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Repeat pulmonary resection for recurrent lung metastases from colorectal cancer: an analysis of prognostic factors

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Abstract

OBJECTIVES: The purpose of this study was to investigate the prognostic factors for repeat lung metastasectomy in patients with colorectal cancer, which may be clinically helpful in defining a subset of patients who are most likely to benefit from repeat lung metastasectomy.

METHODS: In total, 138 patients underwent complete lung resection for the first time due to metastases of colorectal cancer between January 2004 and December 2013 at Fujita Health University School of Medicine. Among them, 33 underwent repeat pulmonary metastasectomy for lung tumour recurrence. Kaplan–Meier survival curves and log-rank tests were used to analyse the survival rates.

RESULTS: No patient died as a direct result of surgery, and all patients were discharged after the repeat pulmonary metastasectomy. The 5-year survival rate after the initial pulmonary resection of the 33 patients who underwent repeat lung resection was 64%, which was not significantly different from that of the 105 patients who did not undergo repeat lung resection (5-year survival rate, 61%; $P = 0.779$). Univariate analysis identified only one significant prognostic factor: preoperative serum carcinoembryonic antigen (CEA) level ($P = 0.002$). The 5-year survival rates of patients with high preoperative CEA levels and normal CEA levels after repeat metastasectomy were significantly different at 47 and 90%, respectively.

CONCLUSIONS: Prethoracotomy serum CEA levels affect survival rates after repeat pulmonary resection. The preoperative assessment of serum CEA levels before repeat metastasectomy is important when considering repeat pulmonary resection, and prethoracotomy CEA levels should be taken into account when selecting patients for repeat lung resection.

Keywords: Colorectal cancer • Lung metastasis • Repeat metastasectomy

INTRODUCTION

Colorectal cancer is one of the most common cancers worldwide [1], and it frequently metastasizes to the liver and lungs [2, 3]. Recently, the development of chemotherapy for metastatic colorectal cancer has been reported [4], but surgical resection for lung metastasis is still considered to be the optimal treatment where possible [5]. However, the main cause of death after pulmonary metastasectomy for colorectal carcinoma is tumour recurrence, which involves the lungs in approximately half of the patients [6, 7]. Although many studies have reported on the survival and prognostic factors for patients undergoing pulmonary metastasectomy for colorectal carcinoma [8–15], few studies have investigated prognostic factors after repeat pulmonary metastasectomy for recurrent lung metastases from colorectal carcinoma [7, 16–19]. Therefore, we reviewed a recent series of consecutive patients who underwent repeat pulmonary metastasectomy at Fujita Health University School of Medicine. The main purpose of this study was to investigate the prognostic factors of repeat lung metastasectomy in patients with colorectal cancer, which may be clinically helpful in defining a subset of patients who are most likely to benefit from repeat lung metastasectomy.

MATERIALS AND METHODS

One hundred and thirty-eight patients underwent lung resection for the first time due to the metastases of colorectal cancer between January 2004 and December 2013 at our institution. Among these 138 patients, 33 underwent repeat pulmonary metastasectomy for lung tumour recurrence following colorectal cancer.

All patients who underwent resection of their pulmonary metastases met the following criteria: (i) the primary tumour was controlled; (ii) there was no evidence of extrathoracic metastasis except liver metastasis; (iii) complete resection of recurrent lung disease was considered to be possible at presentation regardless of the number of lesions; (iv) the patient was in a good general condition and had adequate respiratory function to tolerate lung resection. The detailed regimens of chemotherapy were different

among patients; however, all 33 patients underwent pre- or postoperative chemotherapy. The patients were followed up until August 2015.

We reviewed each patient's medical records to obtain clinicopathological information, which included the following: (i) age at the repeat metastasectomy (dichotomized at the median age of 65), (ii) gender, (iii) smoking history (never- or ever-smoker), (iv) prethoracotomy serum carcinoembryonic antigen (CEA) level before repeat pulmonary metastasectomy (cut-off at the normal upper limit of 5 ng/ml), (v) primary site (colon or rectum), (vi) prior resection of liver metastasis (yes or no), (vii) Dukes' stage of the primary tumour (A-B or C-D), (viii) histological differentiation of the primary tumour (well differentiated or moderately/poorly differentiated), (ix) number of pulmonary metastases (≤2 or >2), (x) largest diameter of the resected tumour (≤1 or >1 cm), (xi) the disease-free interval (DFI) between the colorectal resection and repeat pulmonary resection (≤36 or >36 months) and (xii) the DFI between the initial pulmonary resection and the repeat pulmonary resection (≤12 or >12 months).

