Prognostic Factors in the Pulmonary Metastasectomy and Efficacy of the Repeat Pulmonary Metastasectomy from Colorectal Cancer

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Research

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Abstract

Background

Pulmonary metastasectomy from colorectal cancer (CRC) has improved with recent advances in chemotherapy, diagnostic techniques, and surgical procedures. The purpose of this study was to investigate the prognostic factors of response to pulmonary metastasectomy and the efficacy of repeat pulmonary metastasectomy.

Methods

This study was a retrospective, single-institution study of 126 CRC patients who underwent pulmonary metastasectomy between 2000 and 2019 at the Gifu University Hospital. Among these 126 patients, 47 cases (37.3%) had pulmonary re-recurrence after initial pulmonary metastasectomy, and 26 cases (20.6%) underwent the second pulmonary metastasectomy.

Results

The 3- and 5- year survival rates of all 126 patients who underwent complete pulmonary metastasectomy were 84.9% and 60.8%, respectively. Univariate analysis in survival identified seven significant factors: 1) gender ($p = 0.04$), 2) past history of extra thoracic metastasis ($p = 0.04$), 3) maximum tumor size ($p = 0.002$), 4) hilar or mediastinal lymph node metastasis ($p = 0.02$), 5) preoperative carcinoembryonic antigen (CEA) level ($p = 0.01$), 6) preoperative carbohydrate antigen 19-9 (CA19-9) level ($p = 0.03$), and 7) repeat pulmonary metastasectomy for pulmonary re-recurrence ($p < 0.001$). On the multivariate analysis, only hilar or mediastinal lymph node metastasis ($p = 0.02$, risk ratio: 8.206, 95% confidence interval (CI): 1.566-34.962) and repeat pulmonary metastasectomy for pulmonary re-recurrence ($p < 0.001$, risk ratio: 0.054, 95% CI: 0.010-0.202) were significant. Furthermore, there was no significant difference in clinical and surgical characteristics between the initial and the second pulmonary metastasectomy except for intraoperative blood loss [10 (range 0-1130) mL vs 20 (range 0-220) mL, $p = 0.008$].

Conclusions

Repeat pulmonary metastasectomy is likely to be safe and effective for re-recurrent cases that meet the indication. However, hilar or mediastinal lymph node metastasis was a significant independent prognostic factor of worse overall survival.

Introduction:

Colorectal cancer (CRC) is one of the most common cancers, and it is known to metastasize frequently to the liver and lungs via the systemic blood flow. Because of recent advances in chemotherapy, diagnostic techniques, and surgical procedures, pulmonary resection is widely accepted as the optimal treatment for pulmonary metastases [1–8]. However, the clinical results of pulmonary metastasectomy for pulmonary recurrence of CRC have not yet been fully evaluated. We herein report the surgical outcomes of

pulmonary metastasectomy from CRC at our institutes. The main purpose of this study was to answer the following questions: i) What are potential prognostic factors for patients undergoing pulmonary metastasectomy? ii) What is the role of repeat pulmonary metastasectomy for re-recurrent metastatic CRC?

Patients And Methods:

Study population

A total of 126 consecutive patients underwent pulmonary metastasectomy at the Department of Thoracic Surgery, Gifu University Hospital between March 2000 and December 2019. The study's retrospective protocol was approved by our institutional review board (approval number '2019 – 253'). Among these 126 patients, 47 cases (37.3%) had pulmonary re-recurrence after initial pulmonary metastasectomy, and 26 cases (20.6%) who met the surgical indications underwent the second pulmonary metastasectomy (Fig. 1).

All patients who underwent pulmonary metastasectomy met the following indications based on the Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines for the treatment of CRC [9]: (i) The patient was capable of tolerating surgery, (ii) The primary colorectal tumor was controlled or could be controlled, (iii) The metastatic lung tumor could be completely resected, (iv) There were no extra thoracic metastases or they could be controlled, and (v) The function of the remaining lung would be adequate.

Hilar and mediastinal lymph node dissection was performed if the diagnosis was positive based on the intraoperative consultation or if lymph node metastasis was suspected in the preoperative examination (short axis ≧ 10 mm or positron emission tomography examination positive).

The surgery was considered curative if all known pulmonary nodules were removed. Patients who had complete resection of all known pulmonary disease were included in this study. We reviewed each patients' medical records to obtain clinicopathological information of the initial and second pulmonary metastasectomy.

We collected information on patients and primary colorectal tumor characteristics including gender, age at the initial pulmonary metastasectomy, smoking habits (non-smoker or smoker), Brinkman index, primary colorectal tumor location (colon or rectum / right side or left side), histological differentiation of the primary colorectal tumor (well-, moderately-, or poorly differentiated), pathological Union for International Cancer Control-TNM classification (8th edition) [10] of the primary colorectal tumor, past history of extra thoracic metastasis (present or absent), adjuvant chemotherapy after the primary colorectal operation (yes or no), and the number of pulmonary metastasectomy.

The clinical characteristics of pulmonary metastases included diagnosis period (synchronous or metachronous), number (solitary or multiple), location (unilateral or bilateral), disease-free interval, maximum tumor size, hilar or mediastinal lymph node metastasis (positive or negative), preoperative

carcinoembryonic antigen (CEA) (normal or elevated, normal upper limit at 5 ng/ml), preoperative carbohydrate antigen 19 – 9 (CA19-9) (normal or elevated, normal upper limit at 37 ng/ml), perioperative chemotherapy (yes or no), recurrence after pulmonary metastasectomy (yes or no), and recurrent organ. In this study, lung lesions diagnosed within 1 year from resection of the primary colorectal tumor were defined as synchronous metastases, and those diagnosed after 1 year were defined as metachronous metastases. The disease-free interval (DFI) referred to both the period from primary colorectal tumor resection to diagnosis of the initial pulmonary metastasis and the period from the initial pulmonary metastasectomy to diagnosis of the second pulmonary metastasis. In our department, as a general rule, perioperative chemotherapy was indicated in cases excluding solitary pulmonary metastasis with DFI > 1 year.

