

Surgical resection of synchronous and metachronous lung and liver metastases of colorectal cancers

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Purpose: Surgical resection of isolated hepatic or pulmonary metastases of colorectal cancer is an established procedure, with a 5-year survival rate of about 50%. However, the role of surgical resections in patients with both hepatic and pulmonary metastases is not well established. We aimed to analyze overall survival of these patients and associated factors.

Methods: Data retrospectively collected from 66 patients who underwent both hepatic and pulmonary metastasectomy after colorectal cancer surgery from August 2002 through August 2013 were analyzed. In univariate analysis, the log-rank test compared patient survival between groups. $P < 0.1$ was considered indicative of significance. Multivariate analysis of the significance data using a Cox proportional hazard model identified factors associated with overall survival. The synchronous group ($n = 57$) was defined as patients who had metastasectomy within 3 months from primary colorectal cancer surgery. The remaining nine patients constituted the metachronous group.

Results: Median follow-up was 126 months from the primary colorectal cancer surgery. The 5-year survival was 73.4%. There was no difference in overall survival between the synchronous and metachronous groups, consistent with previous studies. Distribution (involving one hemiliver or both, $P = 0.010$ in multivariate analysis) of liver metastases and multiplicity of the pulmonary metastasis ($P = 0.039$) were predictors of poor prognosis.

Conclusion: Sequential or simultaneous resection of both hepatic and pulmonary metastasis of colorectal cancer resulted in good long-term survival in selected patients. Thus, an aggressive surgical approach and multidisciplinary decision making with surgeons seems to be justified.

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Key Words: Colorectal cancer, Liver metastasis, Lung metastasis, Synchronous metastasis

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers. About half of all CRC patients will develop hepatic metastases and 20% will develop pulmonary metastases during the course of their disease [1]. For metastatic CRC, prognosis without any treatment is poor. The 5-year survival rate of colon cancer with distant metastasis is about 13% in the United States [2,3]. With isolated hepatic metastasis, metastasectomy is an established treatment for resectable metastasis. Previous studies on patients with hepatic metastases treated with surgical treatment re-

ported a 58% of 5-year survival rate [4,5]. Surgical treatment of pulmonary metastases is common for CRC patients and studies have demonstrated 5-year survival rates up to 56% [6,7]. Encouraged by these results, many centers contemporarily offer pulmonary and hepatic metastasectomy to selected patients with both pulmonary and hepatic metastases.

However, such an aggressive approach is controversial [8]. The role of surgery in the management of patients who have both liver and lung metastases is not well defined. There were 12 articles reporting survival after hepatic and pulmonary metastasectomy following CRC surgery (Table 1) [9-20]. The

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Table 1. Previous reports about survival of sequential hepatic and pulmonary metastasectomy following CRC surgery

Study	Published year	No.	Median survival (mo)	5-Year survival (%)	Negative prognostic factor
After resection of primary CRC					
Our data		66	126	73.2	
Lee et al. [12]	2007	32		60.8	
After first metastasectomy					
Our data		66	100	73.4	
Takahashi et al. [13]	2007	30	60	70	
Shah et al. [14]	2006	39	87	74	
Marudanayagam et al. [15]	2009	43	42	53.9	
Neeff et al. [16]	2009	55		42	
Kawano et al. [17]	2012	35	39.5	36.7	
After second metastasectomy					
Our data		66	100	56.4	
Murata et al. [18]	1998	30	30	43.8	Synchronous, bilateral lung metastases
Robinson et al. [9]	1999	25		11	Multiple liver metastasis, advanced age, short disease free interval
Kobayashi et al. [10]	1999	47		31	Multiple lung metastasis, multiple liver metastasis
Miller et al. [11]	2007	131	40	31	Multiple liver metastasis, short disease free interval
After first pulmonary metastasectomy					
Regnard et al. [19]	1998	43	19	11	High CEA level, low number of lung resections
Headrick et al. [20]	2001	58		30	High CEA level, mediastinal nodes involvement

CRC, colorectal cancer.

conditions and outcomes varied, and factors associated with prolonged survival were debatable. Five-year survival rates as high as 11% from the second metastasectomy was reported [9], with 5-year survival rate as high as 70% reporting from the first metastasectomy [13].

