Efficacy of Surgery for Lung Metastases from Colorectal Cancer Synchronous to or Following that for Liver Metastases

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Abstract. Aim: To evaluate the validity of surgical therapy for isolated hepatic and pulmonary colorectal metastases. Patients and Methods: Among 256 patients with liver resection for colorectal cancer metastases, 31 patients underwent resection for lung metastases synchronously or following liver resection. Results: Twenty-nine patients (93.5%) underwent pulmonary resection for lung metastases after hepatectomy. Two patients (6.5%) with synchronously identified liver and lung metastases underwent staged liver and lung resection. The 5- and 10-year overall survival rates were 77.5% and 39.5% after the initial liver resection and were 44.7% and 38.2% after the pulmonary resection, respectively. By multivariate analysis, the presence of three or more pulmonary metastases (risk ratio=3.692, 95% confidence interval C I=1.039-13.118, p=0.043) was an independent adverse prognostic factor. Conclusion: Surgical resection for both hepatic and pulmonary metastases from colorectal cancer appears feasible and efficacious in patients with <3 pulmonary metastases.

The liver and lung are the most frequent sites of metastases originating from colorectal cancer (1). Liver resection for hepatic metastases from colorectal cancer is now accepted as the most effective therapy and is associated with low morbidity and acceptable rates of long-term survival (2-5). Pulmonary metastasectomy has also proven to be a safe procedure, with a 5-year survival rate of 37-56% (6-8).

However, the role of surgery in the management of patients who have both liver and lung metastases (detected either simultaneously or metachronously) has not been thoroughly investigated; only six such studies have each evaluated more than 30 patients (9-14).

The aim of this study was to determine the indication criteria for surgical resection in patients with both hepatic and pulmonary metastases from colorectal cancer.

Patients and Methods

Patients. Data were collected from the medical records of 256 patients who underwent hepatic resection for liver metastases originating from colorectal cancer between 1992 and 2006 at University-affiliated hospitals (Graduate School of Medicine, Yokohama City University, Yokohama City University Medical Center) were collected. Among these, patients who underwent both lung and liver resections for metastatic colorectal cancer were included in this study. Demographic, perioperative, survival data and variables were evaluated by retrospective chart review. To evaluate extrahepatic disease in patients with liver metastases from colorectal cancer, chest, abdominal, and pelvic computed tomography (CT) scans are mandatory at the study’s hospitals. Bone scans are rarely helpful, so are not performed routinely. Imaging by positron-emission tomography was introduced for preoperative staging after April 2002.

Operative procedure for hepatic resection. Patients with liver metastases from colorectal carcinoma were treated according to the following protocol (15, 16). First, hepatic resection was attempted regardless of the number or distribution of liver metastases, provided that the procedure was potentially curative and that the patient was able to tolerate it. Second, the presence of extrahepatic metastases, other than resectable lung metastases, was usually considered to be a contraindication for surgery, and the decision to operate was made on a case-by-case basis. Hepatectomy might or might not have conformed to the principles of anatomical resection; performing a heptectomy that ensured tumor-free margins was the guiding principle. In patients for whom there was concern that the amount of residual liver might be insufficient to maintain hepatic function, either preoperative portal vein embolization (17, 18), or a two-stage hepatectomy (19) was performed. Intraoperative techniques for heptectomy were performed as described previously (15, 16, 20, 21). The terminology used for liver anatomy and resections followed the Brisbane 2000 Terminology of the International Hepato-Pancreato-Biliary Association (22).
Operative procedure for pulmonary resection. The criteria for pulmonary resection were as follows: (i) metastatic thoracic lesions confined to the lung and technically resectable, (ii) no extrathoracic metastasis except resectable hepatic metastasis, and (iii) sufficient cardiorespiratory function to allow complete resection of all pulmonary tumors. The timing of the detection of hepatic and pulmonary metastases, and the number of prior resections for metastases did not influence whether a patient met these criteria, so the selection criteria for further resections necessitated by recurrences after hepatic and pulmonary resections were the same as the above. During pulmonary resection, hilar or mediastinal lymph node dissection was used to obtain samples from the lymph nodes of most patients who had a lobectomy.

