



# Outcomes After Resection of Hepatocellular Carcinoma: Intersection of Travel Distance and Hospital Volume

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Received: 15 February 2019 / Accepted: 15 April 2019 / Published online: 8 May 2019  
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## Abstract

**Background** Data on the impact of hospital volume and travel distance on patient outcomes after major abdominal surgery remain poorly defined. We sought to characterize the relationship of travel distance, hospital volume, and long-term outcomes of patients undergoing surgical resection of hepatocellular carcinoma (HCC).

**Methods** The 2004–2015 National Cancer Database was used to identify patients who underwent resection of HCC. Patients were stratified according to travel distance and hospital volume quartiles, and multivariable regression models were utilized to examine the impact of travel distance, hospital volume, and travel distance/hospital volume on overall survival (OS).

**Results** Among the 12,266 patients identified, procedures included wedge/segmental resections ( $N = 7354$ , 59.9%), hemihepatectomy ( $N = 4003$ , 32.6%), and extended hepatectomy ( $N = 909$ , 7.5%). Stratifying data into quartiles, travel distance to surgical care was  $\leq 5.7$  miles (mi),  $> 5.7$ –14.2 mi,  $> 14.2$ –44.4 mi, and  $\geq 44.4$  mi, while hospital volume quartiles determined on the hospital level were  $\leq 1$  case per year, 1.1–4, 4.1–12.5, and  $\geq 12.5$ . On multivariable analysis, increased hospital volume was associated with decreased hazard of mortality (HR 0.69, 95% CI 0.45–0.82,  $p < 0.001$ ). Travel distance was not significantly associated with hazard of mortality. Furthermore, only hospital volume was associated with mortality (HR 0.67, 95% CI 0.56–0.80,  $p < 0.001$ ) after controlling for both travel distance and hospital volume.

**Conclusions** Only hospital volume was associated with increased hazard of mortality. The benefits of undergoing resection for HCC at a high-volume hospital appear to outweigh the inconvenience of longer travel distances.

**Keywords** Travel distance · Hospital volume · Hepatocellular carcinoma

## Introduction

Liver cancer is the second leading cause of cancer-related death worldwide. In the USA, the age-adjusted incidence of liver cancer has more than tripled between 1975 and 2011, increasing from 2.6/100,000 to 8.6/100,000.<sup>1</sup> Seventy to 90% of primary liver cancers worldwide are hepatocellular carcinoma (HCC)—a cancer likely to increase in incidence in the upcoming years.<sup>1,2</sup> Current evidence suggests that the major risk factors for HCC are sustained virological response of hepatitis C and suppressed hepatitis B on treatment, as well as alcoholic and non-alcoholic fatty liver disease.<sup>3,4</sup>

Curative treatment options for early HCC include ablative techniques, resection, and liver transplantation, with each of these offering the possibility of long-term response and improved survival.<sup>5</sup> Non-curative therapies, aimed at slowing tumor progression and improving survival, include transarterial chemoembolization (TACE), stereotactic body radiation therapy (SBRT), and systemic chemotherapy.<sup>5</sup> Given the multitude of potential treatment options and complex decision making involved in treating patients, HCC is best managed by a multidisciplinary team composed of medical, surgical, and radiation oncologists, transplant surgeons, and interventional radiologists.<sup>6</sup> In fact, implementation of multidisciplinary tumor board review for patients with HCC has led to improved survival.<sup>7</sup>

Increasing evidence has suggested that survival of patients treated for HCC may be influenced by institution volume and the experience of the operating surgeon. In a study of the Texas Cancer Registry, patients with HCC who received treatment at high-volume hospitals were likely to receive curative

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therapies, and, thus exhibit improved survival.<sup>8</sup> In addition, recent analyses from the National Cancer Database (NCDB) revealed that patients undergoing resection at transplant centers and high-volume cancer programs had an improved 10-year survival compared with patients treated at low-volume hospitals.<sup>9,10</sup> Similarly, patients with HCC undergoing radiofrequency ablation also had improved overall and cancer-specific survival when treated at high-volume hospitals.<sup>11,12</sup>

In order to access care at high-volume hospitals, a significant proportion of patients may have to travel long distances. The impact of travel distance on outcomes of patients undergoing major abdominal surgery has not yet been clearly defined. Some studies have reported an increase in mortality associated with increased distance, whereas other studies have demonstrated improved short- and long-term outcomes among patients receiving treatment at high-volume hospitals despite increased travel distance.<sup>13,14</sup> Interestingly, a recent study examining outcomes of patients undergoing cystectomy for invasive bladder cancer demonstrated that the association between longer travel distances and improved outcomes was mediated by hospital volume.<sup>15</sup> Nevertheless, the combined impact of travel distance and hospital volume among patients undergoing resection for HCC has not been examined. Therefore, the objective of the current study was to characterize the association between travel distance and hospital volume relative to short- and long-term outcomes following resection of HCC.

