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TECHNICAL NOTE

Radiofrequency Ablation Combined with Hepatic Artery Embolization Using a Tris-acryl Gelatin Microsphere for Colorectal Liver Metastases -Initial Experience

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Abstract:
Purpose: We aim to evaluate retrospectively the feasibility, safety, and initial therapeutic outcomes of radiofrequency ablation combined with hepatic artery embolization using a tris-acryl gelatin microsphere for colorectal liver metastases.
Material and Methods: Six consecutive patients (4 men and 2 women) with median age of 68 years (range 57-78 years) underwent computed tomography fluoroscopy-guided radiofrequency ablation immediately after hepatic artery embolization using microspheres. This study evaluated tumor visibility on noncontrast-enhanced computed tomography immediately after hepatic artery embolization; analyzed local tumor progression; defined technical success as the coverage of the tumor by the ablative zone; and assessed adverse events based on Common Terminology Criteria for Adverse Events v5.0.
Results: Ten tumors with median maximum diameter of 9 mm (range 5-52 mm) were treated in nine sessions. Eight tumors (80%, 8/10 tumors) were detected as high-attenuation nodules. One tumor was treated in two sessions because follow-up computed tomography revealed an insufficient ablative margin. Therefore, the primary and secondary technical success was 90% (9/10 tumors) and 100% (10/10 tumors), respectively. Grade 2 pneumothorax was observed in one session (11%, 1/9 sessions). No grade 3 or higher adverse event was observed. The local tumor progression rate was 20% (2/10 tumors) during the median follow-up of 14 months.
Conclusions: Radiofrequency ablation following microsphere embolization may be a feasible, safe, and useful therapeutic option for controlling small colorectal liver metastases.

Keywords:
colorectal cancer, embolization, liver metastasis, microsphere, radiofrequency ablation

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Introduction

In patients with colorectal cancer, the liver is the most common site of metastasis. In fact, 50% of patients with colorectal cancer develop liver metastases [1].

Hepatectomy is the most effective treatment for colorectal liver metastases (CRLM). When CRLM are resected, the median overall survival (OS) has been reported to be 40-53 months [2]. However, surgical candidates are approximately 25% due to poor general condition or tumor status. The patients without surgical candidates end up receiving systemic chemotherapy or best supportive care (BSC). After systemic chemotherapy and BSC, the median OS decreased to approximately 20 and 8 months, respectively [2-4]. Therefore, controlling liver metastases is necessary to achieve longer survival [2-4].

Radiofrequency (RF) ablation is another therapeutic option for the management of unresectable CRLM. Several studies of image-guided RF ablation for CRLM have indicated the median OS and local tumor progression rate as 35-48 months and 8.8%-14.2%, respectively, when tumors are ≤30 mm [5]. However, this recurrence rate is higher than that of hepatectomy: 4.0%-5.5% [6]. Therefore, a more effective therapeutic strategy should be established to improve

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Table 1. The Patients and Tumors Characteristics.

Patients	
Gender	
Male/Female	4/2
Age	
Median	68
Range (years)	57-78
Performance status	
0/1	4/2
Child-pugh score	
A/B/C	6/0/0
Primary lesion	
Colon/Rectum	4/2
Stage at the time of primary lesion resection	
I/II/III/IV	1/2/1/2
Previous liver resection	
Yes/No	5/1
Previous chemotherapy	
Yes/No	5/1
Tumors	
Liver metastasis	
Tumor number; 1/2/3	3/2/1
Maximum tumor diameter (mm)	
Median	9
Range	5-52
≤30 mm/30 mm<	7/3
Extrahepatic lesion at the time of RFA	
Yes/No	1/5
Carcinoembryonic antigen (ng/mL)	
Positive/Negative	5/1
Median	11.8
Range	2.6-244
Fong classification 0-2/3–5	1/5

the local tumor control of CRLM.

