ESTRO School

ESTRO Course Book

Hematological Malignancies

3 – 5 September 2015
London, United Kingdom

NOTE TO THE PARTICIPANTS

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Faculty

Lena Specht and Joachim Yahalom

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The faculty of the teachers for this event has disclosed any potential conflict of interest that the teachers may have.

Programme

Thursday, 3 September		
Time	**Lecture Topic**	**Lecturer**
08.20-08.30	Welcome and Practical Information	Specht
08.30-09.00	The role of the radiation oncologist in the multimodality treatment of lymphomas	Specht
	General principles of treatment	
09.00-09.45	Radiotherapy	Specht
09.45-10.30	Chemotherapy	Engert
10:30-10:45	*Coffee or Tea*	
10:45-11:10	Immunotherapy	Engert
11:10-11:35	Radioimmunotherapy and new immunological approaches	Illidge
11:35-12:20	Combined modality treatments	Engert
12:20-13:05	*Lunch*	
13:05-13:50	Long term toxicity	Aleman
13:50-14:05	Hodgkin lymphoma: Lymphocytic predominance, the role of radiotherapy	Mikhaeel
	Classic Hodgkin lymphoma, the role of radiotherapy	
14:05-14:35	Early stage	Illidge
14:35-14:55	Advanced stage	Engert
14:55-15:05	Advanced stage, comments on radiation therapy	Yahalom
15:05-15:20	*Coffee or Tea*	
15:20-15:40	Relapsed/refractory disease	Yahalom
15:40-15:50	Relapsed/refractory disease, comments on chemotherapy	Engert
15:50-16:20	Radiotherapy volumes, doses and techniques	Ricardi
16:20-17:20	Hodgkin case discussion	**Ricardi** Yahalom/ Aleman/ Engert

Friday, 4 September		
Time	**Lecture Topic**	**Lecturer**
	Indolent nodal non Hodgkin lymphoma, the role of radiotherapy	
08.00-08.20	Early stage	Illidge
08.20-08.40	New agents for advanced stage	Illidge
08.40-08.50	Advanced stage, comments on radiation therapy	Mikhaeel
08.50-09.10	Role of radiation therapy in relapsed/refractory disease	Yahalom
09.10-09.30	Volumes, doses and techniques	Ricardi
09.30-10.30	Indolent nodal non Hodgkin case discussion	**Mikhaeel** Illidge/ Specht
10.30-10.50	*Coffee or Tea*	
10.50-11.20	Motion management and deep inspiration breath hold DIBH technique	Aznar
11:20-11:50	Contouring - Guideline Presentation	Specht
11:50-12:40	Contouring Group 1 - *Lunch Group 2*	De Bari/ Specht/ Berthelsen/ Aleman
12:40-13:20	Contouring Group 2 - *Lunch Group 1*	De Bari/ Specht/ Berthelsen/ Aleman
13:20-14:20	Presentation and Discussion of Participant Contours	Specht/ Berthelsen/ Aleman
	Aggressive nodal non Hodgkin lymphoma, the role of radiotherapy	
14:20-14:50	Early stage	Ricardi
14:50-15:20	Advanced stage	Aleman
15:20-15:40	*Coffee or Tea*	
15:40-16:10	Relapsed/refractory disease	Mikhaeel
16:10-16:30	Volumes, doses and techniques	Aleman
16:30-17:30	Aggressive nodal non Hodgkin case discussion	**Illidge** Mikhaeel/ Ricardi/ Davies
	Other indications: Role of radiotherapy, special techniques	
17:30-17:50	Myeloma - Solitary & Disseminated	Ricardi
17:50-18:00	Granulocytic sarcoma (Chloroma)	Yahalom
18:00-18:10	Total body irradiation as part of the conditioning regimen for transplant	Yahalom
18:10-18:15	Splenomegaly, hypersplenism	Specht

Saturday, 5 September		
Time	**Lecture Topic**	**Lecturer**
08.00-09.00	Pathology: WHO Classification (morphology, immunophenotype, genetics)	Wilkins
09.00-09.45	Imaging for radiotherapy of lymphomas	Mikhaeel/ Berthelsen
	Extranodal lymphomas: Characteristics, the role of radiotherapy, volumes doses and techniques	
09.45-10.15	Head and neck	Specht
10.15-10.35	Thyroid	Mikhaeel
10.35-10.55	*Coffee or Tea*	
10.55-11.25	Orbital (ocular adnexae)	Ricardi
11.25-11.55	Gastric	Yahalom
11.55-12.25	Skin	Specht
12:50-13:50	*Lunch*	
13:50-14:05	Testicular	Aleman
14:05-14:20	Breast	Aleman
14:20-14:35	Lung	Ricardi
14:35-14:55	Systemic approaches to early and advanced marginal zone lymphoma	Davies
14:55-15:10	Bone	Ricardi
15:10-15:40	CNS	Yahalom
15:40-16:00	Other, rarer sites	Mikhaeel
16:00-16:20	*Coffee or Tea*	
16:20-17:20	Extranodal lymphoma case discussion	Yahalom Specht/ Aleman/ Davies
17:20-17:40	Evaluation and farewell	All

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The role of the radiation oncologist in the multimodality treatment of lymphomas

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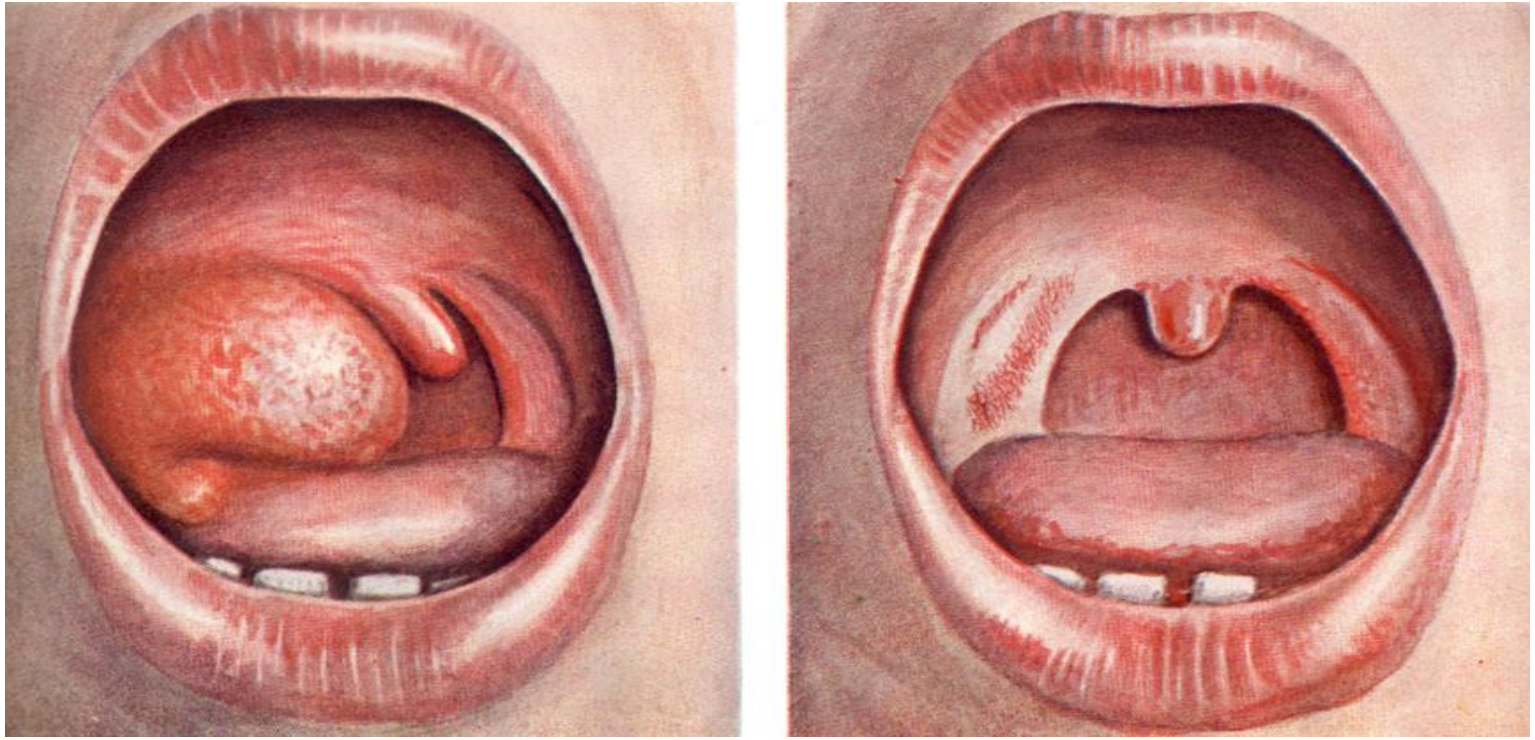
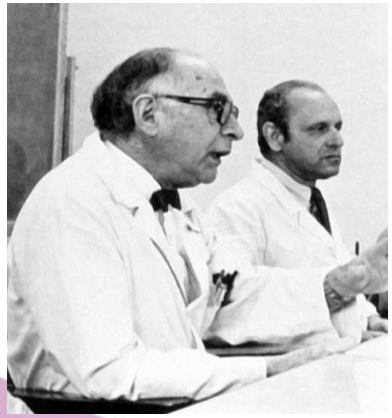
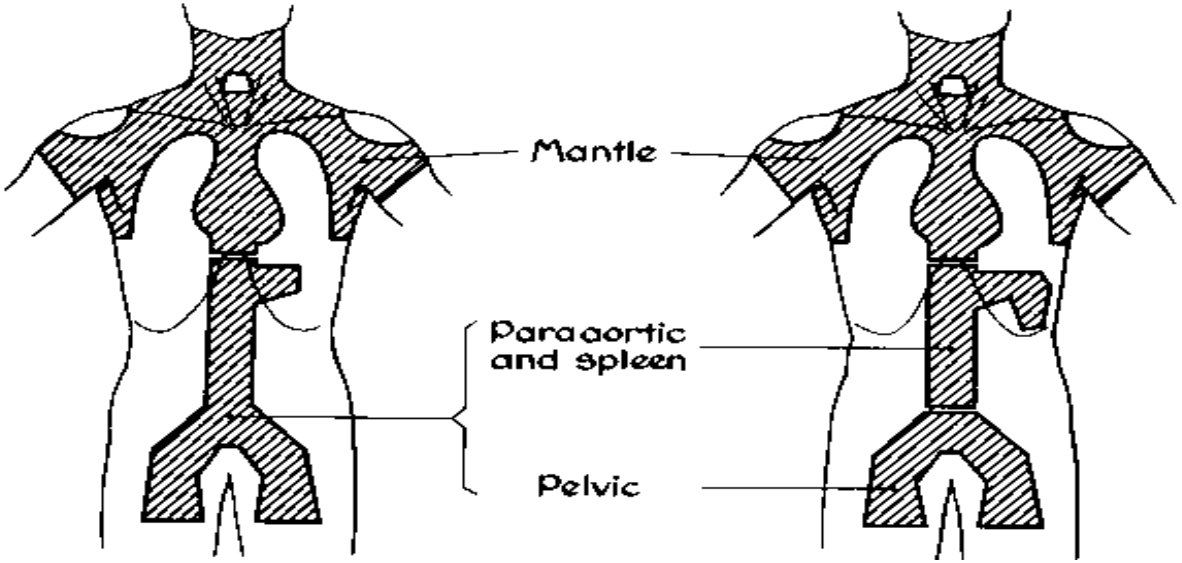


Lymphosarcoma of right tonsil, before treatment November 1916, alive and free of symptoms April 1930

Prophylactic irradiation of clinically uninvolved regions → extended field RT





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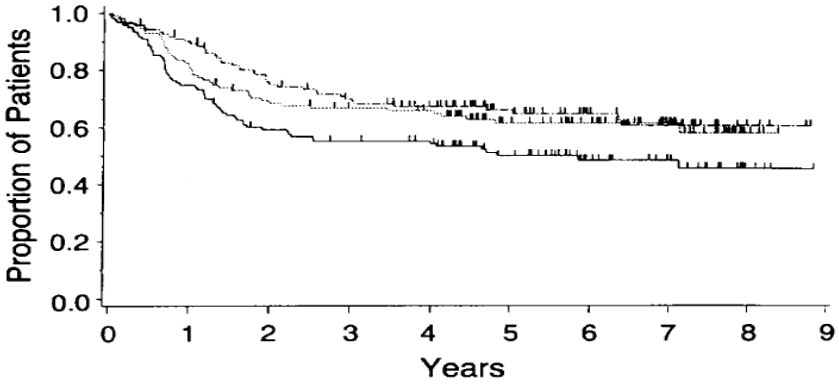
Effective chemotherapy was developed

Hodgkin lymphoma
Canellos et al. NEJM 1992; 327: 1478-84



Regimen	No. of Patients	No. (%) of Treatment Failures	Median Survival
MOPP	123	62 (50)	4.84
ABVD	115	44 (38)	None
MOPP–ABVD	123	43 (35)	None
All	361	149 (41)	—

Figure 1. Failure-free Survival According to Primary Chemotherapeutic Regimen.

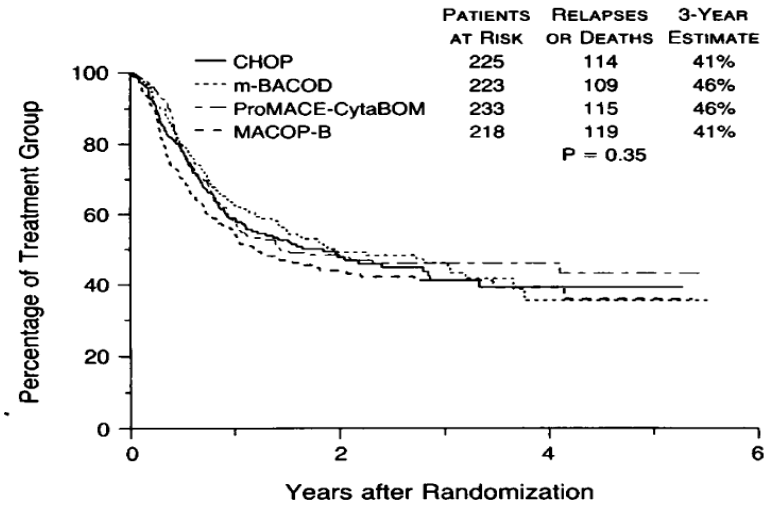


Figure 1. Time to Treatment Failure in the Treatment Groups. The three-year estimate is of survival without disease.

Aggressive non-Hodgkin lymphoma
Fisher et al. NEJM 1993; 328: 1002-6

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

James O. Armitage

- Its role has changed
- Now part of combined modality treatment in most situations
- Often as consolidary treatment after primary chemotherapy

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Challenges in lymphoma treatment

- > 70 different diseases, classified on the basis of morphology, immunophenotype, genetic and clinical features:

  Expert pathology is needed

- The diseases may be localized or disseminated, nodal or extranodal, anywhere in the body:

  Expert imaging is needed

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Challenges in lymphoma treatment

- Modern treatment includes:
  - Radiotherapy
  - "Classical" chemotherapy
  - Antibodies
  - Small molecules

Expert radiation and medical oncology are needed

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Role of radiotherapy

Primary treatment for early stage indolent lymphomas

Consolidation therapy for early stage aggressive lymphomas (inc. HL)

Treatment of bulky or residual mass in advanced aggressive lymphoma

Treatment of recurrent disease +/- systemic treatment

Part of conditioning for autologous transplant for recurrent/refractory disease

Palliative treatment in advanced indolent lymphoma

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Role of radiation (and medical) oncology

- Close collaboration from the outset between systemic treatment (medical oncologist/ hematologist/clinical oncologist) and local treatment (radiation oncologist/clinical oncologist)
- The entire treatment strategy must be planned from the outset to allow optimal treatment
- Treatment modifications during treatment must be decided with due regard to both local and systemic treatment options
- Treatment interactions must be considered

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Multidisciplinary set-up

Haemato-pathology

Radiology,

Nuclear Medicine

Medical Oncology, Haematology, Clinical Oncology

Radiation Oncology,

Clinical Oncology

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Responsibilities of the radiation oncologist

- Ensure that all information necessary for optimal target definition is available for radiotherapy planning
- Relevant imaging of all lymphoma involvement before chemotherapy (and operation)
- Optimally see the patient before any treatment

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

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Ensure that the unique biology of lymphoid malignancies is exploited in RT planning and delivery

In general no survival advantage has been demonstrated with the extended fields of the past

The unique radiosensitivity of lymphoid malignancies means that dose constraints for normal tissues used for solid tumours are not applicable

Modern conformal techniques should be used for lymphomas, not primarily as in solid tumours to allow a high target dose to be delivered, but to minimize the risk of long-term complications

Different techniques are applicable to different disease localizations and disease volumes, no two patients are the same

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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

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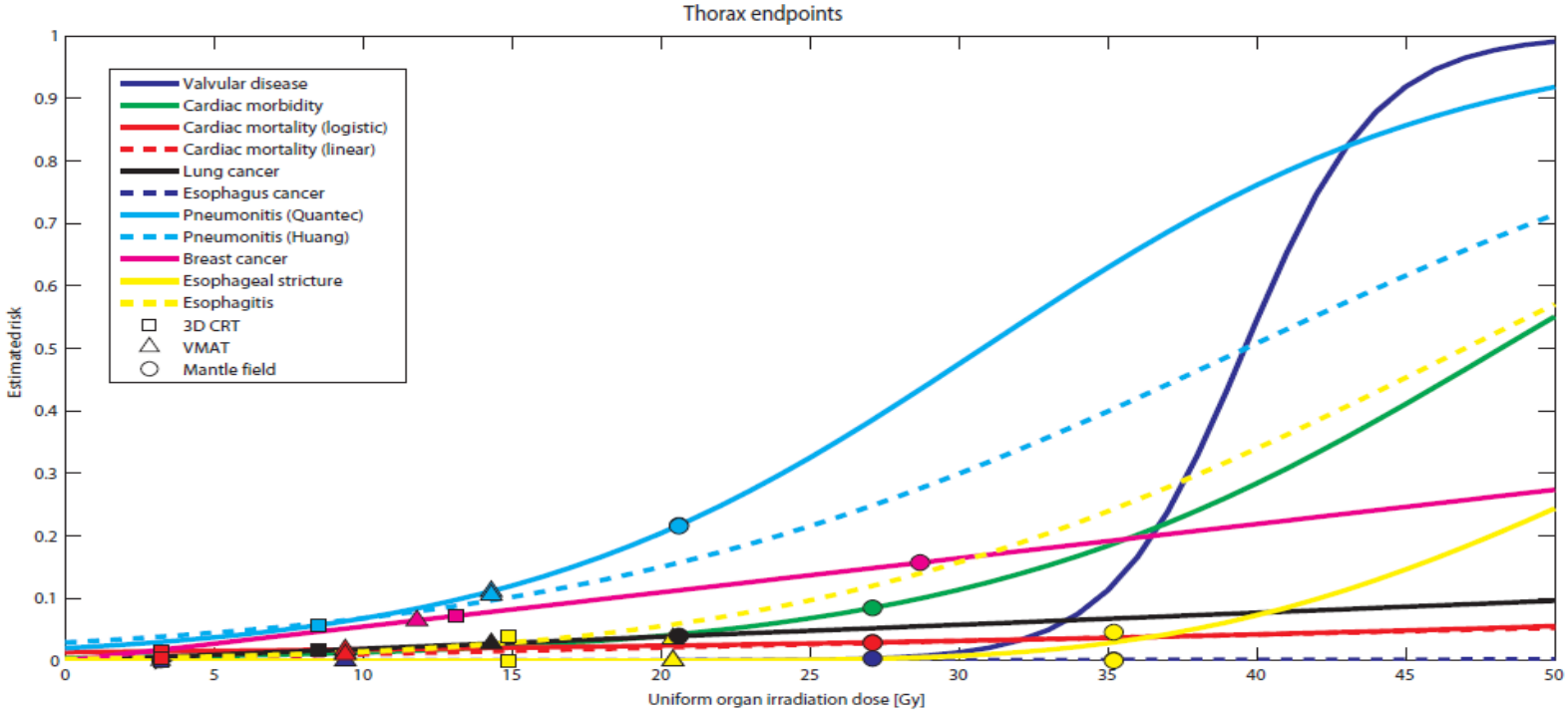
Ideally, normal tissue complication probability models for all relevant risk organs should be combined for each treatment plan



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

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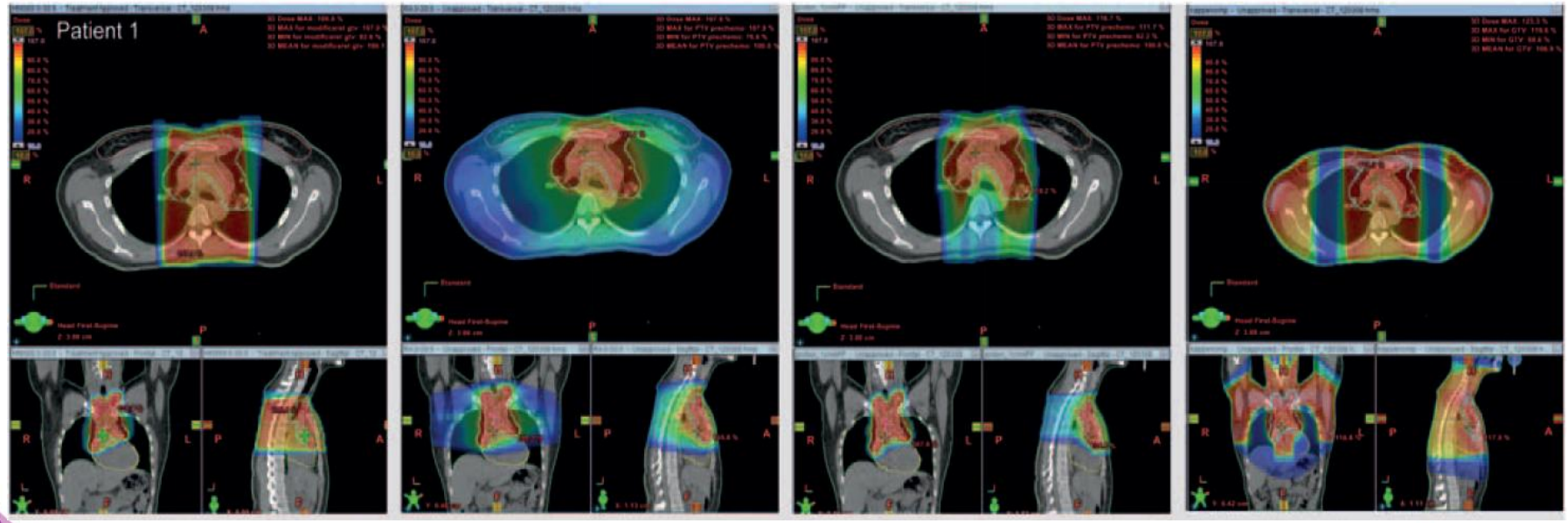
Different modern techniques vs. extended fields of the past

AP-PA IMRT IMPT Mantle field



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

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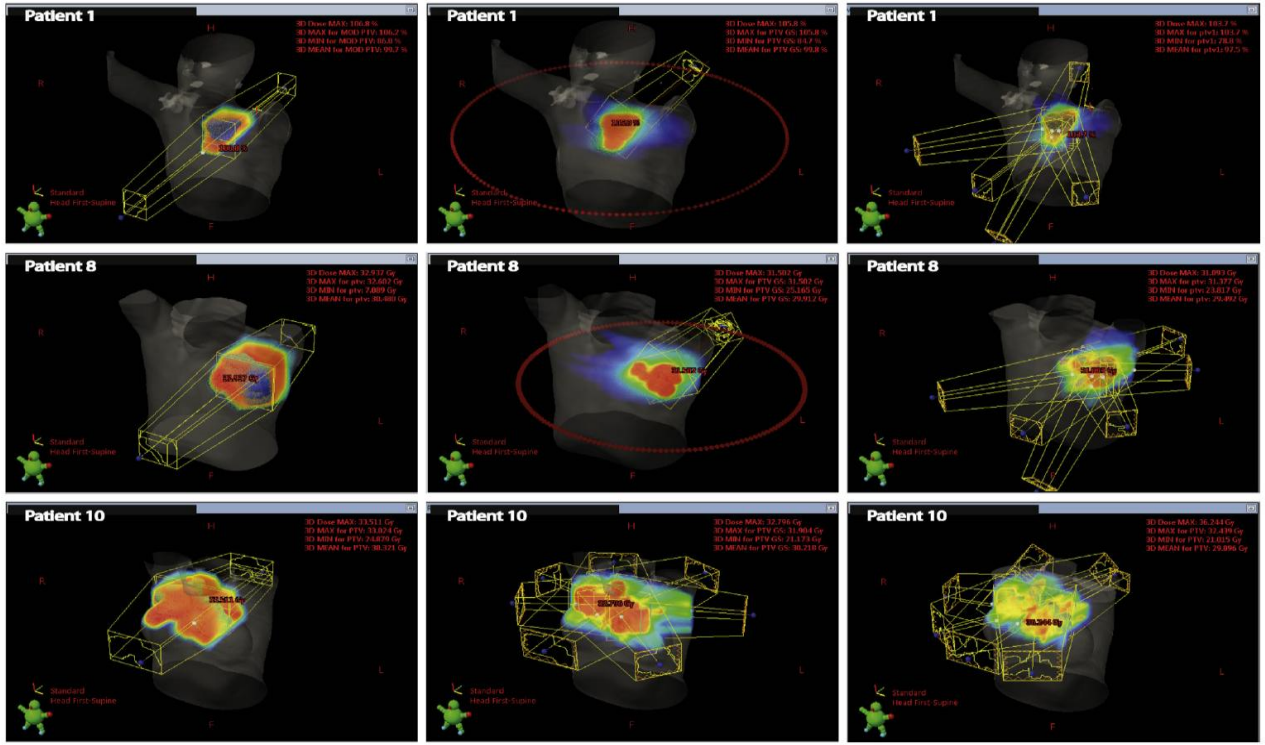
Same patient, different solutions



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

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Thank you for your attention

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General principles of treatment: Radiotherapy

Lena Specht MD DMSc
Professor of Oncology, University of Copenhagen, Denmark
Chief Oncologist, Depts. of Oncology and Haematology, Rigshospitalet, Copenhagen
Vice-chairman, International Lymphoma Radiation Oncology Group

Facts about radiotherapy in lymphomas

- Most lymphoma types are highly radiosensitive
- Radiotherapy was the first modality to cure lymphomas
- Radiotherapy has serious long-term sequelae
- Modern highly conformal limited and fairly low dose radiotherapy has markedly decreased these risks

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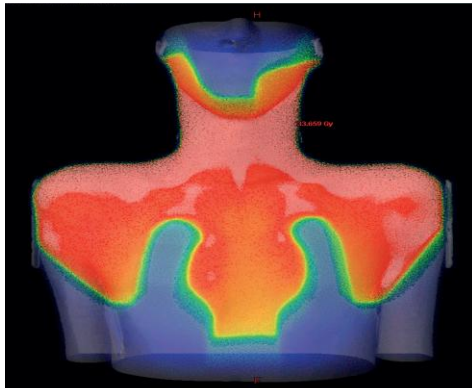
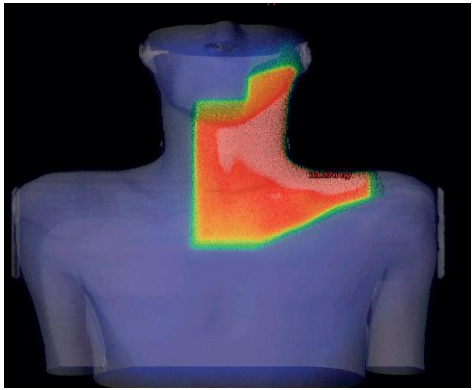
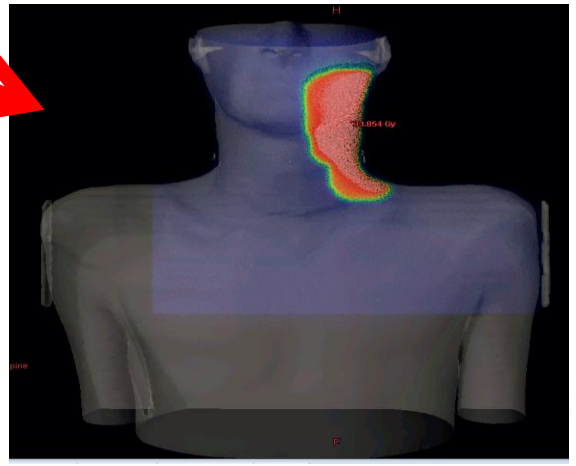
Mantle field (EFRT) or involved field (IFRT)





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

Target volume for radiation therapy depends on lymphoma type and stage

- Aggressive lymphomas
  - Effective chemotherapy deals with microscopic disease (true for B-cell lymphomas, less so for T-cell lymphomas)
  - Target in early stage disease is only the tissue volume which initially contained macroscopic lymphoma
  - Target in advanced disease is only residual disease, or intially bulky or extranodal disease
- Indolent lymphomas
  - Incurable with chemotherapy only
  - In early stage disease RT is the primary treatment. Target is the macroscopic lymphoma and adjacent nodes in that site with a generous margin
  - In advanced disease RT is palliative. Target is localized symptomatic disease

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Extranodal lymphomas

Aggressive lymphomas

- Same principles as for nodal lymphomas
- In many organs (e.g., stomach, salivary glands, thyroid gland, CNS) lymphoma is multifocal. Hence, the whole organ is treated even if apparently only partially involved
- Even with modern imaging it may be difficult to accurately define the exact extent of disease in many extranodal sites. Hence, the whole organ is treated even if apparently only partially involved

Indolent lymphomas

- Same principles as for nodal lymphomas
- Whole organ is usually treated even if apparently only partially involved (for the same reasons as for aggressive lymphomas)
- Uninvolved nodes are not routinely included in the CTV. First echelon nodes of uncertain status close to the primary organ may be included

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Modern radiotherapy guidelines developed by

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- Previous wide field and involved field replaced by limited volumes based solely on detectable involvement at presentation
- ICRU concepts of GTV, CTV, ITV, and PTV are used
- New concept, Involved Site RadioTherapy (ISRT), defines CTV on this basis
- Previous doses were higher that necessary, replaced by lower doses in most lymphoma types

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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)

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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

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Internal target volume (ITV) (ICRU 83)

- Defined in ICRU 62, optional in ICRU 83
- CTV + margin for uncertainties in size, shape, and position of the CTV
- Mostly relevant when the target is moving (chest and upper abdomen)
- Margins may be obtained from 4-D CT, fluoroscopy or from expert clinician
- Margins should be added quadratically: $\sigma' = \sqrt{(\sigma^2_m + \sigma^2_s)}$

Equation for right-angled triangle

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Planning target volume (PTV) (ICRU 83)

- Accounts for set-up uncertainties in patient position and beam alignment during planning and through all treatment sessions
- Function of immobilization device, body site, and patient cooperation
- Geometrical concept introduced to ensure that CTV and/or ITV are properly covered
- Applied by clinician or treatment planner

ISRT scenarios

- Optimal pre-chemo imaging of all the initially involved lymphomas is available and image fusion with the planning CT-scan is possible:
  - INRT
- Pre-chemo imaging (CT, PET, or MR) of all the initially involved lymphomas is available, but image fusion with the planning CT-scan is not possible:
  - Contour with pre-chemo images as a visual aid, allowing for uncertainties of the contouring and differences in positioning
- Pre-chemo imaging not available:
  - Gather as much information as possible from the pre-chemo physical examination, location of scar tissue, patient's and family's recollections, making generous allowance for the many uncertainties in the process

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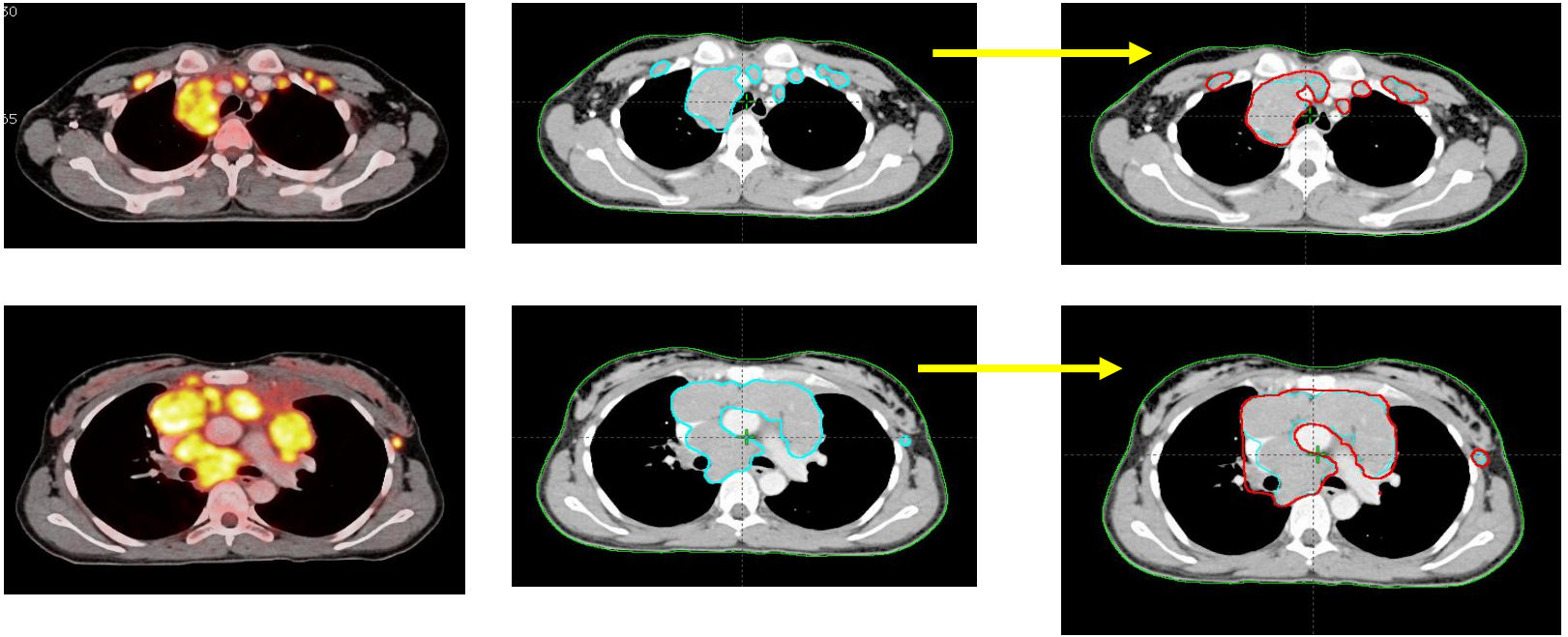
Pre-chemo PET/CT scan

PET+ volume

Gross tumour volume GTV
(pre-chemo)



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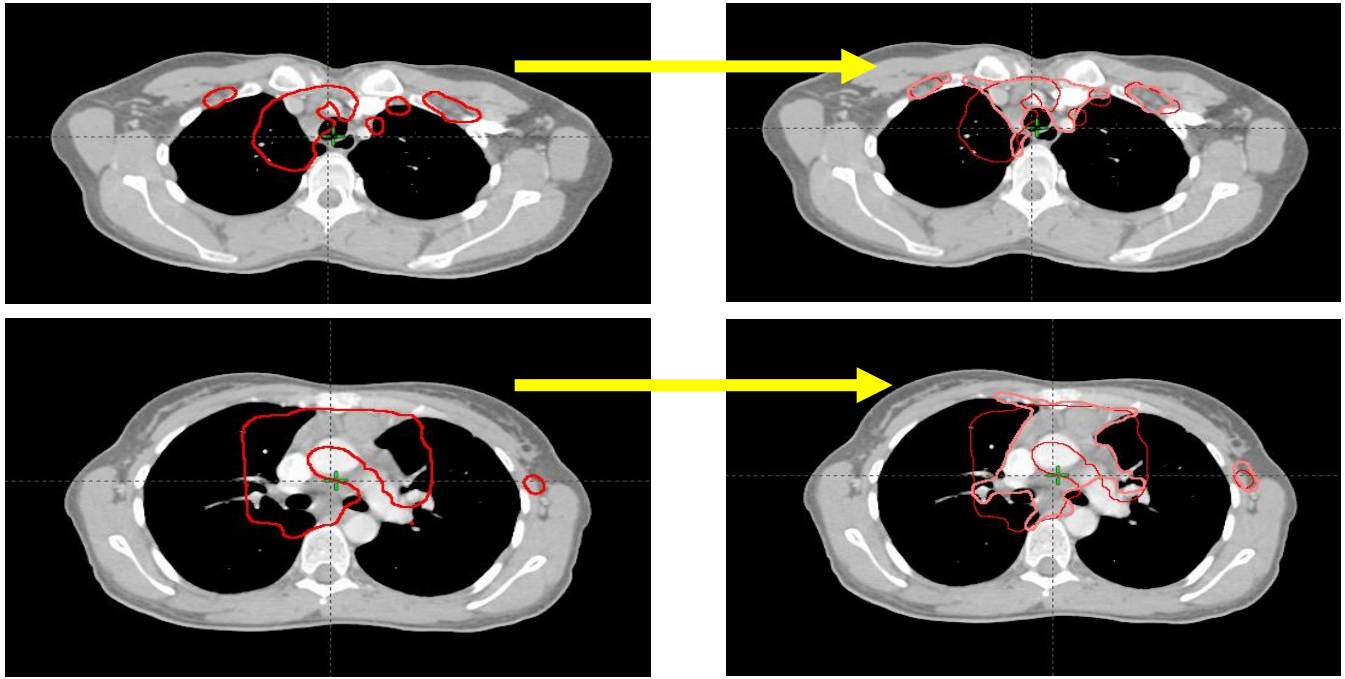
Post-chemo planning CT scan

Pre-chemo gross tumour volume

Post-chemo clinical target volume



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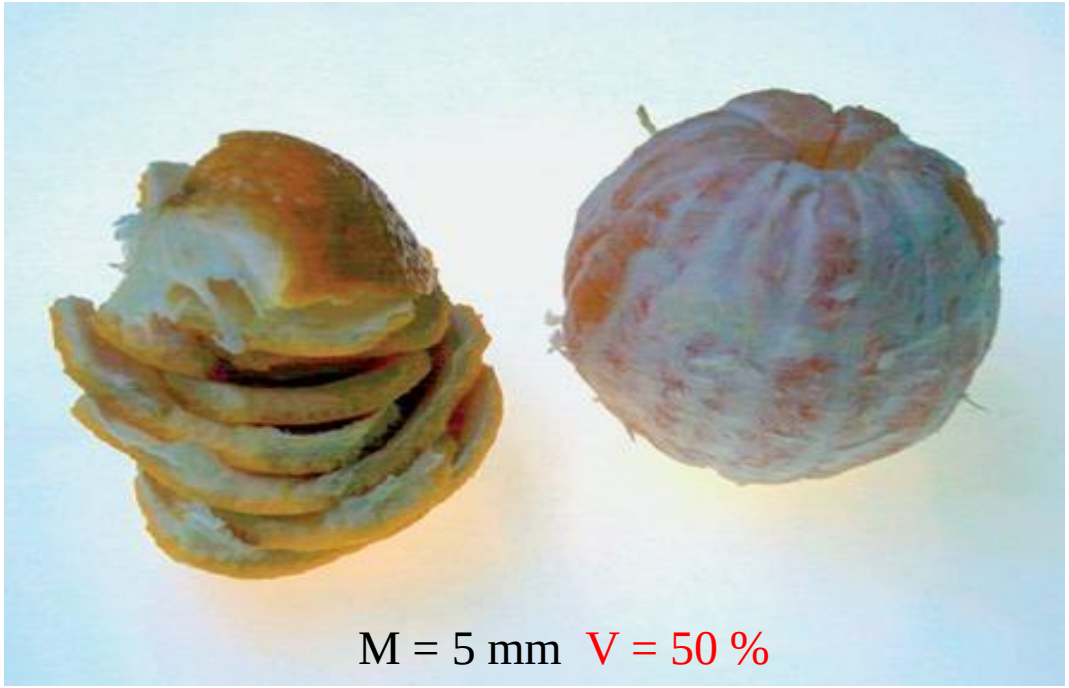
Margins and corresponding tissue volumes



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

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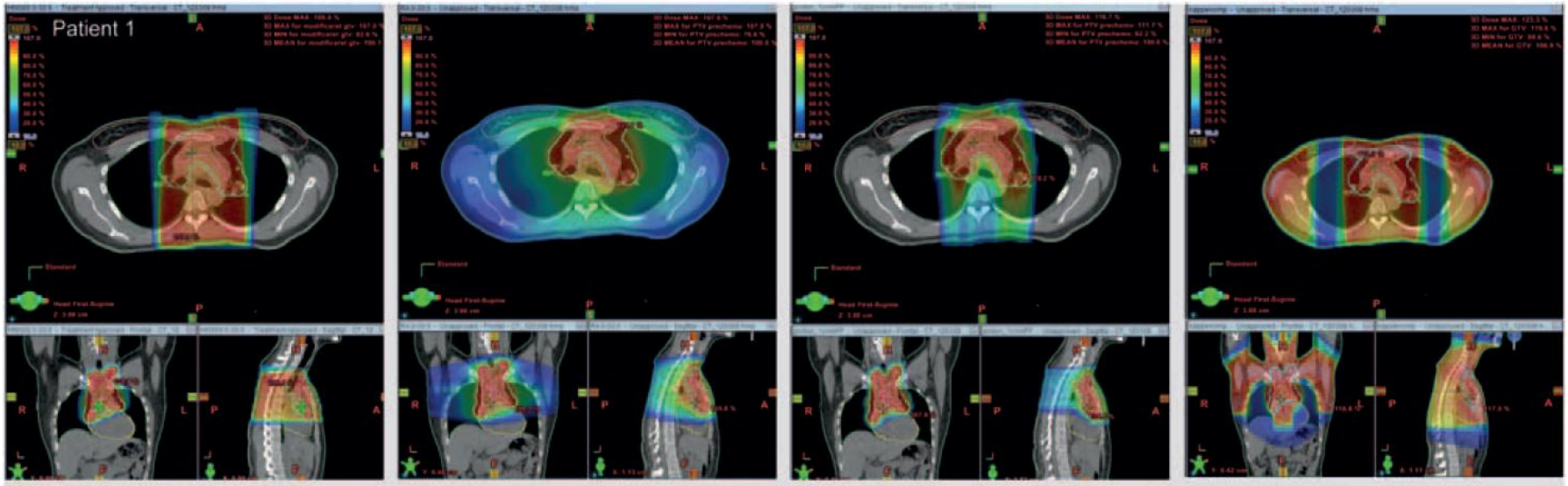
Different modern techniques vs. extended fields of the past

