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Research Article

Drug Eluting Beads for Unresectable Hepatocellular Carcinoma: Does it Need Another Look? Egyptian Single Center Pilot Study

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Abstract

Background: Transarterial chemoembolization (TACE) is a commonly used primary treatment for unresectable hepatocellular carcinoma (HCC). Drug eluting beads is a system that potentially can improve TACE outcome.

Aims: This study was held to compare between conventional TACE (cTACE) and TACE using drug eluting beads (DEB) regarding safety, progression free survival and overall survival.

Methods: In this non-randomized pilot study fifty HCC proven patients were allocated to either conventional TACE group (n = 25) or using drug eluting beads group (n=25) during the period from April 2011 till October 2014. Patients were followed up for tumour progression and survival till October 2017. Repeated TACE sessions were performed individually on demand according to the allocated line of treatment.

Results: Fifty patients with HCC (5 BCLC A and 45 BCLC B) with mean age 56.78 ± 6.3 years were included. Both groups were matched regarding baseline characteristics, tumour burden, Child class and BCLC stage. TACE using DEB was associated with less hepatotoxicity. Median time to progression was four months in both groups' Patients who underwent TACE using drug eluting beads showed significant better o median survival time than those underwent cTACE (26 versus 18 months respectively with p value 0.014). Three years survival was 32% in conventional TACE and 44% in drug eluting beads. In conclusion TACE using DEB was associated with less hepatotoxicity. Patients received TACE using drug eluting beads showed significantly better median survival time.

Trial registration number: ClinicalTrials.gov (NCT03007225)

***Keywords**: Drug Eluting Beads; Egypt; HCC; Survival; TACE*

Introduction

Globally, hepatocellular carcinoma (HCC) is an aggressive tumor and although it is the sixth leading cause of cancer, it is the third leading cause of cancer-related death worldwide [1].

In Egypt, situation is more disastrous with national survey confirmed that HCC is the most common primary malignant tumor [2]. This is mainly due to high HCV burden in Egypt.

Transarterial chemoembolization (TACE) is considered the standard of care for treating intermediate-stage hepatocellular carcinoma (HCC). However, intermediate-stage HCC includes a heterogeneous population of patients with varying tumor burdens, liver function (Child-Pugh A or B) and disease etiology [3].

Chemoembolization achieves partial responses in 15 - 55% of patients, and significantly delays tumor progression and macrovascular invasion [4].

In 2002, two randomized controlled trials from Spain [4] and Hong Kong [5]. showed a survival benefit for TACE compared to the best conservative treatment.

Many post-embolization adverse events were reported such as acute liver failure, renal impairment, upper gastrointestinal bleeding and systemic toxicity of the chemotherapeutic agent if systemic leak occurred. All adverse events may be reversible or irreversible [6].

Therefore, there is a requirement for treatment regimens that improve response rates and survival, while reducing the risk of post-TACE complications.

Drug eluting beads (Biocompatibles. UK) is a drug embolization system for loading with doxorubicin in the treatment of malignant hypervascularized tumors [7]. It has been shown to be clinically effective in primary (HCC) and some metastatic liver cancers [8].

Drug eluting Beads provide a simple method of accurate loading of doxorubicin into embolization microspheres and therefore give the pharmacist and the interventional radiologist a device for a controlled and targeted intra-arterial delivery of the chemotherapeutic agent [9].

These beads prolong drug delivery time and decrease systemic toxicity**.** Accordingly, DEB treatment can potentially enhance the therapeutic efficacy of regional, liver-directed transcatheter chemoembolization for patients with unresectable HCC [9].

Although some early reports suggested better response results, others didn't find survival or response benefits in patients with HCC using DEB.

This study was held to compare between conventional TACE (cTACE) and drug eluting beads (DEB) regarding maneuver related adverse events, progression free survival and overall survival in Egyptian patients with HCC.

Patients and Methods

This prospective controlled pilot study was conducted at the Department of Tropical Medicine and HCC Clinic, Ain Shams University Hospitals (Cairo, Egypt), after obtaining the approval of the Research and Ethics Committee of Ain Shams University, in accordance with local research governance requirements. The study was performed in accordance with the 1964 Declaration of Helsinki and all subsequent revisions. The trial was registered with the federal clearing house for randomized trials: ClinicalTrials.gov (NCT03007225).

