Doxorubicin-eluting beads versus combined conventional transarterial chemoembolization and percutaneous alcohol injection in the treatment of large hepatocellular carcinoma

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Introduction
Hepatocellular carcinoma (HCC) is a primary tumor of the liver, which usually develops in the setting of chronic liver disease, particularly in patients with chronic hepatitis B and hepatitis C. Current guidelines recommend transarterial chemoembolization (TACE) as the standard treatment of Barcelona Clinic Liver Cancer-B patients. The aim of this work is to compare the efficacy, safety, feasibility, and cost-effectiveness of drug-eluting bead (DEB)-TACE versus combined conventional transarterial chemoembolization (c-TACE)+percutaneous ethanol injection (PEI) for improving the outcome of large HCC.

Patients and methods
In all, 75 patients with large HCC were included in this study: 30 patients were treated by combined c-TACE + PEI and 45 patients were treated by DEB-TACE.

Results
By comparison of the results of the combined c-TACE + PEI group with the DEB-TACE group, there was no significant difference in tumor response, with better results in the combined c-TACE + PEI group and significant decrease in the median value of the serum level of α-fetoprotein after treatment among patients treated with combined c-TACE + PEI ($P = 0.004$), and a statistically significant difference in the median value after treatment between the two groups ($P = 0.036$).

Conclusion
Results of combined c-TACE + PEI and DEB-TACE are comparable, but the cost of a DEB-TACE session is three times that of c-TACE + PEI, and thus cost-effectiveness analyses recommend the use of combined c-TACE + PEI (less cost) in the treatment of large HCC; in addition, there was a significant reduction in the level of α-fetoprotein after combined c-TACE+PEI treatment.

Keywords:
doxorubicin beads, hepatocellular carcinoma, percutaneous alcohol, transaretrial chemoembolization

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common form of cancer worldwide, and it is the second leading cause of cancer-related deaths worldwide [1]. In Egypt, HCC is the first cause of cancer mortality [2].

The ideal transarterial chemoembolization (TACE) scheme should allow maximum and sustained concentration of the chemotherapeutic drug within the tumor with minimal systemic exposure combined with calibrated tumor vessel obstruction [3].

The use of TACE + percutaneous ethanol injection (PEI) is either to reduce the size of large tumors to subsequently apply percutaneous treatment or to combine the necrotizing effects of both procedures to achieve a more complete tumor necrosis [4]. It was found that the combination of conventional transarterial chemoembolization (c-TACE) and PEI was associated with higher survival rates and higher tumor response compared with c-TACE alone for HCC more than 3 cm in diameter [5].

Although conventional TACE with administration of an anticancer drug in oil emulsion followed by embolic agents has been the most popular technique, the introduction of embolic, drug-eluting beads (DEB) has provided an attractive alternative to lipiodol-based regimens [6]. This characteristic allows for the delivery

of large amounts of drugs to the tumor for a prolonged period of time, thereby decreasing plasma levels of the chemotherapeutic agent and potentially the related risk of systemic effects (e.g. cardiotoxicity) [7].

The 3-year recurrence-free survival was higher in DEB-TACE-treated patients than in c-TACE-treated patients (87.4 vs. 61.5%, $P = 0.0493$) [8].

In our study, we aimed to compare the efficacy, safety, feasibility, and cost-effectiveness of DEB-TACE versus combined c-TACE + PEI in the treatment of large HCC.

Patients and methods

Patients

Between January 2013 and May 2016, 75 cirrhotic patients with large HCC were included in this study and admitted to the Department of Tropical Medicine and Gastroenterology, Assiut University Hospital, Al-Rajhy Liver Hospital and National Cancer Institute, Cairo University. All our patients were diagnosed as having HCC by one imaging technique, showing the HCC radiological hallmark (contrast uptake in arterial phase and rapid washout in venous or delayed phase) [9].

