

## Article

# Impact of Low-Dose Irradiation of the Lung and Heart on Toxicity and Pulmonary Function Parameters after Thoracic Radiotherapy

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**Simple Summary:** To assess the impact of thoracic (low) dose irradiation on pulmonary function changes after thoracic radiotherapy (RT) data of 62 patients were analyzed. There were several significant correlations between pulmonary function and dose parameters of the lung and heart, most of which remained significant in the multivariate analysis.

**Abstract:** Objective: To assess the impact of (low) dose irradiation to the lungs and heart on the incidence of pneumonitis and pulmonary function changes after thoracic radiotherapy (RT). Methods/Material: Data of 62 patients treated with curative thoracic radiotherapy were analyzed. Toxicity data and pulmonary function tests (PFTs) were obtained before RT and at 6 weeks, at 12 weeks, and at 6 months after RT. PFTs included ventilation (e.g., vital capacity) and diffusion parameters (e.g., diffusion capacity for carbon monoxide (DL<sub>CO</sub>)). Dosimetric data of the lung and heart were extracted to assess the impact of dose on PFT changes and radiation pneumonitis (RP). Results: No statistically significant correlations between dose parameters and changes in ventilation parameters were found. There were statistically significant correlations between DL<sub>CO</sub> and low-dose parameters of the lungs (V<sub>5Gy</sub>–V<sub>30Gy</sub> (%)) and irradiation of the heart during the follow-up up to 6 months after RT, as well as a temporary correlation of the V<sub>60Gy</sub> (%) on the blood gas parameters at 12 weeks after RT. On multivariate analysis, both heart and lung parameters had a significant impact on DL<sub>CO</sub>. There was no statistically significant influence of any patient or treatment-related (including dose parameters) factors on the incidence of ≥G2 pneumonitis. Conclusion: There seems to be a lasting impact of low dose irradiation to the lung as well as irradiation to the heart on the DL<sub>CO</sub> after thoracic radiotherapy. No influence on RP was found in this analysis.

**Keywords:** respiratory function tests; lung neoplasms; radiation injuries; organs at risk



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## 1. Introduction

Pulmonary function test (PFTs) are commonly performed in patients that require thoracic radiotherapy (RT). Before treatment, they are a part of the medical workup to assess the suitability of the patient for radiation treatment, and after radiotherapy, they may help to evaluate radiation induced lung damage. PFT parameters are known to change after radiotherapy. Ventilation parameters such as vital capacity (VC) can both decrease or

improve after treatment, presumably due to the re-opening of obstructed airways [1–7]. The diffusion, commonly measured using the diffusion capacity for carbon monoxide ( $DL_{CO}$ ), however, has often been reported to decrease after RT [1,2,8–19] and to show little to no recovery [5,12,20].

In clinical practice, the PFT changes are usually not a factor to be considered in treatment planning. The dose constraints used for the organs at risk (OAR) derive from the risk for acute and late treatment-related toxicities [21,22]. For the lung, this usually refers to radiation pneumonitis, for which the percentage of the volume receiving 20 Gy ( $V_{20Gy}$  (%)) or 30 Gy ( $V_{30Gy}$  (%)) as well as the mean lung dose measured in Gy ( $D_{mean}$  (Gy)) have proven to be prognostic parameters [7,15,23–30].

However, many of the data on dose constraints come from the area of 3D conformal radiotherapy or even 2D planning. With the introduction of multiple fields intensity modulated radiotherapy (IMRT) or volumetric arc radiotherapy (VMAT), there is a tendency for increased low dose irradiation of the healthy lung tissue.

There are some data suggesting that low-dose irradiation, as assessed by the dose–volume parameters of the lung (e.g.,  $V_{5Gy}$  (%)), has an influence on outcome and toxicities [31–33]. However, data on this topic are scarce.

Therefore, in this analysis, we focused on the effect of dose–volume parameters, especially in terms of low-dose irradiation of the lungs and heart as the most critical OARs in thoracic radiation on radiation pneumonitis as well as PFT changes after RT.

