Original Article

Prognostic Analysis of Colorectal Cancer Patients after Surgical Resection of Pulmonary Metastasis – Case Series from a Single Center

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Purpose. Pulmonary metastasectomy had been widely performed for colorectal cancer with lung metastasis with favorable outcomes. However, there is currently no standard surgical indication for the procedure. This study aim to identify the patient groups who might benefit from pulmonary metastasectomy.
Methods. We reviewed 42 patients who underwent curative resection of pulmonary metastasis from colorectal cancer between February 2002 and January 2015. The prognostic factor for overall survival was analyzed.
Results. Twenty-four male and 18 female were included, and the median age at pulmonary resection was 66.7 years (range, 36-92 years). The median interval between colorectal and pulmonary resection was 2.3 years (range, 0 to 8.9 years), and the median follow-up period after pulmonary resection was 30.7 months (range, 2.1 to 102.3 months). The 3 year overall survival after pulmonary resection was 57.3%. Univariate analysis revealed that younger than 65 years, rectal cancer origin, initial pathological stage IV, multiple lung metastases, previously-treated liver metastasis, CEA and CA 19-9 level, positive resection margin and thoracic lymph node involvement were significant adverse indicators of disease-free survival. In multivariate analysis, previously-treated liver metastasis was the only significant independent prognosticator identified.
Conclusions. The current study highlighted the importance of selection criteria for pulmonary metastasectomy from colorectal cancer. If the patient had history of previously-treated liver metastasis, aggressive treatment strategy should be considered.
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Colorectal cancer (CRC) is one of the common causes of cancer death worldwide. Lung ranked the second leading site of metastasis from colorectal cancer, with 5-20% colorectal cancer patients developing lung metastasis.[1-6] A 30-years population study showed that the frequency of lung metastases increased significantly over time, from 5.75% between 1976 and 1985 to 17.0% between 1996 and 2005.[4] In 1995,[7] it was proposed that a clinical state of oligometastases existed 'amenable to a curative therapeutic

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strategy'. The oligometastatic state is generally limited to five or fewer metastases,[8] which may be in more than one organ.[9] With curative intent, liver metastasectomy for resectable liver metastasis can improve five year survival close to 25%.[11] Does surgical resection for lung metastasis have the same favorable impact on survival? Overall five year survival for all patients with lung metastasis is 6.9%, whereas the overall survival for patients who underwent lung metastasectomy is 27-68%.[11-13] The seemingly drastically improvement in survival data all came from retrospective studies.[14] The first and the only randomized controlled trial to date regarding lung metastasectomy was the PulMiCC, which opened to recruitment in 2010, and was ongoing.[15] The criteria for pulmonary metastasectomy was raised by by Kondo et al.[16] — an update of the well-known Thomford criteria.[17]

1. The patient must be a good risk for surgical intervention.
2. The primary site is controlled.
3. No other metastatic disease; or, if present, it can be controlled by surgery or another treatment modality.
4. Pulmonary metastases are thought to be completely resectable.

Currently, we aim to identify the prognostic factors associated with survival after lung metastasectomy, in order to identify the subgroups of patients that might benefit from this surgical strategy.

Material and Methods

Between February 2002 and January 2015, 63 consecutive CRC patients receiving 79 lung resections at Taipei Veterans General Hospital were analyzed. After reviewing the pathologic reports, 21 lung diseases were proved to be primary lung carcinoma, or benign diseases such as tuberculosis, fungal microorganism, pneumonia, granuloma and lipoma. The medical records of the remaining 42 patients who underwent lung resection for synchronous or metachronous lung metastasis from CRC were reviewed. All 42 patients underwent resection for primary colorectal cancer and lung metastasis with curative intent. Hepatic metastasis was allowed as long as it is treated with radiofrequency ablation or metastasectomy with curative intent. The following variables were recorded and included in the analysis: (1) patient's demographic information (age at first lung resection and gender), (2) primary tumor characteristics (location, initial TNM stage), (3) detail of lung metastasis (synchrounous or metachronous, pre-metastasectomy tumor markers (CEA/CA 19-9), disease-free interval from primary colorectal resection to detection of lung recurrence, the number, size and sidedness of tumor, (4) detail of lung metastasectomy (microscopic feature, year of resection, surgical approach (video-assisted thoracic surgery, sternotomy or thoracotomy), extent of resection (wedge resection, segmentectomy, lobectomy or pneumonectomy), lymph node dissection), and (5) adjuvant chemotherapy/target therapy and recurrence patterns after lung metastasectomy.