## Methods

### Data Source

The National Cancer Database (NCDB) is jointly administrated by the American College of Surgeons Commission on Cancer and the American Cancer Society and was designed as a quality improvement initiative. The available data include patients treated between 2004 and 2015 who received at least a portion of their care at a site accredited by the Commission on Cancer, representing 30% of US hospitals and 70% of patients with newly diagnosed cancer.<sup>16</sup> Data in the NCDB include sociodemographic information, Charlson-Deyo comorbidity score, cancer diagnosis, disease stage, treatment details and survival, surgical procedures, length of stay, readmission to the index hospital, death within 30 and 90 days of surgery, and long-term survival.<sup>17</sup>

For purposes of the current analysis, patients were included in the analytic cohort who had a primary site of the liver (PRIMARY\_SITE = C220), hepatocellular carcinoma (HISTOLOGY = 8170), and underwent resection (RX\_SUMM\_SURG\_PRIM\_SITE = 20–59, 65–66). Patients with fibrolamellar HCC and/or metastatic disease were excluded.

### Analytic Variables

Demographic data were obtained including age, race, Charlson-Deyo comorbidity score, insurance status, patient area of residence (metropolitan vs urban vs rural), median income (median household income in each area of residence), and education level (number of adults in the area of residence who did not graduate from high school). Tumor and treatment variables including cN stage, cT stage, pN stage, pT stage, preoperative chemotherapy, positive surgical margins, surgical delay (surgery > 90 days from date of diagnosis), and overall survival were also obtained. The exposures of interest were travel distance and hospital volume among patients undergoing resection of HCC. Annual hospital surgical volume for HCC cases was calculated using the entire cohort of patients with HCC and assigned to each individual patient as a continuous variable, as described previously.<sup>15</sup> Travel distance in the NCDB is defined as “great circle” distance in miles between the patient’s residence and the hospital, calculated using zip codes and the haversine formula.<sup>17</sup> Quartiles for travel distance and hospital volume were determined.

Overall survival, calculated as the time from the date of diagnosis to the date of last follow-up or death from any cause, was the primary outcome. Secondary outcomes included surgical delay greater than 3 months and positive surgical margin. The primary independent variables—travel distance and hospital volume—were considered as continuous and categorical data (i.e., quartiles). Travel distance was divided into first quartile/short travel (ST), second quartile/intermediate travel (IT), third quartile/intermediate long travel (ILT), and fourth quartile/long travel (LT). Hospital volume was divided into first quartile/low volume (LV), second quartile/intermediate low volume (ILV), third quartile/intermediate high volume (IHV), and fourth quartile/high volume (HV).

### Statistical Analysis

Descriptive statistics were calculated for the overall cohort and for each quartile of travel distance and reported as frequencies and proportions for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. Chi-square tests and Kruskal-Wallis one-way analysis of variance were used to determine associations between travel distance quartiles, demographics, and clinical variables. Fisher’s exact tests were used where appropriate. Kaplan-Meier curves were constructed and log-rank tests were performed to assess the association of travel distance and hospital volume relative to overall survival. The association between travel distance and hospital volume relative to mortality was determined using multivariable Cox proportional-hazards models controlling for relevant covariates. Multivariable logistic regression analyses were constructed and evaluated to assess the

association between travel distance and hospital volume relative to secondary outcomes.

Three different multivariable models to assess possible associations of hospital volume, travel distance, and outcomes were performed. The first and second models evaluated the independent effect of travel distance alone and hospital volume alone; in contrast, the third multivariable model assessed the impact of travel distance combined with hospital volume. Sensitivity analyses were also performed using travel distance and hospital volume as continuous variables. This analytic approach had been used in previous studies to examine the relative contributions of travel distance and hospital volume on overall survival for other surgical procedures.<sup>15,18,19</sup> Statistical significance was assessed at  $p = 0.05$ . All analyses were performed using SAS v9.4 (Cary, NC).

## Results

### Study Cohort

A total of 12,266 patients with non-metastatic HCC were analyzed. Among the patients identified, procedures included wedge/segmental resections ( $N = 7354$ , 59.9%), hemihepatectomy ( $N = 4003$ , 32.6%), and extended hepatectomy ( $N = 909$ , 7.5%). Hospital volume, travel distance, patient demographics, and clinical characteristics are summarized in Table 1. Median patient age was 64 years (IQR 57–72); the majority of patients were male ( $N = 8653$ , 70.5%) and Caucasian ( $N = 8290$ , 67.6%). Most patients had a Charlson-Deyo score of zero ( $N = 6406$ , 52.2%). The majority of patients had Medicare ( $N = 5633$ , 47.3%) followed by private insurance ( $N = 4549$ , 38.2%). The vast majority of patients lived in a metropolitan area ( $N = 10,443$ , 86.9%), and most individuals had an income  $\geq \$48k$  ( $N = 7036$ , 57.4%) per year. Most patients with available preoperative staging data had stage cT1 ( $N = 5278$ , 43.3%) followed by cT2 ( $N = 2126$ , 17.4%) disease, as well as cN0 disease ( $N = 9,401$ , 76.9%).

