Research Paper

Impact of Systemic Therapy and Recurrence Pattern on Survival Outcome after Radiofrequency Ablation for Colorectal Liver Metastases

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Abstract

Background: Most patients undergoing radiofrequency ablation (RFA) of colorectal liver metastasases (CLM) develop disease recurrence, but little is known about the effect of recurrence patterns and/or systemic therapy on outcome. In this study, we examined the recurrence patterns and survival after systemic therapy plus RFA in patients with unresectable CLM without extrahepatic disease. The aims were to analyze the effect of recurrence patterns on survival and to assess the relative benefit contributed by systemic therapy and local ablation to disease control and patient outcome.

Methods: From January 2002 to December 2012, 113 patients underwent RFA of liver-limited CLM after systemic therapy. Univariate and multivariate analyses for associations between clinical and/or treatment-related variables, recurrence-free survival (RFS), recurrence patterns, and overall survival (OS) were carried out.

Results: Of 113 patients, 105 (92.8%) had disease recurrence (median RFS: 6.1 months). Lower post-recurrence OS was observed after early (≤6 months) than after late recurrence (8.5 versus 24.0 months, p < 0.001). Recurrence sites were RFA-sites only (4.8%), liver-only (57.1%), lung-only (10.5%), or multiple (27.6%); the corresponding post-recurrence OS was 21, 19, 39, and 7 months (p < 0.001), respectively. Response to pre-RFA systemic therapy was the strongest predictor for OS (hazard ratio [HR] 5.28), RFS (HR 3.30), early (odds ratio [OR] 6.34) and multiple-site recurrence (OR 3.83) (p < 0.01), respectively; only responders achieved 5-year OS and RFS (29% and 12% versus 0% and 0% for non-responders, p < 0.001, respectively).

Conclusions: Survival after RFA for liver-limited CLM is strongly linked to the timing and pattern of non-local disease recurrence. Local ablation efficacy is necessary but not sufficient to obtain long-term disease control. Effective pre-RFA systemic therapy does favourably affect the incidence, timing and patterns of recurrence and long-term survival and appears essential for the tailoring of RFA application to maximize patient benefit.

Key words: Colorectal cancer, metastases, radiofrequency ablation, recurrence, survival.

Introduction

The treatment options for patients with unresectable colorectal liver metastases (CLM) have evolved markedly, especially with the modern-agent systemic and local ablative therapies now available for routine use [1,2]. Among ablative therapies, radiofrequency ablation (RFA) is the most widely used for complete eradication of unresectable CLM.[3] Local recurrence (LR) rates after RFA of small (≤3-4 cm) CLM in current studies are low (<10%) [4], and reported 5-year overall survival (OS) rates following

RFA for liver-limited CLM range between 17 to 51% [5-9]. However, the standard treatment for unresectable CLM is systemic therapy, and the precise place of RFA within the treatment algorithm is not defined.

Treatment of liver-only CLM evolves towards combining local and systemic therapy, owing to the fact that it represents a systemic disease. The randomized phase II CLOCC trial supports this concept and documents improved 5-year OS from adding RFA upfront to chemotherapy in patients with up to 9 liver-limited CLM [10,11]. However, >80% of patients' experience disease recurrence distant from RFA-treated CLM within 12 months, and virtually no RFA-treated patient achieves 5-year recurrence-free survival (RFS) [12]. Therefore, it is reasonable to consider that the recurrence pattern may play a role for survival outcome. However, while some data on recurrence patterns after RFA of liver-limited CLM exist [13,14], little is known about the effect of these recurrence patterns on survival outcome.

With the availability of effective antineoplastic agents, response to modern-agent regimens has become an important prognostic factor and has been shown to convert unresectable CLM to respectability [15,16]. This raises the increasing need to define the results and place of RFA of CLM with regard to the responsiveness of disease to systemic therapy. Based on prior data suggesting a potential for long-term RFS after RFA of liver-limited CLM responding to chemotherapy [17,18], we considered that the more common inverse phenomenon of disease recurrence was worthy of further study. An analysis of the relationship between response to pre-RFA systemic therapy, post-RFA recurrence patterns, and survival outcome may help to better define the current place of RFA in the multimodality treatment of unresectable liver-limited CLM and also aid to improve multimodal concepts and/or patient stratification in future clinical trials. Therefore, such analysis may be of interest for both clinical and research settings.

In the present study, we evaluated the incidence, timing, and patterns of recurrence and survival after systemic therapy plus RFA in patients with unresectable CLM without extrahepatic disease (EHD). The aims were to assess the effect of recurrence pattern on survival and to assess the relative benefit contributed by systemic therapy and local ablation to disease control and patient outcome.

Materials and methods

Patient selection

We performed a retrospective review of a prospectively collected database of patients who had received RFA of liver-limited CLM after systemic therapy at the Asklepios Hospital Barmbek between January 2002 and December 2012. The study was approved by the Ethics Committee the Asklepios Hospital Barmbek and carried out in accordance with the Declaration of Helsinki. All patients included into the database provided written informed consent for scientific evaluation of the data. Inclusion criteria for RFA treatment were: ≤5 unresectable liver-only CLM of ≤5 cm maximum size, and anticipated life expectancy of ≥6 months. Non-resectability was determined by two hepatobiliary surgeons and defined as technically impossible to achieve a margin-negative resection with preservation of ≥30% liver parenchyma (i.e. a margin-negative resection requires resection of 3 hepatic veins or both portal veins; or, a resection leaves <2 adequately perfused and drained segments). Inoperability was determined by two surgeons, one oncologist, and one anaesthetist and defined as contraindications to general anaesthesia (deterioration of general condition and/or cardio respiratory disease), inadequate liver function, Karnofsky performance score of less than 70%, or patient's refusal. Exclusion criteria for RFA were proximity of CLM to major biliary structures or bleeding disorders.

