

Original Article

Debulking treatment with CT-guided percutaneous radiofrequency ablation and hepatic artery infusion of floxuridine improves survival of patients with unresectable pulmonary and hepatic metastases of colorectal cancer

Sheng Li, Ni He, Wang Li and Pei-Hong Wu

Abstract

The survival of most patients with both unresectable hepatic and pulmonary metastases of colorectal cancer is poor. In this retrospective study, we investigated the efficacy of computed tomography (CT)-guided radiofrequency ablation (RFA) and systemic chemotherapy plus hepatic artery infusion of floxuridine (HAI-FUDR). Sixty-one patients were selected from 1,136 patients with pulmonary and hepatic metastases from colorectal cancer. Patients were treated with RFA and systemic chemotherapy plus HAI-FUDR (ablation group, $n = 39$) or systemic chemotherapy plus HAI-FUDR (FUDR group, $n = 22$). Patients in the two groups were matched by sex, age, number of metastases, and calendar year of RFA or FUDR. Survival data were evaluated by using univariate and multivariate analyses. Clinical characteristics were comparable between the two groups. All patients in the ablation group underwent RFA and chemotherapy. Median follow-up was 56.8 months. The 1-, 3-, and 5-year overall survival (OS) rates were 97%, 64%, and 37%, respectively, for the ablation group, and 82%, 32%, and 19%, respectively, for the FUDR group. The 1-, 3-, and 5-year survival rates after metastasis were 97%, 49%, and 26% for the ablation group, and 72%, 24%, and 24% for the FUDR group, respectively. The median OS times were 45 and 25 months for the ablation and FUDR groups, respectively. In the multivariate analysis, treatment allocation was a favorable independent prognostic factor for OS ($P = 0.001$) and survival after metastasis ($P = 0.009$). These data suggest that the addition of RFA to systemic chemotherapy plus HAI-FUDR improves the survival of patients with both unresectable hepatic and pulmonary metastases from colorectal cancer.

Key words Hepatic metastases, pulmonary metastases, colorectal cancer, radiofrequency ablation, hepatic artery infusion of floxuridine

Colorectal cancer with both hepatic and pulmonary metastases has long been regarded as a terminal disease, but in strictly selected patients, sequential resection can bring survival benefits^[1,2]. Less-than-complete resection or ablation has not been recommended by the expert panel in the National Comprehensive Cancer

Network (NCCN) because this treatment intent was believed to be unsuitable^[3]. In most patients with both hepatic and pulmonary metastases, the lesions are unresectable and the survival is poor^[4]. A previous study on resection of hepatic and extrahepatic metastases from colorectal cancer demonstrated that only 39% of patients with pulmonary metastases had a complete resection, and other patients developed evidence of disease progression during the interval period while awaiting pulmonary surgery^[5]. A similar report also indicated that only 52% patients with pulmonary metastases from colorectal cancer underwent a complete resection, and others failed to receive such an operation due to disease progression during the waiting period^[6].

In our practice, we have encountered 2 patients with unresectable colorectal cancer metastases to the liver and lungs who were treated

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with a combination of radiofrequency ablation (RFA), systemic chemotherapy, and hepatic artery infusion of floxuridine (HAI-FUDR). The patients' survival in either group was long (> 90 months). HAI-FUDR prolongs the survival of patients with hepatic metastasis of colorectal origin and has become a standard care for these patients^[7,8]. RFA is associated with a quick recovery and can be repeated after short interval, and major progression seldom occurs during this short period. By contrast, longer intervals are required between sequential resections of hepatic and pulmonary metastases, and tumor progression often occurs during this long period. That is why a complete resection is not feasible in many patients. RFA can be repeated^[9] and is less invasive than surgical resection for patients with metastatic disease. In addition, the combination of RFA and FUDR may further prolong survival by reducing tumor burden.

There are several long-term studies of RFA alone for hepatic or pulmonary metastases from colorectal cancer with favorable results^[10-12]. The results from the combination of RFA with liposomal chemotherapy are also encouraging^[13-15]. To determine whether the addition of RFA provides survival benefits, we retrospectively compared the efficacy of debulking treatment with RFA and chemotherapy plus HAI-FUDR to the efficacy of systemic chemotherapy plus HAI-FUDR in patients with both hepatic and pulmonary colorectal metastases.

Materials and Methods

Patients and their clinicopathologic characteristics

The study was reviewed and approved by the Institutional Review Board of Sun Yat-sen University Cancer Center (China). All patients in our study had pathologic confirmation of colorectal carcinoma, presenting with both hepatic and pulmonary metastases on computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET-CT) imaging.

The inclusion criteria were as follows: (1) patients receiving systemic chemotherapy and HAI-FUDR; (2) patients with unresectable metastases in the liver and lungs due to additional metastatic sites, poor performance status, impaired liver or lung function, or positive margin; (3) patients with Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2; and (4) patients with a diagnosis of hepatic and pulmonary metastases of colorectal origin prior to the procedure.

