
SURGICAL TREATMENT FOR BOTH PULMONARY AND HEPATIC METASTASES FROM COLORECTAL CANCER

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Objective: The role of surgery in the treatment of patients with pulmonary and hepatic metastases from colorectal cancer has not been delineated. **Methods:** Of the 351 patients enrolled in the Metastatic Lung Tumor Study Group of Japan between June 1988 and June 1996 who underwent thoracotomy for pulmonary metastases from colorectal cancer, 47 also underwent hepatic resection for metastatic tumors. The records of these patients were studied. **Results:** The 47 patients who underwent pulmonary and hepatic resection had a 3-year survival of $36\% \pm 8\%$, a 5-year survival of $31\% \pm 8\%$, and an 8-year survival of $23\% \pm 9\%$. The longest survival was 98 months. This patient was alive without recurrence. There was a significant difference in the cumulative survival of the patients with a solitary pulmonary metastasis and the patients with multiple pulmonary metastases ($P = .04$). Neither age, sex, location of the primary tumor, maximum diameter of the pulmonary metastases, method of pulmonary resection, number of hepatic metastases, nor method of hepatic resection was correlated with survival. However, 9 of 10 patients who survived 3 years or more after the initial thoracotomy had only one or two hepatic metastases. **Conclusion:** Surgical treatment of a solitary pulmonary metastasis concurrent with or after resection of hepatic metastases from colorectal cancer may be appropriate if the hepatic metastases are resectable for cure. Patients with a solitary pulmonary metastasis and a small number of hepatic metastases are good candidates for resection. Long-term survival can be expected. (J Thorac Cardiovasc Surg 1999;118:1090-6)

Surgical treatment for pulmonary metastases from colorectal cancer has been discussed since Thomford, Woolner, and Clagett¹ first reported the criteria for the resection of metastatic lung tumors in 1965. The utility of surgery in the treatment of patients with pulmonary metastases from colorectal cancer is generally accepted, despite the fact that no prospective study demonstrated its efficacy. In practice, many patients survive more than 5 years after resection of their pulmonary metastases. The effectiveness of the resection of pulmonary metastases from colorectal cancer in

patients with hepatic metastases has not been discussed extensively because of a general understanding that involvement of other organs is a contraindication to surgery.¹

Of the 351 patients in the Metastatic Lung Tumor Study Group of Japan (MLTSGJ) who underwent pulmonary resection for metastatic tumor from colorectal cancer, 47 patients underwent hepatectomy for metastatic tumors. We reviewed the characteristics of these 47 patients in an attempt to elucidate the effectiveness of surgical treatment in this population.

Patients and methods

A total of 351 patients from 11 hospitals in the Greater Tokyo Metropolitan Area who underwent thoracotomy for pulmonary metastases resulting from colorectal cancer were registered in the MLTSGJ between June 1988 and June 1996. Of these patients, 47 underwent curative pulmonary and hepatic resection for metastatic tumors. These patients' characteristics are shown in Table I. Twenty-one patients had a solitary pulmonary metastasis. The average number of metastatic pulmonary tumors was 2.5. Of the 26 patients with

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Table I. Characteristics of 47 patients undergoing resections of both hepatic and pulmonary metastases

	No. of patients
Sex	
Male	30
Female	17
Age	
≥60 y	27
<60 y	19
Unknown	1
Average	59
Range	40-82
No. of pulmonary metastases	
Solitary	21
2-3	17
4-5	5
≥6	4
Maximum size of pulmonary metastases	
<2.0 cm	19
2.0-2.9 cm	11
3.0-4.9 cm	12
≥5.0	3
Unknown	2
No. of hepatic metastases	
Solitary	30
2	11
3	2
4	4
Mode of pulmonary resection	
Wedge resection	18
Segmentectomy	14
Lobectomy	15
Location of primary cancer	
Colon	26
Ascending	4
Sigmoid	22
Rectum	17
Unknown	4
Interval between primary and pulmonary metastases	
Synchronous	8
<1 y	6
1≤, <2 y	13
2≤, <3 y	4
3≤, <4 y	10
4 y≤	6
Combination therapy for hepatic metastases	
Done	27
No	13
Unknown	7

multiple pulmonary metastases, 9 had bilateral metastases. Bilateral thoracotomies were performed simultaneously in 7 of these patients. Thirty patients had a solitary hepatic metastasis. The average number of hepatic metastases was 1.6. Pulmonary surgery included wedge resection (n = 18), segmentectomy (n = 14), and lobectomy (n = 15). Hepatic surgery included partial resection or enucleation (n = 15), subsegmentectomy or segmentectomy (n = 12), bisegmentec-

