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ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Prof. Claudio Casella is Associate Professor of Surgery at the University of Brescia, Italy. He graduated from the University of Brescia Medical School in 1987. His post-graduate education culminated with a Digestive Surgery and Endoscopy Surgery degree in 1992. He is currently a general surgeon and oncology and endocrine surgeon specialist. His surgical track-record (in elective, urgent and emergency cases) covers all fields of general surgery, applying traditional and the latest minimally-invasive techniques. His scientific activity focuses on research of hormones and cancers, colorectal cancers, tumor markers in surgical oncology, and endocrine surgery, resulting in over 100 publications of scientific papers and communications in national and international journals. He participated in the International Study Group "Complications after Gastrectomy for Cancer". (L-Editor: Filipodia)

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Retrospective Study

Oncological outcomes and predictors of radiofrequency ablation of colorectal cancer liver metastases

Chuan-Zhuo Wang, Guang-Xin Yan, He Xin, Zhao-Yu Liu

ORCID number: Chuan-Zhuo Wang 0000-0002-7426-2738; Guang-Xin Yan 0000-0002-6686-451X; He Xin 0000-0001-9478-5803; Zhao-Yu Liu 0000-0002-4226-6099.

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Chuan-Zhuo Wang, Guang-Xin Yan, He Xin, Zhao-Yu Liu, Department of Radiology, Shengjing Hospital of China Medical University, Shenyang 110004, Liaoning Province, China

Corresponding author: Zhao-Yu Liu, MD, Chairman, Chief Doctor, Department of Radiology, Shengjing Hospital of China Medical University, No. 36 Sanhao Street, Heping District, Shenyang 110004, Liaoning Province, China. liushjh@163.com

Abstract

BACKGROUND

Surgical resection is considered the standard treatment option for long-term survival in colorectal cancer liver metastasis (CRLM) patients, but only a small number of patients are suitable for resection following diagnosis. Radiofrequency ablation (RFA) is an accepted alternative therapy for CRLM patients who are not suitable for resection. However, the relatively high rate of local tumor progression (LTP) is an obstacle to the more widespread use of RFA.

AIM

To determine the oncological outcomes and predictors of RFA in CRLM patients.

METHODS

A retrospective analyze was performed on the clinical data of 85 consecutive CRLM patients with a combined total of 138 liver metastases, who had received percutaneous RFA treatment at our institution from January 2013 to December 2018. Contrast-enhanced computed tomography was performed the first month after RFA to assess the technique effectiveness of the RFA and to serve as a baseline for subsequent evaluations. The Kaplan-Meier method was used to calculate overall survival (OS) and LTP-free survival (LTPFS). The log-rank test and Cox regression model were used for univariate and multivariate analyses to determine the predictors of the oncological outcomes.

RESULTS

There were no RFA procedure-related deaths, and the technique effectiveness of the treatment was 89.1% (123/138). The median follow-up time was 30 mo. The LTP rate was 32.6% (45/138), and the median OS was 36 mo. The 1-, 3-, and 5-year OS rates were 90.6%, 45.6%, and 22.9%, respectively. Univariate analysis revealed that tumor size and ablative margin were the factors influencing LTPFS, while extrahepatic disease (EHD), tumor number, and tumor size were the factors influencing OS. Multivariate analysis showed that tumor size larger than 3 cm

Data sharing statement: No additional unpublished data are available.

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and ablative margin of 5 mm or smaller were the independent predictors of shorter LTPFS, while tumor number greater than 1, size larger than 3 cm, and presence of EHD were the independent predictors of shorter OS.

CONCLUSION

RFA is a safe and effective treatment method for CRLM. Tumor size and ablative margin are the important factors affecting LTPFS. Tumor number, tumor size, and EHD are also critical factors for OS.

Key Words: Colorectal cancer liver metastasis; Radiofrequency ablation; Local tumor progression; Local tumor progression-free survival; Overall survival

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Core Tip: Relatively high rate of local tumor progression (LTP) is an obstacle to more widespread use of radiofrequency ablation (RFA) in colorectal cancer liver metastasis (CRLM) patients. The purpose of this retrospective study was to determine the oncological outcomes and predictors of RFA in CRLM patients. The median overall survival (OS) of the 85 patients was 36 mo, and the rate of LTP was 32.6% in 138 lesions. Multivariate analysis showed that tumor size and ablative margin were independent predictors of LTP-free survival, while tumor number, tumor size, and extrahepatic disease were independent predictors of OS.

