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Prediction of health-related quality-of-life results after lung stereotactic body radiotherapy using dose-volume parameters from functional mapping on Gallium-68 perfusion PET/CT

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Abstract

Background The PEGASUS trial was the first study to evaluate and demonstrate the benefits of ^{68}Ga-perfusion PET/CT in the lung stereotactic body radiotherapy (SBRT) planning process in preserving functional lung volumes while respecting target volume coverage and doses to other organs at risk. Here we report the prespecified exploratory endpoint of SBRT on health-related quality of life (HRQoL).

Methods In this single-center prospective study, we recruited patients planned to be treated in our radiotherapy department with SBRT for primary or secondary lung tumors. Patient-reported outcomes were assessed at the first visit, 1 month, 3 months and every 3 months until 12 months after SBRT using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 items (QLQ-C30), the EORTC Quality of Life Questionnaire Lung Cancer 13 items (QLQ-LC13), and the European Quality of Life 5 Dimensions-5 Level (EQ-5D-5 L) questionnaire. The key exploratory HRQoL endpoints (analyzed for all patients who completed at least QLQ-C30 at least one time point after SBRT) were baseline-to-early change (between 1 month and 3 month) and baseline-to-late change (between 6 month and 12 month) in the QLQ-C30 global health status (GHS)/quality-of-life (QoL) score and in the deterioration of the dyspnea (patient-reported lung toxicity). Explorative analysis of the impact of baseline HRQoL, patient- and SBRT-related characteristics, including PET perfusion-based functional parameters, on the change in HRQoL from baseline was analyzed using univariate analysis.

Results Of the 60 patients included, 39 were analyzable as early-onset and 22 as late-onset. Thirteen (33%) and 7 (32%) patients had a deterioration of QoL. In univariate analysis, maximal dose to the heart, doses to the functional

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lung volume and pulmonary functional test parameters were significantly associated with the early deterioration of HRQoL. Only doses to the functional lung volume were significantly associated with the late deterioration of HRQoL.

Conclusion In our study, increased radiation doses in functional lung volume PET bases dose parameters were significantly associated with a decrease of HRQoL unlike anatomic lung parameters. Functional lung avoidance planning guided by perfusion PET/CT may be a simple and noninvasive method to improve HRQoL in patients treated with lung SBRT.

Introduction

Health-related quality of life (HRQoL) is a multidimensional measure that assesses and quantifies the patient's experience of the impact of illness and treatment on physical, role, social, cognitive, emotional, sexual and spiritual functioning [1]. The diagnosis of cancer and its treatment can lead to changes in quality of life that vary according to the characteristics of the patient, the disease and the treatment carried out [2–6]. In recent years, the use of HRQoL instruments has increased in clinical trials and daily practice and is recommended for evaluating treatments in complement to traditional outcomes [7–9]. Several validated HRQoL instruments have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency for use in assessing the benefit of treatments [1, 10, 11].

However, many challenges remain in the assessment of HRQoL. In primary and secondary lung tumors, the treatment landscape is rapidly evolving, particularly with the development of stereotactic body radiotherapy (SBRT). In most previous studies, HRQoL of patients treated for a lung tumor focused primarily on those treated with systemic treatment. Nevertheless, radiotherapy also causes toxicity and studies on HRQoL receiving SBRT are sparse. Radiation-induced toxicity may negatively impact short and long-term HRQoL, as demonstrated in head-and-neck and breast cancer patients [12–14]. For example, HRQoL is a more accurate prognostic indicator of survival than other clinical prognosticators, such as performance status (PS); and it is particularly useful to evaluate the benefits and toxicity of therapy [15]. Not surprisingly, improving and maintaining HRQoL in oncology patients has become a key aspect of personalized medicine. Treatment-decision making should therefore balance between clinical evidence and patient preferences, which is influenced by their current and anticipated future HRQoL.

Differences in the severity of radiation-induced toxicity can depend on various factors such as the volume of normal tissues irradiated and intrinsic differences in radiosensitivity of the normal tissues between individuals [16]. Side effects can be described as acute or late [17]. Acute adverse events occur up to 90 days post-radiotherapy. They generally resolve completely, but may affect quality of life significantly and may even cause death [18]. Acute side effects that do not heal can lead to late tissue damage, the so-called "consequential late damage" [19]. Late adverse events are mainly irreversible and progressive and have therefore a more prolonged and significant impact on patients' daily life. However, it remains important to assess the impact of HRQoL local treatments and to identify the factors associated with impaired quality of life.

Recently the PEGASUS study, a prospective single-center trial (ClinicalTrials.gov identifier, NCT04942275) whose primary aim was to show the feasibility of decreasing the doses delivered to the lung functional volumes (FVs) by integration of pulmonary functional mapping guided by gallium 68 lung perfusion positron emission tomography (PET)/computed tomography (CT) (68Ga-perfusion PET/CT) while maintaining target volume coverage and doses to other organs at risk (OARs) [20]. Authors also showed that the predictive value of PET perfusion-based functional parameters outperforms the standard CT-based dose volume parameters for the risk of grade ≥ 2 acute radiation-induced lung toxicity as assessed with CTCAE version 5.0 at 3 months [21]. However, they did not report the HRQoL.

Therefore, this analysis aimed to describe the characteristics of HRQoL of primary or secondary lung tumors patients receiving SBRT using validated HRQoL instruments and explore its influencing factors, especially dosimetric parameters.

Methods

Study design and participants

The PEGASUS trial is a single-center prospective study. The eligible study population consisted of patients aged > 18 years who planned to be treated in the radiation therapy department of our institute with SBRT for primary or secondary lung tumors. Exclusion criteria included the inability to give informed consent, patients under guardianship or curatorship, pregnant or breast feeding women, and contraindication to the administration of human albumin macroaggregates. The study was approved by the Nord Ouest IV Ethics Committee (ID RCB: 2021-002224-20) and registered in Clinical Trial.gov registry (NCT04942275). Written informed consent was obtained from all participants.

Treatment

All patients were treated with SBRT and underwent 68Ga-perfusion PET/CT imaging before treatment. Detailed treatment protocols are available in [20, 21]. Briefly, All treatments were delivered by volumetric modulated arc therapy (VMAT) using a TrueBeamTM STX 2.0 linac linear accelerator (Varian Medical Systems, Palo Alto, CA, United States) equipped with Varian RPM gating system (Varian Medical Systems, Palo Alto, CA, United States) with a prescription dose of 48 to 60 Gy in 3 to 8 fractions depending on proximity to organs at risk (OAR). As per the protocol of this pilot study, and given that doses to the target volume and the OARs were respected, either the anatomical plan or functional plan could be delivered to the patient. We only selected the functional plan if it allowed for equal or superior coverage of the target volumes, as well as equal or lower doses to organs at risk, and if the staging assessment (^{18}F-FDG PET/CT and brain imaging) was less than 4 weeks old. However, in the majority of cases, due to the time required to optimize the functional plan to meet al.l dosimetric constraints, it was not ready within the allotted time of less than 4 weeks from the staging assessment. In fact, the anatomical plan was used for 51 patients and the functional plan for the remaining 8.

HRQoL assessment

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Module (EORTC QLQ-C30), the QLQ-LC13 lung cancer–specific questionnaire were used to evaluate HRQoL. The scoring procedures were conducted following EORTC guidelines. The EORTC QLQ-C30 assesses global QoL, functioning scores, including physical functioning, and a range of patient reported symptoms, including dyspnea and fatigue. EORTC QLQ-C30 scores were linearly transformed to a 0-to-100 scale. Symptoms were further assessed with the lung-specific QLQ LC-13 scales which include symptoms of dyspnea, cough, hemoptysis and chest pain. Higher scores on the functional HRQoL scales indicate better functioning, whereas higher scores on the symptom scales indicate more severe symptoms. Quality of life/Global health status (QoL/GHS), dyspnea, physical function (PF), emotional function (EF) and fatigue were previously defined to be of primary interest [22]. The endpoint of the present analysis was a decrease in one of these indices at 3 months (early change) and 12 months (late change) relative to the baseline. A clinically relevant change was defined as a change in HRQoL scores of greater than or equal to 10 points, as generally accepted in the current literature. Radiation induced lung toxicity (RILT) was assessed prospectively by a radiation oncologist, without access to dose statistics for the functional pulmonary volume, every 3 months until 12 months after completion of SBRT, based on clinical and imaging evaluation according to NCI CTCAE version 5.0 (pneumonitis or fibrosis).

Clinical and dosimetric parameters

Clinical parameters included in the analysis were age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), smoking history including pack-years, histology (primary vs. secondary), tumor volume, spirometry including forced expiratory volume in one second (FEV1) and diffusion capacity of the lung for carbon monoxide (DLCO).

