Chemoembolization of Hepatocellular Carcinoma with Drug-Eluting Polyethylene Glycol Embolic Agents: Single-Center Retrospective Analysis in 302 Patients

Filipe Veloso Gomes, MBChB, BSc, João A. Oliveira, MD, Mariana Tomé Correia, MD, Nuno Vasco Costa, MD, João Abrantes, MD, Daniel Torres, MD, Pedro Pereira, MD, Ana Isabel Ferreira, MD, José Hugo Luz, MD, Erik Spaepen, MSc, Tiago Bilhim, MD, PhD, and Élia Coimbra, MD

ABSTRACT

Purpose: To evaluate the efficacy and safety of transarterial chemoembolization with polyethylene glycol (PEG) drug-eluting embolic agents in the treatment of hepatocellular carcinoma (HCC).

Materials and Methods: A single-center retrospective study of 302 patients (258 men; 85.4%) with HCC treated during a 20-month period was conducted. The mean patient age was 66 years ± 10; 142 (47%) had Barcelona Clinic Liver Cancer stage A disease and 134 had (44.4%) stage B disease; 174 (57.6%) had a single HCC tumor, 65 (21.5%) had 2, and 62 (20.9%) had 3 or more. Mean index tumor size was 36.6 mm ± 24.8. One-month follow-up computed tomography (CT) response per modified Response Evaluation Criteria In Solid Tumors and clinical and biochemical safety were analyzed. Progression-free and overall survival were calculated by Kaplan–Meier method.

Results: Median follow-up time was 11.9 months (95% confidence interval, 11.0–13.0 mo). One-month follow-up CT revealed complete response in 179 patients (63.2%), partial response in 63 (22.3%), stable disease in 16 (5.7%), and progressive disease in 25 (8.8%). The most frequent complications were postembolization syndrome in 18 patients (6%), liver abscess in 5 (1.7%), and puncture-site hematoma in 3 (1%). Biochemical toxicities occurred in 57 patients (11.6%). Survival analysis at 12 months showed a progression-free survival rate of 65.9% and overall survival rate of 93.5%. Patients who received transplants showed a 57.7% rate of complete pathologic response.

Conclusions: Chemoembolization with PEG embolic agents for HCC is safe and effective, achieving an objective response rate of 85.5%.

ABBREVIATIONS

CI = confidence interval, CR = complete response, DEE = drug-eluting embolic, EASL = European Association for the Study of the Liver, HCC = hepatocellular carcinoma, mRECIST = modified Response Evaluation Criteria In Solid Tumors, PEG = polyethylene glycol, PR = partial response, RF = radiofrequency, ROC = receiver–operating characteristic

From the Interventional Radiology Unit, Hepato-Biliary-Pancreatic and Transplant Center (F.V.G., M.T.C., N.V.C., D.T., J.H.L., T.B., É.C.), Hospital Curry Cabral, Centro Hospitalar Lisboa Central, Rua da Beneficência 8, 1050-099, Lisbon, Portugal; Department of Radiology (J.A.O.), Hospital Geral de Santo António, Centro Hospitalar do Porto, Porto, Portugal; Department of Radiology (J.A.), Hospital Nossa Senhora do Rosário, Centro Hospitalar Barreiro-Montijo, Barreiro, Portugal; Department of Radiology (P.P.), Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal; Department of Radiology (A.I.F.), Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte, Lisbon, Portugal; SBD Analytics (E.S.), Bekkevoort, Belgium; and Department of Radiology (T.B.), NOVA Medical School, Universidade NOVA de Lisboa, Lisbon, Portugal. Received December 13, 2017; final revision received January 31, 2018; accepted February 4, 2018. **Address correspondence to** F.V.G.; E-mail: fvgomes@gmail.com

F.V.G. receives statistical support and personal fees from Terumo (Tokyo, Japan). T.B. receives statistical support from and is a paid consultant of Terumo and receives personal fees from Merit Medical (South Jordan, Utah). None of the other authors have identified a conflict of interest.

J Vasc Interv Radiol 2018; 29:841–849

https://doi.org/10.1016/j.jvir.2018.02.004

Transarterial chemoembolization is currently indicated for the treatment of patients with intermediate-stage hepatocellular carcinoma (HCC) according to the American Association for the Study of Liver Diseases and European Association for the Study of Liver Diseases (EASL)/European Organization for Research and Treatment of Cancer recommendations on the management of HCC (1,2). Chemoembolization, either conventional or with the use of drug-eluting embolic (DEE) agents (3), is also one of the recommended options as a "bridge" therapy for liver transplantation candidates with stage T1 and T2 HCC tumors while on the waiting list based on assessment of the patient's liver function, expected waiting time, and the organ allocation policy of each country or region (2). However, no specific locoregional therapy has been recommended over the others, including thermal ablation, combination treatments, or radioembolization, raising the need for continuous research in this area. Currently, there are a number of DEE agents available on the market, and an in vitro comparison of a variety of characteristics of each of the microspheres was published recently (4), describing their drug-loading and elution properties, diameter changes after loading, changes after 2 weeks in storage, and time in suspension. Two preliminary studies by the same group (5,6) have reported clinical experiences with the recently developed polyethylene glycol (PEG) LifePearl microspheres (Terumo, Tokyo, Japan) for DEE chemoembolization in a cohort of 20 patients with primary and metastatic liver cancer (5) and in a cohort of 42 patients with HCC (6).

The purpose of the present study is to evaluate the efficacy and safety of DEE chemoembolization with the use of PEG embolic agents in the treatment of HCC in 302 patients during a 20-month period of time.

MATERIALS AND METHODS

Study Design

The present study was conducted in a single liver transplantation center and retrospectively reports a 20-month experience between September 2015 and April 2017, during which 302 patients with HCC were treated with DEE agent chemoembolization. The time frame of the study was chosen to allow an extensive number of patients to be included to strengthen the analysis. This study was approved by the local ethics committee. The manuscript was written based on the Strengthening the Reporting of Observational Studies in Epidemiology Statement.

