Original Article

Lung Metastasectomy for Colorectal Carcinoma in Patients with a History of Hepatic Metastasis

Fengshi Chen, MD, Tsuyoshi Shoji, MD, Hiroaki Sakai, MD, Ryo Miyahara, MD,
Toru Bando, MD, Kenichi Okubo, MD, and Hiroshi Date, MD

Background: We reviewed resection of pulmonary metastases preformed by the Department of Thoracic Surgery at Kyoto University Hospital to confirm the clinical significance of this surgery in patients with colorectal carcinoma and a history of hepatic metastasis.

Methods: From 1992 to 2006, 19 patients with colorectal carcinoma and a history of hepatic metastasis underwent a pulmonary metastasectomy . Surgical outcomes of these patients were investigated in terms of various perioperative variables.

Results: Sixteen of 19 patients showed metachronous presentation of hepatic and pulmonary metastases, while 3 patients showed synchronous presentation. Overall survival rate after the pulmonary resection was 93%, at 1 year; 75%, at 3 years and 60% at 5 years. Three years after the pulmonary resection, none of the patients with synchronous hepatic and pulmonary metastases survived, while patients with metachronous metastases had an overall survival rate of more than 80%. Interestingly enough, the overall survival curve of the patients with colorectal carcinoma and a history of hepatic metastasis, who underwent a pulmonary metastasectomy was almost the same as that of patients who did not have the surgery, during the same period.

Conclusion: Aggressive resection of pulmonary metastases in a select group of colorectal cancer patients with a history of liver metastases might result in prolonged survival.

Key words: colorectal carcinoma, liver, lung, metastasectomy

Introduction

Surgical resection has become the standard therapy for various metastatic malignancies to the lungs and has been consistently shown to prolong survival among patients with pulmonary metastases.[1, 2] Similar results have been obtained for lung metastases from colorectal carcinomas.[3–8] Most of the patients with resection of col-

orectal carcinoma are likely to have a recurrence, and the liver as well as the lungs are the most frequent sites for its recurrence.[9] Furthermore, around 10% of patients with colorectal carcinomas will have both liver and pulmonary metastases.[10] Although a large number of published case series have confirmed the effectiveness of surgical resection of lung metastases from colorectal carcinoma,[3–8] the management of patients with both hepatic and pulmonary metastases from colorectal carcinoma is far more controversial. Therefore, we reviewed the clinical data of patients with colorectal carcinoma and a history of hepatic metastasis, who underwent a pulmonary metastasectomy in the Department of Thoracic Surgery at Kyoto University Hospital to determine the long-term results and the prognostic predictors of survival in this subset of patients.

Patients and Methods

Study design

Between April 1992 and March 2006, according to our medical records, 75 patients had received curative pulmonary resection for the first time due to metastasis of colorectal carcinoma. Of 75 patients, 19 (25%) had a history of hepatic metastasis, while 56 (75%) did not.

Preoperative investigation

Detection of metastatic pulmonary nodules was made by x-radiography and computed tomography that was routinely examined at several monthly intervals, after the first diagnosis of the primary tumor. Tumor markers, such as carcinoembryonic antigen (CEA), were also used as a possible indicator of tumor recurrence. Further examinations were also performed to exclude extrapulmonary metastases. Preoperative pathologic diagnosis was not confirmed routinely, and pathologic diagnosis was done upon examination of a frozen section, intraoperatively. A definitive diagnosis was finally made after examination of a formalin-embedded specimen.

Selection criteria for pulmonary metastasectomy

All patients who underwent resection of their pulmonary metastases met the following criteria: (1) radiological examinations confirmed that pulmonary lesions were resectable (2) clinical condition of the patient was acceptable for surgery, (2) no distant metastases, except for pulmonary and hepatic lesions were observable, (3) both pulmonary and hepatic metastases could be removed completely, if present, and (4) locoregional control of the primary cancer was obtained or obtainable.

Surgical technique

Complete resection was defined as the absence of tumor cells at the surgical margin of the resected lung, examined macroscopically and histologically. All the visible and palpable nodules were resected during the surgery, and the histological examinationconfirmed the diagnosis of metastases. The surgical approach was chosen according to the location and number of pulmonary nodules. All surgical procedures were performed by open thoracotomy until 1997, while video-assisted thoracic surgery has been utilized since 1998. The detailed regimens of chemotherapy were different among patients and times; however, almost all the patients underwent preoperative and/or postoperative chemotherapy.

