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ORIGINAL ARTICLE

Factors affecting local control of pulmonary oligometastases treated with stereotactic body radiotherapy

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ABSTRACT

Background: Oligometastases refers to a state of limited metastatic disease. The use of local ablative therapies to patients with oligometastases can result in durable state of remission or long-term cure. Stereotactic body radiotherapy (SBRT) is a highly conformal radiation technique that delivers ablative doses to the target. The study aimed to evaluate local control (LC) and identify factors associated with poor LC in patients with pulmonary oligometastases treated with SBRT. Primary endpoint of the study was to assess LC; secondary endpoint was to determine factors associated with LC.

Material and methods: Criteria used for selection of patients with oligometastases included: metastatic disease limited to a maximum of two organs and no more than five metastatic lesions at time of treatment. Peripheral tumors were treated with 51–60 Gy in three fractions or a single fraction of 30 Gy. Central tumors received a dose of 45–60 Gy in 5–8 fractions.

Results: In 206 patients, 327 pulmonary oligometastases were treated with SBRT. Median follow-up was 22 months (range 2–100). LC at 2 and 3 years was 85% and 83%, respectively. On univariate analysis, biological equivalent dose assuming an α/β ratio of 10 (BED_{10}) < 100 Gy (HR 3.09), single-fraction SBRT (HR 2.83), synchronous metastasis (HR 1.99), and pre-SBRT chemotherapy (HR 2.79) were significantly associated with inferior LC. In the multivariable analysis BED_{10} <100 Gy (HR 3.59), pre-SBRT chemotherapy (HR 2.61) and presence of synchronous metastasis (HR 2.21) remained independently associated with poor LC.

Conclusions: SBRT achieved an excellent LC of 85% at 2 years. Although retrospective in nature, our study identified three factors associated with inferior LC. These factors may help to refine SBRT practice for pulmonary oligometastases in the future.

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Introduction

Oligometastases represents a state of metastatic disease characterized by limited number of metastatic tumors that involve either a single organ or limited number of organs. In 1995, Hellman and Weichselbaum were the first to hypothesize the presence of a disease status intermediate between widespread metastatic disease and locally confined disease. This state was thought to be amenable to curative localized therapies [1]. The potential for aggressive metastasis directed therapies has been investigated either with curative intent with the assumption that oligometastases are the only burden of disease or in the hope that reduction of tumor burden may increase the efficacy of chemotherapy [2–6]. With the use of metastasis directed therapies, a subset of patients with oligometastases has experienced long-term survival. Results of retrospective studies for pulmonary and hepatic metastasectomy show that 20–45% of the patients can achieve 5-year survival [2–6].

The lung is one of the most commonly involved sites of distant metastasis, and metastases to the lung can be seen in most cancer types [7]. In the past, development of pulmonary metastases was considered fatal in less than 2 years [8,9]. At present, surgical resection is a mainstay of treatment for patients with pulmonary oligometastases and can result in long-term survival or cure [2,4]. Other treatment options for patients diagnosed with pulmonary oligometastases include stereotactic body radiotherapy (SBRT), radiofrequency ablation (RFA), laser therapy, and chemotherapy. For appropriately selected patients, complete metastasectomy can achieve survival rates as high as 26% at 10 years and 22% at 15 years [2]. However, not all patients are suitable for radical excision, and, for those patients, SBRT is an alternative treatment option.

SBRT is a radiation technique that delivers very high ablative doses of radiation in a few (often 3–8) fractions in a short overall treatment time. Recently, evidence has

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accumulated to suggest that SBRT achieves similar outcomes as surgical resection for patients with early-stage non-small cell lung cancer (NSCLC) [10,11]. Appropriate dose fractionation schedules result in treated metastasis control rates of at least 85% with minimal treatment-related side effects irrespective whether the tumor is located centrally or peripherally in the lungs [12,13]. SBRT has also emerged as a novel treatment option for patients with pulmonary oligometastases [14–21]. Unlike early stage NSCLC, pulmonary oligometastases may differ in their response to SBRT [20]. Therefore, we aimed to investigate local control (LC) and factors affecting LC in patients with pulmonary oligometastases treated with SBRT.

