

Surgical Resection for Lung Metastases from Colorectal Cancer

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Purpose: The lung is the second most common site of metastasis from colorectal cancer. Of all patients who undergo a curative resection for colorectal cancer, 10% to 15% will develop lung metastasis. As a hepatic resection of colorectal liver metastases results in improved survival, many reports have suggested that a pulmonary resection of a colorectal lung metastasis would also improve survival. The aim of this study was to analyze the postoperative outcomes of and the prognostic factors for a surgical resection of a lung metastasis.

Methods: Between August 1997 and March 2006, 27 patients underwent surgical resections for colorectal lung metastases at Seoul St. Mary's hospital. A retrospective review of patients' characteristics and various tumor factors was performed.

Results: The mean interval between colorectal resection and lung metastasis was 24.0 ± 15.1 months. The overall 3- and 5-year survival rates were 76.5% and 22.2%, respectively. The mean follow-up after pulmonary resection was 39.5 ± 21.6 months (range, 3.3 to 115 months). Except for the existence of hilar-lymph-node metastasis ($P < 0.001$), no risk factors that we studied were statistically significant. Two patients had hilar-lymph-node metastasis. They survived for only for 3.3- and 11.6-months, respectively.

Conclusion: In our study, we found that a pulmonary resection for metastases from colorectal cancer may improve survival in selected patients.

Keywords: Colorectal neoplasms; Neoplasm metastasis; Lung

INTRODUCTION

Colorectal cancer is one of cancers whose incidence is most rapidly increasing in Korea. With the increasing incidence of colorectal cancer, the number of patients with distant metastasis is also increasing, and for this, various treatment methods have been introduced, and treatment protocols have been changed [1]. Among the distant metastases, hepatic metastasis is presently the representative distant metastasis of colorectal cancer, and numerous studies have reported that surgical re-

section contributes to improving the survival rate of the patients [2, 3]. The lung is the most frequent extraperitoneal metastatic site, and lung metastasis has been shown to develop in approximately 10% of the patients who undergo a curative resection for colorectal cancer [4]. Since most lung metastases are in a disseminated state at the time of diagnosis, cases for which a curative resection is indicated are rare, so most cases are treated by using conservative treatment or chemotherapy, which have been shown to be only limited help to patients [1]. Nevertheless, since Blalock reported a surgical resection for lung metastasis from colorectal cancer for the first time in 1944, surgical resection of lung metastasis has been performed for selected cases, and the 5-year survival rate after surgical resection of lung metastasis has been reported to range from 9% to 60%, depending on the investigator [1-6]. Therefore, in our study, among patients who underwent a curative resection for colorectal cancer, the outcomes of the surgical resection of lung metastasis and the prognostic factors affecting the survival rate were examined.

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METHODS

One thousand two-hundred sixty-nine patients underwent surgery for colorectal cancer from August 1997 to March 2006 at Seoul St. Mary's Hospital, The Catholic University of Korea, and lung metastasis was diagnosed in 259 cases. Surgical resection for lung metastasis was performed on 29 patients. Excluding 2 patients without sufficient data, the medical records of the remaining 27 patients (10.4%) were examined retrospectively. Studies were conducted only on patients without other distant metastases and with metastases limited to the lung at the time of the detection of the lung metastasis, as confirmed by comprehensive preoperative evaluations. Factors affecting the survival rate were analyzed by examining age, gender, the site of the primary tumor, the disease stage, the interval from radical resection for colorectal cancer to the detection of lung metastasis, the carcinoembryonic antigen (CEA) value at the time of the detection of lung metastasis, the number of lung metastasis lesions, the size of the largest lesion, the surgical method for removing the lung metastasis, and the presence or absence of hilar-lymph-node metastasis. Based on the time of the detection of lung metastasis, we performed a Kaplan-Meier survival analysis, and the survival rates were compared by using the log-rank test; P-values less than 0.05 were considered to be significant.