Adjuvant therapy. After resection for liver metastases or extrahepatic metastases, adjuvant chemotherapy was carried out via hepatic artery infusion or intravenous infusion, generally with 5-fluorouracil (5-FU) and folinic acid (FA), with or without addition of cisplatin (CDDP), or irinotecan. In patients who received prehepatectomy chemotherapy, the preoperative chemotherapy was continued postoperatively as adjuvant therapy.

Patient follow-up. Patients were followed up monthly at our outpatient clinic. Data were obtained and recorded, and long-term outcomes were determined through clinical follow-up, cancer registry follow-up, and contact with the patient, family, or referring physician when necessary. No patients were lost to follow-up. Serum carcinoembryonic antigen (CEA) levels were measured monthly, CT was performed every 3 months, and a chest x-ray was obtained every 6 months. The median follow-up time was 62.2 months.

Statistics. Continuous variables were expressed as the median with range and were compared using the Mann-Whitney U-test. Categorical variables were compared using the Fisher exact test if appropriate. Survival rates were calculated and evaluated using the Kaplan-Meier method, and the statistical analysis of differences in survival curves was carried out using the log-rank test. Multivariable regression analysis was carried out by a proportional-hazard method using a Cox model, beginning with factors identified in univariate analysis by a p-value below 0.1. All statistical analyses were
performed using SPSS version 10.0 for data analysis software for Windows® (SPSS, Inc., Chicago, IL, USA). Probability (p) values <0.05 were considered to be statistically significant.

Results

The study included 31 patients who underwent lung resections synchronous to or following liver resection for metastatic colorectal cancer. Two out of the 31 patients (6.5%) underwent staged resection for liver and lung metastases identified synchronously. The other 29 patients (93.5%) underwent sequential pulmonary resection after hepatectomy because of lung metastasis following liver metastasis. Patient demographics and features of the primary tumor are shown in Table I. The tumor originated in the colon in 18 (58.1%) patients and the rectum in 13 (41.9%) patients. Regional lymph node metastases from the primary tumor were identified in 18 (58.1%) patients.

Features of the first liver resection. The characteristics of the patients’ first liver resection are listed in Table II. In 16 (51.6%) cases, resection of the liver metastases was performed simultaneously with resection of the colonic primary tumor. The median number of liver tumors was 2 (range 1 to 20 tumors) and 14 patients had bilobular disease. The median size of the largest tumor was 2.7 cm (range 0.5 to 8 cm). In 11 (35.5%) patients, a hemihepatectomy or more extensive resection was required to remove all gross disease. No patients died within 30 days after surgery. Twenty (64.5%) patients received adjuvant chemotherapy after liver resection. Seven (22.6%) patients underwent a second hepatectomy for subsequent recurrence within the liver.

Features of the first pulmonary resection. The characteristics of the patients’ first lung resection are listed in Table III. In only 1 (3.2%) case was resection of lung metastasis performed simultaneously with resection of the recurrent liver tumor. The median number of metastatic nodules was 2 (range 1 to 10) and 13 (41.9%) patients had metastatic disease in both lungs. The median size of the largest tumor was 1.5 cm (range 0.4 to 6.0 cm). A large majority of patients (83.9%) had a wedge resection; lobectomy was required in only 5 (16.1%) patients. Six (19.4%) patients underwent repeat pulmonary resection for subsequent recurrence in the lung.

Survival. The 5-, and 10-year overall survival rates after primary tumor resection and after liver resection were 81.9% and 41.9% and 77.5% and 39.5%, respectively. Median survival time from the first resection of liver metastasis was 86.5 months.

From the time of first resection of pulmonary metastasis, the 5-, and 10-year overall survival rates were 44.7% and 38.2%, respectively. Median survival time from resection of the first pulmonary metastasis was 55.2 months.

