Pulmonary metastasectomy for 165 patients with colorectal carcinoma: A prognostic assessment

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Objective: The purpose of this study was to analyze our entire experience with pulmonary resection for metastatic colorectal carcinoma to determine prognostic factors and critically evaluate the potential role of extended metastasectomy.

Methods: We analyzed the postoperative survival of 165 patients who underwent curative pulmonary surgery at eight institutions in the Kansai region of western Japan (Kansai Clinical Oncology Group) from 1990 to 2000.

Results: Overall survivals at 5 and 10 years were 39.6% and 37.2%, respectively. Cumulative survival of patients who underwent simultaneous bilateral metastasectomy was significantly lower than that of the patients who underwent unilateral metastasectomy or sequential bilateral metastasectomy ($P = .048$). Five-year survival was 53.6% for patients without hilar or mediastinal lymph node metastasis, versus 6.2% at 4 years for patients with metastases ($P < .001$). Five-year survival of patients with a prethoracotomy carcinoembryonic antigen level less than 10 ng/mL was 42.7%, versus 15.1% at 4 years for patients with a carcinoembryonic antigen level 10 ng/mL or greater ($P < .0001$). Twenty-one patients underwent a second or third thoracotomy for recurrent colorectal carcinoma. Overall 5-year survival from the date of the second thoracotomy was 52.1%. The 34.1% 10-year survival for the 26 patients with hepatic metastasis resected before thoracotomy did not differ significantly from that of patients without hepatic metastases ($P = .38$).

Conclusions: The status of the hilar or mediastinal lymph nodes and prethoracotomy carcinoembryonic antigen level were significant independent prognostic factors. Patients with pulmonary metastases potentially benefit from pulmonary metastasectomy even when there is a history of solitary liver metastasis. Careful follow-up is warranted, because patients with recurrent pulmonary metastases can undergo repeat thoracotomy with acceptable long-term survival. Simultaneous bilateral metastasectomy confers no survival benefit. Prospective studies may determine the significance of this type of pulmonary metastasectomy.

Pulmonary resection for metastatic colorectal carcinoma was first performed by Blalock¹ in 1944. In 1965, Thomford and coworkers² reported an experience with surgical resection of pulmonary metastases from various malignancies. They mentioned that surgical treatment might not be indicated in patients with metastasis in organs other than the lung such as the liver, or with simultaneous pulmonary metastases. They reported that indications for pulmonary metastasectomy include

control of the primary site, no other distant metastatic disease than the lung, a technically feasible operation, and adequate cardiopulmonary reserve of the patient. Since that time, however, extended pulmonary metastasectomy has become practical in patients with bilateral pulmonary metastases or with distant metastasis such as a solitary liver metastasis. The eligibility criteria for pulmonary metastasectomy proposed by Thomford have been extensively modified. Operative approaches have also changed to improve the resectability of pulmonary metastases, from unilateral thoracotomy to median sternotomy, transsternal bilateral thoracotomy ("clamshell" thoracotomy), and video-assisted thoracic surgery. More recently, an increasing number of patients undergo polysurgery (repeat thoracotomies). However, the potential role of extended metastasectomy has not been critically evaluated. The value of an aggressive surgical approach for the patients with bilateral lung metastases or with solitary liver metastases is controversial.

The purpose of this review was to analyze our entire experience with pulmonary resection for metastatic colorectal carcinoma in an attempt to answer the following questions: What are potential prognostic factors for patients undergoing pulmonary metastasectomy? Is there significant prognostic value in performing extended simultaneous pulmonary metastasectomy in patients with bilateral lung metastases? Is pulmonary metastasectomy indicated in patients who have localized extrapulmonary disease, such as solitary liver metastasis, if it has been resected or treated before thoracotomy? What is the role of repeat thoracotomy for recurrent metastatic colorectal carcinoma?