Inclusion criteria were unresectable intermediate-stage HCC [Barcelona Clinic Liver Cancer (BCLC) classification stage B or Child–Pugh class A/B with large or multifocal HCC (5.1–11 cm)], with no vascular invasion or extrahepatic spread. Exclusion criteria were Child–Pugh C score, bilirubin greater than 3 mg/dl, ascites, platelet less than 50 000/dl, serum creatinine greater than 1.5 mg/dl, main portal vein thrombosis, pregnancy, and hepatic encephalopathy. Our patients were divided into two groups (based on financial item of the patients): the DEB-TACE group included 45 patients and the c-TACE and PEI group included 30 patients. The study protocol was approved by our institutional review board and by the ethical committee, and a written informed consent was obtained from all patients.

Methods

Procedure for conventional transarterial chemoembolization

Using the Seldinger [10] technique, the common femoral artery was punctured and the Cobra catheter (5 Fr; Radio Focus, Japan) was passed through a 5 Fr introducer guided by a hydrophilic guide wire (035 Fr diameter, Laureate; Merit, South Jordan, UT, USA), for selective catheterization of the hepatic artery. Then, a microcatheter (Renegade HI-FLOKIT; Boston Scientific, Boston, MA, USA) was passed into the proper hepatic artery branch (s) supplying the tumor, a blood vessel(s) supplying the tumor was selected, and aliquots of the chemotherapy dose [doxorubicin (Adriamycin (Pfizer, NY, USA)) 50–100 mg + 3–5 cm saline+3–6 cm Ultravist+8 cm Lipidol (ethyl ester of iodized oil; Guerbet, Cedex, France)], followed by embolization with polyvinyl alcohol 250–355 μm (Contour Embolization Particles; Boston Scientific, Boston, MA, USA) suspended in 50% saline and contrast are injected through the catheter until cessation of blood flow; next, postembolization angiogram was performed after removal of the microcatheter to assess the degree of devascularization.

PEI was started 2 weeks after c-TACE with a session of alcohol per week until the lesion(s) was saturated sector by sector with alcohol in each session or until contraindication developed for the procedure (e.g., ascites and rupture of HCC).

Procedure of drug-eluting bead-transarterial chemoembolization

This procedure is the same as c-TACE, but in DEB-TACE 50–100 mg of doxorubicin coupled with one to two vials of 30–60 or 50–100 μm dry eluting beads (Hepasphere Microspheres (Merit Medical, Soth Jordan, UT, USA)) were injected. Particle embolization was performed in addition if necessary.

Technique of percutaneous ethanol injection

After fasting, good sedation was provided with 5 mg of intravenous midazolam, and skin sterilization was performed at the site of needle insertion. The PEI needle (a 22-G needle) was introduced percutaneously into the tumor under real-time ultrasonographic guidance, and 2–10 ml of absolute ethanol was injected each time, depending on the tumor size and ethanol diffusion, which will be monitored by real-time ultrasonography.

Follow-up

Clinical examination and abdominal ultrasound were performed 2 weeks after c-TACE or DEB-TACE, and laboratory tests were performed when indicated (complete blood count, liver function tests, prothrombin time and concentration, serum electrolyte, blood urea, and serum creatinine).

Clinical examination, laboratory tests [complete blood count, liver function tests, prothrombin time and concentration, serum electrolyte, blood urea, serum

creatinine, and serum α-fetoprotein (AFP) level], and abdominal enhanced MRI with diffusion were performed 2 months after the procedures, and the oncologic standard for determining tumor response is according to modified Response Evaluation Criteria in Solid Tumors.

Statistical analysis

Data entry and data analysis were performed using SPSS (statistical package for the social science; version 19). c^2-test was used to compare between qualitative variables. Independent samples *t*-test was used to compare between two quantitative variables, and Mann–Whitney test was performed in case of nonparametric data. Paired samples *t*-test was performed to compare quantitative data before and after treatment and Wilcoxon's signed rank test was performed in case of nonparametric data. Multiple logistic regression analysis was applied to rank the different risk factors. *P* value was considered statistically significant when *P* value less than 0.05.

