

Outcomes After Hepatic and Pulmonary Metastasectomies Compared With Pulmonary Metastasectomy Alone in Patients With Colorectal Cancer Metastasis to Liver and Lungs

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Abstract

Background Surgical resection is the most effective treatment for colorectal cancer that has metastasized to the liver. Similarly, surgical resection improves survival for selected patients with pulmonary colorectal metastases. However, the indication for pulmonary metastasectomy is not clear in patients with both hepatic and pulmonary colorectal metastases. Therefore, we evaluated outcomes after pulmonary resection of colorectal metastases in patients with or without a history of curative hepatic metastasectomy.

Methods We retrospectively analyzed 96 patients who underwent pulmonary metastasectomy from March 1999 to November 2009. Patients were grouped according to treatment: resection of pulmonary metastases alone (lung metastasectomy group) or resection of both hepatic and pulmonary metastases (liver and lung metastasectomy group). Overall survival (OS) and disease-free survival (DFS) were evaluated by Kaplan–Meier analysis. Survival curves were compared using the log-rank test.

Results The 5-year OS for all patients was 61.3 %, and the 5-year DFS was 26.7 %. Group comparisons showed that the 5-year OS of the lung metastasectomy group was significantly better than that of the liver and lung metastasectomy group (69 vs. 43 %; $p = 0.030$). However, the 5-year DFS rates of the lung metastasectomy group (25.8 %) and liver and lung metastasectomy group (28.0 %) did not differ

significantly. Recurrence was higher after resection of both hepatic and pulmonary metastases than after pulmonary metastases alone (79 vs. 45 %; $p = 0.025$).

Conclusions Resection of pulmonary colorectal metastases may increase survival. However, the combination of liver and lung metastasectomies had a worse prognosis than pulmonary metastasectomy alone. In selected patients, combined liver and lung metastasectomy can be beneficial and result in acceptable DFS.

Introduction

The most frequent sites of distant metastases from colorectal cancer are the liver and lung [1]. After curative resection for colorectal cancer, hepatic metastases are detected in 8–30 % of patients [2, 3] and pulmonary metastases in 10–20 % [4, 5].

Surgical resection is the most effective treatment for colorectal cancer that has metastasized to the liver. This treatment is widely accepted and has produced 5-year survival rates of 25–58 % [6–10]. Lung metastases were previously thought to be incurable and were treated primarily with systemic chemotherapy. However, recent studies have shown that resection of pulmonary metastases from colorectal cancer is beneficial for selected patients, reporting 5-year survival rates of 30–48 % [11–17]. Also, some reports have suggested that resection of both hepatic and pulmonary colorectal metastases can increase survival after colorectal cancer has metastasized to both liver and lungs [18, 19]. In these patients, the outcome of pulmonary metastasectomy after previous hepatic resection is unclear. For example, Ike et al. [20] reported that survival rates did not differ between patients who underwent sequential hepatic and pulmonary resections compared with those who underwent pulmonary

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resection alone. In the present study, we evaluated outcomes after pulmonary resection of colorectal metastases in patients with or without a history of curative hepatic metastasectomy.

Materials and methods

Between March 1999 and November 2009, a total of 96 patients underwent pulmonary resection for metastatic colorectal cancer at the Aichi Cancer Center. These patients were divided into two groups based on treatment: resection of pulmonary metastases alone (lung metastasectomy group) or resection of both hepatic and pulmonary metastases (liver and lung metastasectomy group). Demographic, perioperative, and survival data were evaluated by retrospective review.

