Original Article

Centers with more therapeutic modalities are associated with improved outcomes for patients with hepatocellular carcinoma

Julie M. Jiang[1], Nitin Ohri[1], Justin Tang[1], Renee Moadel[2], Jacob Cynamon[3], Andreas Kaubisch[4], Milan Kinkhabwala[5], Madhur K. Garg[1], Chandan Guha[1], Rafi Kabarriti[1]

[1]Departments of Radiation Oncology, [2]Departments of Radiology (Nuclear Medicine), [3]Departments of Radiology (Vascular & Interventional Radiology), [4]Departments of Medicine (Oncology), [5]Departments of Surgery, Albert Einstein College of Medicine-Montefiore Medical Center, Bronx, NY, USA

Contributions: (I) Conception and design: JM Jiang, R Kabarriti; (II) Administrative support: MK Garg, C Guha, R Kabarriti; (III) Provision of study materials or patients: R Kabarriti; (IV) Collection and assembly of data: JM Jiang, R Kabarriti; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Rafi Kabarriti, MD. Department of Radiation Oncology, Montefiore Medical Center, 111 210th Street, Bronx, NY 10467, USA. Email: rkabarri@montefiore.org.

Background: Higher facility volume is correlated to better overall survival (OS), but there is little knowledge on the effect of facility treatment modality number on OS in hepatocellular carcinoma (HCC).

Methods: This is a retrospective analysis of data from the National Cancer Database (NCDB) from 2004–2014 on patients with non-metastatic HCC. Treatment modalities assessed were surgical resection, transplantation, ablation, radioembolization, stereotactic body radiation therapy (SBRT), single-agent chemotherapy, and multi-agent chemotherapy. Facilities were dichotomized at the median of the listed treatment modalities.

Results: There were a total of 112,512 patients with non-metastatic HCC. Of a total of 1,230 sites, 830 (67.5%) used four or fewer modalities. Average survival for patients treated at facilities using fewer modalities was 12.0 and 23.5 months for those treated at facilities with more modalities [hazard ratio (HR) =0.52, 95% confidence interval (CI): 0.51–0.53, P<0.001]. After adjusting for facility volume, liver function, tumor and patient characteristics and other prognostic factors in a multivariable Cox model, treatment at a multi-modality facility still provided a survival advantage (HR =0.60, 95% CI: 0.52–0.70, P<0.001). This benefit also persisted after propensity score matching. Sensitivity analysis varying the cut point from 2 to 6 modalities for dichotomization showed that the benefit persisted. Subgroup stratified analyses based on stage showed that the benefit in OS was highest for patients with stage I and II (P≤0.002) but was not significant for stage III or IVa.

Conclusions: Institutions that offered more treatment modalities had improved OS for patients with non-metastatic HCC, especially for those with stage I and II.

Keywords: Hepatocellular carcinoma (HCC); number of treatment modalities; National Cancer Database (NCDB); stereotactic body radiation therapy (SBRT)

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and is the third most common cause of cancer death worldwide. Management of HCC has many different treatment modalities (1). While surgery and transplantation are potential curative options, the majority of patients are not candidates for these therapies (2). For patients with unresectable disease,

locoregional therapies include ablation, arterially directed therapies such as transarterial chemoembolization (TACE) or radioembolization, or stereotactic body radiation therapy (SBRT). Systemic therapy options include newer kinase inhibitors, such as, sorafenib, which has provided marginal increases in life span for advanced HCC patients (3). Chemotherapy options such as gemcitabine and oxaliplatin have demonstrated efficacy with overall disease control rates of 66% and 8.5% of the patients were subsequently eligible for curative-intent therapies after downstaging (4). More recently, immunotherapy using checkpoint blockade has demonstrated promise for the management of advanced HCC (5).

It has been well documented that treatment at high-volume facilities is associated with improved survival across many different disease sites (6-10). However, it is unknown if sites that offer multiple modalities of treatment, regardless of site volume, have improved overall survival (OS). We hypothesized that access to these multi-modality treatments for patients with HCC could result in improvement in OS. We conducted a nationwide cancer database analysis to assess if patients treated at facilities with more treatment modalities for HCC have improved OS.

Methods

Data source and study population

The study population used for this analysis was derived from the National Cancer Database (NCDB), which is a joint program of the Commission on Cancer and the American Cancer Society. The Commission on Cancer's NCDB and the hospitals participating in the NCDB are the source of the deidentified data used in this study. It is estimated that the NCDB captures about 70% of newly diagnosed cancer cases in the United States (11). Patients were included in this analysis if they were diagnosed with non-metastatic HCC from 2004 to 2014.

