

Transarterial chemoembolization for treatment of hepatocellular carcinoma: A single center experience

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Background/aims: We aimed to determine the effect of transarterial chemoembolization treatment on survival in patients with hepatocellular carcinoma and to investigate the efficacy and tolerability of two different transarterial chemoembolization procedures, conventional transarterial chemoembolization and drug-eluting beads, in these patients. **Materials and Methods:** A total of 40 patients with hepatocellular carcinoma treated with transarterial chemoembolization between January 2007 and March 2011 were included. Thirty-seven patients had Child-Pugh class A and the remaining 3 had class B. Intra-arterial administration of doxorubicin with lipiodol-based conventional transarterial chemoembolization or drug-eluting beads-transarterial chemoembolization was performed. Eighty sessions were performed with a median of 2 sessions. Sixteen patients were treated with conventional transarterial chemoembolization and 11 with drug-eluting beads-based transarterial chemoembolization, and 13 were treated with both treatment procedures in separate sessions. Primary outcome was defined as patient survival after treatment. **Results:** The median follow-up was 19 months. The median overall survival of patients was 23.2 months. The survival of patients with Child-Pugh class A was significantly better than that of patients with class B (24 vs 6 months, $p=0.004$). No statistically significant difference in survival was observed between conventional transarterial chemoembolization and drug-eluting beads-based transarterial chemoembolization treatments ($p>0.05$). Baseline low serum albumin level ($p=0.003$) and the presence of portal vein thrombosis ($p=0.011$) negatively affected patient survival. Side effects of conventional transarterial chemoembolization and drug-eluting beads-based transarterial chemoembolization were similar. **Conclusions:** Based on the results of this study and in comparison with the findings in the literature, transarterial chemoembolization treatment was seen to improve overall survival and provide better outcome in selected patients with hepatocellular carcinoma. No differences in survival or side effects were observed between the two transarterial chemoembolization treatment modalities.

Key words: Chemoembolization, hepatocellular carcinoma, drug-eluting beads

Hepatoselüler karsinom tedavisinde transarteriyel kemoembolizasyon: Tek merkez deneyimi

Amaç: Hepatoselüler karsinomlu hastalarda transarteriyel kemoembolizasyon tedavisinin sağkalım üzerine olan etkisi ve iki farklı transarteriyel kemoembolizasyon yöntemi olan konvansiyonel transarteriyel kemoembolizasyon ve ilaç salınımlı partiküllü transarteriyel kemoembolizasyon tedavilerinin etkinlik ve tahammül edilebilirliğinin araştırılmasıdır. **Gereç ve Yöntem:** Ocak 2007-Mart 2011 tarihleri arasında transarteriyel kemoembolizasyon ile tedavi edilmiş toplam 40 hepatoselüler karsinom hastası çalışmaya dahil edildi. Otuz yedi hasta Child-Pugh sınıf A ve 3 hasta sınıf B idi. Konvansiyonel transarteriyel kemoembolizasyon veya ilaç salınımlı partiküllü-transarteriyel kemoembolizasyon yöntemleri ile Doksorubisinin transarteriyel uygulaması yapıldı. Ortanca 2 seans, toplam 80 seans transarteriyel kemoembolizasyon tedavisi gerçekleştirildi. Onaltı hastaya konvansiyonel transarteriyel kemoembolizasyon, 11 hastaya ilaç salınımlı partiküllü-transarteriyel kemoembolizasyon, 13 hastaya ise farklı seanslarda her iki tedavi yöntemi uygulandı. Tedavi etkinliğinde sonuç, tedavi sonrası sağ kalım olarak tanımlandı. **Bulgular:** Ortanca takip süresi 19 ay, ortanca tedavi sonrası sağkalım 23,2 ay olarak bulundu. Child-Pugh A hastaların sağ kalımı Child-Pugh B hastalara göre anlamlı derecede iyiydi (24 ay ile 6 ay, $p=0.004$). Sağ kalım açısından konvansiyonel transarteriyel kemoembolizasyon ve ilaç salınımlı partiküllü-transarteriyel kemoembolizasyon yöntemleri arasında istatistiksel anlamlı farklılık bulunmadı ($p>0.05$). Tedavi öncesi düşük albümin seviyesi ($p=0.003$) ve portal ven tromboz varlığı ($p=0.011$) hasta sağkalımını negatif etkilediği saptandı. Konvansiyonel transarteriyel kemoembolizasyon ve ilaç salınımlı partiküllü-transarteriyel kemoembolizasyon yan etkilerinin benzer olduğu görüldü. **Sonuç:** Bu çalışmanın sonuçları değerlendirildiğinde ve literatür bulgularıyla karşılaştırıldığında, transarteriyel kemoembolizasyon tedavisi seçilmiş hepatoselüler karsinomlu hastaların sağ kalımını arttırmakta ve daha iyi seyir sağlamaktadır. İki farklı tedavi yöntemi ile sağ kalım ve yan etki farklılığı gözlenmedi. Karaciğer fonksiyon kapasitesi ve portal ven tutulumu transarteriyel kemoembolizasyon ile tedavi edilen hepatoselüler karsinomlu hastaların hastalık seyrini etkilediği gözlemlendi.