In this study, clinical-, pathologic-, and treatment-related features of 66 patients who underwent hepatic and pulmonary metastasectomies at a single institution were prospectively collected over 11 years. Our goal was to compare the outcomes between synchronous and metachronous metastasectomy groups, and to define prognostic factors for survival in this patient group. The data should be useful in patient selection.

METHODS

Patients

Data collected retrospectively from 92 patients who underwent both hepatic and pulmonary metastasectomy after CRC surgery from August 2002 to August 2013 at a single institution, Samsung Medical Center, in Seoul, Korea. Through March 2015, the patients were offered hepatic and pulmonary metastasectomy only if oncologically curative resection was possible. There were no well-established criteria used in selection of patients. Selection of patients for resection of multiple site metastatic disease was at the discretion of the surgeon. Patient information included tumor, treatment, recurrence, and death-related information. Twenty-six patients

were excluded; 16 patients failed to achieve R0 resection in metastasectomy and required palliative surgery, 2 patients confirmed to have no lung metastasis after lung resection, and 8 patients had other site of metastasis. Finally, 66 patients were included in this analysis.

Definitions

Synchronous metastasis was defined as metastasis to the liver or lung at the time of resection of the primary CRC or the first metastasectomy done within 3 months from primary CRC surgery. The metachronous group was defined as patients who had the first metastasectomy later than 3 months from the primary colorectal tumor resection (Fig. 1). The occurrence of bilateral lung metastases represented one episode of metastasis regardless of whether the disease was resected during one operation or staged thoracotomies. Radiofrequency ablation (RFA) was also counted as metastasectomy of hepatic metastasis if the RFA procedure was done according to the radiologists' reports. Disease-free intervals (DFI) were calculated as the time between surgeries. The primary DFI was between primary CRC surgery and first site metastasectomy as well as the secondary DFI was between the first site metastasectomy and second site metastasectomy. Primary DFI was 0 to 3 months in the synchronous metastasectomy group. Secondary DFI was 0 in patients presenting with simultaneous liver and lung metastases.