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INTRODUCTION

Colorectal cancer (CRC) is among the most common malignant tumors of the gastrointestinal system. In 2018, for example, more than 1.1 million individuals were diagnosed with CRC worldwide and the number of deaths exceeded 550000^[1,2]. In CRC, most disease-related deaths are secondary to metastatic disease, with the liver being the most common site of metastasis^[3]. It has been reported that more than half of CRC patients develop liver metastases during disease progression^[4,5]. The survival and prognosis of patients therefore depend on how effective the treatment is. Surgical resection is considered the first-line treatment for the cure or long-term survival of colorectal cancer liver metastasis (CRLM) patients, with 5-year overall survival (OS) rates of 32%-58%^[5-10]. Unfortunately, when the patient's clinical state and the surgical resection criteria are taken into consideration, only 10%-20% of patients are suitable for resection at the time of diagnosis of liver metastasis^[11,12].

Image-guided radiofrequency ablation (RFA) is widely used in clinical practice as an alternative to resection, especially for selected smaller tumors that can be ablated with margins^[13,14]. RFA combined with chemotherapy increases the 5-year OS rate of patients with unresectable CRLM to 24%-48%, which is close to that of patients undergoing surgical resection^[15-17]. Moreover, the left lobe of the liver can be well visualized using endoscopic ultrasound (EUS)^[18-21], making it possible to perform EUS-PFA^[22]. In addition, RFA has been shown to be safe, with few side effects; being a minimally invasive treatment, the rate of major complications of RFA is 0.9%-7.2% and the mortality rate is less than 1%^[23,24]. Despite these gratifying results, however, the relatively high local tumor progression (LTP) rate is still an obstacle to the widespread use of RFA^[25,26].

The aim of this study was to determine the oncological outcomes of CRLM after RFA, to evaluate the risk predictors affecting OS and LTP-free survival (LTPFS), to identify the group of CRLM patients who benefit most from RFA, and to provide a reference framework for personalized treatment strategies.

MATERIALS AND METHODS

Study population

In compliance with the principles of the World Medical Association Declaration of Helsinki, patients in this retrospective study were exempt from the need to provide informed consent, and the study was approved by the Medical Ethics Committee of Shengjing Hospital of China Medical University. Between January 2013 and December 2018, 85 consecutive CRLM patients who received percutaneous RFA were enrolled in the study and followed until January 2019. The patients comprised 56 males and 29 females, with a mean age of 59.1 ± 10.9 years (range, 35–76 years). A total of 138 liver metastases were detected in these 85 patients, with a mean tumor size of 2.8 ± 1.0 cm (range, 0.8–5.0 cm). Of these 85 patients, 45 had a single lesion, 27 had two lesions, and 13 patients had three lesions, with a mean of 1.6 ± 0.7 lesions per patient. Twenty-two (25.9%) out of the 85 patients had imaging evidence of extrahepatic disease (EHD), which was located in the lungs ($n = 14$), lymph nodes ($n = 4$), lungs and lymph nodes ($n = 3$), and a solitary vertebral body ($n = 1$). Sixty-three (74.1%, 63/85) patients were considered unsuitable for hepatectomy, because of multiple liver metastases, EHD, unfavorable tumor location, or comorbidities. The other 22 (25.9%, 22/85) patients refused surgical intervention. Seventy-six (89.4%, 76/85) patients underwent systemic chemotherapy regimens prescribed by oncologists, such as irinotecan, leucovorin and 5-fluorouracil, and oxaliplatin, leucovorin, and 5-fluorouracil. We stopped chemotherapy for 2 wk or so before RFA treatment took place, without any intervention in the actual chemotherapy regimen.

