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# Optimizing SABR delivery for synchronous multiple lung tumors using volumetric-modulated arc therapy

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**ABSTRACT**

**Background:** Volumetric-modulated arc therapy (VMAT) delivery for stereotactic ablative radiotherapy (SABR) of multiple lung tumors allows for faster treatments. We report on clinical outcomes and describe a general approach for treatment planning.

**Material and methods:** Patients undergoing multi iso-center VMAT-based SABR for ≥2 lung lesions between 2009 and 2014 were identified from the VU University Medical Center and London Health Sciences Centre. Patients were eligible if the start date of the SABR treatment for the different lesions was within a time range of 30 days. SABR was delivered using separate iso-centers for lesions at a substantial distance from each other. Tumors were either treated with a single fraction of 34 Gy, or using three risk-adapted dose-fractionation schemes, namely three fractions of 18 Gy, five fractions of 11 Gy, or eight fractions of 7.5 Gy, depending on the tumor size and the location. Multivariable analysis was performed to assess factors predictive of clinical outcomes.

**Results:** Of 84 patients (188 lesions) identified, 46% were treated for multiple metastases and 54% for multiple primary NSCLC. About 97% were treated for two or three lesions, and 56% had bilateral disease. After a median follow-up of 28 months, median overall survival (OS) for primary tumors was 27.6 months, and not reached for metastatic lesions ($p = .028$). Grade ≥3 toxicity was observed in 2% of patients. Multivariable analysis showed that grade 2 or higher radiation pneumonitis ($n = 9$) was best predicted by a total lung $V35_{Gy}$ of ≥6.5% (in 2Gy/fraction equivalent) ($p = .007$).

**Conclusion:** Severe toxicity was uncommon following SABR using VMAT for up to three lung tumors. Further investigations of planning parameters are needed in patients presenting with more lesions.

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## Introduction

The lung is a common site of metastatic disease from most solid tumors, including non-small cell lung cancer (NSCLC). In recent years, patients with more limited metastatic disease have been treated radically using stereotactic ablative radiotherapy (SABR) [1–3]. SABR to multiple lung targets has also been employed in the setting of multiple primary lung cancers [4,5]. Although the likelihood of severe radiation pneumonitis is low in patients undergoing SABR for a single lung lesion, concerns exist about the potential for radiation-induced toxicity in patients with multiple lung lesions [6]. Consequently, some centers have administered treatment to just one lesion at a time, or have excluded patients who have more than four synchronous lesions [3,7].

Volumetric-modulated arc therapy (VMAT) has been in use since 2008, including for lung SABR, and it allows delivery of conformal treatment plans in a shorter treatment time than conventional static beam plans [8]. Faster delivery is patient-friendly, and may help to minimize the risk of a geographic miss due to intrafraction tumor displacement, both of which are considerations for SABR delivery to multiple pulmonary lesions. To the best of our knowledge, practical descriptions of VMAT planning for treatment of multiple lung lesions are lacking. Furthermore, although recent studies in solitary lung lesions have shown that some dosimetric parameters are important predictors for SABR induced lung toxicity, predictors for toxicity after VMAT-SABR for multiple lesions are unknown [9,10].

Selected patients presenting with a limited number of lesions currently undergo SABR using VMAT at both the VU University Medical Center (VUmc) and the London Health Sciences Centre (LHSC). The aim of this retrospective analysis is to perform a multivariable regression analysis to identify significant predictors for clinical outcomes in this patient group, and to derive a practical approach for treatment planning in such cases.

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Supplemental data for this article can be accessed here.

## Material and methods

### Patient selection

Institutional databases from the VUmc and the LHSC were queried to identify consecutive lung SABR patients with multiple primary or oligometastatic lung tumors. Eligible patients had to commence multi iso-center VMAT for $\geq$2 parenchymal lung lesions within a 30-d period, and to a $BED_{10}$ (biologically effective dose with $\alpha/\beta = 10$) of at least 100 Gy. Patients with two tumors in close proximity that were treated with a single iso-center were not included, as the treatment planning of these patients was not different from patients treated for a single lesion. Patients receiving prior, synchronous, or subsequent non-SABR thoracic radiotherapy or chemoradiotherapy, were excluded. Patients who were treated in the randomized phase II SABR-COMET trial were also excluded [11]. No patients with more than three lesions were eligible for treatment with SABR at the LHSC. The resulting study population consisted of 84 patients, 74 patients were from the VUmc and 10 patients from the LHSC, treated between 2009 and 2014.

