Research Article

DEB-TACE in hepatocellular carcinoma

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Evaluation of the effectiveness of drug-eluting transarterial chemoebolization in hepatocellular carcinoma

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Abstract

Background and Aim: Transarterial Chemoembolization (TACE) therapy is currently considered as first option therapy in the intermediate stage HCC. The purpose of our study is to assess the efficacy and prognostic factors related to the DEB- TACE therapy.

Materials and Methods: The data from 133 patients with unresecetable HCC who were treated with DEB-TACE and followed between January 2011-March 2018 were retrospectively evaluated. To assess the efficacy of therapy, control imagings were performed at 30th and 90th days after the procedure. Response rates, survival outcomes, and prognostic factors were investigated.

Results: According to the Barcelona staging system, 16 patients (13%) were in the early stage, 58 patients (48%) were in the intermediate stage and 48 patients (39%) were in the advanced stage. There were complete response (CR) in 20 patients (17%), partial response (PR) in 36 patients (32%), stable disease (SD) in 24 patients (21%) and progressed disease (PD) in 35 (30%) patients. Median follow-up time was 14 months (range 1-77 months). Median PFS and OS were 4 months and 11 months, respectively. In multivariate analysis, posttreatment AFP ≥400 ng/ml was found to be an independent prognostic factor on both PFS and OS. Child-Pugh classification and tumor size >7 cm were independent prognostic factors on OS.

Conclusion: DEB-TACE is effective and a tolerable treatment method for unresectable HCC patients.

Keywords: DEB-TACE; Hepatocellular carcinoma; Prognostic factors

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and fourth most common cause of cancer-related deaths in the worldwide.[1] HCC is an aggressive tumor, often associated with chronic liver disease or cirrhosis. Most HCC cases are detected during screening programs of high-risk individuals or incidentally, and most of them are usually asymptomatic until the advanced stage. The median life expectancy after diagnosis of HCC is approximately six to twenty months.[2] Although, the standard treatment modality for the early stage is surgical resection, only less than 30% of patients are eligible for surgical resection at the time of diagnosis. According to Barcelona staging, since most patients receive a diagnosis at the intermediate or advanced stage, staging should consider other treatment options such as, liver transplantation, radiofrequency ablation, Transarterial Chemoembolization (TACE), Transarterial Radioembolization (TARE), systemic chemotherapy, and molecular targeted therapies.[3]

TACE, which also falls into the category of locoregional therapy, has an important role in the treatment of HCC patients with intermediate or advanced stages. In prospective studies, comparing TACE with best supportive therapy in patients with unresectable intermediate-stage HCC showed that TACE has beneficial effect on survival for this patient group.[4,5] Also, in a systematic review including randomized trials has shown that unresectable HCC patients who underwent TACE have a median survival of 2 years which is significantly higher than control groups.[6] However, impaired liver function tests due to underlying chronic liver disease cause limitations for TACE. That is to say, TACE is considered as one of the standard treatment modalities in patients with early-stage unsuitable to curative options and intermediate stage, but with preserved liver reserve and without vascular invasion and distant metastasis.[3-7]

In the present study, we aimed to evaluate the efficacy and prognostic factors for survival in patients with unresectable HCC who underwent DEB-TACE, which is a relatively new endovascular treatment.

Materials and Methods

We retrospectively collected the data of 136 HCC patients who underwent DEB-TACE therapy between January 2011 and March 2018 in Marmara University Pendik Training and Research Hospital Hospital. Inclusion criterias were histological or radiological diagnosis of HCC patients who were treated with DEB-TACE and with complete medical records. Three patients were excluded from the study because of the terminal stage. Patients treated with other treatment modalities were also excluded. As a result, 133 patients were included in the study.

The DEB-TACE Procedure

The DEB-TACE procedure was performed after eight hours of fasting. IV hydration and broad-spectrum antibiotic prophylaxis were applied to the patients who were taken to the angiography room. After local disinfection and anesthesia, with the Seldinger Technique, a 4F vessel sheath was inserted percutaneously into the right main femoral artery. Then, diagnostic celiac and superior mesenteric artery angiographies were performed with the help of 4F Simmons 2 diagnostic angiography catheter to identify the hepatic arterial anatomy and the potential presence of anatomic variants. The particle size and chemotherapeutic drug dose were determined according to tumor size. Doxorubicin was used as a chemotherapeutic agent, that dosage of 50 mg was injected into each box of particles. The recommended maximum dose is 150 mg, which was not exceeded in any our patients. Superselective injection of the microspheres through a 2.7 F microcatheter is insisted on each lesion.