Anahtar kelimeler: Kemoembolizasyon, hepatoselüler kanser, ilaç salınımlı partikül

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INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) is increasing in many countries (1,2). Unfortunately, curative treatment modalities become impossible in the majority of cases because of late diagnosis or underlying advanced liver disease (3-5). The recurrent disease after curative treatment is another challenge.

Transarterial chemoembolization (TACE) is widely used to treat HCC patients, and has currently become the standard treatment in selected patients (6). Standard TACE treatment for HCC has been performed using lipiodol and intra-arterial chemotherapy followed by embolization with Gel-foam particles. Doxorubicin and cisplatin are the widely used chemotherapeutic agents in TACE treatment (7,8). Lipiodol is generally mixed with chemotherapeutic agents in TACE treatment (7,8); however, lipiodol may mask the assessment of residual vascularity on computerized tomography (CT) imaging after TACE treatment (8). The recently developed technique, drug-eluting beads (DEB)-based TACE, represents an advantageous technique over conventional TACE (cTACE), and promises an efficient treatment with minimum side effects as a result of delivering a higher dose of chemotherapeutic agent into the tumor area and diminishing its delivery into the systemic circulation.

The aims of the present study were to determine the effect of TACE treatment on survival in selected patients with HCC and to investigate the efficacy and tolerability of two different TACE treatment modalities, cTACE and DEB-based TACE, in these patients.

MATERIALS AND METHODS

Between January 2007 and March 2011, a total of 40 patients with HCC (M/F: 34/6; mean age, 59.6±10.3 years), who underwent TACE treatment were included in this retrospective study.

The eligibility criteria were as follows: (1) confirmed diagnosis and stage of HCC according to non-invasive diagnostic criteria of the American Association for the Study of Liver Disease (AASLD) guidelines (or tissue biopsy when available) and the Barcelona Clinic Liver Cancer (BCLC) staging classification; (2) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and (3) preserved liver function (Child–Pugh Class A or B). Patients with potentially resectable

or ablative lesions but at high risk for surgery and/or radiofrequency ablation (RFA), patients with progressive disease despite surgery or local ablative therapies, and patients with portal vein thrombosis (PVT) were also included.

The exclusion criteria were: (1) secondary primary tumor; (2) advanced liver disease (bilirubin levels >3 mg/dl, and an aspartate aminotransferase (AST) or alanine transaminase (ALT) >5x the upper limit of normal); (3) impaired renal functions; and (4) ECOG status score of 2 and above. The study was approved by our institutional Ethics Review Board and was conducted in compliance with the Declaration of Helsinki.

Serum ALT, gamma-glutamyl transpeptidase (GGT), total bilirubin, creatinine, alpha fetoprotein (AFP), and international normalized ratio (INR) were measured by our central laboratory using standard reagents. Clinical and laboratory examination was documented before and after TACE procedures. All patients provided written informed consent for TACE treatment before the procedures. Data were retrospectively collected from the patients' hospital charts.

