Stereotactic Radiotherapy for Pulmonary Oligometastases From Colorectal Cancer: A Systematic Review and Meta-Analysis

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Stereotactic Radiotherapy for Pulmonary Oligometastases From Colorectal Cancer: A Systematic Review and Meta-Analysis

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Abstract

Purpose: The purpose of this study was to determine whether pulmonary oligometastases from colorectal cancer have greater radioresistance than that of pulmonary oligometastases from other cancers and whether good local control can be achieved by dose escalation in stereotactic body radiotherapy. **Materials and Methods:** This systematic review and meta-analysis were conducted according to the preferred reporting items for systematic reviews and meta-analyses statement and methods. Studies were obtained from a database search of PubMed, Web of Science, and Google Scholar for publications using search terms designed to identify studies on "oligometastases," "lung," "stereotactic radiotherapy," and "colorectal cancer." For meta-analysis 1, studies that showed the number of local failures after stereotactic body radiotherapy for pulmonary metastases from colorectal carcinoma and other cancers were included. For meta-analysis2, studies in which a comparison was made of local control rates of pulmonary metastases from colorectal carcinoma by stereotactic body radiotherapy with a higher dose and that with a lower dose were included. A meta-analysis was performed using Mantel-Haenszel statics with the fixed or random-effect model by Review Manager 5.3. **Results:** Eighteen retrospective studies with 1920 patients with pulmonary oligometastases were used in meta-analysis 1. The local control rate in patients with pulmonary oligometastases from colorectal cancer was significantly lower than that in patients with pulmonary oligometastases from other cancers (odds ratio = 3.10, $P < .00001$). Next, 8 retrospective studies with 478 patients were included in meta-analysis 2 for dose escalation. Better local control was achieved by a higher prescription dose than by a lower prescription dose (odds ratio = 0.16, $P < .00001$). **Conclusion:** Our meta-analysis indicated that local control of pulmonary oligometastases from colorectal cancer by stereotactic body radiotherapy was significantly worse than that of pulmonary metastases from other cancers; however, our results also indicated that good local control of pulmonary oligometastases from colorectal cancer can be achieved by dose escalation.

Keywords

oligometastases, colorectal cancer, stereotactic radiotherapy, lung metastases, meta-analysis

Abbreviations

CI, confidence interval; OR, odds ratio; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PTV, planning target volume; SBRT, Stereotactic body radiotherapy.

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Pulmonary oligometastases from colorectal cancer should be resected as much as possible.[1] Stereotactic body radiotherapy (SBRT) for pulmonary oligometastases has been used commonly as an alternative method to metastomy in patients who cannot receive surgery; however, some studies have shown that pulmonary oligometastases from colorectal cancer are more difficult to control by SBRT than are pulmonary