AP-PA IMRT IMPT Mantle field



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

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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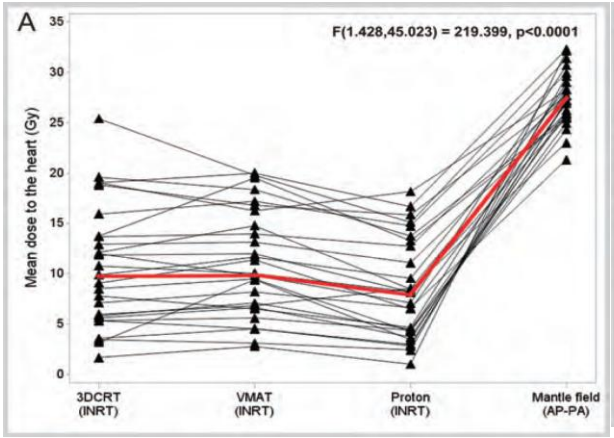
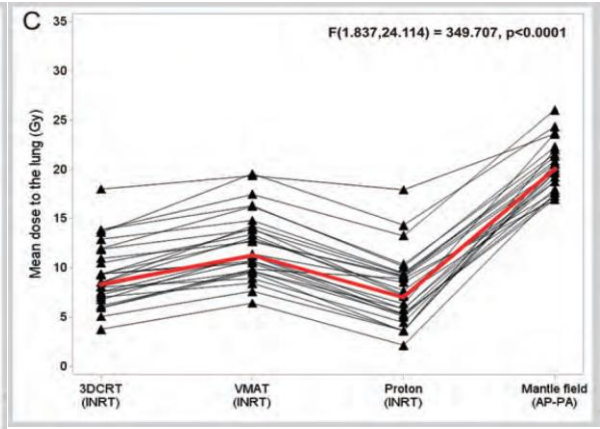
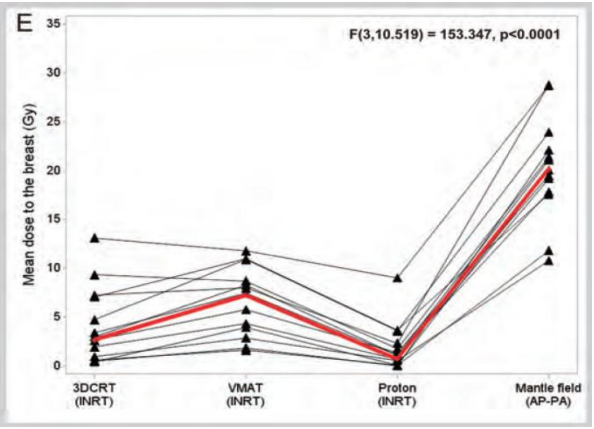
Mean doses to heart, lungs, and breasts in 27 early stage HL patients with mediastinal involvement with different techniques

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







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

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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

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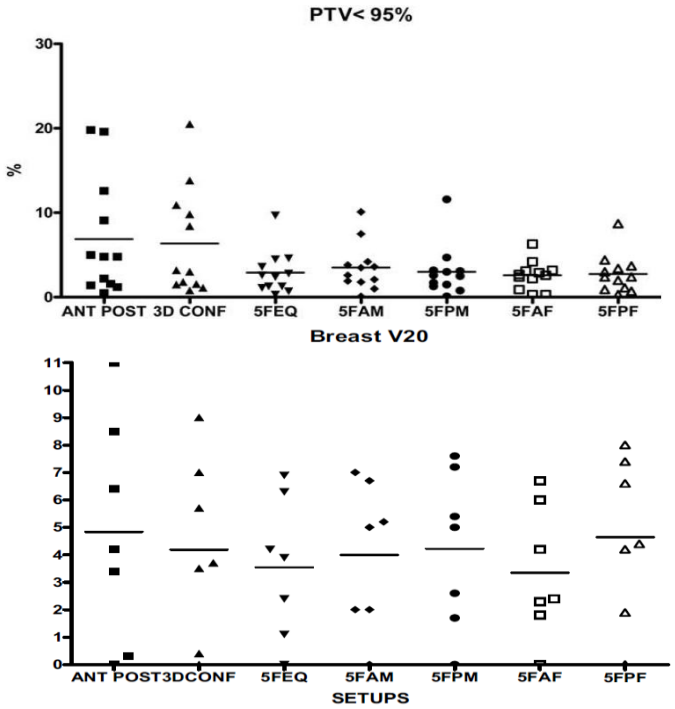
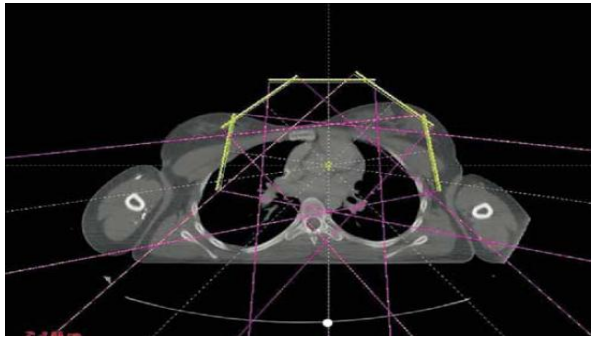
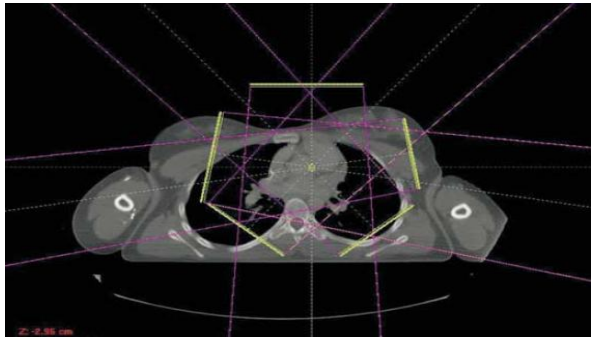
Optimizing IMRT with ”intelligent” beam orientation





Focus on anterior mass (FAM)



Avoid the breasts (FAF)

Girinsky et al. IJROBP 2006; 64: 218-26

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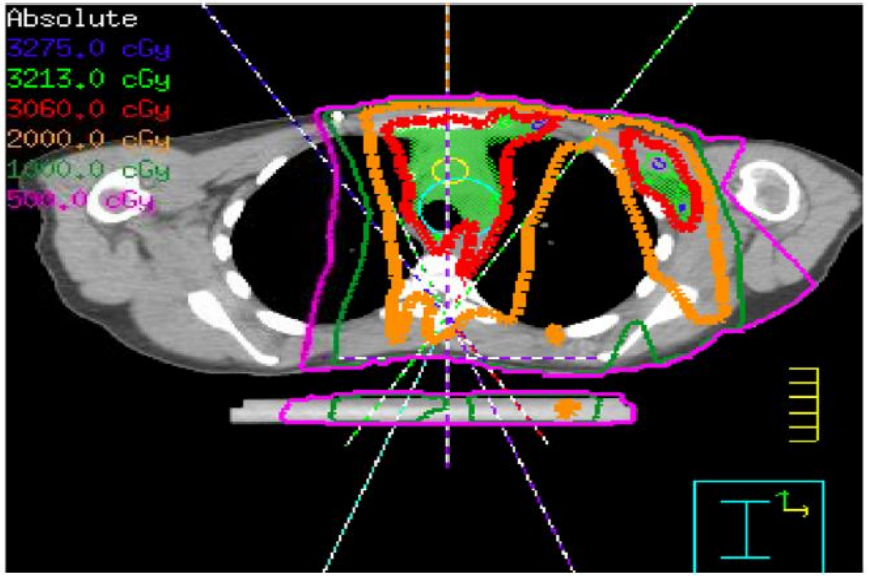
Optimizing IMRT with ”intelligent” beam orientation

”Butterfly technique”



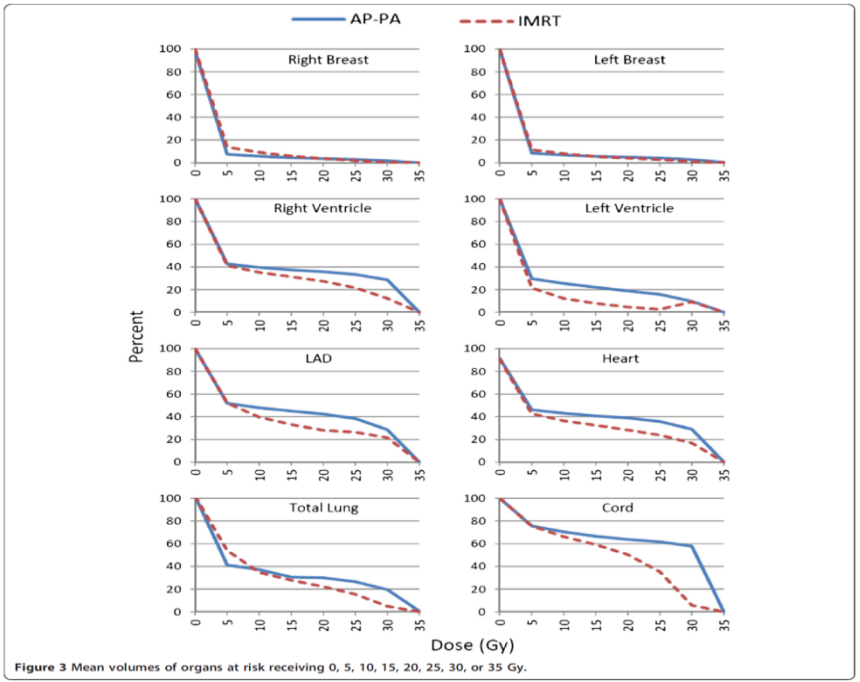


Figure 3 Mean volumes of organs at risk receiving 0, 5, 10, 15, 20, 25, 30, or 35 Gy.

Voong et al. Radiat Oncol 2014; 9: 94

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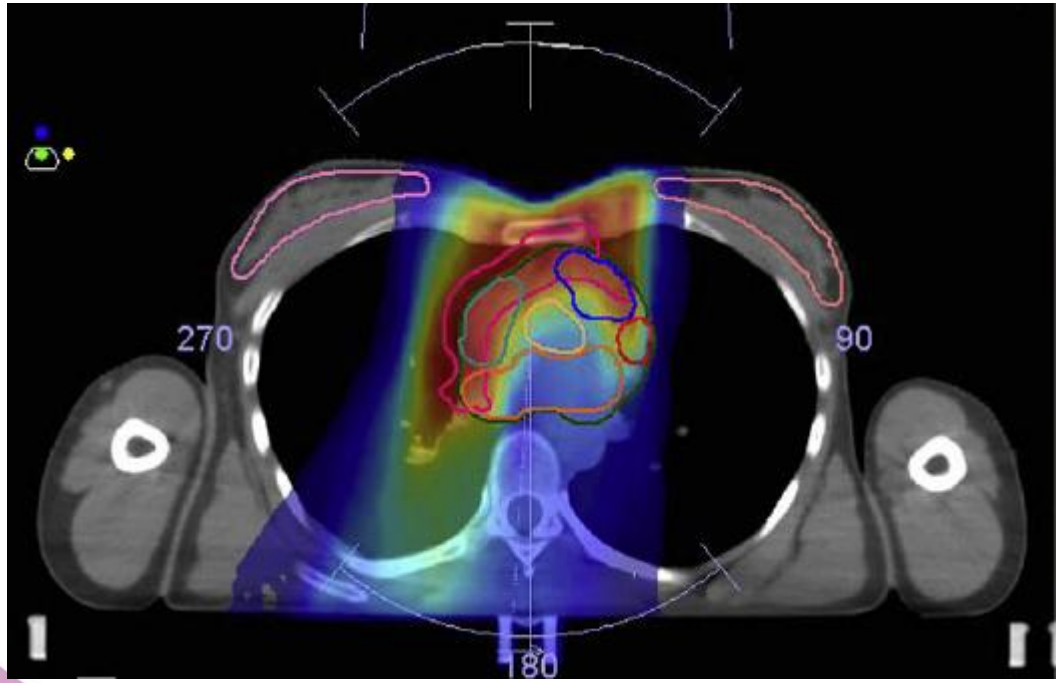
Optimizing IMRT with ”intelligent” beam orientation

2 coplanar arcs + 1 non-coplanar



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

Target	Mean OED and SD		*P* value
	3D-CRT	VMAT	
Lung			
All	2.16 ± 0.84	2.28 ± 0.73	.025
No neck	1.59 ± 0.73	1.91 ± 0.62	.001
Unilateral neck	2.31 ± 0.85	2.46 ± 0.81	.03
Bilateral neck	2.33 ± 0.76	2.22 ± 0.57	.23
Breast			
All	0.22 ± 0.15	0.22 ± 0.16	.72
No neck	0.17 ± 0.13	0.20 ± 0.13	.34
Unilateral neck	0.26 ± 0.18	0.25 ± 0.19	.88
Bilateral neck	0.20 ± 0.12	0.16 ± 0.09	.02
Thyroid			
All	3.29 ± 1.77	3.34 ± 1.75	.35
No neck	0.30 ± 0.16	0.41 ± 0.36	.29
Unilateral neck	3.65 ± 0.83	3.73 ± 0.81	.48
Bilateral neck	4.83 ± 0.62	4.83 ± 0.68	.94

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

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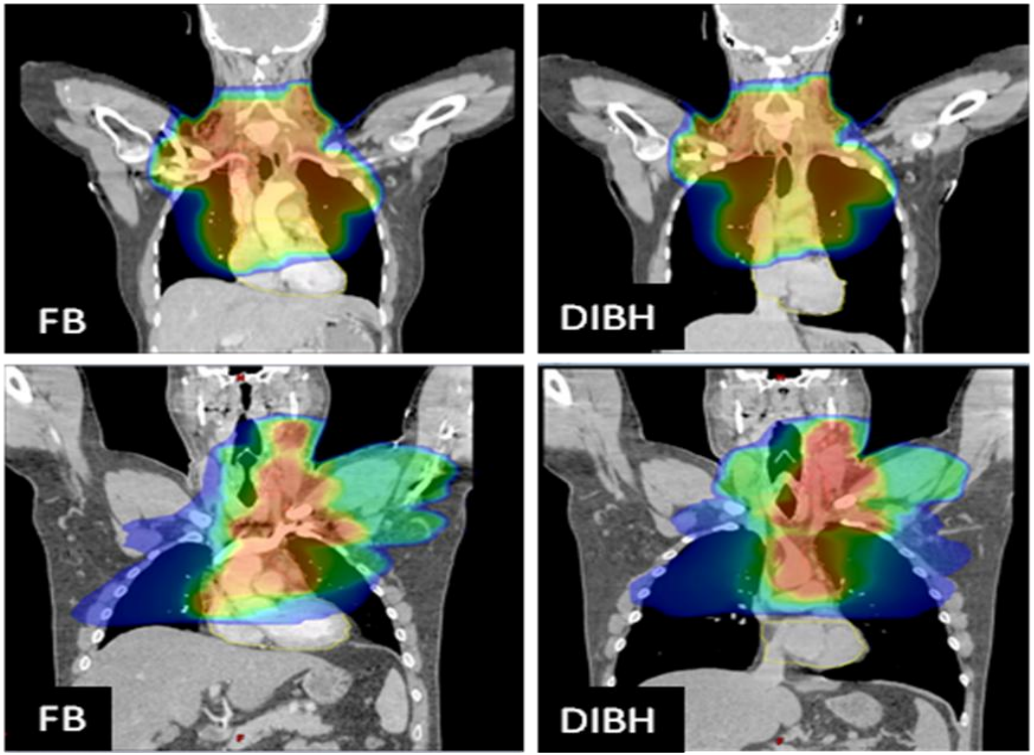
Breathing adapted RT



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

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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

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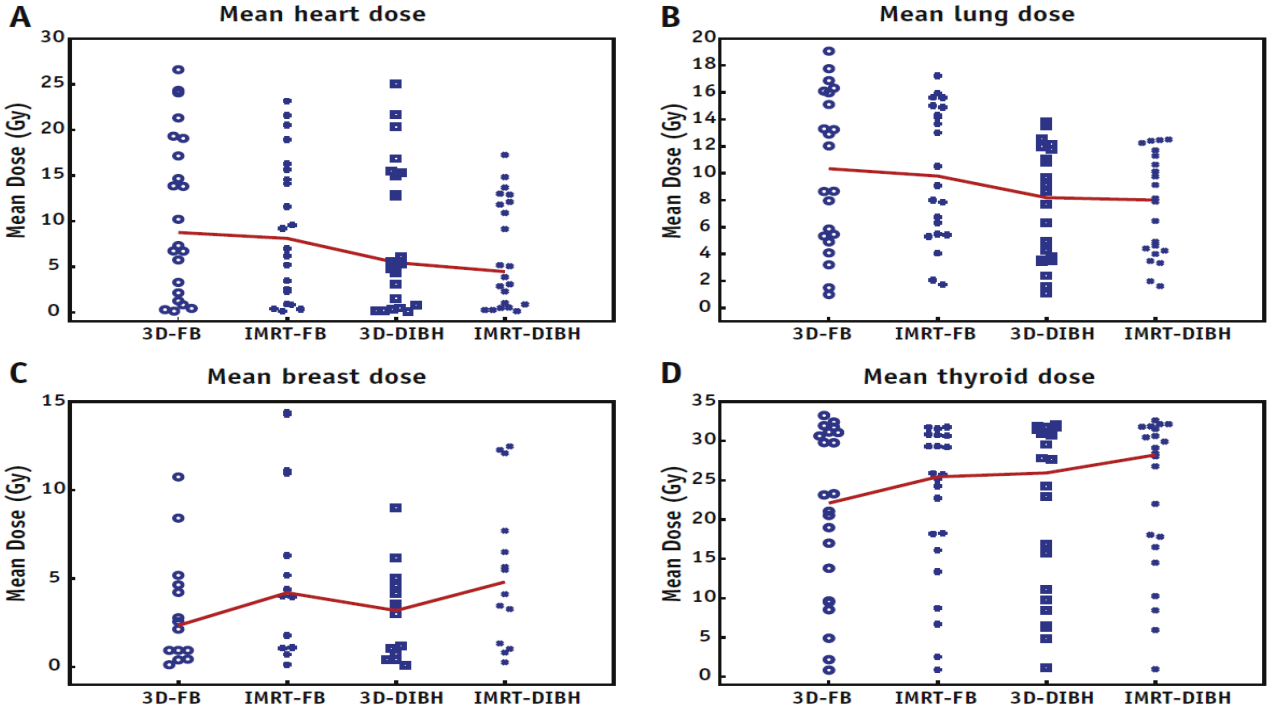
Breathing adaptation and highly conformal treatment (IMRT), what can we achieve?



Aznar et al. IJROBP 2015; 92: 169-74

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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

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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

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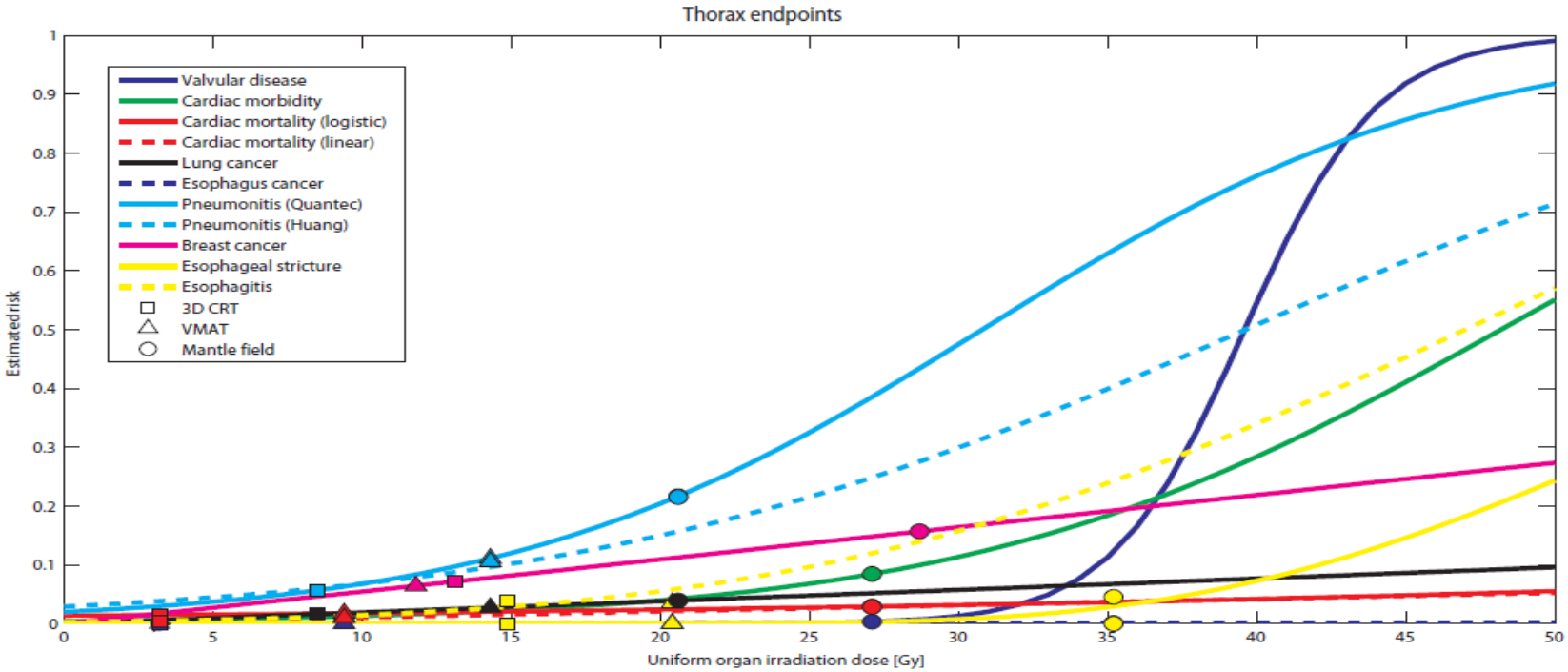
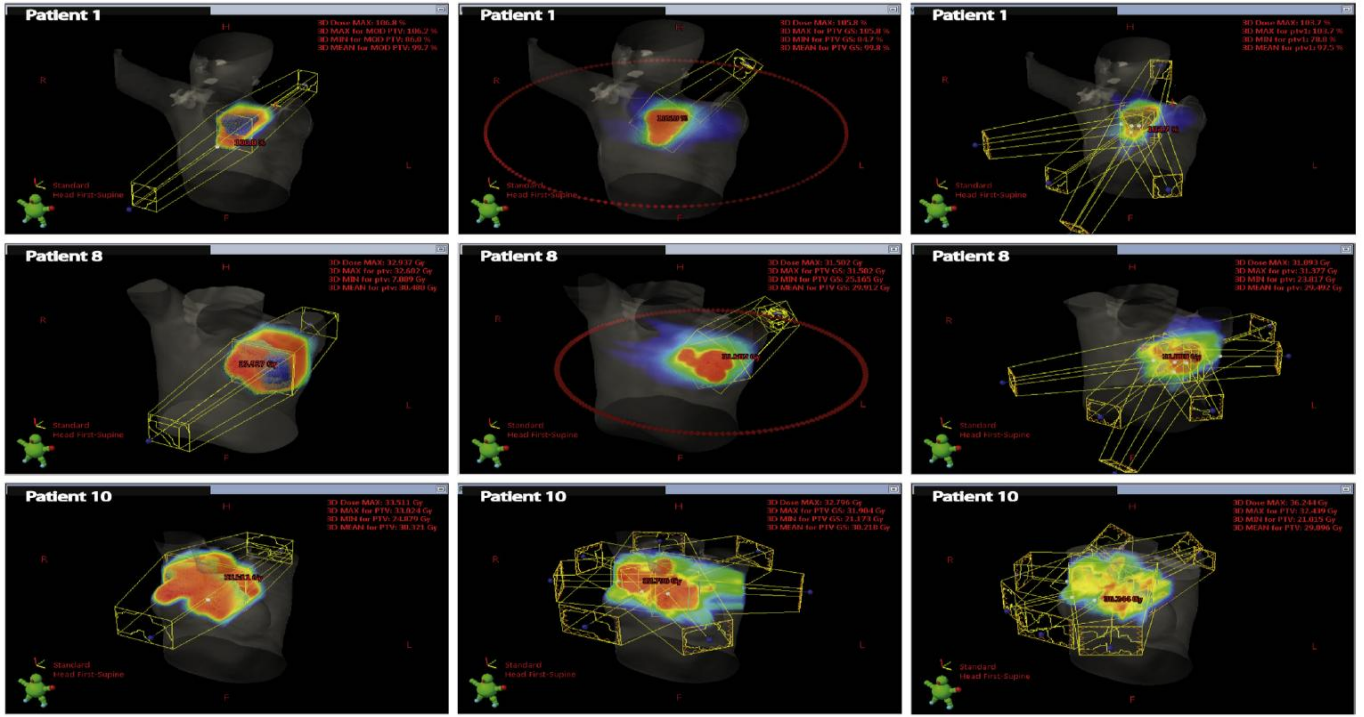
Ideally, normal tissue complication probability models for all relevant risk organs should be combined for each treatment plan



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

Same patient, different solutions



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

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Current approaches and emerging therapies in the treatment of malignant lymphoma

Andreas Engert, MD

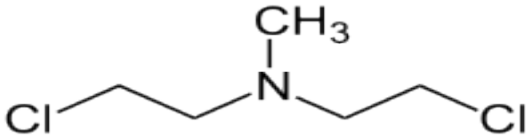
Chairman, German Hodgkin Study Group
University Hospital of Cologne

Chemotherapy of malignant lymphoma

- History of and principles of chemotherapy
- Hodgkin lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma
- Summary

Mechlorethamin

The first cytostatic drug in lymphoma

Name	**Mechlorethamin**	**Strukturformel:**
Other names	**N,N-Bis(2-chlorethyl)-N-methylamin** **Chlormethin** **Stickstofflost** **N-Lost** **HN2**	

Mechlorethamin (Stickstoff-Lost) is an alkylating agent, and is mainly used in the chemotherapy of Hodgkin lymphoma (trade name *Mustargen*®, USA, CH)

Mustargen and the history of alkylating agents

- **Mustargen as antitumor agent evolved from observed effects of mustard gas in ww1**
- **Depression of the hematopoietic system was observed in survivors**
- **Nitrogen mustard is an alkylating agent**
- **First non-hormonal chemical demonstrating clear clinical antitumor activity**
- **Studies published in 1946 demonstrated regression especially of lymphomas**
- **Nitrogen mustard (mechlorethamine, mustargen) and other less toxic and more clinically effective derivatives were developed**

Colvin OM. History of the alkylating agents; 19(3):363-371.
Cancer Principley & Practice of Oncology, de Vita V, et al (eds), 2001

MOPP

Combination chemotherapy

(M)ustargen (also known as mechlorethamine, mustine, or nitrogen mustard)
(O)ncovin (also known as Vincristine or VCR)
(P)rocarbazine (also known as Matulane or Natulan)
(P)rednisone (also known as Deltasone or Orasone)

Drug	Dose	Mode	Days
(M)ustargen	6 mg/m^2	iv bolus	1 + 8
(O)ncovin	1.4 mg/m^2 (max 2)	iv bolus	1 + 8
(P)rocarbazine	100 mg/m^2	po qd	1 - 14
(P)rednisone	40 mg/m^2	po qd	1 - 14

MOPP

Major Side effects

Alopecia (hair loss)

Skin sensitivity

Nausea, vomiting

Chills, constipation

Sterility (dose and age dependent)

Second cancer

https://en.wikipedia.org/wiki/MOPP

COPP

Combination chemotherapy

Drug	Dose	Mode	Days
(C)yclophosphamide	600 mg/m^2	iv infusion	1 + 8
(O)ncovin	1.4 mg/m^2 (max. 2 mg)	iv bolus	1 + 8
(P)rocarbazine	100 mg/m^2	PO qd	1 - 10
(P)rednisone	40 mg/m^2	PO qd	1 - 14

Major side effects of COPP

Myelosuppression

Hair loss

Nausea and vomiting

Infection

Fatigue

Bleeding

Peripheral neuropathy

Gonadal toxicity

Infertility

ABVD

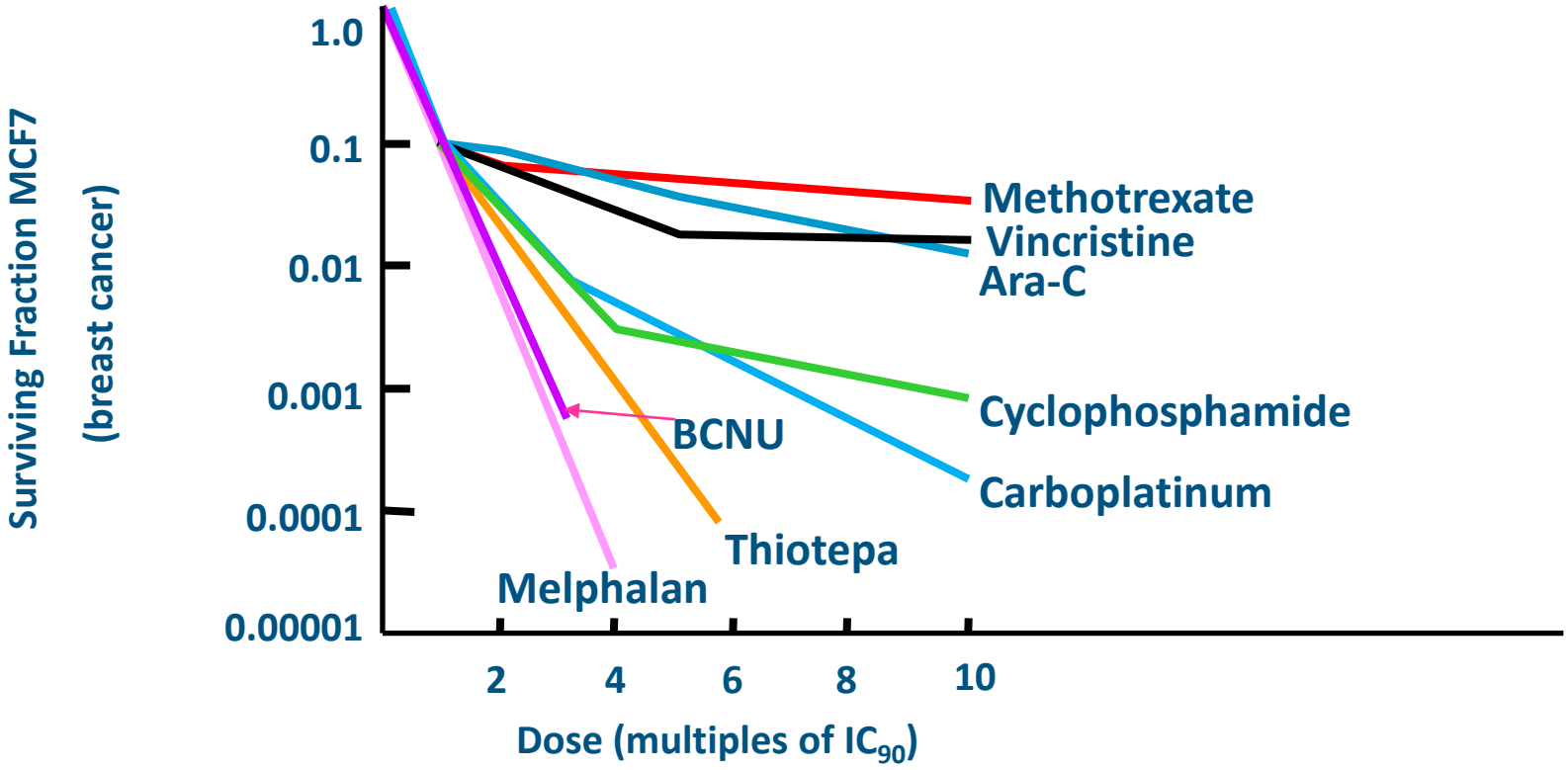
Combination chemotherapy

(A)driamycin (also known as doxorubicin/(H)ydroxydaunorubicin, designated as H in CHOP)
(B)leomycin
(V)inblastine
(D)acarbazine (similar to (P)rocarbazine, designated as P in MOPP and in COPP)

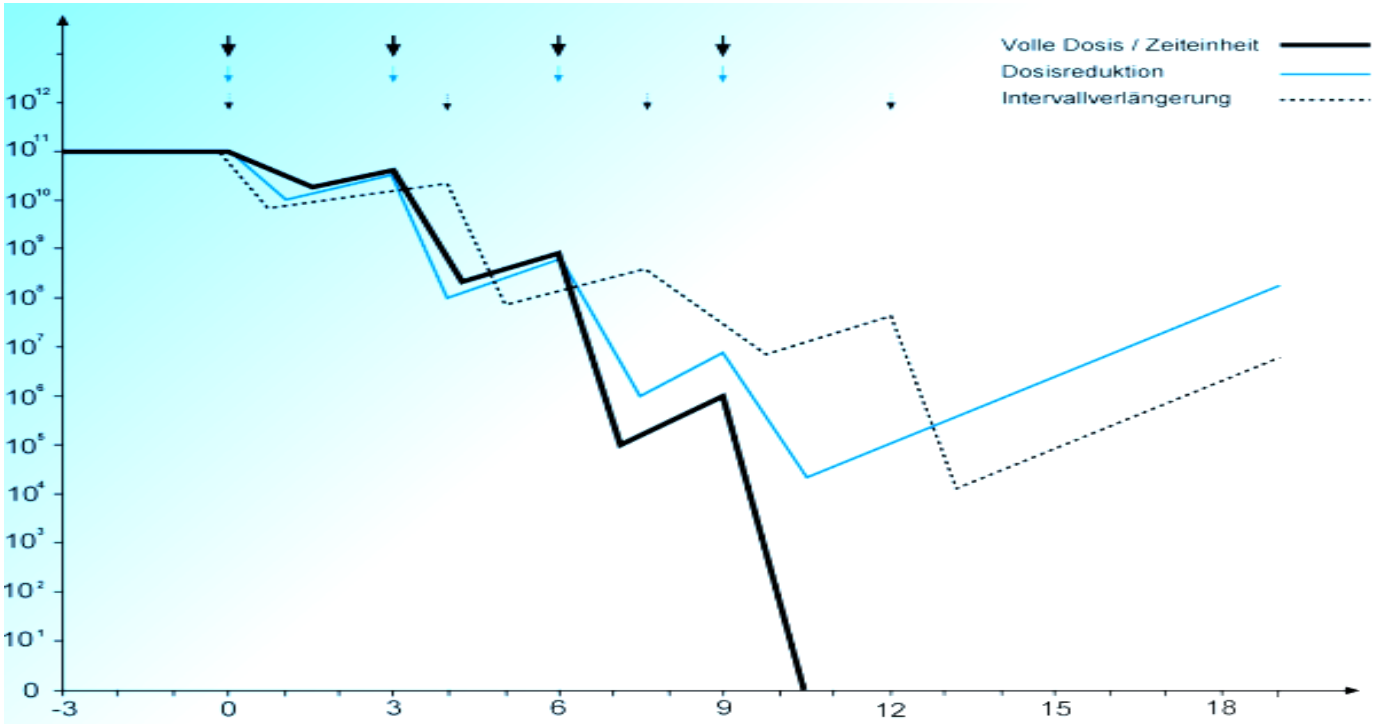
Drug	Dose	Mode	Days
(A)driamycin	**25 mg/m²**	**iv bolus**	**1 + 15**
(B)leomycin	**10 IU/m²**	**iv bolus**	**1 + 15**
(V)inblastine	**6 mg/m²**	**iv bolus**	**1 + 15**
(D)acarbazine	**375 mg/m²**	**iv infusion**	**1 + 15**

Correlation of dose and efficacy

Cytostatic drugs *in vitro*



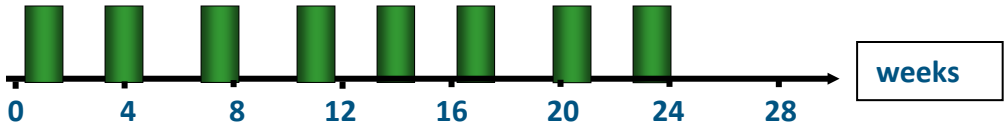
Correlation of dose density and response
Chemosensitive malignancies



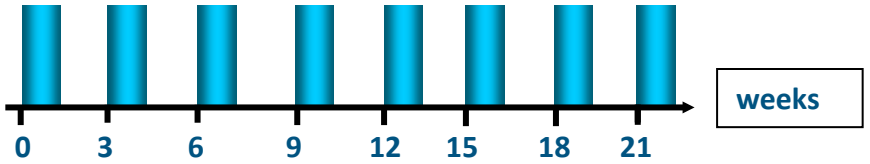
C. Jackisch

Dose-intensification strategies
for first-line Lymphoma treatment

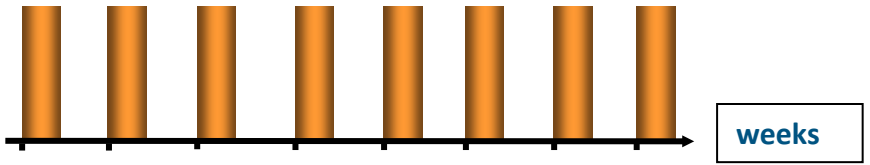
Conventional chemo



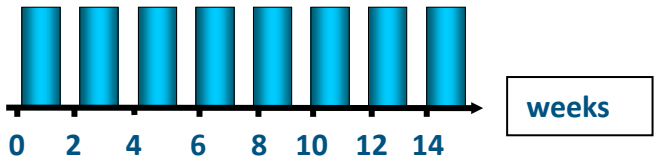
BEACOPP baseline



BEACOPP escalated



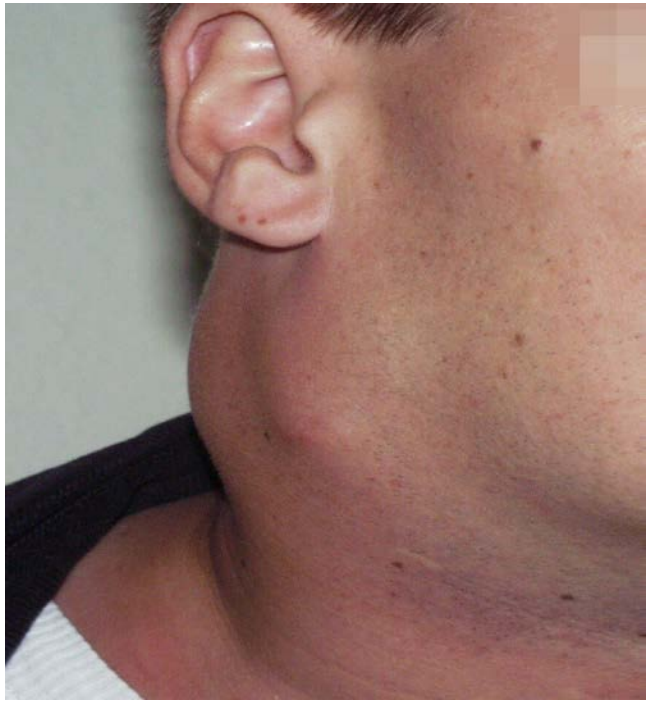
CHOP-14, BEACOPP-14

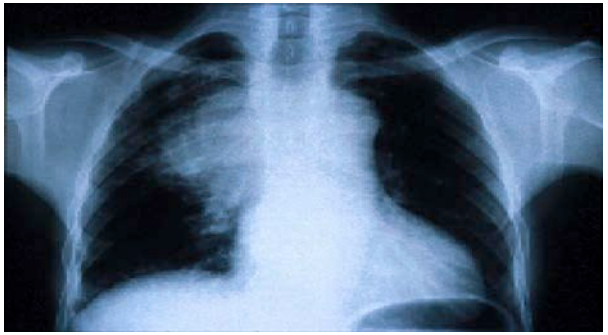


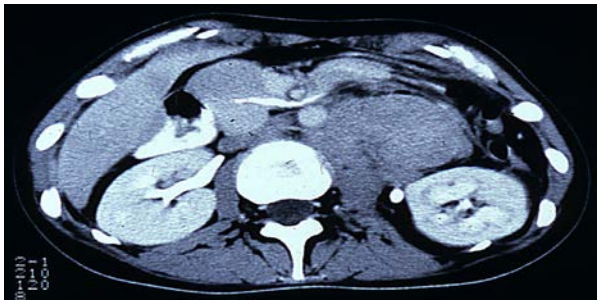
Chemotherapy of malignant lymphoma

- History and principles of chemotherapy
- Hodgkin lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma
- Summary

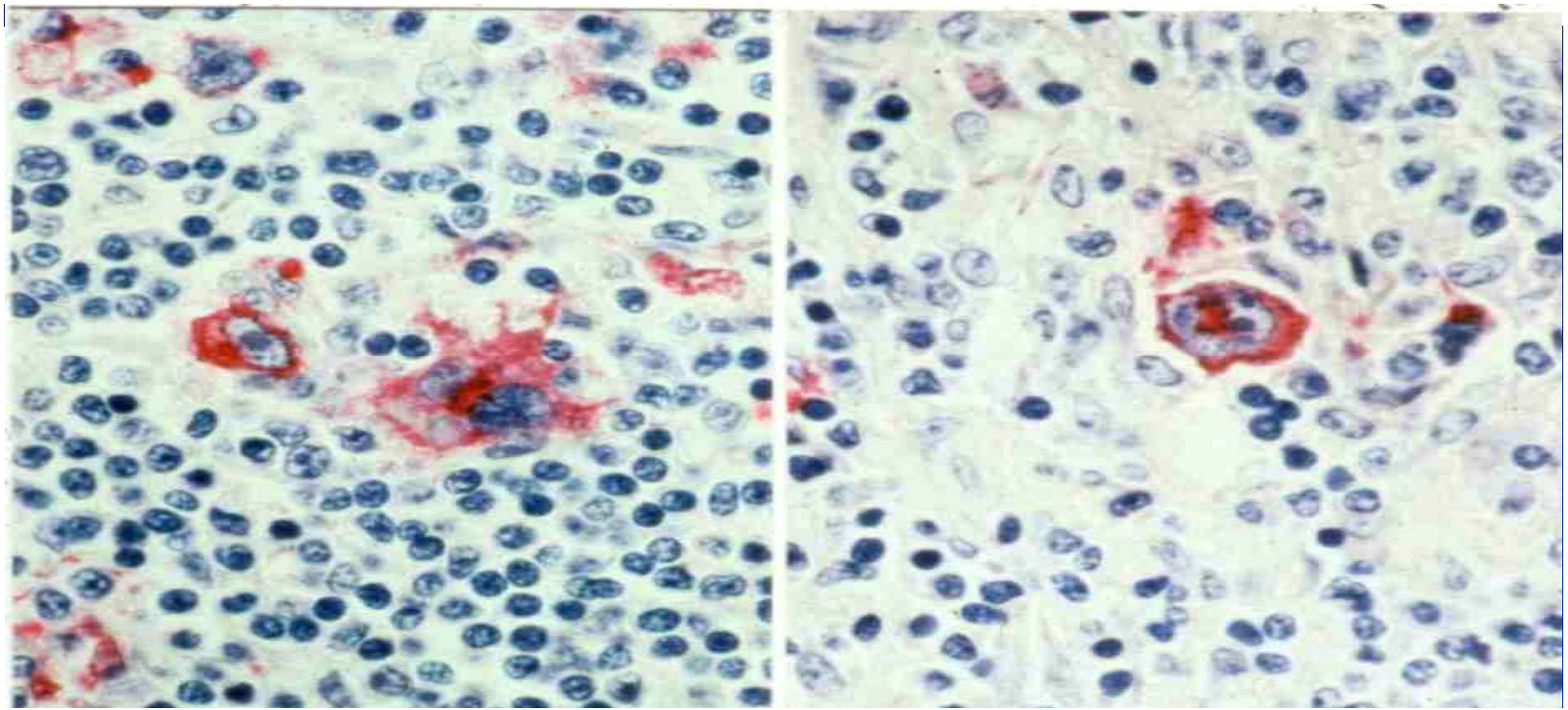
Hodgkin Lymphoma
Clinical Presentation







Hodgkin Lymphoma
Immunohistology



WHO Classification for HL (2001)

