

Review

Factors Affecting Survival in Patients with Lung Metastases from Colorectal Cancer. A Short Meta-analysis

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Abstract. Liver and pulmonary metastases (PMs) are relatively common in patients with colorectal cancer. The majority of metastases are suitable for surgical resection, and the effectiveness of metastasectomy is usually assessed based on overall survival (OS). Metastasectomy provides a mean 5-year OS rate of approximately 50%, but the results are better in patients with liver metastases compared to those with PMs. Unfortunately, the presence of bilateral or multiple PMs represents a relative contraindication to surgical metastasectomy. Unresectable PMs can be safely treated with percutaneous radiofrequency ablation or radiotherapy, but the reported results vary widely. Several clinical prognostic factors affecting OS after metastasectomy have been reported, such as number of PMs, hilar or mediastinal lymph node involvement, disease-free interval, age and gender, resection margins, size of the metastases, neoadjuvant chemotherapy administration, and histological type of the primary cancer. The accurate evaluation of all clinical prognostic factors, circulating and immuno-histochemical markers, and the study of gene mutational status will lead to a more accurate selection of patients scheduled to metastasectomy, with the aim of improving outcome.

*This article reports in part the discussion about the abstract presented at the European Lung Cancer Conference (ELCC), Geneva (Switzerland) 15-18 April, 2015 (32).

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Key Words: Colorectal cancer, metastatic colorectal cancer, pulmonary metastases, lung metastases, prognostic factor, review.

Colorectal cancer (CRC) is a common malignancy, with approximately 1,360,000 new cases each year worldwide (1). However, in the USA, an annual decline in CRC incidence rate of 3.6% has been observed during the past five years (2). The postoperative overall survival (OS) of patients varies widely, ranging between 90% and 10%, according to the stage of the disease at the time of surgery (3). In the European Union, the estimated death rates per 100,000 people for the year 2015 were 10.19% and 9.36% in men and women, respectively (4). Preoperative staging of CRC requires both endoscopic and radiographic studies. In the primary diagnosis of CRC and early detection of cancer, colonoscopy is the best diagnostic tool. In selected patients, not scheduled for colonoscopy, contrast-enhanced multi-detector computed tomography (CT) colonography (virtual colonoscopy) is considered a validated diagnostic modality, having a high accuracy in the definition of T and M, but little sensitivity and specificity in the definition of N (5, 6).

Metastases from Colorectal Cancer

In patients with CRC, liver metastases (LMs) and pulmonary metastases (PMs) are common, and approximately 20% of patients present with stage IV disease at the time of diagnosis (7). In the presence of either LMs or PMs from CRC surgical metastasectomy still represents the treatment of choice, prolonging OS and providing several long-term benefits (8, 9). The data obtained from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) registry show that the majority (67.4%) of patients with stage IV CRC underwent primary tumor resection, and that the overall postoperative survival rate increased progressively over the two past decades (10). However, especially in patients with multiple or surgically difficult-to-remove metastases, other therapeutic options should be considered, such as cytotoxic chemotherapy and targeted

therapies (11), external radiotherapy (12, 13) and radiofrequency ablation (14-16). It has been reported that 5-6% of colon cancers and 10-18% of rectal cancers spread to the lung, with an overall incidence of PMs up to 15% (17). Another review study found that the incidence of isolated PMs was 6% and 12%, respectively, and that isolated PMs were uncommon (18). According to the Danish Colorectal Cancer Group (DCCG) database, the occurrence of a synchronous PM in patients with CRC accounts for 7.5%, and approximately one third are exclusively localized in the lung (19). The National Institute of Clinical Excellence (NICE) recommends the use of CT scanning of both the thorax and upper and lower abdomen for staging CRC (20). Unfortunately, CRC patients usually have a relatively advanced age, and thus pulmonary nodules are very common findings, ranging from 4% to 42% of all chest CT performed (21). However, the risk that one of these nodules can be a metastasis is less than 30%, and some studies suggest selecting patients at risk of LMs, such as those with lymph node involvement and LMs, before performing CT study (17, 21). According to a recent meta-analysis, contrast-enhanced magnetic resonance imaging (MRI) is the imaging study of choice in evaluating LMs, especially after neoadjuvant chemotherapy, and ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F -FDG PET) should be considered a second-line imaging modality (22, 23). Kim *et al.* (24) reviewed 319 patients (median age=60 years, range=26-89 years) with CRC and no LMs, and found that 136 (42.6%) had indeterminate lung nodules on CT, out of which 14.7% were PMs. A prospective analysis study found that 8.5% and 4.3% had PMs or other pulmonary malignancies, respectively, suggesting to use chest CT as screening imaging study, followed by ^{18}F -FDG PET combined with perfusion CT (PET/CT) in the presence of pulmonary nodules revealed on CT (25). Other imaging studies for staging patients with CRC are available, including dynamic enhanced MRI and diffusion-weighted MRI, but they are not routinely used (26).

