

CEASE HCC:
Comparative Effectiveness Analysis of Sorafenib and Embolization
for Hepatocellular Carcinoma

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Abstract

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Background: Transarterial embolization and sorafenib are the two main first-line therapeutic options for patients with hepatocellular carcinoma (HCC) who are not candidates for curative treatments. As no prospective trials or comparative studies exist on the relative effectiveness of these two treatment strategies, this study aimed to compare the clinical effectiveness of embolization and sorafenib as practiced in real-world settings.

Materials and Methods: Using the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database, patients aged ≥ 65 diagnosed with primary liver cancer between 2007-2011 who received embolization or sorafenib were identified. Patients were excluded if they had insufficient claims records, a diagnosis of intrahepatic cholangiocarcinoma, other primary cancers, liver transplantation, or combination therapy. The primary outcome of interest was overall survival. Inverse-propensity for treatment weighted (IPW) models were used to control for selection bias.

Results: 1,017 patients met inclusion and exclusion criteria. IPW models showed good balance between treatment groups. Compared to those who underwent embolization, patients who received sorafenib had significantly higher hazard of earlier death from time of treatment (HR=1.87, 95% CI 1.46, 2.37; p<0.0001) and from time of cancer diagnosis (HR=1.87, 95% CI 1.46, 2.39; p<0.0001). The survival advantage after embolization was seen in both intermediate and advanced stage disease.

Conclusion: This comparative effectiveness study of Medicare patients with HCC demonstrated significantly longer overall survival following treatment with embolization when compared with sorafenib. As these findings conflict with expert opinion-based guidelines for treatment in advanced stage disease, prospective randomized comparative trials in this subpopulation would be justified.

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This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The author acknowledges the efforts of the Applied Research Program, NCI; the Office of Research, Development, and Information, MCS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and Ends Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death worldwide.¹ In the United States, HCC mortality rates increased at the highest rate of all cancer types during the same period when overall cancer mortality rates decreased.² Less than 30% of HCC patients are candidates for potentially curative treatments such as surgical resection, liver transplantation, and ablation. For the remainder of patients, transarterial embolization therapies, with the most common form being transarterial chemoembolization (TACE), was the mainstay of therapy until 2008. In 2008, results were published from the first randomized clinical trial to show a survival advantage for sorafenib, a systemic agent for treatment of HCC, compared to placebo.³ Sorafenib remains the only FDA approved first-line systemic agent for HCC and is considered the standard of care for treating advanced stage HCC.⁴

No head-to-head comparative study of transarterial embolization versus sorafenib has been reported and limited information exists on the comparative effectiveness of these therapies in real-world settings. In the absence of randomized prospective trials, large well-controlled retrospective comparative effectiveness studies may provide evidence to guide clinical management decisions. This study therefore aimed to compare the clinical effectiveness of these two treatment strategies in a Medicare patient population as practiced in real-world settings. Prior efficacy studies have demonstrated an improvement in median survival of 8-16 months with TACE and 2-3 months with sorafenib^{3,5} when compared to best supportive care or placebo. Based upon these results, we hypothesized that, in a population that is otherwise similar, transarterial embolization would confer a survival benefit when compared to sorafenib.

MATERIALS AND METHODS

Data source

Data were extracted from the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database. The National Cancer Institute's SEER program pools clinical, pathologic, and cause of death information from 18 tumor registries comprising a non-random sample of about 26% of the U.S. population. This database is considered an accurate representation of the overall U.S. cancer population and is one of the premier cancer registries worldwide.⁶ The SEER-Medicare database links SEER registry variables to claims data from the Centers for Medicare and Medicaid Services, the largest healthcare payer in the country. SEER-Medicare data for patients diagnosed with liver cancer from January 1, 2007 to December 31, 2011 were used. Medicare claims from January 1, 2007 to December 31, 2012 from the hospital, hospital outpatient, physician/supplier, prescription medication (Part D), home health, hospice, and durable medical equipment files were used. The data were maintained and results reported in accordance with a data use agreement with the National Cancer Institute. Institutional review board approval was obtained from the University of Washington for this study.

