Original Article

Comparison of transarterial bland embolization and drug-eluting beads transarterial chemoembolization for very early and early hepatocellular carcinoma not amenable for surgery or ablation: a single center retrospective data analysis

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Background: Transarterial chemoembolization (TACE) is the accepted therapy for intermediate hepatocellular carcinoma (HCC). Although recent data suggests that bland transarterial embolization (TAE) is equally effective in intermediate HCC, not much is known about the efficacy in very early and early HCC not amenable for ablation or resection. We aimed to compare the outcome of patients with very early and early HCC treated by drug-eluting beads TACE (DEB-TACE), a specific technique of TACE using DC beads, and TAE using microparticles with a size of 100 µm up to 700 µm.

Methods: Clinical data of totally 95 patients with very early and early HCC not amenable for surgery or ablation, treated between 2009 and 2019 at the Department of Visceral Surgery and Medicine and the Interdisciplinary Center of Vascular Interventions, University Hospital Bern, Switzerland, were retrospectively analyzed (52 patients in DEB-TACE and 42 patients in TAE group, respectively). All images were assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Primary endpoint was overall survival (OS). Secondary endpoints were local response rate and time to local progression.

Results: Most patients presented with Child-Pugh A. Thrombocytes were significantly lower in patients treated by TAE. Minor side effects occurred equally in both groups. No differences were detected in terms of OS, local tumor recurrence and response rate.

Conclusions: Compared with DEB-TACE, TAE is an equally effective and save therapy for very early and early HCC not amenable for resection or ablation without differences in local tumor control and OS.

Keywords: Hepatocellular carcinoma (HCC); bland embolization; drug-eluting transarterial chemoembolization (TACE); transarterial embolization (TAE)

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Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer related mortality with increasing incidence worldwide. Current guidelines recommend transarterial chemoembolization (TACE) as accepted therapy for HCC classified as Barcelona Clinic of Liver Cancer (BCLC) intermediate stage B and as an alternative treatment option for patients with very early and early HCC (BCLC 0 and A) not amenable for resection, ablation or transplantation (1-4). For latter patients, TACE is the accepted embolization procedure, performed either with lipiodol or with drug-eluting beads (DEB) plus chemotherapeutic agents, despite very little evidence in the literature (5,6). So far, only two studies investigated the feasibility of doxorubicin-eluting bead TACE (DEB-TACE) in patients with very early and early HCC (7,8). No data for bland transarterial embolization (TAE) in patients with very early and early HCC is available. In addition, the superiority of DEB-TACE compared with TAE is still under debate. While TAE delivers its anti-tumoral activity only by vascular occlusion, DEB-TACE combines it with the effects of chemotherapy (9).

Up to date, only few studies addressed the non-inferiority of TAE compared with DEB-TACE in patients with HCC (10,11). Even though no study specifically compared DEB-TACE with TAE in very early or early-stage HCC, a previous published study investigated up to 24% of patients with BCLC A indicating that early HCCs are routinely treated by embolization techniques (11).

Overall survival (OS) is the benchmark of research and treatment choice for patients with HCC (12).

We therefore aimed to analyze the outcome, local response and toxicity of TAE compared with DEB-TACE in our own retrospective and monocentric patient cohort of very early and early HCC not amenable for resection or ablation. We present this article in accordance with the TREND reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-261/rc).

Highlight box

Key findings

- Transarterial bland embolization (TAE) is equally safe and effective as drug-eluting beads transarterial chemoembolization (DEB-TACE) in very early and early-stage hepatocellular carcinoma (HCC).

What is known and what is new?

- According to current guidelines, TACE is recommended for the treatment of HCC.
- This study showed no difference in outcome, local response and toxicity of TAE compared with DEB-TACE in very early and early HCC.

What is the implication, and what should change now?

- TAE is safe and might be equally effective as DEB-TACE for very early and early HCC.

Methods

Study design

All patients with early or very early HCC receiving either DEB-TACE or TAE at the Bern University Hospital (Department of Visceral Surgery and Medicine, Interdisciplinary Center of vascular Interventions, and Radiology) in Switzerland between December 2009 and December 2019 were retrospectively enrolled. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Regional Ethics Review Board of Bern, Switzerland (No. KEK-Nr.2018-00416). All patients signed a general informed consent.

Study population

Patients were included with either histologically proven HCC or HCC diagnosis based on radiological non-invasive criteria according to the European Association of the Study of the Liver (EASL) guidelines (3). Each patient was presented and discussed individually at the institutional multidisciplinary tumor board. Embolization was recommended as treatment whenever the tumor was deemed unresectable and/or unablatable including patients awaiting liver transplantation (LT).

In this study we compare chemoembolization performed by DEB-TACE. Therefore, all interventions using lipiodol or ethanol were excluded. Further exclusion criteria were poor quality of pre- and postinterventional imagining without sufficient visibility of the lesions/treatment effect. Furthermore, patients receiving both kind of embolization, or patients with simultaneous systemic therapy were excluded.

