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CLINICAL INVESTIGATION **Lung**

PULMONARY FUNCTION FOLLOWING HIGH-DOSE RADIOTHERAPY OF NON–SMALL-CELL LUNG CANCER

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Purpose: To study changes of pulmonary function tests (PFTs) after radiotherapy (RT) of non–small-cell lung cancer (NSCLC) in relation to radiation dose, tumor regression, and changes in lung perfusion.

Methods and Materials: Eighty-two patients with inoperable NSCLC were evaluated with PFTs (forced expiratory volume in 1 s [FEV_1] and diffusion capacity [$T_{L,COc}$]), a computed tomography (CT) scan of the chest, and a single photon emission CT (SPECT) lung perfusion scan, before and 3–4 months after RT. The reductions of PFTs and tumor volume were calculated. The lung perfusion was measured from pre- and post-RT SPECT scans, and the difference was defined as the measured perfusion reduction (MPR). In addition, the perfusion post-RT was estimated from the dose distribution using a dose–effect relation for regional lung perfusion, and compared with the pre-RT lung perfusion to obtain the predicted perfusion reduction (PPR). The difference between the actually measured and the PPR was defined as reperfusion. The mean lung dose (MLD) was computed and weighted with the pre-RT perfusion, resulting in the mean perfusion-weighted lung dose (MpLD). Changes of PFTs were evaluated in relation to tumor dose, MLD, MpLD, tumor regression, and parameters related to perfusion changes.

Results: In a multivariate analysis, the total tumor dose and MLD were not associated with reductions of PFTs. Tumor regression resulted in a significant improvement of FEV_1 ($p = 0.02$), but was associated with a reduction of $T_{L,COc}$ ($p = 0.05$). The MpLD and the PPR showed a significant ($p = 0.01$ to 0.04) but low correlation ($r = 0.24$ to 0.31) with the reduction of both PFTs. The other parameters for perfusion changes, the MPR and reperfusion were not correlated with changes in PFTs.

Conclusion: The perfusion-related dose variables, the MpLD or the PPR, are the best parameters to estimate PFTs after RT. Tumor regression is associated with an improvement of FEV_1 and a decline of $T_{L,COc}$. Reperfusion was not associated with an improvement of global pulmonary function. © 2003 Elsevier Science Inc.

Pulmonary function, SPECT, Perfusion, Tumor response, Mean lung dose.

INTRODUCTION

Radiotherapy of tumors located within or around the thoracic cavity inevitably results in partial irradiation of the surrounding normal lung tissue. Lung damage after radiotherapy has been reported in breast cancer (1), Hodgkin's lymphoma (2–4), esophageal and lung cancer (5–8). Radiation-induced respiratory toxicity ranges from an often asymptomatic impairment of lung function to fibrosis and radiation pneumonitis, which can develop into a life-threatening complication (9). Several investigators have found that simple dose–volume parameters such as the mean lung dose (MLD) (10, 11), the percentage of lung volume receiving more than a threshold dose of 20 Gy (12) or 30 Gy (13) solely or in combination with biologic factors like transforming growth factor beta (TGF-β) levels (14), can be used to predict radiation pneumonitis.

In addition to the prediction of radiation pneumonitis, which is a binary type of complication, it is clinically relevant to evaluate and predict the graded response of lung tissue to radiation. This response can be quantified by

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changes in pulmonary function tests (PFTs) (2, 8). Abratt *et al.* noted a worsening of the dyspnea score in patients who had more than 10% decrease of their diffusion capacity (8, 15). Moreover, predicting PFTs post-radiotherapy (post-RT) is of particular interest in patients with non–small-cell lung cancer (NSCLC). The majority of lung cancer patients already have an impaired pulmonary function before RT, which often leads to a therapeutic nihilistic approach. Several authors (5, 6, 16) have tried to estimate the post-RT pulmonary function by taking into account the percentage of perfused lung in the estimated irradiated volume. In general, the residual lung function post-RT was better than predicted. This inconsistency was attributed to the applied methodology, which did not consider the full three-dimensional (3D)-dose distribution.

We previously assessed changes of lung function in patients with Hodgkin's lymphoma post-RT using full 3D single photon emission computed tomography (SPECT) lung perfusion and ventilation scans and spatially correlated pretreatment computed tomography (CT) scans (17). We showed that the average reduction of local perfusion significantly correlated with the reduction of PFTs. Theuws *et al.*(18) extended this work and reported that in patients with relatively healthy lungs (breast cancer and lymphoma), the reduction of PFTs strongly correlated with the predicted perfusion reduction (PPR) as well as with the MLD, which is a pure dose parameter.

For patients with lung cancer, it is, however, more intricate to estimate the amount of functional lung damage. The majority of these patients suffer from preexisting lung disease, which is frequently associated with inhomogeneous lung perfusion and fluctuating pulmonary function. Furthermore, tumor progression can contribute to functional damage. Conversely, shrinkage of central lung tumors initially obstructing the blood flow through pulmonary vessels can lead to perfusion recovery and hence compensate for radiation-induced injury (19). It has also been reported that lung cancer patients may experience an improvement of their PFTs after radiotherapy (7).