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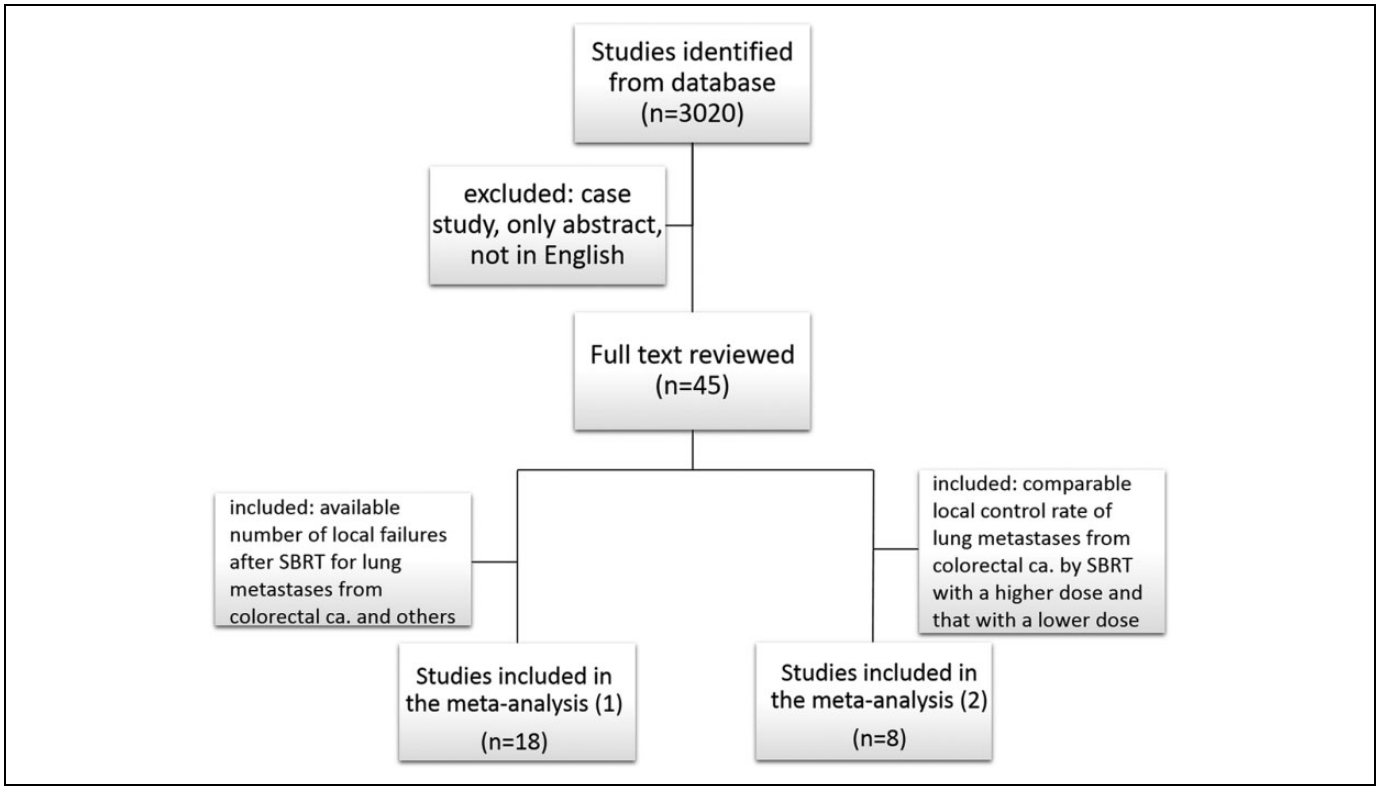

Figure 1. Flow diagram of the search process.

oligometastases from other cancers.[2-4] On the other hand, some researchers have reported that there was no significant difference in local control.[5] All of the studies were relatively small studies, and to the best of our knowledge, there has been no prospective study in which this issue was evaluated. Whether SBRT can be a practical alternative treatment to metastomy has remained controversial. We therefore evaluated local control by SBRT for pulmonary oligometastases from colorectal cancer compared to local control by SBRT for pulmonary oligometastases from other cancers using pooled analysis. There have been some studies showing that dose escalation could achieve better local control in patients who received SBRT for pulmonary oligometastases from colorectal cancer.[4,6] Unfortunately, there has also been no prospective study on this issue. Since pulmonary oligometastases from colorectal cancer might have greater radioresistance, we also evaluated the efficacy of dose escalation in SBRT for pulmonary oligometastases from colorectal cancer using meta-analyses.

Purpose

The purpose of this study was to determine whether pulmonary oligometastases from colorectal cancer have greater radioresistance than that of pulmonary oligometastases from other cancers and whether good local control can be achieved by dose escalation in SBRT.