Primary endpoint and covariates

The primary endpoint is the effect of facility treatment modality number on OS. The treatment modalities assessed were surgical resection, transplantation, ablation, radioembolization, SBRT, single-agent chemotherapy, and multi-agent chemotherapy. A facility was classified as using a particular modality if any patient treated at that site had been treated with that modality. The total number of modalities used for each facility was called the final treatment modality number. For illustrative purposes, facilities were dichotomized at the median as using ≤4 *vs.* ≥5 of the listed treatment modalities. Those using four or fewer modalities were classified as few-modality facilities and those using five or more modalities were classified as multi-modality facilities. Sensitivity analyses were also performed for cut points at two, three, five, and six modalities.

Other covariates included in the analysis were age, sex, race, insurance status (government *vs.* non-government), household income of patient's zip code, education level of patient's zip code, Charlson-Deyo comorbidity score (0 *vs.* 1 or 2), year of diagnosis, type of facility (academic *vs.* non-academic), geographical location of the facility, facility volume, clinical T stage, clinical N stage, tumor size, multiple *vs.* single tumor, presence of fibrosis, creatinine, bilirubin, and international normalized ratio (INR).

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics. Categorical variables were compared using the chi-squared test and continuous variables were assessed using the Student *t*-test or Mann-Whitney U test as appropriate. Facility treatment modality number was used as a dichotomous variable. Years of follow-up served as the time scale and were calculated beginning with the date of diagnosis to either final follow-up date or death, whichever occurred earliest. Kaplan-Meier survival curves were fit to visualize the distributions of time to death. The statistical significance between few-modality *vs.* multi-modality facilities was evaluated using the log rank test. Cox proportional hazard models were used to examine the multivariate association between facility modality number and OS. The proportional hazards assumption was tested using sums of weighted residuals.

To adjust for nonrandom patient assignment to facilities that may have been influenced by patient, disease, and/or geographically related characteristics potentially confounding survival estimates, we performed a propensity score analysis. Propensity scores were generated using multivariate logistic regression with the dichotomized variable facility modality number as the intervention of interest, and then subsequently compared the matched samples with OS as the outcome of interest. A 1:1 propensity score matching was used to match patients who were treated at a few *vs.* multi-modality facility, not allowing replacement and using a caliper width equal to 1.05

(0.2 of the standard deviation of the logit of the propensity score) (12). In the survival analysis, patients were propensity matched based on the following variables: facility volume, tumor size, single *vs.* multiple tumors, invasion into a major vessel, T stage, age, gender, year of diagnosis, race, insurance status, academic *vs.* community facility, location, Charlson-Deyo comorbidity score, income, education, level of fibrosis, creatinine, bilirubin, and INR. Kaplan-Meier curves for OS were generated for patients who were treated at a few *vs.* multi-modality facility.

Finally, sensitivity analyses were conducted changing the cut point from four to two, three, five, and six. Additional sensitivity analyses were conducted by removing the patients who had received rare treatment modalities. These modalities were defined as treatments which less than ten percent of the population received. These treatments were SBRT (0.7%), radioembolization (1.6%), transplant (7.0%), and ablation (7.3%). To determine this effect on different stages, stratified analyses based on stage were conducted. All analyses were conducted in Stata, version 12 (College Station, Texas, USA).

Results

Baseline characteristics stratified by few vs. multi-modality facility

Baseline characteristics are summarized in *Table 1*. There was a total of 1,229 facilities. Of these, 829 (67.5%) used four or fewer treatment modalities and 400 (32.5%) used five or more treatment modalities. The median follow-up time for the entire population was 10.1 months (IQR: 2.6–28.2 months). There were 82,034 (72.9%) deaths in the population. In brief, there were 28,290 (22.2%) patients who were treated at few-modality facilities and 99,191 (77.8%) patients treated at multi-modality facilities. A much larger percentage of patients in the multi-modality facility group (67.2%) were treated at academic/research centers compared to 18.4% of patients in the few-modality facility group. Additionally, the median patient volume in the multi-modality facility group was 62.1 and 5.5 in the few-modality group. There was correlation (r=0.66, P<0.001) between facility volume and facility modality number.

Table 2 shows the distribution of modality type by facility modality number. Single agent chemotherapy is the most commonly used treatment modality in the initial management of HCC patients and is the primary modality used in few-modality facilities. The next most common modalities used in the initial management of patients are multi-agent chemotherapy, surgical resection, and ablation. SBRT, transplant, and radioembolization are more rarely used in few-modality facilities. As facilities use more modalities, SBRT and transplant remain the least commonly used modalities.

