ORIGINAL ARTICLE

Best radiological response to trans-arterial chemoembolization for hepatocellular carcinoma does not imply better outcomes

Jon C. Henry[1], Lavina Malhotra[1], Hooman Khabiri[2], Gregory Guy[2], Anthony Michaels[3], James Hanje[3], Marcela Azevedo[1], Mark Bloomston[1] & Carl R. Schmidt[1]

Departments of [1]Surgery, [2]Radiology and [3]Medicine, The Ohio State University College of Medicine, Columbus, OH, USA

Abstract

Introduction: Regional therapy with trans-arterial chemoembolization (TACE) is a common treatment for unresectable hepatocellular carcinoma (HCC). Outcomes were examined in patients with the best radiological response (BR) after the initial TACE.

Methods: This was a retrospective cohort study of patients who underwent TACE as the initial treatment for HCC between the years 2000 and 2010. BR was defined as complete disappearance of the tumour or no enhancement with contrast on the first cross-sectional imaging study after the initial TACE.

Results: Seventy-eight out of 104 total consecutive patients were identified with the potential for a BR to TACE therapy for unresectable HCC, and 24 met the criteria for BR. Patients with BR had a median survival of 12.8 months (2.2–54.9) compared with 18.9 months(1.3–56.7) for the entire cohort ($P = 0.313$). The median time to progression was 10.6 months (1.2–24.3) in the BR group and 3.2 months (0.7–49.2) in the patients without a BR ($P = 0.003$).

Discussion: BR to initial TACE for unresectable HCC is associated with comparable survival to those without BR in spite of a longer time to cancer progression. It may be reasonable to consider further therapy such as repeat TACE or biological/systemic therapy in patients with HCC even when the radiological response to the initial TACE is favourable.

Correspondence

Carl R. Schmidt, Division of Surgical Oncology, M-256C Starling-Loving Hall, 320 West 10th Avenue, Columbus, OH 43210-1240, USA. Tel: +1 614 293 5644. Fax: +1 614 293 3465. E-mail: carl.schmidt@osumc.edu

Introduction

Liver cancer has a devastating global impact being the third leading cause of cancer-related death worldwide. Hepatocellular carcinoma (HCC) compromises 70–85% of liver cancer diagnoses resulting in well over 500 000 deaths worldwide each year.[1,2] While this disease is most prevalent in the African and Asian continents, its incidence is on the rise in the United States with liver cancers as a whole being the fastest growing group of cancers over the past decade.[1,3] In spite of the prevalence of this disease treatment options are limited resulting in a 1-year survival rate of less than 50% for all stages worldwide.[3,4]

Potentially curative treatment with surgical resection or transplantation is limited to a small subset of HCC patients.[3,5] Many patients are not candidates for these procedures because of

This manuscript was presented at the annual AHPBA meeting, Miami, 7–11 March 2012.

advanced cirrhosis precluding safe resection or tumours outside transplant criteria.[5] While other options such as local ablative therapy are available these are limited by the extent of cirrhosis and the size and location of tumour(s).[6] Therefore a commonly used treatment for HCC in the presence of cirrhosis is trans-arterial chemoemboization (TACE).[7] TACE has been shown to be safe and improve survival in patients with unresectable HCC compared with no therapy or best supportive care.[8–11] As expected outcomes are best in patients with compensated or Child's A cirrhosis, TACE has also been used by some in properly selected patients with more advanced cirrhosis.[12] Favourable outcomes from TACE are associated with Child's Class A cirrhosis[13] lack of ascites,[13] age younger than 60 years,[14] alkaline phosphatase less than 120 U/l,[14] albumin greater than 35 g/l,[14] smaller tumours,[15] solitary tumours,[15] good baseline performance status,[16] low billirubin level,[7,16] and multiple TACE procedures.[15,16]

A best or complete radiological response to TACE has been defined as a lack of contrast enhancement on imaging after the

procedure.[7,15–18] Such a best response to TACE has been associated with improved survival in patients with recurrent HCC after a hepatectomy[15] and in patients with class A and B cirrhosis.[7,16] Of note, some of these previous studies allowed for multiple serial TACE procedures to be done in order to achieve a best response after the final TACE.[7,15,16] One study by Imai suggested that a favourable response after subsequent TACE is associated with the response seen at previous TACE procedures (not specifically the initial TACE), but the present study did not examine survival outcomes based upon response.[17] In this study, outcomes for individuals having a best response (BR) after initial TACE for unresectable HCC are compared with the individuals who do not have a BR.