Patients and Methods

Between January 1, 1990, and December 31, 2000, a total of 165 patients underwent curative pulmonary resection for metastatic colorectal carcinoma at eight institutions in the Kansai region of western Japan (Kansai Clinical Oncology Group). Resection was considered curative if all known pulmonary nodules were removed at thoracotomy. Patients who had complete resection of all known pulmonary disease were included in this study. Patients who had pulmonary biopsy only were excluded. The record of each patient was reviewed for age and sex, disease-free interval, prethoracotomy serum carcinoembryonic antigen (CEA) level, number and maximum diameter of the nodules, operative procedures and extent of pulmonary resection, presence of hilar or mediastinal lymph node metastasis, number of pulmonary metastasectomy, and duration of survival. When multiple metastases were present, the largest diameter was recorded. Operative mortality included patients who died within the first 30 days after thoracotomy and those who died later but during the same hospitalization. Survival was calculated from the time of first metastasectomy to the last date follow-up. Statistical calculations were carried out with StatView software (SAS Institute, Inc, Cary, NC). The actuarial overall survivals were analyzed by the Kaplan-Meier method, and differences in their distributions were evaluated by the log-rank test. The

Cox proportional hazards models was used for multivariate analysis.

Results

There were 97 men and 68 women. Median age was 61.6 years (range 33-84 years). Thirty-seven patients (22.4%) were 70 years old or older. The primary colorectal neoplasm was a solitary adenocarcinoma in all patients and was located in the colon in 70 patients (42.4%) and in the rectum in 95 (57.6%). All patients were evaluated for local recurrence of the colorectal carcinoma. Barium enema, endoscopy, and abdominal computed tomography were the procedures most commonly used. Bone and brain scans were performed if there were clinical signs suggestive of metastases in these areas. The median interval between colorectal resection and lung resection was 28.4 months (range 0-111 months). Seventy-eight patients had a tumor-free interval of less than 2 years. Conventional chest computed tomography revealed a solitary pulmonary nodule in 104 patients (63.0%), multiple unilateral nodules in 37 (22.4%), and bilateral nodules in 24 (14.6%). The CEA level was measured in 108 patients and found to be elevated in 44.

All pulmonary resections were performed at a Kansai Clinical Oncology Group institution. Pulmonary resection followed colon resection in 163 patients; 2 patients, however, had initial lung resection that led to the subsequent diagnosis of a colorectal carcinoma. Lateral thoracotomy was performed in 147 patients, median sternotomy was performed in 17 patients, and clamshell thoracotomy was performed in patient. Six patients with simultaneous bilateral metastases underwent staged thoracotomies for bilateral pulmonary metastasectomy. Wedge resection was done in 103 patients. Thirty-seven patients underwent lobectomy, 4 underwent bilobectomy, 3 underwent pneumonectomy, and 18 underwent lobectomy combined with wedge excision. At the operation, pulmonary metastases were unilateral in 141 patients (79 right and 62 left) and bilateral in 24. A total of 104 patients had solitary metastases, 23 had two metastases, and 38 had three or more. Median diameter of the metastases was 25 mm (range 3-100 mm). Twenty-six patients had liver metastases, which were resected before pulmonary metastasectomy. Hilar or mediastinal lymph nodes were dissected or sampled in 138 patients (Table 1).

There were no postoperative deaths in our series. Metastatic colorectal carcinoma recurred in 102 patients (61.8%). Recurrence was limited to the lungs in 53 patients, the abdomen in 13, the brain in 7, the bone in 3, the mediastinal lymph node in 2, and to other locations in 3. Recurrence occurred in multiple organ systems in 21 patients, all of whom had lung involvement. Altogether, recurrence involved the lung in 74 patients (72.5% of those with recurrence). Sixty-one patients currently are alive. Deaths of the remaining 104 patients resulted from recurrent colorectal carcinoma in 102 cases and unknown causes in 2.

Figure 1. Pulmonary metastasectomy for colorectal carcinoma. Overall survival.

Mean follow-up was 56.5 months (range 5-135 months). Overall survivals at 5 and 10 years were 39.6% and 37.2%, respectively (Figure 1, Table 2). Survival was not influenced by age or sex. Likewise, 5-year survival for the 78 patients with a disease-free interval of less than 2 years was 35.1% and did not differ significantly from the 42.0% observed for the 87 patients with a tumor-free interval of greater than 2 years.

