

# Effect of primary tumor location and tumor size on the response to radiotherapy for liver metastases from colorectal cancer

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**Abstract.** Metastatic liver tumors (MLTs) from colorectal cancer (CRC) are often treated with stereotactic body radiation therapy (SBRT). The present study aimed to examine the predictive factors for response of MLTs to SBRT. A total of 39 MLTs from 24 patients with CRC were retrospectively analyzed. Radiotherapy for MLT was typically performed with a prescribed dose equivalent to a biologically effective dose (BED)<sub>10</sub> of 100 Gy. The median follow-up period was 16 months (range, 5-64 months). The median prescribed dose and total BED<sub>10</sub> were 56 Gy (range, 45-72 Gy) and 97.5 Gy (range, 71.7-115.5 Gy), respectively, in a median of 8 fractions (range, 4-33 fractions). The 1- and 2-year local control rates were 67.2 and 35.9%, respectively. For patients with MLT treated with ablative SBRT (BED<sub>10</sub> ≥ 100 Gy in ≤ 5 fractions), the 1- and 2-year local control rates were 83.3 and 62.5%, respectively. Univariate analysis showed that primary tumor location (left-sided colon), maximum tumor diameter (≤ 30 mm) and ablative SBRT (BED<sub>10</sub> ≥ 100 Gy in ≤ 5 fractions) were significantly associated with improved local control (P=0.0058, P=0.0059 and P=0.0268, respectively). Multivariate analysis showed that tumor diameter was significantly associated with improved local control (P=0.0314). In addition, patients who received ablative SBRT had significantly prolonged overall survival times compared with those treated with non-ablative SBRT (P=0.0261). To conclude, tumors ≤ 30 mm that can be treated with ablative SBRT are associated with good local control rates. The primary tumor location may affect the radiosensitivity of MLTs.

## Introduction

Patients with colorectal cancer (CRC) often have metastases at initial presentation or during follow-up (1,2). The liver is one of the most frequent sites of metastasis (1,2). Newly developed chemotherapeutic agents, including targeted therapies, have improved the progression-free and overall survival times of patients with metastatic CRC (3,4). There is also evidence supporting the benefit of surgery to treat metastases from CRCs, with surgery improving overall survival time (5-7). The prolonged survival times of patients have highlighted the importance of local therapy for CRC and limited metastatic disease. In patients who are unfit for surgery, alternative local therapeutic approaches, including radiofrequency ablation (RFA), are available to treat liver metastases; these approaches are minimally invasive and can achieve good local control (8,9). However, their indication is currently limited to relatively small tumors that are located far away from critical structures (8,9).

Modern radiotherapeutic techniques, including intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT), have recently become more frequently utilized to curatively treat limited metastatic tumors (10-14). SBRT, also termed stereotactic ablative radiation therapy, is a proven curative treatment for medically inoperable small tumors in the lung and liver; it delivers highly conformal radiation in a limited number of high-dose fractions, providing excellent primary tumor control with minimal toxicity (12-21). Radiotherapy in alternatively fractionated regimens with a greater number of fractions may be required to reduce the biologically effective doses (BEDs) to normal tissues when treating liver tumors located in the hepatic portal regions. In those cases, IMRT may be considered a more conventional schedule (22). However, there are limited data that compare SBRT with conventionally fractionated radiotherapy of curative intent.

The present study aimed to evaluate the optimal radiotherapy regimen for liver metastases from CRC.

## Materials and methods

**Patients.** The present study was conducted according to the principles of the Declaration of Helsinki. The institutional

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review board of Miyakojima IGRT Clinic (Osaka, Japan) approved data collection and analysis (approval no. 9). A total of 39 liver tumors in 24 patients who received definitive radiotherapy at Miyakojima IGRT Clinic between November 2007 and December 2014 were analyzed. All eligible patients were histologically diagnosed with primary colorectal adenocarcinoma and radiographically diagnosed with liver metastases using computed tomography (CT) or magnetic resonance imaging (MRI). Tumors from patients who were followed up for <6 months without any failures were excluded. Written informed consent for radiotherapy was obtained from all patients. Patient characteristics are shown in Table I.

