# La terapia del Linfoma di Hodgkin

# La Radioterapia

Umberto Ricardi

DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

# RT in classical Hodgkin Lymphoma

- In most HL patients, RT is used in combination with chemotherapy
- Chemotherapy has evolved with increasing efficacy to play a major role in the management of HL
- RT continues to have an important place in ensuring locoregional control and improving overall outcome in the combined modality treatment programs for HL

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

# Classical Hodgkin Lymphoma

- ✓ Early stages:

  Without risk factors (Favourable)

  With risk factors (Unfavourable)

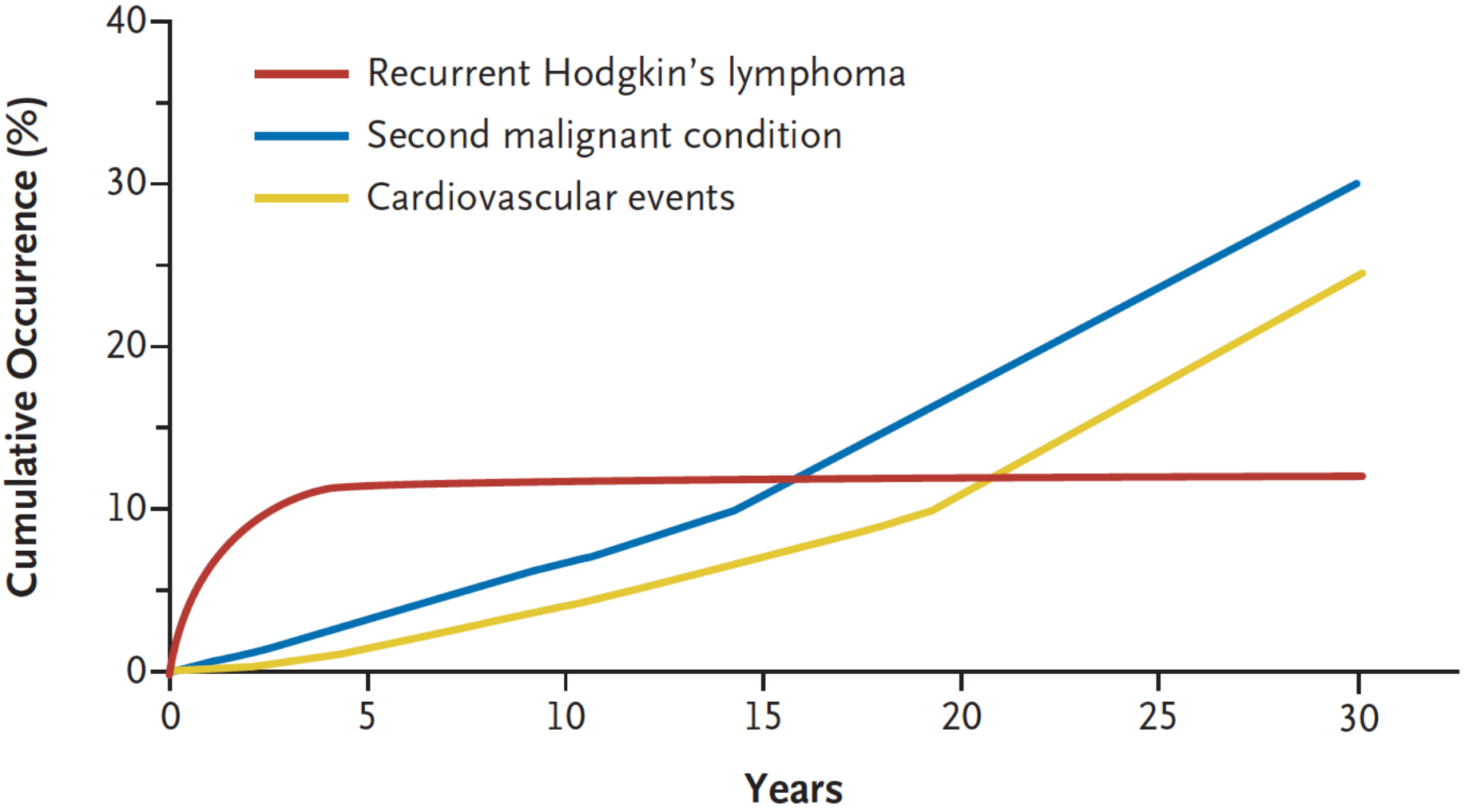
- ✓ Advanced stages (bulky sites, residual disease)

DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

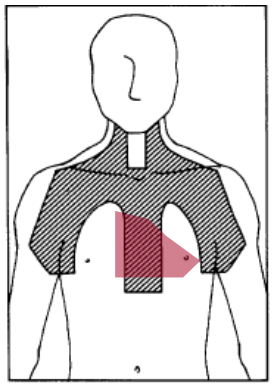
# Overall results of therapy for early disease

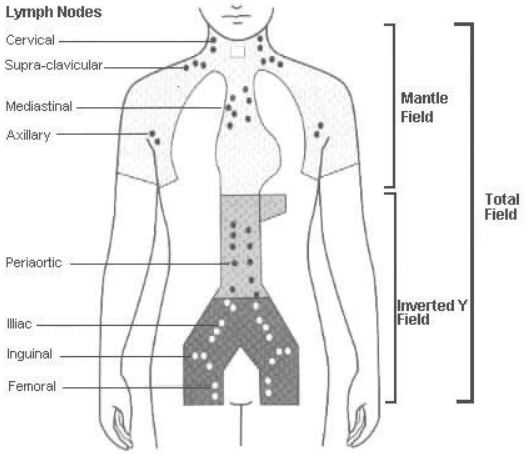
- Up to 90% cures with first line therapy
- About 95% alive at 5 years
- Primary focus of research is to
  - maintain (? improve) this result
  - minimise toxicity

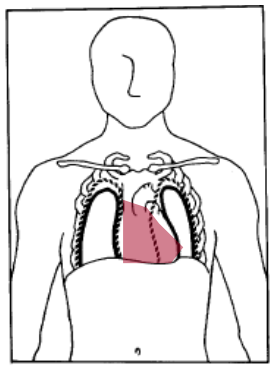
# The price of success

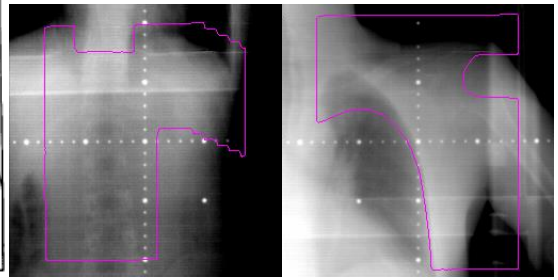


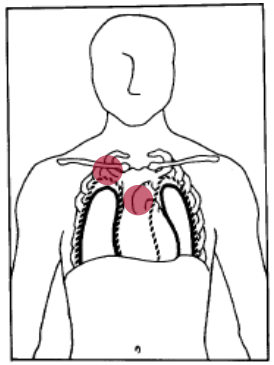
# Timeline of major changes in RT in Hodgkin's Lymphoma

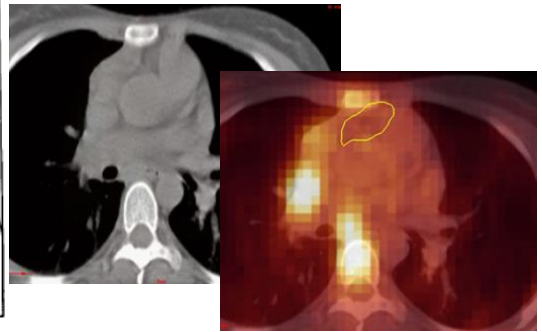










Extended fields

DFT≈40 Gy

MOPP

Involved fields

DFT≈30 Gy

ABVD

Involved nodes/sites

DFT≈20 Gy

**1960**

**Now**

# In the Era of Combined Modality Therapy Bigger is not Better (Radiation Fields)

**Milan Trial**

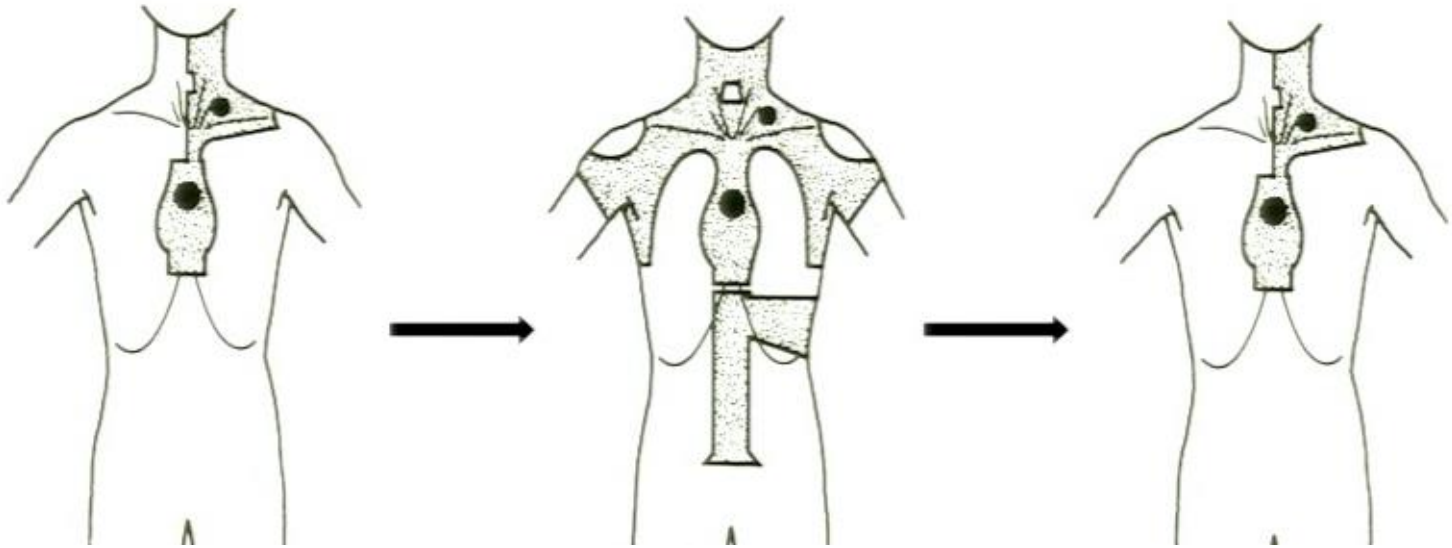
Bonadonna et al., *J Clin Oncol.* 2004;22(14):2835-2841.

**EORTC H8**

Ferme et al., *N Engl J Med.* 2007;357(19): 1916-1927.

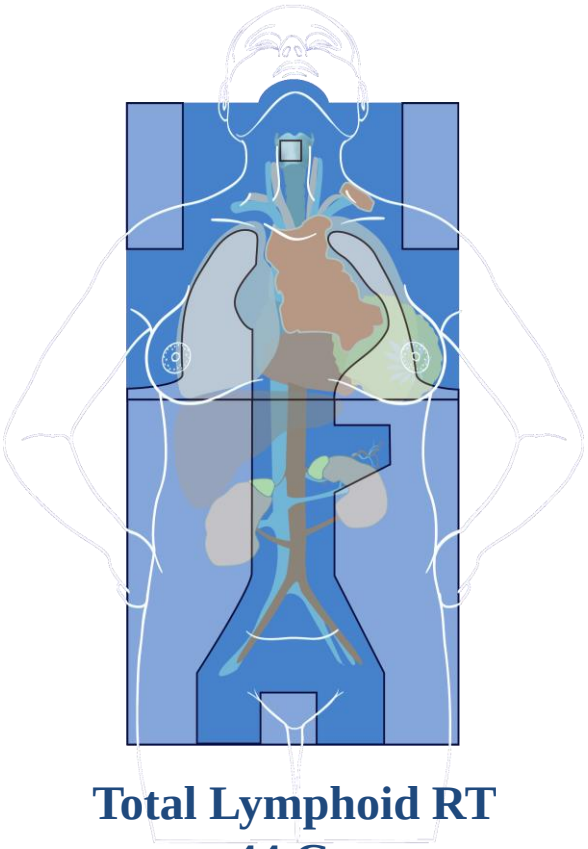
**GHSG HD8**

Engert et al., *J Clin Oncol.* 2003; 21(19):3601-3608.



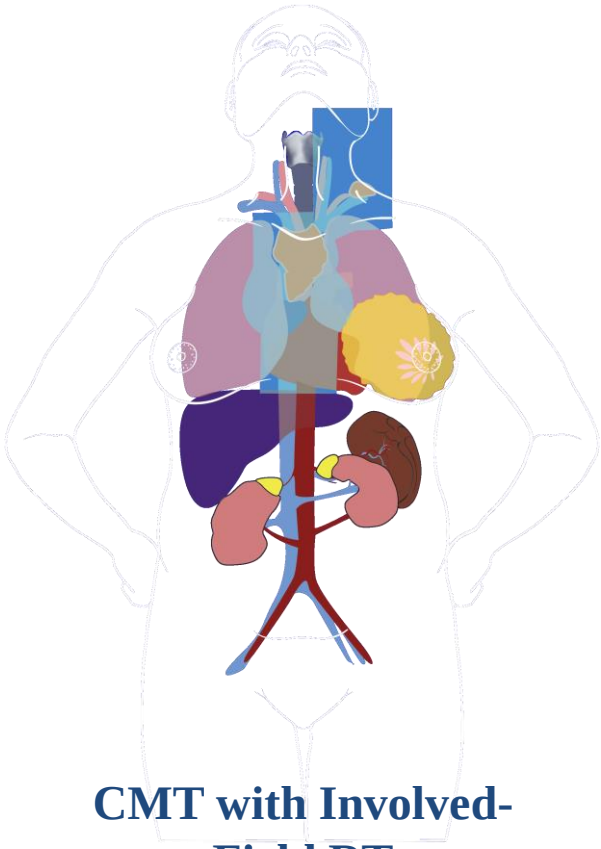
# Hodgkin Lymphoma
## Evolution of Radiotherapy

**1970**

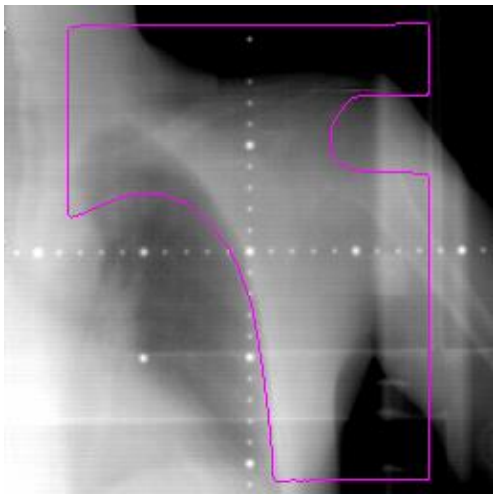


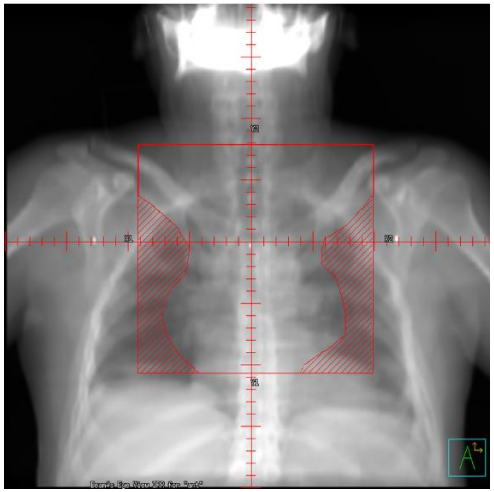
**Total Lymphoid RT**
**44 Gy**

**1995**



**CMT with Involved-Field RT**
**36 Gy**





DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 24, 2015 VOL. 373 NO. 26

# Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma

Michael Schaapveld, Ph.D., Berthe M.P. Aleman, M.D., Ph.D., Anna M. van Eggermond, M.Sc., Cécile P.M. Janus, M.D., Augustinus D.G. Krol, M.D., Ph.D., Richard W.M. van der Maazen, M.D., Ph.D., Judith Roesink, M.D., Ph.D., John M.M. Raemaekers, M.D., Ph.D., Jan Paul de Boer, M.D., Ph.D., Josée M. Zijlstra, M.D., Ph.D., Gustaaf W. van Imhoff, M.D., Ph.D., Eefke J. Petersen, M.D., Ph.D., Philip M.P. Poortmans, M.D., Ph.D., Max Beijert, M.D., Marnix L. Lybeert, M.D., Ina Mulder, Ph.D., Otto Visser, Ph.D., Marieke W.J. Louwman, Ph.D., Inge M. Krul, M.Sc., Pieternella J. Lugtenburg, M.D., Ph.D., and Flora E. van Leeuwen, Ph.D.

# Results

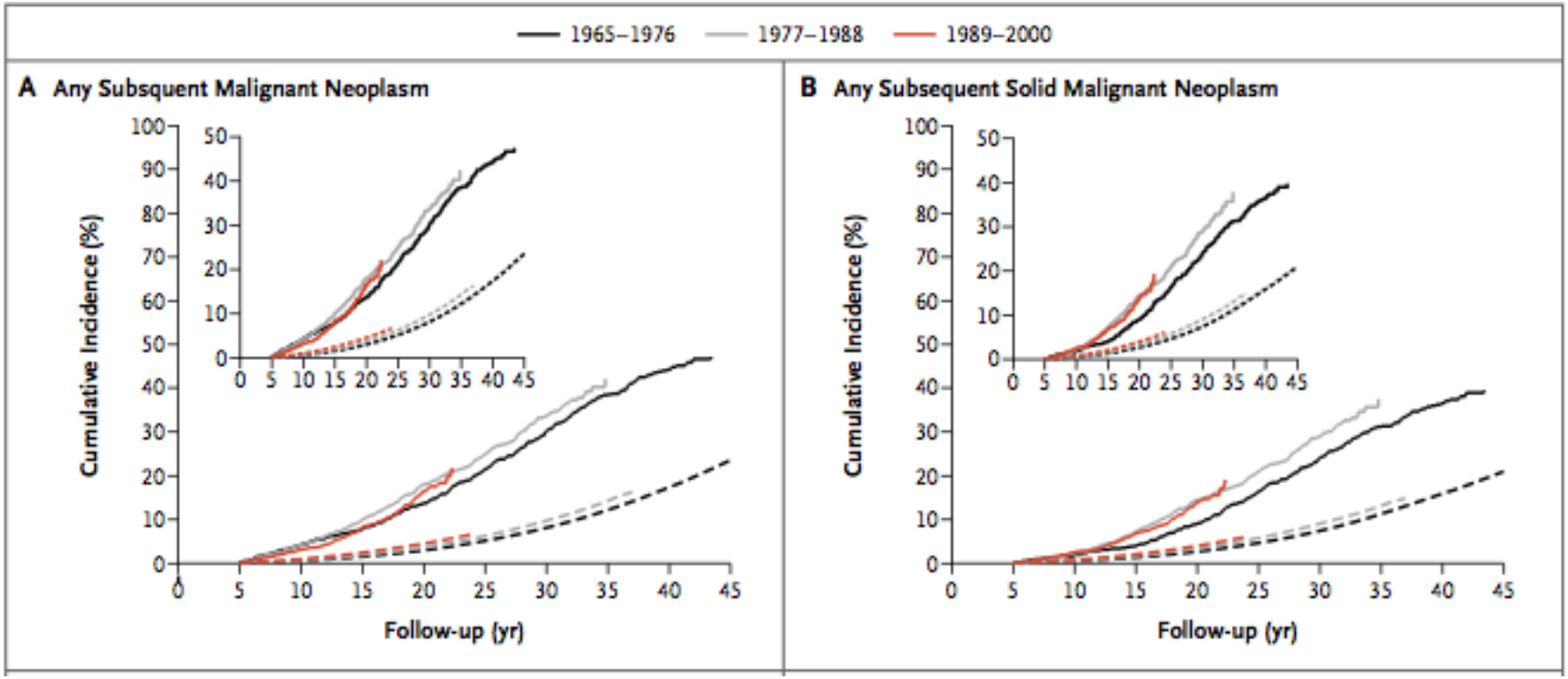



**Figure 2. Cumulative Incidence of Subsequent Malignant Neoplasms, According to Treatment Period, with Death as a Competing Risk.**
Solid lines represent the observed incidence, and dashed lines the expected incidence in the general population. The insets show the same data on enlarged y axes.

