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CLINICAL INVESTIGATION

Safety Profile of Sequential Transcatheter Chemoembolization with DC Bead™: Results of 237 Hepatocellular Carcinoma (HCC) Patients

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Abstract
Introduction Complications of chemoembolization performed with DC Bead™ loaded with doxorubicin (DEBDOX) of diameters 100–300 μm and 300–500 μm are presented in this paper. These diameters are currently the smallest available in drug-eluting technology.
Methods Included are 237 patients who were treated with sequential DEBDOX with doxorubicin loaded at 37.5 mg/ml of DC Bead. The National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) were used to categorize complications.
Results Thirty-day mortality was 1.26% (3/237). Incidence of grade 5 complications was 1.26% (3/237). Overall, grade 4 complications resulted in 5.48% (13/237) (irreversible liver failure, cholecystitis). Grade 2 liver function deterioration developed in 10 patients (4.2%). Cholecystitis/grade 2 and 4 incidents were observed in 3.6–5.06% across sessions (overall 13 patients; 5.48%). Postembolization Syndrome (PES) grade 1 or 2 was observed in up to 86.5%; however, grade 2 was observed in 25–42.19% across treatments. Pleural effusion was seen in eight patients (overall 3.37%; grade 1 in 1.8–3.7% across

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treatments; grade 3 in 0.42%). Grade 1 procedure-related laboratory pancreatitis was seen in 0.45%, and grade 2 gastrointestinal bleeding was seen in 0.84%. Procedure-associated skin erythema/grade 1 was seen in 0.84%. There was no correlation of liver failure or transient liver function deterioration with the diameter of the beads ($p = 0.25$–0.37 and $p = 0.14$–0.89, respectively). Stratifying with the diameter of the beads correlation values was: for cholecystitis ($p = 0.11$–0.96 across treatments), PES ($p = 0.35$–0.83), temporary/grade 1 elevation of liver enzymes ($p = 0.002$–0.0001), and bilirubin ($p = 0.04$–0.99).

Conclusions DEBDOX chemoembolization is safe and small calibres do not result in increased complication rates compared with results of series using larger diameters of beads.

Keywords Interventional oncology · Endovascular treatment · Liver/hepatic

Introduction

Transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) is an established procedure in Barcelona Clinic Liver Cancer (BCLC) stage B patients with proven survival benefit [1–3]. TACE data performed with DC Bead™ loaded with doxorubicin (DEBDOX) (Biocompatibles, Terumo) until now showed that it is an effective targeted locoregional treatment with objective response rates in the range of 44–82% [4–10]. In addition, DEBDOX has shown lower chemotherapeutic-related systemic complications compared with conventional chemoembolization (c-TACE) as proven by a recent large randomized prospective trial [10]. However, the majority of these trials have mainly been performed with bead diameters >300 μm because there was a reservation for smaller bead diameters safety (risk of perisinusoidal vessel occlusion and biliary wall necrosis). In our department, we have routinely used a combination of beads of 100–300 μm and 300–500 μm of DC Bead™ with good clinical results and low complication rates [6, 7, 9].

In this study, we report the spectrum of adverse events observed in patients treated with DEBDOX for HCC. Potential effects on the myocardium are not included in this study. The classification of the complications in this paper is descriptional reflecting the precise medical condition, and severity grading was performed according to the National Cancer Institute Common Terminology Criteria. This qualitative and quantitative description is useful for setting safety standards and for accurate comparisons between studies. This is the largest study focusing exclusively in safety and the first series reporting on complications of DC Bead™ of diameters 100–300 μm and 300–500 μm loaded with doxorubicin. These diameters are currently the smallest available in drug eluting chemoembolization technology.

Materials and Methods

Included in this cohort are 237 patients with documented HCC, treated with sequential DEBDOX performed at set time intervals every 2 months until three sessions/6-month follow-up. Six patients did not proceed to the second session and 189 of the 237 completed three embolization sessions. Data were prospectively obtained in the context of efficacy and safety protocols designed to assess this treatment ($n = 173$) and the rest ($n = 64$) were assessed retrospectively from patient records. Patients who had BCLC B stage of HCC were Eastern Cooperative Oncology Group performance status, ECOG 0–1, and Child-Pugh class A ($n = 116$; 48.9%) and B ($n = 121$; 51%) cirrhosis. Selection criteria included bilirubin <3 mg/dl, AST, ALT <270 IU/l. Patients with portosystemic shunts, thrombus within main portal vein, or extrahepatic metastases were excluded.

Procedure

After hepatic and superior mesenteric artery angiography to map liver vascular anatomy, check for arteriovenous shunts, and identification of arterial tumor supply, feeding artery/ies were superselectively catheterized with the use of a 2.7-Fr microcatheter (Progreat, Terumo). Slow injection of the DC Bead™ loaded with doxorubicin followed until the complete intended dose was administered or until intratumoral vascularity was obliterated and slow flow was observed. Lesions supplied from extrahepatic arteries also were treated—always with the use of microcatheter with the endpoint of intratumoral vessel blockade. For each vial of reconstituted and loaded beads, 10 cc of contrast was used for dilution. The diameter of the beads chosen was based on the size of the lesion, the feeder/s diameter, and vascularity. In all patients, two different sizes of DC Bead™ were used: 100–300 μm and/or 300–500 μm (Biocompatibles, Terumo). In the first 80 patients, loaded beads of 100–300 μm and 300–500 μm were used regardless of the diameter of the tumor, until flow stasis within the tumor was achieved or until the administration of the two vials. After this initial period, during which confidence for small diameters was achieved, the smallest size of DC Bead™ was preferably used; for lesions <60 mm (without fluoroscopically visible arteriovenous shunts), only beads of 100–300 μm were administered, whereas in larger tumor diameters or lesions that were multilobulated or presented obvious satellites, 1 vial of 100–300 μm and 1 vial of 300–500 μm were injected. Depending on the vascularity of the lesion—in cases in which intratumoral flow stasis was not achieved—additional