Response Evaluation

The response of first DEB-TACE was evaluated with abdominal magnetic resonance imaging (MRI) or conventional computer tomography (CT) which were performed on between thirtieth day or the ninetieth day. Response evaluation was conducted according to mRecist criteria by an abdomen radiologist retrospectively. According to mRECIST criteria, Complete response (CR) was defined as the absence of enhanced tumor areas during the arterial phase, reflecting complete tissue necrosis; Partial response (PR) was defined as at least a 30% decrease, Progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameter in the enhanced tumor areas; and Stable disease (SD) was defined as neither sufficient shrinkage for partial response nor a sufficient increase for progressive disease.[8] The disease control rate (DCR) was defined as the sum of complete response, partial responses and stable disease. The objective response rate (ORR) was defined as the sum of complete response and partial response. We evaluated the alfa-feto protein (AFP) measured at the first month after DEB-TACE as post-treatment AFP response.

Progression-free survival (PFS) was defined as the time starting from the date of first DEB-TACE till radiological progression, death or last visit date. Overall survival (OS) was defined as the time starting from the date of first DEB-TACE until death any reason or last visit date. Age, gender, AFP level, vascular invasion, presence of extrahepatic metastasis, tumor size, number of tumor, Child-Pugh classification and Barcelona staging were investigated as prognostic factors for PFS and OS. Follow-up monitoring of all patients was performed until July 2018.

Statistical Analysis

OS and PFS were calculated using the Kaplan-Meier method. Prognostic factors were compared using the log-rank test in univariate analysis. Hazard ratios (HR) with 95% confidence intervals (CI) were also calculated. All p values were 2-sided in the tests, and p values of 0.05 were considered statistically significant. Multivariate analysis was carried out using the Cox proportional hazards model to assess the effect of prognostic factors on PFS and OS. SPSS 22 program was used for statistical analysis.

Results

Patients Demographic and Clinical Characteristics Outcomes

Data from a total of 133 HCC patients who underwent DEB-TACE were analyzed retrospectively. One hundred and three patients were male (77.4%), and thirty patients were female (22.6%). The median age was 65 years (40-91). The most common etiologic factor was chronic hepatitis B infection. One hundred and twenty-two patients had cirrhosis. Baseline demographics and disease characteristics for the entire study cohort are outlined in Table 1. In the whole group, the median pre-treatment AFP was 32.05 ng/ml (min 1.27-max 23967). The median AFP in cirrhotic patients was 30 ng/ml (min 1.27 ng/dl -max 23.960 ng/dl), and there was no statistical difference compared to non-cirrhotic patients (p>0.05).

Table 1. Baseline demographics and disease characteristics findings

Characteristic	n	%
Gender		
Male	103	77.4
Female	30	22.6
Age (years) (median)	65 (min 40-max 91)	
Etiolgy		
Hepatitis B	76	57.1
Hepatitis C	23	17.3
Alcohol	5	3.8
Nonalcoholic steatohepatitis	4	3
Cryptogenic	24	18.4
Others	1	0.8
ALT (IU/l (Median)	35 (min 10-max 168)	
Total bilirubin (mg /dl) (median)	0.89 (min 0.4- max 4.5)	
Albumin (g/dl) (median)	3,4 (min 1-max 4.7)	
Creatinin (mg/dl) (median)	0.8 (min 0.42-max 4.33)	
International normalized ratio (INR) (median)	1.24 (min 0.94-2.24)	
AFP level (ng/ml) (median)	32.05 (min 1.27-max 23967)	
AFP level (ng/ml)		
<400	88	76
≥400	27	24
Tumor size (median) (centimeter)	6.6 (min 1.7-max17)	
Number of tumor (median)	1 (min 1-max 4)	
Non-cirrhotic patient	11	8
Cirrhotic patient (n=122)		
Child-pugh classification		
Child A	78	64
Child B	44	36
Barcelona staging (BCLC)		
Early (BCLC-A)	16	13
Intermediate (BCLC-B)	58	48
Advanced (BCLC-C)	48	39
Treatment modality of pre-TACE		
Surgical resection	6	4.5
Radiofrekans ablation	16	12
Systemic treatment	2	15
No	109	82

ALT: Alanine aminotransferase; AFP: Alfa-feto protein; TACE Transarterial chemoembolization.

