Outcomes and prognostic factors after pulmonary metastasectomy in patients with colorectal cancer with previously resected hepatic metastases

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ABSTRACT

Objectives: Outcomes and prognostic factors remain obscure in patients with colorectal cancer after pulmonary metastasectomy who had previously received a curative hepatic metastasectomy.

Methods: We collected data of 757 patients with pulmonary metastasis from colorectal cancer who underwent curative metastasectomy between 2004 and 2008 from 46 Japanese institutions, from which we extracted data on patients who previously received curative hepatic metastasectomy. Disease-free survival, overall survival, and prognostic factors were analyzed.

Results: The subjects of this study were 160 patients, of whom 44% had primary rectal tumor, 73% had a single pulmonary metastasis, 11% had a bilateral pulmonary metastasis, and 39% had high (>5 ng/mL) serum carcinoembryonic antigen. Patients' median age was 66 years, and 58% were male. The median follow-up was 64 months. Five-year overall survival and disease-free survival were 65.2% (95% confidence interval, 56.8-72.5) and 33.5% (95% confidence interval, 26.1-41.0), respectively. In multivariable analyses, high prethoracotomy carcinoembryonic antigen level was an independent prognostic factor for overall survival (hazard ratio, 2.01; 95% confidence interval, 1.16-3.47) and disease-free survival (hazard ratio, 2.10; 95% confidence interval, 1.41-3.12). Five-year overall survival and disease-free survival of patients with normal prethoracotomy carcinoembryonic antigen level were 76.4% (95% confidence interval, 66.1-83.9) and 40.7% (95% confidence interval, 30.5-50.5), respectively.

Conclusions: After pulmonary metastasectomy, approximately two thirds of patients with colorectal cancer with a history of curative hepatic metastasectomy survived for 5 years—half of them disease-free. Our results indicate that patients with colorectal cancer with pulmonary metastasis and a history of curative hepatic metastasectomy may benefit from sequential pulmonary metastasectomy, especially if prethoracotomy serum carcinoembryonic antigen levels are within normal range. (*J Thorac Cardiovasc Surg* 2019;157:2049-57)

OS in patients who underwent both hepatic and pulmonary metastasectomies.

Central Message

Patients with pulmonary metastases and history of curative hepatic metastasectomy may benefit from sequential pulmonary metastasectomy, especially if prethoracotomy serum CEA levels are 5 ng/mL or less.

Perspective

Pulmonary metastasectomy can benefit patients with colorectal carcinoma, history of curative hepatic metastasectomy, and prethoracotomy serum CEA levels 5 ng/mL or less.

See Commentaries on pages 2058 and 2060.

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Abbreviations and Acronyms

ACT = adjuvant chemotherapy
 CEA = carcinoembryonic antigen
 CI = confidence interval
 CRC = colorectal cancer
 DFS = disease-free survival
 HR = hazard ratio
 OS = overall survival
 PM = pulmonary metastasis

Scanning this QR code will take you to the article title page to access supplementary information.

The most common sites of metastasis from colorectal adenocarcinoma are the liver and lung. Hepatic metastases occur in 8% to 30% of patients after curative resection of colorectal cancer (CRC), and pulmonary metastases (PMs) occur in 5% to 20% of patients.¹⁻³

Surgical resection is considered to be the most effective treatment for hepatic metastases from CRC and has produced a 5-year survival of 25% to 58%.⁴⁻⁹ PMs were previously thought to be incurable and were primarily treated with systemic chemotherapy. However, many surgeons have performed pulmonary metastasectomies in selected patients, with reported 5-year survival ranging from 27% to 68%.¹⁰⁻¹⁴ Recently, patients with histories of completely resected hepatic metastases have more widely received pulmonary metastasectomies, although no consensus is available on identifying patients most likely to benefit from sequential pulmonary metastasectomy among those with histories of completely resected hepatic metastases.¹⁵⁻²³

The aim of this study was to clarify the long-term outcomes of patients who underwent sequential curative hepatic followed by pulmonary metastasectomies and to identify factors affecting their survival, based on the data from a large population of patients who underwent metastasectomy of PMs from CRC at 46 Japanese institutions.