Pre-RFA assessments

Assessments included performance status evaluation, liver function tests, carcinoembryonic antigen (CEA) evaluation, and contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis. Response to systemic therapy was classified as partial response (PR), stable disease (SD), or progressive disease (PD) using the Cancer Response Evaluation Criteria In Solid Tumours (RECIST) [19].

RFA procedure

RFA was performed percutaneously under conscious sedation and analgesia and guided by ultrasonography (US) or CT. A 15-gauge multi-tined expandable RF needle electrode (LeVeen, Boston Scientific, Natick; 3 or 4 cm in diameter) was used connected to an RF generator (RF 3000, Boston Scientific, Natick, MA, USA). After stepwise increase of power, primary end points for a technically successful ablation were ≥2 increases in tissue impedance. Routinely, contrast-enhanced US (SonoVue, Bracco, Milan, Italy) guided additional ablations if the ablation volume achieved was insufficient compared to the pre-RFA tumour size and/or margin. An RFA procedure was considered to be complete when the ablated area, as determined by the absence of contrast enhancement at US,

encompassed the RFA-treated CLM by including a ≥0.5 cm ablative margin.

Post-RFA assessments

Assessments included contrast-enhanced CT of the chest, abdomen, and pelvis and CEA evaluation. Initial post-RFA CT imaging was performed 4 weeks after RFA treatment to establish a new baseline, thereafter every 3 months for the first 2 years, and then 6 monthly. Each follow-up study was compared to the contrast-enhanced CT images before RFA and the new baseline CT studies after RFA. Treatment efficacy was determined on according to the criteria proposed by the International Working Group on Image-Guided Tumour Ablation [3]. Local recurrence was defined as the development of new focal areas of contrast enhancement at follow-up CTs, either within or adjacent to the edge of RFA-treated CLM that were previously considered to be completely ablated. All other new contrast-enhancing focal lesions at other intra-/ and extrahepatic sites were considered new metastases and defined as intra- and/or extrahepatic recurrence. Procedural complications were determined according to the Society of Interventional Radiology (SIR) classification system [20]. Major complications were defined as events associated with substantial morbidity and disability, requiring surgical or radiological interventions, blood transfusion, significant medical therapies or longer hospital stay. All other complications were considered minor.

Statistical analysis

Quantitative and qualitative variables were summarized in terms of median (range), mean (standard deviation), and frequency (percentage). Comparisons between groups were analyzed with the chi-square or Fisher exact test for categorical variables and the Mann-Whitney U test for continuous variables, as appropriate. Survival curves for OS and RFS were calculated using the Kaplan-Meier method and compared using log-rank tests. All variables associated with survival or recurrence patterns with p ≤ 0.05 in the univariate analyses were subsequently entered into a Cox multivariate proportional hazard model to assess their independent influence. Estimated hazards ratios (HRs) for survival duration and odds ratios (ORs) for predicting recurrence were ranked to assess the most important factor among independent factors identified on multivariate analysis. For all tests, p-values ≤ 0.05 were considered statistically significant. Statistical analyses were performed using the SAS Statistical Software Version 9.1 (SAS, Institute Inc.; Cary, North Carolina, USA).

Results

Patient characteristics

Table 1 shows the baseline characteristics of the study population, which included a total of 113 patients (69 men, 44 women, median age: 70 years) with 279 CLM. The median number of RFA-treated CLM per patient was 2.5 (range 1-5), with a median size of the largest RFA-treated CLM of 2.8 cm (range: 0.6 to 5.0 cm). With respect to the total exposure to antineoplastic agents, patients had received on average 3 (range 1-5) lines of systemic therapies before and after RFA: a total of 106 patients (94%) had been treated with FOLFOX, 107 (95%) with FOLFIRI, 63 (55%) with bevacizumab, and 23 (20%) with cetuximab. Details with respect to chemotherapy before RFA were as follows: a total of 66 patients (58%) underwent RFA after one line, 36 (32%) after two lines, and 11 (10%) after 3 lines of prior systemic therapy. Most frequently applied last line pre-RFA regimens were FOLFOX (47% [53/113] and FOLFIRI (37% [42/113]). RFA was performed after PR in 63 patients (56%); 21 patients (19%) had SD, and 29 patients (25%) had PD after the last line pre-RFA systemic therapy.

RFA-related Efficacy and Complications

Primary technical success was obtained in 93.6% (261 of 279) CLM. Secondary technical success was obtained in 100% (18 of 18) re-ablated CLM with residual enhanced tumour on follow-up CT ≤4 weeks. Local RFA-site recurrence rates were 7.2% (20/279) on lesion basis, and 14.1% (16/113) on patient basis. Adverse events related to the RFA procedure were observed in 10.6% of patients (12/113). Three patients (2.6%) developed major complications (3x infected biloma requiring drainage and antibiotic therapy). The remaining 9 patients had one or more self-limiting minor complications (7 post ablation syndromes, 5 pleural effusions, 2 intrahepatic hematomas). There were no RFA-related deaths.

Survival Outcome

After a median follow-up from the date of RFA of 107 months (Interquartile range 83-127 months), the median OS for the entire cohort (n=113) was 25.0 months (95% confidence interval [95% CI] 20.1-31.9), and the 5-year OS rate was 16.3% (95% CI 9.9-23.9). Median RFS was 6.9 months (95% CI 5.0-8.9) with a 5-year RFS rate of 7.1% (95% CI 3.1-12.5). OS was significantly higher for responders to systemic therapy before RFA (median 36.0 months; 29.1% [95% CI 18.3-42.2] at 5 years) than for non-responders (median 12.0 months; 0% at 5 years, p < 0.001) (Figure 1). Similarly, RFS was different between responders

(median 10.0 months; 12.7% [95% CI 5.7-21.9] at 5 years) and non-responders (median 4.0 months, 0% at 5 years, p < 0.001 (Figure 1).