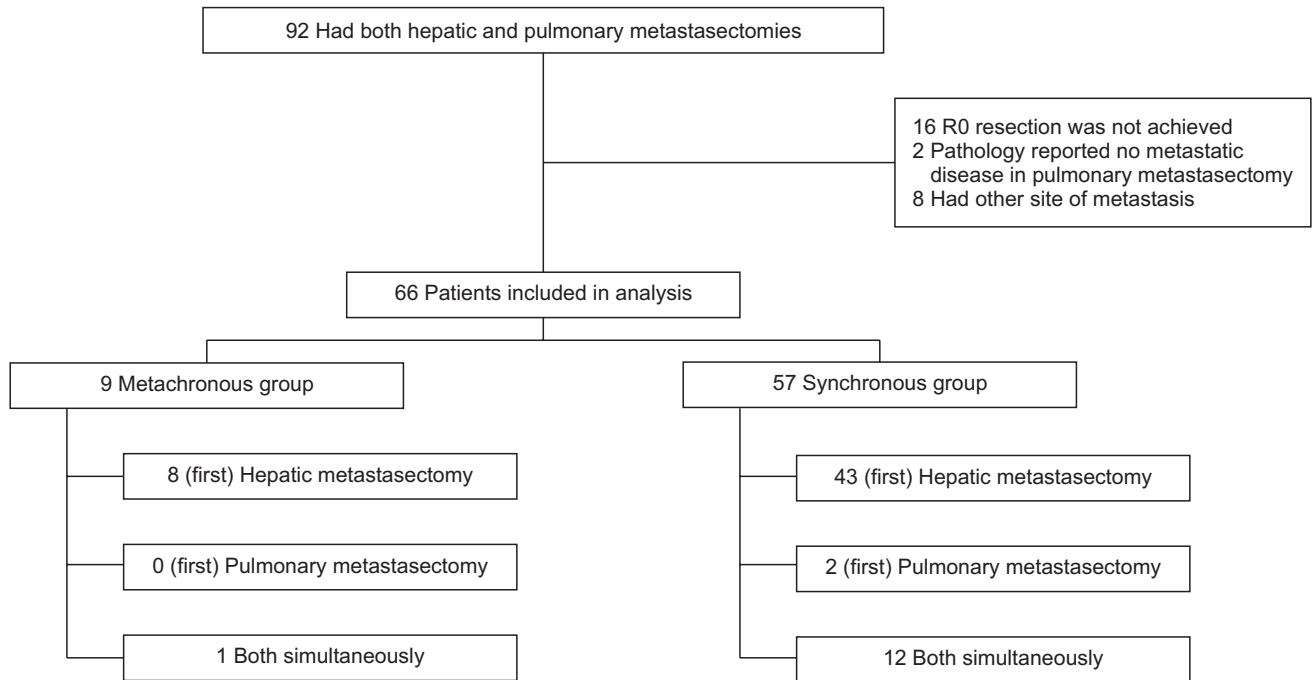


Fig. 1. Patient grouping according to initial presentation and sequence of metastasis site.

Statistical analysis

Survival and its associated factors were analyzed by univariate and multivariate analyses. Some continuous or categorical variables were converted into dichotomous variables, such as age (<60 years vs. ≥60 years), T stage (0–2 vs. 3, 4), N stage (0 vs. 1, 2), and DFI (<12 months vs. ≥12 months). Survival analysis used IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). Actuarial survival was determined by Kaplan-Meier analysis. Relationships of patient, tumor, and treatment characteristics to outcomes were tested by log-rank test. Multivariate analysis was done with the Cox proportional hazards model explaining the overall survival after first metastasectomy. In univariate analysis, factors whose P-values were <0.1 were selected for multivariate analysis. All factors whose P-values were <0.05 in multivariate analysis were considered statistically significant.

RESULTS

Sixty-six patients were included in the analysis. They had both liver and lung metastasectomies after CRC surgery during the period of study. Table 2 shows the clinicopathologic and operative characteristics. Median age was 59 years (range, 25 to 79 years) at first diagnosis. Forty-five were male patients and 21 were female. Nine patients were in the metachronous group and 57 patients were in the synchronous group (M1 stage). Twenty-five patients had CRC originating from the colon, while 41 patients had CRC originating from the rectosigmoid junction or rectum. The majority of the subjects was T3 (47, 71.2%). Four

Table 2. Patient demographics

Variable	Value
Sex	
Male	45 (68.2)
Female	21 (31.8)
Age (yr), median (range)	59 (25–79)
Chronology	
Metachronous (M0)	9 (13.6)
Synchronous (M1)	57 (86.4)
Colorectan cancer site	
Colon	25 (37.9)
Rectum or rectosigmoid junction	41 (62.1)
T	
T2 or less	4 (6.1)
T3	47 (71.2)
T4	15 (22.7)
N	
N0	25 (37.9)
N1	20 (30.3)
N2	21 (31.8)

Values are presented as number (%) unless otherwise indicated.

patients were less than T2 and 15 subjects were T4. In nodal status, 25 (37.9%) was negative. Twenty-one patients (31.8%) were N2 and 20 (30.3%) were diagnosed with N1. 1 of them has proven to achieve pathologic complete remission (ypT0N0) in primary surgery (colon and liver). Ten patients received

neoadjuvant chemotherapy before primary CRC surgery.

