Survival of patients with hepatocellular carcinoma in the San Joaquin Valley: a comparison with California Cancer Registry data

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Abstract

Background Variation in the survival of patients with hepatocellular carcinoma (HCC) is related to racial differences, socioeconomic disparities and treatment options among different populations.

Methods A retrospective review of the data from medical records of patients diagnosed with HCC were analyzed at an urban tertiary referral teaching hospital and compared to patients in the California Cancer Registry (CCR) – a participant in the Survival Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI). The main outcome measure was overall survival rates.

Results 160 patients with the diagnosis of HCC (M/F=127/33), mean age 59.7±10 years, 32% white, 49% Hispanic, 12% Asian and 6% African American. Multivariate analysis identified tumor size, model for end-stage liver disease (MELD) score, portal vein invasion and treatment offered as the independent predictors of survival (p <0.05). Survival rates across racial groups were not statistically significant. 5.6% received curative treatments (orthotopic liver transplantation, resection, radiofrequency ablation) (median survival 69 months), 34.4% received nonsurgical treatments (trans-arterial chemoembolization, systemic chemotherapy) (median survival 9 months), while 60% received palliative or no treatment (median survival 3 months) (p <0.001).

Conclusion There was decreased survival in our patient population with HCC beyond 2 years. 60% of our study population received only palliative or no treatment suggesting a possible lack of awareness of chronic liver disease as well as access to appropriate surveillance modalities. Ethnic disparities such as Hispanic predominance in this study in contrast to the CCR/SEER database may have been a contributing factor for poorer outcome.

Keywords Hepatocellular carcinoma, cirrhosis, ethnic, disparities, survival

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver neoplasm and the fourth most common malignancy worldwide [1]. There were an estimated 696,000 deaths from liver cancer in 2008 and, because of its high fatality, HCC is the third most common cause of death from cancer worldwide [2]. Chronic hepatitis C (CHC) infection is the major risk factor for HCC in the US, particularly among individuals of white and African American (AA) ethnicity, whereas chronic hepatitis B (CHB) remains the main risk factor among patients of Asian ethnicity [3]. The incidence is currently 4.1 per 100,000 individuals and has steadily increased over the past 30 years [4]. The prognosis of symptomatic HCC is poor, with an overall 5-year survival rate of 3-7% [5-7]. The
prognosis is uniquely affected due to underlying cirrhosis [8].

Potentially curative therapies including surgical resection, transplantation, and percutaneous ablation are only available to patients with limited disease, which includes only one third of the cases [9]. The surveillance for HCC has proven to be vital in improving survival but is possible only when the potentially high-risk individuals are identified and entered into surveillance programs. However, it appears that there are inconsistencies in HCC surveillance and myriad reasons, such as geographic location combined with patient characteristics and provider preferences being contributing factors [10]. Despite incremental technological advances in cross-sectional imaging techniques, standard imaging methods can underestimate or overestimate the extent of HCC in up to 25% of cases, compared with pathological findings of the explanted liver [11]. The role of tumor markers, such as α-fetoprotein, lens culinaris agglutinin-reactive α-fetoprotein, and des-carboxyprothrombin has recently been reported to predict survival in HCC [12]. More recently, molecular profiling has led to a better understanding of HCC biology and specific microRNAs and epigenetic changes in the clinical setting have been described as potential tools for clinical outcomes [13-15].

Racial and socioeconomic disparities exist in the incidence and outcomes of HCC [16-19]. Hispanics in the US have high rates of HCC that are second only to Asians/Pacific Islanders [16]. Several environmental and cultural risk factors, such as CHC infection, heavy alcohol consumption, and nonalcoholic steatohepatitis related to obesity and diabetes mellitus may be responsible for these observations [20,21].

