

Survival differences among patients with hepatocellular carcinoma based on the stage of disease and therapy received: pre and post sorafenib era

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Background: The incidence of hepatocellular carcinoma (HCC) is increasing. Development of newer therapeutic modalities has changed the paradigm of HCC treatment in recent years. So, the aim of our study is to analyze the impact of these treatment modalities into the survival of HCC patients, based on the stage of HCC in real life practice.

Methods: We analyzed the data from the SEER database: Incidence – SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2015 Sub (1973–2013 varying). Relative survival rates (RSRs) and hazard ratios (HRs) were measured for patients diagnosed with HCC between 2001 and 2013. Rates were compared between pre sorafenib [2001–2007] and post sorafenib [2008–2013] eras.

Results: A total of 50,088 patients (21,435 in pre sorafenib era and 28,653 in the post-sorafenib era) were included with HCC from SEER database. The median relative survival for the entire population was 14 months with 5-year RSR of 21.20%; 11 months for those diagnosed in 2001–2007 with 5-year RSR 19.30% and 17 months for those diagnosed in 2008–2013 with 5-year RSR 22.40% ($P < 0.01$). This survival improvement was largely limited to HCC patients with single nodule (5-year RSR; 35.1% vs. 37.00% for pre and post sorafenib era respectively; P value < 0.01) and multiple nodules without vascular invasion (5-year RSR; 19.90% vs. 22.60% for pre and post sorafenib era respectively; P value < 0.01). RSR remained extremely poor with no significant improvement for advanced stage HCC who had vascular invasion ($P = 0.37$) or distant metastasis ($P = 0.10$), respectively for pre and post sorafenib era in each category. Survival improved since 2008, for HCC patients who received either no surgical intervention ($P < 0.01$) or received tumor-directed therapy ($P < 0.01$), however, it remained significantly poor compared to the patients who received lobectomy or hepatectomy and transplant. Approximately 70% of patients from our study population did not receive any HCC directed surgical intervention and among this, more than 40% of patients were with single nodule in the liver.

Conclusions: Survival in patients with HCC has improved since 2008, which is limited to early stage HCC. Survival of advanced stage HCC patients is extremely poor and has not shown any significant improvement since the approval of sorafenib, emphasizing the need for better therapeutic options. Not receiving any surgical intervention is associated with significantly poor prognosis. Large numbers of early stage HCC patients were not able to receive surgical interventions. This can impose a significant financial burden, as these patients would progress on to the advanced stage, where treatment options are very limited and not as cost-effective. This emphasizes the need for further research to identify various barriers and the possible need for healthcare policy changes.

Keywords: Carcinoma; hepatocellular; sorafenib; Surveillance, Epidemiology and End Results (SEER)

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Introduction

The cancer death rate has dropped by 23% since 1991. Despite this progress, death rates are increasing for liver cancers (1). Hepatocellular carcinoma (HCC) remains the leading cause of cancer death worldwide (1). For last three decades, the incidence of HCC has continued to increase (1.9 per 100,000 *vs.* 3.1 per 100,000 *vs.* 4.9 per 100,000 during 1983–1992, 1993–2002 and 2003–2012 respectively) (2). It develops mostly in the cirrhotic liver and the common risk factors known to be responsible includes, hepatitis B and C infection, alcoholic liver disease, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD) (3). While survival from HCC seemed to have been improving [relative survival rate (RSR) at 5 years; 4.7% *vs.* 10.6% *vs.* 18.2 % during 1983–1992, 1993–2002 and 2003–2012 respectively] (4), mortality from HCC has continued to rise (5). Multiple factors such as demographic features, comorbidities, stage and extent of the disease, therapy options can play a vital role in the survival from HCC. The emergence of multiple newer treatment modalities has changed the paradigm of HCC treatment (6). Local tumor-directed therapies have been perfected, such as radio-frequency ablation, novel agents for transarterial chemoembolization (TACE) along with improvements in hepatic resection and liver transplantation. There is also an emergence of new molecular-targeted agents such as Sorafenib. Sorafenib inhibits molecular components of the RAF-MEK-ERK signaling pathway, which suppresses tumor growth and vascular endothelial growth factor receptors, affecting tumor angiogenesis (7). Sorafenib was approved by FDA in 2007 for the treatment of advanced stage HCC with vascular invasion and distant metastasis, based on the results of the pivotal SHARP clinical trial (7). Sorafenib has become the standard first-line therapy for advanced stage HCC (6,8). The American Association for the Study of Liver Diseases (AASLD), National Comprehensive Cancer Network (NCCN) and European Association for the Study of the Liver (EASL) endorsed Sorafenib as the first-line therapy for Barcelona Clinic Liver Cancer (BCLC) stage C patients (those with unresectable