embolization with Beadblock particles (Biocompatibles, Terumo) followed. Each patient received a maximum of 150 mg of doxorubicin loaded in two vials of DC Bead™ (4 ml total), which represents bead loading with 37.5 mg of doxorubicin/ml of reconstituted beads. No lipiodol was used. Vigorous hydration was administered before and after embolization. All patients received antibiotic prophylaxis (cefuroxime sodium/Zinacef 750 mg IVq 8 h, 500 mg metronidazole), 500 mg Solucortef or 10 mg dexamethasone, 100 mg ranitidine IV (Zantac) and antiemetic drug (8–16 mg ondansetron/Zofron IV). Pain was controlled individually with nonsteroidal anti-inflammatory drugs or opioids. After the first year of application of this technique in patients complaining for medium to severe pain during and after the procedure, we performed routinely an ultrasound of the right abdomen before discharge.

The size/s of the beads used were classified as: size 1 (small beads of 100–300 μm only), size 2 (100–300 μm followed by 300–500 μm), and size 3 (those in which additional to the initial two vials of DC Bead™ Bead block of similar diameters was used; Biocompatibles, Terumo). In addition, quantity of the beads in vials/cc (1 vial = 2 cc of reconstituted beads) and set volumes were recorded (1, 2, 3, or 4 ml of beads). No accurate measurement of the quantity of the administered beads was possible. The type of embolization was classified as superselective/subsegmental (SS), selective/segmental (S), or embolization of more than one segment (>S).

Imaging Follow-up

Patients were followed up at 1, 3, 5–6 months, i.e., 1 month after each procedure with computed tomography (CT), or magnetic resonance imaging (MRI). CT scans were of three phases performed on a helical CT scanner (high-speed Advantage scanner, General Electric Medical Systems Milwaukee, WI, USA). CT parameters were: 5-mm collimation; 5-mm/sec table speed (pitch, 1.0) during a single breath-hold helical acquisition of 25–30 s, depending on the size of the liver, and a 5-mm reconstruction interval. The hepatic arterial, portal venous, and delayed phases were performed at 30 s, 60 s, and 180 s, respectively, after the start of the injection of 120 mL of nonionic iodinated contrast material, iopamidol (Iopamiro 300; Bracco, Milano, Italy), via a peripheral vein at a rate of 3 mL/sec by power injector. MRI included T1 fat-suppressed images, T2 fat-suppressed sequences, and dynamic fat-suppressed T1 sequences with gadolinium enhancement. Imaging measurements were made by consensus by two radiologists (KM and MP). Contrast-enhanced ultrasound (CEUS) was performed with a Siemens Acuson, Sequoia 512 equipment using Sonovue (Bracco) as an enhancing agent with a compatible logistic program. Raw data and videos during contrast enhancement were recorded. Ultrasound without contrast was done before patient discharge in patients with severe pain.

Imaging evaluation for complications included search for visually detected complications including ascites, intratumoral gaz collection, intraparenchymal fluid collections, cholecystitis, biliary tree dilatation pleural effusion, and pancreatic edema. Imaging response was classified according to the EASL criteria (European Association of the Study of the Liver) and by percentage of necrosis.

Safety was monitored by follow-up of liver enzymes at discharge (after each procedure) and synchronously with the scheduled imaging follow-up visits. Liver function tests included bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), serum glutamic oxaloacetic transaminase (SGOT), and albumin levels. Amylase levels were obtained in cases of prolonged abdominal pain (≥3 days). Left ventricular function was not monitored routinely. The latest National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) [11, 12] were used to grade severity of complications. Grade 1 complications are mild, require no intervention, and include asymptomatic complications. Grade 2 events require bedside medical management and medication. Grade 3 complications are severe and require additional intervention. Grade 4 complications are those that are life-threatening and/or result in chronic disability, and a Grade 5 complication is a death related to the adverse event. Complications, bilirubin levels, and liver enzymes were stratified against size of beads, the volume of reconstituted beads used (quantity of beads and doxorubicin), and the extent of embolization.

Data Analysis

Pairwise comparisons through multivariate analysis and cross-tabulations were performed to identify differences between the mean values of bilirubin, AST, ALT (in abovementioned time points), and the postembolic complications in relation to the levels of the independent variable (DC Bead™ and Beadblock size and quantity, extent of embolization). SPSS software version 11.5.0 was used, and the statistical level of significance was set on 0.05.