Table 1. Baseline data of the study cohort.

Characteristic	Value
Patients, n	113
Male, n (%)	69 (61)
Female, n (%)	44 (39)
Median age (range), years	70 (36-88)
Mean age ± SD, years	68.6 ± 8.58
Primary tumor	
Colon, n (%)	89 (79)
Rectum, n (%)	24 (21)
Node status	
Positive, n (%)	79 (70)
Negative, n (%)	34 (30)
Presentation of CLM	
Synchronous, n (%)	24 (21)
Metachronous, n (%)	89 (79)
Number of CLM	
Median number (range)	2.5 (1-5)
Mean number ± SD	2.7 ± 0.16
Number of 1-3 CLM, n (%)	87 (77)
Number of 4-5 CLM, n (%)	26 (23)
Size of CLM, cm	
Median maximum size (range)	2.8 (0.6-5.0)
Mean maximum size ± SD	2.9 ± 0.21
Maximum size ≤ 3 cm, n (%)	79 (70)
Maximum size > 3-5 cm, n (%)	34 (30)
CEA levels before RFA, ng/mL	
Median CEA level (range)	125.5 (3-1.578)
Mean CEA level ± SD	81.3 ± 15.6
CEA ≤ 100, n (%)	71 (63)
CEA > 100, n (%)	42 (37)
Main cause of unresectability and/or inoperability	
Expected liver remnant ≤ 30%, n (%)	19 (17)
Proximity to critical structures, n (%)	25 (22)
Medical comorbidity, n (%)	52 (46)
Patients refusal, n (%)	17 (15)
Systemic therapies before RFA	
Median number of lines (range)	1.5 (1-3)
Mean number of lines ± SD	1.5 ± 0.07
≥2 lines of systemic therapy, n (%)	47 (41)
5-Fluorouracile monotherapy, n (%)	43 (38)
Oxaliplatin-based combination therapy (FOLFOX), n (%)	75 (66)
Irinotecan-based combination therapy (FOLFIRI), n (%)	54 (48)
+ Bevacizumab, n (%)	30 (27)
+ Cetuximab, n (%)	8 (7)
Systemic therapies before and after RFA	
Median number of lines (range)	3 (1-5)
Mean number of lines ± SD	3.1 ± 0.1
5-Fluorouracile monotherapy, n (%)	76 (67)
Oxaliplatin-based combination therapy (FOLFOX), n (%)	106 (94)
Irinotecan-based combination therapy (FOLFIRI), n (%)	107 (95)
+ Bevacizumab, n (%)	63 (56)
+ Cetuximab, n (%)	23 (20)
Response to last line regimen before RFA	
Partial remission, n (%)	63 (56)
Stable disease, n (%)	21 (19)
Progressive disease, n (%)	29 (25)

CEA, carcinoembryonic antigen; CLM, colorectal liver metastases; RFA, radiofrequency ablation.

Factors associated with Survival Outcome

At the time of RFA treatment, five factors were independently associated with OS (Table 2): CEA level (p = 0.012), size of CLM (p = 0.022), number of CLM (p < 0.001), number of lines of systemic therapy before RFA (p = 0.001), and response to systemic therapy before RFA (p < 0.001). Four factors were independently associated with RFS: size of CLM (p = 0.001), number of CLM (p < 0.004), number of lines of systemic therapy before RFA (p = 0.017) and response to systemic therapy before RFA (p < 0.001). Ranking of HRs revealed response to systemic therapy before RFA as the most important factor affecting OS (HR: 5.28, p < 0.001) and RFS (HR: 3.30; p < 0.001) (Table 2).

Recurrence Pattern

A total of 105 of the 113 (92.8%) patients had recurrent disease (median time to recurrence: 6.1 months [range 1-24 months]). Most patients (83.8% [88/105]) developed intrahepatic disease as a component of recurrence, and 65 (61.9%) presented with liver-limited recurrence. Of the 41 patients (39.0%) who experienced extrahepatic recurrence, 24 (58%), 9 (22%), 5 (12%), 2 (5%) and 1 (2.5%) failed in the lung, regional lymph nodes, peritoneum, bone, and spleen, respectively, as the site of recurrence. There were 11 patients (10.5%) who had recurrence only in the lung. Single organ site recurrences (n = 76) predominated over multiple organ site recurrences (n = 29). The 65 liver-only recurrences accounted for the majority (85.5%) of single site recurrences. Only 5 patients (4.8%) had a local RFA-site recurrence as the sole site of recurrence.

Recurrence Pattern and Survival Outcome

After a median follow up from the date of recurrence of 99 months (Interquartile range 76-123 months), the median OS for the whole recurrence group (n = 105) was 16.0 months (95% CI 12.9-20.1) with a 5-year OS rate of 4.7% (95% CI 1.3-9.9). Post-recurrence OS was significantly lower after early (≤6 months) compared to later (>6 months) recurrence (median 8.5 versus 24 months; 0% and 4.2% [95% CI 2.6-18.9%] at 5 years, p < 0.001, Figure 2). With respect to the recurrence pattern, post-recurrence OS was as follows: a lung-only recurrence was associated with the best OS (median 39.9 months; 10.2% [95% CI 0.2-35.5%] at 5 years); the next best OS was for patients with liver-only recurrence (median 19.1 months, 6.2% [95% CI 1.4-14.0%] at 5 years), whereas those with multiple-site recurrence had the worst outcome (median 7.0 months, 0% at 5 years, p < 0.001; Figure 2).

