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The Assessment of Prognostic Factors for Lung Metastasectomy in Colorectal Cancer Patients With Previously Resected Liver Metastases

Ayumi Hachimaru, Ryo Maeda, Takashi Suda, Yasushi Takagi

Division of Thoracic and Cardiovascular Surgery, Fujita Health University School of Medicine, Toyoake, Japan

The purpose of this study is to investigate the prognostic factors of lung metastasectomy in patients with previously resected liver metastases. Thirty-three patients underwent complete resection of lung metastases after previous liver metastasectomy from colorectal cancer between January 2004 and December 2013. In univariate analyses, all cumulative survival curves were estimated using the Kaplan-Meier method, and differences in variables were evaluated using the log-rank test. Multivariate analyses were performed using the Cox proportional hazards regression model. The 5-year survival rate of all 33 patients after lung metastasectomy was 31%. Univariate analysis identified 2 significant prognostic factors: preoperative serum carcinoembryonic antigen level ($P = 0.035$) and maximum tumor size ($P = 0.029$). Subgroup analysis with a combination of these 2 independent prognostic factors revealed 2-year survival rates of 100%, 92.3%, and 0% for patients with 0, 1, and 2 risk factors, respectively. We identified 2 independent poor prognostic factors for pulmonary metastasectomy in patients with previously resected liver metastases: high serum carcinoembryonic antigen level before lung metastasectomy, and maximum size of lung metastases. When these 2 factors are combined, higher- and lower-risk subgroups can be identified, which may help select patients with previously resected liver metastases who benefit most from lung metastasectomy.

Key words: Colorectal cancer – Lung metastasis – Liver metastasis – Prognostic factor

Colorectal cancer is the most common tumor type diagnosed in developed countries.[1] Despite improved recent outcomes obtained by advances in chemotherapy, surgical technique, and curative surgery, it remains one of the leading causes of cancer death worldwide.[1] A quarter of patients with colorectal cancer have metastatic lesions at diagnosis, and in nearly half of these

Corresponding author: Ryo Maeda, MD, Division of Thoracic and Cardiovascular Surgery, Fujita Health University School of Medicine, 1-98, Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192 Japan.
Tel.: +81 562 93 9030; Fax: +81 562 93 5845; E-mail: r-maeda@fujita-hu.ac.jp

patients, metastases will develop often in liver. Surgery has been consistently reported as a potentially curative option for liver-limited disease, with 5-year survival rates of 34% to 55%.[2–6]

The lung is also one of the most frequently affected metastatic sites in patients with colorectal cancer. Thus far, several studies have demonstrated the efficacy of lung metastasectomy in colorectal cancer patients.[7–10] In particular, for a selected group of patients with metastases limited to the lungs, 5-year survival rates of 33% to 67% have been reported,[7–10] with higher percentages in the last 5 years, probably due to better patient selection.

Although surgical resection for liver or pulmonary metastases from colorectal cancer has been widely accepted and performed, the efficacy and indications for resecting both liver and pulmonary metastases are unknown. Some studies have reported significantly reduced survival for patients with lung and liver metastases compared with patients having lung-only disease.[11,12] However, the influence of previous liver surgery on patients with lung metastases remains unknown because of heterogeneity among published studies. Therefore, we reviewed a series of consecutive patients with previously resected liver metastases who underwent complete resections for lung metastases from colorectal cancer at our institution. The main purpose of this study was to investigate the prognostic factors of metastasectomy in patients with previously resected liver metastases, which may be clinically helpful for defining a subset of patients who are most likely to benefit from lung metastasectomy.

Patients and Methods

A total of 138 patients underwent complete lung resection for the first time due to metastases of colorectal cancer between January 2004 and December 2013 at our institution. Among the 138 patients, 33 underwent resection of lung metastases after previous liver metastasectomy from colorectal cancer.

All patients who underwent resection of their pulmonary metastases met the following criteria: (1) no evidence of extrathoracic metastasis except liver metastasis, (2) no evidence of uncontrolled primary site, (3) chest computed tomography demonstrating that complete resection could be warranted regardless of the number of lesions, and (4) good general condition and adequate respiratory function to tolerate lung resection. Lymph node dissection was not routinely performed. The detailed regimens of chemotherapy were different among patients; however, all 33 patients with previously resected liver metastases underwent preoperative or postoperative chemotherapy.