Among all hospitals included in the study, median hospital HCC surgical volume was 3 (IQR 1, 7) cases per year. Hospital surgical volume quartiles were categorized as first quartile/LV  $\leq 1$  case per year, second quartile/ILV 1.1–4, third quartile/IHV 4.1–12.5, and fourth quartile/HV  $\geq 12.5$  cases per year.

Median patient travel distance to receive surgical care was 14.2 (IQR 5.7–44.4) miles. Travel distance quartiles were further categorized as first quartile/ST  $\leq 5.7$  miles, second quartile/IT  $> 5.7$ –14.2 miles, third quartile/ILT  $> 14.2$ –44.4 miles, and fourth quartile/LT  $\geq 44.4$  miles. Among patients treated at hospitals within the 1st volume quartile, 45.3% traveled  $< 5.7$  miles, whereas 27.2% of patients treated at high-volume hospitals traveled  $> 44.4$  miles to ensure access to surgical care (Fig. 1).

### Overall Survival by Travel Distance and Hospital Volume

Multivariable Cox regression models evaluating the association between travel distance, hospital volume, and mortality are shown in Table 2. When only travel distance was included in the model, none of the distance quartiles were associated with decreased hazard of mortality (IST: HR 0.97, 95% CI 0.90–1.05; ILT: HR 0.99, 95% CI 0.92–1.08; LT: HR 0.98, 95% CI 0.90–1.06, all  $p > 0.05$ ). In contrast, when only hospital volume was included in the model, high-volume hospitals were associated with a substantial decrease in the hazard of mortality (HR 0.69, 95% CI 0.58–0.82,  $p < 0.001$ ). Moreover, when both travel distance and hospital volume were included in the model, high case volume remained associated with a decreased hazard of mortality (HR 0.67, 95% CI 0.56–0.80,  $p < 0.001$ ). Of note, sensitivity analysis with travel distance and hospital volume as continuous variables demonstrated that either higher hospital volume alone (HR 0.981, 95% CI 0.977–0.984,  $p < 0.001$ ) or combined with longer travel distance (HR = 0.981, 95% CI 0.977–0.984,  $p < 0.001$ ) was associated with improved survival.

Importantly, patients treated at high-volume hospitals ( $> 12.5$  cases per year) had the highest median survival (median survival; 1st 30.49 months vs 2nd 31.84 months vs 3rd 37.65 months vs 4th 51.7 months, log-rank  $p$  value = 0.030, Fig. 2).

### Quality of Care Indicators by Travel Distance and Hospital Volume

Multivariable logistic regression models examining the associations between travel distance, hospital volume, and quality of care indicators including surgical delay and surgical margins are shown in Tables 3 and 4.

In examining surgical delay (SD, Table 3), when only travel distance was included in the model, increasing travel distance was not associated with increased risk of SD (IST: OR 1.04, 95% CI 0.92–1.17; ILT: OR 1.00, 95% CI 0.89–1.14; LT: OR 1.16, 95% CI 0.99–1.32; all  $p > 0.05$ ). Similarly, when only hospital volume was included in the model, none of the volume quartiles were associated with increased risk of SD (LV: OR 1.03, 95% CI 0.71–1.48; IHV: OR 0.89, 95% CI 0.63–1.25; HV: OR 0.88, 95% CI 0.65–1.21; all  $p > 0.05$ ). When both travel distance and hospital volume were included in the model, traveling longer distances or undergoing surgery at high-volume hospitals was not associated with increased risk of SD. In fact, sensitivity analysis demonstrated that increasing hospital volume alone (OR 0.99, 95% CI 0.987–0.996,  $p < 0.001$ ) and combined with travel distance (OR 0.99, 95% CI 0.987–0.996,  $p < 0.001$ ) were associated with a slight decrease in the risk of SD.

**Table 1** Hospital Volume, travel distance, patient demographics and clinical characteristics of overall cohort stratified by travel distance

