Clinical safety and tumor response rate of DEB-TACE for the treatment of hepatocellular carcinoma

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ABSTRACT

Clinical safety and tumor response rate of DEB-TACE for the treatment of hepatocellular carcinoma

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OBJECTIVE: To assess the tumor response rate and clinical safety of transarterial chemoembolization using drug-eluting beads (DEB-TACE) in patients with hepatocellular carcinoma.

MATERIALS AND METHODS: Between September 2009 and January 2011, eighty-one patients with 100 HCCs were included in this study. All patients underwent pre-procedural MDCT or magnetic resonance imaging for evaluation of tumor stage. Four experienced interventional radiologists had performed DEB-TACE for hypervascular HCC. Before and after treatment, liver function status (Child-Pugh class) and tumor stage (BCLC and mUICC criteria) were evaluated. MDCT and MRI were performed 4~8 weeks after

DEB-TACE to evaluation of tumor response. And, statistical correlation was calculated between angiographic findings and tumor response. Also, relation tumor stage and tumor response was calculated. Finally, post-procedural complications were evaluated by symptoms and image findings.

RESULTS: For total of 81 patients, 71 were Child-Pugh class A and 10 were Child-Pugh class B before treatment, and 67 were Child-Pugh class A, 13 were Child-Pugh class B and 1 were Child-Pugh class C after treatment. For a total of 100 treated HCCs, immediate complete response (CR) according to mRECIST and EASL was seen in 74 lesions. Partial response (PR) lesions were 14 according to mRECIST and 13 in EASL, stable disease (SD) were 5 according to mRECIST and 6 in EASL, and disease progression (PD) were 7 according two response criteria. Tumor progression free survival rate were 65.2% during 1-year follow-up. There was no statistical significance between tumor stage and tumor response. Of angiographic findings, feeder hypertrophy, neovascularization and multiple feeder were correlated with tumor response, showing statistical significance. Of total 81 patients, localized bile duct dilatation were shown in 39 patients (48.1%), peritumoral parenchymal ischemic change were shown in 10 patients (12.4%) and post-embolization syndrome were shown in 7 patients (8.6%).

CONCLUSION: DEB-TACE was considered as a safe modality for the treatment of HCC, and showed acceptable tumor response rate as well as tumor progression free rate in this mid-term result.

Key words : hepatocellular carcinoma, drug-eluting bead, transarterial chemoembolization, tumor response rate, angiographic findings, post-procedural complication.

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I. INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world and the third most common frequent cause of death of cancer [1, 2]. Although liver transplantation or surgical resection is the curative option with good survival rates, locoregional treatment is usually the only option for the majority of patients with HCC [3-5].

Image-guided treatment for patients with unresectable HCC includes catheter-based approaches (transarterial chemoembolization (TACE)) and ablative techniques (ethanol ablation, radiofrequency ablation) [6]. According to the Barcelona Clinic Liver Cancer (BLCL), TACE is recommended for intermediate-stage HCC patients with multinodular disease but no vascular

invasion, which is the most common stage at the date of diagnosis [7-9]. Recently, the use of TACE with drug-eluting beads (DEB-TACE; DC Beads; Biocompatibles, Terumo) has shown that it provides a combined ischemic and cytotoxic effect locally, while the systemic levels of doxorubicin are low [10]. In recent study, doxorubicin-related complications were lower with DEB-TACE compared with conventional TACE for the same dose of doxorubicin (150 mg; $p < 0.001$) [11].

The purpose of this study was to assess the tumor response rate and clinical safety of transarterial chemoembolization using drug-eluting beads (DEB-TACE) in patients with hepatocellular carcinoma.

II. MATERIALS AND METHODS

1. Patients

Informed consent forms for DEB-TACE were obtained from all patients. Approval by the institutional review board was waived because the study was retrospective.