The exclusion criteria were as follows: (1) patients with other malignancies; (2) patients with only hepatic metastasis; (3) patients with resectable hepatic and pulmonary metastases, undergoing resection or complete ablation of hepatic and pulmonary metastases before receiving HAI-FUDR, or only undergoing HAI-FUDR; (4) patients with a life expectancy less than 3 months; (5) patients with viral hepatitis and liver cirrhosis; (6) patients only undergoing systemic chemotherapy or best supportive therapy; (7) patients with uncontrolled severe diabetes, acute infection, or allergy to iodine; (8) patients with bleeding tendency or severe jaundice; or (9) patients with a follow-up duration of less than 3 months.

Between December 2004 and September 2012, 61 patients

were selected from 1,136 patients with colorectal cancer hepatic metastasis. Thirty-nine patients were treated with CT-guided percutaneous RFA, HAI-FUDR, and systemic chemotherapy (the ablation group), and 22 patients were treated with systemic chemotherapy and HAI-FUDR (the FUDR group). The selection of patients in the FUDR group was based on matching with patients in the ablation group, in accordance with the following variables: sex, age, number of metastases, maximal diameter of metastases, interval between hepatic and pulmonary metastases, and calendar year of RFA or FUDR (**Table 1**). Patients in the FUDR group were reluctant to receive RFA or could not afford RFA, or RFA was unavailable at the time of treatment. The last follow-up was on April 10, 2013.

CT-guided percutaneous radiofrequency ablation

Vital signs were monitored during the procedure and 3–6 h after the procedure. Moderate sedation and local anesthesia were given during RFA. Following intraoperative chest or abdominal CT scan, a 17-gauge, cooled-tip electrode (Cool-Tip system; Valleylab, MA, USA) was inserted into the tumor at a specific angle step by step. The power and exposure time were selected according to the standard recommendations from the manufacturer of Cool-Tip systems, the operators' experience, and the intraoperative efficacy evaluation. A maximum of 3 tumors in the liver or unilateral lung were treated in the same session for safety reasons. These methods have been described in detail in previous studies^[16,17].

Chemotherapy

HAI-FUDR was conducted with a port catheter system for 14 consecutive days, with FUDR 0.1–0.2 mg/kg daily. While the catheter was in situ in the appropriate hepatic artery, the gastroduodenal artery was embolized with coils. All patients underwent the oxaliplatin, leucovorin, and fluorouracil regimen (FOLFOX4) as first line systemic chemotherapy; the irinotecan, leucovorin, and fluorouracil regimen (FOLFIRI) was given if the disease progressed after FOLFOX4.

Both FUDR and systemic chemotherapy were initiated at the same time, and treatment was repeated every 3 weeks. Timing of ablation depended upon response to chemotherapy and tumor status. If the lesion influenced the quality of life or was life-threatening, RFA was offered first. However, RFA was initially offered after 2 cycles of chemotherapy in the ablation group and repeated every 2 cycles of chemotherapy if necessary. HAI-FUDR and systemic chemotherapy were discontinued 2 weeks before ablation.

The targeted metastases were ablated by several sessions of RFA between intervals of chemotherapy, whereas the micrometastases were treated with chemotherapy. Chemotherapy was stopped when the tumor had shrunken and the toxicity was not severe. Patients then underwent palliative ablation and continued to undergo HAI-FUDR to control hepatic metastases, in addition to systemic chemotherapy for systematic metastases. Hence chemotherapy cycles were lessened or postponed, and possible toxicity due to additional chemotherapy was avoided. Another consideration was that during continuous and repeated chemotherapy, the disease might progress or even become

undetectable on CT or MRI. An invisible lesion in the liver or lungs was not considered suitable for RFA because the lesion location could not be confirmed. Therefore, timely RFA after several chemotherapy cycles was provided. A high concentration and continuous infusion of FUDR was given through the proper hepatic artery.

To determine which lesion to ablate in patients with extensive metastases, the following selection criteria were used: (1) lesions that influenced quality of life or were life-threatening, such as painful lesions or tumors compressing the hepatic hilum or bronchus; (2) tumors located in sites with high metastatic potential; and (3) tumor location and size readily amenable to ablation. If the lesion was situated in extremely risky positions and not influencing quality of life, the lesion was followed up until marked progression had occurred. Finally, in cases of bilateral pulmonary metastases, one lung was treated at any given time for safety reasons.

Outcome assessment

A special follow-up team consisting of 5 staff members who were unfamiliar with the treatment plan conducted telephone interviews on a regular basis. CT or MRI scans were performed and related tumor markers were tested every 3 months after the procedure in most patients according to our routine protocol. Only on four occasions did 2 patients not receive a CT scan every 3 months, and this was due to casual delay. This did not affect the calculation of survival.