Demographic and clinical data were retrieved from patient's medical records. During the study period, 147 patients were treated with DEB-TACE or TAE, respectively.

Angiogram and embolization technique

DEB-TACE was the standard embolization technique at

Table 1 Categories of mRECIST

Categories	Description
CR	No sign of remaining viable tumor tissue with contrast enhancement
PR	Reduction of the sum of diameters of embolized target lesions ≥30%
SD	Neither response nor progression
PD	Increase of ≥20% of the sum of the diameters of the embolized lesions

mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

our hospital between 2009 and 2014 and was performed using doxorubicin as the chemotherapeutic agent, applicated by DEB (DC beads, Boston Scientific®, USA; Table S1). The loaded bead size was between 300–700 µm. For small and large supplying arteries, bead sizes of 100–300 and 500–700 µm were applied, respectively. Per embolization, a dose of 25–150 mg doxorubicin was administered. Since 2014, TAE became the standard embolization technique at our institution using microparticles or microspheres with a size of 100 µm up to 700 µm (Embozene, Varian®, USA; Hydropearls, Terumo®, Japan; PVA foam embolization particles, Cook®, USA; Table S1).

All embolizations were guided by 2D angiography and, if necessary and available, cone-beam computed tomography (CT) control. First overview angiographies of the coeliac trunk and the superior mesenteric artery were performed using 4–5 Charrière catheters as chosen by interventional radiologists' preference. The embolization position was defined and the diagnostic catheter or a microcatheter was placed as desired. After angiography control of the correct catheter position the embolization was performed. The procedure was finished by a final angiogram from a central position.

For the TAE approach, the embolization was done as superselective as possible, meaning embolization in a subsegmental position as close to the tumor as possible. In general, for TAE the smallest possible particle size was used to achieve distal/intratumoral vessel occlusion, as this was thought to produce more necrosis. Overall goal was to use 100 µm microspheres, if considered safe by the interventionalist, judged by the angiography and previous imaging. If considered unsafe, larger spheres or PVA were used. For DEB-TACE, on the other hand, a more central embolization position was usually accepted. DC beads were used in all cases for DEB-TACE with a standard size of 300–500 or 500–700 µm. Endpoint of the embolization was the lack of tumor blush with obtained antegrade perfusion for DEB-TACE and complete stasis of the superselective tumor feeder for TAE, respectively.

Intervention time was considered as time between the first angiography and the final one.

Radiological analysis

Diagnosis of HCC was defined by typical behavior on liver imaging by multiphase contrast enhanced CT or multiparametric contrast enhanced MRI (13). Radiological data were extracted from imaging files in the picture archiving and communication system (PACS) of the clinic. For this study, all hepatic lesions in all patients were retrospectively re-analyzed and re-confirmed by two radiologists with a subspecialisation in abdominal and liver imaging (Mertineit N and Maurer MH). All intra-procedural images/angiographies were retrospectively analyzed by a subspecialised interventional radiologist with training and experience in TAE and DEB-TACE (Mertineit N). Imaging follow-up was performed 1–3 months after the embolization and then 3-monthly by either magnetic resonance imaging (MRI), CT or contrast enhanced ultrasound (CEUS; since 2016 CEUS was additionally performed 2 weeks after TAE as an early assessment of treatment response). To evaluate treatment efficiency of the embolization, modified Response Evaluation Criteria in Solid Tumors (mRECIST) was used (*Table 1*) (14,15).

Outcome and variables

Local recurrence (LR) was defined as the presence of a detectable tumor after an initial complete response (CR). In contrast, new lesions within the liver other than the embolized tumor were considered as overall progression (OP).

Patients showing a partial response (PR) underwent re-TACE or re-TAE, if no contraindication was present. Cases were re-discussed in the interdisciplinary tumor board, if no

