Original Article

Retrospective analysis of stereotactic ablative radiotherapy (SABR) for metastatic lung lesions (MLLs) in comparison with a contemporaneous cohort of primary lung lesions (PLLs)

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Background: The net benefit from local ablative therapy for pulmonary oligometastases remains unknown. The outcomes of stereotactic ablative radiotherapy (SABR) for metastatic lung lesions (MLLs) were analyzed retrospectively and compared with those of SABR for primary lung lesions (PLLs).

Methods: Medical records of patients treated with lung SABR between 2011 and 2014 were retrospectively reviewed. Basic patient, lesion and treatment characteristics were compared using the Pearson chi-square test for categorical and Mann-Whitney U test for continuous variables. To estimate the rates of local control (LC), progression-free survival (PFS), survival after the first progression post-SABR (SAPF) and overall survival (OS), the Kaplan-Meier method was used, and the differences between groups were assessed by means of the log rank test. The uni- and multivariate Cox proportional hazards regression model was used to identify predictive factors for these endpoints.

Results: Twenty-nine MLLs in 18 consecutive patients and 51 PLLs in 42 patients were treated stereotactically and included in the study. Median follow-up was 14 months (range, 4–40 months). Although patients with MLLs had a significantly better cardiopulmonary function (P=0.0001), more conservative dose-fractionation schedules were prescribed (P=0.0001), but this did not result in a significant difference in LC (P=0.98), PFS (P=0.06) and OS (P=0.14). Multivariate analysis revealed that the dose per fraction (≥ or <12 Gy) was an independent predictor for LC (P=0.02) and PFS (P=0.01) for the whole population, and for PFS (P=0.02) in the PLLs group. Late toxicities ≥ G2 occurred in six patients with PLLs, compared with none in the metastatic group.

Conclusions: SABR for MLLs was as successful as for PLLs with respect to LC and OS with lower long-term toxicity in patients with MLLs. Dose per fraction ≥12 Gy turned out to be an independent, favorable prognostic factor.

Keywords: Lung cancer; stereotactic ablative radiotherapy (SABR); lung metastases; oligometastatic state

Submitted Nov 13, 2016. Accepted for publication Feb 09, 2017.
doi: 10.21037/jtd.2017.03.07
View this article at: http://dx.doi.org/10.21037/jtd.2017.03.07

Introduction

Based on conceptual theories of breast cancer growth and dissemination, Hellman and Weichselbaum inferred the existence of a clinically and biologically relevant group of oligometastatic patients, in whom aggressive local therapy may prolong survival and even be a curative treatment option (1). The incentive for using stereotactic ablative radiotherapy (SABR) for metastatic lung lesions (MLLs) came from favorable results of surgical removal of oligometastases in different types of solid tumors (2). High rates of survival in treated compared with untreated patients have also been demonstrated for lung metastasectomy (3). However, the temporal and locational burden of oligometastatic state remains blurred and diffuse and—until now—no clear guidelines have been defined for the selection of patients who would really benefit from local ablative treatment.

During the past decade, SABR emerged as a new standard of care for medically inoperable patients with early stage non-small-cell lung cancer. For oligometastatic diseases the benefit from SABR has been extrapolated from the experience with primary lung lesions (PLLs). However, patients with MLLs represent a clinically and biologically distinct population regarding the different clinical basic characteristics and the biology of the already disseminated cancer, therefore the efficacy and safety of SABR would not be expected to be identical to that of patients with PLLs. In this population, the progression-free survival (PFS) remains the crucial endpoint. There is some evidence that cancer metastases themselves may become the source of additional metastases (4). Patients with MLLs may gain benefit from a high local control (LC) of their oligometastases, if they are at a very low risk to develop further distant metastases (5). There have been a few studies that addressed the issue of comparison between MLLs and PLLs patients (5-8). In contrast to them, lung lesions of pulmonary origin, i.e., metastases from lung cancer were strictly excluded from the MLLs group. Also, the presented study provides a more holistic approach by analyzing a multitude of patient-, lesion- and treatment-related factors, which potentially determine the treatment outcome.

Methods

Patients

A positive statement of the local ethics committee (Ärztekammer des Saarlandes) was obtained prior to the data acquisition with the need for approval being waived due to use of anonymized data only. Between October 2011 and October 2014, we identified 80 lesions in 60 patients with lung tumors, who were consecutively treated with SABR after informed consent. All patients had previously been discussed by a multidisciplinary tumor board with a final consensus decision for lung SABR. Three patients were lost to follow-up and excluded, leaving a total of 28 lesions in 17 patients with lung metastases and 49 lesions in 40 patients with primary lung cancer which were retrospectively analyzed.

MLLs were defined as the presence of a new or an enlarging nodule or mass detected on routine chest imaging during the regular follow-up of a previously treated primary cancer (except for primary lung cancer, germ cell tumors and hematological malignancies). In 13 of 17 (76.5%) patients, the diagnosis of MLLs was based on computed tomography (CT), and confirmed with biopsy in only two patients. In two other patients, the MLLs were diagnosed based on positron-emission-tomography-computed tomography (PET-CT). Ten inoperable patients with metastatic disease were considered as ineligible for either first-line or continuation of chemotherapy. Two patients with renal cell cancer (RCC), who had previously undergone pulmonary metastasectomy, refused further surgical resection for recurrent metastases in a different lung lobe. The majority of patients had one or two lung lesions (n=8; n=6, respectively), only three patients presented with three metastases. Two patients later received a second SABR for metachronous recurrent lesions. The primary tumors in the patients with MLLs were head and neck cancer (n=2), colorectal cancer (n=7), RCC (n=2), urothelial cancer (n=1), breast cancer (n=2), ovarian cancer (n=1), endometrial cancer (n=1) and sarcoma (n=1). At the time of SABR delivery, all these primary tumors were locally controlled, and all patients except for two patients with additional liver and brain metastases, which were simultaneously treated with liver and brain SABR—had no further extrathoracic manifestations.

PLLs were defined as a malignant lesion of pulmonary origin, i.e., either a first diagnosis of histologically proven or suspected non-small-cell lung cancer or pulmonary metastases in the context of a prior diagnosis of non-small-cell lung cancer. All cases of PLLs were either medically or technically inoperable. Twelve of 40 patients with PLL had a previous history of a primary lung cancer and were considered as recurrent (either locally or at a distant intrathoracic site), in five of whom the cancer was histologically proven, whereas in seven the diagnosis was based on CT (n=2) or PET-CT criteria (n=5). In this subgroup three patients recurred as multiple recurrent lung cancer (3 lesions, n=1; 2 lesions,

n=2). Twenty eight patients with PLLs were *de novo*, in 24 of whom the cancer was histologically proven, whereas in 4 the diagnosis was based on PET-CT criteria. In five of these *de novo* cases, the disease manifested initially as multiple primary lung cancer (each had two lesions). FDG-PET staging was available in 36 patients with PLLs. In two patients with histologically proven PLLs, there was no pathologic metabolism on PET-CT.

Treatment technique

The treatment technique was previously described elsewhere (9). Each patient was immobilized in supine position in a dual vacuum BodyFIX system (Medical Intelligence, Schwabmuenchen, Germany). Planning CT scan of the chest was acquired with a 16-slice 4D-spiral-CT (Brilliance CT Big Bore, Philips, Best, The Netherlands). Gross tumor volume (GTV) was defined as the maximum intensity projection at each voxel during the entire respiratory cycle and was contoured in all ten phases. The GTVs were fused to create the internal target volume (ITV). The planning target volume (PTV) was generated by adding 5 mm to ITV in all directions. SABR treatment plans were created in the Philips Pinnacle^{3}™ treatment planning system (TPS) v.08 and v.09 (Philips, Best, The Netherlands) using 6 MV photons. The dose distributions were calculated with a collapsed cone algorithm for heterogeneity corrections. Dose-volume-histograms were evaluated according to the dose-constraints suggested by the AAMP Task Group 101 (10). Patient alignment was verified by means of kV cone beam CT (CBCT) before each treatment. Translational set-up uncertainties up to 3 mm and rotations up to 3 degrees were tolerated.

Three-dimensional conformal treatment (3D) plans were used in 50 lesions, and intensity-modulated radiation therapy (IMRT) in 27 lesions. Routinely, three fractions of SABR were administered per week with a minimum interval between fractions of 40 hours. Different dose-fractionation schemes were applied with a median dose per fraction (prescribed to the isodose surrounding the PTV) of 12 Gy (range, 3.6–18 Gy) and a total dose of 48 Gy (range, 25–60 Gy) in 4 fractions (range, 3–10 fractions) delivered in 9 days (range, 5–23 days). The most common dose-fractionation schedules were 4×12 Gy (n=21), 5×12 Gy (n=15) and 8×7.5 Gy (n=12).

Endpoints and follow-up

Endpoints of this retrospective study were PFS, LC, SAFP, OS, timing and location of treatment failure, and treatment related late toxicity.

Six weeks after SABR, all patients underwent clinical examination and chest-CT. Then, they were followed every 3 months in the first 2 years, and every 6 months thereafter. PET-CT was performed only in case of differential diagnosis between recurrence and radiation-induced consolidation. Toxicity was assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analysis

Time to any of the pre-defined events was calculated from the first day of SABR to the date of an event. Data were censored, when the patients showed no evidence of an event at their last follow-up during the period of analysis. Furthermore, survival after the first progression post-SABR (SAPF) was calculated from the date of the diagnosis of the first disease progression after SABR treatment to the date of the death or the loss of follow-up. For between-group comparison, the Pearson chi-square test was used for categorical and Mann-Whitney test for continuous variables. To estimate the rates of local failure, PFS and OS, the Kaplan-Meier method was used, and the differences between groups were compared by means of the log-rank test.

The uni- and multivariate Cox proportional hazards regression model was used to identify prognostic factors for endpoints. Tumor and treatment-related factors were used to assess the PFS and LC, whereas clinical factors were used to assess SAFP and OS. In the multivariate analysis, a stepwise selection of covariates was done and all predictors with P value <0.10 were retained in the final model. Continuous variables were dichotomized at the median value, or converted into categorical variables. Hazard ratio and the 95% confidence interval were also reported. All statistical tests were 2-sided, and P value <0.05 was considered significant. Data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

There was no difference between groups regarding age, gender, pre- and post-SABR lung local treatment (surgery, irradiation), post-SABR chemotherapy and cardiovascular disease (CVD). However, patients in the MLLs group had a significantly higher Karnofsky performance status (KPS) (P=0.01). Pretreatment lung function variables

including forced expiratory volume during the first second (FEV_1), diffusion capacity of the lung for carbon monoxide (DLCO) and the need of supplemental oxygen were also significantly better in patients with MLLs. There was a higher percentage of chronic obstructive pulmonary disease (COPD) in the PLLs group (75% *vs.* 12%, P=0.001). This difference remained significant, when COPD + CVD were considered as one variable (P=0.001). All patient basic characteristics are illustrated in *Table 1*.

