Rigshospitalet
Department of Oncology,
Section of Radiotherapy

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

REGION

Modern radiotherapy for Hodgkin lymphoma

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Vice Chairman, International Lymphoma Radiation Oncology Group

GLOBAL EXCELLENCE IN HEALTH

Issues in Hodgkin lymphoma radiotherapy

- The disease may be located everywhere in the body, both within and outside the lymphatic system
- May be localized or widely disseminated
- Often curable, many long-term survivors
- Highly radiosensitive, but long-term side effects are a major issue
- Effective chemotherapy exists which can manage microscopic disease
- Long-term side effects of chemotherapy have not yet been well examined

The Journal of the American Medical Association

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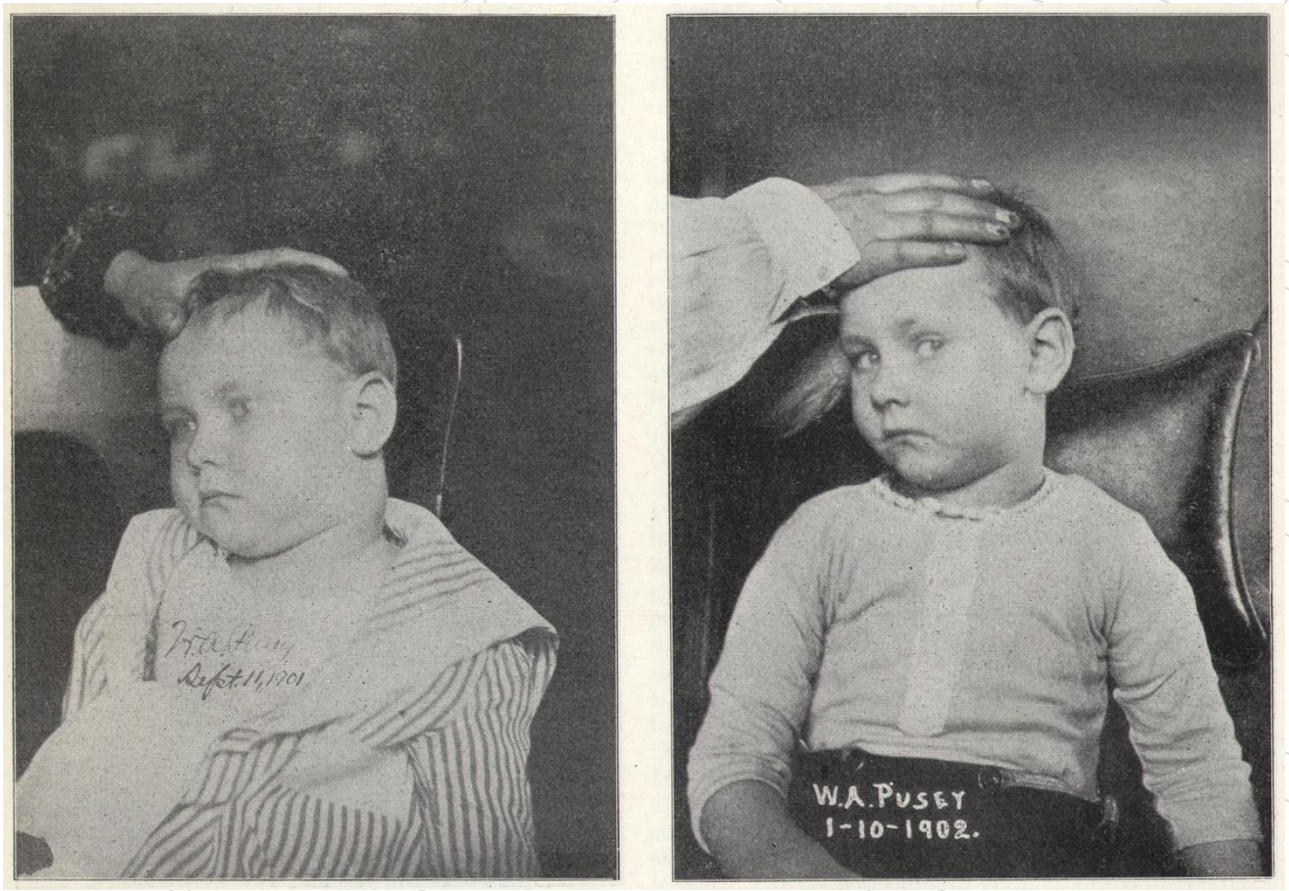
VOL. XXXVIII. CHICAGO, ILLINOIS, JANUARY 18, 1902. No. 3.

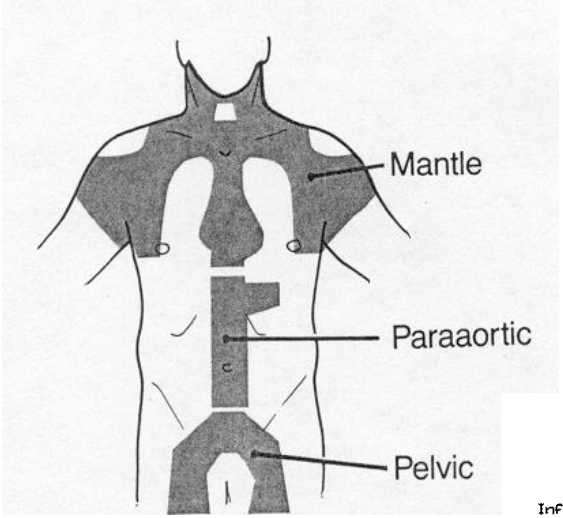


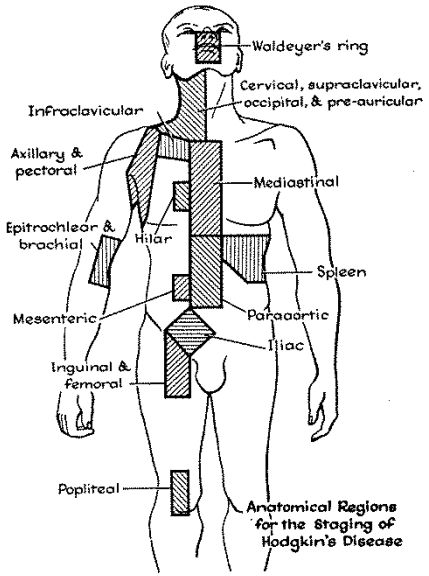
”There is no doubt that radiation remains the most active single modality in the treatment of most types of lymphoma”

James O. Armitage

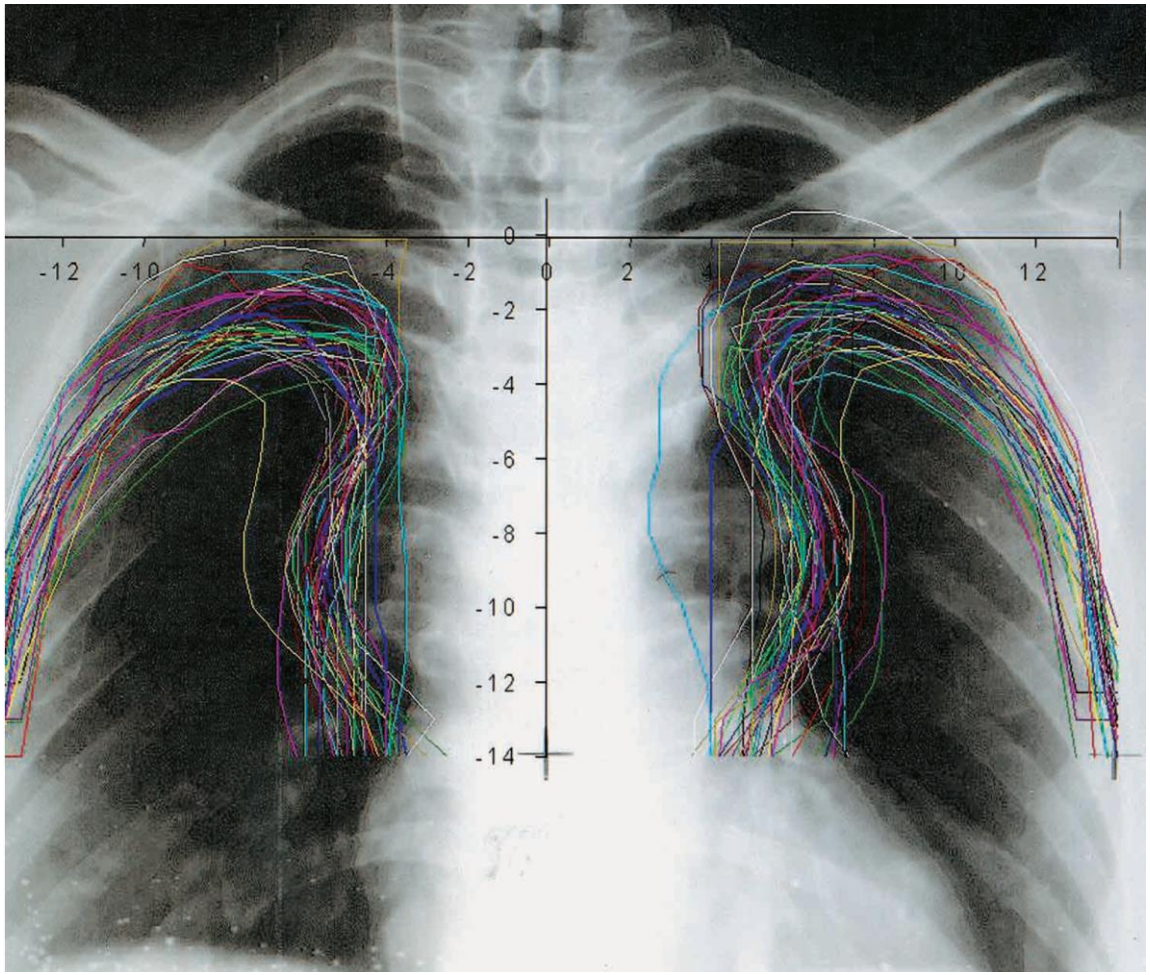
Radiotherapy, the first curative treatment of lymphoma