Between September 2009 and January 2011, 94 patients with 113 HCCs were referred for DEB-TACE. Of these, 9 patients with previous TACE using lipiodol, 2 who underwent palliative DEB-TACE due to huge mass, one with previous RFA, and one who had previous holmium treatment were excluded. The remaining 81 patients (64 men, 17 women; age range 8~83; mean age, 30.1) with 100 HCCs who underwent DEB-TACE that included the study population. All patient were decided liver function status (Child-Pugh class) and tumor stage (BCLC and mUICC stage) before and after treatment. In the study, 90 patients had risk factor as hepatitis B (n=78), hepatitis C (n=10), or alcoholism (n=2). Tumor response rate were evaluated, according to the

mRECIST criteria and the EASL criteria.

The HCCs ranged from 1.0cm to 11.0cm in diameter (mean, 2.9cm). All patients were considered to be HCC based on the basis characteristic imaging (MDCT, MRI and angiography) findings or elevated serum tumor marker (α-fetoprotein level greater than 200ng/mL).

2. Chemoembolization

Before TACE, angiography of the hepatic and mesenteric artery was performed to map liver vascular anatomy, to check for arteriovenous shunts, and to identify arterial feeders of the tumor. In large lesions segmental arteries were catheterized selectively, while for smaller lesions –if feasible- the vessels catheterized were generally subsegmentary branches. Feeding arteries were superselectively catheterized with a microcatheter (2.7F Progreat; Terumo, Europe N.V, Leuven, Belgium) through which the DEB were delivered to the tumor. In patients with larger tumors, both segmental and subsegmental TACE was performed. The type of DEB used was DC-Beads (Biocompatibles, Surrey, UK), and each patient received 2 ml DC Beads with a diameter of 100 to 300 μm or 2 ml DC Beads with a diameter of 300 to 500 μm. One hour before intervention, DC Beads were loaded with doxorubicin (Adriblastina, Pfizer N.V, Puurs, Belgium) at a dose 35 - 37.5 mg doxorubicin/ml of bead suspension, to a maximum of 150 mg of doxorubicin loaded in two vials of DC Beads (4 ml total). Loaded DC Bead suspension was mixed an equal volume of nonionic contrast medium before delivery. The successful embolization end point was defined as stasis of blood flow at the level of the segmental arteries. Pain and fever attributed to postembolization syndrome were controlled individually with nonsteroidal anti-inflammatory drugs and opioids.

3. Image Analysis

All CT and MRI images were archived with a picture arching and communication system (PACS; PathSpeed Workstation; GE Medical System). Two experienced abdominal radiologists reviewed the CT and MRI images at the PACS workstation, without knowledge of the final outcomes of the patients. The radiologists knew the patients had been referred for an evaluation after DEB-TACE of HCC, and were unaware of all other information regarding the patients' detailed medical history, laboratory results, findings from other imaging modalities, and the final diagnosis. Each radiologist reviewed all the CT and MRI images of precontrast and arterial phase obtained for 1st follow up evaluation after treatment. A standard questionnaire was completed for each patient. A final decision was made with consensus.

4. Statistical analysis

Numerical differences between groups were assessed by chi-square test for categorical variables. Kaplan-Meier survival curves were plotted for progression free survival rate. All statistical computations were performed using SPSS software (version 17.0, SPSS Inc, Chicago, Illinois). The statistical results were considered to indicate significance if the P-value was less than 0.05.

III. Results

For total of 81 patients, 71 were Child-Pugh class A and 10 were Child-Pugh class B before treatment, and 67 were Child-Pugh class A, 13 were Child-Pugh class B and 1 were Child-Pugh class C after treatment. Following BCLC staging system, 15 were stage 0, 43 were stage A, 11 were stage B, and 12 were stage C. According to mUICC staging system, 17 were stage I, 19 were stage II, 20 were stage III, and 5 were stage IV.