TACE Procedure

All procedures were performed in the Interventional Radiology Unit. Vital signs and cardiac status were monitored throughout the procedure. All procedures were performed under local anesthesia (1% lidocaine) with conscious sedation with intravenous midazolam and/or fentanyl. Routine aortogram and superior mesenteric and celiac arteriography were performed to assess overall anatomy, vascularity and portal vein patency before all procedures in addition to the pre-procedural cross-sectional imaging work-up. After catheterization of the tumoral artery selectively or superselectively, intra-arterial administration of the anti-cancer agent with cTACE or DEB-based TACE treatment was performed.

The cTACE group was treated only with intra-arterial doxorubicin (50-100 mg) or a combination of intra-arterial mitomycin-C (5-10 mg) or cisplatin (50-100 mg) in a mixture of lipiodol (5-10 mg). Drug administration was followed by injection of embolic materials (polyvinyl alcohol [PVA] particles) until stasis in segmental or subsegmental arterial branches. Patients in the DEB-based TACE group received a maximum dose of 4 ml of DC bead (Terumo) (diameter 100–500 micron) or He-

pasphere (Biocompatibles) (50-100 micron) loaded with 50 mg of doxorubicin per 2 ml of beads until stasis in the tumor feeders was achieved angiographically.

All HCC patients received at least one session of TACE treatment. The decision of doing cTACE or DEB-based TACE was made simply according to the experience level of the operators with DEB. As the DEB data with detailed pharmacokinetics was published in 2007, it has become increasingly more popular over time, and DEB-based TACE has almost become the standard of treatment over cTACE since the end of 2009 (19). Thus, in this study, while the patients from 2007 and 2008 were treated with cTACE only, the patients after 2010 were treated with DEB-based TACE only. Thereafter, DEB-based TACE treatment was also used in patients who had been treated previously with cTACE between 2007 and 2010 (mixed group).

The decision of performing multiple TACE sessions for any patient was made according to the following factors: (1) in case of bilobar multiple tumors (lobar treatment strategy) and (2) residual or recurrent tumors during routine follow-up using imaging tools.

Definitions

Primary outcome was defined as patient survival after TACE treatment. Treatment response was defined according to CT findings as: complete response, no evidence of neoplastic disease; partial response, reduction in total tumor load of more than 50%; no change, reduction of less than 50% or increase of less than 25%; and progressive disease: increase of more than 25% (9).

Follow-up

All patients were followed through 48 hours at the hospital, and were seen at one month and at three-month intervals after TACE treatment in the outpatient clinic. Vital signs, physical examination, laboratory examination, tumor evaluation, and patient compliance were assessed. Blood was drawn for determining biochemical parameters. Patients underwent liver imaging evaluation with multiphasic multidetector-row spiral CT scanners (Siemens, Germany) before and after TACE treatment. Post-contrast scans were obtained during arterial phase using bolus-tracking method, portal phase in 70 seconds (s) and equilibrium phase in 120 s. Contrast agent was injected intravenously at a rate of 3 ml/s through a power injector.

Statistical Analyses

The survival estimations were performed using Kaplan-Meier method, and the comparison between groups was evaluated with log-rank test. Median survival times were given with their standard errors and 95% confidence intervals (95% CI). Life tables were used for cumulative survival proportions and respective standard errors. Relationships between survival times and patient characteristics were evaluated using Spearman or Pearson correlation coefficients as appropriate. A p-value <0.05 was considered statistically significant (Statistical Package for the Social Sciences (SPSS) ver.15.0, Chicago, IL, USA).

RESULTS

Male gender was predominant (85%). All patients had compensated cirrhosis classified based on the Child-Pugh score. The most common causes of the cirrhosis were hepatitis B virus (HBV)-induced cirrhosis in 20 patients (50%), followed by hepatitis C virus (HCV)-induced cirrhosis in 10 patients (25%). Thirty-seven patients (92.5%) had Child-Pugh A and the remaining 3 had class B. Median serum AFP levels were 72.0 U/L (range, 0.52 - 131707 ng/ml). The baseline characteristics of the HCC patients who underwent TACE treatment are summarized in Table 1.

