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Comparison of changes in pulmonary function following stereotactic body radiotherapy versus conventional 3D conformal radiotherapy for stage I and IIa non-small cell lung cancer: an analysis of the TROG 09.02 (CHISEL) phase III trial.

Nicholas W. Bucknell MBBS (Hons) , Tomas Kron PhD , Alan Herschtal PhD , Nicholas Hardcastle , Louis Irving MBBS, FRACP , Michael MacManus MB, MD, MRCP, FRANZCR , Gerard G. Hanna MB PhD, MRCP, FRCR, FRANZCR , Alisha Moore BMedSci, MPhil , Andrew Murnane MApplSci , Shankar Siva MBBS, FRANZCR, PhD , David Ball MBBS, MD, FRANZCR, FACR(Hon) , On behalf of the CHISEL co-authors

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Title Page

Title

Comparison of changes in pulmonary function following stereotactic body radiotherapy versus conventional 3D conformal radiotherapy for stage I and IIa non-small cell lung cancer: an analysis of the TROG 09.02 (CHISEL) phase III trial.

Short Title

Comparison of changes in pulmonary function following stereotactic ablative body radiotherapy

Authors:

Nicholas W. Bucknell, MBBS (Hons)[1, 2]
Tomas Kron, PhD[2,3]
Alan Herschtal, PhD [5]
Nicholas Hardcastle[2,3, 4]
Louis Irving, MBBS, FRACP [6,7]
Michael MacManus, MB, MD, MRCP, FRANZCR[1, 2]
Gerard G. Hanna, MB PhD, MRCP, FRCR, FRANZCR [8]
Alisha Moore, BMedSci, MPhil[9]
Andrew Murnane, MApplSci[10]
Shankar Siva MBBS, FRANZCR, PhD[1, 2]
David Ball, MBBS, MD, FRANZCR, FACR(Hon)[1, 2]
On behalf of the CHISEL co-authors
Author Affiliations
[1] Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia
[2] Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia
[3] Department of Physical Sciences, Peter MacCallum Cancer Centre, Melbourne, Australia
[4] Centre for Medical Radiation Physics, University of Wollongong, NSW, 2522, Australia
[5] Centre for Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre, Melbourne, Australia
[6] Department of Respiratory Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia
[7] Department of Medicine, University of Melbourne, Melbourne, Australia
[8] Queen's University of Belfast, Belfast, United Kingdom

[9] TROG Cancer Research, Waratah, New South Wales, Australia
[10] ONTrac at Peter Mac, Victorian Adolescent and Young Adult Cancer Service, Peter MacCallum Cancer Centre, Melbourne, Australia.
Corresponding Author:
Nicholas Bucknell, Department of Radiation Oncology, Peter MacCallum Cancer Centre, 305 Grattan St, 3002, Melbourne, Victoria, Australia
Phone: +61385595000
Email: nick.bucknell@petermac.org

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Data sharing statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Conflict of Interest Statement

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Abstract

Background

The [Anonymized for Review] trial compared conventional radiotherapy (CRT) with stereotactic body radiation therapy (SBRT) in patients with inoperable early-stage non-small cell lung cancer. Patients randomised to SBRT had less local failure and improved overall survival. This analysis reports differences in pulmonary function tests (PFTs) and the six-minute walk test (SMWT) between patients who received SBRT and those who received CRT.

Methods

We analyzed the PFTs and SMWT of all patients recruited to the [Anonymized for Review] trial. During this trial, patients underwent serial PFTs. Linear regression models were used to compare parameters between SBRT and CRT at 3 and 12-months post-treatment.

Results

101 patients were enrolled, 33 patients were treated with CRT, 61 with SBRT and 7 did not receive treatment. Primary tumor size was similar between arms, SBRT 25mm (SD 9mm) and CRT 28mm (SD 9mm). On regression analysis, at 3 and 12 months, there was no evidence of a difference between arms in PFT decline or distance walked in the SMWT. PTV size was significantly larger in the CRT arm, 142.79 cc (SD 61.14cc) compared to the SBRT group 46.15 cc (SD 23.39 cc). The mean Biological Equivalent Dose (BED) received by the target was significantly larger in the SBRT group 125.92 Gy (SD 21.58 Gy) compared to CRT 65.49 Gy (6.32Gy). Mean dose to the lungs – iGTV was 8.9 Gy (SD 2.34 Gy) in the CRT group and 4.37 Gy (SD 1.42 Gy) in the SBRT group.

