Radiotherapy for lung cancer
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Pulmonary function changes after radiotherapy in non-small cell lung cancer patients with a long-term disease free survival

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Abstract

Purpose: To evaluate the changes in pulmonary function after high-dose radiotherapy (RT) for non–small-cell lung cancer in patients with a long-term disease-free survival.

Methods and Materials: Pulmonary function was measured in 34 patients with inoperable non–small-cell lung cancer before RT and at 3 and 18 months of follow-up. Thirteen of these patients had a pulmonary function test (PFT) 36 months after RT. The pulmonary function parameters (forced expiratory volume in 1 s [FEV1], diffusion capacity [Tlcc], forced vital capacity, and alveolar volume) were expressed as a percentage of normal values. Changes were expressed as relative to the pre-RT value. We evaluated the impact of chronic obstructive pulmonary disease, radiation pneumonitis, mean lung dose, and PFT results before RT on the changes in pulmonary function.

Results: At 3, 18, and 36 months, a significant decrease was observed for the Tlcc (9.5%, 14.6%, and 22.0%, respectively) and the alveolar volume (5.8%, 6.6%, and 15.8%, respectively). The decrease in FEV1 was significant at 18 and 36 months (8.8% and 13.4%, respectively). No recovery of any of the parameters was observed. Chronic obstructive pulmonary disease was an important risk factor for larger PFT decreases. FEV1 and Tlcc decreases were dependent on the mean lung dose.

Conclusion: A significant decrease in pulmonary function was observed 3 months after RT. No recovery in pulmonary function was seen at 18 and 36 months after RT. The decrease in pulmonary function was dependent on the mean lung dose, and patients with chronic obstructive pulmonary disease had larger reductions in the PFTs.
Introduction
Lung cancer is still one of the leading causes of cancer mortality [1]. About 80% of these tumors are histologically non-small cell lung cancers (NSCLC). Eighty percent of these NSCLC patients receive radiotherapy because many patients are inoperable due to metastases, loco regional spread (technically inoperable) or because of a poor pulmonary function (medically inoperable) [2].

Radiotherapy to the thoracic region is associated with important side effects. Several investigators found various parameters such as the Mean Lung Dose (MLD), or the percentages of lung volume receiving more than a threshold dose of 13 Gy, 20 Gy or 30 Gy to be predictive for radiation pneumonitis [3-7]. These parameters can currently be taken into account to estimate the risk of this type of complication.

It is more complicated to estimate graded responses in the lung such as changes in pulmonary function. For patients with healthy lungs (breast cancer and lymphoma patients) Theuws et al. [8] was able to show a significant recovery in pulmonary function tests (PFTs) at 18 months after an initial reduction at 3 months following irradiation. For lung cancer patients it is more difficult to estimate PFT changes. First, lung cancer patients are often suffering from pulmonary comorbidities such as chronic obstructive pulmonary disease (COPD) and emphysema, mainly due to the high incidence of smokers. These underlying lung diseases increase the variability of PFTs [9], and therefore makes it more difficult to objectify the pulmonary toxicity of irradiation. Secondly, the estimation of pulmonary function changes on the long term is hampered by the poor prognosis of NSCLC patients.

Radiotherapy modalities, such as dose escalation [10-13] and combined chemo-radiation [14-18] may improve local control and even the prognosis of NSCLC patients. Long-term toxicity following irradiation in medically inoperable NSCLC patients is of great interest, especially if tumor control improves in these patients. Long-term follow-up data are however scarce for this group of patients. Seven patients experienced a progressive decrease of PFTs 3 years after radiotherapy in a study by Miller et al. [7]. But clearly, data of more patients is needed to clarify the respiratory condition following irradiation of inoperable NSCLC patients with a long-term disease free survival.

To investigate the development of pulmonary function in the long term, we evaluated the PFT changes of inoperable NSCLC patients with locally controlled disease with at least a follow up of 18 months. We investigated the impact of patient- and treatment- related factors on the PFTs.

