Original Article

Prognostic Factors of Overall and Disease-free Survival among Patients with Colorectal Cancer Lung Metastasis after Pulmonary Resection

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Key Words
Colorectal cancer;
Lung metastasis;
Pulmonary resection

Purpose. The lungs and liver are the two organs most commonly affected by metastatic colorectal cancer (CRC). Postoperative follow-up is crucial because most metastases occur within 3 years of primary tumor resection. Pulmonary resection is the most effective treatment for CRC lung metastasis. This study explored the prognostic factors of overall and disease-free survival among patients with CRC lung metastasis after pulmonary resection.

Methods. We conducted a retrospective study of patients who underwent pulmonary resection for CRC lung metastasis between January 2011 and December 2020. Patient demographics, tumor characteristics, disease-free survival rates, and overall survival rates were analyzed.

Results. Thirty-three patients were consecutively enrolled into this study. The mean age of participants was 61 years, and the mean follow-up time was 54.6 months. Three-year disease-free survival and overall survival in all patients was 33.3% and 78.8%, respectively. Carcinoembryonic antigen (CEA) levels more than 5 ng/mL is a negative prognostic factor of 3-year disease-free survival, and the occurrence of lung metastasis less than 12 months after primary tumor resection is a negative prognostic factor of 3-year overall survival.

Conclusion. Lung resection is a safe and effective treatment for metastatic CRC, and it should be considered for eligible patients to improve their survival. Patients with CEA levels more than 5 ng/mL or lung metastasis within 12 months of primary tumor resection should be followed intensively because of their risk of poor prognosis.

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According to the statistics from Taiwan's Cancer Registry annual report in 2019,[1] Colorectal cancer (CRC) is the most prevalent cancer and the third leading cause of cancer-related death in Taiwan.[1,2] The incidence rate of CRC in Taiwan has been increasing in recent years, which highlights the need for effective treatment and prevention strategies. While the 5-year survival rate of CRC in the United States is 64%,[3] the survival rate for metastatic CRC remains low. The most effective treatment for non-metastatic CRC is

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surgery. Postoperative adjuvant chemotherapy or radiotherapy decreases the cancer recurrence rate among high-risk patients.[2,4-6]

The most commonly affected organs by metastatic CRC are the liver and lungs. For CRC liver metastasis, liver resection of metastatic tumors is an effective treatment option. Similarly, the current treatment principle for CRC lung metastases is the resection of all metastases.[2] It is worth noting that some studies have reported that around 10%-16% of patients with CRC experience lung metastasis.[7-9] The median survival time for CRC patients with lung metastasis is about 18 months.[10] However, the site of the primary tumor, including colon or rectal cancer, can also influence the prognosis.[11-13] Additionally, factors such as R0 resection, pre-operative carcinoembryonic antigen (CEA) and CA-199 levels, lymph node involvement rate, perineural involvement rate, and number of lesions are important factors affecting the prognosis of colorectal cancer patients with lung metastases. However, the findings regarding these factors are still somewhat controversial.[11-13]

Given these complex considerations, the current study aims to investigate the prognostic factors of patients with CRC lung metastasis after pulmonary resection. It is hoped that this study will elucidate on potential avenues for improving the prognosis and treatment of CRC patients with lung metastasis.

Materials and Methods

Patients and data collection

We conducted a retrospective study using the data of all patients who underwent colorectal surgery for primary CRC at Shuang-Ho Hospital from January 2011 to December 2020 and follow up more than 3 years. Patients who underwent curative video-assisted thoracoscopic pulmonary resection for a synchronous or metachronous lung metastasis from CRC were enrolled into this study. The exclusion criteria were no metastases in the pathology report or no surgical treatment.

We collected information on sex, age, body mass index, American Society of Anesthesiologists score, location of primary CRC, primary tumor stage, preoperative CEA and CA-199 levels, time from primary tumor resection to pulmonary metastasis, pulmonary tumor side, tumor size, tumor location, liver metastasis before thoracotomy, overall and disease-free survival. Overall and disease-free survival rates were defined as the time from thoracotomy to death and recurrence, respectively.

