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# Chemoembolization With Doxorubicin-Eluting Beads for Unresectable Hepatocellular Carcinoma: Five-Year Survival Analysis

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**Abstract**
*Purpose* The purpose of this study was to report on the 5-year survival of hepatocellular carcinoma (HCC) patients treated with DC Bead loaded with doxorubicin (DEB-DOX) in a scheduled scheme in up to three treatments and thereafter on demand.
*Materials and Methods* 173 HCC patients not suitable for curable treatments were prospectively enrolled (mean age 70.4 ± 7.4 years). Child-Pugh (Child) class was A/B (102/71 [59/41 %]), Okuda stage was 0/1/2 (91/61/19 [53.2/35.7/11.1 %]), and mean lesion diameter was 7.6 ± 2.1 cm. Lesion morphology was one dominant ≤5 cm (22 %), one dominant >5 cm (41.6 %), multifocal ≤5 (26 %), and multifocal >5 (10.4 %).
*Results* Overall survival at 1, 2, 3, 4, and 5 years was 93.6, 83.8, 62, 41.04, and 22.5 %, with higher rates achieved in Child class A compared with Child class B patients (95, 88.2, 61.7, 45, and 29.4 % vs. 91.5, 75, 50.7, 35.2, and 12.8 %). Mean overall survival was 43.8 months (range 1.2–64.8). Cumulative survival was better for Child class A compared with Child class B patients ($p = 0.029$). For patients with dominant lesions ≤5 cm 1-, 2-, 3-, 4-, and 5-year survival rates were 100, 95.2, 71.4, 66.6, and 47.6 % for Child class A and 94.1, 88.2, 58.8, 41.2, 29.4, and 23.5 % for Child class B patients. Regarding DEB-DOX treatment, multivariate analysis identified number of lesions ($p = 0.033$), lesion vascularity ($p < 0.0001$), initially achieved complete response ($p < 0.0001$), and objective response ($p = 0.046$) as significant and independent determinants of 5-year survival.
*Conclusion* DEB-DOX results, with high rates of 5-year survival for patients, not amenable to curative treatments. Number of lesions, lesion vascularity, and local response were significant independent determinants of 5-year survival.

**Keywords** Hepatocellular carcinoma · Transarterial chemoembolization · Drug-eluting beads · Survival · Doxorubicin loaded drug eluting beads · Embolization in unresectable hepatocellular carcinoma

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## Introduction

Chemoembolization is considered a palliative treatment indicated for intermediate-stage hepatocellular carcinoma (HCC) according to the Barcelona Clinical Liver Cancer

(BCLC) stage system. Level 1 evidence has shown that chemoembolization definitively prolongs survival compared with best supportive care as documented by the cornerstone randomized studies of Llovet *et al.* and Lo et al. [1, 2]. During the last 6 years, a new chemoembolization technique with novel drug-eluting embolizing agents has been introduced into medical practice [3–11]. DC Bead (Biocompatibles, Terumo) is one drug-eluting bead with proven favorable pharmacokinetics in a significant number of clinical series with good local results and short-term survival [3–9]. More importantly, the Precision V randomized comparison of chemoembolization with DC Bead loaded with doxorubicin (DEB-DOX) versus conventional chemoembolization with lipiodol, doxorubicin, and particles (conventional chemoembolization [c-TACE]) showed that DEB-DOX provides superior local response in more advanced patients (Child class B, Eastern Cooperative Oncology Group [ECOG] status 1, bilobar, and recurrent disease) [3]. In addition, the same study documented that DEB-DOX embolization presents fewer doxorubicin-related systemic side effects compared with c-TACE [3]. The safety profile of DEB-DOX in the treatment of intermediate-stage HCC has been shown in a large series with 273 patients in which, among others, it was shown that bead diameters of 100–300 μm are not associated with increased complication rates compared with the larger beads used in Precision V study [12]. However, data on survival >3 years have not yet been reported in a large series. The purpose of this study was to evaluate 5-year survival rates in patients with intermediate-stage HCC treated with DEB-DOX using the smallest available bead sizes and to identify the factors significantly determinant of long-term survival.

## Material and Methods

This was a multi-institutional study including 173 patients with HCC. From the initial cohort, 12 patients were lost to follow-up and were excluded (initial cohort = 185 patients with 173 finally analysed).

Patient prospective recruitment started November 2004 until the end of 2007. All centers used the same inclusion and exclusion criteria. Also included in the study are the data of 34 patients recruited for the DEB-DOX arm of prospective randomized studies within this time frame. These comprised 38 patients with single lesions [7] and 23 patients with multiple lesions [8] who were included in previous prospective studies describing immediate and mid-term results, respectively. Institutional Review Board approval was obtained, and all patients signed the informed consent. Documentation of HCC complied with guidelines from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (EASL) 13, 14], and biopsy documentation was performed in 61 patients. The present analysis was performed at a time point when patients had either died or completed 5-year follow-up.