Treatment of Pulmonary Metastases

The optimal treatment strategy of pulmonary metastasectomy (PMx) requires a careful definition of patients with potentially resectable PMs, according to both clinical and non-clinical parameters. The feasibility and usefulness of PMx was described for the first time in the 1940s (27, 28). Since then, a number of studies have reported on the advantages of surgery in patients with PMs of different origin. Currently, PMx is routinely performed worldwide, representing an effective option strategy in patients with metastatic CRC, but the short- and long-term results vary widely. The criteria used in selecting patients and the multimodal adjuvant treatment administered may justify the

different OS rates reported by the authors (19, 29). In some studies, patients who underwent simultaneous PMx and liver metastasectomy had similar or slightly reduced OS compared to those with exclusively PMs, and the number of metastases represented an independent factor affecting survival (30-32). Adjuvant chemotherapy usually improves the disease-free interval (DFI) after surgery (33). Patients with PMs as first site of metastasis have a worse outcome, while re-metastasectomy may lead to OS rates up to 70%, justifying an aggressive surgical approach (34, 35). However, other studies report that the 5-year OS after repeated PMx ranges from 32% to 42% (36, 37). Unfortunately, patients with previously resected LMs and multiple PMs, have shorter DFI and OS (35-38).

CT-guided radiofrequency ablation causes coagulation necrosis of the metastatic tissue and is usually suggested in selected patients with multiple and surgically difficult-to-treat PMs. The results are promising, and the estimated 3- and 5-year OS range between 44-65% and 20-51%, respectively, but the 3-year tumor-free survival is approximately 15% (14, 15). Radiotherapy for isolated PMs, using different radiation techniques, can be effective in patients unsuitable for surgery, achieving 3-year OS rates ranging from 40% to 60%, but a 5-year overall relapse-free survival less than 20% (12, 13).

Prognostic Factors Affecting Outcome

Several clinical prognostic factors (PFs), including serum tumor markers, affecting outcome have been described. We analyzed the results of 15 studies involving a total of 1,669 patients (median=89, range=51-229 patients per study) that met the following criteria: (i) at least 50 patients with PMs from CRC surgically resected with curative intent; (ii) 5-year OS reported in the study; (iii) both univariate and multivariate analysis of PFs of survival presented. The mean 5-year OS was 49% (median 45%, range 25-72%) (Figure 1). No correlation was found ($R=0.20$, $p=0.48$) between number of patients and OS rate, and thus the surgical experience does not seem to affect outcome.

Table I resumes the PFs reported in the studies selected for our analysis (8, 9, 29, 39-50). The main independent predictors of worse results were elevated preoperative serum levels of carcinoembryonic antigen (CEA), the presence of multiple or bilateral PMs *vs.* single or unilateral PMs, hilar or mediastinal lymph node involvement, and a shorter DFI from PMx (Figure 2). Negative PFs were also no neoadjuvant chemotherapy administration (9, 47), younger (<60) or older (>60) age (43, 8), and incomplete (R1) *vs.* complete (R0) pulmonary resection (9, 49). Other negative PFs were male gender, size of the PMs, shorter interval for development of PMs from CRC resection, and histological type other than well-differentiated adenocarcinoma (8, 43, 45, 46). Many

