Current Guidelines for Chemoembolization for Hepatocellular Carcinoma: Room for Improvement?

Jared A. White,[1] Stephen H. Gray,[1] Peng Li,[1] Heather N. Simpson,[1] Brendan M. McGuire,[1] Devin E. Eckhoff,[1] Ahmed Mohamed Kamel Abdel Aal,[1] Souheil Saddekni,[1] and Derek A. Dubay[2]

Transarterial chemoembolization (TACE) is the most common oncologic therapy used according to the American Association for the Study of Liver Diseases (AASLD) guidelines established in 2005, revised in 2011. The purpose of this study was to determine how AASLD criteria for the management of hepatocellular carcinoma (HCC) have impacted TACE practice in the community. Clinical, demographic, and cause of death information were collected for patients diagnosed with HCC in the 2012 linkage of the Surveillance, Epidemiology, and End Results Medicare database. Propensity score survival analysis was used to compare survival outcomes in patients whose HCC tumor characteristics were less than, met, or were beyond AASLD criteria. The proportion of patients with HCC receiving TACE who met the AASLD-recommended criteria increased after the 2005 guidelines were published. Up to 17% of patients treated with TACE had tumor characteristics less than the AASLD criteria and were not offered potentially curative therapies. Propensity score matching demonstrated the largest survival advantage in patients with HCC whose tumor characteristics met the AASLD criteria (hazard ratio, 0.42; 95% confidence interval, 0.38-0.47). A significant survival advantage was also observed in patients with HCC whose tumor characteristics exceeded the AASLD criteria. *Conclusion*: The AASLD criteria successfully identify a population of patients with HCC that maximally benefit from TACE therapy. However, patients with HCC with tumor characteristics beyond the AASLD criteria also appear to receive a significant survival advantage with TACE. Further studies are necessary to improve referral patterns and appropriate use of chemoembolization in the management of unresectable HCC. (*Hepatology Communications* 2017;1:338–346)

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy in the United States and worldwide and is the leading cause of death among patients with cirrhosis.[1] HCC is the third most common cause of cancer-related deaths worldwide, and the incidence of HCC in developed countries has almost doubled in the last 2 decades, largely as a result of cirrhosis and the prevalence of chronic hepatitis.[2] With a 5-year survival less than 5%, HCC has the fastest growing death rate of any cancer in the United States, and survival has been shown to be worse among patients who do not receive any liver-specific therapy.[3]

Several staging systems have been validated to varying degrees for the diagnosis and management of HCC.[4] Currently, the Barcelona Clinic Liver Cancer (BCLC)

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AJCC, American Joint Committee on Cancer; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; ICD-9, International Classification of Diseases, Ninth Revision; SEER, Surveillance Epidemiology, and End Results; TACE, transarterial chemoembolization.

Received November 4, 2016; accepted April 12, 2017.
Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1046/suppinfo.

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep4.1046

Potential conflict of interest: Nothing to report.

strategy has been endorsed by the American Association for the Study of Liver Diseases (AASLD) and is used to stratify patients according to outcome, simultaneously linking it with the appropriate treatment by stage of HCC at presentation.[1,5-7] Surgical resection, transplantation, and ablation are the only potential curative management strategies of early stage HCC, with a 5-year survival ranging from 60% to 70%. However, the majority of patients present with intermediate to advanced stages or with compromised liver function[8] and are only eligible for life-prolonging palliative treatments.[9-11] The most common palliative HCC treatment is transarterial chemoembolization (TACE).[12] Population-based data demonstrate that more patients with HCC are treated with TACE than all other HCC therapies combined.[12] TACE is also the most common bridging therapy offered to >70% of wait-listed patients with HCC for liver transplants in the United States.[13]

Despite being the most common oncologic therapy for HCC in the United States, most clinical data supporting the use of TACE come from single-center studies[7,13-17] and older, multicenter, randomized clinical trials,[18-23] limiting the ability to develop contemporary data-driven treatment recommendations. The AASLD practice guidelines currently state that "TACE is recommended as first line non-curative therapy for non-surgical patients," which includes "asymptomatic patients with multi-nodular tumors that have not invaded vessels nor disseminated outside the liver."[5]

It is unclear, however, how the AASLD criteria have impacted TACE use in the community. Furthermore, there is a gap in the literature assessing the survival advantage of patients with HCC who meet the AASLD criteria on a population-based level. The goal of this study was to measure 1) the proportion of TACE patients whose HCC tumor pattern met the AASLD criteria and 2) TACE survival outcomes in patients whose HCC tumor characteristics met the AASLD criteria and compared to the survival outcomes in patients whose HCC tumor characteristics were less than or exceeded the AASLD criteria for TACE.