Patients

Eligible participants included 333 patients with inaugural HCC, referred from a multidisciplinary tumor board, consecutively treated with DEE chemoembolization at a single interventional radiology (IR) unit. Only the 302 patients who had 1-month follow-up contrast-enhanced computed tomography (CT) after treatment and/or follow-up blood tests, obtained as long as 3 months after treatment, were included (**Fig 1**). The indication for chemoembolization was HCC diagnosed per EASL/American Association for the Study of Liver Diseases criteria. Contraindications for chemoembolization included extrahepatic disease, bilirubin levels greater than 2 mg/dL, and complete portal vein thrombosis or tumor portal vein invasion. During the 20-month study period, 302 patients were treated with DEE chemoembolization: 258 men (85.4%) and 44 women (14.6%), with a mean age of 66 years ± 10. The baseline characteristics of the patients and tumors are summarized in **Table 1**.

DEE Chemoembolization Procedure

All DEE chemoembolization procedures were performed by three interventional radiologists with 4–25 years of experience. One day before treatment, patients were admitted to the hospital and evaluated according to the admission protocol, including clinical and biochemical evaluation. At the IR unit, patients received intravenous prophylactic antibiotic therapy (cefazolin 2 g) and sedative/analgesic therapy (midazolam 1 mg, paracetamol 1 g, metamizole magnesium 2 g). Vascular access was achieved through the common femoral artery. A 5-F Simmons catheter (Cordis, Somerset, New Jersey) was used to catheterize the celiac trunk or anatomic variant to gain access to the hepatic arteries, which was achieved with a 2.7-F Progreat microcatheter (Terumo). Diagnostic angiographic runs were obtained at the celiac trunk and proper hepatic and right and left hepatic arteries to define tumor arterial supply. DEE chemoembolization was performed after superselective catheterization of the tumor-feeding artery (or arteries), and 1 or 2 vials of LifePearl microspheres (Terumo), charged with 75 mg of doxorubicin each for a maximum dose of 150 mg per session, were administered until near-stasis was achieved, defined as stasis of contrast medium during 5 heartbeats (7). A final manual angiographic run was performed to confirm effective embolization. In patients with large tumors and remaining arterial feeding vessels on control angiography, a second chemoembolization procedure was planned 3–4 weeks later.

Evaluation of Tumor Response

The efficacy of DEE chemoembolization was the primary outcome of this study. Efficacy was measured as the response on 1-month follow-up contrast-enhanced CT according to modified Response Evaluation Criteria In Solid Tumors (mRECIST) (8), categorized into four groups: complete response (CR), partial response (PR), stable disease, or progressive disease. Evaluation of response was performed by three radiologists with 4–25 years of experience in reading follow-up CT images for the purpose of evaluation of tumor response after DEE chemoembolization.

Evaluation of Safety

Safety was measured clinically, with symptoms (pain, nausea, vomiting) and vital signs (heart rate, blood pressure,

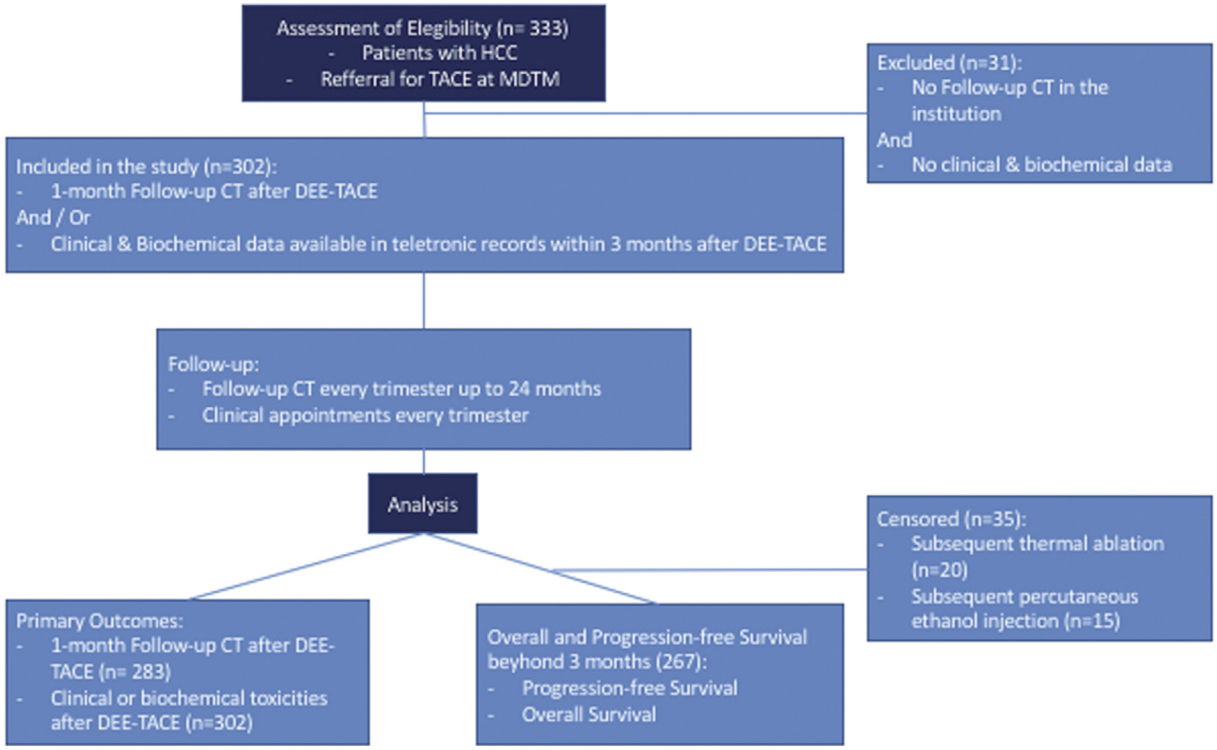


Figure 1. Patient flowchart.

temperature) recorded on the patients' charts. Grade 3 complications were recorded per Society of Interventional Radiology Quality Improvement Guidelines for the Reporting and Archiving of Interventional Radiology Procedures (9). Minor complications are usually not recorded, so it was not possible to accurately account for them retrospectively. Blood test results collected before and as long as 3 months after the procedure were evaluated in all patients and were reported when white blood cell count, aspartate/alanine aminotransferase level, total bilirubin level, albumin level, and International Normalized Ratio changed after chemoembolization.

