



XXIII CONGRESSO  
**AIRO2013**

Taormina, 26-29 ottobre  
Giardini Naxos

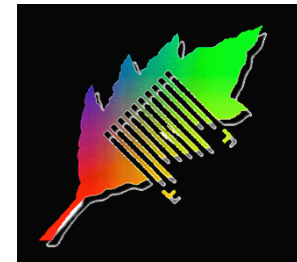
# WORKSHOP

## Trattamenti integrati nel NSCLC III stadio

# Tecniche di trattamento



Marco Trovò





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Giardini Naxos

## DICHIARAZIONE

Relatore: MARCO TROVO'

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board: **NIENTE DA DICHIARARE**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**

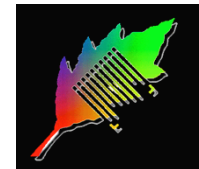


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# Outline

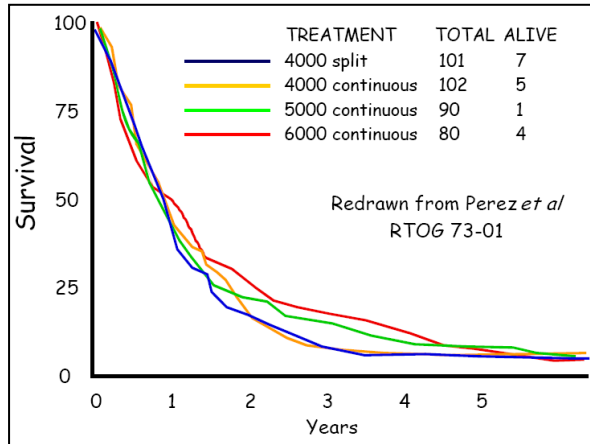
- Background
- Tecniche di trattamento
  - Treatment Planning
    - 4D-CT Simulation
    - PET-CT
  - Treatment Delivery
    - 3D-CRT
    - IMRT
    - SBRT
- Direzioni future





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2D-RT

*timeline*

'73-'80

doseline

60 Gy



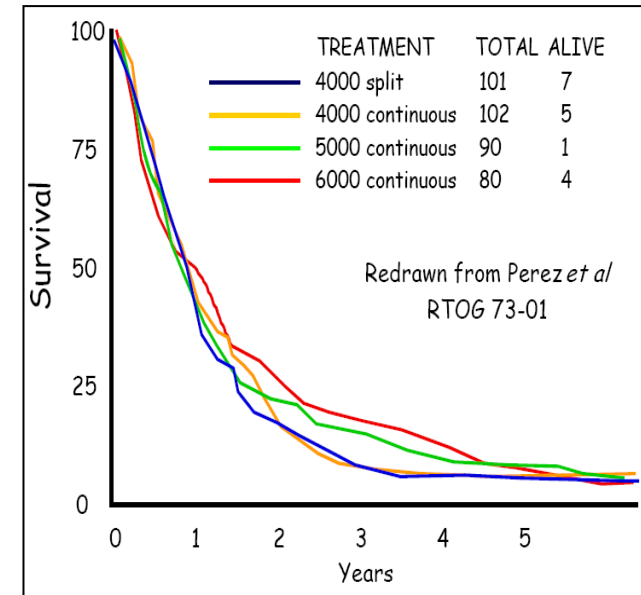
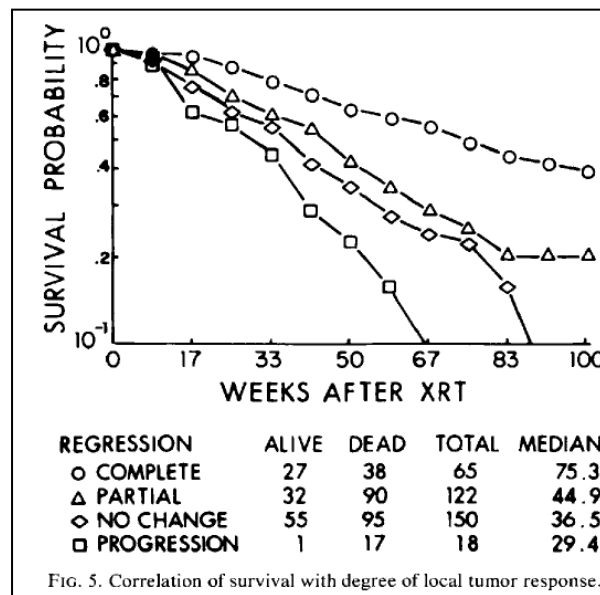
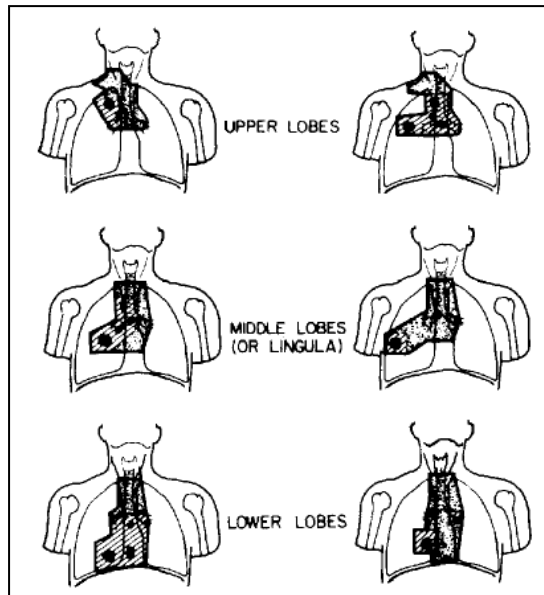
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## A Prospective Randomized Study of Various Irradiation Doses and Fractionation Schedules in the Treatment of Inoperable Non-Oat-Cell Carcinoma of the Lung

*Preliminary Report by the Radiation Therapy Oncology Group*

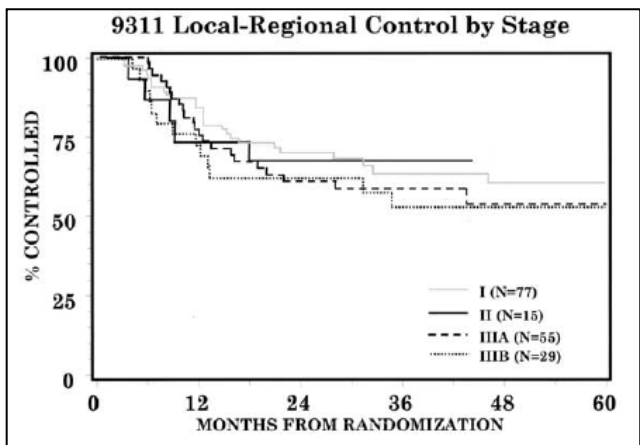
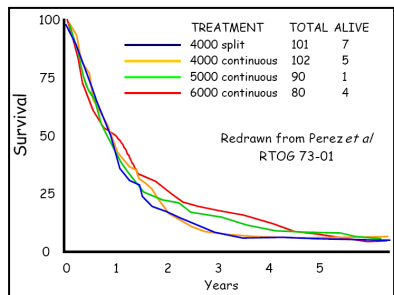
C. A. PEREZ, MD,\* K. STANLEY, PhD,† P. RUBIN, MD,‡ S. KRAMER, MD§, L. BRADY, MD,¶ R. PEREZ-TAMAYO, MD,# G. S. BROWN, MD,¶ J. CONCANNON, MD,\*\* M. ROTMAN, MD,†† AND H. G. SEYDEL, MD‡‡





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2D-RT

3D-CRT

*timeline*

'73-'80

'93-'95

*doseline*

60 Gy

83 Gy





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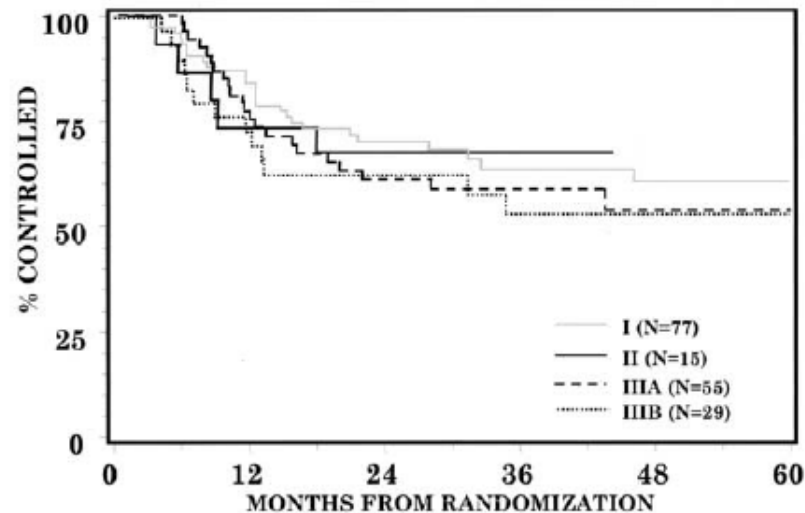
**CLINICAL INVESTIGATION**

**Lung**

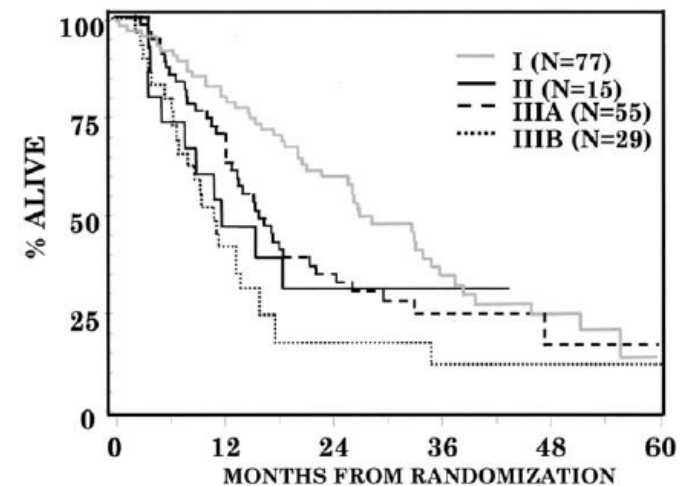
**TOXICITY AND OUTCOME RESULTS OF RTOG 9311: A PHASE I-II DOSE-ESCALATION STUDY USING THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY IN PATIENTS WITH INOPERABLE NON-SMALL-CELL LUNG CARCINOMA**

JEFFREY BRADLEY, M.D.,\* MARY V. GRAHAM, M.D.,<sup>†</sup> KATHRYN WINTER, M.S.,<sup>‡</sup>  
JAMES A. PURDY, PH.D.,<sup>§</sup> RITSUKO KOMAKI, M.D.,<sup>||</sup> WILSON H. ROA, M.D.,<sup>¶</sup> JANICE K. RYU, M.D.,<sup>#</sup>  
WALTER BOSCH, D.Sc.,<sup>§</sup> AND BAHMAN EMAMI, M.D.\*\*

**9311 Local-Regional Control by Stage**



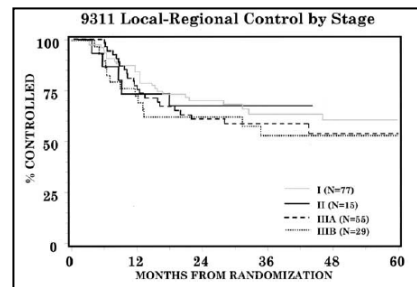
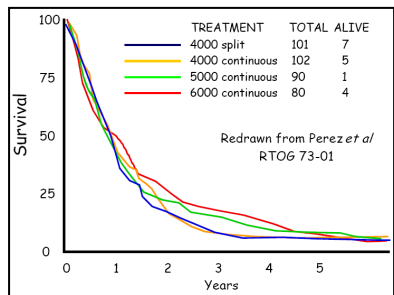
**9311 Overall Survival by Stage**





