Modern radiotherapy in the combined modality treatment of lymphomas

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Disclosures

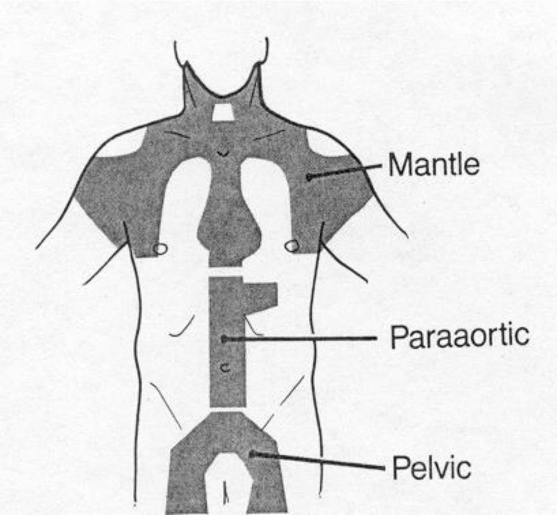
- Member of Advisory Board and Principal Investigator, Takeda
- Research Agreement, Varian Medical Systems

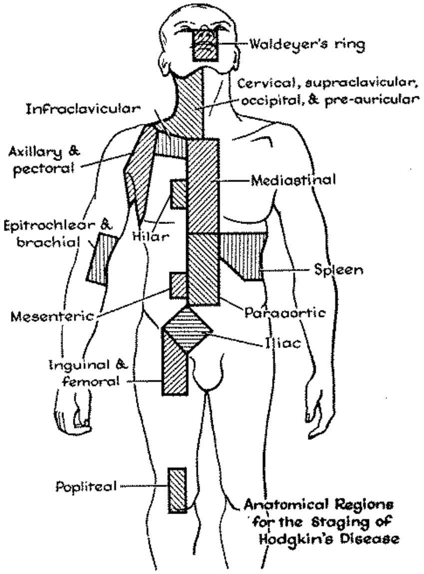
”There is no doubt that radiation remains the most active single modality in the treatment of most types of lymphoma”

James O. Armitage

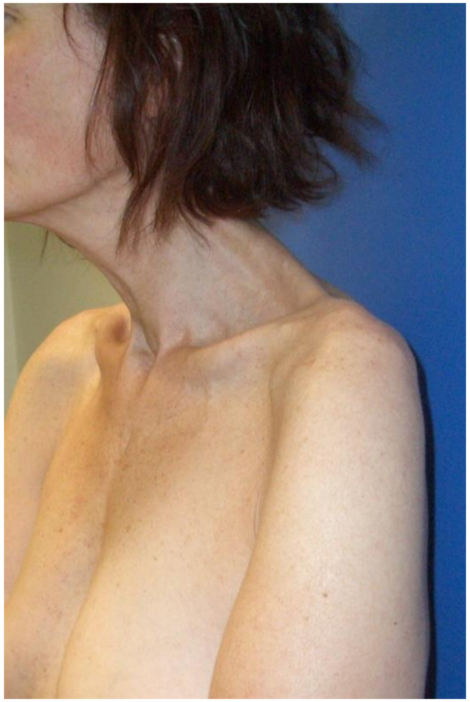
Radiotherapy, the first curative treatment of lymphoma

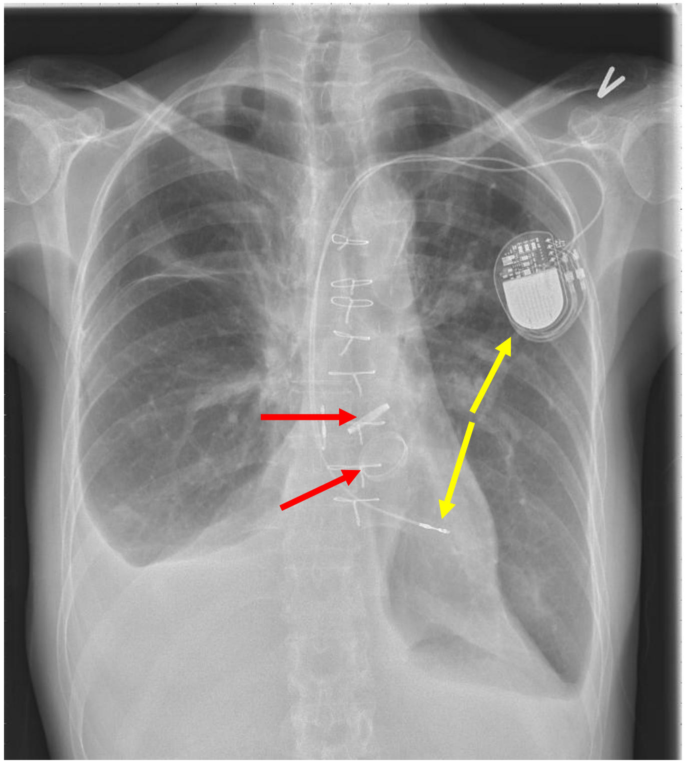
- Prophylactic irradiation of clinically uninvolved volumes
- Very large treatment fields, especially for Hodgkin lymphoma
- Regional irradiation, based on Ann Arbor region definition





Irraditing these very large volumes caused serious long-term sequelae in patients surviving many decades





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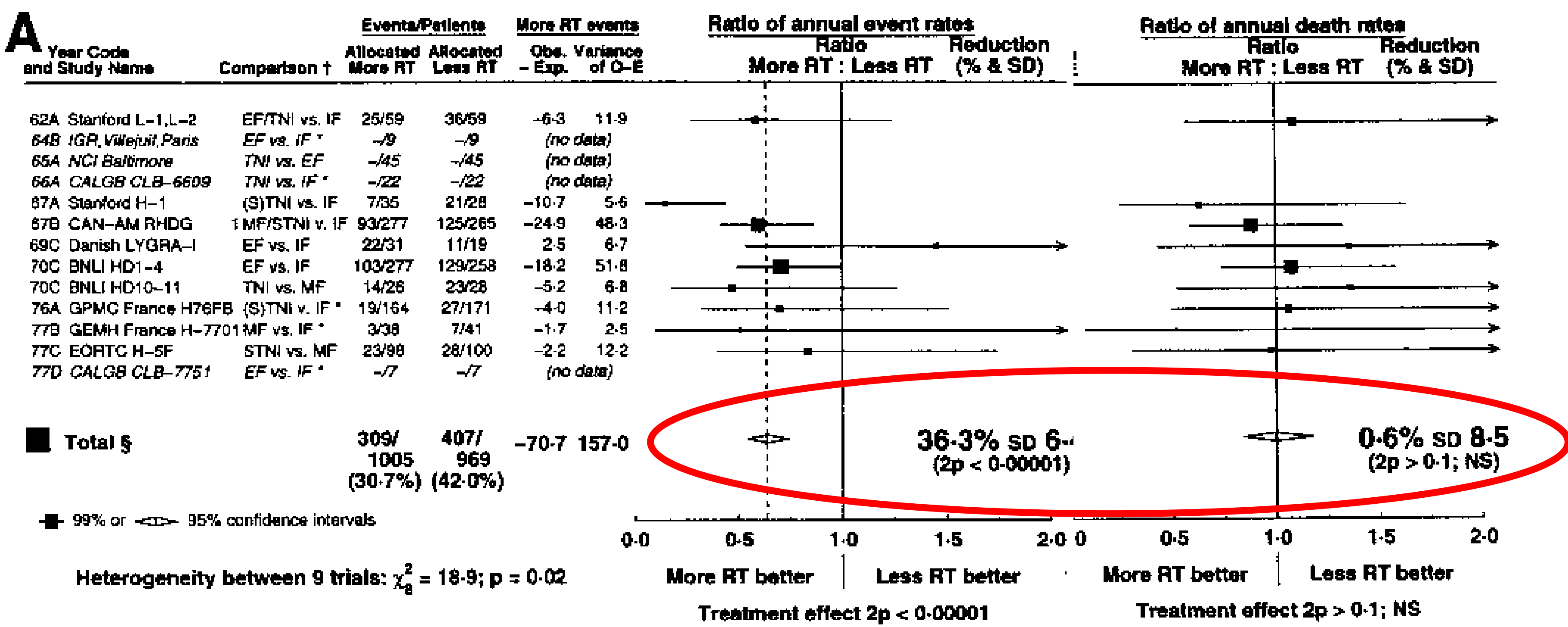
Meta-analysis of randomized trials of more vs. less extensive radiotherapy

