Original Article

A systematic review and meta-analysis of stereotactic body radiation therapy for colorectal pulmonary metastases

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Background: There is growing evidence to support the hypothesis that radical treatment of pulmonary oligometastatic disease with stereotactic body radiation therapy (SBRT) can improve oncological outcomes. However, some reports suggest colorectal cancer (CRC) pulmonary metastases are associated with radioresistance. The present systematic review aimed to assess the local control (LC), overall survival (OS), and progression-free survival (PFS) of patients with CRC pulmonary metastases treated by SBRT. Secondary outcomes included assessment of peri-procedural complications and identification of prognostic factors on LC.

Methods: Electronic databases were systematically searched from their dates of inception using predefined criteria. Summative statistical analysis was performed for patients with CRC pulmonary metastases, and comparative meta-analysis was performed for patients with CRC versus non-CRC pulmonary metastases.

Results: Using predefined criteria, 18 relevant studies were identified from the existing literature. LC for CRC pulmonary metastases treated by SBRT at 1-, 2-, and 3-year were estimated to be 81%, 66%, and 60%, respectively. OS and PFS at 3-year were 52% and 13%, respectively. Patients with CRC pulmonary metastases were associated with significantly lower LC compared to non-CRC pulmonary metastases [HR, 2.93; 95% confidence interval (CI), 1.93–4.45; P<0.00001], but higher OS (HR, 0.61; 95% CI, 0.45–0.82; P=0.001). There were no reported periprocedural mortalities and low incidences of periprocedural morbidities.

Conclusions: These findings may have implications for patient and treatment selection, dose fractionation, and support the hypothesis that CRC pulmonary metastases may require higher biological effective doses while respecting normal tissue constraints when treated with SBRT.

Keywords: Stereotactic body radiation therapy (SBRT); colorectal cancer (CRC); pulmonary metastasis; systematic review; meta-analysis

Submitted May 29, 2019. Accepted for publication Nov 15, 2019.
doi: 10.21037/jtd.2019.12.12
View this article at: http://dx.doi.org/10.21037/jtd.2019.12.12

Introduction

Stereotactic body radiation therapy (SBRT) has emerged as a safe and efficacious treatment modality for selected patients with pulmonary metastases (1,2). Encouraging results from phase I and II trials have been followed by large multi-institutional databases to refine the patient selection process (3,4). The increased utilisation of SBRT for patients with pulmonary metastases was reflected in a recent European survey involving 30 centres from six countries, in which 90% of the responding radiation oncology centres were treating pulmonary metastases with SBRT (5). There is now growing evidence to support the hypothesis that radical treatment of oligometastatic disease with SBRT can improve oncological outcomes (6-8).

Approximately 10–15% of all patients with colorectal cancer (CRC) develop pulmonary metastases, and CRC represents the second most common origin of all secondary pulmonary tumours (2,4,9,10). Previous reports have demonstrated that the high doses per fraction delivered by SBRT have the ability to overcome differences in intrinsic radiosensitivity of different histologies in spinal metastases (11,12). However, other reports suggest that SBRT for pulmonary metastases from colorectal origin may not achieve as high local control (LC) rates as pulmonary metastases of other primary histologies (13,14). More recently, gene expression analyses have suggested an intrinsic radioresistance of colorectal pulmonary metastases, indicating that adjusted doses of SBRT may be necessary to achieve LC (15,16). These findings are somewhat surprising, as CRCs in their primary location are considered fairly radiosensitive and responsive to fractionated radiotherapy.

The primary objectives of the present systematic review were to assess the LC, overall survival (OS), and progression-free survival (PFS) outcomes of patients with CRC pulmonary metastases treated by SBRT. Meta-analysis was performed to compare these endpoints between patients with CRC pulmonary metastases and patients with non-CRC pulmonary metastases. Secondary outcomes included assessment of peri-procedural complications and identification of prognostic factors on local disease control.

Methods

Literature search strategy

The systematic review was performed using electronic databases EMBASE and Ovid Medline, from their dates of inception to November 2018. To ensure adequate sensitivity of the search, we combined the terms (pulm* or lung) and (metasta* or oligometasta*) and (sbrt or sabr or stereotactic body radiotherapy or stereotactic radiotherapy or radiosurgery) as either Medical Subject Headings or keywords. All identified articles were then assessed by applying the predefined selection criteria.