PATIENTS AND METHODS**Patients**

We retrospectively reviewed the medical records of patients who underwent metastasectomies of PMs from CRC at 46 Japanese institutions from January 2004 to December 2008. This period was selected because

FIGURE 1. Flowchart of patient selection for analyses. *PM-CRC*, Pulmonary metastasis from colorectal cancer.

5-fluorouracil with leucovorin plus irinotecan or oxaliplatin was approved for metastatic CRC in 2004 in Japan. Although indications and procedures for pulmonary metastasectomy varied by surgeons and institutions, metastasectomy was generally considered suitable in patients for whom (1) all pulmonary lesions are considered to be resectable; (2) hepatic metastasis has been curatively treated by hepatic metastasectomy; and (3) the expected surgical procedure can be tolerated. Inclusion criteria for this study were (1) no prior metastasectomy for PM; (2) pulmonary metastasectomy performed with curative intent for synchronous or simultaneous lesions with the primary tumor or hepatic metastases; (3) pathological confirmation of the resected lesions as metastases from CRC; and (4) metastasectomy with pathologically confirmed complete resection. Patients with extrathoracic lesions (other than hepatic metastasis) were excluded, even if those lesions had been treated with curative intent before hepatic or pulmonary metastasectomy. Hepatic and pulmonary metastases were considered simultaneous when diagnosed less than 3 months apart and sequential when diagnosed more than 3 months apart. Patients with PMs from appendix cancer or anal cancer were also excluded. Because this is a retrospective study, indications for postpulmonary metastasectomy adjuvant chemotherapy (ACT), hepatic resection procedures, and follow-up intervals after treatment also varied by institution. However, most recurrences were assessed with respect to the follow-up recommendation after primary tumor resection in the clinical guideline of Japanese Society for Cancer of the Colon and Rectum.²⁴ Briefly, this entailed interviews and examinations, including tumor markers, every 3 months after initial CRC surgery for 3 years and then every 6 months. The cutoff date for our analysis data was August 31, 2013. This study was approved by the institutional review board of each participating institution.

Data Collection

All patients who fulfilled these criteria in participating institutions were registered. Clinical data were collected on prespecified case report forms that covered patients' demographic information, primary disease status, ACT after primary CRC resection, premetastasectomy status, details of metastasectomies, pathological findings of resected PMs, ACT after pulmonary metastasectomy, and prognosis.

Statistical Analysis

Overall survival (OS) was defined as the time between the date of pulmonary metastasectomy and the date of death from any cause. Patients who were alive at last follow-up were censored from the analysis at that time, regardless of disease status. Disease-free survival (DFS) was defined as the time between the date of pulmonary metastasectomy and the date of the first detection of recurrence or death. Patients who did not experience recurrence or death were censored at the date of last follow-up. Survival was estimated with the Kaplan–Meier method and compared with the log-rank test. Cox models were used for univariable and multivariable survival analyses. Variables for which the *P* value was less than .1 in univariable analysis and previously reported prognostic factors were included in the multivariable analysis.

RESULTS

Patients

We collected case report forms of 1237 patients who underwent pulmonary metastasectomies. After evaluation by a central review board, 955 patients were judged to be suitable for analysis (Figure 1). We excluded 116 patients who underwent noncurative resection before data collection. We also excluded 198 patients from the final analysis, including 113 who underwent preoperative chemotherapy for pulmonary metastasis (PM) (because we could not

