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ORIGINAL REPORT

Actual 10-Year Survival After Resection of Colorectal Liver Metastases Defines Cure

James S. Tomlinson, William R. Jarnagin, Ronald P. DeMatteo, Yuman Fong, Peter Kornprat, Mithat Gonen, Nancy Kemeny, Murray F. Brennan, Leslie H. Blumgart, and Michael D'Angelica

From the Departments of Surgery, Epidemiology and Biostatistics, and Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY; Division of Surgical Oncology, University of California, Los Angeles, Greater Los Angeles Healthcare System, Los Angeles, CA; and Department of Surgery, Medical University of Graz, Graz, Austria.

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Address reprint requests to Michael D'Angelica, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021; e-mail: dangelim@mskcc.org.

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ABSTRACT

Purpose
Resection of colorectal liver metastases (CLM) in selected patients has evolved as the standard of care during the last 20 years. In the absence of prospective randomized clinical trials, a survival benefit has been deduced relative to historical controls based on actuarial data. There is now sufficient follow-up on a significant number of patients to address the curative intent of resecting CLM.

Methods
Retrospective review of a prospectively maintained database was performed on patients who underwent resection of CLM from 1985 to 1994. Postoperative deaths were excluded. Disease-specific survival (DSS) was calculated from the time of hepatectomy using the Kaplan-Meier method.

Results
There were 612 consecutive patients identified with 10-year follow-up. Median DSS was 44 months. There were 102 actual 10-year survivors. Ninety-nine (97%) of the 102 were disease free at last follow-up. Only one patient experienced a disease-specific death after 10 years of survival. In contrast, 34% of the 5-year survivors suffered a cancer-related death. Previously identified poor prognostic factors found among the 102 actual 10-year survivors included 7% synchronous disease, 36% disease-free interval less than 12 months, 25% bilobar metastases, 50% node-positive primary, 39% more than one metastasis, and 35% tumor size more than 5 cm.

Conclusion
Patients who survive 10 years appear to be cured of their disease, whereas approximately one third of actual 5-year survivors succumb to a cancer-related death. In well-selected patients, there is at least a one in six chance of cure after hepatectomy for CLM. The presence of poor prognostic factors does not preclude the possibility of long-term survival and cure.

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INTRODUCTION

The concept of resecting metastatic disease with curative intent is counterintuitive to the concept that metastases represent a systemic disease. However, if one envisions the disease to be regionally confined to a specific organ, then acceptance of a local therapy as potentially curative is reasonable. Such has been the thinking in the surgical treatment of metastatic colorectal cancer to the liver during the last few decades.[1-3] It has been shown that 60% to 70% of recurrences after resection of a primary colorectal tumor involve the liver. Moreover, 20% to 35% of patients with metastatic disease have the liver as their sole site of disease and could be considered potentially to have regionally confined metastases.[4,5]

During the last 20 years, resection of colorectal liver metastases (CLM) in selected patients has been slowly adopted as the standard of care. The largest single-institution surgical series report actuarial 5-year survival rates of 27% to 39% for resected patients.[1-3,6] As these series mature, a substantial number of actual 5-year survivors are being reported after resection, even though a significant number of them experience a recurrence at some point.[7] In comparison, patients with untreated but potentially resectable metastases have an approximately 6- to 12-month median survival and rarely survive longer than 3 years.[8,9] The use of modern chemotherapy regimens now results in median survival of up to 21 months in patients with unresectable disease.[10] However, chemotherapy is rarely, if ever, associated with durable resolution of disease or long-term survival beyond 5 years. On the basis of these data, the enthusiasm and optimism in favor of a resectional approach seems justified. Still, the survival advantage has been called into question by some because it is based on retrospective natural

history studies. These arguments suggest that lead time bias and extreme selection of patients with limited disease may be responsible for the improved survival associated with resected metastases.[11-13] Although these questions could be answered in a randomized prospective trial, such a trial is not feasible because of the overwhelming evidence in favor of resection.