### Treatment planning and delivery

A 10 phase four-dimensional CT (4D-CT) scan was performed for each patient in the supine position during uncoached, quiet respiration on a 16 slice CT scanner [12]. A respiratory monitoring system (Respiratory Position Management, Varian Medical Systems, Palo Alto, CA) was used to record breathing patterns. For each tumor, an internal target volume (ITV) based on the positions of the gross tumor volume on 4D-CT was defined. The planning target volume (PTV) was created by adding an isotropic expansion of 5 mm to the ITV. For VUmc patients, treatment planning was performed on the average intensity projection (Ave-IP) of the 4D-CT using VMAT RapidArc (Varian Medical Systems, Palo Alto, CA). For LHSC patients, treatment planning was performed on the untagged average CT scan and generated using SmartArc VMAT (Philips Medical Systems, Fitchburg, WI), and patients with substantial tumor movement, usually defined as $\geq$7 mm, were treated using respiratory gating. Patients were treated on a Varian linear accelerator (Varian Medical Systems, Palo Alto, CA) in both centers.

SABR was delivered using separate iso-centers for each lesion in patients with either unilateral or bilateral multiple lung lesions which were at a substantial distance from each other. Tumors were either treated using a single fraction of 34 Gy [13], or using a risk-adapted dose-fractionation scheme, namely three fractions of 18 Gy, five fractions of 11 Gy, or eight fractions of 7.5 Gy, depending on the tumor size and the location [6]. At the VUmc, all dose calculations were performed using the Eclipse AAA algorithm (Varian Medical Systems, Palo Alto, CA) up to April 2014, and Acuros thereafter. At the LHSCs, all dose calculations were performed using Collapsed Cone Convolution algorithm of the Pinnacle treatment planning system (Philips Medical Systems, Fitchburg, WI). Both institutional guidelines required that 95% and 99% of the PTV, respectively, received at least 100% and 90% of the prescription dose, and that the PTV has a heterogeneous dose distribution with a maximum point dose between 110 and 140%. Treatment plans were optimized to limit doses to organs at risk (OARs), such as the chest wall, brachial plexus, esophagus, and spinal canal (Supplemental Table 1). Substantial priority was placed on minimization of the contralateral lung dose, using partial arcs or an avoidance sector, and methods such as an optimization objective of $V_{5Gy} = 0$ or a goal of $V_{5Gy} < 5\%$ in the final treatment plan. Planning objectives for the total lung volume were generally not used. Online setup on each tumor was performed using cone beam CT scans (CBCT). In some cases, an additional CBCT was performed between the two arcs in order to correct for possible intra-fraction tumor motion. As far as possible, patients at the VUmc underwent treatment to all lesions during a single treatment session. However, at the LHSC, each patient was treated for a maximum of two lesions per day due to scheduling efficiency, with the remaining lesion(s), if any, treated on the following day, and alternating thereafter.

### Delineation and dosimetry

Contours of both lungs (minus PTV) were automatically generated and edited where necessary on the Ave-IP (or subset average, for gated patients) reconstruction of the 4D-CT using the treatment planning systems described above. For the purposes of this study, treatment plans of each lesion were separately exported to Velocity™ Medical Systems and scaled to biologically equivalent in 2 Gy/fraction equivalents ($EQD_2$) using the formula $EQD_2 = \frac{Biologically\ effective\ dose}{1+\left(\frac{2}{\alpha/\beta}\right)}$ with an $\alpha/\beta$-ratio of 10 for the ITV and three for the lung structure. A combined $EQD_2$ plan was then generated for each patient. For LHSC patients, lungs (minus PTV) were defined in Pinnacle and $EQD_2$ values were computed using MIM version 6.5 (MIM Software, Cleveland, OH). All dosimetric parameters in this study are reported in $EQD_2$ values.

### Assessment of clinical outcomes

Available patient records and clinical data from referring physicians and general practitioners were used to evaluate clinical outcomes. Any toxicity recorded after 6 weeks of start of SABR was retrospectively assessed using the CTCAE version 4.03 by a clinical panel including at least two clinical physicians. In cases of doubt, a third physician specialized in lung cancer treatment was consulted. In cases where the relationship of an adverse event with treatment could not be excluded, such events were scored as toxicity.