The selection criteria for resection of hepatic metastases were (1) control of the primary colorectal cancer; (2) no extrahepatic metastases except resectable pulmonary metastases; (3) completely resectable liver lesions diagnosed by preoperative imaging; (4) liver function that was sufficient for resection of all liver lesions. Liver resection procedures (partial resection, segmentectomy, lobectomy) were selected with curative intent regardless of tumor size, number, or location. The selection criteria for resection of pulmonary metastases were (1) control of the primary colorectal cancer; (2) no extrathoracic metastases; (3) completely resectable lung lesions diagnosed by preoperative imaging; (4) respiratory function that was adequate for resection of all lung lesions. Lung resection procedures included partial resection for lesions in the peripheral lung or tumors ≤ 3.0 cm in diameter and lobectomy performed for multiple tumors in the same lobe or tumors > 3.0 cm in diameter. In all, 207 patients did not fulfill the selection criteria for resection: recurrence at the primary site ($n = 11$), extrahepatic or extrathoracic metastases ($n = 85$), unresectable liver lesions ($n = 81$), unresectable lung lesions ($n = 30$). When metastasis to the liver and/or lung was detected at the time of diagnosis of colorectal cancer, we resected the primary tumor first and, in the absence of disease progression, performed the metastasectomy 3 months later [21]. When patients presented with simultaneous liver and lung metastases, we resected the hepatic lesion(s) first to rule out extrahepatic abdominal lesions. Pulmonary resection was performed about 4 weeks later.

Patient characteristics are shown in Table 1. The primary tumor originated in the rectum in 39 patients (58 %) of the lung metastasectomy group and in 16 patients (55 %) of the liver and lung metastasectomy group. Regional lymph node metastases from the primary tumor were identified in 43 patients (64 %) of the lung

Table 1 Patient characteristics

| Characteristic | Lung metastasectomy ($n = 69$) | Liver and lung metastasectomy ($n = 29$) | p |
|---|-------------------------------------|---|------|
| Median age at pulmonary resection (years) | 63 (36–84) | 60 (46–75) | |
| Sex (M:F) | 27:40 | 17:12 | 0.12 |
| Location of primary tumor | | | |
| Colon | 28 | 13 | 0.82 |
| Rectum | 39 | 16 | |
| Lymph node metastasis of primary tumor | | | |
| Present | 43 | 19 | 0.97 |
| Absent | 20 | 9 | |
| Disease-free interval (months) | 20 | 17 | 0.35 |
| No. of pulmonary metastases | | | |
| Solitary | 37 | 20 | 0.26 |
| Multiple | 30 | 9 | |
| Location of pulmonary metastasis | | | |
| Unilateral | 52 | 26 | 0.25 |
| Bilateral | 15 | 3 | |
| Maximum size of pulmonary metastasis (cm) | | | |
| > 3 | 13 | 8 | 0.19 |
| ≤ 3 | 54 | 21 | |
| Prethoracotomy CEA level (ng/ml) | | | |
| ≥ 5 | 21 | 8 | 0.81 |
| < 5 | 44 | 20 | |

CEA carcinoembryonic antigen

metastasectomy group and 19 patients (66 %) of the liver and lung metastasectomy group. The disease-free interval (DFI) was calculated as the interval between the day of primary tumor resection and the day of pulmonary metastasectomy. The median DFI was 20 months in the lung metastasectomy group and 17 months in the liver and lung metastasectomy group. Most cases of lung metastasis exhibited solitary, unilateral tumors < 3 cm and a prethoracotomy carcinoembryonic antigen (CEA) value < 5 ng/ml; these results did not differ significantly between the two patient groups.

The primary endpoint for this study was overall survival (OS), defined as the interval from the date of pulmonary resection to the date of last follow-up or death. The secondary endpoint was disease-free survival (DFS), defined as the interval from the date of pulmonary resection to the date of disease recurrence. OS and DFS were evaluated by Kaplan–Meier analysis, and survival curves were compared using the log-rank test. Multivariate analysis was performed using the Cox proportional hazard regression model to identify independent survival factors. Statistical significance was set at $p < 0.05$.