It is incumbent on the clinicians who regularly perform resections of CLM based on retrospective data to continually evaluate and define the true benefit offered by such therapy. The basis for performing resection of CLM is the intent to cure, yet this end point has not been well defined. Long-term disease-free survival is the true measure of a curative therapy, yet few studies have had enough patients with sufficient follow-up to define cure. In fact, most studies report actuarial 5-year survival statistics as evidence of an adequate oncologic outcome. This study is based on a large, single-institutional experience with at least 10-year follow-up to address the true curative intent of resection of CLM. The aims of this study are to define cure after resection of CLM, determine the cure rate based on actual survivors, and identify clinical characteristics associated with a cured patient to improve patient selection for surgical therapy.

METHODS

With approval of the Institutional Review Board and in accordance with Health Insurance Portability and Accountability Act regulations, a prospectively maintained hepatobiliary database was used to identify 644 consecutive patients who underwent resection of CLM at Memorial Sloan-Kettering Cancer Center (New York, NY) from 1985 to 1994. Postoperative deaths (n = 32) were excluded. Guidelines for resectability were medical fitness for major laparotomy, no evidence of disseminated disease, and a resection strategy encompassing all liver disease with an adequate remnant liver for recovery. A preoperative extent-of-disease evaluation included chest x-ray, abdominal/pelvic computed tomography, and colonoscopy.

Variables studied included age, sex, site and node status of the primary, synchronous versus metachronous metastases, disease-free interval (DFI; defined as time elapsed from primary resection to hepatic recurrence), prehepatectomy carcinoembryonic antigen (CEA) level, presence or absence of bilobar disease, and size and number of hepatic tumors. Postoperative variables evaluated were hepatic resection margin status, extent of resection, and whether adjuvant hepatic-arterial infusional chemotherapy (HAIC) was administered. Accurate documentation of postoperative systemic chemotherapy in other patients was not available. A margin was considered positive if tumor was less than 1 mm from the cut edge. Extent of resection was recorded as less than a hemihepatectomy, hemihepatectomy, or greater then a hemihepatectomy. A hemihepatectomy refers to a left hepatectomy (resection of segments 2, 3, and 4) or a right hepatectomy (resection of segments 5 through 8). Resections that are classified as less than a hemihepatectomy refer to segmentectomies and wedge resections, alone or in combination, that do not add up to removal of a hemiliver. Resections considered greater than a hemihepatectomy are left or right hepatectomies plus additional contralateral resections, as well as extended right or left hepatectomies.

In a previous study from Memorial Sloan-Kettering Cancer Center, a preoperative clinical risk score (CRS) was developed to predict survival after resection of liver metastases of colorectal origin. The CRS was based on five preoperative factors: node-positive primary, DFI less than 12 months, number of hepatic metastases more than one, largest hepatic metastasis more than 5 cm, and CEA more than 200 ng/mL. If present, each factor was assigned one point and the total score (0 to 5) was tallied for each patient. In this study, we investigated the CRS to reassess its value in predicting long-term survival and cure. Patients were grouped according to CRS score, and Kaplan-Meier survival curves were constructed and compared by the log-rank test.

Disease-specific survival (DSS) was calculated from the time of initial hepatectomy until cancer-related death. Survival curves were generated by Kaplan-Meier method.[14] Patients were censored at the time of loss to follow-up or death as a result of noncancer causes. Univariate analysis for factors associated with DSS was conducted using the log-rank test.[15] Statistical analysis was performed using the SPSS (version 12; SPSS Inc, Chicago, IL). *P* values $\leq .05$ were considered statistically significant.

RESULTS

Patient Characteristics and Follow-Up Status

Six hundred twelve patients underwent resection of CLM from 1985 through 1994 and had the potential for at least 10 years of follow-up. The median age at the time of resection was 62 years and 60% of the patients were male. The original site of primary was located within the colon 73% of the time. Disease status at last follow-up identified 132 patients (22%) with no evidence of disease (NED), 24 patients (4%) alive with disease (AWD), 438 patients (72%) dead as a result of disease, and 18 patients (3%) dead as a result of other causes. Seventy-three (12%) patients were lost to follow-up before 10 years and thus death earlier than 10 years or survival for longer than 10 years was unknown. Median follow-up of this group was 70 months. The disease status of these 73 patients includes 49 patients who were NED, 22 patients who were AWD, and two patients who died as a result of other causes. Of note, median survival for the 49 patients who were NED was 72 months and 35 of these patients (71%) survived at least 5 years.