Table 2. Univariate and multivariate analysis of factors associated with overall survival and recurrence-free survival after systemic therapy plus radiofrequency ablation of colorectal liver metastases.

Variables	No. of patients	Overall survival					Recurrence-free survival				
		Univariate analysis			Multivariate analysis		Univariate analysis			Multivariate analysis	
		Median months (95% CI)	5-years, % (95% CI)	p-value	HR (95% CI)	p-value	Median months (95% CI)	5-years, % (95% CI)	p-value	HR (95% CI)	p-value
Patient and tumor characteristics											
Age				0.690					0.254		
≤ 60 years	21	21.9 (15.9-38.0)	15.7 (3.4-34.7)				7.0 (4.9-10.9)	14.3 (3.0-32.0)			
> 60 years	92	25.0 (20.9-31.0)	16.5 (9.5-25.0)				6.9 (5.0-9.0)	5.4 (2.7-10.9)			
Gender				0.643					0.730		
Male	69	25.0 (18.0-31.1)	15.2 (7.4-25.1)				6.97 (5.0-9.9)	7.3 (2.4-14.5)			
Female	44	25.0 (18.1-36.0)	18.2 (8.3-30.8)				6.97 (4.9-9.0)	6.8 (1.6-16.0)			
Primary tumor				0.527					0.505		
Colon	89	24.0 (18.0-31.1)	15.1 (8.2-23.6)				6.9 (5.0-8.9)	6.7 (2.5-12.8)			
Rectum	24	30.0 (22.0-36.9)	20.8 (7.3-38.9)				7.0 (5.9-10.9)	8.3 (0.8-22.3)			
Node status				0.924					0.967		
Positive	79	28.0 (21.9-33.9)	14.4 (7.4-23.1)				6.9 (5.0-9.1)	7.6 (2.8-14.4)			
Negative	34	20.0 (16.0-31.9)	21.5 (9.1-37.4)				6.4 (4.9-10.0)	5.8 (0.6-16.1)			
CLM				0.967					0.056		
Synchronous	24	25.5 (22.0-36.0)	13.9 (3.0-31.0)				9.5 (6.0-11.9)	4.2 (0.7-15.6)			
Metachronous	89	25.0 (18.0-33.0)	17.0 (9.7-25.7)				6.0 (4.9-7.1)	7.8 (3.2-14.3)			
CEA level before RFA				<0.001	1.68 (1.10-2.57)	0.012			0.004		
≤ 100 ng/ml	71	31.1 (25.0-36.0)	21.5 (12.6-32.2)				8.9 (6.9-10.0)	9.8 (4.1-17.8)			
> 100 ng/ml	42	15.5 (11.1-25.0)	7.5 (1.5-17.6)				5.0 (4.0-6.0)	2.4 (0.6-9.1)			
Maximum size of CLM				<0.001	1.78 (1.09-2.90)	0.022			<0.001	2.18 (1.36-3.48)	0.001
≤ 3 cm	79	31.9 (24.0-36.0)	22.3 (13.6-32.5)				9.0 (6.9-10.0)	10.1 (4.5-17.7)			
3-5 cm	34	14.5 (10.0-22.0)	2.94 (2.0-11.1)				4.0 (3.0-5.0)	0 (.-.)			
Number of CLM				<0.001	2.68 (1.62-4.46)	<0.001			0.012	1.99 (1.25-3.17)	0.004
1-3	87	29.0 (23.0-35.0)	20.17 (12.3-29.3)				7.0 (6.0-9.0)	9.2 (4.1-16.1)			
4-5	26	13.5 (10.0-26.9)	0.00 (-)				4.5 (3.0-9.0)	0 (.-.)			
Systemic therapy before RFA											
Lines of therapy received				0.002	1.88 (1.21-2.92)	0.001			0.012	1.67 (1.10-2.55)	0.017
1	66	31.9 (26.9-36.0)	18.2 (9.7-28.7)				9.0 (7.03-10.02)	6.1 (1.6-13.0)			
≥2	47	13.0 (10.0-17.9)	13.7 (5.3-25.2)				4.0 (3.02-5.03)	8.5 (2.3-18.1)			
Oxaliplatin used in last line				0.482					0.160		
Yes	53	24.0 (18.0-35.0)	20.1 (10.4-31.9)				7.9 (5.0-10.1)	9.4 (3.2-18.6)			
No	60	26.0 (18.0-31.9)	12.6 (5.2-22.7)				6.0 (5.0-8.0)	5.0 (1.0-11.9)			
Irinotecan used in last line				0.673					0.140		
Yes	42	25.0 (15.9-33.0)	13.2 (4.2-26.1)				5.5 (4.9-7.0)	7.1 (1.4-16.7)			
No	71	25.0 (18.0-34.0)	17.7 (9.7-27.5)				7.9 (5.9-9.9)	7.0 (2.3-14.1)			
Bevacizumab used in last line				0.425					0.920		
Yes	24	23.0 (18.0-33.0)	24.1 (8.7-43.9)				6.0 (4.9-7.0)	12.5 (2.6-28.3)			
No	89	26.0 (18.0-33.0)	14.4 (7.8-22.6)				6.9 (5.0-9.9)	5.6 (1.8-11.3)			
Cetuximab used in last line				0.236					0.126		
Yes	8	34.5 (22.0-38.5)	25.0 (3.1-58.4)				11.0 (6.0-12.0)	12.5 (0.2-42.3)			
No	105	25.0 (18.0-29.9)	15.6 (9.2-23.4)				7.0 (5.0-8.0)	6.7 (2.7-12.2)			
Response to last line regimen				<0.001	5.28 (3.18-8.77)	<0.001			<0.001	3.30 (2.09-5.20)	<0.001
Partial remission	63	36.0 (32.9-46.9)	29.1 (18.3-41.2)				10.0 (9.0-12.0)	12.7 (5.7-22.0)			
Stable disease	21	21.9 (15.9-25.0)	0.00 (.-.)				5.9 (4.9-7.0)	0 (.-.)			
Progressive disease	29	9.03 (8.0-10.9)	0.00 (.-.)				3.0 (2.9-4.0)	0 (.-.)			