Methods

After Institutional Review Board approval, the medical records of 104 patients with unresectable HCC treated with initial TACE therapy between 2000 and 2010 were reviewed. All patients had the diagnosis of HCC made by characteristic radiographical findings on pre-procedure liver magnetic resonance imaging (MRI) or computed tomography (CT); ultrasound or a CT-guided biopsy was done if tumour features were suggestive, but not diagnostic for HCC. Patients with extra-hepatic disease or major vascular invasion were excluded. Patients without post-TACE imaging were also excluded.

TACE therapy was generally offered to patients with unresectable HCC, Child's class A or B cirrhosis, an Eastern Cooperative Oncology Group performance status of 0–2, no encephalopathy and no ascites detectable on physical examination. Very rarely, patients with Child's C cirrhosis were offered TACE. TACE therapy was triple drug TACE (cisplatin 50 mg, doxorubicin 30 mg, and mitomycin C 20 mg with Visipaque at 320 mg/ml) using a 10-ml Lipiodol carrier and most of the procedures targeted the right or left lobar distribution. After 2009, LC Beads (coated with 100 mg of doxorubicin) (Biocompatibles, Farnham, Surrey, UK) were used for all TACE procedures in any patient with HCC. Some patients received bland embolization. Most patients were discharged the day after TACE. A physical examination and laboratory studies were conducted within a few days after discharge from the initial hospitalization in the outpatient setting. Liver protocol CT or MRI was done around 1 to 2 months after TACE, and if no further therapy was needed, surveillance imaging and labs were repeated every 3 months for the first year then every 6 months for at least another 2 years.

A radiological BR to TACE therapy was determined using the first imaging study available at least 2 weeks after the initial TACE therapy. Both abdominal contrast-enhanced MRI and multiphase CT were allowed. BR was defined as no abnormal enhancement or density consistent with a viable tumour present at the previous target site(s) for TACE or complete disappearance of tumour(s) after the initial TACE without any new tumours within the liver or abdomen concerning early progression. For the patients that received Lipiodol, areas of enhancement that had washout or obvious tumour lesions without Lipiodol contrast were considered to have a residual tumour. If a patient had additional TACE therapy less than 2 months after the intial TACE, they were considered to not have a BR.

Clinical tumour characteristics and outcomes were compared between those with BR after the initial TACE for unresectable disease to those without BR using Student's *t*-test for parametric, continuous data, Mann–Whitney *U*-test for non-parametric, continuous data, and Fisher' exact test for all nominal data. From data obtained through the chart review, the Child–Pugh score, model of end-stage liver disease (MELD) score, and TACE survival score[14] were calculated for each patient. Overall survival was defined as the time from initial TACE therapy to date of death or censored at last follow-up. Time to progression was defined as the time from the initial TACE to the first sign of progression after TACE. Kaplan–Meier curves were used to compare groups and significance was determined by the log-rank test. Factors were considered to be associated with overall survival when a *P*-value of less than 0.05 was obtained by univariate analysis. All statistics were performed using Statistical Package for Social Sciences (SPSS) Version 19 (SPSS Inc., Chicago, IL, USA).

Results

There were 104 patients who underwent TACE for initial treatment of unresectable HCC between 2000 and 2010. A total of 26 (25%) patients were excluded from the analysis. Seven had extra-hepatic disease, five had major vascular invasion and two had a combination of these findings on pre-procedure imaging. Twelve patients did not have post-TACE imaging owing to the following reasons: six died in less than 2 months after the TACE procedure, one was assumed to need additional TACE procedures without imaging because of the size of the original tumour, one had a secondary malignancy discovered that prioritized their therapy, one had a brain metastasis discovered after the procedure that altered the plan of therapy, one patient had a liver transplant and two had reasons that were unknown. Of the remaining patients, 24 (30.8%) met the criteria for BR whereas 54 (79.2%) did not have BR (Fig. 1). A small number of patients in the study (*n* = 11) underwent TACE for recurrent HCC after previous potentially curative ablation or surgical resection; none of these recurrences were local. There were no significant differences in patient demographics between patients in the BR group and the remaining portion of the TACE cohort who did not have a BR. A difference was observed in the synthetic liver function between the groups, but not any other lab values. All patients had liver cirrhosis and the degree of liver impairment was not significantly different between the two groups (Table 1).