Disease-Specific and Disease-Free Survival

Figure 1 illustrates the Kaplan-Meier DSS curve for the entire cohort (n = 612). The median survival is 44 months and the survival curve reaches a plateau after 10 years from the time of hepatic resection. This plateau represents 102 actual 10-year survivors, demonstrating a minimum cure rate of 17% (102 of 612). If one considers the 49 patients who were NED but did not have follow-up beyond 10 years, the maximum cure rate is 25% (151 of 612). One disease-specific death occurred among patients who survived 10 years from the time of hepatectomy. This is in contrast to the 214 patients who

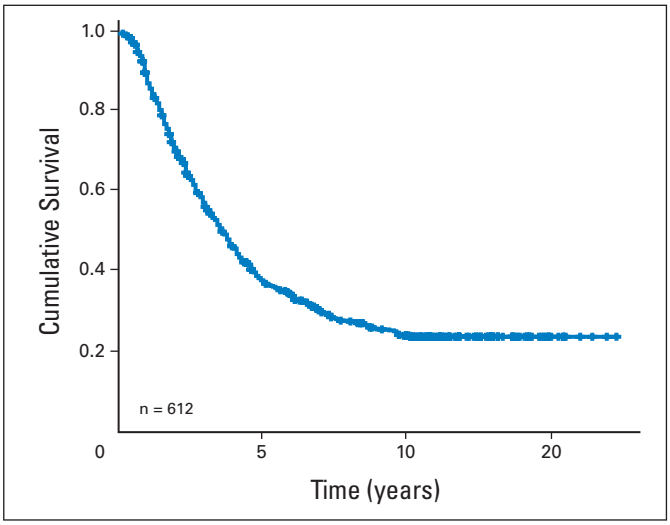

Fig 1. Kaplan-Meier plot of disease-specific survival for 612 patients with potential 10-year follow-up who underwent resection of colorectal liver metastases from 1985 to 1994 at Memorial Sloan-Kettering Cancer Center.

survived at least 5 years from the time of liver resection, in which 73 (34%) were documented ultimately to have a cancer-related death. Of these 73 patients, 42 (58%) had documented evidence of recurrence before 5 years of survival, 17 (23%) had a documented first recurrence after 5 years, and 14 (19%) had inadequate data to accurately document the timing of recurrence.

Actual 10-Year Survivors

Of the 102 actual 10-year survivors, 99 were NED, two were AWD, and one patient died as a result of disease at last follow-up. Median follow-up for the 10-year survivors is 146 months (Table 1). Eighty-six of the 102 actual 10-year survivors remained disease-free after a single hepatectomy. However, disease recurrence after initial hepatectomy occurred in 16 patients. In seven patients, recurrences were isolated to the liver and these patients underwent a second liver resection. All seven patients remained NED after their second hepatectomy. Six patients had recurrences limited to the lungs, which were resected, resulting in five patients remaining disease free. One patient experienced an additional pulmonary recurrence and is AWD. Two patients had recurrences involving both the liver and the lung. These patients underwent both a second liver and lung resection, resulting in one patient free of disease, whereas the other patient is considered AWD secondary to additional pulmonary recurrences. Only one patient had a recurrence that involved the liver, lung, and the peritoneal cavity, and was treated with chemotherapy. This patient represents the only disease-specific death that occurred after 10 years of survival from initial hepatectomy. The vast majority (92 of 102) of the 10-year survivors had liver-only disease throughout their course.

