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Analyses of local control and survival after stereotactic body radiotherapy for pulmonary oligometastases from colorectal adenocarcinoma

Takaya Yamamoto[1,*], Yuzuru Niibe[2,3], Yasuo Matsumoto[4], Hiroshi Onishi[5], Masahiko Aoki[6], Atsushi Nishikawa[7], Ryoong-Jin Oh[8], Takashi Shintani[9], Katsuya Yahara[10], Masatoki Ozaki[11], Yoshihiko Manabe[12] and Keiichi Jingu[1]

[1]Department of Radiation Oncology, Graduate School of Medicine, Tohoku University, Sendai, Japan
[2]Department of Radiology, Toho University Omori Medical Center, Tokyo, Japan
[3]Department of Public Health, Kurume University School of Medicine, Kurume, Japan
[4]Department of Radiation Oncology, Niigata Cancer Center, Niigata, Japan
[5]Department of Radiology, Yamanashi University, Chuo, Japan
[6]Department of Radiation Oncology, Hirosaki University, Hirosaki, Japan
[7]Department of Radiation Oncology, Shikoku Cancer Center, Matsuyama, Japan
[8]Department of Radiology, Miyakojima IGRT Clinic, Osaka, Japan
[9]Department of Radiation Oncology and Image-Applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[10]Department of Radiology, University of Occupational and Environmental Health, Fukuoka, Japan
[11]Department of Radiation Oncology, Shizuoka City Shimizu Hospital, Shizuoka, Japan
[12]Department of Radiology, Nagoya City University, Nagoya, Japan
*Corresponding author. Department of Radiation Oncology, Tohoku University School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan.
Tel: +81-22-717-7312; Fax: +81-22-717-7316; Email: t.yamamoto@rad. med. tohoku.ac.jp
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ABSTRACT

This study is a subset analysis of a retrospective multicenter study performed in Japan and its purpose was to investigate the effectiveness of stereotactic body radiotherapy (SBRT) for pulmonary oligometastases from colorectal cancer. Local control (LC), freedom from further metastases, relapse-free survival and overall survival (OS) after SBRT were retrospectively analyzed. The Kaplan–Meier method was used to estimate lifetime data and the log-rank test was performed as univariate analyses. The Cox proportional hazards model was applied in multivariate analyses. Data for 330 patients with 371 tumors were used for analyses. The median follow-up period was 25.0 months. The 3-year LC, freedom from further metastases, relapse-free survival and OS rates were 64.9, 34.9, 24.9 and 63.4%, respectively. The results of multivariate analyses showed that a higher LC rate was associated with no history of local therapy for oligometastases ($P = 0.01$), SBRT without concurrent chemotherapy ($P < 0.01$), type B calculation algorithm ($P < 0.01$) and higher biological effective radiation doses ($\geq$115 Gy, $P = 0.04$). A longer OS was associated with no history of local therapy for oligometastases ($P = 0.04$), a more recent period of SBRT (2010–15, $P = 0.02$), tumor located in the upper or middle lobe ($P < 0.01$) and higher biological effective radiation doses ($\geq$115 Gy, $P = 0.01$). In conclusion, OS after SBRT was good, but LC rate was relatively low. The use of high biological effective radiation doses can improve both LC and OS outcomes.

Keywords: stereotactic body radiotherapy (SBRT); pulmonary oligometastasis; colorectal cancer; colorectal metastasis

INTRODUCTION

Metastasectomy for lung metastases from colorectal cancer is a part of the standard treatment for colon cancer and rectal cancer [1, 2]. For patients who are amenable to surgical resection, stereotactic body radiotherapy (SBRT) is regarded as one of the alternative treatments. However, due to insufficient evidence regarding the efficacy and safety of SBRT, it has not become an upfront local therapy for colorectal metastases. According to the National Comprehensive Cancer Network guidelines, radiotherapy should not be used in the place of surgical resection. It has been shown that the local control (LC) rates for pulmonary oligometastases from colorectal cancer (CRC) are lower than LC rates for pulmonary oligometastases from other cancers or LC rates for early-stage non-small cell lung cancer [3, 4]. This radioresistance feature of pulumonary CRC metastases would be the same for liver metastases from CRC [5]. The results of the meta-analysis also suggested that higher LC rates would be obtained by dose escalation of SBRT, and it was shown in another study that an excellent LC rate was achieved with a maximum dose of 83–100 Gy in five fractions [6]. Another feature of CRC was that some patients with CRC showed better overall survival (OS) than patients with other malignancies, although LC rates of SBRT for CRC oligometastases were relatively low, therefore, the role of LC in survival was controversial [5, 7]. These interesting features of oligometastases from CRC motivated us to perform subset analyses using data from a nationwide multicenter retrospective study of SBRT for pulmonary oligometastases that was performed in Japan [8]. The aim of the study was to determine factors affecting LC, development of further metastases and survival after SBRT for pulmonary oligometastases from CRC.