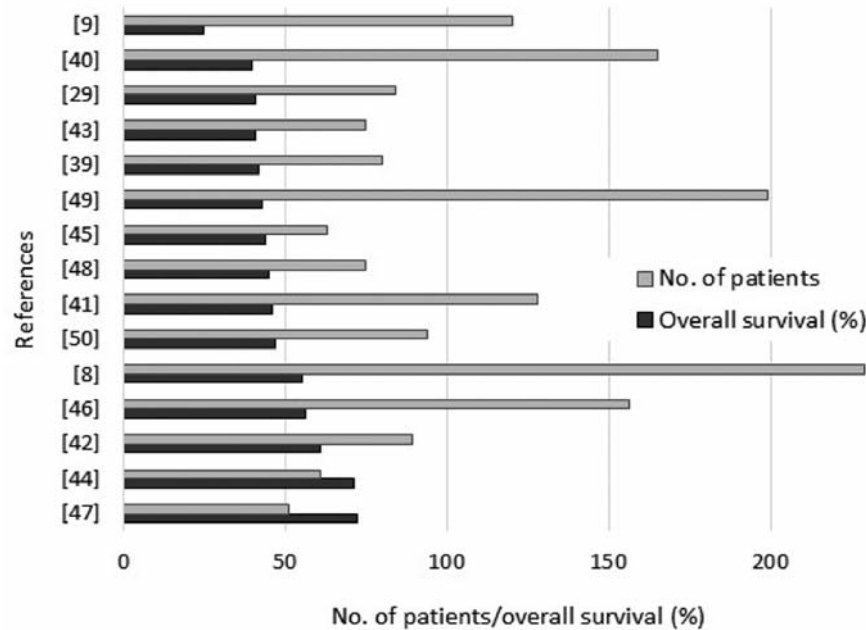


Figure 1. Five-year overall survival of patients with pulmonary metastases from colorectal cancer who underwent metastasectomy and number of treated patients (8, 9, 29, 39-50).

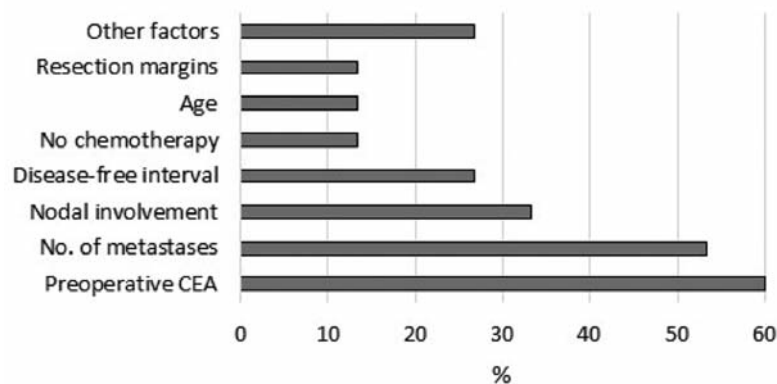


Figure 2. Main independent prognostic factors for survival at the multivariate analysis in patients with pulmonary metastases from colorectal cancer who underwent metastasectomy. The data are expressed as percentage of authors who reported them (8, 9, 29, 39-50).

serum tumor markers other than CEA, such as carbohydrate antigen (CA) 19-9 and tissue polypeptide-specific antigen (TPS), alone or in combination have been reported to be useful in predicting the onset of metastases and results of PMx (48, 51, 52). Simultaneous multi-analyte assay of a panel of circulating markers, including CEA, CA 19-9, CA 72-4, cytokeratin fragment (CYFRA) 21-1 and osteopontin, can be used for CRC screening, but not for revealing metastases, while baseline preoperative C-reactive protein measurement inversely correlates with OS, regardless of the presence of

PMs (53, 55). In addition, several immunohistochemical markers, including the overexpression of FBJ murine osteosarcoma viral oncogene homolog B (FOS-B), tumor-suppressor protein p53, cellular proliferation protein Ki-67 and stromal expression of heat-shock protein 27 (Hsp27) may correlate to survival of patients with metastasized CRC (56-59). In certain studies, the intratumoral expression of thymidylate (TS), orotate phosphoribosyltransferase (OPRT) and dihydropyrimidine dehydrogenase (DPD) are closely related with efficacy of chemotherapy (60).

Table I. Main prognostic factors affecting overall survival of patients with pulmonary metastases from colorectal cancer at uni- and multivariate analysis (8, 9, 29, 39-50).