Comparison of the Survival Extremes

To identify characteristics that may preclude long-term survival and cure, we compared the frequency of known poor prognostic factors present within specific survival cohorts defined as less than 2, 2 to 5, 5 to 10, and more than 10 years. These results are listed in Table 2. The frequency of poor prognostic factors found among the 102 actual 10-year survivors included 7% with synchronous disease, 36% with a DFI less than 12 months, 25% with bilobar metastases, 50% with node-positive primary tumor, 39% with more than one metastasis, and 35% with a hepatic tumor more than 5 cm. Although each poor prognostic factor decreases in frequency compared with the worst survival cohort (< 2 years), no single preoperative prognostic factor was sufficiently discriminating to preclude long-term survival and cure. In considering postoperative prognostic factors, there were no patients who survived 10 years who had a positive margin. Overall, 95% of the 10-year survivors had three or fewer hepatic metastases. The frequency of resections classified as ≥ hemihepatectomy was the only factor that did not change among the survival cohorts.

Complete information on the use of adjuvant systemic chemotherapy was not available on most patients. However, we were able to document treatment with adjuvant HAIC in 55 patients treated on prospective trials. Interestingly, 21 of these 55 patients were 10-year survivors. In contrast, there were 81 10-year survivors of the 557 other patients (15%; $P < .0001$). In analyzing the potential confounding prognostic factors, there was a slightly lower margin positivity rate (2% *v* 11%; $P = .03$) and patients with CEA more than 200 (9% *v* 13%; $P = .04$) in the patients receiving HAIC. All of the other factors were equivalent between these two groups, including the CRS.

Revisiting the CRS

We next stratified the DSS of the entire cohort based on the CRS as defined.[1] Patients with a CRS of 0, 1, or 2 (n = 359) had similar survival that was not statistically different. Likewise, there was no statistical difference in survival between patients with a CRS of 3, 4, or 5 (n = 161; data not shown). This allowed us to group the individual CRS values into a high group (CRS = 3, 4, or 5) and low group (CRS = 0, 1, or 2), as illustrated in Figure 2. The median survival of 57 months for the low group is significantly better when compared with median survival of 30 months associated with the high group ($P < .0001$). Both groups contained actual 10-year survivors, with 16 patients (10%) in the high-risk group and 74 patients (21%) in the low-risk group.

Table 1. Characteristics of 102 Actual 10-Year Survivors

Characteristic	No. of Patients
Disease status	
NED	99*
AWD	2
DOD	1
Median follow-up, months	146
Disease recurrence	16
Liver	7
Lung	6
Liver/lung	2
Peritoneum	1

Abbreviations: NED, no evidence of disease; AWD, alive with disease; DOD, dead as a result of disease.
*Patients who experienced a non–cancer-related death but were considered NED at last follow-up are listed as NED.

DISCUSSION

During the last 20 years, resection of CLM in selected patients with limited disease has been increasingly accepted by surgeons and medical oncologists. This is the result of the decreasing surgical morbidity/mortality of liver resection and the overwhelming evidence in favor of an associated survival benefit. The evidence for such a benefit is based on retrospective studies reporting actuarial 5-year survival rates of 25% to 40% for patients undergoing resection as compared with patients treated with chemotherapy or untreated who rarely survive 5 years.[8,9,16-19] Currently, it is considered the standard of care that patients with resectable CLM are offered a resection as their only chance of cure. However, no study to date has been able to address adequately the cure rate associated with resection. Previous studies have been limited by small sample sizes and limited long-term follow-up. Documentation of durable, long-term, disease-free survival after resection of CLM would provide evidence of the potentially curative nature of hepatic resection.

The data from the current study were extracted from a large, single-institution experience, including more than 600 patients who underwent resection of their CLM and had the potential for 10 years of follow-up. Moreover, these patients underwent resection of their CLM before the introduction of modern chemotherapeutic agents such as irinotecan, oxaliplatin, and bevacizumab. This is an important point because as the efficacy of newer agents improves, evaluating the independent therapeutic benefit afforded by surgical resection of