Conclusion

Despite the considerably higher biologically effective doses delivered to the tumor in SBRT, there was no difference in decline in respiratory function observed between the two groups.

Introduction

SBRT is the standard of care in patients with peripheral stage I and IIa non-small cell lung cancer who have significant cardiovascular, respiratory, or other co-morbidities that preclude surgical management or who refuse surgery. The [Anonymized for Review] compared conventional radiotherapy (CRT) administered over a period of four to six weeks with stereotactic ablative body radiotherapy in 3 or 4 fractions in patients who were medically inoperable or who declined operative management.(1) SBRT is a technically complex method that allows precise irradiation of early-stage peripheral lung cancers. In the [Anonymized for Review] trial, patients randomised to the SBRT arm had superior freedom from local failure and longer overall survival.

Prior to this randomized study there were no prospective randomised phase III comparisons between these two radiation therapy modalities. The prior SPACE study did collect lung function metrics on follow up however this was a phase 2 study and pulmonary function between the two arms were not compared.(2) Other descriptive studies of pulmonary function tests in SBRT and CRT cohorts do exist however these are largely retrospective studies.(3-5)

SBRT treatment has a number of key differences from CRT. SBRT techniques are technically complex treatments that deliver higher doses in fewer fractions than CRT which results in significantly higher biologically effective doses (BED).(6) Inhomogeneous dose prescription results in a significantly increased dose being delivered to a portion of the tumor.(7) It is common for portions of the tumor to receive doses higher than 125% of the prescribed dose.(7) Improved motion management also allows treatment to involve smaller margins resulting in a smaller volume of normal tissue being irradiated to high doses.(7) SBRT has been hypothesised to be a potential non-surgical alternative to lung volume reduction surgery resulting in lung volume reduction in the irradiated volume and converse lung volume expansion in the adjacent unirradiated volumes. SBRT has therefore been suggested as a potential mechanism to improve lung function in highly selected patients.(8) It should be noted

that this SBRT approach would involve targeting areas of lung compromised by chronic obstructive pulmonary disease (COPD) rather than regions of lung affected by tumors.(8)

The primary aim of this post-hoc analysis was to compare prospectively measured pulmonary function tests (PFTs) between SBRT and conventional radiation treatment (CRT) using absolute measured values. This analysis also describes the longitudinal changes in respiratory function over time in the two treatment arms.

Methods and Analysis

We conducted an analysis of all patients recruited to the [Anonymized for Review] trial. This trial was approved by the [Anonymized for Review] Ethics Committee. All patients gave written informed consent. Patients were assessed as per treatment received.

During the prospective [Anonymized for Review] trial participants were subjected to lung function and spirometry tests; Forced Expiratory Volume in one second (FEV1), Diffusing capacity of the lungs for carbon monoxide (DLCO), Distance Walked in 6 minutes measured in meters (SMWT) and Vital Capacity (VC) at baseline, 1 month, 3 months, then 3 monthly until 24 months and 6 monthly thereafter. Each of these lung function measures was modelled using a linear mixed effects (LME) model to estimate the mean lung function at each time point for each arm. Arm and time point (considered as a factor) were fixed effects in the model and patient identity was a random effect. The interaction between the arm and time point was also included in the model. Time was measured in months since baseline, and all lung function measures were modelled relative to the baseline lung function measure. The baseline lung function measure was also controlled for as a covariate in the model. LME estimates of lung function for each arm at the mean value of the baseline lung function measure, as well as for the difference between the arms at each time point were described.

Linear regression models were used to compare FEV1, FVC and DLCO between SBRT and CRT. Separate models at 3 and 12-months post-treatment were created to assess the two different processes impacting lung function post-radiation therapy (acute pneumonitis and chronic fibrosis). Linear regression models were used to assess the association of baseline PFT measures with changes in respiratory function at 3 and 12 months. Planning target volumes and doses received between both arms were compared and described.

All statistical analyses were performed in the R statistical software package version 3.5.1 using standard and validated statistical procedures. Statistical methods consisted of standard reporting of descriptive baseline statistics and linear mixed effects regression methods, all carried out using the base package of the R language for statistical computing and commonly used add-on packages. All statistical analysis results and their interpretation were independently reviewed by a qualified statistician.

