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Factors Predicting Survival after Transarterial Chemoembolization of Unresectable Hepatocellular Carcinoma

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Abstract

Background: Transarterial chemoembolization is the preferred treatment for unresectable, intermediate-stage hepatocellular carcinoma. Survival after transarterial chemoembolization can be highly variable. The purpose of this study is to identify the factors that predict overall survival of patients with unresectable hepatocellular carcinoma who undergo transarterial chemoembolization as the initial therapy.

Methods: We included patients who underwent transarterial chemoembolization from 2007 to 2012 in this study. Patient's age, gender, cause of cirrhosis, Child-Turcotte-Pugh score, model of end-stage liver disease score, Cancer of the Liver Italian Program score, Okuda stage, alpha- fetoprotein level, site, size and number of tumors were recorded. Radiological response to transarterial chemoembolization was assessed by computerized tomography scan at 1 and 3 months after the procedure. Repeat sessions of transarterial chemoembolization were performed according to the response. We performed survival assessment and all patients were assessed for survival at the last follow-up.

Results: Included in this study were 71 patients of whom there were 57 (80.3 %) males, with a mean age of 51.9±12.1 years (range: 18-76 years). The mean follow-up period was 12.5±10.7 months. A total of 31 (43.7%) patients had only one session of transarterial chemoembolization, 17 (23.9%) underwent 2 and 11 (15.5%) had 3 or more sessions. On univariate analysis, significant factors that predicted survival included serum bilirubin (P=0.02), esophageal varices (P=0.002), Cancer of the Liver Italian Program score (P=0.003), tumor size (P=0.005), >3 sessions of transarterial chemoembolization (P=0.006) and patient's age (P=0.001). Cox regression analysis showed that tumor size of <5cm (P=0.025), absence of varices (P=0.035), Cancer of the Liver Italian Program class (P=0.015), and >1 transarterial chemoembolization session (P=0.004) were associated with better survival.

Conclusion: Our study demonstrates that survival after transarterial chemoembolization is predicted by tumor size, Cancer of the Liver Italian Program classification, bilirubin <2.0 mg/dl, absence of varices and >3 transarterial chemoembolization sessions.

Keywords: Cirrhosis, Hepatocellular carcinoma, Prognosis, Survival, Transarterial chemoembolization

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Introduction

Hepatocellular carcinoma (HCC) accounts for 70%-85% of primary liver cancer burden worldwide.[1] Although resection and liver transplantation are the only curative interventions, the majority of patients fail to undergo surgery due to multiple factors such as large tumor size, severe co-morbidities, advanced tumor stage and poor liver reserve.[2] Therefore, in unresectable HCC, radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) are possible palliative modalities.[3] Transarterial chemoembolization is generally accepted as a palliative approach and has been shown to improve survival in unresectable HCC.[4,5]

The common adverse event related to TACE is post-TACE syndrome (fever, abdominal pain, nausea and vomiting, leukocytosis and elevated liver enzymes lasting for a few hours to a few days),[6] decompensation of cirrhosis,[7] liver abscess and tumor lysis syndrome.[8,9] Hepatic failure and renal failure which, although infrequent, are among the major treatment related complications that may lead to significant morbidity and burden to health care services.[10,11]

In Asian and European studies, various prognostic factors including early tumor stage,[2] small tumor size,[12] and localized disease[13] have been associated with improved survival after TACE. A previous study in Pakistan[14] has enlightened the prognostic factors of unresectable HCC but no study reported factors predictive of survival after TACE in this country.

For third world countries like Pakistan where resources are scarce, it is important to select suitable candidates for this procedure in order to decrease the health care burden and ensure appropriate use of resources. Therefore, the objective of this study is to explore the prognostic factors in patients who undergo TACE for unresectable HCC.

