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Predictors of Mortality in Patients with Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization

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Abstract

Background/Aim—Transarterial chemoembolization (TACE) is the recommended treatment for patients with Barcelona stage B hepatocellular carcinoma; however, community practice varies from these American Association for the Study of Liver Diseases guidelines. In this study, we sought to assess factors determining outcome after TACE and examine adherence to guidelines.

Methods—From January 2006 to December 2012, 308 patients with newly diagnosed HCC were treated at the Veterans Affairs (VA) Ann Arbor Healthcare System. Of these, 109 patients underwent TACE. The primary outcome measured mortality. Kaplan–Meier analysis was used to determine the cumulative probability of death. Cox regression was used to assess the predictors of mortality.

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Conflict of interest None.

Results—The median age of the 109 patients was 60 years (48–90), 97 % were males and 82 % had chronic HCV infection. The median size of the largest lesion was 4 cm, 51 % were multifocal, and portal vein thrombosis was present in 3.6 %. Sixty-two patients died after median 333 days from the index TACE treatment. Median overall survival from index TACE was 11.2 months. Unadjusted 1-, 2-, and 3-year survival was 64, 35, and 24 %, respectively. CTP score (B vs. A: HR 2.51, $p = 0.002$; C vs. A: HR 7.96, $p < 0.0001$) and presence of complete response to TACE (HR 0.51, $p = 0.004$) were independent predictors of mortality. Barcelona stage ($p = 0.88$) and performance status as measured by ECOG ($p = 0.98$) were not associated with mortality after TACE.

Conclusions—In this community based, single VA center study, we found a significant number of patients beyond Barcelona stage B were treated with TACE. Advanced TNM stage, poor liver synthetic function and achieving CR with TACE were better predictors of mortality than guideline-directed decisions based on Barcelona stage. These factors may be useful to guide future patient selection for TACE.

Keywords

Hepatocellular carcinoma; Transarterial chemoembolization; Barcelona Clinic Liver Cancer; Mortality; Predictors

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and represents 4 % of all new cancer diagnoses [1]. HCC has been identified as the fastest rising cause of cancer-related death in the USA, with a dismal 5-year survival of <12 % [2]. Low survival rates are due to lack of observable symptoms in the early stages, aggressiveness of the cancer with concomitant hepatic failure, and limited curative options in the later stages.

HCC surveillance can be effective in early detection of malignant lesions and improving mortality. However, it is significantly underutilized with <20 % of eligible patients receiving appropriate screening [3, 4]. A survey studied showed that one quarter of physicians did not know the appropriate management of a positive result, thereby limiting the overall effectiveness of HCC surveillance [5]. The natural history of HCC is such that nearly two-thirds of the diagnoses are thus made at an advanced stage [6]. Only a minority are diagnosed at a stage where potentially effective curative therapies such as liver transplantation (LT) and resection are available, as outlined by Barcelona Clinic Liver Cancer (BCLC) guidelines [7].

In the absence of viable curative options, transarterial chemoembolization (TACE) has become the first-line therapy for many patients who exceed transplantation criteria and for whom radio frequency ablation (RFA) are precluded due to tumor size and location [8]. Although the American Association for the Study of Liver Diseases (AASLD) guideline recommends TACE for only intermediate stage HCC (Barcelona stage B) [7], it is not clear whether these guidelines are strictly adhered to in the community or whether other factors may be useful in determining outcomes after TACE.

The primary aim of this study was to determine the factors associated with mortality after TACE procedure among patients with HCC receiving TACE at a single center. The secondary aim was to determine the incidence of response and recurrence as well as factors associated with HCC response and recurrence after the TACE procedure.

Methods

Patients/Materials

From the period of 2006 to 2012, 308 patients with newly diagnosed HCC were treated at the VA Ann Arbor Healthcare System. The patients were identified through the Liver Tumor Board as well as from clinical administrative databases using the ICD-9 codes of 155.0 and 155.2. Retrospective chart review was performed to verify all diagnosis. Of the 308 patients, 109 patients received TACE procedure, whose data were analyzed.

Diagnosis of HCC was made based on radiological criteria or histology per AASLD guidelines [7]. Ninety-eight percent of the patients were seen by the Gastroenterology Consultation service, and 91 % were formally reviewed by the Liver Tumor Board. A treatment algorithm was used where all patients were assessed for resection or LT if they were within Milan criteria and/or met the United Network for Organ Sharing (UNOS) criteria. Patients who were not candidates for resection or LT were then considered for RFA or TACE. Of note, six patients did receive subsequent LT after initial intervention with RFA (n = 2), TACE (n = 3), or RFA followed by TACE (n = 1).