For a total of 100 treated HCCs, immediate complete response (CR) according to mRECIST and EASL was seen in 74 lesions. Partial response (PR) lesions were 14 according to mRECIST and 13 in EASL, stable disease (SD) were 5 according to mRECIST and 6 in EASL, and disease progression (PD) were 7 according two response criteria. Of 100 lesions, 63 HCCs were shown size reduction 1-month after treatment (1.0~3.6cm; mean : 0.5cm). There was no statistical significance between tumor stage and tumor response. (p=0.789, BCLC; p=0.525, mUICC). And, tumor progression survival rate were 65.2% during 1-year follow-up.

Of angiographic findings, feeder hypertrophy, neovascularization and multiple feeders were correlated with tumor response, showing statistical significance. ($p<0.05$). There was no statistically significant correlation between embolization level with tumor response rate. (p=0.238).

Of total 81 patients, localized bile duct dilatation were shown in 39 patients (48.1%), peritumoral parenchymal ischemic change were shown in 10 patients (12.4%) and post-embolization syndrome were shown in 7 patients (8.6%). On immediate post procedural period, liver enzymes level (AST/ALT) were elevated statistically significant ($p < 0.05$). However, follow-up laboratory findings after 2 weeks and 1 month, liver enzyme levels show no statistically difference, comparing to initial liver enzyme level.

Table 1. Pre- and post-procedural liver function status (Child-Pugh score)

Post-procedural C-P score	Pre-procedural C-P score			
	A	B	C	total
A	67	0	0	67
B	4	9	0	13
C	0	1	0	1
Total	71	10	0	81

Table 2. Tumor response rate by mRECIST and EASL

Response rate					
	mRECIST				total
EASL	CR	PR	SD	PD	
CR	74	0	0	0	74(%)
PR	0	13	0	0	13(%)
SD	0	1	5	0	6(%)
PD	0	0	0	7	7(%)
total	74(%)	14(%)	5(%)	7(%)	100(%)

Table 3. Tumor complete response rate correlated with patient factors, angiographic findings and procedural factors. *p-value

	mRECIST	EASL
BCLC stage	0.789	0.789
mUICC stage	0.525	0.525
Feeder hypertrophy	0.025	0.025
Neovascularization	0.031	0.031
Multiple feeder	0.238	0.238
Embolization level	0.023	0.023

Table 4. Numbers of patients with complication after DEB-TACE.

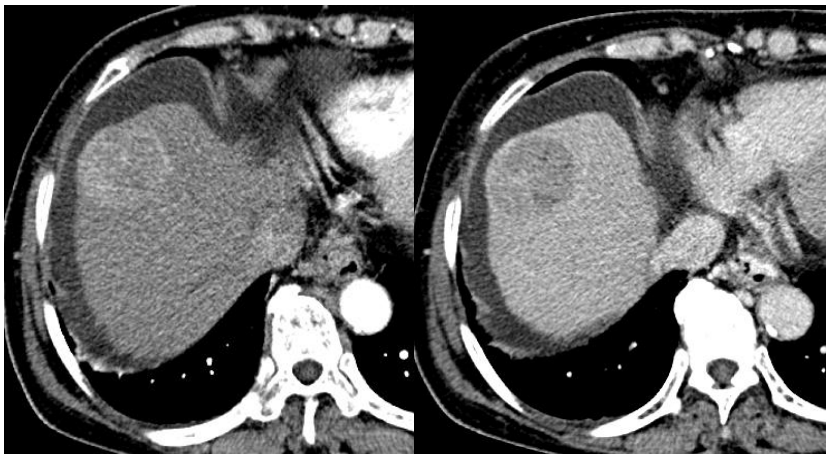
Complications	Present	Absent
Localized bile duct dilatation	39 (48.1%)	42 (51.9%)
Peritumoral parenchymal ischemic change	10 (12.4%)	71 (87.7%)
Post-embolization syndrome	7 (8.6%)	74 (91.4%)

