CLINICAL INVESTIGATION

Transarterial Chemoembolization for Hepatocellular Carcinoma with Drug-Eluting Microspheres: Preliminary Results from an Italian Multicentre Study

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Abstract The purpose of this article is to present the early results of a multicentre trial using HepaSphere microspheres loaded with chemotherapeutic agents for transarterial chemoembolization (TACE) in patients with unresectable hepatocellular carcinoma. From December 2005 to March 2007, 50 patients (36 male and 14 female, mean age 68.4 years) were treated by selective TACE using HepaSphere microspheres loaded with doxorubicin or epirubicin. The diameter of the treated lesions ranged from 20 to 100 mm (mean 42.5; maximum of 4 tumor nodules). Tumor response was evaluated by computed axial tomography according to the World Health Organization criteria as modified by the European Association for the Study of Liver Diseases. All of the procedures were technically successful, and there were no major complications. At 1-month follow-up, complete tumor response was observed in 24 of 50 (48%), partial response in 18 of 50 (36%), and stable disease in 8 of 50 (16%) patients, and there were no cases of disease progression. At 6-month follow-up (31 of 50 patients), complete tumor response was obtained in 16 of 31 (51.6%), partial response in 8 of 31 (25.8%), and progressive disease in 7 of 31 (22.6%)
patients. Within the initial 9-month follow-up, TACE with HepaSphere was successfully repeated twice in 3 patients, whereas 3 patients underwent the procedure 3 times. Our initial multicentre experience demonstrates that TACE using HepaSphere is feasible, is well tolerated, has a low complication rate, and is associated with promising tumor response. When complete tumor response in not achieved, additional treatments can be performed without difficulties. Longer follow-up on larger series is mandatory to confirm these preliminary results.

Keywords TACE · Hepatocellular carcinoma · Hepatic embolization · Drug-loaded microspheres · Interventional radiology

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Introduction

Hepatocellular carcinoma (HCC) represents the fifth most common cancer in the world and ranks third among cancer-related deaths, and its annual incidence continues to increase. HCC patients almost invariably suffer from a concomitant chronic liver disease that is mainly caused by viral hepatitis.

The choice of treatment for HCC should take into account several prognostic factors, including number and size of tumor nodules, portal invasion, presence or absence of cirrhosis, and degree of deterioration in liver function [1].

Patients diagnosed with early-stage HCC are candidates for potentially curative treatments, such as surgical resection, liver transplantation, and percutaneous ablation techniques [2, 3], all of which are capable of eradicating the tumor and prolonging survival. Currently, the 5-year survival rate in patients with early-stage HCC treated with

radical intent is approximately 70%; however, when the disease has reached the intermediate or advanced stage, the 3-year survival rate decreases to 10–50% [4]. However, ≤80% of patients are diagnosed at an intermediate stage of disease [1, 4]. In these patients, transarterial chemoembolization (TACE) is recommended as first-line noncurative treatment [5–8] because it is able to improve survival compared with conservative therapy and transarterial embolization.

Standard TACE consists of the intra-arterial selective injection of an emulsion of chemotherapeutic agent and oily contrast medium (lipiodol) followed by embolization with absorbable particles. Lipiodol seems to be able to act like a carrier, enabling concentration of the chemotherapeutic agent into the tumor [9].

Recently two types of drug-loaded carriers have been introduced: DC Beads (Biocompatible UK Limited, Surrey, UK) and HepaSphere microspheres (Biosphere Medical, France). They are represented by nonabsorbable microspheres loaded with the anticancer drug, which can be released in a controlled and prolonged manner into the tumor with lower systemic toxic exposure [10].

Thus far, encouraging data on animals models using DC Beads have been published [11, 12], and initial clinical results have confirmed the favourable pharmacokinetic profile of the beads with good tumor response and low complication rates [13, 14]. On the contrary, only one animal study has been recently published regarding the use of HepaSphere microspheres in HCC, confirming the stability of the spheres and the persistent occlusion of the vascular bed [15].

The aim of this study was to present the 1- and 6-months clinical results of an Italian multicentre registry (Cuneo: $n = 19$ patients; Pisa: $n = 13$ patients; Milan: $n = 10$ patients; and Pavia: $n = 8$ patients) using HepaSphere microspheres loaded with a chemotherapeutic agent (doxorubicin or epirubicin) for TACE treatment of patients with unresectable HCC.

Materials and Methods

From December 2005 to March 2007, 50 patients (36 male and 14 female, mean age 68.4 years) with HCC were treated by selective TACE using HepaSphere microspheres loaded with a chemotherapeutic agent. The procedure was performed after informed written consent was obtained from all patients; approval of an ethics committee was not required.