MATERIALS AND METHODS

Eligibility criteria, data collection and definitions

This study was a subset analysis of a retrospective multicenter study performed in Japan. Methods and inclusion criteria for the whole study were as described elsewhere [8]. The whole study was conducted in 68 institutions in Japan. Rewritable compact disks (CD-RWs) containing research items (excel format) were sent from the secretariat office to each institution. Radiation oncologists at each institution filled in the research items fundamentally based on medical records, image interpretation reports, the radiological information system and treatment planning system. After confirming that there was no private information in the CD-RW, they returned the CD-RW to the secretariat office by using 'the Letter Pack' which provided a tracking service. The main inclusion criteria were that the number of pulmonary metastases $\leq$5, the primary lesion and extrathoracic metastases needed to be treated before the start of SBRT, SBRT was performed between 2004 and 2015, and a biological effective dose (BED_{10}) $\geq$75 Gy or more was needed for SBRT. BED_{10} was calculated using the following formula: $BED = n \times d\,[1 + d/(\alpha/\beta)]$, where n is the number of fractions, d is dose per fraction and the α/β ratio is applied for 10 Gy for the tumors. Of a total of 1378 patients in the database, there were 345 patients with pulmonary oligometastases of colorectal origin. Two cases of non-adenocarcinoma pathology (squamous cell carcinoma and endocrine cell carcinoma) were excluded from analysis. Data for 330 patients with 371 tumors from 51 institutes were analyzed in this study (Fig. 1).

Patients' characteristics are shown in Table 1, and oligometastatic tumor and SBRT characteristics are summarized in Table 2. The number of oligometastases was counted at the time of emergence of the pulmonary oligometastases targeted by SBRT. Prior local therapy or combination with another local therapy such as surgical resection was allowed. Disease-free interval (DFI) was defined as the interval between the date when the primary site was controlled and the date when the first metastasis was confirmed. Oligo-recurrences, sync-oligometastases and unclassified oligometastases were defined as DFIs of $\geq$6, 0 and 0–6 months, respectively. Located lobe was defined as the lung lobe in which irradiated tumor was located. When SBRT was performed metachronously, located lobe was judged based on initially irradiated tumor location. When SBRT was performed to multiple sites synchronously, at least one oligometastatic tumor located in the upper or middle lung lobe was classified into upper of middle lobe involvement. The type B dose calculation algorithm included superposition, an equivalent algorithm or a newer generation algorithm such as the Monte Carlo algorithm and type A was an older generation algorithm such as Pencil Beam Convolution.

LC was defined as freedom from local failure, and local failure was defined as enlargement of the irradiated tumor. Freedom from further metastases (FFFM) was defined as the time until emergence of any recurrence or metastasis excluding local failure. Relapse-free survival (RFS) was defined as freedom from any recurrences, any metastases, local failures or death. Toxicity that was judged to be caused by SBRT was reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 translated by the Japan Clinical Oncology Group (CTCAE-JCOG).

Ethics

The previous study was a retrospective multicenter study in Japan. The previous study and this study were approved by the ethical committee of a senior facility (Ethics Committee of Toho University Omori Medical Center, reference number: 27–148) and informed consent was waived due to the study design. All participating institutions were guaranteed the chance to opt out of participation in this study by being given the information about the study via the Internet or posters, and opt-out consent was obtained for all patients.

Data analysis

Follow-up periods and time-to-event outcomes were calculated from the first day of SBRT to the day that an event was confirmed. Cumulative LC rate, FFFM rate, RFS rate and OS rate were calculated from the Kaplan–Meier estimator, and then time-to-event outcomes were summarized using the Kaplan–Meier estimator with a log-rank test to compare stratified outcomes. Continuous covariates were divided at the median value to create stratification factors. Regarding BED_{10} for LC, other cut-off BED_{10} values of 106 and 150 Gy were used to create three groups: classic standard SBRT dose in Japan (48 Gy in 4 fractions) or less group ($<$106 Gy), higher than standard dose but less than ablative dose group (106–150 Gy) and ablative dose group ($>$150 Gy) [5]. The Kaplan–Meier curves were also described according to this group separation. In multivariate analyses (MVA), the Cox proportional hazards model was applied for factors with a log-rank P-value < 0.20 by using a stepwise backward elimination/forward

