The development of early ascites is associated with shorter overall survival in patients with hepatocellular carcinoma treated with drug-eluting embolic chemoembolization

CURRENT STATUS: UNDER REVISION

BMC Gastroenterology

María Pipa-Muniz
Hospital de Cabuenes

ORCiD: https://orcid.org/0000-0003-2176-0423

Susana Sanmartino
Hospital Universitario Central de Asturias

Alicia Mesa
Hospital Universitario Central de Asturias

Carmen Alvarez-Navascués
Hospital Universitario Central de Asturias

Maria Luisa González-Diéquez
Hospital Universitario Central de Asturias

Valle Cadahía
Hospital Universitario Central de Asturias

José Eduardo Rodríguez
Hospital Universitario Central de Asturias

Florentino Vega
Hospital Universitario Central de Asturias

Manuel Rodríguez
Hospital Universitario Central de Asturias

Serafín Marcos Costilla-García
Hospital Universitario Central de Asturias

Maria Varela Calvo
Abstract
Background: A single-centre cohort study was performed to identify the independent factors associated with the overall survival (OS) of hepatocellular carcinoma (HCC) patients treated with transarterial chemoembolization with drug-eluting beads (DEB-TACE).

Methods: A total of 216 HCC patients who underwent DEB-TACE from October 2008 to October 2015 at a tertiary hospital were consecutively recruited. The analysis of prognostic factors associated with DEB-TACE complications was performed.

Results: The objective response (OR) rate (Modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria) to the first DEB-TACE (DEB-TACE-1) was 70.3%; the median OS from DEB-TACE-1 was 27 months (95% confidence interval (CI), 24-30). In the multivariate analysis, basal Barcelona Clinic Liver Cancer (BCLC) stage and serum alkaline phosphatase were independent factors for survival following DEB-TACE-1. The most important clinical event associated with poor survival was the development of early ascites after DEB-TACE-1 (median OS, 17 months), which was closely related to the history of ascites, albumin and hemoglobin but not to tumour load or to response to therapy.

Conclusions: Early ascites post-DEB-TACE is associated with the survival of patients despite adequate liver function and the use of a supra-selective technical approach. History of ascites, albumin and hemoglobin are major determinants of the development of early ascites post-DEB-TACE.

Declarations
Ethics approval: The protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the Hospital Universitario Central de Asturias (Approval No. 120/19).

Consent to participate (provide consent): yes. All patients provided signed consent to perform the DEB-TACE and the follow-up CT scan. No specific individual consent was obtained regarding the publication of data.

Consent to publish: not applicable

Availability of data and materials: The datasets used and/or analysed during the current study
are available from the corresponding author on reasonable request.

**Competing interests:** Pipa-Muñiz M, Sanmartino S, Mesa A, Cadahía V, Rodríguez JE, Vega F, and Costilla-García SM: none. Álvarez Navascués C: speaking fees and advisory roles for Gilead, Abbvie, and Intercept. González-Diegués ML: speaker fees from Gilead, Abbvie and Novartis and consultancy fees from Gilead. Manuel Rodríguez M: speaking fees and advisory fees from Gilead, Abbvie, Intercept, and MSD. Varela M: speaker fees from Bayer and Gilead; consultancy fees from Roche, Bristol-Myers-Squibb, SIRTEX, Bayer, IPSEN, and BTG-Boston.

**Funding:** none

**Authors’ Contributions:** Concept and design of the study: M Varela and M Pipa; data collection: M Pipa, S Sanmartino, A Mesa, C Alvarez-Navascués, ML González-Diégués, V Cadahía, JE Rodríguez, F Vega; statistical analysis: M Pipa, M Rodríguez, M Varela; analysing the results and writing of article: M Pipa, S Sanmartino, A Mesa, JE Rodríguez, SM Costilla-García, M Rodríguez and M Varela. All authors approved the last version of the manuscript.

**Acknowledgements:** Susana Díaz-Coto and Pablo Martínez-Camblor (statistical support).

**Background**

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and is the fourth-leading cause of cancer-related mortality\(^1,2\). According to the European and American guidelines\(^3,4\), transarterial chemoembolization (TACE) is the first-line treatment for asymptomatic patients with Barcelona Clinic Liver Cancer (BCLC) B stage disease (which includes multinodular HCC beyond the Milan criteria, without portal invasion or extrahepatic disease) and compensated liver function. TACE is performed not only in BCLC-B patients but also in early-stage patients if resection, ablation or liver transplantation is not feasible. Thus, TACE candidates represent a heterogeneous group of patients with variable tumour burden and liver function\(^5\).