Assuming the six months disease control outcome in BCLC stage B is about 75% in DEB-TACE compared to nearly 30% in cTACE [10] giving a sample size 23 in each group. Assuming 6 months survival in BCLC stage B is about 85% in DEB-TACE compared to nearly 45% in cTACE [11] a sample of 23 in each group is enough to detect such difference at 0.05 alpha error and 0.8 power of test. Sample size has been calculated using tenth version of STATA program.

Out of 62 patients fulfilling inclusion criteria during the period from April 2011 till October 2014 and after exclusion of 12 patients (7 due to unmeasurable disease and 5 refused to participate) Fifty HCC proven patients, based on AASLD practice guidelines [12] were enrolled in this study after signing a comprehensive informed consent. Patients were then followed for tumour response and survival till October 2017.

No randomization has been performed due to economic reasons; however, strict eligibility criteria have been set to be applied to both the conventional and beads groups Eligibility criteria were: Confirmed diagnosis of HCC according to AASLD practice guidelines [10]. intermediate stage HCC using the Barcelona Clinic Liver Cancer (BCLC) staging system (Stage B), and early stage HCC (BCLC stage A) whenever curative measures were contraindicated and finally patients with patent portal vein and its main branches.

On the other hand, Patients with Child class C according to Child Pugh classification (BCLC D), patients with diffuse HCC (non-measurable lesion), patients with thrombosis of main portal vein or one of its main branches (BCLC C), patients with extra hepatic spread, performance status more than one were excluded from the study.

Patients were then allocated (one to one ratio) to either group I (who underwent Chemoembolization with Drug eluting beads, n = 25) and group II (who underwent conventional Chemoembolization (cTACE) n = 25). was signed by All included patients were subjected to Full history taking and thorough clinical examination, laboratory investigations including Complete blood picture (CBC), serum creatinine, AST (aspartate aminotransferase), ALT (alanine aminotransferase), serum bilirubin (total and conjugated), serum albumin and prothrombin time. Viral markers including HBsAg, HCV antibodies by enzyme linked immunosorbent assay (ELISA) and HCV RNA by Real-Time PCR. Serum Alpha-fetoprotein (AFP) by electro-chemiluminescence.

Radiological investigations including abdominal ultrasound to detect patients with hepatic focal lesions as part of standard of care for cirrhotic patients and triphasic spiral abdominal CT to confirm the diagnosis and staging. All CT scan studies were performed with a 16-slice multidetector CT (Light speed, General Electric Medical Munich, Germany). CT examination was performed using a 4-phase protocol including a non-enhanced acquisition. Arterial phase (delay 20 - 30s), portal venous phase (delay 60s) and delayed venous phase (delay 80s) were obtained using 120 mL of contrast (Iopromide 300 mg I/L, Schering, Germany) at a rate of 4 mL/s. The images were acquired with slice thickness 1.25 mm, collimation 2.5 mm and table speed 7.5 mm per gantry rotation.

Procedure

Conventional TACE (cTACE) procedure

TACE procedures were performed by fluoroscopy (Toshiba INFINIX-8000V). The procedure was performed after advising the patient to have an overnight fast. The femoral artery was catheterized under local anesthesia, with a 4F catheter with Copra head configuration. Conventional angiography of the Coeliac and Hepatic arteries was done to delineate the feeding arteries of the tumors and to exclude portal venous shunting. Then vascular catheter was inserted super-selectively into the branch of the hepatic artery that was believed to be the main feeder of the tumor. Chemoembolization was then performed using ten milliliters of Lipiodol was mixed with 100 mg of Doxorubicin hydrochloride and 5 ml of Urografin emulsified to create a milky solution.

TACE with Drug Eluting Beads procedure:

The same procedure as cTACE was followed till the super selective catheterization of the feeding artery.

