PULMONARY RESECTION FOR METASTATIC COLORECTAL CANCER: EXPERIENCES WITH 159 PATIENTS

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We reviewed the clinical courses of 159 patients between February 1967 and May 1995 for the purpose of examining the survival of patients who had pulmonary resection for metastatic colorectal cancer. The cumulative survivals at 5 years and 10 years were 40.5% and 27.7%, respectively. Fifteen patients (10%) were alive more than 10 years after the thoracotomy without any evidence of recurrence. The cumulative survival at 5 years for 39 patients who had hepatic metastases before thoracotomy was 33%. There was a statistically significant difference in survival between patients with extrapulmonary metastases and those with only intrapulmonary metastases before thoracotomy. The number of pulmonary metastases and the presence of hilar or mediastinal lymph node metastases affected postthoracotomy survival. There was no significant difference in survival on the basis of sex, age, location of the primary cancer, size of the pulmonary tumors, mode of operation, or disease-free interval. Surgical treatment for pulmonary metastases from colorectal cancer in selected patients, even those who had hepatic metastases before thoracotomy, might improve prognosis. (*J Thorac Cardiovasc Surg* 1996;112:867-74)

Surgical therapy has been attempted for metastatic lung tumors since Thomford, Woolner, and Clagett¹ published the principles for surgical treatment of metastatic lung tumors in 1965. As for resection of pulmonary metastases from colorectal cancer, documented 5-year survivals after resection of pulmonary metastases varied among institutions, ranging from 22% to 42%.²⁻¹⁰ We⁷ also reported our experience with 62 patients who underwent resection of pulmonary metastases from colorectal cancer in 1988. In that series, we could not show that surgical resection of pulmonary metastases improved the cure rate. Furthermore, the significance of pulmonary metastatectomy for patients who had hepatic metastases before thoracotomy was unknown. In the present series, the clinical courses of 159 patients were reviewed and followed for a much longer time. In addition, this study included 39

patients who had hepatic metastases before thoracotomy. Therefore we believe it is possible to examine the significance of pulmonary resection for metastatic colorectal cancer more accurately than in our previous report.

Patients and methods

A total of 162 patients underwent pulmonary resection for metastatic lesions from colorectal cancer between February 1967 and May 1995 in the National Cancer Center Hospital in Japan. There were three hospital deaths within 30 days of the operation, and 159 patients were available for review in this study. Criteria for resection of pulmonary metastases were as follows: (1) The patient must be able to tolerate the required surgical procedure and the remaining respiratory function is considered to be good enough for ordinary life. (2) Unilateral or bilateral lung lesions can be seen on a chest roentgenogram or a computed tomographic scan and those lesions presumably could be completely resected. (3) There are no distant metastases without pulmonary lesions and there was no evidence of local recurrence of the primary cancer. (4) It is possible to completely remove both hepatic and pulmonary metastases, if present.

Table I summarizes the characteristics of the 159 patients. We divided the patients into three groups. Group A consisted of 111 patients who had no extrapulmonary metastatic lesions before thoracotomy. Group B included 39 patients who had hepatic metastases before or at the time of thoracotomy. Ten patients who underwent simultaneous resection of pulmonary and hepatic metastases were included in group B. Group C was composed of nine

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Table I. Characteristics of 159 patients who underwent resection of pulmonary metastases from colorectal cancer

	No. of patients
Sex	
Male	95
Female	64
Age (yr)	
Average	58.7
Range	28-82
Location of primary cancer	
Colon	82
Ascending	19
Transverse	4
Descending	4
Sigmoid	55
Rectum	73
Unknown	4
Grade of primary tumor	
Dukes' A	11
Dukes' B	30
Dukes' C	64
Unknown	54
No. of Pulmonary metastases	
Solitary	107
Multiple	52
Site of metastases before thoracotomy	
No metastases (group A)	111
Liver (group B)	39
Local (group C)	9
Location of pulmonary metastases	
Left lung	65
Right lung	62
Both	32
Mode of operation	
Pneumonectomy	7
Lobectomy	85
Wedge or segmental resection	67

patients who had undergone resection of local recurrence before thoracotomy (Table I).

