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ORIGINAL ARTICLE

Effect of colorectal resection combined with intraoperative radiofrequency ablation in treating colorectal cancer with liver metastasis and analysis of its prognosis

Tao Fu[1]*, Liu He[1]*, Feide Liu[2]

[1]Department of Gastrointestinal Surgery, Peking University Cancer Hospital & Institute; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Beijing, China. [2]Department of General Surgery, the Fourth Medical Center of PLA General Hospital, Beijing, China.

*Tao Fu and Liu He contributed equally to this work.

Summary

Purpose: *To explore the efficacy and safety of colorectal resection combined with intraoperative radiofrequency ablation (RFA) in the treatment of colorectal cancer (CRC) with liver metastasis.*

Methods: *The clinical data of 106 CRC patients with liver metastasis were retrospectively analyzed. There were 53 cases treated with CRC resection combined with RFA (RFA group) and 53 cases treated with surgical resection of CRC and liver metastasis (surgery group). The clinicopathological features, and perioperative and postoperative complications were compared between the two groups, and the patient's survival and tumor recurrence were recorded via follow-up. Moreover, the risk factors for survival and recurrence in patients were analyzed via univariate and multivariate Cox regression analyses.*

Results: *In the RFA group, the amount of intraoperative blood loss and the number of cases of blood transfusion were significantly smaller than those in the surgery group, and the postoperative hospital stay was obviously shorter than that in the surgery group. In the surgery group, the median recurrence-free survival was 16.4 months, and the 1-, 2- and 3-year tumor-free survival rates were 56.6%, 37.7% and 15.1%, respectively. In the RFA group, the median recurrence-free survival was 10.5 months, and the 1-, 2- and 3-year tumor-free survival rates were 41.5%, 17.0% and 7.5%, respectively. Log-rank test showed no statistically significant difference in overall survival between the two groups (p=0.151), but found in tumor-free survival (p=0.028). Besides, the results of univariate and multivariate analyses showed that the number of metastases, the maximum diameter of liver metastases and the N stage of the primary tumor were independent influencing factors for the postoperative overall survival of patients. The number of metastases >1, N1-2 stage of primary tumor and combined RFA were independent risk factors for tumor recurrence in patients.*

Conclusions: *Compared with resection of CRC and liver metastasis, colorectal resection combined with RFA can significantly reduce the intraoperative blood loss and shorten the hospital stay, with a comparable long-term survival, but the tumor recurrence rate is higher than that in patients with resection.*

Key words: *colorectal cancer, liver metastasis, radiofrequency ablation, surgery, prognosis*

Introduction

According to the 2014 tumor data in China, the incidence and mortality rates of colorectal cancer (CRC) rank 3rd and 5th among malignant tumors [1]. Due to its special blood supply and anatomic location, the liver is the most vulnerable organ to metastasis of CRC, and 15-25% of CRC patients have

Corresponding author: Feide Liu, MD. Department of General Surgery, the Fourth Medical Center of PLA General Hospital, 51 Fucheng Rd, Haidian District, 100048 Beijing, China.
Tel: +86 013472855519, Email: feide301@163.com
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liver metastasis at the time of diagnosis [2,3]. Liver metastasis is also a major cause of death in CRC patients [4]. However, only less than 20% of patients have the opportunity of surgical resection, and surgery is not appropriate for most patients due to extensive liver disease or severe complications, so these patients often can only undergo chemotherapy, with poor long-term prognosis [5]. Currently, there are many alternative treatments for CRC patients with liver metastasis who are not suitable for surgical resection. As a minimally invasive treatment, radiofrequency ablation (RFA) can effectively control focal malignant tumors, with fewer complications, so it has been widely used in the treatment of liver metastasis [6]. It has been confirmed that colorectal resection with liver metastasis is safe and effective in such cases [7]. Colorectal resection combined with RFA has also been proved to be safe and feasible for those patients who are not suitable for surgical resection [8,9].