Seppenwoolde *et al.*(20) have correlated perfusion changes on SPECT scans and 3D-dose distributions in patients with NSCLC and derived a dose–effect relation. They compared the reduction of local perfusion as predicted based on this dose–effect relation with the actually measured perfusion loss as assessed from the follow-up SPECT. Eighteen of 25 evaluated NSCLC cases experienced a perfusion loss, which was on average 7.2% less than predicted, and this was defined as local reperfusion.

Because of the parallel structure of the lung (21), it can be hypothesized that the sum of changes in regional perfusion may correlate with the overall lung function as measured by PFTs (22, 23). Furthermore, lung perfusion is often inhomogeneous in NSCLC patients, so that it is conceivable to assume that the radiation dose delivered to nonperfused regions contributes less to functional lung damage.

Therefore, the main objective of this study was to evaluate changes in overall pulmonary function (as measured by PFTs) after high-dose radiotherapy in relation to perfusion, dose, and perfusion-related dose parameters. Following the observation that PFTs can improve in patients with NSCLC after radiotherapy, we further examined the impact of tumor regression and reperfusion (recovery of functional [perfusion] damage) on PFTs.

Table 1. Patient, tumor, and treatment characteristics

Male/female	63/19
Age (year)	
median	74
range	48–88
Tumor stage	
Stage I (IA/IB)	26 (12/14)
Stage II (IIA/IIB)	14 (2/12)
Stage III (IIIA/IIIB)	42 (26/16)
GTV, preradiotherapy (cm^3)	
mean	113
range	2–901
Tumor location	
Central	48
Peripheral	34
Upper lobe/middle lobe/lower lobe	63/7/12
Elective nodal field + boost to a total dose of 70 Gy	20
Involved field (60.8–94.5 Gy)	62
Radiotherapy dose to GTV (Gy)	
mean	74.8
range	60.8–94.5
Chemotherapy before radiotherapy/ radiotherapy alone	4/78

Abbreviation: GTV = gross tumor volume.

METHODS AND MATERIALS

Patient, tumor, and treatment characteristics

Eighty-two patients with medically inoperable or locally advanced NSCLC and good prognostic factors (weight loss $<10\%$, Eastern Cooperative Oncology Group performance status ≤ 2) referred to the department for radical RT were included in this study (Table 1). Eligibility criteria were: presence of visible tumor on a diagnostic chest CT scan, availability of CT and SPECT scans before irradiation and at 3–4 months follow-up (all acquired in RT treatment position, which was supine with the arms raised above the head in a forearm support), baseline PFTs (see below), with at least a forced expiratory volume in 1 s (FEV_1) and/or diffusion capacity for carbon monoxide ($T_{L,COc}$) at 3–4 months follow-up. Patients with disease progression were excluded from the study to avoid the confounding effect of tumor progression on the evaluation of radiation-induced toxicity.

It has been hypothesized that regression of central tumors is likely to result in reperfusion (19). Consequently, we classified tumors in two groups according to their location (Table 1). A central lung tumor was defined as a tumor involving the hilum or mediastinum, or both, by either the primary tumor or metastatic lymph nodes (19).

For all patients, 3D conformal RT plans were created,

including either an elective nodal field irradiation or an involved field radiotherapy (Table 1), encompassing the primary tumor with lymph nodes pathologic at mediastinoscopy, on CT scan according to the 1-cm diameter criterion or, when a positron emission tomography (PET) scan was available, all lymph nodes showing 18-fluoro-2-deoxyglucose (FDG) uptake. Only 4 patients received chemotherapy, which was administered at least 6 weeks before radiotherapy.

The standard RT regimen consisted of 70 Gy delivered in 35 fractions and 7 weeks in 36 patients. Forty-six patients were treated within the context of an ongoing Phase I/II dose escalation trial (dose range 60.8–94.5 Gy/2.25 Gy per fraction/overall treatment time 6 weeks) (24). Patients were entered in this trial after an informed consent was obtained, and the trial was approved by the hospital's ethics committee.

Pulmonary function tests

PFTs were performed using the Jaeger Masterlab equipment (Würzburg, Germany). Data were collected at baseline (within 2 weeks before RT) and at 3–4 months follow-up. For this study, the FEV_1 and the $T_{L,CO}$ were analyzed as these PFTs are most reported. FEV_1 was measured with spirometry. $T_{L,CO}$ was determined using the single breath method. The diffusion capacity was corrected for the actual hemoglobin level (Hb) in the peripheral blood ($T_{L,COc}$) according to the formula $T_{L,COc} = T_{L,CO} * (6.12 + Hb)/(1.7 * Hb)$. PFTs were expressed as percentage of the predicted normal value according to Quanjer *et al.*(25). Changes in PFTs were expressed as relative reductions defined by the difference between pre- and post-RT value relative to the pre-RT value.

Radiotherapy dose to the lungs

All patients had CT-based 3D-dose computations performed in our treatment planning system [U-MPlan, University of Michigan (26)], as described previously (17). Corrections for lung density were based on an equivalent pathlength algorithm. To correct for the effect of dose per fraction, the local dose was converted to the normalized total dose (NTD) (27), which is defined as the total biologically equivalent dose delivered in 2 Gy per fraction, using the linear quadratic model with an α/β ratio of 3 Gy (28). All doses reported hereafter are NTD-corrected.

