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Surgical Outcomes After Resection of Both Hepatic and Pulmonary Metastases From Colorectal Cancer

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Abstract

Background The efficacy and the indications of resection of synchronous or metachronous hepatic and pulmonary metastases from colorectal cancer (CRC) are controversial. This study retrospectively reviewed the cases of CRC patients who underwent both liver and lung resection to define the appropriate indications for surgical resection in patients with hepatic and pulmonary metastases.

Methods A total of 39 patients with both hepatic and pulmonary metastases from CRC underwent both liver and lung resection from January 1987 to December 2009. The relapse-free survival (RFS) and overall survival (OS) from the resection for the first metastasis were evaluated by a Kaplan–Meyer analysis. Prognostic factors were analyzed using the log-rank test and a Cox proportional hazards model.

Results The median RFS and the 5-year RFS rate of all patients were 12 months and 2.6 %, respectively. The median survival time (MST) and 5-year OS rate of all patients were 66 months and 48.3 %, respectively. The MST of the patients with a long (>1 year) disease-free interval (DFI) could not be calculated, but their 5-year OS rate was 73.7 %. In contrast, the MST and 5-year OS rate of the patients with a short (<1 year) DFI were 29 months and 37.5 %, respectively. The short DFI was the only prognostic factor in the multivariate analysis.

Conclusions Aggressive surgical resection of both hepatic and pulmonary metastases from CRC should be undertaken in selective patients, including those with a long DFI.

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Introduction

Liver and lung are the most common sites of distant metastases from colorectal cancer (CRC). Approximate 60 % of all patients with CRC develop hepatic metastases [1]. The 5-year survival rates of patients with metastatic CRC treated with best supportive care alone range from 0.4 to 4.0 % [2]. Surgical resection of localized hepatic metastases is widely accepted as the most effective therapy. The 5-year survival rates after resection of hepatic metastasis were 25–38 % during the 1990s and 58 % in the most recent study [3–7]. On the other hand, 10–20 % patients who undergo curative resection of CRC develop pulmonary metastases [8, 9]. Similarly, surgical resection of localized pulmonary metastases from CRC is thought to be beneficial, and the 5-year survival rates after resection of pulmonary metastasis are >40 % [10–12]. It should be noted that the efficacy and the indications for resecting both hepatic and pulmonary metastases from CRC is controversial, regardless of whether they are synchronous or metachronous. Several studies have reported the usefulness of resecting both hepatic and pulmonary metastases from CRC, reporting 5-year survival rates of 27–74 % [13–18]. Various prognostic factors have been reported, and there is no consensus on the appropriate indications for resection.

This study retrospectively reviewed the cases of CRC patients who underwent both liver and lung resection. We aimed to define the indications for resection in patients

with both hepatic and pulmonary metastases and clarify the prognostic factors in these patients.

Patients and methods

A total of 39 patients with both hepatic and pulmonary metastases from CRC underwent surgery at the Department of Gastroenterological Surgery, National Kyushu Cancer Center, Fukuoka, Japan from January 1987 to December 2009. All of the patients underwent hepatic and pulmonary resection.

Patients were evaluated preoperatively for hepatic and pulmonary metastases using abdominal ultrasonography (US), abdominal and thoracic computed tomography (CT), and/or magnetic resonance imaging (MRI). In addition, we started using positron emission tomography (PET)-CT to evaluate patients in 2006. The surgical indications for liver and lung resection for metastasis from CRC in our institution were as follows: (1) the patient could physically tolerate surgery; (2) the organ function would be preserved after surgery; (3) R0 complete resection was achievable. There were two exclusion criteria: (1) the patient could not tolerate the surgery because of his or her poor general condition and/or organ function; (2) R0 complete resection could not be achieved.

Synchronous metastases were defined as those identified within 3 months from the time of resecting the primary CRC. Metastases identified >3 months from the time of resection of the primary CRC were categorized as metachronous. The occurrence of bilateral pulmonary metastases was counted as one episode of metastasis, regardless of whether the tumors were resected simultaneously or sequentially. The disease-free interval (DFI) was determined as the time from the resection of the first metastasis to the development of any second metastasis, including at the same organ. The DFI was zero in patients who presented with simultaneous liver and lung metastases. The patients were divided into two groups with a short DFI (<1 year) and a long DFI (≥1 year). Relapse-free survival (RFS) and overall survival (OS) were also calculated from the time of resection of the first metastasis.

