

Case Analysis

## Surgical Management of Pulmonary Metastases of Colorectal Cancer

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### Key Words

Pulmonary metastasis;

Colorectal cancer;

Surgical management

**Purpose.** The most common metastatic sites of colorectal cancer are the liver and lung. Patients with untreated stage IV colorectal cancer have a very poor prognosis. Only surgical intervention seems to be effective in cases of pulmonary metastases, for which there exists no definitive prognostic factors. Therefore, in this study we analyzed case records and attempted to identify potential prognostic factors and more effective methods of management of pulmonary metastases.

**Methods.** Forty consecutive cases of pulmonary metastases from January 1998 to December 2007 in which curative pulmonary metastasectomy was performed were examined retrospectively by reviewing medical charts and the outcome assessed, the primary endpoint being death and the secondary endpoint being disease recurrence.

**Results.** The five-year disease-free and overall survival rates in these patients were 36.8% and 38.8%, respectively. A total of 47 lung resections were performed, with no instances of postoperative mortality. Only the post-thoracotomy disease-free interval and tumor size less than 3 centimeter were found to be a meaningful prognostic factor of five-year overall survival, although the normal serum CA199 level seemed to contribute to a better outcome.

**Conclusion.** Pulmonary metastasectomy in cases of colorectal cancer is relatively safe and assists in improving survival.

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Colorectal cancer is one of the most common malignancies and a leading cause of cancer-related death worldwide. The prognosis of colorectal cancer after primary surgery is related to subsequent or concurrent distant metastasis and local recurrence; at least one-third of patients will develop metastases/recurrence, the most common sites of metastases being the liver and lung.<sup>1</sup> Unfortunately, there is no definitive successful chemotherapy and target therapy regimen for patients with lung metastases,<sup>2-4</sup> although pulmonary metastasectomy has seemed to have a positive effect since its introduction in the 1980s.<sup>1,5,6</sup> In addition,

no clear prognostic factor of survival following pulmonary resection has been identified. Therefore, in this study we examined the outcome in patients who underwent pulmonary metastasectomy and attempted to identify potential prognostic factors.

## Materials and Methods

### Patients

The records of 40 consecutive cases of colorectal

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cancer with lung metastases in which curative metastasectomy was performed at National Cheng Kung University Hospital from 1998 January to 2007 December were retrieved and examined. The criteria for curative resection of pulmonary metastases included unilateral or bilateral lung lesions, which were removed during the operation, no local recurrence of primary lesions, no extrapulmonary lesions except prior or simultaneous resectable liver metastases, and a respiratory function following the pulmonary resection sufficient for normal daily life. Our patients routinely underwent chest radiography every three months in order to identify any pulmonary metastases, and a chest CT was performed every six months for patients with a high risk of lung metastases or to evaluate possible lung metastases if any suspicious lesions were identified on the chest radiograph or if an elevated carcinoembryonic antigen (CEA) level was detected. In recent years, we have also used F<sup>18</sup>-fluorodeoxyglucose positron emission tomography (FDG PET) to evaluate possible metastatic sites. All patients underwent chemotherapy and/or target therapy following a diagnosis of metastases.

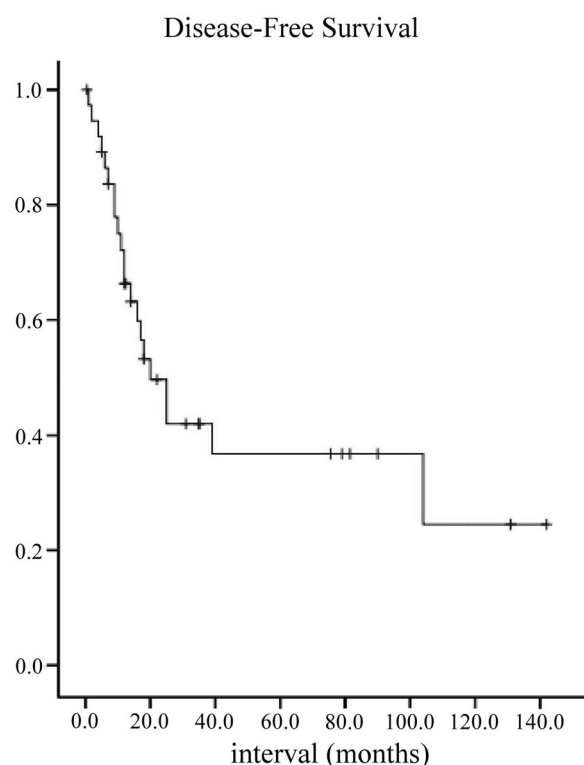
Patients' gender, primary tumor site and stage (according to the tumor-node-metastasis (TNM) system), CEA level, location of metastatic lesions, size and number of metastatic lesions, type of pulmonary resection, presence of metastatic lymph nodes with hilum, liver metastasis status, interval between primary tumor resection and lung metastasis, and disease-free and overall survival were recorded. Overall survival was measured as the interval between the date of pulmonary surgery and death, while recurrence was defined as the appearance of a new tumor on a chest radiograph or computed tomography scan subsequent to the pulmonary resection.