Materials and Methods

This systematic review and meta-analysis were conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and methods. Studies were obtained from a database search of PubMed, Web of Science, and Google Scholar for publications up until December 2017 using search terms designed to identify studies on "oligometastases," "lung," "stereotactic radiotherapy," and "colorectal cancer." The exclusion criteria were as follows: (1) case report, editorial, and specialist experience; (2) only abstract; and (3) articles written in languages other than English (Figure 1). Two investigators (K.J. and H.M.) selected trials independently for 2 meta-analyses to determine whether pulmonary oligometastases from colorectal cancer have greater radioresistance than pulmonary oligometastases from other cancers (meta-analysis 1) and whether good local control can be achieved by dose escalation in SBRT (meta-analysis 2). For meta-analysis 1, studies that showed the number of local failures after SBRT for lung metastases from colorectal carcinoma and other cancers were included. For meta-analysis 2, studies in which a comparison was made of local control rates for lung metastases from colorectal carcinoma by SBRT with a higher dose and that with a lower dose were included.

The corresponding authors of the candidate studies were contacted via e-mail in the case of missing data or the requirement for additional information regarding their studies.

Table 1. Characteristics of Studies Included in the Meta-Analysis 1.

Author		No. of Patients	No. of Failures	Median Follow-up Period	Dose/Fraction	Median BED10	Local Control Rate
Aoki[7]	CRC*	15	3	31.7 months	50 Gy/5 fractions	100 GyBED	3 years: 47.6%
	non-CRC	61	1				3 years: 97.5%
Baschnagel[8]	CRC	17	4	27.6 months	60 Gy/4 fractions	132 GyBED	2 years: 80%
	non-CRC	30	0				2 years: 100%
Binkley[9]	CRC	26	9	22 months	25 Gy/1 faraction or 50 Gy/4 fractions	85 GyBED	2 years: 57.6%
	non-CRC	96	9				2 years: 90.1%
Franceschini[10]	CRC	99	19	24.2 months	48 Gy/4 fractions	105.6 GyBED	3 years: 75.7%
	non-CRC	101	8				3 years: 88.2%
Hamamoto[12]	CRC	8	6	19 months	48 Gy/4 fractions	105.6 GyBED	25%
	non-CRC	4	1				75%
Helou[4]	CRC	101	24	22 months	52 Gy/4 fractions	119.6 GyBED	2 years: 76.4%
	non-CRC	83	5				2 years: 91.7%
Inoue[13]	CRC	37	7	NA	48 Gy/4 fractions	105.6 GyBED	81%
	non-CRC	50	4				92%
Navarria[14]	CRC	29	3	18 months	48 Gy/4 fractions	105.6 GyBED	89.7%
	non-CRC	15	4				73.3%
Norihisa[21]	CRC	9	3	27 months	48 Gy/4 fractions	105.6 GyBED	66.7%
	non-CRC	25	1				96%
Oh[15]	CRC	7	1	21 months	60 Gy/5 fractions	132 GyBED	85.7%
	non-CRC	60	2				96.7%
Okunieff[16]	CRC	14	3	14.9 months	50 Gy/ 10 fractions	75 GyBED	78.6%
	non-CRC	35	5				85.7%
Osti[5]	CRC	23	1	15 months	30 Gy/1 fraction	120 GyBED	95.7%
	non-CRC	53	9				83.0%
Rieber[11]	CRC	153	20	14.3 months	NA	84.4 GyBED	86.9%
	non-CRC	545	53				90.3%
Singh[17]	CRC	13	5	16.7 months	50 Gy/5 fractions	100 GyBED	61.50%
	non-CRC	21	0				100%
Sulaiman[18]	CRC	11	5	17 months	NA	110 GyBED	54.50%
	non-CRC	36	5				86.10%
Takahashi[19]	CRC	7	2	20 months	48 Gy/4 fractions	105.6 GyBED	2 years: 67%
	non-CRC	35	4				2 years: 89%
Takeda[3]	CRC	21	8	29 months	50 Gy/5 fractions	100 GyBED	2 years: 73%
	non-CRC	23	0	15 months			2 years: 94%
Yamamoto[2]	CRC	29	12	35 months	48 Gy/4 fractions	105.6 GyBED	2 years: 25.5%
	non-CRC	28	6				2 years: 70.0%

Abbreviations: BED, biological effective dose; CRC, colorectal cancer; NA, not available.

