

Is it necessary to follow up surveillance of the extra-hepatic metastasis after RFA for HCC?

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Background/Aims: Characteristics of EHM of HCC after radiofrequency ablation (RFA) are not fully understood and guidelines for adequate surveillance for detection of extra-hepatic metastasis is still lacking. Therefore, we aimed to elucidate the characteristics of EHM of HCC and the need for follow up surveillance of EHM following RFA. **Methods:** We enrolled 661 patients who underwent RFA as a first-line treatment for HCC between 2006 and 2017. Baseline clinical and tumor characteristics, complications of RFA, status of recurrence, recurrence free survival, and rescue treatment methods were analyzed. **Results:** 44 patients (6.7%) were diagnosed to have EHM during median follow-up period of 1,204 days. Baseline tumor stage of enrolled patients as follows; BCLC 0 (39%), BCLC A (57.1%), BCLC B (3.9%) and mUICC I (45%), mUICC II (47.7%), mUICC III (7.3%). Recurrence rate and median recurrence free survival during study period was 49% and 778 days, respectively. Most common initial recurrence site was intra-hepatic lesion. Extra-hepatic recurrence at initial recurrence was only 1.2%. Median time to diagnosis of EHM was 2.68 years and most EHM occurred after multiple intra-hepatic recurrences. The locations of EHM were as follows; intra-abdominal lymph nodes (36.3%), bone (25%), lung (29.5%) and peritoneum (27.3%). Abdomen CT/MRI was used for diagnosis of EHM for 33 patients (75%), spine MRI was used for 3 patients (6.8%), PET CT was used for 5 patients (11.4%) and chest CXR/CT for 6 patient (13.6%). Thirty patients (79%) had increment of tumor marker at the time diagnosis of EHM. At multivariate analysis, recurrence free survival less than 2 years, ratio of ablation zone by RFA and tumor size less than two and AFP > 400 IU/ML at 1st recurrence were associated with high risk of EHM. **Conclusions:** Most patients had intra-hepatic lesions or intra-abdominal lesions at the time of initial recurrence. Only 1.2% was diagnosed with EHM at first recurrence and most EHM occurred after multiple intra-hepatic recurrences. Abdomen CT, AFP could detect most of first recurrence including EHM, and role of chest computed tomography was limited.

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 (year)	66.9±10.20	66.8±10.2	67.4±9.98	0.301
Male	487 (73.7%)	469 (76.0%)	18 (40.9%)	0.066
Etiology of liver cancer				0.084
Alcoholic	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 (3.4%)	18 (2.9%)	4 (9.1%)	
Platelet (10 ³ /μL)	127.8±35.1	127±34.7	141.2±83.1	0.304
AST (U/L)	48.9±45.8	48.6±45.2	54.7±72.1	0.40
ALT (U/L)	37.2±48.8	36.7±44.9	43.0±69.2	0.392
ALP (U/L)	97.4±38.6	96.7±38.7	107.4±51.2	0.076
Albumin (g/dL)	4.3±2.9	4.3±3.0	3.9±0.8	0.013
Total bilirubin (mg/dL)	0.89±0.85	0.92±0.84	1.10±0.87	0.378
AFP (U/L)	209.7±1159.3	185.3±1103.8	348.3±2179.0	0.283
PDCA (mAU/mL)	331.9±2603.4	336.3±2673.6	246.1±1542.6	0.807
BCLC stage				0.034
0	257 (39.0%)	248 (40.2%)	9 (20.5%)	
A	378 (57.1%)	347 (56.3%)	31 (70.5%)	
B	26 (3.9%)	24 (3.9%)	2 (4.5%)	
mUICC stage				0.096
I	298 (45.1%)	28 (46.0%)	11 (25.0%)	
II	318 (48.3%)	281 (45.6%)	37 (83.6%)	
III	45 (6.8%)	40 (6.5%)	5 (11.4%)	
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	1.75±0.74	0.001
Tumor number	1.19±0.42	1.19±0.44	1.18±0.37	0.316
Recurrence rate	322 (48.9%)	289 (46.8%)	44 (100.0%)	0.000
Recurrence free duration (days)	778 (49.3-844)	821 (49.3-844)	389 (79.2-841)	0.000
Rescue treatment				0.840
Resected tumor	157 (23.7%)	148 (24.2%)	11 (25.0%)	
Subcapsular tumor	283 (42.8%)	240 (39.0%)	23 (52.3%)	
Follow-up duration (days)	1204	1175	1179	0.270
Median, range	(183.2-1518)	(183.2-1518)	(181.4-1541)	

*Values are presented as mean ± SD

Table 2. Characteristics of 1st recurrence following RFA

	Patients without extrahepatic metastasis (n=370)	Patients with extrahepatic metastasis (n=44)	p-value
1 st recurrence site			0.000
Edo site	33 (13.3%)	7 (15.9%)	
Subcapsule	143 (38.7%)	20 (45.5%)	
Diffuse intra	60 (16.2%)	8 (18.2%)	
Buddhi	31 (8.4%)	1 (2.3%)	
Extra-hepatic site	0 (0.0%)	8 (18.2%)	0.000
mUICC stage at 1 st recurrence			
I	140 (38.1%)	17 (38.6%)	
II	161 (43.5%)	13 (29.5%)	
III	18 (4.9%)	4 (9.1%)	
IV	1 (0.3%)	2 (4.5%)	
IVb	0 (0.0%)	8 (18.2%)	

Table 3. Univariate and multivariate analysis of factors associated with extrahepatic metastasis

	Univariate analysis	Multivariate analysis	
	OR (95% CI)	OR (95% CI)	p-value
BCLC stage (I vs. A, B)	2.87	1.38 (0.4-5.0)	0.001
mUICC stage (I vs. II, III)	2.84	2.84	0.004
Post-RFA complications (fever, abscess)	2.18	2.18	0.000
Resection of metastases	0.69	0.69 (0.08-5.63)	0.000
AFP > 400 IU/L	2.29	2.29	0.000
1 st recurrence free survival < 2 years	3.89	3.89	0.000
Ratio of ablation zone and tumor size > 2	3.84	3.84	0.000
Presence of transarterial hemorrhage	2.27	2.27	0.024
AFP > 400 IU/L at 1 st recurrence	4.82	4.82	0.000
mUICC stage > 2 at 1 st recurrence	2.49	2.49	0.001
	2.49	2.49	0.001

BCLC, Barcelona Clinic Liver Cancer; mUICC, modified UICC for International Cancer Control; RFA, radiofrequency ablation; AFP, alpha-fetoprotein; AFP, alpha-fetoprotein.