### Statistical analysis

Descriptive statistics were generated for baseline characteristics stratified by laterality and tumor type, compared using the Chi-square test, Fisher's exact test, two sample *T*-test, or

Wilcoxon rank sum test (for volumetric and dosimetric variables) as appropriate. Univariable and multivariable regression analyses were performed to identify significant predictors of clinical outcomes using logistic regression. All available factors composed of baseline patient and treatment characteristics, including doses delivered to the lung ($V_{5Gy}$–$V_{50Gy}$ in 5 Gy intervals), were, therefore, used. Variables significant or associated from univariable regression ($p < .10$) were incorporated into a multivariable regression model and sequentially removed using backward elimination techniques until all remaining covariates had $p$ values <.10. Variables with higher rates of missing data ($n < 50$) were omitted from regression analysis. Kaplan–Meier estimates were generated for all survival outcomes and compared using the Log-rank test. Median follow-up times were calculated using reverse Kaplan–Meier method [14]. All statistical analysis was performed using SAS version 9.4 software (SAS institute, Cary NC), using two-sided statistical testing at the 0.05 significance level.

## Results

### *Patient, tumor, and treatment characteristics*

A total of 84 patients with 188 lesions were identified (Table 1 and Figure 1). The median age was 69 years (range 38–87). Baseline WHO performance status, available for 96% of patients, was scored WHO 0–1 in 75% of them. A PET-scan was performed in 77%, with pathological diagnosis of at least one of the treated lesions available in 41% of patients. Thirty-nine patients (46%) were treated for multiple lung metastasis, and 45 patients (54%) for multiple primary lung cancers. Twenty-six patients (31%) received chemotherapy pre-SABR, with a median time to start of SABR of 18.5 months (range 0.9–62.3). Nineteen patients (23%) received chemotherapy after SABR (median time to chemotherapy was 9.5 months (1.1–25.2)). Six (7%) and 11 (13%) patients received prior and adjuvant SABR, respectively. Thirty-seven patients (44%) had unilateral lesions (13 of them left-sided only) and 47 patients (56%) bilateral lesions. Most patients (81%) underwent treatment for two lesions, with 51% of the 68 having bilateral lesions. Thirteen patients (15%) were treated for three lesions (77% of these were bilateral), two patients for four lesions (one of them had bilateral lesions), and one patient was treated for five bilateral lesions. In 35 patients (42%), different fractionation schemes were used for the lesions. SABR was delivered in 1, 3, 5, or 8 fractions in 4%, 24%, 43%, and 30% of lesions, respectively. The doses delivered to different lesions varied in 12 patients having unilateral lesions (14%), and in 23 patients with bilateral lesions (27%). Median total ITV, which was a summation for all

**Table 1.** Baseline patient, tumor and treatment characteristics for all patients ($n = 84$), patients with unilateral ($n = 37$), and bilateral lesions ($n = 47$).

