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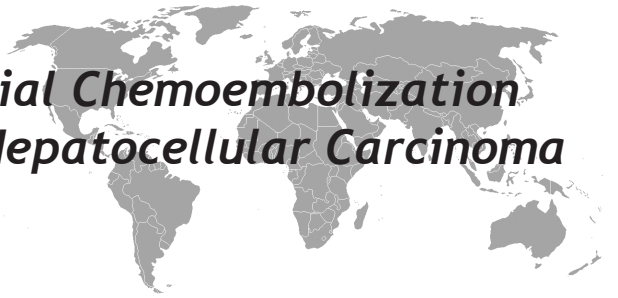
Original Article

The Efficiency of Transarterial Chemoembolization with Drug-Eluting Beads in Hepatocellular Carcinoma



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ABSTRACT

Transarterial chemoembolization (TACE) with drug-eluting beads (DEB) is a new palliative treatment method for patients with hepatocellular carcinoma (HCC). Little is known about the efficiency of DEB-TACE for patients with HCC. The purpose of our study was to evaluate the treatment efficacy (survival rate, tumor response) and safety of DEB-TACE for inoperable HCC and to identify the predictors of survival in patients with unresectable HCC. Twenty-six patients (18 Child-Pugh A, 8 Child-Pugh B) underwent chemoembolization with doxorubicin DEB, including 5 women and 21 men with a mean age of 67.04 years (range 40-86 years). Twenty patients had one DEB-TACE procedure, while the remaining six had two procedures. Overall median survival and survival at 6 and 12 months were calculated. Meanwhile, the response rate was assessed using response evaluation criteria in solid tumors criteria on computed tomography/magnetic resonance imaging at 1 and 6 months. Overall survival rates at 6 months and 1 year from the first administration of doxorubicin DEB-TACE were 80% and 57%, respectively. At 1 and 6 months, objective tumor response rates were 46.2% and 57.1%, respectively. Child-Pugh class, Okuda staging, Cancer of the Liver Italian Programme score, Barcelona Clinic Liver Cancer staging, serum albumin level, Eastern Cooperative Oncology Group performance status, and tumor morphology and volume were found to be prognostic factors for survival. All of the procedures were technically successful, and there were no major complications. Eighteen patients died during the study period and eight survived.Transarterial chemoembolization with DEB is safe and well tolerated in patients with inoperable HCC. Additional prospective randomized controlled studies are required to assess the efficiency of DEB-TACE.

Key words: *Hepatocellular carcinoma, drug-eluting beads, transarterial chemoembolization,*

Hepatoselüler karsinom tedavisinde ilaç yüklü mikrosferlerle yapılan transarteriyel kemoembolizasyonun etkinliği

ÖZET

İlaç yüklü partiküllerle yapılan transarteriyel kemoembolizasyon (DEB-TAKE); inoperatif hepatosellüler karsinomun (HCC) paliyatif tedavisinde yeni bir seçenektir. Literatürde HCC'li hastaların tedavisinde DEB-TAKE'nin etkinliği hakkında sınırlı bilgi vardır. Bu çalışmanın amacı inoperatif HCC olgularında DEB-TAKE tedavisinin etkinliğini (sağkalım, tümör cevabı) ve güvenliliğini değerlendirmek; aynı zamanda bu hastalarda DEB-TAKE sonrası sağkalımda prognostik faktörleri belirlemektir. İnoperatif HCC'si olan, 40-86 yaş arası (ort. 67.04) 5'i kadın ,21'i erkek toplam 26 HCC olgusuna (18 Child-Pugh A ve 8 Child-Pugh B) doksorubisin yüklü partikülle kemoembolizasyon uygulandı. 20 hastaya tek, kalan 6 hastaya çift girişim uygulandı. Grupların 6. ve 12. ay ortanca sağkalım süreleri hesaplandı. DEB-TAKE'nin ilk uygulanmasını takiben olguların 6.ay ve 1 yıllık yaşam süreleri sırasıyla %80 ve %57 olarak saptandı. 1. ve 6.ayda objektif tümör yanıt oranları sırasıyla %46.2 ve %57.1 olarak bulundu. Child-Pugh evresi, Okuda evresi, Cancer of the Liver Italian Programme (CLIP) skoru, Barcelona Clinic Liver Cancer (BCLC) evresi, serum albumin seviyesi, Eastern Cooperative Oncology Group (ECOG) performans statüsü (PS), tümör morfolojisi ve hacmi DEB-TAKE sonrası sağkalımda prognostik faktörler olarak saptandı. Bütün girişimler teknik olarak başarıyla tamamlandı ve işleme bağlı majör komplikasyon görülmedi.Takiplerde 18 hasta öldü, 8 hasta yaşamaktadır. Çalışmamız sonucunda inoperatif HCC olgularında DEB-TAKE'nin seçilmiş hasta gruplarında güvenli ve iyi tolere edilebilir bir yöntem olduğu sonucuna varılmıştır. Bununla birlikte tedavi etkinliğini değerlendirecek prospektif randomize kontrollü çalışmalara ihtiyaç vardır.

