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Combined Hepatic Resection and Radio-frequency Ablation for Patients with Colorectal Cancer Liver Metastasis: A Viable Option for Patients with a Large Number of Tumors

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Abstract. *Background/Aim: Radiofrequency ablation (RFA) is thought to result in inferior prognosis than hepatic resection among patients with colorectal liver metastasis (CRLM). However, resection plus RFA may be an option for patients with a large number of tumors (≥4 liver lesions) and borderline resectability. Materials and Methods: A total of 717 patients with CRLM who underwent hepatic resection +/– RFA at two tertiary institutions between 09/01/2000-12/01/2015 were eligible for inclusion in this study. Results: Among patients with <4 lesions (n=568), OS in the resection + RFA group (n=48) was significantly worse than in the resection alone group (n=520) (5-year OS: 34.4 % versus 58.9%, p=0.007). Conversely, in patients with ≥4 lesions, OS in the resection + RFA (n=68) and resection alone(n=81) groups were not significantly different (5-year OS: 31.9% versus 34.1%, p=0.48). In patients with <4 lesions, carcinoembryonic antigen (CEA) ≥30 ng/ml, extrahepatic metastasis, preoperative chemotherapy and resection + RFA were independently associated with poor prognosis. Interestingly, in patients with ≥4 lesions, positive primary lymph nodes, KRAS mutation, CEA ≥30 ng/ml and extrahepatic metastasis were independent predictors of poor prognosis; however, the combination of hepatic resection with RFA was not associated with worse survival (p=0.93). Conclusion: Although surgeons should always strive for R0 resection when feasible, combined resection and RFA may be a viable alternative for CRLM patients with a large number of tumors.*

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Currently, the principal treatment strategy for patients with colorectal cancer liver metastasis (CRLM) is systemic chemotherapy, while hepatic resection can further improve survival in carefully selected patients (1-5). On the contrary, many reports concur that radio-frequency ablation (RFA) results in inferior outcomes than hepatic resection in patients with CRLM and should only be employed when surgical resection cannot be performed (6-9).

Nonetheless, the presence of extensive metastatic tumor number in the liver, (especially four or more lesions) often precludes a curative hepatic resection due to either technical challenges or inadequate remnant liver function and is a well-known poor prognostic factor (4, 5, 10-12). In fact, historically, specifically ≥4 CRLM, was considered to be a contraindication for liver resection (13, 14). Similarly, a study on a contemporary cohort (treated after 2005) demonstrated that the prognosis of patients with ≥4 CRLM who undergo surgery has not improved despite the development of modern chemotherapies (14). Interestingly, our group and others have demonstrated that hepatectomy + RFA may achieve long-term outcomes that are comparable to hepatectomy alone (15, 16).

Nonetheless, the impact of combined resection and RFA on survival among patients with different levels of tumor number

Table I. *Baseline characteristics of colorectal cancer liver metastasis patients with <4 and ≥4 tumors.*

	Patients with tumors <4 (n=568)	Patients with tumors ≥4 (n=149)	*p*-Value
Age, mean	59.6±12.5	57.7±11.6	0.09
Gender			
Male	342 (60.2%)	88 (59.1%)	0.85
Female	226 (39.8%)	61 (40.9%)	
Primary tumor location			
Colon	419 (73.8%)	114 (76.5%)	0.53
Rectum	149 (26.2%)	35 (23.5%)	
Primary N status			
Negative	184 (32.4%)	52 (34.9%)	0.56
Positive	384 (67.6%)	97 (65.1%)	
Concurrent primary tumor resection			
Yes	126 (22.2%)	30 (20.1%)	0.66
No	442 (77.8%)	119 (79.9%)	
KRAS mutation*			
Mutant	151 (38.0%)	37 (38.1%)	>0.99
Wild	246 (62.0%)	60 (61.9%)	
CEA (ng/ml)**	35.3±122.4	84.4±607.2	0.10
Extrahepatic metastasis			
Present	54 (9.5%)	13 (8.7%)	0.87
Absent	514 (90.5%)	136 (91.3%)	
Preoperative chemotherapy			
Yes	395 (69.5%)	127 (85.2%)	<0.001
No	173 (30.5%)	22 (14.8%)	
Tumor size (cm)	3.19±2.26	2.94±2.07	0.22
Tumor number, median (IQR)	1 (1-2)	5 (4-8)	<0.001
Combination of RFA			
Yes	48 (8.5%)	68 (45.6%)	<0.001
No	520 (91.5%)	81 (54.4%)	

*Data obtained from 494 patients. **Data obtained from 593 patients.

