Pulmonary function and quality of life after VMAT-based stereotactic ablative radiotherapy for early stage inoperable NSCLC: A prospective study

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Highlights

•SABR may cause a small decline in lung volumes and DLCO.

•Baseline pulmonary function was not associated to radiation-induced lung toxicity and survival.

•Radiation-induced lung toxicity was not clearly associated with dose-volume parameters.

•Quality of life was globally not impaired, with only a slight decline in one item (fatigue).

Abstract

Objectives

To analyze changes in pulmonary function and quality of life (QoL) at different time points after Stereotactic Ablative Radiotherapy (SABR) for early stage inoperable lung cancer, and potential correlations between radiation dose-volume parameters and pulmonary toxicity or changes in pulmonary function tests (PFT) and QoL.

Materials and methods

From July 2012 to October 2013, 30 patients were enrolled in this prospective observational study. Complete PFT were performed and Lung Cancer Symptoms Scale (LCSS) questionnaire administered prior to SABR; all patients then underwent Computed Tomography (CT) scan and PFT at 45, 135, 225 and 315 days after SABR, together with LCSS questionnaire. Clinical lung toxicity and radiological toxicity (acute and late) were prospectively recorded by using the Radiation Therapy Oncology Group (RTOG) scoring system.

Results

A decline in Slow Vital Capacity (SVC), Forced Expiratory Volume in 1 s (FEV_1), Single-breath lung diffusing capacity (D_LCO) and blood partial pressure of oxygen (PaO_2) was seen at 135 days post-SABR. PaO2 values rescued to normal levels at 315 days. None of the baseline PFT parameters resulted to be associated with the occurrence of pulmonary toxicity or with late radiological changes. Mean V5, V10, and V20 and MLD_{2Gy} were higher in patients who developed radiation pneumonitis, even if not significantly associated at Cox regression analysis. LCSS QoL showed a significant worsening of the single item fatigue at 135 days after SABR.

Conclusions

A small (mean 10%) but significant decline in lung volumes and D_LCO was recorded after SABR, with clinical impact of such change difficult to estimate in individual patients. Global QoL was not significantly impaired. Dose-volume parameters did not emerge as significantly predictive of any clinical, radiological or functional toxicity.

Keywords

- Stereotactic ablative radiotherapy;
- Stereotactic body radiotherapy;
- Pulmonary function;
- Radiation pneumonitis;
- Lung cancer;
- Early stage

1. Introduction

Stereotactic Ablative Radiotherapy (SABR) is currently recognized as the gold standard for patients with inoperable stage I non-small cell lung cancer (NSCLC) [1]. This recommendation is based on the results of several prospective phase II trials [2], [3], [4], [5] and [6], as well as large observational studies [7], [8] and [9], with variable follow-up intervals: most of them were limited to spirometric parameters and diffusing capacity for carbon monoxide (Diffusion Lung capacity for Carbon monoxide, D_LCO). Recently, a more comprehensive analysis of "complete" Pulmonary Function Tests (including blood gas analysis) was reported, on a series of patients enrolled in the RTOG 0236 phase II trial of SABR in inoperable patients [10].

Primary aim of this prospective study was to investigate changes in pulmonary function after SABR and correlation between baseline pulmonary function tests and any pulmonary toxicity and efficacy. Additional goals were to analyze possible correlation between radiation-dose volume parameters and lung toxicity (clinical or radiological) or impairment in pulmonary function and patient-reported quality of life.

2. Material and methods

2.1. Patients

From July 2012 to October 2013, 30 patients affected with inoperable Stage I NSCLC accepted to be enrolled in the study. Eligibility criteria for SABR were: (a) medical contraindications to surgery after multidisciplinary evaluation (thoracic surgeon, medical oncologist and pneumologist), (b) ECOG Performance Status ≤2, (c) complete staging including 18 fluorodeoxyglucose-Positron Emission Tomography (18FDG-PET) and brain Computed Tomography (CT) scan, (d) no prior radiation therapy to the site of SABR. Histological diagnosis was not mandatory. In the absence of the cyto-histological evidence of

malignancy, a new or growing lesion on CT scan was considered consistent with malignancy, in conjunction with an increased uptake of 18FDG-PET (according to the concept of “clinical proof of malignancy”).

