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CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

Five-Years Outcome Analysis of 142 Consecutive Hepatocellular Carcinoma Patients Treated with Doxorubicin Eluting Microspheres 30–60 μm: Results from a Single-Centre Prospective Phase II Trial

K. Malagari[1,2,3] · H. Moschouris[4] · Th. Kiakidis[1,3] · S. Harward[5] · A. Kelekis[1,2,3] · S. Vrakas[6] · D. Koundouras[7,8] · D. Filipiadis[1,2] · G. Glantzounis[9] · E. Emmanouil[1,3] · A. Chatziioannou[3,10] · V. Vergadis[11] · I. Elefsiniotis[12] · J. Koskinas[7,8] · S. Dourakis[7,8] · N. Kelekis[1,2,3]

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Abstract

Purpose To assess prospectively long-term results of doxorubicin-loaded HepaSphere 30–60 μm in consecutive patients with hepatocellular carcinoma (HCC) not amenable to curative treatments.

Patients and Methods Single-center study from June 2011 to December 2015 in 151 patients treated with 75 mg of doxorubicin per HepaSphere vial. Baseline: Barcelona Clinic Liver Cancer BCLC A/B was 49.3%/50.7%, and median diameter 6.1 cm (mean 6.7 ± 2.0). Liver function, local response (mRECIST), liver time to progression (LTTP), progression-free survival (PFS), overall survival (OS) and adverse events (AEs) were recorded.

Results Final analysis included 142 patients with median follow-up of 46.8 months (range 4–72) without grade 4/5 AEs, and 30-day mortality was 0%. Mean number of scheduled treatments was 2.6 (range 1–3) and on demand 3 (range 1–8). Complete response for single tumor ≤ 5 cm was 75.0% and 66.7% for Child A and Child B, while for > 5 cm was 28.6% and 11.8%, respectively. OS was 31.0 months (mean 33.3 ± 15.2; range 8–69), notably for BCLC A 41 months (mean 41.1 ± 15.3; range 13–69) and for BCLC B 26.0 (mean 26.0 ± 10.5; range 8–51). OS at 1, 3 and 5 years: 95.8%, 75.7% and 21.4% for BCLC A, and 94.4%, 36.1% and 2.7% for BCLC B. Median LTTP for BCLC A was 11 months (mean 11.9 ± 4.7; range 3–24) and 7.5 for BCLC B (mean 7.9 ± 2.9). Local response was significant for OS and LTTP ($p < 0.0001$), while size and lesion number affected LPFS and OS ($p < 0.001$).

Conclusions HepaSphere 30–60 μm loaded with doxorubicin provides a safe and effective treatment option for patients with HCC.

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✉ K. Malagari
kmalag@otenet.gr

H. Moschouris
hipmosch@gmail.com

S. Harward
sardis.h.harward@gmail.com

S. Vrakas
sbrakas@yahoo.gr

D. Koundouras
dkountouras@hepatology.gr

D. Filipiadis
dfilippiadis@yahoo.gr

G. Glantzounis
gglantzounis@gmail.com

E. Emmanouil
manolisem@hotmail.com

A. Chatziioannou
achatzi@med.uoa.gr

V. Vergadis
valvergadis@yahoo.gr

I. Elefsiniotis
ielefs@nurs.uoa.gr

J. Koskinas
koskinasj@yahoo.gr

N. Kelekis
kelnik@med.uoa.gr

Keywords Chemoembolization · Drug-eluting beads–microspheres · Hepatocellular carcinoma (HCC) · Long-term survival HCC · HepaSphere · Drug-eluting microspheres-DEM chemoembolization (DEMs)-(DEM TACE)

Abbreviations

DEM	Drug-eluting microsphere
DEM-TACE	Drug-eluting microsphere transarterial chemoembolization
HCC	Hepatocellular carcinoma
BCLC classification	Barcelona Clinic Liver Cancer
mRECIST	Local response
LTTP	Time to progression in the liver
PFS	Progression-free survival
OS	Overall survival
AEs	Adverse events
NACT	HCC not amenable to curative treatments
OS	Overall survival
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive disease

Introduction

Hepatocellular Carcinoma (HCC) is the fifth most frequently diagnosed cancer in men and seventh in women worldwide with varying etiologies across different countries with hepatitis C more common in the western countries and hepatitis B in Mediterranean and Asian countries mostly [1].

Use of embolic drug delivery devices (drug-eluting microspheres—DEMs) is an established tool for treating hepatocellular carcinoma (HCC) not amenable to curative treatments [2–4]. There is a tendency to use smaller diameters of DEMs between 70 and 300 μm and even below 100 μm in some centers [5, 6]. HepaSphere Microspheres (named QuadraSphere Microspheres in the USA; Merit Medical Systems, South Jordan, Utah) were first used as a bland embolic for HCC in 2002 [7]. HepaSphere 30–60 μm hydrated enlarges to 148 ± 45 μm which has been assessed in animal models and in humans [8–10]. Dose escalation studies have proven its safety profile and also demonstrated an advantageous pharmacokinetic profile compared to that of conventional chemoembolization (c-TACE). However, long-term 5-year survival for this particular HepaSphere size is not known. The only two papers presenting data from 5-year survival until now have used DC Bead (BTG, London, UK) with highly selected and non-consecutive patients. The purpose of this study is to report 5-year outcome analysis with HepaSphere 30–60 μm in consecutive HCC patients.