Prognostic factors at univariate analysis	Prognostic factors at multivariate analysis
Age of the patient	Age of the patient
Complete resection of the metastasis	Complete resection of the metastasis
Disease-free interval	Disease-free interval
Extra-pulmonary metastases	Extra-pulmonary metastases
Interval after primary tumor resection	Interval after primary tumor resection
Nodal involvement	Nodal involvement
Number of metastases	Number of metastases
Tissue polypeptide-specific antigen	
Tumor size	
Tumor-node-metastasis stage	
Unilateral vs. bilateral metastasis	

Molecular Prognostic Factors

More recently, molecular markers and oncogene mutations have been found to be related to PMs development, also affecting the results of PMx. Kristen rat sarcoma viral oncogene homologue (*KRAS*) is an essential component the epidermal growth factor receptor (*EGFR*) signaling cascade, and *KRAS* gene mutations promote tumor cells invasion and are usually associated with a poor prognosis (58, 61). *KRAS* and v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) mutations were found to be independent PFs for CRC LMs, and can be useful in selecting patients requiring metastasectomy (62). In patients with CRC, these mutations are associated with high incidence of PMs and reduced OS after PMx (62-65). The VICTOR (Vioxx® in Colorectal Therapy: Definition of Optimal Regime) trial evaluated 859 CRCs, detected oncogene mutations in 4 of 19 oncogenes, including *KRAS*, *BRAF*, the phosphatidylinositol 3-kinase pathway member *PIK3CA* and the neuroblastoma RAS viral oncogene homologue (*NRAS*), and found a strong relationship between *KRAS* mutation and PMs (66). In some studies, the resistance to *EGFR* inhibitors, including gefitinib and lapatinib, was associated with *RAS* and *BRAF* mutations (67).

Conclusion

The majority of PMs are suitable for surgical resection and the effectiveness of PMx is usually assessed based on OS rates, because other validated selection criteria are not reliable (68). In certain studies, the site of primitive tumor (colorectal vs. non-colorectal) and the presence of simultaneous LMs does not significantly affect the results of PMx, which are similar to those obtained in patients with PMs exclusively (30, 32, 69). Unresectable PMs can be

safely treated with percutaneous radiofrequency ablation or radiotherapy, with palliative intent, but the result varies widely (12, 13, 15, 16, 70, 71). A careful evaluation of all clinical PFs, circulating immunohistochemical and molecular markers, and the gene mutational status will lead to a more accurate selection of patients scheduled for metastasectomy, with the aim of improving DFI and OS.

References

- 1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global statistics, 2012. *CA Cancer J Clin* 65: 87-108, 2015.
- 2 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2015. *CA Cancer J Clin* 65: 5-29, 2015.
- 3 Haggard FA and Boushey RP: Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. *Clin Colon Rectal Surg* 22: 191-197, 2009.
- 4 Malvezzi M, Bertuccio P, Rosso T, Rota M, Levi F, La Vecchia C and Negri E: European cancer mortality predictions for the year 2015: Does lung cancer have the highest death rate in EU women? *Ann Oncol* 26: 779-786, 2015.
- 5 de Haan MC, van Gelder RE, Graser A, Bipat S and Stoker J: Diagnostic value of CT-colonography as compared to colonoscopy in an asymptomatic screening population: a meta-analysis. *Eur Radiol* 21: 1747-1763, 2011.
- 6 Narayanan S, Kalra N, Bhatia A, Wig J, Rana S, Bhasin D, Vaiphei K and Khandelwal N: Staging of colorectal cancer using contrast-enhanced multidetector computed tomographic colonography. *Singapore Med J* 55: 660-666, 2014.
- 7 Edwards BK, Ward E, Kohler BA, Ehemann C, Zauberg AG, Anderson RN, Jemal A, Schymura MJ, Lansdorp-Vogelaar I, Seeff LC, van Ballegooijen M, Goede SL and Ries LA: Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer* 116: 544-573, 2010.

