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Computed Tomography-Guided Radiofrequency Ablation Following Transcatheter Arterial Embolization in Treatment of Large Hepatic Hemangiomas

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Abstract: The aim of the study was to evaluate the feasibility, safety, and efficacy of computed tomography (CT)-guided radiofrequency (RF) ablation combined with transcatheter arterial embolization (TAE) to treat large (≥10 cm) hepatic hemangiomas.

We retrospectively reviewed our sequential experience with 15 large hepatic hemangiomas in 15 patients.

The mean diameter of the 15 hemangiomas was 13.0 ± 2.2 cm (10.0–16.0 cm). RF ablation combined with TAE treatment was performed successfully in all patients. The mean diameter of the hemangiomas decreased from 13.0 ± 2.2 to 7.1 ± 2.0 cm ($P < 0.001$) after TAE treatment. Out of 15 hepatic hemangiomas, 14 (93.3%) showed no enhancement on CT or MRI indicating complete ablation after RF treatment. The mean diameter of the ablation zone decreased to 6.1 ± 2.0 cm 1 month after ablation and further decreased to 4.9 ± 1.6 cm 6 months after ablation. There were 6 complications related to the ablation in 4 patients. According to the Dindo–Clavien classification, all the complications were minor (Grade I).

RF ablation combined with TAE is a safe and effective treatment for large hepatic hemangiomas. TAE can improve the disruption of lesion blood supply and reduce lesion size to facilitate subsequent RF ablation and reduce the risk of ablation-related complications.

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Abbreviations: CT = computed tomography, HCC = hepatocellular carcinoma, MRI = magnetic resonance imaging, RF = radiofrequency, TACE = transcatheter arterial chemoembolization, TAE = transcatheter arterial embolization.

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INTRODUCTION

Hepatic hemangiomas are the most commonly diagnosed benign tumor of the liver, with a prevalence ranging from 0.4% to 7.3%.[1–3] A majority of hepatic hemangiomas are asymptomatic and identified incidentally and medical or surgical intervention is often not needed.[3] However, for the giant hemangioma (with a diameter ≥ 5 cm) which poses a higher risk of rupture, presents with uncontrollable abdominal pain by analgesic medication or increases size during follow-up, a radical intervention needs to be considered.[4,5] Conventionally, surgical resection to remove the tumor is the mostly used treatment for symptomatic, enlarging or vulnerable-to-rupture hepatic hemangiomas, but it is a highly invasive procedure, with a periprocedural morbidity and mortality rates of up to 31.5% and 3%, respectively.[4,5]

Radiofrequency (RF) ablation has been successfully used in the management of giant hepatic hemangiomas with a large size ranging from 5 cm to –9.9 cm.[6–12] However, the application of RF ablation in treating hepatic hemangiomas >10 cm still remains in debate because of the great technical challenge and high incidence of ablation-related complications.[8–12] The most severe complication is dangerous hemolysis because a large volume of blood in the giant hemangioma needs a relatively long time of ablation, which induces an abrupt and massive blood cell lysis.[8–12] A feasible solution to this critical problem would be to decrease the volume of hemangiomas in advance of RF ablation.

Some groups have tried transcatheter arterial embolization (TAE) for the treatment of hepatic hemangiomas. However, the treatment is not considered as curative because recurrence is common due to vascular recanalization.[13,14] Several reports have advocated TAE as a temporizing and auxiliary preoperative procedure for large hemangioma or spontaneously ruptured hemangiomas to decrease the risk of surgery. Successful preoperative embolization of hemangiomas has proven to be very useful in reducing the risk of intraoperative hemorrhage.[15,16]

RF ablation as a thermal in situ technique has been proven to be a safe and effective treatment,[6–12,17] as TAE helps to decrease blood flow to the hemangiomas.[13–15] TAE therapy before RF ablation for large hemangiomas would theoretically block the tumor blood supply and reduce tumor size to improve RF ablation outcomes. We reasoned that this combination therapy would help us achieve successful eradication of large hepatic hemangiomas while avoiding ablation-related complications. To the best of our knowledge, whether the combination of RF ablation and TAE can provide therapeutic benefits for large hepatic hemangiomas has not yet been reported.

The purpose of this study was to evaluate the feasibility, safety, and efficacy of computed tomography (CT)-guided RF ablation combined with TAE treatment of large hepatic hemangiomas.