RESULTS

A comparative analysis of the clinical features and the prognostic factors for the 27 patients who underwent a surgical resection for lung metastasis is shown in Table 1. The mean age at the time of the detection of lung metastasis was 61.0 years (range, 42 to 81 years), and regarding gender, 15 patients were males and 12 patients were females. Concerning primary cancer, tumour node metastasis (TNM) stage II was observed in 12 cases, stage III in 9 cases, and stage IV in 3 cases; the three patients with stage IV cancer had simultaneous lung metastasis. As the site of colorectal cancer, rectal cancer was observed in 19 cases and colon cancer in 8 cases. Concerning surgery for colorectal cancer, a low anterior resection was performed in 13 cases, an abdominoperineal resection in 5 cases, an anterior resection in 3 cases, a right colectomy in 3 cases, and a Hartmann's procedure in 2 cases. The mean interval from surgery for colorectal cancer to the detection of lung metastasis was 24.0 ± 15.1 months. The mean follow-up period was 39.5 ± 21.6 months (range, 3.3 to 115 months). The 3-year survival rate and the 5-year survival rate for all entire patients were 76.5% and 22.2%, respectively, and the mean survival period was 55.7 ± 8.1 months (Fig. 1). The average size of the lung metastasis lesions was 2.3 ± 1.6 cm. In regard to their numbers, a single metastasis was noted in 12 cases and multiple metastases were noted in 15 cases, 7 of those being bilateral. In re-

gard to surgery, a wedge resection was performed in 21 cases, and a segmentectomy or a lobectomy was performed in 6 cases. No deaths related to lung resection were noted, and all patients

Table 1. Characteristics of the primary cancer and pulmonary metastasis

Variables	No. (%)	Mean survival (mo)	P-value
Sex			0.811
Male	15 (56)	45.5 ± 3.3	
Female	12 (44)	55.2 ± 12.9	
Tumor location			0.597
Colon	8 (30)	40.2 ± 7.9	
Rectum	19 (70)	60.1 ± 9.9	
Initial stage			0.524
II	12 (44)	50.8 ± 2.9	
III	8 (30)	55.4 ± 15.0	
IV	3 (11)	33.2 ± 8.8	
Adjuvant chemotherapy			0.791
No	1 (3.7)	59.3	
Yes	21 (77.7)	59.3 ± 9.7	
Disease free interval ^a			0.735
Synchronous	3 (11)	33.2 ± 8.8	
Within 24 mo	10 (37)	56.0 ± 10.8	
After 24 mo	14 (52)	40.5 ± 4.1	
Carcinoembryonic antigen (preop.)			0.624
< 5	19 (70)	56.2 ± 8.9	
> 5	7 (26)	37.1 ± 8.0	
Number of metastases			0.876
Solitary	12 (44)	57.2 ± 12.6	
Multiple	15 (56)	44.0 ± 3.5	
Unilateral vs. Bilateral			0.993
Unilateral	20 (74)	54.3 ± 9.4	
Bilateral	7 (26)	45.7 ± 4.5	
Largest diameter of metastases			0.261
Less than 2 cm	17 (63)	40.9 ± 4.4	
Larger than 2 cm	10 (37)	69.2 ± 14.7	
Type of surgery			0.514
Wedge resection	21 (78)	54.1 ± 8.3	
Segmentectomy or lobectomy	6 (22)	40.2 ± 3.5	
Hilar-lymph-node			<0.001
Positive	2 (7)	7.5 ± 4.2	
Negative	25 (93)	59.5 ± 8.3	
Resection margin			0.804
Positive	3 (11)	43.5 ± 2.5	
Negative	24 (89)	55.2 ± 8.4	
Chemotherapy ^b			0.836
No	2 (11.1)	49.7 ± 9.7	
Yes	23 (85.2)	60.1 ± 10.5	

^aFrom colorectal cancer surgery to lung metastasis; ^bChemotherapy after lung resection.