Figure 1. A 72-year-old man with hepatocellular carcinoma

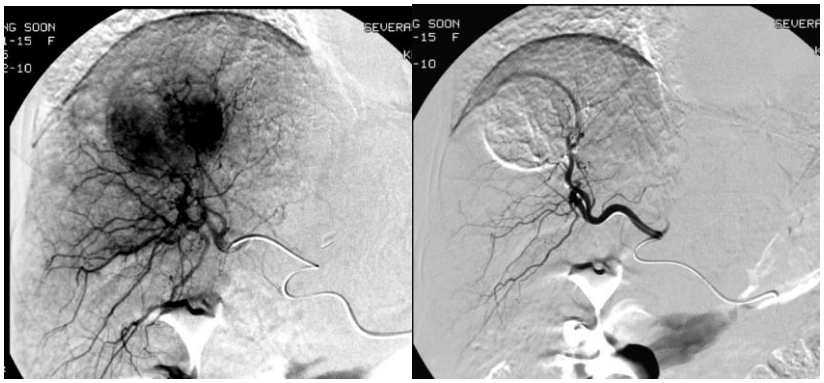
(A) hepatic arterial, (B) portal venous phase image from MDCT scan. The lesion shows increased arterial enhancement on the arterial phase image (A) and washout of contrast enhancement on the portal venous image (B).

(C) Angiographic finding of the tumor before embolization shows intratumoral neovascularization and feeder hypertrophy. (D) Angiographic finding of the tumor after embolization shows complete obstruction of tumor feeder, and stasis of blood flow at the level of the segmental arteries.

(E) Liver dynamic MRI was performed 1-month after treatment, shows complete necrosis of the tumor without intratumoral enhancement. (F) Follow-up MDCT was performed 6-months after treatment shows size reduction of the tumor without enhancement.



(A) (B)



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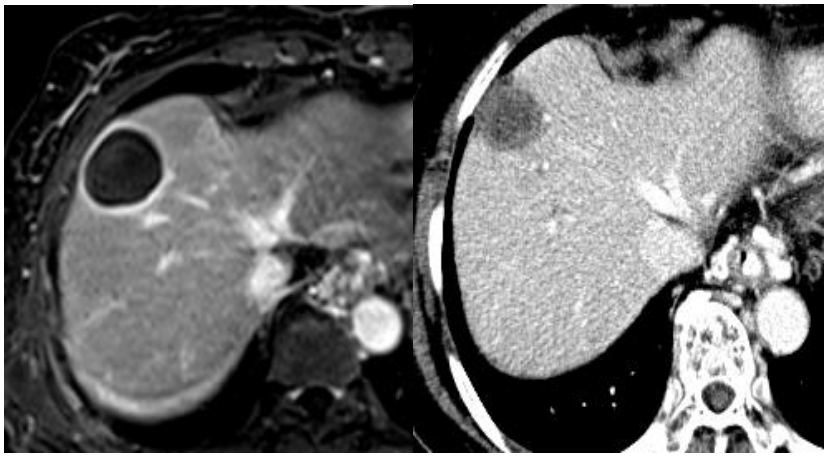


(E) (F)

Fig 2. A 72-year-old man with hepatocellular carcinoma

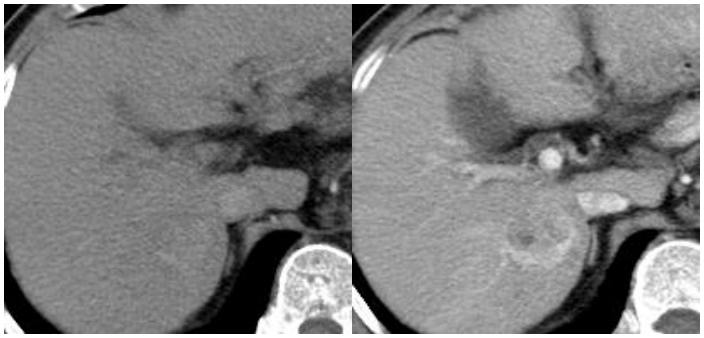
(A)Precontrast, (B) hepatic arterial, (C) portal venous phase images from MDCT scan. A hypoattenuating lesion in seen on the precontrast phase image (A). The lesion shows increased arterial enhancement on the arterial phase image (B) and washout of contrast enhancement on the portal venous(C).