Missing data were not imputed, but rather cases with missing data were deleted from specific analyses as necessary. No adjustment for multiple testing was made. Patients were analyzed according to treatment received, rather than the arm to which they were randomised.

Patients underwent treatment as per the [Anonymized for Review] trial protocol. For patients undergoing SBRT a expansion from iGTV (GTV incorporating motion) to PTV of 5mm was used for SBRT whereas for CRT a margin of 1.5cm from GTV to PTV was used. Rigorous quality assurance was conducted during this trial.(6)

Results

A total of 101 patients were randomised. Five patients in the SBRT arm and 2 in the CRT arm did not receive treatment. Trial recruitment occurred between December 2009 and June 2015. Treatment occurred in 11 centres in Australia and New Zealand. In total 94 patients were treated on trial, 33 with CRT and 61 with SBRT. Patient characteristics were balanced between

each arm and are described in Table 1. At baseline mean FEV1 was 1.44 L in the SBRT group and 1.55 L in the CRT group. The mean DLCO was 12.39 ml/min/mmHg in the SBRT group and 10.84 ml/min/mmHg in the CRT group. Mean forced vial capacity was 2.61 L in the SBRT group and 2.73 L in the CRT group. The mean distance walked in 6 minutes was 344.5 m in the SBRT group and 362.6 m in the CRT. Both arms had a similar size primary tumor at enrolment with the mean size of the tumor in the SBRT group 25mm (SD 9 mm) and a mean size of 28mm (SD 9 mm) in the CRT group.

Data Available

Of the total 94 patients who were treated on trial. At baseline, 57 of the 61 patients treated with SBRT and 32 of the 33 patients treated with conventional radiation therapy had pulmonary function tests available for analysis. At 12 months this number decreased to 42 in the SBRT arm and 24 in the conventional radiation therapy arm. By 24 months post-treatment, this number was 22 in the SBRT arm and 6 in the conventional radiation therapy arm. Fewer patients had available 6MWT data at 3 months: data was available for 32 patients in the SBRT arm and 18 in the conventional radiation therapy arm, by 12 months this number was 23 in the SBRT arm and 4 in the conventional radiation therapy arm. Due to the large amount of data missing after 3 months, only the 3-month SWMT data were compared to the baseline.

Comparison Between Arms

Linear regression models were used to assess the association in PFT measures at 3 and 12 months between treatment arms. The corresponding baseline PFT measures were included as covariates in the models. On regression analysis at 3 months, there was no evidence of a difference between arms in the change from baseline in absolute values of FEV1 (p=0.47), DLCO (p=0.26) or forced VC (p=0.81). At 12 months there were no differences observed in change from baseline of FEV1 (p=0.69), DLCO (p=0.51) nor forced VC (p=0.69) between arms. There was no evidence of a difference in the change from baseline in SMWT between two arms at 3 months (p=0.13). The results of the regression analyses are shown in Table 2.

Comparison of Dose and Volumes

Despite similar tumor size between the groups, the planning tumor volume (PTV) size was much larger in the CRT arm, mean 142.79 cc (SD 61.14cc) compared to the SBRT arm, mean 46.15 cc (SD 23.39 cc). Due to different methods including differences in motion management used in planning CRT and SBRT in the era of the [Anonymized for Review] trial, gross tumor volume (GTV) size could not be compared. The mean Biological Equivalent Dose (BED) planned for delivery to the target was significantly larger in the SBRT group 125.92 Gy (SD 21.58 Gy) compared to CRT 65.49 Gy (SD 6.32Gy). Mean dose to the lungs – iGTV was 8.9 Gy (SD 2.34 Gy) in the CRT group and 4.37 Gy (SD 1.42 Gy) in the SBRT group. In the SBRT group this mean dose to the lungs was delivered over three to four fractions and in the CRT group this was delivered in twenty to thirty three fractions.

Longitudinal Changes in Pulmonary Function

Overall patients in both arms demonstrated similar deterioration in DLCO, VC and FEV1 over time. The LME model describing the longitudinal decline in pulmonary function is demonstrated in **Figure 1**. There was no significant deterioration in the 6-minute walk test over time (appendix 1).

Scatterplots (**figures 2 and 3**) demonstrate the individual changes in patient pulmonary function at the 3- and 12-month time points respectively and **figure 4** demonstrates the changes observed in the 6MWT at the 3-month time point. Table 2 describes the parameters of the regression model to predict PFTs in the CRT and SBRT treatment arms at the 3- and 12-month time points.

