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# Impact of Sublobar Resection on Pulmonary Function: Long-term Results from ACOSOG Z4032 (Alliance)

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## Abstract

**Background—**Sublobar resection (SR) in high-risk operable patients may result in long-term decrease in pulmonary function. We previously reported 3-month pulmonary function outcomes from a randomized phase III study comparing SR alone to SR with brachytherapy (SRB) in patients with non-small cell lung cancer. We now report on long-term pulmonary function after SR.

**Methods—**Pulmonary function was measured at baseline, and at 3, 12 and 24 months. A ≥10% decline from baseline in $FEV_1$% or DLCO% was considered clinically meaningful. The impact of study arm, tumor location, size, approach (VATS vs. thoracotomy), and SR type (wedge vs.

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segmentectomy) on pulmonary function was assessed using a Wilcoxon rank sum test. A generalized estimating equation model was used to assess the impact of each factor on longitudinal data including all 4 time-points.

**Results—**Complete pulmonary function data at all time-points was available in 69 patients. No significant differences were observed in pulmonary function between SR and SRB, thus the study arms were combined for all analyses. A ≥10% decline ($p$=0.02) in $FEV_1$% was demonstrated for lower lobe resections at 3 months, but was not seen at 12 or 24 months. A ≥10% decline ($p$=0.05) in DLCO% was seen for thoracotomy at 3 months but was not seen at 12 or 24 months.

**Conclusions—**Clinically meaningful declines in pulmonary function occurred after lower lobe resection and after thoracotomy at 3 months, but subsequently recovered. This study suggests that SR does not result in sustained decreased pulmonary function in high-risk operable patients.

### Keywords

pulmonary function; lung cancer surgery; lung cancer clinical trials; lobectomy; segmentectomy; wedge resection; statistics (clinical trial)

Sublobar resection (SR) is usually offered for patients with clinical stage IA lung cancer who have limited pulmonary reserve or significant medical comorbidities but are still considered candidates for surgery. However, the premise that sublobar resection preserves pulmonary function more than lobectomy remains controversial. Some retrospective series have shown greater reduction in pulmonary function in patients undergoing lobectomy compared to SR [1, 2]. However, the Lung Cancer Study Group reported no significant difference in pulmonary function among patients randomized to either lobectomy or sublobar resection for clinical stage I lung cancer [3].

The American College of Surgeons Oncology Group (ACOSOG) Z4032 was a randomized trial undertaken to compare SR alone to SR with brachytherapy (SRB) for high-risk operable patients with early-stage non–small cell lung cancer. The primary endpoint of this trial was time to local recurrence. No significant difference was observed in local recurrence rates and this has been reported elsewhere [4]. ACOSOG is now part of the Alliance for Clinical Trials in Oncology.

Patients enrolled in ACOSOG Z4032 underwent pulmonary function testing (PFTs) at baseline and at 3, 12 and 24 months. The impact of SR on pulmonary function at 3 months has been previously reported [5]. In the present analysis we report on the long-term impact of sublobar resection on pulmonary function among the high-risk operable patients enrolled in ACOSOG Z4032.

## Patients and Methods

ACOSOG Z4032 was open to patients with clinical stage IA or 1B lung cancer, who were considered to be high-risk for lobectomy [6]. Enrolled patients were randomized to undergo either sublobar resection alone (wedge or segmentectomy) or sublobar resection with intraoperative brachytherapy. The surgical approach (VATS versus open and wedge resection versus segmentectomy) was at the discretion of the operating surgeon. Each participant

signed an IRB-approved, protocol-specific informed consent in accordance with federal and institutional guidelines.

The primary endpoint of the trial was time to local recurrence. No difference in recurrence-free survival, overall survival or locoregional recurrence was observed between study arms [4].

Secondary endpoints of this trial included describing the impact of treatment on quality of life and pulmonary function [7]. Consequently, patients enrolled in ACOSOG Z4032 underwent pulmonary function testing, including diffusion capacity for carbon monoxide (DLCO) pre-operatively, as well as 3, 12 and 24 months following surgery.

### Statistical analysis

Pulmonary function tests included percentage predicted forced expiratory volume in 1 second ($FEV_1$%) and percentage predicted carbon monoxide diffusing capacity of the lung (DLCO%), both of which were measured preoperatively and at 3, 12 and 24 months after intervention. Chi-squared tests for categorical variables and Wilcoxon rank sum tests for continuous variables were used to compare the baseline patient characteristics between the SR and SRB arms among patients with complete and incomplete PFT data. The impact of study arm, tumor location (lower lobe versus upper/middle lobe), pathological tumor size (≤ or > 2cm), surgical approach (VATS vs. thoracotomy), and sublobar resection type (wedge vs. segmentectomy) on PFTs was assessed. Specifically, the median percentage changes in the DLCO%, and $FEV_1$% from baseline to months 3, 12 and 24 were compared between the different subgroups using a Wilcoxon signed rank test. Additionally, a ≥10% decline from baseline in $FEV_1$% or DLCO% was considered clinically meaningful, and compared between the different subgroups using a Fisher's exact or Chi-squared test at each time point. A generalized estimating equation (GEE) model was subsequently used to assess the impact of each factor on longitudinal PFT data across all 4 time-points [8,9]. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center.