Anahtar kelimeler: *Hepatosellüler karsinom, ilaç yüklü partikül, transarteriyel kemoembolizasyon*

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy and the third leading cause of cancer-related deaths. The incidence of HCC is increasing and it causes more than 600,000 deaths globally per year (1). Most HCC patients have underlying cirrhosis due to chronic viral hepatitis (2). Screening and surveillance programs may raise early detection and diagnosis of HCC when liver function is preserved and there are no cancer-related symptoms. In addition, several active curative treatments and palliative treatments that will potentially improve survival are available (3). Resection, liver transplantation, and ablation are the only curative treatments for HCC, but unfortunately, at first presentation, only 30% of patients are candidates for curative treatments (4). Transarterial chemoembolization (TACE) has become the standard of care for patients with HCC not amenable to surgical or ablative treatment if extrahepatic metastases and advanced liver disease are lacking (5).

There is no generally accepted TACE technique. The rationale for TACE is that the intra-arterial infusion of a such as doxorubicin or cisplatin with or without a viscous emulsion, followed by embolization of the blood vessel with gelatin sponge particles or other embolic agents, will result in a strong cytotoxic effect combined with ischemia (6). However, some studies have shown that systemic release of chemotherapy agents following conventional TACE is high and many patients suffer from systemic side effects (7). With the introduction of drug-eluting beads (DEB) that are ionically bound to negatively charged chemotherapeutic agents (most commonly doxorubicin), treatment can be delivered in a controlled, sustained fashion to the tumor foci. In such an approach, the antitumoral effect can be increased with longer duration of treatment, while patients exhibit better tolerance and a low rate of side effects (8, 9).

Preclinical and clinical studies have demonstrated a higher and prolonged retention of doxorubicin within the tumor after TACE with DC beads (TACE utilizing doxorubicin-DEB), and lower systemic plasma levels of doxorubicin compared to conventional TACE (c-TACE) (8-10). The aim of this study was to evaluate the treatment efficacy (survival rate, tumor response) and safety of DEB-TACE, as well as to identify the prognostic factors that influence survival in patients with unresectable HCC.

MATERIALS AND METHODS

Study population

In this study, data from patients who were treated with DEB-TACE at our angiographic institution from January 2007 to May 2011 were evaluated retrospectively. Patient diagnosis of HCC was confirmed by biopsy or radiological findings, in addition to elevated serum alpha-fetoprotein (AFP). All patients demographic (age, gender) and clinical (etiology, ascites, complications) characteristics, pre-post procedural laboratory parameters (bilirubin, albumin, creatinine, international normalized ratio [INR], AFP, alanine transaminase [ALT], and aspartate transaminase [AST]), and radiological data (number of lesions, tumor burden, size) were collected from patients' case records or by contacting family members.

All patients underwent computed tomography (CT) or magnetic resonance imaging (MRI) within 1 month prior to the procedure to assess the morphological characteristics of the tumor, including diameter, number, tumor burden, presence of portal vein thrombosis, and ascites. The functional capacity of patients' livers was classified according to the Child-Pugh classification (Table 1). Okuda staging, Cancer of the Liver Italian Programme (CLIP) score, and the Barcelona Clinic Liver Cancer (BCLC) staging system have been used to stage HCC (11-13). The Eastern Cooperative Oncology Group (ECOG) system (Table 2) was used to grade performance status (PS) before the procedure (14).