TACE is an image-guided transcatheter tumour therapy that has an ischaemic and cytotoxic effect on tumour tissue. The use of drug-eluting embolic chemoembolization (DEB-TACE) is safe and effective\(^6,7\). However, an improvement in the overall survival (OS) of DEB-TACE compared to that of
conventional TACE has not been confirmed\textsuperscript{8,9}.

Considering the heterogeneity of TACE candidates, patient selection must be carefully carried out. Underlying chronic liver disease is exacerbated by this procedure, especially in patients with diminished liver reserve\textsuperscript{10}. Several algorithms have been recently reported to predict HCC prognosis in an attempt to optimize chemoembolization treatments, but few data have been obtained from DEB-TACE procedures\textsuperscript{11–13}. Moreover, there is also scarce information about the influence of post-DEB-TACE events on OS and hepatic decompensation.

A prior meta-analysis of untreated patients in randomized clinical trials for HCC reported that ascites is strongly linked to a worse outcome in intermediate/advanced BCLC stages\textsuperscript{14}.

Some authors have suggested that a time-dependent covariate analysis that includes all the rounds of DEB-TACE, clinically relevant events and subsequent therapies is needed to properly evaluate the factors that influence the survival of patients.

The aim of our study was to identify predictive factors for survival in HCC patients treated with DEB-TACE, taking into account the basal characteristics, the procedure, the response to treatment and the impact of events after the first DEB-TACE (DEB-TACE-1), in a time-dependent covariate analysis.

Methods

Patients:

From October 2008 to October 2015, patients with HCC diagnosed according to the European Association for the Study of the Liver (EASL) guidelines who were selected for DEB-TACE were referred to a tertiary academic university hospital and were prospectively registered.

The inclusion criteria were as follows: 1) HCC that was diagnosed in the early stage but was not eligible for resection, ablation or liver transplant; 2) HCC with an intermediate BCLC stage; 3) compensated cirrhosis with normal or mildly altered liver function, without ascites or encephalopathy at the time of DEB-TACE; 4) an asymptomatic status, with an ECOG performance status 0; and 5) approval for DEB-TACE after evaluation by the multidisciplinary tumour board. Portal thrombosis, impaired liver function, decompensated cirrhosis, performance status > 0, extrahepatic disease and
contraindication or impossibility for catheterization or chemoembolization were considered exclusion criteria. Patients included in clinical trials or awaiting liver transplantation for whom DEB-TACE was used as a bridge therapy were excluded.

We defined clinically significant portal hypertension (CSPH) as the presence of prior cirrhosis decompensation, oesophageal or gastric varices or low platelet counts (lower than $100 \times 10^9$/mm$^3$). Early ascites was defined as the appearance of ascites after the first round of DEB-TACE.

Clinical, biochemical and radiological examinations were performed at baseline and prior to every DEB-TACE procedure. No general sedation was used, and no antibiotic prophylaxis was indicated, except in patients with prior endoscopic retrograde cholangiopancreatography. If the prothrombin rate was lower than 50% or if the platelet count was less than $50 \times 10^9$/mm$^3$, fresh-frozen plasma was administered and/or platelet infusion was performed. Pain during the procedure was individually managed, and patients were discharged 24 hours later, unless complications were observed.

**DEB-TACE procedure:**

Drug-eluting beads® were loaded with doxorubicin following the manufacturer’s instructions the day before the procedure. Particles that were 300-500 microns (µm) were used until March 2013, when these particles were replaced by 100-300-µm beads to further penetrate the tumour. If embolization was not completely achieved unloaded microspheres were employed to complete the artery obstruction.

Selective angiography of the common hepatic artery was carried out as well as of the right and left hepatic arteries. A supraselective approach for tumour vessels was achieved by using a Progreat 2.7 (Terumo®) microcatheter with 0.21, 0.16 or 0.14 Terumo® microwires, and DC-Beads® were then injected. After angiographic control, the 4F catheter and the introducer were removed, and manual compression was applied.

Starting in February 2015, Cone-Beam-Computed-Tomography software (CBCT, Syngo DynaCT, Siemens®) with contrast injection was employed to help during vascular catheterization, especially if
the nodule was not visible at basal angiography or was in intersegmental nodules, when lesions were proximal to the diaphragm and when extrahepatic vascularization was evaluated. Once the procedure was finished, CBCT without intraarterial contrast was used to evaluate embolization.

**Follow-up:**

All patients received a clinical, analytical and radiological follow-up 6 weeks after each DEB-TACE procedure. Response to treatment was evaluated by contrast-enhanced computed tomography (CT) according to the Modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria\(^\text{17}\), and results were presented to the multidisciplinary tumour board. If partial response, stable disease or treatable progression were observed, a subsequent DEB-TACE was planned\(^\text{18}\). Patients with untreatable progression were evaluated for systemic therapy. Objective response (OR) was defined as the sum of complete response and partial response. The disease control rate (DCR) was defined as the OR as well as the stable disease rate.