The medical charts were examined for age; sex; stage and grade of the primary cancer; location, number, and size of the pulmonary metastases; mode of the operation (Table I). Also evaluated were the presence of hepatic metastasis or local recurrence (or both) and disease-free interval (DFI) between resection of the primary lesion and clinical detection of pulmonary metastases. The survival after thoracotomy was estimated by the method of Kaplan and Meier.¹¹ The significance of each prognostic factor was determined by the log-rank test.¹²

Results

Five of the 159 patients (3.1%) underwent incomplete resection for pulmonary metastases because of numerous small lesions (four patients) or involvement of the main bronchus by metastatic lymph nodes (one patient).

The cumulative survivals at 5 years and 10 years were 40.5% and 27.7%, respectively (Fig. 1). Fifteen of the 16 10-year survivors were alive with no evidence of cancer recurrence and only one patient died of metastatic disease. Seven of the 37 patients who survived more than 5 years died of metastatic disease, and five patients died without recurrence. Two patients were alive with recurrent cancer at the time of this report. The other 23 5-year survivors were free of disease.

Table II shows survivals 5 years after thoracotomy based on potential prognostic factors. The cumulative survival for patients in group A was 44.9% at 5 years, but for patients in group B it was 33.0%. The difference between these two groups was statistically significant. The cumulative survival for patients in group C at 5 years was 25.0%. There was also a statistically significant difference between group A and group C but no significant difference between group B and group C (Table II, Fig. 2).

In group A, the cumulative survival for 78 patients with a solitary pulmonary metastasis was 52.5% at 5 years, whereas that for 33 patients with multiple pulmonary metastases was 25.5% (Fig. 3). The difference between these two groups was statistically significant ($p = 0.019$). Wedge or segmental resection was adopted to preserve respiratory function, especially in the patients with multiple metastases. Fourteen patients (42%) with multiple metastases in group A underwent limited resection, 16 patients (49%) had lobectomy, and three patients (9%) had pneumonectomy. Among the patients with a solitary metastasis in group A, 23 patients (29%) underwent limited resection, 52 (66%) had lobectomy, and three (4%) pneumonectomy. For the patients with a solitary metastasis, the cumulative survivals for the lobectomy and limited resection groups were 45.6% and 73.3%, respectively, at 5 years ($p = 0.080$) (Fig. 4). The intrapulmonary recurrence rates after limited resection for the patients with multiple tumors and a solitary tumor were 50% (7/14) and 39% (9/23), respectively. In this series, we could not examine marginal recurrence after limited pulmonary resection. The cumulative survival for 52 patients with a DFI of more than 24 months was 50.1% at 5 years, whereas that for 57 patients with a DFI of less than 24 months was 40.6%. There was no significant difference in survival based on DFI for the patients in group A ($p = 0.486$).

In group B, the 5-year survival even for the patients who had hepatic metastases before thoracotomy was 33.0%. Twenty patients had a solitary

Fig. 1. Kaplan-Meier survival curve for all 159 patients who underwent resection of pulmonary metastases from colorectal cancer.

Fig. 2. Kaplan-Meier survival curves based on the three groups. *Group A*, Patients without extrathoracic metastasis before thoracotomy. *Group B*, Patients with a history of hepatic metastases. *Group C*, Patients with a history of local recurrences. *n*, Number of patients.

hepatic metastasis, three patients had two hepatic metastases, and four patients had three. In 12 patients the number of hepatic metastases was unknown. There was no significant difference in the

survivals between the group of the patients with solitary hepatic metastases and those with multiple metastases ($p = 0.26$). Two of the four patients who survived more than 5 years died of metastatic dis-

Fig. 3. Kaplan-Meier survival curves for the patients with a solitary metastasis and the patients with multiple metastases in group A ($p = 0.019$).

Fig. 4. Kaplan-Meier survival curves for the patients who underwent limited resection and the patients who underwent lobectomy in group A with a solitary metastasis ($p = 0.08$). n , number of patients.

ease and one patient was alive with recurrent cancer. The other patient was free of disease. The only statistically significant difference in survival for the patients in group B was that concerning the number of pulmonary metastases. The cumulative survival

for 22 patients with a solitary pulmonary metastasis was 43.7% at 5 years, whereas that for 17 patients with multiple pulmonary metastases in group B was 22.3% ($p = 0.047$).

