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Radiobiological modeling of radiation damage to the cardio-pulmonary system and the Hodgkin lymphoma paradigm

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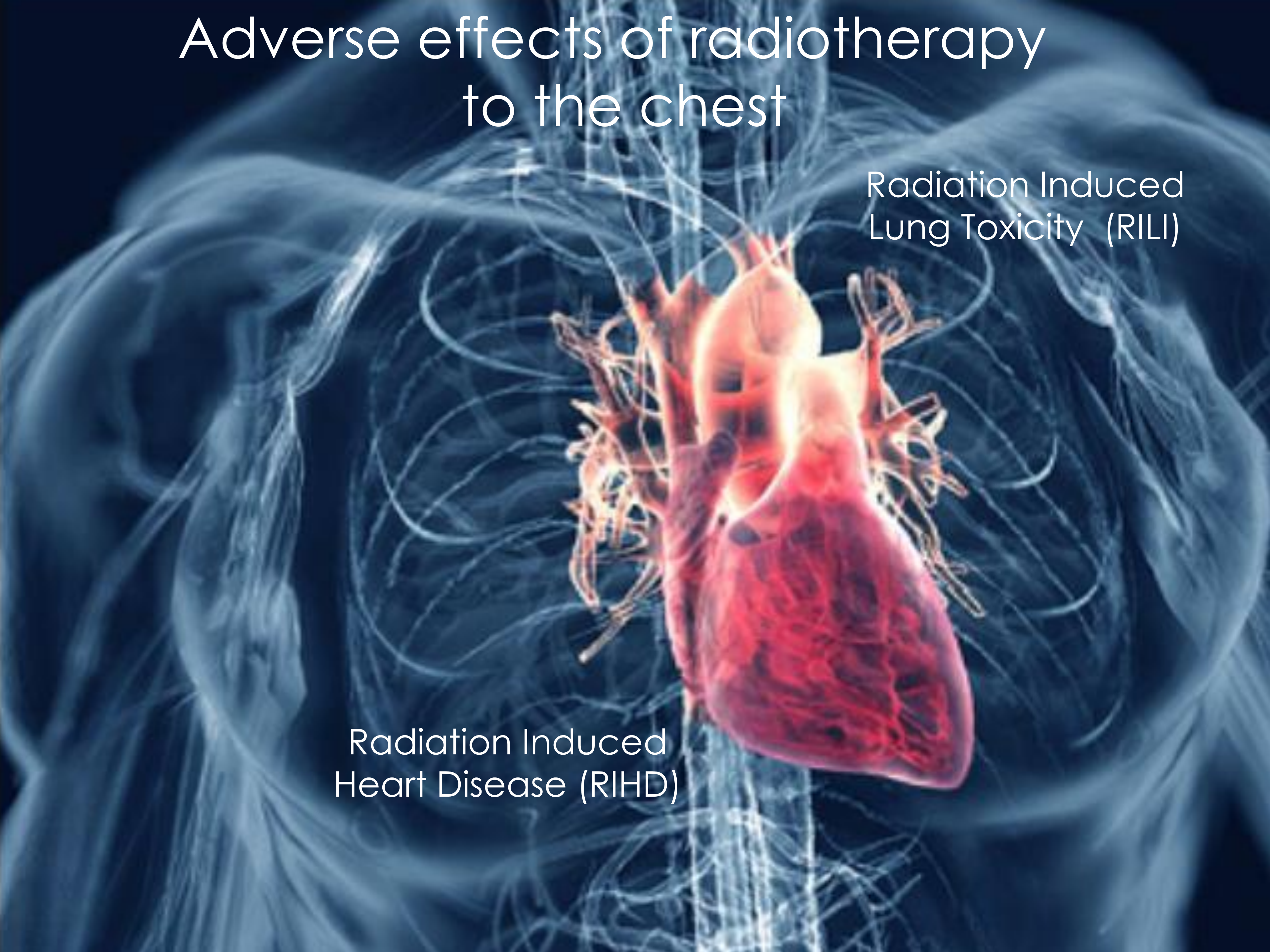
In a modern radiotherapy setting, radiobiological models potentially play an essential role and normal tissue complication probability (NTCP) modeling may help to minimizes side effects for individual patients.

Adverse effects of radiotherapy to the chest



Experimental studies in rats showed that irradiation of heart, lungs, or both independently induces specific cardiac dysfunction and associated pulmonary vascular damage, in a negative synergy

van Luijk P, IJROBP 2007, Ghobadi G, IJROBP 2012

However, clinical studies in radiotherapy patients are necessary in order to link these results to humans