TABLE 1. Patient characteristics

Variables	N (%)
All patients	160 (100)
Age (y)	
Median and IQR	66 (58-72)
Sex	
Male	92 (58)
Female	68 (43)
Primary site	
Colon	90 (56)
Rectum	70 (44)
Primary CRC stage	
I-II	35 (22)
III-IV	125 (78)
Time between primary resection and PM (mo)	
Median and IQR	20.1 (12.4-34.9)
<2 y	94 (59)
≥2 y	66 (41)
ACT after pulmonary metastasectomy	
No	87 (54)
Yes	73 (46)
Prethoracotomy CEA level (ng/mL)	
Median and IQR	3.6 (2.4-7.7)
≤5 ng/mL	97 (61)
>5 ng/mL	63 (39)
Repeat pulmonary resection	
No	139 (87)
Yes	21 (13)
No. of PMs	
<3	140 (88)
≥3	20 (13)
Maximum PM size (mm)	
Median and IQR	15 (11-23)
≤10 mm	26 (16)
>10 mm	134 (84)
Bilateral PMs	
No	142 (89)
Yes	18 (11)
Extent of resection	
Wedge/Seg	122 (76)
Lobectomy	38 (24)
Time between hepatic and pulmonary metastasectomies (mo)	
Median and IQR	13.8 (6.7-26.0)
Type of hepatopulmonary metastases	
Simultaneous	28 (18)
Sequential	132 (83)

ACT, Adjuvant chemotherapy; CEA, carcinoembryonic antigen; CT, chemotherapy; CRC, colorectal cancer; IQR, interquartile range; PM, pulmonary metastasis; Wedge/seg, wedge resection or segmentectomy. Simultaneous denotes both hepatic and pulmonary metastases found within 3 mo.

adjust substantial differences in background characteristics, such as regimen, duration, and objective of chemotherapy) (Figure 1). We then reviewed the remaining 757 patients

FIGURE 2. Kaplan–Meier curves and 95% CIs of OS (A) and DFS (B) after resection of pulmonary metastases from CRC. OS, Overall survival; CI, confidence interval; DFS, disease-free survival.

who underwent pathologically curative metastasectomies and extracted patients who previously underwent hepatic metastasectomies and then pulmonary metastasectomies ($n = 160$).

Table 1 shows the background information of 160 patients, who underwent sequential curative hepatic and pulmonary metastasectomies, analyzed in this study. Their median age at the time of pulmonary metastasectomy was 66 years (IQR, 58–72); 58% were male, and 44% had primary tumors sited in the rectum. The median time between primary resection and PM was 20.1 months (IQR, 12.4–34.9). PMs were solitary in 73% of patients; 18% had simultaneously diagnosed hepatic and pulmonary metastases; 39% had high (>5 ng/mL) prethoracotomy carcinoembryonic antigen (CEA) levels; 76% had PMs removed by wedge resections or segmentectomies.

Outcomes

Death after pulmonary metastasectomy was observed in 55 patients (34%). Figure 2 shows the Kaplan–Meier survival curves. The 5-year OS was 65.2% (95% confidence interval [CI], 56.8–72.5), with a median follow-up of 64 months (censored case, interquartile range, 52–75; Figure 2, A). Ninety-eight patients (61%) experienced recurrences. Pulmonary was the most common site of single-organ recurrence ($n = 35$; 22%), followed by the liver ($n = 28$; 18%) (Table 2). The 5-year DFS was 33.5% (95% CI, 26.1–41.0; Figure 2, B). The simultaneous and sequential groups did not significantly differ in OS (hazard ratio [HR], 1.03; 95% CI, 0.50–2.10; $P = .99$) or DFS (HR, 1.03; 95% CI, 0.50–2.10; $P = .52$) (Figure E1).