| Characteristic | *N* | All patients ($n = 84$) | Unilateral ($n = 37$) | Bilateral ($n = 47$) |
|---|---|---|---|---|
| Age – median (range) | 84 | 69.4 (37.9, 87.2) | 71.0 (49.9, 83.0) | 68.4 (37.9, 87.2) |
| WHO performance status – *n* (%) | 81 | | | |
| 0 | | 31 (38.3) | 14 (40.0) | 17 (37.0) |
| 1 | | 30 (37.0) | 14 (40.0) | 16 (34.8) |
| 2 | | 15 (18.5) | 5 (14.3) | 10 (21.7) |
| 3 | | 5 (6.2) | 2 (5.7) | 3 (6.5) |
| COPD GOLD status – *n* (%) | 78 | | | |
| 1 | | 7 (9.0) | 2 (5.7) | 5 (11.6) |
| 2 | | 13 (16.7) | 8 (22.9) | 5 (11.6) |
| 3 | | 8 (10.3) | 5 (14.3) | 3 (7.0) |
| 4 | | 2 (2.6) | 1 (2.9) | 1 (2.3) |
| Previous lung surgery – *n* (%) | 84 | 18 (21.4) | 8 (21.6) | 10 (21.3) |
| Pathological diagnosis – *n* (%) | 84 | 34 (40.5) | 11 (29.7) | 23 (48.9) |
| Lesion type – *n* (%) | 84 | | | |
| Metastasis | | 39 (46.4) | 15 (40.5) | 24 (51.1) |
| Primary lung | | 45 (53.6) | 22 (59.5) | 23 (48.9) |
| Number of lesions – *n* (%) | 84 | | | |
| 2 | | 68 (81.0) | 33 (89.2) | 35 (74.5) |
| 3 | | 13 (15.5) | 3 (8.1) | 10 (21.3) |
| 4 | | 2 (2.4) | 1 (2.7) | 1 (2.1) |
| 5 | | 1 (1.2) | – | 1 (2.1) |
| Location[a] – *n* (%) | 188 | | | |
| Left lower lobe | | 37 (19.7) | 19 (24.1) | 18 (16.5) |
| Left upper lobe | | 44 (23.4) | 10 (12.7) | 34 (31.2) |
| Right lower lobe | | 40 (21.3) | 16 (20.3) | 24 (22.0) |
| Right middle lobe | | 13 (6.9) | 8 (10.1) | 5 (4.6) |
| Right upper lobe | | 54 (28.7) | 26 (32.9) | 28 (25.7) |
| Combined ITV ($cm^3$) – median (range) | 84 | 17.4 (1.4, 182.2) | 12.3 (1.5, 59.1) | 20.4 (1.4, 182.2) |
| Combined PTV ($cm^3$) – median (range) | 84 | 52.1 (9.6, 325.2) | 39.7 (9.6, 139.0) | 61.2 (11.1, 325.2) |
| Fractionation[a] – *n* (%) | 188 | | | |
| 1 × 34Gy | | 7 (3.7) | – | 7 (6.4) |
| 3 × 18Gy | | 45 (23.9) | 18 (22.8) | 27 (24.8) |
| 5 × 11Gy | | 80 (42.6) | 35 (44.3) | 45 (41.3) |
| 8 × 7.5Gy | | 56 (29.8) | 26 (32.9) | 30 (27.5) |
| $BED_{10}$ (Gy)[a,b] – median (range) | 188 | 115.5 (105.0, 151.2) | 115.5 (105.0, 151.2) | 115.5 (105.0, 151.2) |

[a]Based on per lesion database ($n = 188$).
[b]Biologically effective dose calculated using an $\alpha/\beta$ ratio of 10; COPD: chronic obstructive pulmonary disease; NSCLC: non-small cell lung cancer; NOS: not otherwise specified.

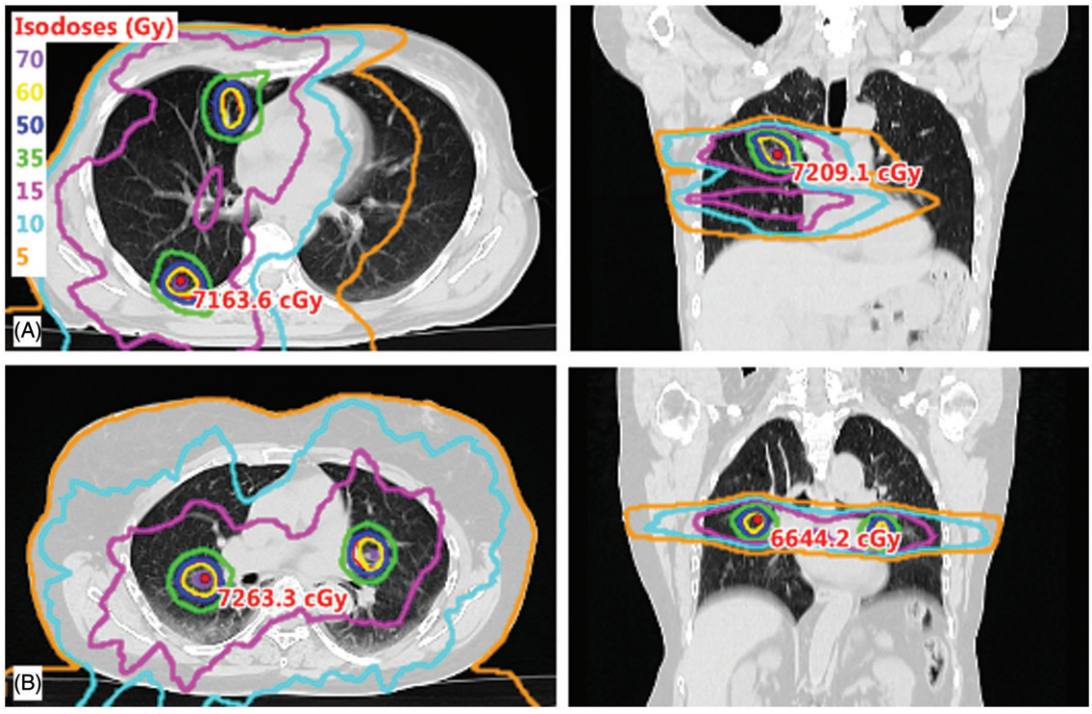


**Figure 1.** Treatment plan of a patient with three unilateral lesions (panel A), and another with two bilateral lesions (panel B).

