

Short-term Efficacy and Safety of CalliSpheres Drug-loaded Microsphere Embolization in Primary Hepatocellular Carcinoma

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Abstract

Background To evaluate the short-term clinical efficacy, side effects, and risk factors affecting the clinical effectiveness of CalliSpheres drug-loaded bead-transcatheter arterial chemoembolization (DEB-TACE) in the treatment of primary hepatocellular carcinoma (HCC).

Methods A total of 172 consecutive patients with HCC undergoing DEB-TACE (loaded with doxorubicin) from August 2016 to July 2018 were prospectively enrolled. Short-term local tumor response was evaluated by the modified RECIST criteria. Postoperative complications and liver function disorders were analyzed based on examinations and clinical symptoms.

Results The median follow-up period was 310 days. Based on the mRECIST criteria, objective response rates (CR+PR) were 78.7%, 71.6% and 63.2%, and disease control rates (CR+PR+SD) were 95.3%, 92.1% and 85.9% at 2, 4 and 6 months post-treatment, respectively. Multivariate logistic regression analysis showed that nodule number >3, high BCLC stage, vascular leak, and previous cTACE treatment were associated with poor ORR ($P < 0.05$). Post-operation, liver function showed transient changes. Postoperative complications were tolerated and relieved by symptomatic treatment. The average interval of TACE before D-TACE was 43 days, compared with 70 days for average interval of DEB-TACE. The average hospital stay was 1.87 days.

Conclusions DEB-TACE has improved short-term efficacy and lower incidence of complications in primary HCC and prolongs the interval of TACE. It significantly increases the ORR, especially in patients with no extra-hepatic metastasis pre-treatment. DEB usage actually improves treatment efficacy and provides more benefits to patients.

Background

Hepatocellular carcinoma (HCC) is growing in incidence, constituting the second major cause of cancer-related death worldwide. Most patients are in middle and late stages at diagnosis, with 5-year survival rates of 50% and 8%, respectively [1]. Transcatheter arterial chemoembolization (TACE) is the most effective first-line therapy and can prolong survival [2]. However, conventional TACE (cTACE) uses lipiodol to load chemotherapeutics, and efficacy and safety are unsatisfactory. Drug-eluting bead-TACE (DEB-TACE) is a novel chemoembolization technique which not only loads and slowly releases high amounts of chemotherapeutics locally to reduce systemic toxicity, but also permanently embolizes supplying vessels of tumors [3]. Multiple studies have demonstrated superior short-term efficacy and safety of DEB-TACE over cTACE [4]. Due to economic limitations, drug-loaded microspheres have not been widely used in China. Few studies have evaluated the efficacy and safety of DEB-TACE in HCC, assessing benefits to patients. The objective of the present study was to investigate the short-term efficacy, safety and factors of CalliSpheres drug-loaded microspheres for HCC, providing a basis for the development of this novel technique.

Methods

Study population

Consecutive HCC patients in Shandong Cancer Hospital and Institute from August 2016 to June 2018 were enrolled into the present prospective study if they met the following criteria: (1) primary HCC diagnosed clinically or pathologically in accordance with the guidelines of the American Association for the Study of Liver Diseases (AASLD); (2) aged over 18 years; (3) Eastern collaborative oncology group (ECOG) score <2; (4) BCLC B stage, inapplicable for radical correction in BCLC A stage, ECOG score ≤ 2 in BCLC C stage, Child-Pugh A or B hepatic function, or expected survival time ≥ 3 m; (5) DEB-TACE required by the patient's wish or clinical situation.

Exclusion criteria were: (1) severe hepatic or renal failure; (2) allergy or contraindication for the chemoembolic agent; and (3) contraindication for hepatic arterial embolization including arteriovenous fistula, portal occlusion, severe coagulation disorders, and severe uncontrolled systemic complications such as infection and diabetes mellitus; (4) severe cardio-cerebrovascular disease; (5) complication with other primary tumors; (6) pregnancy or lactation in women; (7) cognitive impairment or inability to comprehend the present study. The study was approved by the Ethics Committee of Shandong Cancer Hospital [number: SDZLEC-2017-001-01]. All subjects provided written informed consent.