Disease free interval was defined as the period between primary colorectal tumor resection and detection of pulmonary metastasis on CT scans. For pulmonary nodules that were ambiguous of malignancy or were too small to identify its significance, chest CT scans were repeated at 6 month interval. When the nodularity showed progression in size or number, which implied malignant nature, date of the CT scan was designated as date of recurrence. When bilateral lung metastases were present, two-staged surgery with one month interval was performed and was counted as one surgery; survival was calculated from the second lung operation. Follow up strategy was to examine blood CEA ± CA19-9 every three months. Chest and abdominal CT scans were performed alternatively every three months. Colonoscopy was done at one year interval.

Statistical analysis

For comparisons of categorical and continuous variables, chi square, Mann-Whitney U and Fisher's exact test were used as appropriate. Univariate analysis was made by Cox proportional hazards model for the following prognostic factors: gender, age, primary tumor location, initial pathological stage for primary tumor, CEA and CA19-9 level before lung resection, disease-free interval, year of pulmonary resection,

synchronous or metachrounous metastasis, size, number and sidedness of pulmonary metastatic lesions, presence of tumor necrosis or pleural effusion, resection margin, lymph node dissection and involvement, adjuvant chemotherapy or target therapy after lung metastasectomy, and previously-treated liver metastases. Prognostic factors with a *p* value lower than 0.15 in univariate analysis were proceed for multivariate analysis by Cox proportional hazards model, survival analysis by Kaplan-Meier method and log rank test. All statistical analysis was performed using SPSS version 22. The results were considered significant for *p* values less than 0.05.

Results

Patient characteristics

Twenty-four male and 18 female were included, and the median age at pulmonary resection was 66.7 years old (range, 36-92). There were 36 colon cancer patients and 6 rectal cancer patients. Disease free interval was short (< 1 year) in 10 patients and long (≥ 1 year) in 32 patients. Prior to lung metastasectomy, 14 patients had undergone liver resection for colorectal cancer metastasis with curative intent (Table 1).

Lung metastasis was solitary in 33 patients and multiple in 9 (unilateral in 4 and bilateral in 5). Regarding the surgical extent, most patients underwent wedge resection (37, 88.1%) instead of lobectomy (5). Video-assisted thoracic surgery (VATS) was chosen for 38 patients, while thoracotomy was required in 4 patients. The pathologic examination showed tumor necrosis in 23 patients and pleural retraction in 2 patients. Two patients had positive resection margin. Lymph node sampling or dissection was performed in 20 patients, in which 4 (20%) patients were confirmed to have metastatic lymph nodes (Table 2).

The CEA level before pulmonary metastasectomy

Table 1. Patient characteristics

Characteristics	Location of primary cancer			*p* value
	All (n = 42)	Colon (n = 36)	Rectum (n = 6)	
Age, median (range)	66.7 (35.7-92.0)	67.4 (35.7-92.0)	59.0 (41.3-80.7)	0.332
Sex, n (%)				0.685
Male	24	20 (55.6)	4 (66.7)	
Female	18	16 (44.4)	2 (33.3)	
Disease free interval, median (range)	2.3 (0-8.9)	2.3 (0-8.9)	1.7 (0-6.8)	0.408
Initial pathologic stage, n (%)				1
I-III	29	25 (69.4)	4 (66.7)	
IV	13	11 (30.6)	2 (33.3)	
Pre-metastasectomy CEA, mean ± SD	11.4 ± 18.1	12.1 ± 19.2	7.4 ± 11.2	0.693

CEA, carcinoembryonic antigen.

