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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Long-term results of liver thermal ablation in patients with hepatocellular carcinoma and colorectal cancer liver metastasis regarding spatial features and tumor-specific variables

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PURPOSE

Colorectal cancer liver metastasis (CRLM) and hepatocellular carcinoma (HCC) are widely treated using microwave and radiofrequency ablation. Local tumor progression (LTP) may develop depending on the shortest vascular distance and large lesion diameter. This study aims to explore the effect of these spatial features and to investigate the correlation between tumor-specific variables and LTP.

METHODS

This is a retrospective study covering the period between January 2007 and January 2019. One hundred twenty-five patients (CRLM: HCC: 64:61) with 262 lesions (CRLM: HCC: 142:120) were enrolled. The correlation between LTP and the variables was analyzed using the chi-square test, Fischer's exact test, or the Fisher-Freeman-Halton test where applicable. The local progression-free survival (Loc-PFS) was analyzed using the Kaplan–Meier method. Univariable and multivariable Cox regression analyses were performed to identify prognostic factors.

RESULTS

Significant correlations were observed for LTP in both CRLM and HCC at a lesion diameter of 30–50 mm ($P = 0.019$ and $P < 0.001$, respectively) and SVD of ≤3 mm ($P < 0.001$ for both). No correlation was found between the ablation type and LTP (CRLM: $P = 0.141$; HCC: $P = 0.771$). There was no relationship between residue and the ablation type, but a strong correlation with tumor size was observed ($P = 0.127$ and $P < 0.001$, respectively). In CRLM, LTP was associated with mutant K-ras and concomitant lung metastasis ($P < 0.001$ and $P = 0.003$, respectively). In HCC, a similar correlation was found for Child–Pugh B, serum alpha-fetoprotein (AFP) level of >10 ng/mL, predisposing factors, and moderate histopathological differentiation ($P < 0.001$, $P = 0.008$, $P = 0.027$, and $P<0.001$, respectively). In CRLM, SVD of ≤3 mm proved to be the variable with the greatest negative effect on Loc-PFS ($P = 0.007$), followed by concomitant lung metastasis ($P = 0.027$). In HCC, a serum AFP level of >10 ng/mL proved to be the variable with the greatest negative effect on Loc-PFS ($P = 0.045$).

CONCLUSION

In addition to the lesions' spatial features, tumor-specific variables may also have an impact on LTP.

KEYWORDS

Ablation techniques (D055011), colorectal neoplasm (D015179), hepatocellular carcinoma (D006528), local tumor progression (D009364), survival analysis (D016019)

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Colorectal cancer liver metastasis (CRLM) and hepatocellular carcinoma (HCC) are widely treated using local ablation, which provides an increased survival outcome.[1-3] Both radiofrequency ablation (RFA) and microwave ablation (MWA), the most commonly used ablation techniques, cause necrosis through elevated temperatures, but they have different physical parameters that offer advantages in certain situations.[4,5]

After local ablation procedures, local tumor progression (LTP) may be confronted out of favor.[6,7] This situation is more frequent in large tumors that exceed the perimeter of the

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ablation zone and in tumors with a blood vessel in close proximity (heat-sink effect).[8,9] Of these two variables, tumors with a blood vessel in close proximity are considered the highest risk factor for the development of LTP.[5,10,11] Given the extensive literature addressing the development of LTP, it is possible that several non-spatial variables also influence this development in malignancies with different pathogenesis, such as mutant K-ras oncogene in colorectal carcinoma (CRC) and alpha-fetoprotein (AFP) levels before ablation in HCC.

This study has three main objectives. First, to investigate the correlation between common variables (tumor diameter, shortest vascular distance, and the ablation type) and LTP with local progression-free survival (Loc-PFS), which corresponds to the period without LTP. Second, to investigate the association with K-ras mutation, primary tumor location (left- or right-sided), and concomitant lung metastases in CRLM as tumor-specific variables. Third, to investigate the association between the Child–Pugh score, histopathological differentiation grade, serum AFP level, and predisposing factors for chronic liver disease in HCC as tumor-specific variables.

Methods

Study design

This study is a retrospective analysis of liver lesions that received RFA or MWA between January 2007 and January 2019 due to CRLM or HCC. The Hacettepe University Faculty of Medicine Ethics Committee of the institute approved this study (GO-18/429).

The decision for each thermal ablation was made by the multidisciplinary Institutional tumor board, and informed consent was obtained from all enrolled patients.

Imaging-guided ablation therapies were defined according to publications developed by the "International Working Group on Image-Guided Tumor Ablation" and "Results of the SIO and DATECAN Initiative".[12,13]

Main points

- Morphometric features of the lesion, such as larger diameters or shorter vascular proximity, were an effective factor in local tumor progression.
- Colorectal cancer liver metastasis, concomitant lung metastasis, and a host-specific variable had the greatest impact on local progression-free survival after short vascular proximity.
- In hepatocellular carcinoma, a serum alpha-fetoprotein level of >10 ng/mL proved to be the variable with the greatest negative effect on local progression-free survival.

Inclusion criteria

The inclusion criteria for both CRLM and HCC lesions were as follows:

1. Maximum of five liver lesions for each patient with CRC and a maximum of three lesions for each patient with HCC,

2. Maximum diameter of 5 cm for each lesion,

3. Curative intent (the ablation of all liver lesions in the same session),

4. Presence of magnetic resonance imaging (MRI) images within 2 months before the ablation,

5. Presence of follow-up MRI or computed tomography (CT) imaging at 1, 3, 6, and 12 months and semiannually after the first year.

Furthermore, the presence of lung metastasis was not an exclusion criterion.