Statistical analysis

Data are presented as mean ± standard deviation. Comparisons were made using the χ^2 test or one-way analysis of variance for continuous or categorical variables, respectively. Kaplan-Meier curves were drawn for overall survival and disease-free survival. The Cox proportional hazard model was used for survival analysis, and 95% confidence intervals were estimated to determine the influence of the variables on survival outcomes. All tests were considered statistically significant if $p < 0.05$. All statistical analyses were performed using SPSS (version 25; IBM, Armonk, NY, USA).

Results

A total of 33 patients were included in this study. Of these, 16 were men, and 17 were women. The mean age was 61.2 years (range: 42-81), and 20 patients (60.6%) exhibited a primary tumor location at the rectum. Four patients (12.1%) had liver metastases before pulmonary resection, and the mean resection margin of lung metastasis tumor was 8.5 mm (range: 2-30 mm). Stage III (63.3%) was the most common primary tumor stage, and 78.8% of all patients had moderately differentiated primary tumor cells. Detailed patient information is presented in Table 1.

The 3-year overall survival and disease-free survival rates were 78.8% and 33.3%, respectively (Figs. 1 and 2). In the overall survival analysis (Table 2), only time from primary tumor resection to pulmonary metastasis diagnosis was found to be a predictor of overall survival. The 3-year overall survival rate was

Table 1. Characteristics of all patients

	N	SD/%
Sex		
Male/female	16/17	48.5%/51.5%
Age (y)	61.2	10.9
Primary tumor location		
Ascending	3	9.1%
Transvers	1	3%
Descending	2	6.1%
Sigmoid	7	21.2%
Rectum	20	60.6%
Liver metastasis		
Positive	4	12.1%
T stage		
1	2	6.1%
2	24	72.7%
3	5	15.2%
4	2	6.1%
N stage		
0	7	21.2%
1	13	39.4%
2	13	39.4%
M stage		
0	27	81.8%
1	6	18.2%
Stage		
I	2	6.1%
II	4	12.1%
III	21	63.6%
IV	6	18.2%
Tumor differentiation		
Well	4	12.1%
Moderate	26	78.8%
Poor	3	9.1%
Resection margin (mm)		
Colon	21.5	22.95
Lung	8.5	8.5
Lung metastasis side		
Unilateral	28	84.8%
Bilateral	5	15.2%
Procedure		
Wedge	21	63%
Segmentectomy	12	37%
Lung metastasis number		
Single	25	75.8%
Multiple	8	24.2%
Interval of metastasis to lung (months)	32.7	26.3
Follow-up time (months)	54.6	29.1

16.7% for patients who received a pulmonary metastasis diagnosis less than 12 months after primary tumor resection and 92.6% for those who received a pulmonary metastasis diagnosis more than 12 months after primary tumor resection ($p < 0.001$, Fig. 3). In disease-free survival analysis (Table 2), the pre-pulmonary resection CEA level was indicated to be a predictor of disease-free survival. The 3-year disease-free survival rate was 17.4% for patients with a CEA level equal to or greater than 5 ng/mL and 70.0% for patients with a CEA level less than 5 ng/mL ($p = 0.028$, Fig. 4). And the CA-199 level was found to be an independent predictor ($p = 0.016$, Fig. 5). Other factors such as age, sex, primary tumor location, primary tumor stage, primary tumor differentiation, pulmonary tumor location, pulmonary tumor size, num-

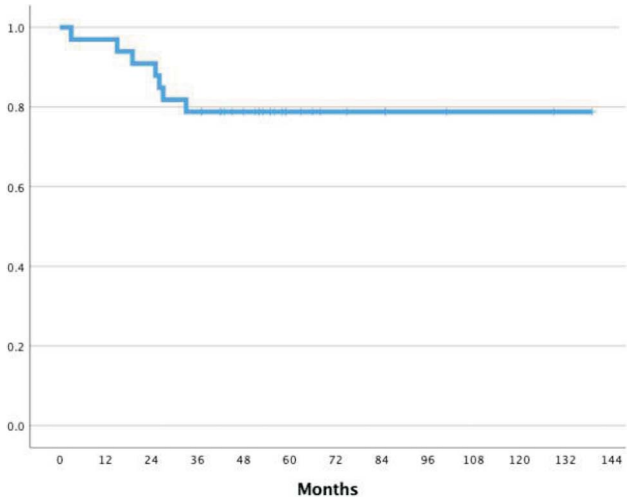

Fig. 1. Overall survival curve for all patients.