Survival

Forty-six of 66 patients (69.6%) survived. Median survival was 100 months (95% confidence interval [CI], 55.3 to 196.7) from primary CRC surgery, 100 months (95% CI not available) from first metastasectomy, and 100 months (95% CI, 40.5 to 159.5 months) from second site metastasectomy. The 5-year survival rate was 73.2% from primary CRC surgery, 73.4% from first metastasectomy, and 56.4% from the second site metastasectomy. Survival curves are shown in Fig. 2.

Synchronous versus metachronous metastasis

Synchronous group (n = 57) was defined as patients who had first metastasectomy within 3 months from primary CRC surgery, the others (who had first metastasectomy after

3 months from the primary CRC surgery) comprised the metachronous group (n = 9). Median survival for synchronous metastasis was 126 months, while the median survival was not available for metachronous metastasis group because of the lack of mortality cases. In synchronous metastases patients, the majority (n = 43, 65%) presented with liver metastasis (liver first group) compared to 8 subjects (12.1%) in the metachronous metastases group. Two patients (3.0%) were in the lung first group in the synchronous metastases group. Twelve of those with synchronous metastases (18.2%) presented with lung and liver metastases simultaneously, compared with 1 patient (1.5%) in the metachronous metastases group.

There was no difference in long-term survival between the synchronous and metachronous group, and this result was consistent with previous studies [9-11]. The 5-year survival rate after primary CRC surgery was 77.8% in the synchronous group,

