Colorectal Cancer Liver Metastases and Concurrent Extrahepatic Disease Treated With Resection

Universe Leung, MBChB, Mithat Gönen, PhD,† Peter J. Allen, MD,* T. Peter Kingham, MD,* Ronald P. DeMatteo, MD,* William R. Jarnagin, MD,* and Michael I. D'Angelica, MD**

Objective: The aim of the study was to evaluate outcomes after resection of colorectal liver metastases (CRLM) and concurrent extrahepatic disease (EHD), and to define prognostic factors.

Background: There is increasing evidence to support resection of liver metastases and concurrent EHD in selected patients. Long-term survival data are lacking, and prognostic factors are not well defined.

Methods: Retrospective review of 219 patients was undertaken between January 1992 and December 2012, who underwent hepatectomy for CRLM and resection of synchronous EHD. Survival outcomes were estimated by the Kaplan-Meier method. Univariate and multivariate analyses of prognostic factors were performed. A scoring system for prognostication was developed.

Results: The median, 3, 5, and 10-year overall survival were 34.4 months, 49%, 28%, and 10%, respectively. Disease recurred in 185 patients (90.2%) at a median of 8 months. There were 8 actual 10-year survivors. The site of EHD affected survival, with portal, retroperitoneal nodes and multiple sites associated with the worst prognoses. The size of the largest CRLM, the number of CRLM, unfavorable site of EHD, and progression of CRLM on neoadjuvant therapy were associated with overall survival on univariate and multivariate analyses. Three variables, assigned 1 point each, were used to create an EHD risk score: largest CRLM greater than 3 cm, greater than 5 CRLM, and unfavorable site of EHD. The resulting score was prognostic of overall and recurrence-free survival.

Conclusions: Long-term survival is possible after resection of liver metastases and concurrent EHD, but true cure is rare. A proposed scoring system may identify patients most likely to benefit from surgery.

Keywords: colorectal cancer, extrahepatic metastases, liver metastases, liver resection

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Colorectal cancer metastasizes to the liver in approximately 50% of patients.[1] Hepatic resection with or without chemotherapy is the standard of care for patients with resectable colorectal liver metastases (CRLM). Resection is associated with the best chance of long-term survival and the only chance of cure. Modern multimodal therapy, including surgery, has resulted in 5-year survival of approximately 50% and 10-year survival of greater than 20%.[2–5] Approximately 2/3 of patients recur within 5 years of resection, and 1/3 of patients who survive 5 years will eventually die of their disease. Patients who are disease-free at 10 years from liver resection can be considered cured.[2,5]

From the *Hepatopancreatobiliary Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; and †Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY.

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Reprints: Michael I. D'Angelica, MD, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. E-mail: dangelim@mskcc.org.

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Resection of CRLM has now become routine. The presence of extrahepatic disease (EHD), however, was once considered a contraindication to liver resection as the prognosis was poor.[6] In the past decade, evidence has emerged that concurrent resection of CRLM and limited EHD is associated with acceptable medium-term survival in well selected patients[7–11] Most patients, however, recur. Some of these recurrences occur rapidly, suggesting that patients may have been better served by a nonoperative approach. Due to small numbers of patients and relatively short follow-up, the factors that affect survival in these patients have not been well defined, and selection criteria for surgery remain unclear. In addition, surgeons sometimes discover unexpected small-volume EHD, particularly in lymph nodes and in the peritoneum, during exploratory surgery for CRLM. They then face the dilemma of whether to proceed with resection.

Our group previously published our experience with concurrent resection of CRLM and EHD between 1992 and 2007, showing a median survival of 36 months and a 5-year overall survival (OS) of 26% in 127 patients. Importantly, we documented that at least 95% of patients will ultimately recur.[9] We now have significantly expanded our experience and generated follow-up data out to beyond 10 years. The aim of this study was to examine the chance of long-term cure, further define prognostic factors, and devise a scoring system using pre and intraoperative factors to predict survival.

METHODS

The Institutional Review Board at Memorial Sloan Kettering Cancer Center (MSKCC) granted a waiver of consent for this retrospective study. Patients who underwent hepatectomy for CRLM and had concurrent EHD resected between January 1, 1992 and December 31, 2012 were identified from a prospectively maintained database. All patients had synchronous EHD identified at the time of their hepatic resection or on preoperative investigations. Concurrent EHD resection was defined as EHD resected at the same time or within 6 months of hepatectomy. An initial search was performed to identify all patients who underwent hepatectomy for CRLM. Patient charts and pathology reports were then reviewed to select patients who underwent concurrent EHD resection as defined above. Patients were eligible if there had been complete gross resection of CRLM (R2 resections excluded), as judged by the operating surgeon. Patients with incompletely resected EHD (R2 resections) were included. Patients who underwent a planned 2-staged liver resection performed within 6 months of each other were included if all liver disease was resected. Patients who had operative ablation of CRLM were included if concomitant resection was performed at the same setting. Patients were excluded if they had inadequate follow-up (<3 mo), benign final pathology of resected EHD, direct invasion of adjacent organs by CRLM as their site of EHD, and if the CRLM was treated with ablation only.