All patients in this study had unresectable tumors, and the resectability criteria were consistent with those previously published^[18], i.e., an R0 resection of metastases and adequate liver or lung remnant. If new lesions appeared after initial treatment, the option to repeat RFA was offered. Complete ablation was defined as no viable metastases on contrast-enhanced CT or MRI. Debulking was defined as over 60% total metastases volume ablated on contrast-enhanced CT or MRI. The percentage of necrosis was assessed with volumetric analysis software in the imaging workstation.

Survival and related information were collected. Overall survival (OS) was defined as the interval from the date the disease was diagnosed to the date of death or last follow-up. Survival after metastasis was defined as the interval from the date that metastasis was first diagnosed to the date of death or last follow-up.

All adverse events of chemotherapy and HAI-FUDR were evaluated according to the Common Terminology Criteria for Adverse Events Version 4.0^[19].

Statistical analysis

Comparisons of continuous data between the two groups were made using independent Student's *t* test, and categorical variables were compared with Pearson's chi-squared test or Yates' correction for continuity. Survival was estimated using the Kaplan-Meier method and the significance was determined by log-rank test. A two-tailed *P* value of < 0.05 was considered statistically significant. The independent prognostic factors in predicting survival were assessed using a multivariate Cox proportional hazard model. All statistical

calculations were performed with SPSS software, version 18.0 (SPSS, Chicago, IL, USA).

Results

No significant differences in clinicopathologic characteristics between two groups

Clinicopathologic characteristics of the 61 patients in the ablation (39 patients) and FUDR groups (22 patients) are listed in **Table 1**. There were no significant differences in these parameters between the ablation and FUDR groups. Representative perioperative changes in CT images in patients are shown in **Figures 1** and **2**. Sixteen patients (26.2%) had three metastatic sites, 2 had five metastatic sites, and 2 had four metastatic sites. Among these patients, 10 had distant lymph node metastases, 4 had adrenal metastases, 10 had bone metastases, 4 had pelvic metastases, and 2 had ovarian metastases. All the above metastases developed after the treatment of hepatic and pulmonary metastases.

The RFA procedure

The average number of radiofrequency applications was 8.1 ± 3.4 , and there were 484 total application times in the ablation group. The average ablation sessions for each patient in the ablation group were 2.6 ± 1.9 (range, 1–8) times.

All hepatic lesions were treated simultaneously if feasible, but pulmonary lesions often required multiple sessions. Approximately 75% of the pulmonary metastases were smaller than 3 cm in diameter, but over 50% of the hepatic metastases were larger than 3 cm in diameter. A complete ablation was achieved in 90% of the targeted pulmonary metastases. After RFA, we observed a visible honeycomb-shaped postablation lesion with low density, which was larger than the baseline nodule in the liver. Lung lesions were low density and exhibited possible cavitation and surrounding ground-glass opacity. There was no contrast enhancement in the necrotic area of targeted lesions on CT. Pneumothorax, hemothorax, and hydrothorax mainly occurred after RFA for pulmonary metastases. Liver dysfunction and elevation of transaminase levels occurred mainly after RFA for hepatic metastases.

In the ablation group, 80% of lesion was treated in the target lesions; of the ablated lesions, > 90% necrosis was ensured for those less than 5 cm in diameter and at least 75% necrosis was achieved in lesions > 5 cm in diameter. We usually perform a complete ablation for lesions less than 3 cm. In this study, the percentage of debulking achieved by RFA was approximate 75% of the target lesions. Eight patients had complete ablation and 31 patients had partial ablation, with a median OS of 45.0 months and 25.0 months, respectively. Characteristics of those patients with a complete ablation were: (1) tumor at least 2 cm away from larger vessels; (2) only hepatic and pulmonary metastases; (3) metastasis smaller than 4 cm in diameter and ≤ 5 lesions in the liver or lungs (including solitary metastasis specially) after chemotherapy.

Most patients had multiple hepatic and metastatic lesions.

Table 1. Clinicopathologic characteristics of 61 patients undergoing different treatments for liver and lung metastases in two groups