Time to failure and overall survival

Specht et al. J Clin Oncol 1998; 16: 830-43



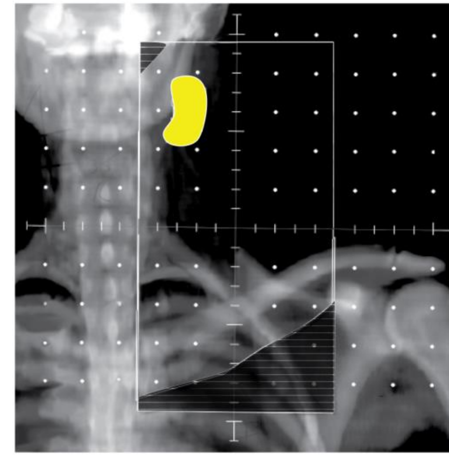
Involved Field Radiotherapy

Symposium article

Annals of Oncology 13 (Supplement 1): 79–83, 2002
DOI: 10.1093/annonc/mdf616

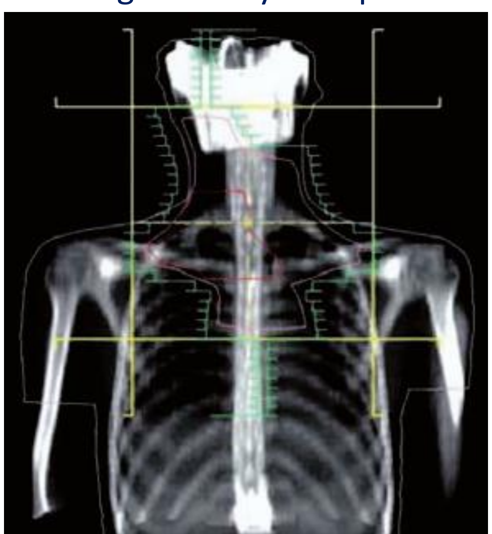
The involved field is back: issues in delineating the radiation field in Hodgkin's disease

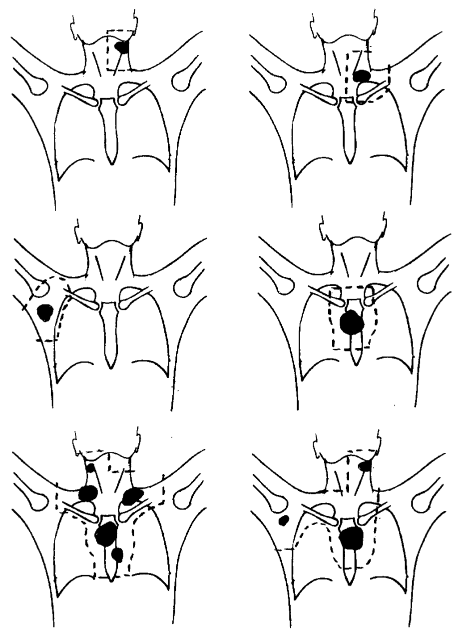
J. Yahalom[1]* & P. Mauch[2]



Many different interpretations

German Hodgkin Study Group

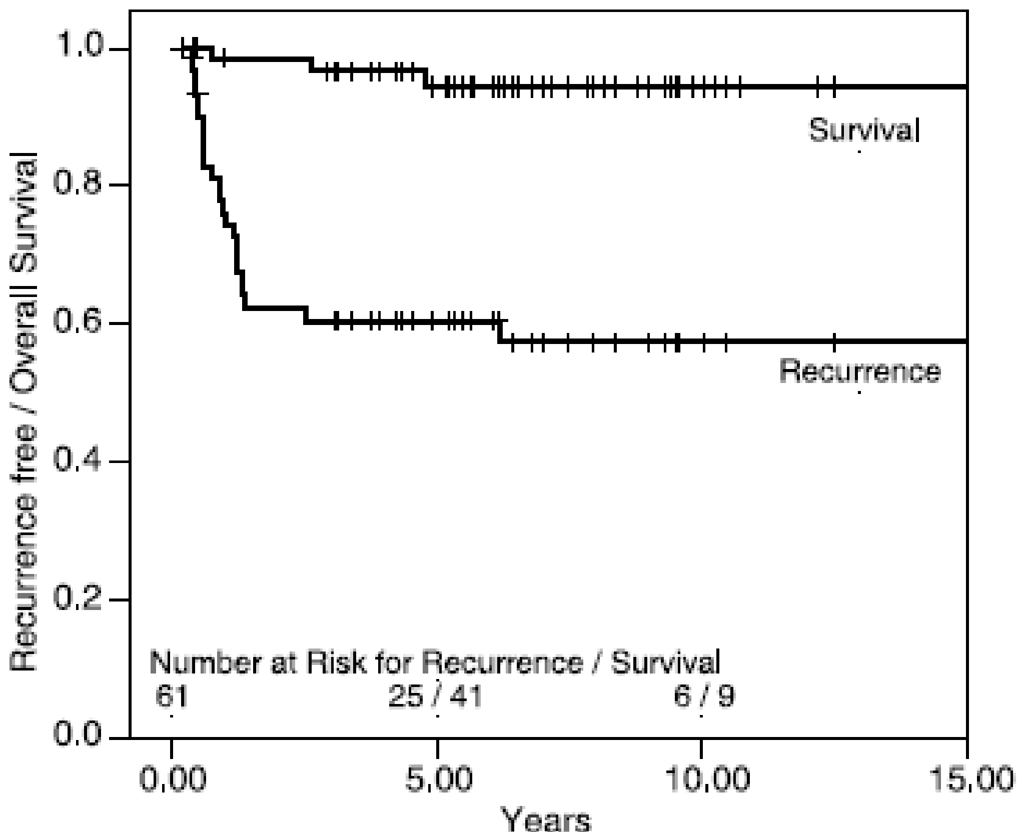




Nordic Lymphoma Group

Site of relapse after chemotherapy alone for stage I and II Hodgkin's disease

Mehdi Shahidi[a], Nahid Kamangari[a], Sue Ashley[b,c], David Cunningham[c], Alan Horwich[a,*]