Table II. *Tumor number and size treated with hepatic resection and RFA.*

	Patients with tumors <4 (n=568)	Patients with tumors ≥4 (n=149)	*p*-Value
Tumor number treated with hepatic resection, median	1 (1-2)	4 (2-7)	<0.001
Tumor size treated with hepatic resection, mean (cm)	3.19±2.26	2.94±2.07	0.22
Tumor number treated with RFA, median	1 (1-2)	2.5 (1-4)	<0.001
Tumor size treated with RFA, mean (cm)	1.25±0.75	1.59±1.22	0.10

has not been well-studied. As such, we aimed to compare the overall survival of patients who underwent hepatic resection plus RFA and hepatic resection alone according to tumor number (with the presence of <4 lesions defined as small number and the presence of ≥4 liver lesions as big number); furthermore, factors associated with poor survival among patients with <4 and ≥4 liver lesions were also assessed.

Materials and Methods

Study design. We performed a retrospective study that included data from patients with CRLM who underwent hepatic resection with or without RFA at two institutions: Johns Hopkins Hospital (eligible patients underwent surgery between January 2003 and October 2015) and Kumamoto University (eligible patients underwent surgery between September 2000 and December 2015). Surgical indications and technical details of the procedures employed at both institutions have been described previously (16-20). At Johns Hopkins University, hepatic resection + RFA was selected when at least one hepatic tumor was considered unresectable because of its location, inadequate liver remnant, proximity of tumor to major vascular structure, or presence of medical comorbidities that precluded major hepatic resection (16). At Kumamoto University, hepatic resection + RFA was performed in patients with initially unresectable multiple metastases and had already received chemotherapy for CRLM (19).

Information on preoperative patient characteristics including age, gender, primary tumor location (colon *vs*. rectum), primary lymph node metastasis (N) status, concurrent primary tumor resection, *KRAS* mutation status, serum carcinoembryonic antigen (CEA) level, presence of extrahepatic metastasis, administration of preoperative chemotherapy, size of the largest liver metastasis and number of CRLM were collected for each included patient. Data on tumor size and number were obtained with the aid of preoperative CT or MRI; information on the size and number of tumors treated with hepatic resection and RFA was also collected, based on the findings of pathology. Patients' survival data after hepatic resection were obtained. This study was approved by both the Johns Hopkins University and Kumamoto University Institutional Review Boards.

Statistical analysis. Patient age, serum CEA level and tumor size were expressed as means±standard deviation and were compared using the Student's *t*-test, while tumor number was expressed as a median with interquartile range (IQR) and were compared using the Mann–Whitney *U*-test. Overall survival rates were calculated with the Kaplan–Meier method and compared with the log rank test. Univariate analyses were performed using the chi square test or Fisher's exact probability test for categorical values and the Student's *t*-test for continuous variables. All factors that were shown to be significant in univariate analysis were incorporated into the multivariate analysis, as was the main variable of interest (performance of RFA in conjunction with hepatic resection). A p-value <0.05 was considered statistically significant. All statistical analyses were performed using Statview software (SAS Institute, Cary, NC, USA).

Results

A total of 717 patients from both institutions were included in the final study cohort. The frequency with which hepatic resection was performed in combination with RFA was 45.6% in patients with ≥4 lesions, compared to 8.5% in

Table III. *Characteristics of patients treated with hepatic resection and hepatic resection + RFA in patients with tumors <4 (n=568).*

Factors	Hepatic resection (n=520)	Hepatic resection + RFA (n=48)	*p*-Value
Age, mean	59.8±12.5	57.6±12.0	0.23
Gender			
Male	311 (59.8%)	31 (64.6%)	0.54
Female	209 (40.2%)	17 (35.4%)	
Primary tumor location			
Colon	378 (72.7%)	41 (85.4%)	0.06
Rectum	142 (27.3%)	7 (14.6%)	
Primary N status			
Negative	168 (32.3%)	16 (33.3%)	0.87
Positive	352 (67.7%)	32 (66.7%)	
Concurrent primary tumor resection			
Yes	117 (22.5%)	9 (18.8%)	0.71
No	403 (77.5%)	39 (81.2%)	
KRAS mutation*			
Mutant	136 (38.3%)	15 (35.7%)	0.87
Wild	219 (61.7%)	27 (64.3%)	
CEA (ng/ml) **	36.6±127.2	22.6±52.4	0.48
Extrahepatic metastasis			
Present	50 (9.6%)	4 (8.3%)	>0.99
Absent	470 (90.4%)	44 (91.7%)	
Preoperative chemotherapy			
Yes	353 (67.9%)	42 (87.5%)	0.005
No	167 (32.1%)	6 (12.5%)	
Tumor size (cm)	3.2±2.3	2.8±1.7	0.20
Tumor number, median (IQR)	1 (1-2)	2 (2-3)	<0.001

*Data obtained from 397 patients. **Data obtained from 347 patients.