Baseline tumour characteristics were similar between the two groups. (Table 2). There was no statistical difference in the type or specify of the TACE therapy used between those with BR and those without, and alpha-feto protein (AFP) levels before and
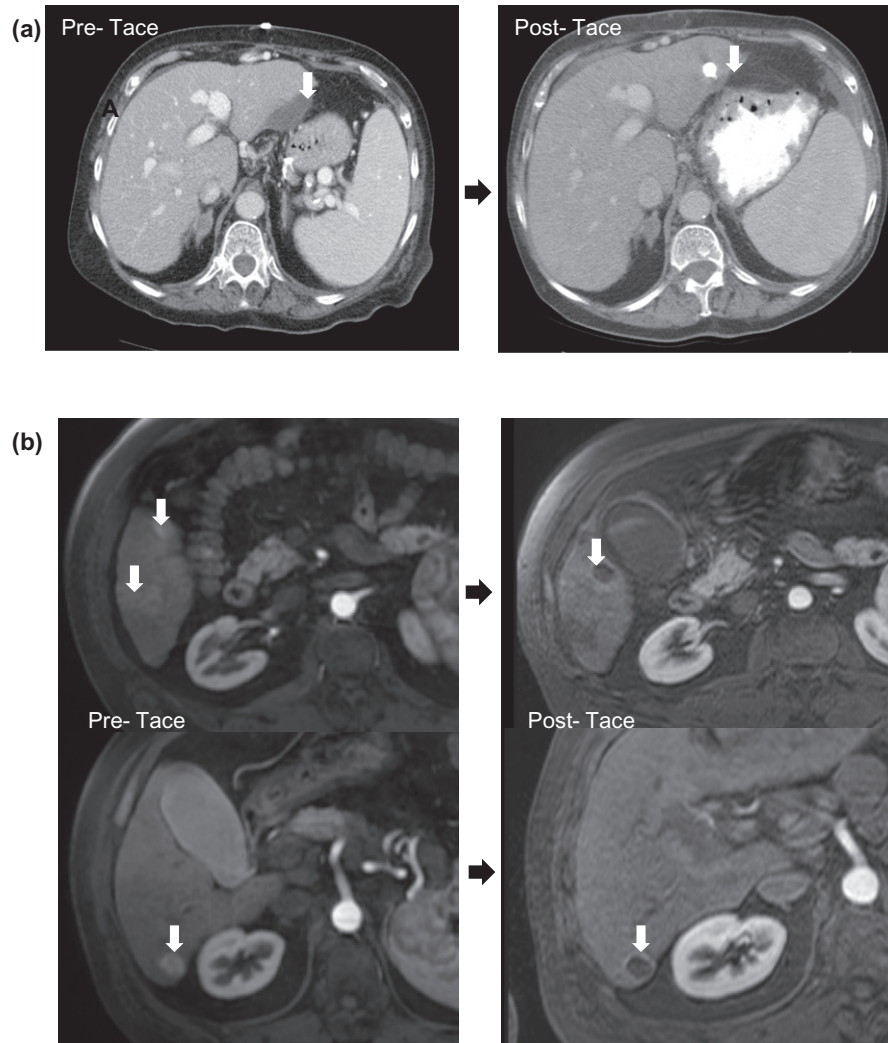
Figure 1 (a) An example of a best response: this is a computed tomography (CT) image from a 76-year-old woman who presented with haemoperitoneum from a bleeding left lateral segment hepatocellular carcinoma (HCC) (arrow, left CT). Multiple comorbidities and portal hypertension made surgical resection not feasible therefore she was treated with trans-arterial chemoembolization (TACE). A CT scan performed 1 month after the initial TACE revealed no evidence of a residual viable tumour (arrow right CT). Several more serial CT scans showed no evidence of a mass until she developed local recurrence/progression 2 years after the initial TACE. (b) An example of not a best response: magnetic resonance imaging (MRI) images are shown from a patient with cirrhosis and three arterial-enhancing tumours in the right liver (arrows, left MRI) treated with TACE. MRI images obtained approximately 1 month after TACE revealed a tumour response with overall loss of enhancement but some residual peripheral enhancement around two of the masses (arrows, right MRI)

after TACE were not different (Table 2). The pre-TACE imaging was performed at this institution for 63 (80.8%) of the patients and all patients had post-TACE imaging performed at this hospital. Imaging was generally obtained at a median of 52 days (15–810) after the initial TACE. The median length of hospital stay was 2 days (1–15) in the entire cohort and 2 days in both the non-BR (1–6 days) and the BR groups (1–15 days) ($P = 0.160$). Only one 60-day mortality occurred in the entire cohort and that was in the non-BR group. There were three patients who experienced major complications in the BR group compared with 15 in the non-BR group ($P = 0.160$). Common complications included infection, hepatic insufficiency and gastrointestinal bleeding. There were three with hepatic failure in the non-BR group and two with hepatic failure in the BR group ($P = 0.641$).

