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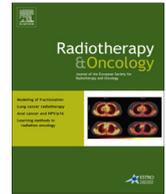
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Late effects in lung cancer

Cardiac comorbidity is an independent risk factor for radiation-induced lung toxicity in lung cancer patients



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ABSTRACT

Purpose: To test the hypothesis that cardiac comorbidity before the start of radiotherapy (RT) is associated with an increased risk of radiation-induced lung toxicity (RILT) in lung cancer patients.

Material and methods: A retrospective analysis was performed of a prospective cohort of 259 patients with locoregional lung cancer treated with definitive radio(chemo)therapy between 2007 and 2011 (ClinicalTrials.gov Identifiers: NCT00572325 and NCT00573040). We defined RILT as dyspnea CTCv.3.0 grade ≥ 2 within 6 months after RT, and cardiac comorbidity as a recorded treatment of a cardiac pathology at a cardiology department. Univariate and multivariate analyses, as well as external validation, were performed. The model-performance measure was the area under the receiver operating characteristic curve (AUC).

Results: Prior to RT, 75/259 (28.9%) patients had cardiac comorbidity, 44% of whom (33/75) developed RILT. The odds ratio of developing RILT for patients with cardiac comorbidity was 2.58 ($p < 0.01$). The cross-validated AUC of a model with cardiac comorbidity, tumor location, forced expiratory volume in 1 s, sequential chemotherapy and pretreatment dyspnea score was 0.72 ($p < 0.001$) on the training set, and 0.67 ($p < 0.001$) on the validation set.

Conclusion: Cardiac comorbidity is an important risk factor for developing RILT after definite radio(chemo)therapy of lung cancer patients.

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Radiation-induced lung toxicity (RILT) is an important dose-limiting complication of radical thoracic radiotherapy (RT). While high radiation doses are expected to provide better locoregional control, associated toxicity, such as RILT, may have a major impact on the quality of life and can even be lethal. About 10%–20% of all lung cancer patients treated with radio(chemo)therapy, R(CH)T, develop RILT within 6 months after start of treatment, with clinical symptoms of dyspnea, cough, and sometimes fever [1]. Notably, the degree of RILT varies greatly among patients treated with similar dose levels to the healthy lung. Identification of patients' susceptibility to RILT prior to RT based on baseline characteristics

may permit (1) dose escalation for low-risk patients, potentially leading to better survival rates at reduced/similar levels of treatment-related side effects [2] and (2) dose reduction/redistribution for high-risk patients to avoid side effects.

Traditional risk factors for RILT include mean lung dose (MLD), V20 Gy (volume of lung receiving at least 20 Gy), age, smoking status, gender, World Health Organization (WHO) performance status, chemotherapy, and the location of the primary lung tumor ([3–14], among others). Unfortunately, prognostic models based on these factors have not provided consistent performance across different studies. Blood biomarkers have likewise shown controversial results, [15–17]. Recently, preclinical [18] and clinical [19] studies have demonstrated a short-term effect of irradiation of a healthy heart on pulmonary dysfunction. Left-sided heart failure is known to lead to dyspnea due to an elevated end-diastolic pressure of the left ventricle, which perpetrates to the pulmonary capillaries and leads to pulmonary edema, [20,21]. Moreover, cardiac comorbidity at the start of treatment among 3864 lung cancer patients with a

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mean age of 67 years has been found to be the most frequent concomitant disease, with incidence twice as high (23%) as in the general population, [22]. We therefore hypothesized that patients with recorded historical treatment of cardiac pathologies are at greater risk of developing RILT after R(CH)T.

