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ABOUT COVER

Editorial Board of *World Journal of Gastroenterology*, Dr. Conrado M Fernandez-Rodriguez is Chief of the Gastroenterology Unit at Alcorcon Foundation University Hospital and Associate Professor of Medicine at University Rey Juan Carlos. His main research interest is chronic liver diseases, for which he has authored more than 140 peer-reviewed publications, including in top gastroenterology and hepatology journals. He serves as Director of the Scientific Committee of the Spanish Society of Digestive Diseases, Associate Editor of Hepatology for *Spanish Journal of Gastroenterology*. He is also a member of the Spanish Steering Committee of Alcohol-Related Liver Disease National Registry (ReHalc) and Scientific Advisor of the Spanish Committee for Hepatitis C virus Elimination, and direct participant in several multicenter international clinical trials (Respond-2, REGENERATE, STELLAR-4) and national trials and registries (TRIC-1, HEPAMet, Hepa-C, ColHai). (L-Editor: Filipodia)

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Retrospective Study

Features of extrahepatic metastasis after radiofrequency ablation for hepatocellular carcinoma

Jae H Yoon, Young J Goo, Chae-Jun Lim, Sung K Choi, Sung B Cho, Sang S Shin, Chung H Jun

ORCID number: Jae H Yoon 0000-0002-4993-2496; Young J Goo 0000-0002-5747-1212; Chae-Jun Lim 0000-0001-7373-7167; Sung K Choi 0000-0002-6878-3385; Sung B Cho 0000-0001-9816-3446; Sang S Shin 0000-0002-5752-7431; Chung H Jun 0000-0002-7136-8350.

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Informed consent requirement was waived because the patient data were de-identified.

Jae H Yoon, Young J Goo, Chae-Jun Lim, Sung K Choi, Department of Gastroenterology, Chonnam National University Hospital and Medical School, Gwangju 61469, South Korea

Sung B Cho, Department of Gastroenterology, Hwasun Chonnam National University Hospital and Medical School, Hwasun 58128, South Korea

Sang S Shin, Department of Radiology, Chonnam National University Hospital and Medical School, Gwangju 61469, South Korea

Chung H Jun, Department of Internal Medicine, Mokpo Hankook Hospital, Mokpo 58643, South Korea

Corresponding author: Chung H Jun, MD, Doctor, Professor, Department of Internal Medicine, Mokpo Hankook Hospital, 483 Yeongsan-ro, Mokpo 58643, South Korea. estevanj@naver.com

Abstract

BACKGROUND

Extrahepatic metastasis (EHM) of hepatocellular carcinoma (HCC) is associated with poor outcomes. However, the clinical features and risk factors of EHM of HCC after radiofrequency ablation (RFA) remain unclear.

AIM

To elucidate the characteristics and risk factors of EHM after RFA for HCC.

METHODS

From January 2008 to December 2017, we retrospectively enrolled 661 patients who underwent RFA as first-line treatment for HCC at 2 tertiary hospitals. The inclusion criteria were age ≥ 18 years, a diagnosis of HCC, and treatment-naivety. Abdominal computed tomography (CT) or magnetic resonance imaging (MRI) and alpha-fetoprotein measurements were routinely performed at 1 mo after RFA and followed-up at intervals of 3-6 mo. Univariate analyses were performed using the chi-squared test or Student's *t*-test, and univariate and multivariate analyses were performed *via* logistic regression, as appropriate.

RESULTS

EHM was diagnosed in 44 patients (6.7%) during a median follow-up period of 1204 days. The 10-year cumulative rate of HCC recurrence and EHM was 92.7% and 33.7%, respectively. Initial recurrence was most often intrahepatic, and the

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rate of extrahepatic recurrence at initial recurrence was only 1.2%. The median time to the diagnosis of EHM was 2.68 years, and 68.2% of patients developed EHM within 2 years of the first recurrence, regardless of recurrence-free survival and 75.0% of patients developed EHM within 5 years after first recurrence. EHM was mostly diagnosed *via* abdominal CT/MRI in 33 (75.0%) and 38 of 44 patients (86.4%) with EHM had either positive abdominal CT scan results or serum AFP level elevation. In multivariate analysis, recurrence-free survival < 2 years, ablation zone/tumor size < 2, and alpha-fetoprotein level > 400 IU/mL were associated with a high EHM risk.

CONCLUSION

EHM occurs following multiple intrahepatic recurrences after RFA and combined contrast-enhanced abdominal CT and serum AFP were useful for surveillance. Patients especially with high-risk factors require close follow-up for EHM.

