Surgical Resection of Colorectal Cancer With Distant Metastases to Other than Liver or Lung

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Abstract. *Background/Aim:* If both distant metastases and the primary tumour of colorectal cancer (CRC) are resectable, resection of the distant metastases is considered. The aim of this retrospective study was to determine the efficacy of curative resection of both primary and metastatic lesions in organs other than liver or lung in CRC patients. *Patients and Methods:* The medical records of 23 CRC patients who received R0 resection for primary and metastatic regions between 2009 and 2018 were retrospectively analyzed. *Results:* The 3-year overall survival (OS) in all 23 cases was 80.0%. There was no clinicopathological factor associated with OS on univariate analysis. *Conclusion:* Curative surgical resection appears to be useful for distant CRC metastases to organs other than liver or lung.

Colorectal cancer (CRC) is one of the most common malignancies in Japan. Of the patients who undergo curative resection of the primary tumour, nearly one third will develop recurrent disease. In addition, patients with stage IV CRC have a very poor prognosis, with the 5-year survival approaching 20% (1). However, if both the distant metastases and the primary tumour of CRC are resectable, curative resection of the primary tumour is performed, and resection of the distant metastases is considered to improve the prognosis (1). In particular, the 5-year overall survival (OS) rates after curative resection of hepatic or pulmonary metastases are well known to be 35-68% (2). Regarding other than hepatic or pulmonary metastases, there are only a

few reports of resection of peritoneal metastases, and almost no reports of other organs. The aim of this retrospective study was to determine the efficacy of curative resection of both primary and metastatic lesions in tissues other than liver or lung in CRC patients.

Patients and Methods

A total of 23 patients with CRC with distant metastases in organs other than liver and lung underwent R0 resection of the primary and metastatic tumours at the Kansai Rosai Hospital from 2009 to 2018. The patients were Stage IV or had distant metastatic recurrence after curative surgery for Stage I-III.

Information on various clinicopathological factors of patients, including age, sex, tumour location, histological type, tumour markers, and status of distant metastatic organs was obtained from medical records and retrospectively analysed. Histological type was categorized as either differentiated (dif, well or moderately differentiated tubular adenocarcinoma) or undifferentiated (undif, mucinous or poorly differentiated adenocarcinoma). Regarding tumour location, those arising from the cecum and the ascending and transverse colon were defined as right-sided tumours, whereas those arising from the descending colon to the rectum were defined as left-sided tumours.

This study was reviewed and approved by the institutional review boards of the participating institutions (Approval number; 20160425).

Statistical analysis. The Kaplan–Meier method was used to generate actuarial survival estimates; these were compared using the log-rank test. All statistical analyses were performed using JMP version 14.0 (SAS Institute, Cary, NC, USA).

Results

The clinicopathological characteristics of all patients (n=23) are presented in Table I. Their median age was 66 years (range=34-87 years). Synchronous resection for Stage IV was performed in 11 cases, and resection of metastatic recurrence after curative surgery was performed in 12 cases. All patients underwent R0 resection. The regimens of chemotherapy before resection of metastases were: CAPOX

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Key Words: Colorectal cancer, metastases, R0 resection.

Table I. Clinicopathological characteristics of the patients.

	All patients (n=23)	(%)
Age (y)		
Median (range)	66	34-87
≥65	10	43.5
<65	13	56.5
Gender		
Male	8	34.8
Female	15	65.2
Tumour location		
Right-sided colon (C/A/T)	5 (2/3/0)	21.7
Left-sided colon (D/S/R)	18 (D/S/R)	78.3
Target		
Stage IV	11	47.8
Metastatic recurrence	12	52.2
Histological type		
Dif	19	82.6
Undif	4	17.4
CEA		
Positive	15	65.2
Negative	8	34.8
CA19-9		
Positive	4	17.4
Negative	19	82.6
M status		
M1a/M1b	11 (10/1)	47.8
M1c	12	52.2
Chemotherapy before metastasectomy		
Yes	7	30.4
No	16	69.6

Dif: Well or moderately differentiated tubular adenocarcinoma; Undif: mucinous or poorly differentiated adenocarcinoma; CEA positive: >5.0 ng/ml, negative: ≤5.0 ng/ml; CA19-9 positive: >37 U/ml, negative: ≤37 U/ml.

(capecitabine + oxaliplatin) + B-mab (bevacizumab), 2 cases; FOLFOXILI (5-FU + oxaliplatin + irinotecan) + B-mab; mFOLFOX6 (5-FU + oxaliplatin) + Bmab; capecitabine + Bmab; CAPOX; and capecitabine.

Table II shows the details of the metastatic sites in all 23 patients. The most common metastatic site was the ovary (7 cases, 30.4%), followed by the peritoneum (6 cases, 26.1%).

