original report

Liver Metastasectomy and Systemic Therapy Improve Overall Survival Compared With Surgery Alone After Curative Liver Resection of Colorectal Metastases in a Developing Country (Costa Rica)

abstract

Background Resection of liver-isolated metastases of colorectal cancer (CRC) offers the greatest likelihood of cure. Nevertheless, recurrence rates after this procedure are high, and chemotherapy is a reasonable choice with inconclusive evidence. We aimed to determine if there is a survival difference between patients receiving systemic therapy with surgery versus surgery alone for resection of liver metastases.

Methods From a source population of 170 patients treated in our National Centre (Centro Nacional de Cirugía Hepatobiliar, San José, Costa Rica), with liver metastases from various primary sites, we selected 51 patients with CRC who underwent hepatic resection with curative intent. We categorized patients according to the treatment received (fluoropyrimidine-based chemotherapy plus or minus monoclonal antibody and surgery *v* surgery alone) and then calculated the overall survival (OS) rate according to the Kaplan-Meier method. A Cox proportional hazard model was used to assess the influence of potential confounding variables on OS.

Results After a median follow-up of 41.6 months, OS was significantly better for patients treated with systemic therapy (before and/or after hepatic resection) versus surgery alone (3-year OS: 66.7% *v* 41.7%; hazard ratio, 0.37; 95% CI, 0.15 to 0.91; log-rank test: $P = .025$). There were no differences among patients who underwent neoadjuvant (48.7%), perioperative (46.2%), and adjuvant therapy (5.1%). The use of systemic therapy was significantly associated with better OS after adjustment for confounding variables (hazard ratio, 0.23; 95% CI, 0.07 to 0.92; $P = .03$).

Conclusion Our findings support the use of systemic therapy (either perioperative, neoadjuvant, or adjuvant) as part of isolated hepatic metastasectomy from CRC.

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Paula Quesada-Soto

Denis Landaverde

Allan Ramos-Esquivel

Paula Quesada-Soto and **Denis Landaverde**, Hospital México; and **Allan Ramos-Esquivel**, Hospital San Juan de Dios, San José, Costa Rica.

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Corresponding author: Allan Ramos-Esquivel, Ciudad Universitario Rodrigo Facio, Escuela de Medicina, Departamento de Farmacología, San José, Costa Rica, Apdo. 2082; e-mail: allan.ramos@ucr.ac.cr.

INTRODUCTION

Colorectal cancer (CRC) is the second and third most common cancer in women and men, respectively; it is a leading cause of cancer-related mortality worldwide.[1] Approximately 50% of patients develop hepatic metastases, and in one-third of cases the liver is the only affected organ. At the time of diagnosis, synchronous isolated liver metastases are detected in approximately 25% of patients. If these lesions become resectable, the reported 5-year survival rate increases from 30% to 65%, and fewer than 2% of patients are still alive 5 years after diagnosis without any medical or surgical treatment.[2]

For this reason, surgical resection of isolated liver metastases is the treatment of choice when feasible. Nevertheless, recurrence rates after this procedure are high, making systemic treatment plausible to achieve longer survival.[3] Although the use of perioperative and adjuvant therapy has

shown some efficacy in patients with resectable liver metastases, the indication of systemic therapy after curative surgery for liver metastases is currently uncertain. There are contradictory results in the literature as the result of scarce data and trials that closed prematurely because of slow accrual. Hence, clear evidence for a survival benefit of systemic treatment compared with observation alone has not been well established.[4,5] Nevertheless, a recent meta-analysis of randomized and observational clinical trials showed a clinical benefit in terms of overall survival (OS) and recurrence-free survival for those patients who underwent hepatic metastasectomy and received systemic chemotherapy.[6]

Furthermore, there is a current debate about the preference of neoadjuvant, perioperative, or adjuvant treatment in these patients, and the best regimen remains to be determined.[7,8] Moreover, there are scarce data regarding this procedure in developing countries, where access to medical care is often limited.

In this retrospective study, we aimed to determine if patients receiving any kind of systemic therapy plus surgery obtain a better OS than patients treated with surgery alone for CRC liver metastases.

METHODS

Between January 2009 and December 2014, we reviewed the clinical records of 170 patients treated in the National Centre of Hepatobiliary Surgery (San José, Costa Rica) who underwent hepatic metastasectomy. We then selected 51 patients who underwent curative hepatic resection of colorectal metastases. The attending surgeon performed the surgical procedure (metastasectomy, segmentectomy, or partial hepatectomy) after multidisciplinary planning. Patients were considered candidates for this approach if they had no significant medical condition that contraindicated the surgical procedure, an Eastern Cooperative Oncology Group performance status score $\leqslant 2$, and no detectable extrahepatic tumor.

