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Hepatectomy for Recurrent Colorectal Liver Metastases after Radiofrequency Ablation

Antoine Brouquet, MD¹, Jean-Nicolas Vauthey, MD, FACS¹, Brian D. Badgwell, MD, MS², Evelyn M. Loyer, MD³, Harmeet Kaur, MD³, Steven A. Curley, MD, FACS¹, and Eddie K. Abdalla, MD, FACS¹

¹Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030

²Department of Surgery, The University of Arkansas for Medical Sciences, Winthrop P. Rockefeller Cancer Institute, Little Rock, Arkansas 72205

³Department of Radiology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030

STRUCTURED ABSTRACT

Background—The results of surgery for recurrent colorectal liver metastases (CLM) after radiofrequency ablation (RFA) have not been evaluated.

Methods—From 1993 to 2009, data on patients who underwent resection or RFA for recurrent CLM were collected prospectively. Inclusion criteria were: RFA as initial treatment of CLM, resection of recurrent CLM after RFA. Postoperative results and oncologic outcome were analyzed.

Results—Twenty-eight patients (median number of tumours 1 [range = 1 – 3], median size 2.75 [range = 2 – 4] cm) met the inclusion criteria. Of these, 22 had recurrence at the site of RFA only, 2 developed new lesions, while 4 had both recurrent and de novo metastases. At the time of resection, patients had a median number of 1 (range = 1 – 13) CLM and median maximum tumour diameter was 5 (range = 1.8 – 11) cm, significantly larger than at the time of RFA ($p = 0.02$). Ninety-day postoperative morbidity and mortality rates were 46% and 7% respectively. After median follow-up of 35 (range = 0 – 70) months, Kaplan-Meier analyzed 3-year and 5-year overall survival rates were 60% and 33% respectively. Carcinoembryonic antigen plasma level > 5 ng/mL at the time of resection and a rectal primary tumour were associated with worse survival ($p = 0.041$ and $p = 0.02$ respectively).

Conclusions—Resection for recurrence after RFA is associated with significant morbidity and modest long-term benefit.

INTRODUCTION

Although radiofrequency ablation (RFA) has not been formally evaluated as an alternative to liver resection in patients with resectable colorectal liver metastases (CLM),^{1–3} it is increasingly used for this indication.⁴ However, RFA is associated with an increased risk of local recurrence, which frequently includes regrowth of the initially ablated tumour.^{5, 6} The survival impact of recurrence after RFA for CLM is controversial, but appears to be associated with shorter overall survival compared to recurrence and survival after resection of CLM.^{6–10} Repeat hepatectomy in the event of recurrence after resection for CLM is well established.^{11–15} For patients with recurrent CLM after RFA, hepatectomy is proposed in select patients, but the feasibility and results of this approach have not been evaluated. The aim of this study was to assess the clinicopathologic characteristics, perioperative results, and oncologic outcomes of patients undergoing hepatectomy for recurrent CLM after RFA.

METHODS

Patient selection

Between December 1993 and December 2009, data on 115 consecutive patients who underwent a laparotomy for recurrent CLM after RFA or resection at The University of Texas MD Anderson Cancer Center were collected prospectively. The study was approved by the Institutional Review Board of MD Anderson Cancer Center.

Diagnosis of recurrent CLM and preoperative assessment

The diagnosis of recurrent CLM was made using helical computed tomography with liver protocol (rapid injection of 150 mL of intravenous contrast material with image reconstruction of 2.5–5 mm through the liver) or magnetic resonance imaging.^{16, 17} Recurrent CLM were defined as local recurrence when they were observed at the site of previous RFA.¹⁸ Other recurrent CLM were defined as new lesions (Figure 1).^{17–19} Beginning in 1998, 9-fluorodeoxyglucose positron emission tomography (FDG-PET) was used in some patients with uncertain findings of recurrence or to rule out extrahepatic disease (Figure 1).²⁰ When recurrence of CLM was suspected but not confirmed after the initial imaging work-up, a new evaluation including computed tomography and FDG-PET was generally repeated approximately 1 month later to detect additional changes. When the diagnosis of recurrence was confirmed, the patient's performance status was carefully evaluated. In most patients, the decision whether surgery for recurrent CLM was indicated was made during a multidisciplinary meeting including hepatobiliary surgeons, imaging radiologists, interventional radiologists, and medical oncologists. Final pathology confirmed recurrence of cancer in all patients.