- 8 Blackmon SH, Stephens EH, Correa AM, Hofstetter W, Kim MP, Mehran RJ, Rice DC, Roth JA, Swisher SG, Walsh GL and Vaporciyan AA: Predictors of recurrent pulmonary metastases and survival after pulmonary metastasectomy for colorectal cancer. *Ann Thorac Surg* 94: 1802-1809, 2012.
- 9 Younes RN, Abrao F and Gross J: Pulmonary metastasectomy for colorectal cancer: long-term survival and prognostic factors. *Int J Surg* 11: 244-248, 2013.
- 10 Hu CY, Bailey CE, You YN, Skibber JM, Rodriguez-Bigas MA, Feig BW and Chang GJ: Time trend analysis of primary tumor resection for stage IV colorectal cancer: Less surgery, improved survival. *JAMA Surg* 150: 245-251, 2015.
- 11 Ciombor KK, Wu C and Goldberg RM: Recent therapeutic advances in the treatment of colorectal cancer. *Annu Rev Med* 66: 83-95, 2015.
- 12 Lee S, Kim DY, Kim SY, Koom WS, Lee SY, Kang JK and Kim MS: Curative radiotherapy using different radiation techniques for isolated lung metastasis from colorectal cancer. *Tumori* 99: 68-75, 2013.
- 13 Takahashi W, Nakajima M, Yamamoto N, Yamada S, Yamashita H, Nakagawa K, Tsuji H and Kamada T: Carbon ion radiotherapy for oligo-recurrent lung metastases from colorectal cancer: A feasibility study. *Radiat Oncol* 9: 68, 2014.
- 14 Hiraki T, Gobara H, Iguchi T, Fujiwara H, Matsui Y and Kanazawa S: Radiofrequency ablation as treatment for pulmonary metastasis of colorectal cancer. *World J Gastroenterol* 20: 988-996, 2014.
- 15 Matsui Y, Hiraki T, Gobara H, Iguchi T, Fujiwara H, Nagasaka T, Toyooka S and Kanazawa S: Long-Term Survival following Percutaneous Radiofrequency Ablation of Colorectal Lung Metastases. *J Vasc Interv Radiol* 26: 303-310, 2015.
- 16 Ferguson J, Alzahrani N, Zhao J, Glenn D, Power M, Liauw W and Morris DL: Long term results of RFA to lung metastases from colorectal cancer in 157 patients. *Eur J Surg Oncol* 41: 690-695, 2015.
- 17 Parnaby CN, Bailey W, Balasingam A, Beckert L, Eglinton T, Fife J, Frizelle FA, Jeffery M and Watson AJ: Pulmonary staging in colorectal cancer: A review. *Colorectal Dis* 14: 660-670, 2012.
- 18 Tan KK, Lopes Gde L Jr and Sim R: How uncommon are isolated lung metastases in colorectal cancer? A review from database of 754 patients over 4 years. *J Gastrointest Surg* 13: 642-648, 2009.
- 19 Nordholm-Carstensen A, Krarup PM, Jorgensen LN, Wille-Jørgensen PA and Harling H; Danish Colorectal Cancer Group: Occurrence and survival of synchronous pulmonary metastases in colorectal cancer: A nationwide cohort study. *Eur J Cancer* 50: 447-456, 2014.
- 20 Yongue G, Hotouras A, Murphy J, Mukhtar H, Bhan C and Chan CL: The diagnostic yield of preoperative staging computed tomography of the thorax in colorectal cancer patients without hepatic metastases. *Eur J Gastroenterol Hepatol* 27: 467-470, 2015.
- 21 Grossmann I, Avenarius JK, Mastboom WJ and Klaase JM: Preoperative staging with chest CT in patients with colorectal carcinoma: not as a routine procedure. *Ann Surg Oncol* 17: 2045-2050, 2010.
- 22 Niekel MC, Bipat S and Stoker J: Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: A meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology* 257: 674-684, 2010.
- 23 van Kessel CS, Buckens CF, van den Bosch MA, van Leeuwen MS, van Hillegersberg R and Verkooyen HM: Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: A meta-analysis. *Ann Surg Oncol* 19: 2805-2813, 2012.
- 24 Kim HY, Lee SJ, Lee G, Song L, Kim SA, Kim JY, Chang DK, Rhee PL, Kim JJ, Rhee JC, Chun HK and Kim YH: Should preoperative chest CT be recommended to all colon cancer patients? *Ann Surg* 259: 323-328, 2014.
- 25 Jess P, Seiersen M, Ovesen H, Sandstrøm H, Maltbæk N, Buhl AA and Roikjær O: Has PET/CT a role in the characterization of indeterminate lung lesions on staging CT in colorectal cancer? A prospective study. *Eur J Surg Oncol* 40: 719-722, 2014.
- 26 Kekelidze M, D'Errico L, Pansini M, Tyndall A and Hohmann J: Colorectal cancer: current imaging methods and future perspectives for the diagnosis, staging and therapeutic response evaluation. *World J Gastroenterol* 19: 8502-8514, 2013.
- 27 Blalock A: Recent advances in surgery. *N Engl J Med* 231: 261-267, 1944.
- 28 Alexander J and Haight C: Pulmonary resection for solitary metastatic sarcomas and carcinomas. *Surg Gynecol Obstet* 85: 129-146, 1947.
- 29 Cho S, Song IH, Yang HC and Jheon S: Prognostic factors of pulmonary metastasis from colorectal carcinoma. *Interact Cardiovasc Thorac Surg* 17: 303-307, 2013.
- 30 Kamiyoshihara M, Igai H, Kawatani N, Ibe T, Tomizawa N, Obayashi K, Shimizu K and Takeyoshi I: Lung metastasectomy for postoperative colorectal cancer in patients with a history of hepatic metastasis. *Gen Thorac Cardiovasc Surg* 62: 314-20, 2014.
- 31 Andres A, Mentha G, Adam R, Gerstel E, Skipenko OG, Barroso E, Lopez-Ben S, Hubert C, Majno PE and Toso C: Surgical management of patients with colorectal cancer and simultaneous liver and lung metastases. *Br J Surg* 102: 691-699, 2015.
- 32 Lumachi F, Mazza F, Del Conte A, Chiara GB and Basso SMM: Factors affecting survival in patients with pulmonary metastases from colorectal cancer with previously resected liver metastases who underwent lung metastasectomy [abstract]. *Ann Oncol* 26(Suppl 1): i47, 2015.
- 33 Brandi G, Derenzini E, Falcone A, Masi G, Loupakakis F, Pietrabbissa A, Pinna AD, Ercolani G, Pantaleo MA, Di Girolamo S, Grazi GL, de Rosa F and Biasco G: Adjuvant systemic chemotherapy after putative curative resection of colorectal liver and lung metastases. *Clin Colorectal Cancer* 12: 188-194, 2013.
- 34 Neeff H, Hörth W, Makowiec F, Fischer E, Imdahl A, Hopt UT and Passlick B: Outcome after resection of hepatic and pulmonary metastases of colorectal cancer. *J Gastrointest Surg* 13: 1813-1820, 2009.
- 35 Tsukamoto S, Kinugasa Y, Yamaguchi T and Shiomi A: Survival after resection of liver and lung colorectal metastases in the era of modern multidisciplinary therapy. *Int J Colorectal Dis* 29: 81-87, 2014.
- 36 Chen F, Sakai H, Miyahara R, Bando T, Okubo K and Date H: Repeat resection of pulmonary metastasis is beneficial for patients with colorectal carcinoma. *World J Surg* 34: 2373-2378, 2010.
- 37 Gonzalez M, Robert JH, Halkic N, Mentha G, Roth A, Perneger T, Ris HB and Gervaz P: Survival after lung metastasectomy in colorectal cancer patients with previously resected liver metastases. *World J Surg* 36: 386-391, 2012.