Patients and Methods

DATA SOURCE

The 2012 linkage of Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database, which includes outcome data through December 31, 2011, was used in this study. Cancer patients' clinical, demographic characteristics, and cause of death information were collected from SEER cancer registries, while health care services were captured from Medicare claims from the time of a person's Medicare eligibility until death.[24] The SEER-Medicare linked database used in this study contained information on HCC cases diagnosed between 1991 and 2010 from 16 cancer registries in eight states (Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah) and nine metropolitan areas (Atlanta, Greater Georgia, Greater California, Detroit, Los Angeles, San Francisco/Oakland, San Jose-Monterey, Seattle-Puget Sound, and Rural Georgia), accounting for about 25% of the Medicare-insured population in the United States. Socioeconomic information based on geographic location from the U.S. Census Bureau is also included in this database. The diagnosis and procedure codes and the dates of each diagnosis and procedure from 1991 to 2011 for those patients with HCC were included in the Medicare claims. These data include inpatient and outpatient procedures, physician-generated and laboratory-generated claims, home health, and hospice claims.[25]

ARTICLE INFORMATION:

From the [1]University of Alabama at Birmingham, Birmingham, AL; [2]Medical University of South Carolina, Charleston, SC.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Jared A. White, M.D.
University of Alabama at Birmingham
722 Lyons-Harrison Research Building
1720 2nd Ave South
Birmingham, AL 35294
Tel.: + 1-205-975-0317
E-mail: jaredwhite@uabmc.edu

STUDY COHORT

A total of 43,594 patients with HCC were identified from the SEER cancer registries. Patients were excluded from this study based on the following exclusion criteria: 1) being diagnosed with an intrahepatic bile duct carcinoma only, 2) the diagnosis date before 1991, 3) the diagnosis date being missing, and 4) unspecified cancer characteristics. A total of 32,023 patients with HCC diagnosed between 1991 and 2010 met study criteria and were included. In the data analyses, either the total study cohort or subsamples from the total cohort were used depending on the study objectives. This study was approved by the Institutional Review Board of the University of Alabama at Birmingham.

OUTCOMES OF INTEREST

Sociodemographic and Tumor Characteristics

The sociodemographic characteristics include age at diagnosis, sex, ethnicity, functional status, risk factors, and median household incomes. The median household income was generated from Census 2000 data (included in the SEER 2012 data set). HCC risk factors, including hepatitis B virus, hepatitis C virus, alcoholism, diabetes and obesity, rare genetic diseases associated with HCC, and the presence of cirrhosis, were identified using the International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes (Supporting Table S1).[24] The nonliver comorbidities were quantified by the Charlson comorbidity index with Klabunde modification,[26] which was calculated from hospital and physician claims in the 12 months before the HCC diagnosis. Specific tumor characteristics include tumor size (maximal diameter of the largest tumor), tumor number, intrahepatic location versus extrahepatic extension, presence of metastasis, presence of vascular invasion, and American Joint Committee on Cancer (AJCC) HCC stage.

Hospital Characteristics

The hospital information was captured from the Hospital File included in the SEER-Medicare database. The size of the hospital was defined according to the American Hospital Association[27] as follows: small (<100 beds), medium (100 to 400 beds), and large (>400 beds).

Treatment Identification

HCC-related treatments, such as TACE, surgical resection, ablation, liver transplantation, and radiotherapy, were identified using the ICD-9 procedure codes and Healthcare Common Procedure Coding System codes (Supporting Table S2). Patients with Nexavar treatment after 2007 were identified from the Medicare Part D 2007-2010 data set by using the brand name "Nexavar," generic name "Sorafenib Tosylate," or the National Drug Code numbers (50419048858 and 00026848858). For patients who received multiple treatments, the initial treatment and the order of successive treatments were identified using the Medicare claim dates. In the survival analysis, patients with any identified oncologic treatment other than TACE were excluded so that TACE (including multiple TACEs) was the only treatment effect evaluated.

AASLD Criteria

Patients were classified as meeting the AASLD criteria *for TACE* if meeting all of the following: 1) no cancer-related curative surgical procedures performed, 2) unifocal HCC with tumor size greater than 3 cm or multifocal HCC, 3) no vascular invasion, and 4) no extrahepatic disease. Based on these HCC tumor characteristics, patients were categorized into three groups: less than AASLD criteria (single tumor less than 3 cm without vascular invasion or extrahepatic disease), meeting AASLD criteria, or beyond AASLD criteria (presence of vascular invasion or extrahepatic disease).