Association between facility modality number and OS

The Kaplan-Meier curve for *Figure 1* illustrates the unadjusted relationship between facility modality number and OS (log-rank P<0.001). Cox proportional hazards models adjusting for age, sex, race, insurance status, household income of patient's zip code, education level of patient's zip code, Charlson-Deyo comorbidity score, year of diagnosis, type of facility, geographical location of the facility, facility volume, clinical T stage, clinical N stage, tumor size, multiple *vs.* single tumor, presence of fibrosis, creatinine, bilirubin, and INR can be seen in *Table 3*. Propensity matched analyses found similar results. The Kaplan-Meier curve (*Figure 2*) illustrates the propensity matched relationship between facility modality number and OS (log-rank P=0.032). In summary, increased facility modality usage was associated with a better OS [hazard ratio (HR) =0.60, 95% confidence interval (CI): 0.52–0.70, P<0.001] after adjusting for the above variables, including facility volume, age, race, insurance status, income, Charlson-Deyo comorbidity score, facility location, T stage, N stage, tumor size, presence of fibrosis, bilirubin, and INR were also significant predictors of OS.

Sensitivity analyses were also performed. Varying the cut point from two to six showed that the adjusted HRs all remained significant [ranging from 0.36 (95% CI: 0.25–0.50, P<0.001) for a cut off of two to 0.89 (95% CI: 0.81–0.99, P=0.026) for a cut off of six] (*Table 4*). Less frequently used treatments were multi-agent chemotherapy (9.5%), ablation (8.2%), transplant (7.8%), radioembolization (1.6%), and SBRT (0.7%). Excluding patients who received these treatments in their initial management showed that treatment at a multi-modality facility continued to provide a survival advantage (adjusted HR =0.66, 95% CI: 0.56–0.77, P<0.001).

To determine if the benefit of higher modality number persisted across all stages, we conducted stratified analyses based on stage. For patients with stage I and II, facility modality number remains a predictor of OS in adjusted analyses (stage I: HR =0.48, 95% CI: 0.38–0.60, P<0.001; stage II: HR =0.64, 95% CI: 0.48–0.85, P=0.002). Facility

Table 1 Patient baseline characteristics

Characteristic	Few-modality facility	Multi-modality facility	P value
Total patient number (%)	28,290 (22.2)	99,191 (77.8)	
Age, mean (SD), years	66.0 (12.1)	62.4 (11.0)	<0.001
Sex, No. (%)			0.201
Male	21,312 (75.3)	75,092 (75.7)	
Female	6,978 (24.7)	24,099 (24.3)	
Race, No. (%)			0.053
White	21,120 (75.2)	72,521 (74.4)	
Black	4,074 (14.5)	15,365 (15.8)	
Asian	2,423 (8.6)	7,465 (7.7)	
Other	468 (1.7)	2,156 (2.2)	
Insurance status, No. (%)			<0.001
Government	18,344 (67.5)	57,883 (59.5)	
Private	6,755 (24.9)	34,278 (35.2)	
Not insured	2,062 (7.6)	5,110 (5.3)	
Median household income of zip code, No. (%)			<0.001
<$38,000	6,359 (23.0)	22,826 (23.4)	
$38,000–$47,999	7,349 (26.6)	22,914 (23.5)	
$48,000–$62,999	7,030 (25.5)	25,567 (26.2)	
>$63,000	6,858 (24.9)	26,145 (26.8)	
Education level of zip code, No. (%)			<0.001
≥21% did not graduate high school	7,578 (27.4)	24,462 (25.1)	
13–20.9% did not graduate high school	8,034 (29.1)	26,753 (27.4)	
7–12.9% did not graduate high school	7,937 (28.7)	28,201 (28.9)	
<7% did not graduate high school	4,068 (14.7)	18,093 (18.6)	
Charlson-Deyo comorbidity score, No. (%)			<0.001
0	14,754 (52.2)	45,551 (45.9)	
1	6,977 (24.7)	27,308 (27.5)	
2	6,559 (23.2)	26,332 (26.6)	
Facility type, No. (%)			<0.001
Academic/research	5,134 (18.4)	65,571 (67.2)	
Comprehensive community	15,964 (57.1)	18,750 (19.2)	
Integrated network	700 (2.5)	12,450 (12.8)	
Community	6,169 (22.1)	878 (0.9)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Few-modality facility	Multi-modality facility	P value
Facility location, No. (%)			<0.001
Northeast	5,286 (18.9)	21,095 (21.6)	
South	5,504 (19.7)	18,814 (19.3)	
Central	10,465 (37.4)	37,672 (38.6)	
West	6,712 (24.0)	20,068 (20.5)	
Facility volume, median (IQR)	5.5 (3.3–9.9)	62.1 (23.5–95.2)	<0.001
Tumor stage, No. (%)			<0.001
1	6,198 (31.1)	31,576 (40.3)	
2	3,221 (16.2)	19,311 (24.6)	
3	6,395 (32.1)	19,768 (25.2)	
4	4,088 (20.5)	7,710 (9.8)	
Presence of severe fibrosis/cirrhosis, No. (%)	1,937 (65.6)	17,606 (77.9)	<0.001
Creatinine, median (IQR), mg/dL	1.1 (0.8–2)	1 (0.8–1.5)	<0.001
Bilirubin, median (IQR), mg/dL	1.4 (0.7–3)	1.2 (0.7–2.3)	<0.001
INR, median (IQR)	1.2 (1.1–1.4)	1.2 (1.1–1.4)	<0.001