Radiotherapy and Oncology 78 (2006) 1–5

Modern lymphoma treatment

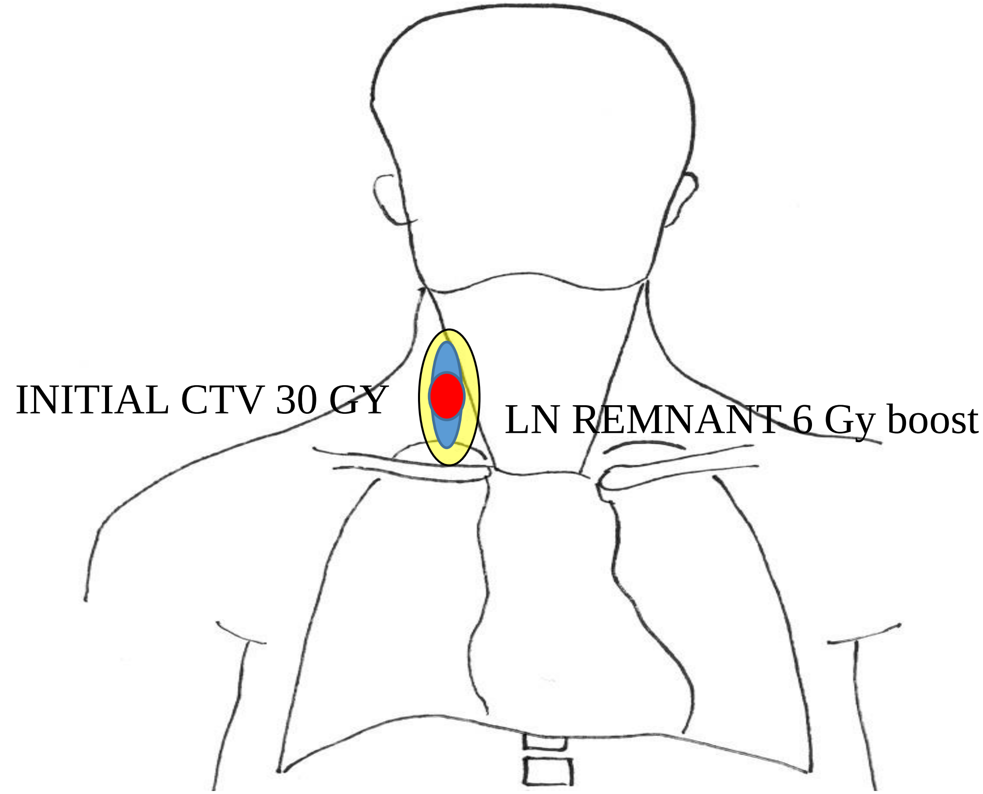
- In Hodgkin lymphoma and aggressive non Hodgkin lymphomas effective chemotherapy exists which eradicates microscopic disease
- Recurrences after chemotherapy alone usually occur in initial macroscopic involvement
- In the combined modality setting we only need to irradiate the volume which contained macroscopic disease from the outset before chemotherapy
- The extended fields of the past are no longer necessary
- Modern imaging and treatment planning and delivery have enabled dramatic reductions in the irradiated volume

EORTC European Organisation for Research and Treatment of Cancer

EORTC Lymphoma Group pioneered conformal RT for HL:
Involved node radiotherapy (INRT)

Requirements:

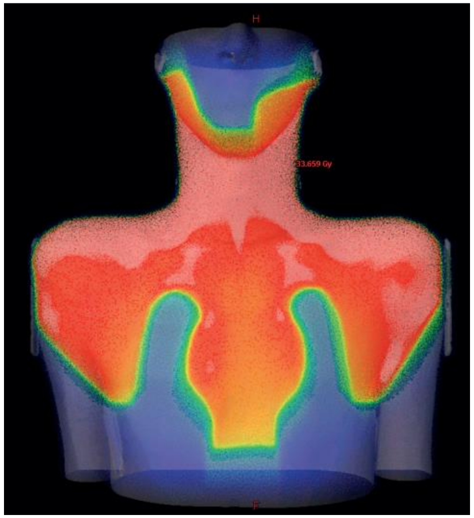
- Good pre-chemo imaging with PET/CT in treatment position
- Image fusion with post-chemo planning CT
- Contouring target volume of tissue which contained lymphoma at presentation

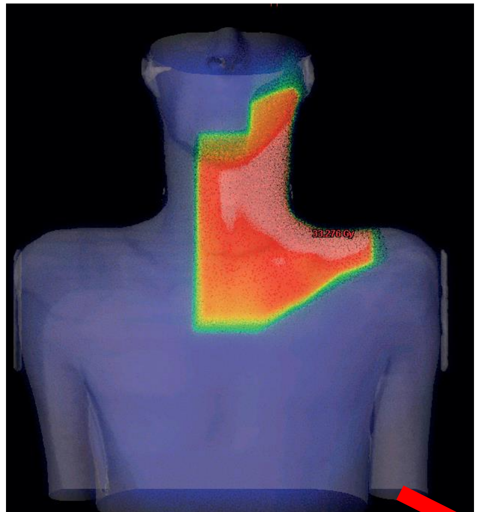


Girinsky el al. Radiother Oncol 2006; 79: 270-7

Paradigm shift in lymphoma radiotherapy

Mantle field (EFRT) or involved field (IFRT)

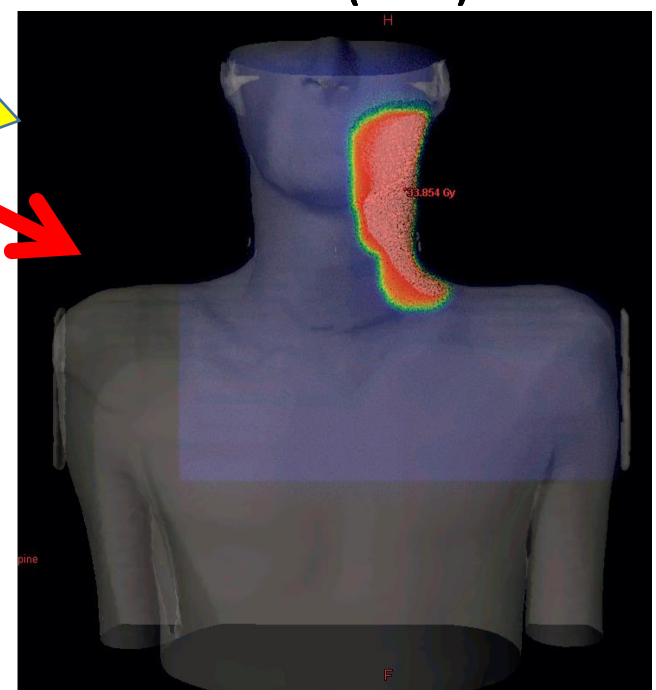




Based on:

- 2 D planning
- Regions
- Bony landmarks defining fields
- ”Fixed” margins

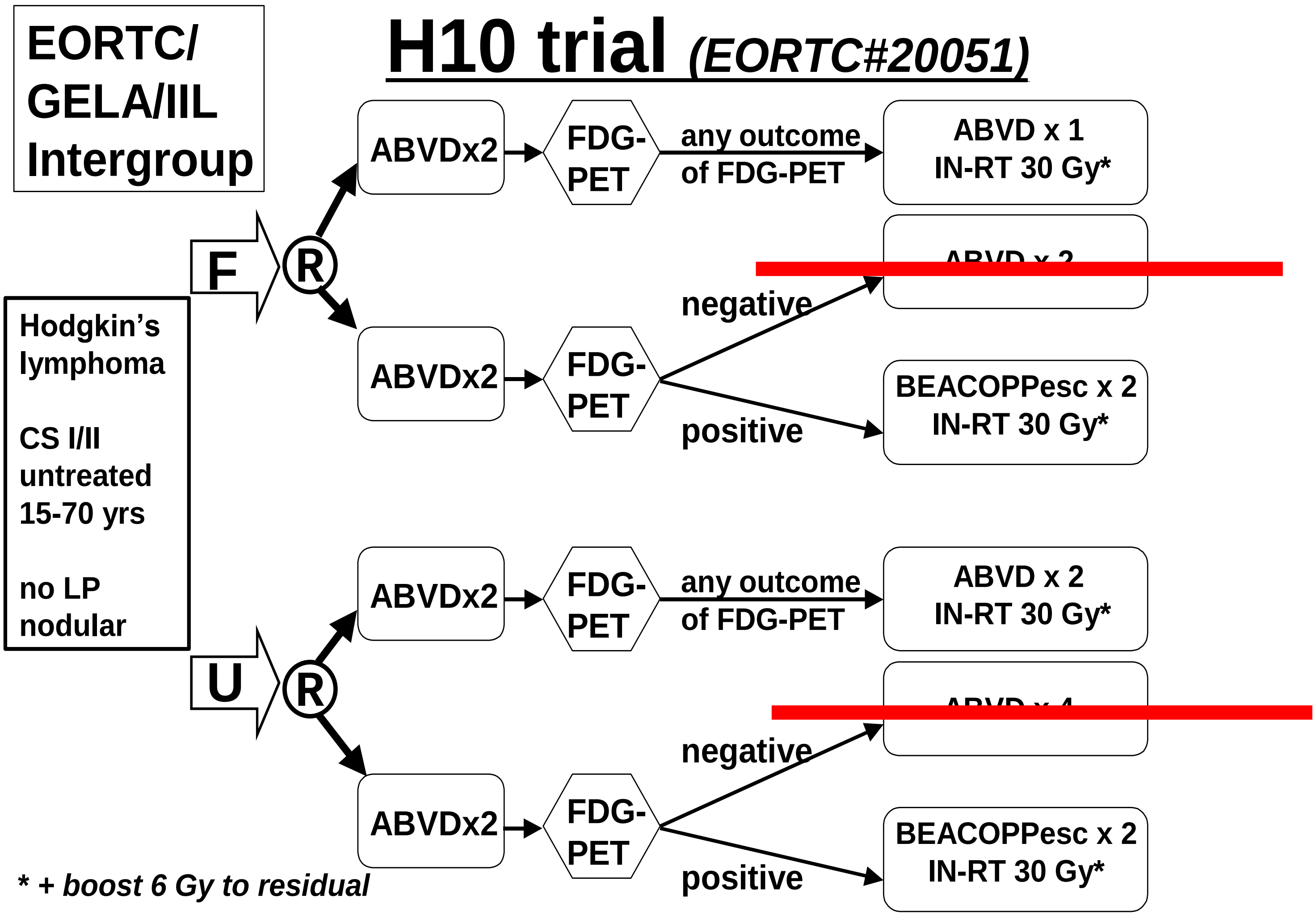
Involved site (ISRT) or involved node (INRT)