(D) Angiographic finding of the tumor before embolization shows intratumoral neovascularization and feeder hypertrophy.

(E) MDCT was performed 1-month after treatment, shows complete necrosis

of the tumor without intratumoral enhancement.

(F), (G) Follow-up MDCT was performed 6-months after treatment shows size reduction of the tumor without enhancement (F) with asymptomatic localized bile duct dilatation (G).



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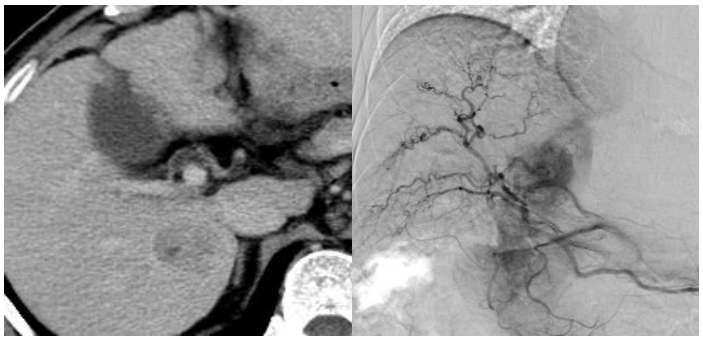

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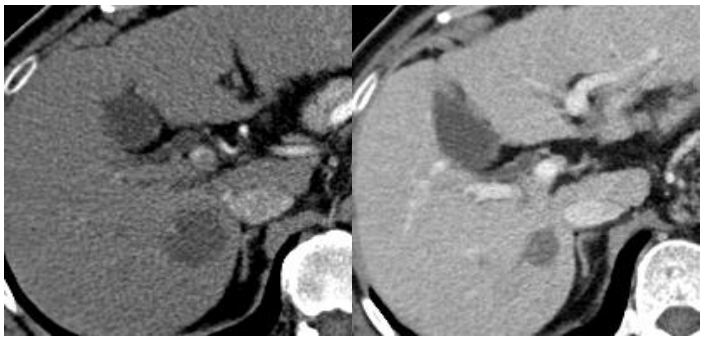

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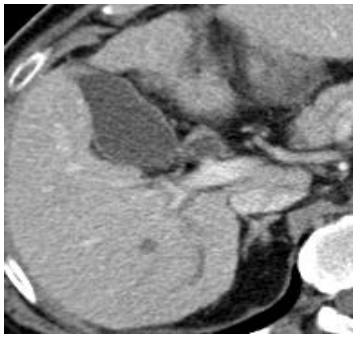


(G)

Fig 3. Kaplan-Meier analysis for disease progression free survival during 1-year follow-up. 1-year progression free survival rate was 65.2%.