Seventy-one patients with CRC and 67 patients with HCC who underwent ablation with "curative intent" were identified. However, due to insufficient follow-up, seven patients with CRC (9.85%) and six patients with HCC (8.95%) were excluded. Finally, the remaining 64 patients with CRC (142 lesions) and 61 patients with HCC (120 lesions) were enrolled in this study.

For further information please see the flowchart (Figure 1).

Ablation procedure and follow-up

All procedures were done with ultrasound guidance. StarBurst® (AngioDynamics®) electrodes were used for RFA, while Acculis®/Solero® (AngioDynamics®) antennas were used for MWA. All procedures were performed according to the manufacturer's instructions, with an ablation margin of at least 5–10 mm.[14]

After the ablation, contrast-enhanced CT and MRI were performed within the first month. Patients with no residual disease were accepted as "complete ablation". Tumor development during follow-up in patients with complete ablation was classified as LTP. Loc-PFS was calculated for each lesion, starting with ablation until the development of LTP or patient death, and it was censored at the last follow-up date. The censor date for Loc-PFS estimation was February 2, 2020.

Data collection

All data were reviewed and collected with the consensus of two radiologists (A.G.E. and O.A.) at two different time points to ensure external and internal validity in both patient selection and data collection.

The segmental distribution, LTP development, thermal ablation type (MWA or RFA), and shortest vascular distance of each lesion were recorded. The measurement of the shortest vascular distance was performed on volumetric dynamic T1W slices from the patient's last MRI before ablation. The shortest perpendicular distance to the vessel with a width of ≥3 mm was estimated through multiplanar reformation images (Figure 2). The longest axial and craniocaudal diameter of each lesion was also recorded.

The complications, ablation type and technique (percutaneous or intraoperative), and the segment of the relevant lesion were recorded.

The presence of K-ras mutation, the site of primary disease (right or left colon), and concomitant lung metastasis were considered CRC-specific variables. In the HCC group, predisposing factors (non-alcoholic steatohepatitis and hepatitis B or C virus), degree of histopathologic differentiation, AFP level, and Child–Pugh score within one month before ablation were recorded.

Histopathologic diagnoses were available in both the CRC and HCC groups that participated in this study. However, in patients with CRC with multiple liver metastases, only one of the lesions was biopsied. In addition, K-ras mutations were analyzed using DNA derived from formalin-fixed paraffin-embedded tumors obtained from primary sites in the colon. The presence of microsatellite instability was also analyzed.

Statistical analysis

The data were processed using the IBM-SPSS® Statistics 24.0, StataCorp LCC-STATA® 14 software, and R® version 4.0.3. Categorical variables were reported as frequencies and percentages, and continuous variables were reported as means and standard deviations.

Categorical variables were evaluated using the chi-square test or the Fisher-Freeman-Halton test where applicable. For all tests, a two-tailed *P* value of less than 0.05 was considered statistically significant.

The Kaplan–Meier method was used for estimates of Loc-PFS, and the log-rank test was used to compare survival groups. Cox

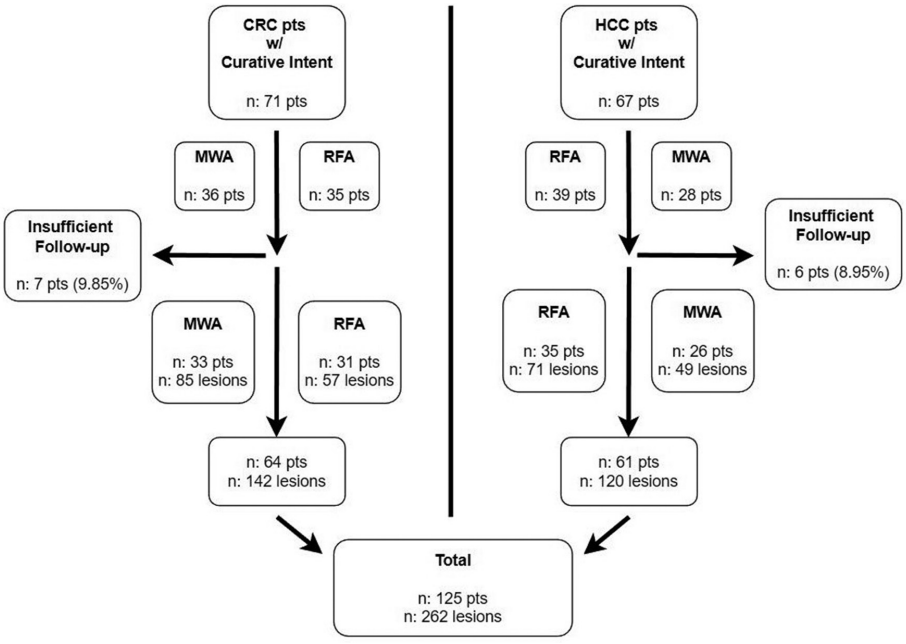

Figure 1. The flowchart of patient selection. CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; MWA, microwave ablation; RFA, radiofrequency ablation.

regression models were used to assess the effects of confounding factors on overall survival. Variables with a *P* value of <0.20 in the univariable analyses were analyzed in multivariable Cox regression models to explore prognostic factors of overall survival. The results are reported with hazard ratios and 95% confidence intervals.[15]

Results

Background data and complications

The detailed baseline characteristics of 262 lesions and 125 patients are shown with all aspects in Table 1.

The complications of the included patients were biliary obstruction, abscess, and costochondritis (Figures 3-5). Seventeen lesions (out of 262 lesions, 6.48%) were complicated: eight of them were percutaneous (out of 198 lesions, 4.04%) and nine of them were intraoperative (out of 64 lesions, 14.06%). A significant correlation was found between intraoperative ablation and the occurrence of complications: when all 17 complications were included and when only the abscess [three percutaneous (3/198 = 1.51%) and six intra-operative (6/64 = 9.37%) lesions] were included ($P < 0.005$). Six of the nine abscesses had a history of hepaticojejunostomy (two lesions) and endoscopic sphincterotomy (four lesions) due to gallstones. All lesions (n = 7, 2.67%) that developed biliary dilatation were in the central segments (segments 1, 4b, and 5) ($P < 0.001$). A transient costochondritis complication was observed in only one patient with a subcapsular localized lesion in segment eight.