The characteristics of the patients, primary tumor, metastatic tumors, and surgical data were obtained retrospectively from the patients' records. Data concerning the surgical outcome were obtained from outpatient clinical visits. The clinical stage of the CRC was described according to the TNM classification of malignant tumors. All patients agreed to the use of their data by giving their written informed consent.

The data were entered into the Microsoft Excel software program (Microsoft, Redmond, WA, USA) for analysis. Kaplan-Meyer survival curves and the log-rank test were used to analyze the survival rates. A Cox proportional hazards model was used to analyze the prognostic factors. Statistical significance was defined as $p < 0.05$.

Results

Clinicopathologic features

The characteristics of all patients and primary tumors are shown in Table 1. A total of 28 men and 11 women (median age 63 years, range 31–82 years) underwent surgery for both hepatic and pulmonary metastases from CRC. The primary tumor was located in the colon and rectum in 33 and six patients, respectively. Most tumors were differentiated-type tumors and invaded deeper than the subserosa. Lymphatic and venous infiltration was recognized in 31 and 26 patients, respectively. Regional lymph node metastases from the primary tumor were recognized in 28 patients. In all, 15 patients were diagnosed as stage IV because of synchronous hepatic and/or pulmonary metastasis.

Hepatic and pulmonary metastases

The characteristics of hepatic and pulmonary metastases are shown in Table 2. The median size of the hepatic metastases was 25 mm (range 10–180 mm), and the median number of metastases was one (range 1–8). Altogether, 17 patients had multiple hepatic metastases, but only five patients had bilateral hepatic metastases. Hepatic resection was repeated in eight patients. On the other hand, the median size and number of pulmonary metastasis were 12 mm (range 5–45 mm) and 2 (range 1–8), respectively. In all, 20 patients had multiple pulmonary metastases, and ten patients had bilateral pulmonary metastases. Pulmonary resection was repeated in 13 patients. Various types of

Table 1 Clinicopathologic characteristics of all patients ($n = 39$)

Variable	Data
Age (years), median (range)	63 (31–82)
Sex (M/F)	28/11
Tumor size (mm), median (range)	40 (10–95)
Tumor location (colon/rectum)	33/6
pT factor (2/3/4)	1/23/15
pN factor (0/1a/1b/2a/2b)	11/9/12/5/2
Histologic classification (well diff./moderately diff./mucinous)	20/18/1
Lymphatic infiltration (present/absent)	31/8
Venous infiltration (present/absent)	26/13
Synchronous metastases (present/absent)	15/24
pTNM stage (IIA/IIIA/IIIB/IIIC/IV)	3/1/18/2/15

diff differentiated

Table 2 Characteristics of hepatic and pulmonary metastases in 39 patients

Variable	Data
Hepatic metastasis	
Size (mm), median (range)	25 (10–180)
Tumors (no.), median (range)	1 (1–8)
Single/multiple	22/17
Location (unilaterality/bilaterality)	34/5
Repeat resection (yes/no)	8/31
Adjuvant chemotherapy (yes/no)	28/11
Pulmonary metastasis	
Size (mm), median (range)	12 (5–45)
Tumors (no.), median (range)	2 (1–8)
Single/multiple	19/20
Location (unilaterality/bilaterality)	29/10
Repeat resection (yes/no)	13/26
Adjuvant chemotherapy (yes/no)	12/27

Table 3 Patterns of metastasis

Variable	No. of patients	DFI (months)
Synchronous with primary tumor	15	
Simultaneous in liver and lung	3	0
Liver followed by lung	11	15.6 (4.8–25.4)
Lung followed by liver	1	5.9 (5.9)
Metachronous from primary tumor	24	
Simultaneous in liver and lung	6	0
Liver followed by lung	14	24.5 (6.4–60.7)
Lung followed by liver	4	26.5 (7.2–65.8)
All	39	13.5 (0–65.8)

Numbers in parentheses are the ranges

DFI disease-free interval

adjuvant chemotherapy were administered after the hepatic ($n = 28$) and pulmonary ($n = 12$) resections.

The patterns of metastasis are shown in Table 3. Synchronous and metachronous metastases with the primary CRC were recognized in 15 and 24 patients, respectively. Simultaneous hepatic and pulmonary metastases were recognized in three patients who had metastases synchronous with the primary CRC. Also, there were six patients with simultaneous hepatic and pulmonary metastases among those with metastases metachronous with the primary CRC. The DFI was zero for these nine patients. The median DFI was 13.5 months (range 0–65.8 months).