Finally, the surgical characteristics of pulmonary metastasectomy were operation method (partial resection, segmentectomy, or lobectomy/video-assisted thoracic surgery (VATS) or open surgery), operation time, intraoperative blood loss, preoperative percent vital capacity (%VC), preoperative forced expiratory volume percent in 1 second ($FEV_{1.0}$%), preoperative respiratory dysfunction (absent or present), postoperative complications after pulmonary metastasectomy (Clavien-Dindo classification [11] Grade ≥ 2: yes or no), postoperative mortality, and hospital stay.

Statistical analysis

For comparisons of variables between the initial and second pulmonary metastasectomy groups, Fisher's exact test was used for categorical variables, and Mann-Whitney U test was used for continuous and ordinal variables.

Overall survival was calculated in months from the date of the initial pulmonary resection to the date of the last follow-up. All cumulative survival curves were estimated using the Kaplan-Meier method, and the log-rank test was used to evaluate differences between groups for univariate analysis. A Cox relative risk regression model was used to estimate risk ratios and 95% confidence intervals (CIs) for multivariate analysis. The significance level was set at < 0.05. All statistical analyses were performed using JMP software (SAS Institute Inc., Cary, NC, USA).

Results:

Characteristics of patients and primary colorectal tumor underwent initial and second pulmonary metastasectomy

Characteristics of patients and primary colorectal tumor underwent initial and second pulmonary metastasectomy are presented in Table 1. The cohort consisted of 85 males (67.5%) and 41 females (32.5%). The age at the initial pulmonary metastasectomy ranged from 37 to 84 years, with a median of 66 years. The primary tumor location was the colon in 59 cases (46.8%) and the rectum in 66 cases (52.4%). The pathological tumor stage was stage I in 8 cases (6.3%), stage II in 25 cases (19.8%), stage III

in 56 cases (44.4%), and stage IV in 31 cases (24.6%). Forty-five patients (35.7%) had a past history of extra thoracic metastasis, and the liver (33 cases, 26.2%) was the most frequent site of metastasis.

Table 1
Characteristics of patients and primary colorectal tumor underwent initial and second pulmonary metastasectomy

Characteristics	The initial pulmonary metastasectomy n = 126	The second pulmonary metastasectomy n = 26	p-value
Gender, n (%)	Male 85 (67.5) Female 41 (32.5)	Male 16 (61.5) Female 10 (38.5)	0.56
Age¶, median [range]	66 [37–84]	62.5 [37–77]	0.04*
Smoking habits, n (%)	Non-smoker 39 (31.0) Smoker 79 (62.7)	Non-smoker 10 (38.5) Smoker 13 (50.0)	0.34
Brinkman index, median [range]	457.5 [0-2100]	107 [0-2000]	0.46
Primary colorectal tumor location, n (%)	Colon 59 (46.8) Rectum 66 (52.4)	Colon 11 (42.3) Rectum 16 (57.7)	0.65
	Right side 23 (18.2) Left side 102 (81.0)	Right side 3 (11.5) Left side 23 (88.5)	0.38
Histological differentiation of the primary colorectal tumor, n (%)	Well- 55 (43.6) Moderately- 53 (42.0) Poorly- 6 (4.8)	Well- 8 (30.8) Moderately- 9 (34.6) Poorly- 1 (3.8)	0.54
Pathological T Stage‡, n (%)	T1 7 (5.6) T2 11 (8.7) T3 61 (48.4) T4 37 (29.4)	T1 1 (3.8) T2 0 (0.0) T3 15 (57.7) T4 6 (23.1)	0.19
Pathological N Stage‡, n (%)	N0 43 (34.1) N1 47 (37.3) N2 24 (19.0)	N0 7 (27.0) N1 9 (34.6) N2 5 (19.2)	0.92

¶: Age at the initital pulmonary metastasectomy

: Brinkman index = (the number of cigarette smoked per day) × (the number of years of smoking)

‡: UICC TNM classification(the 8th edition)

*: $p < 0.05$ ** :$p < 0.01$ ***: $p < 0.001$

Characteristics	The initial pulmonary metastasectomy n = 126	The second pulmonary metastasectomy n = 26	p-value
Pathological Stage‡, n (%)	8 (6.3) 25 (19.8) 56 (44.4) 31 (24.6)	0 (0.0) 5 (19.2) 12 (46.2) 8 (30.8)	0.35
Past history of extra thoracic metastasis, n (%)	Present 45 (35.7) Absent 81 (64.3)	Present 10 (38.5) Absent 16 (61.5)	0.79
Adjuvant chemotherapy, n (%)	Yes 61 (48.4) No 57 (45.2)	Yes 16 (61.5) No 8 (30.8)	0.18
Number of pulmonary metastasectomy, n (%)	-	2times 14 (53.9) 3times 7 (26.9) 4times 5 (19.2)	-
¶: Age at the inititial pulmonary metastasectomy			
: Brinkman index = (the number of cigarette smoked per day) × (the number of years of smoking)			
‡: UICC TNM classification(the 8th edition)			
*: $p < 0.05$ ** :$p < 0.01$ ***: $p < 0.001$			

In the second pulmonary metasetasectomy group, the mode and maximum number of repeat pulmonary metastasectomy were 2 (14 cases, 53.9%) and 4 (5 cases, 19.2%), respectively. The age at the initial metastasectomy was significantly younger (p = 0.04). However, there was no significant difference in other patient and primary colorectal tumor characteristics between the two groups.

Characteristics of pulmonary metastases underwent initial and second pulmonary metastasectomy

Characteristics of pulmonary metastases underwent initial and second pulmonary metastasectomy are presented in Table 2. There was no significant difference in 10 clinical characteristics between two groups. Although the DFI was not significantly different between two groups [541.5 (range 0-4664) days vs 409 (range 27-1334) days, p = 0.13], the recurrence rate tended to be higher in the second pulmonary resection group (53.2% vs 65.4%, p = 0.07). Furthermore, the lung was the most common metastatic organ in both groups (37.3% and 46.4%, respectively).