Table 1. General background data

	Colorectal cancer		Hepatocellular carcinoma		Total	
	RFA	MWA	RFA	MWA	RFA	MWA
Patients* (n)	31 (48.73%)	33 (51.57%)	35 (57.37%)	26 (42.63%)	66 (52.80%)	59 (47.20%)
Gender (M:F)	20:11	20:13	22:13	17:9	42:24	37:21
Age†	57.74 ± 11.88	61.25 ± 5.58	61.88 ± 9.62	61.20 ± 11.03	59.15 ± 10.93	61.24 ± 9.85
Lesions* (n)	57 (40.14%)	85 (59.86%)	71 (52.98%)	49 (47.02%)	128 (48.85%)	134 (51.15%)
<30 mm (n)	42 (36.52%)	73 (63.48%)	60 (61.22%)	38 (38.78%)	102 (47.88%)	111 (52.12%)
30–50 mm (n)	15 (55.55%)	12 (44.45%)	11 (50.00%)	11 (50.00%)	26 (53.06%)	23 (46.94%)
R-L diameter†	17.87 ± 7.76	20.42 ± 7.80	16.78 ± 7.42	18.67 ± 9.37	17.11 ± 7.71	20.11 ± 9.01
A-P diameter†	16.87 ± 7.31	19.52 ± 7.60	16.71 ± 7.22	17.91 ± 8.48	16.75 ± 7.24	18.84 ± 8.20
C-C diameter†	16.95 ± 7.72	19.85 ± 7.96	16.94 ± 7.43	18.69 ± 9.29	16.94 ± 7.52	19.18 ± 8.44
Segmental distribution* (n)						
Segment-1	1 (33.33%)	2 (66.66%)	2 (100.0%)	0 (0.00%)	3 (60.00%)	2 (40.00%)
Segment-2	4 (30.76%)	9 (69.24%)	4 (57.14%)	3 (42.86%)	8 (40.00%)	12 (60.00%)
Segment-3	3 (42.85%)	4 (57.15%)	6 (75.00%)	2 (25.00%)	9 (60.00%)	6 (40.00%)
Segment-4a	9 (47.36%)	10 (52.64%)	8 (53.33%)	7 (46.67%)	17 (50.00%)	17 (50%)
Segment-4b	3 (50.00%)	3 (50.00%)	3 (75.00%)	1 (25.00%)	6 (60.00%)	4 (40%)
Segment-5	9 (40.90%)	13 (59.10%)	17 (73.91%)	6 (26.09%)	26 (57.77%)	19 (42.23%)
Segment-6	9 (40.90%)	13 (59.10%)	11 (55.00%)	9 (45.00%)	20 (47.61%)	22 (52.39%)
Segment-7	8 (40.00%)	12 (60.00%)	6 (40.00%)	9 (60.00%)	14 (40.00%)	21 (60.00%)
Segment-8	11 (36.66%)	19 (63.34%)	14 (53.84%)	12 (46.16%)	25 (44.64%)	31 (55.36%)
The shortest vascular distance* (n)						
≤3 mm (n)	14 (43.75%)	18 (56.25%)	11 (55.00%)	9 (45.00%)	25 (48.07%)	27 (51.93%)
>3 mm (n)	43 (39.09%)	67 (60.91%)	60 (60.00%)	40 (40.00%)	103 (49.04%)	107 (50.96%)

†Mean values are given as millimeters with their ± standard deviations. *The percentages in parentheses show the individual distributions of frequencies within the CRC, HCC, and Total groups, depending on which ablation technique was chosen. A-P, anterior-posterior diameter; C-C, craniocaudal diameter; CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; R-L, right-left diameter; RFA, radiofrequency ablation; MWA, microwave ablation.