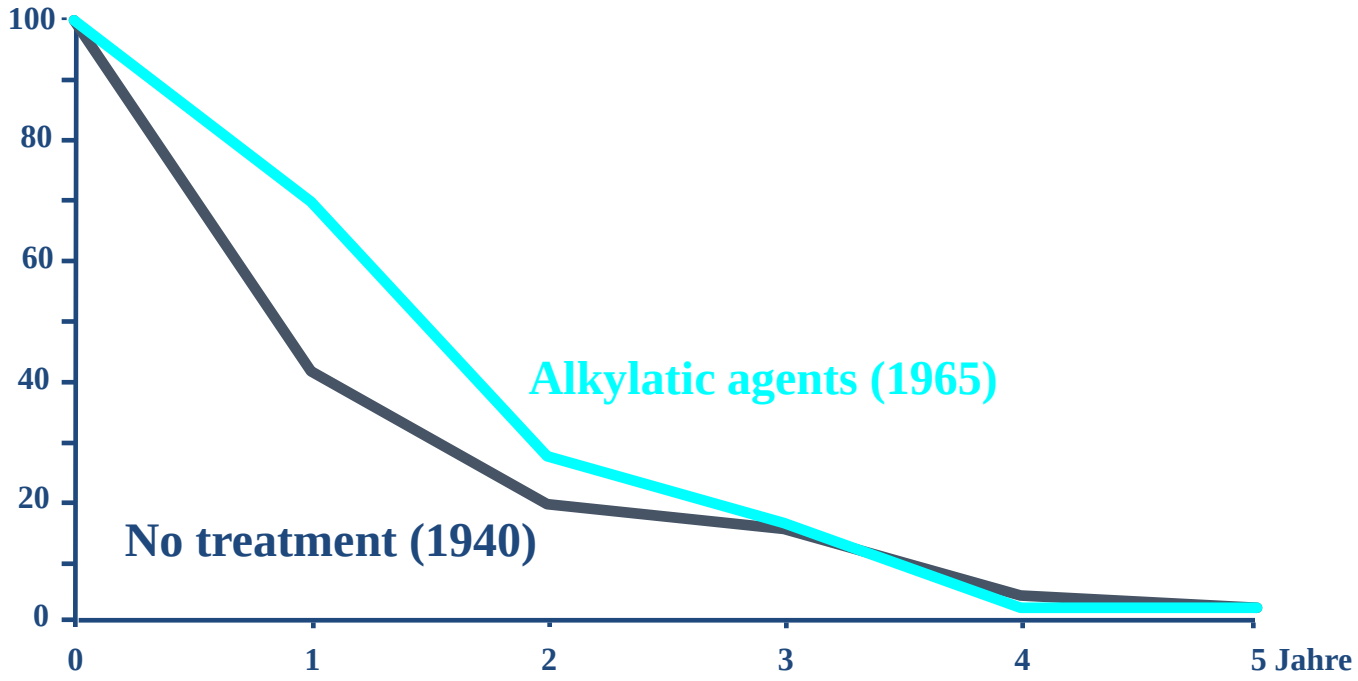
Classical HL (cHL)

- **Lymphocyte-rich classical HL (5%)**
- **Nodular Sclerosis (60-80%)**
- **Mixed Cellularity (25-30%)**
- **Lymphocyte Depletion (1%)**

Nodular Lymphocyte predominant HL (5%)

Hodgkin Lymphoma

Historical prognosis in advanced stages

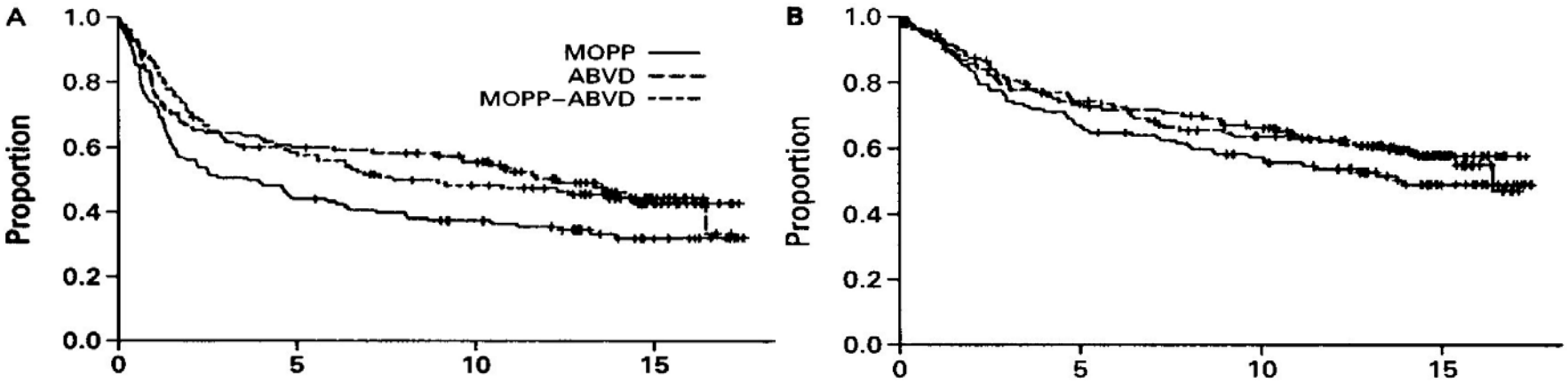


HL treated with MOPP and ABVD

Patients in advanced stages

FFTF

OS

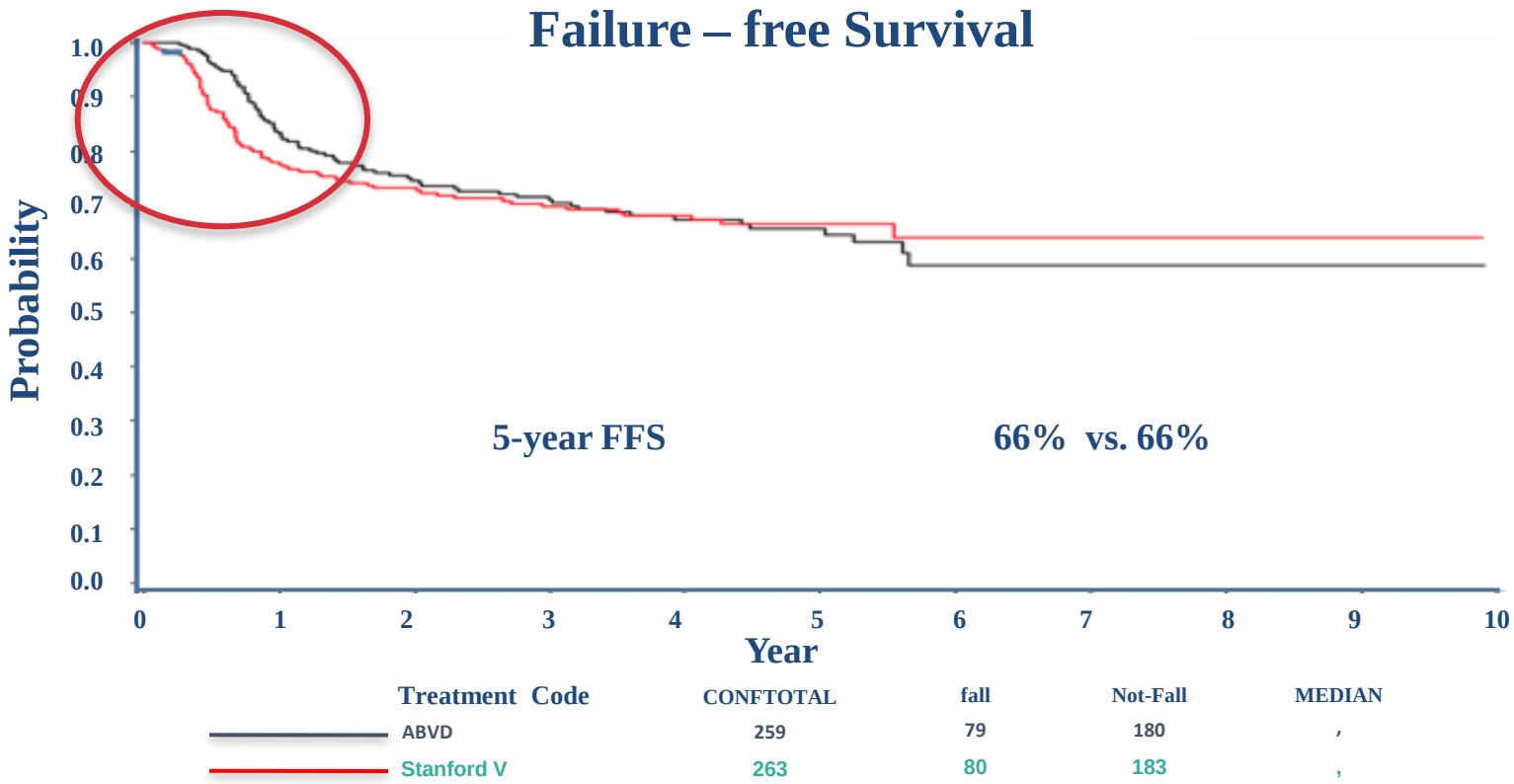


Years after study entry

Canellos G et al NEJM 2002

US Intergroup Trial E2496

ABVD vs Stanford



Gordon et al; JCO 2013

What about ABVD needs improving?

- **Bleomycin lung toxicity with ABVD**
- **Efficacy of ABVD is decreased in certain subgroups**
  - **In patients with stage III/IV disease, the 5-year FFS is about 65%**
  - **In patients >60 years, the 5-year FFS is poor**
  - **In patients with IPS 3-7, the 5-year FFS is about 65%**
- **Long-term tumour control of 70% not good enough**

Improve efficacy!

BEACOPP

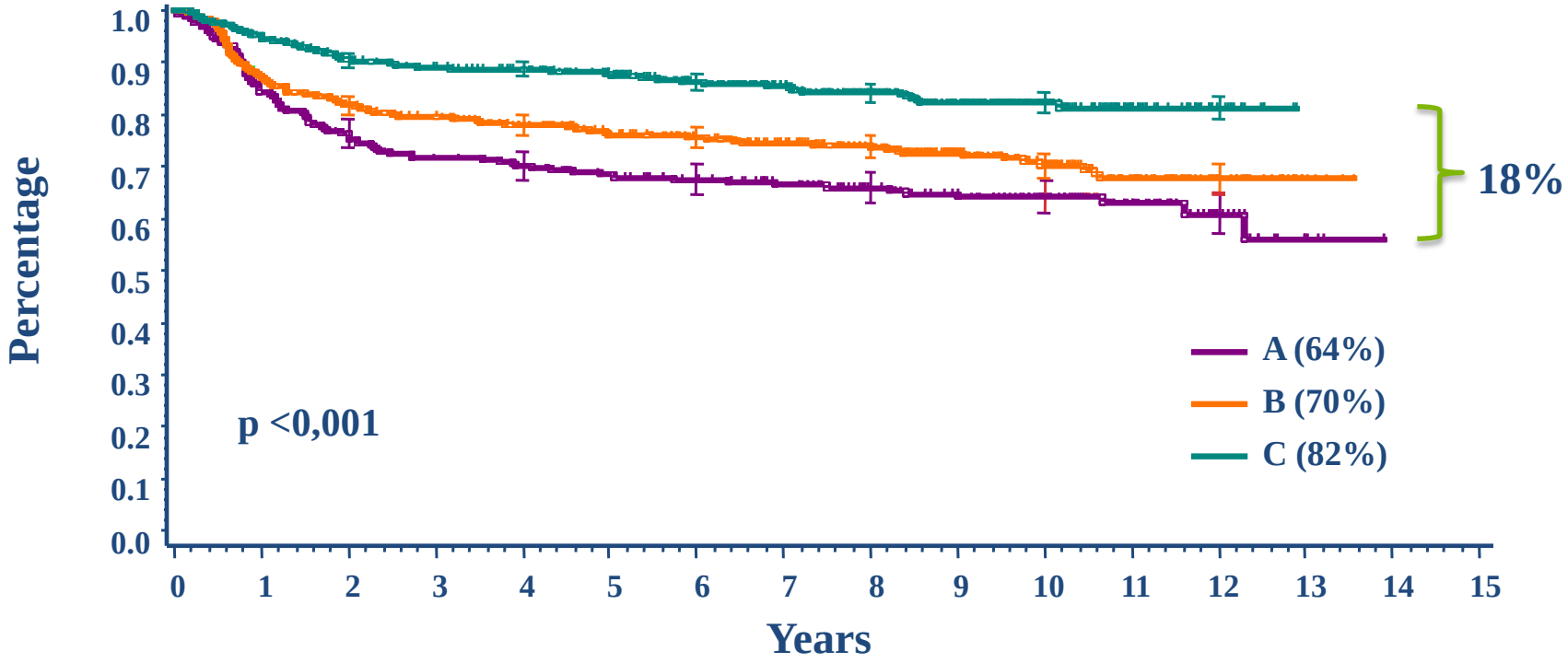
Baseline (base) and escalated (esc)

Drug	base[2]	esc[2]	Route	Schedule
Bleomycin	10	10	iv	8
Etoposide	100	200	iv	1-3
Adriamycin	25	35	iv	1
Cyclophosphamide	650	1250	iv	1
Vincristine	1.4[1]	1.4[1]	iv	8
Procarbazine	100	100	po	1-7
Prednison	40	40	po	1-14
G-CSF	-	+	sc	8-14

[1]max. 2,0mg
[2]mg/m^2

GHSG HD9 trial

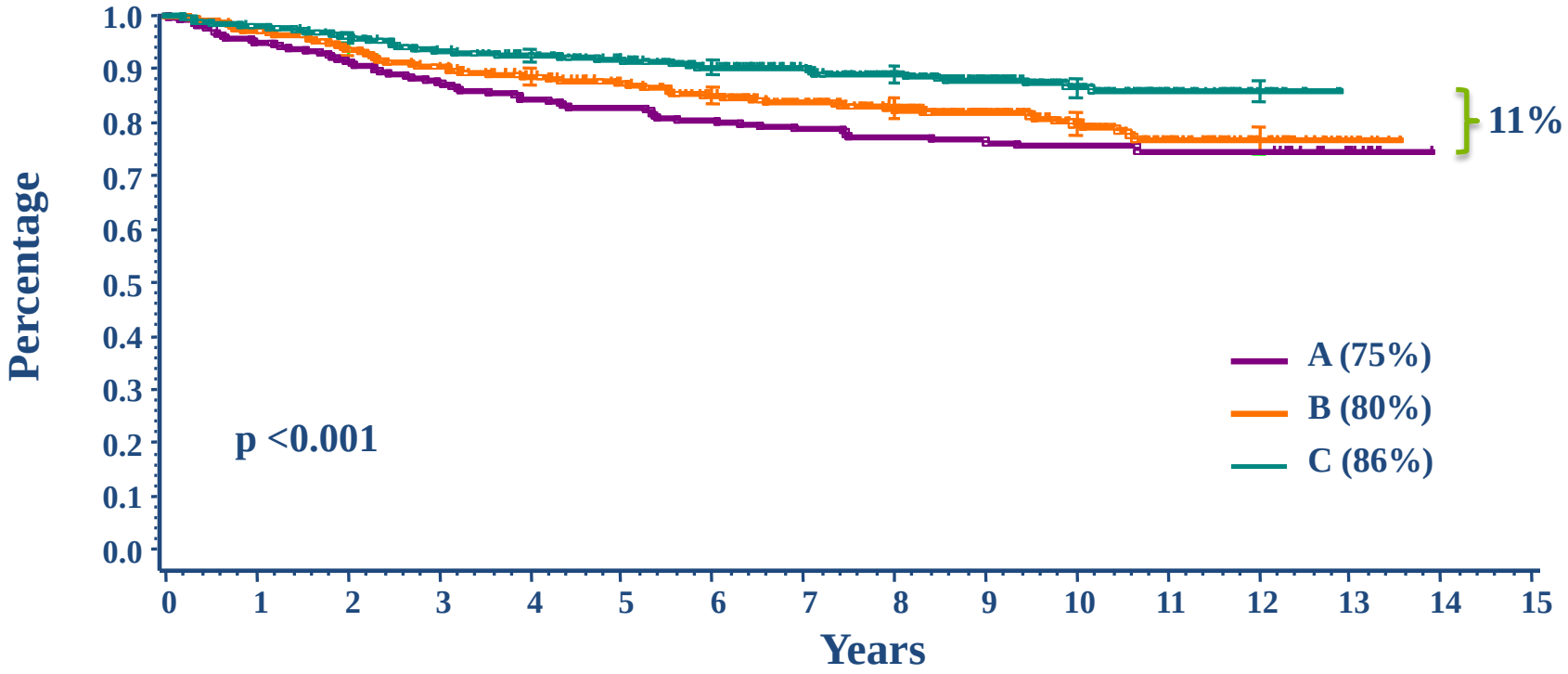
FFTF by treatment arm



Engert A et al, JCO 2009

GHSG HD9 trial

OS by treatment arm



Engert et al; JCO 2009

GHSG HD9 Trial

Causes of death at 10 years (% of all pts)

	C/ABVD n=261	BEAbase n=469	BEAesc n=466
HL	11.5	8.1	2.8
Acute tox. (first-line)	1.9	1.5	1.7
Acute tox. (salvage)	1.9	1.5	0.6
Second malignancy	3.1	3.6	3.2
Cardio-respiratory	1.2	0.9	0.9
Pulmonary	0.4	0.4	0.2
Other/unknown	3.8	3.0	2.1
All deaths	25	20	14

Engert et al; JCO 2009

How can we improve BEACOPP$_{escalated}$?

Early mortality	linked to dose-intensity and Kairos principle, not to a specific drug
sAML/MDS	cyclophosphamide, etoposide, **procarbazine**
Infertility	cyclophosphamide, **procarbazine**
Organ toxicity	**bleomycin**: lung, **vincristine**: PNP, **steroids**: infections

Chemotherapy of malignant lymphoma

- History and principles of chemotherapy
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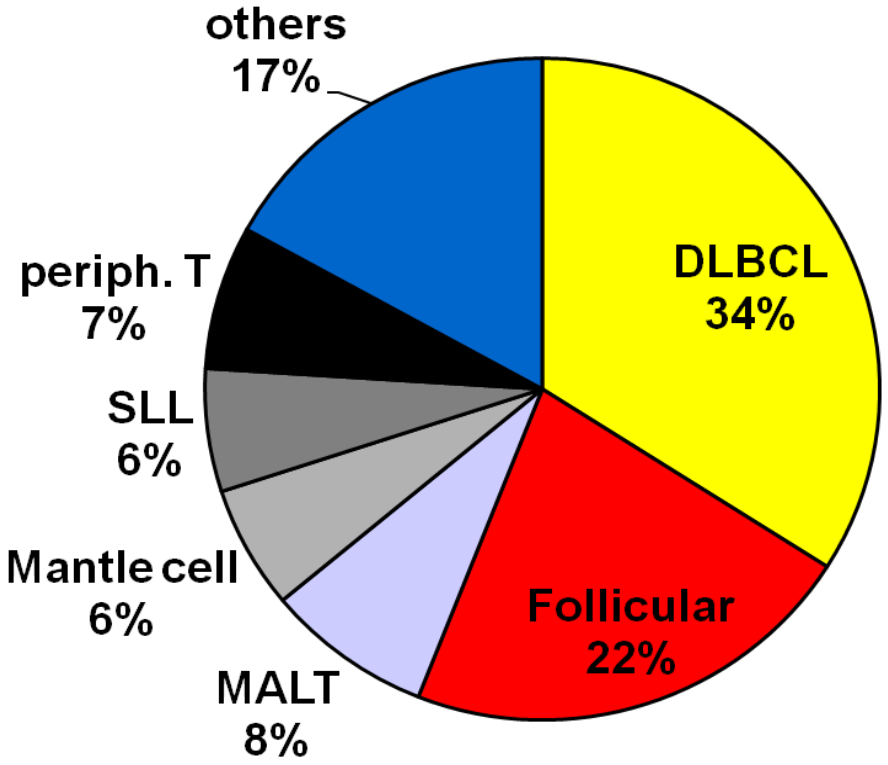
- Follicular lymphoma
- Summary

Non Hodgkin lymphoma

Subtypes



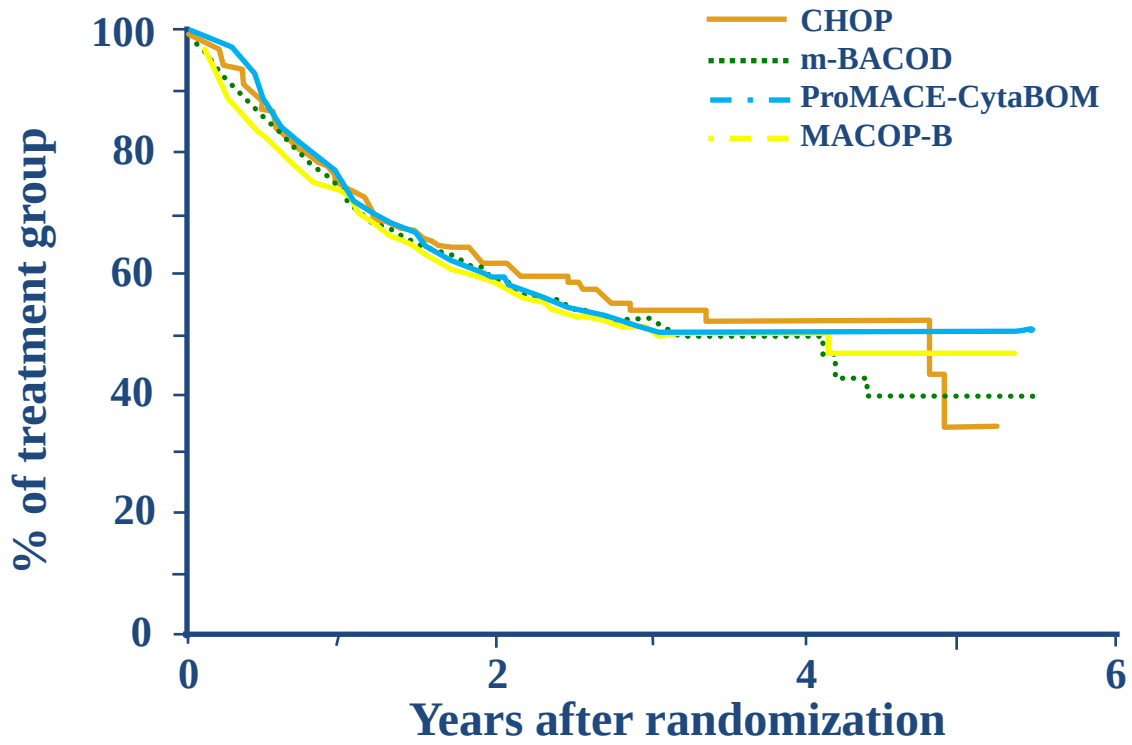
CHOP-21

Combination chemotherapy

(C)yclophosphamid
(H)ydroxydaunorubicin (Doxorubicin)
(O)ncovin®) (Vincristin)
(P)redniso(lo)n

Drug	Dose	Mode	Days
(C)yclophosphamid	750 mg/m^2	iv	1
(H)ydroxydaunorubicin (Doxorubicin)	50 mg/m^2	iv	1
(O)Ncovin® (Vincristin)	1,4 mg/m^2	iv	1
(P)redniso(lo)n	100 mg/m^2	po	1 - 5

SWOG: CHOP *vs* 3 intensive regimens in advanced NHL

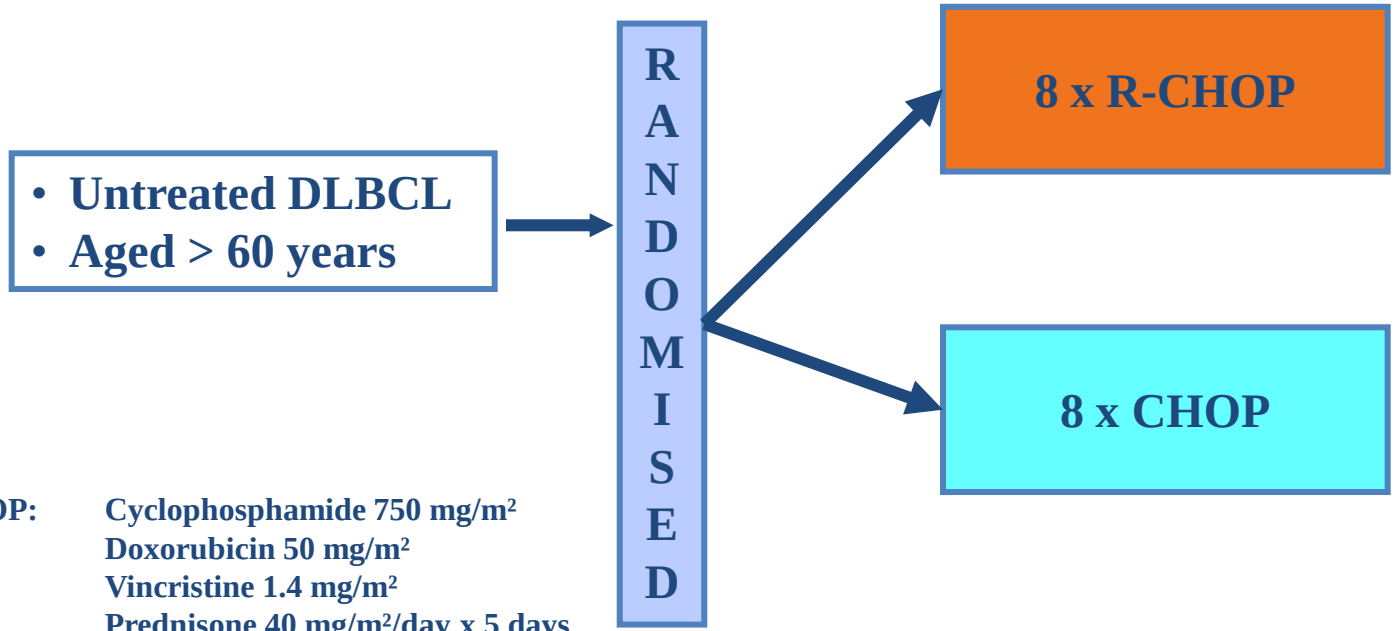


Patients at risk	3-year estimate (%)
225	54
223	52
233	50
218	50

$p = 0.90$

Fischer *et al.* *NEJM* 1993; 328: 1002–6

GELA LNH-98.5: Trial design



CHOP: Cyclophosphamide 750 mg/m²
Doxorubicin 50 mg/m²
Vincristine 1.4 mg/m²
Prednisone 40 mg/m²/day x 5 days

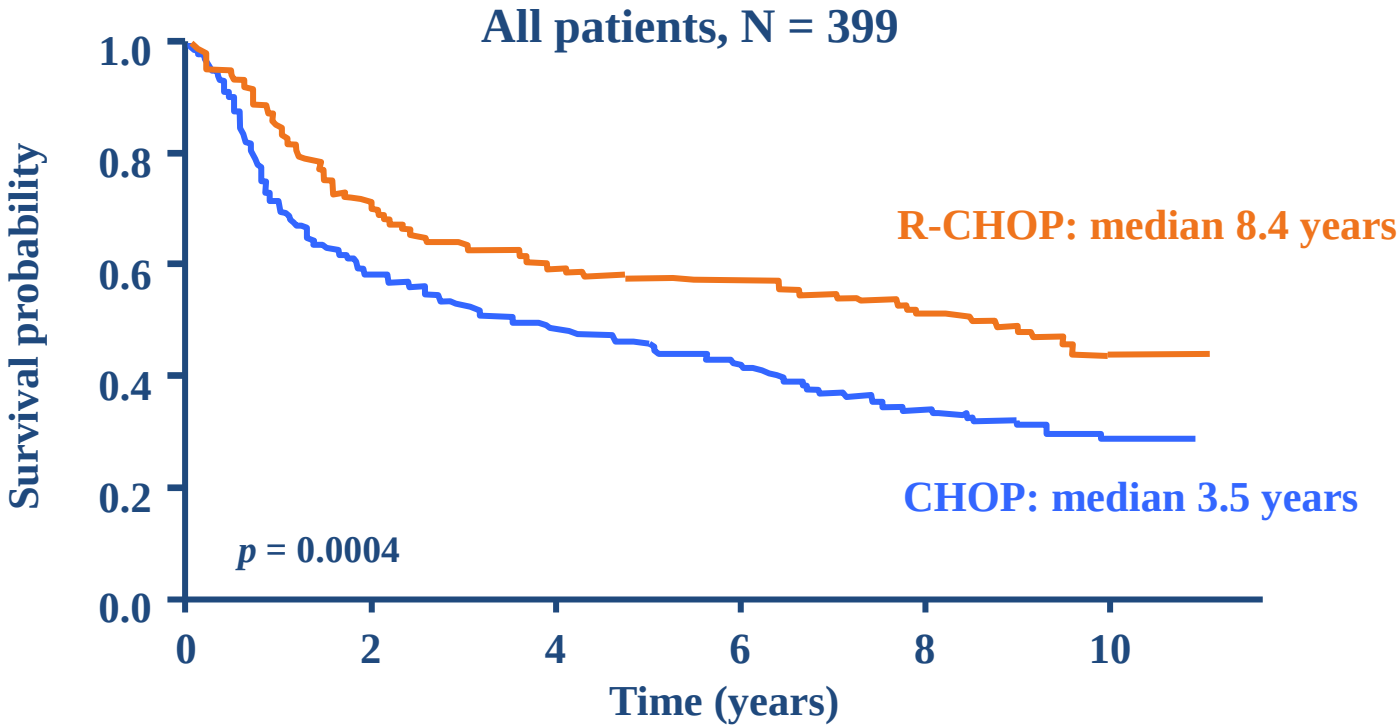
R-CHOP: Rituximab 375 mg/m² Day 1 of each cycle

Cycles every 21 days

Coiffier B, *et al. Blood* 2010; 116:2040–2045.

GELA LNH-98.5 10-year follow-up

Overall survival

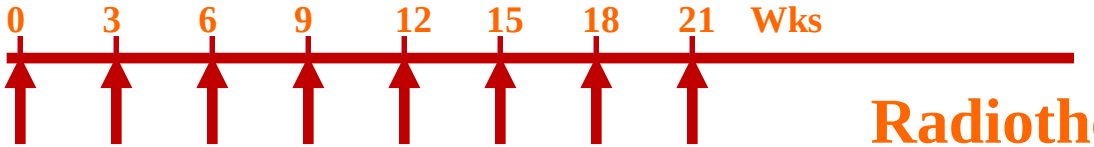


Coiffier B, *et al. Blood* 2010; 116:2040–2045.

Standard Regimen for DLBCL Patients

R-CHOP

R-CHOP 21



Radiotherapy?

Aggressive NHL:
Prognostic factors - aaIPI

- Poor performance status (ECOG 2-4)
- Elevated lactate dehydrogenase (LDH)
- Stage III or IV disease

- **Risk groups:**
- 0 : low risk
- 1 : low-intermediate
- 2 : high-intermediate
- 3 : high risk

The International Non-Hodgkin's Lymphoma Prognostic Factors Project
N Engl J Med 1993; 329:987–994.

Results with R-CHOP in DLBCL

- **5-year survival according to aaIPI & age**
  - **aaIPI score = 0: >85%**
  - **Young, aaIPI score = 1: >80%**
  - **Young, aaIPI score >1: 60%**
  - **Elderly, aaIPI score >0: 50%**
  - **Very old: 30%**
- **For 30-40% of patients, R-CHOP is not satisfactory**

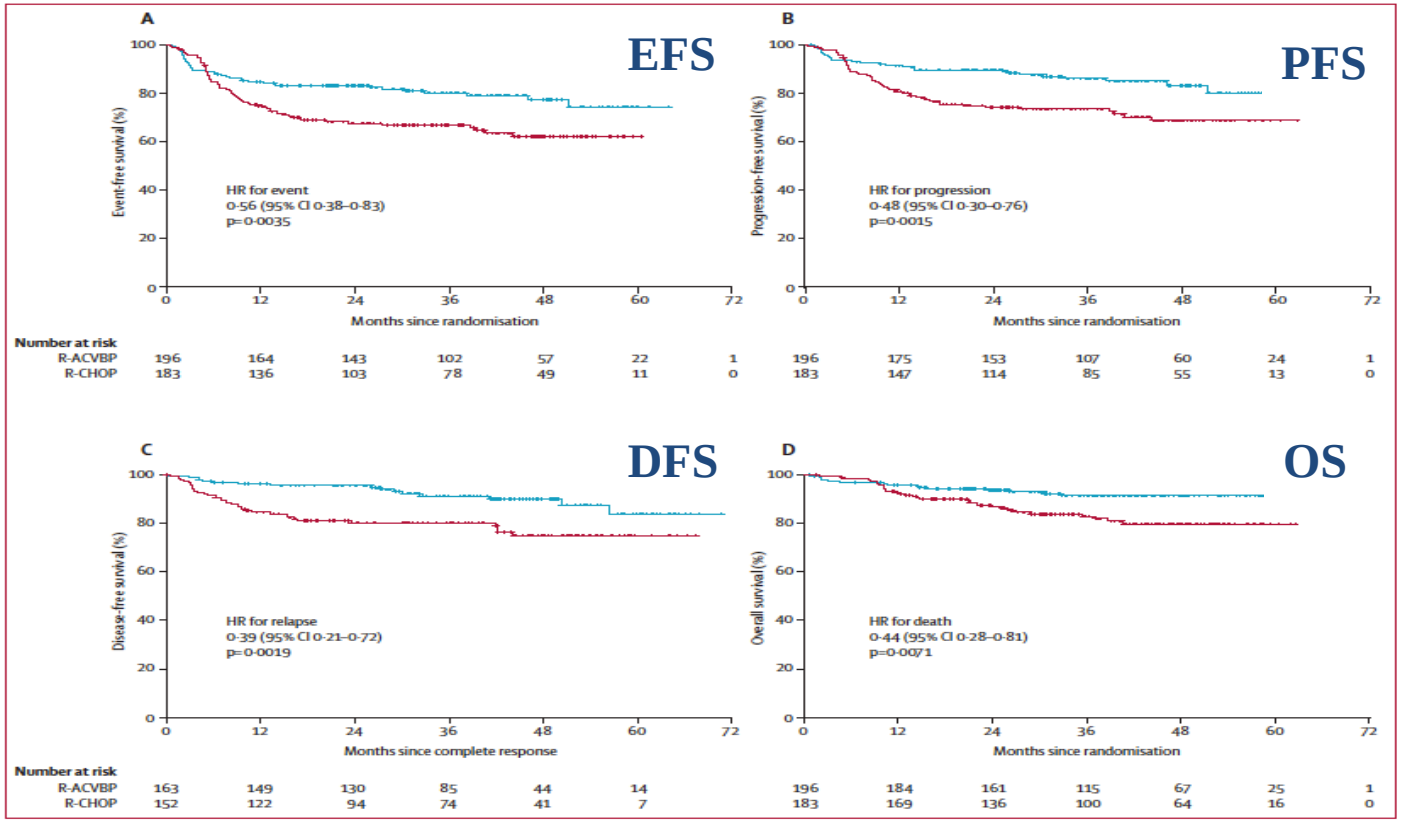
How to further improve DLBCL

- Refractory
  - Use new drugs
  - Subgroup of patients with high risk
- Relapse
  - Higher dose chemotherapy
  - Prevent relapse
- At time of relapse
  - Better salvage regimens

DLBCL: Higher dose regimen

LNH03-2B study

R-ACVBP
R-CHOP



C Rechert et al. Lancet 2011;378:1858

DLBCL: Salvage therapy

- No good regimen
  - R-DHAP, R-ICE, R-ESHAP, R-GDP
  - All identical, few CR, particularly for early relapses
- Necessity to design a New Regimen
  - With all/some new drugs
  - Plus rituximab or another antibody
  - Plus chemotherapy
- Before autologous transplant

DLBCL: Conclusions

- **Medical need: new combinations for poor risk patients**
  - **If possible to identify them**
- **Particularly for refractory/early relapse**
- **New drugs combination at time of relapse**
- **Look at cure**

Chemotherapy of malignant lymphoma

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- Diffuse large B-cell lymphoma (DLBCL)
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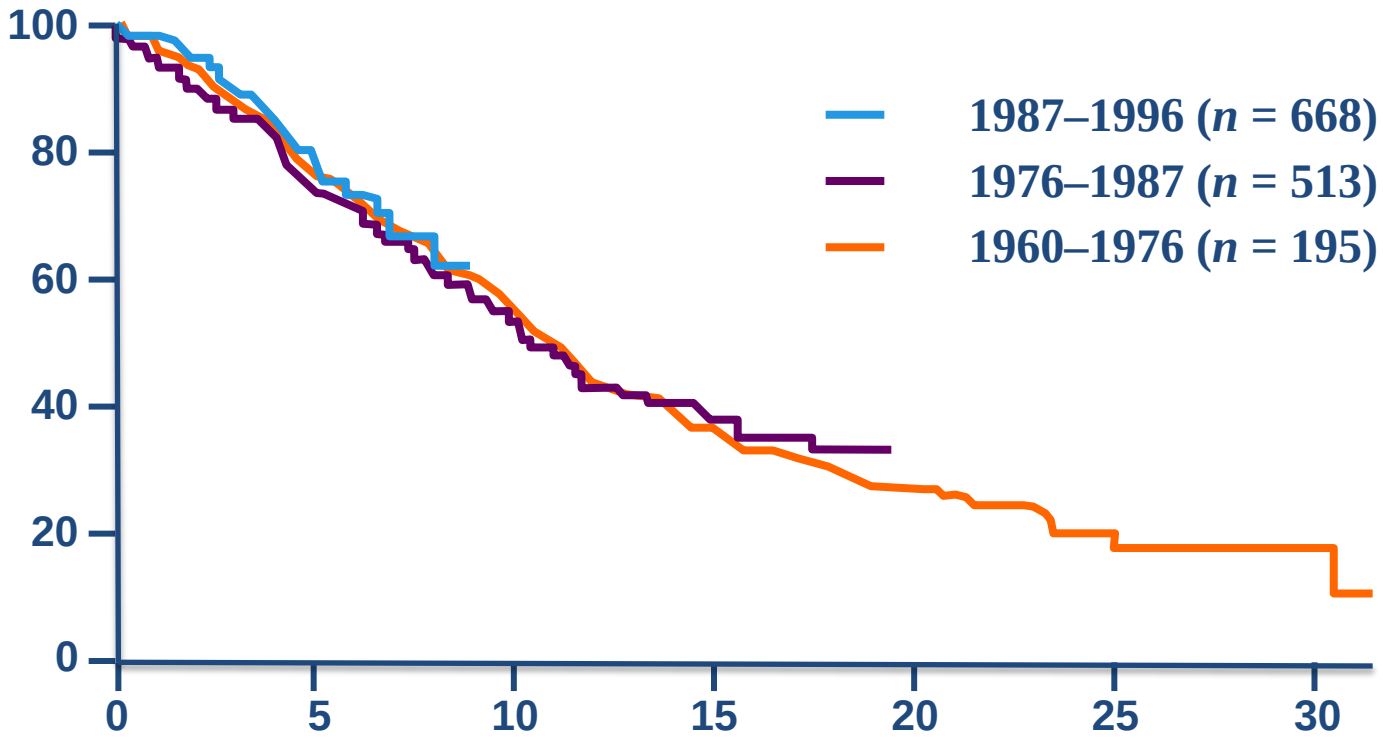
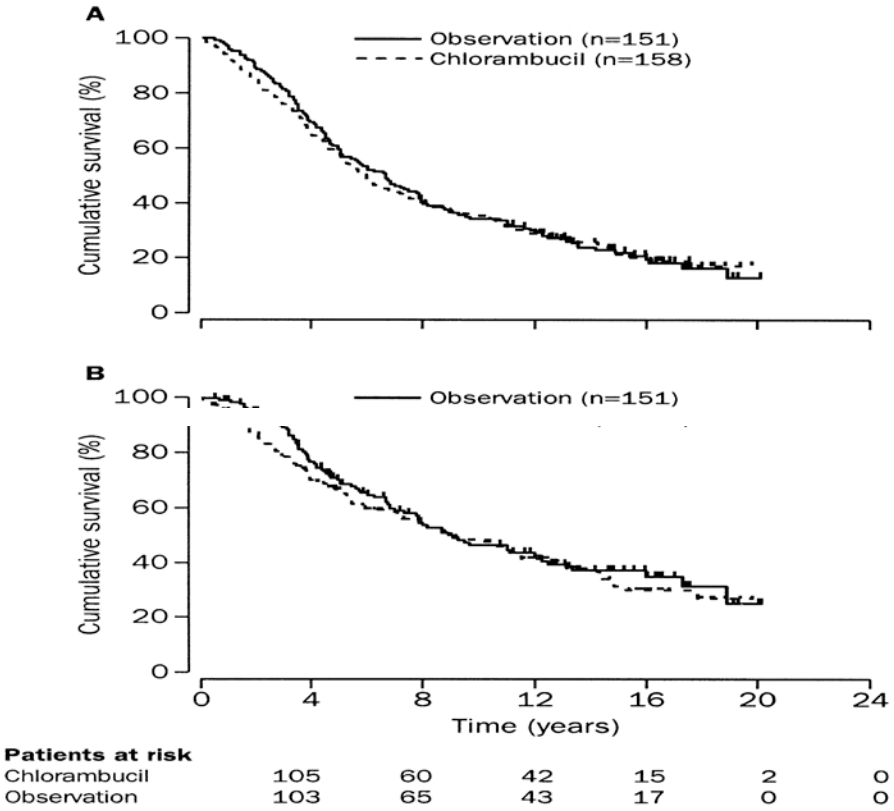
- Summary

Indolent NHL – Overall Survival



Horning. *Semin Oncol*. 1993; 20(suppl 5): 75–88

FL: Watch & wait or early treatment?