## Results

Data were frozen for this analysis on July 15, 2013. A total of 224 patients were randomized to the Z4032 trial, twelve of whom were deemed ineligible. Among the 212 evaluable patients, 155 completed PFTs at 3 months, 111 patients completed PFTs at 3 and 12 months, and 69 patients completed PFTs at all three time points (3, 12 and 24 months). Therefore, the present analysis included 69 patients for whom PFT (DLCO% and $FEV_1$%) data was complete at all time-points (Figure 1). The specific reasons for missing PFT data are listed in Table 1.

Baseline characteristics of these 69 patients are shown in Table 2. Sublobar resection was performed in 27 patients; the remaining 42 patients underwent sublobar resection plus brachytherapy. There were no differences in baseline characteristics and operative factors analyzed between study arms. In addition, there were no differences in baseline characteristics and operative factors analyzed between patients with complete and incomplete PFT data The characteristics of the complete PFT cohort in each study arm (27

SR arm, 42 in SRB arm) was also compared with the cohort of patients with complete data for either DLCO% or FEV1% at each time point (baseline, 3, 12 and 24 months) with no statistically significant differences (data not shown).

### Longitudinal Pulmonary Function Data

The baseline median $FEV_1$% and median DLCO% was 46% and 53% predicted, respectively. The median change from baseline for $FEV_1$% was +2%, +1% and +1% at 3, 12 and 24 months respectively and for DLCO% was −1%, −2% and −2% at 3, 12 and 24 months respectively. No statistically significant changes in median $FEV_1$% or DLCO% were observed between baseline values and those measured at 3, 12 or 24 months (Figure 2).

The proportion of patients who experienced a clinically significant decline in pulmonary function (≥10% decline from baseline in $FEV_1$% or DLCO%) is shown in Table 3. Overall 24.6% and 14.5% of patients were observed to have a long-term reduction in DLCO% and $FEV_1$% at 24 months.

### Tumor location

No differences were observed in baseline median $FEV_1$% (49.5% vs. 55%, $p = 0.06$) or median DLCO% (47.5% vs. 42%, $p = 0.23$) between upper/middle and lower lobe resections. Although median values of $FEV_1$% and DLCO% were comparable at all time-points, patients with lower lobe resections were more likely to have a ≥10% decline in $FEV_1$% compared to those with middle/upper lobe resections at 3 months (28% vs. 6.8%, $p = .02$). This difference was not observed at 12 or 24 months (Figure 3).

### Surgical Technique

No differences were observed in baseline median $FEV_1$% (49% vs. 54%, $p = 0.29$) or median DLCO% (46% vs. 47%, $p = 0.62$) between those who underwent a thoracotomy vs. VATS. Although median values of $FEV_1$% and DLCO% were comparable at all time points, patients who underwent a thoracotomy were more likely to have a ≥10% decline in DLCO% compared to those treated by VATS at 3 months (40% vs. 18.2%, $p = .05$). No differences were observed at 12 or 24 months (Figure 4). The type of sublobar resection (wedge vs. segmentectomy) did not have a significant impact on pulmonary function at any time point.

### Tumor size

A statistically significant relationship was found between pathologic tumor size (≤ or > 2cm) in the median DLCO% at 24 months (47% vs. 38%, $p = .02$). However, no difference in pulmonary function was observed at baseline or at other time points for $FEV_1$% and DLCO %.

### Longitudinal analysis: Generalized Estimating Equation

Results of the GEE model incorporating data from all 4 time points are shown in Table 4. None of the analyzed factors (study arm, tumor location, surgical technique or pathologic tumor size) were found to have an impact on the longitudinal measures of $FEV_1$% or DLCO %.

## Comment

The assessment of risk for patients undergoing pulmonary resection is predicated on an accurate prediction of postoperative pulmonary function [10]. Several tools have been developed to determine this, including quantitative CT scans, perfusion scans, and most commonly, the segment-counting method [11,12,13]. However, longitudinal studies have demonstrated that the measured postoperative pulmonary function does not always correlate with predicted values. Specifically, pulmonary function has been shown to improve over time following surgery, and may return to preoperative values even after lobectomy [14,15].

The Lung Cancer Study Group performed the landmark study evaluating pulmonary function after lung cancer resection [3]. In that publication, the authors observed no significant difference in forced vital capacity (FVC) between patients undergoing lobectomy versus limited resection, and concluded that sublobar resection offered no functional benefit over lobectomy. However, the reduction in $FEV_1$ was significantly greater in the lobectomy group versus the sublobar resection group at both 6 months and 12–18 months.

