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Chemoembolization for hepatocellular carcinoma fed by right internal thoracic artery

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Abstract

The purpose of the study was to evaluate the value of transarterial chemoembolization (TACE) via right internal thoracic artery (RITA) for patients with unresectable hepatocellular carcinoma (HCC).

From January 2000 to June 2016, a retrospective study was conducted of all patients with unresectable HCC who underwent TACE via RITA across 3 medical centers. The technical success, serum alpha-fetoprotein (AFP) level changes, major complications, disease control rate, and survival were evaluated and analyzed.

During the study peroid, in all, 21 patients (men 21; mean age 57.3±7.1 years) were included in this study. Of the 21 patients, all the tumors were located under the capsule of the liver and adjacent to the diaphragm with median tumor diameter of 8.2 cm in 20 patients, and the tumor was located at the surface of the liver due to incisional site metastasis in 1 remaining patient. Lesions fed by the RITA were demonstrated during initial TACE in 2 patients and during repeat TACE therapy in 19 patients. The technical success rate was 100%. The AFP response 1 month after treatment was complete (n=4) and partial (n=9) of 13 patients whose AFP was abnormal before the procedure, and the serum levels of AFP reduced significantly 1 month after treatment (1240.1±347.1 vs 175.2±71.8; $P<.01$). No major complications occurred. The disease control rate was 100% at 3 months after treatment. The median overall survival from the time of TACE therapy via the RITAs was 18.2 months, and 1-year survival after TACE therapy via the RITAs was 76.2%.

Chemoembolization via the RITA can improve the therapeutic efficacy of TACE and reduce the presence of residual HCC.

Abbreviations: AFP = alpha-fetoprotein, CT = computed tomography, DSA = digital subtraction angiography, HCC = hepatocellular carcinoma, mRECIST = modified Response Evaluation Criteria in Solid Tumors, MRI = magnetic resonance imaging, RITA = right internal thoracic artery, TACE = transarterial chemoembolization.

Keywords: chemoembolization, hepatocellular carcinoma, internal thoracic artery

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and the third highest global cause of cancer mortality.[1] Transarterial chemoembolization (TACE) has been widely used in the treatment of unresectable HCC.[2,3] However, the rates of post-treatment residual HCC remain high, and repeated TACE therapy is needed.[4,5] It was reported that an extrahepatic collateral pathway to the tumor play an important role in the presence of residual HCC, which can limit the effectiveness of TACE therapy.[4,6,7] To improve the efficacy of TACE therapy and reduce the presence of residual HCC, these collaterals need to be adequately embolized.[4,7,8]

The right internal thoracic artery (RITA), previously known as the internal mammary artery, is an artery that arises from the subclavian artery and terminates by dividing into superior epigastric and musculophrenic arteries. Although it is uncommon for HCC to be fed by the RITA, the RITA can form a collateral pathway to HCC.[9–11] Although TACE therapy via RITA for unresectable HCC has been reported, the outcome reports of TACE therapy via RITA in the treatment of unresectable HCC are limited. The purpose of this retrospective study was to evaluate the value of TACE therapy via RITA for patients with unresectable HCC.

2. Methods

2.1. Patients

The protocol was approved by all participating institution review boards (Wujin Hospital, No. 2 People's Hospital of Changzhou, and The Third Hospital Affiliated to Soochow University). This study has been performed according to the ethical standards laid down in the 1964 Declaration of Helsinki and its later

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amendments. The diagnosis of HCC was made by histologically or computed tomography (CT) scan and digital subtraction angiography (DSA), in addition to high serum levels of alpha-fetoprotein (AFP). All patients were fulfilling diagnostic criteria for HCC adopted by Barcelona-2000 EASL conference. From January 2000 to June 2016, all patients with unresectable HCC who received TACE therapy via RITA were included in this study. Patient demographics, clinical information, procedural data, and follow-up data were collected from patients' medical records.