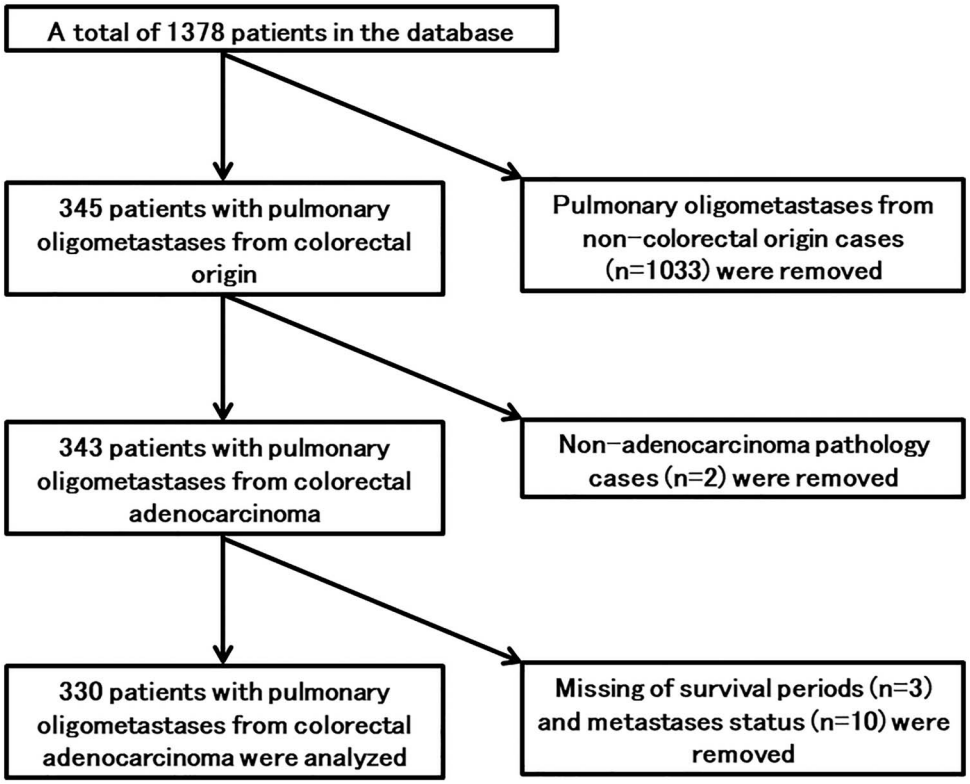

Fig. 1. Flow chart of patients selected from the database of a retrospective multicenter study.

addition approach with the Akaike information criterion (AIC) to construct the best MVA model. A *P*-value < 0.05 was defined as significant. Statistical analyses were performed using EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a modified version of R commander (R Foundation for Statistical Computing, Vienna, Austria) [9].

RESULTS

The median follow-up period for all patients was 25.0 months (range, 0.1–121.3 months). During follow-up, there were 99 local failures and 111 deaths, including death from primary cancer in 83 patients, death from unknown cause in 6 patients, death from toxicity in 2 patients and death from other causes in 20 patients. Of the 330 patients, 187 had failure of FFFM and 236 had failure of RFS. The 1- and 3-year LC rates, FFFM rates, RFS rates and OS rates were 86.1 and 64.9% [95% confidence interval (CI): 81.9–89.5 and 58.6–70.6%], 60.4 and 34.9% (95% CI: 54.7–65.7 and 28.8–41.1%), 52.6 and 24.9% (95% CI: 46.9–58.1 and 19.7–30.5%) and 94.4 and 63.4% (95% CI: 91.1–96.5 and 56.3–69.7%), respectively (Fig. 2). The median FFFM, RFS and OS periods were 19.0 months (95% CI: 15.1–24.5%), 12.6 months (95% CI: 11.2–16.0%) and 51.5 months (95% CI: 40.9–65.6%), respectively. The median time from SBRT to local failure was 12.6 months and it ranged from 4.4 months to 63.3 months. Toxicity was reported in 245 patients, and lung toxicities ≥grade 2 and ≥grade 3 occurred in 33 and 5 patients, respectively. There were two patients with grade 5 toxicity including one patient with pneumonitis and one patient with hemoptysis.

The results of log-rank tests for the variables are shown in Table 3 and the Kaplan–Meier LC curves stratified by BED_{10} of 106 Gy and 150 Gy are shown in Figure 3. By using potential factors that emerged after log-rank tests, MVA for LC, FFFM, RFS and OS revealed several related factors (Fig. 4). A history of local therapy for prior oligometastases [yes vs no, hazard ratio (HR): 1.91, 95% CI: 1.11–3.26, $P = 0.01$], chemotherapy concurrent with SBRT (yes vs no, HR: 4.81, 95% CI: 1.58–14.5, $P < 0.01$), dose calculation algorithm of SBRT (type B vs type A, HR: 0.42, 95% CI: 0.25–0.73, $P < 0.01$) and BED_{10} (≥115 Gy vs <115 Gy, HR: 0.55, 95% CI: 0.30–0.98, $P = 0.04$) showed significant associations with LC. MVA for FFFM showed that a history of local therapy for prior oligometastases (yes vs no, HR: 1.79, 95% CI: 1.21–2.64, $P < 0.01$), chemotherapy concurrent with SBRT (yes vs no, HR: 2.77, 95% CI: 1.07–7.13, $P = 0.03$), maximum oligometastatic tumor diameter (≥1.5 cm vs < 1.5 cm, HR: 1.52, 95% CI: 1.04–2.23, $P = 0.03$) and initially irradiated oligometastatic tumor-located lobe (upper or middle lobe involvement vs lower lobe, HR: 0.66, 95% CI: 0.44–0.98, $P = 0.04$) were significantly associated with FFFM. A history of local therapy for prior oligometastases (yes vs no, HR: 1.81, 95% CI: 1.28–2.55, $P < 0.01$), chemotherapy concurrent with SBRT (yes vs no, HR: 2.90, 95% CI: 1.23–6.81, $P = 0.01$), maximum oligometastatic tumor diameter (≥1.5 cm vs <1.5 cm, HR: 1.45, 95% CI: 1.03–2.06, $P = 0.03$), initially irradiated oligometastatic tumor-located lobe (upper or middle lobe involvement vs lower lobe,