2.2. Pulmonary function evaluation

Fig. 1 illustrates the study flow. Our Institution’s Ethical Review Board approved the study protocol and each patient gave informed consent. Lung volumes were measured according to American Thoracic Society (ATS)/European Respiratory Society (ERS) Standardization [11], with subjects sitting in a body plethysmograph (Vmax Encore 62CareFusion®, Hoechberg Germany) and panting at the end of tidal expiration against a closed shutter at a frequency slightly <1 Hz with their cheeks supported by hands. Total lung capacity (TLC) was obtained as the sum of thoracic gas volume and the linked inspiratory capacity. Functional residual capacity (FRC) was obtained from thoracic gas volume corrected for any difference between the volume at which the shutter was closed and the average end-expiratory volume of the four preceding regular tidal breaths. Residual volume was the difference between TLC and vital capacity (VC). The D_LCO was measured using a gas mixture containing 0.3% CO, 0.3% methane, 21.0% O_2 and balance N_2, according to ATS/ERS recommendations [12]. The D_LCO was corrected for hemoglobin and carboxyhemoglobin obtained by the arterial blood sampling performed on the same day. Predicted values for spirometry, lung volumes and D_LCO were from Quanjer et al. [13]. Always in a seated position, an arterial sample was obtai cid-base balance and the arterial partial pressure nmHg) with an ABL 800® series emogasanalyzer (R

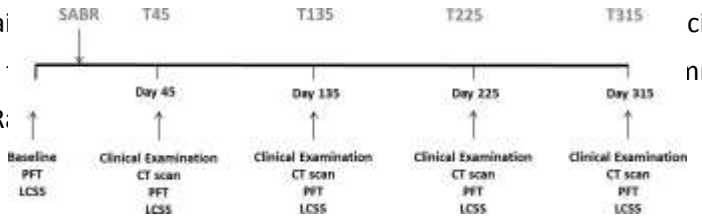

Fig. 1.

Study flow.

2.3. Radiation therapy

Four-dimensions CT was performed in every patient and an Internal Target Volume (ITV) was defined in which the GTV included the tumor position in all phases of the normal respiratory cycle, outlined using a CT windows setting. The ITV was expanded by 3 mm to create the planning target volume (PTV). Treatments were planned as single arc Volumetric Modulated Arc Therapy, and delivered with an Elekta Axesse™ Linear Accelerator (Elekta, Stockholm, Sweden), with 6–10 MV photons and cone-beam CT image-guidance. The total dose ranged from 45 to 60 Gy in 3–8 fractions, on the basis of tumor location (45-54 Gy/3 fractions for parenchymal lesions; 55 Gy/5 fractions for lesions close to chest wall; 60 Gy/8 fractions for central lesions), prescribed at 80% isodose. Mean Lung Dose was kept below 15 Gy_2[14]. Dose constraints for esophagus, heart, great vessels, trachea, main bronchi and spinal cord were derived from the American Association of Physicists in Medicine (AAPM) Task Group 101 recommendation [15].

2.4. Study flow

Clinical examination, total body CT scan and complete PFT were performed at T45, T135, T225 and T315 (Fig. 1). Lung toxicity was graded according to RTOG acute radiation toxicity score (for events occurring within 6 months from the start of radiation treatment) or RTOG late radiation toxicity score (for events occurring after 6 months) (http://www.rtog.org/members/toxicity). Acute radiological toxicity was scored using a five-point scoring system developed by Vrije University, modified from Kimura et al. [16] (1 = diffuse consolidation, 2 = patchy consolidation, 3 = diffuse "ground glass opacity", 4 = patchy "ground glass opacity", 5 = no changes) [17]. Late radiological toxicity was scored according to the Koenig's Scale (0 = absence of changes, 1 = modified conventional pattern, 2 = mass like pattern, 3 = scar like pattern) [18].

2.5. Quality of life

Disease-related symptoms and quality of life were assessed with the patient-reported Lung Cancer Symptom Scale (LCSS) questionnaire [19]. This scale focuses on symptoms and their effect on the patient. Symptoms assessed were loss of appetite (item 1), fatigue (item 2), cough (item 3), dyspnea (item 4), hemoptysis (item 5), pain (item 6), symptom distress (item 7), interference with activity level (item 8), and overall quality of life (item 9). Each item is assessed with a 100 mm visual analogue scale, with lower values representing better quality of life or lower symptom burden than higher values. Patients were expected to complete one LCSS questionnaire at baseline, and then at T135, T225, and T315.