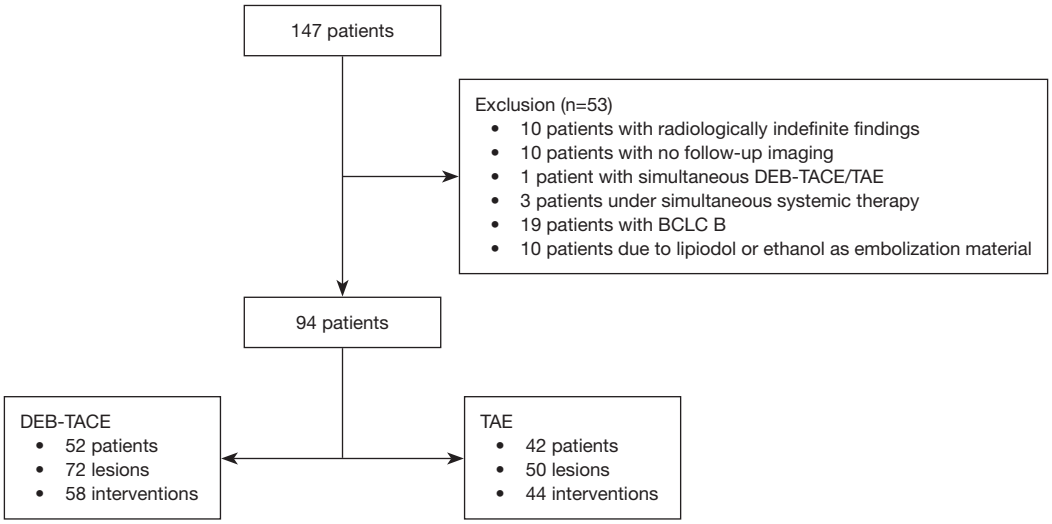

Figure 1 Flow chart showing the number of included patients before and after exclusion and allocation to 2 treatment groups. DEB-TACE, drug-eluting beads transarterial chemoembolization; TAE, transarterial bland embolization; BCLC B, Barcelona Clinic of Liver Cancer intermediate stage B.

CR was present after 2 TACE or TAE. All hepatic lesions were followed until recurrence or progressive disease (PD) and re-treatments like additional TACE or TAE, surgery or additional interventions were documented and were censored for the follow-up analysis. Further sub-group analyses according to the size of DC beads and the doses of doxorubicin within the DEB-TACE group as well as the comparison of size of microparticles in the TAE group in respect to local response were performed and showed no difference (see Table S2). Patient records were analyzed for post-interventional complications such as the commonly reported post-embolization syndrome (nausea, vomiting and abdominal pain) and constitutional syndrome (deterioration of the general condition) (16). At the beginning of the study period, embolizations were performed as outpatient procedures, what changed over time due to the changes in the reimbursement policy requiring a minimum 2-night hospital stay in order to not be deficient. Patients were admitted the day before the intervention and discharged one day after the intervention when pain-free and in an adequate general condition.

Statistical analysis

For statistical analysis using SPSS (version 25), *t*-test and Mann-Whitney *U* test was applied for continuous variables with normal and not normal distribution, respectively. For nominal variables, depending on the size, Chi-square test (total n>120) and Fisher's exact test (total n<120) was performed, respectively. Survival data was evaluated by Kaplan-Meier curve. For the survival analysis, death or end of the study period was considered as the end of follow-up. The threshold for statistical significance was $P \leq 0.05$. Propensity score matching was not achievable due to size of patient groups.

Results

Clinical data

Fifty-three (36.1%) patients were excluded due to the defined exclusion criteria. For the final analyzes, 94 patients (52 DEB-TACE and 42 TAE) were included undergoing a total of 102 interventions of 122 HCC lesions (*Figure 1*).

Patient characteristics are summarized in *Table 2*. There was a predominance of male patients in both groups with no difference of the median age between the groups. At the time of intervention, the Model for End-stage Liver Disease (MELD), Child-Pugh classification and albumin-bilirubin (ALBI) score were not significantly different between DEB-TACE and TAE patients in both groups (*Table 2*). Patients treated with TAE had a more marked thrombocytopenia (DEB-TACE 120×10^9/L, TAE 85×10^9/L; Mann-Whitney *U* test, P=0.003; *Table 2*). In total, 22 patients had previously been treated for other HCC lesions, 11 (21.2%) patients in the DEB-TACE group and 10 (23.8%) patients in the

Table 2 Patients characteristics

Characteristics	DEB-TACE (n=52)	TAE (n=42)	P value
Gender (male), n (%)	48 (92.3)	37 (88.1)	0.51
Age (years), median [range]	63 [45–84]	65.5 [45–85]	0.30
MELD, median [range]	9 [6–22]	9 [6–22]	0.38
BCLC, n (%)			0.77
0	8 (15.4)	5 (11.9)	
A	44 (84.6)	37 (88.1)	
Child-Pugh classification, n (%)			0.48
A	36 (69.2)	25 (59.5)	
B	16 (30.8)	16 (38.1)	
C	0	1 (2.4)	
Albumin-bilirubin score, n (%)			0.36
1	9 (17.3)	8 (19.0)	
2	39 (75.0)	27 (64.3)	
3	4 (7.7)	7 (16.7)	
Thrombocytes ($\times 10^9$/L), median [range]	120 [60–319]	85 [22–241]	0.003
AFP (kU/L), median [range]	10.9 [1.3–9,207.7]	6.1 [1.0–9,263.0]	0.78
Etiology of liver disease, n (%)			0.357
HCV	8 (15.4)	13 (31.0)	
HBV	6 (11.5)	3 (7.1)	
HCV + HBV	0	1 (2.4)	
Alcohol	18 (34.6)	11 (26.2)	
NASH	6 (11.5)	2 (4.8)	
ASH/NASH	3 (5.8)	5 (11.9)	
Combination[†]	3 (5.78)	3 (7.1)	
Other[‡]	8 (15.4)	4 (9.5)	
Embolization as first therapy, n (%)			0.81
Yes	41 (78.8)	32 (76.2)	
No	11 (21.2)	10 (23.8)	
Previous therapy, n (%)			
Surgery	6 (11.5)	7 (16.7)	
Surgery + locoregional therapy	2 (3.8)	1 (2.4)	
Locoregional therapy	2 (3.8)	2 (4.7)	
Radiotherapy	1 (1.9)	0	