Selection criteria and data appraisal

Eligible studies for inclusion in the systematic review were those in which LC, PFS, or OS outcomes were presented for patients with colorectal pulmonary metastatic disease treated by SBRT. When institutions published duplicated studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete or updated reports were included for statistical analysis. Case reports, conference abstracts or presentations, editorials, and publications not written in English were excluded. Studies with less than 10 patients were also excluded. Data were extracted from texts, tables, figures, and supplementary material. The definitions of LC, PFS, and OS were noted for each paper. Prognostic factors were selected based on categorization of the various prognosticators in each report. To assess the methodological quality of the selected studies, the Downs and Black scale was used to evaluate the quality index and categorized each report as good, fair or poor (17). Two investigators (D Wang and C Cao) independently reviewed each retrieved article. Discrepancies between the two reviewers were resolved by discussion and consensus.

Statistical analysis

Summative analysis was performed to examine two patient cohorts: (I) patients with colorectal pulmonary metastases identified from selected studies were analysed for LC, PFS, and OS; (II) when studies presented comparative outcomes for LC, PFS or OS for patients with colorectal pulmonary metastatic disease versus non-colorectal pulmonary metastases, these data were extracted and meta-analysed.

Meta-analysis was performed by combining the reported outcomes of selected studies using a random effect model. Hazard ratio (HR) and standard error were extracted or calculated from each study using the Tierney and Parmar methods described previously (18,19). When calculations were not possible because of inadequate data, HRs were estimated using Kaplan-Meier graphs. I^2 statistic was used to estimate the percentage of total variation across studies

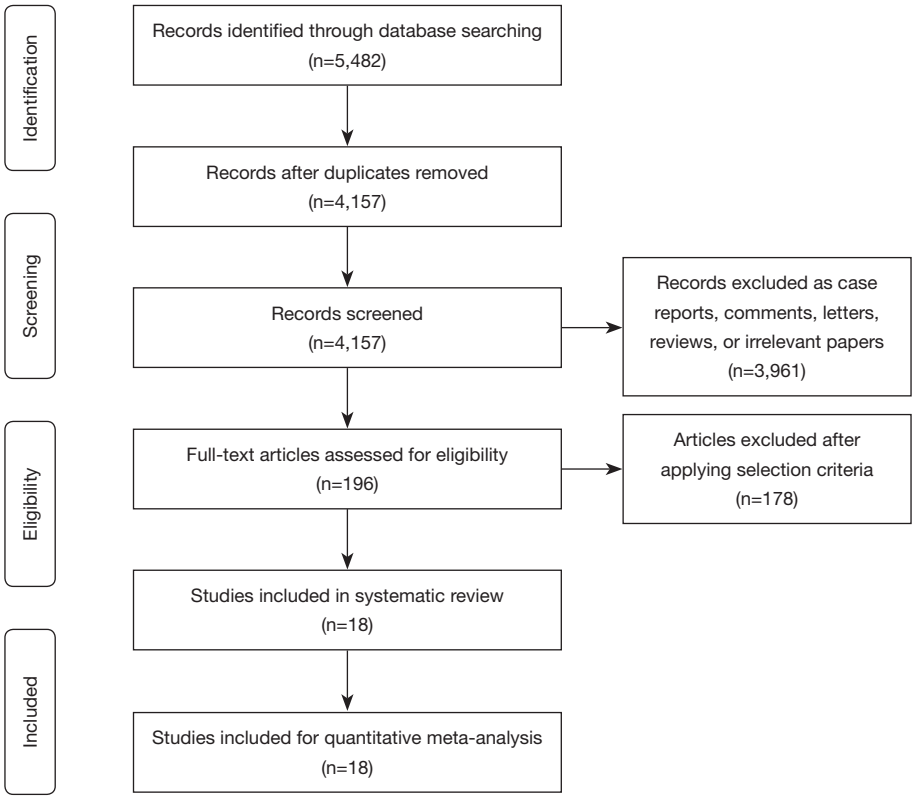

Figure 1 PRISMA flow chart summarizing the literature search strategy in the systematic review on stereotactic body radiation therapy for patients with colorectal and non-colorectal pulmonary metastases.

attributable to heterogeneity rather than chance. Meta-analysis was performed using Review Manager (version 5.1.2, Cochrane Collaboration, Oxford, United Kingdom). All P values were two-sided, and P≤0.05 was considered to indicate statistical significance.

Individual patient survival data were reconstructed using Guyot's iterative algorithm to solve the Kaplan-Meier equations originally used to produce the published graphs (20). This algorithm used digitalized Kaplan-Meier curve data to find numerical solutions to the Kaplan-Meier equations, assuming a constant censoring mechanism. The reconstructed patient data were then aggregated to form the combined Kaplan-Meier curve. Reconstructed analyses were conducted using R (version 3.2.5, R Core Team, Vienna, Austria).