Loading of the beads with Doxorubicin hydrochloride (100 - 150 mg) was done *in vitro* an hour before the beginning of catheterization. The loaded beads were then aspirated from the vial into a syringe filled with nonionic contrast medium. Once the feeding artery was identified and catheter was in placement, the loaded beads were infused slowly under fluoroscopic guidance. Two different sizes of DC beads were used, 100 - 300 and 300 - 500 μm. Starting with the smaller sized beads to occlude the tumoral bed followed by the larger sized one to embolize the proximal vessels.

Post-procedure follows up

All included patients were assessed clinically one week after the procedure to detect early post chemoembolization complications and adverse events were recorded and graded according to CTCAE version 3.

Initial assessment of tumor response was done one month after the procedure date then every 3 months till progression. In each visit patients were subjected to laboratory investigations including: liver function tests, kidney function tests, CBC, serum alpha-fetoprotein and triphasic pelvi-abdominal CT with contrast.

Patients who had tumor progression were then followed for overall survival. Repeated embolization using the same method was scheduled "on demand" basis, if there was residual viable tumor.

The overall response was assessed according to combined assessment of the target lesions, non-target lesions and new lesion either intrahepatic or extrahepatic according to modified radiological criteria [13].

Statistical Analysis

IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. The quantitative variables are summarized as mean and standard deviation, while categorical variables are presented in the form of frequency and percentages. Values of skewed parameters are expressed as median and interquartile range (25^{th} and 75^{th} IQR (–). Unpaired *t* test (*t* value) was used to compare a quantitative variable between the two study groups in parametric data. Mann Whitney test (*Z* value) was used when data is nonparametric (showing skewed distribution and SD > 25% of mean). Chi square (X^2 value) was used to to test association between 2 categorical variables. Spearman correlation test (rho value) was used to identify correlation between different nonparametric variables against each other. P value < 0.05 was considered statistically significant. Kaplan Meier analysis was used to examine the distribution of time to event variables and Log rank test was used to compare time to event variables by levels of a factor variable.

Results

Group I for patients who underwent TACE using drug eluting beads (group I) and group II for those who underwent conventional TACE.

The overall mean age of both groups was (56.78 ± 6.3). Both groups were matched regarding baseline demographic data, baseline liver profile, kidney function tests, Alpha-fetoprotein, complete blood picture, tumour burden, Child class and BCLC stage (Tables 1 and 2).

N %		DEB TACE group (n = 25)		cTACE group (n = 25)		p-value*	Sig
		N	%				
Gender	Male	22	88.0	21	84.0	1	NS
	Female	3	12.0	4	16.0		
Smoking		12	48.0	11	44.0	0.78	NS
Alcohol		1	4.0	0	0.0	1	NS
Diabetes Mellitus		12	48.0	8	32.0	0.25	NS
Hypertension		8	32.0	8	32.0	1	NS
Number of HFLs One Two More than Two		16	64	11	44	0.3	NS
		6	24	9	36		
		3	12	5	20		
Child class A B		19	76	21	84	0.48	NS
		6	24	4	16		
BCLC stage A B		3	12	2	8	1	NS
		22	88	23	92		
		Mean	SD	Mean	SD	P value**	
Diameter of largest lesion		6.7cm	±2.2	5.8cm	±1.6	0.11	NS

Table 1: *Baseline patient characteristics.*

*DEB: Drug Eluting Beads; TACE: Trans Arterial Chemoembolization; cTACE: Conventional Trans Arterial Chemoembolization; HFL: Hepatic Focal Lesion; BCLC: Barcelona Clinic for Liver Cancer. *: Chi Square Test, **: Unpaired t Test.*