Based on:

- 3 D planning
- Actual lymphoma involvement
- Contouring of volumes (GTV, CTV, PTV)
- Margins (GTV→CTV) based on clinical judgement and (CTV→PTV) based on internal and setup uncertainties

Is highly conformal treatment safe?



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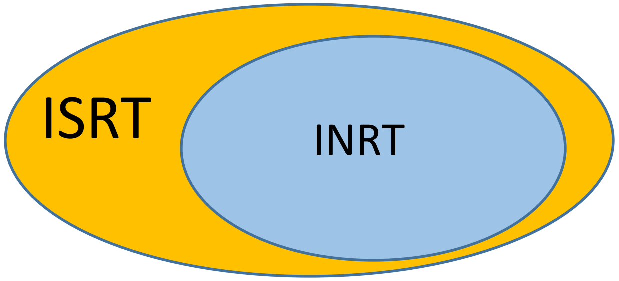
Involved Site Radiotherapy (ISRT)

- 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



Guidelines for radiotherapy of lymphomas
implemented by NCCN and most cooperative groups

Modern Radiation Therapy for Nodal Non-Hodgkin Lymphoma—Target Definition and Dose Guidelines From the International Lymphoma Radiation Oncology Group

Tim Illidge, MD, PhD,* Lena Specht, MD,† Joachim Yahalom, MD,‡ Berthe Aleman, MD, PhD,§ Anne Kiil Berthelsen, MD,|| Louis Constine, MD,¶ Bouthaina Dabaja, MD,# Kavita Dharmarajan, MD,‡ Andrea Ng, MD,** Umberto Ricardi, MD,†† and Andrew Wirth, MD,‡‡, on behalf of the International Lymphoma Radiation Oncology Group

IJROBP 2014; 89: 49-58

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

IJROBP 2014; 89: 854-62

Implementation of contemporary radiation therapy planning concepts for pediatric Hodgkin lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group

David C. Hodgson MD [a, b,*], Karin Dieckmann MD [c], Stephanie Terezakis MD [d], Louis Constine MD, [e] for the International Lymphoma Radiation Oncology Group

Practical Radiation Oncology 2015; 5: 85-92

Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

Joachim Yahalom, MD,* Tim Illidge, MD, PhD,† Lena Specht, MD, PhD,‡ Richard T. Hoppe, MD,§ Ye-Xiong Li, MD,|| Richard Tsang, MD,¶ and Andrew Wirth, MD#, on behalf of the International Lymphoma Radiation Oncology Group

IJROPB 2015; 92: 11-31

Modern Radiation Therapy for Primary Cutaneous Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

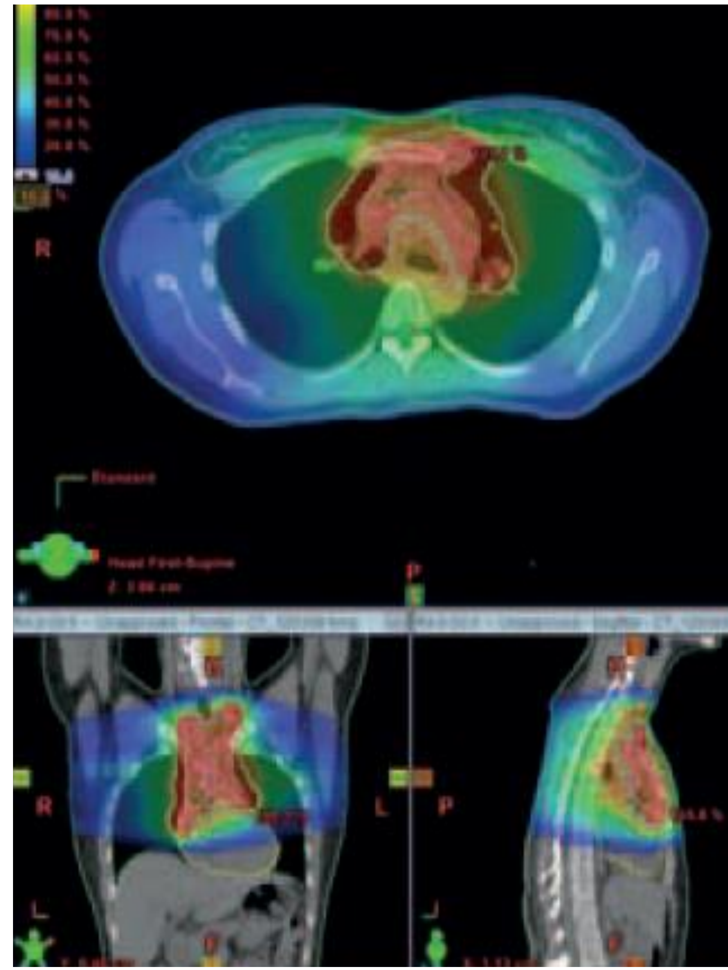
Lena Specht, MD, PhD,* Bouthaina Dabaja, MD,† Tim Illidge, MD, PhD,‡ Lynn D. Wilson, MD,§ and Richard T. Hoppe, MD||, on behalf of the International Lymphoma Radiation Oncology Group

IJROBP 2015; 92: 32-39

Highly conformal radiotherapy

(3D conformal, intensity modulated radiotherapy IMRT, volumetric arc therapy VMAT)