Pre-Procedural Evaluation

Patients with confirmed diagnosis of HCC, an ECOG PS of 0 or 1, preserved liver function (Child-Pugh Class A or B), and who were unsuitable for resection or percutaneous ablation without portal invasion, extrahepatic spread, hepatic encephalopathy, or massive ascites, were eligible for the study. Patients with portosystemic shunts, thrombus within portal vein, extrahepatic metastases, advanced liver disease (bilirubin levels >3 mg/dl, AST or ALT>270 U/l), and any contraindications for doxorubicin administration were excluded. Patients with contraindications against catheter angiography like impaired clotting test platelet count < 50,000/ml, INR >1.5, sepsis, elevated serum creatinine > 1.4 mg/dl, or renal failure were also excluded from the study. Written informed consent was received from all patients before the procedure.

Table 1. *Child-Pugh Score*

Measure	*1 point*	*2 points*	*3 points*
Encephalopathy (grade)	*None*	*1-2*	*3-4*
Ascites	*None*	*Slight*	*Moderate*
Albumin (g/dl)	*>3.5*	*2.8-3.5*	*<2.8*
Prothrombin time (seconds)	*1-3*	*4-6*	*>6*
Bilirubin (mg/dl)	*<2*	*2-3*	*>3*

Child-Pugh A: 5-6 points; Child-Pugh B: 7-9 points; Child-Pugh C: 10-15 points

Procedure

Patients' oral intake was stopped for at least 8 hours before the procedure. Drug-eluting microspheres were prepared using 300–500 μm. Loading of the beads was carried out in vitro an hour before the beginning of catheterization. The loaded beads were then aspirated from the vial into a syringe mixed with nonionic contrast medium using a three-way stopcock at a 50:50 ratio. A total of 4 mL of microspheres (two vials) were mixed with a maximum of 150 mg of doxorubicin according the manufacturer's guidelines. No antibiotic prophylaxis was used before the procedure and no analgesia or general sedation was needed during the procedure. Under local anesthesia, the femoral artery was cannulated followed by the insertion of a 5F sheath.

Prior to chemoembolization celiac, superior mesenteric arteriography was performed with a 5F diagnostic catheter to assess the arterial anatomy and feeding arteries of the tumor, to identify variation in the liver arterial supply and exclude portal venous shunting. Highly selective catheterization was performed with a 2.7F microcatheter in order to obtain complete obstruction of the feeding arteries and avoid damage to the non-tumoral liver. After stable positioning of the microcatheter in the second- or third-order branches of the right or left hepatic artery, superselective chemoembolization with DC beads was performed slowly under fluoroscopic guidance until stasis of blood flow in the arterial feeders to the tumor. As soon as stasis or reflux was observed during the procedure, the chemoembolization was terminated, followed by a control hepatic angiography in order to ensure hepatic artery patency and tumor devascularization. For some patients with inadequate tumor response or different lesions, a second embolization was performed.

Outcome measures

After DEB-TACE, all patients were followed up for at least 24 hours to watch for post-embolization syndrome and other complications in hospital. Medication was administered as necessary. Treatment response was assessed through CT and MRI, AFP assay performed after 1 and 6 months of treatment according to the response evaluation criteria in solid tumors (RECIST criteria; Table 3) (15), and the patients were divided into four groups. Tumor size in HCC with more than one was calculated by the sum of the longest diameter of all measurable tumors according to the RECIST criteria.

Liver functions were evaluated by bilirubin, albumin, AST, and ALT values before embolization and after 1-3 days and 1 month. Initial serum AFP levels were compared with the levels after DEB-TACE. It was recorded when patients exhibited a significant decrease. Complications or death that occurred within 30 days of the embolization was assessed as procedure-related.

Statistical analysis

Survival time is defined as the time from the first doxorubicin DEB chemoembolization to the date of death. All analyses were conducted using SPSS for Windows (version 16.0; SPSS Inc., Chicago, IL, USA). A univariate analysis to test the significance of difference between the survival times of the different groups and identify predictors of survival was performed using the Kaplan-Meier method of survival function by the log rank test. All statistical tests were performed at a significance level of $\alpha = 0.05$.

