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Original article

Modeling the risk of radiation-induced lung fibrosis: Irradiated heart tissue is as important as irradiated lung

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ABSTRACT

Purpose: We used normal tissue complication probability (NTCP) modeling to explore the impact of heart irradiation on radiation-induced lung fibrosis (RILF).
Materials and methods: We retrospectively reviewed for RILF 148 consecutive Hodgkin lymphoma (HL) patients treated with sequential chemo-radiotherapy (CHT-RT). Left, right, total lung and heart dose–volume and dose–mass parameters along with clinical, disease and treatment-related characteristics were analyzed. NTCP modeling by multivariate logistic regression analysis using bootstrapping was performed. Models were evaluated by Spearman *Rs* coefficient and ROC area.
Results: At a median time of 13 months, 18 out of 115 analyzable patients (15.6%) developed RILF after treatment. A three-variable predictive model resulted to be optimal for RILF. The two models most frequently selected by bootstrap included increasing age and mass of heart receiving >30 Gy as common predictors, in combination with left lung V5 (*Rs* = 0.35, AUC = 0.78), or alternatively, the lungs near maximum dose $D_{2\%}$ (*Rs* = 0.38, AUC = 0.80).
Conclusion: CHT-RT may cause lung injury in a small, but significant fraction of HL patients. Our results suggest that aging along with both heart and lung irradiation plays a fundamental role in the risk of developing RILF.
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Thoracic irradiation may be responsible for late-phase subclinical lung radiation-induced injuries such as fibrosis, with radiological lung density changes detectable on radiographic studies or by computed tomography [1]. Radiation-induced lung fibrosis (RILF), even if asymptomatic, may lead to a progressive and irreversible decline in pulmonary function and its prediction is crucial for the long-term quality of life of cancer survivors [2]. The incidence and nature of RILF are likely to be determined by multiple interrelated factors. Although the pathophysiology of the underlying mechanisms is still not completely understood, many studies have shown an overproduction of pro-inflammatory/pro-fibrogenic cytokines, including TGF-β and IL-6, during thoracic irradiation. TGF-β has been widely studied as the main responsible for the activation of fibrotic reaction after lung irradiation [3] as well as after local irradiation of the heart [4]. Also, effects in lung tissue adjacent to the irradiated area (abscopal out-of-field effects) have been observed and attributed to inflammatory-inducing cytokine cascades [1]. Recent preclinical and clinical studies [5–8] suggest that heart irradiation may be critical to understanding lung toxicity following radiotherapy (RT). Therefore, the cardio-pulmonary system should be considered in its entirety to improve the accuracy of RILF predictive model.

In the last years many efforts have focused on the determination of clinically useful indicators (dosimetric, physical and biological parameters) to discriminate between patients at high and low risk of both acute and late pulmonary complications after thoracic RT [9–13]. Recent data [14] suggest that relatively low doses (5–15 Gy) to large volumes of lung are more predictive for acute radiation pneumonitis than the traditionally considered volumes receiving more than 20 or 30 Gy.

The aim of the present study is to investigate clinical and dosimetric predictors of late RILF in Hodgkin lymphoma (HL) survivors treated with sequential chemo-radiotherapy.

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Radiotherapy of HL involving the mediastinum often entails a significant irradiation of heart volume in addition to lungs. As such, these patient cohorts may play a pivotal role in modeling heart–lung complications after thoracic irradiation. Given the multivariate nature of heart–lung complications and the corresponding dataset, we adopted a data-driven multivariate approach for normal tissue complication probability (NTCP) modeling for RILF prediction. Besides dose–volume histograms (DVHs), to provide a better representation of the number of cells damaged by radiation, dose–mass histograms (DMHs) were analyzed. Particularly, DMHs may be more appropriate than DVHs considering the variable alveolar cell density in lungs.

Materials and methods

Patient dataset

Clinical and dosimetric records of 148 HL patients from an inter-institutional dataset (117 patients treated at University Federico II of Naples and 31 patients at S. Camillo-Forlanini Hospital in Rome) were retrospectively reviewed. The study eligibility criteria include: evaluation of pulmonary status before chemotherapy (CHT), after CHT and before RT, and periodically after RT; no pre-treatment lung disease; a follow-up of at least 12 months; and availability of 3-dimentional dose maps.

Patients and treatment characteristics have been described in detail in [9]. Briefly, all patients received post-CHT supradiaphragmatic involved-site RT between 2001 and 2013. Patients were treated with CT-based 3D-CRT with a median total dose of 30.6 Gy (range, 20.8–45.0 Gy) in daily fractions of 1.5–1.8 Gy. When needed, the forward intensity modulated technique was employed [15] to improve dose uniformity. Only three patients were treated with TomoTherapy technique [16]. Calculation algorithms that correct for the presence of heterogeneous tissues were always applied.