Mann-Whitney *U* test for continuous variables with not normal distribution. Fisher's exact for nominal variables. [†], combination: DEB-TACE: HBV/ASH [1], HCV/ASH [1], HBV/NASH [1]; TACE: HCV/ASH [1], HCV/NASH [2]. [‡], other: DEB-TACE: hemochromatosis [2], Alagille syndrome [1], idiopathic [3], primary biliary cholangitis [2]; TAE: autoimmune [1], idiopathic [1], hemochromatosis [2]. MELD, Model for End-stage Liver Disease; BCLC, Barcelona Clinic of Liver Cancer, AFP, alpha-fetoprotein; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, non-alcoholic steatohepatitis; ASH, alcoholic steatohepatitis.

Table 3 Intervention-specific data

Variables	DEB-TACE	TAE	P value
Treated tumors	72	50	
Tumor size (mm), median [range]	23 [6–64]	27.5 [11–100]	0.12
Number of interventions	58	44	
Intervention time			
Available number	52	42	
Median [range], min	42.6 [21.3–116.5]	55.9 [12.5–223.4]	0.08
Side effects, n (%)	5 (8.6)	7 (15.9)	0.35
Postembolic syndrome	2 (3.4)	3 (6.8)	
Constitutional symptoms	1 (1.8)	3 (6.8)	
Liver decompensation	2 (3.4)	0	
Septic shock	0	1 (2.3)	
Hospitalization duration (days), mean [range]	1.7 [1–8]	2 [1–26]	<0.001

Mann-Whitney *U* test for continuous variables with not normal distribution and Student's *t*-test for continuous variables with normal distribution, Fisher's exact for nominal variables (n<120). DEB-TACE, drug-eluting beads transarterial chemoembolization; TAE, transarterial bland embolization.

TAE group, respectively (P=0.81, Fisher's exact test; *Table 2*). Totally, 73 (77.7%) patients were treatment naïve, 41 (78.8%) patients in the TACE group and 32 (76.2%) in the TAE group, respectively (*Table 2*). Mean follow-up time was 39.0 months, with 42.4 months (range, 3–132 months) in the DEB-TACE group and 34.7 months (range, 1–102 months) in the TAE group (P=0.35).

Intervention-specific data

During the study period, 123 lesions were treated during 102 interventions (*Table 2*). In the DEB-TACE group 72 lesions were treated in 58 interventions and in the TAE-group 50 lesions in 44 interventions. While the mean number of performed embolizations was not different between the two groups [mean 1.44 (range, 1–3) for DEB-TACE group and mean 1.2 (range, 1–3) for TAE group; P=0.08; Mann-Whitney *U* test], the intervention time was 42.6 minutes in the DEB-TACE compared to 55.9 minutes in the TAE group (Mann-Whitney *U* test, P=0.08). Median tumor size at the time of intervention was 28.0 mm overall, 23.0 mm (range, 6–64 mm) in the DEB-TACE-group and 27.5 mm (range, 11–100 mm) in the TAE group (P=0.12; Student's *t*-test).

In the DEB-TACE group, 1 lesion (1.4%) was embolized with DC beads 100–300 µm, 30 lesions (41.7%) with DC beads 300–500 µm, 1 (1.4%) with DC beads 500–700 µm and 36 lesions (50.0%) with DC beads 300–500 and 500–700 µm. The data for embolization materials were not available for 4 lesions (5.5%). Applied doxorubicin dose varied from 20 to 150 mg per embolization (median: 95.0 mg). Applied dose of chemotherapeutic agents could not be elicited for 8 (11.1%) lesions. For TAE different types of embolization agents were used including microparticles (n=35; 70%) and DC beads (n=15; 30.0%; see Table S1).

There were no significant differences in terms of adverse events. Side effects occurred after 11.8% of all interventions, showing no differences between the groups (P=0.35; Fisher's exact test, *Table 3*). According to the Society of Interventional Radiology (SIR) classification of adverse events, one patient treated by TAE suffered a grade D category, namely septic shock of unknown origin and needed intensive care (17). Other complications included postembolic syndrome, constitutional symptoms or liver decompensation (*Table 3*).