Clinical data were abstracted from medical chart review including liver tumor board notes and cancer-staging forms. Tumor assessment and staging as well as clinical diagnosis of diabetes, hypertension, and laboratory studies were based on the data, which were closest to the diagnostic imaging study (either MRI or CT) and never >6 months from the date of imaging. Hepatitis C diagnosis was confirmed by serum HCV RNA. Tobacco use included present and past use. Survival was based on date of first intervention to death or censor. Follow-up was censored at date of last visit. No patients were lost to follow-up.

TACE Procedure

We used standard fashion TACE using up to 10 mg mitomycin, 50 mg doxorubicin, 100 mg cisplatin and 20 mL lipodiol until March 2011. We then switched to doxorubicin drug-eluting beads (DEB) with doses up to 150 mg. A follow-up CT scan or MRI with contrast was obtained 6 weeks after the TACE procedure to assess response. Response to initial procedure was determined by mRECIST criteria [9]. Subsequent surveillance imaging was obtained every 3 months for 1 year and 6 months for the following subsequent 2 years. Patients were then continuously followed until either death or last follow-up, and presence of recurrence or progression-free survival was recorded. If disease recurred or progressed, treatment was then decided based on primary hepatologist opinion and recommendation of tumor board, as above. This included further TACE, RFAs, or best supportive care including sorafenib and/or palliative care.

Statistical Analysis

The continuous variables were expressed as median and range, and categorical variables were expressed as percentage. The primary outcome was mortality, and the secondary outcome was recurrence of HCC. Patients were followed from the time of initial diagnosis until death or June 30, 2013.

Kaplan–Meier method was used to estimate the cumulative probability of death. Time to death was counted from the first TACE procedure to death or last follow-up visit. Backwards stepwise Cox regression models were used to assess the predictors of mortality. The variables with $p < 0.05$ in the univariate analysis were further investigated in the multivariate Cox regression analysis. The model was adjusted for age, size of largest lesion, stage, CTP score, MELD, Log AFP, etiology, and response to TACE and ECOG score.

Logistic regression was used to examine the predictors of complete response. A p value <0.05 was considered statistically significant. All analyses were performed in SPSS version 20.

Results

Description and Outcomes of Cohort

One hundred and nine patients underwent TACE procedures as a primary intervention for HCC during the study period. The demographic, clinical, and tumor features are shown in Table 1. The median age was 60 years old (48–90); 97 % males and 82 % had hepatitis C as their primary liver disease. The median MELD score was 9, with 61, 34, and 5 % of patients in Child's class A, B, and C, respectively, and 2, 20, 22, 50, and 7 % in BCLC stage 0, A, B, C, and D, respectively.

The median size of the largest lesion was 4 cm, and 51 % of the patients had multifocal tumor. Of the patients with portal vein thrombosis, only 4 (3.6 %) patients had true tumor thrombus. Two invaded the main/right portal veins and left portal vein, respectively. The other two instances involved thrombus in the main/left portal veins without invasion. The median time from diagnosis to index procedure in the treatment session was 81 days. The average number TACE per patient was 1, with a range of 1–5. The results of the TACE procedures are given in Table 2.

Unadjusted Mortality After TACE Procedure

Sixty-two of the 109 patients died after a median of 333 days from the index TACE treatment. Median overall survival from index TACE was 11.2 months. Median overall survival in patients who achieved CR was 14.5 months compared with 7.7 months in those who did not. The unadjusted 1-, 2-, and 3-year patient survival was 64, 35, and 24 %, respectively. Figure 1 shows the cumulative probability of survival stratified by CTP score.

Independent Predictors of Mortality After TACE Procedure

Table 3 shows the independent predictors of mortality. Patients with Child's Class B and C cirrhosis had 2.1-fold and 3.7-fold higher hazard of death compared with Child's Class A,

respectively. The presence of complete response was associated with a 49 % lower risk of death (HR 0.51, $p = 0.004$). Interestingly, Barcelona stage and performance status as measured by ECOG were not associated with mortality after TACE.

Response to TACE and HCC Recurrence

Figure 2 shows the spectrum of response and outcomes based upon response to TACE. Approximately half of the patients (51 %) achieved complete response after a median of one TACE procedure (range 1–5). Of those with a complete response, 48 % had HCC recurrence during the follow-up period (Fig. 2).

Independent predictors of complete response (Table 4) included number of TACE procedures (OR 0.43; $p = 0.023$), TNM stage (OR 0.43; $p = 0.006$), and lesion size per cm (OR 0.78; $p = 0.029$).

Discussion

In this large VA-based study of American patients undergoing TACE as primary intervention, the 1-year overall survival was 64 % which is similar to prior studies showing a median survival of approximately 20 months with TACE [10, 11]. The cumulative incidence of survival was highest among those with well-preserved liver synthetic function. Our results validate previous findings that residual liver function is important to the success of TACE and survival of patients. Uniquely, our analysis did not demonstrate that a single component of CTP scoring (bilirubin, INR, albumin, ascites, or encephalopathy) was predictive of survival as seen in previous studies: albumin [12], bilirubin [13], and INR [14].