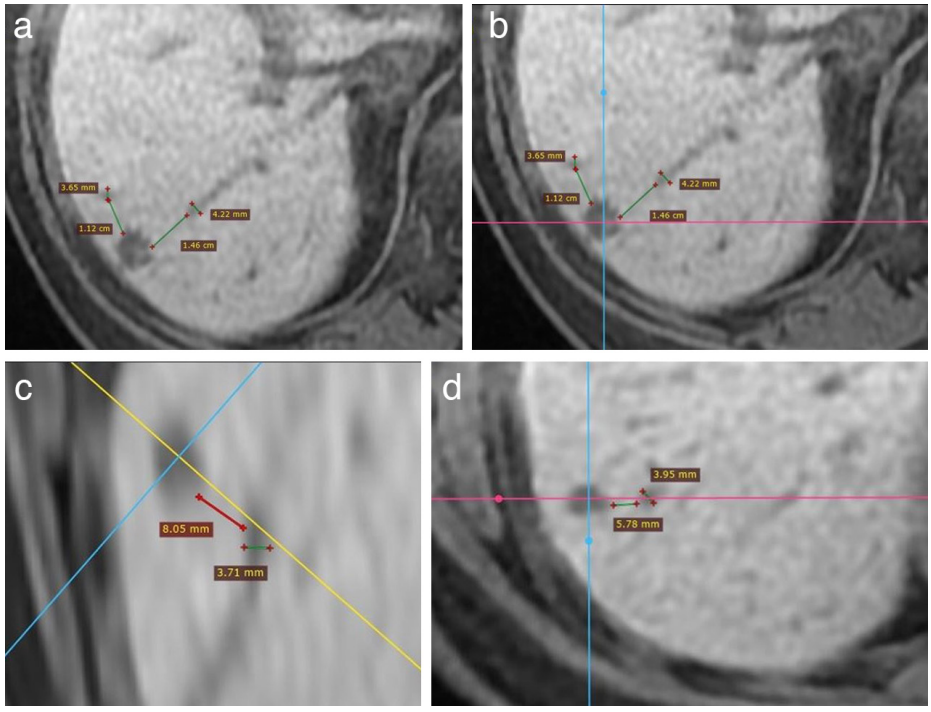

Figure 2. The measurement of the shortest vascular distance. Dynamic T1W volume sections in a patient with CRC metastasis in segment 6 are shown **(a)**. Two vessels with the smallest distance to the lesion, 1.12 mm and 1.46 mm and a width of approximately 4 mm, (3.65 mm and 4.22 mm, respectively) are seen in the axial sections. To determine the exact distance, the dimensional indicators were centered on the lesion **(b)**. Rotating through 360 degrees in the coronal and sagittal planes **(c)**, the closest vessel distance was sought. On this plane represented with the yellow line **(c)**, the exact distance was determined to be 5.78 mm in the axial-oblique section **(d)**. CRC, colorectal carcinoma.

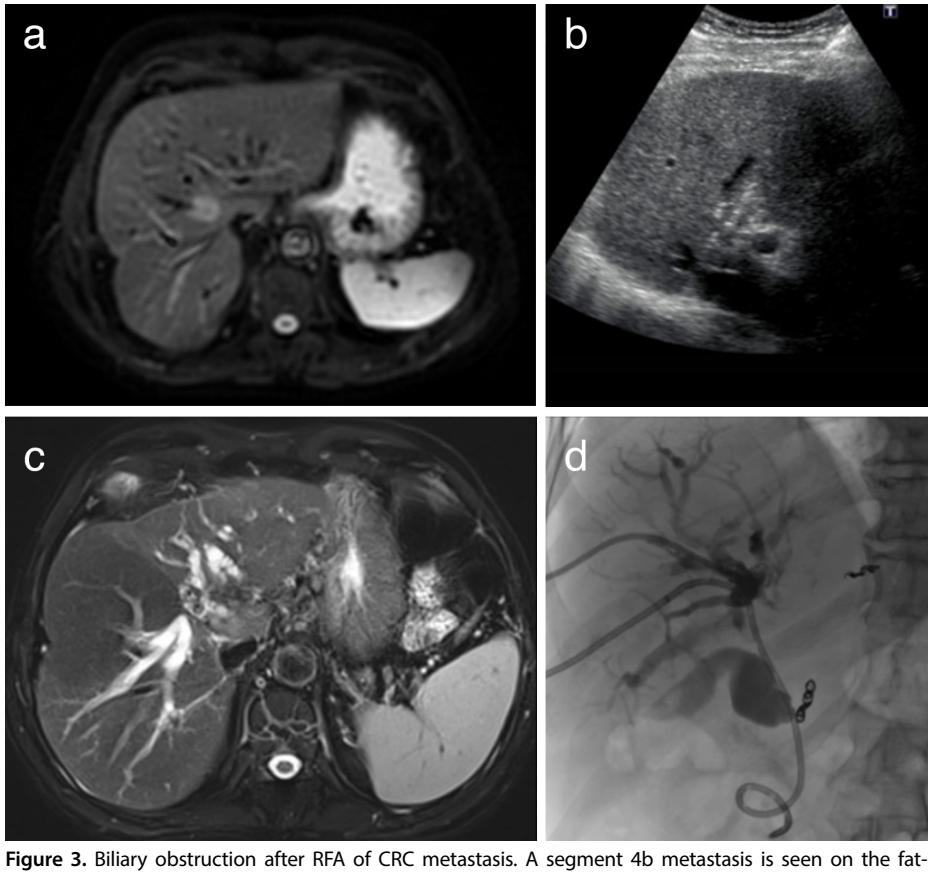

Figure 3. Biliary obstruction after RFA of CRC metastasis. A segment 4b metastasis is seen on the fat-suppressed T2-weighted slice **(a)**. Ultrasound-guided percutaneous radiofrequency ablation is performed **(b)**. Approximately nine months after the procedure, the patient developed biliary dilatation **(c)** due to the central ablation scar, and percutaneous biliary drainage **(d)** was performed. RFA, radiofrequency ablation; CRC, colorectal carcinoma.

Residue occurred in three CRLM (MWA: RFA: 0:3) and four (MWA: RFA: 1:3) HCC lesions, and six of seven residual lesions (out of 262 lesions) were observed after RFA (P = 0.127). Moreover, all six of them had a diameter of 30–50 mm (P < 0.001). For all lesions with residual occurrences, that were reablated with complete ablation, were included in the cohort from the time of complete ablation.

More detailed information on complications and residue is shown in Table 2.

Correlations of common variables with local tumor progression development and local progression-free survival

Regarding the ablation type (MWA or RFA), no statistically significant difference was found for LTP development and Loc-PFS in the CRC group (P = 0.141 and P = 0.161, respectively). In the HCC group, no correlation was found between the development of LTP and Loc-PFS considering the ablation type (P = 0.771 and P = 0.699, respectively).

The development rate of LTP in CRLM was statistically significant in those with a lesion diameter of 30–50 mm (P = 0.019). Loc-PFS also decreased in this group but failed to reach a statistically significant result (P = 0.085). In HCC lesions with a lesion diameter of 30–50 mm, a statistically significant correlation was observed between both LTP development and Loc-PFS (P < 0.001 for both).

The shortest vascular distance of ≤3 mm in both HCC and CRLM was statistically associated with both LTP development (P < 0.001 for each group) and decreased Loc-PFS (P < 0.001 and P = 0.014, respectively).

