Changes in Pulmonary Function After Stereotactic Body Radiotherapy and After Surgery for Stage I and II Non-small Cell Lung Cancer, a Description of Two Cohorts

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Abstract. *Aim: To evaluate changes in pulmonary function tests (PFTs) at different follow-up durations after stereotactic body radiotherapy (SBRT) and surgery in stage I and II non-small-cell lung cancer (NSCLC). Patients and Methods: Differences between pre-treatment- and follow-up PFTs were analyzed in 93 patients treated with surgery and 30 patients treated with SBRT for NSCLC. Follow-up durations were categorized into: early (0-9 months), middle (10-21 months) and late (≥22 months). Wilcoxon signed-rank test was used to analyze differences between pre-treatment and follow-up PFTs. Results: Forced expiratory volume in one second, forced vital capacity and diffusion capacity for carbon monoxide corrected for the actual hemoglobin level significantly diminished after surgery for all follow-up durations: 11-17% of predicted values. After SBRT, PFTs remained stable, but a declining trend of 6% (p=0.1) was observed after 22 months. Conclusion: SBRT might lead to less treatment-related toxicity measured by PFTs than surgery in both the short and long term.*

Lung cancer remains the most lethal form of cancer worldwide for both men and women (1). The most common type of lung cancer in 85-90% of the patients is non-small-cell lung cancer (NSCLC), and 30% of patients are diagnosed with disease at an early stage, defined as stage I and II (2).

The standard treatment for stage I and II NSCLC is surgical resection of the tumor, defined as lobectomy with systematic mediastinal lymph node dissection (3). However, approximately 20% of patients are not eligible for surgery due to a compromised pulmonary function [often pertaining to chronic obstructive pulmonary disease (COPD)] or cardiovascular comorbidity (4). Besides medical inoperability, there are patients who refuse surgical treatment for personal reasons (5). Since the introduction of stereotactic body radiotherapy (SBRT) in 2003-2005, optimum tumor control can now be achieved because the tumor is irradiated very precisely, while the surrounding tissue is spared to the greatest extent possible, achieved by the large dose-gradient fall off outside the tumor target (6).

Recently, retrospective studies have shown survival and local tumor control rates for patients with stage I NSCLC when treated with either SBRT or surgery to be equal (7, 8). In a pooled analysis of two randomized trials, which were both closed prematurely, the authors concluded that SBRT is also an equivalent treatment option for operable patients, and a better pooled estimated 3-year overall survival of 95% after SBRT compared to 79% after surgery was found (9). Even when patients with stage II NSCLC were included, Kastelijn *et al*. showed that by using the propensity score to adjust for confounding by indication, equal outcomes are suggested after surgery and SBRT in patients with early-stage NSCLC (10). Therefore, investigations about other treatment-related outcomes, such as pulmonary function, must be performed to compare the treatments.

Patients with poor pulmonary function, that can be expressed by symptoms such as dyspnea, may have a diminished quality of life (11). Previous studies conclude that after surgery, a decline in pulmonary function is observed shortly after resection, with recovery up to 3-6 months after treatment because the remaining lobe expands and compensates for the resected part (12-15). Pulmonary function after SBRT is likewise not significantly impaired overall or shows only a small decline (16-21). However, long-term follow-up data following SBRT are lacking.

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The purpose of the present study was to evaluate changes in pulmonary function after different follow-up durations, up to more than two years, within an SBRT cohort and a surgery cohort.

Patients and Methods

This retrospective cohort study was performed at the Department of Pulmonology of St. Antonius Hospital, Nieuwegein, the Netherlands. All patients diagnosed with stage I and II NSCLC and treated with SBRT or surgery between 2008 and 2011 in this hospital were included. Data were collected from reviewing electronic patient records. When patients were referred to their own physician at another hospital, pulmonary function test (PFT) values were retrieved. That all patients treated in our hospital were included was verified by consulting the database of the Dutch Cancer Registry.