The role of performance status as measured by ECOG score is a unique component of BCLC staging. While previous studies have shown that lower ECOG score has a significant positive impact on survival [12, 13], we did not find an association between post-TACE survival and ECOG status. Although the AASLD guideline recommends TACE procedure for intermediate stage (BCLC-B) HCC [7], 57 % of our patients who received TACE were advanced stage, BCLC stage C and D. In our patients, advanced BCLC stage did not predict the mortality after TACE, suggesting that with careful patient selection, TACE may be a reasonable option for palliation.

Our study also confirms the findings of Cabibbo et al. [13] that achieving a complete response-affected survival. However, we found that an increasing number of TACE procedures were associated with lower complete response. We speculate that an increase in the number of TACE procedures might be a surrogate for aggressive or harder to treat tumor biology such as undifferentiated or anaplastic HCC.

Curative as well as palliative modalities for HCC tend to vary clinically, especially for intermediate stage. TACE has been used in Asia for many years for intermediate stages and two major RCTs and a systematic review in the early 2000s validated the procedure [15–17]. Since then, the majority of studies examining the predictors of outcomes after TACE are from Asia. The epidemiology of HCC in Asia is different from the USA because of high incidence of hepatitis B and occurrence of HCC in patients with well-preserved hepatic

function. Results from those studies cannot be generalized to patients in the USA. Our results may help guide the patient selection for TACE procedure in this country. Additional unique features strengthening our study are the uniformity of patient selection, standard decision-making criteria using a multidisciplinary tumor board and extremely low loss to follow-up.

Finally, the limitations to our study include that it is a single center study with a predominantly male population and retrospective study design that can result in some bias from unmeasured components. Despite these limitations, this is one of the largest studies that evaluated the risk factors of mortality as well as factors associated with response after TACE procedure in the USA.

In this community based, single VA center study, many patients were beyond BCLC-B stage, with poor ECOG performance status, but these factors were not associated with decrease survival after TACE. In conclusion, patients should be carefully selected based upon their CTP score. Complete response to TACE is associated with lower mortality and dependent upon lower TNM stage and small size of the lesion. Patients who do not respond to TACE after index procedure are less likely to achieve complete response. These results may guide caregivers regarding patient selection for TACE and counseling regarding the outcomes of TACE procedures.

Acknowledgments

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Abbreviations

HCC	Hepatocellular carcinoma
TACE	Transarterial chemoembolization
BCLC	Barcelona clinic liver cancer
CTP	Child–Turcotte–Pugh
AASLD	American association for the study of liver diseases
mRECIST	Modified response evaluation criteria in solid tumors

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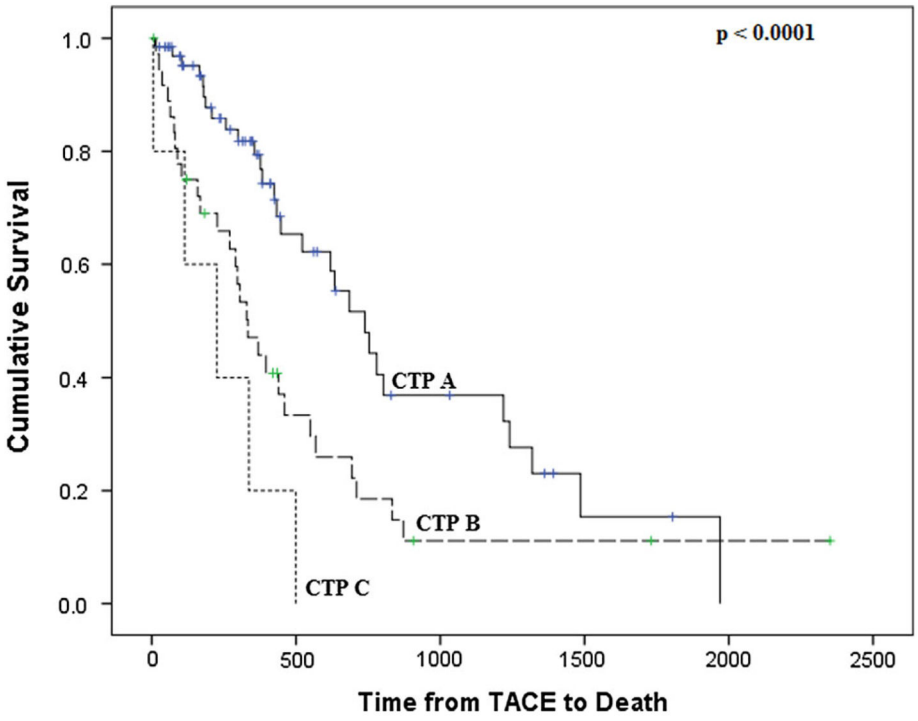