More detailed information on the common variables of both groups can be found in Tables 3 and 4.

Multivariable analysis and correlations of colorectal carcinoma-specific variables with local tumor progression and local progression-free survival

In the Cox regression analysis for the CRC-specific variable model (Supplementary Table 1), the P value was 0.0006.

Mutated K-ras oncogene was found to be statistically correlated with both LTP development and decreased Loc-PFS (P < 0.001 and P = 0.021, respectively). Similar results were observed with the existence of concomitant lung metastasis for both LTP development and decreased Loc-PFS (P = 0.003 and P = 0.044, respectively). Although LTP

Table 2. Residue, complications, and puncture type

	Colorectal cancer		Hepatocellular carcinoma		Total	
	RFA	MWA	RFA	MWA	RFA	MWA
Percutaneous thermoablation†						
Patients (n)	25 (56.81%)	19 (43.19%)	28 (57.14%)	21 (42.86%)	53 (56.98%)	40 (43.02%)
Lesions (n)	49 (49.49%)	50 (50.51%)	58 (58.58%)	41 (41.42%)	107 (54.04%)	91 (45.96%)
Complications						
Biliary dilatation						
Patients (n)	2	-	2	-	4	-
Lesions (n)	2	-	2	-	4	-
Localization	Segment-4b **(1)** Segment-5 **(1)**	-	Segment-5 **(2)**	-	Segment-4b **(1)** Segment-5 **(4)**	-
Abscess						
Patients (n)	-	-	3	-	3	-
Lesions (n)	-	-	3	-	3	-
Localization	-	-	Segment-6 **(2)** Segment-8 **(1)**	-	Segment-6 **(2)** Segment-8 **(1)**	-
Costochondritis						
Patients (n)	-	-	1	-	1	-
Lesions (n)	-	-	1	-	1	-
Localization	-	-	Segment-8 **(1)**	-	Segment-8 **(1)**	-
Intra-operative thermoablation†						
Patients (n)	6 (30.00%)	14 (70.00%)	7 (58.33%)	5 (41.67%)	13 (40.62%)	19 (59.38%)
Lesions (n)	8 (18.60%)	35 (81.40%)	13 (61.90%)	8 (38.10%)	21 (32.81%)	43 (67.19%)
Complications						
Biliary dilatation						
Patients (n)	-	2	1	-	1	2
Lesions (n)	-	2	1	-	1	2
Localization	-	Segment-1 **(1)** Segment-5 **(1)**	Segment-4b **(1)**	-	Segment-4b (1)	Segment-1 **(1)** Segment-5 **(1)**
Abscess						
Patients (n)	1	3	1	1	2	4
Lesions (n)	1	3	1	1	2	4
Localization	Segment-5 **(1)**	Segment-5 **(1)** Segment-7 **(2)**	Segment-5 **(1)**	Segment-4a **(1)**	Segment-5 **(2)**	Segment-4a **(1)** Segment-5 **(1)** Segment-7 **(2)**
Residue*						
Patients (n)	3	-	**3**	**1**	**6**	**1**
Lesions (n)	3	-	**3**	**1**	**6**	**1**
Lesion diameter (n) (m)	3	-	**3**	**0**	**6**	**0**
Shortest vascular distance (n) (≤3 mm)	0	-	**0**	**1**	**0**	**1**

†The percentages in parentheses after the frequency values show individual distributions within groups (CRC, HCC, and total), depending on which ablation technique was chosen. Bold parentheses after the segments show the segmental distribution. *For all lesions with residual occurrences that were reablated with complete ablation and were included in the cohort from the time of complete ablation. CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; MWA, microwave ablation.

development and decreased Loc-PFS were more associated with right-sided CRLM, no statistically significant results were observed ($P = 0.064$ and $P = 0.358$, respectively).

Although microsatellite instability was also analyzed in all patients, it was not detected in any of them.

In the multivariable analysis for CRLMs, the shortest vascular distance of ≤3 mm was found to be the variable with the largest negative effect on Loc-PFS ($P = 0.007$), followed by concomitant lung metastasis ($P = 0.027$).

More detailed information on CRC-specific variables and multivariable analysis can be found in Table 3 and Supplementary Table 1.

Multivariable analysis and correlations of hepatocellular carcinoma-specific variables with local tumor progression and local progression-free survival

In the Cox regression analysis for the HCC-specific variable model (Supplementary Table 1), the *P* value was 0.0002.

Child–Pugh B, a serum AFP level of >10 ng/mL, and moderate histopathological differentiation showed a highly significant statistical correlation with both LTP development and decreased Loc-PFS ($P < 0.001$, $P = 0.008$, and $P < 0.001$, respectively).

Poor histopathologic differentiation was not observed in the entire HCC cohort.

The LTP development rate in lesions with HBV was statistically significant ($P = 0.027$). However, although Loc-PFS decreased in this group, no statistically significant results were obtained ($P = 0.210$).