Key words: Hepatocellular carcinoma; Metastasis; Radiofrequency ablation; Surveillance; Risk factor

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Core tip: Extrahepatic metastasis (EHM) after radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC) takes place in substantial clinical situations and EHM of HCC is related with dismal prognosis. Our study provides characteristics and risk factors for EHM after RFA of HCC. EHM after RFA at the time of the first recurrence is rare; however, cumulative EHM frequently occurs following multiple intrahepatic recurrences. Most of the patients (86.4%) had either positive contrast-enhanced computed tomography scan results or serum alpha-fetoprotein level elevation at EHM. EHM turned out to be related with recurrence-free survival < 2 years, ablation zone/tumor size < 2, and alpha-fetoprotein level > 400 IU/mL.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related death^[1]. Unlike other cancers that cause distant metastasis during progression, HCC has unique characteristics of loco-regional progression with an increase in size, intrahepatic metastasis, and vascular invasion. Therefore, current guidelines in Korea suggest follow-up surveillance after curative HCC treatment using abdominal imaging focusing on the liver and tumor marker such as serum alpha-fetoprotein (AFP) level^[2]. Although enrolled subjects of previous studies represented all stages of HCC, the incidence of extrahepatic metastasis (EHM) of HCC ranged from 14%-37% and the presence of EHM was associated with poor clinical outcomes^[3]. The reported median survival duration of patients with EHM is less than 6 (range, 4.9-5.9) mo, and the 1-year survival rate was reported as 24.9%^[3,4]. Natsuizaka *et al*^[5] suggested that the lung was the most common site of metastasis, and screening tests for lung metastases, as well as abdominal imaging, should be performed periodically for HCC patients. Lam *et al*^[6] reported that when EHM is identified early and surgical resection is possible, the prognosis may be improved. Therefore, early diagnosis of EHM of HCC may help improve the prognosis.

Radiofrequency ablation (RFA) for the treatment of small HCC lesions (tumor diameter < 3 cm) has shown favorable clinical outcomes with less invasiveness and a low complication rate. RFA is recommended as one of the first-line treatment modalities for the management of HCC along with liver transplantation and surgery^[6,7]. However, the recurrence-free survival (RFS) varies substantially (3.2%-38.2%) between studies, and cumulative extrahepatic recurrence rates were reported as

19.1% and 38.2% at 5 and 10 years, respectively^[8,9]. Hence, careful monitoring for intra- and extrahepatic HCC recurrence after RFA is essential, but there is a lack of data regarding the effect of post-treatment surveillance on the prognosis of recurred HCC^[10]. Moreover, few studies have been conducted on individualized post-treatment surveillance for EHM after RFA according to risk factors^[11].

Therefore, we aimed to assess the characteristics and risk factors of EHM among patients who had undergone RFA as initial treatment for HCC and to investigate the appropriate surveillance tool for EHM detection.

MATERIALS AND METHODS

Patients

From January 2008 to December 2017, 1421 patients who underwent RFA for hepatic tumors at 2 tertiary hospitals were assessed. The inclusion criteria for this study were age ≥ 18 years, a diagnosis of HCC, and treatment-naivety. After excluding patients with hepatic tumors other than HCC or a history of HCC treatment, 661 patients were finally enrolled (Figure 1). Baseline clinical and tumor characteristics, complications of RFA, the status of recurrence, RFS, and rescue treatment methods for HCC recurrence were assessed retrospectively. The study protocol was approved by the Institutional Review Board of Chonnam National University Hospital (CNUH-2019-203). The research was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

The indications of RFA for HCC in our institutes were as follows: (1) Ineligible for surgical resection/liver transplantation or patient refusal for surgery; (2) Single nodular HCC < 5 cm in maximum diameter or multinodular HCC (3 in number, each < 3 cm in maximum diameter); (3) No EHM or vascular invasion; and (4) Prothrombin time ratio $> 50\%$ (international normalized ratio < 1.7).

Baseline staging and work-up

HCC was diagnosed according to the guidelines proposed by the Korean Liver Cancer Study Group and the National Cancer Center^[12]. HCC was staged at diagnosis according to the modified Union for International Cancer Control (mUICC) staging system^[13] and the Barcelona Clinic Liver Cancer (BCLC) classification system^[14]. The initial tumor size was based on planning ultrasonography performed before RFA, and ablation size was measured *via* computed tomography (CT) scan performed immediately after RFA. All measurements were reviewed by board-certified radiologists who were experts in abdominal imaging.

Abdominal CT or magnetic resonance imaging (MRI) and AFP measurements were routinely performed at 1 month after RFA and followed-up at intervals of 3-6 mo. Positron emission tomography (PET)-CT, bone scanning, spinal MRI, and chest CT were also performed in cases of clinically suspected metastasis or as intermittent routine follow-up based on the decision of the treating physician.

Diagnosis of extrahepatic metastasis

The time of EHM diagnosis was defined as the date on which EHM was detected *via* imaging study for the first time. Most cases of EHM were diagnosed during routine follow-up studies while few patients were diagnosed during the evaluation of new symptoms or significant AFP/serial AFP elevation without definite intrahepatic lesions. An increase in AFP > 15 ng/mL compared to the previous value within less than 6 months was considered significant; this was regarded as a feasible cutoff point for the prediction of long-term outcome among patients with HCC^[15]. An AFP level that showed an increasing tendency more than twice was considered as serial elevation of AFP.

Statistical analysis

The data are expressed as means \pm standard deviations or medians with ranges. Univariate analyses were performed using the chi-squared test or Student's *t*-test, and univariate and multivariate analyses were performed *via* logistic regression, as appropriate. Variables with *P* values ≤ 0.05 in the univariate analysis were included in the multivariate logistic regression analysis. All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, United States). All analyses items with *P* < 0.05 were considered statistically significant.

