JOURNAL OF THE
ANUS, RECTUM AND COLON
dx.doi.org/10.23922/jarc.2017-021
http://journal-arc.jp

ORIGINAL RESEARCH ARTICLE

Outcomes of stage IV patients with colorectal cancer treated in a single institution: What is the key to the long-term survival?

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Abstract:

Objectives: The purpose of this study is to summarize our short- and long-term treatment results for stage IV colorectal cancer (CRC) and to clarify the factors predicting the favorable long-term survival. Methods: Between January 2008 and December 2015, 149 consecutive patients with stage IV CRC underwent initial treatment at Nagoya University Hospital. Their clinical and pathological characteristics, the treatment methods used, and the outcomes were retrospectively analyzed. Results: The median observation period was 23 months. All of the primary and metastatic lesions were technically resectable in 74 patients; however, the remaining 75 were judged as initially unresectable. R0/1 resection during the treatment course was achieved in 74 patients (50%). For the cohort as a whole, the 5-year overall survival (OS) rate was 35%. The 5-year OS rate in the R0/1 resection group was 57%, which was significantly better than that of the non-R0/1 resection group (6%, $p < 0.001$). In the R0/1 resection group, perioperative chemotherapy significantly improved the outcome (5-year OS; 62% vs. 0%, $p = 0.03$). In the non-R0/1 resection group, primary tumor resection was associated with a significantly higher favorable prognosis (3-year OS; 20.4% vs. 0%, $p = 0.026$). Moreover, the additional use of molecular targeted drugs significantly improved the survival. In multivariate analysis, the differentiated histologic type, R0/1 resection, and parallel use of molecular targeted drugs remained independent factors of a favorable outcome. Conclusions: The present study suggested that aggressive curative resection with perioperative chemotherapy might improve survival and that primary tumor resection might improve the outcome in the non-R0/1 group.

Keywords:

stage IV, colorectal cancer, surgery, long-term survival, chemotherapy

J Anus Rectum Colon 2018; 2(1): 16-24

Introduction

Although the concept of preventive medicine is wide spread and the population undergoing medical checkups has increased, approximately 17-20% of colorectal cancer (CRC) patients are diagnosed as stage IV[1,2]. Surgical resection with perioperative chemotherapy is recommended as a promising option of the treatment for initially resectable disease, including distant metastasis[3]. Alternatively, no contrary opinion exists against the main role of systemic chemotherapy for initially unresectable disease, although the role of primary tumor resection remains controversial[4-7]. The judgment of resectability is an important issue but remains unclear. Resectability must be decided from both oncologic and technical aspects; therefore, it is a matter of course that the judgment is quite different among institutions and physicians. In our institution, the definition of resectable disease has been judged mainly from the technical aspect, and surgical resection played a crucial role for technically resectable or borderline disease.

Several large randomized studies for patients with unresectable and metastatic CRC have been performed world-

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Received: April 21, 2017, Accepted: October 3, 2017

wide. The remarkable advances in cytotoxic drugs and molecular-targeted drugs improve their survival, and it has been reported that the median survival time has reached 28-30 months[8,9]. Moreover, with advances in surgical technique and the following extension of the surgical indication, conversion therapy with curative intent was reported to improve survival;[10] however, these studies included both oncologically unresectable and technically borderline resectable, stage IV and metachronous recurrent disease after curative primary resection. Early liver metastasis after curative resection including stage IV disease has been reported to be a worse prognostic factor[11-13]. Faron et al. reported that 30% of the registered patients had metachronous recurrence in the four large European randomized controlled trials (RCTs)[7]. The true outcome of the pure stage IV patients remained unclear.

The purpose of this study is to summarize our short- and long-term treatment results of stage IV CRC treated in a single institution and to clarify the factors predicting the favorable long-term survival.