Table 1. Patients' characteristics

Patients	Total number	330
Institute	Academic	143 (43.3%)
	Non-academic	187 (56.6%)
Age, years	Median, range	73, 29–93
Sex	Male	202 (61.2%)
	Female	128 (38.7%)
ECOG performance status[a]	0	193 (58.4%)
	1	112 (33.9%)
	2–3	18 (5.4%)
	Missing	7 (2.1%)
Primary origin	Colon	171 (51.8%)
	Rectum	157 (47.5%)
	Missing	2 (0.6%)
DFI, months	Median, range	17.2, 0–133.9
Oligometastatic state	Oligo-recurrence	243 (73.6%)
	Sync-oligometastases	35 (10.6%)
	Unclassified oligometastases	27 (8.1%)
	Missing	25 (7.5%)
History of local therapy for metastases	Yes	122 (36.9%)
	No	131 (39.6%)
	Missing	77 (23.3%)
Chemotherapy before SBRT	Yes	148 (44.8%)
	No	179 (54.2%)
	Missing	3 (0.9%)
Chemotherapy concurrent with SBRT	Yes	8 (2.4%)
	No	322 (97.5%)
Chemotherapy after SBRT	Yes	196 (59.3%)
	No	55 (16.6%)
	Missing	79 (23.9%)
Number of metastases	1	230 (69.6%)
	2–5	97 (29.3%)
	Missing	3 (0.9%)

[a]ECOG, Eastern Cooperative Oncology Group.

HR: 0.68, 95% CI: 0.48–0.95, $P = 0.02$), dose calculation algorithm of SBRT (type B vs type A, HR: 0.65, 95% CI: 0.43–0.96, $P = 0.03$) and BED_{10} ($\geq$115 Gy vs $<$115 Gy, HR: 0.67, 95% CI: 0.47–0.97, $P = 0.03$) showed significant associations with RFS. In MVA for OS, a history of local therapy for prior oligometastases (yes vs no, HR: 1.70, 95% CI: 1.02–2.85, $P = 0.04$), SBRT treatment date (2010–15 vs 2004–09, HR: 0.54, 95% CI: 0.32–0.92, $P = 0.02$), initially irradiated oligometastatic tumor-located lobe (upper or middle lobe involvement vs lower lobe, HR: 0.43, 95% CI: 0.25–0.73, $P < 0.01$) and BED_{10} ($\geq$115 Gy vs $<$115 Gy, HR: 0.48, 95% CI: 0.27–0.86, $P = 0.01$) emerged as significant prognostic factors.

DISCUSSION

The analyses performed in this study are one of the largest-scale analyses of pulmonary oligometastases from CRC after SBRT. Although this study was a retrospective multicenter study, the results indicated possible factors related to outcomes including both pre-SBRT characteristics and treatment factors. Treatment factors would be particularly valuable because these factors such as BED_{10} dose and calculation algorithm can be changed from now on or in the future. The type B dose calculation algorithm of SBRT (equivalent to superposition or newer generation) and higher BED_{10} ($\geq$115 Gy at the isocenter) contributed not only to a higher LC rate but also higher RFS and OS rates. The radiation dose–response relationship of pulmonary oligometastases from CRC was confirmed in the present study [3]. On the other hand, it was shown in the present study that chemotherapy concurrent with SBRT had no beneficial effect on LC or lower rate of LC.