Patients with recurrent disease, lacking follow-up, induction chemotherapy and more than one tumor at the time of diagnosis were excluded. Of this remaining group, patients were included if they had both a pre- and a minimum of one post-treatment PFT.

The diagnosis of stage I and II NSCLC was evaluated by using the regularly updated National Comprehensive Cancer Network (NCCN) guidelines (22). Tumor staging was carried out according to the seventh edition of the tumor, node, metastasis (TNM) classification, which was revised in 2010. Patients treated before 2010, were re-staged according to the current edition (23).

Histological grading was only performed in 20% of patients who underwent SBRT. Due to poor pulmonary function and the risk of complications when performing a biopsy, obtaining a histopathologically confirmed diagnosis was not always possible. Therefore, the single pulmonary nodule calculator was used to generate a percentage probability of malignancy (site: http://www.chestx-ray.com/) (24).

Before treatment, all patients were discussed in the weekly multidisciplinary meeting. This team consisted of a pulmonologist, thoracic surgeon, oncological radiotherapist and a radiologist. Whether the patients underwent surgery or SBRT depended on their pulmonary function and Eastern Cooperative Oncology Group (ECOG) performance status.

The choice of surgical approach (type of surgical resection and type of incision) were at the discretion of the treating surgeon. During surgery, nodal dissection was routinely carried out in accordance with the guidelines of the European Society of Thoracic Surgeons (25). In 2009, video-assisted thoracic surgery (VATS) was introduced.

SBRT was delivered in an outpatient setting at the University Medical Centre Utrecht. Different stereotactic regimens were used depending on tumor size and location: three fractions of 18 Gy, five fractions of 12 Gy, or eight fractions of 7.5 Gy. The biological effective dose was more than 100 Gy. Patients were treated three times a week.

PFTs were performed by spirometry. The equipment used for spirometry was from Jaeger Masterlab, Viasys (Hoechberg, Germany). The following PFT parameters were included: forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and transfer factors: the diffusion capacity of carbon monoxide, corrected for the actual hemoglobin level (DLCOc) and carbon monoxide transfer coefficient (KCOc). The transfer capacity was measured using a single-breath method.

The absolute and predicted percentages were reported. Percentage of predicted values were calculated using the European Coals and Steel Community/European Respiratory Society references, based on gender, age and height (26).

Because many patients had underlying disease, for example COPD, they often used bronchodilators. Inhalation medication use was defined as bronchodilator admitted during spirometry and as chronically used by the patient. To prevent differences caused by medication, rather than by treatment, and to evaluate the maximum pulmonary function, pre-treatment post-inhaled bronchodilator PFT were compared to post-inhaled bronchodilator PFTs after treatment whenever possible.

COPD was classified using the (old, 2011) criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (27)

The follow-up period started on the first day of treatment. There was no routine protocol for assessment of post-treatment PFTs. Spirometry was performed on indication.

Statistical analysis. The primary endpoint was any change in PFT after treatment after different follow-up durations. Normally distributed continuous variables are presented as the mean with standard deviation and compared between the groups using the unpaired *t*-test. Non-normally distributed continuous variables are presented as the median and range and compared with the Mann–Whitney *U*-test. For categorical variables, the Chi-square test was used to compare frequencies of the groups.

Our data showed differences in follow-up durations and differences in the number of PFTs per patient. Therefore patients were categorized into three categories of follow-up durations: early (0-9 months), middle (10-21 months) and late (≥22 months). This distribution was based on the number of patients divided over time to obtain equal groups.

The percentage differences in pulmonary function between preoperative and postoperative values were expressed as the changes relative to the pretreatment value (baseline). A negative relative change from the baseline value represents an increase in pulmonary function since the baseline PFT, while a positive value represents a decline.

Wilcoxon signed-rank test for paired samples was used for analyzing statistical differences between baseline and follow-up PFTs within the groups.