Subsequent studies have challenged the claim that lobectomy and sublobar resection are equivalent in regards to preservation of pulmonary function [16,17]. As an example, a single center review of 83 patients from Japan demonstrated a positive correlation between the number of segments removed and reduction in $FEV_1$ and FVC, and this was most pronounced in lobectomy patients [2]. Similar studies have been published from centers in the United States [1].

Common to all of these reports is the exclusion of high-risk patients. Consequently, patients who underwent segmentectomy in these other studies were potential candidates for lobectomy on the basis of preserved cardiopulmonary function. In contrast, patients enrolled in ACOSOG Z4032 were considered to be at high-risk for lobectomy, and would likely be referred for non-operative ablative therapy if sublobar resection was not performed.

The principal finding of this analysis is that sublobar resection did not lead to a clinically significant reduction (≥10% decline from baseline in $FEV_1$% or DLCO%) in a cohort of high-risk patients. While a thoracotomy and lower lobe resections were associated with a reduction in pulmonary function at 3 months, these effects were transient. Importantly, pulmonary function at 24 months following surgery was equivalent to baseline measurements.

We believe that this observation has important implications for treatment recommendations in high-risk patients. Non-operative therapies, such as radiofrequency ablation and stereotactic radiosurgery, are increasingly being considered for these patients [18]. A potential advantage of non-operative therapy is the preservation of lung parenchyma, in contrast to surgical resection, which mandates the loss of functional lung tissue [19, 20].

However, reductions in pulmonary function have also been observed in patients undergoing non-operative therapy. For instance, a retrospective study of stereotactic radiosurgery demonstrated a significant reduction in DLCO from a baseline of 61.5% to 44.8% at 12 months [21]. A similar study of 20 high-risk patients undergoing stereotactic radiosurgery

showed that while $FEV_1$ did not change at 12 months following treatment, a significant decline of 11% was observed for DLCO [22]. The largest study of pulmonary function following SBRT was an analysis of RTOG 0236, a prospective phase 2 trial that enrolled medically inoperable patients with early-stage lung cancer [23]. A total of 55 patients were evaluable, however only 24 patients completed pulmonary function testing at 2 years following treatment. A reduction in $FEV_1$% and DLCO% was noted at 2 years (−5.8% and −6.3% respectively), however neither was statistically significant. In the present analysis, patients enrolled in ACOSG Z4032 were observed to have a 2% decrease in DLCO at 2 years, and an increase in $FEV_1$ of 1%, neither of which was statistically significant.

This study has important limitations. Among 212 patients eligible for analysis, only 69 (32%) completed pulmonary function testing at all planned time points. While we found no statistically significant difference in either baseline or subsequent pulmonary function in those with complete follow-up and those without, we acknowledge that this is a potential bias. Nonetheless, it is possible that patients with a more favorable postoperative course may have been more likely to undergo pulmonary testing, which would impact the conclusions of this analysis. In addition, we note that a direct comparison between pulmonary function data from this trial and single-arm studies evaluating ablative therapies may be influenced by differences in trial design and inclusion criteria.