95% CI, 95% confidence interval; CEA, carcinoembryonic antigen; CLM, colorectal liver metastases; HR, hazard ratio; RFA, radiofrequency ablation.
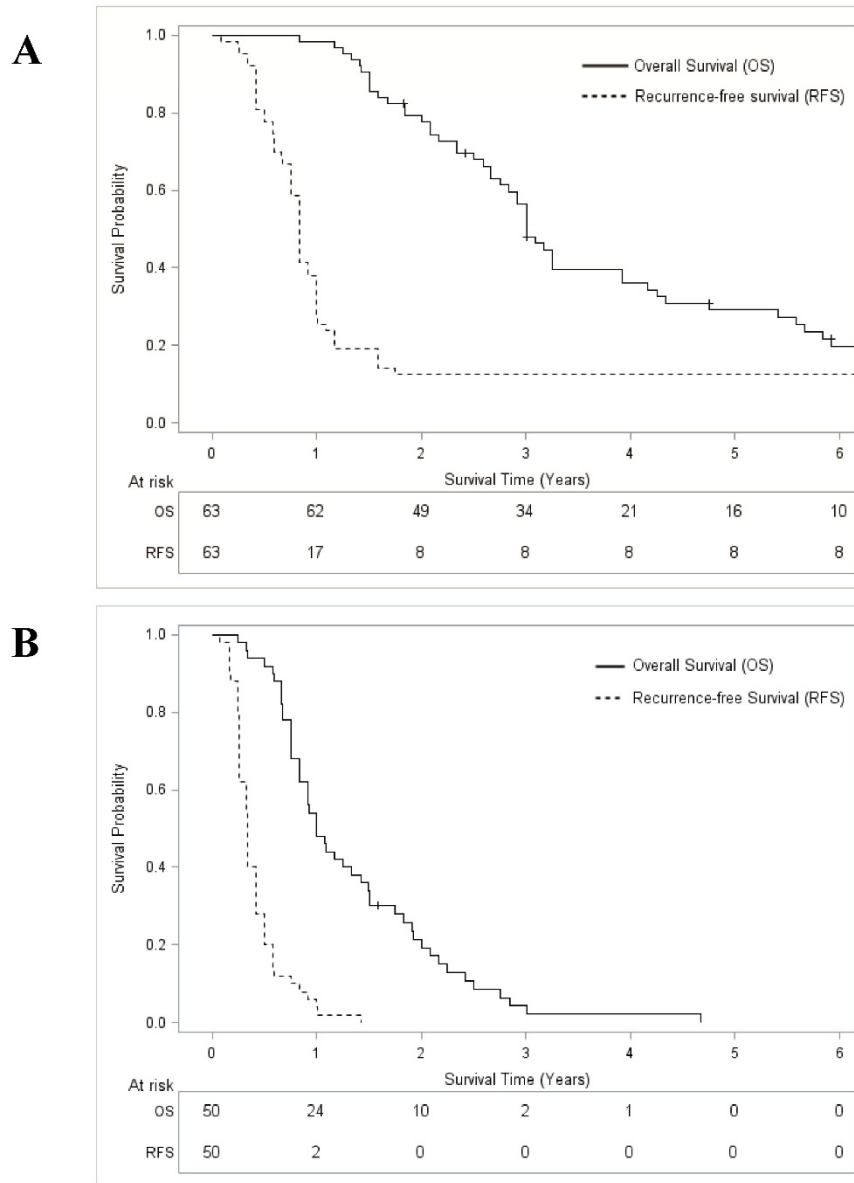
Figure 1. Overall survival and recurrence-free survival curves after systemic therapy plus radiofrequency ablation for colorectal liver metastases. A: Responders to systemic therapy; B: Non-responders to systemic therapy.

Predictors of Recurrence Pattern

At the time of RFA treatment, three parameters were independent predictors of early (≤6 months) recurrence following RFA (Table 3): size of >3 cm of CLM (p = 0.005), number of ≥2 lines of systemic therapy before RFA (p = 0.027), and no response to systemic therapy before RFA (p < 0.001). Two parameters were independent predictors of multiple site recurrence: number of >3 RFA-treated CLM (p = 0.006) and no response to systemic therapy before RFA (p < 0.001). Ranking of ORs identified no response to systemic therapy before RFA as the strongest predictor of early recurrence (OR 6.34, p < 0.001) and multiple site recurrence (OR 3.83, p < 0.001) (Table 3). Associations between the timing and recurrence patterns are detailed in Table 4.