Prognostic factors. The analysis of potential clinicopathologic prognostic factors for overall survival from the time of resection of the lung metastasis is shown in Table IV. Multivariate analysis found the presence of 3 or more pulmonary metastases to be an independent unfavourable prognostic factor for long-term survival (risk ratio=3.692, 95% confidence interval [CI]=1.039-13.118, p=0.043). In contrast, neither the characteristics of the primary tumor (site, lymph node status, venous invasion, time to diagnosis of liver metastasis) nor the characteristics of the liver metastases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>MST (months)</td>
</tr>
<tr>
<td>No. of liver metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>19</td>
<td>115.1</td>
</tr>
<tr>
<td>≥3</td>
<td>12</td>
<td>39.0</td>
</tr>
<tr>
<td>Tumor distribution of the liver metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilobular</td>
<td>17</td>
<td>115.0</td>
</tr>
<tr>
<td>Bilobular</td>
<td>14</td>
<td>64.7</td>
</tr>
<tr>
<td>No. of lung metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>20</td>
<td>109.7</td>
</tr>
<tr>
<td>≥3</td>
<td>11</td>
<td>43.4</td>
</tr>
<tr>
<td>Pre thoracotomy CEA level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 ng/ml</td>
<td>21</td>
<td>109.1</td>
</tr>
<tr>
<td>≥5 ng/ml</td>
<td>9</td>
<td>39.4</td>
</tr>
</tbody>
</table>

MST, Median survival time.
(number, size and distribution) appeared to affect survival. Whether the lung metastasis was synchronous or metachronous with the liver metastasis did not predict outcomes. With respect to the characteristics of the lung metastases, the tumor size, laterality and serum CEA level before lung resection were not associated with shorter survival.

However, the overall cumulative survival results after lung resection in patients with three or more pulmonary metastases (5- and 10-year survival rates 16.6%, median survival 23.4 months) were significantly worse than in patients with fewer than three pulmonary metastases (60.2% at 5 years, 45.1% at 10 years; median, 97.1 months; \( p=0.0071 \)) (Figure 1A). The overall cumulative survival results after initial liver resection in patients with three or more pulmonary metastases (53.3% at 5 years, 17.8% at 10 years; median, 61.0 months) were worse than in patients with fewer than three pulmonary metastases (88.8% at 5 years, 47.6% at 10 years; median, 106.3 months; \( p=0.0180 \)) (Figure 1B).

### Discussion

Colorectal cancer is one of the leading causes of cancer death and most deaths occur in patients with metastases from the primary tumor. Without treatment, the median survival following diagnosis of metastatic colorectal cancer is 6-9 months (23). With chemotherapy, the median survival is at best 16-20 months, even with up-to-date combination regimens (23, 24). Isolated liver resection of hepatic metastases from colorectal cancer is now accepted as being the most effective therapy and is associated with low morbidity and improved long-term survival (2-5), and isolated pulmonary metastasectomy has also proven to be a safe procedure, with a 5-year survival rate of 37-39% (6, 7). However, the role of surgery in the management of patients who have both liver and lung metastases (identified either simultaneously or metachronously) is not well defined. Some surgical centers have taken an aggressive approach to the management of a highly select group of patients with stage IV colorectal cancer, with encouraging survival results. Indeed, Elias and colleagues (25) reported that prolonged survival can be achieved with surgery for metastatic colorectal cancer involving multiple sites. In the literature, there are currently only six articles reporting the outcome of resection of both liver and lung metastases in more than 30 patients (9-12, 14), including only one report of a study with more than 100 patients (13) (Table V).

In the present study, we found better 5-year survival rates in patients who underwent both hepatic and pulmonary resection for colorectal metastases, with 81.9%, 77.5%, and 47.7% surviving 5 years after the time of resection of the primary tumor, liver metastases, and lung metastases, respectively. Reported 5-year survival rates after liver resection of previous series showed large variations ranging between 11% and 74% (8-13). Shah and colleagues (12) reported a 5-year survival rate of 74%, quite similar to our results. The reason for the favourable outcome may be that this cohort represents highly select patients with relatively favorable biology. In particular, patients who redevelop resectable lung metastases after liver resection represent a favourable subgroup compared with entire population of patients who undergo hepatectomy.

It is critical to clearly define prognostic factors in patients with both liver and lung metastases to aid in patient selection for surgery. In the largest case series from the Memorial Sloan Kettering Cancer Center (New York, NY, USA), Miller et al. (13) demonstrated that a longer disease-free interval after liver resection, the presence of only one liver metastasis, and younger age were associated with a better outcome. Other factors, such as the number of metastases, premetastasectomy CEA levels, thoracic lymph node involvement before pulmonary metastasectomy, and the lung as the first metastatic site, have also been identified as significant predictors of outcome (9-12, 14). In our evaluations, we found that the presence of three or more pulmonary metastases was an independent unfavorable

### Table V. Survival and prognostic factors of selected published series after resection of hepatic and pulmonary colorectal metastases.