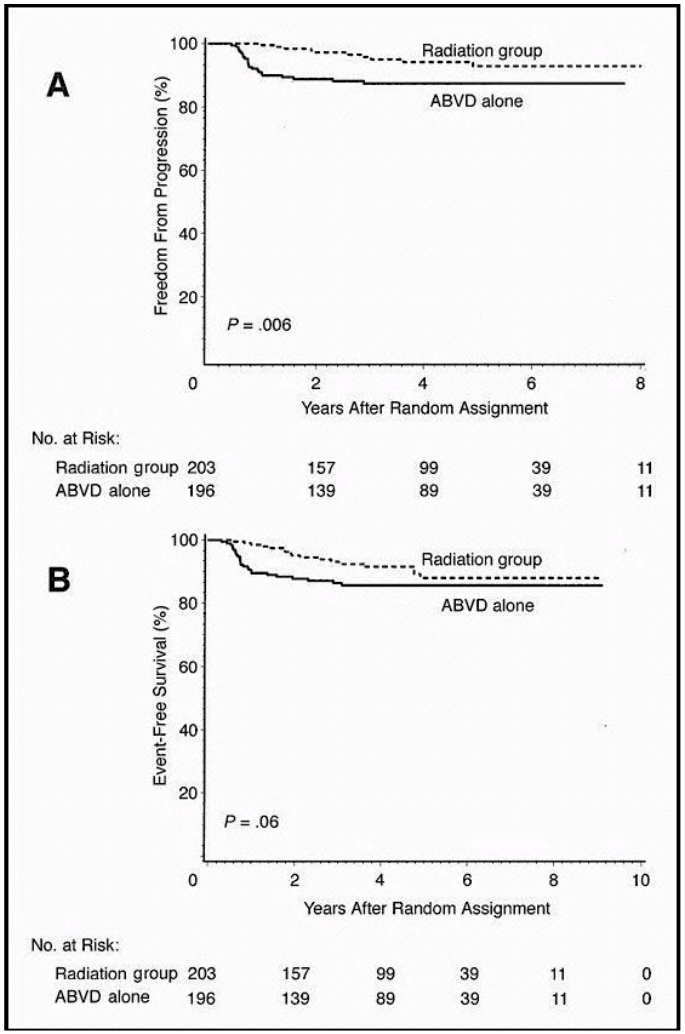
# NCIC/ECOG HD6 study: Omitting radiation completely might be detrimental for disease control…

399 patients with early stage disease

Favourable:
STNI vs ABVD 4-6 cycles

Unfavourable:
2 ABVD + STNI vs ABVD 6 cycles

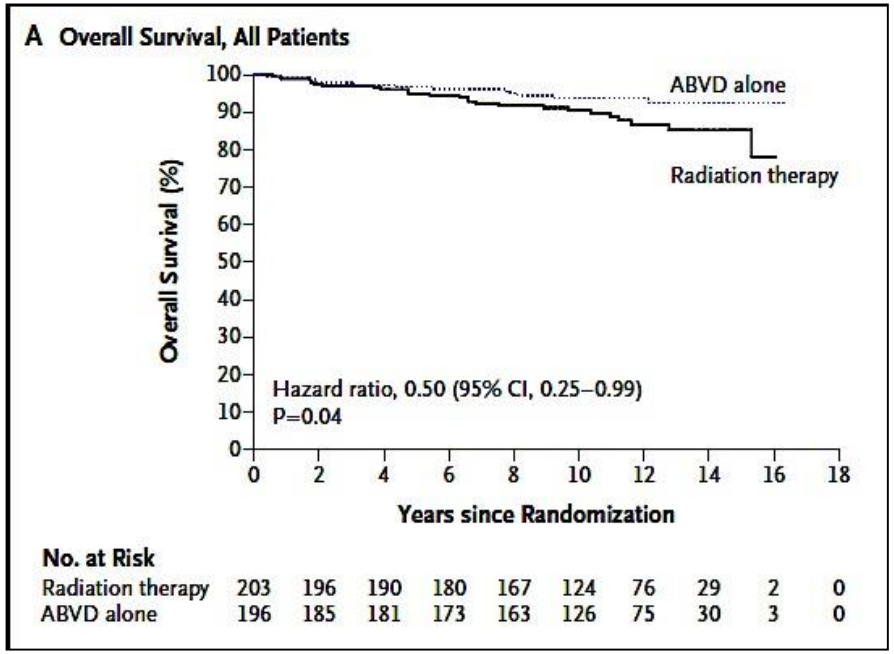
Inferior EFS, FFP with ABVD alone

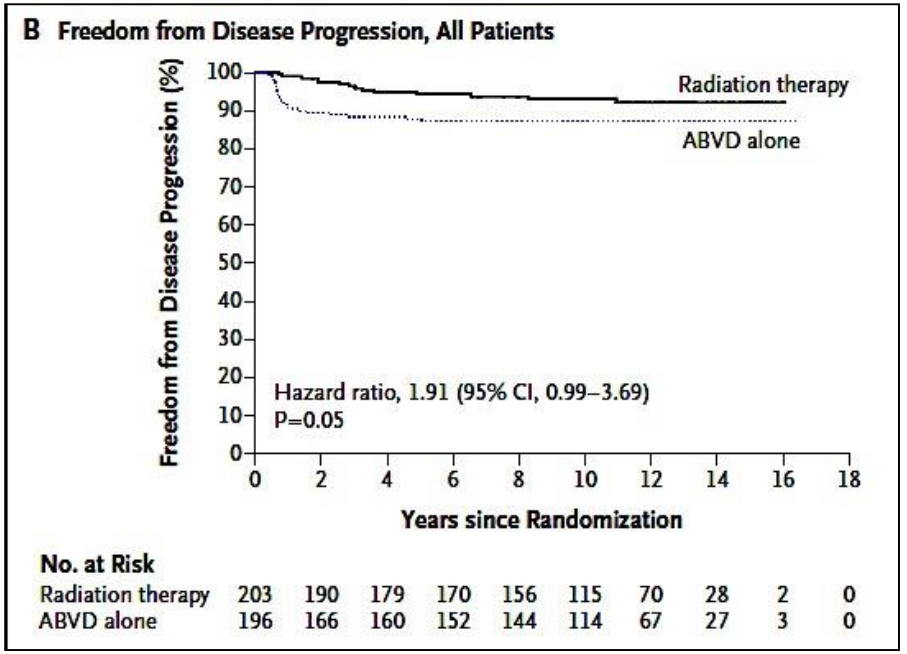



Meyer, R. M. et al. J Clin Oncol; 23:4634-4642 2005

# Omitting RT safer in the long run ?

**Meyer et al., N Engl J Med 2012; 366:399-408**




Median 11.3 yrs follow-up.

OS at 12 yrs 94 vs 87%  EFS 85 vs 80%

Deaths: RT arm: 4 HL (9 2nd cancer, 2 cardiac, 3 infection, 5 other)

ABVD arm: 5 HL (4 2nd cancer, 2 cardiac)

DEPARTMENT OF ONCOLOGY
UNIVERSITY OF TURIN

# NCIC CTG ECOG HD.6 Trial
# Unfavorable Cohort-Causes of Death

| Cause of Death | ABVD alone (137) | ABVD+STNI (139) |
|---|---|---|
| **Hodgkin Lymphoma** | 5 | 4 |
| **Cardiac** | 2 | 2 |
| **Second CA** | 4 | 9 |
| **Infection** | 0 | 3 |
| **Other** | 0 | *5 |
| **TOTAL** | 11 | 23 |

*Alzheimer disease, drowning, suicide, resp failure, unknown

From Meyer R *et al. NEJM* 2012;366:399-408

# What do we learn from NCIC/ECOG HD6 ?

- Improving long term OS depends on :
  - Effective initial therapy. RT leads to better disease control
  - Developing treatment approaches with less late toxicity (second cancers, lung injury, cardiac toxicity, infertility) is important to improving long term survival

# What don't we learn from HD6 ?

- How does full course (4-6) ABVD compare with 2 x ABVD and modern small RT field : PFS and OS, patient tolerability and quality of life

- What are the acute and late consequences of replacing 2 x ABVD and modern small RT field versus more cycles of chemotherapy ?