Discharge and Follow-up

Patients were discharged the day after treatment unless there were signs or symptoms of complications. Follow-up with imaging and clinic appointments took place 1 month after the treatment and every 3 months thereafter. Repeat treatment was performed in all patients with less than a CR at 1-month follow-up CT or with disease progression on subsequent follow-up CT unless a new contraindication arose or if the patient received a transplant during the waiting period.

Liver Transplantation Procedure and Explant Histopathology

Liver transplantation procedures were performed by using the "double-piggyback" technique with deceased donor livers, familial amyloidotic polyneuropathy "domino" liver transplants (10), or living-donor livers. Liver explants were analyzed by 1 of 3 pathologists with more than 10 years of experience in liver pathology. The number of tumors, size of each tumor, percentage of necrosis of each tumor, and presence of vascular and lymphatic invasion were reported. Tumor differentiation was graded according to the Edmonson and Steiner system. Complete necrosis was defined as $\geq$ 90% necrosis of the HCC nodule(s) in the explant liver.

Statistical Methods

As this was an exploratory, retrospective study of consecutively treated patients in a single clinical center, no sample-size calculations were performed. Descriptive statistics are presented as means and standard deviations for continuous variables and frequencies and percentages for categoric variables. The complete response rate at 1 month and overall response rate (including CR and PR) for the duration of the study period are reported. Analyses of time-to-event outcomes such as overall survival and progression-free survival (ie, time to progression or death) are reported per Kaplan–Meier method, with means $\pm$ standard errors and medians with 95% confidence intervals (CIs) of times to event (in months). Censoring was performed at the date of cutoff or loss to follow-up. Additionally, 35 patients were censored after the 1-month contrast-enhanced CT to avoid confounding results because they had undergone treatments other than DEE chemoembolization. Therefore, progression-free and overall survival results are based on the follow-up of patients treated with DEE chemoembolization only. No imputation techniques for missing data were used.

Table 1. Baseline Characteristics of 302 Patients Treated with DEE Chemoembolization

Characteristic	Value
Sex	
Male	258 (85.4)
Female	44 (14.6)
Age (y)	66 ± 10
Cause of liver disease	
Alcohol	132 (45.4)
Hepatitis C virus	57 (19.6)
Alcohol/hepatitis C virus	61 (21)
Other	40 (14)
ECOG PS 0/1	302 (100)
Child–Pugh class	
A	215 (82.7)
B	41 (15.8)
C	4 (1.5)
BCLC class	
0	21 (7)
A	142 (47)
B	134 (44.4)
C	3 (1)
D	2 (0.6)
MELD score	
1–9	209 (76.6)
10–19	61 (22.3)
20–29	3 (1.1)
Liver transplant candidate*	109 (36.1)
Liver transplant performed†	25 (8.3)
No. of tumors	
1	174 (57.6)
2	65 (21.5)
≥ 3	63 (20.9)
Size of index tumor (mm)	38.3 ± 25
Sum of tumor size (mm)	47.4 ± 30.1
α-Fetoprotein > 200 ng/mL	45 (16.9)
No. of treatments	1.5 ± 0.7

Note–Values presented as mean ± standard deviation where applicable. Values in parentheses are percentages.
DEE = drug-eluting embolic; BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group; MELD = Model for End-stage Liver Disease; PS = performance status.
*Disease meets Milan criteria for transplantation, without known contraindications.
†Patients who underwent liver transplantation during the study period.

Univariate analysis and multivariate stepwise selection models with entry and stay P values of $P = .40$ and $P = .15$ were performed, respectively, in an attempt to identify predictors of CR and complications with logistic regression models and to identify predictors of time to disease-free and overall survival with Cox proportional-hazards models. The diagnostic accuracy of 1-month follow-up contrast-enhanced CT to detect complete pathologic necrosis was analyzed by performing receiver–operating characteristic (ROC) curve analysis. Statistical analysis was performed by using STATA (version 13; StataCorp, College Station, Texas) and SAS (version 9.4; SAS, Cary, North Carolina).

Table 2. One-Month Follow-up CT Response per mRECIST after Additional DEE Chemoembolization Sessions

Response	Additional Chemoembolizations			Total (N = 283)
	1 (n = 233)	2 (n = 45)	≥ 3 (n = 5)	
CR	157 (67.4)	19 (41)	3 (60)	179 (63.2)
PR	47 (20.2)	15 (34)	1 (20)	63 (22.3)
SD	11 (4.7)	5 (11.4)	0	16 (5.7)
PD	18 (7.7)	6 (13.6)	1 (20)	25 (8.8)

Note–Values in parentheses are percentages. Nineteen patients had no follow-up CT 1 month after chemoembolization as a result of transplantation (n = 1), death (n = 2), CT at a later date (n = 3), or loss to follow-up (n = 13).
CR = complete response; DEE = drug-eluting embolic; mRECIST = modified Response Evaluation Criteria In Solid Tumors; PD = progressive disease; PR = partial response; SD = stable disease.