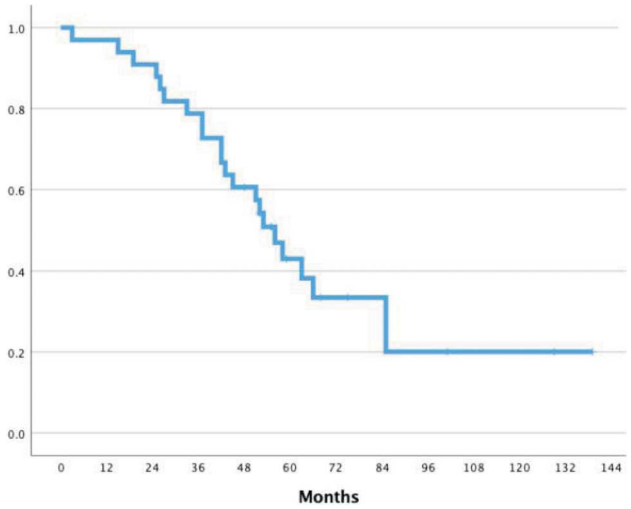

Fig. 2. Disease free survival curve for all patients.

Table 2. Prognostic factor affecting 3-year disease free survival and overall survival rate

	N	3-year DFS	*p* value	3-year OS	*p* value
Age (years)			0.218		0.171
< 60	17	23.5		88.2	
≥ 60	16	43.8		68.8	
Sex			0.622		0.235
Man	16	37.5		87.5	
Woman	17	29.4		70.6	
Tumor location			0.314		0.279
Colon	13	23.1		69.2	
Rectum	20	40		85	
TNM stage			0.237		0.246
1	2	50		100	
2	4	25		75	
3	21	42.9		85.7	
4	6	0		50	
Differencing			0.93		0.836
Good	4	25		75	
Moderate	26	34.6		80	
Poor	3	33		66.7	
Lymphphovascular invasion			0.407		0.385
Positive	24	22.2		88.9	
Negative	9	37.5		75	
Perineural invasion			0.443		0.629
Positive	21	41.7		83.3	
Negative	12	28.6		76.2	
CEA			0.003		0.911
≤ 5	10	70		80	
> 5	23	17.4		78.3	
CA-199			0.016		0.514
≤ 37	18	50		77.8	
> 37	11	0		72.7	
Metastasis side			0.086		0.943
Unilateral	28	39.3		78.6	
Bilateral	5	0		80	
Metastasis number			0.566		0.763
Single	25	36		80	
Multiple	8	25		75	
Largest size			0.407		0.385
< 3 cm	24	29.2		75	
≥ 3 cm	9	44.4		88.9	
Liver metastasis			0.451		0.268
Yes	4	50		75.9	
No	29	31		100	
Interval of lung metastasis (months)			0.056		< 0.001
≤ 12 m	6	0		16.7	
> 12 m	27	40.7		92.6	

ber of pulmonary tumors, and previous liver metastasis were not predictors of either overall survival or disease-free survival.

Discussion

CRC represents the highest proportion of adult

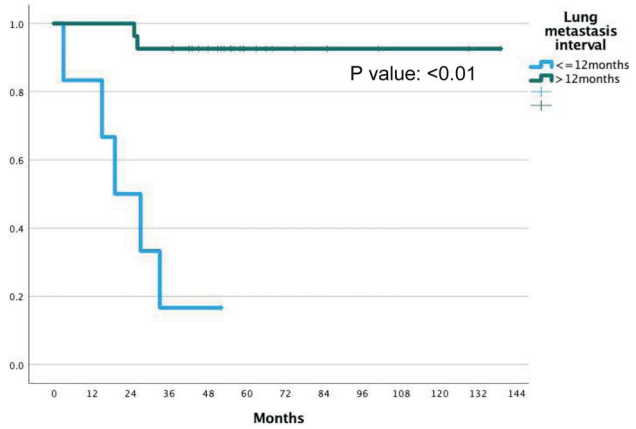

Fig. 3. Overall survival curve for patients with lung metastasis greater than 12 months and less than 12 months. Lung metastasis occur less than 12 months has lower overall survival rate.