2.2. TACE procedure

Transarterial chemoembolization was carried out according to the current practice guidelines.[12] Arteriography was routinely performed using a 5-Fr Rosch hepatic catheter (Cook, Bloomington, IN) in all patients before chemoembolization. TACE was performed using a 2.7-Fr microcatheter (Progreat; Terumo, Japan). Lipiodol, gelatin sponge particles, and polyvinyl alcohol were used as embolic agents. All tumor arteries were embolized with an emulsion of iodized oil and epirubicin or oxaliplatin at a ratio of 10 mL of lipiodol to 10 mg epirubicin or 50 mg oxaliplatin. The dose of lipiodol used depended on the size and vascularity of the tumor. Lipiodol injection was stopped when the flow stasis. Additional embolization of gelatin sponge particles or polyvinyl alcohol was performed until there was no longer any tumor staining after repeat angiography in whom flow stasis of feeding artery could not have been obtained with the lipiodol.

2.3. Postprocedural management

All patients were admitted for TACE procedure, and received postprocedural supportive treatment, which included hydration, treatment with antiemetics, and pain control.

2.4. Tumor response and tumor marker changes

Contrast-enhanced CT and/or magnetic resonance imaging (MRI) scans were obtained within 30 days before TACE therapy to serve as a baseline. After TACE therapy via RITA, follow-up imaging was obtained at 1 and every 3 months. Tumor response was evaluated at 3 months post-treatment according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Two radiologists evaluated the tumor response independently and a third assisted in resolving the differences. Disease control rate was defined as the percentage of patients who achieved complete response, partial response, and stable disease at 3 months after TACE therapy via RITA.

Serum AFP (normal $\leq$25 μg/L) levels were analyzed at baseline and after therapy. The type of response was defined as complete if the levels normalized, partial if the decrease was >20% from baseline, no response if the decrease was <20% of increase <20%, or progression if the elevation was >20%.

2.5. Follow-up

Major complications related to TACE therapy via RITA were evaluated during follow-up, and was defined by the Society of Interventional Radiology,[13] including admission to a hospital for therapy, higher level of care required, substantially longer hospital stay (>48 hours) required, and the occurrence of permanent adverse sequelae or death. Routine survey of procedure-related complications was carried out post-treatment with bedside visit and clinical follow-up.

Clinical follow-up was scheduled on the first and third months after treatment, and every 3 months thereafter. More frequent evaluations were done when needed. During follow-up, contrast-enhanced MRI and routine laboratory work-up were obtained, including complete blood count, liver enzymes and bilirubin, and serum AFP level. Mortality data were obtained by searching our electronic medical chart system.

2.6. Definitions

Technical success was defined as successful catheterization and completion of TACE therapy via RITA. Survival was calculated from the date of first TACE therapy via RITA for unresectable HCC to the date of death or last follow-up.

2.7. Statistical analysis

SPSS version 17.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. The values of serum AFP levels were recorded as mean ± SD. A *t* test was used to compare the differences in serum AFP levels before and 1 month after treatment. A *P* value less than .05 was considered statistically significant.

3. Results

3.1. Patients

From January 2000 to June 2016, in all, 21 patients who underwent TACE therapy via RITA for unresectable HCC were included in this study. All the 21 patients were male with mean age of 57.3 ± 7.1 years (range 40–74 years). The demographic information and disease characteristics are detailed in Table 1. The tumors were located under the capsule of the liver and adjacent to the diaphragm with median tumor diameter of 8.2 cm (range 6–15 cm) in 20 patients (Fig. 1), and the tumor was located at the surface of the liver due to incisional site

Table 1

Baseline characteristics for 21 study participants.

Characteristic	Value
Age, y	57.3 ± 7.1 (40–74)
Sex	
Male	21 (100)
Female	0
ECOG performance status	
0	8 (38.1)
1	13 (61.9)
Child-Pugh classification	
A	12 (57.1)
B	9 (42.9)
AFP, μg/L	
Positive	13 (61.9)
Negative	8 (38.1)
Number of lesions	
Solitary	5 (23.8)
Multifocal	16 (76.2)
Extrahepatic metastases	
Yes	0
No	21 (100)

Values are presented as mean ± SD (range) or n (%).
AFP = alpha-fetoprotein, ECOG = Eastern Cooperative Oncology Group.