From the 3D-dose data, the mean dose to the lungs (MLD) was calculated. The lung volume was defined on the CT scan by binary thresholding (a threshold value was chosen at a density of 0.7 g/mL), excluding any gross tumor volume (GTV) embedded in lung tissue. For the calculation of the mean perfusion-weighted lung dose (MpLD), the dose in each lung voxel was weighted with the normalized pretreatment perfusion in that voxel as measured by SPECT (see below). In case of a homogeneous lung perfusion, the MpLD is (per definition) equal to the MLD.

Quantification of tumor regression

All CT scans (5-mm slice thickness) were acquired during free breathing in RT treatment position pre-RT and at 3–4 months follow-up. The GTV was delineated on the pre- and post-RT CT scans using the appropriate level and window settings (lung and mediastinum). The GTV was defined as the primary tumor solely except for hilar tumors in which the primary tumor is often contiguous with adjacent lymph nodes. As CT scans only provide morphologic information, differentiation between residual tumor and RT-induced fibrosis is not always easy. Fusion of pre- and post-RT CT scans was performed to assist and improve consistency in delineation. The relative tumor reduction was expressed as the difference of the pre- and post-RT tumor volume divided by the pre-RT tumor volume. Complete disappearance of all radiographic abnormalities is rare after RT for lung cancer. Tumor regression was also scored 100% (complete remission) in case of near complete disappearance (scar-like residue) of radiographic abnormalities that remained unchanged for at least 12 months according to Green *et al.* (29). Tumor volume regression of at least 65% was scored as partial response according to the Response Evaluation Criteria in Solid Tumors (RECIST) (30). Tumors with less than 65% regression and no progression were scored as stable disease.

Quantification of perfusion changes

SPECT lung perfusion scans were obtained before RT and at 3–4 months post-RT after injection of 4 mCi of 99m-technetium-labeled macroaggregated albumin. All SPECT scans were performed within 1 week of the companion CT and PFT exams.

The reevaluation time point was set at 3–4 months post-RT, as this time point is consistent with our previous research on radiation-induced lung injury and is based on observations by Prato *et al.* who reported a maximal perfusion decrease at approximately 150 days after radiation treatment for breast cancer (31, 32).

SPECT image acquisition and reconstruction were performed as reported previously (20). Normalization of these SPECT scans (see Appendix) allows quantification of perfusion changes. SPECT and CT scans were matched to correlate these perfusion changes with the locally delivered dose within the CT-defined lung contours. In an earlier paper by our group, the obtained dose–effect data for perfusion changes in individual patients were averaged over the patient population and fitted with a sigmoid-shaped function according to a logistic model with a D_{50} of 63 Gy and k of 1.7 (20). The logistic model can be written as:

$$E(D) = \frac{1}{1 + \left(\frac{D_{50}}{D}\right)^{k}}$$

with E(D) = the dose–effect relation for perfusion changes (Fig. 1), D = the total dose, D_{50} = the dose at which the

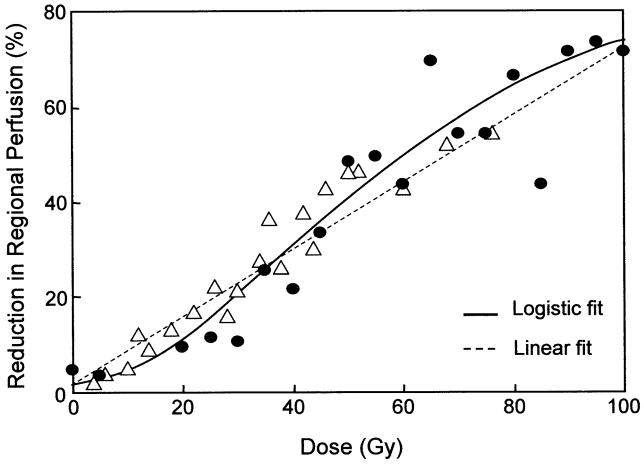

Fig. 1. Dose–effect data for perfusion changes in patients with breast cancer, lymphoma, and NSCLC treated at the Netherlands Cancer Institute (20) (triangles) and at Duke University (39) (circles). Logistic and linear fits were used for the analysis.

effect is 50%, and k = the steepness parameter. The data were also fitted with a linear relation with a slope S of 0.67% per gray (Fig. 1).

The following parameters were defined to quantify lung perfusion changes:

The *measured perfusion reduction (MPR)* was defined as the difference between the average lung perfusion measured from the pre-RT SPECT and the average lung perfusion measured from the post-RT SPECT, relative to pre-RT value.

For each individual patient, a post-RT perfusion scan can be predicted by combining the dose–effect relation for perfusion changes (Fig. 1) with the patient's pre-RT SPECT and individual 3D-dose distribution. In analogy to the MPR, the *predicted perfusion reduction (PPR)* was defined as the difference between the average lung perfusion measured from the pre-RT SPECT and the average lung perfusion measured from the predicted post-RT SPECT, relative to pre-RT value.

Reperfusion was defined as the difference between the average lung perfusion measured from the actual post-RT SPECT and the average lung perfusion measured from the predicted post-RT SPECT, relative to the pre-RT value. By definition, the reperfusion is equal to the difference between the measured (actual) perfusion reduction and the PPR.

