

The effect of transarterial chemoembolization therapy on survival in patients with non-resectable hepatocellular carcinoma: Single-center study results

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Abstract

Background and Aim: This study was designed to investigate the tumor response and effect of drug-eluting transarterial chemoembolization (DEB-TACE) treatment on survival in patients diagnosed with hepatocellular carcinoma (HCC).

Materials and Methods: The records of 40 patients who underwent DEB-TACE between March 2018 and November 2020 were retrospectively analyzed. Follow-up included abdominal computed tomography and measurement of serum albumin, bilirubin, prothrombin time, and alpha-fetoprotein values. The treatment response was evaluated using the European Association for the Study of the Liver criteria.

Results: A total of 70 TACE sessions were performed in the 40 study patients with HCC. The etiology was chronic hepatitis B virus (n=32), secondary biliary cirrhosis (n=2), cryptogenic (n=2), or chronic hepatitis C virus (n=4). Based on the TACE response, complete response was observed in 22 patients, a partial response in 8 patients, and progression in 10 patients. Liver transplantation was performed for 4 patients who had a complete response. The formation of new nodules was observed in 8 patients during the follow-up period. In all, 29 patients survived and 11 died.

Conclusion: The findings of this study suggest that DEB-TACE had a positive effect on the survival of patients diagnosed with HCC who could not be treated surgically.

Keywords: Chronic liver disease; hepatocellular carcinoma; transarterial chemoembolization.

Introduction

Liver cancer ranks as the fifth most common cancer globally, and the second most frequent cause of cancer-related mortality. Hepatocellular carcinoma (HCC) constitutes more than 90% of liver cancer cases and is an important worldwide health problem.^[1-3] Surgery is the main treatment strategy for liver cancer, however, the cancer is considered unresectable at the time of diagnosis in a majority of cases. In recent years, management of HCC has significantly improved. Several treatment methods have been used effectively, even in patients with advanced disease.^[4,5]

In cases of HCC, local destruction occurs in the liver and that damage subsequently progresses to liver failure and death. Therefore, local treatment methods, such as transarterial chemoembolization (TACE) or tumor ablation, have become important in the management of HCC. TACE has been widely accepted as a method of treatment for unresectable HCC and has become the standard treatment for patients with intermediate-stage or unresectable HCC according to the Barcelona Clinical Liver Cancer staging system (BCLC).^[4,6-9]

This study was an evaluation of data related to patients with unresectable HCC who underwent drug-eluting bead TACE (DEB-TACE). The objective was to evaluate the effect of TACE treatment and to try to identify the effect of other factors, such as age, gender, and the Child-Pugh score on HCC survival.

Materials and Methods

This study was designed and conducted according to the Declaration of Helsinki and ethics committee approval was granted (no: 28928.28/04/2021).

The medical records of patients diagnosed with HCC at the Harran University Faculty of Medicine between May 2018 and January 2021 were retrospectively evaluated. Of those, only patients treated with TACE were included in the study. The inclusion criteria were (i) patients with Child-Pugh score A or B cirrhosis, (ii) the presence of at least 1 HCC tumor, (iii) BCLC A stage but unsuited to ablative therapy, and (iiii) computed tomography (CT) performed before the TACE procedure and during follow-up. The exclusion criteria were (i) extra-hepatic disease, (ii) Child-Pugh score C cirrhosis, (iii) more than 3 HCC tumors, and (iv) systemic treatment before TACE.

Statistical Analysis

IBM SPSS Statistics for Windows, Version 23.0 software (IBM Corp.,

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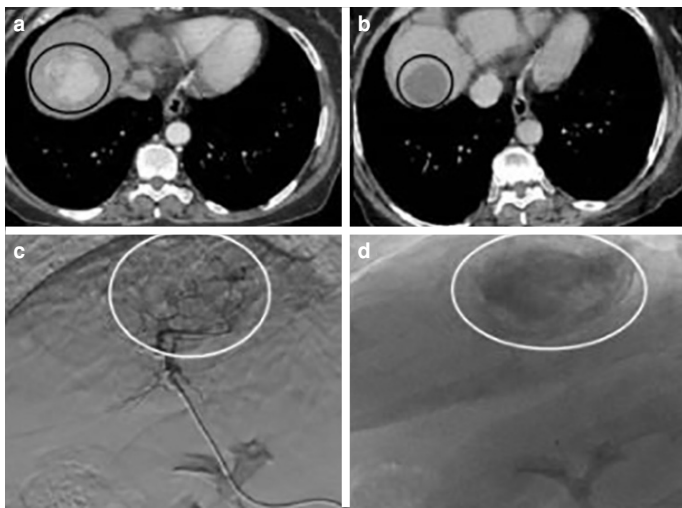