HepaSphere microspheres are expandable biocompatible microspheres made of sodium acrylate/vinyl alcohol copolymer. The product is approved and indicated in Europe for hepatic embolisation and chemoembolization.

First developed in Japan by Hori and produced by Biosphere Medical (France), the microspheres are sold in dehydrated form. When placed in contact with physiologic saline solution or nonionic (isotonic) contrast medium, they increase in volume in a controlled manner. The polymer contained within HepaSphere is anionic and carries a negative electrical charge. This anionic property captures molecules with an opposite electrical charge, such as doxorubicin or epirubicin; this property, together with a reservoir effect, enables large quantities of chemotherapeutic agent to be carried within the microsphere; the extimated loading capacity is 50 mg/vial of beads. When used during a TACE procedure, the associated benefit of sequestering the chemotherapeutic agent within the sphere is limited systemic exposure of drug, thus minimizing chemotherapeutic systemic effects and toxicity.

The preparation of HepaSphere is relatively simple and consists of placing the chemotherapeutic solution mixed with physiologic saline or nonionic isotonic contrast medium (270 mg/ml Visipaque [iodixanol]; Amersham Health) in direct contact with the dehydrated microspheres by injecting the mixture directly into the vacuum-sealed vial of HepaSphere. It is necessary to wait at least 20 minutes to be certain that >90% of the chemotherapeutic solution has been absorbed by the microspheres. Then the drug-loaded microspheres are aspirated from the vial, and additional contrast medium or saline is added to obtain a final injectable volume of 20 cc.

The inclusion criteria of the study were presence of unresectable HCC with no less four lesions <10 cm in diameter. In addition, the lesions had to be preferentially localized in the same liver lobe. Subjects were to retain adequate liver function (Child-Pugh class A or B). Patients with portal vein occlusion, neoplastic infiltration of the vessel, or extrahepatic tumor spread were excluded.

Angiographic study of the superior mesenteric artery (SMA), celiac trunk, and common hepatic artery was performed to identify all of the vessels feeding the HCC nodule and to assess patency of the portal vein. In some patients, selective angiography of the phrenic or intercostal arterial branches was required.

The arterial branches feeding the tumor were selectively cannulated by microcatheters to proceed with TACE and to ensure better preservation of the surrounding nontumoral liver tissue. The injection of the spheres was performed far from the origin of the gastroduodenal, right gastric, and cystic arteries.

TACE was performed by way of a slow injection of the mixture of the HepaSphere microspheres loaded with chemotherapeutic agent and the nonionic isotonic contrast medium, which improves the radiopacity of the mixture, to perform a controlled injection under fluoroscopic guidance. Any reflux that may have occurred and revealed

contrastographic impregnation within and around the target lesions, up to the complete embolisation of the arteries feeding the lesions, was avoided. Patients received intravenous analgesic and antiemetic medications before and/or during the procedure. Antibiotics were not routinely prescribed.

The four interventional radiology centres enrolled a total of 50 patients (36 men and 14 women; aged 54 to 80 years (mean 68.4); 46 patients presented with Child-Pugh score A and 4 patients with Child-Pugh score B. Among the treated patients, 35 of 50 had hepatitis C virus (HCV)-related liver cirrhosis, 3 of 50 had hepatitis B virus (HBV)-related liver cirrhosis, 4 of 50 had alcohol-induced cirrhosis, 5 of 50 had cryptogenic cirrhosis, 1 of 50 had HCV- and alcohol-related cirrhosis, 1 of 50 had HBV- and alcohol-related cirrhosis, and 1 of 50 had HBV- and hepatitis D virus (HDV)-correlated liver cirrhosis. The diameter of the treated lesions ranged from 10 to 100 mm (mean 42.5; Table 1). The initial study plan included the use of 100- to 150-µm HepaSphere microspheres (the only size of microspheres available at the beginning the study) in 15 patients.

Subsequently, 50- to 100-µm HepaSphere microspheres were used to treat 35 patients in the attempt to obtain more distal embolisation. In our early experience, we prepared HepaSphere microspheres using a solution of doxorubicin or epirubicin (50 mg/vial) in NaCl 0.9% (5 ml). After injecting this solution into the HepaSphere vial, we waited 20 minutes for the spheres to expand and absorb the drug. We then added 5 ml nonionic isotonic contrast medium (270 mg/ml Visipaque). The 10-ml suspension of doxorubicin- or epirubicin-loaded HepaSphere was then aspirated into a syringe and injected in a manner consistent with a regular embolisation procedure.