Lesion characteristics

There was a significant difference between MLLs and PLLs regarding the method by which the diagnosis was established (biopsy *vs.* PET *vs.* CT, P=0.0001), the histological type of cancer (squamous cell *vs.* adenocarcinoma *vs.* others, P=0.004), the anatomic location (P=0.003) and the topography of tumor in relation to organs at risks (OARS) (peripheral *vs.* parenchymal *vs.* central, P=0.002). Furthermore, GTV as a continuous or categorical variable was not significantly different between groups. The

Table 1 Patients characteristics

Variable	Total, n=57 (%)	Patients with primary lesions, n=40 (%)	Patients with metastatic lesions, n=17 (%)	P value* (level of significance)
Age at diagnosis (years)				
Median	69.0	68.1	71.0	
Range	44–86	55–84	44–86	
Mean	67.8	68.1	66.9	0.84
Age dichotomized (No.)				
≥70 years	28 [49]	18 [45]	10 [59]	
<70 years	29 [51]	22 [55]	7 [41]	0.34
Gender				
Male	35 [61]	25 [62]	10 [59]	
Female	22 [39]	15 [38]	7 [41]	0.79
Performance status KPS				
>70%	37 [65]	22 [55]	15 [88]	
≤70%	20 [35]	18 [45]	2 [12]	0.01
Pretreatment lung function				
FEV_1 in (% of predicted)				
Available	52 [91]	39 [97]	13 [76]	
Not available	5 [8]	1 [3]	4 [24]	0.01
Median	57.5	49	90	
Range	18–128	18–128	40–116	
Mean	62.8	54.2	88.6	0.0001
FEV_1 dichotomized				
≤40%	13 [25]	12 [30]	1 [7]	
>40%	39 [75]	27 [70]	12 [93]	0.09

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Total, n=57 (%)	Patients with primary lesions, n=40 (%)	Patients with metastatic lesions, n=17 (%)	P value* (level of significance)
DLCO (% of predicted)				
Available	32 [56]	26 [65]	6 [35]	
Not available	25 [44]	14 [35]	11 [65]	0.04
Median	48	41	68	
Range	14–137	14–84	57–137	
Mean	47.8	40.5	79.3	0.002
DLCO dichotomized				
>40%	19 [57]	13 [50]	6 [100]	
≤40%	13 [43]	13 [50]	0 [0]	0.03
O_2-supplementary				
Yes	13 [23]	13 [32]	0 [0]	
No	44 [77]	27 [68]	17 [100]	0.007
Comorbidity				
CVD				
Yes	25 [44]	20 [50]	5 [29]	
No	32 [66]	20 [50]	12 [71]	0.15
COPD				
Yes	32 [66]	30 [75]	2 [12]	
No	25 [44]	10 [25]	15 [88]	0.0001
Cardiopulmonary dysfunction				
Both CVD + COPD	13 [23]	12 [30]	1 [6]	
One of them	31 [64]	26 [65]	5 [29]	
None	13 [23]	2 [5]	11 [65]	0.0001
Pre-SABR chemotherapy				
Yes	24 [42]	12 [30]	12 [70]	
No	33 [68]	28 [70]	5 [30]	0.005
Post-SABR chemotherapy				
Yes	21 [37]	13 [32]	8 [47]	
No	36 [63]	27 [68]	9 [53]	0.29
Pre and post-SABR				
Both pre and post-SABR	13 [23]	7 [16]	6 [35]	
One of them	19 [33]	11 [28]	8 [47]	
None	25 [44]	22 [54]	3 [18]	0.03

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Total, n=57 (%)	Patients with primary lesions, n=40 (%)	Patients with metastatic lesions, n=17 (%)	P value* (level of significance)
Previous lung surgery				
Yes	14 [25]	8 [20]	6 [35]	
No	43 [75]	32 [80]	11 [65]	0.22
Previous lung irradiation				
Yes	5 [9]	5 [14]	0 [0]	
No	52 [91]	35 [86]	17 [100]	0.12
Pre-SABR lung local treatment				
Both surgery and irradiation	2 [4]	2 [6]	0 [0]	
One of them	15 [26]	9 [22]	6 [35]	
None	40 [70]	29 [72]	11 [65]	0.42
Post-SABR lung surgery				
Yes	3 [5]	2 [5]	1 [6]	
No	54 [95]	38 [95]	16 [94]	0.81
Post-SABR lung irradiation				
Yes	5 [9]	2 [5]	3 [18]	
No	52 [91]	38 [95]	14 [82]	0.12
Post-SABR lung local treatment				
Both surgery and irradiation	1 [2]	0 [0]	1 [6]	
One of them	6 [10]	4 [10]	2 [12]	
None	50 [88]	36 [90]	14 [82]	0.29
No. lesion per patient	1.4	1.2	1.7	0.01
No. of treated lesions				
Single lesion	40 [70]	32 [80]	8 [47]	
More than one	17 [30]	8 [20]	9 [53]	0.01

*, pearson chi-square test for categorical and Mann-Whitney U test for continuous variables. KPS, Karnofsky performance status; FEV_1, forced expiratory volume during the first second; DLCO, diffusing capacity of the lung for carbon monoxide; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; SABR, stereotactic ablative radiotherapy.

lesions' characteristics are shown in *Table 2*.

Treatment characteristics

Time interval, calculated from the date of first diagnosis of MLLs or PLLs to the first day of SABR, treatment duration, number of fractions and treatment planning techniques were not significantly different between groups. Although PTV volume was not significantly different between MLLs and PLLs, MLLs were—on average—treated with more conservative SABR-regimens with respect to total dose (P=0.001) and BED_{10} <105 (P=0.0001). The dose-fractionation in MLL-patients, in whom the toxicity and benefit were at that time unclear, has been more conservative. Further treatment characteristics are highlighted in *Table 3*.

Table 2 Characteristics of lesions

Variable	Total, n=77 (%)	PLLs, n=49 (%)	MLLs, n=28 (%)	P value* (level of significance)
Diagnostic method				
Biopsy proven	36 [47]	33 [68]	3 [11]	
PET-CT criteria	14 [18]	12 [24]	2 [7]	
CT criteria	27 [35]	4 [8]	23 [82]	0.0001
Histologic type				
Squamous cell carcinoma	24 [31]	21 [43]	3 [11]	
Adenocarcinoma	37 [48]	17 [34]	20 [71]	
Others	16 [21]	11 [23]	5 [18]	0.004
Anatomic location				
Left upper lobe	11 [14]	11 [23]	0 [0]	
Left lower lobe	6 [8]	2 [4]	4 [14]	
Right upper lobe	27 [35]	18 [37]	9 [33]	
Right middle lobe	7 [9]	1 [2]	6 [21]	
Right lower lobe	16 [20]	12 [24]	4 [14]	
Left hilum	4 [6]	1 [2]	3 [11]	
Right hilum	6 [8]	4 [8]	2 [7]	0.003
OARS related location				
Peripheral	40 [51]	33 [68]	7 [25]	
Parenchymal	24 [32]	11 [23]	13 [47]	
Central	13 [17]	5 [9]	8 [28]	0.002
GTV				
Median	8.1	9.9	5.7	
Range	0.5–55.6	0.5–55.6	0.8–47.8	
Mean	11.6	12.7	9.7	0.13
GTV dichotomized				
≥14 mL	25 [32]	19 [39]	6 [21]	
<14 mL	52 [68]	30 [61]	22 [79]	0.11
Pretreatment SUV_{max}				
Available	48 [82]	43 [88]	5 [18]	
Not available	29 [38]	6 [12]	23 [82]	0.0001
Median	6.9	7.2	5.4	
Range	0–23	0–23	2.5–13.7	
Mean	8.5	8.7	8.7	0.51
Pretreatment SUVmax				
<6.9	24 [50]	20 [46]	4 [80]	
≥6.9	24 [50]	23 [54]	1 [20]	0.15

*, pearson chi-square test for categorical and Mann-Whitney U test for continuous variables. PLLs, primary lung lesions; MLLs, metastatic lung lesions; PET, positron emission tomography; CT, computed tomography; OARS, organs at risks; GTV, gross tumor volume; SUV_{max}, maximal standardized uptake volume.

Table 3 Treatment characteristics

Variable	Total, n=77 (%)	PLLs, n=49 (%)	MLLs, n=28 (%)	P value* (level of significance)
Interval between the first diagnosis and the start of SABR (in days)				
Median	48.0	48.0	52.0	
Range	14–170	14–170	20–141	
Mean	57.2	57.9	56.0	0.79
Interval dichotomized				
≤48 days	39 [51]	26 [54]	13 [47]	
>48 days	38 [49]	23 [46]	15 [53]	0.57
SABR duration (in days)				
Median	9.0	9.0	7.0	
Range	5–23	5–23	5–19	
Mean	9.6	10.0	8.9	0.12
SABR duration dichotomized				
<9 days	37 [48]	23 [46]	14 [50]	
≥9 days	40 [52]	26 [54]	14 [50]	0.79
No. of fractions				
Median	5.0	5.0	5.0	
Range	3–10	3–10	3–8	
Mean	5	5.4	4.3	0.03
No. of fractions dichotomized				
<5 fractions	35 [45]	22 [45]	13 [47]	
≥5 fractions	42 [55]	27 [55]	15 [53]	0.89
Dose per fraction in Gy				
Median	12	12	12	
Range	3.6–18	3.6–18	5–12.5	
Mean	10.2	10.4	9.9	0.86
Dose per fraction dichotomized				
≥12 Gy	46 [60]	30 [61]	16 [57]	
<12 Gy	31 [40]	19 [39]	12 [43]	0.72
Total dose in Gy				
Median	48	48	36	
Range	25–60	30–60	25–60	
Mean	47.9	52	40.5	0.001
Total dose dichotomized				
≤48 Gy	49 [64]	26 [53]	23 [82]	
>48 Gy	28 [36]	23 [47]	5 [18]	0.01

Table 3 (*continued*)

Table 3 (*continued*)

Variable	Total, n=77 (%)	PLLs, n=49 (%)	MLLs, n=28 (%)	P value* (level of significance)
Prescription isodose line				
80–95%	60 [78]	48 [98]	12 [43]	
60–65%	17 [22]	1 [2]	16 [57]	0.0001
BED_{10} (peripheral)				
Median	105	105	79	
Range	37–151	48–151	37–132	
Mean	97.2	105.8	82	0.0001
BED_{10} dichotomized				
≥105 Gy	48 [62]	41 [84]	7 [25]	
<105 Gy	29 [38]	8 [16]	21 [75]	0.0001
Treatment planning technique				
3D conformal	50 [65]	33 [67]	17 [60]	
IMRT	27 [35]	16 [33]	11 [40]	0.56
PTV volume in mL				
Median	27	29	20	
Range	4–147	5–147	4–98	
Mean	33.8	37	28	0.12

*, pearson chi-square test for categorical and Mann-Whitney U test for continuous variables. PLLs, primary lung lesions; MLLs, metastatic lung lesions; SABR, stereotactic ablative radiotherapy; BED_{10}, biologic effective dose at α/β=10 Gy; 3D, three dimensional; IMRT, intensity-modulated radiation therapy; PTV, planning target volume.

Temporal and locational distribution of the first disease progression

With a median follow-up of 14 months (range, 4–40 months), progression occurred in 22 of 49 (45%) PLLs compared with 18 of 28 (64%) MLLs (P=0.1). However, there was a significant difference in the time to progression between groups (P=0.003) with a median onset of 8 months (range, 6–24 months) in PLLs compared with 4.5 months (range, 1–26 months) for MLLs. There was no significant difference between MLLs from colorectal cancer and non-colorectal cancer (P=0.2) and between PLLs of squamous *vs.* non-squamous histology (P=0.29). The difference in progression was independent of the type of PLLs (*de novo vs.* recurrent, P=0.06).