**No RCT to address questions**

DEPARTMENT OF ONCOLOGY
UNIVERSITY OF TURIN

# Early Stage classical Hodgkin Lymphoma

- Combined modality treatment

- Chemo followed by “modern” radiotherapy

# Hypothesis: Is more dose better?

# German HD 10 study: reducing therapy in early favourable disease

1370 pts 1998-2003
Early Favourable disease:
$I_A/II_A$

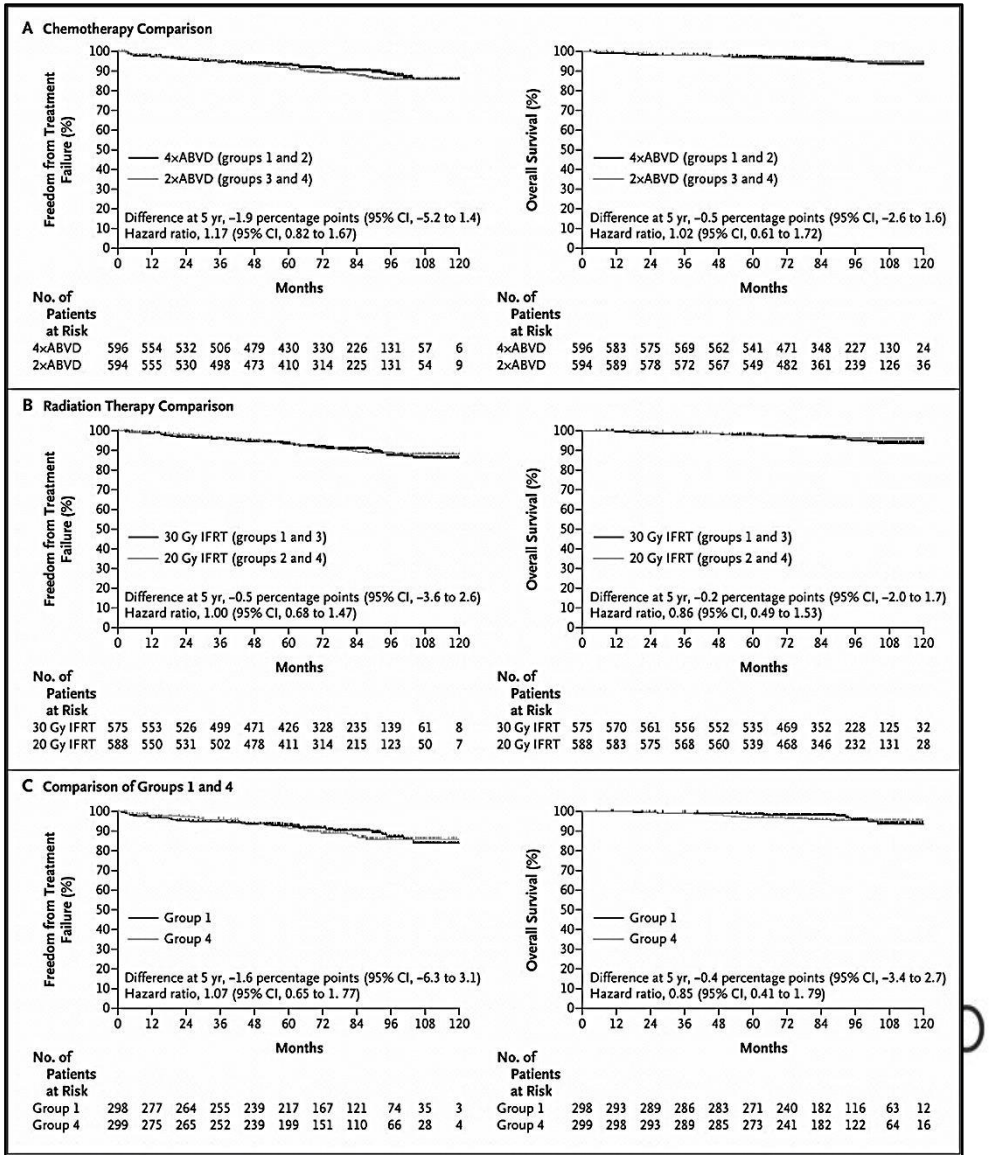
ABVD

2 cycles 4 cycles

Involved field RT

20 Gy 30 Gy

Results equivalent for all 4 arms: 5yr FFTF 92% OS 97%




**Engert A et al. N Engl J Med 2010;363:640-652.**

# German HD 11 Study:
## Lower threshold of therapy for early unfavourable disease

1395 pts 1998-2003
Early Unfavourable disease

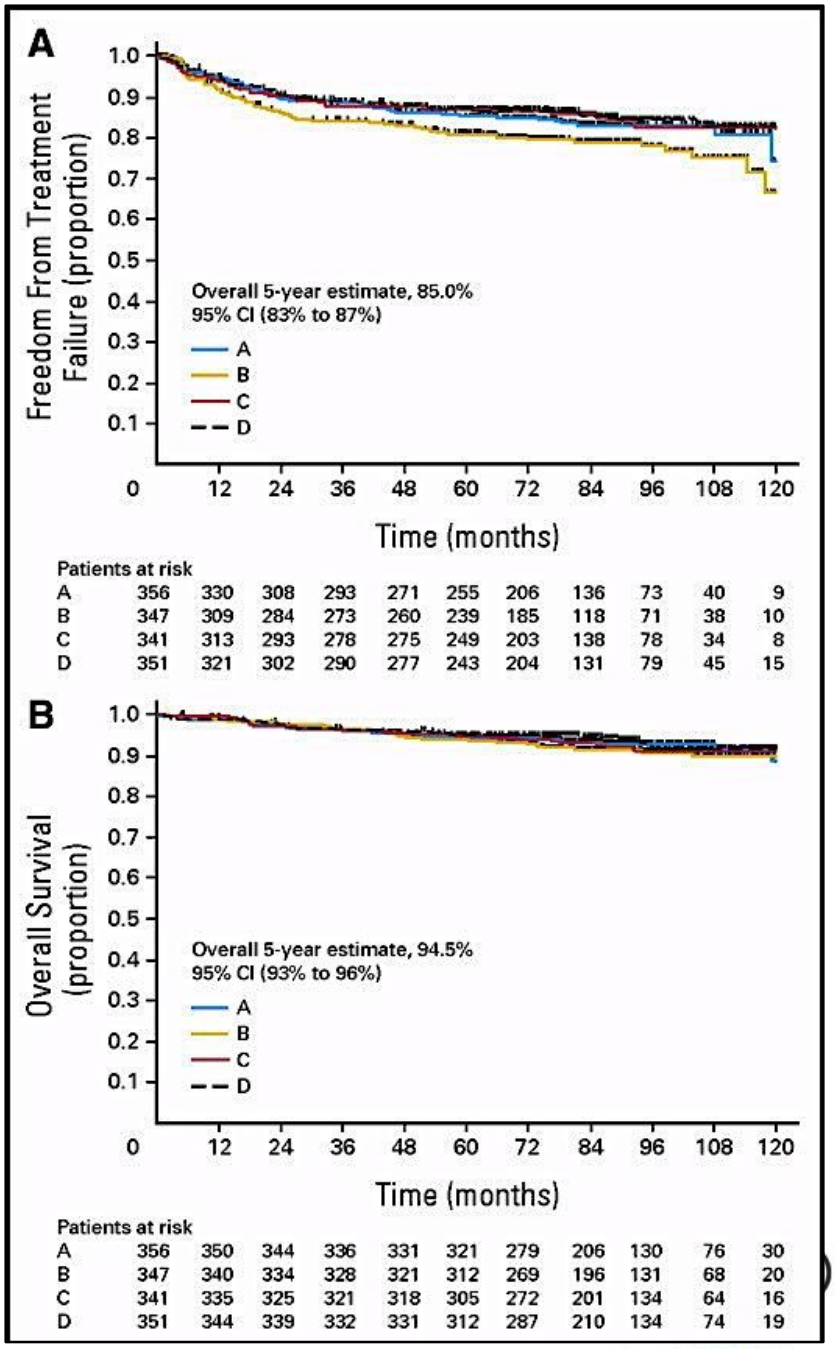
Chemotherapy

4 ABVD 4 BEACOPP

Involved field RT

20 Gy 30 Gy

ABVD + 20 Gy inferior on FFTF

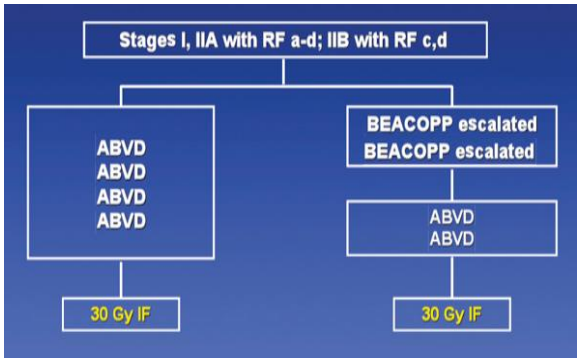



**Eich H T et al. J Clin Oncol 2010;28:4199-4206**

VOLUME 30 · NUMBER 9 · MARCH 20 2012

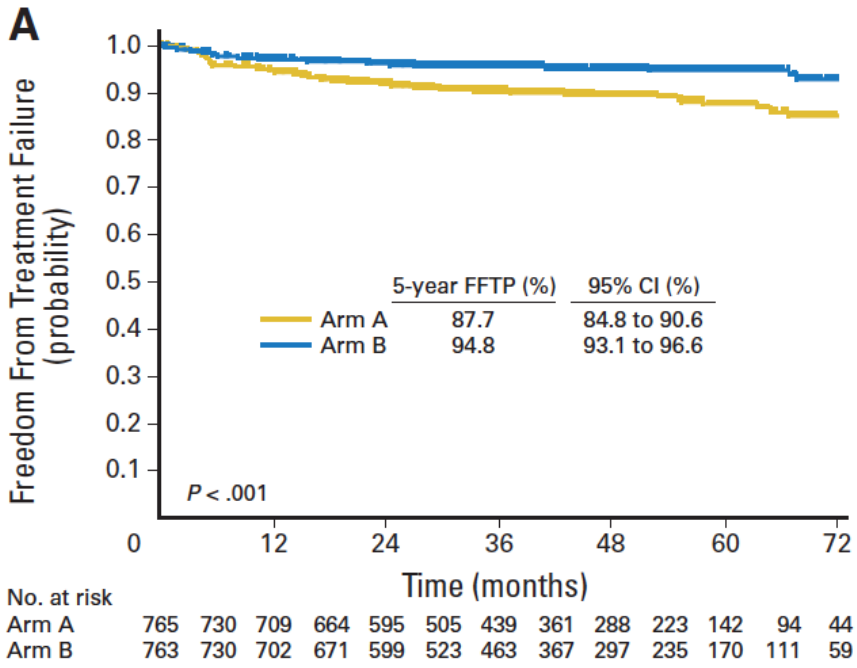
JOURNAL OF CLINICAL ONCOLOGY

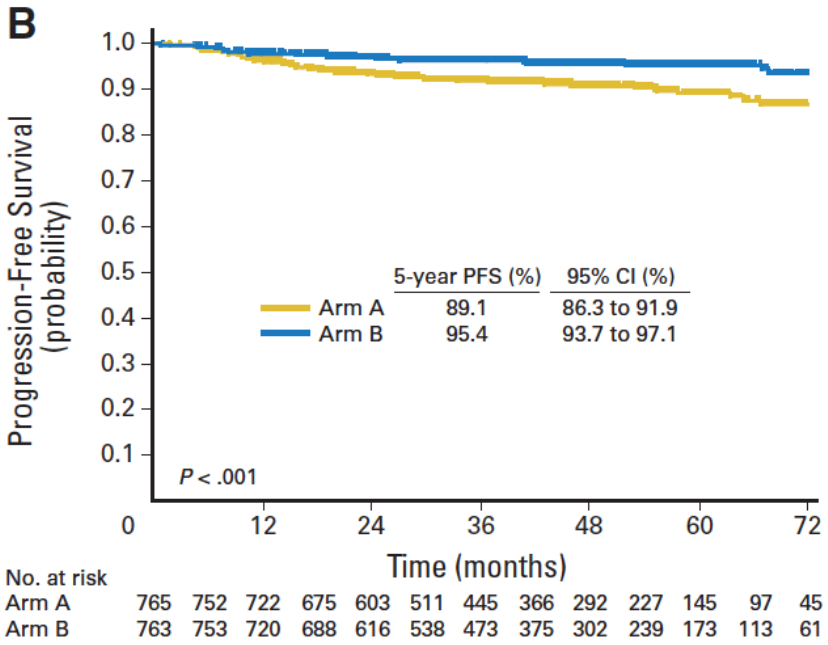
ORIGINAL REPORT




# Dose-Intensification in Early Unfavorable Hodgkin's Lymphoma: Final Analysis of the German Hodgkin Study Group HD14 Trial

*Bastian von Tresckow, Annette Plütschow, Michael Fuchs, Beate Klimm, Jana Markova, Andreas Lohri, Zdenek Kral, Richard Greil, Max S. Topp, Julia Meissner, Josée M. Zijlstra, Martin Soekler, Harald Stein, Hans T. Eich, Rolf P. Mueller, Volker Diehl, Peter Borchmann, and Andreas Engert*



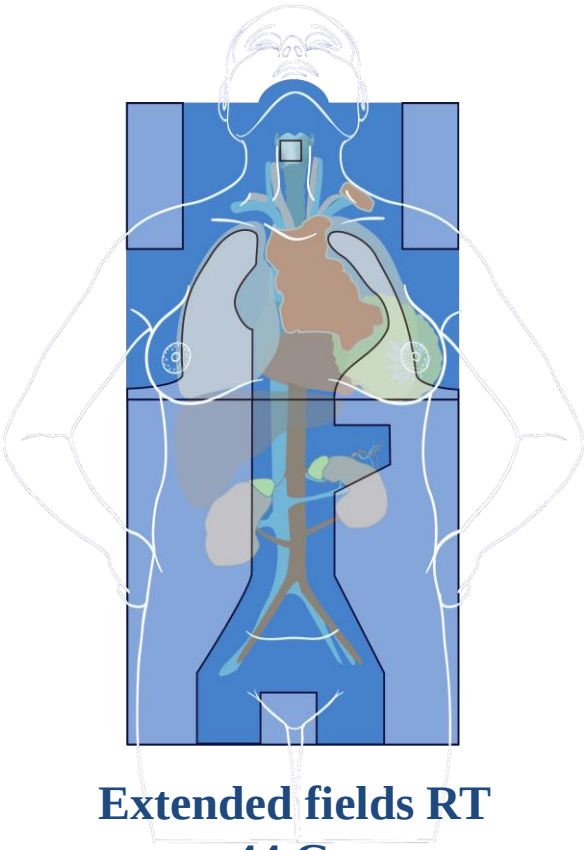




There was more acute toxicity associated with 2+2 than with ABVD, but there were no overall differences in treatment-related mortality or secondary malignancies

# Hodgkin Lymphoma

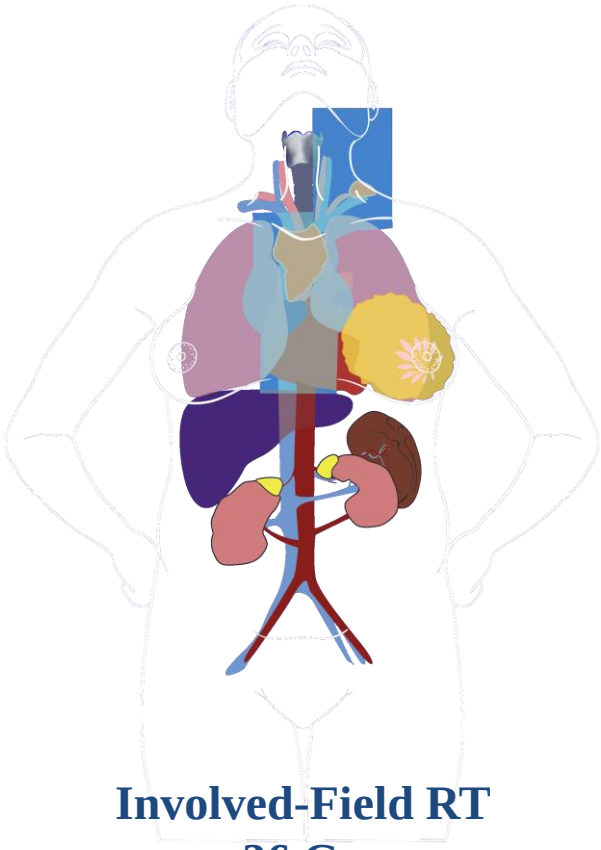
## Evolution of Radiotherapy: Volumes

**1970**



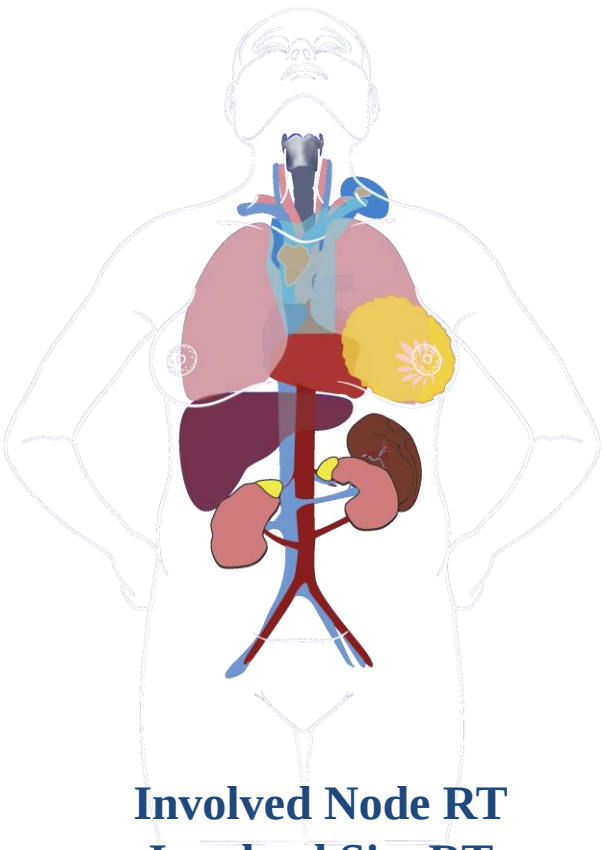
**Extended fields RT**
**44 Gy**

**1995-2008**



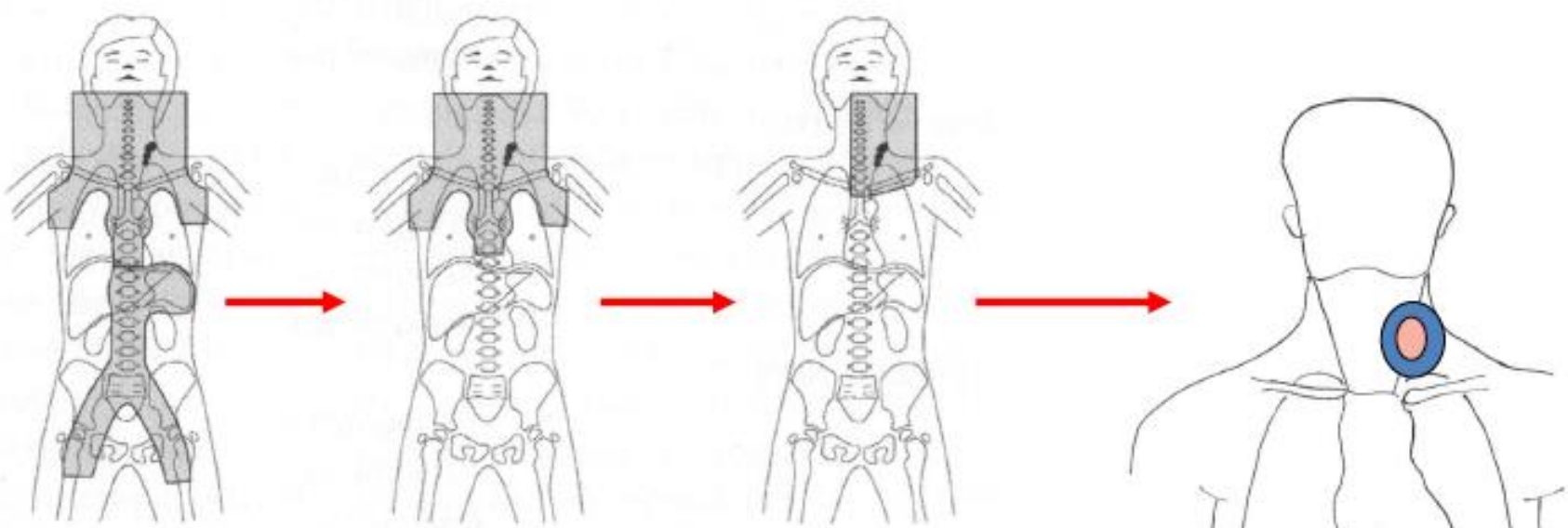
**Involved-Field RT**
**36 Gy**

**2008-2016**



**Involved Node RT**
**Involved Site RT**
**20-30 Gy**

# Development of RT volumes



Total nodal

Mantle

Involved field

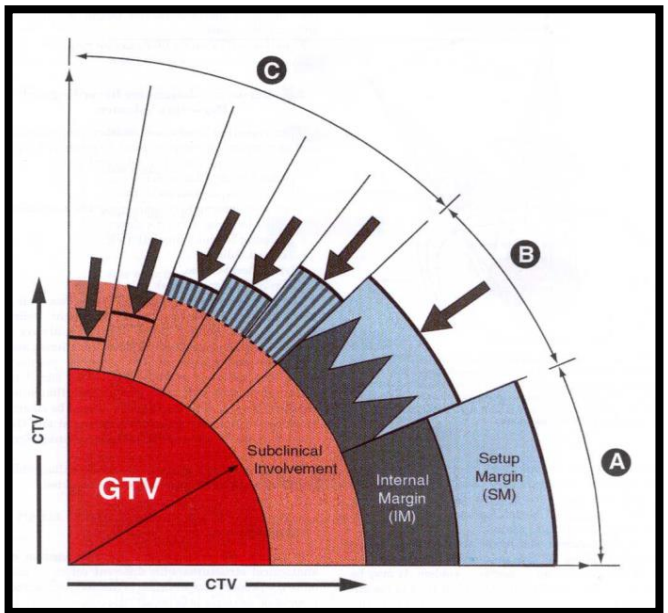
2D planning, based on bony landmarks

Involved node

3D planning, based on lymphoma volume

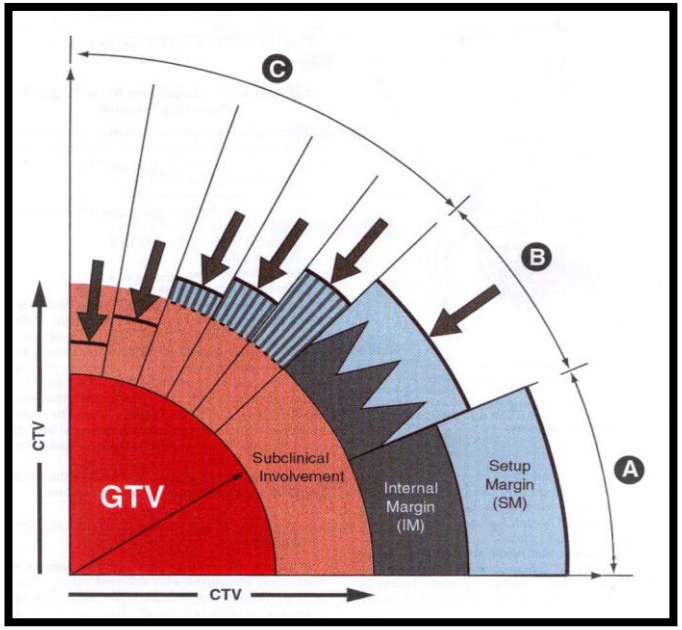
# Gross tumor volume (GTV) (ICRU 83)

- Gross demonstrable extent and location of the tumor (lymphoma)
- Original (before any treatment) lymphoma: pre-chemo GTV
  - Seen on CT: pre-chemo GTV(CT)
  - Seen on FDG-PET: pre-chemo GTV(PET)
- Residual (after systemic treatment) lymphoma: post-chemo GTV
  - Seen on CT: post-chemo GTV(CT)
  - Seen on FDG-PET: postchemo GTV(PET)



# Clinical target volume (CTV) (ICRU 83)

- Volume of tissue that contains a demonstrable GTV and/or subclinical malignant disease with a certain probability of occurrence considered relevant for therapy
- Encompasses the original (before any treatment) lymphoma (pre-chemo GTV), modified to account for anatomic changes if treated with chemotherapy up front
- Normal structures (e.g., lungs, kidneys, muscles) that were clearly uninvolved should be excluded
- Residual lymphoma (post-chemo GTV) is always part of the CTV




ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

# Defining CTV relies upon

- the quality and accuracy of imaging;
- knowledge of the spread patterns of the disease, as well as potential subclinical extent of involvement, and adjacent organ at risk constraints

**all of which depend on clinical judgment and experience**

Critical Review

# Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG)

Lena Specht, MD, PhD,* Joachim Yahalom, MD,† Tim Illidge, MD, PhD,‡ Anne Kiil Berthelsen, MD,§ Louis S. Constine, MD,|| Hans Theodor Eich, MD, PhD,¶ Theodore Girinsky, MD,# Richard T. Hoppe, MD,** Peter Mauch, MD,†† N. George Mikhaeel, MD,‡‡ and Andrea Ng, MD, MPH††, on behalf of ILROG

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

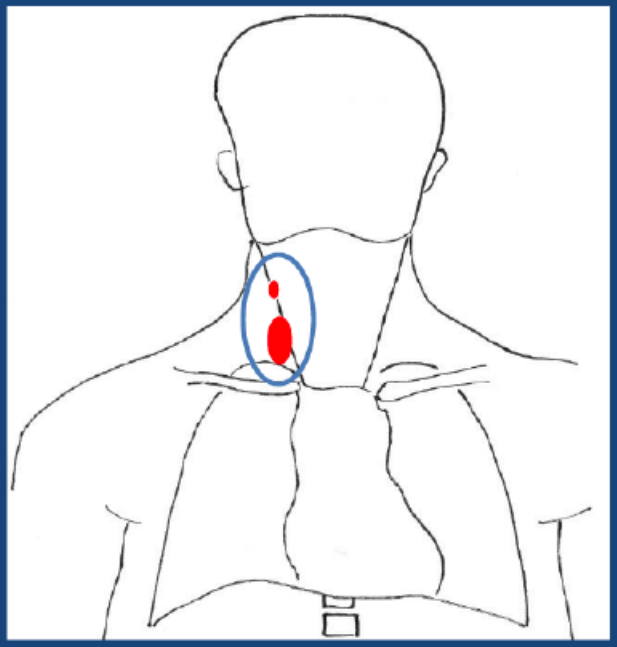
ESTRO School

# The concepts of INRT and ISRT

## EORTC-GELA Lymphoma Group Guidelines

”Involved node radiotherapy”

INRT



Girinsky el al. Radiother Oncol 2006; 79: 270-7

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

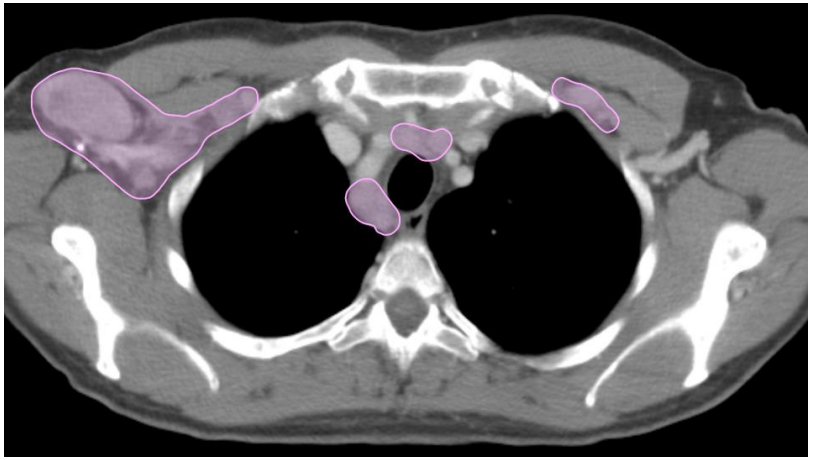
EORTC Lymphoma Group pioneered conformal RT for HL:

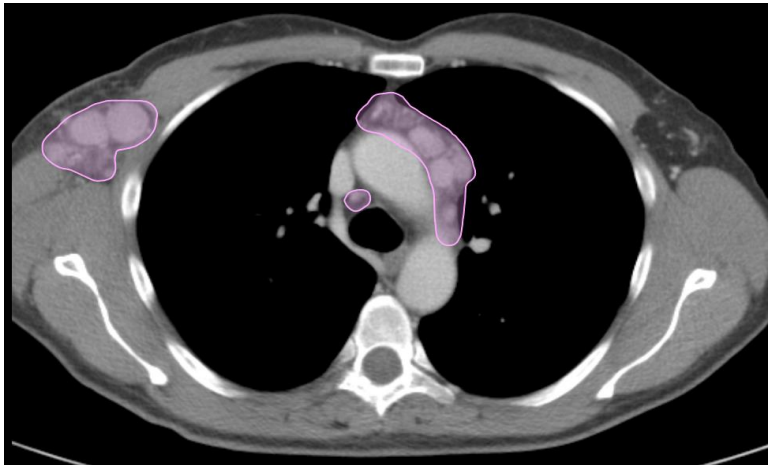
# Involved node radiotherapy (INRT)

Requirements:

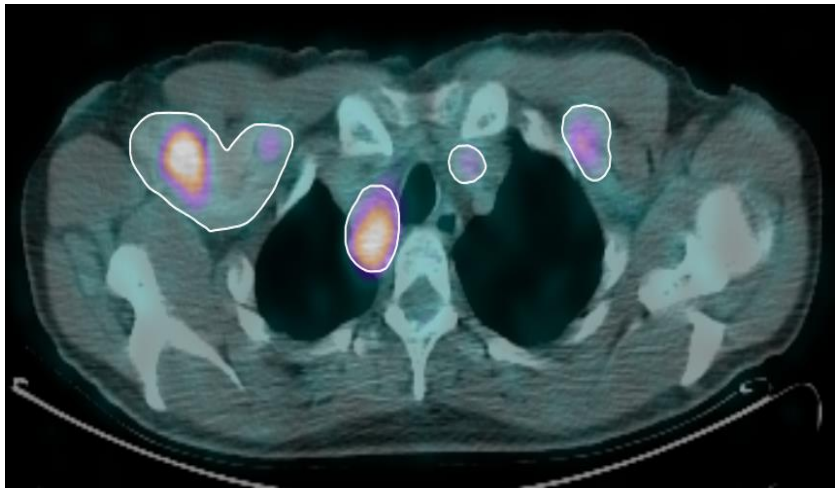
- Good pre-chemo imaging with PET/CT in treatment position
- Image fusion with post-chemo planning CT
- Contouring target volume of tissue which contained lymphoma at presentation

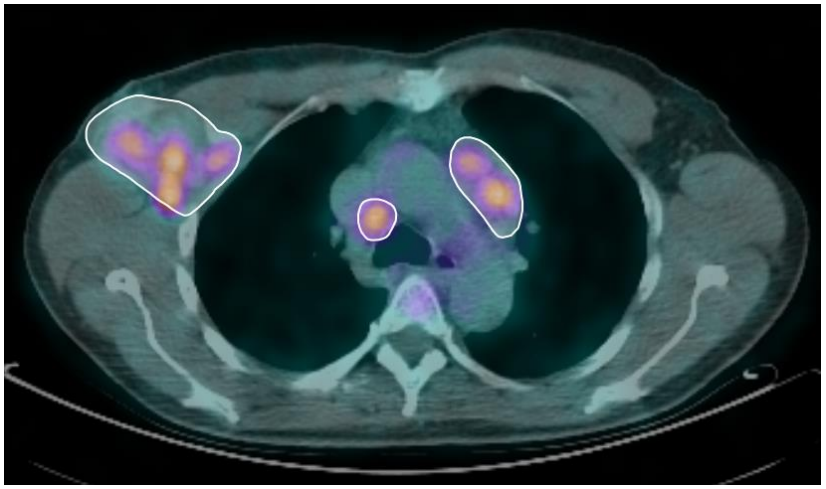
# GTV on pre-chemotherapy CT

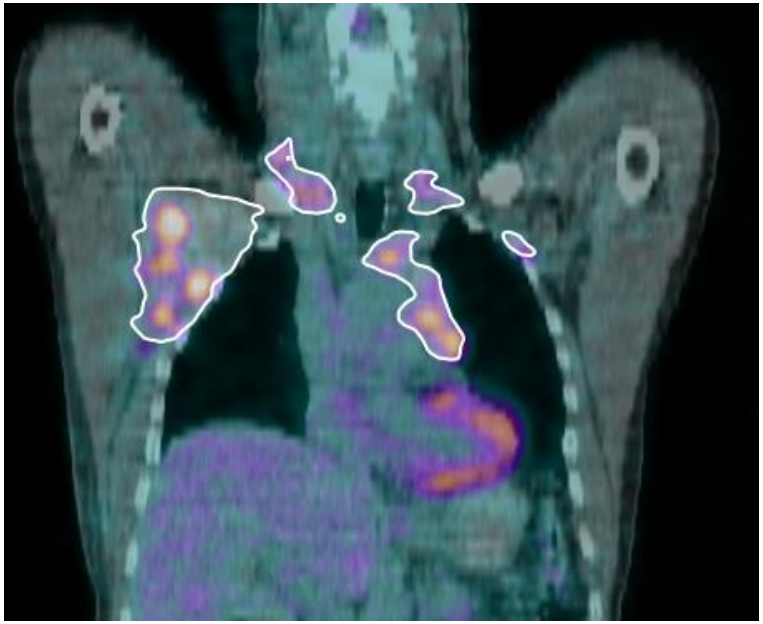


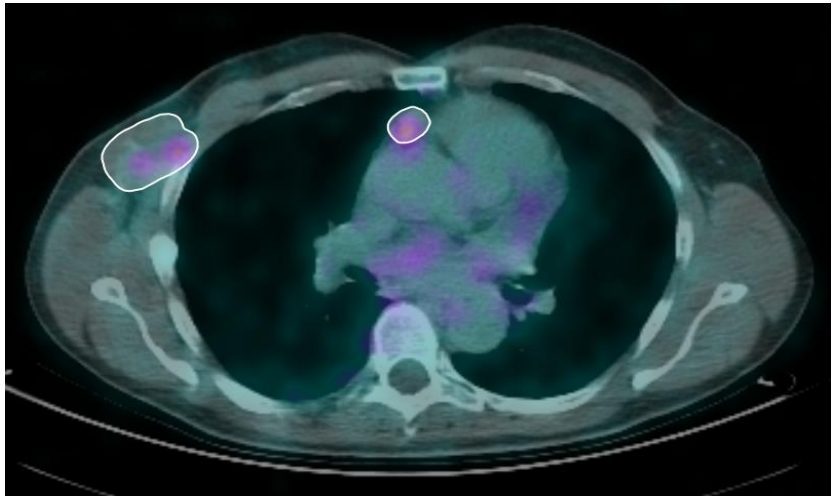


# GTV on pre-chemotherapy PET

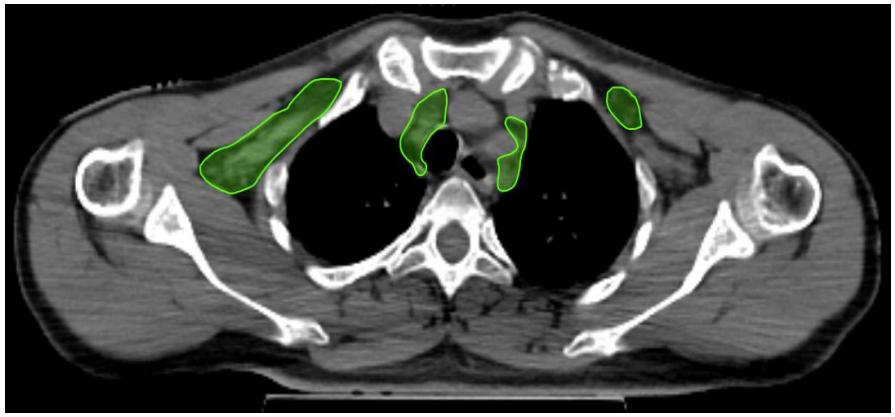


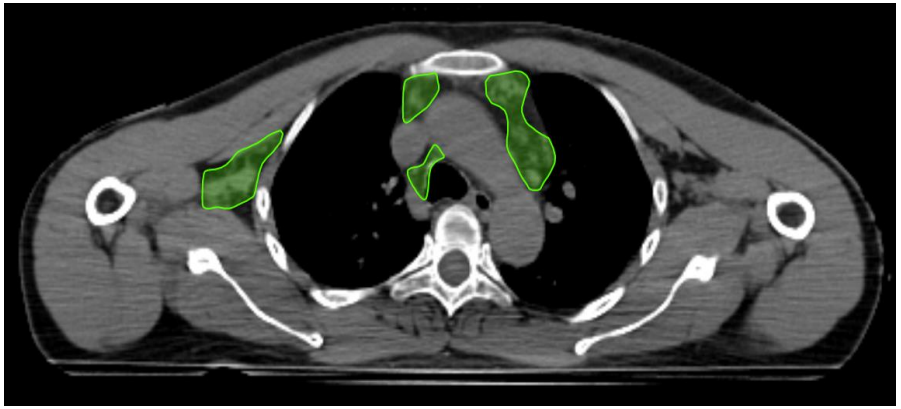


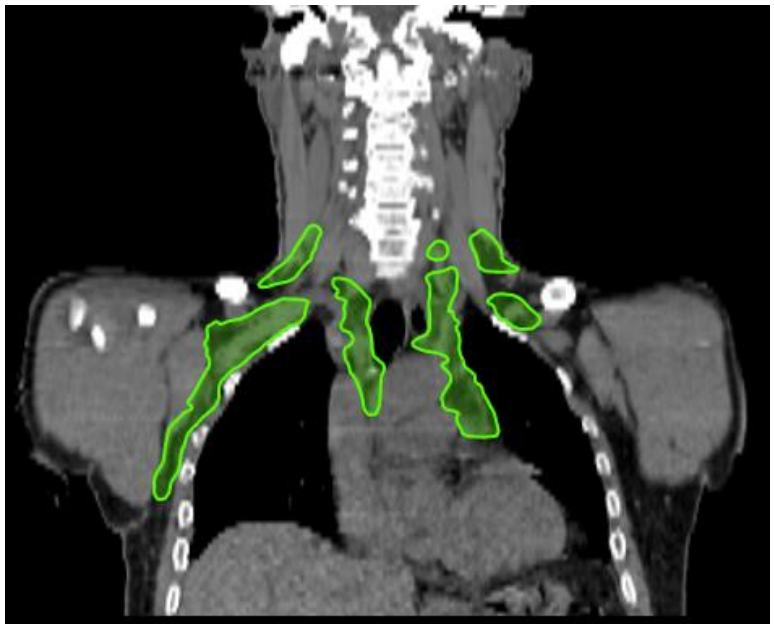


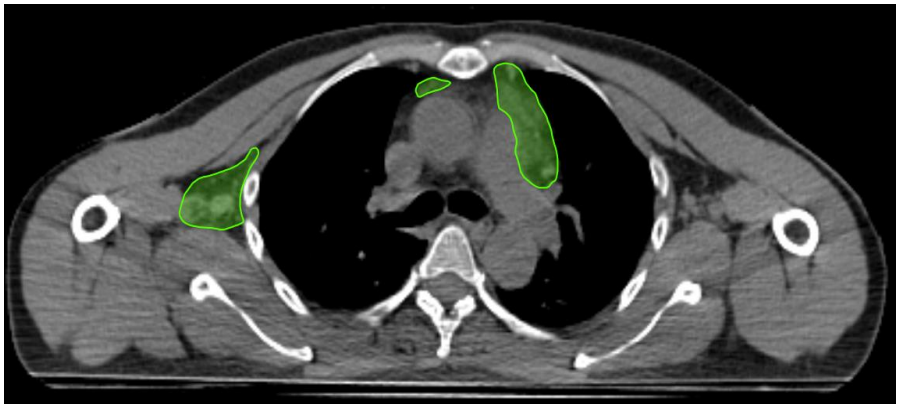


$GTV_{CT}$ and $GTV_{PET}$ import on planning CT→ CTV definition by modifying GTVs according to response and normal tissues displacement → **INRT**









ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

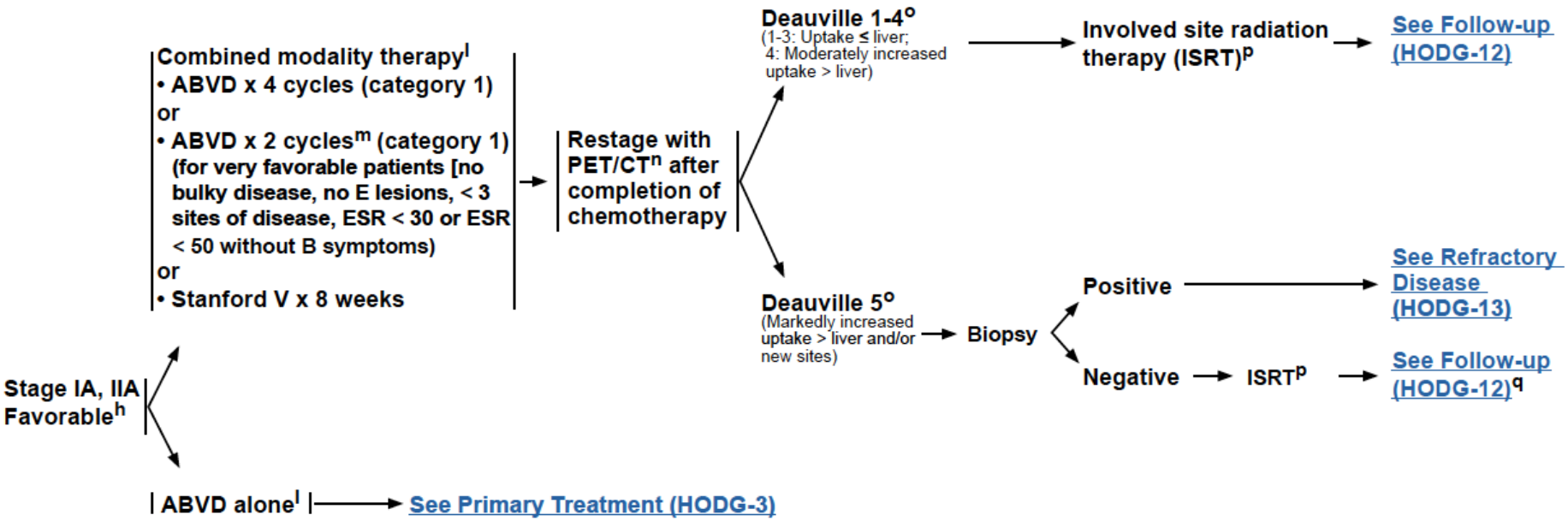
# Involved Site Radiotherapy (ISRT)

- Detailed pre-chemotherapy information and imaging is not always optimal in standard clinical practice
- Compared to INRT slightly larger volumes needed to ensure irradiation of all initially involved tissue volumes, but the same principles apply
- In most situations, ISRT will include significantly smaller volumes than IFRT

Specht et al, IJROBP 2013

DEPARTMENT OF ONCOLOGY
UNIVERSITY OF TURIN

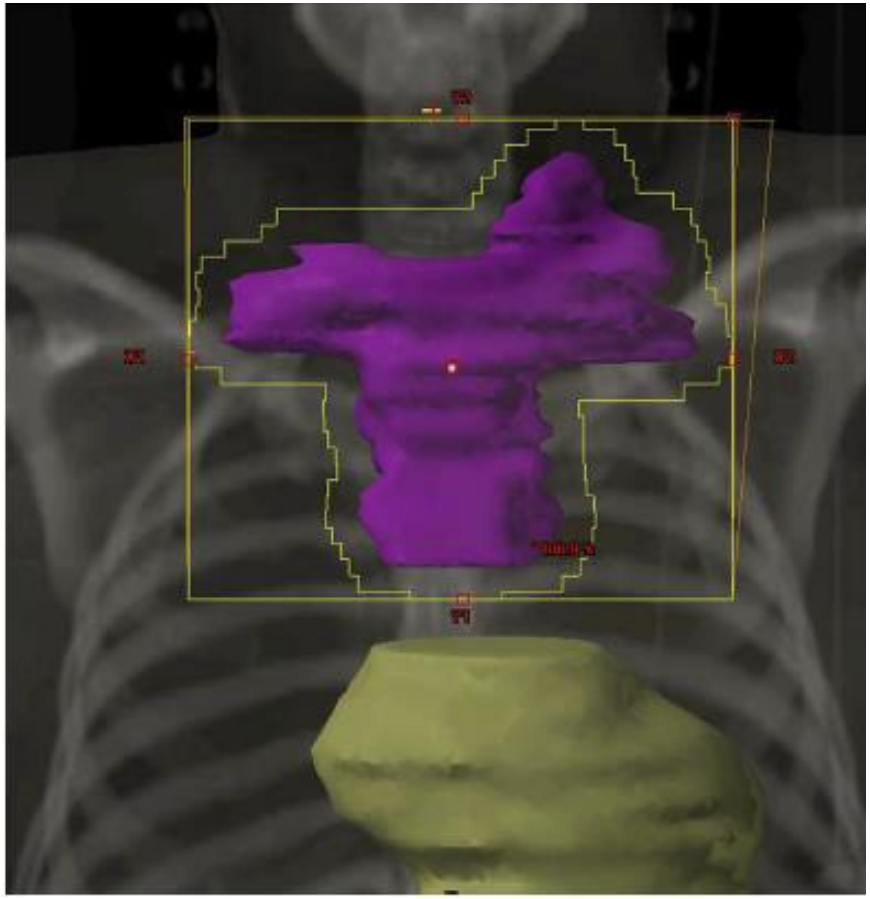
**PRIMARY TREATMENT[k]**

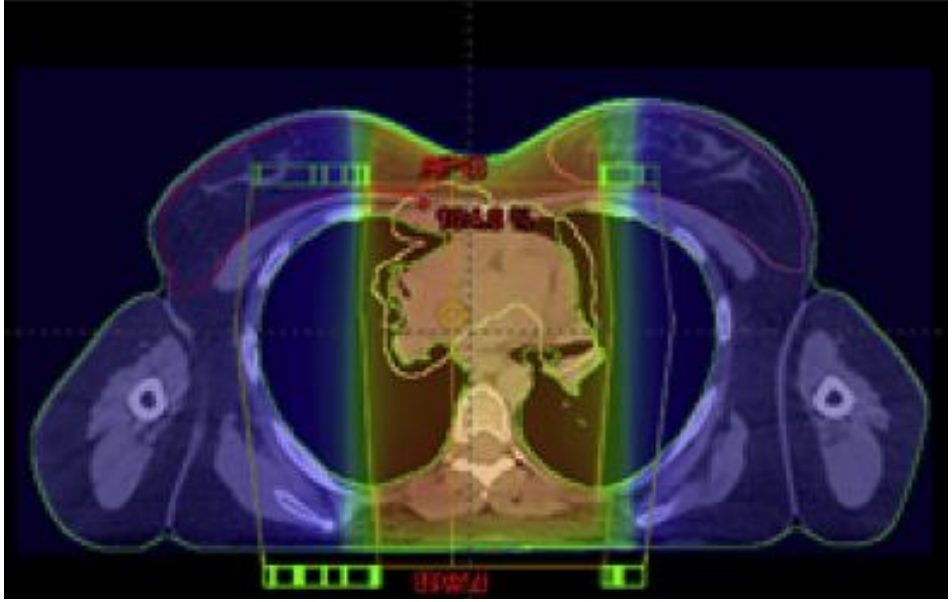


# Responsibilities of the radiation oncologist

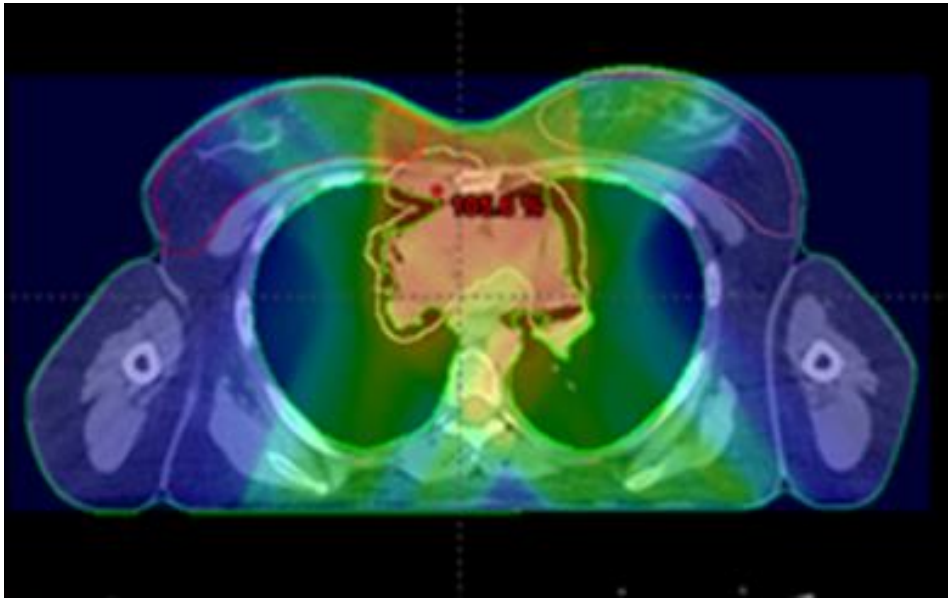
- Ensure that the advantages that can be obtained with modern radiotherapy are used to the benefit of the patient:
  - Optimal target coverage
  - Lowest target dose necessary for the highest chance of local lymphoma control
  - Lowest possible risk of significant long-term side effects