Hepatic artery embolization (HAE), which is known to reduce the heat sink effect during RF ablation, enlarges the ablation zone and achieves better local tumor control in patients with hepatocellular carcinoma [7, 8]. Therefore, we hypothesize that combination therapy of RF ablation and HAE might enhance the local control of CRLM. Among the various embolic materials, the tris-acryl gelatin microsphere is officially approved for the treatment of CRLM [6, 8].

This study was conducted to evaluate retrospectively the feasibility, safety, and initial therapeutic outcomes of RF ablation combined with HAE using tris-acryl gelatin microspheres for CRLM.

Material and Methods

Patients

Our institutional review board approved this single center retrospective study. Written informed consent to participate in this study was waived because of its retrospective nature.

From May 2020 to December 2021, six patients with CRLM had nine sessions of RF ablation combined with HAE using microspheres. **Table 1** shows the patient and tumor characteristics. Four and two patients were men and women, respectively. Their median age was 68 years (range 57-78 years). The total number of CRLM was 10 tumors: one, two, and three tumors in three, two, and one patient, respectively. The median maximum tumor diameter was 9 mm (range 5-52). Three of the 10 tumors (30%) were >30 mm in diameter. Eight tumors were invisible on plain computed tomography (CT) imaging. The remaining two tumors measuring 32 and 38 mm showed slightly low attenuation as compared with the surrounding liver parenchyma. Calcification was observed in a tumor measuring 32 mm with slightly low attenuation. All patients were regarded as nonsurgical candidates because of a previous history of hepatectomy or refusal of surgery. CRLM was diagnosed on the basis of contrast-enhanced CT (CECT), gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) magnetic resonance (MR) imaging, and F18 fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT imaging findings and high carcinoembryonic antigen level (**Fig. 1 a**).

Biopsy was not used for diagnosis in this study population.

HAE and RF ablation

In this study, RF ablation combined with HAE was performed on an inpatient basis. First, hepatic angiography was performed using a femoral approach with a 4-Fr catheter and a 1.7-Fr microcatheter (Progreat λ; Terumo Corp., Tokyo, Japan). After angiographic evaluation of the arteries supplying the CRLM, 100- to 300-μm microspheres (Embosphere; Nippon Kayaku, Tokyo, Japan) diluted 4 times with contrast medium (Iomeron injections; Eisai Co., Tokyo, Japan) were injected at the optimal catheter position in the hepatic artery. After confirming stasis of hepatic arterial blood flow on angiography, non-CECT was performed (**Fig. 1b**).

Immediately after HAE, RF ablation was performed under moderate sedation and local anesthesia. Fentanyl (fentanyl injection; Terumo Corp., Tokyo, Japan), dexmedetomidine (dexmedetomidine intravenous syringe; Nipro Corp. Co. Ltd., Osaka, Japan), and lidocaine (Xylocaine Polyamp; AstraZeneca International PLC, Osaka, Japan) were used for analgesia, sedation, and local anesthesia, respectively. Real-time CT fluoroscopy was used to place 17-gauge electrodes (Cool-Tip RF ablation system; Covidien, Boulder, CO or arfa RF ablation system; Japan Lifeline Co., Ltd., Tokyo, Japan (**Fig. 1c**)).

The placement of RF electrodes and tip exposure length were determined on the basis of the tumor size. When the tumor diameter was ≤20 mm, the exposure length was determined to be 10 mm longer than the maximum tumor diameter. When the tumor diameter was >20 mm, electrodes with 30-mm exposure length were placed at two to three sites of the tumor; then, a switching algorithm was adapted.

