Beperken van cardiale toxiciteit bij radiotherapie voor longtumoren

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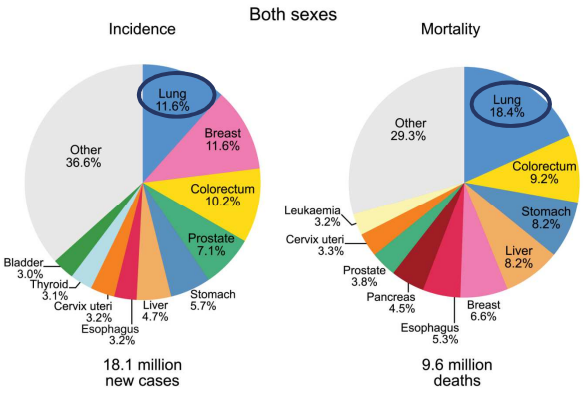
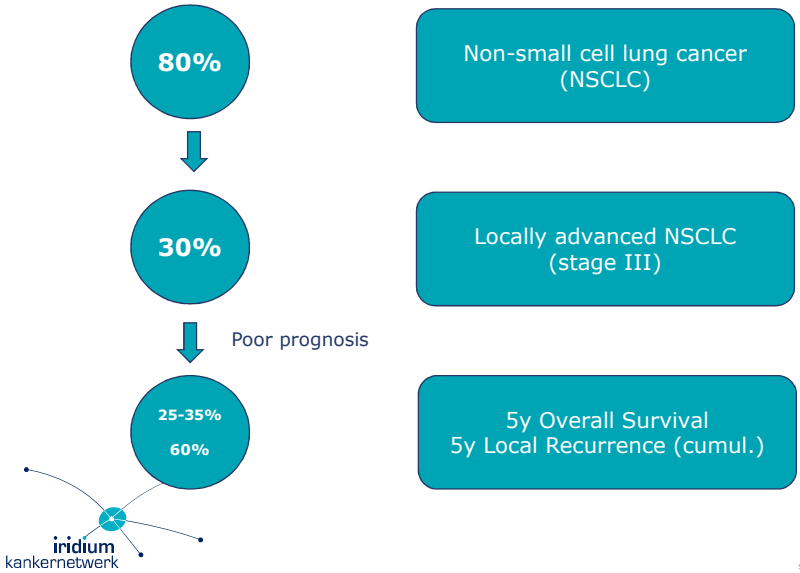
Lung cancer



Estimates of incidence and mortality worldwide for 36 cancers in 185 countries

GLOBOCAN 2018;

Non-small cell lung cancer (NSCLC)



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Slide 3 14/06/2019

Locally advanced NSCLC

- Standard treatment

= concurrent (or sequential) chemo-radiotherapy (CRT)

+ adjuvant PD-L1 inhibitor (Durvalumab)

OR surgical multimodality treatment for selected cases

- Radiation treatment (RT)

= 33 x 2 Gy

  - 6-7 weeks
  - local therapy
  - to involved tumor +/- lymph nodes

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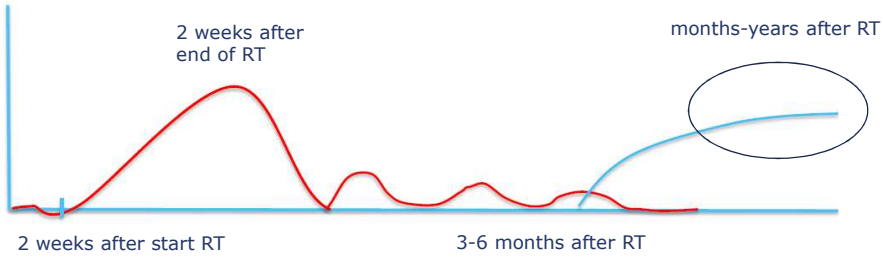
RT Toxicity

- Toxicity: acute vs. late



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RT Toxicity

- Acute:
  - Skin erythema
  - Esophagus esophagitis
  - Lung dyspnea, cough
  - Fatigue
- Late:
  - Skin fibrosis, teleangiectasia
  - Esophagus stricture, stenosis
  - Lung radiation pneumonitis
  - Heart ???