Patients had BCLC B stage HCC ($n = 135$) or BCLC A stage HCC not amenable to curative treatments (surgery, local ablation) due to high surgical risk or location of the lesion(s) next to the hilum or diaphragmatic dome ($n = 38$). Patients were evaluated by a multidisciplinary group that included a hepatologist, a liver surgeon, and interventional radiologists. The clinical features and morphology of the lesion(s) are listed in Table 1. Liver function criteria included bilirubin <3 mg/dl, aspartate amino transferase (AST), and alanine amino transferase (ALT) < 270 IU/l. Patients with arteriovenous shunts, thrombus within main portal vein, or extrahepatic

**Table 1** Clinical features of study patients

| | |
|---|---|
| Age (year) | 70.4 ± 7.4 |
| Sex (M/F) | (132/41) |
| Cause of cirrhosis (*n*) | 173 |
| HBV (%) | 80 (46.2) |
| HCV (%) | 44 (25.4) |
| HBV + HCV (%) | 44 (25.4) |
| Other (%) | 5 (2.9) |
| AFP (ng/ml) | 1725 ± 4692 |
| >500 | 58 |
| <500 | 115 |
| Child class A/B (%) | 102/71 (59/41) |
| Radiological ascites (% yes) | 16 (9.2) |
| ECOG status 0/1 (%) | 154/19 (89/11) |
| BCLC stage A/B | 38/135 |
| Okuda stage (%) | |
| 0 | 91 (53.2) |
| 1 | 61 (35.7) |
| 2 | 19 (11.1) |
| Performance status (%) | 97.7 ± 5.5 |
| Vascular invasion (portal branch) | 7 |
| Sum lesion diameter (cm) | 7.6 ± 2.1 |
| Lesion morphology | |
| One dominant ≤ 5 cm ± 0–2 satellites | 38 (22) |
| One dominant > 5 cm ± 0–2 satellites | 72 (41.6) |
| Multifocal ≤ 5 | 45 (26) |
| Multifocal > 5 | 18 (10.4) |
| Lesion vascularity[a] | |
| Hypervascular (%) | 138 (79.8) |
| Hypovascular (%) | 35 (20.2) |

*HBV* hepatitis B virus, *HCV* hepatitis C virus

[a] Hypervascular-hypovascular as assessed in angiography at baseline (enhancement on CT or MRI was seen also in lesions that were characterized as hypovascular on angiography)

metastases were excluded. All patients were chemo-naive, and previous treatment with local ablation or surgery was not criteria for exclusion. No cases that were on the transplantation list were included in this study.

Treatment consisted of a series of scheduled DEB-DOX every 2 or 3 months (in 61 patients embolized in the initial period of application of DEB-DOX, the 3, scheduled treatments were performed every 3 months, whereas later embolizations, including 112 patients, were performed every 2 months). Three procedures were the routine number of scheduled sessions unless complete response was achieved with two treatments. During the scheduled DEB-DOX sessions, patients were not receiving any additional treatment with the exception of antiviral medication. After the initial period of scheduled embolizations, patients were followed-up up (imaging and AFP) every 3 months, and additional embolizations were performed only in cases of disease progression (i.e., embolization on demand) using DEB-DOX. The number of additional DEB-DOX sessions and the time interval between sessions were recorded. Additional radiofrequency or microwave ablation, depending on the morphology and the location of new lesion/s, was applied when suitable. Local ablation was considered, if feasible, in these cases instead of a repeat DEB-DOX session because of the small diameter of the new lesions (<2 cm). The number of sessions was recorded and assessed as a variable in the statistical analysis. Decisions were consensus-driven by the interventional radiologist and the referring hepatologist. During follow-up, antiangiogenesis treatment, i.e., sorafenib 400 mg twice daily, was administered in a number of patients. Sorafenib indications in this population included the development of multiple new lesions or diffuse disease, the need to reembolize more frequently than 4 months (after the initial three scheduled sessions), the development of vascular invasion, and the inability to perform DEB-DOX due to progression to BCLC stage C or D disease. The final decision was made by the hepatologist.The impact of sorafenib was assessed by multivariate analysis. The follow-up period ranged between 2 and 68 months, i.e., until time of death or time of analysis.