The locational distribution of progression was also significantly different between groups (P=0.01). Whereas all types of progression were seen in PLLs, the pattern of failure in MLLs was mainly distant, either isolated or combined with local recurrence (LR). Post-SABR, the lung parenchyma was the predominant site for distant failure in both groups. In only two patients with MLLs and a prior history of extrapulmonary manifestations, additional metastases occurred in the brain from breast cancer and in the liver from colorectal cancer. In the PLLs groups, isolated extrapulmonary distant failure occurred in four patients (liver, n=1; bone, n=2; adrenal gland, n=1).

The main salvage treatment after first progression post-SABR in the MLL-group was chemotherapy (n=7) and a second course of SABR (n=2). In the PLLs patients, salvage chemotherapy was administered in seven patients and nine patients received no further treatment or best supportive care, respectively. The difference in receiving salvage treatments after the first progression was also significant (P=0.005). There was a significant difference regarding the percentage of deceased patients after the first progression post-SABR (75% for PLL *vs.* 34% for MLL, P=0.041).

LR was diagnosed in 11 PLLs and 6 MLLs (P=0.9). With

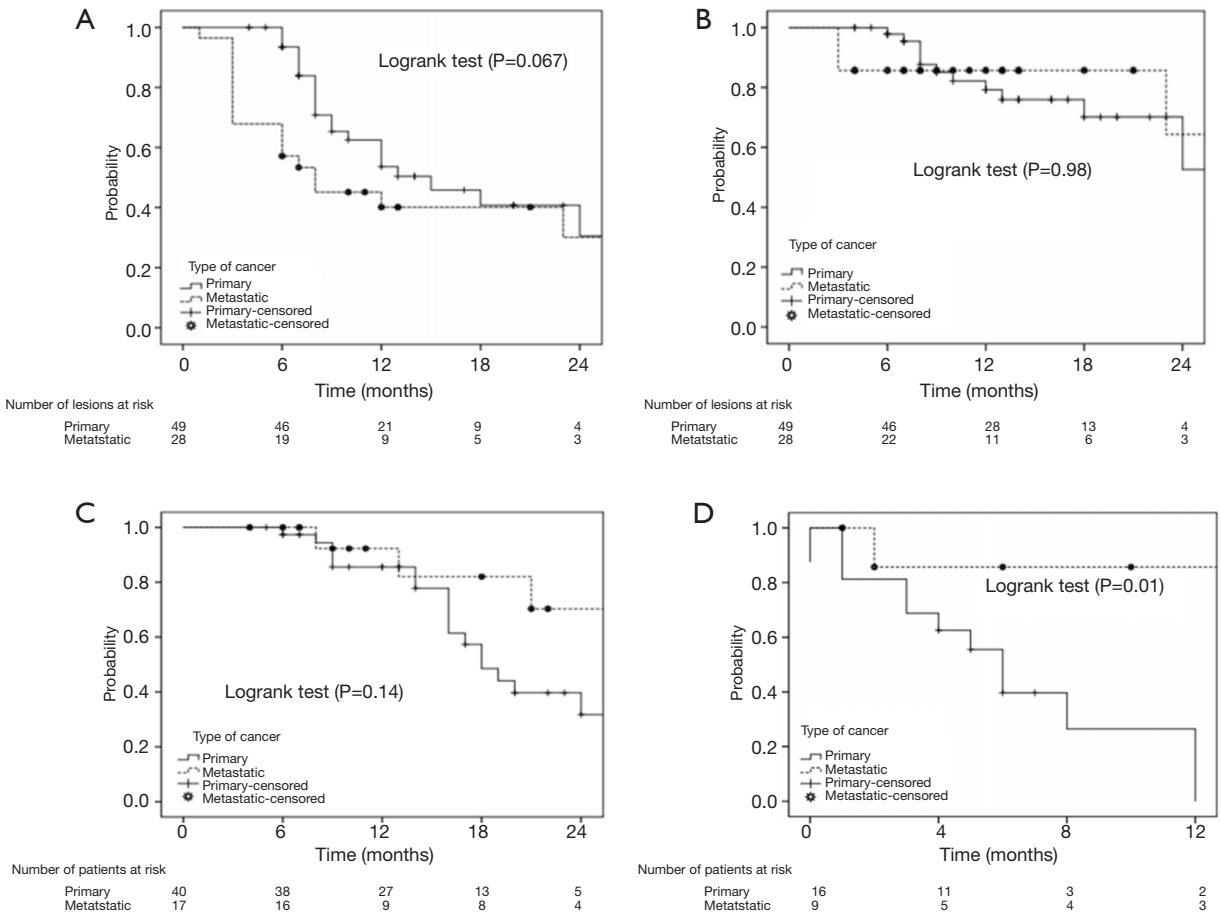

Figure 1 Kaplan-Meier survival curves stratified by the origin of lesions [primary lung lesions (PLLs) *vs.* metastatic lung lesions (MLLs)]. (A) Progression-free survival (PFS) for PLLs compared with MLLs; (B) local control (LC) rate for PLLs compared with MLLs; (C) overall survival (OS) in patients with PLLs compared with those with MLLs; (D) survival after the first progression after "stereotactic ablative body radiotherapy" (SABR) in patients with PLLs compared with those with MLLs.

a median onset of 9 months (range, 6–24 months) for PLLs and 3 months (range, 3–26 months) for MLLs, there was no significant difference in the time until LR (P=0.22) The diagnosis was based on biopsy in one patient with PLLs, PET-CT in 3 PLLs *vs.* 2 MLLs, and CT in 7 PLLs and 4 MLLs.

LC and PFS

The actuarial 1- and 2-year LC rates were 79.3% (95% CI: 66.4–92%) and 52.6% (95% CI: 20.3–85%) in PLLs compared with 85.7% (95% CI: 72.8–98.7%) and 64.3% (95% CI: 26.7–85.4%) in MLLs, P=0.25 and P=0.47 respectively. There was no significant difference in the LR free survival (log-rank, P=0.98) (*Figure 1*).

The actuarial 1- and 2-year PFS rates were 53.6% (95% CI: 37.5–69.6%) and 30.5 % (95% CI: 9–52.4%) in PLLs compared with 40% (95% CI: 20.9–59.3%) and 30% (95% CI: 8–52.4%) in MLLs, P=0.37 and P=0.48. There was no significant difference in the PFS (log-rank, P=0.06) (*Figure 1*).

In the multivariate analysis, only dose per fraction (> or <12 Gy) was an independent prognostic factor for both LC (HR =0.09, 95% CI: 0.01–0.76, P=0.02) and PFS (HR =0.12, 95% CI: 0.02–0.61, P=0.01) for all patients, and remained predictive for PFS for the PLLs subgroup (HR =0.14, 95% CI: 0.02–0.8, P=0.02). No prognostic factors in the subgroup analysis for LR were found.

Survival after the first progression post-SABR and OS

MLLs patients had significantly better survival after

progression post-SABR as compared to PLLs patients (log-rank, P=0.01) (*Figure 1*). The actuarial 6-month SAFP was 45% (95% CI: 17.3–73%) in PLLs patients and 85.7% in MLLs patients (95% CI: 59.8–100%), P=0.37.

There was no difference between groups regarding the median OS (log-rank, P=0.14) (*Figure 1*). The 1- and 2-year OS rates were 85.5% (95% CI: 73.8–97.3%) and 39.6% (95% CI: 20.2–59%) in PLLs compared with 92.3% (95% CI: 77.8–100%) and 70% (95% CI: 41–99%), P=0.5 and P=0.09 respectively.

In the multivariate analysis, the gender was the only predictive factor for longer SAFP (HR =0.16; 95% CI: 0.02–0.89; P=0.036). For the whole population, the need for supplemental oxygen (HR =3.48; 95% CI: 1.26–9.56; P=0.016) was an independent predictive factor for worse OS.

To get more insight and entire view, univariate and multiple explorative statistical analyses including more than 45 covariates have been performed in addition. The interested reader is referred to supplementary appendix online (*Tables S1-S7*, *Figures S1-S7*).

Late toxicity

Adverse events after 90 days post-SABR occurred in six patients (10%) with PLLs. No long-term toxicity (grade ≥2) was observed in the MLLs group. There was a correlation between clinical symptoms and macroscopic damages caused in radiation in three of them (rib fracture, bronchial necrosis and radiation pneumonitis), whereas the other three toxicities were rather related to COPD exacerbation (dyspnea) (*Table 4*,*Figure 2*). Due to the low incidence of radiation pneumonitis, no DVH analysis was performed.

Discussion

The net benefit from SABR for MLLs remains unclear and has been basically extrapolated from the experience with early stage lung cancer. Patients with MLLs were frequently included in series on SABR for primary lung cancer, making the interpretation of treatment impact on the outcomes of SABR for this population difficult. Conversely, PLLs were also included in studies for MLLs. In a recent published systematic review (11), all five studies on stereotactic radiosurgery included lesions of pulmonary origins with a median percentage of 34% (range, 6–51%), and 11/13 studies of SABR included such lesions with a median percentage of 22% (range, 8–62%).

There have been a few studies that addressed the issue of comparison between MLL and PLL patients. Wulf *et al.* (5) compared the outcomes of 51 MLLs with that of 20 PLLs and found no difference in LC, freedom from systematic progression and OS. In another study from the same institution (6), where 118 MLLs were compared with 41 PLL, there was no difference in LC and OS at 3 years. Takeda *et al.* (7) compared the outcomes of 44 MLLs from colorectal cancer and other primary cancers with 115 PLLs, and found worse LC rate for MLLs compared with PLLs (P=0.001), and in the subgroup analysis worse LC for MLLs form colorectal cancer compared with MLLs of other origins. Similar results were found in another study (8), in which the LC between MLLs and PLLs was significantly different (P=0.01), and the difference in LC for MLLs from colorectal cancer was significant (P=0.022). In the presented study, LR occurred in lung metastases from ovary (n=2), sarcoma (n=2), and head and neck cancer (n=2).

The locational distribution of the treatment failure are compared with published literature and illustrated in *Table S7*. In our study, the lung parenchyma was the common site for the first new metastases post-SABR. Milano and colleagues (12) reported in detail the patterns of recurrence after curative-intent radiation of oligometastases confined to one organ and found that the first new metastases in patients with MLLs occurred in the lung parenchyma (40% compared with 27% in a distant organ) with a median onset of 6 months (range, 3–69 months).

In concordance with the policy of other institutes (13,14) and because of the unknown toxicity and efficacy of SABR for oligometastases at the time of SABR implementation in our institute, more conservative dose-fractionation schedules were used for this cohort. Now in the absence of severe toxicity, and similar efficacy of SABR, we are moving toward treating MLLs and PLLs with the same dose-fractionation schedule.