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| Study                     | Radiation MTD (Gy) |
|---------------------------|--------------------|
| RTOG 0117 <sup>34</sup>   | 74                 |
| NCCTG 0028 <sup>35</sup>  | 74                 |
| UNC <sup>36</sup>         | 74                 |
| Wake Forest <sup>37</sup> | 74                 |
| CALGB 30105 <sup>38</sup> | 74                 |

IMRT

2D-RT

3D-CRT

*timeline*

'73-'80

'93-'00

'03-'05

*doseline*

60 Gy

83 Gy

Conc-CT

74Gy





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## Primary Analysis of the Phase II Component of a Phase I/II Dose Intensification Study Using Three-Dimensional Conformal Radiation Therapy and Concurrent Chemotherapy for Patients With Inoperable Non-Small-Cell Lung Cancer: RTOG 0117

*Jeffrey D. Bradley, Kyoung-hwa Bae, Mary V. Graham, Roger Byhardt, Ramaswamy Govindan, Jack Fowler, James A. Purdy, Jeff M. Michalski, Elizabeth Gore, and Hak Choy*

**Table 2.** Overall and Progression-Free Survival Outcomes (n = 53)

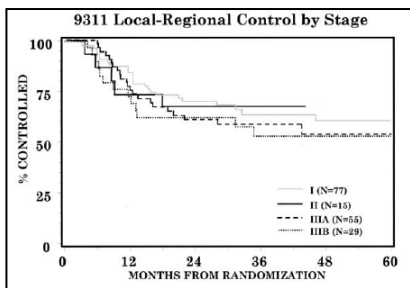
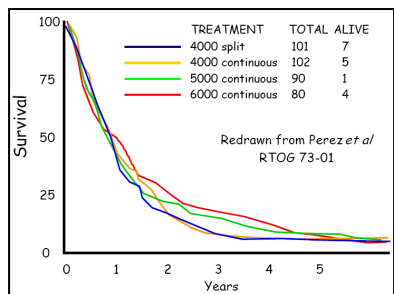
| Survival Time                             | RTOG 0117 Overall Survival |              |             |                    | RTOG 0117 Progression-Free Survival |              |             |                    | RTOG 9410 CON-QD Arm Overall Survival |              |             |                    |
|---|----------------------------|--------------|-------------|--------------------|-------------------------------------|--------------|-------------|--------------------|---------------------------------------|--------------|-------------|--------------------|
|   | % Alive                    | 95% CI       | No. at Risk | No. Dead/No. Alive | % Alive                             | 95% CI       | No. at Risk | No. Dead/No. Alive | % Alive                               | 95% CI       | No. at Risk | No. Dead/No. Alive |
| Time, months                              |                            |              |             |                    |                                     |              |             |                    |                                       |              |             |                    |
| 0   | 100                        |              | 53          |                    | 100                                 |              | 53          |                    | 100                                   |              | 195         |                    |
| 3   | 94.3                       | 83.5 to 98.1 | 50          |                    | 88.7                                | 76.5 to 94.7 | 47          |                    | 95.4                                  | 91.3 to 97.6 | 186         |                    |
| 6   | 88.7                       | 76.5 to 94.7 | 47          |                    | 69.8                                | 55.5 to 80.3 | 37          |                    | 84.1                                  | 78.2 to 88.5 | 164         |                    |
| 9   | 77.4                       | 63.6 to 86.5 | 41          |                    | 52.8                                | 38.6 to 65.2 | 28          |                    | 74.4                                  | 67.6 to 79.9 | 145         |                    |
| 12  | 75.5                       | 61.5 to 85.0 | 40          |                    | 50.9                                | 36.9 to 63.4 | 27          |                    | 62.1                                  | 54.8 to 68.4 | 120         |                    |
| Median survival time, months              | 25.9                       | 17.1 to NA   |             |                    | 12.2                                | 7.2 to 17.4  |             |                    | 17                                    | 14.0 to 20.2 |             |                    |
| No. of patients surviving at end of study | 28/53                      |              |             |                    | 36/53                               |              |             |                    | 185/195                               |              |             |                    |

Abbreviations: RTOG, Radiation Therapy Oncology Group; CON QD, concurrent delivery beginning with day 1; NA, not applicable.

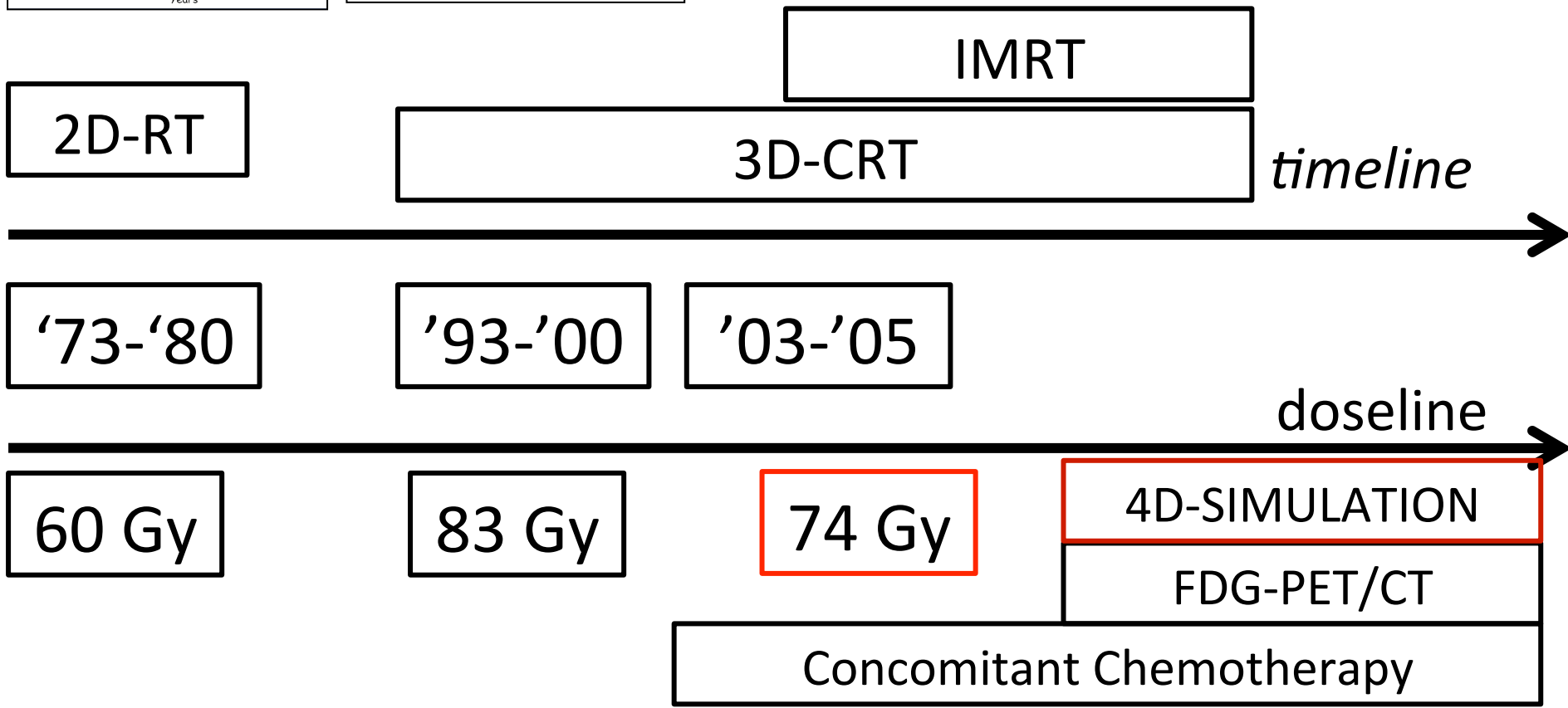


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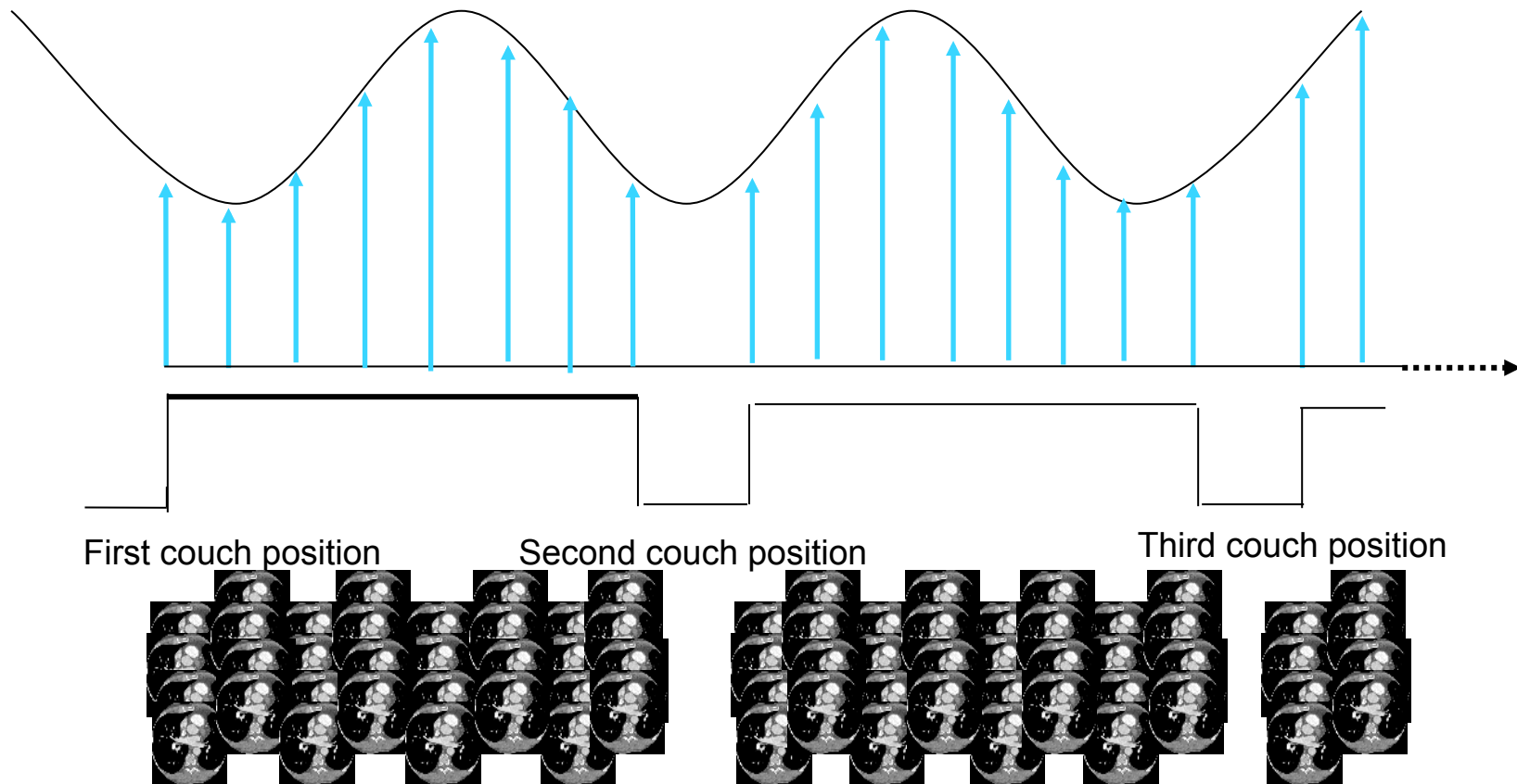