portal vein invasion, extrahepatic spread), with reasonable performance status (ECOG 0–2), and good liver function (Child-Pugh class A or B) (9,10).

The aim of our study is to analyze the impact of these treatment modalities into the survival of HCC patients, based on the extent of HCC in real life practice. We accessed and analyzed data on HCC patients from 2001–2013, from the Surveillance, Epidemiology, and End results (SEER) database (11). To evaluate the difference in survival since the approval of sorafenib, we have analyzed the data dividing into two groups; patient diagnosed between 2001–2007 and 2008–2013.

Methods

The SEER database is derived from cancer registries representing approximately 28% of the U.S. population and is maintained by the National Cancer Institute (www.seer.cancer.gov) (11). The SEER population-based cancer registries contain information on cancer incidence and survival in selected geographic areas. Selection of the included geographic areas was based on the quality of their cancer reporting systems and population diversity.

A retrospective cohort study was performed using data from the SEER database, based on the November 2015 submission, which was released in April 2016. Data was examined from 2001 through 2013 from eighteen SEER registries. The SEER data set includes information on patient demographics, tumor characteristics, cancer-associated treatments, use of cancer-directed surgery, and survival for individuals with cancer. Surgical intervention is coded in the SEER database as a separate variable, whenever it is performed. The actual surgical procedure directed at the primary site is coded as a separate variable. No record of chemotherapy is available in this database. BCLC classification is most widely accepted currently, they have categorized HCC patients into five categories based on the extent of disease, Child-Pugh score, and performance status. SEER does not provide details to calculate Child-Pugh score and information on performance status, hence, accurate BCLC staging information could not be obtained.

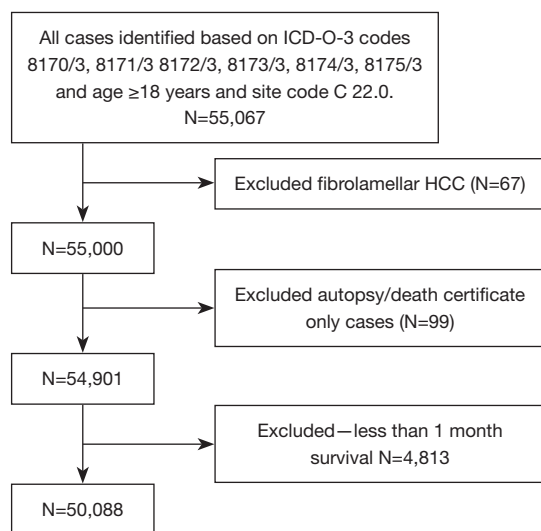


Figure 1 Schema showing patient selection process of study population.

Study population

SEER*Stat version 8.3.2 was used for all data collection and survival analysis. Patient inclusion criteria based on the site recode International Classification of Diseases for Oncology, third Edition (ICD-O-3) [2008] for HCC (C22.0), and year of diagnosis (2001 through 2013). HCC are histologically defined by the following ICD-O-3 histology codes for malignant cases: HCC (8170/3, 8172/3, 8173/3, 8174/3, 8175/3). Eighteen years or older patients were included. Only actively followed or treated cases were included. Cases identified on autopsy or reported only on a death certificate were excluded. Patients with the fibrolamellar variant of HCC were excluded as they differ in clinical course and prognosis, compared to conventional HCC (12). Diagnosis made based on only clinical suspicion without radiological, laboratory or microscopic confirmation were excluded. Patients with death reported within the first month of diagnosis were excluded, as SEER data reports their survival as zero months. Step by step patient selection process is shown in *Figure 1*.