Materials and Methods

Patients

This study included all patients diagnosed as

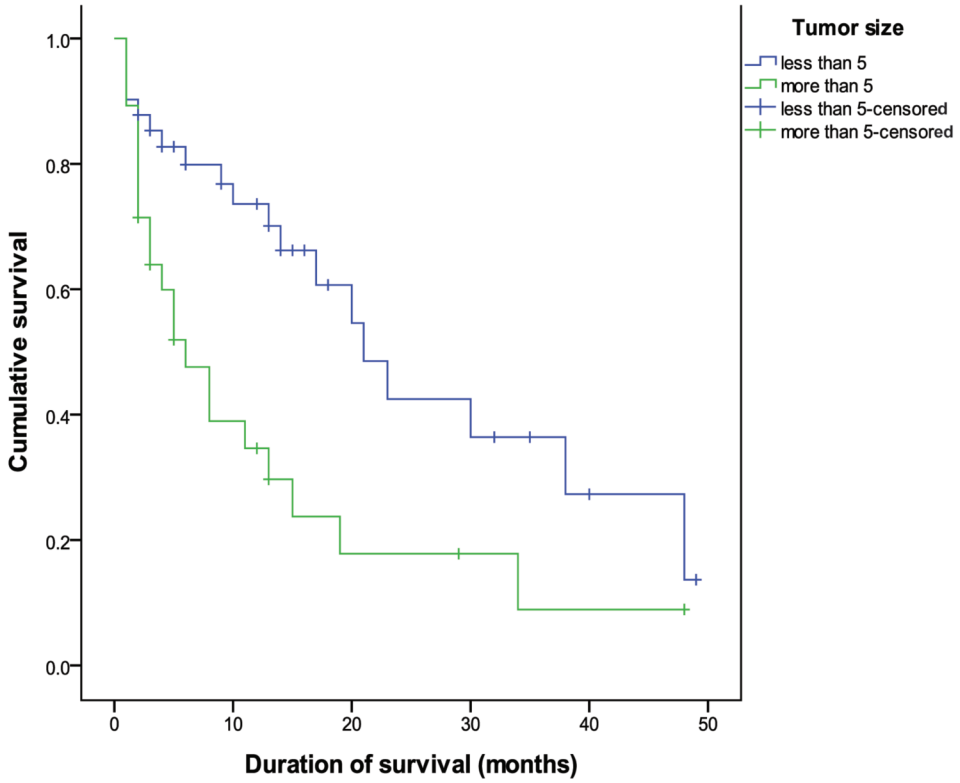

Figure 1. Kaplan-Meier survival analysis showing according to tumor size less than or greater than 5 cm. There was a significant difference in survival (P=0.025).

HCC according to American Association Study of Liver Disease (AASLD) criteria[15] and found eligible for TACE for five years, from September 2007 to September 2012. We excluded patients who presented within 6 months of any previous intervention such as RFA or surgical liver resection for HCC.

Inclusion criteria

All consecutive patients of all ages and both sexes diagnosed with non-resectable and non-ablatable HCC were enrolled as potential candidates. We defined cases of HCC as non-resectable when any one or more of these conditions were found: severe comorbidity that precluded the administration of general anesthesia; liver dysfunction and/or portal hypertension that contraindicated parenchyma loss during radical tumor resection. Ablation therapy was not indicated when the maximum diameter of the tumor was >5 cm, when the tumor was in close proximity to major vascular or biliary structures, or if there was multifocal disease.

Methods

This was a retrospective observational study. Approval was obtained from the Ethical Review Committee (ERC) of Sindh Institute of Urology and Transplantation (SIUT). We included 71 patients in this study. The TACE procedure was performed in the Radiology Department and involved injection of a chemotherapeutic agent (doxorubicin) mixed with lipoidal into selectively or super selectively catheterized branches of the arteries feeding the tumor followed by injection of gelfoam particles to reinforce the effect of treatment. After the procedure, the patient was shifted to the Gastroenterology Ward for observation. A structured proforma was used to collect data and included demographics (age, gender), clinical (etiology), laboratory parameters [serum bilirubin, albumin, creatinine, international normalized ratio (INR), and alpha-fetoprotein (AFP)] and imaging (number of lesions, size, and lobe involved). Data were collected from patient case records. Child-Turcotte-Pugh (CTP) score, Model of end-stage liver disease (MELD)