Lung volumes were defined as follows [23]. The whole-lung anatomic volume (AV) was delineated on CT images based on Hounsfield unit value and then visually adjusted to match normal contours if required. Within the AV, 3 lung functional volume (FVs) were defined using an automated relative to whole-lung function segmentation method, delineating the minimal volume containing 50% (FV50%), 70% (FV70%), and 90% (FV90%) of the total activity within the AV, respectively. We also defined a low functional lung volume (LFV) as follows: LFV = AV - FV90%. Dosimetric parameters included the maximum dose to organs at risk (OARs), mean lung dose (MLD), percentage volume of lung getting 5 to 30 Gy dose (Vx) extracted from 5 lung volumes: the AV, 3 lung FVs (FV50%, FV70%, and FV90), and the LFV. We also reported the Biologically Effective Dose (BED), using the formula $BED = D \times (1 + [d / (\alpha/\beta)])$ where variables are as follows: d = Dose per fraction, in Gy, D = Total dose (number of fractions x dose per fraction), in Gy, and α/β ratio = 3 for the lungs.

Statistical analysis

Early and late changes in QoL from baseline were descriptively analyzed based on the total QoL sample. Explorative analysis of the impact of patient- and SBRT-related characteristics, including PET perfusion-based functional parameters, on the change in QoL from baseline was analyzed using univariate analysis, paired Student's t tests or, in case of non normally distributed differences (normality checked by use of skewness and visual inspection of histograms) paired Wilcoxon tests, for each of the five primary interest QoL scales. We evaluated the association between clinician-scored RILT using NCI CTCAE v5 and HRQoL with each of the 5 indices using the Fischer test. The area under the curve (AUC) of each ROC curve for the five lung volumes as predictors of decrease of QoL (AV, FV50%, FV70%, FV90%, LFV) was calculated. Multivariate statistical tests were not performed due to the small sample size and low number of patients experiencing decrease of QoL.

All analyses were performed using the R + + platform for statistical programming, version 1.5.03.

Results

Between July 2021 and January 2022, 60 consecutive patients with primary or secondary lung tumors were enrolled into this prospective study. Lung SBRT was not performed in 1 patient with NSCLC due to a brain progression of the disease for which systemic treatment was initiated. Thirty-nine (66%) and twenty-two (37%) patients were evaluable for early- and late-change in HRQoL. Patient-, tumor-, and treatment-related characteristics and the analysis of their impact on early and late-changes of HRQoL are provided in Tables 1, 2, 3 and 4.

Baseline HRQoL scores

Details of baseline HRQoL scores and their impact on changes in quality of life assessment are summarized in Table S1-S10. The median score (IQR) for QoL/GHS, PF, EF, fatigue, and dyspnea were 66.7 (50.0–75.0), 80.0 (53.3–93.3), 75.0 (66.7–91.7), 33.3 (11.1–55.6) and 33.3 (0.0-66.7). No initial indices had a significant association with early or late-changes of HRQoL.

Early changes

The mean change (standard deviation (SD)) in QoL/GHS, dyspnea, PF, EF and fatigue were 2.0 (20.6), -0.9 (27.0), 0.9 (16.1), 1.4 (18.2) and − 2.3 (21.4) (Fig. 1). The number of patients with impairment of QoL/GHS, dyspnea, PF, EF and fatigue were 8/39 (21%), 6/39 (15%), 8/39 (21%), 6/39 (15%) and 16/39 (41%), respectively.

The results of the univariate analysis assessing the association between clinical and dosimetric parameters and a decline in one of the 5 indices are presented in Tables 1 and 2 and S11-S13. Among the clinical characteristics tested, only a FEV1 < 80% was associated with a decline of QoL/GHS. Only heart Dmax was significantly higher in patient with decline of QoL/GHS, physical function. AV and LFV dose-volume parameters were not statistically different between patients with and without decline of QoL. The majority of PET perfusion-based functional parameters based on FV50% and FV70% were significantly higher in patients with decline of QoL. ROC curves assessing the ability of the MLD AV, LFV, FV50%, FV70% and FV90% and V20 AV, LFV, FV50%, FV70% and FV90% to discriminate between patients with and without early changes of QoL are shown in Figures S1-S2.

Late changes

The mean change (SD) in QoL/GHS, dyspnea, PF, EF and fatigue, and were 1.9 (15.6), 0.0 (23.0), -0.5 (16.1), 3.8 (13.5) and 3.3 (17.9) (Fig. 2). The number of patients with impairment of QoL/GHS, dyspnea, PF, EF and fatigue were 5/22 (23%), 3/22 (14%), 4/22 (18%), 5/22 (23%) and 4/22 (18%), respectively.

The results of the univariate analysis assessing the association between clinical and dosimetric parameters and a decline in one of the 5 indices are presented in Tables 3 and 4 and S14-S16. Among the clinical characteristics tested, none was found to be significantly higher in patients with a decline of the 5 indices. Dose-volume parameters in the AV and LFV were not statistically different between patients with and without decline of QoL. The majority of PET perfusion-based functional parameters based on FV50% and FV70% were significantly higher in patients with decline of QoL. ROC curves assessing the ability of the MLD AV, LFV, FV50%, FV70% and FV90% and V20 AV, LFV, FV50%, FV70% and FV90% to discriminate between patients with and without late changes of QoL are shown in Figures S3-S4.

Association between clinician-scored RILT and HRQoL

The 5 indices were significantly associated with the NCI CTCAE v5 assessment of the acute grade ≥ 2 RILT ($p < 0.05$) but not with long-term grade ≥ 2 RILT tables S17-S18. Among the 39 patients and 22 patients evaluable for early- and late-change, 6/39 (15%) and 2/22 (10%) had acute and long-term grade ≥ 2 RILT, respectively. For QoL/GHS, 5/6 and 1/2 patients with acute and long-term grade ≥ 2 RILT had an early- and late-decline of QoL/GHS. For dyspnea, 4/6 and 1/2 patients with acute and long-term grade ≥ 2 RILT had an early- and late-decline of dyspnea.

Discussion

This analysis of early and late changes in HRQoL in our prospective single-center study showed that dosimetric lung functional volume parameters had a significant impact on the risk of HRQoL decline. To the best of our knowledge, this is the first study investigating the usefulness of functional mapping in preserving HRQoL for patients treated with SBRT.

In accordance with the literature, we found few clinically significant changes in HRQoL scores after lung SBRT [24–31] unlike after surgical resection [32, 33]. A study of 380 patients reported no clinically significant worsening of quality-of-life scores, even up to two years after SBRT [28]. However, to our knowledge, prior studies have not directly analyzed the influence of lung-functional parameters on QoL. The most interesting result of our analysis is that in patients who have a decline in one of the most relevant indices, no standard lung dosimetric parameters were statistically different between patients with and without decline of QoL unlike PET perfusion-based functional parameters. Some studies have reported a significant improvement in quality in patients with a low initial quality of life score [22, 26, 28]. A secondary analysis of STRIPE trial in 97 patients found a significative improvement in QoL/GHS, EF and fatigue at 7 weeks after SBRT for patients with a baseline QoL below the median [22]. In our study, a poorer basic

Table 1 Impact of baseline patient, tumor and dosimetric parameters on early-change of quality of life/global health status

		Impairment of quality of life/Global health status			
		No **31 (79.5%)**	**Yes** **8 (20.5%)**	**Overall** **39 (100%)**	***P* value**
Histology					0.69
	Primary	20 (64.5%)	6 (75.0%)	26 (66.7%)	
	Secondary	11 (35.5%)	2 (25.0%)	13 (33.3%)	
Age					0.64
	Median [Q1, Q3]	68 [63, 72]	71 [63.8, 75]	69 [63, 72.5]	
Gender					1.00
	Male	16 (51.6%)	4 (50.0%)	20 (51.3%)	
	Female	15 (48.4%)	4 (50.0%)	19 (48.7%)	
Performance status					0.87
	Median [Q1, Q3]	1 [0, 1]	0.5 [0, 1.3]	1 [0, 1]	
Tobacco					1.00
	Non smoker	8 (25.8%)	2 (25.0%)	10 (25.6%)	
	Active or former smoker	23 (74.2%)	6 (75.0%)	29 (74.4%)	
Prior thoracic irradiation					1.00
	No	23 (74.2%)	6 (75.0%)	29 (74.4%)	
	Yes	8 (25.8%)	2 (25.0%)	10 (25.6%)	
Thoracic surgery					1.00
	No	25 (80.7%)	7 (87.5%)	32 (82.1%)	
	Yes	6 (19.3%)	1 (12.5%)	7 (17.9%)	
SBRT dose					0.51
	54 Gy	10 (32.3%)	1 (12.5%)	11 (28.2%)	
	48 Gy	15 (48.4%)	6 (75.0%)	21 (53.9%)	
	60 Gy	6 (19.3%)	1 (12.5%)	7 (17.9%)	
Localization					1.00
	central	6 (19.3%)	1 (12.5%)	7 (17.9%)	
	peripheral	25 (80.7%)	7 (87.5%)	32 (82.1%)	
PTV volume in cc					0.38
	Median [Q1, Q3]	16.9 [9.7, 26.9]	11.3 [8.2, 18.9]	15.2 [9.0, 26.9]	
ITV volume in cc					0.44
	Median [Q1, Q3]	7.0 [3.7, 13.1]	4.7 [3.4, 8.7]	6.6 [3.6, 13.1]	
Spinal cord Dmax					0.88
	Median [Q1, Q3]	6.9 [5.5, 12.0]	11.2 [5.1, 13.3]	7.0 [5.4, 12.8]	
Left bronchi Dmax					0.26
	Median [Q1, Q3]	4.1 [1.6, 7.9]	7.3 [4.8, 12.6]	4.9 [1.8, 10.4]	
Right bronchi Dmax					0.64
	Median [Q1, Q3]	5.5 [1.7, 12.5]	6.2 [3.5, 13.2]	5.5 [2.7, 12.9]	
Trachea Dmax					0.30
	Median [Q1, Q3]	6.7 [0.7, 13.3]	1.0 [0.5, 5.0]	5.4 [0.5, 12.7]	
Esophagus Dmax					0.40
	Median [Q1, Q3]	8.4 [6.5, 16.0]	8.3 [5.8, 9.9]	8.4 [6.4, 15.0]	
Pulmonary artery Dmax					0.30
	Median [Q1, Q3]	4.2 [0.6, 11.9]	8.0 [2.9, 12.1]	4.53 [1.0, 11.9]	
Aorta Dmax					0.38
	Median [Q1, Q3]	12.3 [7.8, 24.3]	8.7 [6.5, 18.0]	11.8 [7.4, 24.3]	
Brachial plexus Dmax					0.40
	Median [Q1, Q3]	0 [0, 0.05]	0 [0, 0]	0 [0, 0]	
Heart Dmax					0.26
	Median [Q1, Q3]	3.4 [0.5, 12.6]	11.3 [4.0, 14.0]	4.9 [0.7, 13.7]	
FEV1 < 80%					0.10
	Yes	18 (58.1%)	3 (37.5%)	21 (53.8%)	
	No	13 (41.9%)	5 (62.5%)	18 (46.2%)	