Material and methods

Patient cohort

This retrospective study was approved by the institutional medical ethics committee of the Erasmus Medical Center (EMC). Patients were treated with SBRT if they had inoperable pulmonary metastases, refused surgery, or were technically unresectable and were >18 years in age. Criteria used for selection of patients with oligometastases included: metastatic disease limited to a maximum of two organs and no more than 5 metastatic lesions at time of treatment. Exclusion criteria were patients with oligoprogression or dominant metastatic progression or patients with prior thoracic radiotherapy. All tumors located in the lung were treated with SBRT and tumors in another organ than the lung were treated with surgery, SBRT or RFA, depending on the advice of the multidisciplinary tumor board. The local progression of these tumors did not count as local progression of the metastasis in the lung. All patients treated with stereotactic radiotherapy are entered in a prospective database. Patients who fulfilled the inclusion criteria were selected for the study. Histopathological confirmation of oligometastases was performed in 42% of the patients. It was not done if it was deemed not to be safe or feasible.

Treatment planning and delivery

Details of the SBRT procedure performed at the institution have been described previously [16]. All patients were treated with real-time tumor tracking. During treatment, tumor motion was detected by radiopaque markers implanted in or around the tumor. Gross tumor volume (GTV) was defined as visible tumor on the CT scan in lung window. A uniform margin of 5 mm was added to the GTV to create the planning treatment volume (PTV) [17]. The radiation schedule depended on the size and location of the metastasis, and on the algorithm used for dose calculation. Before May 2011, dose calculation was performed with the Ray Tracing algorithm using a one-dimensional equivalent path length correction to account for variation in tissue density. Large peripheral tumors (>3 cm) received 60 Gy in three fractions and small peripheral tumors (<3 cm) received 30 Gy delivered in a single fraction. Central tumors (located within 2 cm of trachea and main bronchus) received 45–60 Gy in five fractions except when located close to esophagus, in which case the tumor was treated with 6–7 fractions of 8 Gy (48 Gy, 56 Gy). After the introduction of a Monte Carlo (MC) dose calculation algorithm in 2011, the prescribed dose was corrected to match the prior Ray Tracing prescription dose [22]. Peripheral tumors were treated with 51 Gy or 54 Gy in three fractions, central tumors received 55 Gy in five fractions and tumors located close to esophagus received 49 Gy in seven fractions. Treatment planning was done on the OnTarget treatment planning system before 2011 and with the Multiplan treatment planning system (Accuray, Sunnyvale, CA) thereafter. Dose to PTV was prescribed to the 70–90% isodose line (median 78%), covering at least 95% of the PTV. Similar biological effect for different dose fractionation schedules was achieved by calculating biological equivalent dose, assuming an α/β ratio of 10 (BED_{10}). To account for the dose calculation inaccuracy of the Ray Tracing versus the Monte Carlo algorithm [22,23], the BED_{10} calculated with the Ray Tracing algorithm was corrected by reducing it by 12% for central tumors and 17–21% for peripheral tumors [22].

Follow-up

Clinical follow-up was performed at 3 weeks after SBRT and at 3, 6, 12, 18, and 24 months after treatment, and yearly thereafter. All available follow-up CT scans performed at our center and referring hospitals were used to evaluate local control. Follow-up PET scans were only obtained for evaluation of CT abnormalities. Toxicity was defined as acute if it occurred within 6 months and late if it occurred thereafter. All acute and late adverse events were reported and scored for severity using NCI Common Terminology Criteria for Adverse Events, version 3.0. Only the highest score of acute and late toxicity of each patient was used to determine the toxicity of the whole group.