Responders versus Non-responders to pre-RFA Systemic Therapy

RFA was performed in 63 patients (56%) during response (PR group) and in 50 patients (44%) without response (non-PR group) after systemic therapy. Response was not related to the agents and/or regimens used, but both timing and patterns of recurrence differed significantly between the PR and non-PR group (Table 5). Response was associated with a 6 months longer RFS (p < 0.001) and a higher rate of lung-only recurrence (18.2% vs. 2.0%, p = 0.007). By contrast, significantly higher rates of local RFA-site recurrence (24.0% vs. 7.3%), multiple site recurrence (40.0% vs. 16.4%), and intrahepatic recurrence (90.0% vs. 68.2%) were observed in the non-PR group (p < 0.05, respectively, Table 5).
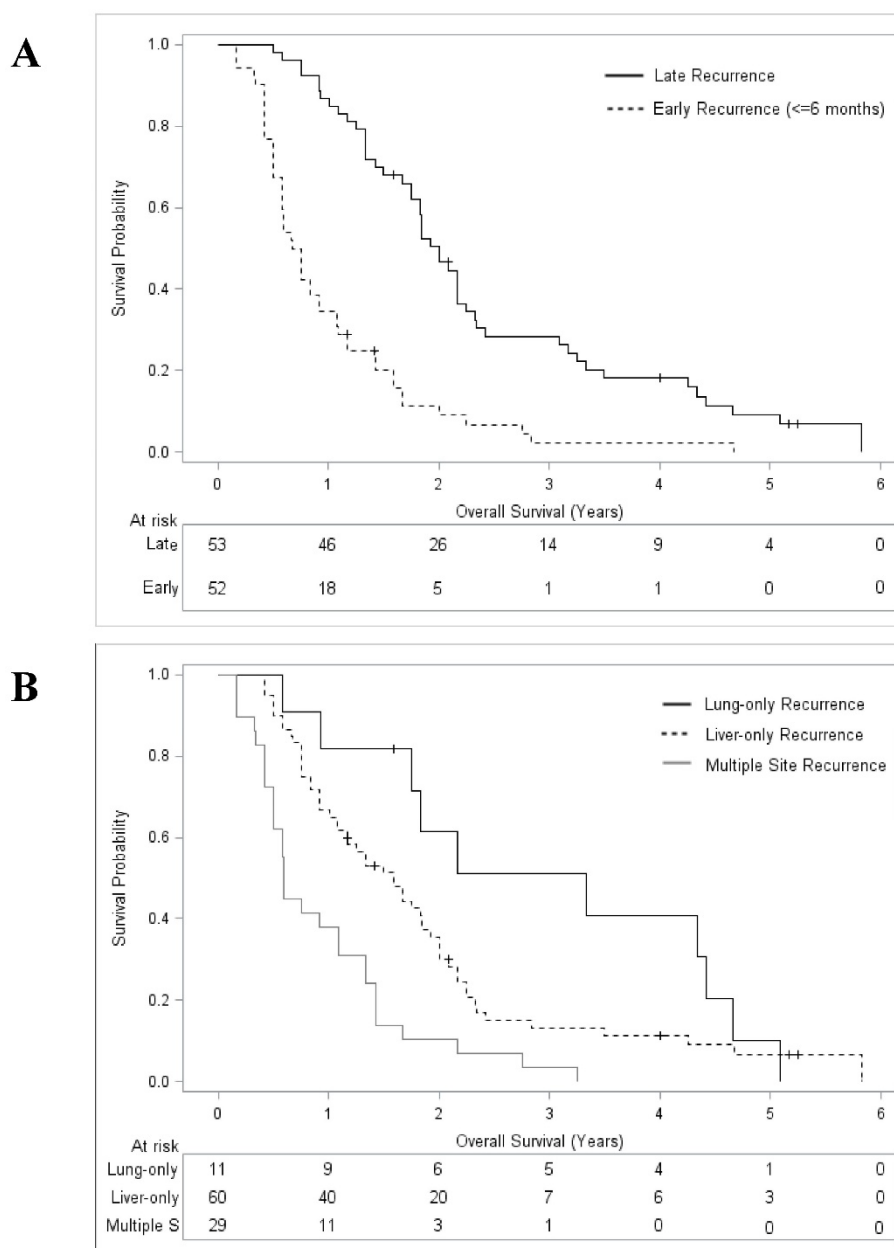
Figure 2. Overall survival curves from initial recurrence of disease after systemic therapy plus radiofrequency ablation for colorectal liver metastases. A: Stratified by recurrence timing; B: Stratified by recurrence sites.

Table 3. Univariate and multivariate analysis of factors associated with multiple (≥2) site recurrence and early (≤6 months) recurrence after systemic therapy plus radiofrequency ablation of colorectal liver metastases.

Variable	No. of patients	Multiple site recurrence				Early recurrence			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		Multiple site recurrences n, (%)	p-value	OR (95% CI)	p-value	Early recurrences n, (%)	p-value	OR (95% CI)	p-value
Patient and tumor characteristics									
Age			0.257				0.965		
≤ 60 years	18	7 (38.9)				9 (50)			
> 60 years	87	22 (25.3)				43 (49.4)			
Gender			0.137				0.903		
Male	64	21 (32.8)				32 (50)			
Female	41	8 (19.5)				20 (48.8)			
Primary tumor			0.967				0.363		
Colon	83	23 (27.7)				43 (51.8)			
Rectum	22	6 (27.3)				9 (40.9)			