Onishi *et al.* (15) from Japan were the first who described the SABR-thoracic dogma of BED_{10} >100 Gy as prerequisite for better LC for primary lung cancer. This concept was confirmed by another study (6), and extrapolated for MLLs (8,16). However, this dogma is based on chi-square test (15) and log rank (6) univariate analysis and remains therefore controversial (17). In a meta-analysis (18), the OS for medium BED_{10} (range, 83.2–105 Gy) was even as high as for medium to high BED_{10} (range, 106–146 Gy). Notwithstanding, our data showed similar dose-relationship on the univariate analysis. BED_{10} >105 Gy was found to be a significant predictor for PFS for the whole population (HR =0.43; 95% CI: 0.23–0.81; P=0.01) and for LC in the patients with PLLs

Table 4 Characteristics of patients with late adverse events ≥ G2

Pat. ID	1	3	7	26	51	55
type/grade	Chest wall pain G2	Dyspnea G3	Dyspnea G3	Necrosis G3; stenosis G3	Dyspnea G3	Dyspnea G4
Age (years)	62	73	71	63	77	71
Gender	Male	Male	Male	Male	Male	Female
Symptoms at baseline	Chest wall pain G1 after lung surgery	Dyspnea G2 by COPD stage III	Dyspnea G2 by CVD and COPD stage II	Dyspnea G3 by COPD stage IV	None	Dyspnea G3 by COPD stage IV
Previous treatments	Lung surgery, chemotherapy	Lung surgery	None	None	None	None
Post-SABR treatments	None	Chemotherapy	Chemotherapy, lung irradiation	None	None	Endoscopic lung volume reduction
Type of cancer	Primary	Primary	Primary	Primary	Primary	Primary
Cancer location	Right LL, peripheral	Right UL and LL, peripheral	Right LL, peripheral	Right Hilary, central	Right and left UL, peripheral	Right UL, peripheral
PTV volume	24.3 mL	31.3 mL, 33 mL	29.4 mL	89 mL	20 mL, 24 mL	8 mL
Treatment schedule	5×12 Gy	Each 8×7.5 Gy	5×12 Gy	8×7.5 Gy	4×12 Gy	8×7.5 Gy
BED_3	300	210	300	210	240	210
Onset in month	24	6	6	7/9	6	3
Changes during follow-up	Stabilization, alive	Worsening, died 1 year later	Improvement, died 14 months later	Worsening, died 7 months later	Improvement, alive	Improvement, alive
Dosimetric evaluation	Chest wall: D_{mean}=24 Gy; D_{max}=73 Gy; dorsal 8; Rib: D_{mean}=30 Gy; D_{max}=68.9 Gy	V5=32%; V10=24%; V20=12%; MLD=7.7 Gy; 750 mL >10 Gy; 500 mL >15 Gy	V5=25%; V10=17%; V20=6%; MLD =5 Gy; 750 mL >6 Gy; 500 mL >10 Gy	Main and intermediate bronchus: D_{max}=74 Gy; D_{mean}=58 and 65 Gy respectively	Left lung: V5=25%; V10=14%; V20=6%; MLD=4.5 Gy; Right lung:V5=14%; V10=10%; V20=6%; MLD =4 Gy	Right lung: V5=12%; V10=10%; V20=6%; MLD =3.2 Gy
Risk assessment	Rib fracture correlated with D_{max}=68.9 Gy was seen on chest CT	No lung consolidation on chest-CT. Decline in PFT (FEV_1% decreased by 35% from 41% to 27%). At the onset cancer progression and exacerbation of COPD	Minimal lung consolidation on chest CT. Decline in PFT (FEV_1% decreased by 33% from 54% to 36%). COPD exacerbation at the onset	Necrosis correlated with D_{max}; large tumor volume; entire main and intermediate bronchus within PTV; secondary atelectasis in middle lobe	Dyspnea correlated with interstitial consolidation within radiation field in both right and left lung lobe	No sign of lung consolidation within radiation field; COPD exacerbation, decline in DLCO by 28% (from 22% to 15.8%) but no changes in FEV_1%
Interventions	Occasionally non-opioid pain medication	Hospitalization permanente O_2 supplementary, inhaltive drugs	Hospitalization, inhaltive drugs, and O_2 supplementary	Hospitalization, endoscopic debridement removing	Hospitalization, inhalative drugs, and cortison treatment	Hospitalization, endoscopic lung volume reduction

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; LL, lower lobe; UL, upper lobe; PTV, planning target volume; BED_3, biologic effective dose at α/β=3 Gy; D_{mean}, mean dose; D_{max}, maximal dose; Vn, P% the percentage of organ volume that received n Gy; MLD, mean lung dose; CT, computed tomography; PFT, pulmonary function test; FEV_1, forced expiration at the first second; DLCO, diffusing capacity of the lung for carbon monoxide; COPD, chronic obstructive pulmonary disease.

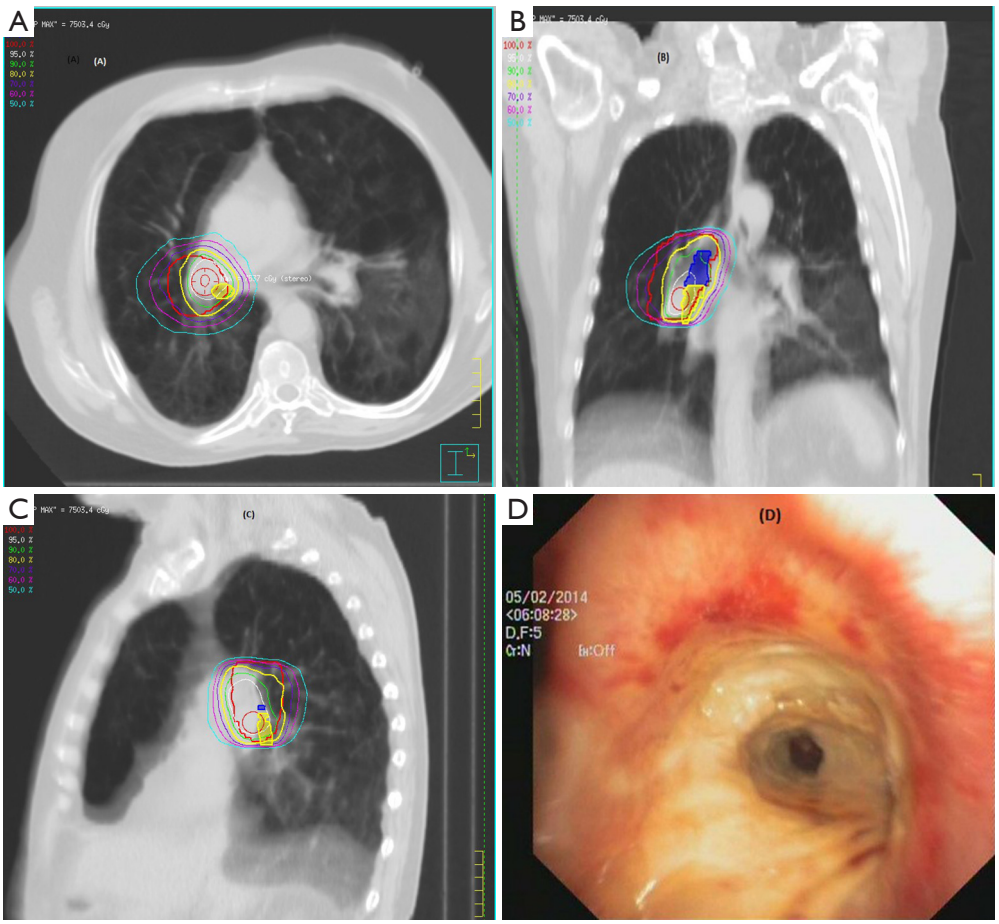

Figure 2 Transversal, coronal and sagittal slices of the treatment planning computer tomography and corresponding endoscopic finding in the patient who developed bronchial necrosis after SABR for the central primary lung lesions (PLLs) in right hilum. Transversal (A) coronal (B) and sagittal (C) slices showed that a significant portion of the right main bronchus (blue) and the right intermediate bronchus (yellow) were within the planning target volume (PTV) and received dose maximum of more than 70 Gy. In the distal right main bronchus (D), the bronchoscopy revealed an area of hypervascularization above a circular area of necrosis that was located in the main right intermediate bronchus and lemon-yellow discolored necrotic cartilage.

(HR =0.18; 95% CI: 0.05–0.68; P=0.01). Furthermore, the PFS in the patients with MLLs was significantly better with increased BED_{10} as continuous variable (HR =0.97; 95% CI: 0.94–0.99; P=0.02). Multivariate analysis revealed the dose per fraction (≥ or <12 Gy) was an independent predictor for LC (P=0.02) and PFS (P=0.01) for the whole population, and for PFS (P=0.02) in the PLLs group. Indeed, there is evidence that LC may be improved with higher fractional dose. In a dose-escalation series on patients with lung and liver metastases (19), the LC was improved on the uni- and multivariate analysis with greater nominal dose, i.e., with greater dose per fraction, since the number of fractions remained constant. A similar observation was reported in patients with hepatocellular carcinoma (20). Timmerman *et al.* (21) observed in a dose-escalation study on early-staged primary lung cancer no treatment failures in patients treated with a dose greater than 18 Gy/fraction. Similarly, PLLs in the Stage IB were locally better controlled, when the dose was escalated from 10 to 12 Gy/fraction (22). In another study (23) on pulmonary and hepatic metastases from RCC and malign melanoma, Log rank comparison revealed dose per fraction (>11 *vs.* <11 Gy/fraction, P<0.01) to be significant predictors of LC. Similar results were reported in another study on metastatic RCC (24), in which a univariate analysis revealed dose per fraction ≥9 Gy (HR =0.631; 95% CI, 0.429–0.931; P=0.021) to be predictive factor for

radiographic LC. The dose per fraction ≥9 Gy (HR =0.396; 95% CI, 0.163–0.962; P=0.042) was a significant predictor for clinical LC in another report as well (25). These data support the concept that a dose per fraction >10 Gy may independently of the histological type of the cancer induce severe vascular damage leading to indirect cell death (26).

The toxicity results are consistent with the published literature even for central MLLs (27). The most serious SABR complication in our study was a bronchial necrosis. Indeed, radiation necrosis has been infrequently reported in SABR-literature. There are other three cases of bronchial necrosis that resulted in different clinical scenarios, i.e., fatal hemoptysis (28), atelectasis (29) and bronchial fistula formation (30). Regarding the difficulty to distinguish SABR complications from those of exacerbation of cardiopulmonary comorbidity, the reader is referred to our previous discourse on this issue (31).

Our study had several limitations including the inherent risk of bias due to its retrospective nature, small sample size of MLLs, widely different treatment protocol, method of dose prescription, and variety of dose-fractionation schemes. One relevant bias is the questionable definition of LR based solely on CT-criteria in the majority of patients, which may have overestimated the rate of tumor LR (32,33).

Conclusions

Despite significant differences in patient, lesion and treatment-related characteristics, SABR for MLLs provided similar results without long-term toxicity, when compared with those of primary lung cancer. Dose per fraction ≥12 Gy as complementary to the concept of BED_{10} >100 Gy may be radiobiologically meaningful to explain the ablative potential of SABR.

Acknowledgements

None.

Footnote

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

Ethical Statement: In response to our formal request and notification of the study, the responsible ethics committee (Ärztekammer des Saarlandes) waived the need for approval and patients' informed consent for this retrospective study as the analysis was based on non-identifiable, anonymized data only. Written informed consent was obtained from all patients.