Material and Methods

Patients with baseline pulmonary function tests (PFTs) 2 weeks before the start of
radiotherapy, and at 3 and 18 months follow up were included. Patients with tumor recurrence, progression and/or metastases were excluded. One hundred and sixty-nine patients with medically or technically inoperable non-small cell lung cancer (NSCLC) were referred to the department for radical or curative RT between 1996 and 2002. According to these inclusion criteria, 34 patients were eligible. In 13 of these 34 patients PFTs were evaluated at 36 months, as well.

Patient and tumor characteristics are shown in Table 1. The majority of patients were former (47 %) or current (41 %) smokers. Half of the patients suffered from chronic obstructive pulmonary disease (COPD). COPD was diagnosed according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria [19]. COPD was defined in patients having symptoms of cough, sputum production, or dyspnea, and/or a history of exposure to risk factors (smoking) for the disease. A postbronchodilator forced expiratory volume (FEV1) of less than 80 % and a ratio of FEV1 / forced vital capacity (FVC) of less than 70 % can confirm the diagnosis.

Thirteen patients received a standard radiotherapy regimen of 70 Gy delivered in 35 fractions in 7 weeks. The remaining 21 patients were included in a Phase I/II dose escalation study (10) and were treated with doses between 60.8 and 94.5 Gy (2.25 Gy per fraction, fixed overall treatment time of 6 weeks).

Three radiotherapy patients received chemotherapy, which was administered at least 6 weeks before the start of the irradiation. Radiation pneumonitis (RP) was scored according to the Southwest Oncology Group (SWOG) toxicity criteria. Five patients developed RP grade 2 and one patient developed grade 3 RP (grade 2 is scored when steroids are required for treatment, grade 3 is scored when oxygen is needed).

**Pulmonary function tests**

Pulmonary function tests (PFTs) were performed using the Jaeger Masterlab equipment (Würzburg, Germany). In this study, we evaluated the FEV1, forced vital capacity (FVC), transfer factor for carbon monoxide corrected for the actual hemoglobin (Hb) level in the peripheral blood (Tlccoa) and the alveolar volume (VA). The transfer factor for carbon monoxide (Tlcco) was corrected for the actual hemoglobin (Hb) level according to the formula Tlccoc=Tlco*(6.12+Hb)/(1.7*Hb) [mmol / min/ kPa]. PFTs were expressed as a percentage of the normal value (based on weight, height and gender) [20]. Changes of the PFTs 3, 18 and 36 months post-RT were expressed as the difference between the pre-RT and post-RT PFT relative to the pre-RT value: (PFTpre – PFTpost) / PFTpre (%).

**Lung dose**

CT based dose calculations were performed as previously described [21] using a 3-D treatment planning system [U-Mplan, University of Michigan]. Corrections for tissue inhomogeneities were based on an equivalent path length algorithm.
All doses reported in this paper were corrected for fractionation. The local dose was converted to the normalized total dose (NTD) [22], defined as the biologically equivalent dose delivered in 2 Gy per fraction. The linear quadratic model with an $\alpha/\beta$ ratio of 3 Gy was used [23]. For calculating the mean lung dose (MLD), the gross target volume (GTV) was excluded from total volume of both lungs. The lung was defined on the CT scan by a binary threshold. The mean perfusion weighted lung dose (MpLD), a parameter correlating better with PFT changes at 3 months compared to the MLD [24], was not evaluated because perfusion data were not available for a significant number of patients.

**Statistical analysis**

To evaluate changes in the PFT parameters following irradiation, we compared the pre-RT values with the 3, 18 and 36 months follow-up values using the paired t-test. To study whether a parameter remained constant or changed after 3 months, we compared the values at 18 months with both pre-RT and 3-month values. Similarly, the values at 36 months were compared with the measurements at earlier points (i.e. pre-RT, 3 months and 18 months). To investigate whether PFT values and the PFT changes were different between specific subgroups, the unpaired t-test was used.

