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Multicentre prospective study of drug-eluting bead chemoembolisation safety using tightly calibrated small microspheres in non-resectable hepatocellular carcinoma

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ABSTRACT

Purpose: To assess the safety and tolerability of transarterial drug-eluting bead chemoembolisation (DEB-TACE) using tightly calibrated 100-μm microspheres in hepatocellular carcinoma (HCC).

Method: This multicentre prospective study included 131 patients with a 2-year follow-up. All patients had Child-Pugh scores ≤ B7, a good performance status, and Barcelona Clinic Liver Cancer stage A or B. Beads were loaded with 50 mg of doxorubicin per millilitre. Overall, 223 nodules were treated (mean size: 27.6 mm, average number of nodules per patient: 1.7). Toxicity was assessed using Common Terminology Criteria for Adverse Events 4.03 and response according to the modified Response Evaluation Criteria in Solid Tumours. The primary endpoint was safety. Secondary endpoints included technical success, post-embolisation syndrome (PES), local tumour response, and 2-year survival.

Results: A total of 214 DEB-TACE procedures were performed (mean per patient: 1.64), with a technical success rate of 97.6 % and a PES rate of 9.3 %. Major complications occurred in 6.8 % of patients and 4.1 % of procedures. There were no treatment-related deaths. Doxorubicin dose was an independent predictor of complications ($p = 0.01$). Four patients were lost to follow-up and 18 received liver transplants. Objective response rates were 74.6 %, 45.7 %, and 44.1 % at 6, 12, and 24 months, respectively. The cumulative 24-month overall survival rate was 55.96 %. Median survival was 22 months (interquartile range = 13–24). Co-morbidities and tumour response were independent predictors of survival ($p = 0.0012$ and 0.0052, respectively). Complications did not affect survival ($p = 0.24$).

Conclusions: DEB-TACE with tightly calibrated 100-μm beads is safe and not associated with increases in biliary toxicity or complications. Tumour response and survival are in the expected range for chemoembolisation therapy. (Clinical trials ID: NCT02670122).

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1. Introduction

In randomised studies, drug-eluting bead transarterial chemoembolisation (DEB-TACE) for the treatment of hepatocellular carcinoma (HCC) has not achieved better overall survival (OS) than conventional chemoembolisation (cTACE) [1–3]. Nonetheless, DEB-TACE has several proven advantages such as the delivery of higher concentrations of the chemotherapy drug in the tumour, lower systemic toxicity, a need for fewer sessions, controlled and sustained release of the drug, greater efficacy in advanced-stage or large tumours, and better standardisation of the procedure itself [4–6].

There is no consensus on the optimal size of the microparticles for DEB-TACE treatment [7]. Animal studies have shown that small microspheres penetrate deeper and more homogenously into tumours, causing more intense ischaemia and achieving a higher intratumoural concentration of the chemotherapy [8,9]. This would imply a better objective local response. The DEBs most commonly used in current clinical practice are 100–300 μm; DEBs sized ≤100 μm are used less often, as they are considered potentially more dangerous [10].

Biliary toxicity of DEB-TACE attributed to the ischaemic injury of the peribiliary plexus, associated with local doxorubicin toxicity, has been a particular source of concern. It has been suggested that this type of toxicity may be more intense when small microspheres are used, thus placing limits on their use [11]. Several uncontrolled retrospective studies have reported significantly higher rates of biliary complications with DEB-TACE than with cTACE [12,13]. In this context, the question of the most suitable microsphere size for use in DEB-TACE remains unanswered.

The objective of this multicentre prospective study was to assess whether DEB-TACE using small microspheres (100 μm) is associated with a higher rate of complications compared with cTACE and with DEB-TACE using bigger microspheres.

2. Material and methods

2.1. Study design and endpoints

This was a multicentre prospective study to assess the safety and tolerability of DEB-TACE of non-resectable HCC, using 100-μm doxorubicin-loaded microspheres (Embozene Tandem™, CeloNova BioSciences, Boston Scientific, San Antonio, TX, USA). Institutional Review Board approval was obtained at all the participating institutions. All patients provided written informed consent.

The safety of selective DEB-TACE with tightly calibrated 100-μm microspheres loaded with 50 mg of doxorubicin per millilitre of microspheres was the primary endpoint of this study. Technical complications, 30-day mortality, and minor and major adverse events were assessed in accordance with the Common Terminology Criteria for Adverse Events 4.03 [14]. Particular focus was placed on the potential biliary toxicity of these small DEBs. Secondary endpoints included technical success; post-embolisation syndrome (PES); 6-, 12-, and 24-month local tumour response; and 2-year OS.