Data management

All patients were retrospectively analyzed for age, gender, location of primary tumors, metastasis at the time of primary tumor diagnosis, recurrence of primary tumor ahead of lung metastasis, CEA levels before pulmonary metastasectomy, number and location of pulmonary metastases, maximum tumor size, disease-free interval (DFI), types of surgical resection, and number of metastasectomy for pulmonary recurrence, regarding long term survival. DFI was defined as the duration from the resection of the primary tumor to the initial diagnosis of the metastatic pulmonary tumor. The endpoint was overall survival (OS) and disease-free survival (DFS) after the first pulmonary metastasectomy.

Statistical analysis

Statistical analysis was performed using the StatView (version 4.5) software package (Abacus Concepts, Berkeley, CA). The patient characteristics were analyzed with the Fisher's exact probability test. The postoperative survival rate was analyzed by the Kaplan-Meier method. The prognostic influence of variables on survival was analyzed using the Log-rank test for univariate analyses. Differences were considered significant when $P < 0.05$.

Results

Patient characteristics

From 1997 till 2006, 19 patients with a history of hepatic metastasis underwent a thoracotomy and resection for pulmonary metastasis from colorectal carcinoma. The patients were 5 males and 14 females with a median age of 63 years (range, 42 to 74 years, **Table 1**). In terms of metastasis at the time of primary tumor diagnosis, 5 of 7 patients showed liver metastases and the rest 2 patients presented liver and lung metastases. Furthermore, 2 of 7 patients who had liver metastasis at the time of colorectal carcinoma diagnosis, and who had a complete resection of both lesions developed liver metastasis again before the first pulmonary metastasectomy. As of recurrence of primary tumors ahead of lung metastases, 11 of 14 patients showed only liver metastases and the remaining 3 patients, presented with liver and locoregional metastases.

Liver metastasis

Sixteen of 19 patients showed a metachronous presentation of hepatic and pulmonary metastases, while the remaining 3 patients showed a synchronous presentation.

Table 1 Patient characteristics.

Age (years)		42-74
(mean)		(63)
Gender	Male	14
	Female	5
Location of primary tumors	Colon	10
	Rectum	9
Metastasis at the time of rimary tumor diagnosis	Yes	7
	No	12
Recurrence of primary tumor ahead of lung metastasis	Yes	14
	No	5
CEA levels before pulmonary metastasectomy	> 5 ng/ml	6
	≤ 5 ng/ml	13
Number of pulmonary metastases	1-4	14
	≥ 5	5
Location of metastases	Unilateral	13
Bilateral		6
Maximum tumor size of pulmonary metastases	≥ 3 cm	4
	< 3 cm	15
Disease-free interval (months)		0-84
(mean)		(32)
Surgical operation (First metastasectomy)	Wedge resection or segmentectomy	17
	Lobectomy	2
Number of meastasectomy for pulmonary recurrence	1	13
	≥2	6

Table 2 Sites for recurrence first. (n = 10)

Sites for recurrence	No. of cases
Lungs	8
Brain	1
Lymph nodes	0
Locoregional	1
Liver	0
Bone	0

In 16 patients with metachronous presentation, 7 patients showed simultaneous liver metastases at the time of detection of primary colorectal cancer. In 3 patients with a synchronous presentation, 2 patients showed simultaneous liver and lung metastases at the time of the detection of primary colorectal cancer, while 1 patient presented with simultaneous liver and lung metastases, one year after the curative resection of primary colorectal cancer. Eighteen of 19 patients underwent curative surgical resection for liver metastasis, and only one patient underwent a transarterial embolization instead of a surgical resection.

Surgical resection

Three of 6 patients with bilateral tumors underwent simultaneous bilateral thoracotomy, whereas we had planned and completed a staged bilateral thoracotomy for bilateral lesions in three patients. As for the number of surgeries, staged bilateral thoracotomies were counted as one operation. An attempt was made to conserve as much lung tissue as possible. This was reflected by the fact that wedge resections were the most common procedures performed. We preformed a lobectomy in only 2 of 19 patient. No patients died directly of surgery and all patients were discharged home after pulmonary metastasectomy.

Recurrent disease

Ten out of 19 patients had a recurrence after the first pulmonary metastasectomy. As shown in **Table 2**, most of the first recurrent sites after the pulmonary metastasectomy were in the lungs. There were no patients who developed liver metastasis first after the pulmonary resection. Repeat pulmonary resections were undertaken in 6 patients (**Table 1**).