Table 2
Characteristics of pulmonary metastases underwent initial and second pulmonary metastasectomy

Characteristics		The initial pulmonary metastasectomy n = 126	The second pulmonary metastasectomy n = 26	p-value
Diagnosis period, n (%)		Synchronous 41 (32.5) Metachronous 85 (67.5)	-	-
Number of pulmonary metastasis, n (%)	Solitary	89 (70.6)	16 (61.5)	0.27
	Multiple	34 (27.0)	10 (38.5)	
Location, n (%)	Unilateral	108 (85.7)	23 (88.5)	0.71
	Bilateral	18 (14.3)	3 (11.5)	
Disease free interval (days), median [range]		541.5 [0-4664]	409 [27-1334]	0.13
Maximum tumor size (mm), median [range]		12.0 [5–70]	12.0 [8–40]	1.00
Metastasis of hilar or mediastinal lymph node, n (%)	Negative	117 (92.9)	25 (96.2)	0.95
	Positive	5 (4.0)	1 (3.8)	
Preoperative CEA level, n (%)	Normal	86 (68.3)	15 (57.7)	0.61
	Elevated	36 (28.6)	8 (30.8)	
Preoperative CA19-9 level, n (%)	Normal	97 (77.0)	21 (80.8)	0.74
	Elevated	12 (9.5)	2 (7.7)	
Chemotherapy before operation, n (%)	Yes	28 (22.2)	9 (34.6)	0.09
	No	96 (76.2)	15 (57.7)	
Chemotherapy after operation, n (%)	Yes	40 (31.7)	9 (34.6)	0.50
	No	74 (58.7)	12 (46.2)	
Recurrence after pulmonary metastasectomy, n (%)	Yes	67 (53.2)	17 (65.4)	0.07
	No	59 (46.8)	7 (26.9)	

CEA: Carcinoembryonic antigen level, normal upper limit at 5 ng/ml

CA19-9: Carbohydrate antigen 19 – 9 level, normal upper limit at 37 ng/ml

*: $p < 0.05$ ** :$p < 0.01$ ***: $p < 0.001$

Characteristics	The initial pulmonary metastasectomy n = 126	The second pulmonary metastasectomy n = 26	p-value
Recurrent organ, n (%)	Lung 47 (37.3) Liver 12 (9.5) Abdominal lymph node 6 (4.8) Pelvic local recurrence 6 (4.8) Bone 5 (4.0) Brain 5 (4.0) Peritoneal dissemination 3 (2.4) Pleural dissemination 2 (1.6) Bone marrow 1 (0.8) Adrenal 1 (0.8)	Lung 13 (46.4) Pleural dissemination 2 (7.2) Thoracic lymph node 2 (7.2) Liver 1 (3.6) Bone 1 (3.6) Brain 1 (3.6) Pancreas 1 (3.6)	
CEA: Carcinoembryonic antigen level, normal upper limit at 5 ng/ml			
CA19-9: Carbohydrate antigen 19 − 9 level, normal upper limit at 37 ng/ml			
*: $p < 0.05$ ** :$p < 0.01$ ***: $p < 0.001$			

Surgical characteristics of patients underwent initial and second pulmonary metastasectomy

Surgical characteristics of patients underwent initial and second pulmonary metastasectomy are presented in Table 3. The amount of intraoperative blood loss was significantly higher in patients undergoing second pulmonary metastasectomy [10 (range 0-1130) mL vs 20 (range 0-220) mL, p = 0.008], and the percentage of patients undergoing segmentectomy also tended to be higher among those receiving second pulmonary metastasectomy [31 (24.6%) vs 11 (42.3%), p = 0.09]. However, there were no significant differences in postoperative complications, postoperative mortality, and hospital stay between two groups.

Table 3
Surgical characteristics of patients underwent initial and second pulmonary metastasectomy

Characteristics		The initial pulmonary metastasectomy (n = 126)	The second pulmonary metastasectomy (n = 26)	p-value
Operation, n (%)	Partial resection	65 (51.6)	8 (30.8)	0.09
	Segmentectomy	31 (24.6)	11 (42.3)	
	Lobectomy	30 (23.8)	5 (19.2)	
	VATS	106 (84.1)	17 (65.4)	0.12
	Open	20 (15.9)	7 (26.9)	
Operation time (min), median [range]		163 [40–645]	217 [62–505]	0.15
Intraoperative blood loss (ml), median [range]		10 [0-1130]	20 [0-220]	0.008**
Preoperative %VC (%), median [range]		109.8 [56.7–154]	109.0 [56.4–147]	0.23
Preoperative $FEV_{1.0}$% (%), median [range]		74.9 [46.8-102.6]	72.7 [59.8–97.1]	0.99
Preoperative respiratory dysfunction, n (%)	Absent	77 (61.1)	13 (50.0)	0.91
	Present	44 (34.9)	10 (38.5)	
	Restrictive-	4 (3.2)	2 (7.7)	
	Obstructive-	39 (31.0)	8 (30.8)	
	Mixed-	1 (0.8)	0 (0.0)	
Postoperative complication (≧ CD□-grade2), n (%)	Yes	5 (3.9)	0 (0.0)	0.32
	No	115 (91.3)	24 (92.3)	

□: Clavien-Dindo classification

VATS: Video-assisted thoracic surgery

%VC: percent vital capacity

$FEV_{1.0}$%: forced expiratory volume percent in 1 second

*: $p < 0.05$ ** :$p < 0.01$ ***: $p < 0.001$

Characteristics	The initial pulmonary metastasectomy (n = 126)	The second pulmonary metastasectomy (n = 26)	p-value
	Fistula 2 (1.6) Pneumonia 1 (0.8) Air leakage 1 (0.8) Pleural effusion 1 (0.8)	-	
Postoperative mortality, n (%)	0 (0.0)	0 (0.0)	-
Hospital stay (day), median [range]	7 [2–55]	8 [3–19]	0.51
: Clavien-Dindo classification			
VATS: Video-assisted thoracic surgery			
%VC: percent vital capacity			
$FEV_{1.0}$%: forced expiratory volume percent in 1 second			
*: $p < 0.05$ ** :$p < 0.01$ ***: $p < 0.001$			

Survival of the pulmonary metastasectomy from CRC

The median follow-up period after the primary pulmonary metastasectomy was 37 months (range 1-209 months). Of the 126 patients, 33 (24.3%) died after pulmonary metastasectomy: 24 (19.0%) of the primary disease, 8 patients (6.3%) of another disease, and 1 (0.8%) of unknown causes.