Results

Surgical resection procedures and complications

The pulmonary resection procedure was partial resection for 45 patients (67 %) of the lung metastasectomy group and 18 patients (62 %) of the liver and lung metastasectomy group. Regarding liver resection procedures, 9 patients (31 %) underwent partial resection and 13 (45 %) underwent lobectomy (Table 2).

Five patients experienced minor postoperative complications. One patient in each group had a pulmonary infection. The complications after liver resection were abdominal abscess ($n = 2$) and bile leakage ($n = 2$). No patients required laparotomy for complications, and no deaths occurred during surgery or during the postoperative period (Table 2).

Adjuvant chemotherapy after pulmonary resection

In all, 21 patients (31 %) of the lung metastasectomy group and 8 patients (28 %) of the liver and lung metastasectomy group received postoperative chemotherapy following the pulmonary resection. Among the patients who received adjuvant chemotherapy, 15 in the lung metastasectomy group (15/21, 71 %) received oral chemotherapy such as UFT and TS-1. Four patients of the liver and lung metastasectomy (4/8, 50 %) group received oxaliplatin-based chemotherapy.

Overall survival and disease-free survival

The median follow-up after pulmonary resection was 50.8 months. For all patients, the 5-year survival rate was

61.3 %. Group comparison revealed a significantly better 5-year survival rate in the lung metastasectomy group than in the liver and lung metastasectomy group (69 vs. 43 %; $p = 0.030$) (Fig. 1). The 5-year DFS rate was 26.7 % for all patients and did not differ significantly between groups (lung metastasectomy 25.8 %; liver and lung metastasectomy 28.0 %; $p = 0.616$) (Fig. 2).

Recurrence after pulmonary metastasectomy

Recurrence after pulmonary metastasectomy is shown in Table 3. In all, 43 patients (64.2 %) in the lung metastasectomy group experienced tumor recurrence: liver only ($n = 2$), lung only ($n = 22$), liver + lung ($n = 1$), liver + lymph node ($n = 2$), lung + lymph node ($n = 10$), lung + brain or bone ($n = 3$), other organs ($n = 3$). Altogether, 19 patients (65.5 %) in the liver and lung metastasectomy group experienced tumor recurrence: liver only ($n = 3$), lung only ($n = 1$), liver plus lung ($n = 2$), lung plus lymph node ($n = 4$), liver plus brain or bone ($n = 3$), lung plus brain or bone ($n = 3$), other organs ($n = 3$). Most patients in the lung metastasectomy group who experienced recurrence (24/43, 55 %) had only one metastatic organ (e.g., remnant lung). In contrast, most patients in the liver and lung metastasectomy group who experienced recurrence (15/19, 79 %) had two or more metastatic organs (e.g., remnant lung, liver, brain, bone, lymph node) ($p = 0.025$).

Repeat pulmonary resection

Among patients with remnant lung recurrence, 18 (50 %) in the lung metastasectomy group and 2 (20 %) in the liver and lung metastasectomy group underwent repeat resection. Postoperative morbidity occurred in 10 %. The complications were wound infection ($n = 1$) and

Table 2 Types of surgical resection and complications

| Parameter | Lung metastasectomy ($n = 67$) | Liver and lung metastasectomy ($n = 29$) |
|----------------------------|----------------------------------|--|
| Pulmonary resection | | |
| Partial resection | 45 | 18 |
| Segmentectomy | 8 | 2 |
| Lobectomy | 14 | 9 |
| Hepatic resection | | |
| Partial resection | | 9 |
| Segmentectomy | | 7 |
| Lobectomy | | 13 |
| Complications | | |
| Pulmonary infection | 1 | 1 |
| Abdominal abscess | | 2 |
| Bile leakage | | 2 |