## Procedure

The embolization procedure was performed as selectively as possible using a 2.7F or 2.4F microcatheter (Progreat; Terumo). DC Bead, 100–300 μm and/or 300–500 μm (Biocompatibles, Terumo) in size was used for lesions >6 cm; DC Bead 100–300 μm in size was only used for lesions ≤6 cm. Bead loading was performed at 37.5 mg doxorubicin/ml reconstituted beads (intended dose 150 mg/patient). There was no adjustment of doxorubicin for body surface area or bilirubin levels, and the final dose administered was not recorded in all patients; therefore, this information was not entered into the analysis. After loading the beads from each vial, the fluid was removed from the suspension and the beads were diluted in 15 ml contrast material. However, in the initial period of the first 6 months, a dilution with 10 ml was performed. The end point of embolizations was obliteration of neovascularity within the target tumor(s). In the first 61 patients, when this end point was not achieved by the intended dose, additional embolic of the same diameter was given until neovascularity disappeared. However, but this was suspected of causing an increased number of abscesses, so the rest of the patients were treated only with the intended dose. Vascularity was assessed at angiography, and tumors were recorded subjectively as hypervascular or hypovascular. In patients with a high number of repeat embolizations, the quantity of the drug that was feasible to be administered was significantly less, and neovascularity was frequently absent or not prominent. In patients with poor blush, intraprocedural contrast-enhanced ultrasonography (CEUS) was often to facilitate selection of the appropriate tumor feeder. For this, diluted intra-arterial ultrasound contrast material (Sonovue; Bracco, Milan, Italy) was injected through the microcatheter, and appearance of new echoes within the lesion confirmed the right position. Contrast dilution was necessary to avoid a curtain-like artifact. Patients with bilobar disease were embolized in one session in a segmental/subsegmental manner. If this was not feasible, the rest of the lesions were treated in the next scheduled session and not in an additional session. Complications of embolizations during the entire follow-up were recorded and graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) that was available at that time [13, 14].

## Imaging Follow-Up

During the first two to three scheduled treatments, patients underwent imaging at 1 month after each scheduled embolization; later the patients underwent followed-up imaging every 3 months. Local response to treatment was assessed with the EASL criteria ($n = 17$) because it was also performed in the Precision V trial [3]. Complete response (CR) was considered when there was (1) complete necrosis documented by complete absence of tumor uptake on the arterial phase of contrast studies, (2) complete disappearance of all viable tumor/s, and (3) no new lesions (i.e., no viable tumor characterized by contrast uptake on the arterial phase of magnetic resonance imaging [MRI] or computed tomography [CT] scan). Partial response (PR) was determined when a decrease ≥50 % of viable tumoral area of all measurable lesions was detected; progressive disease (PD) was determined when there was an increase ≥25 % of viable tumor or appearance of new lesions; and stable disease (SD) was considered in all other cases. Objective response (OR) was considered the sum of CR and PR.

Imaging was performed with MRI at baseline and at 1 month after each embolization session, whereas follow-up after this time was performed every 3 months with MRI exclusively for patients with one dominant lesion and with MRI or CT in patients with multiple lesions. CEUS was performed as an adjunct in questionable cases of local recurrence and before retreatment. CT scans during the last 3 years were performed with a 64-slice multidetector scanner (Brilliance-64; Philips) in three phases: arterial, portal, and equilibrium. Earlier CT studies were performed in three phases on a helical CT scanner (high-speed Advantage scanner; General Electric, Milwaukee, WI). 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 between two radiologists (K. M. and M. P). Image evaluation was not blinded. CEUS was performed with Siemens Acuson (Sequoia 512) equipment using a second-generation echo-enhancer (Sonovue; Bracco, Milan, Italy) with dedicated software and a low-mechanical index imaging technique.

### Data Analysis

Cumulative survival rates were calculated. Kaplan–Meier 5-year survival curves were plotted for various subgroups, and differences between curves were analyzed using log-rank test. Possible variables predictive of survival were analyzed by univariate analysis using chi-square test with Yates' correction (or Fisher's exact test where appropriate). Analyzed variables included AFP $< 500$ or $>500$ ng/ml, Child class, radiologically detectable ascites, ECOG status, Okuda stage, lesion morphology (multifocal *vs*. one dominant), bilobar versus unilobar disease, lesion vascularity on angiography (hypervascular *vs*. hypovascular), additional ablation, additional sorafenib administration, number of embolizations, and the initially achieved (after the two or thee scheduled treatments) CR or OR (CR + PR). Portal branch thrombosis was not assessed as a separate variable because of small numbers. Parameters that were shown to be significant in the univariate analysis were tested also with the multivariate Cox proportional hazard model. For continuous variables, preliminary analysis of the prognostic significance of different cut-off values for each variable was performed. Relative risk and $p$-values were calculated. Statistical significance was defined as $p < 0.05$. Data processing and analysis were performed with SPSS 17.0 software (SPSS, Chicago IL).

## Results

Patient demographics, clinical characteristics, and tumour(s) are listed in Table 1. The mean sum of the longest diameter of tumor(s) treated was $7.6 \pm 2.1$ cm (range 3–15.5). Nine patients had tumour(s) that were surgical recurrences, and 11 patients had tumors that were recurrences after RFA. Local responses ≤6 months after each of the scheduled DEB-DOX embolizations are listed in Table 2. Mean AFP levels were $1725 \pm 4692$ ng/ml (Table 1). No repeat embolization was performed as a staged procedure in bilobar disease because all lesions were treated in one session in a segmental fashion. This was feasible because of the patients with multifocal disease, 45 had 1–5 lesions and only 18 had >5 lesions (Table 1). Of the latter group, 13 had bilobar disease, and if the lesions were not treated in the same session, the remaining were treated in the next session 2 months later. The mean number of embolizations was 5.6 (range 1–9). Statistical analysis showed no significant differences in survival between the 61 patients treated with DEB-DOX every 2 months and the 112 patients treated every 3 months. Forty-four patients received local ablation of a local recurrence (if accessible) or a new lesion during follow-up [mean number of ablations in the 44 patients = 1.4 (range 1–3)]. On long-term follow-up, sorafenib was given in 51 patients as an adjunct to DEB-DOX ($n = 14$) or eventually as a sole treatment due to untreatable progression ($n = 37$).