Patients in the DEB-TACE-group had a shorter hospital stay than patients in the TAE-group (mean: 1.7 *vs.* 3.8 days; P<0.001, Mann-Whitney *U* test, *Table 3*).

Radiological response

The radiological analyses showed no significant difference

Table 4 Radiological response

Variables	DEB-TACE (n=72)	TAE (n=50)	P value
Radiological response[†], n (%)			0.59
Complete response	33 (45.8)	24 (48.0)	
Partial response	37 (50.0)	19 (38.0)	
Stable disease	2 (2.8)	5 (10.0)	
Progressive disease	1 (1.4)	2 (4.0)	
Local recurrence after complete response, n (%)	17 (40.5)	8 (33.3)	0.70
Time to local re-occurrence (months), median (range)	7.5 (1.8–62.0)	19.4 (4.4–61.2)	0.8
Local progression, n (%)	9 (24.3)	6 (31.6)	0.66
Time to local progression (months), median (range)	9.1 (0.83–48.9)	6.7 (1.0–11.0)	0.74
Subsequent treatment, n (%)	28 (38.9)	28 (56.0)	0.06

Mann-Whitney *U* test for continuous variables with not normal distribution. Chi-square test and Fisher's exact test for nominal variables. [†], response after the first embolization. DEB-TACE, drug-eluting beads transarterial chemoembolization; TAE, transarterial bland embolization.

in the radiological response between the DEB-TACE and the TAE group (P=0.59, Chi-square test; *Table 4*). At the first follow-up imaging 1–3 months after the first intervention, 33 (45.8%) out of 72 DEB-TACE-lesions and 24 (48.0%) out of 50 TAE-lesions showed a CR. PR rate and stable disease and PD rate were similar between the two groups. After up to a maximum of 3 embolizations (range, 1–3), a total of 42 (58.3%) DEB-TACE lesions and 25 (50.0%) TAE lesions showed a CR. Twenty-five (34.7%) of DEB-TACE lesions and 19 (38.0%) of TAE lesions showed a PR, 2 (2.8%) of DEB-TACE and 4 (8.0%) of TAE lesions showed stable disease. In the DEB-TACE group, 3 (4.2%) lesions presented with a PD compared to 2 (4.0%) lesions in the TAE group (P=0.53; Chi-square test), results are not shown in *Table 4*. Of the lesions showing a CR after 1–3 treatments, 17 (40.5%) of all 42 DEB-TACE lesions and 8 (33.3%) of all 24 TAE lesions re-occurred after a median time of 7.5 months (range, 1.8–62.0 months) and 19.4 months (range, 4.4–61.2 months), respectively (P=0.8, Chi-square test; P=0.20, respectively, Mann-Whitney *U* test, *Table 4*).

Fifty-four (44.3%) lesions with residual activity received either stereotactic microwave ablation, systemic therapy (sorafenib) or were operated including atypical resection, hemihepatectomy or LT. In the long-time follow-up, local PD occurred in 9 (24.3%) of 37 DEB-TACE lesions with PR and 6 (31.6%) of 19 TAE lesions with PR (P=0.74; Chi-square test; *Table 4*).

Progression free survival (PFS)

Overall disease progression occurred in 12 (23.1%) of 52 DEB-TACE patients and 6 (14.3%) of 42 TAE patients (P=0.31; Fisher's exact test). Time to overall disease progression was not significantly different [mean 6.8 (range, 1.1–27.5) *vs.* mean 6.9 (range, 0.9–11.4) months; P=0.78; Mann-Whitney *U* test]. Further, PFS was not significantly different (P=0.41; Kaplan-Meier curve; *Figure 2A*). Patients with alpha-fetoprotein (AFP) >20 ng/mL (=16.5 kU/L) showed significant more overall disease progression (P=0.001; Kaplan-Meier curve, Figure S1). No other association was found (Table S3).

OS

Mean OS was 42.4 months (range, 3–132 months) for DEB-TACE patients and 34.7 months (range, 1–102 months) for TAE patients until death or end of the study period (P=0.42; Kaplan-Meier curve, *Figure 2B*). Additionally, mean survival considering transplantation or death as endpoint was not different (see Figure S2). The overall 1-, 2- and 3-year survival rate was 75.0%, 55.8% and 48.1% in the DEB-TACE group 81.0%, 52.4% and 35.7% in the TAE group, respectively (P=0.30; Fisher's exact test). Again, patients with an AFP above 20 ng/mL (=16.5 kU/L) showed a significantly worse survival irrespective of whether they received DEB-TACE or TAE (P=0.005; Kaplan-Meier curve, Figure S3).