Methods

Patients

The patients of the present study were selected from our prospective colorectal cancer database, which is maintained at Nagoya University Hospital in Nagoya, Japan. Between January 2008 and December 2015, 149 consecutive patients with stage IV CRC underwent initial treatment at Nagoya University Hospital. All patients were histologically confirmed as having colorectal adenocarcinoma by endoscopic biopsy. The metastatic lesions were diagnosed using enhanced computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)-CT. Before the diagnosis of colorectal cancer, nine patients revealed a history of receiving a treatment for the other malignant diseases (breast cancer: $n = 3$, gastric cancer: $n = 2$, bladder cancer: $n = 2$, gallbladder cancer: $n = 1$, tongue cancer: $n = 1$); however, none of the diseases had an influence on their outcomes. Their clinical and pathological characteristics, treatment methods, and the outcomes were retrospectively analyzed.

Study parameters

Data collected included age, gender, performance status, observation period, primary tumor location, histological type, metastatic sites, presence of symptoms due to the primary tumor, technical resectability of the tumor during initial diagnosis, KRAS oncogene mutation status, initial treatment, induction of systemic chemotherapy with or without molecular targeted drugs, achievement of curative resection, recurrence after curative resection, and overall survival (OS). Transverse colon cancer was included in the category of right-sided cancer. Histologic type was divided into the differentiated type (well or moderately differentiated) and the undifferentiated type (poorly differentiated, signet ring cell, or mucinous). The technical resectability was assessed during the pretreatment multidisciplinary conference by the medical oncologists and colorectal, liver, and pulmonary surgeons. Curative resection was defined as the complete macroscopic resection of both primary and all metastatic lesions during the treatment course, including R0 and R1 resection. The patients were divided into two groups: the R0/1 resection group and the non-R0/1 resection group, which included patients with R2 resection and nonsurgical resection.

Statistical analysis

The Kaplan-Meier method and log-rank test were used to compare the survival curves. The Cox proportional hazards model was used to clarify the factors predicting long-term survival. P values of <0.05 were considered as statistically significant. All of the statistical analyses were performed using the SPSS software program (version 23.0; SPSS Inc., Chicago, Ill., USA).

Results

The clinical and pathological characteristics of 149 patients are presented in Table 1. The median observation period was 22.9 months. The primary tumor was located at the right side of the colon in 41 patients (27.5%), at the left side of the colon in 46 patients (30.9%), and at the rectum in 62 patients (41.6%). In 63 patients (42.3%), the primary tumor was symptomatic owing to bowel stenosis or bleeding, requiring initial bowel resection, bypass, or stoma creation. No patients underwent colonic stent. Regarding histological type, the differentiated type was dominant in 128 patients (85.9%) and the undifferentiated type was proven in 14.1% patients. Although the metastatic lesions were localized on a single organ in 106 patients (71.1%), the other 43 patients (28.9%) initially revealed multiple-organ metastases. In 106 patients (71.1%) the liver was the dominant metastatic site and 70 patients (47.0%) revealed liver limited metastases. All of the primary and metastatic lesions were technically resectable in 74 patients (49.7%); however, the other 75 (50.3%) were judged as having an initially unresectable disease. The KRAS oncogene test was examined in 100 patients, and 52 of them were confirmed to have the mutation.

The treatment results are presented in Table 2. As an induction treatment, some form of surgical intervention was performed in 110 patients (73.8%). The primary tumor was initially resected in 85 patients (57.0%). Systemic chemotherapy was introduced without any surgical intervention in 33 patients (22.1%). In the patients with technically resectable disease, five patients failed to achieve curative re-

Table 1. Patients' Characteristics (n=149).

Age (years)	67 (28-91)
Gender (male/female)	90/59
Performance status (%)	
0	85 (57.0)
1	56 (37.5)
2	8 (5.5)
Primary tumor location (%)	
Colon	87 (58.4)
Right-sided	41 (27.5)
Left-sided	46 (30.9)
Rectum	62 (41.6)
Observation period (months)	22.9 (0.4-98.8)
Histologic type (%)	
Differentiated	128 (85.9)
Undifferentiated	21 (14.1)
Serum level of CEA (ng/ml)	35.6 (0.5-19000)
Number of metastatic sites (%)	
1	106 (71.1)
2	31 (20.9)
3	8 (5.3)
4	4 (2.7)
Metastatic site (including overlap) (%)	
Liver	106 (71.1)
Lung	33 (22.1)
Peritoneum	28 (18.8)
Distant LN	28 (18.8)
Others	13 (8.8)
Symptoms (%)	
Yes	63 (42.3)
No	86 (57.7)
Initial resectability (%)	
Resectable	74 (49.7)
Unresectable	75 (50.3)
KRAS mutation type (%)	
Wild	52 (34.9)
Mutated	48 (32.2)
Unknown	49 (32.9)