Definition of endpoints

Time to local recurrence was defined as the number of months from the first session of SBRT to date of diagnosis of a local recurrence. Time to death was calculated in months for patients who died before experiencing a local recurrence from the first session of SBRT to date of death. A local recurrence was defined as a relapse within the PTV area. Overall survival (OS) was calculated from date of first SBRT session to date of death or date of last follow-up for alive patients. Progression-free survival (PFS) was calculated from date of first SBRT session to date of local, regional or distant relapse, which ever happened first. Patients who did not experience local recurrence and who were alive at date of last follow-up were censored. In the absence of biopsy confirming viable carcinoma, local recurrence was defined as a 20% increase in tumor size on CT scan compared with the previous CT scan according to the Response Evaluation Criteria In Solid Tumors (RECIST, version 1.0). In addition, a corresponding avid lesion on PET scan was required.

Table 1. Patient, disease and tumor characteristics.

Age	$N = 206$	Percentage (%)
Median	68 years	<70 years = 63.1%
Range	28 years–87 years	≥70 years = 36.9%
Gender	N = 206	
Male	120	58.3%
Female	86	41.7%
Comorbidity index	$N = 206$	
Charlson (range)	Median 1 (0–13)	Score 0 = 36.4%
		Score 1–2 = 32.5%
		Score ≥3 = 31.1%
Cumulative illness score (range)	Median 1 (0–13)	Score 0–4 = 86.4%
		Score ≥5 = 13.6%
Primary tumor	$N = 206$	
Colorectal	118	57.3%
Lung (Non small cell)	36	17.5%
Melanoma	11	5.3%
Sarcoma	10	4.9%
Breast	7	3.4%
Others	24	11.6%
Location of lung	$N = 327$	
Peripheral	244	74.6%
Central	83	25.4%
Biological equivalent dose (Gy)	$N = 327$	
≥100	244	74.6%
<100	83	25.4%
Tumor size	$N = 327$	
<3 cm	259	79.2%
≥3 cm	68	20.8%
Development of metastasis	$N = 327$	
Synchronous	86	26.3%
Metachronous	241	73.7%
Pre-SBRT chemotherapy	$N = 327$	
Yes	159	48.6%
No	168	51.4%
Location of metastases in lung	$N = 327$	
Lower lobe	157	48%
Other lobes	170	52%

Factors evaluated for local control

Variables assessed as prognostic factors for LC included: metachronous versus synchronous metastasis, delivery of pre-SBRT chemotherapy, primary site, location in lower lobes versus other location, central versus peripheral lung metastasis, tumor size, single-session versus fractionated SBRT, BED_{10}, Ray Tracing versus MC dose calculation, and time interval after diagnosis of pulmonary oligometastases to initiation of SBRT (Table 1). Synchronous metastasis was defined as the presence of metastases within 5 months after diagnosis of the primary tumor. Previously treated oligometastases that occurred as pulmonary oligorecurrence were categorized into the synchronous group if initial oligometastases developed within 5 months of diagnosis of primary tumor. Time period before initiation of SBRT was calculated from date of diagnosis of pulmonary metastasis to date of first fraction of SBRT and dichotomized at 4 months. To compare whether three fractions of SBRT used for treating peripheral tumors was equivalent to 5 or more fractions used for treating central tumors, patients were further grouped into four categories. Category 1 included tumors treated with $BED_{10} > 100$ Gy in three fractions ($n = 208$), category 2 included tumors treated with $BED_{10} > 100$ Gy in five or more fractions ($n = 36$), category 3 included tumors treated with $BED_{10} < 100$ Gy ($n = 51$), and category 4 included tumors treated with single-fraction SBRT ($n = 32$).

Statistical considerations

The cumulative incidence of local recurrence was analyzed using Fine and Gray's proportional subhazards model (competing risk regression) [24], where death was considered to be the only competing risk. The cumulative incidence rate was calculated on the number of tumors. The subhazard ratio (HR), 95% confidence interval (CI), and p-values for various covariates were obtained by the univariate analysis and covariates with a p-value of ≤.10 were taken as input for the multivariable analysis. The backward selection method was used to find the combination of factors associated with LC, where a threshold of $p < .05$ was used. The proportional subhazards assumption was checked using cumulative hazard plots, addition of time-varying covariates, and Schoenfeld residuals. No violations of this assumption were found. All analyses were performed using IBM SPSS statistics version 22.0 software package (SPSS Inc., Chicago, IL) and Stata version 14.0 (StataCorp. 2015; Stata: Release 14; Statistical Software; StataCorp LP, College Station, TX).