Results

Patients' demographics, underlying disease, and HCC characteristics are shown in Table 1. Results are reported as intention to treat. Procedures were 13.8–16.5% subsegmental (SS), 55.2–63.5% segmental (S), and in 22.8–28.3% involved more than one segment (>1S) (Table 2). Additional Beadblock was used in 8.9% of the procedures. MRI

Table 1 Demographics of 237 study participants

Variables	
Age (mean ± SD)	69.9 ± 5.9 (range 46–82)
Sex	
Male	175 (73.8%)
Female	62 (26.2%)
Etiology	
HBV	129 (54.4%)
HCV	35 (14.8%)
HBV + HCV	68 (28.7%)
Alcohol	2 (0.8%)
Steatosis	2 (0.8%)
Other, unknown	1 (0.4%)
Child stage	
A	116 (48.9%)
B	121 (51%)
Tumor/s diameter (mean ± SD)	6.9 ± 2.5 (range 3–14)

Table 2 Extent of embolization per session

	SS	S	>1S
Embo 1	16.5	55.2	28.3
Embo 2	15.8	57.5	26.7
Embo 3	13.8	63.5	22.8

S segmental embolization; *SS* supersegmental; *>1S* more than one segment

follow-up was performed in 181 patients (76.3%), whereas CT only was performed in 56 (23.7%). CEUS was performed in 177 patients (always as an additional evaluation and never as a single-imaging modality). The mean hospital stay was 1.37 days.

Using the EASL criteria at 6 months, complete response was achieved in 22.36%, partial response in 40.5%, stable disease in 27%, and progressive disease in 9.7%. Mean relative decrease in AFP (%) was 63.46 ± 20.2 ng/ml.

There were no periprocedural deaths. Overall, 30-day mortality was 1.26% (3/237): all procedure-related. Complications not including PES were recorded in 31 patients (13.08%). The type of complications and total numbers are seen in Table 3. Correlations with the size of the beads per session are displayed in Table 4. Procedure-related grade 5 complications were seen in 1.26% (3/237): one fatal periprocedural sepsis (death on day 11 postembolization) and two liver abscesses that led to death (days 16 and 29 postembolisation respectively) despite early percutaneous drainage.

Abscess formation was seen in six patients overall (2.53%; 6/237), also including the sepsis case of which the 50% led to death (3/6 patients). One liver abscess was treated conservatively (considered grade 2 complication). Two patients with liver abscess were treated with minor invasive procedures: one patient with abscess responded well to drainage and antibiotics, whereas in the second fine needle aspiration was performed for cultures and was subsequently treated with antibiotics (both cases classified as grade 3 complications). Abscess presented as body temperature >38°C, leucocytosis (white blood cell count >10.000/mm^3), and persistent severe right abdominal pain. The complete spectrum of manifestations of abscess with fever, leucocytosis, and pain was apparent 5–7 days postembolization. All patients had gas collection and liquidation of the embolized areas confirmed by CT and ultrasound. Three of the cases with abscess had diameter >6 cm. Four of the patients with abscess also had pleural effusion ipsilaterally. Serum AST and ALT levels were elevated three times the normal values in all abscess cases, whereas γ-GT and alkaline phosphatase were less affected in three patients. One patient had a small accumulation of perihepatic ascites at the time of abscess diagnosis. Table 4 reveals no correlation of abscess and size of the beads. In four cases with abscesses (3 of them fatal), additional Beadblock was used after DC Bead™.

Liver failure as grade 4 complication resulted in 1.68% of the cases (4/237) (irreversible liver failure that led to the discontinuation of TACE (3 after the first session and 1 after the third). Grade 2 liver function deterioration (in the form of transient encephalopathy and/or ascites and increase of liver enzymes) developed in 10 pts (4.2%), 3 of which had also cholecystitis (Table 3). The number of events of transient ascites or encephalopathy is seen in Table 4 and shows no correlation with the diameter of the beads used. No correlation was found with the extent of embolization ($p = 0.3$–0.44 across the three sessions).

Liver enzymes presented a statistically significant increase from base line at 1–5 days postembolization ($p = 0.002$–0.0001) that returned to preembolization levels at measurements 1 month after each procedure. AST, and ALT values were statistically significantly higher with smaller beads ($p < 0.0001$), while no differences were seen for SGOT and γ-GT (Table 5). Liver enzyme values were positively correlated with the extent of embolization (SS vs. S: $p < 0.0001$; SS vs. >S $p < 0.0001$; S vs. >S $p = 0.001$) and the quantity of beads (2 ml vs. 3 ml: $p = 0.2$; 2 ml vs. 4 ml: $p < 0.0001$ and 3 ml vs. 4 ml: $p = 0.009$). No significant changes of liver enzymes were seen at months 1, 3, 6 postembolization compared to baseline.