The size of the metastasis, when patients were divided into those with tumors less than 20 mm in maximum diameter and those with tumors 20 mm or more, was not associated with a statistical difference in 5-year survival. There was no significant difference in the survival of the lobectomy group (lobectomy and lobectomy with wedge resection) and limited resection group (segmental and wedge resection), with survivals of 22.2% and 47.6%, respectively, at 10 years ($P = .282$). However, the cumulative survival of patients who underwent simultaneous bilateral metastasectomy was significantly lower than that of patients who underwent unilateral metastasectomy or sequential bilateral metastasectomy ($P = .048$, Figure 2). Five-year survival was 42.6% for patients with solitary metastases, versus 35.7% for patients with two or more metastases ($P = .043$, Figure 3).

Hilar or mediastinal lymph nodes were dissected or sampled in 138 patients, revealing metastases in 20 patients. Five-year survival was 48.5% for the patients without hilar or mediastinal lymph node metastasis, versus 6.2% at 4 years for the patients with metastases ($P < .001$, Figure 4).

Five-year survival for the 81 patients with a prethoracotomy CEA level less than 10 ng/mL was 42.7%, versus 15.1% at 4 years for the 27 patients with a CEA level 10 ng/mL or greater ($P < .0001$, Figure 5). More important, all

TABLE 1. Patient features

Age (y, mean and range)	61.6 (33-84)
Sex	
Male	97
Female	68
Site of primary lesion	
Colon	70
Rectum	95
Disease-free interval (no.)	
0 mo	9
1-11 mo	25
12-23 mo	44
24-35 mo	40
≥ 36 mo	47
Pulmonary metastases (no.)	
1	104
2	23
≥ 3	38
Approach (no.)	
Unilateral	
Thoracotomy	124
Video-assisted thoracoscopic surgery	6
Bilateral	
Sequential thoracotomy	17
Simultaneous	
Sternotomy	17
Clamshell	1
Resection	
Wedge or segment	103 (86/17)
Lobe	59
Pneumonectomy	3
Diseased nodes	
N0	118
N1-2	20
Not sampled	27
Chemotherapy	
Postoperative	63
None	102
Operations (no.)	
1	142
2	19
3	4
Prethoracotomy CEA level	
Normal (≤ 5 ng/mL)	64
Abnormal (> 5 ng/mL)	44
Not measured	57

27 patients who had an elevated prethoracotomy CEA level had recurrence of colorectal carcinoma after thoracotomy. Only 4 patients survived for longer than 3 years.

The number of pulmonary metastases, mode of operation, lymph node metastasis, and serum CEA level influenced survival.

Twenty-three patients underwent a second or third thoracotomy for recurrent colorectal cancer (second 19 patients, third 4 patients). At the time of second thoracotomy, a wedge excision was performed in 18 patients and lobectomy was performed in 3. The median interval between the first and second pulmonary resections was 14 months (range

TABLE 2. Survivals and univariate analysis of prognostic factors of 165 patients undergoing pulmonary metastasectomy

Variables	Patients	5-y survival (%)	10-y survival (%)	P value
Overall	165	39.6	37.2	
Sex				
Male	97	45.5	42.3	.1900
Female	68	24.7	— (24.7% at 9-y)	
Age				
<50 y	24	22.2	— (22.2% at 6-y)	.4458
≥50 y	141	41.4	38.7	
Location of primary carcinoma				
Colon	70	34.5	— (34.5% at 8 y)	.6847
Rectum	95	42.4	38.6	
Disease free interval				
<24 mo	78	35.1	35.1	.5289
≥24 mo	87	42.0	— (37.8% at 9 y)	
Maximum tumor size				
< 20 mm	57	44.7	44.7	.5921
≥20 mm	108	38.3	35.6	
Pulmonary metastases				
Single	104	42.6	39.4	.0434
Multiple	61	35.7	— (35.7% at 7 y)	
Operative procedure				
Wedge or segmental	103	47.6	47.6	.2819
Lobectomy	59	27.8	22.2	
Pneumonectomy	3	33.3	— (33.3% at 6 y)	
Mode of operation				
Unilateral or sequential	147	41.6	39.0	.0483
Bilateral (simultaneous)	18	— (16.2% at 4 y)		
Operation				
Single	142	36.2	33.2	.3908
Repeat	23	54.6	54.6	
Prethoracotomy CEA				
<10 ng/mL	81	42.7	42.7	<.0001
≥10 ng/mL	27	— (15.1% at 4 y)		
Hilar or mediastinal lymph node metastases				
Negative	118	48.5	45.5	<.001
Positive	20	— (6.2% at 4 y)		
Postoperative chemotherapy				
Yes	63	34.1	34.1	.3376
No	102	43.5	38.6	
Hepatic metastases				
Resected before thoracotomy	26	34.1	34.1	.3846
None	139	40.6	37.5	