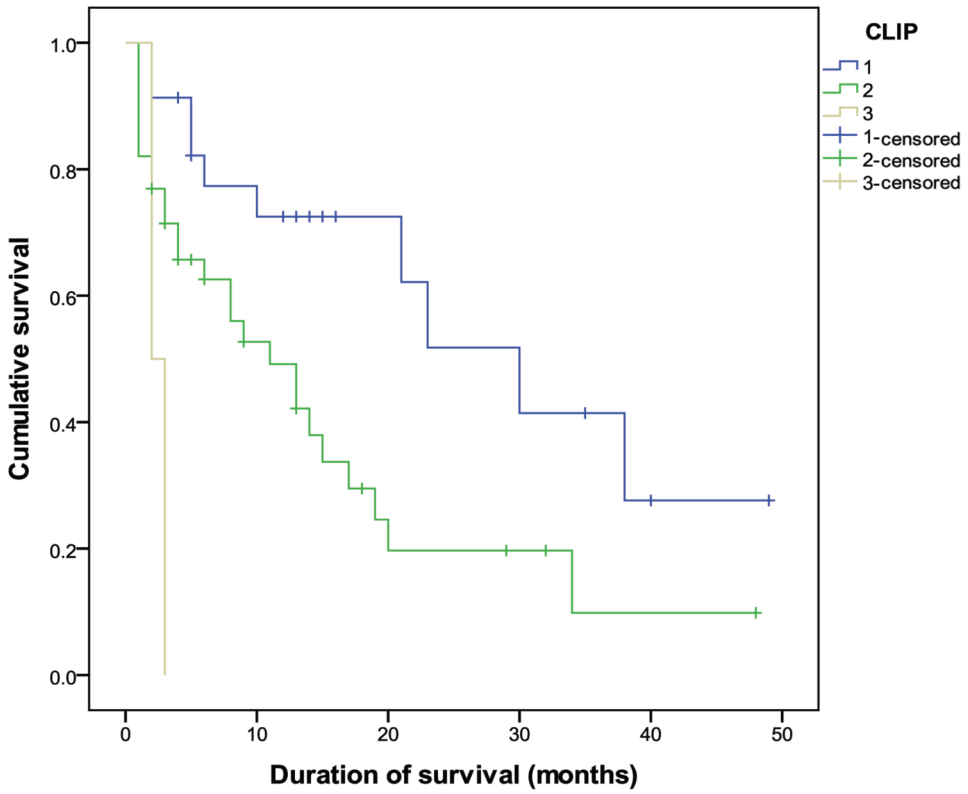

Figure 2. Kaplan-Meier survival analysis showing according to the Cancer of the Liver Italian Program (CLIP) class. There was a significant difference in survival among the three classes (P=0.015).

score, Cancer of the Liver Italian Program (CLIP) score, and Okuda staging system were used to stage HCC, as in our previous study.[14] At the end of 6 weeks, a computerized tomography (CT) scan of the abdomen was performed as per the TACE protocol. Response of TACE was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria[16] after first session of TACE. Inquiry was made through telephone calls to determine the patient's survival status.

Statistical analysis

The data were statistically analyzed using Statistical Package for the Social Sciences (SPSS) software version 19.0 (Chicago, IL, USA). The frequency and percentages were computed for different categorical variables such as gender and cause of HCC. Mean and standard deviation were computed for age. We employed the two-sided Fisher's exact test to analyze the dichotomous variables before and after TACE. Univariate analysis and multivariate analysis were also performed. *P*-value of <0.05 was considered significant. Survival was calculated using Kaplan-Meier estimates, with comparisons generated using the log rank test.