Variables	Overall (N = 12,266)	1st quartile (N = 3040)	2nd quartile (N = 3067)	3rd quartile (N = 3091)	4th quartile (N = 3068)	p value
Hospital volume per case median (IQR)	49 (18–106)	26 (9–68)	41 (13–82)	26 (21–110)	79 (36–133)	< 0.001
Travel distance, miles median (IQR)	14.2 (5.7–44.4)	3.1 (1.8–4.3)	9.1 (7.2–11.3)	24.0 (18.3–32.1)	91.8 (60.9–152.8)	< 0.001
Age (median (IQR))	64 (57–72)	64 (57–73)	64 (56–72)	65 (57–73)	65 (57–72)	0.170
Gender						0.014
Male	8653 (70.5%)	2162 (71.1%)	2148 (70.0%)	2189 (70.8%)	2154 (70.2%)	
Female	3613 (29.5%)	878 (28.9%)	919 (30.0%)	902 (29.2%)	914 (29.8%)	
Race						< 0.001
White	8290 (67.6%)	1602 (52.7%)	1852 (60.4%)	2328 (75.3%)	2508 (81.7%)	
Black	1846 (15.0%)	746 (24.5%)	540 (17.6%)	291 (9.4%)	269 (8.8%)	
Other	2130 (17.4%)	692 (22.8%)	675 (22.0%)	472 (15.3%)	291 (9.5%)	
Charlson-Deyo Score						0.008
0	6406 (52.2%)	1626 (53.5%)	1662 (54.2%)	1532 (49.6%)	1586 (51.7%)	
1	3612 (29.4%)	859 (28.3%)	878 (28.6%)	972 (31.4%)	903 (29.4%)	
≥ 2	2248 (18.3%)	555 (18.3%)	527 (17.2%)	587 (19.0%)	579 (18.9%)	
Insurance status						< 0.001
Private	4549 (38.2%)	1035 (34.6%)	1168 (38.9%)	1246 (41.3%)	1100 (38.1%)	
Medicare	5633 (47.3%)	1367 (45.6%)	1367 (45.5%)	1447 (48.0%)	1452 (50.3%)	
Medicaid and other government	1373 (11.5%)	481 (16.1%)	379 (12.6%)	255 (8.5%)	258 (8.9%)	
Not insured	350 (2.9%)	112 (3.7%)	90 (3.0%)	69 (2.3%)	79 (2.7%)	
Residence Area						< 0.001
Metropolitan	10,443 (86.9%)	2947 (98.8%)	2986 (99.1%)	2667 (88.5%)	1843 (61.3%)	
Urban	1411 (11.7%)	36 (1.2%)	28 (0.9%)	323 (10.7%)	1024 (34.0%)	
Rural	164 (1.4%)	0 (0.0%)	0 (0.0%)	23 (0.76%)	141 (4.7%)	
Median income						< 0.001
< \$38,000	2418 (19.7%)	894 (29.4%)	412 (13.4%)	319 (10.3%)	793 (25.9%)	
\$38,000–\$47,000	2801 (22.9%)	607 (20%)	615 (20.1%)	573 (18.6%)	1006 (32.8%)	
\$48,000–\$62,999	3261 (26.6%)	742 (24.4%)	842 (27.5%)	860 (27.8%)	817 (26.7%)	
≥ 63,000	3775 (30.8%)	794 (26.1%)	1196 (39%)	1336 (43.3%)	449 (14.6%)	
Education level						< 0.001
≥ 21%	2730 (22.3%)	1014 (33.4%)	645 (21.0%)	431 (14.0%)	640 (20.9%)	
13–20%	3229 (26.3%)	726 (23.9%)	750 (24.5%)	821 (26.6%)	932 (30.4%)	
7–12.9%	3684 (30.1%)	712 (23.4%)	913 (29.8%)	1025 (33.2%)	1034 (33.7%)	
< 7%	2616 (21.3%)	586 (19.3%)	757 (24.7%)	812 (26.3%)	461 (15.0%)	
cN Stage						0.003
cN0	9401 (76.9%)	2345 (77.3%)	2384 (77.8%)	2404 (78%)	2268 (74.4%)	
≥ cN1	135 (1.1%)	22 (0.7%)	35 (1.1%)	35 (1.1%)	43 (1.4%)	
cNx	2692 (22%)	666 (22%)	644 (21%)	645 (20.9%)	737 (24.2%)	
cT stage						0.012
cT1	5278 (43.3%)	1364 (45.1%)	1344 (44.1%)	1319 (43%)	1251 (41.1%)	
cT2	2126 (17.4%)	497 (16.4%)	559 (18.3%)	545 (17.7%)	525 (17.3%)	
cT3	1473 (12.1%)	342 (11.3%)	344 (11.3%)	376 (12.2%)	411 (13.5%)	
cT4	220 (1.8%)	65 (2.2%)	56 (1.8%)	53 (1.7%)	46 (1.5%)	
cTX	3090 (25.3%)	755 (25%)	747 (24.5%)	778 (25.4%)	810 (6.6%)	
pN Stage						0.009
pN0	5212 (46.5%)	1250 (45.2%)	1285 (46%)	1278 (45.4%)	1399 (49.3%)	
≥ pN1	121 (1.1%)	24 (0.9%)	27 (1%)	32 (1.1%)	38 (1.3%)	
pNx	5878 (52.4%)	1492 (53.9%)	1484 (53.1%)	1502 (53.4%)	1400 (49.3%)	