**Statistical analysis:**

Quantitative variables are expressed as the median and interquartile range, and categorical variables are expressed as the count and proportion. Continuous quantitative variables were categorized according to the median value for the analysis. Differences between subgroups were evaluated with a Chi-squared test, Fisher’s exact test and a Student’s T-test, depending on the type of variable. A conventional p-value of less than 0.05 was considered significant.

Patient survival probability was estimated using the Kaplan-Meier method. OS was calculated from DEB-TACE-1 to death or to the end of follow-up for two periods: from baseline (\(t_0\)), taking into account clinical, demographic and radiological data prior to DEB-TACE-1, and from 6 weeks after DEB-TACE-1 (\(t_1\)), also considering complications and the radiological response to treatment.

Variables with univariate significance (p<0.10) and clinical relevance were included in the Cox proportional hazards model for the multivariable analysis with the forward selection method.
The factors associated with the development of early ascites were analysed, bearing in mind the baseline characteristics, the response to treatment and other complications. The time was censored at ascites development, death or the second DEB-TACE (DEB-TACE-2).

All calculations were performed with SPSS version 23 (SPSS Inc., Chicago, IL).

An additional time-dependent covariate analysis was performed by using R (www.r-project.org) to identify factors associated with mortality. A backward method based on the Akaike information criteria was employed.

The protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the Hospital Universitario Central de Asturias (Approval No. 120/19).

Results
From October 2008 to October 2015, 242 consecutive patients with HCC who were diagnosed according to EASL guidelines were referred for DEB-TACE, but only 216 of these patients met the inclusion criteria. Table 1 summarizes the baseline characteristics. The predominant aetiology of liver disease was alcohol (45%), followed by hepatitis C virus infection (36%). Most of the patients were BCLC-B (59.7%) and Child-Pugh class A 5 (64%). Sixty-one percent had oesophageal varices, 32% were on a low-salt diet and / or diuretic and 73% presented CSPH.

The median number of DEB-TACE sessions was 2 (IQR, 1-3), and a total of 443 procedures were performed (Figure 1).

The median follow-up was 26.5 months, and follow-up was censored at death, loss to follow-up or the last visit (April 1, 2019).

Response to treatment:
According to the mRECIST criteria at week 6 after DEB-TACE-1, complete response was achieved in 25.5% of patients, partial response was achieved in 45% and stable disease was achieved in 11%; in contrast, 35 patients presented progressive disease after DEB-TACE-1 (69% BCLC-B and 31% BCLC-C).
**Follow-up and post-DEB-TACE events:**

During the follow-up, DEB-TACE was discontinued in 71 patients after the first session. **Figure 1** shows the different causes for the discontinuation of DEB-TACE after the first or subsequent rounds. Post-procedure events within the first 90 days after DEB-TACE-1 are described in **Supplementary table 1.** A total of 73 of 216 patients experienced post-DEB-TACE-1 events (33.7%): 23 patients (31.5%) experienced radiological events, 41 patients (56.2%) experienced clinical events and 9 patients (12.3%) experienced both clinical and radiological events. Ascites was the most frequent adverse event and was present in 27 patients.

At the end of follow-up, 27 patients were alive; 70 patients had moved to sorafenib and 9 to second-line regorafenib.

**Overall Survival:**

The median OS from DEB-TACE-1 was 27 months (95% confidence interval (CI), 24.193-29.807) (**Figure 2**). The cumulative survival rates were 82%, 58%, 32% and 16% at 1, 2, 3 and 5 years, respectively.

Univariate and multivariate analyses prior to DEB-TACE-1 (**t₀**) and at 6 weeks after DEB-TACE-1 (**t₁**) are shown in **Tables 2 and 3.** The independent factors associated with OS at **t₀** were BCLC stage and alkaline phosphatase, and the independent factors associated with OS at **t₁** were albumin, BCLC stage, alkaline phosphatase and ascites. A second model with the independent factors of survival in the **t₁** period was constructed that included the liver function, as estimated by the Child-Pugh score, and DCR, as estimated by mRECIST, after DEB-TACE-1.

**Post-DEB-TACE events:**

The most important clinical event associated with shorter survival was the presence of ascites after DEB-TACE-1 (**Figure 3**). Patients with ascites (n=27) had a median OS of 17 months (95% CI, 8.566-
25.434; p < 0.05); in contrast, patients without ascites had a median OS of 28 months (95% CI, 25.519-30.481). Cumulative survival rates at 1, 2, 3 and 5 years are shown in Figure 3.