In this study, the clinical data of 106 CRC patients with liver metastasis treated in our hospital from April 2013 to April 2017 were retrospectively analyzed, and the efficacy and safety were compared between colorectal resection combined with RFA and colorectal resection alone in the treatment of CRC with liver metastasis, hoping to provide a basis for developing the clinical therapeutic strategy for such patients.

Methods

General data

The clinical data of 106 CRC patients with liver metastasis treated in our hospital from April 2013 to April 2017 were collected. The study included 68 males and 38 females aged 40.3-71.8 years with an average of 56.7±9.8 years. *Inclusion criteria:* 1) patients diagnosed with CRC with liver metastasis via pathological examination; 2) those who had no extrahepatic metastatic le-

Table 1. Demographics and general clinical data of all studied patients

Parameters	*Surgery group (n=53)*	*RFA group (n=53)*	*p value*
Gender (Male/Female)	36/17	32/21	0.544
Age (years)	56.24±9.71	57.78±10.11	0.426
Number of metastasis tumors, n (%)			0.401
1	21 (39.6)	16 (30.2)	
2	19 (35.8)	18 (34.0)	
3	13 (24.5)	19 (35.8)	
Largest metastasis tumor diameter (cm)	4.2±0.9	3.9±0.8	0.073
Primary tumor location, n (%)			0.624
Left colon	24 (45.3)	29 (54.7)	
Right colon	12 (22.6)	10 (18.9)	
Rectum	17 (32.1)	14 (26.4)	
Primary tumor T staging, n (%)			0.560
T1-3	26 (49.1)	29 (54.7)	
T4	27 (50.9)	24 (45.3)	
Primary tumor N staging, n (%)			0.314
N0	22 (41.5)	17 (32.1)	
N1-2	31 (58.5)	36 (67.9)	
ASA Grade, n (%)			0.696
1	30 (56.6)	28 (52.8)	
>1	23 (43.4)	25 (47.2)	
CEA (μg/L) , n (%)			0.522
≥10	36 (67.9)	39 (73.6)	
<10	17 (32.1)	14 (26.4)	
Child-Pugh class, n (%)			0.367
A	38 (71.7)	42 (79.2)	
B	15 (28.3)	11 (20.8)	
Preoperative chemotherapy, n (%)			0.136
Yes	40 (75.5)	46 (86.8)	
No	13 (24.5)	7 (13.2)	

RFA: Radiofrequency ablation; ASA: American Society of Anesthesiologists; CEA: Carcinoembryonic antigen

sions before surgery; 3) those with maximum diameter of liver metastases <5 cm; and 4) those with number of liver metastases ≤3. *Exclusion criteria:* 1) patients with extrahepatic metastasis in other sites found preoperatively or intraoperatively; 2) those with recurrence after previous surgery, RFA or interventional therapy; 3) those with severe dysfunction of the heart, lung or kidney; or 4) those who could not tolerate surgery.

The patients were divided into surgery group (n=53, treated with surgical resection only) and RFA group (n=53, treated with surgery+intraoperative RFA). The baseline data, such as age, gender distribution, liver function, Child-Pugh grade, primary tumor stage, maximum diameter of metastatic tumor, number of metastatic tumors and carcinoembryonic antigen (CEA) level, had no statistically significant differences between the two groups (p>0.05), and they were comparable (Table 1). All patients enrolled adhered to the *Declaration of Helsinki* and signed the informed consent. This study was approved by the Ethics Committee of Peking University Cancer Hospital & Institute.

Treatment methods

Preoperative preparation: All patients underwent fiber colonoscopy before surgery and they were pathologically diagnosed with CRC. Abdominal and pelvic enhanced CT examinations were performed to determine the site and size of CRC primary lesions and liver metastases and lymph node metastasis. Enhanced MRI was also performed to further reveal the condition of liver metastases. Then, blood routine tests, blood coagulation, serum biochemistry and tumor markers were assessed, and electrocardiography and lung X-ray examination were conducted as well. Based to the medical history results it was decided whether a patient was suitable for surgical treatment or not.