Figure 1. (a) There is severe contrast enhancing HCC in the liver dome (black circle). (b) Completely necrosis of the tumor after TACE (black circle). (c) Angiographic image of the tumor made from the feeding artery (white circle). (d) Angiographic image showing that the mixture of particle-doxorubicin injected into the tumor is taken up by the tumor (white circle).

Armonk, NY, USA) was used to perform the analysis of data. Survival relationships were examined using an independent sample t-test and one-way analysis of variance. A *p* value of <0.05 was considered statistically significant. The impact of categorical variables on survival rate was determined using Kaplan-Meier survival analysis.

Transarterial Chemoembolization Procedure

TACE was implemented using local analgesia, heparin (5000 IU), antibiotic prophylaxis (cephalosporin), and antiemetic (granisetron) drugs. Angiography was performed according to a standardized protocol prior to intervention. Superselective catheterization of the hepatic artery and the artery supplying the tumor was performed using a 2.7-F microcatheter (Progreat; Terumo Corp., Tokyo, Japan) in all cases. DEB-TACE was then applied to the feeding vessel with a combination of DC beads (Biocompatibles; Terumo Corp., Tokyo, Japan) loaded with doxorubicin (Fig. 1). The microsphere size (100–300 μm and 300–500 μm) of the beads was chosen according to the size of the tumor. DC beads 100–300 μm and/or 300–500 μm in size were used for lesions >6 cm, while beads 100–300 μm in size were used for

lesions <6 cm in size. Doxorubicin was administered in a maximum dose of 150 mg per embolization contingent on the tumor size. After loading the beads, the fluid was removed from the suspension and the beads were diluted in 15 mL contrast material (Ultravist 300 mg/mL; Bayer AG, Leverkusen, Germany). The intervention was terminated when imaging confirmed no contrast agent drainage into the tumor and appropriate blood flow blockage.

Treatment Response and Follow-Up

The European Association for the Study of the Liver (EASL) criteria were used to evaluate treatment outcome. No sign of intratumoral arterial enhancement was considered a complete response, a reduction of 50% in all arterial enhancement areas was classified as a partial response, and a 25% increase in the size of arterial enhancement areas, or the formation of new lesions was considered treatment failure or non-response.

The alpha-fetoprotein (AFP), albumin, and bilirubin values of all of the patients were assessed, along with CT examination, before and 1 month after a TACE procedure. For patients with a partial response demonstrated on CT, second or third TACE procedures were performed (Fig. 2). Additional TACE sessions were not performed for patients who did not respond to the therapy.

Results

A total of 40 patients (30 male) with median age of 65 years (range: 52–83 years) at the time of HCC diagnosis were included in the study. The general characteristics of the study population are presented in Table 1. The etiology of the HCC was chronic hepatitis B virus (HBV) ($n=32$), secondary biliary cirrhosis ($n=2$), cryptogenic ($n=2$), and chronic hepatitis C virus (HCV) ($n=4$). Sixteen patients had a Child-Pugh score classification of A, 18 patients were ranked as Child-Pugh score B, and the remaining 6 patients were ranked as Child-Pugh C. Thirty patients had a single HCC nodule, 8 had 2 nodules, and 2 patients had 3 nodules. A total of 70 TACE sessions were performed in 40 patients. In all, 22 patients had 1 TACE procedure, 13 patients had 2 sessions, and 5 patients had 3 or more. The median length of follow-up was 16 months (range: 10–25 months) after the first TACE procedure. Among 40 treated patients, 22 patients demonstrated a complete response to TACE, 8 patients had a partial response, and 10 patients were considered non-responders.