Overall survival

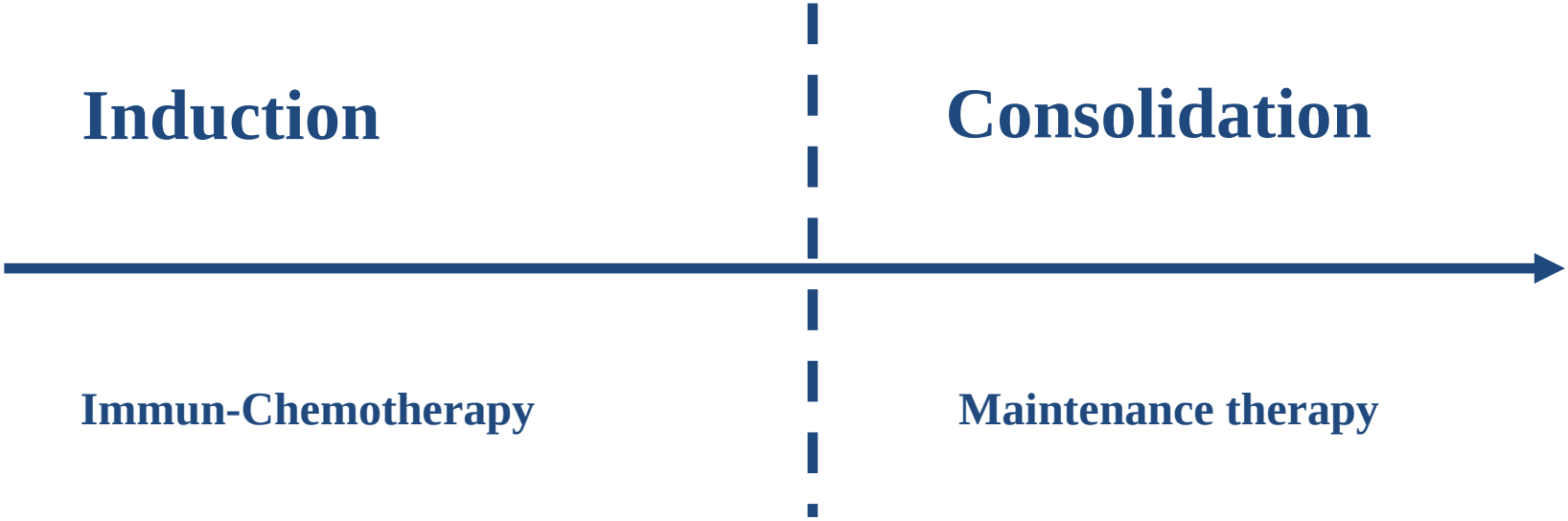
Disease-associated survival

Ardeshna KM et al. Lancet 262: 516, 2003

FL: Reasons to initiate treatment

- **B-symptoms**
- **Hematopoietic failure**
  (Hb<11g/dl, granulocytes <1.500/µl, platelets <100.000 /µl)
- **Large tumor burden**
  (3 areas >5 cm or 1 area >7.5 cm)
- **Rapid progression**
  (increase of tumor mass >50% within 6 months)
- **Complications due to disease**
  (pain, infarction of spleen, hyperviscosity syndrome, etc.)
- **No role for FLIPI, LDH, B2M, age, stage, or bone marrow involvement**

Treatment strategies in indolent lymphomas



Standard of care in pts with indolent lymphomas

- Still a role for watch & wait in asymptomatic pts
- Wait for indication of treatment
- Combined R-chemo standard; R-CHOP most often used
- No clear superiority of R-CHOP over R-CVP
- BR with longer PFS and lower toxicity
- R-chemo plus R-maintenance current best option in follicular particularly in relapsed disease
- No relevant role for high-dose chemo and ASCT
- Perspectives: Bortezomib, Lenalidomide, Obinutuzumab (GA101), Ofatumumab, Temsirolimus, Ibrutinib, Idelalisib, ABT-199

Chemotherapy of malignant lymphoma

- History and principles of chemotherapy
- Hodgkin lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma
- Summary

Chemotherapy of malignant lymphoma

- **Development of multi-agent chemo led to cure in lymphoma patients**
- **Most frequently used today are CHOP, ABVD and BEACOPP**
- **Typical side effects include alopecia, aplasia, infection, neuropathy, fatigue and infertility**
- **Major long-term effects are 2nd neoplasia and organ failure**
- **Prognosis of pts much worse at relapse (DLBCL, HL)**
- **New less toxic drugs have become available and might improve the long-term prognosis**

ESTRO School

WWW.ESTRO.ORG/SCHOOL

Immunotherapy of malignant lymphoma

Andreas Engert, MD

Chairman, German Hodgkin Study Group
University Hospital of Cologne

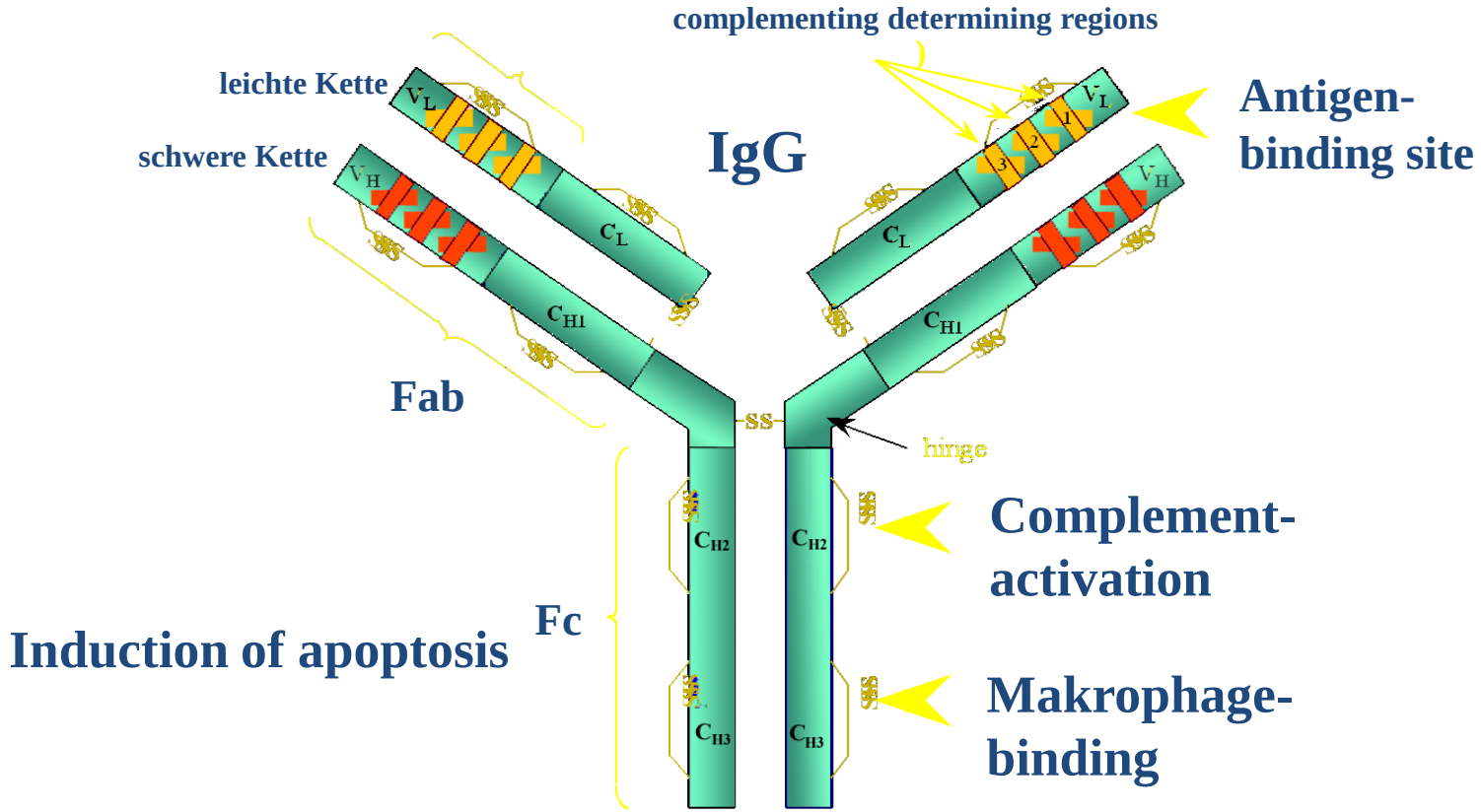
Rationale for immunotherapy of malignant lymphoma

- Long term side effects of chemo- and radiotherapy
- Poor prognosis of patients with relapse or refractory disease
- Small amount of malignant cells (Hodgkin)
- Residual dormant cells lead to relapse
- Good target antigens (CD20, CD30, others)
- Lymphoma well vascularized

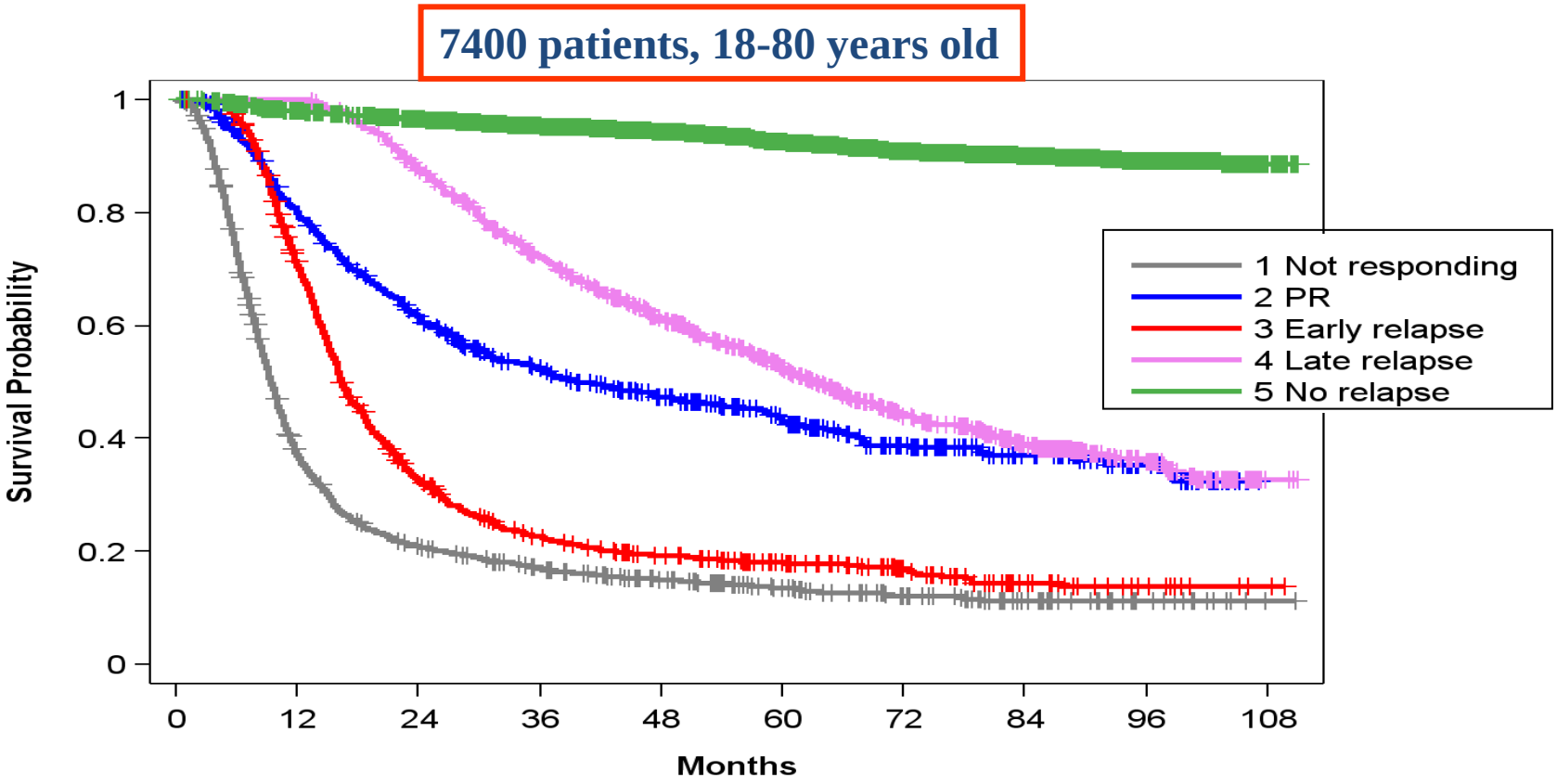
Immunotherapy of malignant lymphoma

- **Diffuse large B-cell lymphoma (DLBCL)**
- **Follicular lymphoma**
- **Hodgkin lymphoma**
- **Summary**

Structure of a monoclonal Antibody



DLBCL in Gela trails: OS



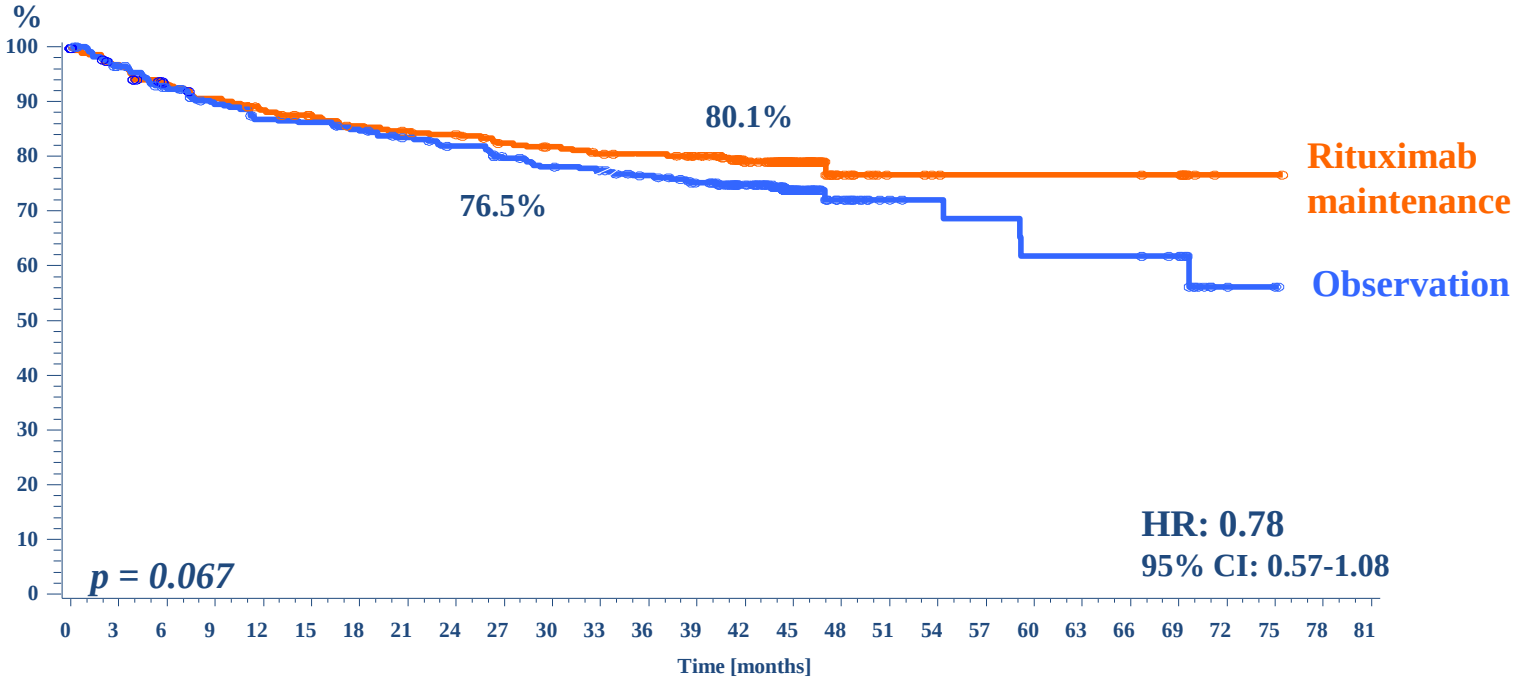
R-CHOP + X

- **RA-CHOP: stopped due to Avastin tox**
- **R2-CHOP: lenalidomide (phase II, not better)**
- **R-CHOP + bortezomib**
- **R-CHOP + enzastaurin**
- **R-CHOP + ibrutinib**
- **R-CHOP + idelalisib**
- **R-CHOP + ABT-199**

Maintenance in DLBCL

- **Rituximab**
  - **3 studies → No benefit**
- **Enzastaurin**
  - **2 studies → No benefit**
- **Lenalidomide**
  - **2 studies → Possible benefit**

Event Free Survival by Treatment Arm
(ITT population; N=683)

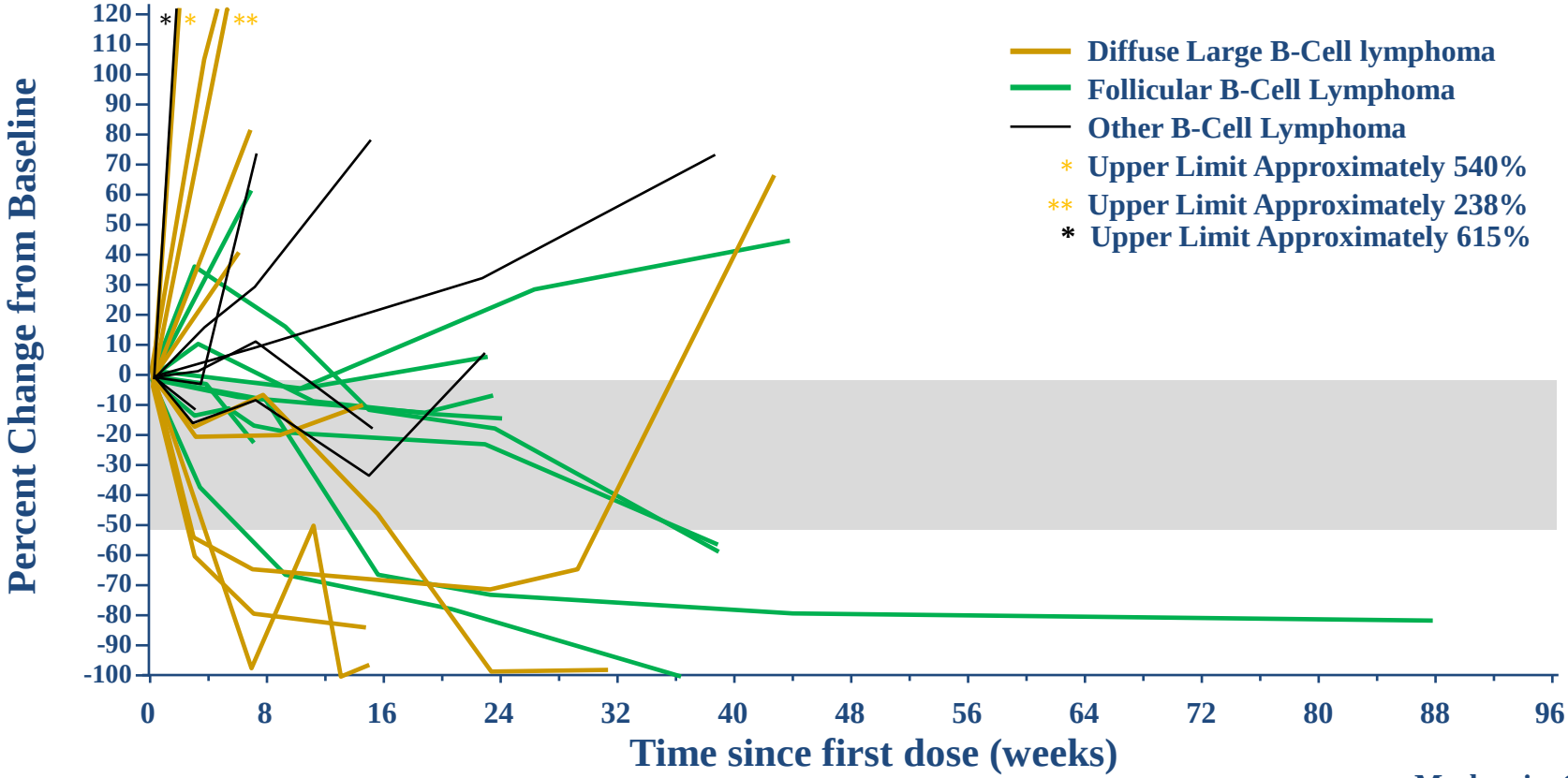


N at risk														
Rituximab	338	302	283	269	261	249	242	204	23	13	12	12	1	0
Observation	342	308	283	275	261	245	234	198	34	20	18	17	3	0

U Yäger et al. ICML 2013

Nivolumab in clinical trials

All B-Cell Lymphoma Patient Responses



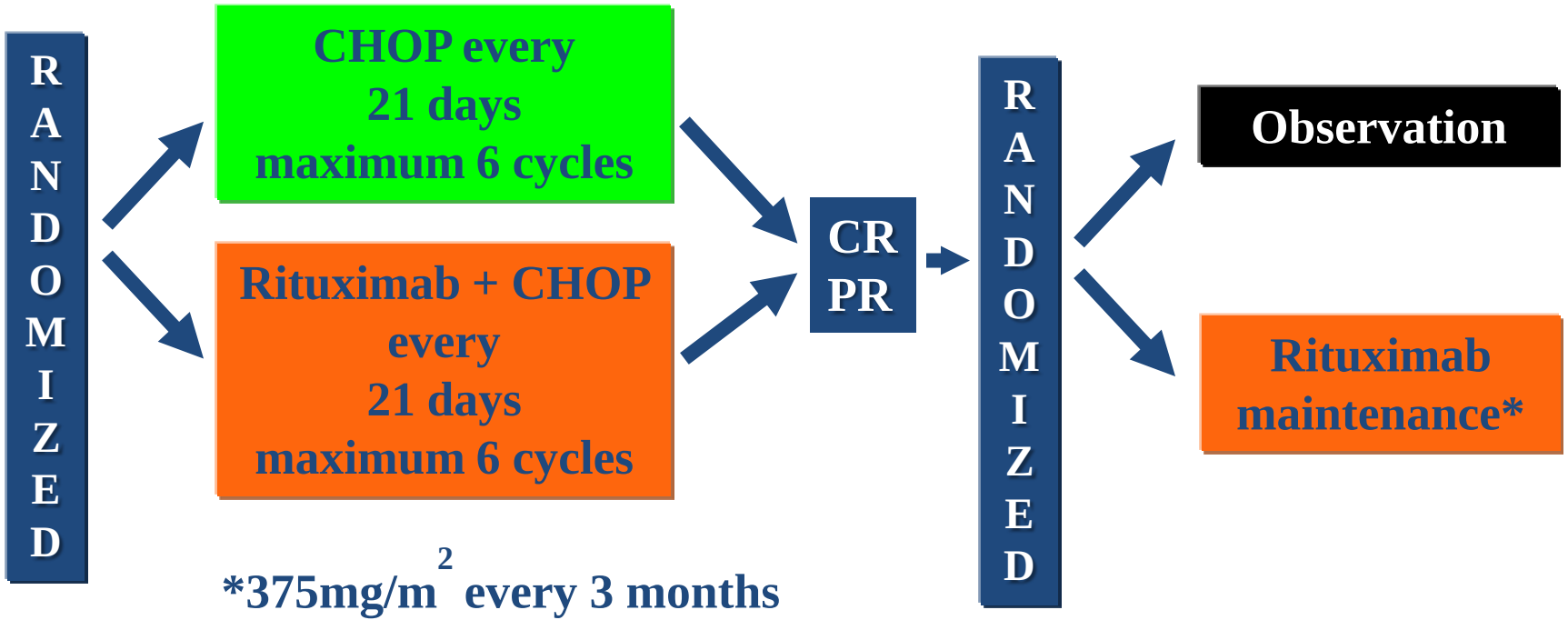
Moskowitz C, ASH 2014

Immunotherapy of malignant lymphoma

- **Diffuse large B-cell lymphoma (DLBCL)**
- **Follicular lymphoma**
- **Hodgkin lymphoma**
- **Summary**

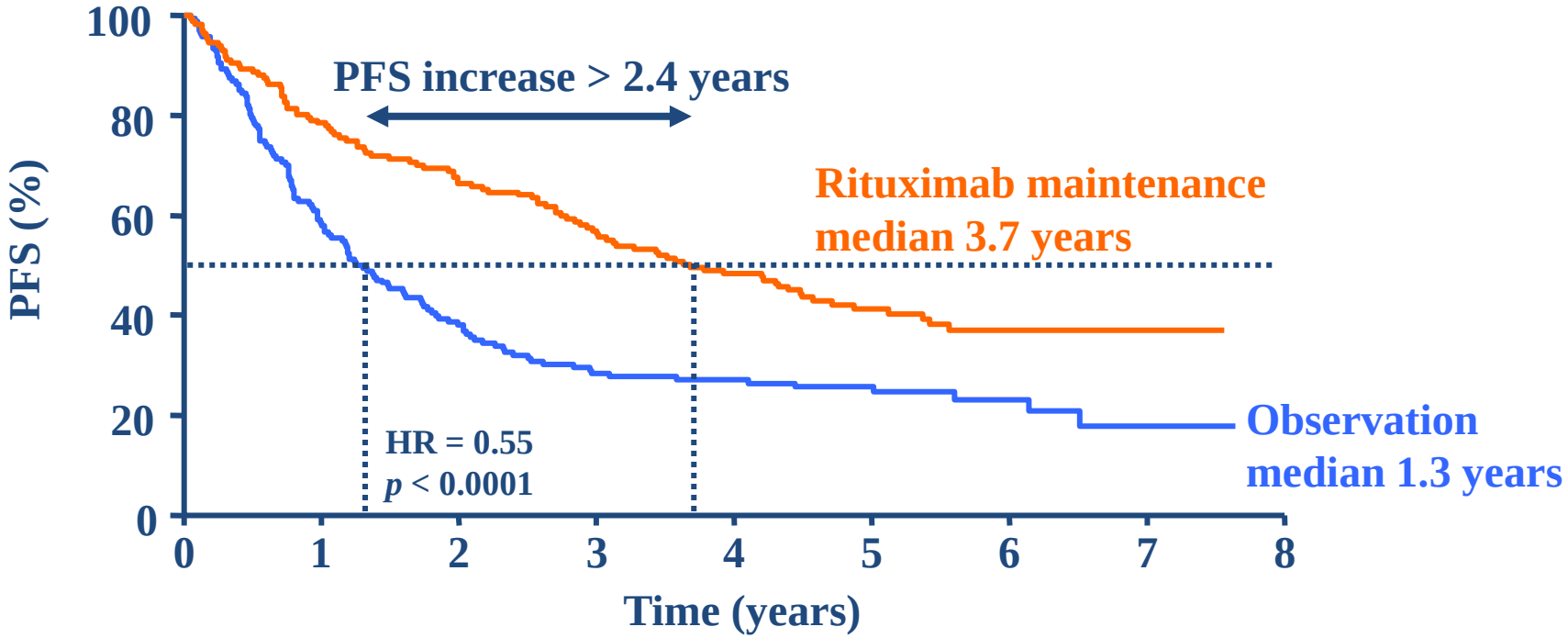
EORTC 20981:

Rituximab maintenance vs observation in relapsed FL



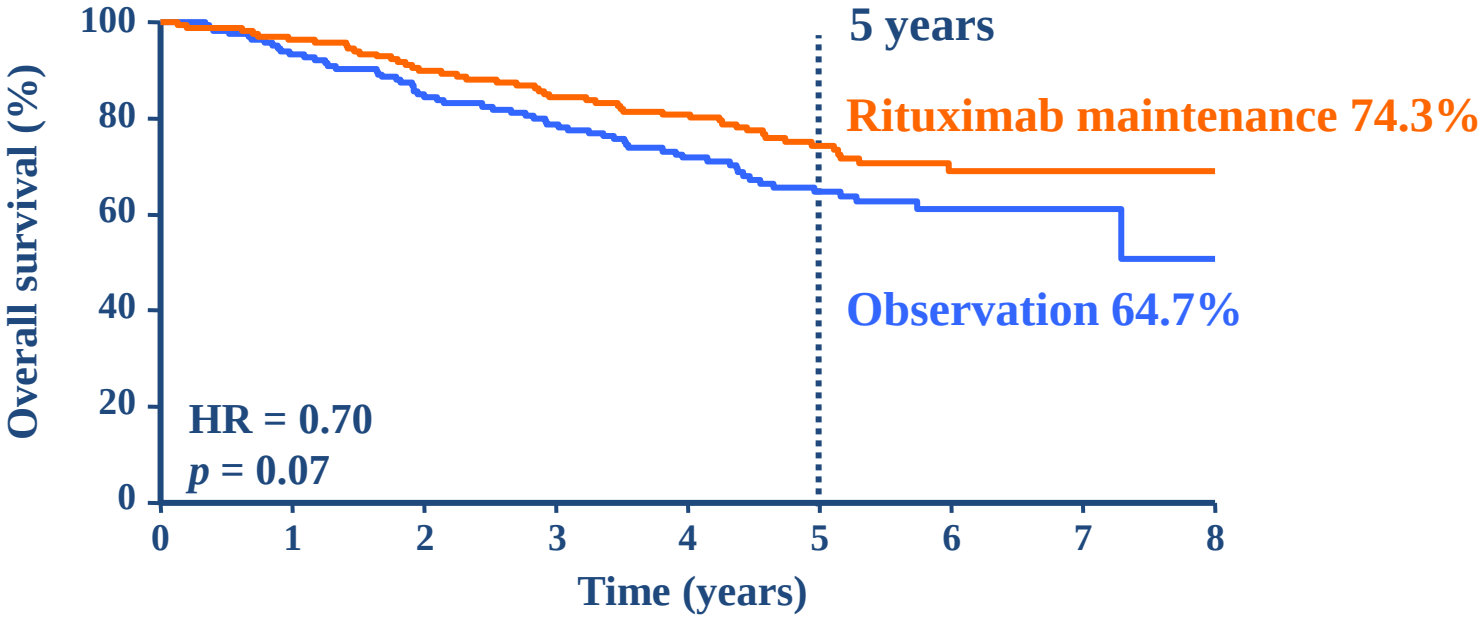
van Oers MHJ, et al. JCO 2010; 28:2853–2858

Rituximab maintenance vs observation
in relapsed FL (EORTC 20981): PFS



van Oers MHJ, et al. J Clin Oncol 2010; 28:2853–2858.

Rituximab maintenance vs observation in relapsed FL (EORTC 20981): Overall survival



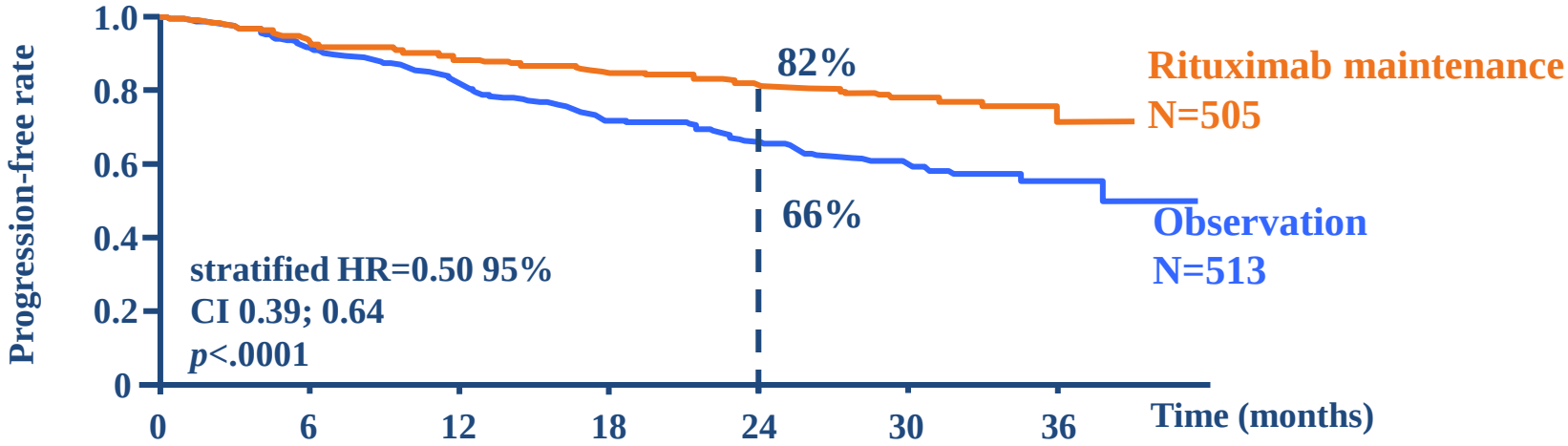
Number of patients at risk

167	161	150	141	124	86	44	13
167	155	139	128	104	67	28	9

van Oers MHJ, et al. J Clin Oncol 2010; 28:2853–2858.

PRIMA: Progression-free survival

Rituximab maintenance significantly reduced the risk of progression by 50%

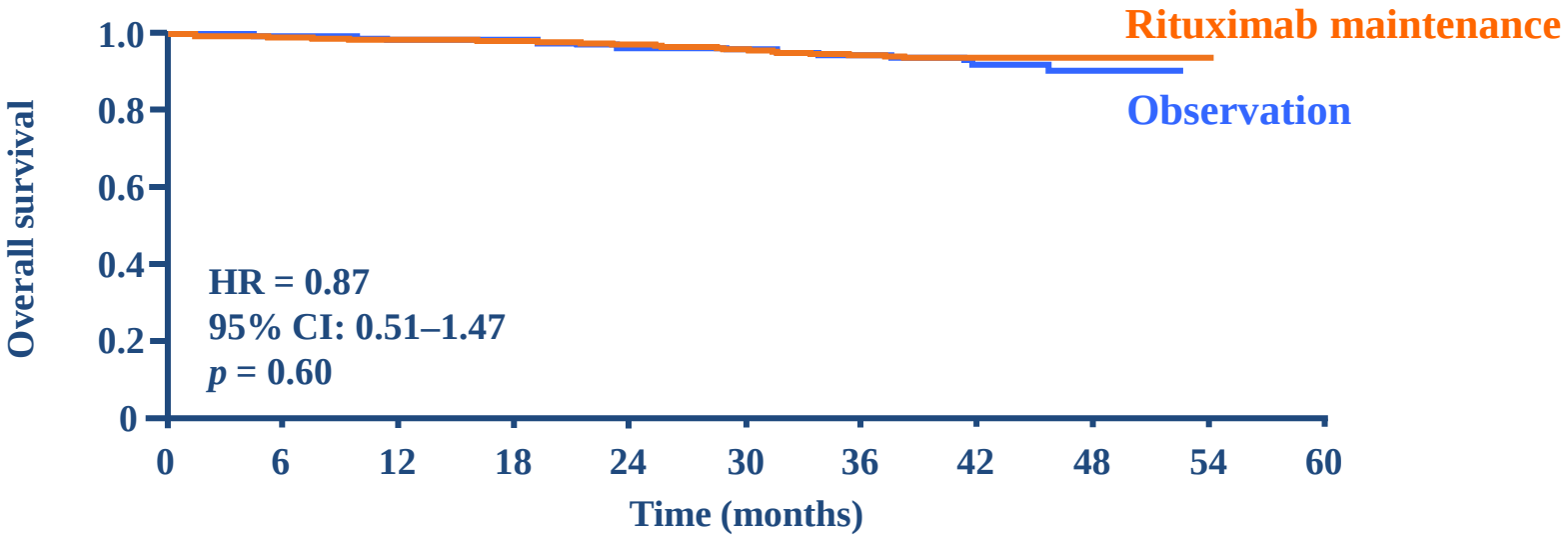


Patients at risk

505	472	443	336	230	103	18
513	469	411	289	195	82	15

Salles G, et al. Lancet 2011; 377:42–51

PRIMA: Overall survival

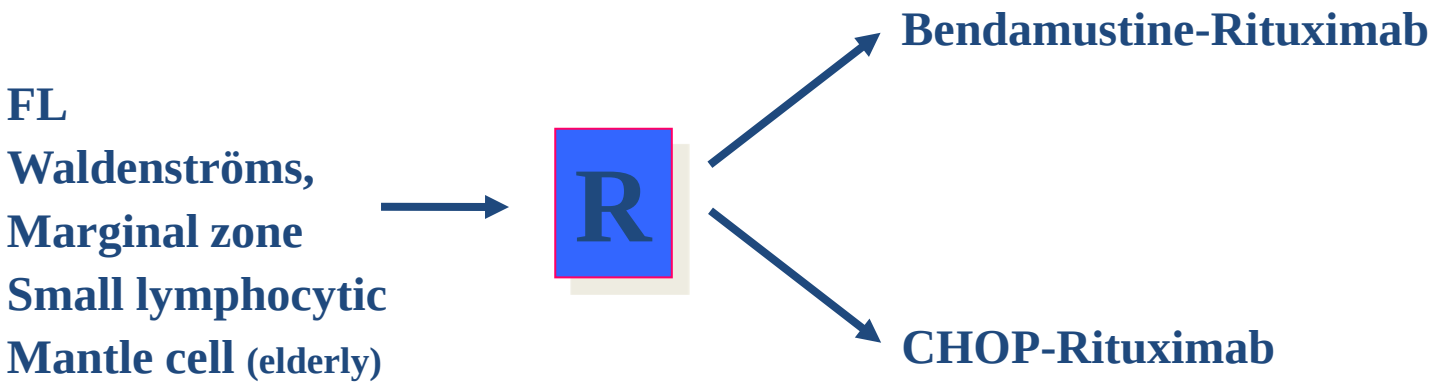


Rituximab	505	499	492	483	474	365	246	108	22	1	–
Observation	513	507	501	492	472	381	243	97	26	0	–

Salles G, et al. Lancet 2011; 377:42–51.

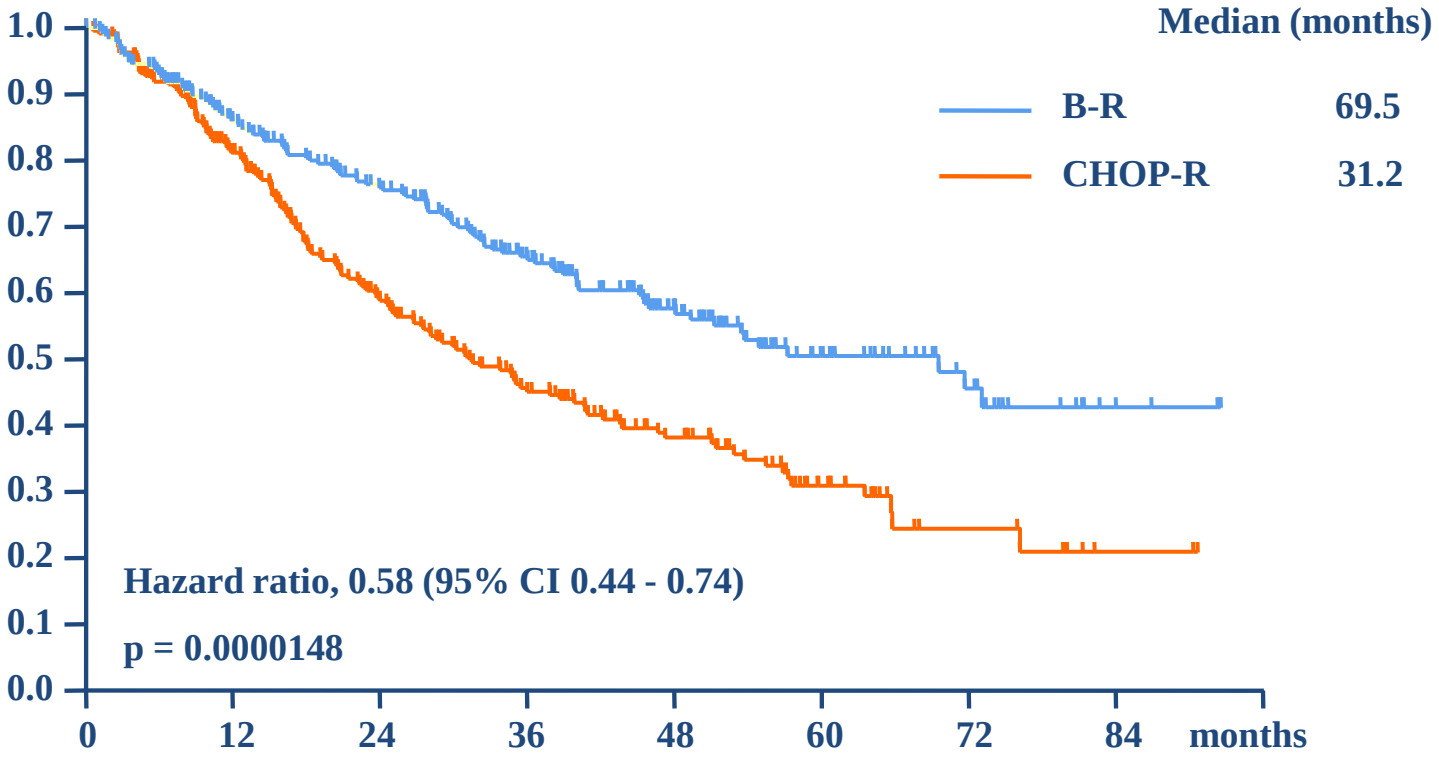
Bendamustine-Rituximab (B-R) vs CHOP-R

StiL NHL 1-2003



Bendamustine 90 mg/m^2 day 1+2 + R day 1, max 6 cycles, q 4 wks. CHOP-R, max 6 cycles, q 3 wks.

