The Safety and Efficacy of Transarterial Chemoembolization with Bleomycin for Hepatocellular Carcinoma Unresponsive to Doxorubicin:A Prospective Single-center Study

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Research article

Keywords: Hepatocellular carcinoma, Chemoembolization, Bleomycin

Posted Date: December 23rd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-132442/v1

Abstract

Purpose To investigate the safety and efficacy of transarterial chemoembolization (TACE) with bleomycin for hepatocellular carcinoma (HCC) unresponsive to doxorubicin.

Methods We did a randomized controlled trial in HCC patients resistant to TACE with doxorubicin to assess the survival benefits of the experimental group (TACE with bleomycin) compared with the control group (TACE with doxorubicin). 170 patients were allocated randomly between December 2015 and December 2017 and 80 patients of each group were accomplished and analyzed finally. The modified response evaluation criteria in solid tumors (mRECIST) was used to evaluated the tumor response every 4-6 weeks. The primary endpoint was median progression-free survival (mPFS) and median overall survival (mOS). Safety was assessed by post-procedure complications.

Results The study was stopped in October 2018. Objective response rate (ORR) of the experimental group was 27.5% (22/80) , mPFS and mOS was 5.8 and 8.1 months. ORR of the control group was 7.5% (6/80) , mPFS and mOS was 2.9 and 4.0 months. The ORR were significantly different between two grous (χ^2= 0.348, P<0.05). The differences of mPFS and mOS between the two groups were statistically significant (χ^2 = 2.865, P<0.05 and χ^2 = 0.926, P<0.05, respectively). There were no significant difference in post-procedure complications (P>0.05) and no major complications occurred.

Conclusion It is suggested that TACE with bleomycin is a safe and effective method for HCC and bleomycin can be a second-line chemotherapeutic agent for the HCC patients unresponsive to TACE with doxorubicin.

Background

HCC is the second most common cause of cancer-related deaths in the world with accounting for 9% of total deaths from cancer, the fifth most common cancer in men, the ninth most common cancer in women[1]. TACE is the current standard treatment for patients classified as intermediate stage in accordance with the Barcelona Clinic Liver Cancer (BCLC) staging system [2, 3]. The rationale for conventional TACE is intra-arterial chemotherapy using the mixture of lipiodol and chemotherapeutic agents and then selective vascular embolization, which result in a severe cytotoxic effect and ischemia [4, 5]. Unfortunately, there is no enough data about the choice of chemotherapeutic agent and whether the combination of chemotherapeutic agents over another or not at present[6]. Doxorubicin is the most common chemotherapeutic agent worldwide, mitomycin and platinum analogue were also used with lipiodol[7]. TACE is regularly administrated with doxorubicin in our department, however, resistance to TACE with doxorubicin often occurred after therapy repetition. Bleomycin is an anti-tumour antibiotic that causes DNA strand scission through formation of an intermediate metal complex[8]. To our knowledge, however, there is less information about the safety and efficacy of bleomycin for the treatment of HCC. The purpose of our study was to examine the safety and efficacy of TACE with bleomycin for HCC unresponsive to doxorubicin.

Methods

Patients

Entry criteria were the patients with unresectable HCC at the time of diagnosis of HCC (HCC diagnosis was confirmed according to biopsy or the criteria recommended by American Association for the Study of Liver Diseases) had undergone TACE therapy and were considered TACE-resistant now, which were defined as the HCC showed progressive disease according to modified response evaluation criteria in solid tumors(mRECIST)after at least two continuous courses of TACE with doxorubicin. Eastern cooperative oncology group (ECOG) performance status of 0–2; adequate liver function (Child-Pugh class A or B); sufficient hematopoietic function (platelet count is more than 50×10^9/L and leukocyte count is more than 3×10^9/L). Exclusion criteria were receiving concomitant chest radiation; advanced liver disease (Child-Pugh class C); refractory ascites; encephalopathy; active gastrointestinal bleeding; the whole portal obstruction, hepatic arteriovenous shunt.