Mean bilirubin showed no statistically significant differences between baseline and months 1, 3, and 6 ($p > 0.1$). Mean bilirubin values for patients treated with small diameter vs. the larger diameters of beads presented low correlation comparing beads of 100 μm only (size 1) with sizes 2 and 3 ($p = 0.03$ and 0.04) and absence of correlation ($p = 0.99$) comparing size 2 to size 3. No correlation was found between bilirubin levels and quantity

Table 3 Complication incidents per session and overall incidence and grading

Complication	Embo 1 ($n = 237$) (% of incidents per session)	Embo 2 ($n = 221$) (% of incidents per session)	Embo 3 ($n = 189$) (% of incidents per session)	Overall (%)	Overall Score (%)
Abscess[a]	3 (1.3%)	3 (1.35%)	0	2.53	Grade 5: 1.26% Grade 3: 1.8%
Liver failure (irreversible)[a]	1 (0.42%)	2 (0.9%)	1 (0.5%)	1.68	Grade 4: 1.68%
Ascites/encephalopathy	8 (3.37%)	10 (4.52%)	8 (4.23%)	4.2	Grade 2: 4.2%
PES	205 (86.5%)	179 (80.99%)	100 (52.91%)	86.5	Grade 1: 57.81–75% Grade 2: 25–42.19%
Cholecystitis	12 (5.06%)	8 (3.6%)	7 (3.7%)	5.48	Grade 2: 2.95% Grade 4: 2.53%
Pleural effusion	7 (2.95%)	4 (1.8%)	5 (2.64%)	3.37	Grade 3: 0.42% Grade 1: 1.8%
GI bleeding	0	0	2 (1.05%)[c]	0.84	Grade 2: 1.05%
Pancreatitis	0	1 (0.45%)	0	0.42	Grade 2: 0.45%
Skin erythema	2 (0.8%)[b]	1 (0.45%)	0	0.84	Grade 1: 0.8%
Death[a]	3 (1.26%)	0	0	1.26	Grade 5: 1.26%

[a] Number of these complications represents incident per session. However, the total number of patients who had this complication in this series is of more clinical significance than the rate per session because the event occurs only once. The rate for abscess is 6 of 237 patients (2.53%) and 4 of 237 (1.68%) for irreversible liver failure

[b] Only one of the two was related to the procedure; the other was considered an allergic reaction

[c] Only one of the two was related to the procedure; the other was variceal bleeding

of beads ($p = 0.8$), but significant correlation was found with the extent of embolization ($p < 0.001$).

Overall postembolization syndrome (PES) expressed as right abdominal pain, fatigue, nausea, and vomit was observed in up to 86.5% (Table 3). Included in this rate are cases that required and those that did not require additional symptomatic medical treatment the second day after embolization (grades 1 and 2 complications). However, if we limited this diagnosis to grade 2, the incidence of this condition decreased to 25–42.19% across treatments. There was no statistical correlation of PES with the size of the beads (Table 4). Fever and pain in our study was recorded more often in more extensive embolization ($p < 0.005$). PES as a separate condition is not included in the Terminology Criteria for further quantification of severity.

Cholecystitis documented with ultrasound was seen in 3.6–5.06% across the three sessions (12/8/7 to first/second/third session). Cholecystitis manifested as right abdominal pain, positive Murphy sign on physical examination and on ultrasound, and was associated with wall thickening. The total number of patients who developed cholecystitis was 13 (5.48%; some patients developed cholecystitis more than once). Follow-up 1 month postembolization with MRI or CT revealed persistent but asymptomatic gallbladder wall thickening in six patients (2.53%). Incident of cholecystitis was grade 2 in seven patients (2.95%) and grade 4 in six (2.53%). *P* values shown in Table 3 reveal no correlation with the size of the beads used. A significant correlation with the extent of embolization was found for the first session only ($p < 0.0001$). All cases of cholecystitis were due to inadvertent embolization of the cystic artery. No other biliary abnormalities were observed in this series.

Pleural effusion documented by ultrasound before discharge from the hospital was observed in 1.8–3.7% across treatments (7/4/5 to first/second/third session). It was asymptomatic grade 1 severity, and in only one it was a grade 3 event requiring drainage (0.42%). In the series of the 237 patients, the total number of patients who developed pleural effusion was eight (3.37%; some patients developed pleural effusion more than once). Four of the patients with pleural effusion also had liver failure, and two had skin erythema. Table 4 shows that no correlation was found with the diameter of the beads used, but there was a correlation with the extent of embolization ($p < 0.005$).

A laboratory pancreatitis developed in one patient (0.42%) with elevated amylase (1.5XULN- upper limits of normal; grade 1). Two patients had gastrointestinal bleeding that was related to the procedure (0.84%); one patient had limited gastrointestinal bleeding associated with gastroduodenal erosions—most likely due to inadvertent embolization, which that was treated conservatively (grade 2). One additional patient had variceal bleeding within 1 month from embolization; this complication was

Table 4 Distribution of complications by bead size (per embolization session and overall frequency)