Materials and Methods

The study was conducted prospectively after approval by the Institutional Review Board and written informed consent. Recruitment period started in June 2011 and ended in December 2015, and the time of the end of follow-up and final analysis was June 2018. The primary objective of this prospective study is 5-year overall survival (OS) with doxorubicin-loaded HepaSphere 30–60 μm (Dox HS/30–60) in consecutive patients with hepatocellular carcinoma (HCC) not amenable to curative treatments (NACT)

[1] 2nd Department of Radiology, Medical School, National and Kapodistrian University of Athens, 19 Monis Kyccou, 15669 Papagou, Athens, Greece

[2] Attikon Hospital, Chaidari, Greece

[3] Evgenidion Hospital, Athens, Greece

[4] Radiology Department of Tzanion General Hospital, Athens, Greece

[5] University of Massachusets Medical School, Worcester, MA, USA

[6] Tzanion Hospital, Athens, Greece

[7] 2nd Clinic of Medicine and Hepatology Medical School, National and Kapodistrian University of Athens, Athens, Greece

[8] 2nd Clinic of Internal Medicine University of Athens Hippokration Hospital, Athens, Greece

[9] Department of Surgery, University Hospital of Ioannina (UOI), Ioannina, Greece

[10] 1st Department of Radiology, Medical School, National and Kapodistrian University of Athens, Athens, Greece

[11] Radiology Department of Laikon University Hospital, Athens, Greece

[12] Department of Internal Medicine and Hepatology Unit, Agioi Anargyroi General and Oncology Hospital of Kifissia Hospital Timiou Stavrou and Noufaron, Kalyftaki, Athens, Greece

Table 1 Baseline descriptive and functional characteristics of study cohort

Variable	Cohort value (mean; %)
Age (years)	70.1 ± 8.5
Sex—*n* (%)	
Male	105 (73.9)
Female	37 (26.1)
Etiology—*n* (%)	
Hepatitis B (HBV)	80 (56.3)
Hepatitis C (HCV)	32 (22.5)
HBV and HCV	15 (10.6)
Alcohol	4 (2.8)
Steatosis	3 (2.1)
Hemosiderosis	2 (1.4)
HBV and hemosiderosis	4 (2.8)
HCV and hemosiderosis	2 (2.8)
Documentation	
Biopsy	56 (39.4)
Imaging and AFP–AASLD criteria	86 (60.6)
AFP (mean ± SD) range (ng/ml)	184 ± 358 (3.02–2.3)
< 400	109 (83.9)
≥ 400	21 (16.2)
Child–Pugh stage-*n* (%)	
A	104 (73.2)
Single ≤ 5	35
Single > 5	35
Multiple ≤ 3	27
Multiple > 3	7
Encapsulated	43
Infiltrative	29
B	38 (26.8)
Single ≤ 5	11
Single > 5	17
Multiple ≤ 3	7
Multiple > 3	3
Encapsulated	8
Infiltrative	14
Karnofsky performance status	97.1 ± 5.5
BCLC stage	
A	70 (49.3)
B	72 (50.7)
Sum of tumor diameters (cm)	6.7 ± 2.0
Median	6.1
One dominant/single ≤ 5 cm	47 (33.1)
One dominant/single > 5 cm	52 (36.6)
Multiple ≤ 3 in number	34 (23.9)
Multiple > 3 in number	9 (6.3)
Tumor boarders	
Encapsulated	51 (35.9)
Infiltrative	43 (30.3)
Indeterminate	48 (33.8)
Number of tumors—*n* (%)	
1	98 (69.0)
≤ 3	34 (24.0)
> 3	10 (7.1)
Tumor vascularity—*n* (%)	
Hypervascular	122 (85.9)
Hypovascular	20 (14.1)
Initiation of sorafenib	
Time from baseline (mo)	13.3 ± 7.8 (4–43)

not published before. Secondary objectives are progression-free survival (PFS), liver time to progression (LTTP), local response and local recurrence rates at the site of the index tumor or new lesions as defined by mRECIST. Safety and long term-related toxicity were also evaluated.

Diagnosis of HCC was confirmed either by biopsy or by the AASLD (American Association for the Study of the Liver Diseases) criteria [1]. Follow-up was until patients' death. Inclusion criteria were: no previous embolization (embolization-naïve), ECOG (Eastern Cooperative Oncology Group) stage 0, Child–Pugh A-B7 and BCLC A-B with tumors < 50% of liver volume. Exclusion criteria were: patients with portal vein thrombosis (main trunk or branches), extrahepatic metastasis, non-treatable arteriovenous shunts, or patients on antiangiogenesis medication, patients with bilirubin > 2 mg/dl and transaminases > × 5 of normal values. Causes for not choosing resection or transplantation included high risk for surgery from the tumor board (resection not considered due to impaired liver function, high-risk American Society of Anesthesiologists—ASA status, poor candidacy for transplantation waiting list > 12 months or outside Milan criteria). Criteria for not considering ablation included subcapsular exophytic lesions, proximity to liver hilum and presence of satellites. Patients downstaged for surgery or bridged for transplantation were recorded and were censored from statistical curves (8 in number). Despite Child A status, nine patients were not candidates for resection due to Mediterranean hemolytic anemia with hemosiderosis and von Willebrand's disease. Follow-up included imaging, hematology, liver function and tumor marker examinations every 3 months unless there was a significant abnormality that warranted reexamination earlier. It is noted that the percentage of alcohol intake as a cause of cirrhosis in our patients is low, and the leading cause was viral hepatitis due to poor population screening of elderly patients. Hemosiderosis was also a considerable cause due to the

high rates of patients with homozygous hemolytic anemias who survive to adulthood.