### Statistical analysis

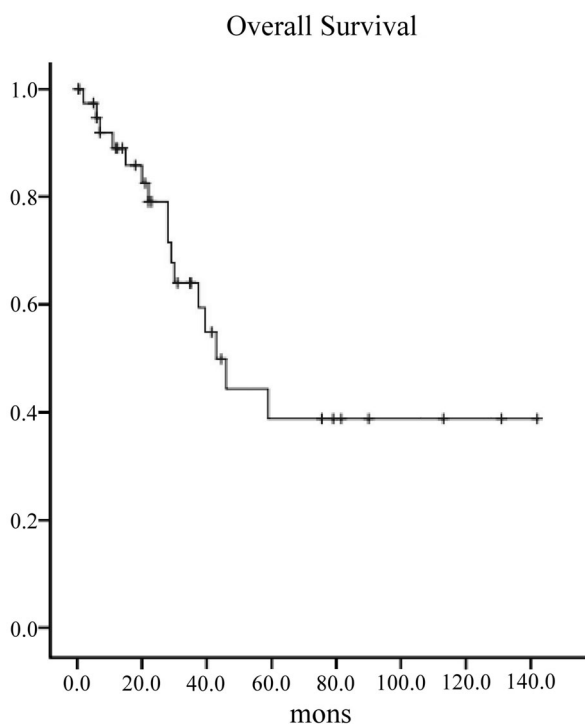
Disease-free and overall survival rates were calculated by the Kaplan-Meier method. Differences between subgroups were compared by the long-rank test. For multivariate analysis, the Cox regression model was used. Analyses were regarded as statistically significant at a probability value lower than 0.05.

## Results

The 40 patients included 24 males and 16 females, 20 of whom were over 60 years of age. Thirty patients developed pulmonary metastases more than one year after surgery for primary lesions, and in four cases liver metastases developed prior to thoracotomy. In our series, the five-year disease-free and overall survival rates were 36.8% and 38.8%, respectively; the median of the disease-free interval was 18 months (Figs. 1 and 2). Twenty-two patients got tumor recurrence within 24 months after pulmonary metastasectomy. Six patients developed recurrence after 36 months, and the longest duration was 74.5 months. Two prognostic factors of five-year overall survival, pulmonary metastases sizes and disease-free interval (post-thoractomy disease-free interval) after pulmonary metastasectomy, were identified in this study as being statistically significant ( $p = 0.02$  and  $< 0.01$ , respectively; Table 1). Patients with metastatic lesions



**Fig. 1.** Five-year disease-free survival curve for patients with pulmonary metastasectomy of colorectal cancer. The median was 18 months. Five-year disease-free survival rate was 36.8%.



**Fig. 2.** Five-year overall survival curve for patients with pulmonary metastasectomy of colorectal cancer. Five-year overall survival rate was 38.8%.

of diameter larger than 3 centimeter and shorter median disease-free interval ( $\leq 18$  months) had poor prognosis (13.5% vs 53.0% and 0% vs 62.9%; Table 1). CEA level, primary tumor stage, hilar lymph node involvement ( $p = 0.81$ , data not shown), blood loss or blood transfusion ( $p = 0.18$ , data not shown), age, operation methods, and interval between surgery for primary lesions and development of pulmonary metastases were not found to be important factors, although an increasing trend of carbohydrate cell surface antigen 19-9 (CA199) level appeared to be correlated with increasingly poor five-year overall survival rate ( $p = 0.08$ ). However, the CA199 data were missing or not obtained in around half of the cases examined, and it may cause the misinterpretation. The disease-free interval, and size of metastatic lesions were then included in the multivariate analysis, of which only the disease-free interval was found to be significant in five-year overall survival ( $p < 0.01$ , Table 2).