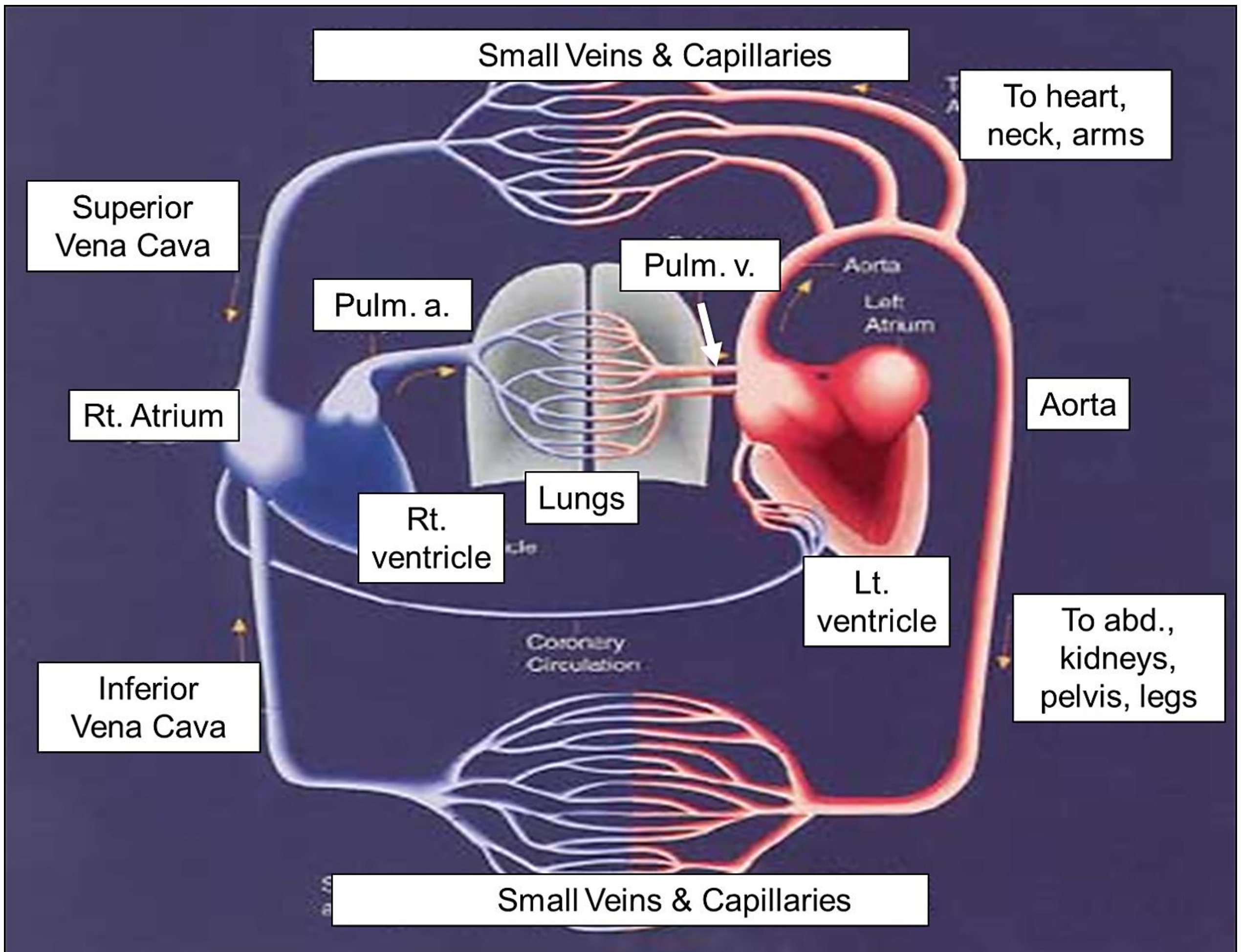
Studied patients population for RIHD & RILI

- Hodgkin's lymphoma
  Heidenreich J Clin Oncol. 2007, Eriksson R&O 2000, Fox IJROBP 2012
- Breast cancer
  Darby N Engl J Med. 2013 , Lind IJROBP 2006
- Lung cancer
  Hope, IJROBP 2006, Dang Acta Oncol 2013
- Esophageal cancer
  Konski R&O 2012, Wei IJROBP 2006 , Gayed I, Int J Cardiovasc Imaging 2009

Lung and heart have been historically considered separately in radiation induced side effects study

but….

Organs' "partnership" should be considered



For the proposition

LUNG CANCER PATIENTS

- Co-irradiation of heart enhances the risk and severity of RILI

  Hope, IJROBP 2006; Huang, Acta Oncol 2011

- Cardiac comorbidity is an independent risk factor for RILI

  Nalbantov, R&O 2013

- Radiation-induced fibrosis of the lung and its vessels may affect cardiac functions

  Adams, Crit Rev Oncol Hematol 2003

Against the proposition

- The incorporation of heart parameters did not significantly improve RILI risk prediction

  Tucker, Acta Oncol 2014

Clinical Radiobiology

Our basic idea is to perform a “clinical” radiation biology studies through the development of robust predictive Normal Tissue Complication Probability (NTCP) models

Modeling:
Data driven approach to NTCP

We have followed a multivariate modeling approach of radio-induced complication risk for heart-lung system without making a-priori hypotheses.

"A data-driven and exploratory approach to NTCP analyses allows for consideration of a wider range of dosimetric, spatial, and clinical-biological covariates within the same model-building exercise"

Deasy and El Naqa, Radiation Oncology Advances , Springer 2008

Modeling steps

1. Model size estimated by bootstrapping
2. Model regression coefficients estimated using forward selection on multiple bootstraps sample (the most frequently selected model is the optimal one)
3. Model predictive power was quantified by use of Spearman's coefficient Rs
4. AUC of ROC curve used to evaluate the discriminating ability of model fit

Application of data-driven multivariate NTCP modeling exercise

- Input variables: lung + heart dosimetric parameters + clinical data
- Logistic regression model:

$$NTCP = \frac{1}{1+e^{-g(x)}} \qquad g(x) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_n x_n$$

$x_1, x_2 \ldots\ldots x_n$ input variables,
$\beta_0, \beta_1 \ldots\ldots \beta_n$ the corresponding regression coefficients