Surgical procedure

Liver resections were performed only with curative intent, i.e., only if it was believed that all tumour deposits could be completely resected. During laparotomy, the peritoneal cavity was inspected in order to rule out extrahepatic disease. Palpation and intraoperative ultrasonography were carried out in all patients to better define the location of the metastases in the liver and their relationship with portal pedicles and hepatic veins. When

dense adhesion of recurrent CLM to an adjacent organ was found, en bloc resection was performed to avoid peritoneal dissemination of disease. Parenchymal transection was performed using an ultrasonic dissector, and haemostasis was achieved with the saline-linked cautery as previously described.^{21, 22} Major hepatectomy was defined as liver resection including three or more contiguous liver segments. CLM number and size (diameter of the largest metastasis) were evaluated on resected specimens in all patients; in patients who had previously undergone RFA, the size of the scar was excluded from the size of the metastasis. The margin width was defined as the distance between tumours and the closest inked section as previously described.²³

Postoperative and long-term outcomes

Postoperative morbidity, 30-day mortality, and 90-day mortality rates were evaluated. Major postoperative complications were defined as complications of grade 3 or higher in the Dindo classification (i.e., necessitating a surgical, endoscopic, or radiologic procedure).²⁴ Postoperative liver insufficiency was defined as a postoperative bilirubin peak level ≥ 7 mg/dL.²⁵ Overall survival was calculated from the time of the hepatectomy for recurrent CLM. After hepatectomy, whether postoperative chemotherapy was indicated was discussed between oncologists and surgeons at a multidisciplinary meeting; factors taken into account included the completeness of the resection, the extent and toxicity of previously delivered chemotherapy, and the macroscopic and microscopic response to it.^{26, 27}

Statistical analysis

Quantitative and qualitative variables were expressed as mean $\pm$ standard deviation, median (range), and frequency. Overall and disease-free survival were calculated from the date of resection of recurrent CLM using the Kaplan-Meier method and compared using the log-rank test. For the detection of factors associated with survival in patients who underwent resection of recurrent CLM after RFA, univariable analysis was used to examine the relationship between survival and the following variables: location of the primary tumour; lymph node status at the time of diagnosis of the primary tumour; synchronous (vs. metachronous CLM, synchronous metastases were defined as liver metastases diagnosed at the same time or within 6 months after the diagnosis of primary colorectal cancer), number of initial CLM (single or multiple); initial CLM size (<3 cm vs. ≥ 3 cm); time to recurrence (≥ 12 months vs. < 12 months); CEA plasma level at time of resection of recurrent CLM (≤ 5 ng/mL vs. > 5 ng/mL); local recurrence only (vs. new lesions with or without local recurrence), number of recurrent CLM (single or multiple); size of recurrent CLM (< 3 cm vs. ≥ 3 cm); and presence or absence of extension of CLM to an adjacent organ, preoperative chemotherapy before resection of the recurrent CLM, positive surgical margin at the time of resection of the recurrent CLM, need for transfusion during surgery for the recurrence, occurrence of major postoperative complications, and postoperative chemotherapy. All variables associated with survival with $P \leq 0.2$ in the univariable proportional hazard model were subsequently entered into a Cox multivariable regression model with backward elimination. P values < 0.05 were considered statistically significant. Comparisons between groups were analyzed with the chi-square or Fisher exact test for proportions and the Mann-Whitney U test as appropriate. Statistical analysis was performed using the statistical software package SPSS version 17.2 (SPSS, Chicago, IL).

RESULTS

Clinicopathologic features at first treatment of CLM and at recurrence of CLM

Between December 1993 and December 2009, 115 patients underwent a laparotomy for recurrent CLM. Details of procedures performed in these patients are listed in Table 1. Clinicopathologic features of the 28 patients who underwent hepatectomy for recurrent CLM after RFA are summarized in Table 2.

At the time of first treatment of CLM, 6/28 patients underwent RFA for multiple CLM, while 22/28 underwent RFA for solitary CLM. CLM subsequently presented as local recurrence in 22 patients, local recurrence associated with new lesions in 4 patients and new lesions only in 2 patients. The majority of patients underwent RFA as first treatment in the pre-referral setting and were seen at our institution at the time of recurrence (20/28 patients). Median time from the initial treatment to recurrence was 12 months (2–147 months).

Recurrent CLM were significantly larger than the initially treated lesions (5 cm, range = 1.8 – 11 vs. 2.75 cm, range = 2 – 4, $p < 0.001$), but the median number of lesions was similar (1, [range = 1 – 3] vs. 1, range [1 – 13]). Fourteen patients (15%) had FDG-PET at the time of diagnosis of recurrent CLM. Decision-making regarding resection of recurrent CLM was discussed formally at multidisciplinary meeting in the majority of patients (23/28).