More recently, to simplify the process, we injected a solution of doxorubicin or epirubicin (50 mg/vial) and nonionic contrast medium (270 mg/ml Visipaque) (5 ml) directly into the HepaSphere vial and waited 20 minutes for the drug to load into the spheres. After the HepaSphere absorbed the drug, we aspirated the contents of the HepaSphere vial and add another 5 ml contrast. In all patients, we dispersed the drug-loaded spheres using an additional volume of contrast medium to obtain a final injection volume of 20 ml.

Microspheres were loaded with doxorubicin in 18 patients (mean dose 43.6 ± 8.7 mg) or with epirubicin in 32 patients (mean dose 41.7 ± 14.6 mg), according to each centre's drug availability. In particular, epirubicin was used in 3 of 4 hospitals. No significant difference was observed between the administered doses of epirubicin and doxorubicin ($P = .6$).

Tumour response to treatment was assessed by multislice computed tomography (MSCT) using a multiphase protocol, including a nonenhanced acquisition followed by intravenous injection of iodized contrast media (120 ml) at a flow rate of 3 ml/second. Arterial (delay 30 s), venous (delay 80 s) and delayed (delay 180 s) scans were obtained with 5-mm slice thickness and 2.5-mm reconstruction intervals. In select patients, contrast-enhanced ultrasonography and magnetic resonance imaging were used. Follow-up was conducted at 1 and again at 6 months after treatment.

Tumour response to TACE was evaluated according to the World Health Organization (WHO) criteria as modified according to the amendments of European Association for the Study of Liver Diseases (EASL) [1], that take into account the amount of necrotic tumor as represented by a persistently hypodense area after contrast medium administration. MSCT images were reviewed by two expert radiologists by consensus. When the residual viable tumor was at least 1 cm in maximum axial diameter, further treatments were scheduled (TACE "on demand"). Patients undergoing different treatment modalities (percutaneous ethanol injection, radiofrequency ablation, orthotopic liver transplantation, surgical resection, conventional TACE) were censored at the time of the repeat procedure.

Results

Procedural technical success, which was defined by complete devascularization of all target lesions at the end of the procedure, was 100%. The 30-day mortality rate was 0%, whereas the overall mortality rate at 6 months was 6% (3 of 50 patients); 1 patient death was caused by hepatic failure at 2 months after TACE, and 2 patient deaths were reported at 5 and 6 months after treatment secondary to cardiovascular disease. Finally, another patient (2%) died 9 months after TACE because of hepatic failure unrelated to the procedure.

No periprocedural major complications were observed. Nine of 50 patients (18%) reported nausea and mild abdominal pain immediately after the procedure and had febrile temperatures >38°C (mild postembolization syndrome). In 1 patient (2%), the posttreatment period was complicated by pancreatitis, which responded well to medications and extended hospitalization. The pancreatitis was most likely caused by reflux of the drug into the gastroduodenal artery through a right segmentary aberrant hepatic artery with an origin rising from the gastroduodenal artery itself.

Laboratory tests carried out periprocedurally showed no evident variations in blood parameters regarding liver and renal function. Of 26 of 50 (51%) patients, in whom preprocedural alpha-fetoprotein (AFP) was increased (mean 617 ± 1409 ng/ml; range 21.3 to 3,810 L), 24 of 26 (92.3%) patients showed a significant ($P = .007$) reduction of AFP levels after TACE (mean 20.6 ± 12.2 ng/ml; range 5.9 to