Figure 2. (a) Tomography image of the mass compatible with HCC with significant contrast enhancement in the right lobe posterior segment of the liver (black circle). (b) After the first session of TACE, there are contrast-enhancing residual tumor tissues in the mass (black arrows). (c) After the second session of TACE, it is seen that the mass has developed complete necrosis (white circle).

Table 1. Survival and p values according to findings in HCC patients

Variables	Complete response (n=22)	Progression (n=10)	Partial response (n=8)	p
Gender				
Female	10 (45.5%)	0 (0%)	0 (0%)	0.000
Male	12 (54.5%)	10 (100%)	8 (100%)	
HCC etiology				
HBV	16 (72.7%)	10 (100%)	6 (75%)	0.304
Secondary biliary cirrhosis	2 (9.1%)	0	0	
Cryptogenic	0	0	2 (25%)	
HCV	4 (18.2%)	0	0	
Child-Pugh score				
A	8 (36.4%)	4 (40%)	4 (50%)	0.002
B	10 (45.5%)	4 (40%)	4 (50%)	
C	4 (18.2%)	2 (20%)	0	
Number of nodules				
n=1	18 (81.8%)	7 (70%)	5 (62.5%)	0.037
n=2	4 (18.2%)	1 (10%)	3 (37.5%)	
n=5	0	2 (20%)	0	
Mass diameter				
≥50 mm	14 (63.7%)	6 (60%)	4 (50%)	0.680
>50 mm	8 (36.3%)	4 (40%)	4 (50%)	
Baseline AFP value				
≥400 ng/mL	4 (18.2%)	2 (20%)	2 (25%)	0.232
<400 ng/mL	18 (81.8%)	8 (80%)	6 (75%)	
AFP value after TACE				
≥400 ng/mL	6 (27.3%)	8 (80%)	4 (50%)	0.973
<400 ng/mL	16 (72.7%)	2 (20%)	4 (50%)	
New nodule formation during follow-up				
Yes	2 (9.1%)	6 (60%)	0	0.198
No	20 (90.9%)	4 (40%)	8 (100%)	

AFP: Alpha-fetoprotein; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; TACE: Transarterial chemoembolization.

In all, 29 patients in this study were alive and 11 died. Kaplan-Meier survival analysis of patients with HCC according to TACE response are illustrated in Figure 3.

Analysis indicated that the overall survival was significantly higher in females than males (p=0.000). The number of nodules was inversely correlated with survival (p=0.037). Complete response to TACE was significantly associated with better survival (p=0.011).

Overall survival was better in patients with a Child-Pugh A status than those with Child-Pugh B or C status (p=0.002). The baseline AFP value (<400 ng/mL vs >400 ng/mL), post-TACE AFP value (<400 ng/mL and >400 ng/mL), etiology of HCC, number of TACE procedures, and the diameter of nodules (>50 mm vs <50 mm) were not associated with survival.

Discussion

We observed that DEB-TACE treatment had a positive effect on survival in HCC patients. Our results confirm previous studies that have reported favorable effects of DEB-TACE on the survival of patients with HCC.^[10-12]

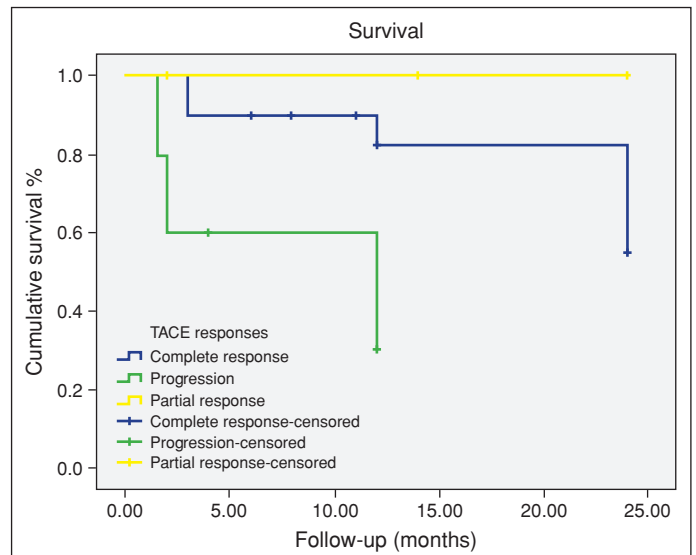


Figure 3. Illustration of Kaplan-Meier survival analysis based on response to transarterial catheterization (TACE).