Variable	Ablation group	FUDR group	P value
Sex ^a			0.309
Male	23	10	
Female	16	12	
Age ^a			0.274
≤ 70 years	32	21	
> 70 years	7	1	
Performance status ^a			0.236
0	15	13	
1	22	8	
2	1	1	
Primary tumor ^a			0.080
Colon	25	9	
Rectum	14	13	
Dead or censored ^a			0.871
Dead	24	14	
Censored	15	8	
Duke stage ^a			0.680
B	13	5	
C	8	5	
D	18	12	
T category ^a			0.945
T2	2	1	
T3	21	11	
T4	16	10	
Maximal diameter of hepatic metastases ^a			0.902
≤ 5 cm	30	18	
> 5 cm	9	4	
Maximal diameter of pulmonary metastases ^a			0.768
≤ 5 cm	35	21	
> 5 cm	4	1	
Location of hepatic metastases ^a			0.426
One lobe	20	11	
Two lobe	19	11	
Location of pulmonary metastases ^a			0.351
Unilateral lung	19	8	
Bilateral lung	20	14	
Other metastatic sites ^a			0.629
Yes	17	11	
No	22	11	
Metastatic number of liver ^a			0.309
Limited	23	10	
Extensive	16	12	
Metastatic number of lungs ^a			0.113
Limited	23	7	
Extensive	16	15	
Total metastatic number ^a			0.283
Limited (≤ 7)	12	4	
Extensive (> 7)	27	18	

(To be continued)

Table 1. Clinicopathologic characteristics of 61 patients undergoing different treatments for liver and lung metastases in two groups (continued)

Variable	Ablation group	FUDR group	P value
ALB level ^a			0.594
≤ 40 g/L	16	10	
> 40 g/L	24	12	
PLT level ^a			0.520
≤ 100 × 10 ⁹ /L	5	5	
> 100 × 10 ⁹ /L	34	17	
CEA ^a			1.00
≤ 200 ng/mL	31	17	
> 200 ng/mL	8	5	
CA19-9 ^a			0.089
≤ 200 U/mL	28	11	
> 200 U/mL	11	11	
Chemotherapy cycle	10.0 ± 6.2	10.1 ± 4.6	0.942
ALB	40.98 ± 4.71	41.01 ± 4.79	0.980
PLT	186.10 ± 88.54	222.27 ± 130.99	0.257
Metastatic type ^a			0.382
Metachronous	24	11	
Synchronous	15	11	
HB decrease	12.04 ± 23.12	12.82 ± 9.74	0.881
Interval between pulmonary and hepatic metastases (cm)	7.5 ± 9.0	4.5 ± 4.6	0.088
Maximal diameter of metastasis (cm)			
Hepatic metastasis	4.02 ± 1.98	3.52 ± 2.17	0.360
Pulmonary metastasis	2.07 ± 2.15	1.68 ± 0.95	0.419

^aThe values of these variables are presented as number of cases. HB, hemoglobin; ALB, albumin; PLT, platelet; FUDR, floxuridine; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; other metastatic sites, additional organ metastasis (beyond liver and lungs).

Thirteen patients had 7 or fewer hepatic or pulmonary metastases. Solitary lesions were observed in 10 patients with pulmonary metastasis and in 11 patients with hepatic metastasis. The largest hepatic or pulmonary metastatic lesions were greater than 5 cm in diameter, and such lesions occurred in 15 patients. Ten patients had no or minor symptoms. The interval between hepatic metastases and pulmonary metastases was from 0 to 10 months.

Overall survival and survival after metastasis

At the time of last follow-up, 37 patients had died, and 10 patients were still alive without disease progression. Median follow-up duration was 56.8 months (range: 5–165 months), and 3 patients were lost to follow-up. The 1-, 3-, and 5-year OS were 97%, 64%, and 37% for the ablation group, respectively, and 82%, 32%, and 19% for the FUDR group, respectively (**Figure 3A**). The 1-, 3-, and 5-year survival rates after metastasis were 97%, 49%, and 26% for the ablation group, respectively, and 72%, 24%, and 24% for the FUDR group, respectively (**Figure 3B**). The median OS were 45.0 and 25.0 months for the ablation and FUDR groups, respectively. The median survival after metastasis was 35.6 and 19.0 months for the ablation and FUDR groups, respectively.

Factors affecting survival

Univariate analysis was first carried out for factors that might affect patient survival (**Table 2**). Per the results, three parameters were related to survival: the type of treatment, the maximal diameter of hepatic metastases, and more than one extrahepatic metastasis.

Multivariate analysis was performed, and the results indicated that treatment allocation (RFA vs. FUDR), CEA level (≤ 200 ng/mL), and maximal diameter of hepatic metastases (≤ 5 cm) were favorably independent prognostic factors for OS; treatment allocation (RFA vs. FUDR) was an independent prognostic factor for survival after metastasis. The CEA level [$P = 0.023$, hazards ratio (HR) = 2.334, 95% CI: 1.122–4.857] and the maximal diameter of hepatic metastases ($P = 0.038$, HR = 2.184, 95% CI = 1.046–4.560) were also independent prognostic factors for OS. Treatment allocation (FUDR and chemotherapy) was used to independently predict worse OS ($P = 0.001$, HR = 3.586, 95% CI = 1.743–7.377) and worse survival after metastasis ($P = 0.009$, HR = 2.505, 95% CI = 1.261–4.978). OS and survival after metastasis were not associated with age ($P > 0.05$), or number of lesions (≤ 7 and > 7 lesions, $P > 0.05$).