2.6. Statistics

All statistical analyses were done on SPSS 20.0 (SPSS Inc., Chicago, USA). Changes in PFT were calculated by comparison of the mean values at any time point by Student's T test. Logistic regression models were used to investigate the relationship between PFT and clinical (RTOG any grade, RTOG grade ≥2) and radiological status (late toxicity according to Koenig, 0 vs. 1–3). The possible relation between normal lung radiation dose and the occurrence of pulmonary toxicity was performed using Fisher's exact test; statistical significance was established at $p < 0.05$. All the categorical variables were evaluated by Pearson's Chi-Square Test or Fisher's Exact test, as appropriate. Survival curves were generated using Kaplan–Meier method, starting from the end of radiotherapy, and comparisons were performed using the Mantel–Cox log-rank test. The relationship between PFT and overall survival was evaluated using the Cox proportional hazards model.

3. Results

3.1. Descriptive analysis

Detailed patients characteristics are presented in Table 1. Mean age was 77 years old (range 61–84); most patients were male, with good performance status and stage IA disease. Histologic or cytological diagnosis was available in 70% of the cases. The majority of patients were considered medically inoperable for concomitant cardiovascular disease and/or poor pulmonary function.

Table 1.

Patients' characteristics.

Age (mean, range)	**77 (61–84)**
Male	23 (76.7%)
Female	7 (23.3%)
Former smokers	19 (63.3%)
Active smokers	8 (26.7%)
Never smokers	3 (10%)
Performance status (ECOG)	
0	23 (76.7%)
1	6 (20%)
2	1 (3.4%)
AA Charlson CI (mean, range)	6.9 (3–14)
<7	16 (53.3%)
≥7	14 (46.7%)
Stage	
IA	17 (56.7%)
IB	13 (43.3%)
Tumor max diameter, mm (mean, range)	25.5 (12–55)
Histology	
Adenocarcinoma	9 (30%)
Squamous cell carcinoma	8 (26.7%)
NSCLC NOS	4 (13.3%)
Unknown	9 (30%)

Age (mean, range)	**77 (61–84)**
Treatment schedules	
45–54 Gy/3 fr	9 (30%)
55 Gy/5 fr	11 (37%)
60 Gy/8 fr	10 (33%)

Abbreviations: AA Charlson CI (age-adjusted Charlson comorbidity index); NSCLC (non small cell lung cancer); VMAT (volumetric-modulated arc therapy); Gy (gray); fr (fractions).

*T-stage according to the revised 7th edition of the TNM classification for lung cancer.

3.2. Baseline and changes in PFT

PFT distribution at baseline is presented in Table 2. At days 45, 135, 225 and 315, 30 patients (100%), 28 patients (93.3%), 25 patients (83.3%) and 20 (66.7%) patients were evaluable, respectively. Main reasons of drop-off were death (4 patients) and poor compliance (6 patients).

Table 2.

Pulmonary function tests distribution.

Pulmonary function test	**Baseline (*n* = 30)**		**Days 45 post-SABR**			**Days 135 post-SABR**			**Days 225 post-SABR**			**Days 315 post-SABR**		
	N	**Raw**	***n***	**Raw**	**Change since baseline**	***n***	**Raw**	**Change since baseline**	***n***	**Raw**	**Change since baseline**	***n***	**Raw**	**Change since baseline**
FEV_1 (liters)	30	1.7 ± 0.5	30	1.7 ± 0.5	−0.01 ± 0.18	28	1.6 ± 0.5	−0.73 ± 0.22	25	1.6 ± 0.5	−0.79 ± 0.23	20	1.5 ± 0.5	−0.19 ± 0.33
FEV_1 (% predicted)	30	75.3 ± 23.1	30	75.5 ± 24.4	−0.49 ± 7.53	28	72.4 ± 25.1	−3.21 ± 9.18	25	72.9 ± 26.3	−3.26 ± 9.49	20	64.3 ± 23.4	−7.57 ± 11.66
FEV_1/SVC	30	61.6 ± 13.3	30	60.0 ± 12.9	−1.12 ± 3.74	28	59.8 ± 13.1	−0.93 ± 4.26	25	59.1 ± 14.2	−0.84 ± 5.68	20	57.1 ± 14.0	−1.85 ± 6.85
FEV_1/SVC	3	82.2 ± 19.	3	80.3 ± 18.	−1.41 ± 5.2	2	79.7 ± 18.	−1.19 ± 6.4	2	78.7 ± 1	−0.72 ± 7.3	2	76.1 ± 19.	−2.14 ± 9.3

