Korean J Hepatobiliary Pancreat Surg 2016;20:110-115
http://dx.doi.org/10.14701/kjhbps.2016.20.3.110

Original Article

Aggressive surgical resection for concomitant liver and lung metastasis in colorectal cancer

Sung Hwan Lee[1], Sung Hyun Kim[1], Jin Hong Lim[2], Sung Hoon Kim[3], Jin Gu Lee[4], Dae Joon Kim[4], Gi Hong Choi[1], Jin Sub Choi[1], and Kyung Sik Kim[1]

[1]*Department of Surgery, Yonsei University College of Medicine, Seoul,*
[2]*Department of Surgery, Yongin Severance Hospital, Yongin,*
[3]*Department of Surgery, Yonsei University Wonju College of Medicine, Wonju,*
[4]*Department of Thoracic and Cardiovascular Surgery, Yonsei University College of Medicine, Seoul, Korea*

Backgrounds/Aims: Aggressive surgical resection for hepatic metastasis is validated, however, concomitant liver and lung metastasis in colorectal cancer patients is equivocal. **Methods:** Clinicopathologic data from January 2008 through December 2012 were retrospectively reviewed in 234 patients with colorectal cancer with concomitant liver and lung metastasis. Clinicopathologic factors and survival data were analyzed. **Results:** Of the 234 patients, 129 (55.1%) had synchronous concomitant liver and lung metastasis from colorectal cancer and 36 (15.4%) had metachronous metastasis. Surgical resection was performed in 33 patients (25.6%) with synchronous and 6 (16.7%) with metachronous metastasis. Surgical resection showed better overall survival in both groups (synchronous, p=0.001; metachronous, p=0.028). In the synchronous metastatic group, complete resection of both liver and lung metastatic lesions had better survival outcomes than incomplete resection of two metastatic lesions (p=0.037). The primary site of colorectal cancer and complete resection were significant prognostic factors (p=0.06 and p=0.003, respectively). **Conclusions:** Surgical resection for hepatic and pulmonary metastasis in colorectal cancer can improve complete remission and survival rate in resectable cases. Colorectal cancer with concomitant liver and lung metastasis is not a poor prognostic factor or a contraindication for surgical treatments, hence, an aggressive surgical approach may be recommended in well-selected resectable cases. **(Korean J Hepatobiliary Pancreat Surg 2016;20:110-115)**

Key Words: Colorectal cancer; Liver cancer; Lung cancer; Metastasis

INTRODUCTION

The liver is the most frequent site of metastatic colorectal cancer, and metastatic lesions from colorectal cancer are frequently detected in the lungs, bones, and brain.[1,2] As surgical managements such as operative equipment innovation, operation strategy, and perioperative management have advanced, morbidity and mortality associated with surgical resection are reduced to acceptable levels. Since the first report of liver or lung metastasectomy due to colorectal cancer,[3] surgical resection of liver and lung metastatic lesions is considered the only therapeutic option for long-term survival.[4] In addition, perioperative chemotherapy improves the resectability of metastasectomy with minimal safety margins, which is an accepted standard procedure that is frequently performed worldwide.[5] A safety resection margin of $>$1 cm, or a 3-mm margin, is widely used for surgical resection of metastasis of colorectal cancer.[6,7] Several clinical guidelines recommend surgical resection for synchronous or metachronous resectable metastatic lesions before or after systemic chemotherapy.[2,8] However, the role of surgical resection in concomitant liver and lung metastasis is not clearly defined, and aggressive surgical resection may be a contributing factor in improvement of survival outcomes in patients with confirmed concomitant liver and lung metastasis.[9] The aim of this study was to evaluate the efficacy of surgical resection in concomitant synchronous or

Received: March 15, 2016; **Revised:** April 14, 2016; **Accepted:** May 10, 2016
Corresponding author: Kyung Sik Kim
Department of Surgery, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-2125, Fax: +82-2-313-8289, E-mail: kskim88@yuhs.ac

metachronous liver and lung metastasis from colorectal cancer.

MATERIALS AND METHODS

Patient selection

Data regarding patients with liver and lung metastasis from colorectal cancer from January 2008 to December 2012 were reviewed retrospectively in our institutional cohort. Patients with concomitant liver and lung metastasis showing solitary or multiple lesions were then selected for the study, excluding non-surgical patients and patients with other metastasis besides liver and lung. Clinicopathologic and pathologic data was obtained and survival outcomes were analyzed in these patients (Fig. 1).