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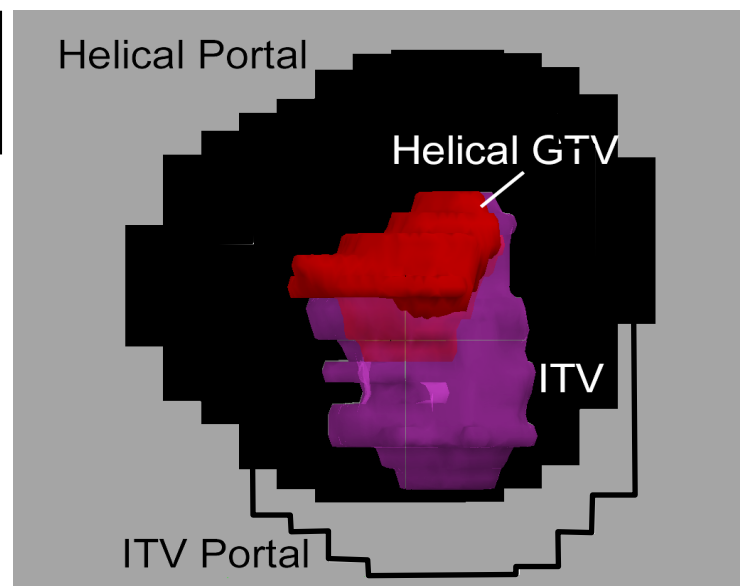
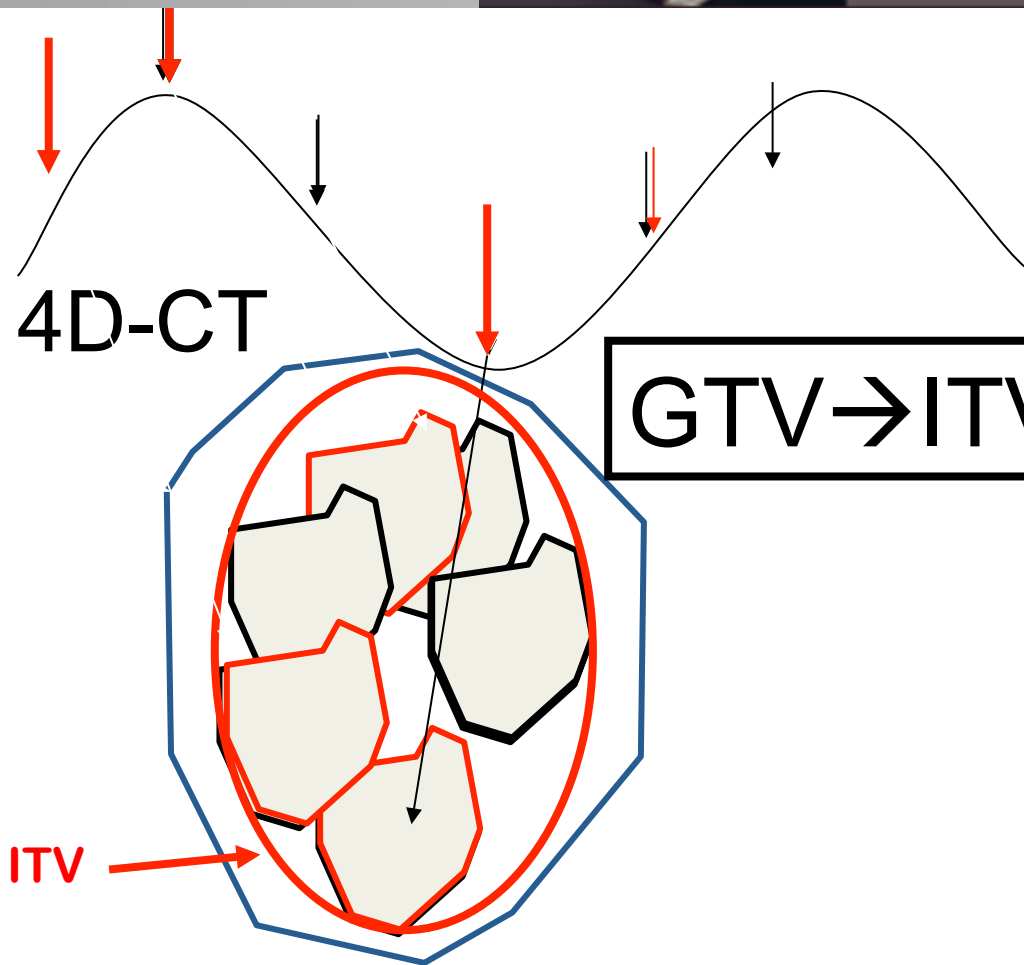
# 4D-CT SIMULATION





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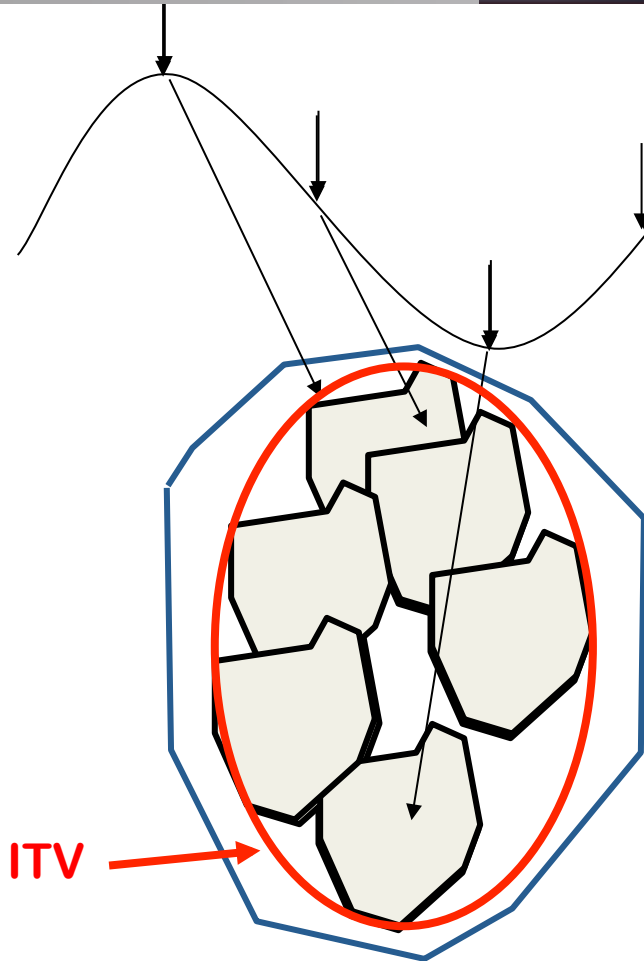
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## 4DCT: Generating target volumes

Underberg, Lagerwaard et. al. 2005



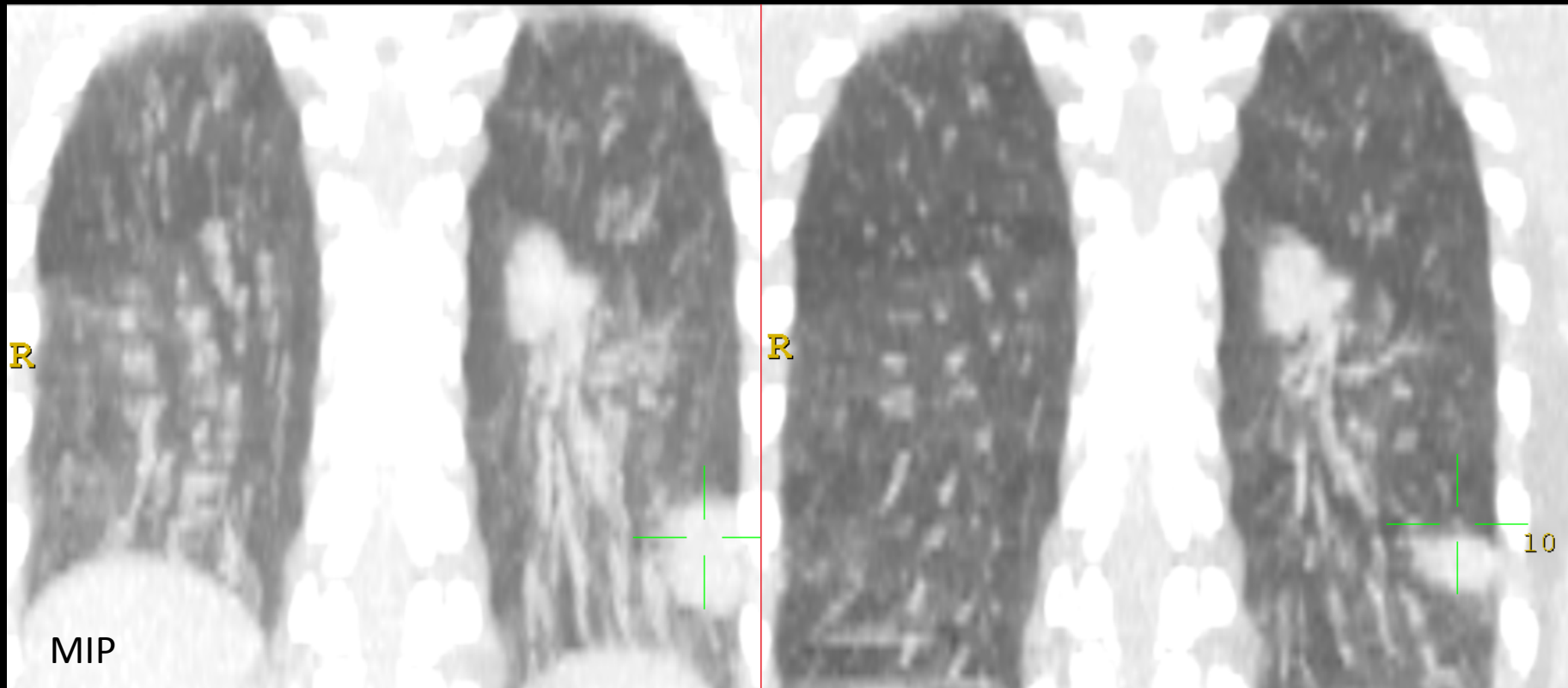
- **Max Intensity Projection (MIP):** maximum value of a pixel over all phases; indicates any location where tumor present over all phases.
- **Min IP:** minimum value of each pixel over all phases; indicates only those locations where tumor is constantly present over all phases.
- **Mean IP:** mean value of each pixel over all phases; represents the time-weighted location of the tumor.