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





Variation in RT fields

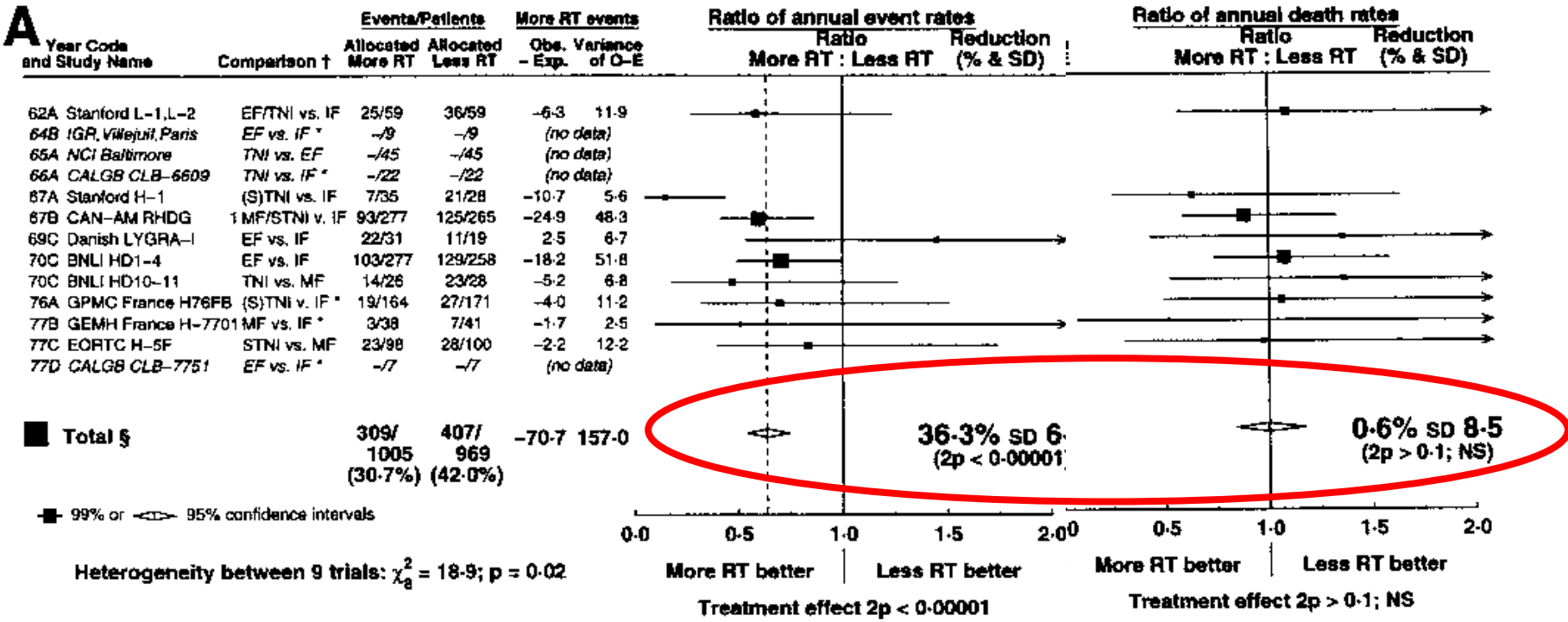


Barton MA *et al., Australas Radiol 2000; 44:433-8*

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



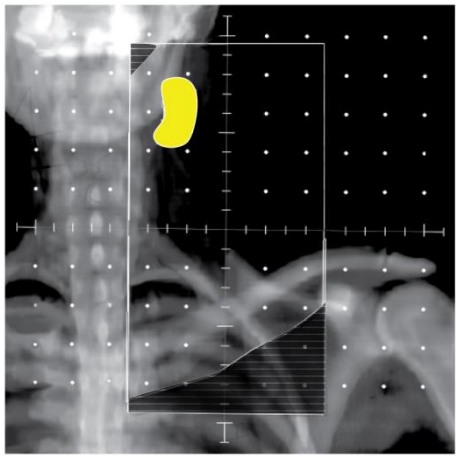
Involved Field Radiotherapy

Symposium article

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

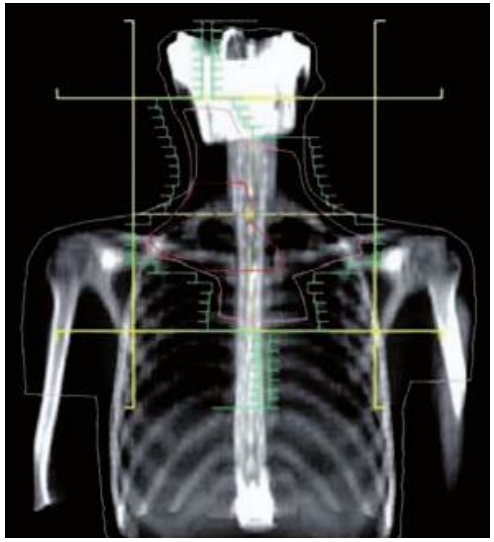
The involved field is back: issues in delineating the radiation field in Hodgkin's disease

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

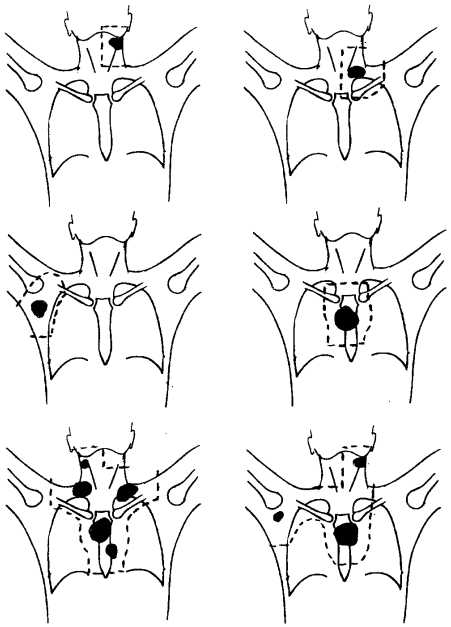


Many different interpretations

German Hodgkin Study Group

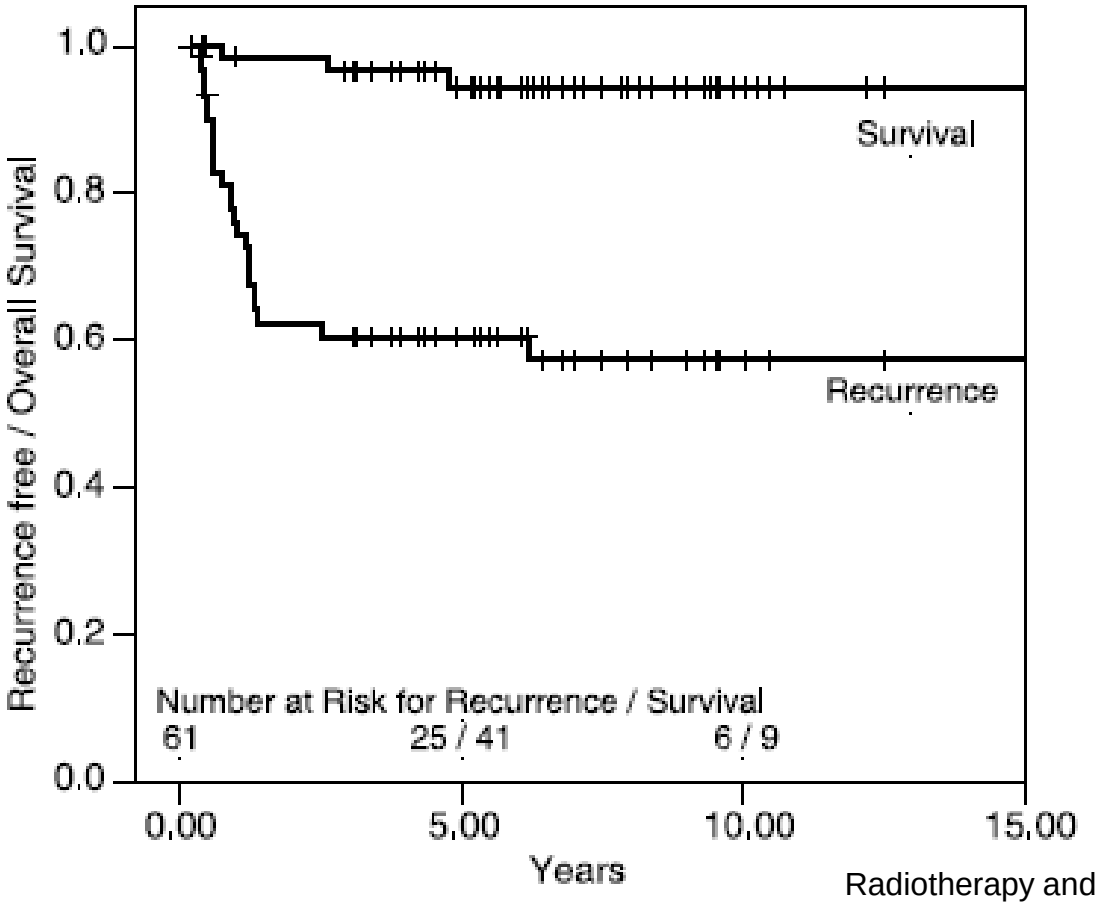


Nordic Lymphoma Group



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

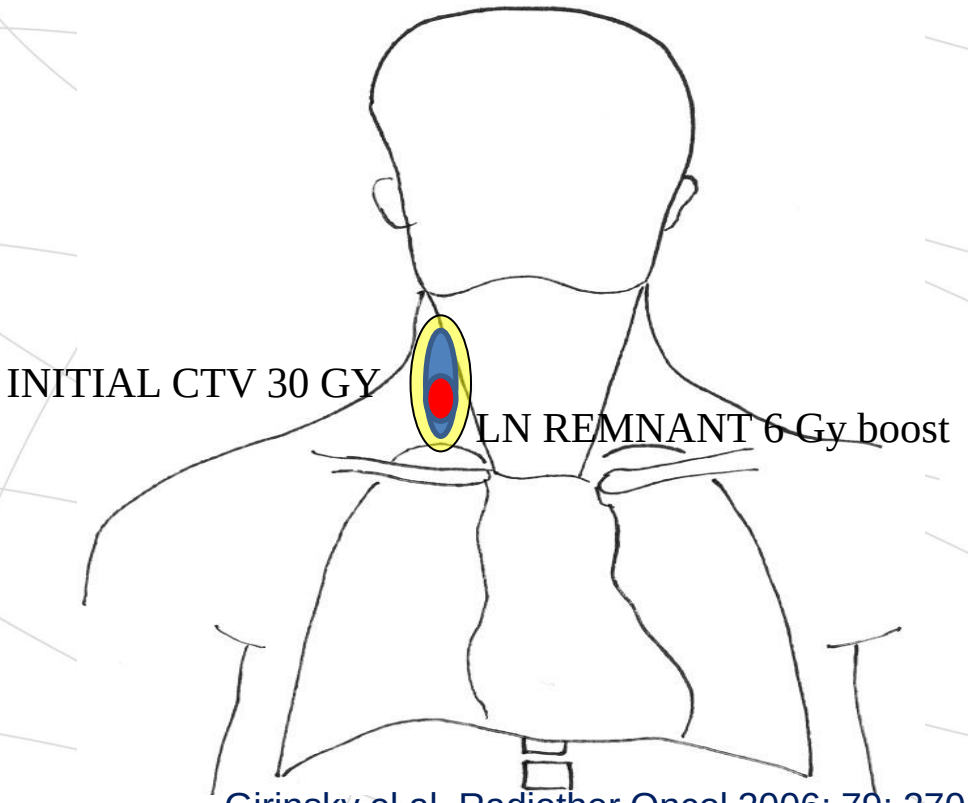
EORTC
European Organisation for Research and Treatment of Cancer

