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ORIGINAL RESEARCH

Clinical Outcomes of Radiofrequency Ablation Combined with Transarterial Chemoembolization Using Degradable Starch Microsphere Mixed with Mitomycin C for the Treatment of Non-hepatocellular Carcinoma Malignant Liver Tumors

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Abstract:
Purpose: To retrospectively evaluate the outcomes of radiofrequency ablation combined with transarterial chemoembolization using degradable starch microspheres for non-hepatocellular carcinoma malignant liver tumors.
Material and Methods: A total of 15 patients (13 men, 2 women; median age, 67 years) who underwent radiofrequency ablation immediately after transarterial chemoembolization using degradable starch microspheres for liver tumors between July 2011 and September 2020 were included in this study. Thirteen patients had liver metastases from colorectal cancer (n = 6), esophageal cancer (n = 2), lung cancer (n = 2), and other tumors (n = 3), and 2 patients had primary liver tumor of cholangiocellular carcinoma (n = 1) and gastrinoma (n = 1). Twenty tumors (median size, 16 mm) were treated in 17 sessions. Technical success, safety, local tumor progression, and overall survival were evaluated. Safety was assessed according to the clinical practice guideline of the Society of Interventional Radiology.
Results: All treatment procedures were successfully completed. There were no major complications. Grade-B complications of self-limiting pneumothorax (n = 1), vomiting (n = 1), and fever (n = 1) occurred in 1 session each. Local tumor progression developed in two tumors (local tumor progression rate, 10%, 2/20). The local tumor progression rates were 5% and 11% at 1 year and at 3 and 5 years, respectively. Tumor size of more than 20 mm (P = 0.0003) and contact with major vessels (P = 0.03) were significant risk factors for local tumor progression. The patients were treated with repeat radiofrequency ablation combined with transarterial chemoembolization using degradable starch microspheres. During median follow-up of 48 months (range, 4-77 months), 5 patients died (33%, 5/15). The overall survival rates were 100%, 85%, and 57% at 1, 3, and 5 years, respectively. The median overall survival time was 69 months.
Conclusions: Radiofrequency ablation combined with transarterial chemoembolization using degradable starch microspheres was safe and showed favorable local control for non-hepatocellular carcinoma malignant liver tumors.

Keywords:
liver metastases, radiofrequency ablation, transarterial chemoembolization

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Introduction

Radiofrequency ablation (RFA) is widely performed for malignant liver tumors. It is less invasive than hepatic resection and can be applied to patients who are not surgical candidates due to comorbid disease or multiple tumors. RFA has been reported to offer comparable outcomes of recurrence-free survival (RFS) and overall survival (OS) with surgical resection for hepatocellular carcinoma (HCC) [1, 2], and RFA is described as locoregional treatment for HCC in several guidelines [3-5]. However, the rate of local tumor progression (LTP) was higher after RFA than after hepatic resection. In particular, the LTP rate was significantly higher for tumors located close to the blood vessels [6]. One reason is the heat sink effect, which occurs because blood flowing in the vasculature around the target tumor

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Table 1. Details of Patients and Tumors.

Case	Sex	Age (y)	Primary lesion	Primary or metastatic liver tumor	Previous history of metastases	Previous treatment for metastases	Number of liver tumors	Maximum liver tumor diameter (mm)
1	M	69	CRC	Metastatic	Liver	Chemotherapy, surgery	3	16, 13, 7
2	M	75	CRC	Metastatic	No		2	25, 16
3	M	74	CRC	Metastatic	Liver	Chemotherapy, surgery	1	17
4	M	64	CRC	Metastatic	Liver	Chemotherapy, surgery	1	23
5	M	76	CRC	Metastatic	Liver	Chemotherapy, surgery	1	29
6	M	53	CRC	Metastatic	Liver	Chemotherapy, surgery	2	11, 6
7	M	72	Esophageal Ca	Metastatic	No		1	11
8	M	67	Esophageal Ca	Metastatic	Liver	Chemotherapy, surgery	1	25
9	M	77	CCC	Primary	No		1	17
10	M	54	CCC	Metastatic	No		2	16, 10
11	M	56	Lung adenocarcinoma	Metastatic	Adrenal gland	Chemotherapy, surgery	1	14
12	M	53	Lung small cell Ca	Metastatic	LN	Chemotherapy	1	17
13	F	43	Bronchial ACC	Metastatic	Bone	Cryoablation	1	12
14	F	81	Stomach GIST	Metastatic	No		1	17
15	M	64	Liver gastrinoma	Primary	No		1	10