Pulmonary function test	Baseline (*n* = 30)		Days 45 post-SABR			Days 135 post-SABR			Days 225 post-SABR			Days 315 post-SABR		
	N	Raw	*n*	Raw	Change since baseline	*n*	Raw	Change since baseline	*n*	Raw	Change since baseline	*n*	Raw	Change since baseline
(%predicted)	0	1	0	3	3	8	5	8	5	9.9	3	0	9	5
SVC (liters)	30	2.9 ± 0.8	30	2.9 ± 0.8	0.06 ± 0.24	28	2.8 ± 0.9	−0.10 ± 0.33	25	2.8 ± 0.7	−0.12 ± 0.34	20	2.7 ± 0.7	−0.26 ± 0.66
SVC (% predicted)	30	92.1 ± 21.8	30	94.5 ± 23.5	1.05 ± 8.45	28	91.2 ± 25.9	−2.56 ± 14.67	25	92.3 ± 23.9	−3.12 ± 10.62	20	84.3 ± 20.8	−7.33 ± 16.88
RV (liters)	30	3.2 ± 1	30	3.0 ± 1	−0.12 ± 0.54	28	3.0 ± 1.0	−0.97 ± 0.54	25	2.8 ± 0.9	−0.34 ± 0.52	20	3.0 ± 1.2	−0.22 ± 0.69
RV (% predicted)	30	130.4 ± 47.0	30	123.6 ± 46.8	−5.02 ± 21.26	28	123.9 ± 49.3	−4.4 ± 21.53	25	117.6 ± 45.4	−14.28 ± 20.39	20	123.3 ± 58.7	−8.94 ± 28.38
TLC (liters)	30	6.0 ± 1.4	30	5.9 ± 1.4	−0.11 ± 0.54	28	5.7 ± 1.5	−0.19 ± 0.61	25	5.6 ± 1.3	−0.46 ± 0.73	20	5.7 ± 1.5	−0.47 ± 0.97
TLC (% predicted)	30	103.2 ± 20.2	30	100.9 ± 20.9	−2.11 ± 8.77	28	99.3 ± 22.5	−3.73 ± 11.09	25	96.9 ± 21.7	−8.46 ± 10.45	20	96.2 ± 25.7	−7.81 ± 14.25
D_LCO (ml/min/mm Hg)	30	14.7 ± 4.5	30	13.3 ± 4.4	−1.48 ± 2.36	28	13.5 ± 3.9	−1.50 ± 2.63	25	13.1 ± 3.3	−1.73 ± 3.22	20	11.6 ± 4.6	−3.57 ± 3.55
D_LCO (% predicted)	30	67.0 ± 18.5	30	60.8 ± 18.8	−6.35 ± 11.34	28	62.2 ± 16.4	−6.32 ± 11.56	25	60.6 ± 17.2	−6.84 ± 14.83	20	51.6 ± 17.6	−14.61 ± 14.85
D_LCO/VA (ml/min/mm Hg)	30	3.5 ± 1.4	30	3.1 ± 0.9	−0.4 ± 1.23	28	3.2 ± 0.9	−0.41 ± 1.34	25	3.2 ± 0.8	−0.39 ± 15.2	20	2.9 ± 0.8	−0.68 ± 1.43
D_LCO/VA (% predicted)	30	90.2 ± 27.3	30	84.0 ± 26.3	−5.9 ± 12.45	28	86.5 ± 29.5	−5.32 ± 14.72	25	85.0 ± 24.3	−3.92 ± 15.2	20	77.6 ± 23.9	−10.0 ± 16.33
PaO_2	3	75.1 ± 8.5	3	73.1 ± 9.7	−1.7 ± 7.89	2	72.7 ± 8.8	−3.11 ± 7.5	2	76.2 ± 6.	−1.14 ± 7.6	2	74.6 ± 10.	−1.02 ± 8.8

Pulmonary function test	Baseline (*n* = 30)		Days 45 post-SABR			Days 135 post-SABR			Days 225 post-SABR			Days 315 post-SABR		
	N	Raw	*n*	Raw	Change since baseline	*n*	Raw	Change since baseline	*n*	Raw	Change since baseline	*n*	Raw	Change since baseline
(mmHg)	0		0			8		6	5	4	3	0	3	3
$PaCo_2$ (mmHg)	30	38.3 ± 4.4	30	37.4 ± 3.7	−0.95 ± 4.05	28	37.7 ± 4.5	−0.48 ± 3.5	25	37.8 ± 3.6	0.32 ± 3.16	20	37.8 ± 4.7	−0.66 ± 5.18

Abbreviations: FEV_1 = forced expiratory volume in the first second; SVC = slow vital capacity; RV = residual volume; TLC = total lung capacity; D_LCO = diffusing capacity for carbon monoxide; D_LCO/VA diffusing capacity for carbon monoxide / alveolar volume; PaO_2 = partial pressure of arterial oxygen; $PaCO_2$ = partial pressure of arterial carbon dioxide; SABR = stereotactic ablative radiation therapy.