## 2. Results

### 2.1. Correlation between Dose Parameters and the Difference in PFTs

In this cohort, the ventilation parameters (e.g., VC) showed variable changes after RT with up to half of the patients experiencing an improvement after RT. The  $DL_{CO}$ , however, largely declined, with 85% of patients showing a decrease in  $DL_{CO}$  at any time point after RT, half of whom showed a decrease of more than 20%. The median lung volume of patients was 3847 mL (range 2101–6777 mL) with a median volume of the gross tumor volume of 79.1 mL (range 12.4–406.8 mL) and 328.3 mL (102.7–1014.1 mL) for the planning tumor volume.

Regarding the correlations between pulmonary function changes and dose and dose–volume parameters, there were statistically significant correlations between the  $D_{mean}$  of the lung and the ventilation parameter forced expiratory volume within 1s ( $FEV_1$ ) 12 weeks after RT (correlation coefficient ( $R$ ) =  $-0.276$ ,  $p = 0.035$ ) and VC 6 months after RT ( $R = -0.397$ ,  $p = 0.006$ ).

Regarding diffusion parameters, there were several statistically significant correlations for the gross tumor volume (GTV) volume as well as  $D_{mean}$  and  $V_{5Gy}$ – $V_{30Gy}$  of the lung that are shown in Table 1. There was no significant correlation for  $>V_{30Gy}$  of the lung.

**Table 1.** Correlation of GTV volume and lung  $V_{5Gy}$ – $V_{30Gy}$  (%) with  $\Delta$  diffusion capacity for carbon monoxide ( $DL_{CO}$ ) after thoracic radiotherapy (RT) ( $R$  (sign.)).

GTV and Lung Parameters	$\Delta DL_{CO}$ at 6 Weeks	$\Delta DL_{CO}$ at 12 Weeks	$\Delta DL_{CO}$ at 6 Months
GTV Volume (mL)	n.s.	n.s.	−0.312 (0.047)
Lung $D_{mean}$ (Gy)	−0.471 (<0.001)	−0.338 (0.011)	−0.487 (0.018)
Lung $V_{5Gy}$ (%)	−0.323 (0.016)	−0.352 (0.008)	−0.465 (0.002)
Lung $V_{10Gy}$ (%)	−0.336 (0.012)	−0.324 (0.016)	−0.423 (0.006)
Lung $V_{15Gy}$ (%)	−0.381 (0.004)	n.s.	−0.417 (0.007)
Lung $V_{20Gy}$ (%)	−0.370 (0.005)	n.s.	−0.403 (0.009)
Lung $V_{25Gy}$ (%)	−0.309 (0.022)	n.s.	−0.333 (0.034)
Lung $V_{30Gy}$ (%)	−0.286 (0.034)	n.s.	−0.316 (0.044)

n.s.:  $p > 0.05$ .

For the blood gas analysis (partial pressure of carbon dioxide ( $p\text{CO}_2$ ) and partial pressure of oxygen ( $p\text{O}_2$ )), there were statistically significant correlations with  $V_{60\text{Gy}}$  (%) 12 weeks after treatment ( $p\text{CO}_2$ :  $R = 0.294$ ,  $p = 0.0031$ ;  $p\text{O}_2$ :  $R = 0.282$ ,  $p = 0.0039$ ), as well as the  $D_{\text{mean}}$  6 months after treatment ( $p\text{O}_2$ :  $R = -0.351$ ,  $p = 0.0018$ ).

Regarding the heart dose parameters, there were several statistically significant correlations with  $\Delta$  diffusion parameters but also with VC at 12 weeks after RT. The correlation coefficients are shown in Table 2.

**Table 2.** Correlation of dosimetric heart values with  $\Delta$  vital capacity (VC) and  $\Delta$  diffusion parameters after RT (R (sign.)).

