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Long-term outcomes in patients undergoing resection, ablation, and trans-arterial chemoembolization of hepatocellular carcinoma in the United States: a national cancer database analysis

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Abstract: In the United States, hepatocellular carcinoma (HCC) incidence rates were approximately three times higher in over 30 years. To investigate the long-term outcomes of patients who underwent resection, ablation, and trans-arterial chemoembolization (TACE) of HCC, we analyzed the National Cancer Data Base (NCDB), which is a nationwide oncology outcomes database and covers approximately 70% of new cancer cases in the United States. A total of 56,512 patients with HCC in the NCDB during 2004-2013 were retrospectively analyzed. Results showed that liver resection (48.5%) and ablation (57.0%) were performed more frequently than TACE (31.5%) in patients with AJCC stage I HCC. The 5-year overall survival (OS) was significantly higher in patients undergoing resection (52.4%) than in patients undergoing ablation (40.5%; $P < 0.001$) and patients undergoing TACE (36.1%; $P < 0.001$). For patients with AJCC stage I, the 5-year OS of patients undergoing resection (51.6%; $P < 0.001$) and patients undergoing ablation (51.1%, $P = 0.005$) remains significantly better than patients undergoing TACE (40.0%). However, the 5-year OS did not differ significantly between patients undergoing resection and patients undergoing ablation ($P = 0.486$). Additionally, the findings of our study confirm that the sub-stratification of T1 category by HCC diameter in the AJCC staging eighth edition (*i.e.*, T1a, HCC diameter ≤ 2 cm and T1b, HCC diameter > 2 cm) is valid, with a 5-year OS of 54.1% and 50.4%, respectively ($P = 0.031$).

Keywords: Hepatocellular carcinoma, liver resection, ablation, trans-arterial chemoembolization, long-term outcome, United States of America

Introduction

Liver cancer is predicted to be the sixth most common cancer and the fourth leading cause of cancer-related death in 2018, worldwide (*1*). For males, rates of incidence and mortality are approximately 2-3 times higher than for females, with liver cancer being the fifth most common cancer and the second leading cause of death (*1*). Hepatocellular carcinoma (HCC) is the most common primary liver cancer and accounts for 75-85% of diagnoses, followed by intrahepatic cholangiocarcinoma (10-15%), and other rare liver histologies. The major epidemiological risks of HCC are chronic viral infections with hepatitis B virus and/or hepatitis C, alcoholic hepatitis, and non-alcoholic steatohepatitis (*1,2*).

In the United States, HCC incidence is increasing, and age-adjusted incidence rates of HCC were approximately three times higher in 2005 than in 1975 (*3*). HCC has several treatment options including liver resection, transplantation, ablation, trans-arterial chemoembolization (TACE), and systemic therapy. Herein, we sought to evaluate long-term outcomes of patients who underwent resection, ablation, and TACE for HCC using the National Cancer Database (NCDB).

Methods

Data source

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB is a nationwide oncology outcomes database, which covers approximately 70% of new cancer cases in the USA and has more than 34 million patient records (*4,5*). This analysis of a publically available deidentified data set was exempt from the institutional review board.

Study cohort and variables analyzed

From NCDB during 2004-2013, HCC patients were

identified using primary site code C22 and histology code 8170. According to the primary surgery recode, patients with the code 20-90 were defined as those who underwent resection, and patients with the code 11-17 were defined as those who underwent ablation. A variable, RX_SUMM_CHEMO in the NCDB, was used for defined patients who underwent TACE. Patients who underwent 'single agent' (code 2) or 'multi-agent' (code 3) of chemotherapy variables as the first treatment were defined as those who underwent TACE. Age, sex, Charlson-Deyo score,7 years of diagnosis, largest diameter of HCC, the American Joint Committee on Cancer (AJCC) stage (6th and 7th editions), and survival were assessed.