Overall rates of survival of specific subgroups are listed in Table 3, whereas Kaplan–Meier curves of cumulative survival for Child classes A and B is shown in Figure 1. Mean overall survival was 43.8 months (range 1.2–64.8), notably 48.7 months for Child class A and 36.7 months for Child class B. Overall survival at 1, 3, and 5 years was 93.6, 62, and 22.5 %, respectively, with higher rates achieved in Child class A compared with class B

**Table 2** Results of local response according to EASL criteria ($n = 15$) after each session of the initial scheduled treatments (≤6 months)

| Child class | Local response | No. of scheduled embolization sessions | | |
|---|---|---|---|---|
| | | First (%) | Second (%) | Third (%) |
| A ($n = 102$) | CR | 8 (**7.8**) | 15 (**14.7**) | 24 (**23.5**) |
| | PR | 31 (**30.4**) | 42 (**41.2**) | 50 (**49**) |
| | SD | 61 (**59.8**) | 41 (**40.2**) | 23 (**22.5**) |
| | PD | 2 (**2**) | 4 (**3.9**) | 5 (**4.9**) |
| B ($n = 71$) | CR | 5 (**7**) | 12 (**16.9**) | 16 (**22.5**) |
| | PR | 17 (**23.9**) | 26 (**36.6**) | 33 (**46.5**) |
| | SD | 46 (**64.8**) | 28 (**39.4**) | 16 (**22.5**) |
| | PD | 3 (**4.2**) | 5 (**7**) | 6 (**8.4**) |

*CR* Complete response (complete disappearance of all viable tumor and no new lesions)

*PR* Partial response (decrease >50 % of viable tumoral area of all measurable lesions)

*PD* Progressive disease (increase >25 % of viable tumor or appearance of new lesions)

*SD* Stable disease (all other cases)

**Table 3** Rates of survival overall and in patient subgroups

| Child class (*n*) | | 1 year (%) | 2 year (%) | 3 year (%) | 4 year (%) | 5 year (%) |
|---|---|---|---|---|---|---|
| A | | | | | | |
| 21 | One dominant ≤ 5 cm | 100 | 95.2 | 71.4 | 66.6 | 47.6 |
| 37 | One dominant > 5 cm | 97.3 | 89.1 | 85.1 | 43.3 | 32.4 |
| 31 | Multinodular ≤ 5 cm | 93.5 | 90.3 | 61.3 | 41.9 | 25.8 |
| 13 | Multinodular > 5 cm | 84.6 | 69.2 | 46.1 | 15.3 | 0 |
| 102 | Overall | 95 | 88.2 | 61.7 | 45 | 29.4 |
| B | | | | | | |
| 17 | One dominant ≤ 5 cm | 94.1 | 88.2 | 58.8 | 41.2 | 23.5 |
| 35 | One dominant > 5 cm | 91.4 | 71.4 | 54.2 | 37.1 | 11.4 |
| 14 | Multinodular ≤ 5 cm | 85.7 | 75 | 25 | 14.3 | 0 |
| 5 | Multinodular > 5 cm | 100 | 60 | 20 | 0 | 0 |
| 71 | Overall | 91.5 | 75 | 50.7 | 35.2 | 12.8 |
| Total | | 93.6 | 83.8 | 62 | 41.04 | 22.5 |

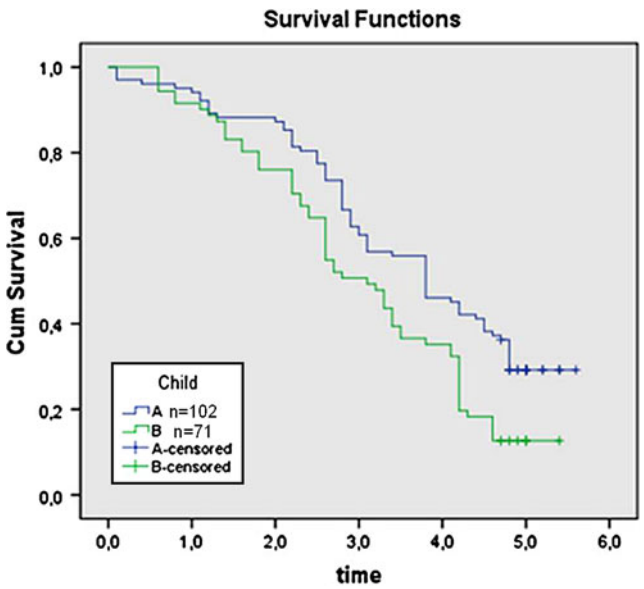


**Fig. 1** Graph illustrates survival-over-time (months) outcome for Child class A and B patients with a statistical significant difference (log-rank test $p = 0.029$). The two curves diverge after 15 months