To describe longitudinal changes in PFT parameters and 6MWT a linear mixed effects model was created for each treatment arm and time point. Figure 1 demonstrates the linear effects model for each PFT parameter.

Discussion

In this analysis no differences observed in respiratory function parameters including FVC, DLCO, FEV1 between the SBRT and CRT treatment arms at 3 and 12 months. There were no differences observed in SMWT between treatment arms. Despite the considerably higher biologically effective doses delivered to the tumor in SBRT no statistically significant detriments to pulmonary function measurements were observed. This likely relates to SBRT's ability to deliver a higher integral dose delivered to the tumor but with relative sparing of lung tissue due to the steep dose gradients and reduced margins that are possible. The large difference in PTV volumes between the SBRT and CRT groups are explained by the reduced margins allowed by SBRT due to the use of advanced motion management. In the [Anonymized for Review] trial protocol iGTV to PTV expansion of 5mm was used for SBRT whereas for conventional radiation therapy a margin of 1.5cm was used. The smaller volumes being irradiated with SBRT and the higher BED able to be achieved supports the hypothesis that SBRT has resulted in an improvement in the therapeutic ratio over conventional radiation therapy in the management of peripheral NSCLC.

In the SBRT literature, several studies have described changes in pulmonary function over time. Ferrero et al. found that a patient's baseline pulmonary function was not associated with treatment-related toxicity.(9) Over 6 to 12 months post-SBRT, there was a mean 10% reduction in mean total lung volumes, no change in FEV1 and a 10% reduction in DLCO.(9) Takemoto et al. conducted a prospective observational trial involving 75 patients and found there was a significant correlation with PTV size and decline in FVC and FEV1.(10) Pulmonary function was measured at baseline and between 18 to 24 months post-treatment and the authors found mean change in FVC was −5.9% (SD 11.1%) and FEV1 −4.6% (SD 12.1%).(10) These declines were smaller than those described by Takeda et al. in a retrospective series of 292 patients with a median follow-up of 21 months the authors found a mean decline in FEV1 of 7.9% in patients with mild or moderate COPD 7.9% and 7.4% in patients with severe

COPD.(11) In a large retrospective series of 191 patients treated with SBRT, Guckenberger et al demonstrated a modest decrease in PFTs in the first 6 months following treatment with SBRT treatment with reductions of FEV1 of 1.4% and DLCO of 7.6% In the period 7-24 months post-SBRT, further reductions were observed in FEV1 of 8.1% and DLCO of 12.4%.(12) These reductions in pulmonary function were not correlated to tumor size, PTV dose, MLD or other lung dose-volume histogram parameters.(12)

In this study both groups experienced a significant decline in lung function over time. This is consistent with progressive decline following treatment with SBRT observed in similar studies. In the [Anonymized for Review] study population, most patients were deemed medically inoperable due to advanced airway disease (COPD). The natural history of advanced COPD is for patients to experience a progressive decline in pulmonary function dependent on the severity of the disease with declines in FEV1 the order of 35-80 ml/year.(13)

Although SBRT treatment was well tolerated in the studied population, patients with interstitial lung disease (ILD) have been demonstrated to be at high risk of excessive treatment-related morbidity and mortality. Neither CRT nor SBRT arms had any patients with known ILD. The safety of SBRT in this population is not well defined and is the subject of the ASPIRE-ILD study which is seeking to define the optimal dose and fractionation or provide the option of no treatment for lung cancer in this population.(14)

A limitation in this analysis is a large amount of missing data in particular after 12 months for PFT and 3 months for SMWT. This is despite few patients experiencing local disease recurrence or death at these time points. Future trials should consider ways to increase the completion rate of these investigations. The primary way to do this is to minimize the burden on patients. Firstly, the number of PFT and 6MWT investigations should be rationalized. We suggest a baseline test, a short-term post-treatment test at 3-6 months and a longer-term post-treatment test at 12 or 24 months. In trial design, the PFT testing timepoint should coincide

with other visits and attention should be paid to minimizing patient inconvenience. The co-location of PFT testing and other post-treatment investigations would further minimize patient inconvenience. For example, a micro-spirometry device could be used to perform both post-treatment PFT and imaging in the same location. Micro-spirometry devices are not typically recommended for PFTs that will be used clinically however these devices have been validated for respiratory function testing in patients with COPD.(15, 16) In a research setting, the convenience for patients of access to a bedside test compared to requiring formal testing in a respiratory laboratory may increase protocol compliance.