Results

In all, 75 patients having large HCC were included in this study (30 patients were treated by combined c-TACE+PEI and 45 patients were treated by DEB-TACE), and the results were analyzed as follows.

All patients enrolled in this study were classified as stage B according to the BCLC classification. Sociodemographic data and risk factors presented in Table 1 show that there was a significant difference in sex and residence between the two groups (male more than female and rural more than urban) and no significant differences as regards age, smoking, or diabetes mellitus between the two groups. Most of our patients were hepatitis C virus (HCV)-infected: 93.3% of patients in the combined c-TACE + PEI group and 95.6% of patients in the DEB-TACE group.

The two treatment groups were comparable as regards number, anatomical site, and size of the lesions, as shown in Table 2.

Although there was a higher response rate in combined c-TACE + PEI than in DEB-TACE, this was not a statistically significant difference, as shown in Table 3.

There was no statistically significant difference between the two groups before and after treatment as regards the Child–Pugh score. However, there was significant deterioration after DEB-TACE treatment (the mean score increased from 5.78 to 6.16, $P = 0.018$), as shown in Table 4.

Table 1 Sociodemographic data and risk factors of combined conventional transarterial chemoembolization + percutaneous ethanol injection versus drug-eluting bead-transarterial chemoembolization treatment groups of patients

	c-TACE+PEI (*n*=30) (*N* (%))	DEB-TACE (*n*=45) (*N* (%))	*P*
Age			
<60 years	13 (43.3)	24 (53.3)	0.396
≥60 years	17 (56.7)	21 (46.7)	
Mean±SD	62.03±9.15	60.18±6.64	0.312
Sex			
Male	27 (90.0)	32 (71.1)	0.050*
Female	3 (10.0)	13 (28.9)	
Residence			
Rural	26 (86.7)	28 (62.2)	0.021*
Urban	4 (13.3)	17 (37.8)	
Smoking			
Smoker	12 (40.0)	19 (42.2)	0.377
Exsmoker	10 (33.3)	9 (20.0)	
Nonsmoker	8 (26.7)	17 (37.8)	
Diabetes mellitus			
Diabetic	9 (30.0)	11 (24.4)	0.594
Nondiabetic	21 (70.0)	34 (75.6)	
Etiology			
HCV	28 (93.3)	43 (95.6)	0.547
HBV	1 (3.3)	0 (0.0)	
Combined infections (HCV + HBV)	1 (3.3)	2 (4.4)	

*Statistically significant; cTACE, conventional transarterial chemoembolization; DEB, drug-eluting bead; HBC, hepatitis B virus; HCV, hepatitis C virus; PEI, percutaneous ethanol injection.

Table 2 Comparison of the characters of hepatocellular carcinoma lesions in combined conventional transarterial chemoembolization + percutaneous ethanol injection versus drug-eluting bead-transarterial chemoembolization treatment groups of patients

	c-TACE + PEI (*n*=30) (*N* (%))	DEB-TACE (*n*=45) (*N* (%))	*P*
Number of lesions			
Single	25 (83.3)	43 (95.6)	0.168
Multiple	5 (16.7)	2 (4.4)	
Site of lesions			
Right lobe	23 (65.7)	39 (83.0)	0.140
Left lobe	11 (31.4)	8 (17.0)	
Right and Left lobes	1 (2.9)	0 (0.0)	
Size of lesions (cm)			
5-6	20 (66.7)	34 (75.6)	0.401
>6	10 (33.3)	11 (24.4)	
Mean±SD	6.49±1.70	6.11±1.10	0.244
Range	5.1 : 11	5.1 : 10	

cTACE, conventional transarterial chemoembolization; DEB, drug-eluting bead; PEI, percutaneous ethanol injection.

There was a significant decrease in the median value of the serum level of AFP after combined TACE+PEI treatment ($P = 0.004$), with a statistically significant difference after treatment between the two groups ($P = 0.036$), as shown in Table 5.