Table 1 (continued)

	Impairment of quality of life/Global health status			
	No **31 (79.5%)**	**Yes** **8 (20.5%)**	**Overall** **39 (100%)**	***P* value**
DLCO < 70%				1.00
No	16 (51.6%)	4 (50.0%)	20 (51.3%)	
Yes	15 (48.4%)	4 (50.0%)	19 (48.7%)	
MLD AV (Gy)				0.77
Median [Q1, Q3]	2.9 [2.2, 3.5]	2.5 [2.2, 4.6]	2.9 [2.1, 3.8]	
MLD FV50% (Gy)				0.01
Median [Q1, Q3]	2.7 [1.3, 3.9]	4.1 [4.0, 5.6]	3.0 [1.6, 4.2]	
MLD FV70% (Gy)				0.02
Median [Q1, Q3]	2.7 [1.7, 3.7]	4.0 [3.4, 4.6]	3.1 [1.8, 3.9]	
MLD FV90% (Gy)				0.16
Median [Q1, Q3]	2.8 [1.7, 3.5]	3.1 [2.7, 4.8]	2.9 [1.8, 3.7]	
MLD LFV (Gy)				0.38
Median [Q1, Q3]	2.8 [1.2, 5.0]	2.3 [0.7, 3.3]	2.7 [1.2, 4.6]	
V5Gy AV (%)				0.96
Median [Q1, Q3]	13.9 [10.0, 16.8]	12.8 [10.6, 16.5]	13.2 [10.2, 16.8]	
V5Gy FV50% (%)				0.01
Median [Q1, Q3]	12.5 [6.1, 18.0]	22.2 [18.5, 25.4]	16.5 [8.3, 20.8]	
V5Gy FV70% (%)				0.03
Median [Q1, Q3]	12.5 [8.0, 17.9]	18.9 [14.7, 22.8]	13.7 [9.4, 19.5]	
V5Gy FV90% (%)				0.24
Median [Q1, Q3]	13.4 [8.0, 16.9]	15.0 [12.6, 19.0]	13.4 [9.8, 16.9]	
V5 LFV (%)				0.67
Median [Q1, Q3]	0.2 [0.1, 0.2]	0.1 [0.05, 0.2]	0.2 [0.07, 0.2]	
V20Gy AV (%)				0.85
Median [Q1, Q3]	3.3 [2.2, 4.6]	2.5 [2.2, 6.7]	3 [2.2, 4.9]	
V20Gy FV50% (%)				< 0.001
Median [Q1, Q3]	2.2 [0.8, 3.6]	5.2 [4.4, 7.7]	3.2 [1, 4.7]	
V20Gy FV70% (%)				0.02
Median [Q1, Q3]	2.8 [1.2, 4]	4.6 [3.9, 6.8]	3.2 [1.4, 4.9]	
V20Gy FV90% (%)				0.24
Median [Q1, Q3]	3.4 [1.5, 4.5]	3.3 [2.9, 7.4]	3.4 [1.6, 4.7]	
V20Gy LFV (%)				0.31
Median [Q1, Q3]	0.04 [0.02, 0.06]	0.02 [0.01, 0.06]	0.03 [0.02, 0.06]	
MLD AV (Gy) BED				0.85
Median [Q1, Q3]	7.5 [5.9, 9.7]	7.0 [6.0, 11.1]	7.5 [5.9, 9.7]	
MLD FV50% (Gy) BED				< 0.001
Median [Q1, Q3]	4.9 [2.7, 6.8]	11.5 [10.3, 17.5]	5.8 [3.1, 11.2]	
MLD FV70% (Gy) BED				< 0.001
Median [Q1, Q3]	6.2 [3.7, 7.7]	10.3 [9.5, 14.2]	6.7 [4.1, 9.8]	
MLD FV90% (Gy) BED				0.07
Median [Q1, Q3]	7.1 [4.2, 8.9]	8.8 [7.5, 12.2]	7.7 [4.3, 9.4]	
MLD LFV (Gy) BED				0.28
Median [Q1, Q3]	8.3 [2.9, 12.3]	4.8 [2.5, 7.0]	6.0 [2.8, 11.5]	
V5Gy AV (%) BED				0.93
Median [Q1, Q3]	16.5 [12.4, 20.2]	15.6 [13.1, 20.4]	16.1 [13.0, 20.2]	
V5Gy FV50% (%) BED				< 0.001
Median [Q1, Q3]	10.2 [7.4, 19.7]	26.3 [22.2, 31.3]	14.3 [8.3, 22.9]	
V5Gy FV70% (%) BED				< 0.001
Median [Q1, Q3]	11.6 [8.9, 18.9]	22.6 [18.1, 26.9]	14.0 [9.2, 22.6]	
V5Gy FV90% (%) BED				0.05
Median [Q1, Q3]	13.4 [9.3, 18.8]	18.2 [15.9, 22.2]	14.8 [9.6, 19.4]	

Table 1 (continued)

	Impairment of quality of life/Global health status			
	No **31 (79.5%)**	**Yes** **8 (20.5%)**	**Overall** **39 (100%)**	***P* value**
V5Gy LFV (%) BED				0.67
Median [Q1, Q3]	14.3 [6.1, 26.8]	14.6 [4.0, 17.1]	14.3 [4.0, 25.7]	
V20Gy AV (%) BED				0.55
Median [Q1, Q3]	6.8 [5.3, 8.5]	7.5 [5.2, 10.9]	6.9 [5.1, 8.9]	
V20Gy FV50% (%) BED				< 0.001
Median [Q1, Q3]	3.7 [1.9, 6.0]	11.8 [9.2, 15.2]	5.3 [2.3, 9.8]	
V20Gy FV70% (%) BED				< 0.001
Median [Q1, Q3]	4.8 [3.1, 6.2]	10.2 [8.7, 13.2]	5.9 [3.5, 9.0]	
V20Gy FV90% (%) BED				0.01
Median [Q1, Q3]	5.4 [3.2, 7.7]	9.5 [6.7, 11.1]	5.6 [3.8, 9.0]	
V20Gy LFV (%) BED				0.42
Median [Q1, Q3]	7.1 [1.5, 14.6]	4.6 [1.2, 8.4]	7.1 [1.4, 13.1]	

Abbreviations: FEV1 = forced expiratory volume in the first second; DLCO = diffusing capacity for carbon monoxide; PTV = planning target volume; ITV = internal target volume; AV = anatomic volume; BED = biologically effective dose; EQD2 = equivalent dose in 2-Gy fractions; FV = functional volume; LFV = low functional volume; MLD = mean lung dose; VxGy = percentage of lung volumes receiving xGy

general condition (PS) tended to be associated with less early decline in the QoL/GHS indice. Only one study in 55 patients showed that higher lung dose in anatomical volume increased the risk of impaired quality of life [34]. However, this study used a different questionnaire to evaluate QoL (the Functional Assessment of Cancer Therapy-Lung-Trial Outcome Index).