Surgical procedures

Liver and lung resections were performed by hepatobiliary surgeons and thoracic surgeons at a single institution. All surgical procedures were performed to completely remove the metastatic lesions in the liver or lung. Resections of the liver and lung were conducted for solitary or multiple lesions as one-step or two-step procedure based on the surgeons' discretion.

Follow-up and survival outcome

Patients who underwent surgical resection for liver or lung metastatic lesions were examined regularly after surgery. Physical examination, blood test, and computerized tomography (CT) scan of the abdomen and thorax were performed at each evaluation. Patients were followed until the latest visiting days, including the date of death or loss to follow-up.

Statistics

Continuous variables were expressed as mean±standard deviation and categorical variables were expressed as frequencies with percentages. The Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables were used to determine significant associations between parameters. The Kaplan-Meier method and log-rank test were used for survival analysis. Multivariate analysis using Cox-regression was done to identify significant prognostic factors for overall survival. Statistical significance was determined if the p-value was <0.05.

RESULTS

Patient characteristics

The age of patients with synchronous metastasis was

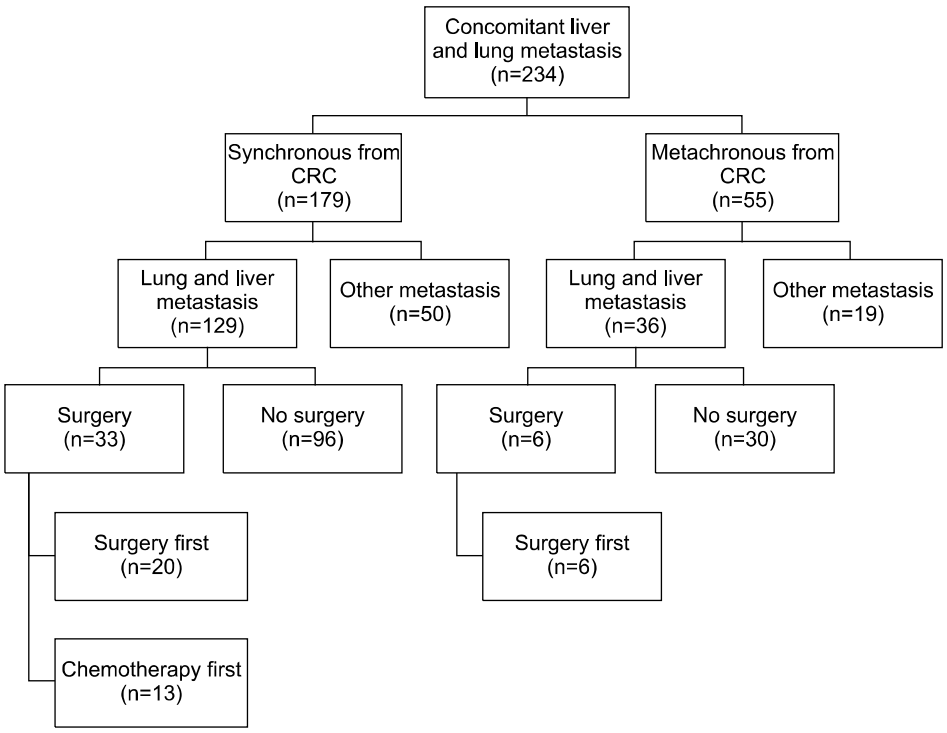

Fig. 1. Selection of study patients. Flow chart describes the characteristics of patients included in the analyses. CRC, colorectal cancer.

significantly higher than that of patients with metachronous metastasis, and female patients were frequently identified with metachronous metastasis. T stage, N stage, and location of primary colorectal cancer was not significantly different between synchronous and metachronous metastasis patients (Table 1).

Detailed pattern of metastasis

There were more liver lesions in synchronous than metachronous metastasis, without significant difference in largest size of solitary or multiple metastatic lesions between the two groups. In addition, synchronous metastasis showed multiple metastatic lesions in both liver lobes compared to metachronous metastasis, and the surgical method was not remarkably different between the two groups.

Multiple metastatic lesions of lung in the synchronous metastases were more frequent than in the metachronous metastasis, though size of lung metastases were not significantly different for either groups. Bilateral lung metastasis was more frequent in synchronous metastasis compared to metachronous metastasis, and the surgical method was not statistically different between both groups (Table 1).

