Journal of Surgical Oncology 2016;114:75–79

Control of Primary Lesions Using Resection or Radiotherapy Can Improve the Prognosis of Metastatic Colorectal Cancer Patients

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Background: Control of the primary lesions in metastatic colorectal cancer (mCRC) is still controversial. For rectal cancer patients, not only resection but also irradiation is expected to provide palliative effects. We investigated the effects of resection and irradiation of primary lesions (local control) on the prognosis of mCRC patients.
Patients: Forty-seven patients with mCRC at our institute were examined, with 34 in the local controlled group and 13 in the uncontrolled group.
Results: The median survival time (MST) of the local controlled and uncontrolled groups were 2.90 and 1.39 years ($P = 0.028$). Cox proportional hazard regression analysis showed that local control was an independent prognostic factor ($P < 0.05$). The patients who underwent primary lesion resection had significantly longer MST (2.90 vs. 1.39 years, $P = 0.032$) than those in the uncontrolled group. In rectal cancer patients, the patients who underwent irradiation to control the primary lesions had a significantly longer MST than the uncontrolled patient group (1.97 vs. 1.39 years, $P = 0.019$).
Conclusions: Local control of primary lesions may improve the prognosis in mCRC patients. In rectal cancer patients with metastasis, not only resection but also irradiation of the primary lesions may be a useful therapeutic strategy.
J. Surg. Oncol. 2016;114:75–79. © 2016 Wiley Periodicals, Inc.

KEY WORDS: metastatic colorectal cancer; primary lesion; surgical resection; radiotherapy

INTRODUCTION

The incidence rate of colorectal cancer (CRC) is increasing worldwide [1,2]. Although the mortality rate of CRC patients has decreased over time [3] because of improvements in the efficacy of treatments, it is still relatively high [1–3]. Patients with incurable metastatic CRC (mCRC) are generally treated with multimodal therapy [4,5]. In such cases, the resection of the primary lesions is often performed before starting chemotherapy with the intent of controlling the symptoms caused by the primary lesions. However, it is still unclear whether the control of primary lesions has any impact on prognosis.

Stillwell et al. claimed that the resection of primary lesions results in better prognoses for patients with stage IV CRC on the basis of meta-analysis [6]. Ahmed et al. also reported the beneficial effect of resection on prognosis in a clinical trial [7]. On the other hand, Seo et al. and Cirocchi et al. claimed that the resection of primary lesions did not have any impact on the prognoses of stage IV CRC patients, particularly in patients who did not present any symptoms [8,9]. Furthermore, the risk of complications from the surgery and the effects of these complications on the subsequent chemotherapy need to be considered [10]. Thus, the efficacy of resecting primary lesions is still controversial.

Another method of controlling primary lesions is irradiation. Palliative radiotherapy is sometimes performed to relieve the symptoms caused by primary lesions; thus, avoiding the potential complications of surgery [11]. Palliative radiotherapy can improve the quality of life for symptomatic patients [12,13]. However, to our knowledge, the effects of irradiation on prognosis have not been reported.

The objective of this study was to compare the prognoses of patients who underwent resection or irradiation to control the primary lesions with that of patients who did not undergo primary lesion control. The effects of resection and irradiation on patient survival were also evaluated.

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PATIENTS AND METHODS

Patient Groups

The clinical records of 47 patients with unresectable mCRC were retrospectively selected from the database of the Department of General Surgical Science, Graduate School of Medicine, Gunma University, Maebashi, Japan, from April 2005 to August 2012. All clinical data in this study were used in accordance with institutional guidelines and the Helsinki Declaration after obtaining written informed consent from all participants. All the patients were chemotherapy naive. Twenty-nine patients underwent primary lesion resection before chemotherapy, whereas five patients received irradiation alone for the primary lesions. These 34 patients were sorted into the "local controlled" group. The remaining 13 patients did not undergo resection nor irradiation and were

Abbreviations: CRC, colorectal cancer; mCRC, metastatic colorectal cancer; MST, median survival time; CTC, circulating tumor cells.

Conflicts of interest: None.

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Received 30 October 2015; Accepted 26 March 2016

DOI 10.1002/jso.24255

Published online 25 April 2016 in Wiley Online Library (wileyonlinelibrary.com).

sorted into the "uncontrolled" group. The treatment of each case was determined by attending physician's judgment.