Results

Quantity and quality of trials

Applying the predefined selection criteria, a total of 5,482 records were found through the electronic search. After identification of additional records through other sources and removal of duplicate studies, 4,157 articles remained for screening. Of these, 3,961 were excluded on the basis of title or abstract content. After review of the full text of the remaining 196 articles, 18 were found to meet the selection criteria for the systematic review (13,21-37). All of the selected studies were non-randomized observational studies, with 9 studies presenting comparative clinical data on patients with colorectal pulmonary metastatic disease with non-colorectal pulmonary metastatic disease (13,21,25,27-29,31,34,37). Quality assessment using the Downs and Black scale reported scores that indicated good (13,21,23,24,26-28,35) or fair quality (22,25,29-34,36,37). A summary of the study selection process is presented in the PRISMA chart in *Figure 1*. Patients were treated according to institutional regimens, with different doses, motion management, and beam management, as detailed in *Table 1*. *Table S1* displays SBRT regimens, including Gy and fractions, by study.

Table 1 Summary of baseline characteristics of patients who underwent stereotactic body radiation therapy for pulmonary metastases

Country	Authors	N patients		N tumors		Median age		Female (%)		Median tumor size (cm)		Median GTV (cc)		Follow-up (months)	
		CRC	NC	CRC	NC	CRC	NC	CRC	NC	CRC	NC	CRC	NC	CRC	NC
Italy															
2017	Francheschini	99	101	NR	NR	69		39		NR	NR	NR	NR	24.2[M]	
2017	Pasqualetti	33	NA	56	NA	67	NA	24	NA	NR	NA	2.3	NA	22.8	NA
2017	Agolli	44	NA	69	NA	70[M]	NA	27	NA	1.4	NA	NR	NA	36	NA
2015	Filippi	40	NA	59	NA	70	NA	50	NA	1.5	NA	NR	NA	20	NA
2013	Osti	23	43	103		68		52		NR	NR	NR	NR	15	
Japan															
2017	Jingu	93	NA	104	NA	69	NA	36	NA	1.5	NA	NR	NR	28	NA
2015	Niibe	5	29	NR	NR	69.5		35		1.6		NR	NR	20	
2014	Yamamoto	37		29	28	63		35		NR	NR	NR	NR	35	
2011	Takeda	15	19	21	23	61	69	13	35.7	1.8	1.9	NR	NR	29	15
USA															
2018	Qiu	42	NA	NR	NA	NR	NA	NS	NA	NR	NA	NR	NA	6.4	NA
2015	Binkley	77		26	96	60		48		NR	NR	3.7		22	
2017	Ricco	115	332	NR	NR	69		49		NR	NR	10.58		13	
Korea															
2015	Jung	50	NA	79	NA	65	NA	NR	NA	NR	NA	1.5	NA	42.8	NA
2009	Kim	13	NA	18	NA	54	NA	54	NA	2.1	NA	5.9	NA	28	NA
Canada															
2014	Thibault	NR	NR	45	38	NR	NR	NR	NR	NR	NR	NR	NR	20.8	
France															
2017	Kinj	53	NA	87	NA	69	NA	66	NA	1.6	NA	3.2	NA	33	NA
Netherlands															
2018	Sharma	118	88	NR	NR	68		41		NR	NR	NR	NR	26	
Spain															
2015	Carvajal	13	NA	13	NA	66.5	NA	31	NA	1	NA	NR	NA	9.2	NA
Q1		23	35	26	28	65	67	33	36	1.5	1.7	2.5	5.4	20	15
Q3		77	91	79	96	69	69	50	48	1.7	1.8	5.4	8.9	29	24

CRC, colorectal; NC, non-colorectal; NA, not applicable; NR, not reported; NS, not specified; GTV, gross tumor volume; [M], mean.

Patient characteristics

A summary of baseline patient characteristics is presented in *Table 2*. The median age was 68 years for CRC patients and 68.5 for non-CRC patients. The median percentage of females was 39% for CRC patients and 40% for non-CRC patients. Median length of follow-up was 23.5 months for CRC patients, and 20.8 months for non-CRC patients.