Statistical analysis

For the univariate analyses, linear regression was used. Multiple factors were explored in a multivariate analysis to investigate their association with the reduction of PFTs using logistic regression with a stepwise backward elimination approach. At each step, the least significant variable was left out when the significance level was above 0.05. Values of *p* were not corrected for multiple comparisons. Analysis was carried out using SPSS 9 (Superior Performing Software Systems). Given the very low number of patients that received chemotherapy before high-dose radiotherapy, chemotherapy was not entered as an independent variable in the model.

Table 2. Pulmonary function tests

Lung function parameter	Baseline	Reduction at 3–4 months
FEV_1		
mean (%)	60	6
1 SD (%)	20	16
range (%)	28 to 121	−34 to +41
n	82	82
$T_{L,COc}$		
mean (%)	69	14
1 SD (%)	23	19
range (%)	20 to 128	−33 to +44
n	74	63

Average baseline (pretreatment) pulmonary function parameters (% of predicted value) and their (relative) reductions at 3–4 months after radiotherapy. The range and SD are also tabulated. Negative values indicate an improvement of pulmonary function. *n* represents the number of patients in whom PFTs were performed.

RESULTS

Pulmonary function tests

The average baseline values for FEV_1 and $T_{L,COc}$ were 60% and 69%, respectively (Table 2). It should be noted that before radiotherapy $T_{L,COc}$ values were missing in 8 of 82 patients. In these patients breath-holding during 10 s could not reliably be performed.

At 3–4 months post-RT FEV_1 decreased on average by 6%, whereas reductions of $T_{L,COc}$ were larger and on average 14%. In addition to reductions, improvements of PFTs were also observed (negative values in Table 2). Thirty-eight percent of the patients experienced an improvement of FEV_1. $T_{L,COc}$ improved in 21% of the patients. Sixty-two percent of patients with an improvement of $T_{L,COc}$ experienced an improvement of their FEV_1, whereas only 32% of improvements of FEV_1 were associated with a simultaneous improvement of $T_{L,COc}$.

Lung dose and perfusion-weighted lung dose

The MLD was on average 14.9 Gy (1 SD 4.8 Gy) and was larger in the subset of central tumors as compared with peripheral tumors (17.3 Gy vs. 11.4 Gy, respectively) (right shift of datapoints, Fig. 2). The average perfusion-weighted mean lung dose (MpLD) was overall 13.9 Gy (1 SD 4.7 Gy). For peripheral tumors, the average MpLD was 11.6 Gy and similar to the average MLD. In the subgroup of central tumors, the average MpLD was 15.7 Gy and lower than the average MLD of 17.3 Gy (Fig. 2). For most individual patients, the MpLD differed from the MLD, due to the inhomogeneous perfusion pattern in these patients (Fig. 2).

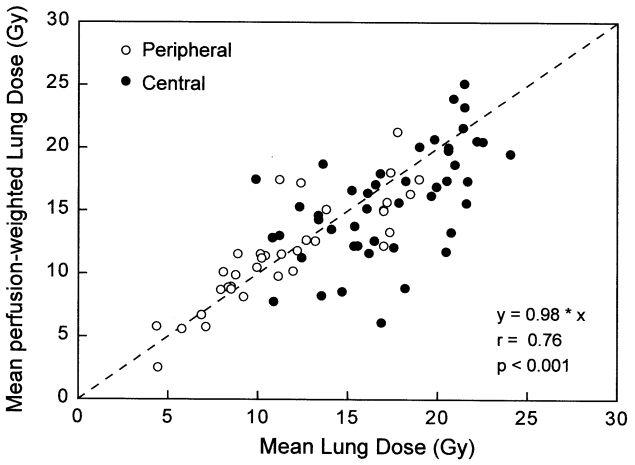

Fig. 2. Correlation between the MpLD and the MLD for central and peripheral lung tumors. The dotted line is the line of identity.

Quantification of tumor regression

Tumor volume was reduced by on average 74.6% (range 16–100%) at 3–4 months post-RT. A complete remission was scored in 12 of 82 included patients. Forty-five patients (55%) experienced a partial response. Twenty-five patients (30%) had less than 65% tumor volume regression and were scored as stable disease.