Table 2. *ECOG performance status*

Grade	*ECOG*
0	*Fully active, able to carry on all pre-disease performance without restriction*
1	*Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work*
2	*Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours*
3	*Capable of only limited self-care, confined to bed or chair more than 50% of waking hours*
4	*Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair*

Table 3. *Definition of treatment response according to the RECIST criteria*

RECIST	*Change in sum of longest diameter*
Complete response (CR)	*Disappearance of all target lesions*
Partial response (PR)	*At least 30% reduction in the sum of the longest diameter of target lesions*
Stable disease (SD)	*Neither PR nor PD criteria are met*
Progressive disease (PD)	*At least 20% increase in the sum of the longest diameter of target lesions, or appearance of new lesions smallest sum longest diameter recorded since treatment started or the appearance of new lesions*

RESULTS

Thirty-one DEB-TACE procedures were performed in 26 patients (5 women and 21 men with a mean age of 67.04 years) with inoperative HCC at our angiographic institution from January 2007 to May 2011. The procedures were technically successful in all patients. Demographic, clinical, laboratory, tumor staging, and imaging characteristics are summarized in Table 4 and distribution according to staging system is shown in Figure 1. At the time of data analysis, 18 patients had died (69.2%). Median duration of follow-up was 13.7 months (range 2–26 months). Overall median survival was 18.0 months, and survival rates at 6–12 months from the first administration of DEB-TACE were 81% and 65%, respectively. Figure 2 shows the post-procedural Kaplan-Meier survival curve for all patients.

Tumor response to the procedure was evaluated according to the amount of tumor necrosis detected on follow-up CT or MR imaging as recommended by the RECIST criteria. At the 1 month follow-up, partial response was documented in 12 patients (46.2%). Thirteen patients

Table 4. *Patient demographics, clinical characteristics, and univariate analysis p values of prognostic factors*

	Category	*n (%)*	*p value*
Age (years)	*>65*	*15 (57.7)*	*0.644*
	<65	*11 (42.3)*	
	Median: 67.04 (40-86)		
Sex	*Male*	*21 (80.8)*	*0.758*
	Female	*5 (19.2)*	
Etiology	*HBV*	*18 (69.2)*	*0.252*
	HCV	*6 (23.1)*	
	Idiopathic	*2 (7.7)*	
ECOG PS	*0*	*17 (65.4)*	*0.001*
	1	*9 (34.6)*	
Tumor morphology	*Nodular*	*13 (50)*	*0.072*
	Multinodular	*7 (26.9)*	*0.001*
	Diffuse	*6 (23.1)*	
Tumor size	*>5 cm*	*21 (80.8)*	*0.918*
	<5 cm	*5 (19.2)*	
Tumor burden	*>50% of liver*	*4 (15.4)*	*0.003*
	<50% of liver	*22 (84.6)*	
Albumin	*>3 gr/dl*	*17 (65.4)*	*0.007*
	<3 gr/dl	*9 (34.6)*	
Bilirubin	*>1.5 mg/dl*	*7 (26.9)*	*0.524*
	<1.5 mg/dl	*19 (73.1)*	
AFP	*>400 ng/dl*	*10 (38.5)*	*0.098*
	<400 ng/dl	*16 (61.5)*	
Prothrombin time (PT)	*>15 sn*	*14 (53.8)*	*0.911*
	<15 sn	*12 (46.2)*	
Ascites	*+*	*13 (50)*	*0.009*
	-	*13 (50)*	
Procedure number	*1*	*20 (76.9)*	*0.852*
	>1	*6 (23.1)*	
PES	*+*	*23 (88.4)*	*0.715*
	-	*3 (11.6)*	

Table 5. *Survival rates after DEB-TACE according to the staging systems*

Stage	6 months (%)	1 year (%)	p value
Child-Pugh Class A	90	79	0.001
B	57	0	
Okuda Stage I	86	78	0.025
II	67	34	0.074
III	34	0	0.001
CLIP score <3	90	60	0.001
≥3	28	14	
BCLC Stage A-B	100	78	0.001
C-D	38	25	

(50%) showed stable disease and one (3.8%) showed progressive disease. At the 6 month follow-up, five patients who had died were excluded from the results, so that partial response was documented in 12 patients (57.1%). Eight patients (38.1%) showed stable disease and one patient (4.8%) showed progressive disease. To ensure statistical homogeneity between the groups, one patient with progressive disease was added to the stable disease group. There was no doxorubicin systemic toxicity (alopecia, marrow suppression, or cardiac failure) or procedural complications documented in these patients. The 30-day procedural mortality was zero (0%). Pleural effusion in our series was seen in two patients (7.6%) and ascites in two patients (7.6%). Post-embolization syndrome (PES), defined as fever, nausea, vomiting, or abdominal pain, was observed in 23 (88.5%) patients following the procedure. In our patients, a transient increase of AST and ALT was seen 1–3 days after the procedure.