Inclusion and exclusion criteria

All patients age 65 or older who were diagnosed with primary liver cancer between 2007-2011 and received either transarterial embolization or sorafenib were included. Patients with insufficient claims records (those without continuous Part A, Part B, and Part D Medicare coverage or those enrolled in a Health Maintenance Organization) in the 6 months prior to and following diagnosis were excluded. In order to achieve a homogenous HCC population, patients were excluded if they had a diagnosis of intrahepatic cholangiocarcinoma or had other primary cancers. Liver transplantation confers a significant survival benefit in these patients and

transarterial embolization is commonly used as a bridge to transplantation. To prevent confounding from this group with anticipated superior outcomes, we excluded all patients who received liver transplantation. Similarly, to prevent confounding by patients who may have received treatment as part of planned combination therapy, we excluded patients who received resection or thermal ablation within one month of embolization or sorafenib. Those who received both transarterial embolization and sorafenib on the same day were also considered as having received combination therapy and were excluded.

Group and covariate definition

Treatment group assignment was determined by “intent-to-treat” method, with patients assigned by the first treatment type received, regardless of subsequent crossover to the other treatment. Sensitivity analysis was also performed in which patients who received both treatments during the study period were excluded. Patients that had billing data that showed transarterial embolization therapy to the liver for HCC were categorized in the “embolization” group. Therefore this group may include TACE, transarterial (“bland”) embolization or radioembolization. Subgroup analysis was performed to assess differences in outcomes between TACE/bland embolization and radioembolization. Patients within the embolization group were identified as having received radioembolization if they had Healthcare Common Procedure Coding System codes for “yttrium-90 brachytherapy” or “complex interstitial radiation source application” in combination with an embolization code. All other patients in the embolization group were assumed to have received either TACE or bland embolization.

Demographic variables were obtained from the SEER registry data. Charlson comorbidity index using the Deyo adaptation⁷ was calculated using Medicare hospital and physician/supplier claims from the 6 month period prior to treatment. Etiology of cirrhosis

(hepatitis B, hepatitis C, alcohol) and major risk factors for poor outcomes (hepatic encephalopathy, ascites, portal vein thrombosis) were identified using claims from the 6-month period prior to treatment. Performance status is considered a significant predictor of survival for many cancers, including HCC. We used a validated claims-based algorithm to determine disability status: this measure was developed as a claims-based proxy for Eastern Cooperative Oncology Group performance status.^{8,9} American Joint Committee of Cancer (AJCC) stage was coded directly within the SEER registry. Barcelona Clinic Liver Cancer (BCLC) stage was estimated using a combination of available covariates. Specifically, a patient was classified with advanced BCLC stage disease if there was nodal or metastatic disease, portal vein thrombosis, or poor disability status. All other patients were classified as having intermediate BCLC stage disease.

Outcomes

The primary outcomes of interest were 1) overall survival (OS) from time of receipt of first embolization or sorafenib to death and 2) OS from time of diagnosis to death. Secondly, we examined the cumulative incidences of cancer-specific mortality from the time of first treatment and from the time of diagnosis. The cause of death, based on state death certificates, was coded in the SEER database. Patients were censored if they were alive at end of the study period on December 31, 2012. Because only the month and year of diagnosis were provided by SEER, diagnosis dates were recoded as the first day of the month.

Statistical analysis

Given that this was a retrospective study using observational data, controlling for potential selection bias was of critical importance. We used inverse-propensity for treatment weighted (IPW) models to control for selection bias, as this considered one of the most robust

methods to control for confounding in observational data¹⁰ Propensity score matching, another highly effective method for controlling confounding, was used in sensitivity analyses.

Propensity scores were calculated with multivariate logistic regression with inclusion of all available covariates considered to have possibly influenced outcomes,¹¹ including: age, year of diagnosis, sex, race, median income of census tract, AJCC stage, disability status, Charlson comorbidity index, prior hepatic resection, history of encephalopathy, history of ascites, history of portal vein thrombosis, etiology of liver disease, and presence of nodal or distant metastatic disease. To ensure sufficient similarity between the comparison groups, patients with propensity scores that did not significantly overlap between the two groups (i.e. no common support) were excluded. After inverse-propensity score weighting, standardized differences between groups were calculated for all covariates and differences; standardized differences of <10% were considered to represent good balance between groups.¹²

Kaplan-Meier curves were used to estimate median survival times. To preclude potential for lead-time bias and avoid bias from patients who may have died prior to receipt of treatment, analyses of survival from time of diagnosis accounted for delayed entry into the risk set. Cox regression was used to compare hazard ratios (HR). When using IPW Cox regression, model-based methods of calculating variance have been shown to result in bias¹³ and therefore 95% confidence intervals (CI) for HR were calculated using bootstrapping. For cancer-specific death, competing risk analysis was performed, with cumulative incidence functions estimated with nonparametric methods and cancer-specific subhazard ratios calculated according to the model described by Fine and Gray.¹⁴

Two-tailed tests for statistical significance were used, with an α level of 0.05. All statistical analyses were performed with Stata 13 software (StataCorp, College Station, TX).