The 3- and 5- year survival rates of all 126 patients who underwent complete pulmonary metastasectomy were 84.9% and 60.8%, respectively (Fig. 2). Table 4 lists the 3- and 5-year survival rates after the pulmonary metastasectomy according to 21 clinicopathological features for all 126 patients. Univariate analysis identified seven significant factors: 1) gender {p = 0.04, Fig. 3(a)}, 2) past history of extra thoracic metastasis {p = 0.04, Fig. 3(b)}, 3) maximum tumor size {p = 0.002, Fig. 3(c)}, 4) hilar or mediastinal lymph node metastasis {p = 0.02, Fig. 3(d)}, 5) preoperative CEA level {p = 0.01, Fig. 3(e)}, 6) preoperative CA19-9 level {p = 0.03, Fig. 3(f)}, and 7) repeat pulmonary metastasectomy for pulmonary re-recurrence (p < 0.001, Fig. 4). Multivariate analysis using a Cox relative risk regression model indicated that of these features (Table 5), only hilar or mediastinal lymph node metastasis (p = 0.02, risk ratio: 8.206, 95% CI: 1.566–34.962) and repeat pulmonary metastasectomy for pulmonary re-recurrence (p < 0.001, risk ratio: 0.054, 95% CI: 0.010–0.202) were significant.

Table 4
Survival of the pulmonary metastasectomy from CRC in univariate analysis

Prognostic factors		n (%)	3-year overall survival after the initial pulmonary metastasectomy (%)	5-year overall survival after the initial pulmonary metastasectomy (%)	p-value
Gender	Male	85 (67.5)	80.1	54.5	0.04*
	Female	41 (32.5)	94.0	77.0	
Age (years)	≧ 70	41 (32.5)	77.0	53.8	0.34
	< 70	85 (67.5)	87.6	63.1	
Brinkman index	≧ 400	58 (46.0)	85.1	64.5	0.78
	< 400	48 (38.1)	84.5	59.2	
Primary colorectal tumor location	Colon	59 (46.8)	87.4	53.4	0.31
	rectum	66 (52.4)	82.5	69.1	
	Right sided	23 (18.2)	78.6	57.3	0.50
	Left sided	102 (81.0)	84.3	61.3	
Pathological T stage‡	T4	37 (29.4)	81.2	55.2	0.21
	T < 4	79 (62.7)	86.0	63.9	

: Brinkman index = (the number of cigarette smoked per day) × (the number of years of smoking)

‡: UICC TNM classification(the 8th edition)

CRC: Colorectal cancer

CEA: Carcinoembryonic antigen level, normal upper limit at 5 ng/ml

CA19-9: Carbohydrate antigen 19 – 9 level, normal upper limit at 37 ng/ml

*: p < 0.05 ** :p < 0.01 ***: p < 0.001

Prognostic factors		n (%)	3-year overall survival after the initial pulmonary metastasectomy (%)	5-year overall survival after the initial pulmonary metastasectomy (%)	p-value
Pathological N stage‡	N ≧ 1	71 (56.3)	86.9	61.6	0.99
	N0	43 (34.1)	78.6	60.5	
Past history of extra thoracic metastasis	Presence	45 (35.7)	78.6	53.1	0.04*
	Absence	81 (64.3)	88.7	65.4	
Past history of liver metastasis	Presence	33 (26.2)	70.4	52.4	0.05
	Absence	93 (73.8)	87.2	64.3	
Adjuvant chemotherapy after primary colorectal resection	Yes	61 (48.4)	90.1	68.5	0.07
	No	57 (45.2)	79	53.9	
Diagnosis period of pulmonary metastases	Synchronous	41 (32.5)	92.9	63.7	0.48
	Metachronous	85 (67.5)	80.9	59.3	
Number of pulmonary metastases	Solitary	89 (70.6)	81.8	62.2	0.75
	Multiple	34 (27.0)	91.6	55	
Location of pulmonary metastases	Unilateral	108 (85.7)	84.9	62.9	0.56

: Brinkman index = (the number of cigarette smoked per day) × (the number of years of smoking)

‡: UICC TNM classification(the 8th edition)

CRC: Colorectal cancer

CEA: Carcinoembryonic antigen level, normal upper limit at 5 ng/ml

CA19-9: Carbohydrate antigen 19 – 9 level, normal upper limit at 37 ng/ml

*: $p < 0.05$ ** :$p < 0.01$ ***: $p < 0.001$

Prognostic factors		n (%)	3-year overall survival after the initial pulmonary metastasectomy (%)	5-year overall survival after the initial pulmonary metastasectomy (%)	p-value
	Bilateral	18 (14.3)	78.3	52.9	
Maximum tumor size (mm)	≧ 20	27 (21.4)	52.0	31.2	0.002**
	< 20	94 (74.6)	89.2	66.1	
Metastasis of hilar or mediastinal lymph node	Positive	5 (4.0)	20.0	20.0	0.02*
	Negative	117 (74.6)	86.6	60.8	
Preoperative CEA level	Normal	86 (68.3)	88.5	67.7	0.01*
	Elevated	36 (28.6)	63.3	37.3	
Preoperative CA19-9 level	Normal	97 (77)	87.8	64.1	0.03*
	Elevated	12 (9.5)	63.5	31.8	
Disease free interval after primary colorectal resection (years)	≧ 2	81 (64.3)	85.7	59.9	0.91
	< 2	45 (35.7)	79.9	62.4	
Perioperative chemotherapy	Yes	60 (47.6)	78.1	55.3	0.13
	No	65 (51.6)	87.1	68.4	

