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Correlation between the Changes in Lung Function and Lung Density Changes in Patients Following Radio- (Chemo-) Therapy for Thoracic Carcinomas

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Abstract

Purpose: In this analysis we focused on the correlation of patients' lung function (PFT) data and lung density changes (ΔHU) detected in follow-up CTs. **Material and Methods:** PFT and lung function data were available for 58 patients 12 weeks and 47 patients 6 months after radio- (chemo-) therapy for thoracic carcinomas (NSCLC, SCLC and esophageal carcinoma). The follow-up CT scans were matched with the planning CT scans of each patient and then subtracted to calculate ΔHU for each voxel using customized research software. PFT data regarding e.g. vital capacity (VC), total lung capacity (TLC) and diffusion capacity for carbon monoxide (DL_{CO}) were collected before and at several follow-up appointments after treatment. **Results:** 12 weeks after therapy there was a statistically significant correlation between difference in DL_{CO} and the maximum ΔHU as well as the difference in TLC and the minimum ΔHU. 6 months after treatment there was a significant correlation between the difference in VC and DL_{CO} with numerous lung density parameters, e.g. the mean and median lung density changes and the 75th percentile of ΔHU. There was no significant correlation between the PFT parameters FEV1, pCO_2 and pO_2 and any lung density parameter at any follow-up appointment. **Conclusion:** There is a significant correlation between DL_{CO} and ΔHU 6 months after treatment that most likely reflects the underlying pathological mechanisms in terms of the development of fibrotic lung tissue after RT. The relevance of the significant correlations 12 weeks after RT is questionable.

Keywords

Lung, Thoracic Neoplasms, Radiation Injuries, Pulmonary Fibrosis, Lung Function

1. Introduction

There are numerous ways to examine radiation therapy (RT) related injuries to the lung tissue. On the one hand, there are simple but nonetheless crucial aspects like treatment related side effects; on the other hand, there are parameters that allow an analysis of the influence of RT in more detail and even give the opportunity to quantify the treatment induced lung damage. Two of these parameters are the changes in pulmonary function and the changes in lung density detectable by follow-up CT scans.

Pulmonary function tests (PFT) are easy to perform and often part of treatment preparation. Therefore, they have been the subjects of a number of studies in the past. There are some common results in most of these studies like the decrease of the diffusion capacity for carbon monoxide (DL_{CO}) after RT [1]-[8]. Other lung function parameters, mostly regarding ventilation parameters, lead to different results about their course over time [9] [10].

There are only a few studies regarding lung density changes in CT scans, probably due to the fact that there is no commercially available software for this, so that research software has to be customized [1] [11]-[19]. Because of the lack of commercial software for an automated analysis, older studies were often performed by using X-rays or the manual evaluation of just a few CT slides per patient. Common results were an increase in lung density after RT, regarding the influence of dose and time after treatment different results were published though [11]-[19].

In addition to the aspects of changes in PFT and lung density after RT the question arises if and how the density changes in the follow-up CTs influence the patient's pulmonary function. Are they relevant to a patient's pulmonary capacity and therefore possibly influencing his physical functioning? This aspect has rarely been analyzed before. Therefore, we analyzed prospectively collected data focusing on the correlation of the patient's PFT data and changes in pulmonary density measured with the help of a customized computer program for matching and analyzing follow-up CT scans. We focused on common PFT parameters regarding diffusion (DL_{CO}), ventilation (e.g. vital capacity (VC)) and blood gas analysis.

2. Methods and Material

2.1. Patient Characteristics

Included in this analysis were curatively treatable patients with intrathoracical carcinoma (NSCLC, SCLC, esophageal carcinoma) with a written consent of participation and a Karnofsky index (KI) of at least 70%. Patients with a lung operation in the patient's medical history, a relevant pleural effusion visible in the planning CT, a forced expiratory volume in 1 second (FEV1) of less than 1 liter, the refusal of participation or a KI of less than 70% were excluded. From April 2012 to October 2015 81 patients with thoracic carcinomas received radio-(chemo-) therapy. NSCLC patients were treated with a total radiation dose of 74 Gy, SCLC patients with 60 Gy and patients with esophageal carcinoma with 66 Gy. Fraction dose was 2 Gy each. During concurrent RCT patients with NSCLC received Cisplatin (80 mg/m^2) and Vinorelbin (15 mg/m^2). Patients with SCLC received Cisplatin (75 mg/m^2) and Etoposid (120 mg/m^2) simultaneously. Patients with esophageal carcinomas were treated with Cisplatin (75 mg/m^2) and 5-Fluoruracil (5 FU) (800 mg/m^2/24 h). If the glomerular filtration rate was lower than 60 ml/min patients received Carboplatin AUC 5 instead of Cisplatin. 58 of those patients received both a follow-up CT and pulmonary function testing 12 weeks after RT and 47 patients 6 months after RT. Further patient characteristics are shown in Table 1.