BR vs CHOP-R (PFS; 45 months)



Lancet 2013; 381: 1203–10

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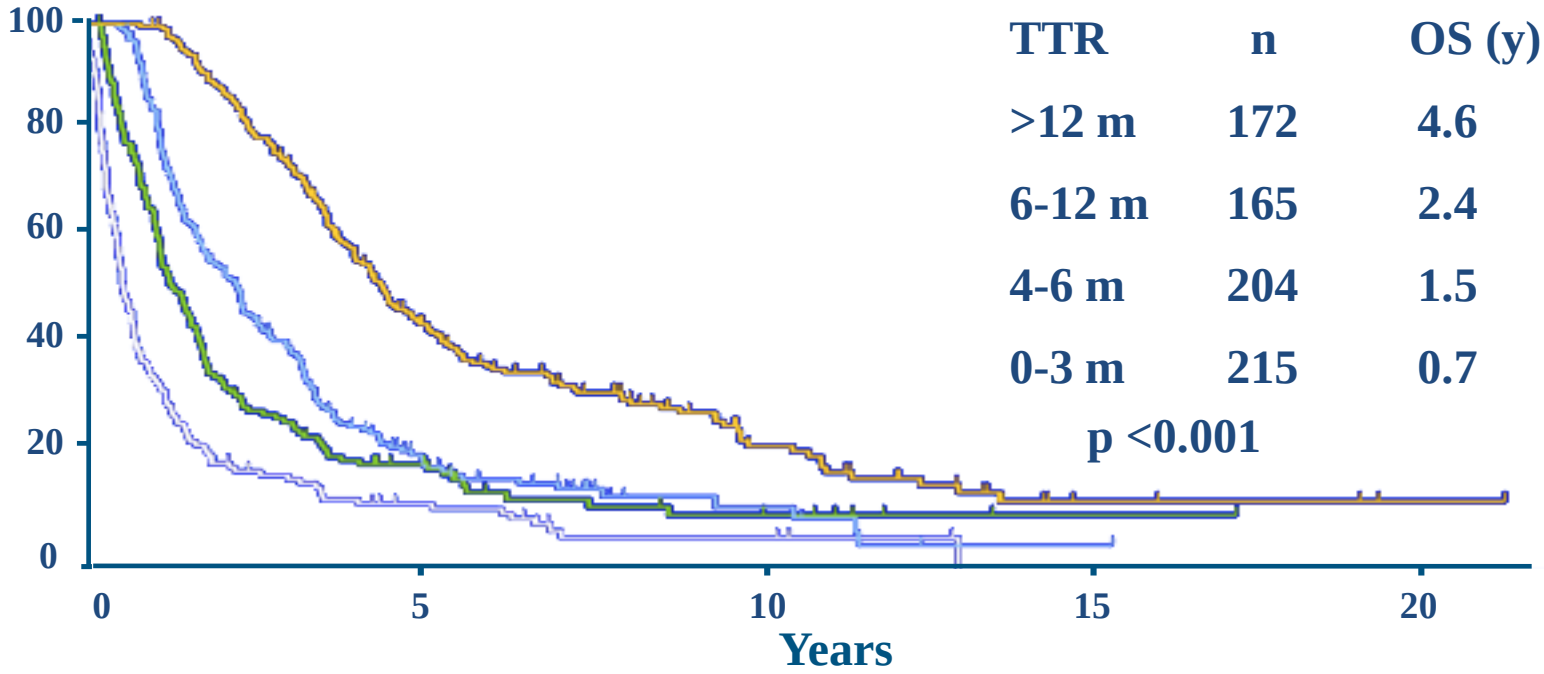
- R-Benda with longer PFS and lower toxicity
- No clear superiority of R-CHOP over R-CVP
- R-chemo plus R-maintenance current best option in follicular, particularly in relapsed disease
- High-dose chemo and ASCT in r&r or transformed pts
- Perspectives: Bortezomib, Lenalidomide, Obinutuzumab (GA101), Ofatumumab, Temsirolimus, Ibrutinib, Idelalisib, ABT-199

Immunotherapy of malignant lymphoma

- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma
- Hodgkin lymphoma
- Summary

Relapse After Auto-TX

OS by time to relapse after TX (n=756)

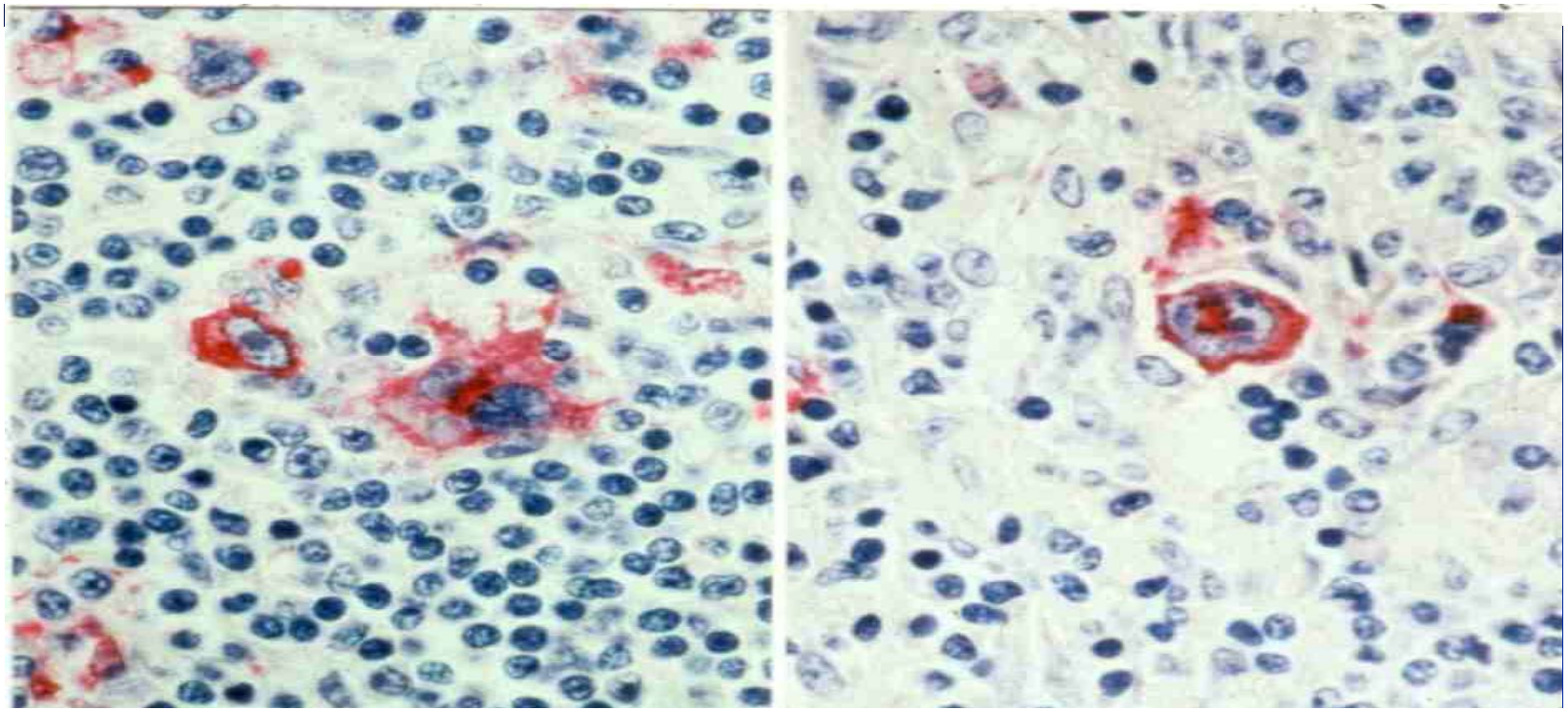


TTR	n	OS (y)
>12 m	172	4.6
6-12 m	165	2.4
4-6 m	204	1.5
0-3 m	215	0.7

p <0.001

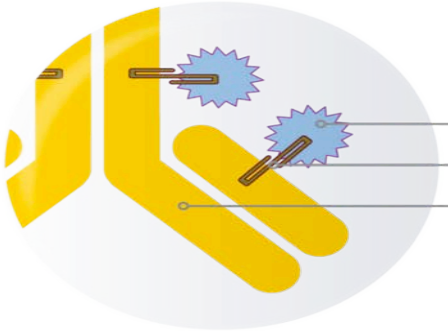
Arai et al. Leukemia & Lymphoma 2013

Hodgkin Lymphoma
Immunohistology



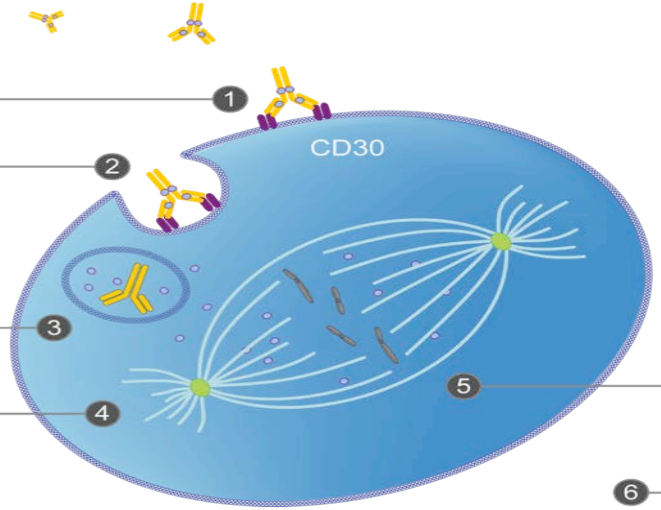
Brentuximab Vedotin (SGN-35)

Mechanism of action



Brentuximab vedotin (SGN-35) ADC

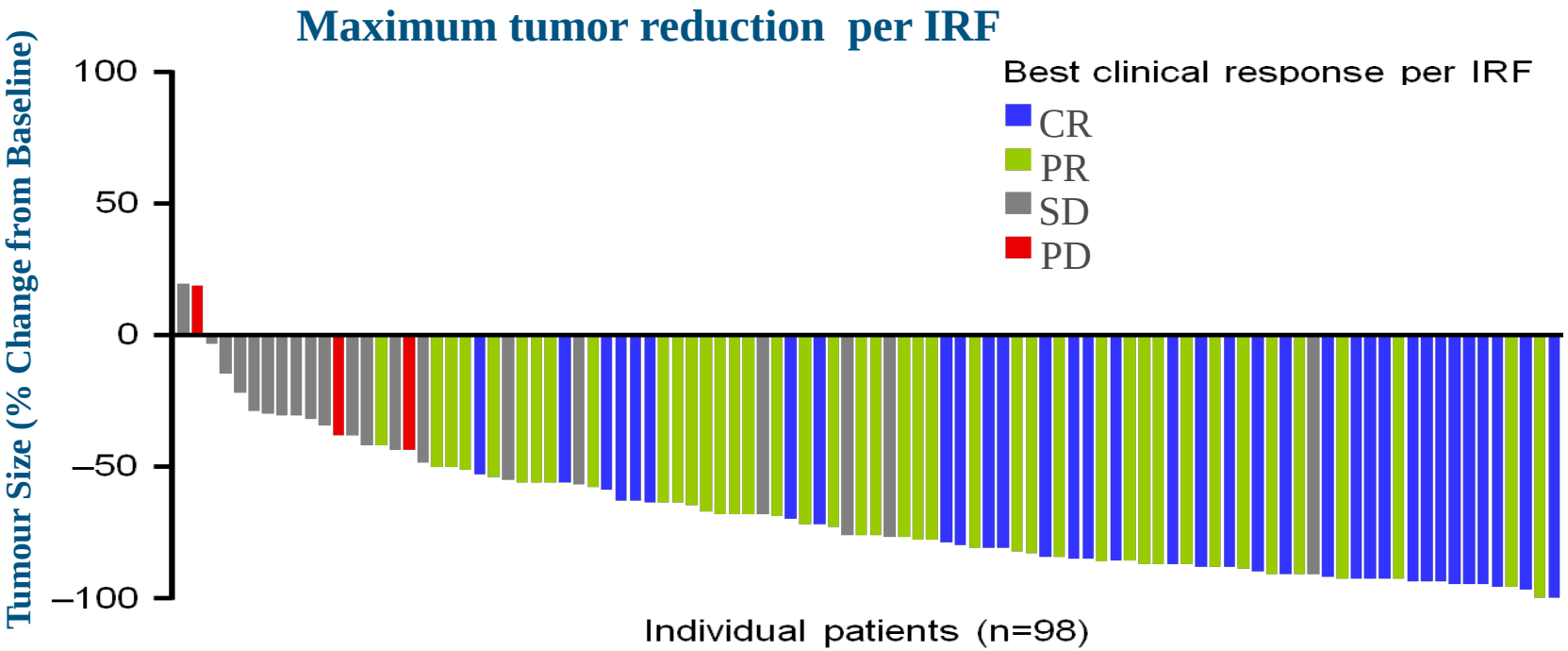
- monomethyl auristatin E (MMAE), potent antitubulin agent
- protease-cleavable linker
- anti-CD30 monoclonal antibody



1. ADC binds to CD30
2. ADC-CD30 complex traffics to lysosome
3. MMAE is released
4. MMAE disrupts Microtubule network
5. G2/M cell cycle arrest
6. Apoptosis

Phase II Pivotal Study of BV

Patients with R/R HL post ASCT



Younes A et al, J Clin Oncol 2012;30: 2183-2189.

Phase II Pivotal Study of BV

Safety (AEs in ≥20% of pts)

Adverse event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Peripheral sensory neuropathy	47	9	0
Fatigue	46	2	0
Nausea	42	0	0
Upper respiratory tract infection	37	0	0
Diarrhoea	36	1	0
Pyrexia	29	2	0
Neutropenia	22	14	6
Vomiting	22	0	0
Cough	21	0	0

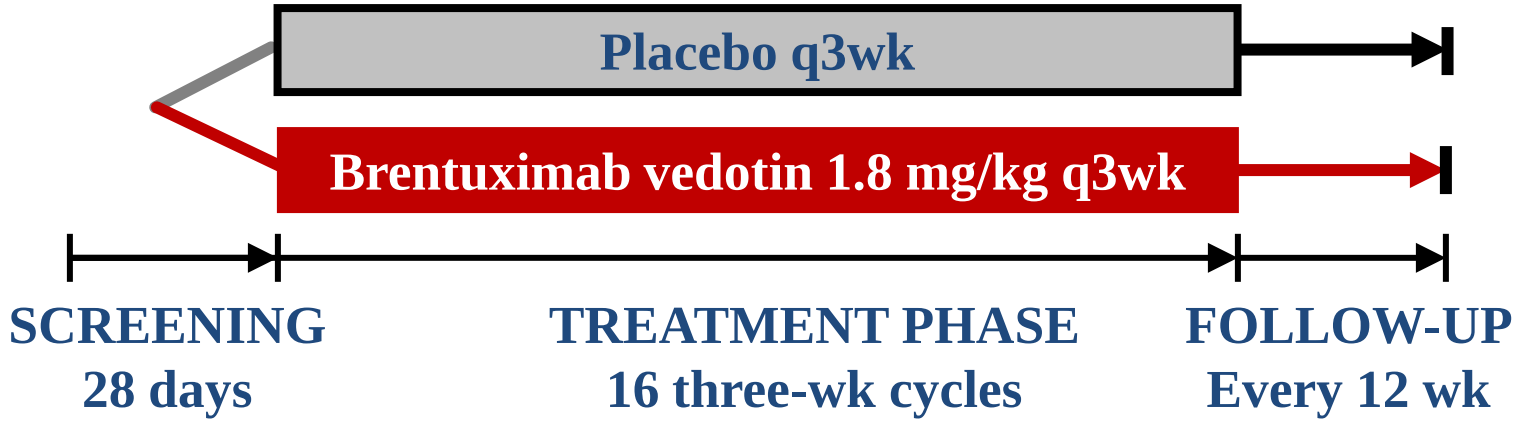
BV – brentuximab vedotin; AEs – adverse events; pts – patients

Adapted from Chen R et al. ASH 2012, abstract A3689

Random. Phase III (AETHERA)

BV in HL pts

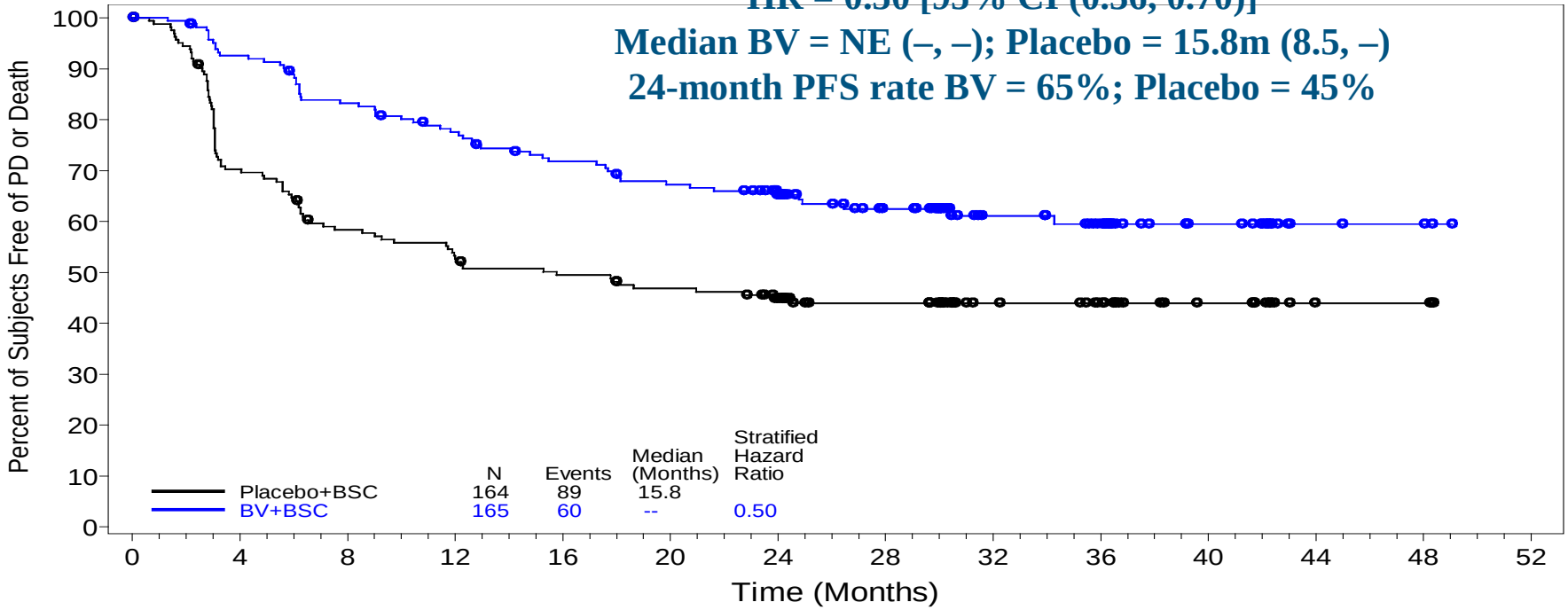
N = 322 HL post ASCT
high risk (no CR, r/r <12 mo, ex-nodal)



Assessments: 3, 6, 9, 12, 18, 24 mo, then every 6 mo
Follow-up: every 12 wk until death

AETHERA

PFS per Investigator

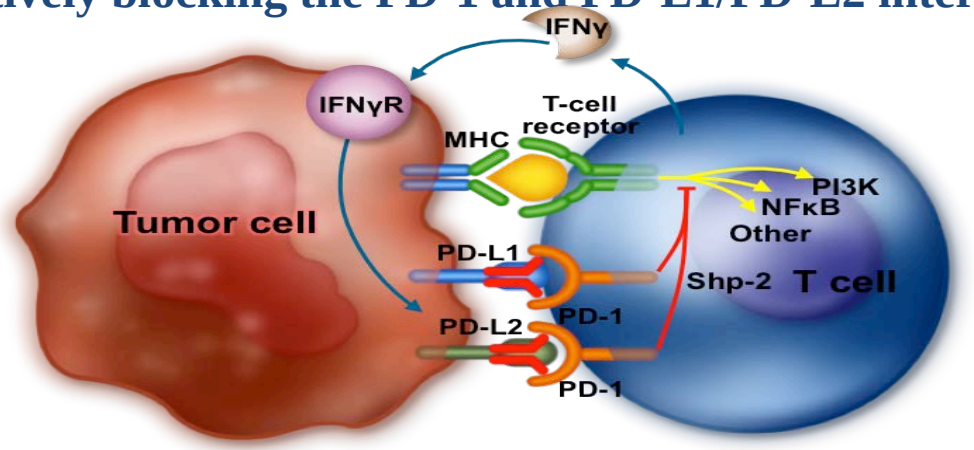


N at Risk (Events)

Pla+BSC	164 (0)	113 (48)	92 (67)	83 (76)	77 (81)	71 (85)	61 (88)	45 (89)	28 (89)	23 (89)	13 (89)	3 (89)	3 (89)	0 (89)
BV+BSC	165 (0)	149 (12)	133 (27)	122 (36)	111 (45)	103 (52)	90 (55)	62 (58)	40 (59)	33 (60)	16 (60)	4 (60)	3 (60)	0 (60)

PD-1 Blockade

- PD-1 engagement by its ligands results in transient down-regulation of T-cell function (T-cell exhaustion).
- Nivolumab (BMS) and Pembrolizumab (MSD) fully human/humanized anti-PD-1 antibody selectively blocking the PD-1 and PD-L1/PD-L2 interaction.

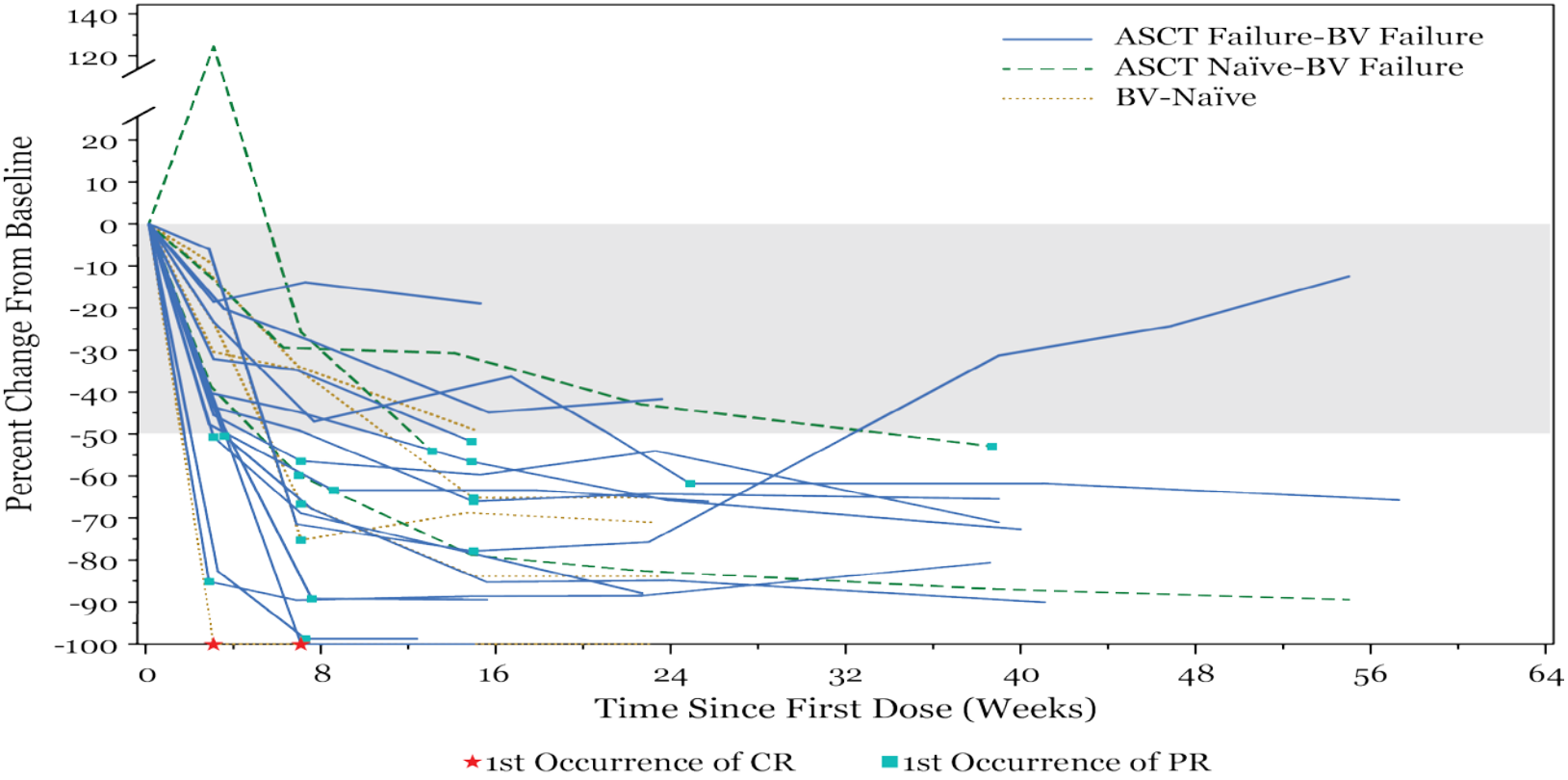


- PD-1 blockade through monoclonal antibody therapy has single-agent activity in a range of solid tumors

Brahmer et al, NEJM 2012;366:2455. Topalian et al, NEJM 2012;366:2443-54

Nivolumab Phase I in r&r HL

Response Kinetics



Armand P, ASH 2014

Immunotherapy of malignant lymphoma

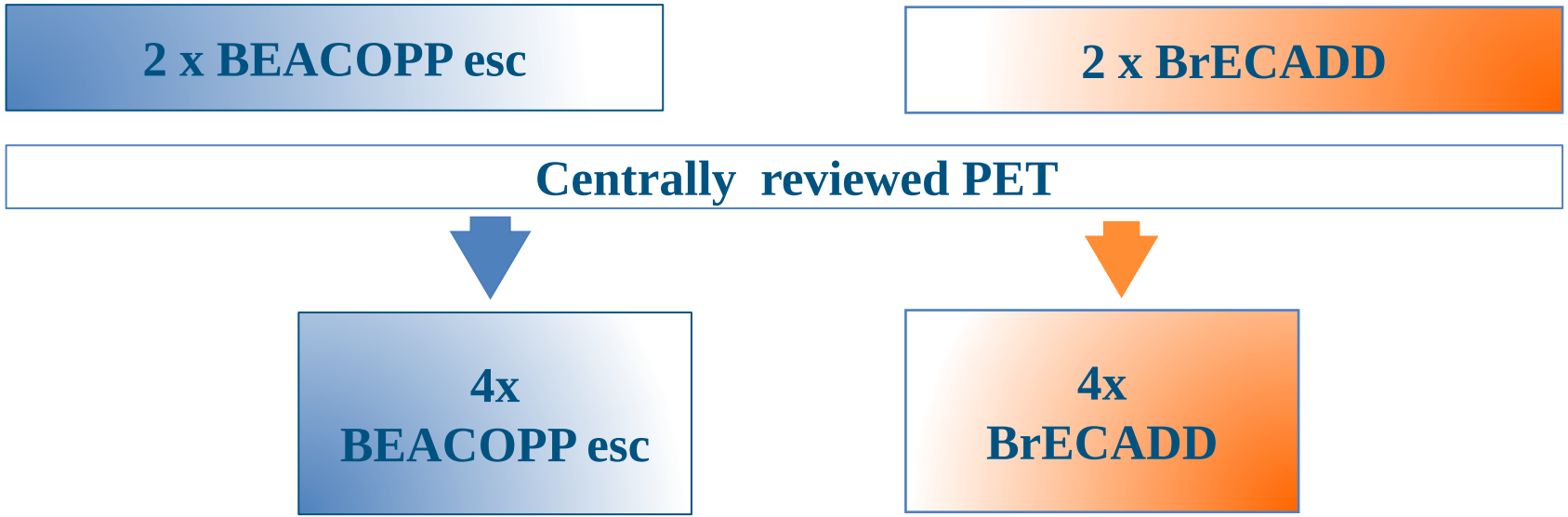
- **Diffuse large B-cell lymphoma (DLBCL)**
- **Follicular lymphoma**
- **Hodgkin lymphoma**
- **Summary**

Immunotherapy of malignant lymphoma

- **R-chemo SoC in most B-cell lymphoma including DLBCL and low-grade lymphoma**
- **MoAb-based maintenance established in low grades and cHL; role of maintenance in DLBCL unclear**
- **Anti-PD1 moabs extremely promising, mainly in HL**
- **Immunotherapy might at least in part replace chemo- and radiotherapy in the future**

HD21: GHSG Perspective

BV in advanced stage HL



End of therapy and residual nodes > 2.5 cm:

PET positiv: **Rx**

PET negative: **Follow up**

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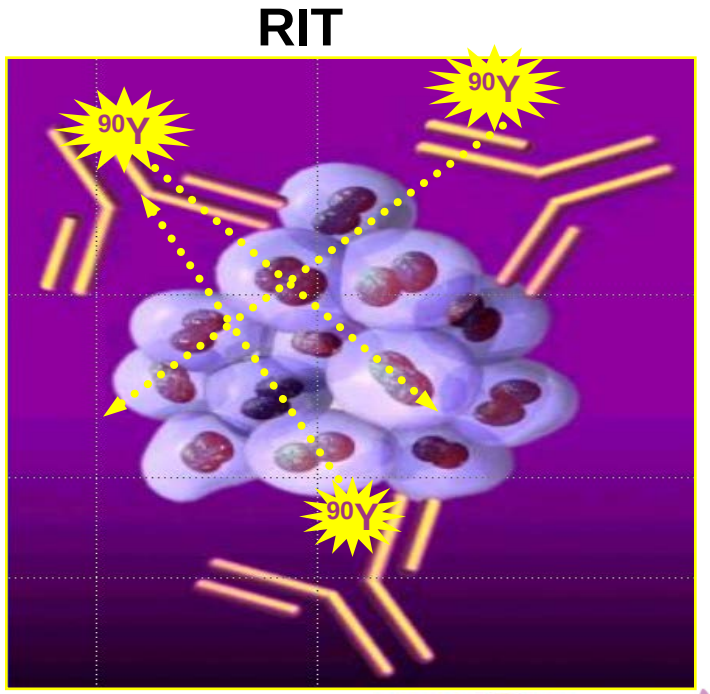
Radioimmunotherapy and Radiotherapy and immunotherapy combinations

Tim Illidge
Professor of Targeted Therapy and Oncology
BSc PhD DRCOG FRCP FRCR FRCPath

Institute of Cancer Sciences
Manchester Academic Health Sciences Centre
Manchester University
The Christie Hospital
Manchester , UK

Radioimmunotherapy – a unique tool targeting radiosensitivity

- Lymphoma cells are inherently sensitive to radiation
- Radiotherapy effective in chemotherapy-refractory patients
- Continuous delivery of low-dose radiation and antibody effector mechanisms
- Radiation also destroys tumour cells distant from targeted tumour cell



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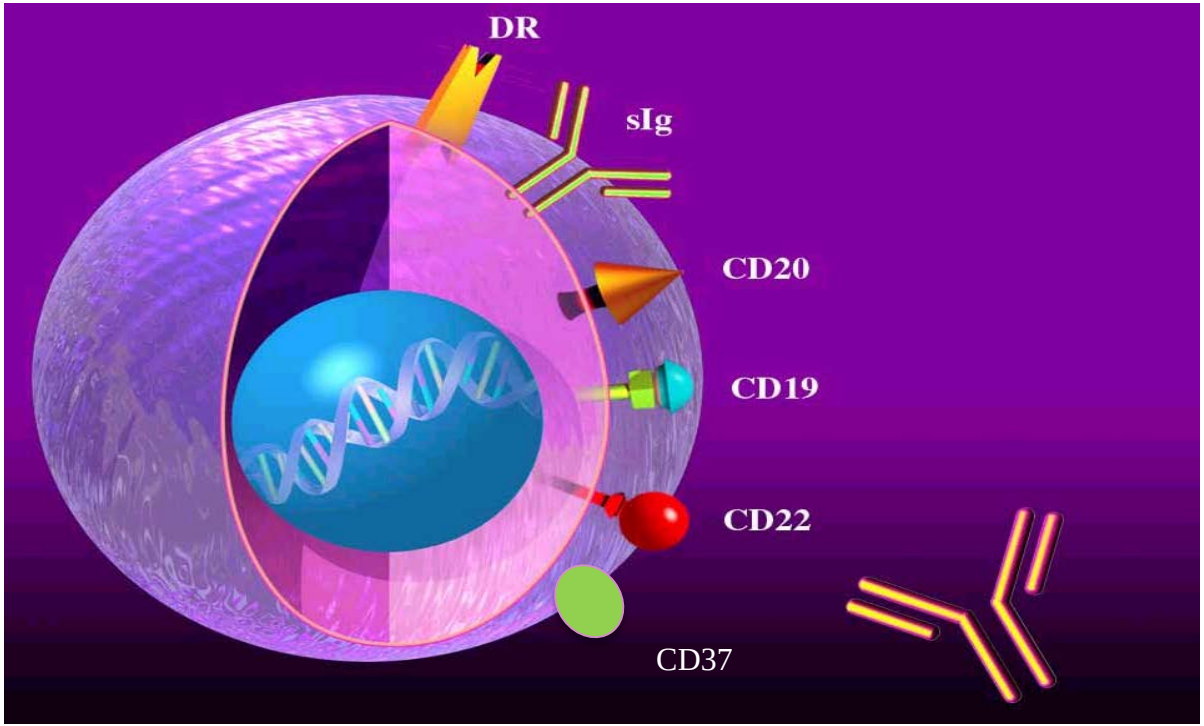
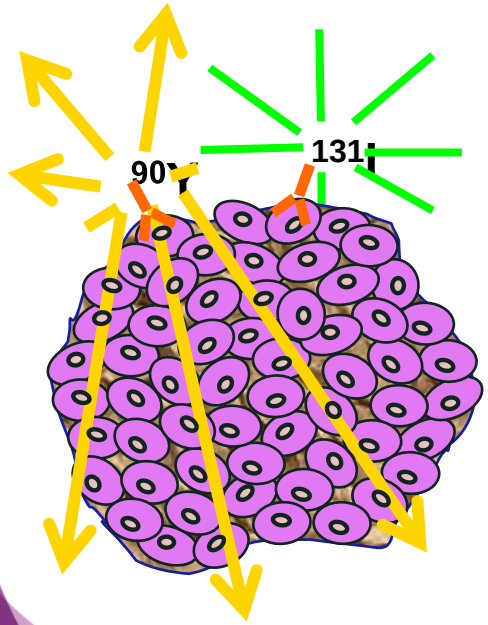
B-cell lymphomas express several antigens that can be targeted



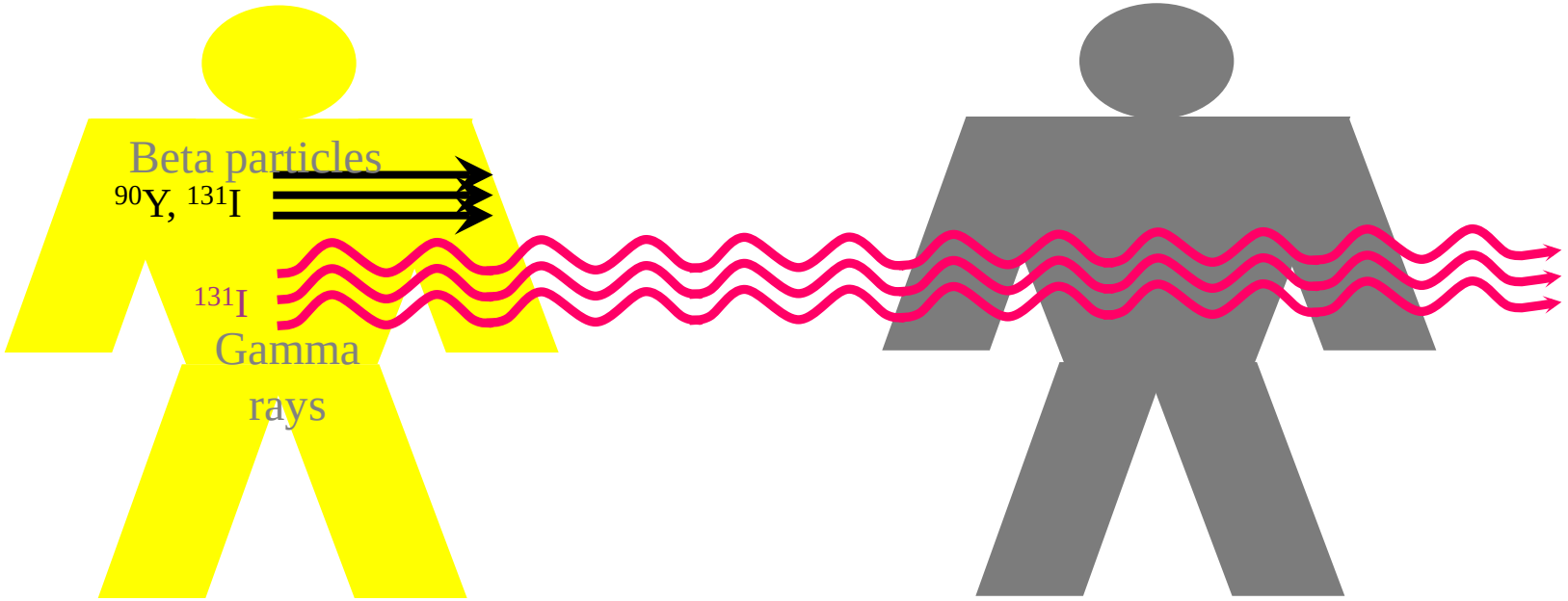
Adapted from Press, OW. *Semin Oncol* 1999; 26: 5(Suppl 14) 58–65

Choice of radioisotope



Properties	^{90}Yttrium	^{131}Iodine
Half-life	64 hours	192 hours
Energy emitter	Beta (2.3 MeV)	Gamma (0.36 MeV) Beta (0.6 MeV)
Path length	χ_{90} 5 mm	χ_{90} 0.8 mm
Urinary excretion	Minimal 7% in 7 days	Extensive/variable 46 - 90% in 2 days
Dosing	Based on weight and platelet count	Clearance based dosing using whole body dosimetry
Administration	Outpatient	Inpatient or restrictions to protect family/public

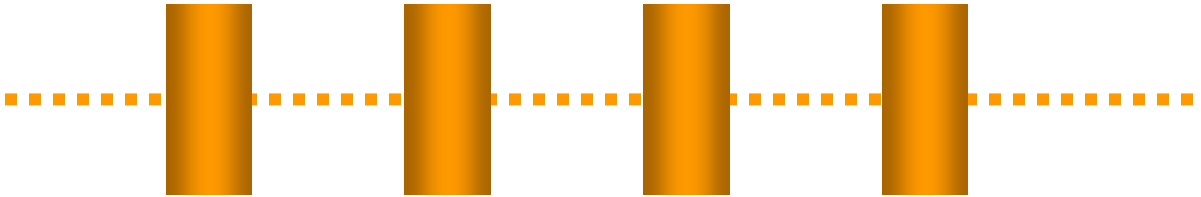
Penetration of Particulate and Electromagnetic Radiation



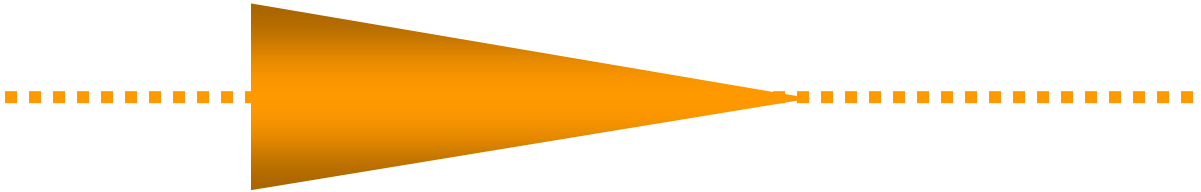
Radiation delivery profile of conventional radiotherapy versus targeted radiotherapy

Radioimmunotherapy delivers radiation at a lower rate, and continuous delivery may provide less opportunity for DNA repair

Fractionated external beam radiotherapy



Targeted radiotherapy



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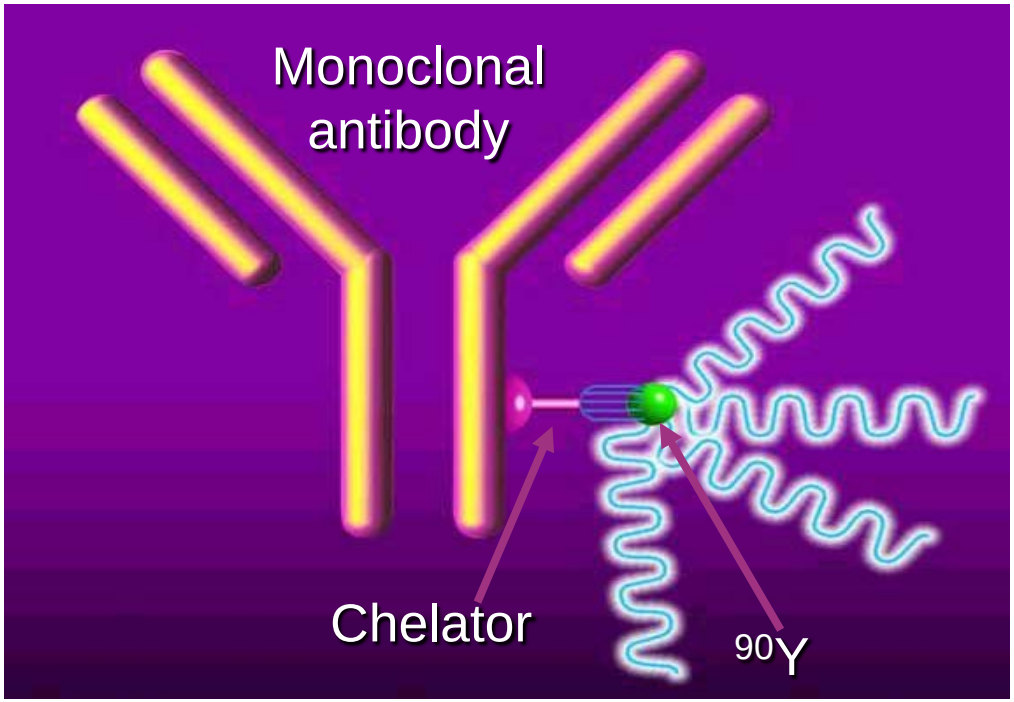
Yttrium-90 Ibritumomab tiuxetan (Zevalin™)



- Ibritumomab
  - Murine monoclonal antibody parent of Rituximab
- Tiuxetan

  Conjugated to antibody, forming strong urea-type bond

  Stable retention of ^{90}Y
- 90Y – Beta emitter

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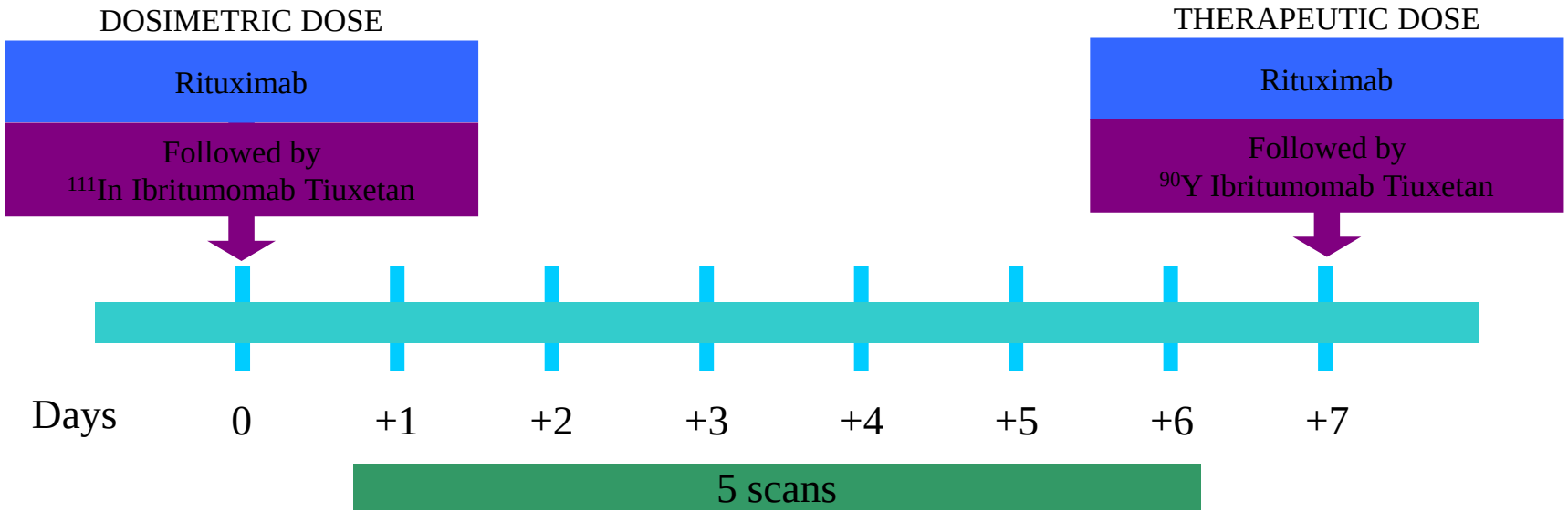
^{90}Y Ibritumomab Tiuxetan treatment is completed in 7 days



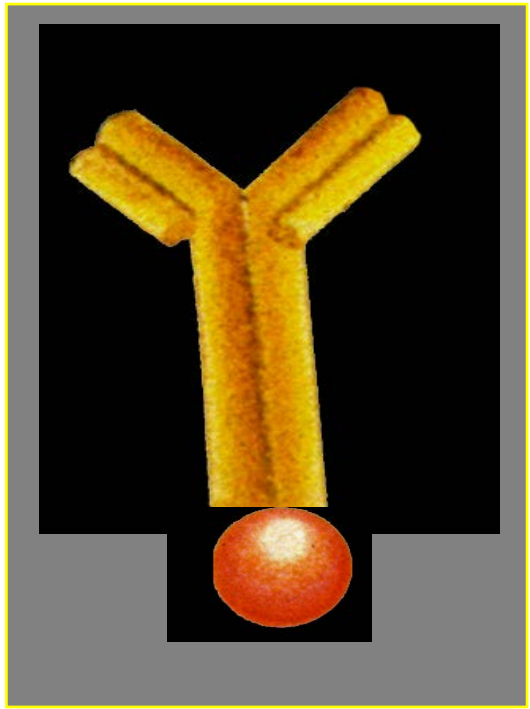
Dosimetric dose: Rituximab 250 mg/m^2; ^{111}In Ibritumomab Tiuxetan 5mCi ^{111}In, 1.6 mg Ibritumomab Tiuxetan