- 38 Kim CH, Huh JW, Kim HJ, Lim SW, Song SY, Kim HR, Na KJ and Kim YJ: Factors influencing oncological outcomes in patients who develop pulmonary metastases after curative resection of colorectal cancer. *Dis Colon Rectum* 55: 459-464, 2012.
- 39 Rena O, Casadio C, Viano F, Cristofori R, Ruffini E, Filosso PL and Maggi G: Pulmonary resection for metastases from colorectal cancer: factors influencing prognosis. Twenty-year experience. *Eur J Cardiothorac Surg* 21: 906-912, 2002.
- 40 Saito Y, Omiya H, Kohno K, Kobayashi T, Itoi K, Teramachi M, Sasaki M, Suzuki H, Takao H and Nakade M: Pulmonary metastasectomy for 165 patients with colorectal carcinoma: A prognostic assessment. *J Thorac Cardiovasc Surg* 124: 1007-1013, 2002.
- 41 Inoue M, Ohta M, Iuchi K, Matsumura A, Ideguchi K, Yasumitsu T, Nakagawa K, Fukuhara K, Maeda H, Takeda S, Minami M, Ohno Y and Matsuda H; Thoracic Surgery Study Group of Osaka University: Benefits of surgery for patients with pulmonary metastases from colorectal carcinoma. *Ann Thorac Surg* 78: 238-244, 2004.
- 42 Shiono S, Ishii G, Nagai K, Yoshida J, Nishimura M, Murata Y, Tsuta K, Nishiwaki Y, Kodama T and Ochiai A: Immunohistochemical prognostic factors in resected colorectal lung metastases using tissue microarray analysis. *Ann Thorac Surg* 79: 278-282, 2005.
- 43 Iizasa T, Suzuki M, Yoshida S, Motohashi S, Yasufuku K, Iyoda A, Shibuya K, Hiroshima K, Nakatani Y and Fujisawa T: Prediction of prognosis and surgical indications for pulmonary metastasectomy from colorectal cancer. *Ann Thorac Surg* 82: 254-260, 2006.
- 44 Rama N, Monteiro A, Bernardo JE, Eugénio L and Antunes MJ: Lung metastases from colorectal cancer: surgical resection and prognostic factors. *Eur J Cardiothorac Surg* 35: 444-449, 2009.
- 45 Lin BR, Chang TC, Lee YC, Lee PH, Chang KJ and Liang JT: Pulmonary resection for colorectal cancer metastases: duration between cancer onset and lung metastasis as an important prognostic factor. *Ann Surg Oncol* 16: 1026-1032, 2009.
- 46 Kanzaki R, Higashiyama M, Oda K, Fujiwara A, Tokunaga T, Maeda J, Okami J, Tanaka K, Shingai T, Noura S, Ohue M and Kodama K: Outcome of surgical resection for recurrent pulmonary metastasis from colorectal carcinoma. *Am J Surg* 202: 419-426, 2011.
- 47 Hawkes EA, Ladas G, Cunningham D, Nicholson AG, Wassilew K, Barbachano Y, Ratnayake G, Rao S and Chau I: Peri-operative chemotherapy in the management of resectable colorectal cancer pulmonary metastases. *BMC Cancer* 12: 326, 2012.
- 48 Vodicka J, Spidlen V, Treska V, Fichtl J, Simanek V, Safranek J, Vejvodova S, Mukensnabl P and Topolcan O: Surgical treatment of colorectal cancer pulmonary metastases: 12-year results. *Anticancer Res* 34: 4239-4245, 2014.
- 49 Zampino MG, Maisonneuve P, Ravenda PS, Magni E, Casiraghi M, Solli P, Petrella F, Gasparri R, Galetta D, Borri A, Donghi S, Veronesi G and Spaggiari L: Lung metastases from colorectal cancer: analysis of prognostic factors in a single institution study. *Ann Thorac Surg* 98: 1238-1245, 2014.
- 50 Suzuki H, Kiyoshima M, Kitahara M, Asato Y and Amemiya R: Long-term outcomes after surgical resection of pulmonary metastases from colorectal cancer. *Ann Thorac Surg* 99: 435-440, 2015.