Baseline characteristics are summarized in Table 1. The mean diameter of tumors treated was 6.7 ± 2.0 cm (range 4–10.5; median 6.1). Liver function status was Child–Pugh A in 104 patients (73.2%) and B in 38 (26.8%). Seventy patients were in BCLC stage A (49.3%), and 72 were in BCLC stage B (50.7%). In 12 patients, TACE was performed because of tumor recurrence after liver surgery and in 17 patients, TACE was performed because of tumor recurrence after ablation with multiple nodules/satellites and/or tumor located in the liver hilum.

Technique of embolization: Embolization was performed according to the quality improvement guidelines and technical recommendation for drug-eluting microspheres [11]. HepaSphere Microspheres (named QuadraSphere Microspheres in the USA; Merit Medical Systems, South Jordan, Utah) are superabsorbent polymer microspheres (SAP-MS) capable of being loaded with doxorubicin, epirubicin and cisplatinum [12–14]. SAP consists of sodium acrylate and vinyl alcohol copolymer that has the ability to absorb fluids and swell within minutes by a factor of four from the dry state. As a first step, tumor vascularity was assessed by selective angiography and immediately previously with contrast-enhanced ultrasound. HepaSphere microspheres were loaded with 37.5 mg/ml (75 mg of dry doxorubicin diluted with 15 ml saline per microsphere vial with maximum intended dose 2 vials) that had been solubilized in normal saline. Loading was performed in two steps as recommended per product IFU (physician Instructions for Use) and previously described [9, 12, 13]. The embolic suspension was diluted up to 30 ml using a 50/50% solution with nonionic contrast and normal saline administered as selectively as possible with microcatheters 1.9.–2.4F and after intra-arterial injection of 100–200 μg of nitrate. The intended dose of doxorubicin per session was 150 mg, lowered to 100 mg in Child–Pugh B7 [15]. Periprocedural medication included antiemetics, prophylactic antibiotics, gastroprotection, analgesia as described previously to avoid post-embolization syndrome [9] and IV dexamethasone/Decadron 10 mg. Procedural operators were KM, HM, A Ch and V V with 15/15/15/and 10 years of experience of chemoembolization with DEMs and evaluating results.

Schedule of embolizations: Patients received 1–3 scheduled procedures 3–6 weeks apart and then on demand upon progression. Sessions were performed subsegmentally (< 1S), segmentally (S) or involved more than one or two segments (> 2S). The goal of scheduled procedures was maximum local response, as this has been found to be an independent and significant predictor of survival [16–18]. Imaging included dynamic MDCT or contrast-enhanced 3.0 T MR at baseline, 1 month post each embolization, and every 3 months thereafter. Imaging was performed with MDCT or MRI including arterial phase, portal venous phase and delayed imaging in the equilibrium phase and ADC values. MDCT was performed with a Brilliance-64, Philips Medical Systems, and MRI was performed with a 3 Tesla, Philips Medical Systems, including T2 fat-suppressed sequences and dynamic fat-suppressed T1 sequences with gadolinium enhancement and DWI axial images as suggested in the literature [19].

Clinical response assessment: Efficacy was evaluated by α-fetoprotein (AFP) levels, imaging outcome according to mRECIST as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), objective response (OR: CR + PR) [20], liver time to progression (LTTP), analyzed as recurrence of the target tumor or new lesions, liver progression-free survival (LPFS) and overall survival (OS) up to 5 years. Crossover to sorafenib or downstaging to surgery was recorded, and patients were censored at the time of crossover. No patients included in the study received sorafenib during chemoembolization sessions. Adverse events (AEs) were classified using the National Cancer Institute Common Terminology Criteria v.3.0 [33] (not v 4 as the study was initiated in 2011). Patency of vessels at repeat embolization was recorded.

Statistical analysis: Statistical analysis used Stata® for Mac, version 14.1 (StataCorp, College Station, TX). Additional to descriptive statistics, nonparametric analysis used Shapiro–Wilkinson tests. Outcome variables included LTTP, LPFS and OS. Continuous variables were described as means with standard deviations and categorical variables were described as percentages. Comparisons of continuous variables between two groups were conducted using the Mann–Whitney U test, comparisons between three or more groups were made using the Kruskal–Wallis H test with correction for ties, and comparisons of categorical variables were done using Fisher's exact test. A two-sided p value less than 0.05 was considered significant. Reports of Kaplan–Meier analyses include error ranges or 95% confidence intervals and censoring for sorafenib or downstage to surgery. Variables entered into the multivariate analysis included: age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, cirrhosis stage (Child–Pugh Class), tumor-related characteristics (sum of diameters, presence of capsule or infiltrative margins) and composite variables (BCLC classification).

Results

From the 151 consecutive patients with documented HCC, 142 patients were eventually analyzed (nine lost to follow-up); documentation was done by AASLD criteria in 89

Table 2 Tumor response according to mRECIST criteria by Child–Pugh status after the scheduled treatments