RESULTS

Tumor Response

Median follow-up time was 11.9 months (95% CI, 11.0–13.0). Response rates per mRECIST at 1-month contrast-enhanced CT after DEE chemoembolization are shown in Table 2 for 233 patients after a single treatment session, for 45 patients after two treatment sessions, and for 5 patients after three treatment sessions. Response rates and the numbers of patients at 1, 3, 6, 9, and 12 months of follow-up per mRECIST are shown in Table 3. Among the 104 patients who did not show CR at 1-month contrast-enhanced CT (Table 2), 14 had no further treatments, 55 had at least one more DEE chemoembolization treatment, 20 underwent percutaneous microwave ablation, and 15 underwent percutaneous ethanol injection. The introduction of different therapies confounds survival analysis and even subsequent follow-up imaging. Therefore, the 35 patients who had further treatments other than DEE chemoembolization were excluded from subsequent tumor response and survival analysis. Identification of predictors of CR with univariate analysis and multivariate analysis showed that patients with multiple tumors were less likely to show CR at 1-month contrast-enhanced CT, although this did not reach statistical significance ($P = .0748$). Regarding the best overall CR during the study period, multivariate analysis identified patients with larger total tumor size ($P = .0188$) as less likely to show CR.

Safety and Complications

The major complications observed were postembolization syndrome in 18 patients (6%), liver abscess in 5 (1.6%), puncture-site complications in 3 (1%), portal vein thrombosis in 2 (0.7%), cholecystitis requiring cholecystectomy in 2 (0.7%), alopecia in 2 (0.7%), nontarget embolization of

Table 3. Tumor Response per mRECIST after DEE Chemoembolization

Response	Follow-up				
	1 mo (n = 283)	3 mo (n = 147)	6 mo (n = 115)	9 mo (n = 81)	12 mo (n = 57)
CR	179 (63.2)	104 (70.8)	69 (60)	50 (61.7)	39 (68.4)
PR	63 (22.3)	2 (1.4)	5 (4.3)	2 (2.5)	0
SD	16 (5.7)	9 (6.1)	7 (6.1)	15 (18.5)	4 (7)
PD	25 (8.8)	32 (21.7)	34 (29.6)	14 (17.3)	14 (24.6)

Note–Values in parentheses are percentages.
CR = complete response; DEE = drug-eluting embolic; mRECIST = modified Response Evaluation Criteria In Solid Tumors; PD = progressive disease; PR = partial response; SD = stable disease.

the stomach and spleen in 1 (0.3%), cardiovascular toxicity in 1 (0.3%), and death in 2 (0.7%). The two deaths were caused by liver failure 1 month after treatment in one case, in a patient with previous episodes of hepatic decompensation requiring admission to the hospital, and acute leukemia in the other case, also 1 month after treatment. Nontarget embolization to the stomach and spleen occurred in one patient with a left lobe tumor and a variant left hepatic artery originating from the left gastric artery, resulting in gastric ulcer documented by endoscopy, which was treated conservatively, and spleen embolization documented by CT, both attributed to control angiography inadvertently performed with a power injector. Biochemical toxicities at 1–3 months after treatment occurred in 57 patients (11,6%), with increased aspartate/alanine aminotransferase levels in 14 (4.6%), increased bilirubin level in 12 (4%), leukopenia in 2 (0.7%), and other biochemical abnormalities in 7 (2.3%). Univariate statistical analysis identified Child–Pugh class B/C disease and multiple tumors as predictors of clinical or biochemical toxicities. However, only the presence of multiple tumors remained a significant predictor on multivariate analysis (Table 4). Specifically regarding the risk of developing postembolization syndrome, univariate and multivariate analyses could not identify specific predictors.

Progression-Free and Overall Survival

The Kaplan–Meier estimate of progression-free survival, censored at cutoff or loss to follow-up, was 65.1% (95% CI, 58.4%–71.0%) at 12 months, with a mean time to event and standard error of 14.3 months ± 0.5 and median time to event not estimable because of the low number of events. Overall survival at 12 months, censored at cutoff or loss to follow-up, was 93.2% (95% CI, 87.8%–95.9%), with a mean time to event of 18.6 months ± 0.4 and median time to event not estimable because of the low number of deaths. Both Kaplan–Meier curves are shown in Figure 2.

Identification of predictors of progression-free and overall survival was performed with Cox regression using a multivariate stepwise selection model, with entry and stay P values of $P = .40$ and $P = .15$, respectively.

Table 4. Logistic-Regression Model Predictors of Primary Outcomes

Outcome/Predictor	Odds Ratio (95% CI)	*P* Value
CR at 1-mo CT		
Multiple tumors	0.74 (0.532–1.031)	.0748
Best overall CR		
Total tumor size	0.937 (0.888–0.989)	.0188
Any clinical or biochemical toxicity		
Multiple tumors	2.159 (1.035–3.651)	.0388

Note–Multivariate stepwise selection model: entry and stay P values of $P = .40$ and $P = .15$, respectively. Variables included female sex, age, transplantation candidacy, cause of chronic hepatic disease, Barcelona Clinic Liver Cancer class, Child–Pugh score, Model for End-stage Liver Disease score, α-fetoprotein level, multiple tumors, and total tumor size.
CI = confidence interval; CR = complete response; OR = odds ratio.