All CRLM patients were treated with RFA under the following conditions: Surgical resection of colorectal tumors had been performed and histopathological results had confirmed primary colorectal malignant tumors; imaging evidence supported the diagnosis of liver metastasis; the number of intrahepatic metastases was 3 or less and the maximum diameter was 5 cm or smaller; there were no uncorrectable coagulation abnormalities; and they were not candidates for resection of the metastases or had refused surgical resection. All patients provided informed consent before undergoing RFA. RFA procedures were performed under computed tomography (CT) guidance, local anesthesia, analgesia, and hemodynamic monitoring. CelonLab POWER (Olympus Surgical Technologies Europe, Hamburg, Germany) or RF3000 Radio Frequency Generator (Boston Scientific, Natick, MA, United States) was used, depending on the tumor size, shape, location, and the operator's preference. According to the manufacturer's instructions, impedance-based control of the generator was adjusted to transmit the radiofrequency energy. For larger tumors, RFA was performed repeatedly to create overlapping ablation zones and safe ablative margins (≥ 5 mm, ideally > 10 mm).

Follow-up

Contrast-enhanced CT examination was performed the first month after RFA treatment to assess the technique effectiveness and to serve as a new baseline for future comparisons. Additional CT examinations were performed every 2 to 4 mo to evaluate the progression of the disease. Additional MRI or PET/CT were performed for those patients with an unclear diagnosis. According to standardized terminology and reporting criteria for tumor ablation^[27,28], technique effectiveness is defined as no evidence of residual tumor within 1 cm of the ablation defect; LTP is defined as any new peripheral or nodular enhancement within 1 cm or enlargement of the baseline ablation defect. Patients with multiple new intrahepatic lesions and/or new extrahepatic lesions detected during follow-up were not considered for RFA re-treatment, while patients with a single new intrahepatic lesion and/or LTP lesions were considered for RFA re-treatment.

Complications

Complications were classified as either major or minor. Major complications were defined as those events that led to an increased level of care, prolonged hospital stay, or that caused permanent adverse sequelae, including any cases requiring blood transfusion or interventional drainage^[29]. Any other complications were classified as minor.

Statistical analysis

SPSS 16.0 software (SPSS, Inc., Chicago, IL, United States) was used for data analyses. Continuous variables are presented as the mean \pm SD and categorical variables are expressed as frequencies (percentages). The primary endpoints of the study were the

OS for each patient and the time of LTPFS for each tumor. The Kaplan-Meier method was used to calculate OS and LTPFS from the time of RFA as well as to plot the survival curve. The log-rank test was used for univariate analysis. Variables with $P < 0.05$ in the univariate analysis were introduced into the Cox multivariate regression model to identify independent predictors affecting OS and LTPFS and to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). $P < 0.05$ was considered statistically significant.

RESULTS

A total of 140 RFA sessions were performed on 138 CRLM lesions in 85 patients, of whom 56 received one session of RFA, 12 received two sessions, ten received three sessions, five received four sessions, and two received five sessions. All RFA procedures were completed as planned. A total of 123 out of 138 lesions showed complete ablation at the first month of enhanced CT follow-up, with a technique effectiveness rate of 89.1%. The failures of the first ablation of 15 CRLM lesions were related to poor tumor coverage by the ablation area due to the large tumor volume, irregular morphology requiring overlapping ablation, or tumor proximity to larger vessels leading to heat loss.

Local tumor progression

The median follow-up time of 138 CRLM lesions in the 85 patients was 30 mo. The clinical features are shown in Tables 1 and 2. By the end of follow-up, 45 (32.6%, 45/138) lesions in 42 (49.4%, 42/85) patients developed LTP. Of these, 32 (23.2%, 32/138) LTP lesions were found in 29 (34.1%, 29/85) patients in the first year, and eight (5.8%, 8/138) LTP lesions were found in eight (9.4%, 8/85) patients in the second year. Thus, 71.1% (32/45) of LTP lesions occurred within the first year after RFA, and 88.9% (40/45) occurred by the end of the second year.

Of the 45 LTP lesions in the 42 patients, 31 (68.9%, 31/45) LTP lesions in 29 (69.0%, 29/42) patients received RFA re-treatment; while 14 (31.1%, 14/45) LTP lesions in 13 (31.0%, 13/42) patients did not receive RFA re-treatment due to disease progression or patient preference. Among 31 re-treated LTP lesions, 17 (54.8%, 17/31) LTP lesions in 16 (55.2%, 16/29) patients were controlled, while 14 (45.2%, 14/31) LTP lesions in 13 (44.8%, 14/29) patients were not controlled. In summary, the CRLM lesions of 69.4% (59/85) patients were controlled by repeated RFA. The total control rate of CRLM lesions was 79.7% (110/138).