We reviewed each patient's medical record to obtain clinicopathologic information, which included age (dichotomized at the median age of 67 years), sex, smoking history (never or ever smoker), ratio of prethoracotomy forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC; $>70\%$ or $<70\%$), prethoracotomy serum carcinoembryonic antigen (CEA) level (cutoff at the normal upper limit of 5 ng/mL), primary site (colon or rectum), Dukes' stage of the primary tumor (A–B or C–D), histologic differentiation of the primary tumor (well differentiated or moderately/poorly differentiated), the disease-free interval between the colorectal resection and the first pulmonary resection ($\leq$24 months or $>$24 months), tumor laterality (hemilateral or bilateral), time from liver metastasectomy to lung metastasectomy ($\leq$12 months or $>$12 months), number of pulmonary metastases, and largest diameter of the resected tumor ($\leq$1 cm or $>$1 cm).

The duration of overall survival rate was calculated in months from the date of pulmonary metastasectomy to the date of death due to any etiology or the date of the last follow-up. In univariate analyses, all cumulative survival curves were estimated using the Kaplan–Meier method, and differences in variables were evaluated using the log-rank test. Multivariate analyses were performed using the Cox proportional hazards regression model. All p values reported were 2-sided, and the significance level was set at less than 0.05. Analyses were performed using the statistical software SPSS 11.0 (Dr. SPSS II for Windows, Standard Version 11.0, SPSS Inc., Chicago, Illinois, USA).

Results

The 5-year survival rate of all 138 patients who underwent complete lung resection was 61.7%. Of the 138 patients, 33 underwent resection of lung metastases after previous liver metastasectomy from colorectal cancer. Characteristics of patients who underwent resection of lung metastases after previous liver metastasectomy are shown in Table 1. The median follow-up period was 22 months (range, 5–69 months). The cohort consisted of 19 women and 14 men. The age ranges from 41 to 79 years with a median of 67 years. Seventeen patients with previously resected primary colorectal cancer first

Table 1 Patient characteristics and 5-year survival rates according to the clinicopathologic features

Characteristic	No. (%) of patients	Five-year survival rates after the pulmonary resection, %	Univariate *P* value[a]
Overall	33	30.5	
Age			
≤67 y	16	33.2	
>67 y	17	32.5	0.661
Sex			
Women	19	19.2	
Men	14	49.5	0.093
Smoking habits			
Nonsmoker	14	17.6	
Current or former smoker	10	23.7	0.422
Unknown	9		
FEV_1/FVC			
≥70%	18	34.4	
<70%	9	17.8	0.229
Unknown	6		
CEA			
Within normal range	16	61.5	
Elevated	16	13.2	0.035*
Unknown	1		
Primary site			
Colon	16	25.6	
Rectum	17	68.1	0.199
Dukes' stage			
A–B	8	48.6	
C–D	16	19.0	0.111
Unknown	9		
Histologic differentiation			
Well differentiated	6	41.7	
Moderately/poorly differentiated	21	18.4	0.797
Unknown	6		
Time from primary tumor resection to lung metastasectomy			
≤24 mo	18	36.4	
>4 mo	15	44.9	0.238
Time from liver metastasectomy to lung metastasectomy			
≤12 mo	15	22.2	
>12 mo	18	45.5	0.757
Tumor laterality			
Hemilateral	26	24.1	
Bilateral	7	66.7	0.383
No. of pulmonary metastases			
1	17	32.0	
≥2	16	29.9	0.647
Maximum tumor size			
≤1 cm	17	44.7	
>1 cm	15	22.3	0.029*
Unknown	1		

[a]Log-rank test.

CEA, preoperative serum CEA level (normal upper limit at 5 ng/mL); FEV_1/FVC, ratio of forced expiratory volume in 1 second to forced vital capacity.