$$LLH = \sum_{yi=1} \ln NTCP + \sum_{yi=0} \ln(1 - NTCP)$$

- Data analysis performed by CERR+DREES open source packages

El Naqa, Phys Med Biol 2006


MEB

Traditional dose-volume based NTCP models

Lyman-Kutcher-Burman

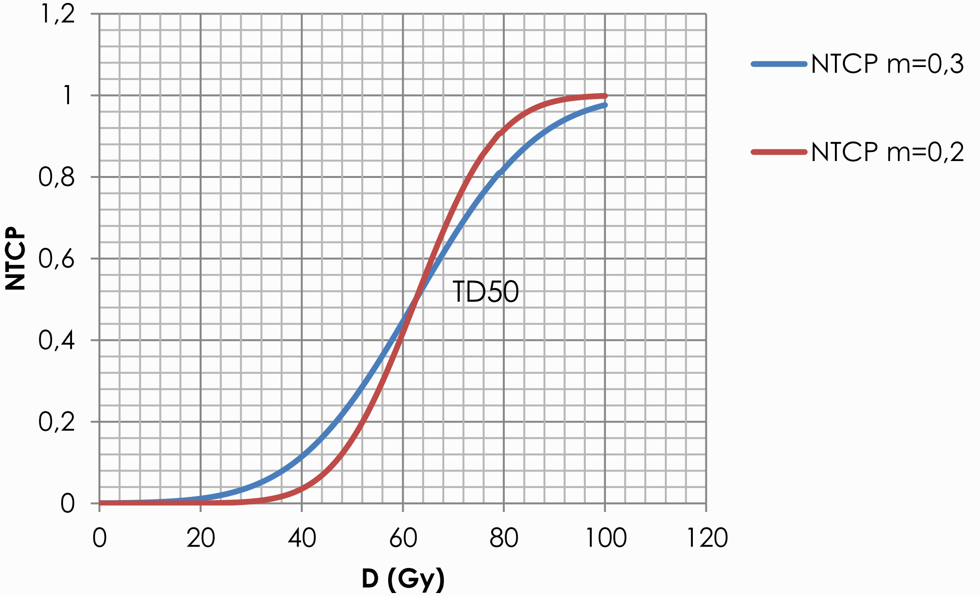
Kutcher and Burman, IJROBP 1989

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{u} e^{-t^2/2} dt$$

$$u = \frac{D - \mathrm{TD50}(V)}{m \times \mathrm{TD50}(V)}$$

$$\mathrm{TD50}(V) = \mathrm{TD50}(1)/V^n$$

$$V = \Sigma_i (D_i/D)^{1/n} \Delta V_i$$



(3 parameters: TD50(1), m, n)

Why Hodgkin's lymphoma survivors

Compared with other thoracic malignancies, Hodgkin lymphoma (HL) patient population is generally characterized by:

- High cure rates (90%) and prolonged survival

Late chronic toxicities, including cardiovascular disease and lung injuries, are of major concern in patients treated for HL

- lower median age
- better performance status
- different smoking history
- different chemotherapy regimens
- lower radiation doses prescribed
- Intact lungs

These patient cohorts may play a pivotal role in modeling heart-lung complications after thoracic irradiation

Our database

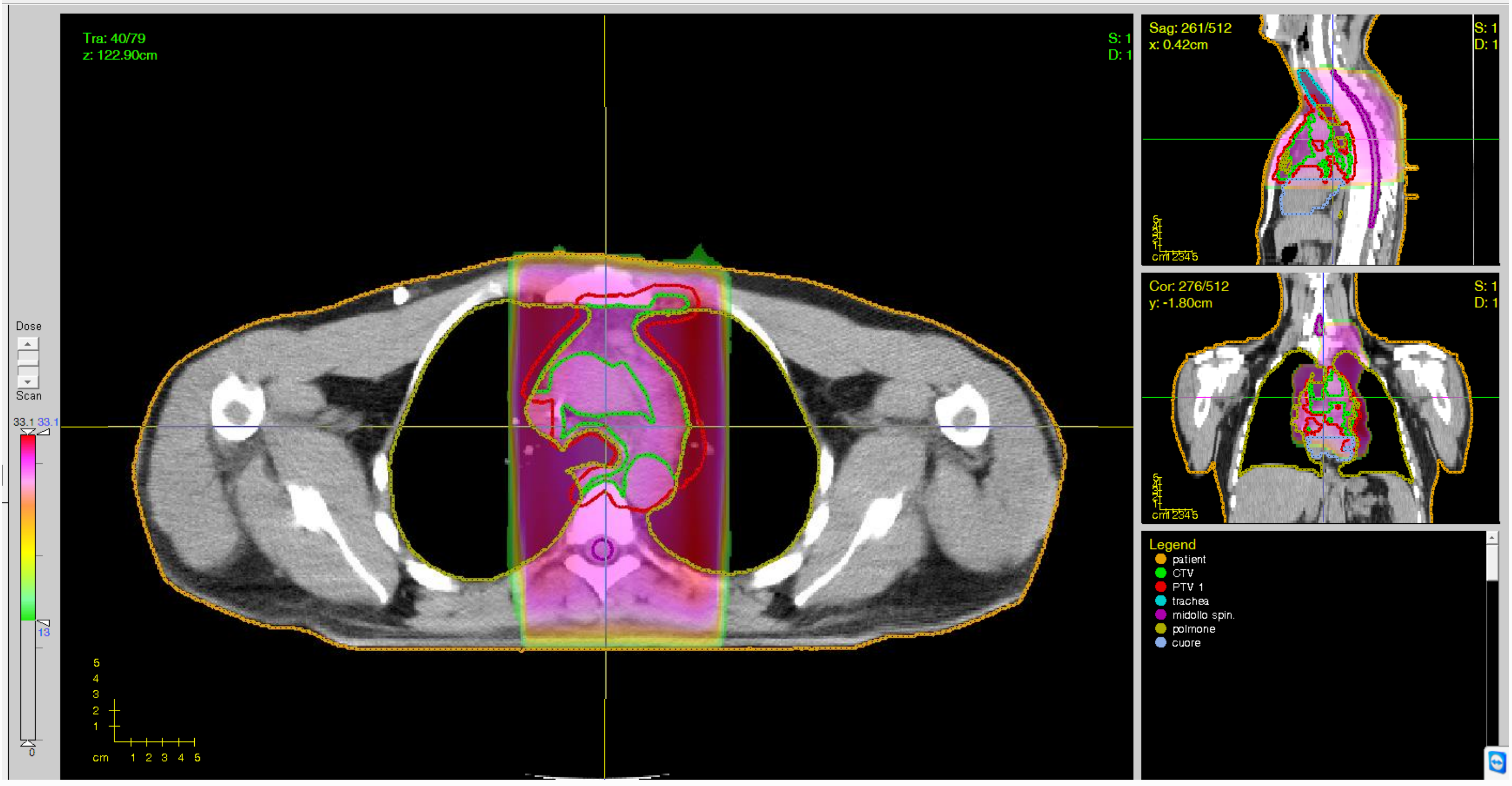
Consecutive HL patients treated with chemotherapy and subsequent supradiaphragmatic radiation therapy (2001-2013)

Radiation Oncology Department of Federico II University School of Medicine of Naples (117 pts)

+

S. Camillo-Forlanini Hospital in Rome (31 pts)

A representative patient



Patient characteristics

- Median total dose: 30.6 Gy (range 20.8-45.0 Gy)
- AP-PA fields with 6-20 MV photon beams
- Median Age: 28 years (13-71 years)
- Gender : 54% female, 46% male
- Chemotherapy: 38% ABVD, 59% VEBEP, 3% BEACOPP