: Brinkman index = (the number of cigarette smoked per day) × (the number of years of smoking)

‡: UICC TNM classification(the 8th edition)

CRC: Colorectal cancer

CEA: Carcinoembryonic antigen level, normal upper limit at 5 ng/ml

CA19-9: Carbohydrate antigen 19 – 9 level, normal upper limit at 37 ng/ml

*: $p < 0.05$ ** :$p < 0.01$ ***: $p < 0.001$

Prognostic factors		n (%)	3-year overall survival after the initial pulmonary metastasectomy (%)	5-year overall survival after the initial pulmonary metastasectomy (%)	p-value
Chemotherapy before pulmonary metastasectomy	Yes	28 (22.2)	63.7	49.6	0.17
	No	96 (76.2)	88.4	62.6	
Chemotherapy after pulmonary metastasectomy	Yes	40 (31.7)	84.0	60.6	0.77
	No	74 (58.7)	82.5	59.7	
Repeat pulmonary metastasectomy for pulmonary re-recurrence	Yes	26 (38.8)	96.2	76.9	< 0.001***
	No	41 (61.2)	68.8	8.7	
: Brinkman index = (the number of cigarette smoked per day) × (the number of years of smoking)					
‡: UICC TNM classification(the 8th edition)					
CRC: Colorectal cancer					
CEA: Carcinoembryonic antigen level, normal upper limit at 5 ng/ml					
CA19-9: Carbohydrate antigen 19 − 9 level, normal upper limit at 37 ng/ml					
*: $p < 0.05$ ** :$p < 0.01$ ***: $p < 0.001$					

Table 5
Survival of the pulmonary metastasectomy from CRC in multivariate analysis

Prognostic factors	p-value	Risk ratio	95% Confidence interval
Gender (Male / Female)	0.60	1.324	0.484–4.381
Past history of extra thoracic metastasis (Presence / Absence)	0.67	1.205	0.511–2.922
Preoperative CEA level (Elevated / Normal)	0.89	1.083	0.356–3.547
Maximum tumor size (≧ 20 mm / < 20 mm)	0.74	1.203	0.401–3.646
Metastasis of hilar or mediastinal lymph node (Positive / Negative)	0.02*	8.206	1.566–34.962
Repeat pulmonary metastasectomy for the pulmonary re-recurrence (Yes / No)	< 0.001***	0.054	0.010–0.202
CRC: Colorectal cancer			
CEA: Carcinoembryonic antigen level, normal upper limit at 5 ng/ml			
*: p < 0.05 ** :p < 0.01 ***: p < 0.001			

Discussion:

The number of new CRC cases has been increasing annually worldwide. In 2002, the number of new diagnoses was estimated to be about 1.02 million globally [12], but in 2018, the number had increased to about 1.8 million [13]. Accordingly, the number of patients with pulmonary metastases from CRC is inevitably increasing. However, the development of multidrug chemotherapy regimens such as FOLFOX and FOLFIRI and the emergence of molecular targeting drugs such as anti-VEGF antibody and anti-EGFR antibodies have dramatically improved CRC outcomes. Treatment strategies for pulmonary metastasis of CRC have received attention for the purpose of further improving prognosis [1–8].

In the past, pulmonary metastasis was considered to be a condition in which cancer spread throughout the body, and aggressive treatment was commonly avoided. However, since Thomfold et al. [14] proposed the principles of surgical treatment for pulmonary metastases, pulmonary metastasectomy has been performed on patients who meet the operative indication, and the prognosis after treatment is relatively good. The 5-year survival rate after pulmonary resection is reported to be 30–68% [1–8]; a similar result

was observed in this study (60.8%). In the multicenter aggregate in the JSCCR project study [8], the 5-year survival rate of lung resection cases was 46.7% and the cumulative 5-year relapse-free survival rate was 33.7%, whereas the 5-year survival rate of non-resected cases was 3.9%. However, the efficacy of lung resection has not been shown in cohort studies or randomized controlled trials, and assessment of surgical outcomes and prognostic factors after pulmonary resection in a large sample size (at least 100 cases or more) is unexpectedly rare. According to some reports [1–8, 15–21], the number of metastases, bilateral lung metastasis, hilar or mediastinal lymph node metastasis, CEA before pulmonary metastasectomy, primary colorectal tumor factors (T factor and N factor), and disease-free interval after resection of the primary colorectal tumor were found to be prognostic factors. In this study, past history of extrathoracic metastasis, maximum tumor size, hilar or mediastinal lymph node metastasis, and elevated tumor marker level before pulmonary metastasectomy were also identified as important prognostic factors. Multivariate analysis identified hilar or mediastinal lymph node metastasis as an independent predictor of poor prognosis. Therefore, excluding cases of hilar or mediastinal lymph node metastasis, our results suggest that pulmonary metastasectomy could lead to improved prognosis in patients who met the operative indication, regardless of the characteristics of not only the patients and the primary colorectal tumor but also the pulmonary metastases.

Hilar or mediastinal lymph node metastasis in patients with pulmonary metastases is considered to reflect the spread of the cancer to the entire body and is therefore likely to be a poor prognostic factor. In our study, although the number of hilar or mediastinal lymph node-positive cases was small number, all had past histories of extrathoracic metastasis. Furthermore, distant metastases to other extrathoracic organs such as the brain, liver, and bone occurred within 1 year after surgery in these patients. Several studies suggested an association of hilar or mediastinal lymph node metastasis with an increased risk of death [15, 17, 18, 21], and a meta-analysis [20] showed poor 5-year survival among patients with lymph node metastasis (range, 0–33.5%) compared to those without lymph node metastasis (range, 38.7–71%). Our results suggest that lymph node dissection for patients with hilar or mediastinal lymph node metastasis has low therapeutic efficacy for those with other poor prognostic factors, and preventive systematic thoracic lymph node dissection is likely not necessary. Welter et al. [22] suggested it is more important to offer adjuvant chemotherapy after metastasectomy in cases of nodal metastasis than to perform radical or systematic lymph node dissection in patients with stage IV disease, understanding the risk of recurrence in extrapulmonary organs. In our study, there was no significant difference in survival based on receiving perioperative chemotherapy. Prospective studies on the efficacy and appropriate indications of perioperative chemotherapy are necessary in the future.