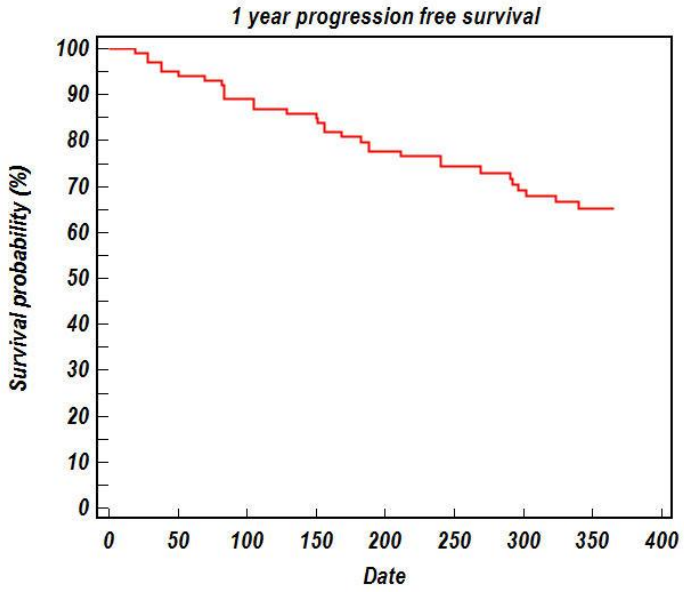
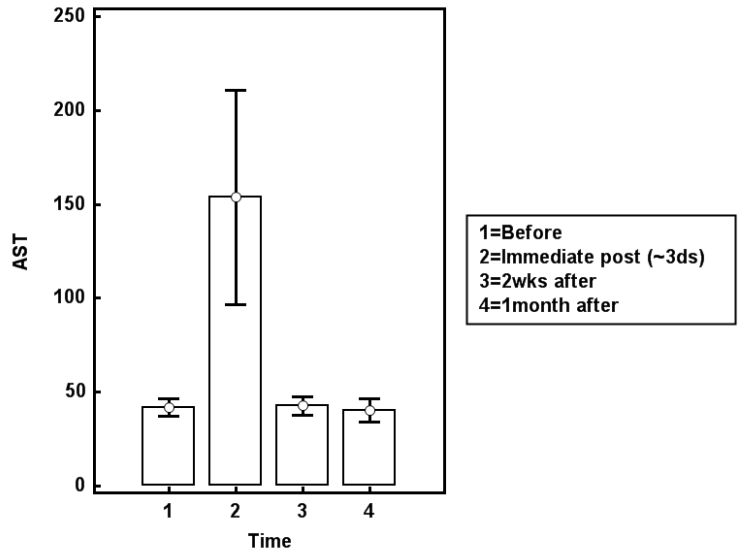
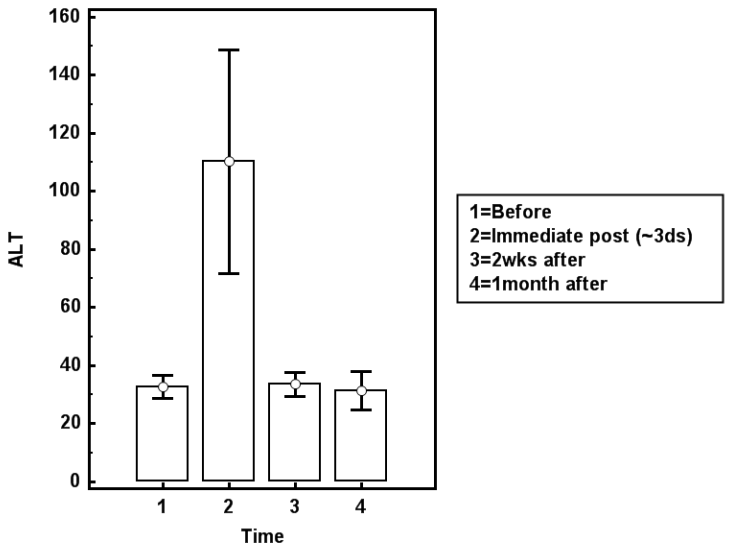


Fig 4. Liver enzyme level comparison before and after DEB-TACE procedure.





IV. DISCUSSION

TACE is an overall accepted palliative treatment approach in unresectable HCC for the reduction of cancer progression and the improvement of survival compared to patients treated with best supportive care [12]. DEB-TACE was first introduced in 2006. The use of TACE with drug-eluting beads (DEB-TACE; DC Beads; Biocompatibles, Terumo) has shown that it provides a combined ischemic and cytotoxic effect locally, while the systemic levels of doxorubicin are low [10]. In recent study, doxorubicin-related complications were lower with DEB-TACE compared with conventional TACE for the same dose of doxorubicin (150 mg; $p < 0.001$) [11]. Reviews of current treatment results are promising as they consider DC beads to be an efficient chemoembolization material with good pharmacokinetic profile [10, 12, 13]. In our study shows acceptable immediate tumor response rate without decreased liver function.