Table 2 also describes all changes at different time points for any parameter. A statistically significant decline in SVC, FEV_1, D_LCO and PaO_2 was seen at 135 days post-SABR; in details, change from baseline was 0.10 L for SVC ($p = 0.04$), 0.73 L for FEV_1 ($p = 0.02$), 1.50 ml/min/mmHg for D_LCO ($p = 0.001$) and 3.11 mmHg for PaO_2 ($p = 0.04$). At 315 days, a significant change of TLC, FEV_1, and D_LCO was also evident ($p = 0.03$, 0.007 and 0.0001, respectively); conversely, PaO_2 values increased at 315 days towards baseline values. For D_LCO, mean decline at 135 days was 10.6%, while at 315 days 23.2%. The ratio between D_LCO and alveolar volume didn't show any statistical significant change. No significant correlations were found between different tumor location (upper versus lower lobe and central versus peripheral) and changes in PFT.

3.3. Toxicity

Clinical pulmonary toxicity according to RTOG scoring system was recorded in 16 patients; 5 patients experienced G1 (15%), 6 G2 (20%), 4 G3 (13.3%) and 1 G4 toxicity (3.3%), respectively. At logistic regression analysis, none of the baseline PFT parameters resulted to be associated with the occurrence of pulmonary toxicity of any grade and of grade ≥2 (Table 3). Other symptoms reported by the patients were asthenia (15 patients), cough (3 patients) and thoracic pain (1 patient, treated for a tumor in close proximity to the chest wall).

Table 3.

Logistic regression model analysis of baseline pulmonary function tests and toxicity.

Pulmonary function test	Any pulmonary toxicity			Grade 2+ pulmonary toxicity			Any late radiological toxicity (Koenig)		
	No. of events/total	OR (95% CI)	*p* Value	No. of events/total	OR (95% CI)	*p* Value	No. of events/total	OR (95% CI)	*p* Value
FEV_1 (liters)	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	16 (0.1–200)	0.26
FEV_1 (%predicted)	16/30	1.5 (0.1–22)	0.75	11/30	3.1 (0.4–21.4)	0.26	7/24	NA-unstable	–
FEV_1/SVC	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	NA-unstable	–
FEV_1/SVC (%predicted)	16/30	0.02 (0–7.7)	0.2	11/30	0.02 (0–7)	0.18	7/24	NA-unstable	–
SVC	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	0.1 (0.003–7.8)	0.34
SVC (%predicted)	16/30	0.1 (0–5)	0.22	11/30	0.1 (0–6.7)	0.21	7/24	NA-unstable	–
RV (liters)	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	NA-unstable	–
RV (%predicted)	16/30	5.04 (0.4–75.2)	0.24	11/30	8.6 (0.5–150.3)	0.14	7/24	NA-unstable	–
TLC (liters)	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	0.7 (0.1–3.6)	0.68
TLC (%predicted)	16/30	0.03 (0–5.5)	0.19	11/30	0.008 (0–2.8)	0.11	7/24	NA-unstable	–
D_LCO (ml/min/mmHg)	16/30	NA-unstable	–	11/30	0.001 (0–6.5)	0.12	7/24	0.9 (0.6–1.2)	0.39
D_LCO (%predicted)	16/30	8.8 (0.6–136)	0.12	11/30	8.8 (0.7–105.4)	0.09	7/24	NA-unstable	–

Pulmonary function test	Any pulmonary toxicity			Grade 2+ pulmonary toxicity			Any late radiological toxicity (Koenig)		
	No. of events/total	OR (95% CI)	*p* Value	No. of events/total	OR (95% CI)	*p* Value	No. of events/total	OR (95% CI)	*p* Value
D_LCO/VA (ml/min/mmHg)	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	NA-unstable	–
D_LCO/VA (%predicted)	16/30	3.9 (0.3–55)	0.31	11/30	3.7 (0.2–75.2)	0.4	7/24	NA-unstable	–
PaO_2 (mmHg)	16/30	1.0 (0.8–1.3)	0.94	11/30	0.9 (0.5–1.6)	0.72	7/24	1.1 (0.9–1.3)	0.41
$PaCo_2$ (mmHg)	16/30	0.8 (0.1–4.3)	0.75	11/30	0.3 (0.1–1.3)	0.12	7/24	NA-unstable	–

Abbreviations: CI = confidence interval; OR = odds ratio; NA = not applicable; all others abbreviation are as shown in Table 2.