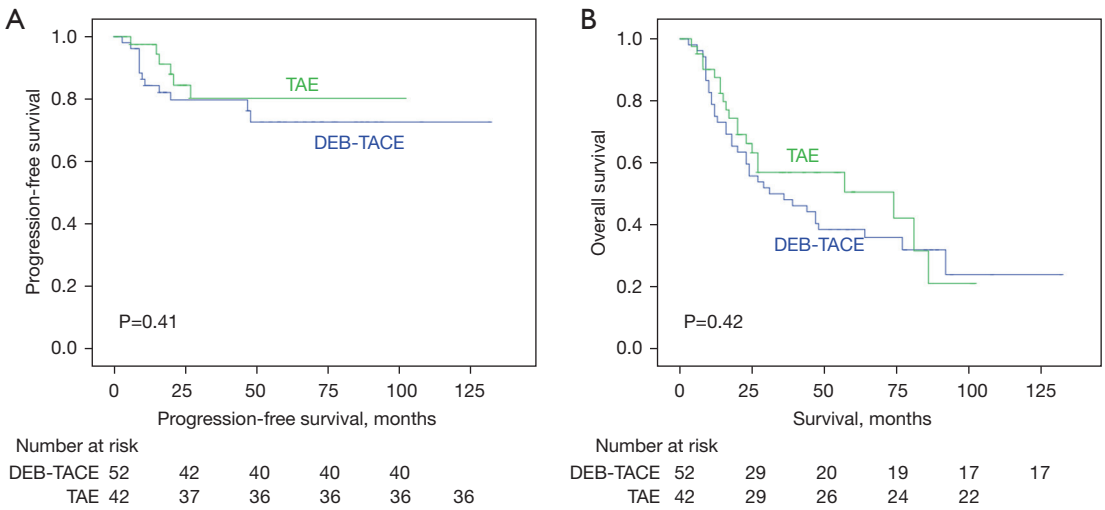

Figure 2 Kaplan-Meier curves showing (A) progression-free survival of patients receiving DEB-TACE versus TAE; (B) overall survival of patients receiving DEB-TACE versus TAE until death or end of study period. DEB-TACE, drug-eluting beads transarterial chemoembolization; TAE, transarterial bland embolization.

No other association was found (Table S3).

During the study period, 29 (55.8%) DEB-TACE patients and 19 (45.2%) TAE patients were listed for LT (P=0.41, Fisher's exact test). Seven (24.1%) of these 29 DEB-TACE patients and 4 (21.1%) of the 19 listed TAE patients dropped out of the waiting list due to disease progression (P=0.53, Fisher's exact test, *Table 4*).

Post-transplant histological analysis

In total, 30 (81.1%) explanted livers of 37 transplanted patients with 32 (71.1%) of 45 embolized hepatic lesions were available for histological analysis (DEB-TACE =19, TAE =13). Six (31.6%) and 5 (38.5%) completely necrotic lesions were detected in DEB-TACE and TAE treated patients, respectively (P=0.50; Fisher's exact test). Remaining vital HCC nodules were identified in 13 (68.4%) and 6 (46.2%) of DEB-TACE and TAE treated lesions, respectively. Two (15.3%) lesions with local progression were treated by microwave ablation after TAE so the effect of embolization could not be elicited.

Discussion

Our retrospective single-center analysis showed no significant differences in terms of local tumor control and OS in patients treated with DEB-TACE or TAE for very early and early HCC.

In 2009, Malagari *et al.* compared DEB-TACE with TAE finding better local response, fewer recurrences and a longer time to progression in favor of DEB-TACE without a survival benefit within 1 year (10). In contrast, the more recently published randomized controlled trial by Brown *et al.* found no difference in terms of response rates and survival comparing bland embolization with DEB-TACE (11). Our data supports the latter results for patients with early and very early HCC.

According to the BCLC guidelines, embolization is commonly recommended for patients with BCLC stage B in a non-curative approach (12,18). Furthermore, embolization is a therapeutic option for patients who do not qualify for resection or ablation or as a bridging or downstaging therapy for patients awaiting LT (19-21). In our cohort, 51.1% of all patients were listed for transplantation, of which 77.1% could be transplanted. Until 2014, patients with HCC in a very early or early stage, unsuitable for surgery or ablation, were routinely treated with DEB-TACE. In 2014 stereotactic microwave ablation was introduced offering an additional curative therapy for inoperable patients with HCC (20).

Despite the retrospective design of our study, the clinical features of the two cohorts were very similar, except for the degree of thrombocytopenia, which was significantly more severe in the TAE group. In the literature, most studies excluded patients with thrombocytopenia below 50×10^9/L or the thrombocytes were not considered in the patients'

characteristics at all (22,23). However, it's known, that thrombocytopenia is correlated with the severity of portal hypertension in cirrhosis pointing to the fact that patients in the TAE group had a more advanced underlying liver disease compared to those in the DEB-TACE group (24).

In the literature, an upper size limit between 7 and 10 cm is discussed, in our patients, only 2 patients (4.8%) presented with a tumor above 7 cm, both treated by TAE (25-27).