Table 1. Patient characteristics.

		n (%)
sex	male	47 (81)
	female	11 (19)
chemotherapy	no	18 (31)
	yes	40 (69)
entity (total radiation dose)	SCLC (60 Gy)	10 (17)
	Esophageal CA (66 Gy)	25 (43)
	NSCLC (74 Gy)	23 (40)
smoking history	never	5 (9)
	present	30 (52)
	former	23 (40)
UICC stage * NSCLC/SCLC	IIIa	2 (3)
	IIIb	11 (19)
	IIIc	17 (29)
	IV	3 (5)
UICC stage * Esophageal carcinoma	Ib	2 (3)
	IIIa	4 (7)
	IIIb	12 (21)
	IV	7 (12)
total		58 (100)

2.2. Treatment Characteristics

All patients were treated with intensity-modulated treatment techniques (IMRT with "sliding window" technique or volumetric modulated radiation treatment in "rapid arc"™ (Varian medical Systems) technique). The treatment plans were calculated by a medical physicist using Eclipse software™ (Varian medical Systems) with an AAA algorithm for dose calculation. All treatment plans had to match intradepartmental dose constraints. Dose constraints for the lung were V20 Gy < 30 %, V30 Gy < 20 Gy and V20 Gy < 1000 ml; for the spinal cord a maximum dose (Dmax) < 47 Gy; for the esophagus a Dmax < 74 Gy and for the heart a mean dose < 35 Gy, D (33%) < 60 Gy und D (50%) < 45 Gy. All these dose values refer to biological doses.

2.3. Analysis of Follow-Up CT Scans

Patients received follow-up CT scans 12 weeks and 6 months after RT. For all CT scans a Sensation open CT (Siemens™) with 2 mm slices was used. To calculate the density changes of the lung tissue over time a patient's follow-up CT scans had to be matched to the original treatment planning CT. Because of the unavoidably always slightly different positioning and breathing position of a patient a deformation of one of the scans was necessary prior to the matching. Since the treatment planning CT was linked to the dose data and structure files the follow-up CT had to get deformed. To calculate the differences in lung density (in Hounsfield units) the treatment planning and the follow-up scan where then subtracted. Because the focus was supposed to be on changes in the lung parenchyma, structures with higher density like the tumor itself, adjacent organs, blood vessels etc. were subtracted with a small safety margin.

Since no commercial software was available research software had to be customized. This included CERR (Computational Enviroment for Radiotherapy Research), an open source library for medical research by the US National Institutes of Health and 3D-Slicer, also open source library for medical research by the National Alliance for Medical Image Computing (NA-MIC). The original data sets were imported, analyzed and ΔHU with the corresponding dose were exported into Microsoft Excel. For the present analysis the minimum and maximum ΔHU, mean ΔHU, median ΔHU, 5^{th}, 25^{th}, 75^{th} and 95^{th} percentile were calculated for each patient.

2.4. Pulmonary Function Tests

Lung function data were collected before radiation treatment, 6 weeks, 12 weeks and 6 month after RT. Data of patients that were not able to attend all appointments but had received both PFT testing and follow-up CT scans 12 weeks or 6 months post RT were also used for analysis. The following lung function parameters were analyzed: vital capacity (VC), total lung capacity (TLC), forced expiratory volume in 1 second (FEV1), diffusion capacity for carbon monoxide (DL_{CO}) and capillary blood gas analysis (pCO_2, pO_2). For further analysis, the difference between the pre-treatment PFT value and the value at the follow-up appointment was calculated.

