Radiotherapy and Oncology 109 (2013) 100–106

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

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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ARTICLE INFO

Article history:
Received 30 May 2013
Received in revised form 21 August 2013
Accepted 25 August 2013
Available online 14 September 2013

Keywords:
Lung cancer
Cardiac comorbidity
Radiotherapy
Dyspnea
Radiation-induced lung toxicity

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 $\geqslant 2$ 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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http://dx.doi.org/10.1016/j.radonc.2013.08.035

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 $\leqslant$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 $\geqslant$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* $\geqslant$*2*, our main clinical hypothesis being that we reject such independence;
(2) *the independence of cardiac comorbidity and post-treatment dyspnea* $\geqslant$*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* $\geqslant$*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 α/β = 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 $\geqslant$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 $\geqslant$*2*

The odds ratio of post-RT dyspnea $\geqslant$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