In summary, we found that sublobar resection performed in a high-risk operable patient population did not lead to a clinically or statistically significant reduction in pulmonary function with long-term follow-up. Although a direct comparison of surgical resection versus ablative therapy awaits appropriately powered randomized trials, this observation should be considered when treatment recommendations are developed for this cohort of patients.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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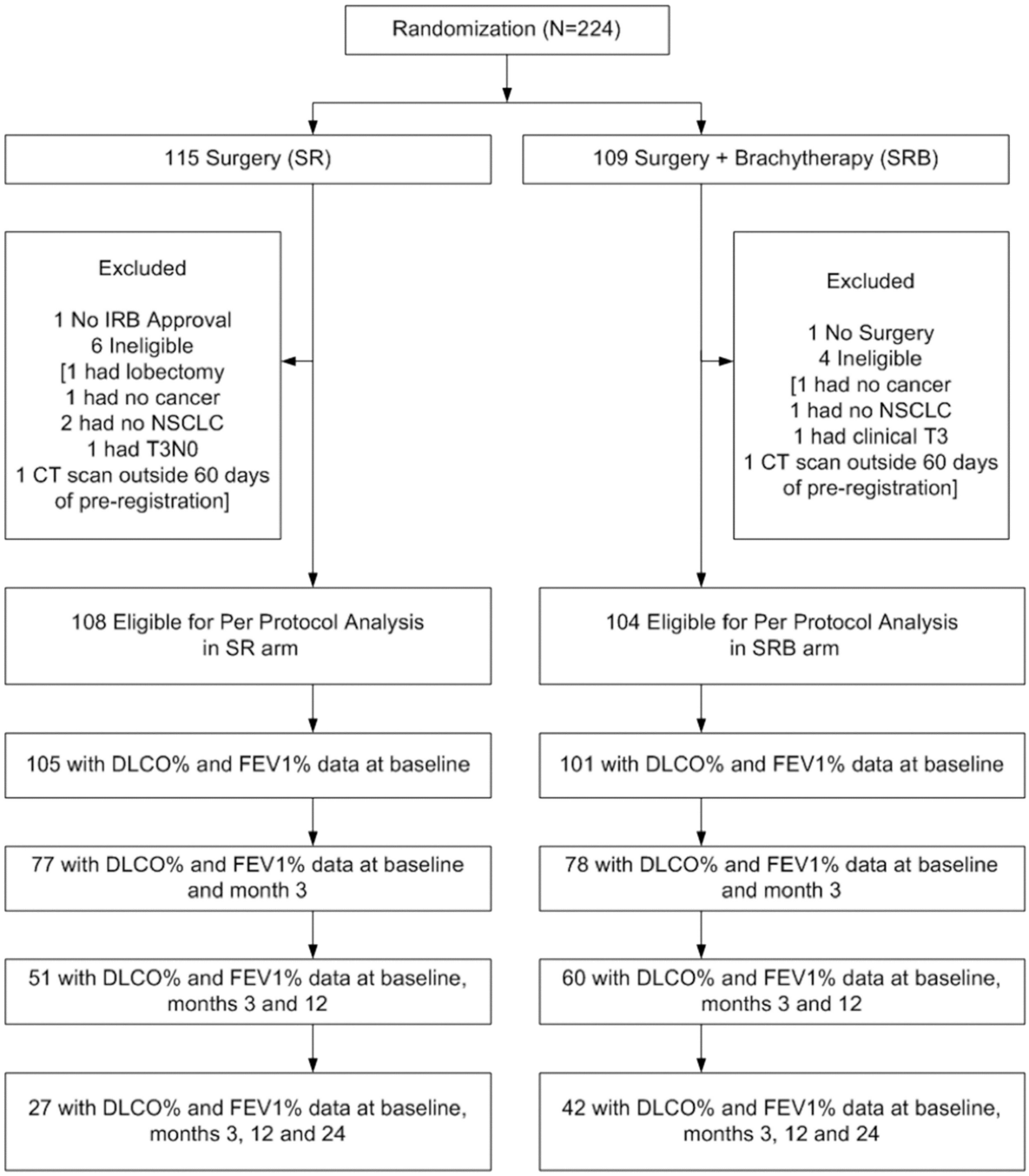


**Figure 1.**

Patient CONSORT Diagram. IRB, institutional review board; DLCO%, percentage predicted diffusing capacity of the lung for carbon monoxide; $FEV_1$%, percentage predicted forced expiratory volume in 1 second.