We found a significant association between the RILT assessed with NCI CTCAE v5 and HRQoL scores at early-stage. This result is in line with a previous study about 435 patients treated with radiation therapy that already showed that lung toxicity had an impact on HRQoL [35]. However, we did not find this association at late-stage. This may be explained by the lack of power, with few patients evaluable over the long term for HRQoL. Moreover, in our study, there were more patients reporting impaired HRQoL than RILT reported by the physician, showing the importance of HRQoL assessment.

The findings of this innovative study could have practical implications for lung SBRT planning. In a previous study, authors showed the feasibility of significantly decreasing the doses delivered to the lung functional volumes using 68Ga-perfusion PET/CT while still respecting target volume coverage and doses to other organs at risk [20]. They also found that functional lung imaging dose parameters outperformed anatomic lung parameters to predict the risk of acute RILT grade ≥ 2 after SBRT for primary or secondary lung tumors [21]. Thus, functional lung avoidance planning guided by perfusion PET/CT may be a simple and noninvasive method to reduce lung toxicity and the risk of impaired HRQoL in patients treated with lung SBRT while delivering an optimal dose to the tumor.

This analysis has limitations. The patient population in this study is heterogeneous, with patients treated for ES-NSCLC or pulmonary metastases with curative intent. With a questionnaire response rate of 66% and 37% for early and late HRQoL assessments, participating patients, who experienced long-term survival, may have contributed to an upward-biased response. Patients who were not alive at the time of analysis or who refused to participate in the HRQoL study may have seen their QoL deteriorate and side effects increase over the course of their treatment. Their absence from this study contributes to an incomplete picture of quality of life. However, we found a significant correlation between physician-rated dyspnea (NCI CTCAE 5.0) and HRQoL, and in a previous analysis we found the predictive value of PET perfusion-based functional parameters on the risk of increased dyspnea [21].

Conclusion

In our study, increased radiation doses in functional lung volume PET bases dose parameters were significantly associated with decreased of HRQoL unlike anatomic lung parameters. Functional lung avoidance planning guided by perfusion PET/CT may be a simple and non-invasive method to improve HRQoL in patients treated with lung SBRT.

Table 2 Impact of baseline patient, tumor and dosimetric parameters on early-change of dyspnea

		Impairment of dyspnea			
		No **33 (84.6%)**	**Yes** **6 (15.4%)**	**Overall** **39 (100%)**	***P* value**
Age					0.25
	Median [Q1, Q3]	68 [63, 72]	73 [65.8, 75]	69 [63, 72.5]	
Gender					0.66
	Male	16 (48.5%)	4 (66.7%)	20 (51.3%)	
	Female	17 (51.5%)	2 (33.3%)	19 (48.7%)	
Performance status					0.46
	Median [Q1, Q3]	1 [0, 1]	1 [0.25, 1.75]	1 [0, 1]	
Tobacco					0.31
	Non smoker	10 (30.3%)	0 (0.0%)	10 (25.6%)	
	Active or former smoker	23 (69.7%)	6 (100.0%)	29 (74.4%)	
Prior thoracic irradiation					1.00
	No	24 (72.7%)	5 (83.3%)	29 (74.4%)	
	Yes	9 (27.3%)	1 (16.7%)	10 (25.6%)	
Thoracic surgery					0.57
	No	26 (78.8%)	6 (100%)	32 (82.1%)	
	Yes	7 (21.2%)	0 (0%)	7 (17.9%)	
FEV1 < 80%					0.66
	Yes	17 (51.5%)	4 (66.7%)	21 (53.8%)	
	No	16 (48.5%)	2 (33.3%)	18 (46.2%)	
DLCO < 70%					1.00
	No	18 (54.5%)	2 (33.3%)	20 (51.3%)	
	Yes	15 (45.5%)	4 (66.7%)	19 (48.7%)	
Histology					0.64
	Primary	21 (63.6%)	5 (83.3%)	26 (66.7%)	
	Secondary	12 (36.4%)	1 (16.7%)	13 (33.3%)	
PTV volume in cc					0.15
	Median [Q1, Q3]	16.4 [9.0, 26.7]	13.9 [9.5, 26.4]	15.2 [9.0, 26.9]	
ITV volume in cc					0.83
	Median [Q1, Q3]	6.6 [3.6, 11.9]	6.3 [4.1, 12.7]	6.6 [3.6, 13.1]	
SBRT dose					0.36
	54 Gy	10 (30.3%)	1 (16.7%)	11 (28.2%)	
	48 Gy	16 (48.5%)	5 (83.3%)	21 (53.9%)	
	60 Gy	7 (21.2%)	0 (0.0%)	7 (17.9%)	
Localization					0.57
	Central	7 (21.2%)	0 (0.0%)	7 (17.9%)	
	Peripheral	26 (78.8%)	6 (100.0%)	32 (82.1%)	
Spinal cord Dmax					0.82
	Median [Q1, Q3]	6.9 [5.4, 12.5]	11.2 [6.3, 12.9]	7.1 [5.4, 12.8]	
Left bronchi Dmax					0.35
	Median [Q1, Q3]	4.4 [1.7, 8.7]	8.3 [5.0, 14.8]	4.9 [1.8, 10.4]	
Right bronchi Dmax					0.35
	Median [Q1, Q3]	4.5 [2.0, 11.8]	10.6 [4.8, 14.1]	5.5 [2.7, 12.9]	
Trachea Dmax					0.67
	Median [Q1, Q3]	6.0 [0.4, 13.3]	2.2 [0.8, 9.1]	5.4 [0.5, 12.7]	
Esophagus Dmax					0.98
	Median [Q1, Q3]	8.4 [6.2, 15.5]	8.9 [7.1, 11.2]	8.4 [6.4, 15.0]	
Pulmonary artery Dmax					0.13
	Median [Q1, Q3]	3.2 [0.7, 11.9]	10.4 [7.1, 14.2]	4.5 [1.0, 11.9]	
Aorta Dmax					0.71
	Median [Q1, Q3]	12.3 [7.5, 24.0]	8.7 [7.0, 24.4]	11.8 [7.4, 24.3]	
Brachial plexus Dmax					0.64

Table 2 (continued)

	Impairment of dyspnea			
	No	**Yes**	**Overall**	***P* value**
	33 (84.6%)	**6 (15.4%)**	**39 (100%)**	
Median [Q1, Q3]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	
Heart Dmax				0.47
Median [Q1, Q3]	3.7 [0.5, 13.4]	11.3 [3.4, 13.7]	4.9 [0.7, 13.7]	
Chest wall Dmax				0.92
Median [Q1, Q3]	43.6 [33.5, 58.6]	46.9 [42.0, 55.2]	44.8 [34.2, 58.4]	
Ribs Dmax				0.89
Median [Q1, Q3]	40.9 [32.3, 59.2]	48.6 [35.3, 56.0]	43.7 [31.7, 59.0]	
V5Gy AV (%)				0.65
Median [Q1, Q3]	13.9 [10.1, 16.7]	12.8 [11.3, 22.9]	13.2 [10.2, 16.8]	
V5Gy FV50% (%)				< 0.001
Median [Q1, Q3]	12.5 [6.3, 18.2]	23.1 [21.7, 29.7]	16.5 [8.3, 20.8]	
V5Gy FV70% (%)				0.01
Median [Q1, Q3]	12.5 [8.7, 17.5]	20.7 [18.9, 23.6]	13.7 [9.4, 19.5]	
V5Gy FV90% (%)				0.10
Median [Q1, Q3]	13.3 [8.6, 16.4]	15.9 [14.6, 24.7]	13.4 [9.8, 16.9]	
V5Gy LFV (%)				0.56
Median [Q1, Q3]	0.1 [0.08, 0.2]	0.2 [0.07, 0.3]	0.2 [0.07, 0.2]	
V20Gy AV (%)				0.83
Median [Q1, Q3]	3.3 [2, 4.7]	2.5 [2.2, 5.6]	3 [2.2, 4.9]	
V20Gy FV50% (%)				< 0.001
Median [Q1, Q3]	2.2 [0.8, 3.7]	6.2 [4.6, 7.9]	3.2 [1, 4.7]	
V20Gy FV70% (%)				0.02
Median [Q1, Q3]	2.8 [1.2, 4.2]	4.6 [4.1, 7.1]	3.2 [1.4, 4.9]	
V20Gy FV90% (%)				0.24
Median [Q1, Q3]	3.4 [1.4, 4.6]	3.3 [3.0, 6.7]	3.4 [1.6, 4.7]	
V20Gy LFV (%)				0.66
Median [Q1, Q3]	0.03 [0.02, 0.06]	0.03 [0.01, 0.05]	0.03 [0.02, 0.06]	
MLD AV (Gy)				0.75
Median [Q1, Q3]	2.9 [2.0, 3.7]	2.5 [2.3, 4.5]	2.9 [2.1, 3.8]	
MLD FV50% (Gy)				< 0.001
Median [Q1, Q3]	2.8 [1.3, 4.1]	4.8 [4.1, 5.9]	3.0 [1.6, 4.2]	
MLD FV70% (Gy)				0.02
Median [Q1, Q3]	2.7 [1.8, 3.8]	4.0 [3.6, 5.1]	3.1 [1.8, 3.9]	
MLD FV90% (Gy)				0.18
Median [Q1, Q3]	2.8 [1.7, 3.5]	3.1 [2.9, 4.9]	2.9 [1.8, 3.7]	
MLD LFV (Gy)				0.48
Median [Q1, Q3]	2.8 [1.2, 4.8]	2.3 [1.1, 3.0]	2.7 [1.2, 4.6]	
V5Gy AV (%) BED				0.69
Median [Q1, Q3]	16.3 [13.0, 19.9]	15.6 [13.8, 28.3]	16.1 [13.0, 20.2]	
V5Gy FV50% (%) BED				< 0.001
Median [Q1, Q3]	10.5 [7.5, 19.9]	27.9 [26.1, 35.5]	14.3 [8.3, 22.9]	
V5Gy FV70% (%) BED				< 0.001
Median [Q1, Q3]	12.0 [8.9, 18.3]	24.7 [22.4, 27.6]	14.0 [9.2, 22.6]	
V5Gy FV90% (%) BED				0.03
Median [Q1, Q3]	13.6 [9.4, 18.2]	19.3 [17.6, 27.8]	14.8 [9.6, 19.4]	
V5Gy LFV (%) BED				0.83
Median [Q1, Q3]	14.3 [4.2, 26.0]	14.6 [6.1, 18.4]	14.3 [4.0, 25.7]	
V20Gy AV (%) BED				0.43
Median [Q1, Q3]	6.8 [5.0, 8.6]	7.5 [5.7, 12.7]	6.9 [5.1, 8.9]	
V20Gy FV50% (%) BED				< 0.001
Median [Q1, Q3]	3.9 [2.0, 6.6]	12.8 [11.5, 19.3]	5.3 [2.3, 9.8]	