The site of EHD was categorized anatomically. The size and number of CRLM were defined by the final pathological report whenever possible, otherwise by preoperative cross-sectional imaging. Intra-abdominal nodal involvement was divided by anatomic region into portal nodes (along proper hepatic artery, portal vein, and

common hepatic artery) and retroperitoneal nodes (celiac, retropancreatic, para-aortic, and aorto-caval). More distant nodal disease was grouped into ''other,'' including mesenteric and internal iliac nodes not associated with an intact primary tumor. EHD found in organs adherent to a subcapsular liver metastasis was considered direct invasion and excluded. Patients with colorectal anastomotic recurrence or pelvic recurrence after rectal surgery as their site of EHD were called locoregional failure. Patients with more than 1 site of EHD were analyzed as ''multiple sites.''

Patients with CRLM and concurrent EHD were selected for surgery if they had limited and resectable EHD. Other factors taken into account include patient age and fitness, and site and volume of disease. Response to chemotherapy was also considered. All patients were discussed at multidisciplinary disease management meetings and treatment tailored individually. All patients underwent preoperative cross-sectional imaging of the chest, abdomen, and pelvis, with a combination of computed tomography (CT) and/or magnetic resonance imaging (MRI). Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scans were obtained at the discretion of the treating physicians. Extrahepatic disease was detected either on imaging or intraoperatively during exploration. Patients were staged according to the 7th edition of the American Joint Committee on Cancer (AJCC) manual. Clinical risk scores (CRS) were calculated using a previously reported scoring system based on 5 factors (node-positive primary, disease-free interval of CRLM <12 mo, >1 CRLM, size of largest CRLM >5 cm, and CEA >200 ng/mL, each scoring 1 point).[6]

Liver resections were performed open, laparoscopically, or robotically. Intraoperative ablation was used as an adjunct in patients in whom complete resection leaving an adequate remnant was not possible or when maximal parenchymal preservation was desired. The choice of ablation modality (radiofrequency, microwave, or irreversible electroporation) was at the discretion of the treating surgeon. EHD resection was reported as complete (R0 or R1) or incomplete (R2) on a macroscopic level as judged by the treating surgeon. Liver resection margin was reported as microscopically greater than or equal to 1 mm (R0), or less than 1 mm (R1).

Systemic chemotherapy with or without hepatic artery infusional chemotherapy was offered on an individual basis after discussion with the involved physicians. Neoadjuvant chemotherapy was defined as treatment within 6 months before hepatectomy specifically to treat CRLM. Adjuvant chemotherapy referred to chemotherapy given after hepatectomy. Hepatic artery infusional chemotherapy consisted of floxuridine infusion via a pump over a 4-week cycle, with systemic therapy given concurrently. Floxuridine was infused for 14 days, followed by 14 days of heparin and saline infusion. Progression of disease while on neoadjuvant therapy was defined at the time of surgery by radiological report, whenever available, or in cases in which that information was not available, was defined by the treating surgeon or oncologist.

After surgery, patients underwent regular cross-sectional imaging every 3 to 6 months. Time of recurrence was defined as the time of the first imaging that reported definitive or suspicious new tumors. In patients with pre-existing indeterminate radiological lesions, the time of radiologic progression was defined as the time of recurrence. For patients with biopsy-proven recurrence, the date of positive cytological or histological results was defined as the time of recurrence. Survival was calculated from time of index hepatectomy. Salvage therapy was defined as complete gross resection or ablation of recurrent disease regardless of location.

Statistical analyses were performed using Prism (version 6.0, GraphPad) and SPSS (version 21.0, IBM). OS and recurrence-free survival (RFS) were estimated using the Kaplan-Meier method and compared using the log-rank test for univariate comparisons and Cox proportional-hazards regression for multivariate comparisons. A P value of less than 0.05 was considered statistically significant.

An EHD risk score was developed using pre and intraoperative factors identified as significant predictors for OS in the univariate and multivariate analyses. Cut-off levels were determined based on statistical significance and clinical relevance, and points were weighted according to relative hazard ratios (HRs).

RESULTS

Between January 1, 1992 and December 31, 2012, 2693 patients underwent hepatectomy for CRLM, of which 299 were eligible. Eighty patients were excluded due to ablation only (40), direct invasion (21), inadequate follow-up (9), R2 resection of CRLM (7), and benign EHD histology (3). A total of 219 patients therefore were analyzed. Patient demographics and oncologic characteristics are summarized in Table 1. Plasma Carcinoembryonic antigen (CEA) level was available in 178 patients and the median was

TABLE 1. Demographics and Characteristics of Primary Tumor, Liver Metastases, and Extrahepatic Disease

Total patients, N	219
Age, y, median (range)	59 (25–90)
Male, n (%)	99 (45.2)
Primary site, n (%)	
Colon	152 (69.4)
Rectum	67 (30.6)
Primary T, n (%)	
T0†	1 (0.5)
T1	0 (0)
T2	29 (13.2)
T3	138 (63.0)
T4	46 (21.0)
Primary N	
N0	54 (24.7)
N1	96 (43.8)
N2	66 (30.1)
Liver metastases, n (%)	
First metastases	186 (84.9)
Recurrent metastases	33 (15.1)
Synchronous‡	94 (42.9)
Metachronous	125 (57.1)
Median disease-free interval (LM), mo	8.1
Largest liver tumor diameter, cm, median (range)	3.5 (0.2–21.5)
No. of liver tumors, median (range)	2 (1–17)
Preop CEA, ng/mL, median (range)	8.9 (0.6–687)
Median clinical risk score	2
Site of extrahepatic disease, n (%)	
Lung	57 (26.0)
Portal lymph nodes*	40 (18.2)
Retroperitoneal lymph nodes*	19 (8.7)
Ovaries	13 (5.9)
Anastomotic/pelvic recurrence	14 (6.4)
Peritoneum	33 (15.7)
Adrenal	3 (1.4)
Mesenteric/iliac nodes	9 (4.1)
Other§	8 (3.7)
Multiple sites¶	14 (6.4)
Diagnosis of EHD	
Preoperative	127 (58.0)
Intraoperative	92 (42.0)

*Portal lymph nodes defined as nodes along the hepatic artery proper, portal vein, and common hepatic artery. Retroperitoneal lymph nodes defined as nodes along the celiac axis, retropancreatic, para-aortic, and aortocaval regions.