*Indicates significance.

underwent resection of liver metastases and then surgery for lung metastases (Figure 1). The primary tumor, the liver and pulmonary metastasis were simultaneously detected in 3 patients (Figure 1). The simultaneous liver and pulmonary metastasectomies were performed in 6 patients. Three patients underwent pulmonary resection after simultaneous primary colorectal cancer and liver metastases resection (Figure 1). Video-assisted thoracic surgery (VATS) was performed in all the 33 patients. No patients died as a direct result of surgery, and all patients were discharged home after pulmonary metastasectomy.

The 5-year survival rate of the 33 patients was 30.5%, which was significantly lower than that of 105 patients with pulmonary metastasectomy alone (5-year survival rate, 62.4%; $P = 0.011$; Fig. 1A). Table 1 lists the survival rates at 5 years after the first pulmonary resection according to clinicopathologic features in all 33 patients. Univariate analysis (log-rank test) identified 2 significant prognostic factors: preoperative serum CEA level and maximum tumor size (Table 1). The 5-year survival rates of the patients with a high preoperative CEA level and those with a normal CEA level were 13.2% and 61.5%, respectively ($P = 0.035$; Fig. 2). The 5-year survival rate of the patients with maximum tumor size greater than 1 cm was 22.3%, which was significantly lower than that of the patients with maximum tumor size of 1 cm or less (44.7%; $P = 0.029$; Fig. 3). On multivariate analysis using the Cox regression model, preoperative serum CEA level ($P = 0.030$) and maximum tumor size ($P = 0.021$) remained statistically significant independent prognostic factors (Table 2).

Subgroup analysis with a combination of these 2 independent prognostic factors (preoperative serum CEA level and maximum tumor size) revealed 2-year survival rates of 100%, 92.3%, and 0% for patients with 0, 1, or 2 risk factors, respectively (Fig. 4). The difference in survival rates was statistically significant between the 0 and 2 risk factor groups ($P < 0.001$) and between the 1 and 2 risk factor groups ($P < 0.001$), but not between the 1 and 2 risk factor groups ($P = 0.239$; Fig. 5). When we divided the patients into 2 groups with 2 factors, or either 0 risk factors or 1 risk factor, the 5-year survival rates were 0% and 95.2%, respectively ($P < 0.001$).

Discussion

Iida *et al*[13] proposed that metastasis to the lungs and the upstream organs, or to the liver, can be regarded

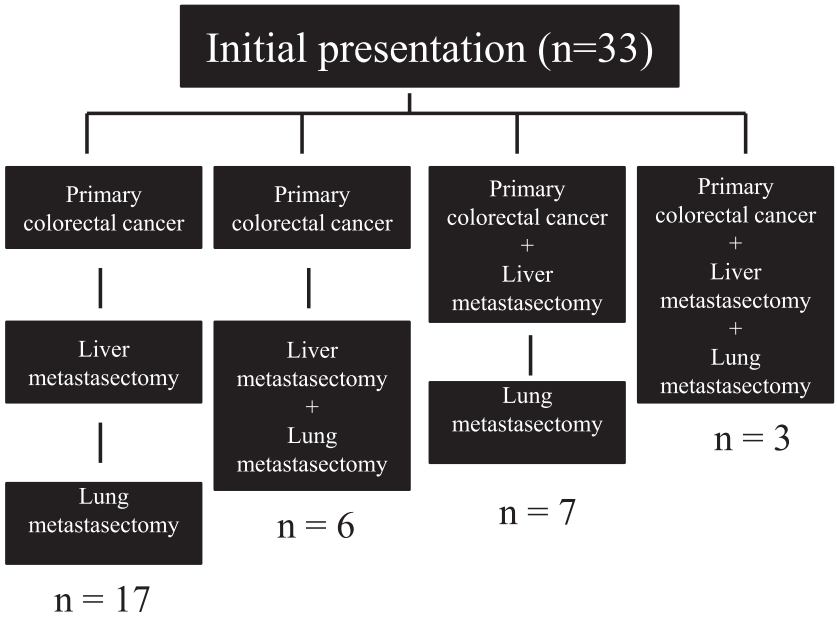

Fig. 1 Sequence of liver and lung metastases after the resection of the primary colorectal cancer.