Prognostic Factors

The results of univariable and multivariable analyses for patients' background factors and outcomes are detailed in Tables 3 and 4. We included the factors that were significant in univariable analysis and reported prognostic factors such as the number of PMs and ACT after pulmonary metastasectomy to variables for multivariable analysis. Multivariable analysis revealed that only prethoracotomy serum CEA level greater than 5 ng/mL was significantly associated

TABLE 2. Recurrence pattern after pulmonary metastasectomy

Variable	N (%)
All patients	160 (100.0)
All recurrences	98 (61.3)
Single-site recurrence	
Lung	35 (21.9)
Liver	28 (17.5)
Abdominal cavity	6 (3.8)
Bone	3 (1.9)
Brain	3 (1.9)
Multisite recurrence	
Lung + liver	11 (6.9)
Lung + other*	5 (3.1)
Liver + other†	3 (1.9)
Primary site + brain	1 (0.6)
Brain + bone	1 (0.6)
Unknown	2 (1.3)
No recurrence	62 (38.8)

*Adrenal gland, primary site + skin, bone, brain + bone + kidney. †Brain, stomach, chest wall.

TABLE 3. Univariable and multivariable analyses of overall survival

	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
Age				
<65 y				
≥65 y	1.62 (0.94-2.80)	.082	1.81 (1.01-3.24)	.045
Sex				
Male	1.08 (0.63-1.85)	.772		
Female				
Primary site				
Colon				
Rectum	1.75 (1.03-2.97)	.040	1.73 (1.00-2.98)	.050
Primary CRC stage				
I-II				
III-IV	0.82 (0.44-1.53)	.528		
Prethoracotomy CEA				
≤5 ng/mL				
>5 ng/mL	2.20 (1.30-3.74)	.004	2.01 (1.16-3.47)	.012
Extent of PM				
Unilateral				
Bilateral	1.44 (0.71-2.95)	.316		
The number of PMs, n				
<3				
≥3	1.37 (0.69-2.73)	.366	1.59 (0.76-3.30)	.216
Maximum PM size				
≤10 mm				
>10 mm	2.72 (0.98-7.51)	.054	1.02 (0.99-1.05)	.224
ACT after pulmonary metastasectomy				
No				
Yes	0.79 (0.46-1.34)	.376	0.85 (0.49-1.48)	.569
Extent of pulmonary resection				
Wedge/Seg				
Lobectomy	1.29 (0.70-2.36)	.416		
Time between primary resection and hepatic metastasectomy				
<1 y				
≥1 y	0.86 (0.44-1.66)	.651		
Hepatopulmonary met timing				
Sim				
Seq	1.03 (0.50-2.10)	.944		

Bold denotes statistically significant. HR, Hazard ratio; CI, confidence interval; CRC, colorectal cancer; CEA, carcinoembryonic antigen; ACT, adjuvant chemotherapy; PM, pulmonary metastasis; Wedge/seg, wedge resection or segmentectomy; met, metastases; Sim, simultaneous (both hepatic and pulmonary metastases found within 3 mo); Seq, sequential.

with both shorter OS (HR, 2.01; 95% CI, 1.16-3.47; $P = .012$) and DFS (HR, 2.10; 95% CI, 1.41-3.12; $P < .001$). Five-year OS of normal versus high prethoracotomy CEA levels was 76.4% versus 47.6%, respectively, and 5-year DFS was 40.7% versus 22.4%, respectively (Figure 3). There was a trend that patients with a higher serum level of prethoracotomy CEA showed worse survival (Figure E2). Age (HR, 1.81; 95% CI, 1.01-3.24; $P = .045$) was significantly associated with shorter OS (Table 3). Male sex (HR, 1.68; 95% CI, 1.12-2.52; $P = .013$) was associated with shorter DFS (Table 4).

DISCUSSION

This study demonstrated that clinical outcomes of patients who underwent curative hepatic metastasectomy followed by pulmonary metastasectomy were OS of 65.2% and DFS of 33.5%. These data seemed to be better than previous reports of OS ranging from 11% to 54% and DFS ranging from 13% to 28%,¹⁵⁻²³ although we limited them to patients with R0. Most previous studies investigated small numbers of patients or used time frames longer than 10 years to obtain adequate numbers of patients.^{15-21,23} Therefore, it is unclear whether those previous reports

