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Single-center randomized trial comparing conventional chemoembolization versus doxorubicin-loaded polyethylene glycol microspheres for early- and intermediate-stage hepatocellular carcinoma

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According to Barcelona Clinic Liver Cancer classification (BCLC), transarterial chemoembolization (TACE) is preferred treatment for stage B and in certain cases for stage A hepatocellular carcinoma (HCC). Conventional TACE (c-TACE) and drug-eluting microspheres TACE (DEM-TACE) are available intraarterial therapies. Screening of patients with cirrhosis is of great importance for early detection of malignant liver nodules. Primary endpoint of this study was to compare DEM-TACE with c-TACE in terms of 12- and 24-month survival. Secondary endpoints were comparison of intensity and duration of the postembolization syndrome (PES) and severe adverse events. We randomized 60 patients with unresectable HCC one-to-one with c-TACE or DEM-TACE and followed them for at least 24 months or until death. TACE was repeated 'on-demand'. Of all, 28 were in the c-TACE and 32 in the DEM-TACE group. Most patients underwent two TACE sessions and the median hospital stay was 3 days for c-TACE and 2 days for DEM-TACE group. The overall 12- and 24-month survival rates were 89.8 and 70.7%, respectively, precisely 85.7 and 63.6% after c-TACE and 90.2 and 75.8% after DEM-TACE, without any significant difference (P=0.18). Median overall survival was 21.1 months. Significant difference in the overall 12- and 24-month survival was found in patients with Child-Pugh A compared to Child-Pugh B class (P=0.001). Postprocedural pain was similar in both arms. Febrility occurred markedly more after c-TACE (P=0.001). Child-Pugh class, AST levels and ascites independently predicted survival (P=0.003). Both, DEM-TACE and c-TACE showed excellent 12- and 24-month survival rates. No significant difference in terms of adverse events was found. PES was slightly more severe after c-TACE, because of elevated temperature. DEM-TACE requires shorter in-hospital stay. *European Journal of Cancer Prevention* XXX: 000–000

European Journal of Cancer Prevention 2020, **XXX**:000–000

Keywords: adverse events, chemoembolization, doxorubicin, hepatocellular carcinoma, interventional radiology, liver, microspheres, prevention, survival

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Received 7 May 2020 **Accepted** 4 August 2020

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common type of cancer, currently representing the second leading cause of tumor-related death worldwide. It accounts for 90% of all primary liver malignancies with annual incidence of approximately 850 000 new cases (Takayasu *et al.*, 2006, 2012; El-Serag, 2012; Gao *et al.*, 2013; Hui *et al.*, 2015; EASL Guidelines, 2018). Prevention of risk factors that lead to chronic liver disease is of crucial importance. Worldwide, more than 80% of HCCs are related to HBV or HCV infection, leaving approximately 15% associated with other causes such as alcohol abuse, nonalcoholic steatohepatitis and aflatoxin exposure. Primary prevention of cirrhosis and HCC can be achieved with HBV vaccination, alcohol abuse programs, avoidance of toxic materials and so on. Successful antiviral therapy reduces but does not eliminate the risk of HCC development. Screening and regular follow-up of patients with chronic liver disease are essential, and can be helpful in early detection of malignant liver nodules. Median survival in early-stage HCC reaches up to 50–70% at 5 years after resection, transplantation or loco-regional treatment in selected candidates. Transarterial chemoembolization (TACE) is also used in patients with early-stage HCC when curative treatments are not possible or as a bridge to liver transplantation. This is why early diagnosis of HCC is the key to greater treatment success and better survival rates. Although TACE is the

DOI: 10.1097/CEJ.0000000000000623

<zdoi;10.1097/CEJ.0000000000000623>

first-line treatment option for intermediate-stage HCC according to Barcelona Clinic Liver Cancer classification (BCLC), in real life approximately 30% of chemoembolizations are performed in early stages. Two surveys have shown that TACE is widely used outside intermediate HCCs (Bargellini *et al.*, 2014; Park *et al.*, 2015; EASL Guidelines, 2018). Definitive agreement regarding the best TACE technique has not yet been reached, and various options concerning patient selection, delivery systems, selectivity of treatment, drugs and embolic agents, as well as repetition schedules for TACE are still in use.