A two-tailed *p*-value of less than 0.05 was considered statistically significant and all statistical analys were performed using IBM SPSS statistics 22 (SPSS Inc., Chicago, IL, USA). Graphs were made by using GraphPad Prism 6.00 for Windows (GraphPad Software, La Jolla, CA, USA).

Results

Among 228 patients, 123 patients had both pre- and a minimum of one post-treatment PFT. Out of the 123 patients, 30 patients were treated with SBRT and 93 patients with surgery.

Patient characteristics are shown in Table I. The surgically-treated group consisted of more males, while in the SBRT group, females dominated. SBRT patients were older, more often had COPD GOLD II and III, and were diagnosed with smaller tumors. No differences in body mass index, smoking status, tumor location and clinical TNM stage were assessed between the two treatment groups.

The average time between pre-treatment PFT and starting of treatment was one month (range=0-6 months). Most patients were not represented in each of the follow-up categories because follow-up was not performed routinely. Therefore, the categories do not represent an individual course, but they do

Table I. *Baseline characteristics of both cohorts. Continuous data are presented as median with range (minimum–maximum), unless otherwise specified.*

Characteristic	No. of patients (%)		*p*-Value
	SBRT	Surgery	
Total number		n=30	n=93
Gender			
Male	11 (37)	54 (58)	0.041
Female	19 (63)	39 (42)	
Age, years	73 (52-90)	66 (35-80)	0.009
Mean BMI (SD), kg/m^2	25.40 (5.1)	26.56 (4.1)	0.209
Smoking			
No smoker or unknown	2 (2)	6 (7)	0.334
Current or former smoker	28 (93)	87 (94)	
COPD			
GOLD I	0 (0)	18 (19)	<0.0001**
GOLD II	14 (47)	29 (31)	
GOLD III	11 (37)	3 (3)	
GOLD IV	2 (7)	0 (0)	
No COPD	3 (10)	39 (42)	
Histology			
No biopsy	24 (80)	0 (0.0)	<0.0001
Adenocarcinoma	1 (3)	59 (63)	
Squamous cell carcinoma	4 (13)	27 (29)	
Large cell/other/NSCLC	1 (3)	7 (8)	
Tumor location			
Left lower lobe	6 (20)	25 (27)	0.878
Left upper lobe	7 (23)	34 (37)	
Right lower lobe	12 (40)	18 (19)	
Right middle and upper lobe	5 (17)	16 (17)	
Surgery			
VATS		38 (41)	
Open thoracotomy		55 (59)	
Lobectomy		81 (87)	
Pneumonectomy		5 (5)	
Other (bilobectomy, wedge, sleeve)		7 (8)	
SBRT			
3×18 Gy/5×12 Gy/8×7.5 Gy	10/10/10	n.a.	
Clinical tumor stage			
IA	23 (77)	52 (56)	0.068**
IB	3 (10)	18 (19)	
IIA	1 (3)	14 (15)	
IIB	3 (10)	9 (10)	
Pathological tumor stage			
IA	n.a.	39 (42)	
IB		20 (22)	
IIA		14 (15)	
IIB		13 (14)	
IIIA		7 (8)	
Clinical tumor diameter (cm)	1.85 (1-7)	2.20 (1-10)	0.023
Pathological tumor diameter (cm)	n.a.	3.07 (2)	
ECOG PS			
0	12 (40)	85 (91)	<0.0001**
1	17 (57)	8 (9)	
2	1 (3)	0 (0)	

SBRT: Stereotactic body radiotherapy; BMI: body mass index; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ECOG PS: Eastern Cooperative Oncology Group performance score; n.a.: not applicable; clinical tumor diameter was measured by computed tomographic scan and pathological tumor diameter during pathological examination. **For three variables the Chi-square test could not be performed due to the small number of patients (<5) in the groups. Therefore, Chi-square was performed when COPD was dichotomized into normal pulmonary function and COPD. For cTNM and ECOG PS, the Mann–Whitney *U*-test was performed.

give information about PFTs after treatment at different time points. When patients had more than one PFT in one follow-up category, the average value was calculated.