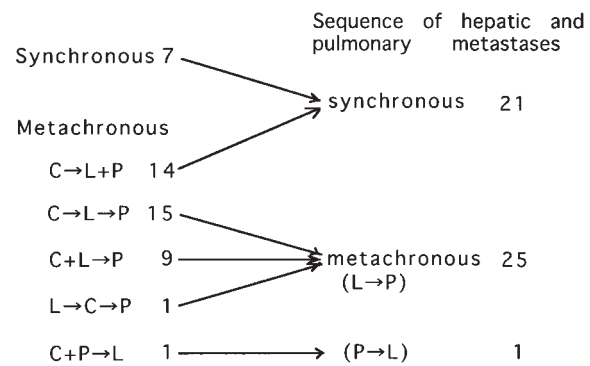


Fig 1. Timing and sequence of pulmonary metastases, hepatic metastases, and primary colorectal cancer. C, Colorectal cancer; L, hepatic metastases; P, pulmonary metastases.

tomy (n = 2), and lobectomy (n = 16). The type of hepatic operation was unknown in 2 patients.

Timing and sequence of pulmonary and hepatic metastases in relation to colorectal cancer resection are shown in Fig 1. In 25 patients, hepatic metastases were resected before the pulmonary metastases were detected. The mean interval between the 2 resections was 23.8 months. No patient in this subset had a recurrent hepatic tumor or evidence of residual hepatic tumor when the pulmonary metastases were discovered. Of the 21 patients with both pulmonary and hepatic metastases detected simultaneously, 13 underwent hepatectomy before thoracotomy. The interval between operations ranged from 1 to 7 months (mean 2.6 months). Six of the 21 patients underwent hepatectomy and thoracotomy at the same time. In 2 patients, thoracotomy was followed by hepatectomy. In 1 patient the pulmonary metastases were detected 9 months before the hepatic metastasis.

Vital status was available in the respective databases. For 21 patients alive when their medical records were retrieved, the interviews were performed at the outpatient offices of the respective hospitals to update vital status. Five patients were lost to follow-up at this time. Follow-up periods of these patients after last resections were 4, 11, 23, 28, and 35 months.

In the analysis of survival, 2 types of time 0 were used. One type of the time 0 was set to be the time at which last resection of metastases was undertaken. This is the time at which all the patients had both hepatic and pulmonary metastases resected. Another type of the time 0 was set to be the time at which initial resection of metastases was undertaken. This is the time at which 3 patients underwent pulmonary resection and the other patients underwent hepatectomy or both hepatectomy and pulmonary resection for their initial metastasectomy.

As this study was multi-institutional, pathologic diagnoses were made by the pathologists belonging to the respective institutions. When the specimens of pulmonary metastatic lesions required pathologic analysis to eliminate second primary tumors, they were necessarily compared with the spec-