Perioperative results and oncologic outcome

Operative details and postoperative complications are summarized in Table 2. Among the 12 patients who underwent resection of adjacent organs, 11 had en bloc diaphragmatic resection, and in 2 of these patients the diaphragmatic resection was combined with resection of the pericardium ($n = 1$) or lung wedge en bloc resection ($n = 1$). Seven patients developed major complications: two patients died intraoperatively when attempts to mobilize the right liver surrounding the ablation cavity led to vena cava and hepatic vein injury. This led to a change in operative technique for tumours in this location – the anterior approach with hanging maneuver has been used subsequently eliminating the possibility of this complication.^{28, 29} Three patients developed an intraabdominal collection requiring radiologic percutaneous drainage, and two patients developed a pleural effusion requiring chest drainage.

The median follow-up for the entire population was 35 months from the date of resection of recurrent CLM (range: 0–148 months). Median overall survival was 47 months (confidence interval 95% = 27 – 67 months). Three-year and 5-year overall survival rates after resection of recurrent CLM after RFA were 60% and 33% respectively (figure 2). Eighteen patients (62%) developed a further recurrence after hepatectomy for recurrent CLM after RFA. Three-year and 5-year disease-free survival rates after resection of recurrent CLM after RFA were 29% and 11%, respectively, in patients who had recurrent CLM after RFA (Figure 2). Among the 18 patients who developed a second recurrence after hepatectomy for recurrent CLM, 5 had liver-only recurrences, 11 had extrahepatic recurrences, and 2 had liver and extrahepatic recurrences.

Predictors of survival

Results of univariable analysis of factors associated with survival in patients undergoing resection of recurrent CLM are summarized in Table 3. Univariable analysis revealed that the following factors were associated with worse survival: rectal primary tumour, CEA plasma level at the time of resection of recurrent CLM > 5 ng/mL. In multivariable analysis, none of these factors were significantly associated with survival.

DISCUSSION

This study evaluated outcomes after resection of recurrent CLM in patients initially treated with RFA. Findings indicate that hepatectomy after RFA is feasible, but complex and associated with significant morbidity. Additionally, hepatectomy for recurrent CLM after RFA can be associated with prolonged survival, but the chance for definitive cure of metastatic disease in this context is low. In contrast, repeat hepatectomy for recurrent CLM after resection is generally associated with good long-term outcome with 5-year survival ranging from 41% to 88%.^{11, 12, 14} The excellent outcome for patients with recurrence after initial resection is attributed to the “biological” selection of patients with oncologically favorable tumors, e.g., those with oligonodular recurrence.^{11, 30} Unfortunately, despite using the same criteria for resection of patients with recurrence after RFA, the 5-year overall survival rate is only 33%, and the survival curve never reaches a “plateau” – only a small minority of patients experience prolonged disease free survival.

The concept that incomplete treatment may create a microenvironment that promotes tumour growth is supported by the current study, based on the finding of the larger recurrent tumour size compared to initial ablated lesion size and on regrowth of tumor surrounding the RFA cavity.^{17, 18} Carefully reviewed imaging demonstrates recurrence with acceptable accuracy and complete treatment with ablation is typically associated with a stable or collapsing ablation cavity, not increase in the size of the ablation zone. Evaluation of the completeness of ablation on early post procedure imaging may help to predict recurrence and to tailor imaging follow-up in high risk patients.

Findings in this study heighten the concern surrounding calls to use RFA as an alternative to resection for CLM in a fashion analogous to RFA use for hepatocellular carcinoma in cirrhotic patients, where RFA use may be better supported by outcome data.³¹ Poor overall and disease-free survival found in this study despite salvage resection, and the markedly inferior outcome of RFA vs. resection for solitary CLM⁶ further undermine any proposal for a randomized trial comparing RFA and resection for CLM.^{2, 9} The statement that the modality of initial local treatment (i.e. RFA rather than resection) may not affect overall survival of patients with potentially curable CLM is further suspect given results of a recent study confirming increased local recurrence rate and shorter time to progression when RFA was compared with resection as a treatment for CLM.⁹ Strong evidence from previous studies demonstrates that local recurrence rates are higher and survival is shorter in patients treated with RFA for initial CLM than in patients treated with liver resection for initial CLM.^{1, 3, 5, 6} This series includes only patients who had resectable recurrence after RFA. The full denominator of patients with recurrence after RFA could be determined because this study includes patients who underwent ablation prior to referral to our institution.