In the univariate analysis, CA199 level ( $p = 0.02$ ),

and liver metastasis before thoracotomy ( $p < 0.01$ ) were observed to be statistically correlated with five-year disease-free survival (Table 1). In this series, we have four patients with liver metastases before thoracotomy. One patient got simultaneous liver and lung metastases. Two patients received partial hepatectomy and others had radiofrequency ablation for liver metastases. And all of them were free from liver metastases before pulmonary surgery. After multivariate analysis, only an elevated CA199 level (hazard ratio = 12.2,  $p = 0.015$ ) was identified as being significantly correlated with poorer prognosis in five-year disease-free survival (Table 2).

In the 40 cases included in this study, a total of 47 thoracotomies were performed. One patient received the operation three times, and another five patients underwent this surgery twice. There were no significant differences between the patients undergoing a single metastasectomy and those receiving multiple surgeries in terms of five-year overall and disease-free survival ( $p = 0.43$  and  $0.38$ , Table 1). Besides, 38 patients (95%) received chemotherapy after pulmonary surgery with either FOLFOX/FOLFIRI or Xeloda prescription.

Only two patients (5%) experienced major postoperative complications (Table 3): one developed empyema after undergoing a wedge resection; the other suffered gastric ulcer bleeding and urosepsis following a lobectomy. Neither patient had any underlying diseases. None of the patients included in this analysis died within thirty postoperative days.

## Discussion

The development of novel chemotherapy and target therapy regimens has moved the treatment of patients with stage IV colorectal cancer into a new era; however, these treatment regimens appear to be useful only when combined with surgery in cases of liver metastases.<sup>7</sup> Since the 1980s, several studies have been performed to investigate the role of chemotherapy in combination with surgery and identify possible prognostic factors of pulmonary metastases in cases of colorectal cancer.<sup>8-18</sup> In the guidelines of the National Comprehensive Cancer Network (NCCN),<sup>19</sup>

**Table 1. Univariate analysis of prognostic factors and survival rates after pulmonary resection**

Characteristic	Patient numbers	5-year overall survival (%)	<i>p</i> value	5-year disease-free survival (%)	<i>p</i> value
Age (years)					
≥ 60	20	53.4	0.34	39.6	0.89
< 60	20	22.9		34.3	
Sex					
Male	24	38.7	0.75	38.5	0.89
Female	16	35.9		31.8	
Primary tumor site					
Colon	14	58.2	0.44	55.6	0.51
Rectum	26	27.5		26.2	
CEA					
Elevated	17	43.9	0.99	42.4	0.73
Within normal	16	55.5		42.4	
CA199					
Within normal	17	52.0	0.08	70.4	<b>0.02</b>
Elevated	4	37.5		0.00	
Primary tumor stage					
I + II	17	52.8	0.30	43.1	0.39
III + IV	21	27.0		26.3	
Pulmonary metastasis interval (months) <sup>a</sup>					
≤ 12	10	25.7	0.73	29.2	0.62
12-24	12	47.6		34.3	
> 24	18	37.0		42.9	
No. of metastasectomies					
1	34	44.8	0.43	38.5	0.38
> 1	6	20.8		25.0	
OP method					
Wedge resection	20	48.2	0.19	54.1	0.25
Segmentectomy or Lobectomy	13	16		25.8	
Tumor laterality					
Unilateral	35	39.4	0.78	39.2	0.52
Bilateral	5	31.3		25.0	
Number of metastases					
1	28	36.9	0.53	43.2	0.43
> 1	12	42.2		26.7	
Liver metastasis before thoracotomy					
Yes	4	0	0.45	0	<b>&lt; 0.01</b>
No	36	42.6		40.1	
Tumor size					
≤ 3 cm	21	53.0	<b>0.02</b>	56.3	0.12
> 3 cm	13	13.7		18.0	
Disease-free interval <sup>c</sup>					
≤ Median	20	0	<b>&lt; 0.01</b>	-	-
> Median	20	62.9		-	