No significant difference was found between the two groups as regards any of the major complications,

Table 3 Response according to modified Response Evaluation Criteria in Solid Tumors criteria

Responses	c-TACE + PEI (*n*=30) (*N* (%))	DEB-TACE (*n*=45) (*N* (%))	*P*
Complete response	15 (50.0)	16 (35.6)	0.393
Partial response	10 (33.3)	21 (46.7)	–
Stable disease	2 (6.7)	1 (2.2)	–
Progressive disease	3 (10.0)	7 (15.6)	–
Objective response	25 (83.3)	37 (82.2)	0.901
Disease control	27 (90.0)	38 (84.4)	0.729

cTACE, conventional transarterial chemoembolization; DEB, drug-eluting bead; PEI, percutaneous ethanol injection.

Table 4 Child-Pugh score of combined conventional transarterial chemoembolization + percutaneous ethanol injection versus drug-eluting bead-transarterial chemoembolization groups of patients before and after treatment

Child-Pugh score	c-TACE + PEI (*n*=30)	DEB-TACE (*n*=45)	*P*
Child-Pugh before			
Mean±SD	5.90±0.88	5.78±0.74	0.518
Range	5.0-8.0	5.0-7.0	
Child-Pugh after			
Mean±SD	6.23±1.57	6.16±1.09	0.800
Range	5.0-11.0	5.0-9.0	
P	0.245	0.018*	

*Statistically significant; cTACE, conventional transarterial chemoembolization; DEB, drug-eluting bead; PEI, percutaneous ethanol injection.

Table 5 α-Fetoprotein before and after combined conventional transarterial chemoembolization + percutaneous ethanol injection versus drug-eluting bead-TACE treatment

	c-TACE + PEI (*n*=30) (*N* (%))	DEB-TACE (*n*=45) (*N* (%))	*P*
AFP before			
<100	14 (46.7)	19 (43.2)	0.498
100-1000	11 (36.7)	21 (47.7)	
>1000	5 (16.7)	4 (9.1)	
Median (range)	100 (0.5-9143.0)	200 (2.2-14 103.0)	0.555
AFP after			
<100	23 (76.7)	23 (53.5)	0.052
100-1000	4 (13.3)	17 (39.5)	
>1000	3 (10.0)	3 (7.0)	
Median (range)	21 (1.0-10 000.0)	71 (2.0-37 300.0)	0.036*
P	0.004*	0.187	

*Statistically significant; AFP, α-fetoprotein; cTACE, conventional transarterial chemoembolization; DEB, drug-eluting bead; PEI, percutaneous ethanol injection.

whereas the minor complication 'postablation syndrome' occurred in all patients of the TACE+PEI group (P = 0.000) and 'postembolization syndrome' occurred in 12 (40%) patients in the TACE+PEI treatment group and in 24 (53.3%) patients in the DEB-TACE group, with no statistically significant difference, as shown in Table 6.

By using multivariate logistic regression analysis for all factors, there were no significant predictors for improving the response of the treatment in the studied groups.

Discussion

The number of deaths per year in HCC is virtually identical to the incidence throughout the world, underscoring the high case fatality rate of this aggressive disease [11]. The HCC epidemic in Egypt is associated with HCV infection; up to 90% of the HCC cases in the Egyptian population were attributed to HCV [12].

The study by Bartolozzi *et al*. [13] had better results than our study results, which could be because of the difference in the size of HCC lesions between this study (from 3 to 8 cm) and our study (from 5.1 to 11 cm) and the number of sessions of PEI (from 6 to 16 sessions in this study and three to fourth sessions in our study).