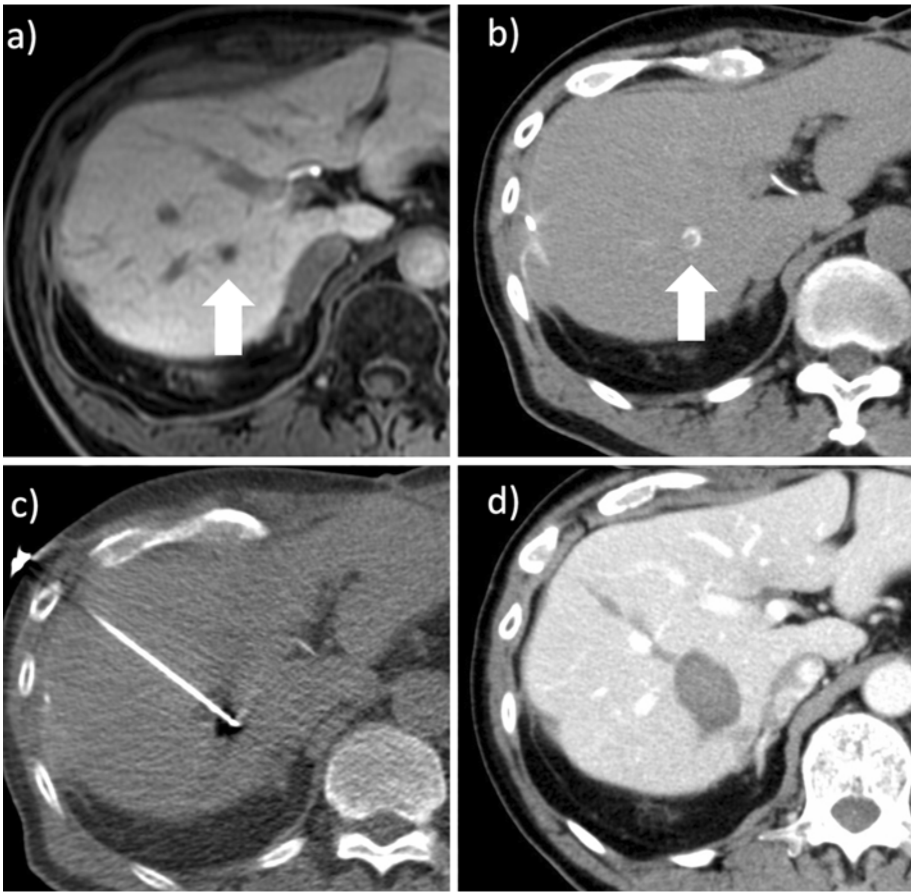

Figure 1. (a) Fat suppression T1WI in the hepatobiliary phase show a liver metastasis from colon cancer in the right lobe in a male patient in his 60s. (b) Noncontrast-enhanced CT images after embolization using microspheres show a collection of contrast medium in the tumor. (c) CT fluoroscopy images during RF ablation shows microbubbles in the tumor. (d) Contrast-enhanced CT performed on the second day of RF ablation shows an ablative zone encompassing the tumor with a sufficient ablative margin.

Follow-up

The initial therapeutic response was evaluated using CECT within 1 week after the combination therapy. The ablative safety margin was defined as complete coverage of the nonenhanced liver tissue with an ablative margin of ≥5 mm. Routine physical examination, laboratory tests, and CECT were performed every 3 months thereafter (**Fig. 1d**).

Gd-EOB-DTPA MR imaging or FDG/PET-CT was also performed as needed when local tumor progression was suspected from CT studies.

Assessment

Tumor visibility, adverse event, technical success, and local tumor progression were evaluated retrospectively. Tumor visibility was assessed by operators during the procedure, and the CT values of pre-HAE and post-HAE were measured. When the tumor was detected as a high-density nodule on non-CECT immediately after HAE, the tumor was defined as visible. Adverse events were evaluated per session based on Common Terminology Criteria for Adverse Events v5.0 [9]. Common procedural side effects, including periprocedural pain, fever, and transient increase of liver enzyme levels, were voided from the evaluation. Technical success was evaluated using CECT within 1 after the treatment. The primary and secondary technical success was defined as the percentage of tumors treated successfully after the initial and repeated treatment, respectively. Local tumor progression was defined as the appearance of tumor foci at the edge of the ablation zone and was assessed on the basis of the tumor size.