CEA, carcinoembryonic antigen; LN, lymph node

Table 2. Treatment Results (n=149).

Induction treatment (%)	
For initially resectable patients	74 (49.7)
Surgery	
Resection of both primary and metastasis	20
Resection of primary tumor	26
Resection of metastasis	1
Colostomy	3
Chemotherapy	18
Others	6
For initially unresectable patients	75 (50.3)
Surgery	
Resection of primary tumor	39
Resection of metastases	1
Bypass or colostomy	20
Chemotherapy	15
R0/1 resection (%)	
Yes	74 (49.7)
Perioperative chemotherapy	
Yes with targeted drugs	37
Yes without targeted drugs	26
No	11
No	75 (50.3)
Primary tumor resection during the treatment course	
Yes	45
No	30
Induction of chemotherapy	
Yes with targeted drugs	49
Yes without targeted drugs	13
No	13
Recurrence after R0/1 resection (n=74) (%)	
Yes	46 (62.2)
Re-resection of recurrent disease	13
No	28 (37.8)
5-year overall survival rate in the whole (%)	34.5

section. The reasons included their systemic comorbidity (n = 2), tumor progression (n = 2), and peritoneal disseminationon laparotomy (n = 1). In the patients with initially unresectable disease, five patients underwent successful conversion surgery after chemotherapy. Eventually, R0/1 resection during the treatment course was achieved in 74 patients (49.7%) and 63 of them received perioperative chemotherapy. Although recurrence after R0/1 resection developed in 46 patients, recurrent lesions could be curatively re-resected in 13 patients. Furthermore, re-recurrence was detected in 11 of 13 patients (85%); 8 of them could undergo a third resection. In the non-R0/1 group, 45 patients finally underwent primary resection and 49 patients were treated with targeted drugs. Figure 1 represents a detailed flow chart.

For the cohort as a whole, the 5-year OS rate was 34.5%. The 5-year OS rate in the R0/1 resection group was 57.0%, which was significantly better than that of the non-R0/1 resection group (5.9%, $p < 0.001$; Figure 2A). In the R0/1 resection group, perioperative chemotherapy significantly improved the survival (5-year OS; 61.8% vs. 0%, $p = 0.03$; Figure 2B); however, the parallel use of molecular-targeted drugs did not affect the outcome. Alternatively, in the non-R 0/1 resection group, primary tumor resection was associated with a significantly higher favorable prognosis (3-year OS; 20.4% vs. 0%, $p = 0.026$; Figure 2C). Moreover, the addition of molecular-targeted drugs to chemotherapy significantly improved the survival in 62 of 75 patients who received chemotherapy (3-year OS; 21.1% vs. 0%, $p < 0.001$; Figure 2D). KRAS oncogenic mutation had no impact on the outcome (Figure 3A). The patients with right-sided colon cancer had a trend of worse prognosis but revealed no significant difference from the patients with left-sided or