Complication	Embo 1 ($n = 237$)			Embo 2 ($n = 221$)			Embo 3 ($n = 189$)			Total		
Bead size	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3
Abscess	0 (0%)	1 (0.4%)	2 (0.9%)	0 (0%)	2 (1.6%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0.5%)	3 (0.5%)
N	69	102	62	33	55	41	54	89	48	156	246	151
Total observations	233 [$p = 0.2$]			129 [$p = 0.38$]			191			N 653 [$p = 0.084$]		
Liver failure leading to discontinuation of treatment	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0.9%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	3 (1.3%)	1 (0.2%)
N	69	102	61	60	103	55	54	88	49	183	293	165
Total observations	232 [$p = 0.26$]			218 [$p = 0.37$]			101 [$p = 0.25$]			N 641 [$p = 0.26$]		
Transient ascites/encephalopathy (incidents not patients)	2 (0.9%)	3 (1.4%)	3 (1.4%)	3 (1.4%)	4 (1.8%)	3 (1.4%))	3 (1.6%)	3 (1.6%)	0 (0%	8 (1.3%)	10 (1.6%)	6 (1%)
N	69	96	53	60	103	55	53	88	47	182	287	155
Total observations	218 [$p = 0.69$]			218 [$p = 0.89$]			188 [$p = 0.14$]			N 624 [$p = 0.9$]		
PES	58 (24.9%)	88 (37.8%)	56 (24%)	48 (25.4%)	81 (42.9%)	49 (25.9%)	25 (25%)	45 (45%)	30 (30%)	131 (25.1%)	214 (41%)	135 (25.9%)
N	69	102	62	49	87	53	25	45	30	143	234	145
Total observations	233 [$p = 0.55$]			189 [$p = 0.35$]			100 [$p = 0.4$]			N 522 [$p = 0.83$]		
Cholecystitis	2 (0.9%)	6 (2.6%)	4 (1.7%)	5 (2.3%)	2 (0.9%)	1 (0.5%)	2 (1.1%)	3 (1.6%)	2 (1.1%)	9 (1.4%)	11 (1.7%)	7 (1.1%)
N	69	102	62	60	102	55	54	89	46	183	294	162
Total observations	233 [$p = 0.56$]			217 [$p = 0.11$]			189 [$p = 0.96$]			N 639 [$p = 0.82$]		
Pleural effusion	0 (0%)	3 (1.3%)	4 (1.7%)	1 (0.5%)	3 (1.4%)	0 (0%)	1 (0.5%)	2 (1.0%)	2 (1.0%)	2 (0.3%)	8 (1.2%)	6 (0.09%)
N	69	102	62	60	102	55	54	89	49	183	293	166
Total observations	233 [$p = 0.047$]			217 [$p = 0.27$]			189 [p = 0.76]			N 642 [$p = 0.26$]		

Incidents of complications recorded once or twice only, i.e., GI bleeding, pancreatitis, and skin erythema are not included in this table

size 1, small beads of 100–300 μm only; *size 2,* 100–300 μm followed by 300–500 μm; *size 3,* those in which after 100–300 μm and 300–500 μm additional bead block of similar diameters was used

Table 5 Correlation values of liver enzymes stratified per diameter of beads used

	SGOT	AST	ALT	γ-GT
Size 1 vs. 2	0.5	<0.0001	0.0001	0.07
Size 1 vs. 3	0.2	<0.0001	0.0001	0.6
Size 2 vs. 3	0.04	0.4	0.4	0.2

size 1, small beads of 100–300 μm only; *size 2,* 100–300 μm followed by 300–500 μm; *size 3,* those in which after 100–300 μm and 300–500 μm additional bead block of similar diameters was used

assessed as not related to inadvertent embolization but was possibly related to the procedure.

Skin erythema was seen in a total of three patients. One was considered an allergic reaction (diffuse in the ventral and dorsal areas of the body). The other two patients (0.84%) presented a lower rib distribution asymptomatic grade 1. In both of these patients, there was a small amount of pleural effusion ipsilaterally. Because both of these patients were embolized through the inferior phrenic artery, it was attributed to advertent embolization of skin branches.

Doxorubicin related toxicity (alopecia, skin discoloration, mucositis, and bone marrow suppression) was not seen in our series. In this series, there are no sufficient data for left ventricular function because ejection fraction was not monitored routinely.

Of other complications post-TACE that are reported in the literature, no pulmonary or diaphragmatic complications were seen in this series. No tumor rupture was observed. There were no cases of renal function decompensation.

The extent of embolization was found to associate with the frequency of several complications, in particular, fever and pain ($p < 0.0001$ and 0.006, respectively). Other complications, such as pleural effusion, cholecystitis, and gastrointestinal bleeding, presented more frequently after segmental embolization compared with subsegmental or the embolization of more than one segments ($p = 0.005$, $p < 0.0001$, and 0.005, respectively).

Grading of complications is analyzed in Table 3. Overall grade 4 complications were seen in 13 patients (5.48%): notably 3 patients with lung abscess who eventually recovered after treatment, 4 patients who developed irreversible liver failure, and 6 patients with cholecystitis who presented persistent gallbladder wall thickening. Grade 5 complications were three liver abscesses cases that led to death (1.26%).

Discussion

Grade 4 complications developed in 5.48% and grade 5 in 1.26%. Overall, treatment-related complications in this series (not including PES and skin erythema) were recorded in 31 of the 237 patients (13.08%). If PES and skin erythema are added, the incidence of complications increases to 86%. These rates are within the previously reported with DC Bead™ in which overall treatment-related complications not including PES ranged between 4.2 and 16.1% [4–10, 13]. It is worth mentioning that in the cases included in this study are the results of the learning curve phase.

Treatment-related 30-day mortality was 0–1% in the published DC Bead™ studies [4–10, 13]. In our series, 30-day mortality was 1.26%—all cases were due to abscess formation. Overall, treatment-related deaths in DC Bead™ papers for HCC are reported as 0% [5–7, 9], 1% [8], and 3.7% [4]. The most severe complication in this study was abscess formation, which contributed to 100% of the 30-day mortality rate. Among the severe adverse events in the study by Poon et al., four occurred within 30 days from embolization (11.4%)—all associated with large tumors—and included liver rupture of a tumor of 10 cm, and liver failure in a patient with 22 cm HCC [5]. Kettembach et al. report 2% serious adverse events (including temporary liver failure and cholecystitis) [8]. In the study by Malagari et al., the incidence of complications was 4.2% ($n = 3/71$, including cholecystitis, liver abscess, and pleural effusion) [7]. In their study, liver abscess and cholecystitis were considered serious adverse events (2.8%) and were clearly related to the procedure.