Survival

Median follow-up time was 23 months. After the pulmonary resection, the OS rate was 93.3% at 1 year; 74.7% at three years; and 59.7% at 5 years (**Fig. 1**). In patients with metachronous liver and pulmonary metastases after the pulmonary resevtion, the OS rate was 92.3% at 1 year, 82.1% at 3 years, and 65.6% at 5 years. None of the patients with synchronous metastases had survived beyond 3 years ($P = 0.23$, **Fig. 2**). The DFS rate after the pulmonary resection was 75.5%, at 1 year, 18.9% at 3 years, and 18.9% at 5 years. There was no significant prognostic factor for a better OS or DFS (**Table 3**). When the group of patients with a history of hepatic metastasis was compared with those without a history (n = 56) in the same period, there was no significant difference in the OS curve between the two groups ($P = 0.95$, **Fig. 1**). Likewise, there was also no significant difference between the groups in terms of DFS ($P = 0.32$).
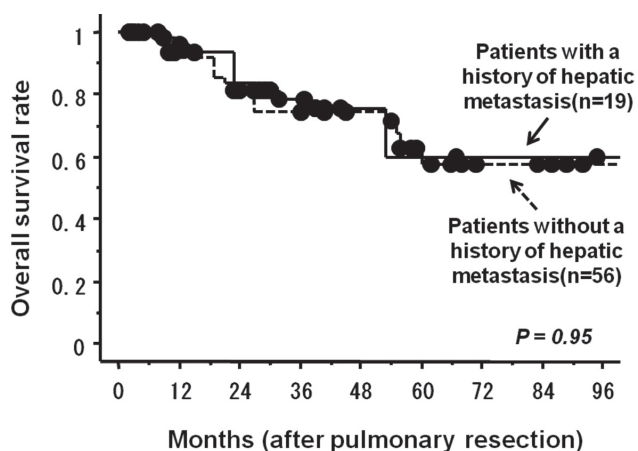
Fig. 1 Overall survival of patients after pulmonary resection with or without a history of hepatic metastases.
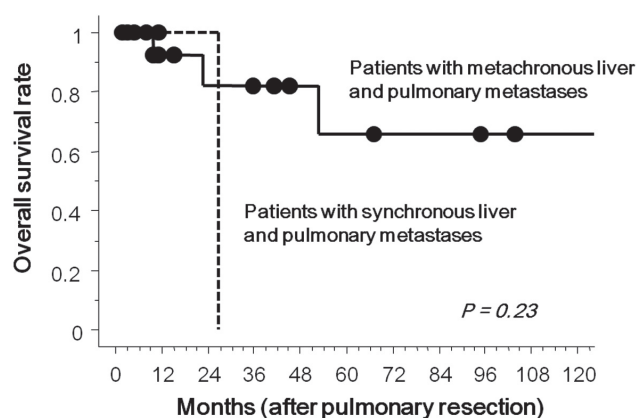
Fig. 2 Overall survival of patients with metachronous or synchronous liver and lung metastases.

Table 3 Univariate analysis for overall survival and disease-free survival.

Variables	Overall survival			Disease-free survival	
	Number of patients	5-Year OS (%)	*P* value	2-Year DFS (%)	*P* value
Age					
< 60y	6	37.5	0.66	50.0	0.58
≥ 60y	13	75.0		48.2	
Gender					
Male	5	66.7	0.85	30.0	0.13
Female	14	57.9		55.6	
Location of primary tumors					
Colon	10	75.0	0.59	25.0	0.26
Rectum	9	54.7		61.0	
Metastasis at the time of primary tumor diagnosis					
Yes	7	80.0	0.85	40.0	0.18
No	12	53.6		52.4	
Recurrence of primary tumor ahead of lung metastasis					
Yes	14	56.3	0.89	47.5	0.42
No	5	75.0		50.0	
CEA levels before pulmonary metastasectomy					
> 5 ng/ml	6	66.7	0.75	66.7	0.71
≤ 5 ng/ml	13	51.9		38.2	
Number of pulmonary metastases					
< 5	14	68.2	0.89	42.9	0.91
≥ 5	5	0		75.0	
Location of metastases					
Unilateral	13	68.2	0.89	42.9	0.91
Bilateral	6	0		75.0	
Maximum tumor size of pulmonary metastases					
≥ 3 cm	15	59.7	0.89	44.9	0.25
< 3 cm	4	50.0		50.0	
Disease-free interval					
< 3 y	13	36.0	0.37	41.6	0.16
≥ 3 y	6	80.0		60.0	
Surgical operation (First metastasectomy)					
Wedge resection or segmentectomy	17	53.8	-	41.1	-
Lobectomy	2	100		100	
Number of metastasectomy for pulmonary recurrence					
One	13	71.1	0.88		
≥2	6	40.0			