**Table 2.** Summary of lung parameters for all patients ($n = 84$), patients with unilateral ($n = 37$), and bilateral lesions ($n = 47$). All doses were reported in $EQD_2$ values.

| **Total lung minus PTV** | | | |
|---|---|---|---|
| Median (range) | All patients | Patients with unilateral tumors | Patients with bilateral tumors |
| Minimum lung dose (Gy) | 0.1 (0.0, 0.3) | 0.1 (0.04, 0.3) | 0.1 (0.0, 0.3) |
| Mean lung dose (Gy) | 7.1 (2.3, 16.7) | 5.9 (2.3, 16.7) | 7.8 (2.5, 16.1) |
| Maximum lung dose (Gy) | 194.0 (72.5, 342.1) | 192.5 (143.9, 311.2) | 198.5 (72.5, 342.2) |
| $V_{5Gy}$ (%) | 25.3 (8.1, 54.8) | 19.7 (8.1, 42.1) | 27.5 (9.0, 54.8) |
| $V_{15Gy}$ (%) | 12.1 (2.5, 31.9) | 10.0 (2.5, 31.9) | 12.7 (2.5, 31.6) |
| $V_{20Gy}$ (%) | 8.9 (1.6, 27.6) | 8.2 (1.6, 27.6) | 10.5 (1.6, 26.1) |
| $V_{25Gy}$ (%) | 7.2 (1.0, 22.8) | 6.9 (1.0, 22.8) | 8.1 (1.7, 22.0) |
| $V_{35Gy}$ (%) | 4.9 (0.5, 15.3) | 4.7 (0.5, 15.0) | 5.3 (1.1, 15.3) |
| $V_{50Gy}$ (%) | 3.1 (0.1, 9.0) | 2.6 (0.1, 9.0) | 3.3 (0.1, 8.6) |
| **Summary of lung parameters for patients with unilateral lesions ($n = 37$)** | | | |
| Median (range) | Contralateral lung | Ipsilateral lung minus PTV | |
| Minimum lung dose (Gy) | 0.1 (0.0, 0.3) | 0.1 (0.0, 0.6) | |
| Mean lung dose (Gy) | 1.0 (0.3, 2.3) | 12.1 (4.2, 32.8) | |
| Maximum lung dose (Gy) | 6.7 (2.7, 24.2) | 192.5 (143.9, 311.2) | |
| $V_{5Gy}$ (%) | 0.09 (0.0, 13.3) | 38.0 (11.10, 80.2) | |
| $V_{15Gy}$ (%) | 0.0 (0.0, 3.9) | 20.0 (0.0, 67.3) | |
| $V_{20Gy}$ (%) | 0.0 (0.0, 2.8) | 15.3 (0.0, 58.2) | |
| $V_{25Gy}$ (%) | 0.0 (0.0, 2.2) | 12.8 (0.0, 48.0) | |
| $V_{35Gy}$ (%) | 0.0 (0.0, 1.5) | 8.4 (0.0, 31.6) | |
| $V_{50Gy}$ (%) | 0.0 (0.0, 1.0) | 5.5 (0.0, 18.9) | |

PTV: planning target volume.

treated lesions in each patient, was 17.4 $cm^3$ (range 1.4–182.2), and median total PTV was 52.1 $cm^3$ (range 9.6–325.2). Table 2 shows details of doses (in $EQD_2$) delivered to the lung.

## *Disease control*

Disease progression at any location was recorded in 44 patients (52%) (Figure 2). Median progression-free survival (PFS) was 12.0 months for all patients, 25.3 months for patients with unilateral lesions, and 11.0 months for patients with bilateral lesions ($p = .059$). Patients presenting with primary lung tumors had a median PFS of 15.5 months, while this was 11.2 months in patients with metastatic lesions ($p = .224$). Isolated distant progression at one or more sites was the most common pattern (38%). Four patients (5%) had an isolated local recurrence, one patient (1%) had both local and distant relapse, six (7%) had both regional and distant relapse, and one patient (1%) had both loco-regional and distant relapse. There were no patients with an isolated loco-regional recurrence.