The log-rank univariate analysis showed that gender, age, location of primary tumor, TNM stage, tumor differentiation, liver resection history, EHD, and tumor number had no significant effect on LTPFS (Table 1, $P > 0.05$). However, tumor size larger than 3 cm and ablative margin of 5 mm or smaller were associated with shorter LTPFS (Figure 1, $P < 0.05$). By introducing the above two variables into the multivariate Cox model, tumor size larger than 3 cm ($P < 0.001$, HR = 3.712, 95%CI: 1.894-7.277) and ablative margin of 5 mm or smaller ($P = 0.003$, HR = 3.077, 95%CI: 1.479-6.405) were shown to be independent predictors of shorter LTPFS (Table 1). In addition, of the 15 lesions with ablative margin more than 10 mm, only one lesion developed LTP. The LTP rate was thus 6.7% (1/15). Among the 12 lesions with ablative margin of 0 mm, 11 lesions developed LTP, thus the LTP rate for no ablative margin was 91.7% (11/12).

Overall survival

The median OS of the 85 patients was 36 mo. The 1-, 3-, and 5-year OS rates were 90.6%, 45.6%, and 22.9%, respectively. Log-rank univariate analysis indicated that gender, age, location of primary tumor, TNM stage, tumor differentiation, liver resection history, and tumor number had no significant influence on OS (Table 2, $P > 0.05$). However, tumor number greater than 1, tumor size larger than 3 cm, and presence of EHD were associated with shorter OS (Figure 2A-C, $P < 0.05$). The multivariate Cox model was used to analyze the above three variables, and the results showed that tumor number greater than 1 ($P = 0.029$, HR = 2.475, 95%CI: 1.099-5.573), tumor size larger than 3 cm ($P = 0.001$, HR = 3.641, 95%CI: 1.732-7.654), and presence of EHD ($P = 0.001$, HR = 3.676, 95%CI: 1.730-7.811) were the independent predictors of shorter OS (Table 2). In this study, the median OS of patients with a single tumor, size of 3 cm or smaller, and no EHD was up to 62 mo, and the 5-year OS rate was 55.5%.

The median OS of 42 patients with LTP and 43 patients who were LTP-free were 33 mo and 50 mo, respectively; the difference was statistically significant (Figure 2D, $P =$

Table 1 Univariate and multivariate analyses for local tumor progression-free survival

Variable	Number of tumors (<i>n</i> = 138)	LTP rate (%)	Univariate	Multivariate	
			<i>P</i> value	HR (95%CI)	<i>P</i> value
Gender			0.052		
Male	91	27.5			
Female	47	42.6			
Age (yr)			0.653		
≤ 60	76	30.3			
> 60	62	35.5			
Location of primary tumor			0.868		
Colon	99	32.3			
Rectum	39	33.3			
TNM classification			0.502		
I, II, or III	81	30.9			
IV	57	35.1			
Tumor differentiation			0.591		
Well or moderate	81	34.6			
Poor	57	29.8			
Previous liver resection			0.120		
No	105	29.5			
Yes	33	42.4			
EHD			0.522		
No	93	32.3			
Yes	45	33.3			
Tumor number			0.799		
1	45	35.6			
2 or 3	93	31.2			
Tumor size			< 0.001	3.712 (1.894-7.277)	< 0.001
≤ 3 cm	86	15.1			
> 3 to 5 cm	52	61.5			
Ablative margin			< 0.001	3.077 (1.479-6.405)	0.003
≤ 5 mm	67	52.2			
> 5 mm	71	14.1			

LTP: Local tumor progression; LTPFS: Local tumor progression-free survival; EHD: Extrahepatic disease; HR: Hazard ratio; CI: Confidence interval.

0.007). Of the 42 patients with LTP, 13 who did not receive RFA re-treatment had a median OS of 19 mo, and 29 who received RFA re-treatment had a median OS of 36 mo; this difference was statistically significant (Figure 2E, *P* = 0.047).