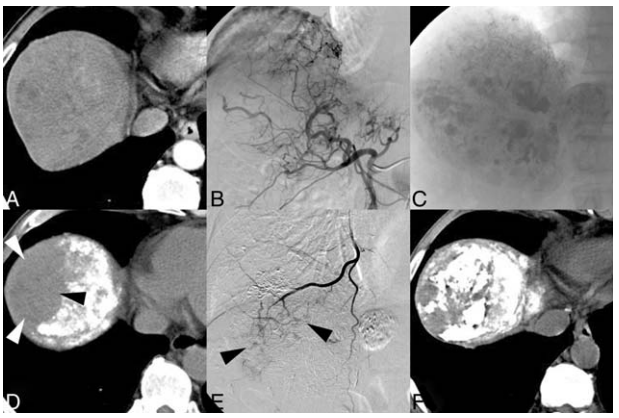

Figure 1. (A) A 53-year-old man with huge HCC in the right lobe of the liver, which was located under the capsule of the liver and adjacent to the diaphragm with tumor diameter of 11.6 cm. (B) Staining of the tumor on the proper hepatic arteriogram was demonstrated. (C) Lipiodol retention in the tumor after TACE via right hepatic artery. (D) Defective lipiodol retention of the peripheral portion of the tumor (arrow heads) one month after TACE via right hepatic artery. (E) Staining of the tumor (arrow heads) on the right internal thoracic arteriogram was demonstrated during repeat TACE. (F) Lipiodol retention of the peripheral portion of the tumor 3 months after TACE via the right internal thoracic artery. HCC = hepatocellular carcinoma, TACE = transarterial chemoembolization.

metastasis in 1 remaining patient (Fig. 2). Serum AFP levels were abnormal at baseline in 13 patients with the mean level of 1240.1 ± 347.1 μg/L.

3.2. Treatment

Lesions fed by the RITA were demonstrated during initial TACE therapy in 2 patients and during repeat TACE therapy (mean 2.4 sessions; range 2–5 sessions) in 19 patients. Also, 7 patients (33.3%,7/21) had extrahepatic collateral inferior phrenic artery feeding HCC, additional to extrahepatic collateral RITA. TACE via the RITA was performed successfully in all patients, with a technical success rate of 100%. Lipiodol was used as an embolic agent in all patients (mean 6.5 ± 2.3 mL; range 5–10 mL); gelatin sponge particles was used in 12 patients and polyvinyl alcohol was used in 3 patients. There were no major embolization-related complications occurred.

3.3. AFP changes and tumor response

The AFP response 1 month after treatment was complete (n = 4) and partial (n = 9) of 13 patients whose AFP was abnormal before the procedure, and the serum levels of AFP reduced significantly 1 month after treatment (1240.1 ± 347.1 vs 175.2 ± 71.8; $P < .01$). The disease control rate was 100% at 3 months after TACE therapy, with partial tumor response seen in 19 (90.5%) patients and stable disease seen in 2 (9.5%) patients.

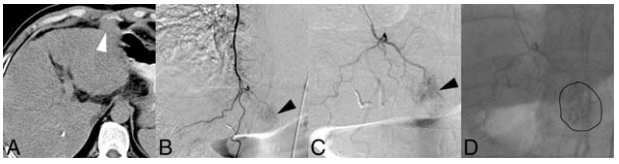

Figure 2. (A) A 47-year-old man with tumor located at the surface of the liver due to incisional site metastasis (arrow head). (B, C) Staining of the tumor (arrow head) on the right internal thoracic arteriogram was demonstrated. (D) Lipiodol retention of the tumor after TACE via right internal thoracic artery. TACE = transarterial chemoembolization.

3.4. Survival

At the time of this analysis, 15 (71.4%, 15/21) patients expired and 6 (28.6%, 6/21) patients were still alive with a mean follow-up of 15.6 ± 5.7 months (range 6–27 months) after TACE therapy via the RITAs. The median overall survival from the time of TACE therapy via the RITAs was 18.2 months. The 1-year survival after TACE therapy via the RITAs was 76.2%.