as a "semilocal" disease and can explain favorable outcomes after lung and liver metastasectomy in colorectal cancer patients. They also suggested that once the filtering system in the lungs is collapsed by tumor growth, distant metastases will develop in the organs downstream from the lung, such as the brain and bones, which are generally unresectable and are associated with a poor prognosis. Therefore, even if there are multiple pulmonary metastases, surgical resection still has the potential for better survival as long as the lung's defense system is functioning and preventing tumor cells from spreading to downstream organs. Although surgical resection for lung metastases from colorectal cancer has been widely accepted and performed, the efficacy and indications for resecting both liver and lung metastases are unknown. Several studies have reported the usefulness of resecting both liver and lung metastases from colorectal cancer, reporting 5-year survival rates of 27% to 74%.[14–19] However, Riquet *et al*[11] reported a series of 127 patients who underwent lung metastasectomy; 29 of them (23%) had undergone previous liver surgery for liver metastases. Their data indicate that prior

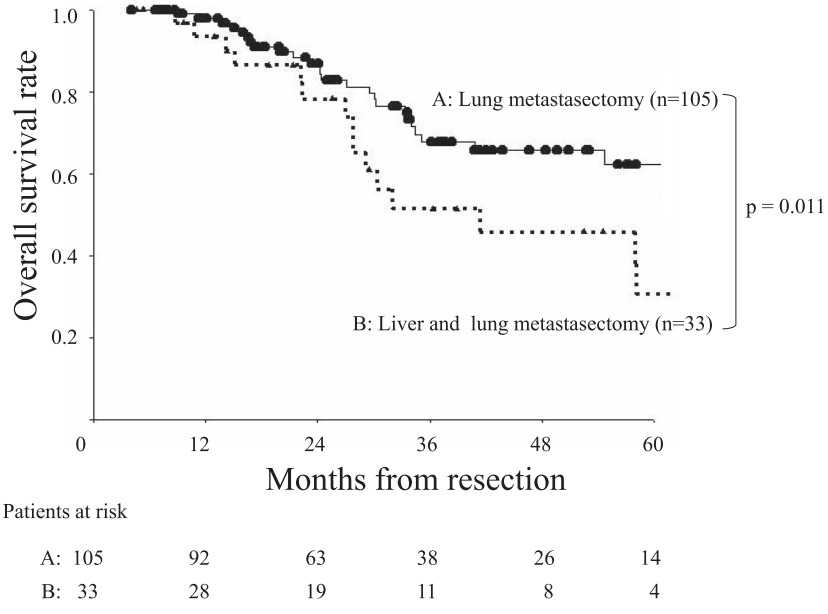

Fig. 2 Overall survival curves for patients according to the history of the prior resection of liver metastases.

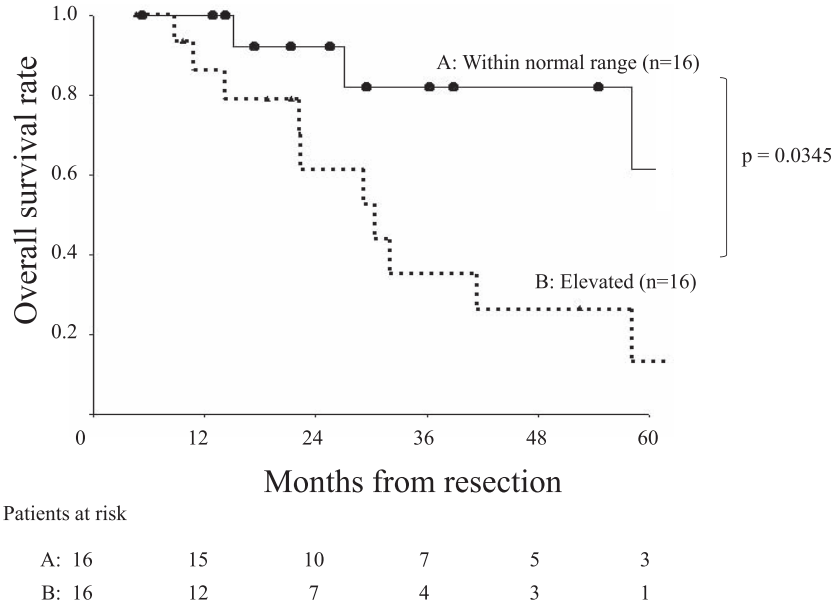

Fig. 3 Overall survival curves for patients according to the prethoracotomy serum CEA level.