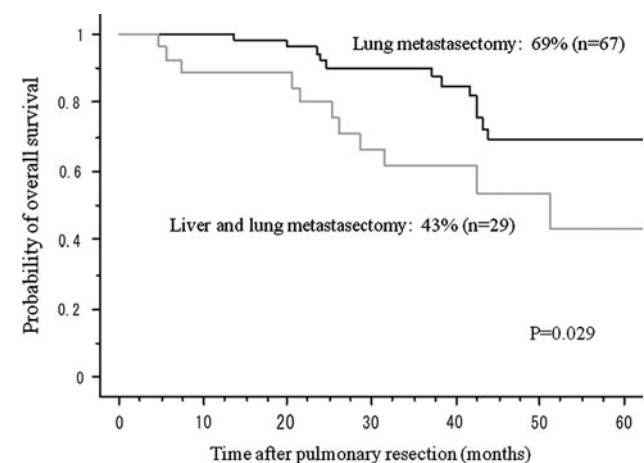


Fig. 1 Overall survival for the two patient groups

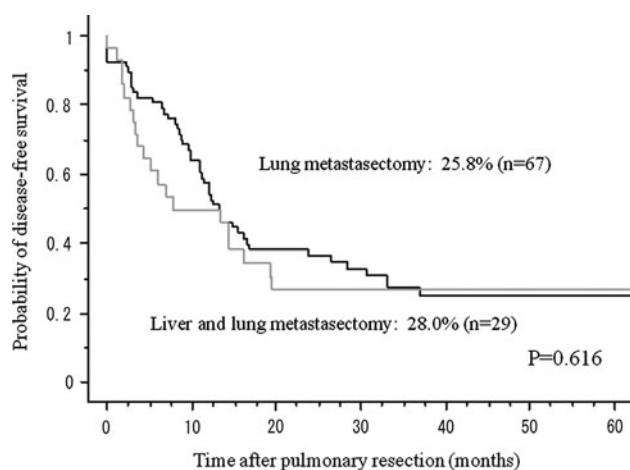


Fig. 2 Disease-free survival for the two patient groups

Table 3 Outcome of recurrence after pulmonary metastasectomy

| Recurrence parameters | Lung metastasectomy (n = 67) | Liver and lung metastasectomy (n = 29) | p |
|-----------------------|------------------------------|--|-------|
| Recurrence rate | 43 (64.2 %) | 19 (65.5 %) | |
| Recurrence pattern | | | |
| Liver only | 2 | 3 | |
| Lung only | 22 | 1 | |
| Liver + lung | 1 | 2 | |
| Liver + lymph node | 2 | – | |
| Lung + lymph node | 10 | 4 | |
| Liver + brain or bone | – | 3 | |
| Lung + brain or bone | 3 | 3 | |
| Other | 3 | 3 | |
| Metastatic sites | | | 0.025 |
| One organ | 24 | 4 | |
| Two or more organs | 19 | 15 | |

pulmonary infection ($n = 1$). No postoperative mortality was observed. Of the 20 patients who underwent repeat pulmonary resection, overall and disease-free 5-year survivals were 69.0 and 35.5 %, respectively, after the second metastasectomy.

Prognostic factors

Table 4 shows the results of univariate analysis of prognostic factors and survival after pulmonary resection. Factors associated with prognosis were regional lymph node metastases from the primary tumor ($p = 0.015$), previous liver resection ($p = 0.035$), DFI ($p = 0.030$), and prethoracotomy serum CEA level ($p = 0.018$). Multivariate analysis revealed that regional lymph node metastases from the primary tumor ($p = 0.016$), previous liver

resection ($p = 0.008$), and DFI ($p = 0.017$) were independent predictors of survival (Table 5).

Discussion

The liver and lung are common sites of colorectal cancer metastasis. Although chemotherapy has significantly improved overall survival [22], chemotherapy alone cannot cure metastatic colorectal cancer. Surgical resection of metastatic colorectal cancer is the only curative treatment [23]. Surgical resection of hepatic colorectal metastases has been shown to be safe, with reported mortality rates of 0–5 % and morbidity rates of 11–42 % [24–26]. Resection of pulmonary colorectal metastases provides similar outcomes, with mortality rates of 0–4 % and a morbidity rate of 12.2 % [11, 27, 28]. In the present study, the perioperative mortality rate was 0 %, and morbidity rates after liver and lung resection were 14 and 2 %, respectively. These results were acceptable. All four complications were minor, and none required reoperation.