**Table 1** (continued)

Variables	Overall (N = 12,266)	1st quartile (N = 3040)	2nd quartile (N = 3067)	3rd quartile (N = 3091)	4th quartile (N = 3068)	<i>p</i> value
pT Stage						<i>0.008</i>
pT1	4962 (41.6%)	1242 (42.2%)	1231 (41.3%)	1268 (42.1%)	1221 (40.7%)	
pT2	2996 (25.1%)	694 (23.6%)	786 (26.3%)	765 (25.4%)	751 (25.1%)	
pT3	1823 (15.3%)	408 (13.9%)	451 (15.1%)	452 (15%)	512 (17.1%)	
pT4	381 (3.2%)	107 (3.6%)	87 (2.9%)	100 (3.3%)	87 (2.9%)	
pTx	1772 (14.9%)	490 (16.7%)	429 (14.4%)	426 (14.1%)	427 (14.2%)	
Positive surgical margins	1107 (9%)	288 (9.5%)	256 (8.3%)	271 (8.8%)	292 (9.5%)	0.310
Surgical delay (> 3 months)	3296 (26.9%)	817 (26.9%)	817 (26.6%)	797 (25.8%)	865 (28.2%)	0.200

Hospital volume summary statistics are presented on the patient level. Quartiles were derived on the hospital level and had the following median (IQR): 3<sup>1.7</sup>. The *p*-values in italics are those that are statistically significant using a *p*-value threshold <0.05 Fischer's exact test

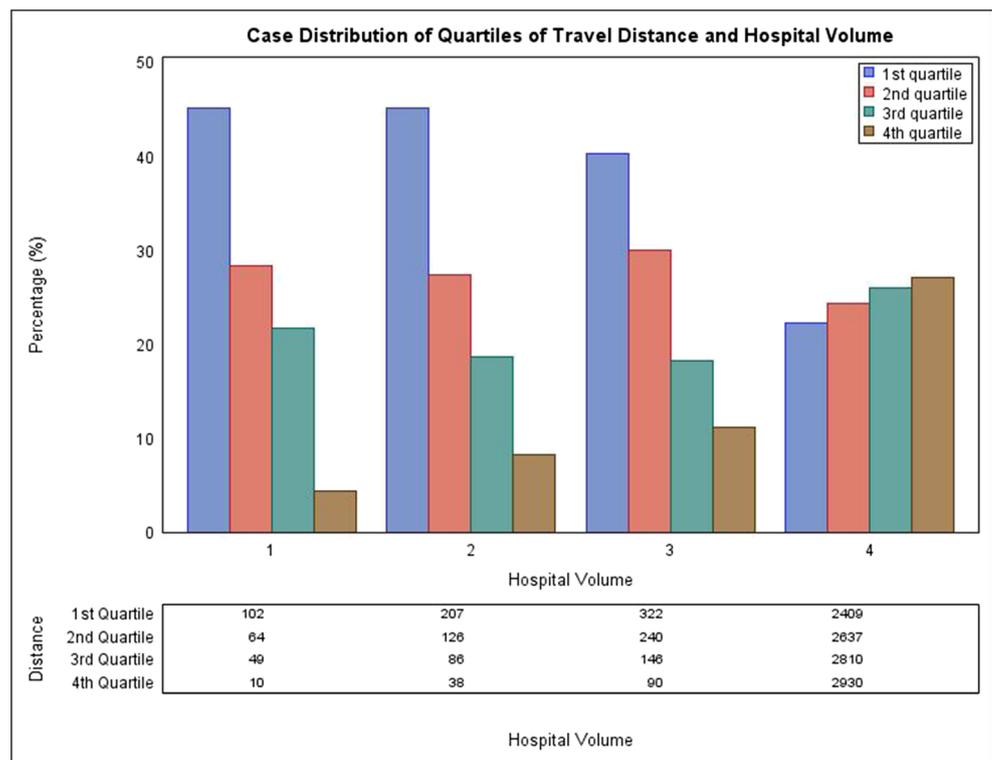
Regarding positive surgical margins (PSM, Table 4), when only travel distance was included in the model, none of the quartiles were associated with decreased risk of PSM. Similarly, when only hospital volume was included in the model, higher hospital volume was not associated with decreased risk of PSM (HV: OR 0.72, 95% CI 0.47–1.12). In addition, when both hospital volume and travel distance were included, neither variables were associated with decreased risk of PSM (HV: OR 0.71, 95% CI 0.46–1.10; LT: OR 1.05, 95% CI 0.86–1.29) (all *p* > 0.05). However, on sensitivity analysis with travel distance and hospital volume as continuous

variables, higher hospital volume alone (OR 0.976, 95% CI 0.967–0.985, *p* < 0.001) and combined with travel distance (OR 0.976, 95% CI 0.968–0.985, *p* < 0.001) were associated with decreased odds of PSM.