LC

LC was generally defined as the absence of growth within

Table 2 Summary of baseline characteristics of patients who underwent stereotactic body radiation therapy for pulmonary metastases

Country	Authors	N patients		N tumors		Median age		Female (%)		Median tumor size (cm)		Median GTV (cc)		Follow-up (months)	
		CRC	NC	CRC	NC	CRC	NC	CRC	NC	CRC	NC	CRC	NC	CRC	NC
Italy															
2017	Francheschini	99	101	NR	NR	69		39		NR	NR	NR	NR	24.2[M]	
2017	Pasqualetti	33	NA	56	NA	67	NA	24	NA	NR	NA	2.3	NA	22.8	NA
2017	Agolli	44	NA	69	NA	70[M]	NA	27	NA	1.4	NA	NR	NA	36	NA
2015	Filippi	40	NA	59	NA	70	NA	50	NA	1.5	NA	NR	NA	20	NA
2013	Osti	23	43	103		68		52		NR	NR	NR	NR	15	
Japan															
2017	Jingu	93	NA	104	NA	69	NA	36	NA	1.5	NA	NR	NR	28	NA
2015	Niibe	5	29	NR	NR	69.5		35		1.6		NR	NR	20	
2014	Yamamoto	37		29	28	63		35		NR	NR	NR	NR	35	
2011	Takeda	15	19	21	23	61	69	13	35.7	1.8	1.9	NR	NR	29	15
USA															
2018	Qiu	42	NA	NR	NA	NR	NA	NS	NA	NR	NA	NR	NA	6.4	NA
2015	Binkley	77		26	96	60		48		NR	NR	3.7		22	
2017	Ricco	115	332	NR	NR	69		49		NR	NR	10.58		13	
Korea															
2015	Jung	50	NA	79	NA	65	NA	NR	NA	NR	NA	1.5	NA	42.8	NA
2009	Kim	13	NA	18	NA	54	NA	54	NA	2.1	NA	5.9	NA	28	NA
Canada															
2014	Thibault	NR	NR	45	38	NR	NR	NR	NR	NR	NR	NR	NR	20.8	
France															
2017	Kinj	53	NA	87	NA	69	NA	66	NA	1.6	NA	3.2	NA	33	NA
Netherlands															
2018	Sharma	118	88	NR	NR	68		41		NR	NR	NR	NR	26	
Spain															
2015	Carvajal	13	NA	13	NA	66.5	NA	31	NA	1	NA	NR	NA	9.2	NA
Q1		23	35	26	28	65	67	33	36	1.5	1.7	2.5	5.4	20	15
Q3		77	91	79	96	69	69	50	48	1.7	1.8	5.4	8.9	29	24

CRC, colorectal; NC, non-colorectal; NA, not applicable; NR, not reported; NS, not specified; GTV, gross tumor volume; [M], mean.

the irradiated site. Overall, 15 studies with 686 colorectal pulmonary metastases were identified and analysed in the present systematic review for LC. A cumulative Kaplan-Meier graph is presented in *Figure 2A*, demonstrating an estimated 1-, 2-, and 3-year LC rate of 81%, 66%, and 60%, respectively. Five studies provided comparative LC data for colorectal pulmonary metastases versus non-colorectal pulmonary metastases, with a forest plot demonstrating statistically significantly lower LC for colorectal pulmonary metastases [HR, 2.93; 95% confidence