Therapeutic dose: Rituximab 250 mg/m^2; ^{90}Y Ibritumomab Tiuxetan 0.4mCi ^{90}Y for patients with platelet count >150,000 cells/mm^3 or 0.4 mCi/kg for a platelet count 100,000–149,000 cells/mm^3

Wiseman GA, *et al*. *Eur J Nucl Med* 2000; 27: 766–77

^{131}I Tositumomab (Anti-B1): Mechanism Of Action

- **Tositumomab**
  - Murine IgG2a anti-CD20 mAb
  - Triggers apoptosis, via unique epitope
- **Iodine-131 radioisotope**
  - Beta emission
    - Short pathlength “crossfire” effect (~1 mm)
  - Gamma emission
    - Allows individual dosimetry
    - Essential component of treatment



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Treatment Regimen for ^{131}I Tositumomab (Licensed in USA – no longer available)

Thyroprotection: Day -1 continuing through 14 days post-therapeutic dose

Day 0

Dosimetric dose
(450 mg tositumomab,
5 mCi ^{131}I tositumomab
[35 mg])

- Unlabeled predose infused over 1 hour
- Dosimetric dose used to determine individual pharmacokinetics

→ Whole body counts x 3 →

Day 7–14

Therapeutic dose
(450 mg tositumomab,
mCi dose of
^{131}I tositumomab [35 mg] to deliver
desired cGy TBD)

- Unlabeled predose infused over 1 hour
- Administered mCi activity determined by gamma counts

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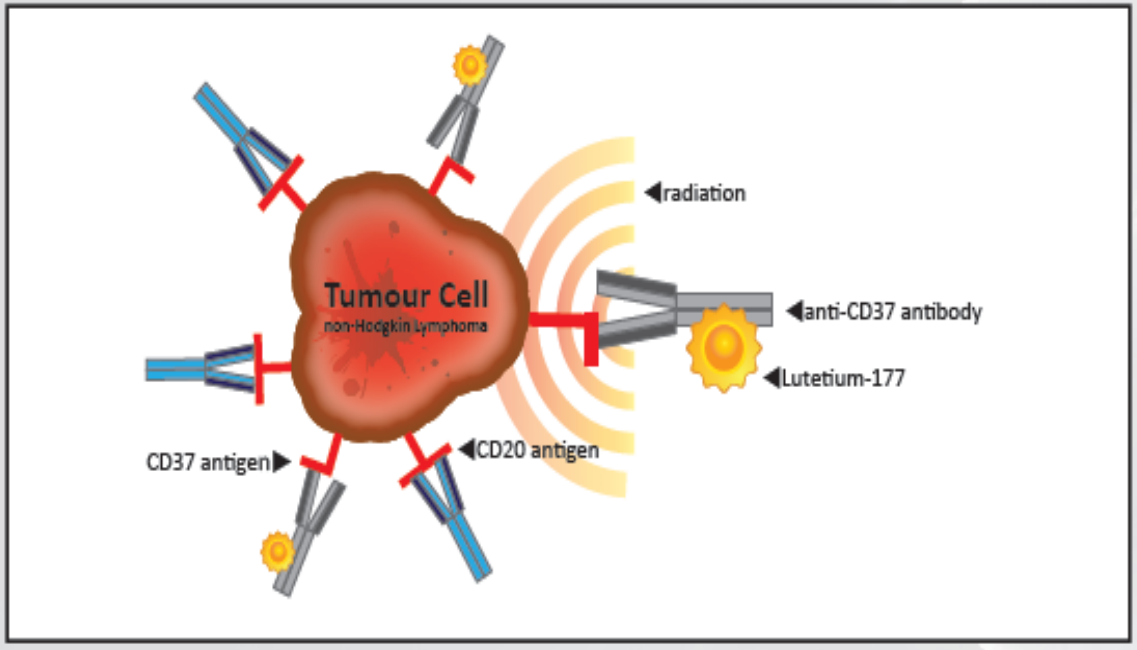
Results of a phase 1 study of ^{177}Lu-DOTA-HH1 anti body radionuclide (Betalutin) conjugate for patients with relapsed CD37+ non-Hodgkin lymphomas – Lugano 2015



177Lu-DOTA-HH1 (Betalutin)

- Murine mAb HH1
- Chelate to chemical linker DOTA
- Beta emitting lutetium-177 (t1/2= 6.7 days)

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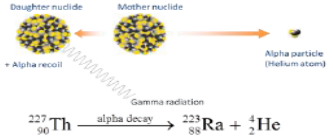
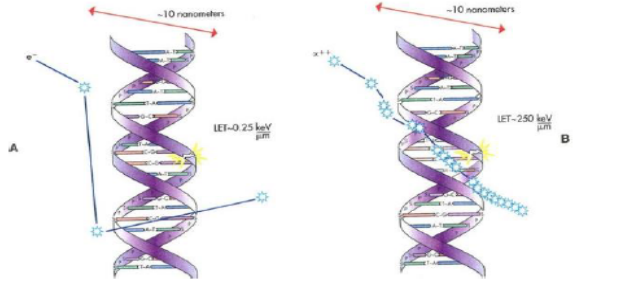
Alpha: Mechanism of Action



- The alpha-particle: a high energy, heavy charged particle
  - High Linear Energy Transfer (LET) = energy deposited per unit path length
  - High Relative Biological Effectiveness (RBE) = ratio of the effectiveness of one type of ionising radiation relative to another given the same amount of absorbed energy
- Alpha-particles deposit all their energy over a very short distance (2-10 cell diameters)
  - High propensity for Double Strand Breaks (DSB) due to direct DNA damage
  - No special shielding requirements when administering the dose

Low LET radiation vs. High LET radiation



LET: Beta (~0.2 keV/µm) Alpha (>100 keV/µm)

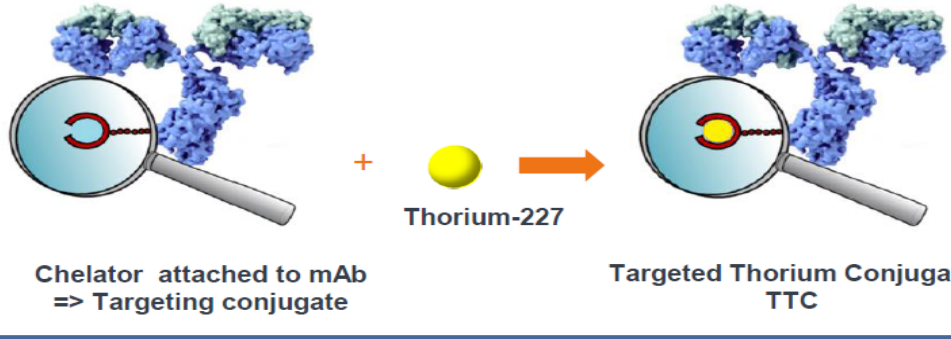
β-RIT for B-Cell Non-Hodgkins Lymphoma

- **Epratuzumab**: humanised mAb to CD22
- Clinical studies performed in NHL patients using naked mAb, beta emitters ^{131}I and ^{90}Y
  - 90Y-epratuzumab; 53% ORR (N=17) in DLBCL (3 median prior treatments), 5 of 6 at MTD (6 mCi/m^2)

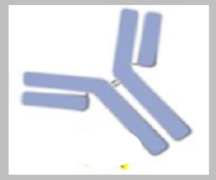
Thorium-227 anti-CD22

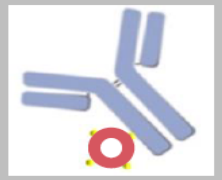
What Makes Thorium-227 Unique?

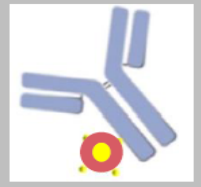
- Half-life (18.7 days) ideal for manufacture and commercial distribution
- Optimal physical half-life for tumor delivery by mAbs
- Radium-223 daughter has a 'clean' well understood clearance route
- Th(IV) forms highly stable complexes with specific chelators at ambient temp.



Three principal forms of mAb being injected:


mAb
20%


mAb conjugate
80%


Th-labelled mAb conjugate
<0.1%

Three key components:

- Thorium-227
- Chelator
- Targeting molecule antibody

Defining features of RIT in relapsed Follicular Lymphoma

- High response rates
- Durable remissions
  - in chemo-refractory disease
  - in rituximab-refractory disease

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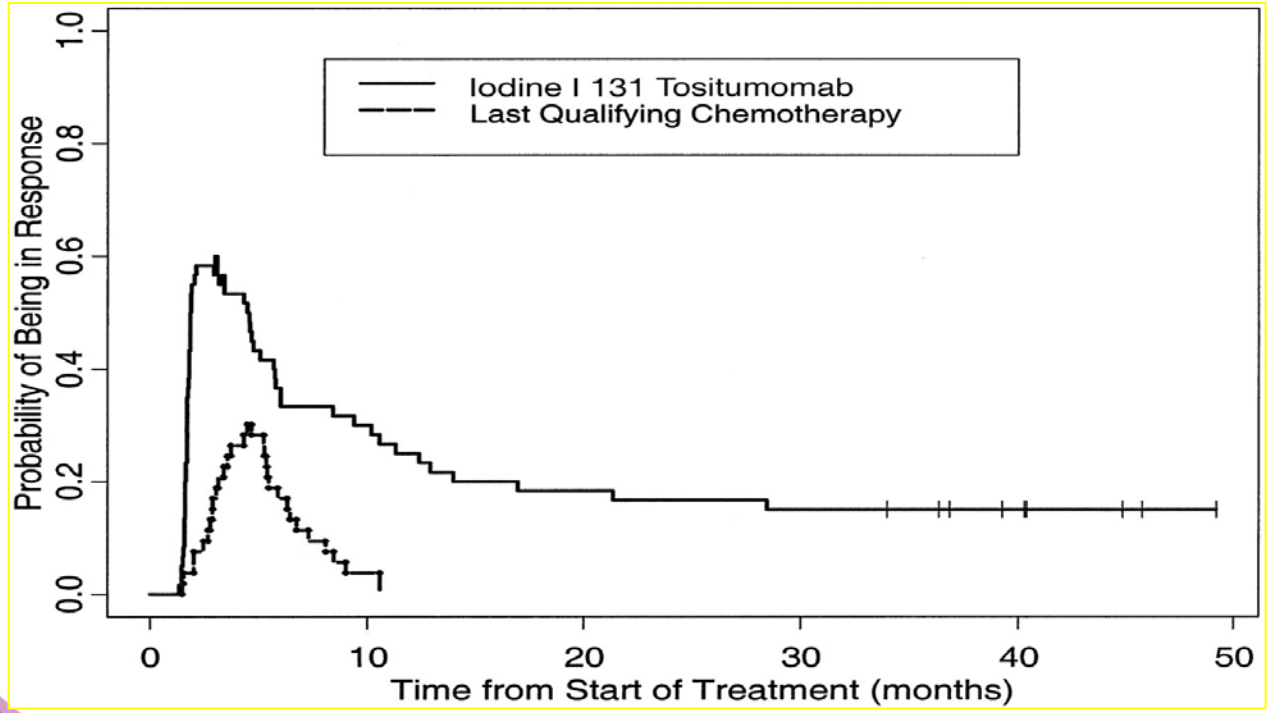
Pivotal Study of ^{131}I Tositumomab

Kaminski MS, et al. *J Clin Oncol*. 2001;19:3918–3928

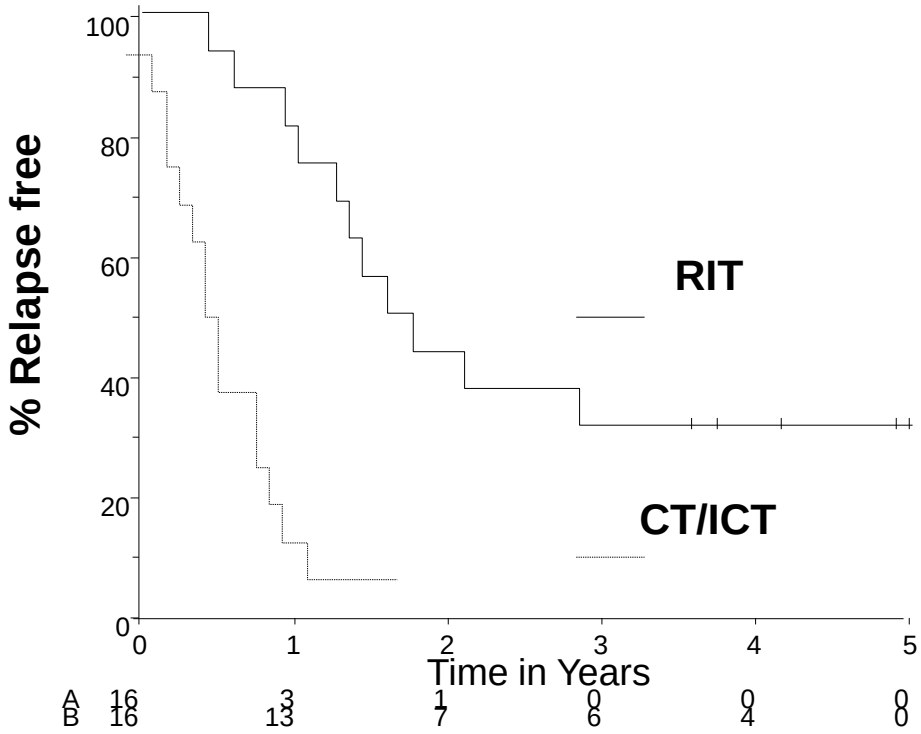


- **9 of 12 CR patients remain in CR 7 years**
- **7 patients in CR 4.9 to 7.2 years after RIT**

Kaminski MS, et al. *J Clin Oncol*. 2001;19:3918–3928.

Progression Free Survival of 131I Rituximab vs Last qualifying chemotherapy.

Illidge et al Blood 2009



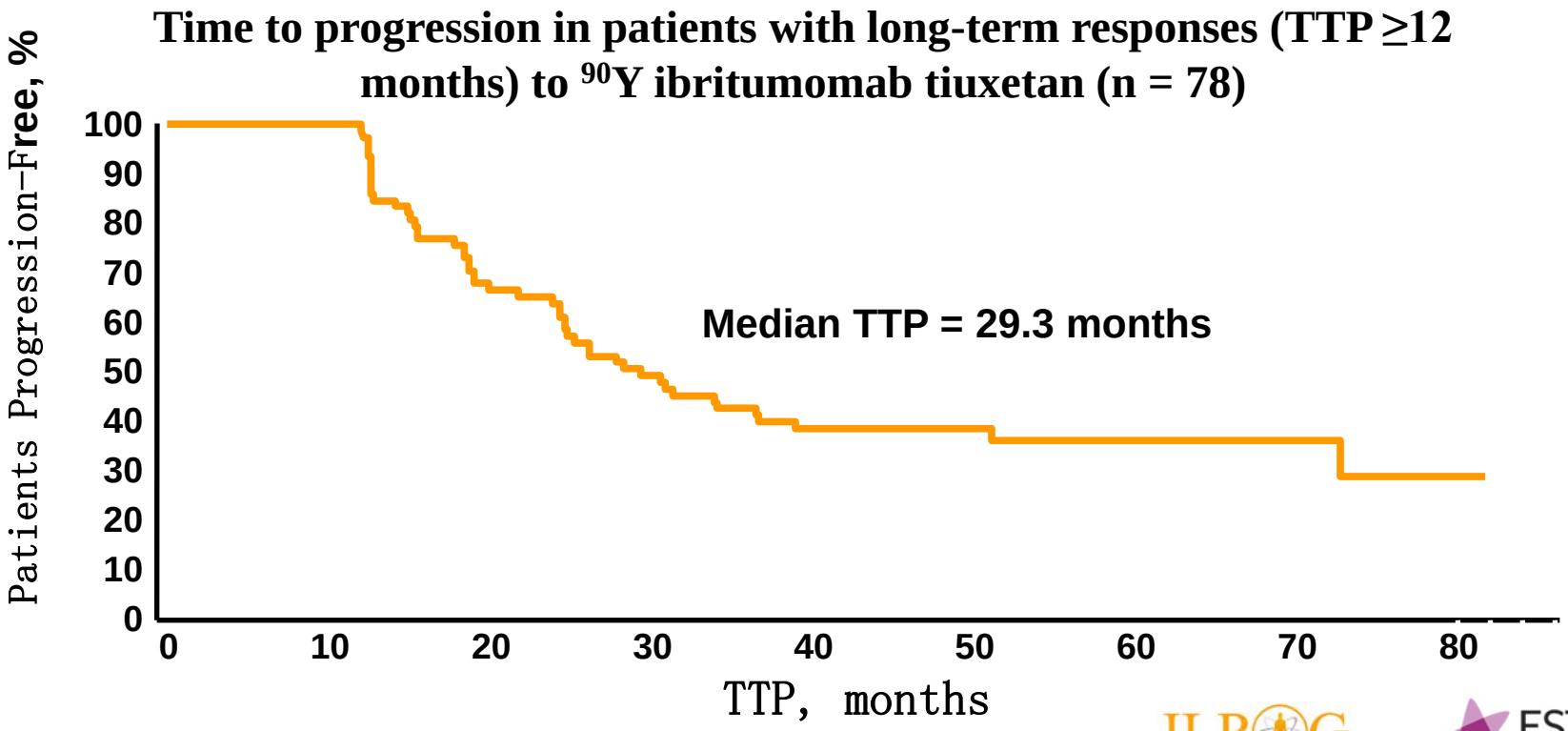
Duration of Response in ^{90}Y Ibritumomab Tiuxetan Trials

	Phase I-II *n* = 51	Phase II *n* = 30	Phase III *n* = 73
Overall Response, %	73	83	80
Median DR, months	11.7	11.5	13.9
CR/CRu, %	29*	47	34
Median DR, months	28*	23	23
Ongoing CR/CRu, %	19	14	32
Median DR, months	62.1	41.2	42.2
Range	60+ to 66+	40+ to 42+	33+ to 48+

*Patients with CR only.

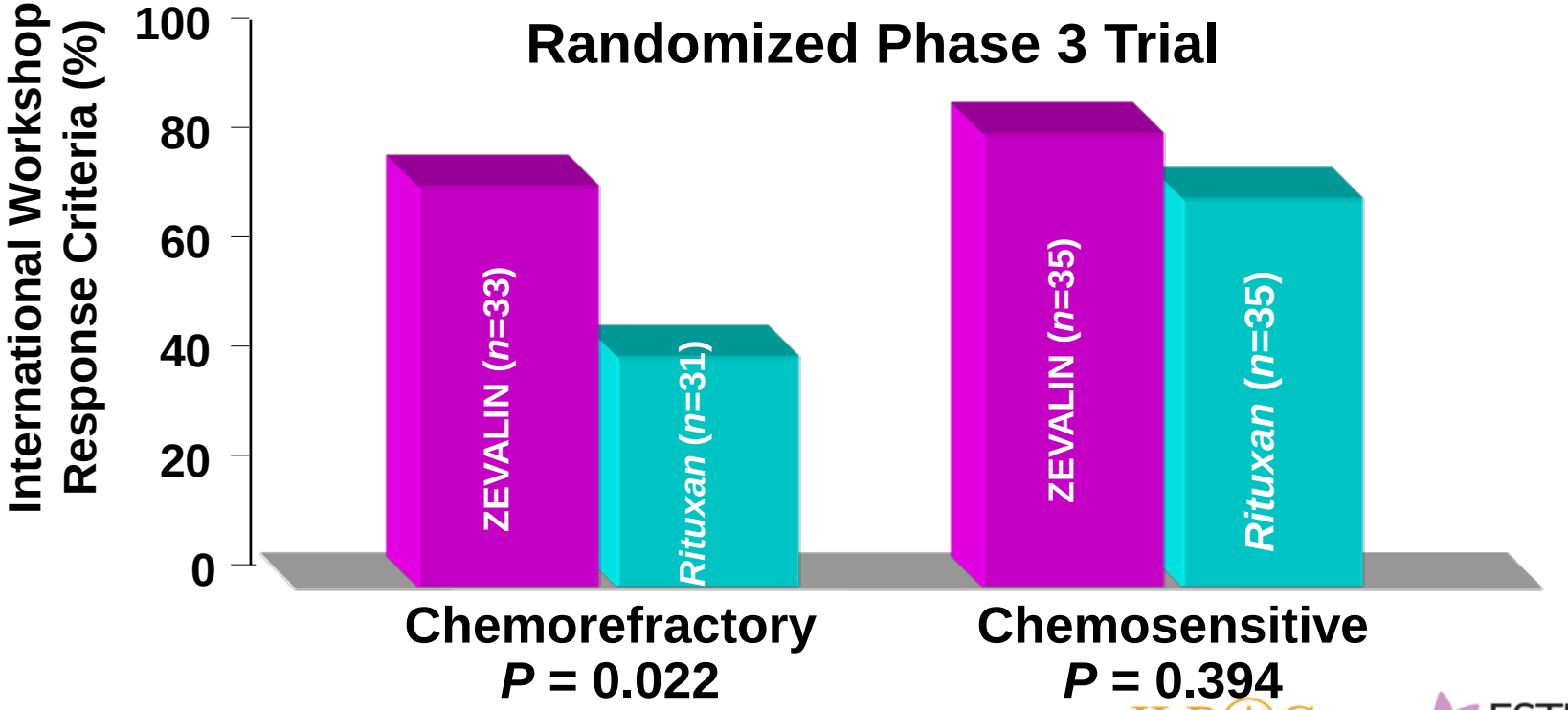
Gordon et al. Blood 2004.

Durability of Clinical Responses with ^{90}Y Ibritumomab Tiuxetan



Wiseman GA, et al. *Cancer Biother Radiopharm*. 2005;20(2):185-188.

^{90}Y Ibritumomab tiuxetan : Active in Chemorefractory NHL



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Multivariate analysis of prognostic factors correlated with response to Zevalin for NHL

- Analysis of 4 clinical registrational studies
- Patients with extensive prior therapy (1-9 regimens), bulky disease, splenomegaly
- Disease bulk (< 5 cm) correlated with overall response rate (89 patients ORR 90% ($p<0.001$)
- Other unfavourable characteristics (high LDH, extranodal disease, splenomegaly, extensive prior therapy, elevated peripheral B cell count) that might have been expected to confer a reduced probability of response failed to do so

Czuczman et al Proc ASCO 2002

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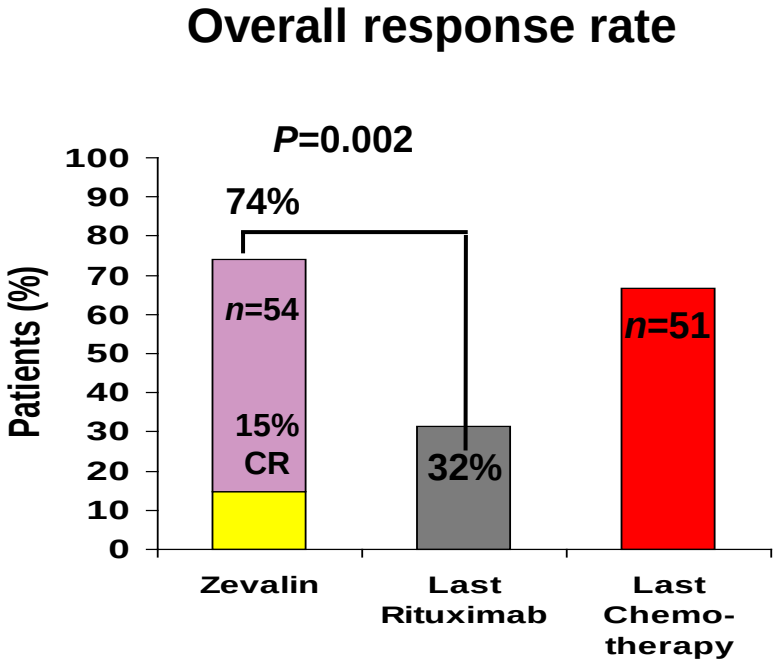
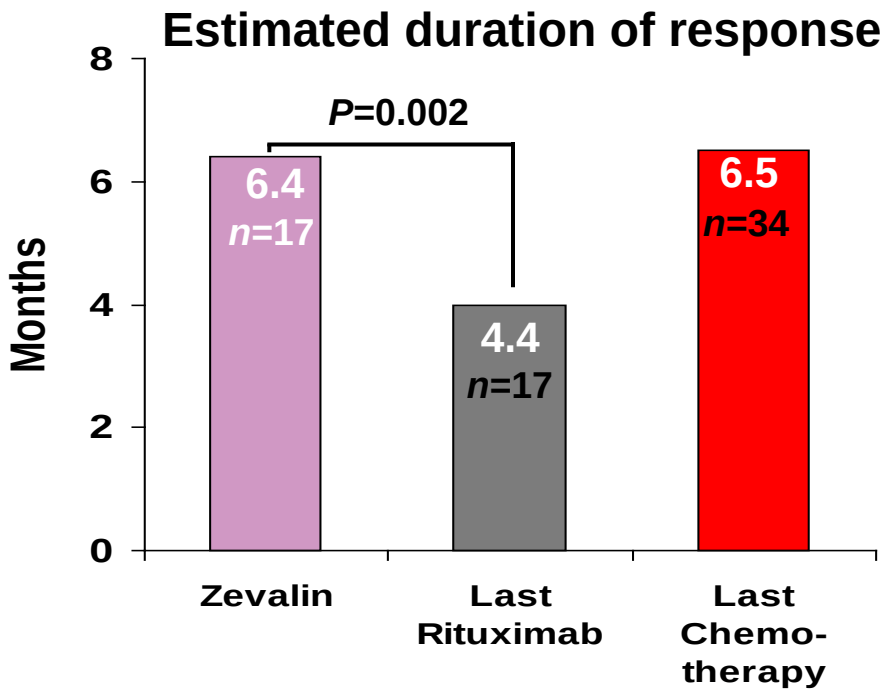
Rituximab-Refractory Trial: Patient Response to Zevalin



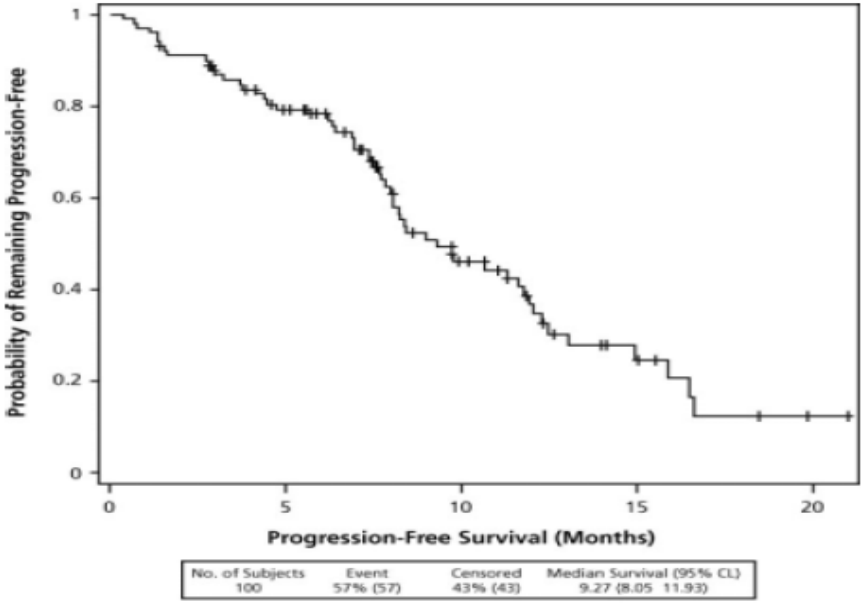


Median TTP in responders 9.1 months (range: 3.5 to 25.9+ months)

Bendamustine in Rituximab refractory FL

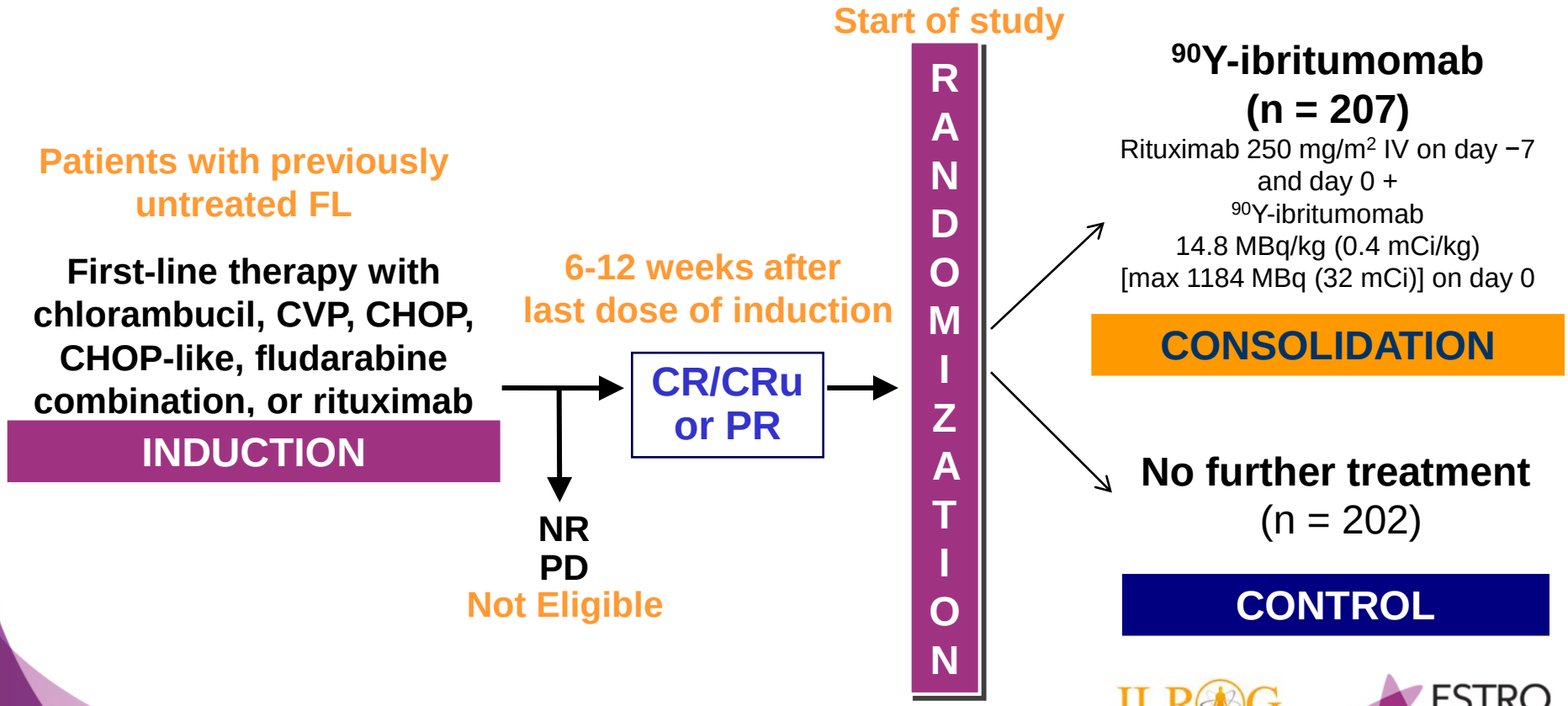
100 patients rituximab refractory
Bendamustine: 120 mg/m^2

ORR: 75%
CR: 14%
Median PFS: 9 months



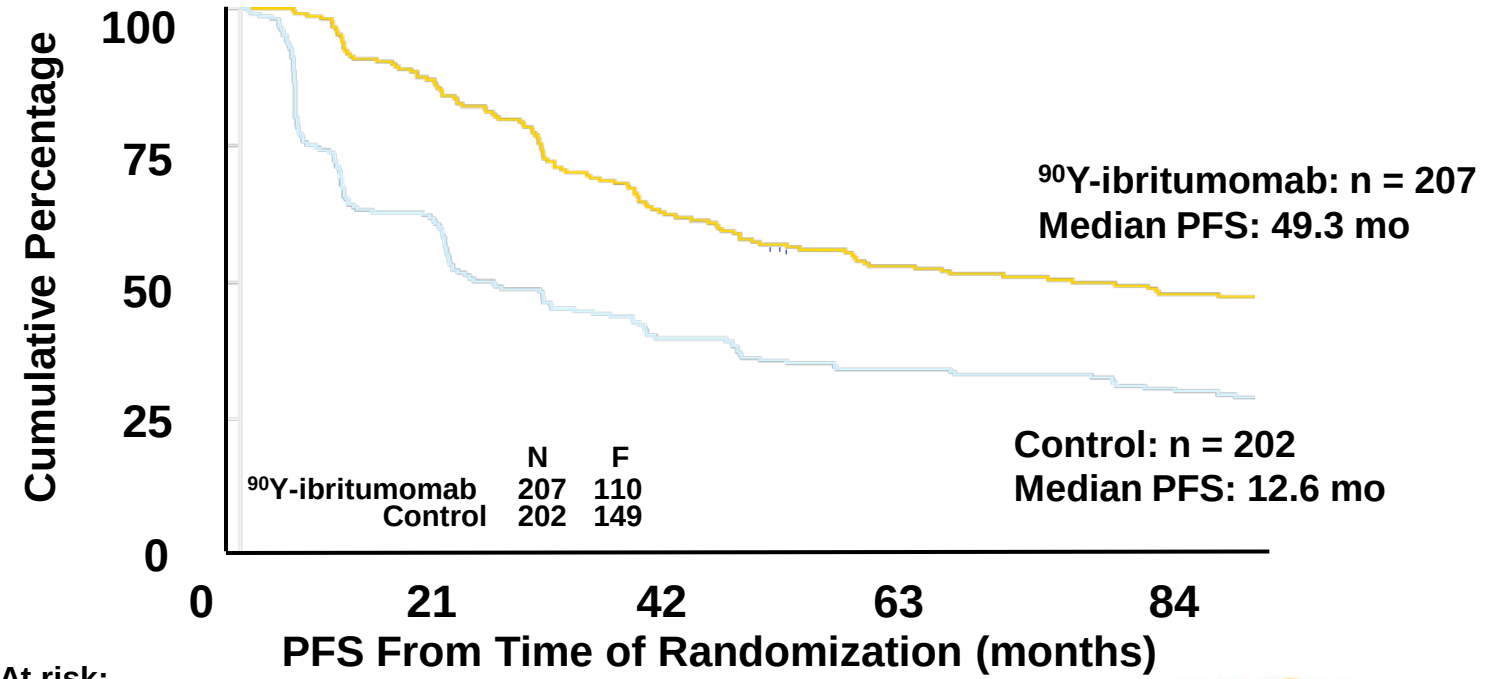
Kahl BS, et al. *Cancer.* 2010;116(1):106-114.

Radioimmunotherapy consolidation FIT Study



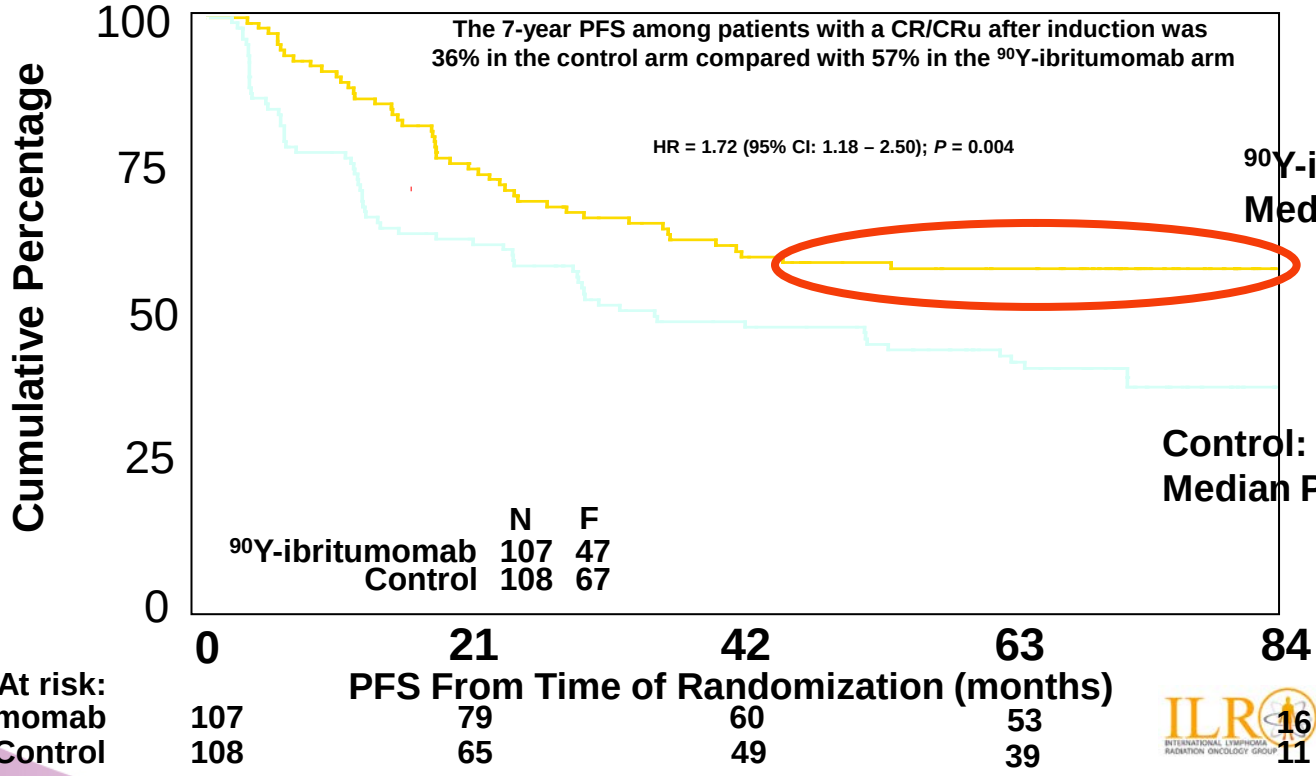
Morschhauser et al. *J Clin Oncol*. 2008;26:5156-5164

Overall PFS For Treatment Groups



90Y ibritumomab tiuxetan consolidation of first remission in advanced-stage follicular non-Hodgkin lymphoma: updated results after a median follow-up of 7.3 years from the International, Randomized, Phase III First-Line Indolent trial.

Morschhauser F, et al J Clin Oncol. 2013 ;31(16):1977-83.

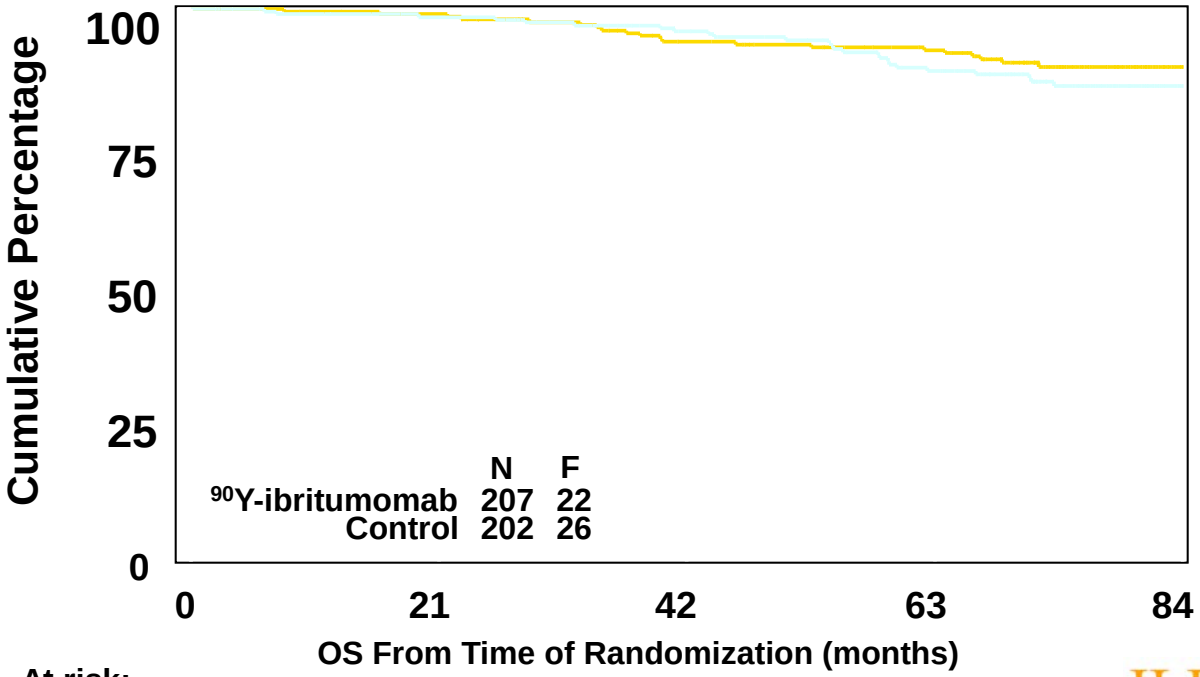


Overall Survival for Treatment Groups

7-year OS 86% in control arm compared with 89% in the ^{90}Y-ibritumomab arm
HR = 1.50 (95% CI: 0.84 – 2.68); *P* = 0.478

^{90}Y-ibritumomab: n = 207
Median OS: > 110 mo

Control: n = 202
Median OS: > 113 mo



At risk:					
^{90}Y-ibritumomab	207	200	178	166	47
Control	202	192	175	152	45

FIT TRIAL
Conclusions after 7 years Follow-up

- ^{90}Y-Ibritumomab consolidation confers a durable PFS benefit for patients with advanced FL
  - 3-year PFS advantage for patients in the ITT population
  - At least a 6-year PFS advantage for patients with a CR/CRu after induction > 5-year advantage in time to next treatment

- No unexpected toxicities emerging

  Annualized rate of secondary MDS/AML was 0.55% in the Zevalin arm

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Does ^{90}Y Ibritumomab Consolidation after first line R-Chemo Induction in Follicular Lymphoma improve outcome?

➢FIT study (R-chemo subgroup; n=59)

- CR rate after Zevalin : 93% (controls: 71%)
- PFS at 84 months: 64% Zevalin vs 23% controls (median follow-up: 71.6 months)

- ECOG 1496 6-8 x chemo - CR/PR/SD randomised 16 cycles of Rituximab – similar results for PFS

➢Randomised (^{90}Y Ibritumomab) vs in Rituximab maintenance (ROZETTA study) no significant difference in PFS

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Responses rates of Zevalin monotherapy versus R-chemo in first line therapy of Follicular NHL

	ORR (%)	CR (%)	Reference
R-CHOP	96	20	Hiddemann et al., 2005
R-CVP	81	41	Marcus et al., 2005
R-MCP	92	50	Herold et al., 2005
Zevalin	84	53	Scholz et al., 2012
Zevalin	96	70	Illidge et al 2014
Bexxar	95	75	Kaminski et al., 2010

Conclusions – Role of RIT in Follicular lymphoma

- RIT simple and effective treatment; most active drug in NHL, unique mechanism of action
  - Effective (high response rate, durable remission) and underused single treatment in relapsed and rituximab refractory disease
  - Patients in ^{90}Y-ibritumomab arm had a greater than 5-year advantage in time to next treatment in FIT trial as consolidation
  - Phase II data as single agents Zevalin RIT in untreated follicular lymphoma show high response rates and durable remission
  - Novel Radioimmunconjugates are being developed but pathways to registration and routine clinical use are challenging.