### Discussion

Treatment at specialized cancer centers has long been considered to provide superior outcomes compared with low-volume, community-based institutions. As regionalization of care

**Fig. 1** Distribution of travel distance by hospital volume quartile



**Table 2** Multivariable Cox regressions for mortality with alternately including travel distance, hospital volume, and both variables in the model

Primary analysis*	Travel distance		Hospital volume		Travel distance + hospital volume	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
<b>Travel distance</b>						
1st quartile (ST)	Reference	–	–	–	Reference	–
2nd quartile (IST)	0.97 (0.90–1.05)	0.454	–	–	1.00 (0.93–1.08)	0.908
3rd quartile (ILT)	0.99 (0.92–1.08)	0.953	–	–	1.06 (0.98–1.14)	0.174
4th quartile (LT)	0.98 (0.90–1.06)	0.545	–	–	1.08 (0.98–1.17)	0.092
<b>Hospital volume</b>						
1st quartile (LV)	–	–	Reference	–	Reference	–
2nd quartile (ILV)	–	–	1.11 (0.90–1.37)	0.323	1.10 (0.89–1.36)	0.369
3rd quartile (IHV)	–	–	0.97 (0.79–1.18)	0.734	0.96 (0.78–1.17)	0.662
4th quartile (HV)	–	–	0.69 (0.58–0.82)	< 0.001	0.67 (0.56–0.80)	< 0.001
<b>Sensitivity analysis*</b>						
Travel distance (continuous, per 100 miles)	0.99 (0.97–1.01)	0.328	–	–	0.999 (0.978–1.021)	0.927
Hospital volume (continuous, per 10 cases)	–	–	0.981 (0.977–0.984)	< 0.001	0.981 (0.977–0.984)	< 0.001

The *p*-values in italics are those that are statistically significant using a *p*-value threshold <0.05

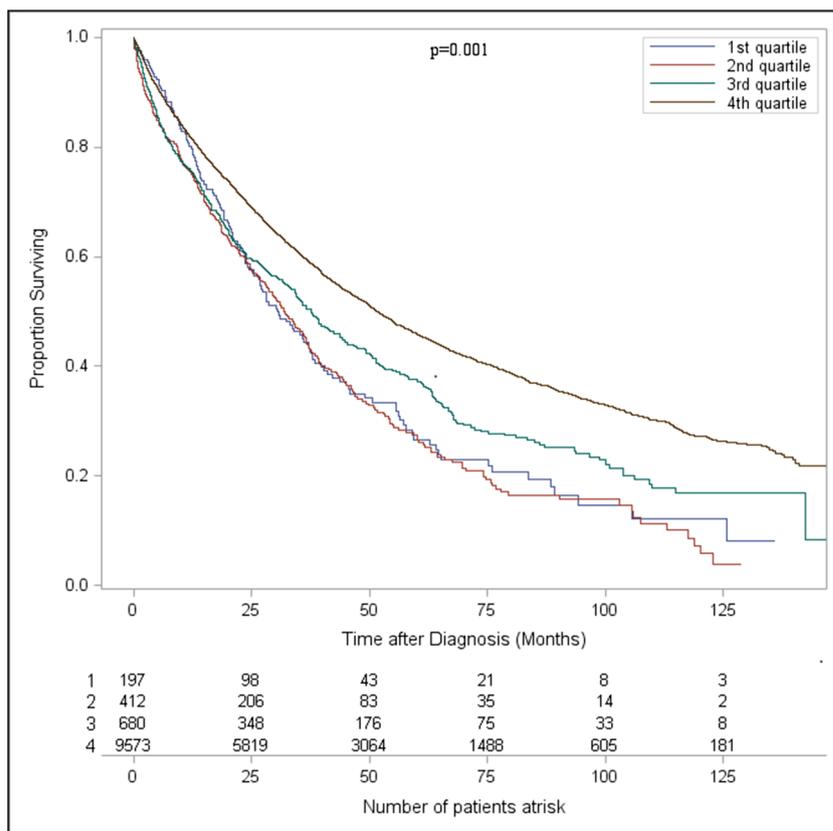
HR, hazard ratio; CI, confidence interval; ST, short travel; IST, intermediate short travel; ILT, intermediate long travel; LT, long travel; LV, low volume; ILV, intermediate low volume; IHV, intermediate high volume; HV, high volume

\*Analysis adjusted for age, sex, race, Charlson-Deyo score, insurance status, patient residence area, median income, education level, cT stage, and cN stage

increases, specialized surgical care may only be available at high-volume centers. Patients with HCC are particularly

complex as decisions about the tumor frequently need to be considered in light of underlying liver disease and patient

**Fig. 2** Kaplan-Meier curve for overall survival comparing volume quartiles



**Table 3** Multivariable logistic regressions for surgical delay with alternately including travel distance, hospital volume, and both variables in the model