Progression of disease occurred in 69 of the 78 (82.2%) patients within the cohort. In the BR group, 17 out of 24 had progression of disease compared with 52 of the 54 within the non-BR group. The median time to progression (TTP) after the initial TACE was 4.6 months (0.7–54.9) in the entire cohort, and the BR group experienced a median TTP of 10.6 months (1.2–54.9) compared

Table 1 Patient demographics and baseline liver function

	TACE cohort (n = 78)	No BR (n = 54)	BR (n = 24)	P-value
Age, years [median (range)]	60 (31–83)	59 (31–81)	59 (48–83)	0.380
Gender [n, (% male)]	58 (74.4)	42	16	0.400
HBV [n (%)]	9 (11.5)	8	1	0.261
HCV [n (%)]	33 (42.3)	22	11	0.805
Total bilirubin [median (range)]	1.1 (0.4–4.4)	1.0 (0.5–3.8)	1.2 (0.40–4.40)	0.173
Albumin [median (range)]	3.1 (1.5–4.9)	3.1 (1.7–4.9)	2.8 (1.5–3.7)	**0.014**
INR [median (range)]	1.2 (0.9–2.0)	1.2 (0.9–2.0)	1.2 (1.1–1.7)	**0.042**
Creatinine [median (range)]	0.82 (0.46–4.94)	0.86 (0.52–4.94)	0.79 (0.46–1.66)	0.309
Ascites [n (%)]	18 (23.1)	13	5	1.000
C-P score [median (range)]	6 (5–11)	6 (5–11)	7 (5–10)	0.071
Class A (n, %)	42 (54.8)	31	11	0.461
Class B (n, %)	34 (43.6)	23	11	0.803
Class C (n, %)	2 (2.6)	0	2	0.092
MELD score [median (range)]	9.5 (6.4–23.8)	9.1 (6.4–23.8)	9.7 (7.9–17.0)	0.059
TACE prognostic survival score [mean]	1.55	1.44	1.79	0.129

C-P, Child-Pugh; HBV, Hepatitis-B Virus; HCV, Hepatitis-C Virus; INR, International Normalized Ratio; TACE, trans-arterial chemoembolization. Bold values indicated significant P-values in the comparison of BR to non-BR groups.

Table 2 Tumour characteristics and trans-arterial chemoembolization (TACE) treatment among the cohort

|	TACE cohort (n = 78)	No BR (n = 54)	BR (n = 24)	P-value
Pre-procedure AFP level [median, (range)]	47.0 (1.3–524 000)	47.0 (1.3–524 000)	44.5 (2.0–4787)	0.830
Post-procedure AFP level [median, (range)]	24.6 (1.4–58 623)	37.6 (1.8–58 623)	23.1 (1.4–2668)	0.922
Diameter of largest tumour (cm) [median (range)]	4.4 (0.7–12.1)	4.2 (0.7–12.1)	4.8 (2.1–12.1)	0.700
More than one tumour [n (%)]	48 (61.5)	34	14	0.802
Location of tumour (s)				
Right lobe [n (%)]	36 (46.2)	22	14	0.219
Left lobe [n (%)]	7 (9.0)	4	3	0.670
Bilobar [n (%)]	35 (44.8)	28	7	0.085
TACE procedure details				
Selective TACE (smaller than hepatic arteries) [n (%)]	9 (11.5)	6	3	1.000
Chemotherapy TACE [n (%)]	37 (47.5)	23	14	0.227
TACE with chemo-coated beads [n (%)]	24 (30.7)	17	7	1.000
Bland TACE (embolization) [n (%)]	17 (21.8)	14	3	0.242

AFP, Alpha-feto protein.

with 3.2 months (0.7–49.2) in the non-BR group (P = 0.003, Fig. 2). The most common site of progression was an intrahepatic tumour in both groups (n = 12 and n = 41, respectively), and the most common therapy given for progression after the initial TACE was another TACE (n = 8 and n = 18, respectively). Two (2.6%) patients in the entire cohort underwent liver transplantation after the initial TACE.