Results

In 206 patients, 327 pulmonary oligometastases were treated with SBRT between 2005 and 2015. Patient, disease and tumor characteristics are shown in Table 1. Primary site of pulmonary oligometastases per patient included colorectal carcinoma ($n = 118$), lung carcinoma ($n = 36$), melanoma ($n = 11$), sarcoma ($n = 10$), breast carcinoma ($n = 7$), and other tumors sites ($n = 24$). Two-hundred and ninety-five out of 306 pulmonary oligometastases were treated with fractionated SBRT and 244 were treated with a BED_{10} >100 Gy. Two-hundred and forty-four oligometastases were peripheral in location and 157 were located in lower lobes. The diameter of the majority of the oligometastases ($n = 259$) was less than 3 cm. Of the 206 patients, 119 (57%) had only metastases to the lung. Median follow-up in the study was 22 months (range 2–100 months). Local recurrence in the entire cohort is shown in Figure 1(a). Local recurrence rate at 2 and 3 years was 15% and 17%, respectively.

On univariate analysis (Table 2), BED_{10} <100 Gy (HR 3.09, 95% CI 1.80–5.32, $p < .001$) (Figure 2(a)), pre-SBRT chemotherapy (HR 2.79, 95% CI 1.56–5.00, $p = .001$) (Figure 2(b)), the presence of synchronous metastasis (HR 1.99, 95% CI 1.13-3.48, $p = .016$) (Figure 2c), and single-fraction radiotherapy (HR 2.83, 95% CI 1.43–5.59, $p = .003$) were associated with inferior LC. Tumors treated with BED_{10} >100 Gy (either in three or five fractions) had significantly better LC than single-fraction radiotherapy or treatment with BED_{10} <100 Gy (Figure 1(b)). Based on pair-wise comparison there was no significant difference in LC between BED_{10}>100 Gy in three fractions and BED_{10}>100 Gy in five fractions (HR 0.98, 95% CI 0.33–2.91, $p = .975$). However, in comparison with the BED_{10} >100 Gy in the three-fraction group, the groups treated with BED_{10} <100 Gy and single-fraction SBRT experienced significantly worse LC with HR 2.73 (95% CI 1.42–5.23, $p = .002$) and HR 3.63 (95% CI 1.74–7.57, $p = .001$), respectively.

In the multivariable analysis (Table 3), BED_{10} <100 Gy (HR 3.59, 95% CI 2.00–6.44, $p < .001$), delivery of pre-SBRT