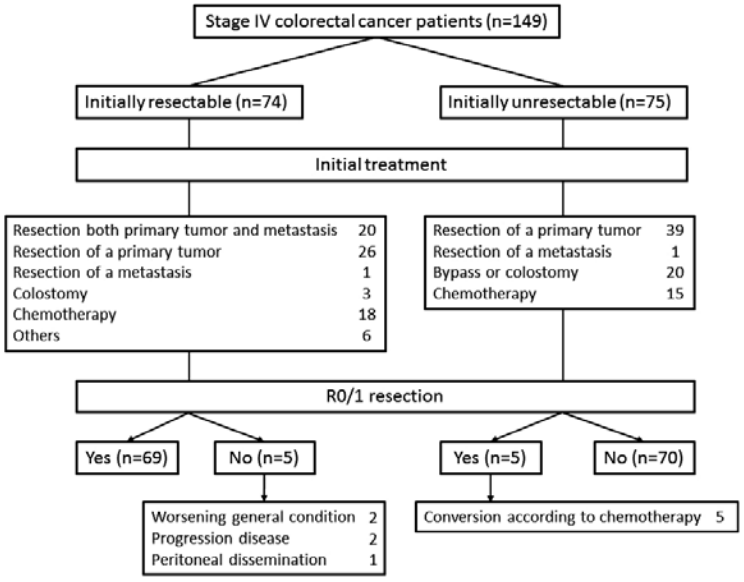

Figure 1. A detailed flow chart.