**SBRT technique.** Radiotherapy for liver tumors was performed as previously described (23). Briefly, CT and MRI scans for treatment planning were obtained using a 4-slice BrightSpeed Excel<sup>®</sup> (GE Healthcare Bio-Sciences, Pittsburgh, PA, USA) between November 2007 and June 2014, and a 64-slice SOMATOM Definition AS Open RT Pro edition (Siemens AG, Munich, Germany) from July 2014 onward, as well as the SIGNA EXCITE HDx 1.5T (GE Healthcare Bio-Sciences), respectively. Planning contrast-enhanced 4-dimensional CT scans and gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced MRI images were used to determine gross tumor volume. Planning target volume (PTV) was created by adding a 4-8-mm margin in all directions to the internal target volume (ITV). The prescribed radiation doses were documented at the reference point using conformal beams in 17 tumors, or designed to deliver the prescribed dose to cover 95% of the PTV using IMRT in 22 tumors. A prescribed dose equivalent to a BED<sub>10</sub> of ~100 Gy was administered to the liver metastases from CRC. Radiotherapy was performed using a 6-MV linear accelerator (Novalis BrainLAB AG, Feldkirchen, Germany).

**Follow-up.** Local control was defined as the absence of local failure. Local control and survival times were defined as the intervals between the start of radiotherapy and the date of diagnosis of local failure or the date of mortality, respectively. Local failures were identified by experienced physicians using CT and MRI, and defined by any regrowth of the target tumor or the appearance of tumor staining in the target tumor on contrast-enhanced images. Toxicity was evaluated for the 29 treatments for 39 tumors in 24 patients. No hematological toxicities were considered to exist in patients who exhibited hematological abnormalities prior to radiotherapy and developed no apparent changes from the baseline. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events version 4.0 (24).

**Statistical analysis.** The data are expressed as the medians, with the ranges in parentheses, unless otherwise indicated. Cumulative local control and survival estimates were calculated using the Kaplan-Meier method, and statistical differences were evaluated by the log-rank test. The Cox proportional hazards model was performed to evaluate factors affecting local control and survival. Results are reported as hazard ratios (HR) and corresponding 95% confidence intervals (CI). Variables with P<0.2 by univariate analysis were entered into the multivariate model. Multivariate analyses

were performed with a Cox regression analysis. All statistical analyses were performed using JMP software version 12.2.0 (SAS Institute, Cary, NC, USA). P<0.05 was considered to indicate a statistically significant difference.

## Results

**Eligible patients and tumors.** Of the 24 eligible patients, 14 patients received radiotherapy for a single liver metastasis, 3 patients received radiotherapy for two different lesions simultaneously, 3 patients received radiotherapy for two different lesions that occurred sequentially, and 2 patients received radiotherapy for three different lesions simultaneously. In addition, 1 patient received radiotherapy for one lesion and then for three lesions simultaneously 4 months later, and 1 patient received radiotherapy for two lesions simultaneously and then for one lesion 1 month later. The median follow-up times were 11 months (range, 5-52 months) and 16.5 months (range, 6-64 months) for local control and survival, respectively. Ablative SBRT, defined as BED<sub>10</sub> ≥100 Gy in ≤5 fractions, was performed for 16 tumors in 8 patients.

Grade 1 nausea and fatigue were observed in 2 patients including 1 patient who developed grade 1 alkaline phosphatase (ALP) elevation and grade 2  $\gamma$ -glutamyl transpeptidase (GGT) elevation following radiotherapy. Furthermore, 1 patient developed grade 1 aspartate aminotransferase (AST), alanine aminotransferase (ALT) and ALP elevation, and grade 2 GGT elevation following two different treatments. One patient developed grade 1 ALP elevation alone. In addition, 1 patient developed grade 1 AST, ALT and ALP elevation and grade 3 GGT elevation due to chemotherapy. One patient developed grade 2 AST and ALP elevation, and grade 3 GGT and blood bilirubin elevation due to cholangitis caused by a recurrent tumor. Furthermore, 1 patient developed a hemorrhagic duodenal ulcer; however, there was no evident causal association between that event and radiotherapy.