†Complete pathological response after neoadjuvant chemotherapy.

‡Liver metastases present at time of diagnosis of primary tumor.

§Subcutaneous 2, mediastinal lymph nodes 1, pericardial lymph nodes 1, chest wall 1, pleura 1, abdo wall 1, spleen 1, brain 1.

¶For analysis of single vs multiple sites, portal nodes and retroperitoneal nodes were analyzed as a single site.

8.9 (range 0.6-687). The median CRS was 2. In 42 patients, the CRS was unable to be calculated due to missing data. Eighty per cent of patients had their EHD resected at the same time as their CRLM; 20% were resected within 6 months.

Treatment Factors

Most of the liver resections required a major hepatectomy (3 or more segments) (49.8%). Almost all patients received systemic chemotherapy, including 56.2% receiving neoadjuvant and 82.2% receiving adjuvant therapy. Modern chemotherapy agents (FOLFOX or FOLFIRI, ± bevacizumab or cetuximab) were used in 93.4% of neoadjuvant regimens and 71.1% of adjuvant regimens. Hepatic arterial infusion with floxuridine combined with systemic chemotherapy was administered to 23.3% of patients as neoadjuvant and/or adjuvant therapy. Neoadjuvant chemotherapy was given for a median of 5 months (range 1–29 mo). Among the patients treated with neoadjuvant chemotherapy, progression of disease was observed in 38 (30.9%) patients, responsive disease in 61 (49.6%) patients, and stable disease in 24 (19.5%) patients. Margin negative (R0) resection of liver disease was achieved in 87.7%, and resection of EHD was grossly complete in 94.1%. The reasons for incomplete resection of EHD were extensive nodal disease in 8 patients, low-volume lung metastases (in addition to resected EHD at another site) that were intended for later resection, but never proceeded due to disease progression in 3 patients, extension of tumor onto right atrium in 1 patient, and palliative portal node resection for bile duct obstruction in 1 patient. Treatment details are summarized in Table 2.

Overall and Recurrence-free Survival

The median follow-up for survivors was 31.2 months. The median OS in the entire cohort was 34.4 months, with an estimated 3, 5, and 10-year survival of 49%, 28%, and 10% respectively. There were 37 actual 5-year and 8 actual 10-year survivors. The estimated 3, 5, and 10-year RFS was 9%, 5%, and 3%, with a median of 8.3 months. The estimated OS and RFS are shown in Figure 1A and B.

Recurrence Patterns and Treatment

In 14 patients, follow-up data were insufficient for analysis of recurrence. Disease recurred in 185 of the remaining 205 patients (90.2%). Intrahepatic recurrence occurred in 118 (57.6%) patients at a median of 8.1 months, and systemic recurrence occurred in 173 (84.4%) at a median of 8.0 months. One hundred six patients (51.7%) recurred both in and outside the liver. When EHD recurred, 76.9% did so outside the initial site of EHD resection. Sites of systemic recurrence included isolated lung (73, 42.2%), abdominal lymph nodes (all sites) (18, 10.4%), peritoneum (9, 5.2%), other (25, 14.5%, including stomach, spleen, bone, pancreas, brain, muscle, heart), and multiple sites (48, 27.7%). Following recurrence, 41 of 185 patients (22.3%) underwent salvage surgery or ablation (7 liver only, 26 EHD only, 8 both liver and EHD), with an associated median survival of 57 months, and a 3 and 5-year survival of 66% and 48%, respectively, from the time of salvage. Median follow-up for survivors after salvage procedures was 22 months (range 1–190) as measured from the date of salvage therapy.

TABLE 2. Surgery and Chemotherapy Details

Surgery, n (%)	
Major hepatectomy (>3 segments)	109 (49.8)
Minor hepatectomy	110 (50.2)
Ablation, n (%)	29 (13.2)
Radiofrequency	5 (2.3)
Microwave	21 (9.6)
Irreversible electroporation	3 (1.4)
Liver margin, n (%)	
R0	192 (87.7)
R1	27 (12.3)
Completeness of EHD resection, n (%)	
R0/R1	206 (94.1)
R2	13 (5.9)
Systemic chemotherapy, n (%)	216 (98.6)
Neoadjuvant	123 (56.2)
Adjuvant	180 (82.2)
Hepatic artery infusional chemotherapy, n (%)	51 (23.3)
Neoadjuvant	21 (9.6)
Adjuvant	39 (17.8)
Duration of neoadjuvant chemotherapy, mo, median (range)	5 (1–29)
Progression of disease while on neoadjuvant chemotherapy, n (%)	38 (30.9)

Cure Rate

At 5 years from index hepatectomy, there were 37 actual survivors, including 6 patients who never recurred, 5 who recurred, but were salvaged and had no evidence of disease (NED), and 26 alive with disease (AWD). There were 166 patients who had 5 or more years of follow-up or had died before 5 years; therefore the NED rate at 5 years was 11/166 (6.6%). At 10 years, there were 8 actual survivors, with 2 who never recurred, 3 who recurred, but were salvaged and rendered NED, and 3 AWD. There were 154 patients who had 10 or more years of follow-up or had died before 10 years; therefore the NED rate at 10 years was 5/154 (3.2%). At 15 years, there was 1 survivor who had 3 recurrences and underwent gastrectomy, repeat hepatectomy, and adrenalectomy to remain NED.