PATIENTS AND METHODS

Study Design

We retrospectively reviewed the medical records of patients with large hepatic hemangiomas who had been treated by RF ablation combined with TAE at the Fifth Affiliated Hospital of Wenzhou Medical College from October 2007 to May 2015.

The inclusion criteria for patients who were selected to receive RF ablation combined with TAE include: (1) persistent abdominal pain or discomfort directly caused by hemangioma without any evidence of potential gastrointestinal diseases; (2) the lesions gaining size increase of > 1 cm on regular imaging follow-up within a 2-year observation period; (3) patient's refusal to surgical treatment.[8–12]

An experienced interventional radiologist (Ji J) performed all the procedures. This study was conducted in accordance with the Declaration of Helsinki of the World Medical Association. This study was approved by our Institutional Ethics Committee of the Fifth Affiliated Hospital of Wenzhou Medical College, Zhejiang, China. Written informed consent was obtained from all patients before the treatment.

TAE Procedures

All patients were medicated with analgesia and sedated throughout the procedures. The Seldinger technique was used to establish the access to the femoral artery. After a celiac and superior mesenteric arteriography through a 5-French catheter (Cook, Bloomington, IN), the hepatic artery was catheterized. After a confirmation of the feeding arteries originating from either the right or left hepatic artery, a superselective cannulation of the tumor feeding arteries was performed using a 3-French microcatheter (Microferret®, Cook). Thereafter, the feeding vessels were selectively embolized by infusing an emulsion of pingyangmycin (PYM®, Zhejiang Hisun Pharmaceutical CO., Ltd, China, bleomycin A5 hydrochloride for injection) in iodized oil (Lipiodol®, Andre Gurbet, Aulnay-sous-Bois, France), followed by a further embolization by an injection of gelatin sponge particles (1–2 mm in diameter) (Gelfoam®, Upjohn, Kalamazoo, MI). Pingyangmycin is an antitumor glycopeptide antibiotic belonging to the bleomycin family, which is produced by *Streptomyces verticillus var. pingyangensis n. sp.*, a variety of *S verticillus*, which functions to damage the endothelia cells of the tumor vessels and ultimately induce the blood coagulation in the vessel. The pingyangmycin-in-lipiodol mixture was prepared by emulsifying 2 mL of 5% glucose solution with 8 mg of pingyangmycin in 20 mL iodized oil. Under the monitoring of fluoroscopy, a continuous infusion of the emulsion was performed till a complete blockade of the blood flow in the tumor feeding vessel was achieved. After embolization, angiography was performed to assess the extent of vascular embolization and identify any presence of residual lesion staining.

CT-guided RF Ablation Procedures

CT-guided RF ablation was performed 1 month after TAE. The patient was placed on the table in a supine position. Under CT guidance, the optimal puncture site was identified. After local anesthesia infiltration, the RF electrode (RITA StarBurst® Xli-enhanced RF electrode, Radiofrequency Interstitial Thermal Ablation Medical Systems, Mountain View, CA) was placed in the targeted tumor via a percutaneously transhepatic approach. After an optimal position of the electrode was confirmed by CT, RF ablation was carried out according to the established protocol.

To achieve a safe and effective ablation of the hemangioma, we followed the protocol to perform the RF ablation strictly: (1) to prevent the bleeding from the hemangiomas, RF electrode was advanced via a percutaneous transhepatic approach and keep the trajectory of the probe through the liver parenchyma; (2) ablation was started from the tumor margin, where the heat-sink effect is minimal and the likelihood of bleeding is relatively small; (3) an overlapped RF ablation were warranted by placing the electrode in multiple sites of the tumor to ensure a substantial ablation of the entire tumor; (4) we minimized the possibility of injuring surrounding liver tissue; (5) RF electrode trajectory was ablated to prevent the bleeding along with the withdrawal of the electrode.[10–12]

Postoperative Evaluation

All patients underwent contrast material-enhanced CT or MRI 1 month postablation to follow up the treatment effect. Complete ablation was defined as no nodular or irregular enhancement within the ablated zone on contrast-enhanced CT or MRI images. Incomplete ablation was identified as irregular, peripherally enhancing foci in the ablated zone. For the cases with complete ablation, subsequent CT or MRI examinations were repeated at a 6-month interval for 2 years. For the patients with incomplete ablation, RF ablation procedures were repeated in case the residual tumor progressed significantly during a 6-month imaging follow-up.[10–12]

Study Endpoints

The primary evaluated variables at the endpoint of the study include the rate of technical success, major or minor complications, mean hospital stay, and confirmed complete ablation. The secondary evaluated variables at the endpoint include improvement in symptoms, change in size of the ablated tumor, recurrence of the residual tumor, and life quality improvement. The endpoints of the study were set at 6 months after RF ablation treatment.