Table 2. Association of surgical management and pathologic finding on the location of primary colorectal cancer

Variable	Location of primary cancer			*p* value
	All (n = 42)	Colon (n = 36)	Rectum (n = 6)	
Multiple nodules, n (%)	9	7 (19.4)	2 (33.3)	0.593
Maximal tumor size > 20 mm, n (%)	15	14 (38.9)	1 (16.7)	0.395
Bilateral metastasis, n (%)	5	4 (11.1)	1 (16.7)	0.557
Lymph node dissection performed, n (%)	20	18 (50.0)	2 (33.3)	0.665
Lymph node metastasis, n (%)	4	3 (8.3)	1 (16.7)	0.474
Extent of resection, n (%)				1
Wedge resection	37	31 (86.1)	6 (100.0)	
Lobectomy	5	5 (13.9)	0 (0.0)	
Surgical approach				0.474
Thoracotomy/sternotomy	4	3 (8.3)	1 (16.7)	
Video-assisted thoracic surgery	38	33 (91.7)	5 (83.3)	

was elevated in 10 patients. Adjuvant chemotherapy was administered to 31 patients after pulmonary resection. 17 patients received target therapy after pulmonary metastasectomy.

Survival analysis

The median follow-up period after pulmonary resection was 30.7 months (range, 2.1 to 102.3 months), with 85.7% three-year follow-up rate. The median interval between colorectal and pulmonary resection was 2.3 years (range, 0 to 8.9 years). The 3 year disease free survival and overall survival after pulmonary resection were 23.8% and 57.3%, respectively (Fig. 1). Twenty-six patients (61.9%) developed pulmonary recurrence after lung resection, with 9 of them underwent second lung resection. Twenty-four (57.1%) patients developed extra-thoracic recurrence in liver, bone, brain, kidney or eye.

All 42 patients were included in univariate and multivariate analysis to identify the prognostic factor for disease free survival after pulmonary resection. Univariate analysis revealed that younger than 65 years, rectal origin, initial pathological stage IV, multiple lung metastases, previously-treated liver metastasis, CEA and CA 19-9 level, positive resection margin and thoracic lymph node involvement were significant adverse indicator of disease free survival (Table 3). The 3-year disease free survival for younger patients and older patients were 5.3% and 39.1%, respectively (p = 0.013). Patients with previously-treated liver metastasis had shorter 3-year disease free survival (7.1%) than those who did not (32.1%) (p = 0.002). Positive resection margin was also an adverse prognosticator that reduced 3-year disease free survival from 20.0% to 0.0% with significance (p = 0.033). With lymph node involvement, 3-year disease free survival decreased from 26.0% to 0.0% (p = 0.001). In multivariate analysis, previously-treated liver metastasis was the only factor identified as significant independent prognosticator for disease free survival (p = 0.04) (Fig. 2).

As for overall survival, initial pathological stage IV and lymph node involvement were poor prognostic factors in univariate analysis (p = 0.022 and 0.044 respectively). Furthermore, there was no identified independent prognostic factor for overall survival after multivariate analysis (data not shown).

Discussion

It is not surprising that pathological stage had an impact on overall survival after lung metastasectomy, since the AJCC staging categorizes TNM stage by prognosis. Onaitis and associates reported from a prospective study of 378 patients who underwent lung metastasectomy from colorectal cancer between 1998 and early 2007 that primary stage > 3 (HR 2.04, 95% CI 1.40-2.98) and age < 65 (HR 0.71, 95% CI 0.51-0.99) were independent poor predictors of recurrence after pulmonary resection.[18]