Variable	No. of patients	Multiple site recurrence				Early recurrence			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		Multiple site recurrences n, (%)	p-value	OR (95% CI)	p-value	Early recurrences n, (%)	p-value	OR (95% CI)	p-value
Node status			0.939				0.625		
Positive	73	20 (27.4)				35 (47.9)			
Negative	32	9 (28.1)				17 (53.1)			
CLM			0.215				0.038		
Synchronous	23	4 (17.4)				7 (30.4)			
Metachronous	82	25 (30.5)				45 (54.8)			
CEA level before RFA			0.453				0.002		
≤ 100 ng/ml	64	16 (25.0)				24 (37.5)			
> 100 ng/ml	41	13 (31.7)				28 (68.3)			
Maximum size of CLM			0.009				<0.001	4.91 (1.63-14.82)	0.005
≤ 3 cm	71	14 (19.7)				26 (36.6)			
3-5 cm	34	15 (44.1)				26 (76.5)			
Number of CLM			0.003	3.47 (1.33-8.65)	0.006		0.337		
1-3	79	16 (20.2)				37 (46.8)			
4-5	26	13 (50.0)				15 (57.7)			
Systemic therapy before RFA									
Lines of therapy received			0.346				<0.001	3.33 (1.15-9.64)	0.027
1	62	15 (24.2)				20 (32.3)			
≥2	43	14 (32.6)				32 (74.4)			
Oxaliplatin used in last line			0.745				0.488		
Yes	48	14 (29.2)				22 (45.8)			
No	57	15 (26.3)				30 (52.6)			
Irinotecan used in last line			0.579				0.058		
Yes	39	12 (30.8)				24 (61.5)			
No	66	17 (25.7)				28 (42.4)			
Bevacizumab used in last line			0.913				0.435		
Yes	21	6 (28.6)				12 (57.1)			
No	84	23 (27.4)				40 (47.6)			
Cetuximab used in last line			0.091				0.113		
Yes	7	0 (0 %)				1 (14.3)			
No	98	29 (29.6)				51 (52.0)			
Response to last line regimen			0.002	3.83 (1.48-10.85)	0.001*		<0.001*	6.34 (2.29-17.56)	<0.001
Partial remission	55	9 (16.4)				13 (23.6)			
Stable disease	21	6 (28.5)				11 (52.4)			
Progressive disease	29	14 (48.3)				28 (96.5)			

95% CI, 95% confidence interval; CEA, carcinoembryonic antigen; CLM, colorectal liver metastases; OR, odds ratio; RFA, radiofrequency ablation.

Table 4. Patterns and timing of disease recurrence after systemic therapy plus radiofrequency ablation of colorectal liver metastases.

Variable	Any recurrence (n = 105)	Early recurrence ≤ 6 months (n = 52)	Late recurrence > 6 months (n = 53)	p-value*
Patterns of recurrence				
Any local recurrence (LR), n (%)	16 (15.2)	8 (15.4)	8 (15.1)	0.967
LR, only n, (%)	5 (5.8)	2 (3.8)	3 (5.7)	1.000
Any intrahepatic recurrence n, (%)	88 (83.8)	48 (92.3)	40 (75.5)	0.019
Liver, only n, (%)	65 (61.9)	30 (57.7)	30 (56.6)	0.910
Any extrahepatic recurrence, n (%)	41 (39.0)	21 (40.4)	20 (37.7)	0.781
Lung, only n, (%)	11 (10.5)	1 (1.9)	10 (18.9)	0.005
Disseminated Recurrence				
≥2 sites (disseminated), n, (%)	29 (27.6)	19 (36.5)	10 (18.9)	0.043

* Pairwise comparison between early and late recurrence.

Table 5. Comparison of systemic therapy and recurrence patterns between responders and non-responders to the last line systemic therapy before RFA treatment.

Variable	Responder (PR)	Non-Responder (SD,PD)	p-values
Number of patients (%)	63 (56)	50 (44)	
Systemic therapy received before RFA			
Median number of lines (range)	1.2 (1-3)	1.8 (1-3)	<0.001
≥2 lines of chemotherapy, n (%)	14 (22.2)	33 (66.0)	<0.001
Oxaliplatin used in last line	30 (47.6)	23 (46.0)	0.864
Irinotecan used in last line	22 (34.9)	20 (40.0)	0.579

Bevacizumab used in last line	12 (19.1)	12 (24.0)	0.523
Cetuximab used in last line	5 (7.9)	3 (6.0)	1.000
Systemic therapy received before and after RFA			
Median number of lines (range)	2.9 (1-5)	3.2 (2-5)	0.011
Oxaliplatin	57 (90.5)	49 (98.0)	0.131
Irinotecan	57 (90.5)	50 (100)	0.033
Bevacizumab	37 (58.7)	26 (52.0)	0.474
Cetuximab	10 (15.9)	13 (26.0)	0.184
Timing of recurrence after RFA			
Median time (range) to recurrence, months	10.0 (9.0-12.0)	4.0 (3.0-5.0)	<0.001
Time to recurrence ≤ 6months (early)	13 (23.6)	39 (78.0)	<0.001
Time to recurrence > 6 months (late)	42 (76.4)	11 (22.0)	
Patterns of recurrence after RFA			
No recurrence	8 (12.8)	0 (0)	0.009
Any local RFA-site recurrence (LR)	4 (7.3)	12 (24.0)	0.028
LR, only	2 (3.2)	3 (6.0)	0.867
Any intrahepatic recurrence	43 (68.2)	45 (90.0)	0.039
Liver, only	34 (61.8)	26 (52.0)	0.310
Any extrahepatic recurrence	19 (30.2)	22 (44.0)	0.581
Lung, only	10 (18.2)	1 (2.0)	0.007
Number of recurrence sites			
≥2 sites (disseminated)	9 (16.4)	20 (40.0)	0.007

PD, progressive disease; PR, partial remission; RFA, radiofrequency ablation; SD, stable disease.

Discussion

Traditionally, RFA has been used as single procedure for eradication of CLM from the liver to offer inoperable patients the chance of long-term OS. As a main problem following RFA involves the high risk of non-local disease recurrence, adjuvant systemic therapy may be an option to address occult microscopic disease, however, with uncertain responsiveness of macroscopic disease. The present study evaluates the prognostic importance of recurrence patterns in patients with liver-limited CLM rendered clinically disease-free after systemic therapy plus subsequent RFA treatment. The clinical importance of recognizing the prognostic impact of post-RFA recurrence patterns with known pre-RFA response of CLM is 2-fold: First, it reveals the relative benefits and limitations of RFA for disease control and patient outcome, and it provides direction for adjuvant strategies in the future.