Complications

Minor complication rate for all treatments in this study was 12.1% (17/140), and major complication rate was 4.3% (6/140). The major complications included pneumothorax (*n* = 2), pleural effusion (*n* = 1), biloma (*n* = 1), liver abscess (*n* = 1), and subcapsular hematoma (*n* = 1). All the major complications were improved by percutaneous catheter drainage combined with intravenous antibiotics. No technology-related deaths were reported.

Table 2 Univariate and multivariate analyses for overall survival

Variable	Number of patients (<i>n</i> = 85)	Median OS (mo)	Univariate	Multivariate	
			<i>P</i> value	HR (95%CI)	<i>P</i> value
Gender			0.341		
Male	56	42			
Female	29	35			
Age (yr)			0.504		
≤ 60	44	35			
> 60	41	36			
Location of primary tumor			0.229		
Colon	62	42			
Rectum	23	33			
TNM classification			0.208		
I, II, or III	52	45			
IV	33	33			
Tumor differentiation			0.100		
Well or moderate	56	36			
Poor	29	34			
Previous liver resection			0.084		
No	65	36			
Yes	20	34			
EHD			< 0.001	3.676 (1.730-7.811)	0.001
No	63	50			
Yes	22	26			
Tumor number			< 0.001	2.475 (1.099-5.573)	0.029
1	45	50			
2 or 3	40	26			
Maximum tumor diameter			< 0.001	3.641 (1.732-7.654)	0.001
≤ 3 cm	48	45			
> 3 to 5 cm	37	26			
Minimum ablative margin			0.367		
≤ 5 mm	44	33			
> 5 mm	41	36			

OS: Overall survival; EHD: Extrahepatic disease; HR: Hazard ratio; CI: Confidence interval.

DISCUSSION

Affected by various factors such as tumor location, size, and shape, CRLM is unevenly heated during the RFA process and the surrounding tissue may not reach the temperature required to cause the death of tumor cells. Thus, there may be residual tumor tissue, and this is the main cause of LTP^[29]. In previous studies, the LTP rate in CRLM patients treated with RFA ranged from 3.6% to 60%^[30]. This wide variability may be explained by the differences among study populations and inclusion criteria. Most researchers concur that LTP is an important factor affecting the efficacy of RFA, and early detection and intervention of LTP are crucial in improving treatment outcomes in CRLM patients^[31]. We followed 138 CRLM lesions in 85 patients and found that the LTP rate was 32.6% (45/138) and LTP occurred more frequently in the