Reported rates of overall survival after liver and lung metastasectomy are shown in Table 6. The 5-year survival rates after both liver and lung metastasectomy have previously been reported as ranging from 11 to 50 % [12, 15, 20, 28–35]. Comparisons of patient outcomes after lung metastasectomy alone with outcomes after both liver and lung metastasectomies showed that 5-year survival rates did not differ significantly [12, 15, 20, 29–32]. In the present study, the 5-year survival of all patients after pulmonary resection was 61.3 %, which was higher than that reported by many previous studies [11–17]. We found that the 5-year survival rate in the lung metastasectomy group was significantly better than that of the liver and lung metastasectomy group (69 vs. 43 %; $p = 0.030$). Multivariate analysis identified three independent prognostic factors for survival after lung metastasectomy: regional lymph node metastases from the primary tumor, DFI, previous liver metastasectomy. Previous studies reported the following independent prognostic factors after lung metastasectomy: number of pulmonary metastases [11, 13], hilar or mediastinal lymph node metastasis [12, 13, 28], time when pulmonary metastases were detected [29], prethoracotomy CEA level [36, 37], distribution of pulmonary metastases [12], liver metastasectomy before thoracotomy [28]. The better prognosis in our study may be because many of the lung tumors were solitary, unilateral, and <3 cm. We also excluded patients for whom hilar or mediastinal lymph node enlargement was detected by computed tomography. Patients with liver and lung metastases are thought to have two metastasizing lymphatic drainage routes: one through the portal venous system to the liver and the other through the systemic venous system to the lung. Thus, malignant cells can

Table 4 Univariate analysis of prognostic factors for overall survival after pulmonary metastasectomy

| Prognostic factors | No. | 5-Year survival (%) | <i>p</i> |
|---|-------|---------------------|----------|
| Median age at pulmonary resection | | | |
| ≥60 | 57 | 45.2 | 0.096 |
| <60 | 39 | 71.1 | |
| Sex (M/F) | 44/52 | 48.8/74.6 | 0.191 |
| Location of primary tumor | | | |
| Colon | 41 | 69.5 | 0.279 |
| Rectum | 55 | 56.4 | |
| Lymph node metastasis of primary tumor | | | |
| Present | 62 | 50.0 | 0.015 |
| Absent | 29 | 87.7 | |
| Previous liver resection | | | |
| Yes | 29 | 43.0 | 0.035 |
| No | 67 | 69.0 | |
| Disease-free survival | | | |
| ≥6 months | 79 | 67.1 | 0.030 |
| <6 months | 17 | 35.6 | |
| No. of pulmonary metastases | | | |
| Solitary | 57 | 65.4 | 0.364 |
| Multiple | 39 | 50.9 | |
| Location of pulmonary metastasis | | | |
| Unilateral | 78 | 64.8 | 0.051 |
| Bilateral | 18 | 44.6 | |
| Maximum size of pulmonary metastasis (cm) | | | |
| ≥3 | 21 | 64.9 | 0.761 |
| <3 | 74 | 60.0 | |
| Prethoracotomy CEA level | | | |
| ≥5.0 | 30 | 41.4 | 0.018 |
| <5.0 | 66 | 73.5 | |
| Adjuvant chemotherapy after pulmonary resection | | | |
| Yes | 29 | 73.2 | 0.312 |
| No | 67 | 59.8 | |

spread through both routes in these patients, resulting in a worse prognosis. Surgical resection of both liver and lung metastases from colorectal cancer is thought to prolong survival in highly selected patients. Therefore, prospective data analysis is needed to establish operative indications.