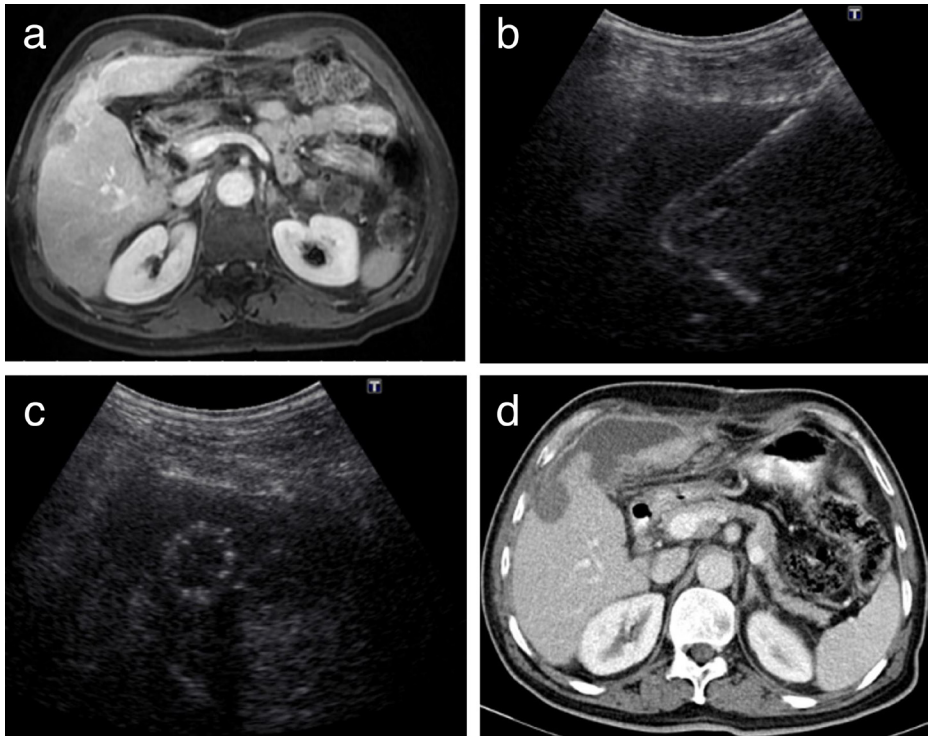

Figure 4. Abscess formation after MWA of CRC metastasis. A segment-5 metastasis is visible on the portal venous phase enhanced MRI **(a)**. Ultrasound-guided intraoperative MWA and the ablation zone with echogenic borders are seen **(b, c)**. On the fourth day after surgery, an abscess associated with the ablation zone and subcapsular suppuration were observed on contrast-enhanced abdominal CT examination **(d)**, which was performed after the addition of fever to persistent right upper quadrant pain. CRC, colorectal carcinoma; MWA, microwave ablation; CT, computed tomography; MRI, magnetic resonance imaging.

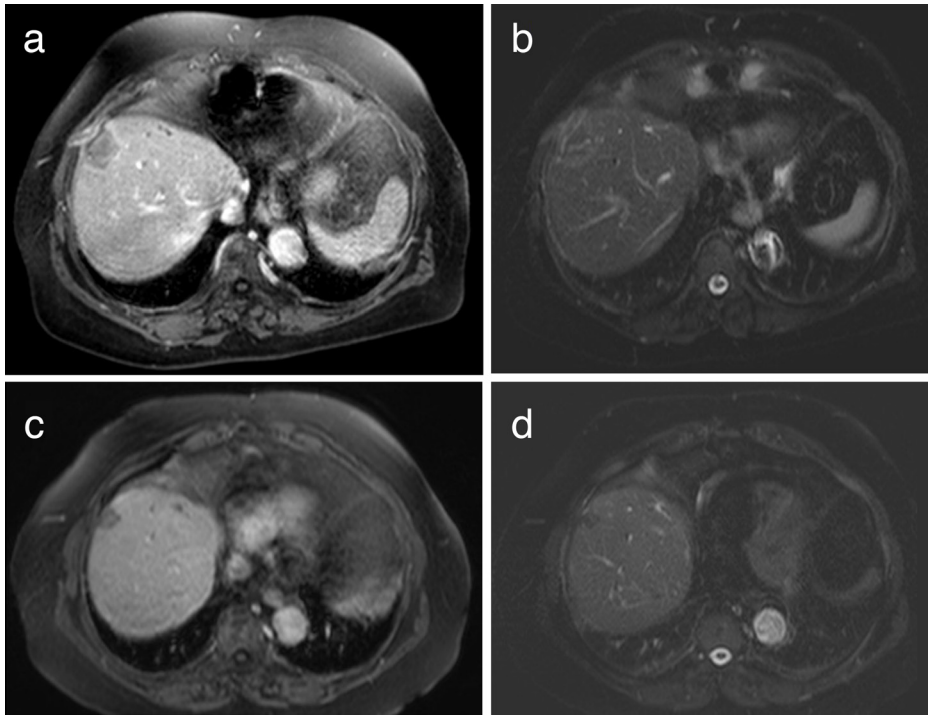

Figure 5. Costochondritis after RFA of HCC. A patient with segment 8 HCC who underwent RFA one month ago has right upper quadrant pain that does not resolve. Follow-up MRI in the first month shows a costochondral inflammatory signal increase adjacent to the ablation zone in the postcontrast T1 **(a)** and fat-suppressed T2 slices **(b)**. At the sixth month follow-up, the postcontrast fat-suppressed T1 **(c)** and fat-suppressed T2 **(d)** slices show a regression of costochondral inflammation and a shrunken ablation cavity. RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging.

In the multivariable analysis for HCC lesions, a serum AFP level of >10 ng/mL was found to be the variable with the largest negative effect on Loc-PFS ($P = 0.045$).

More detailed information on HCC-specific variables and multivariable analysis can be found in Table 4 and Supplementary Table 1.

Discussion

This study's results showed that in both CRLM and HCC lesions, albeit with lower LTP rates in the lesions treated with MWA, there was no significant difference between RFA and MWA. In contrast, two other common variables in both lesion groups were statistically associated with LTP: the shortest vascular distance of ≤3 mm and a lesion diameter of 30–50 mm. Important results were obtained from the observations for tumor-specific variables. A significant correlation of CRC-specific variables was observed with mutant K-ras and concomitant lung metastasis, while the same was observed for HCC-specific variables with Child–Pugh B, a serum AFP level of >10 ng/mL, HBV, and moderate histopathological differentiation.