The actuarial local control rates at 1 and 3 years were 96.9% and 84.7%, respectively, for all patients (Figure 2). For patients with primary lung tumors, this was 93.1% and

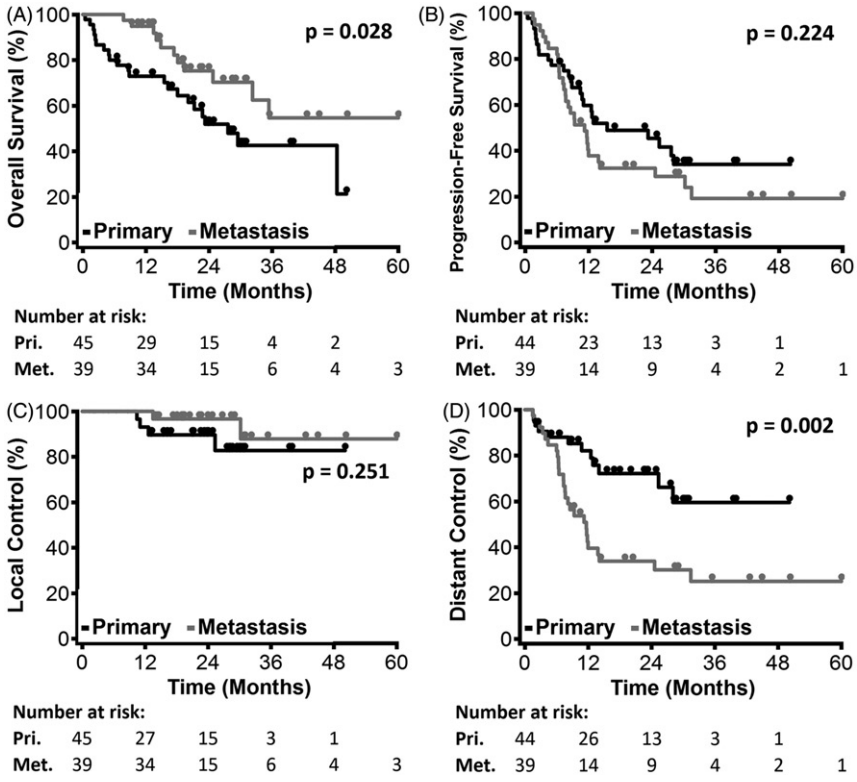


**Figure 2.** Kaplan–Meier plots for (A) overall survival, (B) progression-free survival, (C) local control, and (D) distant control stratified by lesion type (primary lung versus metastasis).

82.8%, respectively. In metastatic tumors, the corresponding rates were 100% and 87.9%, respectively. There were no significant differences in local control and regional control (not shown) between patients with primary or metastatic lesions. Actuarial distant control rates were 82.1% and 59.5% at 1 and 3 years for patients with primary tumors, as opposed to 39.6% and 25.1%, respectively, for those presenting with lung metastases ($p = .002$).

### *Treatment toxicity*

In total, 17 patients (20%) were considered to have grade $\geq$2 toxicity at $\geq$6 weeks after the start of treatment. Grade $\geq$3 toxicity ($\geq$G3) was observed in two patients (2%). The most common $\geq$G2 toxicities were radiation pneumonitis (RP) (11%) and chest wall pain (6%). Eight patients presented with G2 RP, and in one patient G5 RP could not be excluded (see below). Four patients presented with G2 chest wall pain (CWP) and one patient with G3 CWP, two patients with G2 rib fracture, and one patient with G2 dyspnea. The actuarial rate of $\geq$G2 RP was 9.3% at 12 months post-SABR, and 13.2% at 24 months. For $\geq$G2 CWP, this was 4.0% and 8.5%, respectively. Multivariable analysis (Supplemental Table 2) showed that $\geq$G2 RP was significantly associated with a primary lung tumor (OR 0.11; 95% confidence interval [CI] 0.01–0.97; $p = .047$) and a total lung $V_{35Gy}$ of $\geq$6.5% (OR 10.85; 95% CI 1.93–61.05; $p = .007$).

### *Overall survival*

At a median follow-up of 28.1 months (95% CI 22.6–30.2), median OS for all patients was 35.4 months, with 1- to 5-year survivals being 83.2%, 62.1%, 46.3%, 46.3%, and 38.6% (Figure 2). For patients with unilateral lesions, median OS was 48.3 months, and for patients with bilateral lesions, this was 24.7 months ($p = .068$). For primary lung lesions, median OS was 27.6 months, and for metastatic lung lesions, the median was not reached ($p = .028$). Multivariable analysis revealed that WHO performance status, lesion type, lesion laterality, and history of chemotherapy post-SABR, were all significant predictors for survival (Supplemental Table 2). Dosimetric variables did not show any significant associations for OS on univariable and multivariable analysis.