The effect of additional chemotherapy on peri-SBRT was unclear. Chemotherapy concurrent with SBRT showed higher HRs in LC, FFFM and RFS. Although chemotherapy concurrent with SBRT was performed in only 8 patients with 11 tumors, it was shown that concurrent chemotherapy had no benefit for LC and was possibly a disadvantageous factor. On the other hand, chemotherapy prior to SBRT showed a marginally significant lower HR for LC, though the patients

Table 2. Characteristics of pulmonary oligometastatic tumors and SBRT

Irradiated oligometastatic tumors	Total number	371
SBRT date	2004–09	143 (38.5%)
	2010–15	228 (61.4%)
Maximum tumor diameter, cm	Median, range	1.5, 0.5–5.3
Located lobe	Upper or middle lobe	143 (38.5%)
	Lower lobe	143 (38.5%)
	Missing	85 (22.9%)
Field coplanarity	Coplanar field	102 (27.4%)
	Non-coplanar field	269 (72.5%)
Beam	Static	260 (70.0%)
	Arc	111 (29.9%)
Dose prescription	Isocenter	256 (69.0%)
	D95 of PTV[a]	79 (21.2%)
	Others	36 (9.7)
Calculation algorithm	A	143 (38.5%)
	B[b,*]	225 (60.6%)
	Missing	3 (0.8%)
Energy	6 MV only	300 (80.8%)
	Others	71 (19.1%)
BED_{10} dose of IC, Gy	Median, range	115.3, 75.0–289.5
OTT[c] of SBRT, days	Median, range	7, 3–61

[a]Dose covering 95% of the planning target volume.
[b]Type B calculation algorithm included superposition, equivalent algorithm or newer generation algorithm.
[c]Overall treatment time.

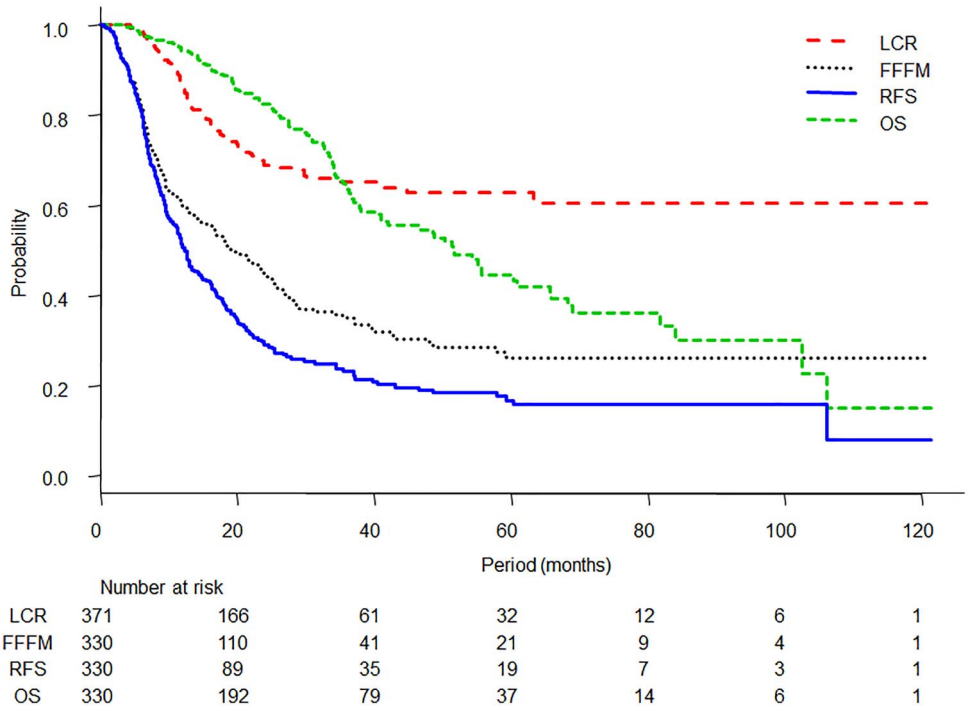

Fig. 2. Kaplan–Meier curves of LC, FFFM, RFS and OS.

who received chemotherapy prior to SBRT included 8 patients with 10 tumors who also received chemotherapy concurrent with SBRT. There were opposite results that chemotherapy prior to SBRT showed higher HR for LC and systemic therapy prior to SBRT showed higher

Table 3. Comparison of outcomes using the Kaplan–Meier estimator with log-rank tests for stratified outcomes