In this paper, abscess was seen in six patients (2.53%; 6/237) of which in 50% it was fatal (grade 5). In the published series with DC Bead™, abscess formation was seen in 3.7% (2/27) and 1.4% (1/71) in the Varela and Malagari papers respectively [4, 7]. In the first of these two series, one abscess healed with conservative treatment and the other lead to patient death 3 months after the procedure from liver failure [4]. In the Poon's study with DC Bead™, no abscess was reported but only a spontaneous bacterial peritonitis [5]. The more alarming signs for the diagnosis of abscess were morning fever, leucocytosis, pain, and chills present from the fourth to fifth day postembolization—features that are not seen in PES. Similar to our results, none of the patients in the DC Bead™ series had any known predisposing factor (i.e., bilioenteric anastomosis or portal thrombosis) [14], whereas this complication developed despite systematic antibiotic prophylaxis. Regarding the size of beads and extent of embolization, no correlation was found. However, the strength of statistics is low because of the small numbers, but at least it merits mentioning that no abscesses were seen in patients who were treated only with the smallest bead diameter (Table 4). Of our patients who developed this complication, three had tumors >6 cm and three had smaller lesions. Therefore, our data do not show a predilection of this complication to large tumors with extensive necrosis postembolization.

However, because all patients who developed abscess had been embolized with increased quantity of additional Beadblock, we may infer that overembolization (with the use of additional embolic material after the initial quantity of the two vials of DEBDOX) maybe a risk factor to the development of this complication. Therefore, in large tumors in which intratumoral vascularity cannot be entirely obliterated with the use of the two vials of DEBDOX, additional embolization should be avoided or performed with small additional quantity. Staging of the procedure should be preferred. In a letter to the editor referring to the study by Varela et al., Del Poggio et al. speculated that abscess formation is greater with DEBDOX compared with c-TACE inferring that the beads are not reabsorbed [15]. However, the stronger evidence provided by the randomized trial comparing DEBDOX with c-TACE (PRECISION V) did not confirm this hypothesis [10].

Abscess is attributed to the inoculation and migration of blood circulating bacteria to the ischemic and necrotic area of the lesion postembolization [14, 16]. The frequency of this complication in c-TACE is 0.26–3.12% [14, 16–21]. These data—compared with ours—indicate that abscess formation occurs if not lower than at least at equally frequent rates with c-TACE.

Irreversible acute liver failure that leds to discontinuation of TACE in our series developed in 1.68% of our patients (classified as grade 4 complication by the National Cancer Adverse Events grading). Overall, liver toxicities developed in 11% in the DC Bead™ embolization arm of the PRECISION V study, of which 3.6% were grade 3 and 5.4% were grade 4 [10, 13]. Similarly, low rates were observed in other studies with DC Bead™; in one patient in Poon's series (2.85%; 1/35) and in one patient who developed liver abscess and eventually died from liver failure 3 months postembolization in the series by Varela et al. [4, 5].

Irreversible acute liver failure as a complication of TACE is attributed to inadvertent embolization of the adjacent to the lesion liver parenchyma with preexisting impaired liver function and portal vein thrombosis (parameters recognized as risk factors for this complication) [20, 22, 23]. In our series, the low rate of this complication (1.68%) is attributed to the exclusion of Child Pugh C patients, cases with portal vein thrombosis, and the selectivity of the procedures. We also showed that there was no correlation of liver failure with the size of the beads that we used in this series. In c-TACE literature studies that have excluded Child C cirrhosis, the reported frequency ranges from 2.1 to 20% [1, 17, 20, 21, 24–26]. The high rates are due to the fact that embolization sessions frequently involved large liver areas. Llovet et al. [2] reported liver failure without progression in 5% and hepatic failure that led to death in 4 of 40 patients in the c-TACE group (12.5%) despite the exclusion of patients with Child Pugh C cirrhosis.

Grade 2 liver function deterioration (in the form of transient encephalopathy and/or ascites and increase of liver enzymes) developed in ten patients (4.2%), three of which also had cholecystitis. The number of events of transient ascites or encephalopathy is seen in Table 4 and shows no correlation with the diameter of the beads used. In addition, no correlation was found with the extent of embolization ($p = 0.3$–044 across the three sessions). These rates are similar to those of other DEBDOX papers and also comparable with studies with conventional TACE that excluded Child C patients. Although there are various reports of severity criteria in the literature overall, in 27 trials c-TACE encephalopathy and increasing ascites are reported from 1.8% (range, 0–16%) to 8.3% (range, 0–51.6%) [20, 22, 23].