($p = 0.029$) (Table 3, Fig. 1). Figure 2 shows that Child class A patients with one dominant lesion had longer survival than those with multiple lesions (log-rank test $p < 0.0001$). However, for Child class B patients, Kaplan–Meier curves of those with one dominant lesion >5 cm and <5 cm overlap (log-rank test $p = 0.86$), but Kaplan–Meier curves are distinctly different from those with multiple lesions at all times (log-rank test $p < 0.0001$) (Fig. 2B). For the initial period ≤30 months, patients with one dominant lesion >5 cm had similar survival with those with one dominant <5 cm, whereas after that period patients with a dominant lesion <5 cm clearly had longer survival (log-rank test $p = 0.041$). Patients with multiple lesions had lower survival rates at any time period (Fig. 2A).

Univariate analysis of pretreatment (baseline) patient characteristics identified that AFP values <500 ng/ml, Child class A, absence of radiologically detectable ascites, ECOG status 0, Okuda stage 1, lesion hypervascularity, and presence of one dominant lesion were significantly associated with an increased probability of 5-year survival (Table 4). Log-rank test also showed that additional local ablation ($p < 0.0001$), additional administration of sorafenib ($p = 0.004$), segmental embolization ($p < 0.0001$), and initial CR or OR ($p < 0.0001$) had a greater probability for longer survival (Table 4). The number of embolizations did not have a significant impact on survival ($p = 0.455$). Multivariate analysis identified number of lesions, lesion hypervascularity, additional local ablation, sorafenib administration, and initially achieved CR and OR as significant and independent determinants of 5-year survival (Table 4). The beneficial impact of initially achieved CR or OR after the scheduled sessions is also shown in Fig. 3.

Thirty-day mortality was 1.2 % and was procedure-related (two patients with liver abscess and sepsis). Overall incidence of adverse events included abscess (2.9 %), irreversible liver failure (1.7 %), transient liver decompensation (4.6 %), cholecystitis (5.8 %), pleural effusion (1.2 %), and postembolization syndrome that wad treated symptomatically (73.9 %). Grade 5 complications were seen in 2.9 % and grade 4 in 1.2 % of patients. Of the grade 5 complications, two cases were due to abscess and sepsis and three to irreversible liver failure. The evaluation of patients who developed grade 5 complications (soon after the events) showed that in the two abscess patients, additional bland embolization had been performed due to persistent neovascularity of large tumors (after administration of the intended dose of the embolic); since then this practice was abandoned early during the course of the

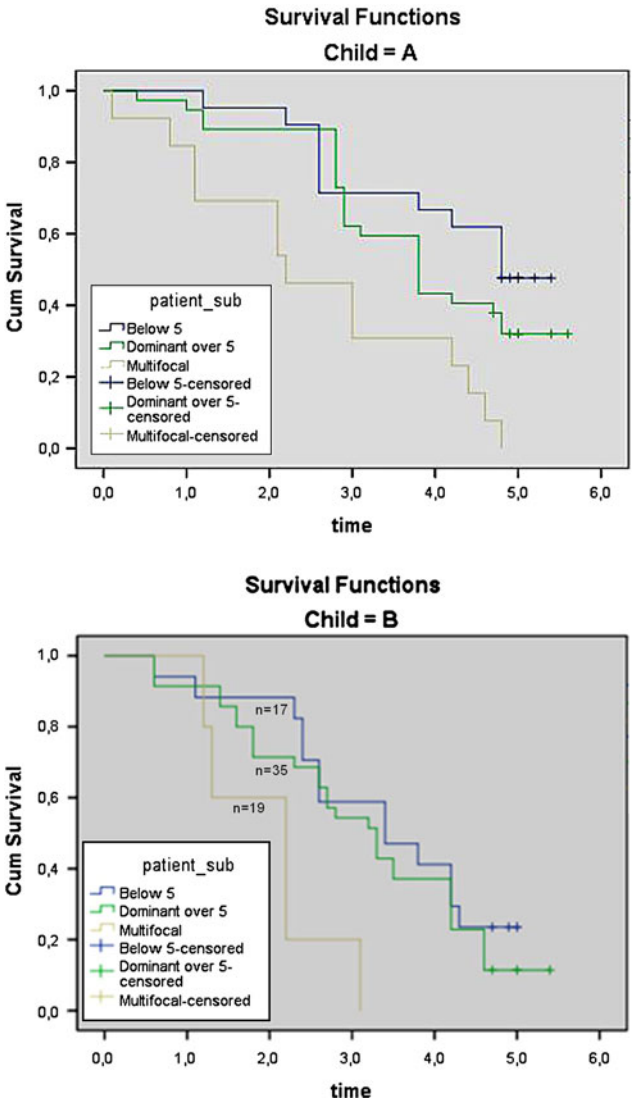


**Fig. 2** **A** Comparison of cumulative survival rates among Child class A patients with different diameters and multiplicity of tumors. Patients with one dominant tumor had significantly longer survival than those with multifocal lesions (log-rank test $p < 0.0001$). When the dominant lesion was <5 cm, survival was slightly higher compared with patients having a dominant lesion >5 cm in diameter (log-rank test $p = 0.041$). **B** In Child class B patients, survival was statistically significantly better in those with one dominant lesion regardless of size compared with those having multiple lesions (log rank test $p < 0.0001$), whereas there was no difference between patients with one dominant lesion >5 cm or <5 cm (log-rank test $p = 0.86$)