Child–Pugh stage	CR *n* (%)	PR *n* (%)	SD *n* (%)	PD *n* (%)	OR *n* (%)
Child–Pugh A (n = 104)					
Overall	44 (42.3)	44 (42.3)	14 (13.5)	2 (1.9)	88 (84.6)
Single/dominant ≤ 5 cm (n = 35)	28 (80.0)	7 (20.0)	0 (0.0)	0 (0.0)	35 (100)
Single/dominant > 5 cm (n = 35)	10 (28.6)	16 (45.7)	8 (22.9)	1 (2.9)	26 (74.3)
Multiple ≤ 3 in number (n = 27)	6 (22.2)	16 (59.3)	4 (14.9)	1 (3.7)	22 (81.5)
Multiple > 3 in number (n = 7)	0 (0.0)	5 (71.4)	2 (28.6)	0 (0.0)	5 (71.4)
Encapsulated (n = 43)	36 (83.7)	7 (16.3)	0 (0.0)	0 (0.0)	43 (100)
Infiltrative (n = 29)	4 (13.8)	11 (37.9)	12 (41.4)	2 (6.9)	15 (51.7)
* p = 0.001 (obtained by Fisher's Exact Test)					
Child–Pugh B (n = 38)					
Overall	7 (18.4)	23 (60.5)	4 (10.5)	4 (10.5)	30 (78.9)
Single/dominant ≤ 5 cm (n = 11)	5 (45.5)	6 (54.5)	0 (0.0)	0 (0.0)	11 (100)
Single/dominant > 5 cm (n = 17)	2 (11.8)	11 (64.7)	2 (11.8)	2 (11.8)	13 (76.5)
Multiple ≤ 3 in number (n = 7)	0 (0.0)	4 (57.1)	2 (28.6)	1 (14.3)	4 (57.1)
Multiple > 3 in number (n = 3)	0 (0.0)	2 (66.7)	0 (0.0)	1 (33.3)	2 (66.7)
Encapsulated n = 8)	3 (37.5)	4 (50.0)	0 (0.0)	0 (0.0)	7 (87.5)
Infiltrative (n = 14)	0 (0.0)	5 (35.7)	6 (42.8)	4 (28.6)	5 (35.7)
* p = 0.002 (obtained by Fisher's Exact Test)					

Local response evaluation by mRECIST abbreviations: Complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) and objective response (OR) = CR + PR

(62.7%) and biopsy in 53 (37.32). The median follow-up was 46.8 months (range 4–72).

Mean number of scheduled embolizations was 2.6 (range 1–3), and hospitalization was 1.1 days (range 1–6). Patients presenting with stable disease (SD) or progressive disease (PD) according to mRECIST criteria after two scheduled sessions of TACE, and upon agreement with the oncology review board, did not receive a third scheduled session (total of ten patients). The median number of additional (on demand) embolizations until untreatable progression (developing contraindications for intra-arterial or ablative procedures) or death was 3 (range 1–8). After the first session of TACE, early feeding vessel stasis due to proximal occlusion was seen in 16 patients (11.3%). In these patients, it was possible to inject 60–70% of one vial, with complete coverage of the tumor and disappearance of residual vascular blush in 90.8% of patients. However, these patients required prolonged injection times.

Local response stratified by Child–Pugh stage is summarized in Table 2 with an objective response (OR) rate (CR + PR) of 84.6% in Child–Pugh A and in 78.9% in B. PD occurred at the highest rate in patients with diffuse infiltrative lesions (Table 2). Table 3 demonstrates that better local response is associated with longer OS. AFP levels significantly decreased during the follow-up of patients from 184 ± 358 (3.0–2.3) to 33.4 ± 94 (3.1–509.3) ($p < 0.001$).

Table 3 Mean overall survival by mRECIST response status

mRECIST response	Mean survival (months)
CR	34.8 ± 9.6
PR	28.2 ± 10.2
SD	22.1 ± 8.5
PD	10.0 ± 1.8

*p = 0.0007 (obtained from Fisher's exact test)

OS per tumor characteristics, Child–Pugh and BCLC stage are summarized in Table 4. The median OS of the entire cohort was 31.0 months (mean 33.3 ± 15.2; range 8–69) that for BCLC stage A was 41 months (mean 41.1 ± 15.3; range 13–69), while for BCLC B was 26.0 months (mean 26.0 ± 10.5; range 8–51). OS for BCLC A patients at 1, 3 and 5 years was 95.8%, 75.7% and 21.4%, and 94.4%, 36.1% and 2.7% for BCLC B (Table 5). OS at 1, 3 and 5 years in patients with recurrences post-tumor resection was 85.2%, 53.4% and 19.2%. The Kaplan–Meier curves of overall survival for BCLC stage subgroups and target lesion characteristics subgroups are illustrated in Fig. 1 demonstrating significantly longer survival in patients with OR ($p < 0.0001$) and selectivity of embolization ($p < 0.0001$). Over the follow-up period, crossover to sorafenib was prescribed in 39 patients and was censored for survival calculations. Censored were also nine patients who were downstaged to surgery.

Table 4 Liver time to progression (LTTP), time to progression for development of new lesions and overall survival per Child and BCLC stage