Table 2. Initial and salvage treatment characterestic and survival outcomes for whole cohort

Characteristic	n	%
Median Follow-up duration (months)	14 (min 1- max 77)	
Response		
Complete (CR)	20	17
Partial (PR)	36	32
Stable (SD)	24	21
Progression (PD)	35	30
Objective response rate (ORR)	56	49
Disase control rate (DCR)	80	70
Post-treatment AFP level (ng/ml) (median)	23.3 (min 1.7 -max 26.700)	
AFP level (ng/ml)		
<400	85	79
≥400	22	21
Progression (n=111)		
Yes	87	78
No	24	22
Second line treatment (n=87)		
Best supportive care	26	30
Surgical resection	3	4
TACE	28	32
TARE*	5	6
Radiofrekans ablatition	7	8
Systemic treatment	18	20
Mortality (n=133)		
Exitus	95	72
Alive	38	28
PFS (95% CI)		
Median (months)	4 (2.7-5.7)	
1 years (%)		23
2 years (%)		14
OS (95%CI)		
Median (months)	11 (9.0-12.91)	
1 years (%)		58
2 years (%)		47

AFP: Alfa-fetoprotein; CI: Confidence interval; PFS: Progression-free survival; OS: Overall survival; TACE: Transarteriel chemoembolization; TARE: Transarteriel radioembolization.

The median AFP was found to be 29 ng/ml (min 1.27 ng/dl-max 23.960 ng/ml) in patients with chronic hepatitis B and there was no statistically significant difference between patients with other etiologic risk factors (p>0.05). Seventy-eight (59%) patients had a single lesion. Median tumor size in the whole group was 66 mm (min 17mm-max170mm). Tumor size (median) was 65 mm, and 120 mm in cirrhotic and non-cirrhotic patients respectively. There was a statistically significant difference between the two groups (p=0.001). Vascular invasion and extrahepatic metastatis was present in 15 (12%) and 7 (5%) patients respectively. All 18 (13%) patients with portal vein thrombosis were cirrhotic. Portal lymphadenopathy was present in 39 (28%) patients (36 of cirrhotic patients, 3 of non-cirrhotic patients, p=0.012).

A total of 208 DEB-TACE procedures were performed in one hundred thirty- three HCC patients, and it has been performed median once in patients (min 1-max 5). Eighty-two patients had one DEB-TACE procedure, 32 patients had two, 15 patients had three, 3 patients had four, and 1 had five procedures. Technical success was achieved in all procedures. In the first 27 procedures of our study, DC-BEAD (Boston Scientific, Marlborough, Massachusetts, USA) was used in 19 patients (13 patients 1 procedure, 5 patients 2 procedures, 1 patient 4 procedures). Lifepearl (Terumo, Tokyo, Japan) was used in a total of 181 procedures (1 procedure for 69 patients, 2 procedures for 27 patients, 3 procedures for 15 patients, 4 procedures for 2 patients, and 5 procedures for 1 patient) in the next 114 patients. A total of 60 vials of DC-BEAD (1 vial in 15 procedures, 2 vials in 9 procedures, 3 vials in 3 procedures; mean 2.22 vials/procedure), 378 vials of Lifepearl (1 vial in 48 procedures, 2 vials in 69 procedures, 3 vials in 64 procedures; mean 2.09 vial/procedure) was used.

The mean number of vials used per procedure was 2.11 (min 1-max 3), and the mean number of vials used per patient was 3.29 (min 1-max 11). 100-300 micron and 300-500 micron particles were preferred for DC-BEAD, 200 micron and 400 micron particles were preferred for Lifepearl. Each vial microsphere was loaded with 50 mg of Doxorubicin, and the dose of 150 mg of Doxorubicin was not exceeded in any patients. The mean Doxorubicine dose per procedure was 75.5 mg (min 35 mg-max 150 mg), and the mean Doxorubicine dose per patient was 146.5 mg (min 35 mg-max 1650 mg). After DEB-TACE treatment, three patients undergo surgical resection (early stage: two patients and intermediate stage: one patient). Liver transplantation has not been performed on any patients.

Treatment Outcomes

Adverse Events Outcomes

After DEB-TACE procedure, the median hospital length of stay was one day (min 1 -14 days). None of the patients had grade 4 (Potentially life-threatening) adverse events. The most common side effects observed after the DEB-TACE were elevated liver enzyme (Grade 1: 19%, Grade 2: 6.3% and Grade 3: 5.4%), abdominal pain (22.1%) and nausea-vomiting (4.4%). Liver abscess developed in one patient. Two patients passed away within thirty days of the post-DEB-TACE procedure period. The thirty-day mortality rate was 1.5%.