- 51 Lin PC, Lin JK, Lin CC, Wang HS, Yang SH, Jiang JK, Lan YT, Lin TC, Li AF, Chen WS and Chang SC: Carbohydrate antigen 19-9 is a valuable prognostic factor in colorectal cancer patients with normal levels of carcinoembryonic antigen and may help predict lung metastasis. *Int J Colorectal Dis* 27: 1333-1338, 2012.
- 52 Holdenrieder S, Stieber P, Liska V, Treska V, Topolcan O, Dreslerova J, Matejka VM, Finek J and Holubec L: Cytokeratin serum biomarkers in patients with colorectal cancer. *Anticancer Res* 32: 1971-1976, 2012.
- 53 Lumachi F, Marino F, Orlando R, Chiara GB and Basso SMM: Simultaneous multianalyte immunoassay measurement of five serum tumor markers in the detection of colorectal cancer. *Anticancer Res* 32: 985-988, 2012.
- 54 Swede H, Hajduk AM, Sharma J, Rawal S, Rasool H, Vella AT, Tobet RE and Stevens RG: Baseline serum C-reactive protein and death from colorectal cancer in the NHANES III cohort. *Int J Cancer* 134: 1862-1870, 2014.
- 55 Lumachi F, Basso SMM, Santeufemia DA, Ermani M, Lo Re G and Chiara GB: Preoperative serum C-reactive protein and its prognostic significance in patients with stage III-IV colorectal cancer. *Anticancer Res* 34: 7263-7266, 2014.
- 56 Pfannschmidt J, Bade S, Hoheisel J, Muley T, Dienemann H and Herpel E: Identification of immunohistochemical prognostic markers for survival after resection of pulmonary metastases from colorectal carcinoma. *Thorac Cardiovasc Surg* 57: 403-408, 2009.
- 57 Lumachi F, Orlando R, Marino F, Chiara GB and Basso SMM: Expression of p53 and Ki-67 as prognostic factors for survival of men with colorectal cancer. *Anticancer Res* 32: 3965-3968, 2012.
- 58 Ivanecz A, Kavalar R, Palfy M, Pivec V, Sremec M, Horvat M and Potrč S: Can we improve the clinical risk score? The prognostic value of p53, Ki-67 and thymidylate synthase in patients undergoing radical resection of colorectal liver metastases. *HPB (Oxford)* 16: 235-242, 2014.
- 59 Schweiger T, Nikolowsky C, Starlinger P, Traxler D, Zimmermann M, Birner P, Hegedüs B, Dome B, Bergmann M, Mildner M, Klepetko W, Hoetzenecker K and Ankersmit HJ: Stromal expression of heat-shock protein 27 is associated with worse clinical outcome in patients with colorectal cancer lung metastases. *PLoS One* 10: e0120724, 2015.
- 60 Kaira K, Okumura T, Ohde Y, Takahashi T, Murakami H, Kondo H, Nakajima T and Yamamoto N: Prognostic significance of thymidylate synthase expression in the adjuvant chemotherapy after resection for pulmonary metastases from colorectal cancer. *Anticancer Res* 31: 2763-2771, 2011.
- 61 Brand TM and Wheeler DL: KRAS mutant colorectal tumors. *Small GTPases* 3: 34-39, 2012.
- 62 Chang YY, Lin JK, Lin TC, Chen WS, Jeng KJ, Yang SH, Wang HS, Lan YT, Lin CC, Liang WY and Chang SC: Impact of KRAS mutation on outcome of patients with metastatic colorectal cancer. *Hepatogastroenterology* 61: 1946-1953, 2014.
- 63 Pereira AA, Rego JF, Morris V, Overman MJ, Eng C, Garrett CR, Boutin AT, Ferrarotto R, Lee M, Jiang ZQ, Hoff PM, Vauthey JN, Vilar E, Maru D and Kopetz S: Association between KRAS mutation and lung metastasis in advanced colorectal cancer. *Br J Cancer* 112: 424-428, 2015.
- 64 Teng HW, Huang YC, Lin JK, Chen WS, Lin TC, Jiang JK, Yen CC, Li AF, Wang HW, Chang SC, Lan YT, Lin CC, Wang HS and Yang SH: BRAF mutation is a prognostic biomarker for colorectal liver metastasectomy. *J Surg Oncol* 106: 123-129, 2012.