OS, overall survival; DFS, disease-free survival; CEA, carcinoembryonic antigen

Discussion

Pulmonary metastasectomy for colorectal carcinoma has become the standard therapy, although there are controversial studies that have examined prognostic factors for these pulmonary resections.[3–8] Colorectal cancer patients with untreated metastatic disease have a median survival of 6–9 months and a 5-year survival of less than 5%.[11, 12] Furthermore, median survival is at best between 16 and 20 months, even with the newer chemotherapies or biological agents.[12, 13] Thus, surgery still remains the mainstay in treatment for patients with resectable metastasis from colorectal carcinoma. The lungs and the liver are the most frequent sites for metastasis in colorectal carcinomas, and approximately 5% to 10% of patients with colorectal carcinomas will have both liver and pulmonary metastases.[10] This is why the management of patients with both hepatic and pulmonary metastases from colorectal carcinoma is definitely important. Therefore, we decided to report our experience with pulmonary metastasectomy in patients with colorectal carcinoma with a history of hepatic metastasis and to evaluate its role in their treatment focusing on OS and DFS.

The 5-year OS rate for patients who underwent a complete resection of pulmonary metastases for colorectal carcinomas was approximately 50%, ranging from 30%–60% in several reports.[3–8] By contrast, the 5-year OS rate for patients who underwent a combined hepatic and pulmonary metastasectomy for colorectal carcinoma reportedly seemed lower, varying from 11 to 52%.[14–19] In comparison with these previous reports, our outcomes of pulmonary metastasectomy for colorectal carcinomas appeared to be acceptable in terms of the OS rate. Furthermore, interestingly enough, the OS rate of pulmonary metastasectomy for colorectal carcinomas with a history of hepatic metastases was almost the same as that without a history of hepatic metastasis in the same period.

Patients with liver and lung metastasis are thought to have two metastasizing drainage routes, that is, through the portal venous system to the liver and through the systemic venous system to the lung. The spread of malignant cells through the two drainage routes to systemic organs is likely to make the disease more resistant to treatment and reduces survival, especially for the patients with synchronous metastasis. In our study, the OS and DFS were not affected by the existence of a history of hepatic metastasis. This could be understood when it might be considered that majority of the patients were metachronous liver and lung metastasis in this study since the spread of malignant cells through the two drainages at the same time, that is, simultaneous metastasis was considered an adverse prognostic factor.[20] Although there was no significant differences in the OS between the patients with metachronous liver and pulmonary metastases and those with synchronous metastases in our study ($P = 0.23$, **Fig. 2**), but this would probably be due to the small number of cases in the group of synchronous metastases. In fact, there were no patients with synchronous metastases who survived more than 3 years, while the OS rate in patients with metachronous liver and pulmonary metastases was more than 80% at 3 years after the pulmonary resection. Our results also imply that aggressive treatment is recommended for patients with metachronous liver and pulmonary metastases.

To date, several parameters, such as stage of the primary tumor,[6, 8] DFI,[4] CEA levels,[4] vascular invasion of the metastatic lesion,[5] and number of lesions[7] have been reported as prognostic factors for pulmonary metastasectomy of colorectal carcinoma. In the current study, we did not find any prognostic factors for pulmonary metastasectomy in the patients with a history of liver metastases. It is difficult to interpret the results of this study, but it might be mainly related with the patient numbers inthe subgroup, and further studies would also be necessary.

There are several limitations to this study. Firstly, this study dealt with a select group of patients with metastatic colorectal carcinoma, who were considered for pulmonary metastasectomy after liver metastases from their well-controlled original diseases. Secondly, the retrospective design is the most practical way of addressing our question, but the results should be interpreted with caution. Last but not least, chemotherapeutic regimens and surgical strategies have evolved substantially and rapidly over the last decade and continue to be highly individualized. In this study, we did not analyze the patients in this respect, but preoperative and/or postoperative chemotherapy might have some influence on our results. In the near future, prospective study would be necessary in terms of a combination of metastasectomy and adjuvant chemotherapy for several subsets of patients with pulmonary and liver metastases from colorectal carcinoma.

Conclusions

Our study demonstrated that overall survival after pulmonary metastasectomy for colorectal carcinoma

with a history of hepatic metastasis was as we had expected. Resection of pulmonary colorectal metastases might improve survival in selected patients who underwent hepatic resection for colorectal liver metastases at an earlier stage.