A total of 172 patients were eligible, including 139 males and 33 females with an average age of 54.62 ± 11.25 years. Of these, 130 patients (75.6%) had type B hepatitis and 16 (9.3%) had type C hepatitis. The ECOG score was 0 in 116 patients and 1 in 56 individuals. Thirteen patients were in BCLC stage A, with 89 in stage B and 70 in stage C. One-hundred fifty one patients were classified as Child-Pugh A and 21 as Child-Pugh B. Seventy one patients had multiple foci and 98 had a single focus. Sixteen patients (66.7%) were treated previously surgically, 6 with targeted therapy, and 8 with radiofrequency ablation. A total of 98 patients had received c-TACA once to twice, with a median of 1 time.

Treatment

CalliSpheres drug-loading microspheres (Jiangsu Hengrui Medicine Co. Ltd., Jiangsu, China) were used (300–500 μm or 100–300 μm). Percutaneous right femoral artery puncture intubation with a modified Seldinger technique was performed. Then, a 5F-Yashiro or RH (Terumo, Japan) catheter was introduced through a 5-F vascular sheath into the common hepatic artery under DSA guidance for celiac angiography to assess hepatic arterial anatomy and the potential existence of variants, location, size, number and staining of tumors, as well as tumor thrombus in the portal vein and hepatic arteriovenous fistulas. In case arteries supplying the tumors were not developed, arteriography was continued of the superior mesenteric artery, bilateral inferior phrenic arteries, internal thoracic arteries, and the aortic suprarenal artery to confirm these arteries supplying the tumors. Then, a 2.7F micro-catheter (Terumo, Japan) was advanced super-selectively to the supplying artery of the tumor. CalliSpheres beads were fully loaded Epirubicin at a dosage of 60-80 mg and mixed with Ioversol at a volume ratio of 1:1-1.2,

followed by standing for 5 minutes. Before use, the sample was mixed and placed in a 1 ml injector. The bead diameter and injecting sequence depended on the tumor size and supplying vessels. Subsequently, the mixture was manually injected in a pulsed mode into the tumor-supplying artery at a rate of 1 ml/min under fluoroscopic monitoring until the developer was stable or approached stability. Angiography was repeated 5 minutes after embolization to assess whether embolization was complete. If there were still tumors, embolization was continued until tumor-supplying vessels slowed down and contrast agent disappeared after 2-5 heart beats. Imaging examinations were conducted every 4-6 weeks, and the next TACE treatment was based on imaging results. Post-operation, liver protection and pain relief treatments were provided. If necessary, antibiotics were also administered to prevent infection.

Follow-up and imaging evaluation

All patients were followed up during hospitalization or by telephone. Based on modified response evaluation criteria in solid tumors (mRECIST) [5], CT and/or MRI were performed 4-6 weeks after DEB-TACE to evaluate local response. The objective response rate (ORR) was defined as the proportion of patients gaining CR or PR, and the disease control rate (DCR) as that of patients showing CR, PR, and SD. In case of PD even after two D-TACE procedures for the same tumor focus, the patient no longer received drug-loaded microsphere embolization. Treatment efficacy in months 2, 4, and 6 was evaluated as well as the associated factors. The tumor lesions were evaluated by two independent experienced (more than 5 years of working experience) abdominal radiologists in cooperation with our department.

Safety was evaluated with changes of liver function, including albumin (ALB), total bilirubin (TBIL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), and the tumor marker α -fetoprotein (AFP) one week pre-operation, and one week and one month post-operation. Adverse events such as pain, fever, nausea, and vomiting one month post-DEB-TACE were recorded according with common terminology criteria for adverse events (CTCAE) established by the National Cancer Institute (NCI) [6].

Statistical analysis

SPSS22.0 was used for statistical analysis. Measurement data were expressed as mean \pm standard deviation (SD) and compared by the t test. Qualitative data were expressed as proportion (%) and compared by the χ^2 test. Factors predicting ORR were analyzed by univariate and multivariate logistic regression analyses. $P < 0.05$ was considered statistically different.

Results

Factors influencing treatment response and tumor relapse

All CalliSpheres drug-loaded microsphere treatments were successfully conducted, and the technical success rate was 100%. A typical case is shown in Figure 1. All 172 patients were

followed up, and efficacy was evaluated with the mRECIST criteria (Table 1).