Table IV. *Characteristics of patients treated with hepatic resection and hepatic resection + RFA in patients with tumors ≥4 (n=149).*

Factors	Hepatic resection (n=81)	Hepatic resection + RFA (n=68)	*p*-Value
Age, mean	56.9±12.4	58.7±10.6	0.37
Gender			
Male	45 (55.6%)	43 (63.2%)	0.40
Female	36 (44.4%)	25 (36.8%)	
Primary tumor location			
Colon	58 (71.6%)	56 (82.4%)	0.17
Rectum	23 (28.4%)	12 (17.6%)	
Primary N status			
Negative	30 (37.0%)	22 (32.4%)	0.61
Positive	51 (63.0%)	46 (67.6%)	
Concurrent primary tumor resection			
Yes	20 (24.7%)	10 (14.7%)	0.008
No	61 (75.3%)	58 (85.3%)	
KRAS mutation*			
Mutant	17 (33.3%)	20 (43.5%)	0.40
Wild	34 (66.7%)	26 (56.5%)	
CEA (ng/ml) **	134.4±831.8	28.6±89.4	0.33
Extrahepatic metastasis			
Present	6 (7.4%)	7 (10.3%)	0.57
Absent	75 (92.6%)	61 (89.7%)	
Preoperative chemotherapy			
Yes	66 (81.5%)	61 (89.7%)	0.17
No	15 (18.5%)	7 (10.3%)	
Tumor size (cm)	3.1±2.4	2.8±1.6	0.45
Tumor number, median (IQR)	5 (4-7)	5 (4-10)	0.10

*Data obtained from 97 patients. **Data obtained from 82 patients.

patients with <4 lesions ($p<0.001$). The administration of preoperative chemotherapy was also significantly more common among patients with ≥4 lesions, than in patients with <4 lesions ($p<0.001$). Patient age, gender, primary tumor location, primary tumor lymph node status, concurrent primary tumor resection, KRAS mutation status, serum CEA level, the presence of extrahepatic metastasis and tumor size were not significantly different between patients with <4 and ≥4 lesions (Table I).

Tumor number of patients treated with both hepatic resection ($p<0.001$) and RFA ($p<0.001$) were significantly higher in those with tumors ≥4 than those with <4. Tumor size treated with hepatic resection ($p=0.22$) or RFA ($p=0.10$) were not significantly different between the groups (Table II).

In patients with tumors <4 (n=568), preoperative chemotherapy ($p=0.005$) and tumor number (<0.001) were higher in the group of hepatic resection + RFA even though all patients had three or less tumors (Table III). Patient age, gender, primary tumor location, primary N status, concurrent primary tumor resection, KRAS mutation, serum CEA level, extrahepatic metastasis and tumor size were not different between the groups. In patients with tumors ≥4 (n=149), concurrent primary tumor resection was lower in the hepatic resection + RFA group ($p=0.008$) (Table IV). Patient age, gender, primary tumor location, primary N status, KRAS mutation, serum CEA level, extrahepatic metastasis, preoperative chemotherapy, tumor size and median tumor number were not different between the groups.

Overall survival of patients who underwent hepatic resection with and without RFA. Patients who underwent hepatic resection + RFA (n=116) had a significantly worse prognosis than those who underwent hepatic resection alone (n=601) (1, 3, and 5-year overall survival: 89.2%, 53.2% and 33.1% *versus* 94.9%, 70.9% and 55.3%, respectively; $p<0.001$) (Figure 1). Similarly, among patients with fewer than 4 hepatic lesions, overall survival in the group that underwent hepatic resection + RFA (n=48) was significantly