**Local control.** In all 39 liver metastases, the local control rates were 67.2 and 35.9% after 1 and 2 years, respectively (Fig. 1). When patients were divided into three groups based on tumor size (maximum diameter of GTV, ≤30, 30-50 and >50 mm), patients with tumors ≤30 mm in maximum diameter had significantly improved local control compared with the other two groups (Fig. 2A). When patients were stratified according to the primary tumor, defined as right-sided colon (cecum, ascending and transverse colon), left-sided colon (descending, sigmoid and rectosigmoidal) or rectal cancers, liver metastases from rectal cancer were shown to be associated with a significantly poorer local control rate compared with those from the left-sided colon (Fig. 2B).

Univariate analyses showed that colon cancer, left-sided location of primary tumor, the use of ablative SBRT and tumor size ≤30 mm were significantly associated with improved local control rates. In addition, multivariate analysis showed that tumor size <30 mm was a significant independent predictor of local control (Table II).

**Survival times.** For all 24 patients, the overall survival rates were 81.3 and 67.1% at 12 and 24 months, respectively (Fig. 3). In univariate analyses, ablative SBRT, BED<sub>10</sub> ≥100 Gy, an

Table I. Characteristics of the patients (n=24) and tumors (n=39).

Characteristics	n (%)	Median (range)
Gender		
Male	14 (58.3)	-
Female	10 (41.7)	-
Age, years	-	64 (43-84)
Performance status		
0	14 (58.3)	-
1	10 (41.7)	-
Primary tumor location		
Right-sided colon	4 (16.7)	-
Left-sided colon	14 (58.3)	-
Rectum	6 (25.0)	-
Interval between the initial treatment and radiotherapy, months	-	34 (5-145)
Number of liver metastasis at the initial radiotherapy		
1	18 (75.0)	-
2	4 (16.7)	-
3	2 (8.3)	-
Usage of chemotherapy after initial surgery to radiotherapy		
Yes	21 (87.5)	-
No	3 (12.5)	-
Presence of metastasis at the initial diagnosis		
Yes	8 (33.3)	-
No	16 (66.7)	-
History of local therapy <sup>a</sup> for metastasis		
Yes	16 (66.7)	-
No	8 (33.3)	-
History of chemotherapy		
Yes	21 (87.5)	-
No	3 (12.5)	-
History of radiotherapy		
Yes	4 (16.7)	-
No	20 (83.3)	-
Presence of extra diseases outside the field of radiotherapy		
Yes	5 (20.8)	-
No	19 (79.2)	-
Primary tumor location		
Right-sided colon	7 (17.9)	-
Left-sided colon	22 (56.4)	-
Rectum	10 (25.6)	-
GTV, cc	-	8.7 (0.4-134.7)
Size of maximum diameter, mm		35.6 (7.0-116.9)
≤30	18 (46.2)	-
30-50	13 (33.3)	-
>50	8 (20.5)	-
PTV, cc	-	52.8 (12.3-243.0)
Total dose, Gy	-	56.0 (45.0-72.0)
Number of fractions	-	8 (4-33)
Fraction size, Gy	-	7.0 (2.0-12.0)
Total prescription BED <sub>10</sub> , Gy	-	97.5 (71.7-115.5)

<sup>a</sup>Local therapy included surgery, radiofrequency ablation, and radiotherapy. GTV, gross tumor volume; PTV, planning target volume; BED, biologically effective dose.