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Cite this article as: Oskan F, Dzierma Y, Wagenpfeil S, Rübe C, Fleckenstein J. Retrospective analysis of stereotactic ablative radiotherapy (SABR) for metastatic lung lesions (MLLs) in comparison with a contemporaneous cohort of primary lung lesions (PLLs). J Thorac Dis 2017;9(3):742-756. doi: 10.21037/jtd.2017.03.07

Supplementary

Table S1 Univariate and multivariate analysis of predictive factor for progression-free and local control (LC) for the whole population

Characteristics	PFS				LC			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Type of cancer								
Primary	1.74 (0.93–3.26)	0.08	1.44 (0.59–3.51)	0.41	0.99 (0.36–2.70)	0.98	–	–
Metastatic	–	–	–	–	–	–	–	–
Tumor location								
Parenchymal	2.15 (0.99–4.68)	0.05	2.25 (0.92–5.5)	0.07	–	–	–	–
Non-parenchymal	–	–	–	–	–	–	–	–
SUV_{max}								
<6.9	0.52 (0.21–1.29)	0.16	–	–	0.41 (0.10–1.62)	0.20	–	–
≥6.9	–	–	–	–	–	–	–	–
SUV_{max} (continuous)	1.01 (0.94–1.08)	0.68	–	–	1.05 (0.96–1.16)	0.24	–	–
GTV								
<14 mL	0.76 (0.38–1.5)	0.43			1.30 (0.48–3.47)	0.60	–	–
≥14 mL	–	–	–	–	–	–	–	–
GTV (continuous)	1.00 (0.97–1.03)	0.99	–	–	1.03 (0.99–1.07)	0.13	–	–
SABR-duration								
<9 days	1.14 (0.68–2.14)	0.67	–	–	0.48 (0.18–1.3)	0.15	–	–
≥9 days	–	–	–	–	–	–	–	–
SABR-duration (continuous)	1.00 (0.92–1.08)	0.96	–	–	0.95 (0.83–1.09)	0.53	–	–
Interval to SABR[§]								
<60 days	1.03 (0.55–1.93)	0.94	–	–	0.42 (0.15–1.16)	0.09	0.45 (0.16–1.2)	0.13
≥60 days	–	–	–	–	–	–	–	–
Interval to SABR[§] (continuous)	1.00 (0.99–1.01)	0.09	1 (1–1.01)	0.04	1 (0.98–1.01)	0.85	–	–
No. of fractions								
<5 fractions	0.96 (0.51–1.81)	0.92	–	–	1.26 (0.46–3.47)	0.65	–	–
≥5 fractions	–	–	–	–	–	–	–	–
No. of fractions (continuous)	1.03 (0.86–1.23)	0.72	–	–	1.06 (0.82–1.39)	0.62	–	–
Dose per fraction								
<12 Gy	0.36 (0.19–0.68)	0.002	0.12 (0.02–0.61)	0.01	0.31 (0.11–0.85)	0.02	0.09 (0.01–0.76)	0.02
≥12 Gy	–	–	–	–	–	–	–	–
Dose per fraction (continuous)	0.86 (0.77–0.96)	0.007	1.08 (0.75–1.54)	0.67	0.85 (0.72–1.02)	0.083	1.4 (0.93–2.11)	0.10
Total dose								
<48 Gy	0.66 (0.34–1.29)	0.22	–	–	0.68 (0.25–1.88)	0.46	–	–
≥48 Gy	–	–	–	–	–	–	–	–
Total dose (continuous)	0.95 (0.92–0.97)	0.007	0.91 (0.82–1.02)	0.11	0.97 (0.93–1.02)	0.38	–	–
Prescription IDL								
80% IDL	2.27 (1.14–4.54)	0.02	4.22 (1.36–13.09)	0.01	0.3 (0.04–2.33)	0.25	–	–
60% IDL	–	–	–	–	–	–	–	–
Treatment technique								
3D	1.72 (0.89–3.32)	0.10	–	–	1.72 (0.62–4.74)	0.29	–	–
IMRT	–	–	–	–	–	–	–	–
BED_{10}								
<105 Gy_{10}	0.43 (0.23–0.81)	0.01	4.21 (0.84–20.97)	0.07	0.49 (0.18–1.3)	0.15	–	–
≥105 Gy_{10}	–	–	–	–	–	–	–	–
BED_{10} (continuous)	0.98 (0.96–0.99)	–	1.01 (0.95–1.08)	0.57	0.98 (0.96–1.00)	0.09	0.98 (0.96–1.01)	0.31

[§], interval to SABR was calculated from the first date of diagnosis (biopsy, PET, CT) to the first day of SABR. PFS, progression-free survival; LC, local control; HR, hazard ratio;SUV_{max}, maximal Standardized uptake volume; GTV, gross tumor volume; SABR, stereotactic ablative radiotherapy; IDL, isodose line; 3D, three dimensional; IMRT, intensity-modulated radiation therapy; BED_{10}, biologic effective dose at α/β=10 Gy; PET, positron-emission-tomography; CT, computed tomography.

Table S2 Univariate and multivariate analysis of predictive factor for progression-free and LC for PLLs

Characteristics	PFS				LC			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P Value	HR (95% CI)	P value	HR (95% CI)	P value
Type of primary								0.47
De novo	2.09 (0.90–4.85)	0.08	1.17 (0.45–3.04)	0.73	2.97 (0.86–10.23)	0.08	1.65 (0.41–6.56)	
Recurrent	–	–	–	–	–	–	–	
Histology								–
Squamous	0.19 (0.39–2.15)	0.84	–	–	0.38 (0.09–1.51)	0.17	–	
Non-squamous	–	–	–	–	–	–	–	
SUV_{max}								–
<6.9	0.57 (0.22–1.50)	0.25	–	–	0.31 (0.05–1.67)	0.17	–	
≥6.9	–	–	–	–	–	–	–	
SUV_{max} (continuous)	1 (0.93–1.08)	0.81	–	–	1.07 (0.96–1.19)	0.17	–	
GTV								–
<14 mL	0.71 (0.29–1.71)	0.44	–	–	0.79 (0.22–2.78)	0.71	–	
≥14 mL	–	–	–	–	–	–	–	
GTV (continuous)	0.99 (0.95–1.03)	0.70	–	–	0.99 (0.93–1.06)	0.88	–	–
SABR-duration								0.10
<9 days	1.06 (0.45–2.49)	0.89	–	–	0.31 (0.09–1.08)	0.06	0.16 (0.02–1.45)	
≥9 days	–	–	–	–	–	–	–	
SABR-duration (continuous)	1.03 (0.93–1.16)	0.49	–	–	0.84 (0.67–1.04)	0.12	–	–
Interval to SABR[§]								0.15
<60 days	0.57 (0.24–1.34)	0.19	–	–	0.27 (0.07–1.05)	0.05	0.33 (0.07–1.52)	
>60 days	–	–	–	–	–	–	–	
Interval to SABR[§] (continuous)	1 (0.99–1.01)	0.15	–	–	0.98 (0.96–1.00)	0.19	–	–
No. of fractions								–
<5 fractions	0.92 (0.39–2.15)	0.84	–	–	0.52 (0.15–1.76)	0.29	–	
≥5 fractions	–	–	–	–	–	–	–	
No. of fractions (continuous)	1.14 (0.92–1.42)	0.20			0.86 (0.59–1.26)	0.46		–
Dose per fraction								–
<12 Gy	0.30 (0.12–0.71)	0.006	0.14 (0.02–0.80)	0.02	0.42 (0.12–1.41)	0.16	–	
≥12 Gy	–	–	–	–	–	–	–	
Dose per fraction (continuous)	0.87 (0.76–1.00)	0.06	1.19 (0.88–1.62)	0.25	0.95 (0.76–1.18)	0.67		–
Total dose								–
<48 Gy	0.94 (0.40–2.2)	0.90	–	–	0.42 (0.12–1.47)	0.17	–	
≥48 Gy	–	–	–	–	–	–	–	
Total dose (continuous)	0.99 (0.94–1.05)	0.94	–	–	0.93 (0.86–1.01)	0.08	1.06 (0.86–1.30)	0.57
Prescription IDL								–
80% IDL	1.19 (0.15–9.00)	0.86	–	–	3.14 (0.39–25.30)	0.82	–	
60% IDL	–	–	–	–	–	–	–	
Treatment technique								–
3D	1.24 (0.48–3.12)	0.64	–	–	0.65 (0.14–3.05)	0.58	–	
IMRT	–	–	–	–	–	–	–	
BED_{10}								0.73
<105 Gy_{10}	0.69 (0.23–2.08)	0.51	–	–	0.18 (0.05–0.68)	0.01	0.63 (0.04–8.89)	
>105 Gy_{10}	–	–	–	–	–	–	–	
BED_{10} (continuous)	0.98 (0.97–1.00)	0.14	–	–	0.97 (0.95–1.00)	0.09	0.96 (0.0.87)	0.42

[§], interval to SABR was calculated from the first date of diagnosis (biopsy, PET, CT) to the first day of SABR. LC, local control; PLLs, primary lung lesions; PFS, progression-free survival; CT, computed tomography; HR, hazard ratio; SUV_{max}, maximal standardized uptake volume; GTV, gross tumor volume; SABR, stereotactic ablative radiotherapy; IDL, isodose line; 3D, three dimensional; IMRT, intensity-modulated radiation therapy; BED_{10}, biologic effective dose at α/β=10 Gy; PET, positron-emission-tomography; CT, computed tomography.

Table S3 Univariate and multivariate analysis of predictive factor for progression-free and LC for MLLs

Characteristics	PFS				LC			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Histology								–
Colorectal	0.56 (0.19–1.63)	0.29	–	–	–	–	–	
Non-colorectal	–	–	–	–	–	–	–	
GTV								–
<14 mL	1.19 (0.39–3.65)	0.75	–	–	3.21 (0.64–16.05)	0.15	–	
≥14 mL	–	–	–	–	–	–	–	
GTV (continuous)	1.02 (0.98–1.06)	0.31	–	–	1.07 (1.01–1.13)	0.01	0.98 (0.87–1.10)	0.75
SABR-duration								–
<9 days	1.26 (0.49–3.24)	0.62	–	–	0.74 (0.14–3.83)	0.72	–	
≥9 days	–	–	–	–	–	–	–	
SABR-duration (continuous)	0.99 (0.88–1.11)	0.91	–	–	1.06 (0.88–1.27)	0.51	–	–
Interval to SABR[§]								0.22
<60 days	2.04 (0.76–5.51)	0.15	–	–	1.01 (0.20–5.12)	0.98	–	
≥60 days	–	–	–	–	–	–	–	
Interval to SABR[§] (continuous)	1.00 (0.99–1.02)	0.26	–	–	1.01 (0.99–1.03)	0.06	1.01 (0.99–1.04)	–
No. of fractions								–
<5 fractions	1.15 (0.45–2.95)	0.76	–	–	–	–	–	
≥5 fractions	–	–	–	–	–	–	–	
No. of fractions (continuous)	1.03 (0.70–2.95)	0.86	–	–	2.15 (1.20–3.85)	0.01	5.2 (0.63–43.70)	0.12
Dose per fraction								0.22
<12 Gy	0.42 (0.16–1.08)	0.07	0.05 (0.00–2.28)	0.12	0.14 (0.01–1.25)	0.07	126 (0.05–not reached)	
≥12 Gy	–	–	–	–	–	–	–	
Dose per fraction (continuous)	0.83 (0.70–1.00)	0.05	1.92 (0.94–3.92)	0.07	0.66 (0.44–0.97)	0.03	0.42 (0.11–1.59)	0.20
Total dose								–
<48 Gy	0.47 (0.10–2.08)	0.32	–	–	1.83 (0.32–10.24)	0.48	–	
≥48 Gy	–	–	–	–	–	–	–	
Total dose (continuous)	0.93 (0.88–0.99)	0.03	0.96 (0.83–1.12)	0.68	1 (0.92–1.09)	0.96	–	–
Prescription IDL								–
80% IDL	1.86 (0.64–5.40)	0.25	–	–	–	–	–	
60% IDL	–	–	–	–	–	–	–	
Treatment technique								–
3D	2.49 (0.91–6.82)	0.07	10.61 (2.23–50.48)	0.003	–	–	–	
IMRT	–	–	–	–	–	–	–	
BED_{10}								–
<105 Gy_{10}	0.25 (0.05–1.15)	0.07	0.43 (0.02–6.77)	0.55	0.87 (0.14–5.29)	0.88	–	
≥105 Gy_{10}	–	–	–	–	–	–	–	
BED_{10} (continuous)	0.97 (0.94–0.99)	0.02	0.97 (0.89–1.06)	0.61	0.98 (0.94–1.01)	0.29	–	–

[§], interval to SABR was calculated from the first date of diagnosis (biopsy, PET, CT) to the first day of SABR. LC, local control; MLLs, metastatic lung lesions; PFS, progression-free survival; CT, computed tomography; HR, hazard ratio; GTV, gross tumor volume; SABR, stereotactic ablative radiotherapy; IDL, isodose line; 3D, three dimensional; IMRT, intensity-modulated radiation therapy; BED_{10}, biologic effective dose at α/β=10 Gy; PET, positron-emission-tomography; CT, computed tomography.