Surgery group: Liver metastasis, mesenteric lymph node enlargement and pelvic floor conditions were explored. R_0 resection was performed for liver metastases. The mesocolon, lateral peritoneum and great omentum were dissociated, and the blood vessels were clamped. The lymph nodes near the colorectum, in the mesentery and at the root of mesentery were dissected. The lesioned intestine was cut off using a stapler, and then the intestinal tract was reconstructed using a tubular stapling device. Then, the abdominal cavity was rinsed, drainage tube was placed, and the incision was sutured layer by layer. RFA group: The Radionics Cool-tip™ RF Ablation System (Valleylab, USA) was used. According to the preoperative ultrasound/CT/MRI examination and intraoperative ultrasound and exploration, the placement direction and depth of electrodes and the scope of ablation were determined. Then, the electrode needle was inserted into the tumor under the initial energy of 90 W. After preheating for 10 min, the energy of the device was adjusted to 200 W, the automatic feedback balance was controlled, and the energy output ranged from 96 W to 142 W for 20 min. According to the number and size of tumors, multi-point multi-needle ablation was adopted, so that it could completely cover the tumor for thorough ablation. Colorectal resection was performed in the same way in the surgery group. All patients underwent B-mode ultrasound and enhanced CT to review the necrosis of liver metastases after RFA within 3-7 d after surgery.

Observation indexes

Operation-related indexes: The time of operation, amount of intraoperative blood loss and amount of blood transfusion were recorded in both groups. The postoperative hospital stay and the incidence of postoperative complications (wound infection, abdominal infection, pleural effusion, ascites, bile leakage, liver dysfunction and intestinal obstruction) were recorded.

At 1 month after surgery, upper abdominal plain scan+enhanced MRI were routinely performed. The tumor markers and liver ultrasound were examined every 3 months within 2 years after surgery, and every 6 months after 2 years. In the case of abnormalities, upper abdominal x-ray film + enhanced MRI or abdominal plain scan + enhanced CT, chest and pelvic enhanced CT were performed, as well as PET-CT if necessary. The patient's survival and tumor recurrence were recorded via follow-up.

Recurrence is defined as recurrent lesions definitely found via imaging (enhanced CT, enhanced MRI, and PET-CT). In this study, three recurrence states were defined as follows: 1: Local recurrence: the recurrent tumors were located around the site of surgical resection or RFA. 2: Intrahepatic recurrence: the recurrent tumors were located in the liver, but not around the site of surgical resection or RFA. 3: Systemic recurrence: the recurrent tumors were located anywhere outside the liver. After recurrence, secondary resection, RFA, chemotherapy, targeted therapy or supportive therapy were selected based on the patient's conditions.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean±standard deviation and *t*-test was performed for intergroup comparison. Enumeration data were expressed as rate (%), and x^2 test was performed for intergroup comparison. The survival curves were plotted using the Kaplan-Meier method and log-rank test was used to detect significant survival differences between two groups. P<0.05 suggested statistically significant difference.

Results

Comparison of operation-related indexes between the two groups

The time of operation in the RFA group was significantly shorter than that in the surgery group [(245.2±61.3) min *vs.* (252.5±56.4) min], but there was no statistically significant difference (p=0.525). In the RFA group, the amount of intraoperative blood loss and the number of cases with blood transfusion were significantly smaller