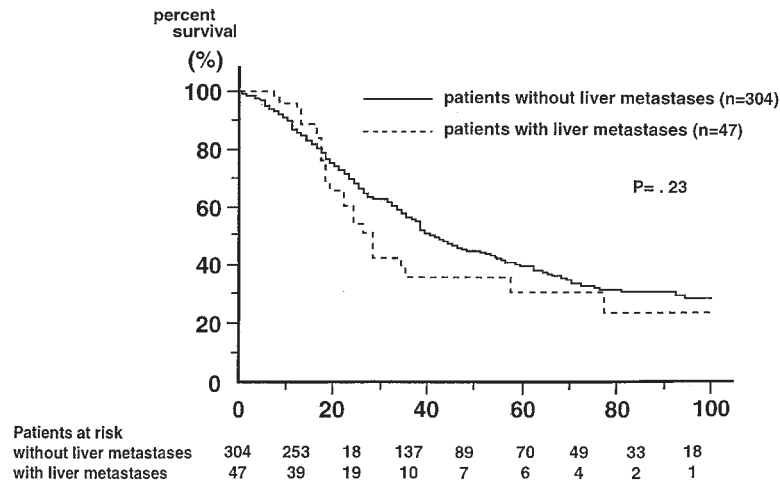


Fig 2. Kaplan-Meier survival analysis: Months after the last resection of metastases of the patients with liver metastases and the patients without liver metastases. The *P* value of overall log-rank test is .23.

imens of primary colorectal tumors. When they had the same pathologic features as those of the primary lesions, they were diagnosed as pulmonary metastases.

Statistical analysis. The survival from the initial or the last metastasectomy was calculated by means of the Kaplan-Meier method.² The significance of each prognostic factor was determined by means of the log-rank test.

For the identification of prognostic factors, multivariable analyses were done by the Cox semiparametric proportional hazards regression. The following variables were entered into the multivariable analyses: age, sex, site of colorectal primary tumor (colon or rectum), date of colorectal resection, sequence of metastases, number of hepatic metastases, number of pulmonary metastases, date of pulmonary resection, date of hepatic resection, follow-up date, and vital status. A *P* value < .05 was considered prognostic.

Results

The cumulative survival from the last metastasectomy was calculated for the 47 patients who underwent resection of pulmonary and hepatic metastases and the 304 patients who underwent resection of only pulmonary metastases (Fig 2). The patients who underwent pulmonary and hepatic resection had a 3-year survival of 36% ± 8%, a 5-year survival of 31% ± 8%, and an 8-year survival of 23% ± 9%. The longest survival was 98 months. This patient was alive without recurrence. The patients who underwent pulmonary resection alone had a 3-year survival of 56% ± 3%, a 5-year survival of 40% ± 3%, and an 8-year survival of 28% ± 3%. No significant difference was noted in survival between these 2 groups at confidence intervals of 95% (*P* = .23).

The cumulative survivals after the last metastasecto-

my and after the initial metastasectomy were calculated for the 21 patients in whom the hepatic and pulmonary metastases were detected simultaneously and the 25 patients in whom the hepatic metastases were detected before the pulmonary metastases (Figs 3 and 4). There was no significant difference in survival after the last metastasectomy between these 2 groups (*P* = .97). On the other hand, the cumulative survival at 5 years after the initial metastasectomy was 22% ± 12% in the patients with the hepatic and pulmonary metastases simultaneously and 50% ± 11% in the patients in whom the hepatic metastases were detected before the pulmonary metastases. There was a significant difference in survival after the initial metastasectomy between these 2 groups (*P* = .009).

The cumulative survival from the last metastasectomy was calculated for the 21 patients with a solitary pulmonary metastasis and the 26 patients with multiple pulmonary metastases (Fig 5). The patients with a solitary pulmonary metastasis had a 3-year survival of 48% ± 12%, a 5-year survival of 40% ± 12%, and an 8-year survival of 40% ± 12%. The patients with multiple pulmonary metastases had a 3-year survival of 30% ± 12%, a 5-year survival of 22% ± 11%, and an 8-year survival of 0%. A significant difference in cumulative survival was seen between these 2 groups (*P* = .04).

In the 21 patients with a solitary pulmonary metastasis, a wedge resection (*n* = 7), segmentectomy (*n* = 7), or lobectomy (*n* = 7) was performed. In the 26 patients with multiple pulmonary metastases, a wedge resection (*n* = 11), segmentectomy (*n* = 7), or lobectomy (*n* = 8) was performed. The 5-year survival of the 32 patients who underwent wedge resection or segmentectomy