Tumor and underlying disease variables	LTTP (mo) (range) to the target tumor				TTP to new lesions				Overall survival—OS (mo)			
	Median (range)	Mean	SD	Interquartile range	Median (range)	Mean	SD	Interquartile range	Median (range)	Mean	SD	Interquartile range
Child–Pugh A												
Overall (n = 104)	9 (3–24)	10.1	4.4	6	15 (3–58)	20.5	14.3	14.5	35 (9–69)	36.5	14.8	23.3
One dominant target tumor $\leq$ 5 cm	15 (8–24)	14.44	4.2	6.5	32 (9–58)	32.1	15.9	32	51 (23–69)	48.9	11.2	14.5
One dominant target tumor > 5 cm	9 (3–19)	9.4	3.9	6	13 (3–45)	15.7	10.6	13.8	27 (9–62)	29.5	13.0	19
Multiple tumors $\leq$ 3	8 (4–18)	8.4	3.4	3	13 (3–26)	13.2	5.6	7	31 (16–51)	31.4	10.3	14
Multiple tumors > 3	7.5 (5–9)	7.3	1.2	1.8	12 (9–17)	12.5	2.8	5.8	21 (10–40)	23.6	9.9	18
Encapsulated with or without satellites	14.5 (8–24)	14.1	3.9	5.5	27 (11–58)	30.1	15.2	25.5	44 (20–69)	23.6	12.9	21
Infiltrative—ill-defined boarders	7 (3–20)	8.4	4.3	4	9 (3–43)	12.1	8.8	9	25 (9–58)	29.4	14.6	25
Child–Pugh B												
Overall (n = 38)	8 (3–10)	8.4	3.8	3	11 (4–25)	12.1	4.9	5.8	23.5 (8–54)	24.6	11.5	16.8
One dominant target tumor $\leq$ 5 cm	9 (7–20)	11.6	5.1	11	12 (9–25)	14.6	5.5	9.5	29 (17–41)	28.3	8.1	15
One dominant target tumor > 5 cm	8 (3–11)	7.9	2.3	4	11 (5–17)	11.2	3.9	5	18 (8–38)	21.0	8.7	16
Multiple tumors $\leq$ 3	6.5 (3–9)	6.3	2.0	3.8	11 (8–17)	12.2	3.1	6	25 (9–30)	21.7	7.7	17
Multiple tumors > 3	5 (4–7)	5.0	2.0	N/A	7 (4–10)	7.0	3.0	N/A	1 (10–20)	13.7	4.5	N/A
Encapsulated with or without satellites	9 (8–20)	12.2	5.2	11.3	24 (9–58)	27.6	14.7	21	30 (17–39)	29.6	7.6	17
Infiltrative—ill-defined boarders	6 (3–9)	5.6	2.1	4	9 (3–54)	12.5	10.6	9	15.5 (8–29)	16.2	5.9	9
Entire cohort (n = 142)	9 (2–24)	9.6	4.3	4.8	15 (3–58)	18.5	13.0	10	31 (8–69)	33.3	15.2	22.3
BCLC stage A/B: 70/72												
A	11 (3–24)	11.9	4.7	6.8	18.5 (3–58)	22.9	14.6	19.8	41 (13–69)	41.1	15.3	23.3
B	7.5 (3–18)	7.9	2.9	3	13 (3–54)	13.6	9.1	6.8	26 (8–51)	26.0	10.5	14.0

N/A: not applicable due to small number

Table 5 Overall survival per year stratified by Child stage, lesion characteristics and BCLC stage

	1st year (%)	2nd year (%)	3rd year (%)	4th year (%)	5th year (%)	> 60 mo (%)	Still alive (%)
Child A (n = 104)	102	92	66	39	23	13	5
	98.1	88.5	63.5	37.5	22.1	12.5	4.8
Single/dominant ≤ 5 cm (n = 35)	35	35	31	23	12	9	5
%	**100**	**100**	**94.9**	**65.7**	**34.3**	**25.7**	**14.3**
Single/dominant > 5 cm (n = 35)	34	27	14	5	3	2	0
%	**97.1**	**77.1**	**40**	**14.3**	**8.6**	**5.7**	**0**
Multiple ≤ 3 (n = 27)	26	21	13	5	0	0	0
%	**96.3**	**77.8**	**48.1**	**18.5**	**0**	**0**	**0**
Multiple > 3 (n = 7)	6	6	2	0	0	0	0
%	**85.7**	**85.7**	**28.6**	**0**	**0**	**0**	**0**
Encapsulated (n = 43)	42	41	36	21	12	9	0
%	**100**	**97.6**	**85.7**	**50**	**28.6**	**21.4**	**0**
Infiltrative (n = 29)	27	17	13	5	1	0	
%	**96.4**	**60.7**	**46.4**	**17.9**	**3.6**	**0**	**0**
Child B (n = 38)	34	20	8	4	1	0	0
	89.5	52.6	20.1	10.5	2.6	0	0
Single/dominant ≤ 5 cm (n = 12)	12	9	6	3	0	0	0
%	**100**	**75**	**50**	**25**	**0**	0	0
Single/dominant > 5 cm (n = 17)	15	7	1	0	0	0	0
%	**88.2**	**41.2**	**5.8**	**0**	**0**	0	0
Multiple ≤ 3 (n = 7)	6	4	1	1	1	1	0
%	**85.7**	**57.1**	**28.6**	**14.3**	**14.3**	**0**	0
Multiple > 3 (n = 2)	1	0	0	0	0	0	0
%	**50.0**	**0**	**0**	**0**	**0**	**0**	0
Encapsulated (n = 8)	8	6	3	1	0	0	0
%	**100**	**75.0**	**37.5**	**12.5**	**0**	**0**	0
Infiltrative (n = 14)	9	2	1	0	0	0	0
%	**64.3**	**14.3**	**7.1**	**0**	**0**	**0**	0
BCLC A (n = 70)	69	64	53	35	15	15	5
%	95.8	91.4	75.7	50	21.4	21.4	7.1
BCLC B (n = 72)	68	51	26	7	2	2	0
%	94.4	70.8	36.1	9.7	2.7	2.7	

Bold values indicate statistically significant ($p < 0.001$)