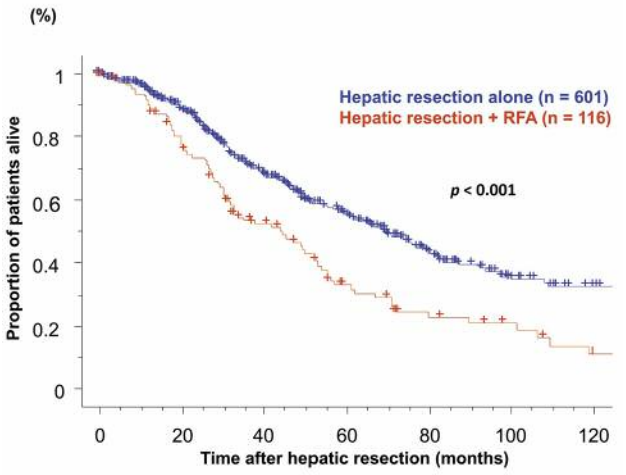

Figure 1. *Overall survival of CRLM patients who underwent hepatic resection plus RFA and hepatic resection alone. Overall survival of CRLM patients who underwent hepatic resection + RFA (n=116) was significantly worse than those who underwent hepatic resection alone (n=601)(1-, 3-, and 5-year overall survival: 89.2%, 53.2% and 33.1% versus 94.9%, 70.9% and 55.3%, respectively; p<0.001).*

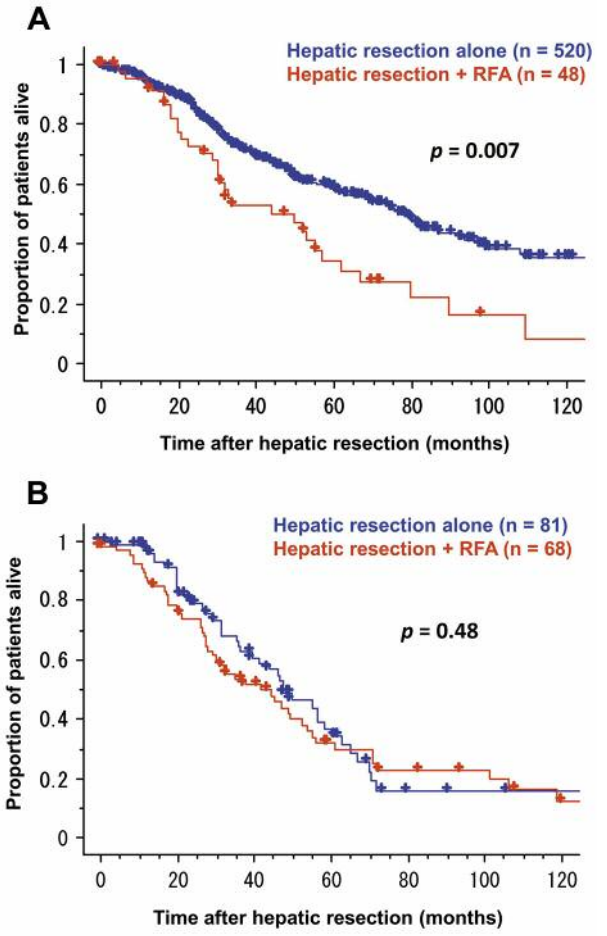

Figure 2. *Overall survival of CRLM patients with tumors <4 (A) and ≥4 (B) who underwent hepatic resection + RFA and hepatic resection alone. In patients with tumors <4, overall survival of patients who underwent hepatic resection + RFA (n=48) was significantly worse than those who underwent hepatic resection alone (n=520) (1-, 3-, and 5-year overall survival: 93.3%, 52.8% and 34.4 % versus 94.5%, 72.3% and 58.9%, respectively; p=0.007) (A). In patients with tumors ≥4, overall survival of patients who underwent hepatic resection + RFA (n=68) and hepatic resection alone (n=81) were not significantly different (1, 3, and 5-year overall survival: 87.9%, 53.4% and 31.9% versus 98.7%, 64.3% and 34.1%, respectively; p=0.48) (B).*

worse than in the group that underwent hepatic resection alone (n=520) (1, 3, and 5-year overall survival: 93.3%, 52.8% and 34.4 % *versus* 94.5%, 72.3% and 58.9%, respectively; p=0.007) (Figure 2A). On the other hand, in patients with ≥4 lesions, overall survival in the groups that underwent hepatic resection + RFA (n=68) and hepatic resection alone (n=81) were not found to be significantly different (1, 3, and 5-year overall survival: 87.9%, 53.4% and 31.9% *versus* 98.7%, 64.3% and 34.1%, respectively; p=0.48) (Figure 2B).