AJCC Staging Manual, 6th, 7th, and 8th Editions

Recently, the AJCC has released the new staging manual, 8th edition (*6*) (Table 1), which has several changes to the T category from the 7th edition (*7*) (Table 2). The newest 8th edition staging system divided T1 category (solitary tumor in the seventh edition) into T1a category (solitary tumor ≤ 2 cm) and T1b category (solitary tumors > 2 cm without vascular invasion). The AJCC stage of our study is based on the 7th edition for patients treated from 2010-2013 and based on the 6th edition (*8*)

Table 1. AJCC staging Manual, 8th edition for HCC*

Primary tumor (T)				Regional lymph nodes (N)		Distant metastases (M)	
T1a	Solitary tumor ≤ 2 cm with/without vascular invasion			Nx	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T1b	Solitary tumor > 2 cm without vascular invasion			N0	No regional lymph node metastasis	M1	Distant metastasis
T2	Solitary tumor >2 cm with vascular invasion or multifocal tumors, none >5 cm			N1	Regional lymph node metastasis		
T3	Multifocal tumors at least one of which is >5 cm						
T4	Single tumor or multifocal tumors of any size involving a major branch of the portal vein or hepatic vein or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum						
Stage							
IA	T1a	N0	M0				
IB	T1b	N0	M0				
II	T2	N0	M0				
IIIA	T3	N0	M0				
IIIB	T4	N0	M0				
IVA	Any T	N1	M0				
IVB	Any T	Any N	M1				

HCC, hepatocellular carcinoma. *According to the *AJCC Cancer Stating Manual*, 8th editions (*6*).

Table 2. AJCC staging Manual, 7th edition for HCC*

Primary tumor (T)				Regional lymph nodes (N)		Distant metastases (M)	
T1	Solitary tumor without vascular invasion			Nx	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T2	Solitary tumor with vascular invasion, or multifocal tumors, none >5 cm			N0	No regional lymph node metastasis	M1	Distant metastasis
T3a	Multifocal tumors at least one of which is >5 cm			N1	Regional lymph node metastasis		
T3b	Single tumor or multifocal tumors of any size involving a major branch of the portal vein or hepatic vein						
T4	Tumor with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum						
Stage							
IA	T1	N0	M0				
IB	T2	N0	M0				
II	T3a	N0	M0				
IIIA	T3b	N0	M0				
IIIB	T4	N0	M0				
IVA	Any T	N1	M0				
IVB	Any T	Any N	M1				

HCC, hepatocellular carcinoma. *According to the *AJCC Cancer Stating Manual*, 7th editions (*7*).

(Table 3) for patients treated from 2004-2009.

Statistical analysis

Categorical variables are expressed in numerical figures and percentages and were compared among groups using Fisher's exact test or χ^2 test, as appropriate. Continuous variables were expressed as median values with the interquartile range (IQR) and were compared using the Kruskal-Wallis test. Overall survival (OS) was estimated using the Kaplan-Meier method. $P \leq 0.05$ was considered to indicate statistical significance, and all tests were two-sided. Statistical analysis was conducted with SAS (SAS Institute, Cary, NC).

Results

Study population

A total of 56,512 patients with HCC who underwent resection, ablation, and TACE was found in the NCDB from 2004-2013. Demographic characteristics are shown in Table 4. Median (IQR) age was 61 (55-69) years, and female sex was 24.4% of the cohort. There

Table 3. AJCC staging Manual, 6th edition for liver (including intrahepatic bile duct cancer)*

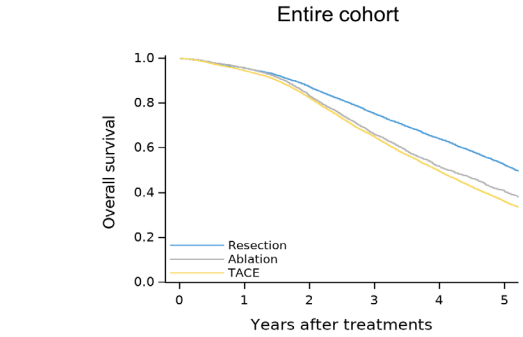
Primary tumor (T)				Regional lymph nodes (N)		Distant metastases (M)	
TX	Primary tumor cannot be assessed			Nx	Regional lymph nodes cannot be assessed	MX	Distant metastasis cannot be assessed
T0	No evidence of primary tumor			N0	No regional lymph node metastasis	M0	No distant metastasis
T1	Solitary tumor without vascular invasion			N1	Regional lymph node metastasis	M1	Distant metastasis
T2	Solitary tumor with vascular invasion, or multiple tumors none more than 5 cm						
T3	Multiple tumors more than 5 cm or tumor involving a major branch of the porta or hepatic vein(s)						
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum						
Stage							
I	T1	N0	M0				
II	T2	N0	M0				
IIIA	T3	N0	M0				
IIIB	T4	N0	M0				
IIC	Any T	N1	M0				
IV	Any T	Any N	M1				