A meta-analysis was performed using Mantel-Haenszel statics with the fixed or random-effect model by Review Manager 5.3 (Cochrane Collaboration, London, United Kingdom). Dichotomous data were calculated by the odds ratio (OR) with 95% confidence intervals (CIs).

The Q test was used to calculate the inconsistency index I^2 value. Due to the low sensitivity of the Cochrane Q test, the significance level $\alpha = 0.1$ was used for conservation, with $P > .1$ indicating no statistical heterogeneity between studies and $P < .1$ indicating heterogeneity. Inconsistency index I^2 was used to quantitatively evaluate heterogeneity. When I^2 was <25%, the fixed effect model was used for meta-analysis. When I^2 was more than 25% and less than 50%, the random effect model was used. When $I^2$was more than 50%, the source of the heterogeneity was analyzed first, and if there was no obvious clinical heterogeneity and the source of heterogeneity could not be found, the random effect model was used. A $P < .05$ was considered significant for all analyses.

Results

Figure 1 shows the results of the search strategy and all of the studies that were included and excluded. Data from 18 retrospective studies with 1920 patients were used in the meta-analysis. The patients included 619 patients with pulmonary oligometastases from colorectal cancer treated by SBRT and 1301 patients with pulmonary oligometastases from other cancers treated by SBRT (meta-analysis 1;[2-5,7-20] Table 1). The local control rate in patients with pulmonary oligometastases from colorectal cancer was significantly lower than that in patients with pulmonary oligometastases from other cancers (OR = 3.17, 95% CI: 1.98-5.08, $P < .00001$) with