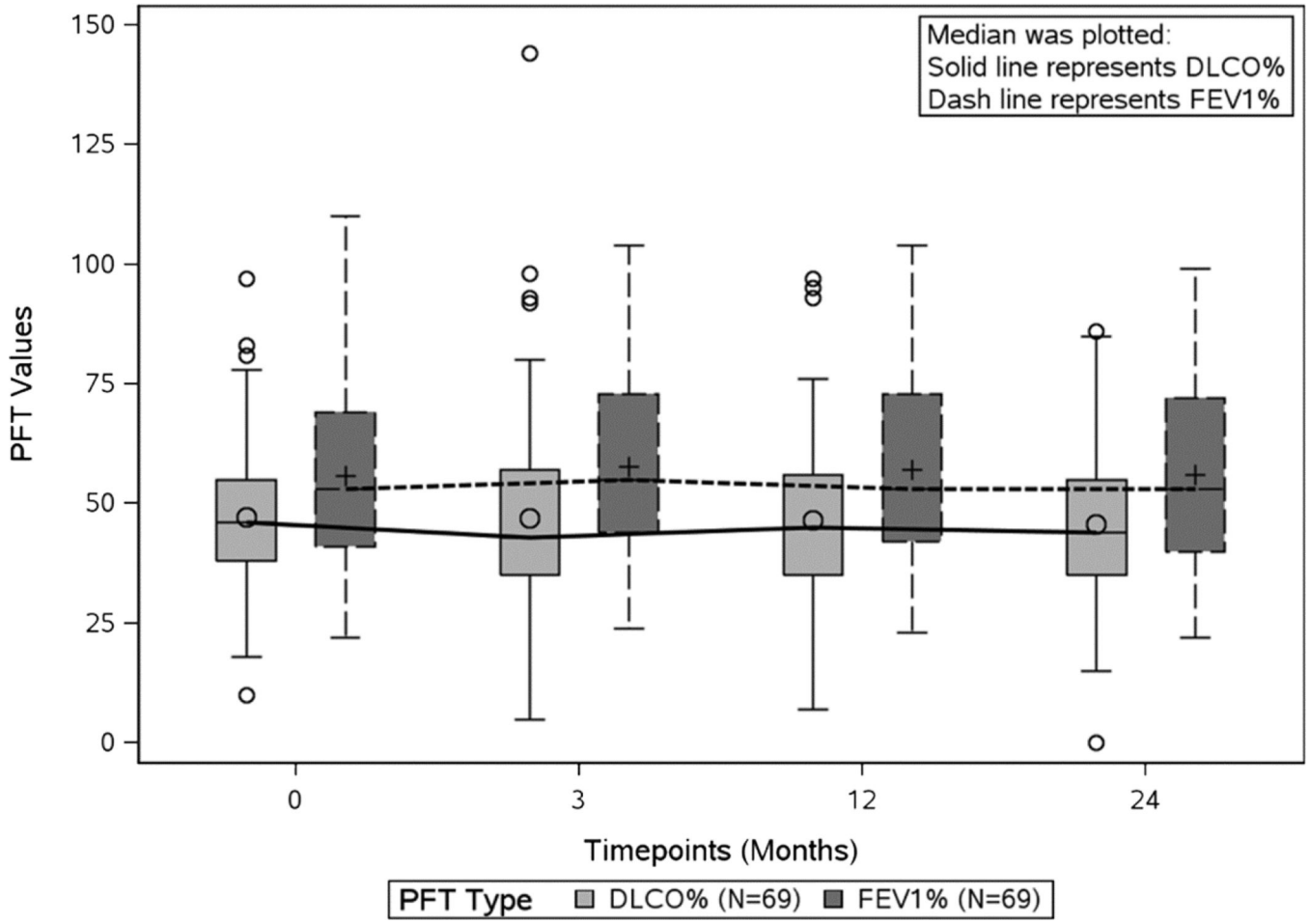


**Figure 2.**

Changes in median $FEV_1$% and DLCO% over 24 months. DLCO%, percentage predicted diffusing capacity of the lung for carbon monoxide; $FEV_1$%, percentage predicted forced expiratory volume in 1 second.