CRC: Colorectal cancer, Ca: Carcinoma, CCC: Cholangiolocellular carcinoma, GIST: Gastrointestinal stromal tumor, ACC: Adenoid cystic carcinoma, LN: Lymph node

causes a cooling effect and reduces ablation volume [7]. To overcome such an effect, the combination therapy of transarterial chemoembolization (TACE) and RFA has been reported to be an effective technique for HCC [8-10].

Liver metastases are also common malignant liver tumors. When patients have liver metastases, they are considered to have systemic progression and are generally given systemic treatment, such as chemotherapy or immunotherapy. However, if the number and size of liver metastases are limited, locoregional treatment of such metastases has come to be performed in the concept of "oligo-metastases" [11-14]. RFA is also used as locoregional treatment for such oligometastatic liver tumors [15-21].

To achieve complete ablation, combination therapy of TACE and RFA might be useful in the treatment of liver metastases. Although ethiodized oil (Lipiodol; Guerbet Japan KK, Tokyo, Japan) is often used in TACE for HCC, it does not always sufficiently accumulate in liver metastases, especially in hypovascular tumors [22, 23]. Degradable starch microsphere (DSM) is another embolic material used at the time of TACE for liver metastases [24]. The contrast medium remains in the tumor on computed tomography (CT) image obtained immediately after DSM-TACE for liver metastases; thus, TACE using DSM may be compatible with CT-guided RFA. From this perspective, Yamakado et al. conducted a prospective study about combination therapy of TACE using DSM mixed with mitomycin C (MMC) and RFA for colorectal cancer (CRC) liver metastases and reported promising results [25]. However, whether this combination therapy is also useful for other malignant liver tumors has not been well investigated. This study aimed to evaluate the safety and efficacy of RFA combined with DSM-TACE for non-HCC malignant liver tumors.

Material and Methods

Patients

This retrospective study was approved by our institutional review board. The need for informed consent for study inclusion was waived, but informed consent to perform RFA combined with DSM-TACE was obtained from each patient before the procedure. Preoperatively, a multidisciplinary team discussed how to treat liver metastases, considering available systemic therapy, tumor progression, and each patient's general condition. The inclusion criteria for combination therapy were (a) non-surgical candidate for liver tumors, (b) primary lesion resected or controlled if the liver tumor was metastasis, (c) 3 or fewer liver tumors of 3 cm or smaller, and (d) nonexistent or controllable extrahepatic lesions. The exclusion criteria were (a) previous history of biliary reconstruction, (b) abnormality in a major organ, and (c) abnormal coagulability, with a platelet count of 50,000/mL or less or an international normalized ratio of 1.5 or greater.

From July 2011 to September 2020, RFA combined with DSM-TACE was planned for 15 patients with 20 liver tumors. The patients' background and nodule characteristics are presented in **Table 1**. There were 13 men and 2 women, with a median age of 67 years (range, 43-81 years). Diagnosis of liver metastases was made based on imaging findings obtained with serial follow-up abdominal CT and magnetic resonance imaging (MRI). New liver masses that had emerged and increased in size were regarded as liver metastases. Two patients had primary liver tumors. One patient was diagnosed with cholangiocellular carcinoma *via* percutaneous needle biopsy. The other patient who was referred to our hospital due to high serum gastrin level underwent endoscopic ultrasound-guided fine-needle aspiration for the