Of the 5 patients who had NED at 10 years, all had a single-liver metastasis, gross complete resection of EHD, and received adjuvant chemotherapy. All patients either did not receive neoadjuvant chemotherapy or had stable or responsive disease while on neoadjuvant chemotherapy. The size of CRLM ranged from 1.2 to 9 cm. Four patients had an R0 liver margin and 1 had an R1 margin. The initial site of EHD was anastomotic in 2 patients, chest wall in 1, internal iliac node in 1, and multiple sites (lung, mesenteric node, small bowel) in 1 patient.

Univariate Analysis of Factors Predictive of Overall Survival

Factors predictive of OS are summarized in Table 3. The CRS was significantly associated with survival. However, of the individual components of the CRS, only size greater than 5 cm and number of CRLM above 1 retained prognostic significance (HR 1.459, $P = 0.030$; and HR 1.496, $P = 0.019$, respectively). There was no difference in survival between patients who received neoadjuvant chemotherapy and those who did not ($P = 0.308$). However, patients who received neoadjuvant chemotherapy and had progression of their liver disease while on treatment had a worse survival than patients who either received no neoadjuvant chemotherapy, or had stable/responsive disease (HR 1.578, $P = 0.002$). An R1 liver resection margin was associated with a median survival of 26.2 months compared with a median of 40.2 months for R0 status (HR 1.534, $P = 0.001$). Incomplete resection of EHD was associated with an even worse prognosis, with a median survival of 19.9 months and no survivors beyond 3.5 years, compared with median of 37.4 months for complete gross resection (HR 1.879, $P = 0.001$).

The survival figures by EHD site are summarized in Table 4. There was no difference in survival between patients with metastases to portal nodes vs retroperitoneal nodes ($P = 0.768$). Patients with involved portal/retroperitoneal nodes, or multiple sites, had the poorest prognosis. The sites of EHD were divided into 2 groups based on prognosis—a poorer prognostic group consisting of portal