No patients died during treatment with RFA, HAI-FUDR, or

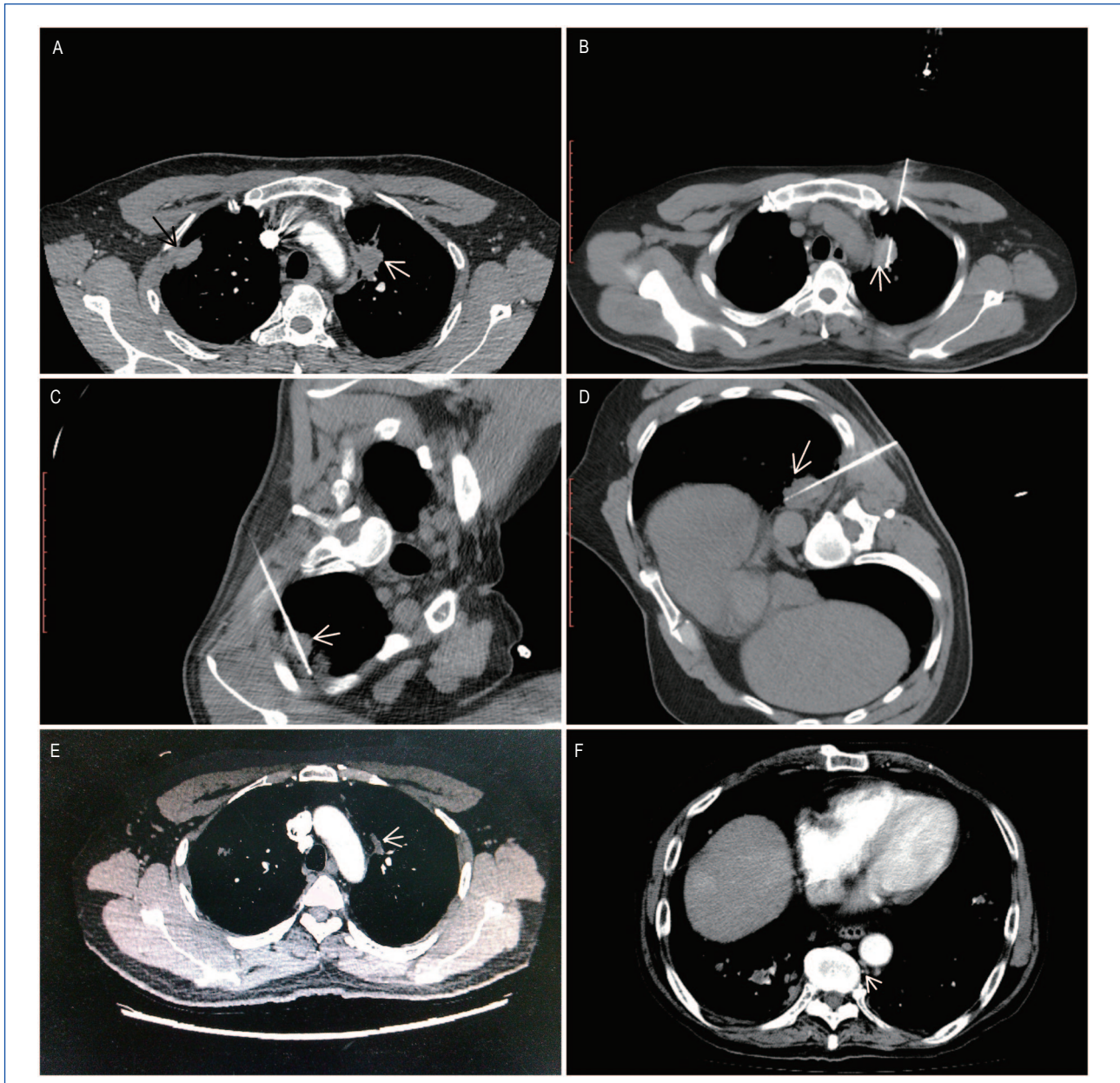


Figure 1. Radiofrequency ablation for pulmonary metastases of colorectal cancer origin. A, two pulmonary metastases of colorectal origin are shown in preablation computed tomography (CT) imaging; B–D, the process of puncturing pulmonary metastases during radiofrequency ablation as shown on CT images; E and F, postablation CT imaging shows tumors decrease after radiofrequency ablation, suggesting successful ablation.

chemotherapy. Major complications are listed in **Table 3**.