Table 2. Comparison of Prognostic Factors Among Survival Cohorts

Factor	< 2-Year Survival* (n = 175)		2- to 5-Year Survival* (n = 189)		5- to 10-Year Survival* (n = 73)		> 10-Year Survival (n = 102)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Preoperative								
Synchronous disease	23	13	20	11	4	5	7	7
Node-positive primary†	111	63	101	53	38	52	51	50
Preoperative CEA > 200 ng/mL†	28	16	21	11	6	8	7	7
DFI < 12 months†	89	51	86	46	26	36	37	36
No. of hepatic tumors > 1†	103	59	96	51	23	32	40	39
Median	2		2		1		1	
1	72	41	90	48	50	69	60	60
2	41	23	50	27	12	16	24	24
3	22	13	15	8	3	4	11	11
≥ 4	40	23	31	16	8	11	5	5
Size of hepatic tumor > 5 cm†	92	53	78	41	30	41	36	35
Median size of largest hepatic tumor, cm	5		4		4		3.8	
Postoperative								
Margin positive	35	20	18	10	6	9	0	0
Resection ≥ hemihepatectomy	109	62	114	60	44	60	66	64
Bilateral resection	80	46	55	29	21	29	25	25

Abbreviation: CEA, carcinoembryonic antigen; DFI, disease-free interval; CRS, clinical risk score.
*Only patients who experienced a cancer-related death were included in cohorts with less than 10 years of survival.
†Prognostic factors included in CRS.

CLM will be increasingly difficult. During the time period of this study, the only available perioperative chemotherapy agents were fluorouracil based and had minimal efficacy. Although the systemic chemotherapy of this era was ineffective, it has been shown that HAIC with floxuridine is effective for controlling liver disease. A small proportion of patients in this study did receive adjuvant HAIC on prospective trials.[20,21] Irinotecan and oxaliplatin were first used at our institution after 1996, and it is possible that some of the long-term survivors received these agents as part of the treatment for recurrent disease. Given that the vast majority of 10-year survivors did not experience recurrence, these chemotherapeutic agents cannot account for their long-term survival. In considering the adjuvant and palliative chemotherapy used during the time period of this study, combined with the marginal benefit associated with fluorouracil-based therapies, this cohort represents the most reasonable group of patients in which to investigate the true benefit of surgical resection of CLM.

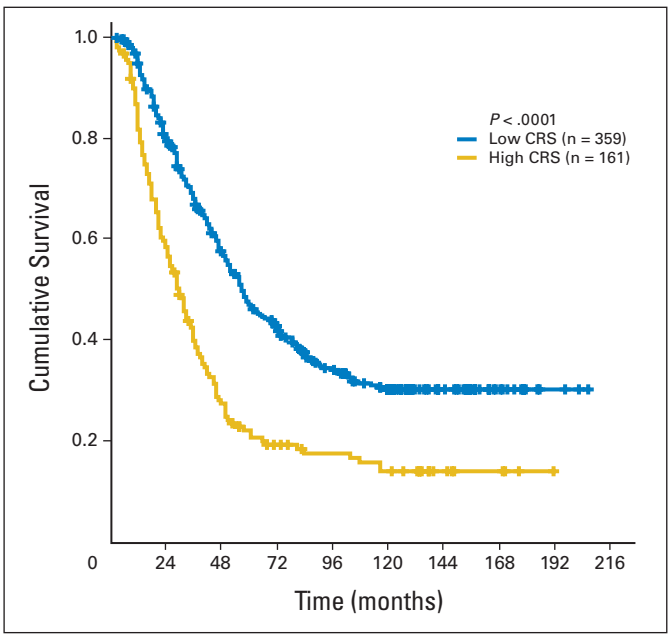

Fig 2. Kaplan-Meier plots of disease-specific survival stratified by low-risk clinical risk score (CRS; top curve) and high-risk CRS (bottom curve).

The principal aim of this study was to define cure after resection of CLM. On observation of the Kaplan-Meier plot of DSS of the entire cohort, it is immediately obvious that the curve reaches a plateau after 10 years of survival. The time point from hepatectomy in which disease-specific death becomes an extremely rare event is the basis of our definition of cure. Of the 102 actual 10-year survivors representing this plateau in the curve, only one patient experienced a cancer-related death. We therefore define cure as 10 years of survival after resection of CLM. It should be noted that 16 of these actual 10-year survivors did experience a recurrence and all but one underwent additional surgical therapy to treat their recurrent metastatic disease. The one patient who suffered a cancer-related death had such extensive recurrence involving the peritoneal cavity, liver, and lung that reresection was not an option. The vast majority, 99 (98%) of 102 actual 10-year survivors, were NED at last follow-up. The cure rate after resection of CLM is therefore at least 17%. If we use only actual survivors to define cure, we have negated the chance of censored patients to contribute to the rate of cure. Of note, 49 patients were lost to follow-up before 10 years but were NED at last follow-up. The median follow-up of this group of patients was 72 months. It is likely that a proportion