RESULTS

Study population

Figure 1 summarizes the total number of patients that fit inclusion and exclusion criteria to arrive at the final study population. 1,017 patients meeting inclusion and exclusion criteria had a mean follow-up period of 18.0 (SD=13.7) months. 648 (63.7%) patients received embolization and 369 (36.3%) received sorafenib as their initial treatment. Demographic and baseline data are summarized in Table 1. As expected, there were differences between the two groups. A greater proportion of patients who initially received embolization had a previous diagnosis of cirrhosis. The patients who received sorafenib first came from census tracts with lower median income and a greater proportion had history of prior liver resection. Consistent with some degree of adherence to treatment algorithms, patients who received sorafenib, had higher AJCC stage and were more likely to have been diagnosed with nodal or metastatic disease prior to treatment. During application of inverse propensity of treatment weighting, 13 patients were excluded due to a missing value for a covariate used in the propensity score model or for being outside the range of the common support in propensity scores between the groups. After propensity score weighting, these differences were successfully balanced, with <10% standardized differences across all covariates.

Overall Survival

As shown in Figure 2 and summarized in Table 2, patients who received embolization had significantly improved OS ($p<0.0001$). Median survival following embolization and sorafenib were 19.5 and 10.8 months, respectively. Estimated probability of OS at 3, 6, 12, and 24 months were 96.9%, 90.2%, 68.5%, and 40.7% following embolization and 94.1%, 80.0%, 46.7%, and 18.3% following sorafenib. Compared to those who underwent embolization,

patients who received sorafenib had significantly higher hazard of earlier death (HR=1.87, 95% CI 1.46, 2.37).

In order to account for potential differences in outcomes due to differences in times to treatment, an analysis of OS from time of diagnosis was performed and results were similar (Table 2). Patients who received embolization had significantly improved OS ($p < 0.0001$). Median survival from time of HCC diagnosis was 21.0 months for the embolization group and 14.1 months for the sorafenib group. Compared to those who underwent embolization, patients who received sorafenib had significantly higher hazard of earlier death (HR=1.87, 95% CI 1.46, 2.39).

Subgroup Analyses

To assess if HCC stage influenced differences in treatment effectiveness, we stratified patients by BCLC and AJCC stage. When patients were stratified by intermediate versus advanced BCLC stage, both subgroups showed a survival advantage after embolization (Table 2; Figures 3a, 3b). In intermediate BCLC stage patients, patients who received sorafenib had higher hazard of dying (HR=1.86 95% CI 1.40, 2.51) and median survivals following embolization or sorafenib of 21.0 and 10.0 months, respectively. In advanced BCLC stage patients, patients who received sorafenib had higher hazard rate for death (HR=1.85 95% CI 1.15, 2.88) and median survivals following embolization or sorafenib of 16.4 and 11.2 months, respectively. Similarly, when patients were stratified by AJCC stage, patients who received sorafenib had higher hazard of dying in all subgroups (all $p < 0.05$) (Table 2; Figures 4a-d), although for stage 3-4 disease, the 95% CI for HRs were not statistically significant when we used a more conservative bootstrap method for variance calculations.

Finally, we explored whether the specific type of embolization technique affected outcomes. No difference in OS was seen between these groups (HR=1.07, 95% CI 0.69, 1.70; p=0.693) (data not shown). Differences between TACE and bland embolization groups were not tested, as billing codes were not felt to be able to reliably discriminate between the two and current evidence suggests no difference in survival outcomes between the two techniques.¹⁵

Cancer-specific mortality

As seen in Figure 5, patients who received sorafenib had significantly increased incidence of cancer-specific mortality from time of treatment (sub-HR=1.69, 95% CI 1.39, 2.07; p<0.001). Estimated probability of cancer-specific death at 3, 6, 12, and 24 months were 4.2%, 17.4%, 46.8%, and 71.0% following sorafenib treatment and 2.2%, 7.6%, 25.7%, and 47.9% following embolization.

Similarly, a model of cancer-specific mortality from time of diagnosis showed increased odds of mortality following sorafenib (sub-HR=1.72, 95% CI 1.41, 2.11; p<0.001). Estimated probability of cancer-specific death at 6, 12, and 24 months after HCC diagnosis were 0%, 36.3%, and 65.2% in the sorafenib group and 0%, 17.2%, and 43.3% in the embolization group.

Sensitivity analyses

Using a model where patients in each group were matched one-to-one using propensity scores, we found very similar results, with the sorafenib group again having almost 2 times the hazard of death compared with embolization group (HR=1.92, 95% CI 1.48, 2.23; p<0.0001).