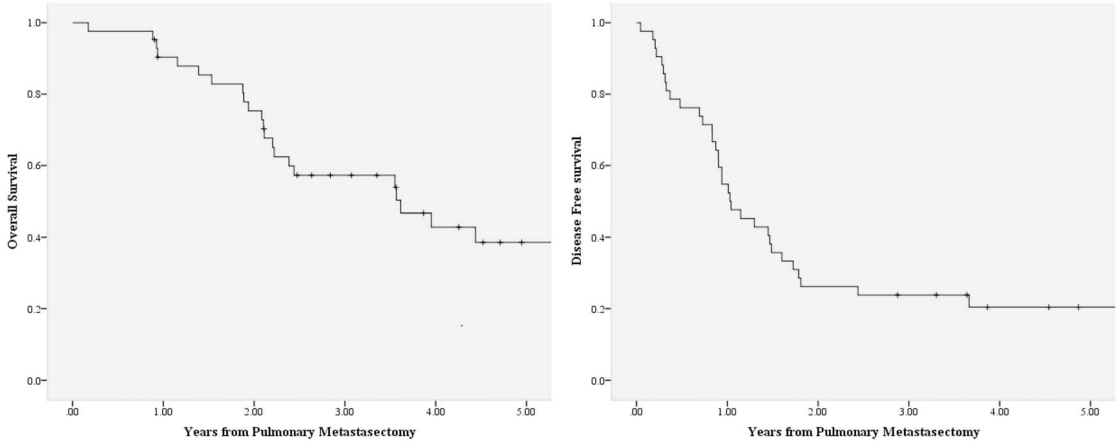

Fig. 1. The 3 year overall survival and disease free survival after pulmonary resection were 57.3% and 23.8%, respectively.

Table 3. Univariate analysis of disease free survival and overall survival after pulmonary resection

Variables	No.	3-year DFS	*p* value	3-year OS	*p* value
Gender		(%)			(%)
Male	24	20.8	0.975	55.4	0.885
Female	18	27.8		59.3	
Age, y					
< 65	19	5.3	0.013	55.7	0.360
≥ 65	23	39.1		58.4	
Year of resection					
Between 2002 and 2012	24	20.8	0.306	59.5	0.772
Between 2013 and 2015	18	27.8		54.2	
Primary site					
Colon	36	25.0	0.124	55.5	0.689
Rectum	6	16.7		66.7	
Initial pathologic stage					
Stage I-III	29	31.0	0.149	67.5	0.022
Stage IV	13	7.7		33.6	
Synchronous or metachronous lung metastasis					
Synchronous	6	16.7	0.868	50.0	0.773
Metachronous	36	25.0		58.6	
Disease-free interval					
< 1 year	10	20.0	0.840	50.0	0.554
≥ 1 year	32	25.0		59.7	
Size of pulmonary metastases (largest lesion)					
< 20 mm	27	18.5	0.552	52.4	0.365
≥ 20 mm	15	33.3		65.5	
Number of pulmonary metastases					
Solitary	33	30.3	0.014	48.7	0.245
Multiple	9	0.0		88.9	
Laterality of pulmonary metastases					
Unilateral	37	27.0	0.222	55.3	0.842
Bilateral	5	0.0		75.0	
Previously-treated liver metastases					
No	28	32.1	0.002	61.6	0.174
Yes	14	7.1		49.0	
CEA level before pulmonary resection					
Normal	32	12.5	0.020	52.7	0.256
Elevated	10	60.0		70.0	
Adjuvant chemotherapy after pulmonary resection					
No	11	18.2	0.730	51.1	0.547
Yes	31	25.8		58.9	
Adjuvant target therapy after pulmonary resection					
No	25	32.0	0.159	60.5	0.201
Yes	17	11.8		52.9	
Tumor necrosis					
Absent	23	26.1	0.619	53.8	0.893
Present	19	21.1		61.1	
Pleural retraction					
Absent	30	21.1	0.451	58.2	0.566
Present	4	50.0		50.0	
Resection margin					
Negative	35	20.0	0.033	54.8	0.362
Positive	2	0.0		50.0	
Lymph node sampling					
No	22	18.2	0.597	54.7	0.428
Yes	20	30.0		60.0	
Lymph node involvement					
Negative	38	26.3	0.001	60.9	0.044
Any positive	4	0.0		25.0	

CEA, carcinoembryonic antigen, CEA > 5 is categorized as elevated. DFS, disease free survival; OS, overall survival.