Material and methods

Patient population and inclusion criteria

Between 2008 and 2011 a total of 399 lung cancer patients, all treated in two hospitals with cardiology departments, were referred to our institute for radiation treatment and used in our retrospective study. Of these, 259 patients retrospectively met the inclusion criteria of the study, namely: stage I–IIIB, (chemo)radiotherapy with curative intent, radiation fraction dose ≤ 3 Gy. Stereotactic body irradiation treatments were excluded. All patients underwent a FDG-PET/CT scan for treatment planning purposes, on which the heart and lungs (manual contouring in either mediastinal or lung WW/WL-setting as appropriate) were delineated. The treatment planning system used was XiO (4.3.4, CMS, St. Louis, USA) using the superposition dose calculation algorithm. Patients were treated with concurrent or sequential chemoradiotherapy, (postoperative) radiotherapy with subsequent adjuvant chemotherapy, or with radiation alone. Sequential chemotherapy consisted of carboplatin on day 1 and gemcitabine on day 1 and 8. The majority of the patients received 3 cycles (range 1–6). Concurrent chemo radiation consisted of cisplatin on day 1 and 8 and etoposide on day 1–3 of a three-weekly cycle. In total three cycles were given. The patients were examined weekly during RT and every three months thereafter by either the radiation oncologist or the chest physician. Patient characteristics for the training ($n = 259$) as well as the validation dataset ($n = 107$ from Ghent University Hospital and $n = 44$ from Radboud University Nijmegen Medical Centre) are given in Table 1.

Toxicity scoring

RILT was scored using the Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3.0) before, weekly during and every 3 months after RT by either a chest physician or a radiation oncologist. A value of dyspnea ≥ 2 within 6 months after RT was considered as acute manifestation of RILT and used as primary endpoint in the analysis. In the CTCAE3.0 system, grade 0 is no dyspnea; grade 1 is dyspnea on exertion, but can walk 1 flight of stairs without stopping; grade 2 is dyspnea on exertion but unable to walk 1 flight of stairs or 100 meters without stopping; grade 3 is dyspnea with ADLs (Activities of Daily Living. Basic ADLs include eating, dressing, getting into or out of a bed or chair, taking a bath or shower, and using the toilet.); grade 4 is dyspnea at rest, intubation/ventilator indicated; and grade 5 is death.

Cardiac comorbidity scoring

Cardiac comorbidity was defined as a recorded historical treatment of any cardiac disorder at a cardiology department before the start of RT, irrespective of its severity. Cardiac comorbidity for all patients was scored by a cardiologist from the academic hospital azM Maastricht using the cardiac specific anamnesis from the cardiology departments. Patient dyspnea scores were not provided to the cardiologist.

Statistical analysis

We tested four statistical hypotheses:

- (1) the independence of cardiac comorbidity and post-treatment dyspnea ≥ 2 , our main clinical hypothesis being that we reject such independence;
- (2) the independence of cardiac comorbidity and post-treatment dyspnea ≥ 2 , given pretreatment dyspnea < 2 , to determine whether cardiac comorbidity might be a risk factor only for patients who already have high dyspnea levels at the start of RT;
- (3) the independence of cardiac comorbidity and post-treatment dyspnea ≥ 3 , to determine the robustness of the first hypothesis, in case it is not rejected;
- (4) the independence of cardiac comorbidity and pretreatment dyspnea, In case cardiac comorbidity is a risk factor for post-RT dyspnea, it may be also be more likely that presence of cardiac comorbidity is associated with higher levels of pretreatment dyspnea.

The univariate and multivariate logistic regression analyses were performed in SPSS version 19 (IBM Corp., Armonk, NY) and MATLAB (MathWorks Inc., Natick, MA). The following variables were considered as inputs for the prediction models: MLD, existing cardiac comorbidity at the start of radiotherapy, smoking status, type of chemotherapy, age, gender, forced expiratory volume in 1 s adjusted for gender and age (FEV_1 , in%), lung surgery performed in the past before RT, WHO performance status (WHOPs), tumor location, lung volume, prescribed tumor dose expressed as equivalent radiation dose in 2 Gy fractions corrected for overall treatment time ($EQD_{2,t}$) [23] using $\alpha/\beta = 10$ Gy and accelerated repopulation kick-off time of 28 days, overall treatment time, and the level of dyspnea at the start of RT. In addition, mean heart dose (MHD) was available for the patients in the training set, which is available online at www.cancerdata.org/?q=10.1016/j.radonc.2013.08.035. The variables for the multivariate model were selected via a wrapper feature selection procedure, [24], on the training set using a 10-fold cross validation with AUC set as a performance criterion. This feature selection method was performed in WEKA (Waikato Environment for Knowledge Analysis, [25]). An alpha value of 0.05 was used as a threshold for statistical significance. The p -values for nominal variables were computed using a chi-square test. Model performance was evaluated using the area under the receiver operator characteristic curve (AUC) estimated from a 10-fold cross-validation procedure to avoid the problem of overfitting; p -values for the difference in AUC vis-à-vis AUC = 0.5 (random model) were calculated using 1000 bootstrap samples. Univariate and multivariate analyses were performed on the training set and validated on the validation set.