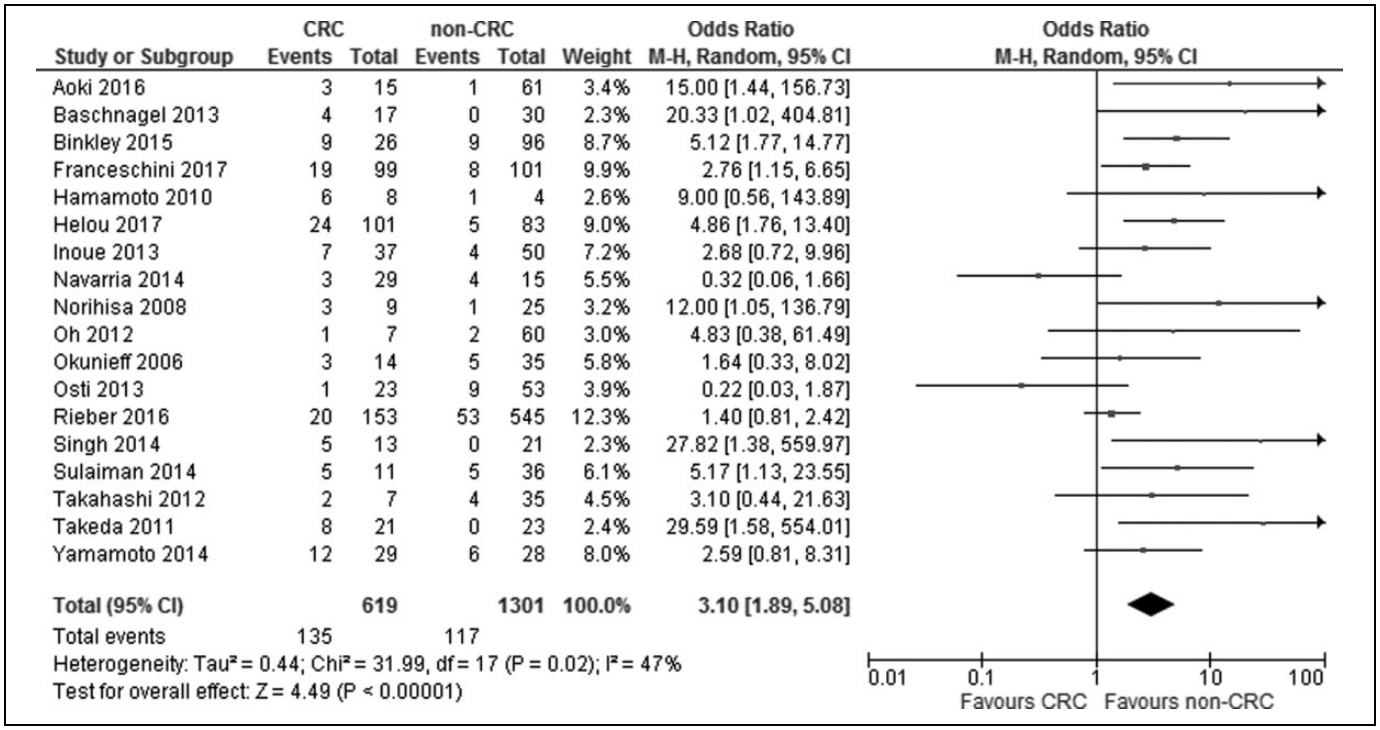

Figure 2. Forest plot showing the association between local control rate and subgroup (colorectal cancer vs others).

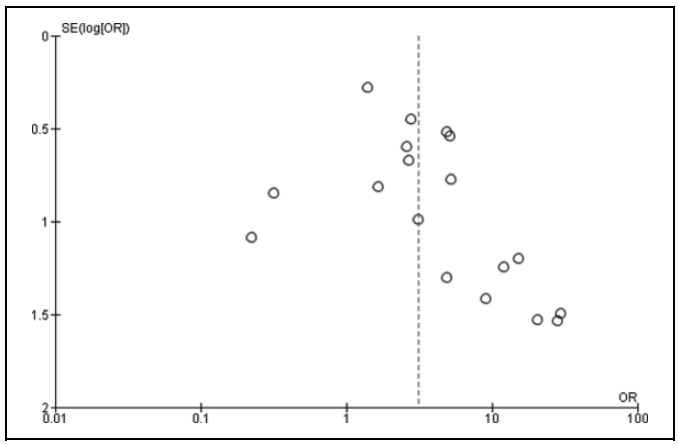

Figure 3. Funnel plots for publication bias for local control in patients with pulmonary metastases from colorectal cancer compared with that in patients with pulmonary metastases from other cancers.

substantial heterogeneity ($P = .02$, $I^2 = 47\%$; Figure 2). Funnel plots showed that there was no significant publication bias (Figure 3).

Among the studies on SBRT for pulmonary metastases from colorectal cancer, 8 retrospective studies with 478 patients were included in the meta-analysis for dose escalation: 222 patients who were treated with a higher dose and 256 patients who were treated with a lower dose (meta-analysis [2])[4,6,9,20-24] (Table 2). Better local control was achieved by a higher prescription dose than by a lower prescription dose (OR = 0.16, 95% CI: 0.09-0.28, $P < .00001$) with no statistical heterogeneity ($P = .36$, $I^2 = 9\%$; Figure 4). Funnel plots showed that there was no significant publication bias (Figure 5).

Discussion

First, our results showed that it was more difficult to control pulmonary oligometastases from colorectal cancer by SBRT than pulmonary oligometastases from other cancers.

Some investigators have reported that metastases from colorectal cancer have radioresistance. Laarhoven *et al* showed that metastases of colorectal cancer contain large amounts of hypoxic cells compared to those in metastases of other cancers and are therefore radioresistant[25]; however, this must be only one of the reasons for local control by SBRT for metastases from colorectal cancer being poor. In our previous study, we showed that pulmonary oligometastases from colon cancer was more difficult to control by SBRT than those from rectal cancer.[6] This may be due to molecular differences (eg, KRAS and BRAF status and microsatellite instability); however, the exact reasons are also unknown.

Next, the present meta-analysis indicated that dose escalation was important for local control of pulmonary oligometastases from colorectal cancer as well as hepatic oligometastases[26]; however, the appropriate total dose and appropriate dose per fraction in SBRT for pulmonary oligometastases from colorectal cancer have still not been determined. In past studies, there were notable differences in prescription methods (eg, for the isocenter and for the periphery of the planning target volume [PTV]) as well as in total dose and dose per fraction. In some studies, 2- to 3-year local

Table 2. Characteristics of Studies Included in the Meta-Analysis 2.