There was a moderate degree of crossover in the patient groups, with 28.7% of patients subsequently receiving the other treatment. In the embolization group, 34.5% subsequently received sorafenib a mean time of 259 (SD=280) days after receiving embolization. Among those in the sorafenib group, 18.5% subsequently received embolization a mean time of 113

(SD=151) days after receiving their first prescription for sorafenib. To test the robustness of the results in light of this degree of crossover, an analysis was also performed excluding patients who received both treatments. The overall conclusions were not affected, with similar differences found for overall survival similar compared to the primary analysis (HR=1.98, 95% CI 1.56, 2.56; $p<0.0001$).

Additionally, we wanted to preclude the possibility that patients who received both treatments as a planned combined therapy affected results. Therefore we excluded those who received embolization or initiated sorafenib within a month of each other. The overall conclusions were again not affected, with continued greater hazard of early death in the sorafenib group (HR=1.96, 95% CI 1.51, 2.51; $p<0.0001$).

DISCUSSION

The majority of patients with HCC present with non-curative disease. Without any form of cancer treatment, the prognosis for these patients is extremely poor, with reported median survival of less than seven months.¹⁶ In recent decades, liver-directed and systemic options have demonstrated efficacy relative to best-supportive care or placebo in multiple randomized clinical trials. However, evidence on the comparative effectiveness of these therapies is lacking, making the clinical choice between treatments challenging for providers. Many providers turn to published guidelines for assistance, with the most well-known being the on BCLC staging-treatment algorithm linked system, which are not based on data from comparative trials. Furthermore, simple algorithms do not take into consideration the combination or sequential therapies that patients often receive in the real world.

In this study using population-based data, we found a significant survival advantage in patients who received embolization compared to those who received sorafenib, after adjusting

for expected baseline differences between treatment groups. Those who received sorafenib had almost double the hazard of mortality compared to those who received embolization, regardless of whether we modeled survival from time of treatment or time of diagnosis. We found a median OS of 10.8 months following treatment initiation in the sorafenib group that almost exactly matched the median OS of 10.7 months reported the SHARP trial,³ suggesting that treatment effectiveness under real-world circumstances are consistent with those in controlled trials.

We also found that a large number of patients were being treated outside of BCLC guidelines, with a large number of intermediate BCLC stage patients receiving sorafenib as initial therapy, as well as advanced stage patients receiving embolization. Importantly, we found that the survival advantage following embolization persisted in the both the intermediate and advanced BCLC stage groups. These findings indicate that existing treatment guidelines recommending sorafenib for all patients with advanced disease may be flawed, and that reconsideration of these recommendations may be warranted. Specifically, identification of particular subsets of patients with advanced disease who might benefit from catheter-based approaches is needed.

While the reasons behind non-adherence to BCLC guidelines are beyond the scope of this study, it is notable that in the unweighted groups, those that received embolization lived in census tracts with significantly higher median incomes. Prior investigators have found associations between low socioeconomic status and lower treatment rates¹⁷; this study suggests that socioeconomic status may also influence the type of treatment received. This, in turn, likely contributes to socioeconomic disparities in HCC outcomes.¹⁸

HCC mostly occurs in patients with significant comorbidities, including chronic liver disease. Our data confirmed this, with over 90% of the study population having at least one comorbidity and over 67% having a Charlson comorbidity index >2. In such a population, non-cancer causes of death compounded with deleterious effects of treatment may impact survival. We found no evidence that this substantively affected the comparative effectiveness of the two treatments, as a competing risk model also showed differences in cancer-specific mortality between the two groups, again with a significant survival advantage in those who underwent embolization.

Our data also confirmed results from published comparative studies of specific embolization techniques. Salem et al. recently published results of a prospective trial which randomized HCC patients to radioembolization versus TACE and was unable to demonstrate a difference in overall survival.¹⁹ We were similarly unable to show a difference in survival in our exploratory analysis comparing radioembolization to TACE or bland embolization. Of note, we were unable to confidently distinguish between those two received TACE from those who received bland embolization, but studies have also shown no difference in outcomes between these two categories of embolization therapies.¹⁵ Similar to our study, one prospective comparative study and a meta-analysis showed no survival differences when sorafenib was combined with embolization relative to receipt of embolization alone.^{20,21}

