

# Is Cure Possible After Sequential Resection of Hepatic and Pulmonary Metastases From Colorectal Cancer?

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## Abstract

**Retrospective analysis of 150 patients who had undergone sequential surgery for liver and lung metastasis from colorectal cancer identified prognostic factors for survival and cure. Median and 5-year overall survival were 76 months and 60% respectively. Twenty percent of patients were potential cured by this onco-surgical strategy.**

**Background:** Surgical resection is an established therapeutic strategy for colorectal cancer (CRC) metastasis. However, controversies exist when CRC liver and lung metastases (CLLMs) are found concomitantly or when recurrence develops after either liver or lung resection. No predictive score model is available to risk stratify these patients in preparation for surgery, and cure has not yet been reported. **Patients and Methods:** All consecutive patients who had undergone surgery for CLLMs at our institution during a 20-year period were reviewed. Our policy was to propose sequential surgery of both sites with perioperative chemotherapy, if the strategy was potentially curative. Overall survival, disease-free survival, and cure were evaluated. **Results:** Sequential resection was performed in 150 patients with CLLMs. The median number of liver and lung metastases resected was 3 and 1, respectively. The median follow-up period was 59 months (range, 7-274 months). The median, 5-year, and 10-year overall survival was 76 months, 60%, and 35% respectively. CRC that was metastatic at the initial diagnosis ( $P = .012$ ), a prelung resection carcinoembryonic antigen level  $> 100$  ng/mL ( $P = .014$ ), a prelung resection cancer antigen 19-9 level  $> 37$  U/mL ( $P = .034$ ), and an interval between liver and lung resection of  $< 24$  months ( $P = .024$ ) were independent poor prognostic factors for survival. The 5-year survival was significantly different for patients with  $\leq 2$  and  $\geq 3$  risk factors (77.3% vs. 26.5%). Of 75 patients with  $\geq 5$  years of follow-up data available from the first metastasis resection, 15 (20%) with disease-free survival  $\geq 5$  years were considered cured. The use of targeted therapy was the only independent predictor of cure. **Conclusion:** Curative-intent surgery provides good long-term survival and offers a chance of cure in select patients. Patients with  $\leq 2$  risk factors are good candidates for sequential resection.

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## Introduction

One half of the patients undergoing radical resection of colorectal adenocarcinoma (CRC) will develop metastatic disease, with liver and

lung being the most frequent sites of distant metastases.<sup>1,2</sup> Although chemotherapeutic regimens have evolved significantly during the past decade with the addition of biologic therapies, long-term survival and

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## Cure After Hepatic and Pulmonary Metastasis Resection

cure have been achieved only in patients who have undergone resection of all CRC liver metastases.<sup>3-10</sup> With respect to CRC liver and lung metastases (CLLMs), various studies have reported survival after staged resection of both sites comparable to the survival observed after hepatic resection in patients without extrahepatic disease (EHD).<sup>9-12</sup> However, no study has yet clearly established the best method to select patients for surgery, especially when metastases are found concomitantly in both organs or when patients who have undergone either liver or lung resection develop recurrence in the other organ.<sup>5,7,13-15</sup> The potential for cure in these patients is still questioned. We aimed to determine whether disease cure is possible in this cohort of patients who develop CLLMs. The additional objective was to identify the predictive factors for long-term survival and cure.

### Patients and Methods

#### Study Cohort

All consecutive patients who had undergone sequential resection of CLLMs from January 1990 to December 2012 were identified from our prospective database and included in the present study. Patients with metastasis from neuroendocrine or noncolorectal primary tumors were excluded.

#### Preoperative Management

Once the radiologic diagnosis of liver and/or lung metastasis was confirmed in the tumor board by a multidisciplinary team consisting of surgeons, oncologists, and radiologists, our policy was to propose potentially curative resection of all metastatic sites with a combination of chemotherapy (CTx) with or without biologic agents. The response to CTx was evaluated every 2 to 3 months using the Response Evaluation Criteria In Solid Tumors and the following serum tumor markers: carcinoembryonic antigen (CEA; normal, 5 ng/mL) and carbohydrate antigen 19-9 (CA19-9; normal, 37 U/mL).<sup>8</sup> Surgery was considered when the overall strategy could eradicate both hepatic and EHD. Disease progression during CTx was considered a relative contraindication to curative surgery. Staged hepatic and EHD resection was performed, with CTx given during the interval between the 2 surgeries to prevent disease progression.