Table 2 (continued)

	Impairment of dyspnea			
	No	**Yes**	**Overall**	***P* value**
	33 (84.6%)	**6 (15.4%)**	**39 (100%)**	
V20Gy FV70% (%) BED				< 0.001
Median [Q1, Q3]	5.3 [3.3, 6.4]	12.1 [9.6, 13.9]	5.9 [3.5, 9.0]	
V20Gy FV90% (%) BED				0.01
Median [Q1, Q3]	5.4 [3.5, 7.7]	9.5 [7.4, 12.8]	5.6 [3.8, 9.0]	
V20Gy LFV (%) BED				0.61
Median [Q1, Q3]	7.1 [1.4, 14.5]	4.6 [1.6, 9.2]	7.1 [1.4, 13.1]	
MLD AV (Gy) BED				0.66
Median [Q1, Q3]	7.5 [5.8, 9.5]	7.0 [6.3, 13.7]	7.5 [5.9, 9.7]	
MLD FV50% (Gy) BED				< 0.001
Median [Q1, Q3]	5.5 [3.0, 7.0]	14.2 [11.5, 19.2]	5.8 [3.1, 11.2]	
MLD FV70% (Gy) BED				< 0.001
Median [Q1, Q3]	6.2 [3.8, 7.8]	12.0 [9.8, 15.9]	6.7 [4.1, 9.8]	
MLD FV90% (Gy) BED				0.06
Median [Q1, Q3]	7.1 [4.2, 9.0]	8.8 [7.8, 15]	7.7 [4.3, 9.4]	
MLD LFV (Gy) BED				0.56
Median [Q1, Q3]	6.0 [2.8, 11.7]	5.2 [3.1, 8.5]	6.0 [2.8, 11.5]	

Abbreviations: FEV1 = forced expiratory volume in the first second; DLCO = diffusing capacity for carbon monoxide; PTV = planning target volume; ITV = internal target volume; AV = anatomic volume; BED = biologically effective dose; EQD2 = equivalent dose in 2-Gy fractions; FV = functional volume; LFV = low functional volume; MLD = mean lung dose; VxGy = percentage of lung volumes receiving xGy

Table 3 Impact of baseline patient, tumor and dosimetric parameters on late-change of quality of life/global health status

		Impairment of quality of life/Global health status			
		No **17 (77.3%)**	**Yes** **5 (22.7%)**	**Overall** **22 (100.0%)**	***P* value**
Histology					1.00
	Primary	12 (70.6%)	3 (60.0%)	15 (68.2%)	
	Secondary	5 (29.4%)	2 (40.0%)	7 (31.8%)	
Age					0.33
	Median [Q1, Q3]	64 [63, 72]	72 [71, 72]	69 [63, 72]	
Gender					0.61
	Male	7 (41.2%)	1 (20.0%)	8 (36.4%)	
	Female	10 (58.8%)	4 (80.0%)	14 (63.6%)	
Performance status					0.58
	Median [Q1, Q3]	1 [0, 1]	0 [0, 1]	1 [0, 1]	
Tobacco					0.12
	Non smoker	2 (11.8%)	3 (60.0%)	5 (22.7%)	
	Active or former smoker	15 (88.2%)	2 (40.0%)	17 (77.3%)	
Prior thoracic irradiation					0.59
	No	13 (76.5%)	3 (60.0%)	16 (72.7%)	
	Yes	4 (23.5%)	2 (40.0%)	6 (27.3%)	
Thoracic surgery					1.00
	No	12 (70.6%)	4 (80.0%)	16 (72.7%)	
	Yes	5 (29.4%)	1 (20.0%)	6 (27.3%)	
SBRT dose					1.00
	54 Gy	6 (35.3%)	2 (40.0%)	8 (36.4%)	
	48 Gy	6 (35.3%)	2 (40.0%)	8 (36.4%)	
	60 Gy	5 (29.4%)	1 (20.0%)	6 (27.2%)	
Localization					1.00
	central	5 (29.4%)	1 (20.0%)	6 (27.3%)	
	Peripheral	12 (70.6%)	4 (80.0%)	16 (72.7%)	
PTV volume in cc					0.34
	Median [Q1, Q3]	17.0 [11.7, 33.0]	14.9 [8.9, 22.6]	16.4 [10.0, 29.2]	
ITV volume in cc					0.23
	Median [Q1, Q3]	7.1 [4.4, 17.6]	5.5 [2.8, 9.0]	6.6 [3.5, 14.0]	
Spinal cord Dmax					0.94
	Median [Q1, Q3]	9.8 [5.6, 13.1]	14.0 [5.4, 14.2]	10.1 [5.5, 14.2]	
Left bronchi Dmax					0.65
	Median [Q1, Q3]	4.4 [1.7, 19.9]	5.1 [0.9, 9.6]	4.7 [1.5, 13.7]	
Right bronchi Dmax					0.25
	Median [Q1, Q3]	4.5 [3.4, 23.4]	3.4 [0.4, 8.5]	4.2 [2.5, 13.8]	
Trachea Dmax					0.31
	Median [Q1, Q3]	7.9 [6.0, 25.4]	6.5 [2.4, 18.0]	7.1 [2.8, 21.8]	
Esophagus Dmax					0.36
	Median [Q1, Q3]	9.2 [7.4, 20.4]	8.0 [6.5, 10.0]	8.8 [6.8, 16.2]	
Pulmonary artery Dmax					0.70
	Median [Q1, Q3]	4.6 [0.7, 15.9]	3.0 [1.2, 9.7]	4.6 [0.8, 11.4]	
Aorta Dmax					0.49
	Median [Q1, Q3]	16.0 [8.7, 24.4]	14.3 [7.4, 22.3]	15.3 [8.6, 24.3]	
Brachial plexus Dmax					0.15
	Median [Q1, Q3]	0 [0, 1.1]	0 [0, 0]	0 [0, 0.5]	
Heart Dmax					0.53
	Median [Q1, Q3]	3.4 [0.5, 14.0]	10.0 [7.7, 22.1]	6.5 [0.5, 19.7]	
Chest wall Dmax					0.54
	Median [Q1, Q3]	43.6 [32.9, 62.1]	38.3 [35.2, 40.8]	41.7 [33.8, 56.0]	
Ribs Dmax					0.49

Table 3 (continued)