Baseline characteristics associated with the development of ascites are shown in Supplementary table 2. History of ascites decompensation, hemoglobin and albumin were independently related to the development of early ascites (Table 4). The development of ascites after DEB-TACE was independent of the radiological response (the OR rate was similar in patients who developed ascites, indicating that this was not related to tumour progression, p=0.13). The median time from DEB-TACE-1 to the onset of early ascites was 40 days (interquartile range (IQR), 33-57), and the median time between DEB-TACE-1 and DEB-TACE-2 was 140 days (IQR, 81 -177). Lastly, 9 patients recovered from hepatic decompensation and received DEB-TACE-2.

In the time-dependent covariate analysis, the variables that were independently associated with survival were basal alpha-fetoprotein (HR 1.66; 95% CI, 1.31-2.10; p < 0.001), time-dependent bilirubin (HR 4.47; 95% CI, 1.80-11.09; p < 0.001) and time-dependent alkaline phosphatase (HR 1.68; 95% CI, 1.41-2.01; p < 0.001) (Supplementary tables 3 and 4 and Supplementary figure 1).

Discussion

Several publications have described the safety of DEB-TACE6–9, but an in-depth analysis of the impact of adverse events on patient progression has not been examined. Our study determined that the development of early ascites was negatively related to the overall survival of compensated patients treated with DEB-TACE. This finding was related to low albumin, low hemoglobin and prior episodes of clinical ascites. The presence of significant portal hypertension and/or worse liver function might suggest that patients are predisposed to complications in chemoembolization procedures and to the consequent impairment in OS. Currently, the presence of CSPH precludes patients from undergoing surgical resection for HCC19, but less attention has been paid to other loco-regional therapies. However, two studies have recently reported that CSPH is a major negative prognostic factor in patients treated with DEB-TACE10,20.

It should be noted that the OS of this cohort was lower than that at other sites21–29(Supplementary
table 5), despite similar patient selection, supra-selective procedures and response to therapy. We speculate that although alcohol aetiology is not an independent predictor of survival, alcohol consumption can impair liver function due to acute-on-chronic liver failure\textsuperscript{30} or alcoholic hepatitis\textsuperscript{31,32}. The poor prognosis of alcohol-related HCC has been specifically observed in some French cohort studies\textsuperscript{33,34} and in patients treated with Y\textsuperscript{90}.radioembolization in the SORAMIC study\textsuperscript{35}. Indeed, these patients had more comorbidities than those affected by hepatitis C, and in some cases, refused to undergo additional sessions of DEB-TACE. In our series, 6 patients presented a second primary tumour after DEB-TACE (1 pyriform sinus, 1 bladder, 1 colorectal and 3 lung cancers), and 13% of patients died from other causes that were not related to tumour progression or cirrhosis decompensation. Finally, some post-DEB-TACE events were handled out of the tertiary hospital, and the suboptimal care of cirrhosis complications could have influenced the survival of our patients. This study had several weaknesses. This was an observational cohort study that was performed over many years, during which changes in the state-of-the-art technology occurred. However, the multidisciplinary core team and the main interventional radiologists did not change over the course of the study. Furthermore, nor the change in the DEB particles size (March 2103) nor the introduction of CBCT (February 2015) have influenced the objective response rate or the global overall survival (data not shown).

The second weakness was that no clinical events were identified in the time-dependent covariate analysis.

In contrast, the main advantage of this study was the prospective collection of a large number of patients who were treated with a homogeneous protocol and the collection of adverse effects after DEB-TACE, including asymptomatic radiological abnormalities.

Conclusions
In conclusion, adverse events reduce OS following DEB-TACE, especially when ascites is present. Although compensated chronic liver disease is a requirement for loco-regional therapy, the appearance of early ascites seems to be related to the history of prior ascites, lower hemoglobin levels and lower albumin. These factors could be relevant for properly select the best candidates for
DEB-TACE when different therapeutic options are available.

Abbreviations

BCLC: Barcelona Clinic Liver Cancer

CBCT: cone-beam computed tomography

CI: Confidence interval

CT: Computed tomography

CR: Complete response

CSPH: clinically significant portal hypertension

CDR: disease control rate

DEB-TACE: drug-eluting embolic chemoembolization

EASL: European Association for the Study of the Liver

HCC: Hepatocellular carcinoma

HR: Hazard ratio

IQR: interquartile range

mRECIST: modified Response Evaluation Criteria in Solid Tumors

OR: objective response

OS: overall survival

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394-424.

2. Fact Sheets by Population-Globocan-IARC [Internet]. http://globocan.iarc.fr/Pages/factsheets_population.aspx

3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018; 69: 182-236.

4. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for
the Study of Liver Diseases. Hepatology 2018; 68: 723-750.

5. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018 Mar 31;391(10127): 1301-1314.

6. Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007; 46: 474-481.

7. Poon RT, Tso WK, Pang RW et al. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. Clin Gastroenterol Hepatol 2007; 5 (9): 1100-8.

8. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010; 33: 41-52.

9. Golfieri R, Giampalma E, Renzulli M, et al. Randomised controlled trial of doxorubicin-eluting beads vs. conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 2014; 111: 255-264.

10. Kim NH, Lee T, Cho YK, Kim BI, Kim HJ. Impact of clinically evident portal hypertension on clinical outcome of patients with hepatocellular carcinoma treated by transarterial chemoembolization. J Gastroenterol Hepatol. 2018; 33(7): 1397-1406.

11. Sieghart W, Hucke F, Pinter M, et al. The ART of Decision Making: Retreatment With Transarterial Chemoembolization in Patients With Hepatocellular Carcinoma. Hepatology. 2013; 57 (6): 2261-73.

12. Kadalayil L, Benini R, Pallan L, et al. A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. Ann Oncol. 2013; 24 (10): 2565-70.

13. Adhoute X, Penaranda G, Naude S, et al. Retreatment with DEB-TACE: The ABCR...
14. Cabibbo G, Enea M, Attnasio M, Bruix J, Craxì A, Cammà C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. 2010; 51(4): 1274-83.

15. García-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal Hypertensive Bleeding in Cirrhosis: Risk Stratification, Diagnosis, and Management: 2016 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2017; 65 (1): 310-335.

16. Prajapati HJ, Xing M, Spivey JR, et al. Survival, efficacy, and safety of small versus large doxorubicin drug-eluting beadsDEB-TACE chemoembolization in patients with unresectable HCC. AJR Am J Roentgenol. 2014; 203(6): W706-14.

17. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010; 30(1): 52-60.

18. Forner A, Gilabert M, Bruix J, Raoul JL. Treatment of intermediate-stage hepatocellular carcinoma. Nat Rev Clin Oncol. 2014; 11 (9): 525-35.

19. Berzigotti A, Reig M, Abraldes JG, Bosch J, Bruix J. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: a systematic review and meta-analysis. 2015; 61(2): 526-36.

20. Choi JW, Chung JW, Lee DH, et al. Portal hypertension is associated with poor outcome of transarterial chemoembolization in patients with hepatocellular carcinoma. Eur Radiol. 2018; 28(5): 2184-2193.

21. Malagari K, Pomoni M, Moschouris H, et al. Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. Cardiovasc Intervent Radiol 2012; 35(5): 1119-28.

22. Burrel M, Reig M, Forner A, et al. Survival of patients with hepatocellular carcinoma
treated by transarterial chemoembolisation (DEB-TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. J Hepatol. 2012; 56(6): 1330-5.

23. Terzi E, Terenzi L, Venerandi L, Croci L. The ART score is not effective to select patients for transarterialchemoembolization retreatment in an Italian series. Dig Dis. 2014; 32(6): 711-6.

24. Chen L, Ni CF, Chen SX, et al. A Modified Model for Assessment for Retreatment with TransarterialChemoembolization in Chinese Hepatocellular Carcinoma J Vasc Interv Radiol. 2016; 27(9): 1288-1297.

25. Facciorusso A, Mariani L, Sposito C, et al. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma.J Gastroenterol Hepatol. 2016;31 (3):645-653.

26. Pipa-Muñiz M, Castells L, Pascual S, et al. The ART-SCORE is not an effective tool for optimizing patient selection for DEB-TACE retreatment. A multicentre Spanish study. Gastroenterol Hepatol. 2017; 40(8): 515-524.

27. Zhang YQ, Jiang LJ, Wen J, et al. Comparison of α-Fetoprotein Criteria and Modified Response Evaluation Criteria in Solid Tumors for the Prediction of Overall Survival of Patients with Hepatocellular Carcinomafter Transarterial Chemoembolization. J Vasc Interv Radiol. 2018; 29(12): 1654-1661.

28. Biolato M, Gallusi G, Iavarone M, et al. Prognostic ability of BCLC-B Subclassification in Patients with Hepatocellular Carcinoma Undergoing TransarterialChemoembolization. Ann Hepatol. 2018; 17(1): 110-118.

29. Sánchez-Delgado J, VergaraM, Machlab S, et al. Analysis of survival and prognostic factors in treatment of hepatocellular carcinoma in Spanish patients with drug-eluting bead transarterial chemoembolization. Eur J Gastroenterol Hepatol.2018; 30(12): 1453-1460.
30. Moreau R, Jalan R, Ginés P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013; 144: 1426-1437.