The follow-up consisted of clinical evaluation performed at least every 6 weeks during the first year and at least every 3 months thereafter. Evaluation included physical examination, serum carcinoembryonic antigen levels, and at least three annual thorax and abdomen computed tomography scans or an abdominal ultrasound every 4 or 6 months. Patients received conversion (ie, neoadjuvant), perioperative, adjuvant, or no systemic therapy, according to the recommendation of the multidisciplinary team. For the purpose of this work, we considered conversion (neoadjuvant) chemotherapy solely as the administration of preoperative treatment for resectable or borderline-resectable liver metastases. The administration of chemotherapy before and after the surgical procedure was considered perioperative treatment. Lastly, adjuvant therapy refers to systemic treatment received after surgical resection.

The tumor board decided upon the most suitable chemotherapeutic regimen (fluoropyrimidine based) with or without the addition of any monoclonal antibody (bevacizumab or cetuximab). Individual patient data were collected, including age, sex, tumor stage and grade, as well as primary site, number, and size of liver metastases.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Because of the retrospective nature of this study, formal consent was not required.

Categorical variables are presented as percentages and were compared by the χ^2 test or Fisher's exact test when applicable. Continuous variables are presented as the mean $\pm$ standard deviation and were analyzed by the Mann-Whitney *U* test as appropriate. Follow-up time was calculated as the time from surgery to death or to August 1, 2014. Disease-free survival (DFS) and OS were calculated using the Kaplan-Meier method, measuring time from the date of surgery to the date of failure at any site (determined by RECIST 1.1) or to the date of death from any cause, respectively. Using the log-rank test, we compared patients who received systemic treatment plus surgery with those who underwent only the surgical procedure. The Cox proportional hazards regression model was used to calculate crude hazard ratios.

A P value $< .05$ was considered statistically significant. Data were analyzed using SPSS for Mac version 20.0 (SPSS, Chicago, IL).

RESULTS

Patients had a median follow-up of 41.6 months (interquartile range: 29.2 to 44.4 months). Patient demographics and clinical variables stratified according to treatment received are presented in Table 1. Treatment modalities were as follows: neoadjuvant therapy (conversion therapy), 19 patients (48.7%); perioperative chemotherapy, 18 patients (46.2%); and adjuvant therapy, two patients (5.1%). The regimen used most frequently was capecitabine plus oxaliplatin (XELOX)

Table 1 – Clinical Characteristics of the Studied Population According to Treatment Received

Variable	Patients (n = 51)	Surgery Only (n = 12)	Systemic Treatment and Surgery (n = 39)	*P*
Male sex, No. (%)	39 (76.5)	7 (58.3)	32 (82.1)	.09
Age, years (mean ± SD)	61.72 ± 14.5	63.83 ± 19.7	61.07 ± 12.8	.90
T (primary site), No.(%)				.69
T1	3 (5.9)	1 (8.3)	2 (5.1)	
T2	8 (15.7)	2 (16.7)	6 (15.4)	
T3	33 (64.7)	7 (58.3)	26 (66.7)	
T4	7 (13.7)	2 (16.7)	5 (12.8)	
N (primary site), No. (%)				.95
N0	3 (5.9)	1 (8.3)	2 (5.1)	
N1	12 (23.5)	3 (25)	9 (23.1)	
N2	15 (29.4)	3 (25)	12 (30.8)	
Nx (fewer than 12 harvested nodes)	10 (19.6)	2 (16.7)	8 (20.5)	
Unknown	11 (21.6)	3 (25)	8 (20.5)	
Clinical stage (%)				.76
II	3 (5.9)	1 (8.3)	2 (5.1)	
III	20 (39.2)	10 (83.3)	10 (25.6)	
IV	28 (54.9	1 (8.3)	27 (69.2)	
Primary origin (%)				.54
Colon	27 (52.9)	6 (50)	21 (53.8)	
Rectum	24 (47.1)	6 (50)	18 (46.2)	
Synchronicity of liver metastases (%)				< .001*
Synchronous	28 (54.9)	1 (8.3)	27 (69.2)	
Methacronous	23 (45.1)	11 (91.7)	12 (30.8)	
Mean size of liver metastases (cm)	3.01 ± 1.8	3.19 ± 1.5	3.07 ± 1.9	.87
More than three hepatic lesions (%)	13 (28.9)	1 (8.3)	12 (30.8)	.13
Incomplete resection rate (R1; %)	7 (13.7)	2 (16.7)	5 (12.8)	.63
Recurrence proportion after metastasectomy during follow-up	36 (70.6)	10 (83.3)	26 (66.7)	.23