The duration of the overall survival rate was calculated in months from the date of initial or repeat pulmonary metastasectomy to the date of death due to any aetiology or the date of the last follow-up. All cumulative survival curves were estimated using the Kaplan–Meier method, and differences between groups were evaluated using log-rank tests. The significance level was set at <0.05. Analyses were performed using the statistical software SPSS 11.0 (Dr SPSS II for Windows, Standard Version 11.0, SPSS, Inc., Chicago, IL, USA).

RESULTS

The 5-year survival rate of all 138 patients who underwent complete lung resection was 61.7%. Of the 138 patients, 71 had recurrence after the first lung resection, with 35 developing recurrence in the lungs. Of these patients, 33 underwent repeat lung resection for recurrent lung metastases (Fig. 1). Postoperative morbidities were observed in 6 patients: prolonged air leak in 4 patients, pleural effusion in 1 patient and arrhythmia in 1 patient. No patient died as a direct result of the repeat surgery, and all patients were discharged after the repeat pulmonary metastasectomy. Patient characteristics are presented in Table 1. The cohort consisted of 14 women and 19 men. The ages ranged from 28 to 82 years with a median of 65 years. Video-assisted thoracic surgery (VATS) for the initial metastasectomy was performed in 31/33 (94%) patients and for the repeat metastasectomy in 21/31 (68%) patients. The number of metastases ranged from 1 to 6 with a median of 2. The surgical method for repeat pulmonary resection was a wedge resection in 20 patients, segmentectomy in 5, lobectomy in 7 and completion pneumonectomy in 1. All repeat pulmonary metastasectomies were curative resections. The median time interval between the initial and repeat pulmonary resections was 12 months (range: 5–37 months). The median follow-up period after repeat metastasectomy was 51 months (range: 8–127 months). Of the 33 patients, 9 were alive with no evidence of disease and 9 were alive with disease at the end of the follow-up period of the study. One had died of another disease, and 14 had developed recurrences and died of the disease.

The 5-year survival rate after the initial pulmonary resection for the 33 patients who underwent repeat lung resection was 64.3%,

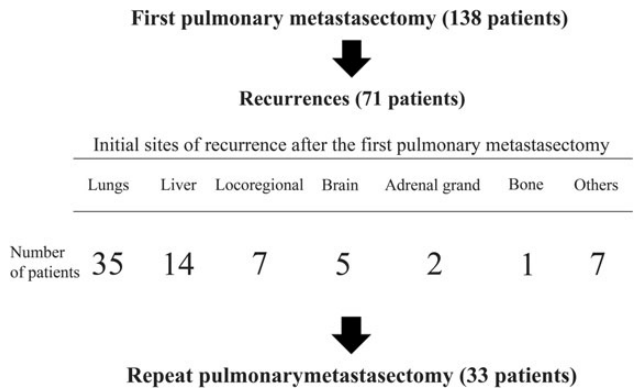

Figure 1: Patients who underwent complete lung resection for the first time due to metastases of colorectal cancer.

Table 1: Patient characteristics

Characteristics	Number of patients
Overall	33
Age at the second pulmonary resection	
Median	65
Range	28–82
Gender	
Women	14
Men	19
Smoking habits	
Non-smoker	13
Current or former smoker	10
Unknown	10
CEA before the second pulmonary resection	
Within normal range	16
Elevated	16
Unknown	1
Primary site	
Colon	12
Rectum	21
Prior resection of liver metastasis	
Yes	10
No	23
Dukes' stage	
A-B	6
C-D	18
Unknown	9
Histological differentiation	
Well differentiated	8
Moderately/poorly differentiated	19
Unknown	6
Number of pulmonary metastases	
1	12
2	10
3–6	11
Maximum tumour size (cm)	
Median	1
Range	0.2–5
Interval between the primary resection and the second pulmonary resection (months)	
Median	36
Range	13–92
Interval between the first pulmonary resection and the second pulmonary resection (months)	
Median	12
Range	5–37

CEA: preoperative serum carcinoembryonic antigen levels, normal upper limit at 5 ng/ml.