Results

A total of 71 patients with HCC who underwent chemoembolization with doxorubicin and lipoidal satisfied the study inclusion criteria and were included in the study. There were 14 (19.7%) women and 57 (80.3%) men with a mean age of 51.9±12.1 years (range: 18 to 76 years). A total of 41 (57.7%) patients died during the study period. The demographic, clinical, laboratory, tumor staging and imaging characteristics are summarized in Table 1. The main clinicopathological characteristics of the tumors are shown in Table 2. The mean duration of follow-up was 12.5±10.7 months (range:

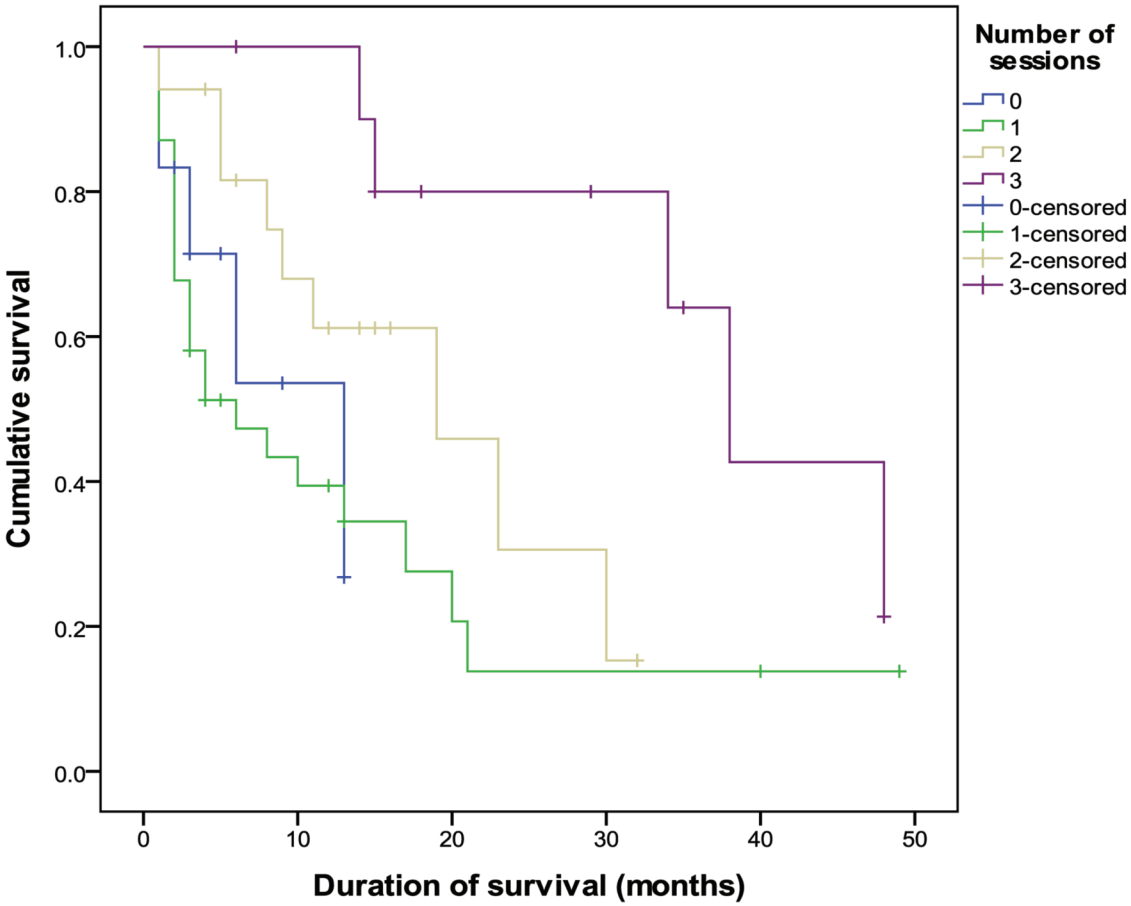

Figure 3. Kaplan-Meier survival analysis according to the number of TACE sessions. The survival was significantly better in patients who received three or more sessions (*P*=0.004).