Table 1. Clinicopathologic factors and detailed patterns of liver and lung metastasis in resected cases

	Synchronous metastasis (n=33)	Metachronous metastasis (n=6)	*p*-value
Age (range, median)	63 (29-78)	46 (35-58)	0.01
Sex (Male/Female)	21 (63.6%)/12 (36.4%)	2 (33.3%)/4 (66.6%)	0.03
Preoperative CEA (ng/ml)	34.3 (3.4-85.4)	12.8 (2.5-56.3)	0.01
Primary CRC			
T stage (T1/T2/T3/T4)	0/3/26/4	0/0/6/0	0.686
N stage (N0/N1/N2)	9/12/12	1/4/1	0.147
Location			
Colon	17 (51.5%)	2 (33.3%)	0.124
Rectum	16 (48.5%)	4 (66.7%)	
Liver metastasis			
Number of lesions			
(range, median)	1-15 (7)	1-3 (1)	0.001
(solitary/multiple)	6 (18.2%)/27 (81.8%)	4 (66.7%)/2 (33.3%)	
Largest size (cm)	2.1 (0.8-4.5)	2.4 (1.0-3.4)	0.684
Distribution			
Unilateral (Right/Left lobe)	11 (33.3%)/7 (21.2%)	4 (66.6%)/2 (33.3%)	0.003
Bilateral	15 (45.5%)	0	
Operation			
None	2 (6.1%)	1 (16.7%)	0.576
Wedge resection	18 (54.4%)	2 (33.3%)	
Segmentectomy	6 (18.2%)	2 (33.3%)	
Lobectomy	3 (9.1%)	1 (16.7%)	
Extended lobectomy	1 (3%)	0	
Intraoperative RFA	3 (9.1%)	0	
Lung metastasis			
Number of lesions			
(range, median)	1-12 (5)	1-2 (1)	0.001
(solitary/multiple)	12 (36.4%)/27 (63.6%)	5 (83.3%)/1 (16.7%)	
Largest size (cm)	0.9 (0.5-3.1)	1.0 (0.6-2.8)	0.849
Distribution			
Unilateral (Right/Left lobe)	9 (27.3%)/7 (21.2%)	2 (33.3%)/4 (66.6%)	0.002
Bilateral	17 (51.5%)	0 (0%)	
Operation			
None	13 (39.4%)	0 (0%)	0.492
Wedge resection	18 (54.5%)	6 (100%)	
Lobectomy	2 (6.1%)	0 (0%)	
Adjuvant treatment	13 (39.4%)	2 (33.3%)	0.824

SD, standard deviation; CEA, carcinoembryonic antigen; CRC, colorectal cancer; RFA, radiofrequency ablation

Clinical and oncologic outcomes

The median follow-up periods for synchronous and metachronous metastasis were 22.2 and 21.6 months, respectively, from the time of the operation. Preoperative adjuvant treatments were performed for 39.4% and 33.3% of patients in synchronous and metachronous groups, respectively. Complete surgical resections confirmed by postoperative imaging study were conducted for 54.6% and 83.3% of patients in each group. Unresected metastatic lesions in liver were treated by radiofrequency ablation (RFA) (Table 1).

There was no postoperative mortality within 30 days after operation (Table 2). Recurrence after surgical resection was 63.6% and 83.3% in the synchronous and metachronous groups, respectively. Survival analysis was performed using the Kaplan-Meier method and log-rank test. In the synchronous metastasis group, the resection group had statistically better survival, as compared to the non-resection group ($p < 0.001$). Furthermore, complete resection of both liver and lung metastasis had significantly better survival than the incomplete resection group (p=0.037). Additionally, in the metachronous group, the resection group had significantly better survival, as compared to the non-resection group (p=0.028) (Fig. 2).

Prognostic factors

Multivariate analysis for prognostic factors of overall survival was performed using previously known prognostic factors and potential clinical markers. Rectal primary cancer was marginally significant (p=0.06, hazard ratio (HR)=0.988-2.318), and incomplete surgical resection for metastatic lesions was most significant (p=0.003, HR=1.477-6.441) for predicting poor outcomes in concomitant liver and lung metastasis from colorectal cancer (Table 3).