The study by Grosso *et al*. [14] regarding DEB-TACE had better results than our study; this may be because the small diameter of the treated lesions ranged from 20 to 100 mm (mean: 42.5) compared with our study in which the diameter of the treated lesions ranged from 51 to 100 mm (mean: 60.1). However, our study had better results than the study by Reyes *et al*. [15] regarding DEB-TACE, because the tumor size in our study had a smaller diameter (6.1 vs. 6.9 cm) and better Child–Pugh score (in our study, Child–Pugh class A was found in 82.2% of patients and Child–Pugh class B in 17.8% of patients, and in the study of Reyes *et al*. [15] Child–Pugh class A was found in 30% of patients, Child–Pugh class B in 10% of patients, and Child–Pugh class C in 60% of patients). In addition, our results are better than those of Nawawi *et al*. [16] regarding DEB-TACE because of the difference in Child–Pugh score, as well as the number of lesions (Child–Pugh class A and class B were 63.2 and 36.8%, respectively, in the study by Nawawi *et al*. [16]; in our study, single lesion was found in 95.6% of patients and multiple lesions were found in 4.4% of patients, whereas in the study by Nawawi *et al*. [16] single lesion was found in 36.8% of patients and multiple lesions were found in 63.2% of patients).

By comparison of combined c-TACE + PEI group with the DEB-TACE group results in our study, there were better results in tumor response in the combined c-TACE + PEI group, but with no significant difference between the median value of AFP after treatment in both groups (P = 0.036).

The results of our study were consistent with those of Facciorusso *et al*. [17] in a meta-analysis that concluded a nonsuperiority of drug-eluting bead chemoembolization

Table 6 Complications of combined conventional transarterial chemoembolization + percutaneous ethanol injection versus drug-eluting bead-transarterial chemoembolization

Complications	c-TACE + PEI (*n*=30) (*N* (%))	DEB-TACE (*n*=45) (*N* (%))	*P*
Minor complications			
Postablation syndrome	30 (100.0)	0 (0.0)	0.000*
Postembolization syndrome	12 (40.0)	24 (53.3)	0.258
Skin infection	3 (10.0)	0 (0.0)	0.118
Major complications			
Acute hepatic decompensation	3 (10.0)	5 (11.1)	0.879
Liver cell failure	5 (16.7)	3 (6.7)	0.321
Portal vein thrombosis	0 (0.0)	1 (2.2)	0.411
Hepatic encephalopathy	3 (10.0)	4 (8.9)	0.871

cTACE, conventional transarterial chemoembolization; DEB, drug-eluting bead; PEI, percutaneous ethanol injection.

with respect to conventional chemoembolization in HCC patients as regards safety and efficacy.

Post embolization syndrome (abdominal pain, nausea, vomiting, and fever) was more in the DEB-TACE group than in the combined c-TACE+PEI group, with no statistically significant difference, which may be because of the possibility of prolonged duration of action of the chemotherapeutic agent in the DEB-TACE group than in the combined c-TACE+PEI group, which is consistent with our study; postembolization syndrome was seen in all patients of DEB-TACE studies by Nawawi *et al*. [16] and Kalva *et al*. [18].

Major complications that occurred in our study in the form of acute hepatic decompensation (10.66%), liver cell failure (10.66%), portal vein thrombosis (1.33%), and hepatic encephalopathy (9.33%) showed no statistically significant difference in both groups and no reported deaths during the period of the study.

c-TACE+PEI are feasible and can be used effectively for unresectable large HCC. In our country, the cost of DEB-TACE session is three times that of c-TACE+PEI Therefore, cost-effectiveness analysis recommends that combined c-TACE+PEI (less cost) can substitute DEB-TACE (more cost) in the treatment of large HCC.

The limitations in our study are the short duration of follow-up and the limited number of patients enrolled. Despite these limitations, we believe that our study could contribute to the comprehensive evaluation of DEB-TACE versus combined c-TACE+PEI that might support clinical decision making.

Conclusion

(1) Management of HCC is best performed in a multidisciplinary setting
(2) Patients diagnosed at an early HCC stage are optimal candidates for resection, liver transplantation, or percutaneous ablation. TACE is recommended as first-line noncurative therapy for nonsurgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread according to BCLC classification
(3) By comparison of the combined c-TACE + PEI group with the DEB-TACE group, there was no significant difference in tumor response and significant difference between the median value of AFP after treatment in both groups ($P = 0.036$)
(4) With regard to major complications, there was no statistically significant difference between the two studied groups and no reported deaths during the period of the study
(5) There were no significant predictors for improving the response of the treatment in our study by using multivariate logistic regression analysis for all studied factors.