*According to the *AJCC Cancer Stating Manual*, 6th editions (*8*).

Table 4. Demographic characteristics by treatments

Characteristic	All	Resection	Ablation	TACE	*P*
Number of patients	56,512	14,663	6,323	35,526	
Age, median (IQR), yr	61 (55–69)	61 (54-69)	62 (56-71)	61 (55-69)	< 0.001
Sex, n (%)					< 0.001
Male	42,700 (75.6)	10,732 (73.2)	4,611 (72.9)	27,357 (77.0)	
Female	13,812 (24.4)	3,931 (26.8)	1,712 (27.1)	8,169 (23.0)	
Charlson-Deyo Score (*9*)					< 0.001
0	26,148 (46.3)	6,710 (45.8)	2,733 (43.2)	16,705 (47.0)	
1	16,176 (28.6)	4,326 (29.5)	1,810 (28.6)	10,040 (28.3)	
2	14,188 (25.1)	3,627 (24.7)	1,780 (28.2)	8,781 (24.7)	
Year of diagnosis					< 0.001
2004-2006	9,891 (17.5)	3,867 (26.4)	1,416 (22.4)	4,608 (13.0)	
2006-2009	16,030 (28.4)	4,582 (31.3)	1,646 (26.0)	9,802 (27.6)	
2009-2013	30,591 (54.1)	6,214 (42.4)	3,261 (51.6)	21,116 (59.4)	
Largest diameter of HCC, cm	4.0 (2.5-7.0)	3.7 (2.2-6.7)	2.7 (2.0-3.8)	4.5 (2.8-7.5)	
AJCC stage,* *n* (%)					< 0.001
Stage I	6,219 (43.6)	4,471 (48.5)	354 (57.0)	1,394 (31.5)	
Stage II	4,714 (33.1)	3,015 (32.7)	201 (32.4)	1,498 (33.9)	
Stage III	2,213 (15.5)	1,502 (16.3)	42 (6.8)	669 (15.1)	
Stage IV	1,111 (7.8)	225 (2.4)	24 (3.9)	862 (19.5)	
Unavailable	42,255	5,450	5,702	31,103	

TACE, trans-arterial chemoembolization; IQR, interquartile range; HCC, hepatocellular carcinoma. *According to the *AJCC Cancer Stating Manual*, sixth and seventh editions (*7,8*).



Median survival (95% CI), yr	
Resection	5.2 (5.1–5.3)
Ablation	4.2 (4.0–4.3)
TACE	4.0 (3.9–4.0)

Patients at risk						
Resection	14663	11621	9185	6965	5315	3922
Ablation	6323	4790	3185	1929	1177	748
TACE	35526	20402	11996	7150	4469	2830

5-year OS (95% CI)	HR (95% CI)	*P* value
52.4% (51.4%–53.5%)	0.68 (0.66–0.70)	< 0.001
40.5% (38.6%–42.4%)	0.87 (0.83–0.91)	< 0.001
36.1% (35.1%–37.0%)	1 (reference)	–
Resection vs. Ablation	0.77 (0.74–0.81)	< 0.001

Figure 1. OS of the entire cohort. OS, overall survival.

were 14,663 patients (25.9%) who underwent resection (resection group), 6,323 (11.2%) who underwent ablation (ablation group), and 35,526 (62.9%) who underwent TACE (TACE group). Demographic characteristics were significantly different between the three groups (Table 4). Median largest diameter of HCC was significantly different between the three groups: resection group, 3.7 (IQR, 2.2-6.7) *vs*. ablation group, 2.7 (IQR, 2.0-3.8) *vs*. 4.5 (2.8-7.5), $P < 0.001$. Liver resection (48.5%) and ablation (57.0%) were performed more frequently than TACE (31.5%) in patients with AJCC stage I HCC.