	LC		FFFM		RFS		OS	
Factors[a]	3-Year LC	*P*	Median time	*P*	Median time	*P*	Median time	*P*
Institute								
Academic	68.3		17.9		12.7		42.0	
Non-academic	62.6	0.22	21.3	0.61	12.0	0.81	55.6	0.21
Age, years								
<73	61.7		19.0		11.3		51.4	
≥73	66.4	0.27	19.7	0.24	14.3	0.13	55.6	0.80
Sex								
Male	64.8		21.3		12.0		55.6	
Female	65.1	0.41	17.9	0.44	12.4	0.65	48.8	0.50
ECOG Performance Status								
0	66.5		18.0		12.9		60.3	
1	60.9		23.0		12.0		40.1	
2–3	65.6	0.46	21.6	0.89	10.0	0.50	33.1	0.01
Primary origin								
Colon	64.0		23.5		14.2		55.2	
Rectum	66.5	0.75	17.8	0.12	11.7	0.06	51.7	0.75
DFI								
<17.2 months	62.3		18.2		11.7		38.0	
≥17.2 months	67.2	0.34	25.4	0.04	14.7	0.09	60.3	0.26
Oligometastatic state								
Oligo-recurrence	64.4		23.2		12.9		55.6	
Sync-oligometastases	70.9		9.4		9.4		35.9	
Unclassified oligometastases	59.5	0.47	17.9	0.08	12.6	0.29	37.6	0.40
History of local therapy for metastases								
Yes	73.3		14.3		10.6		42.0	
No	63.9	0.06	27.2	<0.01	17.5	<0.01	65.6	0.16
Chemotherapy								
Before SBRT - yes	69.8		12.7		11.3		55.6	
Before SBRT - no	59.5	0.09	25.0	<0.01	14.7	<0.01	48.8	0.36
Concurrent SBRT - yes	N/A		6.6		6.9		34.2	
Concurrent SBRT - no	65.8	0.01	21.3	0.02	12.6	0.01	54.3	0.16
After SBRT - yes	68.8		13.1		11.7		50.3	
After SBRT - no	68.5	0.92	23.2	0.08	12.7	0.41	51.5	0.66
Number of metastases								
1	60.7		25.0		12.9		55.8	
2–5	73.6	0.09	13.1	<0.01	11.3	0.15	35.8	0.07
SBRT date								
2004–09	58.8		20.4		12.6		48.6	
2010–15	69.3	0.03	19.0	0.83	12.4	0.64	60.8	0.11
Maximum tumor diameter								
<1.5 cm	69.4		23.5		16.0		55.6	
≥1.5 cm	56.1	0.07	16.3	0.03	11.3	0.02	48.6	0.01
Located lobe								
Upper or middle lobe involvement	70.3		25.0		16.5		60.8	
Lower lobe	67.9	0.75	14.2	<0.01	11.1	0.02	36.6	0.02
Field coplanarity								
Coplanar field	60.3		23.0		13.3		54.3	
Non-coplanar field	66.7	0.41	18.5	0.67	12.4	0.99	51.5	0.50

(Continued)

Table 3. Continued

	LC		FFFM		RFS		OS	
Beam								
Static	54.5		21.3		12.7		55.6	
Arc	69.2	0.02	16.9	0.36	10.1	0.29	42.0	0.76
Dose prescription								
Isocenter	57.4		18.8		12.0		48.8	
D95 of PTV	86.3		25.0		16.3		68.9	
Others	77.7	<0.01	31.3	0.96	9.2	0.28	N/A	0.62
Calculation algorithm								
Type A	54.5		18.8		11.6		51.4	
Type B	72.7	<0.01	20.4	0.41	13.1	0.17	51.7	0.60
Energy								
6 MV only	65.1		19.0		12.6		51.4	
Others	65.1	0.62	23.5	0.54	12.0	0.89	55.6	0.70
BED_{10} dose of IC								
<115 Gy	56.5		17.0		11.7		41.0	
≥115 Gy	70.3	0.06	23.4	0.12	12.7	0.06	84.0	0.01
OTT of SBRT								
<7 days	67.1		18.5		12.7		50.3	
≥7 days	69.2	0.54	19.7	0.45	12.4	0.47	51.5	0.74

[a]ECOG = Eastern Cooperative Oncology Group, N/A = not applicable, D95 of PTV = dose covering 95% of the planning target volume, IC = isocenter, OTT = overall treatment time.