Local response to treatment is relevant for the investigation of new therapeutic options. The assessment of loco-regional treatment requires a careful assessment of the treated HCC by imaging techniques. Many studies used tumor response according to the European Association for the Study of Liver Disease (EASL) and modified RECIST (mRECIST) criteria [10, 11, 14-16]. Unlike RECIST, EASL criteria and mRECIST criteria assesses tumor response according to amount of enhancing tissue [15, 16]. DEB-TACE induces tumor necrosis with almost no interference with the systemic circulation. In our study, tumor response rate after DEB-TACE were evaluated according to EASL criteria and mRECIST criteria using MDCT and MRI.

Following our knowledge, there was no previous report about relation angiographic findings and tumor response rate after DEB-TACE. We

evaluated angiographic findings, which can be influence on tumor response rate. As a result, feeder hypertrophy, neovascularization and multiple feeder are correlated with tumor response rate after DEB-TACE, that show statistically signifincance.

Conventional TACE was reported a safe technique, with a very low rate of major complication. The most common reported serious adverse events of conventional TACE are liver abscess, liver infarction and cholecystitis, which develop in up to 2% of the patients [17]. In our study, there was no major complication, such as liver abscess of liver infarction. Localized bile duct dilatation, peritumoral parenchymal ischemic change and post-embolization syndrome were shown as complication in our study. Peritumoral parenchymal ischemic change was improved on follow up MDCT scan after few months. Overall, conventional TACE related mortality is less than 4% and 30-day mortality is 1% [18]. In our study, procedure-related mortality and 1-year mortality was 0%.

Our study has some limitation. First, we had no pathologic proof of the all treated lesions. Surgical excision, angiography, and serial follow-up were used to confirm whether progression or stable lesion. Second, tumor response rate was evaluated on immediate period after treatment (4~8 weeks).

V. CONCLUSION

We conclude that DEB-TACE was considered as a safe modality for the treatment of HCC, and showed acceptable tumor response rate as well as tumor progression free rate in this mid-term result.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94(2):153-6.
2. Liu Q, Song Y, Zhou Y, Qiao L. A useful agent for chemoprevention of hepatocellular carcinoma? Cancer Biol Ther 2006;5(12):1674-6.
3. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42(5):1208-36.
4. Hong K, Georgiades CS, Geschwind JF. Technology insight: Image-guided therapies for hepatocellular carcinoma--intra-arterial and ablative techniques. Nat Clin Pract Oncol 2006;3(6):315-24.
5. Jansen MC, van Hillegersberg R, Chamuleau RA, van Delden OM, Gouma DJ, van Gulik TM. Outcome of regional and local ablative therapies for hepatocellular carcinoma: a collective review. Eur J Surg Oncol 2005;31(4):331-47.
6. Rhim H, Lim HK, Kim YS, Choi D, Lee WJ. Radiofrequency ablation of hepatic tumors: lessons learned from 3000 procedures. J Gastroenterol Hepatol 2008;23(10):1492-500.
7. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19(3):329-38.
8. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002;35(3):519-24.
9. Llovet JM, Fuster J, Bruix J. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transpl 2004;10(2 Suppl 1):S115-20.
10. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead

embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010;33(1):41-52.

11. Malagari K, Pomoni M, Spyridopoulos TN, Moschouris H, Kelekis A, Dourakis S, et al. Safety profile of sequential transcatheter chemoembolization with DC Bead: results of 237 hepatocellular carcinoma (HCC) patients. Cardiovasc Intervent Radiol 2011;34(4):774-85.
12. Sadick M, Haas S, Loehr M, Elshwi M, Singer MV, Brade J, et al. Application of DC beads in hepatocellular carcinoma: clinical and radiological results of a drug delivery device for transcatheter superselective arterial embolization. Onkologie 2010;33(1-2):31-7.
13. Malagari K. Drug-eluting particles in the treatment of HCC: chemoembolization with doxorubicin-loaded DC Bead. Expert Rev Anticancer Ther 2008;8(10):1643-50.
14. Kloeckner R, Otto G, Biesterfeld S, Oberholzer K, Dueber C, Pitton MB. MDCT versus MRI assessment of tumor response after transarterial chemoembolization for the treatment of hepatocellular carcinoma. Cardiovasc Intervent Radiol 2010;33(3):532-40.
15. Riaz A, Memon K, Miller FH, Nikolaidis P, Kulik LM, Lewandowski RJ, et al. Role of the EASL, RECIST, and WHO response guidelines alone or in combination for hepatocellular carcinoma: radiologic-pathologic correlation. J Hepatol 2011;54(4):695-704.
16. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35(3):421-30.
17. Bargellini I, Sacco R, Bozzi E, Bertini M, Ginanni B, Romano A, et