Protocol of Irradiation

The primary lesions and the pararectal lymph nodes were included in the irradiation range. Irradiation was combined with 5-fluorouracil/calcium folinate in one case, and with mFOLFOX6 in four cases. The irradiation range was 50–60 Gy (50 Gy in three cases, and 56 and 60 Gy for one case each). Weekly regional hyperthermia with 8 MHz radiofrequency was used with irradiation in three cases. Initiation of post-radiation multidrug chemotherapy was based on the attending physician's judgment, and chemotherapy was started within 8 weeks after irradiation.

Clinical Staging

The depth of tumors (cT) was evaluated by computed tomography (CT), colonoscopy, and endoscopic ultrasonography. The lymph node metastasis was evaluated by CT. Invasion to other organs was diagnosed by CT. The accuracy of CT in diagnosing invasions to other organs is reported to be 70–100% [14,15]. According to Japanese classification of colorectal carcinoma [16], we classified the burden of liver metastasis into H0–H3 (H0, no liver metastasis; H1, one to four metastatic tumors all of which are 5 cm or less in maximum diameter; H2, other than H1 or H3; H3, five or more metastatic tumors at least one of which is more than 5 cm in maximum diameter) based on CT imaging.

Statistical Analysis

For continuous variables, the data were expressed as the mean ± standard deviation. The relationships between the characteristics of the local controlled and uncontrolled groups were analyzed using Student's *t*-test, chi-square test, and analysis of variance. Overall survival was measured from the day of the first multidrug chemotherapy and was plotted according to the Kaplan–Meier method; the log-rank test was used for comparisons. Differences were considered statistically significant at the level of $P < 0.05$. The relative multivariate significance of potential prognostic variables was examined. Cox proportional hazard regression analysis was used to test he independent prognostic contributions of the local control methods. All statistical analyses were performed with R script generated by EZR [17].

RESULTS

Patient Characteristics

Table I shows the characteristics of the local controlled and uncontrolled groups. The local controlled group consisted of 34

TABLE I. Patient Characteristics

	Uncontrolled n = 13	Local controlled n = 34	*P* value
Gender			
Male	10	18	0.189
Female	3	16	
Age (years)	59.5 (38–75)	63.1 (39–77)	0.285
ECOG PS			
0	5	20	0.416
1	6	11	
2	2	3	
Location of primary lesions			
Colon	8	18	0.746
Rectum	5	16	
Location of metastatic lesions			
Only liver	7	18	1
Extrahepatic lesions	6	16	
Depth of tumor (cT)			
T1	1	1	0.537
T2	0	0	
T3	4	14	
T4	8	19	
Lymph node metastasis (cN)			
Present	3	4	0.377
Absent	10	30	
Pretherapeutic CEA	565.6 ± 1,003	269.9 ± 939.4	0.348
1st line chemotherapy			
FOLFOX ± Bmab	9	21	0.897
CapeOX ± Bmab	3	5	
FOLFIRI ± Bmab	1	2	
FOLFIRI + Cmab	0	1	
Others	0	5	
Curative resection			
Present	0	3	0.550
Absent	13	31	
KRAS state			
Wild type	0	7	0.237
Mutant	3	8	
unknown	10	19	
Burden of liver metastasis			
H0	8	11	0.156
H1	0	6	
H2	1	8	
H3	4	9	

CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status.

TABLE II. Characteristics of the Primary Lesion

	Controlled group n = 34	Uncontrolled group n = 13	*P* value
Gastrointestinal symptoms[a]			
Present	17	8	0.746
Absent	17	5	
Stenosis of colorectal tract[b]			
Present	14	7	0.745
Absent	20	6	
Tumor invasion to other organs (T4b)[c]			
Present	8	5	0.467
Absent	26	8	

[a]Subjective gastrointestinal symptoms at first visit, such as abdominal pain, bloody stool, and constipation.
[b]Stenosis was defined as when the colonoscope could not be inserted into the primary tumor.
[c]Invasions were determined using image diagnosis (mainly computed tomography).

patients, including 18 males and 16 females, with a mean age of 63.1 years, whereas the uncontrolled group consisted of 13 patients, including 10 males and three females, with a mean age of 59.5 years. The clinical characteristics of the two groups are shown in Table I (Eastern Cooperative Oncology Group performance status, depth of tumor, lymph node metastasis, pretherapeutic carcinoembryonic antigen, first-line chemotherapy, and KRAS status), and no significant differences were found between the two groups. In the local controlled group, three patients underwent curative resection of the metastatic lesions; however, the difference between the two groups was not statistically significant ($P = 0.550$). There is no significant difference of tumor barden of liver metastasis between two groups ($P = 0.156$). Table II summarizes the characteristics of the primary lesions at each patient's first visit. None of these characteristics (subjective gastrointestinal symptoms, stenosis of the colorectal tract, and tumor invasion to other organs (T4b)) were significantly different between the two groups.