	Impairment of quality of life/Global health status			
	No **17 (77.3%)**	**Yes** **5 (22.7%)**	**Overall** **22 (100.0%)**	***P* value**
Median [Q1, Q3]	35.7 [31.4, 62.0]	33.5 [33.4, 33.5]	34.1 [31.5, 61.0]	
FEV1 < 80%				0.87
Yes	9 (52.9%)	3 (60.0%)	12 (54.5%)	
No	8 (47.1%)	2 (40.0%)	10 (45.5%)	
DLCO < 70%				0.84
No	9 (52.9%)	2 (40.0%)	11 (50.0%)	
Yes	8 (47.1%)	3 (60.0%)	11 (50.0%)	
MLD AV (Gy)				0.45
Median [Q1, Q3]	2.9 [2.4, 4.1]	2.9 [2.0, 2.9]	2.9 [2.3, 4.0]	
MLD FV50% (Gy)				0.08
Median [Q1, Q3]	1.7 [1.0, 3.2]	4.1 [3.6, 4.2]	2.9 [1.3, 4.0]	
MLD FV70% (Gy)				0.19
Median [Q1, Q3]	2.6 [1.7, 3.6]	3.8 [3.1, 3.9]	2.8 [1.9, 3.9]	
MLD FV90% (Gy)				0.70
Median [Q1, Q3]	2.8 [2.1, 3.9]	3.3 [2.5, 3.3]	2.8 [2.2, 3.8]	
MLD LFV (Gy)				0.10
Median [Q1, Q3]	4.3 [2.8, 5.1]	1.3 [0.8, 1.4]	3.6 [1.6, 4.8]	
V5Gy AV (%)				0.22
Median [Q1, Q3]	14.3 [9.7, 20.4]	13.2 [8.8, 14.0]	14.0 [9.3, 18.0]	
V5Gy FV50% (%)				0.13
Median [Q1, Q3]	9.4 [3.0, 16.5]	17.2 [13.0, 17.7]	10.4 [4.4, 17.6]	
V5Gy FV70% (%)				0.27
Median [Q1, Q3]	10.4 [6.4, 17.9]	13.9 [12.4, 16.3]	11.9 [9.4, 17.5]	
V5Gy FV90% (%)				0.94
Median [Q1, Q3]	13.3 [9.4, 17.3]	12.8 [11.1, 15.3]	13.2 [10.3, 16.4]	
V5Gy LFV (%)				0.12
Median [Q1, Q3]	0.2 [0.1, 0.2]	0.1 [0.1, 0.2]	0.2 [0.1, 0.2]	
V20Gy AV (%)				0.64
Median [Q1, Q3]	2.7 [2.6, 6.1]	3.0 [2.2, 3.9]	2.9 [2.6, 5.8]	
V20Gy FV50% (%)				0.02
Median [Q1, Q3]	1.8 [0.5, 3.5]	4.8 [3.8, 4.9]	3.2 [0.7, 3.7]	
V20Gy FV70% (%)				0.15
Median [Q1, Q3]	2.8 [1.2, 3.8]	4.2 [3.4, 5.1]	3.1 [1.4, 4.8]	
V20Gy FV90% (%)				0.51
Median [Q1, Q3]	3.4 [1.7, 4.4]	3.7 [2.7, 4.6]	3.4 [1.8, 4.6]	
V20Gy LFV (%)				0.27
Median [Q1, Q3]	0.05 [0.03, 0.07]	0.03 [0.01, 0.06]	0.05 [0.02, 0.07]	
MLD AV (Gy) BED				0.54
Median [Q1, Q3]	7.5 [7.1, 10.2]	7.7 [6.5, 9.1]	7.5 [6.8, 9.8]	
MLD FV50% (Gy) BED				0.04
Median [Q1, Q3]	3.5 [2.1, 6.6]	8.9 [6.3, 11.4]	5.3 [2.5, 9.2]	
MLD FV70% (Gy) BED				0.22
Median [Q1, Q3]	6.5 [3.7, 7.4]	9.5 [6.3, 10.1]	6.6 [4.7, 9.1]	
MLD FV90% (Gy) BED				0.59
Median [Q1, Q3]	8.0 [5.3, 9.0]	7.7 [7.1, 10.6]	7.8 [5.4, 9.2]	
MLD LFV (Gy) BED				0.06
Median [Q1, Q3]	9.4 [5.8, 13.3]	2.9 [2.8, 5.4]	8.8 [4.4, 12.6]	
V5Gy AV (%) BED				0.19
Median [Q1, Q3]	18.5 [13.0, 22.4]	14.9 [11.1, 16.3]	16.7 [12.0, 21.1]	
V5Gy FV50% (%) BED				0.06
Median [Q1, Q3]	9.0 [4.5, 13.6]	14.3 [14.0, 21.6]	9.6 [6.2, 14.2]	

Table 3 (continued)

	Impairment of quality of life/Global health status			
	No **17 (77.3%)**	**Yes** **5 (22.7%)**	**Overall** **22 (100.0%)**	***P* value**
V5Gy FV70% (%) BED				0.25
Median [Q1, Q3]	9.8 [8.9, 14.4]	15.1 [13.6, 17.5]	10.8 [9.1, 16.9]	
V5Gy FV90% (%) BED				0.94
Median [Q1, Q3]	14.6 [9.4, 19.3]	13.8 [12.1, 16.3]	14.2 [9.9, 19.0]	
V5Gy LFV (%) BED				0.07
Median [Q1, Q3]	24.3 [15.9, 28.2]	10.5 [5.8, 17.8]	18.7 [10.6, 27.1]	
V20Gy AV (%) BED				0.49
Median [Q1, Q3]	6.8 [6.0, 11.2]	7.1 [5.3, 8.0]	7.0 [6.0, 9.6]	
V20Gy FV50% (%) BED				0.01
Median [Q1, Q3]	3.3 [1.5, 5.3]	7.8 [7.4, 9.7]	5.2 [1.8, 7.4]	
V20Gy FV70% (%) BED				0.10
Median [Q1, Q3]	5.4 [3.3, 7.5]	7.8 [6.0, 9.0]	6.0 [4.0, 7.8]	
V20Gy FV90% (%) BED				0.59
Median [Q1, Q3]	5.6 [4.0, 9.6]	7.1 [6.5, 8.7]	6.8 [4.5, 9.4]	
V20Gy LFV (%) BED				0.03
Median [Q1, Q3]	11.1 [6.4, 17.4]	5.1 [1.4, 7.1]	8.9 [5.4, 13.8]	

Abbreviations: FEV1 = forced expiratory volume in the first second; DLCO = diffusing capacity for carbon monoxide; PTV = planning target volume; ITV = internal target volume; AV = anatomic volume; BED = biologically effective dose; EQD2 = equivalent dose in 2-Gy fractions; FV = functional volume; LFV = low functional volume; MLD = mean lung dose; VxGy = percentage of lung volumes receiving xGy

Table 4 Impact of baseline patient, tumor and dosimetric parameters on late-change of dyspnea

		Impairement of dyspnea			
		No **19 (86.4%)**	**Yes** **3 (13.6%)**	**Overall** **22 (100%)**	***P* value**
Age					0.15
	Median [Q1, Q3]	64.0 [62.0, 72.0]	72.0 [71.5, 75.0]	69.0 [63.0, 72.0]	
Gender					1.00
	Male	7 (36.8%)	1 (33.3%)	8 (36.4%)	
	Female	12 (63.2%)	2 (66.7%)	14 (63.6%)	
Perfomance status					0.75
	Median [Q1, Q3]	1.0 [0.0, 1.0]	0.0 [0.0, 1.0]	1.0 [0.0, 1.0]	
Tobacco					1.00
	No	4 (21.0%)	1 (33.3%)	5 (22.7%)	
	Yes	15 (79.0%)	2 (66.7%)	17 (77.3%)	
Prior thoracic irradiation					1.00
	No	14 (73.7%)	2 (66.7%)	16 (72.7%)	
	Yes	5 (26.3%)	1 (33.3%)	6 (27.3%)	
Thoracic surgery					1.00
	No	14 (73.7%)	2 (66.7%)	16 (72.7%)	
	Yes	5 (26.3%)	1 (33.3%)	6 (27.3%)	
Histology					1.00
	Primary	13 (68.4%)	2 (66.7%)	15 (68.2%)	
	Secondary	6 (31.6%)	1 (33.3%)	7 (31.8%)	
PTV volume in cc					0.41
	Median [Q1, Q3]	16.9 [9.6, 31.6]	12.6 [11.3, 12.7]	16.4 [10.0, 29.2]	
ITV volume in cc					0.41
	Median [Q1, Q3]	7.0 [3.5, 16.1]	5.0 [4.2, 5.5]	6.6 [3.5, 14.0]	
SBRT dose					0.43
	54 Gy	6 (31.6%)	2 (66.7%)	8 (36.4%)	
	48 Gy	8 (42.1%)	0 (0.0%)	8 (36.4%)	
	60 Gy	5 (26.3%)	1 (33.3%)	6 (27.2%)	
Localization					1.00
	Central	5 (26.3%)	1 (33.3%)	6 (27.3%)	
	Peripheral	14 (73.7%)	2 (66.7%)	16 (72.7%)	
Spinal cord Dmax					0.93
	Median [Q1, Q3]	9.8 [5.6, 13.9]	14.0 [9.5, 14.1]	10.1 [5.5, 14.2]	
Left bronchi Dmax					0.46
	Median [Q1, Q3]	4.1 [1.2, 17.2]	9.6 [7.3, 10.4]	4.7 [1.5, 13.7]	
Right bronchi Dmax					0.72
	Median [Q1, Q3]	3.8 [2.1, 18.0]	8.5 [6.0, 11.3]	4.2 [2.5, 13.8]	
Trachea Dmax					0.32
	Median [Q1, Q3]	7.9 [5.7, 25.0]	3.5 [1.9, 7.7]	7.1 [2.8, 21.8]	
Esophagus Dmax					0.72
	Median [Q1, Q3]	9.2 [6.8, 18.5]	8.0 [7.3, 11.7]	8.8 [6.8, 16.2]	
Pulmonary artery Dmax					0.46
	Median [Q1, Q3]	4.5 [0.7, 12.7]	9.7 [6.3, 10.8]	4.6 [0.8, 11.4]	
Aorta Dmax					0.46
	Median [Q1, Q3]	16.0 [8.6, 26.6]	14.3 [10.6, 18.3]	15.3 [8.6, 24.3]	
Brachial plexus Dmax					0.30
	Median [Q1, Q3]	0.0 [0.0, 0.9]	0.0 [0.0, 0.0]	0.0 [0.0, 0.5]	
Heart Dmax					0.34
	Median [Q1, Q3]	3.4 [0.5, 17.8]	10.0 [8.9, 16.1]	6.5 [0.5, 19.7]	
Chest wall Dmax					1.00
	Median [Q1, Q3]	42.7 [33.2, 59.8]	40.8 [39.6, 42.8]	41.7 [33.8, 56.0]	
Ribs Dmax					0.52