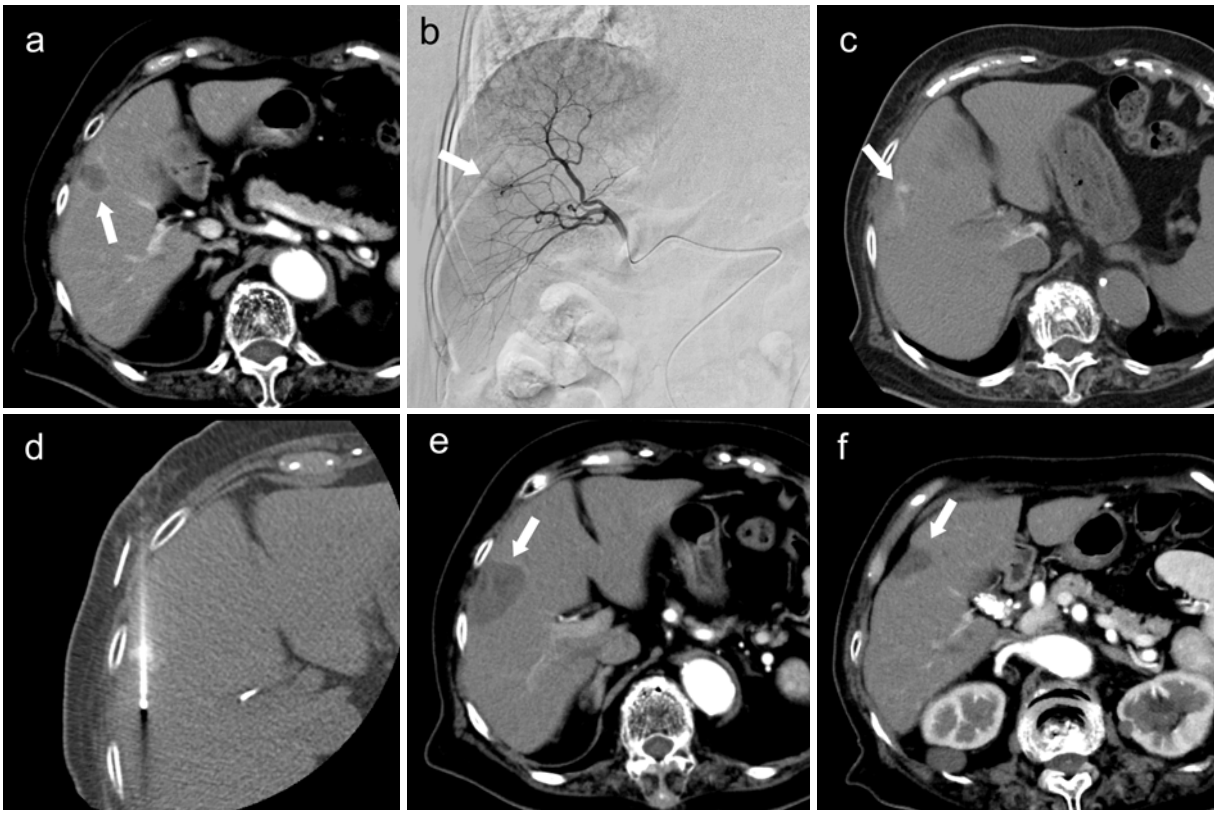

Figure 1. An 81-year-old woman with liver metastasis from a stomach gastrointestinal stromal tumor.
(a) CT reveals a 17-mm liver metastasis (arrow) in the right lobe. (b) Angiogram from the anterior branch of the right hepatic artery shows tumor stain (arrow). A degradable starch microsphere (DSM) is injected from the anterior branch. (c) CT immediately after DSM injection reveals DSM deposition (arrow) partially on the tumor. (d) Radiofrequency ablation is performed under CT fluoroscopic guidance. (e) CT obtained 1 month after the procedure shows tumor fully covered by the ablation area (arrow). (f) CT obtained 3 years after the procedure shows no local tumor progression around the shrunken ablation area (arrow).

liver tumor, and the pathological finding was neuroendocrine tumor. No extrahepatic tumors were detected *via* upper endoscopy, colonoscopy, CT, and somatostatin receptor scintigraphy, and the patient was diagnosed with primary liver gastrinoma. The median nodule size was 16 mm (range, 6-29 mm). Seven nodules (35%, 7/20) contacted the major portal vein or hepatic vein of 3 mm or greater in axial diameter.