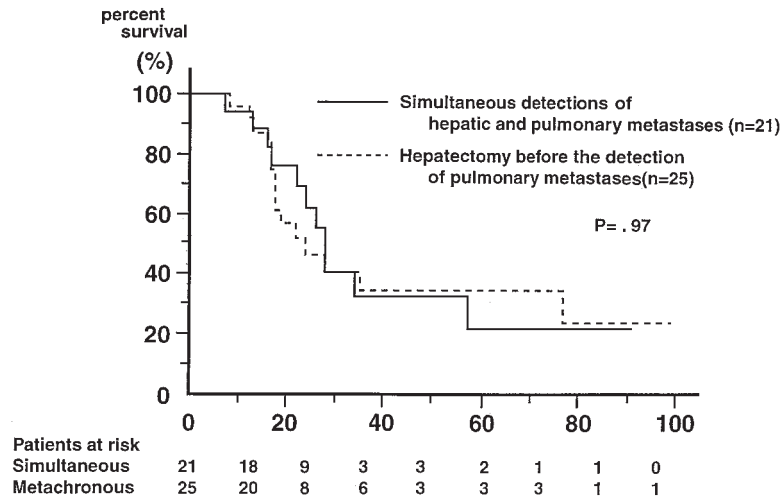


Fig 3. Kaplan-Meier survival analysis: Months after the last resection of metastases of the patients with simultaneously detected hepatic and pulmonary metastases and the patients who underwent hepatectomy before the detection of pulmonary metastases. The *P* value of the overall log-rank test is .97.

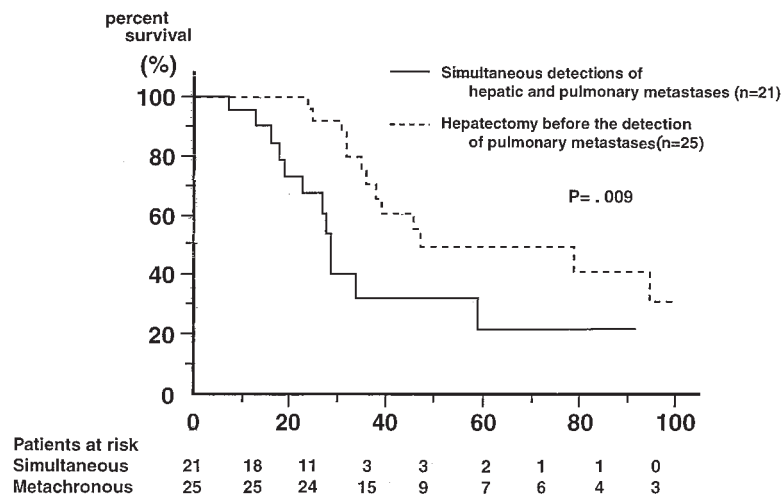


Fig 4. Kaplan-Meier survival analysis: Months after the initial resection of metastases of the patients with simultaneously detected hepatic and pulmonary metastases and the patients who underwent hepatectomy before the detection of pulmonary metastases. The *P* value of the overall log-rank test is .009.

was worse than that of the 15 patients who underwent lobectomy (22% vs 44%, respectively). However, there was no significant difference in the survivals between these 2 groups (*P* = .40). Although the number of hepatic metastases did not affect the cumulative survival after thoracotomy, there were no 8-year survivors among the patients with multiple hepatic metastases.

Multivariable analysis shows that the only prognostic factor after the last metastasectomy was the number of pulmonary metastases (*P* = .045, Table II). On the other hand, prognostic factors after the initial metastasecto-

my were revealed to be the number of pulmonary metastases (*P* = .011) and the timing of the detection of hepatic and pulmonary metastases (*P* = .002, Table III).