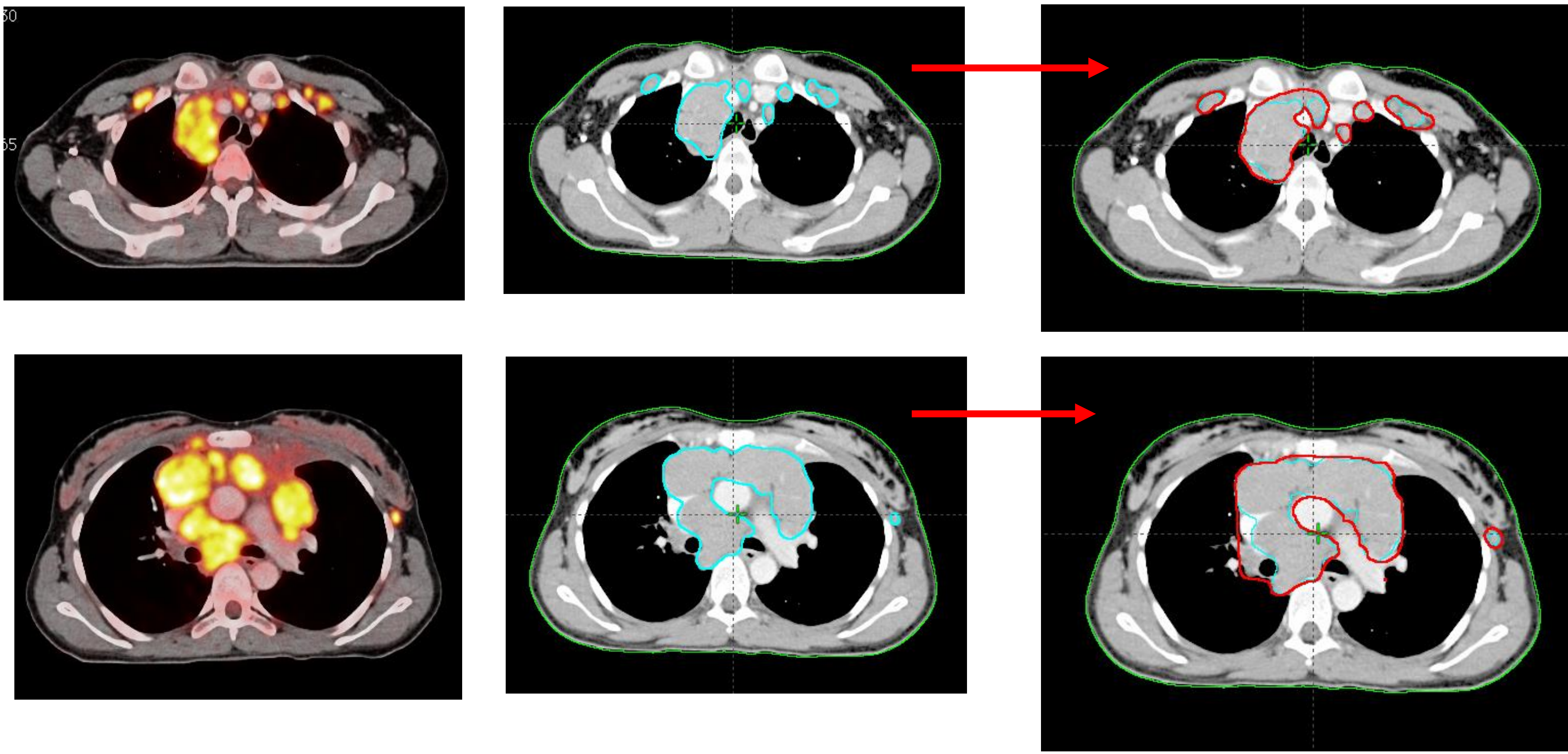
- High dose volume conforms almost precisely to the target we contour
- Very steep dose gradients around the target
- Precise target definition is crucial
- If we contour too small we will miss lymphoma and jeopardize the patient's chance of cure
- If we contour too large unnecessary radiation will be given to normal structures