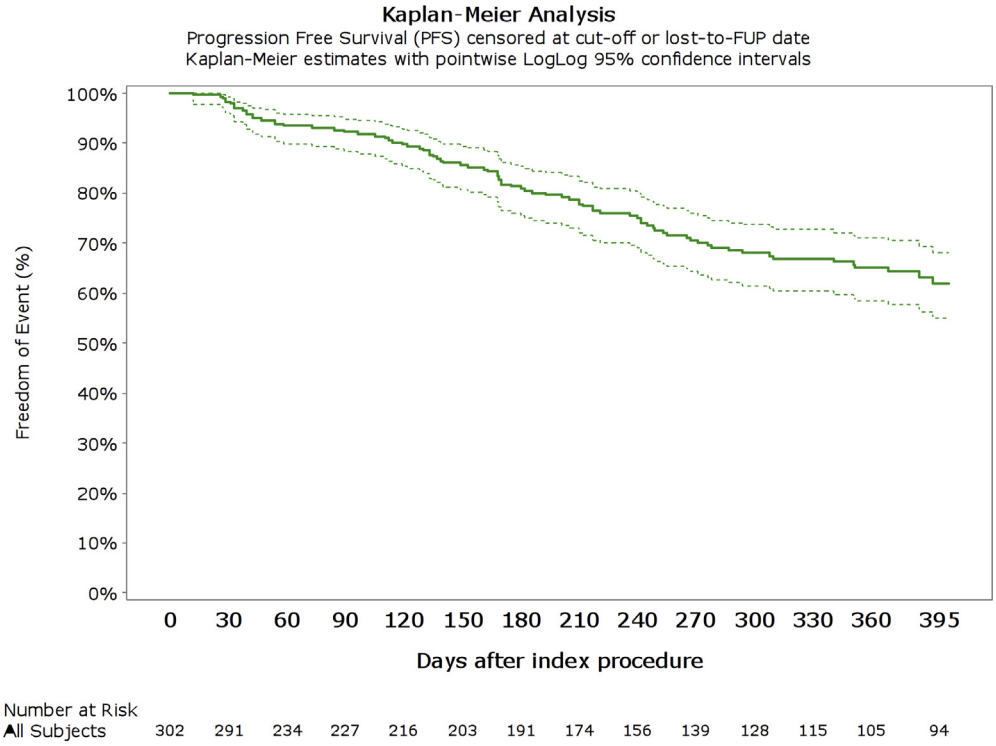
Intermediate or advanced disease stage per Barcelona Clinic Liver Cancer criteria ($P < .0001$), Child–Pugh class B/C disease ($P = .0002$), and α-fetoprotein level > 200 ng/mL ($P = .0025$) were identified as predictors of earlier progression (Table 5). Child–Pugh class B/C disease ($P = .0089$) and total tumor size ($P = .0061$) were identified as a predictors of earlier mortality (Table 6).

Transplant Recipients

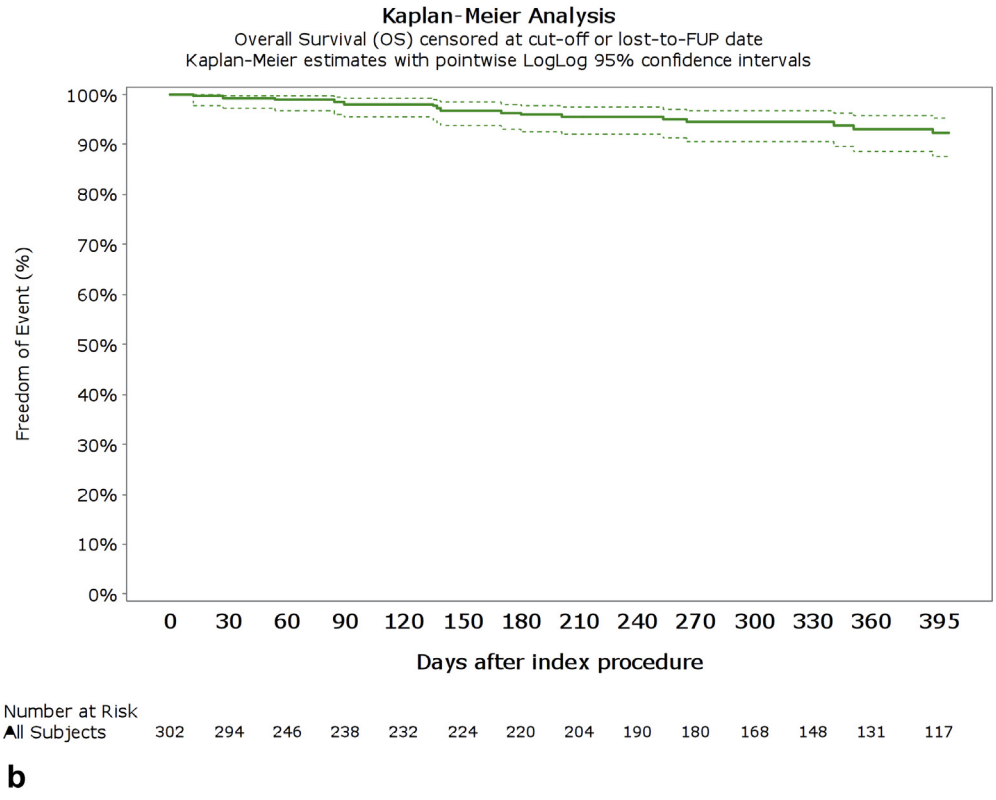
During the study period, 26 of 109 eligible patients (23.9%) whose disease met the Milan criteria underwent liver transplantation. The mean time from DEE chemoembolization to liver transplantation was 176.1 days ± 107.8 (range, 37–447 d). Pathologic analysis of the explants revealed a mean of 73% ± 27 tumor necrosis, with 57.7% of patients (15 of 26) showing a complete pathologic response (ie, > 90% necrosis) in the explant liver, 38.5% (10 of 26) showing a PR (ie, 30%–89% necrosis), and 3.9% (1 of 26) showing no response (ie, < 30% necrosis). Only 19.2% of patients (5 of 26) had less than 50% necrosis. All 15 patients with a complete pathologic response on explant analysis showed CR on 1-month contrast-enhanced CT. Among the 11 patients without a complete pathologic response, 7 had CR on 1-month contrast-enhanced CT, 3 had PR, and 1 had stable disease. The complete pathologic response rate for patients who received transplants was 57.7%. Figure 3 illustrates a case of CR on 1-month contrast-enhanced CT with complete pathologic response. ROC curve analysis was performed to determine the accuracy of 1-month contrast-enhanced CT to detect a complete pathologic response and showed a sensitivity of 100%, specificity of 55%, and area under the curve of 0.7727.