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which was not significantly different from that for the 105 patients who did not undergo the repeat lung resection (5-year survival rate, 61.3%; $P = 0.779$). Table 2 lists the 5-year survival rates after the repeat pulmonary resection according to clinicopathological features for all 33 patients. Univariate analysis (log-rank test) identified only one significant prognostic factor: preoperative serum CEA levels prior to repeat thoracotomy (Table 2). The 5-year survival rates for patients with a high preoperative CEA level and normal CEA level were significantly different at 46.9 and 90.0%, respectively ($P = 0.002$, Fig. 2).

DISCUSSION

The lungs are one of the most frequently affected metastatic sites in patients with colorectal cancer [2, 3]. Lung metastases are sequentially or simultaneously detected in ∼10% of patients with colorectal cancer [20]. Several studies have demonstrated the efficacy of lung metastasectomy in colorectal cancer patients [5, 8–15]. Various factors associated with prolonged survival after surgery for lung metastases from colorectal cancer have been identified, including (i) a single isolated metastasis <3 cm in size [8–10], (ii) a long DFI [11–13], (iii) the absence of thoracic lymph node invasion [14, 15] and (iv) prethoracotomy CEA level [5, 14]. This knowledge is clinically helpful for defining a subset of patients who are most likely to benefit from surgical resection. Although approximately half of the patients developed lung tumours after pulmonary metastasectomy for colorectal carcinoma [6, 7], there are few studies investigating the prognostic factors after repeat pulmonary metastasectomy for recurrent lung metastases from colorectal carcinoma. Because there is no consensus on appropriate indications for the resection of repeat lung metastases, we

Table 2: Five-year survival rates according to clinicopathological features

Characteristic	No. of patients	5-year overall survival after the second pulmonary resection (%)	Univariate analysis		
			P-value[†]	HR	CI
Overall	33	55			
Age (years)					
≤65	16	72			
>65	17	46	0.108	1.931	0.629–5.933
Gender					
Women	14	53			
Men	19	66	0.831	0.738	0.248–2.203
Smoking habits					
Non-smoker	13	61			
Current or former smoker	10	50	0.806	1.226	0.342–4.388
Unknown	10				
CEA					
Within normal range	16	90			
Elevated	16	47	0.002*	3.749	1.031–13.632
Unknown	1				
Primary site					
Colon	12	44			
Rectum	21	79	0.221	0.544	0.181–1.632
Prior resection of liver metastasis					
Yes	23	76			
No	10	39	0.128	2.261	0.748–6.832
Dukes' stage					
A-B	6	72			
C-D	18	58	0.298	2.293	0.366–23.376
Unknown	9				
Histological differentiation					
Well differentiated	8	82			
Moderately/poorly differentiated	19	56	0.183	2.764	0.550–13.878
Unknown	6				
Number of pulmonary metastases					
≤2	22	53			
>2	11	59	0.298	0.556	0.121–2.552
Maximum tumour size (cm)					
≤1	17	58			
>1	16	52	0.531	1.19	0.376–3.772
Interval between the primary resection and the second pulmonary resection (months)					
≤36	15	47			
>36	18	59	0.478	0.606	0.201–1.825
Interval between the first pulmonary resection and the second pulmonary resection (months)					
≤12	18	49			
>12	15	60	0.554	0.706	0.236–2.114

CEA: preoperative serum carcinoembryonic antigen levels, normal upper limit at 5 ng/ml; HR: hazard ratio for death; CI: confidence interval.
[†]Log-rank test.
*Significance.