2.5. Statistical Analysis

The correlation between the difference in a patient's lung function and lung density parameters was calculated using Pearson's correlation (correlation coefficient r). Additionally the correlation was analyzed graphically using scatter plots. If statistical outliers were detected those were removed from the analysis. For statistical analysis, SPSS version 24 was used.

3. Results

At 12 weeks after therapy there was a statistically significant correlation between difference in DL_{CO} and the maximum increase in lung density (ΔHU_{max}, $r = -0.374$, $p = 0.007$) as well as the difference in TLC and the minimum increase in lung density (ΔHU_{min}, $r = -0.348$, $p = 0.012$). 6 months after treatment there was a significant correlation between the difference in VC and DL_{CO} with numerous lung density parameters, e.g. the mean and median lung density changes (ΔHU_{mean} and ΔHU_{median}). There was no significant correlation between the PFT parameters FEV1, pCO_2 and pO_2 and any lung density parameter at any follow-up appointment. Table 2 shows the lung function and lung density parameters with a statistically significant correlation with corresponding correlation coefficients. Figures 1-6 show the correlation between VC and DL_{CO} with ΔHU_{mean}, ΔHU_{median} and $\Delta HU_{75percentile}$ 6 months after treatment.

4. Discussion

12 weeks after treatment only the DL_{CO} and the TLC proved to have a significant correlation with a lung density parameter, in this case ΔHU_{max} and ΔHU_{min}. Especially in case of the correlation of the TLC and ΔHU_{min} the relevance of this

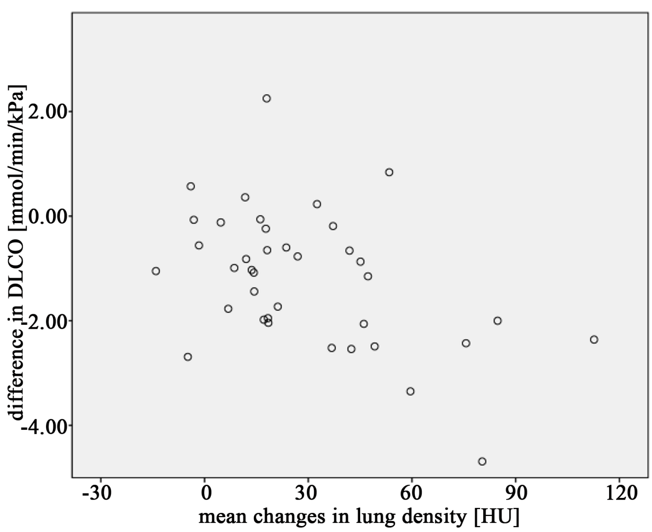

Figure 1. DL_{CO} vs. mean ΔHU—6 months post RT (n = 47).

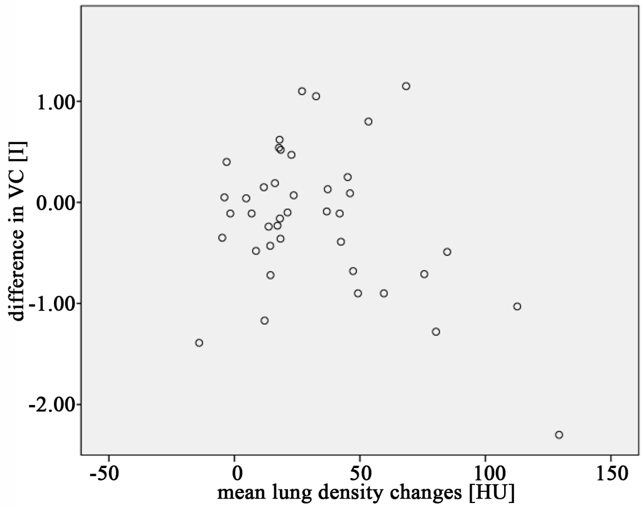

Figure 2. VC vs. mean ΔHU—6 months post RT (n = 47).