DISCUSSION

The present study demonstrates transarterial chemoembolization with PEG DEE agents loaded with 75 mg of



a



b

Figure 2. Kaplan–Meier estimates of progression-free **(a)** and overall survival **(b)** censored at cutoff or loss to follow-up.

doxorubicin to be a safe and effective treatment for intermediate-stage HCC per Barcelona Clinic Liver Cancer criteria and in liver transplantation candidates (per Milan criteria) as a bridge to transplantation.

DEE chemoembolization has been established as an alternative to conventional chemoembolization in the treatment of HCC, with recent meta-analysis reporting a statistically significant advantage of DEE chemoembolization

Table 5. Cox Regression Model Predictors of Progression-Free Survival

Predictor	HR (95% CI)	*P* Value
BCLC class B/C	2.982 (1.978–4.495)	< .0001
Child–Pugh class B/C	2.345 (1.491–3.689)	.0002
AFP level > 200 ng/mL	2.122 (1.303–3.457)	.0025

Note–Multivariate stepwise selection model: entry and stay *P* values of $P = .40$ and $P = .15$, respectively. Variables included female sex, age, transplantation candidacy, cause of chronic hepatic disease, BCLC class, Child–Pugh score, Model for End-stage Liver Disease score, AFP level, multiple lesions, and total lesion size.
AFP = α-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; CI = confidence interval; HR = hazard ratio.

Table 6. Predictors of Overall Survival on Multivariate Cox Regression Analysis

Predictor	HR (95% CI)	*P* Value
Child–Pugh class B/C	3.172 (1.335–7.534)	.0089
Total lesion size	1.182 (1.049–1.332)	.0061

Note–Multivariate stepwise selection model: entry and stay *P* values of $P = .40$ and $P = .15$, respectively. Variables included female sex, age, transplantation candidacy, cause of chronic hepatic disease, Barcelona Clinic Liver Cancer class, Child–Pugh class, Model for End-stage Liver Disease score, α-fetoprotein level, multiple lesions, and total lesion size.
CI = confidence interval; HR = hazard ratio.

over conventional chemoembolization in achieving CR and fewer adverse events (11–13). In addition, a recent cost-effectiveness analysis demonstrated the superiority of DEE chemoembolization, even though this may vary depending on reimbursement schemes and costs of products (14).

Treatment response to DEE chemoembolization should be assessed 1 month after treatment with contrast-enhanced CT or magnetic resonance imaging (7). mRECIST and EASL criteria have been shown to be reproducible and well-correlated with pathologic necrosis (15). In addition, evaluation at 1 month with mRECIST may be predictive of survival (16) and a valid criterion for selection for liver transplantation (17). Previous studies of chemoembolization in HCC have shown varied but consistent results in terms of CT response at 1 month per mRECIST or EASL criteria. Reported results in the literature show an overall CR rate between 38.5% and 70% and an objective response rate (ie, CR plus PR) between 72.7% and 100% (6,17–19). The present results show a CR rate of 63.2% and objective response rate of 85.5%.

The accuracy of 1-month contrast-enhanced CT in detecting a complete pathologic response in the 26 patients who received transplants, based on ROC curve analysis, supports the previously described finding that CT overestimates the response after chemoembolization in comparison with pathologic findings (20). Although overestimation of response by CT may be the result of technical limitations, it may also be influenced by the presence of residual microscopic tumor in the treatment area, the presence of undetected satellite tumors before the treatment, or the growth of new tumors.

In cases of bridge therapy for liver transplantation candidates with HCC, Nicolini et al (21) showed a better response and recurrence-free survival after transplantation when patients were treated with DEE chemoembolization rather than conventional chemoembolization and hypothesized that the inflammatory fibrotic reaction observed around the microspheres, also previously demonstrated by Namur (22), could possibly lead to better local tumor control. Frenette et al (23) found that both chemoembolization techniques were similar in terms of local tumor control on explant pathologic analysis and in limiting rates of dropout from the transplant waiting list.

There is controversy regarding the need for a complete pathologic response in the context of bridge treatment before liver transplantation. Agopian et al (24) have shown that complete pathologic response can increase recurrence-free survival after liver transplantation in patients undergoing chemoembolization, radiofrequency ablation, or combined chemoembolization and radiofrequency ablation. However, in a study by Beal et al (25) in a cohort of patients who underwent bridge therapy with chemoembolization (both conventional and with drug-eluting microspheres) or thermal ablation (radiofrequency and microwave) before liver transplantation, the authors concluded that serial bridging in an attempt to achieve a complete pathologic response is not needed and that a CR observed on follow-up CT suffices before transplantation in the context of HCC, as the outcomes were similar in both settings. Only 19.2% of patients (5 of 26) had less than 50% necrosis on explant pathologic analysis, which has been previously associated with a worse 5-year recurrence-free survival rate after liver transplantation (26).