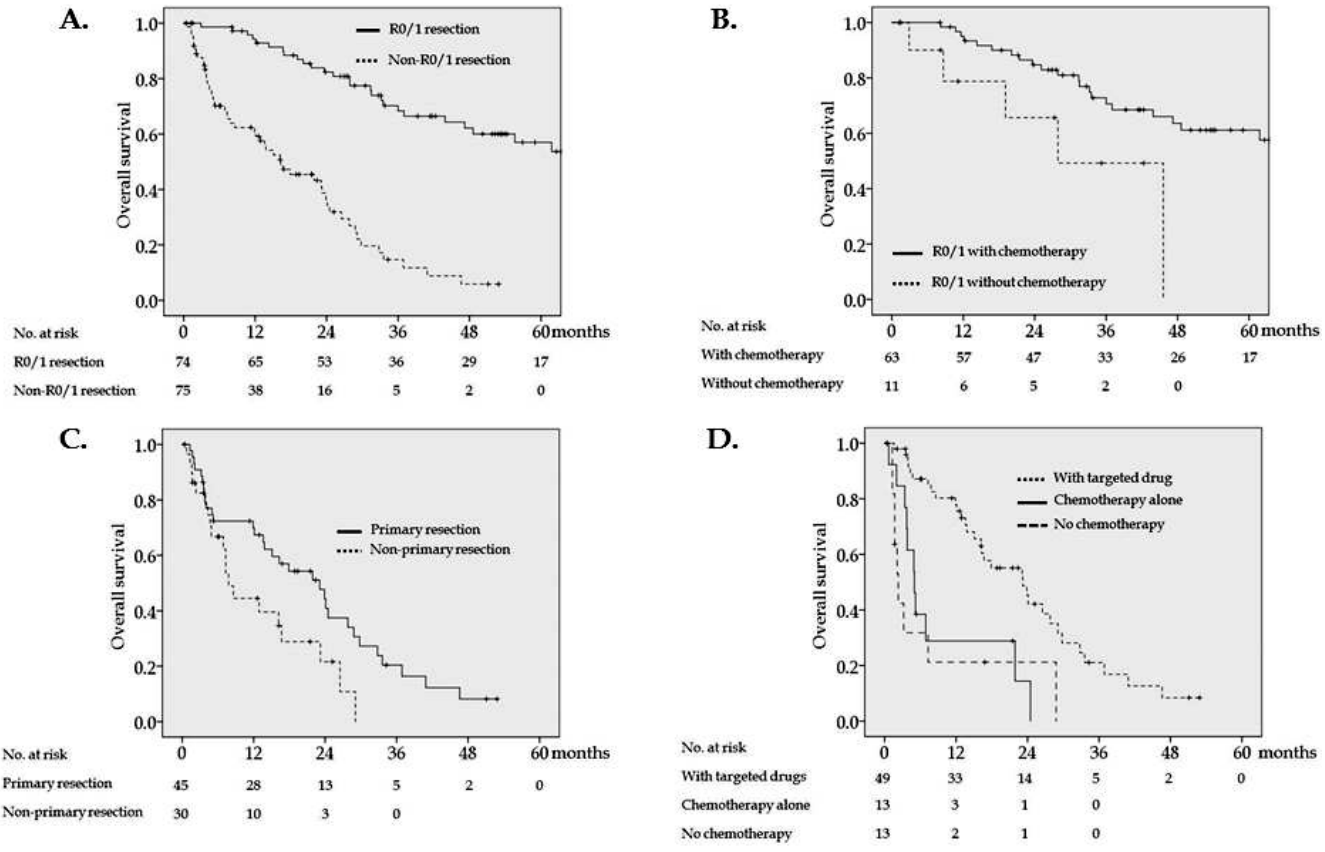

Figure 2.

A. The 5-year OS rate in the R0 resection group was significantly better than that of the non-R0 resection group (57.0% vs. 5.9%, $p < 0.001$).

B. In the R0/1 resection group, perioperative chemotherapy significantly improved survival (5-year OS; 61.8% vs. 0%, $p = 0.03$).

C. In the non-R0/1 resection group, the primary tumor resection was associated with a significantly higher favorable prognosis (3-year OS; 20.4% vs. 0%, $p = 0.026$).

D. In the non-R0/1 resection group, additional targeted drugs significantly improved the survival compared to chemotherapy alone (3-year OS; 21.1% vs. 0%, $p < 0.001$).