SD, standard deviation; INR, international normalized ratio; IQR, interquartile range.

Table 2 Distribution of modalities by facility modality number

Modality	Facility modality number							Overall
	1	2	3	4	5	6	7	
Single-agent chemotherapy (%)	80.4	94.2	98.7	99.6	100	100	100	94.3
Multi-agent chemotherapy (%)	8.8	42.8	68.8	90.5	98.5	98.4	100	71.8
Surgical resection (%)	8.8	47.6	75.8	95.7	99.5	100	100	75.4
Ablation (%)	1.0	12.5	42.9	83.0	98.5	100	100	61.4
SBRT (%)	0.0	1.0	5.6	10.7	27.0	52.5	100	19.4
Transplant (%)	0.0	0.0	1.3	5.5	24.5	59.8	100	17.7
Radioembolization (%)	1.0	1.9	6.9	15.0	52.0	89.3	100	28.5

modality number is not a significant predictor of OS for stage III (HR =0.83, 95% CI: 0.58–1.18, P=0.29) or stage IVa (HR =0.65, 95% CI: 0.34–1.27, P=0.21).

Discussion

To our knowledge, this is the first study to show that facilities that provide more treatment modalities have better OS after controlling for facility treatment volume. Several studies have shown that facilities with more treatment volume have better OS (6-10), but none have examined this relationship in HCC.

A possible reason for the effect seen is that patients being treated at centers with multi-modality therapy have access to the additional modalities once their disease progresses after initial management. This is consistent with the available data demonstrating that addition of locoregional therapies (13,14) or sorafenib (15,16) can improve survival

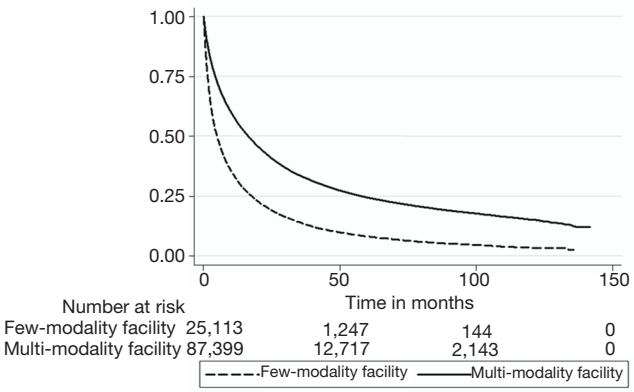

Figure 1 Unadjusted OS Kaplan-Meier curves. OS, overall survival.

when compared to best supportive care.

Another possibility is that increasing number of modalities maybe a proxy for quality of care delivered at these facilities (17). We tried to control for this in these analyses by adding facility volume and facility type to the model. Although we may not be able to completely control for this as there was correlation between facility volume and facility modality number, it is interesting to note that the HR for facility volume was 1.00 and facility type was not a significant predictor for OS. This shows that after accounting for facility modality number, facility volume and facility type are not significant predictors of OS. It is possible that facility modality number is a better proxy for the quality of care than facility volume (17). It is possible that facilities with more modalities available also have more collaborative tumor boards where patients are able to receive treatments that are better suited for their particular situation.