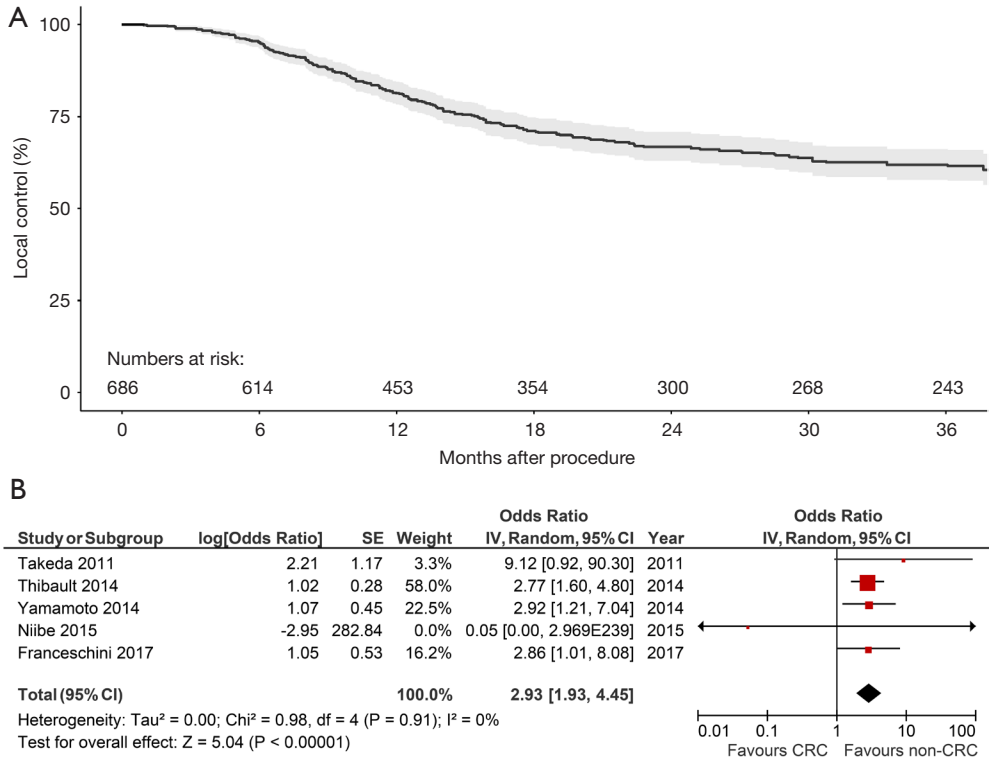

Figure 2 Local control. (A) Cumulative Kaplan-Meier graph demonstrating estimated local control of colorectal pulmonary metastases after stereotactic body radiation therapy. Shaded region indicates 95% confidence interval (CI). (B) Forest plot of the odds ratio (OR) of local control in patients with colorectal pulmonary metastases versus non-colorectal pulmonary metastases after stereotactic body radiation therapy. The estimate of the OR of each study corresponds to the middle of the squares and the horizontal line shows the 95% CI. On each line, the numbers of events as a fraction of the total number randomized are shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics.

interval (CI), 1.93–4.45; P<0.00001, I^2=0%, *Figure 2B*]. A summative reconstructed Kaplan-Meier graph comparing these two cohorts is shown in *Figure 3A*.

OS

Eleven studies with 567 colorectal pulmonary metastases were analysed in the present systematic review for OS. The cumulative Kaplan-Meier graph is presented in *Figure 3B*, demonstrating an estimated 3-year OS rate of 52%. All of the selected studies only included patients with oligometastatic disease, which was defined as five or fewer metastases in the specified studies. Three studies provided comparative OS data for colorectal pulmonary metastases versus non-colorectal pulmonary metastases, with a forest plot demonstrating statistically significantly increased OS for colorectal pulmonary metastases (HR, 0.61; 95% CI, 0.45–0.82; P=0.001, I^2=0%, *Figure 3B*). A summative reconstructed Kaplan-Meier graph comparing these two cohorts is shown in *Figure 4A,B*.

PFS

PFS was generally defined as the lack of progression or relapse at any site after the commencement of SBRT. Six studies with 265 colorectal pulmonary metastases were analysed in the present systematic review for PFS. The cumulative Kaplan-Meier graph is presented in *Figure 5*, demonstrating an estimated 3-year PFS rate of 13%. There were an insufficient number of studies that compared colorectal pulmonary metastases versus non-colorectal pulmonary metastases for statistical analysis.