Pre-chemo PET/CT scan

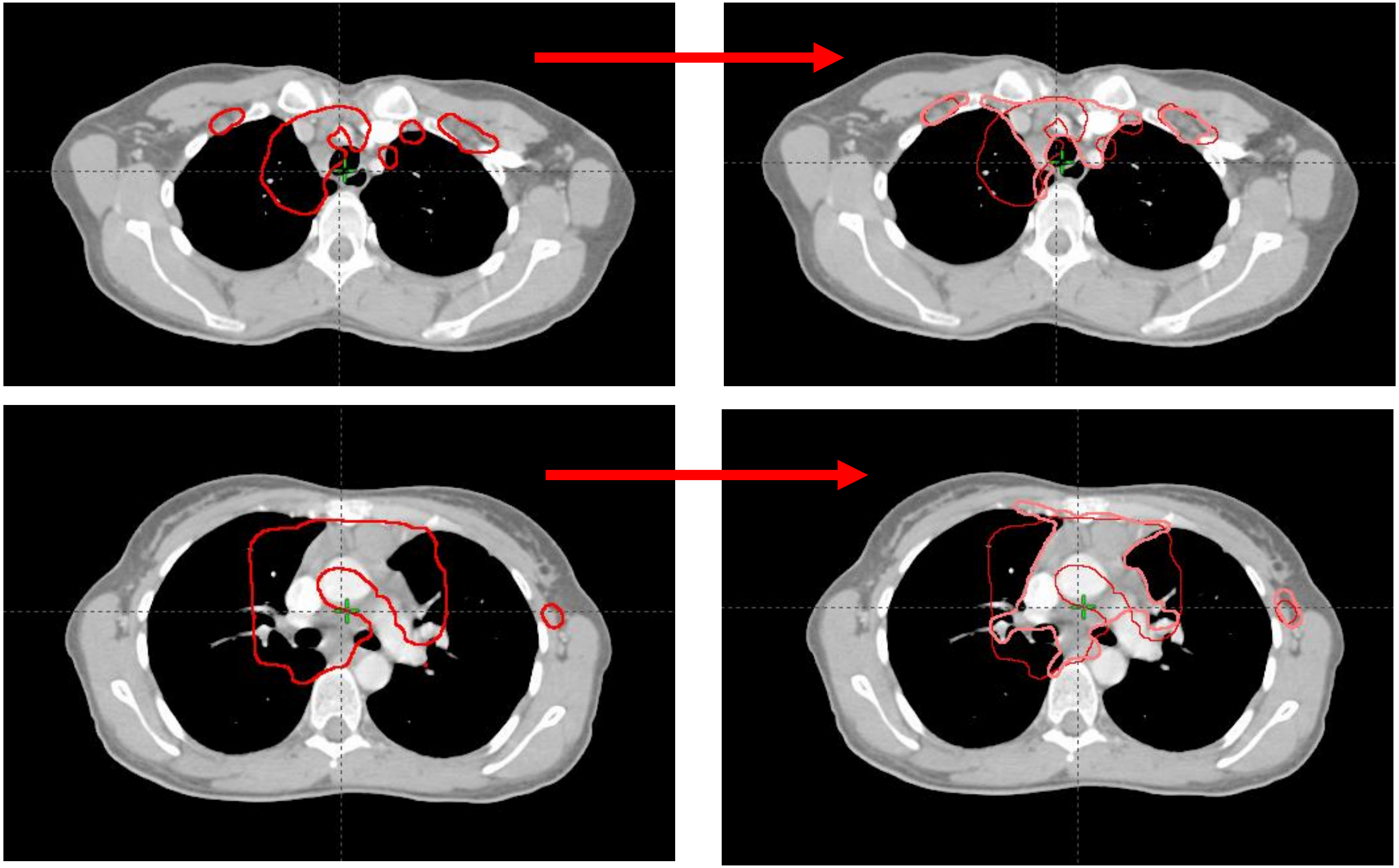
PET+ volume

Gross tumour volume GTV



Post-chemo planning CT scan

Pre-chemo gross tumour volume | Post-chemo clinical target volume



Margins and corresponding tissue volumes

Verellen D et al. Nat Rev Cancer 2007; 7: 949-60

Radiation dose for combined modality treatment

- Hodgkin lymphoma, early stage favourable: 20 Gy

  GHSG HD10, Engert A et al, N Engl J Med 2010; 363: 640-52

- Hodgkin lymphoma, early stage unfavourable: 30 Gy

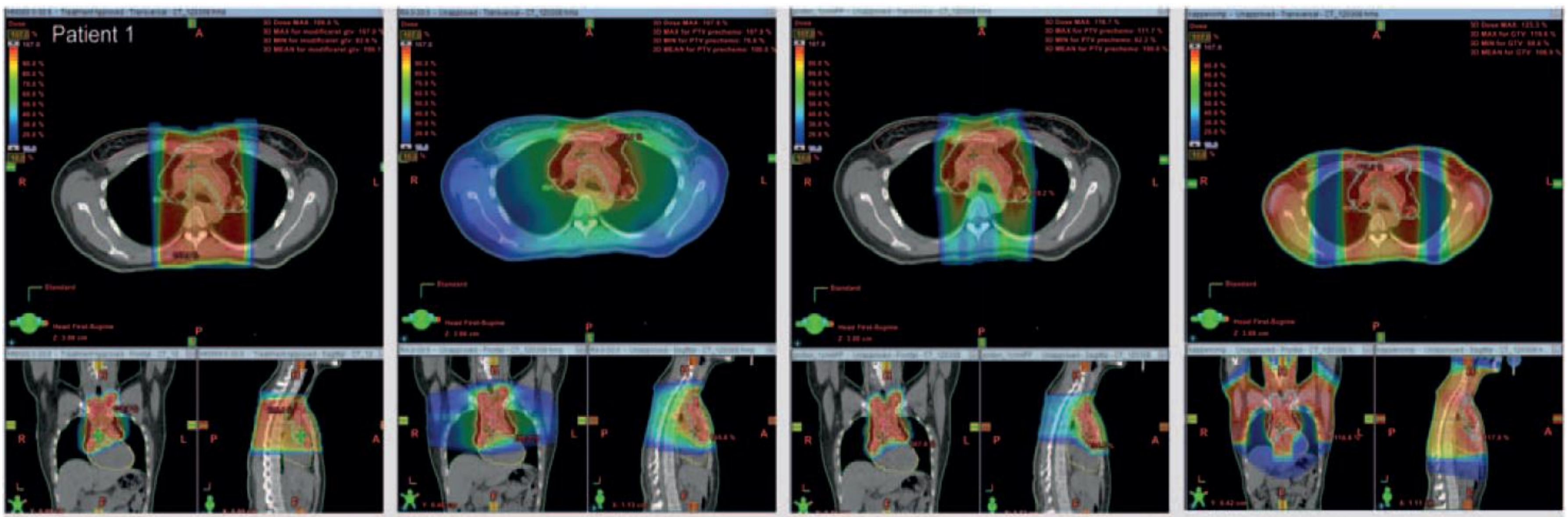
  GHSG HD11, Eich HT et al, JCO 2010; 28: 4199-206

- Non Hodgkin lymphoma, aggressive: 30 Gy

  Lowry L et al, Radiother Oncol 2011; 100: 86-92

Different modern techniques vs. extended fields of the past

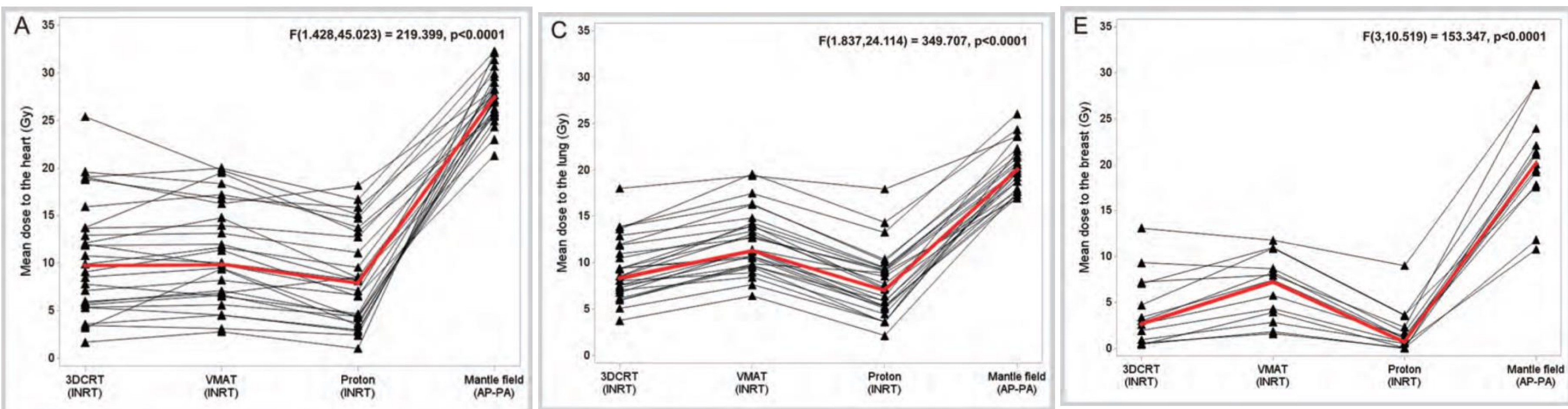
AP-PA | IMRT | IMPT | Mantle field



Maraldo M et al. Ann Oncol 2013; 24: 2113-8

Mean doses to heart, lungs, and breasts in 27 early stage HL patients with mediastinal involvement with different techniques

3D conformal, IMRT (volumetric arc), proton therapy, and conventional mantle field



Maraldo M et al. Ann Oncol 2013; 24: 2113-8

Lifetime excess risks in 27 early stage HL patients with mediastinal involvement with different techniques

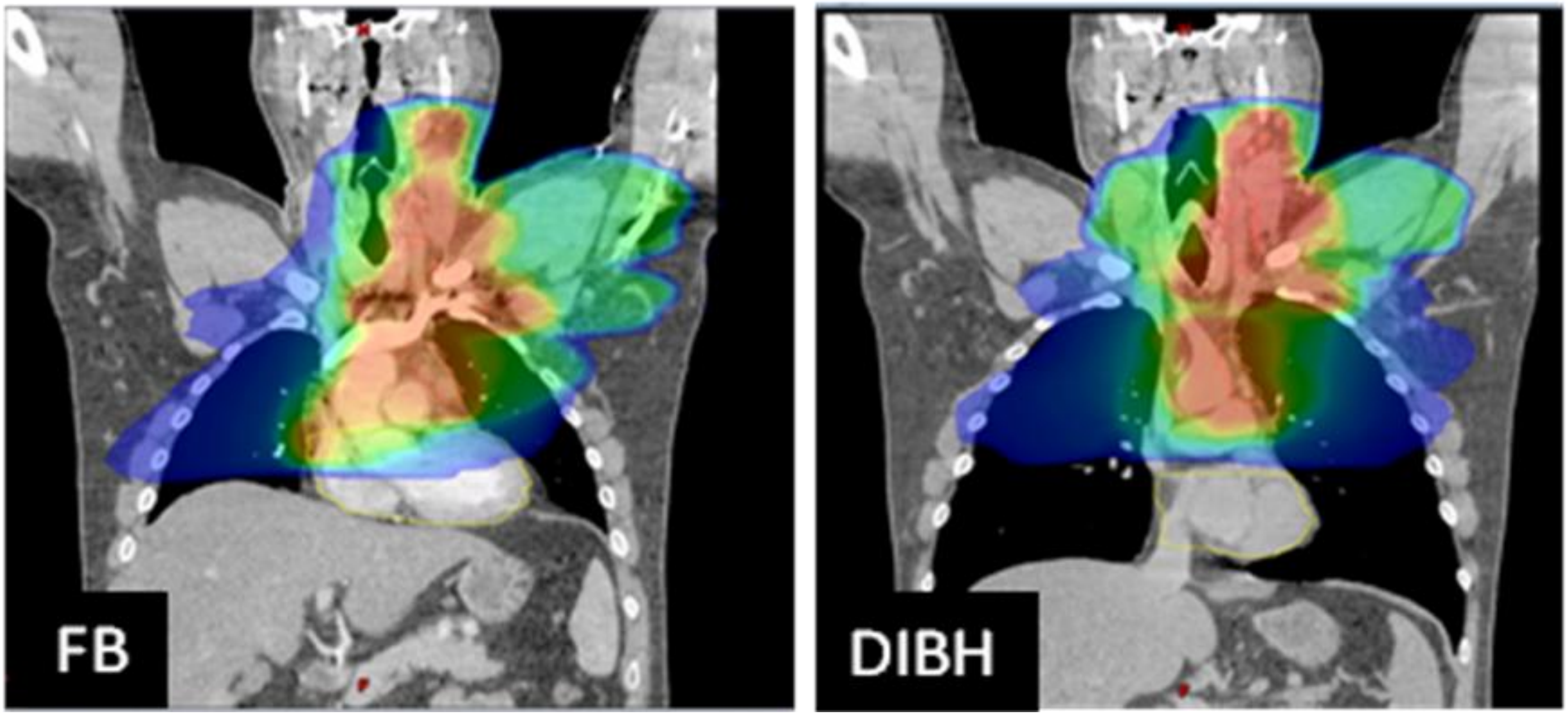
3D conformal, IMRT (volumetric arc), proton therapy, and conventional mantle field