Table 4 (continued)

	Impairement of dyspnea			
	No **19 (86.4%)**	**Yes** **3 (13.6%)**	**Overall** **22 (100%)**	***P* value**
Median [Q1, Q3]	34.6 [31.6, 61.8]	33.4 [32.3, 34.0]	34.1 [31.5, 61.0]	
DLCO < 70%				0.18
Yes	10 (52.6%)	1 (33.3%)	11 (50.0%)	
No	9 (47.4%)	2 (66.7%)	11 (50.0%)	
FEV1 < 80%				0.47
Yes	10 (52.6%)	2 (66.7%)	12 (54.5%)	
No	9 (47.4%)	1 (33.3%)	10 (45.5%)	
V5Gy AV (%)				0.46
Median [Q1, Q3]	14.1 [9.4, 19.4]	13.2 [11, 13.6]	14.0 [9.3, 18]	
V5Gy FV50% (%)				0.36
Median [Q1, Q3]	9.6 [3.4, 17.6]	17.2 [13.8, 17.5]	10.4 [4.4, 17.6]	
V5Gy FV70% (%)				0.50
Median [Q1, Q3]	11.2 [7.9, 19.3]	13.9 [12.7, 15.1]	11.9 [9.4, 17.5]	
V5Gy FV90% (%)				0.86
Median [Q1, Q3]	13.3 [9.7, 16.9]	12.8 [12.0, 14.1]	13.2 [10.3, 16.4]	
V5Gy LFV (%)				0.16
Median [Q1, Q3]	0.17 [0.11, 0.23]	0.11 [0.07, 0.13]	0.16 [0.11, 0.21]	
V20Gy AV (%)				0.92
Median [Q1, Q3]	2.7 [2.6, 5.55]	3 [2.6, 4.9]	2.9 [2.6, 5.8]	
V20Gy FV50% (%)				0.02
Median [Q1, Q3]	2.2 [0.6, 3.6]	4.9 [4.4, 5.3]	3.2 [0.7, 3.7]	
V20Gy FV70% (%)				0.15
Median [Q1, Q3]	2.8 [1.2, 4.4]	4.2 [3.8, 5.3]	3.1 [1.4, 4.8]	
V20Gy FV90% (%)				0.39
Median [Q1, Q3]	3.4 [1.7, 4.5]	3.7 [3.2, 5.5]	3.4 [1.8, 4.6]	
V20Gy LFV (%)				0.36
Median [Q1, Q3]	0.05 [0.03, 0.07]	0.02 [0.01, 0.04]	0.05 [0.02, 0.07]	
MLD AV (Gy)				1.00
Median [Q1, Q3]	2.9 [2.3, 4.0]	2.9 [2.5, 3.7]	2.9 [2.3, 4.0]	
MLD FV50% (Gy)				0.13
Median [Q1, Q3]	2.4 [1.1, 3.4]	4.1 [3.9, 4.1]	2.9 [1.3, 4.0]	
MLD FV70% (Gy)				0.16
Median [Q1, Q3]	2.6 [1.8, 3.8]	3.8 [3.4, 4.1]	2.8 [1.9, 3.9]	
MLD FV90% (Gy)				0.46
Median [Q1, Q3]	2.8 [2.0, 3.8]	3.3 [2.9, 4.0]	2.8 [2.2, 3.8]	
MLD LFV (Gy)				0.19
Median [Q1, Q3]	3.8 [2.3, 5.0]	1.3 [1.0, 2.5]	3.6 [1.6, 4.8]	
V5Gy AV (%) BED				0.65
Median [Q1, Q3]	17.0 [12.3, 21.9]	16.3 [13.7, 17.5]	16.7 [12.0, 21.1]	
V5Gy FV50% (%) BED				0.05
Median [Q1, Q3]	9.1 [5.2, 13.7]	21.6 [18.0, 24.3]	9.6 [6.2, 14.2]	
V5Gy FV70% (%) BED				0.11
Median [Q1, Q3]	9.8 [9.0, 14.0]	17.5 [16.3, 20.5]	10.8 [9.1, 16.9]	
V5Gy FV90% (%) BED				0.46
Median [Q1, Q3]	13.4 [9.6, 18.7]	16.3 [15.1, 18.6]	14.2 [9.9, 19.0]	
V5Gy LFV (%) BED				0.11
Median [Q1, Q3]	24.2 [12.3, 28.2]	10.5 [6.4, 13.4]	18.7 [10.6, 27.1]	
V20Gy AV (%) BED				1.00
Median [Q1, Q3]	6.8 [6.0, 10.2]	8.0 [6.6, 8.9]	7.0 [6.0, 9.6]	
V20Gy FV50% (%) BED				0.02
Median [Q1, Q3]	3.9 [1.6, 5.5]	9.7 [8.8, 10.0]	5.2 [1.8, 7.4]	

Table 4 (continued)

	Impairement of dyspnea			
	No **19 (86.4%)**	**Yes** **3 (13.6%)**	**Overall** **22 (100%)**	***P* value**
V20Gy FV70% (%) BED				0.05
Median [Q1, Q3]	5.9 [3.6, 6.8]	9.0 [8.4, 9.2]	6.0 [4.0, 7.8]	
V20Gy FV90% (%) BED				0.26
Median [Q1, Q3]	5.6 [4.2, 8.6]	8.7 [7.6, 9.5]	6.8 [4.5, 9.4]	
V20Gy LFV (%) BED				0.19
Median [Q1, Q3]	10.8 [6.3, 15.9]	5.1 [3.3, 6.5]	8.9 [5.4, 13.8]	
MLD AV (Gy) BED				1.00
Median [Q1, Q3]	7.5 [6.9, 10.0]	9.1 [7.8, 9.3]	7.5 [6.8, 9.8]	
MLD FV50% (Gy) BED				0.03
Median [Q1, Q3]	4.9 [2.2, 6.5]	11.4 [10.2, 12.3]	5.3 [2.5, 9.2]	
MLD FV70% (Gy) BED				0.02
Median [Q1, Q3]	6.3 [4.1, 7.2]	10.1 [9.8, 11.1]	6.6 [4.7, 9.1]	
MLD FV90% (Gy) BED				0.11
Median [Q1, Q3]	7.1 [5.2, 8.9]	10.6 [9.1, 10.6]	7.8 [5.4, 9.2]	
MLD LFV (Gy) BED				0.09
Median [Q1, Q3]	9.4 [5.3, 13.1]	2.9 [2.9, 4.2]	8.8 [4.4, 12.6]	

Abbreviations: FEV1 = forced expiratory volume in the first second; DLCO = diffusing capacity for carbon monoxide; PTV = planning target volume; ITV = internal target volume; AV = anatomic volume; BED = biologically effective dose; EQD2 = equivalent dose in 2-Gy fractions; FV = functional volume; LFV = low functional volume; MLD = mean lung dose; VxGy = percentage of lung volumes receiving xGy