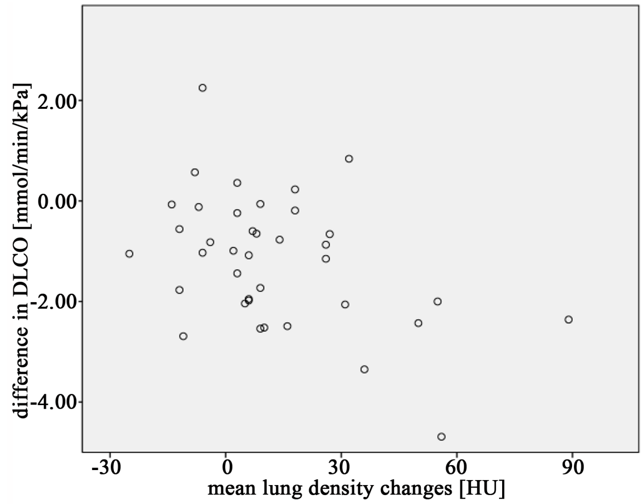

Figure 3. DL_{CO} vs. median ΔHU—6 months post RT (n = 47).

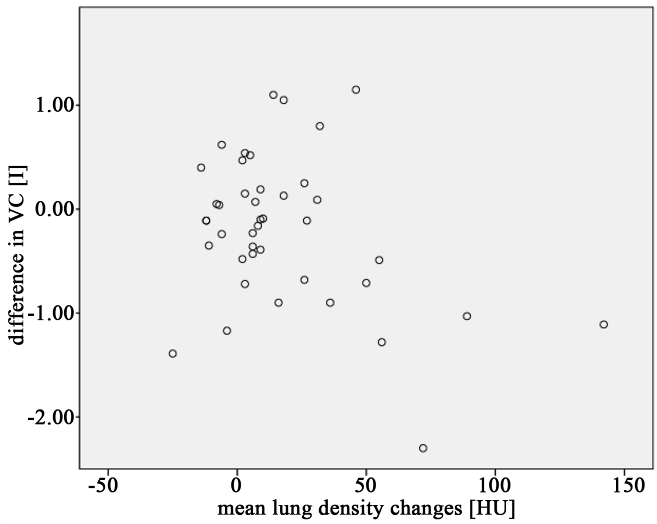

Figure 4. VC vs. median ΔHU—6 months post RT (n = 47).

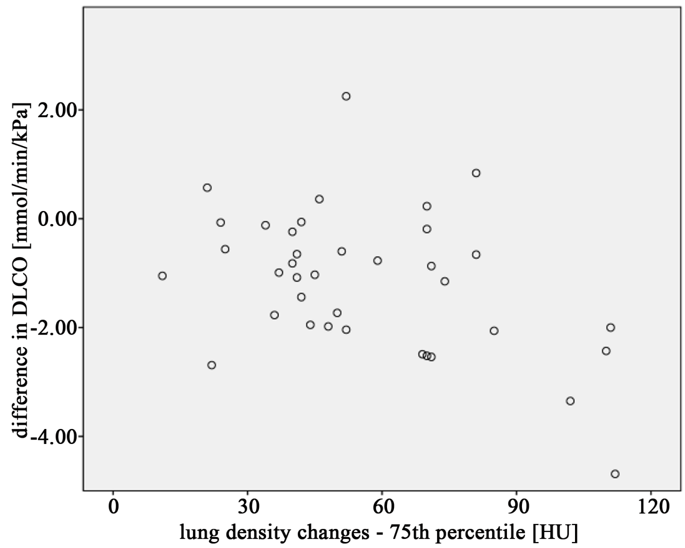

Figure 5. DL_{CO} vs. ΔHU 75th percentile—6 months post RT (n = 47).

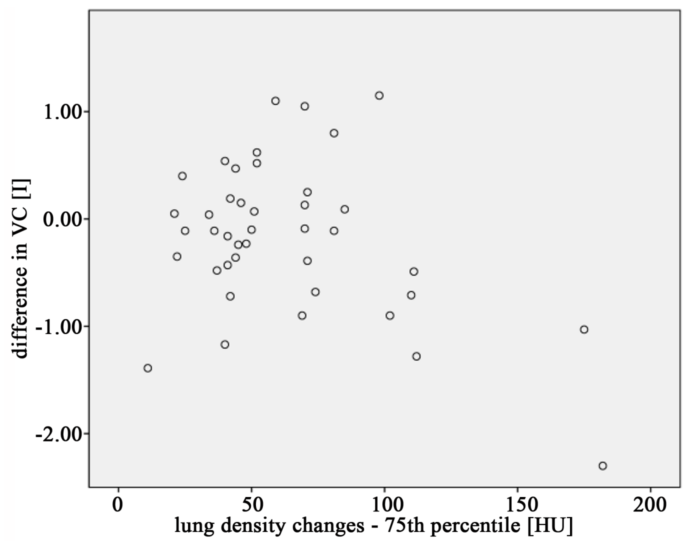

Figure 6. VC vs. ΔHU 75th percentile—6 months post RT (n = 47).