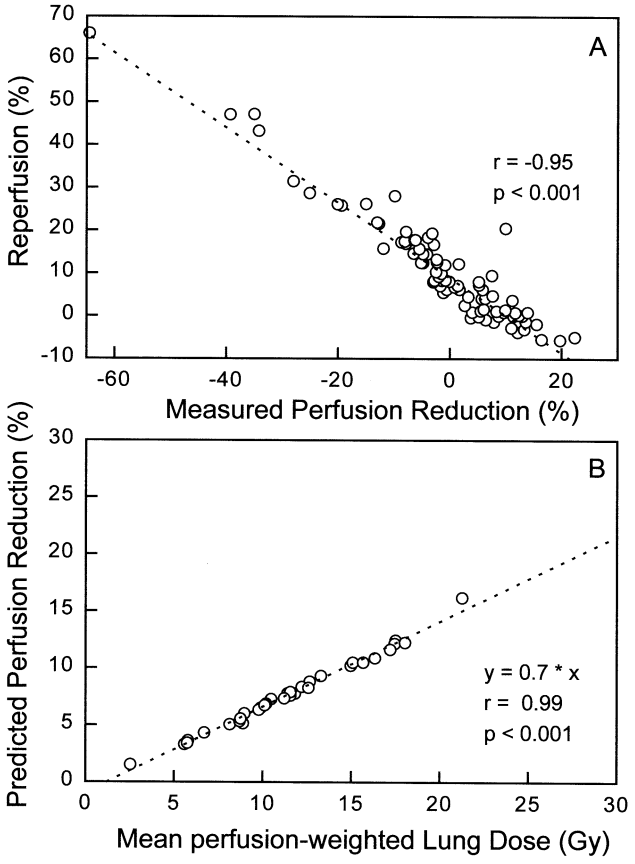

Fig. 3. (A) Correlation between the reperfusion and the MPR. The solid line represents the regression line. (B) Correlation between the PPR and the MpLD. The dotted line represents the regression line.

Table 3A. Variables assessed for an association with changes in pulmonary function tests in the univariate analysis*

	Reduction of FEV_1	Reduction of $T_{L,COc}$
Total tumor dose	0.56	0.07
Mean lung dose (MLD)	0.24	0.05†
Mean perfusion-weighted lung dose (MpLD)	0.03†	0.01†
Predicted perfusion reduction (PPR)	0.02†	0.02†
Tumor reduction	0.07	0.02†
Measured perfusion reduction (MPR)	0.22	0.92
Reperfusion	0.53	0.70

*Correlation of different variables with the (relative) reductions of FEV_1 and $T_{L,COc}$. The *p* values are tabulated.
†Statistically significant *p* values.

Quantification of perfusion changes

The MPR was on average −1.2% (1 SD 13.8%), indicating a small overall increase of perfusion, possibly due to reperfusion.

The PPR was on average 9.5% (1 SD 3.5%) and thus larger than the actually MPR. This is because the MPR also takes into account the occurrence of reperfusion. The strong ($p < 0.001$) inverse correlation ($r = -0.9$) between reperfusion and MPR is illustrated in Fig. 3A.

The PPR was strongly correlated with the MpLD (Fig. 3B). It can be shown (see Appendix) that the PPR is identical to S times the MpLD if the PPR is calculated using a linear dose–effect relation with slope S (Fig. 1). Because we used a sigmoid-shaped dose–effect relation that is nearly linear for the calculation of the PPR (Fig. 1), the coefficient of correlation between the PPR and the MpLD differs slightly from 1 (Fig. 3B).

Reperfusion was on average 10.9% (1 SD 13%, range −6 to 66%). Sixty-seven of 82 patients showed regions of reperfusion. The impact of tumor regression on reperfusion was studied. Only in univariate analysis and in a subgroup of centrally located lung tumors a trend for a correlation ($r = 0.3$, $p = 0.08$) between reperfusion and tumor regression was observed.

Estimation of changes in PFTs

Different variables (Table 3A) were first tested in a univariate analysis for their association with the reduction of the PFTs. The reductions of both PFTs were significantly albeit weakly associated with the PPR and MpLD. This is not surprising because the PPR and MpLD parameters are strongly correlated (Fig. 3B).

The tumor dose, MLD, MPR, and reperfusion were not associated with functional outcome as measured by the PFTs (Table 3), although for $T_{L,COc}$ a significant but less strong association with MLD was observed.

Figure 4 summarizes in different panels the correlations

Table 3B. Variables significantly associated with changes in pulmonary function tests in the multivariate analysis; the *p* values are tabulated

	Reduction of FEV_1	Reduction of $T_{L,COc}$
Mean perfusion-weighted lung dose (MpLD)	0.01	0.04
Predicted perfusion reduction (PPR)	0.01	0.04
Tumor reduction	0.02	0.05

between the reductions of both PFTs and the MLD (Panels B) and the MpLD (Panels C). For comparison, the correlations ($r = 0.58$ to 0.69) between the reductions of $T_{L,COc}$ and FEV_1 and the MLD are also displayed for a group of reference patients (breast cancer and lymphoma) who received incidental partial irradiation of their (healthy and homogeneously perfused) lungs [Panels A, adapted from Theuws *et al.*(18)]. As these patients have a homogeneous lung perfusion, the MLD is nearly identical to the MpLD for these patients. The slopes of the regression lines indicate a 1% reduction of $T_{L,COc}$ and FEV_1 per gray MLD (or MpLD) (Panels A). In NSCLC, the reduction of PFTs is best correlated with the MpLD. The regression line shows a smaller reduction (approximately 0.5% per gray MpLD) for FEV_1, compared with the regression line for $T_{L,COc}$.

In a subgroup analysis according to tumor location (central vs. peripheral), the association between tumor regression and reduction of $T_{L,COc}$ was significant in peripheral tumors only ($p = 0.01$, $r = 0.51$). Overall, a trend for an improvement of FEV_1 with tumor regression was found (Table 3B, Fig. 5). In a subgroup analysis, this trend was observed in centrally located tumors only ($p = 0.06$, $r = -0.27$).