The present study also showed that repeat pulmonary metastasectomy for pulmonary re-recurrence is likely to be effective. Repeat pulmonary metastasectomy is a well-established procedure with satisfactory survival [1, 2, 4, 5, 15, 16, 19]. We had 26 patients (20.6% in all 126 cases and 55.3% in 47 pulmonary re-recurrent cases) who underwent repeat pulmonary metastasectomy. They had 1- and 3-year survivals of 90.7% and 84.6% after the second pulmonary metastasectomy, which are similar to the outcomes after the initial metastasectomy (97.4% and 84.9%, respectively). Furthermore, there was no significant difference between two groups in not only clinical characteristics of the primary colorectal tumor and the

pulmonary metastases but also the surgical outcomes including postoperative complications, mortality, and length of hospital stay. Only the amount of intraoperative blood loss was significantly higher in the second pulmonary metastasectomy group, probably because of the higher rate of segmentectomy. Therefore, at least one repeat pulmonary metastasectomy can be performed relatively safely and expected to improve the prognosis by strictly complying with operative indications.

Some limitations of this study have to be addressed. First, the major limitation of our study is the single-institution, retrospective design. Second, there was a potential for selection bias, which was compounded by the retrospective design. Inclusion of patients was highly selective, with patients having presumed good performance status and few comorbidities, which might have contributed to the observed long-term survival. These limitations should be considered when evaluating the results of the present study. It is necessary to carry out a prospective study at multiple institutions that have a unified definition of operative indication and treatment strategy.

Conclusions:

Pulmonary metastasectomy carries a potential survival benefit for patients with metastatic CRC. In our retrospective study, status of hilar or mediastinal lymph nodes was significant independent prognostic factor. Therefore, the presence or absence of hilar or mediastinal lymph node metastases must be accurately determined by preoperative examination and should be taken into consideration when deciding whether to perform pulmonary metastasectomy. Furthermore, careful follow up after the initial pulmonary metastasectomy is warranted, because at least one repeat pulmonary metastasectomy can lead to improve the prognosis.

Abbreviations:

CRC - colorectal cancer

JSCCR – Japanese Society for Cancer of the Colon and Rectum

CEA – carcinoembryonic antigen

CA19-9 – carbohydrate antigen 19-9

DFI – disease-free interval

VATS – video-assisted thoracic surgery

%VC – percent vital capacity

$FEV_{1.0}$% - forced expiratory volume percent in 1 second

CIs – confidential intervals

Declarations:

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Authors' contributions:

MF conceived the study concept and planned the design as the principal investigator.

MF interpreted the results and wrote the manuscript draft.

NM, HI, KD and KY revised the manuscript draft by adding intellectual insights and provided critical advice.

MF, NM, TT, HY, KS, HI, KD and KY obtained the data and provided their critical comments to improve the manuscript and gave final approval for submission.

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Availability of data and materials:

The datasets used during this study are available from the corresponding author on reasonable request

Ethics approval and consent to participate:

The present study was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of Gifu University (approval number '2019-253'). As this study was a retrospective study and did not include any potentially identifiable patient data, informed consent was not obtained from the enrolled patients. The institutional review board gave the ethics approval for this retrospective study.

Consent for publication:

Not applicable.

Competing of interests:

K. Yoshida has received honoraria for lectures from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Eli Lilly and Company, Daiichi Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., Novartis Pharma K.K., and Sanofi K.K.; and

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T. Takahashi has received honoraria for lectures from Takeda Pharmaceutical Co., Ltd. All remaining authors declare that they have no conflicts of interests.