STATISTICAL ANALYSIS

Descriptive statistics were summarized as proportions for categorical variables. Multivariate logistical regression was used to identify the factors associated with TACE use. Survival was calculated as the time from diagnosis to death from any cause. Patients who were still alive were censored on December 31, 2011, the date of last follow-up in Medicare claims. The overall survival was estimated by the Kaplan-Meier method, and group comparisons were performed using the log-rank test. The primary outcome of interest was survival from the time of HCC diagnosis for patients who met or did not meet the AASLD criteria. To address the imbalance of covariates in the survival outcome analysis, propensity score matching was performed. In the propensity score analysis, patients receiving only TACE were selected as cases and patients without any HCC-related treatments were

selected as controls. The propensity score for each patient's likelihood of receiving TACE was calculated from a logistic regression with sociodemographic and tumor characteristics as covariates. Based on the propensity score, a 1:1 case-control match without replacement was performed using a greedy algorithm.[28] The survival outcomes of cases and controls were estimated by the Kaplan-Meier curves, and group comparisons performed by an F test in a Cox proportional hazards model stratified for the matched pairs. There were no significant differences in the balance of covariates between TACE cases and controls (Supporting Tables S3-S6). All data analyses were performed using SAS 9.4 (Cary, NC).

Results

PATIENT DEMOGRAPHICS

Patient, tumor, and treating hospital characteristics are summarized in Table 1. Of the 32,023 patients with HCC identified within the SEER-Medicare linked data set, 6,421 (20.1%) were treated with TACE. The typical Medicare patient was a Caucasian male in his 70s with nonalcoholic steatohepatitis cirrhosis as the etiology of liver disease. The majority of patients with HCC were located in the West region (58.4%) and treated in medium to large hospitals (91%). The unadjusted proportion of TACE use has slowly increased from 8.2% of Medicare beneficiaries in 1991 to a peak of 21.2% in 2010 (Supporting Fig. S1).

PREDICTORS OF TACE USE

Characteristics predictive of receiving TACE are summarized in Table 2. Younger age was associated with TACE use. Compared to Caucasians, Asians were more likely to receive TACE, whereas Blacks were less likely to receive TACE. Hepatitis B, hepatitis C, diabetes/ obesity, rare genetic diseases, and cirrhosis were all associated with TACE use. Increasing socioeconomic status was also predictive of receiving TACE. The following tumor characteristics were associated with receiving TACE: multifocal disease, vascular invasion, and larger tumors. Patients with HCC with AJCC stage I and II disease were more likely to receive TACE. The likelihood of receiving TACE was less during the 2001-2010 era compared to the 1991-2000 era on multivariable analysis.

TABLE 1. DEMOGRAPHICS AND TUMOR CHARACTERISTICS OF PATIENTS WITH HCC IN THE SEER-MEDICARE LINKED DATABASE 1991-2010

Characteristics	Mean (SD) or Frequency (%)
N	32,023
Age	72.9 (10.6)
Male	21,508 (67.2%)
Ethnicity	
White	21,210 (66.2%)
Black	3,184 (9.9%)
Hispanic	1,567 (4.9%)
Asian	3,531 (11.0%)
Other	2,531 (7.9%)
HCC risk factors*	
HCV	11,191 (35.0%)
HBV	3,488 (10.9%)
Alcohol	8,237 (25.7%)
Diabetes/Obesity	18,634 (58.2%)
Rare genetic diseases	1,299 (4.1%)
Cirrhosis present	17,466 (54.4%)
Charlson score	
0	11,033 (34.5%)
1	2,084 (6.5%)
2	3,287 (10.3%)
≥3	15,619 (48.8%)
Intrahepatic disease	20,226 (63.2%)
Unifocal	9,436 (46.7%)
Multifocal	8,393 (41.5%)
Unspecified	2,397 (11.9%)
Vascular invasion	
YES	3,896 (12.2%)
NO	14,389 (44.9%)
UNKNOWN	13,738 (42.9%)
Tumor size	
Mean size (cm)	6.3 (4.3)
Median size (cm)	5.1
<2 cm	1,456 (4.6%)
2-5 cm	8,082 (25.2%)
>5 cm	9,674 (30.2%)
UNKNOWN	12,806 (40.0%)
AJCC	
I	4,900 (15.3%)
II	2,417 (7.6%)
III	2,870 (9.0%)
IV	2,292 (7.2%)
UNKNOWN	19,539 (61.0%)
TACE	6,421 (20.0%)
Region	
Northeast	4,859 (15.2%)
South	4,980 (15.6%)
Midwest	3,490 (10.9%)
West	18,694 (58.4%)
Teaching hospital	16,664 (52.1%)
Hospital bed size	
Small	2,878 (9.0%)
Medium	16,249 (50.8%)
Large	12,882 (40.2%)

*Can have more than one HCC risk factors.