Heart Parameters	$\Delta$ VC at 12 Weeks	$\Delta$ DL <sub>CO</sub> at 6 Weeks	$\Delta$ DL <sub>CO</sub> at 12 Weeks	$\Delta$ DL <sub>CO</sub> at 6 Months	$\Delta$ pCO <sub>2</sub> at 6 Weeks	$\Delta$ pO <sub>2</sub> at 6 Weeks
Heart $D_{\text{mean}}$ (Gy)	−0.346 (0.008)	−0.302 (0.025)	−0.416 (0.002)	−0.371 (0.017)	0.272 (0.037)	0.319 (0.014)
Heart $D_{33\%}$ (Gy)	−0.340 (0.009)	−0.274 (0.043)	−0.371 (0.005)	−0.365 (0.019)	n.s.	0.299 (0.022)
Heart $D_{50\%}$ (Gy)	−0.359 (0.006)	n.s.	−0.366 (0.006)	−0.351 (0.024)	0.284 (0.029)	0.297 (0.023)

n.s.:  $p > 0.05$ .

As possible confounders, the influence of clinically apparent ( $\geq$ Common Terminology Criteria for Adverse Events (CTCAE) G2, medical intervention indicated) radiation pneumonitis ( $n = 7$ ) and locally progressive disease ( $n = 9$ ) on the difference in DL<sub>CO</sub>,  $p\text{O}_2$ , and  $p\text{CO}_2$  after RT was analyzed. No statistically significant impact of pneumonitis or progression on the change of any diffusion parameter after radiotherapy was found.

### 2.2. Impact of Clinical and (Low) Dose Parameters on Clinically Apparent Pneumonitis

The seven patients with a  $\geq$ G2 pneumonitis predominantly suffered from primary lung tumors ( $n = 6$ ); one patient suffered from an esophageal carcinoma. The median planning target volume (PTV) volume for those patients was 355.8 mL (range 102.7–857.9 mL) with a median  $V_{20\text{Gy}}$  of 38.9% (range 17.1–50.5%) and a median  $D_{\text{mean}}$  of the lung of 19.5 Gy (range 9.9–22.2 Gy). When looking at the DL<sub>CO</sub> changes for those patients after radiotherapy, they showed a variable course. Two patients showed an improvement or stable DL<sub>CO</sub> at the point of their last follow-up, while the other 5 patients had a decrease in DL<sub>CO</sub>, all of which had a decrease of more than 20%.

There was no statistically significant difference of patient-related parameters (gender, T-Status, tumor entity, total treatment dose, chemotherapy, smoking history) for patients with or without  $\geq$ G2 pneumonitis. Additionally, there was no statistically significant difference for any dose parameter of either the lung or the heart.

### 2.3. Multivariate Analysis

In the multivariate analysis, several dose parameters of both the lungs and heart proved to have a statistically significant influence on  $\Delta$  DL<sub>CO</sub> after treatment. For  $\Delta$  DL<sub>CO</sub> at 6 weeks after treatment,  $V_{15\text{Gy}}$ ,  $V_{25\text{Gy}}$ , and  $V_{30\text{Gy}}$  (%) and  $D_{\text{mean}}$  (Gy) of the lung as well as  $D_{\text{mean}}$  (Gy) of the heart, and for  $\Delta$  DL<sub>CO</sub> at 12 weeks after RT,  $D_{\text{mean}}$  and  $D_{50\%}$  (Gy) of the heart remained significant. For  $\Delta$  DL<sub>CO</sub> after 6 months, those values were  $V_{20\text{Gy}}$ ,  $V_{25\text{Gy}}$ , and  $V_{30\text{Gy}}$  (%) of the lung.

## 3. Discussion

The goal of this analysis was to assess the impact of (low) dose–volume parameters of the lung and heart on changes in lung function after RT and pulmonary toxicity assessed by clinically apparent pneumonitis.