This study has some limitations. First, as an observational study, there is potential for selection bias. Our study aimed to compare the effectiveness of two treatments using a well-established methodology for reducing selection bias and results were robust in stratified and sensitivity analyses. Nonetheless, methods to reduce bias can only account for measured variables. Child Pugh class, presence of vascular invasion, and performance status all influence

treatment decisions and outcomes but these variables were not available. Variables for history of encephalopathy and ascites were used as proxies for Child Pugh status, but no data was available on bilirubin or albumin levels. Although it is imperfect, we used a history of portal vein thrombosis as a surrogate for vascular invasion. Similarly, we used a validated method to determine poor disability as a proxy for poor performance status. All of these claims-based methods rely on accurate coding and likely underestimated the prevalence of the entities. Furthermore, BCLC stage was derived from these proxies, limiting the accuracy of stage assignment. Also, subgroup analysis by AJCC stage was affected by small numbers in higher stages and should be interpreted with caution. Finally, the results of this study are not generalizable to younger patients who are not represented in the Medicare population.

In conclusion, in this study of Medicare patients treated under real world conditions, we demonstrated significantly longer overall and cancer-specific survival following treatment with embolization when compared with sorafenib. Survival differences were found in both intermediate and advanced stages of disease. Given that these findings conflict with expert opinion-based guidelines for treatment in advanced stage disease, prospective randomized comparative trials in this subpopulation would be justified. The large effect sizes we found suggest that adequate power to demonstrate differences could be achieved with reasonable enrollment targets.

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FIGURES AND TABLES

Figure 1: Inclusion and exclusion criteria to arrive at final study population

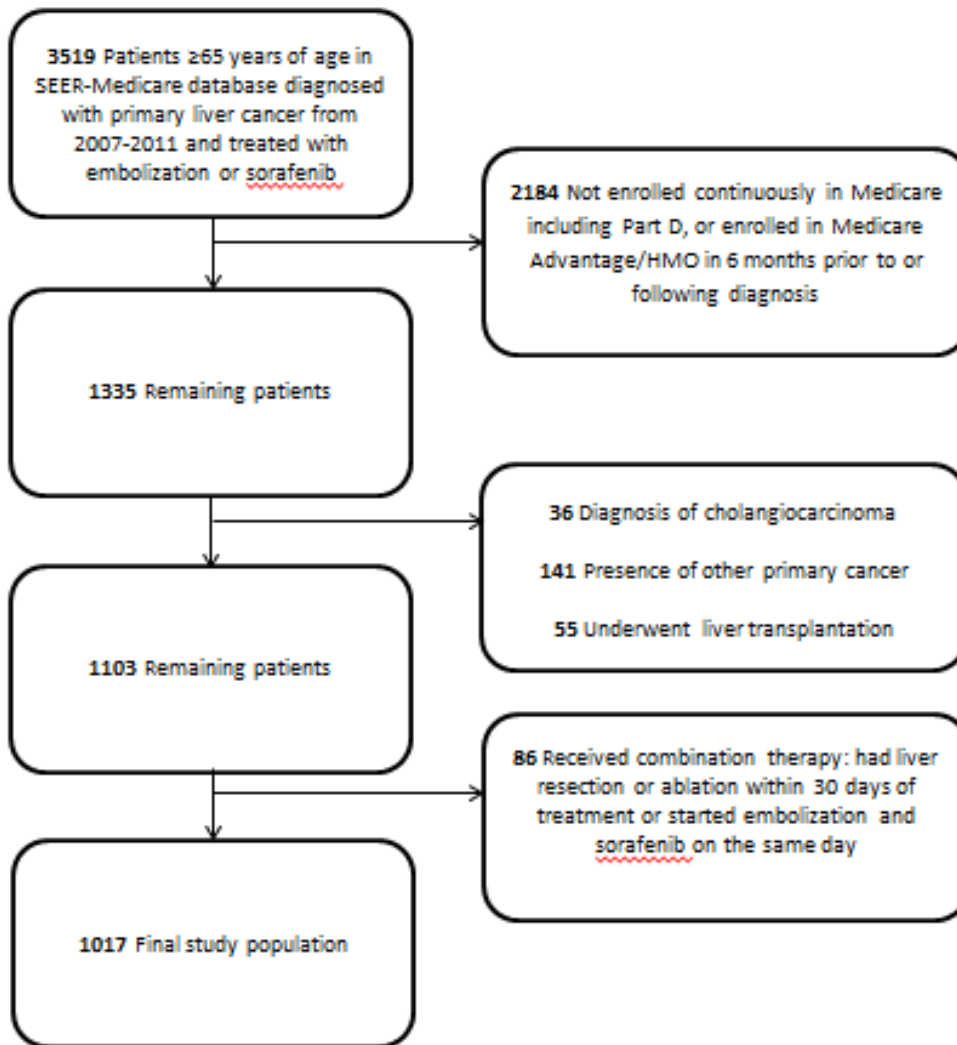


Table 1: Baseline demographic and clinical patient characteristics, before and after inverse-probability weighting