The median time between treatment and follow-up for the early group was 5 months (range=2-9 months) after SBRT and 6 months (range=1-9 months) after surgery; for the middle group it was 14 months for both (range=10-20/21 months), and for the late group it was 31 months (range=24-55 months) after SBRT and 36 months (range=22-62 months) after surgery. All pulmonary functions in the SBRT group worsened more than those in the surgical group ($p<0.001$), especially in the long run. Differences in PFTs are shown in Table II and the relative differences in Figure 1.

FEV_1, FVC and DLCOc as a percentage of their predicted values significantly diminished after surgery for all follow-up durations. After 22 months, the KCOc as a percentage of the predicted value remained stable with a relative change of 2.94% ($p=0.074$). The relative changes for the other parameters in the long-term were 16.69% for FEV_1; 11.19% for FVC and 15.45% for DLCOc. After SBRT, absolute FEV_1 and FVC values remained stable up to 22 months. After 22 months, a statistically significant change was observed (relative changes for FEV_1 and FVC were ±11% $p=0.008$). This difference was not observed for the percentage of predicted values (both ±6%; $p=0.122$). DLCOc and KCOc were not significantly impaired after SBRT (11.23% and 6.81%, respectively; $p=0.091$).

Discussion

Because equivalent survival and local control rates after surgery and SBRT might be assumed from prior work, there is need for assessment of other treatment-related parameters to compare these two treatments for patients with stage I-II NSCLC (4, 7-9, 28). The current retrospective study provides long-term data, up to more than two years, of PFT changes after SBRT and surgery.

Numerous retrospective studies have examined PFT changes after SBRT. In three studies, pulmonary function (FEV_1 and FVC) remained stable within 24 months after treatment of variable sample sizes of 30-90 patients (16, 19, 20). In contrast to these studies, Guckenberger *et al*. reported a decline in FEV_1 of 8.1% of the predicted value after a median follow-up of 12 months among 191 patients (17). A decline of 3% of predicted FEV_1 and FVC was also revealed by the only study examining PFT long-term changes, up to more than four years after treatment (21).

For diffusion capacity, several results have been published, ranging from no change, a decline and even a small increase in pulmonary function of 4-9% of predicted absolute difference (16, 18, 20). It is suggested that improvement may have been due to tumor shrinkage. On the other hand, a decline was observed from 12% of relative change of predicted by value Guckenberger *et al*. (17), while Stanic *et al*. observed only a

Table II. *The distribution of pulmonary function test (PFT) results. All data are presented as the median values with range (minimum-maximum). Significances were calculated for the differences in each category between follow-up PFTs and baseline PFTs. PFT% results are percentages of the predicted values.*