study. In the three patients who developed irreversible liver damage, overembolization in Child class B disease was assumed to be the most likely cause. The two patients who developed grade 4 complications presented cholecystitis that resulted in chronic thickening of the gallbladder as documented by follow-up ultrasound; neither of the two required surgery. The remaining cholecystitis events presented temporary thickening of the gallbladder, abdominal pain without fever, or laboratory abnormalities and were treated conservatively; ultrasound follow-up showed complete resolution of gallbladder abnormalities. Review of the films of the patients who presented cholecystitis showed that close location of the treated vessel was the most likely cause in two patients, but in the rest there was no proximity but rather an embolization of multiple segments. At any event, inadvertent embolization was the most likely cause. Grade 3 complications included nonfatal abscess events and one pleural effusion that required drainage.

## Discussion

To be considered effective, treatments of intermediate HCC should surpass the 3-year 50 % survival rate, which occurs at this stage of the disease without treatment [15]. c-TACE has a wide range of survival rates between clinical series reflecting patient group differences and various chemoembolization techniques [16–21]. Only a few reports with c-TACE using doxorubicin are available for ≥5-year or survival, which ranged from 1 to 13 %, the majority of which were conducted in Asian populations [19, 20]. This study is one of the first to report on 5-year survival after DEB-DOX for intermediate-stage HCC. Because it was not randomized, only historical comparison with literature results of studies with patient groups similar to ours is feasible (applicable only if objective and detailed patient description is available). Overall, recent reviews and meta-analyses found that in studies after 2000, survival rates after c-TACE at 1, 2, 3, and 5 years were 71 ± 18 %, 48 ± 16 %, 34 ± 13 %, and 14 ± 10 %, respectively [16–19]. However, all of the above-mentioned survival studies of chemoembolization precede the use of sorafenib. In addition, in our series, we cannot precisely assess the impact of sorafenib or local ablation on survival other than with the results of the multivariate analysis. Our overall survival rate is clearly greater compared with a number of c-TACE studies with similar mean tumor diameters and underlying disease; in randomized studies that documented the impact of c-TACE on survival, Llovet et al. and Lo et al. presented significantly lower survival rates [1, 2]. O'Suilleabhain et al. [20], with 81 % Child class A patients and median tumor size of 9 cm, presented a 5-year survival rate of 8 %. Survival rates comparable with those in our series have been published in c-TACE studies having a mean tumor diameter smaller than ours. In the large series by Takayasu et al. [21], with 8150 patients (Child class A in 51 %, maximum tumor size ≤5 cm in 75 %, and maximum tumor size >5 cm in 25 %), survival rates were 82, 47, 26, and 16 % at 1, 3, 5, and 7 years, respectively. The survival rates of patients with Child class B disease are quite high in our study, a fact that is in accordance with the

**Table 4** Results of univariate and multivariate analysis

| Parameters/risk factors | Univariate analysis (log-rank test) | Multivariate analysis (Cox proportional hazard model) | | |
|---|---|---|---|---|
| | *p* | Hazard ratio | 95% CI | *p* |
| Sex (M vs. F) | 0.414 | 1.108 | 0.672–0.825 | 0.688 |
| AFP (≤500 vs. >500 ng/ml)[a] | 0.019 | 1.468 | 0.965–2.232 | 0.073 |
| Child class (B vs. A) | 0.003 | 1.024 | 0.365–2.868 | 0.965 |
| Radiological ascites (yes vs. no) | 0.000 | 1.494 | 0.446–5.002 | 0.515 |
| ECOG status (1 vs. 0) | 0.000 | 1.633 | 0.616–4.331 | 0.325 |
| Okuda stage (2 vs. 1) | 0.000 | 2.193 | 0.816–5.894 | 0.119 |
| Lesion morphology (multifocal vs. one dominant) | 0.014 | 1.662 | 1.042–2.651 | 0.033 |
| Lesion morphology (bilobar vs. unilobar) | 0.000 | 0.420 | 0.196–0.522 | 0.000 |
| Lesion vascularity (hypervascular vs. hypovascular) | 0.000 | 0.290 | 0.149–0.564 | 0.000 |
| Additional local ablation (yes vs. no)[b] | 0.000 | 0.326 | 0.202–0.526 | 0.000 |
| Additional sorafenib (yes vs. no)[c] | 0.004 | 0.316 | 0.188–0.531 | 0.000 |
| No. of embolizations (1–6 vs. >6)[a] | 0.455 | 0.900 | 0.493–1.646 | 0.733 |
| Extent of embolization (s vs. >2 s)[a] | 0.000 | 1.508 | 0.869–2.615 | 0.144 |
| Initial CR | 0.000 | 0.134 | 0.059–0.303 | 0.000 |
| Initial OR (CR + PR) | 0.000 | 0.534 | 0.267–1.067 | 0.046 |