Treatment Responses and Survival Outcomes

Median follow-up time was 14 months (range 1-77 months). During the follow-up, 78% of all patients progressed. After the progression, second-line treatment was given to sixty-one patients. Median PFS and OS were 4 months and 11 months, respectively (Fig. 1a, b). 12 months PFS rate was 23% and 24 months OS rate was 47%. We performed the response evaluation analysis in one hundred- fifteen patients because 18 patient's radiologic results could not be reached. For the whole cohort, there were 20 (17%) patients in CR, 36 (32%) patients in PR, 24 (21%) patients in SD and 35 (30%) patients in PD. DCR and ORR was found to be 70% and 49%, respectively. The median post-treatment AFP was 23.3 ng/ml (min 1.7 ng/ml -max 26.700 ng/ml). The AFP response rate was 61%. Initial and salvage treatment characteristics and overall clinical outcomes are outlined in Table 2.

There was no statistical difference in response rates according to Barcelona staging system in cirrhotic patients (p>0.05). However, according to the Child-Pugh classification, there was a statistically significant difference between Child A and Child B patients in terms of both ORR and DCR (p=0.04 and p=0.006, respectively). The treatment response

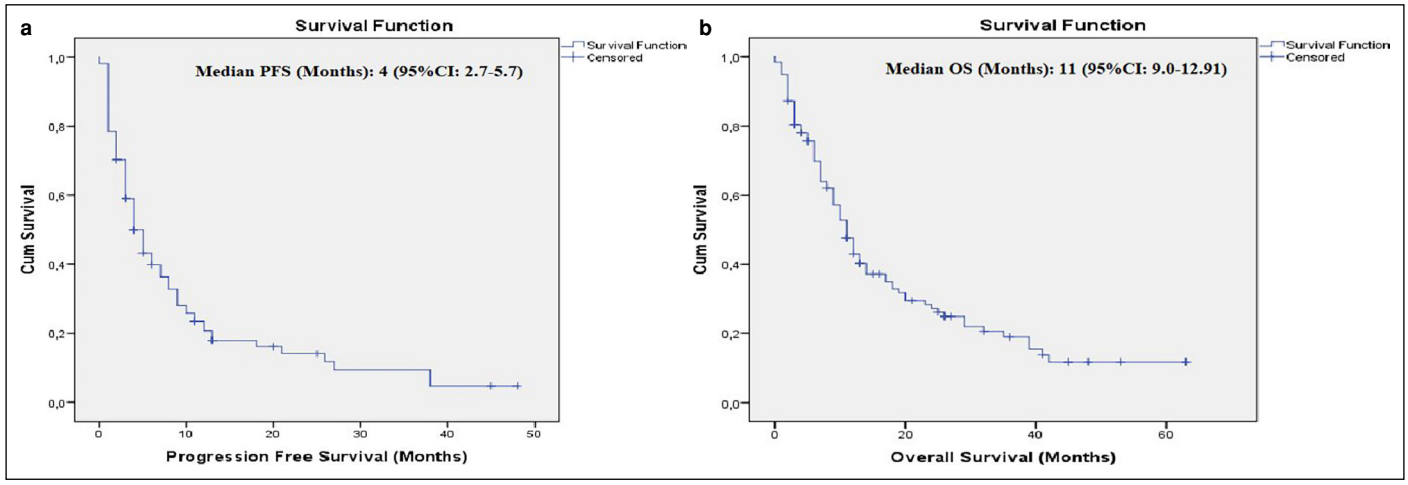

Figure 1. Survival outcomes for whole cohort by Kaplan-meir graphic. **(a)** Progression-free survival graphic. **(b)** Overall survival graphic.

Table 3. The response rates according to Barcelona staging system and child-pugh classification

	mRecist													
	Response								Response rate					
	CR		PR		SD		PD		ORR		p	DCR		p
	n	%	n	%	n	%	n	%	n	%		n	%	
Barcelona staging system											>0.05			>0.05
Early (n=13)	4	31	2	15	5	39	2	15	6	46		11	85	
Intermediate (n=50)	11	22	18	36	8	16	13	26	29	58		37	74	
Advanced (n =44)	4	9	14	31	8	18	18	40	18	40		26	59	
Child-pugh classification											**0.04**			**0.006**
A (n=75)	15	20	29	39	12	16	19	25	44	59		56	75	
B (n =32)	4	12	5	6	9	28	14	44	9	28		18	56	
Total (cirrhotic patients) (n=107)	19	17	34	32	21	20	33	31	53	49		74	69	

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate; DCR: Disease control rate.

outcomes according to Barcelona staging system and Child-Pugh classification were shown in Table 3. For survival outcomes, there was a statistically significant difference between PFS and OS according to both the Barcelona stage and Child-Pugh classification (Fig. 2a-d). Survival outcomes according to Barcelona staging system and Child-Pugh classification are given in Table 4.