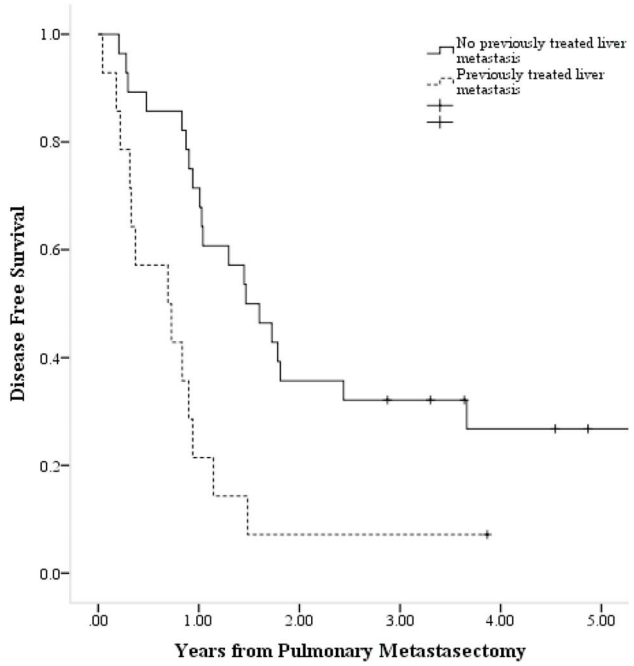

Fig. 2. There exist significant difference in disease free survival between patient groups with and without previously treated liver metastasis ($p = 0.002$).

Sourrouille and associates reviewed 69 patients operated on for colorectal cancer pulmonary metastasis, and attested that rectal cancer patient survived shorter than colon cancer patients with significance ($p = 0.04$).[19] The trend for lowered survival was also demonstrated in our study. Three-year disease survival of patients with colon and rectal cancers was 25.0% and 16.7%, respectively. The observation was supported by several researchers.[20-22]

The proportion of rectal cancer with lung metastasis among the whole study group was only 14.3%. This proportion was around 60% in a retrospective study conducted by Lan et al., recruiting 395 patients in our institute who underwent curative surgery for colorectal cancer during 2000 and 2005, with median follow up period of 69.2 months.[38] Rectal cancer has higher incidence for lung metastasis than colon cancer. This observation holds true in the parent group of colorectal cancer patients in Taipei Veterans General Hospital. However, in this study, only those patients who had undergone lung metastasectomy were extracted as subgroup. Therefore, the proportion of rectal cancer in the subgroup exhibited discrepancy from the parent group and may not represent the proportion in parent group.

Suzuki and coworkers concluded from a retrospective study of 136 surgical resections performed on 102 patients for pulmonary metastasis from colorectal cancer that multiple pulmonary metastases had poorer survival than those with solitary metastasis.[20] The difference was not significant (35.1% vs. 52.1%, $p = 0.058$), while in our study, the significance was demonstrated (0% vs. 30.3%, $p = 0.014$). When the lung metastatic nodules were multiple instead of solitary, it raises the concern of undetected pulmonary nodule at the time of resection.

In the retrospective study conducted by Cho et al. including 626 colorectal patients who underwent lung metastasectomy, thoracic lymph node metastasis was described as an independent adverse prognostic factor ($p = 0.020$).[22] Other studies had narrowed the range of involved lymph nodes to mediastinum, namely paratracheal, pre-vascular, retrotracheal, hilar, interlobar, lobar, segmental and subsegmental lymph nodes. Similar poor prognostic indication with mediastinal lymph node metastasis was confirmed by a meta-analysis of 14 studies of pulmonary metastasectomies for colorectal cancer.[13,21] Likewise, positive thoracic lymph node also had an adverse impact on overall survival in our study. Lymph node sampling or dissection was not routinely performed in our hospital. It may be performed when more advanced disease was suspected, which might contributed to selection bias.

