Predictors of Safety and Efficacy of 2-Stage Hepatectomy for Bilateral Colorectal Liver Metastases

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BACKGROUND: In patients with bilateral colorectal liver metastases (CLM) not resectable in 1 operation, 2-stage hepatectomy is the standard surgical approach. The objective of this study was to determine factors associated with safety and efficacy of 2-stage hepatectomy.

STUDY DESIGN: The study included all 109 patients for whom 2-stage hepatectomy for CLM was planned during 2003 to 2014. The *RAS* mutation status and other clinicopathologic factors were evaluated for association with major complications and survival using multivariate analysis.

RESULTS: Two-stage hepatectomy was completed in 89 of 109 patients (82%). Reasons for dropout after the first stage were disease progression (n = 12), insufficient liver growth (n = 5), and complications after first stage or portal vein embolization (n = 3). More than 6 cycles of preoperative chemotherapy were associated with failure to proceed to the second stage (p = 0.009). Rates of major complications (26% vs 6%; p < 0.001) and 90-day mortality (7% vs 0%; p = 0.006) were higher after the second stage. The cumulative rate of major complications was 15% (n = 29). Factors independently associated with major complications were rectal primary tumor, metachronous CLM, and more than 1 lesion resected at first stage. At median follow-up of 29.5 months, 3-year (68% vs 6%; p < 0.001) and 5-year overall survival rates (49% vs 0%; p < 0.001) were better after 2-stage hepatectomy completion than noncompletion. Factors independently associated with poor overall survival were rectal primary tumor (p = 0.044), more than 5 CLMs (p = 0.043), need for chemotherapy after first stage (p = 0.046), and *RAS* mutation (p < 0.001).

CONCLUSIONS: The *RAS* mutation independently predicts the oncologic efficacy of 2-stage hepatectomy and may help guide patient selection for this aggressive surgical strategy. (J Am Coll Surg 2016; 223:99–108. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Advances in chemotherapy and surgical techniques during the past decade have improved the prognosis of patients with colorectal liver metastases (CLM) considerably. Two-stage hepatectomy, first described in 2000,[1] in combination with systemic chemotherapy, has become the standard of care for patients with bilateral CLM that cannot be resected in 1 operation because of insufficient volume of the future liver remnant.[2] The main problems with 2-stage hepatectomy are morbidity rates of 20% to 59%, mortality rates of up to 7%,[2-8] and progression after first-stage resection resulting in noncompletion of second-stage resection in 20% of patients.[9]

During the past decade, mutations in the rat sarcoma viral oncogene homolog (*RAS*) have been found in 15% to 35% of patients with resectable CLM and have been associated with worse survival.[10-12] Clinical parameters

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Abbreviations and Acronyms
CLM = colorectal liver metastases
OS = overall survival
PFS = progression-free survival
PVE = portal vein embolization

initially reported as prognostic factors after CLM resection, including CLM size, number of CLM, and carcinoembryonic antigen level, have limited clinical value in the era of modern chemotherapy.[13] Clinicopathologic score[3] and pathologic response[14,15] have been reported to be major prognostic factors but can only be evaluated postoperatively after examination of the resected surgical specimen. Unlike clinical parameters, *RAS* mutation appears to remain a reliable prognostic factor over time, even after interval chemotherapy,[16] and does not depend on pathologic analysis of the resected surgical specimen. Recently, *RAS* mutation status was reported to be a major biologic prognostic factor after liver resection for CLM.[17] To date, no study has evaluated the effect of *RAS* mutation status on outcome after 2-stage hepatectomy.

Because of the low numbers of patients with bilateral CLM amenable to resection, it has been difficult to determine factors influencing postoperative outcomes and survival after 2-stage hepatectomy. The purpose of our study was to determine factors associated with safety and oncologic efficacy after 2-stage hepatectomy using a large institutional prospective database of patients undergoing resection of bilateral CLM.

METHODS

Patient population

The Institutional Review Board of The University of Texas MD Anderson Cancer Center approved this study protocol (IRB 15-0203). A total of 1,502 patients underwent surgical resection of CLM between November 2003 and September 2014 and had their clinicopathologic factors prospectively recorded in a liver-resection database. Of these patients, 109 were considered for 2-stage hepatectomy. Their computerized medical records were queried for data on clinicopathologic factors, including *RAS* mutation status, treatment variables, perioperative details, pathologic response, recurrence, and survival.

RAS mutation profiling

As previously described,[12] DNA from CLM was used to determine *RAS* mutation status. Routine polymerase chain reaction-based primer extension assay was performed to screen for mutations in *KRAS* codons 12 and 13 in all patients and for mutations in *KRAS* codons 61 and 146 and *NRAS* codons 12, 13, and 61 in the majority of patients treated since 2012. The lower limit of detection of this assay was approximately 1 mutant allele in a background of 9 wild-type alleles. Single mutations in the various codons of *KRAS* and *NRAS* were analyzed together and reported as *RAS* mutations.

Two-stage hepatectomy

Two-stage hepatectomy was considered for patients with advanced bilateral CLM who responded to chemotherapy, when CLM could be completely resected with a future liver remnant volume of 20% to 30% of the total liver volume with adequate inflow and outflow.[18] Portal vein embolization (PVE) was performed before second-stage resection when the future liver remnant volume was deemed insufficient, as previously described.[19] Interval chemotherapy was not used routinely, but was used in patients with progressive disease or insufficient growth of the future liver remnant after first-stage resection. For patients with progressive disease after first-stage resection, response was re-evaluated after 2 months of chemotherapy, and if disease had remained stable or responded, second-stage resection was performed. For patients with insufficient growth of the future liver remnant, repeat PVE including segment IV, or hepatic vein embolization was considered. Liver growth was re-evaluated 4 weeks after repeat embolization, and if the future liver remnant was deemed sufficient at that time, second-stage resection was considered. For patients in whom 2-stage hepatectomy was completed, adjuvant chemotherapy was recommended to complete a total of 12 cycles, including preoperative and postoperative chemotherapy.[20] Regarding management of the primary tumor, a reverse staged approach was preferred, but a combined primary resection could be considered during the first stage. Extrahepatic disease at the time of the first-stage hepatectomy was not considered a contraindication to liver resection if the extrahepatic lesion was deemed resectable and at least stable after systemic chemotherapy.

Morbidity and mortality

Postoperative 90-day morbidity and mortality were prospectively recorded. Morbidity was graded according to the Dindo classification.[21] Postoperative hepatic insufficiency was defined as a peak total bilirubin level greater than 7 mg/dL.[22]