Table S4 Univariate and multivariate analysis of predictive factor for OS and survival after the first progression post-SABR for the whole patients

Characteristics	OS				Survival after the first progression post-SABR			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (continuous)	1.00 (0.95–1.05)	0.89	–	–	1.02 (0.97–1.08)	0.34	–	–
Age							–	–
<70 years	0.86 (0.36–2.05)	0.74	–	–	1.40 (0.47–2.21)	0.54	–	
≥70 years	–	–	–	–	–	–	–	
Gender								
Male	0.78 (0.31–1.97)	0.60	–	–	0.33 (0.10–1.10)	0.07	0.15 (0.02–0.88)	0.03
Female	–	–	–	–	–	–	–	
FEV_1 (continuous)	0.99 (0.97–1.01)	0.46	–	–	0.99 (0.97–1.02)	0.85	–	–
FEV_1								–
<40% of predicted	0.47 (0.17–1.26)	0.13	–	–	0.38 (0.07–1.93)	0.42	–	
≥40% of predicted	–	–	–	–	–	–	–	
DLCO (continuous)	0.98 (0.95–1.00)	0.15	–	–	0.98 (0.95–1.01)	0.31	–	–
DLCO								–
<40% of predicted	0.98 (0.95–1.00)	0.16	–	–	0.88 (0.16–4.85)	0.88	–	
≥40% of predicted	–	–	–	–	–	–	–	
Supplemental O_2								–
Needed	3.49 (1.52–10.25)	0.005	3.40 (1.25–9.22)	0.01	1.68 (0.46–6.18)	0.43	–	
Not-needed	–	–	–	–	–	–	–	
KPS								0.08
≤70%	0.42 (0.17–1.01)	0.05	0.51 (0.20–1.32)	0.16	0.33 (0.09–1.22)	0.09	0.16 (0.02–1.27)	
>70%	–	–	–	–	–	–	–	
CVD								–
Yes	1.27 (0.53–3.05)	0.58	–	–	0.76 (0.26–2.19)	0.62	–	
No	–	–	–	–	–	–	–	
COPD								–
Yes	1.43 (0.59–3.48)	0.60	–	–	1.97 (0.66– 5.91)	0.22	–	
No	–	–	–	–	–	–	–	
Comorbidity								–
One or more	1.46 (0.42–5.06)	0.54	–	–	2.18 (0.47–9.95)	0.31	–	
None	–	–	–	–	–	–	–	
Pre-chemotherapy								–
Yes	0.79 (0.33–1.89)	0.60	–	–	0.70 (0.24–2.05)	0.51	–	
No	–	–	–	–	–	–	–	
Post-chemotherapy								0.36
Yes	0.85 (0.35–2.07)	0.73	–	–	0.37 (0.11–1.17)	0.09	0.47 (0.09–2.39)	
No	–	–	–	–	–	–	–	
Chemotherapy								–
One or both pre or post	0.80 (0.32–1.98)	0.63	–	–	0.48 (0.14–1.67)	0.25	–	
None	–	–	–	–	–	–	–	
Pre-lung irradiation								–
Yes	0.86 (0.20–3.71)	0.84	–	–	0.96 (0.21–4.37)	0.96	–	
No	–	–	–	–	–	–	–	
Pre-lung surgery								0.71
Yes	0.78 (0.30–2.03)	0.62	–	–	0.24 (0.05–1.15)	0.07	0.63 (0.05–7.71)	
No	–	–	–	–	–	–	–	
Pre-lung treatment								–
One or both	0.71 (0.28–1.78)	0.47	–	–	0.33 (0.08–1.29)	0.11	–	
None	–	–	–	–	–	–	–	
Post-lung irradiation								–
Yes	0.68 (0.16–2.95)	0.61	–	–	0.52 (0.06–4.13)	0.53	–	
No	–	–	–	–	–	–	–	
Post-lung surgery								–
Yes	1.06 (0.14–0.7.98)	0.95	–	–	–	–	–	
No	–	–	–	–	–	–	–	
Post- lung treatment								–
One or both	0.72 (0.16–3.12)	0.66	–	–	–	–	–	
None	–	–	–	–	–	–	–	
Lung local treatment								0.84
One or both pre or post	0.64 (0.26–1.53)	0.32	–	–	0.22 (0.05–0.86)	0.03	1.30 (0.09–18.97)	
None	–	–	–	–	–	–	–	
Number of lesions								–
One lesion	1.83 (0.77–4.36)	0.17	–	–	0.47 (0.14–1.57)	0.22	–	
More than one	–	–	–	–	–	–	–	
Type of cancer								0.10
Primary	0.45 (0.15–1.36)	0.15	–	–	0.11 (0.01–0.88)	0.03	0.17 (0.02–1.44)	
Metastatic	–	–	–	–	–	–	–	
After progression								–
Salvage treatments	1.28 (0.45–3.67)	0.63	–	–	0..40 (0.13–1.22)	0.11	–	
No treatments	–	–	–	–	–	–	–	

OS, overall survival; SABR, stereotactic ablative radiotherapy; HR, hazard ratio; FEV_1, forced expiration at the first second; DLCO, diffusing capacity of the Lung for carbon monoxide; KPS, Karnofsky`s performance status; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease.

Table S5 Univariate and multivariate analysis of predictive factor for OS and survival after the first progression post-SABR for PLLs

Characteristics	OS				Survival after the first progression post-SABR			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (continuous)	0.99 (0.94–1.04)	0.79	–	–	1.01 (0.93–1.08)	0.8	–	–
Age								–
<70 years	0.89 (0.34–2.31)	0.81	–	–	1.37 (0.43–4.3)	0.59	–	
≥70 years	–	–	–	–	–	–	–	
Gender								–
Male	0.68 (0.23–1.94)	0.47	–	–	0.54 (0.16–1.80)	0.31	–	
Female	–	–	–	–	–	–	–	
FEV_1 (continuous)	0.99 (0.98–1.01)	0.85	–	–	1.00 (0.98–1.03)	0.42	–	–
FEV_1								–
<40% of predicted	0.63 (0.21–1.85)	0.40	–	–	0.46 (0.08–2.41)	0.35	–	
≥40% of predicted	–	–	–	–	–	–	–	
DLCO (continuous)	0.96 (0.93–1.00)	0.08	0.98 (0.49–1.02)	0.43	1.01 (0.96–1.07)	0.53	–	–
DLCO								–
<40% of predicted	0.54 (0.14–2.03)	0.36	–	–	1.45 (0.26–8.03)	0.67	–	
≥40% of predicted	–	–	–	–	–	–	–	
Supplemental O_2								–
Needed	3.43 (1.25–0.43)	0.01	4.02 (0.52–30.55)	0.17	0.87 (0.22–3.37)	0.84	–	
Not-needed	–	–	–	–	–	–	–	
KPS								–
≤70%	0.61 (0.23–1.62)	0.32	–	–	0.68 (0.16–2.78)	0.59	–	
>70%	–	–	–	–	–	–	–	
CVD								–
Yes	0.95 (0.36–2.48)	0.92	–	–	0.51 (0.16–2.78)	0.25	–	
No	–	–	–	–	–	–	–	
COPD								–
Yes	0.85 (0.30–2.45)	0.77	–	–	0.71 (0.20–2.46)	0.59	–	
No	–	–	–	–	–	–	–	
Comorbidity								–
One or more	0.14 (0.01–1.31)	0.08	NA	0.99	0.14 (0.01–1.54)	0.10	–	
None	–	–	–	–	–	–	–	
Pre-chemotherapy								–
Yes	1.27 (0.48–3.35)	0.62	–	–	0.79 (0.23–2.76)	0.72	–	
No	–	–	–	–	–	–	–	
Post-chemotherapy								–
Yes	1.07 (0.39–2.90)	0.89	–	–	0.91 (0.28–2.93)	0.88	–	
No	–	–	–	–	–	–	–	
Chemotherapy								–
One or both pre or post	1.09 (0.42–2.84)	0.85	–	–	0.82 (0.23–2.92)	0.75	–	
None	–	–	–	–	–	–	–	
Pre-lung irradiation								–
Yes	0.71 (0.16–3.13)	0.65	–	–	0.47 (0.10–2.25)	0.35	–	
No	–	–	–	–	–	–	–	
Pre-lung surgery								–
Yes	0.84 (0.27–2.60)	0.53	–	–	0.31 (0.06–1.49)	0.14	–	
No	–	–	–	–	–	–	–	
Pre-lung treatment								–
One or both	0.70 (0.24–2.02)	0.51	–	–	0.38 (0.09–1.51)	0.17	–	
None	–	–	–	–	–	–	–	
Post-lung irradiation								–
Yes	1.59 (0.36–7.07)	0.53	–	–	1.2 (0.14–10.07)	0.86	–	
No	–	–	–	–	–	–	–	
Post-lung surgery								–
Yes	4.21 (0.50–35.27)	0.18	–	–	–	–	–	
No	–	–	–	–	–	–	–	
Post- lung treatment								–
One or both	1.88 (0.42–8.32)	0.40	–	–	–	–	–	
None	–	–	–	–	–	–	–	
Lung local treatment								–
One or both pre or post	0.90 (0.34–2.38)	0.83	–	–	–	–	–	
None	–	–	–	–	–	–	–	
Number of lesions								–
One lesion	2.86 (0.97–8.39)	0.05	2.00 (0.36–11.05)	0.42	0.21 (0.02–1.74)	0.15	–	
More than one	–	–	–	–	–	–	–	
Type of primary								–
De novo	0.70 (0.24–2.02)	0.51	–	–	–	–	–	
Recurrent	–	–	–	–	–	–	–	
Histology								–
Squamous	–	–	–	–	–	–	–	
Non-Squamous	0.89 (0.34–2.34)	0.82	–	–	0.61 (0.19–1.95)	0.40	–	
After progression								–
Salvage treatments	2.02 (0.56–7.22)	0.27	–	–	–	–	–	
No treatments	–	–	–	–	–	–	–	

OS, overall survival; SABR, stereotactic ablative radiotherapy; PLLs, primary lung lesions; HR, hazard ratio; FEV_1, forced expiration at the first second; DLCO, diffusing capacity of the lung for carbon monoxide; KPS, Karnofsky's performance status; CVD, cardiovascular Disease; COPD, chronic obstructive pulmonary disease.