In the prospective [Anonymized for Review] trial, we did not observe a difference in pulmonary function decline between SBRT and conventional radiation therapy treatment arms. This work is the first randomised data supporting the use of SBRT over conventional radiation therapy which demonstrates improved local control and survival without any worsening of respiratory function. A major limitation of this work is a large amount of missing data for the SMWT and for the PFT measures as time post-treatment increased. There were a limited number of toxicities and no grade 4 or 5 respiratory adverse events in either arm. There is a possibility that the data are missing not at random, and this may induce a bias in the findings.

Conclusion

Despite the considerably higher biologically effective doses delivered to the tumor in SBRT there was no difference in decline in respiratory function observed between the two groups. SBRT is a highly effective tool for treating peripheral tumors with low toxicity rates, improved local control and relative preservation of lung function. SBRT treatment is an effective and safe treatment option in patients with poor lung function or other comorbidities. Randomised trials including VALOR (NCT02984761) and STABLEMATES (NCT02468024) are currently underway to rigorously compare surgery with SBRT.

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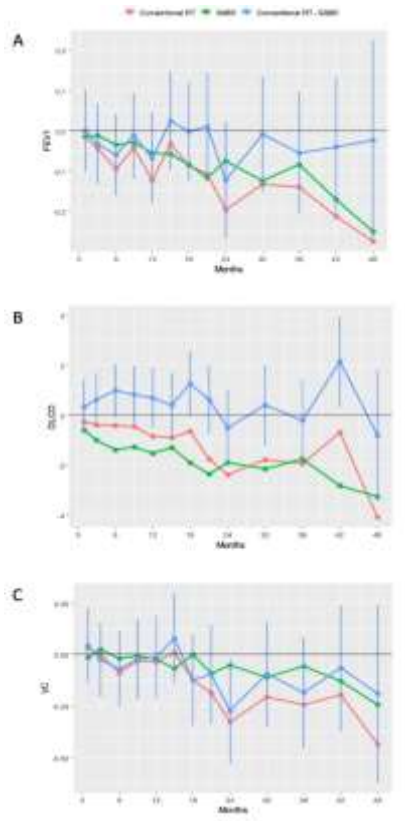

Figure 1 caption

Figure 1A describes the results of a linear mixed effects model for FEV1 (L) as a function of Treatment Arm and Months.

Figure 1B describes the results of a linear mixed effects model for DLCO (ml/min/mmHg) as a function of Treatment Arm and Months.

Figure 1C describes the results of a linear mixed effects model for VC (L) as a function of Treatment Arm and Months.