HOSPITAL CHARACTERISTICS AND TACE

Although the highest proportion of patients diagnosed with HCC in the SEER-Medicare cohort were located in the West (Table 1), the highest percentage use of TACE by region was observed in patients with HCC in the Northeast. Patients with HCC were more likely to receive TACE at larger hospitals (23.5%) when compared to medium (18.1%) and small hospitals (15.5%). Patients with HCC were also more likely to receive TACE in teaching hospitals (22.4%) compared to nonteaching hospitals (17.5%).

TABLE 2. MULTIVARIATE ANALYSIS OF THE ASSOCIATION BETWEEN PATIENTS' CHARACTERISTICS AND THE USE OF TACE

Predictors	Odds Ratio	95% Confidence Limits	
Age	0.995	0.992	0.998
Female	0.978	0.914	1.045
Race (reference White)			
Asian	1.158	1.052	1.275
Black	0.893	0.8	0.996
Hispanic	0.923	0.803	1.061
Other	0.928	0.83	1.037
HCC risk factors			
HCV	1.764	1.644	1.893
HBV	1.678	1.532	1.838
Alcohol	1.015	0.942	1.094
Diabetes/Obesity	1.486	1.389	1.591
Rare genetic diseases	1.444	1.261	1.654
Cirrhosis	2.246	2.074	2.432
Charlson score (reference 0)			
1	1.885	1.651	2.153
2	1.915	1.718	2.133
≥3	1.524	1.41	1.647
Median household income (reference Q1)			
Q 2	1.085	0.994	1.183
Q 3	1.109	1.016	1.211
Q 4	1.336	1.225	1.459
Intrahepatic disease	0.939	0.728	1.211
Multifocal	1.134	1.020	1.262
Vascular invasion	1.178	1.059	1.309
Tumor size (reference < 2 cm)			
2-5 cm	1.483	1.293	1.701
>5 cm	1.855	1.605	2.144
AJCC stage (reference stage I)			
Stage II	1.032	0.891	1.195
Stage III	0.779	0.67	0.906
Stage IV	0.325	0.271	0.389
Era 2001-2010 vs. 1991-2000	0.879	0.805	0.959

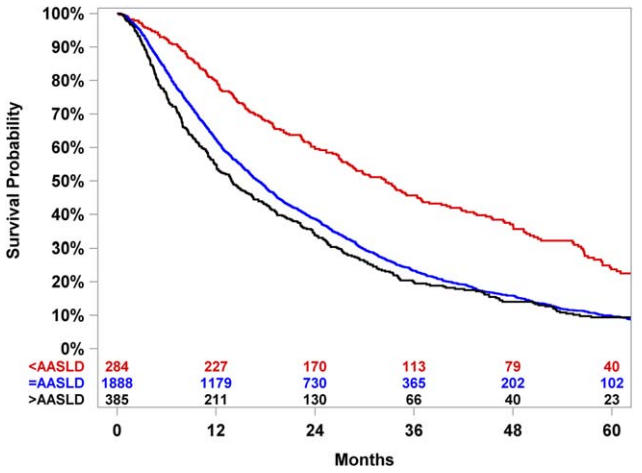

FIG. 1. Survival in patients with TACE-only treatment, stratified by AASLD criteria. Median survival was greatest in patients treated with TACE whose HCC tumors were less than AASLD criteria (32.6 months), followed by patients whose HCC tumors met the AASLD criteria (17.1 months), and lowest in patients whose HCC tumors exceeded the AASLD criteria (13.9 months; $P < 0.0001$).

SURVIVAL, TACE, AND AASLD CRITERIA

Unadjusted median survival was greatest in patients receiving TACE whose HCC tumor characteristics were less than AASLD (32.6 months) compared to those whose HCC tumor characteristics met AASLD criteria (17.1 months) and was least in patients whose HCC tumor characteristics exceeded the AASLD criteria (13.9 months; $P < 0.0001$; Fig. 1). There was a significant difference in the proportion of patients with HCC receiving TACE who met the AASLD-recommended criteria after the 2005 guidelines were published (37.2% era 2006-2009) compared to before 2005 (25.8% era 2001-2005; $P < 0.0001$; Supporting Fig. S2).

HCC Tumor Characteristics Less Than AASLD Criteria

In this cohort, 17% (2,503) of the patients with HCC had tumor characteristics that were less than AASLD criteria, among which 284 patients received only TACE and the others received no identified oncologic treatment. Propensity score analysis including 264 cases and 264 controls demonstrated significantly improved median survival in TACE-only treatment compared to no oncologic treatments in

patients whose HCC tumor characteristics were less than AASLD criteria (32.6 months TACE versus 18.9 months no TACE; hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.37-0.65; Fig. 2A).