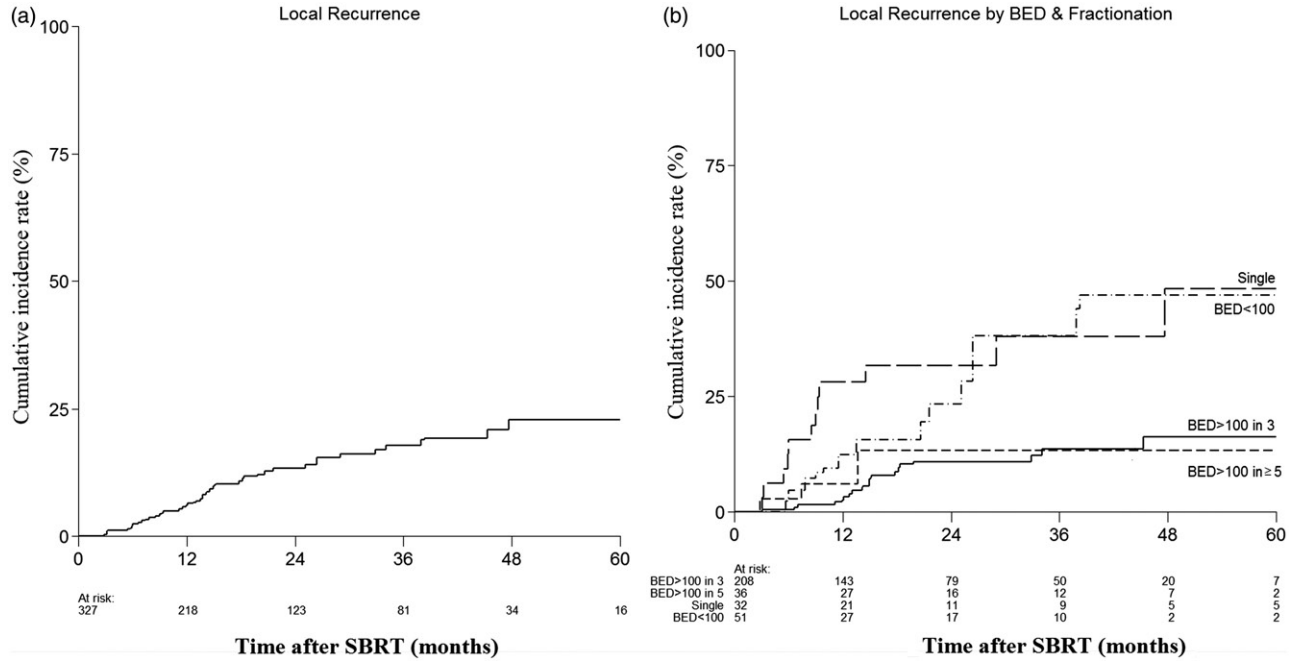

Figure 1. (a) Cumulative incidence of local recurrence (b) Cumulative incidence of local recurrence by Groups. Group1 pulmonary oligometastases treated with $BED_{10} > 100$ Gy in three fractions, group 2 tumors treated with $BED_{10} > 100$ Gy in ≥ 5 fractions, group 3 tumors treated with $BED_{10} < 100$ Gy, and group 4 tumors treated with single-fraction SBRT. The cumulative incidence rate is based on the number of tumors. BED_{10}: biologically equivalent dose with an α/β of 10; SBRT: stereotactic body radiation therapy.

Table 2. Univariate analysis of factors affecting local control for pulmonary oligo metastasis.

Covariate	2 yr Local control	3 yr Local control	4 year Local control	HR[a] 95%CI	*p* Value
1. Timing of metastasis					
Synchronous (86)	77%	74%	71%	1.99 (1.13–3.48)	.016
Metachronous (241)	88%	86%	84%		
2. Pre-SBRT chemotherapy					
Yes (159)	78%	74%	71%	2.79 (1.56–5.00)	.001
No (168)	92%	90%	89%		
3. Primary location					
Colorectal (202)	83%	80%	77%	1.69 (0.94–3.06)	.081
Others (125)	89%	87%	86%		
4. Lobe location					
Lower lobe (157)	86%	84%	82%	0.89 (0.52–1.54)	.689
Other lobes (170)	85%	82%	80%		
5. Location of lung					
Peripheral (244)	85%	83%	81%	0.98 (0.54–1.78)	.937
Central (83)	85%	82%	80%		
6. Tumor size (cm)					
<3 (259)	85%	83%	81%	0.97 (0.51–1.83)	.918
≥ 3 (68)	85%	82%	80%		
7. Fractionation of SBRT					
Single (32)	68%	63%	59%	2.83 (1.43-5.59)	.003
Fractionated (295)	87%	85%	83%		
8. Biological equivalent dose					
<100 (83)	72%	68%	64%	3.09 (1.80–5.32)	$<.001$
≥ 100 (244)	90%	88%	87%		
9. Algorithm					
Ray Tracing (146)	83%	80%	77%	1.51 (0.87–2.64)	.147
Monte Carlo (181)	88%	86%	84%		
10. Initiation of SBRT (after diagnosis of pulmonary metastases)					
≥ 4 months (207)	83%	80%	77%	1.68 (0.91–3.07)	.096
<4 months (120)	89%	87%	86%		

[a]HR is subhazard ratio from Fine & Gray model.

chemotherapy (HR 2.61, 95% CI 1.46–4.64, $p = .001$) and presence of synchronous metastasis (HR 2.21, 95% CI 1.22–4.00, $p = .009$), remained as independent factors associated with LC.