Thirteen of the 40 patients had solitary tumor (32.5%), 5 (12.5%) had two nodules, and 22 (55.0%) had more than two nodules. Seven patients (18.5%) had BCLC stage A, 14 (35%) had stage B and the remaining 19 (47.5%) had stage C. Among the 7 patients with BCLC stage A, 2 were awaiting liver transplantation, 2 had recurrence after RFA, 1 had recurrence after surgical resection, and the remaining 2 patients did not accept curative treatment modalities for HCC. Overall, 11 patients had recurrent disease - 4 after surgical resection and 7 after RFA. Twelve of the 40 patients had PVT (3 had total right PVT, 2 had total left PVT, 1 had main PVT, and the remaining 6 had partial right PVT). Twelve had detectable intraabdominal lymphadenopathy (Table 1).

TACE Treatment

A total of 80 sessions were performed with a median of 2 sessions (range, 1-7 sessions). Drug infusion via segmental catheterization was performed in 53 sessions (66.3%), via subsegmental in 24 sessions (30%) and via intercostal and/or with inferior phrenic artery in 3 sessions (3.8%). cTACE was

Table 1. Characteristics of the 40 patients with HCC who underwent TACE treatment

	Total cohort n=40	cTACE n=16	DEB-TACE n=11	Mixed n=13
Age (years)	59.6±10.3 (60)	58.6±12.4 (59.5)	58.2±8.5 (58)	61.9±8.9 (64)
Gender (M/F)	34/6	14/2	9/2	11/2
Child-Pugh class A/B	37/3	15/1	9/2	13/0
BCLC stage A/B/C	7/14/19	3/6/7	1/3/7	3/5/5
Performance status 0/1	37/3	15/1	11/0	11/2
Serum ALT levels (N: <37 U/L)	48.4±29.6 (42.5)	51.1±32.5 (45)	51.7±20.7 (50)	42.7±33.0 (37)
Serum GGT levels (N: 10-55 U/L)	128.4±201 (77)	121.1±103 (70)	193.2±373 (89.5)	87.1±52 (78)
Total bilirubin levels (N: 0.3-1.2 mg/dl)	1.06±0.86 (0.87)	1.18±1.2 (0.82)	1.20±0.7 (0.92)	1.16±0.07 (1.16)
Albumin levels (N: 3.5-4.5 g/dl)	3.8±0.6 (3.8)	3.7±0.5 (3.7)	3.9±0.7 (3.8)	3.9±0.5 (3.8)
Serum creatinine level (N:0.4-0.9 mg/dl)	0.82±0.22 (0.82)	0.82±0.3 (0.83)	0.81±0.2 (0.81)	0.85±0.1 (0.82)
INR level	1.19±0.13 (1.18)	1.25±0.18 (1.23)	1.15±0.07 (1.15)	1.16±0.07 (1.16)
AFP level (N: 0-9 ng/ml)	5421.9±23320.8 (72)	2920.7±7998.9 (120)	370.5±540 (74)	12033.3±39691.5 (7)

cTACE: Conventional transarterial chemoembolization. DEB-TACE: Drug-eluting beads transarterial chemoembolization. M: Male. F: Female. BCLC: Barcelona Clinic Liver Cancer. ALT: Alanine transaminase. GGT: Gamma-glutamyl transpeptidase. INR: International normalized ratio. AFP: Alpha fetoprotein.