1 to 49 months). Univariate analyses of patient- and tumor-related variables along with various prognostic scoring systems are given in Table 3. The prognostic factors found to be associated with survival on univariate analysis were age >50 years, >3 sessions of TACE, absence of varices, repeat TACE sessions, CTP class, early Okuda stage, CLIP score, bilirubin <2.0 mg/dl and tumor <5 cm (Figures 1, 2 and 3). Gender, creatinine, INR, serum albumin, AFP, and number of lesions were not significant prognostic factors. On multivariate analysis, tumor size <5 cm, age >50 years, >3 sessions of TACE, stage I CLIP and bilirubin <2 mg/dl were significant predictors of survival (Table 4).

Table 1. Patients' demographic, clinical and laboratory characteristics.

Age (years)	
<50, n (%)	26 (36.6)
≥50, n (%)	45 (63.4)
Gender	**n (%)**
Male	57 (80.3)
Female	14 (19.7)
Etiology	**n (%)**
Non-B, Non-C	10 (14.1)
Hepatitis C	45 (63.7)
Hepatitis B	8 (11.3)
Hepatitis B and C	5 (7)
Other	3 (4.2)
Varices	**n (%)**
Present	30 (43.5)
Absent	24 (34.8)
Ascites	**n (%)**
Present	57 (80.3)
Absent	12 (16.9)
Number of TACE sessions	**n (%)**
1	31 (43.7)
2	17 (23.9)
≥3 sessions	11 (15.5)
Follow-up (months) mean (range)	12.15+10.7 (1-49)
Repeat TACE, n (%)	28 (47.5)
Serum creatinine, mmol/l, mean (range)	0.93 (0.56-1.78)
Serum albumin, g/dl, mean (range)	2.89 (1.4-4.8)
INR, mean (range)	1.26 (1-1.83)
Serum total bilirubin, mg/dl, mean (range)	1.48 (0.39-6.3)

INR: International normalized ratio

Discussion

Although TACE is associated with a significant survival advantage in the management of non-resectable HCC, there is a higher morbidity and mortality associated with the management of advanced liver cancer. The survival advantage of TACE has been validated in many randomized control trials. Llovet et al.[4] reported 63% two-year survival while Lo et al.[5] reported 26% three-year survival in patients who underwent TACE. A recent meta-analysis also supported the benefit of chemoembolization in selected patients.[17] Therefore, TACE has been accepted as a treatment of choice in patients with unresectable HCC.

Chronic hepatitis C appears to be the major risk factor for the development of HCC[18] which is consistent with our study population where HCV has accounted for 63.7% of patients. On the contrary, in the studies from India, China, and Korea,[1] hepatitis B virus (HBV) infection emerged as the most common factor for HCC. Multiple prognostic factors associated with better outcomes have been observed in previous studies and include the absence of diffuse disease,[13] low MELD score, reduction in serum AFP after TACE, small tumor size,[12] and increased number of sessions of TACE. Chen et al.[19] reported that age had a paradoxical effect on HCC outcome and that younger patients had poor survival in the earlier years of diagnosis, however they had the best outcome thereafter. A study at a single Canadian center[2] also reported younger age group as a predictor of survival after TACE on univariate analysis. This finding contrasted the results of the current study in which patients' age above 50 years was a better predictor of survival than age below 50 years. This could partly be attributed to the fact that the majority of the current study patients were above 50 years of age.

In decompensated liver cirrhosis, Ueno et al.[20] reported that absence of esophageal varices, solitary tumor, small tumor, high albumin, and low AFP were favorable survival factors for HCC patients. Elia et al.[21] observed that TACE in 15 patients with esophageal varices had no influence on the hepatic venous pressure gradient (HVPG) and variceal bleed occurred in 1.5% of 125 patients. However no study has reported esophageal varices as a prognostic factor of survival in patients with unresectable HCC. In our study esophageal varices were absent in 34.8% of the participants; these patients fared well

in survival analysis (*P*=0.035).