In a subsequent multivariate analysis, the reductions of both PFTs remained significantly associated with the MpLD

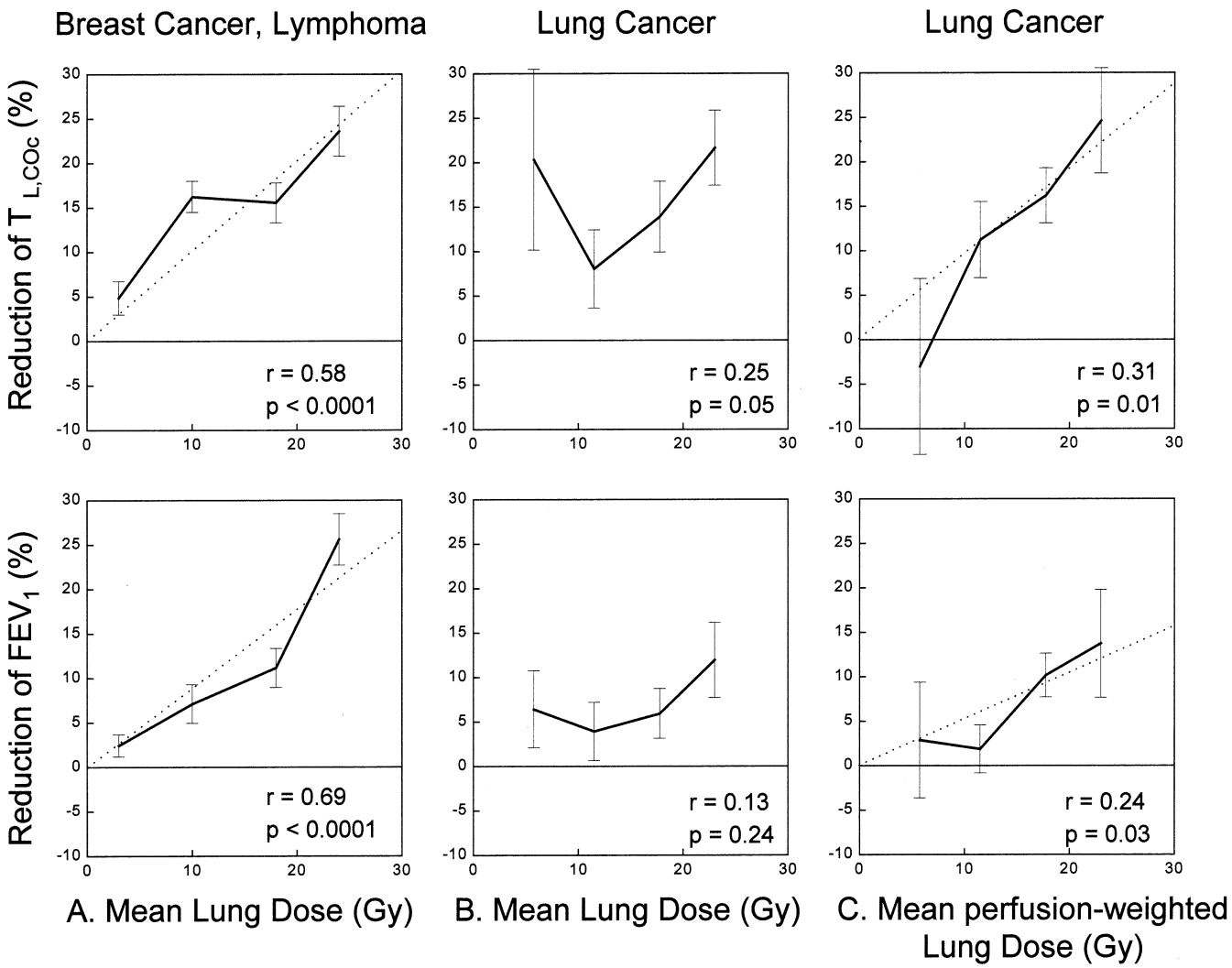

Fig. 4. The relative reductions of $T_{L,COc}$ and FEV_1 as a function of the MLD for reference patients with breast cancer and lymphoma [Panels A, adapted from Theuws *et al.*(3)] and studied NSCLC patients (Panels B). For the NSCLC patients, the reductions are also displayed as a function of the MpLD (Panels C). Data are binned for the display. The error bars represent ±1 standard error of the mean. The regression lines are dotted.