Despite the development of different types of drug-eluting microspheres (DEM), conventional TACE (c-TACE) is still considered as the 'gold standard' method worldwide, as it has been historically the first chemoembolization technique. On the other hand, DEM-TACE is becoming treatment of choice in many centers including ours, mainly due to the possibility for easier technique standardization. Despite ~~the seappealing premise~~, the superiority of DEM-TACE over c-TACE in terms of survival still needs to be demonstrated. Two retrospective studies from Dhanasekaran *et al.* (2010) and Song *et al.* (2012), affected by several biases, have suggested the superiority of DEM-TACE whereas other two randomized controlled trials performed by Sacco *et al.* (2011) and Golfieri *et al.* (2014) have not confirmed this. To elucidate this key point, we conducted a prospective, single-center randomized controlled trial involving a relatively small cohort of mainly cirrhotic patients with HCC not amenable to curative therapies.

Materials and methods

The present study is a prospective, single-center, randomized trial conducted from November 2015 to November 2018. A total of 60 patients with unresectable HCC were included and randomized one-to-one to undergo c-TACE or DEM-TACE. Institutional review board approval was waived by the ethics committee of the Medical Faculty in Skopje and local ethics committee at City General Hospital '8th September'.

All patients provided written informed consent before enrolment. The decision for TACE treatment was made on a multidisciplinary tumor board meeting. Preprocedural examinations included abdominal ultrasound, contrast-enhanced multiphasic multidetector computed tomography (MDCT) or MRI, laboratory tests (liver enzymes, bilirubin level, coagulation parameters and protein status), as well as alfa fetoprotein (AFP) serum levels.

The inclusion criteria were: patients >18 years of age diagnosed with HCC according to the EASL criteria, liver function Child-Pugh class A or B7-9, with an ECOG 0–1, no more than six tumors in both liver lobes, ALP < 300 U/L, AST < 50 U/L, ALT < 42 U/L, LDH < 430 U/L, GGT < 64 U/L and total bilirubin < 50 µmol/L.

The exclusion criteria were as follows: extrahepatic metastasis, contrast agent intolerance, portal vein thrombosis, previous systemic chemotherapy (sorafenib and cisplatin), pregnancy, INR > 2.0, concomitant malignant disease and advanced liver disease with total bilirubin >50 mmol/L. Previous treatment with surgery or ablation were not contraindications for enrolment.

Study design

This study represents a prospective, single-center, randomized trial in which patients were stratified one-to-one to undergo c-TACE or DEM-TACE. Our protocol required follow-up of at least 24 months after the treatment or until their death.

Patients underwent transarterial chemoembolization as follows

Patients in the c-TACE group received a mixture of 50–100 mg of doxorubicin emulsified with 10–15 mL lipiodol (Ultrafluid, Guerbet, France) in a ratio 1:2.5, followed by administration of polyvinyl alcohol or polyethylene glycol microspheres (Contour 45–355 µm in diameter, Boston Scientific, USA or HydroPearl 75–400 µm, Terumo, Japan); patients in the DEM-TACE group received polyethylene glycol drug-eluting microspheres (LifePearl, Terumo, Japan), 100–400 µm, volume of 2–4 mL preloaded with 50–100 mg of liquid doxorubicin. When needed, additional embolic agents for bland embolization were used, mostly polyethylene glycol particles, 75–200 µm, (HydroPearl) at the discretion of the operator. Chemoembolization was terminated when a dose of 100 mg of doxorubicin per session was administered or until full saturation of the tumor feeding arteries was achieved. In all cases, TACE was performed in a selective or superselective manner using 2.4–2.8°F microcatheters (Progreat, Terumo).

Chemoembolization sessions were repeated 'on demand', every 3–6 weeks until complete response based on imaging criteria was achieved. The response to treatment was evaluated by MDCT or MRI, and reported according to the modified RECIST criteria (mRECIST) as (1) complete response, (2) partial response, (3) stable disease and (4) progressive disease.