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Cardiac toxicity

- Long latency of RT-associated heart injury
- Limited number of long-term survivors

→ *Limited clinical relevance*

The NEW ENGLAND JOURNAL of MEDICINE

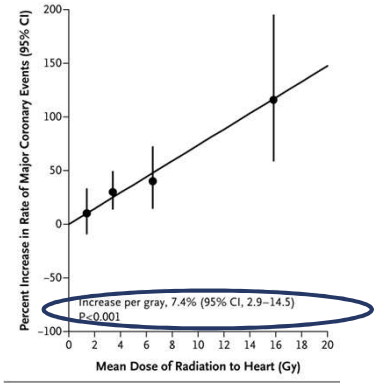
ESTABLISHED IN 1812 MARCH 14, 2013 VOL. 368 NO. 11

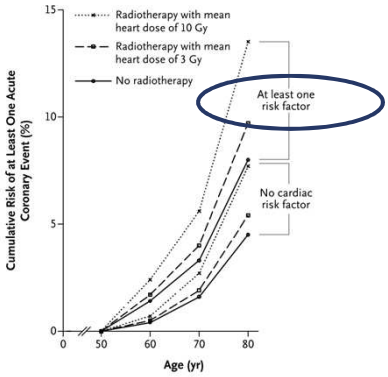
Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.

- Radiotherapy for breast cancer -> exposure of the heart to ionizing radiation
- population-based case–control study
- 963 women with major coronary events and 1205 controls

Darby et al. N Engl J Med 2013;





- **Results:**
  - Rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy with no apparent threshold.
  - Begins within a few years after exposure, and continues for at least 20 years.
  - Women with preexisting cardiac risk factors have greater absolute increases in risk from radiotherapy than other women.

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Darby et al. N Engl J Med 2013;

RT-associated cardiac toxicity in breast cancer

- **Discussion:**
  - The greatest percentage increase in rate of events per gray (Gy) of irradiation to the heart occurs within the first 4 years after radiotherapy
  - Possible mechanism: radiation causes accelerated late atherosclerosis of major bloodvessels and early microvascular changes

➡ Important to minimize mean heart dose

➡ Early onset of damage

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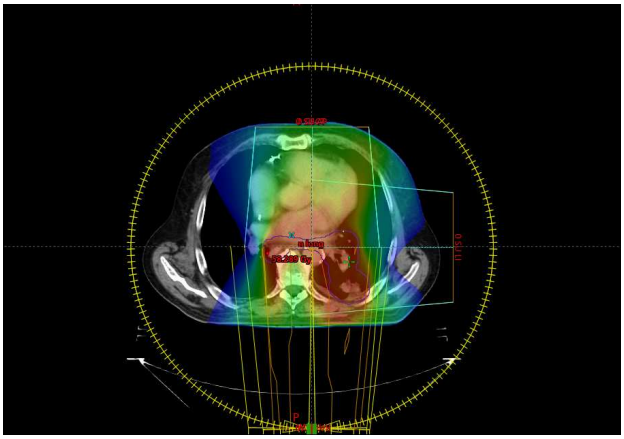
Darby et al. N Engl J Med 2013;

Lung Cancer



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Lung Cancer

- Radiotherapy (RT) –associated heart toxicity recognized for breast cancer or Hodgkin lymphoma
- Impact of radiotherapy (RT)–associated cardiac injury for stage III non–small-cell lung cancer (NSCLC) is unclear
  - Increasing long-term survivors after lung cancer
  - Also possible at earlier time intervals (cfr. breast cancer)
  - More comorbid risk factors (smoking and pre-existing cardiac disease): lower reserve and predispose them to earlier events: increasing risk and perhaps shortening the latency between RT and heart disease
  - High heart doses in stage III NSCLC

➡ **Increasing interest in (RT) –associated heart toxicity in NSCLC**

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RT-associated cardiac toxicity in lung cancer