1972 consecutively registered patients diagnosed as HCC from December 1, 2015 to December 1, 2017 were admitted to our department for treatment. All patients underwent a multidisciplinary evaluation to determine the treatment methods. In 284/1972 patients who met the entry criteria, 57 patients received targeted treatment, 18 patients received liver transplantation and 39 patients refused to participate, other 170 patients who agree to participate were enrolled and randomly assigned to TACE with bleomycin (n = 85) and TACE with doxorubicin (n = 85). The Consort diagram for the study was shown in Fig. 1.

Design and procedures

According to the standards of the Declaration of Helsinki, the study was approved by the ethics committee of our hospital and every patient gave written informed consent. Randomization was stratified blocked. Randomization was done with a computer-generated allocation and sealed envelopes to give in equal proportions: patients receiving TACE with bleomycin; patients receiving TACE with doxorubicin. Double-blind and double-dummy techniques were abandoned because the nature of the treatment. The femoral artery was catheterized under local anesthesia, celiac trunk and superior mesenteric arteriograms were routinely performed via a 4-F RH catheter to show parenchymal tumor. The total volume of contrast medium was 16 ml with a flow rate of 4 ml/s. The 2.7F microcatheter (Progreat, Terumo Corporation, Tokyo, Japan) was placed to the feeding artery and the emulsion was injected into the feeding artery under careful fluoroscopic guidance. The emulsion was performed by the administration of doxorubicin (50–60 mg/m^2) or bleomycin (0.5–1.5 wu) dissolved in 5–15 ml lipiodol (Lipiodol Ultra-Fluide, France) and then it was mixed with contrast agends (Ultravist, Bayer, Germany) at the ratio of 1:1. The dose of lipiodol ranged from 5 to 15 ml and varied according to tumor size and number. The feeding artery was embolized by gelfoam slurry subsequently. The procedure was stopped when the target vessel reach total stasis .

Follow-up and clinic evaluation

The follow-up and clinic evaluation was performed by clinical visits until the end of the study (October 1, 2018) or death. Efficacy was assessed based on tumor response and mOS, mPFS. Safety was assessed by post-procedure complications according to national cancer institute common terminology criteria for adverse events version 5.0 (NCI-CTCAE V 5.0). The tumor response was assessed by enhanced CT/MRI scans according to mRECIST [9] every 4–6 weeks. OS was defined as the duration between the initial chembolization and the last follow-up or death. PFS was defined as the interval between the initial chemoembolization and the first tumor progression which was showed by radiological evidence or death for any reasons.

Statistical analysis

Data were analyzed with IBM SPSS statistics version 24.0. The measurement data was compared by one-way ANOVA analysis. The chi-square test was utilized to compare the noncategoric variables. Survival curves were calculated by Kaplan–Meier method and compared by log-rank test. A two-tailed P value < 0.05 was regarded as statistically significant.

Results

1.Patient characteristics

3 patients (1.7%) (2 patients in the experimental group and 1patient in the control group) did not receive allocated intervention, 7 patients (4.1%) (3 patients in the experimental group and 4 patients in the control group) lost to follow-up, 80 patients of each group were accomplished and included in analysis finally. There were 135 males (84.4%) and 25 females (15.6%) with average age 57.4 ± 7.9 years (range from 35 to 74 years). Hepatitis B was present in 134 patients (83.7%) of all patients and hepatitis C in 2 patients (1.2%).131 patients (81.8%) had liver cirrhosis diagnosed on imaging. Vascular invasion occurred in 23 patients (14.3%) and extrahepatic metastasis in 36 patients (22.5%). The baseline characteristics of the patients are showed in Table 1. There were no significant difference in baseline characteristics of patients between the two groups (P>0.05).