The statistical methods of this study were reviewed by Ja Young Baek from

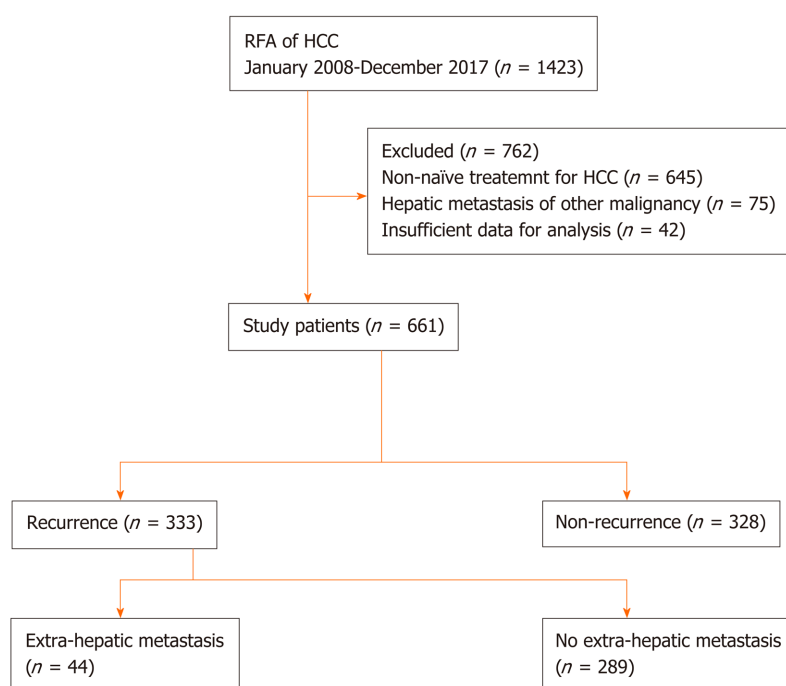


Figure 1 Flowchart indicating the method of patient enrollment. HCC: Hepatocellular carcinoma; RFA: Radiofrequency ablation.

Biomedical Research Institute, Hwasun Chonnam National University Hospital.

RESULTS

Baseline characteristics of enrolled patients

We identified 661 patients who underwent RFA as initial treatment for newly diagnosed HCC, and EHM occurred among 44 patients during the study period. We compared the baseline characteristics between the groups with and without EHM among the enrolled patients (Table 1). The mean age was 66.9 years, and 75.2% of the patients were male. The serum albumin level was lower among patients with EHM (4.3 mg/dL *vs* 3.9 mg/dL, $P = 0.015$). A higher proportion of patients in the EHM group had initial BCLC stage A and mUICC stage II disease compared to patients in the group without EHM who had a higher prevalence of BCLC stage 0 and mUICC stage I disease. There were no differences in tumor size and numbers between the 2 groups; however, the ratio of the ablation zone to tumor size was smaller in the group with EHM (2.07 *vs* 1.57, $P = 0.001$). There were no significant differences in the initial HCC recurrence site and mUICC tumor stage. The median follow-up duration of the enrolled patients was 1204 d.

Characteristics of first recurrence following RFA

Among 661 enrolled patients, 289 (43.7%) developed recurrent lesions without EHM, and 44 (6.7%) were diagnosed with EHM during the follow-up period. The median AFP level was higher at diagnosis of EHM than before the diagnosis of EHM in 79.0% of patients. The 10-year cumulative rates of HCC recurrence and EHM were 92.7% and 33.7%, respectively (Figure 2). Among the 661 patients, the median time to the detection of first HCC recurrence after RFA was 1.75 years, and the median duration to the development of EHM was 2.68 years. In addition, 68.2% of patients developed EHM within 2 years after the first recurrence regardless of RFS, and 75.0% of patients developed EHM within 5 years of the first recurrence (Figure 3). The most common site of initial recurrence was intrahepatic; initial extrahepatic recurrence occurred in only 1.2% (8/661) of patients. Most cases of EHM occurred after multiple intrahepatic recurrences, and the HCC stages at first recurrence are shown in Table 2. In addition, the peritoneum was the most common site of first EHM among 8 patients with EHM (5/8, 62.5%) followed by the lymph nodes (3/8, 37.5%). There was no case of pulmonary metastasis as the first recurrence in this study. Transcatheter arterial chemoembolization and RFA were mostly used as rescue treatment modalities (45.9%