1. **Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study**

Jeffrey D Bradley, Rebecca Paulus, Ritsuko Komaki, Gregory Masters, George Blumenschein, Steven Schild, Jeffrey Bogart, Chen Hu, Kenneth Forster, Anthony Magliocca, Vivek Kavadi, Yolanda I Garces, Samir Narayan, Puneeth Iyengar, Cliff Robinson, Raymond B Wynn, Christopher Koprowski, Joanne Meng, Jonathan Beitler, Rakesh Gaur, Walter Curran Jr, Hak Choy

- Randomized phase III trial - multicentric
- Stage IIIA/B NSCLC patients receiving concurrent chemoradiotherapy
- 2007 - 2011
- 544 patients
- Two-by-two randomization
  - Standard dose (60 Gy) vs. High dose (74 Gy) in 2 Gy fractions
  - +/- cetuximab

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Bradley et al. Lancet Oncol 2015;

RT-associated cardiac toxicity in lung cancer

- **Results:**
  - Median OS 28m vs. 20m

  -> Lower OS in high dose group!
  - No OS difference for +/- cetuximab
  - No statistical differences in grade 3 or worse toxic effects between radiotherapy groups
  - Predicting factors for OS in multivariate analysis (all patients):
    - Standard radiation dose (60 Gy)
    - Maximum oesophagitis grade
    - planning target volume
    - Heart V5 and V30

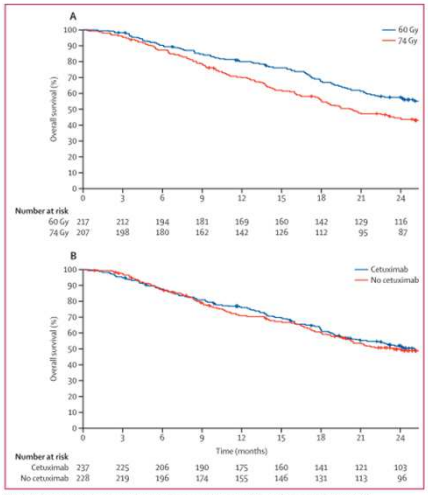

Figure 2: Kaplan-Meier overall survival curves for radiation dose (A) and the use of cetuximab (B)
(A) One-sided log-rank p=0·0042. (B) one-sided log-rank, p=0·2938.

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Bradley et al. Lancet Oncol 2015;

RT-associated cardiac toxicity in lung cancer

- **Conclusions:**
  - Increasing dose to 74 Gy did not improve OS + is potentially harmful
  - addition of concurrent cetuximab (anti-EGFR antibody) did not improve OS

- **Discussion:**
  - Similar planning target volumes
  - Higher mean lung dose in high-dose group (mean 16·5 Gy vs 18·9 Gy; p<0·0001)
  - Higher heart dose in high-dose group
  - Higher rates of treatment-related deaths in high-dose group
  - Higher rates of non-compliance to RT in high-dose group

Toxicity related

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Bradley et al. Lancet Oncol 2015;

RT-associated cardiac toxicity in lung cancer

- **Hypothesis**
  - Heart dose might explain why patients given 74 Gy had worse survival than patients given 60 Gy, especially because patients in the 74-Gy arm received higher cardiac doses.
  - Heart radiation dose was associated with worse OS with a median follow-up of 2 years, suggesting a contribution of radiation-induced cardiac morbidity relatively soon after treatment

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Bradley et al. Lancet Oncol 2015;

RT-associated cardiac toxicity in lung cancer

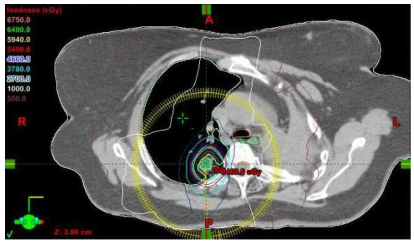
- **Secondary analysis:**

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non–Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial

Stephen G. Chun, Chen Hu, Hak Choy, Rituuko U. Komaki, Robert D. Timmerman, Steven E. Schild, Jeffrey A. Bogart, Michael C. Dobelbower, Walter Bosch, James M. Galvin, Vivek S. Kavadi, Samir Narayan, Puneeth Iyengar, Clifford G. Robinson, Raymond B. Wynn, Adam Raben, Mark E. Augspurger, Robert M. MacRae, Rebecca Paulus, and Jeffrey D. Bradley

- Impact of RT technique?
  - Comparison of conventional RT vs IMRT (intensity modulated radiotherapy)



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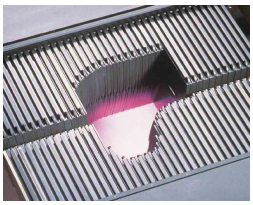
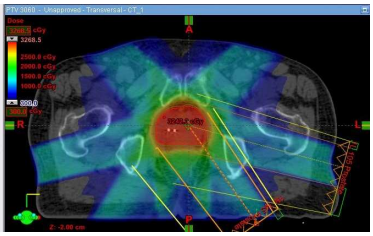
Chun et al. J Clin Oncol 2016;

Intensity modulated radiotherapy

- Conventional = STATIC
- **IMRT** = "Intensity modulated beams"
  (dynamic leafs)
  + more homogene dose distribution
  + sharp dose fall-off
  + lower dose to critical organs nearby





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RT-associated cardiac toxicity in lung cancer

- **Results:**
  - 53% 3D-CRT vs. 47% with IMRT
  - No difference in 2y overall survival, progression-free survival, local failure, and distant metastasis–free survival
  - However
    - Less grade 3 pneumonitis (7.9%v 3.5%, p=.039)
    - Lower heart doses (p<0.05) (and heart radiation dose was associated with worse OS in trial RTOG 0617)
- **Conclusion:**
  - **IMRT associated with lower lung toxicity and heart dose**
  - **Routine use of IMRT for locally advanced NSCLC recommended**

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Chun et al. J Clin Oncol 2016;

RT-associated cardiac toxicity in lung cancer

2.

VOLUME 35 · NUMBER 13 · MAY 1, 2017
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Cardiac Toxicity After Radiotherapy for Stage III Non–Small-Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy

Kyle Wang, Michael J. Eblan, Allison M. Deal, Matthew Lipner, Timothy M. Zagar, Yue Wang, Panayiotis Mavroidis, Carrie B. Lee, Brian C. Jensen, Julian G. Rosenman, Mark A. Socinski, Thomas E. Stinchcombe, and Lawrence B. Marks

- Pooled analysis of 6 prospective dose-escalation trials
- All stage III NSCLC patients receiving chemoradiotherapy
- RT dose all >70 Gy
- 1996 – 2009
- 127 patients
- Primary end point: symptomatic cardiac events

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Wang et al. J Clin Oncol 2017;

RT-associated cardiac toxicity in lung cancer

- **Results**:
- 2- and 4-year rates of symptomatic cardiac events were 14% and 32%
- Patients with events:
  - higher heart doses than patients without events (mean dose 20 Gy vs 10 Gy; V5Gy, 56% vs 34%; V30Gy, 29% v 12%)
  - higher rates of baseline coronary artery disease
- Subgroups according mean heart dose:
  - significantly higher rate of cardiac events in mean heart dose >20 Gy (HR, 5.47; P<.001)

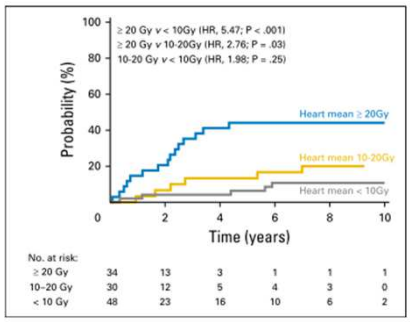

Fig 2. Cumulative incidence of competing risk–adjusted symptomatic cardiac events in patients with heart mean dose ≥ 20 Gy (blue), 10 to 20 Gy (gold), and < 10 Gy (gray).