Results

Among the 259 patients from the training dataset, 76 (29.3%) had a maximum dyspnea score ≥ 2 after RT. Out of them, 33 (43.4%) had a cardiac comorbidity at the start of RT. As the total number of patients with cardiac comorbidity was 75, this means that 44% (33/75) of the cardiac-comorbidity patients developed RILT. Conversely, 23.4% (43/184) of the patients without cardiac comorbidity experienced RILT.

Cardiac comorbidity and dyspnea ≥ 2

The odds ratio of post-RT dyspnea ≥ 2 for patients with versus without cardiac comorbidity was 2.6 ($p = 0.0009$, 95% confidence interval (CI): 1.5–4.5; Table 3 and Supplement Figure 1). These findings were confirmed on the combined validation set from two university hospitals ($n = 151$), with corresponding odds ratio of 2.3 ($p = 0.039$, 95% CI: 1.03–4.9). The relative risk of RILT in

Table 1
Patient characteristics.

Variable	No. of patients (%)		
	Training set (n = 259)	Ghent set (n = 107)	Nijmegen set (n = 44)
Gender			
Male	163(62.9)	94(87.8)	36(81.8)
Female	96(37.1)	13(12.2)	8(18.2)
Smoking status			
Current smoker	77(29.7)	34(31.8)	11(25.0)
Histopathology			
NSCLC	198(76.5)	88(93.5)	43(97.7)
SCLC	49(18.9)	11(10.3)	0(0)
NSCLC + SCLC	0(0)	1(0.9)	0(0)
cT-stage			
0 or 1	48(18.5)	9(8.4)	10(22.7)
2	75(29.0)	33(30.8)	14(31.8)
3	40(15.4)	32(29.9)	11(25.0)
4	95(36.7)	20(18.7)	9(20.5)
cN-stage			
0	67(25.9)	17(15.9)	2(4.5)
1	19(7.3)	9(8.4)	2(4.5)
2	112(43.2)	47(44.0)	35(79.5)
3	60(23.2)	23(21.5)	5(11.4)
WHO-ps			
0	63(24.3)	52(48.6)	25(56.8)
1	153(59.1)	48(44.9)	14(31.8)
≥2	43(16.6)	6(5.61)	5(11.4)
Chemotherapy			
Yes	197(76.1)	98(91.6)	41(93.2)
Concurrent	148(57.1)	39(36.4)	22(50.0)
Sequential before RT	39(15.1)	56(52.3)	19(43.2)
Adjuvant (after surgery)	9(0.03)	0(0)	0(0)
Palliative	1(0.01)	0(0)	0(0)
Concurrent + adjuvant	0(0)	3(0.03)	0(0)
No	44(17.0)	9(8.41)	3(6.8)
Cardiac comorbidity			
No	184(71.0)	86(80.4)	13(29.5)
Yes	75(29.0)	21(19.6)	31(70.5)
Baseline dyspnea score			
0	78(30.1)	46(43.0)	15(34.1)
1	140(54.1)	25(23.4)	25(56.8)
2	22(8.5)	19(17.8)	4(9.1)
3	15(5.8)	2(1.9)	0(0)
4	1(0.4)	0(0)	0(0)
Maximal dyspnea score			
0	49 (18.9)	19 (17.8)	4 (9.1)
1	134 (51.7)	47 (44.0)	28 (63.6)
2	40 (15.4)	34 (31.8)	8 (18.2)
3	32 (12.4)	5 (4.7)	4 (9.1)
4	4 (1.5)	2 (1.9)	0(0)
Tumor location			
Lower/middle lobe	76 (29.3)	33 (30.8)	15 (35.7)
Upper lobe	83 (32.1)	67 (62.6)	27 (64.3)
Lung surgery before RT			
Yes	23 (8.9)	15 (14.0)	0(0)
No	236 (91.1)	92 (86.0)	44 (100.0)
	Mean (SD)		
OTT	30.21 (7.45)	47.8 (11.1)	43.37 (3.49)
Age, years	67.5 (10.1)	64.0 (8.8)	65.94 (7.69)
Prescribed tumor dose, Gy	62.4 (9.92)	64.5 (8.58)	64.66 (4.13)
EQD _{2,t}	58.83 (9.51)	51.97 (5.94)	54.60 (2.35)
Dose per fraction	1.836 (0.342)	1.981 (0.172)	2.02 (0.15)
MLD, Gy	15.65(4.44)	13.1 (4.31)	16.23 (3.12)
V20 Gy	25.45 (9.87)	19.35 (7.71)	Not available
FEV ₁ (in%)	75.96 (21.86)	75.7 (20.56)	77(17.44)