HCC Tumor Characteristics Met the AASLD Criteria

In this cohort, 66% (9,757) of the patients with HCC had tumor characteristics that met the AASLD criteria, among which 1,888 patients received TACE-only treatment and the others received no identified oncologic treatment. Propensity score analysis, including 1,750 cases and 1,750 controls, also demonstrated significantly improved median survival in TACE-only treatment compared to no oncologic treatments in patients whose HCC tumor characteristics met the AASLD criteria (17.0 months, TACE versus 5.8 months, no TACE; HR, 0.42; 95% CI, 0.38-0.47; Fig. 2B).

HCC Tumor Characteristics Exceeded the AASLD Criteria

In this cohort, 17% (2,450) of the patients with HCC had tumor characteristics that exceeded AASLD criteria, among which 385 patients received TACE-only treatment and the others received no identified oncologic treatment. Propensity score analysis, including 362 cases and 362 controls, demonstrated significantly improved median survival in TACE-only treatment compared to no oncologic treatments in patients whose HCC tumor characteristics exceeded AASLD criteria (13.7 months, TACE versus 5.4 months, no TACE; HR, 0.52; 95% CI, 0.42-0.64; Fig. 2C) The most common HCC tumor factor that led to a beyond AASLD criteria designation was the presence of vascular invasion. A secondary survival analysis was performed with patients with HCC who had vascular invasion. The TACE-only treatment(s) significantly improved median survival compared to no oncologic treatment in those patients in a propensity score analysis (13.8 months TACE versus 4.2 months no TACE; HR, 0.42; 95% CI, 0.34-0.53; Fig. 3).

Discussion

Based on the best clinical evidence and expert consensus, the AASLD treatment recommendations for HCC were developed and published in 2005 in concert with promotion of the BCLC HCC staging classification (updated in 2011).[5,6] In this system, TACE