Pulmonary function tests are easy to assess and help to identify radiation-induced damage of lung tissue after RT [1–3,8–10,12,13,20,34,35]. In particular, diffusion parameters such as DL<sub>CO</sub> have proven to be reliable as they show the largest decline and least recovery after RT [1,2,8–19]. This also holds true for this cohort and was published in an earlier report [13].

When looking at the correlations between PFT changes and dose values of the lung, there were mostly significant correlations for  $\Delta DL_{CO}$ . All these correlations had a negative correlation coefficient, in this case meaning that with increased dose, there was a greater decline in  $DL_{CO}$ . Interestingly, larger correlation coefficients were found for lower doses like  $V_{5Gy}$  and  $V_{10Gy}$ . Notably, there were no statistically significant correlations for  $>V_{30Gy}$ , suggesting a larger impact of the low dose bath on  $DL_{CO}$ . For  $\Delta pO_2$  and  $\Delta pCO_2$ , assessed by blood gas analysis, the opposite was the case. These values significantly correlated with  $V_{60Gy}$ . However, this correlation was only significant at 12 weeks after RT and therefore a temporary phenomenon, unlikely to be clinically relevant.

There have been some studies regarding the correlation of dose–volume parameters with PFT changes in the past. Some found no correlation between  $DL_{CO}$  changes and dose–volume parameters of the lung [10,15,17], while others were able to show significant correlations of  $DL_{CO}$  with both heart and lung parameters [9,14,16,18,19]. As for radiation pneumonitis, most studies focused on  $V_{20Gy}$  as an important dose parameter. For example, Bral et al. and Enache et al. showed a significant impact of  $V_{20Gy}$  [16,19]. A correlation of  $DL_{CO}$  decline with low-dose irradiation (percent or absolute volume receiving 700–1000 cGy) of the lungs was shown for a cohort of patients with esophageal carcinomas by Gergel et al. [14].

Lopez-Guerra et al. demonstrated that in addition to dose parameters of the lung ( $V_{20Gy}$  (%)), heart parameters had a significant impact on  $DL_{CO}$  decline as well [9]. This also holds true in this cohort, where we found several significant correlations of heart dose values and PFT changes after RT. For  $DL_{CO}$ , this correlation remained until the last PFT follow-up at 6 months after RT.

In addition, on multivariate analysis, the heart doses proved to have a significant impact on  $\Delta DL_{CO}$  after treatment. At 6 months after treatment,  $D_{mean}$  (Gy) of the heart remained statistically significant next to  $V_{20Gy}$ – $V_{30Gy}$  (%) of the lungs. This suggests that the very low-dose bath (e.g.,  $V_{5Gy}$ ) does not have a significant impact on long-term  $DL_{CO}$  changes when other dose parameters for both the lung and heart are taken into account. A significant impact of the low dose bath was only seen 6 weeks after treatment, where  $V_{10Gy}$  (%) remained one of the significant parameters, suggesting that very low-dose irradiation seems to only have a transient and not a lasting clinical effect. For the later time points, dose–volume parameters of the lung in the mid-dose range ( $V_{15Gy}$ – $V_{30Gy}$ ) have a larger impact on  $DL_{CO}$ .

The clinical relevance of diffusion reduction lies in the fact that a reduction in  $DL_{CO}$  can have a significant impact on a patient's well-being and quality of life after treatment. This especially holds true if they already had a substantial impairment before therapy. In this case, further reduction could mean an increase in physical impairment or even oxygen dependency. However, existing planning objectives largely focus on radiation pneumonitis as the most common radiation-induced lung toxicity, for which  $V_{20Gy}$  (%) and  $D_{mean}$  (Gy) are known to be significant predictors [7,15,23–26].