To assess the impact of various parameters on the change of the PFTs, an univariate linear regression analysis was performed. Significant (and borderline significant) factors in the univariate analysis were explored in the multivariate linear regression analyses to evaluate their association with PFT changes. A stepwise backward approach was used. Differences were considered significant when the p-value was < 0.05. Analyses were carried out using SPSS version 10.0.0 (statistical package for the social sciences).
Chapter 5

Results

Pulmonary function before radiotherapy
Values for the FEV1, FVC, Tlcoc and VA were available for all patients. The Tlcoc and VA values were available in 25 of the 34 patients. The absolute FEV1 values ranged between 0.7 to 3.7 L/s. The mean values for FEV1, FVC, Tlcoc and VA were 60 %, 84 %, 69 % and 85 %, respectively.

Pulmonary function after radiotherapy
The mean values for FEV1, FVC, Tlcoc and VA, 3 months following irradiation, were 56 %, 80 %, 62 % and 80 %, respectively. Eighteen months after radiotherapy the mean values for FEV1, FVC, Tlcoc and VA were 54 %, 80 %, 59 % and 80 %, respectively. For the PFT at 36 months the mean values for FEV1, FVC, Tlcoc and VA were 56 %, 76 %, 58 % and 75 %, respectively. The time trend of the mean relative change of all the different PFT parameters is illustrated in Figure 1. Tlcoc and VA showed a statistically significant decrease at all points compared to the pre-RT values. The FEV1 decreased significant at 18 and 36 months. The FVC did not decrease significant.

In addition, the PFT values at 18 and 36 months were compared with the PFT values of previous PFTs (i.e. 3 and 18 months, respectively), using the paired t-test. Decreases were observed for all parameters although these decreases were not significant with respect to each other in the period from 3 to 36 months.

Patients with an improvement or deterioration of more than 10 % of the PFT parameters after 18 and 36 months are indicated in Figure 2.

Figure 1. Mean relative change of the FEV1, Tlcoc, FVC and VA values at 3, 18 and 36 months following irradiation. The error bars indicate the standard error of the mean. n = number of patients, p = significance of the paired t-test.
Long-term pulmonary function changes after RT in NSCLC patients

A change of 10% was regarded as no change, since the reproducibility of PFT measurements is approximately 10% (20,25). For Tlcc and FEV₁, the majority of the patients showed a decrease of more than 10%. After 36 months none of the patients showed an improvement in Tlcc, FEV₁ and VA of 10% or more, but the number of patient was smaller.

Changes of PFT parameters and patient related factors

The pulmonary function of COPD patients was worse than that of non-COPD patients. The mean pre-RT FEV₁, was as expected, statistically significantly different in COPD vs. non-COPD patients (50% and 67%, respectively, p = 0.006). The FEV₁ also remained significantly different between the non-COPD and COPD patients at 3 (43% vs. 67%, p < 0.001), 18 (42% vs. 64%, p < 0.001) and 36 months (45% vs. 66%, p = 0.03). For the FVC and Tlcc, at all time periods, the mean values were lower for COPD patients compared to non-COPD patients. The difference was significant for FVC at 18 months (72% vs. 87%, p = 0.02) and for the Tlcc at 36 months (44% vs. 72% p = 0.03). For the VA a significantly lower mean value was observed for COPD compared to non-COPD patients at 36 months (62% vs. 87%, p = 0.03).