Univariate and Multivariate Outcomes

Univariate and multivariate analysis results are summarized in Table 5. In multivariate analysis, Child-Pugh Classification, post-treatment AFP value and tumor size were found to be independent prognostic factors for OS. Post-treatment AFP value were independent prognostic factors for PFS. Median PFS was 5 months in patients with post-treatment AFP <400 ng/ml, 2 months in patients ≥400 ng/ml (HR: 2.5 95% CI: 1.45-4.45; p=0.01). Median overall survival was 12 months in patients with post-treatment AFP <400 ng/ml, 6 months in patients ≥400 ng/ml (HR: 2.4 95% CI: 1.41-4.40; p=0.02). Also, median overall survival was 12 months in patients with tumor size ≤7 centimeter(cm), 9 months in patients >7 cm (HR: 1.78 95% CI: 1.06-2.99; p=0.02).

Discussion

In this study, we evaluated the efficacy, safety and prognostic factors of treatment in patients with hepatocellular carcinoma who underwent DEB-TACE. The complete response rate was 17%, the partial response rate was 31%, and the objective response rate was 48.1%. Median PFS and OS were 4 months, and 11 months respectively. In univariate and multivariate analysis, Child-Pugh classification and post-treatment AFP ≥400 ng/ml were independent prognostic factors for survival. DEB-TACE treatment was well tolerated and manageable side effects in HCC patients.

TACE is the most commonly used primary treatment modality in the treatment of patients with unresectable HCC, and according to Barcelona staging (BCLC), it is recommended as a first-line treatment modality in patients with intermediate-stage HCC.[9] A randomized placebo-controlled study, which included 112 patients with Child A-B and Okuda stage 1-2 HCC who were not eligible for curative treatment, has been reported that overall survival was 28.7 months in the TACE group, 21.7 months in the transarterial embolization (TAE) group, and 17.9 months in the placebo group. One-year and two-year survival rates in the TACE group were 82% and 63%, respectively. There was a statistically significant difference in the groups.[10]