Table 1 Baseline characteristics of enrolled patients

	Total (n = 661)	Patients without extrahepatic metastasis (n = 617)	Patients with extrahepatic metastasis (n = 44)	P value
Age (yr)	66.9 ± 10.20	66.8 ± 10.2	68.4 ± 9.98	0.301
Male, n (%)	497 (75.2)	469 (76.0)	28 (63.6)	0.066
Etiology of liver cirrhosis, n (%)				0.084
Alcohol	137 (20.7)	131 (21.2)	6 (13.6)	
HBV	351 (53.1)	322 (52.2)	29 (65.9)	
HCV	111 (16.8)	108 (17.5)	3 (6.8)	
Combined	40 (6.1)	38 (6.2)	2 (4.5)	
Others	22 (3.3)	18 (2.9)	4 (9.1)	
Platelet (× 10 ³ /μL)	127.8 ± 55.1	127 ± 54.7	141.2 ± 63.1	0.304
AST (IU/mL)	49.0 ± 45.6	48.6 ± 43.2	54.7 ± 72.1	0.40
ALT (IU/mL)	37.2 ± 46.8	36.7 ± 44.9	43.0 ± 69.2	0.392
ALP (U/L)	97.4 ± 38.6	96.7 ± 38.7	107.4 ± 35.2	0.076
Albumin (mg/dL)	4.3 ± 2.9	4.3 ± 3.0	3.9 ± 0.6	0.015
Total bilirubin (mg/dL)	0.93 ± 0.83	0.92 ± 0.84	1.04 ± 0.67	0.378
Serum AFP (IU/mL)	209.7 ± 1558.3	185.5 ± 1503.8	548.3 ± 2179.0	0.283
PIVKA-II (mAU/mL)	331.9 ± 2901.4	336.3 ± 2973.6	246.1 ± 542.6	0.907
BCLC stage, n (%)				0.034
0	257 (39.0)	248 (40.2)	9 (20.5)	
A	378 (57.1)	345 (55.8)	33 (75.0)	
B	26 (3.9)	24 (3.9)	2 (4.5)	
mUICC stage, n (%)				0.096
I	298 (45.0)	28 (46.0)	13 (29.5)	
II	316 (47.7)	288 (46.6)	28 (63.6)	
III	48 (7.3)	45 (7.3)	3 (6.8)	
Tumor size (cm)	2.42 ± 1.02	2.41 ± 1.02	2.62 ± 1.05	0.18
Ablation size/tumor size ratio	2.04 ± 0.97	2.07 ± 0.97	1.57 ± 0.74	0.001
Tumor number	1.19 ± 0.45	1.19 ± 0.46	1.16 ± 0.37	0.356
Encapsulated tumor, n (%)	157 (23.7)	146 (24.2)	11 (25.6)	0.840
Subcapsular tumor, n (%)	263 (39.7)	240 (39.4)	23 (53.5)	0.069
Follow-up duration, d (median, range)	1204 (183-5016)	1175 (183-5016)	1379 (187-4541)	0.270

Values are presented as mean ± SD. SD: Standard deviation; HBV: Hepatitis B virus; HCV: Hepatitis C virus; AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; AFP: Alpha-fetoprotein; PIVKA-II: Protein induced by vitamin K absence or antagonist-II; BCLC: Barcelona Clinic Liver Cancer; mUICC: Modified Union for International Cancer Control.

and 36.9%, respectively) for recurrent HCC (Table 2).

Clinical features of patients with extrahepatic metastasis

Forty-four patients with EHM were assessed for clinical features related to metastasis (Table 3). The location of metastasis was distributed evenly in the lymph nodes, bone, lung, and peritoneum. In 68.2% of patients, abdominal CT was used for the diagnosis of EHM (12 patients with lymph node, 11 patients with peritoneum, 6 patients with lung, and 5 patients with bone metastasis including 3 patients with multiple EHM), and 3 (6.8%) patients were diagnosed *via* chest X-rays during routine follow-up

Table 2 Characteristics of patients with first recurrence following radiofrequency ablation (n = 333)

	Patients without extrahepatic metastasis (n = 289)	Patients with extrahepatic metastasis (n = 44)	P value
AFP level			
Initial (median, range)	8.13 (0.70-30000.0)	21.750 (0.836-13148.0)	0.291
1 st recurrence (median, range)	7.08 (0.93-50000.0)	28.15 (0.73-70000.0)	0.274
CTP score, n (%)			0.044
A	277 (95.8)	39 (88.6)	
B	12 (4.2)	5 (11.4)	
Recurrence free survival, d (median, range)	821 (49-3944)	389 (79-2041)	< 0.001
First recurred site, n (%)			< 0.001
RFA site	53 (18.3)	7 (15.3)	
Same hepatic lobe	145 (50.2)	20 (45.5)	
Different hepatic lobe	60 (20.8)	8 (18.2)	
Both hepatic lobe	31 (10.7)	1 (3.1)	
Extrahepatic area	0 (0.0)	8 (18.2)	
Peritoneum		5	
Lymph nodes		3	
mUICC stage at 1 st recurrence, n (%)			< 0.001
I	140 (48.4)	17 (38.6)	
II	101 (34.9)	13 (29.5)	
III	38 (13.1)	4 (9.1)	
IVa	5 (1.7)	2 (4.5)	
IVb	0 (0.0)	8 (18.2)	
Rescue Treatment modalities, n (%)			0.003
TACE	138 (47.7)	15 (34.1)	
RFA	110 (38.2)	13 (29.5)	
Sorafenib	1 (0.3)	-	
Surgery	8 (2.8)	3 (6.8)	
Radiotherapy	1 (0.3)	3 (6.8)	
Liver transplantation	1 (0.3)	-	
TACE	11 (3.8)	3 (6.8)	
RFA PEIT	1 (0.3)	-	
None	9 (3.1)	5 (11.4)	
Follow-up loss	9 (3.1)	2 (4.5)	

RFA: Radiofrequency ablation; AFP: Alpha-fetoprotein; CTP: Current procedural terminology; mUICC: Modified Union for International Cancer Control; TACE: Transarterial chemoembolization; PEIT: Percutaneous ethanol injection therapy.

examinations. Three patients (6.8%) were diagnosed *via* abdominal MRI: 1 patient during HCC surveillance and 2 patients while evaluating elevated tumor marker levels without definite HCC recurrence on abdominal CT. Spine MRI was used for the diagnosis of spinal metastasis among 3 patients who presented with new-onset back pain. Five patients (11.4%) underwent PET-CT for re-staging of HCC without signs of intrahepatic recurrence, and EHM was detected in the lung, lymph nodes, and bone.