2.2. Patients and tumours

A total of 131 patients were included between March 2015 and November 2016, and 223 HCCs were treated, with a mean tumour size of 27.6 mm (standard deviation = 17.4) and a mean of 1.7 tumours per patient. Table 1 summarises the characteristics of these patients. The diagnosis of HCC was confirmed in accordance with the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases guidelines, and HCC was staged according to the Barcelona Clinic Liver Cancer (BCLC) system [15]. The indication for DEB-TACE was made following clinical practice guidelines [16,17]. Inclusion and exclusion criteria are listed in Table 2. Patients with HCC were treated if they had BCLC stage B or stage A and were not

Table 1
Baseline demographic characteristics of the 131 patients included.

	N (%)	mean (SD)
Sex (male/female)	103/28 (78.62/21.37)	
Age in years		68.64 (10.85)
Etiology of chronic liver disease		
HCV	63 (48.09)	
Alcohol abuse	41 (31.29)	
HBV	6 (4.58)	
HCV and alcohol abuse	9 (6.87)	
Others[a]	9 (6.87)	
HBV and alcohol abuse	1 (0.76)	
HCV, HBV, alcohol abuse	1 (0.76)	
HBV and HCV	1 (0.76)	
BCLC Classification		
A	75 (57.25)	
B	56 (42.75)	
ECOG performance status		
0	116 (88.54)	
1	15 (11.45)	
Child-Pugh score		
A5	93 (70.99)	
A6	24 (18.32)	
B7	14 (10.68)	
Liver lobes involved, N (%)		
Unilobar HCC	104 (79.38)	
Bilobar HCC	27 (20.61)	
Tumors treated	223	
Tumors per patient	1.70 (1.1)	
Mean size, mm	27.6 (17.4)	
Tumors ≤3 cm	159 (71.3)	
Tumors 3–6 cm	46 (20.6)	
Tumors ≥6 cm	18 (8.1)	
Comorbidities, Yes/No	74/ 57 (56.68/43.51)	
Diabetes mellitus	37 (28.24)	
Heart disease	11 (8.39)	
History of other tumors[b]	10 (7.6)	
COPD	9 (6.87)	
Patients on anticoagulation	7 (5.34)	
Kidney failure	4 (3.05)	
Others[c]	43 (32.85)	
Previous Treatments, Yes/No	35 / 96 (27.4 / 72.6)	
Previous TACE	12 (9.16)	
Previous thermoablation	8 (6.1)	
Previous TACE + thermoablation	6 (4.58)	
Previous surgery	2 (1.52)	
Previous surgery + thermoablation	1 (0.76)	
Unknown	6 (4.58)	
Pretreatment laboratory test results		
Platelets (x1000)		120 (5871)
Bilirubin, mg/dl		1.03 (0.55)
Albumin, g/L		3.82 (0.47)
Quick value, %		82.29 (18.59)
α-fetoprotein, ng/mL		96.99 (254.68)
HCC diagnosis confirmation		
Non-invasive criteria (EASL/AASLD)	106 (80.91)	
Biopsy/fine needle aspiration	23 (17.55)	
Unknown	2 (1.52)	

N: Frequency, %: Percentage, SD: standard deviation, HBV: hepatitis B virus, HCV: hepatitis C virus, HCC: hepatocellular carcinoma, BCLC Barcelona Clinic Liver Cancer, ECOG Eastern Cooperative Oncology Group, EASL: European Association for the Study of the Liver, AASLD: American Association for the Study of Liver Disease.

[a] Others: autoimmune hepatitis, steatohepatitis, hemochromatosis, primary biliary cirrhosis.

[b] On complete or partial response at the time of DEB-TACE. ENT, 3; Lung, 2; bladder, 1: colon 1; breast, 1; stomach, 1; and pancreas intraductal papillary mucinous, 1.

[c] Others: hypertension, dyslipidemia.

Table 2
Inclusion and Exclusion Criteria.

Inclusion Criteria	
1	Confirmed diagnosis of HCC and staged according to BCLC system
2	Indication for DEB-TACE following usual practice
3	Adults (male or female) ≥18 years of age
4	Written informed consent
5	Child-Pugh score ≤ B7
6	ECOG performance status 0 or 1
7	No tumor invasion in the major blood vessels
8	Adequate blood, liver, renal and heart function, based on test results obtained no more than 2 weeks before starting
9	No current infections requiring antibiotic therapy
10	Measureable disease as per the modified Response Evaluation Criteria in Solid Tumors (mRECIST)
11	Life expectancy of more than 6 months
Exclusion Criteria	
1	Child-Pugh class ≥ B8
2	ECOG performance status > 1
3	HCC with vessel or biliary duct invasion
4	Diffuse HCC or extrahepatic spread
5	Bilirubin levels > 3 mg/dl
6	WBC < 2000 cells/mm^3
7	Contraindications to the use of doxorubicin, MRI or CT
8	Cardiac ejection fraction < 50 %
9	Blood creatinine ≥2 mg/dl
10	Impaired clotting test, transaminase > 5 x ULN or, when greater > 250 U/L
11	Known hepatofugal blood flow, arterio-venous shunt, arterio-portal shunt
12	Main stem portal vein occlusion
13	Pregnancy or breastfeeding
14	Tumor burden of more than 50 % of the liver
15	Objective signs of active bacterial, viral, or fungal infection

ULN upper limit of normal.

candidates for radical curative treatment. DEB-TACE was also indicated as a bridge therapy for liver transplantation or for down-staging.