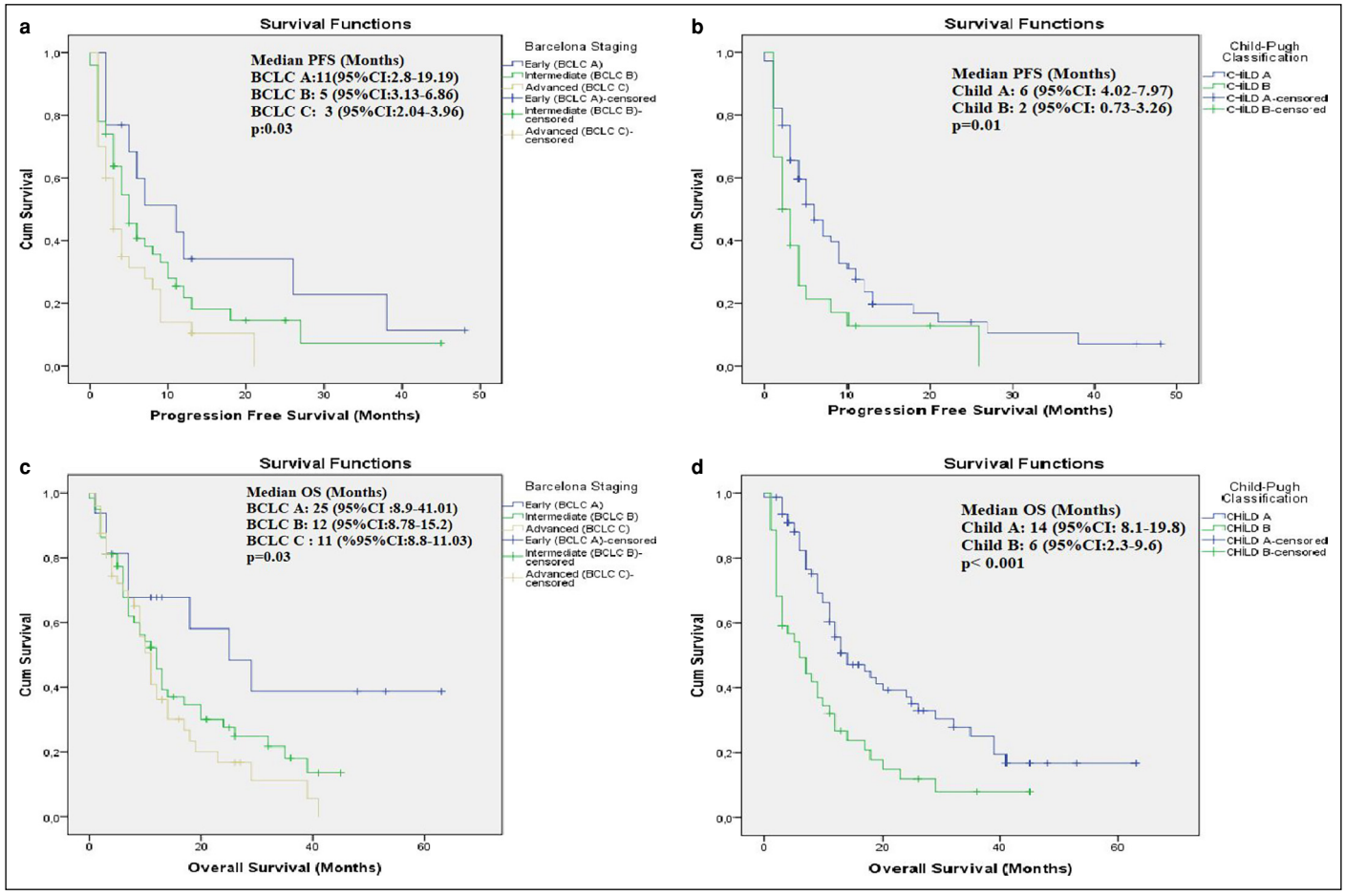

Figure 2. Survival outcomes according to barcelona stage and child-pugh classification by kaplan meier graphic. **(a)** progression-free survival graphic for Barcelona stage system. **(b)** Progression-free survival graphic for child-pugh classification. **(c)** Overall survival graphic for barcelona stage system. **(d)** Overall survival graphic for child-pugh classification.

Table 4. Survival outcomes according to Barcelona staging system and child-pugh classification

	Survival							
	PFS				OS			
	Median, Months (%95 CI)	1 years (%)	2 years (%)	p	Median, Months (%95 CI)	1 years (%)	2 years (%)	p
Barcelona staging system				**0.03**				**0.03**
Early	11(2.8-19.19)	42	34		25 (8.9-41.01)	67	58	
Intermediate	5 (3.13-6.86)	25	14		12 (8.78-15.2)	52	30	
Advanced	3 (2.04-3.96)	14	0		11 (8.8-11.03)	41	16	
Child-pugh classification				**0.01**				**<0.001**
A	6 (4.02-7.97)	27	14		14 (8.1-19.8)	60	39	
B	2 (0.73-3.26)	12	0		6 (2.3-9.6)	32	14	
Total (cirrhotic patients)	5 (3.63-6.36)	23	13		12 (9.5-14.4)	50	28	

CI: Confidence interval; PFS: Progression-free survival; OS: Overall survival.

Lammer et al.[11] compared conventional TACE and DEB-TACE, in a randomized controlled phase study which included two hundred twelve cirrhotic patients.They showed that the complete response, ORR and DCR was 27%, 52%, and 63%, respectively. Although, the DEB-TACE group had numerically higher rates of response compared with the cTACE group, the hypothesis of superiority was not met (one-sid-

Table 5. Cox-regression model of progression-free survival (PFS) and overall survival (OS) in hepatocellular carcinoma

Variable	Characterestics	PFS				OS			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
Age	<65	0.88	0.5			0.88	0.5		
	≥65	(0.57-1.3)				(0.58-1.3)			
Gender	Female	1.13	0.6			1.05	0.8		
	Male	(0.65-1.9)				(0.6-1.7)			
Pretreatment AFP (ng/ml)	<400	1.66	0.05			1.7	**0.02**		
	≥400	(0.99-2.7)				(1.05-2.7)			
Barcelona stage	Early+Intermediate	1.63	**0.03**			2.16	**0.04**		
	Advanced	(1.03-2.5)				(1.03-4.5)			
Child-P	A	1.74	**0.02**			2.21	**0.00**	2.48	**0.001**
	B	(1.07-2.8)				(1.4-3.4)		(1.4-4.1)	
Vascular invasion	No	1.07	0.8			1.84			
	Yes	(0.55-2.08)				(1.01-3.3)			
Post-treatment AFP (ng/ml)	<400	2.32	**0.02**	2.50	**0.01**	2.25	**0.02**	2.49	**0.02**
	≥400	(1.35-4)		(1.45-4.45)		(1.3-3.7)		(1.4-4.4)	
Number of tumor	Single	1.27	0.2			1.33	0.1		
	Multiple	(0.83-1.9)				(0.8-2)			
Tumor size (centimeter)	≤5	1.47	0.1			1.44	0.1		
	>5	(0.92-2.3)				(0.9-2.2)			
	≤7	1.25	0.2			1.53	**0.03**	1.78	**0.02**
	>7	(0.82-1.9)				(1.02-2.2)		(1.06-2.9)	