The median overall survival (OS) was 16.0 months (1.3–56.7) after the initial TACE. In the group with BR after TACE, the median OS was 12.8 months (2.2–54.9) compared with 18.9 months (1.3–56.7) in the remaining patients without BR (P = 0.313, Fig. 3). In the patients with compensated cirrhosis (Child's A), the median OS after TACE in the BR group was not different

compared with the without BR group (P = 0.675, Fig. 4). Other factors associated with overall survival in the entire cohort included Child's class and MELD score (Table 3).

Discussion

After the initial TACE for HCC, a best or complete radiological response is not a rare occurrence and can be seen in the range of 14–70% of TACE procedures for HCC.[7,15–17] The TACE best response rate of 31% in this study falls within this range, and notably represents a response after the initial TACE whereas some other studies with higher rates allowed for multiple TACE procedures to achieve BR.[15] These studies have also demonstrated that a
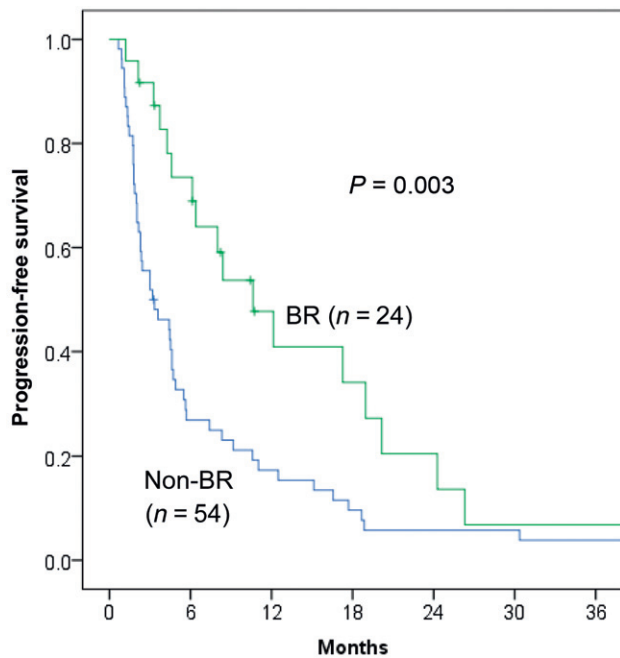
Figure 2 Time to progression of hepatocellular carcinoma (HCC) after the initial trans-arterial chemoembolization (TACE) comparing patients with a best response (BR) and those without response BR
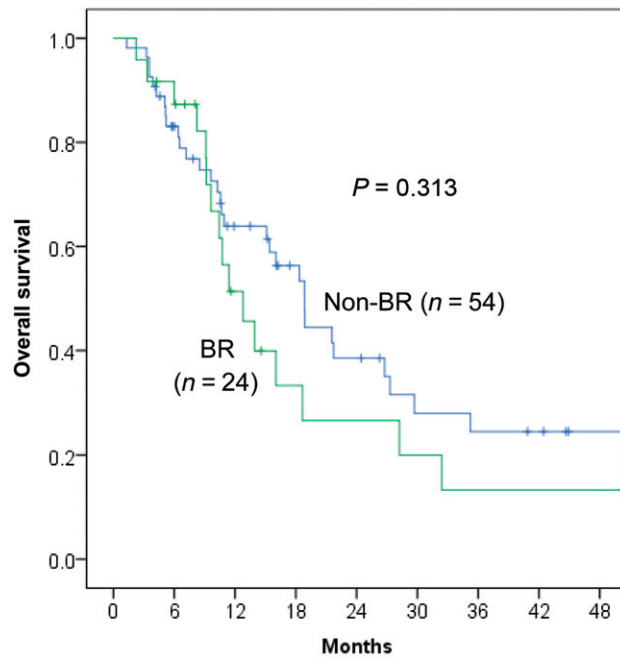
Figure 3 Overall survival compared between patients with a best response (BR) and without after an initial trans-arterial chemoembolization (TACE) for unresectable hepatocellular carcinoma (HCC)

complete response after TACE is associated with improved survival. While BR in this study's patients was associated with improved progression-free survival, outcomes were otherwise similar between the BR and non-BR groups.