than those in the surgery group (158.8±120.9 mL *vs.* 204.2±114.9 mL, p=0.042; 3 cases *vs.* 13 cases, p=0.001), and the postoperative hospital stay was obviously shorter than that in the surgery group (8.7±6.3 d *vs.* 11.3±7.7 d, p=0.047). The incidence rate of postoperative complications was 24.5% and 18.9%, respectively, in the two groups, but the difference was not statistically significant (p=0.480). In the surgery group and the RFA group, there were 2 cases (3.8%) and 1 case (1.9%) of postoperative wound infection, 2 cases (3.8%) and 3 cases (5.7%) of abdominal infection, 0 case and 1 case (1.9%) of gastrointestinal bleeding, 2 cases (3.8%) and 1 case (1.9%) of pleural effusion (relieved after puncture aspiration), 3 cases (5.7%) and 1 case (1.9%) of ascites (relieved after abdominal drainage), 1 case (1.9%) and 0 case of biliary fistula (closed spontaneously after drainage), as well as 1 case (1.9%) of intestinal fistula and 2 cases (3.8%) of intestinal obstruction in each group (improved after symptomatic treatment) (Table 2). All patients were discharged successfully after active treatment. In the RFA group, no incomplete ablation of tumor was found using B-mode ultrasound and enhanced CT reexamination before discharge. There were no deaths in the perioperative period in both groups.

Follow-up results of patient's survival

In the RFA group, FOLFOX, FOLFIRI and XELOX regimens were used for postoperative chemotherapy in 13 cases, 6 cases and 22 cases, respectively. In the surgery group, the above three

Table 2. Comparison of parameters related to surgery

Parameters	*Surgery group n=53*	*RFA group n=53*	*p value*
Operation time (min)	252.5±56.4	245.2±61.3	0.525
Blood loss (ml)	204.2±114.9	158.8±120.9	0.042
Blood transfusion (cases)	13	3	0.007
In-hospital time (days)	11.3±7.7	8.7±6.3	0.047
Complications, n (%)	13 (24.5)	10 (18.9)	0.480
Incision infection	2 (3.8)	1 (1.9)	
Abdominal infection	2 (3.8)	3 (5.7)	
Gastrointestinal hemorrhage	0 (0)	1 (1.9)	
Pleural effusion	2 (3.8)	1 (1.9)	
Ascites	3 (5.7)	1 (1.9)	
Biliary fistula	1 (1.9)	0 (0)	
Intestinal fistula	1 (1.9)	1 (1.9)	
Ileus	2 (3.8)	2 (3.8)	