surgery for liver metastases is associated with a higher risk for tumor recurrence and death after lung metastasectomy. Hattori *et al*[12] recently also reported that the survival rate after both liver and lung metastasectomies was worse than the survival rate after lung metastasectomy alone. In this study, the 5-year survival rate of patients who underwent lung metastasectomy after liver resection for metastatic liver tumor from colorectal cancer was significantly lower than that of patients who underwent lung metastasectomy alone in this study. The main purpose of this study was to investigate the prognostic factors of metastasectomy in patients with previously resected liver metastases, which may be clinically helpful for defining a subset of patients who are most likely to benefit from pulmonary metastasectomy.

Various factors associated with prolonged survival after surgery for lung metastases from colorectal have been identified, including: (1) a long disease-free interval[20–22]; (2) prethoracotomy CEA level[7,8,23–25]; (3) a single isolated metastasis less than 3 cm in size[26–28]; and (4) the absence of thoracic lymph node invasion.[8,29] Among the patients who underwent lung metastasectomy after liver resection, univariate analysis identified 2 significant prognostic factors: preoperative serum CEA level and maximum tumor size in this study. In addition, high CEA level before metastasectomy and maximum size of lung metastases remained statistically significant independent poor prognostic factors also on multivariate analysis using the Cox regression model.

Preoperative CEA levels may serve as a biochemical marker for postresection outcome. CEA participates in intracellular recognition and metastasis by functioning as an attachment factor.[30] CEA levels may therefore reflect the highly malignant nature of cancer cells that undergo systemic dissemination. In the current study, preoperative CEA was also an independent poor prognostic factor in patients with previous liver metastasectomy. Therefore, the preoperative CEA level should be taken into account when selecting patients for a lung resection.

Table 2 Multivariate analysis of prognostic factors

Factors	Unfavorable	Favorable	HR	95% CI	*P* value
Gender	Women	Men	1.501	0.200–11.233	0.693
Primary site	Colon	Rectum	2.971	0.477–18.529	0.244
Dukes' stage	C–D	A–B	2.233	0.388–12.848	0.368
CEA	Elevated	Within normal range	8.961	1.237–64.891	0.030*
Maximum tumor size, cm	>1	<1	18.894	1.567–227.881	0.021*

CEA, preoperative serum carcinoembryonic antigen level; CI, confidence interval; HR, hazard ratio for death.

*Indicates significance.

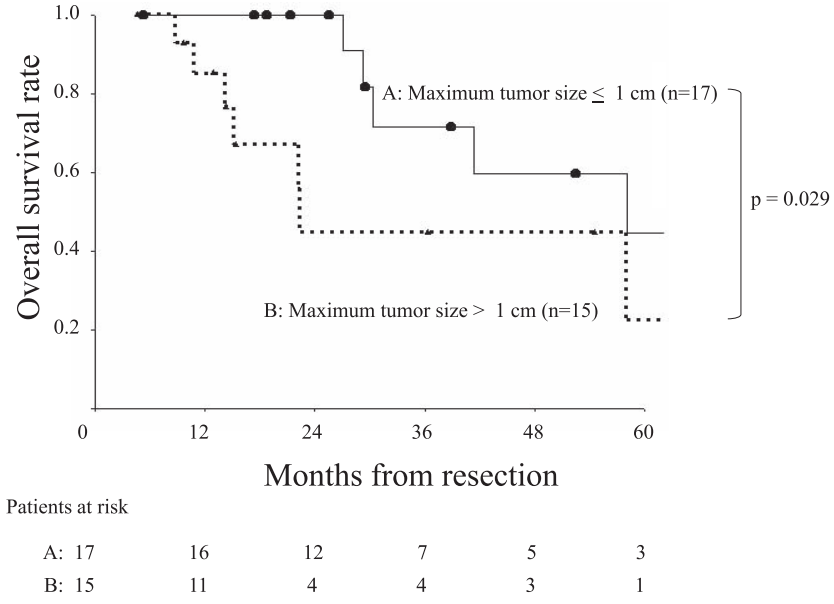

Fig. 4 Overall survival curves for patients according to the maximum size of lung metastases.