The factors analyzed included gender (male vs. female), age (≤65 years vs. >65 years), etiology (HBV vs. HCV and idiopathic), ECOG performance status (0 vs. 1), tumor burden (tumor volume less than vs. more than 50% of liver), ascites (absent or present), serum albumin (<3 vs. > 3 g /dl) and bilirubin (<1.5 vs. > 1.5 mg /dl) , maximum tumor size (>5 cm vs. <5 cm), tumor number (nodular vs. multinodular vs. diffuse), AFP (>400 ng/dl vs. <400 gr/dl) values, Child-Pugh score (A vs. B), CLIP stage (0-2 vs. >2), BCLC stage (A-B vs. C-D), Okuda stage (I vs. II vs. III), and the number of re-treatments (1 vs. 2). Survival rates of our patients after DEB-TACE according to the staging system are shown in Table 5. The median overall survival times following DEB-TACE in the Child-Pugh A and B groups were 19 and 6 months, respectively. There were significant differences in the median survival of patients in Child-Pugh class A and B after DEB-TACE (p=0.001). The median overall survival times after DEB TACE were 18.6, 12, and 6 months in Okuda I, II, and III, respectively. There were no significant differences in median survival of patients in Okuda stages II and III (p=0.074), but there

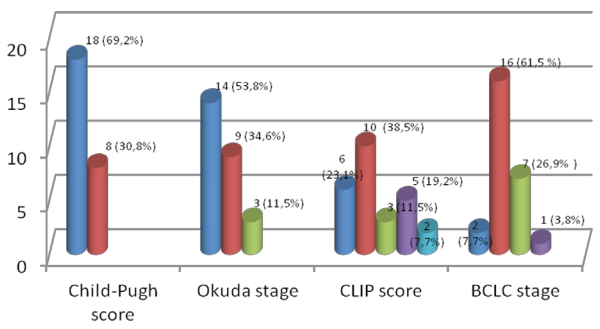

Figure 1. Distribution of the patients according to tumor staging systems

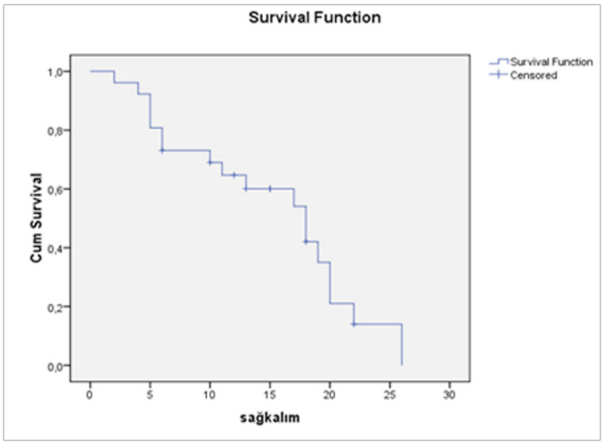

Figure 2. Kaplan-Meier survival graphic for all groups

were significant differences in median survival of patients in Okuda stage I in relation to the other stages (p=0.025, 0.01). In terms of CLIP score, patients were classified into two groups—those with a score of less than 3 and those with a score of 3 and above. There were significant differences in median survival of patients with CLIP score <3 compared to ≥3 after DEB-TACE (p=001). The 1-year survival rates in those with a CLIP score of <3 and ≥3 after DEB-TACE were 60% and 14%, respectively. BCLC stage A and B patients' overall median survival was statistically significantly better than that of stage C and D patients.