	All Patients	Unweighted			PS-Weighted		
		Embolization	Sorafenib	p-value	Embolization	Sorafenib	Std diff
Count	1017	648	369				
Age at diagnosis, mean (SD)	73.9 (6.28)	73.7 (6.06)	74.2 (6.65)	0.229	74.2	74.0	-3%
Year of Diagnosis, % (n)				0.162			
2007	15.7 (160)	14.7 (95)	17.6 (65)		17.3	16.7	-2%
2008	18.6 (189)	17.0 (110)	21.4 (79)		18.0	17.9	0%
2009	21.1 (215)	21.5 (139)	20.6 (76)		20.3	20.6	1%
2010	20.8 (212)	21.5 (139)	19.8 (73)		19.8	19.0	-2%
2011	23.7 (241)	25.5 (165)	20.6 (76)		24.5	25.8	3%
Male, % (n)	61.1 (621)	60.2 (390)	62.6 (231)	0.447	61.0	62.0	3%
Race, % (n)				0.64			
White	55.2 (561)	54.2 (351)	56.9 (210)		56.7	56.3	-1%
Black	9.0 (91)	9.4 (61)	8.1 (30)		8.5	9.3	3%
Native American	ND	ND	ND		ND	ND	2%
Asian Pacific Islander	34.7 (353)	35.5 (230)	33.3 (123)		33.7	33.1	-1%
Unknown/other	ND	ND	ND		ND	ND	-1%
Census Tract Median Income, median (SD)	49,119 (24,044)	51,774 (25,273)	26,607 (22,558)	<0.001	48,761	49,445	3%
AJCC summary stage, % (n)				<0.001			
Stage 1	37.5 (381)	42.6 (276)	28.5 (105)		56.7	36.5	-1%
Stage 2	18.3 (186)	20.5 (133)	14.4 (53)		8.5	16.3	3%
Stage 3	24.4 (248)	22.5 (146)	27.6 (102)		0.8	26.7	2%
Stage 4	6.00 (61)	2.31 (15)	12.5 (46)		33.7	6.2	-1%
Unknown	13.9 (141)	12.0 (78)	17.1 (63)		0.3	14.3	-1%
Estimated ECOG Performance Status >2, % (n)	15.2 (155)	13.9 (90)	17.6 (65)	0.112	14.0	14.0	0%
Charlson comorbidity index, % (n)				0.511			
0	9.1 (93)	8.18 (53)	10.8 (40)		10.5	9.2	-5%
1	12.7 (129)	13.0 (84)	12.2 (45)		13.4	13.7	1%
2	10.6 (108)	10.3 (67)	11.1 (41)		10.4	10.2	-1%
>2	67.6 (687)	68.5 (444)	65.9 (243)		65.6	66.9	3%
History of liver resection, % (n)	12.9 (131)	7.87 (51)	21.7 (80)	<0.001	17.0	14.0	-8%
History of hepatic encephalopathy, % (n)	5.21 (53)	6.17 (40)	3.52 (13)	0.068	5.0	5.0	1%
History of ascites, % (n)	14.1 (143)	13.1 (85)	15.7 (58)	0.251	15.0	14.0	-2%
History of portal vein thrombosis, % (n)	1.57 (16)	ND	ND	0.531	ND	ND	0%
History of cirrhosis, % (n)	49.5 (503)	55.6 (360)	38.8 (143)	<0.001	47.0	47.0	0%
Etiology of liver disease							
Hepatitis B	3.83 (39)	4.17 (27)	3.25 (12)	0.465	3.0	3.0	2%
Hepatitis C	2.56 (26)	2.16 (14)	3.25 (12)	0.289	2.0	3.0	5%
Alcohol	10.0 (102)	11.0 (71)	8.40 (31)	0.192	10.0	11.0	3%
Nodal or metastatic disease, % (n)	9.0 (92)	4.94 (32)	16.3 (60)	<0.001	12.0	9.0	-7%