In this study, the 5-year survival rate of the patients with maximum metastatic tumor size greater than 1 cm was significantly lower than that of patients with maximum metastatic tumor size 1 cm or less. Patients who have undergone liver metastasectomy undergo intensive surveillance in the postoperative follow-up program after liver metastasectomy. Therefore, the larger size of the tumor may indicate more aggressive biology for a rapid growth, ultimately determining poorer overall survival.

When we divided patients into groups of 0, 1, or 2 risk factors using these risk factors (serum CEA level and maximum size of lung metastases) described above, we found 2-year survival rates of 100%, 92.3%, and 0%, respectively. This may help select patients who benefit most from pulmonary metastasectomy.

This was a retrospective study, and the analyses conducted had several limitations. In particular, this study had a retrospective design and consisted of a small patient population. The other drawback is that the recent development of systemic chemotherapy in combination with molecular targeting agents has resulted in prolonged survival for patients with

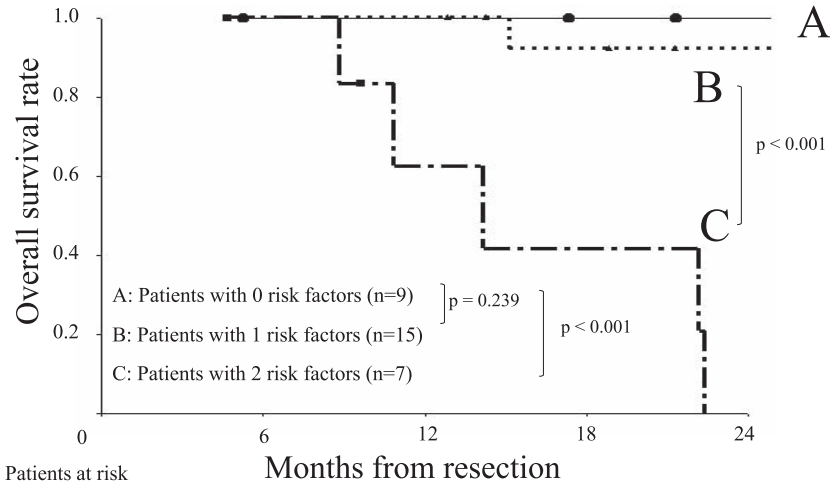

Fig. 5 Overall survival curves for the patients according to the number of prognostic factors.

metastases from colorectal cancer. Although adjuvant and/or neoadjuvant systemic chemotherapy is thus thought to play an important role in patients with both liver and pulmonary metastases from colorectal cancer, we did not analyze the patients in this respect.

Conclusion

In conclusion, we identified 2 independent poor prognostic factors for lung metastasectomy in patients with previously resected liver metastases from colorectal cancer: high serum CEA level before lung metastasectomy and larger maximum tumor size. When these 2 factors are combined, higher- and lower-risk subgroups can be identified, which may help select patients with previously resected liver metastases who benefit most from lung metastasectomy.