# Modern RT in lymphoma and treatment planning





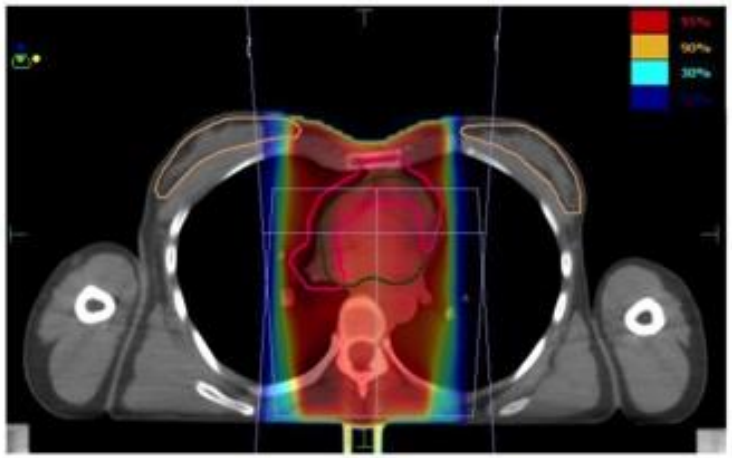
**3D-CRT**



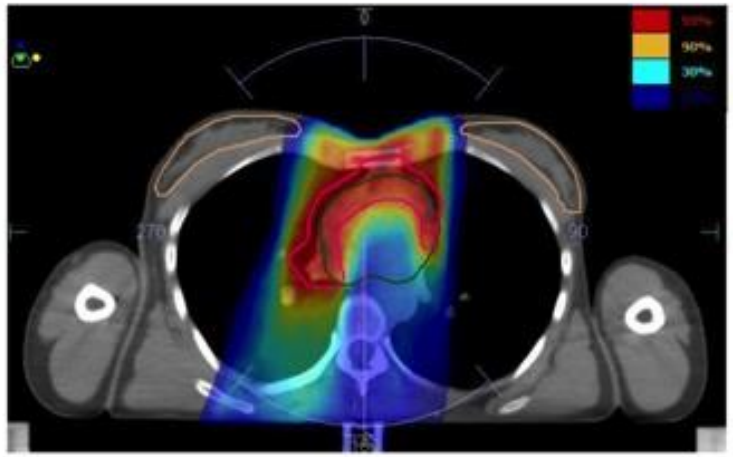
**IMRT**

# Highly conformal RT

- Only the target volume is treated to the full dose
- Better sparing of normal tissues
- Low-dose bath to the surrounding normal tissues



**3D-CRT**



**IMRT (VMAT)**

# IMRT in lymphoma RT

IMRT has been thought to be less useful and still not regarded as a standard option in hematological malignancies because:

- Lower prescribed doses, generally well below tolerance dose of normal tissues
- Fear of late effects secondary to low-dose exposure of larger volumes of healthy tissues
- Theoretical increased risk of geographic miss, as the dose gradients are steeper around the target volumes

# Modern RT in lymphoma

- Specific constraints in lymphoma RT

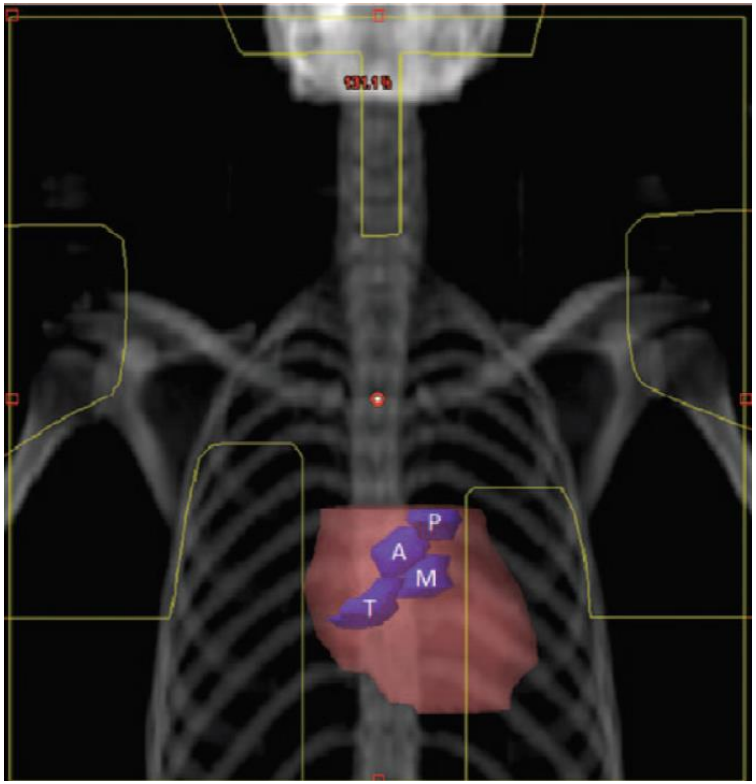
- Do even lower radiation doses, which would be considered safe by conventional criteria (QUANTEC), carry the risk of significant long-term toxicity?

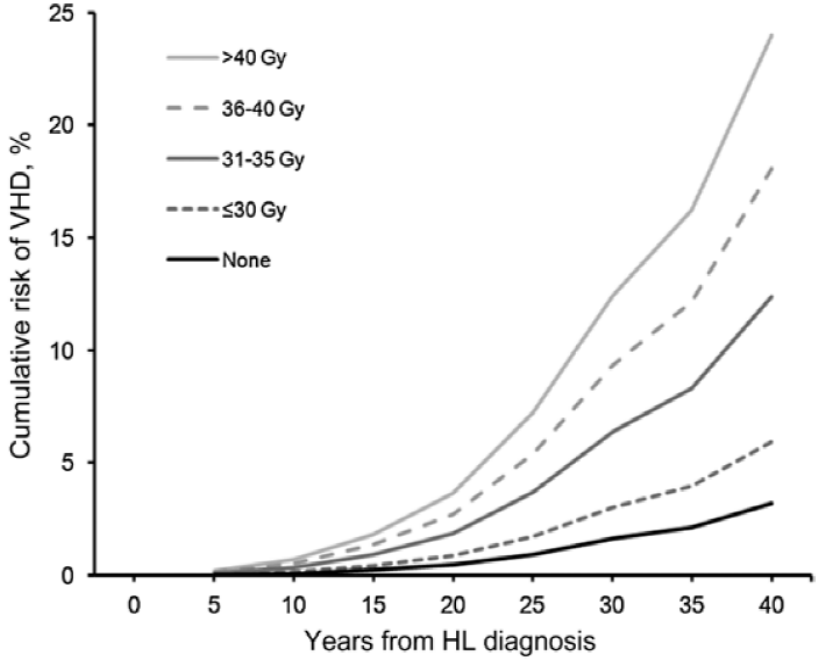
ARTICLE

# Risk of Valvular Heart Disease After Treatment for Hodgkin Lymphoma

David J. Cutter*, Michael Schaapveld*, Sarah C. Darby, Michael Hauptmann, Frederika A. van Nimwegen, Augustinus D. G. Krol, Cecile P. M. Janus, Flora E. van Leeuwen, Berthe M. P. Aleman

*JNCI J Natl Cancer Inst* (2015) 107(4): djv008



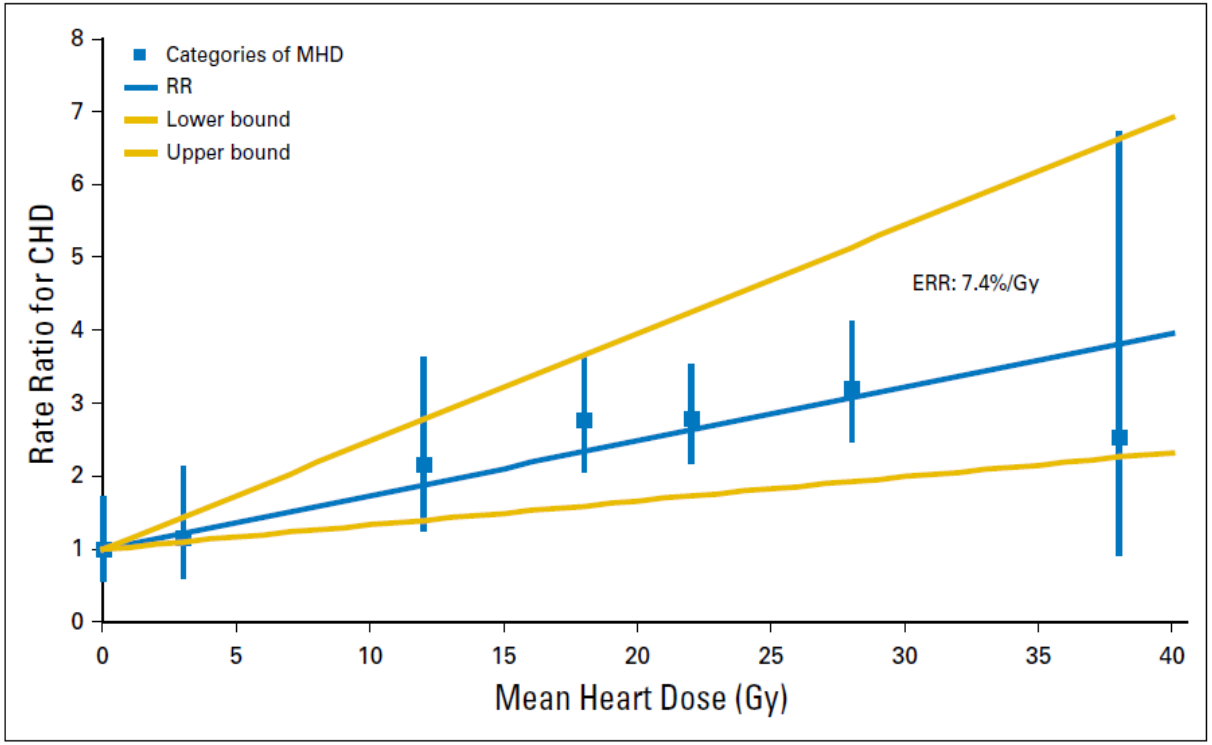




DEPARTMENT OF ONCOLOGY
UNIVERSITY OF TURIN

# Radiation Dose-Response Relationship for Risk of Coronary Heart Disease in Survivors of Hodgkin Lymphoma

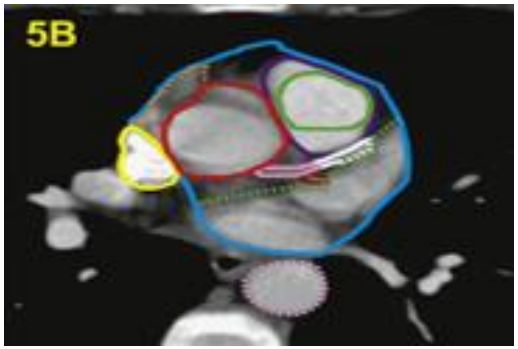
*Frederika A. van Nimwegen, Michael Schaapveld, David J. Cutter, Cècile P.M. Janus, Augustinus D.G. Krol, Michael Hauptmann, Karen Kooijman, Judith Roesink, Richard van der Maazen, Sarah C. Darby, Berthe M.P. Aleman, and Flora E. van Leeuwen*

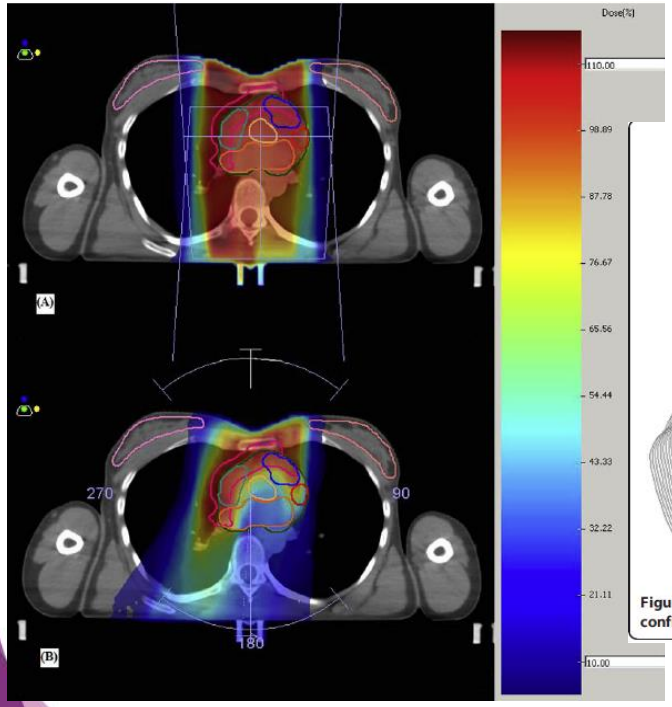
## LINEAR "NO-THRESHOLD" CORRELATION BETWEEN MEAN HEART DOSE AND DEVELOPMENT OF CAD




*J Clin Oncol 2016*

# Cardiac substructures sparing with IMRT




2 coplanar arcs + 1 non-coplanar

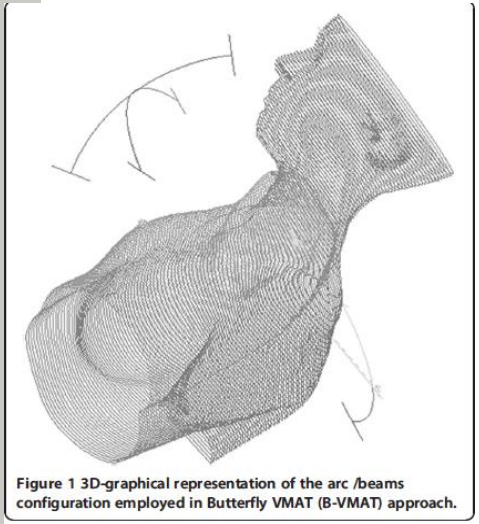


Figure 1 3D-graphical representation of the arc /beams configuration employed in Butterfly VMAT (B-VMAT) approach.

| Site | Mean AER and SD | | *P* value |
|---|---|---|---|
| | 3D-CRT | VMAT | |
| Cardiac diseases | 0.74 ± 1.50 | 0.37 ± 0.45 | .038 |
| Aortic valve | 2.15 ± 2.27 | 0.26 ± 0.63 | <.0001 |
| Pulmonic valve | 3.13 ± 3.24 | 1.36 ± 1.88 | <.0001 |
| Mitral valve | 0.29 ± 1.10 | 0.003 ± 0.007 | .12 |
| Tricuspid valve | 0.73 ± 2.11 | 0.07 ± 0.36 | .045 |
| All valves | 1.57 ± 2.55 | 0.42 ± 1.14 | <.0001 |

Filippi et al. IRJOBP 2015; 92: 161-8

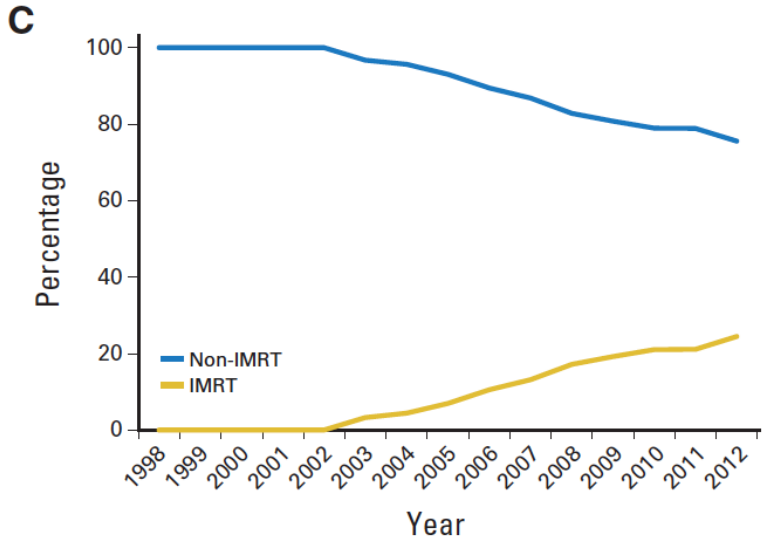
ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

# Big Data: National Cancer Database

Treatment Selection and Survival Outcomes in Early-Stage Diffuse Large B-Cell Lymphoma: Do We Still Need Consolidative Radiotherapy?