All patients underwent routine physical examinations, laboratory tests, and imaging studies, including whole-body CT and abdominal MRI, within 6 weeks preceding treatment (**Fig. 1a**).

Transarterial chemoembolization and radiofrequency ablation

Seventeen sessions of RFA combined with DSM-TACE were performed for 20 tumors on an inpatient basis. The median session number for each patient was 1 (range, 1-2). First, angiography was performed, and CT during arterial portography and hepatic arteriography was obtained (**Fig. 1 b**). All target tumors exhibited ring enhancement on CT during hepatic arteriography. After ruling out an unexpected increase in the number of liver metastases, DSMs (Spherex; Yakult Co. Ltd., Tokyo, Japan) were injected from a lobular or segmental branch of the hepatic artery with a 1.7 F (Progreat λ17, Terumo Corporation, Tokyo, Japan) or 1.9 F microcatheter (Carnelian Si, Tokai Medical Products, Kasugai, Japan) to cover the entire tumor. Before injection, 2-4 mg of mitomycin C (Mitomycin C; Kyowa Hakko Kirin Co. Ltd., Tokyo, Japan) was dissolved with 5 mL of contrast medium (Iopamiron injection 300; Bayer Holding, Ltd., Tokyo, Japan) and mixed with 300 mg of DSMs according to the manufacturer's medical package inserts. For the management of pain during DSM-TACE, fentanyl citrate (Fentanyl; Daiichi Sankyo, Tokyo, Japan) was intravenously administered for analgesia. Fentanyl was also used for managing pain caused by RFA. The embolization endpoint was defined as stasis of blood flow of the artery until two to three heart beats. CT was performed without contrast enhancement after TACE to confirm DSM distribution (**Fig. 1c**).

Percutaneous liver RFA was performed immediately after DSM-TACE under moderate sedation and local anesthesia. Real-time CT fluoroscopy (Aquilion LB; Canon Medical Systems Corp., Otawara, Japan) was used for imaging guidance (**Fig. 1d**). All procedures were performed using an internally cooled electrode (VIVA RF System; STARmed Co., Seoul, Korea). The electrodes were inserted into the tumor and placed in the appropriate position considering the tumor size, shape, and location. The tip exposure length was deter-

mined based on tumor size. Radiofrequency energy was applied until the impedance of each site increased 30 Ω above the baseline five times. Overlapping ablation was not required in all sessions. After RFA, CT was performed again to check for complications. Cefazolin (Cefazolin; Astellas Pharma, Tokyo, Japan) was administered before and for 2 days after RFA as prophylaxis in accordance with our institutional standards and policies.

Follow-up

Laboratory tests were conducted 1 day and 3 days after completing TACE and RFA. The patients were discharged after confirming the absence of infectious complication and peak out of aspartate transaminase (AST) value on laboratory test. Routine physical examinations, laboratory tests, and CT with or without contrast enhancement were performed at 1 month and every 3-4 months thereafter (**Fig. 1e, f**). In surviving patients, data were followed up until death or June 2021.

Assessment

In this study, technical success, safety, LTP, RFS, and OS after combination therapy were evaluated. Technical success was defined as completion of the treatment protocol. Safety was evaluated on a session basis using the clinical practice guideline of the Society of Interventional Radiology [26]. LTP was defined as the appearance of enlarged nodules around the ablated tumor on follow-up CT [27, 28]. RFS was defined as the time from the achievement of the tumor-free condition to the date of LTP or new metastasis development or the last follow-up. OS was defined as the time between the initial combination therapy and the date of death or the last follow-up. LTP was evaluated on a tumor basis and RFS and OS on a patient basis.