Liver is the most common site of metastasis from CRC. We did not exclude patients with previously treated liver metastasis from lung resection. Gonzalez and colleges conducted a meta-analysis reviewing studies published during 2001 and 2011 that focused on surgical management of lung metastasis from colorectal cancer, and hold that liver metastasis had no impact on patient survival.[11] However, there were others who believed that concomitant liver metastasis does have adverse prognostic effect on survival.[2,21,23,24] In our study, patients with previous liver metastasectomy with curative intent had 7.1% 3-year disease free survival, which is lower than that (32.1%) of patients who did not have previous liver metastasis. The difference showed significance in both univariate and

multivariate analysis.

In the previously mentioned study by Lan et al., 75 out of 395 colorectal cancer patient had lung metastasis but no liver metastasis.[38] Twenty-nine (28.7%) patients had colon origin, while 46 (61.3%) patients were rectal cancer patients. Tumor at low rectum may spread via superficial inguinal lymphatic drainage directly to lung, bypassing liver. In 28 patients who exhibited lung metastasis as the only metastatic location without previously-treated liver metastasis, twenty-four (85.7%) had colon origin, while the remaining four (14.3%) originated from rectum. The difference in the proportion of primary tumor location may as well contributed by selection bias.

Literature search for pulmonary recurrence rate after resection of colorectal cancer pulmonary metastasis yielded diverse results. In McAfee's analysis of 139 patients after surgical resection of colorectal lung metastasis, recurrence involved the lung in 75 patients (74.3%).[25] Shiono et al. investigated 553 colorectal lung metastasectomy patients and reported 29.1% intrathoracic recurrence.[26] The author also determined that the recurrences were more frequently seen in patients undergoing wedge resection than segmentectomy. In the reporting of Onaitis et al., age younger than 65 years and female gender predicted recurrence.[18] From a retrospective study of 238 patients with lung metastasis from colorectal cancer, Sponholz and coworkers identified that recurrence was more often detected in the case of multiple metastases.[27] The intrathoracic recurrence rate in our study was 61.9%. Factors contributing to recurrence were not analyzed in this study.

The evidence for repeated pulmonary metastasectomy was conflicting.[28] In a retrospective Japanese multicenter study hosted by Hishida and colleges, repeated lung resection was significantly associated with favorable overall survival in patients with lung-limited recurrence after initial pulmonary metastasectomy of colorectal cancer.[21]

CEA level is a strong indicator of tumor size and volume. Many studies had attested to the worse survival of patients with elevated CEA level before lung resection.[11,20,28-35] Suzuki et al. in a previously mentioned study opined that the high CEA group had a lower disease-free survival after pulmonary metastasectomy than the normal CEA group.[20] In our study, pre-operative CEA level was elevated in only 10 patients (23.8%) and failed to demonstrate reasonable correlation on survival. We detect lung metastasis by routine chest CT exams, instead of survey for metastasis when CEA is elevated. This is perhaps one of the reasons why only a small portion of metastatic patient presented elevation of CEA level.

Trend of CEA level before and after surgery was also an interest of debate. In the 10 patients who had pre-operatively elevated CEA level, six of them had CEA level normalized one month after surgery. Univariate analysis revealed CEA returning to normal postoperatively as a prognostic factor of disease free survival with significance. However, due to small case number, the univariate analysis for CEA returning to normal was abandoned.

From a retrospective study enrolling 385 colorectal patient who underwent curative surgery for colorectal cancer at Taipei Veterans General Hospital, Lin et al. concluded that patients with elevated preoperative CA 19-9 and normal preoperative CEA level had higher lung recurrence rate (23.1%), compared to patients who had normal CA 19-9 and CEA level preoperatively (7.2%).[37] CA 19-9 level was collected in our study, in hope of testifying its reproducibility. On the other hand, Lin et al. also determined CA 19-9 level as a prognostic factor for disease free survival. CA 19-9 level may be obtained prior to primary surgery, in order to individualize follow up strategy. However, CA 19-9 exam has not yet become our pre-operative routine. CA 19-9 data were available in only 20 patients, and was therefore not included in univariate and multivariate analysis to avoid bias.