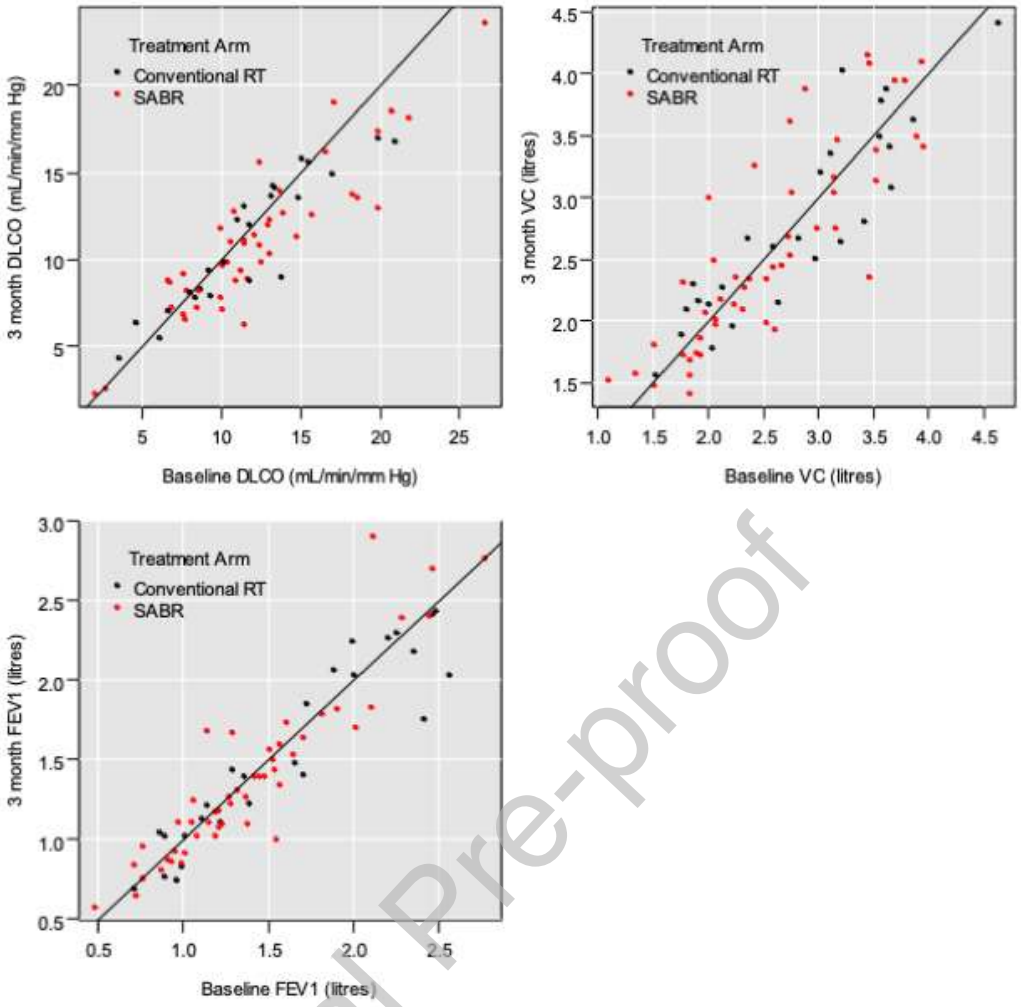

Figure 2 caption

Scatterplots of Baseline DLCO vs. 3-month DLCO, Baseline FEV1 vs. 3-month FEV1 and Baseline VC vs. 3-month VC. The black line is a simple linear regression line describing the data.