1-55 months). The median interval between the second and third pulmonary resections was 12 months (range 2-18 months). There were no major postoperative complications and no operative deaths. Five-year survival for all 23 patients from the date of the second thoracotomy was 52.1%. Eight patients (38.1%) were living without recurrence more than 3 years after the second lung resection. Four patients underwent a third pulmonary resection for recurrent carcinoma. One of them is alive 9 years after the third thoracotomy without evidence of carcinoma.

The presence of hepatic metastases was not an unfavorable prognostic factor. The 34.1% 10-year survival observed for the 26 patients with hepatic metastasis resected

before thoracotomy did not differ significantly from the 40.6% survival observed in the 139 patients without hepatic metastases ($P = .38$).

The potential prognostic factors were tested by univariate analysis (Table 2). Mode of operation, number of pulmonary metastases, prethoracotomy CEA level, and status of hilar or mediastinal lymph nodes were found to be significant prognostic factors. All the remaining factors listed in Table 1 were not prognostic factors. Table 2 shows the results of multivariate analysis. Status of hilar or mediastinal lymph nodes and prethoracotomy CEA level were the characteristics that retained significant independent prognostic impact (Table 3).

Figure 2. Pulmonary metastasectomy for colorectal carcinoma. Mode of operation and survival.

Figure 4. Pulmonary metastasectomy for colorectal carcinoma. Absence versus presence of metastasis and survival.

Figure 3. Pulmonary metastasectomy for colorectal carcinoma. Single versus multiple metastases and survival.

Figure 5. Pulmonary metastasectomy for colorectal carcinoma. CEA less than 10 ng/mL versus 10 ng/mL or more and survival.

Discussion

To date, no effective chemotherapeutic treatment is available for colorectal carcinoma metastatic to the lung. Consequently, resection of pulmonary metastases has been accepted as appropriate therapy by many surgeons.³

In our patients, there were no operative or postoperative deaths regardless of age. Therefore, age alone should not be a contraindication to resection.

Limited wedge excision remains our procedure of first choice for metastatic colorectal carcinoma. Mortality was zero after this procedure, and long-term survival was similar to that seen with more extensive resections of lung, such as lobectomy.

Median sternotomy is a convenient operative approach for patients with bilateral pulmonary lesions. However, a median sternotomy alone is not recommended in patients with simultaneous bilateral multiple pulmonary metastases, because the approach limits removal of all of the metastases. Remaining lesions after metastasectomy by median sternotomy, which we previously performed without endoscopic surgical assistance, could be one reason for the poor prognosis of patients with bilateral multiple metastases.

On the other hand, lateral thoracotomy, which we have done, places no limitation on removal of metastatic lesions because of sufficient operation area relative to that seen with median sternotomy. This also may be one reason why

TABLE 3. Multivariate prognostic factors analysis of the 165 patients according to Cox proportional hazards regression model

Variable	Hazard ratio	95% Confidence interval	P value
Mode of operation			
Unilateral or sequential	1	0.595-6.130	.2765
Bilateral (simultaneous)	1.910		
Pulmonary metastases			
Single	1	0.543-2.526	.6879
Multiple	1.171		
Hilar or mediastinal lymph node metastases			
Positive	1	0.142-0.875	.0246
Negative	0.352		
Prethoracotomy CEA			
<10 ng/mL	1	0.170-0.726	.0047
≥10 ng/mL	0.352		

patients who underwent simultaneous bilateral metastasectomy had significantly lower survival than did patients who underwent unilateral or sequentially bilateral thoracotomy. The survival of patients with bilateral multiple pulmonary metastases could be improved by detecting small metastatic foci before thoracotomy and completely removing all metastatic lesions at the time of operation. This could be achieved through overlapping image reconstruction with helical computed tomography and accurate video-assisted tumor resection with manual palpation of the entire lung, such as a transxiphoid approach.⁴