2.3. Embolisation procedure

Tandem™ microspheres are precisely calibrated and change in size by less than 9 % after drug loading [18]. Each millilitre of microspheres can be loaded with up to 50 mg of doxorubicin. The maximum dose of doxorubicin used per procedure was 150 mg, corresponding to 3 ml of microspheres [19].

All the procedures were selective or super-selective using standard micro-catheters. No anti-reflux micro-balloons or micro-catheters were used. The procedure was considered super-selective when the micro-catheter tip reached the tumour feeding artery and selective when it was placed at a branch upstream of the feeding artery. Each millilitre of microspheres was mixed with 10 ml of non-ionic contrast medium and injected at a rate of 1 mL/min, using 1- or 3-mL Luer-lock syringes under fluoroscopic guidance and avoiding reflux. Cone-beam computed tomography was used as a complementary tool at the operator's discretion.

The embolisation endpoint was vascular stasis or the administration of the maximum doxorubicin dose. In the case of stasis not being achieved in the first TACE, a second procedure was planned within 3–6 weeks. No complementary embolisation using bland microspheres or gelatine sponge was done at the end of each TACE session.

2.4. Follow-up and response assessment

Patients were followed up for a period of 2 years or until they died. Before hospital discharge, the Edmonton Symptom Assessment System was used to assess the PES [20]. Clinical evaluations, blood tests, and imaging controls at 1, 3, 6, 12, and 24 months after the first DEB-TACE procedure were performed. Tumour response was assessed using the modified Response Evaluation Criteria in Solid Tumors assessment for HCC [21].

2.5. Statistical analysis

Descriptive statistics were calculated for categorical variables and means ± standard deviations or medians with interquartile ranges (IQRs) for continuous variables. Univariate analysis was performed to identify variables related to developing complications, using Chi-square tests. To identify risk factors related to mortality, univariate logistic regression models were constructed. For survival analysis, Kaplan-Meier curves and log-rank tests were used. A column graph was used to represent tumour response. All effects were considered significant at $p < 0.05$. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. DEB-TACE procedures

The results are summarised in Fig. 1. A total of 214 DEB-TACE procedures (a mean of 1.64 per patient) were performed, with 46.5 % of the patients undergoing two DEB-TACE procedures and 12.9 %, 3.8 %, and 0.7 % undergoing three, four, and six procedures, respectively. Catheterisation was super-selective in 60.8 % of the procedures and selective in 39.2 %. The endpoint of stasis was achieved in 89.2 % of cases. Doxorubicin dose, based on the volume of microspheres infused, was 50 mg in 24, 75 mg in 53, 100 mg in 46, 125 mg in 16, and 150 mg in 75 procedures, meaning that the maximum allowed dose of doxorubicin was used in only 35 % of the DEB-TACE procedures.

The technical success rate was 97.6 %. It was not possible to complete the DEB-TACE at the first attempt in five of 214 procedures, in one case due to severe spasm, another due to failure to achieve selective catheterisation, and in a third due to micro-catheter clogging. There were two cases of asymptomatic segmental hepatic artery dissection. The TACE procedure was successful in all five of these patients in a second attempt between 3 and 5 weeks later.

3.2. Complications and adverse events

Technical complications occurred in 2.4 % of the patients (five cases). This included the aforementioned dissections as well as two cases of serious groin haematoma resulting in prolongation of hospitalisation and one case of asymptomatic hepatic arterial branch perforation and microsphere leakage into the biliary tree.

Approximately half (51.6 %) of the patients did not experience pain or discomfort after DEB-TACE; in 39 %, symptoms were mild and self-limiting; and 9.3 % reported severe PES requiring intravenous analgesia and extending their hospital stay.

Table 3 shows the 30-day adverse events. There were no deaths attributable to the procedures. Major complications (grade 3 or 4 adverse events) occurred in 6.8 % of the patients and 4.1 % of the procedures. There were minor complications (grade 1 or 2) in 22.1 % of patients and 13.5 % of the procedures. Biliary complications were seen in 6.8 % of patients (nine cases) and 4.2 % of the procedures. Eight patients developed segmental dilatation of the intrahepatic bile ducts, but all were asymptomatic. Six of these patients had received the maximum doxorubicin dose (150 mg). One patient developed an 8-cm biloma that did not require any invasive management.