The San Joaquin Valley is home to 4 million people and spans 300 miles through the center of California. Hispanics constitute 46% of the population and, in addition, there are several Asian minorities including Hmong, Laotian, Thai and south Asian Indians. There are health care disparities in these ethnic minorities which are multifactorial and include cultural practices, language barriers, health care insurance and access to care. Therefore, we set out to examine the survival of HCC in the San Joaquin Valley and identify any specific factors that could be contributing towards a poorer survival compared to the general population. We compared the survival of our patients with HCC with data from the California Cancer Registry (CCR) – a participant in the Survival Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI) to determine if differences exist in overall survival between our study group and that of the California general population.

Materials and Methods

A retrospective review of the medical records of patients diagnosed with HCC was carried out at our hospital, an urban tertiary referral teaching hospital located in the heart of San Joaquin Valley. The study included all patients (age, 18-80 years) diagnosed with HCC presenting to our hospital between January 2002 and December 2008. Initially, a total of 175 patients were identified with diagnosis of HCC and 15 patients were excluded because of the unavailability of the pertinent medical information related to the study.

Demographic information, etiologies, diagnostic labs, tumor characteristics and treatments offered were collected by review of the medical records. The model for end-stage liver disease (MELD) score was calculated. CCR/ SEER data was accessed for the similar period from 2002 to 2008. The NCI’s SEER program is a comprehensive source of population-based information on cancer incidence and survival in the US [22]. The following patient variables (obtained from the CCR/SEER cancer registry for HCC) were examined: race/ethnicity, tumor size, American Joint Committee on Cancer tumor stage, median survival and yearly percentage survival up to 5 years. The main outcome measure was overall survival rates. This study was approved by the University of California, San Francisco, Fresno Medical Education Program (UCSF Fresno MEP) Institutional Review Board.

Statistical analysis

The data collected from the medical charts were analyzed using Stata statistical software, version 11.1. Continuous variables were summarized as mean ± standard deviation and median where appropriate. Comparisons between continuous variables were analyzed using Student t test. Categorical variables are summarized as percentage of the group total and, comparisons between groups were analyzed using either Fisher exact test or Chi-square test. Prevalence values with 95% confidence intervals (CI) were reported where needed. Survival analysis performed using Cox proportional hazard model and displayed with Kaplan-Meier curves. Median survival rates were calculated and yearly survival comparisons were done up to 5 years follow up with CCR/SEER database with Chi-square test (with Yates’ correction for continuity). The univariate and multivariate analyses were carried out to identify the predictors of survival. The Log rank test and Cox regression-Breslow methods for ties were used to calculate p values. A p value <0.05 was considered to be statistically significant.

Results

During 2002-2008, 160 patients with the diagnosis of HCC were identified (men=127; women=33), with a mean age of 59.7±10.3 (range, 27-87 years). Of 160 patients, 32% were white, 49.4% Hispanic, 12% Asian and 5.6% AA. Mean tumor size was 6.2±3.4 cm (Table 1, Fig. 1). 43.8% of the study sample diagnosed with both cirrhosis and HCC at the same time while, 50.6% diagnosed with cirrhosis progressed to HCC with a median duration of 24.5 months (range, 1-113 months). 12.5% of the total sample was found to have received HCC surveillance.

Etiology

The predominant etiology of cirrhosis in the study population was CHC (62%, 95% CI: 53.9-69.4) followed by excess alcohol consumption (44.4%, 95% CI: 36.5-52.4) and CHB (10%, 95% CI, 5.8-15.7). Among Asians, the prevalence
of CHB was significantly higher (62.5%) compared to any other ethnic group (p≤0.001) (Table 2). Males had higher prevalence of hepatitis C virus (HCV), alcohol and hepatitis B virus (HBV) compared to females (p≤0.05). 27% of the study population had both alcohol and CHC as an etiology for cirrhosis. 16 (10%) patients had other etiologies (unknown) and the etiology was not documented in 4 cases.