In this analysis, there was no influence of any dose–volume parameter of the lungs or heart on the incidence of  $\geq G2$  pneumonitis. Additionally, other patient- or treatment-specific parameters failed to show a significant influence. This might be due to the low number of events with seven patients with  $\geq G2$  pneumonitis (11.3%). Published results on pneumonitis come to different results regarding the relevant parameters.  $V_{20Gy}$  (%) of the lungs was identified as a significant factor in some studies [23,25,26], but not in others [28]. Additionally, there are data suggesting an influence of heart parameters on the incidence of RP. Huang et al. found a significant influence of several dose–volume parameters of the heart on the RP incidence [36], but published data are not congruent, as Tucker et al. could not find a significant impact of heart dose parameters [37].

A limitation of this analysis is that as a result of testing several possible correlations at a significance level of 0.05, the risk of encountering an incidentally significant finding is obviously increased, as is the case with many retrospective analyses. While this is especially true for borderline significant findings, several associations were encountered, such as

the relation between  $D_{\text{mean}}$  and VC at 6 months following RT, showing a much stronger correlation which mitigates this risk to a certain degree. However, as retrospective analyses like this can only be considered as hypotheses-generating, prospective studies are needed to confirm our findings. Another limitation lies in the limited number of patients available for analysis and follow-up using PFTs up to 6 months only. However, several previous studies assessed only one time point after RT. The strength of this study though is that PFTs were done at three time points after RT, which enables the differentiation between transient and more permanent radiation-induced lung toxicities.

#### 4. Materials and Methods

##### 4.1. Patient Characteristics

A total of 62 patients receiving curative thoracic radiotherapy for non-small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC), and esophageal carcinoma between April 2012 and October 2015 were included in this analysis. All patients had a Karnofsky performance status score (KPS) of at least 70%. Patients with lung surgery in their medical history, displaying relevant pleural effusion visible in the planning CT scan, and/or a forced expiratory volume within 1s ( $FEV_1$ ) of less than 1 L were excluded from this analysis. NSCLC patients received a total radiation dose of 74 Gy, SCLC patients 60 Gy, and patients with esophageal carcinoma 66 Gy, all with a single-fraction dose of 2 Gy. Of the 34 patients with primary lung tumors, the majority of patients had centrally located tumors (38%). Eligible patients received concomitant chemotherapy according to intradepartmental standards. During concurrent RCT, patients with NSCLC received Cisplatin and Vinorelbine. Patients with SCLC received Cisplatin and Etoposid simultaneously. Patients with esophageal carcinomas were treated with Cisplatin and 5-Fluorouracil (5 FU). If the glomerular filtration rate was lower than 60 mL/min, patients received Carboplatin area under the curve (AUC) 5 instead of Cisplatin. The median age of patients was 66 years. All patients included in this analysis completed the treatment protocol. A total of 62 patients had at least one follow-up appointment, 58 patients had at least two, and 45 patients had all three follow-up appointments. Patient characteristics are shown in Table 3.

**Table 3.** Patient and treatment characteristics.

		<i>n</i> (%)
Gender	Female	12 (19.4%)
	Male	50 (80.6%)
Smoking history	Never	6 (9.7%)
	Present	32 (51.6%)
	Former	24 (38.7%)
	Median pack years	30 (range 5–120)
Tumor entity (treatment dose)	NSCLC (74 Gy)	24 (38.7%)
	SCLC (60 Gy)	10 (16.1%)
	Esophageal Cancer (66 Gy)	28 (45.2%)
UICC stage	Ia–IIb	7 (11.3%)
	IIIa	23 (37.1%)
	IIIb	25 (40.3%)
	IIIc	1 (1.6%)
	IV	6 (9.7%)
RT technique	IMRT	34 (54.8%)
	VMAT	28 (45.2%)
Chemotherapy during primary treatment	Concurrent and/or sequential	44 (71.0%)
	none	18 (29.0%)
Total		62 (100%)

#### 4.2. Treatment Planning and Dose Parameters

All treatment plans had to match intradepartmental dose constraints and were identically standardized using the PTV. Dose–volume parameters were expressed as (1) percentage of the volume of an OAR receiving a certain dose ( $V_{xxGy}$ ), (2) mean and maximum dose in Gy received by a certain OAR ( $D_{mean}$  and  $D_{max}$ ), or (3) dose in Gy received by a certain percentage of the volume ( $D_{xx\%}$ ).