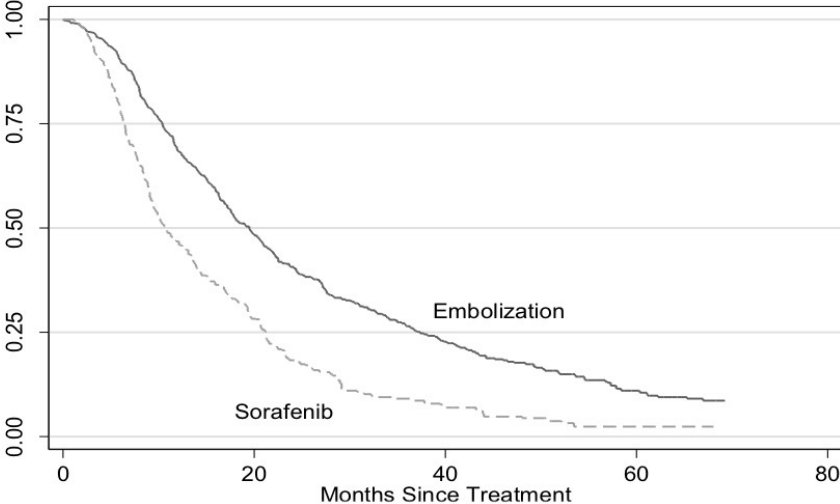
ND=Not displayed due to count ≤ 11 , per National Cancer Institute's minimum cell size restrictions.

PS=Propensity score. SD=Standard deviation. Std Diff=Standardized Differences

Table 2: Summary of survival outcomes

	Median Survival (months)		Hazard Ratio (95% CI)	p-value
	Embolization	Sorafenib		
All				
From time of treatment	19.5	10.8	1.87 (1.46, 2.37)	<0.0001
From time of diagnosis	21.0	14.1	1.87 (1.46, 2.39)	<0.0001
By BCLC stage				
Intermediate	21.0	10.0	1.86 (1.4, 2.51)	<0.0001
Advanced	16.4	11.2	1.85 (1.15, 2.88)	0.0006
By AJCC stage				
Stage 1	22.9	12.1	1.99 (1.37, 2.93)	<0.001
Stage 2	20.4	10.8	1.53 (0.93, 2.82)	0.0371
Stage 3	16.4	11.5	1.55 (1.03, 2.39)	0.0044
Stage 4	27.2	8.0	3.8 (0.74, 24.28)	0.0127

Figure 2: Kaplan Meier curve for overall survival from time of treatment



Figures 3a-b: Kaplan Meier curves for overall survival, stratified by BCLC stage.

Figure 3a: Intermediate BCLC stage. Figure 3b: Advanced BCLC stage.

Figure 3a.

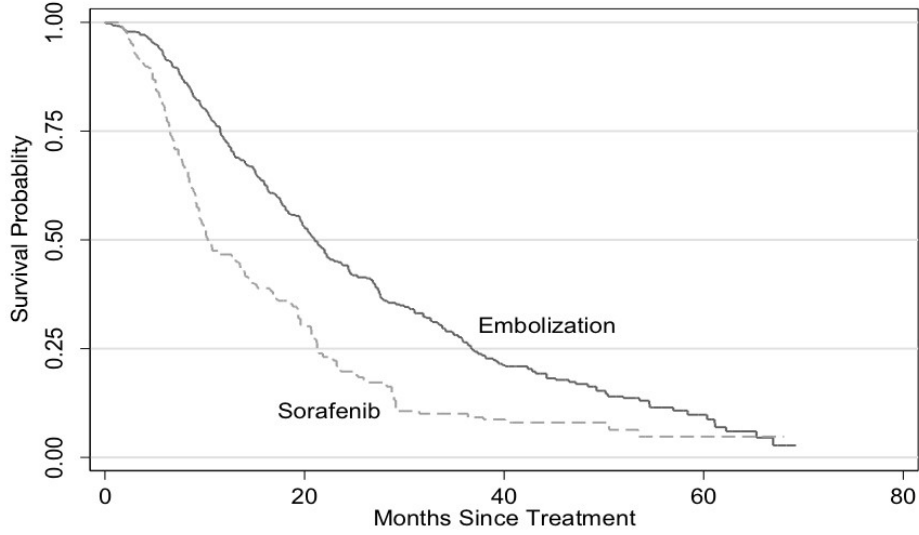
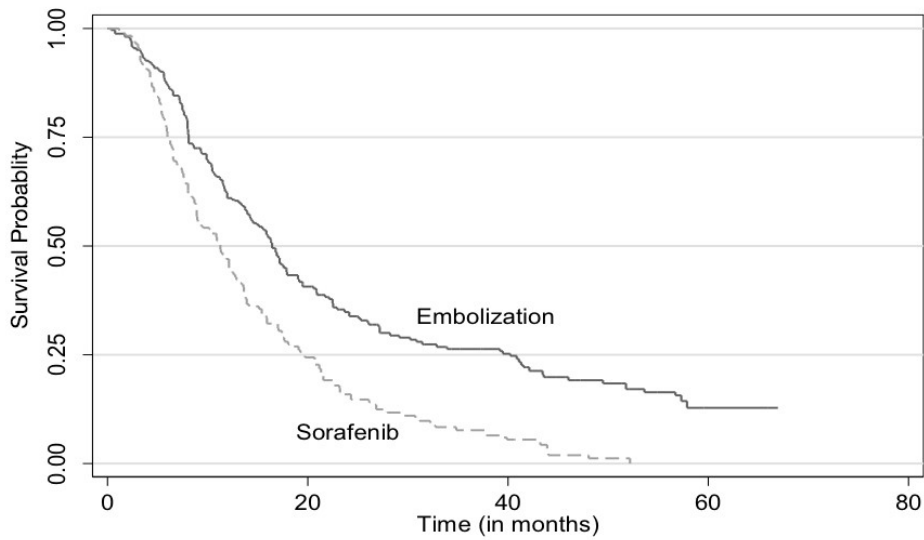


