, and overt discrimination [36, 37]. In addition, major interventions such as transplantation require the fulfillment of rigid criteria for social support, adherence to medical care, etc. Meeting these criteria may be more challenging for immigrant groups or persons of lower socioeconomic status—the groups which are proportionately more likely to include minority populations.

Differences in outcome after specific treatments may also be partially related to the underlying diseases associated with hepatocellular carcinoma, most commonly hepatitis B, hepatitis C, and alcohol abuse. These risk factors are not in the SEER database and could not be evaluated in the current analysis. The biological behavior of hepatocellular carcinoma may differ in the presence of different risk factors. For example, while hepatitis C causing hepatocellular carcinoma is almost always preceded by progressive liver damage resulting in cirrhosis, hepatitis B can lead to hepatocellular carcinoma without liver cirrhosis. These differences likely affect choice of therapy and overall survival. Hepatitis B virus is the main etiological agent for hepatocellular carcinoma in Asians, while hepatitis C virus is more commonly found in blacks and non-Hispanic whites [38–46]. While few studies have reported variations in surgical interventions, one study suggested that compared to non-Hispanic whites, Asians...
with chronic hepatitis B virus had a significantly higher posttransplantation mortality [23]. A differential response to similar interventions between demographic groups suggests the possibility that ethnicity/race may influence posttherapy survival independent of etiology; such differences are well documented for many disorders, including hypertension and the response to antiviral therapies for hepatitis C [47–50]. Potential explanations for the race/ethnicity-specific variations in treatment response in our study include differences in disease severity within limited stage disease, host genetic variations to therapy or the cancer, compliance with therapy, disparities in co-interventions that influence survival, or interactions with environmental factors.

Strengths of this study include the utilization of high-quality data from a population-based cancer registry that represents a large proportion of the US population [27, 28]. Detailed data on race classifications and therapeutic interventions permitted analysis of sex and race/ethnicity-specific responses to each treatment category and the analyses adjusted for several potential major confounders including age, date of diagnosis, and gender among localized cancers.

There are several potential limitations of this study. In Table 1, we presented improvements in 3-year survival between patients with localized hepatocellular carcinoma diagnosed between 1973 and 1997 and those diagnosed between 1998 and 2001. While the increased survival rates likely represent new advances in cancer targeted therapy and improved techniques of potentially curative interventions, lead time bias may also be another contributing factor. In addition, SEER records the initial therapy received after a cancer diagnosis, but not necessarily the most aggressive therapy. Some patients may have received multiple treatments over time; however, this limitation of all registry studies does not alone explain the race/ethnicity differences in treatment patterns or posttreatment survival. Although all patients analyzed had localized disease, a spectrum of disease exists within each recorded cancer stage. While the SEER category of “localized tumors” is defined by lack of nodal or extrahepatic involvement, it is limited in its ability to identify the extent of tumor involvement (size and unifocal vs. multifocal) within the lobe it affects as well as evidence of vascular invasion. Tumor differences within the category of localized disease may influence the utility of therapy for some patients, although it is not clear that racial/ethnic disparities in the spectrum of disease within each stage would fully account for the differences observed in treatment, treatment response, and overall survival. Even if this were the case, it would suggest there are either biological differences in disease aggressiveness within a specific stage between the different race/ethnic groups or differences in the application of techniques (e.g., screening) between the groups to identify less aggressive cancers. Either of these would be important observations for improving treatment outcomes. Finally, additional factors such as disease etiology (e.g., viral hepatitis), underlying liver disease, severity of liver disease as evidenced by MELD scores, other comorbidities, alcohol use, access to timely care within each SEER region, etc., were not available for analysis; variations in these factors may also influence choices of therapeutic intervention employed or survival and may differ by race/ethnicity.

In summary, for localized stage hepatocellular carcinoma, this study described substantial and significant disparities by race/ethnicity in 3-year survival, therapy administered, and stage-specific survival for individual therapies. The differences were not explained by age, date of diagnosis, or geography. Potential explanations include differences in the delivery of health care between demographic groups with similar stages of disease, disease differences within limited stage disease, disease biology, or variations in treatment response.

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