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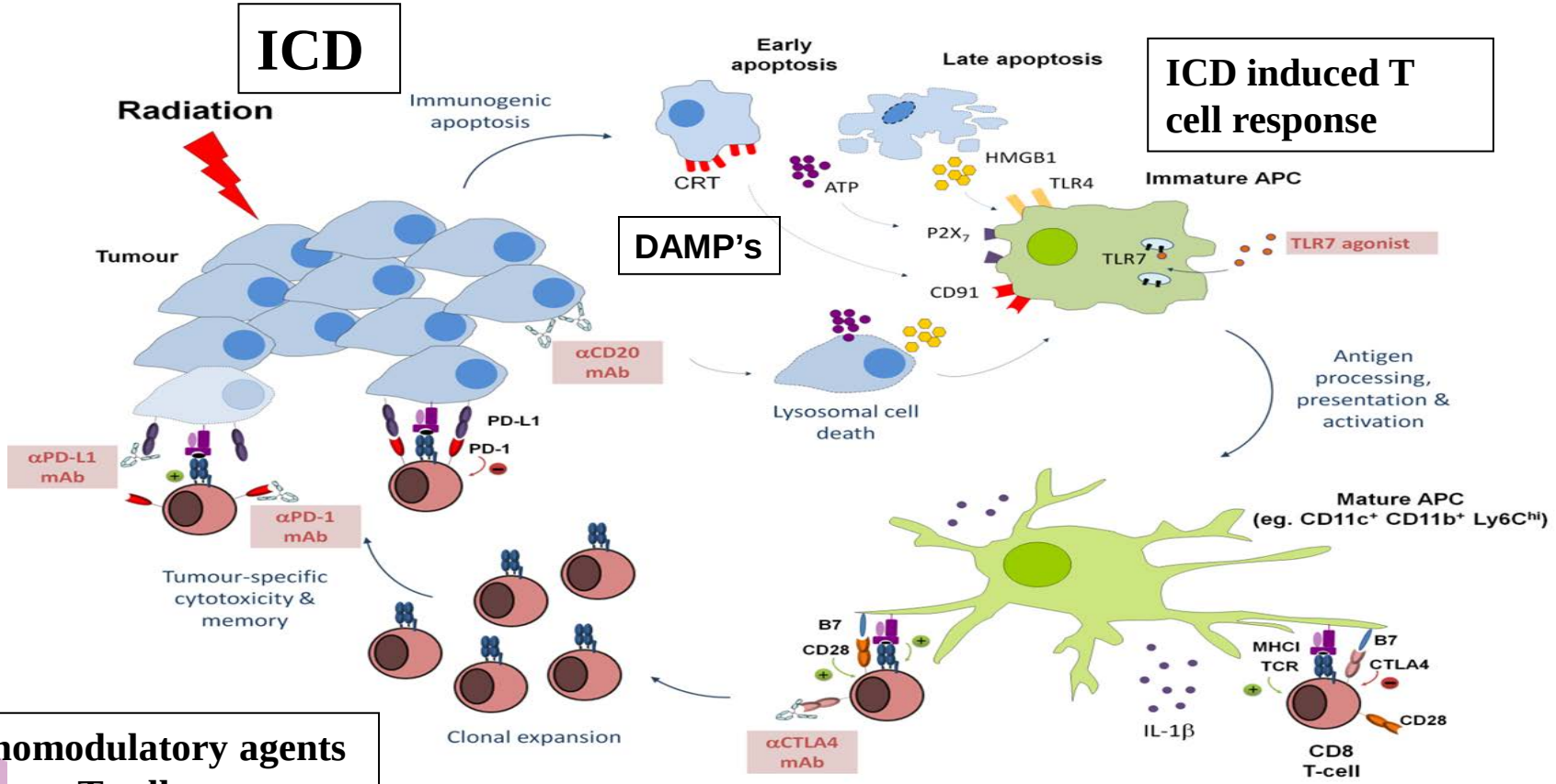
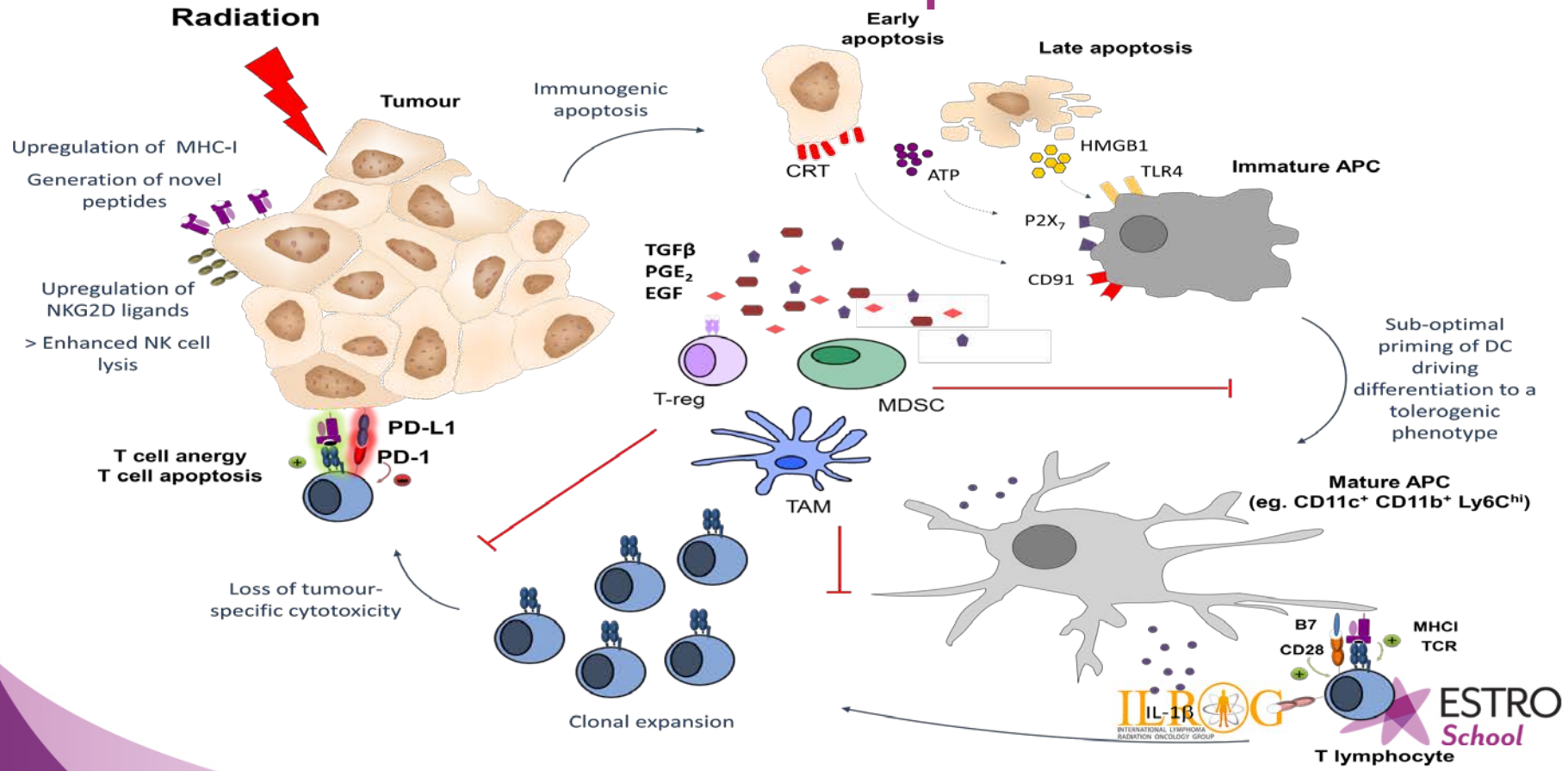
Developing effective combinations of radiotherapy and immunotherapy in cancer

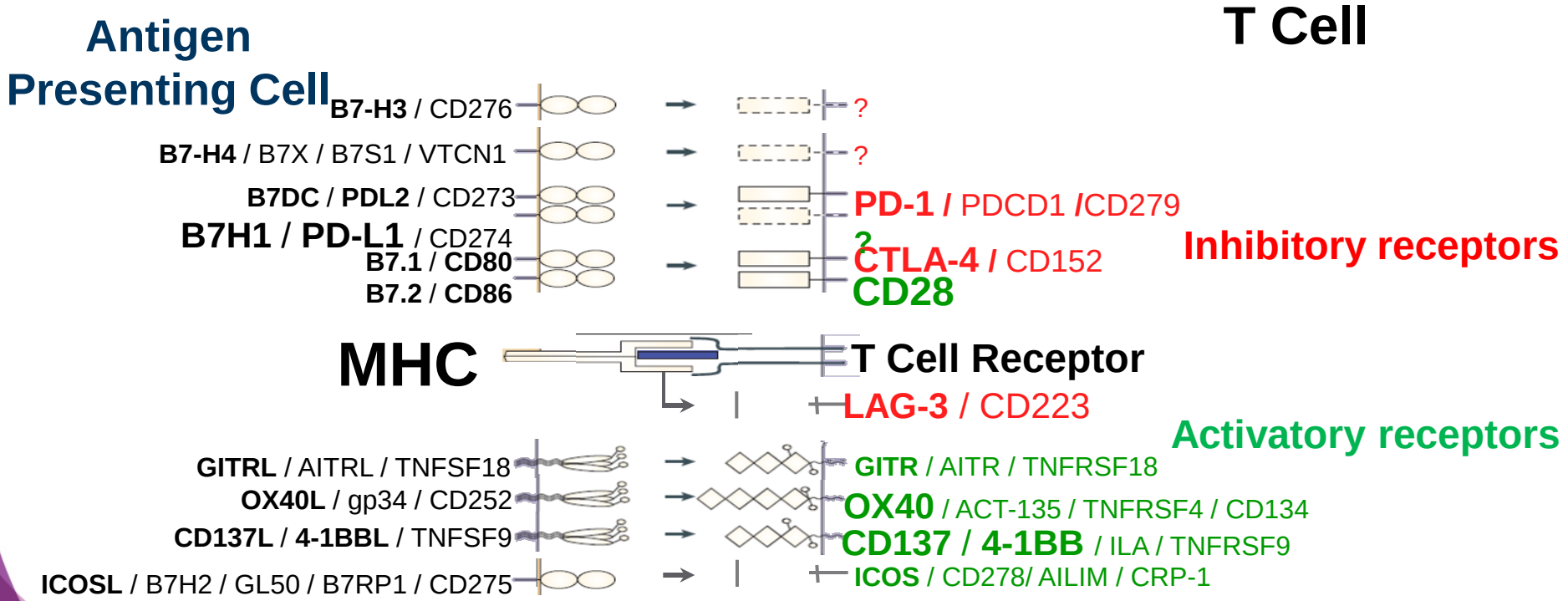


Immunomodulatory agents to enhance T cell response

Tumours generate an environment that suppresses anti-tumour immune responses



Understanding T- cell Immune Check-Points in the Tumour Microenvironment and Reversing Immunosuppression



ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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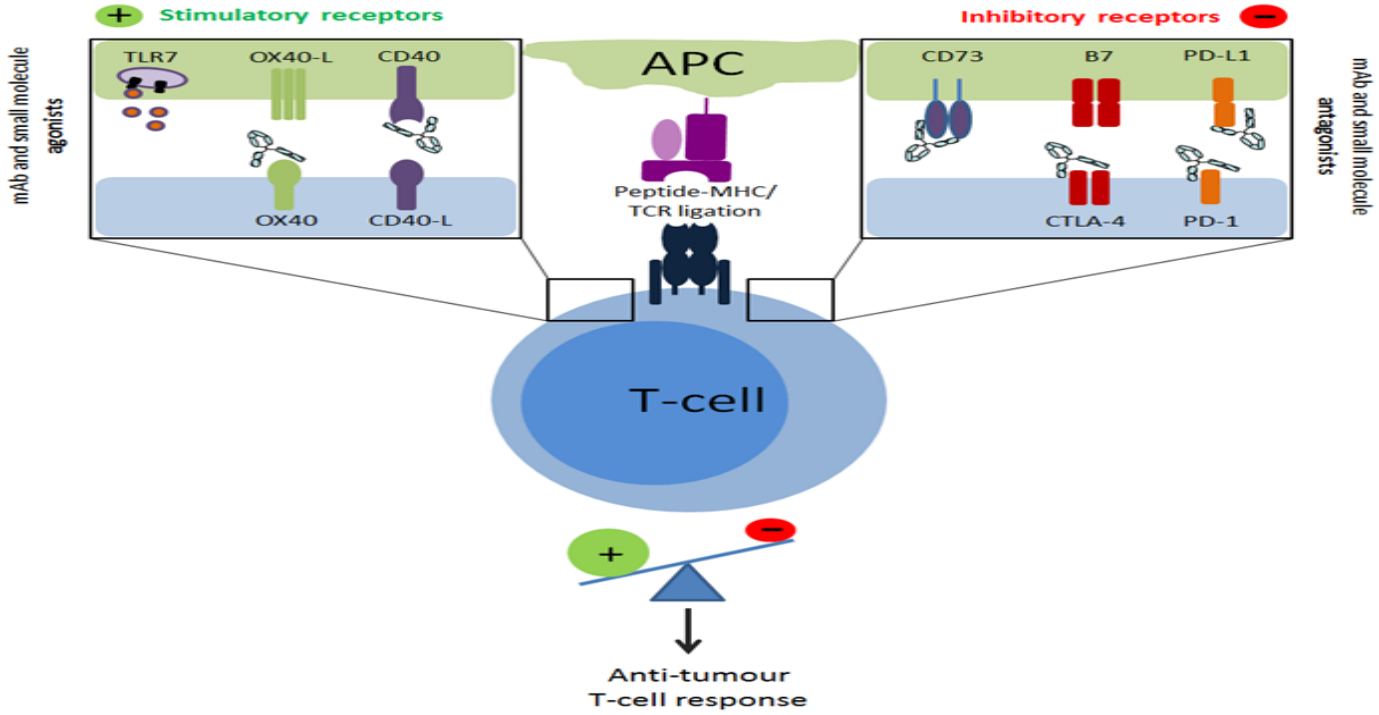
Targeting immuno-regulatory checkpoints to overcome immune suppression in combination with RT

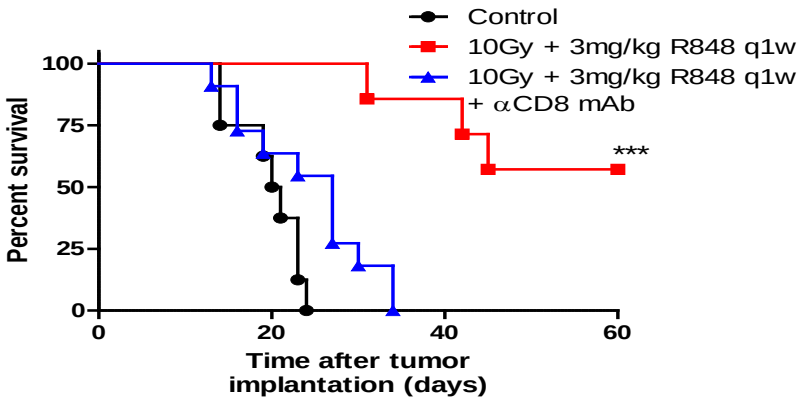


Systemic delivery of a TLR7 agonist in combination with radiation primes durable antitumor immune responses in mouse models of lymphoma

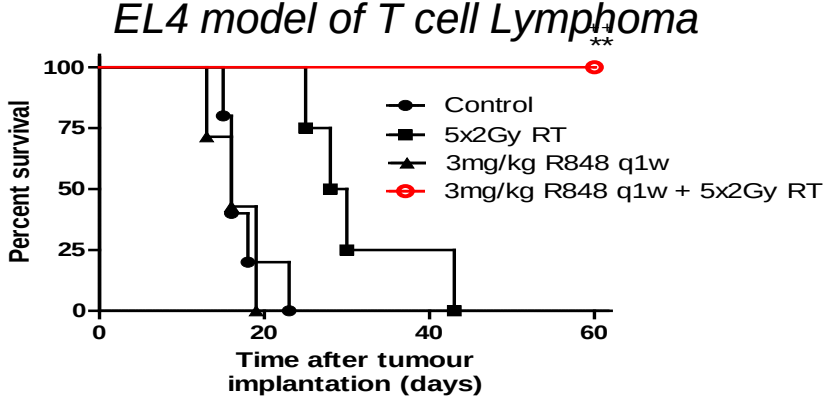
Simon J. Dovedi,[1] Monique H. M. Melis,[1] Robert W. Wilkinson,[2] Amy L. Adlard,[3] Ian J. Stratford,[3] *Jamie Honeychurch,[1] and *Timothy M. Illidge[1]

Plenary paper. Blood, 10 January 2013 · VOLUME 121, NUMBER 2

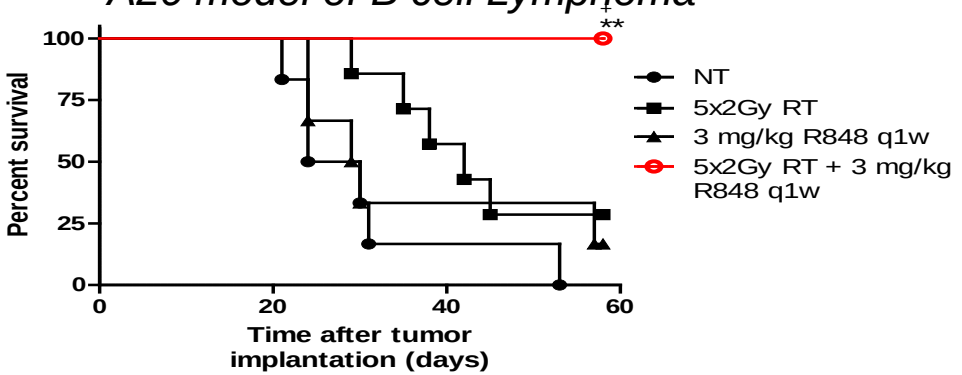
EG7 model of T cell Lymphoma



EL4 model of T cell Lymphoma



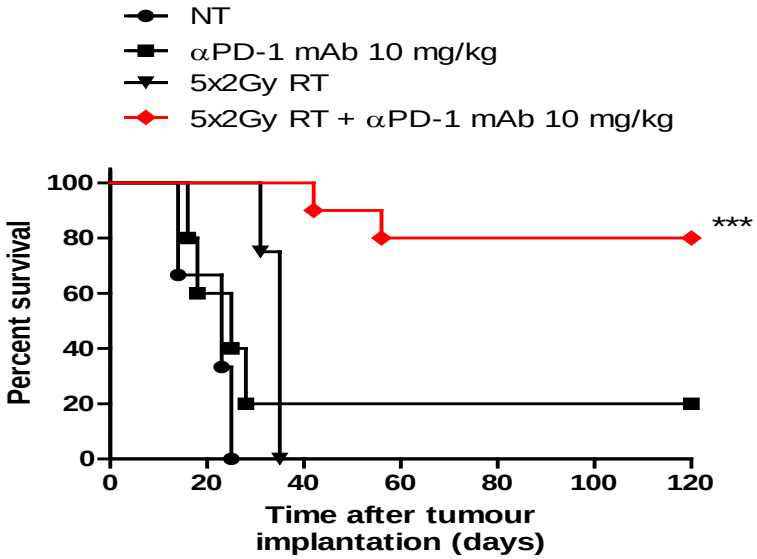
A20 model of B cell Lymphoma

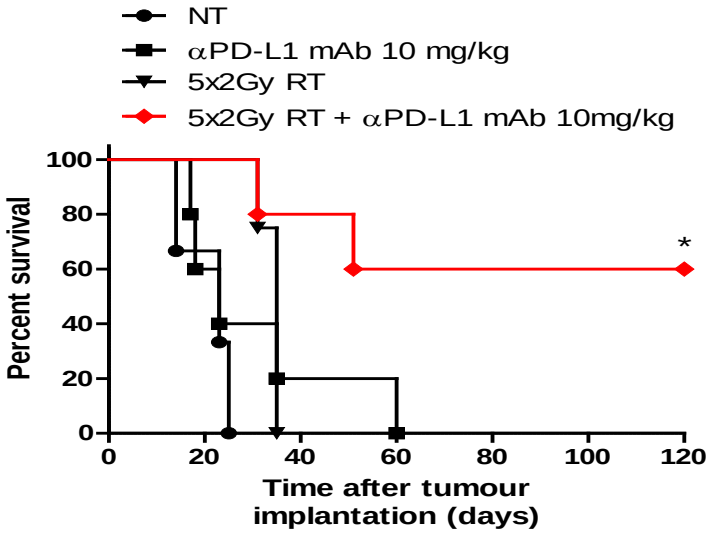


Acquired Resistance to Fractionated Radiotherapy Can Be Overcome by Concurrent PD-L1 Blockade

Simon J. Dovedi[1], Amy L. Adlard[2], Grazyna Lipowska-Bhalla[1], Conor McKenna[1], Sherrie Jones[1], Eleanor J. Cheadle[1], Ian J. Stratford[2], Edmund Poon[3], Michelle Morrow[3], Ross Stewart[3], Hazel Jones[3], Robert W. Wilkinson[3], Jamie Honeychurch[1], and Tim M. Illidge[1]

Cancer Research





Questions

- Thanks for listening

ESTRO School

WWW.ESTRO.ORG/SCHOOL

Combined Modality Treatment of Hodgkin Lymphoma

Andreas Engert, MD

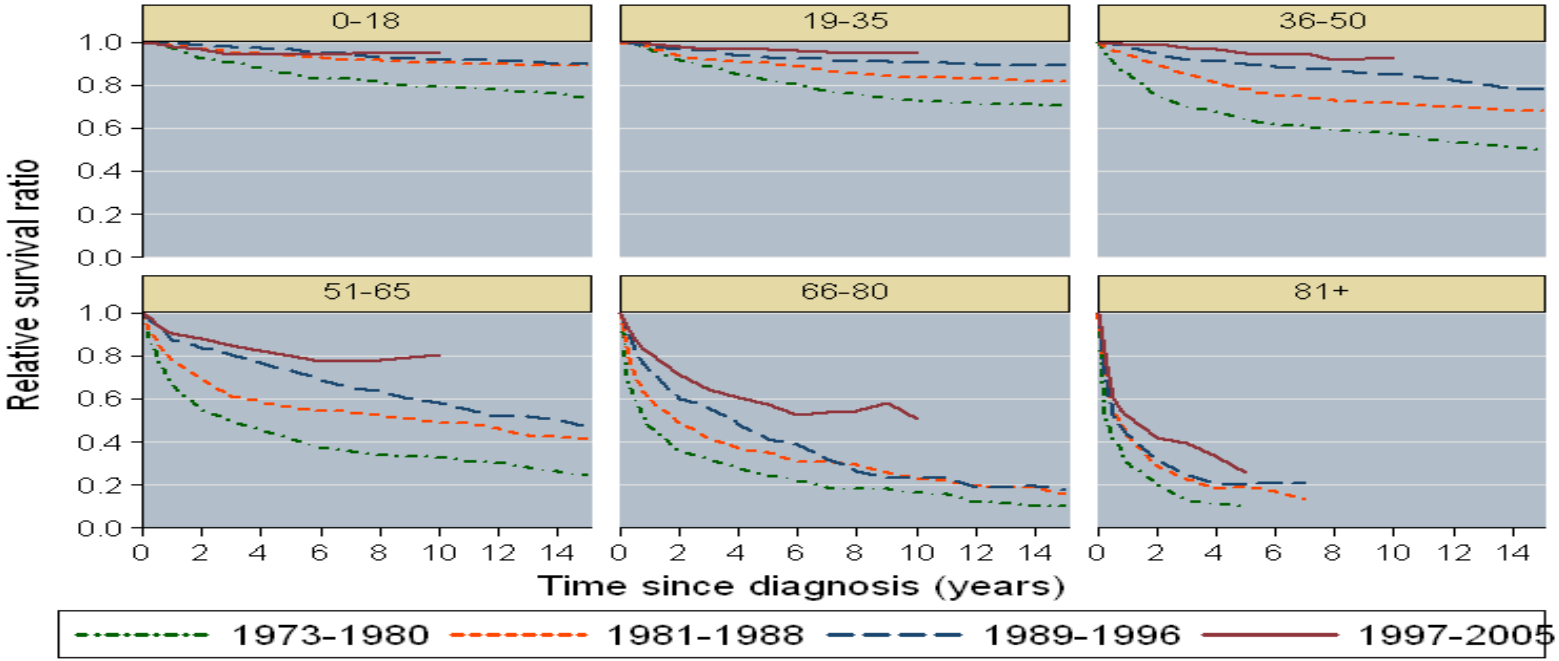
Chairman, German Hodgkin Study Group
University Hospital of Cologne

Combined Modality Treatment of HL

- **Background**
- **Hodgkin lymphoma – early stages**
- **PET-driven trials**
- **Chemo-Immunotherapy**
- **Summary**

Hodgkin Lymphoma

Cumulative relative survival of HL pts in Sweden



Courtesy of Magnus Björkholm 2010

Hodgkin Lymphoma

Late side effects after treatment

- **2nd NPL**
  - **AML**
  - **NHL**
  - **Solid tumours**
- **Organ damage**
  - **Lung**
  - **Heart**
  - **Thyroid**
- **Others**
  - **Fertility**
  - **Fatigue**
  - **Psycho-social**

GHSG Clinical Trials
Patients recruited since 1978

1978 - 88	HD 1 - 3	506
1988 - 94	HD 4 - 6	2035
1994 - 98	HD 7 - 9	2865
1998 - 02	HD10-12	3948
2003 - 08	HD13-15	5171
2008 -	HD16-18	3879
Total		18404

Combined Modality Treatment of HL

- Background
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- Summary

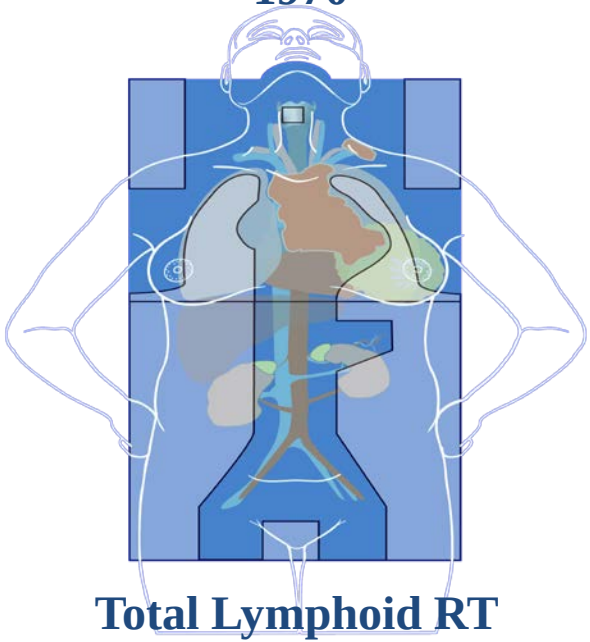
GHSG Risk Allocation for HL patients

	Stage (Ann Arbor)			
Risk factors	**IA, IB, IIA**	**IIB**	**IIIA, IIIB**	**IVA, IVB**
None	**Early favorable**		**Advanced**	
≥3 LN areas	**Early unfavorable**			
Elevated ESR				
Large med mass				
Extranodal disease				

GHSG 2000

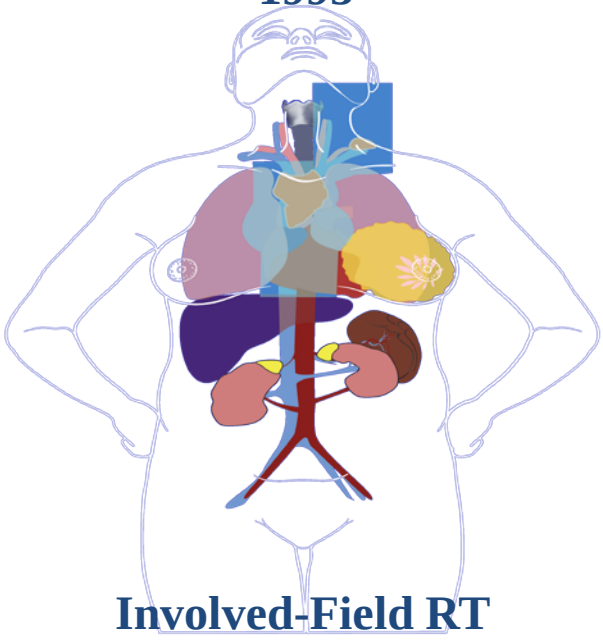
Hodgkin Lymphoma
Evolution of Radiotherapy

1970



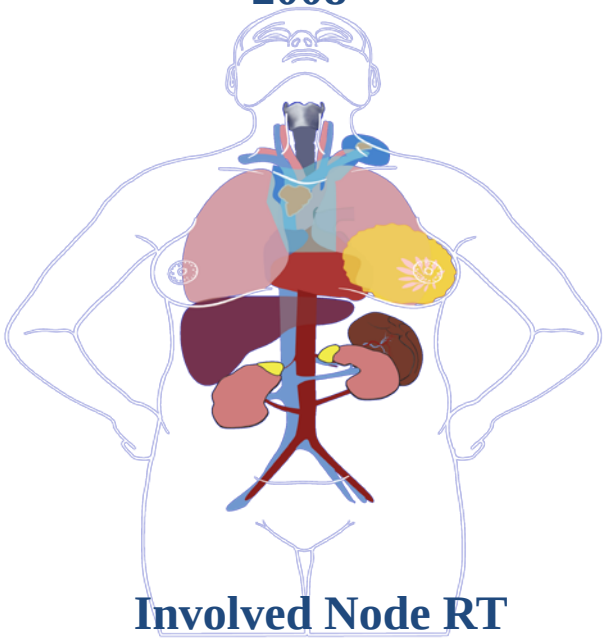
Total Lymphoid RT
44 Gy

1995



Involved-Field RT
36 Gy

2008

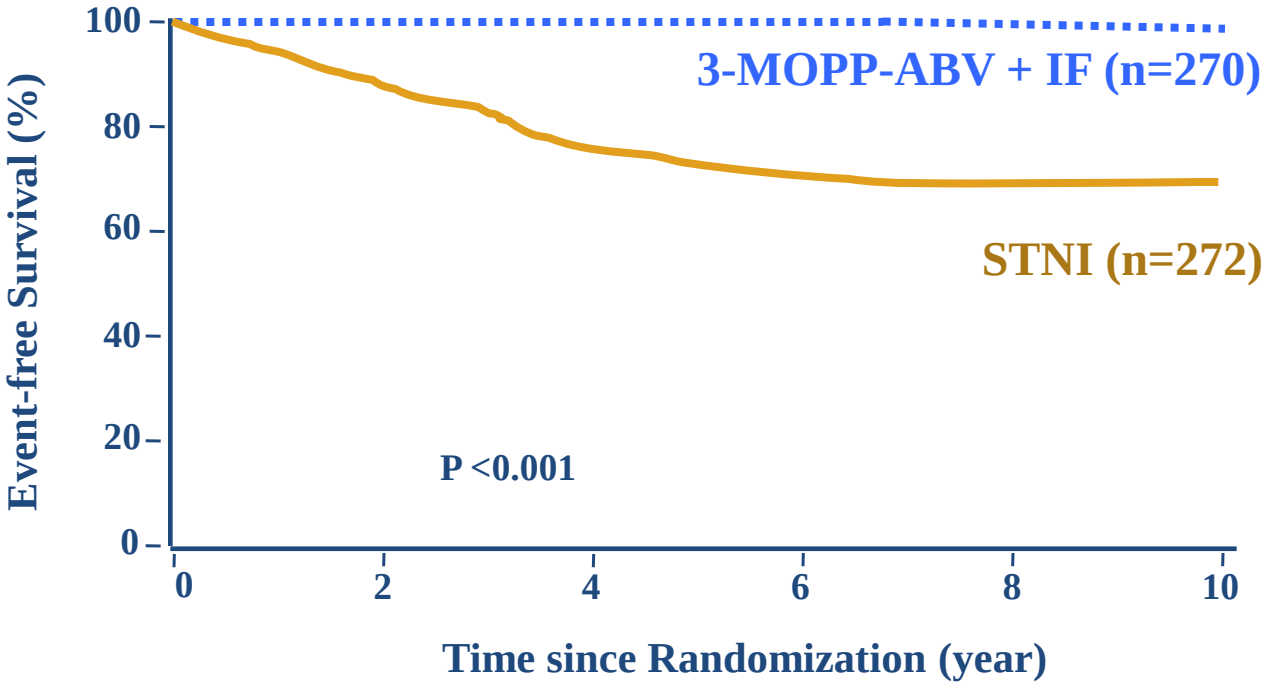


Involved Node RT
20-30 Gy

Adapted from Yahalom, Lugano 2008

EORTC H8F trial

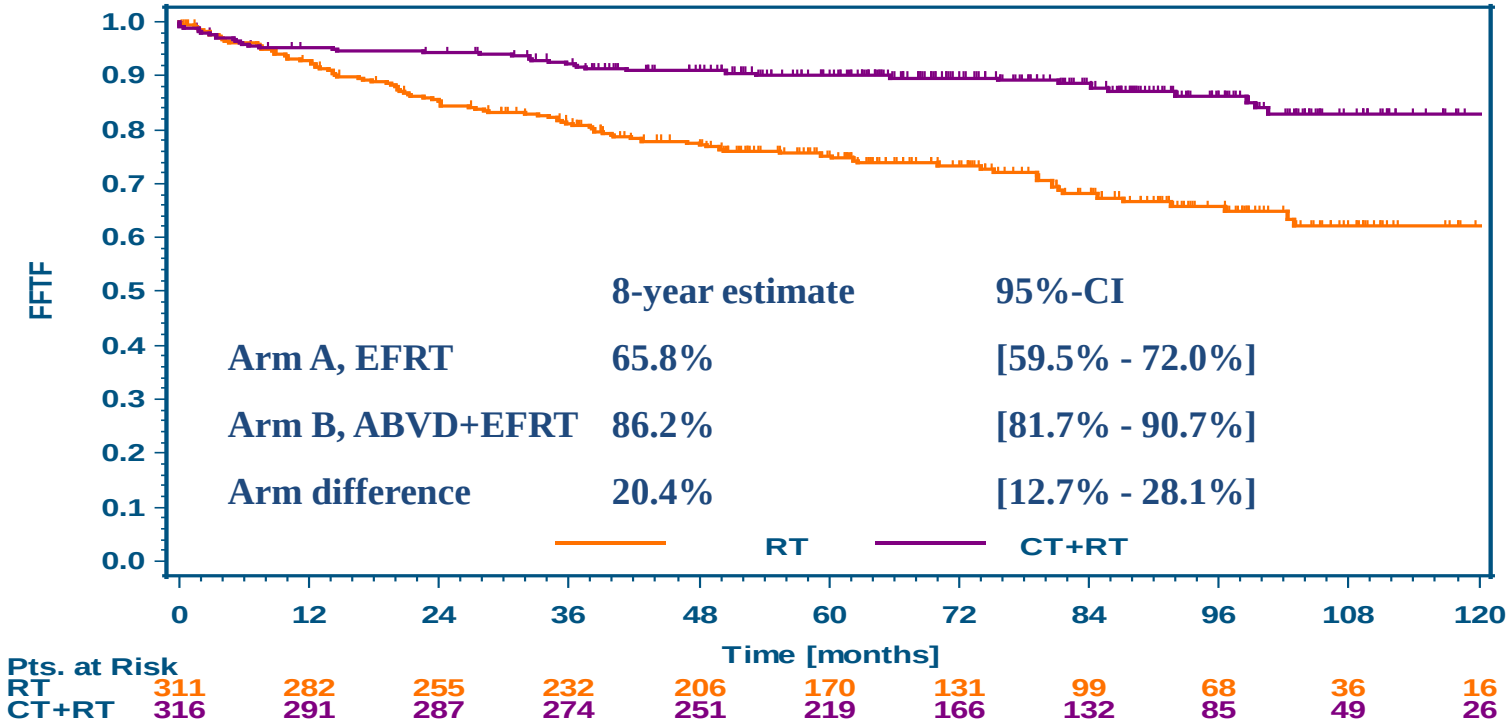
FFTF for pts with early favorable



Ferme et al NEJM 2007

HD7 trial

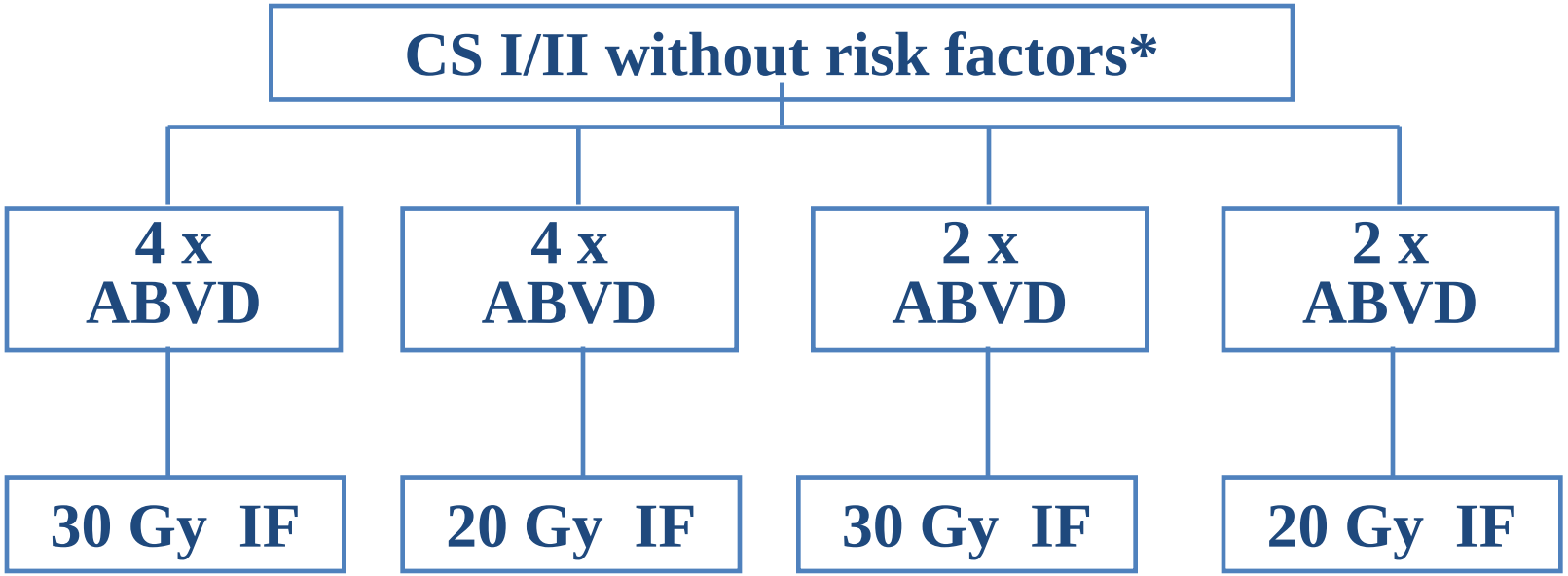
For early favorable HL (FFTF)



Engert et al, JCO 2007

GHSG HD10 Study

Early favorable HL

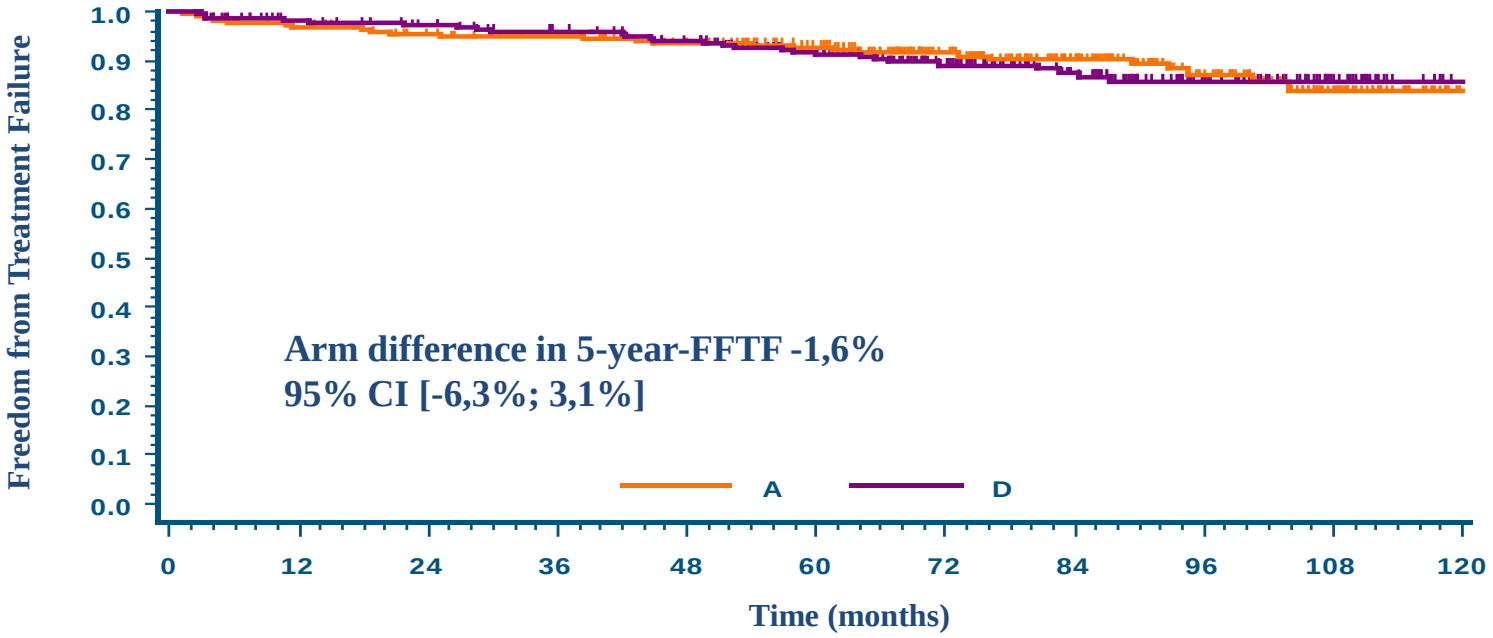


*Large mediastinal mass; extranodal disease; high ERS; 3 or more areas involved

GHSG 2010

GHSG HD10 Study

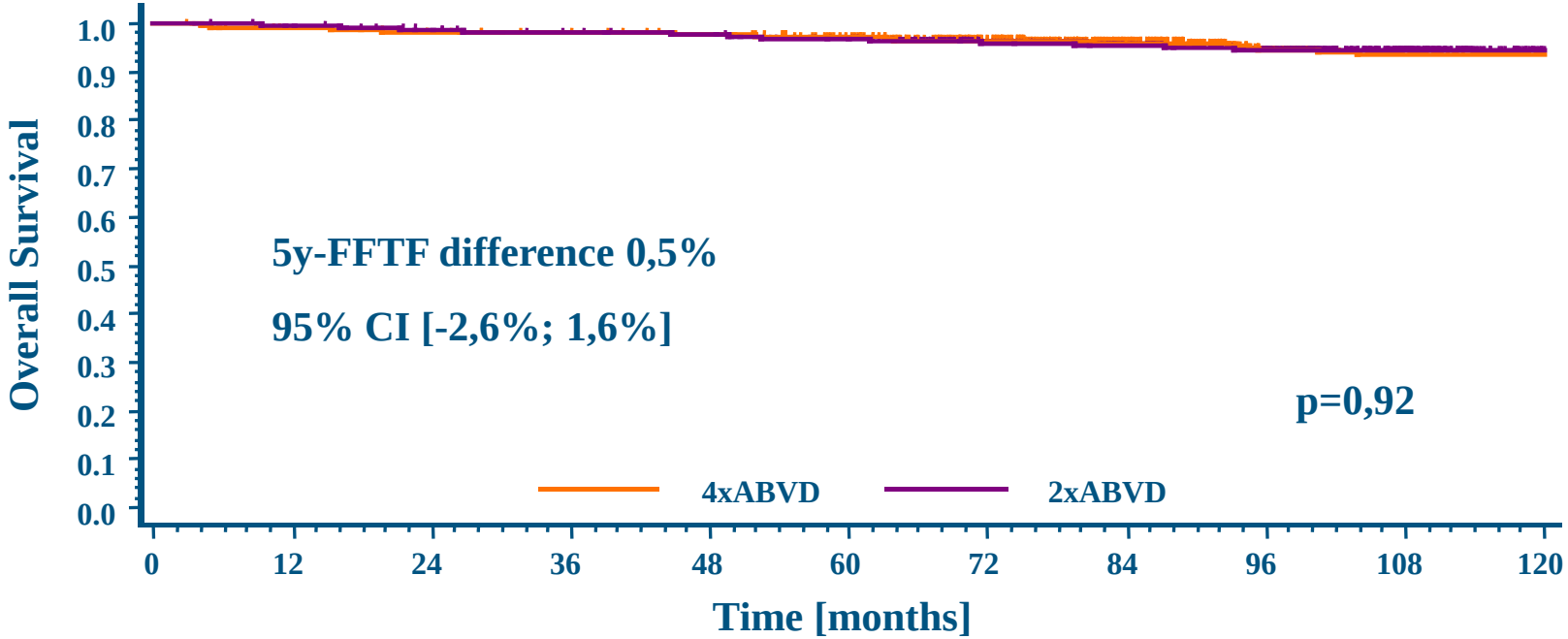
Weakest vs strongest arm (FFTF)