Regarding the liver enzymes, our data show that although there is a statistically significant elevation of liver enzymes 3–5 days postembolization ($p = 0.002$–0.0001), there are no statistically significant differences from baseline 1 month after the procedure. It is interesting to acknowledge in our study that these transient elevations were higher when 100–300 μm were used compared with larger sizes—a fact that reaches statistical significance for AST and ALT but not for SGOT or γ-GT (Table 5). However, the degree of elevation was of no clinical significance with the diameters used in our series. A transient increase of liver enzymes also is seen in c-TACE [26] and was observed in all other studies with DC Bead™—returning to normal 1 month after the procedure [10, 13]. In the large, randomized comparison of DC Bead™ with c-TACE [10, 13], the mean postprocedural ALT increase in the DC Bead™ group was 50% less compared with the c-TACE group and 41% less for the AST at a level of $p < 0.001$ [13]. Similar observations with DC Bead™ embolization were made in animal studies in which a transient increase of liver enzymes was present until day 14 postembolization and returned to near or below pretreatment levels by days 28–90 [27]. Increase of liver enzymes was more significant with the smaller beads compared with the larger ones. The higher elevation of liver enzymes with smaller loaded beads was attributed to the more distal nature of the embolization and the elimination of collateral flow [27]. Although in this study they used healthy porcine hepatic model to demonstrate the significant local toxicity effects of smaller beads, it is expected that rapidly dividing cells within HCC in combination with the increased concentration and extent of exposure to doxorubicin become more susceptible to damage and antitumoral activity can be even higher.

Bilirubin levels showed no difference between the different bead sizes that we evaluated in this study, but levels

correlated with the extent of embolization. Lammer et al. in the Precision V randomized trial showed that there was a greater increase of bilirubin in the c-TACE group compared with the DC Bead™ group (mean 13.53 ± 73.89 μmol/L for the c-TACE and 5.3 ± 15.13 μmol/L for the DC Bead™) [10, 13]—a fact that was possibly related to the additional offending action of lipiodol.

Postembolization syndrome is a self-limited condition that is characterized by the combination of right abdominal pain, fever fatigue, nausea, and vomiting [28]. PES is not described as an entity in the Common Terminology Criteria for Adverse Events and no accepted severity grading has been proposed [11, 12]. Chang et al. and Chung et al. in their papers that report PES in detail define PES as body temperature >38°C and pain that requires analgetics for more than a week [22, 23]. In our paper although PES presented in 60.75–85.65% across the three sessions, grade 2 PES requiring systematic administration of nonsteroidal anti-inflammatory drugs was confined to 24–45%. Because of the lack of standardized criteria, PES is recorded with large differences among the different trials. PES was observed in 27 patients in Poon's series with DC Bead™ (77.1%) and the symptoms were characterized as mild [5]. In the study by Varela et al., it was reported in 10 of the 27 patients (37%), and it responded well to acetaminophen or tramadol [4]. After the second embolization, 18% of their patients presented PES with 32% mild pain and 14% nausea and vomiting; no symptoms remained after 1 week [4]. Malagari et al. reported PES in all patients, which lasted for 1 to 5 days, but no quantification of the severity is reported in any of their previous papers [7]. Lammer et al. reported very low rates of PES in both the c-TACE and DC Bead™ groups in the randomized study comparing these two treatments reaching 25.9 and 24.7% respectively [10]. This complication also is reported frequently in c-TACE at rates ranging from 15.1 to 100% [20, 22, 28–32].

The cause of this condition is attributed to the extent of tumor necrosis and is considered as a positive prognostic sign of increased local response to treatment [22, 23, 33]. In series of c-TACE, it also has been attributed to extensive ethiodol embolization [33]. This explanation of PES in c- TACE has been questioned by Paye et al. and Wigmore et al., who suggest that PES is an adverse event than tumor response and is attributed to damage of the adjacent liver [34, 35]. In their paper, Paye et al. showed that increased alanine aminotransferase (cytolysis) developed in 55.17% of their patients and correlated positively with PES. On the contrary they found that PES was not seen in the absence of cytolysis, regardless of tumor necrosis. However, their study was retrospective and c-TACE was performed with lobar catheterization without selective approach (Paye). Wigmore et al. also correlated PES with cytolysis that was present in 85% of their patients, despite the fact that they performed selective embolization in 89% of the sessions. In this study, we found no correlation of PES with the diameter of beads. Fever and pain in our study correlated with the extent of embolization ($p < 0.005$). The low toxicity rates in our study despite the fact of high rates of PES support that PES is a result of tumor necrosis rather than liver toxicity.

Cholecystitis in this series was observed in 2.95–5.06% across treatments: grade 2 complication 2.95% and grade 4 in 2.53%. Cholecystitis was called in the presence of the combination of right abdominal pain, positive Murphy sign on physical examination, and ultrasound associated with mural thickening. All cases responded well conservatively. We found no correlation with the size of the beads. However, it was found that it was seen more frequently in segmental embolizations compared with those of subsegmental distribution ($p < 0.0001$), and therefore, it can be considered as the result of inadvertent embolization even if the cystic artery is not seen fluoroscopically within the territories of the embolized vessels. Cholecystitis is reported in 1.6–3.3% in other DC Bead™ papers [7, 8] and seems to present at relatively higher rates in this series. Besides the acknowledgement that it represents inadvertent embolization of the cystic artery, it is speculated that it can be falsely diagnosed as PES if ultrasound is not performed. Cholecystitis as complication of c-TACE is reported in 0.2–4.6% in large series [17, 19, 21, 36] responding successfully with conservative treatment, whereas percutaneous cholecystostomy may be required in the presence of gangrenous cholecystitis, perforation, or emphysematous cholecystitis [37]. We consider that in patients with right abdominal pain postembolization ultrasound should be used to differentiate cholecystitis from PES.