DISCUSSION

Colorectal cancer leads to metastatic disease in 60% of cases, with frequent involvement of the liver, lungs, or both.[5] Following several reports of promising results after surgical resection of liver metastasis from colorectal cancer, the paradigm has shifted from limited indication for hepatic resection to an active surgical approach.[1,4] Currently, the only absolute contraindication is the inability to obtain a tumor-free margin and maintain adequate liver function. Surgical resection is the only way to achieve long-term survival in patients with colorectal cancer liver metastases;[10] and several comparative studies have revealed that surgical resection shows better survival outcomes, as compared to systemic chemotherapy alone.[11-13]

Although several studies have explored optimal treatment strategies, there are still limitations for specific guidelines in a patient with synchronous or metachronous concomitant liver and lung metastasis from colorectal cancer.[9,10] Treatment strategy differs between institutions

Table 2. Clinical course and recurrence pattern of resected cases

	Synchronous metastasis (n=33)	Metachronous metastasis (n=6)	*p*-value
Follow-up period (median, range, month)	22 (1-78)	21 (2-38)	0.547
Adjuvant treatment	13 (39.4%)	2 (33.3%)	0.824
Resection pattern			0.04
Complete resection (Simultaneous/Staged)	9 (27.3%)/9 (27.3%)	3 (50%)/2 (33.3%)	
Incomplete resection	15 (45.5%)	1 (16.7%)	
Postoperative CEA (POD 1 month, ng/ml)	3.2 (1.9-12.4)	1.3 (1.2-7.2)	0.01
Postoperative mortality	0 (0%)	0 (0%)	ns
Recurrence rate	21 (63.6%)	5 (83.3%)	0.15
Recurrence interval (months, range)	18 (3-79)	22 (10-68)	0.652
Recurred site			0.754
Liver	4 (12.1%)	2 (33.3%)	
Lung	3 (9.1%)	0 (0%)	
Liver+Lung	8 (24.2%)	0 (0%)	
Carcinomatosis	3 (9.1%)	1 (16.7%)	
Other (Bone, brain, etc.)	3 (9.1%)	2 (33.3%)	