The underlying liver disease (cirrhosis) seems to influence outcomes more than tumour stage or radiological response to therapy in this study. Thirty-six patients (46.2%) in this study had Child's B or C compared with rates of 13–23% in other (mostly prospective) studies which excluded patients with more advanced cirrhosis.[7–9,15–17] The overall survival reported in this study reflects this inclusion of more patients with baseline poorer liver function. In other studies similar to this one with higher rates of advanced cirrhosis (34–63%) and survival rates range from 6–21 months.[19–21] In Dhanasekaran *et al.* 's work on prognostic factors in doxorubicin-bead TACE therapy in HCC, they found 7 out of 10 reported prognostic factors were associated with liver function rather than tumour stage.[20]

The present study has several limitations. As stated, outcomes were examined based only on radiological response to the initial TACE. Others have found a complete or best response to correlate with outcomes allowing for more than one TACE procedure, and such a treatment strategy when feasible may result in better

outcomes overall. As stated above, almost half of the patients in this study had more advanced cirrhosis. This likely explains why only 26 out of 69 patients in the cohort with disease progression went on to receive additional TACE therapy. It may be that combination therapies or a use of selective TACE over multiple sessions when feasible may improve outcomes in patients with unresectable HCC compared with a single lobar TACE followed by observation. The use of selective TACE has increased at this institution since 2009. Finally, the first post-TACE imaging study was used at a median of 52 days to determine BR or no BR, but this may not be the ideal timing in terms of measuring this response outcome.

In summary, the best response to the initial TACE was not associated with a survival advantage in patients with unresectable HCC in spite of an improved time to progression. It may be reasonable to offer other therapies such as systemic/biological therapy even in patients who have a favourable radiological response to the initial TACE. A radiological response is inadequate as a sole variable for determining prognosis in patients with HCC who undergo regional therapy. Therefore, better molecular information and biomarkers are needed to determine outcomes and personalize therapies.
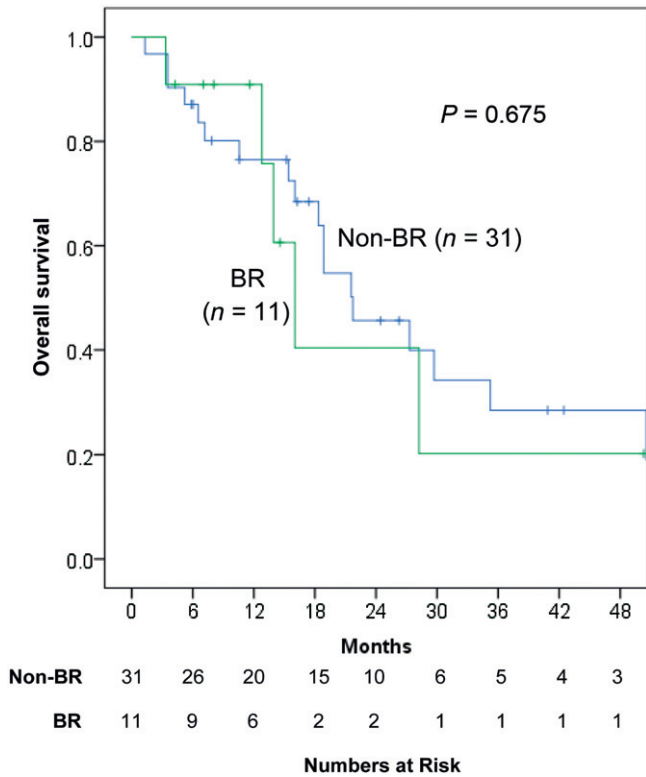
Figure 4 Overall survival compared between patients with Child's A cirrhosis and with or without a best response to an initial transarterial chemoembolization (TACE) for unresectable hepatocellular carcinoma (HCC)

Table 3 Factors associated with overall survival among the entire cohort

Factor	Univariate
Demographics	
Age	0.147
Gender	0.289
Liver function	
Child's class	**0.024**
MELD score	**0.031**
HCC tumour burden	
AFP	0.755
Milan criteria	0.167
More than 1 tumour	0.132
Largest diameter	0.758
TACE therapy	
Specific TACE	
Bland TACE	0.244
Chemotherapy with embolization	0.940
Bead Therapy	0.155

AFP, alpha-feto Protein; MELD, model for end-stage liver disease.

Conflicts of interest

None declared.

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