Patient race was categorized as white, black, Asian (Asian/Pacific Islander), and native American (American Indian/Alaska native) based on SEER coding scheme (11). Based on SEER Summary staging manual [2000], the extent of the HCC at diagnosis was defined as localized, regional disease, distant disease, or missing. AJCC (American Joint Committee on Cancer) stage of HCC was obtained based on Collaborative Stage Data Set Type (CS extension codes)

and divided into single nodule without vascular invasion, multiple nodules in different lobes without vascular invasion, any number of nodules with vascular invasion. Presence or absence of metastasis was categorized using CS metastasis codes. Therapy received was categorized using SEER site-specific therapy of primary site codes and divided into four groups: no surgery received, tumor-directed therapy, hepatic resection/lobectomy, and hepatectomy with a transplant. Tumor-directed therapy included heat radiofrequency ablation, photodynamic therapy, electrocautery, fulguration, cryosurgery, laser, or alcohol and acetic acid ablation.

Statistical analysis

Statistical methods used were non-parametric Kaplan-Meier survival estimates and Cox proportional hazards models. Equality of survival curves was tested using Cox-regression based tests and log-rank tests. Akaike and Bayesian information criterion in addition to graphical exploration of residuals using the Cox-Snell and Martingale residual fit were used as model diagnostics for selecting best models that fitted the data. Proportionality of hazards assumptions was also assessed to avoid gross violations of these model assumptions. Descriptive statistics of the patient's demographics were analyzed using proportions, and Chi-square test of independence for categorical variables whereas Medians, Means, and standard errors were estimated if variables were continuous. Non-parametric Kaplan-Meier survival estimates together with semi-parametric Cox proportional hazards models were fitted to a continuous-time varying data, where the survival time was recorded in months from the SEER database. Stata statistical software, release 14 was used for analysis (13). Models examined the different rates of survival (or hazards) by mainly focusing on HCC staging, summary staging, therapy received while controlling for age at diagnosis and sex. In addition to the overall survival from the complete data, the analysis was also performed by stratifying the data into two groups; patients diagnosed between 2001–2007 and 2008–2013. Missing observations were considered to be missing at random and therefore dropped during the analysis.

Results

We identified a total of 50,088 HCC cases that met the inclusion criteria from SEER database. Demographic features are mentioned in the *Table 1*.

Table 1 Demographic and tumor related features of patients with HCC diagnosed between 2001 and 2013 at 18 SEER sites

Variable characteristics	Overall sample size (N=50,088)	
	2001–2007	2008–2013
Number of patients by year of diagnosis	21,435 (42.79)	28,653 (57.21)
Median age at diagnosis (years)	62	62
Mean age at diagnosis: mean age (st error of mean)	62.8 (0.083)	63.5 (0.064)
Gender: n (%)		
Female	5,228 (24.39)	6,617 (23.09)
Male	16,207 (75.61)	22,036 (76.91)
Race		
American Indian/Alaska Native	229 (1.07)	367 (1.28)
Asian or Pacific Islander	4,401 (20.53)	4,571 (15.95)
Black	2,557 (11.93)	3,917 (13.67)
White	14,248 (66.47)	19,798 (69.10)
Age group in years: n (%)		
0–44	1,032 (4.81)	744 (2.60)
35–54	4,860 (22.67)	4,676 (16.32)
55–64	6,055 (28.25)	11,228 (39.19)
65+	9,488 (44.26)	12,005 (41.90)
HCC stage: n (%)		
Single nodule	3,981 (18.57)	8,568 (29.90)
Multiple nodules w/o vascular invasion	2,987 (13.94)	6,980 (24.36)
Vascular invasion	2,690 (12.55)	5,896 (20.58)
Missing	11,777 (54.94)	7,209 (25.16)
Metastasis: n (%)		
Absent	19,727 (92.03)	25,170 (87.84)
Present	1,690 (7.88)	3,436 (11.99)
Missing	18 (0.08)	47 (0.16)
Summary stage: n (%)		
Localized	10,516 (49.06)	15,405 (53.76)
Regional	5,917 (27.60)	7,787 (27.17)
Distant	3,064 (14.29)	3,689 (12.87)
Missing	1,938 (9.04)	1,772 (6.18)
Type of therapy: n (%)		
No surgery	14,635 (68.29)	20,902 (72.94)
Tumor directed therapy	3,715 (17.33)	4,689 (16.39)
Lobectomy	1,030 (4.80)	1,126 (3.92)
Hepatectomy	2,043 (9.53)	1,906 (6.65)
Missing	12 (0.05)	30 (0.10)
Mortality		
Alive	2,798 (13.05)	10,847 (37.86)
Dead	18,637 (86.95)	17,806 (62.14)