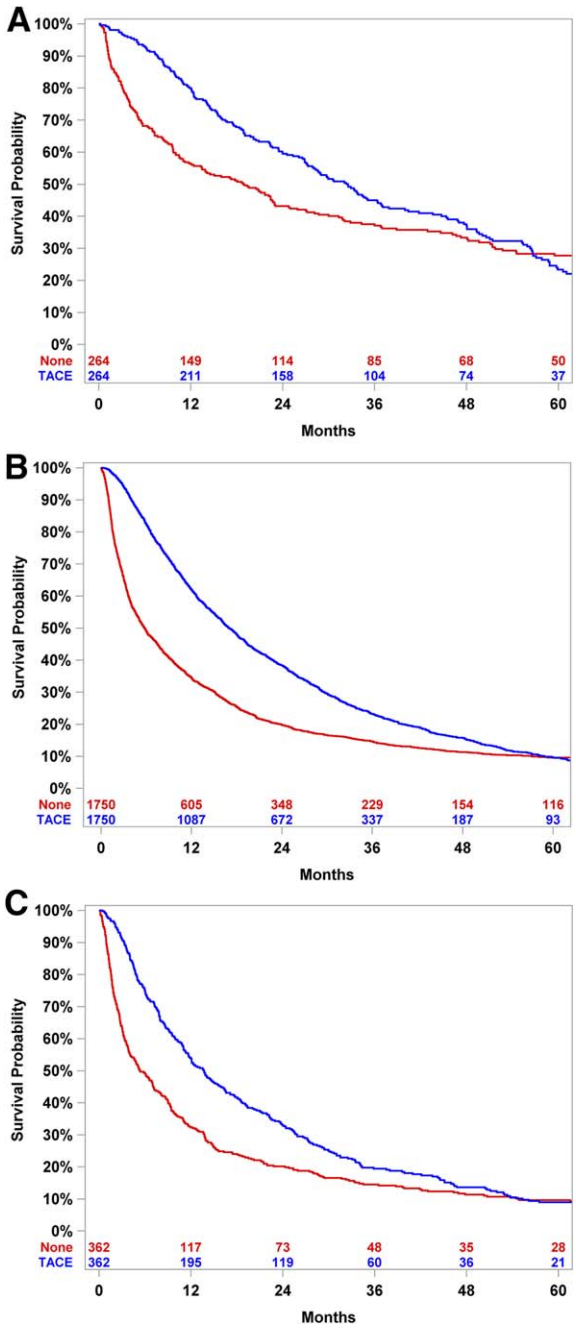

FIG. 2. Kaplan-Meier survival analysis by AASLD guidelines for HCC tumors less than (A), meeting (B) or exceeding (C) criteria for TACE therapy. (A) Survival of patients whose HCC tumors were less than the AASLD criteria. After propensity score matching, the median survival was 32.6 months in patients treated with TACE compared to 18.9 months in patients with no oncologic treatment ($P < 0.0001$). (B) Survival of patients whose HCC tumors met the AASLD criteria. After propensity score matching, the median survival was 17.0 months in patients treated with TACE compared to 5.8 months in patients with no oncologic treatment ($P < 0.0001$). (C) Survival of patients whose HCC tumors exceeded the AASLD criteria. After propensity score matching, the median survival was 13.7 months in patients treated with TACE compared to 5.4 months in patients with no oncologic treatment ($P < 0.0001$). Actual numbers are masked per the SEER-Medicare requirement for credential reasons.

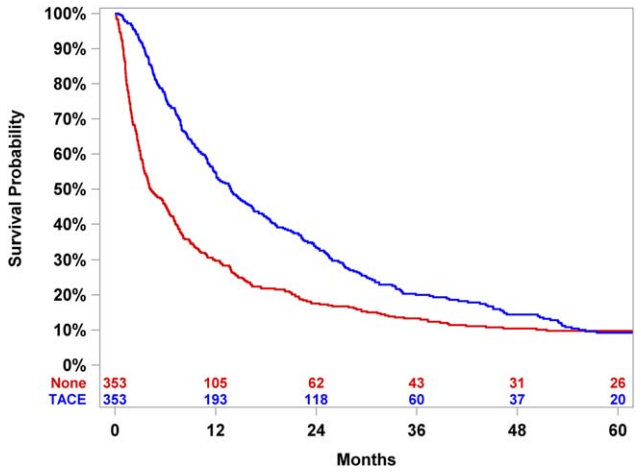

FIG. 3. Survival of patients with HCC with vascular invasion. After propensity score matching, the median survival was 13.8 months in patients treated with TACE compared to 4.2 months in patients with no oncologic treatment ($P < 0.0001$). Actual numbers are masked per the SEER-Medicare requirement for credential reasons.

is indicated for BCLC B "intermediate" stage patients, which include the following characteristics: Child-Turcotte-Pugh A-B, performance status 0, unifocal over 3 cm or multifocal HCC, no vascular invasion, no nodal disease, and no distant metastatic disease.[5] The AASLD practice guidelines further state that "patients who present with a more advanced stage because of liver failure or tumor growth with vascular involvement/extrahepatic spread or physical impairment reflected by a markedly impaired performance status (<2) will not benefit from any treatment options, even one with known efficacy in earlier disease."[5,13,14,17,18,29]

The principle findings of this population-based study were that a significantly higher proportion of patients who met criteria for TACE were appropriately treated following publication of the AASLD practice guidelines compared to preceding years. However, less than 40% of Medicare patients who met AASLD criteria were treated with TACE. Surprisingly, there also was a better than expected survival advantage observed in TACE patients whose HCC tumor characteristics exceeded the AASLD criteria.

Perhaps the largest public health issue raised by this population-based analysis was the vast underuse of AASLD-recommended treatment guidelines for HCC. Studies suggest that nearly 75% of Medicare patients received no oncologic treatment for their HCC, despite having similar demographic and tumor characteristics as those who received treatment.[11,30] An inappropriately low number of patients are considered for HCC treatment. The reasons for underuse of treatment are not clear. Anecdotally, HCC diagnosis is commonly made during the first hepatic decompensation event during which a patient's hepatic function may seem inadequate for HCC treatment. Appropriate referral and care of reversible liver dysfunction by a hepatologist will subsequently make many of these patients candidates for potentially curative or palliative HCC treatments.

TACE use conferred an 8.3-month survival advantage in patients whose HCC characteristics exceeded the AASLD criteria on propensity score matching analysis. A prospective study by Luo et al.[31] comparing patients with portal vein invasion receiving TACE versus conservative management showed an overall survival of 7.1 months versus 4.1 months. The major HCC criteria that classified the patients as beyond AASLD criteria was the presence of vascular invasion, generally thought to be a contraindication for TACE use. On detailed analysis of the effect of vascular invasion on survival, TACE resulted in a 9.6-month survival prolongation. Patients with vascular invasion who received TACE undoubtedly were a highly select population of patients, likely with favorable synthetic function and tumor characteristics. Nevertheless, it may be prudent in the AASLD guidelines to note that select patients with advanced tumor characteristics may benefit from select locoregional therapies, such as TACE.