OS of the entire cohort

For the entire cohort, the 5-year OS was significantly better in the resection group (52.4%) than the ablation group (40.5%; $P < 0.001$) and TACE (36.1%; $P < 0.001$) group and higher in the ablation group than the TACE group ($P < 0.001$) (Figure 1).

OS of patients with AJCC stage I

For the cohort including patients with AJCC stage I, the 5-year OS of the resection group (51.6%; $P < 0.001$) and ablation group (51.1%, $P = 0.005$) remains significantly better than the TACE group (40.0%) (Figure 2A). However, the 5-year OS was not significantly different between the resection and ablation groups ($P = 0.486$). OS curve of the resection group was further stratified by HCC diameter. Within the resection group, patients with HCC diameter ≤ 2 cm were significantly associated with better survival than patients with HCC diameter > 2 cm, with 5-year OS, 54.1% *vs*. 50.4%, $P = 0.031$ (Figure 2B).

Discussion

This large retrospective cohort study from a large nationally representative dataset, showed that resection and ablation were performed more frequently in patients with lower AJCC stage. When local therapy was chosen, TACE was more often selected for patients with higher AJCC stage. The 5-year OS survival of patients with HCC is 52.4% after resection, 40.5% after ablation, and 36.1% after TACE.

A recent report based on the Surveillance, Epidemiology, and End Results Program demonstrated that the 5-year relative survival rates for liver cancer in the United States between 2008-2014, was 31% for localized disease and 2% for distant metastases (*10*). In the current NCDB study, patients undergoing resection were associated with better survival, more than 50% at 5 years, although confounders among the three groups (resection, ablation, and TACE) were not adjusted. Additionally, the findings of our study confirm that the sub-stratification of T1 tumors by diameter in the AJCC staging 8th edition (*i.e*., T1a, HCC diameter ≤ 2 cm *vs*. T1b, HCC diameter > 2 cm) is valid. Similar to our results, a recent meta-analysis showed that ablation was associated with worse overall survival at 5 years than resection for patients with a single HCC of any size and up to 3 tumors all less than 3 cm (hazard ratio, 1.91; $P = 0.001$) (*11*). Another meta-analysis showed that resection had significantly better OS than TACE for patients with multiple tumors (hazard ratio, 0.65; $P < 0.001$) (*12*).

Liver transplantation has the advantage of removing the diseased liver together with HCC and it is regarded as an ideal treatment option for HCC patients associated with chronic liver diseases if donors are available. Liver transplantation is generally recommended in patients within the Milan criteria (single lesion ≤ 5 cm or up to three separate lesions, none larger than 3 cm) (*13*). Studies reported that the 5-year OS is similar between patents who have HCC within the Milan criteria and patients who had other indications. As a result, the Milan criteria is included in the Barcelona Clinic Liver