Statistical Analysis

Values are expressed as mean $\pm$ SD. Continuous variables between groups were compared by use of Student's *t*-test and analysis of variance. Two-tailed P values of < 0.05 were deemed significant. Statistical analysis was performed using SPSS Statistics (version 15.0 for Windows®, SPSS, Chicago, IL).

RESULTS

Baseline Characteristics

Of the 15 patients, 6 (40.0%) were men and 9 (60.0%) women. The mean diameter of the 15 hemangiomas was 13.0 ± 2.2 cm (10.0–16.0 cm). The patients' demographic characteristics and characteristics of the tumors are provided in Table 1.

RF ablation Combined With TAE Procedure

Outcome data for the TAE treatments are given in Table 2. Follow-up radiological examinations showed significant regression in the mean size of the hemangiomas. The mean largest diameter of the hemangiomas decreased from 13.0 ± 2.2 to 7.1 ± 2.0 cm ($P < 0.001$) after TAE treatment.

TABLE 1. Characteristics of 15 Patients With Hepatic Hemangiomas 10 cm or Larger

Characteristics	n = 15
Age (years)	43.5 ± 7.5 (29–54)
Sex (male:female)	6:9
Concomitant illness	
Chronic hepatitis B	2 (13.3 %)
Diabetes	1 (6.7%)
Liver cyst	3 (20.0%)
Reasons for RF ablation	
Abdominal pain or discomfort	3 (20.0%)
Enlargement of hemangioma	4 (26.7 %)
Abdominal pain and enlargement hemangioma	8 (53.3%)
Mean diameter (cm)	13.0 ± 2.2 (10.0–16.0)
Location of hemangioma	
Right liver lobe	8 (53.3%)
Left liver lobe	2 (13.3%)
Bilateral	5 (33.3%)

RF = radiofrequency.

Outcome data for the RF ablation treatments are given in Table 2. Ablation treatment was conducted according to the predefined protocols; there were no technical failures (Figure 1). All the patients required only a single RF ablation session.

Out of 15 hepatic hemangiomas, 14 (93.3%) were completely ablated. One hemangioma was incompletely ablated, showing subtle enhancement of the periphery on follow-up CT.

Complications

Within 72 hours after the TAE, 8 patients experienced postprocedural pain which need pethidine injection. Within 48 hours after RF ablation, 4 patients required a pethidine injection to manage the procedure-related pain.

Four patients (26.7%, 4/15) experienced ablation-related complications. According to the Dindo–Clavien complication classification system,[18] 4 patients had minor complications (Grade I) and 2 patients experienced moderate fevers at 38°C to 39°C that lasted for 2 to 5 days, which resolved spontaneously without requirement of medications. Elevated serum alanine transaminase and aspartate transaminase (> 80 U/L) were seen in 4 patients, which spontaneously restore to normal level within 1 to 2 weeks postablation.

No TAE or ablation-related major complications, including pulmonary fibrosis, hepatic abscess, hemoglobinuria, hemolytic jaundice, pneumothorax, injury to the abdominal viscera, or liver/kidney failure were seen in the patients after the intervention. The mean hospital stay after TAE treatment was 2.2 ± 0.9 (1–3) days, and the mean hospital stay after RF ablation was 3.0 ± 1.0 (3–5) days.