We detected an overall complication rate of 11.8%, including 3.4% post-embolization syndromes in the DEB-TACE-group and 6.8% in the TAE-group, respectively, with no difference between the two treatment groups. The retrospective character of available studies may underestimate mild forms of post-embolization syndromes.

The length of hospital stay was also significantly different between the two groups, which can be explained in part by changing reimbursement policies in Switzerland during the study period requiring either an ambulant procedure or a 2-day hospital stay. Further reasons may include the fact that TAE is a painful procedure, even this study found no differences in the adverse event (28). Principally, however, embolization is an intervention that can be performed in an out-patient setting (18). However, a large range of hospitalization time up to 41 days has been described (29).

Due to the retrospective character of the study, embolization was not standardized. For DEB-TACE, DC beads were used and the particle size was chosen depending on the supplying artery of the hepatic lesion and the preferences of the interventionalist in charge. For TAE, overall size of the particles was smaller and more adapted to the individual patient as the most necrotic effect was expected if the embolization material reaches the microvasculature of the tumor. However, the subanalysis according to the size and type of the embolization material showed no significant difference.

To analyze the radiological effect, we used mRECIST criteria which are recommended to evaluate the response rate after embolization (30). The overall CR rate was 45.9% without significant difference between the 2 groups. Confirming this radiological finding, no difference of histologically proven necrosis was observed in the liver explants among the two groups. The much longer time to progression in the TAE group might be, at least partly, explained by the more selective and therefore maybe longer-lasting embolization. Due to the small sample size this would have to be validated in a separate and ideally prospective study.

For a more detailed analysis, we further stratified in OS and PFS. Differences were solely found in AFP >20 ng/mL (=16.5 kU/L) (Table S3 and Figure S1). Finally, OS, PFS and recurrence after CR was equal in both groups.

Even though combination of different therapies is known to potentiate the effect (23), this study is lacking a comparison with percutaneous or systemic treatments. In the recent years, the introduction of stereotactic image-guided microwave ablation led to a change in our treatment algorithm offering a curative approach even to invisible lesions or those being deemed as not amenable for ablation due to their complicated anatomic location in the liver (31,32).

Clearly, the retrospective character of the study, the potential bias due to the change in our treatment algorithm and the change of clinical practice over time as well as the small patient collective with no possible matching, limits the interpretation of our results. In particular, the further development of minimal invasive procedures, imaging modalities and also the compounds and devices used for embolotherapy in the treatment landscape of HCC most likely limit the interpretation of the current study results. On top of that, no comparison to conventional TACE is available. Nevertheless, our data demonstrate the feasibility and safety of TAE compared with DEB-TACE in early and very early-stage HCC, in particular considering the fact that patients in the TAE group had more advanced and larger tumors.

Conclusions

In conclusion, our monocentric retrospective study showed no difference in local tumor control and OS between DEB-TACE and TAE. These findings indicate that TAE might be a valid treatment alternative for patients with very early and early HCC.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-261/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-261/coif). IB is receiving consulting fees/honoraria from educational grant Terumo und Boston Scientific. AB is receiving consulting fees from Boehringer Ingelheim and General Electrics. MHM has been receiving consulting fees/honoraria from Johnson&Johnson, Bayer Healthcare and CAScination. AL is receiving consulting fees/honoraria from Johnson&Johnson, Histoconics, CAScination and the Swiss Association of the Study of the Liver. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Regional Ethics Review Board of Bern, Switzerland (No. KEK-Nr.2018-00416). All patients signed a general informed consent.

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Supplementary

Table S1 Embolization material

Embolization materials	Brands	Size (treated lesions)
DEB-TACE (n=72)		
DC beads	Boston Scientific®	100–300 µm (n=1); 300–500 µm (n=30); 500–700 µm (n=1); 300–500 µm/500–700 µm (n=36); not available (n=4)
TAE (n=50)		
DC beads	Boston Scientific®	100–300 µm (n=11); 300–500 µm (n=2); not available (n=2)
Embozene	Varian®	40 µm (n=1); 100 µm (n=6); 250–500 µm (n=11); 500–700 µm (n=2); not available (n=3)
Hydropearls	Terumo®	75 µm (n=4); 200 µm (n=4); 75 µm/200 µm (n=1); not available (n=2)
PVA foam embolization particles	Cook®	not available (n=1)

DEB-TACE, drug-eluting beads transarterial chemoembolization; TAE, transarterial bland embolization; PVA foam, polyvinyl alcohol foam.