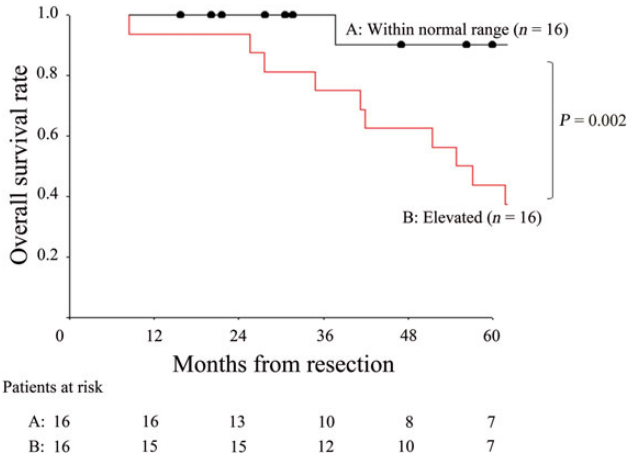

Figure 2: Overall survival curves after the second lung resection for the patients according to prethoracotomy serum CEA levels before the second thoracotomy. CEA: carcinoembryonic antigen.

investigated a recent series of patients with repeat resected lung metastases from colorectal cancer in our current study. The main purpose of this study was to investigate the prognostic factors of repeat metastasectomy in patients with previously resected lung metastases, which may be clinically helpful in defining a subset of patients who are most likely to benefit from repeat pulmonary metastasectomy.

In the current study, a high CEA level before the repeat thoracotomy was shown to be the only poor prognostic factor. Earlier studies have also shown that a high preoperative CEA level is associated with poorer survival in patients with pulmonary metastases from colorectal cancer [5, 14]. The elevation of serum CEA is considered to be an indication of increased malignancy and rapid, aggressive growth of the tumour [21, 22], which leads to multiple lesions and a poorer prognosis. CEA levels may therefore reflect the highly malignant nature of cancer cells that undergo systemic dissemination. We concluded that the group with high CEA levels prior to repeat thoracotomy should be carefully selected for the resection of recurrent lesions. If we apply appropriate surgical treatment for recurrent lesions, careful postoperative follow-up with frequent CEA measurement and periodic computed tomography (CT) scans to check for early recurrence may be the key to improved survival in some patients with high preoperative CEA levels.

In the current study, there were no occurrences of operative major morbidity or mortality regardless of whether the patient underwent repeat thoracotomy. Our results may be a result of VATS because 31/33 (94%) of initial metastasectomy procedures were performed using VATS. Recently, VATS has become a very popular method for minimally invasive surgery, and it is increasingly being used for pulmonary metastasectomy [23]. Although its efficacy for pulmonary metastasectomy is controversial, in our study, 94% of the patients underwent VATS metastasectomy and showed a comparable survival rate to those undergoing open surgery [5, 8–15]. The main disadvantages of VATS metastasectomy are establishing the localization of small nodules and the loss of non-visualized additional nodules. However, in terms of the loss of non-visualized nodules, Nakas *et al.* [24] reported no difference in the incidence of missed lesions and concluded that VATS metastasectomy in conjunction with multidetector CT was justified. Therefore, if complete resection of pulmonary metastasectomies using VATS is promising and no additional detection of nodules during open surgery is required due to precise CT results, VATS can certainly be the ideal approach for lung metastasectomy from colorectal cancer, especially for future repeat lung metastasectomy.

There are several limitations to our analysis. Firstly, we studied a small sample size. Secondly, because this is a retrospective study on surgical cases, the patients included in the analysis were carefully selected, and our sample may not represent a cross section of all patients with recurrent pulmonary metastases from colorectal cancer. A prospective, large-scale study with multiple institutions would be necessary to confirm the current results.

CONCLUSION

Prethoracotomy serum CEA levels affect survival after the second pulmonary resection. Preoperative assessment of serum CEA levels before repeat thoracotomy is important for repeat pulmonary resection. Furthermore, prethoracotomy CEA levels should be taken into consideration when selecting patients for repeat lung resection. In a carefully selected subset of patients who develop resectable recurrence in the lungs following initial metastasectomy of colorectal cancer lung metastasis, repeat resection is feasible.

Conflict of interest: none declared.