	Follow-up duration							
	Baseline		Early		Middle		Late	
Parameter	SBRT	Surgery	SBRT	Surgery	SBRT	Surgery	SBRT	Surgery
FEV_1	n=30	n=93	n=14	n=33	n=13	n=49	n=18	n=60
	1.22 (0.53-2.63)	2.33 (1.00-5.44)	1.24 (0.43-2.33)	1.91 (0.96-4.02)*	1.25 (0.46-2.07)	1.84 (0.95-3.78)*	1.08 (0.46-2.00)*	1.92 (0.85-3.86)*
FEV_1%	n=30	n=93	n=14	n=33	n=13	n=49	n=18	n=60
	54.61 (24.40-128.90)	86.90 (45.50-135.00)	48.51 (26.77-118.70)	75.30 (39.70-114.50)*	58.30 (22.20-108.30	75.35 (41.10-104.30)*	49.80 (19.90-84.90)	72.15 (35.40-115.45)*
FVC	n=30	n=90	n=14	n=31	n=13	n=46	n=18	n=60
	2.59 (1.15-3.43)	3.41 (1.75-6.74)	2.52 (1.28-3.36)	2.96 (1.31-5.21)	2.93 (1.97-3.47)	2.91 (1.37-5.48)	2.38 (1.01-3.12)*	3.01 (1.30-4.83)*
FVC%	n=30	n=90	n=14	n=31	n=13	n=47	n=18	n=60
	79.00 (46.30-129.00)	102.95 (69.10-145.40)	85.95 (57.00-120.00)	97.75 (31.70-141.90)*	87.80 (58.10-135.10)	95.30 (44.97-148.90)*	83.00 (35.30-101.80)	90.65 (51.20-138.95)*
DLCOc	n=25	n=85	n=9	n=25	n=7	n=32	n=8	n=43
	4.31 (1.70-7.43)	6.05 (2.98-11.73)	3.81 (1.38-6.58)	4.92 (2.86-9.57)*	3.95 3.66-6.41)	5.18 (2.88-8.39)*	3.25 (1.61-6.31)	4.89 (1.87-9.57)*
DLCOc%	n=25	n=87	n=9	n=25	n=7	n=32	n=8	n=43
	57.00 (23.00-94.0)	70.90 (33-110.50)	50.00 (18.50-89.80)	64.40 (38.40-86.70)*	59.60 (42.80-88.10)	64.30 (39.80-89.60)*	42.30 (22.20-91.20)	60.25 (23.50-99.30)*
KCOc	n=25	n=85	n=9	n=25	n=7	n=32	n=8	n=43
	0.88 (0.40-1.58)	1.15 (0.57-1.73)	0.86 (0.37-1.35)	1.25 (0.56-1.51)	0.95 (0.76-1.31)	1.13 (0.62-1.58)	0.77 (0.52-1.17)	1.04 (0.39-1.68)*
KCOc%	n=8	n=25	n=9	n=25	n=7	n=32	n=8	n=43
	73.49 (29.34-118.70)	84.30 (38.30-126.70)	74.90 (25.10-118.70)	88.09 (41.70-111.40)	72.10 (51.50-116.10)	81.90 (40.10-115.20)	51.15 (34.00-106.30)	82.35 (26.60-120.33)

FEV_1: Forced expiratory volume in one second; FEV_1%: percentage of predicted forced expiratory volume in one second; FVC: forced vital capacity; FVC%: percentage of predicted forced vital capacity ; DLCOc: diffusion capacity for carbon monoxide corrected for the actual hemoglobin level ; DLCOc%: percentage of predicted diffusion capacity for carbon monoxide corrected for the actual hemoglobin level; KCOc: carbon monoxide transfer coefficient; KCOc%: percentage of predicted carbon monoxide transfer coefficient. *$p<0.05$.

decline for up to three months (−5.39% of predicted relative change, $p=0.007$) (19).

The most important implication of the current study is that even after a median follow-up time of 31 months (range=24-55 months), all PFT values remained stable after SBRT. This is in accordance with other studies, where stable PFT results within 24 months were observed. Although after 22 months a significant decline in absolute FEV_1 and FVC was observed, this decline disappeared when adjustment for age, height and gender was made. But we should address the fact that declining trends were observed (with *p*-values of 0.1), suggesting that significance might not have been reached due to the small sample size.

In patients who were treated with surgery, the extent of removal of lung parenchyma correlates with pulmonary function loss (29). Following pneumonectomy, a 35% decline in FEV_1 and FVC might be expected, following a lobectomy: 10% decline, and following the most limited resection: a sublobar resection, a decline of around 3% might be expected (12, 14, 15). Within six months, the maximum permanent loss due to the operation is reached and one study observed a plateau after 12 months (14). We did analyze pulmonary function after surgery in the long-term in order to be able to give a fair comparison of changes within the groups.

In our study, significant relative changes in FEV_1, FVC and DLCOc were between 11-17% for all follow-up durations. Previous research evaluating FEV_1 after lobectomy revealed the same results, with a decline ranging from 8 to 15% in FEV_1 (12, 14, 15). KCOc did not change postoperatively in this study, because KCO is independent of lung volume and will remain normal (30).