Table S6 Univariate and multivariate analysis of predictive factor for OS and survival after the first progression post-SABR for MLLs

Characteristics	OS				Survival after the first progression post-SABR			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (continuous)	1.03 (0.91–1.15)	0.61	–	–	1.27 (0.58–2.77)	0.54	–	–
Age								–
<70 years	1.00 (0.13–7.81)	0.99	–	–	–	–	–	
≥70 years	–	–	–	–	–	–	–	
Gender								–
Male	1.59 (0.20–12.09)	0.65	–	–	–	–	–	
Female	–	–	–	–	–	–	–	
FEV_1 (continuous)	0.97 (0.92–1.03)	0.41	–	–	–	–	–	–
FEV_1								–
<40% of predicted	0.15 (0.01–2.57)	0.19	–	–	–	–	–	
≥40% of predicted	–	–	–	–	–	–	–	
KPS								–
≤70%	0.87 (0.65–1.16)	0.34	–	–	–	–	–	
>70%	–	–	–	–	–	–	–	
CVD								–
Yes	1.96 (0.26–14.39)	0.50	–	–	1.58 (0.09–27.19)	0.75	–	
No	–	–	–	–	–	–	–	
COPD								–
Yes	2.41 (0.21–27.03)	0.47	–	–	–	–	–	
No	–	–	–	–	–	–	–	
Comorbidity								–
One or more	1.38 (0.18–10.36)	0.75	–	–	–	–	–	
None	–	–	–	–	–	–	–	
Pre-chemotherapy								–
Yes	0.37 (0.03–4.30)	0.43	–	–	0.40 (0.01–8.66)	0.56	–	
No	–	–	–	–	–	–	–	
Post-chemotherapy								–
Yes	0.91(0.12–6.54)	0.92	–	–	–	–	–	
No	–	–	–	–	–	–	–	
Chemotherapy								–
One or both pre or post	0.6 (0.01–3.68)	0,87	–	–	–	–	–	
None	–	–	–	–	–	–	–	
Pre-lung surgery								–
Yes	1.18 (0.16–8.40)	0.86	–	–	–	–	–	
No	–	–	–	–	–	–	–	
Histology								–
Colorectal	0.31 (0.02–3.63)	0.35	–	–	–	–	–	
Non-colorectal	–	–	–	–	–	–	–	

OS, overall survival; SABR, stereotactic ablative radiotherapy; MLLs, metastatic lung lesions; HR, hazard ratio; FEV_1, forced expiration at the first second; DLCO, diffusing capacity of the lung for carbon monoxide; KPS, Karnofsky's performance status; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease.

Table S7 Pattern of failure after SABR for primary lung cancer in selected literature

Study (year)	Total No. of failure	LF, n (%)	RF, n (%)	DF, n (%)	LF + RF, n (%)	LF + DF, n (%)	RF + DF, n (%)	LF + RF + DF, n (%)
Baumann 2006 (34)	44	4 (9.0)	3 (7.0)	22 (50.0)	2 (4.0)	9 (20.0)	3 (7.0)	1 (2.0)
Guckenberger 2009 (6)	18	1 (2.0)	4 (10.0)	11 (27.0)	0	0	2 (5.0)	0
Bradely 2010 (35)	21	3 (14.0)	1 (5.0]	10 (47.0)	2 (10.0)	1 (5.0)	3 (14.0)	1 (5.0)
Olsen 2011 (36)	25	4 (16.0)	7 (28.0)	6 (24.0)	3 (12.0)	0	4 (16.0)	1 (4.0)
Haasbeck 2011 (37)	17	1 (6.0)	0	10 (59.0)	1 (6.0)	1 (6.0)	3 (17.0)	1 (6.0)
Taremi 2012 (38)	31	7 (22.0)	6 (19.0)	12 (39.0)	1 (3.0)	1 (3.0)	3 (9.0)	1 (3.0)
Lee 2013 (39)	21	4 (19.0)	1 (95.0)	8 (38.0)	1 (5.0)	3 (14.0)	3 (14.0)	1 (5.0)
Presented study	40	6 (15.0)	6 (15.0)	12 (30.0)	1 (2.5)	5 (12.5)	5 (12.5)	5 (12.5)
PLLs	22	4 (18.0)	3 (13.0)	3 (13.0)	1 (5.0)	1 (5.0)	5 (23.0)	5 (23.0)
MLLs	18	2 (11.0)	3 (17.0)	9 (50.0)	0	4 (22.0)	0	0

SABR, stereotactic ablative radiotherapy; LF, local failure; RF, regional failure; DF, distant failure; PLLs, primary lung lesions; MLLs, metastatic lung lesions.

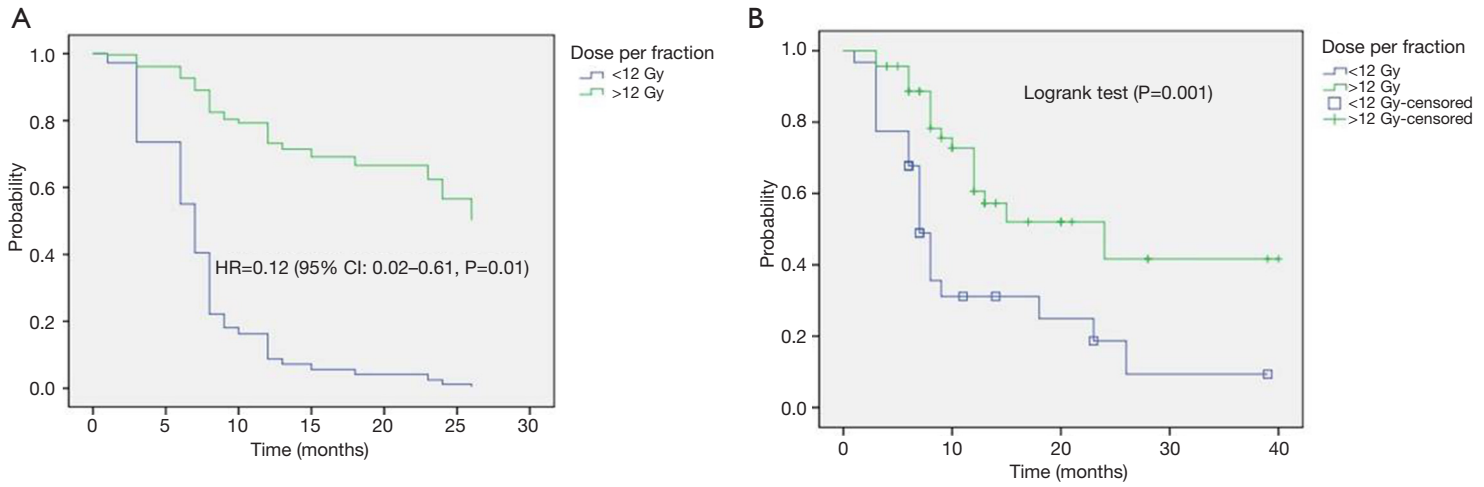

Figure S1 Survival curves for progression-free survival (PFS) for the whole population stratified by dose per fraction (> or <12 Gy). (A) Cox regression; (B) Kaplan-Meier.

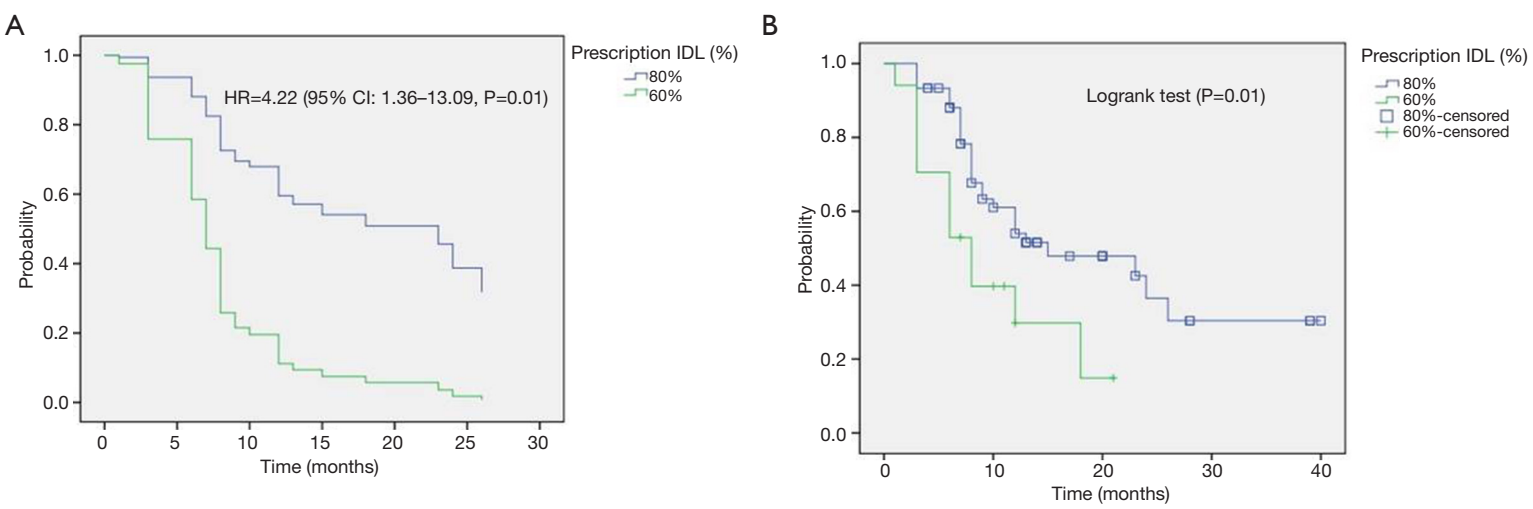

Figure S2 Survival curves for progression-free survival (PFS) for the whole population stratified by prescription isodose line (IDL) (80% or 60%). (A) Cox regression; (B) Kaplan-Meier.

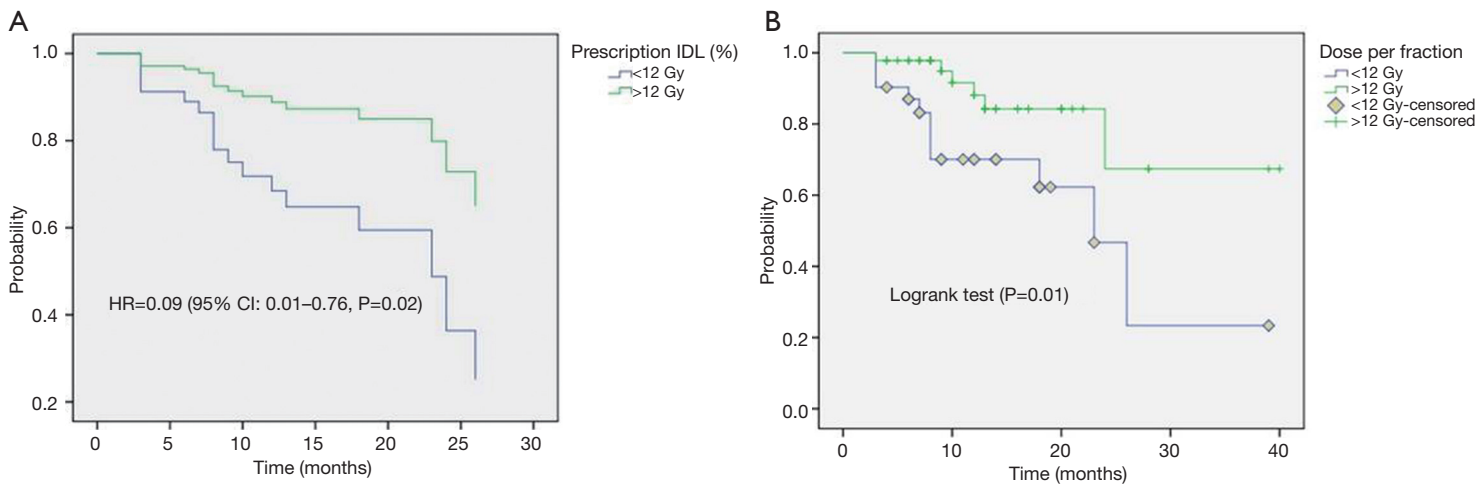

Figure S3 Survival curves for local control (LC) for the whole population stratified by dose per fraction (> or <12 Gy). (A) Cox regression; (B) Kaplan-Meier.