Table 1 Patients enrolled in the study and HCC lesions

Patient no.	Age (y)	Sex	Child-Pugh score	Etiology	Number of tumor nodules	Tumour size (mm)	Drug
1	62	M	A	N	1	50	Doxorubicin
2	76	M	A	HCV	1	70	Doxorubicin
3	74	M	A	ALC	2	45	Doxorubicin
4	66	M	A	HCV	2	45	Doxorubicin
5	71	M	A	HCV	1	40	Doxorubicin
6	80	M	A	HCV	1	43	Doxorubicin
7	67	F	A	HCV	1	45	Doxorubicin
8	58	F	A	N	2	40	Doxorubicin
9	67	M	A	HCV	1	55	Doxorubicin
10	68	F	A	N	1	25	Epirubicin
11	70	M	A	ALC	1	50	Doxorubicin
12	74	M	A	N	1	40	Doxorubicin
13	75	M	A	HCV	1	60	Doxorubicin
14	73	M	A	N	1	60	Doxorubicin
15	71	F	A	HCV	1	40	Doxorubicin
16	74	M	A	HCV	2	65	Doxorubicin
17	76	M	A	HCV	1	35	Doxorubicin
18	76	F	A	HCV	1	45	Doxorubicin
19	75	M	A	HCV	4	25	Doxorubicin
20	73	M	A	HBV	1	25	Epirubicin
21	76	M	A	HCV	1	20	Epirubicin
22	76	M	A	HCV	1	25	Epirubicin
23	54	F	A	HCV	1	30	Epirubicin
24	62	M	A	ALC	1	40	Epirubicin
25	66	M	A	HCV	1	50	Epirubicin
26	66	F	A	HCV	1	20	Epirubicin
27	69	F	A	HCV	1	55	Epirubicin
28	68	M	A	ALC	3	90	Epirubicin
29	77	M	A	HCV	1	100	Epirubicin
30	72	F	A	HCV	1	20	Epirubicin
31	56	M	A	HBV	1	45	Epirubicin
32	53	M	B	HCV + ALC	1	50	Epirubicin
33	65	M	A	HBV + ALC	1	25	Epirubicin
34	58	M	B	HBV + HDV	1	38	Epirubicin
35	77	F	B	HCV	1	60	Epirubicin
36	65	F	A	HCV	2	60	Epirubicin
37	59	M	A	HCV	1	50	Epirubicin
38	77	F	B	HCV	1	10	Epirubicin
39	64	M	A	HBV	4	32	Epirubicin
40	57	M	A	HCV	1	17	Epirubicin
41	74	M	A	HCV	1	15	Epirubicin
42	57	M	A	HCV	3	55	Epirubicin
43	60	M	A	HCV	1	42	Epirubicin
44	80	M	A	HCV	1	40	Epirubicin
45	66	F	A	HCV	1	40	Epirubicin
46	65	F	A	HCV	1	40	Epirubicin
47	73	M	A	HCV	3	50	Epirubicin

Table 1 continued

Patient no.	Age (y)	Sex	Child-Pugh score	Etiology	Number of tumor nodules	Tumour size (mm)	Drug
48	65	M	A	HCV	2	40	Epirubicin
49	76	M	A	HCV	1	32	Epirubicin
50	60	M	A	HCV	1	30	Epirubicin

ALC = alcohol-induced; HDV = hepatitis D virus; N = cryptogenetic

45). In the 2 cases in whom AFP increased, the 1-month tumor response was considered insufficient (stable disease).

One month after treatment, MSCT showed complete tumor response in 24 of 50 (48%) (Fig. 1), partial response in 18 of 50 (36%) (Fig. 2), and stable disease in 8 of 50 (16%) patients, and there were no cases of disease progression. Tumor response was significantly associated with tumor size (Table 2; $P = .03$). Six-month CAT follow-up was available in 31 of 50 (62%) patients because 3 patients died, 12 patients underwent other treatments (Table 3), and 4 patients were lost to follow-up. MSCT at 6 months showed a complete response in 16 of 31 (51.6%) (Fig. 3), partial response in 8 of 31 (25.8%), and progressive disease in 7 of 31 (22.6%) patients (Table 4). Within the initial 9-month follow-up, TACE with HepaSphere was successfully repeated twice in 3 patients, whereas 3 patients underwent the procedure 3 times.

Discussion

In the absence of vascular invasion and extrahepatic tumor spread, TACE represents the first-line approach in patients with HCC that is not suitable for curative treatment [8]; it can improve 1 and 2-year survival [5–7].

Conventional TACE technique consists of the injection of an emulsion of the chemotherapeutic agent with iodized oil followed by the embolization with absorbable particles. However, there is no standard method to perform TACE for HCC, and the choice of chemotherapeutic agent and embolization material varies from centre to centre, often driven more by toxicity issues and experience rather than clinical data [12, 16, 17].

In the attempt to increase local efficacy and reduce the side effects of the procedure, several vendors have developed microspheres, either to be used for bland embolization or to be loaded with chemotherapeutic agents [18]. HepaSphere microspheres and DC Beads belong to the latter group of embolic agents.

Up to now, the majority of published data deal with the use of DC Beads, whereas not much is yet known about HepaSphere. In vitro and animal studies [10–12] have proven that TACE with DC Beads is associated with increased tumor necrosis together with mild and transient increase of liver enzymes and reduced plasma levels of doxorubicin.

Moreover, initial clinical trials have confirmed the benefits of DC Beads in terms of reduced local and systemic side effects, with a 75–80% objective response rate [13, 14], which is higher than the 35% objective response rate reported by Llovet et al. with traditional TACE [6].