### Survival analysis

Median survival in the study population was found to be 5 months (Fig. 2). Table 3 lists the univariate and multivariate analysis of various factors affecting mortality with p values. Univariate analysis was carried out using Log-rank test of equality and univariate Cox proportional hazard regression-Breslow methods for ties for categorical and continuous predictor variables respectively. Predictor variables with p value less than 0.2 on univariate analysis were included in the multivariate analysis. Multivariate analysis identified tumor size, treatment class, MELD score and portal vein invasion as the independent predictors of survival (p<0.05), whereas the prothrombin time, hypoalbuminemia, hyperbilirubinemia, and metastases were identified as the predictors of survival only on univariate analysis (p < 0.05) (Table 3). No statistical significance was identified in survival rates across racial/ethnic groups. MELD score >15 was associated with significantly lower survival (median survival of 3 months) when compared with MELD score ≤15 (median survival of 19 months) (p <0.001). Patients with no ascites had a median survival of 9 months compared with those with ascites (median survival of 4 months) (p=0.054) (Table 3).

### Tumor characteristics

51% of the study population had more than one tumor and 34% were found to have metastatic disease. Most common site for extra-hepatic metastases was found to be the lung (51%) followed by bone including spinal metastases and abdominal lymph nodes. Other metastatic sites include peritoneum and the adrenal gland. 53% of the study population had tumor size >5 cm, 44% had 2-5 cm, while 4% had tumors <2 cm. Though not statistically significant, median survival was considerably

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**Table 1** Baseline characteristics of hepatocellular carcinoma (HCC) study patients, 2002-2008

| Characteristics       | Values                  |
|------------------------|-------------------------|
| Age in years (mean ±SD)| 59.7 ± 10.3             |
| Gender                 |                         |
| Male - no (%)          | 127 (79.4)              |
| Female - no (%)        | 33 (20.6)               |
| Race/Ethnic group - no (%) |                |
| White                  | 51 (31.9)               |
| Hispanic               | 79 (49.4)               |
| Asian                  | 19 (11.9)               |
| African American       | 9 (5.6)                 |
| Others                 | 2 (1.3)                 |
| Time to HCC in months* | 24.5                    |

*71 patients diagnosed with HCC at the time of diagnosing cirrhosis and were excluded in calculating the time to progress to HCC.
^MELD > 40 taken as 40. j Median.
SD, standard deviation; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease; AFP, alpha fetoprotein
lower (4 months) in patients with tumor size ≥5 cm compared to those with tumor size ≤5 cm (>14 months; p=0.09). When the tumor size was compared across ethnicities, no major differences were noted.

### Treatment modalities

Only 5.6% received curative treatments [orthotopic liver transplantation (OLT), resection, radiofrequency ablation (RFA)] and 34.4% received nonsurgical treatments [transarterial chemoembolization (TACE), systemic chemotherapy], while 60% received palliative care or no treatment. The median survival of 69 months was noted in curative treatment class followed by 9 months in nonsurgical and 3 months in palliative care/no treatment class (p <0.001) (Table 4, Fig. 4). 89% of AA received palliative/no treatment followed by Asians (68%), whites (59%) and Hispanics (57%) (p=0.024). 39% of whites received nonsurgical treatment followed by Hispanics (38%) and Asians (21%) while, AA did not receive any nonsurgical treatments in the study sample (p=0.024) (Table 5).

### Comparison with CCR/SEER data

15,094 HCC patients from the CCR/SEER database were identified. The median survival, survival by race and tumor size was estimated. The predominant ethnic group in CCR/SEER database were whites (39%) followed by Hispanics (29%) in contrast to our study population where Hispanics were the majority (49%) followed by whites (32%). Asians represented 26% of CCR/SEER population while it was only 12% in our study population. AA had the lowest representation of 7.3% in CCR/SEER versus 6% in our population.

The median survival in the CCR/SEER population was 7 months compared to 5 months in our study population. The breakdown in survival differences between our patients and CCR/SEER patients by race/ethnicity was as follows: Asians (10 versus 5 months), Hispanics (8 versus 5 months) and AA (5 versus 3 months) (Table 6). No survival difference was noted among patients with a tumor size greater than 5 cm. However, with tumor size between 2 and 5 cm, CCR/SEER patients showed better survival (22 months compared to 14 months in our study population).