Progression-free survival in the liver (LPFS) was 13.1 ± 5.9 months in patients OR as opposed to 6.9 ± 2.4 in patients with SD ($p < 0.001$ Wilcoxon rank sum tests) (Fig. 2). The median time to liver progression (LTTP) of the target tumor for the entire cohort was 9 months (mean 9.6 ± 4.3; range 2–24) (Table 4). Median LTTP was 11 and 7.5 months for BCLC A and B, respectively. Well-defined encapsulated tumors without visible microsatellites presented a median LTTP of 14.5 months in Child–Pugh A patients (mean 14.1 ± 3.9; range 8–24) that dropped to a median LTTP of 7 months (mean 8.4 ± 4.3; range 3–20) in infiltrative ill-defined tumors (Table 4). Table 4 also displays that the time to development of new lesions during follow-up for the entire cohort appeared at a median time of 15 months (mean 18.5 ± 13.0; range 3–58). Median LTTP for recurrences post-liver resection was 10.2 months (mean 10.7 ± 3.1). Anova regression—univariate and multivariate analysis, for OS is displayed in Table 6 (supplement) and indicates that the sum of diameters and local response are clearly correlated with OS ($p < 0.001$), while multivariate analysis results for LPFS (Table 7, supplement) demonstrate that achievement of CR is statistically significant ($p < 0.001$).

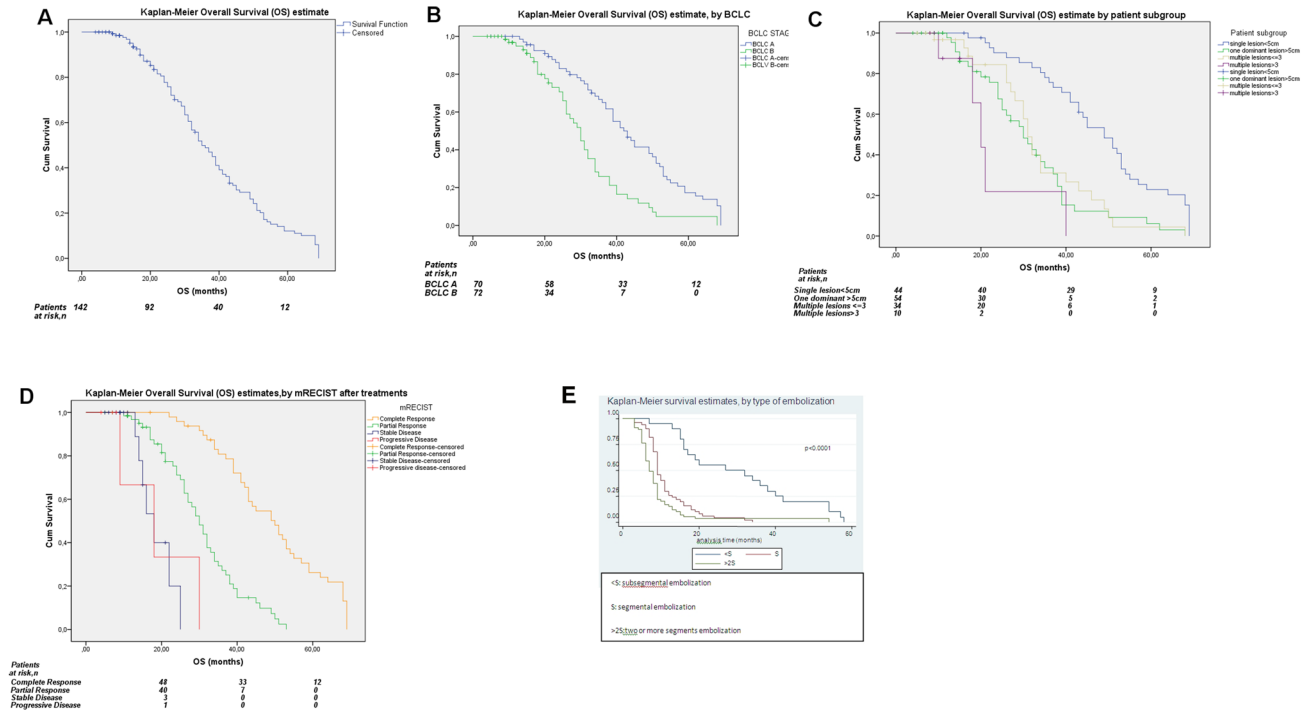

Fig. 1 **A** Overall survival (OS) for the entire cohort. It demonstrates a fast drop during months 20–40 while less than 25% of patients live longer than 40 months. **B** Better survival is seen for BCLC A patients ($p = 0.0001$). **C** Size and number of lesions and local response correlate with OS at statistically significant level ($p < 0.0001$). **D** Survival stratified per local response shows longer survival in objective response (CR + PR) ($p < 0.0001$). **E** OS stratified per selectivity of embolization. All curves indicate patients at risk