Table 2. Correlation between the difference lung function and the lung density changes ΔHU 6 months after therapy (n = 47).

lung function parameter	lung density parameter	correlation coefficient (r)	p-value
VC	ΔHU_{mean}	−0.358	0.022
VC	ΔHU_{median}	−0.349	0.024
VC	$\Delta HU_{75percentile}$	−0.366	0.018
DL_{CO}	ΔHU_{mean}	−0.456	0.004
DL_{CO}	ΔHU_{median}	−0.427	0.008
DL_{CO}	$\Delta HU_{25percentile}$	−0.370	0.022
DL_{CO}	$\Delta HU_{75percentile}$	−0.433	0.007
DL_{CO}	$\Delta HU_{95percentile}$	−0.478	0.002

correlation is questionable. The problem with both the minimum and maximum density change is that these might be isolated values which do not necessarily represent the overall change in lung density like e.g. the mean or median density change. Therefore they can easily be outliers due to an extreme density change in a volume that might only be the size of a voxel. It is highly unlikely that a volume this size would have any influence on a patient's PFT, especially the TLC. Furthermore no lung density parameter that represents a larger amount of voxels like the mean, median or any other percentile proved to have any significant correlation 12 weeks after treatment. However 6 months after treatment both the DL_{CO} and the VC show a number of significant correlations with several lung density parameters. At 6 months after RT the predominant toxicity is the radiation-induced lung fibrosis whereas the radiation pneumonitis (RP) as the most common radiation induced lung toxicity is more likely to occur in the first 3 months after RT [10] [20]-[26]. A fibrotic remodeling of lung tissue leads to an increase in lung density, which can be detected in follow-up CT scans [1] [10] [13]. The DL_{CO} as a diffusion parameter is more sensitive in reflecting RT induced changes in lung tissue [1]-[7] [26] [27]. It is also the PFT parameter that is commonly reported to show a stable decline after RT [1] [2] [3] [7] [26] [27]. Therefore it is not surprising that there are 5 significant correlations between the DL_{CO} and lung density parameters. The correlation coefficients however are not large, but with −0.370 to −0.478 larger that those reported by Ma *et al.* with a correlation coefficient ranging from 0.17 to 0.29 [28].

Ventilation parameters like FEV1 and VC are reported to show a more diverse dynamic after RT [2] [4] [6] [10] [26]. They do not only show a decline, but e.g. due to the opening of atelectases also an improvement after treatment. Regarding the correlation between ventilation parameters and lung density changes Ma *et al.* found a significant correlation between FEV1 and the lung density changes (r = 0.3 - 0.37) and Lind *et al.* described an greater decline in VC in patients with a greater lung density increase assed by the Arriagada score [28] [29]. In this analysis there was no significant correlation between the FEV1 and any lung density parameter 12 weeks or 6 months after RT. There was a significant correlation between the VC and several parameters 6 months after RT. The fibrotic remodeling of lung tissue would lead to both an increase in lung density and a decrease in VC. However one would also expect to see a decrease in FEV1 and TLC with a corresponding significant correlation between an increase in ΔHU and a decrease of those PFT parameters as well. The reason there is no significant correlation for those parameters might be the large dynamic of those values after RT and the interindividual differences between patients [2] [4] [26].

Limitations of this analysis are certainly the small number of patients given the large interindividual differences regarding both the PFT and the lung density changes. Further trials with a larger patient number are certainly desirable.

5. Conclusion

There are significant correlations between the DL_{CO} and ΔHU_{max} as wells as the

TLC and ΔHU_{min} whose relevance is questionable. However, the significant correlations between the DL_{CO} and VC with several lung density parameters suggest that both reflect an underlying RT induced change of lung tissue. Especially, the correlation between the decline in DL_{CO} which shows a loss of diffusion capacity, possibly due to remodeling of lung tissue and the increase in lung density, which also shows an increase in connective tissue due to remodeling of lung tissue reflects the effects of RT induced lung fibrosis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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