	3D CRT		VMAT		PT		MF	
	Median	Range	Median	Range	Median	Range	Median	Range
Risk estimates (%)								
Cardiac mortality (CMort)	1.0	(0.2–2.7)	1.1	(0.3–2.1)	0.9	(0.1–1.9)	2.9	(2.2–3.4)
Cardiac morbidity (CMorb)	1.3	(0.5–7.1)	1.3	(0.6–4.0)	1.1	(0.5–3.3)	8.6	(4.6–14.3)
Myocardial infarction (MI)	5.5	(0.7–30.1)	5.9	(1.1–23.8)	4.7	(0.4–20.4)	19.8	(6.9–37.7)
Valvular disease (VD)	0	(0–0.2)	0	(0)	0	(0)	0.4	(0–3.7)
Radiation-induced lung cancer (LC)	4.4	(2.4–9.7)	6.0	(3.1–11.4)	3.3	(1.4–9.7)	10.5	(6.3–15.1)
Radiation-induced breast cancer (BC)	3.7	(0.2–11.8)	8.0	(0.6–13.4)	1.4	(0–8.1)	23.0	(7.5–34.5)
Life years lost (LYL)								
Total LYL	0.9	(0.2–1.6)	1.1	(0.2–2.3)	0.7	(0.1–1.6)	2.1	(0.6–3.6)

Maraldo M et al. Ann Oncol 2013; 24: 2113-8


H
R
R
L
Standard
Head First-Supine
Y: -28.46 cm
F
90

Breathing adapted RT

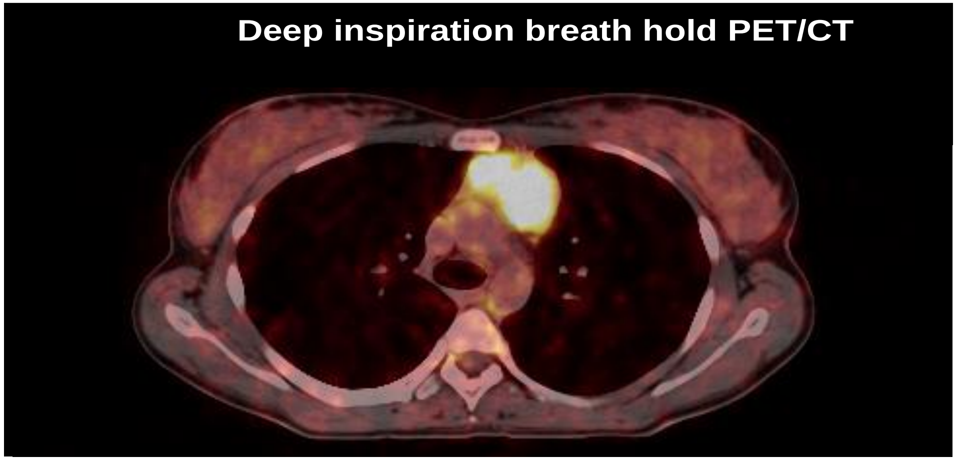


Petersen PM et al. Acta Oncol 2015; 54: 60-6

Table II. Dose characteristics with free breathing (FB) and deep inspiration breath-hold (DIBH).

	FB (median, range)		DIBH (median, range)		Difference (median, range)		p-Value*
Target							
PTV volume (cm^3)	1198	(132, 1877)	945	(131, 1949)	62	(−361, 634)	0.07
CTV volume (cm^3)	213	(21, 511)	198	(14, 561)	3	(−126, 209)	0.60
PTV $V_{95\%}$ (%)	94	(61, 98)	93	(78–97)	1	(−18, 7.4)	0.12
Lung							
Lung volume (cm^3)	2924	(1908, 5228)	4936	(3391, 8776)	−2300	(−5272, −1093)	<0.01
Mean lung dose (Gy)	8.5	(0.95, 18.9)	7.2	(1.0, 12.5)	2.0	(−0.08, 6.4)	<0.01
Lung V_{20Gy} (%)	14	(0, 46)	11	(0, 32)	5.3	(−1, 17)	<0.01
Heart							
Mean heart dose (Gy)	6.0	(0.12, 23)	3.9	(0.10, 17)	1.4	(0, 8.6)	<0.01
Heart V_{20Gy} (%)	15	(0.00, 76)	4.1	(0.00, 66)	6.3	(−2.7, 32)	<0.01
Heart V_{30Gy} (%)	2.0	(0.00, 35)	0.00	(0.00, 27)	0.8	(−7, 16)	0.01
Mean aortic valves dose (Gy)	26	(0.23, 31)	16	(0.20, 31)	1.9	(−1.8, 14)	<0.01
Mean mitral valve dose (Gy)	7.1	(0.12, 30)	1.9	(0.10, 29)	0.58	(−1.3, 16)	<0.01
Mean tricuspid valves dose (Gy)	2.6	(0.11, 30)	1.7	(0.10, 30)	0.43	(−4.6, 20)	0.01
Mean pulmonic valves dose (Gy)	26	(0.26, 32)	15	(0.23, 32)	1.4	(−1.9, 21)	<0.01
Mean LAD dose (Gy)	8.9	(0.10, 29)	5.0	(0.09, 27)	0.80	(−1.8, 14)	<0.01
Mean LMA dose (Gy)	25	(0.25, 32)	18	(0.20, 32)	3.0	(−11, 21)	<0.01
Mean LC dose (Gy)	11	(0.18, 31)	7.7	(0.15, 31)	0.40	(−4.0, 25)	0.02
Mean RCA dose (Gy)	27	(0.16, 31)	17	(0.01, 32)	0.29	(−17, 24)	0.06
Breast							
Mean dose right breast (Gy)	5.0	(0.11, 15)	6.4	(0.074, 13)	0.00	(−4.8, 2.2)	0.47
Mean dose left breast (Gy)	3.7	(0.11, 15)	3.2	(0.090, 13)	0.01	(−3.6, 6.8)	0.22

Using breath hold PET for radiotherapy planning



RT risks vs. benefits

- Cure with first treatment is important
  - Recurrence is usually treated with high dose chemotherapy and stem cell transplantation
  - These patients experience much more acute and long term toxicity
  - Only about 50 % achieve long term remission

- Modern radiotherapy is associated with much less long term complication probability than the extended fields of the past

- Chemotherapy is also associated with long term complications, but less data are available

Which treatment strategy is preferable?