Aims of the study

The primary aim of this study was to compare the 12- and 24-month survival rates between the two arms. Secondary endpoints were comparison of intensity and duration of postembolization syndrome (PES) after c-TACE and DEM-TACE and reporting of any serious adverse events after both methods, then impact of liver function, number of treatments and duration of hospital admission.

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Statistical analysis

The statistical analysis was performed by an external statistician using SPSS for Windows 23.0.

The variable distribution was checked with the Kolmogorov–Smirnov test, the values with symmetrical distribution are reported as mean ± SD, and the values with asymmetrical distribution as median and range.

Bivariate analysis was obtained for comparison between c-TACE and DEM-TACE groups, where on Chi-square and Fisher's exact tests were carried out for qualitative values, or Mann–Whitney and Student's *t*-test for quantitative values.

The Kaplan–Meier method was used to calculate the 12- and 24-month survival rates and the log Rank (Mantel-Cox) test for treatment comparisons.

Univariate and multivariate Cox regression analysis with calculation of Hazard ratios were used to determine the lethality prognostic factors.

Results

A total number of 60 patients were enrolled in this study. Patient demographics and tumor characteristics are reported in Tables 1 and 2. No significant differences were observed in clinical and tumor characteristics among the two arms. T1 T2

Study population

Table 1 shows the characteristics of the patients who were enroled in the study. Among all, 28 (46.7%) were treated with c-TACE, and 32 (53.3%) were treated with DEM-TACE. Most of the patients underwent two sessions of TACE 28 (46.7%), in the c-TACE group 13 (46.4%) and 15 (46.9%) in the DEM-TACE group. More than two sessions were performed in 13 (46.4%) patients in c-TACE group and in 12 (37.5%) patients in DEM-TACE group without any statistical significance concerning the number of sessions between the two arms ($P = 0.46$), see Table 3. AQ13 T3

Survival

Of all 60 patients, 17 (28.3%) died during the follow-up period of 2 years.

Divided by groups, 10 (35.7%) were from the c-TACE and 7 (21.9%) from the DEM-TACE group.

In the entire population, the 12- and 24-month survival rates were 89.8 and 70.7%, respectively. Based on the type

Table 1 Baseline characteristics of the patients

Variable	Total (*n*=60)	c-TACE (*n*=28)	DEM-TACE (*n*=32)
Clinical characteristics			
Age (mean ± SD)	68.40 ± 7.2	67.93 ± 7.4	68.81 ± 7.0
Age groups *n* (%)			
53–60	11 (18.33)	6 (21.43)	5 (15.63)
61–70	24 (40)	11 (39.29)	13 (40.63)
>71	25 (41.67)	11 (39.29)	14 (43.75)
Gender *n* (%)			
Male	41 (68.33)	20 (71.43)	21 (65.63)
Female	19 (31.67)	8 (28.57)	11 (34.38)
Child-Pugh score *n* (%)			
A	24 (40)	15 (55.56)	9 (30)
B	33 (55)	12 (44.44)	21 (70)
Hepatitis B/C cirrhosis *n* (%)	33 (55)	18 (66.67)	15 (50)
AFP (ng/mL) (mean ± SD)	94.11 ± 138.8	64.93 ± 70.9	119.65 ± 175.6
AFP *n* (%)			
≤150	50 (83.33)	25 (89.29)	25 (78.12)
>151	10 (16.67)	3 (10.71)	7 (21.88)
Ascites (%)	15 (25)	9 (32.14)	6 (18.75)
AST (U/L) (mean ± SD)	53.92 ± 36.4	52.25 ± 27.6	55.37 ± 42.9
AST *n* (%)			
5–37	24 (40)	10 (35.71)	14 (43.75)
>37	36 (60)	18 (64.29)	18 (56.25)
ALT (U/L) (mean ± SD)	66.33 ± 40.6	66.78 ± 32.9	65.94 ± 46.8
ALT *n* (%)			
10–63	36 (60)	16 (57.14)	20 (62.5)
>63	24 (40)	12 (42.86)	12 (37.5)
LDH (U/L) (mean ± SD)	197.65 ± 103.4	204.18 ± 80.8	191.94 ± 120.8
LDH (U/L) *n* (%)			
81–234	38 (63.33)	17 (60.71)	21 (65.63)
>235	22 (36.67)	11 (39.29)	11 (34.38)
Bilirubin (mean ± SD)	18.03 ± 12.0	18.43 ± 12.4	17.69 ± 11.9
Bilirubin *n* (%)			
5–12	30 (50)	14 (50)	16 (50)
>12	30 (50)	14 (50)	16 (50)
ECOG PS *n* (%)			
0	39 (65)	18 (64.29)	21 (65.63)
1	21(35)	10 (35.71)	11 (34.38)