Extensive meta-analyses have shown that the most important difference in the clinical outcome between MWA and RFA is the size of the larger liver lesion treated, with RFA having some possible disadvantages over LTP.[9,16,17] In this study, although residues were seen more frequently in tumors treated with RFA, all of these lesions were 30–50 mm in diameter. Although no statistically significant results were obtained in this cohort, LTP was more frequent, and Loc-PFS was shorter in patients treated with RFA. In accordance with this study, numerous articles have been published in the literature showing the association of tumor size and shortest vascular distance with LTP.[7,11,18-20]

Recent retrospective studies have shown a strong correlation between the K-ras mutation, which is one of the CRC-specific variants, and LTP.[21,22] In the study by Jiang et al.[23], which is one of the most recent studies conducted in this context, similar results were obtained, but they only included lesions with RFA. The second tumor-specific variable studied in CRLM lesions was the primary origin of the tumor. There are few studies in the literature that address primary origins. Zhou et al.[24], who studied patients with MWA, and Gu et al.[25], who studied patients with RFA, conduct-

Table 3. LTP development and Loc-PFS of CRLMs

	LTP development			Loc-PFS				
	Developed	Not developed	*P* value*	1-year survival	3-year survival	5-year survival	Median survival (months)	*P* value*
Ablation type								
MWA	15 (17.64%)	70 (82.36%)	0.141	80.00% (n = 64)	43.52% (n = 37)	29.41% (n = 25)	57.26	0.161
RFA	16 (28.07%)	41 (71.93%)		73.68% (n = 42)	68.42% (n = 39)	68.42% (n = 39)	98.31	
Lesion diameter								
<30 mm	19 (16.52%)	96 (83.48%)	0.019	74.78% (n = 86)	60.00% (n = 69)	49.56% (n = 57)	78.41	0.085
3–50 mm	12 (44.44%)	15 (55.55%)		74.07% (n = 20)	25.92% (n = 7)	25.92% (n = 7)	45.74	
The shortest vascular distance								
≤3 mm	23 (71.87%)	9 (28.13%)	<0.001	62.50% (n = 20)	37.50% (n = 12)	15.62% (n = 5)	8.06	<0.001
>3 mm	8 (7.27%)	102 (92.73%)		78.18% (n = 86)	58.18% (n = 64)	53.63% (n = 59)	78.11	
K-ras oncogene								
Wild	5 (6.75%)	69 (93.25%)	<0.001	83.78% (n = 62)	77.02% (n = 57)	77.02% (n = 57)	47.02	0.044
Mutated	26 (38.23%)	42 (61.77%)		61.76% (n = 42)	27.94% (n = 19)	10.29% (n = 7)	105.71	
Right/left sided								
Right colon	10 (34.48%)	19 (65.52%)	0.064	75.86% (n = 22)	48.27% (n = 14)	31.03% (n = 9)	40.77	0.358
Left colon	21 (18.58%)	92 (81.42%)		74.33 (n = 84)	54.86% (n = 62)	48.67% (n = 55)	87.13	
Concomitant lung metastasis								
Yes	14 (40.00%)	21 (60.00%)	0.003	42.85% (n = 15)	25.71% (n = 9)	25.71% (n = 9)	22.32	0.021
No	17 (15.88%)	90 (84.12%)		77.77% (n = 91)	57.26% (n = 67)	47.01% (n = 55)	87.11	

*These *P* values indicate the results of univariate Cox regression analysis. RFA, radiofrequency ablation; MWA, microwave ablation; LTP, local tumor progression; Loc-PFS, local progression-free survival; CRLM, colorectal cancer liver metastasis.

Table 4. LTP development and Loc-PFS of HCC lesions

	LTP Development			Loc-PFS				
	Developed	Not developed	*P* value	1-year survival	3-year survival	5-year survival	Median survival (months)	*P* value *
Ablation type								
MWA	6 (12.24%)	43 (87.76%)	0.771	57.14% (n = 28)	57.14% (n = 28)	57.14% (n = 28)	60.36	0.699
RFA	10 (14.08%)	61 (85.92%)		76.05% (n = 54)	54.92% (n = 39)	54.92% (n = 39)	77.33	
Lesion diameter								
<30 mm	7 (7.14%)	91 (92.86%)	<0.001	71.42% (n = 70)	64.28% (n = 63)	64.28% (n = 63)	26.72	<0.001
30–50 mm	9 (40.90%)	13 (59.10%)		54.54% (n = 12)	18.18% (n = 4)	18.18% (n = 4)	100.60	
The shortest vascular distance								
≤3 mm	10 (50.00%)	10 (50.00%)	<0.001	40.00% (n = 8)	25.00% (n = 5)	25.00% (n = 5)	45.82	0.014
>3 mm	6 (6.00%)	94 (94.00%)		74.00% (n = 74)	62.00% (n = 62)	62.00% (n = 62)	82.94	
Serum AFP level								
≤10 ng/mL	1 (2.32%)	42 (97.68%)	0.008	95.34% (n = 41)	95.34% (n = 41)	95.34% (n = 41)	118.06	<0.001
>10 ng/mL	15 (19.48%)	62 (80.52%)		53.24% (n = 41)	33.76% (n = 26)	33.76% (n = 26)	22.72	
Child–Pugh score								
Child-A	5 (5.81%)	81 (94.19%)	<0.001	82.55% (n = 71)	73.25% (n = 63)	73.25% (n = 63)	98.36	
Child-B	11 (32.35%)	23 (67.65%)		32.35% (n = 11)	11.76% (n = 4)	11.76% (n = 4)	12.02	<0.001
Cellular differentiation								
Well	2 (2.35%)	83 (97.65%)	<0.001	84.70% (n = 72)	78.82% (n = 67)	78.82% (n = 67)	106.33	<0.001
Moderate	14 (40.00%)	21 (60.00%)		28.57% (n = 10)	0.00% (n = 0)	0.00% (n = 0)	11.63	
Predisposing factor								
HBV	12 (23.07%)	40 (76.93%)	0.027	50.00% (n = 26)	42.30% (n = 22)	42.30% (n = 22)	49.10	0.210
HCV	3 (8.10%)	34 (91.90%)		78.37% (n = 29)	48.64% (n = 18)	48.64% (n = 18)	82.35	
NASH	1 (3.22%)	30 (96.78%)		87.09% (n = 27)	87.09% (n = 27)	87.09% (n = 27)	49.98	