HCC, hepatocellular carcinoma; w/o, without.

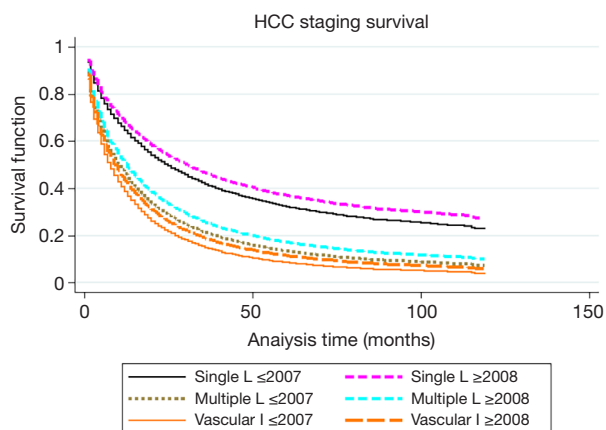


Figure 2 Kaplan Meier survival curves of HCC patients based on the AJCC staging: pre and post sorafenib era. HCC, hepatocellular carcinoma; METS, metastasis.

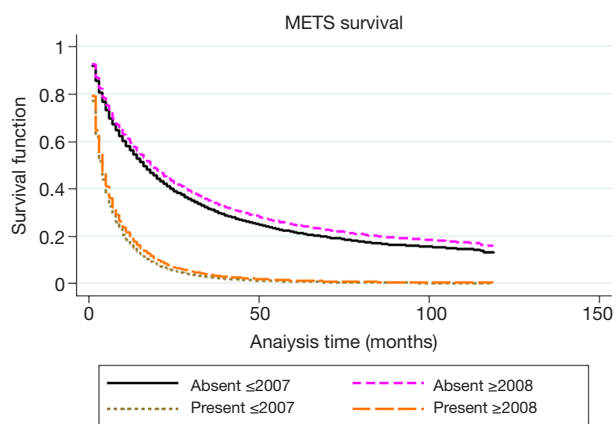


Figure 3 Kaplan Meier survival curves of HCC patients based on the presence or absence of distant metastasis: pre and post sorafenib era. HCC, hepatocellular carcinoma.

Out of the 50,088 patients, 36,443 (73%) died. The median relative survival for the entire population was 14 months with 5-year RSR of 21.20%; 11 months for those diagnosed in 2001–2007 with 5-year RSR 19.30% and 17 months for those diagnosed in 2008–2013 with 5-year RSR 22.40%, which was statistically significant, $P < 0.01$. Survival rates were significantly lower for patients with age 65 years or older when compared to the groups with age less than 65 years (5-year RSR was 13% for 65+ years old *vs.* 24.8% for age group 18–44 years, 21.1% for 45–54 years, 20.7% for 55–64 years; $P < 0.001$). Although survival remained poor, the 65+ years group had the highest increase in RSR since 2008, when compared

to other age groups (5-year RSR was 11.10% *vs.* 14.20% for patients diagnosed in 2001–2007 and 2008–2013 respectively; P value < 0.001).