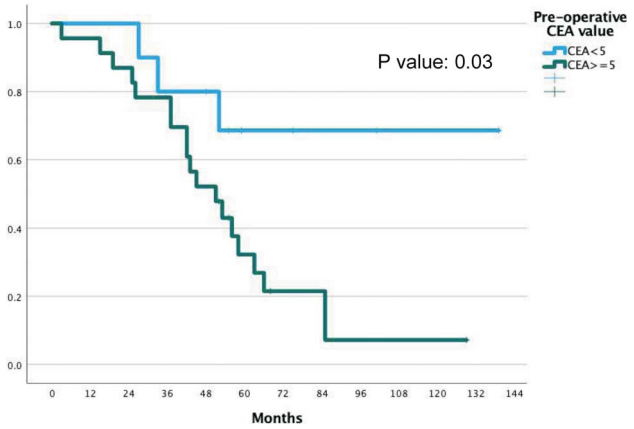

Fig. 4. Disease free survival curve for patients with pre-operative CEA ≥ 5 ng/ml and < 5 ng/ml. Pre-operative CEA levels more than 5 ng/mL with lower disease-free survival rate.

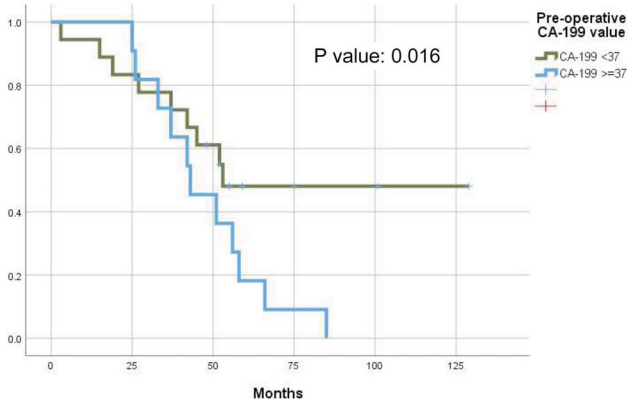

Fig. 5. Disease free survival curve for patients with pre-operative CA-199 < 37 U/ml and ≥ 37 U/ml. Pre-operative CA-199 levels more than 37 U/mL with lower disease-free survival rate.

cancers and it is the third leading cause of cancer-related death in Taiwan.[1,2] The main reason for treatment failure is metastasis, including local recurrence or distant organ metastasis. The liver and lungs are the two organs most affected by distant metastasis from CRC. Lung metastases account for approximately 16% of all CRC metastases.[9]

The treatment of metastatic CRC is the removal of metastatic tumors.[14-16] Numerous studies have reported risk factors for pulmonary metastasis from CRC,[9,17] including the number of lung metastases, lung helium lymph node metastasis, preoperative CEA level, and primary tumor stage. In this study, preoperative CEA levels of more than 5 ng/mL were determined to be a negative prognostic factor of disease-free survival, and time between primary tumor resection and lung metastasis was determined to be a predictor of overall survival.

In CRC liver metastasis, intervals of less than 12 months from primary tumor resection to liver metastasis is the main prognostic factor of resectable CRC liver metastasis.[18-20] In this study, the same result was found. Intervals of less than 12 months between primary tumor resection and lung metastasis is a negative prognostic factor of overall survival. It may be assumed that lung metastasis occurs in less than 12 months has a greater invasiveness potential rate[21] compared with other groups. Therefore, frequent and careful outpatient follow-up after the primary tumor section is required in high-risk patients.