*These *P* values indicate the results of univariate Cox regression analysis. HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; LTP, local tumor progression; Loc-PFS, local progression-free survival; HCC, hepatocellular carcinoma; MWA, microwave ablation.

ed their studies considering "patient-based" survival and observed better outcomes in patients with left-sided primary origin. In this "lesion-based" study, where more variables were considered, LTP was observed more frequently in CRLMs originating from the right colon. However, the study failed to achieve significant results. Concomitant lung metastasis, another CRC-specific variable, is one of the most important variables affecting survival and LTP.[26,27] In the study by Shady et al.[26], which only included patients with RFA, the presence of lung metastases was targeted as one of the most important prognostic factors. In this study, which included more comprehensive variables, the presence of lung metastases had an impact on LTP and Loc-PFS, and it proved to be more important than the primary origin of metastases and K-ras mutations. This suggests that concomitant lung metastases may be an important overall indicator of aggressive neoplastic behavior. Moreover, in the multiples analysis, it was found to be the second most important factor in lowering Loc-PFS after the shortest vascular distance of ≤3 mm.

There are numerous articles in the literature that include HCC-specific variants. One of the largest prospective studies that included patients with RFA and MWA, by Chong et al.[28] and Vietti Violi et al.[29], examined predisposing factors, the Child–Pugh score, and AFP levels, but they were not included in the statistical analysis. In another study comparing RFA with liver resection, in which 109 patients were treated with RFA, these three HCC-specific variables were included, and no effect of these three variables on "disease-free survival" was reported.[30] In a study examining 48 lesions with RFA, in addition to these three HCC-specific variables, the degree of histopathological differentiation was also included, of which only a high AFP level before ablation was correlated with "intrahepatic distant recurrence".[31] There are other studies that correlate with higher AFP levels.[32,33] In this study, a correlation was found between all these four variables and LTP. In addition, the multiples analysis revealed that the AFP level was the most important variable affecting the poor Loc-PFS outcome. This result is valuable in that it indicates that a host factor such as the AFP level is an important poor prognostic factor that outperforms even a tumor-based variable such as the shortest vascular distance of ≤3 mm or large tumor size.

Complications were also investigated in this study as ancillary findings. Previous retrospective studies have shown that there was no difference in safety between ablation types.[8,34,35] A significant association was found between the occurrence of complications and intraoperative ablation, either when only the abscess or all complications were included. This could be due to a more invasive procedure and greater surface area of the peritoneum. There was also a strong correlation between the dilation of the bile duct and the ablation of the central segments (segments 1, 4b, and 5). It is understandable that the ablation of zones closer to the portal hilum may lead to this biliary obstruction. Costochondritis was observed in only one patient with a subcapsular lesion. The ablation of a subcapsular lesion in close proximity to the costochondral arcus may have caused this inflammation. This is the first time such a case was reported with the corresponding images.

This study has some limitations. First, it is a single-center, retrospective study. However, it represents the results of a large tertiary oncology center with a long-established thermal ablation protocol. Second, although an inspection was carried out, no patients with CRC with microsatellite instability and no patients with HCC with poor histopathological morphology were detected. Third, there were only three predisposing factors for chronic liver disease, and no other chronic liver diseases were included. However, this study provides a suitable basis for future thermal ablation studies to include more tumor-specific variables.

In conclusion, large tumor size and the shortest vascular distance of ≤3 mm are important factors with effects on LTP. However, host variables such as concomitant lung metastasis in patients with CRC and high pre-ablation AFP levels in patients with HCC may be important indicators of poor prognosis. Prospective randomized studies with tumor-specific variables and spatial characteristics are needed to explain the exact effects.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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Supplementary Table 1. Results of the Cox regression and multiples analysis of the variables' effect on Loc-PFS*

	Hazard ratio	Confidence interval (95%)	P value
CRLM			
Ablation technique (MWA vs. RFA)	0.619	0.166–2.311	0.476
K-ras (Mutant vs. wild)	1.940	0.520–7.229	0.323
Lesion diameter (30–50 mm vs. <30 mm)	1.065	0.348–3.259	0.911
Concomitant lung metastasis (yes vs. no)	6.437	1.661–24.946	0.027
SVD (≤3 mm vs. >3 mm)	6.604	1.065–40.941	0.007
HCC			
Serum AFP level (>10 ng/mL vs. ≤10 ng/mL)	6.323	1.038–38.494	0.045
Cellular differentiation (moderate vs. poor)	2.134	0.915–8.191	0.068
Child–Pugh score (Child-B vs. Child-A)	2.510	0.611–10.303	0.101
Lesion diameter (30–50 mm vs. <30 mm)	1.329	0.433–4.079	0.618
SVD (≤3 mm vs. >3 mm)	1.924	0.894–3.917	0.090

*Only variables with $P < 0.20$ values were included in the multiples analysis. AFP, alpha-feto protein; CRLM, colorectal cancer liver metastasis; HCC, hepatocellular carcinoma; SVD, shortest vascular distance; RFA, radiofrequency ablation; MWA, microwave ablation; Loc-PFS, local progression-free survival.