<sup>a</sup> Interval between pulmonary metastases and primary lesion surgery

<sup>b</sup> For patients with single metastasis only

<sup>c</sup> Interval between recurrence/metastases after pulmonary metastectomy

only a few carefully-selected patients are recommended for pulmonary metastasectomy, the criteria for which include technically resectable metastases, tolerable general and functional risk to the patient, a

controlled primary tumor, and no extrathoracic lesions except liver lesions. The five-year survival rates have been reported to vary from 24% to 61.4% regardless of R0 or R1 resection, and low postoperative

**Table 2. Multivariate analysis of prognostic factors and survival rates after pulmonary resection**

Variable	Hazard ratio	95% confidence interval	<i>p</i> value
5-year overall survival			
Tumor size*			
≤ 3 cm	0.62	0.207-1.87	0.398
> 3 cm	1		
Disease-free interval			
≤ 18 months (median)	8.435	2.394-29.718	<b>0.001</b>
> 18 months	1		
5-year disease-free survival			
Liver metastasis before thoracotomy			
Yes	5.072	0.646-39.831	0.123
No	1		
CA199 level			
Elevated	12.2	1.634-91.068	0.015
Within normal	1		

\* For patients with single pulmonary metastasis

**Table 3. Postoperative morbidity and mortality**

Characteristic	Patients, n (%)
Major Complications	2 (5%)
Pneumonia	0
Prolonged ventilation	0
Bronchopleural fistula	0
Empyema	1 (2.5%)
Gastric ulcer bleeding	1 (2.5%)
Arrhythmia/Angina/AMI	0
Urosepsis/Urinary Tract Infection	1 (2.5%)
Mortality (30 days)	0

mortality rates were reported in these papers.<sup>8-17</sup> The outcome for lung metastectomy from colorectal cancer seems better than surgical resection for colorectal liver metastases.<sup>18</sup> The five-year overall survival rate in our series was 38.8%, and there was no postoperative mortality or respiratory decompensation. Thus, pulmonary metastasectomy was deemed safe and useful for the patients selected to undergo the procedure in our hospital.

The possible prognostic factors reported for five-year overall survival are diverse.<sup>8-17,20</sup> Chiba and colleagues<sup>9</sup> claimed that age (continuous data) significantly affects five-year survival, but the results of Osaka and colleagues<sup>8</sup> and our study are not in agreement with this finding. Other common factors can be divided into several different categories, such as char-

acteristics of the primary tumor (e.g., location, histology, TNM stage), pulmonary metastases characteristics (number, size, laterality, timing of metastases, thoracic lymph node status), type of thoracotomy (wedge resection, lobectomy), liver metastases status, pre-thoracotomy embryonic antigen (CEA) level, etc. DeMatteo and colleagues<sup>16</sup> reported that the disease-free interval between resection of the primary tumor and pulmonary metastases was a prognostic factor only when patients underwent combined liver and lung resection, while Pfannschmidt and colleagues<sup>18</sup> reviewed the existing literature and concluded that the pre-thoracotomy serum level of carcinoembryonic antigen was the only potential prognostic indicator in patients undergoing metastasectomy. According to these reports, there remains a debate with regards to operative and postoperative prognostic factors.<sup>8-20</sup> Whatever the surgical approach used, including variations in the surgical procedure, radicality of resection, repeat pulmonary resection, combination of liver and lung resection, and even (neo) adjuvant chemotherapy, no prognostic significance of long-term survival has been confirmed. In our series, the metastatic tumor size and post-thoracotomy disease-free interval were found to be significant in univariate analysis, but only post-thoracotomy disease-free interval remained significant after multivariate analysis in relation to the five-year overall survival rate. This result indicates that if recurrence or metastases develop soon after the pulmonary resection, the overall survival of the patient is worse, although a repeat metastasectomy and advanced chemotherapy with target therapy would be performed. With regards to the five-year disease-free survival, liver metastasis was identified as being significant in univariate analysis, and elevation of serum CA199 level was found to be significant in both univariate and multivariate analysis. Interestingly, we also found serum CA199 level, not CEA, to be related to the five-year overall survival in this group of patients. CA199, a tumor-associated antigen, has been reported to be a diagnostic and independent prognostic factor of colorectal cancer.<sup>21</sup> The characteristics of tumors with increased serum CA199 levels differ<sup>22</sup> from those exhibiting elevated serum CEA levels and may belong to another subtype of colorectal cancer. However, CA199 data were missing in a

high proportion of cases included in our study, and it is possible that an increased serum level of CA199 in tumors was positively correlated with the subsequent development of lung metastases but had no obvious influence on prognosis; it is also possible that no relationship exists.