Analysis based on AJCC HCC stage

To further categorize and understand the improvement in survival for patients diagnosed after 2007, we performed Kaplan-Meier analysis based on the stage of the disease, as shown in *Figures 2* and *3*. As shown in *Table 2*, the survival significantly improved for the group of patients with single nodule (30 *vs.* 36 months) or multiple nodules without vascular invasion (14 *vs.* 19 months), respectively for 2001–2007 and 2008–2013 in each category ($P < 0.05$). Survival for advanced cases remained significantly poor without any real improvement since 2008, 8 months for patients with vascular invasion and only 4 months for patients with distant metastasis. Moreover, as shown in *Table 3*, when compared with patients diagnosed before 2008, hazards of having vascular invasion or presence of distant metastasis was significantly higher for patients diagnosed after 2008, $P < 0.05$.

Analysis based on summary stage

Median relative survival for patients diagnosed in 2001–2007 was 23, 8, and 4 months, respectively for localized, regional and distant stages. While patients diagnosed in 2008–2013 had better survival; 31, 11, and 5 months respectively for localized, regional and distant stages. As shown in *Table 3*, regional and distant stages showed poorer prognosis after 2008 with higher hazard ratios (HRs).

Analysis based on therapy received

Approximately 70% of patients from our study population did not receive any HCC directed surgical intervention and among this more than 40% of patients were with early stage HCC with single nodule only. Median relative survival for those who did not receive any surgery was significantly lower when compared with patients who received any sort of surgical procedure (9 months for patients with no surgery *vs.* 38 months for patient received tumor-directed therapy *vs.* 49 months who received lobectomy; $P < 0.001$). Even though survival for those who did not receive any surgery remained extremely low, it improved significantly after 2007 (as shown in *Table 2*). This survival improvement in the group of no surgery was limited only to patients with the

Table 2 Relative survival rates based on HCC stage and type of therapy received at 18 SEER sites stratified by year of diagnosis, with number of patients in parentheses

Variable	Number of months	2001–2007, %	2008–2013, %	P value
HCC stage—AJCC				
Single nodule	12	68.60±0.50 (3,981)	74.80±0.50 (8,568)	<0.01
	60	35.10±0.50	37.00±0.90	<0.01
Multiple nodules without vascular invasion	12	52.60±0.90 (2,987)	60.30±0.60 (6,980)	<0.01
	60	19.90±0.70	22.60±0.80	<0.01
Vascular invasion	12	39.50±0.90 (2,690)	41.10±0.60 (5,896)	0.20
	60	15.50±0.70	15.30±0.60	0.37
Distant metastasis	12	17.40±0.70 (1,690)	18.20±0.50 (3,436)	0.12
	60	2.40±0.30	2.90±0.30	0.10
Type of therapy				
No surgery	12	33.20±0.30 (14,635)	45.40±0.30 (20,902)	<0.01
	60	7.60±0.30	11.70±0.30	<0.01
Tumor directed therapy	12	75.40±0.80 (3,715)	85.80±0.60 (4,689)	<0.01
	60	31.60±0.90	39.90±1.40	<0.01
Lobectomy	12	76.90±1.50 (1,030)	83.40±1.40 (1,126)	<0.01
	60	42.50±1.80	47.30±2.7	<0.01
Hepatectomy, transplant	12	87.30±0.90 (2,043)	89.70±0.9 (1,906)	<0.01
	60	67.00±1.10	71.50±1.60	<0.01

Data are mean ± standard error of the mean. HCC, hepatocellular carcinoma; AJCC, American Joint Committee on Cancer.

Table 3 Hazard ratio (HR) for HCC patients based on AJCC staging, summary stage, type of therapy received at 18 SEER sites

Variable	HR (95% CI)		P value
	2001–2007	2008–2013	
AJCC staging			
Single nodule			
Multiple nodules without vascular invasion	1.73 (1.65–1.81)	1.81 (1.74–1.88)	
Vascular invasion	1.92 (1.82–2.02)	2.37 (2.27–2.48)	<0.05
SEER summary stage			
Localized			
Regional	1.86 (1.79–1.92)	2.11 (2.03–2.18)	<0.05
Distant	3.28 (3.14–3.43)	4.17 (3.99–4.35)	<0.05
Metastasis			
Absent			
Present	2.86 (2.72–3.02)	3.26 (3.13–3.39)	< 0.05
Type of therapy			
No surgery			
Tumor directed therapy	0.42 (0.40–0.44)	0.32 (0.31–0.34)	< 0.05
Lobectomy	0.35 (0.32–0.38)	0.31 (0.28–0.34)	
Hepatectomy and transplant	0.18 (0.17–0.19)	0.16 (0.15–0.18)	

HR, Hazard ratio; CI, confidence interval, AJCC, American Joint Committee on Cancer.