CEA, carcinoembryonic antigen; POD, postoperative day

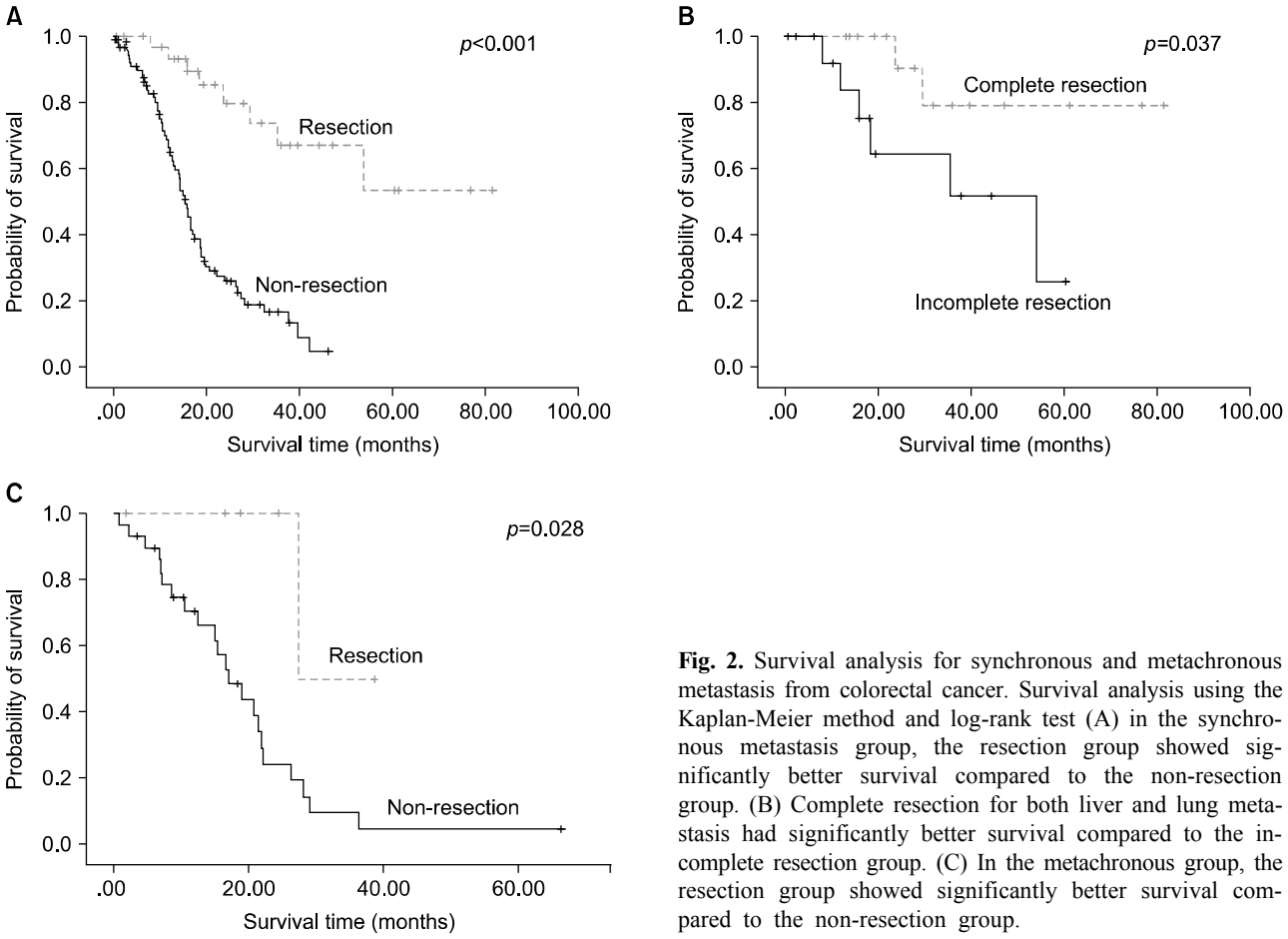

Fig. 2. Survival analysis for synchronous and metachronous metastasis from colorectal cancer. Survival analysis using the Kaplan-Meier method and log-rank test (A) in the synchronous metastasis group, the resection group showed significantly better survival compared to the non-resection group. (B) Complete resection for both liver and lung metastasis had significantly better survival compared to the incomplete resection group. (C) In the metachronous group, the resection group showed significantly better survival compared to the non-resection group.

Table 3. Multivariate analysis for prognostic factors of overall survival

Cox proportional hazard analysis	*p*-value	HR	95% Confidential interval	
Age (>60 yrs)	0.646	1.156	0.623	2.144
Sex (Male/Female)	0.664	1.092	0.733	1.626
Pattern of metastasis (Metachronous/Synchronous)	0.665	0.819	0.331	2.026
T stage of CRC (T3,4/T1,2)	0.116	1.386	0.922	2.083
N stage of CRC (Positive/Negative)	0.113	1.531	0.904	2.593
Bilateral distribution (Bilateral/Unilateral)	0.735	0.769	0.231	2.452
Surgical resection (Complete/Incomplete)	0.003	3.084	1.477	6.441
Primary location of CRC (Rectum/Colon)	0.06	1.475	0.988	2.318
Preoperative CEA	0.09	2.481	0.842	12.458

HR, hazard ratio; CRC, colorectal cancer; CEA, carcinoembryonic antigen

due to differing clinical situations of patients and the institute's management plan. Nevertheless, several studies emphasize the importance of complete surgical resection in patients with concomitant liver and lung metastasis with colorectal cancer.[14-16] In this study, the pattern of clinicopathologic factors, particularly the preoperative and postoperative levels of carcinoembryonic antigen (CEA), were evaluated for synchronous or metachronous metastasis from primary colorectal cancer. Although several clinical features differed based on the timing of metastasis from primary colorectal cancer, only complete resection of the metastatic liver and lung lesions improved survival outcomes.

The prognostic factors for liver and lung metastasis from colorectal cancer in terms of CEA, rectal primary cancer, bilateral lung metastasis, and multiple metastases

have been recently reported.[14,17,18] In particular, complete surgical resection of both liver and lung metastasis is the most significant prognostic factor for patients with concomitant liver and lung metastasis with colorectal cancer, according to a study on the synchronism of liver and lung metastasis.[9] The resectability of liver and lung metastasis has gradually increased due to the progress in surgical skill and technique, and improvement of perioperative management. Recent advances in molecular biology have also offered new prognostic factors, e.g., KRAS, BRAF, NRAS, and PIK3CA mutations, for patients with metastatic colorectal cancer in the era of precision medicine.[19]

This study has several limitations in terms of retrospective design, single-center study, and small study population. The heterogeneous clinical status of the enrolled population is another limitation. However, the evidence regarding the clinical situation for concurrent liver and lung metastasis in colorectal cancer is relatively rare and the strategy for this situation is not yet established. Therefore, this study increases our current understanding of concurrent liver and lung metastasis in colorectal cancer.

In conclusion, the results of this study indicated that the resection of hepatic and pulmonary metastases from colorectal cancer is safe and can offer long-term survival to selected patients. Surgery should be considered only if resection of all metastatic sites are potentially curative. Furthermore, resections should be as limited as possible to allow for repeat resections for eventual disease recurrence.

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