RFA: Radiofrequency ablation

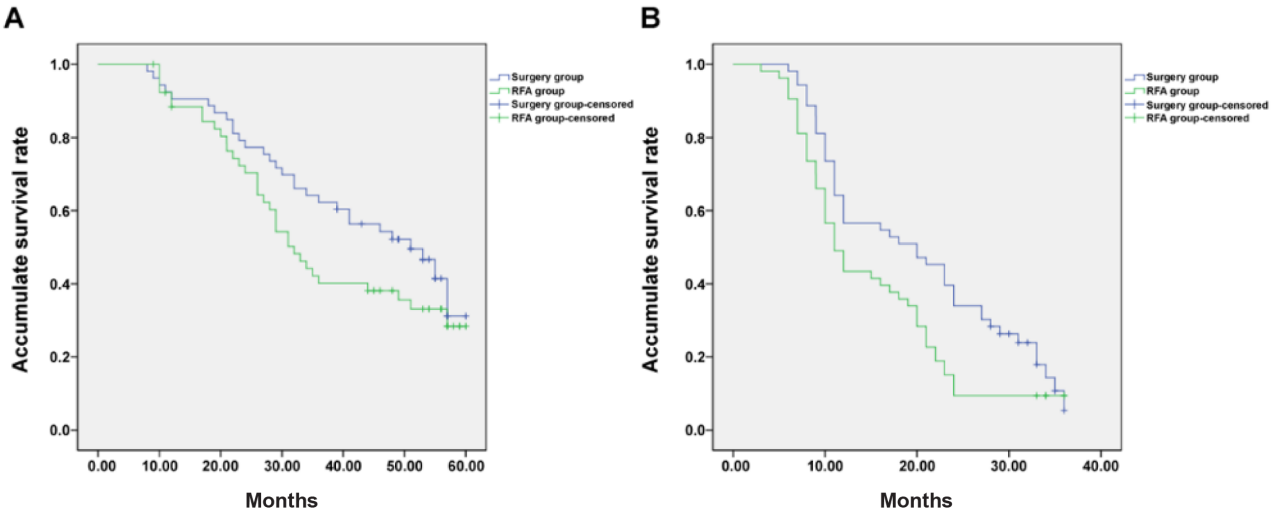

Figure 1. Kaplan-Meier survival curves of patients in Surgery group and RFA group. **A:** The difference between overall survival rate of patients between Surgery group and RFA group had no statistical significance (p=0.151). **B:** The tumor-free survival rate of patients in Surgery group was significantly higher than that of patients in RFA group (p=0.028).

chemotherapy regimens were administered to 17, 9 and 16 cases, respectively, showing no statistically significant differences between the two groups (p>0.05). All patients were followed up for 6-60 months, and the 1-, 3- and 5-year overall survival rates were 90.6%, 62.3% and 45.3% in the surgery group, and 94.3%, 49.1% and 35.8% in the RFA group, respectively. Kaplan-Meier survival curves and log-rank test showed no statistically significant difference in overall survival rate between the two groups (p=0.151) (Figure 1A). Besides, in the surgery group, the median recurrence-free survival time was 16.4 months, and the 1-, 2- and 3-year tumor-free survival rates were 56.6%, 37.7% and 15.1%, respectively. There was no case with local recurrence, 21 cases had intrahepatic recurrence, and 13 cases showed systemic recurrence. In the RFA group, the median recurrence-free survival time was 10.5 months, and the 1-, 2- and 3-year tumor-free survival rates were 41.5%, 17.0% and 7.5%, respectively. There was no local recurrence, 37 cases had intrahepatic recurrence, and 7 cases showed systemic recurrence. Five out of 21 patients with intrahepatic recurrence in the surgery group were treated with local treatment of liver (surgical excision, RFA, cyberknife), while 17 out of 37 patients with intrahepatic recurrence in the RFA group were treated with local treatment of liver (surgical resection, RFA and cyberknife). The tumor-free survival curves in the two groups were plotted using the Kaplan-Meier method, and a statistically significant difference was found in tumor-free survival rate according to the log-rank test (p=0.028) (Figure 1B).

Table 3. Univariate analysis of predictors for 5-year overall survival rate in patients with colorectal liver metastases

Parameters	*Cases*	*5-year overall survival rate, %*	*p value*
Age (years)			0.064
≤60	66	42.4	
>60	40	37.5	
Number of metastasis tumors			0.001
1	37	73.0	
>1	69	23.2	
Largest metastasis tumor diameter (cm)			0.036
<3	38	42.1	
≥3	68	39.7	
Primary tumor location			0.089
Left colon	53	35.8	
Right colon	22	40.9	
Rectum	31	48.4	
Primary tumor T staging			0.374
T1-3	55	43.6	
T4	51	37.3	
Primary tumor N staging			0.019
N0	39	51.3	
N1-2	67	34.3	
CEA (μg/L)			0.483
≥10	75	38.7	
<10	31	45.2	
Treatment			0.141
Surgery	53	45.3	
RFA	53	35.8	
Surgical margin			0.015
R_0	73	46.6	
R_1	33	27.3	
Preoperative chemotherapy			0.001
Yes	86	45.3	
No	20	20.0	

RFA: Radiofrequency ablation; CEA: Carcinoembryonic antigen

Table 4. Univariate analysis of predictors for 3-year tumor-free survival rate in patients with colorectal liver metastases