The applied dose constraints for the lungs were as follows:  $V_{20Gy} < 30\%$ ,  $V_{30Gy} < 20\%$ , and  $V_{20Gy} < 1000$  mL. The dose constraint for the spinal cord was  $D_{max} < 47$  Gy, and for the esophagus was  $D_{max} < 74$  Gy. The dose constraints used for the heart were:  $D_{mean} < 35$  Gy,  $D_{33\%} < 60$  Gy, and  $D_{50\%} < 45$  Gy. The treatment plans were calculated using an anisotropic analytical algorithm (AAA) in Eclipse software™ (Varian Medical Systems, Inc., Palo Alto, CA, USA).

For our analyses, the following dose–volume parameters were analyzed: lung  $D_{mean}$ ,  $V_{5Gy}$ – $V_{60Gy}$  in 5 Gy steps, as well as heart  $D_{mean}$ ,  $D_{33\%}$ , and  $D_{50\%}$ . Furthermore, the GTV and PTV volumes in mL were analyzed.

#### 4.3. Follow-Up and Pulmonary Function Testing

Patients received regular clinical follow-up visits during radiotherapy, as well as at 6 weeks, at 12 weeks, and at 6 months after treatment. During clinical follow-up visits, toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Pulmonary function tests (PFT) were done before radiation treatment, as well as at 6 weeks, 12 weeks, and at 6 months after RT. Both ventilation and diffusion parameters were measured. For ventilation, the parameters were vital capacity (VC), total lung capacity (TLC), and forced expiratory volume within 1 s ( $FEV_1$ ). The diffusion capacity for carbon monoxide ( $DL_{CO}$ ) was measured, and capillary blood gas analysis was performed to obtain the partial pressure of carbon dioxide ( $pCO_2$ ) and partial pressure of oxygen ( $pO_2$ ).

#### 4.4. Statistical Analysis

The differences ( $\Delta$ ) in PFT compared to the baseline were calculated. Pearson's correlation coefficient was calculated to assess the correlation between dose–volume parameters and  $\Delta$  PFT. The Mann–Whitney U-Test was applied to assess the influence of local progression within the first 6 months after RT, as well as radiation pneumonitis on the  $\Delta$  diffusion parameters after RT. To assess the influence of patient and dose related factors on pneumonitis, U-Test and Chi-Square tests were used. Further, multivariate analysis was used for multivariate linear regression. A  $p$ -value of  $\leq 0.05$  was considered statistically significant. All statistical analyses were done with International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 25 (IBM, Armonk, NY, USA).

### 5. Conclusions

In conclusion, there seems to be a significant lasting impact of low-dose irradiation in the range of  $V_{15Gy}$ – $V_{30Gy}$  to the lungs, as well as irradiation to the heart ( $D_{mean}$ ,  $D_{50\%}$  (Gy)) on the  $DL_{CO}$  after thoracic radiotherapy. The impact of very low-dose irradiation to the lungs ( $<V_{15Gy}$ ) seems to be transient with being only present at 6 weeks after RT and not thereafter if other parameters are taken into account. Still, the low dose bath should also be taken into account when planning patients' treatments, especially in patients that present with a low  $DL_{CO}$  before treatment, as they might be clinically affected even by transient effects. Within known dose constraints, an individual weighing of the risk radiation-induced side effects on the lung for different dose levels (e.g.,  $V_{20Gy}$ ,  $D_{mean}$  for pneumonitis,  $V_{10Gy}$ – $V_{30Gy}$  for  $DL_{CO}$  decline, higher doses for fibrosis) should be done according to each patient's specifics on an individual basis.

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**Data Availability Statement:** The data presented in this study are available on request from the corresponding author. The data are not publicly available due to insitutional guidelines.

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