Fig. 1.
Unadjusted patient survival by CTP score

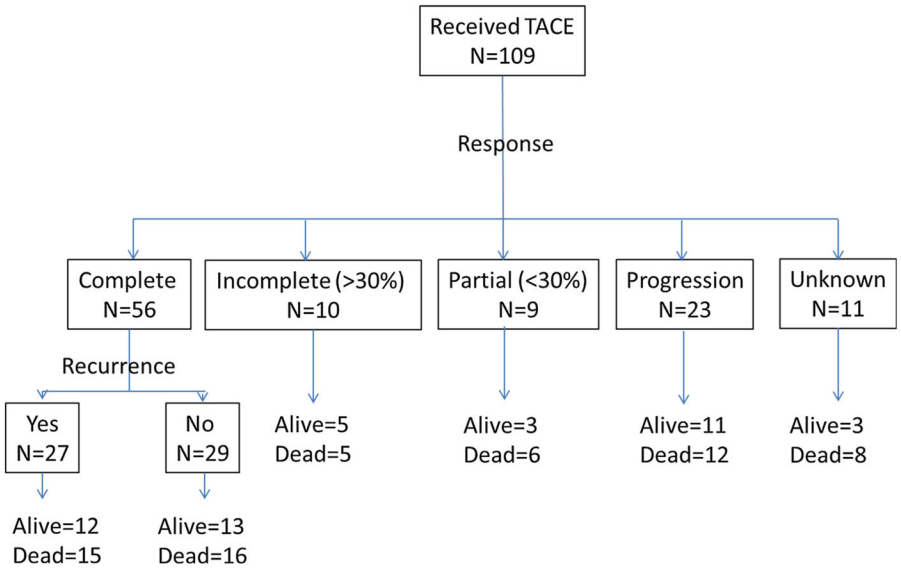

Fig. 2.

Outcomes based upon response to TACE

Table 1

Baseline characteristics of cohort

Variables	**Median (range)/number (%)** ***N*** **= 109**
Age at diagnosis (years)	60 (48–90)
Male	106 (97 %)
Female	3 (3 %)
White	46 (42 %)
AA	30 (27.5 %)
Other	1 (0.1 %)
Unknown	32 (29.4 %)
HCV	89 (82 %)
Size of largest lesion	4 (1–24)
Multifocal	56 (51 %)
PVT	8 (7.3 %)
ECOG score	1 (0–3)
MELD score	9 (6–18)
CTP	6 (5–11)
A/B/C	67 (61 %)/37 (34 %)/5 (5 %)
Barcelona stage 0–A–B–C–D	2 (1.8 %)–21 (19.3 %)–24 (22 %)–54 (49.5 %)–8 (7.3 %)
Stage I/II/III/IV	50 (45.8 %)/41 (37.6 %)/17 (15.6 %)/1 (1 %)
BMI	26.6 (20–42)
Log AFP	1.48 (0.02–4.65)
Albumin	3.2 (1.9–4.6)
Ascites: none/mild/mod-severe	87 (80 %)/21 (19 %)/1 (1 %)
HE: none/Gr 1–2/Gr 3–4	98 (90 %)/10 (9 %)/1 (1 %)
DM	27 (25 %)
HTN	73 (67 %)
Smoking	88 (81 %)

Table 2

Results of TACE procedures

Variables	**Median (range)/number (%)** ***N*** **= 109**
Number of TACE procedures/patient	1 (1–5)
Complete response	56 (51.4 %)
Recurrence	27
No recurrence	29
Incomplete response (> 30 % necrosis)	10 (9.2 %)
Partial response (< 30 % necrosis)	9 (8.3 %)
Progression (increase in size)	23 (21 %)
Unknown	11 (10.1 %)
Deaths	62 (57 %)
Time from diagnosis to death (days)	413 (41–2,491)
Time from diagnosis to TACE	81 (8–648)
Time from TACE to death	333 (28–2,351)

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Table 3

Independent predictors of survival

Covariates	HR (95 % CI)	*p* value
Log AFP	1.34 (0.96–1.86)	0.085
CTP	2.13 (1.25–3.6)	0.006
B (vs. A)	3.72 (2.34–10.4)	0.012
C (vs. A)		
Complete response to TACE (vs. not)	0.51 (0.28–0.92)	0.004

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Table 4

Independent predictors of complete response

Covariates	OR (95 % CI)	*p* value
Number of TACE procedures	0.43 (0.21–0.89)	0.023
TNM stage	0.43 (0.23–0.78)	0.006
Largest lesion (per cm)	0.78 (0.60–0.97)	0.029