	Normal values	DEB TACE group (n = 25)		cTACE group (n = 25)		p - value*	Sig
		Mean	SD	Mean	SD		
SGPT	7 - 31 IU/L	44.68	31.59	55.64	36.61	0.263	NS
SGOT	7 - 31 IU/L	62.44	29.30	61.68	25.85	0.923	NS
T. Bilirubin	(0.3 - 1.2 mg/dl)	1.23	0.66	1.01	0.53	0.204	NS
Albumin	(3.5 - 5.1 g/dl)	3.70	0.45	3.40	0.45	0.123	NS
INR		1.20	0.17	1.25	0.19	0.307	NS
Hemoglobin	12 - 15 g/dl	12.78	2.00	12.55	1.45	0.46	NS
Leucocytic count	4000 - 11,000/uL	4.99	2.38	4.92	1.92	0.913	NS
Platelets	140,000 - 400,000/uL	149.76	70.02	141.72	78.67	0.704	NS
Serum creatinine	0.4 - 1.1 mg/dl	0.92	0.21	0.81	0.18	0.055	NS
Sodium	136 - 145 mmol/L	136.20	6.44	138.96	3.59	0.069	NS
Potassium	3.5 - 5.1 mmol/L	4.20	0.61	4.07	0.56	0.428	NS
		Median	IQR	Median	IQR	Z value **	Sig
Alkaline phosphatase	64 - 306 U/L	116.00	95 - 126	118.00	91 - 214	0.356	NS
Alpha foeto protein	0 - 10 ng/ml	40.00	20 - 470	31.80	8.2 - 509	0.669	NS

***Table 2**: Baseline laboratory results.*
*DEB: Drug Eluting Beads; TACE: Trans Arterial Chemoembolization; cTACE: Conventional Trans Arterial Chemoembolization; *: Unpaired t test; **: Mann Whitney test.*

Regarding the aetiology of the liver disease in the current study, both groups were matched. 82% of included patients had HCV related cirrhosis, 4% had HBV and 8% had combined HCV and HBV infection. Six percent (3 patients) had negative viral markers, one of them had alcoholic cirrhosis and the other two turned out to have cryptogenic cirrhosis.

Mean number of sessions was 1.48 in DEB TACE group, while it was 1.6 sessions in cTACE group. We assessed and graded adverse events after every session.

No procedure related mortality noticed in our study. There was no statistically significant difference between the studied groups regarding occurrence of constitutional and GIT adverse events except for nausea which occurred more after sessions of conventional TACE.

Hepatotoxicity in the form of elevation in SGPT and SGOT was noticed less frequently in patients underwent TACE using DEB in significant statistical manner. Also, the drop-in serum albumin level showed statistically significant difference between both groups.

Post procedure thrombocytopenia occurred more common in patients who underwent conventional TACE. All recorded adverse events (after each session) and their grades are shown in table 3.

N		DEB TACE group (n = 37)		cTACE group (n = 40)		P- value	Sig
		%	N	%			
Fever	No Grade 1 Grade 2 Grade 3	11 7 15 4	29.7 18.9 40.5 10.8	10 16 13 1	25.0 40.0 32.5 2.5	0.16	NS
Fatigue syndrome	No Grade 1 Grade 2 Grade 3	4 13 19 1	10.8 35.1 51.4 2.7	3 17 20 0	7.5 42.5 50.0 0.0	0.79	NS
Weight loss	No Grade 1 Grade 2	25 11 1	67.6 29.7 2.7	32 7 1	80.0 17.5 2.5	0.53	NS
Abdominal pain	No Grade 1 Grade 2 Grade 3	6 10 20 1	16.2 27.0 54.1 2.7	7 11 22 0	17.5 27.5 55.0 0.0	0.98	NS
Anorexia	No Grade 1 Grade 2 Grade 3	5 17 13 2	13.5 45.9 35.1 5.4	5 21 14 0	12.5 52.5 35.0 0.0	0.65	NS
Nausea	No Grade 1 Grade 2	17 13 7	45.9 35.1 18.9	7 23 10	17.5 57.5 25.0	0.03	S
Vomiting	No Grade 1 Grade 2	21 10 6	56.8 27.0 16.2	14 13 13	35.0 32.5 32.5	0.12	NS
Diarrhea	No Grade 1	36 1	97.3 2.7	37 3	92.5 7.5	0.62	NS
Hematemesis and /or Melena	No Grade 1	35 2	94.6 5.4	38 2	95.0 5.0	1	NS
Elevated bilirubin	No Grade I Grade II Grade III	32 4 0 1	86.5 10.8 0 2.7	28 5 7 0	70 12.5 17.5 0	0.06	NS
Elevated liver enzymes	No Grade I Grade II Grade III	33 4 0 0	89.2 10.8 0 0	14 20 4 2	35 50 10 5	< 0.001	S
Albumin decrease	No Grade I Grade II	13 13 11	35.1 35.1 29.7	4 13 23	10 32.5 57.5	0.01	S
Ascites	No Grade I Grade II	30 5 2	81.1 13.5 5.4	26 10 4	65 25 10	0.29	NS
Anemia	No Grade I Grade II Grade III	30 4 2 1	81.1 10.8 5.4 2.7	33 6 1 0	82.5 15 2.5 0	0.67	NS
Leucopenia	No Grade I	37 0	100 0	35 5	87.5 12.5	0.55	NS
Thrombocytopenia	No Grade I Grade II	37 0 0	100 0 0	32 5 3	80 12.5 7.5	0.01	S