Parameters	*Cases*	*3-year tumor-free survival rate, %*	*p value*
Number of metastasis tumors			0.001
1	37	24.3	
>1	69	4.3	
Largest metastasis tumor diameter (cm)			0.001
<3	38	21.1	
≥3	68	5.9	
Primary tumor location			0.179
Left colon	53	9.4	
Right colon	22	13.6	
Rectum	31	12.9	
Primary tumor T staging			0.213
T1-3	55	12.7	
T4	51	9.8	
Primary tumor N staging			0.016
N0	39	20.5	
N1-2	67	6.0	
CEA (μg/L)			0.228
≥10	75	10.7	
<10	31	12.9	
Treatment			0.021
Surgery	53	17.0	
RFA	53	5.7	
Surgical margin			0.010
R_0	73	13.7	
R_1	33	6.1	
Preoperative chemotherapy			0.001
Yes	86	12.8	
No	20	5.0	

RFA: Radiofrequency ablation; CEA: Carcinoembryonic antigen

Table 5. Multivariable Cox regression analysis of predictors for patients with colorectal liver metastases

Parameters	*HR value*	*95% CI*	*p value*
5-year overall survival rate			
Number of metastatic tumors	3.37	1.89-4.69	0.016
Largest metastasis tumor diameter	2.72	1.55-2.56	0.011
Primary tumor N staging	3.95	1.16-5.84	0.007
Surgical margin (R_0/R_1)	0.74	0.46-1.28	0.185
Preoperative chemotherapy	1.23	0.64-2.10	0.456
3-year tumor-free survival rate			
Number of metastatic tumors	2.92	1.71-4.43	0.009
Largest metastatic tumor diameter	1.88	0.85-2.71	0.311
Primary tumor N staging	3.79	1.49-5.85	0.001
Treatment (Surgery/ RFA)	2.14	1.17-4.34	0.010
Surgical margin (R_0/R_1)	0.73	0.54-2.24	0.676
Preoperative chemotherapy	1.47	0.66-2.57	0.482

HR: Hazard ratio; CI: Confidence interval; RFA: Radiofrequency ablation

Influencing factors for patient's survival and tumor recurrence

Univariate analysis showed that the overall survival rate of CRC patients with liver metastasis was related to the number of liver metastases, the maximum diameter of liver metastases, the N stage of primary tumor, the surgical margin of tumor and the presence or absence of preoperative chemotherapy, while the postoperative recurrence was related to the number of liver metastases, the maximum diameter of liver metastases, the N stage of primary tumor, RFA combined or not, the surgical margin of tumor and the presence or absence of preoperative chemotherapy ($p<0.05$) (Tables 3 and 4). Besides, the results of multivariate analyses showed that the number of metastases, the maximum diameter of liver metastases and the N stage of the primary tumor were independent influencing factors for the postoperative overall survival rate of patients [hazard ratio (HR)=3.37, p=0.016. HR=2.72, p=0.011. HR=3.95, p=0.007]. The number of metastases >1, N1-2 stage of primary tumor and combined RFA were independent risk factors for tumor recurrence (HR=2.92, p=0.009. HR=3.79, p<0.001. HR=2.14, p=0.010) (Table 5).

Discussion

Resection of the primary tumor lesions and liver metastases is currently recognized as the only way to cure CRC with liver metastasis. In recent years, with the rapid development of local minimally invasive treatment for liver metastases, RFA has been widely applied in the treatment of malignant hepatic tumors, which is safe and minimally invasive, obtaining satisfactory results [10]. There is a new consensus that RFA can achieve better efficacy on CRC with liver metastasis (diameter <3 cm and number of metastases ≤5) and liver metastases able to be completely ablated in a better condition (diameter <5 cm), and the postoperative 5-year overall survival rate can be up to 48%, with an effect comparable to that of surgical resection [6]. Therefore, CRC resection combined with RFA may be a potential opportunity to cure CRC patients with liver metastases, especially those unsuitable for surgical resection.