PFS: Progression-free survival, OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; AFP: Alfa-feto protein.

ed p=0.11). On the other hand, post hoc analyses have been reported that patients with Child-Pugh B, ECOG 1, bilobar disease, and recurrent disease demonstrated a significant increase in objective response (p=0.038) compared to cTACE.[11] Similarly, in a retrospective database study, Kloeckner et al.[12] reported that statistical similar overall survival between DEB-TACE and cTACE (12.3 months vs 13.6 months respectively. The two groups had similar clinical and demographic characteristics, but patients with DEB-TACE received fewer treatment sessions than those with cTACE (2.9 vs. 4; p=0.01). The authors of this study concluded that DEB-TACE might be considered as a more suitable treatment option compared to cTACE because fewer treatment sessions were required to achieve similar survival outcomes. In another retrospective trials, Liu et al.[13] evaluated the five-year follow-up results of two hundred-seventy three patients who underwent TACE or DEB-TACE treatment.

During the 5-year follow-up period, the mortality rates were higher in patients treated with cTACE than those treated with DEB-TACE (76.1% and 66.7%, respectively, p=0.045). Besides, they showed that there was a statistically significant difference between the groups in terms of PFS. Median PFS was 11 months for cTACE and 16 months for DEB-TACE (p=0.019). In another retrospective study which included patients treated DEB-TACE, conducted by Zhou et al.,[14] reported that DCR was 75.8%, the CR was 16.2%, and the PR was 59.6%. Other two retrospective trials have reported ORR rates of were thirty-nine percent and sixty percent for patients treated with TACE.[15,16] Although our response rates were similar to the literature, our survival results were lower than the literature. Unlike other trials, there was no cirrhosis in 8% of our patients, and 39% of cirrhotic patients had advanced stage according to Barcelona staging. Also, we calculated survival outcomes from the date of DEB-TACE instead of the date of diagnosis. After progression, 30% of our patients did not receive a second-line treatment. This issue may have affected our survival outcomes.

According to BCLC staging; median PFS and OS at BCLC-A were 11 months and 25 months in our study, respectively. Robert et al.[17] have compared the effectiveness of TACE and curative treatment in their study which included 253 patients with BCLC 0 and A stage. They reported that complete response and 1-year OS rates were 47% and 91.7% respectively in BCLC 0 and A patients. However, compared to curative treatments, OS and recurrence free survival were found to be significantly lower statistically. In our study, 1-year OS was 67% in the BCLC A. Unlike the aforementioned study, we did not have a very early patient group. In another study, Zhe Gou et al.[18] reported that the one-year OS rate was 57% in BCLC-A patients who underwent TACE. This result was similar to our study. Our results in advanced-stage patients were similar to those in the intermediate stage patients. In a retrospective study comparing sorafenib and TACE in advanced-stage patients, the median OS was 9.2 months and the 1-year survival rate was 42% in the TACE treated group, and no statistically significant difference was found with sorafenib.[19] Therefore, if there are no contraindications, TACE is generally considered as an alternative treatment modality in these patients group.

Table 6. Review of current literature investigating the clinical efficacy of DEB-TACE in patients with hepatocellular carcinoma