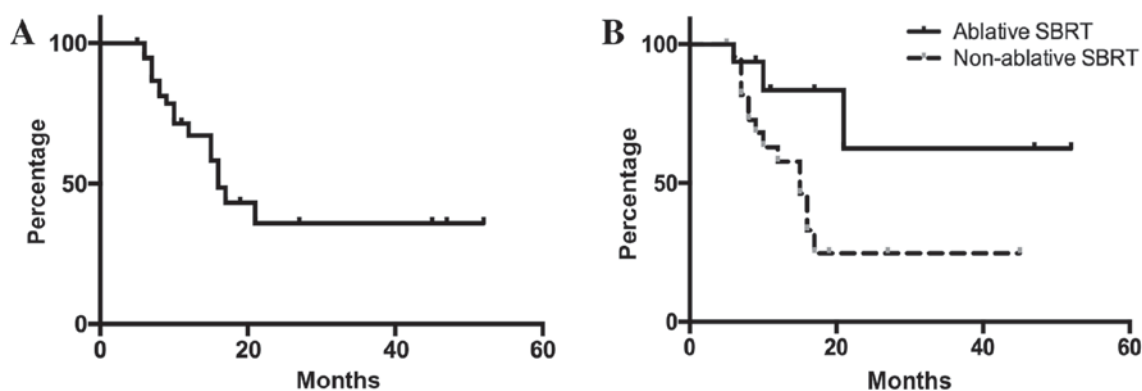


Figure 1. Local control in all eligible patients. (A) Outcomes following radiotherapy for metastatic liver tumors. For 39 metastatic tumors, the median local control time among the patients was 16 months. (B) The 1- and 2-year local control rates were 83.3 and 62.5% in the ablative SBRT group and 57.7 and 24.7% in the non-ablative SBRT group, respectively ( $P=0.0320$ ).

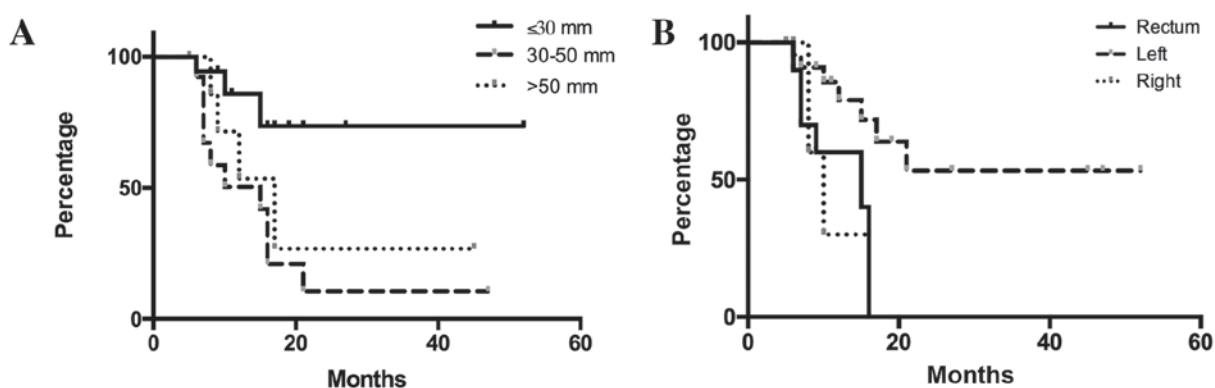


Figure 2. Differences in local control according to tumor sizes and the primary tumor location. (A) The 1- and 2-year local control rates were 85.9 and 73.6% for patients with tumors  $\leq 30$  mm, 50.4 and 10.5% for patients with tumors measuring 30-50 mm and 71.4 and 26.8% for patient with tumors  $> 50$  mm, respectively. A significant difference in local control rates was observed among the three groups ( $P=0.0174$ ). In the two-group analyses, the P-values were  $P=0.0053$  ( $\leq 30$  vs. 30-50 mm),  $P=0.0869$  ( $\leq 30$  vs.  $> 50$  mm) and  $P=0.4148$  (30-50 vs.  $> 50$  mm). (B) The 1-year local control rates were 30.0, 85.6 and 60.0% in liver metastases from the right-sided colon, left-sided colon and rectum, respectively. A significant difference was observed among the three groups ( $P=0.0115$ ). In the two-group analyses, the P-values were  $P=0.0043$  (rectum vs. left-sided colon),  $P=0.7001$  (rectum vs. right-sided colon) and  $P=0.0608$  (right-sided vs. left-sided colon).

interval between the initial surgical treatment for the primary tumor and radiotherapy  $\geq 35$  months, and presence of a single liver metastasis were significantly associated with improved survival outcomes (Table III). No significant independent factors were detected by multivariate analysis.