Local Controlled Group Had Better Prognosis Than the Uncontrolled Group

The local controlled group had prolonged survival compared with the uncontrolled group; the median survival time (MST) and 5-year

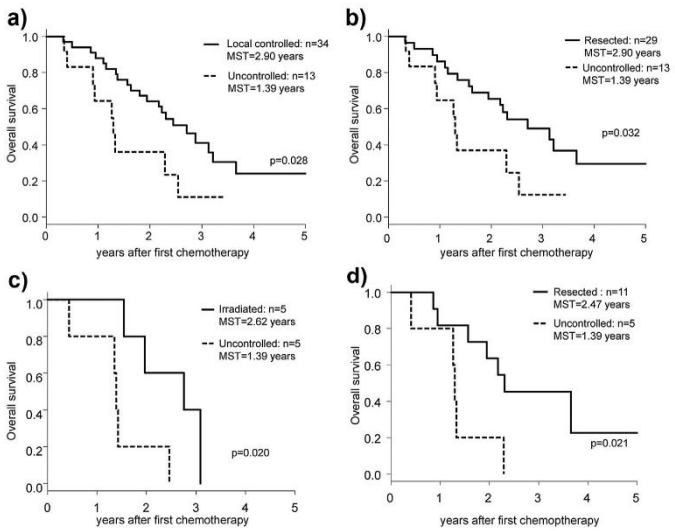

Fig. 1. (**a**) Overall survival after induction of chemotherapy. Local controlled group versus uncontrolled group ($P = 0.028$, log-rank test). (**b**) Overall survival after induction of chemotherapy. Resected group versus uncontrolled group ($P = 0.032$, log-rank test). Resected group: patients group that underwent resection of the primary lesion. (**c**) and (**d**): overall survival of rectal cancer patients after the induction of chemotherapy. (**c**) Irradiated** group versus uncontrolled patients ($P = 0.020$, log-rank test). (**d**) Resected* group versus uncontrolled patients ($P = 0.021$, log-rank test). *Resected group: patients who underwent the resection of the rectal primary lesion. **Irradiated group: patients who underwent irradiation of the rectal primary lesion. MST, median survival time.

TABLE III. Univariate and Multivariate Analysis Between Overall Survival and Clinicopathological Variables

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	*P* value	Hazard ratio	95% confidence interval	*P* value
Gender	1.18	0.562–2.50	0.657	1.11	0.493–2.50	0.801
Age	0.989	0.957–1.02	0.508	0.998	0.961–1.04	0.922
T (T2,T3/T4)	1.08	0.526–2.23	0.829	0.949	0.443–2.03	0.892
N (N0/N1,2,3)	3.60	0.855–15.1	0.0808	5.65	1.23–26.0	0.0262
Pretherapeutic CEA[a]	1.00	1.00–1.001	0.0666	1.00	0.999–1.001	0.155
Local control (+/−)	0.411	0.185–0.916	0.0298[b]	0.300	0.124–0.727	0.00762[b]

[a]CEA, carcinoembryonic antigen.
[b]$p < 0.05$.

survival rates were 2.90 years and 25.2%, and 1.39 years and 0% for the local controlled and uncontrolled groups, respectively ($P = 0.028$; Fig. 1a). The results of the univariate analysis and multivariate analysis by the Cox proportional hazard method are shown in Table III. Local control was an independent prognostic factor among these patients ($P < 0.05$). The prognosis of the patients who underwent primary lesion resection ("resected group") was compared with that of the uncontrolled group (Fig. 1b), and the data show that the resected group had a significantly longer MST than the uncontrolled group (2.90 vs. 1.39 years, $P = 0.032$). Five patients with rectal cancer were irradiated to control the primary lesions, and the MST of these patients was significantly longer than that of the uncontrolled rectal cancer patients (1.97 vs. 1.39 years, $P = 0.019$; Fig. 1c). The resected group also had significantly longer MST than the uncontrolled patients (2.47 vs. 1.39 years, $P = 0.021$; Fig. 1d).

