
Time-to-Surgery and Survival Outcomes in Resectable Colorectal Liver Metastases: A Multi-Institutional Evaluation



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- BACKGROUND:** Resection of colorectal liver metastases (CRLM) is associated with improved survival; however, the impact of time to resection on survival is unknown. The current multi-institutional study sought to evaluate the influence of time from diagnosis (Dx) to resection (Rx) on survival outcomes among patients with resectable, metachronous CRLM and to compare practice patterns across hospitals.
- STUDY DESIGN:** Medical records of patients with ≤ 4 metachronous CRLM treated with surgery were reviewed and analyzed retrospectively. Time from Dx to Rx was analyzed as a continuous variable and also dichotomized into 2 groups (group 1: Dx to Rx < 3 months and group 2: Dx to Rx ≥ 3 months) for additional analysis. Survival time distributions after resection were estimated using the Kaplan-Meier method. Between-group univariate comparisons were based on the log-rank test and multivariable analysis was done using Cox proportional hazards model.
- RESULTS:** From 2000 to 2010, six hundred and twenty-six patients were identified. Type of initial referral ($p < 0.0001$) and use of neoadjuvant ($p = 0.04$) and/or adjuvant ($p < 0.0001$) chemotherapy were significantly different among hospitals. Patients treated with neoadjuvant chemotherapy ($n = 108$) and those with unresectable disease at laparotomy ($n = 5$) were excluded from final evaluation. Median overall survival and recurrence-free survival were 74 months (range 63.8 to 84.2 months) and 29 months (range 23.9 to 34.1 months), respectively. For the entire cohort, longer time from Dx to Rx was independently associated with shorter overall survival (hazard ratio = 1.12; 95% CI, 1.06–1.18; $p < 0.0001$), but not recurrence-free survival. Median overall survival for group 1 was 76 months (range 62.0 to 89.2 months) vs 58 months (range 34.3 to 81.7 months) in group 2 ($p = 0.10$). Among patients with available data pertaining to adjuvant chemotherapy ($N = 457$; 318 treated and 139 untreated), overall survival (87 months [range 71.2 to 102.8 months] vs 48 months [range 25.3 to 70.7 months]; $p < 0.0001$), and recurrence-free survival (33 months [range 25.3 to 40.7 months] vs 22 months [range 14.5 to 29.5 months]; $p = 0.05$) were improved significantly.
- CONCLUSIONS:** In select patients undergoing initial resection for CRLM, longer time from Dx to Rx is independently associated with worse overall survival. In addition, despite uniform disease characteristics, practice patterns related to definitely resectable CRLM vary significantly across hospitals. (J Am Coll Surg 2016;222:766–779. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)
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CME questions for this article available at <http://jacscme.facs.org>

Disclosure Information: Authors have nothing to disclose. Timothy J Eberlein, Editor-in-Chief, has nothing to disclose.

Support: This study was supported in part by NIH/NCI P30 CA008748 (Cancer Center Support Grant).

Received August 17, 2015; Revised January 18, 2016; Accepted January 19, 2016.

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Abbreviations and Acronyms

CRLM	= colorectal cancer liver metastases
CRS	= Clinical Risk Scores
Dx	= diagnosis
HR	= hazard ratio
OS	= overall survival
Rf	= initial referral
RFS	= recurrence-free survival
Rx	= resection

Complete resection of colorectal cancer liver metastases (CRLM) is the only treatment consistently associated with long-term survival and potential cure in up to 16% of patients.¹ Unfortunately, resection is only feasible in 10% to 20% of patients at presentation² and, despite improved overall survival (OS) after hepatectomy, disease recurrence is common.³ As a consequence, the potential use of chemotherapy among patients with clearly resectable CRLM has been of clinical interest. Initial results of the European Organization for Research and Treatment of Cancer prospective randomized trial of surgery with or without perioperative chemotherapy for resectable CRLM suggested a small but significant benefit in progression-free survival at 3 years in the chemotherapy treatment arm,⁴ however, this benefit disappeared with longer follow-up.⁵ Additionally, retrospective series have shown that outcomes in patients with minimal liver-only metastatic disease treated with surgery first are superior to those observed in patients treated with neoadjuvant chemotherapy.^{6,7} These findings suggest that patients with clearly resectable, metachronous, liver-only CRLM do not benefit from chemotherapy before hepatectomy and primary treatment should be directed at definitive oncologic resection.

Determining resectability is challenging and differing notions of resectable disease can give rise to uncertainty as to when, and in whom, surgical referral is appropriate. The number and location of metastases, length of disease-free interval, and presence of extrahepatic disease are the most common clinical factors used to ascertain resectability^{8,9}; however, the relative importance of each is debatable and subject to individual and institutional variability. Given the lack of uniformity in defining resectability and differing attitudes about chemotherapy, significant heterogeneity in referral and treatment of metachronous CRLM amenable to surgical resection exists. Lack of consensus about management in this setting can lead to unnecessary time delays to definitive treatment and potentially impact clinical and oncologic outcomes.

Time delay to definitive treatment has been evaluated for a number of primary cancers, with mixed results.¹⁰⁻¹⁹ However, no study has specifically evaluated the influence

of time to surgery on clinical and oncologic outcomes in patients with resectable CRLM. The primary objective of this multi-institutional study was to evaluate the potential association between time from diagnosis to resection on survival outcomes in patients with resectable, metachronous CRLM and to characterize and compare practice patterns across study centers. To minimize variability related to institutional differences in the treatment of patients with very advanced disease, the current study specifically focused on patients with minimal, liver-only, metastatic disease with the most favorable risk.

METHODS

Study design

Four academic referral hospitals participated in this multi-institutional study. Ethics approval was obtained through institutional review at each site. Patients with metachronous, resectable CRLM diagnosed from 2000 to 2010 were identified from institutional databases and retrospectively reviewed. Colorectal cancer liver metastases were considered metachronous if disease-free interval was longer than 6 months, and resectable if there were ≤ 4 tumors amenable to complete resection in a single-stage operation. Patients were excluded based on the following: presence of extrahepatic disease, use of ablative therapy to achieve R0 resection, recurrent CRLM, concomitant malignancy, and/or use of neoadjuvant chemotherapy.

Data collection

Demographic and clinicopathologic characteristics were obtained from institutional databases and supplemented with information from the medical record where necessary. Date of diagnosis was defined as the first radiographic evidence of CRLM and date of referral as the initial clinic visit addressing CRLM. Clinically relevant time intervals included time from diagnosis (Dx) to initial referral (Rf), Rf to resection (Rx), and Dx to Rx. Clinical Risk Scores (CRS) were calculated as described previously by Fong and colleagues.²⁰ Modified CRS were tabulated for patients with missing data pertaining to 1 or 2 variables ($n = 116$), no score was assigned if >2 variables were missing ($n = 5$). Patients were then stratified into either low-risk (CRS 0–2) or high-risk (CRS 3–5) categories before analysis. Operative reports were reviewed and patients with unresectable disease at laparotomy were excluded from final analysis. Resection margin positivity was defined by the presence of tumor cells at the inked margin. Postoperative complications were graded on a scale from 1 to 5,²¹ with complications graded ≥ 3 considered major.

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