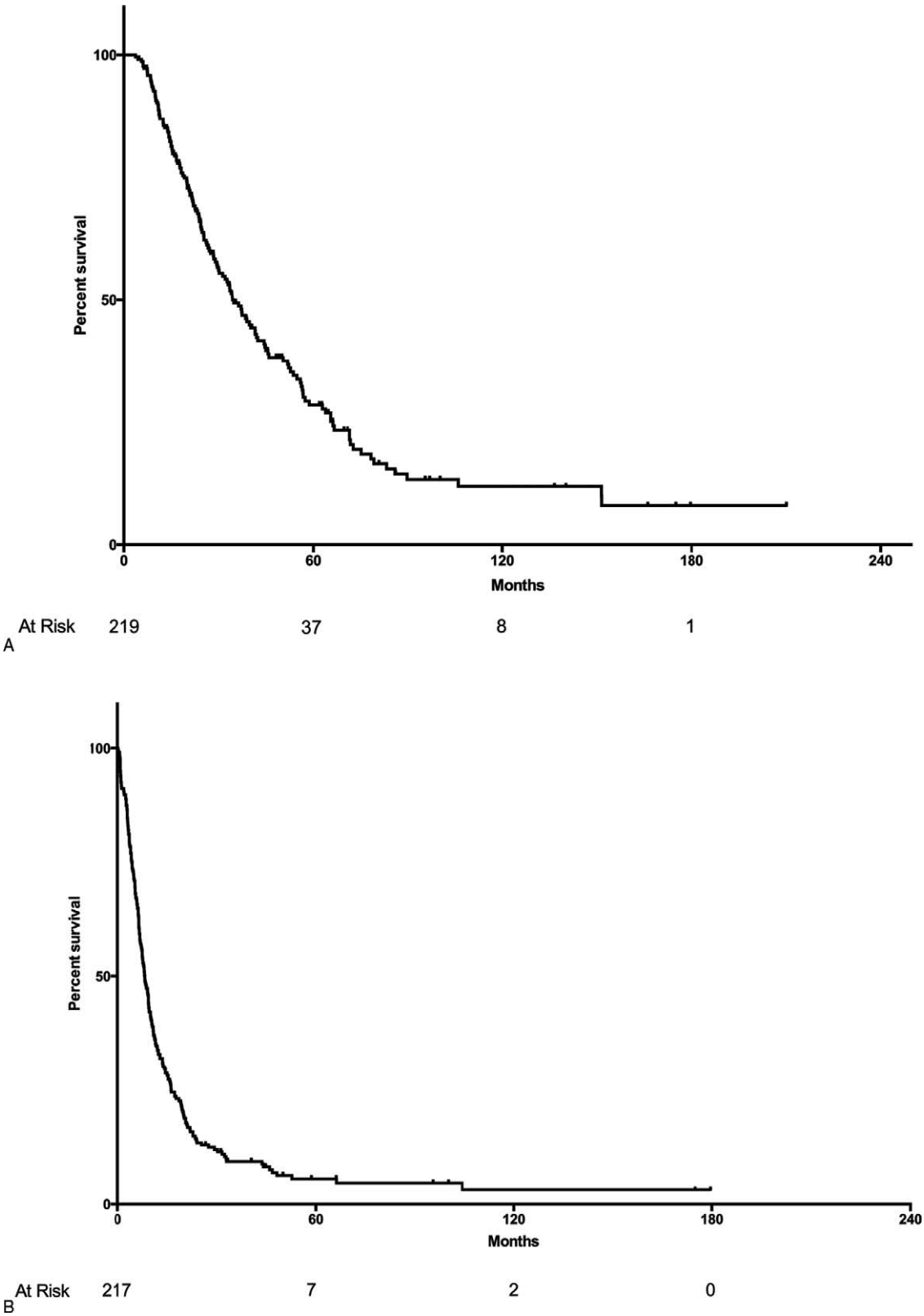


FIGURE 1. (A) Overall survival and (B) recurrence-free survival.

TABLE 3. Univariate and Multivariate Analyses of Factors Predictive of Overall Survival

	Univariate		Multivariate	
Variables	**Hazard Ratio**	***P***	**Hazard Ratio**	***P***
Age*	0.994	0.370		
Male sex	1.077	0.655		
Clinical risk score*,†	1.299	0.004		
Size of largest LM*	1.047	0.037	1.674‡	0.004
Number of LM*	1.117	0.001	1.891§	0.012
Node positive primary	1.280	0.196		
Disease-free interval (LM) <12 m	1.161	0.366		
Preoperative CEA >200 ng/mL	1.697	0.117		
Site of EHD¶	1.813	<0.001	1.783	0.001
Incomplete resection of EHD	1.879	0.001		
Positive liver resection margin (R1)	1.534	0.001		
Neoadjuvant therapy	1.187	0.308		
Progression of liver metastases on neoadjuvant therapy	1.578	0.002	1.829	0.012
Adjuvant chemotherapy	1.194	0.474		

*Continuous variables.
†Fong et al[6]
‡For multivariate analysis, size of largest LM was analyzed as a binary variable: above 3 vs below 3 cm.
§For multivariate analysis, number of LM was analyzed as a binary variable: above 5 vs below 5.
¶Portal/retroperitoneal nodes and multiple sites vs all other sites.

nodes, retroperitoneal nodes, and multiple sites; and a better prognostic group consisting of all other sites. Survival was significantly worse in the poorer prognostic group (5-y survival of 13.2% vs 36.5%, median survival 25.2 vs 45.7 mo; HR 1.813, $P < 0.001$).

Multivariate Analysis of Factors Predictive of Overall Survival

A multivariate analysis was performed using 4 covariates: size of LM greater than 3 cm, number of LM above 5, site of EHD (portal/retroperitoneal nodes or multiple sites vs all other sites), and progression of LM on neoadjuvant therapy. All 4 factors retained statistical significance as predictors of OS.

Extrahepatic Disease Risk Score

A new clinical risk score was developed using 3 variables: size of largest CRLM greater than 3 cm, number of CRLM above 5, and site of EHD (portal/retroperitoneal nodes or multiple sites vs all other sites). Each variable was assigned 1 point, giving a total score of 0 to 3. Although progression of disease while on neoadjuvant chemotherapy was an independent predictor of prognosis on multivariate analysis, not all patients received neoadjuvant chemotherapy. Furthermore, addition of this factor into the risk score model did not improve its prognostic value; therefore it was omitted from the final model. An increasing score correlated with reduced OS and RFS. Patients who scored zero (low risk) had 3, 5, and 10-year survival of 76%, 43%, and 18%, respectively, and a median survival of 56.7 months. Patients who scored 3 (high risk) had a 3-year survival of 12%, with no survivors beyond 5 years, and a median survival of 23.8 months (Fig. 2A).

When the model was applied to RFS, patients who scored 3 all recurred or died within 6 months, with a median RFS of 1.4 months. Patients who scored 2 all recurred within 3 years with a median RFS of 7.1 months (Fig. 2B).