Table 1 Follow-up results based on the mRECIST criteria (n%)

	2 months post-treatment	4 months post-treatment	6 months post-treatment
CR	12 (7.0%)	11 (6.4%)	6 (3.5%)
PR	89 (51.7%)	71 (41.3%)	68 (39.5%)
SD	56 (32.6%)	68 (39.5%)	79 (45.9%)
PD	15 (8.7%)	22 (12.8%)	19 (11.1%)
ORR(CR+PR)	78.7	71.6	63.2
DCR (CR+PR+SD)	95.3	92.1	85.9

No residual DEB-DSA was found in DAS after DEB-TACE. Of the 325 tumor nodules in all patients, 146 (44.9%) relapsed 1-4 months post-DEB-TACE (Table 3). The median follow-up period of CT was 1.6 months (1-4 months). Univariate analysis showed that BCLC stage (p=0.001), tumor number (p=0.002), previous cTACE (p=0.010), AFP (p=0.009), tumor border (p=0.005), and no vascular leak (p=0.001) were significantly associated with tumor relapse (P<0.05) (Table 2).

The 6 factors were further assessed by logistic regression analysis. The results showed that CLC stage (OR=3.46, 95%CI 1.93-34.76, p=0.004), tumor number (OR=3.83, 95%CI 1.14-14.9, p=0.0038), previous cTACE (OR=5.640, 95%CI 1.160-27.415, p=0.0032), and no vascular leak (OR=7.713, 95%CI 1.521-39.112, p=0.014) were significantly associated with reduced ORR post-DEB-TACE (Table 3).

Table 2 Univariate analysis of factors associated with local relapse post-DEB-TACE

	Treatment efficacy of nodules (n=325)		P
	Local relapse(n=146)	No local relapse(n=179)	
Age (x±S)	62.90 ± 9.34	61.56 ± 10.12	0.2162
Sex			0.783
Male	104	115	
Female	42	64	
Hepatitis			0.104
HBV	70	102	
No	76	77	
Child-Pugh stage			0.963
A	108	132	
B	38	47	
BCLC stage			0.001
A	12	26	
B	58	95	
C	76	58	
Tumor diameter (mm)(x±S)	29.65 ± 19.34	28.21 ± 16.76	0.479
Tumor number			0.002
≤3	39	100	
>3	107	79	
Previous cTACE			0.010
Yes	51	88	
No	95	91	
AFP (ng/ml)			0.009
≥ 100	85	78	
<100	61	101	
Tumor border			0.005

Irregular	88	80	
Regular	58	99	
Viral load (copies/ml)			0.223
≥ 103	46	68	
≤103	90	111	
Embolization segments			0.785
Hepatic segment and sub-segment	72	91	
Hepatic lobe	74	88	
Tumor location			0.722
S1 or S4	62	78	
Others	74	101	
Vascular leak			0.001
Yes	51	103	
No	95	76	

Table 3 Multivariate logistic analysis

	HR	95%CI	P
BCLC stage (A:B:C)	3.46	1.93~34.76	0.004
Tumor size (≤3:≥3)	3.83	1.14-14.9	0.038
AFP (≥ 100:≤ 100)	1.726	0.071~2.413	0.129
Previous cTACE (Yes/No)	5.640	1.160~27.415	0.032
Vascular leak (No/Yes)	7.713	1.521~39.112	0.014

Treatment intervals and hospitalization durations

The average interval of D-TACE was 70 days (28 to 198 days) and that of TACE before D-TACE was 43 days (28 to 84 days). The average hospitalization stay after D-TACE was 1.87

days (Table 4). The interval of TACE treatment was significantly prolonged after TACE.

Table 4 Hospitalization durations of patients with primary HCC

Postoperative hospitalization duration	Number of patients	Percentage	Average stay (days)
1	62	36.04%	1.87
2	79	45.93%	
3	24	13.96%	
4	6	3.49%	
5	1	0.58%	

Changes of hepatic function and laboratory parameters pre- and post-treatment

The CTCAE grades of ALB, TBIL, ALT, and AST pre-treatment ranged from 0 to 2, with grade 0 being most common (Table 5). One week post-treatment, ALB was significantly decreased, while TBIL, ALT, and AST were significantly increased, as well as CTCAE grade ($P < 0.001$). All parameters returned to normal one to three weeks post-treatment ($P = 0.852$, $P = 0.167$, $P = 0.228$, and $P = 0.422$, respectively). AFT was significantly decreased post-treatment ($P < 0.05$).