Abbreviations: No./n, number; SD, standard deviation; cT-stage, clinical tumor stage; cN-stage, clinical lymph node stage; NSCLC, non-small-cell lung cancer; SCLC, small-cell-lung cancer; WHO-ps, World Health Organization performance status; OTT, overall treatment time (in days); EQD_{2,t}, equivalent radiation dose at 2 Gy per fraction, adjusted for time; MLD, mean lung dose; V20 Gy, volume of the healthy lung receiving a dose of at least 20 Gy; FEV₁ (in%), forced expiratory volume in 1 s (in%) adjusted for age and gender. Dyspnea is measured according to the Common Toxicity Criteria for Adverse Effects, version 3.0; maximal dyspnea is measured within 6 months after the start of R(CH)T.

the validation data set was 50% for the patients with cardiac comorbidity (17/34).

Cardiac comorbidity and maximal dyspnea ≥2, given baseline dyspnea <2

The odds ratio of post-RT dyspnea in this case turned out to be similar to the one found without the restriction on baseline dyspnea grade: 2.6 ($p = 0.005$, 95% CI: 1.3–5.1; [Table 3](#)).

Cardiac comorbidity and maximal dyspnea ≥3

With this test we checked the robustness of the main finding, which is confirmed: the odds ratio is 2.5 ($p = 0.009$, 95% CI: 1.2–5.2, see [Table 3](#)). Even though the corresponding odds ratio on the validation set was 2.1, the chi-square test was not performed due to the insufficient (less than 5) number of patients with both cardiac comorbidity and maximal dyspnea ≥3.

Cardiac comorbidity and baseline dyspnea

Cardiac comorbidity is an independent cause of dyspnea, so therefore it is likely that the presence of cardiac comorbidity is associated with higher levels of baseline dyspnea. In this study,

we rejected the independence of these two factors on the training set: the odds ratio of observing baseline dyspnea ≥2 for patients with cardiac comorbidity was 2.2 ($p = 0.02$, 95% CI: 1.1–4.5; [Supplement Table 1](#)).

MHD, cardiac comorbidity and dyspnea ≥2

We performed a Kruskal–Wallis test for significant difference between median MHDs across the following four groups in the training set: patients with/without cardiac comorbidity and with/without maximal dyspnea ≥2. The p -value of the test was 0.71, suggestive of no significant difference across the four groups ([Supplement Figure 2](#)).