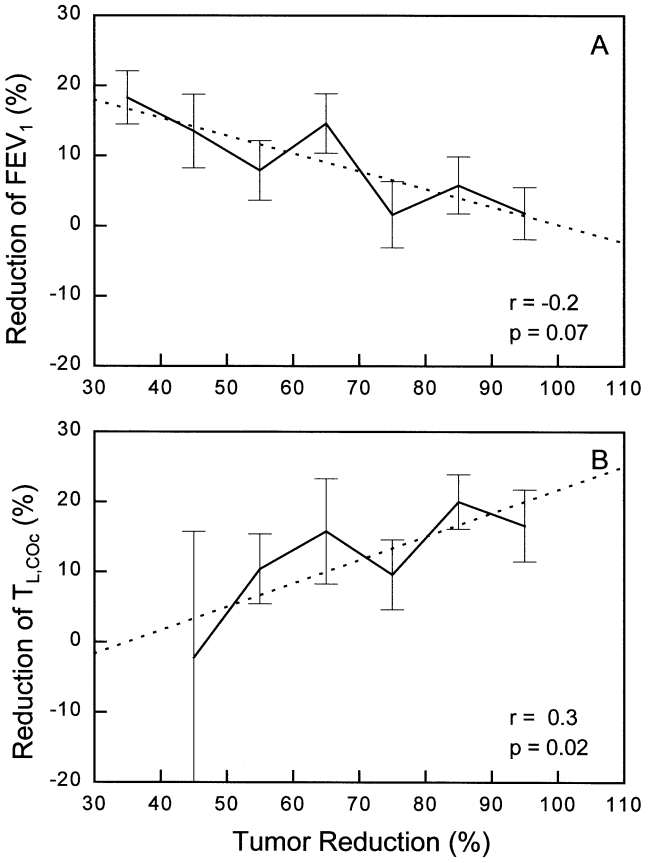

Fig. 5. Reductions of FEV_1 (A) and $T_{L,COc}$ (B) and as a function of tumor reduction. Data are binned for the display. The error bars represent ± 1 standard error of the mean. The regression lines are dotted.

or PPR (Table 3B). Furthermore, the FEV_1 significantly improved with tumor reduction ($p = 0.02$), whereas the opposite effect was observed for the $T_{L,COc}$ which tended to decline ($p = 0.05$) after tumor reduction (Table 3B). Given the impact of the tumor location on the correlation between tumor regression and reductions of PFTs in the univariate analysis, the multivariate analysis was also performed incorporating tumor location as a dummy variable (0 = peripheral, 1 = central). In the multivariate analysis, the associations between tumor regression and the reductions of PFTs were independent of tumor location.

DISCUSSION

Pulmonary function tests

Many investigators have quantified PFTs after thoracic radiotherapy as their decline has been correlated with clinical symptoms (3–5, 13, 16, 18, 22). The low PFT values at baseline (Table 2) reflect the presence of a compromised pulmonary function in the studied group, in part related to the presence of tumor, in part related to preexistent pulmonary disease. Fifty percent of the studied patients had a history of chronic obstructive pulmonary disease. The lung volume parameter FEV_1 declined on average by 6% after RT. We measured an average decrease of the diffusion capacity $T_{L,COc}$ of 14%. These figures compare favorably with the results of other studies reported in lung cancer (5, 16, 22, 33). The pattern of PFT changes is, however, different from that seen after surgery where a similar decrease in both PFTs is observed.

Lung dose and perfusion-weighted lung dose

So far, the ability to predict the magnitude and direction of changes in overall pulmonary function as measured by PFTs has yielded rather disappointing results in patients with NSCLC (22, 23). This is in contrast with the prediction of PFTs in patients with healthy lungs undergoing incidental partial lung irradiation. In a group of 81 breast cancer and lymphoma patients, Theuws *et al.*(18) showed that the MLD (a combination of radiation dose and irradiated volume) is the strongest predictor for changes in PFTs. They found a relative decrease in PFTs of approximately 1% per gray. In NSCLC patients, a dose–volume parameter like the MLD does not correlate with the reduction of FEV_1. The MLD was significantly correlated with the reduction of $T_{L,COc}$, but only in the univariate analysis (Fig. 4, Panels B and Table 3A). In fact, this is not surprising as the MLD implicitly assumes that each part of the lung contributes equally to the overall lung function (3). For patients with NSCLC, this assumption does not hold due to the presence of cancer but also due to preexisting lung diseases associated with unequal perfusion throughout the lungs. The MpLD takes into account this unequal perfusion by weighing the local dose with the local perfusion. The consistent and statistically significant (albeit weak) association of the reduction of PFTs with the MpLD supports the hypothesis that for patients with unequal perfusion the radiation dose delivered to nonperfused lung regions contributes less to functional lung damage. By directing radiation beams preferentially through hypoperfused lung regions, the MpLD can be minimized resulting in less functional lung damage (34). We have recently shown that the incorporation of perfusion information in the optimization of RT plans is feasible (35).

Tumor regression

The observed tumor response rates at 3–4 months follow-up were 15%, 55%, and 30% for complete response, partial response, and stable disease, respectively. The percentages reported by Werner-Wasik *et al.*(36) for partial response are higher (73%), but this study defined tumor response at maximal tumor shrinkage, which was observed at a median of 11 months from RT completion. It is hoped that the advent of functional imaging modalities like FDG-PET will improve the accuracy of response scoring by facilitating differentiation between RT-related changes and tumor.

The impact of tumor regression on changes in PFTs was studied. The multivariate analysis showed that tumor regression results in an improvement of FEV_1. This is not surprising as the reduction of a lung tumor can relieve airway obstruction and thus improve airflow. An increase of

ventilation is, however, not necessarily associated with an increase of gas exchange, because this requires also an adequate perfusion and intact alveolar/capillary membrane. This may explain the paradoxical effect observed for $T_{L,COc}$, namely a decrease with increasing tumor regression (Fig. 5B).