Survival rates of our study group was found to be similar to that of CCR/SEER data for the first 24 months but, lower survival rates were noted at 3, 4 and 5 years respectively (Fig. 3). This inferior survival was especially prominent among our Hispanic population, a predominant ethnic group in our study, with median survival of 5 months (Fig. 1, Table 6).

### Discussion

The incidence of HCC in the US has risen to 4.1 per 100,000 from 1.6 per 100,000 over the last 20 to 30 years [4,23]. The increased incidence is attributed, in part, to the rise in end stage liver disease related to chronic hepatitis B and C infections as well as non-alcoholic fatty liver disease (NAFLD) [24-26]. Men are affected 3 times more frequently with HCC than women. The ethnic minority population in the US is growing and projected to increase considerably in the coming years. It is widely known that health care disparities...
exist in minorities compared to whites. Asians are affected 2 times more frequently with HCC than AA, and Hispanics are affected 2 times more often than whites [16,26]. In our study population, 79% were men, and Hispanics (49.4%) were the main ethnic group (Fig. 1). The predominant etiology for HCC in the study sample was CHC followed by alcohol consumption and CHB. We had a very low representation of Asians in our study population and as expected, the majority of them had CHB as the predominant etiology for HCC.

Geographic variation in HCC surveillance is well described with published literature reporting that less than 20% of patients with cirrhosis who developed HCC received regular surveillance [10,27]. The San Joaquin Valley is home to diverse ethnic populations and our study examined the HCC survival at a tertiary referral care center with a large catchment area from this region. The diagnosis of HCC is usually made during routine surveillance of cirrhotic patients, though in some cases, it is made after the patient develops a symptomatic lesion. The stage at diagnosis is important as potentially curative treatments can be offered for early stages. HCC surveillance has been proved to be effective in improving HCC related morbidity and mortality [28-30]. However, it appears that a significant proportion of patients are not benefitting from surveillance modalities as evidenced from the advanced stage of their disease on diagnosis. 44% of patients in our study sample were diagnosed with HCC and cirrhosis at the same time, hence, depriving them of early surveillance and curative treatment options. Delayed diagnosis of HCC was further evident in our study population, as 53% of the study sample had tumors larger than 5 cm, 51% had more than one tumor and 34% of the study population had metastases.

A multidisciplinary approach is used in the treatment of HCC and includes hepatologists, surgeons, interventional radiologists, pathologists and oncologists under the auspices

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**Table 3** Results of the regression analysis of multiple variables predicting survival in hepatocellular carcinoma study patients, 2002-2008

| Characteristics       | Univariate* | Multivariate* |
|-----------------------|-------------|---------------|
| Treatment             |             |               |
| Surgical/curative     | <0.0001     | 0.009         |
| Nonsurgical           |             |               |
| Palliative/no treatment|            |               |
| MELD score ≤15        | 0.001       | 0.025         |
| MELD score >15        |             |               |
| Ascites Yes           | 0.054       | 0.143         |
| Ascites No            |             |               |
| Prothrombin time (sec) | 0.002      | 0.05          |
| 20.5 ± 10.7           |             |               |
| Albumin (g/dL)        | 0.009       | 0.145         |
| 2.7 ± 0.7             |             |               |
| Bilirubin (mg/dL)     | 0.01        | 0.702         |
| 6.1 ± 7.4             |             |               |
| Tumor size (cm)       | 0.01        | 0.019         |
| 6.2±3.5               |             |               |
| Portal vein invasion  | 0.07        | 0.029         |
| Yes                   |             |               |
| No                    |             |               |
| Metastasis Yes        | 0.03        | 0.845         |
| Metastasis No         |             |               |
| Creatinine            | 0.09        | 0.377         |
| Alpha feto-protein    | 0.102       | 0.265         |