Little is yet known regarding the use of HepaSphere. These microspheres differ from DC Beads mainly because they are provided in "dry state"; when exposed to aqueous-based media, they absorb fluid and swell to a predictable size [19]. The swollen particle is reported to be soft, deformable, and easily delivered through the majority of the currently available microcatheters; moreover, these particles are stable and adapt to the morphology of the vessel lumen, warranting its persistent occlusion [15]. The final size of the swollen particle is predictable and ranges from 200 to 400 μm (for 50- to 100-μm "dry-state" spheres) to 600 to 800 μm (for 150- to 200-μm "dry-state" spheres). Therefore, even the smallest HepaSphere microsphere is larger than the smallest size DC Bead (100 to 300 μm). No clinical data have yet been published regarding the results of TACE using HepaSphere.

The results of our clinical trial demonstrated the feasibility and safety of TACE with HepaSphere; the technical success rate was 100%, and there were no major complications. The procedure was well tolerated by the majority of the patients; 18% of patients reported mild postembolization syndrome, whereas 3% had some other minor complications. Moreover, no evident increase in liver enzyme levels was observed periprocedurally. Thus, low systemic drug toxicity can be supposed, as already demonstrated with DC Beads.

The use of a permanent embolic agent implies the need for superselective catheterization to spare the nontumoral parenchyma. For this reason, TACE with microspheres should not be performed in patients with multiple and diffuse tumor nodules or with nodules supplied by cystic or phrenic arteries. Moreover, it is essential to avoid distant liver embolization by small-size particles, which might block collateral supply and cause severe necrosis of the nontumoral parenchyma. Extrahepatic embolization has also been advocated as having a possible collateral effect, particularly when using small particles. In our experience, one patient

Fig. 1 Multislice CAT in the coronal (A) and axial (B) planes demonstrates the presence of a 35-mm HCC nodule in the VIII hepatic segment; the common hepatic artery rises from the SMA. (C) TACE with HepaSphere is successfully performed (D and E). One-month CAT control in the arterial (F) and venous (G) phases shows complete tumor response with no enhancing areas within the tumor nodule
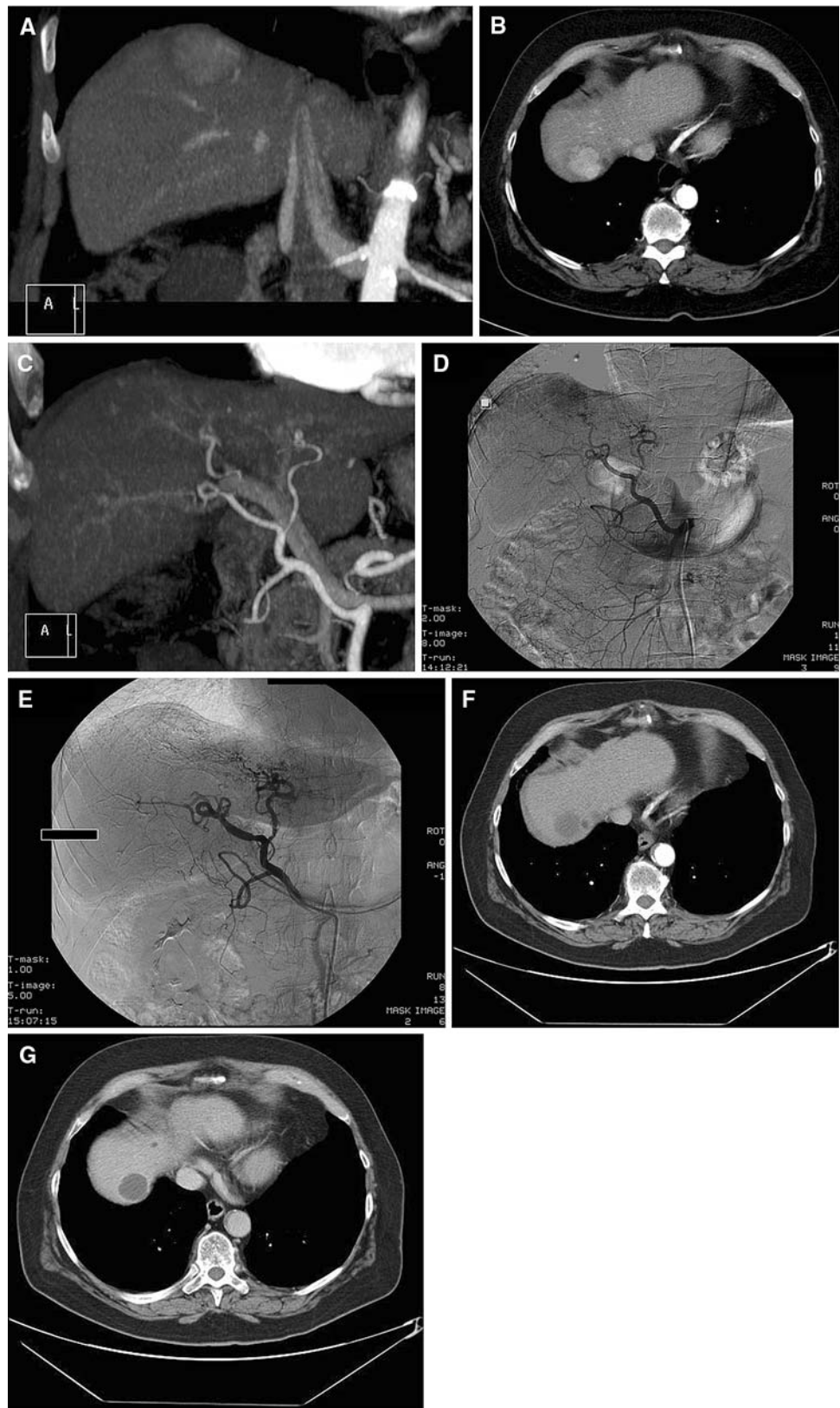
developed postprocedural pancreatitis, which was most likely caused by reflux of the drug into the gastroduodenal artery through a right segmentary aberrant hepatic artery.