Univariate analysis found a significant association between complications and the administered dose of doxorubicin ($p = 0.01$). Furthermore, 52 % of minor complications and 71 % of major complications occurred in the group of patients who received the highest dose of doxorubicin (2.1 – 3 mL of microspheres). Complications were not associated with Child-Pugh, BCLC, selective or super-selective catheterisation, co-morbidities, or treatment response.

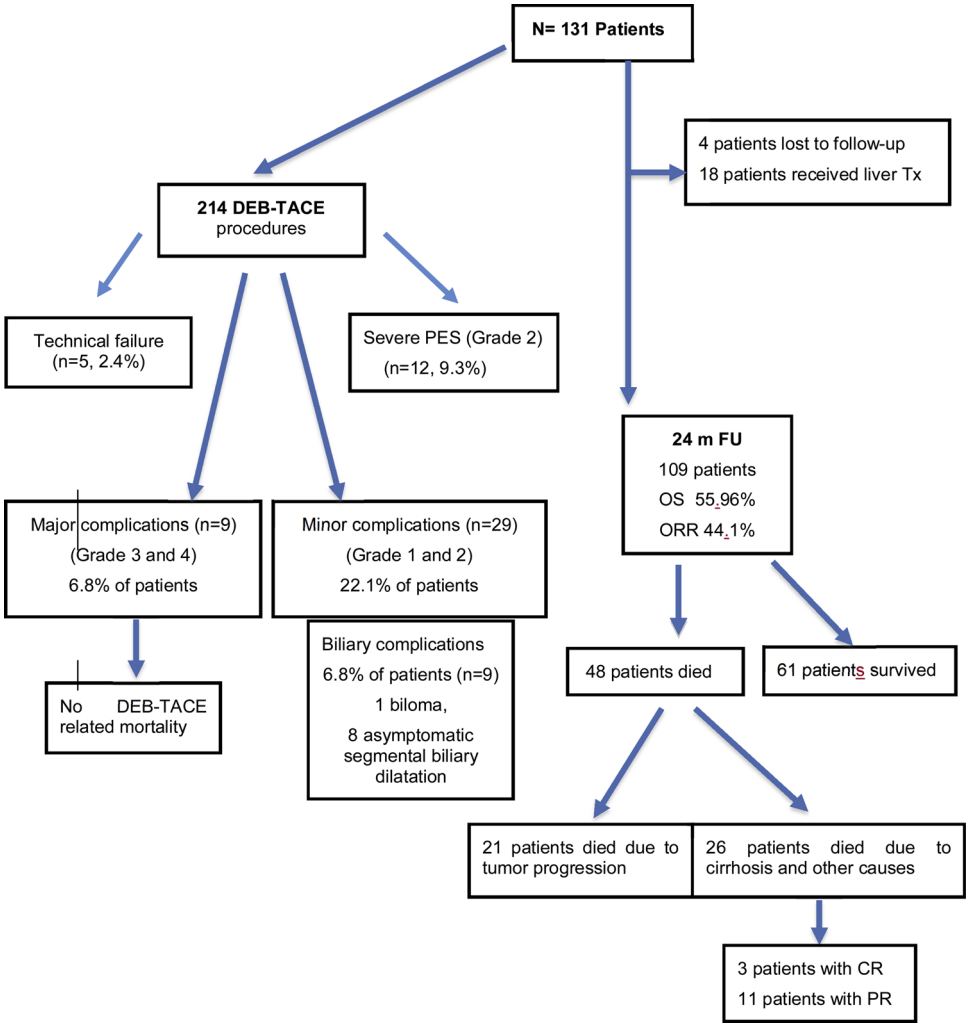


Fig. 1. Flow of patients through the study. Maximum follow-up of 24 months.

3.3. Follow-up, response, and survival

Four patients were lost to follow-up, and 18 received liver transplants. Of the other 109 patients, 61 remained alive at the end of the study. Tumour response at 6, 12, and 24 months is presented in Fig. 2. The cumulative 24-month survival rate was 55.96 %. The median survival of this cohort was 22 months (IQR = 13 – 24 months). Complications after DEB-TACE did not affect 2-year survival (p = 0.24) (Fig. 3). Regarding patient deaths, 45.8 % were due to tumour progression, 23 % due to cirrhosis-related complications, and 31.2 % due to other causes (Table 4). In the univariate analysis of mortality predictors, as well as tumour progression, the risk of death was 3.6-fold higher in patients who had co-morbidities (p = 0.001) (Table 5).