Primary analysis*	Travel distance		Hospital volume		Travel distance + hospital volume	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
<b>Travel distance</b>						
1st quartile (ST)	Reference	–	–	–	Reference	–
2nd quartile (IST)	1.04 (0.92–1.17)	0.583	–	–	1.04 (0.92–1.17)	0.503
3rd quartile (ILT)	1.00 (0.89–1.14)	0.943	–	–	1.02 (0.89–1.15)	0.786
4th quartile (LT)	1.16 (0.99–1.32)	0.276	–	–	1.18 (0.97–1.35)	0.136
<b>Hospital volume</b>						
1st quartile (LV)	–	–	Reference	–	Reference	–
2nd quartile (ILV)	–	–	1.03 (0.71–1.48)	0.896	1.01 (0.70–1.47)	0.954
3rd quartile (IHV)	–	–	0.89 (0.63–1.25)	0.488	0.87 (0.61–1.23)	0.421
4th quartile (HV)	–	–	0.88 (0.65–1.21)	0.444	0.85 (0.62–1.16)	0.295
<b>Sensitivity analysis*</b>						
Travel distance (continuous, per 100 miles)	1.005 (0.973–1.038)	0.767	–	–	1.009 (0.977–1.043)	0.569
Hospital volume (continuous, per 10 cases)	–	–	0.99 (0.987–0.996)	< 0.001	0.99 (0.987–0.996)	< 0.001

The *p*-values in italics are those that are statistically significant using a *p*-value threshold <0.05

OR, odds ratio; CI, confidence interval; ST, short travel; IST, intermediate short travel; ILT, intermediate long travel; LT, long travel; LV, low volume; ILV, intermediate low volume; IHV, intermediate high volume; HV, high volume

\*Analysis adjusted for age, sex, race, Charlson-Deyo score, insurance status, patient residence area, median income, education level, cT stage, and cN stage

performance status. As such, multidisciplinary tumor board review of patients with HCC in experienced centers has been associated with improved patient outcomes.<sup>7</sup> Although

several previous reports described a relationship between hospital volume and patient outcomes, no study had examined the interaction of travel distance and hospital volume among

**Table 4** Multivariable logistic regressions for positive surgical margin with alternately including travel distance, hospital volume, and both variables in the model

Primary analysis*	Travel distance		Hospital volume		Travel distance + hospital volume	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
<b>Travel distance</b>						
1st quartile (ST)	Reference	–	–	–	Reference	–
2nd quartile (IST)	0.84 (0.70–1.01)	0.068	–	–	0.87 (0.72–1.04)	0.132
3rd quartile (ILT)	0.88 (0.73–1.06)	0.171	–	–	0.93 (0.77–1.12)	0.430
4th quartile (LT)	0.97 (0.79–1.18)	0.747	–	–	1.05 (0.86–1.29)	0.608
<b>Hospital volume</b>						
1st quartile (LV)	–	–	Reference	–	Reference	–
2nd quartile (ILV)	–	–	1.18 (0.70–1.98)	0.536	1.16 (0.69–1.95)	0.564
3rd quartile (IHV)	–	–	0.97 (0.60–1.58)	0.896	0.96 (0.59–1.561)	0.862
4th quartile (HV)	–	–	0.72 (0.47–1.12)	0.146	0.71 (0.46–1.10)	0.124
<b>Sensitivity analysis*</b>						
Travel distance (continuous, per 100 miles)	0.970 (0.915–1.028)	0.308	–	–	0.984 (0.931–1.041)	0.577
Hospital volume (continuous, per 10 case)	–	–	0.976 (0.967–0.985)	< 0.001	0.976 (0.968–0.985)	< 0.001

The *p*-values in italics are those that are statistically significant using a *p*-value threshold <0.05

OR, odds ratio; CI, confidence interval; ST, short travel; IST, intermediate short travel; ILT, intermediate long travel; LT, long travel; LV, low volume; ILV, intermediate low volume; IHV, intermediate high volume; HV, high volume

\*Analysis adjusted for age, sex, race, Charlson-Deyo score, insurance status, patient residence area, median income, education level, cT stage, and cN stage

patients treated for HCC.<sup>8–12</sup> Therefore, the current study was important as we specifically examined the relationships between travel distance, hospital volume, and survival among patients undergoing resection of HCC. The current study demonstrated that traveling longer distances was not associated with increased odds of surgical delay. Of note, similar to previous reports, patients treated at high-volume hospitals had a decreased hazard of mortality after controlling for baseline characteristics, irrespective of travel distance.<sup>8–12</sup>

With the increasing trend in centralization of care for complex surgical procedures observed in the past decade, patients with HCC have been increasingly referred to “centers of excellence” to receive surgical care. This centralization phenomenon has been driven by evidence among several surgical specialties that patients who undergo complex surgery at high-volume hospitals have improved survival.<sup>20–24</sup> Regionalization of care, however, may result in a great proportion of patients having to travel long distances in order to have access to surgery at high-volume hospitals.<sup>25</sup> In fact, in the current study, as hospital volume increased, a concomitant increase in the proportion of patients traveling longer distances was noted. For instance, while less than 5% of patients traveled a long distance to receive care at hospitals in the lowest quartile of volume, roughly 30% of the patients traveled long distances to undergo surgical resection of HCC at a high-volume center. Specifically, mean travel distance in the highest distance quartile totaled 91.8 miles, with a proportion of patients traveling as far as 153 miles to receive surgical care.