Table 3 Clinical features of patients with extrahepatic metastasis (*n* = 44), *n* (%)

Clinical features	Value
Location of metastasis ¹	
Lymph nodes	16 (36.3)
Bone	12 (27.3)
Lung	13 (29.5)
Solitary/multiple	4 (30.7)/9 (69.2)
Unilateral/Bilateral	4 (30.7)/9 (69.2)
Lower lobe/non-lower lobe/all lobes	2 (15.4)/9 (69.2)/2 (15.4)
Peritoneum	12 (27.3)
Diagnostic modality	
Abdomen enhanced CT	30 (68.2)
Abdomen enhanced MRI	3 (6.8)
Spine MRI	3 (6.8)
PET-CT	5 (11.4)
Chest X-ray	3 (6.8)
Chest enhanced CT	3 (6.8%)
Tumor marker increment (AFP, PIVKA)	
Both	14 (36.8)
Either	17 (44.7)
AFP/PIVKA	15 (39.5)/2 (5.3)
None	7 (18.4)
N/A	6
Patients diagnosed of EHM with either of abdomen enhanced CT or serum AFP elevation (> 15 IU/mL)	38 (86.4)
Time to extrahepatic metastasis (years, median, range)	2.68 (0.38-10.6)
Intra-hepatic HCC status at diagnosis of EHM (mUICC T stage)	
T0/T1/T2	19 (43.2)/5 (11.4)/7 (15.9)
T3/T4a	2 (4.5)/11 (25.0)

¹Nine patients had multiple EHM occurrences (3 patients: lymph node and bone, 3 patients: Lymph node and lung, 1 patient: bone and lung, and 1 patient: Bone and peritoneum). CT: Computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; AFP: Alpha-fetoprotein; PIVKA-II: Protein induced by vitamin K absence or antagonist-II; N/A: Not applicable; EHM: Extrahepatic metastasis; HCC: Hepatocellular carcinoma; mUICC: Modified Union for International Cancer Control.

In detail, 9 patients (20.5%) had multiple sites of EHM at first diagnosis. Among 13 patients with pulmonary metastasis, 7 (53.8%) were diagnosed *via* abdominal CT, 3 (23.1%) *via* chest X-ray, and 3 (23.1%) *via* chest CT.

Thirty-one patients (31/38, 81.5%) had increased tumor marker levels at the time of diagnosis of EHM. A diagnosis of EHM was made in most patients (86.4%) based on either contrast-enhanced CT findings or elevated serum AFP levels. Intrahepatic tumor status categorized according to the mUICC T stage at the time of EHM diagnosis was assessed; 43.2% of patients had no findings of intrahepatic HCC remnant tumor (T0), and 25.0% of patients had stage T4a disease.

Factors associated with extrahepatic metastasis

Multiple factors that might be relevant to EHM were assessed (Table 4). In the univariate analysis, more advanced stage, the presence of intrahepatic recurrence, serum alkaline phosphatase level > 97 U/L, first RFS within less than 2 years, ablation zone/tumor size > 2, and AFP level > 400 IU/mL at first HCC recurrence were

Table 4 Univariate and multivariate analysis of factors associated with extrahepatic metastasis

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
BCLC stage (0 vs A, B)	2.93 (1.38–6.20)	0.003		
mUICC stage (I vs II, III)	2.04 (1.04–3.96)	0.034		
Post-RFA complication (fever, abscess)	2.78 (1.31–5.92)	0.050		
Presence of intra-hepatic recurrence	48.8 (6.68–356.63)	0.000		
ALP > 97 U/L	2.29 (1.23–4.26)	0.008		
1 st recurrence free survival < 2 yr	2.88 (1.54–5.38)	0.001	2.44 (1.16–5.14)	0.019
Ratio of ablation zone and tumor size < 2	3.84 (1.76–8.39)	0.001	3.33 (1.34–8.27)	0.010
Presence of tumoral thrombosis	2.57 (1.13–5.84)	0.024		
AFP > 400 IU/mL at 1 st recurrence	4.52 (2.03–10.07)	0.000	3.35 (1.33–8.43)	0.010
mUICC stage > 2 at 1 st recurrence	2.49 (1.22–5.06)	0.012		

OR: Odds ratio; CI: Confidence interval; BCLC: Barcelona Clinic Liver Cancer; mUICC: Modified Union for International Cancer Control; RFA: Radiofrequency ablation; ALP: Alkaline phosphatase; AFP: Alpha-fetoprotein.