*John A. Vargo, Beant S. Gill, Goundappa K. Balasubramani, and Sushil Beriwal*

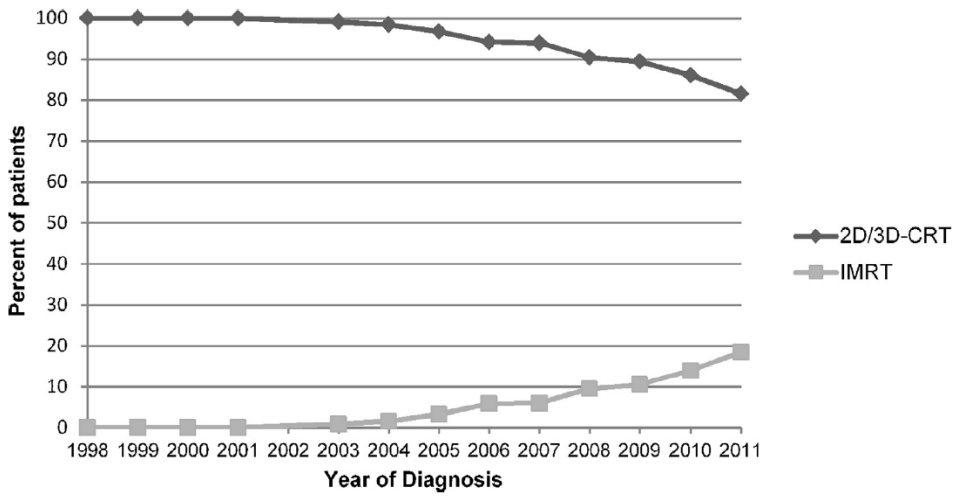



VOLUME 33 · NUMBER 32 · NOVEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

Association of intensity-modulated radiation therapy on overall survival for patients with Hodgkin lymphoma

Rahul R. Parikh [a,*], Michael L. Grossbard [b], Louis B. Harrison [c], Joachim Yahalom [d]

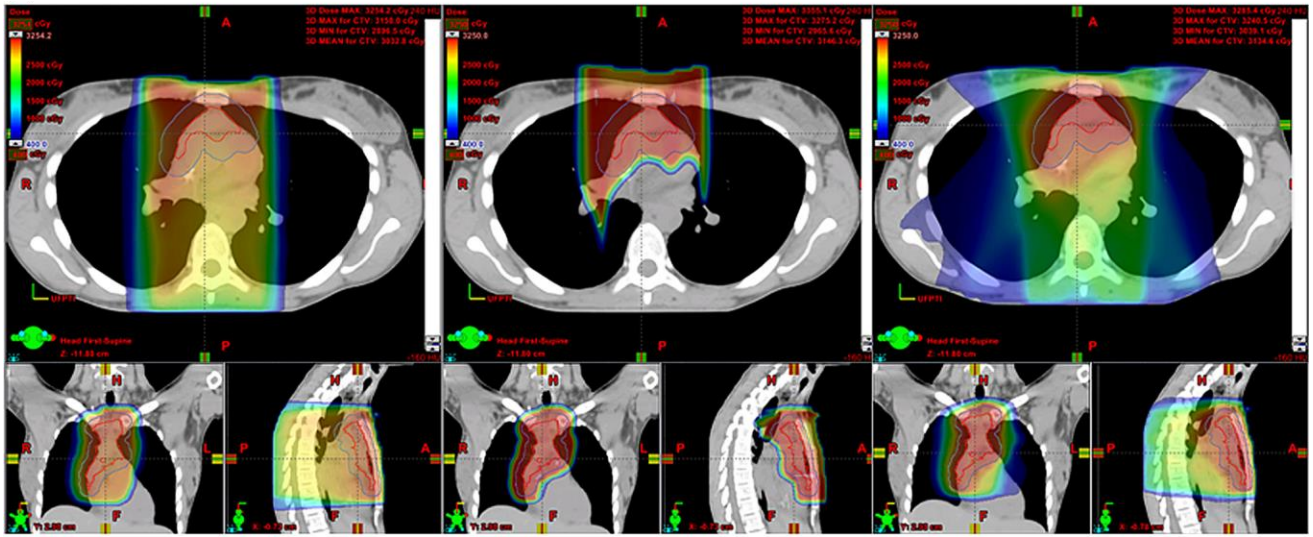



Radiotherapy and Oncology 118 (2016) 52–59

# Involved-Node Proton Therapy in Combined Modality Therapy for Hodgkin Lymphoma: Results of a Phase 2 Study☆

International Journal of Radiation Oncology biology • physics

www.redjournal.org



| Structure | 3DCRT | | IMRT | | PT | |
|---|---|---|---|---|---|---|
| | Mean | ±SD | Mean | ±SD | Mean | ±SD |
| Integral dose (joules) | 122.9 | 62.3 | 103.8 | 48.6 | 53.6 | 32.0 |
| Heart (Gy) | 16.5 | 7.6 | 12.3 | 6.2 | 8.9 | 5.1 |
| Lung (Gy) | 11.6 | 3.7 | 9.8 | 2.8 | 7.1 | 2.5 |
| Breast (Gy) | 6.3 | 3.5 | 6.0 | 3.4 | 4.3 | 3.0 |
| Thyroid (Gy) | 19.3 | 10.1 | 17.7 | 9.3 | 15.8 | 9.7 |
| Esophagus (Gy) | 20.3 | 4.8 | 16.4 | 3.9 | 13.4 | 5.6 |

*Hoppe BS et al, IJROBP 2014;89(5):1053-1059*

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

# Early stage disease

- Reducing size of the radiation field is safe
- Reducing the radiation dose is possible for good prognosis disease, or after adequate chemotherapy
- Omitting radiotherapy altogether ?

**Chemotherapy alone versus chemotherapy plus radiotherapy for early stage HL: Herbst C et al, Cochrane Database Syst Rev 2011**

***Systematic review with meta analysis of RCT, Five RCTs involving 1245 patients.***

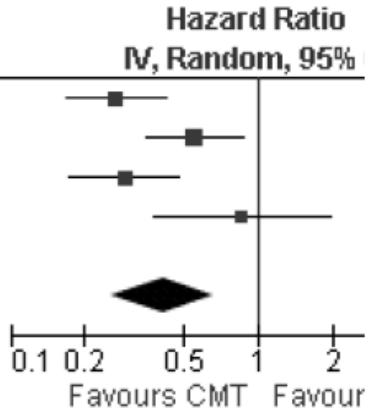
→ ***Adding radiotherapy to chemotherapy improves tumour control and OS***

## Progression-free survival

| Study or Subgroup | log[Hazard Ratio] | SE | CMT Total | CT-alone Total | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| EORTC-GELA H9-F | -1.32 | 0.24 | 448 | 130 | 27.6% | 0.27 [0.17, 0.43] |
| GATLA 9-H-77 | -0.6 | 0.23 | 135 | 142 | 28.2% | 0.55 [0.35, 0.86] |
| Mexico B2H031 | -1.24 | 0.26 | 102 | 99 | 26.4% | 0.29 [0.17, 0.48] |
| MSKCC trial #90-44 | -0.16 | 0.42 | 76 | 76 | 17.8% | 0.85 [0.37, 1.94] |
| **Total (95% CI)** | | | **761** | **447** | **100.0%** | **0.41 [0.25, 0.66]** |

Heterogeneity: Tau² = 0.16; Chi² = 9.47, df = 3 (P = 0.02); I² = 68%

Test for overall effect: Z = 3.64 (P = 0.0003)

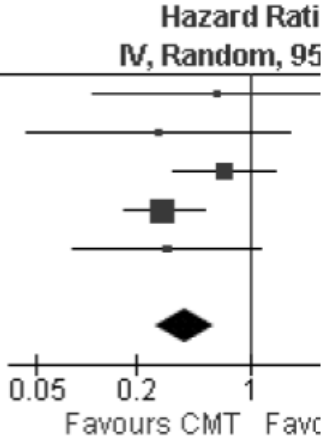



## Overall survival

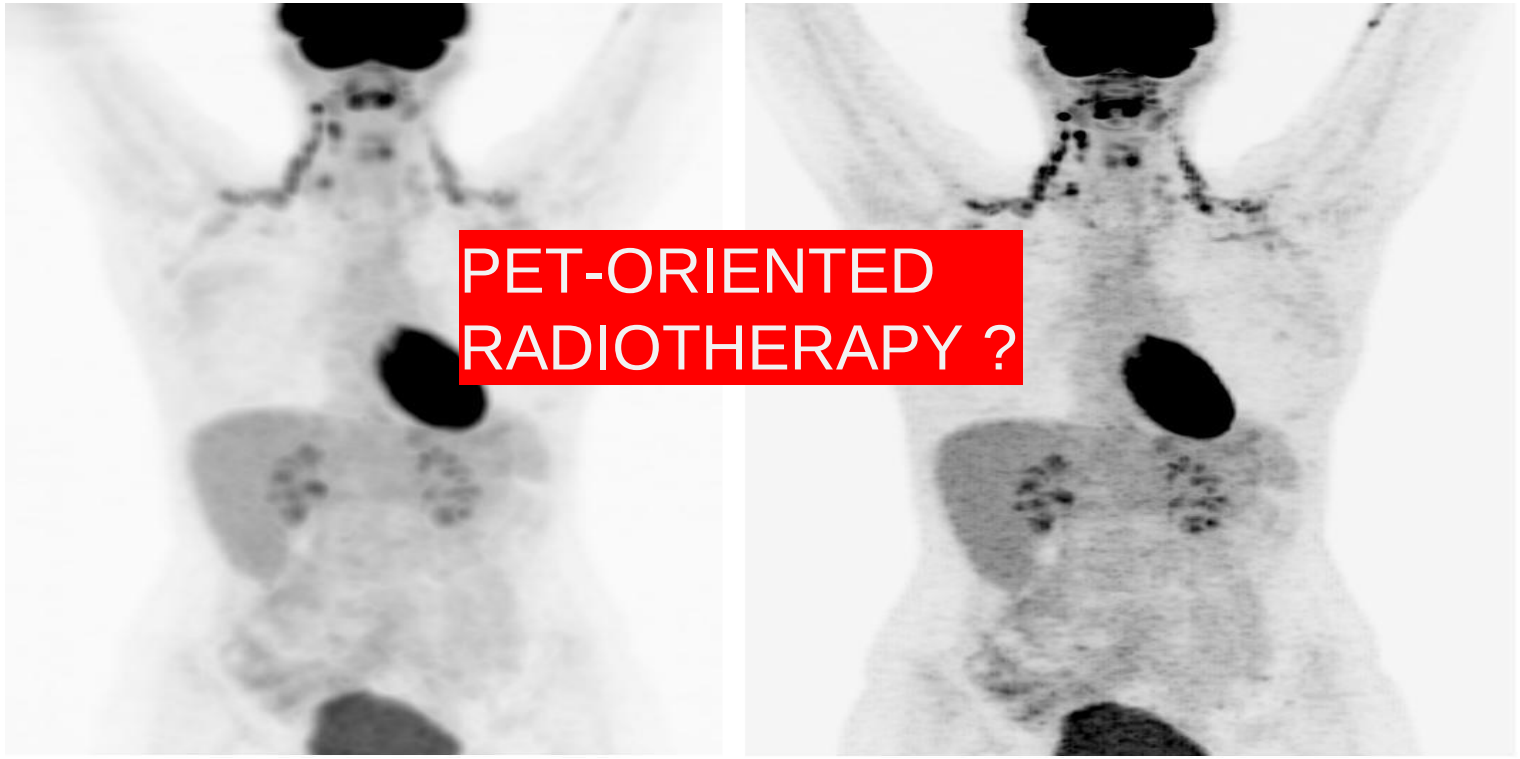
| Study or Subgroup | log[Hazard Ratio] | SE | CMT Total | CT-alone Total | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| CALGB 7751 | -0.47 | 0.9 | 19 | 18 | 5.1% | 0.63 [0.11, 3.65] |
| EORTC-GELA H9-F | -1.2925 | 0.9426 | 448 | 130 | 4.6% | 0.27 [0.04, 1.74] |
| GATLA 9-H-77 | -0.3786 | 0.3651 | 135 | 142 | 30.7% | 0.68 [0.33, 1.40] |
| Mexico B2H031 | -1.2245 | 0.2852 | 102 | 99 | 50.4% | 0.29 [0.17, 0.51] |
| MSKCC trial #90-44 | -1.1733 | 0.6667 | 76 | 76 | 9.2% | 0.31 [0.08, 1.14] |
| **Total (95% CI)** | | | **780** | **465** | **100.0%** | **0.40 [0.27, 0.59]** |

Heterogeneity: Tau² = 0.00; Chi² = 3.89, df = 4 (P = 0.42); I² = 0%

Test for overall effect: Z = 4.57 (P < 0.00001)



# To irradiate or not to irradiate ?



# The Challenge of $^{18}$FDG PET CT in HL : Converting large SUV numbers into Binary (Positive / Negative) and making sense of it

- Can we use FDG-PET to select patients who can be cured with less chemotherapy and no RT ?
- Primary objective UK NCRI RAPID and EORTC H10 trials
  - Is chemotherapy alone as effective - but less toxic to combined modality treatment in patients with CS I/II HL in terms of PFS in patients who are FDG-PET scan negative* after 3 cycles (UK NCRI) or two cycles (EORTC H10) of ABVD? *(non-inferiority)*

Published Ahead of Print on March 17, 2014 as 10.1200/JCO.2013.51.9298
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.51.9298

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

J Clin Oncol. 2014 Apr 20;32(12):1188-94

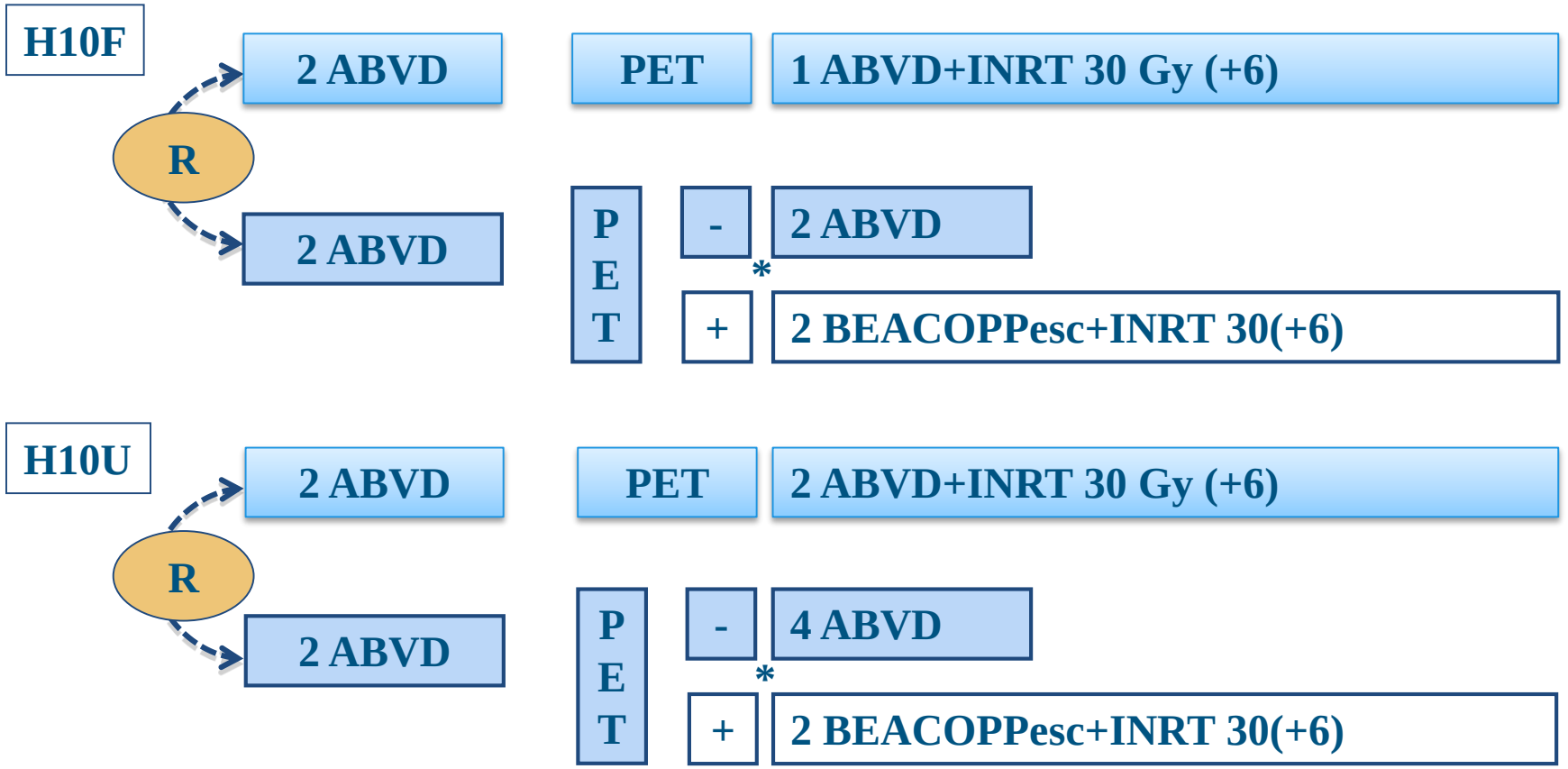
# Omitting Radiotherapy in Early Positron Emission Tomography–Negative Stage I/II Hodgkin Lymphoma Is Associated With an Increased Risk of Early Relapse: Clinical Results of the Preplanned Interim Analysis of the Randomized EORTC/LYSA/FIL H10 Trial

*John M.M. Raemaekers, Marc P.E. André, Massimo Federico, Theodore Girinsky, Reman Oumedaly, Ercole Brusamolino,† Pauline Brice, Christophe Fermé, Richard van der Maazen, Manuel Gotti, Reda Bouabdallah, Catherine J. Sebban, Yolande Lievens, Allessandro Re, Aspasia Stamatoullas, Frank Morschhauser, Pieternella J. Lugtenburg, Elisabetta Abruzzese, Pierre Olivier, Rene-Olivier Casasnovas, Gustaaf van Imhoff, Tiana Raveloarivahy, Monica Bellei, Thierry van der Borght, Stephane Bardet, Annibale Versari, Martin Hutchings, Michel Meignan, and Catherine Fortpied*

# EORTC/GELA/IIL H10 Study

## For early favorable and unfavorable

### H10 (#20051): study design




*PET-/+ according to protocol criteria

Hodgkin - CS I/II – untreated - 15-70 yrs – supradiaphragmatic - no NLPHL

**Table 2.** Results of Interim Analysis in Patients With Early PET-Negative Disease

| Subset | No. of Patients | No. of Observed Events | HR | Adjusted CI* | P† | 1-Year PFS | |
|---|---|---|---|---|---|---|---|
| | | | | | | % | Adjusted CI* |
| Favorable | | | | | .017 | | |
| Standard | 188 | 1 | 1.00 | | | 100.00 | |
| Experimental | 193 | 9 | 9.36 | 2.45 to 35.73 | | 94.93 | 91.89 to 96.85 |
| Unfavorable | | | | | .026 | | |
| Standard | 251 | 7 | 1.00 | | | 97.28 | 95.17 to 98.48 |
| Experimental | 268 | 16 | 2.42 | 1.35 to 4.36 | | 94.70 | 92.11 to 96.46 |

Abbreviations: HR, hazard ratio; PET, positron emission tomography; PFS, progression-free survival.
*Confidence level adjusted to significance level used in interim test: 79.6% CI for favorable group and 80.4% CI for unfavorable group.
†One-sided Wald-test *P* value of superiority test.