Author	Median Follow-up Period	Higher Dose Group				Lower Dose Group			
		Median BED10	No. of Patients	No. of Failures	Local Control Rate	Median BED10	No. of Patients	No. of Failures	Local Control Rate
Jingu[6]	28 months	132 GyBED	24	1	3 years: 95.5%	105.6 GyBED	51	28	3 years: 59.6%
Norihisa[20]	27 months	132 GyBED	6	0	3 years: 100%	105.6 GyBED	3	2	NA
Bae[21]	28 months	180 GyBED	29	5	3 years: 69%	124.8 GyBED	12	9	3 years: 49%
Helou[4]	22 months	150 GyBED	45	3	2 years: 90%	119.6 GyBED	56	21	2 years: 70%
Kinj[22]	33 months	180 GyBED	75	14	2 years: 82.1%	87.5 GyBED	12	5	2 years: 57.1%
Comito[23]	24 months	180 GyBED	6	0	3 years: 100%	105.6 GyBED	54	13	3 years: 70%
Jung[24]	42.8 months	150 GyBED	23	3	3 years: 84%	105.6 GyBED	56	16	3 years: 64.6%
Binkley[9]	22 months	112.5 GyBED	14	4	2 years: 62.5%	87.5 GyBED	12	6	2 years: 16.7%

Abbreviations: BED, biological effective dose; NA, not available.

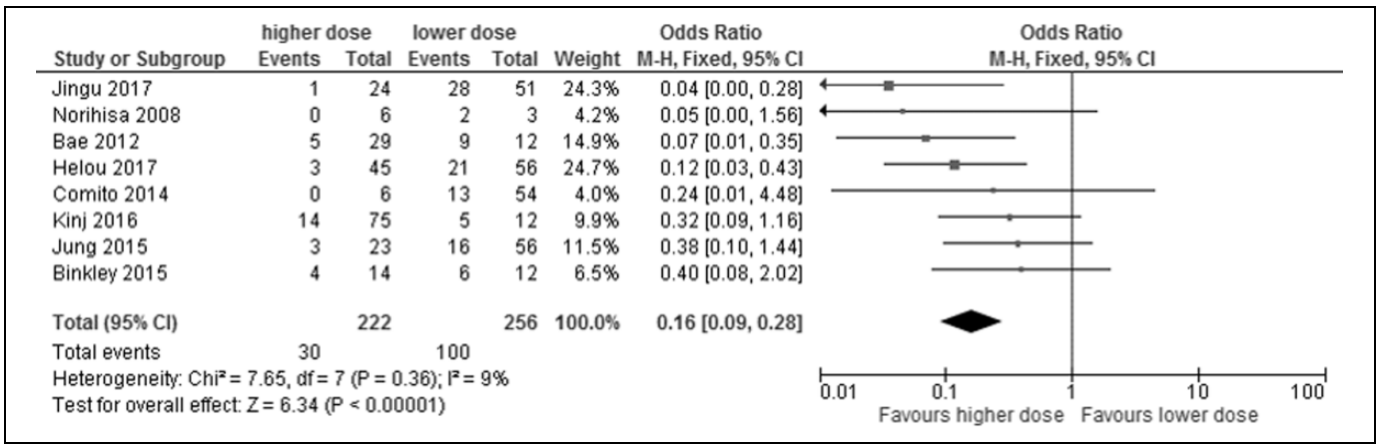

Figure 4. Forest plot showing the association between local control rate and subgroup (higher dose vs lower dose) in patients with pulmonary oligometastases from colorectal cancer.