Inclusion criteria

- Availability of cardiac and lung evaluation before CHT, after CHT before RT, after RT
- Availability 3-dimensional treatment planning data (extraction of dosimetric parameters)
- follow-up at least:
  - ❖ 3 years endpoint RIHD
  - ❖ 2 years endpoint RILI

Endpoint: RIHD ↔ Asymptomatic Valve Dysfunction

- A wide spectrum of adverse effects on the cardiovascular system (pericarditis, cardiomyopathy, coronary artery disease, valvular disease)
- The manifestations of RIHD (most often become clinically apparent several years (~10) after irradiation
- In the spectrum of RIHD, asymptomatic valve defects may be regarded as an early predictor and/or precursor of clinically relevant cardiac dysfunction

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Morbidity of mediastinal irradiation

Dosimetric predictors of asymptomatic heart valvular dysfunction follow mediastinal irradiation for Hodgkin's lymphoma

Laura Cella[a,b], Raffaele Liuzzi[a,b], Manuel Conson[b], Gabriella Torre[b], Michele Caterino[b], Nicol Marco Picardi[c], Luigi Camera[b], Raffaele Solla[a,b], Antonio Farella[b], Marco Salvatore[b], Roberto
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PLOS | ONE

Complication Probability Models for Radiation-Induced Heart Valvular Dysfunction: Do Heart-Lung Interactions Play a Role?

Laura Cella[1,2*], Giuseppe Palma[1], Joseph O. Deasy[3], Jung Hun Oh[3], Raffaele Liuzzi[1,2], Vittoria D'Avino[1], Manuel Conson[1,2], Novella Pugliese[4], Marco Picardi[4], Marco Salvatore[2], Roberto Pacelli[1,2]
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biology ● physics
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Clinical Investigation: Lymphoma

Multivariate Normal Tissue Complication Probabil Modeling of Heart Valve Dysfunction in Hodgkin Lymphoma Survivors

Laura Cella, PhD,*,† Raffaele Liuzzi, PhD,*,† Manuel Conson, MD,*,† Vittoria D'Avino, MSC,* Marco Salvatore, MD,† and Roberto Pacelli, MD*
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Acta Oncologica, 2015; Early Online: 1–8
informa healthcare

ORIGINAL ARTICLE

Predicting radiation-induced valvular heart damage

LAURA CELLA[1,2], JUNG HUN OH[3], JOSEPH O. DEASY[3], GIUSEPPE PALMA[1], RAFFAELE LIUZZI[1,2], VITTORIA D'AVINO[1], MANUEL CONSON[1,2], MARCO PICARDI[4], MARCO SALVATORE[2] & ROBERTO PACELLI[1,2]
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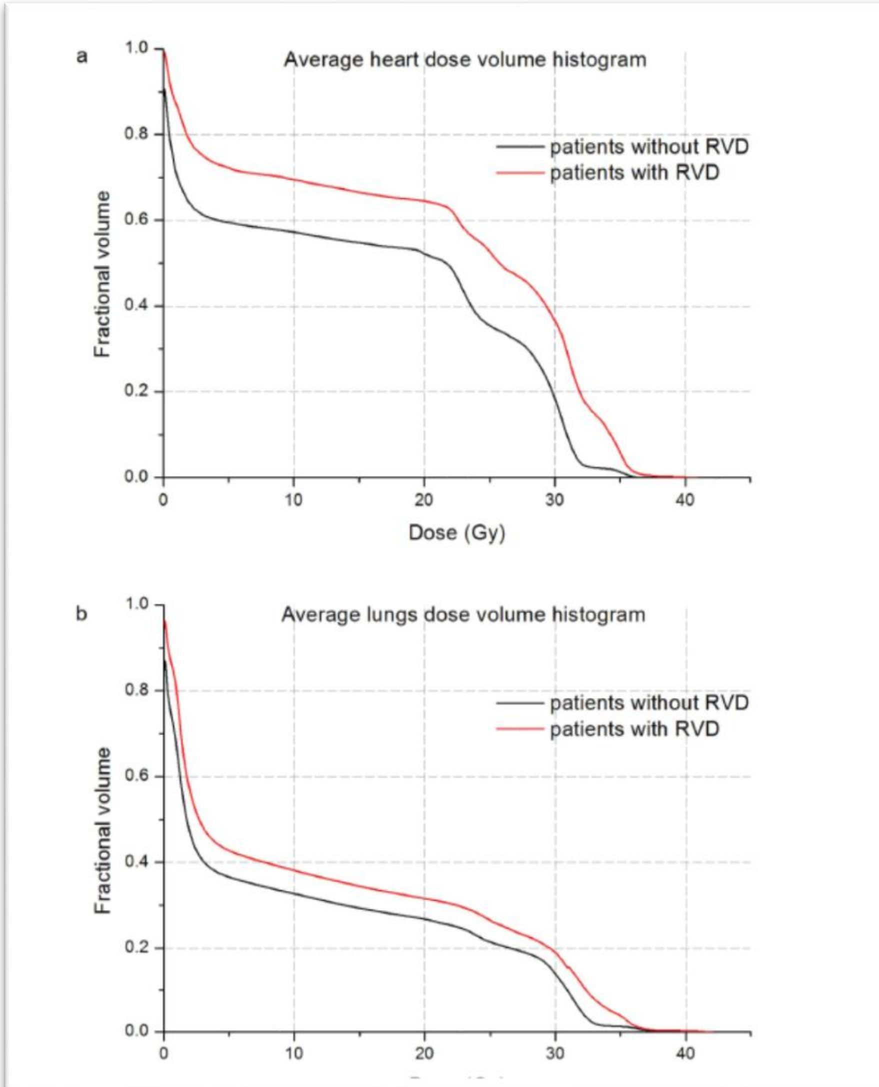
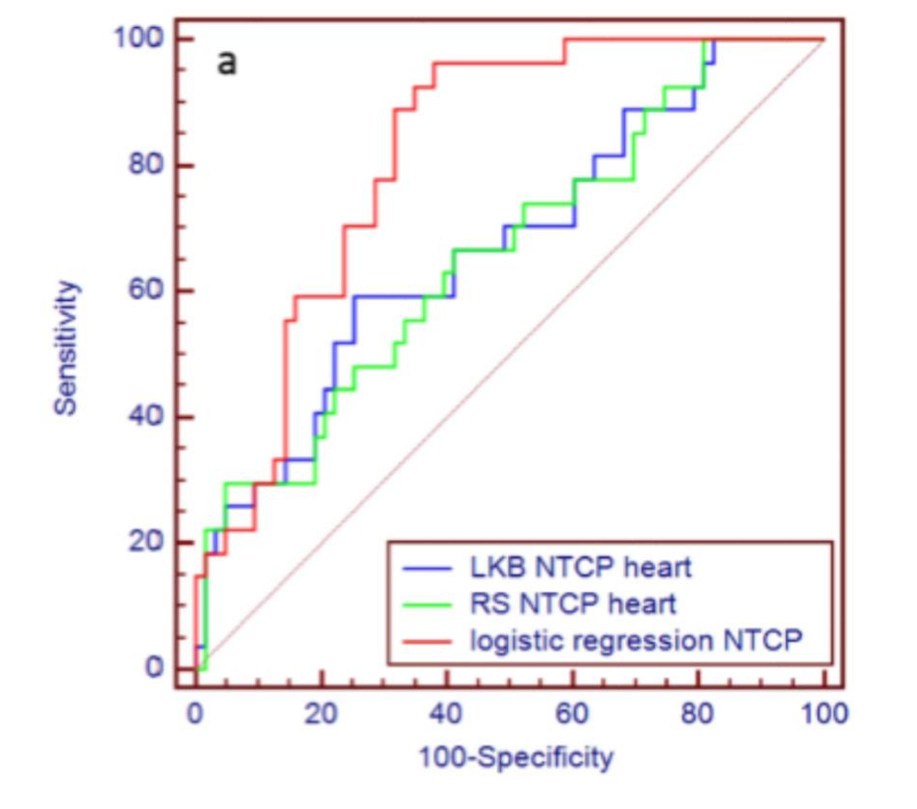
Heart → RESULTS:

- 30% of patients manifested at least one kind of RVD (mild or moderate) at a median time of 55 months (range, 12-92)
- Higher incidence of left-sided RVD(64%)
- The risk of radiation-induce RVD cannot be modeled using NTCP models only based on heart dose-volume distribution (LKB)
- An improved performance can be obtained with the inclusion of clinical variables such as heart and lung volume sizes

Cella, R&O 2011; Cella, IJROBP 2013; Cella, PlosOne 2014

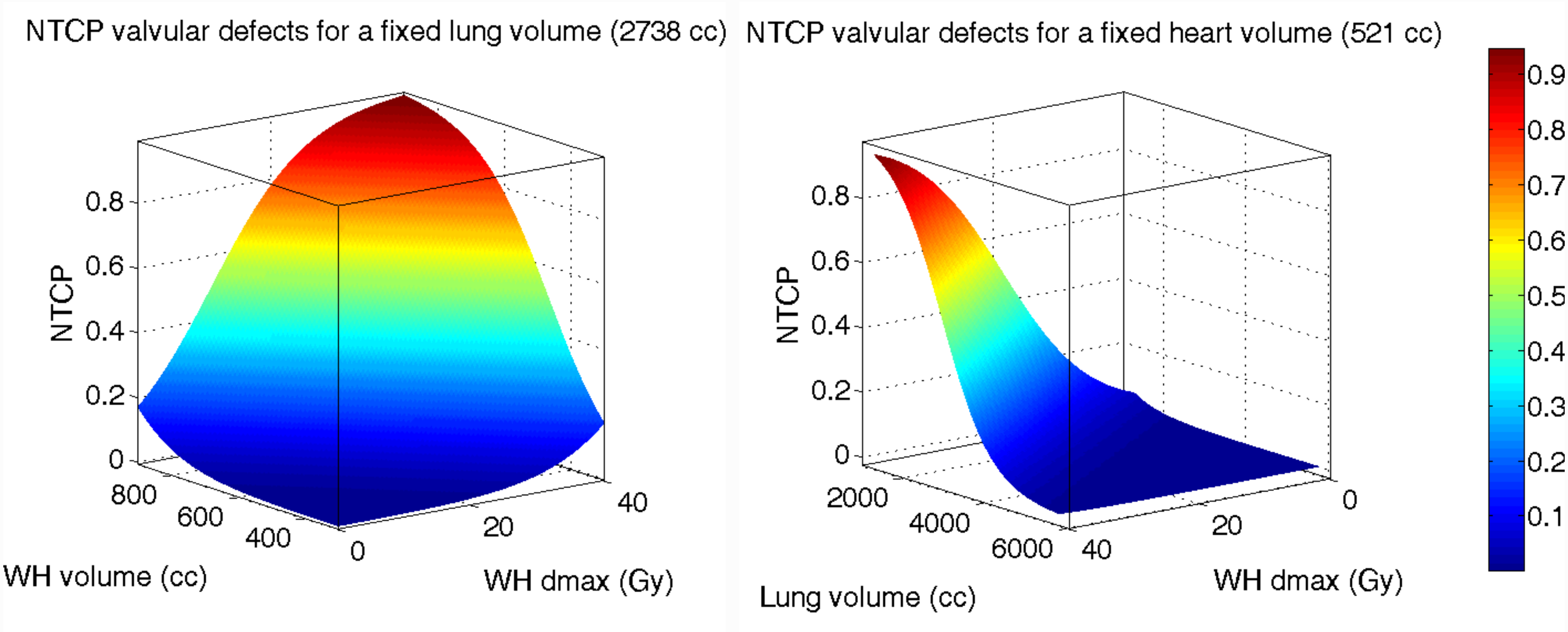


AUC(log)= 0.8
AUC(LKB or RS)= 0.7

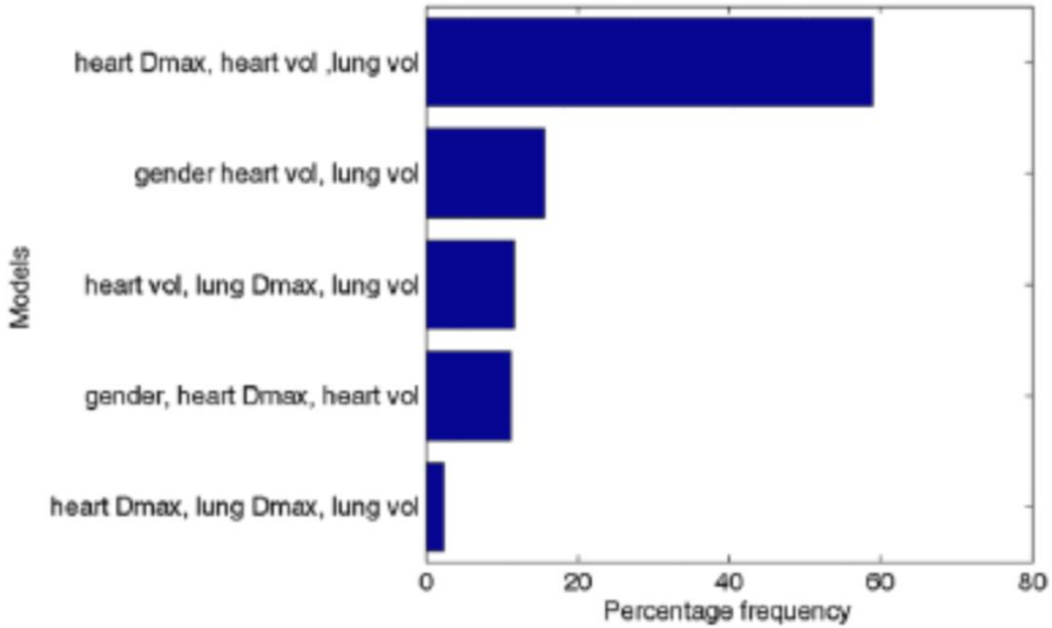


Cella, PlosOne 2014

NTCP (log)=
f(HeartDmax(Gy), Heart vol(cc), lung vol (cc))



Cella, IJROBP 2013



Model	Parameter	Estimated coefficient	SE	P value	OR
Model 1					
	Dmax (Gy)	0.1430	0.0751	.043	1.150
	Heart volume (cc)	0.0095	0.0036	.020	1.010
	Lung volume (cc)	–0.0017	0.0006	.011	0.998
	constant	–5.65			

Improved method for variable selection

- Least absolute shrinkage and Selection operator (LASSO)

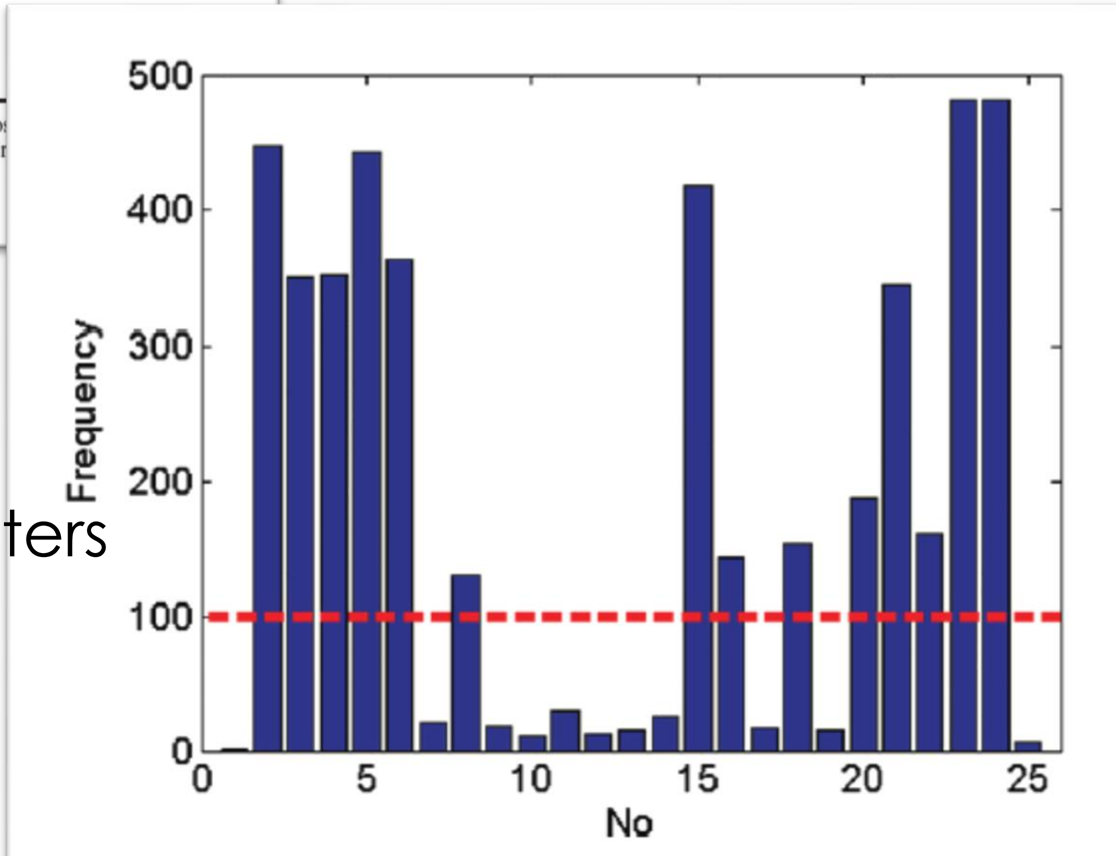