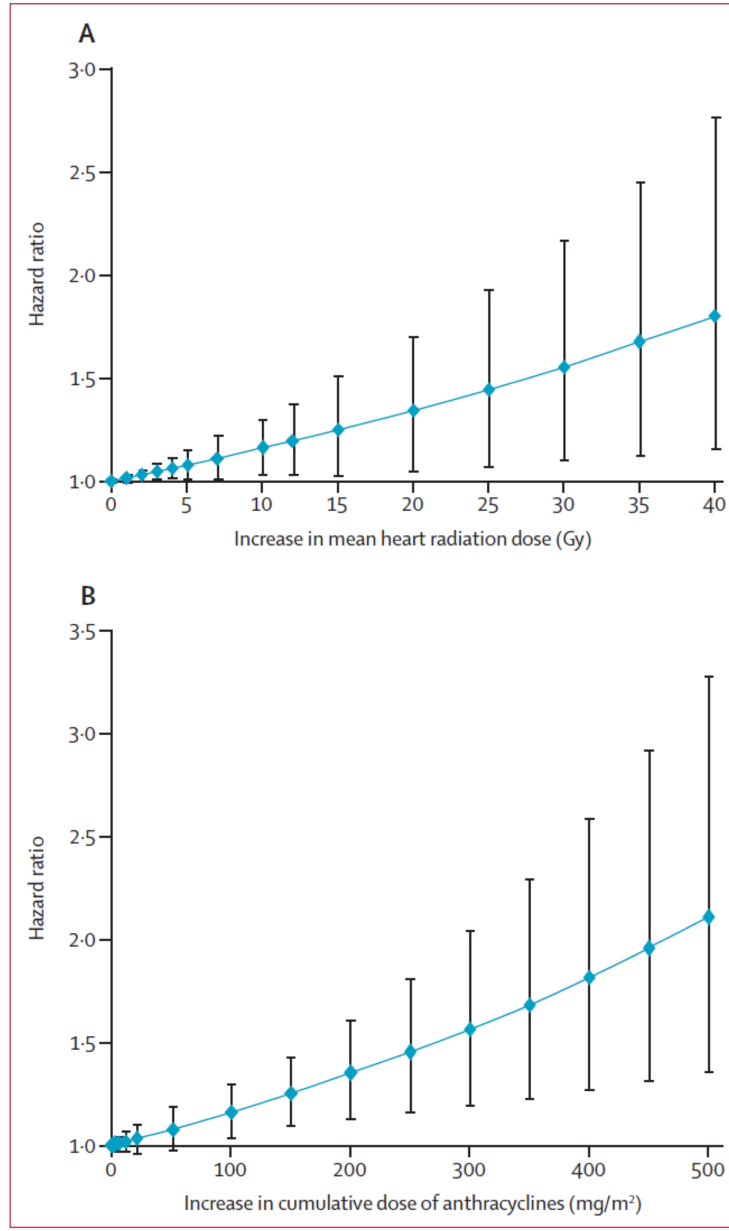
- Depends on the location of the disease
- Doses to different organs with different strategies should be compared
- Considerations of normal tissue toxicity varies between patients depending on:
  - Age
  - Gender
  - Comorbidities
  - Risk factors for other diseases
- Even low radiation doses to normal tissues, previously considered safe, result in significant risks of morbidity and mortality in long-term survivors
- Doses to all normal structures should be kept as low as possible

Dose-response data for cardiotoxicity

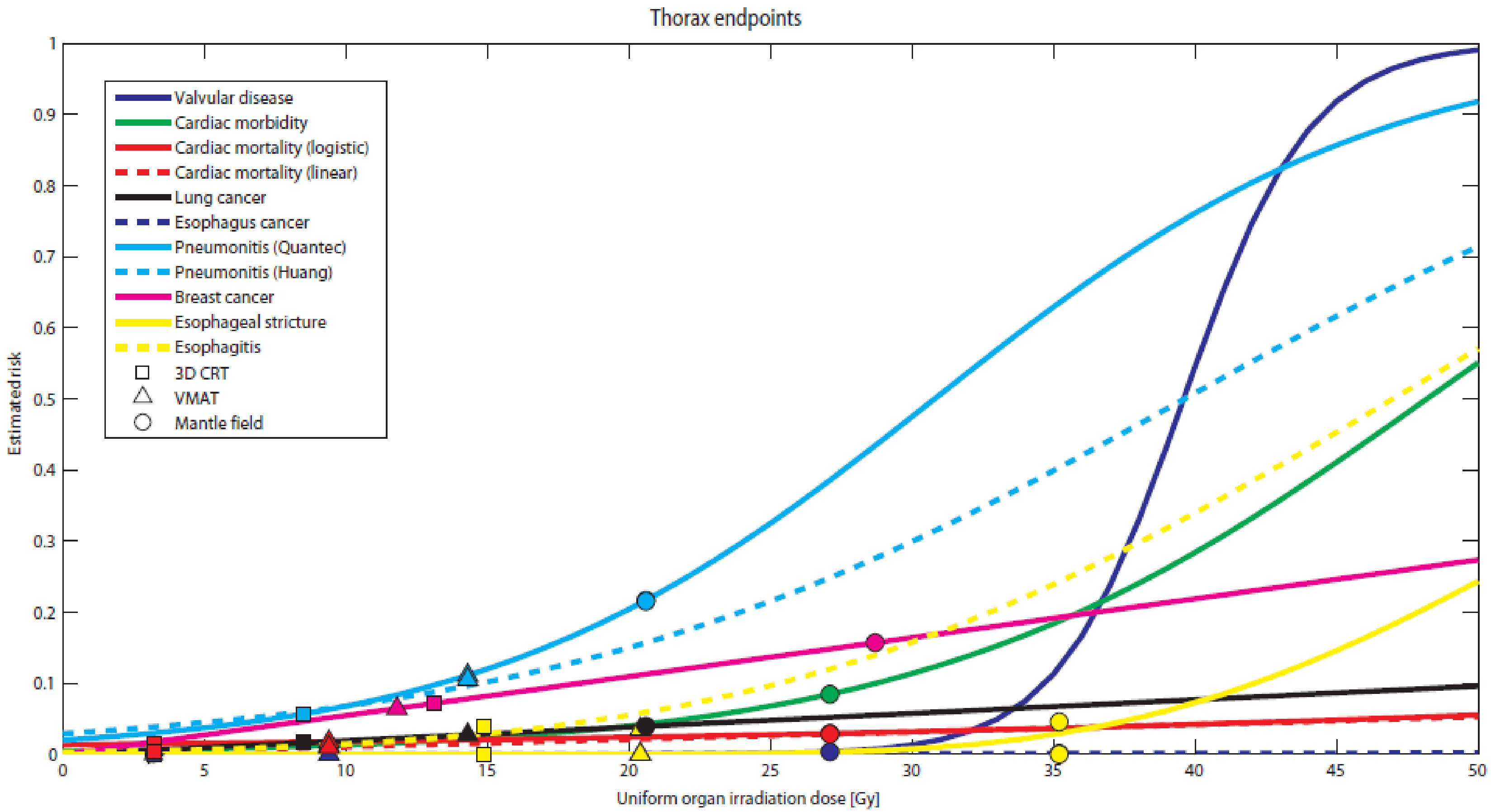
- Hazard ratio for cardiac event:
  - 1.015 per 1 Gy mean heart dose
  - 1.077 per 50 mg/m^2 doxorubicin

5 Gy mean heart dose corresponds to 1 cycle of ABVD

Maraldo MV et al. Lancet Haematol (e-print ahead of publ.)



Ideally, normal tissue complication probability models for all relevant risk organs should be combined for each treatment strategy



Brodin NP et al, IJROBP 2014;88:433-45

Radiotherapy for lymphomas

- If radiotherapy were considered a drug it would be one of the most effective agents available

- More and more data support its use
  - Most often as part of multimodality treatment
  - Modern advanced imaging and treatment technique to minimize risks of long term complications
  - Individualized multispectral risk calculations needed to determine the optimal treatment strategy for each patient

Thank you for your attention

RH

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