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

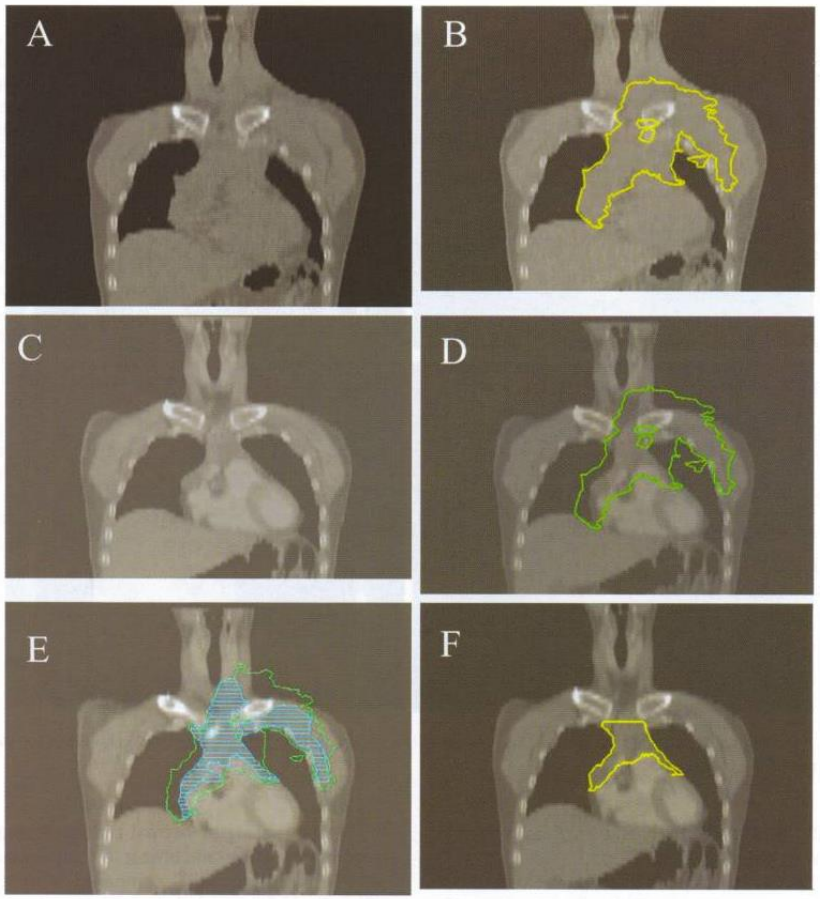


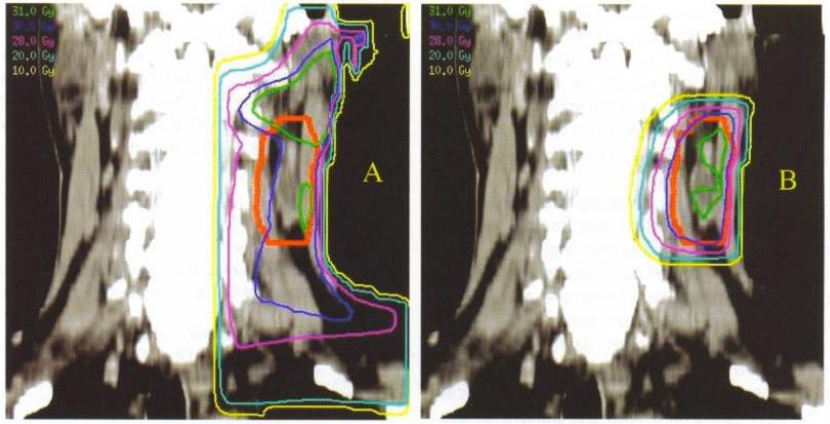
Girinsky el al. Radiother Oncol 2006; 79: 270-7

Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: Concepts and guidelines

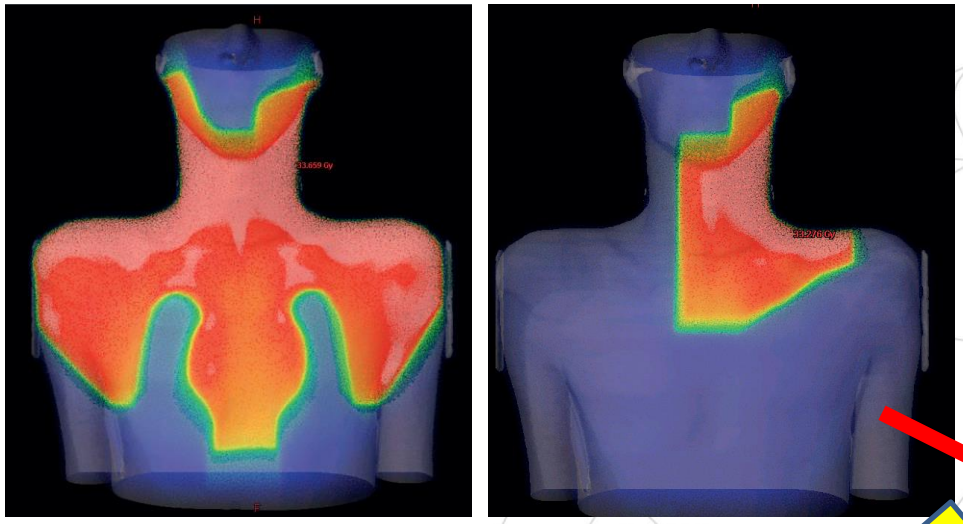
Theodore Girinsky[a,*], Richard van der Maazen[b], Lena Specht[c], Berthe Aleman[d], Philip Poortmans[e], Yolande Lievens[f], Paul Meijnders[g], Mithra Ghalibafian[a], Jacobus Meerwaldt[h], Evert Noordijk[i], on behalf of the EORTC-GELA Lymphoma Group

Radiother Oncol 2006; 79: 270-7



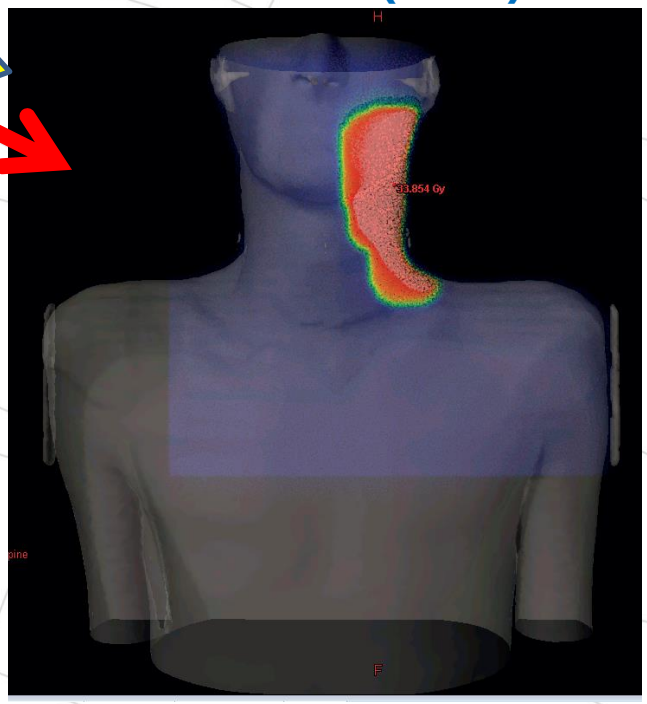


Mantle field (EFRT) or involved field (IFRT)



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

Involved site (ISRT) or involved node (INRT)

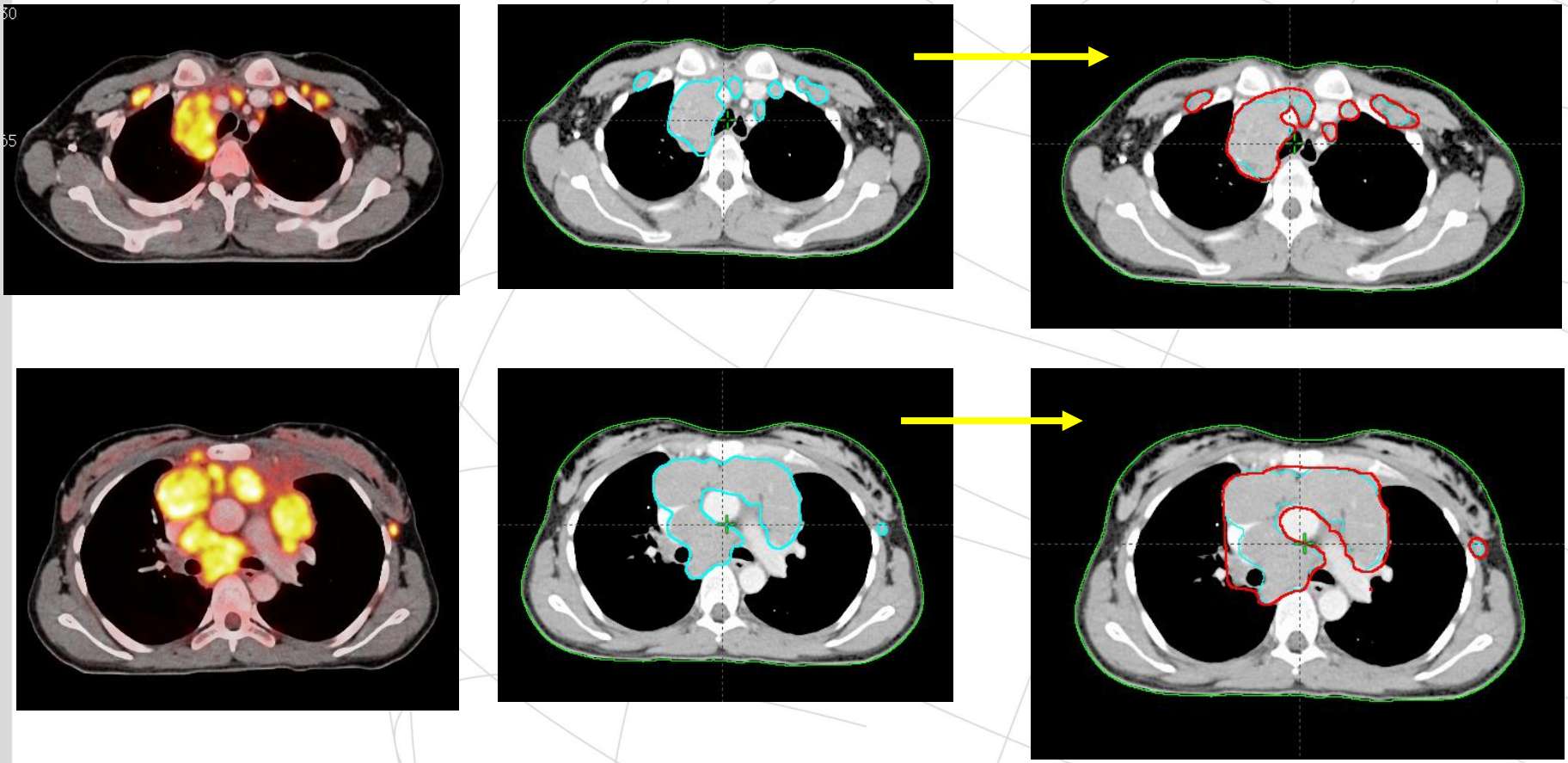


Based on:
- 3 D planning
- Actual lymphoma involvement
- Contouring of volumes (GTV, CTV, PTV)
- Margins (GTV→ CTV) based on clinical judgement and (CTV→ PTV) based on internal and setup uncertainties