Cardiac comorbidity and maximal dyspnea ≥2, given that the patient received chemotherapy

Considering the subgroup of patients who received chemotherapy: the odds ratio of post-RT dyspnea ≥2 for patients with versus without cardiac comorbidity was 2.6 ($p = 0.005$, 95% CI: 1.3–5.1; [Supplement Table 2](#)). These findings were confirmed on the combined validation set ($n = 139$), with corresponding odds ratio of 2.3 ($p = 0.05$, 95% CI: 0.97–5.3).

Table 2

Results for univariate and multivariate logistic regressions for all variables and selected variables based on the wrapper approach. Dependent variables: maximal dyspnea ≥2 within 6 months from the start of RT.

Variable	Univariate			Multivariate: all variables			Multivariate: selected variables			
	Coefficient	S.E.	p -value*	Coefficient	S.E.	p -value*	Coefficient	S.E.	p -value*	
Intercept				0.803	1.614	0.619	1.512	0.664	0.023	
Smoking status	0.029	0.302	0.924	0.185	0.306	0.546	n.a	n.a	n.a	
Sequential chemotherapy	0.671	0.363	0.064	0.601	0.449	0.180	0.610	0.394	0.122	
Concurrent chemotherapy	-0.789	0.290	0.007	-0.016	0.416	0.969	n.a	n.a	n.a	
Gender	0.094	0.284	0.741	-0.005	0.313	0.988	n.a	n.a	n.a	
Cardiac comorbidity	0.969	0.289	0.001	0.817	0.307	0.008	0.826	0.312	0.008	
Surgery	0.057	0.475	0.904	-0.196	0.533	0.713	n.a	n.a	n.a	
Tumor location	-0.185	0.369	0.616	-0.421	0.314	0.180	-0.290	0.347	0.404	
WHO-ps	0.055	0.176	0.755	0.077	0.191	0.684	n.a	n.a	n.a	
Age	0.025	0.014	0.078	-0.016	0.016	0.340	n.a	n.a	n.a	
FEV1 (in %)	-0.016	0.007	0.018	-0.012	0.007	0.077	-0.007	0.007	0.330	
MLD	0.005	0.031	0.872	-0.02	0.034	0.565	n.a	n.a	n.a	
EQD2,t	0.022	0.014	0.126	0.007	0.018	0.713	n.a	n.a	n.a	
Overall treatment time	0.002	0.018	0.914	0.017	0.018	0.345	n.a	n.a	n.a	
Baseline dyspnea score	1.015	0.196	<0.000	1.106	0.203	<0.000	0.990	0.210	<0.000	
<i>Model performance (AUC)</i>									AUC	
Training set, 10-fold cross validation									0.723	<0.01
Validation set									0.674	<0.01

S.E. standard error, n.a. not applicable; abbreviations, see [Table 1](#).

* p -values for coefficients were calculated by multivariate logistic regression; p -values for AUCs were calculated by 1000 bootstraps and a 1-sided Student's t -test testing if the AUC was different from 0.5 (a flip-of-a-coin model).

Table 3

Contingency tables, odds ratios (with 95% CI) and p -values for the hypotheses that (1) maximal dyspnea ≥2 and cardiac comorbidity are independent, even when (2) the baseline dyspnea is ≤1, or (3) the outcome is maximal dyspnea ≥3. Results are shown for both the training set and the validation set. A p -value is not computed when a contingency table contains cells with counts <5.

Dataset	Training set		Validation set		Training set		Validation set		Training set		Validation set	
					Baseline dyspnea = 0 or 1							
	max dyspn <2	max dyspn ≥2	max dyspn <2	max dyspn ≥2	max dyspn <2	max dyspn ≥2	max dyspn <2	max dyspn ≥2	max dyspn <3	max dyspn ≥3	max dyspn <3	max dyspn ≥3
With CC	42	33	17	17	38	20	15	11	58	17	30	4
No CC	141	43	81	36	133	27	60	25	165	19	110	7
Odds ratio (95% CI)	2.58 (1.46–4.55)		2.25 (1.03–4.90)		2.59 (1.31–5.12)		1.76 (0.71–4.36)		2.55 (1.24 – 5.23)		2.10	
p -value	0.0009		0.039		0.005		0.219		0.009		n.a.	
n	259		151		218		111		259		151	

CC, cardiac comorbidity; CI, confidence interval; n , number; max dyspn, maximal dyspnea (within 6 months from the start of RT).