## Discussion

The recommended treatment for patients with oligometastases in the liver is surgical resection (10,11). However, the resection rate of hepatic metastases has been reported to be only 0.8-22% (25). Liver metastases are known to have different sensitivities to radiation therapy based on the location of the primary tumor; it has been reported that liver metastases derived from CRCs were significantly more resistant to radiation compared with liver metastases derived from non-colorectal cancers (15-17). Thus, patients with CRC metastases may benefit from dose escalation. In addition, a hypoxic cell radiosensitizer may potentially improve local control (26).

The present data indicated that liver metastases from rectal cancer were more resistant to radiotherapy compared with

those from colon cancer. Conversely, patients with metastases from left-sided colon cancer showed favorable local control rates following radiotherapy. CRC biological behavior was previously shown to depend on tumor location, as it varies for tumors originating from the right-sided colon, left-sided colon and rectum (27-33). Significant overexpression of p53 that can affect the response to radiotherapy in rectal cancer in comparison with colon cancer has been reported (33,34). Ayiomamitis *et al* (33) reported significant overexpression of p53 in rectal cancer compared with colon cancer tissue samples. In addition, Spitz *et al* (34) reported that p53 immunohistochemical staining of pretreatment biopsy specimens correlated with the extent of residual disease following chemoradiation in patients with rectal cancer. To the best of our knowledge, this is the first study to investigate the association between the radiosensitivity of liver metastases and primary tumor location.

Treatment with ablative SBRT, which was defined as a prescribed  $BED_{10} \geq 100$  Gy in  $\leq 5$  fractions, was found to lead to improved local control and survival rates compared with a conventional fractionated schedule. High-dose regimens have been described for metastatic liver tumors (16,18,19).

Table II. Factors associated with local control in 39 tumors.

Factor	n (%)	MST, months	Univariate analysis		Multivariate analysis	
			P-value	HR (95% CI)	P-value	HR (95% CI)
Age, years						
<65	19 (48.7)	16	0.9486	1.000	-	-
≥65	20 (51.3)	17		0.969 (0.368-2.600)		
Gender						
Male	25 (64.1)	16	0.7442	1.000	-	-
Female	14 (35.9)	21		0.839 (0.261-2.309)		
Performance Status						
0	25 (64.1)	17	0.8508	1.000	-	-
1	14 (35.9)	12		0.908 (0.344-2.649)		
Primary tumor location						
Left-sided colon	22 (56.4)	N/A	0.0058	1.000	0.1068	1.000
Other	17 (43.6)	10		4.370 (1.529-14.199)		3.728 (0.766-23.295)
Ablative SBRT						
Yes	16 (41.0)	N/A	0.0268	1.000	0.4817	1.000
No	23 (59.0)	15		3.558 (1.144-15.594)		2.292 (0.205-24.041)
BED <sub>10</sub> , Gy						
<100	20 (51.3)	15	0.0751	1.000	0.7181	1.000
≥100	19 (48.7)	N/A		0.401 (0.126-1.094)		1.464 (0.148-9.748)
Maximum diameter of the GTV, mm						
≤30	18 (46.2)	N/A	0.0059	1.000	0.0314	1.000
>30	21 (53.8)	15		4.625 (1.506-20.084)		3.940 (1.121-18.692)
PTV margin, mm						
<8	17 (43.6)	16	0.1350	1.000	0.6641	1.000
8	22 (56.4)	21		0.478 (0.177-1.265)		1.441 (0.296-9.156)
Interval between the initial treatment and radiotherapy, months						
≥35	19 (48.7)	16	0.5991	1.000	-	-
<35	20 (51.3)	21		0.771 (0.284-2.051)		

MST, median survival time; HR, hazard ratio; CI, confidence interval; SBRT, stereotactic body radiation therapy; BED, biologically effective dose; GTV, gross tumor volume; PTV, planning target volume; N/A, not applicable.