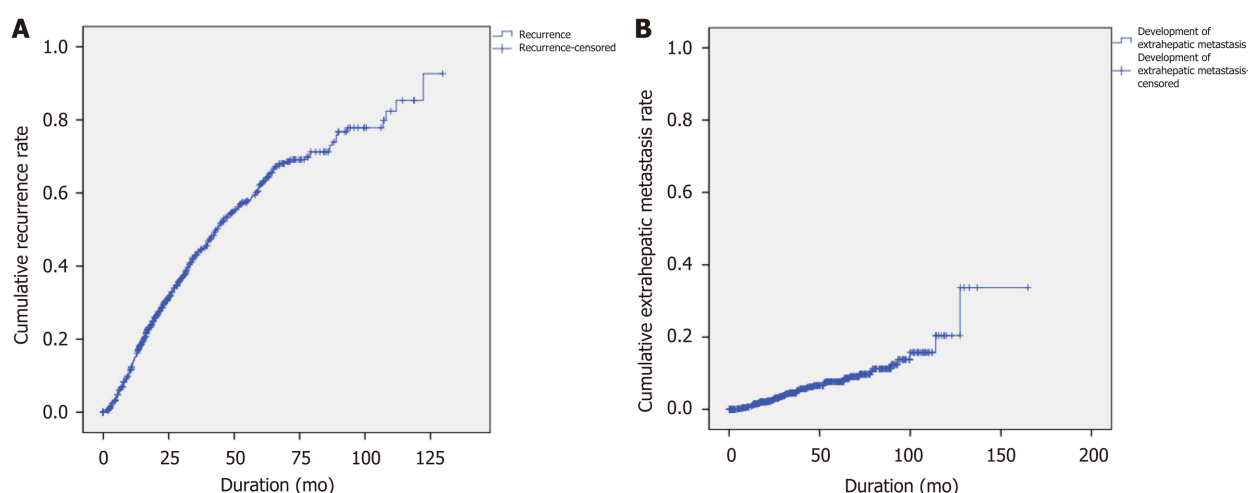


Figure 2 Recurrence curves of 661 patients with hepatocellular carcinoma treated with radiofrequency ablation. A: Cumulative rates of recurrence. The 1-, 3-, 5-, 8-, and 10-year cumulative rates of recurrence were 15.1%, 43.8%, 62.5%, 77.9%, and 92.7%, respectively; B: Cumulative rates of extrahepatic metastasis. The 1-, 3-, 5-, 8-, and 10-year cumulative rates of extrahepatic metastasis were 1.0%, 2.9%, 8.1%, 15.7%, and 33.7%, respectively.

associated with a high risk of EHM. Among these factors, a first HCC RFS < 2 years [odds ratio (OR), 2.44; $P = 0.019$], ablation zone/tumor size < 2 (OR, 3.33; $P = 0.01$), and AFP > 400 IU/mL at first recurrence (OR, 3.35; $P = 0.01$) were identified as significant factors in the multivariate analysis. We stratified the patients who had recurrence after RFA by numbers of risk factors related to EHM occurrence, and in proportion to the numbers of risk factors, the cumulative occurrence of EHM showed an increase (Figure 4).

DISCUSSION

Although RFA is one of the most effective curative treatment modalities for HCC along with surgical resection and liver transplantation, our study and previous studies showed that there is a substantial possibility of EHM even if intrahepatic lesions are stable^[8,16,17]. Most other studies showed that the most common initial site of recurrence is intrahepatic and that most cases of EHM occur after multiple intrahepatic recurrences with several treatments^[8]. This study focused on the characteristics and

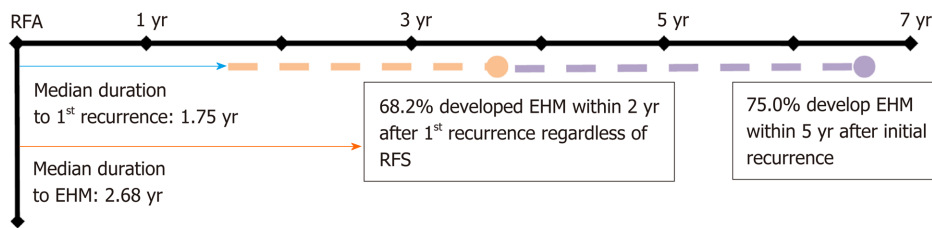


Figure 3 Timelines of recurrence of extrahepatic metastasis after radiofrequency ablation for hepatocellular carcinoma. RFA: Radiofrequency ablation; EHM: Extrahepatic metastasis; RFS: Recurrence-free survival.