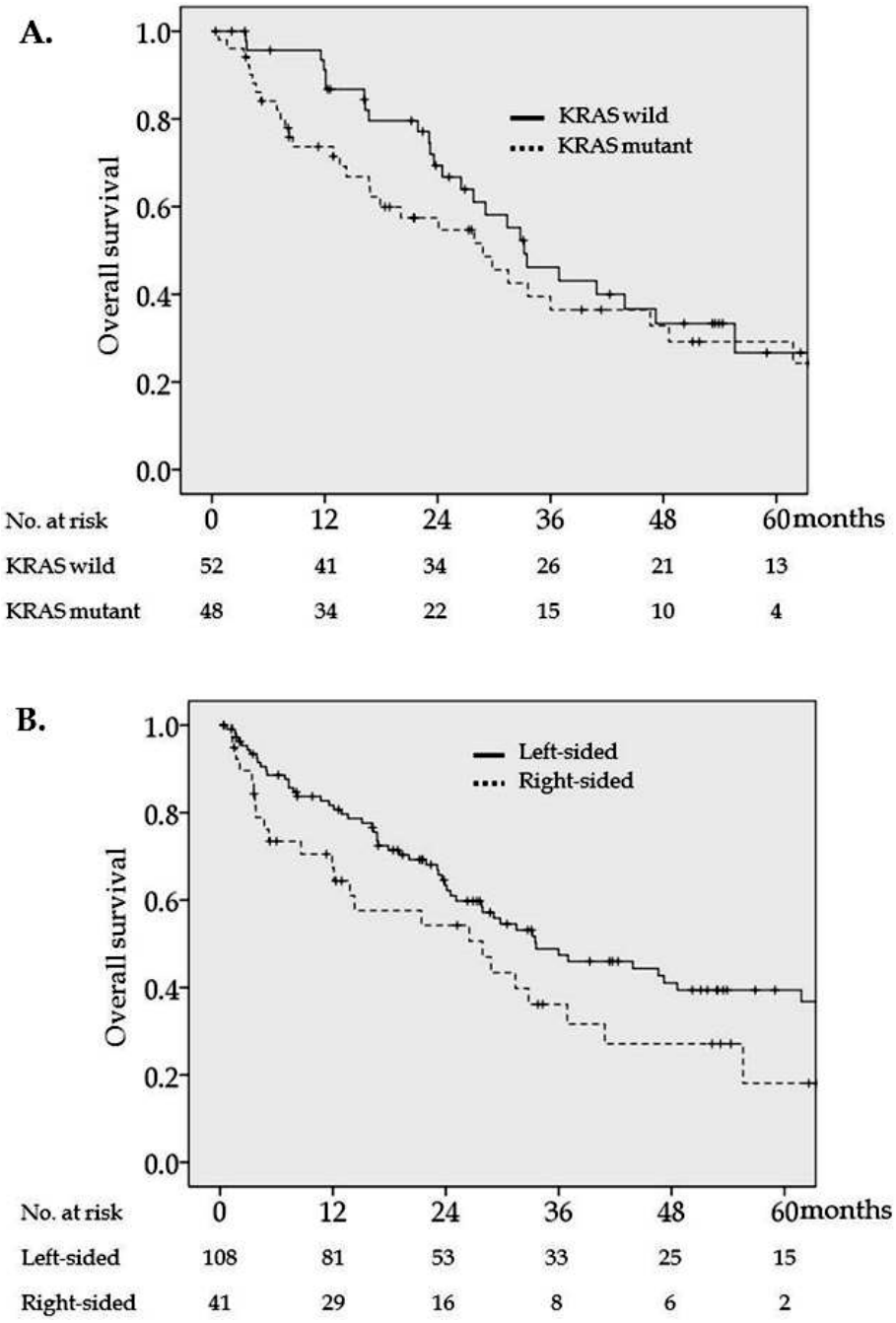

Figure 3.

A. Survival curve according to the KRAS oncogenic type (n = 100). KRAS oncogenic mutation had no impact on the outcome.

B. Survival curves according to the primary tumor location. The patients with right-sided colon cancer revealed a trend of worse prognosis; however, there were no significant differences.

rectal cancer (Figure 3B).

Table 3 presents the factors affecting the long-term outcome. Univariate analysis revealed that the differentiated histological type, single-site metastasis, presence of liver metastasis, absence of distant lymph node metastasis or peritoneal metastasis, R0/1 resection, receiving chemotherapy, and parallel use of molecular-targeted drugs were significant indicators for a favorable prognosis. In multivariate analysis, the differentiated histological type, R0/1 resection, and parallel use of molecular-targeted drugs remained independent factors for a favorable outcome.

Table 4 presents the patients' characteristics according to

Table 3. Univariate and Multivariate Analysis of OS Using the Cox Proportional Hazards Regression Model.

Variables	n	Univariate		Multivariate	
		HR (95% CI)	P	HR (95% CI)	P
Primary tumor location					
Right-sided	41	1.587 (0.980-2.570)	0.069	1	0.988
Left-sided	108	1		1.006 (0.476-2.122)	
Serum level of CEA (ng/ml)					
>30	69	1.072 (0.690-1.664)	0.758	1.134 (0.608-2.117)	0.565
<30	80	1		1	
Histologic type					
Differentiated	128	1	0.032	1	0.004
Undifferentiated	21	1.888 (1.057-3.374)		3.761 (1.529-9.251)	
KRAS mutation status					
Wild	52	1.306 (0.778-2.192)	0.312	1.063 (0.566-1.997)	0.820
Mutant	48	1		1	
Number of metastatic site					
Single-organ	106	1	0.004	1	0.191
Multiple-organs	43	2.030 (1.253-3.290)		2.185 (0.676-7.062)	
Liver metastasis					
Presence	106	1	0.006	1	0.066
Absence	43	1.893 (1.197-2.994)		2.266 (0.918-5.589)	
Plumonary metastasis					
Presence	33	1.206 (0.703-2.067)	0.497	1	0.501
Absence	116	1		1.345 (0.489-3.704)	
Peritoneal metastasis					
Presence	28	2.016 (1.182-3.437)	0.010	1	0.080
Absence	121	1		2.370 (0.903-6.224)	
Distant LN metastasis					
Presence	25	1.755 (1.008-3.057)	0.047	1	0.638
Absence	124	1		1.190 (0.442-3.207)	
Bowel symptom					
Presence	63	1	0.169	1.541 (0.808-2.940)	0.212
Absence	86	1.364 (0.876-2.123)		1	
R0/1 resection					
Yes	74	1	<0.001	1	<0.001
No	75	5.689 (3.413-9.481)		8.531 (3.759-19.358)	
Induction of chemotherapy					
Yes	127	1	<0.001	1.048 (0.280-3.917)	0.944
No	22	3.593 (1.960-6.584)		1	
Use of molecular-tergeted drugs					
Yes	94	1	0.021	1	0.011
No	33	1.689 (1.063-2.686)		2.641 (1.263-5.520)	