Univariate analysis of variables predicting the survival of all patients using the log rank test is also given in Table 4. This analysis showed that age, sex, etiology, tumor size, serum AFP–bilirubin level, and prothrombin time before the procedure were not related to outcome. The significant factors found were Child-Pugh class, Okuda staging, CLIP score, BCLC staging, serum albumin level, ECOG PS, tumor morphology, tumor burden, and presence of ascites.

DISCUSSION

HCC is the third most common cause of cancer-related death worldwide (16). Since the application of curative therapies, including resection, liver transplantation, and percutaneous ablation, is limited in patients with HCC (17), the prognosis of patients with unresectable HCC who receive no treatment due to underlying cirrhosis and the cancer stage is very poor, with median survival less than 1 year (11). In these groups, treatment options are currently so limited that any treatment that can improve survival and quality of life with few adverse events is beneficial (18). HCC is resistant to chemotherapy (7). It was shown that in randomized controlled trials, TACE improved survival in intermediate stage patients to between 19 and 20 months (17). On the other hand, the lack of standardization, variations in chemotherapeutic agents and dosage has led to a wide range of results and severe complications (19, 20). In an attempt to improve the effectiveness of TACE, a new embolic material (DEB) has been found that binds to chemotherapeutic agents and causes controlled and sustained release, as well as high intratumoral concentration and tumor response for a sufficient period with lower systemic toxicity and adverse events (9). The safety and effectiveness of this procedure have been evaluated through preclinical and clinical studies (8, 10, 21, 22).

PRECISION V was the first randomized, prospective, multicenter, trial comparing doxorubicin delivered by c-TACE with TACE utilizing doxorubicin-DEB for the treatment of primary unresectable HCC. The DEB-TACE group showed higher rates of complete response, objective response (primary endpoint), and disease control compared to the c-TACE group (27% vs. 22%, 52% vs. 44%, and 63% vs. 52%, respectively) (23). However, individuals with Child-Pugh B, ECOG 1, bilobar disease, and recurrent disease showed a significant increase in objective response (p=0.038) compared to c-TACE. There were fewer adverse events (including liver and systemic toxicities) after chemoembolization with DEBs than with conventional chemoembolization. In this study, a significant survival difference was not shown between the groups. Dhanasekaran et al. reported that the transcatheter therapy with DEB offers a survival advantage over conventional chemoembolization for individuals with unresectable HCC (24). The investigators concluded that TACE with DC beads and doxorubicin showed improved tolerability, with a significant reduction in serious liver toxicity and doxorubicin-related side effects in comparison with c-TACE (23, 24).

The survival rates in our study at 6 months and 1 year were 59% and 32%, respectively, which is comparable to those reported in previous DEB-TACE studies (7, 25). In addition, the existence of different studies that have shown high survival rates can be explained by patient selection bias, the underlying etiology of cirrhosis, and other comorbidities (8). Between 36% and 84% objective tumor response rates have been reported in patients with intermediate-stage HCC after DEB-TACE in the literature (18). In our study, at 1 and 6 months, the objective tumor response rates were 46.2% and 57.1%, respectively, according to the RECIST criteria. In our study, survival of the patients in the partial response group was found to be statistically significantly better than that of the stable disease group. In most studies, tumor stage has been found to be a significant predictor of survival after conventional chemoembolization (25). However, there have been limited DEB-TACE studies evaluating the factors which influence survival after this therapy. In their DEB-TACE studies, Reyes (145) and Kalva et al. (7) looked at Child-Pugh score, while Dhanasekeran et al. (25) focused on Child-Pugh score, Okuda stage, BCLC stage, and CLIP as prognostic factors. In our study, patients with Okuda stage I, Child–Pugh class A, CLIP score <3, and BCLC stage A–B tumors had better survival rates after DEB-TACE.