Trials	Design	Patients	Result
Llovet JM et al.[10]	Randomised controlled Arterial embolisation or Chemoembolisation vs conservative treatment	Not suitable for curative treatment, Child-Pugh class A or B and Okuda stage I or II	Survival probabilities 1 year and 2 years Embolisation: 75% and 50%, Chemoembolisation: 82% and 63%, Control: 63% and 27% (chemoembolisation vs control p=0.009)
Lammer et al.[11]	Prospective randomized, Phase 2 study DEB-TACE vs conventional TACE (cTACE)	Child-Pugh A/B cirrhosis and large and/or multinodular, unresectable	CR: 27% vs 22%, ORR: 52% vs 44% and DCR: 63% vs 52%, The hypothesis of superiority was not met (one-sided p=0.11)
Kloeckner et al.[12]	Retrospective, To compare the overall survival outcomes cTACE vs DEB-TACE	A total of 520 patients received cTACE, and 154 received DEB-TACE, child A/B/C	Overal survival; DEB-TACE vs cTACE: 369 days (95% CI: 310-589 days) vs 409 days (95% CI: 321-488 days), p=0.76
Liu et al.[13]	Retrospective, observational Five years follow up results cTACE vs DEB-TACE	Child A/B cirrohis and BCLC stage A-B-C	The mortality rates; cTACE vs DEB-TACE: %76.1 vs %66.7, p=0.04), Median time to disease progression was 11.0 months for cTACE and 16.0 months for DEB-TACE (p=0.019)
Robert et al.[17]	Retrospective, comparing the efficacy of curative therapies with TACEin early (BCLC-0/A) stage hepatocellular carcinoma	BCLC 0/A patients	TACE vs Curative therapies Median survival; 2.7 vs 6.7 years, p<0.0001) and recurrence-free survival; 1.3 vs 2.7 years, p<0.001), On multivariate analysis; TACE was an independent poor prognostic predictor for overall survival (HR 1.70, p=0.04)
Our study	Retrospective, The purpose of study to assess the efficacy and prognostic factors related to the DEB- TACE therapy.	Child A/B BCLC stage A/B/C Non-Cirrhotic patients	ORR: 49% DCR: 70%, 12 months PFS rate was 23% and 24 months OS rate was 47%. On multivariate analysis; Child-Pugh classification and tumor size> 7 cm were found to be independent prognostic factors regarding OS, while posttreatment AFP>400 ng/ml had a worse prognostic influence on PFS and OS.

AFP: Alfa-feto protein; BCLC: Barcelona staging; DEB: Drug-eluting bead; TACE: Transarterial chemoembolization; ORR: Objective response rate; OS: Overall survival.

Many prognostic factors such as BCLC stage, tumor diameter, vascular invasion, AFP level and number of TACE procedure have found to affect survival in the literature. Only AFP was reported as an independent prognostic factor affecting survival,[12,13,20] however, the AFP predictive threshold for survival is not clearly. Several estimation values have been investigated in the literature. A prospective study by Chia-Yang Hsu et al.[21] analyzing 2579 HCC patients followed between 2002-2012 has evaluated the predictive value for AFP for prognostic prediction in patients with HCC. In particular, four AFP estimation values; 20, 200, 400 and 1000 ng/mL were determined. A statistically significant difference was found between patients with AFP <20 ng/mL and patients with AFP 20 to 400 ng/mL, and those with AFP ≥400 ng/mL in terms of long-term survival. The prognostic significance of AFP was also evaluated in a study analyzing 590 patients with BCLC-intermediate stage treated with TACE and AFP levels >20 ng/ml.

There was a statistically significant difference in OS in patients with and without AFP response (median OS: 20 vs 12 months). They also reported AFP as an independent prognostic factor in multivariate analysis. In our study, we investigated the predictive value of AFP 400ng/ml before and after DEB-TACE. There was no statistically significant difference in both overall survival and progression-free survival in patients with AFP levels below or above 400 ng/ml before DEB-TACE. Nevertheless, there was a statistically significant difference in both OS and PFS in patients with AFP ≥400 ng/ml after treatment compared with those who have AFP <400 ng/ml. We revealed that AFP >400 ng/ml level after DEB-TACE was an independent prognostic factor for both PFS and OS by multivariate analysis [HR: 2.5 (95%CI: 1.4-4.4), p=0.01 and HR: 2.4 (1.4-4.4), p=0.02, respectively]. Besides, we showed that Child-Pugh Classification and tumor diameter (7 cm) as an independent prognostic factor for OS different from other trials [HR: 2.4 (95%CI: 1.4-4.1), p=0.001 and HR: 1.7 (1.06-2.9), p=0.02, respectively]. Current studies investigating the efficacy of DEB-TACE in hepatocellular carcinoma patients are outlined in Table 6.

There are many limitation factors in our study. Firstly our study was a single institutional retrospective cohort analysis. Secondly, during follow-up, we could not reach the DEB-TACE response data of seventeen percent of our patients. This may have affected our results. As a positive point, unlike other trials, our cohort consisted only of patients who underwent DEB-TACE, and we have just presented response rate and survival data of the first DEB-TACE treatment.

In conclusion, we found that the Child-Pugh classification, tumor diameter (7 cm) and AFP (400 ng/ml) were independent factors affecting survival. To our knowledge, this is the first retrospective trial in HCC patients who underwent DEB-TACE which reports that AFP (400 ng/ml), tumor diameter (7 cm), and Child-Pugh classification may be a prognostic marker for survival. Well designed prospective studies involving more patients are needed to verify our results.

Ethics Committee Approval: The Marmara University Clinical Research Ethics Committee granted approval for this study (date: 01.06.2018, number: 09.2018.412).

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