Results

A total of sessions of combined therapy were performed. RF ablation was performed for one and two tumors in seven and two sessions, respectively. One tumor was treated in two sessions because CECT after the initial treatment revealed an insufficient margin. HAE was performed at the segmental and lobar artery in five and four sessions, respectively. Eight tumors (80%, 8/10 tumors) were detectable as high-attenuation nodules on non-CECT immediately after embolization. The median CT value of pre- and post-HAE was 42.7 and 75.0 Hounsfield units, respectively. In five sessions, a single electrode with exposure length 10 mm longer than the maximum tumor diameter was adapted. In the other four sessions, multiple electrodes with 30-mm exposure length were adapted using a switching algorithm.

Grade 2 pneumothorax developed after one session (11%, 1/9). In this patient, transpulmonary puncture was unavoidable. No grade 3 or higher adverse event was observed.

The primary technical success was 90% (9/10 tumors). The diameter of the tumor for which technical success was not achieved was 14 mm. This tumor was visible on plain CT immediately after HAE. Because of slight insufficient of safety ablative margin, additional RF ablation was performed immediately after HAE at 3 weeks after the first ablation. Therefore, the secondary technical success was 100% (10/10 tumors).

Local tumor progression developed in two tumors (20%, 2/10 tumors) during the median follow-up of 14 months (range 9-17 months). Both tumors were >30 mm. Therefore, 67% of tumors (67%, 2/3) measuring ≥30 mm developed local tumor progression. Local tumor progression was not found in tumors <30 mm (0%, 0/7).

Discussion

Results of our preliminary study indicated that combination therapy of RF ablation and HAE using microspheres was safe and effective for treating CRLM.

Eighty percent of tumors were detectable as high-attenuation nodules on non-CECT immediately after embolization. The technique can contribute appropriate electrode placement and accurate ablation. In an earlier study, Yamakado et al. also reported the feasibility of combination therapy of RF ablation and chemoembolization using degradable starch microsphere and mitomycin C [8]. In this study, RF ablation combined with HAE is apparently safe. No procedure-related death occurred. Grade 2 pneumothorax was the only adverse event requiring treatment. Embolization with microspheres seems not to increase the ratio of adverse events of RF ablation compared with that of a previous study, 8% [8].

Tumor size is known to be a significant factor affecting local tumor progression, as described in an earlier study [5]. In this study, all tumors <30 mm were controlled after repeat ablation therapy, although the follow-up period was short. Two of three tumors (67%) measuring ≥30 mm developed local tumor progression. This finding was similar to that of earlier reports of RF ablation for CRLM >30 mm: local tumor progression rates were reported as 50%-70% [5, 8]. Just a combination of HAE and RF ablation may be challenging for locally controlling CRLM >30 mm. Further study is needed to enhance the effectiveness of RF ablation even in larger tumors.

This study has several limitations. First, the small sample size and short follow-up period are apparent limitations. Second, the study design is retrospective and noncomparative and for a single center. Despite these limitations, these results indicate the safety and efficacy of this combination therapy. This combination therapy must be evaluated in additional studies that include larger clinical trials.

Conclusion

RF ablation following tris-acryl gelatin microsphere embolization may be a feasible, safe, and useful therapeutic option for controlling CRLM.

Conflict of Interest: None
Author Contribution: Taiki Moriyama, Haruyuki Takaki, Atsushi Ogasawara, Hiroshi Kodama, Yasukazu Kako, Kaoru Kobayashi, and Koichiro Yamakado planned the study. Taiki Moriyama, Haruyuki Takaki, Motonori Takahagi, and Junichi Taniguchi collected the data. Taiki Moriyama, Haruyuki Takaki, and Junichi Taniguchi analyzed the data. Taiki Moriyama prepared the first draft of the manuscript.
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