The policy on subjecting patients to repeat TACE sessions depends on the center. Some perform the procedure on pre-decided intervals,[4,5] while others decide on the basis of follow-up imaging findings.[22,23] We performed repeat TACE sessions on the findings of a follow-up CT scan taken at 6 weeks after TACE. It is known that TACE is more efficacious when performed on the basis of follow-up imaging findings rather than scheduled intervals.[24]

Because the tumor cells remain viable after TACE, a complete tumor response following TACE is rare (0-4.8%).[23] We have achieved complete response in 26.9% of patients, while partial response was seen in 32.7%. In this study, 43 patients underwent one session of TACE while 11 patients underwent more than 3 sessions. Farinati et al.[25] reported the number of TACE sessions as one of the significant prognostic factors which supported the current study results (*P*=0.004).

Brown et al.[26] showed CTP score as superior to MELD score in predicting the outcome of patients undergoing TACE for unresectable HCC. A recent study of patients with unresectable HCC who underwent doxorubicin drug eluting beads (DEB) TACE reported that CTP class, Okuda staging, low MELD score, and CLIP score were found to be prognostic markers of survival after treatment.[27,28] In our study CTP, CLIP and Okuda stages showed statistical significance on univariate analysis. However on multivariate analysis only CLIP classification (*P*=0.015) was associated with improved survival.

Both albumin and bilirubin are part of CLIP, CTP and Okuda scoring systems and have been evaluated as important predictors of survival in patients undergoing TACE for HCC.[27] In our study serum albumin was not a statistically significant factor, however serum bilirubin levels >2 mg/dl were associated with poor outcome, which was consistent with previous studies.[12,26]

In addition, HCC size at the commencement of TACE is an important factor in predicting ultimate response and survival. Complete necrosis after TACE is rarely observed in HCC larger than 5 cm.

Table 2. Tumor characteristics.

Number	
Single	38 (54.3)
2-3	9 (12.7)
More than 3	23 (32.4)
Size	**n (%)**
<5 cm	41 (59.4)
≥5 cm	28 (40.6)
Location	**n (%)**
Right lobe	41 (61.2)
Left lobe	16 (23.9)
Bilobed	10 (14.9)
Vascular invasion	**n (%)**
Present	5 (7)
Absent	66 (93)
CTP class	
A	34 (47.9)
B	31 (43.7)
C	4 (5.6)
CLIP classification	
Early	23 (35.9)
Intermediate	39 (60.9)
Advanced	2 (3.1)
Okuda classification	**n (%)**
Stage I	15 (21.1)
Stage II	47 (66.2)
Stage III	6 (8.5)
MELD Score, median (range)	
<15	54 (84.4)
≥15	10 (15.6)
TACE sessions	
1	43 (60.6)
2	17 (23. 9)
≥3	11 (15. 5)
TACE response after 1st session	**n (%)**
Complete response	14/52 (26.9)
Partial response	17/52 (32.7)
Serum AFP level, median (range)	9204.9 (1.25-300000)
Rise in AFP level after TACE	12 (16.9)
Recurrence	45 (63.7)

CTP: Child-Turcotte-Pugh; CLIP: Cancer of the Liver Italian Program; MELD: Model of end-stage liver disease; AFP: Alpha-fetoprotein.

Large tumor size has been reported previously to be associated with poor outcome after TACE,[13,22,23] which is consistent with our finding. In the current study,[28] of 71 patients (39.43%) had tumor size 5 cm which was associated with poor outcome (*P*= 0.025).

To the best of our knowledge, no study has been performed to predict prognostic factors of survival after TACE for HCC patients in Pakistan. Previous studies have emphasized HCC screening, not only due to its cost effectiveness and as the only method

Table 3. Univariate analysis of patient and tumor characteristics.