Favorable: PET-negativity 85.8%

Unfavorable: PET-negativity 74.8%

**Conclusion**

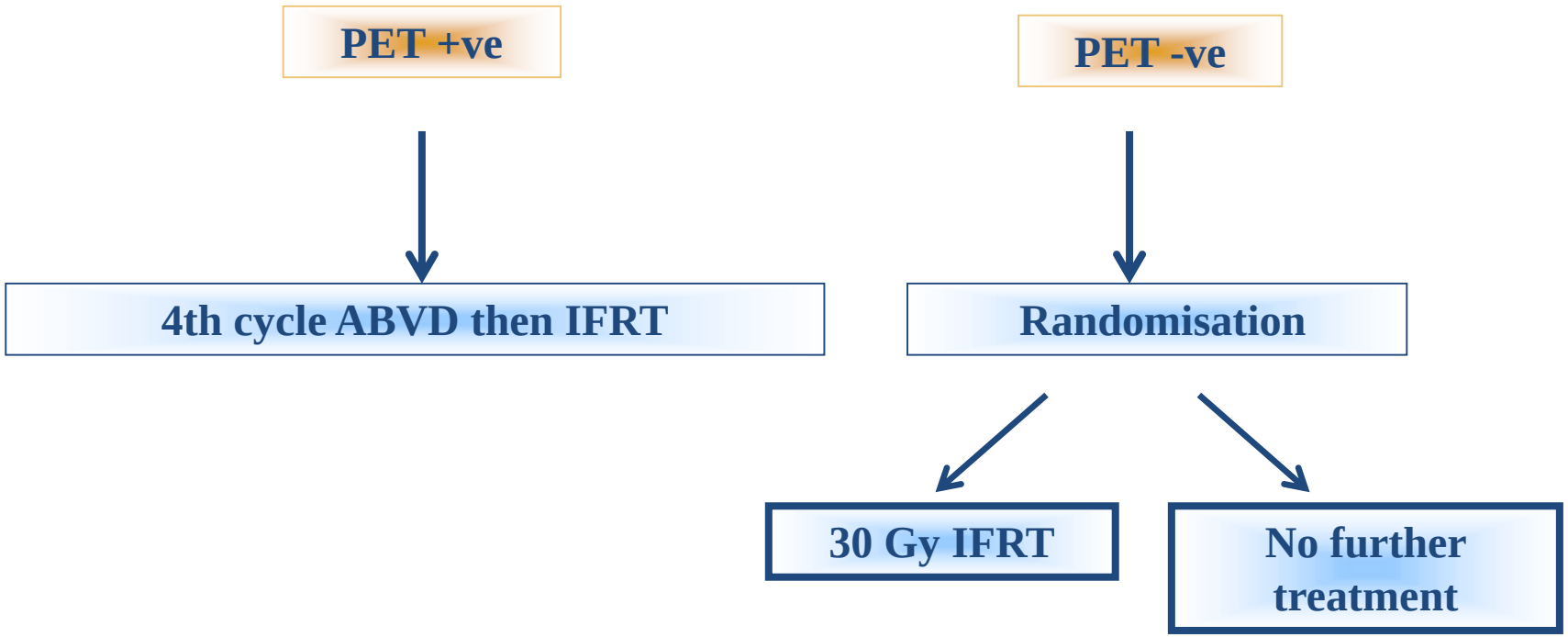
On the basis of this analysis, combined-modality treatment resulted in fewer early progressions in clinical stage I/II HL, although early outcome was excellent in both arms. The final analysis will reveal whether this finding is maintained over time.

# UK NCRI RAPID trial

## In early stage HL (70% of patients: favorable by GHSG)

**Initial treatment:** 3xABVD

**Re-assessment:** if response, PET scan performed



# UK NCRI RAPID study

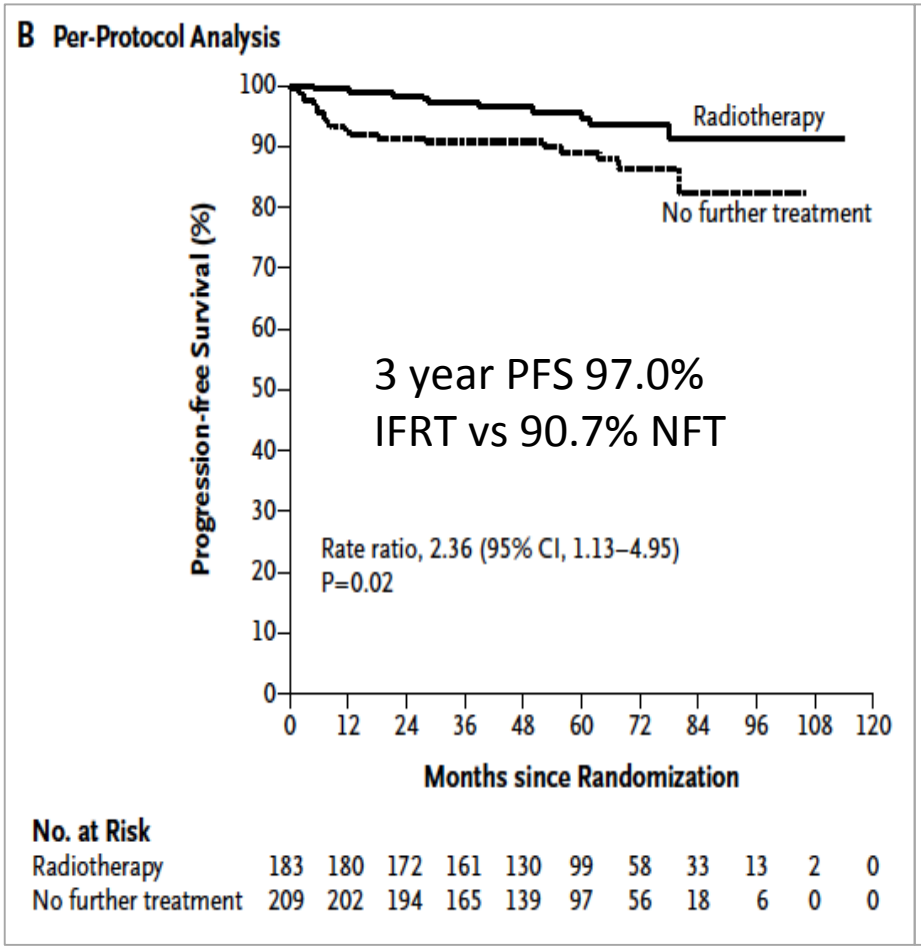
## PET scores after 3 cycles ABVD

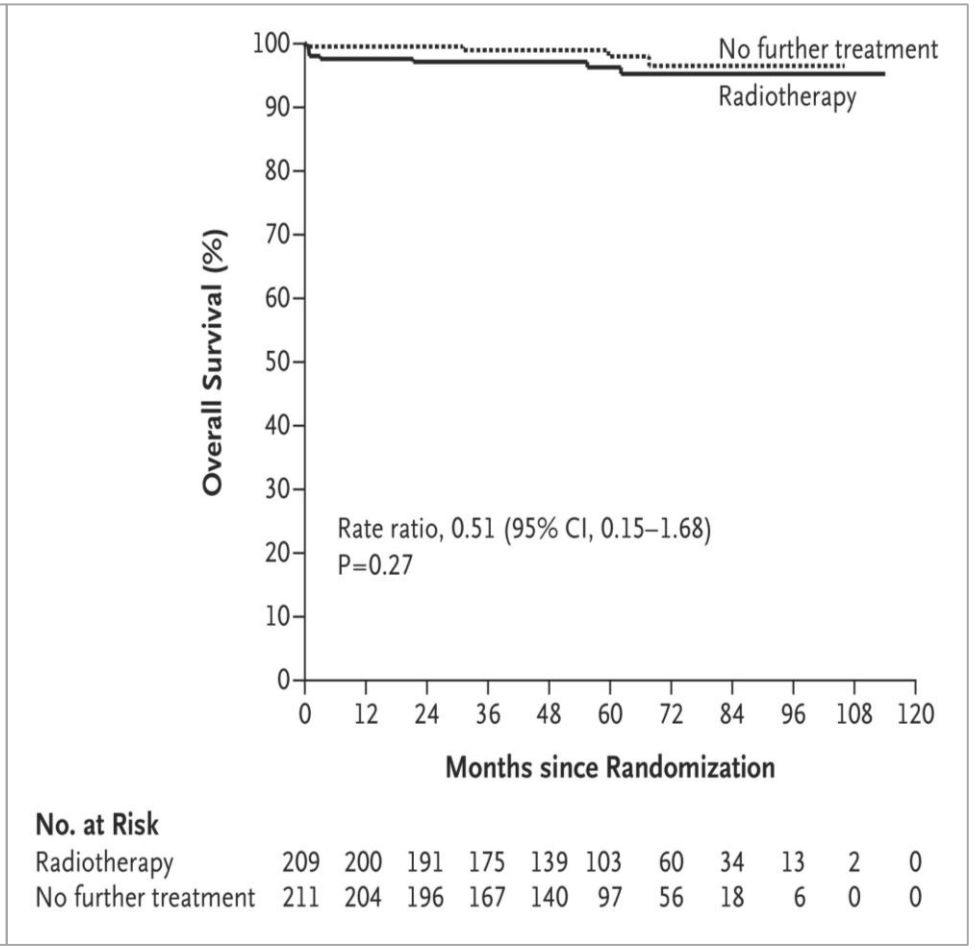
- After 3 cycles ABVD - 571 pts had FDG PET CT scan :
- Deauville 5 point score :
  - Score 1 : 301 (52.7%) **74.7% PET NEGATIVE**
  - Score 2 : 125 (22.0%)
  - Score 3 : 90 (15.7%) **25.3% PET POSTIVE**
  - Score 4 : 32 (5.6%)
  - Score 5 : 23 (4.0%)
- 420 of 426 PET –ve pts randomised to IFRT (209) or NFT (211)
- 6 not randomised; pt choice 3, clinician choice 2, error 1

DEPARTMENT OF ONCOLOGY
UNIVERSITY OF TURIN

# UK NCRI RAPID trial

## Early stage HL




Radford J et al NEJM (2015) 372;17:1598-1605

**Table 3. Causes of Death.**

| PET Status, Sex, and Age at Registration | Time from End of Therapy to Death | Cause of Death |
|---|---|---|
| Negative PET findings, radiotherapy group | | |
| Male, 71 yr* | 3 wk | Pneumonia |
| Male, 70 yr*† | 4 wk | Pneumonitis |
| Male, 62 yr* | 7 wk | Cerebral hemorrhage |
| Female, 73 yr*† | 9 wk | Pneumonitis |
| Male, 61 yr*‡ | 4 mo | Angioimmunoblastic T-cell lymphoma |
| Male, 28 yr§ | 20 mo | Myocardial fibrosis and heart failure |
| Female, 74 yr | 54 mo | Hodgkin's lymphoma |
| Male, 67 yr | 60 mo | Mycosis fungoides |
| Negative PET findings, group with no further treatment | | |
| Female, 75 yr | 3 wk | Bronchopneumonia |
| Female, 64 yr | 31 mo | Small-cell carcinoma of lung |
| Male, 64 yr | 60 mo | Diffuse large-B-cell lymphoma |
| Male, 51 yr | 69 mo | Mantle-cell lymphoma |

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Results of a Trial of PET-Directed Therapy for Early-Stage Hodgkin's Lymphoma

John Radford, M.D., Tim Illidge, M.D., Ph.D., Nicholas Counsell, M.Sc., Barry Hancock, M.D., Ruth Pettengell, M.D., Peter Johnson, M.D., Jennie Wimperis, D.M., Dominic Culligan, M.D., Bilyana Popova, M.Sc., Paul Smith, M.Sc., Andrew McMillan, M.B., Alison Brownell, M.B., Anton Kruger, M.B., Andrew Lister, M.D., Peter Hoskin, M.D., Michael O'Doherty, M.D., and Sally Barrington, M.D.

N ENGL J MED 372;17 NEJM.ORG APRIL 23, 2015

**CONCLUSIONS**

The results of this study did not show the noninferiority of the strategy of no further treatment after chemotherapy with regard to progression-free survival. Nevertheless, patients in this study with early-stage Hodgkin's lymphoma and negative PET findings after three cycles of ABVD had a very good prognosis either with or without consolidation radiotherapy. (Funded by Leukaemia and Lymphoma Research and others; RAPID ClinicalTrials.gov number, NCT00943423.)

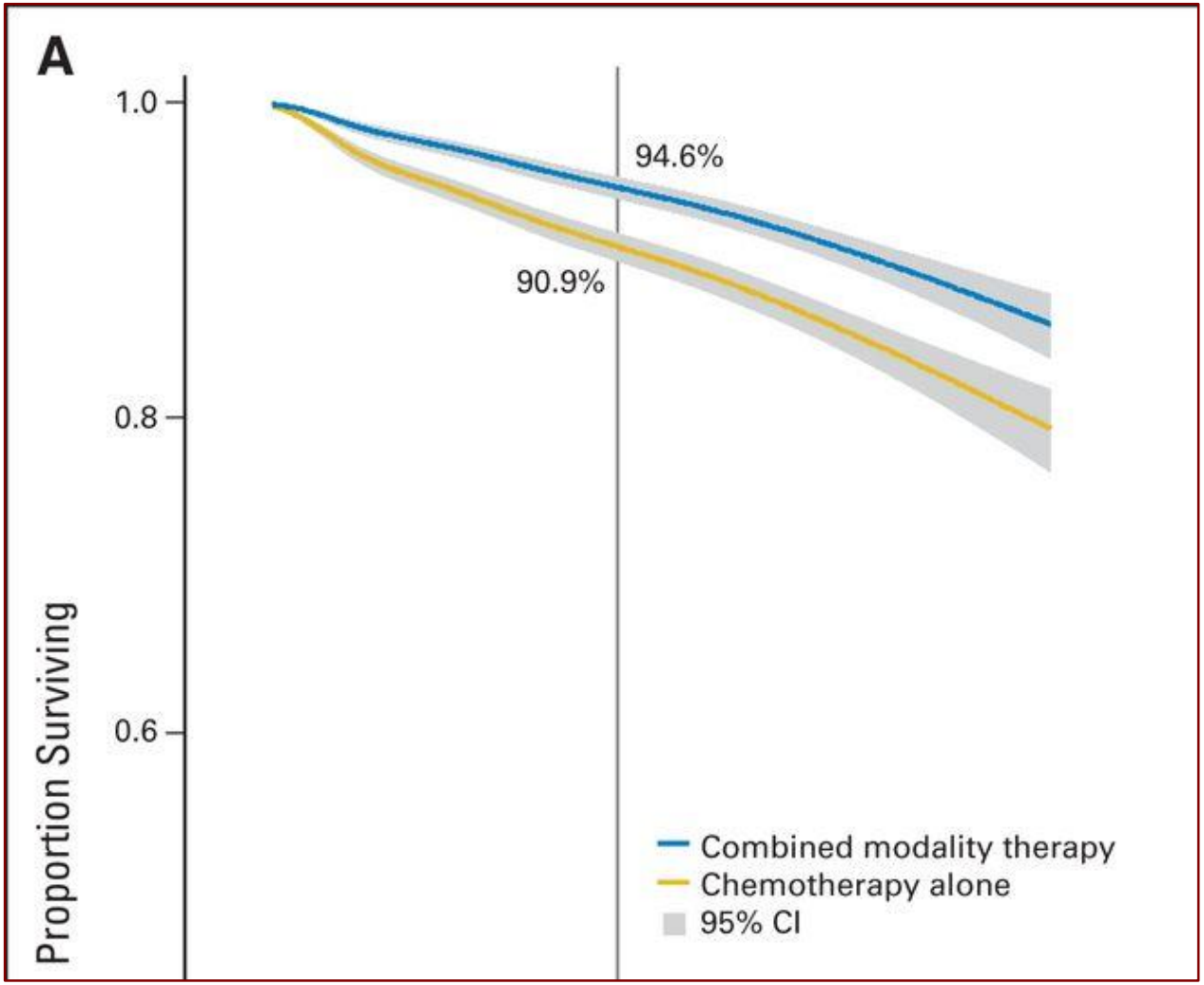
- Interim-PET studies confirmed that even PET-negative patients are more likely to fail without RT (yet this group may be smaller)

- If chemotherapy alone is considered, the patient should also have a discussion with a radiation oncologist to hear about PROS and CONS of RT in her/his particular case

- This is how a lymphoma team should approach an individually tailored curative treatment in 2016, being generalizations, dogma and scare the ways of the past

# CMT or chemo alone in early cHL

Data from USA indicate a decrease in the use of RT and worse OS for patients receiving chemo alone




Olszewski et al. JCO 2015;33:625-633

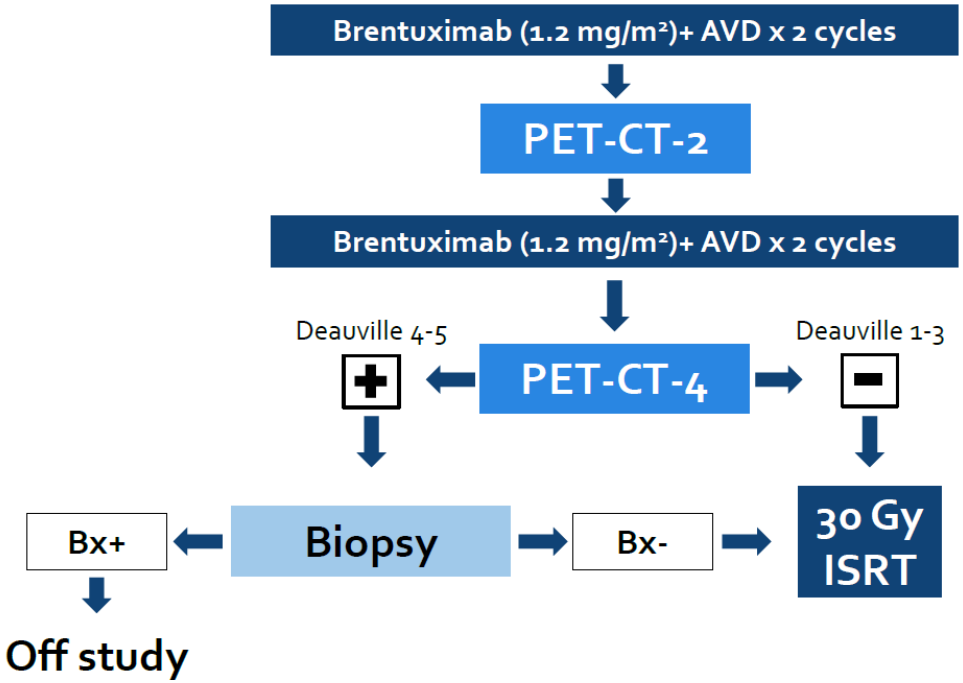
# Combined Modality Treatment of Lymphoma

- **In early favorable, 2xABVD+20Gy IFRT; more chemo not better**
- **In early unfavorable, 2+2+IFRT or 4xABVD+IFRT; 6x chemo not better (H8U)**
- **CMT standard of care in early stage HL (OS better!)**
- **RAPID and H10 gave conflicting results; PET+ pts in H10 benefit from dose escalation with Besc.**
- **Need to develop less toxic regimen; BV and anti-PD1 might at least in part replace chemo- and radiotherapy in HL**