31. Shah ND, Ventura-Cots M, Abraldes JG, et al. Alcohol related Liver Disease is Rarely Detected at Early Stages Compared With Liver Diseases of Other Etiologies Worldwide. Clin Gastroenterol Hepatol. 2019 Jan 29. pii: S1542-3565(19)30073-4.

32. Marot A, Henrion J, Knebel JF, Moreno C, Deltenre P. Alcoholic liver disease confers a worse prognosis than HCV infection and non-alcoholic fatty liver disease among patients with cirrhosis: An observational study. PLoS One. 2017;12(10): e0186715.

33. Adhoute X, Pénaranda G, Raoul JL, et al. Barcelona clinic liver cancer nomogram and others staging/scoring systems in a French hepatocellular carcinoma World J Gastroenterol. 2017;23(14):2545-2555.

34. Collette S, Bonnetain F, Paoletti X, et al. Prognosis of advanced hepatocellular carcinoma: comparison of three staging systems in two French clinical trials. Ann Oncol. 2008;19(6):1117-26.

35. Ricke J, Klümpen HJ, Amthauer H, et al. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. J Hepatol. 2019; 71: 1164-1174.

Tables
Table 1: Baseline characteristics of the patients (n=216).
| Predictor                                           | Value                  |
|-----------------------------------------------------|------------------------|
| Age (yr), median (IQR)                              | 70 (63-76)             |
| Gender (Male/Female), n                             | 180/36                 |
| Alcohol/HCV/other etiologies, n                     | 97/ 78/ 41            |
| Prior radiological ascites (no / yes), n            | 198 / 18               |
| Diuretic treatment (no/yes), n                      | 67 / 84                |
| Esophageal varices (yes/no/not available), n        | 72/131/13              |
| Child-Pugh (A5/A6/B/ not available), n              | 139/39/18/20           |
| BCLC-B (0/A/B), n                                   | 10/77/129              |
| Bilirubin (mg/dL), median (IQR)                     | 1 (0.93-1.33)          |
| Albumin, (g/L), median (IQR)                        | 40 (36-43)             |
| AFP (ng/mL), median (IQR)                           | 12.8 (4.9-60.3)        |
| Cr (mg/dL), median (IQR)                            | 0.84 (0.72-0.99)       |
| Sodium (mEq/L), median (IQR)                        | 141 (138-142)          |
| AST (IU/L), median (IQR)                            | 50 (32-84)             |
| ALT (IU/L), median (IQR)                            | 38 (25-76.5)           |
| GGT (IU/L), median (IQR)                            | 120 (67-212)           |
| AP (IU/L), median (IQR)                             | 108 (86.5-138.5)       |
| PT (%), median (IQR)                                | 84 (75-94)             |
| Platelets (x 10^9/mL), median (IQR)                 | 113 (79-159)           |
| Hemoglobin (g/dL), median (IQR)                     | 13.6 (12.4-14.9)       |
| Clinically Significant Portal Hypertension (yes/no), n | 157/ 59               |
| Main nodule diameter (mm), median (IQR)             | 35 (23-48)             |
| Previous treatment (ablation/resection), n          | 44/8                   |
| ALBI 1/2/3/not available, n                         | 81/96/1/38             |
| Beads size 300-500 mm/ 100-300 mm, n                | 187 / 29               |
| Use of Cone Beam CT (no/yes), n                     | 135 / 81               |
| Dose of doxorubicin (mg), median (IQR)              | 90 (70-140)            |

Yr: year; IQR: interquartile range; HCV: hepatitis C virus; BCLC: Barcelona Clinic Liver Cancer; AFP: alpha-fetoprotein; Cr: serum creatinine; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl-transpeptidase; AP: alkaline phosphatase; PT: prothrombin time.