Outcomes and prognostic factors

The complications after surgery are shown in Table 4. Surgical-site infection, ileus, biloma, and ascites occurred after hepatic resection in two, two, one, and one patients, respectively. Similarly, air leakage and pleural effusion occurred after pulmonary resection in two and one patients, respectively. All of these patients recovered with conservative treatment, and there were no surgery-related deaths.

Table 4 Complications after surgery

Variable	Number
Complications after hepatic resection	
Surgical-site infection	2
Ascites	2
Biloma	1
Ileus	1
Complications after pulmonary resection	
Air leakage	2
Pleural effusion	1

The RFS and OS curves for all patients are shown in Fig. 1. The median follow-up period was 46 months. The median RFS and 5-year RFS rate for all patients were 12 months and 2.6 %, respectively. The median survival time (MST) and 5-year OS rate for all patients were 66 months and 48.3 %, respectively.

There were no surgery-related deaths. The results of the univariate and multivariate analyses for prognostic factors are shown in Table 5. The location of the primary tumor, the presence of synchronous metastasis with primary CRC, the number of pulmonary metastases, and a short DFI were significant prognostic factors in the univariate analysis. Using these four factors, the multivariate analysis showed that only a short DFI was a prognostic factor. The OS curves of the patients with a short and long DFI are shown in Fig. 2. The MST of the patients with a long DFI could not be calculated, and the 5-year OS rate for them was

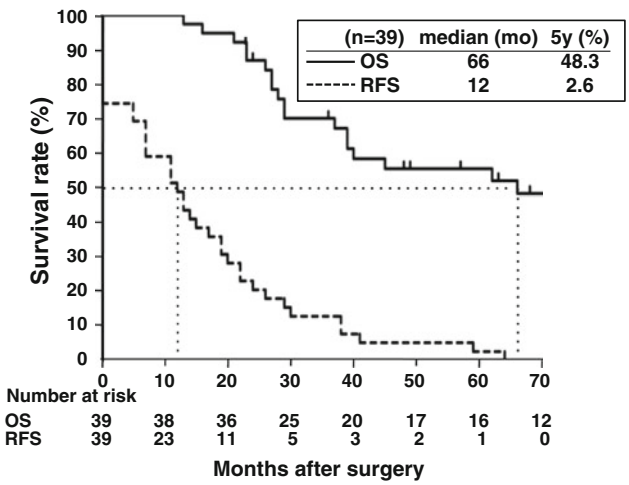

Fig. 1 Relapse-free survival (*RFS*) and overall survival (*OS*) curves for all patients

Table 5 Univariate and multivariate analyses of prognostic factors after the first operation for metastatic lesions

Variable	Number of patients ($n = 39$)	Univariate analysis			Multivariate analysis		
		HR	95 % CI	p	HR	95 % CI	p
Age (years)							
≤60	16	1.050	0.46–2.42	0.906			
>60	23						
Sex							
Male	28	0.695	0.30–1.63	0.404			
Female	11						
Size of primary tumor (mm)							
≤40	24	1.239	0.55–2.91	0.590			
>40	15						
Location of primary tumor							
Colon	33	**0.371**	**0.05–0.88**	**0.033**	0.920	0.27–3.11	0.893
Rectum	6						
pT factor							
2/3	18	1.228	0.54–2.83	0.606			
4	21						
pN factor							
N0	11	0.564	0.25–1.31	0.183			
≥N1	28						
Synchronous metastases							
M0	24	**2.725**	**1.15–6.07**	**0.022**	2.633	0.90–7.69	0.077
M1	15						
Size of hepatic metastases							
≤25	19	0.913	0.40–2.05	0.822			
>25	20						
Size of pulmonary metastases							
≤10	17	1.253	0.54–2.98	0.577			
>10	22						
No. of hepatic metastases							
Single	19	0.907	0.40–2.04	0.809			
Multiple	20						
No. of pulmonary metastases							
Single	22	**2.189**	**1.01–5.44**	**0.047**	2.208	0.81–5.99	0.120
Multiple	17						
Adjuvant chemotherapy							
Yes	31	0.412	0.20–1.24	0.135			
No	8						
Interval between metastases (years)							
≤1	19	**2.528**	**1.19–6.55**	**0.018**	**3.170**	**1.27–7.89**	**0.013**
>1	20						

Bold values indicate statistically significance

HR hazard ratio; *CI* confidence interval

73.7 %. The MST and 5-year OS rate for the patients with a short DFI were 29 months and 37.5 %, respectively.