References

1) Pastorino U. History of the surgical management of pulmonary metastases and development of the international registry. Semin Thorac Cardiovasc Surg 2002; **14**: 18–28.

2) Sternberg DI, Sonett JR. Surgical therapy of lung metastases. Semin Oncol 2007; **34**: 186–96.

3) Chen F, Hanaoka N, Sato K, Fujinaga T, Sonobe M, et al. Prognostic factors of pulmonary metastasectomy for colorectal carcinomas. World J Surg 2009; **33**: 505–11.

4) Rena O, Casaido C, Viano F, Cristofori R, Ruffini E, et al. Pulmonary resection for metastases from colorectal cancers: factors influencing prognosis. Twenty-year experience. Eur J Cardiothoracic Surg 2002; **21**: 906–12.

5) Shiono S, Ishii G, Nagai K, Yoshida J, Nishimura M, et al. Histopathologic prognostic factors in resected colorectal lung metastases. Ann Thorac Surg 2005; **79**: 278–83.

6) Melloni G, Doglioni C, Bandiera A, Carretta A, Ciriaco P, et al. Prognostic factors and analysis of microsatellite instability in resected pulmonary metastases from colorectal carcinoma. Ann Thorac Surg 2006; **81**: 2008–13.

7) Watanabe I, Arai T, Ono M, Sugito M, Kawashima K, et al. Prognostic factors in resection of pulmonary metastasis from colorectal cancer. Br J Surg 2003; **90**: 1436–40.

8) Inoue M, Ohta M, Iuchi K, Matsumura A, Ideguchi K, et al. Benefits of surgery for patients with pulmonary metastases from colorectal carcinoma. Ann Thorac Surg 2004; **78**: 238–44.

9) Galandiuk S, Wieand HS, Moertel CG, Cha SS, Fitzgibbons RJJ, et al. Pattern of recurrence after curative resection of carcinoma of the colon and rectum. Surg Gynecol Obstet 1992; **174**: 27–32.

10) Pihl E, Hughes ES, McDermott FT, Johnson WR, Katrivessis H. Lung recurrence after curative surgery for colorectal cancer. Dis Colon Rectum 1987; **30**: 417–9.

11) Simmonds PC. Palliative chemotherapy for advanced colorectal cancer: systemic review and meta-analysis. Colorectal Cancer Collaborative Group. BMJ 2000; **321**: 531–5.

12) Porschen R, Arkenau H, Kubicka S, Greil R, Seufferlein T, et al. Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: a final report of the AIO colorectal study group. J Clin Oncol 2007; **25**: 4217–23.

13) Diaz-Rubio E, Tabernero J, Gomez-Espana A, Massuti B, Sastre J, et al. Phase III study of capecitabine plus oxaliplatin compared with continuous-infusion fluorouracil and leucovorin plus oxaliplatin as first-line therapy in metastatic colorectal cancer: final report of the Spanish cooperative group for the treatment of digestive tumors trial . J Clin Oncol 2007; **25**: 4224–30.

14) Headrick JR, Miller DL, Nagorney DM, Allen MS, Deschamps C, et al. Surgical treatment of hepatic and pulmonary metastases from colon cancer. Ann Thorac Surg 2001; **71**: 975–9.

15) Elias D, Ouellet J-F, Bellon N, Pignon JP, Pocard M, et al. Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. Br J Surg 2003; **90**: 567–74.

16) Regnard J-F, Grunenwald D, Spaggiari L, Girard P, Elias D, et al. Surgical treatment of hepatic and pulmonary metastases from colorectal cancer. Ann Thorac Surg 1998; **66**: 214–8.

17) Okumura S, Kondo H, Tsuboi M, Nakayama H, Asamura H, et al. Pulmonary resection for metastatic colorectal cancer: experiences with 159 patients. J Thorac cardiovasc Surg 1996; **112**: 867–74.

18) Murata S, Moriya Y, Akasu T, Fujita S, Sugihara K. Resection of both hepatic and pulmonary metastases in patients with colorectal carcinoma. Cancer 1998; **83**: 1086–93.

19) Smith JW, Fortner JG, Burt M. Resection of hepatic and pulmonary metastases from colorectal cancer. Surg Oncol 1992; **1**: 399–404.

20) Nagakura S, Shirai Y, Yamato Y, Yokoyama N, Suda T, et al. Simultaneous detection of colorectal carcinoma liver and lung metastases does not warrant resection. J Am Coll Surg 2001; **193**: 153–60.