Table 2. Predictors of overall survival from DEB-TACE-1 (period t₀) with pre-DEB-TACE variables (n=216) based on multivariate Cox regression.
| Variable                  | Categories     | n =216 | Overall survival (months) | p-val |
|---------------------------|----------------|--------|---------------------------|-------|
|                           |                |        | median                | median 95% CI |       |
| Esophageal varices        | No varices     | 72     | 30                     | 22.795 - 37.205 | 0.02! |
|                           | Varices        | 131    | 25                     | 21.219 - 28.781 |       |
| ≥ 3 nodules               | No             | 180    | 27                     | 23.853 - 30.147 | 0.02! |
|                           | Yes            | 33     | 23                     | 18.632 - 27.368 |       |
| Tumor size                | ≤ 36.5 mm      | 128    | 30                     | 26.946 - 33.054 | 0.02! |
|                           | > 36.5 mm      | 84     | 22                     | 17.509 - 26.491 |       |
| AFP pre-TACE 1            | ≤ median       | 105    | 30                     | 25.759 - 34.241 | 0.00! |
|                           | > median       | 105    | 23                     | 19.244 - 26.756 |       |
| Bil pre-TACE 1            | ≤ median       | 130    | 28                     | 24.174 - 31.826 | 0.05! |
|                           | > median       | 79     | 25                     | 21.332 - 28.668 |       |
| Alb pre-TACE1             | ≤ median       | 110    | 24                     | 20.271 - 27.729 | 0.11! |
|                           | > median       | 98     | 28                     | 24.344 - 31.656 |       |
| AP preTACE-1              | ≤ median       | 105    | 32                     | 28.016 - 35.984 | < 0.(|
|                           | > median       | 105    | 24                     | 20.771 - 27.229 |       |
| Hb pre-TACE1              | ≤ median       | 108    | 24                     | 19.020 - 28.980 | 0.15! |
|                           | > median       | 105    | 28                     | 25.661 - 30.339 |       |
| Ascites preTACE-1         | No             | 197    | 27                     | 24.361 - 29.639 | 0.06! |
|                           | Yes            | 19     | 21                     | 16.985 - 25.015 |       |
| BCLC-preTACE-1            | BCLC-0/A       | 90     | 33                     | 28.931 - 37.069 | 0.00! |
|                           | BCLC-B         | 126    | 23                     | 19.826 - 26.174 |       |
| CSPH                      | No             | 59     | 30                     | 22.482 - 37.518 | 0.04! |
|                           | Yes            | 157    | 26                     | 22.257 - 29.743 |       |
Cl: confidence interval; HR: hazard ratio; TACE: transarterial chemoembolization; BCLC: Barcelona Clinic Liver Cancer; CSPH: clinically significant portal hypertension.; AFP: alpha-fetoprotein; Bil: bilirubin; Alb: albumin; AP: alkaline phosphatase; Hb: Hemoglobin.

AFP pre-TACE 1 median value 12.95 ng/mL; Bil pre-TACE 1 median value 1.00 mg/dL; Alb preTACE-1 median value 40 g/L; AP preTACE-1 median value 108.50 IU/L; Hb preTACE-1 median value 13.5 g/dL;

Other variables evaluated in the multivariate analysis: sex (p=0.156), etiology (0.197); diabetes (p=0.929); AST (p=0.340); ALT (p= 0.791); GGT (p=0.289); Creatinine (p=0.847); Na (P=0.944);

† Tumor size (cut-off estimated by AUROC); platelets (p=0.611); DynaCT use (p=0.495); DEB size (p=0.283).

Table 3. Predictors of overall survival in the $t_1$ period (from DEB-TACE-1 assessment) including pre and post-procedure variables (n=216) based on multivariate Cox regression.
| Variable                        | Categories | n  | Overall survival, months | p-ν |
|--------------------------------|------------|----|--------------------------|-----|
|                                |            |    | Median                   | Median 95% CI |
| BCLC-stage pre-DEB-TACE        | BCLC 0/A   | 88 | 33           | 29.461 - 36.539 | <0    |
|                                | BCLC-B     | 123| 22          | 18.190 - 25.810 |
| CSPH                           | No         | 58 | 29          | 19.055 - 38.945 | 0.0   |
|                                | Yes        | 153| 25         | 21.645 - 28.346 |
| Post-TACE 1 events             | No         | 142| 27          | 24.308 - 29.692 | 0.0   |
|                                | Yes        | 69 | 22          | 15.090 - 28.910 |
| Albumin post-TACE1             | ≤ median   | 106| 21          | 18.519 - 23.481 | < (< |
|                                | > median   | 100| 34          | 29.103 - 38.897 |
| AFP post-TACE 1                | ≤ median   | 105| 28          | 23.406 - 32.594 | 0.0   |
|                                | > median   | 104| 22          | 18.450 - 25.550 |
| Bilirubin post-TACE 1          | ≤ median   | 138| 28          | 24.296 - 31.704 | 0.0   |
|                                | > median   | 71 | 23          | 19.909 - 26.071 |
| AP post-TACE 1                 | ≤ median   | 103| 32          | 28.409 - 35.591 | < (< |
|                                | > median   | 99 | 23          | 20.156 - 25.844 |
| Ascites post-TACE 1            | No         | 180| 28          | 24.835 - 31.165 | < (< |
|                                | Yes        | 28 | 16          | 9.650 - 22.350  |
| ALBI post-TACE 1               | 1          | 76 | 33          | 26.161 - 39.839 | <0    |
|                                | 2          | 124| 22          | 19.407 - 24.593 |
|                                | 3          | 6  | 20          | 6.797 - 33.203  |
| Child post-TACE 1              | A5         | 122| 29          | 24.525 - 33.479 | < (< |
|                                | Other      | 71 | 21          | 18.178 - 23.822 |
| MELD post-TACE 1               | ≤ 8        | 99 | 28          | 22.981 - 33.019 | 0.0   |
|                                | > 8        | 97 | 23          | 20.131 - 25.869 |
| Progressive disease to TACE-1 (mRECIST) | Yes   | 35 | 21          | 18.241 - 23.759 | 0.0   |
|                                | No         | 176| 27          | 24.473 - 29.527 |
CI: confidence interval; HR: hazard ratio; TACE: transarterial chemoembolization; BCLC: Barcelona Clinic Liver Cancer; CSPH: clinically significant portal hypertension.; AFP: alphafetoprotein; Bil: bilirubin; Alb: albumin; AP: alkaline phosphatase; Hb: Hemoglobin. Alb post-TACE1 median value 38 g/L; AFP posTACE 1 median value 8.5 ng/mL; Bil postTACE 1 median value 1.00 mg/dL; AP post-TACE 1 median value 128 IU/L; MELD postTACE 1 median value 8.