The left and right lung tissues and the whole heart were retrospectively contoured on planning CTs following RTOG 1106 and heart atlas contouring guidelines [17,18]. Along with the left and right lungs, the total lung was also considered.

Pulmonary evaluation and follow-up

All patients have been monitored for lung disease/injury as part of the clinical routine during CHT, after CHT and before RT, and after RT. Baseline and follow-up evaluations consisted of history and physical examination along with periodic total body CT scans [9]. A diagnosis of RILF was based on the presence of radiological lung density changes evaluated on follow-up CT scans using the planning CT as baseline comparison. The RTOG late pulmonary toxicity scoring system [19] was used for grading. Any pretreatment lung disease or any CHT-related lung toxicity along with comorbidities were recorded. Radiation-induced cardiac toxicity was also recorded.

Time to RILF was computed from the beginning of RT to the first radiological signs. Patients were followed up for a median time of 67 months (range 13–140 months).

Dosimetric analysis

For each patient, individual DICOM RT plans (CT scans, doses and contoured organs) were converted into Matlab-readable format (MathWorks, Natick, MA) using the CERR (Computational Environment for Radiotherapy Research) software [20] and DVHs from planning data were extracted. DMHs were computed following the method described by Forster et al. [21]. Accordingly, the volume of each CT voxel was weighted by its local mass density estimated from Hounsfield units. An in-house developed library for Matlab was used for this purpose. For each patient and each organ, the mean and standard deviation of the dose–mass density function (DMH/DVH) were calculated.

DVH and DMH metrics were extracted for modeling: the minimum dose to *x%* highest dose–volume (*Dx*); the percentage volume or mass receiving at least *x* dose (*Vx* or *Mx*); the absolute volume or mass receiving at least *x* dose (AV*x* or AM*x*). Of note, *Dx* included $D_{2\%}$ and $D_{50\%}$, that is the near-maximum and the median absorbed dose [22].

The Atlas of Complication Incidence (ACI) method was adopted for reporting toxicity and dose–volume data [23]. For each organ, ACI maps and the associated probability maps for RILF endpoint were generated, as described by Jackson et al., using all patients DMH and DVH.

Table 1
Clinical variables and correlation coefficient (*Rs*) with RILF incidence.

Characteristics			Univariate analysis	
			R_s	*P*-value
Continuos variables		Median (range)		
Age (*y*)	*N* (%)	28 (13–71)	.204	.029
13–25	40 (34.8)			
25–35	41 (35.6)			
35–45	17 (14.8)			
45–55	8 (7.0)			
55–65	6 (5.2)			
65–71	3 (2.6)			
Total lung volume (cm^3)		2678.4 (1363.1–5729.4)	−.103	.273
Left lung volume (cm^3)		1254.2 (732.0–3048.0)	−.153	.103
Right lung volume (cm^3)		1480.2 (664.1–2792.5)	−.079	.402
Heart volume (cm^3)		534.9 (336.0–1459.4)	−.028	.762
Total lung mass (g)		944.0 (598.3–1442.7)	−.111	.237
Left lung mass (g)		436.8 (231.7–764.1)	−.163	.082
Right lung mass (g)		498.9 (308.6–934.8)	−.032	.731
Heart mass (g)		540.4 (344.2–1510.1)	−.030	.748
Categorical variables		*N* (%)		
Gender				
Female		62 (53.9)		
Male		53 (46.1)	−.062	.509
Radiation induced heart disease				
None		35 (30.4)	.008	.935
Yes		80 (69.6)		
Histology				
Nodular sclerosis		85 (73.9)		
Mixed cellularity		29 (25.2)		
Lymphocyte-rich-classical		1 (0.9)		
Stage				
0 (I–II)		89 (77.4)		
1 (III–IV)		26 (22.6)	−.061	.516
Radiation therapy dose				
<30 Gy		4 (3.5)		
30–31 Gy		67 (58.3)		
32–33 Gy		29 (25.2)		
35–36 Gy		12 (10.4)		
>36 Gy		3 (2.6)	.167	.075
Chemotherapy regimen				
ABVD		44 (38.3)		
VEBEP		68 (59.1)		
BEACOPP		3 (2.6)	.010	.911
Risk factors				
None		84 (73.0)		
Yes		31 (27.0)	.021	.834
Smokers		12 (10.4)		
Diabetes		2 (1.7)		
Hypertension		6 (5.2)		
Cardiac disease		12 (10.4)		

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