The current study shows that resection for recurrent CLM after initial treatment with RFA can be complex and associated with a significant risk of intraoperative difficulties and postoperative complications. The frequent need for resection of structures adhered to the liver as a result of prior ablation (43%), the risk of bleeding related to reoperative surgery¹² and to friable character of the hepatic parenchyma and vessels near the ablation zone (mean estimated blood loss > 500 mL) probably contribute to the morbidity associated with this type of surgery. Use of techniques such as the anterior approach to right-sided tumors has enabled avoidance of the problems of cracking of the liver and hepatic veins associated with mobilization of the liver after ablation.^{28, 29} Regardless of the presence of actual tumour invasion, en-bloc resections of adherent diaphragm are often required to facilitate safe resection because of the loss of normal tissue planes between the liver and adjacent structures.

In the present series, rectal primary tumour and preoperative CEA plasma level were associated with outcome after resection of recurrent CLM after RFA. These factors were not independent predictors of survival probably due to limited sample size. Neither the characteristics of CLM at the time of presentation nor at the time of recurrence significantly impacted survival underscoring that concept that the number or the size of recurrent CLM should not define indications or contraindications for surgery. The potential to remove all tumour deposits preserving an adequate remnant liver combined with assessment of patient performance status are more likely to guide the appropriate selection of candidates for demanding surgery of this type.

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Figure 1.
Single segment VI CLM on CT before RFA (A), 1 months after RFA (B), 6 months after RFA with local recurrence on PET-CT (D).

Figure 2. Overall (dotted line) and disease-free (continuous line) survival of patients who underwent hepatectomy for recurrent CLM after RFA.

Table 1

Procedures used in 115 patients who underwent a laparotomy for recurrent CLM

Procedures	Recurrent CLM (n = 115)
Resection after RFA	28 (24%)
Resection after resection	43 (37%)
Resection after resection + RFA	32 (28%)
Resection + RFA after resection	8 (7%)
RFA after resection	4 (3%)

Table 2

Comparison of clinicopathologic features and outcomes of patients who underwent hepatectomy for recurrent CLM after RFA *

Feature	RFA N = 28
<i>Initial diagnosis of CLM</i>	
Median age (range)	61 (35 – 80) years
Sex (M/F)	20/8
Mean body mass index $\pm$ SD	29 $\pm$ 7
Rectal primary tumour	7
Node-positive primary tumour	20 (71)
Liver metastases	
Synchronous (vs. metachronous)	12 (43)
Median number of liver deposits (range)	1 (1 – 3)
Median maximum tumour diameter (range)	2.75 (2 – 4) cm
Treatment of metastases	
Major liver resection ($\geq$ 3 liver segments)	-
Percutaneous RFA	14
Intraoperative RFA	14
<i>Recurrence of CLM</i>	
Mean time to recurrence $\pm$ SD	16 $\pm$ 12 months
Liver metastases	
Median number of liver deposits (range)	1 (1 – 13)
Median maximum tumour diameter in cm (range)	5 (1.8 – 11)
New lesions	2
Local recurrence $\pm$ new lesions	26
Preoperative chemotherapy before liver surgery	12 (43)
Type of resection	
Major liver resection ($\geq$ 3 liver segments)	19 (67)
Resection of adjacent organ(s)	12 (32)
Positive surgical margin	9 (32)
Pringle maneuver	13 (46)
Median estimated blood loss (range)	725 mL (50–10000)
Blood transfusion	9 (32)
Median operating time (range)	203 (82 – 447) min
Postoperative mortality	2 (7)
Postoperative morbidity	13 (46)
Bleeding	2
Intraabdominal collection	3
Liver insufficiency	1
Pleuropulmonary complication	2

Feature	RFA N = 28
Major complication rate [†]	7 (25%)
Median length of hospital stay (range)	7 (4 – 12) days

* Values in table are number of patients (percentage) unless otherwise indicated.

[†] Major complication was defined as requiring surgical, endoscopic or radiographic intervention

Table 3

Univariable and multivariable analysis of factors associated with survival in patients who underwent hepatectomy for recurrent CLM after RFA

	Univariate analysis	Multivariable analysis
	P	P
<i>Initial diagnosis of CLM</i>		
Rectal primary tumour	0.02	0.23
Nodal metastases	0.51	
Liver metastases		
Synchronous	0.45	
Multiple	0.18	0.32
Maximum tumour diameter ≥ 3 cm	0.75	
<i>Recurrence of CLM</i>		
Time to recurrence < 12 months	0.8	
Local recurrence only	0.4	
Preoperative chemotherapy before liver surgery	0.28	
CEA plasma level > 5 ng/mL	0.04	0.42
Liver metastases		
Multiple	0.48	
Maximum tumour diameter ≥ 3 cm	0.51	
Tumour extension to adjacent organs	0.48	
Blood transfusion	0.9	
Major postoperative complication	0.85	
Positive surgical margin	0.66	
Postoperative chemotherapy	0.21	

RFA: Radiofrequency ablation

CEA: Carcinoembryonic antigen