The use of localized treatment methods to treat HCC has increased in recent years. Percutaneous ablation and angiographic embolization remain the primary methods used with HCC patients.^[13] However, TACE is the most frequently used local treatment method. There are 2 different techniques available: conventional TACE and DEB-TACE. The difference is in the agents loaded with the chemotherapeutic drug. A meta-analysis recorded no significant difference between the techniques in 3-year surveys.^[6] In another meta-analysis, the complete tumor response and general survey results of DEB-TACE were superior to conventional TACE, with fewer side effects.^[7] DEB-TACE was used in the present study to evaluate its effect on survival.

The purpose of local treatment methods, such as TACE, for patients with HCC is to effect tumor necrosis. Reducing the tumor burden is an important parameter.^[14] Dynamic CT and magnetic resonance imaging are considered the gold standards in the evaluation of therapeutic response after TACE treatment.^[15] Dynamic imaging modalities, which can reveal tumor vascularity and viability, are essential tools for the evaluation of treatment efficacy. The presence of necrosis and a decrease in enhancement are indicators of success in response to treatment.^[16,17] In this study, we evaluated tumor response according to the EASL criteria, which evaluates the tumor's response according to the amount of arterial enhancement and necrosis. We found that overall survival was better in patients who developed complete necrosis than those who did not.

The prognosis of HCC is related to several tumor qualities and factors related to hepatic function.^[18] Factors such as the etiology, size and diameter, number of nodules, vascular invasion, extrahepatic metastasis, and liver reserve, are important. Analysis of the relationship between gender and survival in this study indicated that, while the mortality rate was higher among men, the uneven sample distribution prohibited a conclusive evaluation of the effect on women. We observed a significant relationship between the number of nodules and survival. The survival rate among all patients decreased as the number of nodules increased. However, no significant relationship was found between the size of nodules and survival. The survival rate was higher in the patients with a Child-Pugh A stage diagnosis. Similarly, other studies have reported that survival decreased with a more severe Child-Pugh score and a greater number of nodules.^[19,20]

Although liver transplantation is a curative treatment for HCC, most patients are identified at an advanced stage beyond the BLCL transplant criteria. Therefore, treatment that can provide for effective regression of the tumor stage may provide a potential advantage for transplantation.^[21] In this study, regression in tumor staging was observed in 4 patients after the procedure and transplantation was performed.

Several complications, such as liver abscess, tumor rupture, bile duct injury, renal failure, necrotizing pancreatitis, or new-onset or worsening hepatic encephalopathy, have been reported after TACE.^[22,23] In our study, no major complications developed in any of the patients. Minor complications were seen: pain post-embolization was noted in 24 patients, and vomiting was recorded in 18 patients.

Liver function reserve was found to have prognostic value in this study. These include the Child-Pugh score, and acid presence, bilirubin, and serum albumin values. In cases of localized spread of HCC, the already-poor liver function further deteriorated. Arterial chemoembolization can be an effective treatment to control the local spread of HCC.

The small number of patients and the retrospective nature of this study are the principal limitations to the interpretation of the results. In addition,

different drug doses may affect the overall survival and outcome of individual patients. Nonetheless, the efficacy and safety of TACE demonstrated in our study population could be useful to additional prospective and large-population studies.

In conclusion, TACE is an effective palliative treatment method that provides local control of a tumor in patients diagnosed with HCC who cannot be treated surgically, increases survival, and can make some patients suitable for transplantation by providing for regression in tumor staging.

Ethics Committee Approval: The Harran University Clinical Research Ethics Committee granted approval for this study (date: 28.04.2021, number: 28928).

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Author Contributions: Concept – MK; Design – MK; Supervision – MK; Fundings – OD; Materials – SS; Data Collection and/or Processing – SS; Analysis and/or Interpretation – OD; Literature Search – OD; Writing – MK; Critical Reviews – SS.

Conflict of Interest: The authors have no conflict of interest to declare.

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