The Local Controlled Group Tended to Have Good Chemosensitivity Compared With the Uncontrolled Group

The response rates to chemotherapy between the local controlled group and uncontrolled group were compared (Table IV). The response rate in the former was 47.1%, whereas that of the latter was 15.4%, and although it was not significantly different ($P = 0.0911$), the efficacy of chemotherapy tended to be higher in the local controlled group than in the uncontrolled group.

DISCUSSION

Our results suggest that control of primary lesions may improve the prognosis of mCRC patients. Not only resection but also irradiation of the primary lesions can potentially prolong survival.

Ahmed et al. noted that surgical resection of the primary tumor before the induction of chemotherapy improved prognoses in unresectable CRC patients [18]; the MST of the resected patients was 18.3 months, whereas that of the non-resected patients was 8.4 months. In our study, the MST of the resected group was 15.2 months (range: 10–30.7 months), whereas that of the uncontrolled group was 11.4 months (range: 3–22 months). Our results are consistent with those of the previous report. Some reports have claimed that there is no relationship between primary resection and prognosis [8,9], but the patients included in these studies exhibited no symptoms caused by the primary lesions. On the other hand, Ahmed et al. reported that primary resection improved prognosis, and 39.5% of their cases exhibited symptomatic disease [7]. In our study, 54.1% of the patients had some subjective symptoms; therefore, we believe that primary lesion resection may improve the prognosis of CRC patients, especially symptomatic patients.

Palliative radiotherapy of the primary lesions in mCRC patients is sometimes performed to avoid complications caused by the primary lesions (pain, bleeding, obstruction, etc.) and to improve patients' quality of life [11,12]. Our results suggest that palliative radiotherapy may improve the prognosis of mCRC patients because the MST of the irradiated patients (1.97 years) was longer than that of the non-irradiated patients (1.39 years). Tyc-Szczepaniak et al. claimed that the palliative effect of radiation can be sustained in the long term; in their study, 67% of the patients exhibited good control of symptoms 2 years after radiotherapy [13]. Our results showed that irradiation is useful for controlling the primary lesions in rectal cancer patients because rectal surgery results in higher complication rates [10].

We demonstrated that local control leads to better prognosis. A previous report noted that the reduction of complications (such as obstruction of the intestinal tract, bleeding from the primary lesions, and perforation) in CRC patients treated with local control resulted in improved prognosis [6]. In our study, two cases in the uncontrolled group needed hospitalization to treat complications caused by the primary lesions. One case underwent partial ileectomy and ileum–ileum bypass to treat the invasion of the primary lesion into the ileum. The other case developed a perineal abscess caused by the invasion of the primary lesion. Neither of these cases were able to continue chemotherapy after discharge. These complications were not lethal, but the dropout from the chemotherapy may have led to shorter survival time. Such complications derived from primary lesion did not observed in local control group. In two cases of "resected group," major surgical complication occurred. One is the post-operative ileus and the other is the anastomotic leakage. In both cases, hospitalization was prolonged about a month, but they were able to start chemotherapy immediately after discharge.

In renal cell carcinoma and ovarian carcinoma, control of the primary lesions improves the therapeutic effect of chemotherapy [19,20]. In CRC, a similar effect may result from the control of the primary lesions. In our study, the response rate to chemotherapy tended to be higher in the local controlled group than in the uncontrolled group (Table IV). In the case of CRC, cytoreductive surgery to treat peritoneal dissemination should result in improved prognosis [21]; however, the effect of reductive surgery of the primary lesions or at other metastatic sites is unclear. Merogi et al. and Barth

TABLE IV. Comparison of Response Rate Between Local Controlled Group and Uncontrolled Group

Best overall response	Uncontrolled group	Local controlled group	*P* value
Stable disease or progressive disease	11	18	0.0911
Complete response or partial response	2	16	
Response rate	15.4%	47.1%	

et al. suggested that the secretion of cytokines by primary lesions may affect the progression of cancer and the therapeutic effect of chemotherapy [22,23]. Further, Kim et al. showed that circulating tumor cells (CTCs) can colonize their tumors of origin in a process termed "self-seeding" [24]. They also showed that self-seeding can accelerate tumor growth, angiogenesis, and stromal recruitment through seed-derived factors. Improvement of patient prognosis by local control could be due to the control of CTCs and humoral factors such as cytokines. Local control using resection or irradiation may improve chemotherapy sensitivity in mCRC.

CONCLUSION

In mCRC patients, local control of the primary lesions may improve prognosis by reducing complications and increasing chemosensitivity. Particularly, in rectal cancer patients with metastasis, not only resection but also irradiation of the primary lesions may be a useful therapeutic strategy.

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