The tumor response was evaluated according to the WHO criteria as modified according to the EASL recommendations [1], which take into account only residual

Fig. 2 Diagnostic angiography (**A**) depicts a 40-mm hypervascular HCC nodule; TACE with HepaSphere microspheres was selectively performed by means of a microcatheter. (**B**) One-month CAT control in the arterial (**C**) and venous (**D**) phases demonstrates a partial tumor response with a persistent enhancing area
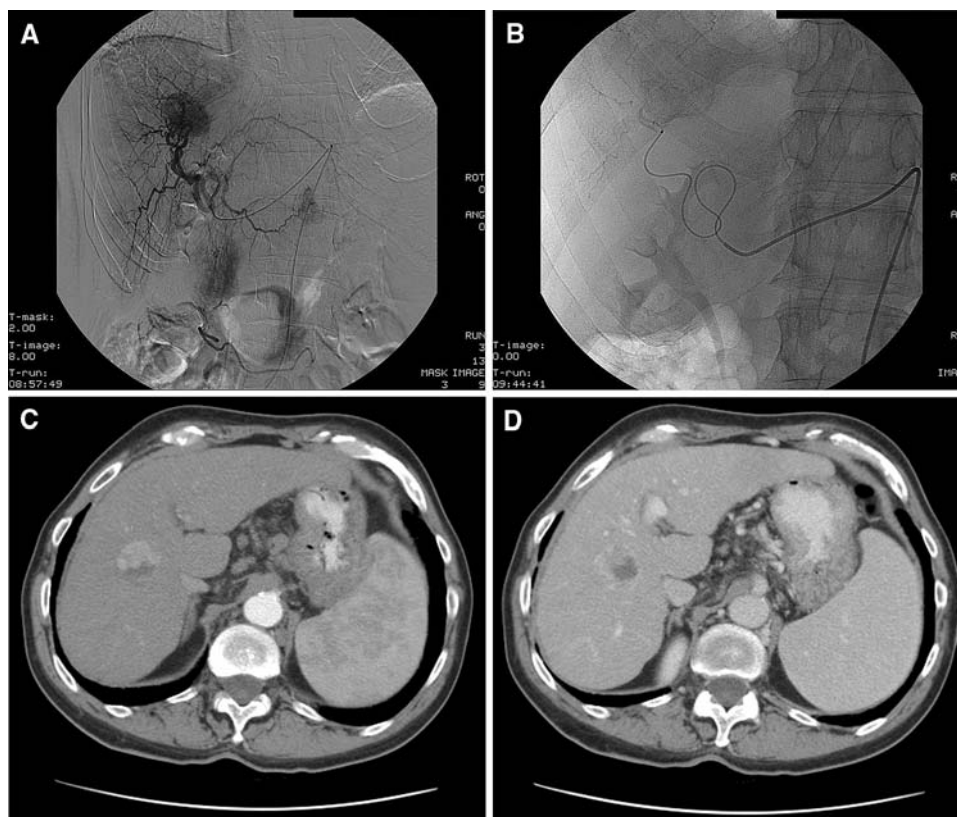