Pre-chemo PET/CT scan

PET+ volume

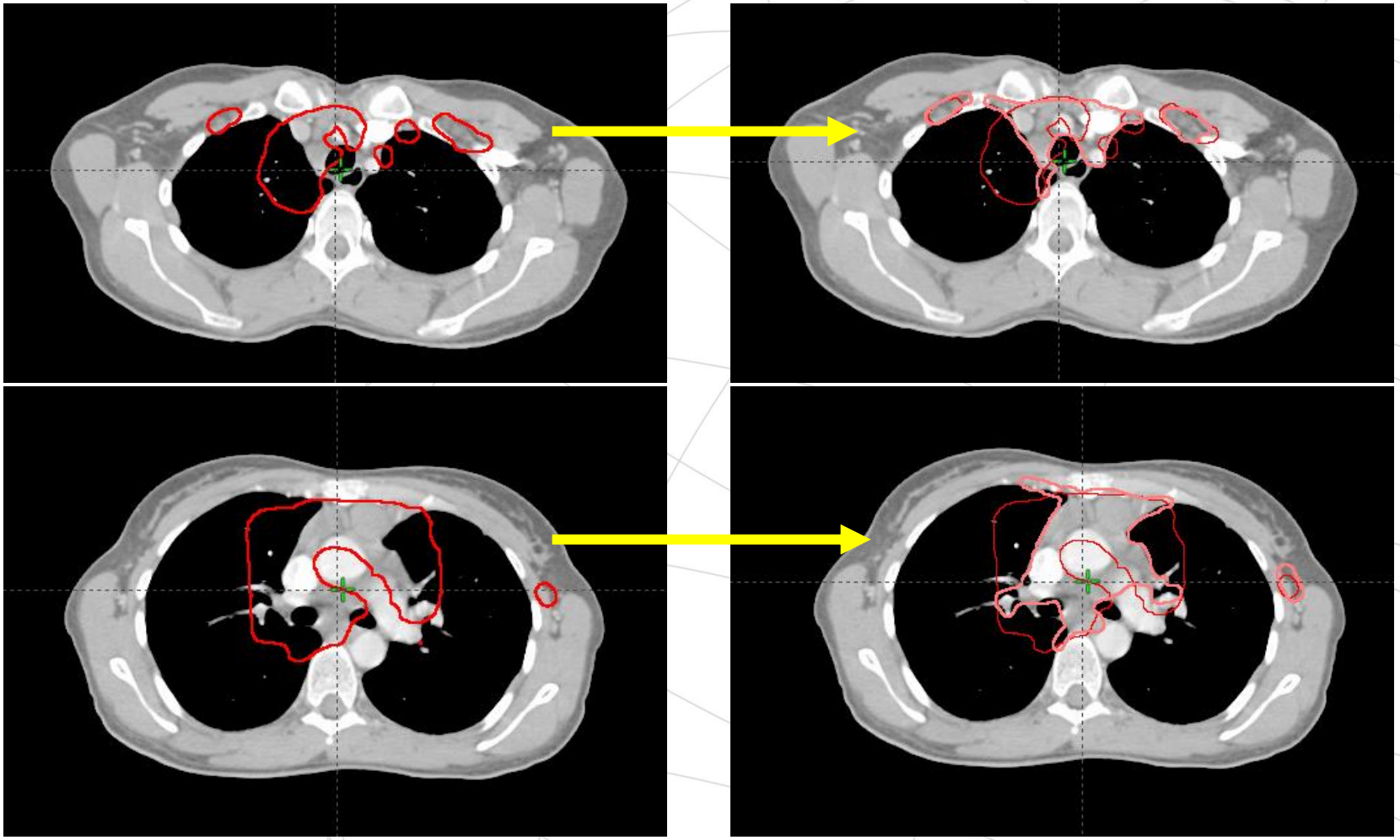
Gross tumour volume GTV



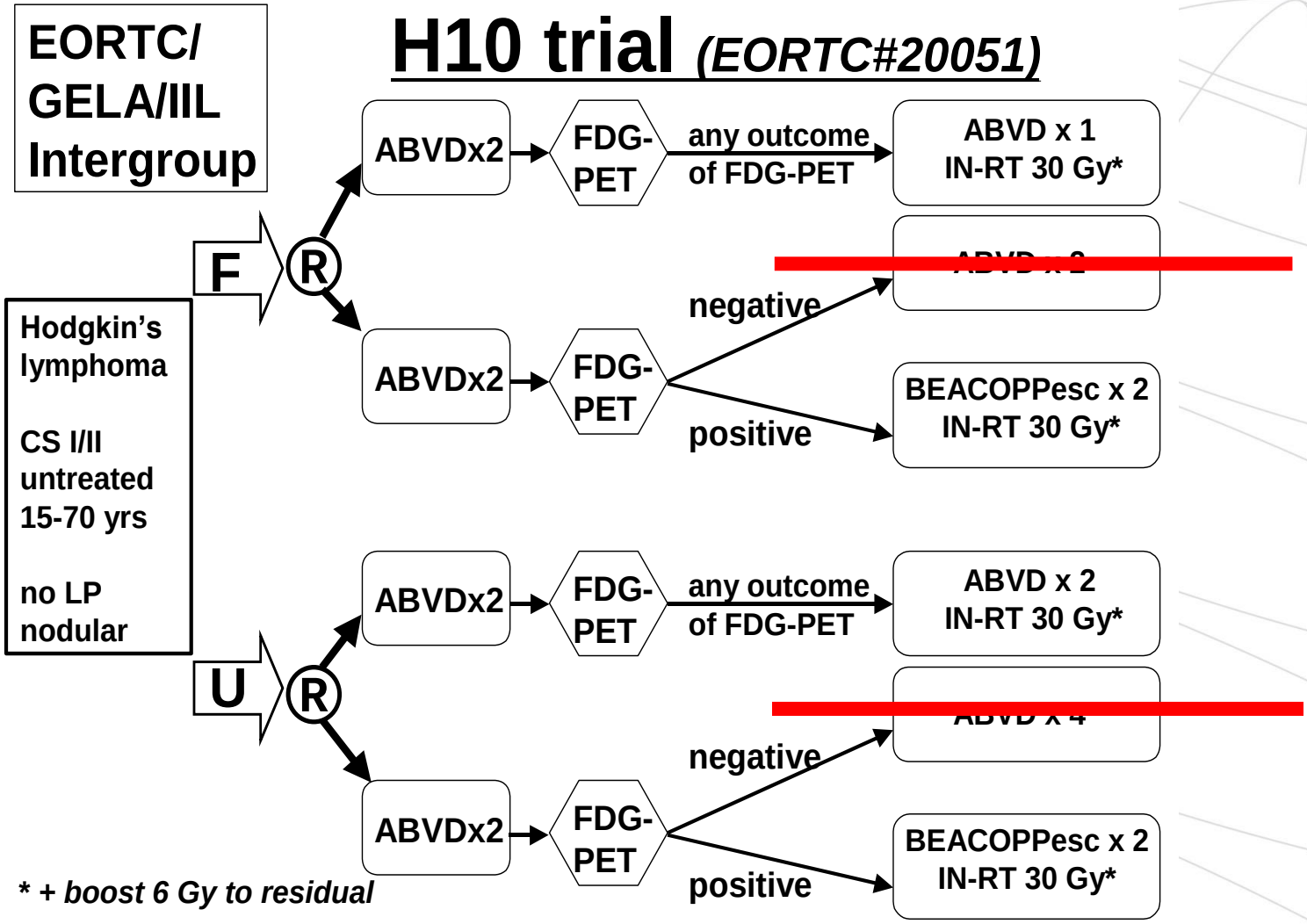
Post-chemo planning CT scan

Pre-chemo gross tumour volume

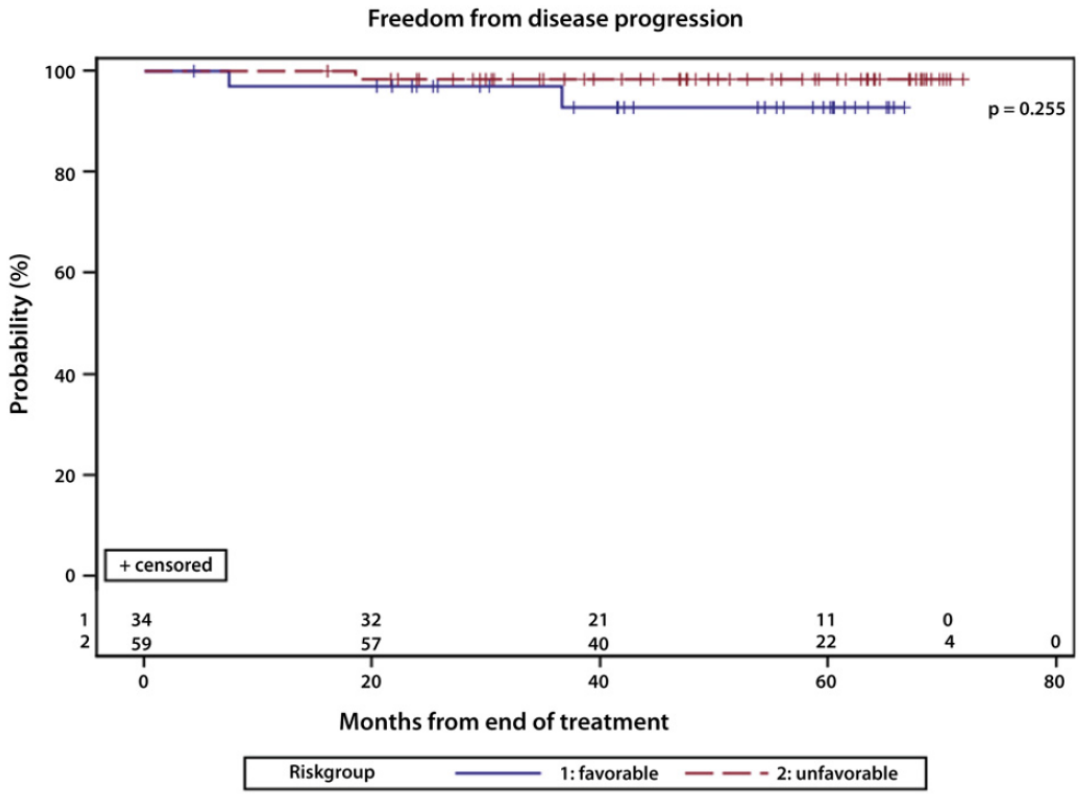
Post-chemo clinical target volume



Is highly conformal treatment safe?



Is highly conformal treatment safe?