In our series, resecting pulmonary metastases was not worthwhile in patients who had hilar or mediastinal lymph node metastases. We understand that pulmonary metastasis with subsequent lymph node metastasis is part of the metastatic cascade.⁵ We have no evidence that hilar and mediastinal lymph node dissection can control disease. Evaluation and sampling of hilar and mediastinal lymph nodes are important for predicting the clinical course after thoracotomy and therefore should be attempted.⁶⁻⁸

Mediastinal or hilar lymph nodes were examined in 138 of our patients. The survival among patients with a lymph node metastasis was worse than among those without. A prospective study is required to investigate whether lymph node dissection improves the survival of patients with a pulmonary metastasis from colorectal carcinoma. However, the presence of lymph node metastasis might be a possible contraindication to surgical resection.⁷

An elevated CEA level greater than 10 ng/mL was a poor prognostic finding in our series. Preoperative CEA levels do appear to be a significant predictor of survival after resection of pulmonary metastases. Among our patients undergoing pulmonary metastasectomy, CEA levels correlated with recurrence and reduction in overall patient survival.⁷ Serum CEA level is an indication of the total tumor mass and the ability of tumor cell to express CEA.⁹ This antigen

is known to participate in intracellular recognition as well as to promote adhesion of tumor cells to host cells, which possibly explains the decreased survival.¹⁰

Traditional criteria for resection of colorectal pulmonary metastases include absence of extrapulmonary disease. However, in our series the presence of resectable metastatic colorectal carcinoma in the liver was not associated with a decreased survival; overall 5-year survival was identical to that of patients without liver metastasis. We advocate combined or staged surgical resection in carefully selected patients with solitary liver metastases before thoracotomy. Although Thomford and coworkers² excluded patients with extrapulmonary metastases as candidates for thoracotomy, there have been several reports about pulmonary resection for patients with extrapulmonary metastases. McAfee and colleagues¹¹ said that the presence of resectable extrapulmonary metastases before or at the time of thoracotomy was not associated with a decreased survival. Yano,¹² Regnard,⁹ Headrick,¹³ and their colleagues also reported that the presence of resectable or controllable hepatic metastases did not decrease survival. The 5-year survival for patients who underwent hepatic resection for metastases for colorectal cancer ranged from 25% to 47.9% in these reports. These results suggest that metastasectomy might be beneficial only when the metastasis is confined to the liver—the first filter for hematogenous metastases from the primary tumor—and may have no effect when secondary metastasis from the first filter organ occurs or when two filter organs, liver and lung, are affected by different pathways, the portal and systemic vein systems. In our series, the presence of hepatic metastases was not an unfavorable prognostic factor. Our 26 patients with a solitary liver metastasis had a 5-year survival of 34.1%. At present, it appears that patients with a solitary pulmonary metastasis potentially benefit from pulmonary resection even when there is a history of hepatic metastasis.

Several authors have advocated repeat thoracotomies for

recurrent pulmonary metastases.¹⁴ Our conclusion is similar. Survival among our patients who underwent a second thoracotomy was satisfactory. Importantly, patients undergoing repeat thoracotomy had no increase in either morbidity or mortality. Repeated metastasectomy for recurrent pulmonary metastasis may be considered in patients without a relapse in another site and with sufficient pulmonary function. We therefore offer at least one repeat thoracotomy to those selected patients who can tolerate further resection.

Conclusion

Pulmonary metastasectomy carries a potential survival benefit for patients with metastatic colorectal carcinoma. In our retrospective study, status of the hilar or mediastinal lymph nodes and prethoracotomy CEA level were significant independent prognostic factors. Patients with pulmonary metastases potentially benefit from pulmonary metastasectomy even when there is a history of solitary liver metastasis. Pulmonary metastasectomy is indicated for patients who have a solitary liver metastasis if the metastasis has been resected or treated before thoracotomy. Careful follow-up is warranted, because patients with recurrent pulmonary metastases can undergo repeat thoracotomy with acceptable long-term survival. Repeated metastasectomy may be considered in patients without a relapse at another site and sufficient pulmonary function. However, simultaneous bilateral metastasectomy has no survival benefit to the patient. Further prospective studies should be done to determine the significance of this type of pulmonary metastasectomy.

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