$$\max_{(\beta_0,\beta)\in R^{p+1}} \left[\sum_{i=1}^{n} r_i \log p(x_i) + (1-r_i)\log(1-p(x_i)) - \lambda \sum_{k=1}^{m} |\beta_k| \right]$$

Tibshirani (1996), "Regression Shrinkage and Selection via the Lasso"

- Reduce the number of predictors in a generalized linear model.
- Identify important predictors.
- Select among redundant predictors
- Produce shrinkage estimates with potentially lower predictive errors

No	Variable	No	Variable	No	Variable
1	D5 left lung	11	D95 lungs	21	**AV30 heart**
2	**D15 left lung**	12	V30 lungs	22	**Dmax heart**
3	**D25 left lung**	13	V35 lungs	23	**Heart volume**
4	**D95 left lung**	14	AV35 lungs	24	**Left lung volume**
5	**Dmax left lung**	15	**Dmax lungs**	25	Right lung volume
6	**D25 right lung**	16	**D10 heart**	26	Lungs volume
7	V30 right lung	17	D35 heart		
8	**Dmax right lung**	18	**V30 heart**		
9	D5 lungs	19	AV20 heart		
10	D20 lungs	20	**AV25 heart**		

Abbreviations: AVX = absolute volume receiving x Gy, Dmax = maximum do[...]
dose to x% highest dose volume, Vx = percentage volume receiving x Gy, Fr[...]
variables are in bold.