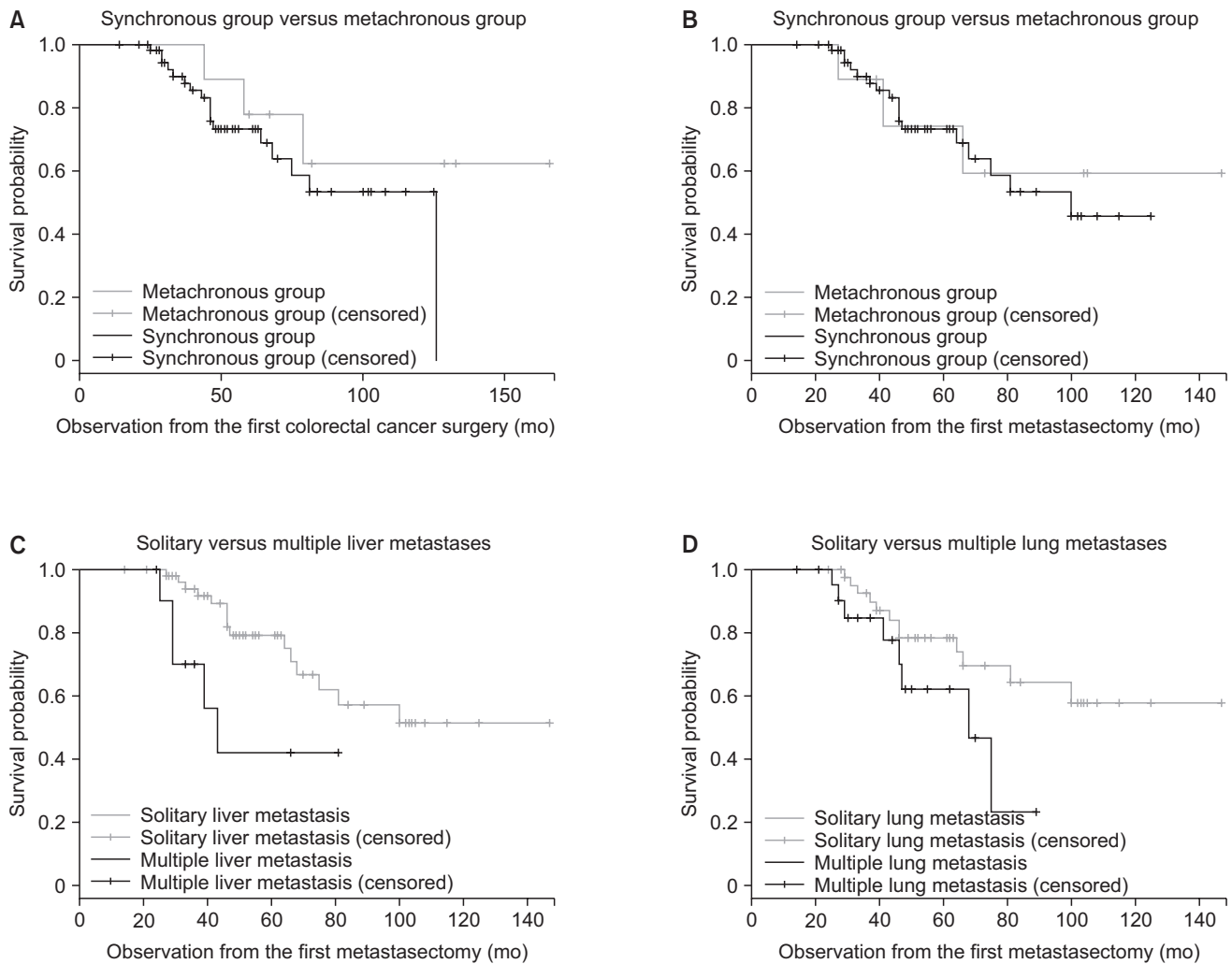


Fig. 2. Survival results. (A) Synchronous versus metachronous survival analysis, by log-rank test ($P = 0.327$, by log-rank) (1, metachronous; 2, synchronous). (B) Survival from first metastasectomy by log-rank test ($P = 0.813$, by log-rank). (C) Comparison between liver metastases involving single lobe or both lobe in survival from first site metastasectomy ($P = 0.031$, by log-rank). (D) Comparison between single and multiple lung metastasis in survival from first site metastasectomy ($P = 0.784$, by log-rank).

similar to the metachronous group (73.1%). The 5-year survival rate of the synchronous and metachronous group following first metastasectomy was 74.1% and 73.2%, respectively. In log-rank test, P was 0.327 after first CRC surgery and 0.819 after first metastasectomy.

In the synchronous metastasis group, 5 patients received primary colectomy, hepatic metastasectomy, and pulmonary metastasectomy within a month. Three patients received those surgeries in the same day, and the others received colectomy and hepatic metastasectomy first and then pulmonary metastasectomy within 7 to 14 days. The aforementioned 5 patients displayed no 30-day mortality and surgery-related morbidities.

Liver metastasis

Fifty-five patients (83.3%) presented with single lobe involvement no matter, while only 11 patients (16.7%) had multiple metastasis involving both hepatic lobes. Fifty-three (65.2%) patients had single metastasis and 23 patients (34.8%) had multiple metastases at first presentation of liver metastasis. Fifty-seven of patients (86.3%) received hepatic metastasectomy only once, 7 had 2 hepatic metastasectomies, and 2 had 3 hepatic metastasectomies. Median survival for single hepatic lobe involvement group was 125 months (95% CI, 33 to 212) and 42 months (95% CI, 33 to 52) for both hepatic lobe involvement group. While multiple liver metastasis versus single liver metastasis did not differ ($P = 0.661$; hazard ratio [HR], 1.123; 95% CI, 0.483 to 3.151) in log-rank test, bilobar involvement of liver metastasis did show poor prognosis compared to single lobar involvement in first liver metastasis ($P = 0.022$; HR, 3.36; 95% CI, 1.192 to 9.474). Fig. 2 shows cumulative survival curve from primary CRC surgery depending on the multiplicity and bilobar distribution of liver metastases.

Lung metastasis

Concerning lung metastasis, 51 patients (77.3%) had lung lesions on one side, while 15 (22.7%) had both lungs involved at first pulmonary metastases. Forty-four patients (66.7%) had single metastasis and 22 (33.3%) had multiple lung metastases at first presentation of lung metastases. Single lung metastasis group was compared with the multiple lung metastasis group; no difference was evident ($P = 0.078$). Both lung involvement groups were compared with the single lung (right or left only) metastasis group; concerning survival, no difference was evident ($P = 0.086$). Fig. 2 shows cumulative survival curve from primary CRC surgery depending on the multiplicity and lobar distribution of lung metastases.