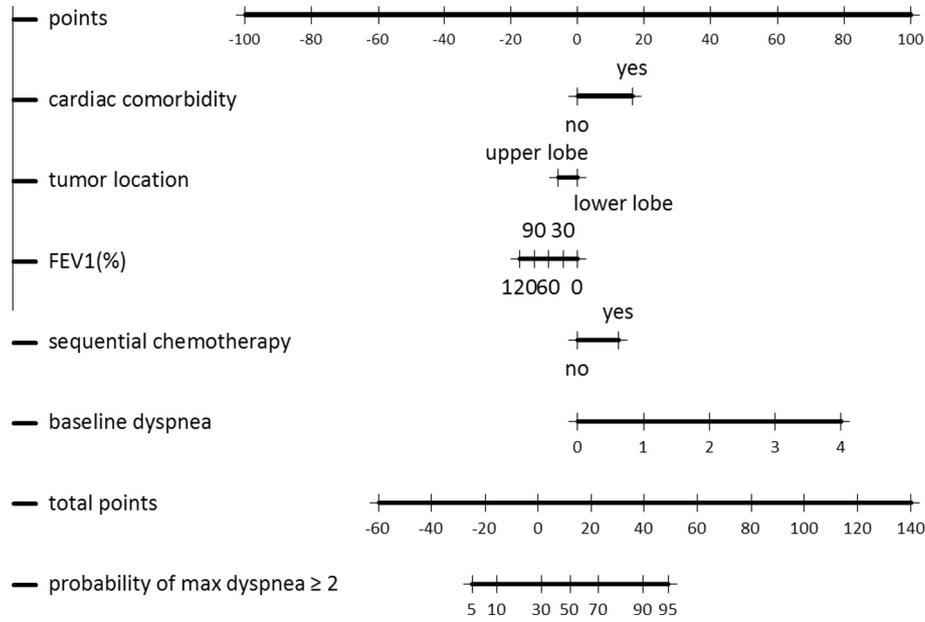


Fig. 1. A nomogram for the multivariate model (with variable selection) for the prediction of maximal dyspnea ≥ 2 within six months after RT (probability of max dyspnea ≥ 2).

Cardiac comorbidity and smoking status

We tested for an association between cardiac comorbidity and smoking status, which we refuted on both the training and validation sets (Supplement Table 1).

Univariate and multivariate analyses: cardiac comorbidity, baseline dyspnea score, and FEV₁ were found to be statistically significant factors in univariate logistic regression analysis (Table 2). Regarding chemotherapy, sequential chemotherapy was marginally significant and concurrent was significant (having opposite sign of the sequential). The wrapper-based feature selection on the training set resulted in the following subset of variables, which

we used in our multivariate model: cardiac comorbidity, tumor location, FEV₁, lung volume, and value of pretreatment dyspnea. The AUC's for the multivariate model were 0.72 ($p < 0.001$) on the training set, and 0.67 ($p < 0.001$) on the validation set. Cardiac comorbidity, lung volume and baseline dyspnea score came out as having the lowest p -values in the model. The AUCs of the “golden standard” model having only MLD as input were 0.49 and 0.37 on the training and the validation sets, respectively. A nomogram and the ROC curves for the multivariate model on the training set (computed using 10-fold cross-validation) and test sets are shown in Fig. 1 and Fig. 2, respectively. Fig. 2 depicts also the ROC curve for the MLD-only model. The multivariate model will be available on www.predictcancer.org. Supplementary Figure 3 further demonstrates the added value of the model at two specific points on the ROC curve of the training-set model.