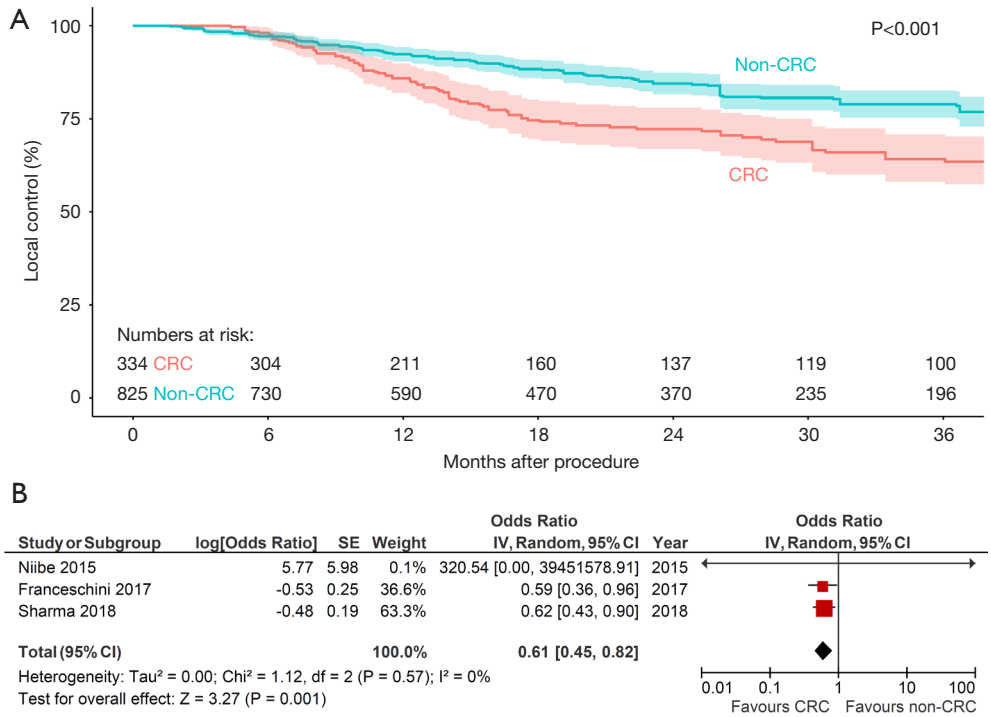

Figure 3 Local control. (A) Cumulative Kaplan-Meier graph demonstrating local control of colorectal pulmonary metastases versus non-colorectal pulmonary metastases after stereotactic body radiation therapy. Shaded regions represent 95% confidence interval (CI). (B) Forest plot of the odds ratio (OR) of local control in patients with colorectal pulmonary metastases versus non-colorectal pulmonary metastases after stereotactic body radiation therapy. The estimate of the OR of each study corresponds to the middle of the squares and the horizontal line shows the 95% CI. On each line, the numbers of events as a fraction of the total number randomized are shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics.

Mortality and morbidity

There was no periprocedural mortality reported in any of the 18 studies identified in the present systematic review. Periprocedural morbidities included pneumonitis, esophagitis, dyspnoea, erythema, fatigue, and chest pain. The most common and serious complications included pneumonitis and dyspnoea, although their incidences were very low, as presented in *Table 3*.

Prognostic factors

A number of patient-, tumor- and treatment-related factors were identified from individual studies to have significant impact on local disease control. These included gender, age, histopathology, number and size of lesions, standardized uptake value (SUV) max, biologically effective dose (BED) of SBRT, and completeness of response. A summary of these prognostic factors is presented in *Table S2*.

Discussion

With increased clinical experience, pulmonary metastases are increasingly being treated by SBRT with minimal peri-procedural toxicity. Previous studies have suggested differing oncological efficacies of SBRT based on the histology of the primary cancer (13,28). More recently, multigene expression models have been developed to estimate the radiosensitivity index (RSI) of different tumor types (15,38). Some have proposed the utilization of genomically-adjusted radiation dosing to personalize radiation therapy for patients with oligometastatic pulmonary metastases (39). Patients with radioresistant subtypes of lesions have been postulated to benefit from escalated BEDs, although these findings have largely been based on models using surgically resected specimens rather