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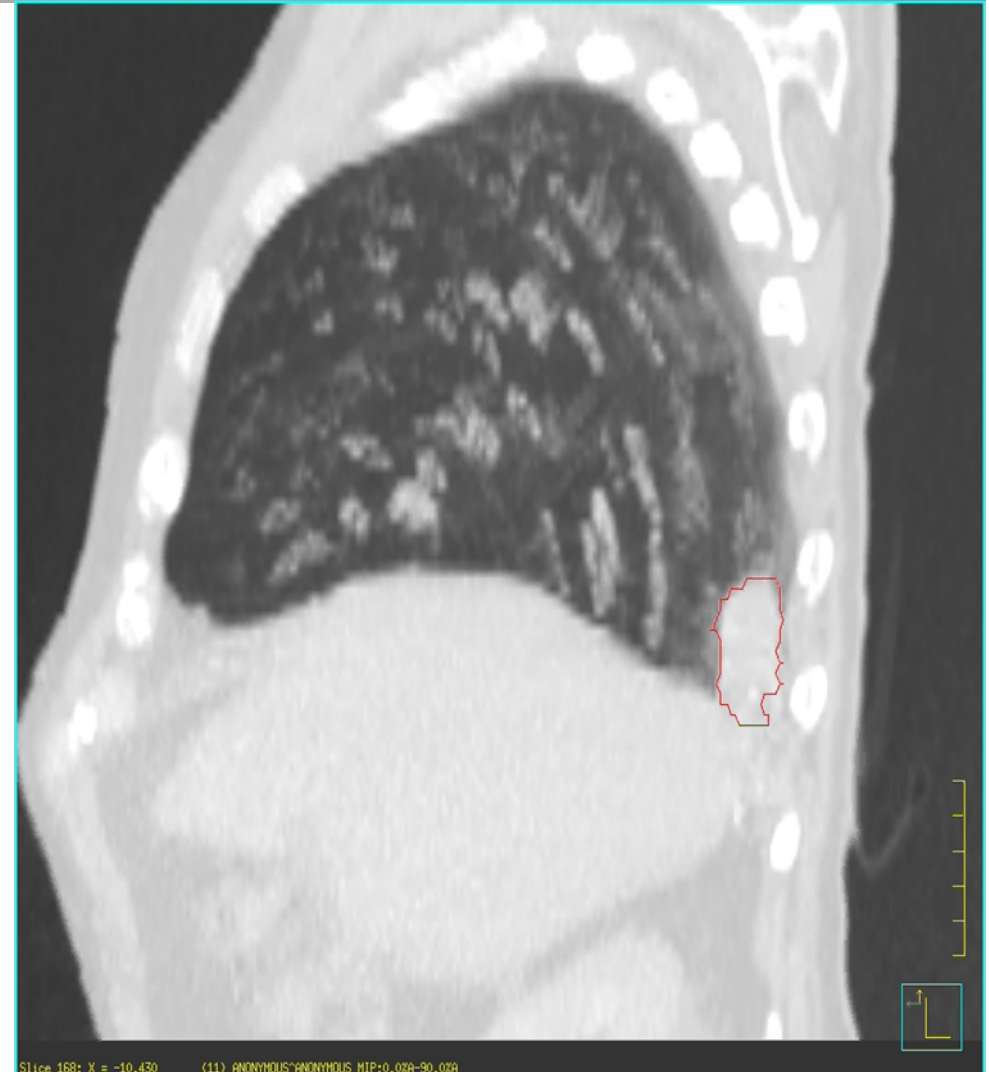


Courtesy of JD Bradley



## MIPs can be problematic

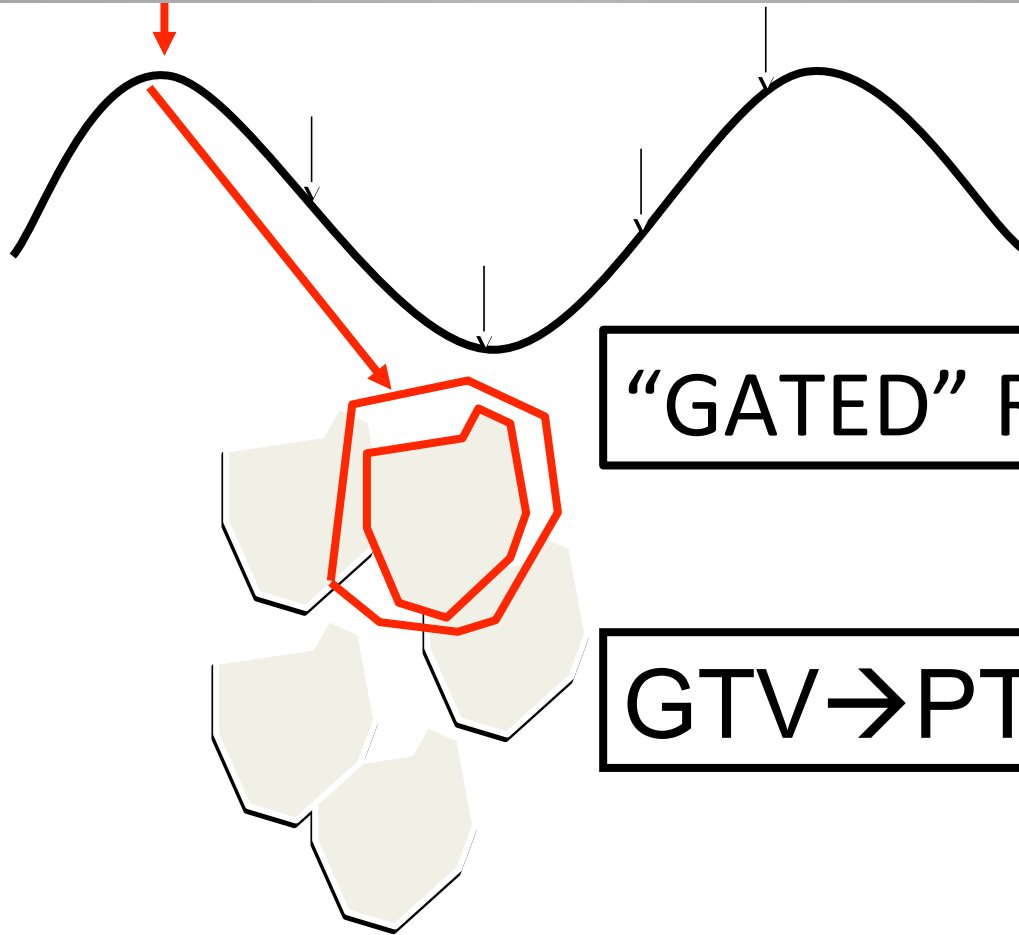
- Where background and tumor have similar HU, tumor is not as clearly defined
- Example: Caudal extent of ITV may not be correct due to overlap with diaphragm
- Review individual phases
- For this case, send additional scans, e.g. max inhale and max exhale scans to help MD assess tumor motion





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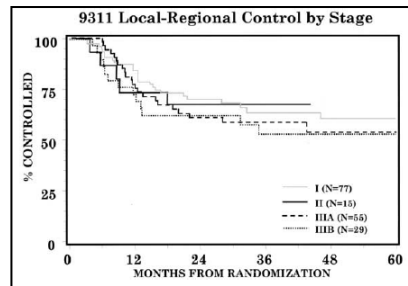
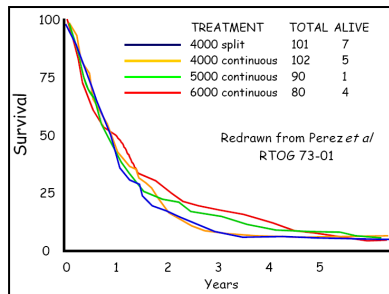