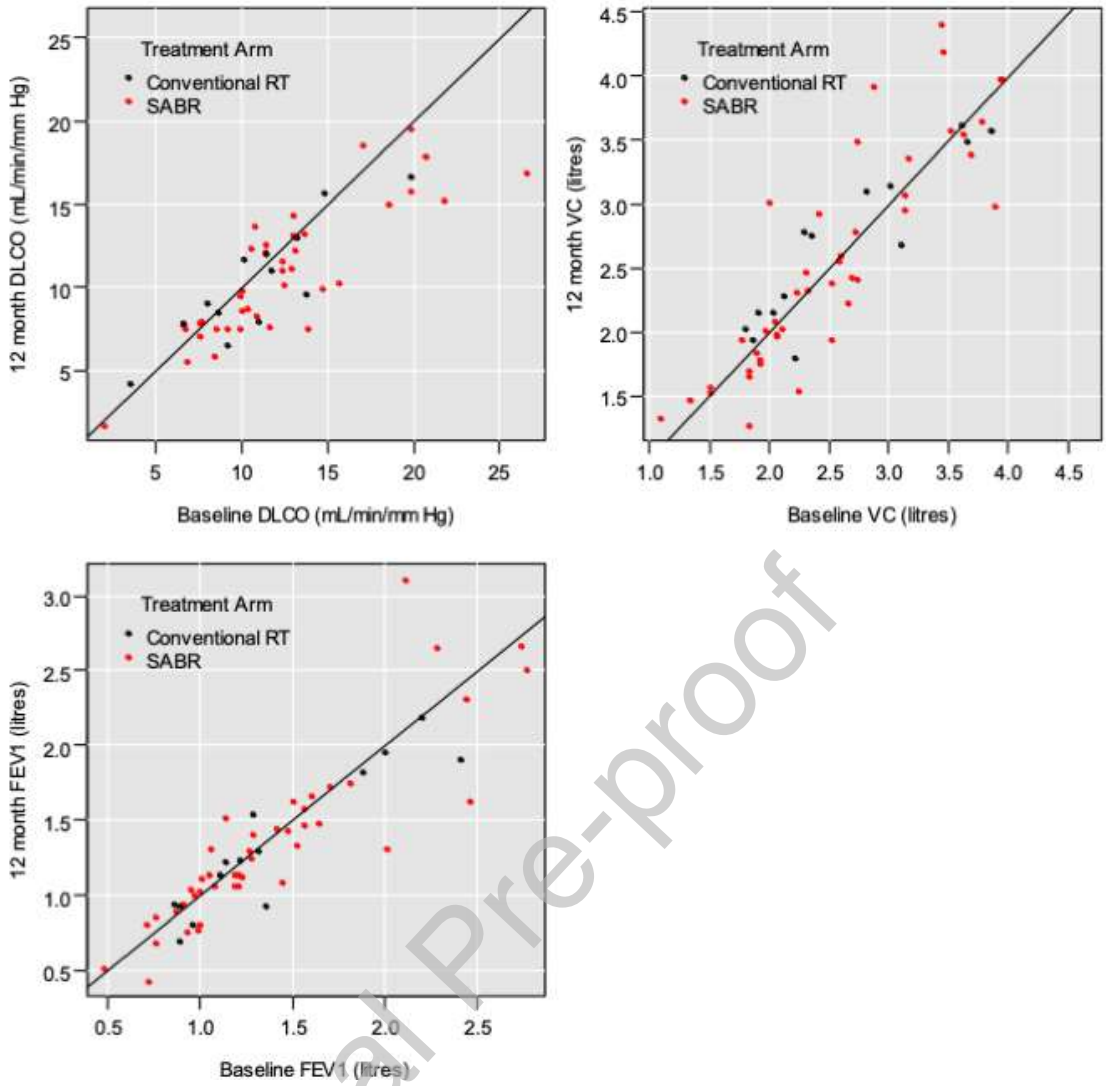

Figure 3 caption

Scatterplots of Baseline DLCO vs. 12-month DLCO, Baseline FEV1 vs. 12 month FEV1 and Baseline VC vs. 12 month VC. The black line is a simple linear regression line describing the data.