4. Discussion

Since the Precision V study, many researchers have attempted to optimise the DEB-TACE procedure [1]. The size and characteristics of the DEB is a key issue. Doxorubicin disseminates a maximum of 150 µm from the surface of the microsphere, and the density of microspheres inside the tumour should be as high as possible [22]. Animal studies have confirmed that small DEBs achieve deeper intra-tumour penetration and more uniform intra-tumour coverage, improving doxorubicin distribution and tumour ischaemia, and thereby also a stronger antitumour effect [8,9]. This hypothesis has been confirmed in humans. Small DEBs are associated with higher survival rates and lower complication rates than DEB-TACE with microspheres sized 300 – 500 µm or 500 – 700 µm [23,24]. In liver explants using microspheres sized 100 – 300 µm, only 42 % of intra-tumour blood vessels were occluded. Given this, it seems rational to use smaller microspheres [25]. However, precise calibration would allow a more homogenous distribution, avoiding premature stasis and proximal occlusion of tumour-feeding arteries caused by the larger ones [19].

Hydrogel core Tandem™ microspheres are second-generation DEBs. Their greatest strengths rely on being uniformly spherical and tightly calibrated. Other advantages include a higher loading dose of doxorubicin, a size reduction after loading of only 9 %, consistent and sustained doxorubicin release inside the tumour, a reduced inflammatory response, and a longer and more stable suspension time [18,19].

Different studies have reported high rates of biliary toxicity associated with DEB-TACE. Guiu et al. [12] observed that 17.2 % of patients had biliary toxicity, which was attributable to having treated non-cirrhotic livers and not having carried out selective embolisation. Monier [13] reported a biliary toxicity rate as high as 36.8 %, and a recent Korean registry reported a rate of 19.7 % [26]. This may seem alarming, however, most of these biliary complications were only accidental

Table 3
Adverse events (N) within 1st month (CTCAE 4.03) and treatment.

Grade 1 (13)
- Asymptomatic segmental bile duct/biliary tree dilatation (8).
- Asymptomatic segmental hepatic artery dissection (2).
- Asymptomatic segmental hepatic artery perforation (1).
- Periumbilical bruise due to non-target falciform artery embolization (1).
- Partial alopecia (1).

Grade 2 (16)
- Asymptomatic coagulative thrombosis of a segmental portal branch (1); LMWH.
- Biloma (1); conservative treatment, painkillers.
- Larger groin hematoma (2); prolonged hospitalization.
- Severe post-embolization syndrome (12); prolonged hospitalization.

Grade 3 (7)
- Hepatic abscess (3); 1 percutaneous drainage, 2 conservative treatment.
- Cholecystitis; conservative management in both cases.
- Worsening of severe COPD (1); symptomatic treatment.
- Colitis, uncertain origin (low cardiac output/infectious) (1); symptomatic treatment.

Grade 4 (2)
- HCC rupture and bleeding (1); embolization 10 h after TACE, discharged 10 days later.
- SIRS + Prerenal failure in CKD (1); required admission in ICU for 20 days.

Grade 5 (0)

CTCAE Common Terminology Criteria for Adverse Events, LMWH low molecular weight heparin, COPD chronic obstructive pulmonary disease, SIRS systemic inflammatory response syndrome, CKD chronic kidney disease. ICU intensive care unit.