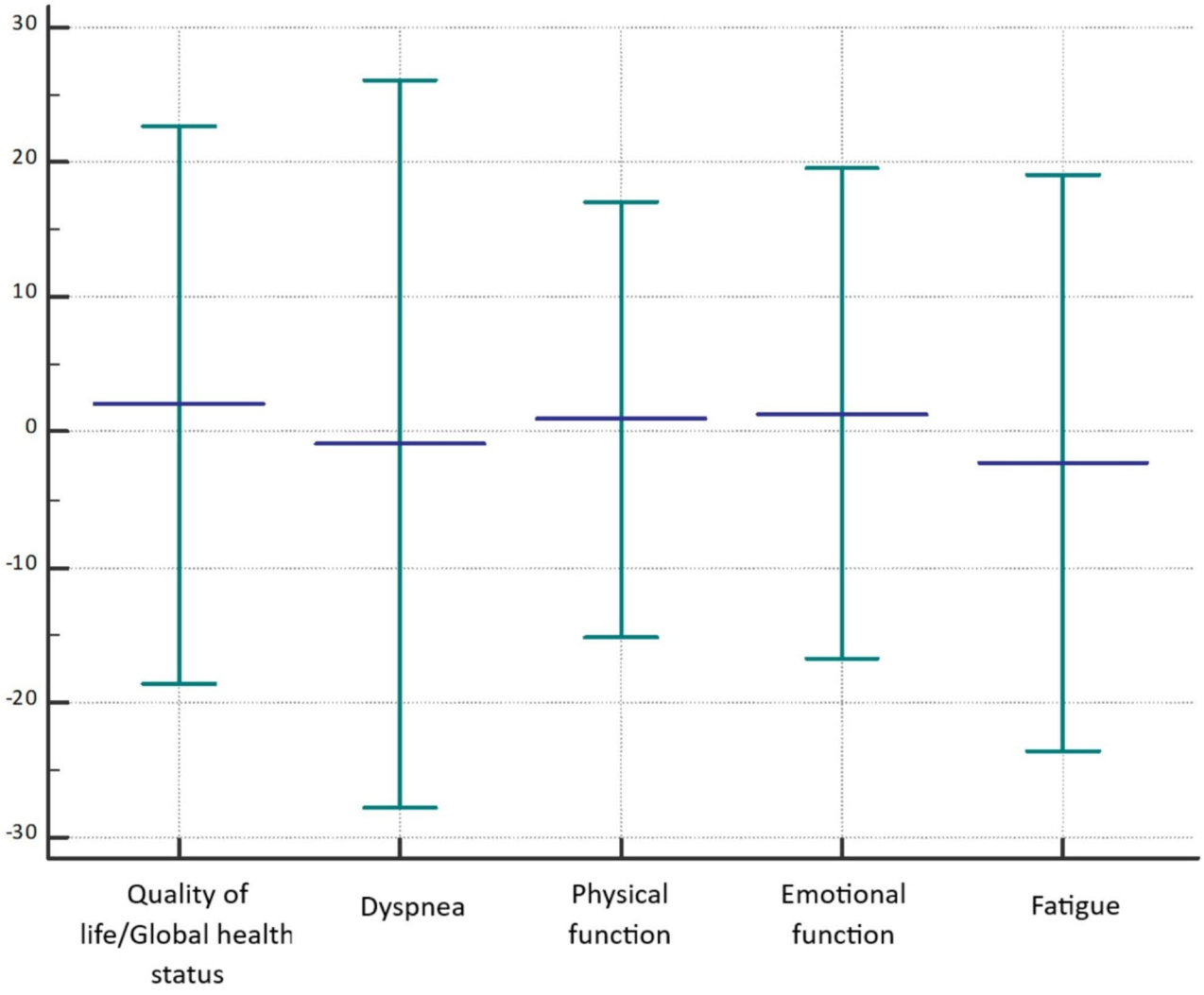

Fig. 1 Early change of health-related Quality of life (HRQoL) assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 and the QLQ LC13 lung cancer-specific questionnaire

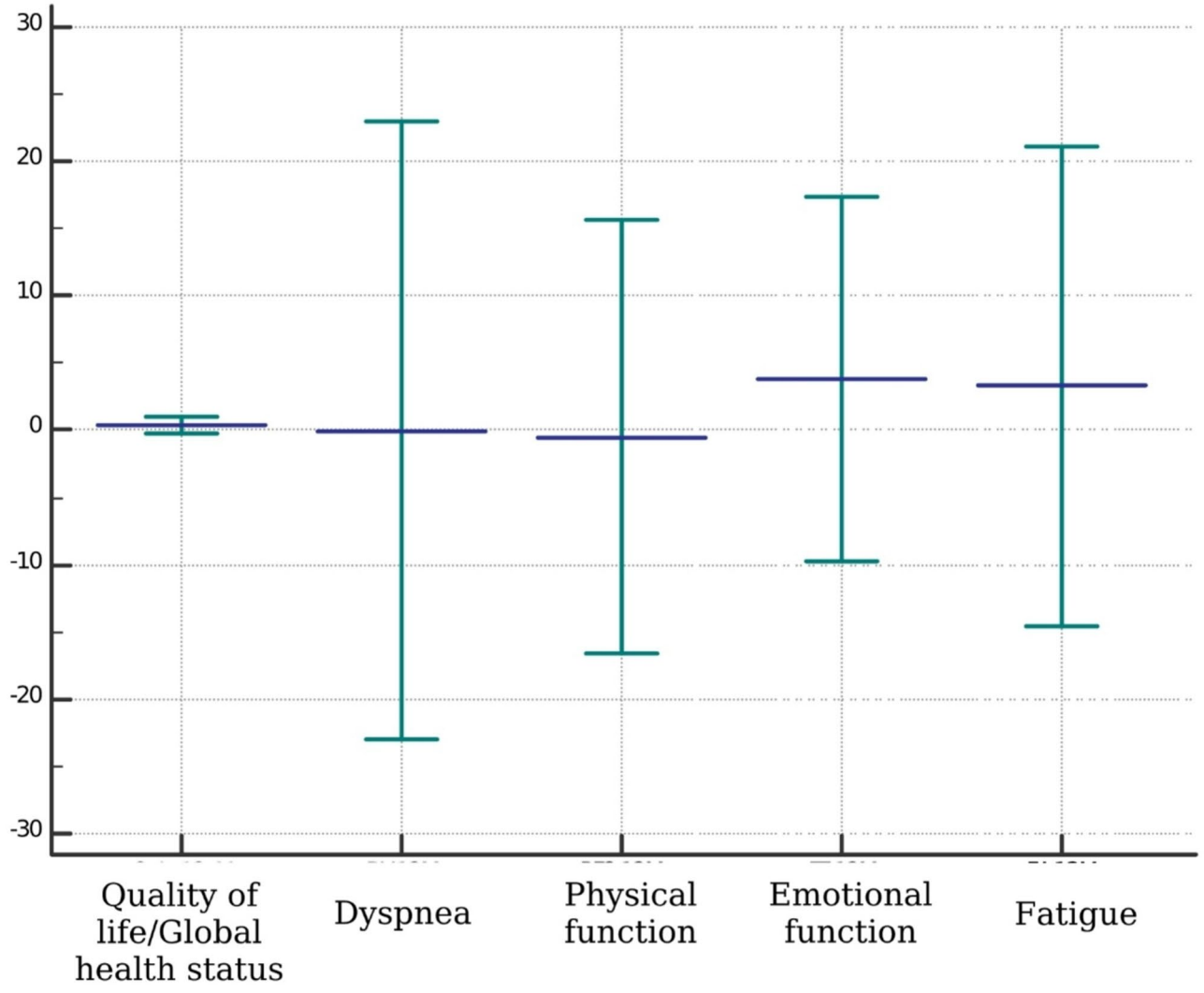

Fig. 2 Late change of Quality of life (QoL) assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 and the QLQ LC13 lung cancer-specific questionnaire

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13014-025-02685-w.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

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Author contributions
François Lucia: Conceptualization, Funding acquisition, Data curation, Writing-Original draft preparation, Visualization, Formal analysis, Methodology. Jacques Lamour: Data curation, Writing- Reviewing and Editing. Margaux Geier: Data curation, Writing- Reviewing and Editing. Vincent Bourbonne: Data curation, Writing- Reviewing and Editing. Fanny Pinot: Data curation, Writing-Reviewing and Editing. Malik Nebbache: Data curation, Writing- Reviewing and EditingFréderique Blanc-Béguin: Software, Writing- Reviewing and Editing. Simon Hennebicq: Software, Writing- Reviewing and Editing. Maelle Mauguen: Data curation, Writing- Reviewing and Editing. Kevin Kerleguer: Data curation, Writing- Reviewing and Editing. Ulrike Schick: Supervision, Writing- Reviewing and Editing. Olivier Pradier: Supervision, Writing-Reviewing and Editing. Grégoire Le Gal: Methodology, Writing- Reviewing and Editing. Pierre-Yves Salaun: Supervision, Writing- Reviewing and Editing, Methodology. David Bourhis: Software, Data curation, Writing- Reviewing and Editing, Methodology. Pierre-Yves Le Roux: Conceptualization, Data curation, Supervision, Funding acquisition, Writing- Reviewing and Editing, Methodology.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Consent for publication
N/A.

Competing interests
The authors declare no competing interests.

Ethics approval
All procedures were performed in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study design and exemption from informed consent were approved by the Institutional Review Board of Brest University Hospital.

Consent to participate
The study was approved by the Nord Ouest IV Ethics Committee (ID RCB: 2021-002224-20) and registered in ClinicalTrial.gov registry (NCT04942275). Written informed consent was obtained from all participants.

Disclosure of conflicts of interest
No potential conflicts of interest financial were disclosed.

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