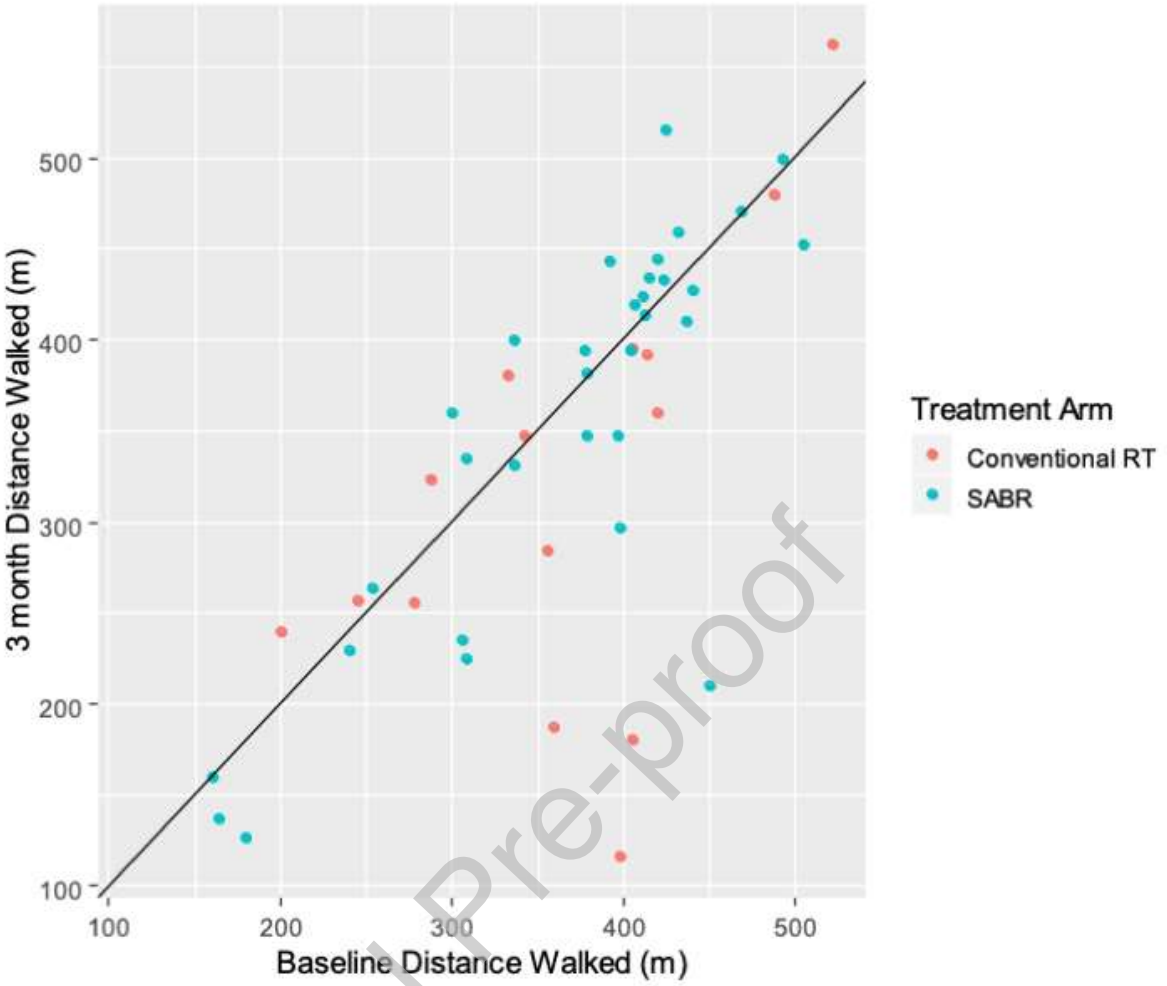

Figure 4 caption

Figure 4 displays the scatterplot of 3-month Distance Walked by the baseline Distance Walked. Cyan dots represent the population who received SBRT and red dots represent the population who received CRT.

Table 1 - Patient Characteristics

Statistic / Level	Treatment Arm	
	SBRT (n = 66)	**Standard RT (n = 35)**
Treatment Received		
No	5 (7.6%)	2 (6.5%)
Yes	61 (92.4%)	33 (94.3%)
Withdrew		
Yes	4 (6.1%)	4 (11.4%)
Sex		
Male	36 (55%)	20 (57%)
Female	30 (45%)	15 (43%)
Age (years)		
Mean (SD)	74 (8)	75 (7)
Median [range]	73.2 [55.9 - 89.7]	77 [61.9 - 86]
Interquartile range	68.9 - 78.6	69.6 - 81.2
Current Smoker		
No	45 (69%)	21 (60%)
Yes	20 (31%)	14 (40%)
Missing	1	0
Current or Prior Smoker		
No	2 (3%)	0 (0%)
Yes	63 (97%)	35 (100%)
Missing	1	0
Prior Cancer		
No	37 (57%)	23 (66%)

Yes	28 (43%)	12 (34%)
Missing	1	0
T stage		
1	47 (71%)	24 (69%)
2	19 (29%)	11 (31%)
Lung Lesion Longest Diameter		
Mean (SD)	25 (9)	28 (9)
Median [range]	22.5 [3.1 - 43]	27 [13 - 49]
Interquartile range	19 - 31	20.5 - 32
Missing	2	0
Smoker No. of Pack-Years		
Mean (SD)	53 (29)	48 (28)
Missing	3	0
Mean baseline lung function measurements		
FEV1 (L)	1.44	1.55
DLCO (ml/min/mmHg)	12.39	10.84
Distance walked at 6 minutes (m)	344.5	362.6
Forced vital capacity (L)	2.61	2.73

Table 1 key: describes the patient characteristics between the two treatment arm

Table 2 Linear Regression Model

3-month PFT Outcome (Change between baseline and 3 months)	**Treatment Arm**	**beta**	**beta 95% CI**	**N**
DLCO (mL/min/mm Hg)	Conventional RT	-	-	24
	SBRT	-0.50	[-1.4, 0.37]	44
FEV1 (litres)	Conventional RT	-	-	26
	SBRT	0.037	[-0.063, 0.14]	49
VC (litres)	Conventional RT	-	-	26
	SBRT	0.024	[-0.17, 0.22]	49
12-month PFT Outcome (Change between baseline and 12 months)	**Treatment Arm**	**beta**	**beta 95% CI**	**N**
DLCO (mL/min/mm Hg)	Conventional RT	-	-	13
	SBRT	-0.43	[-1.7, 0.84]	40
FEV1 (litres)	Conventional RT	-	-	14
	SBRT	0.031	[-0.12, 0.18]	44
VC (litres)	Conventional RT	-	-	14
	SBRT	0.047	[-0.28, 0.18]	44

Table 2 key: The parameters of the regression model to predict PFTs in the CRT and SBRT treatment arms at the 3 and 12 months timepoints