CEA, carcinoembryonic antigen; LN, lymph node

the R0/1 resection. In the R0/1 group, the patients with rectal cancer received preoperative chemotherapy more frequently (p = 0.062). In the non-R0/1 resection group, the patients with colonic cancer underwent palliative primary resection more often (p = 0.107).

Discussion

Stage IV CRC is an extremely heterogeneous subgroup, and patients' outcome is regulated by various factors. In this entire cohort of consecutive stage IV patients, the 5-year OS rate of 35% was beyond our expectation and fairly favorable compared to the previous reports (8.5-18.8%)[2,14,15]. The reason may be that all patients were treated in the era of newly developed chemotherapy. Although the differentiated histological type, R0/1 resection, and parallel use of molecular-targeted drugs were demonstrated as independent prognostic factors in this study, R0/1 resection and use of targeted

Table 4. Patients' Characteristics According to the R0/1 Resection.

	R0/1 resection (n=74)			Non-R0/1 resection (n=75)		
	Perioperative chemotherapy (+) (n=63)	Perioperative chemotherapy (-) (n=11)	P	Primary resection (+) (n=45)	Primary resection (-) (n=30)	P
Age (years)	67 (28-86)	68 (40-87)	0.226	67 (33-91)	65 (29-84)	0.480
Gender (male/female)	45/18	5/6	0.619	24/21	16/14	>0.999
PS (%)			0.674*			0.330*
0	50 (79.4)	10 (90.9)		18 (40.0)	7 (23.3)	
1	12 (19.0)	1 (9.1)		24 (53.3)	19 (63.3)	
2	1 (1.6)	0		3 (6.7)	4 (13.4)	
Primary tumor location (%)			0.062**			0.107**
Colon	29 (46.0)	9 (81.8)		36 (80.0)	15 (50.0)	
Right-sided	10 (15.9)	4 (36.4)		19 (42.2)	8 (26.7)	
Left-sided	19 (30.1)	5 (45.5)		17 (37.8)	7 (23.3)	
Rectum	34 (54.0)	2 (18.2)		9 (20.0)	15 (50.0)	
Observation period (months)	23.2 (1.2-98.8)	25.2 (1.5-55.6)		23.1 (0.4-52.9)	21.5 (0.4-29.1)	
Histologic type (%)			0.393			0.618
Differentiated	57 (90.5)	9 (81.8)		38 (84.4)	24 (80.0)	
Undifferentiated	6 (9.5)	2 (18.2)		7 (15.6)	6 (20.0)	
Serum level of CEA (ng/ml)	34.6 (0.8-19000)	31.7 (3-79.4)	0.631	34.6 (1.6-12500)	34.6 (0.5-1713)	0.154
Number of metastatic sites (%)			0.393***			>0.999***
1	57 (90.5)	9 (81.8)		24 (53.3)	16 (53.3)	
2	6 (9.5)	2 (18.2)		16 (35.6)	7 (23.3)	
3	0	0		3 (6.7)	5 (16.7)	
4	0	0		2 (4.4)	2 (6.7)	
Metastatic site (including overlap) (%)						
Liver	47 (74.6)	7 (63.6)	0.759	33 (73.3)	19 (63.3)	0.693
Lung	7 (11.1)	2 (18.2)	0.566	15 (33.3)	9 (30.0)	0.827
Peritoneum	5 (7.9)	4 (36.4)	0.029	8 (17.8)	11 (36.7)	0.160
Distant LN	10 (15.9)	0	-	8 (17.8)	7 (23.3)	0.631
Others	0	0	-	9 (20.0)	4 (13.3)	0.528
Symptoms (%)			0.773			0.873
Yes	21 (33.3)	3 (27.2)		24 (53.3)	15 (50.0)	
No	42 (66.7)	8 (72.8)		21 (46.7)	15 (50.0)	
Initial resectability (%)			0.858			0.073
Resectable	58 (92.1)	11 (100)		5 (11.1)	0	
Unresectable	5 (7.9)	0		40 (88.9)	30 (100)	
KRAS mutation type (%)			0.637****			0.817****
Wild	19 (30.2)	4 (36.4)		16 (35.6)	13 (43.4)	
Mutated	21 (76.3)	3 (27.2)		14 (31.1)	10 (33.3)	
Unknown	23 (36.5)	4 (36.4)		15 (33.3)	7 (23.3)	