Median OS in the entire cohort was 32 months. The 2 and 3 year OS rates were 63% and 47%, respectively. Median progression PFS was 13 months. The 2 year and 3 year PFS rates were 36% and 25%, respectively.

SBRT was generally very well tolerated. There were no grade 4 or 5 events. Two percent of the patients experienced grade 3 acute or late toxicities. Three patients experienced grade 3 dyspnea, one patient experienced grade 3 chest

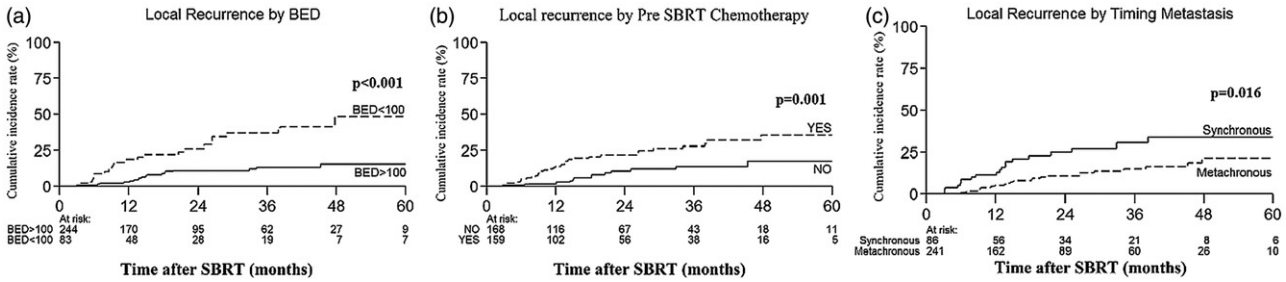

Figure 2. (a) Cumulative incidence of local recurrence at $BED_{10} > 100$ Gy. (b) Cumulative incidence of local recurrence in pre-SBRT chemotherapy. (c) Cumulative incidence of local recurrence by timing of metastasis. BED_{10}: biologically equivalent dose with an α/β of 10; SBRT: stereotactic body radiation therapy

Table 3. Multivariate analysis of factors affecting local control for pulmonary oligo metastasis.

Covariate	HR[a] 95%CI	*p* Value
1. Biological equivalent dose		
<100 (83)	3.59 (2.00–6.44)	<.001
≥100 (244)		
2. Pre-SBRT chemotherapy		
Yes (159)	2.61 (1.46–4.64)	.001
No (168)		
3. Timing of metastasis		
Synchronous (86)	2.21 (1.22–4.00)	.009
Metachronous (241)		

[a]HR is subhazard ratio from Fine & Gray model.

pain, and one patient experienced both grade 3 dyspnea and grade 3 fatigue. Acute grade 2 toxicities were experienced by less than 5% of the patients whereas 7.5% of the patients experienced late grade 2 cough and 6% experienced late grade 2 fatigue.

Discussion

SBRT is the standard treatment option for inoperable early stage NSCLC [10–13]. In this largest, single-center experience treating inoperable pulmonary oligometastases with SBRT, we demonstrated that SBRT achieved excellent LC. The 2-year LC rate in our study was 85%, and our results are consistent with literature where delivery of SBRT for pulmonary oligometastases is associated with LC rates of 80% or higher at 2 years [14,18–21,25]. Our study identified three factors independently associated with inferior LC. These factors are BED_{10} <100 Gy (HR 3.59), delivery of pre-SBRT chemotherapy (HR 2.61), and synchronous metastasis (HR 2.21).