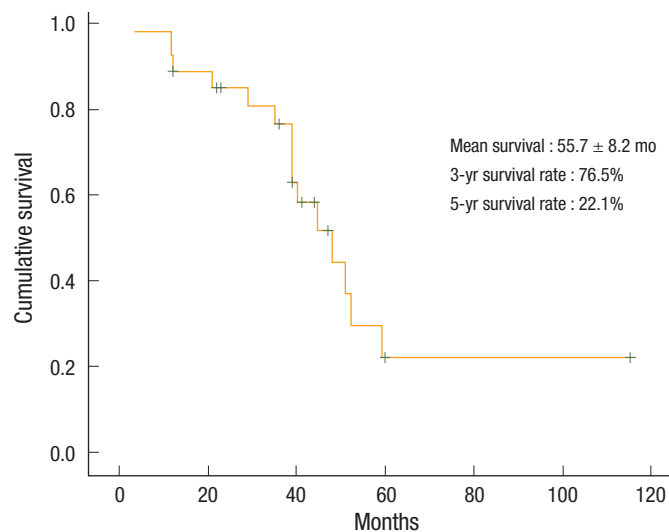


Fig. 1. Overall survival of patients who underwent a pulmonary resection for colorectal lung metastasis.

Table 2. Recurrence after a metastasectomy for colorectal lung metastases

Recurrence site	No. (%)
Lung	8 (57)
Bone	2 (14)
Brain	1 (7)
Chest wall	2 (14)
Cervical lymph nodes	1 (7)
Intraabdominal lymph nodes	2 (14)

recovered without special complications. Hilar-lymph-node metastasis was diagnosed in 2 cases, and the patients died after 3.3 months and 11.6 months, respectively. As chemotherapy after pulmonary resections, the FOLFOX regimen was administered in 13 cases, the FOLFIRI regimen was administered in 3 cases, 5-FU/leucovorin was administered in 4 cases, capecitabine was administered in 3 cases, and no chemotherapy was administered in 2 cases. Recurrence was noted in 14 cases during the follow-up observation period, and recurrence in the lung, 8 cases, was most prevalent. Among those 8, a re-resection was performed in 6 cases, and the remaining 2 patients were treated with chemotherapy. Other distant metastases were brain metastasis, bone metastasis, etc. (Table 2).

In our study, when a surgical resection was performed for lung metastasis, depending on the presence or absence of hilar-lymph-node metastasis, a significant difference in survival was shown ($P < 0.001$) (Fig. 2). No differences in survival due to other factors such as age, gender, the location of the primary tumor, the disease stage, the interval from resection of colorectal cancer to the detection of lung metastasis, the CEA value

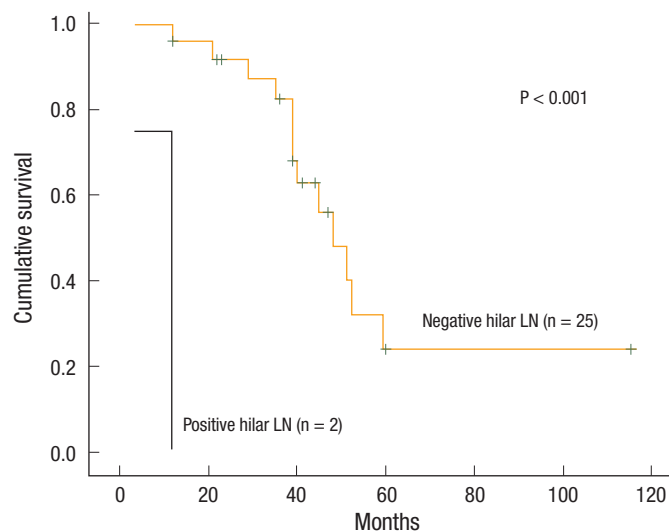


Fig. 2. Cumulative survivals for positive and negative hilar-lymph-node (LN) metastases.

at the time of the detection of lung metastasis, the number of metastasis lesions, the size of the largest metastasis lesion, the surgical method used to treat the lung metastasis, and the presence or absence of residual cancer on the lung resection surface were observed (Table 1). In the multivariate analysis, the presence or absence of hilar-lymph-node metastasis was the only significant prognostic factor ($P = 0.007$).