In this study, the 5-year DFS rate of all patients after pulmonary metastasectomy was 26.7 %. Group comparison showed 5-year DFS rates of 25.8 % in the lung metastasectomy group and 28.0 % in the liver and lung metastasectomy group. Recurrence after pulmonary metastasectomy was ~60 %. The most common site of recurrence in both groups was the remnant lung, although the recurrence pattern differed between groups. In patients who underwent both liver and lung metastasectomy, tumors were later detected in bone, brain, and adrenal

Table 5 Multivariate analysis of prognostic factors after pulmonary metastasectomy

| Variable | Relative risk | 95 % CI | <i>p</i> |
|--|---------------|-------------|----------|
| Lymph node metastasis of primary tumor | | | |
| Present | 1 | | |
| Absent | 0.155 | 0.034–0.708 | 0.016 |
| Previous liver resection | | | |
| Present | 1 | | |
| Absent | 0.307 | 0.129–0.732 | 0.008 |
| Disease-free interval (months) | | | |
| <6 | 1 | | |
| ≥6 | 0.344 | 0.143–0.829 | 0.017 |
| Prethoracotomy CEA level (ng/ml) | | | |
| <5.0 | 1 | | |
| ≥5.0 | 1.864 | 0.804–4.322 | N.S. |

CI confidence interval

Table 6 Survival after pulmonary metastasectomy for colorectal cancer: lung metastasectomy alone versus liver and lung metastasectomy

| Study | Year | Lung metastasectomy alone 5-year survival (%) | Liver and lung metastasectomy 5-year survival (%) | <i>p</i> |
|-----------------------|------|---|---|----------|
| Okumura et al. [28] | 1996 | 45 | 33 | 0.009 |
| Regnard et al. [30] | 1998 | 27 | 11 | NS |
| Kobayashi et al. [31] | 1999 | 40 | 31 | 0.23 |
| Nagakura et al. [32] | 2001 | 46 | 27 | 0.29 |
| Ike et al. [20] | 2002 | 73 | 50 | 0.57 |
| Saito et al. [12] | 2002 | 41 | 34 | 0.38 |
| Iizasa et al. [15] | 2006 | 44 | 32 | 0.39 |
| Koga et al. [29] | 2006 | 24 | 41 | 0.26 |
| Brouquet et al. [33] | 2011 | – | 50 | – |
| Gonzalez et al. [34] | 2012 | – | 39 | – |
| Sakamoto et al. [35] | 2012 | – | 48 | – |
| Present case | 2012 | 69 | 43 | 0.029 |

gland. There were significantly more metastatic organs in the liver and lung metastasectomy group than in the lung metastasectomy group. After recurrence in the remnant lung, 18 patients (50 %) of the lung metastasectomy group and 2 patients (20 %) of the liver and lung metastasectomy group underwent repeat lung resection. In previous studies, the 5-year survival rate after repeat lung resection for

recurrence of colorectal cancer has been reported at 30–40 % [11, 15, 29]. The 5-year survival rate for the 20 patients who underwent a second metastasectomy was 69.0 %. This result was favorable when compared with that of the initial metastasectomies performed in our institution and was a lot better when compared with previous reports. We did not perform a second metastasectomy in cases of bilateral lesions. This is one reason that can explain the better prognosis. Repeated pulmonary resection may provide good outcomes in patients who can undergo resection.

Conclusions

Surgical resection for lung metastases alone or for both liver and lung metastases produced good outcomes. However, the survival rate after both liver and lung metastasectomies was worse than the survival rate after lung metastasectomy alone. The number of metastatic organs was significantly higher after resection of hepatic and pulmonary metastases than after lung metastasectomy alone. Thus, the different survival rates may be due to differential patterns of recurrence after pulmonary resection. Tumor recurrence after pulmonary metastasectomy is high. Therefore, multimodality therapy with systemic chemotherapy may provide a survival benefit.

Conflict of interest None

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