A short disease free interval between primary tumor resection and development of lung metastasis was demonstrated to increase the risk of death.[11] From the IRLM database of 5206 pulmonary metastasectomies from all cancer types at 18 thoracic centers worldwide over the years 1991-1995,[37] it is concluded that disease-free interval strongly affects outcomes, as patients presenting with early pulmonary metastases had a median survival of 29 months, whereas those presenting with late metastases had a median survival of

49 months. This is not in concordance with our results. Lung CT scan was not performed routinely at time of primary resection. That is to say, lung recurrence shortly after primary tumor resection may actually be synchronous lung metastasis.

There are several limitations to the present study. Above all is the small case number of study group. Multi-disciplinary combine meeting in Taipei Veterans General Hospital can be dated back to 2006. However, it was not until 2013 did thoracic surgeons join the meeting. Referral from colorectal surgeons to thoracic surgeons for lung resection in colorectal cancer patient was scarce between 2002 and 2013. 18 (42.9%) lung metastasectomies in our study were performed during 2013 and 2015. Three-year survival of the two time period groups were indifferent in univariate analysis. In addition, follow-up period for surgeries performed after 2015 were not sufficient to calculate 5-year survival for the time being.

Small case number and single-institute data contributed to selection bias. Proportion of rectal cancer in patient with lung metastasis only was lower than parent group. This proportion among all lung metastatic patients was also lower than parent group. Moreover, in univariate analysis, CEA elevation, multiple pulmonary metastasis and bilateral pulmonary metastasis was identified as a favorable factor for 3-year survival. These results contradicted other study results, but had no significance in multivariate analysis. These limitations should be bear in mind when interpretating the analysis.

Conclusion

Based on the retrospective single center study, previously-treated liver metastases was an independent poor prognostic factor for disease-free survival. Younger than 65 years, rectal origin, initial pathological stage IV, multiple lung metastases, previously-treated liver metastasis, CEA and CA 19-9 level, positive resection margin and thoracic lymph node involvement might have adverse impact on disease-free survival for CRC patients receiving lung metastasectomy. If the patient had history of previously-treated liver metastases, more aggressive treatment strategy should be considered.

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原　著

結直腸癌患者手術切除肺轉移後的預後分析 – 來自單一醫學中心的病例分析

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目的　大腸直腸癌之肺部轉移切除是被廣泛接受的術式，且成效良好。然而，目前尚未制定此術式之適應症。本研究將探討大腸直腸癌之肺部轉移切除術對哪些族群的病人較有益。

方法　本研究收錄 42 名在 2002 年 2 月至 2015 年 1 月間接受大腸直腸癌之肺部轉移切除術的病人，並分析影響存活率的預後因子。

結果　本研究收錄 24 名男病患及 18 名女病患，接受肺切除時的年齡中位數為 66.7 歲 (範圍 36-92 歲)。大腸直腸癌切除術至肺切除術之間的時間間隔中位數為 2.3 年 (範圍 0-8.9 年)。肺切除術後的追蹤期間中位數為 30.7 個月 (範圍 2.1-102.3 個月)，三年總存活率是 57.3%。單變項分析結果顯示，年齡、原發腫瘤部位、初診斷期別、肺轉移腫瘤數、已切除之肝轉移、腫瘤指數、切除邊緣及肺淋巴結轉移為無病存活率之顯著不良預後因子。在多變項分析中，已切除之肝轉移為無病存活率之獨立預後因子。

結論　本研究點出慎選病人進行大腸直腸癌之肺轉移切除術之重要性，若病人曾接受肝轉移之切除，需更積極的治療。

關鍵詞　大腸直腸癌、肺轉移、肺轉移切除術、存活率分析。