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References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;**61**(2):69–90
2. Oh SY, Kim do Y, Suh KW. Oncologic outcomes following metastasectomy in colorectal cancer patients developing distant metastases after initial treatment. *Ann Surg Treat Res* 2015;**88**(5):253–259
3. Kuo IM, Huang SF, Chiang JM, Yeh CY, Chan KM, Chen JS *et al*. Clinical features and prognosis in hepatectomy for colorectal cancer with centrally located liver metastasis. *World J Surg Oncol* 2015;**13**(4):92
4. Kulaylat AN, Schubart JR, Stokes AL, Bhayani NH, Wong J, Kimchi ET *et al*. Overall survival by pattern of recurrence following curative intent surgery for colorectal liver metastasis. *J Surg Oncol* 2014;**110**(8):1011–1015
5. Cokmert S, Ellidokuz H, Demir L, Fuzun M, Astarcioglu I, Aslan D *et al*. Survival outcomes of liver metastasectomy in colorectal cancer cases: a single-center analysis in Turkey. *Asian Pac J Cancer Prev* 2014;**15**(13):5195–5200
6. Frankel TL, D'Angelica MI. Hepatic resection for colorectal metastases. *J Surg Oncol* 2014;**109**(1):2–7
7. 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**(2): 435–440
8. 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**(4):1238–1245
9. Cho JH, Hamaji M, Allen MS, Cassivi SD, Nichols FC III, Wigle DA *et al*. The prognosis of pulmonary metastasectomy depends on the location of the primary colorectal cancer. *Ann Thorac Surg* 2014;**98**(4):1231–1237
10. Meimarakis G, Spelsberg F, Angele M, Preissler G, Fertmann J, Crispin A *et al*. Resection of pulmonary metastases from colon and rectal cancer: factors to predict survival differ regarding to the origin of the primary tumor. *Ann Surg Oncol* 2014;**21**(8): 2563–2572
11. Riquet M, Foucault C, Cazes A, Mitry E, Dujon A, Le Pimpec Barthes F *et al*. Pulmonary resection for metastases of colorectal adenocarcinoma. *Ann Thorac Surg* 2010;**89**(2):375–380
12. Hattori N, Kanemitsu Y, Komori K, Shimizu Y, Sano T, Senda Y *et al*. Outcomes after hepatic and pulmonary metastasectomies compared with pulmonary metastasectomy alone in patients with colorectal cancer metastasis to liver and lungs. *World J Surg* 2013;**37**(6):1315–1321
13. Iida T, Nomori H, Shiba M, Nakajima J, Okumura S, Horio H *et al*; Metastatic Lung Tumor Study Group of Japan. Prognostic factors after pulmonary metastasectomy for colorectal cancer and rationale for determining surgical indications: a retrospective analysis. *Ann Surg* 2013;**257**(6):1059–1064
14. Kobayashi K, Kawamura M, Ishihara T. Surgical treatment for both pulmonary and hepatic metastases from colorectal cancer. *J Thorac Cardiovasc Surg* 1999;**118**(6):1090–1096
15. Nagakura S, Shirai Y, Yamato Y, Yokoyama N, Suda T, Hatakeyama K. Simultaneous detection of colorectal carcinoma liver and lung metastases does not warrant resection. *J Am Coll Surg* 2001;**193**(2):153–160
16. Mineo TC, Ambrogi V, Tonini G, Bollero P, Roselli M, Mineo D *et al*. Longterm results after resection of simultaneous and sequential lung and liver metastases from colorectal carcinoma. *J Am Coll Surg* 2003;**197**(3):386–391
17. Reddy RH, Kumar B, Shah R, Mirsadraee S, Papagiannopoulos K, Lodge P *et al*. Staged pulmonary and hepatic metastasectomy in colorectal cancer–is it worth it? *Eur J Cardiothorac Surg* 2004;**25**(2):151–154
18. Shah SA, Haddad R, Al-Sukhni W, Kim RD, Greig PD, Grant DR *et al*. Surgical resection of hepatic and pulmonary

metastases from colorectal carcinoma. *J Am Coll Surg* 2006; **202**(3):468–475

19. Miller G, Biernacki P, Kemeny NE, Gonen M, Downey R, Jarnagin WR *et al*. Outcomes after resection of synchronous or metachronous hepatic and pulmonary colorectal metastases. *J Am Coll Surg* 2007;**205**(2):231–238
20. 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**(5):906–912
21. 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**(7):68–75
22. 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**(4):1026–1032
23. Onaitis MW, Petersen RP, Haney JC, Saltz L, Park B, Flores R *et al*. Prognostic factors for recurrence after pulmonary resection of colorectal cancer metastases. *Ann Thorac Surg* 2009;**87**(6): 1684–1688
24. Iisaza T, Suzuki M, Yoshida S, Motohashi S, Yasufuku K, Iyoda A *et al*. Prediction of prognosis an surgical indications for pulmonary metastasectomy from colorectal cancer. *Ann Thorac Surg* 2006;**82**(1):254–260
25. Inoue M, Ohta M, Iuchi K, Fujiwara K, Fukuhara K, Yasumitsu T. Surgery for pulmonary metastases from colorectal cancer. *Ann Thorac Surg* 2000;**70**(2):380–383
26. 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**(3):732–739
27. 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**(8):1066–1071
28. 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**(10):643–648
29. 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**(2):167–172
30. 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**(19):8809–8817