Transarterial chemoembolization with DEE agents is associated with fewer complications than conventional chemoembolization, particularly regarding systemic effects, according to previous reports (27). The main complications described in the literature include postembolization syndrome, a constellation of pain, nausea, and fever, which is not clearly defined and may vary among reports, affecting 15%–85% of patients (28). Systemic complications of DEE chemoembolization may affect as many as 12% of patients. In the present cohort, the three most frequent major complications were postembolization syndrome in 18 patients (6%), liver abscesses in 5 (1.6%), and puncture site (ie, femoral artery) complications in 3 (1%). Regarding systemic complications, alopecia occurred in 2 patients (0.7%), nontarget embolization in 1 (0.3%), and cardiovascular toxicity in 1 (0.3%), and there were 2 fatalities within 30 days of the procedure (0.7%). Regarding the most common complication, postembolization syndrome, the present study could not identify any independent predictors of risk. This is in contrast with a previous study (29) performed at the

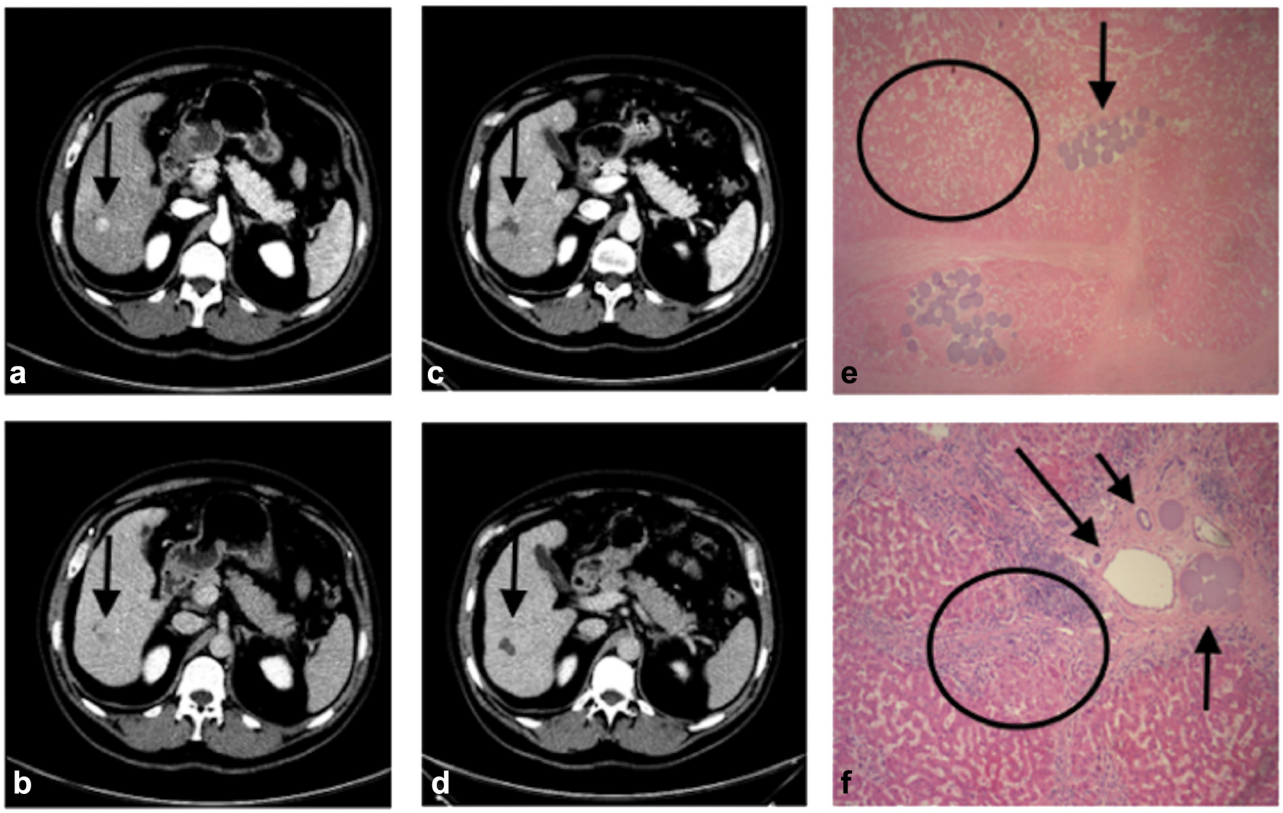


Figure 3. Images from a 50-year-old man with hepatitis C virus–associated cirrhosis and a single 1.6-cm HCC nodule in segment VI. **(a)** Hypervascular tumor (arrow) is shown on arterial-phase contrast-enhanced CT before treatment. **(b)** Washout (arrow) is shown on portal venous-phase contrast-enhanced CT before treatment. **(c)** No enhancement (arrow) is shown on arterial-phase contrast-enhanced CT at 1-month follow-up. **(d)** No enhancement (arrow) is shown on portal venous-phase contrast-enhanced CT at 1-month follow-up. **(e)** Complete tumor necrosis is marked by the circle. (Hematoxylin and eosin stain; original magnification, 10×.) LifePearl microspheres are shown in light purple (arrow). **(f)** Liver fibrosis is marked by the circle. (Hematoxylin and eosin stain; original magnification, 10×.) The portal triad is marked, with the portal vein (long diagonal arrow), bile ductule with epithelial lining (short diagonal arrow), and peripheral arterial branches occluded by microspheres (vertical arrow). LifePearl microspheres are shown in light purple.

present authors' institution in a completely different cohort of 276 patients treated with DEE chemoembolization with different embolic agents, which identified the dose of doxorubicin, the size of the largest tumor, and female sex as risk factors for the development of PES after DEE chemoembolization.

Limitations of the present study include the retrospective nature of the study in a single center, the heterogenous nature of the patient sample typical of an HCC cohort, and the lack of evaluation of patient-reported outcomes, which has not been standardized in the authors' practice. Additionally, the study period was too short to allow a robust evaluation of overall survival, particularly because the results in the present cohort were affected by early transplantation complications. Finally, survival analysis should be interpreted with caution, given the absence of matched controls to compare causes of death and comorbidity profiles.

In conclusion, transarterial chemoembolization with PEG DEE agents is effective and safe for the treatment of HCC and as a bridge therapy for patients awaiting liver transplantation, achieving a high CR rate at 1-month follow-up contrast-enhanced CT and a low rate of major complications.