Discussion

In this study, patient characteristics were comparable between the ablation and FUDR groups. Our data indicate that the addition of RFA to systemic chemotherapy plus HAI-FUDR improves the survival of patients with both unresectable hepatic and pulmonary metastases of colorectal origin. The results also demonstrate

that less-than-complete ablation can still bring survival benefits, a conclusion that differs from those of previous studies that have been cited in related part of the NCCN Guidelines for Colon and Rectal Cancers^[20] in patients with unresectable metastases of colorectal origin. Considering that debulking treatment with RFA, HAI-FUDR, and systemic chemotherapy was minimally invasive and well tolerated, the role of debulking treatment for unresectable hepatic and pulmonary metastases should be reconsidered.

There were 1,136 patients with colorectal cancer hepatic

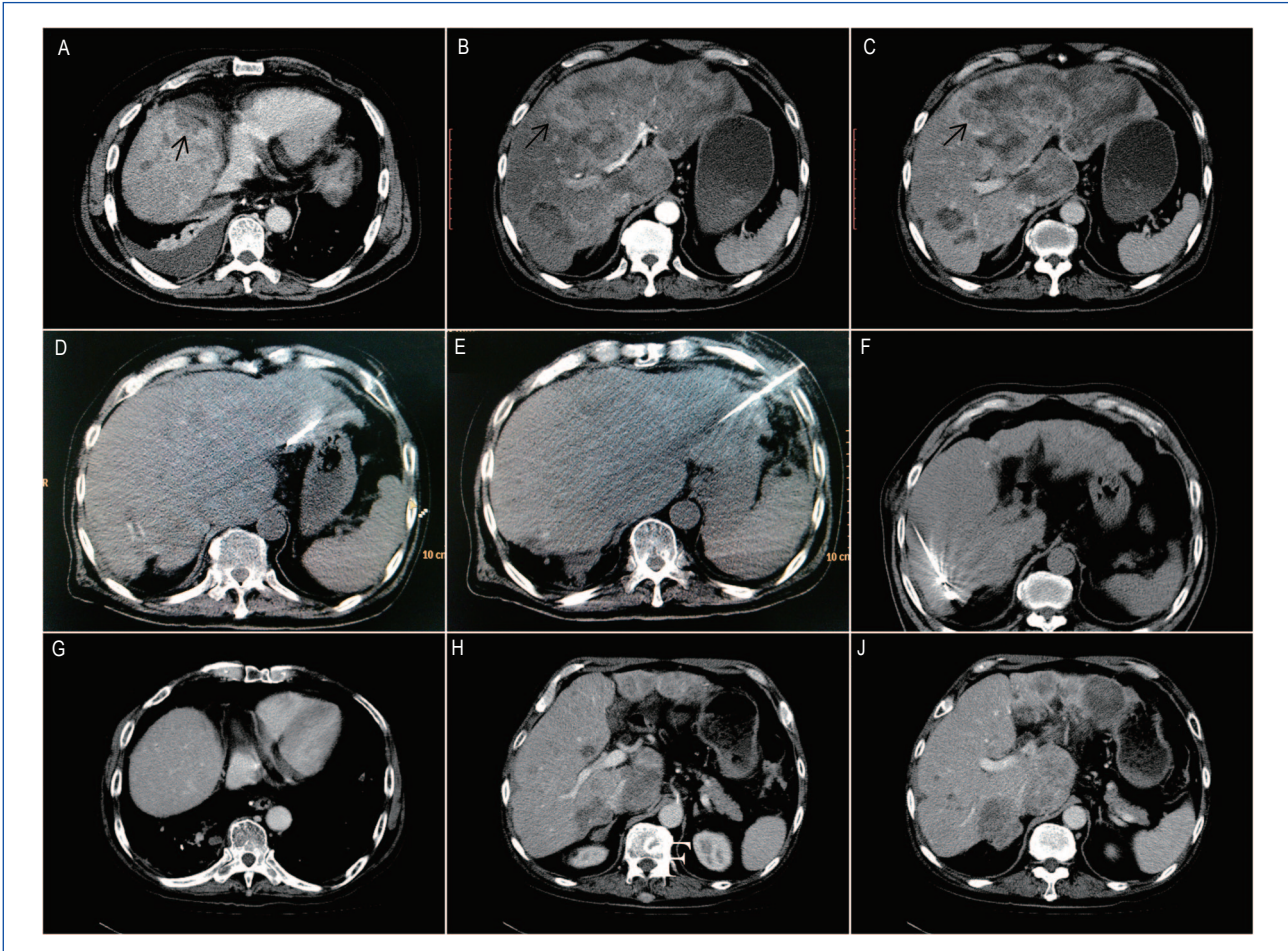


Figure 2. Radiofrequency ablation for hepatic metastases of colorectal cancer origin. A–C, preoperative CT scans show large liver metastases; D–F, the process of puncturing hepatic metastases during radiofrequency ablation; G–J, postoperative CT scans show decreased liver metastases.