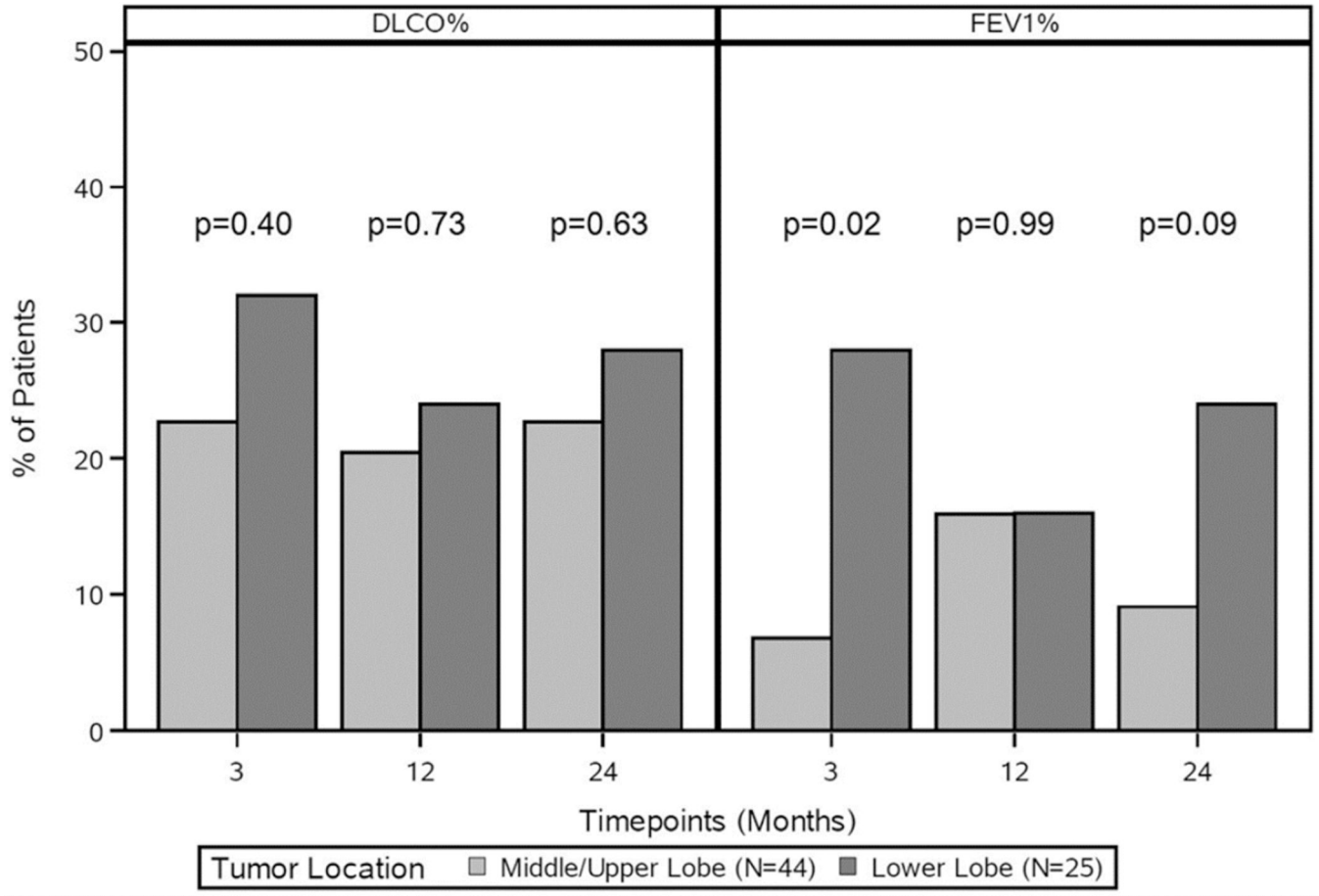


**Figure 3.**

Changes in DLCO% and $FEV_1$% by tumor location over 24 months. DLCO%, percentage predicted diffusing capacity of the lung for carbon monoxide; $FEV_1$%, percentage predicted forced expiratory volume in 1 second.

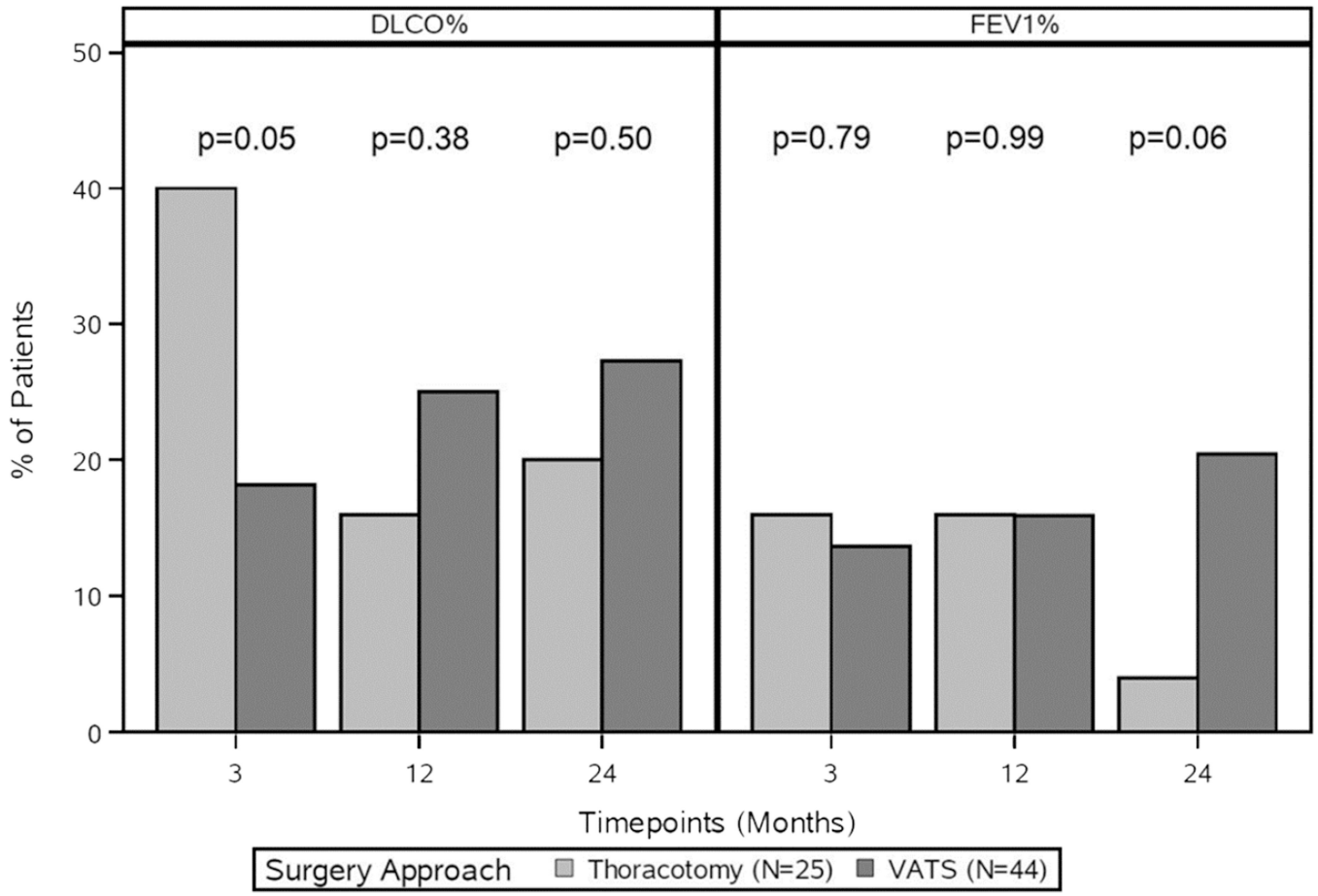


**Figure 4.**

Changes in DLCO% and in $FEV_1$% by surgery approach over 24 months. DLCO%, percentage predicted diffusing capacity of the lung for carbon monoxide; $FEV_1$%, percentage predicted forced expiratory volume in 1 second; VATS, video-assisted thoracoscopic surgery.