TABLE 4. Univariable and multivariable analyses of disease-free survival

	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
Age				
<65 y				
≥65 y	1.46 (0.99-2.16)	.057	1.49 (0.99-2.24)	.057
Sex				
Male	1.50 (1.01-2.23)	.043	1.68 (1.12-2.52)	.013
Female				
Primary site				
Colon				
Rectum	1.30 (0.89-1.91)	.177		
Primary stage				
I-II				
III-IV	1.00 (0.63-1.60)	.978		
Prethoracotomy CEA				
≤5 ng/mL				
>5 ng/mL	1.96 (1.33-2.87)	.001	2.10 (1.41-3.12)	<.001
Extent of PM				
Unilateral				
Bilateral	1.55 (0.90-2.68)	.116		
No. of PMs, n				
<3				
≥3	1.57 (0.93-2.63)	.091	1.72 (1.00-2.98)	.051
Maximum PM size				
≤10 mm				
>10 mm	1.17 (0.69-2.00)	.559		
ACT after pulmonary metastasectomy				
No				
Yes	1.08 (0.74-1.58)	.697	1.06 (0.72-1.56)	.778
Extent of pulmonary resection				
Wedge/seg				
Lobectomy	1.34 (0.86-2.07)	.195		
Time between primary resection and hepatic metastasectomy				
<1 y				
≥1 y	0.79 (0.50-1.26)	.324		
Hepatopulmonary met timing				
Sim				
Seq	0.86 (0.54-1.37)	.517		

Bold denotes statistically significant. *HR*, Hazard ratio; *CI*, confidence interval; *CEA*, carcinoembryonic antigen; *PM*, pulmonary metastasis; *ACT*, adjuvant chemotherapy; *Wedge/seg*, wedge resection or segmentectomy; *met*, metastases; *Sim*, simultaneous (both hepatic and pulmonary metastases found within 3 mo); *Seq*, sequential.

reflect current practice and their patient cohort of pulmonary metastasectomy after curative hepatic metastasectomy is identical to this study. The present study is a multicenter study of patients who underwent pulmonary metastasectomy with a curative intent over a relatively narrow period of 5 years between 2004 and 2008. This period was the first 5 years after approval of current standard chemotherapy for CRC such as 5-fluorouracil with leucovorin plus irinotecan or oxaliplatin in Japan. We also had a long follow-up period (median, 64 months) to provide the latest long-term outcomes. Our

study shows the results of current pulmonary metastasectomy practices in patients who previously underwent hepatic metastasectomy with similar backgrounds. However, because we selected only patients with curative resections, more than 70% had solitary pulmonary metastases, which could lead to better outcomes.

Recently, the LiverMetSurvey, a prospective international registry of patients undergoing surgery for colorectal hepatic metastases at 253 centers in 66 countries, reported that among patients with simultaneous pulmonary and hepatic metastases (ie, identified within 3 months), those

FIGURE 3. Kaplan–Meier curves and 95% CIs of OS (A) and DFS (B) after resection of pulmonary metastases from CRC according to serum levels of CEA (cutoff value 5 ng/mL). CEA, Carcinoembryonic antigen.

who underwent resections of both pulmonary and hepatic metastases had a higher 5-year OS (40.7%) than those who only underwent hepatic metastasectomies (9.4%).²² The 5-year OS of patients with simultaneous pulmonary and hepatic metastases who underwent both metastasectomies was slightly lower (40.7%) than for patients with isolated hepatic metastases who underwent hepatic metastasectomy (50.0%).²² We do not have a clear explanation for the relatively high 5-year OS of simultaneous patients in our study (62.1%; Figure E1, A) compared with the LiverMetSurvey study, except that the number of our patients was small. The LiverMetSurvey registry data and our results suggest that the presence of resectable hepatic metastases or history of curative hepatic metastasectomy is not a contraindication to pulmonary metastasectomy.