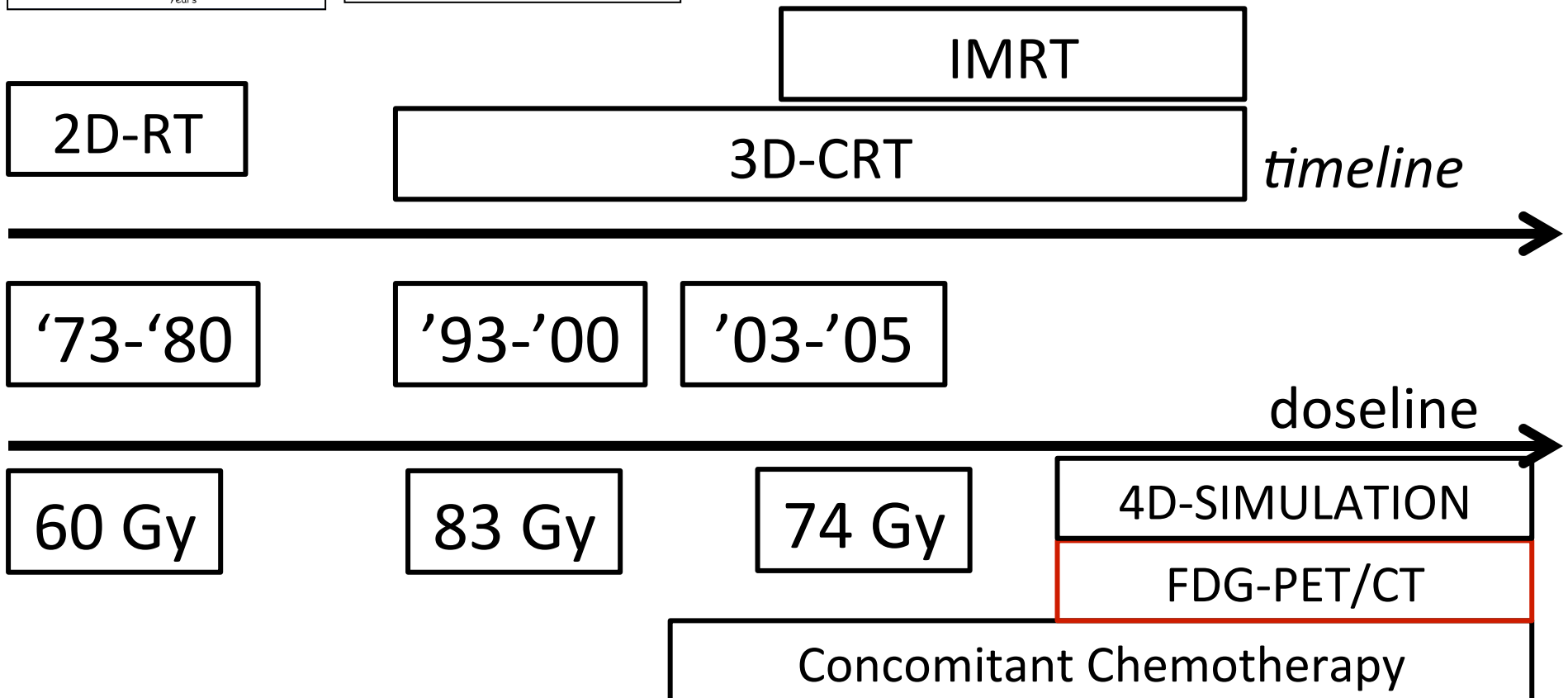


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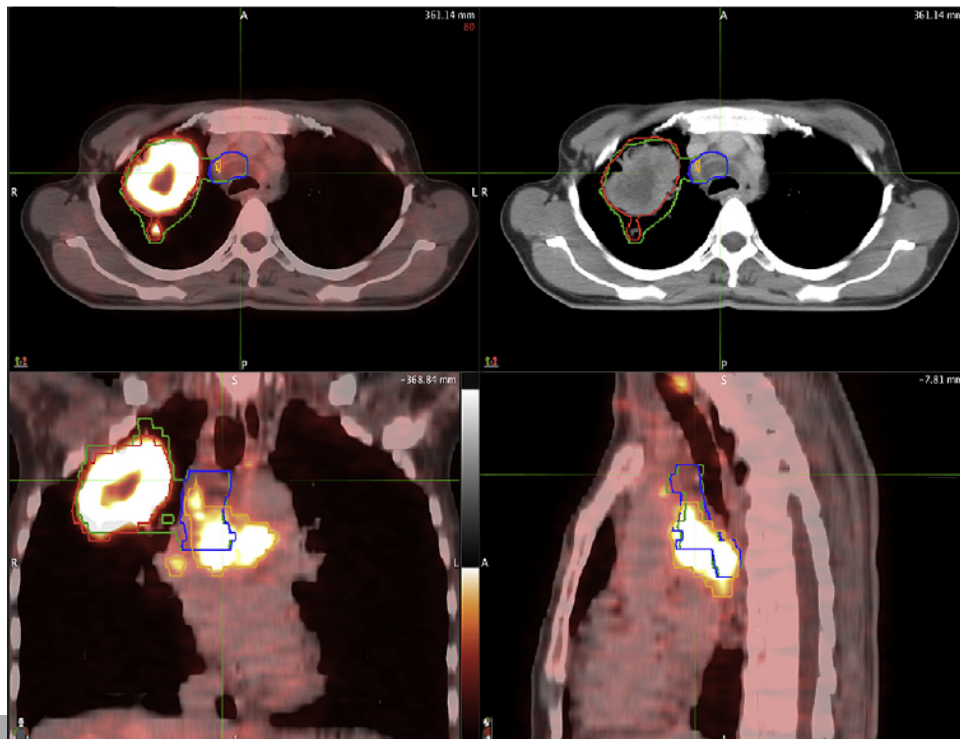
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**CLINICAL INVESTIGATION**

**Thoracic Cancer**

**A PHASE II COMPARATIVE STUDY OF GROSS TUMOR VOLUME DEFINITION WITH OR WITHOUT PET/CT FUSION IN DOSIMETRIC PLANNING FOR NON-SMALL-CELL LUNG CANCER (NSCLC): PRIMARY ANALYSIS OF RADIATION THERAPY ONCOLOGY GROUP (RTOG) 0515**

JEFFREY BRADLEY, M.D.,\* KYOUNGHWBAE, PH.D.,† NOAH CHOI, M.D.,‡ KEN FORSTER, PH.D.,§  
BARRY A. SIEGEL, M.D.,\* JACQUELINE BRUNETTI, M.D.,|| JAMES PURDY, PH.D.,¶ SERGIO FARIA, M.D.,\*\*  
TONI VU, M.D.,†† WADE THORSTAD, M.D.,\* AND HAK CHOY, M.D.‡‡



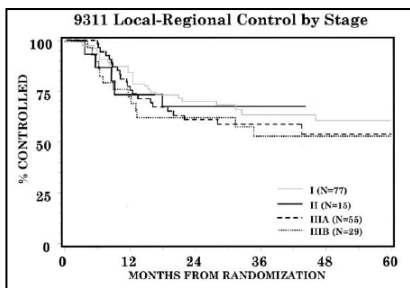
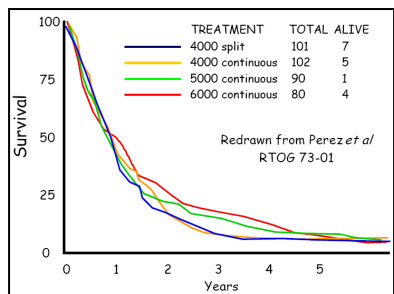
Nodal contour  
altered by PET: 51%

Elective nodal  
failure: 2%

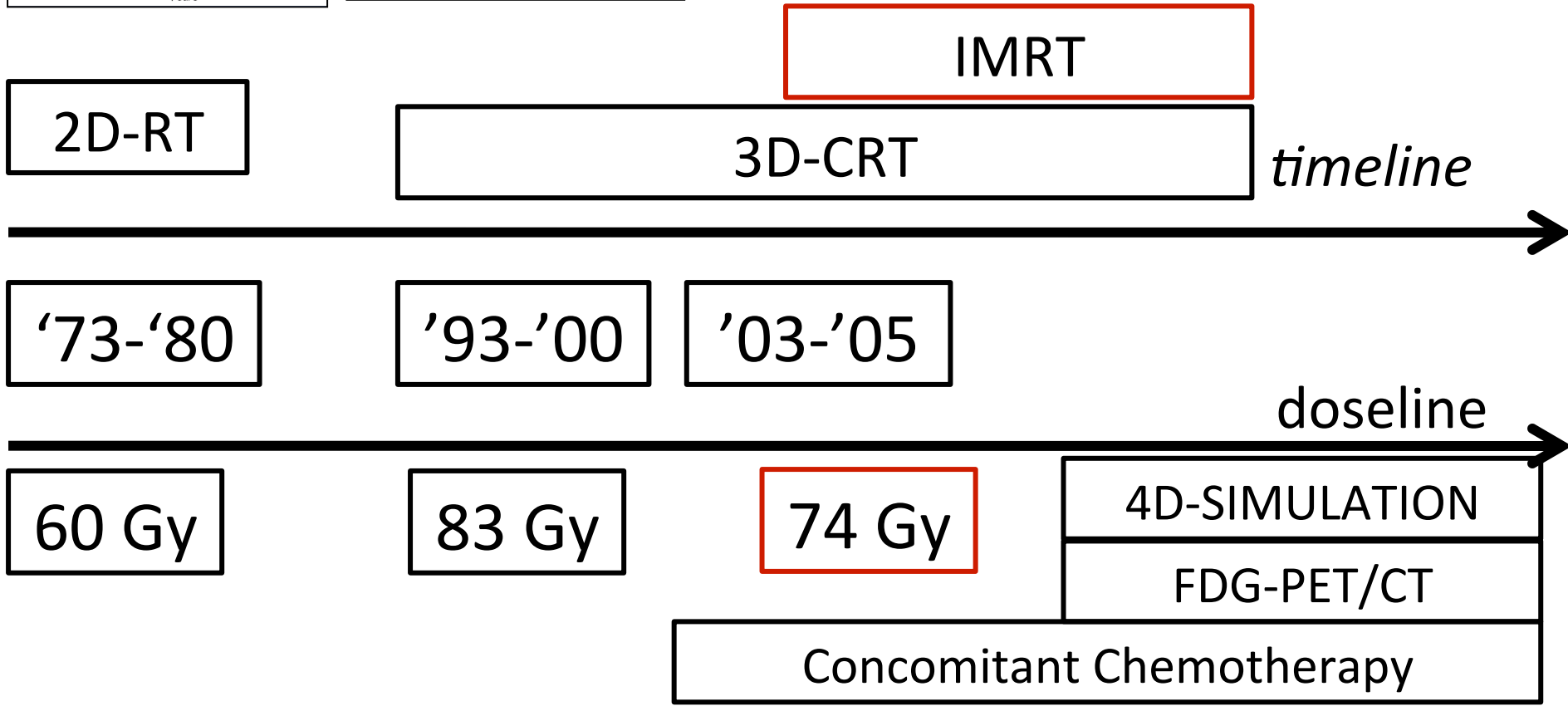


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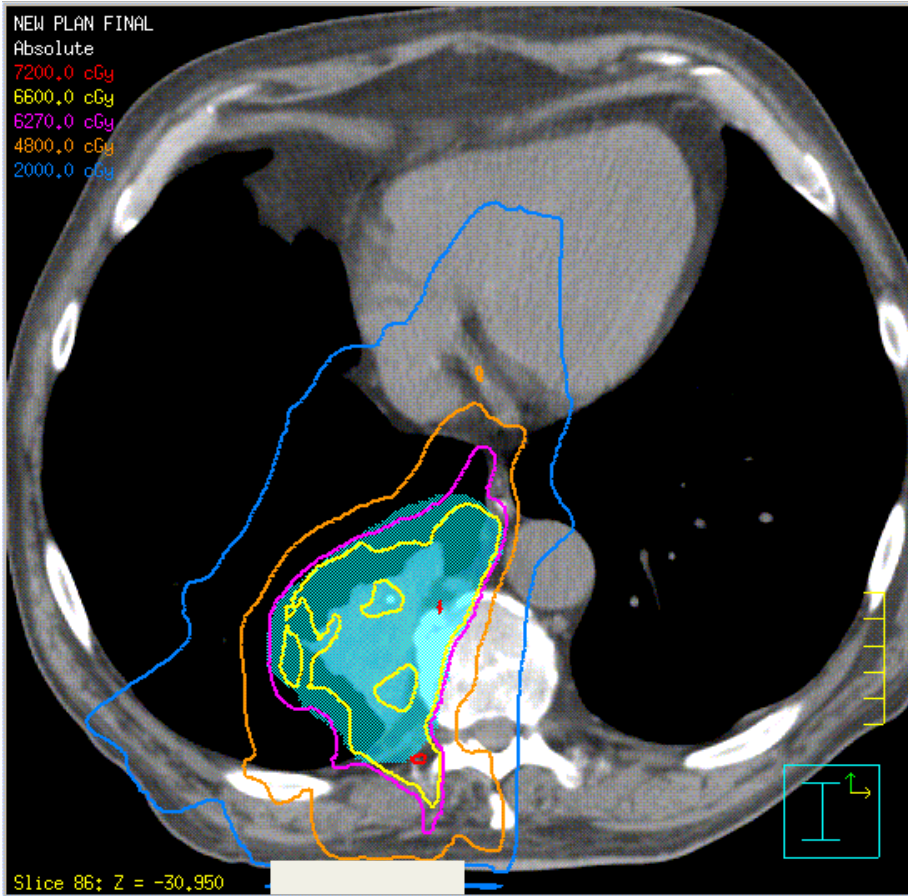
# IMRT

- ❖ IMRT reduces normal lung volumes (MLD; V20)
- ❖ IMRT reduces heart volumes
- ❖ Easier to cover PTV near spine with IMRT
- ❖ Better QOL with lung IMRT? (Movsas et al. ASTRO 2013)
- ❖ IMRT choices
  - Static leaf
  - Dynamic leaf
  - VMAT