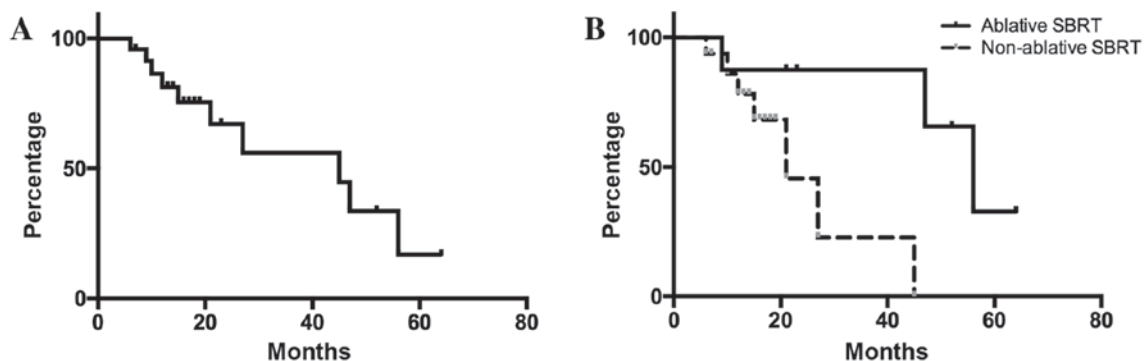


Figure 3. Overall survival of all eligible patients. (A) Outcomes following radiotherapy for patients with metastatic liver tumors. For the 24 patients, the median survival time was 45 months. (B) The 2- and 3-year overall survival rates were 87.5 and 87.5% in the ablative SBRT group, and 45.6 and 22.8% in the non-ablative SBRT group, respectively. Patients who received ablative SBRT showed significantly prolonged survival compared with those who received non-ablative SBRT (P=0.0261).

Table III. Factors associated with overall survival in 24 patients.

Factor	n (%)	MST, months	Univariate analysis		Multivariate analysis	
			P-value	HR (95% CI)	P-value	HR (95% CI)
Age, years						
<65	13 (54.2)	47	0.3912	1.000	-	-
≥65	11 (45.8)	27		1.964 (0.412-10.545)		-
Gender						
Male	14 (58.3)	27	0.7355	1.000	-	-
Female	10 (41.7)	47		0.801 (0.212-3.001)		-
Performance Status						
0	14 (58.3)	27	0.5065	1.000	-	-
1	10 (41.7)	47		0.636 (0.151-2.398)		-
Primary tumor location						
Colon	18 (75.0)	45	0.6331	1.000	-	-
Rectum	6 (25.0)	21		1.414 (0.295-5.256)		-
Left-sided colon	11 (45.8)	45	0.5105	1.000	-	-
Other	13 (54.2)	21		1.562 (0.385-5.691)		-
Ablative SBRT						
Yes	8 (33.3)	56	0.0182	1.000	0.4688	1.000
No	16 (66.7)	12		8.673 (1.387-169.233)		1.121x10 <sup>-8</sup> (0-25.088)
BED <sub>10</sub> , Gy						
<100	13 (54.2)	21	0.0060	1.000	0.1802	1.000
≥100	11 (45.8)	56		0.092 (0.005-0.544)		3.133x10 <sup>-9</sup> (0-9.697x10 <sup>-39</sup> )
Maximum diameter of the GTV, mm						
≤30	9 (37.5)	27	0.4843	1.000	-	-
>30	15 (62.5)	45		1.715 (0.409-11.580)		-
≤50	17 (70.8)	47	0.3458	1.000	-	-
>50	7 (29.2)	45		2.066 (0.416-8.634)		-
PTV margin, mm						
<8	11 (45.8)	21	0.2071	1.000	-	-
8	13 (54.2)	45		0.445 (0.113-1.573)		-
Interval between the initial treatment and radiotherapy, months						
≥35	11 (45.8)	21	0.0028	1.000	0.4246	1.000
<35	13 (54.2)	56		0.079 (0.004-0.456)		0.353 (0.010- 3.807)
Presence of metastasis at the initial diagnosis						
Yes	8 (33.3)	45	0.3683	1.000	-	-
No	16 (66.7)	27		1.984 (0.475-13.384)		-
History of local therapy <sup>a</sup> for metastasis						
Yes	16 (66.7)	45	0.4530	1.000	-	-
No	8 (33.3)	N/A		0.564 (0.084-2.313)		-
History of chemotherapy						
Yes	21 (87.5)	45	0.3970	1.000	-	-
No	3 (12.5)	N/A		2.903 (0.147-20.092)		-
History of radiotherapy						
Yes	4 (16.7)	15	0.1113	1.000	0.1131	1.000
No	20 (83.3)	45		0.201 (0.033-1.545)		0.154 (0.013-1.629)