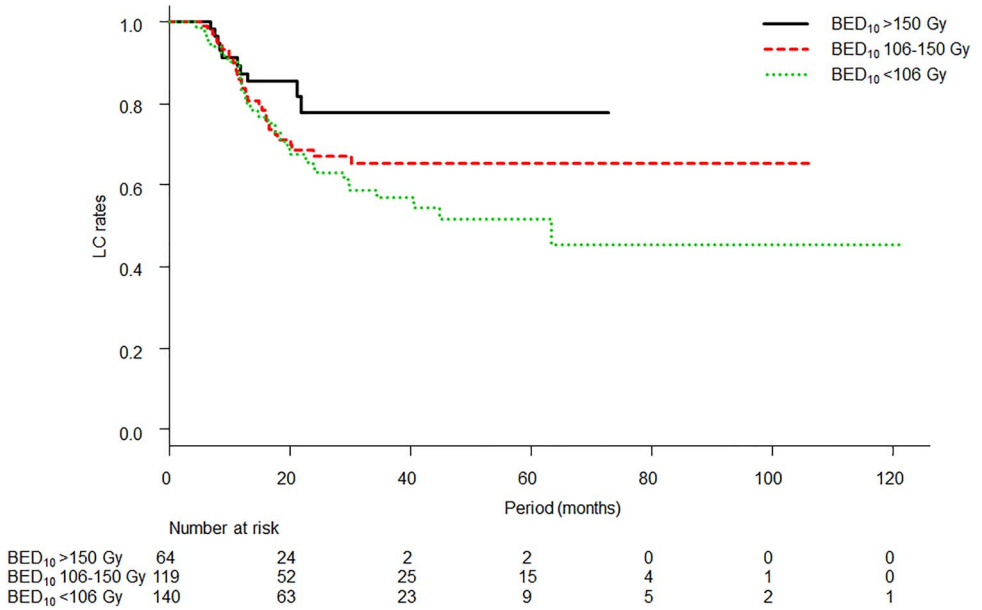

Fig. 3. Kaplan–Meier curves of LC according to group separation: classic standard SBRT dose or less group (BED_{10} < 106 Gy), higher than standard dose but less than ablative dose group (BED_{10} 106–150 Gy) and ablative dose group (BED_{10} > 150 Gy). The 3-year LC rates of each group were 57.0% (95% CI: 46.4–66.3%), 65.3% (95% CI: 54.1–74.4%) and 77.7% (95% CI: 61.0–88.0%), respectively. A log-rank test for the three curves was not significant (P = 0.13).

HR for OS [10, 11]. Another factors might affect these controversial results and one of possible factors, is time from diagnosis of metastases to SBRT, but this factor was not investigated in this study [11]. Chemotherapy after SBRT showed no significant relationship with outcomes. There was a report showing that chemotherapy after SBRT improved LC [12]. In multiple pulmonary oligometastases, adjuvant chemotherapy after metastasectomy might have a benefit for survival [13]. However, other reports showed that there was no association

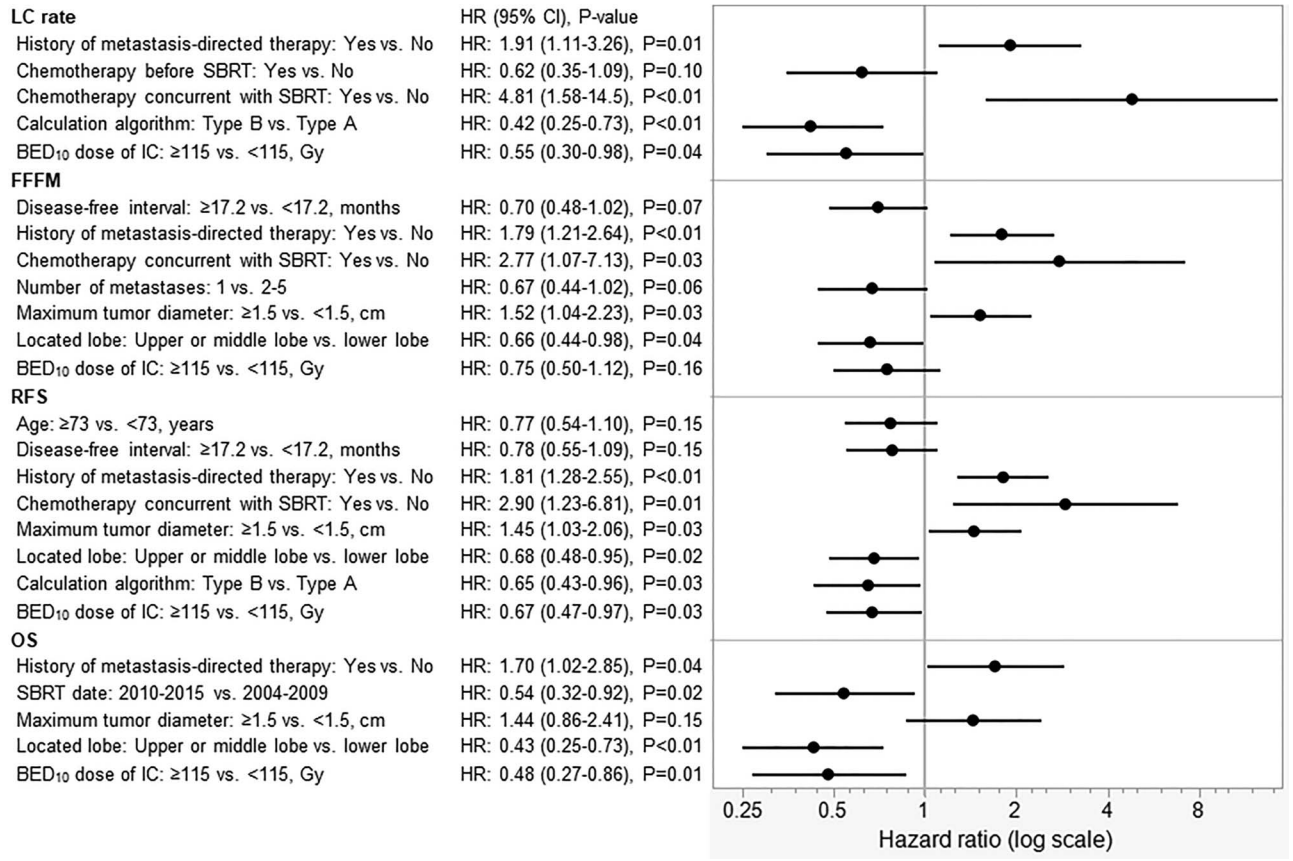

Fig. 4. Results of multivariate Cox regression analyses for LC, FFFM, RFS and OS.

between SBRT or metastasectomy and chemotherapy [14, 15]. The role of additional chemotherapy is therefore controversial.