Table S2 Radiological outcome stratified by embolization material

Radiological response[†]	DEB-TACE[‡]		TAE[§]	
	Doxorubicin <100 mg (n=29)	Doxorubicin ≥100 mg (n=30)	Doxorubicin <250 µm (n=46)	Doxorubicin ≥250 µm (n=12)
Complete response	17 (58.6%)	15 (50.0%)	24 (52.2%)	7 (58.3%)
Partial response	10 (34.5%)	13 (43.3%)	18 (39.1%)	5 (41.7%)
Stable disease	1 (3.4%)	1 (3.3%)	2 (4.3%)	0
Progressive disease	1 (3.4%)	1 (3.3%)	2 (4.3%)	0
P	0.98		1.0	

Mann-Whitney *U* test for continuous variables with not normal distribution. Chi-square test and Fisher's exact test for nominal variables. †, response after first embolization. ‡, DEB-TACE: lesions embolized by DC beads 300–700 µm stratified according to dose of doxorubicin. §, TAE: lesions embolized by Embozene, stratified according to size of the particles. DEB-TACE, drug-eluting beads transarterial chemoembolization; TAE, transarterial bland embolization.

Table S3 Association of clinical factors with OS and PFS

Variables	P value
AFP >20 ng/mL	
OS	0.005
PFS	0.001
Tc >100×10^9/L	
OS	0.96
PFS	0.50
Age >60 years	
OS	0.45
PFS	0.80
CHILD	
OS	0.65
PFS	0.80
BCLC	
OS	0.25
PFS	0.54
MELD ≥9	
OS	0.55
PFS	0.58
Embolization as first therapy	
OS	0.95
PFS	0.54
Tumor size (>2 cm)	
OS	0.76
PFS	0.20

For P value log-rank (mantel cox) was used. OS, overall survival; PFS, progression free survival; AFP, alpha-fetoprotein; Tc, thrombocytes; CHILD, Child Pugh classification; BCLC, Barcelona Clinic of Liver Cancer; MELD, Model for End-stage Liver Disease.

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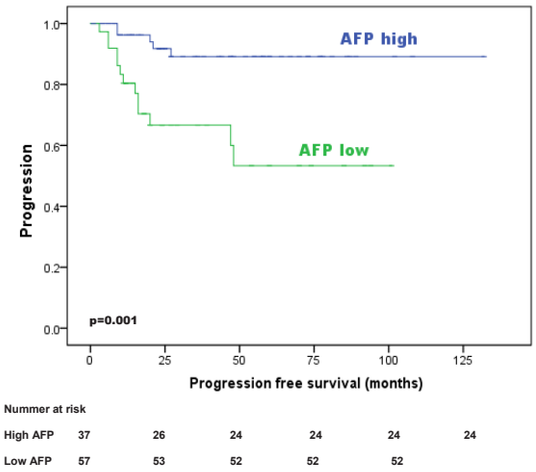

Figure S1 Overall disease free survival in patients with high AFP (>20 ng/mL =16 kU/L) in comparison with patients with low AFP (≤20 ng/mL). AFP, alpha-fetoprotein.

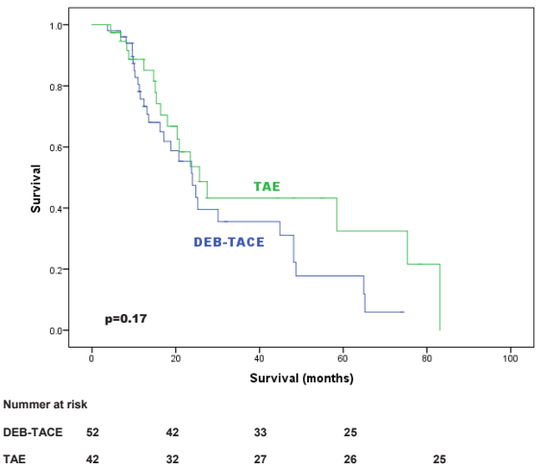

Figure S2 Kaplan-Meier curve showing overall survival of patients receiving DEB-TACE versus TAE until death, end of study period or liver transplantation. DEB-TACE, drug-eluting beads transarterial chemoembolization; TAE, transarterial bland embolization.

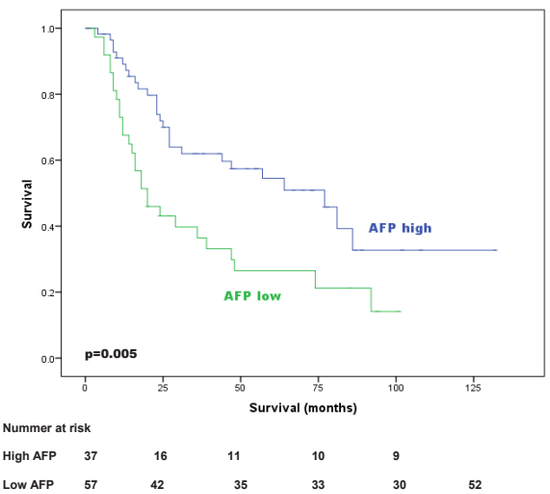

Figure S3 Overall survival in patients with high AFP (>20 ng/mL =16 kU/L) in comparison with patients with low AFP (≤20 ng/mL). AFP, alpha-fetoprotein.

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