Table 2 Tumor size and response at 1-month follow-up[a]

Lesion diameter (mm)	Number of patients by tumor response (%)		
	Complete	Partial	Stable
Mean ± SD (mm)	39.2 ± 14.5	50.8 ± 20.9	33.4 ± 9.5
<30 mm	6 (12)	2 (4)	3 (6)
30–49 mm	12 (24)	6 (12)	5 (10)
≥50	6 (12)	10 (20)	0

[a] There was a significant relation between tumor response at 1 month and tumor size (P = .03)

Table 3 Number of patients treated by other modalities at 1- and 6-month follow-up

Centre	TAE	TACE	RF	OLT	PEI	CT	SG
Cuneo			3				
Milan		1		2	1		1
Pisa		2				1	
Pavia	1						
Total	1	3	3	2	1	1	1	12

TAE = transcatheter arterial embolization; RF = radiofrequency ablation; OLT = orthotopic liver transplantation; PEI = percutaneous ethanol injection; CT = systemic chemotherapy; SG = Surgery

viable tumor tissue as represented by persistent intratumoral arterial contrast uptake. At 1 month follow-up, we observed a high objective response rate (84%), which is comparable with the reported results obtained with DC Beads [13, 14].

In our series, TACE was repeated only "on demand," in the presence of residual viable tumor at least 1 cm in diameter; during follow-up 6 patients repeated treatments 2 or 3 times. On the contrary, other trials have been based on multiple embolizations routinely repeated every 2–3 months. In our opinion, this approach may not represent the right treatment schedule for all patients. Varela et al. [13] reported a response rate at 6-month follow-up of 75% (66% on an intention-to-treat basis) in a series of 27 patients treated with DC Beads; 22 patients (81.5%) underwent 2 cycles of embolization. This result is similar to that reported by Malagari et al. [14] in a series of 62 patients, the majority of whom were treated by 2 or 3 embolizations. Despite the similar tumor response rates, the incidence of major complications was higher in these series, compared with our results: we had ≤3% periprocedural mortality [13]. Therefore, when reviewing the treatment protocol, we must identify the optimal strategy in terms of increased efficacy and decreased complications.

Of interest, tumor response was significantly associated with tumor size because partial remission (PR) was observed larger tumor nodules (mean diameter 51 mm) compared with the size of the nodules in which complete remission (CR) was obtained (mean diameter 39 mm). Therefore, we could assume that routinely repeated TACE