Disease-free interval

Median primary DFI was 0 months (range, 0 to 31 months) and median secondary DFI was 16 months (range, 0 to 78 months). In primary DFI, 59 patients were categorized as

Table 3. Univariate (Cox regression) and multivariate analysis (Cox proportional hazard model) for overall survival after synchronous or sequential pulmonary and hepatic metastasectomy

Variable	Univariate (under Cox)	Multivariate	Hazard ratio
Age (<60 yr, ≥60 yr)	0.991	0.675	-
Sex	0.832	0.439	-
TNM in initial diagnosis			
T	0.638	0.492	-
N	0.705	0.184	-
Primary tumor size (<2 cm, ≥2 cm)	0.124		
Elevated CEA (≥5 ng/mL)	0.419	-	-
Liver metastasis			
Involvement of both liver lobe	0.040	0.010	12.28
Multiplicity	0.846	-	-
Lung metastasis			
Involvement of both lung	0.097	0.231	-
Multiplicity	0.087	0.039	3.75
Synchronous metastasis to metachronous metastasis (M stage)	0.749	-	
Disease free interval			
Primary DFI	0.846	-	
Secondary DFI	0.017	0.615	
CRC location			
Colon or rectum	0.705	-	

DFI, disease-free interval; CRC, colorectal cancer.

shorter primary DFI (<1 year) and the other 7 patients as longer primary DFI. Twenty-two patients were categorized as shorter secondary DFI, and the other 44 patients as longer secondary DFI. Comparison between shorter DFI groups and longer DFI groups; the difference was not significant for primary DFI ($P = 0.89$), but was for secondary DFI ($P = 0.013$).

Prognostic factors

Analysis of potential prognostic factors for survival from the time of resection of the first metastasis is shown in Table 3. Involvement of both liver lobe and lung, multiplicity of lung metastasis, and longer secondary DFI were counted possible prognostic factors and included in multivariate analysis. In multivariate analysis with Cox-proportional hazard model, involvement of both liver lobe ($P = 0.010$) and multiplicity of lung metastasis ($P = 0.039$) were inversely associated with prolonged survival.

DISCUSSION

In this analysis, as many previous studies have shown, metastasectomies of CRC in selected patients showed accept-

able and good survival prognosis. This result is comparable with 5-year survival of pulmonary metastasectomy of CRC [21]. During the time of this study, our institution offered CRC surgery with curative intent for 7,531 patients. Of these, 1,032 presented with metastatic disease (M1). Regardless of the cause of the death, the overall 7,531 patients had a 5-year survival rate of 49.1%, while those with metastatic disease had a rate of 49.3%. Sixty-six patients with both pulmonary and hepatic metastasectomies had a 5-year survival rate from CRC surgery of 73.4% and 56.4% from the first metastasectomy. This result indicates that patients with both pulmonary and hepatic metastasectomies may be strictly selected for resectability.

Median follow-up was 48 months (ranging from 14 to 147 months) from the first metastasectomy, and 31 (ranging from 1 to 107 months) from the second site metastasectomy. At the end of the period of observation, 20 patients had died and

46 patients were still alive. Among the survivors, disease had progressed in 13, partial response or stable disease was evident in 3, and the remaining 30 patients showed no evidence of disease recurrence. Table 4 summarizes long-term outcomes of several recent studies on metastatic CRC. Survival after sequential and simultaneous metastasectomies of liver and lung for metastatic CRC was reported 12 articles including more than 25 patients. Survival varied widely and could be partly due to differences in patient selection and study method.