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Figures

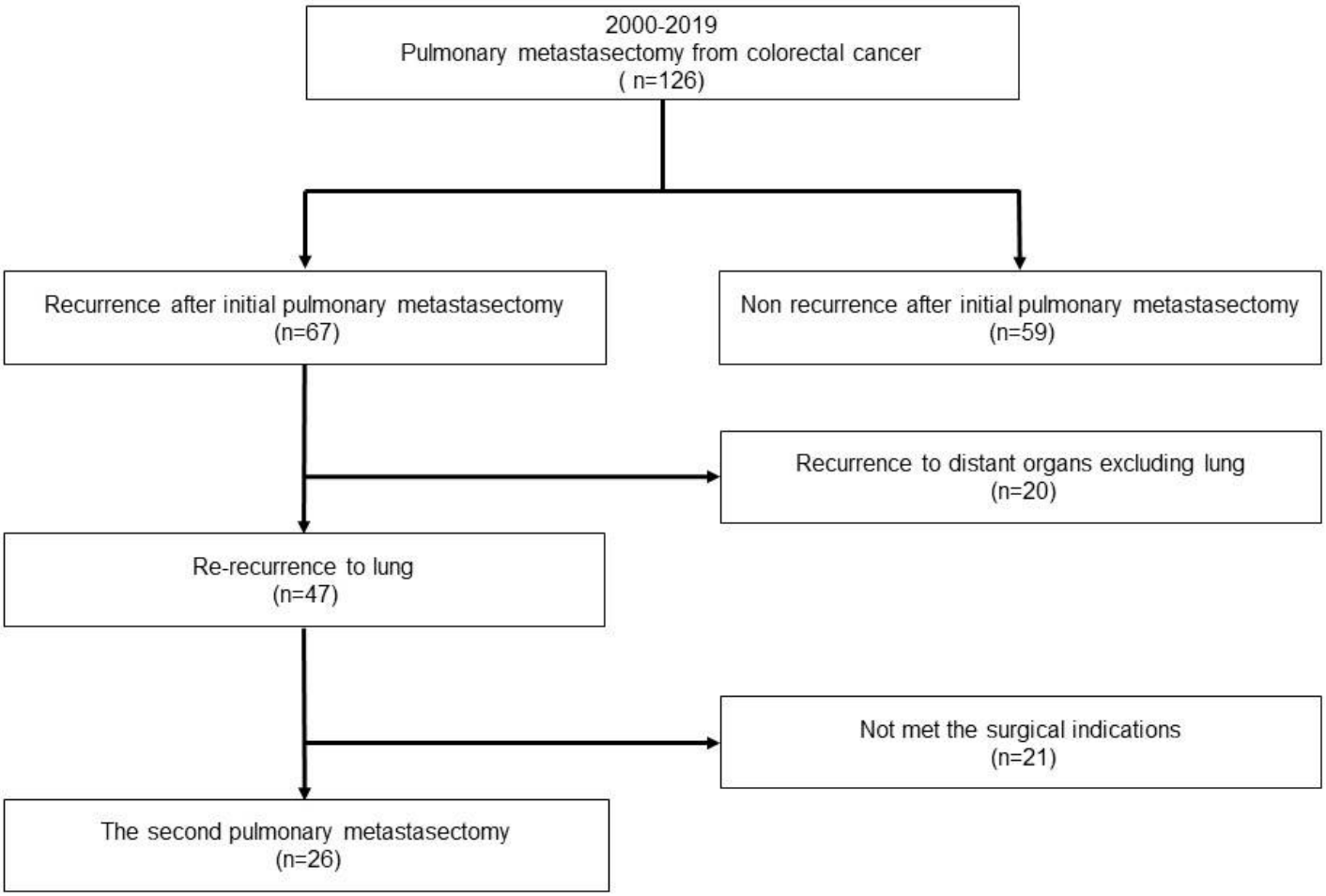

Fig.1

Figure 1

Patients' flow diagram of this study

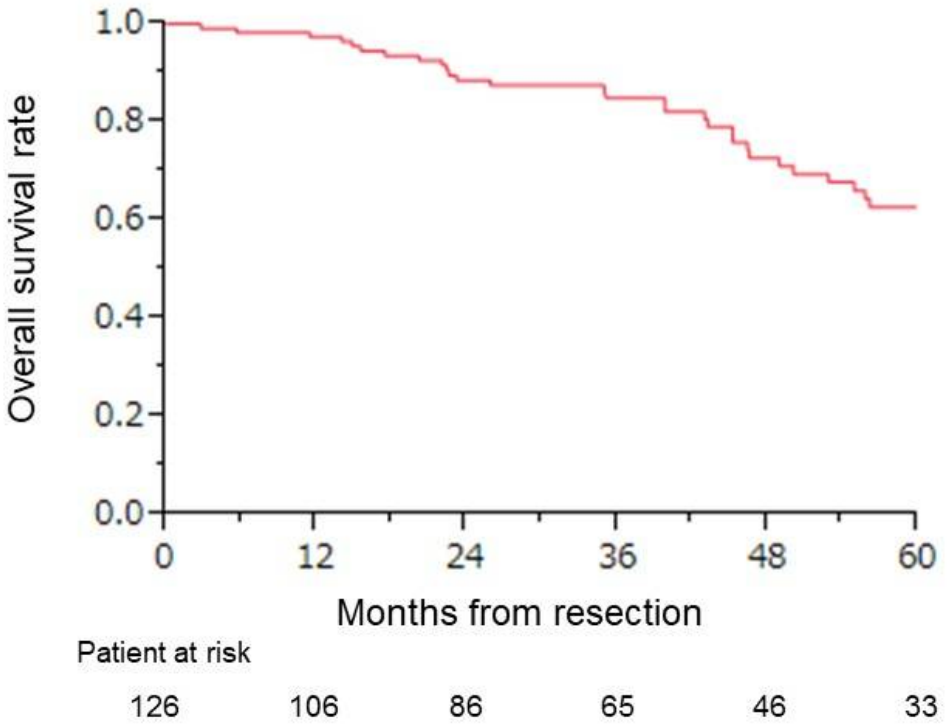

Fig.2

Figure 2

Overall survival of pulmonary metastasectomy for colorectal cancer

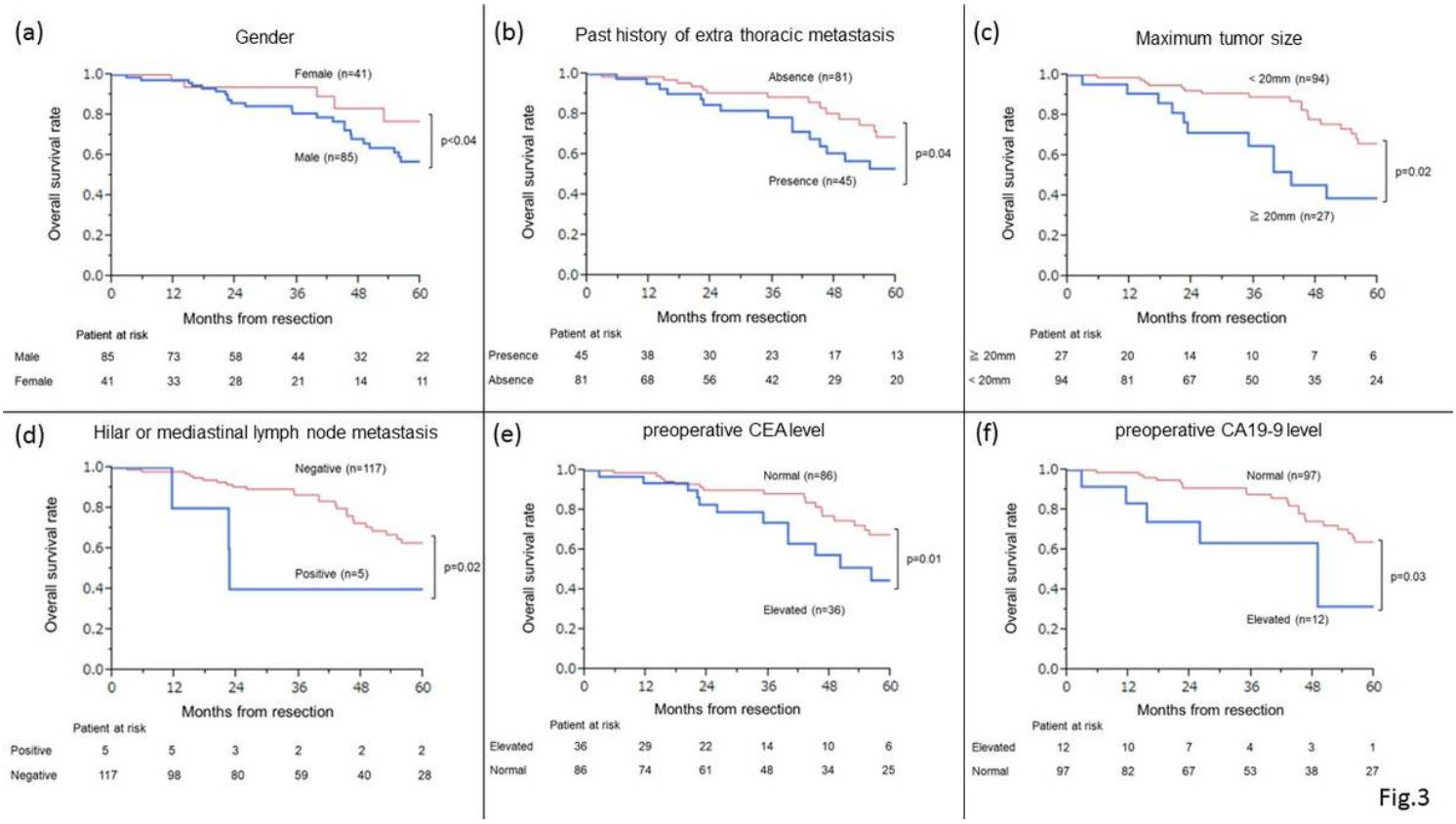

Figure 3

Prognostic factors of pulmonary metastasectomy for colorectal cancer and survival (a) Male versus female and survival. (b) Absence versus presence