Table 1
Patients characteristics

Parameter	Category	Experimental group(n = 80)	Control group(n = 80)	*p* value
Age	18–60 y	55	61	0.288
Gender	>60 y	25	19	0.276
Hepatitis	male	65	70	0.906
ECOG PS	female	15	10	0.329
Child-Pugh class	HBV	68	66	0.391
BCLC stage	HCV	1	1	0.701
Liver cirrhosis	absent	11	13	0.837
Vascular invasion	1	61	66	0.499
Extrahepatic metastasis	2	19	14	0.705
Tumor number	A	69	65	0.317
Tumor size	B	11	15	0.199
	B	55	56	
	C	25	24	
	present	66	65	
	absent	14	15	
	present	13	10	
	absent	67	70	
	present	19	17	
	absent	61	63	
	single	7	11	
	multiple	73	69	
	≤ 5 cm	46	35	
	5-10cm	21	30	
	≥ 10 cm	13	15	

2.Tumor response and survival analysis

The tumor response was assessed by enhanced CT/MRI scans according to mRECIST every 4–6 weeks. 7 cases of 80 patients showed complete response (CR) in experimental group, 15 cases showed partial

response (PR), 23 cases showed stable disease (SD) and 35 cases showed progressive disease (PD) with ORR of 27.5% (22/80). Otherwise, 0 cases of 80 patients showed CR in control group, 6 cases showed PR, 14 cases showed SD and 60 cases showed PD with ORR of 7.5% (6/80). The ORR were significantly different between two groups (χ^2= 0.348, *P*<0.05). The median OS was 8.1 months in experimental group and 4.0 months in control group. The median PFS was 5.8 months in experimental group and 2.9 months in control group. The OS and PFS of two group were assessed using the Kaplan–Meier method and compared by a log-rank test, which revealed significantly different between both groups (χ^2 = 2.865, *P*<0.05; χ^2 = 0.926, *P*<0.05). (Fig. 2,3)

3. Hematologic toxicity and post embolization syndrome

In terms of hematologic toxicity, 4 patients (5%) developed grade 3 thrombocytopenia, 1 patient (1.25%) developed grade 3 leukopenia and 4 patients (5%) developed grade 4 AST elevation in experimental group, 5 patients (6.25%) developed grade 3 thrombocytopenia, 1 patient (1.25%) developed grade 3 leukopenia and 3 patients (3.75%) developed grade 4 AST elevation in control group (Table 2). In terms of postembolization syndrome, there were mainly grade 1–2 fever, nausea, vomiting, abdominal pain, chills and no grade 3–4 adverse reactions in the both group (Table 3). There were no significant difference in hematologic toxicity and postembolization syndrome between the two groups (*p*>0.05). No major complications occurred in the two groups and no bleomycin pulmonary toxicity was found according to chest CT examination during follow-up.

Table 3
Postembolization syndrome according to NCI-CTCAE version 5.0

Parameter	Experimental group (n)				Control group (n)			
	1	2	3	4	1	2	3	4
Abdominal pain	34	6	0	0	40	5	0	0
Fever	55	10	0	0	58	9	0	0
Nausea	27	1	0	0	30	1	0	0
Vomiting	30	2	0	0	28	3	0	0
Chills	5	0	0	0	7	0	0	0
Diarrhea	0	0	0	0	2	0	0	0
Hypotension	0	0	0	0	0	0	0	0

4. Cause of death

The study was stopped in October, 2018. The median follow-up time was 8.1 months (range from 1.5 to 20.7 months) of the 160 patients. Finally, 26 patients (43.3%) died and 54 patients survived in the experimental group, 18 patients of all dead patients died of tumor recurrence, 4 patients died of

gastrointestinal bleeding, 1 patient died of liver abscess and 3 patients died of liver failure. Otherwise, 35 patients (58.3%) died and 45 patients survived in control group, 20 patients of all dead patients died of tumor recurrence, 6 died of gastrointestinal bleeding and 9 patients died of liver failure.

Discussion

TACE is the main treatment for patients with HCC who are not eligible for curative surgery,some randomized controlled trials and meta-analysis have reported the survival benefits of TACE [10–12]. Unfortunately, TACE-resistance can occur frequently during the repetition of embolization and there is no clear evidence about the optimal chemotherapeutic agent for TACE. Bleomycin which was first discovered in 1966 [13] and obtained FDA approval in 1973 as a cytotoxic antibiotic with renowned anticancer activity is clinically used to treat germ cell tumors and lymphomas [14]. To our knowledge, there is no information about the safety and efficacy of bleomycin for TACE-resistant HCC patients. In this study, bleomycin was used as the second-line chemotherapeutic agent for TACE-resistant HCC patients.