REFERENCES

1. European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. Eur J Cancer 2012; 48:599–641.
2. Heimbach JK, Kulik LM, Finn R, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2017; 67:358–380.
3. Gaba RC, Lewandowski RJ, Hickey R, et al. Transcatheter therapy for hepatic malignancy—standardization of terminology and reporting criteria. J Vasc Interv Radiol 2016; 27:457–473.
4. de Baere T, Plotkin S, Yu R, Sutter A, Wu Y, Cruise GM. An in vitro evaluation of four types of drug-eluting microspheres loaded with doxorubicin. J Vasc Interv Radiol 2016; 27:1425–1431.
5. Aliberti C, Carandina R, Sarti D, et al. Hepatic arterial infusion of polyethylene glycol drug-eluting beads for primary and metastatic liver cancer therapy. Anticancer Res 2016; 36:3515–3521.
6. Aliberti C, Carandina R, Sarti D, et al. Chemoembolization adopting polyethylene glycol drug-eluting embolics loaded with doxorubicin for the treatment of hepatocellular carcinoma. AJR Am J Roentgenol 2017; 209: 430–434.
7. Lencioni R, de Baere T, Burrel M, et al. Transcatheter treatment of hepatocellular carcinoma with doxorubicin-loaded DC Bead (DEBDOX): technical recommendations. Cardiovasc Intervent Radiol 2012; 35:980–985.

8. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010; 30:52–60.
9. Omary RA, Bettmann MA, Cardella JF, et al. Quality improvement guidelines for the reporting and archiving of interventional radiology procedures. J Vasc Interv Radiol 2003; 14(suppl):S293–S295.
10. Marques HP, Ribeiro V, Almeida T, et al. Long-term results of domino liver transplantation for hepatocellular carcinoma using the "double piggyback" technique: a 13-year experience. Ann Surg 2015; 262:749–756.
11. Zou JH, Zhang L, Ren ZG, Ye SL. Efficacy and safety of cTACE versus DEB-TACE in patients with hepatocellular carcinoma: a meta-analysis. J Dig Dis 2016; 17:510–517.
12. Facciorusso A, Di Maso M, Muscatiello N. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: a meta-analysis. Dig Liver Dis 2016; 48:571–577.
13. Xie ZB, Wang XB, Peng YC, et al. Systematic review comparing the safety and efficacy of conventional and drug-eluting bead transarterial chemoembolization for inoperable hepatocellular carcinoma. Hepatol Res 2014; 45:190–200.
14. Cucchetti A, Trevisani F, Cappelli A, et al. Cost-effectiveness of doxorubicin-eluting beads versus conventional trans-arterial chemo-embolization for hepatocellular carcinoma. Dig Liver Dis 2016; 48:798–805.
15. Dioguardi Burgio M, Ronot M, Bruno O, et al. Correlation of tumor response on computed tomography with pathological necrosis in hepatocellular carcinoma treated by chemoembolization before liver transplantation. Liver Transpl 2016; 22:1491–1500.
16. Yeo DM, Choi JI, Lee YJ, Park MY, Chun HJ, Lee HG. Comparison of RECIST, mRECIST, and choi criteria for early response evaluation of hepatocellular carcinoma after transarterial chemoembolization using drug-eluting beads. J Comput Assist Tomogr 2014; 38:391–397.
17. Bargellini I, Vignali C, Cioni R, et al. Hepatocellular carcinoma: CT for tumor response after transarterial chemoembolization in patients exceeding Milan criteria–selection parameter for liver transplantation. Radiology 2010; 255:289–300.
18. 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.
19. Boatta E, Corona M, Cannavale A, Fanelli F, Cirelli C, de Medici L. Endovascular treatment of hepatocellular carcinoma with drug eluting microparticles (DC-Beads): CT evaluation of response to the treatment. Indian J Radiol Imaging 2013; 23:126–133.
20. Bargellini I, Bozzi E, Campani D, et al. Modified RECIST to assess tumor response after transarterial chemoembolization of hepatocellular carcinoma: CT-pathologic correlation in 178 liver explants. Eur J Radiol 2013; 82:e212–e218.
21. Nicolini D, Svegliati-Baroni G, Candelari R, et al. Doxorubicin-eluting bead vs conventional transcatheter arterial chemoembolization for hepatocellular carcinoma before liver transplantation. World J Gastroenterol 2013; 19:5622–5632.
22. Namur J, Citron SJ, Sellers MT, et al. Embolization of hepatocellular carcinoma with drug-eluting beads: doxorubicin tissue concentration and distribution in patient liver explants. J Hepatol 2011; 55: 1332–1338.
23. Frenette CT, Osorio RC, Stark J, et al. Conventional TACE and drug-eluting bead TACE as locoregional therapy before orthotopic liver transplantation: comparison of explant pathologic response. Transplantation 2014; 98:781–787.
24. Agopian VG, Morshedi MM, McWilliams J, et al. Complete pathologic response to pretransplant locoregional therapy for hepatocellular carcinoma defines cancer cure after liver transplantation: analysis of 501 consecutively treated patients. Ann Surg 2015; 262: 536–545.
25. Beal EW, Dittmar KM, Hanje AJ, et al. Pretransplant locoregional therapy for hepatocellular carcinoma: evaluation of explant pathology and overall survival. Front Oncol 2016; 6:52–57.
26. Kornberg A, Witt U, Küpper B, Wildgruber M, Friess H. Postinterventional tumor necrosis predicts recurrence-free long-term survival in liver transplant patients with advanced hepatocellular carcinoma. Transplant Proc 2013; 45:1913–1915.
27. 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.
28. Malagari K, Pomoni M, Spyridopoulos TN, et al. Safety profile of sequential transcatheter chemoembolization with DC Bead™: results of 237 hepatocellular carcinoma (HCC) patients. Cardiovasc Intervent Radiol 2011; 34:774–785.
29. Lima M, Dutra S, Veloso Gomes F, Bilhim T, Coimbra E. Risk factors for the development of postembolization syndrome after transarterial chemoembolization for hepatocellular carcinoma treatment. Acta Med Port 2018; 31:22–29.