DEM-TACE, drug-eluting microspheres transarterial chemoembolization; ~~TACE~~, transarterial chemoembolization.

of TACE performed, corresponding figures were 85.7 and 63.6%, respectively after c-TACE, and 90.2 and 76.8% after DEM-TACE ($P=0.18$) (Table 4). No statistically significant difference in terms of 12- and 24-month survival rates were found between the two groups ($P=0.018$).

The median survival rate was similar in both arms, around 22 months for all patients (Table 5, Fig. 1).

The univariate Cox regression analysis did not confirm the type of intervention as a significant prognostic factor influencing survival in patients with unresectable HCC ($P=0.195$). Namely, patients in the c-TACE group had approximately 1.7 times more chances of dying than those treated with DEM-TACE, without statistical significance [hazard ratio = 1.898, 95% confidence interval (CI), 0.721–4.999].

In the period of 24 months follow-up after TACE, only one patient with Child-Pugh class A liver cirrhosis died from the primary malignancy, while 14 (42.4%) with Child-Pugh B. In the subanalysis that we performed it was found that 12- and 24-month survival rates were 95.8% in the Child-Pugh A, and 84.4 and 55.7%, respectively, in the Child-Pugh B group ($P=0.001$). This difference was statistically significant. The median survival rates were 23.5 months in Child-Pugh A, and 19.4 months in patients who had Child-Pugh B liver cirrhosis (Table 6, Fig. 2).

Table 7 demonstrates the clinical and tumor characteristics that underwent univariate regression analysis, where Child-Pugh score, AFP level, ascites, AST, LDH and serum bilirubin level were confirmed to influence survival. When these were included in the multivariate model, only the Child-Pugh score ($P=0.041$), the presence of ascites preprocedural ($P=0.03$) and elevated values of AST ($P=0.003$) remained as significant independent prognostic factors which directly influenced the survival.

According to this statistical model, patients with Child-Pugh class B, had three-fold greater risk of dying, compared to those who presented with Child-Pugh class A cirrhosis initially (hazard ratio = 3.232%, CI, 2.911–7.425); when ascites was present before TACE the mortality risk

Table 2 Tumor characteristics

Solitary (%)	37 (61.67)	18(64.29)	19 (59.38)
Multicentric (%)	23 (38.33)	10 (35.71)	13 (40.63)
Diameter of the ~~TU~~ (cm) (mean ± SD)	6.04 ± 2.5	5.82 ± 2.4	6.23 ± 2.6

Table 3 Number of interventions

	TACE			
Number of interventions	Total *n* (%)	c-TACE *n* (%)	DEM-TACE *n* (%)	*P* value
1	7 (11.67)	2 (7.14)	5 (15.63)	$Z=0.74$; $P=0.46$ ns
2	28 (46.67)	13 (46.43)	15 (46.88)	
3	18 (30)	10 (35.71)	8 (25)	
4	5 (8.33)	2 (7.14)	3 (9.38)	
5	2 (3.33)	1 (3.57)	1 (3.13)	

P (Mann–Whitney test).
c-TACE, conventional transarterial chemoembolization; DEM-TACE, drug-eluting microspheres transarterial chemoembolization; TACE, transarterial chemoembolization.