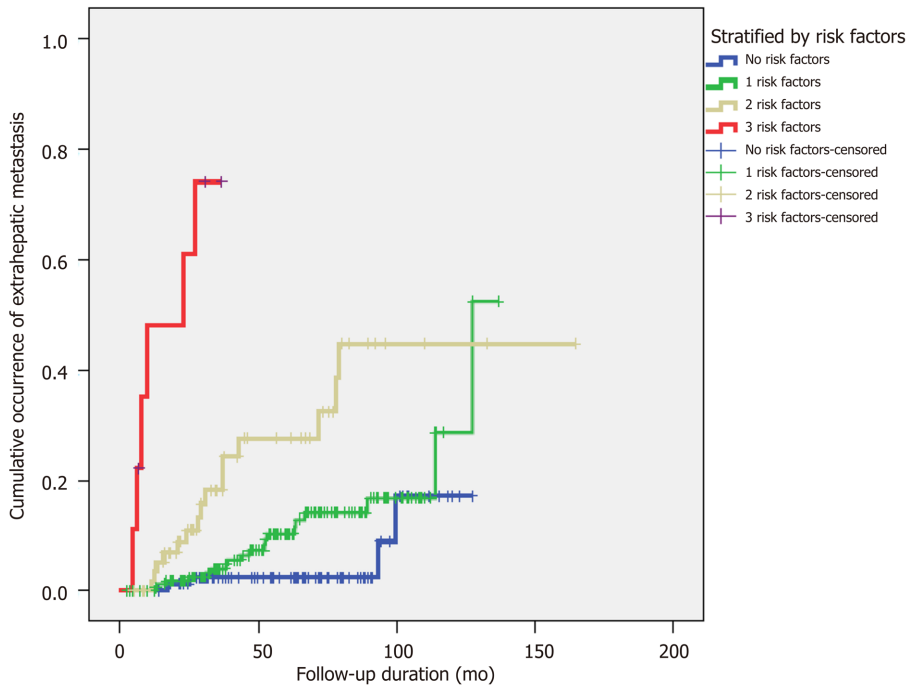


Figure 4 Cumulative occurrence of extrahepatic metastasis in patients with recurrence of hepatocellular carcinoma after radiofrequency ablation: Stratified by numbers of risk factors.

risk factors of extrahepatic recurrence after RFA and whether regular surveillance for EHM is needed. The results are of particular interest because data on the pattern of EHM in HCC after RFA and the role of regular surveillance for EHM are limited, and there have been no reports regarding surveillance methods for EHM in HCC.

In the present study, 289 patients experienced tumor recurrence without EHM, and 44 experienced EHM during a median follow-up period of 1204 d. The 1-, 3-, 5-, 8-, and 10-year cumulative rates of HCC recurrence and EHM development were concordant with the results of previous studies^[8,9], but only 1.2% of the enrolled patients presented with EHM as the first recurrence of HCC. The median time to the detection of EHM was 2.68 years, and 68.2% of patients developed EHM within 2 years after the first recurrence regardless of RFS. Furthermore, 75% of patients developed EHM within 5 years of the first recurrence (Figure 3).

Other studies that reported the locations of EHM showed predominance in the lung (39%-54%), lymph nodes (34%-40%), and bone (25%-39%)^[3,11,18]. In the present study, the location of EHM was relatively evenly distributed among the intra-abdominal lymph nodes (36.3%), bone (25.0%), lung (29.5%), and peritoneum (27.3%). The proportions of extrahepatic metastatic sites in our study may have differed from those identified in previous studies as our population comprised post-RFA patients who had early-stage disease, while the other studies included patients with diverse stages of HCC ranging from early to terminal. The median duration of peritoneal seeding was 883 d (range: 138-3878); however, in 3 patients, the time from RFA to EHM was less than 1 year, suggesting the possibility that peritoneal dissemination occurred *via* RFA in some patients. There was no case of pulmonary metastasis as the first recurrence in

this study. Most pulmonary metastases occurred after intrahepatic recurrences.

The spread pattern of lung metastasis at the initial diagnosis of recurrent HCC is important because of the possible value of metastectomy, which was reported to yield favorable outcomes in some studies^[19,20]. We found that at the time of HCC recurrence 69.2% of patients had multiple lung metastatic lesions, and 69.2% had bilateral lung metastasis for which metastectomy was not indicated. Thus, the option of metastectomy after RFA may be of limited value in the group we studied.

Regarding the detection method, EHM was diagnosed *via* abdominal imaging (CT/MRI) in most patients (75.0%). The backbone of surveillance after RFA for HCC is abdominal imaging, and only 14/661 patients (2.1%) required other diagnostic modalities such as PET-CT, spine MRI, chest CT, or chest X-ray. Considering the small proportion of diagnostic modalities other than abdominal imaging and the low incidence (1.2%) of EHM as the first recurrence of HCC, the need for regular surveillance tools other than abdominal imaging may not be very high. In particular, 38/44 patients (86.4%) with EHM had either positive abdominal CT scan results or serum AFP elevation, which we currently use as surveillance tools for HCC after RFA in clinical practice. Considering the high cost of spine MRI, PET-CT, and chest CT in general, the cost-effectiveness of routine surveillance using these modalities may be high however, an individualized approach in accordance with each country's reimbursement policy is needed.

A correlation between serum PIVKA-II levels and EHM was reported previously^[21,22]. In our study, 31/38 patients (81.5%) had increasing tumor marker levels (serum AFP or protein induced by vitamin K absence-II [PIVKA-II]), and serum AFP levels were elevated in 29/38 (76.3%) which showed correlation with the development of EHM, as reported in other studies^[23]. Although the PIVKA-II level was only assessed in 24 patients, 16 (66.7%) showed elevated serum levels at EHM development. Regarding the pattern of HCC recurrence, the most common initial site of recurrence was intrahepatic. Although the rate of extrahepatic initial recurrences in our population was only 1.2%, 43.2% of the patients had no sign of intrahepatic HCC at the time of diagnosis of EHM. This implies that even if loco-regionally managed HCC lesions are stable, close surveillance for possible EHM is warranted. In particular, when tumor marker levels increase without definite aggravation of previous HCC lesions, additional examination for EHM development should be considered. Refaat *et al*^[17] reported that among 65 patients who underwent loco-regional therapy for HCC and had elevated serum AFP levels, 10 (15.4%) had EHM without intrahepatic tumor recurrence. In addition, Chen *et al*^[16] reported that among 26 patients who had elevated serum AFP levels without findings of recurrence on conventional imaging studies, 8 (30.8%) experienced EHM.