DISCUSSION

In the past, lung metastasis of colorectal cancer was considered to be a disseminated disease and thus incurable, and chemotherapy and conservative treatments were considered to be major treatment options [1]. Nevertheless, recently, surgical resection for metastatic lesions has been reported to prolong survival; thus, surgical treatment for lung metastasis that developed after a curative resection of colorectal cancer has been used widely, and numerous studies on treatment methods after metastasis and on prognostic factors have been conducted [1, 2, 4-6]. In studies reported recently, the 5-year survival rate after a pulmonary resection varies from 9 to 60%, but this is noticeably better than the approximately 5% survival rate in patients without treatment after lung metastasis, and in most studies, postsurgical complications or death was infrequent. Thus, a pulmonary resection is accepted as a safe and effective treatment method [5].

Generally accepted indications of surgery for metastatic lung lesions is 1) a complete resection of primary cancer can be performed, 2) distant metastases other than lung metastasis are absent, 3) metastatic lung lesions can be completely resected, and 4) the patient should be able to withstand surgery [7]. Nevertheless, recently, with efforts to improve pulmonary resec-

tion techniques and to perform more aggressive treatments, the indications of pulmonary resection have been expanded in some cases. Indeed, in some cases, at the time of the detection of lung metastasis of colorectal cancer, metastases to other organs such as the liver have been present. MacAfee et al. [8] reported that a liver metastasis detected prior to surgery for lung metastasis was not a contraindication provided a curative liver resection was performed. In addition, pulmonary resections, which were applied to solitary lesions during the early period of performing pulmonary resections, have recently been applied to cases with bilateral lung metastasis provided a complete resection was possible, and good results were obtained [9-11]. In our study, a pulmonary resection was performed in 15 cases involving multiple metastatic lesions of which 7 involved bilateral metastasis. For cases with multiple lesions, as well as cases with bilateral metastasis, surgical resections of all lesions were performed, and the patients recovered without special complications. In the statistical analysis, the survival rates were not significantly different when surgical resection for solitary lesions and surgical resection for lesions restricted to one side were compared.

Several studies analyzed prognostic factors affecting survival after a pulmonary resection. They reported serum CEA levels immediately prior to surgical treatment for lung metastasis lesions, the interval from radical resection for colorectal cancer to the diagnosis of lung metastasis lesions, and the presence or absence of previously-mentioned multiple lung lesions as prognostic factors [1, 7, 9, 11-13]. The serum CEA level is an index showing the size of the entire tumor, and it has been considered to be an index representing the ability of tumor cells to express serum CEA [14]. In addition, CEA itself has been shown to attach to cells and, thus, to be involved in the adhesion of tumor cells to host cells [15]. Hence, in patients whose serum CEA value is elevated higher than normal, the survival rate after surgical resection for metastatic lung lesions has been predicted to be poor. Nevertheless, even if the serum CEA value is elevated, the survival after surgical resection of metastatic lesions is better than it is in the untreated group; thus, an elevated serum CEA level should not be a contraindication of surgical treatment [8, 10]. Particularly, in cases with multiple metastases or bilateral metastases, if the serum CEA value is elevated during tests on patients on whom a pulmonary resection is to be performed, special attentions should be paid and a comprehensive examinations of organs other than the lung and of the surgical area for colorectal cancer should be performed. In our study, when cases with elevated preoperative serum CEA were compared with normal cases, survival rates were not significantly different. In addition, in cases with multiple metastases, the serum CEA value was shown to be significantly elevated ($P = 0.03$); nonetheless, that did not affect the survival rates, which is thought to be related to the fact that our study was conducted on a limited number of pa-

tients, so studies conducted on more patients are required.