Multivariate analysis model 1: includes BCLC-stage, albumin, alkaline phosphatase, ascites. Multivariate analysis model 2: includes Child-Pugh and response to treatment.

Table 4: Predictors of development of early ascites based on multivariate Cox regression, censoring the time of follow-up at death, early ascites, or second DEB-TACE.

| Predictor                                | p-value | Exp(B) | Exp(B) 95% CI |
|------------------------------------------|---------|--------|---------------|
|                                          |         |        |               | Lower | Higher |
| CSPH (yes/no)                            | 0.348   | 0.366  |               | 0.045 | 2.995  |
| Esophageal varices (yes/no)              | 0.430   | 0.607  |               | 0.175 | 2.100  |
| BCLC 0/ A (yes/no)                       | 0.201   | 1.804  |               | 0.730 | 4.459  |
| Bilirubin                                | 0.152   | 1.529  |               | 0.855 | 2.735  |
| Hemoglobin                               | 0.007   | 0.666  |               | 0.497 | 0.893  |
| Child A5 (yes / no)                      | 0.001   | 0.217  |               | 0.089 | 0.528  |
| Albumin                                  | 0.029   | 0.313  |               | 0.110 | 0.885  |
| Ascites prior to DEB-TACE                | 0.000   | 0.116  |               | 0.042 | 0.322  |

CSPH: clinically significant portal hypertension.

Model 1: Child A 5 plus Hemoglobin; Model 2: Hemoglobin plus prior ascites plus albumin.

Figures
242 patients were proposed to perform DEB-TACE

229 were treated at least with 1 DEB-TACE

13 patients did not meet inclusion criteria
9 awaiting liver transplantation.
1 prior RE-Y⁹₀.
3 DEB-TACE within clinical trial.

216 patients treated with 1 DEB-TACE met inclusion criteria

4 patients did RFA between DEB-TACE 1 and DEB-TACE 2

In 145 a second DEB-TACE was performed.

71 stopped after DEB-TACE-1
Complete response: 27
Switch to SOR: 10
Natural history (comorbidity/fragility): 5+7
Natural history (liver impairment): 9
Lost of follow up: 3
DEB-TACE related death: 4
Others: 3 RFA (3 CR); 3 declined subsequent rounds of DEB-TACE.

78 stopped after DEB-TACE-2.
Complete response: 19
Switch to SOR: 17
Natural history (comorbidity/fragility): 24
Natural history (liver impairment): 11
Lost of follow up: 1
DEB-TACE related death: 2
Others: 4 RFA (1 CR)

In 67 a third DEB-TACE was performed.

52 stopped after 3rd DEB-TACE
Complete response: 2
Switch to SOR: 24
Natural history (comorbidity/fragility): 10
Natural history (liver impairment): 8
Lost of follow up: 3
DEB-TACE related death: 1
Others: 2 RFA, 1 RE-Y⁹₀; 1 declined switch to SOR

In 15 a fourth DEB-TACE was performed.

Switch to SOR: 6
Natural history (comorbidity/fragility): 4
Natural history (liver impairment): 2
Others: 1 RE-Y⁹₀; 1 moved to other country; 1 rapid tumor progression

RE-Y⁹₀: radioembolization Yttrium 90. SOR: sorafenib. RFA: radiofrequency ablation

Figure 1
Flowchart of patients enrolled in the study.

Figure 2
Kaplan-Meier graph with the overall survival of the cohort.
Kaplan-Meier graph with the overall survival according to the development of ascites.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- DDS_Supplementary table 5.docx
- DDS_Supplementary table 3.docx
- DDS_Supplementary table 4.docx
- Supplementary figure 1.tif
- DDS_Supplementary table 2.docx
- DDS_Supplementary table 1.docx