*Statistically significant at $P < .05$.

in 20 patients; followed by fluorouracil, leucovorin, and oxaliplatin (FOLFOX-6) plus bevacizumab in nine patients. Other regimens were as follows: FOLFOX-6 in three patients; fluorouracil, leucovorin, and irinotecan (FOLFIRI) in three patients; XELOX plus cetuximab in one patient; and capecitabine alone in the remaining patient.

The majority of surgical procedures consisted of segmentectomy or tumorectomy (in 28 patients); partial hepatectomy was performed in the remaining cases. Seven patients also received radiofrequency ablation of suspected lesions. All of the procedures were done with curative intent. Only five patients (10%) presented with surgical complications, including infection or bleeding. None of these cases were fatal.

The median OS for all patients was 41.8 months (95% CI, 39.25 to 44.36). As depicted in Figure 1, patients who received systemic therapy had a median OS of 44.4 months (95% CI, 39.47 to 44.36) compared with 36.3 months (95% CI, 21.12 to 51.48) for patients who underwent surgery alone ($P = .025$). The 3-year OS rate was 41.7% in patients treated with surgery alone versus 66.7% in those who also received systemic treatment. There were no statistically significant differences among any of the systemic treatment modalities (neoadjuvant, perioperative, or adjuvant; $P = .91$).

During the follow-up period, 36 patients (70.6%) had relapses, and 29 patients (83%) had recurrences confined to the liver. Among these patients, a second metastasectomy followed by fluoropyrimidine-based chemotherapy was

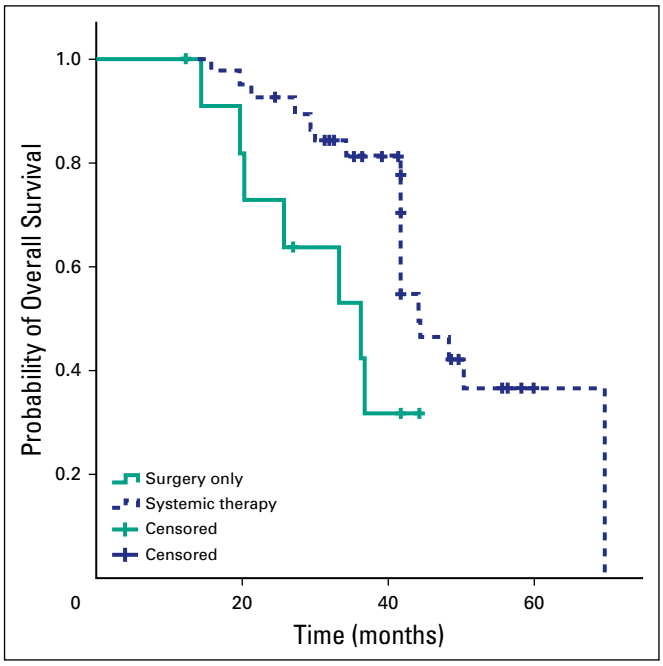

Fig 1 –
Probability of overall survival (Kaplan-Meier method) according to treatment received (hazard ratio, 0.37; 95% CI, 0.15 to 0.91; log-rank test, $P = .025$).

performed in eight cases, and the remaining patients received systemic chemotherapy. Only five patients could not receive further therapy due to a poor performance status score.

Figure 2 shows the probability of DFS according to treatment received. There were no significant differences between surgery-only patients and those who also received systemic therapy ($P = .20$).