Interestingly, the initially irradiated oligometastatic tumor located in the lung lobe showed significant associations with FFFM, RFS and OS. A tumor located in the upper or middle lung lobe was a favorable factor. It is well known that hematogenous spread of metastases is predominant in the lower lung because of the blood distribution heterogeneity in the lung [16]. In contrast, upper lung oligometastases from CRC, which are relatively rare, might tend to be true oligometastases because there is no evidence of metastases in the more sensitive lung lobe. This advantage of location in the upper lung was found even for OS, indicating the possibility of good outcomes for patients with left upper lobe oligometastases. Metastasectomy analyses performed in a previous study showed that patients who received wedge resection had shorter survival than patients who received lobectomy [17]. However, it has been shown that lobectomy of the left upper lobe was a risk factor for cerebral infarction because of thrombosis in the pulmonary vein stump, which has been reported to occur in 13.5% of patients after left upper lobectomy [18, 19]. SBRT for CRC oligometastases located in the left upper lung lobe is possible in the place of metastasectomy.

A history of local therapy for prior oligometastases, also known as metastasis-directed therapy, showed significant associations with LC, FFFM, RFS and OS, while the SBRT treatment period was significantly associated only with OS. Although prior oligometastatic sites were not investigated in this study, a history of liver metastases has been reported to be a negative prognostic factor for survival after surgery [17]. Potential micrometastases might gradually acquire resistance to radiotherapy and chemotherapy through local therapy with or without chemotherapy for tangible oligometastases. As for the SBRT treatment periods, improvement in OS over time seemed to be mainly due to developments in systemic therapy and partly due to advances in SBRT and progress in surgery.

The LC rate of this study was relatively low, as expected from previous findings [3, 4]. Higher BED_{10} tended to achieve higher LC but was not significant because of the effects of other factors such as the dose calculation algorithm (Fig. 3). In MVA, higher BED_{10} ($\geq$115 Gy at the isocenter) was significantly related not only to a higher LC rate but also better RFS and OS. Sharma *et al.* have recently reported that a BED_{10} $\geq$100 Gy contributed significant improvements to both LC and OS [10]. The current study shows that a higher cut-off value of SBRT dose (the median dose of this study) contributes the same improvements and this result dispels concerns over dose escalation because toxicity will increase as the SBRT dose increases. SBRT has mostly been performed for patients who were unfit for surgery. It is important in such cases to achieve a higher LC rate because metastasectomy as a salvage treatment after local failure would be difficult. Although there were very limited data because of the lack of questions about salvage therapy in

this survey, salvage metastasectomy was performed for at least 4 tumors out of 29 in ≥3-year survivors with local failure according to comments from collaborators. LC might be beneficial especially in long survivors. Therefore, dose escalation to achieve higher LC is justified around the range of BED_{10} in this survey (range 75.0–289.5 Gy and interquartile range 105.6–134.4 Gy at the isocenter). If a sufficient SBRT dose is delivered to the tumor, the edge dose, such as the dose covering 95% of planning target volume, might have significance. The results of survival inferiority of wedge resection (vs lobectomy) or positive surgical margins from an individual data meta-analysis for lung metastasectomy suggested that radiation dose at the edge of the target volume might be important [17]. In fact, it was indicated that marginal tumor doses are important as in the case of SBRT for early-stage non-small cell lung cancer [20].

There are some limitations in the present study. Some possible relevant factors such as carcinoembryonic antigen levels, comorbidities in the patients, time from diagnosis of metastases to SBRT and tumor-located lobe which was treated by another local therapy were not investigated in this survey. This study was a retrospective multicenter study and there were therefore missing data for very short-term follow-up and various treatment protocols at the institutions. Some confounding and bias would not have been controlled because of the retrospective nature of this study.

In conclusion, although the LC rate after SBRT is relatively low, the use of high BED_{10} (≥115 Gy) and the use of a type B or newer generation dose calculation algorithm for SBRT can improve LC. Patients who received high BED_{10} also showed prolonged RFS and OS. The role of peri-SBRT chemotherapy remains unclear, but, from the current results, chemotherapy concurrent with SBRT should be avoided. Oligometastases located in the upper or middle lung lobe showed higher FFFM, RFS and OS, therefore, they are good candidates for local therapy and possibly better candidates for SBRT than left upper lobectomy if oligometastases are located in the left upper lung lobe.

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CONFLICT OF INTEREST

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