Concerning acute radiological toxicity, data are available for 30 and 27 patients at 45 days and 135 days, respectively; 22/30 patients (73%) had some nonspecific radiological changes at these time points; 8/22 patients (36.4%) had CT findings of consolidation pattern (patchy in 3 and diffuse in 5), while 14 (63.4%) presented ground-glass opacities (patchy in 5 and diffuse in 9). At 225 days and 315 days after SABR, data of 24 and 16 patients were available, respectively. Eight patients out of 24 (33.3%) did not develop any kind of late radiological changes, while 9/24 (37.5%) developed a mass-like consolidation pattern.

At logistic regression, performed on 24 evaluable patients, baseline PFT did not result associated to late radiological changes.

3.4. Correlation between dose-volume parameters, lung toxicity and changes in PFT

Patients who developed radiation pneumonitis (any grade) had higher volume of normal lung receiving 5, 10 and 20 Gy (V_{5Gy}, V_{10Gy}, V_{20Gy}) and higher Mean Lung Dose (MLD_{2Gy}, converted for fractionation in 2 Gy equivalent). We also considered as a potential predictive parameter of lung toxicity the absolute lung volume spared from a 5 Gy dose (VS5). Logistic regression analysis did not show any significant correlation between these dosimetric parameters and a higher risk of clinical toxicity (Table 4). The same was observed for radiological toxicity and for PFT changes (data not shown).

Table 4.

Normal lungs dose-volume distributions by development of any grade clinical lung toxicity.

Parameter	All patients	Pneumonitis	No pneumonitis		
	(*n* = 30)	(*n* = 14)	(*n* = 16)	OR (95% CI)	*P* value
Ipsilateral lung V_{20Gy} (%)	15.6 ± 5.5	15.1 ± 5.8	16.1 ± 5.4	1.03 (0.91–1.18)	0.61
Ipisilateral lung V_{10Gy} (%)	24.5 ± 6.8	22.9 ± 6.9	26.1 ± 6.5	1.07 (0.96–1.21)	0.22
Ipsilateral lung V_{5Gy} (%)	34.9 ± 8.6	31.7 ± 8.2	38.1 ± 8.0	1.11 (0.99–1.24)	0.058
Ipsilateral mean lung dose (EQD_{2Gy})	11.9 ± 3.5	11.7 ± 3.9	12.1 ± 3.1	1.03 (0.83–1.27)	0.82
Bilateral lung V_{20Gy} (%)	7.8 ± 2.6	7.8 ± 2.8	7.8 ± 2.6	0.99 (0.75–1.32)	0.97
Bilateral lung V_{10Gy} (%)	14.4 ± 5.1	14.6 ± 6.1	14.2 ± 3.9	0.98 (0.85–1.14)	0.84
Bilateral lung V_{5Gy} (%)	24.8 ± 7.4	24.7 ± 8.9	24.8 ± 6.0	1.0 (0.90–1.10)	0.97
Bilateral mean lung dose (EQD_{2Gy})	6.9 ± 1.9	7.0 ± 2.2	6.9 ± 1.6	0.98 (0.66–1.44)	0.91
Absolute lung volume spared from a 5 Gy dose (VS5, in cc)	3088.9 ± 790.3	3157.4 ± 699	3020.4 ± 893.5	1.02 (0.78–1.17)	0.65

Abbreviations: CI = confidence interval; OR = odds ratio; V = volume receiving *n* Gy (e.g., V20 = volume receiving 20 Gy); EQD2Gy = equivalent dose in 2 Gy fractions.

3.5.