However, the high recurrence rate after RFA has attracted extensive attention, and the application of RFA in the treatment of resectable CRC with liver metastasis is also controversial. The study of Reuter et al [11] showed that the median recurrence time after RFA for liver metastases is shorter than that after surgical resection, and the local recurrence rate and intrahepatic recurrence rate in the RFA group are higher than those in the resection group. It was also reported by Otto et al [12] that the disease-free survival time of patients receiving RFA is significantly shortened, but the proportion of patients able to undergo secondary RFA or surgery after recurrence is higher in the RFA group than that in the surgery group, while both tumor-free survival and 3-year survival rates are similar between the two groups after retreatment. Lee et al [13] compared the efficacy of RFA and surgical resection on CRC with liver metastasis, and found that the 3- and 5-year local recurrence-free survival rates in the surgery group (88.0% and 84.6%) are significantly higher than those in the RFA group (53.3% and 42. 6%) ($p<0.01$), and the 5-year survival rate in the RFA group is lower than that in the surgery group (48.5% *vs.* 65.7%), displaying no statistically significant difference ($p>0.05$). Moreover, Aloia et al [14] confirmed in their research on CRC with liver metastasis that surgical resection is superior to RFA in terms of local recurrence and overall survival. In another study on CRC with liver metastasis, the 5-year survival rate and local recurrence rate were similar in patients with lesions <3 cm after surgery and RFA [15]. In a retrospective study of Lee et al [16], it was found that the long-term survival time after RFA is similar to that after surgery in single CRC patients with liver metastasis (≤ 3 cm) or multiple CRC patients with liver metastasis (≤2 cm). However, the clinical and pathological features generally have great differences between the surgery and the RFA group in the above studies.

In this study, there were no statistically significant differences in the baseline clinical and pathological data between the surgery and the RFA group, which were comparable. It was found that the postoperative 1-, 3- and 5-year overall survival rates were higher in the surgery group than those in the RFA group, but the difference was not statistically significant. The surgery group had a higher recurrence-free survival rate than the RFA group, and the difference was statistically significant, basically consistent with previous literature reports.
RFA has unique advantages in the treatment of CRC with liver metastasis, which can avoid and reduce the damage to normal liver tissues and adjacent important blood vessels to the greatest degree. In this study, the amount of intraoperative blood loss and the hospital stay in the RFA group were evidently smaller and shorter than those in the surgery group. Karanicolas et al [17] studied and found that the amount of intraoperative blood loss was smaller and the hospital stay was shorter in the RFA alone or the RFA combined with surgical resection than those in the surgical resection alone for bilaterally distributed CRC with liver metastasis. According to another study, the amount of

blood loss during CRC resection combined with microwave ablation or RFA was smaller and comparable to that during CRC resection alone [18].

The long-term survival rate and tumor recurrence in CRC patients with liver metastasis are affected by many factors. In this study, the results of multivariate analyses showed that the number of metastases, the maximum diameter of liver metastases and the N stage of primary tumor were independent influencing factors for the postoperative overall survival rate of patients, and the number of metastases >1, N1-2 stage of primary tumor and combined RFA were independent risk factors for tumor recurrence in patients, similar to the findings in some other studies [19-21].

As a retrospective study, this study had limited sample size and incomprehensive follow-up content. The results presented in this study remain to be verified using multi-center large-sample prospective clinical research in the future.

Conclusions

Compared with resection of CRC with liver metastasis, colorectal resection combined with RFA can significantly reduce the intraoperative blood loss and shorten the hospital stay, with a comparable long-term survival rate, but the tumor recurrence rate is higher than that in patients receiving resection. The number of metastases, the maximum diameter of liver metastases and the N stage of the primary tumor are independent influencing factors for the postoperative overall survival rate of patients, and the number of metastases >1, N1-2 stage of primary tumor and combined RFA are independent risk factors for tumor recurrence in patients.

Conflict of interests

The authors declare no conflict of interests.

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