In this series, hilar or mediastinal lymph nodes of

Table II. *Survivals 5 years after thoracotomy on the basis of potential prognostic factors*

Variables	No. of patients	Five-year survival (%)	p Value
Sex			
Male	95	37.3	0.639
Female	64	46.1	
Age			
≥65 yr	52	55.9	0.222
<65 yr	107	34.0	
Location of primary cancer			
Colon	82	42.1	0.801
Rectum	73	39.1	
Grade of primary tumor			
Dukes' A	11	$\begin{bmatrix} 74.1 \\ 35.2 \\ 32.5 \end{bmatrix}$ $\begin{matrix} * \\ \ddagger \\ \ddagger \end{matrix}$	0.033*
Dukes' B	30		0.488†
Dukes' C	64		0.011‡
Site of metastases before thoracotomy			
No metastases (group A)	111	$\begin{bmatrix} 44.9 \\ 33.0 \\ 25.0 \end{bmatrix}$ $\begin{matrix} * \\ \ddagger \\ \ddagger \end{matrix}$	0.009*
Liver (group B)	39		0.282†
Local (group C)	9		0.012‡
Size of metastatic lesion ^a			
≥3.0 cm	73	35.3	0.078
<3.0 cm	79	46.8	
No. of pulmonary metastases			
Solitary	107	48.4	0.003
Multiple	52	23.4	
Mode of operation			
Wedge or segmental resection	67	$\begin{bmatrix} 46.7 \\ 39.8 \\ 47.6 \end{bmatrix}$ $\begin{matrix} * \\ \ddagger \\ \ddagger \end{matrix}$	0.489*
Lobectomy	85		0.572†
Pneumonectomy	7		0.703‡
Hilar and/or mediastinal lymph nodes metastases ^b			
Negative	85	50.0	0.0004
Positive	15	6.7	

^aThe size was unknown in seven patients.

^bLymph node involvement was not assessed in 59 patients.

*, †, ‡, The p value with each symbol indicates the statistical comparison of survival between the corresponding two groups with the symbol out of three.

100 patients were dissected or sampled and lymph node metastasis from the pulmonary metastases was observed in 15 patients (Table II). One of these 15 patients was alive after more than 5 years, but she had been receiving chemotherapy for bone metastasis. The other 14 patients died of metastatic disease within 5 years after the thoracotomy. There was a statistically significant difference in survival between the patients who had hilar or mediastinal lymph node metastases and those who did not (Fig. 5).

Although the number of patients whose primary cancer was Dukes' grade A was small (11/159), the 5-year survival for these patients was 74.1%. Dukes' A classification was a favorable prognostic factor (Table II).

We⁷ previously reported that there is a significant difference in survival on the basis of the size of pulmonary metastatic lesions, but in this series the

size of the metastatic tumor had no significant bearing on the survival (Fig. 6). No significant differences in survival were based on sex, age, location of the primary lesion, or extent of the operation (Table II).

In this series, there were three favorable prognostic factors or criteria: (1) The lung should be the first metastatic site after resection of the primary cancer; (2) there should be only one metastatic tumor at the time of thoracotomy; and (3) there should be no metastatic hilar or mediastinal lymph nodes. The survivals at 5 years and 10 years for 69 patients who satisfied these three criteria were 62.1% and 47.0%, respectively (Fig. 7). The survivals at 5 years and 10 years for the 90 patients who did not satisfy these criteria were 22.4% and 10.6%, respectively. There was a statistically significant difference between these two groups ($p < 0.0001$).

Fig. 5. Kaplan-Meier survival curves for patients with or without hilar and/or mediastinal lymph node metastases ($p = 0.0004$). n , Number of patients.

Fig. 6. Kaplan-Meier survival curves according to the size of the pulmonary metastasis (>3.0 cm vs. <3.0 cm) ($p = 0.078$). n , Number of patients.

Discussion

The cumulative survivals for the 159 patients involved in this study at 5 years and at 10 years were 40.5% and 27.7%, respectively. These survivals are not dramatically different from those in earlier

reports.²⁻¹⁰ Wagner and colleagues¹³ reported on the significance of resection of hepatic metastases from colorectal cancer based on the difference between the clinical courses of patients with untreated metastases and those with resected metastases.