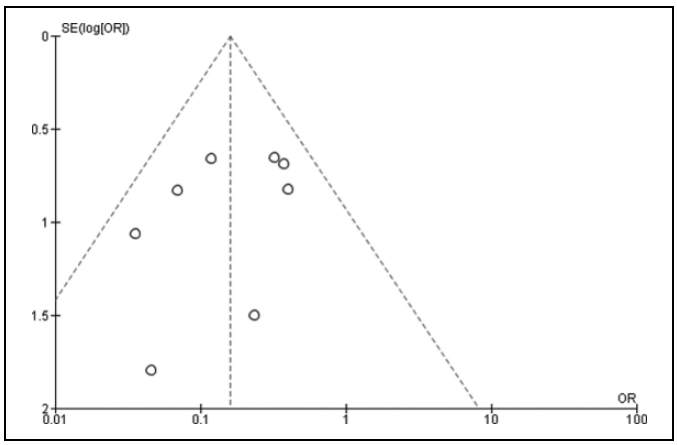

Figure 5. Funnel plots for publication bias for local control with higher dose in patients with pulmonary metastases from colorectal cancer compared to that of lower dose in patients with pulmonary metastases from other cancers.

control rates by 100 to 105.6 $GyBED_{10}$, calculated using the linear-quadratic (LQ) model with $\alpha/\beta = 10$ Gy, with prescription for the isocenter were 24% to 75.7%,[2,4,7,10,19,24,27] while in other studies, 2- to 3-year local control rates by 95.8 to 150 $GyBED_{10}$ with prescription for the periphery of the PTV were 52.7% to 100%,[3,8-10,15,21,22,24,27-31,32] although there were many variations in prescription methods for the periphery of the PTV. Klement reported that the α–β ratio of pulmonary metastases from noncolorectal cancer was 21.6 and that the α–β ratio of pulmonary metastases from colorectal cancer was 43.1.[33] If the α–β ratio of pulmonary metastases from colorectal cancer is very high as Klement reported, both the total dose and dose per fraction are important. He recommended more than 3 × 17 Gy to be given over a course of 5 days to the isocenter in order to control 90% of metastases from colorectal cancer after 1 year. It is difficult to determine the appropriate prescription dose because there are many differences among studies; however, the present meta-analysis suggested that better local control would be achieved by a higher dose. We recommend a prescription dose of >100 Gy of BED_{10} to the periphery of the PTV in SBRT for pulmonary oligometastases from colorectal cancer. In some past studies, oligometastases including those in the liver, lung, and lymph nodes were analyzed collectively. However, Ahmed *et al* showed that control of liver metastases was more difficult than that of lung

metastases.[34] Furthermore, Ahmed *et al* and Fode *et al* revealed that pulmonary metastases could be controlled more easily than metastases in other sites.[28,35] Thus, investigation that includes oligometastases in several organs is not appropriate. In the present study, we therefore used data only for patients with pulmonary oligometastases.

A retrospective study by the Japanese Radiation Oncology Study Group showed, by multivariate analysis, that adjuvant chemotherapy after SBRT was a favorable prognostic factor for local control in patients with pulmonary oligometastases from colorectal cancer.[6] Thibault *et al* also showed by multivariate analysis that previous chemotherapy improved local control of lung metastases treated by SBRT.[36] Systemic therapy with SBRT might improve not only overall survival but also local control; however, the safety and efficacy of systemic therapy with SBRT have still not been established. Prospective studies on SBRT concurrent with systemic therapy including molecular targeted drug therapy for oligometastases are needed.

There was a major limitation in the present study. Most of the data used for analyses were from retrospective studies except for a few phase II studies, which were relatively small-scale studies, because there were no randomized trials to evaluate our queries. However, to the best of our knowledge, this is the first pooled analysis in patients treated by SBRT for pulmonary oligometastases from colorectal cancer. Prospective large randomized trials are needed.

Conclusion

Our meta-analysis indicated that local control of pulmonary oligometastases from colorectal cancer by SBRT was significantly worse than that of pulmonary metastases from other cancers; however, the results of the present study also indicated that good local control of pulmonary oligometastases from colorectal cancer can be achieved by dose escalation.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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