Conversely, 17% of the TACE population had HCC tumor characteristics that were less than the AASLD criteria. Although a significant survival advantage was observed over no treatment, patients with tumor characteristics less than the AASLD criteria should be offered potentially curative therapies, including transplantation, surgical resection, or ablation.[5,6] This study demonstrates that undertreatment, overtreatment, misstreatment, and lack of treatment are disappointingly common. The etiology of these HCC treatment practices are probably due to ingrained referral patterns, a lack of presentation at multidisciplinary tumor boards, and care at centers that do not provide the full gamut of HCC treatments. Reports have documented a survival advantage if more than one specialist evaluates a patient with HCC, highlighting the fact that most HCC specialty evaluations are to consider a patient only for the service that the specialist offers.[32,33]

With all large database studies, these analyses are limited by a lack of data granularity in the clinician

decisions to offer or withhold therapy for HCC. The mean age of Medicare patients represented in this cohort was over 70 years, and thus advanced age probably influenced treatment decisions among clinicians and may underestimate the survival benefit of TACE. Further, important TACE treatment characteristics were not captured in the SEER-Medicare database, including the degree of tumor necrosis, selective versus nonselective technical approach, and use of conventional lipiodol versus newer drug-eluting beads, all of which have been demonstrated to significantly impact post-TACE survival.[34-41] The SEER-Medicare patients with HCC treated with TACE undoubtedly represent a heterogeneous mixture of TACE modalities.

Over the past 2 decades, the treatment of both HCC and chronic liver disease has evolved such that there are likely significant improvements in patient survival that can be attributed to the management of the underlying liver disease as much as or more so than the treatment of the malignancy. As mentioned previously, the AASLD guidelines for curative and palliative treatment of HCC are inconsistently followed such that region-specific, center-specific, and probably physician-specific variations exist when identifying which therapy(s) to offer patients. Carefully selected patients receive multiple TACEs, TACE as a bridge to resection, TACE as a bridge to transplantation, and TACE in combination with other therapies, such as ablation or radiation, regardless of the current guidelines for evidence-based best practice. Although beyond the scope of this study, it is important to consider the possible survival benefit of TACE in combination with the other aforementioned therapies in appropriately selected patients.

Additional limitations of this SEER data set include a large amount of missing data, particularly in regards to liver function, tumor characteristics, and staging. However, the SEER-Medicare database is the largest nationwide HCC cohort available for analysis, and despite the inherent limitations common with most large databases, it is frequently referenced in regards to the management of HCC. Given the advanced age and compounding comorbidities of the patients treated with TACE within this cohort, it is reasonable to infer that carefully selected patients with HCC and preserved hepatic function may benefit from both TACE and/or other liver-directed therapies to confer a survival benefit over best supportive care extending beyond the current AASLD-recommended guidelines. Further efforts are needed to improve the timely diagnosis and referral of patients with HCC and expand the use of curative and palliative strategies beyond the exceedingly low percentage of patients that are currently offered treatment.

In conclusion, the AASLD criteria identify a population of patients with HCC that maximally benefit from TACE therapy. There has been a steady increase in the proportion of patients receiving TACE that meet the AASLD criteria since the 2005 publication. The AASLD criteria, however, may be too restrictive as evidenced by a significant survival advantage in patients receiving TACE whose HCC characteristics exceeded the AASLD criteria. There is a great need to further disseminate the AASLD HCC treatment guidelines to practicing clinicians to increase HCC treatment and to decrease inappropriate HCC treatments.

REFERENCES

1) **Forner A**, **Llovet JM**, **Bruix J**. Hepatocellular carcinoma. Lancet 2012;379:1245-1255.
2) Njei B, Rotman Y, Ditah I, Lim JK. Emerging trends in hepatocellular carcinoma incidence and mortality. Hepatology 2015;61: 191-199.
3) El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011; 365:1118-1127.
4) Subramaniam S, Kelley RK, Venook AP. A review of hepatocellular carcinoma (HCC) staging systems. Chin Clin Oncol 2013;2:33.
5) **Bruix J**, **Sherman M**; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-1022.
6) **Bruix J**, **Sherman M**; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005;42:1208-1236.
7) **Llovet JM**, **Bruix J**. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003;37:429-442.
8) Davila JA, Duan Z, McGlynn KA, El-Serag HB. Utilization and outcomes of palliative therapy for hepatocellular carcinoma: a population-based study in the United States. J Clin Gastroenterol 2012;46:71-77.
9) Garcia-Tsao G, Lim JK; Members of Veterans Affairs Hepatitis C Resource Center Program. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program. Am J Gastroenterol 2009;104:1802-1829.
10) Sherman M, Bruix J, Porayko M, Tran T; AASLD Practice Guidelines Committee. Screening for hepatocellular carcinoma: the rationale for the American Association for the Study of Liver Diseases recommendations. Hepatology 2012;56:793-796.
11) Shah SA, Smith JK, Li Y, Ng SC, Carroll JE, Tseng JF. Underutilization of therapy for hepatocellular carcinoma in the medicare population. Cancer 2011;117:1019-1026.
12) Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999-2008. Am J Transplant 2010;10:1003-1019.