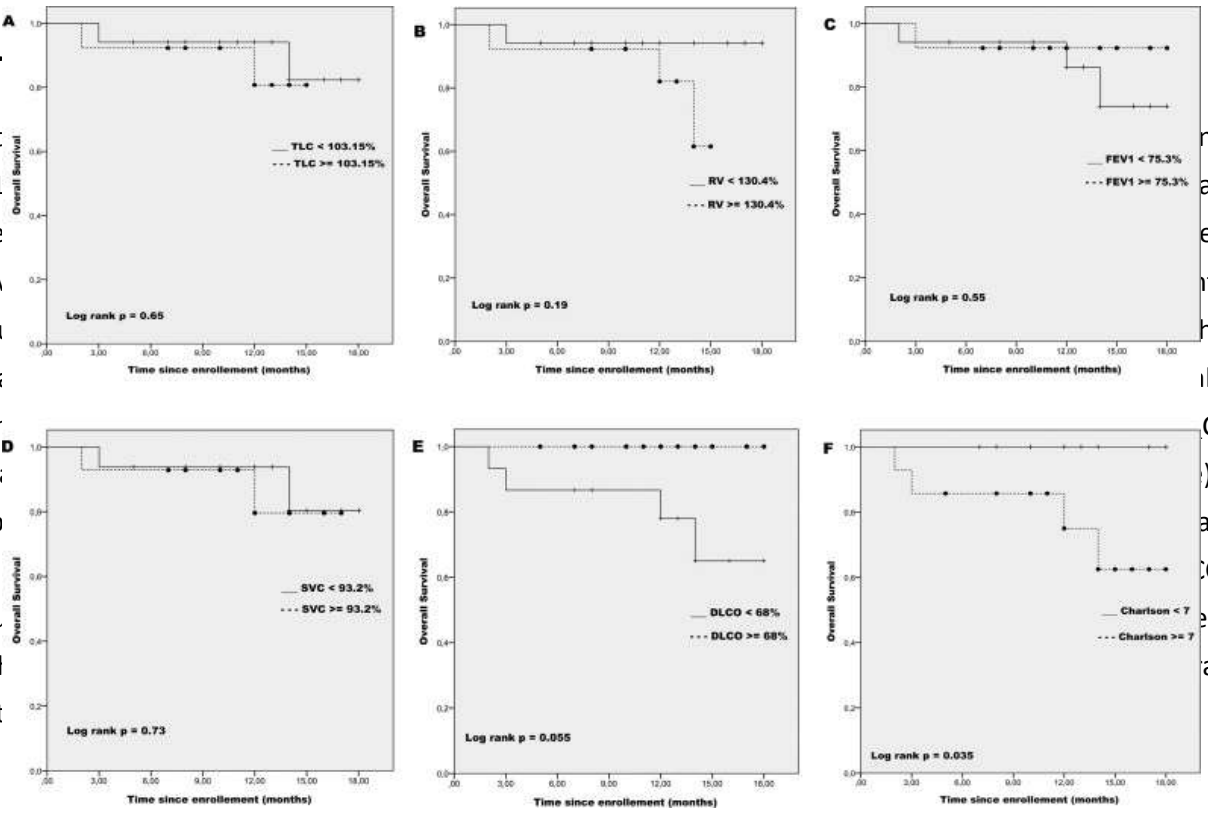

Fig. 2.

Kaplan-Meier overall survival curves of patients with baseline pulmonary function test values greater and less than the mean percentage of predicted values. (2A) Total lung capacity (TLC); (2B) residual volume (RV); (2C) forced expiratory volume in the first second FEV1; (2D) slow vital capacity (SVC); (2E) diffusing capacity for carbon monoxide (DLCO); (2F) age-adjust Charlson's comorbidity index (aa-CCI).

3.6. Quality of life

Compliance for patients completing the LCSS was 80.5% (107 of 133 total assessments); the most common reason for non-compliance was failure in questionnaire administration. The analysis was performed at 135 days, when 22 questionnaires were evaluable. Fig. e3 (Supplementary material) describes the evolution of mean values for every item from basal to 135 days after completion of SABR, showing a statistical significant worsening of the item 2 "Fatigue" (mean basal value = 29, mean value at T135 = 39.8, $p = 0.05$). Non-significant changes were observed for other items; a negative trend in terms of worsening of cough ($p = 0.053$) and daily activity ($p = 0.06$) was registered (Fig. 3, Supplementary material). A similar pattern of LCSS changes was observed at 315 days after SABR (on 10 evaluable patients, data not shown). At logistic regression analysis, no significant correlation was observed between PFT changes and worsening of fatigue.

4. Discussion

In a recent review on the role of SABR for early stage lung cancer, from Louie et al. [20], and accompanying editorial from Brada et al. [21], the Authors emphasize the need for prospective studies with survival and quality of life as primary endpoints, focusing the attention on pulmonary function and morbidity. This is one of the few prospective studies describing changes in pulmonary function and quality of life after SABR, designed with different endpoints: we investigated for a correlation between SABR and changes in pulmonary function, for a potential correlation between baseline pulmonary function tests and overall survival, and between radiation-dose volume parameters and lung toxicity or impairment in pulmonary function and patient-reported quality of life. This prospective series of patients is heterogeneous with regards to the size of lesions, position (central and peripheral) and dose prescription, reflecting clinical practice in an academic environment.