REFERENCES

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
[2] McCormack PM, Burt ME, Bains MS, Martini N, Rusch VW, Ginsberg RJ. Lung resection for colorectal metastases. 10-year results. Arch Surg 1992; 127:1403–6.
[3] Goya T, Miyazawa N, Kondo H, Tsuchiya R, Naruke T, Suemasu K. Surgical resection of pulmonary metastases from colorectal cancer. 10-year follow-up. Cancer 1989;64:1418–21.
[4] Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR *et al.* Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007;25:1539–44.
[5] Suzuki H, Kiyoshima M, Kitahara M, Asato Y, Amemiya R. Long-term outcomes after surgical resection of pulmonary metastases from colorectal cancer. Ann Thorac Surg 2015;99:435–40.
[6] McAfee MK, Allen MS, Trastek VF, Ilstrup DM, Deschamps C, Pairolero PC. Colorectal lung metastases: results of surgical excision. Ann Thorac Surg 1992;53:780–6.
[7] Ogata Y, Matono K, Hayashi A, Takamor S, Miwa K, Sasatomi T *et al.* Repeat pulmonary resection for isolated recurrent lung metastases yields results comparable to those after first pulmonary resection in colorectal cancer. World J Surg 2005;29:363–8.
[8] Pfannschmidt J, Muley T, Dienemann H, Hoffmann H. Prognostic factors and survival after complete resection of pulmonary metastases from colorectal carcinoma: experiences in 167 patients. J Thorac Cardiovasc Surg 2003;126:732–9.
[9] Vogelsang H, Haas S, Hierholzer C, Berger U, Siewert JR, Prauer H. Factors influencing survival after resection of pulmonary metastases from colorectal cancer. Br J Surg 2004;91:1066–71.
[10] Koga R, Yamamoto J, Saiura A, Yamaguchi T, Hata E, Sakamoto M. Surgical resection of pulmonary metastases from colorectal cancer: four favourable prognostic factors. Jpn J Clin Oncol 2006;36:643–8.
[11] Rena O, Casadio C, Viano F, Cristofori R, Ruffini E, Filosso PL *et al.* Pulmonary resection for metastases from colorectal cancer: factors influencing prognosis. Twenty-year experience. Eur J Cardiothorac Surg 2002; 21:906–12.
[12] Takakura Y, Miyata Y, Okajima M, Okada M, Ohdan H. Short disease-free interval is a significant risk factor for intrapulmonary recurrence after resection of pulmonary metastases in colorectal cancer. Colorectal Dis 2010; 12:68–75.

[13] Lin BR, Chang TC, Lee YC, Lee PH, Chang KJ, Liang JT. Pulmonary resection for colorectal cancer metastases: duration between cancer onset and lung metastasis as an important prognostic factor. Ann Surg Oncol 2009;16:1026–32.
[14] Zampino MG, Maisonneuve P, Ravenda PS, Magni E, Casiraghi M, Solli P *et al*. Lung metastases from colorectal cancer: analysis of prognostic factors in a single institution study. Ann Thorac Surg 2014;98:1238–45.
[15] Welter S, Jacobs J, Krbek T, Poettgen C, Stamatis G. Prognostic impact of lymph node involvement in pulmonary metastases from colorectal cancer. Eur J Cardiothorac Surg 2007;31:167–72.
[16] Kanzaki R, Higashiyama M, Oda K, Fujiwara A, Tokunaga T, Maeda J *et al*. Outcome of surgical resection for recurrent pulmonary metastasis from colorectal carcinoma. Am J Surg 2011;202:419–26.
[17] Chen F, Sakai H, Miyahara R, Bando T, Okubo K, Date H. Repeat resection of pulmonary metastasis is beneficial for patients with colorectal carcinoma. World J Surg 2010;34:2373–8.
[18] Kim AW, Faber LP, Warren WH, Saclarides TJ, Carhill AA, Basu S *et al*. Repeat pulmonary resection for metachronous colorectal carcinoma is beneficial. Surgery 2008;144:712–7.
[19] Welter S, Jacobs J, Krbek T, Krebs B, Stamatis G. Long-term survival after repeated resection of pulmonary metastases from colorectal cancer. Ann Thorac Surg 2007;84:203–10.
[20] Watanabe K, Saito N, Sugito M, Ito M, Kobayashi A, Nishizawa Y. Incidence and predictive factors for pulmonary metastases after curative resection of colon cancer. Ann Surg Oncol 2013;20:1374–80.
[21] Blumenthal RD, Hansen HJ, Goldenberg DM. Inhibition of adhesion, invasion, and metastasis by antibodies targeting CEACAM6 (NCA-90) and CEACAM5 (Carcinoembryonic Antigen). Cancer Res 2005;65:8809–17.
[22] Beauchemin N, Arabzadeh A. Carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) in cancer progression and metastasis. Cancer Metastasis Rev 2013;32:643–71.
[23] Landreneau RJ, De Giacomo T, Mack MJ, Hazelrigg SR, Ferson PF, Keenan RJ *et al*. Therapeutic video-assisted thoracoscopic surgical resection of colorectal pulmonary metastases. Eur J Cardiothorac Surg 2000;18:671–6.
[24] Nakas A, Klimatsidas MN, Entwisle J, Martin-Ucar AE, Waller DA. Video-assisted versus open pulmonary metastasectomy: the surgeon's finger or the radiologist's eye? Eur J Cardiothorac Surg 2009;36:469–74.