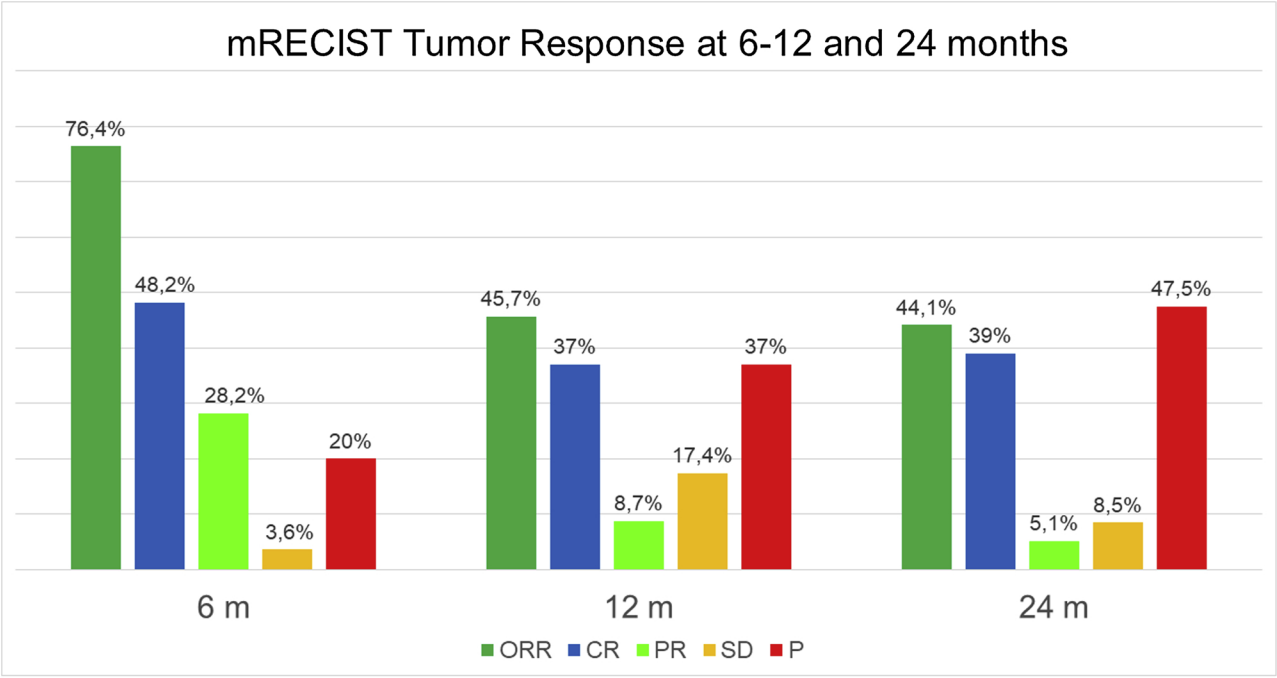
imaging findings that did not have a clinical impact on patient survival. Furthermore, some studies have not found an increase in the rate of biliary toxicity [27,28]. Notably, three studies with 100-, 75-, and 40-μm Tandem™ microspheres reported biliary complications rates of 5.7 %, 0%, and 0%, respectively [29–31]. In the present study, the rate of all types of biliary complications was 6.8 %, similar to that previously reported for cTACE [32,33].

Supporting the suggestion of Malagari [31], we detected a significant association between complications and administration of the highest doses of doxorubicin. A doxorubicin loading of 50 mg/ml DEB rather than the conventional 37.5 mg/ml dose may be a factor that contributes to biliary toxicity. Based on 75-μm Tandem™ microspheres, a recent retrospective study found a grade 1 biliary toxicity rate of 8.3 % using doxorubicin doses of less than 37.5 mg/mL, and hence, it is not clear whether biliary toxicity is only attributable to an increase in doxorubicin dose or also to the larger number of microspheres used in association with such an increase [34]. Overall, optimisation of the chemotherapy drug dose for a given microsphere size seems to be a relevant factor and should be specifically assessed. As well as the dose, the position of the micro-catheter and the endpoint of the embolisation are factors that influence the risk of biloma and biliary toxicity. In the Korean registry, non-selective embolisation and forced stasis were found to be the cause of biliary complications [26].

The reported 30-day mortality and major complication rates of TACE are 0.6 % and 10 %, respectively [7,32,33,35]. In the present study, the 30-day mortality rate was 0 %. Minor complications occurred in 13.5 % and major complications in 4.1 % of the procedures. There were no cases of liver infarction, hepatic decompensation, or persistent liver deterioration. All patients in this cohort had compensated chronic liver disease with Child-Pugh scores of up to B7. These characteristics, together with the super-selective approach with minor or no non-tumour liver parenchyma embolisation, could explain the results.

PES is not considered a true adverse event but represents a reaction to treatment [36]. The rate of PES was as high as 47.7 % in cTACE and 24.7 % in the Precision V trial [4,32]. More recent studies have demonstrated that DEB-TACE is associated with a significantly lower PES rate than is cTACE [37]; however, PES is very variable from mild self-limited abdominal pain to severe symptoms. In our study, 51.6 % of patients had no symptoms at all after DEB-TACE, and only 9.3 % experienced severe PES. This result could be explained by the fact that no bland embolisation was administered after the DEB injection.

This study found an objective response rate of 76.4 % at 6 months, higher than that reported in the Precision studies (51.6 %) and



ORR, objective response rate, CR, complete response; PR, partial response; SD stable disease; P, Progression

Fig. 2. Graph of tumour response.