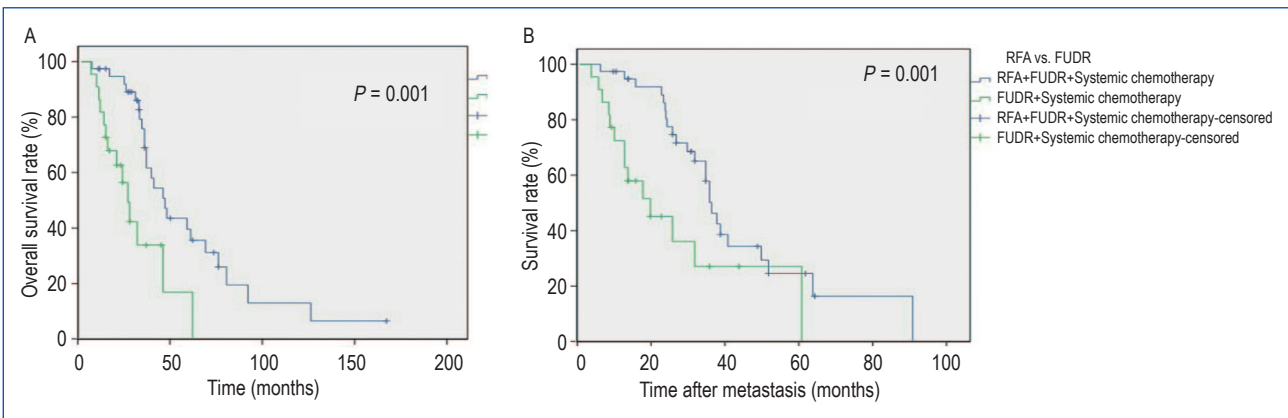


Figure 3. Survival was improved in the ablation group. A, overall survival in the ablation group is better than that in the FUODR group; B, survival after metastasis in the ablation group is better than that in the FUODR group.

metastasis in this study, but only a subset had both pulmonary and hepatic metastases and underwent HAI-FUODR and systemic chemotherapy. Therefore, only 22 patients with unresectable disease

met our selection criteria and were enrolled in the FUODR group. Solitary hepatic or pulmonary metastasis was observed in some patients, but these patients had unresectable metastases at other

Table 2. Univariate survival analysis in 61 patients

Variable	Median overall survival (months)	P value	Median survival after metastases (months)	P value
Sex		0.673		0.673
Male	39		34	
Female	35		35	
Age		0.667		0.667
≤ 70 years	39		31	
> 70 years	35		35	
Performance status		0.124		0.124
0	44		31	
1	39		35	
2	9		9	
Primary tumor		0.955		0.955
Colon	38		34	
Rectum	44		29	
T category		0.498		0.498
T2	29		29	
T3	45		35	
T4	35		34	
Primary N category		0.583		0.583
Negative	44		31	
Positive	38		35	
Metastasis type		0.024		0.024
Metachronous	45		34	
Synchronous	34		31	
Maximal diameter of hepatic metastases		0.012		0.012
≤ 5 cm	44		35	
> 5 cm	31		23	
Maximal diameter of pulmonary metastases		0.796		0.796
≤ 5 cm	38		31	
> 5 cm	44		37	
Location of hepatic metastases		0.110		0.110
One lobe	44		35	
Two lobe	32		25	
Location of pulmonary metastases		0.475		0.475
Unilateral lung	44		35	
Bilateral lung	34		25	
Other metastatic sites		0.377		0.377
Yes	34		25	
No	44		35	
Metastatic number of liver		0.029		0.029
Limited	44		35	
Extensive	33		23	
Metastatic number of lung		0.330		0.330
Limited	44		35	
Extensive	34		25	
Total metastatic number		0.086		0.086
≤ 7 lesions	45		38	
> 7 lesions	34		26	
Treatment allocation		0.001		0.001
RFA group	45		36	
FUHR group	25		19	

(To be continued)

Table 2. Univariate survival analysis in 61 patients (continued)

Variable	Median overall survival (months)	<i>P</i> value	Median survival after metastases (months)	<i>P</i> value
ALB level		0.521		0.521
≤ 40 g/L	34		25	
> 40 g/L	44		35	
PLT level		0.655		0.655
≤ 100 × 10 ⁹ /L	39		31	
>100 × 10 ⁹ /L	37		34	
CEA		0.023		0.023
≤ 200 ng/mL	44		35	
> 200 ng/mL	25		25	
CA199		0.242		0.242
≤ 200 U/mL	38		31	
> 200 U/mL	39		34	

Footnotes as in Table 1.