[a] Cut-off value

[b] Local ablation was used after the initial 6 months (of scheduled treatments) and were only complementary to "on-demand" embolization during follow-up to treat new lesions if they were in suitable locations

[c] Sorafenib was given in a few patients in addition to on-demand embolization in those with a short time to progression

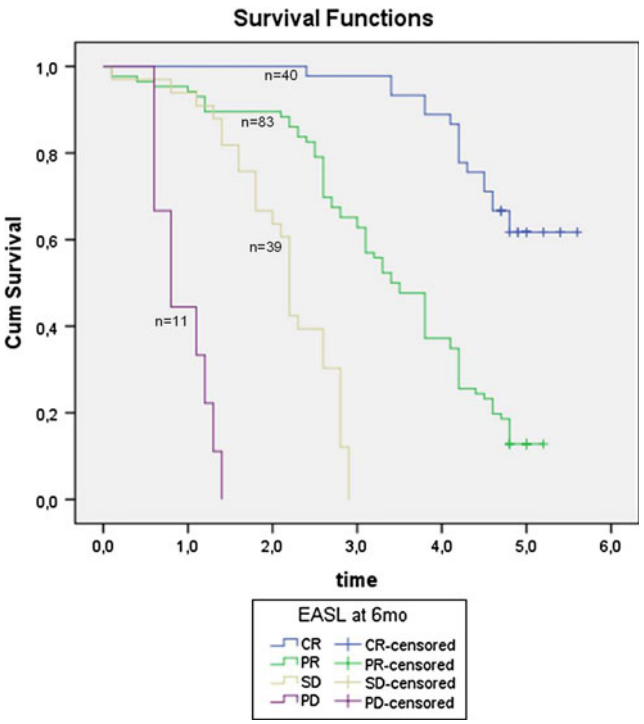


**Fig. 3** Comparison of survival between different local response as evaluated by EASL criteria ($n = 15$) after the initial two to three scheduled treatments (at 6 months). All subgroups present a statistical difference in survival rate at the level of $p < 0.001$)

findings of the Precision V study, showed that patients with more advanced liver disease had a significantly better local response [3].

In our study, higher rates of survival were achieved in our subgroup of patients with one dominant tumor ≤5 cm. Similar results have been published with c-TACE of lesions <3–4 cm [22, 23]. Given that RFA has been classified among the curative treatments, our results in lesions ≤5 cm are close to the survival results with RFA [24–26]. In particular, in the series of Lencioni et al. [24], in which survival was stratified by Child class with lesions ≤5 cm (144 Child class A and 43 Child class B), survival rates were as high as 100, 76, and 51 % for Child class A and 89, 46, and 31 % for Child class B at 1, 3, and 5 years, respectively. Our results are similarly high for the first 2 years; however, not surprisingly from then onward, the decrease in survival is considerable, most likely because of satellite lesions and Child class B cirrhosis. In this series, patients with lesions ≤5 cm were considered eligible for DEB-DOX only if they were unsuitable or at high risk for RFA (mainly because of tumor location next to a major vessel, dome of the liver, or proximity to the liver hilum and biliary tree). Therefore, our results indicate that indeed DEB-DOX proved to be a reasonable alternative if RFA was not feasible. In addition, it must be noted that even in lesions <5 cm, ill-defined borders and small satellites compromise the results of RFA compared with those

mentioned previously [27]. RFA in our series was used after the initial 6 months of the scheduled treatments and only as complementary to "on-demand" embolization during the follow-up to treat new lesions if they were in suitable locations.

It has been inferred that the use of the smallest possible size of beads (100–300 μm) in lesions <6 cm, which allows more distal embolization, has contributed to the high survival rates. The distribution of 100- to 300-μm particles within the tumor has been shown by Lee et al. [28] in their study with iron oxide containing embosphere particles, in which they showed that particles were inside the tumor in 70 % of cases. In contrast, it has been shown that DC Bead diameters of 100–300 μm are not associated with increased complications compared with larger bead diameters [12]. Compared with other studies using DEB-DOX, it is clear that survival is the same for the first 2 years, but no other published studies have longer follow-up periods [3–9]. Similar 5-year survival rates have been reported by Burrel et al. [29] in a single-arm clinical series with DEB-DOX that used larger beads (in all cases >300 μm). However, prospective randomized studies are necessary to compare this with c-TACE.