There remains a concern, however, regarding the impact of travel burden on patient outcomes and the possible association of longer travel distance with fragmentation of care, or even possible delay in initiating treatment of patients with a cancer diagnosis.<sup>15,26,27</sup> For example, Tomaszewski et al. reported that patients with bladder cancer who changed hospitals from the time of diagnosis to surgical treatment were twice as likely to have a surgical delay of > 3 months.<sup>28</sup> Interestingly, in the current study, we found that increasing travel distance was not associated with an increased risk of experiencing surgical delay more than 3 months among patients with HCC. In fact, travel distance did not seem to have any impact on the outcomes analyzed, and the survival benefit of having surgical resection of HCC at a high-volume hospital was not negatively affected by an increase in travel distance. Similar to data in the current study, previous reports have noted that increasing travel distance may be associated with improved outcomes, which is likely mediated by hospital volume.<sup>14,29</sup> In turn, these data suggest that the benefits of receiving treatment at high-volume centers outweigh any possible disadvantages of having to travel a longer distance.

The findings of the current study add to the evidence that patients undergoing resection of HCC at high-volume hospitals have improved outcomes.<sup>9</sup> Although in multivariable analysis the quartiles of hospital volume and travel distance

were not associated with the odds of having a positive surgical margin, sensitivity analysis showed that increasing hospital volume was associated with decreased odds of having positive surgical margins (Table 4). For patients with HCC, negative margin status is directly associated with superior oncologic outcomes, including overall and recurrence-free survival.<sup>30–32</sup> Importantly, patients who underwent surgery at hospitals in the 4th quartile of hospital volume had a 31% lower hazard of mortality compared with patients who underwent surgical resection at hospitals in the lower volume quartile. Moreover, median survival increased from 30.4 months for patients undergoing resection at low-volume hospitals to 51.7 months at high-volume hospitals. The reason why patients who undergo surgery at high-volume hospitals experience superior survival is undoubtedly multifactorial. Even though the exact mechanisms underlying the volume-outcome relationship remain to be elucidated, fundamental aspects of high-volume institutions include higher levels of specialization and compliance to evidence-based processes of care.<sup>33</sup> This is particularly relevant in the context of HCC, which is typically a complex and aggressive tumor occurring in the setting of chronic liver disease and cirrhosis. Indeed, even among patients presenting with similar tumor sizes and stages, treatment options vary widely on the basis of performance status, liver function, and underlying medical comorbidities.<sup>34</sup> In turn, optimal management of patients with HCC includes proper patient selection and evaluation by a multidisciplinary team that encompasses experienced hepatologists, surgeons, diagnostic radiologists, interventional radiologists, radiation oncologists, and medical oncologists.<sup>7,35</sup> In addition, high-volume centers of excellence are more likely to have standardization of postoperative management, which has been associated with significant gains in long-term survival of patients with cancer.<sup>36</sup> Survival outcomes associated with HCC may also be influenced by the follow-up interval and repeat treatments for recurrences. As such, long-term results may not simply be attributable to the quality of surgery alone, but also the overall comprehensive care plan. Collectively, these data suggest that the superior outcomes of patients who do not live close to, but are treated at, specialized centers should outweigh any associated travel burden.<sup>37–40</sup>

There are important limitations to consider when interpreting data from the current study. The National Cancer Database includes only patients who received a portion of their care at a cancer program accredited by the Commission on Cancer (CoC). While this includes 30% of US hospitals and captures 70% of patients with a new diagnosis of cancer, the results may not be broadly applicable to non-CoC hospitals. In particular, compared with CoC-approved and nonapproved hospitals in the USA, CoC hospitals were more frequently accredited by the Joint Commission, designated as a Comprehensive Cancer Center by the National Cancer Institute, affiliated with a medical school or residency program, had more total beds and performed

more operations per year, and were less likely to be critical access hospitals or located in rural areas.<sup>41</sup> The majority of patients included in the current study were from an urban region, and there may be differences in the willingness of patients from urban versus rural areas to travel for surgical care. Travel distance was used to reflect travel burden because NCDB did not contain information about patient resources and ability to travel. Furthermore, the Departments of Veterans Affairs and Department of Defense hospital data is not included in the NCDB Participant User File and was therefore not considered.<sup>16</sup> Given that the data were derived from a US dataset, extrapolation to other countries may also not be appropriate.

In conclusion, results from the current study suggest that the relationship between travel distance and outcomes was mainly mediated by hospital volume for patients undergoing resection for HCC. Patients who traveled longer distances did not experience increased risk of having surgical treatment delay, and a clear survival benefit was observed among patients undergoing surgery for HCC at high-volume centers. The current findings support further regionalization of complex cancer care to high-volume centers of excellence even when longer distances must be traveled.

**Author Contribution** EWB, RM, DIT, AP, KM, MED, JC, AE, and TMP conceived of and designed this work. RM and EWB performed data analysis. EWB drafted the manuscript. EWB, RM, AP, KM, MED, JC, AE, and TMP critically revised the manuscript, provided approval of the final version, and agree to be accountable for all aspects of the work.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

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