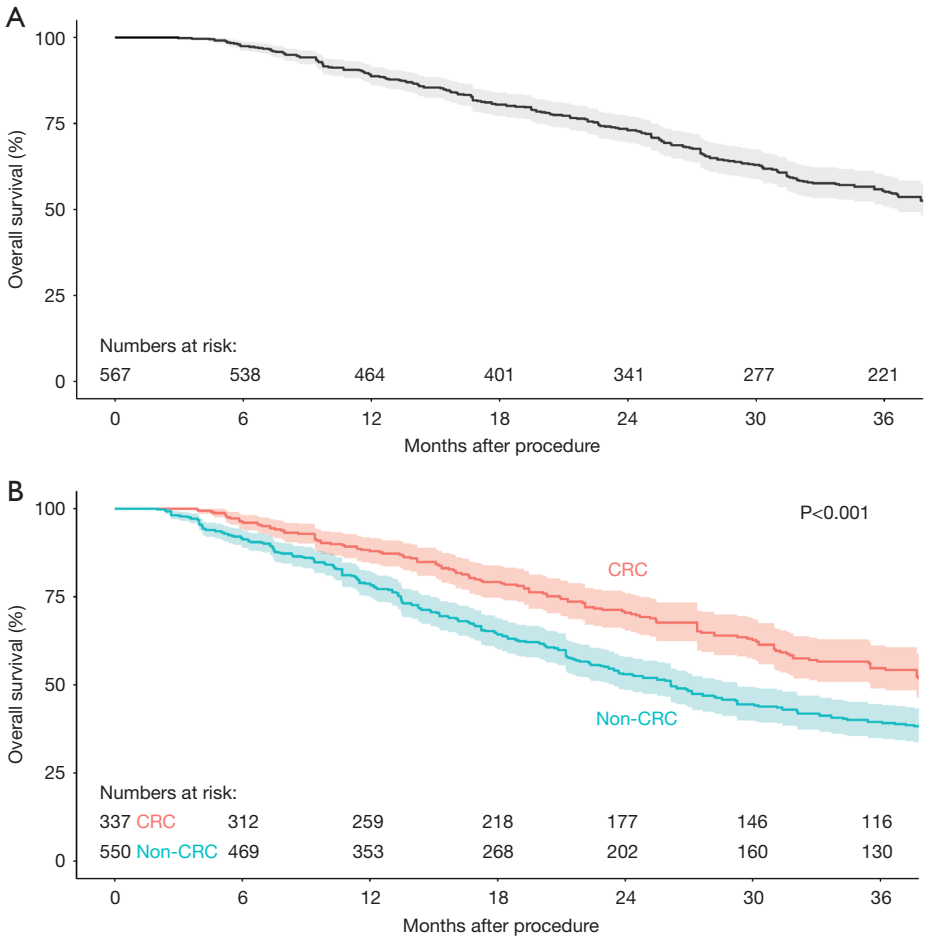

Figure 4 Overall survival. (A) Cumulative Kaplan-Meier graph demonstrating overall survival of patients with colorectal pulmonary metastases after stereotactic body radiation therapy. (B) Cumulative Kaplan-Meier graph demonstrating overall survival of patients with colorectal pulmonary metastases versus non-colorectal pulmonary metastases after stereotactic body radiation therapy. Shaded regions indicate 95% confidence interval.

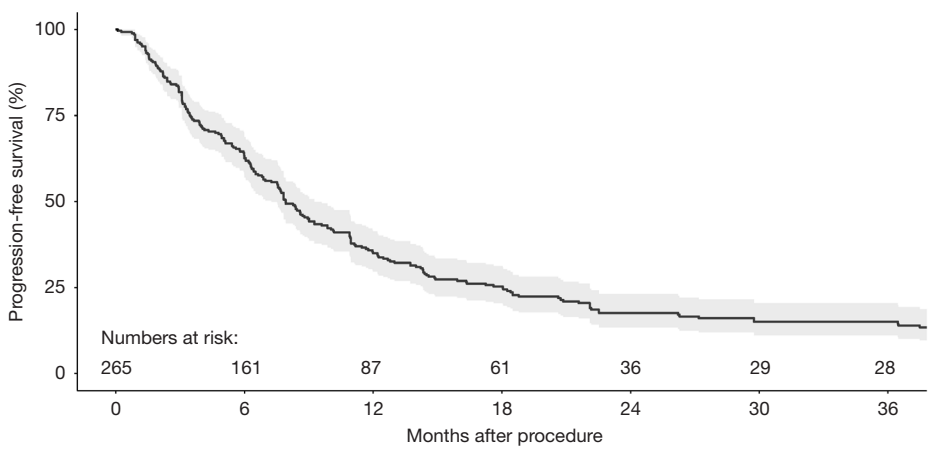

Figure 5 Progression-free survival. Shaded region indicates 95% confidence interval.

Table 3 Summary of morbidity and mortality outcomes in patients who underwent stereotactic body radiation therapy for pulmonary metastases

Author	30-day mortality (%)	Acute toxicities and grades										
		Pneumonitis			Esophagitis	Dyspnea	Erythema		Fatigue		Chest pain	
		Gr 1	Gr 2	Gr 3	Gr 1	Gr 3	Gr 1	Gr 2	Gr 1	Gr 2	Gr 1	Gr 2
Francheschini	0	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Pasqualetti	0	1 (3%)	0	0	0	0	0	0	0	0	0	0
Agolli	0	2 (4.5%)	5 (11.4%)	0	1 (2.3%)	0	1 (2.3%)	0	0	0	0	0
Filippi	0	7 (17.5%)	3 (7.5%)	0	0	0	0	0	0	0	0	0
Osti	0	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Jingu	0	NR	NR	2 (2.2%)	NR	NR	NR	NR	NR	NR	NR	NR
Niibe	0	NR	NR	0	NR	NR	NR	NR	NR	NR	NR	NR
Yamamoto	0	NS	NS	NS	NR	NR	NR	NR	NR	NR	NR	NR
Takeda	0	NS	NS	NS	NR	NR	NR	NR	NR	NR	NR	NR
Qiu	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Binkley	0	0	NS	NS	NS	0	0	0	0	0	0	0
Ricco	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Jung	0	0	2 (4%)	0	0	0	0	0	0	0	0	0
Kim	0	6 (46%)		0	0	0	0	0	0	0	6 (46%)	0
Thibault	0	NS	NS	NS	NR	NR	NR	NR	NR	NR	NR	NR
Kinj	0	2 (5.4%)	2 (5.4%)	0	0	0	0	1 (2.7%)	10 (27%)	1 (2.7%)	1 (2.7%)	0
Sharma	0	0	0	0	0	3 (1.5%)	0	0	0	0	0	1 (0.5%)
Carvajal	0	NR	NR	0	NR	NR	NR	NR	NR	NR	NR	NR

Gr, grade; NR, not reported; NS, not specified.

than direct RSI measurements (16).