Thirty-three patients (39%) had died at the time of this analysis. The cause of death was not available in one patient, and the cause was uncertain in three patients. In total, six patients had a pulmonary cause of death, including one patient with severe COPD (GOLD III/IV) and bilateral lesions (in the left upper lobe and right middle lobe) who died of a possible pneumonia. As a RP could not be excluded, this patient was scored as having a grade 5 RP. A possible cardiac-related death was scored for four patients, and one patient underwent euthanasia. Disease progression was the cause of death in 17 patients, and one patient died as a consequence of another primary tumor. Supplemental Table 3 contains details on patients with a pulmonary cause, cardiac cause, or an uncertain cause of death.

## Discussion

In this two-center retrospective analysis, we describe our approach for multi iso-center VMAT in a selected group of patients with multiple lung lesions: 97% of patients had two

or three lesions, and many had small combined target volumes. SABR was associated with a low incidence of severe toxicity, and multivariable analysis revealed that grade 2 and higher RP was significantly higher in patients with primary lung cancers and when the total lung $V_{35Gy}$ ($EQD_2$) was $\geq$6.5%. Patients with primary lung tumors were significantly older ($p < .001$) had a worse WHO performance status ($p = .02$), higher COPD GOLD status ($p < .001$), a higher total PTV ($p < .001$), and total ITV ($p < .001$), which could all be a contributing factor to the higher rate of RP. It should also be noted that there was a strong attempt made during planning to limit low dose irradiation to the contralateral lung, and also region of low dose irradiation in the ipsilateral lung, based on previous data [10].

Detailed descriptions of the use of VMAT-based SABR for multiple lung lesions are lacking in the literature. Although VMAT plans for a single lung tumor can achieve a superior conformity index and lower $V_{45Gy}$ to the chest wall ($p < .05$) compared with other SABR techniques, it could also increase $V_{5Gy}$ to contralateral lung unless preventive steps such as use of an avoidance sector and strong low dose planning objectives [10]. This may be of concern when bilateral tumors are treated as a contralateral MLD >3.6 Gy, and a contralateral lung $V_{5Gy}$ >26% (both uncorrected for fraction size) are recognized risk factors for radiation pneumonitis [9,10]. When VMAT for this patient group initially commenced, our planning focus was on limiting both the contralateral lung doses (for multiple ipsilateral tumors), and for limiting low-dose regions (when bilateral lesions were irradiated). Follow analysis of the present data, we have generated a flowchart for treatment planning that is presently applied at both centers (Supplemental Figure 1).

Although extensive dosimetric limits in patients treated with VMAT-based SABR for multiple lung tumors are unavailable, data on toxicity have been published. One example is a prospective study that included 30 patients with lung oligometastases, treated with 1–7 fractions using CyberKnife, and where 16 patients had two or more lesions [7]. Chronic grade 3 toxicity was seen in 10% of the total cohort of 30 patients, and no grade 4 or 5 toxicity was reported. Another report on 15 patients with NSCLC who underwent subsequent SABR for a second tumor reported grade 3 RP in 7% [15]. Similarly, Rose et al. [16] observed a total rate of 2% for late high-grade pulmonary toxicity after SABR with VMAT in their study group of 60 NSCLC patients with lung metastatic disease (33% of patients had two or more lesions). A pooled analysis of 88 studies, including 7752 patients, reported a significantly higher MLD ($p = .027$) and $V_{20Gy}$ ($p = .019$) for the total lung volume, in patients who developed grade $\geq$2 lung toxicity [17]. However, only a minority of the patients in this report had multiple lesions.

Despite the relatively high proportion of bilateral lesions in our series, the rate of severe pulmonary toxicity was comparable or lower with that reported by others. The high-priority optimization objectives and avoidance sectors may have contributed to the former. For example, in patients treated for unilateral lesions, the highest contralateral MLD was 2.3 Gy ($EQD_2$) and the highest contralateral $V_{5Gy}$ was 13% ($EQD_2$). For all patients in our cohort, the median total lung $V_{5Gy}$ and $V_{20Gy}$ were 25.3% and 8.9% (both $EQD_2$), respectively. Our only patient with possible G5 radiation pneumonitis had a total lung $V_{5Gy}$ of 27% ($EQD_2$) and was known with severe COPD.