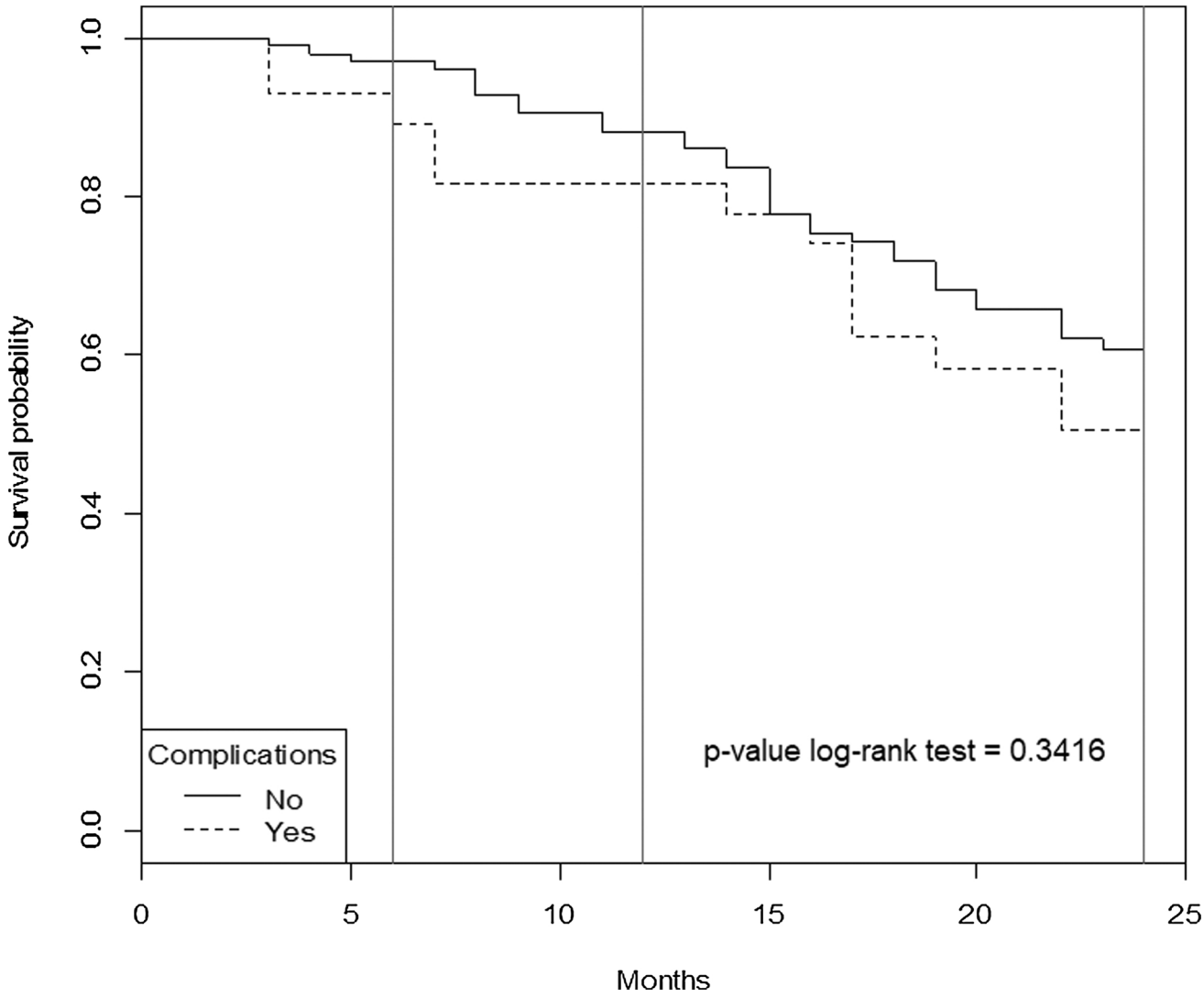


Fig. 3. Kaplan-Meier curves showing overall survival in patients with and without DEB-TACE complications. No significant differences were found (log-rank test p-value = 0.3416).

Table 4
Causes of death (N) at the end of the study, 2 years.

Total (48)
Tumor progression (22)
Cirrhosis complications[a] **(11)**
Other causes (15)
• Pneumonia (5)
• Iatrogenic event[b] (2)
• Other tumors (2) (lung and stomach)
• CHF (1)
• Hemoperitoneum in an anticoagulated patient (1)
• Massive hemoptisis (1)
• PE (1)
• Sepsis (1)
• Not known (1)

N: Frequency.

[a] Liver failure, variceal bleeding, ascites, encephalopathy, spontaneous peritonitis.

[b] Gastric perforation during gastroscopy, massive hemoptysis due to percutaneous lung biopsy CHC, congestive cardiac failure; PE, pulmonary embolism.

somewhat higher than that found in other studies using 100-μm beads [29,31]. The use of spheres that were smaller in size and uniformly calibrated as well as super-selective embolisation may explain the improvements seen in the outcome.

Another characteristic of this research is that it is a post-approval real-world study. Notably, 56.6 % of patients had co-morbidities, and co-morbidities and tumour progression were the only two statistically significant predictors of survival, explaining the fact that only 45.8 % of the deaths by the end of follow-up were associated with tumour progression, with 54.2 % of patients dying due to other causes. Although Malagari et al. [31], using ≤100-μm beads, observed a 2-year survival rate of 88.4 %, recent real-world studies reported a cumulative 2-year survival of between 40 % and 50.5 %, slightly lower than our rate (55.9 %) [34,37]. In the Precision Italy study, the cumulative 2-year survival was 47 %. It should be noted that neither complications nor doxorubicin dose had any effect on survival.