The CEA level is a predictor of CRC prognosis.[4,22] The CEA level is an indicator of tumor mass or the ability of tumor cells to secrete CEA. Numerous studies have reported that elevated CEA is associated with lung metastasis,[6,22,23] and that the CEA level is also a key prognostic factor in patients with pulmonary metastasis from CRC before pulmonary resection.[24-26] This study demonstrated that CEA > 5 ng/mL before thoracotomy is also a prognostic factor predicting lower 3-year disease-free survival rates. The tumor marker CA-199 is a tumor index for CRC. The CA-199 level is one of the prognostic factors of CRC. Zhou et al.[27] reported that patients with stage III CRC had higher

recurrence rates when CA-199 > 24 U/mL before primary tumor resection. However, in our study, high levels of CA-199 before pulmonary resection was not a prognostic factor but lower CA-199 level was found to be an independent predictor with higher 3-year disease-free survival. No significant difference was observed in overall survival rates between patients with CA-199 > 37 U/mL and other group.

Other factors such as age, sex, primary tumor location, TNM stage, location and the number of lung metastases, and the number of metastatic tumors were not determined to be prognostic factors in this study. This result is consistent with the results of other studies. Primary tumor lymphovascular, perineurial invasion, and tumor differentiation have been reported to be prognostic factors of either disease-free survival or overall survival in some studies.[28,29] However, such findings were not observed in this study.

The metastatic tumor size is a potential prognostic factor. Vogelsang et al.[30] and Goya et al.[8] have proposed that tumors larger than 3 cm had an effect on prognosis, but in the present study, the tumor size was not determined to be a prognostic factor of either 3-year disease-free survival or overall survival.

Limitations

This study has some limitations. First, the main limitation is the retrospective study design. All data were obtained from the medical records of a single center with low patient numbers; thus, bias is inevitable. A larger sample size and a longer follow-up time would enable a comprehensive analysis of the data. However, all patients who underwent surgery were followed up at the same institution using the same protocol; this may have reduced the bias. Second, some patients received primary CRC surgery in our institute but underwent pulmonary resection for lung metastasis in another hospital, and we were not able to obtain the data of these patients. Finally, the nature of chemotherapy undertaken before and after pulmonary resection varied widely for each patient. This variation was difficult to account for in the analyses. A greater number of patients may be required to determine the effect of chemotherapy on the prognosis of patients after resection of lung metastases.

Conclusion

In this study, we determined that undergoing primary CRC resection less than 12 months before lung metastasis is a negative prognostic factor of 3-year overall survival. We also determined that CEA levels of more than 5 ng/mL before pulmonary resection is a negative prognostic factor of 3-year disease-free survival. Therefore, close follow-up in patients with higher CEA levels before surgery and patients with less than a 1-year interval between primary tumor resection and lung metastasis is essential.

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原　著

大腸直腸癌肺部轉移經肺切除術後的預後風險因子

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目的 大腸直腸癌最常轉移的器官是肝及肺，而大多數轉移發生在第一次手術後三年內，因此術後的追蹤很重要。對於肺部轉移最有效的治療方式為手術切除。本研究主要是分析大腸直腸癌病人發生肺部轉移接受手術切除的預後風險因子。

研究方法 本研究從 2011 年一月至 2020 年十二月，回溯性的收集大腸直腸癌合併肺部轉移接受手術的病人，評估與分析病人基本資料、腫瘤分類、無病存活率以及整體存活率。

結果 本研究總共收錄了 33 位病人，其中平均年齡為 61 歲，平均追蹤時間為 54.6 個月，三年無病存活率以及整體存活率對於全體病人分別為 33.3% 和 78.8%。結果顯示術前 CEA 指數大於 5 ng/mL 與原發腫瘤切除十二個月內發生肺部轉移為兩個有顯著意義的預後風險因子。

結論 對於大腸直腸癌肺轉移的病人，手術切除對於適當的病人是安全而且有效的治療方式並且可以增加病患存活率。對於不好的預後因子包含術前 CEA 指數大於 5 ng/mL 與原發腫瘤切除 12 個月內發生肺部轉移的這兩類病人需要更密集且小心的追蹤。

關鍵詞 大腸直腸癌、肺轉移、肺切除。