We must note that in contrast to these studies, in our study all kinds of resections were included, although most patients underwent a lobectomy (87%), and we used VATS as well as an open thoracotomy approach in our study. VATS uses smaller incisions and is less destructive than an open thoracotomy, this is expressed in fewer postoperative complications and may influence pulmonary function postoperatively (31). However, according to a study of Handy *et al.*, changes in PFTs postoperatively between these two approaches are not

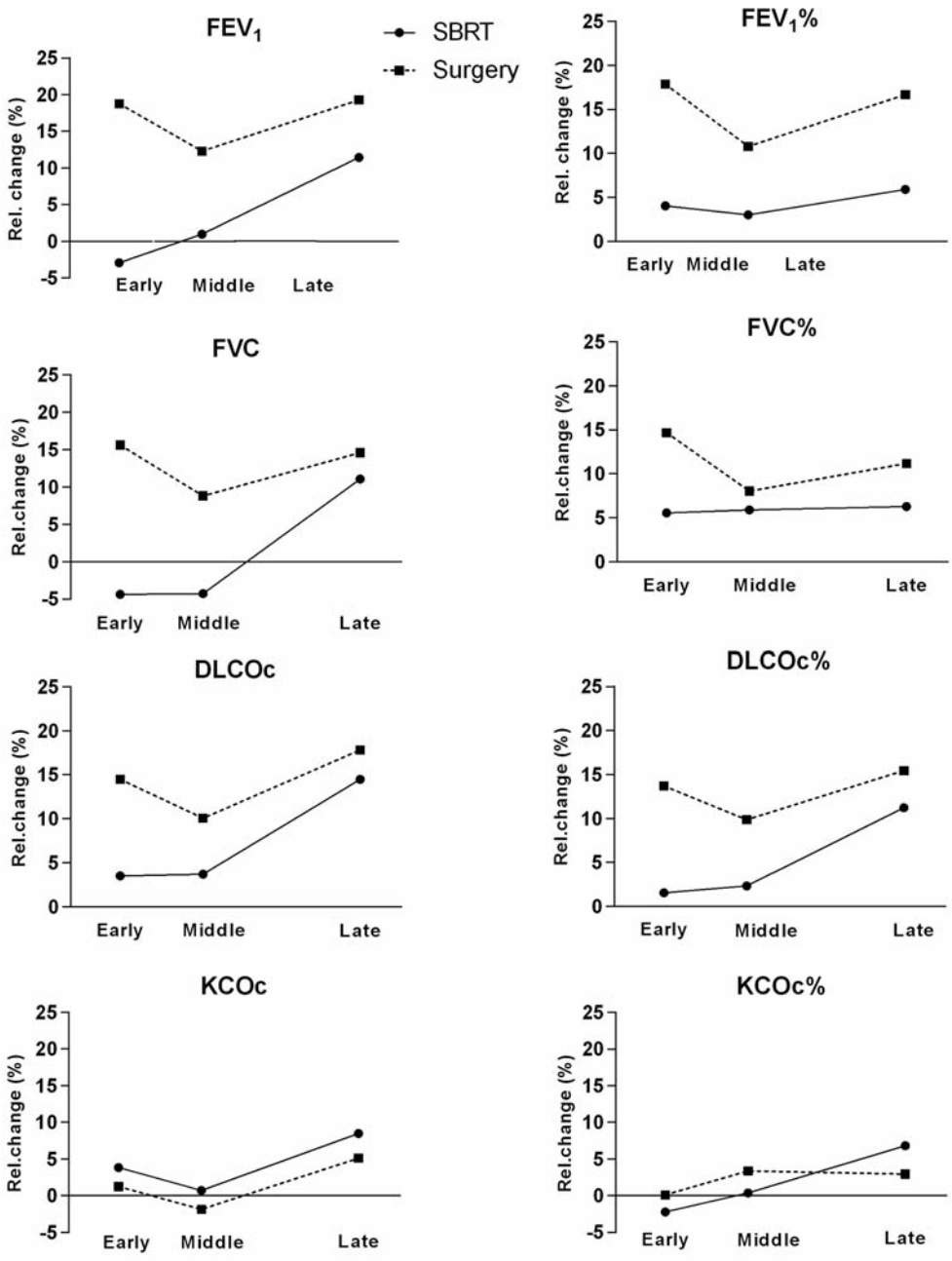

Figure 1. *Average relative changes in pulmonary function test (PFT) values from baseline for three different follow-up durations: early=0-9 months; middle=9-22 months; and late ≥22 months (0=day of treatment). Relative changes were defined as (pre-PFT–post-PFT)/pre-PFT×100. 'PFT'%=percentage of predicted PFT. For the surgical group, all changes in PFTs were significant, except for KCOc. For the stereotactic body radiotherapy (SBRT) group, changes were only significant for absolute FVC and FEV_1.*

significantly different, with a 14% decline in FEV_1 after open thoracotomy *versus* 8.7% decline after VATS within six months after treatment (32). A sub-group analysis of our results for the patients treated with lobectomy (n=83) revealed similar findings, with non-significant declines of 15% after open thoracotomy and 9% after VATS. When we analyzed patients who underwent a lobectomy separately from the other types of resection (which account for 13% of the resections and includes bilobectomy, pneumonectomy as well as wedge and sleeve resections), median PFTs at early follow-up were similar. Therefore, a comparison with other studies including only a lobectomy can be made.

A comparison of changes in PFTs between the groups could not be made because of the small sample size of the SBRT-treated group.

Declines in PFTs must be placed in perspective. A decline of 10-15% is considered clinically significant (33). However, studies about whether and to what degree a decline in pulmonary function is of significance for a patient are scarce. A small decline may be of more relevance in a patient with already compromised pulmonary function, while it might have little effect on a patient with normal pulmonary function before treatment. Because we included long-term follow-up, declines could also have been the result of physiological aging. Per year, a loss of 25-30 cc of FEV_1 might be expected in normal middle-aged adults, but this may increase in patients with COPD, emphysema or current smokers (34). This decline in FEV_1 per year might reveal why significant changes disappeared in the SBRT group when adjustment for age was performed. The same concept was put forward by Takeda *et al.* who observed smaller declines when PFT values were adjusted for age, height and gender (21).