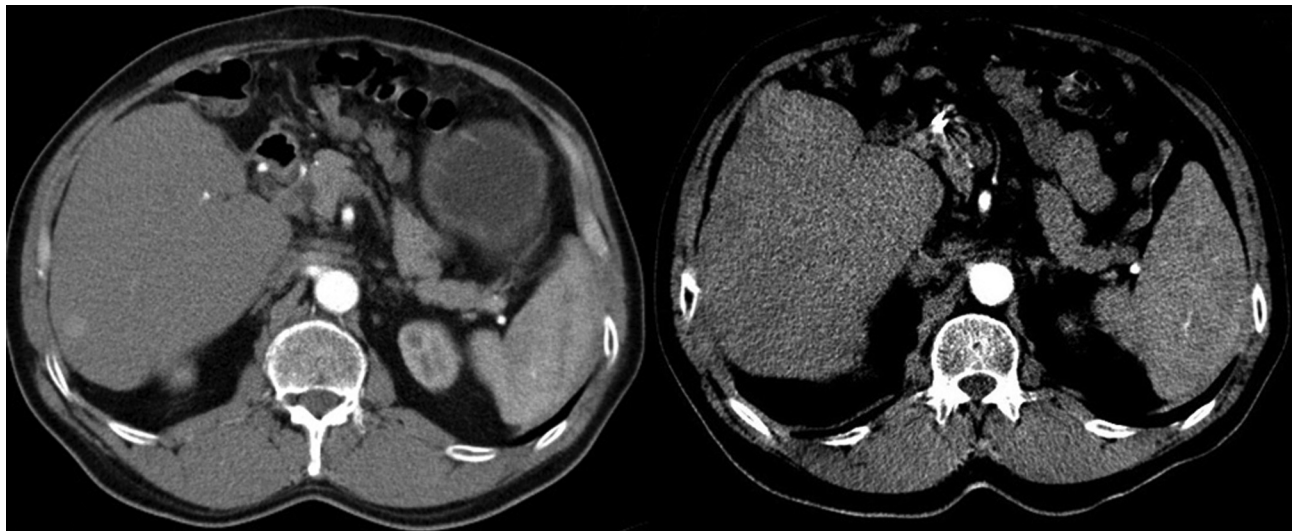


Figure 1. Post-contrast arterial phase computed tomography images of HCC patient with complete response based on RECIST, before and after TACE treatment.

performed in 16 patients (40%, 3 patients BCLC A, 6 patients BCLC B, 7 patients BCLC C), DEB-based TACE in 11 patients (27.5%, 1 patient BCLC A, 3 patients BCLC B, 7 patients BCLC C) and both cTACE and DEB-based TACE in 13 patients (32.5%, 3 patients BCLC A, 5 patients BCLC B, 5 patients BCLC C). The median number of sessions of cTACE, DEB-based TACE and mixed tre-

atment was 1, 2 and 3, respectively. Doxorubicin was infused with lipiodol in 46 sessions and with DEB-based TACE in 34 sessions.

Treatment Response

Based on RECIST criteria, 1 patient had complete response (Figure 1), 6 had partial response, 24 had stable disease, and 8 had progression. The remain-

ning 1 patient received transplantation after chemoembolization. According to their treatment procedure, in the cTACE group (n=16), 3 patients had partial response, 11 had stable disease and 2 had progression, whereas in the DEB-based TACE group (n=11), 2 patients had partial response, 5 had stable disease, 3 had progression, and 1 received transplantation, and in the combined treatment group (n=13), 1 patient had complete response, 1 had partial response, 8 had stable disease, and 3 had progression. No significant difference in terms of the treatment response (partial response and stable disease and liver transplantation) was observed between cTACE and DEB-based TACE treatment groups (87.5%, 14/16 vs 72.7%, 8/11, $p>0.05$).