<table>
<thead>
<tr>
<th>Authors (reference)</th>
<th>Year</th>
<th>Number of patients</th>
<th>5-Year survival after 1st liver resection</th>
<th>Prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regnard et al. (9)</td>
<td>1998</td>
<td>43</td>
<td>11%(a)</td>
<td>Pre-thoracotomy CEA, the number of lung resections and interval between hepatic and pulmonary resections</td>
</tr>
<tr>
<td>Kobayashi et al. (10)</td>
<td>1999</td>
<td>47</td>
<td>50%</td>
<td>Solitary pulmonary metastasis</td>
</tr>
<tr>
<td>Headrick et al. (11)</td>
<td>2001</td>
<td>58</td>
<td>30%(b)</td>
<td>Thoracic lymph node involvement and elevated CEA before pulmonary metastasectomy</td>
</tr>
<tr>
<td>Shah et al. (12)</td>
<td>2006</td>
<td>39</td>
<td>74%</td>
<td>Disease-free interval between metastases, the number of liver metastases, patient’s age</td>
</tr>
<tr>
<td>Miller et al. (13)</td>
<td>2007</td>
<td>131</td>
<td>49%</td>
<td>Lung as the site of first metastasis</td>
</tr>
<tr>
<td>Neeff et al. (14)</td>
<td>2009</td>
<td>44</td>
<td>42%</td>
<td>Three or more lung metastases</td>
</tr>
<tr>
<td>This study</td>
<td>2010</td>
<td>31</td>
<td>78%</td>
<td></td>
</tr>
</tbody>
</table>

\(a\)After first lung resection (=second metastasectomy); \(b\)after first lung resection
prognostic factor that reduced long-term survival (risk ratio=3.692, 95% CI=1.039-13.12, \( p=0.043 \)). The reason for a poor prognosis in patients with three or more pulmonary metastases might be the low rate of repeat pulmonary metastasectomy. The recurrence rate after lung resection in such patients was very high at 9/11, and the rate of repeat lung resection in those patients was only 1/9. On the other hand, in patients with fewer than three lung metastases, the recurrence rate after lung resection was 13/20 and the rate of repeat pulmonary resection was 5/13. Unfortunately, these data were not statistically significant because of the small size of our study population (\( p=0.157 \)). However, in this study, with respect to the long-term outcome after initial hepatectomy for colorectal cancer liver metastases, we found a comparable 5-year survival rate (53.3%) in patients who had three or more pulmonary metastases with multiple centers reporting 5-year survival rates after hepatectomy for colorectal liver metastases of 25% to 58% (3, 5, 26-28). Therefore, these data suggest that aggressive surgical resection might result in long-term survival even those who had three or more lung metastases after hepatic metastasectomy. Further evaluation in a large number of patients will be necessary to confirm this finding.

The median survival time in patients with untreated metastatic colorectal cancer is only 6 months (29). First-line 5-FU-based chemotherapy has been shown to prolong median survival to approximately 12 months (30). More recently, molecular-targeted agents such as bevacizumab, a humanized antibody directed against vascular endothelial growth factor, and cetuximab, a monoclonal antibody directed against the human epidermal growth factor receptor, have been shown to extend survival (31-32). The platinum compound oxaliplatin has been approved for use only since April 2005 by the Japanese health insurance system, therefore CDDP in combination with 5-FU and FA was sometimes given as a neoadjuvant regimen in the present case series. Given the implications of recent advances in chemotherapy and the emergence of surgical adjuncts such as portal vein embolization and ablative therapies, for colorectal cancer metastases, aggressive surgical resection may be performed in patients with stage IV colorectal cancer, which was previously thought to be unresectable (33).

In conclusion, surgical resection of both hepatic and pulmonary metastases from colorectal cancer is associated with prolonged survival in select patients. Further studies should be performed to define the exact role of combined metastasectomy in the context of modern chemotherapeutic modalities.

References


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