*Univariate and multivariate p values
MELD, model for end-stage liver disease

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**Table 4** Median survival among 160 hepatocellular carcinoma patients, 2002-2008, by treatment

| Treatment class       | n (%) | Median Survival* | p value^ |
|-----------------------|-------|------------------|----------|
| Surgical/curative     | 9/160 (5.6) | 69               | <0.0001  |
| Nonsurgical           | 55/160 (34.4) | 9                |          |
| Palliative/No treatment| 96/160 (60) | 3                |          |

*median survival reported in months, ^ Univariate analysis performed with log rank test

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**Table 5** Cross tabulation of treatment class and ethnicity* among 160 hepatocellular carcinoma study patients, 2002-2008

| Race/ethnicity     | Surgical/curative | Nonsurgical | Palliative/No treatment |
|--------------------|-------------------|-------------|-------------------------|
|                    | n (%)             | n (%)       | n (%)                   |
| White              | 1 (2)             | 20 (39)     | 30 (59)                 |
| African American   | 1 (11)            | 0 (0.0)     | 8 (89)                  |
| Asian              | 2 (11)            | 4 (21)      | 13 (68)                 |
| Hispanic           | 4 (5)             | 30 (38)     | 45 (57)                 |
| Other              | 1(50)             | 1 (50)      | 0 (0.0)                 |

*p value = 0.024, calculated by Fisher’s exact test

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*Annals of Gastroenterology 25*
Survival of patients with HCC

Primary treatment modalities for HCC include loco-regional ablative therapies, surgical resection, or OLT in selected patients. Non-curative treatment options include trans-arterial chemoembolization (TACE) and systemic chemotherapy [31]. In the study sample, there was a significant disparity in the survival across treatment groups (Table 4). The fact that a large percentage (94%) of patients did not receive curative treatments in our study population indicates that most tumors are diagnosed in advanced stages and hence, may not have qualified for potentially curative treatments. When we looked at the treatments received by ethnicity, the majority of AA (89%) and Asians (68%) received only palliative treatments compared to whites and Hispanics. However, AA and Asians were also most likely to receive curative treatments in our study population. These findings do not explain the impact of ethnicity on the treatments offered resulting in overall poor survival because of small sample sizes. However, previous studies pointed out the ethnic disparities that exist in the treatments offered, with AA and Hispanics less likely to receive curative treatments [16-19,32]. It is known that the majority of patients diagnosed with HCC are offered only palliative treatment. A population based study found that only 10% of patients receive curative treatments despite advanced imaging modalities and the efforts of national and international societies [9,33]. In our patient group, only 5.6% of total patients were offered curative treatments, while 60% were offered only palliative or no treatment possibly due to delayed diagnosis of HCC.

A lower median survival of 5 months was noted in our study sample when compared with that of CCR/SEER data (7 months) during the similar study period (Fig. 2, Table 6). In addition, the yearly survival of patients in our study group was poorer after 24 months (Fig. 3). This can be explained by the fact that AA, Asians and Hispanics in the CCR/SEER...
database had a better median survival when compared to the median survival in our patient population. Also, the lower survival of Hispanics, the predominant ethnic group, as well as the late diagnosis of HCC in our study sample, could have contributed to the overall poor survival. The condition of the patient with regards to the underlying liver disease with higher MELD score, tumor size and number, portal vein invasion and metastases could have influenced the prognosis and treatment options. Other factors like socioeconomic status, access to care and cultural barriers that were not evaluated in this study could have played a role in the overall outcomes.