Overall Survival

The median follow-up was 19 months (range, 1-52 months). Twenty-eight patients died due to primary disease progression. The median overall survival of all patients was 23.2 months (95% confidence interval (CI): 6.1-37.8) (Figure 2A). The 1-, 2-, 3-, and 4-year cumulative survival rates were 75%, 49%, 22%, and 16%, respectively. The median overall survival rate in patients with BCLC A was better compared to the other groups (35 months [95% CI: 31.2-38.8] vs 19 months [95% CI: 2.1-36] and 14 months [95% CI: 0.3-27.6], respectively) (Figure 2B). However, no statistical significant difference was observed ($p=0.235$). The survival of patients Child-Pugh class A (n=37) was significantly better than that of patients Child-Pugh class B (n=3) (median survival 24 vs 6 months, $p=0.004$). No statistically significant difference in terms of patient survival was observed between the two different TACE treatments ($p=0.186$). The median overall survival of patients treated with cTACE was 18 months (95% CI: 10.2-25.8), with DEB-based TACE was 14 months (95% CI: 1.6-26.4), and with combined c-TACE- and DEB-based TACE was 31 months (95% CI: 13.2-48.8) (Figure 2C).

Baseline low serum albumin level ($p=0.003$) and the presence of PVT ($p=0.011$) were identified for prediction of survival. No other baseline characteristic, including age, gender, serum ALT, GGT, bilirubin, creatinine, AFP levels, or the presence of ascites or intraabdominal lymphadenopathy, was identified as affecting survival ($p>0.05$).

Technical success was 100%. All patients were hospitalized for a mean of 2.3 ± 1.7 days (median, 2

days; range, 1-12 days). No procedure-related major complication or mortality was observed. No significant difference in terms of the TACE-related side effects, including severe hepatotoxicity and

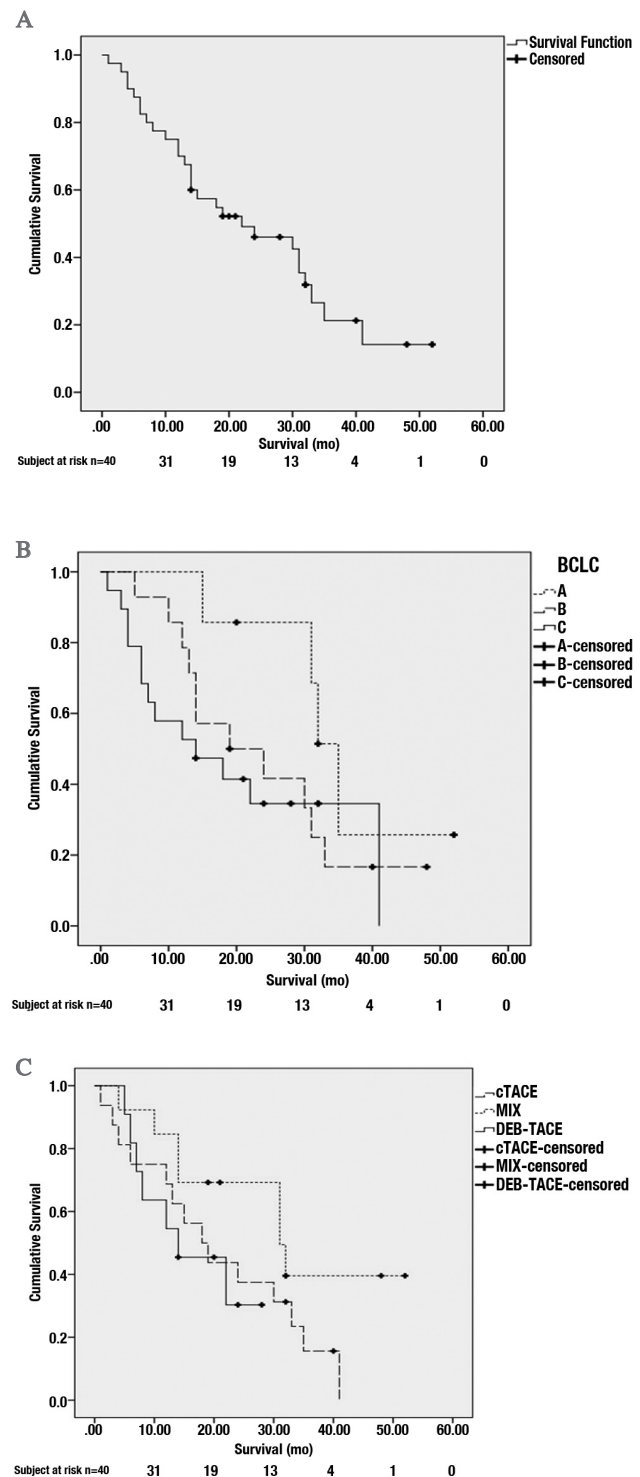


Figure 2. A. Overall survival of the 40 patients with HCC who underwent TACE treatment, according to BCLC stage (B) and treatment modality (C).

pancytopenia, or hospitalization interval was observed between the treatment groups.