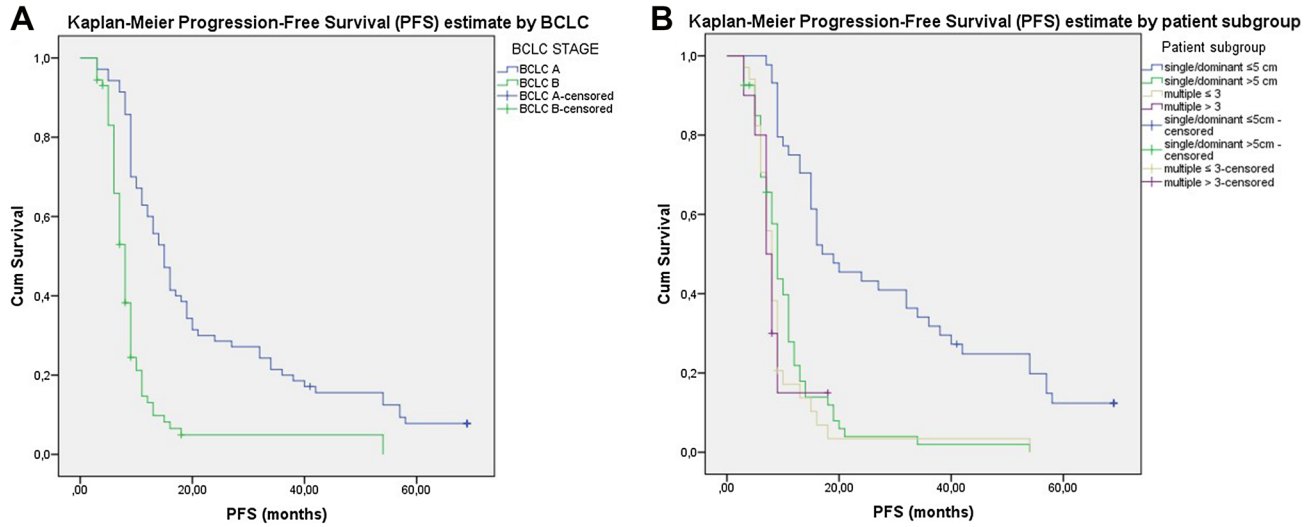

Fig. 2 **A**. Progression-free survival Kaplan–Meier curves stratified per BCLC stage, patient subgroup demonstrating longer PFS for smaller lesions ($p < 0.001$) (**B**)

There were no grade 4 or 5 adverse events, and 30-day mortality was 0%. A summary of the adverse events is shown in Table 6; the most common was post-embolization syndrome (PES) in 24.7% and fever without any other symptoms of PES in 19.7%. There were no instances of biliary injury, or rupture or abscess.

Discussion

The elasticity of HepaSphere 30–60 μm allows conformation to the intima within tortuous and narrow vessels, as demonstrated in in vitro and in animal testing, and the hydrated diameter 148 ± 45 μm allows more distal embolization [10, 21]. Since then, a number of clinical

Table 6 Adverse events of HepaSphere chemoembolization over time

Adverse event	Grade	%
Post-embolization syndrome (PES)	2 or 3	24.7
Fever only without any other symptom of PES	3	19.7
Elevation of transaminases < 100 U/dl	2	27.5
Elevation of bilirubin < 3 mg/dl	2	9.9
Ascitis (only by imaging)	3	4.2
Fatigue and loss of appetite	2	16.2

series have been published using various diameters of this embolic microsphere [9, 22–24]. In this study, 30–60 μm HepaSphere microspheres were evaluated for chemoembolization of 142 consecutive HCC patients meeting inclusion criteria with a median follow-up of 46.8 months (4–72).

The highest tumor response rates in our study were observed in patients with single/dominant lesions ≤ 5 cm with or without microsatellites, who achieved up to 80% CR, while regardless of diameters, CR dropped to 42% (Table 2). Similar results have been reported with HepaSphere 30–60 μm by Bishay et al. [24] achieving a CR and PR in 30 and 35% of patients, respectively. This local response is better than the results of Golfieri et al. [25] treating smaller tumors of a median diameter 2.5 (0.9–9) cm in their DEB TACE arm who reported a CR of 25%. Lee et al. [26] using DC Bead 100–300 μm in 152 patients with 55.3% single tumor of which 11.8% and 33.6% were of less than 2 and 2–5 cm in diameter, respectively, achieved objective response (OR) in 91.4% and CR in 40.1% and at 6 months; the OR and CR were 55.4% and 43.0%, respectively. Yu et al. [27] with DC Bead 100–300 μm achieved CR 40% and 33.3% in bridge for transplantation—treating smaller lesions. Lower OR rates have been reported with the 50–100 HepaSphere reaching 53.3% [23]. The use of even smaller microspheres may achieve better results; Spreafico et al. [28] treating HCC with mean maximum diameters 27 mm (9–143) and using smaller diameter drug-eluting microspheres (70–150 μm) achieved CR of 33% and PR 44.4% as opposed to ours, achieving histopathologically 100% necrosis without severe toxicities. Aliberti et al. [3] with smaller doxorubicin-loaded microspheres of 70–150 μm (M170–DC Bead M1; BTG, London, United Kingdom) in HCC of a mean index tumor diameter of 20.0 mm achieved higher rates of CR reaching 55%, PR 12.8% but also PD in 30.2% without any grade 4 or 5 adverse events.

The hydrated HepaSphere 30–60 μm diameter lies between DC Bead 100–300 μm and M1 (70–150 μm). This diameter range has proven more efficacious and with lower complications compared to larger sizes [4] providing more distal distribution/embolization in histological studies compared to the HepaSphere 50–100 μm [8, 21] and also demonstrated to achieve a lower OR (63.3%) [29]. Although drug-eluting microspheres may not penetrate the portal venules and sinusoids as lipiodol does [30], they extend, cover and distribute over the corona area that contains microsatellites. The importance of the latter has been stressed by Miyayama et al. and is also acknowledged in drug-eluting chemoembolization studies that show that the residual viable tissue or local recurrence lies in the periphery of the treated lesion [30, 31]. Although mechanisms are not fully understood, other than incomplete embolization, peripheral recurrences may also be related to feeders from portal venules that have been documented in well-differentiated HCC [30, 31], or hypoxia-triggered neoangiogenesis [1]. These issues led the interventional community to shift to smaller microspheres for drug-eluting TACE after documentation of their satisfactory safety profile for sizes > 70 μm [2, 4]. Our study, however—as discussed above—achieved high CR rates even for lesions > 5 cm in diameter that for encapsulated tumors ranged from 37.5 to 83.7% (Table 2). Even smaller tightly calibrated microspheres of 40, 75 and 100 μm loaded with doxorubicin may achieve a more distal penetration and have shown good safety profile, but long-term results are still pending [5, 6].