In Figure 3, the mean of the relative changes for COPD and non-COPD patients is given. For the FEV₁, a (borderline) significant larger decrease for COPD patients compared to non-COPD patients was observed at 3 months 13% vs. 0% (p = 0.02), at 18 months 14% vs. 4% (p = 0.09) and at 36 months 23% vs. 5% (p = 0.03). The difference between the relative Tlcc changes in COPD vs. non-COPD patients showed a trend at 3 months (18% vs. 5%, p = 0.09), 18 months (19% vs. 12%, p = 0.3) and at 36 months (33% vs. 11%, p = 0.01). The difference between the relative FVC changes in COPD versus non-COPD patients was significant at 3 months (p = 0.04) and at 18 months (p = 0.008) and for the VA at 36 months (p = 0.03).
We compared patients with pre-RT FEV\textsubscript{1} values above the median to patients with pre-RT FEV\textsubscript{1} values below the median value. The median FEV\textsubscript{1} before treatment was 57%. The higher FEV\textsubscript{1} pre-RT group experienced a (borderline) significant decrease for 18 and 36 months for all parameters ($p = 0.01 - 0.08$) except for the FVC. However, these decreases were not significantly larger than the decreases of the lower FEV\textsubscript{1} pre-RT group. The decreases for the lower pre-RT FEV\textsubscript{1} were significant for the FEV\textsubscript{1} and FVC at 36 months ($p = 0.05$ and $p = 0.02$, respectively) and for the Tlcoc at 18 months ($p = 0.003$).

Patients who developed radiation pneumonitis did not experience a larger decrease of the pulmonary function at any of the follow-up PFTs. No conclusion can be made because of the small number of radiation pneumonitis events. No analyses could be performed to evaluate the influence of smoking on PFT changes because only 4 patients were non-smokers.

**Changes of PFT parameters and treatment related factors.**

The average of the mean lung dose (MLD) was 13.9 Gy (range 2.9 - 21.9 Gy). A statistically significant correlation was found between the MLD and the decrease in FEV\textsubscript{1} at 3 ($p = 0.03$) and 18 months ($p = 0.01$). The same correlation, but not significant, was found at 36 months (Figure 4). The correlation between the MLD and decrease in Tlcoc was (borderline) significant at 3 ($p = 0.03$) and 36 ($p = 0.06$) months, but not significant at 18 months (Figure 4). For the FVC and VA no significant correlations were observed. No analyses could be performed to evaluate
Long-term pulmonary function changes after RT in NSCLC patients

the influence of chemotherapy because only 3 patients received chemotherapy.

Estimation of PFT changes

For the time periods where a trend was observed between the PFT changes and the variables MLD and COPD a multivariate analysis was performed to test their joint effect on the reduction of the PFTs (Table 2). The decrease of FEV$_1$ remained dependent of the MLD and COPD at 3 and 18 months following irradiation. Regarding the Tlcc changes, a trend was observed for the MLD and COPD at 3 months ($p = 0.08$) and at 36 months ($p = 0.07$), respectively. Because the reductions of FVC and VA were only correlated with COPD, no multivariate analyses were performed for these parameters.

Discussion

Non-small cell lung cancer (NSCLC) patients referred for curative radiotherapy experienced a statistically significant decrease of their pulmonary function following irradiation. The decrease observed 3 months following irradiation was additional to a relative poor pulmonary function. Our data showed that the pulmonary function did not recover in patients with a long-term disease free survival. This long-term information is extremely important for inoperable NSCLC patients, especially for

Figure 4. Correlation of the relative reduction ($r$) of FEV1 and Tlcc and the mean lung dose (MLD) at 3, 18 and 36 months following irradiation. Positive values indicate an impairment of pulmonary function. The correlation coefficient ($r$), and p-value are shown. The number of patients in each dose bin is indicated on the right vertical axis.
patients with a poor pulmonary function. In the long-term study of Miller et al. [7], a significant progressive decrease was reported for 7 patients with a follow-up of 3 to 8 years. This decrease was observed after a partial recovery, or plateau, by 12 months. We did not observe this phenomenon in our larger patient group.