The ideal SBRT dose for pulmonary metastases is not known and is an area of active investigation. As with SBRT for early stage NSCLC, BED_{10} <100 Gy was significantly associated with inferior LC for pulmonary oligometastases [26]. Moreover, treating with BED_{10} <100 Gy has the biggest influence on LC in our analyses. There was an absolute reduction of 18% in 2 year LC comparing BED_{10} >100 Gy with BED_{10} <100 Gy (2 year LC of 90% versus 72%, respectively). So when treating with BED_{10} <100 Gy, 1 out of 4 pulmonary oligometastases will develop local recurrence after 2 years.

The current study shows that the delivery of chemotherapy before SBRT was independently associated with poor LC. Pre-SBRT chemotherapy resulted in an absolute reduction in LC of 14% at 2 years and 16% at 3 years. Our results are consistent with findings reported from the multi-center SBRT database within the German Society of Radiation Oncology (DEGRO) [27]. This study also observed that pre-SBRT chemotherapy was significantly associated with lower tumor control probability. The study predicted that metastases treated with pre-SBRT chemotherapy would require substantially higher radiation doses to achieve the similar results. The exact reasons why pre-SBRT chemotherapy is associated with inferior LC remain yet to be elucidated. This could be due to accelerated repopulation of clonogenic tumor cells or the surviving tumor cells could have developed more resistance and may have acquired improved DNA repair capacity after initial exposure to chemotherapy [28–30]. However, there is also evidence supporting that delivery of pre-SBRT chemotherapy for oligometastases is associated with improvement in overall survival [18]. At present the ideal timing of SBRT for pulmonary oligometastases remains unclear and undefined.

Patients with synchronous oligometastases were significantly associated with a decreased risk of local control as compared to patients with metachronous tumors: 2 year LC of 77% versus 88%, respectively. To our knowledge, this study is the first to identify that presence of synchronous metastases is independently associated with inferior LC for pulmonary oligometastases. However, given the retrospective nature of the study, our findings need to be further validated in a prospective cohort study.

In this study, five fractions of SBRT for central tumors was equally effective as three fractions used for peripheral tumors, as long as the BED_{10} was >100 Gy. Single-fraction SBRT of 30 Gy was associated with inferior LC univariately, but disappeared as a predictive factor in the multivariate analyses. Nevertheless, within another analysis single-fraction SBRT was independently associated with worse LC as well [19]. The ongoing TROG SAFFRON study, which is aimed to compare single- versus multi-fraction SBRT for pulmonary oligometastases, will possibly provide a definitive answer [31].

It is recognized that Monte Carlo–based techniques are the most accurate methods of dose calculation available [23,32]. It has also been demonstrated that changing in treatment plan calculation algorithm from equivalent path length (analogous to the Ray Tracing algorithm) to MC in the treatment of lung tumors produces large differences in target and organ doses [23]. One would suspect that switching from Ray Tracing to MC algorithm is associated with improved LC, but our study did not demonstrate any significant improvement in LC with the use of MC algorithms.

In this study, LC was not influenced by tumor size or by primary site. Similar findings have been reported in the

literature [21]. However, some studies have found that patients with colorectal oligometastases are associated with inferior LC [33,34]. In our study, SBRT achieved 83% LC rate at 2 years for patients with colorectal pulmonary oligometastases. This could be clarified by the fact that the majority of pulmonary metastases in our study were treated with BED_{10} >100 Gy. Our findings, based on the largest number of inclusion of colorectal pulmonary oligometastases treated with SBRT, could not underline the hypothesis that SBRT needs to be adapted depending on the primary site. Limitations of the study are its retrospective nature; hence our findings need further validation in future studies.

In our cohort, SBRT achieved excellent LC of 85% and OS of 63% at 2 years. SBRT to pulmonary oligometastases has been reported equivalent to surgery within retrospective analysis [35,36] and this now needs to be addressed in a prospective randomized clinical setting. BED_{10} <100 Gy, delivery of pre-SBRT chemotherapy and synchronous metastasis were independently associated with inferior LC. These factors may help to refine SBRT practice for patients with pulmonary oligometastases in the future.

Disclosure statement

No potential conflict of interest was reported by the authors.

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