eComment. Iterative metastasectomy for recurrent pulmonary disease from colorectal cancer: a challenging issue

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We read the interesting report by Hachimaru and co-workers [1] regarding a very interesting and widely debated topic and we congratulate them on the paper. Surgical removal of pulmonary colorectal carcinoma metastases has become a standard of care. Complete macroscopic resection has been proven to be the most important prognostic factor in this setting and aggressive iterative surgical procedures can also have a role. However, patient selection remains controversial [2]. Previously, Iida and co-workers [3] endeavoured to provide a rationale for pulmonary **metastasectomy** for colorectal cancer by reviewing a large series of patients and identifying prognostic factors for clinical application in order to detect patients who might benefit from surgery Hachimaru and co-workers have the merit of focusing their investigation on the subset of patients who underwent repeat pulmonary resection for recurrent lung metastases from colorectal cancer, proving the role of high preoperative serum carcinoembryonic antigen (CEA) level as significant prognostic factor even in this subset.

We reviewed our experience of 90 patients surgically treated for pulmonary metastasectomy from colorectal cancer from 2000 to 2013. Twenty-one patients (23.3%) underwent repeat pulmonary metastasectomy for lung recurrence. All repeat pulmonary metastasectomies were performed with curative intent. The median number of metastases was 2 (range: 1-7); the median follow-up after first metastasectomy was 29 months (range: 3-156 months). We agree with the authors about the result that 5 year-survival rate after initial pulmonary resection for patients who underwent iterative lung resections is not worse than that for patients without pulmonary recurrence (56% vs 58%, P=0.182 in our series). However, in our data, we did not find significant prognostic factors for this subset of patients. Only a trend toward a survival benefit was observed in patients who did not undergo liver metastasectomy (5-year survival: 85% vs 34%, P=0.008) and in male patients (3-year survival: 63% vs 35%, P=0.07). Instead, by analysing the prognostic factors for 40 patients (44.4%) who underwent both pulmonary and liver resection, we found that pulmonary unilateral vs bilateral disease (5-year survival: 52% vs 23%, P=0.014) and presence of solitary or multiple lung metastases (2-year survival: 67% vs 25%, P=0.004) significantly affected survival. In conclusion, we agree with authors that iterative lung metastasectomy from colorectal cancer disease is feasible and effective in some particular subsets of patients, who must be carefully selected by multidisciplinary cancer teams.

Nevertheless, while waiting for larger multicentre studies, we believe that taking into account all the prognostic factors already reported in the literature could help clinicians in the everyday challenging assessment of patients in the multifaceted scenario of metastatic colorectal disease.

Conflict of interest: none declared.

References

[1] Hachimaru A, Maeda R, Suda T, Takagi Y. Repeat pulmonary resection for recurrent lung metastases from colorectal cancer: an analysis of prognostic factors. Interact CardioVasc Thorac Surg 2016;22:826–30.
[2] Blackmon SH, Stephens EH, Correa AM, Hofstetter W, Kim MP, Mehran RJ *et al*. Predictors of recurrent pulmonary metastases and survival after pulmonary metastasectomy for colorectal cancer. Ann Thorac Surg 2012;94:1802–9.
[3] Iida T, Nomori H, Shiba M, Nakajima J, Okumura S, Horio H *et al*. Prognostic factors after pulmonary metastasectomy for colorectal cancer and rationale for determining surgical indications: a retrospective analysis. Ann Surg 2013;257:1059–64.