Of the 47 patients who underwent pulmonary and hepatic resection, 10 survived more than 3 years after the last metastasectomy. There were 2 deaths due to recurrences in this group, 1 at 57 months and 1 at 76 months. The remaining 8 patients were alive at the time of this study, 41 to 99 months after resection. Two of these patients had recurrent tumors. In 7 of these

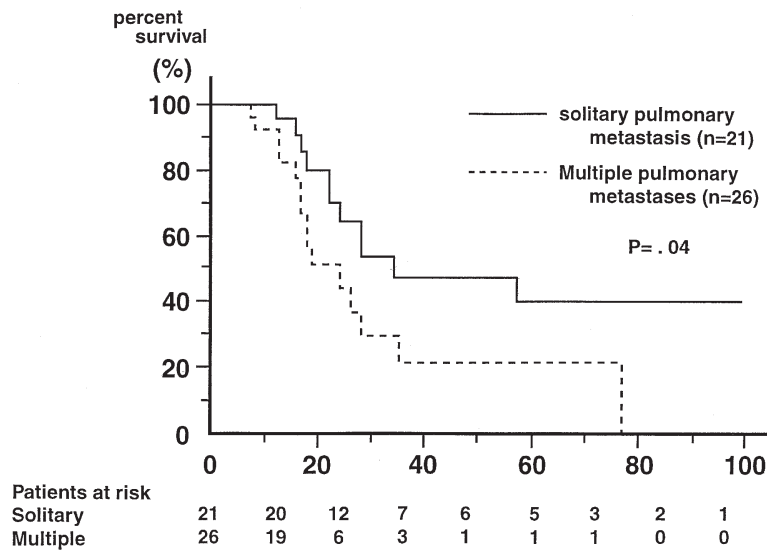


Fig 5. Kaplan-Meier survival analysis: Months after the last resection of metastases of the patients with solitary pulmonary metastasis and the patients with multiple pulmonary metastases. The *P* value of the overall log-rank test is .04.

Table II. Relationship of individual variables to death after the last metastasectomy (Cox proportional hazards method)

Variable/responses	P value	Hazard ratio	95% CL
Sex	.6	1.276	.511-3.186
Age (60≤, 60> y)	.3	.619	.263-1.458
Location of primary cancer (colon/rectum)	.4	.682	.268-1.738
Timing of hepatectomy and pulmonary resection (synchronous/metachronous)	.7	.868	.376-2.001
No. of pulmonary metastases (solitary/multiple)	.04	2.410	1.020-5.696
No. of liver metastases (solitary/multiple)	.9	.965	.398-2.337

CL, Confidence limit.

Table III. Relationship of individual variables to death after the resection of hepatic metastases (Cox proportional hazards method)

Variable/responses	P value	Hazard ratio	95% CL
Sex	.8	1.103	.446-2.726
Age (60≤, 60> y)	.6	.803	.331-1.947
Location of primary cancer (colon/rectum)	.4	.677	.253-1.807
Timing of hepatectomy and pulmonary resection (synchronous/metachronous)	.002	.205	.075-.563
No. of pulmonary metastases (solitary/multiple)	.01	3.640	1.353-9.794
No. of liver metastases (solitary/multiple)	.8	.882	.362-2.146

CL, Confidence limit.

patients, the pulmonary metastasis was solitary. In 6, the hepatic metastasis was solitary. In 5, both metastases were solitary. In 1 patient, the primary colorectal lesion and the pulmonary metastases were detected at the same time. In the other 9 patients, the pulmonary metastases were detected 15 to 44 months after the treatment of the primary colorectal tumor. The intervals were greater than 2 years in 6 patients.

Discussion

Goldberg and associates³ have reported that among 548 patients with recurrent colorectal cancer, 222 (41%) underwent resection, 28 (5.1%) underwent hepatecto-

my, and 20 (3.0%) underwent thoracotomy. Yamamoto and colleagues⁴ have reported that of 974 patients who underwent resection of a primary colorectal cancer, 47 (4.8%) had a hepatic metastasis develop. Among them, 16 (2.9%) underwent reoperation, but only 6 (0.6%) of the reoperations were curative. Of the 35 (3.6%) patients who had pulmonary metastases, only 6 (0.6%) underwent a curative reoperation. The patients enrolled in this study comprised 13% of the 351 cases in the MLTSGJ in which pulmonary metastases from colorectal cancer were resected. Thus these cases are not rare. It is therefore important to determine the criteria for resection of both pulmonary and hepatic metastases.