Furthermore, Treasure<sup>23</sup> made one important but negative observation regarding the performance of pulmonary metastasectomy in cases of colorectal cancer. He states that although the practice of pulmonary metastasectomy is common and widespread, there have been no randomized controlled trials and there exists no strong evidence of the benefits of pulmonary metastasectomy. However, it is very difficult to complete such kinds of randomized studies owing to ethical issues, and no papers have discussed the quality of life of patients after metastasectomy. Recently, Carballo and colleagues<sup>24</sup> proposed that the use of video-assisted thoracic surgery (VATS) for the resection of metastatic adenocarcinoma is an acceptable alternative surgical technique, and the results of a short-term follow-up study showed there to be no increase in thoracic recurrence in patients undergoing surgery for pulmonary metastasectomy by this method. Gillams<sup>25</sup> reported minimally invasive treatments such as radiofrequency ablation to be promising methods for the treatment not only of liver but also pulmonary metastases; moreover, in addition to lowering the pain experienced from surgical wounds and promoting life quality, these methods are less harmful and more suitable for patients with poor general health. The success of these minimal invasive modalities in treating pulmonary metastases in this era maybe related to some factors. They included the more effective chemotherapy and target therapy, advanced surgical techniques, and delicate tools for preoperative evaluation. In our patients, wedge resection performed by VATS attracted no higher an incidence of thoracic recurrence, but there were no statistically significant differences between VATS and segmentectomy/lobectomy groups in the five-year disease-free and overall survival (54.1% vs 25.8% and 48.2% vs 16%;  $p = 0.25$  and  $0.19$ ). Therefore, the statement that the wedge resection is a better option for all patients requiring pulmonary resection must be made with caution, because we only selected patients

with metastases of smaller size and fewer in number for this type of surgery, who may have a naturally relatively good prognosis. Generally speaking, a detailed preoperative survey and careful surgical planning are often more important than the surgical method or instrument employed.

In summary, an analysis of our series of patients demonstrated that resection of pulmonary metastases in cases of colorectal cancer can be performed safely with a low mortality and morbidity rate. Post-thoracotomy disease-free interval was found to be a significant prognostic factor of five-year overall survival rate, and serum CA199 level had a possible positive effect on the five-year disease-free survival rate. Further (randomized) studies of a greater number cases involving diverse treatments, along with careful evaluation of the results, are needed before stronger conclusions can be made and improvements in the management of patients with pulmonary metastases of colorectal cancer can be implemented.

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## 病例分析

# 以手術治療大腸直腸癌肺轉移病患之成果分析

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**目的** 我們知道未治療的第四期大腸直腸癌患者預後極差，而最常發生的大腸直腸癌轉移處為肝臟與肺臟。對肺臟轉移這群病患而言，目前已知可能最有效的治療方法就是手術切除。故作者希望提供成大醫院相關病歷，以進一步探討手術之於大腸直腸肺轉移療效與找出可能的相關預後因子。

**方法** 我們以回溯性方式收集了從 1998 年 1 月至 2007 年 12 月間在成大醫院接受治癒性 (curative) 大腸直腸癌肺轉移的 40 位病患病歷。資料收集終點 (endpoints) 為病患死亡或是疾病復發。

**結果** 這 40 位病患共接受了 47 次肺轉移切除手術，且無任何手術相關致死率。其 5 年無病存活率與總存活率分別為 36.8% 與 38.8%。肺轉移切除後無病存活時間以及肺轉移腫瘤大小與 5 年總存活率是具有統計上的相關性的。至於 5 年無病存活率，則是與術前腫瘤指數 CA199 高低有關。

**結論** 肺轉移切除手術之於大腸直腸癌肺轉移患者相對上而言是安全，且可以延長存活時間的方式。

**關鍵詞** 肺轉移、大腸直腸癌、手術切除。