Besides pulmonary function, quality of life assessments and dyspnea scores would provide additional information by placing declines in pulmonary function in perspective. In a small Dutch study, a slow increase in dyspnea was observed two years after treatment with SBRT, but quality of life was maintained (35).

This study has several limitations. Firstly, the retrospective nature of the study. Secondly, the small sample size of the SBRT group diminished the power of this study and made us choose a non-parametric test. Thirdly, the ideal situation would have been to evaluate post-treatment PFT values in individual patients compared to the same patients' pre-treatment values. Because of lack of routine PFTs, we were forced to categorize patients into three follow-up groups. An alternative approach would have been to group patients into only one follow-up group after treatment, resulting in one large group, thereby providing more power. However, this would not provide an appropriate view of PFT changes over time and could lead to bias, since a PFT after 4 years might be different from one after 6 months of treatment. Fourthly, SBRT for stage I NSCLC is already accepted in some guidelines, but the approach moves up to stage II NSCLC (22, 36). Although we also aimed to provide an overview of patients with stage II disease, most patients were diagnosed with stage I disease, with only four with stage II in the SBRT-treated group. Further research should include a larger number of patients diagnosed with stage II NSCLC.

This retrospective study showed that a patient who underwent SBRT might not have the acute effects on pulmonary function observed after surgery but they might have some degree of pulmonary function loss after 22 months, with the provision that the group of SBRT-treated patients was small. This functional loss is probably more related to physiological aging and underlying comorbidities, such as COPD, rather than to treatment-related toxicity. To work towards a patient-individualized treatment model, these results might be favorable for patients who are on the borderline of medical operability.

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