Tumor size was not found to influence survival after DEB-

TACE in this study, in accordance with that of Reyes et al. (26). However, advanced tumor stage (tumor burden >50% of liver) and diffuse tumor type were found to be negative prognostic factors for survival after treatment with DEB-TACE. Martin also reported that tumor burden and extent of liver involvement less than 25% are positive predictors of overall survival (18). In some studies, AFP was found to be a prognostic factor for survival after DEB-TACE (25). Serum AFP has long been used for the diagnosis and surveillance algorithms of HCC. Some studies have shown that its use is less specific than was once thought (3). In our patient group, initial AFP levels were higher than ≥400 ng/ml in only 10 patients (38%). After DEB-TACE, in spite of effective tumor embolization, AFP levels did not drop in 9 out of 10 patients In addition, no statistically significance relation was found between AFP level and survival. Therefore, like some authors (27), we did not consider AFP to be an effective parameter for treatment response. In our study, liver reserve (Child-Pugh class score), HCC staging (Okuda staging, CLIP score, and BCLC staging), serum albumin level, ECOG PS, ascites, tumor burden, and morphology were found to be predictors of survival after DEB-TACE. The most common complications after DEB-TACE are cholecystitis, liver abscess formation, liver failure, tumor rupture, pancreatitis, pleural effusion, gastric ulcer bleeding, esophageal variceal bleeding, and spontaneous bacterial peritonitis (28, 29). DEB studies have shown a marked reduction in liver toxicity and doxorubicin-related side effects compared with c-TACE (8, 22, 10). Treatment-related 30-day mortality is 0–1.26% in DEB-TACE studies in the literature (8, 23, 29). In our series, no treatment-related death, liver failure, or serious adverse events were observed in the first 30 days after the DEB-TACE procedure. This represents a favorable safety profile compared to other reported studies in the literature (7). Kettembach et al. (30) reported a 2% rate of serious adverse events (including temporary liver failure and cholecystitis). In a study by Malagari et al. (22) the incidence of complications was 4.2% (n=3/71, including cholecystitis, liver abscess, and pleural effusion). We did not encounter serious adverse events like acute cholecystitis, abscess, or liver failure. In our patients, good tolerability of TACE with DC beads can most probably be explained in the choice of patients with preserved liver function (Child-Pugh A and B). We did not consider patients in Child-Pugh stage C or those with portal vein thrombosis for therapy, as they have a high risk of developing toxicity or liver failure. Our superselective chemoembolization technique approach may also have had an additional effect on the low complication ratio.

Pleural effusion, which is assessed as a mild complication, is seen 1 to 5 days after embolization. In our series, pleural effusion was seen in two (7.7%) patients. In the literature, it was reported in 1.8–3.7% of patients across treatments, and found to correlate with the extent of embolization; therefore, it was considered to be the result of inadvertent embolization (26, 29). Post-procedural transient elevation of liver enzymes has also been reported in many TACE studies (27, 29). In our research, although there was a statistically significant elevation of liver enzymes 3 days postembolization, there were no statistically significant differences between baseline and 1 month after the procedure. Encephalopathy and increasing ascites rates have been reported at 1.8% to 8.3% in c-TACE trials. Malagari et al. reported that transient encephalopathy and/or ascites and increase of liver enzymes developed in 10 patients (4.2%) in their DEB studies (29). In our study, ascites was seen in two patients (7.7%), and neither of them developed hepatic encephalopathy after DEB-TACE. In our patients, we observed no doxorubicin systemic toxicity (alopecia, marrow suppression, or cardiac failure). However, systemic toxicity of 11.8% in the DEB group was reported in the randomized study by Lammer et al. However, these events were significantly reduced in the DEB arm compared with the c-TACE arm (25.9%) of their study (23). In this study, PES syndrome was observed in 23 (88.5%) patients following the procedure at different levels. PES is a self-limited condition defined as fever, nausea, vomiting, or abdominal pain following the procedure; it is caused by reduced blood flow to the treatment area. Because of the lack of standardized criteria, there have been large differences in the rates of recorded PES (37–100%) among the different trials (8, 10, 23).

In the present study, Child-Pugh class score, Okuda staging, CLIP score, BCLC staging, serum albumin level before the procedure, ECOG PS, presence of ascites before the procedure, tumor burden, and morphology were found to be predictors of survival after DEB-TACE. The limitations of this study include the small number of patients and relatively short-term follow-up; patients were not randomized to c-TACE and DEB-TACE to assess the superiority of one over the other. Thus, the results must be taken as preliminary.

As a result, TACE with DEB and doxorubicin is safe and well tolerated. Prospective studies with large groups are needed to confirm the improved safety profile of this method and to demonstrate improved efficacy over the conventional procedure. TACE performed with DEB will likely replay. The authors report no conflict of interest in this paper.

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