One interesting observation in our series is that although Child class A patients' cumulative survival depends on lesion parameters (diameter and number) as shown in Fig. 2A, in patients with Child class B the survival outcome is affected more by the number of lesions than by their diameter (Fig. 2B). The survival curve in Child class B patients shows significant overlap between patients with one dominant lesion ≤5 versus >5 cm. This finding indicates that in these patients other features, such as histological type, microvascular invasion, and angiogenesis factors, which were not included in this study, may play a more important role compared with size. Multiplicity of tumors, however, is a clear indicator of poor survival outcome in both Child class A and B patients.

Cox proportional hazard model showed that lesion morphology (dominant vs. multifocal), lesion hypervascularity, additional treatments, and initial remission were independent parameters predicting long-term survival (Table 4). Notably, analysis showed that initial remission as reflected by OR or CR showed better survival rates (Fig. 3) at a statistically significant level ($p < 0.0001$). Similarly, Lee et al. observed that patients with initial remission had better survival compared with these without ($p = 0.002$) [30]. Table 2 lists that improvement of local response can be achieved with the second or third scheduled embolization. Therefore, it can be inferred that pursuit of initial objective response with a number of scheduled treatments is justified because it may prolong survival. However, the frequency and type of locoregional treatments after this initial period must be balanced against the complication rate with special consideration to quality of life. Regarding the number of sessions, our multivariate analysis shows no significant superiority of a certain number. There is literature evidence suggesting that sequential embolizations improve survival [30, 31]; however, patients who require more embolizations on demand are indeed those with poor local response. According to Bruix and Llovet [18], our approach with sequential embolizations for the 6 initial months and thereafter on demand (on evidence of recurrence or tumor progression) is to a certain extent arbitrary and based on previous experience. However, pursuit of an objective response to improve survival has been also suggested by Memon et al. [32]. A greater number of scheduled embolizations than those applied in our study have been shown to cause more liver damage [19, 33, 34], overall more complications [19, 35, 36], and disrupt patients' quality of life [36]. In contrast, on-demand embolizations are associated with less liver damage [19] and fewer complications [34].

The rate of complications and, in particular, liver failure in these series is similar to that reported by other studies with DEB-DOX [3–9]. The two complications that merit more discussion are abscess formation (because two of them were grade 5) and cholecystitis (because the overall rates are quite high). The two cases of grade 5 abscesses may be attributed to additional bland embolization because the patients had no known predisposing factor for abscess formation except that they had large tumors and all received antibiotic prophylaxis. Although at the time it was not known, additional bland embolization is now not recommended for DEB-DOX [37]. The small size of the beads used in our series might be implicated in these complications; however, in a previous study, small bead size did not present more complications compared with beads having larger diameters [12]. Similarly increased incidence of abscesses was also seen in the study of Varela et al.; however, the Precision V trial showed that DEB-DOX and c-TACE have the same incidence of abscess formation [3]. Regarding cholecystitis, it is important to mention that only two cases were grade 4 complications with persistent gallbladder wall thickening, giving a true incidence of cholecystitis of 1.2 %, which is marginally within the accepted threshold [38]. The distinction between grade 4 and 2 is crucial because a gallbladder with wall thickening and malfunction is a disability for the patient, and surgical intervention may be required to relieve symptoms. The remaining cases were grade 2 because they were treated conservatively without any sequelae in the gallbladder (follow-up ultrasound showed normal gallbladder), and the patients presented no symptoms. We believe that these cases could have been mistakenly considered as postembolization syndrome if the patients were not routinely examined with ultrasound in all cases of abdominal pain

the day after embolization. This may be an issue when comparing results with other studies because it clearly overestimates cholecystitis in our series, a fact that is partially counteracted by reporting the severity (grade) of the adverse event. In addition, the overestimation of gallbladder wall thickening with ultrasound is a well known pitfall in patients with cirrhosis. In the three patients who developed irreversible liver damage, overembolization in Child class B disease was the most likely cause. However, the rates are well lower than the accepted standards [38] and similar to other those reported by DEB-DOX studies [3–6]. The high incidence of postembolization syndrome (73.9 %) has also been reported in other DEB-DOX series [3–9] and it may be speculated to be associated with the high dose of doxorubicin used. However, the lack of an objective threshold as to when to call postembolization syndrome was definitely a cause for the high rates in our series.

### Limitations

Among the weaknesses of this study the most important is the fact that it was not randomized, and there is also the confounding effect of the added treatments after the initial scheduled embolization sessions. Another weakness is the small proportion of multinodular disease in both Child class A and B patients, which obviously favors longer survival rates. In addition, during the study there were changes in our protocol regarding time to re-embolize, use of additional bland embolization, and learning curve of the early application period, and all are factors that definitively influenced the data.

Conclusively, this study (1) shows overall survival rates of 93.6, 62, and 22.5 % at 1, 3, and 5 years after sequential sessions of DEB-DOX in HCC patients not amenable to curative treatments and (2) indicates that initially achieved CR and OR are significant and independent determinants of 5-year survival. However, this was a single-arm study, and more solid data are necessary from a randomized study with c-TACE with survival among the primary end points.

**Conflict of interest** None

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