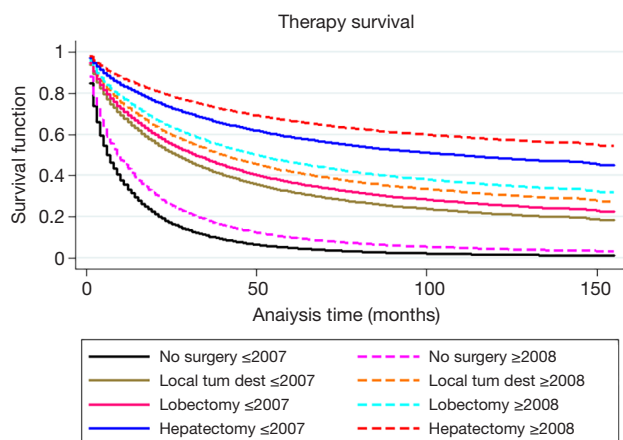


Figure 4 Kaplan Meier survival curves of HCC patients based on the therapy they received: pre and post sorafenib era. HCC, hepatocellular carcinoma.

single nodule, the median survival of 9 months for patients diagnosed in 2001–2007 with 5 years RSR 14.3% *vs.* 17 months for patients diagnosed in 2008–2013 with 5 years RSR 20.10%, $P < 0.05$. As shown in *Figure 4*, hepatectomy with transplant showed the best survival compared to any other mode of therapy (5 years RSR was 69%; $P < 0.01$ when compared to any other groups).

Discussion

The incidence of HCC has continued to rise over last few decades (2), and this could be attributed to the rising prevalence of obesity and type 2 diabetes mellitus (T2DM), the two major risk factors for Non-alcoholic fatty liver disease (NAFLD) (3). NAFLD is rapidly becoming the most common liver disease worldwide (14). The prevalence of NAFLD in the general population of western countries is 20–30%, with about 2–3% of the general population is estimated to have non-alcoholic steatohepatitis (NASH) which can progress to liver cirrhosis and HCC (14). Furthermore, increasing incidence of childhood obesity is quite alarming. Childhood obesity has more than doubled in children and quadrupled in adolescents in past 30 years (15), raises the possibility of even higher incidence of NAFLD and thus HCC in future.

HCC remains one of the leading causes of cancer morbidity and mortality worldwide. The advances in therapeutic modalities have changed the paradigm of HCC treatment in recent years, particularly tumor-directed therapy and molecular targeted therapy. However, to best

of our knowledge, there is limited information on the impact of these on the survival trend of HCC patients in the population. So we present the analysis of HCC patients from SEER database based on the extent of disease and therapy received.

Early stage HCC

Patients with a single nodule or up to 3 nodules ≤ 3 cm in size without vascular invasion are considered as early stage HCC (BCLC staging) (8,9). Treatment also depends on the Child-Pugh score and Eastern Cooperative Oncology Group (ECOG) performance status of the patient. As per NCCN and BCLC guidelines (8,9), various treatment options for early stage HCC, includes tumor resection, transplant or ablation, all of which are potentially curative. Our analysis shows, the survival of patients with single nodule significantly improved since 2008, which was limited to patients who did not have surgical intervention and the patients who had tumor-directed therapy. Since the guidelines recommend essentially surgical options for early stage HCC, survival improvement in patients with single nodule with no surgical intervention can essentially be explained by lead time bias only. As seen in *Table 1*, a higher number of patients were diagnosed with single nodule or localized disease after 2007. This could be secondary to aggressive screening and clinical surveillance protocols of individuals with known risk factors for HCC, with better access to health care (16,17). Local tumor-directed therapies have emerged showing promising results recently (18). Our analysis confirms the survival improvement in early stage HCC patients, who received tumor-directed loco regional therapies. Unfortunately, our analysis revealed, approximately 70% of patients with HCC did not receive any surgical intervention and more than 40% of patients were with single nodule, at the stage which is potentially curable. Unfortunately, SEER data does not provide information on underlying reasons for not receiving the surgical intervention, the analysis suggests, the potentially curative therapies for early stage HCC are underutilized. This could partly be secondary to decreased access to these sophisticated procedures, which are often offered at the tertiary centers only. A similar trend was found in a recently published meta-analysis; early stage HCC patients, who are elderly, non-Caucasian and lower socioeconomic status received significantly lower rates of tumor-directed therapies (19). Further research in this area to identify various underlying reasons would be very vital to