Important variables:
Left lung dose parameters

Cella, Acta Oncol 2015

Endpoint: RILI ↔ symptomatic and radiological signs

- RT induces late-phase subclinical injury → fibrosis detectable by CT
- Fibrosis, even if asymptomatic, may progress over several years and decrease lung compliance

Marks, IJROBP 2010

Acta Oncologica, 2013; Early Online: 1–7

informa healthcare

ORIGINAL ARTICLE

Pulmonary damage in Hodgkin's lymphoma patients treated with sequential chemo-radiotherapy: Predictors of radiation-induced lung injury

LAURA CELLA[1,2], RAFF
ANGELA DI BIASE[2], MA
MARCO SALVATORE[2] &

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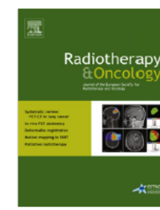

Original article

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

Laura Cella [a,*], Vittoria D'Avino [a], Giuseppe Palma [a], Manuel Conson [a,b], Raffaele Liuzzi [a], Marco Picardi [c], Maria Cristina Pressello [d], Genoveva Ionela Boboc [e], Roberta Battistini [f], Vittorio Donato [e], Roberto Pacelli [a,b]

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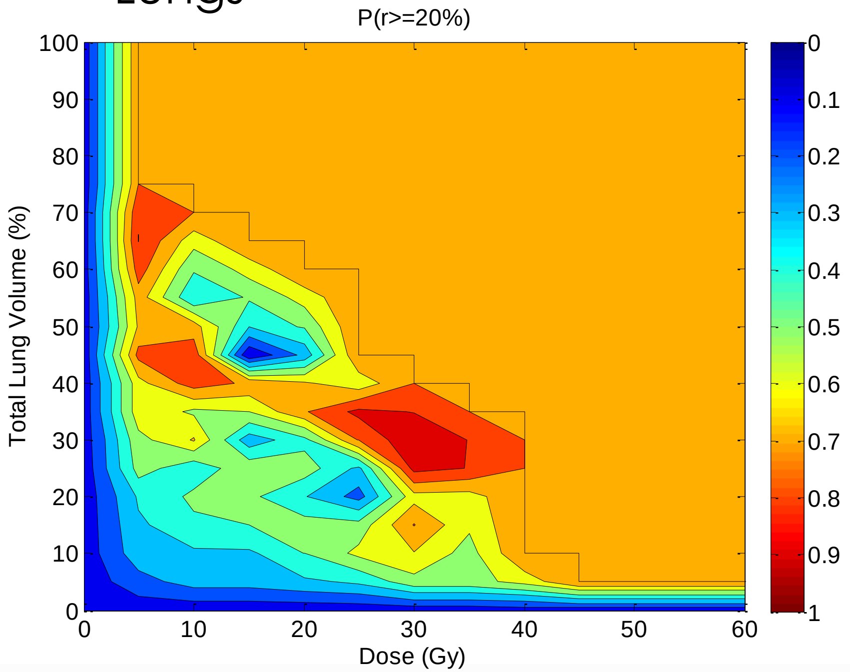
Lung → RESULTS

- 16% of patients developed radiological changes on CT (any grade of RILI) at a median time of 13 months (range, 9-83)
- 9 patients were symptomatic (50%)
- An area of high probability for RILI incidence can be seen in both lungs and heart DVHs
- Aging along with heart and lungs irradiation plays a fundamental role in the risk of RILI