Only in central tumors and in the univariate analysis a trend for an association was observed between tumor regression and reperfusion. This is in agreement with the hypothesis that perfusion recovery is more likely to occur in patients with central tumors. These tumors often cause obstruction and encasement of pulmonary vessels, thereby reducing the regional perfusion (19).

Perfusion changes

Based on the experience in thoracic surgery where the percentage of perfusion of resected lung correlated with the percentage reduction of PFTs (37, 38), it can be postulated that the sum of regional perfusion changes post-RT might correlate with the change in overall pulmonary function as measured by PFTs (22, 23). Following this assumption, we have defined parameters to quantify perfusion changes and evaluated their association with changes of PFTs.

The PPR showed a significant correlation with the reduction of PFTs. This correlation is similar to the correlation found for the MpLD. This is not surprising as these parameters are strongly correlated (Fig. 3B). The MPR was not correlated with the reductions of PFTs. As the MPR differs from the PPR by the reperfusion, this suggests that reperfusion does not contribute to an improvement of pulmonary function. This is confirmed by the absence of association between reperfusion and an improvement of PFTs (Table 3A). In particular, no correlation was observed between reperfusion and an improvement of $T_{L,COc}$. It should be realized that our definition of reperfusion (i.e., the difference between the MPR and the PPR) probably also includes uncertainties in measurements related to setup errors, breathing artifacts, image-fusion mismatches, SPECT artifacts (scatter and blurring), and uncertainties in the dose calculation (20). Nevertheless, the fact that the calculated reperfusion was on average 10.9% makes it rather unlikely that random or interpatient variation has a large impact on this calculated reperfusion parameter.

We hypothesize that radiation induces damage to the alveolar/capillary membrane so that a (potential) perfusion recovery does not necessarily translate into an improvement of overall pulmonary function. It might also be hypothesized that the duration of a perfusion deficit might be critical for the probability of recovery. To our knowledge, no data are available on this issue.

Estimation of changes in PFTs

Although the perfusion-weighted lung parameters MpLD or PPR provide a better estimate of functional outcome (Table 3B, Fig. 4 Panels C) after high-dose radiotherapy of NSCLC than pure dose parameters, the correlations are weak and it remains difficult to accurately predict the global pulmonary function for an individual patient. The group of Duke University observed similar weak correlations between radiation-induced changes in perfusion and changes of PFTs but included patients with diverse diseases. Also, perfusion changes were correlated with averaged (23) or maximal (22) PFT declines. This may explain why these studies did not show that MpLD-based predictions of PFTs are better than MLD-based predictions (22).

PFTs are the only available tests for routine assessment of global pulmonary function. These tests are subject to intrapatient measurement variations that increase in the presence of underlying pulmonary disease (25). Furthermore, the interpatient variation might be increased by heterogeneity in patient-specific factors (age, gender, smoking habits) in addition to individual differences in biologic factors such as TGF-β. Incorporation of these factors in a multiparameter model may improve our ability to predict PFTs.

Our findings suggest a direct impact of tumor regression on PFTs, rather than an indirect impact through reperfusion. The percentage tumor regression, however, cannot be estimated before the start of a radiotherapy course.

CONCLUSIONS

Changes in PFTs post-RT can be best estimated by perfusion-weighted dose parameters. Tumor regression after high-dose radiotherapy of NSCLC can lead to an increase of FEV_1 but reduces $T_{L,COc}$. Reperfusion is not associated with an improvement of global pulmonary function.

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APPENDIX

Normalization of SPECT scans

The interpretation of the SPECT scans is based on the concept of parallel-organized perfused subunits in the lung. The distribution of perfused subunits can be measured by the perfusion scans, in which the number of SPECT counts in a voxel is proportional to the number of perfused subunits

in that voxel. To compare quantitatively the pre- and post-RT scans, the SPECT counts were normalized to the well-perfused low-dose (WPLD) regions. This approach is based on the assumption that the number of perfused subunits remains constant in the low-dose (no radiation effect) and well-perfused (no reperfusion effect) regions (10, 20). Low-dose regions were defined as lung regions receiving a dose less than 8 Gy, well-perfused regions as regions that contain voxels with a perfusion of more than 60% of the maximum perfusion (before treatment) (20).

This normalization allows quantification of perfusion changes and definition of the parameters MPR, PPR, and reperfusion.

For the PPR, it can be shown that the SPECT counts are effectively normalized to the average counts in the whole lung:

$$\mathrm{PPR} = \frac{\frac{1}{N}\sum_{n=1}^{N} \mathrm{Cts}_n^{\mathrm{pre}}(E(D_n))}{\frac{1}{N}\sum_{n=1}^{N} \mathrm{Cts}_n^{\mathrm{pre}}}$$

with N = the total number of voxels in the lungs, Cts_n = the number of SPECT counts in voxel n, $E(D_n)$ = the dose–effect relation for perfusion changes (Fig. 1), and D_n = the radiation dose in voxel n. If we approximate the local dose-effect relation with a linear fit with slope $S = 0.67\%$ per gray (Fig. 1), the PPR equals S times the MpLD, which was defined as the average perfusion-weighted dose to the lungs. For homogeneous lung perfusion, the MpLD is (per definition) equal to the MLD.