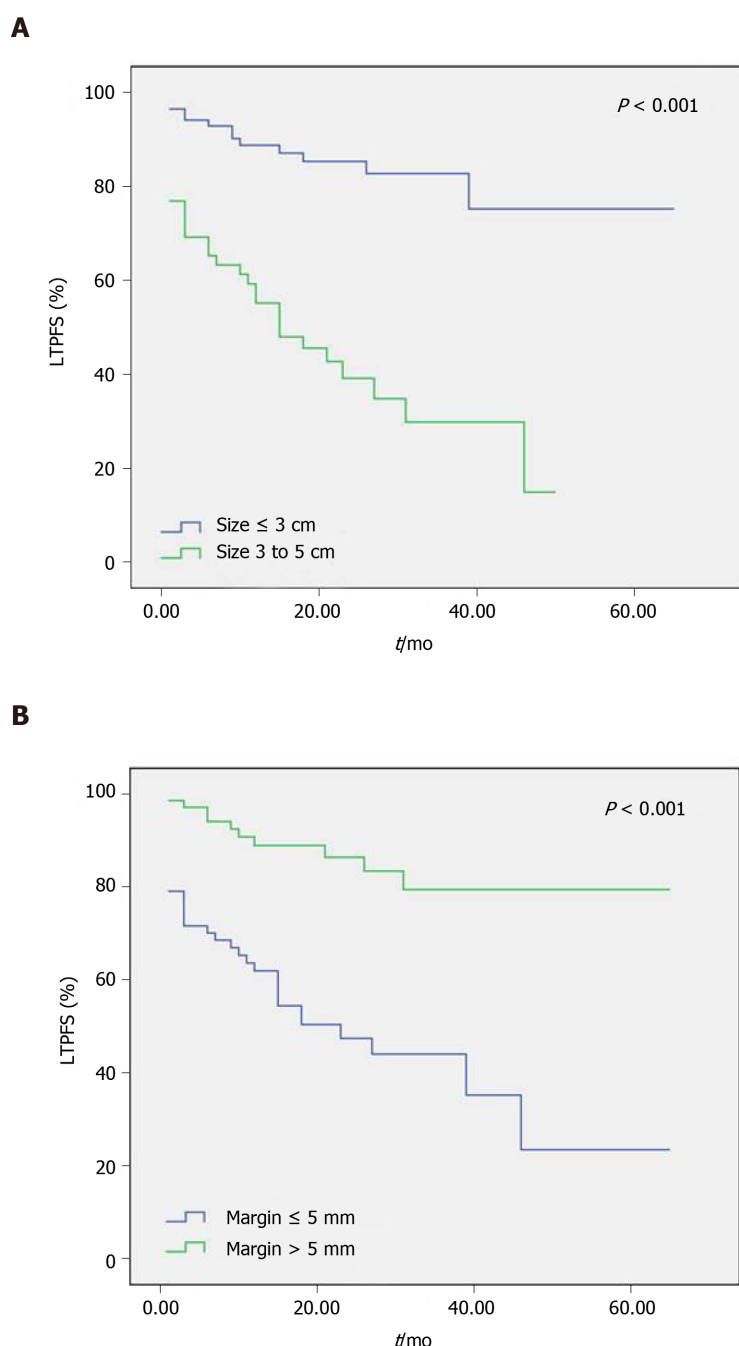


Figure 1 Kaplan-Meier curves of local tumor progression-free survival. A: According to tumor size; B: According to ablative margin. LTPFS: Local tumor progression-free survival.

first year after RFA (71.1%, 32/45).

As the ablation range of the applicator is limited, overlapping ablation is often required to cover large tumors, which increases the risk of LTP. In this study, multivariate analysis shows that tumor size larger than 3 cm ($P < 0.001$, HR = 3.769, 95%CI: 1.921-7.398) was an independent predictor of shorter LTPFS, which is consistent with the results of Shady *et al*^[25] and Hamada *et al*^[32]. Furthermore, surgical margin of liver metastasis is an important factor in predicting recurrence after tumor resection^[33,34]. Similarly in this case, the radiologically estimated ablative margin was used to evaluate oncological outcomes after RFA; ablative margin of 5 mm or smaller ($P = 0.002$, HR = 3.175, 95%CI: 1.524-6.616) was an independent predictor of shorter LTPFS in this study. It is noteworthy that the LTP rate was 91.7% in 12 CRLM lesions with ablative margin of 0 mm, while the LTP rate was only 6.7% in 15 CRLM lesions with ablative margin more than 10 mm. Therefore, expanding the ablative margin is an effective method to prolong LTPFS and local tumor control. Interestingly, the ablative margin was not an independent predictor of OS in patients with CRLM. This