Table 4 Kaplan–Meier analysis for patient survival rate after c-transarterial chemoembolization and drug-eluting microspheres-transarterial chemoembolization

			Survival rate % (SE)	
Type of TACE	Total (*n*)	No. events *N* (%)	12-month	24-month
c-TACE	28	10 (35.7)	85.7 (0.066)	63.6 (0.92)
DEM-TACE	32	7 (21.9)	90.2 (0.04)	76.8 (0.077)

Log rank (Mantel-Cox) = 1.77; $P=0.18$ ns.
c-TACE, conventional transarterial chemoembolization; DEM-TACE, drug-eluting microspheres transarterial chemoembolization; TACE, transarterial chemoembolization.

Table 5 Kaplan–Meier analysis for average and median survival according to the type of transarterial chemoembolization

	Mean and medians for survival time				
				75.0% percentiles	
Variable	Mean	SE	95% CI	Estimate	SEr
c-TACE	20.02	1.059	17.942–22.092	15.0	1.794
DEM-TACE	22.09	0.703	20.716–23.473		

CI, confidence interval; c-TACE, conventional transarterial chemoembolization; DEM-TACE, drug-eluting microspheres transarterial chemoembolization. TACE, transarterial chemoembolization.

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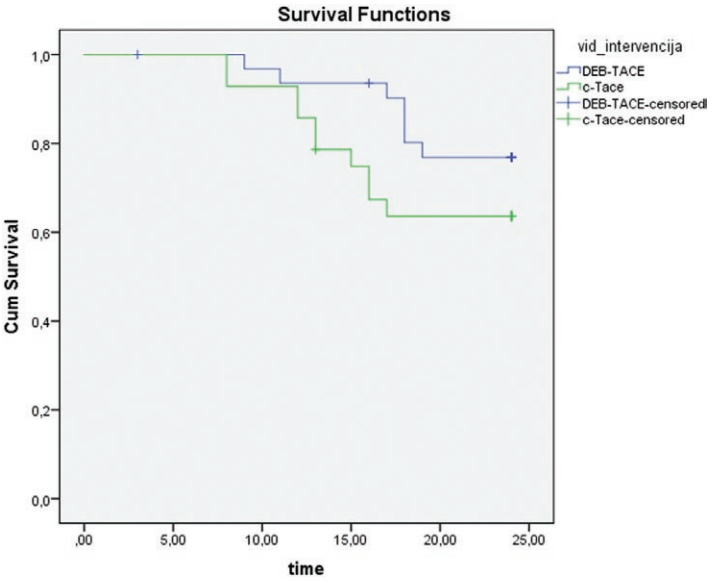
Fig. 1



AQ18 Survival curves in patients with intermediate-stage HCC according to the type of TACE. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

Table 6 Kaplan–Meier analysis for survival rates in accordance with the Child-Pugh score of cirrhosis

			Mean survival % (SE)	
Child-Pugh	Total (*n*)	No. deaths *n* (%)	12-month	24-month
A	24	1 (4.2)	95.8 (0.045)	95.8 (0.045)
B	33	14 (42.4)	84.4 (0.064)	55.7 (0.089)

Log Rank (Mantel-Cox)=10.2; *P*=0.001 sig.
SE, standard error.

was three times higher (hazard ratio = 3.241%, CI, 1.121–9.375) and raise of serum AST values of 1U/L increased the risk for 1.5% (hazard ratio = 1.015%, CI, 1.005–1.025).

Postembolization syndrome

T8 Symptoms of PES are reported in Table 8. No significant difference regarding postprocedural pain, nausea and vomiting was found.

The occurrence of elevated body temperature was almost two-fold more frequent in the c-TACE arm (82.1% against 40.6% in the DEM-TACE arm, $P = 0.001$). In most of the patients (94.4%), elevated temperature was registered up to 2 days postprocedure. Prolonged febrility had two patients only, one after c-TACE (13 days), and one after DEM-TACE (20 days).

The median in-hospital stay was 3 days for c-TACE patients, and 2 days for DEB-TACE (range 1–7days). Statistical analysis showed a significant difference in the in-hospital stay between the two groups ($P = 0.03$), concluding that patients needed longer hospitalization after
T9 c-TACE (Table 9).