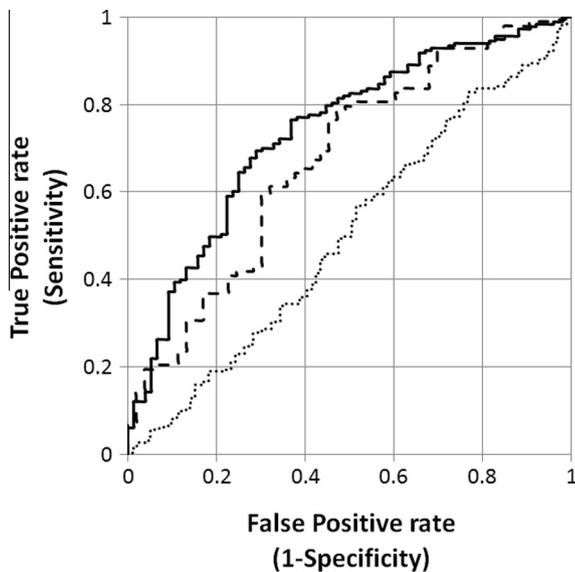


Fig. 2. ROC curves for the multivariable model (with selected variables) for predicting maximal dyspnea ≥ 2 within 6 months after the start of RT on the training set (solid line, cross-validated AUC = 0.72) and the validation set (dashed line, AUC = 0.67), as well as the ROC curve for the model including only mean lung dose as a predictor (dotted line, AUC = 0.50).

Discussion

In this study we tested the hypothesis that pretreatment cardiac comorbidity is associated with the development of RILT after high-dose R(CH)T for lung cancer. Traditionally, the effects of radiation on both organs have not been considered in tandem, most probably due to the short-term (up to 6–9 months) pulmonary toxicity effect and the longer term (5–15 years) cardiac toxicity effect. Short term cardiac toxicity has been considered in the context of high-dose chemotherapy, [26–29], mainly for breast cancer patients. Recently, preclinical [18] and clinical [19] studies discussed the short-term effect of irradiation of a healthy heart on pulmonary dysfunction. They demonstrated that the heart and lungs interact in their reaction to radiation in that excessive heart irradiation leads to pulmonary disorders. This is somewhat surprising, given that the heart has long been considered as the prototype (radiation) dose-resistant organ, based on the long (more than 5 years) rather than short-term increased risk of cardiac events, [30,31]. The short-term pulmonary toxicity from radiation may, however, heavily depend on both the prior condition of the lungs and the heart. Regarding the dose delivered to the heart, we tested whether MHD might be a confounding factor and therefore patients with

relatively higher MHD were actually those who developed dyspnea ≥ 2 . The respective Kruskal–Wallis test for independence between four groups of patients – with/without cardiac comorbidity and with/without maximal dyspnea ≥ 2 – had a rather high *p*-value, suggestive of no significant difference between median MHDs across the four groups.

The model describing the association of cardiac comorbidity and RILT was built on one dataset and externally validated on 151 patients. A major finding of our study is that cardiac comorbidity accounts for approximately 45% of all cases with dyspnea ≥ 2 after RT, even when adjusting for patients with dyspnea grade 0 and 1 at the start of treatment (Table 3). We confirmed the robustness of the results by considering the endpoint of maximal dyspnea ≥ 3 and also by imposing the condition that only patients with pre-treatment dyspnea < 2 are included. The biological mechanism underpinning the short-term interplay between existing cardiac disorders and the effect of radiation on lung toxicity is not clear cut and should be elucidated in the future. Furthermore, more detailed subgroup analyses involving different types of cardiac comorbidity, standardized across multiple institutions, have to be performed in a bigger future study, taking into account also the severity of the cardiac disorder type. Such analyses should be cast against the analyses of cardiac functions and parameters of lung cancer patients who have never been treated for cardiac pathologies in a cardiology department.

Choosing a suitable measure of RILT is likewise challenging, [6,32–35]. Dyspnea is a clinical outcome measured qualitatively, and can be brought about by non-radiotherapy related causes. A chest X-ray or a CT scan can be used as well, whereby radiation pneumonitis (1–6 months) and/or fibrosis (1–2 years) could be detected after lung irradiation, both of which cause dyspnea, [36]. However, in many cases radiation pneumonitis is clinically asymptomatic [6]. We therefore chose for dyspnea as a measure for RILT, since it is clinically the most relevant factor.