Presently, synchronous and metachronous metastasis seemed not to affect prognosis ($P = 0.327$ by log-rank test), similar to other studies [9-11]. Multiplicity of liver metastasis has been associated with poor prognosis [9-11]. This was not evident in the present analysis. In univariate analysis, multiple liver metastasis had a similar survival outcome with single liver metastasis group ($P = 0.659$ in log-rank test). However,

Table 4. Site and chronology of metastases

Variable	No. (%)	Overall survival (%)		Median survival	P-value
		3-Year	5-Year		
Over all	66 (100)	89.8	73.4	100	0.141
Liver first	51 (77.3)	91.6	78.7	N/A	
Lung first	2 (3.0)	100	50.0	39	
Both simultaneously	13 (19.7)	80.0	54.9	N/A	
Chronology group					0.814
Synchronous metastases ^{a)}	57 (86.4)	89.9	73.2	100	
Metachronous metastases ^{b)}	9 (13.6)	88.9	74.1	N/A	
Synchronous metastases ^{a)}	57 (86.4)	89.9	73.2	100	0.120
Liver first	43 (65.2)	92.4	79.8	N/A	
Lung first	2 (3.0)	100.0	50.0	69.5	
Both simultaneously	12 (18.2)	77.8	48.6	47	
Metachronous metastases ^{b)}	9 (13.6)	88.9	77.8	N/A	0.723
Liver first	8 (12.1)	87.5	N/A	N/A	
Lung first	0 (0)	N/A	N/A	N/A	
Both simultaneously	1 (1.5)	100.0	100.0	N/A	
Liver metastasis				N/A	
Single lobe	55 (83.3)	93.8	79.2	N/A	0.031
Both lobe	11 (16.7)	70.0	42.0	43	
Single metastasis	53 (65.2)	91.9	78.3	100	0.843
Multiple metastasis	23 (34.8)	86.4	65.7	N/A	
Lung metastasis					
Single lung	51 (77.3)	93.3	78.0	N/A	0.086
Both lung	15 (22.7)	76.9	54.9	68	
Single metastasis	44 (66.7)	92.4	78.2	N/A	0.078
Multiple metastasis	22 (33.3)	84.7	62.1	68	
Disease free interval					
Primary DFI < 12 mo	59 (89.4)	90.3	74.3	100	0.89
Primary DFI ≥ 12 mo	7 (10.6)	85.7	68.6	N/A	
Secondary DFI < 12 mo	22 (33.3)	72.7	56.9	64	0.013
Secondary DFI ≥ 12 mo	44 (66.7)	97.6	80.4	N/A	

DFI, disease-free interval; N/A, not available.

^{a)}First metastasectomy within 3 months from primary cancer surgery. ^{b)}First metastasectomy after 3 months from primary cancer surgery.

involvement of both lobes in hepatic metastasis was associated with poor prognosis ($P = 0.015$, by log-rank test). This may be because prior studies did not consider the distribution of the liver metastasis rather than multiplicity of the liver metastasis as a prognostic factor. In univariate analysis, distribution of liver metastasis, multiplicity of lung metastasis, and secondary DFI had $P < 0.1$. In multivariate analysis, only the distribution of the liver metastasis and multiplicity of lung metastasis showed $P < 0.05$ (HR, 12.28 and 3.75, respectively).

In this analysis, as many previous studies have done, the data have a limitation that it does not represent wall metastatic CRC patients. Prior survival data (Table 4) involved different and subjective criteria, so the results were not amenable to statistical analysis.

Sequential resection of both hepatic and pulmonary colorec-

tal metastases resulted in good long-term survival in the present subjects. Moreover, distribution of the liver metastases rather than multiplicity was a significantly poor prognosis factor for patients with both hepatic and pulmonary metastases. Thus, an aggressive surgical approach and multidisciplinary decision making with surgeons may be justified with this data. For defining detailed surgical criteria for both hepatic and pulmonary metastases, further studies that include more patients are needed.

CONFLICTS OF INTERESTS

No potential conflict of interest relevant to this article was reported.

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