LTTP in our entire patient cohort was 9.6 ± 4.3 months which are among the higher in drug-eluting chemoembolization clinical studies [42]. TTP is important in HCC because OS is impacted by additional therapies, patient crossover and the underlying cirrhosis. In our study, the LTTP due to local progression of the embolized target tumor was 11.9 ± 4.7 months for BCLC A and dropped to 7.9 ± 2.9 months for BCLC B (Table 4; $p < 0.005$). This is expected since in our study the most frequent reason for BCLC B classification was the presence of small visible satellites around the target tumor. Our LTTP was notably longer than that of the study of Kucukay et al. [32] who report 6.3 ± 5.6 months, most likely attributable to patient selection. In the study of Lee et al. [26], PFS rates at 6 months were 65.0% using DC Bead 100–300 μm. The mean TTP of patients presenting recurrence post-initial resection was 10.2 months in our study, while Covey et al. [33] report as high as 13 months.

In our study, median OS was 31.0 months, with 41.0 months for BCLC A, dropping to 26.0 months for BCLC B (Table 4). These are substantially higher rates than those reported by Gomes et al. [34] in their drug-eluting chemoembolization arm with 300–500 μm and smaller microspheres (100–300) with doxorubicin loading at the same level as in this study; they reported mean and median survival of 28.16 ± 2.75 and 15.00 ± 1.5 months,

respectively, in patients that had not undergone transplantation. Notably, for BCLC A, they report 25.46 ± 3.66 months mean OS and 14.00 ± 1.54 median OS, while for BCLC B patients the respective mean and median survival was 28.00 ± 2.70 and 17.00 ± 1.57 months. In his group with HepaSphere 30–60 μm with 53 patients, Kucukay et al. [32] had achieved 37.4 ± 3.3 mean OS and 6.3 ± 5.6 months TTP that is lower to ours most likely associated to the inclusion of BCLC C patients. Median survival in the DEB TACE arm in the study of Kloeckner et al. [35] was 369 days (12.3 months), notably 627 days (20.3 months) for Child–Pugh stage A and 226 days (7.5 months) for stage B. Lee et al. [26] using DC Bead 100–300 μm in 152 patients with a 67.8% Child–Pugh class A5 69.1% and A6 25% reported a 6-month survival of 97.4%. Chen et al. [36] reporting in 822 patients treated with DEB TACE present similar OS rates at 1, 2 and 3 years. Golfieri et al. [25] demonstrated that for lesions of a mean diameter of 3 cm or less, there is no difference in survival or LPFS between c-TACE and drug-eluting chemoembolization, although survival rates in their study were low in general, 86.2% and 56.8% in 1 and 2 years, respectively, possibly due to patient selection and low dosage of doxorubicin loading at 50 mg per session. Our OS in recurrences post-tumor resection was lower in comparison with the previous studies, most likely due to differences in the tumor load at baseline [33]. Prajapati et al. [4] in their subgroup of patients treated with 100–300 with BCLC B stage recorded OS of 10.1 months (4.3–22.2).

Higher survival than in our study was shown in the study of Aliberti et al. [3] with the smaller diameters 70–150 μm reaching a median OS of 42.0 months, despite the fact that he had included 45.8% patients with BCLC C stage, and from their results, it may be inferred that smaller diameters may achieve better OS. Substantially, higher long-term survival rates have been reported by Burrel et al. [18] with median OS for BCLC A of 40.2 months and 31.9 months for BCLC B and in a previous study with DC Bead 100–300 μm with 5-year rates that reach 22.5% [16]. However, these two studies included highly selected and non-consecutive patients; in Burrel et al. study, 95% of patients were Child–Pugh A. Univariate and multivariate analyses (supplement Tables 6, 7) demonstrated that OS and LPFS were shorter with ill-defined infiltrative borders, larger and multiple lesions ($p < 0.001$), as has also been shown in other studies with drug-eluting microspheres [23, 24].

Patency of vessels post drug-eluting embolization and c-TACE may be compromised [37–39] with authors favoring bland embolization to preserve vessel patency [39]. In our study, proximal feeding vessel occlusion was present in 11.3% not preventing administration of the intended dose in 90.8% most likely attributed to the routine use of nitroglycerine to the feeder, high dilution, however, elongated injection times.

Overall, AEs were below the threshold suggested by the quality improvement guidelines [16] and similarly low to other studies with the same embolic [9, 24] with the most frequent AE being mild post-embolization syndrome up to 67.4% without grade 4 or 5 AEs [2, 3, 24, 40], and without biliary injury that has been reported up to 19.7% in the DEM chemoembolization literature [26]. Post-embolization syndrome was quite mild in our series that may be attributed to the prophylactic administration of dexamethasone [41]. In both the current study and our prior escalation trial with HepaSphere 30–60 loaded with doxorubicin, adverse events were limited and manageable [9].

Limitations of the study include non-availability of control group, a relatively small number of patients, the nature of a single-center study, the fact that a significant amount consists of patients BCLC A with lesions not amenable to curative treatments because of tumor location or comorbidities that all affect the potential for extrapolation of the results. In addition, there are no pathology data with differentiation and high- versus low-grade tumors—that affects local response [42].

In conclusion, this study with 142 consecutive patients within the standard indications for drug-eluting chemoembolization confirms that HepaSphere microspheres 30–60 μm loaded with doxorubicin are safe and effective in local response and long-term survival with good results.

Compliance with Ethical Standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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