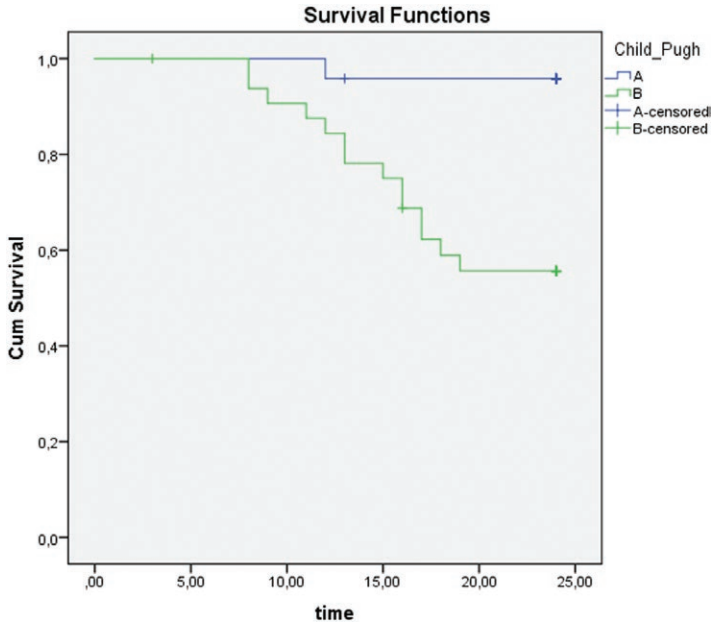
Discussion

TACE is the standard treatment for patients with HCC in intermediate stage (Ernst *et al.*, 1999; Bruix *et al.*, 2011; El-Serag, 2012; Hui *et al.*, 2015), but it can also be considered for early-stage patients excluded from curative treatments. Hence, primary prevention of risk factors for cirrhosis and early detection of HCC is of great importance, which leads to more available treatment options. In some studies like the ones from Varela *et al.* (2007) and Burrel *et al.* (2012), a notable proportion of HCCs are in early stage, and in our study, all patients are BCLC stage B at the most, including several in stage A. Similar to some more recent studies from Sacco *et al.* (2011) and Golfieri *et al.* (2014), our study represents direct comparison between the well-known c-TACE and DEM-TACE in terms of survival rate.

Survival

Regarding patient survival, previous researchers have demonstrated inconsistent and rather conflicting data. The single-center study from Sacco *et al.* (2011), which is very similar to ours regarding patient numbers and

Fig. 2



Survival curves in HCC patients according to the Child-Pugh liver function scores. HCC, hepatocellular carcinoma.

Table 7 Cox regression analysis of factors related to survival in intermediate hepatocellular carcinoma patients

	Univariate		Multivariate	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P* value
Type of TACE				
c-TACE vs. DEM-TACE	1.898 (0.721–4.999)	0.195		
Clinical characteristics				
Women vs. men	2.338 (0.901–6.064)	0.081		
Age	1.055 (0.980–1.135)	0.156		
Child-Pugh B vs. A	5.238 (1.171–13.435)	0.014	3.232 (2.911–7.425)	0.041
Virus-related cirrhosis vs. nonvirus cirrhosis	2.224 (0.708–6.987)	0.171		
AFP>151	4.383 (1.665–11.540)	0.003		
Ascites	4.133 (1.584–10.786)	0.004	3.241 (1.121–9.375)	0.03
AST	1.016 (1.008–1.024)	0.000	1.015 (1.005–1.025)	0.003
ALT	1.015 (1.006–1.025)	0.001		
LDH	1.005 (1.001–1.008)	0.008		
Bilirubin	1.05 (1.012–1.089)	0.01		
Tumor characteristics				
Multiple tumors vs. solitary tumors	1.576 (0.608–4.087)	0.35		
Largest diameter (cm)	1.022 (0.847–1.234)	0.818		

c-TACE, conventional transarterial chemoembolization; DEM-TACE, drug-eluting microspheres transarterial chemoembolization; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

characteristics, failed to demonstrate significant differences between both methods in terms of overall survival, time to tumor progression and tumor recurrence rate. Diversely, the superiority of DEM-TACE was suggested by two retrospective studies, one from Dhanasekaran *et al.* (2010), which has small and disparate groups enrolled in different periods and the other one from Song *et al.* (2012), which showed high survival rates of 88% after DEM-TACE at 18 months follow-up, and 61% after c-TACE.