Cumulative LTP, RFS, and OS curves were generated using the Kaplan-Meier method. The LTP and OS rates were compared *via* univariable analysis using the log-rank test among subgroups categorized by patient or tumor background. A P value of <0.05 was considered significant. Statistical analyses were conducted using commercially available software (SPSS for Windows, version 24; IBM, Armonk, NY).

Results

Safety

All treatment procedures were successfully completed (technical success rate, 100%; 17/17). There were no deaths or major complications associated with the procedures. Grade-B complications of self-limiting pneumothorax (n = 1), vomiting (n = 1), and fever (n = 1) occurred in one session each (18%, 3/17). The median AST levels were 26 IU/L (range, 15-41), 278 IU/L (range, 144-760), and 67 IU/L (range, 30-238) before, 1 day after, and 3 days after the procedure. Patients were discharged from the hospital 3-9 days (median, 6 days) after the procedure. The median AST level was recovered to 28 IU/L (range, 17-52) at 1 month follow-up. The Child-Pugh score did not change between before and 1 month after treatment in all cases, except for one case where the score improved from 6 to 5.

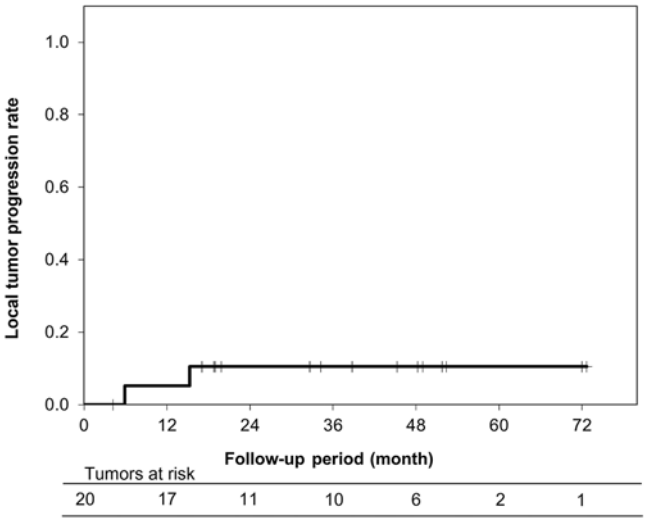

Figure 2. The Kaplan–Meier curve of the local tumor progression rate following RFA combined with TACE using DSMs for liver tumors.

Clinical outcomes

The median follow-up period was 48 months (range, 4-77 months). LTP developed in 23- and 25-mm CRC liver metastases (10%, 2/20), 6 and 15 months after the procedure. The LTP rates were 5% (95% confidence interval [CI], 0%-15%) at 1 year and 11% (95% CI, 0%-24%) at 3 and 5 years (**Fig. 2**). Tumor size of more than 20 mm (P = 0.0003) and contact with major vessels (P = 0.03) were significant risk factors for LTP (**Table 2**). Two LTP cases were both treated with repeat RFA with TACE and were well controlled thereafter.

Seven patients (47%, 7/15) developed new metastases in the liver (n = 3), lymph nodes (n = 2), liver and lymph node (n = 1), and lung and lymph node (n = 1). The median RFS was 8 months (range, 4-73 months), and the RFS rate was 43% (95% CI, 17%-69%) at 1, 3, and 5 years (**Fig. 3**). Three patients with new liver metastases underwent repeat RFA with TACE.

Five patients (33%, 5/15) died of tumor progression. The OS rates were 100% (95% CI, 100%-100%), 85% (95% CI, 65%-100%), and 57% (95% CI, 20%-94%) at 1, 3, and 5 years, respectively (**Fig. 4**). The median OS was 69 months. No significant prognostic factors were identified (**Table 3**).