Table 3: *Recorded grades (according to CTCAE version 3) of adverse events per session (37 sessions of TACE using drug eluting beads in 25 patients and 40 sessions of conventional TACE in 25 patients).*
DEB: Drug Eluting Beads; TACE: Trans Arterial Chemoembolization; cTACE: Conventional Trans Arterial Chemoembolization. Chi square test.

Regarding long term changes in the child classification, progressive deterioration in Child classification after 6 months of first maneuver was significantly more common in group II (P < 0.001) (Table 4).

	Baseline N (%)	1st M N (%)	3rd M N (%)	6th M N (%)	P value♦
Child Class					
DEB TACE group (n = 25)	N = 25	N = 25	N = 23	N = 19	
A B C	19 (76) 6 (24) -	14 (56) 10 (40) 1 (4)	15 (65.2) 7 (30.4) 1 (4.3)	11 (57.9) 8 (42.1) -	0.054 NS
cTACE group (n = 25)	N = 25	N = 25	N = 23	N = 16	
A B C	21 (84) 4 (16) -	17 (68) 5 (20) 3 (12)	11 (45.8) 11 (45.8) 2 (8.3)	8 (50) 7 (43.8) 1 (6.3)	0.008 S

Table 4: *Changes in Child stage during follow up visits. DEB: Drug Eluting Beads; TACE: Trans Arterial Chemoembolization; cTACE: Conventional Trans Arterial Chemoembolization. Friedman test.*

Median time to progression (TTP) was about four months in both groups (Figure 1). In the current study, the overall median survival time in group I was about 26 months while it was 18 months in group II (P = 0.014) (Figure 2).

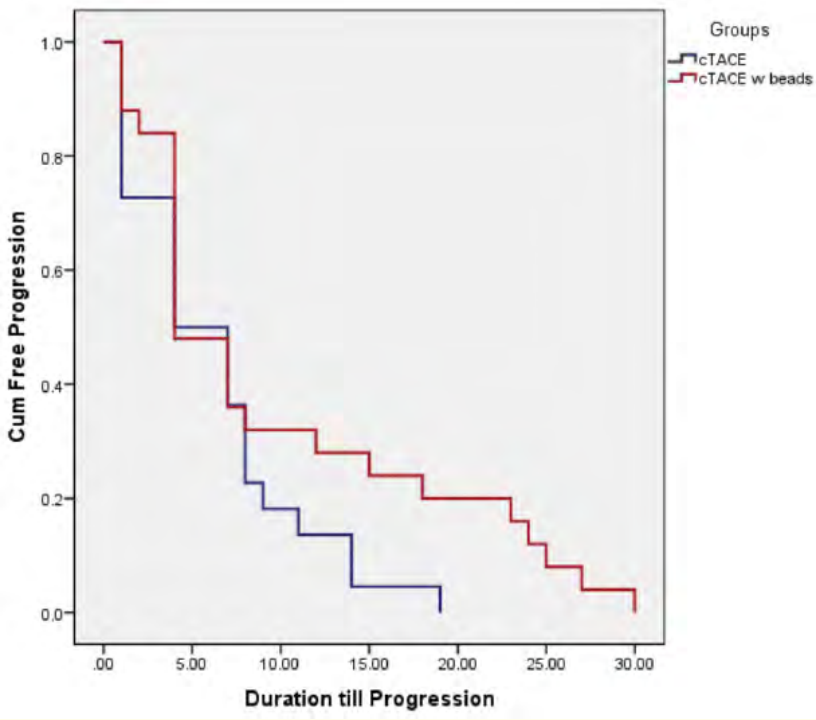

Figure 1: *Median time to Progression in both groups. Time to progression in both groups. cTACE: Conventional Transarterial Chemoembolization; TACE with DEB: Transarterial Chemoembolization with Drug Eluting Beads. Kaplan Meier analysis.*