Wang et al. J Clin Oncol 2017;

RT-associated cardiac toxicity in lung cancer

- **Results:**
  - approximately half of the events occurred within the first 2 years after irradiation.
  - significant arrhythmias, symptomatic pericardial effusions, and myocardial infarctions were most common
  - No statistically significant association between OS and heart doses

Wang et al. J Clin Oncol 2017;

RT-associated cardiac toxicity in lung cancer

- **Conclusions:**
  - Clear association between clinically significant cardiac events and both radiation doses to the heart and baseline cardiac risk
  - Possible dose dependence for RT-associated cardiac toxicity
    - ➡ Heart doses should be minimized (mean dose < 20Gy)
    - ➡ This report clearly associates, for the first time, RT doses with clinically significant cardiac events in patients with locally advanced NSCLC who were treated with modern radiotherapy techniques
  - higher rates of baseline coronary artery disease (35% vs 8%) in patients with cardiac events

    -> pre-existing cardiac disease predisposes to development of radiation-induced major cardiac events and that these events might occur at earlier time points

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Wang et al. J Clin Oncol 2017;

RT-associated cardiac toxicity in lung cancer

- **Critical remarks:**
  - What about normal fractionated RT (this study only dose-escalated trials)?
  - What about chemotherapeutic agents potentiating radiation-induced cardiotoxicity?

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Wang et al. J Clin Oncol 2017;

RT-associated cardiac toxicity in lung cancer

3.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Cardiac Events After Radiation Therapy: Combined Analysis of Prospective Multicenter Trials for Locally Advanced Non–Small-Cell Lung Cancer

Robert T. Dess, Yilun Sun, Martha M. Matuszak, Grace Sun, Payal D. Soni, Latifa Bazzi, Venkatesh L. Murthy, Jason W.D. Hearn, Feng-Ming Kong, Gregory P. Kalemkerian, James A. Hayman, Randall K. Ten Haken, Theodore S. Lawrence, Matthew J. Schipper, and Shruti Jolly

- Combined analysis of 4 prospective multicentric trials
- Stage II-III NSCLC patients receiving chemoradiotherapy
- Hypofractionated radiation (> 2 Gy/fraction) ; median 70 Gy
- 2004 – 2013
- 125 patients
- Primary end point: development of a grade ≥ 3 cardiac event (CTCAE scoring)

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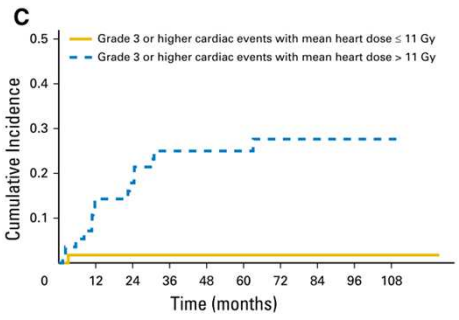
Dess et al. J Clin Oncol 2017;

RT-associated cardiac toxicity in lung cancer

- **Results:**
  - 19 patients (11%) with a grade ≥ 3 cardiac event after 2y
  - 3 patients with grade 5 event
  - Mean heart dose = 11 Gy
  - Significant higher cumulative incidence (1y and 2y) of grade 3+ cardiac events for those with ≥ or < than the median mean heart dose of 11 Gy (p<0.01)
  - Median time for event 11 months
  - No correlation of heart dose with OS



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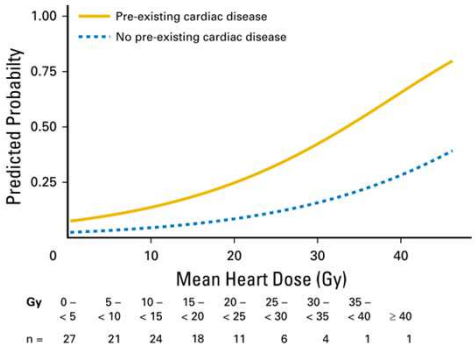
Dess et al. J Clin Oncol 2017;

RT-associated cardiac toxicity in lung cancer

- **Results:**
  - 27% with pre-existing cardiac disease
  - Near three-fold increase in the likelihood of developing a grade 3+ cardiac event over time
  - Predicting factors for grade 3 events in multivariable analysis:
    - pre-existing cardiac disease
    - mean heart dose