The present systematic review identified 18 observational studies on patients with CRC pulmonary metastases that demonstrated 3-year LC, OS and PFS rates of 60%, 52%, and 13%, respectively. These findings may serve as useful benchmarks for future studies and help guide clinicians with their prognostic value. When using the available data to compare patients treated for CRC pulmonary metastases to non-CRC pulmonary metastases, there appeared to be significantly lower LC but higher OS for patients with CRC metastases. There was no reported peri-procedural mortality, and the most common morbidities included pneumonitis, fatigue, and chest pain. A number of prognostic factors were found to be predictive of increased local recurrence for patients with CRC pulmonary metastases, such as increased size of metastatic lesions, increased number of lesions, and lower SBRT dosage. However, other prognostic factors were less consistent, such as colon versus rectal origin of the primary lesion, and the utilization of systemic therapy (26,30,35).

Limitations of the present study included the variable treatment regimens prescribed in each institution, as well as differing baseline patient and tumour characteristics. The significance of adjuvant and neoadjuvant chemotherapy was difficult to interpret, partly due to the heterogenous regimens prescribed by each institution. Patient selection bias may also have caused some studies to report improved LC with adjuvant chemotherapy (26,29), whilst others reported worse OS (30). Future prospective studies are required to improve the understanding of the role of systemic therapy in conjunction with SBRT for oligometastatic pulmonary metastatic disease. In addition, non-colorectal pulmonary metastases varied in histological origin and were sometimes not specified. Colonic and rectal cancers were often presented as a single group, and follow-up protocols also differed between studies. Nonetheless, the present systematic review represents the most comprehensive data to date, and provides a useful overview of oncological outcomes for patients with CRC metastases treated by SBRT.

In conclusion, SBRT in the treatment of colorectal pulmonary metastases has been shown to be safe, with no reported peri-procedural mortality and low rates of morbidity. Patients with colorectal pulmonary metastases are shown to have higher OS, but lower LC rates, when compared to patients with non-colorectal metastases. This supports previous findings that suggest an increased radioresistance of CRCs compared to pulmonary metastases of other primary histologies. These findings may have implications for patient and treatment selection, dose fractionation, or combination with systemic agents, and supports the hypothesis that patients with colorectal pulmonary metastases may require higher BED while respecting normal tissue constraints.

Acknowledgments

Funding: This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Cao C, Wang D, Tian DH, Wilson-Smith A, Huang J, Rimner A. A systematic review and meta-analysis of stereotactic body radiation therapy for colorectal pulmonary metastases. J Thorac Dis 2019;11(12):5187-5198. doi: 10.21037/jtd.2019.12.12

Supplementary

Table S1 Summary of stereotactic body radiation therapy (SBRT) doses by study, for patients with colorectal and non-colorectal pulmonary metastases

Study	SBRT regimen (Gy/F)
Sharma	30/1, 51–60/3–5, 49/7, 48–56/6–7
Franchescini	30/1, 32/4, 36/6, 48/4, 54/3, 60/3, 60/8
Ricco	48–54/1–8
Binkley	25/1, 50/4
Niibe	48–50/4, 35–80/7–10
Thibault	50/5, 52/4
Yamamoto	40/4, 45/3, 46.5/4, 48/4, 50/8, 56.2/8, 60/8, 60/15
Osti	23/1, 30/1
Takeda	50/5
Qiu	50/5, 50/10
Jingu	40–65/3–15
Kinj	25/1, 60/3, 50–75/5
Pasqualetti	24–26/1, 27–42/3
Agolli	23/1, 30/1, 45/3
Carvajal	34/1, 54/3, 60/4, 60/8
Filippi	26/1, 45/3, 48/4, 55/5, 60/8
Jung	40/4, 48/4, 60/3, 60/4
Kim	39–51/3

Gy, Gray; F, fraction.

Table S2 Summary of prognostic factors identified to be significant on local control outcomes for patients with colorectal and non-colorectal pulmonary metastases treated with stereotactic body radiation therapy (SBRT)

Study	Patient characteristics		Tumor characteristics					Treatment characteristics		
	Age	Gender	Histopathology	No. of metastases	Tumor size	SUVmax	CEA level	SBRT dose	Completeness of response	Adjuvant chemotherapy
Sharma										
Franchescini			•	•						
Ricco					•			•		
Binkley			•		•					
Niibe										
Thibault			•					•		
Yamamoto			•		•	•		•		
Osti		•	•		•					
Takeda			•							•
Qiu				•	•			•		
Jingu	•		•					•		•
Kinj			•	•						
Pasqualetti										
Agolli									•	
Carvajal										
Filippi										
Jung					•		•			
Kim					•					

•, data presented. SUV, standardized uptake value; CEA, carcinoembryonic antigen.