Discussion

This study demonstrated that RFA combined with TACE using DSM was a safe and effective treatment for non-HCC malignant liver tumors. DSMs are enzymatically degraded by serum alpha-amylases in the blood, with a half-life of approximately 35-50 min, both *in vivo* and *in vitro*, and partial resumption of blood flow following embolization with

Table 2. Local Tumor Progression Rate by Variable.

Variable	Tumor number	LTP rate (%)			p-value
		1-year	3-year	5-year	
Age (y)					
<60	7	0	0	NA	0.27
≥60	13	8	17	17	
Sex					
Male	18	6	12	12	0.62
Female	2	0	0	NA	
Maximum tumor diameter (mm)					
≤20	16	0	0	0	0.0003
>20	4	33	67	67	
Contact with major vessel					
No	13	0	0	0	0.03
Yes	7	17	33	NA	
Number of liver tumors					
Single	11	10	10	10	>0.99
Multiple	9	0	11	NA	
Primary tumor					
CRC	10	10	20	20	0.17
non-CRC	10	0	0	0	
Total	20	5	11	11	

LTP: Local tumor progression, NA: Not applicable, CRC: Colorectal cancer

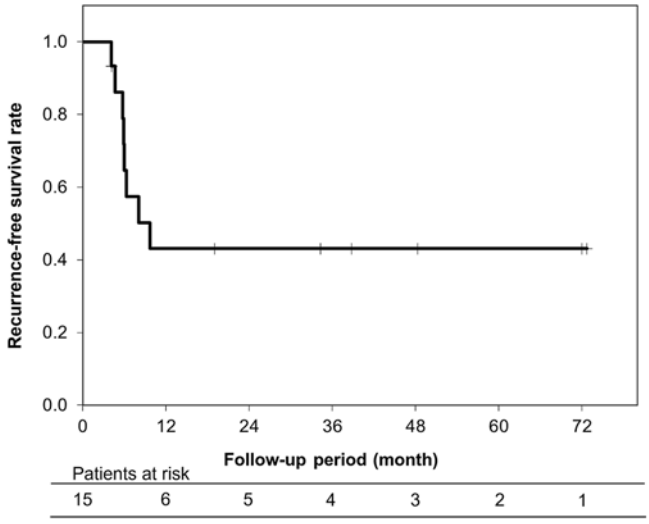

Figure 3. The Kaplan–Meier curve of the recurrence-free survival rate following RFA combined with TACE using DSMs for liver tumors.

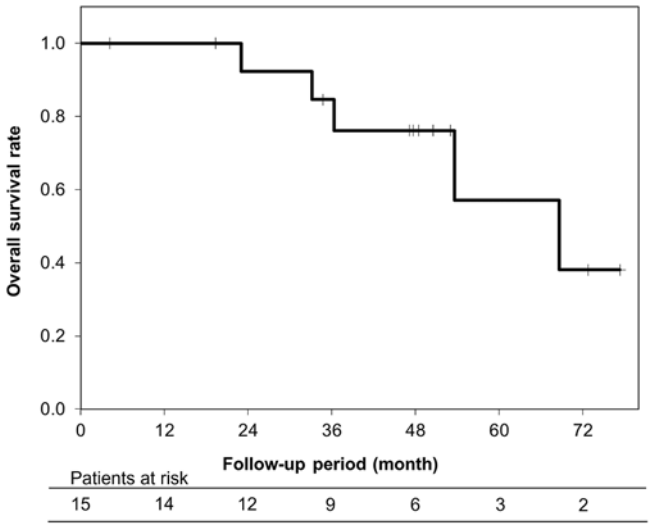

Figure 4. The Kaplan–Meier curve of the overall survival rate following RFA combined with TACE using DSMs for liver tumors.

Table 3. Overall Survival Rate by Variable.