- 65 Renaud S, Romain B, Falcoz PE, Olland A, Santelmo N, Brigand C, Rohr S, Guenot D and Massard G: KRAS and BRAF mutations are prognostic biomarkers in patients undergoing lung metastasectomy of colorectal cancer. *Br J Cancer* **112**: 720-728, 2015.
- 66 Tie J, Lipton L, Desai J, Gibbs P, Jorissen RN, Christie M, Drummond KJ, Thomson BN, Usatoff V, Evans PM, Pick AW, Knight S, Carne PW, Berry R, Polglase A, McMurrick P, Zhao Q, Busam D, Strausberg RL, Domingo E, Tomlinson IP, Midgley R, Kerr D and Sieber OM: PIK3CA and PTEN gene and exon mutation-specific clinicopathologic and molecular associations in colorectal cancer. *Clin Cancer Res* **17**: 1122-1130, 2011.
- 67 Kawazoe A, Shitara K, Fukuoka S, Kuboki Y, Bando H, Okamoto W, Kojima T, Fuse N, Yamanaka T, Doi T, Ohtsu A and Yoshino T: A retrospective observational study of clinicopathological features of KRAS, NRAS, BRAF and PIK3CA mutations in Japanese patients with metastatic colorectal cancer. *BMC Cancer* **15**: 258, 2015.
- 68 Treasure T: Pulmonary Metastasectomy for Colorectal Cancer: Recent Reports Prompt a Review of the Available Evidence. *Curr Colorectal Cancer* **10**: 296-302, 2014.
- 69 Lumachi F, Mazza F, Del Conte A, Lo Re G, Ermani M, Chiara GB and Basso SM: Short-term survival of patients with lung metastases from colorectal and con-colorectal cancer who underwent pulmonary metastasectomy. *Anticancer Res* **35**: 3563-3566, 2015.
- 70 Chua TC, Thornbury K, Saxena A, Liauw W, Glenn D, Zhao J and Morris DL: Radiofrequency ablation as an adjunct to systemic chemotherapy for colorectal pulmonary metastases. *Cancer* **116**: 2106-2114, 2010.
- 71 Inoue T, Oh RJ, Shiomi H, Masai N and Miura H: Stereotactic body radiotherapy for pulmonary metastases. Prognostic factors and adverse respiratory events. *Strahlenther Onkol* **189**: 285-292, 2013.

Received October 5, 2015

Revised November 24, 2015

Accepted December 2, 2015