al. Transarterial chemoembolization in very early and early-stage hepatocellular carcinoma patients excluded from curative treatment: A prospective cohort study. Eur J Radiol 2012;81(6):1173-8.

18. Malagari K, Chatzimichael K, Alexopoulou E, Kelekis A, Hall B, Dourakis S, et al. Transarterial chemoembolization of unresectable hepatocellular carcinoma with drug eluting beads: results of an open-label study of 62 patients. Cardiovasc Intervent Radiol 2008;31(2):269-80.

ABSTRACT(IN KOREAN)

간세포암에서의 DEB-TACE를 이용한 치료의 임상적 안정성과 치료 반응률

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권 준 호

목적: 간세포암 환자에서의 DEB-TACE를 이용한 간동맥 화학색전술의 종양 치료 반응률과 임상적 안정성을 분석한다.

대상 및 방법: 2009년 9월부터 2011년 1월까지 본원에서 DEB-TACE를 시행 받은 81명 환자의 100개의 간세포암이 연구에 포함되었다. 모든 환자는 종양 등급을 알기 위해 시술 전, 후에 MDCT 혹은 MRI를 시행 받았다. 네 명의 중재 방사선학 의사가 DEB-TACE를 시행하였다. 모든 환자에서 시술 전, 후의 간 기능 상태 (Child-Pugh class)와 종양등급

(BCLC와 mUICC criteria)를 평가하였다. 종양의 반응을 알기 위하여 치료 4~8주 후에 MDCT 혹은 MRI를 촬영하였다. 그리고, 혈관촬영 결과와 종양반응에 대한 통계학적 분석이 이루어 졌으며, 종양등급과 종양반응에 대한 분석 또한 이루어졌다. 마지막으로 치료 후 합병증을 환자의 증상과 영상검사를 토대로 판단하였다.

결과: 총 81명의 환자 중 치료 전에 71명의 환자가 Child-Pugh class A, 10명의 환자가 Child-Pugh class B로 평가 되었으며, 시술 후에 67명의 환자가 Child-Pugh class A, 13명의 환자가 Child-Pugh class B, 그리고 1명의 환자가 Child-Pugh class C로 평가되었다. 100개의 치료 받은 병변중 74개가 mRECIST와 EASL criteria에 따라 complete response로 평가 되었다. Partial response는 mRECIST에서 14명, EASL에서는 13명으로 평가 되었으며, stable disease는 mRECIST에서 5명, EASL에서는 6명으로 평가되었다. Disease progression은 두 criteria에서 모두 7명으로 평가 되었다. 종양 등급과 종양 반응률 간에 통계학적으로 유의한 상관관계는 없었다. 혈관촬영상 공급혈관의 비대, 종양 내 신생혈관생성, 그리고 다수의 공급혈관이 있는 경우 통계학적으로 유의하게 종양 반응이 좋은 것으로 나타났다. 81명의 환자 중 국소적 담관 확장이 39명 (48.1%), 종양주변의 경색변화가 10명 (12.4%), 그리고 색전 후 증후군이 7명 (8.6%)에서 나타났다.

결론: DEB-TACE는 간세포암 환자의 치료에 있어서 안전한 치료방법으로 생각되며, 수용할 만한 종양의 치료 반응률을 보이는 것으로 생각된다.

핵심되는 말 : 간세포암, drug-eluting bead, 동맥화학 색전술, 종양 반응률, 혈관촬영 결과, 시술 후 합병증