Variable	Patient number	OS rate (%)			p-value
		1-year	3-year	5-year	
Age (y)					
<60	5	100	60	60	0.25
≥60	10	100	58	58	
Sex					
Male	13	100	82	61	0.33
Female	2	100	100	NA	
Maximum tumor diameter (mm)					
≤20	12	100	72	48	0.87
>20	3	100	100	100	
Number of liver tumors					
Single	11	100	78	65	0.91
Multiple	4	100	100	50	
Primary tumor					
CRC	6	100	100	50	0.21
Non-CRC	9	100	71	54	
Previous metastases					
No	6	100	80	80	0.91
Yes	9	100	88	44	
Total	15	100	85	57	

OS: Overall survival, NA: Not applicable, CRC: Colorectal cancer

DSM is observed after approximately 10-15 min [29]. Since the arterial flow recovers soon after completion of combination procedure, post-embolization syndrome is mild. In fact, in this study, there were no complications requiring any interventions, and no patients developed liver failure. The AST level increased 1 day after the procedure, but it soon peaked out, and the patients were discharged from the hospital, with a median hospital stay of 6 days after the procedure. These facts supported the suggestion that RFA combined with TACE using DSM was safely performed.

In this study, the LTP rate was 10%, which was similar to the LTP rate of 7.9% observed in the prospective study of RFA combined with DSM-TACE for CRC liver metastases [25]. Considering that the LTP rate following percutaneous RFA alone for CRC liver metastases was reported to be 18%-42% [30, 31], the combination with DSM-TACE may work to decrease the LTP rate after RFA. Tumor size of 2 cm or more and contact with major vessels were identified as significant risk factors for LTP. These are well-known risk factors for LTP after liver RFA [6, 16-18, 30, 31]. Although the combination of transarterial embolization and RFA enlarges the ablation area [32], Yamakado et al. showed that tumor size was a risk factor for LTP in the combination of RFA and DSM-TACE for CRC liver metas-

tases [25]. Moreover, DSM-TACE could reduce the arterial blood flow but could not directly reduce portal or hepatic venous flow. Thus, the heat sink effect of the major portal and hepatic veins may remain to some extent. Even when combination therapy is provided, we must follow-up the patients carefully to determine whether LTP develops, especially after treatment of large tumors that are in contact with major vessels. Furthermore, repeat RFA was used for the two LTPs, and they were well controlled. Repeatability for locally advanced tumor is an advantage of RFA; thus, we must detect LTP *via* follow-up CT or MRI before it enlarges beyond the indication for RFA.

This study demonstrated that RFA combined with DSM-TACE provides good outcomes for patients with liver tumors, with a median OS of 69 months. In the previous reports of RFA for CRC liver metastases, the median survival time was reported to be 24-59 months [30, 31]. Though heterogeneity in included patients, the present result seems comparable to these results. Thus, RFA combined with DSM-TACE may be a treatment options for non-HCC malignant liver tumors if they are thought to be oligometastatic condition.

This study has several limitations. First, this was a single-center, retrospective study; thus, selection bias could not be avoided. Second, the follow-up period was short, and the long-term outcomes were unclear. Third, the sample size was too small to conduct multivariate analysis. Forth, the DSMs that were used in this study (Spherex) and mitomycin C were not available. Another DSM product of EmboCept® S (PharmaCept, Berlin, Germany) has been used [33, 34], but it is unclear whether these materials exert similar embolization effect. Further investigation to evaluate the differences between these products is warranted. Finally, the heterogeneity of the tumors makes it difficult to reach conclusions about the effectiveness of this treatment.

Conclusion

RFA combined with TACE using DSM was found to be safe and demonstrated favorable local control for non-HCC malignant liver tumors. However, careful follow-up is needed after treatment of tumors that are larger than 2 cm and are in contact with major vessels.

Conflict of Interest: none

Author Contribution: All authors meet the following criteria of contribution:

Substantial contributions to the conception or design of the research or the acquisition and analysis of data

Drafting the work or revising it critically for important intellectual content

Final approval of the version to be published

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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