# Pilot study of brentuximab vedotin plus AVD/ISRT in previously untreated early-stage, unfavorable-risk HL

**Objectives:** *Primary:* safety, pulmonary toxicity; *Secondary:* prognostic significance of interim PET (Deauville criteria), preliminary efficacy

| Pt Characteristics, N=30 | |
|---|---|
| Median age, yrs (range) | 31 (18–59) |
| CD30+ HL, % | 100 |
| CD20+ | 13 |
| EBV +, n=27 | 11 |
| Stage II, % | 100 |
| Unfavorable risk features, ≥1 (%) | 100 |
| B symptoms, % | 47 |
| ESR >50 or ESR >39 with B-symptoms, % | 67 |
| Nodal sites >2, % | 67 |
| Extranodal involvement, % | 47 |
| Bulk ≥10 cm, % | 47 |
| Anterior mediastinal mass >10 cm, n=14; median size, cm (range) | 13 (10–16.9) |
| Bulky by MSK definition*, n=28 (%) | 86 |

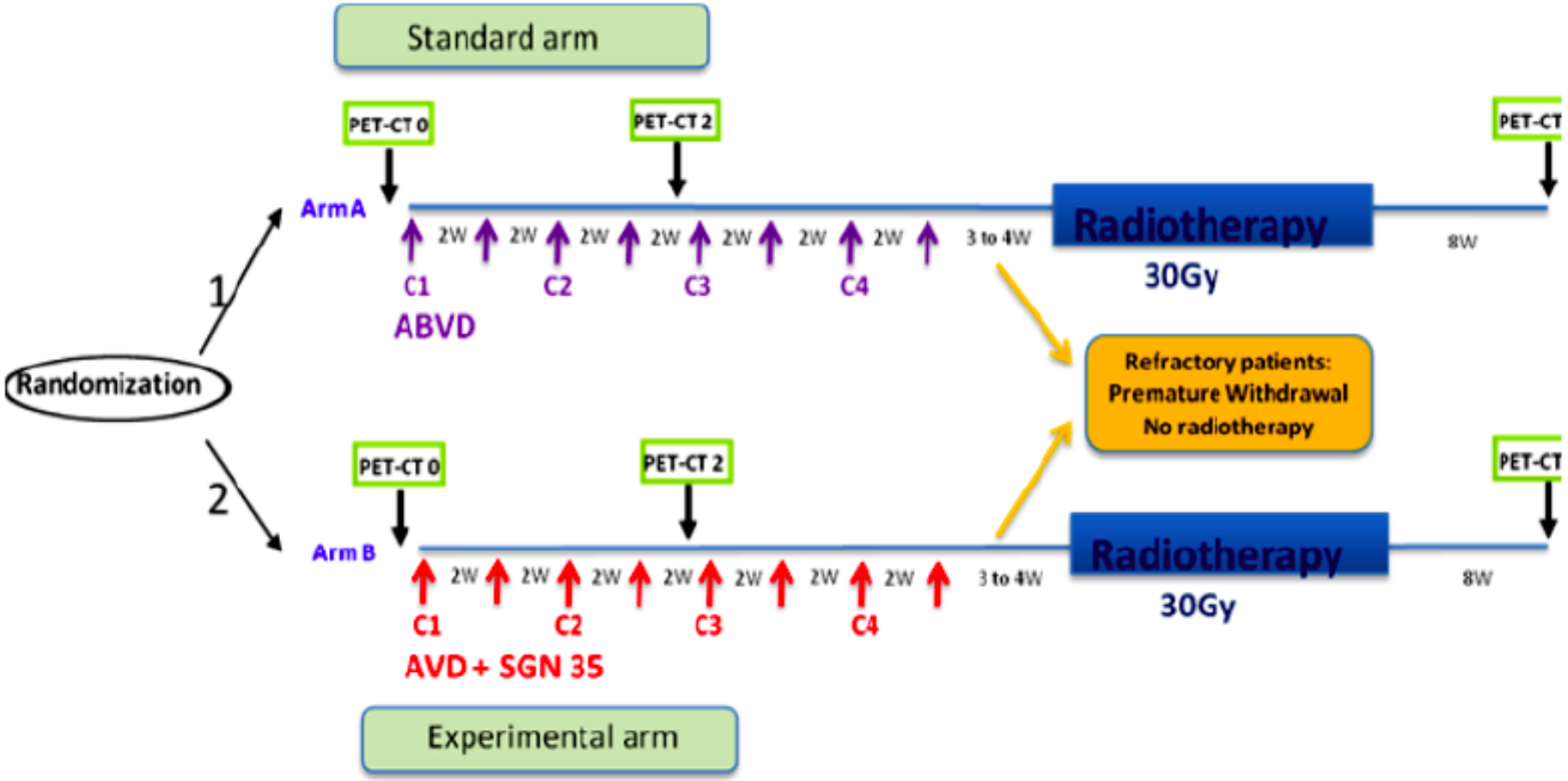



* >7 cm in MTD or >7 cm in MCD

Kumar A et al. ICML 2015, Oral presentation from Abstract #88

# Supra-diaphragmatic stage I –II unfavorable EORTC/GELA

BREACH




**Primary end point**

- PET2 negativity (score 1 and 2): $A^2VD$ >75% of PET negativity

**Secondary end points**

- CR rate ; PFS; OS; Safetyf of Brentuximab vedotin in a combined modality treatment

- **Radiotherapy in advanced stage HL**

# Advanced stage Hodgkin lymphoma IIL-HD0801 protocol


Staging including CT and PET scan or CT-PET

stage IIB-IV

2 ABVD

PET

\- 

\+

2 ABVD

CT scan optional

2 ABVD

salvage

\- 

CT + PET

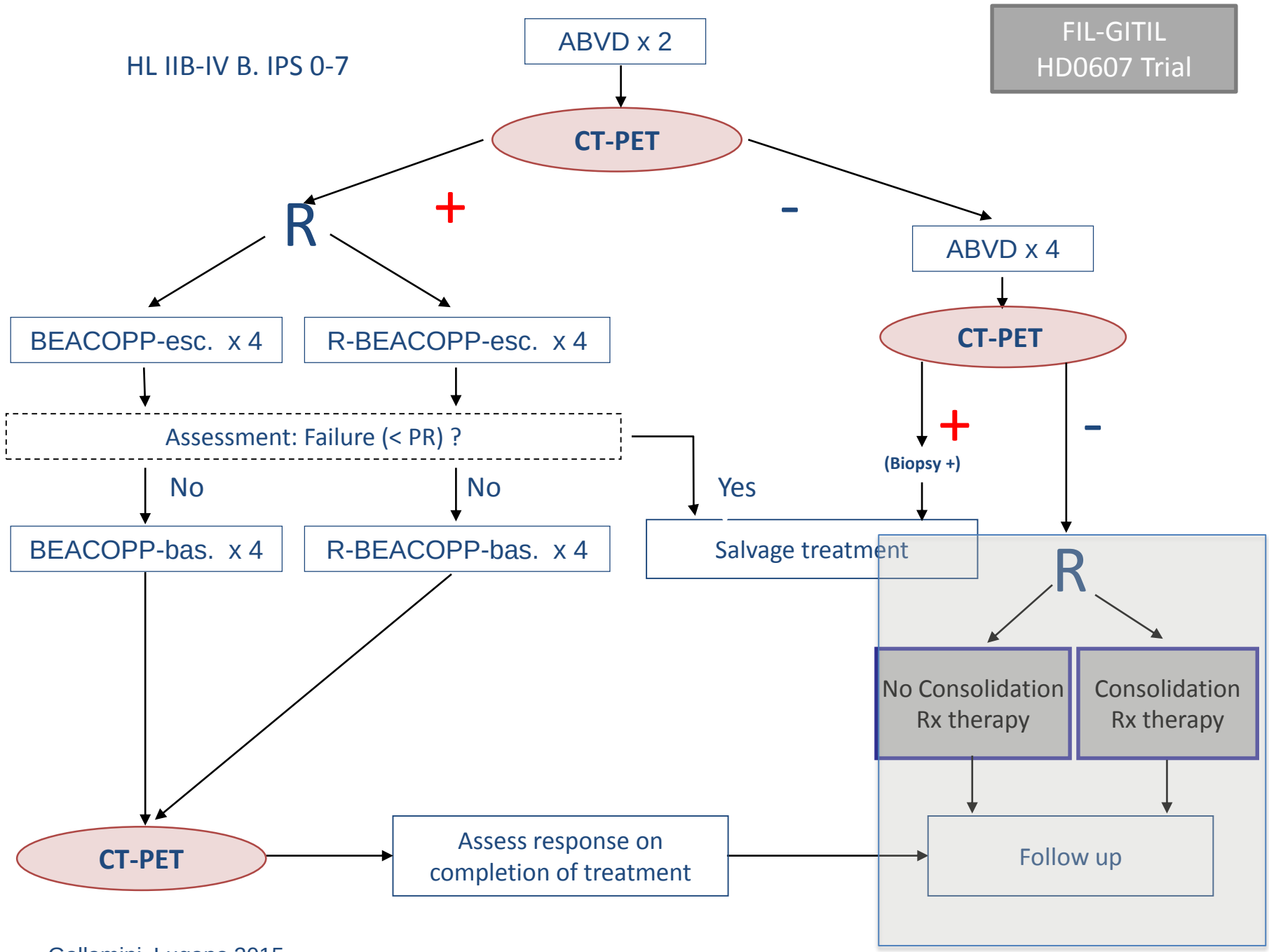
≠

random

RT bulky

No RT

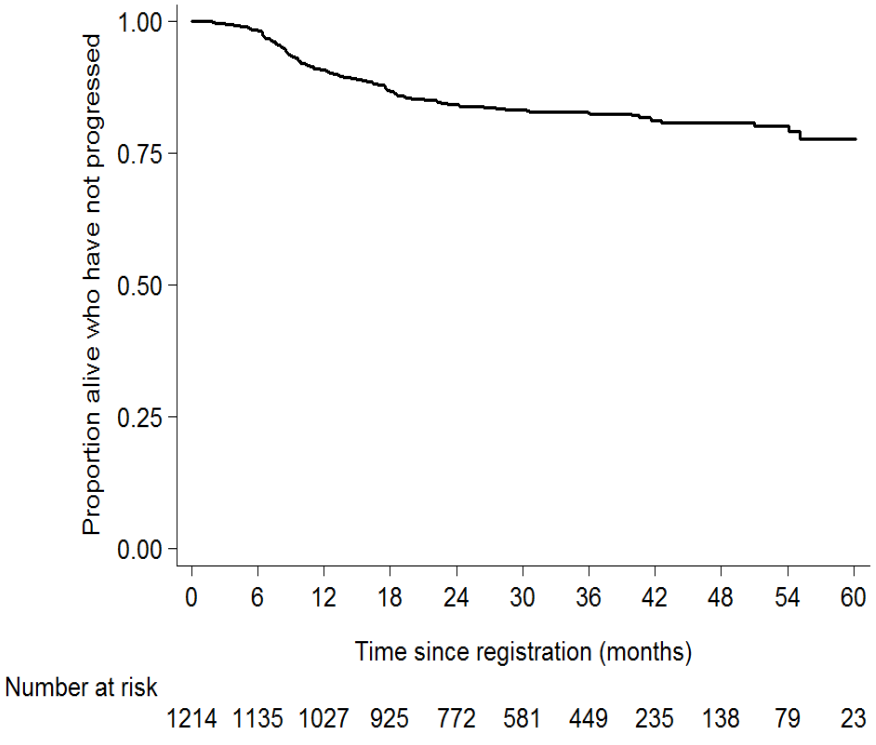
DEPARTMENT OF ONCOLOGY
UNIVERSITY OF TURIN

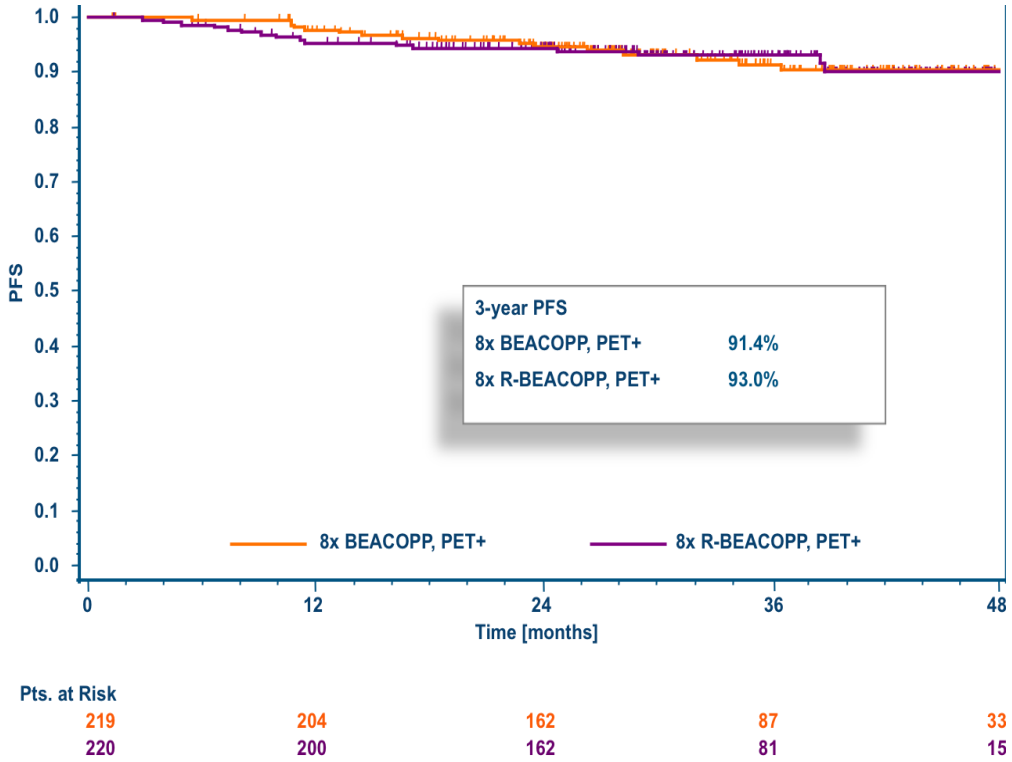



Gallamini, Lugano 2015

# Comparing RATHL and HD18

## PFS at 3 years



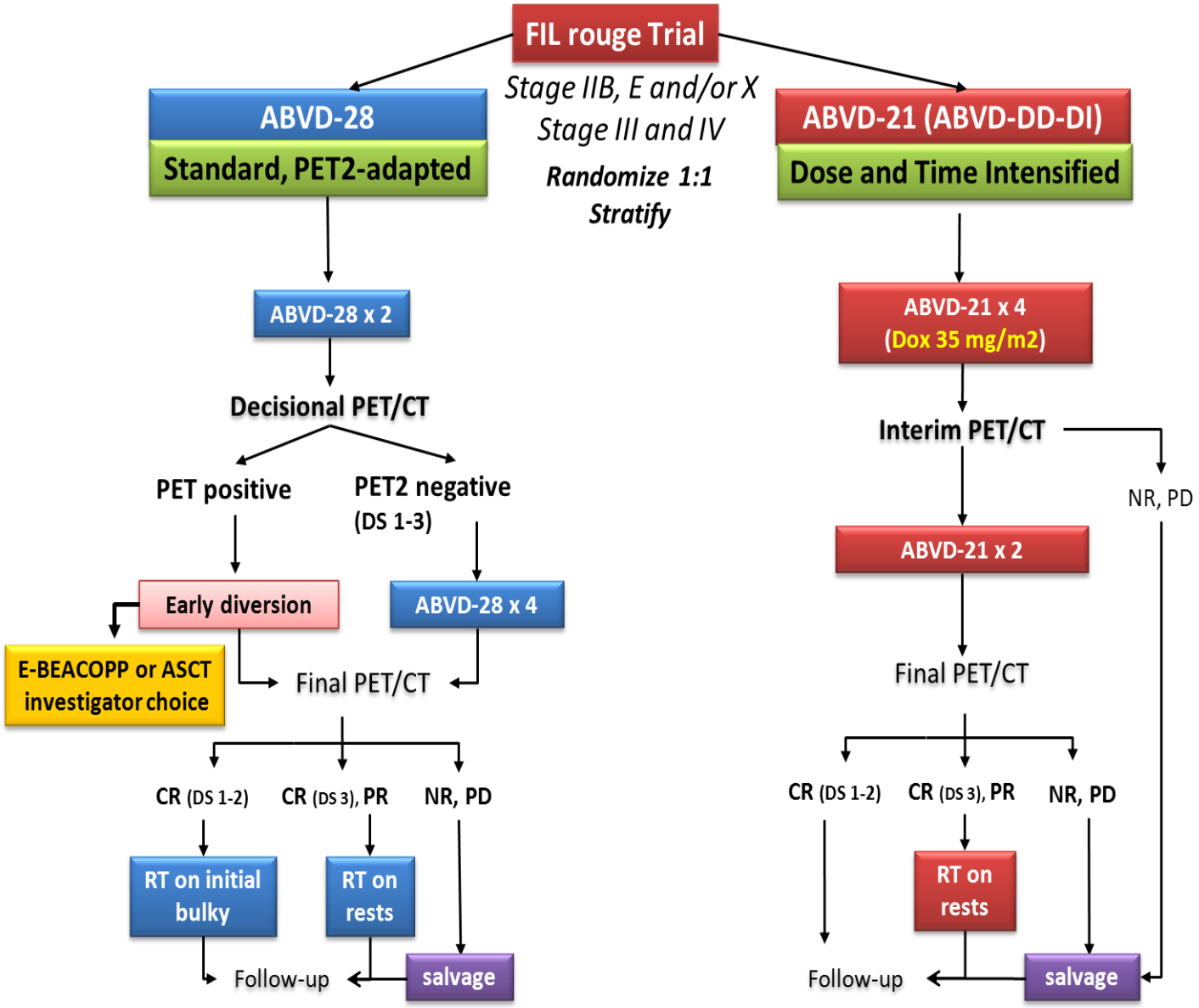




**RATHL (all)**

**3 year PFS: 82.6% (80.2 – 84.8)**

**HD18 (PET+ only):**

**3 year PFS 91.4% – 93.0%**


FIL rouge Trial
Stage IIB, E and/or X
Stage III and IV
Randomize 1:1
Stratify
ABVD-28
Standard, PET2-adapted
ABVD-28 x 2
Decisional PET/CT
PET positive
PET2 negative
(DS 1-3)
Early diversion
ABVD-28 x 4
E-BEACOPP or ASCT
investigator choice
Final PET/CT
CR (DS 1-2)
CR (DS 3), PR
NR, PD
RT on initial bulky
RT on rests
Follow-up
salvage
ABVD-21 (ABVD-DD-DI)
Dose and Time Intensified
ABVD-21 x 4
(Dox 35 mg/m2)
Interim PET/CT
NR, PD
ABVD-21 x 2
Final PET/CT
CR (DS 1-2)
CR (DS 3), PR
NR, PD
RT on rests
Follow-up
salvage

# Modern RT in lymphoma

Radiation therapy has changed dramatically over the last few decades in terms of both irradiated volumes and dose

Smaller treatment volumes, lower radiation dose and advanced conformal radiotherapy can certainly allow a safer radiation delivery, when/if needed (!!!)

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

**”There is no doubt that radiation remains the most active single modality in the treatment of most types of lymphoma”**

James O. Armitage

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School