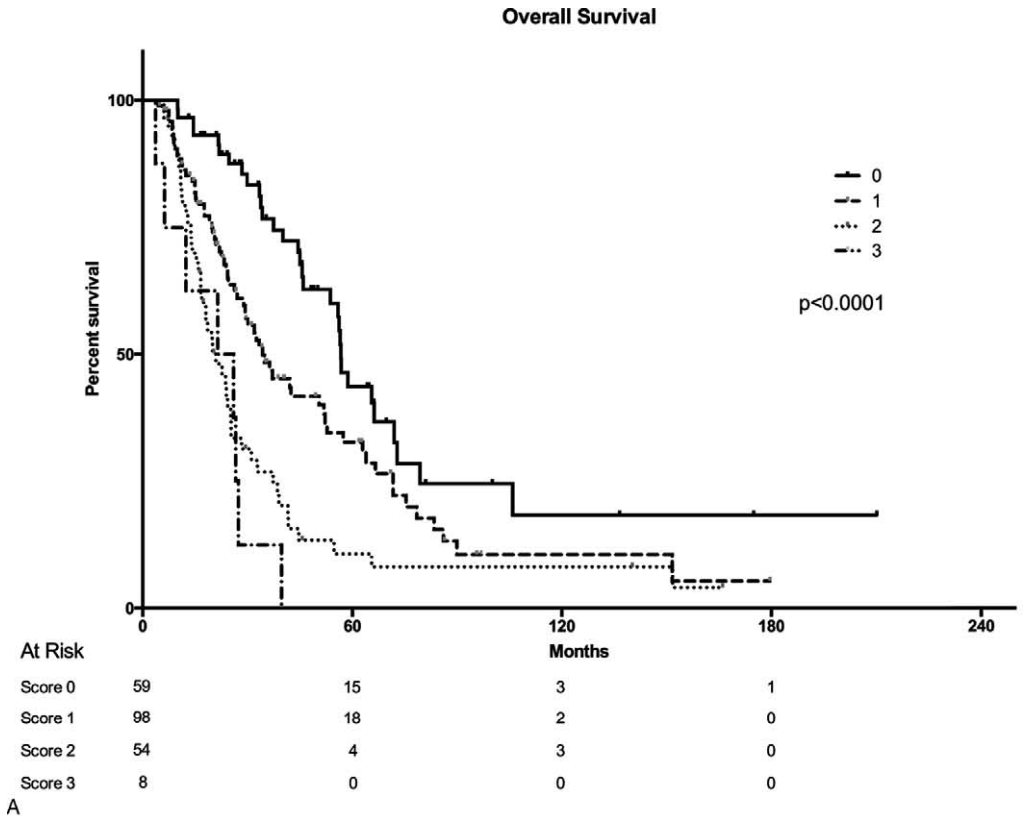
DISCUSSION

Perioperative and oncological outcomes for patients undergoing liver resection for CRLM have improved significantly.[4] This fact, combined with the development of effective systemic chemotherapy for metastatic colorectal cancer, has sparked enthusiasm for consideration of combined hepatic resection and resection of concurrent resectable EHD in selected patients. Recent additions to the literature have provided some evidence that EHD with concurrent liver metastases can be resected to yield promising medium to long-term survival, and thus should no longer be considered an absolute contraindication to curative surgery.[7–11] However, long-term follow-up has not been comprehensively reported, and clinically relevant prognostic factors have not been defined.

TABLE 4. Overall Survival by Site of Extrahepatic Disease

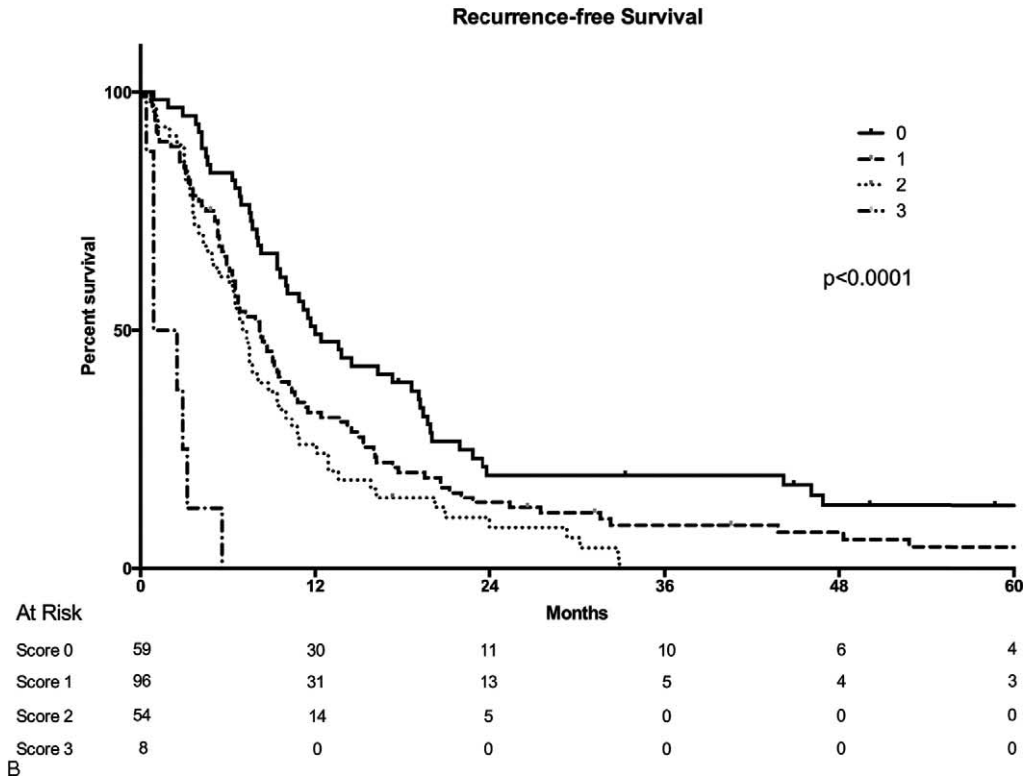
Site	**n**	**Median Survival (Mo)**	**3-y Survival (%)**	**5-y Survival (%)**	**10–y Survival (%)***
Overall	219	34.4	49	28	10
Adrenal	3	Not reached	66	66	—
Anastomotic	14	71.9	64	51	—
Peritoneal	33	40.2	54	42	—
Ovaries	13	32.6	46	34	—
Lungs	57	53.7	68	32	—
Other	8	21.2	32	25	—
Mesenteric/internal iliac nodes	9	23.8	44	22	—
Portal/retroperitoneal Nodes	68	24.3	32	14	—
Multiple	14	30.1	47	11	—

*Too few patients for survival estimates based on individual site.