Table 5 Laboratory parameters pre- and post-DEB-TACE

Pre-operation (n=172)	1 week post-operation (n=165)	1 month post-operation (n=161)	P※	P□
			< 0.001	0.852
155	119	145		
10	36	11		
7	10	5		
0	0	0		
0	0	0		
			< 0.001	0.167
130	58	116		
34	67	42		
8	14	3		
0	23	0		
0	3	0		
			< 0.001	0.228
107	45	99		

61	76	53		
4	22	5		
0	18	4		
0	4	0		
116	47	107	<	0.422
40	65	38		0.001
16	45	13		
0	7	3		
0	1	0		
5326.3±4623.01	5021.5±4562.65	4986.23±4276.34	0.036	0.028

Notes: ALB, Albumin; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; TBil, Total bilirubin. P*, Hepatic function at pre-treatment vs. 1 week post-treatment; P†, Hepatic function at pre-treatment vs. 1 to 3 months post-treatment

Table 6 Adverse events post-D-TACE

Adverse events	Abdominal pain (n)	Vomiting (n)	Fever (n)	Liver abscess (n)	Myelosuppression (n)	Heart toxicity (n)
Grade 0	70	87	60	169	148	171
Grade 1	86	69	72	3	24	1
Grade 2	14	16	39	0	0	0
Grade 3	2	0	1	0	0	0
Grade 4	0	0	0	0	0	0

The most common treatment-related adverse events included abdominal pain, vomiting, fever and myelosuppression. There were 80 patients with mild pain (50.00%), 14 with moderate pain (8.14%), 2 with severe pain (1.16%), and 70 with no pain (40.7%). A total of 85 patients experienced vomiting, including 80 with grade 1 (46.51%) and 5 with grade 2 (2.91%). Only one patient (0.58%) reported cardiac toxicity. There were 60 patients with no fever (34.88%), 72 with low-grade fever (41.86%), 39 with moderate-grade fever (22.67%), and 1 with high-grade fever (9.1%) Table 6.

Discussion

TACE is the standard therapy for advanced HCC. However, chemotherapeutics, and treatment intervals and number in TACE remain controversial [7, 8]. The cTACE treatment usually employs lipiodol to load chemotherapeutics to block supplying arteries of the tumor, which increases the concentration of chemotherapeutics within the tumor, and decreases toxicity to the normal liver parenchyma. However, it also has some disadvantages such as introducing chemotherapeutics into the systemic circulation, which increases the incidence of systemic adverse events, complications and drug resistance, potentially decreasing the survival benefit [9, 10]. The cTACE treatment is associated with improved survival benefit but higher relapse compared with expectant treatment [3, 11]. How to increase the efficacy of TACE in HCC is an urgent topic. The embolization efficacy of TACE is largely dependent upon the embolization material. The optimal material can block supplying arteries of the tumor at high local concentrations and low systemic levels. Compared with lipiodol, drug-loaded microspheres not only block supplying vessels of the tumor but also prolong the time of chemotherapeutics acting on tumor cells. They can induce long-term and sustained release of chemotherapeutics to kill the tumor tissues and decrease the circulating levels. Reportedly, DEB-TACE prolongs the survival time and reduces chemotherapeutic embolization,

being superior to cTACE [12]. However, in clinical practice, some patients firstly select DEB-TACE and others receive multiple cTACEs before considering DEB-TACE. Whether DEB-TACE can shorten the treatment interval and increase treatment efficacy in HCC patients has not been reported. For patients with multiple unsuccessful TACE treatments, DEB-TACE may be a potential key to improve long-term prognosis.

Multiple cohort studies, clinical trials and meta-analyses have shown that DEB-TACE has better treatment response, survival and safety compared with cTACE [13]. A retrospective cohort study suggested that DEB-TACE can be an effective bridge therapy before liver transplantation in late-stage HCC with liver dysfunction [14]. Although DEB-TACE is applicable in advanced HCC, only a few patients are actually treated by this method in clinical practice, and studies and evidences of DEB-TACE treating BCLC C stage HCC are limited.

According to the mRECIST criteria, objective response rates (CR+PR) were 78.7%, 71.6% and 63.2%, and disease control rates (CR+PR+SD) were 95.3%, 92.1% and 85.9% at 2, 4 and 6 months post-treatment, respectively. The one-year survival was 92.6%. Subgroup analysis showed that the CR and ORR were reduced in patients with high BCLC stage and a previous history of cTACE. Logistic regression analysis showed that >3 nodules, high BCLC stage, and previous cTACE treatment may be associated with reduced ORR. Multifocal HCC is considered a risk factor for poor HCC prognosis [15, 16]. Nodule number>3 reflects poor survival post-liver resection [17]. These findings showed that nodule number has a good predictive value, consistent with the current study [18]. Poor ORR in patients with a history of cTACE in the present study may be due to low sensitivity to DEB-TACE post-cTACE. Multiple cTACE treatments worsen vascular injury, hepatic fibrosis, and resistance to chemotherapeutics, affecting the efficacy of subsequent treatment and causing TACE resistance. D-TACE decreases drug spreading into the peripheral system, increases local drug concentration, strengthens the anti-tumor effect of chemotherapeutics, and increases the ORR [19].