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Conflicts of interest
There are no conflicts of interest.

References

1 Globocan2012. Available at: *http://globocan.iarc.fr.* [Last accessed on 2016 Jan].
2 Anwar WA, Khaled HM, Amra HA, *et al.* Changing pattern of hepatocellular carcinoma (HCC) and its risk factors in Egypt: possibilitiesfor prevention. Mutat Res 2008; 659:176–184.
3 Brown DB, Gould JE, Gervais DA, *et al.* Society of Interventional Radiology Technology Assessment Committee, the International Working Group on Image-Guided Tumor Ablation Transcatheter therapy for hepatic malignancy: standardization of terminology and reporting criteria. J Vasc Interv Radiol 2009; 20:425–434.
4 Marelli L, Stiglianor R, Triantos C, *et al.* Treatment outcomes for hepatocellular carcinoma using chemoembolisation in combination with other therapies. Cancer Treat Rev 2006; 32:594–606.
5 Wang S, Zhuang L, Meng Z, et al. Hepatocellular carcinoma more than 3cm in diameter: a systematic review of transcatheter arterial chemoembolization plus percutaneous ethanol injection versus transcatheter arterial chemoembolization alone. ISRN Gastroenterol 2013; 2013:526024.
6 Liapi E, Geschwind JF. Transcatheter arterial chemoembolization for liver cancer: is it time to distinguish conventional from drug-eluting chemoembolization? Cardiovasc Intervent Radiol 2011; 34:37–49.
7 Kettenbach J, Stadler A, Katzler IV, et al. Drug-loaded microspheres for the treatment of liver cancer: review of current results. Cardiovasc Intervent Radiol 2008; 31:468–476.
8 Nicolini D, Baroni G, Candelari R, et al. Doxorubicin-eluting bead vs conventional transcatheter arterial chemoembolization for hepatocellular carcinoma before liver transplantation. World J Gastroenterol 2013; 19:5622–5632.
9 European Association for the Study of the Liver, European Organization for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012; 56:908–943.
10 Seldinger SI. Catheter replacement of the needle in percutaneous arteriography; a new technique. Acta Radiol 1953; 39:368–376.
11 Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J

Clin 2011; 61:69–90.

12 Goldman R, Ressom HW, Abdel-Hamid M, et al. Candidate markers for the detection of hepatocellular carcinoma in low-molecular weight fraction of serum. Carcinogenesis 2007; 28:2149–2153.

13 Bartolozzi C, Lencioni R, Caramella D, et al. Treatment of large hepatocellular carcinoma: transcatheter arterial chemoembolization combined with percutaneous ethanol injection versus repeated transcatheter arterial chemoembolizations. Radiology 1995; 197:812–818.

14 Grosso M, Vignali C, Quaretti P, et al. Transarterial chemoembolization for hepatocellular carcinoma with drug-eluting microspheres: preliminary results from an Italian multicenter study. Cardiovasc Intervent Radiol 2008; 31:1141–1149.

15 Reyes DK, Vossen JA, Kamel IR, et al. Single-center phase II trial of transarterial chemoembolization with drug-eluting beads for patients with unresectable hepatocellular carcinoma: initial experience in the United States. Cancer J 2009; 15:526–532.

16 Nawawi O, Hazman M, Abdullah B, et al. Transarterial embolization of hepatocellular carcinoma with doxorubicin-eluting beads: single centre early experience. Biomed Imaging Interv J 2010; 6:e7.

17 Facciorusso A, Di Maso M, Muscatiello N. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: A meta-analysis. Dig Liver Dis 2016; 48:571–577.

18 Kalva SP, Iqbal SI, Yeddula K, et al. Transarterial chemoembolization with doxorubicin-eluting microspheres for inoperable hepatocellular carcinoma. Gastrointest Cancer Res 2011; 4:2–8.