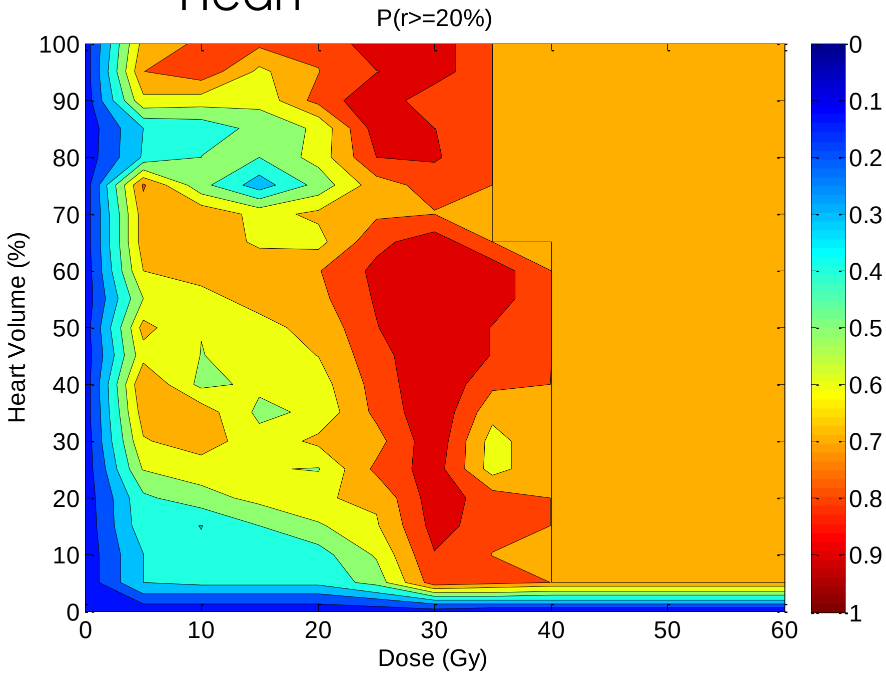
Cella, Acta Oncol 2013; Cella, R&O 2015

Probability maps

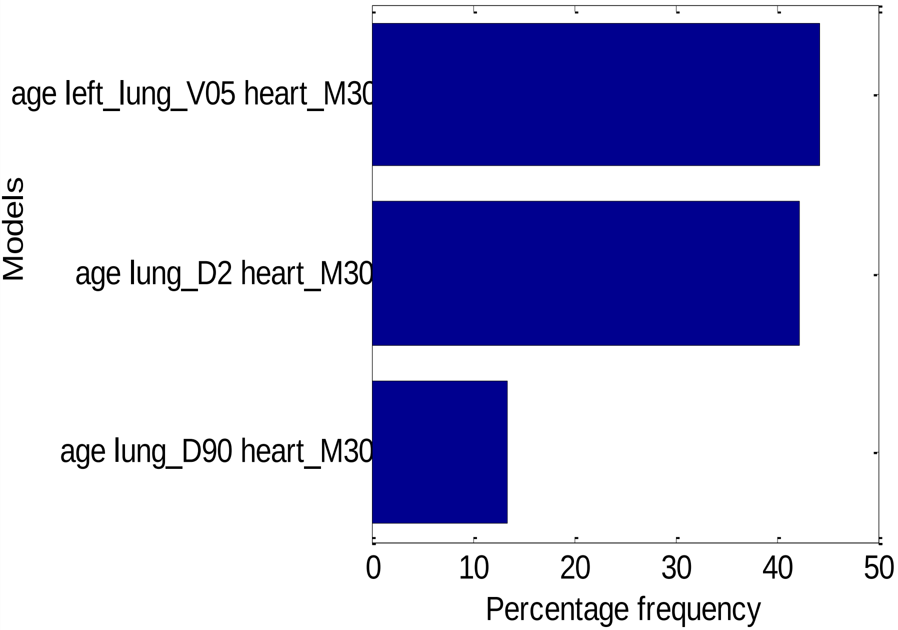
Lungs



Heart

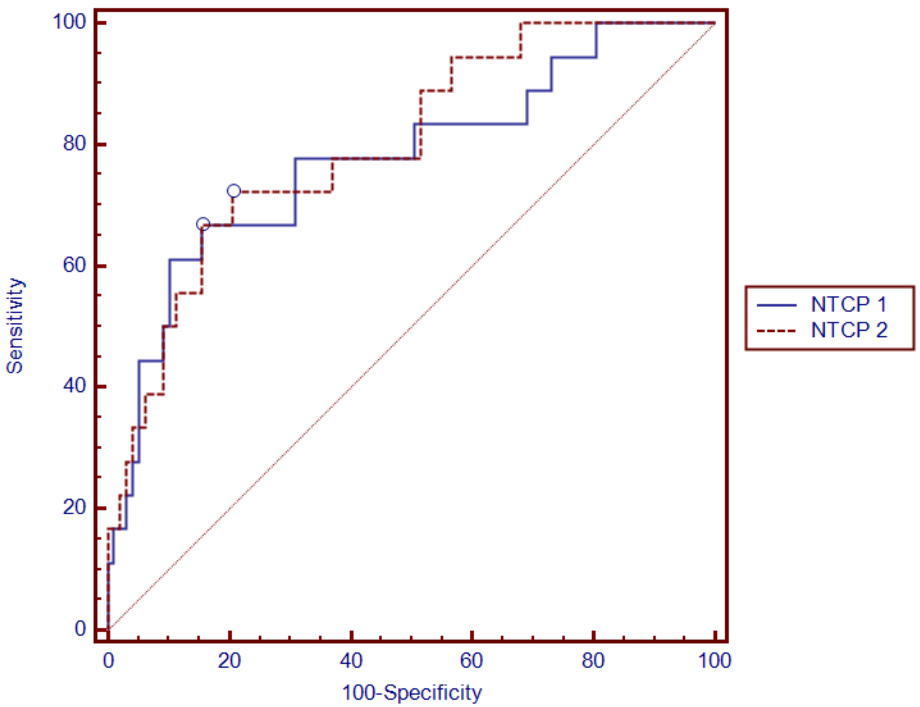


Cella, R&O 2015



Most frequently selected models: competitive models!!!

AUC1≈ AUC2 = 0.8



Cella, R&O 2015

Model 1				
Parameter	Estimated coefficient	SE	*p*-Value	OR
Age	.062	.022	.006	1.064
Heart M30 (%)	.026	.009	.004	1.027
Left lung V5 (%)	.027	.016	.094	1.027
Constant	−5.51			
Performance				
Rs	.347			
AUC (95% CI)	.78 (.65–.91)			
Discrimination value	.20			
Calibration slope	.97 ± .11			
Calibration intercept	.004 ± .0[illegible]			

Model 2				
Parameter	Estimated coefficient	SE	*p*-Value	OR
Age	.068	.023	.003	1.070
Heart M30 (%)	.022	.010	.026	1.022
Lung $D_{2\%}$ (Gy)	.115	.084	.171	1.122
Constant	−8.148			
Performance				
Rs	.376			
AUC (95% CI)	.80 (.69–.91)			
Discrimination value	.18			
Calibration slope	1.02 ± .11			
Calibration intercept	−.004 ± .022			

CONCLUSIONS

1)The importance of lung irradiation and lung volume size in predicting heart toxicity risk.
2) The influence of the left lung irradiation on radiation-induced lung fibrosis
3) The role of heart irradiation on radiation-induced lung fibrosis
4) non-homogeneous lung radiosensitivity

These results obtained in a clinical setting are consistent with those obtained from the Groningen group in animal studies.

The patho-physiological mechanisms of heart-lung interaction in the evolution of late toxicity after thoracic irradiation are still uncertain.

- The obtained models are phenomenological and as such they are consistent with the available data, but the underlying biological mechanisms and causal relations are essentially unknown.

- In several cases, phenomenological models may be an important source of hypothesis-generating information guiding new research

Van der Schaaf et al, Int J Radiat Oncol Biol Phys 2015

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