Preoperative predictors of survival for patients with <4 and ≥4 hepatic lesions. For patients with <4 hepatic lesions, history of positive primary lymph nodes (p=0.034), CEA ≥30 ng/ml (p<0.001), presence of extrahepatic metastasis (p=0.004), administration of preoperative chemotherapy (p=0.005) and combination of hepatic resection with RFA (p<0.001) were predictors of poor prognosis in univariate analysis. In multivariate analysis, CEA ≥30 ng/ml (p<0.001), presence of extrahepatic metastasis (p=0.01), administration of preoperative chemotherapy (p=0.03) and combination of hepatic resection with RFA (p<0.001) were independently associated with poor prognosis (Table V).

Conversely, for patients with ≥4 hepatic lesions, history of positive primary lymph nodes (p=0.004), CEA ≥30 ng/ml (p=0.02), presence of extrahepatic metastasis (p=0.01), administration of preoperative chemotherapy (p=0.024) and the presence of *KRAS* mutation (p<0.001) were predictors of poor prognosis in univariate analysis. Subsequently, we conducted a multivariate analysis that included all aforementioned significant prognostic factors in addition to the concurrent performance of hepatic resection and RFA. Importantly, history of positive primary lymph nodes (p=0.044), the presence of *KRAS* mutation (p<0.001), CEA ≥30 ng/ml (p=0.044) and the presence of extrahepatic metastasis (p<0.001) were shown to be independent predictors of poor prognosis, while the combination of hepatic resection with RFA did not appear to be associated with worse survival (p=0.93) (Table VI).

Table V. *Preoperative prognostic factors for patients with tumors <4 (n=568).*

	Univariate	Multivariate	
	p-Value	Hazard ratio (95%CI)	*p*-Value
Age (≥65)	0.08		
Gender (M)	0.29		
Primary tumor location (rectum)	0.10		
Primary N (positive)	0.034	1.27 (0.91-1.78)	0.16
Concurrent primary tumor resection (Yes)	0.71		
KRAS mutation (mutant)	0.47		
CEA (≥30 ng/ml)	<0.001	2.12 (1.51-2.98)	<0.001
Extrahepatic metastasis (present)	0.004	1.84 (1.15-2.93)	0.01
Preoperative chemotherapy (Yes)	0.005	1.45 (1.03-2.05)	0.03
Tumor size (≥3 cm)	0.07		
Combination of RFA (Yes)	<0.001	1.89 (1.24-2.87)	0.003

Table VI. *Preoperative prognostic factors for patients with tumors ≥4 (n=149).*

	Univariate	Multivariate	
	p-Value	Hazard ratio (95%CI)	*p*-Value
Age (≥65)	0.12		
Gender (M)	0.81		
Primary tumor location (rectum)	0.38		
Primary N (positive)	0.004	1.98 (1.02-3.86)	0.044
Concurrent primary tumor resection (Yes)	0.81		
KRAS mutation (mutant)	<0.001	4.02 (1.91-8.40)	<0.001
CEA (≥30 ng/ml)	0.02	2.36 (1.02-5.43)	0.044
Extrahepatic metastasis (present)	0.01	4.93 (2.04-11.9)	<0.001
Preoperative chemotherapy (Yes)	0.024	2.92 (0.92-9.26)	0.07
Tumor size (≥3 cm)	0.14		
Combination of RFA (Yes)	0.48	1.03 (0.54-1.96)	0.93

Prognosis of patients without extrahepatic metastases and with ≥4 hepatic lesions who underwent hepatic resection + RFA vs. hepatic resection alone. We performed an additional survival analysis of patients with ≥4 hepatic lesions treated with hepatic resection with or without RFA, after first excluding patients with extrahepatic metastases (Figure 3). Importantly, the overall survival of patients who underwent hepatic resection + RFA (n=61) was not found to differ significantly from that of patients who underwent hepatic resection alone (n=75) (p=0.66).