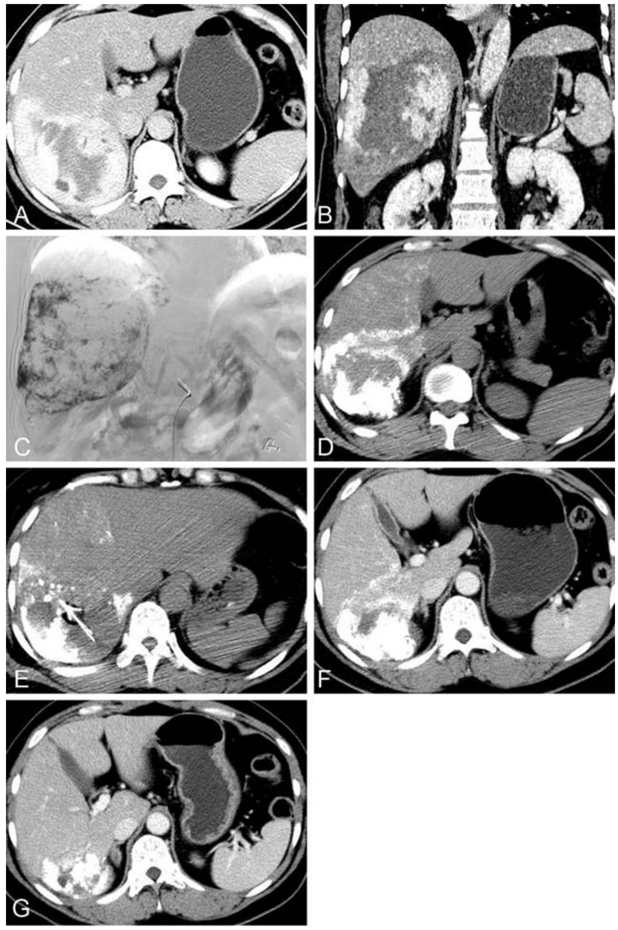

FIGURE 1. A 54-year-old woman had a 13.0 cm hemangioma in the right lobe, as illustrated by contrast-enhanced CT scans (A,B). Fluoroscopy showed that deposited iodized oil completely surrounded the tumor after injection of the mixture of iodized oil and pingyangmycin into the feeding artery (C). One month after TAE, CT scans showed the hemangioma was remarkably smaller (D). RF ablation was performed under CT guidance (E). One month after RF ablation, contrast-enhanced CT scans showed the hemangioma was completely ablated and the ablation zone was smaller (F). Six months after RF ablation, contrast-enhanced CT scans showed that the ablative area became even smaller (G). CT = computed tomography, RF = radiofrequency, TAE = transcatheter arterial embolization.

TABLE 2. Radiofrequency (RF) Ablation Combined With TAE (Transcatheter Arterial Embolization) for 15 Hepatic Hemangiomas 10 cm or Larger

Parameter	(n = 15)
Volume of iodized oil (mL)	14.3 ± 3.1 (10.0–20.0)
Hospital stay after TAE treatment (days)	2.2 ± 0.9 (1–3)
Mean diameter 1 month after TAE (cm)	7.1 ± 2.0 (5–10)
No. of punctures during ablation	5.5 ± 1.1 (4–7)
Ablation time (minutes)	59.2 ± 12.0 (45–80)
Hospital stay after RF ablation (days)	3.0 ± 1.0 (3–5)
Mean diameter 1 month after RF ablation (cm)	6.1 ± 2.0 (4–9)
Mean diameter 6 months after RF ablation (cm)	4.9 ± 1.6 (3–7)

RF = radiofrequency, TAE = transcatheter arterial embolization.

Follow-up Results

The mean diameter of the tumor decreased to 6.1 ± 2.0 cm within 1 month after ablation and continuously decreased to 4.9 ± 1.6 cm at the last imaging follow-up. The remnants of the tumors shrank significantly as well over the follow-up period and required no further intervention. For the 11 patients presenting obvious hemangioma-related symptoms, 10 patients had their symptoms completely resolved and 1 achieved a substantial improvement without any need of additional medication.

During the 6 months of clinical follow-up, no patients developed new hemangiomas-caused symptoms. All patients were evaluated as good to excellent overall health status and quality of life, manifesting as their excellent performance at their full-time or part-time job.

DISCUSSION

The major finding of our study was that RF ablation combined with TAE is a safe and effective nonsurgical alternative for large hepatic hemangiomas. After TAE, the mean diameter of the hemangioma was reduced from 13.0 ± 2.2 cm to 7.1 ± 2.0 cm ($P < 0.001$). The shrinkage of the hemangioma following the embolization resulted in an easier and quicker RF ablation, thus reducing the risk of ablation-related complications. Technical success was achieved in a single RF session in all hemangiomas through multiple overlapping applications. This method was associated with short admission durations of ~3 days for RF ablation treatment, which is significantly shorter than reported hospitalization durations after RF ablation without TAE.[10–12]