Until now, few studies have reported on prognostic factors for patients with CRC who underwent curative resections of both hepatic and pulmonary metastases. Brouquet and colleagues²⁰ reported that serum CEA levels before resection of hepatic metastases and primary rectal tumors were associated with OS in patients who had undergone resections of both hepatic and pulmonary metastases, although the impact of CEA on DFS was not mentioned. Kim and colleagues²³ reported that the time between primary resection and PM less than 12 months and multiple PMs were independent prognostic factors associated with worse OS and DFS, although CEA was not included in their analyzed variables. In our study, high prethoracotomy serum CEA level was an independent prognostic factor associated with both worse OS and DFS, which is also reportedly prognostic for isolated PM from CRC in many

studies.^{2,25,26} This probably reflects the total tumor burden before pulmonary metastasectomy.

This study identifies, for the first time, high prethoracotomy serum CEA level as an unfavorable prognostic factor for both OS and DFS in these patients, which indicates its clinical utility in determining treatment strategy (Figure 4). A history of curative hepatic metastasectomy should not be considered a contraindication for pulmonary metastasectomy in patients with CRC, especially if the prethoracotomy serum CEA level is within normal range. However, the benefit of the systemic chemotherapy before or after pulmonary metastasectomy for patients with high prethoracotomy CEA level is unknown. In the future, the efficacy of perioperative or preoperative chemotherapy to these stratifying patients should be evaluated prospectively. In the present study, age was found to predict shorter OS and male sex was found to predict shorter DFS, which have also been reported in previous studies on pulmonary metastasectomy in patients with CRC.^{14,15,18,27} The prognostic and clinical significance of these factors with respect to OS or DFS should be evaluated further in other large-scale studies.

Study Limitations

This study has some limitations. First, we excluded patients with noncurative resection, which could cause a significant selection bias. We initially tried to demonstrate the survival and prognostic factors in patients after complete resection of both hepatic and pulmonary metastases. However, complete resection cannot always be achieved in all patients. This biased our study and could not reflect clinical reality. Indications for metastasectomy and ACT

FIGURE 4. Graphic schema of OS in patients who underwent both hepatic and pulmonary metastasectomies. Five-year OS of the patients with normal prethoracotomy CEA levels was significantly higher than that of the patients with high prethoracotomy CEA levels (76.4% vs 47.6%). CEA, Carcinoembryonic antigen; OS, overall survival.

differed among institutions because of the retrospective nature of this study, which might influence clinical outcomes. Estimation of DFS was not as precise as it would be in a prospective study. Details of hepatic metastases (eg, number or size) were not available in the database but might affect disease progression.¹⁴ Although we followed up the patients for relatively long periods, the median follow-up period (64 months) was not sufficient and the patient cohort was slightly dated. We also excluded the patients with perioperative or preoperative chemotherapy.

CONCLUSIONS

On the basis of these favorable survival results, we recommend pulmonary metastasectomy in patients with a resectable PM from CRC, even if they previously received a curative hepatic metastasectomy (Video 1).

Conflict of Interest Statement

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OS and DFS curve of patients underwent curative sequential hepatic and pulmonary metastasectomies according to type of hepatopulmonary metastases

Simultaneous group: both hepatic and pulmonary metastases found within 3 months

VIDEO 1. Outcomes and prognostic factors after pulmonary metastasectomy in patients with CRC with previously or simultaneously resected hepatic metastases. Video available at: [https://www.jtcvs.org/article/S0022-5223\(19\)30002-9/fulltext](https://www.jtcvs.org/article/S0022-5223(19)30002-9/fulltext).

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Key Words: pulmonary metastasis, colorectal cancer, CEA, hepatic metastasis, metastasectomy

FIGURE E1. OS (A) and DFS (B) curves for patients after resection of pulmonary metastases who previously (sequential group) and simultaneously (simultaneous group) underwent curative hepatic metastasectomy. The 2 groups did not significantly differ.

FIGURE E2. Kaplan-Meier curves and 95% CIs of OS (A) and DFS (B) after resection of pulmonary metastases from CRC according to serum levels of CEA. CEA, Carcinoembryonic antigen.