It is imperative that patients with risk for HCC be screened for this disease early and routinely in order to give them the best chance of survival by offering them potentially curative options. Regular screening and surveillance for HCC in high-risk populations is recommended by national and international societies which include an ultrasound every 6 months. Although the European and Asian liver societies still use serum alpha-fetoprotein in conjunction with an ultrasound exam, the AASLD recommends using only an ultrasound exam for surveillance [34-36]. However, several gaps in HCC screening currently exist in the US. These include limited HCV testing of current and former injected drug users, pre-1990 transfusion recipients, and incomplete HBV testing of foreign-born Asians/Pacific Islanders [17,37,38]. A variety of cultural and economic barriers to HCC screening of chronic viral carriers also exist [39]. HCC occurs in Asian immigrant CHB patients younger than currently recommended screening guidelines [40]. A recent population-based study showed that CHC infection and Hispanic ethnicity independently increase the risk for HCC-related mortality [20]. A SEER-Medicare linked study of HCC patients diagnosed in the 1990s indicated that only one third of cases with favorable tumor features received potentially curative therapy [33]. In the same token, the San Joaquin Valley population is largely socioeconomically disadvantaged and lagging in several preventive and diagnostic and therapeutic aspects of HCC.

At present, therefore, there is a dire need to identify the barriers that prevent use of these simple screening modalities in the local communities in the Valley. Our study suggests that the currently available surveillance tools may not have been used effectively as evidenced from poor surveillance rates (12.5%) in our study population. Underutilization of these resources might contribute to the delay in diagnosis and hence, poorer overall survival. The local public health services should work in collaboration with the state and national level organizations in eliminating ethnic disparities and, in establishing the required standards, to bring effective screening and surveillance tools to patients in the Valley. This may avoid unnecessary delay in the diagnosis of HCC and thereby, improve overall survival through currently available treatments.

This is a retrospective study with inherent limitations and biases, particularly in inadequate sampling of the patient population of the valley. For example, under sampled Asians, Hmong are included who are a significant population in the Valley with a higher prevalence of hepatitis B [41,42]. Again this is due to many cultural barriers in health care access and socioeconomic conditions described earlier. Another limitation of this study is the absence of information on risk factors related to obesity and diabetes. We did not report staging of HCC in our study as it was inconsistently documented in the medical records, and where reported, was not consistent with CCR/SEER cancer registry’s staging classification. However, we examined study data for local and metastatic disease to get an approximate measure of the disease extent in our study population. It appears that a majority of HCC in our study would fall under BCLC (Barcelona Clinic Liver Cancer) stages, B-D [34]. Another limitation was that we do not know whether the Hispanic population studied was an immigrant population or US-born, as native Hispanic men were noted to have higher HCC rates than immigrant Hispanics [16].

In conclusion there is a marked variation in the outcome of patients with HCC in the San Joaquin Valley as compared to the general population. This study demonstrates the poorer survival after 2 years in the Central Valley when compared with the CCR/SEER data. The higher Hispanic representation, a group which experiences a low median survival in our study group, could have contributed to the overall poor survival. Also, the majority of the study group (60%) that received either palliative or no treatment highlights the delay in the diagnosis of HCC. This could be attributed to the unrecognized cases of cirrhosis (43% in our study sample) that would have benefitted from early HCC surveillance thereby improving overall survival.

Future studies are needed to estimate the current proportion of HCCs that are attributed to CHC and CHB across various ethnic groups, particularly addressing suspected cofactors for HCC such as alcoholism, non-alcoholic steatohepatitis, obesity, and diabetes mellitus. Similarly, aggressive screening programs to diagnose cirrhosis and HBV are required in the Valley to improve early detection rates and hence, improve patient outcome with HCC particularly in the minority groups.
Survival of patients with HCC

Summary Box

What is already known:
- Racial and socioeconomic disparities exist in the incidence and outcomes of hepatocellular carcinoma (HCC)
- Surveillance and early diagnosis is crucial in the management of HCC

What the new findings are:
- Outcome of patients with HCC in the San Joaquin Valley is poorer compared to the general California population
- Higher Hispanic representation coupled with late diagnosis could have contributed to overall poor HCC survival in the San Joaquin Valley
- There is a dire need to improve HCC surveillance in the San Joaquin Valley

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