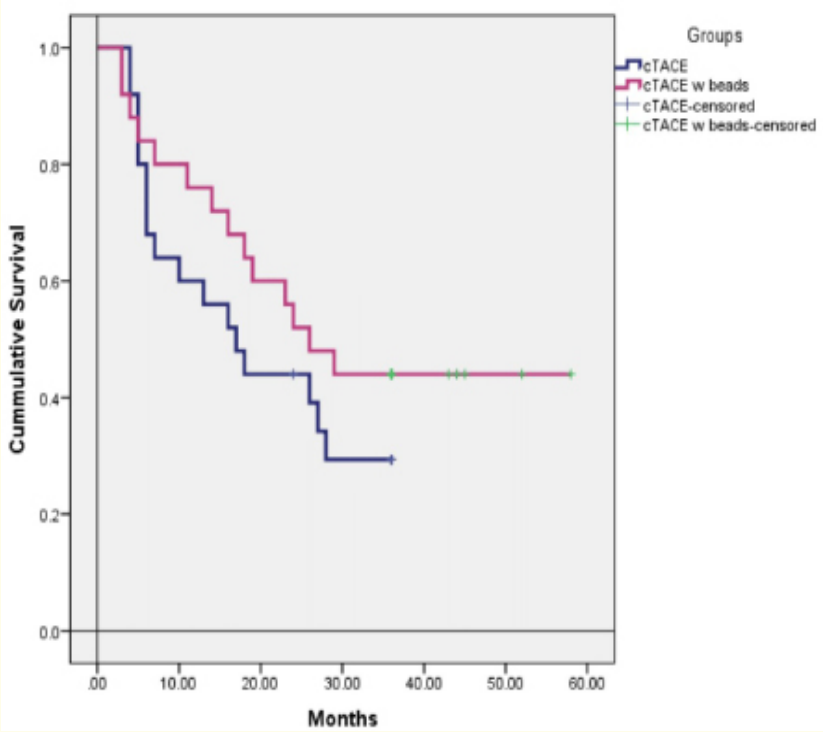

Figure 2: *Overall median survival in both groups. Overall survival in both groups. cTACE: Conventional Transarterial Chemoembolization; TACE with DEB: Transarterial Chemoembolization with Drug Eluting Beads. Kaplan Meier analysis.*

Discussion

The mean age of the studied patients was 56.78 ± 6.3 years. Relatively younger age in the Egyptian patients in comparison to European and American studies can be explained by the high prevalence of HCV among Egyptians and the occurrence of the infection in a young age.

This is consistent with another Egyptian study that was held in our center on 1313 Egyptian patients with HCC and showed that the most frequent age category affected by HCC was between 51 and 60 years [14]. Also, El-Zayadi., *et al.* (2005) reported that there was a slight shift in age distribution among Egyptian patients with HCC from more than 60 years to age group between 40 and 60 [15].

HCV was the main leading cause of liver disease in included patients. These results agree with the study held by Shaker., *et al.* (2013) where 91.32% and 2.5% of the Egyptian HCC cases had HCVAb and HBsAg respectively.

Both groups were matched regarding baseline tumor burden (number of nodules, total tumor size and unilobar or bilobar), Child class and BCLC stage and this was an important point during evaluation of survival and tumor progression and to overcome that no randomization was performed in this study.

Although 5 patients were classified as BCLC stage A, liver transplantation was not done due to either financial issues or non-availability of suitable donor. All these patients had HVPG more than 10 and local ablative therapy was not possible due to inaccessible or risky location.