Variables	Mean Estimate	SE	95%	CI	*P*-value
Tumor size (cm)					0.005
<5	25.435	3.463	18.647	32.223	
≥5	12.637	3.097	6.566	18.708	
Repeat TACE		0.004			
Yes	27.796	3.683	20.577	35.015	
No	13.425	3.357	6.845	20.005	
Number of TACE sessions					0.006
1	13.738	3.151	7.563	19.914	
2	18.495	2.923	12.767	24.224	
≥3	36.927	4.736	27.644	46.209	
Rise in AFP		0.361			
Yes	15.364	3.409	8.682	22.046	
No	24.786	4.298	16.361	33.211	
Age (years)		0.001			
<50	10.721	2.243	6.325	15.118	
≥50	26.169	3.406	19.493	32.844	
Gender					0.866
Male	19.775	2.704	14.476	25.075	
Female	18.986	6.056	7.116	30.856	
Number of lesions					0.619
Single	21.646	3.494	14.797	28.495	
2-3	12.207	3.541	5.267	19.148	
Multiple	14.907	2.860	9.302	20.512	
Ascites					0.278
Absent	20.962	2.909	15.261	26.663	
Present	13.750	4.093	5.729	21.771	
Okuda					0.014
Stage I	24.692	4.858	15.171	34.214	
Stage II	19.315	3.241	12.964	25.667	
Stage III	5.500	2.717	0.174	10.826	
CTP					0.010
A	24.997	3.382	18.368	31.626	
B	15.313	4.094	7.288	23.338	
C	7.250	4.270	0.000	15.618	
CLIP					0.003
1	27.851	4.356	19.315	36.388	
2	14.912	2.799	9.425	20.398	
3	2.500	0.500	1.520	3.480	
Total bilirubin					0.02
<2	21.473	2.868	15.852	27.093	
2-3	9.063	2.830	3.516	14.609	
>3	6.000	3.536	0.000	12.930	
Albumin					0.86
>3.5	25.469	6.091	13.531	37.407	
3.0 to 3.5	20.437	3.017	14.525	26.350	
<3.0	15.301	3.856	7.743	22.860	
Varices					0.002
Yes	19.417	3.523	12.512	26.322	
No	29.134	4.973	19.386	38.882	
MELD					0.89
<15	20.571	3.024	14.644	26.498	
≥15	9.990	3.424	3.279	16.701	
Tumor response					0.112
Complete	31.786	5.489	21.026	42.545	
Partial	26.316	5.450	15.634	36.997	
Progressive disease	17.410	3.406	10.734	24.087	
AFP					0.255
<100	21.459	3.571	14.461	28.458	
≥100	17.081	3.713	9.804	24.358	

CTP: Child-Turcotte-Pugh; CLIP: Cancer of the Liver Italian Program; MELD: Model of end-stage liver disease; AFP: Alpha-fetoprotein.

Table 4. Multivariate analysis of different factors that affect patient survival after TACE therapy.

	Hazard Ratio	*P*-value
Tumor size	0.238	0.025
TACE sessions	0.088	0.004
CLIP classification	0.123	0.015
Total bilirubin	0.240	0.057
Varices	0.241	0.012
Age	3.728	0.010

CLIP: Cancer of the Liver Italian Program; TACE: Transarterial Chemoembolization.

for early diagnosis of HCC, however it can be beneficial for patients who are not candidates for surgery because tumor size is a predictor of patient survival. We also suggest the need for an upper gastrointestinal endoscopy for detection of esophageal varices as we have shown this to be an important predictor of survival in the study population.

Our study had some limitations. This was a single center study with retrospective data collection. Hepatocellular carcinoma was diagnosed on the basis of CT scan as per AASLD criteria. Although rare, the possibility of mixed HCC and cholangiocarcinoma (CC) could not be entirely excluded.

Conclusion

In summary, our study has shown that survival after TACE is determined by tumor size, CLIP classification, bilirubin <2.0 mg/dl, absence of varices and >3 TACE sessions.

Conflict of Interest

No conflict of interest is declared.

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