Table III. Continued.

Factor	n (%)	MST, months	Univariate analysis		Multivariate analysis	
			P-value	HR (95% CI)	P-value	HR (95% CI)
Presence of extra diseases outside the field of radiotherapy						
Yes	5 (20.8)	56	0.6227	1.000	-	-
No	19 (79.2)	27		1.438 (0.354-7.363)		-
Number of liver metastases						
1	18 (75.0)	47	0.0323	1.000	0.1246	1.000
>1	6 (25.0)	21		5.294 (1.160-27.017)		3.845 (0.689-30.348)

\*Local therapy included surgery, radiofrequency ablation, and radiotherapy. MST, median survival time; SBRT, stereotactic body radiation therapy; HR, hazard ratio; CI, confidence interval; BED, biologically effective dose; GTV, gross tumor volume; PTV, planning target volume; N/A, not applicable.

Dose escalation of SBRT for liver metastasis can improve local control (18,19). However, the optimal regimen of SBRT remains unclear. The linear-quadratic (LQ) model has been widely used to compare differentially fractionated radiotherapeutic regimens, despite several limitations (35). Our previous studies have described a prescription using IMRT based on the LQ model (23,36,37). Hypofractionated radiotherapy at higher doses per fraction may increase radiation-induced damages due to direct cytotoxicity, and may lead to microvascular disruption (38-41). It was suggested that liver metastases should be treated by ablative SBRT as often as possible, and the present data support the findings reported in previous studies (15,16).

In the present study, adding margins >8 mm to the ITV led to improved outcomes, although the differences were not significant. When performing SBRT for liver tumors, no margins are usually added to the ITV (12-14,16-21,23). However, only a few studies have demonstrated how many GTV-to-CTV expansions are required in order to reach the gross and microscopic diseases in liver metastasis (41,42). Beginning in July 2012, the PTV margin was reduced from 8 to 4-6 mm in order to minimize focal liver damage. A possible CTV margin of 2-4 mm could therefore exist in tumors with a PTV margin of 8 mm in the present study.

The present study had several limitations. It was a retrospective study with a small sample size and a relatively short follow-up period. In addition, selection bias could exist in the present study, since tumors in the hepatic portal region were often treated with a more conventional regimen. Although a maximum tumor diameter  $\leq 30$  mm was the only prognostic factor for local control by multivariate analysis, the present results were compatible with those in previous studies (20,21). Chemotherapy was less thoroughly described and heterogeneous in the present study. Chemotherapy and other supportive care may differentially affect results, since no significant differences were observed in survival time despite primary tumor location significantly affecting local control in the present study. In addition, molecular biological analysis using

immunohistochemistry and gene evaluation in isolated tissues may reveal differences in biological behavior of metastatic CRCs in future clinical studies.

To conclude, patients with liver metastases  $\leq 30$  mm in size from colorectal adenocarcinoma that received ablative SBRT exhibited favorable local control. Location of the primary tumor may affect the radiosensitivity of liver metastases.

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