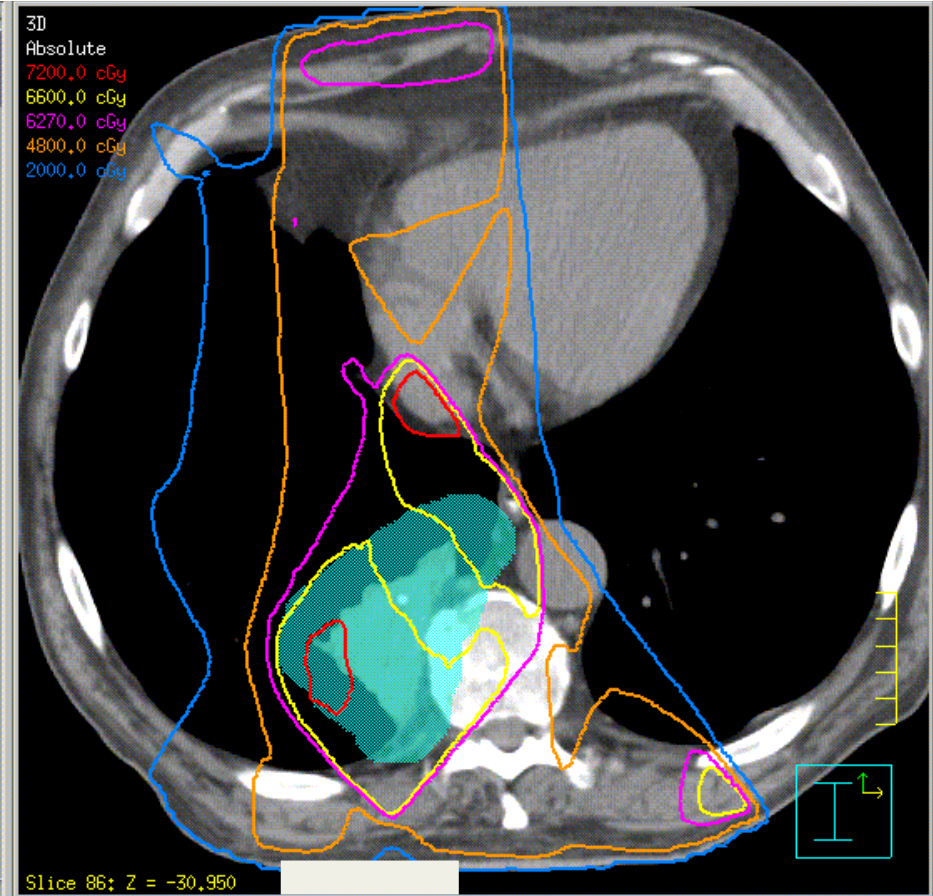


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IMRT



3DCRT

Courtesy of JD Bradley



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# WU RP Risk Calculator

**IMRT**

**3DCRT**

## RP Risk Calculator

## RP Risk Calculator

Patient Name: ANDERSON, ARTHUR,  
Plan: IMRT  
Trial: NEW PLAN FINAL  
Date: 4/18/2008

Most Superior Slice of RT LUNG: **-52.25**  
Most Inferior Slice of RT LUNG: **-26.1501**  
Lung Length: 26.0999  
Slice with GTV center on it: **-34.40005**  
GTV position: 0.32 (0=inferior, 1=superior)  
Mean total lung-gtv Dose (in Gy): **13.48 Gy**

**RP Risk: 0.298** ←

**Desired risk level (RP): 0.2**

**Max MLD to achieve this: 8.81 Gy**

Patient Name: ANDERSON, ARTHUR,  
Plan: IMRT  
Trial: 3D  
Date: 4/18/2008

Most Superior Slice of RT LUNG: **-52.25**  
Most Inferior Slice of RT LUNG: **-26.1501**  
Lung Length: 26.0999  
Slice with GTV center on it: **-34.40005**  
GTV position: 0.32 (0=inferior, 1=superior)  
Mean total lung-gtv Dose (in Gy): **16.95 Gy**

**RP Risk: 0.386** ←

**Desired risk level (RP): 0.2**

**Max MLD to achieve this: 8.81 Gy**



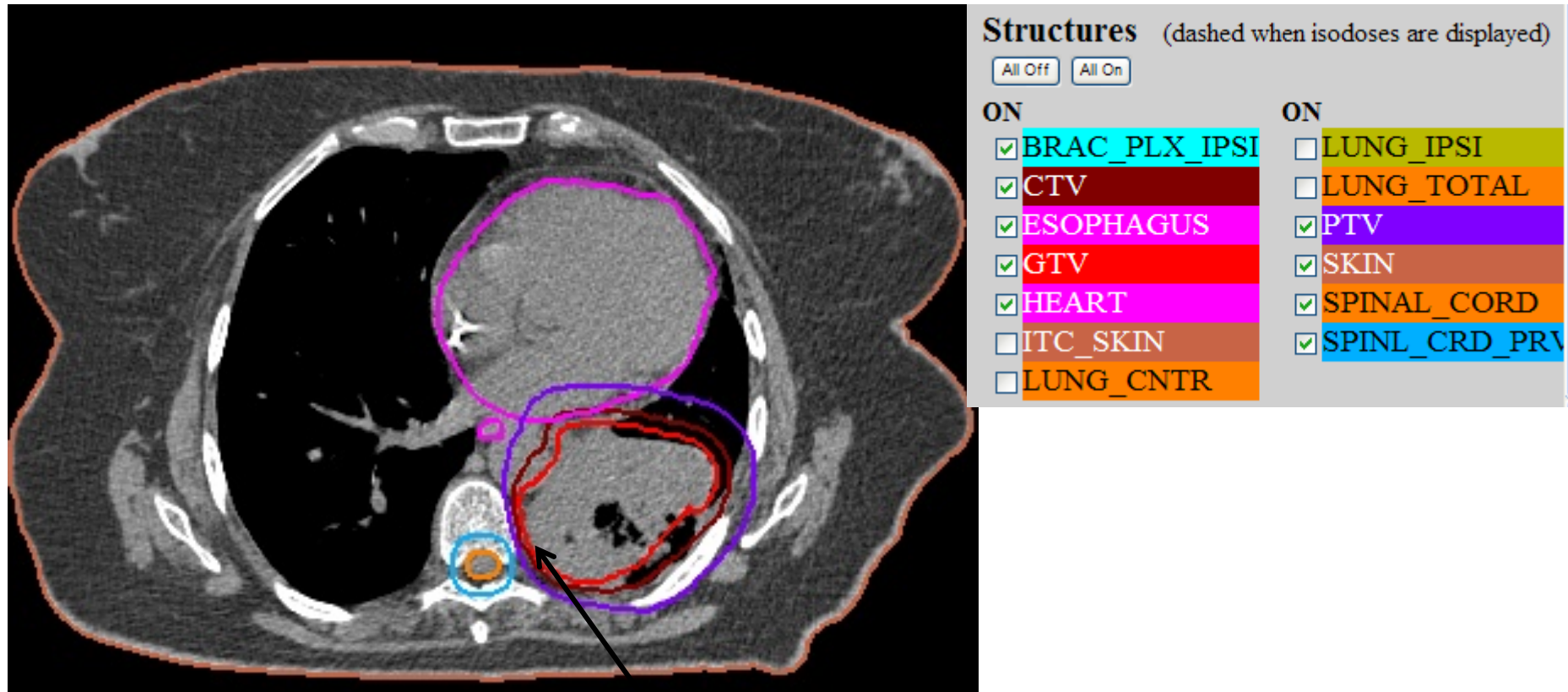
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# IMRT

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  - Static leaf
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# Contouring Problems on RTOG Trials (3)



No margin on GTV





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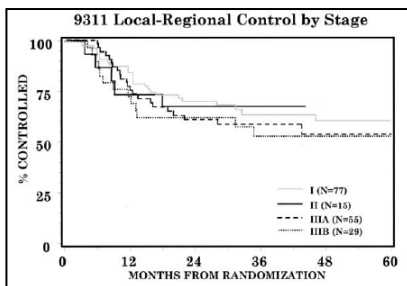
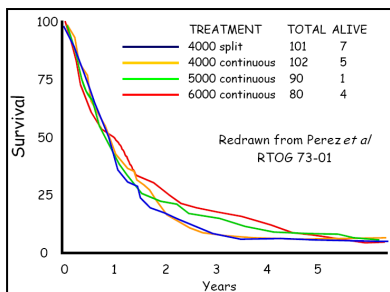
# IMRT

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| CALGB 30105 <sup>38</sup> | 74                 |

**RTOG 0617**  
**60 Gy vs.74 Gy**

2D-RT

IMRT

3D-CRT

*timeline*

'73-'80

'93-'00

'03-'05

'06-'11

*doseline*

60 Gy

83 Gy

74 Gy

4D-SIMULATION

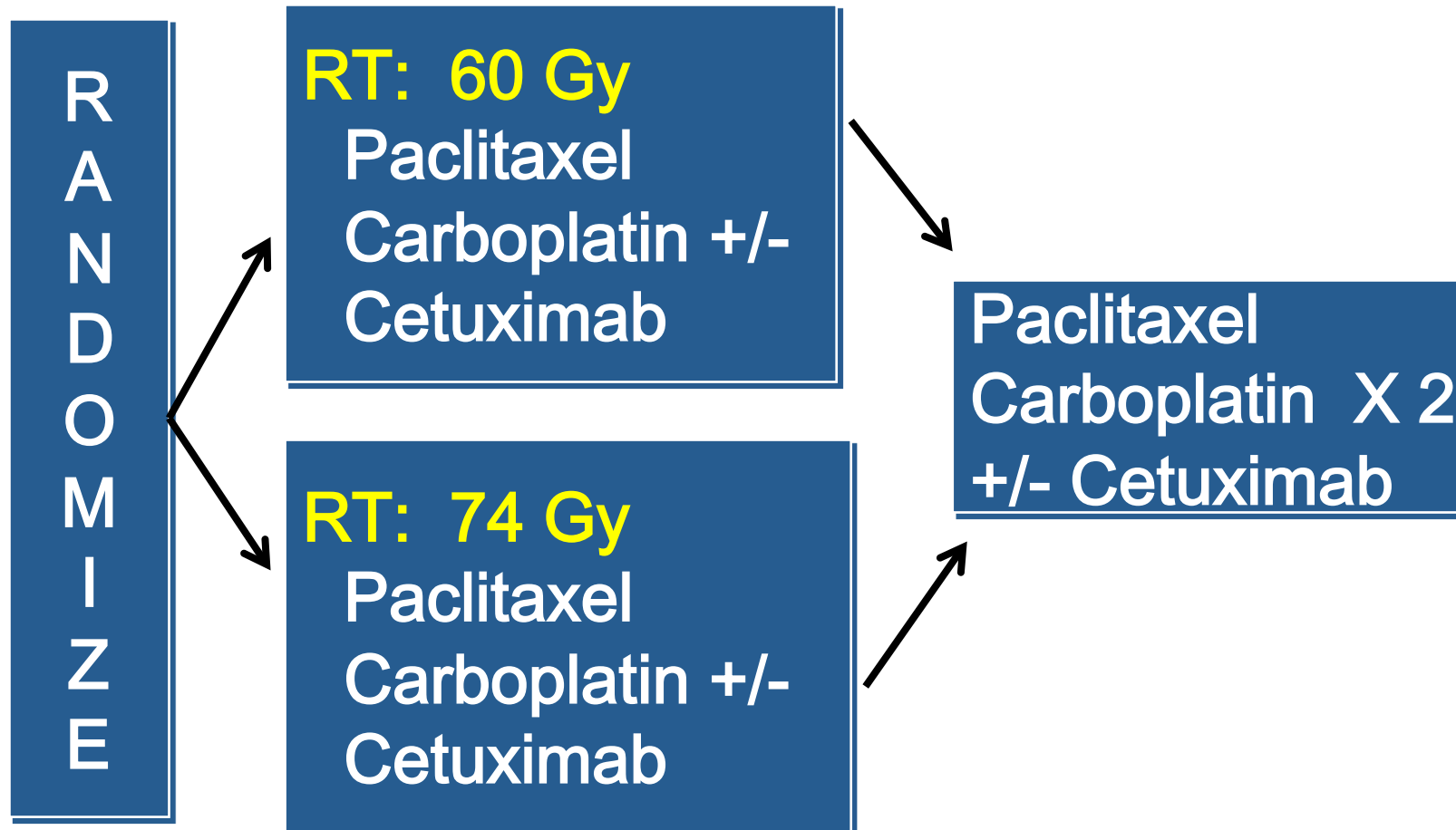
FDG-PET/CT

Concomitant Chemotherapy



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- Newly diagnosed, unresectable Stage IIIA/B NSCLC; patients who present with N2/N3 disease and an undetectable NSCLC primary tumor are also eligible
- No supraclavicular or contralateral hilar adenopathy
- Zubrod 0/1