**Table 1**

Reasons for missing PFT data at baseline, 3, 12 and 24 months

| Reason* | Baseline | 3 months | 12 months | 24 months | Total |
|---|---|---|---|---|---|
| Death | 0 | 24 (24%) | 52 (32%) | 94 (38%) | 170 (33%) |
| Early Termination of follow-up | 0 | 4 (4%) | 20 (12%) | 24 (10%) | 48 (9%) |
| Not done | 6 (100%) | 45 (44%) | 62 (38%) | 96 (39%) | 209 (41%) |
| Missed visit | 0 | 28 (28%) | 26 16%) | 18 (7%) | 72 14%) |
| Missing | 0 | 0 (0%) | 2 (1%) | 16 (6%) | 18 (3%) |
| Total | 6 | 101 | 162 | 248 | 517 |

* Study arms combined, data presented as aggregate for missing DLCO% and $FEV_1$% rather than individual patients

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**Table 2**

Patient characteristics: comparison of complete PFTs (DLCO % and $FEV_1$% at baseline, 3, 12 and 24 months) vs. incomplete PFT cohorts

| | SR [Incomplete PFT] (N=81) | SR [Complete PFT] (N=27) | p value | SRB [Incomplete PFT] (N=62) | SRB [Complete PFT] (N=42) | p value | Complete PFT (SR vs. SRB) p value |
|---|---|---|---|---|---|---|---|
| **Age (in years)** | | | 0.33[1] | | | 0.74[1] | 0.60[1] |
| Median | 70.0 | 70.0 | | 72.0 | 69.5 | | |
| Range | 49.0–85.0 | 58.0–82.0 | | 50.0–87.0 | 53.0–87.0 | | |
| **Sex** | | | 0.31[2] | | | 0.43[2] | 0.35[2] |
| Female | 48 (59.3%) | 13 (48.1%) | | 32 (51.6%) | 25 (59.5%) | | |
| **Ethnicity** | | | 0.07[2] | | | 0.05[2] | 0.36[2] |
| Hispanic/Latino | 0 (0.0%) | 0 (0.0%) | | 0 (0.0%) | 1 (2.4%) | | |
| Not Hispanic/Latino | 72 (88.9%) | 27 (100.0%) | | 50 (80.6%) | 39 (92.9%) | | |
| Unknown | 9 (11.1%) | 0 (0.0%) | | 12 (19.4%) | 2 (4.8%) | | |
| **Race** | | | 0.82[2] | | | 0.57[2] | 0.32[2] |
| White | 76 (93.8%) | 25 (92.6%) | | 58 (93.5%) | 41 (97.6%) | | |
| Black/African American | 5 (6.2%) | 2 (7.4%) | | 3 (4.8%) | 1 (2.4%) | | |
| Unknown | 0 (0.0%) | 0 (0.0%) | | 1 (1.6%) | 0 (0.0%) | | |
| **Performance Status** | | | 0.40[2] | | | 0.59[2] | 0.53[2] |
| 0 | 13 (16.0%) | 6 (22.2%) | | 12 (19.4%) | 11 (26.2%) | | |
| 1 | 46 (56.8%) | 17 (63.0%) | | 37 (59.7%) | 21 (50.0%) | | |
| 2 | 22 (27.2%) | 4 (14.8%) | | 13 (21.0%) | 10 (23.8%) | | |
| **Baseline DLCO %** | | | 0.87[1] | | | 0.34[1] | 0.90[1] |
| Median | 46.5 | 46.0 | | 43.0 | 46.0 | | |
| Range | 18.0–94.0 | 18.0–97.0 | | 8.0–83.0 | 10.0–83.0 | | |
| **Baseline FEV1 %** | | | 0.83[1] | | | 0.46[1] | 0.48[1] |
| Median | 47.0 | 49.0 | | 51.0 | 54.0 | | |
| Range | 26.0–117.0 | 22.0–108.0 | | 25.0–96.0 | 25.0–110.0 | | |
| **Baseline FVC %** | | | 0.13[1] | | | 0.86[1] | 0.90[1] |
| Median | 70.0 | 77.0 | | 77.0 | 77.0 | | |