of this group would have survived 10 years, thus increasing the rate of cure. The maximum 10-year survival rate would be 25% from these calculations. The operative mortality rate in this series was 5%; this number should be factored into the risk/benefit analysis of offering surgical resection. Of note, more recent series report a much lower operative mortality.[22]

Previously determined poor prognostic factors were also analyzed in hopes of identifying factors that may negate the potential for long-term survival and cure. The study group was divided into different survival cohorts to compare the extremes of survival, allowing us to identify trends. When we considered factors that could be established before hepatectomy, no single preoperative factor was sufficiently discriminating to negate the potential for long-term survival and cure. However, patients who had four or more tumors were associated uncommonly with curative resection. With respect to postoperative factors, no patient who had a positive margin survived 10 years. With only marginally effective adjuvant therapy, the inability to remove all disease surgically means that patient cure is unlikely. This finding also validates our selection of an appropriate study cohort with respect to the marginal effect of chemotherapies administered during the study period. Interestingly, the use of adjuvant HAIC was associated with a higher 10-year survival compared with the rest of the patients. It is difficult to interpret these data in the context of a retrospective review, given that complete chemotherapy histories are unknown. Nonetheless, this was an intriguing finding and we continue to study the benefits of adjuvant HAIC.

Given that no single preoperative risk factor precluded the possibility of long-term survival and cure, we analyzed the CRS, which uses the prognostic ability of combining five preoperative factors into a cumulative score. The lower scores of 0, 1, and 2 seem to predict similarly better survival when compared with the higher scores of 3, 4, and 5. This allowed us to define a low-risk CRS (0, 1, and 2) and a high-risk CRS (3, 4, and 5). Both groups contained 10-year survivors, showing that having a high CRS diminishes but does not preclude the possibility of long-term survival and cure. Using the CRS, we are able to refine our estimation of cure rate such that if one has a low CRS, the estimated minimum cure rate associated with surgical resection would be 21%. Likewise, a high CRS score would result in a 10% predicted minimum cure rate. Application of this refined estimation may be used to identify patients who might benefit from a neoadjuvant chemotherapy approach before hepatectomy, especially in light of more effective chemotherapy regimens.

In conclusion, we have defined cure after resection of CLM as 10 years of survival after initial hepatectomy. On the basis of actual 10-year survivors, we have determined the cure rate to be at least 17% and potentially as high as 25%. On investigation of previously determined poor preoperative prognostic factors, we were not able to find any preoperative factors that were sufficiently discriminatory to negate the potential for attaining a cure after resection. A positive margin, however, negated the potential for long-term survival. Identification of novel predictive factors that define tumor biology associated with curable regionally confined metastases clearly is necessary in future attempts to predict outcomes in patients who present with CLM.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: James S. Tomlinson, Michael D'Angelica
Administrative support: William R. Jarnagin, Murray F. Brennan, Leslie H. Blumgart
Provision of study materials or patients: William R. Jarnagin, Ronald P. DeMatteo, Yuman Fong, Nancy Kemeny, Murray F. Brennan, Leslie H. Blumgart, Michael D'Angelica
Collection and assembly of data: James S. Tomlinson, Peter Kornprat, Michael D'Angelica
Data analysis and interpretation: James S. Tomlinson, Mithat Gonen, Michael D'Angelica
Manuscript writing: James S. Tomlinson, Peter Kornprat, Michael D'Angelica
Final approval of manuscript: James S. Tomlinson, William R. Jamagin, Ronald P. DeMatteo, Yuman Fong, Peter Komprat, Mithat Gonen, Nancy Kemeny, Murray F. Brennan, Leslie H. Blumgart, Michael D'Angelica

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