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# Pretreatment Characteristics

|                | <b>60 Gy<br/>(n=216)</b> | <b>74 Gy<br/>(n=208)</b> |
|----------------|--------------------------|--------------------------|
| Age (median)   | 64                       | 64                       |
| Gender         |                          |                          |
| Male           | 127 (58.8%)              | 119 (57.2%)              |
| Female         | 89 (41.2%)               | 89 (42.8%)               |
| RT Technique   |                          |                          |
| 3DCRT          | <b>116 (57.3%)</b>       | <b>113 (54.3%)</b>       |
| IMRT           | <b>100 (46.3%)</b>       | <b>95 (45.7%)</b>        |
| PET Staging    | <b>91.2%</b>             | <b>88.9%</b>             |
| Histology      |                          |                          |
| Adenocarcinoma | 86 (39.8%)               | 73 (35.1%)               |
| Squamous       | 86 (39.8%)               | 96 (46.2%)               |
| NSCLC NOS      | 39 (18.1%)               | 33 (15.9%)               |
| AJCC Stage     |                          |                          |
| Stage IIIA     | 138 (65.7%)              | 131 (63.6%)              |
| Stage IIIB     | 72 (34.3%)               | 75 (36.4%)               |

Courtesy of J.D. Bradley



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## RTOG 0617: Median OS

|                | Standard dose<br>60 Gy | High dose<br>74 Gy |
|----------------|------------------------|--------------------|
| Follow-up 11 m | 21.7 m                 | 20.7 m             |
| Follow-up 17 m | 28.7 m                 | 19.5 m             |



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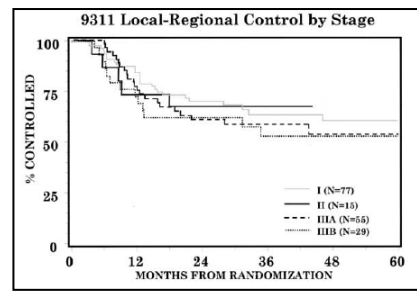
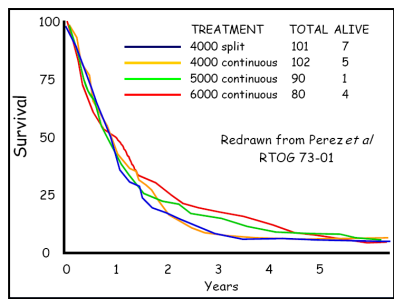
## Multivariate Cox Model Backwards Selection

| <b>Covariate</b>                    | <b>Comparison</b>        | <b>HR (95% CI)</b>          | <b>p-value</b> |
|-------------------------------------|--------------------------|-----------------------------|----------------|
| <b>Radiation dose</b>               | <b>60 Gy v 74 Gy</b>     | <b>1.48 (1.00, 2.22)</b>    | <b>0.038</b>   |
| <b>Histology</b>                    | <b>Non-squam v Squam</b> | <b>1.52 (0.90, 1.99)</b>    | <b>0.025</b>   |
| Age                                 | Continuous               | 1.02 (1.03, 2.77)           | 0.061          |
| <b>GTV (ITV if GTV unavailable)</b> | <b>Continuous</b>        | <b>1.002 (1.000, 1.004)</b> | <b>0.011</b>   |



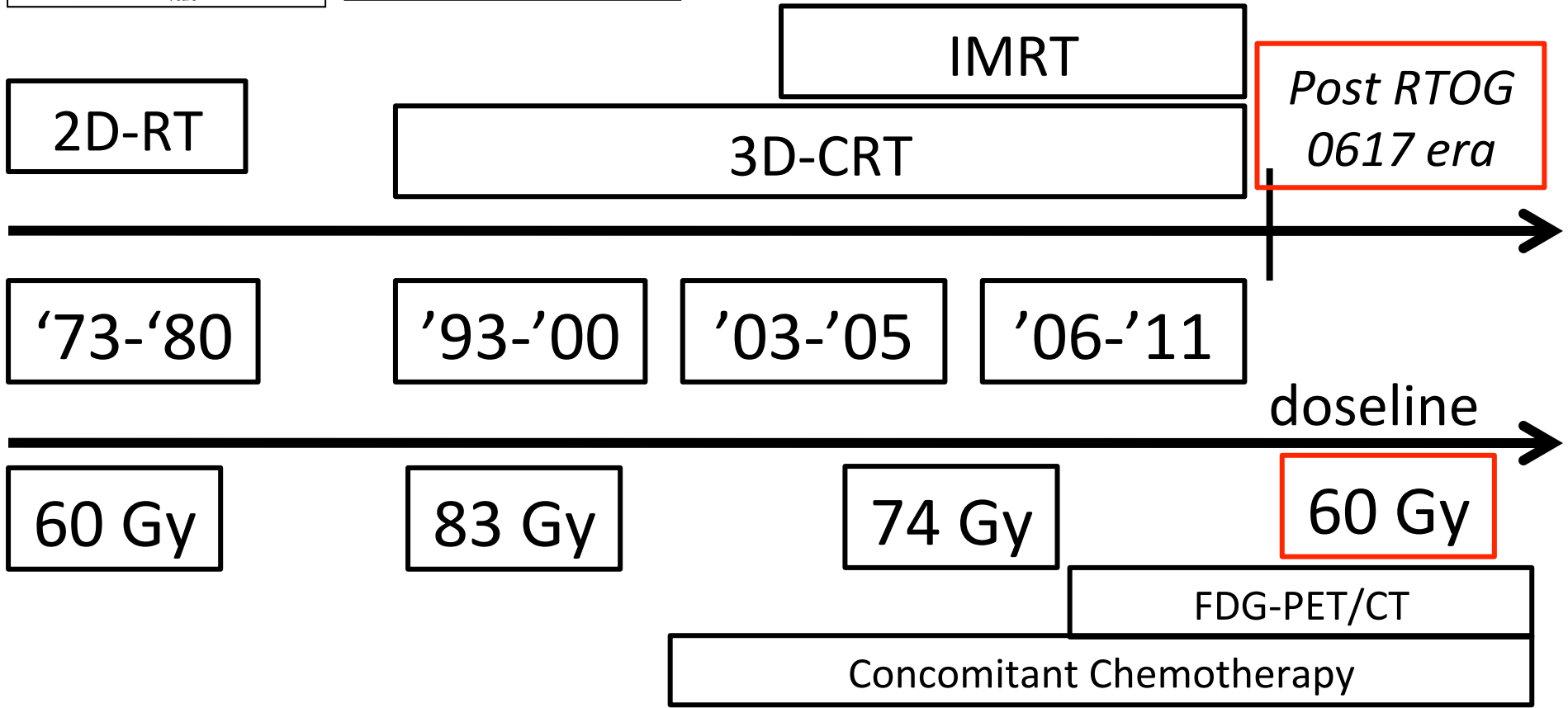
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| Study                     | Radiation MTD (Gy) |
|---------------------------|--------------------|
| RTOG 0117 <sup>34</sup>   | 74                 |
| NCCTG 0028 <sup>35</sup>  | 74                 |
| UNC <sup>36</sup>         | 74                 |
| Wake Forest <sup>37</sup> | 74                 |
| CALGB 30105 <sup>38</sup> | 74                 |

**RTOG 0617**  
60 Gy vs. 74 Gy

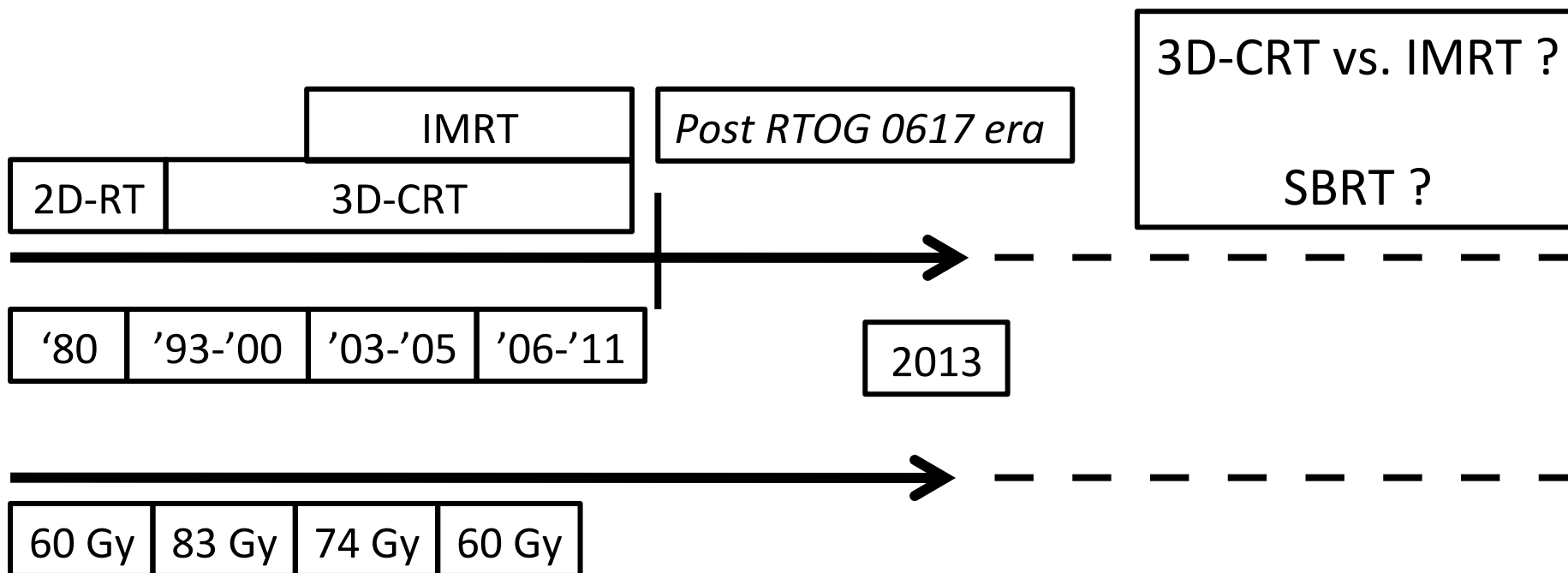






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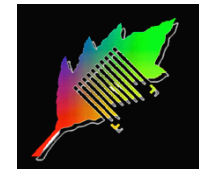


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## 3D vs. IMRT ?