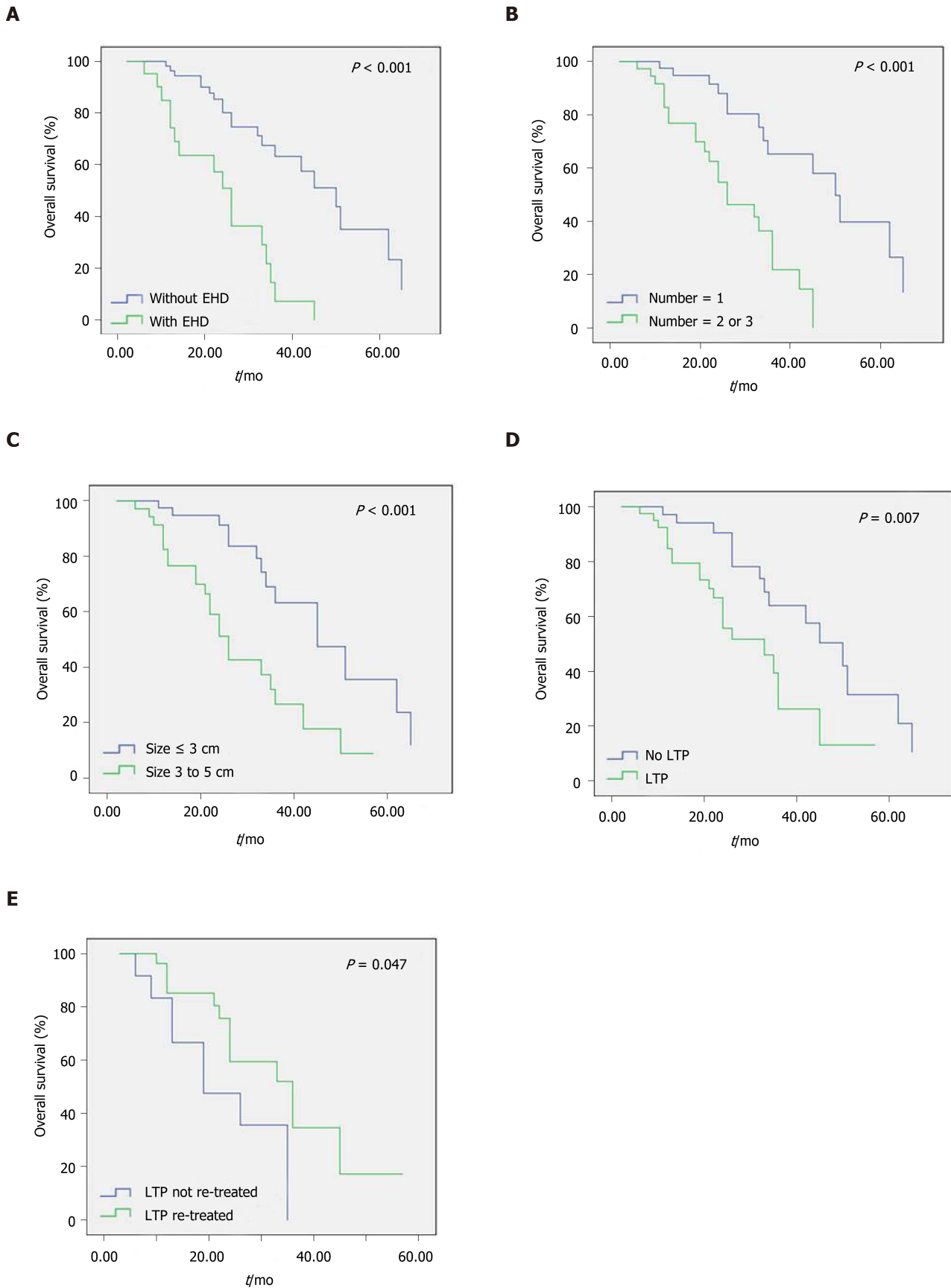


Figure 2 Kaplan-Meier curves of overall survival. A: According to extrahepatic disease; B: According to tumor number; C: According to tumor size; D: According to local tumor progression (LTP); E: According to LTP re-treated. EHD: Extrahepatic disease; LTP: Local tumor progression.

result is similar to that of some surgical resections. As long as the surgical margin of hepatectomy was negative, the width of the margin did not affect the OS of CRLM

patients^[35-37].

The American Society of Clinical Oncology analyzed 73 publications on the RFA treatment of CRLM published from 1996 to 2007. The 1-, 3-, and 5-year OS rates were 72%-95%, 25%-68%, and 17%-31%, respectively, and the median OS was 18-35 mo^[30]. In a 10-year follow-up of 99 patients treated with RFA including 202 small CRLM lesions, Solbiati *et al*^[17] reported that the 5-, 7-, and 10-year OS rates were 47.8%, 25.0%, and 18.0%, respectively, and the median OS of the selected patients was 53.2 mo. Of the 85 patients in this study, 63 were not candidates for hepatectomy and 22 had refused resection. The 1-, 3-, and 5-year OS rates were 90.9%, 47.9%, and 24.3%, respectively, and the median OS was 36 mo.