At Risk				
Score 0	59	15	3	1
Score 1	98	18	2	0
Score 2	54	4	3	0
Score 3	8	0	0	0

A



At Risk						
Score 0	59	30	11	10	6	4
Score 1	96	31	13	5	4	3
Score 2	54	14	5	0	0	0
Score 3	8	0	0	0	0	0

B

FIGURE 2. Survival curves applying the extrahepatic disease risk score to (A) overall survival and (B) recurrence-free survival.

We have previously published our early experience with resection of CRLM and concurrent EHD.[9] In that study, 21/127 patients had locally invasive disease. These patients were excluded from the current analysis since upon reconsideration they probably did not truly have EHD. The current dataset therefore contains 106 original patients and 113 additional patients. To separate the effect on long-term outcome due to incomplete resection of liver disease from incomplete resection of EHD, only patients with macroscopically (determined by surgeon) completely treated liver metastases were included.

There is controversy regarding the prognostic value of the site of EHD in predicting survival after resection. Most studies conclude that the site of EHD is associated with survival,[8–10,12] whereas others did not.[13] Some studies have suggested that patients with metastatic aortocaval lymph nodes did worse than those with portal nodes.[8,12,14] However, we have not found such a difference in the current study. This discrepancy may be due to the lack of a standard anatomical definition of nodal regions, and underlying patient selection. Other factors that have variably been found to be associated with outcome include number of CRLM (ranging from >1 to >6), size of CRLM, use of neoadjuvant therapy, incidental discovery of EHD intraoperatively, and completeness of resection (intra and extrahepatic disease).[7–10] In our previous analysis, we did not find an association between total number of metastases and survival. Furthermore, the counting of systemic metastases can be prone to error; therefore this approach was not undertaken in this study. However, increasing size and number of CRLM were clearly associated with worse survival.

This study showed that incomplete resection of extrahepatic disease strongly predicted a poor prognosis. Therefore, inability to resect all EHD should be considered an absolute contraindication to resection with curative intent. However, no other single factor examined reliably differentiated long-term survivors from patients who met an early demise. Therefore, we sought to develop a scoring system using multiple factors, to help the clinician with preoperative or intraoperative decision-making. A number of scoring systems have been previously derived for patients undergoing resection of CRLM without EHD.[6,15–18] More recently, Adam et al[10] developed a scoring system for patients undergoing resection of concurrent EHD using 5 factors: primary tumor in the right colon, EHD concomitant to recurrence of liver metastases, at least 6 liver metastases, CEA at least 10 ng/mL, and EHD sites other than isolated lung metastases. Here we propose an alternative system using different variables.

The multivariate analysis in this study was performed with development of a scoring system to aid clinical decision in mind. To maximize clinical utility, only variables known preoperatively and/or intraoperatively were included. Therefore, although liver resection margin status and completeness of EHD resection were prognostic of survival on univariate analysis, they were not included in the multivariate analysis. Even though the CRS predicted survival, some patients did not have all the data required for CRS calculation; therefore the CRS was not used in building our predictive model. All 3 factors in the final scoring model were weighted the same (1 point each) due to the comparable HRs (1.67, 1.78, and 1.89 for LM size, EHD site, and number of LM, respectively).

Using this proposed EHD risk scoring system, we identified a group of patients (risk score of 3) who did very poorly after resection. These outcomes are similar to those obtained with modern chemotherapy alone.[19] Therefore, it could be argued that these patients should not undergo resection. In contrast, patients with 0 points had comparable survival to patients with resected liver metastases and no EHD.[4,10] However, it is important to note that even in the best prognostic group, over 90% of patients still recurred. Most of these patients were maintained on long-term and multiple lines of chemotherapy, but were never truly cured.

Due to the retrospective nature of this study, the survival outcomes were heavily influenced by selection bias. The number of patients with CRLM and concurrent EHD who were not offered surgery is unknown. Without such a denominator, the true benefit of concurrent resection is unclear. However, the very poor prognosis of patients who had incomplete resection of EHD (median survival 19.9 mo) would suggest that surgery does have an impact. Patients with diffuse peritoneal carcinomatosis or extensive retroperitoneal lymphadenopathy, and patients who showed marked progression on neoadjuvant therapy would likely have been excluded. Forty-two per cent of patients had EHD discovered intraoperatively, and this group may be biologically different from patients with EHD discovered during preoperative investigations. Intraoperatively diagnosed EHDs are more likely to be portal lymph nodes and peritoneal metastases. Nonetheless, survival for the 2 groups did not differ ($P = 0.93$). FDG-PET scans were not routinely used in this study and this may underestimate the extent of metastatic disease. However, there is evidence from a randomized trial that routine use of preoperative PET in patients with resectable CRLM does not significantly impact management or survival.[20]

Patients with stable or responsive disease while on neoadjuvant therapy fared better than patients who progressed, with an associated median survival of 33.9 months for the former compared with 23.7 months for the latter. Hence disease response on chemotherapy may be an important independent predictor of outcome. However, it should be noted that the definition of progression of liver metastases in this study was not standardized, but was judged retrospectively on the report of CT or MRI results by a radiologist, oncologist, or surgeon. Therefore, we did not draw any firm conclusions from these data, and a separate study to validate this would be recommended. The number of lesions treated may have been overestimated as lesions that were ablated had no histologic confirmation that they were indeed metastases, as they were often small. Their margin status could also not be assessed. Patients who received ablation as part of their treatment, as long as ablation was deemed complete and the resection component had clear margins, were classified as R0. Therefore, the true R0 rate may be lower than reported.