Kawamura et al. [15] reported that the objective tumor response rate of TACE or hepatic arterial infusion (HAI) with platinum analogue was 22.4% in 152 patients with unresectable HCCs unresponsive to TACE with epirubicin–lipiodol emulsion, which is similar to our results, the objective tumor response rate was 27.5% in our study. Maeda et [16] reported the results of TACE or HAI with cisplatin in 51 patients with unresectable HCCs unresponsive to TACE with epirubicin–lipiodol emulsion. The mOS and mPFS was 15.4 and 3.1 months, respectively. Otherwise, Kondo et al. [17] reported the results of HAI with cisplatin and oral sorafenib in 127 HCC patients without extrahepatic metastasis unresponsive to prior TACE at four institutions, The mOS was 11.2 months in the cisplatin group and 10.2 months in the sorafenib group, respectively. However, the mOS and mPFS was 8.1 and 5.8 months in the study, respectively. This may be partly because we enrolled more advanced HCC patients and there were a greater proportion of advanced conditions: tumor size >5 cm in 79 patients (49.3%), multiple tumors in 142 patients (88.7%), vascular invasion in 23 patients (14.3%) and extrahepatic metastasis in 36 patients (22.5%). The study showed the survival benefits of TACE with bleomycin which was used as the second-line chemotherapeutic agent for TACE-resistant HCC patients, however, we can’t confirm better survival benefits of TACE with bleomycin compared with TACE or HAI with cisplatin and sorafenib. So further studies are needed to clarify the optimal chemotherapeutic agent and therapeutic methods for TACE-resistant HCC patients.

Our study showed that TACE with bleomycin was a safe method for the treatment of TACE-resistant HCC patients. Pneumonitis and pulmonary fibrosis are the major complications of bleomycin [18], bleomycin-induced pneumonitis is assessed to be around 10% in the case of germ cell tumors [19]. The incidence of pulmonary toxicity has been reported as high as 18% and 24% mortality of affected cases in patients receiving bleomycin for treatment of lymphoma [20]. However, no major complications and bleomycin pulmonary toxicity were found during follow-up in the study and there were no significant difference in hematologic toxicity and postembolization syndrome between the two groups. The cumulative dose has been described as a cause for toxicity [21] and the route of administration could potentially impact the

level of toxicity. So the lower incidence of complications in the study may be as a result of the lower doses and the route of intra-arterial administration.

There were some limitations in our study. Firstly, it's a small-scale single center trial. Otherwise, the study did not compare results of other chemotherapeutic agent for the HCC patients unresponsive to TACE with doxorubicin. However, that will be the subject of ongoing studies.

Conclusion

In conclusion, the present study reported TACE with bleomycin is safe and effective for HCC and bleomycin can be a second-line chemotherapeutic agent for the HCC patients unresponsive to TACE with doxorubicin.

Abbreviations

HCC
hepatocellular carcinoma
TACE
transarterial chemoembolization
HAI
hepatic arterial infusion
BCLC
Barcelona Clinic Liver Cancer
AST
aspartate transaminase
mRECIST
modified response evaluation criteria in solid tumors
ORR
objective response rate
mPFS
median progression-free survival
mOS
median overall survival

Declarations

Ethics approval and consent to participate

According to the standards of the Declaration of Helsinki, the study was approved by the ethics committee of Chinese PLA General Hospital and every patient gave written informed consent.

Consent for publication

Not applicable

Availability of data and material

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

Our study was supported by big data research and development project of Chinese PLA General Hospital.