overcoming this challenge.

Intermediate stage HCC

Patient with large multinodular HCC with Child-Pugh A or B falls under intermediate stage HCC (8,9). As per guidelines, treatment option mainly includes tumor-directed therapies, mainly trans-arterial chemoembolization (TACE). Various studies have shown a survival benefit of TACE (20,21). Unfortunately, SEER data does not provide specific information on how many patients exactly received TACE.

Advanced stage HCC

Patients with any numbers of nodule with vascular invasion and/or distant metastasis are considered advanced stage HCC (8,9). Treatment would further depend upon the Child-Pugh score and ECOG performance status of the patient. Supportive care used to be the only treatment option for advanced-stage HCC, but sorafenib has become the standard of treatment ever since the FDA approval in 2007 (8,9). SHARP trial showed 3 months survival benefit of sorafenib in advanced stage HCC (7). Since then, sorafenib has been studied as a single agent or in combination with other modalities with inconsistent results (21-26). Our analysis of SEER database shows the survival of advanced stage HCC remains extremely poor with no significant difference after the approval of sorafenib. In an observational study for SEER data, Sanoff *et al.* (27) reported that in Medicare beneficiaries, there was no statistically significant difference in survival of advanced staged HCC patients, whether they received sorafenib or not. This discrepancy between the clinical trial results and real world results could be secondary to several factors including patient health status, socio-economic factors, comorbidities, disease burden, tolerability of the medication, treatment adherence and accessibility to medical care. Parikh *et al.* (28) also reported similar findings showing marginal benefit with no cost effectiveness of using sorafenib in advanced stage HCC Medicare beneficiary patients. Although, SEER does not provide details on chemotherapy rendered to patients, the higher HR of advanced stage HCC since 2008 suggests, efficacious treatment options for advanced stage HCC is still lacking.

Our study has few limitations. First and foremost is retrospective nature of the study. Secondly, while quite detailed, SEER database lacks in the information about the etiology of HCC (cause of cirrhosis), and other

comorbidities. Furthermore, it lacks the information about the chemotherapy rendered to patients. Thirdly, this data also lacks in the information about the Child-Pugh score and functional status of the patient, which directly affects candidacy of patients to different therapies and thus the survival.

In conclusion, the incidence of HCC is increasing and HCC remains one of the commonest cause of cancer deaths worldwide, which is quite concerning. In spite of all the advances in the treatment of the etiology of HCC such as hepatitis B and hepatitis C (16,17) along with the advances in HCC treatment itself, survival from HCC remains extremely poor. This can partially be explained by the poor utility of some of the efficacious treatment options in early stage HCC, and also due to lack of any effective treatment options for advanced stage HCC cases. Not utilizing effective treatment options in early stage HCC, while it is still curable, can impose a significant financial burden. As these patients would progress on to the advanced stage where treatment options are very limited and not as cost-effective. Our study emphasizes the urgent need for efficacious and cost-effective treatment options for advanced stage HCC and also highlights the need for further research to identify various barriers and the possible need for healthcare policy changes to better utilize the existing treatment modalities particularly for early stages of HCC.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: No formal approval of IRB is required as data were collected from a source that was publicly available and did not contain unique patient identifiers. We obtained permission to access research data files of SEER database with the reference number 13253-Nov2014. Given that these data are de-identified and ethics approval is waived, the study did not require informed consent.

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