97 patients CS I-II, treated with INRT 2005-2010 at Rigshospitalet, Copenhagen, Denmark

Median follow-up 50 months

4-year freedom from disease progression 96 % (95 % CI 92-100)

3 recurrences: 2 in field, 1 out of field in previously uninvolved region (contralateral neck)

Maraldo MV et al
Int J Radiation Oncol Biol Phys, Vol. 85, No. 4, pp. 1057–1065, 2013

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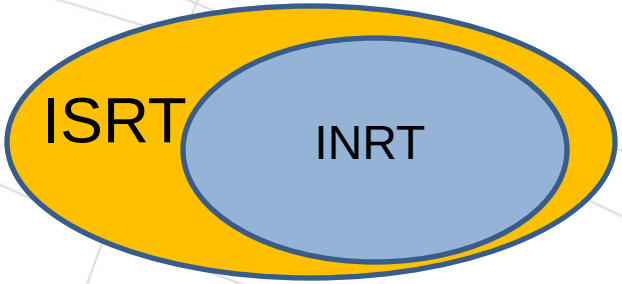
ILROG

INTERNATIONAL LYMPHOMA
RADIATION ONCOLOGY GROUP

www.ilrog.com

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



ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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

Other "INRT/ISRT" guidelines

Involved-Node Radiotherapy in Early-Stage Hodgkin's Lymphoma

Definition and Guidelines of the German Hodgkin Study Group (GHSG)

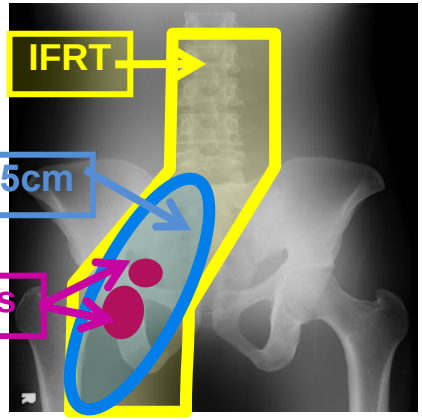
Hans Theodor Eich[1], Rolf-Peter Müller[1] in Cooperation with
Rita Engenhart-Cabillic[2], Peter Lukas[3], Heinz Schmidberger[4], Susanne Staar[5], Normann Willich[6]

Strahlenther Onkol 2008;184:406–10

Involved-Nodal Radiation Therapy As a Component of Combination Therapy for Limited-Stage Hodgkin's Lymphoma: A Question of Field Size

Belinda A. Campbell, Nick Voss, Tom Pickles, James Morris, Randy D. Gascoyne, Kerry J. Savage, and Joseph M. Connors

J Clin Oncol 26:5170-5174. © 2008



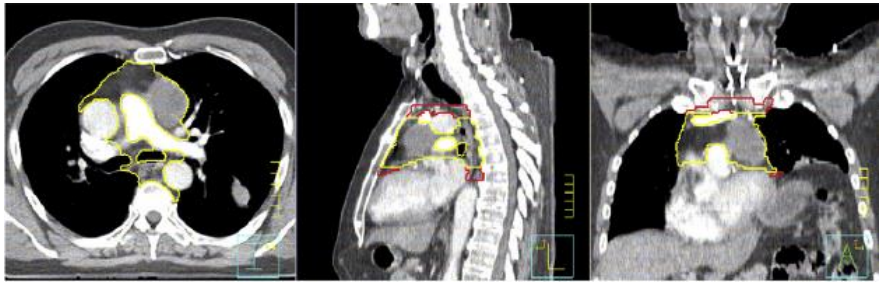
Guidelines

Recommendations for the Use of Radiotherapy in Nodal Lymphoma

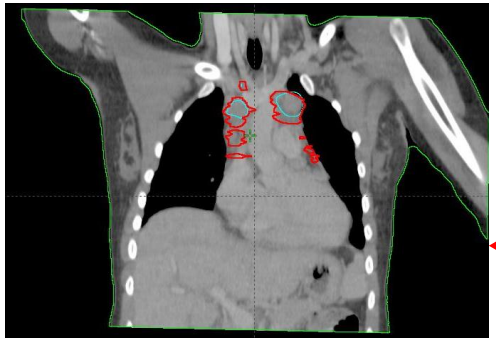
P.J. Hoskin *, P. Díez *, M. Williams †, H. Lucraft ‡, M. Bayne § on Behalf of the Participants of the Lymphoma Radiotherapy Group[a]

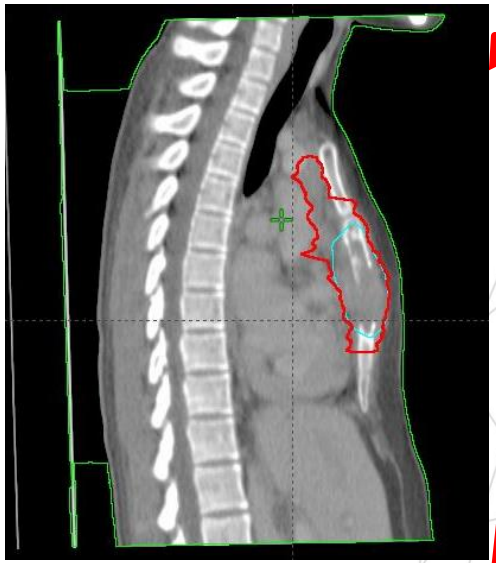
Clinical Oncology 25 (2013) 49–58

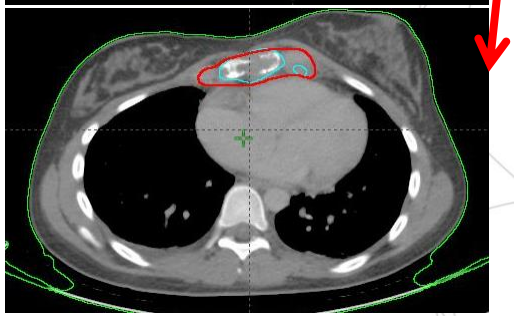
Areas + 1.5 cm margin



Planning without optimal imaging



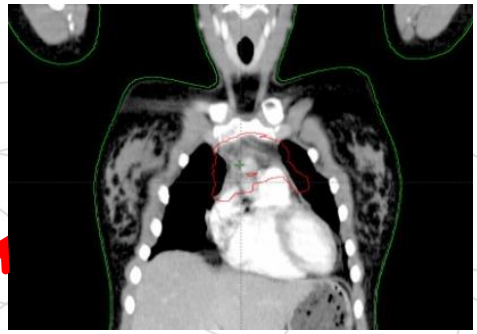


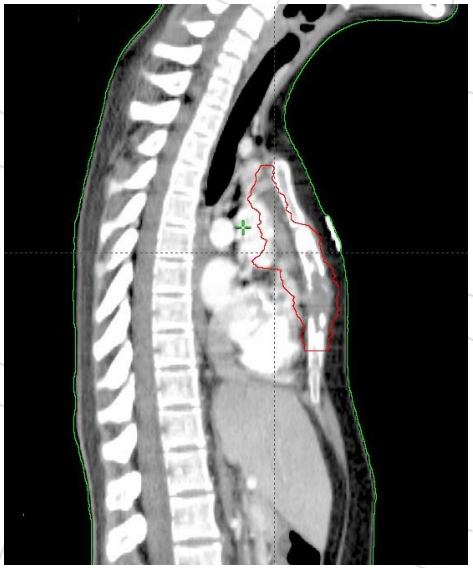


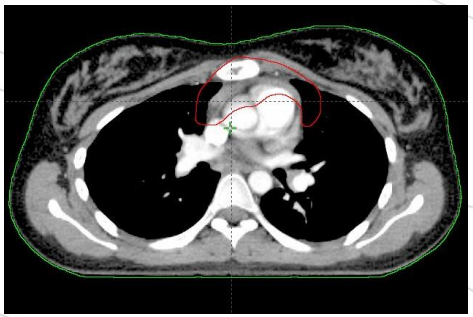
Pre-chemo PET/CT scan with pt. in unsuitable position and on ordinary table top

Post-chemo planning CT scan in treatment position on flat table top

Image fusion is difficult, modifications and margins for uncertainty need to be added

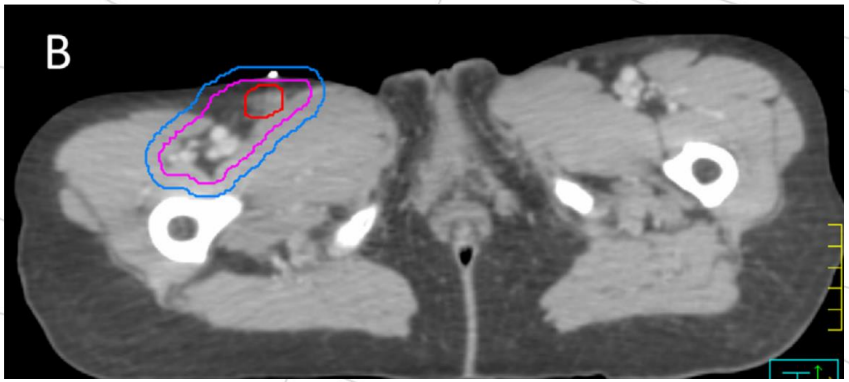






Nodular lymphocyte predominant HL

- For early stage disease RT is the only treatment
- In this situation suspected subclinical disease should be included
- CTV should include the GTV and as a minimum adjacent lymph nodes in that site with a generous margin dictated by the clinical situation
- No advantage has been demonstrated with extended field radiotherapy
- No advantage hase been shown for doses over 30 – 35 Gy



Radiation dose for combined modality treatment

- Hodgkin lymphoma, early stage favourable: 20 Gy

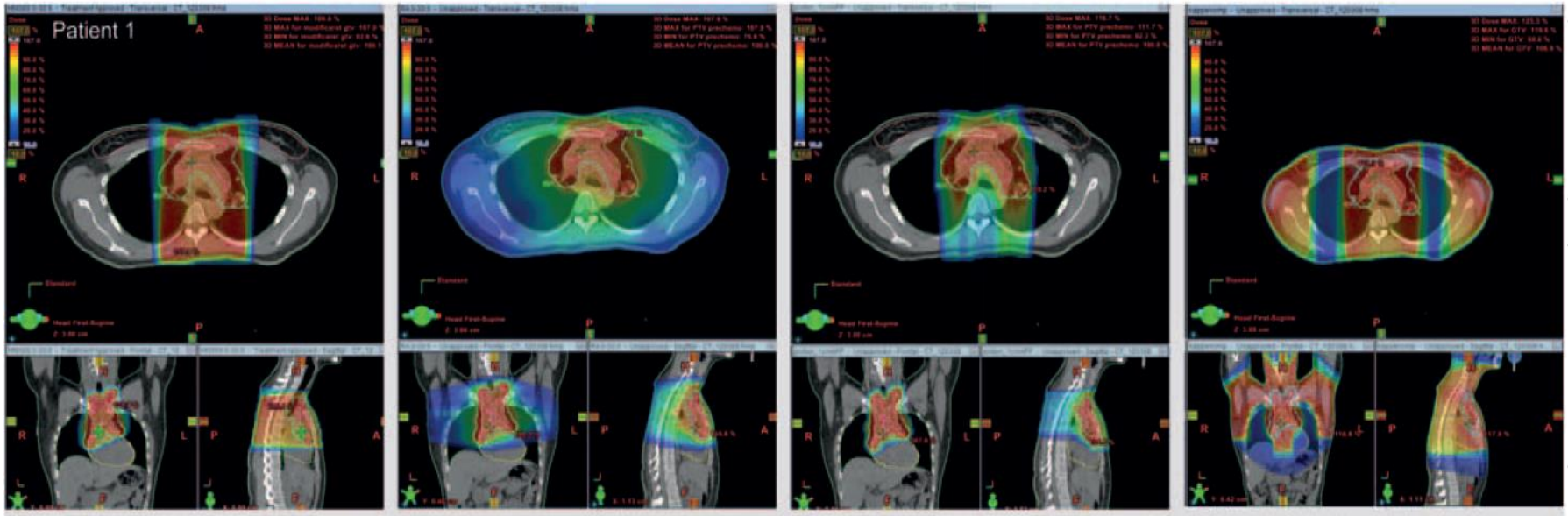
  GHSG HD10, Engert A et al, N Engl J Med 2010; 363: 640-52