Biliary abnormalities other than cholecystitis are reported in conventional TACE in 0.5–2% of patients, of which biloma represent 71%, focal biliary tree stenoses 17%, and diffuse dilatation of intrahepatic bile ducts 12% [19, 38–40]. Biliary complications are attributed to TACE-induced ischemia to the bile ducts because bile ducts do not have a dual blood supply but they receive blood from the peribiliary plexus from the hepatic arteries [38, 39]. In this series, none of these complications was observed regardless of bead size used. The risk of embolization of the peribiliary plexus may be a consideration for particles/beads <100 μm, which we did not use in this series, because for these small diameters safety has yet to be proved.

Pleural effusion in our series was seen in 1.8–3.7% across treatments, and no correlation was found to the diameter of the beads; however, it correlated with the extent of embolization and therefore considered as the result of inadvertent embolization. It was seen 1 to 5 days postembolization; it was indolent/grade 1 complication in

all cases but one with liver abscess that required drainage. We infer that it was associated with the liver failure in four of our patients and with proximity of the tumor to the diaphragm. Pleural effusion was reported in only one patient (3.33%) from Poon's DC Bead™ series [5]. It is most likely that the increased incidence of asymptomatic pleural effusion in this series is due to increase detection associated to the frequent performance of ultrasound before discharge from the hospital in our institution.

Upper gastrointestinal tract bleeding that was treatment-related in our series was observed in 0.84% and was procedure-related. GI bleeding also is a known complication of c-TACE occurring in approximately 5.35% (range, 0–22%) leading to death in 0.2% [17, 20, 40].

Procedure-related skin erythema was observed in two patients in this study (0.84%) after embolization of inferior phrenic artery giving parasitic arterial supply to subdiaphragmatic tumors. Skin erythema was grade 1 in these two cases and was attributed to inadvertent embolization of vessels supplying the skin originating from extrahepatic collaterals that had developed in the superior surface of the liver. Similar cases have been observed after c-TACE embolization of the inferior phrenic artery but also the hepatic falsiform artery, internal mammary artery, intercostal arteries, and epigastric artery [41, 42].

Systemic toxicity, including bone marrow suppression, alopecia, skin discolouration, mucositis, or clinically detectable cardiac failure, was not recorded in this series. We had recorded two patients with mild alopecia in patients who had serial c-TACE before the DEBDOX treatments who are not included in this patients' series (unpublished data). However, systemic toxicity was reported in 11.8% in the DC Bead™ group in the randomized study by Lammer et al. [10]. PRECISION V study and Vogl et al. report that these events were significantly reduced in the DC Bead™ group compared with the c-TACE group ($p = 0.0001$) [10, 13]. In the PRECISION V patient series, alopecia was reported in 2.2% of the DC Bead™ group compared with 19.4% of the c-TACE group [10].

Other complications described in the literature include pulmonary, tumor rupture, and diaphragmatic weakness. No cases of pulmonary complications were recorded in any of the DC Bead™ series—also including this study. Pulmonary embolism is an uncommon but potentially fatal complication if a tumor arteriovenous shunt is missed [43]. It has been reported in bland embolization performed with particles <100 μm. In the study by Maluccio et al., 2 of 322 patients died from emboli that passed to the pulmonary circulation [44]. However, our study confirms that pulmonary embolization is not likely with beads of 100–300 μm and 300–500 μm, which were used in this study. Pulmonary embolization also has been reported after c-TACE [22, 36]. Tumor rupture is a rare complication of TACE, which has been associated with large subcapsular or exophytic tumors [45, 46]. In our series, we observed no rupture. One case was reported in Poon's series with doxorubicin loaded DC Bead™ in a patient with a 22-cm HCC [5]. Other DEBDOX series report no other rupture cases. In c-TACE, it is reported in 0.6–0.8% with a 50% mortality rate [22, 36, 46]. Diaphragmatic weakness is a rare complication reported after c-TACE but was not evaluated in this study with appropriate imaging tests [47]. No signs of this complication were seen on CT/MR imaging postembolization in our series.

The contribution of this study is the correlation of complications with bead diameters, extent of embolization, and quantity of loaded beads—providing correlation with the quantity of doxorubicin used. It is the largest series of DEBDOX in the literature. It has shown that: (1) small DC Bead™ calibers of 100–300 μm are not associated with increased complications or liver function deterioration and are safe to be used in tumors <6 cm in diameter in the absence of fluoroscopically visualized shunt; (2) DEBDOX is not associated with increased liver toxicity, despite the high doses of doxorubicin (37.5 mg/ml of constituted beads reaching up to 150 mg per session); (3) the extent of embolization remains a risk factor for the development of complications; and (4) procedure-related mortality is 1.26%. The most severe and life-threatening complication is liver abscess, which presented with a frequency of 2.53%. It is inferred that overembolization with additional beads may contribute to this complication.

In conclusion, in this series it is demonstrated that the rate of complications from DC Bead™ embolization loaded with doxorubicin at the level of 37.5 mg/ml of reconstituted beads is low, with no increased side effects from the use of beads of diameters of 100–300 μm.

Conflict of interest The authors claim no conflict of interest.

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