of past history of extra thoracic metastasis and survival. (c) Maximum tumor size ≧ 20mm versus < 20mm and survival. (d) Positive versus negative of hilar or mediastinal lymph node metastasis and survival. (e) Elevated versus normal of preoperative CEA level and survival. (f) Elevated versus normal of preoperative CA19-9 level and survival.

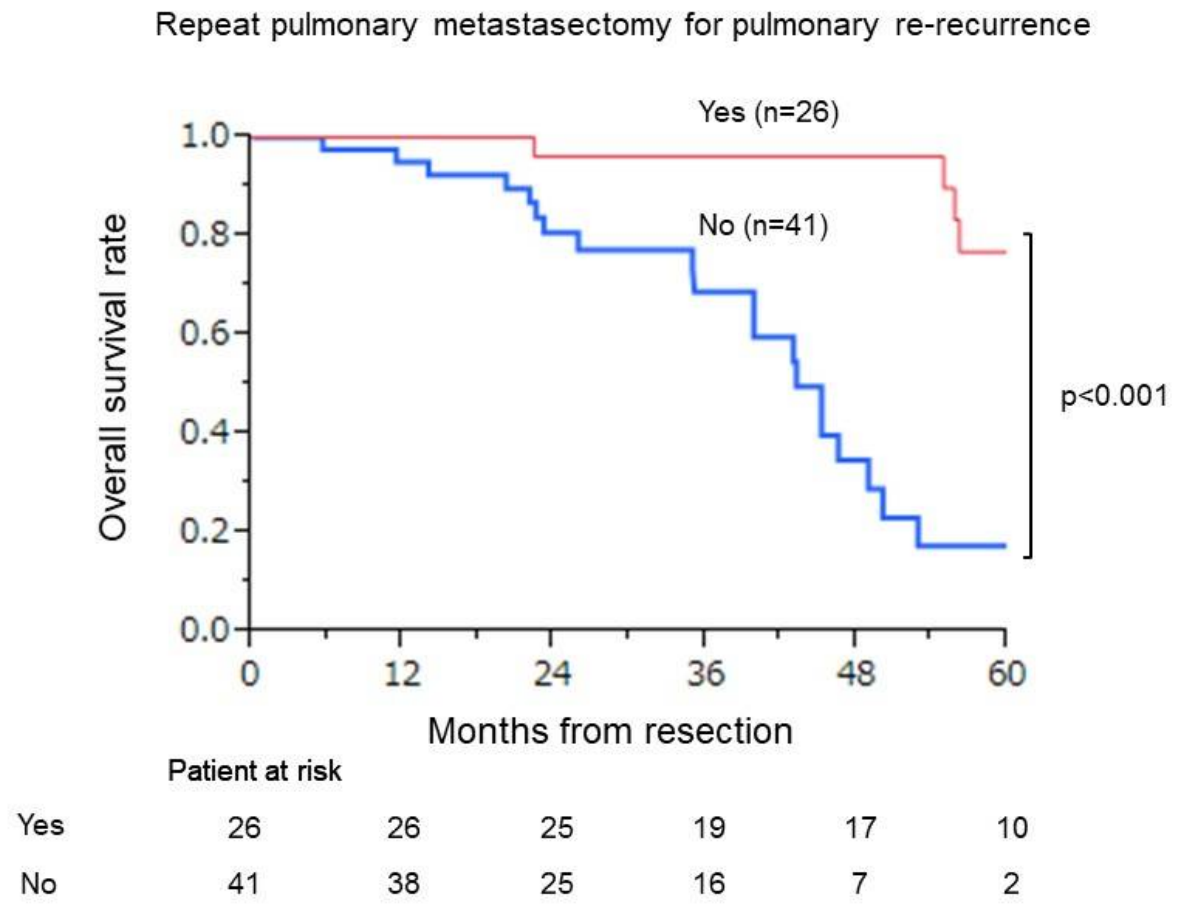

Fig.4

Figure 4

Repeat pulmonary metastasectomy for the pulmonary re-recurrence and survival.