Concerning whether the interval from curative treatment for primary cancer to the development of lung metastasis could be a prognostic factor, it varied with the report. A multicenter study on pulmonary resection for metastatic lung cancer in 5,206 patients reported that the time to the development of lung metastasis might be a factor, together with whether the metastatic lesions had been completely resected or not and the number of metastatic lesions, that could be used to determine a prognosis for patients [11]. In the study reported by Rena et al. [9], the disease-free period was divided into three periods, 0-11 months, 12-35 months, and longer than 36 months, and the survival rates after a pulmonary resection were compared. They reported that as the disease-free period became shorter, a worse prognosis was shown. However, other studies reported that the disease-free period did not have a significant effect on survival. Thus, this issue is still unresolved. In our study, similarly, the time to develop lung metastasis was shown not affect the survival rate of patients after a pulmonary resection. This variation of the disease-free period from one study to another is thought to be due to the differences in the detection times of lung metastasis for various follow-up schedules and methods [16]. If such differences are to be reduced, multicenter studies according to standard treatment guidelines are required. At our hospital, for the detection of lung metastasis after surgery for colorectal cancer, chest X-rays and serum CEA tests are performed every three months for the first 2 years after surgery, then at 6-months intervals for the next three years, and then annually after 5 years. If abnormal findings are detected, additional comprehensive tests, such as CT and PET-CT, were performed. Although some studies have reported that, together with the above prognostic factors, disease stage, the location of primary cancer, and the size of metastatic lesions are valuable as factors that can be used to provide prognosis after a pulmonary resection, in our study, theirs other factors had no statistical significance.

In our study, two patients had hilar-lymph-node metastasis, and the patients died 3.3 months and 11.3 months, respectively, after the pulmonary resection. Since the number of patients was small, it is difficult to consider this result to be statistically significant; nonetheless, hilar-lymph-node metastasis may imply a disease with advanced state and should be considered as a poor prognostic factor. Okumura et al. [17] reported that in 100 patients with lung metastasis of colorectal cancer, hilar-lymph-node metastasis was detected in 15 patients, their 5-year survival rate being 6.7%; a hilar lymphadenectomy did not improve the prognosis. Inoue et al. [18] reported, in a study conducted on 25 patients with lung metastasis, that the 5-year survival rate of patients with hilar-lymph-node metastasis was 14.3%, which was significantly lower than the 49.5% 5-year survival rate of patients without hilar-lymph-node metastasis. Nonetheless, Goya et al. [19] reported, in a study conducted

on 62 patients that the 5-year survival rate of all patients was 42%, and the presence or absence of hilar-lymph-node metastasis did not significantly affect the survival rate of patients after a pulmonary resection for metastatic lung lesions. In cases with metastatic tumors smaller than 3 cm, lymph node metastasis was reported to have been detected only in 8% of the cases whereas in cases with metastatic tumors larger than 3.1 cm, lymph node metastasis was detected in approximately 50% of the patients [1]. Thus one can conclude that as the size of the tumor becomes larger, the possibility of hilar-lymph-node metastasis becomes higher, and the possibility of complete resection is lower. Hence, a large metastatic tumor may indicate poor survival. In fact, hilar-lymph-node metastasis is considered to be a series of processes through which metastatic lung cancer becomes systemic cancer [6]. In such a manner, hilar-lymph-node metastasis may imply disseminated metastasis; thus, attention should be paid to the selection of surgical treatment. In addition, when surgery is selected as the method of treatment, whether or not a broad lymphadenectomy should be performed must be addressed. Based on such results, when a surgical resection for lung metastasis of colorectal cancer is performed, if hilar-lymph-node metastasis is suspected based on preoperative evaluations, comprehensive tests assessing the presence of metastasis in other organs are thought to be required. If surgery is performed, studies on the variation in the outcomes according to the surgical method used for treatment should be conducted, and studies on the necessity of additional treatments, such as postoperative chemotherapy or radiation therapy, should be conducted in parallel.

If a pulmonary resection is selectively performed on patients with lung metastasis after a curative resection of colorectal cancer, the survival rate may be improved. Nonetheless, a pulmonary resection probably will not improve the survival rate of patients with hilar-lymph-node metastasis identified by tests performed prior to the pulmonary resection. In addition, analyses of the effects of pulmonary resection on and of the prognostic factors for lung metastasis patients are thought to be required.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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