Authors' contributions

Jinlong zhang□jieyu yan□kai yuan□bing yuan and yang guan analyzed and interpreted the patient data, and jinxin fu, yan wang, maoqiang wang were major contributors in writing the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

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Figures

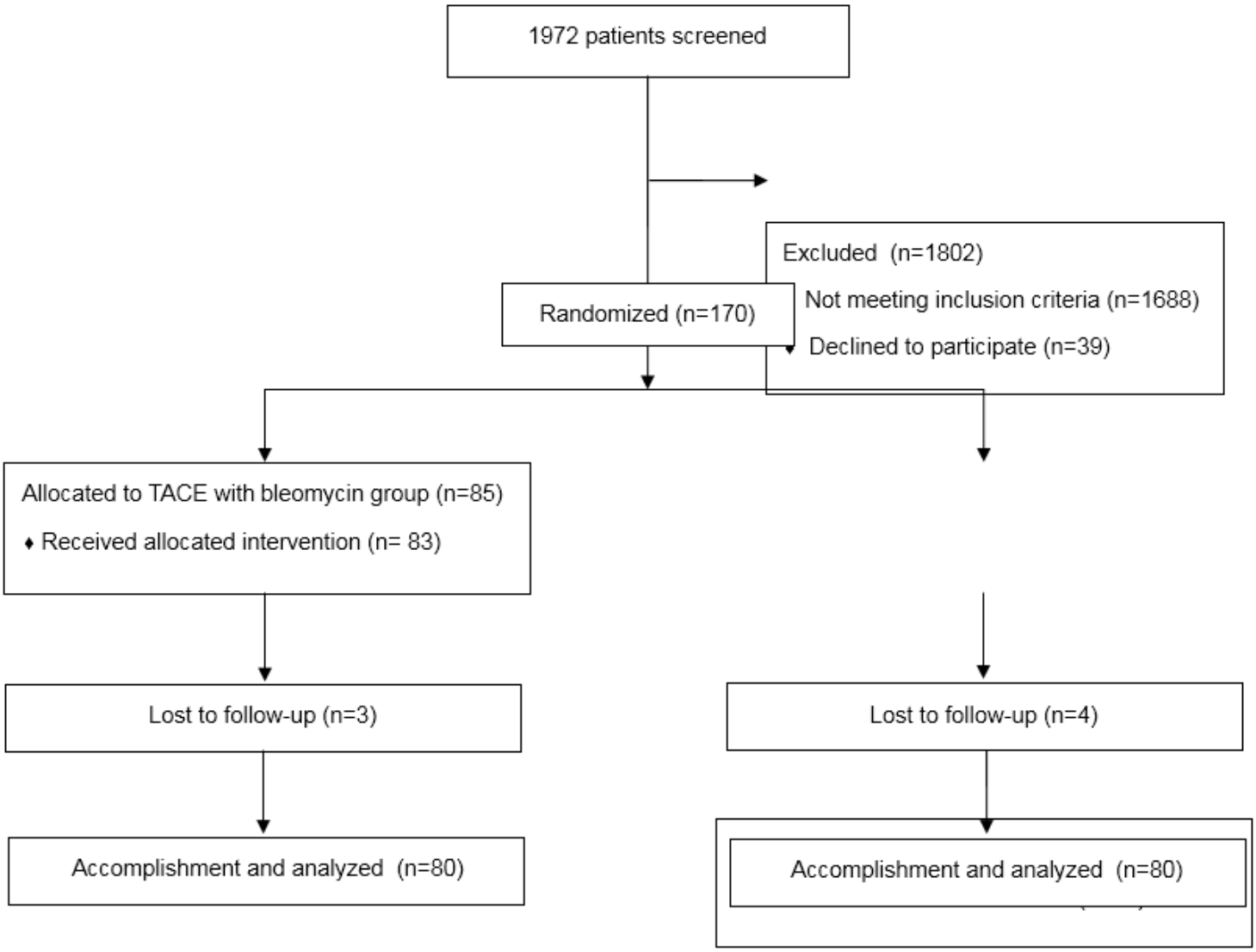

Figure 1

Consort diagram for the study

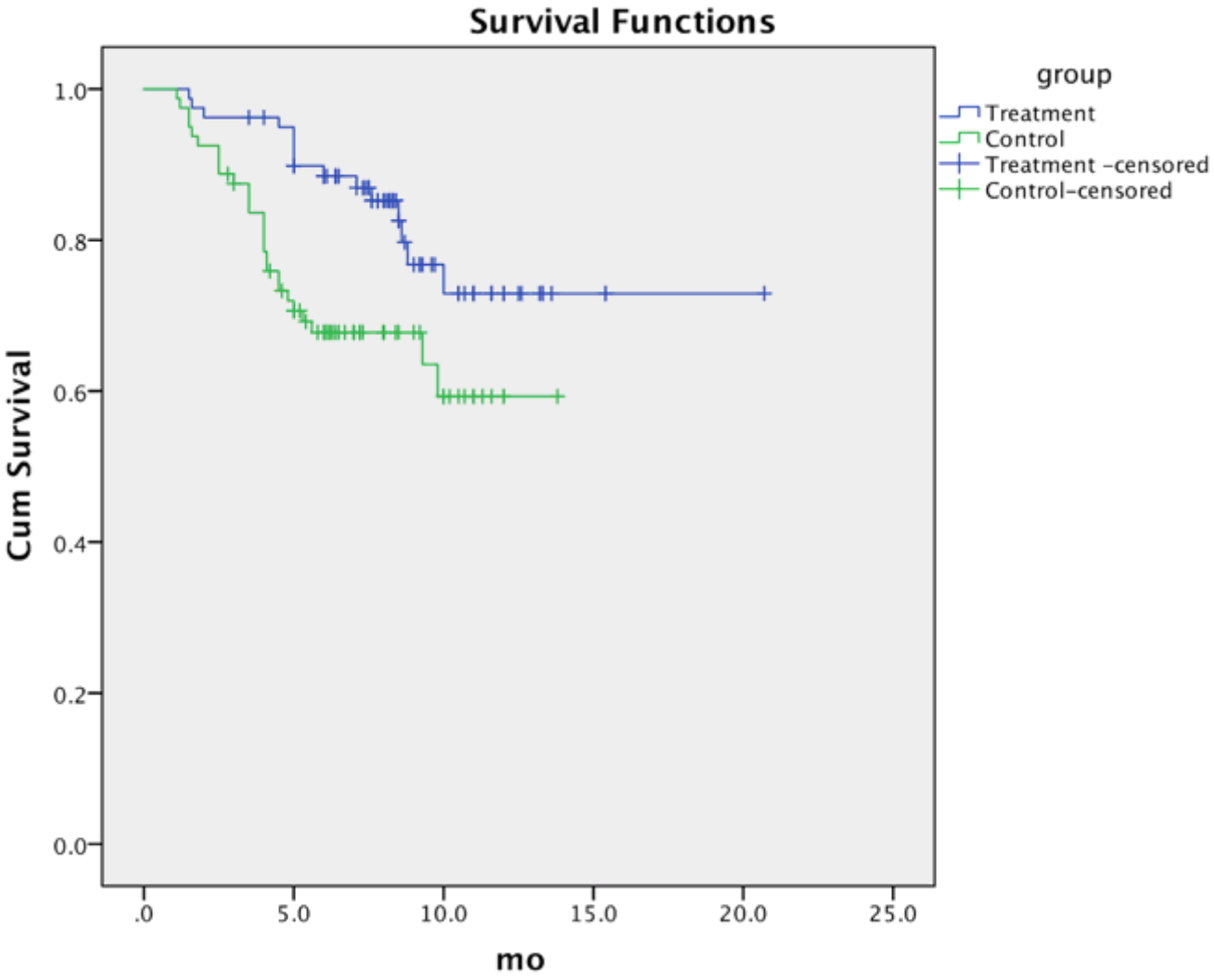

Figure 2

Survival curves of patients for both groups

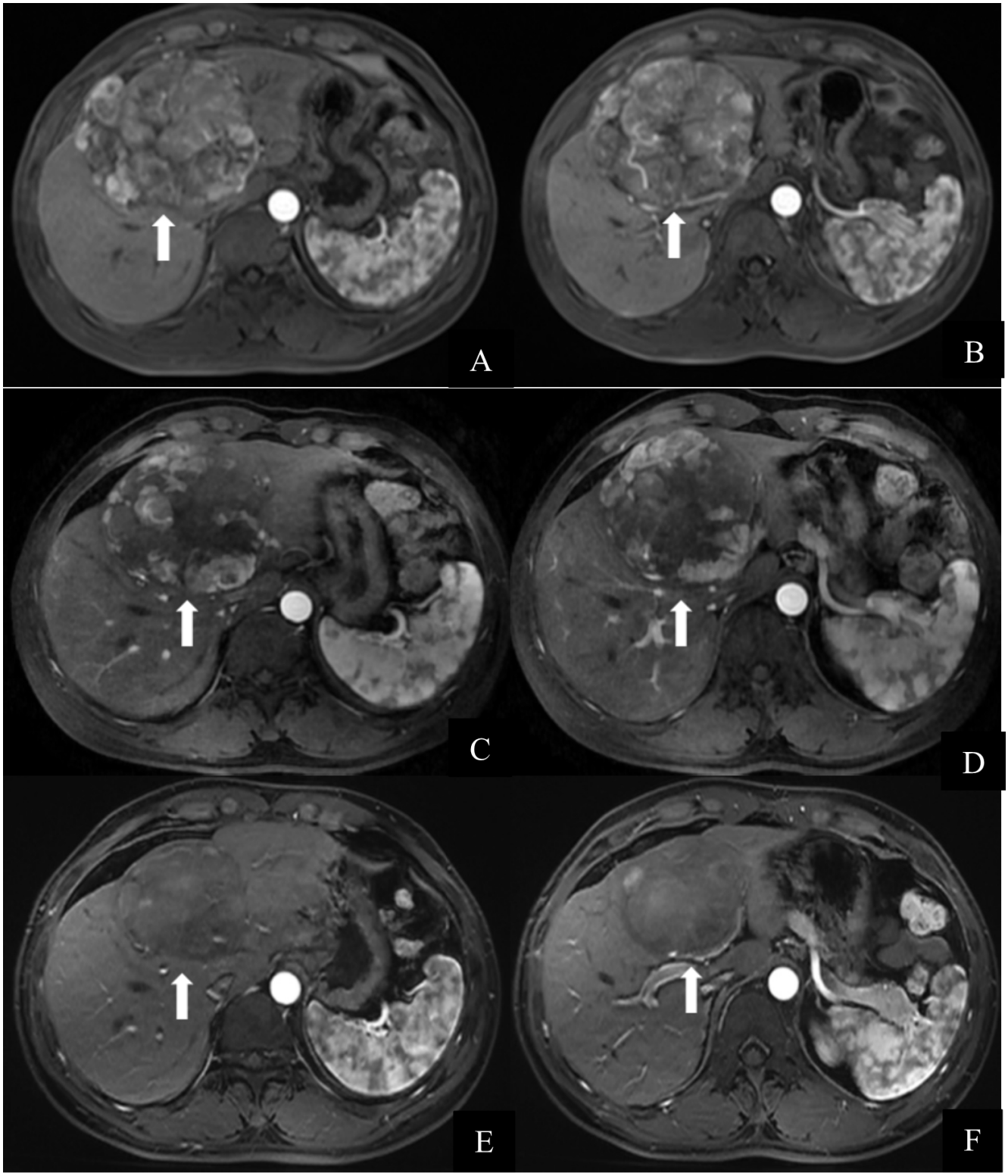

Figure 3

Comparison imaging of before and after TACE using bleomycin for HCC unresponsive to doxorubicin. (A.B) MRI imaging showed a huge hypervascular tumor (arrow) before embolization. (C.D) MRI imaging showed HCC (arrow) began resist to TACE with doxorubicin after PR to initial TACE. (E.F) MRI imaging showed CR (arrow) to TACE using bleomycin.