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-analysis 2, 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 metastases.

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oligometastases from other cancers. On the other hand, some researchers have reported that there was no significant difference in local control. 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. 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 others 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.
A meta-analysis was performed using Mantel-Haenszel statistics 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 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...
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
control rates by 100 to 105.6 GyBED10, calculated using the linear-quadratic (LQ) model with $\alpha/\beta = 10$ Gy, 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 GyBED10 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 $\alpha/\beta$ ratio of pulmonary metastases from noncolorectal cancer was 21.6 and that the $\alpha/\beta$ ratio of pulmonary metastases from colorectal cancer was 43.1.33 If the $\alpha/\beta$ 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 $\times$ 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 BED10 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

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

| Author       | Median Follow-up Period | Higher Dose Group | No. of Patients | No. of Failures | Local Control Rate | Median BED10 | No. of Patients | No. of Failures | Local Control Rate |
|--------------|-------------------------|-------------------|----------------|----------------|--------------------|--------------|----------------|----------------|--------------------|
| Jingu        | 28 months               | 132 GyBED         | 24             | 1              | 3 years: 95.5%     | 105.6 GyBED  | 51             | 28             | 3 years: 59.6%     |
| Norihisa     | 27 months               | 132 GyBED         | 6              | 0              | 3 years: 100%      | 105.6 GyBED  | 3              | 2              | NA                 |
| Bae          | 28 months               | 180 GyBED         | 29             | 5              | 3 years: 69%       | 124.8 GyBED  | 12             | 9              | 3 years: 49%       |
| Helou        | 22 months               | 150 GyBED         | 45             | 3              | 2 years: 90%       | 119.6 GyBED  | 56             | 21             | 2 years: 70%       |
| Kinj         | 33 months               | 180 GyBED         | 75             | 14             | 2 years: 82.1%     | 87.5 GyBED   | 12             | 5              | 2 years: 57.1%     |
| Comito       | 24 months               | 180 GyBED         | 6              | 0              | 3 years: 100%      | 105.6 GyBED  | 54             | 13             | 3 years: 70%       |
| Jung         | 42.8 months             | 150 GyBED         | 23             | 3              | 3 years: 84%       | 105.6 GyBED  | 56             | 16             | 3 years: 64.6%     |
| Binkley      | 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.
metastases. Furthermore, Ahmed et al and Fode et al revealed that pulmonary metastases could be controlled more easily than metastases in other sites. 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. Thibault et al also showed by multivariate analysis that previous chemotherapy improved local control of lung metastases treated by SBRT. 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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