Some limitations of our study deserve mention. Most patients (97%) were treated for two or three lesions which limits the generalizability of our results to this patient population. There were also some differences in treatment planning approaches between the two centers at the start of their VMAT/SABR program. In addition, the retrospective scoring of toxicity from review of case notes could have led to under-reporting of toxicity. In 59% of our patients, a pathological diagnosis was not obtained, although all were assessed by a multi-disciplinary tumor board before referral for SABR. Finally, due to the small number of adverse events, findings of our multivariable analysis must be considered preliminary, and requires external validation.

In conclusion, this retrospective descriptive analysis shows that a structured approach achieves low toxicity rates in patients with two or three lung tumors treated with multi iso-center VMAT-based SABR. The clinical benefits of this approach require further investigation in other patient populations.

## Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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## References

[1] Widder J, Klinkenberg TJ, Ubbels JF, et al. Pulmonary oligometastases: metastasectomy or stereotactic ablative radiotherapy? Radiother Oncol. 2013;107:409–413.
[2] Fode MM, Høyer M. Survival and prognostic factors in 321 patients treated with stereotactic body radiotherapy for oligometastases. Radiother Oncol. 2015;114:155–160.
[3] Siva S, Macmanus M, Ball D. Stereotactic radiotherapy for pulmonary oligometastases: a systematic review. J Thorac Oncol. 2010;5:1091–1099.
[4] Chang JY, Liu Y, Zhu Z, et al. Stereotactic ablative radiotherapy: a potentially curable approach to early-stage multiple primary mung cancer. Cancer. 2013;119:3402–3410.
[5] Griffioen GHMJ, Lagerwaard FJ, Haasbeek CJA, et al. Treatment of multiple primary lung cancers using stereotactic radiotherapy, either with or without surgery. Radiother Oncol. 2013;107:403–408.
[6] Lagerwaard FJ, Haasbeek CJ, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2008;70:685–692.
[7] Nuyttens JJ, Verhoef C, Maat A, et al. Stereotactic body radiation therapy for oligometastases to the lung: a phase 2 study. Int J Radiat Oncol Biol Phys. 2015;91:337–343.
[8] Verbakel W, Senan S, Cuijpers JP, et al. Rapid delivery of stereotactic radiotherapy for peripheral lung tumors using volumetric intensity-modulated arcs. Radiother Oncol. 2009;93:122–124.
[9] Bongers EM, Botticella A, Palma DA, et al. Predictive parameters of symptomatic radiation pneumonitis following stereotactic or

hypofractionated radiotherapy delivered using volumetric modulated arcs. Radiother Oncol. 2013;109:95–99.
[10] Ong CL, Palma D, Verbakel WFAR, et al. Treatment of large stage I-II lung tumors using stereotactic body radiotherapy (SBRT): planning considerations and early toxicity. Radiother Oncol. 2010;97:431–436.
[11] Palma DA, Haasbeek CJA, Rodrigues GB, et al. Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (SABR-COMET): study protocol for a randomized phase II trial. BMC Cancer. 2012;12:305.
[12] Underberg RWM, Lagerwaard FJ, Cuijpers JP, et al. Four-dimensional CT scans for treatment planning in stereotactic radiotherapy for stage I lung cancer. Int J Radiat Oncol Biol Phys. 2004;60:1283–1290.
[13] Videtic GMM, Hu C, Singh AK, et al. A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer: NRG Oncology RTOG 0915 (NCCTG N0927). Radiat Oncol Biol. 2015;93–94:757–764.
[14] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996;17:343–346.
[15] Shintani T, Masago K, Takayama K, et al. Stereotactic body radiotherapy for synchronous primary lung cancer: clinical outcome of 18 cases. Clin Lung Cancer. 2015;16:e91–e96.
[16] Rose FD, Cozzi L, Navarria P, et al. Clinical outcome of stereotactic ablative body radiotherapy for lung metastatic lesions in non-small cell lung cancer oligometastatic patients. Clin Oncol (R Coll Radiol). 2016;28:13–20.
[17] Zhao J, Yorke ED, Li L, et al. Simple factors associated with radiation-induced lung toxicity after stereotactic body radiation therapy of the thorax: a pooled analysis of 88 studies. Int J Radiat Oncol Biol Phys. 2016;95:1357–1366.