On the contrary, a statistically significant better survival rate after c-TACE emerged from one retrospective study by Scartozzi *et al.* (2010).

The 12-and 24-month survival rates of 85.7 and 65.3% after c-TACE and 90.2 and 70.6% after DEM-TACE in our patient groups are slightly exceeding the values reported in many other, and are very close to those from Golfieri *et al.* (2014). Yet, the principal result of our study demonstrated that the type of TACE did not alter significantly the overall 12- and 24-month survival.

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Table 8 Postembolization syndrome related to transarterial chemoembolization procedure

	TACE			
	All *n* (%)	c-TACE *n* (%)	DEM-TACE *n* (%)	*P* value
Postprocedural pain				
Yes	28 (46.67)	16 (57.14)	12 (37.5)	χ^2=2.31; *P*=0.13 ns
No	32 (53.33)	12 (42.86)	20 (62.5)	
Grade 1	23 (82.14)	13 (81.25)	10 (83.33)	Fisher's exact *P*=1.0
Grade 2	5 (17.86))	3 (18.75)	2 (16.67)	
Nausea and vomiting				
Yes	39 (65)	19 (67.86)	20 (62.5)	χ^2=0.19; *P*=0.66 ns
No	21 (35)	9 (32.14)	12 (37.5)	
Elevated body temperature				
Yes	36 (60)	23 (82.14)	13 (40.63)	χ^2=10.7; *P*=0.001 sig
No	24 (40)	5 (17.86)	19 (59.38)	
Grade 1	34 (94.44)	22 (95.65)	12 (92.31)	χ^2=2.31; *P*=0.13 ns
Grade 2	2 (5.56)	1 (4.35)	1 (7.69)	

P (Chi-square test).
c-TACE, conventional transarterial chemoembolization; DEM-TACE, drug-eluting microspheres transarterial chemoembolization; TACE, transarterial chemoembolization.

Table 9 Duration of hospitalization after c-transarterial chemoembolization and drug-eluting microspheres-transarterial chemoembolization

	Days in hospital				
TACE	*n* (%)	Mean±SD	Min–max	Median (IQR)	*P* value
c-TACE	28 (46.67)	3.07±1.3	1–6	3 (2–4)	*Z*=2.2; *P*=0.03 sig
DEM-TACE	32 (53.33)	2.37±1.4	1–7	2 (1–3)	

P (Mann–Whitney test).
c-TACE, conventional transarterial chemoembolization; DEM-TACE, drug-eluting microspheres transarterial chemoembolization; IQR, interquartile range; TACE, transarterial chemoembolization.

We obtained quite high rates of 12- and 24-month survival after TACE, which might be due to several factors. First, we always tried to be as selective as possible using low-profile microcatheters which allowed us reaching maximal targeting of the lesion, thus avoiding dissemination of lipiodol or drug-loaded microspheres in healthy liver. Furthermore, appropriate patient selection is of high importance. In our study, 65% of patients in both arms were in good clinical condition with ECOG0.

Another key fact for such positive survival rates in both arms could be that no Child-Pugh C patients were enrolled. For instance, in other studies such as the one from Dhanasekaran *et al.* (2010), almost half of patients enrolled had Child-Pugh class B or C, and 1-year overall survival after DEM-TACE was 58% but decreased to 32% in Child-Pugh class C.

Our study confirmed the strong prognostic role of preserved liver function, considering that after 24-month follow-up period only one patient with Child-Pugh A cirrhosis died and other 14 (42.4%) with Child-Pugh B. The significance of the preserved extra-tumoral liver had already been observed in patients undergoing DEM-TACE with a 2-year survival rate of 88% in Child-Pugh class A and 75% in class B in the study from Malagari *et al.* (2012).

Postembolization syndrome

Most of the patients after TACE suffer from PES that mainly involves elevated body temperature, abdominal pain, nausea and vomiting. Just to be clear, we do not consider the PES as a complication, but rather as a normal reaction after TACE.