Discussion

The improvements in perioperative care and the surgical techniques and devices has allowed safe resection of localized hepatic or pulmonary metastases from CRC. The surgical mortality rates for liver and lung resections are less than 5 and 1 %, respectively [3, 4, 19]. Thus, surgical resection of localized hepatic or pulmonary metastases from CRC has been performed aggressively and has improved the survival of such patients. However, the efficacy and the indications for resection of both hepatic and pulmonary metastases from CRC are still controversial.

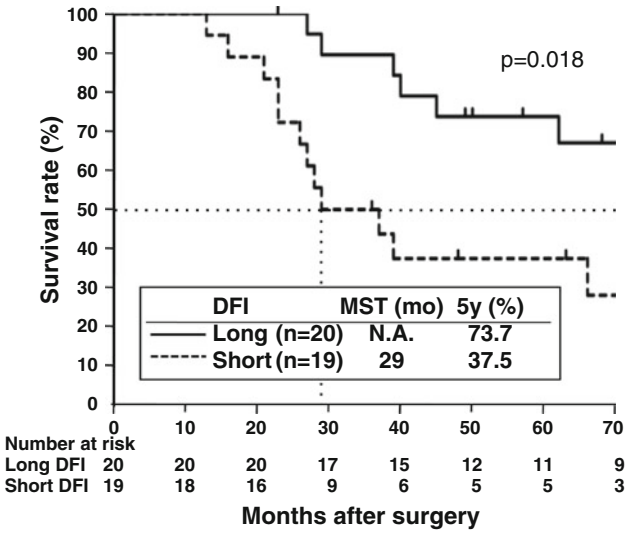

Fig. 2 Comparison of the survival curves of the patients with short and long disease-free intervals (DFI). *MST* median survival time

The results of the current study demonstrate that liver and lung resections can provide good outcomes in selected patients who have both hepatic and pulmonary metastases from CRC. In the current study, achieving low morbidity and mortality rates during hepatic and pulmonary resection was feasible, and the MST and 5-year OS rates after the first resection for metastasis were 66 months and 48.3 %, respectively. Miller et al. reported that the 5-year survival rate was 32 % for patients with both hepatic and pulmonary metastases after the first resection for metastasis [18]. Shah et al. reported the best 5-year survival rate, at 74 % [17]. The reason for the good outcome may be patient selection bias. Several other studies have reported 5-year survival rates ranging from 27 to 51 % [13–16]. Although there are no results reported from a randomized study, it is suggested that aggressive resection of both liver and lung metastases may provide a good outcome.

It is common for repeated metastasis to appear in the same organ. Aggressive resection includes repetitive resection of the liver or lung. In our study, eight and 13 patients underwent repetitive liver and lung resections, respectively. Repetitive resection is necessary to obtain a long survival in patients who can undergo resection.

This study found that the DFI after the first resection for metastasis was the only prognostic factor for improved outcome. This finding was consistent with the largest series reported by Miller et al. [18]. Age and the number of pulmonary metastases have been reported to be prognostic factors in several studies, but they were not prognostic factors in this study [13, 18]. Nagakura et al. [14] and Mineo et al. [15] reported that simultaneous hepatic and pulmonary metastases are a prognostic factor. Their results appear similar to the current results because simultaneous metastases were included in the short-DFI group in this study. The current results support resection in patients with a long DFI.

Recently, the development of systemic chemotherapy—with FOLFOX or FOLFIRI—in combination with a molecular targeting agent has resulted in prolonged survival of patients with metastases from CRC [20–24]. However, data are limited regarding the role of adjuvant and/or neoadjuvant chemotherapy for patients who undergo either liver or pulmonary resection for metastases from CRC. Mitry et al. [25, 26] performed a pooled analysis using two studies and reported the significance of 5-fluorouracil- and leucovorin-based adjuvant chemotherapy for patients with curative resection of liver metastases from CRC. Nordlinger et al. reported the results of a randomized trial showing the advantage of perioperative chemotherapy with the oxaliplatin plus fluorouracil and leucovorin regimen (FOLFOX4) [27]. The trial showed that the rate of progression-free survival at 3 years was significantly increased from 33.2 to 42.4 % in patients who underwent R0 resection. Adjuvant and/or neoadjuvant systemic chemotherapy is thus thought to play an important role in patients with both hepatic and pulmonary metastases from CRC, in particular for the patient with a short DFI.

Conclusions

Aggressive surgical resection of both hepatic and pulmonary metastases from CRC should be undertaken in selective patients. It is particularly indicated for patients with a long DFI.

Conflict of interest None.

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