One study, [37], evaluated treatment-related cardiac toxicity in 64 breast cancer patients treated with sequential RCHT. None of the patients had a cardiovascular history or echocardiographic abnormalities at the start of RT. Left ventricular ejection fraction (LVEF) was measured at baseline as well as during follow-up. Twenty-one patients (32.8%) had a short-term decrease in LVEF, with a median decrease of 10%. These and our findings suggest that future research could concentrate on performing echocardiography before the start of radiotherapy to detect and/or quantify cardiac pathologies and to test whether asymptomatic heart problems are likewise associated with RILT in the same fashion as the symptomatic ones we examined. Another study, [38], did not find a statistically significant association between LVEF $\leq 50\%$ and radiation pneumonitis grade III/IV according to the Common Toxicity Criteria, although the reported odds ratio was 2.15; the overall incidence of radiation pneumonitis was however low: only 3 out of 130 patients (2.3%). Cardiac toxicity blood biomarkers for patients undergoing R(CH)T could also be considered, such as increases in troponin and brain natriuretic peptide, [39,40], but such studies have shown conflicting results, [31].

Patient's smoking status is a potential confounding factor, which could arguably provide an alternative explanation of our main findings. However, current smoking status was not found to be significant in univariate analysis. On the other hand, smoking status is strongly associated with the presence of cardiac disorders, but has also been shown to be protective of RILT, [41]. In general it is the cause of about 15% of all cases of heart failure, [42]. In our (training) dataset, approximately 22% of the patients with cardiac comorbidity were current smokers at the start of RT. We tested therefore for an association between cardiac comorbidity and smoking status, which we refuted. Similarly, we tested for the chemotherapy being a confounding factor and found that for the sub-

group of patients who received chemotherapy the odds ratio for developing RILT was virtually the same as for the patients in the original datasets.

The most commonly used predictive dosimetric parameter for RILT, the mean lung dose, was not found to be significant in our cohort. This is to be expected, as prescribed MLD levels had a relatively low mean with a small standard deviation (15.65 Gy \pm 4.4) due to the fact that MLD was used as a dose-limiting factor during radiotherapy planning. That is why there is arguably insufficient data to detect a stable upward sloping dose-toxicity response relationship, such as reported in the QUANTEC study, [3]. This relative stability of the MLD is actually quite advantageous for the clinical quality of our prediction models, as it gives the opportunity to find important factors for RILT that are not confounded by largely-varying levels of MLD.

The role of ACE (angiotensin-converting-enzyme) inhibitors could also be further investigated. They have been demonstrated to be both vascular protective and preventive of new acute cardiovascular events, and have been proven to play a central role in afterload reduction in patients with congestive heart failure and the improvement of cardiac-driven dyspnea complaints, [43,44]. The role of ACE inhibitors for RILT is not clear cut, however. While a decrease in RILT is reported in preclinical [45] and clinical [46] studies with ACE inhibitors, other investigations did not reveal a protective effect at the dose used for the treatment of hypertension [47].

The role of potential interdependency of cardiac comorbidity, pulmonary toxicity, and overall survival should be further investigated, as higher incidence of comorbidities in general could influence both endpoints. In their study, [48], Firat et al. found that comorbidity influenced overall survival when the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) was used to rate the comorbidity. However, this finding was not observed with the Charlson scale.

The existence of cardiac comorbidity at the start of high-dose RT of lung cancer patients is a major factor for the development of RILT (defined as maximal dyspnea ≥ 2 after radio(chemo)therapy. Moreover, cardiac comorbidity accounted for 43.4% of the incidence of RILT. These results suggest that (1) individualized treatment should be considered for patients with cardiac comorbidity and (2) excluding these patients from dose escalation studies will potentially allow for better targeting/escalation of the rest of the patients. It should further be investigated whether asymptomatic patients with cardiac comorbidity develop RILT to the same extent as the symptomatic ones.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2013.08.035>.

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