This is the largest single-institution series to date of patients undergoing hepatectomy and resection of concurrent extrahepatic metastases. In addition, this is the first study to report a large number of patients with long-term follow-up. We showed that despite the reasonably long survival for our low and medium-risk patients, very few patients can actually be cured. Nonetheless, attempts at curative resection are in line with the modern paradigm in surgical oncology that although many cancers are incurable, effective systemic chemotherapy and salvage treatment with regional therapies, ablation, and further surgery allow such patients to be kept alive long-term with disease.

Finally, due to the relatively small number of patients in the study, we were unable to perform a validation of our prediction model. It has been shown that scoring systems may not generalize well to external datasets.[21] Future studies to validate our scoring system should be performed. However, resection of concurrent EHD remains a relatively uncommon event, even in a high-volume cancer center with an aggressive treatment paradigm (8.1% of patients with resected CRLM at MSKCC); therefore accrual of enough patients for a validation study may be a challenge.

CONCLUSIONS

In well selected patients, resection of CRLM and limited resectable concurrent extrahepatic disease can result in long-term survival. However, recurrence is the rule and patients are rarely

cured. Patients with incomplete resection of EHD have a poor survival. The site of EHD influences outcome, and patients with metastases to portal or retroperitoneal nodes or multiple sites have a particularly poor prognosis. Concurrent resectable EHD in a single site should not be considered an absolute contraindication to curative resection; however, appropriate selection is important. The proposed scoring system may help identify a subset of patients who do not benefit from resection.

REFERENCES

1. Ito K, Govindarajan A, Ito H, et al. Surgical treatment of hepatic colorectal metastasis: evolving role in the setting of improving systemic therapies and ablative treatments in the 21st century. *Cancer J*. 2010;16:103–110.
2. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol*. 2007;25:4575–4580.
3. Nikfarjam M, Shereef S, Kimchi ET, et al. Survival outcomes of patients with colorectal liver metastases following hepatic resection or ablation in the era of effective chemotherapy. *Ann Surg Oncol*. 2009;16:1860–1867.
4. House MG, Ito H, Gonen M, et al. Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. *J Am Coll Surg*. 2010;210:744–752. 752-745.
5. Pulitano C, Castillo F, Aldrighetti L, et al. What defines 'cure' after liver resection for colorectal metastases? Results after 10 years of follow-up. *HPB (Oxford)*. 2010;12:244–249.
6. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg*. 1999;230:309–318 [discussion 318-321].
7. Elias D, Ouellet JF, Bellon N, et al. Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. *Br J Surg*. 2003;90:567–574.
8. Aoki T, Umekita N, Tanaka S, et al. Prognostic value of concomitant resection of extrahepatic disease in patients with liver metastases of colorectal origin. *Surgery*. 2008;143:706–714.
9. Carpizo DR, D'Angelica M. Liver resection for metastatic colorectal cancer in the presence of extrahepatic disease. *Lancet Oncol*. 2009;10:801–809.
10. Adam R, de Haas RJ, Wicherts DA, et al. Concomitant extrahepatic disease in patients with colorectal liver metastases: when is there a place for surgery? *Ann Surg*. 2011;253:349–359.
11. Pulitano C, Bodingbauer M, Aldrighetti L, et al. Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis. *Ann Surg Oncol*. 2011;18:1380–1388.
12. Pulitano C, Bodingbauer M, Aldrighetti L, et al. Colorectal liver metastasis in the setting of lymph node metastasis: defining the benefit of surgical resection. *Ann Surg Oncol*. 2012;19:435–442.
13. Elias D, Liberale G, Vernerey D, et al. Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. *Ann Surg Oncol*. 2005;12:900–909.
14. Adam R, de Haas RJ, Wicherts DA, et al. Is hepatic resection justified after chemotherapy in patients with colorectal liver metastases and lymph node involvement? *J Clin Oncol*. 2008;26:3672–3680.
15. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. *Cancer*. 1996;77:1254–1262.
16. Iwatsuki S, Dvorchik I, Madariaga JR, et al. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. *J Am Coll Surg*. 1999;189:291–299.
17. Nagashima I, Takada T, Adachi M, et al. Proposal of criteria to select candidates with colorectal liver metastases for hepatic resection: comparison of our scoring system to the positive number of risk factors. *World J Gastroenterol*. 2006;12:6305–6309.
18. Konopke R, Kersting S, Distler M, et al. Prognostic factors and evaluation of a clinical score for predicting survival after resection of colorectal liver metastases. *Liver Int*. 2009;29:89–102.
19. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol*. 2004;22:229–237.
20. Moulton CA, Gu CS, Law CH, et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. *JAMA*. 2014;311:1863–1869.
21. Zakaria S, Donohue JH, Que FG, et al. Hepatic resection for colorectal metastases: value for risk scoring systems? *Ann Surg*. 2007;246:183–191.