Changes of SVC, FEV1 and D_LCO at 135 and TLC, FEV_1, and D_LCO at 315 days after SABR resulted to be statistically significant. The ratio between D_LCO and alveolar volume (VA) did not significantly change, suggesting that alveolar volume reduction dose impact on D_LCO more than true diffusion impairment.

Conversely, a decline of PaO_2 was evident at 135 days, but not at 315 days, suggesting a progressive recovery of oxygen level during follow-up. Results of the present study are partially in contrast with the findings of Stanic et al. on pulmonary function changes after stereotactic radiotherapy in patients included in the RTOG 0236 phase II trial, designed for medically inoperable early stage NSCLC patients [10]. In their report, including the data of 55 patients followed over a 2 years interval, the mean percentage in FEV_1 and D_LCO decline were 5.8% and 6.3%, respectively, with minimal changes in blood gases and no significant

decline in oxygen saturation. The Authors concluded that no clinically significant changes in pulmonary function were evident after SABR, at a dose of 54 Gy in 3 fractions. The same statistical methods were used to analyze PFT changes over time, and the two studies may be carefully compared, taking into account that the RTOG study was designed for a selected group of patients with specific characteristics (peripheral tumors, all receiving 54 Gy in 3 fractions). Baseline function tests were better for our patients (mean D_LCO: 14.7 vs. 10.6, mean FEV_1: 1.72 vs. 1.3): we can argue that starting from higher baseline values, the entity of the reduction might be higher as well, as underlined in the report by Guckenberger et al. [22]. Moreover, 33% of our patients (*n* = 8) were treated for centrally located tumors. A difference in treatment planning is also evident, as our series include only VMAT plans, while in the RTOG cohort patients were treated with 3D conformal radiotherapy.

Another important endpoint in our trial was to investigate whether baseline PFT correlates or not with lung toxicity and overall survival. Both studies showed no correlation between baseline PFT and the occurrence of any grade clinical or radiological pulmonary toxicity. Moreover, baseline PFT were not associated to overall survival probability at 1 year. In a previous study by Henderson et al. [23], baseline FEV_1 significantly predicted for post-treatment survival, and patients with poor pulmonary function had significantly better survival. Another study, from Stephans et al. [24], showed similar results. As underlined by Stanic et al. [10], these findings might be explained by the higher rate of deaths in patients medically inoperable for reasons other than poor pulmonary function. In our cohort, patients with higher age-adjusted Charlson's comorbidity index (aa-CCI) showed significantly worse survival than the other patients at univariate analysis, confirmed at Mantel–Cox log-rank test ($p = 0.035$). Particularly, cardiac diseases are associated with a higher risk of death after SABR, and therefore patients with NSCLC and severe cardiac disease appear to have less chance of survival than inoperable patients with poor pulmonary function.

No relationships between MLD2 Gy, V_{5Gy}, V_{10Gy}, V_{20Gy} (ipsilateral and bilateral), VS5 (bilateral) and the occurrence of radiation-induced lung toxicity were observed. A parallel result was obtained when investigating for the correlation between the same lung dose-volume parameters and changes in PFT. Again, these results are similar to what previously shown in the RTOG 0236 cohort, even if the planning technique was different [10]. Notably, the occurrence of lung toxicity in the present study is higher than previously reported (grade ≥3 lung toxicity 16.6%): this finding may be a consequence of several factors, such as the accurate follow-up protocol typical of a prospective study in comparison with retrospective series (toxicity overestimation) or the randomly high number of stage IB (tumors larger than 3 cm) patients enrolled in our cohort (44% vs. 20% in the RTOG 0236 cohort). SABR for larger tumors may translate in higher doses to normal lungs in comparison with the more typical dose distributions achievable in patients with stage IA NSCLC, and the reported toxicity rate for larger tumors is higher [25]. However, as previously mentioned, in the present study we did not find any correlation between normal lung dose-volume parameters and the occurrence of lung toxicity (clinical and radiological). With regards to the possible negative impact of the use of VMAT, a previous publication showed no difference in the incidence of radiation pneumonitis between 3D-CRT and VMAT [17].

SABR was very well tolerated, with a limited impact on daily life. Previous studies also indicated, by means of other scoring systems, that quality of life was not severely impaired by SABR [26], [27] and [28].

In conclusion, results of the present study show that SABR may cause a small decline in lung volumes and D_LCO; however, the clinical impact of such changes seems limited in the whole population, being difficult to estimate in individual patients. The lung function worsening observed after SABR appears however of lower entity if compared with the expected damage caused by thoracic surgery, even after surgical interventions such as wedge resection or segmentectomy.

Conflict of interest statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Appendix A. Supplementary data

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