A possible confounder between facility modality number and OS is liver function. It is unclear which group has worse liver function. The multi-modality group had a higher percentage of patients with severe fibrosis/cirrhosis (78.0% *vs.* 66.2%). The few-modality group had slightly worse bilirubin (median of 1.4 *vs.* 1.3, P<0.001). While there was a statistically significant difference between the groups in bilirubin, INR and creatinine, the medians and IQRs are similar and there may be no clinically significant difference between the two groups. However, the few-modality group had a larger percentage of patients with stage III and IVa disease. To account for this, we ran the adjusted analysis stratifying patients by stage which showed that higher facility modality number was a predictor of OS for stage I and stage II patients but not stage III or IV. This is reassuring that the finding of improved OS remained true for patients with curable disease. It is possible that facility modality number is more important for curable disease because the optimal treatment has the potential to cure the disease and therefore would have a greater effect on

Table 3 Adjusted Cox model

Characteristic	HR (95% CI)	P value
Facility modality number	0.60 (0.52–0.70)	<0.001
Age	1.01 (1.01–1.01)	<0.001
Sex	0.94 (0.86–1.02)	0.140
Race	1.20 (1.10–1.31)	<0.001
Insurance status	1.37 (1.26–1.49)	<0.001
Income	0.90 (0.82–0.98)	0.018
Education	0.96 (0.88–1.04)	0.301
Charlson-Deyo score	1.12 (1.04–1.21)	0.004
Year of diagnosis	1.00 (0.97–1.03)	0.952
Facility type	0.96 (0.88–1.05)	0.336
Facility location		
Northeast	Reference	
South	1.23 (1.06–1.42)	0.007
Central	1.09 (0.97–1.21)	0.140
West	1.06 (0.94–1.18)	0.336
Facility volume	1.00 (1.00–1.00)	<0.001
T stage		
1	Reference	
2	1.31 (1.13–1.52)	0.001
3	2.57 (2.15–3.08)	<0.001
4	0.99 (0.32–3.10)	0.985
N stage	2.01 (1.66–2.44)	<0.001
Tumor size	0.74 (0.72–0.76)	<0.001
Multiple tumors	1.11 (0.96–1.29)	0.167
Fibrosis	1.26 (1.13–1.41)	<0.001
Creatinine	1.01 (1.00–1.01)	0.158
Bilirubin	1.02 (1.02–1.03)	<0.001
INR	1.02 (1.01–1.02)	<0.001

HR, hazard ratio; CI, confidence interval; INR, international normalized ratio.

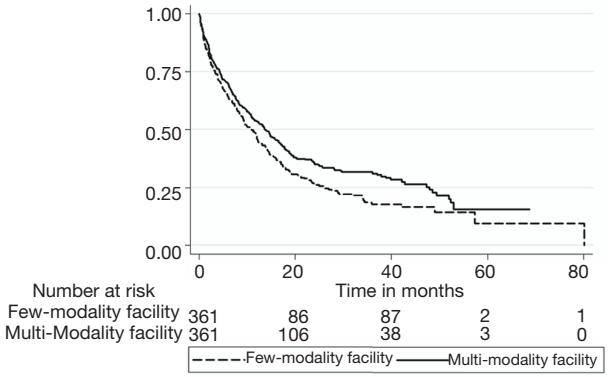

Figure 2 Propensity matched OS Kaplan-Meier curves. OS, overall survival.

Table 4 Changing cut point sensitivity analysis

Cut point	HR	95% CI	P value
2	0.36	0.25–0.50	<0.001
3	0.45	0.35–0.57	<0.001
4	0.60	0.52–0.70	<0.001
5	0.75	0.66–0.85	<0.001
6	0.89	0.81–0.99	0.026

All analyses adjusted for age, sex, race, insurance status, household income of patient's zip code, education level of patient's zip code, Charlson-Deyo comorbidity score, year of diagnosis, type of facility, geographical location of the facility, facility volume, clinical T stage, clinical N stage, tumor size, multiple *vs.* single tumor, presence of fibrosis, creatinine, bilirubin, and INR. HR, hazard ratio; CI, confidence interval; INR, international normalized ratio.

increasing OS.

This study has several limitations. Selection bias cannot be completely ruled out where patients presenting at multi-modality centers maybe different than patients presenting to fewer modality centers. We tried to control for this in our multivariate analysis and by running an additional analysis where patients treated by excluding patients who were treated by the less frequently used treatment modalities. Another limitation of this analysis is that the data is its retrospective and only cases treated at COC accredited programs were reported. The NCDB did not have information related to cancer specific mortality and the Charlson-Deyo comorbidity score was the only available measure of comorbidity. The NCDB also does not provide separate data for TACE, which is why it could not be evaluated as a separate modality. It is possible that some of those patients were included in the radioembolization category or in the single-agent chemotherapy category. Similarly, it is impossible to know what proportion of the patients treated with single-agent chemotherapy were treated with sorafenib.

Conclusions

This study is the first to report to our knowledge that multi-modality facilities have better OS than facilities that use fewer modalities in patients with HCC. This remained true after controlling for facility volume and in sensitivity analysis after removing patients who received the less commonly used treatment modalities.

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Footnote

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

Ethical Statement: This study only used a de-identified national database and was exempt from institutional review board (IRB) review.

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