Occurrence of nausea was statistically higher in patients who were treated by cTACE. Also vomiting was more commonly noticed after cTACE but the difference was not statistically significant. As both groups in the current study were matched regarding the baseline tumor size, and as there was no angiography evidence of regurgitation of the embolic agents into the gastric arteries, so the suggested explanation of the lower rates of nausea and vomiting in DEB TACE is the decreased systemic toxicity by the chemotherapeutic agents.

One of the important observations in our work was that TACE using drug eluting beads was associated with less hepatotoxic effect manifested by elevation of liver enzymes and decrease in serum albumin level. Many other investigators documented same finding [16-18]. As TACE is palliative management and as most of patients need multiple sessions, better safety profile is an important factor that may affect tolerability and survival.

Regarding the occurrence of liver dysfunction or failure as an early complication in the current study (deterioration in the child classification to Child C), it was reported in one patient in group I (it was irreversible) and 5 patients in group II (only one of them was irreversible). Marelli., *et al.* (2007) stated that the deterioration of liver function recovered to the pretreatment level before the next session of cTACE in most of the patients and only 3% of the studied patients had irreversible hepatic decompensation. Also, Malagari., *et al.* (2011) reported DEBTACE related liver failure in 1.68% of their studied patients. On the other hand, long term deterioration in Child classification (assessed after 6 months of first maneuver) was significantly more common in group II ($P < 0.001$).

Median time to progression was 4 months in both groups and as needed retreatment performed according to line of treatment patient allocated to.

Goleferi., *et al.* 2014 also found that there is no difference between studied groups regarding progression free survival, however time to progression in their study was about 9 months in both groups. Better time to progression in their study may be attributed to smaller lesion diameters at baseline [19].

The smaller baseline tumor burden may be also the explanation for the better time to progression observed by Song and colleagues in 2012.

Despite similar median time to progression in both groups, patients who underwent DEB TACE had significant better median survival time. Better survival results despite nearly same time to progression may be a reflection of better safety profile and less hepatoxicity achieved by DEB TACE as evidenced by long term changes in Child classification.

Median survival time in patients who underwent TACE using DEB was 26 months while it was 18 months in those underwent conventional TACE.

The survival results in the current study was agreeable with that of Wiggermann., *et al.* (2011) who found that the median survival in DEB TACE group was 22 months (95% CI; 16.7 - 26.6) and in cTACE was 14 months (95%CI; 10.9 - 16.6). The corresponding one-year survival probability was 70% in DEB TACE and 55% in cTACE [20].

Song., *et al.* (2012) evaluated the mean survival time in DEBTACE and cTACE groups and found that it was 32.2 ± 1.9 and 24.7 ± 1.7 months respectively. Better results than ours can be attributed to smaller baseline tumor size.

Ferrer Puchol*, et al.* (2011) found that there was no significant difference in the median survival time in DEBTACE patients (22.4 months) and cTACE (23.6 months) [21].

One, two and three years survival were achieved in 77%, 60% and 44% in drug eluting beads group and in 60%, 42% and 32% of patients who underwent TACE using conventional TACE.

On the contrary, one and two-year survival was both higher in Golfieri., *et al.* (2014) than in those in the current study. One-year survival in DEB TACE and cTACE was 86.2% and 56% respectively while, two-year survival was 83.5% and 55.4% in DEB TACE and cTACE respectively.

Also, in Song., *et al.* (2012) the cumulative survival rates at 6, 12 and 18 months were 93%, 88% and 88% in DEB TACE group, while rates were 80%, 67% and 61% in cTACE group and this was statistically significant difference (P = 0.005).

The main differences between the last 2 studies and our study are that they studied patients with less tumor burden and hence more favorable prognosis.

Song., *et al.* (2012) started with slightly smaller tumor sizes (mean tumor size was 4.6 ± 3 cm). Also, they used low dose of doxorubicin (50 mg) with planned multiple sessions. While Golfieri., *et al.* (2014) included patients with diameter of largest tumor 3.2 +/-1.8 cm (median 2.6 [0.9 - 10]).

Non-randomization is the main limitation in our pilot trial, however strict inclusion criteria were put in order to match both studied groups to overcome this important limitation.

Conflicts of Interest

The authors declare no conflicts of interest regarding this work.

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