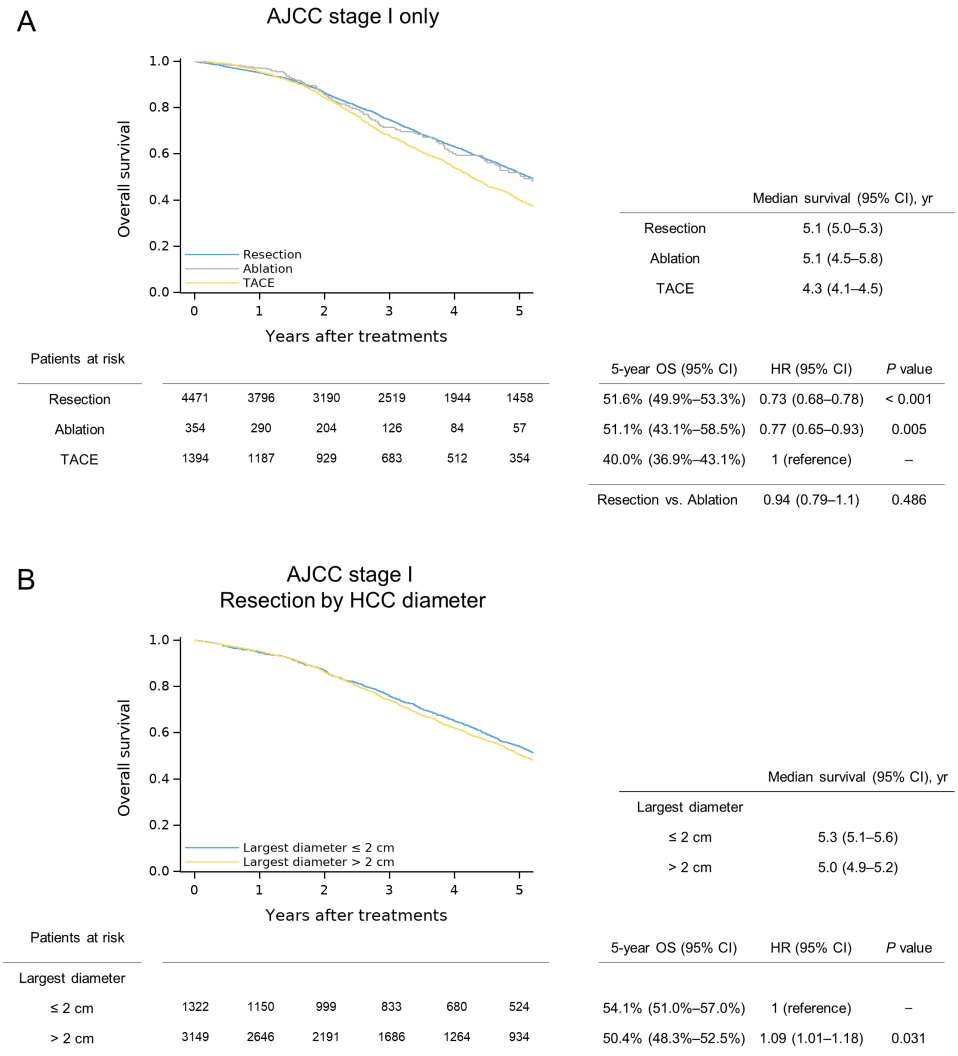


Figure 2. OS of patients with AJCC stage I. (A) By resection, ablation, and TACE; **(B)** Resection by HCC diameter ≤ 2 cm *vs.* > 2 cm. OS, overall survival; TACE, trans-arterial chemoembolization; HCC, hepatocellular carcinoma.

Cancer system and the American Association for the Study of Liver Diseases guideline. The 5-year survival of patients who underwent liver transplantation within Milan criteria is approximately 65-75% (*14,15*). Many studies reported the expanded Milan criteria and showed that patients within their criteria had comparable survival to patients within the Milan criteria. The long-term outcomes in patients beyond the Milan criteria need to be compared not only with patients undergoing liver transplantation within the Milan criteria but also with patients undergoing liver resection. Additionally, donor shortage, cultural limitations on deceased donors, and organ allocation remain unresolved barriers for unlimited deceased-donor and living-donor liver transplantations.

Potential limitations of this study are the direct result of using a national dataset. There are inherent limitations on data granularity such as knowing the surgical quality and understanding the reasons patients were triaged to one treatment modality over another. However, this limitation is counterbalanced by the tremendous statistical power available in a national dataset that no institutional study can offer. Within these confines, this study provides a contemporary overview of current treatment practices for HCC and modern prognostic expectations by stage and treatment.

In conclusion, based on this NCDB study, demographic and clinicopathologic characteristics were different between patients who underwent resection, ablation, and TACE, likely reflecting patient selection. Survival was better in patients undergoing liver resection *vs*. ablation and TACE. Further evaluation is needed to compare long-term outcomes between patients undergoing resection and patients undergoing liver transplantation beyond Milan criteria.

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