With an overall recurrence rate of 92% and the predominance of non-local liver-limited recurrence (57%), our data are close to those reported in previous RFA studies [5-9,21, 22]. To our knowledge, however, this study is the first to show that the timing and patterns of disease recurrence after RFA carry important prognostic significance. Early (≤6 months) recurrence was associated with significantly lower post-recurrence OS than after late recurrence (8.5 versus 24 months), and recurrence in multiple sites was associated with significantly shorter median OS (7 months) when compared to liver-only recurrence (19 months) or lung-only recurrence (39 months). In addition, both early and multiple site recurrence were significantly associated. Therefore, in patients with

complete ablatable CLM at presentation, the tumor biology can differ [23] and the associated course of recurrent disease and prognosis can vary. Despite complete tumor clearance from the liver by RFA, aggressive tumor biology may lead to an aggressive clinical course with poor patient outcome. This poor prognosis group of patients lacking realistic chance of long-term survival after RFA of liver-limited CLM have to be identified to avoid unnecessary RFA treatment.

Multivariate analysis outlined response to pre-RFA systemic therapy as the strongest independent predictor for OS (HR 5.28), RFS (HR 3.30), and prognostically poor early (OR 6.34) and/or multiple-site recurrence (OR 3.83) in our study population. Furthermore, only responders, but none of the RFA-treated non-responders, achieved 5-year survival without disease recurrence or 5-year OS. These effects were only related to response and not related to any particular agent and/or regimen used. Whether response simply identified the disease biology or whether effective systemic therapy modified the course of disease is impossible to prove in our study. We assume that drug efficacy against microscopic disease and indolent disease biology combined to influence for the better RFS and OS in our study population [24]. While the randomized phase II CLOCC trial documents an OS benefit from adding RFA upfront to systemic therapy [11], our study shows that response is prognostically important, rather than the use of systemic therapy itself. In addition to response, number (≥2) of lines of pre-RFA systemic therapy, number (≥4) and size (≥3 cm) of CLM were also independent predictors of early and/or multiple site recurrence and poor outcome in

our study cohort.

Our local (RFA-site) recurrence rate was 14.1% per patient and 7.2% per lesion, which is comparable with rates reported in other RFA studies [4,21,22]. RFA-site recurrence occurred less frequently in responders to systemic therapy, likely because downsizing chemotherapy had eradicated micrometatases surrounding CLM [25]. More importantly, only 5 patients (<5%) developed RFA-site recurrence as the sole site of recurrence, underscoring that non-local recurrence was the key determinant of prognosis in our series. However, outcome did not simply depend upon response to systemic therapy in our study cohort. Local ablation helped systemic agents to control disease at original sites, which was necessary, although not sufficient, to achieve long-term disease control. A long-term-result with a 5-year RFS rate of 12.7% seen in our RFA-treated responders would likely be unrealizable using systemic therapy alone, and supports a positive impact on long-term outcome from RFA-mediated eradication of responding CLM within this subgroup.

The predominant recurrence pattern was non-local liver-limited recurrence (57%) in our study cohort. We and others noted a higher rate of liver-only recurrence after RFA (32-62.5%) [14,21] compared to the 17-34% after resection of CLM [9,26,27], likely because hepatectomy removes parenchymal micrometastases who are at risk for future CLM [22,28]. This provides a rationale to investigate the role of adjuvant post-RFA liver-directed arterial therapy, such as hepatic arterial infusion, to target hepatic micrometastases [29]. In new studies evaluating adjuvant liver-directed arterial therapy, it will be important to assess clinical end points with benefit to patients. Our findings here suggest that RFA-treated responders to systemic therapy might constitute a proper study population to test whether improving hepatic RFS can lead to improved OS as well.

Our findings carry implications and provide direction for both clinical and research settings. First, RFA should not be used as single or upfront therapy for liver-limited CLM with uncertain responsiveness of disease. A selection process (test-of-time approach) by systemic therapy, with the objective to determine the long-term benefit, is necessary to identify those patients who may benefit from RFA and those who will not. Among patients that have progressive disease despite systemic therapy, subsequent RFA is not advocated, even in case of complete ablatable CLM. Second, the optimal timing of RFA is during maximum response and not when disease escapes systemic treatment. The optimal candidates for considering RFA are those with ≤3 liver-limited CLM

which were downsized after 1st-line chemotherapy to less than 3cm in size. Third, following complete ablation of responding CLM, adjuvant liver-directed arterial therapy may be a considerable investigational approach.

The main limitation of this study is the retrospective nature of observing treated patients including a methodically non-avoidable selection bias. In addition, our observations were limited to a single-arm, single-institutional experience. However, we used a prospectively maintained data-base for information on recurrence. Therefore, the detection bias in our ascertainment of recurrence may be low. In addition, the magnitude of effects noted contributed to the significance of our findings. In spite of the limitations, we consider that our work may provide valuable information for the clinical practitioner and serve as a hypothesis-generating data-set for further clinical research.

Conclusions

Several notable findings of this study can be cited. First, local ablation efficacy is not sufficient, although necessary, to obtain long-term disease control following RFA for liver-limited CLM. Second, main challenge of disease control is the frequent occurrence of new metastases distant from RFA-treated CLM within the liver. Third, the timing and patterns of intrahepatic and/or extrahepatic disease recurrence carry important prognostic value. Fourth, effective pre-RFA systemic therapy does favourably affect the risk, timing, recurrence patterns and long-term survival. These findings carry implications for both clinical and research settings. First, a selection process by modern-agent therapy is essential before considering RFA of CLM, thereby allowing for the tailoring of RFA to maximize patient benefit, and following RFA of responding CLM, improving hepatic RFS will be the key to further OS benefit. Prospective multicenter trials are needed to consolidate our findings, ideally designed to evaluate the role of adjuvant post-RFA liver-directed arterial therapy as well.

Competing Interests

The authors have declared that no competing interest exists.

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