In approximately half of the cases, the pulmonary and hepatic metastases were detected at the same time. In the other half, detection of the hepatic metastases preceded detection of the pulmonary metastases. In only 1 case, detection of the pulmonary metastasis preceded that of the hepatic metastases. Although this may be due partly to the fact that the patients in this study were registered mainly by thoracic surgeons, we can assume that resectable hepatic metastases appear before or at the time of detection of pulmonary metastases in most cases. Therefore the cases in which the detection of the hepatic metastases preceded or concurred with the detection of the pulmonary metastases are discussed.

The 5-year survivals after thoracotomy for pulmonary metastases from colorectal cancer have been reported to range from 22% to 42%.⁵⁻⁸ Our data for the 47 patients with both pulmonary and hepatic metastases were also within this range. This means that surgical treatment in patients with both pulmonary and hepatic metastases may be appropriate. Extrahepatic disease has been reported to be a poor prognostic factor for the resection of hepatic metastases from colorectal cancer. In this study, the 5-year survival after metastasectomy in the synchronous group was 22%. This is in contrast to the 5-year survival of 0% to 13% reported for other extrahepatic disease.⁹⁻¹¹ Moreover, the 5-year survivals after hepatic resection of colorectal metastases have been reported to range from 24% to 41%.⁹⁻¹⁵ These data suggest that synchronous pulmonary metastases with hepatic metastases may be different from other extrahepatic diseases and should not be thought of as a poor prognostic factor for hepatectomy.

On the other hand, the 5-year survival of the synchronous group after initial metastasectomy was also significantly poorer than that of the metachronous group. However, in the cumulative survival from the last metastasectomy, there was no significant difference between these 2 groups, because pulmonary metastases developed 23.8 months after hepatectomy in the metachronous group. Multivariable analysis also shows that the prognostic factor after the last metastasectomy was only the number of pulmonary metastases, although the number of pulmonary metastases and timing of the detection of hepatic and pulmonary metastases were prognostic factors after the initial metastasectomy. This means that the prognosis after the last metastasectomy, that is, after pulmonary resection of colorectal metastases, is independent of the timing of metastases. Robinson and coworkers¹⁶ reported a similar conclusion that if the date of last resection is chosen for the calculation of survival, the

timing of metastases is no longer a factor that influences survival.

Only the number of pulmonary metastases affected the survival after the last metastasectomy in patients with both pulmonary and hepatic metastases. Okumura and associates⁵ reported that the 5-year survival after thoracotomy in 22 patients with hepatic metastases and a solitary pulmonary metastasis was 43.7%. In our study, the 5-year survival among patients with a solitary pulmonary metastasis was 40%. Such individuals are good candidates for surgical treatment. The number of liver metastases was not correlated with survival after thoracotomy. However, most of the patients who survived more than 3 years had 1 or 2 hepatic metastases. Therefore surgery may be most effective in patients with few hepatic metastases. More data are needed to establish this pattern as valid.

Among the 21 patients with concurrent pulmonary and hepatic metastases, 6 underwent simultaneous pulmonary and hepatic resection. The operative procedures included lobectomies for pulmonary and hepatic metastases in 1 patient and lobectomy and partial resection for bilateral pulmonary metastases and segmentectomy for a hepatic metastasis in 1 patient. Segmentectomy for pulmonary metastases and partial resection for hepatic metastases was performed in 4 patients. In another 8 patients, the interval between the 2 resections was less than 2 months. When thinking of resection for concurrent pulmonary and hepatic metastases, one must consider the invasiveness of the surgical procedure. After concurrent resection or resection within 2 months, no operative death or deaths within 6 months occurred. This indicates that it is safe to perform these procedures concurrently or at close intervals.

In conclusion, resection of pulmonary metastases concurrent with or after resection of hepatic metastases from colorectal cancer may be appropriate. Patients with a solitary pulmonary metastasis and few hepatic metastases are good candidates for this operation. Long-term survival can be expected in these patients.

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Appendix

The following institutions participated in this study: Keio University, Cancer Institute Hospital, Chiba University, Dokkyo University, Hamamatsu University, National Cancer Center, National Defense Medical College, Saitama Medical School, Tokyo Medical University, Tokyo Metropolitan University, and University of Tokyo.

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