The median length of follow-up for all patients was 32 months (range=10-73 months). The 3-year OS in all 23 cases was 80.0% (Figure 1). There was no clinicopathological factor associated with OS on univariate analysis (Table III).

Discussion

In this study, the prognosis of R0-resected CRC patients with distant metastases in organs other than liver or lung was evaluated. The 3-year OS in all 23 cases was 80.0%. In a multi-institutional study in Japan, it was reported that the 3-year OS after hepatectomy for liver metastases of CRC in

Table II. Metastatic sites.

Metastatic sites	All patients (n=23)	(%)
Ovary	5	21.7
Extra-regional lymph node	3	13.0
Colon	1	4.3
Spleen	1	4.3
Liver+adrenal gland	1	4.3
P1	6	26.1
P1+ovary	1	4.3
P2	1	4.3
P2+ovary	1	4.3
P2+uterus	2	8.7
P3	1	4.3

P1: metastases only to adjacent peritoneum; P2: a few metastases to distant peritoneum; P3: numerous metastases to distant peritoneum.

763 cases was 52.8% (3). The present results compare favourably with this report, suggesting that surgical resection is useful for distant metastases of CRC in tissues other than liver or lung. Another study has reported that patients with R0 resection (n=26) had significantly better survival than those with palliative resection (n=100) (5-year OS: R0 resection vs. palliative resection=55.6% vs. 9.2%, $p<0.001$) (4). However, in that study, the number of patients with metastases in organs other than liver or lung was 50, and the number of R0 resections was not mentioned.

The most common metastatic site in the present study was ovary. It has been reported that isolated ovarian metastases from CRC are rare, representing only 3-8% of metastases (5). Metastasectomy of the ovary is reported to confer a good survival rate (6, 7). However, since the 5-year OS rate after metastasectomy of the ovary in those reports was only 15-25%, metastasectomy of the ovary has not been established.

The second most common metastatic site in this study was peritoneum. One report has shown that the 3-year OS rate (n=78) was 45%, and the 5-year OS rate was 28.7% after R0 resection of peritoneal metastasis (8). The Japanese Society for Cancer of the Colon and Rectum (JSCCR) guideline describes complete resection as desirable for P1 (metastases only to adjacent peritoneum), complete resection is considered for P2 (a few metastases to distant peritoneum) when easily resectable, and the efficacy of resection of P3 (numerous metastases to distant peritoneum) has not been demonstrated (1). Excision for resectable P seems to be recommended.

Finally, clinicopathological factors relating to a poor prognosis were unclear in the present study. Other groups have analysed prognostic factors in patients with stage IV CRC, and they demonstrated that high pT stage and presence of positive node(s) were significant negative prognostic factors (9, 10). A prognostic factor in R0 resection for

Figure 1. Three-year overall survival of the 23 patients.

metastatic CRC patients has not been reported, and no clinicopathological factor associated with OS was identified in the present study.

The main therapy of metastatic CRC at the present time is chemotherapy, but even triplet chemotherapy plus bevacizumab has a 3-year OS of about 40% (11). The present data showed better OS with resection than with chemotherapy alone; thus, R0 resection may extend overall OS, even if recurrence occurs later. We believe that R0 resection also improves the prognosis for metastatic CRC to organs other than liver or lung.

Although advances in chemotherapy have prolonged survival of patients with metastatic colorectal cancer, the combination of R0 metastasectomy and chemotherapy may lead to better outcomes.

This study has certain limitations, such as low patient number, short observation period, and the fact that it was a retrospective, single-institute study. Thus, further large and multi-institutional studies are needed to confirm these findings.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

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Authors' Contributions

Study concepts: Atsushi Naito; Study design: Atsushi Naito; Data acquisition: Atsushi Naito; Quality control of data and algorithms: Yoshinori Kagawa; Data analysis and interpretation: Atsushi Naito;

Table III. Univariate analysis for prognostic variables correlated with 3-year overall survival.

	Number of cases	OS (%)	p-Value
Age (y)			
≥65	10	90.0	0.2899
<65	13	71.6	
Gender			
Male	8	71.4	0.6082
Female	15	84.4	
Tumour location			
Right-sided colon (C/A/T)	5	80.0	0.2285
Left-sided colon (D/S/R)	18	81.2	
Timing of resection			
Simultaneous	11	77.1	0.7035
Recurrent	12	81.8	
Histological type			
Dif	19	88.2	0.0799
Undif	4	50.0	
CEA			
Positive	15	76.2	0.3655
Negative	8	85.8	
CA19-9			
Positive	4	75.0	0.5331
Negative	19	80.0	
M status			
M1a/M1b	11 (10/1)	80.0	0.5328
M1c	12	79.6	
Chemotherapy before metastasectomy			
Yes	7	100	0.7892
No	16	73.1	

Dif: Well or moderately differentiated tubular adenocarcinoma; Undif: mucinous or poorly differentiated adenocarcinoma.

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