The present study suggested that D-TACE could significantly prolong the interval of TACE treatment, i.e. 112 days in 50 patients treated by D-TACE with no previous treatment compared with 69 days in those administered other treatments. After treatment with drug-loading microspheres, the interval of TACE was significantly prolonged, which is beneficial for hepatoprotection, life quality enhancement, and decreasing the social burden. In patients with HCC, protection of hepatic function is also important, except for tumor treatment, and even more important than tumor treatment in some circumstances [20]. Hepatic function directly affects treatment choice, efficacy, and prognosis. Chemotherapeutics and embolic agents can damage hepatic function, and sufficient interval of TACE is required to guarantee recovery of hepatic function. Besides, patients experience varying degrees of adverse events, which decrease the quality of life, affects life and working, increases the nursing load of families and the social burden. Therefore, prolonging the TACE interval is very helpful for hepatic function recovery, life quality increase, and familial and social burden decreases [21].

Usually, hepatic function rapidly worsens one week post-treatment and returns to normal within 1–3 months post-treatment. In the present study, hepatic injury was relatively mild, possibly owing to baseline hepatic function being different from other studies. The rapid alteration of hepatic function 1 week post-treatment may be induced by surgery; liver function recovery 1–3 months post-treatment may be associated with moderate baseline hepatic function, suggesting the self-repair ability of the liver. Previous findings indicate that DEB-TACE can be tolerated, similar to cTACE, with most adverse events being low grade [14]. To some extent, tolerance is better for DEB-TACE compared with cTACE, since no azithromycin-related systemic toxicity in patients with DEB-TACE was previously reported [22]. In a previous study, 7 of 51 patients (13.7%) had low incidence of TACE-related complications such as liver decompensation, hepatic vein thrombosis, pancreatitis, and post-embolization syndrome [23].

In the present study, the most common adverse events pre- and post-treatment included pain, vomiting, hypertension, and fever, most of which were mild to moderate, consistent with previous findings [24]. All these results prove the excellent safety of DEB-TACE. This treatment was well tolerated, and no liver abscess or failure, or bile leakage was reported.

The present study still had limitations. The follow-up period was short, and long-term efficacy such as overall survival was not analyzed. The efficacy and safety of CalliSpheres® DEB-TACE for the treatment of primary HCC was also not evaluated, because the study enrolled 74.4% of patients with a treatment history. Besides, DEB-TACE and CalliSpheres® microsphere treatment is not widely applied in China, and sample size in this study was small.

Conclusions

In conclusion, CalliSpheres® DEB-TACE is effective and well tolerated in Chinese HCC patients. Drug-loading microsphere DEB-TACE should be used as early as possible to reduce treatment time and medical cost, prolonging the TACE interval. BCL stage, nodule number, and a history of cTACE might be associated with treatment efficacy.

List Of Abbreviations

DEB-TACE: drug-loaded bead-transcatheter arterial chemoembolization; HCC: hepatocellular carcinoma; TACE: Transcatheter arterial chemoembolization; AASLD: American Association for the Study of Liver Diseases; TBIL: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AFP: and the tumor marker α -fetoprotein; NCI: National Cancer Institute; SD: mean \pm standard deviation.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Shandong Cancer Hospital number: SDZLEC-2017-001-01]. All subjects provided written informed consent.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests

Funding

Not applicable

Authors' contributions

S JI have made contributions to the conception; X Dw have made contributions to design of the work; L Qr have made contributions to the acquisition, analysis; S Wb have made contributions to the conception; S Cc have made contributions to interpretation of data; L Jp and W N have drafted the work or substantively revised it. All authors read and approved the final manuscript.