4. Discussion

Transarterial chemoembolization has been widely used in the treatment of unresectable HCC because of the advanced stage of the tumor itself and the unfavorable clinical status of the patients. However, the objective of TACE should be tumor control rather than complete eradication, because the pathologically confirmed necrosis rate of HCC after TACE is no more than 90% to 95%.[14,15] In such condition, repeated TACE should be performed to control tumors for those patients with unresectable HCC. Therefore, many problems related to repeated TACE have arisen, which include the development of extrahepatic collateral supplies to the tumor, especially to the patients in whom the tumor is located at the marge of the liver. Various collateral pathways to HCC have been described.[6,16] Among these, the RITA is known to be 1 of the extrahepatic collateral feeders of HCC.[17]

There are many reasons for the formation of extrahepatic collateral feeders of HCC. First, the interruption of the hepatic artery by surgical ligation, and/or arterial injury induced by TACE, can made the extrahepatic collaterals development.[4] Second, adhesion between the liver and other organs exaggerates the degree of extrahepatic collaterals.[18] Third, an extrahepatic blood supply to HCC also develops in the anatomic location of HCC, although the hepatic arterial supply remains intact.[19] Because a potential anastomosis is present between the RITA and the hepatic artery, when hepatic arterial flow is blocked or reduced by TACE, the RITA may exhibit a relative increase in blood flow and develop as an artery feeding the tumor. The present study proved that 90.5% lesions fed by the RITA were demonstrated during repeat TACE therapy, and 95.2% tumors were located under the capsule of the liver and adjacent to the diaphragm.

For tumors located directly beneath the diaphragm, the most likely extrahepatic collateral vessel is the inferior phrenic artery, because the inferior phrenic artery feeds the diaphragm widely and the diaphragm is adjacent to the liver over a large portion of its extent. The inferior phrenic arteries run along the inferior surface of the diaphragm, and their branches are in direct contact with the liver in the region in which no parietal peritoneum covers the diaphragm, the bare area of the liver. Portions of liver S1, S2, and S7 form this bare area. It was reported the inferior phrenic artery frequently supplies lesions located in these segments.[20,21] The present study proved that 33.3% lesions were fed by both of RITA and inferior phrenic artery, which made the operater likely to overlook the RITA. Of the 7 patients who with both of RITA and inferior phrenic artery as feeders of the tumor, the RITAs were disclosed as extrahepatic collateral feeders of HCC with median 4 TACE procedures.

Super-selective catheterization is critical in delivering the chemotherapeutic agents to the target tumor and avoid nontarget

embolization. Once the RITAs were super-selected, further selection of the tumor feeding artery should be carried out due to the fact that RITA has superior epigastric and musculophrenic branches. It is important to place the catheter into the most distal portion of the tumor feeding branch to avoid nontarget embolization; otherwise, the skin necrosis is unavoidable. Of the 21patients, all the RITAs were super-selected and chemoembolized in using a 2.7-Fr microcatheter; there were no RITA embolization-related complications such as skin necrosis.

Considering the results of this study and previous reports, we offer several recommendations. First, if one finds a hypertrophied RITA that runs toward the region of the tumor and/or defective or missing staining of the tumor on the hepatic arteriogram and/or defective lipiodol retention or progression of the peripheral portion of the tumor after TACE in the CT scans, it is mandatory to perform selective RITA arteriograms. Second, extrahepatic collateral RITA has close relationship with the anatomic location of HCC; RITA angiography should be performed for tumors located in the ventral hepatic areas directly beneath the diaphragm in patients with missing staining of the tumor on the hepatic and inferior phrenic arteriogram. Third, intervention radiologist should carefully observe both the CT/MR scans and the angiograms in patients whose tumor beneath the diaphragm to reduce the missed of RITA collateral, especially to the patients with both of RITA and inferior phrenic artery as feeders of the tumor.

The current study is limited by its retrospective nature and the number of patients was small. Also, the observation time was short, which may have biased the results. Prospective randomized clinical trials with large sample sizes and long-term follow-up are needed to validate the value of chemoembolization via the RITA for unresec HCC.

5. Conclusions

In conclusion, the RITA can develop as an extrahepatic collateral supply of HCC and chemoembolization via the RITA can improve the therapeutic efficacy of TACE and reduce the presence of residual HCC.

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