Many studies have confirmed that the number and size of tumors are important factors affecting OS, regardless of whether surgical resection or RFA is employed^[15,38,39]. Cox multivariate analysis in this study likewise confirmed that multiple metastases and large size (> 3 to 5 cm) were the independent predictors of shorter OS in patients treated with RFA. However, whether or not EHD affects the OS of CRLM patients has been controversial. Gillams *et al*^[15] reported that the presence of EHD significantly affected the survival of CRLM patients after RFA and was an independent predictor of shorter OS, while Berber *et al*^[40] concluded that limited amounts of EHD did not appear to adversely affect survival. Hamada *et al*^[32] claimed that EHD kept under control is not a prognostic factor for OS whereas uncontrolled EHD is a poor survival prognostic factor. Our results show that the median OS was 50 mo for patients without EHD and 26 mo for patients with EHD ($P < 0.001$). The presence of EHD was also an independent predictor of shorter OS after RFA in CRLM patients. Therefore, patients with a single tumor, size of 3 cm or smaller, and no EHD benefit most from RFA, with a median OS of 62 mo and a 5-year OS rate of 55.5%. This result is almost consistent with the 5-year OS rate of 55.4% reported by Hur *et al*^[41].

In addition, our study showed that LTP-free patients had the longest median OS (50 mo). The median OS in LTP patients who received re-treatment (36 mo) was significantly longer than those who did not (19 mo). These data would potentially advocate a more aggressive initial RFA strategy and they demonstrate the advantages of RFA as a repeatable, minimally invasive treatment^[17]. Otto *et al*^[42] compared the oncology results of resection and RFA in the treatment of solitary colorectal liver metastasis; although the LTP rate in the RFA group is higher than that of the surgical resection group, the 3-year OS rates are similar. The authors attribute similar ratios of tumor-free patients in both groups to the repeatability of RFA (61% in one and 62% in the other). LTP occurred in 49.4% of patients in this study, but repeated RFA improved the rate of tumor-free patients to 69.4%. Although LTP frequently occurred after RFA in CRLM patients, RFA was still an effective treatment for non-surgical candidates.

Our study had some limitations. First, it was a retrospective study in a single institution with a relatively small number of patients, especially some patients had a short follow-up period. Second, most patients received systemic chemotherapy; thus, OS and LTPFS could not be attributed solely to RFA. In addition, there may have been selection bias when comparing specific patient subgroups, for example, between LTP patients who received repeated RFA treatment and those who did not.

In conclusion, RFA is a safe and effective minimally invasive treatment that can be used as an alternative for patients with unresectable CRLM. Tumor size and ablative margin are important factors influencing LTP, and expanding the ablative margin can effectively reduce the incidence of LTP in these patients. In addition, our study suggests that multiple tumors, large size, and presence of EHD are poor prognostic factors in CRLM patients.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer liver metastasis (CRLM) is a common secondary malignant tumor of the liver and an important cause of tumor-related death. Radiofrequency ablation (RFA) is an accepted alternative therapy for CRLM patients who are unsuitable for resection. However, the relatively high rate of local tumor progression (LTP) is an obstacle to the more widespread use of RFA.

Research motivation

We want to identify the group of CRLM patients who benefit most from RFA, and to provide a reference framework for personalized treatment strategies.

Research objectives

This study aimed to determine the oncological outcomes of RFA in CRLM patients, and to assess predictors that affect LTP-free survival (LTPFS) and overall survival (OS).

Research methods

A retrospective study was conducted. One hundred and thirty-eight lesions in 85 consecutive CRLM patients received RFA treatment from January 2013 to December 2018. Contrast-enhanced computed tomography was performed the first month after RFA to serve as a baseline for subsequent evaluations. The Kaplan-Meier method was used to calculate OS and LTPFS. Univariate and multivariate analyses were performed to determine the predictors of the oncological outcomes.

Research results

There were no RFA procedure-related deaths, and the technique effectiveness rate of the treatment was 89.1% (123/138). The median OS was 36 mo, and the 1-, 3-, and 5-year OS rates were 90.6%, 45.6%, and 22.9%, respectively. Tumor size larger than 3 cm and ablative margin of 5 mm or smaller were the independent predictors of shorter LTPFS, while tumor number greater than 1, size larger than 3 cm, and presence of extrahepatic disease (EHD) were the independent predictors of shorter OS.

Research conclusions

RFA is a safe and effective treatment method for CRLM. Tumor size and ablative margin are the important factors affecting LTPFS, while tumor number, tumor size, and EHD are also critical factors in OS.

Research perspectives

RFA is an effective minimally invasive treatment that can be used as an alternative for patients with unresectable CRLM. Expanding the ablative margin is an effective method to control LTP after RFA. Patients with a single tumor, size of 3 cm or smaller, and no EHD benefit most from RFA.

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