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

Laura Cella
In a modern radiotherapy setting, radiobiological models potentially play an essential role and normal tissue complication probability (NTCP) modeling may help to minimize side effects for individual patients.
Adverse effects of radiotherapy to the chest

Radiation Induced Lung Toxicity (RILI)

Radiation Induced Heart Disease (RIHD)
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.


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

• Breast cancer

• Lung cancer
  Hope, IJROBP 2006, Dang Acta Oncol 2013

• Esophageal cancer
Lung and heart have been historically considered separately in radiation induced side effects study but....
Organs’ “partnership” should be considered
For the proposition

- 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:

\[
NTCP = \frac{1}{1+e^{-g(x)}} \\
\text{where} \\
g(x) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n
\]

- Data analysis performed by CERR+DREES open source packages

\[
LLH = \sum_{y_i=1} \ln NTCP + \sum_{y_i=0} \ln (1 - NTCP)
\]

El Naqa, Phys Med Biol 2006
Traditional dose-volume based NTCP models

Lyman-Kutcher-Burman
Kutcher and Burman, IJROBP 1989

\[
\text{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{u} e^{-t^2/2} dt
\]

\[
u = \frac{D - \text{TD50}(V)}{m \times \text{TD50}(V)}
\]

\[
\text{TD50}(V) = \text{TD50}(1)/V^n
\]

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

(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
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, Nicolò Marco Picardi c, Luigi Camara d, Raffaele Solla a,b, Antonio Farella e, Marco Salvatore f, Roberto

*Institute of Biostructures and Bioimaging, National Research Council of Italy (CNR), Naples, Italy. † Department of Diagnostic Imaging and Radiation Oncology of Biochemistry and Medical Biotechnology, Federico II University School of Medicine, Naples, Italy.

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

Laura Cella1,2, Giuseppe Palma1, Joseph O. Deasy3, Jung Hun Oh3, Raffaele Liuzzi1,2, Vittoria D’Avino1, Manuel Conson1,2, Novella Pugliese4, Marco Picardi5, Marco Salvatore6, Roberto Pacelli1,2

1 Institute of Biostructures and Bioimaging, National Council of Research (CNR), Naples, Italy. 2 Department of Advanced Biomedical Sciences, Federico II University School of Medicine, Naples, Italy. 3 Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York, USA. 4 Department of Clinical Medicine and Surgery, Federico II University School of Medicine, Naples, Italy.

Clinical Investigation: Lymphoma

Multivariate Normal Tissue Complication Probability 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⁎

⁎Institute of Biostructures and Bioimaging, National Council of Research; and ⁎ Department of Advanced Biomedical Sciences, Federico II University School of Medicine, Naples, Italy.

Acta Oncologica, 2015; Early Online: 1–8

ORIGINAL ARTICLE

Predicting radiation-induced valvular heart damage

LAURA CELLA1,2, JUNG HUN OH3, JOSEPH O. DEASY3, GIUSEPPE PALMA1, RAFFAELE LIUZZI1,2, VITTORIA D’AVINO1, MANUEL CONSON1,2, MARCO PICARDI4, MARCO SALVATORE5 & ROBERTO PACELLI1,2

1 Institute of Biostructure and Bioimaging, National Council of Research (CNR), Naples, Italy. 2 Department of Advanced Biomedical Sciences, Federico II University School of Medicine, Naples, Italy. 3 Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York, USA. 4 Department of Clinical Medicine and Surgery, Federico II University School of Medicine, Naples, Italy.
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) = 
\[ f(\text{HeartDmax(Gy), Heart vol(cc), lung vol (cc)}) \]
Improved method for variable selection

- Least absolute shrinkage and Selection operator (LASSO)

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

- 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

Tibshirani (1996), “Regression Shrinkage and Selection via the Lasso"
Important variables:
Left lung dose parameters

<table>
<thead>
<tr>
<th>No</th>
<th>Variable</th>
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<th>Variable</th>
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<td>D95 lungs</td>
<td>21</td>
<td>AV30 heart</td>
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<td>3</td>
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<tr>
<td>8</td>
<td>Dmax right lung</td>
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<td>V30 heart</td>
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<td>D20 lungs</td>
<td>20</td>
<td>AV25 heart</td>
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Abbreviations: AVX = absolute volume receiving x Gy, Dmax = maximum dose to x% highest dose volume, Vx = percentage volume receiving x Gy,Variables are in bold.
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
Pulmonary damage in Hodgkin’s lymphoma patients treated with sequential chemo-radiotherapy: Predictors of radiation-induced lung injury

Laura Cell a,1,2, Raffaele Liuzzi a, Marco Picardi c, Maria Cristina Pressello d, Genoveva Ionela Boboc e, Roberta Battistini f, Vittorio Donato e, Roberto Pacelli a,b

Original article

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

Laura Cell a,1, 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

a Institute of Biostructure and Bioimaging, National Research Council (CNR); b Department of Advanced Biomedical Sciences, Federico II University School of Medicine; c Department of Clinical Medicine and Surgery, Federico II University School of Medicine, Naples; d Department of Health Physics, S. Camillo-Fioranini Hospital, Rome; e Department of Radiation Oncology, S. Camillo-Fioranini Hospital, Rome; and f Department of Hematology, S. Camillo-Fioranini Hospital, Rome, Italy
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
Probability maps

Lungs

Heart
Most frequently selected models: competitive models!!!

AUC1 ≈ AUC2 = 0.8
### Model 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimated coefficient</th>
<th>SE</th>
<th>p-Value</th>
<th>OR</th>
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<td>.022</td>
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<td>Heart M30 (%)</td>
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<td>.009</td>
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**Performance**

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<td>Discrimination</td>
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<td>Calibration slope</td>
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<td>Calibration intercept</td>
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### Model 2

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<th>Parameter</th>
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<td>Age</td>
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<td>.023</td>
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<td>Heart M30 (%)</td>
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<tr>
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**Performance**

<table>
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<th>Rs</th>
<th>.376</th>
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<tbody>
<tr>
<td>AUC (95% CI)</td>
<td>.80 (.69-.91)</td>
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<tr>
<td>Discrimination</td>
<td>.18</td>
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<tr>
<td>Calibration slope</td>
<td>1.02 ± .11</td>
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<td>Calibration intercept</td>
<td>-.004 ± .022</td>
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</table>
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
Radiation Oncology research group

Raffaele Liuzzi, PhD

Giuseppe Palma, PhD

Roberto Pacelli, MD &
Manuel Conson, MD

Vittoria D’Avino, MSc

Consiglio Nazionale delle Ricerche
Istituto di Biostrutture e Bioimmagini