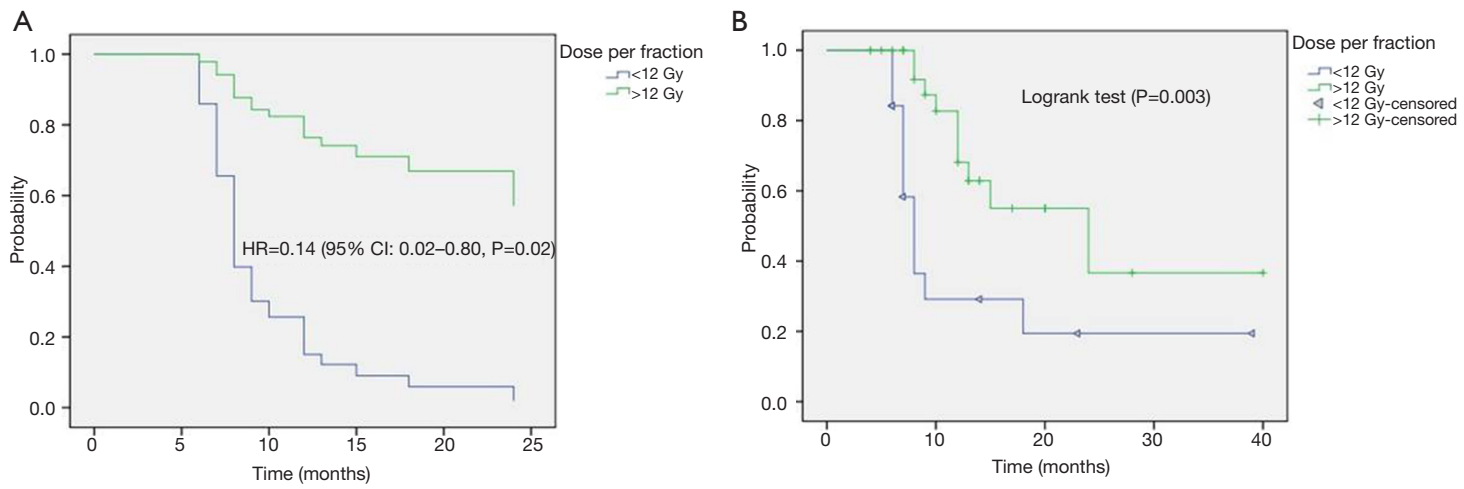

Figure S4 Survival curves for progression-free survival (PFS) for primary lung lesions (PLLs) stratified by dose per fraction (> or <12 Gy). (A) Cox regression; (B) Kaplan-Meier.

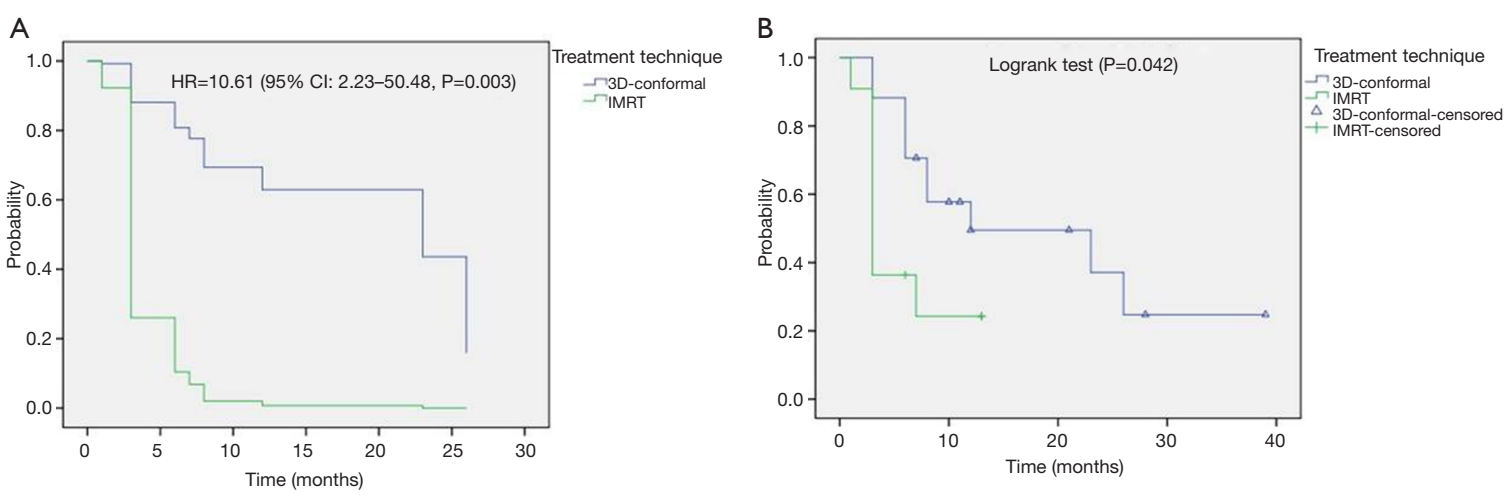

Figure S5 Survival curves for progression-free survival (PFS) for metastatic lung lesions (MLLs) stratified by treatment technique three dimensional (3D) orintensity-modulated radiation therapy (IMRT). (A) Cox regression; (B) Kaplan-Meier.

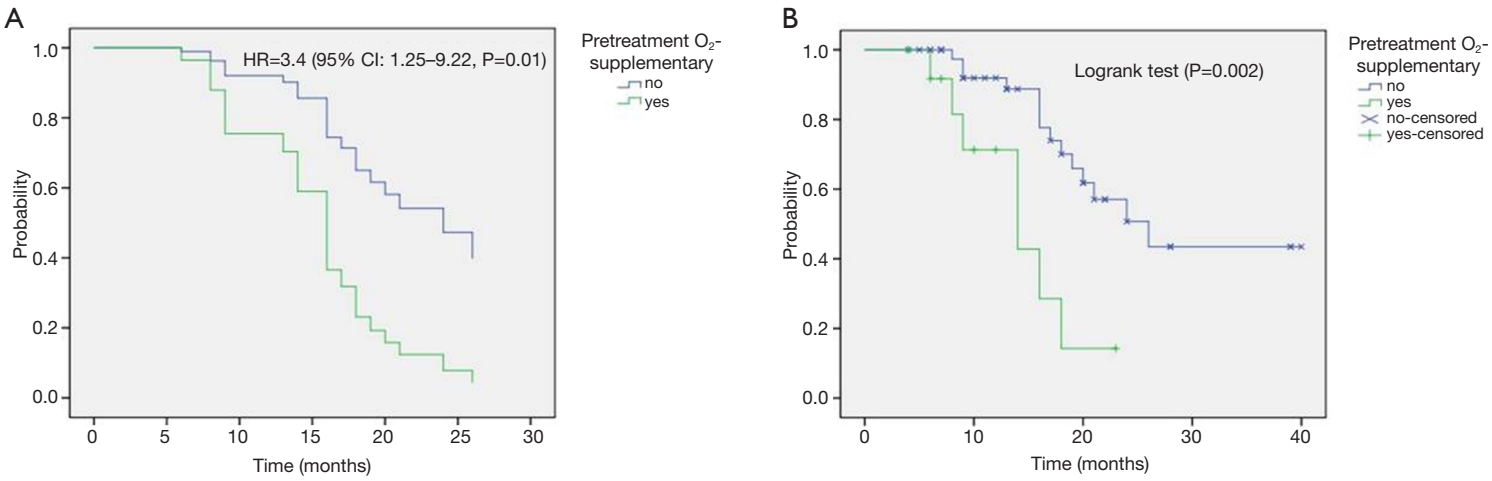

Figure S6 Survival curves for overall survival (OS) for the whole population stratified by the need of supplemental O_2. (A) Cox regression; (B) Kaplan-Meier.

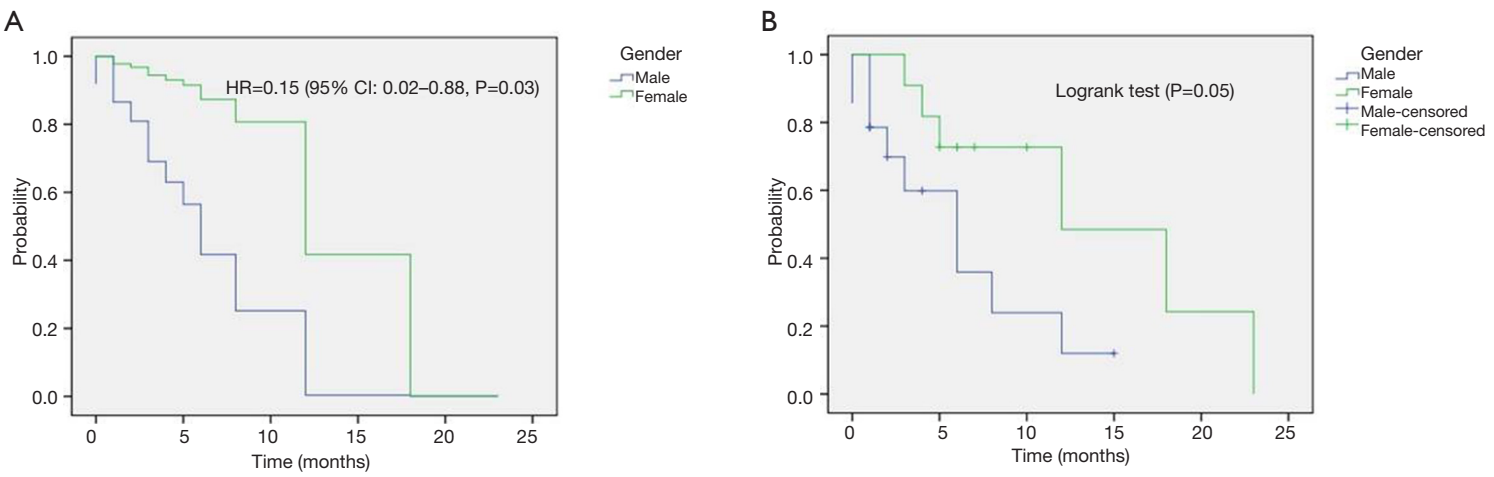

Figure S7 Survival curves for survival after the first progression post-SABR (SAFP) for the whole population stratified by the gender (male or female). (A) Cox regression; (B) Kaplan-Meier.

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