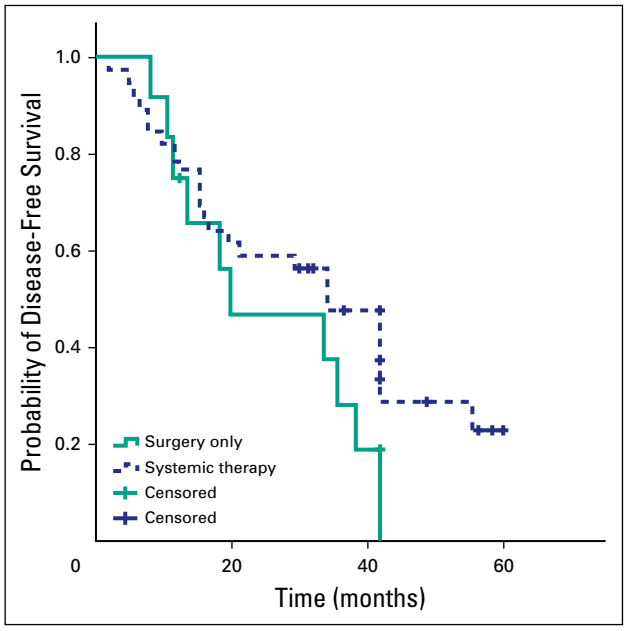

Fig 2 –
Probability of disease-free survival (Kaplan-Meier method) according to treatment received (hazard ratio, 0.62; 95% CI, 0.3 to 1.3; log-rank test, $P = .20$).

DISCUSSION

The survival benefit from complete hepatic resection in patients with limited liver metastases from CRC is well established.[9] Nevertheless, the role of systemic therapy following metastasectomy is currently under debate.[10] Two randomized trials have shown a significant improvement in progression-free survival (as the primary end point) in patients receiving chemotherapy versus observation alone after hepatic resection. Both these trials were prematurely closed because of slow accrual; however, the pooled analysis of these trials showed a nonsignificant trend toward better OS in patients receiving adjuvant therapy.[4,11] On the other hand, the EORTC (European Organization for Research and Treatment of Cancer) 40983 trial did not find any survival benefit after a median follow-up of 8.5 years in patients treated with perioperative FOLFOX4 compared with patients who underwent surgery alone, even when the 3-year progression-free survival increased to an absolute risk of 9.2% in patients who underwent resection.[12]

In our retrospective study, we demonstrate that patients receiving systemic therapy had a better 3-year OS than patients who underwent surgery alone, regardless of the regimen (neoadjuvant, perioperative, or adjuvant). Furthermore, our results are from a real-world setting, showing the clinical efficacy and good outcomes of this treatment modality (ie, the use of systemic therapy and resection of liver metastases).

The discrepancies between our data and those from previous clinical trials could be the result of different regimens used or of different patient populations. For example, among patients in the EORTC 40983 trial, 66% had metachronous disease, whereas the majority of our patients had synchronous metastases. In fact, previous studies have demonstrated that patients with metachronous liver metastases have a poor OS compared with patients diagnosed with synchronous disease.[13] Because the vast minority of our patients with metachronous metastases did not receive systemic treatment, we cannot conclude that there was any real therapeutic benefit of this approach in this particular subgroup. Nevertheless, other authors have also shown the absence of DFS and OS benefit in patients treated with adjuvant FOLFOX after resection of metachronous liver metastases,[13] whereas other authors have shown some efficacy of medical treatment in this subgroup.[14]

In our study, we found that the relapse rate (70.6%) was similar to that reported previously in the literature.[3] It makes it reasonable to administer systemic treatment to these patients to increase DFS and eventually to improve OS. However, we did not find any significant differences among patients

according to treatment received in terms of DFS. This could be attributed to a type II error, because our sample size was small and the study's design was retrospective. Despite these caveats and the low statistical power, we did find a significant difference in OS among patients treated with surgery alone versus those who received any systemic treatment modality before and/or after metastasectomy. These results are in agreement with a recent meta-analysis that showed a 23% improvement in OS among patients treated with liver metastasectomy plus chemotherapy, regardless of the timing of administration.[6]

Our study does have some limitations. The small sample size and the retrospective design of this study could overestimate the magnitude of the reported outcomes.[15] Similarly, selection bias was likely to occur as a result of the nonrandomized selection of the included patients and the retrospective nature of our data.

There are scarce data related to this procedure in Latin American countries. Indeed, the majority of trials have been conducted in developed regions with different ethnic populations. Our results contribute to current evidence supporting the use of systemic therapy as part of the management of patients with resectable liver metastases, although a prospective clinical trial is needed to better clarify this approach.

In summary, our findings support the indication of systemic therapy before and/or after resection of CRC liver metastases because of its significant OS benefit in a real-world population.

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AUTHOR CONTRIBUTIONS

Conception and design: All authors
Administrative support: Paula Quesada-Soto, Allan Ramos-Esquivel
Collection and assembly of data: Paula Quesada-Soto, Denis Landaverde
Data analysis and interpretation: Allan Ramos-Esquivel
Manuscript writing: All authors
Final approval of manuscript: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Paula Quesada-Soto
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Denis Landaverde
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Allan Ramos-Esquivel
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