DISCUSSION

In the present study, we retrospectively investigated the effect and tolerability of interventional TACE treatment in 40 patients with diagnosed HCC. HBV-induced cirrhosis was the most common etiology (50%) in patients with HCC, as previously published in the Turkish population (10). The median overall survival was 23 months in patients with HCC who were treated with TACE, and the 1-, 2-, 3-, and 4-year cumulative survival rates were 75%, 49%, 22%, and 16%, respectively. This result confirms the previous studies, which reported that the 1- and 2-year survival rates of TACE treatment ranged from 57%-82% and 31%-63% in patients with unresectable HCC, as compared to the conservative management group with rates of 32%-63% for 1 year and 11%-27% for 2 years, respectively (11-14). This result indicates that TACE treatment improves survival in patients with unresectable HCC.

In patients with HCC, patient selection is crucial for the success of TACE treatment. Since TACE treats the primary tumor in the liver, asymptomatic HCC patients with intermediate or early stage are the optimal candidates for TACE treatment (15,16). Kim *et al.* (8) demonstrated that Child-Pugh class, serum AFP level, PVT, tumor node metastasis stage, and initial compact lipiodolization were independent predictors of survival in patients with unresectable HCC treated with TACE. Burrell *et al.* (17) reported the median overall survival rates in BCLC A and B patients as 54.2 and 47.7 months in patients with HCC treated by TACE using DC beads. On the other hand, several investigators demonstrated that the recurrence-free survival was significantly better for single HCC treated with TACE compared with multiple HCCs (20 months vs 7.7 months, $p < 0.001$) (8). In the present study, baseline serum albumin level and PVT were identified as affecting survival. The survival of patients with Child-Pugh class A was obviously better than that of patients with Child-Pugh class B (24 vs 6 months). In the analysis of survival based on BCLC staging, no significant difference was

observed among patients according to BCLC groups ($p > 0.05$). However, the median overall survival rate in BCLC A was slightly better than in the others (35 months vs 19 and 14 months).

There are limited data in the literature comparing cTACE and DEB-based TACE in terms of survival and tolerability in patients with HCC. Several investigators reported that TACE using DEB provided better outcomes than cTACE in patients with more advanced HCC (18-22), but this was not confirmed by others (23). The reported data are conflicting. Recently, Song *et al.* (21) investigated the efficacy and safety of c-TACE and DEB-based TACE in HCC patients and reported that DEB-based TACE showed better treatment response and delayed tumor progression compared with cTACE. In the present study, no significant differences in terms of the treatment response and patient survival were observed between the two TACE treatment modalities ($p > 0.05$).

A total of 80 sessions were performed mainly via segmental catheterization. The overall technical success was 100% with a short-term hospitalization of a median 2 days. No procedure-related major complication was observed. The side effects of cTACE and DEB-based TACE were similar in the present study and comparable to those reported in the literature (20-22). However, early clinical experiences confirmed that TACE-related side effects improved gradually with the implementation of DEB-based TACE (19). This result indicates that TACE treatment modalities are safe and tolerable in HCC patients.

There are several limitations to the present study. The study was retrospective in nature and the patient population was heterogeneous with a small sample size. The median treatment sessions according to treatment groups were also heterogeneous.

In conclusion, the present study indicates that TACE treatment improves the overall survival and provides better outcome in selected patients with HCC. No difference in survival or side effects was observed between the two TACE treatment modalities. Liver functional capacity and portal vein invasion appear to negatively affect the disease outcome in HCC patients treated with TACE.

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