- Hodgkin lymphoma, early stage unfavourable: 30 Gy

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

Different modern techniques vs. extended fields of the past

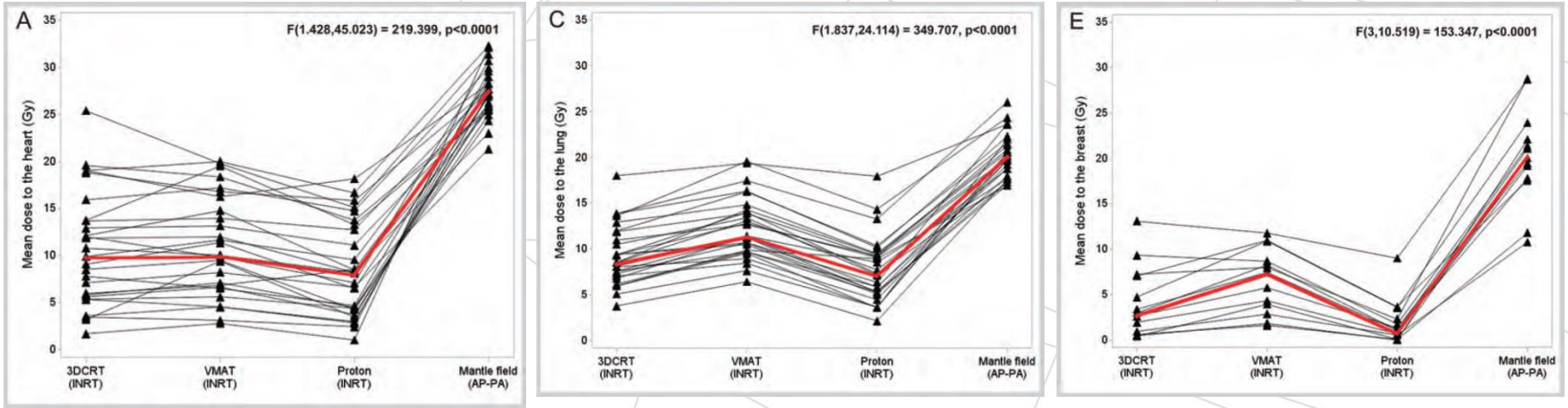
AP-PA IMRT IMPT Mantle field



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

Breathing adapted RT

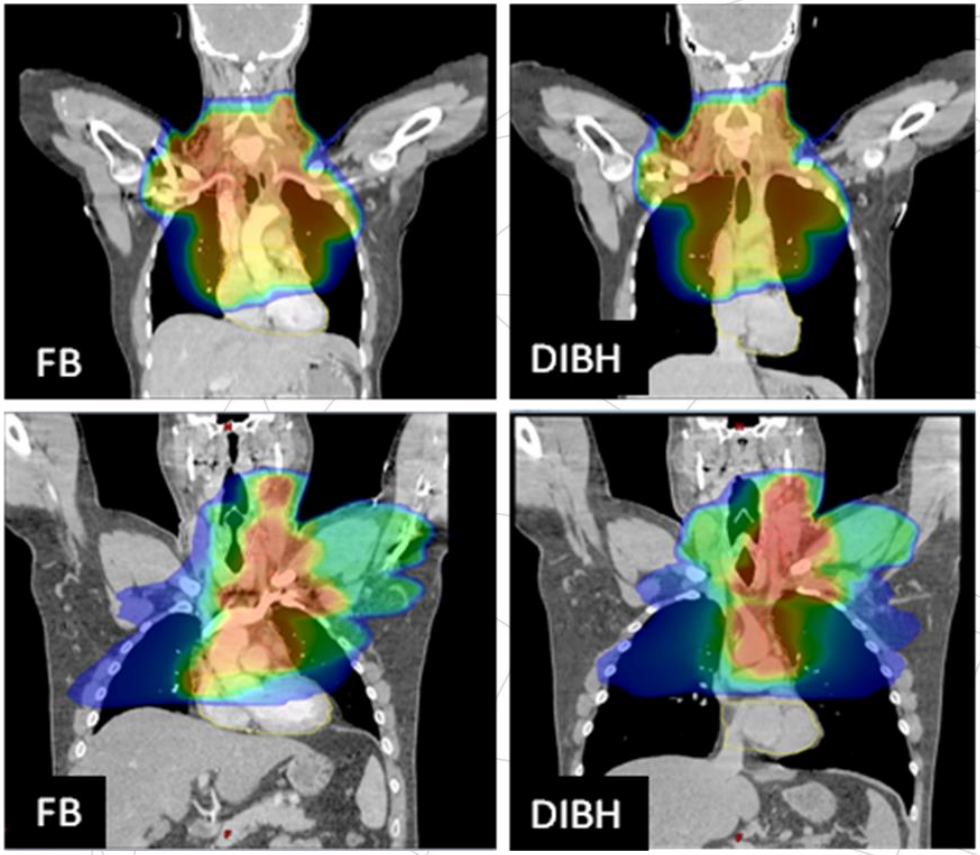


Figure 1. Volume receiving 20 Gy or more with free breathing (FB) and deep inspiration breath-hold (DIBH) in a patient treated with conventional parallel opposing fields (upper panel) and a patient treated with intensity-modulated radiotherapy (lower panel).

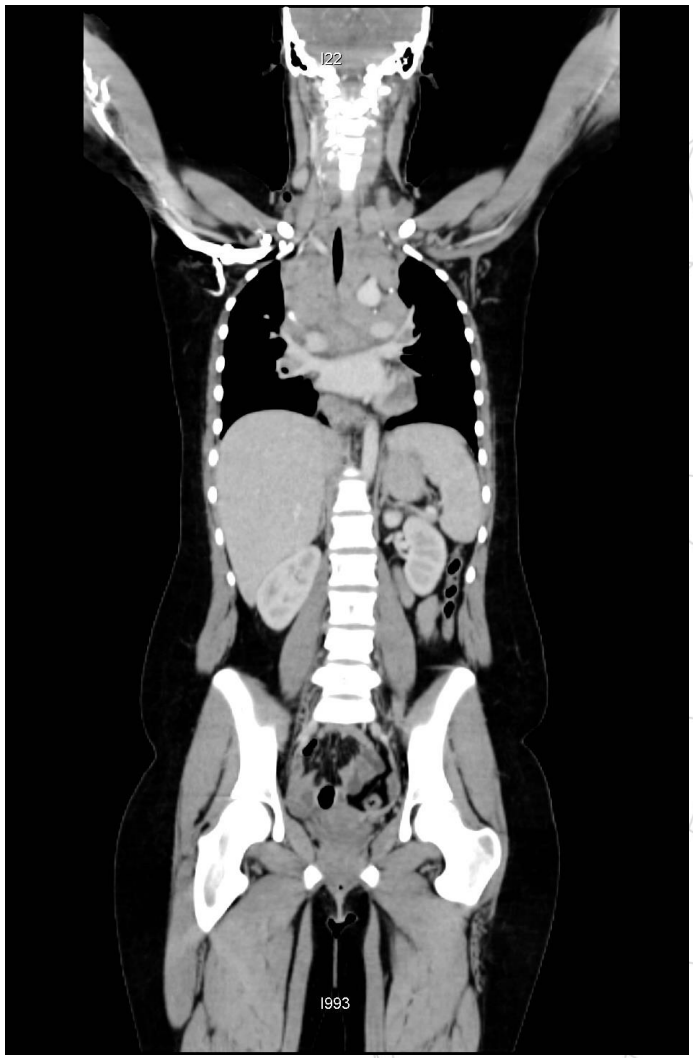
Petersen PM et al. Acta Oncol 2015; 54: 60-6

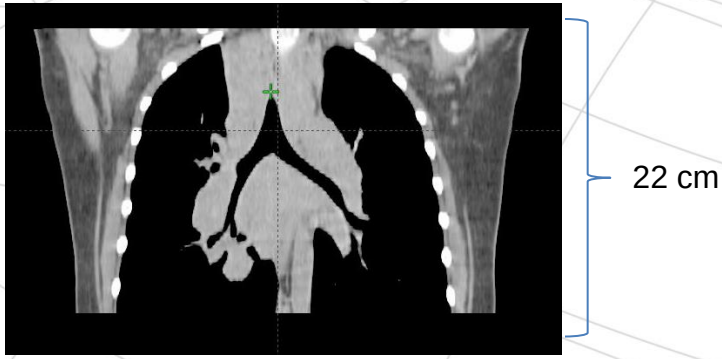
Table II. Dose characteristics with free breathing (FB) and deep inspiration breath-hold (DIBH).