*PS 0/1 vs. 2; **colon vs. rectum; ***1 vs. 2 or more; ****wild vs. mutated; PS, performance status; CEA, carcinoembryonic antigen; LN, lymph node

drugs are the factors in which we can actively intervene. Thus, although it is a matter of course, our results recommended that we should aim for curative resection, and if this is not possible, chemotherapy with molecular-targeted drugs should be introduced.

It is generally accepted that curative resection is a positive indicator of long-term survival[14,15]. A recent retrospective study investigated curatively resected stage IV CRC and reported the 5-year OS rate to be 52.2%[16], which was similar to our results. Kobayashi et al. built a scoring system for stage IV CRC and curative resection was treated as the strongest prognostic factor, being twice as strong as the other factors[14]. A higher rate of curative resection was strongly required for long-term survival. Additionally, several studies reported the safety and efficacy of repeated curative resection for recurrent disease[17-19]. Recurrent surgeries are physically burdensome for patients and postoperative complications might cause delay or suspension of the following therapy. Nevertheless, for strictly selected patients, long-term survival could be expected through repeated sur-

gery for the recurrent disease. In this study, eight patients underwent resection twice or more times for recurrent disease after curative resection.

The efficacy of perioperative chemotherapy for initially resectable metastatic CRC remains unclear[20,21]. Miyoshi et al. reported the outcome of stage IV patients with liver and/or lung metastasis and mentioned that adjuvant chemotherapy, which comprised mainly fluorouracil alone, after curative resection did not affect the survival[22]. In this study, perioperative chemotherapy for patients in the R0/1 group included newly developed cytotoxic drugs in 87% of patients and could improve the outcome.

The efficacy of primary resection for asymptomatic unresectable disease remains controversial[4-7]. In this study, although 52% of the non-R0/1 group had symptomatic primary disease and 60% underwent primary resection, the primary resection improved survival significantly in the non-R 0/1 group; however, notably, this study is a small retrospective study and included selection bias. It is generally well-known that patients with better general condition and lower tumor burden are more likely to undergo primary resection.

Recently, several novel indicators have been reported. The outcome of right-sided cancer has been reported to be worse than that of the left-sided disease[23-26]. Ishihara et al. reported that a right-sided primary tumor was detected to be a worse prognostic factor in stage IV CRC[27]. In this study, the outcome of the patients with right-sided colon cancer revealed a trend toward being worse compared to the left-sided disease (p = 0.06). It has also been reported that mutated KRAS is a worse prognostic factor, although this claim remains controversial;[28,29] however, KRAS mutation type had no impact on the outcome in this study. We need to further investigate the impact of various types of genomic mutations including RAS and BRAF on the outcome.

In conclusion, although this study has several limitations including its small sample-size and retrospective nature, the present study suggested that aggressive curative resection with perioperative chemotherapy might improve survival and that primary tumor resection might improve the outcome in the non-R0/1 group.

Conflicts of Interest

There are no conflicts of interest.

Author contributions

Toshiki Mukai and Keisuke Uehara contributed equally to this work; Toshiki Mukai, Keisuke Uehara, and Masato Nagino designed the research; Tomoki Ebata, Toshisada Aiba performed the research; Hayato Nakamura analyzed the data; Toshiki Mukai and Keisuke Uehara wrote the paper.

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