Model-predicted cumulative incidence of a grade 3+ cardiac event within 24 months of treatment by increasing mean heart dose (A) for those with and without pre-existing cardiac disease

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Dess et al. J Clin Oncol 2017;

RT-associated cardiac toxicity in lung cancer

- **Conclusions:**
  - 2y cumulative incidence of grade 3+ cardiac events exceeded 10% among patients with locally advanced NSCLC (11%) for all patients
  - 2y cumulative incidence of grade 3+ cardiac events in patients with pre-existing cardiac disease was 21%
  - Pre-existing cardiac disease and higher mean heart dose were significantly associated with higher cardiac event rates.
  - mean heart dose, V5Gy and V30Gy were each significantly associated with an increased hazard of cardiac events (P= 0.01)

➡ Importance of minimizing heart dose (mean heart dose, V5Gy and V30Gy)

➡ Individualized, more stringent cardiac dosimetric constraints may be needed in those with pre-existing cardiac disease

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Dess et al. J Clin Oncol 2017;

RT-associated cardiac toxicity in lung cancer

4.

Heart Dose Is an Independent Dosimetric Predictor of Overall Survival in Locally Advanced Non-Small Cell Lung Cancer

Christina K. Speirs, MD, PhD,[a] Todd A. DeWees, PhD,[a] Sana Rehman, MD,[a] Alerson Molotievschi, MD, MBA,[b] Maria A. Velez, MD,[a] Daniel Mullen, DDS,[a] Sandra Fergus, BA,[a] Marco Trovo, MD,[c] Jeffrey D. Bradley, MD,[a] Cliff G. Robinson, MD[a,*]

- Retrospective trial
- Stage II-III NSCLC receiving RT +/- CT
- RT dose median 66 Gy
- 2001 – 2015
- 416 patients

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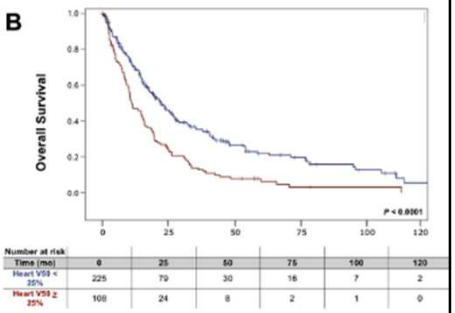
Speirs et al. J Thorac Oncol 2016;

RT-associated cardiac toxicity in lung cancer

- **Results:**
  - Higher heart dose (V50<25% vs V50>25%) correlated with lower OS rates (1-y 70.2% vs. 46.8% and 2-y 45.9% vs. 26.7% (p<0.0001)
- Predicting factors for lower OS in multivariate analysis
  - heart V50 (volume receiving >50 Gy)
  - heart volume
  - bilateral mediastinal LN involvement
  - lung V5 (proportion of the lung structure receiving at least 5 Gy)
  - lack of concurrent chemotherapy.



Cutpoint V50<25%

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Speirs et al. J Thorac Oncol 2016;

RT-associated cardiac toxicity in lung cancer

- **Conclusions:**
  - Heart dose is associated with OS and cardiac toxicity
  - Heart V50 (V50 <25%) was established as the strongest predictor

Speirs et al. J Thorac Oncol 2016;

General conclusions

- **Importance of heart dose in RT for locally advanced NSCLC**
- **Minimizing heart dose can decrease late toxicity and may improve survival.**
- **Important dosimetric factors**
  - Mean heart dose
  - V5
  - V30
  - V50
- **Importance of pre-existing comorbidity**
  - Differentiating heart constraints according to clinical comorbidity?

Future perspectives

- True irradiation dose tolerance of the heart still unclear
  - Exact dosimetric parameters?
  - Certain regions of the heart more susceptible to irradiation damage?
- Ongoing prospective trials to assess serial cardiac biomarkers or imaging (MR and/or echocardiography) in patients before and after thoracic radiotherapy in an attempt to better define the mechanism of early cardiac toxicity

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