13) **Bruix J**, **Llovet JM**. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002;35:519-524.
14) Conill C, Verger E, Salamero M. Performance status assessment in cancer patients. Cancer 1990;65:1864-1866.
15) Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 2010;30:61-74.
16) Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329-338.
17) Sorensen JB, Klee M, Palshof T, Hansen HH. Performance status assessment in cancer patients. An inter-observer variability study. Br J Cancer 1993;67:773-775.
18) Bruix J, Llovet JM, Castells A, Montana X, Bru C, Ayuso MC, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. Hepatology 1998;27:1578-1583.
19) Lin DY, Liaw YF, Lee TY, Lai CM. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma--a randomized controlled trial. Gastroenterology 1988;94:453-456.
20) Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359:1734-1739.
21) Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-1171.
22) Pelletier G, Ducreux M, Gay F, Luboinski M, Hagege H, Dao T, et al. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. Groupe CHC. J Hepatol 1998;29:129-134.
23) Pelletier G, Roche A, Ink O, Anciaux ML, Derhy S, Rougier P, et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatol 1990;11:181-184.
24) Welzel TM, Graubard BI, Quraishi S, Zeuzem S, Davila JA, El-Serag HB, et al. Population-attributable fractions of risk factors for hepatocellular carcinoma in the United States. Am J Gastroenterol 2013;108:1314-1321.
25) Anomyous. Seer-Medicare linked database. http://healthcaredelivery.cancer.gov/seermedicare/. Published 2016. Accessed June 6, 2016.
26) Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. J Clin Epidemiol 2000;53:1258-1267.
27) Anomyous. American Hospital Association DataViewer. Hospital size definition. https://www.ahadataviewer.com/glossary/. Published 2016. Accessed June 6, 2016.
28) Parsons LS. Performing a 1:N case-control match on propensity score. In: SUGI 29 Proceedings; May 9-12, 2004; Montreal, Canada. Paper 165-29.
29) Verger E, Salamero M, Conill C. Can Karnofsky performance status be transformed to the Eastern Cooperative Oncology Group scoring scale and vice versa? Eur J Cancer 1992;28A:1328-1330.
30) Chung GE, Lee JH, Kim HY, Hwang SY, Kim JS, Chung JW, et al. Transarterial chemoembolization can be safely performed in patients with hepatocellular carcinoma invading the main portal vein and may improve the overall survival. Radiology 2011;258:627-634.
31) Luo J, Guo RP, Lai EC, Zhang YJ, Lau WY, Chen MS, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. Ann Surg Oncol 2011;18:413-420.
32) Hyder O, Dodson RM, Nathan H, Herman JM, Cosgrove D, Kamel I, et al. Referral patterns and treatment choices for patients with hepatocellular carcinoma: a United States population-based study. J Am Coll Surg 2013;217:896-906.
33) Chirikov VV, Mullins CD, Hanna N, Breunig IM, Seal B, Shaya FT. Multispecialist care and mortality in hepatocellular carcinoma. Am J Clin Oncol 2015;38:557-563.
34) Haywood N, Gennaro K, Obert J, Sauer PF Jr, Redden DT, Zarzour J, et al. Does the degree of hepatocellular carcinoma tumor necrosis following transarterial chemoembolization impact patient survival? J Oncol 2016;2016:4692139.
35) Lencioni R. New data supporting modified RECIST (mRECIST) for hepatocellular carcinoma. Clin Cancer Res 2013;19:1312-1314.
36) Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52-60.
37) White JA, Redden DT, Bryant MK, Dorn D, Saddekni S, Abdel Aal AK, et al. Predictors of repeat transarterial chemoembolization in the treatment of hepatocellular carcinoma. HPB (Oxford) 2014;16:1095-1101.
38) Sieghart W, Hucke F, Pinter M, Graziadei I, Vogel W, Muller C, et al. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatology 2013;57:2261-2273.
39) Burrel M, Reig M, Forner A, Barrufet M, de Lope CR, Tremosini S, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using drug eluting beads. Implications for clinical practice and trial design. J Hepatol 2012;56:1330-1335.
40) Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010;33:41-52.
41) Shim JH, Lee HC, Kim SO, Shin YM, Kim KM, Lim YS, et al. Which response criteria best help predict survival of patients with hepatocellular carcinoma following chemoembolization? A validation study of old and new models. Radiology 2012;262:708-718.

Author names in bold designate shared co-first authorship.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1046/suppinfo.