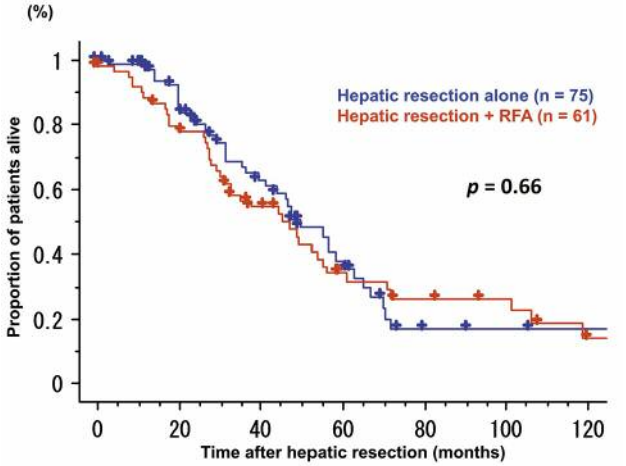

Figure 3. *Overall survival of CRLM patients with tumors ≥4 without extrahepatic metastases who underwent hepatic resection + RFA or hepatic resection alone. The 5-year overall survival of hepatic resection + RFA (n=61) and hepatic resection alone (n=75) were 34.0% and 35.4%, respectively (p=0.66).*

Discussion

This study was primarily conducted to evaluate the prognostic implications of combining RFA with hepatic resection among patients with a large number of liver metastases. Importantly, patients with ≥4 hepatic lesions were shown to have similar prognosis, irrespective of whether they were treated with hepatic resection + RFA or hepatic resection alone; the

exclusion of patients with extrahepatic metastasis from the cohort confirmed these findings. However, combined hepatic resection and RFA was a poor prognostic factor in patients with <4 hepatic lesions. Additional factors that may influence prognosis among patients with either <4 or ≥4 hepatic lesions were also investigated, in an attempt to aid treatment selection in these patient groups.

Importantly, our analysis indicated that the presence of extensive metastatic tumor number in the liver may neutralize the negative prognostic implications associated with the use of RFA (21). Indeed, the presence of 4 or more hepatic tumors has previously been associated with especially poor prognosis and early recurrence in patients undergoing hepatic resection for CRLM (10-12, 22, 23). As such, it is possible that patients with 4 or more lesions have such aggressive underlying disease biology that technical considerations (use of combined resection and RFA *vs*. resection alone) have a comparably minor impact on outcomes. Similarly, previous studies from our group and others have shown that the technical adequacy of a resection as measured by the achievement of negative surgical margins has no measurable impact on outcomes among high-risk patients with aggressive disease biology (24, 25). However, surgeons should still strive for an R0 resection when technically feasible, as the present study lacks the statistical power to conclusively prove the equivalence of combined resection and RFA *vs*. hepatic resection alone (26). Our findings are instead more applicable to borderline cases, where an R0 resection may be feasible, but at the cost of performing extremely aggressive surgery, that may, in turn result in post-hepatectomy liver failure or increase the risk for postoperative recurrence by excessively stimulating liver regeneration (27-29). As RFA is considered to be more successful in sparing liver parenchyma and preserving residual liver function than extensive resection, the combined use of resection and RFA may be a viable alternative for patients with high tumor burden and borderline resectability (30).

We also attempted to quantify the relative importance of various prognostic factors among patients with <4 and ≥4 hepatic lesions with the use of multivariable analysis. In line with previous studies, the presence of extrahepatic metastasis was shown to be an adverse prognostic factor in both groups (31). Nonetheless, recent studies suggest that local therapy for liver metastases might still benefit patients with extrahepatic disease; as such, the use of RFA with or without concurrent resection might be a reasonable option in this setting (32, 33). Previous studies have also identified a high serum CEA level as a predictor of poor prognosis in CRLM patients (12, 34-37). This finding was confirmed in the present study for all patients, irrespective of tumor number. The administration of preoperative chemotherapy was also a poor prognostic factor in patients with fewer than 4 hepatic lesions, which likely reflects the fact that preoperative chemotherapy is commonly administered to patients with advanced, high-risk disease.

The present study had several limitations. The analysis was based on retrospective data from two distinct surgical cohorts; as such, a degree of selection bias was unavoidable, especially since tumor number is an important determinant of treatment among patients with CRLM. Nonetheless, this limitation is inherent to retrospective studies and we attempted to mitigate it by controlling for possible confounders with the aid of multivariable analysis. Furthermore, treatment indications and the composition of each patient population differed somewhat between the two institutional cohorts. More importantly, the number of patients with 4 hepatic lesions or more was limited thus reducing the statistical power of our analysis. As such, our findings would certainly benefit from validation in larger institutional cohorts.

In conclusion, our findings indicate that combined resection and RFA may be a viable option for local treatment in patients with CRLM and a large number of liver lessions. Although in the absence of contradictory data from clinical trials surgeons should strive for complete disease extirpation if feasible, these findings underscore the utility of RFA among patients with borderline resectability and emphasize the primacy of tumor biology over technical considerations in determining the outcomes of patients with advanced disease.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

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