	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

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

Breathing adaptation, technique



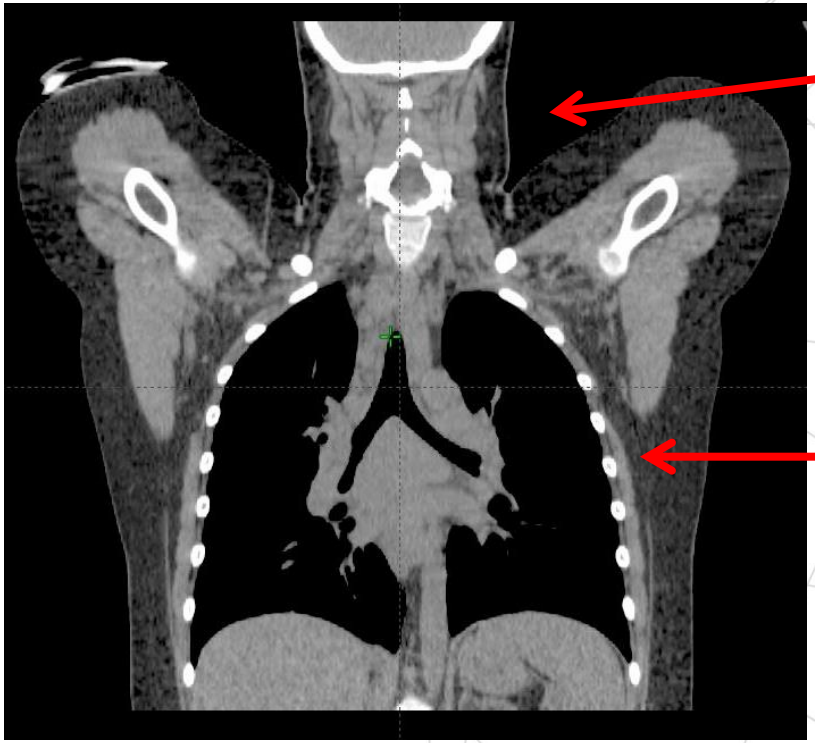


Pre-chemo whole-body PET/CT scan in free breathing in treatment position on flat table top

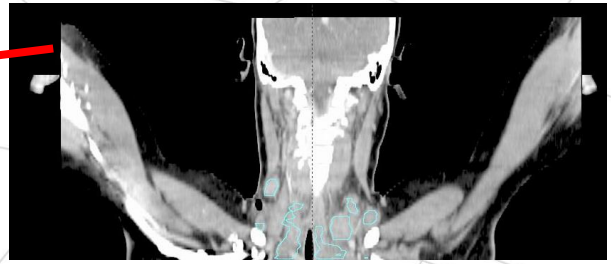
+ deep inspiration PET/CT of the chest

Breathing adaptation, technique

Post-chemo planning CT in DIBH

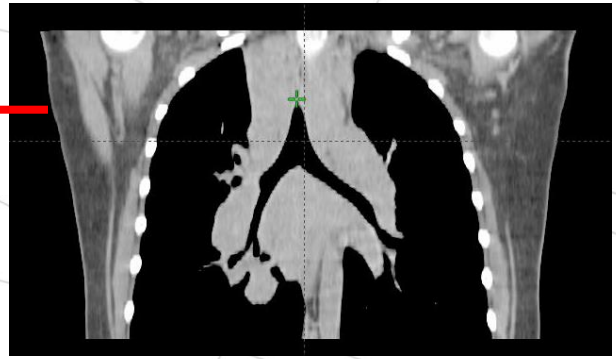


Pre-chemo PET/CT scan



FB

DIBH



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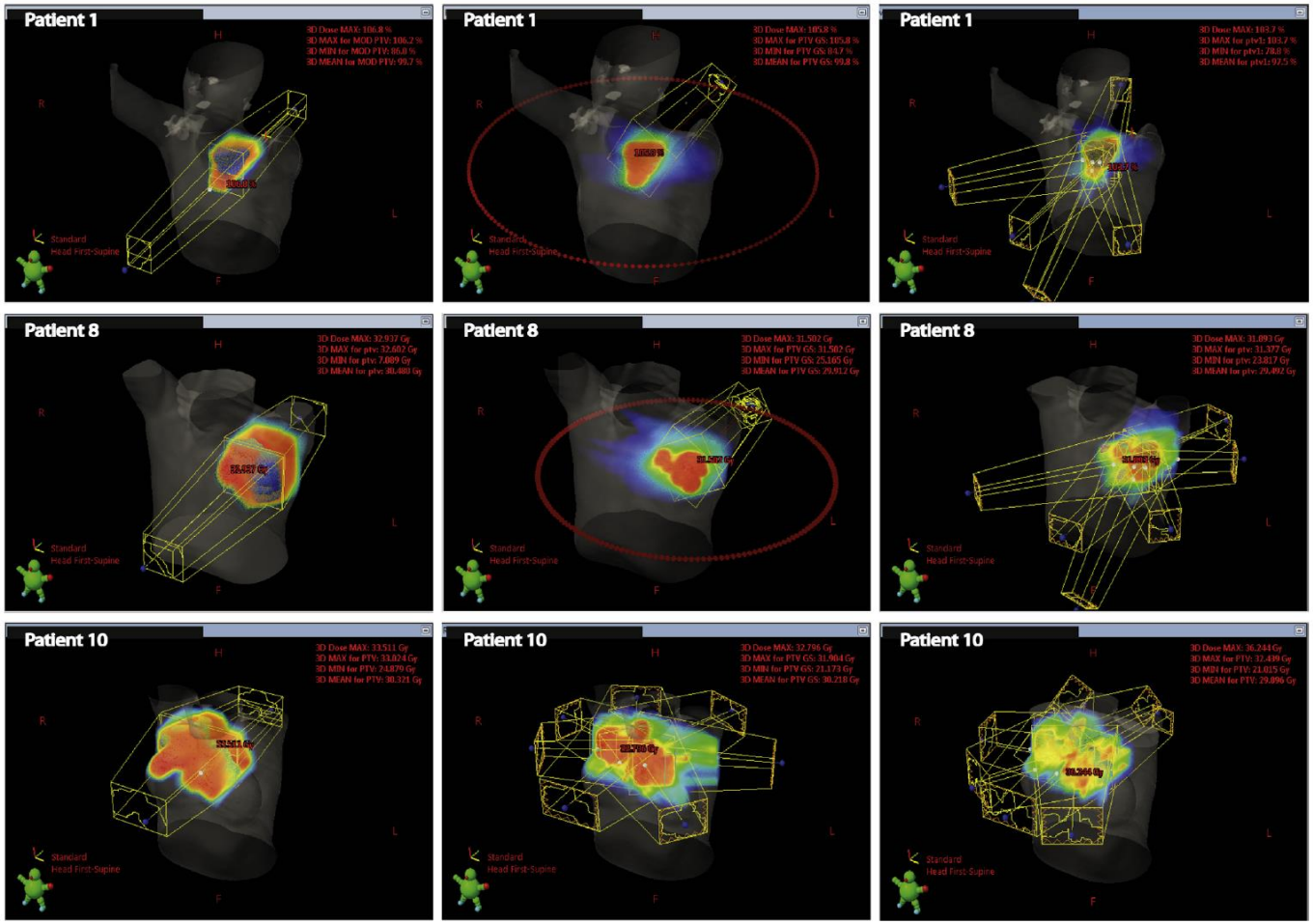
Same patient, different solutions



Maraldo M et al. IJROBP 2015; 92: 144-52

Which technique is preferable?

- Depends on the location of the target
- Dose plans for different alternatives should be compared
- Considerations of normal tissue toxicity varies between patients depending on:
  - Age
  - Gender
  - Comorbidities
  - Risk factors for other diseases
- Even low 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, but some structures are more critical than others

”There is NO advantage to ANY patient for ANY uninvolved tissue to receive ANY dose”

”Primary radiation injury NEVER develops in unirradiated tissues”

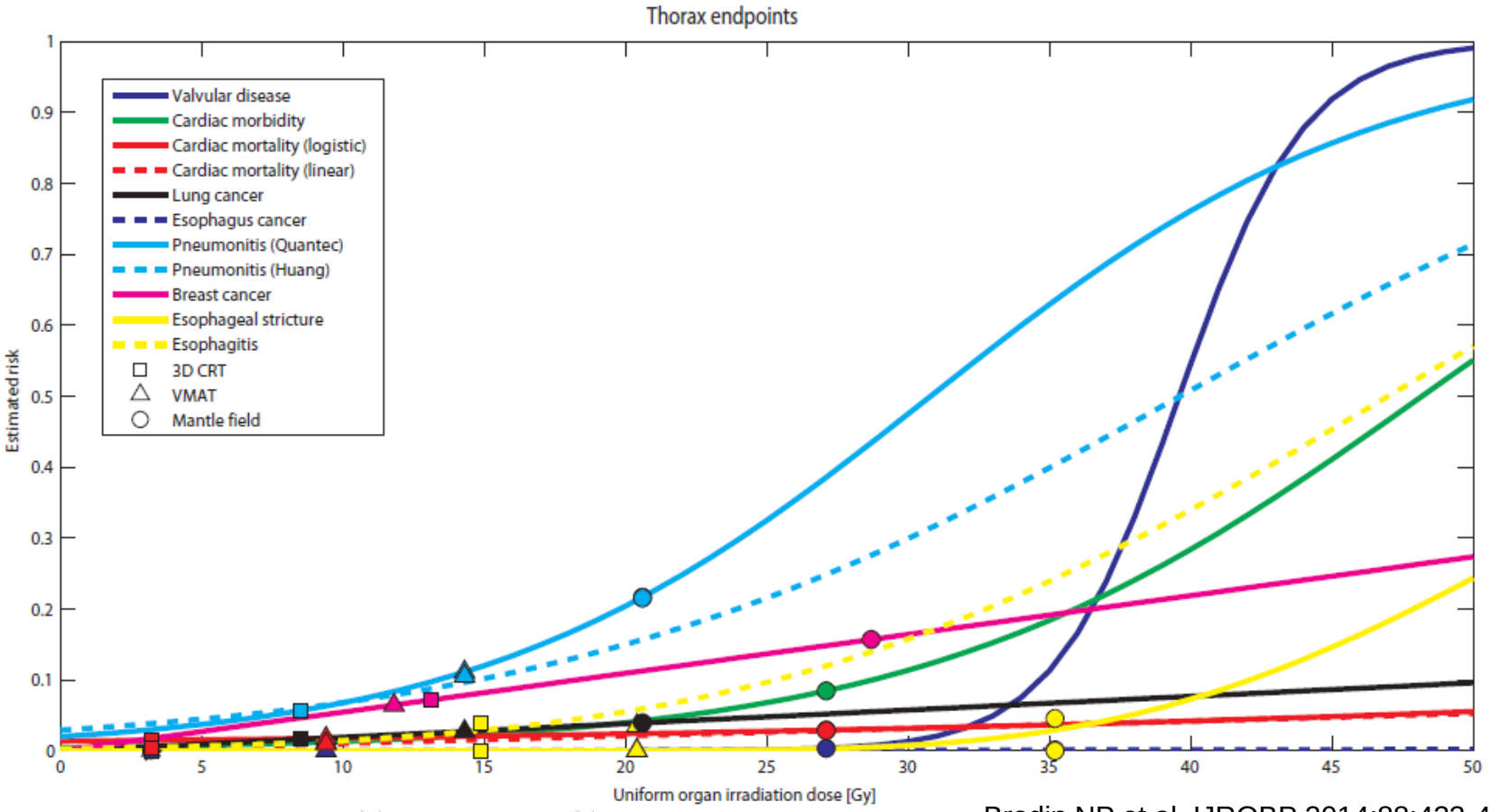
Dr. H. Suit

Constraints, are they useful for lymphomas?