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Figures

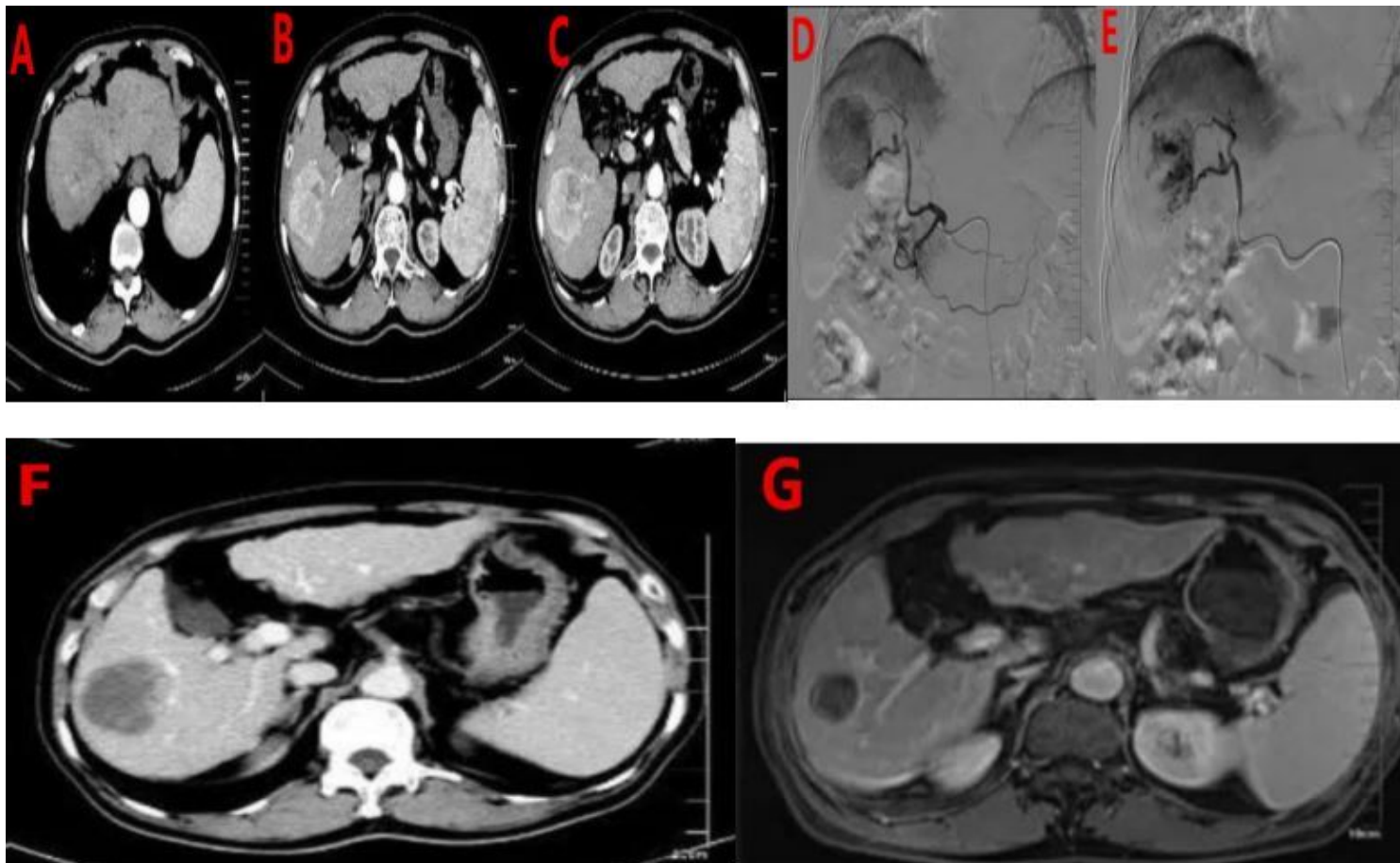


Figure 1

Short-term local tumor response of classic patient treated with CalliSpheres microspheres. A: CT scan showed a circular low-density mass shadow in the right lobe of liver, with the size of 6.8mm×6.5mm; B-C: enhanced CT showed the space-occupying lesion in right lobe tumor was obviously enhanced, showing a classic imaging features of hepatocellular carcinoma (enhanced on arterial phase and washed out on portal venous phase); D: In the interventional procedure, we entered the tumor feeding artery, arteriography showed obvious tumor staining; we used 100~300 μ m CalliSpheres microspheres (loading 60mg Epirubicin) to embolize the feeding artery of tumor; E: Postoperative angiography showed complete embolization of tumor feeding artery; F: Enhanced CT examination at 1 months after surgery showed that the range of the tumor was smaller and the liquefaction necrotic area was enlarged, and the efficacy evaluation was PR. G: Enhanced MRI examination at 3 months after surgery showed no enhanced lesions in the right lobe tumor, and the efficacy evaluation was CR.