We observed a significant decrease of the FEV₁ and Tlcoc at 18 and 36 months in patients with higher pre-RT FEV₁, which was also observed by Choi et al. [26]. They observed a significant decrease at 12 months following irradiation in patients with a pre-RT FEV₁ value > 50 %. We did not observe a significant difference between the decreases of the FEV₁ for the two pre-RT FEV₁ subgroups as was observed by Gopal et al.[27]. They observed a significant difference between the FEV₁ decrease of 9.9 % for patients with a pre-RT FEV₁ ≥ 50 % and the increase of 8.4 % for patients with a pre-RT FEV₁ ≤ 50 %. Both the studies of Choi et al. and Gopal et al. used a pre-RT FEV₁ of 50 % as cut off value which was not feasible in our study because the low number of patients with a FEV₁ < 50 %. In our study, 10 of the 15 COPD patients were in the lower pre-RT FEV₁ group. These 10 patients might be responsible for observing no significant difference between the pre-RT FEV₁ groups.

COPD is a common co-morbidity in NSCLC patients. COPD is a progressive disease characterized by obstructive pulmonary function. Chronic inflammation, oxidative stress and an imbalance of proteinases and antiproteinases are present throughout the airway, parenchyma, and pulmonary vessels. The significant lower baseline FEV₁ in COPD patients is the consequence of the airflow limitation characteristic for COPD. The significant larger decrease of the FEV₁ at 36 months could be due to the progression of COPD. However, the larger decrease of FEV₁ and Tlcoc in COPD patients at 3 months may not (because of the small time interval) be due to COPD alone. Only a very few studies evaluated the influence of COPD on pulmonary function after treatment in lung cancer patients. Maas et al. [28] did not observe a different PFT outcome for COPD patients compared to non-COPD patients after three cycles of gemcitabine and cisplatin in NSCLC patients. This suggests that COPD did not have an influence on PFTs following this particular chemotherapy. The pathogenesis of COPD might reinforce the damage caused by irradiation. Radiation injury, responsible for an early inflammatory and a late fibrotic response in normal lung tissue might be more pronounced in patients suffering from COPD. It could explain both, the significant correlation between COPD and radiation pneumonitis in the study of Rancati et al. [29] and the initial large decrease in FEV₁ and Tlcoc already 3 months following irradiation, observed in our study.

We observed that patients receiving a high MLD, experienced a decrease of the FEV₁ and Tlcoc in the order of 1 % per Gy MLD at all follow-up periods. A similar relation was found for the Tlcoc by Theuws et al.[30] for 81 lymphoma and breast cancer patients. They observed a Tlcoc reduction at 3 months (1.1 % per Gy MLD) that remained unchanged at 18 months (0.9 % per Gy MLD). The decrease of the
volume parameters (FEV₁, VA and FVC) at 3 months (0.8 – 0.9 % per Gy MLD) improved significantly at 18 months (0.3 – 0.4 % per Gy MLD) for these lymphoma and breast cancer patients. We did not observe a recovery for any of the parameters for our lung cancer patients at 18 or 36 months.

The NSCLC patients experienced a significant decrease of the pulmonary function following irradiation. The decrease was observed in the acute phase following irradiation and did not recover after a longer follow-up. Dose-escalation and chemoradiation trials show promising results with better tumor control for inoperable NSCLC patients. For these patients, a sufficient respiratory outcome is important to ensure a satisfying quality of life. The respiratory condition of inoperable NSCLC patients should be optimized before and after radiotherapy and more consideration is required for patients with pulmonary comorbidities like COPD.

**Conclusion**

A significant decrease of the pulmonary function was observed 3 months following irradiation. There was no recovery at 18 and 36 months after radiotherapy. The decrease in pulmonary function was dependent on the mean lung dose and patients with pre-existing lung disease (COPD) had larger reductions in PFTs.
Chapter 5

Reference
16. Curran WJ, Scott CB, Langer CJ et al: Long-term benefit is observed in a phase III
Long-term pulmonary function changes after RT in NSCLC patients