Organ at risk	Limiting dose/volume
Brain stem	If whole organ irradiated, $D_{max} < 54$ Gy to any part of the volume If partial volume irradiated, $D_{1-10\ cm^3} \leq 59$ Gy
Breast	Minimise volume inside PTV, particularly in young women ≤30 years. Mean dose ≤ 2 Gy
Cochlea	Mean dose ≤ 45 Gy
Coronary artery	Minimise volume inside treatment field and keep doses as low as possible without compromising on PTV coverage
Heart	Mean dose < 26 Gy; $D_{100} < 30$ Gy $V_{30} < 46\%$; $V_{33} < 60\%$, $V_{38} < 33\%$, $V_{42} < 20\%$
Kidney	Single kidney irradiated: V_{15} of 65–70%, Both kidneys irradiated: V_{15} of 20–25% for each kidney; mean dose < 18 Gy. Partial kidney irradiation (all constraints are for combined kidneys): mean dose < 18 Gy $V_{28} < 20\%$, $V_{23} < 30\%$, $V_{20} < 32\%$, $V_{12} < 55\%$. If mean dose to one kidney >18 Gy, V_6 for remaining kidney <30%
Lens	Maximum dose of 6 Gy to any part of the volume unless compromising PTV coverage
Liver	Mean dose < 32 Gy; V_{40} of 30–35%; D_{100} of 25 Gy, D_{66} of 28 Gy, D_{33} of 38 Gy
Lung (whole)	$V_{20} \leq 30\%$, Mean lung dose (MLD) ≤ 20 Gy
Oesophagus	Mean dose < 34 Gy, $V_{35} < 50\%$
Optic chiasm	$D_{max} < 55$ Gy to any part of the volume
Optic nerve	$D_{max} < 55$ Gy to any part of the volume
Ovary	D_{max} <10 Gy to any part of the volume outside PTV. If inside PTV discuss individual case with clinician
Parotid	Bilateral irradiation: mean dose < 25 Gy. Unilateral irradiation: mean dose < 20 Gy to the contralateral parotid
Small bowel	For individual loops $V_{15} < 120\ cm^3$ For whole peritoneal cavity $V_{45} < 195\ cm^3$
Spinal cord	$D_{max} \leq 50$ Gy to any part of the volume
Stomach	$D_{100} < 45$ Gy
Testis	Maximum dose of 2 Gy to any part of the volume
Thyroid	$D_{100} < 45$ Gy

Hoskin PJ et al, Clin Oncol 2013; 25: 49-58

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



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

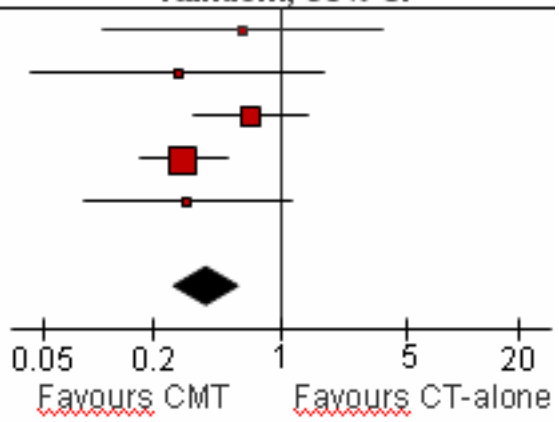
RT risks vs. benefits

- 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

Meta-analysis of overall survival (OS) in patients with early stage Hodgkin lymphoma who were treated with chemotherapy alone (CT) or chemotherapy and radiotherapy (CMT)

Study	Weight	Hazard Ratio Random, 95% CI
CALGB 7751	5.1%	0.63 [0.11, 3.65]
EORTC-GELA H9-F	4.6%	0.27 [0.04, 1.74]
GATLA 9-H-77	30.7%	0.68 [0.33, 1.40]
Mexico B2H031	50.4%	0.29 [0.17, 0.51]
MSKCC trial #90-44	9.2%	0.31 [0.08, 1.14]
Total (95% CI)	**100.0%**	**0.40 [0.27, 0.59]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.89$, $df = 4$ ($P = 0.42$); $I^2 = 0\%$
Test for overall effect: $Z = 4.57$ ($P < 0.00001$)



Herbst C et al. Cochrane Database of Systematic Reviews 2011, Issue 2. Art. No.: CD007110

Early HL selected with PET

Raemaekers JMM et al, JCO 2014; 32: 1188-94

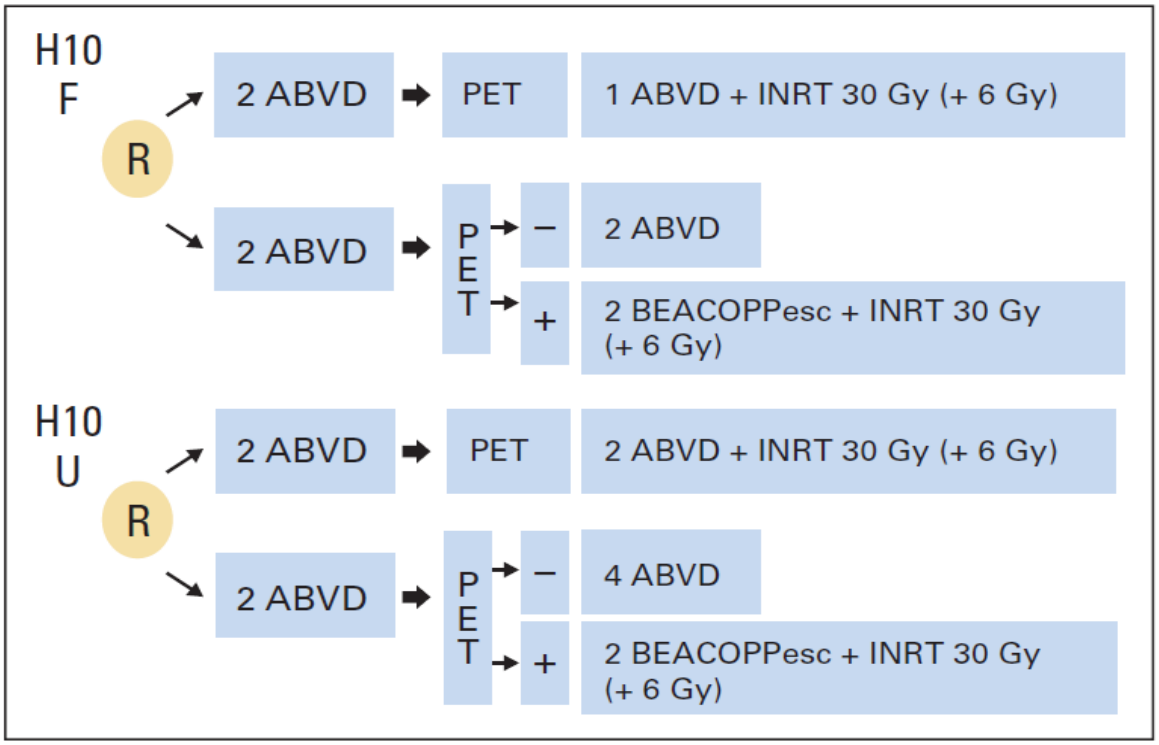


Table 2. Results of Interim Analysis in Patients With Early PET-Negative Disease

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

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

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Extranodal guidelines

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

Int J Radiation Oncol Biol Phys, Vol. 92, No. 1, pp. 11–31, 2015

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

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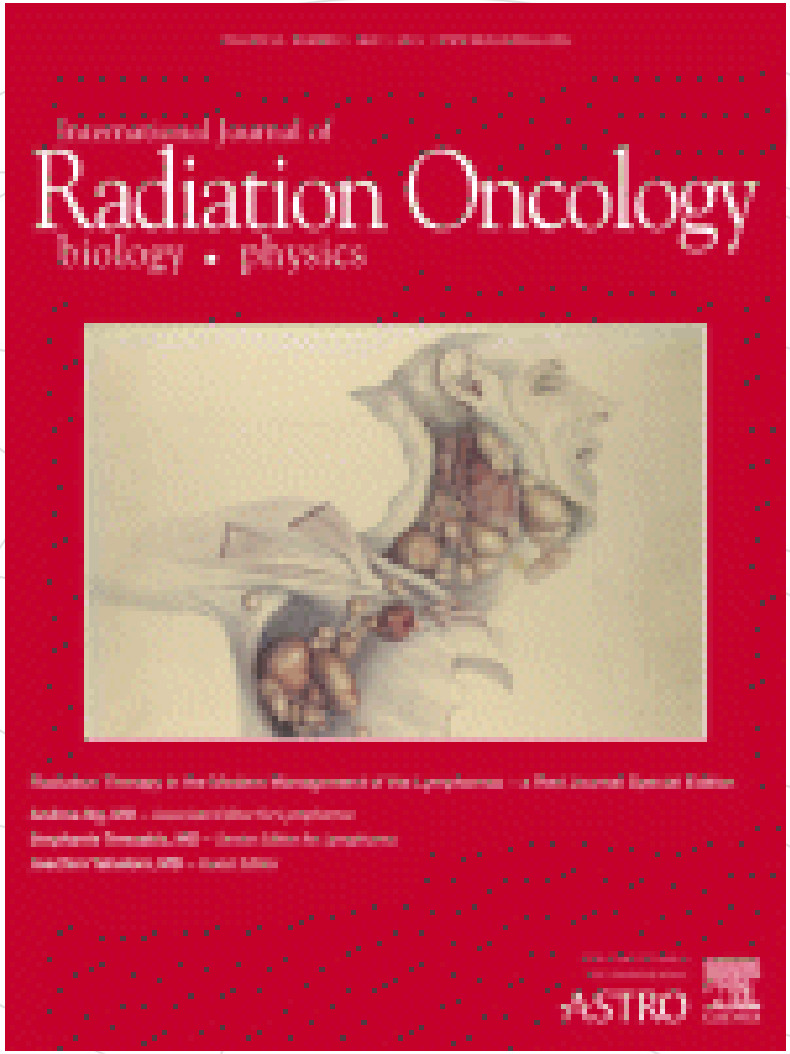
International Journal of Radiation Oncology*Biology*Physics Volume 92, Issue 1, Pages A1-A16, 1-192 (1 May 2015)

Radiation and the Modern Management of Lymphoma

A special edition edited by: Stephanie Terezakis, Andrea Ng & Joachim Yachalom



Special sessions devoted to RADIOTHERAPY, organized in collaboration with ILROG (International Lymphoma Radiation Oncology Group)

- Workshop on **Controversies in the use of Radiation Therapy for Advanced Stage Lymphoma**
Tuesday, June 16, 15:00-18:00, open to all 13-ICML attendees

- Workshop on **Competencies and Technical Challenges for Radiation Oncologists with Special Expertise in Lymphoma**
Thursday, June 18, 13:00-17:00, mainly for radiation oncologists

- **Clinical Case Discussion on Lymphoma Radiotherapy**
Friday, June 19, 9:00-10:30, open to all 13-ICML attendees

- Special session on **Contouring in Modern Lymphoma Radiotherapy Planning**
Saturday June 20, 08:00 – 10:30, for max. 30 lymphoma radiation oncologists
(pre-registration at registration@lymphcon.ch).

Lugano, Switzerland – June 16-20, 2015 – www.lymphcon.ch


13-ICML
13th International Conference on Malignant Lymphoma
Palazzo dei Congressi
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SAVE THE DATE: June 17-20, 2015