- ❖ 60 Gy standard dose
- ❖ Hypofractionation
- ❖ Quality of Life





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# 3D vs. IMRT : Hypofractionation



## *Lung session IV: Toxicity and Fractionation*

Accelerated hypofractionated radiotherapy  
using Tomotherapy plus chemotherapy for  
inoperable locally advanced lung cancer:  
preliminary results of a prospective phase II trial

ELISABETTA PARISI

Department of Radiation Oncology

IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori

Meldola (FC) ITALY

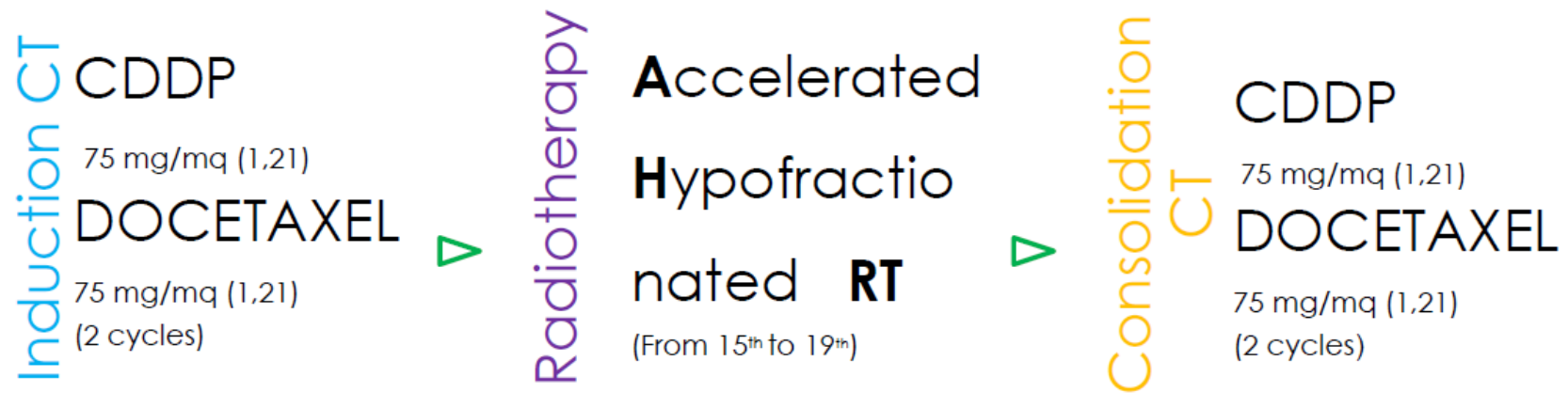


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# 3D vs. IMRT : Hypofractionation

## Program protocol



| Prescription dose |                   |               |
|-------------------|-------------------|---------------|
| T                 | 30 Gy/5 fractions | up to 40 Gy   |
| N                 | 25 Gy/5 fractions | up to 37.5 Gy |



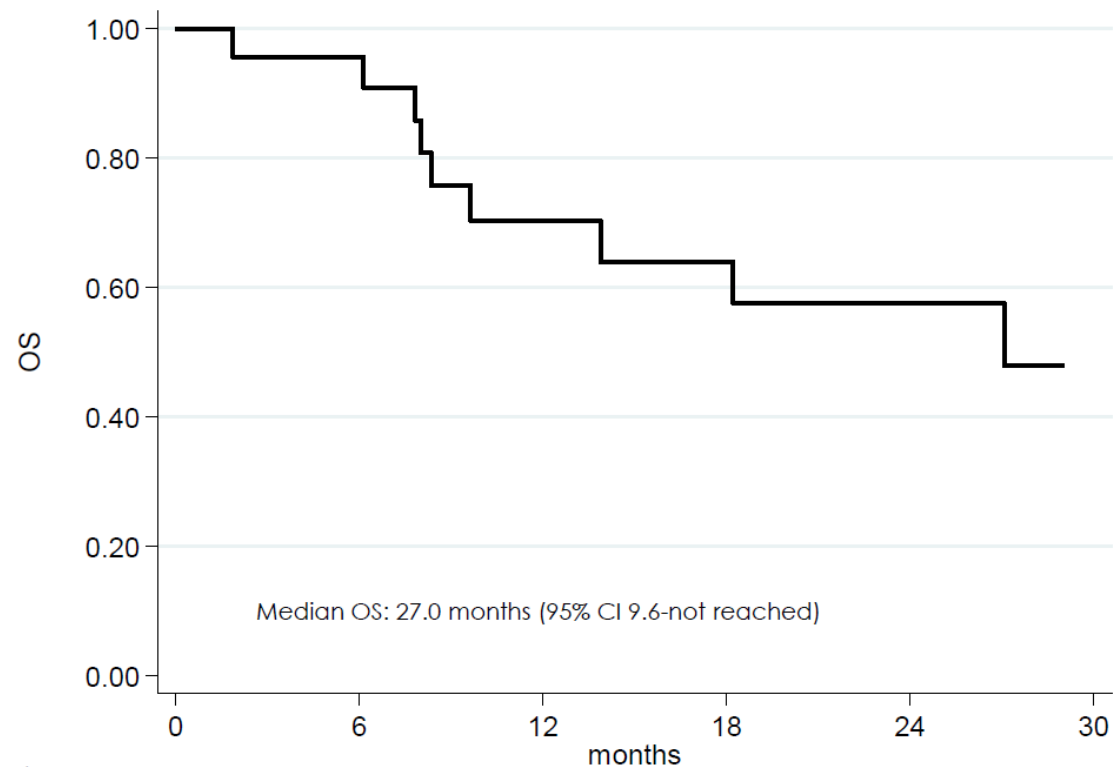
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# 3D vs. IMRT : Hypofractionation

## Overall Survival

(median follow-up : 23 months, range 2-42)



*Courtesy of E.Parisi*



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## 3D vs. IMRT: QoL

### Quality of Life Analysis of the Randomized Radiation Dose-Escalation NSCLC Trial: The Rest of the Story

1. Clinical meaningful decline for 74 Gy was higher (46%) at 3 months than for 60 Gy (31%)  $p=0.02$ .
2. IMRT was associated with significantly less QoL decline than 3D.
3. Base line QoL predicted for survival (at the MVA)
  - May the decline in QoL on the 74 Gy arm account for the survival decrement?
  - The use of IMRT vs. 3D may help enhance the therapeutic window



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# Gruppo di studio Polmone

## Sala Tindari B,

## Martedì 29 ottobre h 14.00



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# Hypofractionation ?





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# **HYPOR**

**RADIOTERAPIA IPOFRAZIONATA  
ACCELERATA DOPO CHEMIOTERAPIA IN  
PAZIENTI AFFETTI DA NSCLC NON  
CHIRURGICO IN STADIO IIIA-IIIIB.**

Andrea R. Filippi, Stefano Arcangeli



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## **HYPORT**

68.75 Gy in 25 frazioni (2.75 x 25),  
BED alfa/beta 10: 72 Gy

Tecnica RT: 3D-CRT o IMRT con IGRT  
e 4D-CT



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## SBRT?

### **Stereotactic Body Radiation Therapy Can Be Used Safely to Boost Residual Disease in Locally Advanced Non-Small Cell Lung Cancer: A Prospective Study**

Jonathan Feddock, MD,<sup>\*</sup> Susanne M. Arnold, MD,<sup>\*,†</sup> Brent J. Shelton, PhD,<sup>‡</sup> Partha Sinha, MD,<sup>§</sup> Gary Conrad, MD,<sup>§</sup> Li Chen, PhD,<sup>‡</sup> John Rinehart, MD,<sup>†</sup> and Ronald C. McGarry, MD, PhD<sup>\*</sup>



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## SBRT?

**P321**

### **L'IRRADIAZIONE CARDIACA È UN FATTORE DI RISCHIO DI TOSSICITÀ POLMONARE SEVERA E MORTALITÀ IN PAZIENTI SOTTOPOSTI A RE-IRRADIAZIONE CON RADIOTERAPIA STEREOTASSICA PER CARCINOMA DEL POLMONE**

M. Trovo, E. Durofil, A. Drigo, E. Minatel, G. Franchin, C. Gobitti, C. Furlan, I. Abu Rumeileh, M.G. Trovo

*Centro di Riferimento Oncologico di Aviano, Italia*



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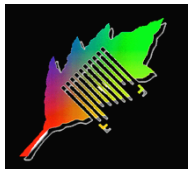
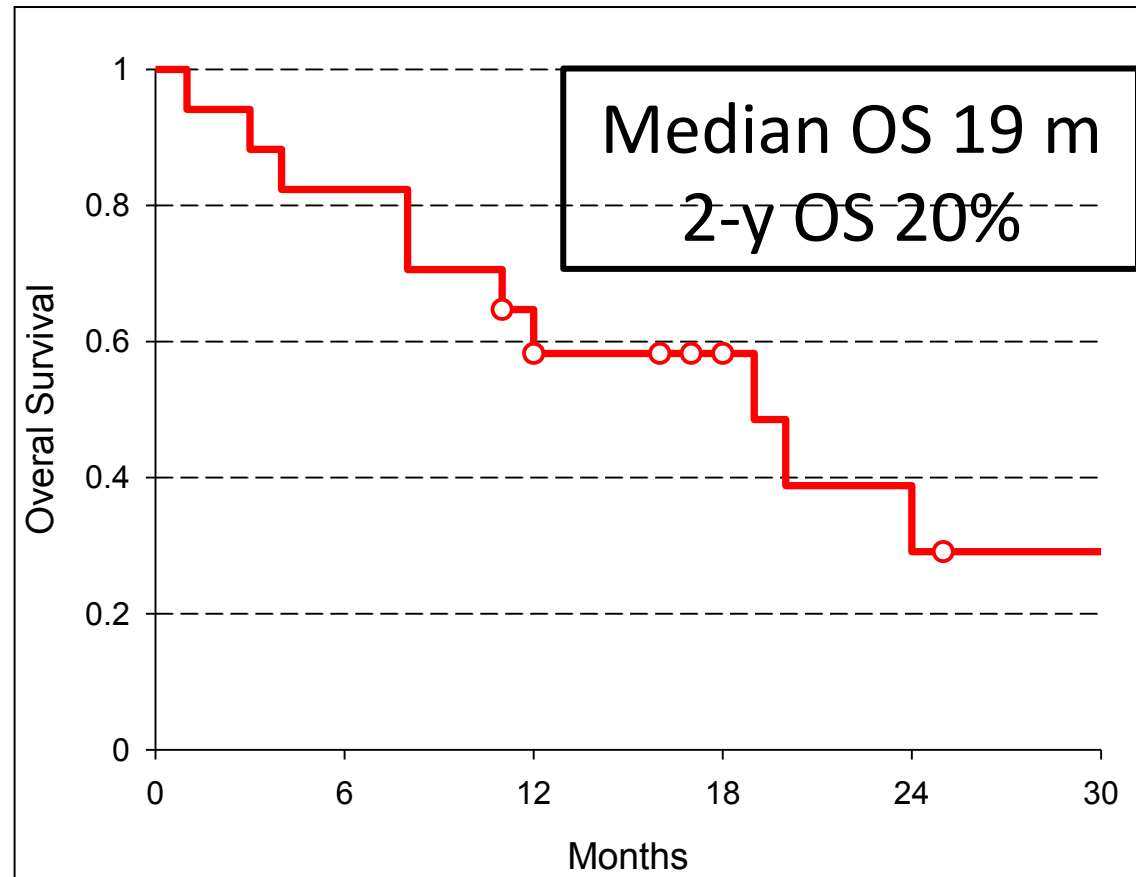
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## SBRT?

17 NSCLC  
stage III

30 Gy/5-6 fr  
SBRT-boost

Median FU 18 m





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## CONCLUSIONI:

La 3D-CRT rappresenta uno (lo) standard terapeutico del LA-NSCLC

(RTOG 06-17 → 60 Gy dose standard)

Il ruolo dell'IMRT può/dovrebbe essere sviluppato nella ricerca clinica

- QoL
- Ipofrazionamento

L'SBRT boost dovrebbe essere investigato in trials clinici (Fase I/II)



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*Grazie per l'attenzione !*

*marco.trovo@cro.it*