Table 3. Major complications of radiofrequency ablation, HAI-FUDR and systemic chemotherapy

Major complication	Ablation group	FUDR group	<i>P</i> value
Pneumothorax	6	0	0.136
Hemothorax	1	0	1.000
Hydrothorax	3	0	0.473
Infection	2	3	0.498
Liver dysfunction	3	4	0.414
Bleeding	1	0	1.000
Grade 3–4 hematological toxicity	2	3	0.498
Grade 3 neurotoxicity	2	2	0.951
Grade 3–4 nausea/vomiting	4	5	0.346
Grade 3 diarrhea	2	2	0.951

Toxicity was assessed by using the common toxicity criteria of the National Cancer Institute, version 4.0. All values are presented as number of cases. HAI-FUDR, hepatic artery infusion of floxuridine.

sites or contraindication to resection, so resection was not performed in these patients.

Approximately 5%–10% of patients who present with metastatic disease of colorectal origin have a combination of hepatic and pulmonary metastases^[18]. A review of 1,142 patients with hepatic and pulmonary colorectal metastasis demonstrated that patients with complete resection had a median survival of 32–46 months, whereas patients with more than one extrahepatic metastatic site had a median survival of 13–25 months^[21]. Median OS in our study was 45.0 months, with 3- and 5-year survival rates of 49% and 26% for the ablation group, and 24% and 24% for the FUDR group, respectively. Different survival rates may be explained by the large number of variables in this complex patient selection process and tumor biology. Our 5-year survival compares favorably with the above studies^[21]. Differences in inclusion criteria and exclusion criteria may contribute to the variations in OS (e.g., patients with fewer and smaller

metastases might have received a complete resection or ablation and would have a better prognosis). Long-term outcomes of RFA alone for hepatic metastases from colorectal cancer are encouraging^[22–24], and the combination of RFA and liposomal chemotherapy is believed to increase hepatic tumor destruction and improve survival^[25,26]. For patients with a third metastatic site, such as distant lymph node metastases, prognosis was worse. However, our results were better than those from previous studies, which we believe was because of our experience with ablating metastatic lymph nodes at difficult sites using RFA^[27], and because multidisciplinary therapies (RFA and chemotherapy) were given to metastatic patients, resulting in prolonged survival.

In the present study, we found a trend toward better overall survival in patients with ≤ 7 metastatic lesions in the ablation group, though without statistical significance, which may be due to small sample size. The hazard ratios of OS and survival after metastasis

were 2.0 (95 % CI: 0.9–4.5, $P = 0.081$) and 1.8 (95 % CI: 1.0–3.2, $P = 0.087$), respectively. Pulitano *et al.*^[31] concluded that the total number of metastases implicated tumor biology, and different survival was found between low-burden and high-burden metastases. We found that OS was significantly different between patients with different lesions (1–3 lesions vs. more than 6 lesions, $P = 0.001$). Schule *et al.*^[28] found that single metastasis in liver and lung indicated a better prognosis in their study with 65 patients ($P = 0.036$). Similar results were reported in two other studies^[29,30].

The mechanisms of action for RFA treatment are not fully understood but several factors should be considered. First, after RFA, most of the metastases are destroyed, including most cancer stem cells (CSC) and the tumor microenvironment^[31]. Second, antitumor immunity is activated after ablation^[32]. The population of CSCs in colorectal cancer are increased after chemotherapy^[33] and are more resistant to conventional chemotherapy^[34].

As shown in our study and other previously published studies, most patients still died of cancer progression, indicating that it was a systemic disease at the time of distant metastasis; systemic chemotherapy was used to control the systemic micrometastasis and possible accelerated repopulation of tumor after ablation. HAI-FUDR is effective in shrinking hepatic metastases and improving survival^[7,8], but repeated chemotherapy may still result in cumulative toxicity. Therefore, the addition of RFA to systemic chemotherapy plus HAI-FUDR can enhance efficiency in destroying metastases (especially hepatic metastases), which may reduce the need for cycles of chemotherapy. The peripheral part of hepatic metastases usually has a rich blood supply, whereas the central part has a poor blood supply. Thus, chemotherapeutic agents can target the peripheral part effectively, whereas RFA can destroy the central part of metastases

more effectively after chemotherapy.

High level of CEA and maximal diameter of hepatic metastases >5 cm were associated with worse prognosis, and the former was validated in two large, randomized phase III studies of metastatic colorectal cancer^[35]. High CEA level may represent advanced stage of metastasis. In addition, larger hepatic metastases may easily lead to hepatic dysfunction and failure, which was a major cause of death in patients with extensive hepatic metastases. By contrast, another study indicated that preoperative CEA level was not an independent prognostic factor for survival^[36].

This study had notable limitations: it was a retrospective study, lacked randomization, and had a relatively small sample size. Randomized controlled trial is needed in the future. However, our results still indicate that further study investigating how to optimize debulking treatment (in terms of extent and frequency) is warranted.

In conclusion, our data indicate that the addition of RFA to systemic chemotherapy plus HAI-FUDR prolonged survival for patients with both unresectable hepatic and pulmonary metastases from colorectal cancer. Future prospective studies are needed to confirm the finding of this retrospective study.

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