This study has several limitations. First is the lack of a comparative arm using larger and/or smaller DEBs or a cTACE. A second is that parameters such as PFS and TTP have not been analysed. Furthermore, histopathological correlation data were not collected from the 18 liver explants. Finally, the data on the doxorubicin dose administered in each TACE are inaccurate because they were calculated considering the volume of microspheres infused.

In conclusion, DEB-TACE with tightly calibrated 100-μm beads was safe and was not associated with higher rates of biliary toxicity or complications. Local tumour response and survival showed a trend to improve on the expected results of DEB-TACE. Further refinement of

Table 5
Mortality data: univariate analysis with logistic regression.

	Total N (%)	Exitus N (%)	β (e.e.)	OR (IC 95 %)	p-value
Total	**131**	**48 (36.64)**			
Child					
A5	93 (71.32)	33 (35.87)	Ref.	Ref.	
A6	23 (17.83)	11 (47.83)	0.49 (0.47)	1.639 (0.652–4.122)	0.2939
B7	14 (10.85)	4 (28.57)	−0.34 (0.63)	0.715 (0.208–2.460)	0.5949
BCLC					
A	81 (62.79)	30 (37.04)	Ref.	Ref.	
B	48 (37.21)	18 (37.50)	0.02 (0.38)	1.020 (0.488–2.134)	0.9580
Selectivity					
Selective	51 (39.23)	20 (39.22)	0.16 (0.37)	1.175 (0.568–2.431)	0.6635
Superselective	79 (60.77)	28 (35.44)	Ref.	Ref.	
Doxorubicin dose[a]					
0–1	9 (6.92)	2 (22.22)	Ref.	Ref.	
1.1–1.5	26 (20.00)	10 (38.46)	0.78 (0.90)	2.187 (0.377–12.701)	0.3831
1.6–2	30 (23.08)	10 (33.33)	0.56 (0.89)	1.750 (0.306–10.022)	0.5297
2.1–2.5	9 (6.92)	2 (22.22)	0 (1.13)	1.000 (0.108–9.229)	1.0000
2.6–3	56 (43.08)	24 (42.86)	0.97 (0.85)	2.625 (0.500–13.781)	0.2540
Comorbidities					
No	57 (43.85)	12 (21.05)	Ref.	Ref.	
Yes	74 (56.15)	36 (49.32)	1.29 (0.40)	3.649 (1.664–7.998)	**0.0012**
Response after 24 m					
Stable disease	15 (11.54)	3 (20.00)	0.18 (0.81)	1.200 (0.245–5.886)	0.8222
Progression	65 (50.00)	32 (49.23)	1.54 (0.55)	4.654 (1.582–13.695)	**0.0052**
Complete response	29 (22.31)	5 (17.24)	Ref.	Ref.	
Partial response	21 (16.15)	8 (38.10)	1.08 (0.67)	2.954 (0.801–10.897)	0.1039
Complications					
No	102 (78.46)	35 (34.31)	Ref.	Ref.	
Yes	28 (21.54)	13 (46.43)	0.51 (0.43)	1.659 (0.711–3.873)	0.2418

N: frequency, %: percentage. β (e.e.): Estimation (standard error). OR: odds ratio. CI: confidence interval.
[a] 50 mg of doxorubicin per mL of beads.

the procedure and super-selective embolisation may result in less biliary toxicity and lower rates of complications using 100-μm DEB-TACE.

CRediT authorship contribution statement

Jose Urbano: Conceptualization, Methodology, Investigation, Data curation, Validation, Writing - original draft, Writing - review & editing, Supervision, Project administration. **J. Javier Echevarria-Uraga:** Investigation, Data curation, Validation, Writing - original draft, Writing - review & editing. **J. Jose Ciampi-Dopazo:** Investigation, Data curation, Validation, Writing - original draft, Writing - review & editing. **Juan A. Sánchez-Corral:** Investigation, Data curation. **Jorge Cobos Alonso:** Investigation, Data curation. **Ane Anton-Ladislao:** Formal analysis, Investigation, Validation. **Borja Peña-Baranda:** Investigation, Data curation. **Veronica Nacarino-Mejias:** Investigation, Data curation. **Rocío González-Costero:** Investigation, Data curation. **J. Joaquín Muñoz Ruiz-Canela:** Investigation, Data curation. **Julian Pérez-Cuesta:** Investigation, Data curation. **Carlos Lanciego:** Investigation, Data curation, Writing - review & editing. **Miguel Angel de Gregorio:** Writing - original draft, Writing - review & editing, Validation, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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