Figure 3b.



Figures 4a-d: Kaplan Meier curves for overall survival, stratified by AJCC stage.

Figure 4a: AJCC Stage 1. Figure 4b: AJCC Stage 2. Figure 4c: AJCC Stage 3. Figure 4d: AJCC Stage 4.

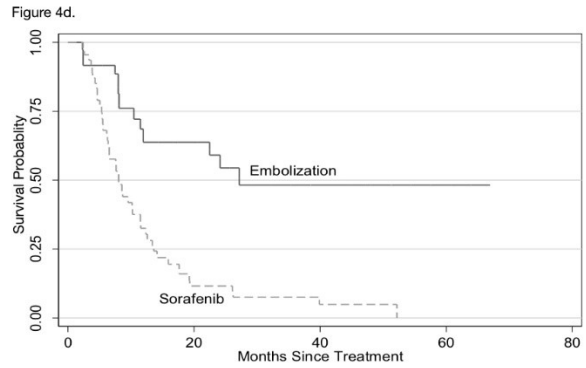
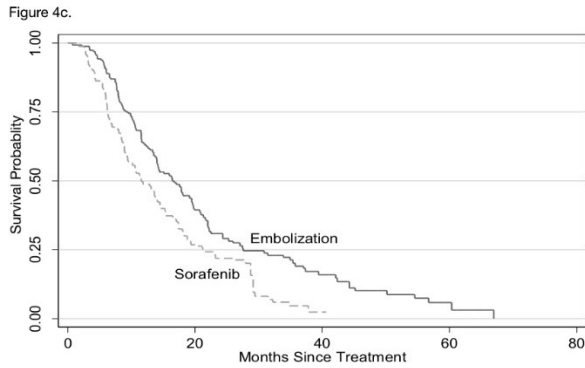
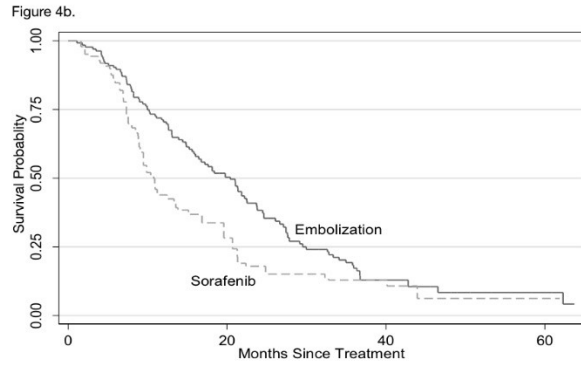
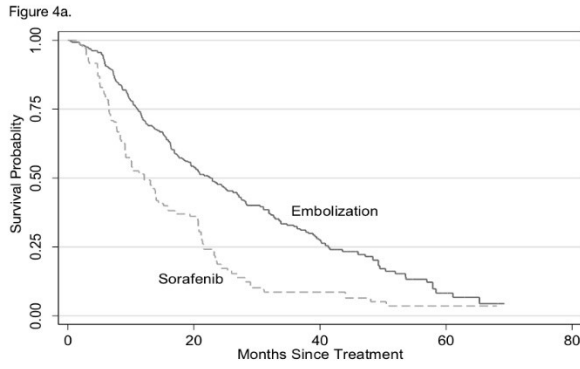


Figure 5: Cumulative incidence curve for cancer-specific mortality