Recurrence of HCC after curative treatment is reported to occur mostly within 2 years^[24]; therefore, guidelines suggest surveillance for HCC recurrence within a short interval of 2-6 mo until the second year after treatment^[25-27]. In the present study, the 1-, 3-, 5-, 8-, and 10-year cumulative rates of HCC recurrence were 15.1%, 43.8%, 62.5%, 77.9%, and 92.7% respectively, and those of EHM development were 1.0%, 2.9%, 8.1%, 15.7%, and 33.7%, respectively. Our results also showed a 1.75-year median time to first recurrence after RFA, a median time to the development of EHM of 2.68 years regardless of RFS, and 75.0% of patients experiencing EHM within 5 years after RFA. Thus, we suggest that it is prudent to pay attention to possible EHM occurrence for at least 5 years after RFA, and patients who experience tumor recurrence may require close observation for the development of EHM, particularly within 2 years after the first recurrence (Figure 3).

In the multivariate analysis of potential risk factors for EHM, first RFS < 2 years, ablation zone/tumor size < 2, and serum AFP level > 400 IU/mL at first recurrence were factors relevant to EHM development. Some studies have suggested that early recurrence is associated with vascular invasion, initial tumor staging, and poor prognosis, and our findings are consistent with these reports^[28,29]. Other studies have assessed the risk of local tumor progression in relation to insufficiently ablated margins after RFA in liver malignancies, a minimal margin of < 2-5 mm being reported as an independent factor for local tumor progression^[30-32]. Our study showed that ablation zone/tumor size was associated with the risk of EHM development. Most patients (97.9%) had minimal margins of > 5 mm, and the margin length between the tumor and ablation zones showed no relevance in the occurrence of EHM. Some studies have reported that higher AFP levels are associated with increased recurrence following liver transplantation for HCC, as well as worse disease-free survival and overall survival^[33,34]. By stratifying patients according to the number of risk factors associated with EHM, the cumulative occurrence of EHM showed an increasing trend related to the number (≥ 2) of risk factors (Figure 4). Therefore, we suggest close

surveillance for EHM after RFA, especially in these high-risk patients.

Our study had some limitations. First, this was a retrospective study based on medical records. Thus, there was no uniform post-treatment or surveillance schedule, and the surveillance modality used for each patient was at the physician's discretion. Second, until the development of EHM, patients underwent different treatment modalities for local HCC recurrence depending on the tumor and patient's status. There may be diverse statuses regarding tumor stage, liver reserve function, and patients' physical performance status. However, we tried to overcome these limitations by using a considerable number of patients with a long-term follow-up duration in multiple tertiary centers.

In conclusion, EHM as the first recurrence after RFA was rare, but cumulative EHM occurred frequently following multiple intrahepatic recurrences. Thus, optimal surveillance for EHM after RFA for HCC is essential according to stratified risk factors (RFS < 2 years, ablation zone/tumor size < 2, and AFP level > 400 IU/mL) related to EHM, and combined contrast-enhanced abdominal CT and serum AFP level have been found useful for this purpose.

ARTICLE HIGHLIGHTS

Research background

Extrahepatic metastasis (EHM) of hepatocellular carcinoma (HCC) is related to dismal prognosis.

Research motivation

The characteristics and risk factors of EHM of HCC after radiofrequency ablation are not elucidated.

Research objectives

To investigate the clinical features and risk factors of EHM after radiofrequency ablation for HCC.

Research methods

Patients who underwent radiofrequency ablation for HCC were identified from the two tertiary hospitals in South Korea from 2008 to 2017. Univariate analyses were performed using the chi-squared test or Student's *t*-test, and univariate and multivariate analyses were performed *via* logistic regression, as appropriate.

Research results

During a median follow-up period of 1,204 days, EHM was diagnosed in 44 patients (6.7%). The 10-year cumulative rate of HCC recurrence and EHM was 92.7% and 33.7%, respectively. The median time to the diagnosis of EHM was 2.68 years, and 68.2% of patients developed EHM within 2 years of the first recurrence, regardless of recurrence-free survival. EHM was mostly diagnosed *via* abdominal CT/MRI in 33 (75.0%) and 38 of 44 patients (86.4%) with EHM had either positive abdominal CT scan results or serum alpha-fetoprotein (AFP) level elevation. In multivariate analysis, recurrence-free survival < 2 years, ablation zone/tumor size < 2, and alpha-fetoprotein level > 400 IU/mL were associated with a high EHM risk.

Research conclusions

EHM occurs following multiple intrahepatic recurrences after radiofrequency ablation and combined contrast-enhanced abdominal CT and serum AFP were useful for surveillance.

Research perspectives

Patients especially with high-risk factors such as recurrence-free survival < 2 years, ablation zone/tumor size < 2, and alpha-fetoprotein level > 400 IU/mL, require close follow-up for EHM.

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