#### Hepatic Resection

The objective of hepatectomy was to resect all detectable lesions with tumor-free margins. When downsizing by CTx would not be sufficient to allow for curative resection owing to contact with a major vessel or bile duct, 3 specific techniques were practiced to increase resectability. Portal vein embolization was performed when the estimated remnant liver volume was < 30%.<sup>16</sup> For bilateral metastases, hemihepatectomy was combined with the radiofrequency ablation if a few contralateral, unresectable, deeply located lesions  $\leq$  3 cm in diameter were present. When multinodular bilobar metastases could neither be completely resected by a single procedure nor treated with hepatectomy combined with radiofrequency ablation, 2-stage hepatectomy was considered.<sup>17</sup> A liver-first strategy was used in certain cases of synchronous presentation when the CRC was not complicated, and the hepatic tumor burden was significant.<sup>18</sup>

#### Pulmonary Resection

Wedge resection, lobectomy, or pneumonectomy of all metastases with tumor-free margins was the objective of surgery.

Pulmonary resection was performed within 2 to 3 months of hepatectomy.<sup>8</sup> In the case of bilateral metastases, staged resection was usually performed. Intrathoracic lymph nodes were resected simultaneously when present.

#### Other Extrahepatic/Pulmonary Resection

The presence of limited synchronous other EHD was not a contraindication for either liver or lung resection when the strategy would be curative. If intra-abdominal EHD (nonregional lymph nodes, localized peritoneal carcinomatosis) was present at the initial liver resection, it was resected simultaneously. Extra-abdominal EHD was resected after liver and lung resection. When other EHD was detected metachronously, resection was performed to achieve cure.

#### Postoperative Management

Postoperative follow-up examinations were performed at 1 month and then every 4 to 6 months with physical examination, serum tumor marker determination, and imaging studies. Our policy was to offer CTx postoperatively for 6 to 8 cycles to decrease the risk of recurrence. In the case of local or distant recurrence, resection was performed if it could be curative.<sup>19</sup>

#### Definitions

Synchronous metastasis was that diagnosed before or within 3 months after resection of the primary colorectal tumor.<sup>20</sup> When the liver and lung metastases were diagnosed within 3 months of each other, they were considered simultaneous liver and lung metastases.<sup>9</sup> Overall survival (OS) was defined as the interval from the first resection of metastasis, either liver or lung, to the last follow-up visit. The disease-free interval from the last metastatic resection, liver, lung, and/or other EHD, to the last follow-up visit was defined as the disease-free survival (DFS). Patients with  $\geq$  5 years of DFS were considered potentially cured among the patients with  $\geq$  5 years of follow-up data available from the initial metastasis resection.<sup>4,21</sup>

#### Statistical Analysis

Continuous variables are expressed as the median and range, and discrete variables are presented as counts and percentages. Survival analysis was performed using the Kaplan-Meier method, and survival curves were compared using the log-rank test. The Cox proportional hazard model was used to define the predictors of survival. Bootstrapped multivariate binary logistic regression analysis was performed to determine the predictors of cure.  $P < .05$  was considered significant. SPSS software, version 20.0 (IBM Corp, Armonk, NY), was used for all statistical calculations.

### Results

From January 1990 to December 2012, 1490 patients had undergone liver resection for CRC liver metastasis, and 156 of these patients had undergone sequential resection of CLLMs. Six patients whose data could not be retrieved were excluded from further analysis. The study cohort consisted of 150 patients (89 men, 61 women) with a median age of 56 years (range, 29-77 years). The patient demographics and tumor and treatment characteristics are summarized in Table 1.

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