Unlike in the study from Golfieri *et al.* (2014), where postprocedural pain is doubly more frequent and severe in the c-TACE group than in DEM-TACE, our study showed insignificant difference in postprocedural pain between both groups.

Our trial reported higher prevalence of elevated body temperature in patients after c-TACE, 23 (82.1%), despite only 13 (40.6%) patients after DEM-TACE. In most of the cases (94%), febrility lasted at most 2 days, only two patients had prolonged elevated body temperature for more than 7 days.

Severe adverse events

Although severe adverse events (SAE) are relatively rare after TACE, some studies as the one from Lammer *et al.* (2010) reported high incidence of SAE, approximately in 20% of the patients with a greater proportion in the c-TACE group, which led to earlier termination of treatment in 13% of enrolled patients.

Higher percentage of SAE might be related to the treatment reiteration, where almost every patient in the trial (82%) was treated with the second session of TACE at a 2-month interval regardless of the response to previous TACE. Another reason could be the high doxorubicin doses injected (around 150 mL) per session.

Elseways, Golfieri *et al.* (2014) noted that only 6.2% of SAE, and systemic adverse events such as alopecia, mucositis and bone marrow depression were not reported at all.

In our study, we observed two cases of SAE among 60 patients. One patient developed transient alopecia after two sessions of c-TACE. After careful reviewing of the images from the first TACE, we realized that it was due to undetected AV fistula in the liver. Alopecia was reported in one patient in a small study of 40 patients treated with DEM-TACE by the group of Richter *et al.* (2017). Our second SAE was after DEM-TACE treatment, when two liver abscesses and large areas of nontarget embolization developed, mainly in the right liver lobe, which led to serious liver decompenzation. Fortunately, patient recovered completely with prolonged conservative treatment and several percutaneous drainages. Abscess formation was also described in two patients by Golfieri *et al.* (2014) and in one case by Richter *et al.* (2017).

Our low rate of SAE may be attributed to the relatively smaller doses of doxorubicin injected, compared to other groups such as Lammer *et al.* (2010). The 'on demand' treatment schedule plays an important role in decreasing the risk of adverse events.

Limitations of the study

One of the major limitations of our study is the small sample size in both groups, but following the results very carefully, we realized that even if we continue enrolment it was very unlikely that a statistically significant difference regarding survival rate will occur. This fact was also suggested by our external statistician.

Another possible limitation of this study could be the fact that we did not enroll any patients with Child-Pugh C liver cirrhosis nor any BCLC stage C, compared to all other trials published so far on this particular topic. On the other hand, this could also be an advantage taking into account the latest EASL-EORTC guidelines, which clearly recommend TACE as a standard treatment for BCLC B patients. However, the situation in this study is not a total reflection on our everyday practice, because we also sometimes ~~threaten~~ BCLC C patients, borderline patients or even ones with poor liver function without other options.

Finally, we should also keep in mind that this is a single-institutional trial defined by certain technical experts, particular methodology and local practice.

Conclusion

Primary prevention of liver cirrhosis and thus HCC development is crucial. This study did not demonstrate any statistically significant difference between c-TACE and DEM-TACE techniques in terms of 12-and 24-month survival rates. In real good candidates, both TACE methods are extremely effective and well tolerated with a great proportion of survival after 24 months. The only objective advantage of DEM-TACE over c-TACE is the shorter in-hospital stay after treatment. Taking into account the current prizes for in-hospital treatment in North Macedonia, this fact does not make any real difference regarding the financial aspect of TACE.

However, in some other health systems such as the USA model, this could be of greater importance.

Hence, the decision of which TACE technique should be utilized as a 'standard' in real clinical practice remains to be a preference of the interventional radiologist himself, personal confidence with one method or the other, and of course the local availability of materials. Both, c-TACE and DEM-TACE should remain as reasonable options for unresectable intermediate stageHCC.

It is very doubtful that any other further investigation on this particular topic will show dramatically different results than ours, so we suggest that future investigations might focus more on combining other therapies and loco regional treatments with TACE in order to achieve greater survival in these fragile patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest. AQ15

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