| | SR [Incomplete PFT] (N=81) | SR [Complete PFT] (N=27) | p value | SRB [Incomplete PFT] (N=62) | SRB [Complete PFT] (N=42) | p value | Complete PFT (SR vs. SRB) p value |
|---|---|---|---|---|---|---|---|
| Range | 33.0–110.0 | 40.0–104.0 | | 38.0–109.0 | 34.0–124.0 | | |
| **Tumor Location** | | | 0.91[2] | | | 0.79[2] | 0.69[2] |
| Middle/Upper Lobe | 55 (67.9%) | 18 (66.7%) | | 40 (64.5%) | 26 (61.9%) | | |
| Lower Lobe | 26 (32.1%) | 9 (33.3%) | | 22 (35.5%) | 16 (38.1%) | | |
| **Surgery Performed** | | | 0.40[2] | | | 0.34[2] | 0.91[2] |
| Thoracotomy | 23 (28.4%) | 10 (37.0%) | | 28 (45.2%) | 15 (35.7%) | | |
| VATS | 58 (71.6%) | 17 (63.0%) | | 34 (54.8%) | 27 (64.3%) | | |
| **Resection Type** | | | 0.47[2] | | | 0.11[2] | 0.23[2] |
| Segmentectomy | 27 (33.3%) | 7 (25.9%) | | 17 (27.4%) | 6 (14.3%) | | |
| Wedge Resection | 54 (66.7%) | 20 (74.1%) | | 45 (72.6%) | 36 (85.7%) | | |
| **Pathological Tumor Size** | | | 0.24[2] | | | 0.93[2] | 0.15[2] |
| <=2 cm | 50 (61.7%) | 20 (74.1%) | | 36 (58.1%) | 24 (57.1%) | | |
| >2 cm | 31 (38.3%) | 7 (25.9%) | | 26 (41.9%) | 18 (42.9%) | | |

[1]Wilcoxon

[2]Chi-Square

Abbreviations: SR, sublobar resection; SRB, sublobar resection plus brachytherapy; PFT, pulmonary function test; DLCO%, percentage predicted diffusing capacity of the lung for carbon monoxide; FEV1%, percentage predicted forced expiratory volume in 1 second; FVC%, percentage predicted forced vital capacity; VATS, video-assisted thoracoscopic surgery.

## Table 3

Summary of 10% Decline in DLCO% and $FEV_1$% from baseline to month 3, 12 and 24

| Change from baseline to: | DLCO% No. of Patients (%) | FEV1% No. of Patients (%) |
|---|---|---|
| **Month 3** | | |
| No 10% Decline | 51 (73.9%) | 59 (85.5%) |
| >=10% Decline | 18 (26.1%) | 10 (14.5%) |
| **Month 12** | | |
| No 10% Decline | 54 (78.3%) | 58 (84.1%) |
| >=10% Decline | 15 (21.7%) | 11 (15.9%) |
| **Month 24** | | |
| No 10% Decline | 52 (75.4%) | 59 (85.5%) |
| >=10% Decline | 17 (24.6%) | 10 (14.5%) |

Abbreviations: DLCO%, percentage predicted diffusing capacity of the lung for carbon monoxide; FEV1%, percentage predicted forced expiratory volume in 1 second.

## Table 4

Results from the multivariable GEE models for DLCO% and $FEV_1$%

| Predictors | DLCO% | | FEV1% | |
|---|---|---|---|---|
| | Estimate | P-value* | Estimate | P-value* |
| Arm: SRB vs. SR | −4.96 | 0.20 | 1.58 | 0.74 |
| Time: Baseline vs. Month 24 | 1.32 | 0.85 | −0.23 | 0.44 |
| Month 3 vs. Month 24 | 1.13 | | 1.73 | |
| Month 12 vs. Month 24 | 0.80 | | 1.16 | |
| Tumor Location: Lower Lobe vs. Middle/Upper Lobe | −2.77 | 0.45 | 6.42 | 0.20 |
| Time: Baseline vs. Month 24 | 1.32 | 0.85 | −0.23 | 0.44 |
| Month 3 vs. Month 24 | 1.13 | | 1.73 | |
| Month 12 vs. Month 24 | 0.80 | | 1.16 | |
| Surgery Approach (VATS vs. Thoracotomy) | 2.46 | 0.46 | 4.77 | 0.32 |
| Time: Baseline vs. Month 24 | 1.32 | 0.85 | −0.23 | 0.44 |
| Month 3 vs. Month 24 | 1.13 | | 1.73 | |
| Month 12 vs. Month 24 | 0.80 | | 1.16 | |
| Resection Type: Wedge vs. Segment | 2.69 | 0.53 | 5.24 | 0.34 |
| Time: Baseline vs. Month 24 | 1.32 | 0.85 | −0.23 | 0.44 |
| Month 3 vs. Month 24 | 1.13 | | 1.73 | |
| Month 12 vs. Month 24 | 0.80 | | 1.16 | |
| Pathological Tumor Size: >2 cm vs. ≤2 cm | −5.58 | 0.12 | 2.57 | 0.61 |
| Time: Baseline vs. Month 24 | 1.32 | 0.85 | −0.23 | 0.44 |
| Month 3 vs. Month 24 | 1.13 | | 1.73 | |
| Month 12 vs. Month 24 | 0.80 | | 1.16 | |

*Wald test p-value

Abbreviations: GEE, generalized estimating equation; DLCO%, percentage predicted diffusing capacity of the lung for carbon monoxide; FEV1%, percentage predicted forced expiratory volume in 1 second; VATS, video-assisted thoracoscopic surgery.