Fig. 3 Multislice CAT in the axial plane (**A**) demonstrates the presence of a hypervascular HCC nodule of hepatic segment VIII confirmed by pre-TACE digital subtraction angiography. (**B**) TACE with HepaSphere is successfully performed. (**C**) One-month CAT control in the arterial phase (**D**) shows complete tumor response with no enhancing areas within the tumor nodule. Persistent complete response is confirmed at 6-month CAT follow-up (**E**); the nodule is fully hypodense and reduced in size
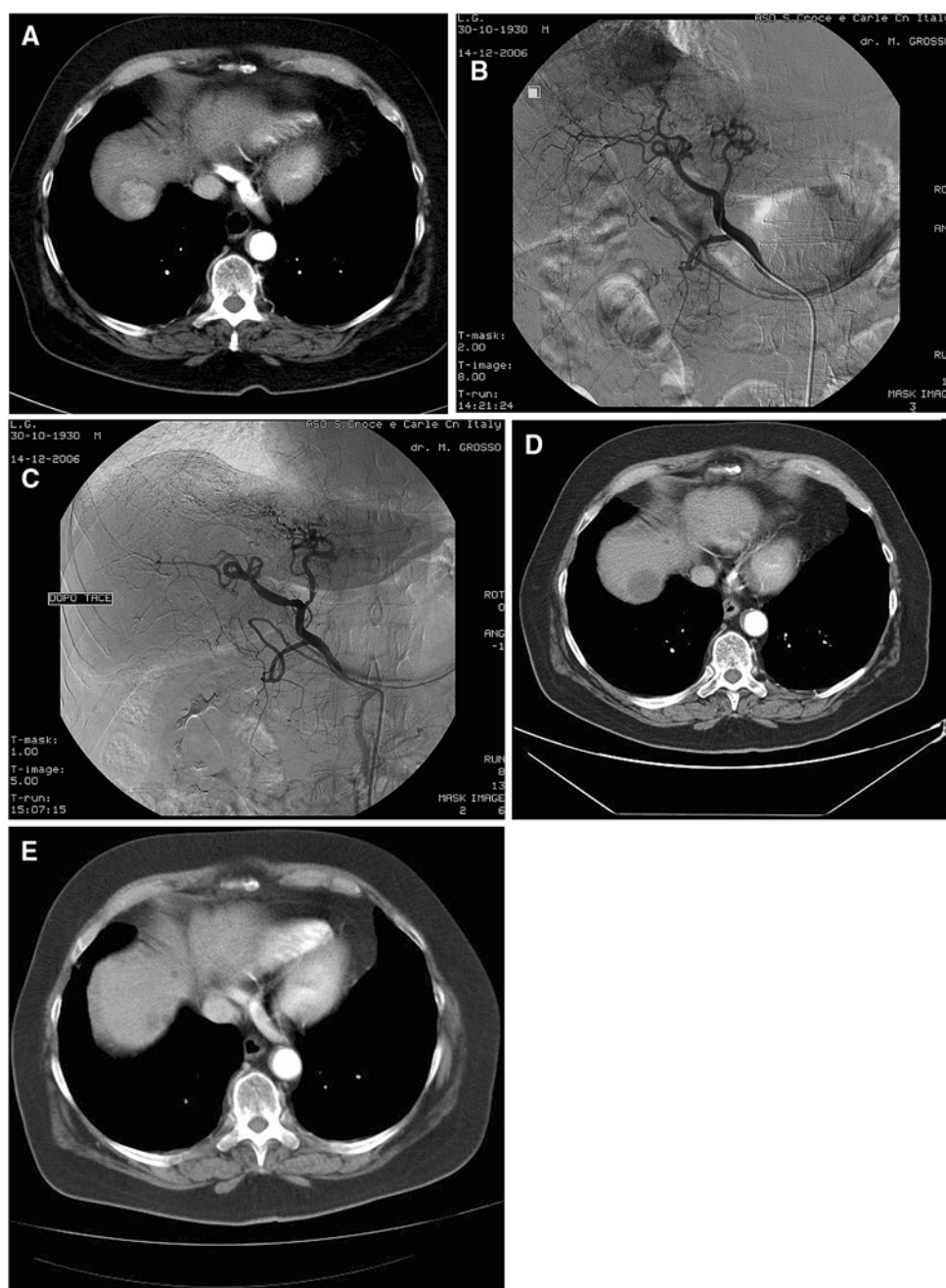

Table 4 Results at 6-month follow-up

Results	Number of patients	%
Complete response	16	32
Partial response	8	16
Stable disease	0	0
Progressive disease	7	14
Death	3	6
Other treatments	12	24
Lost to follow-up	4	8

[13, 18] could be useful for large nodules (e.g., >5 cm), whereas a single cycle of TACE might be sufficient for smaller tumors.

The objective response rate also remained high at 6-month follow-up (76.7%) and was comparable with that of other published series, indicating that the drug-eluting spheres may offer a means for durable tumor necrosis as concluded by in vitro and animal studies [10–12].

Compared with previously published results [13, 14, 18], the mean drug dose used in our study was lower

(approximately 40 mg). Indeed, in our experience, injection of the spheres was interrupted when the nourishing vessels appeared occluded on fluoroscopy. Therefore, a single vial of spheres was often sufficient to achieve this result. We could assume this difference to be related to the larger size of HepaSphere compared with DC Beads, thus achieving earlier embolization. However, lower drug dose did not seem to influence tumor response, which compares favourably with other studies [13, 14, 18]. In addition, a low incidence of complications and side effects was observed periprocedurally. This phenomenon might raise the question of the possible advantages of plain embolization using permanent embolic agents over the use of drug-loaded particles. A randomized trial would be required to answer this question.

The main limitation of our study comes from the relatively limited number of patients enrolled and the nonhomogeneous follow-up. In particular, 19 of 50 (38%) patients were lost to follow-up at 6 months, and 12 of 50 (24%) patients underwent different treatments. In fact, the management of cirrhosis and HCC requires a multidisciplinary approach to provide the patient with the widest range of available treatment options, and the most appropriate treatment modality might change from time to time. Another limit of the study is represented by the use of slightly different drugs (epirubicin and doxorubicin), depending on their availability, in the different institutions involved in the study.

Despite these limitations, our results suggest that TACE with HepaSphere is a safe, well-tolerated, and efficient treatment modality that may provide durable tumor necrosis. Further studies are needed to confirm the efficacy of this treatment and its advantages over other treatment options.

In conclusion, a more extensive evaluation of the use of drug-loaded HepaSphere should consist of loading the microspheres with different chemotherapeutic agents (e.g., tomycin and cisplatin) [20], which would broaden the applications and indications for treatment.

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