Fig. 7. Kaplan-Meier survival curves for 69 patients who satisfied the favorable three criteria given in the text and 90 patients who did not ($p < 0.0001$).

There have been no similar reports on pulmonary metastases or any prospective trials. We⁷ also suggested that the survival of the individual patient might be predetermined by the biologic behavior of the primary tumor, or "length bias." Therefore is it not possible to determine the significance of resection of pulmonary metastases from colorectal cancer. Although several patients died of metastatic tumors in 5 to 10 years, 15 patients in this series were alive after more than 10 years with no evidence of cancer recurrence. In addition, 69 patients with favorable factors in our experience had a cumulative survivals of 62.1% and 47.0% at 5 years and 10 years, respectively (Fig. 7). In light of these results, surgical treatment for pulmonary metastases from colorectal cancer not only may have some survival benefit but also may allow potential cure in selected patients.

Although Thomford, Wollner, and Clagett¹ excluded patients with extrapulmonary metastases as candidates for thoracotomy, there have been several reports about pulmonary resection for patients with extrapulmonary metastases. McAfee and colleagues⁸ said that the presence of resectable extrapulmonary metastases before or at the time of thoracotomy was not associated with a decreased survival. Yano and colleagues⁹ also reported that

the presence of resectable or controllable hepatic metastases did not decrease the survival. In our series, the presence of extrapulmonary metastases was the unfavorable prognostic factor. This difference was probably caused by the differences in the number of patients, the periods of follow-up, and the indications for resection. Muhe, Gall, and Angemann¹⁴ reported the follow-up data of 67 patients who underwent resection for pulmonary metastases from colorectal cancer. That study included 18 patients who had hepatic metastases before thoracotomy, and their 5-year survival was only 18%. The 5-year survival for patients who underwent hepatic resection for metastases for colorectal cancer ranged from 25% to 47.9%.¹⁵⁻¹⁷ In light of these results, metastatectomy might be beneficial only when the metastasis is confined to the organ that is the first hematogenic metastatic filter from the primary tumor, and it might be of no effect when the secondary metastasis from the first filter organ occurs or when two filter organs of different pathways are affected. However, in our series the cumulative survival at 5 years for 22 patients with a solitary metastasis in group B was as high as 43.7%. At present, it appears that a patient with a solitary pulmonary metastasis potentially benefits from pulmonary resection even when there

is a history of hepatic metastasis. Regarding multiple pulmonary metastases in patients who have or had hepatic metastases, the significance of surgical treatment is still unknown. Therefore a prospective studies should be done to determine the significance of resection of pulmonary metastases for patients with extrapulmonary metastases.

As for the extent of pulmonary resection, our preliminary analysis in the middle of the 1980s showed a high incidence (about 30%) of local recurrence at the resected margin in the cases of limited resection. In view of this, we attempted to perform lobectomy in all patients with solitary pulmonary metastases who were expected to have a favorable prognosis. However, the results of this series, as well as of our former report,⁷ show that the extent of pulmonary resection did not appear to affect the prognosis. Limited resection may be a preferable procedure for pulmonary metastasectomy if there is an adequate surgical margin around the tumor.

Cahan, Gastro, and Hajdu¹⁸ found that 10 of 20 patients who underwent resection for pulmonary metastases from colon had hilar or mediastinal lymph node metastases (or both). On the basis of this finding, they advocated lobectomy and lymph node removal for these metastatic lesions. However, in their series, only one patient with metastatic lymph nodes survived more than 5 years. In our series, resecting pulmonary metastases was not worth while in the patients who had hilar or mediastinal lymph nodes metastases, because the dissection of hilar and mediastinal lymph nodes could not control the disease. We believe that pulmonary metastasis with subsequent lymph node metastasis is in advance of the first step in the "metastatic cascade" advocated by Viadana, Bross, and Pickren.¹⁹ Therefore evaluation of hilar and mediastinal lymph nodes is important, and only sampling of those lymph nodes should be attempted to predict the clinical course after thoracotomy.

In conclusion, we believe that pulmonary resection for metastatic tumors from colorectal cancer can improve survival. Furthermore, there appears to be a chance for cure in selected patients with a solitary pulmonary metastasis. Pulmonary metastasectomy has a potential survival benefit to the patient who has multiple pulmonary metastases or who had hepatic metastases before thoracotomy.

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