At present, RF ablation for larger hemangiomas remains controversial.[9–12] Park et al[9] reported a technical failure rate of 40% with percutaneous RF ablation of hemangiomas ≥10 cm in diameter. Gao et al[8] also encountered difficulties when they treated 17 hemangiomas ≥10 cm of 16 patients with RF ablation using multitined electrodes. Although they have achieved a high rate of complete ablation (82.4%, 14/17), ablation-related complications were also seen in all the 16 patients with hemangiomas ≥ 10 cm including significant systemic inflammatory responses and acute respiratory distress syndrome (Grade IV), likely resulting from long ablation times. Thereafter, Gao et al[10] instituted 2 measures to treat 21 large hemangiomas in 21 patients in the hope of having few complications, while still maintaining a successful rate of ablation: (1) cool-tip cluster electrodes were used. (2) During the procedure, if the patient's body temperature exceeded 39°C or hemoglobinuria occurred, they stopped the procedure and scheduled a repeat session. As a result, complete ablation was achieved in 90.5% (19/21) and ablation-related complications reduced to 47.6% (10/21). Moreover, 18 patients required only 1 session, and 3 patients with ≥ 14.0 cm hemangiomas required 2 sessions. Obviously, a complication rate of 47.6% in patients with hemangiomas ≥ 10 cm is not satisfactory although, all were minor (Grade I). The results indicate that there are limitations to single-session RF ablation in the treatment of large hemangiomas because of the long ablation time required.

Transcatheter arterial chemoembolization (TACE) is one of the modalities used to treat unresectable hepatocellular carcinoma (HCC). However, TACE, indirectly through embolism in tumor blood vessels and chemotherapy drug effects, cannot induce necrosis of all HCC cells and can only limit growth.[19] RF ablation has emerged as a curative treatment owing to its safety and effectiveness for small HCCs.[20] In comparison with TACE, the advantage of RF ablation is curative local control of small HCCs smaller than 3 cm, but it is less favorable for complete necrosis of tumors >3 cm. Recently, combined TACE and RF ablation has attracted attention as a more promising technique for improving the local control of HCCs, even lesions with a maximum diameter > 3 cm. The combined use of TACE and RF ablation therapy may reduce local tumor progression arising from larger ablative lesions because of the synergistic effects induced by the decreased blood flow and minimized heat loss.[21–23] However, whether the combination of RF ablation and TAE could provide therapeutic benefits for large hepatic hemangiomas is not clear.

Our study shows that complete and sustained resolution of large hepatic hemangiomas was attained in patients undergoing RF ablation combined with TAE treatment, with a low incidence of ablation-related complications (26.7%, 4/15). Indeed, we found that an initial reduction in size of the hemangiomas after TAE was associated with shorter ablative times undergoing RF ablation subsequently than reported ablative times treated by single RF ablation.[8–10] We adopted the same strategies of ablation of Gao et al;[10] however, we experienced fewer ablation-related complications (26.7% vs 47.6%) and repeat RF ablation was not needed in this study. Exploiting synergies is the underlying principle for combination therapies. The combination therapy of TAE followed by RF ablation for treatment of large hemangiomas has several advantages over either technique alone. First, as a downstage treatment, chemoembolization can block the blood supply of the hemangiomas and decrease volume before RF ablation, thus shortening the ablative time and increasing the completed ablation rates of large hemangiomas. Second, edematous change in the tumors induced by ischemia and inflammation after arterial chemoembolization is expected to enlarge the area of tumor necrosis during RF ablation treatment. Moreover, disruption of intratumoral septa, which usually happens after arterial embolization, facilitates heat distribution within the tumor.[13,14] Third, TAE accurately localizes hemangiomas through iodized oil precipitation and provides guidance for the RF procedure, thus increasing the likelihood of complete ablation of hemangiomas and avoiding the risk of puncture injury to adjacent organs associated with the placement of electrode arrays.

The major limitations of our study include its retrospective nature, the lack of a control group, the small sample size, and the short follow-up period to evaluate the recurrence rate. Moreover, the present data came from the initial experience and the real value of combination therapy might not be fully estimated in the treatment of large hepatic hemangiomas. We felt it important, though, that all the TAE and RF procedures be performed by 1 operator, thus minimizing the chance of bias that might have occurred if multiple doctors had been involved. Larger multicenter studies with longer-term follow-up should be performed to better assess RF ablation combined with TAE for the treatment of large hepatic hemangiomas.

In conclusion, RF ablation combined with TAE appears to be a safe and effective treatment for large hepatic hemangiomas. TAE can improve the blockade of lesion blood supply and reduce lesion size to facilitate subsequent RF ablation and reduces the ablation-related complications.

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