Engert A et al, NEJM 2010

GHSG HD10 Study

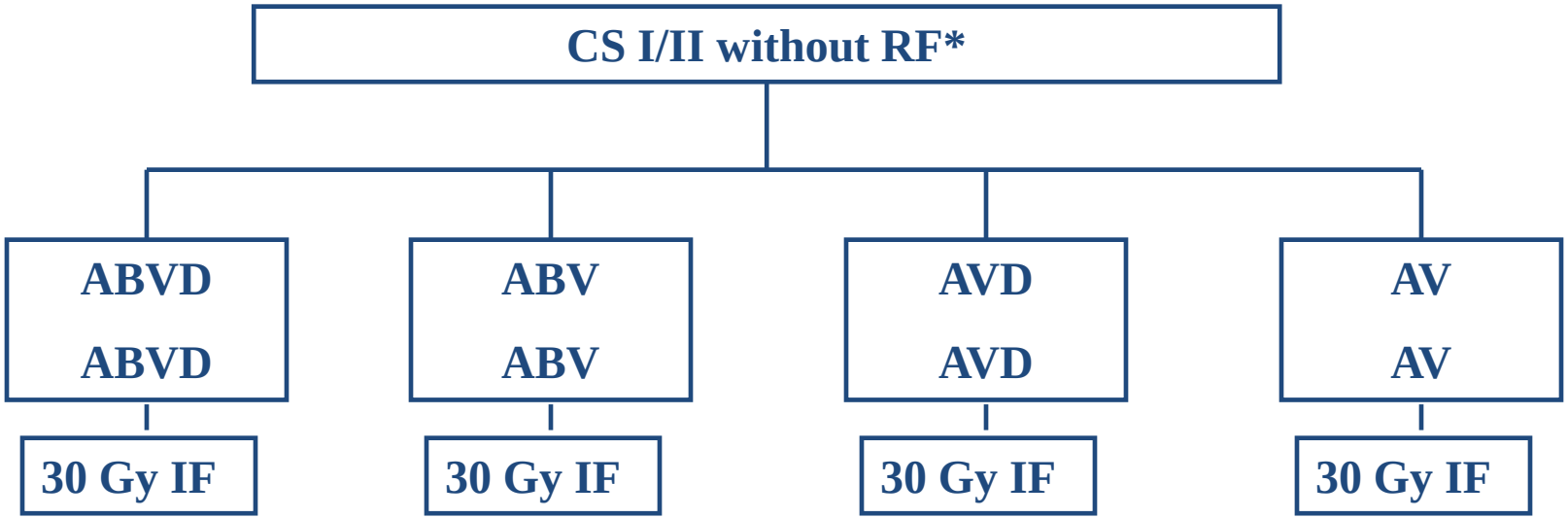
Overall Survival



Engert et al NEJM 2010

HD13 Study

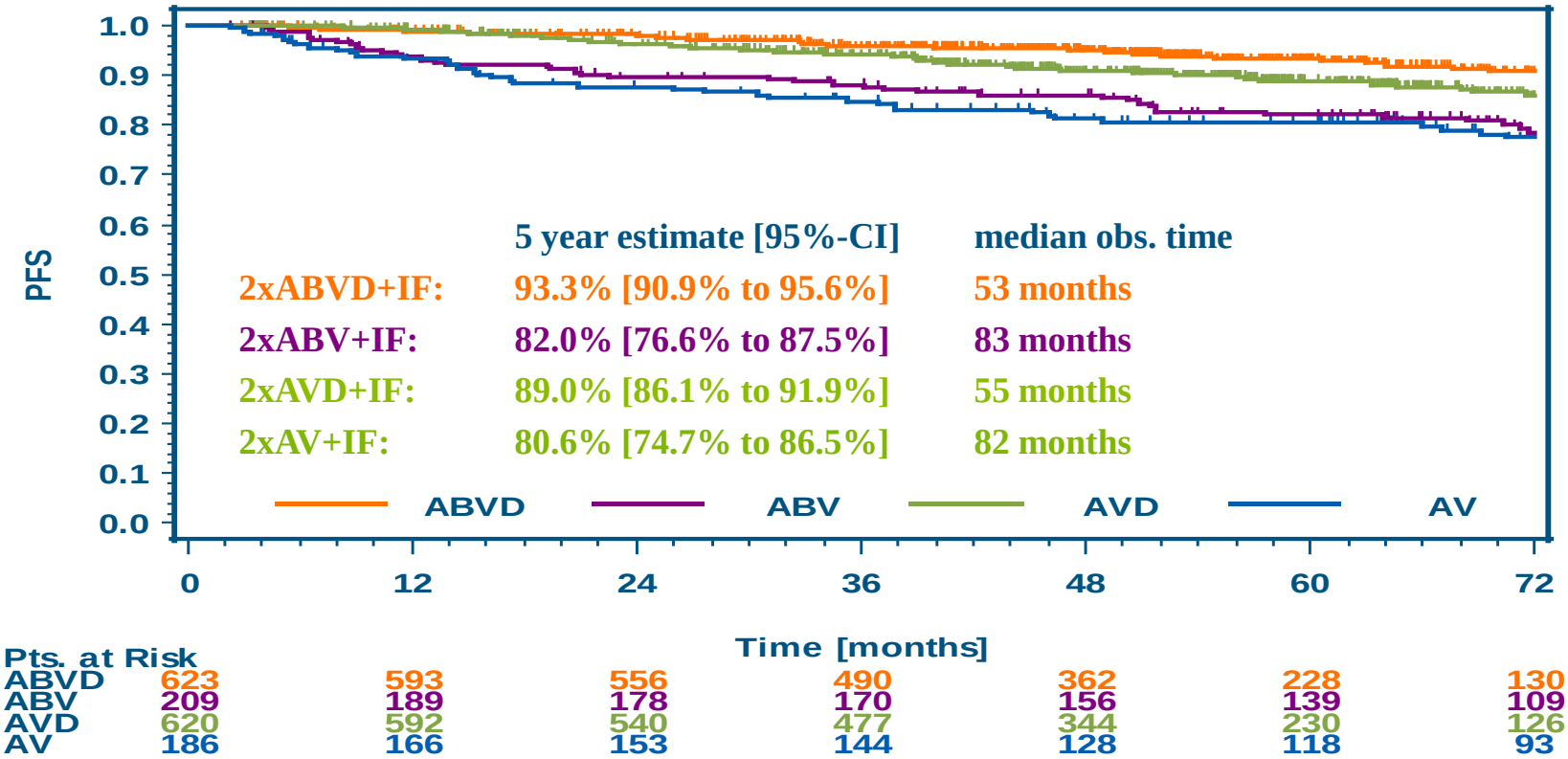
Early favorable HL



*Large mediastinal mass; extranodal disease; high ERS; 3 or more areas involved

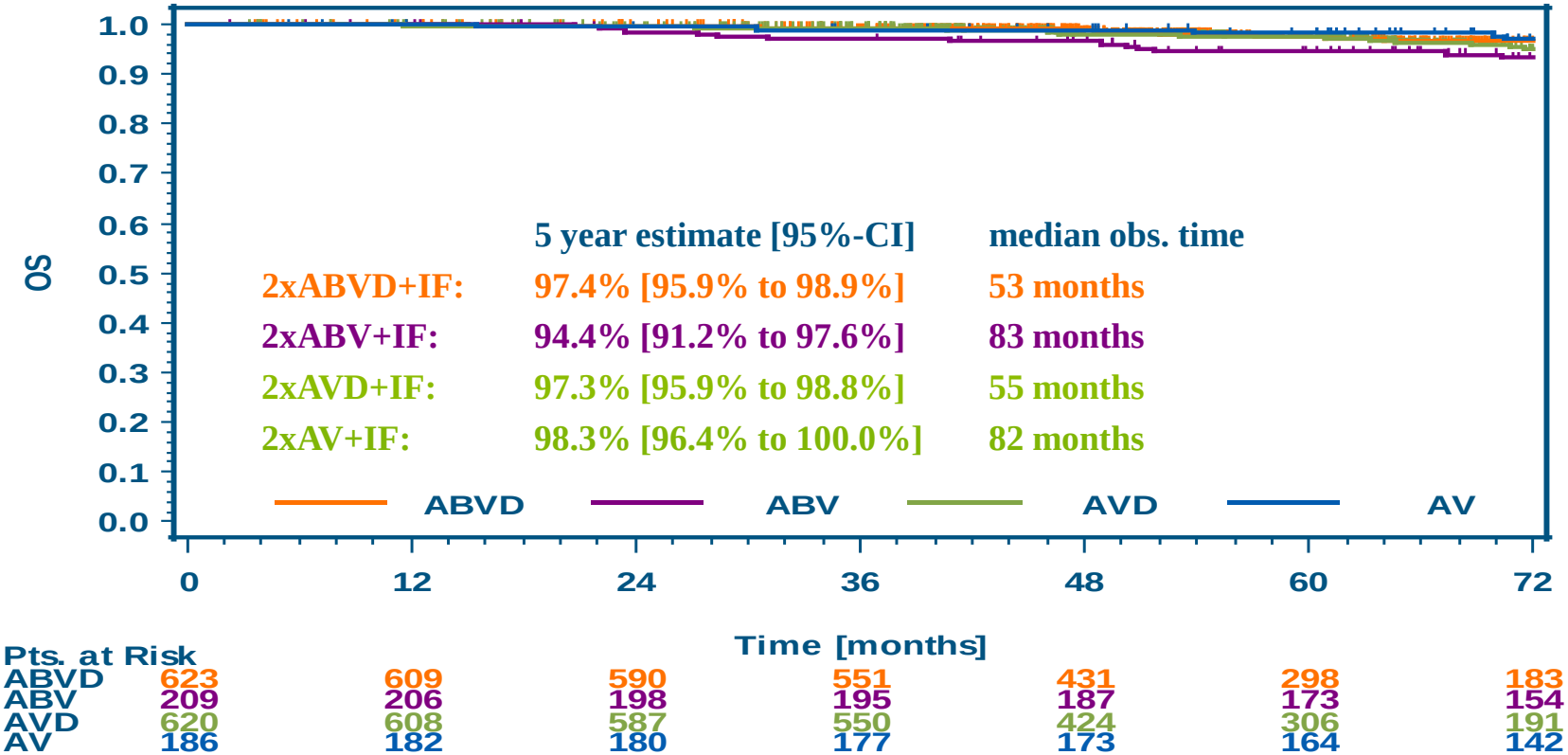
HD13: Progression-free survival

All patients (ITT)



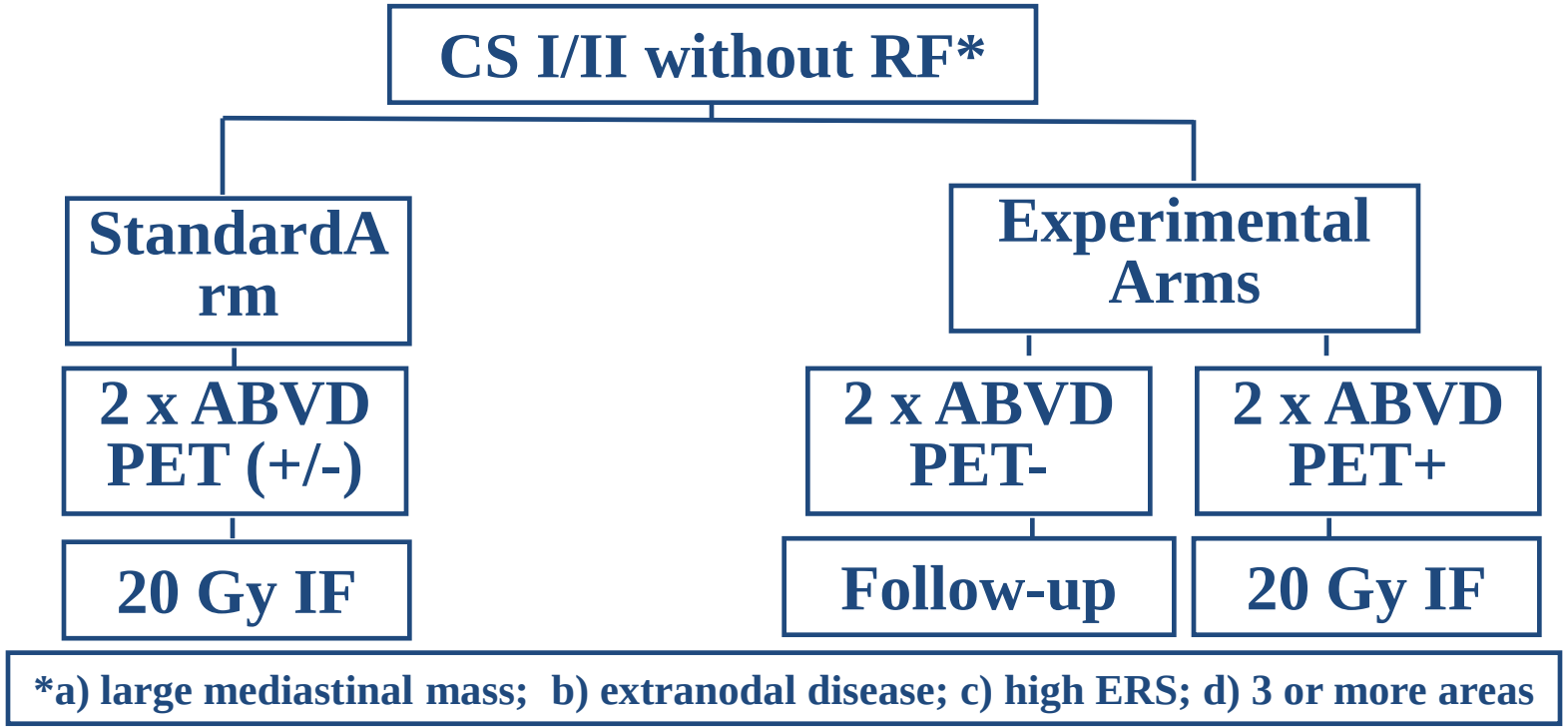
HD13: Overall survival

All patients (ITT)



Ongoing GHSG trial (HD16)

for early favorable HL



GHSG 2010

Combined Modality Treatment of HL

- Background
- Hodgkin lymphoma – early stages
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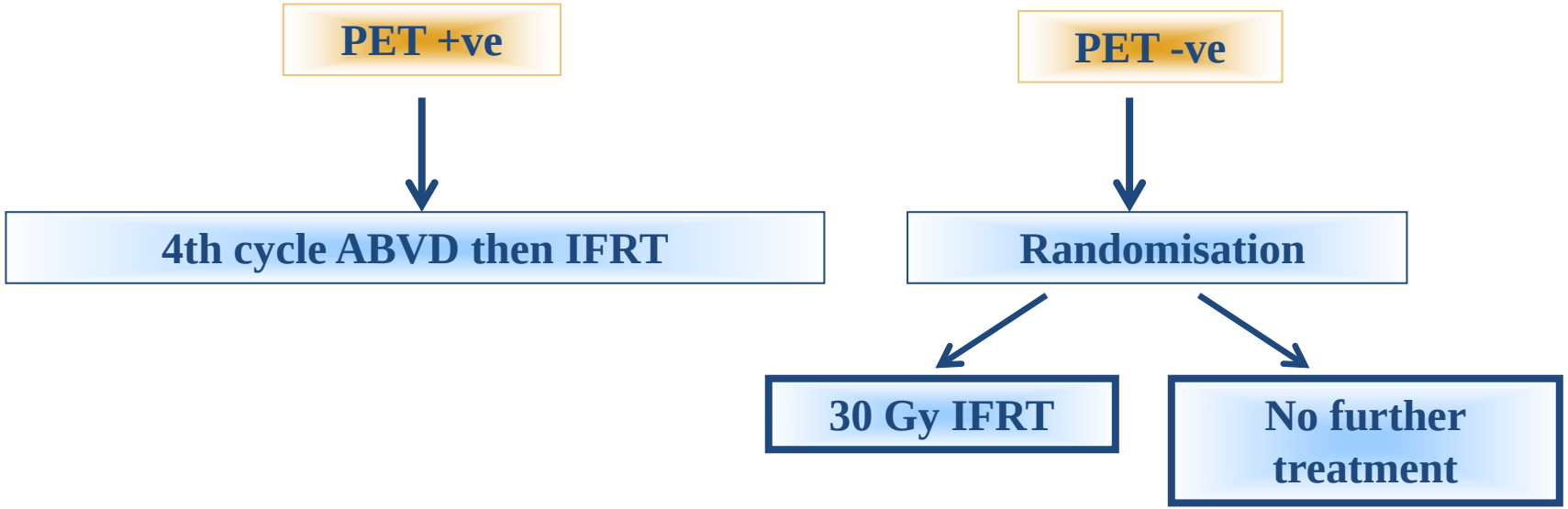
- Summary

UK NCRI RAPID trial

In early stage HL

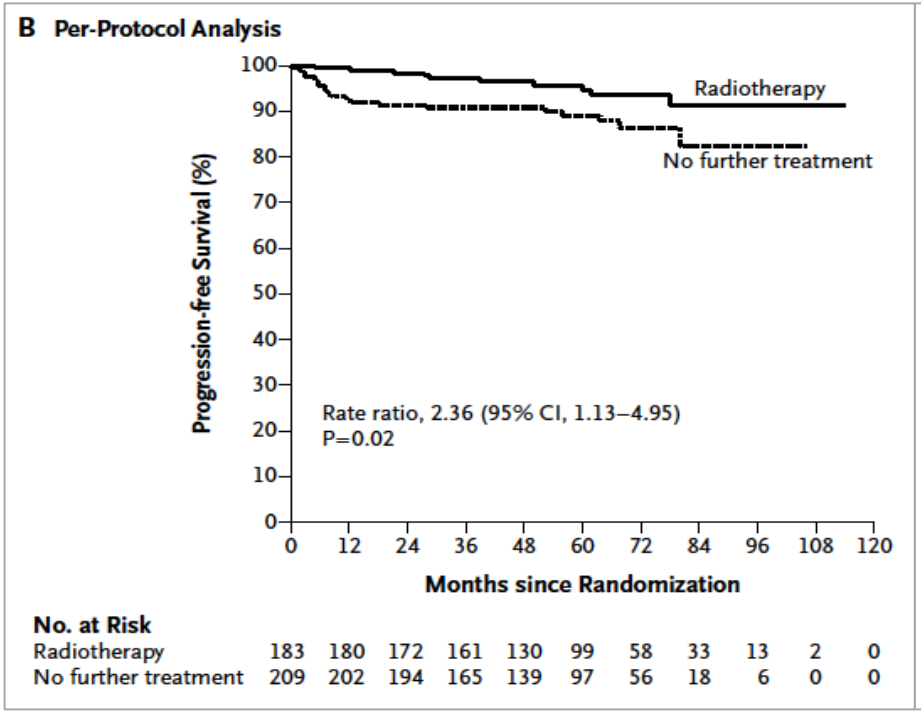
Initial treatment: 3xABVD

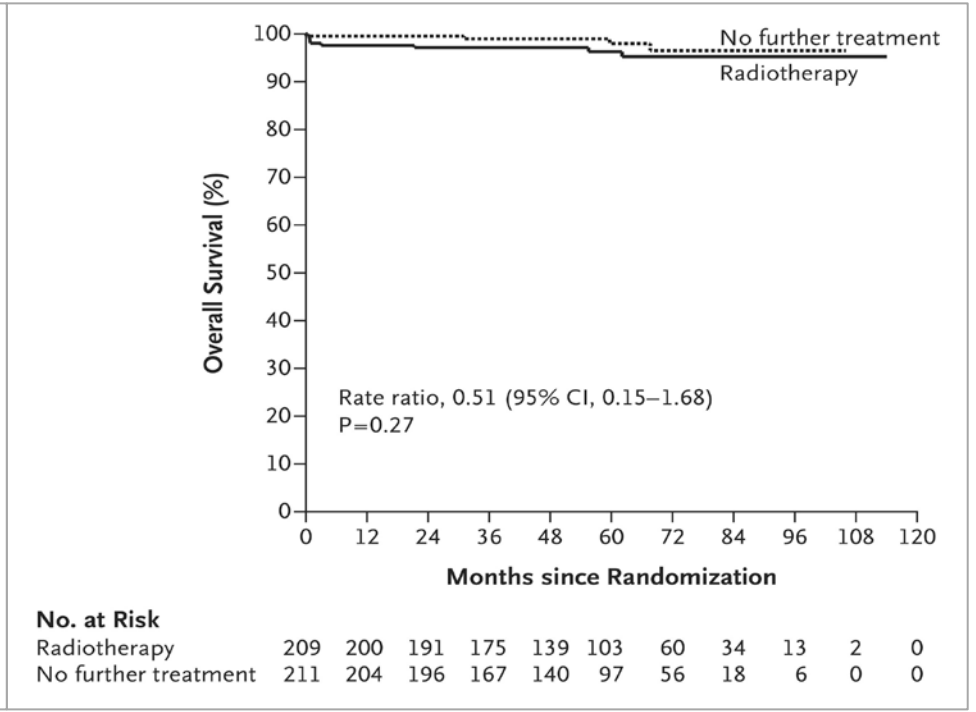
Re-assessment: if response, PET scan performed



UK NCRI RAPID trial

Early stage HL



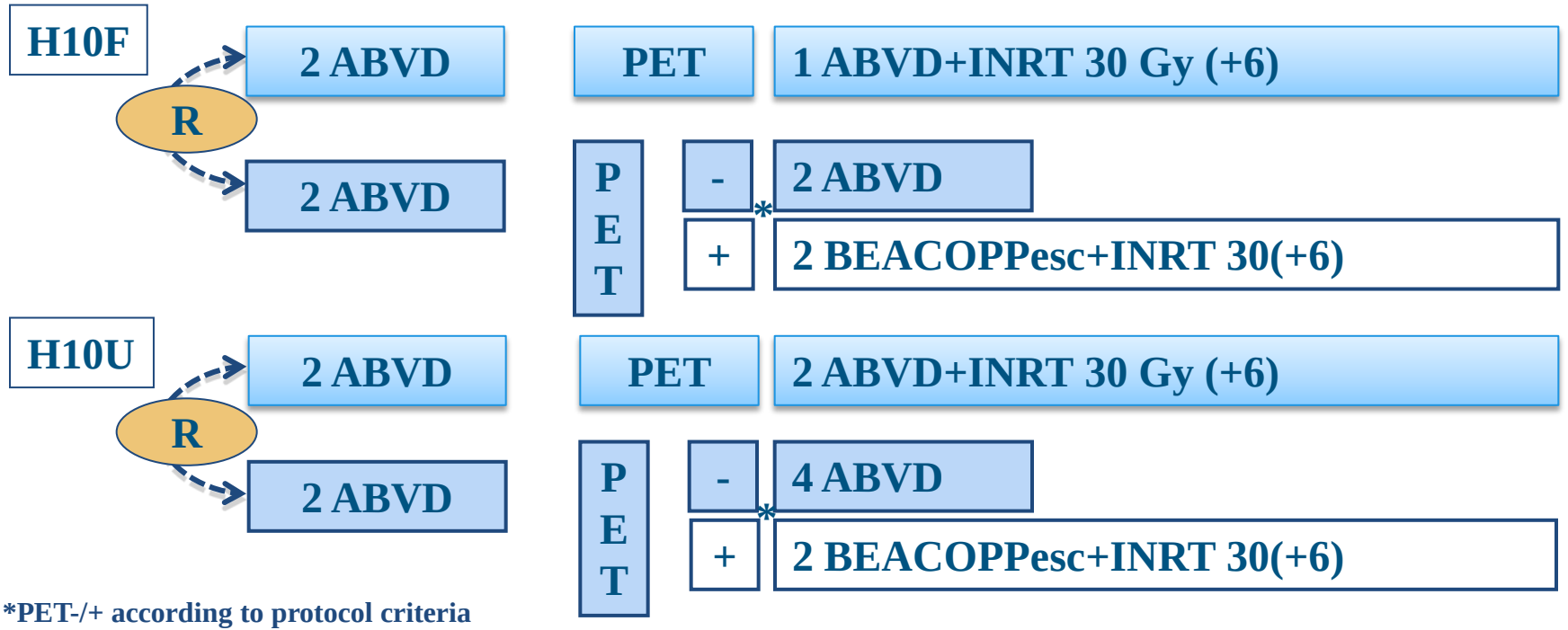


Radford J et al NEJM (2015) 372;17:1598-1605

EORTC/GELA/IIL H10 Study

For early favorable and unfavorable

H10 (#20051): study design



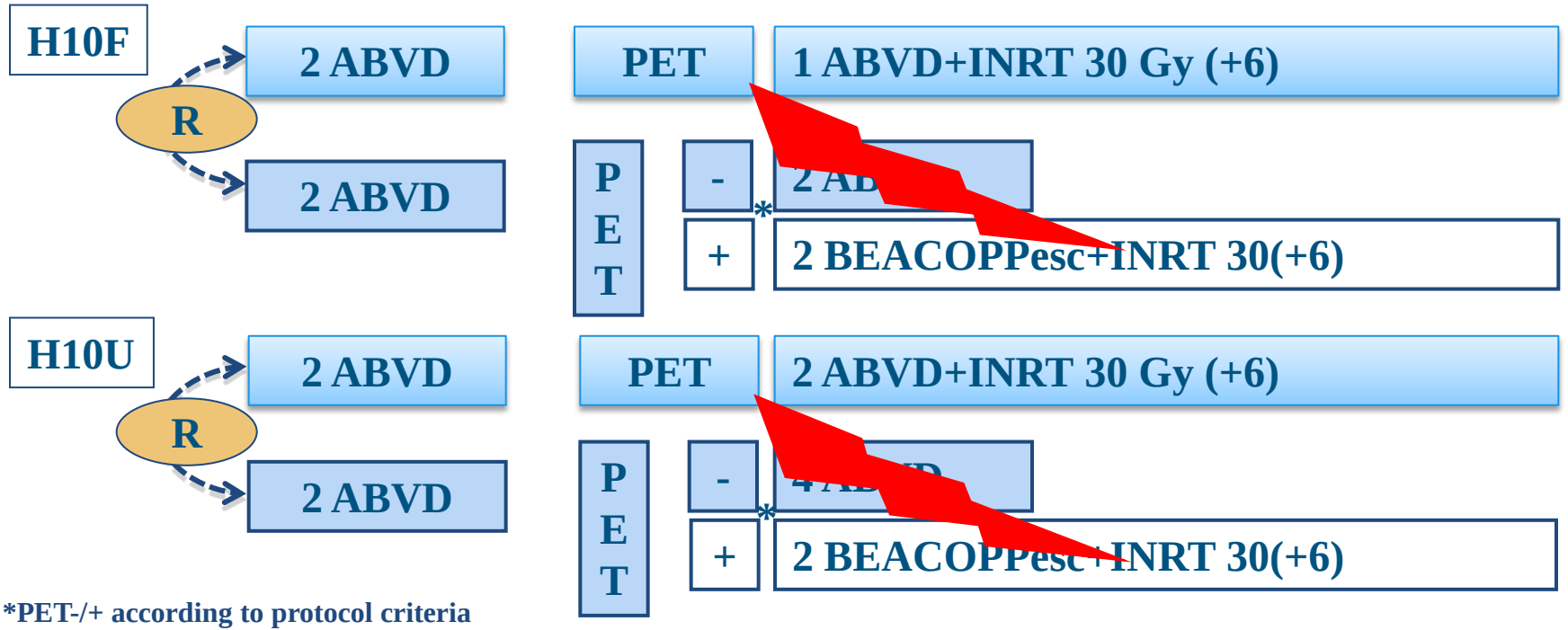
*PET-/+ according to protocol criteria

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

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

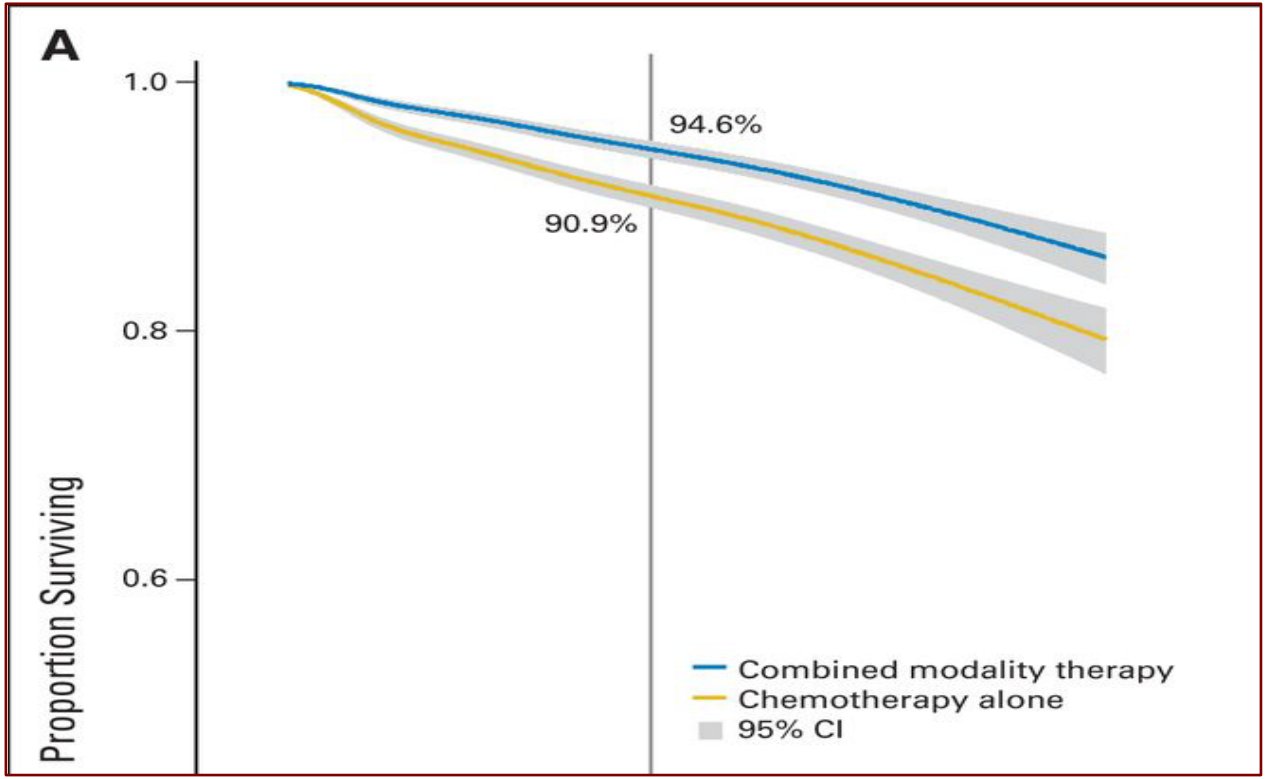
UK RAPID; EORTC/LYSA H10

RT or no RT in PET-negative early stage

- **Central PET review necessary**
- **More events in PET- patients with chemo only**
- **Similar findings but opposite conclusions (8 vs 20 and 8 vs 25 events) between RAPID[1] and H10[2]**
- **Rapid failed to demonstrate non-inferiority (HR 1.57; p=0.27) with PFS differences of up to 8.8% (ITT) and 11.0% (per protocol)**
- **No difference between PET+ and PET- patients –questionable role of PET in this setting!**
- **Deleting RT in PET- early stage HL still experimental**

[1]Radfort et al NEJM 2015
[2]Raemakers et al JCO 2015

CMT or chemo alone in early cHL

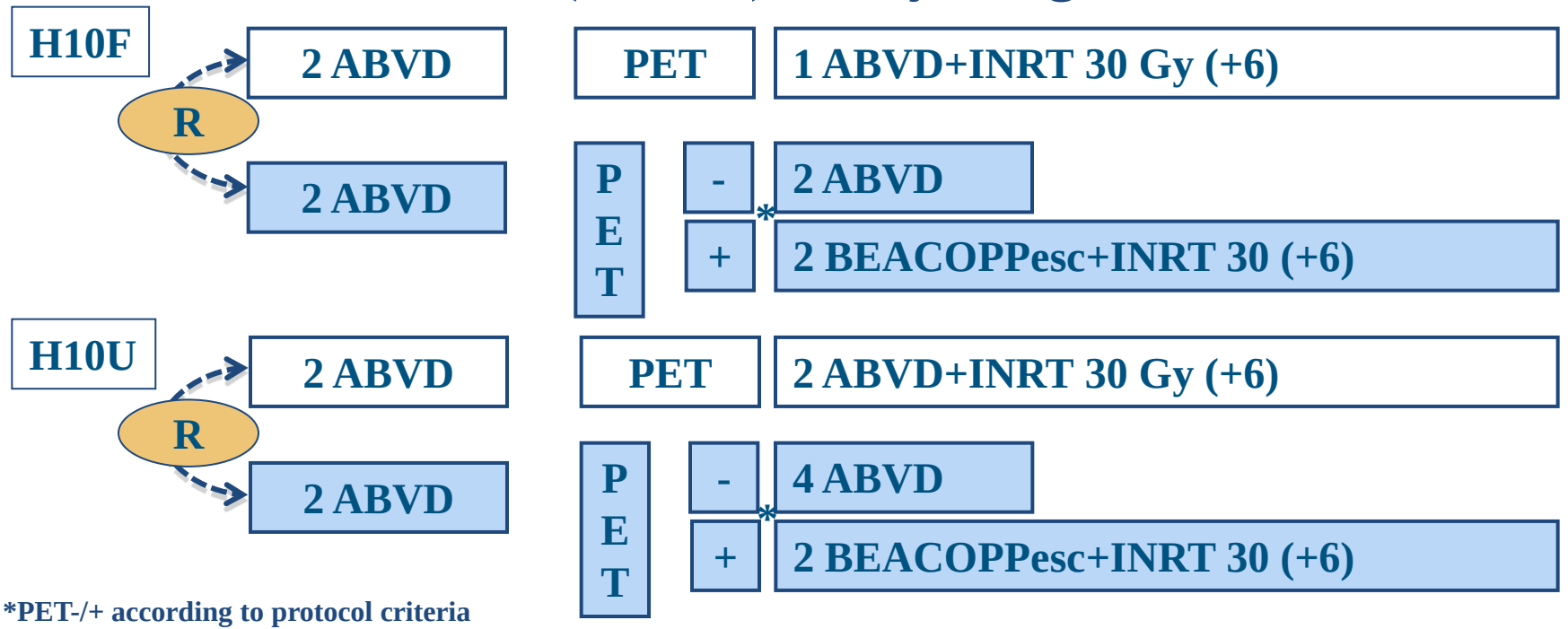


Olszewski et al. JCO 2015;33:625-633

EORTC/GELA/IIL H10 Study

Results of PET+ patients

H10 (#20051): study design

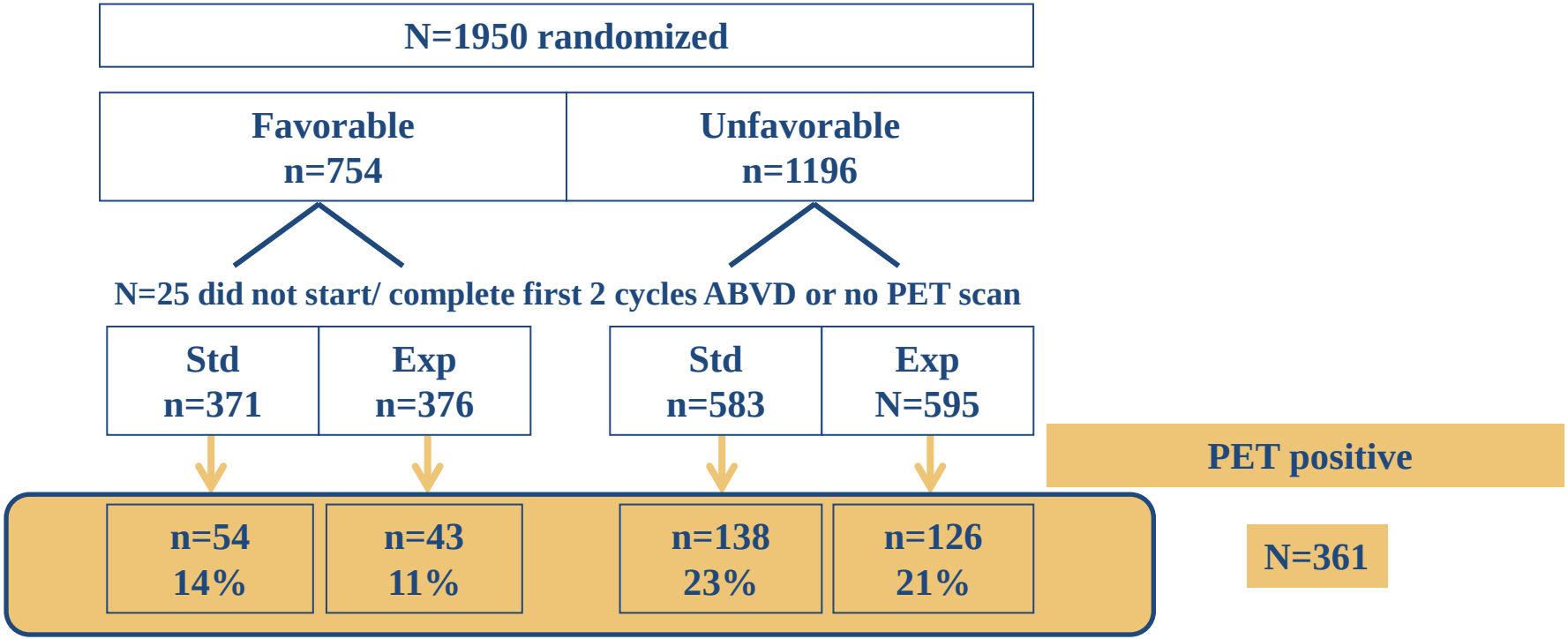


*PET-/+ according to protocol criteria

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

EORTC/GELA/IIL H10 Study

Accrual 2006 - 2011

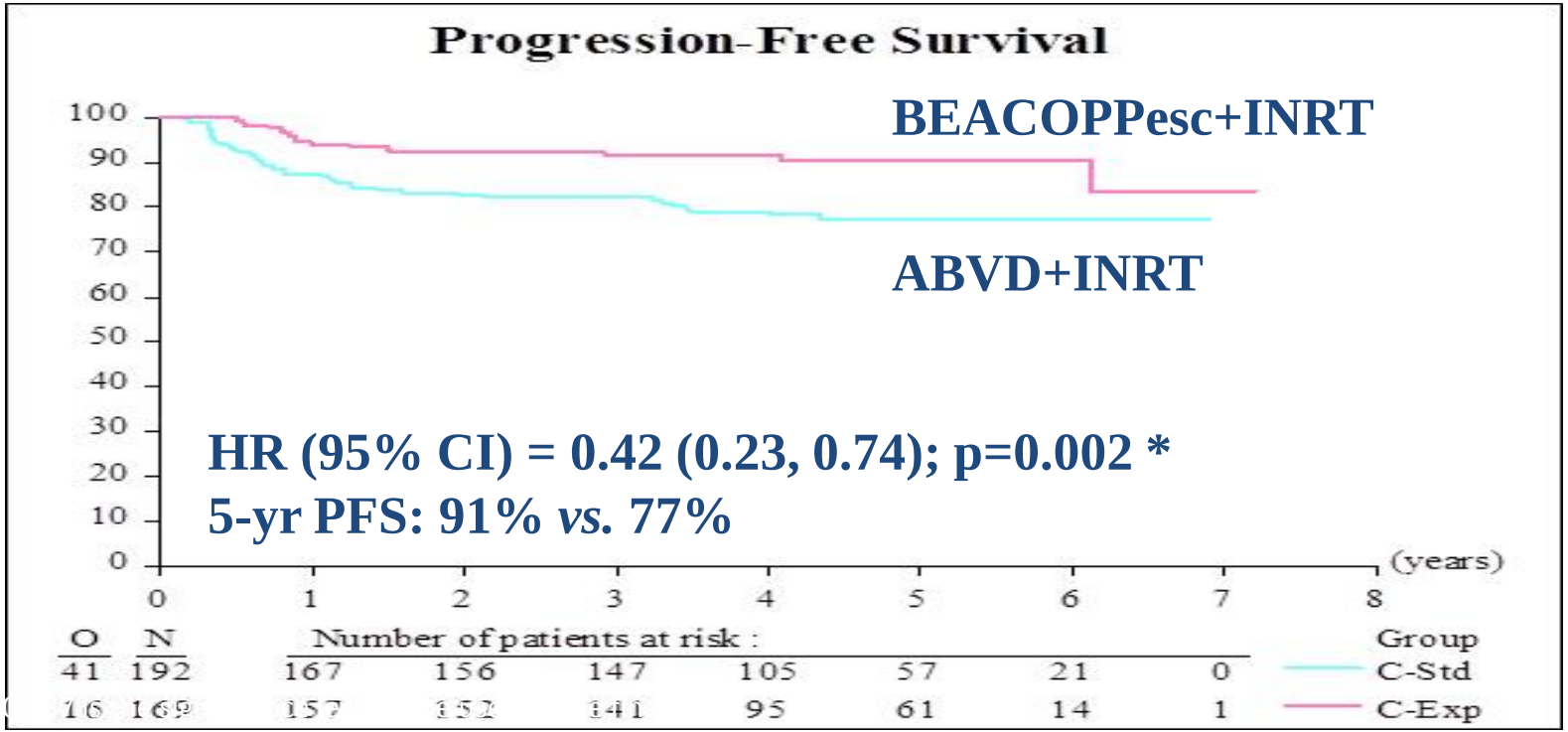


Median FU 4.5 yrs

Raemaekers et at; ICML 2015

PET+ after 2xABVD: B.esc *vs.* ABVD

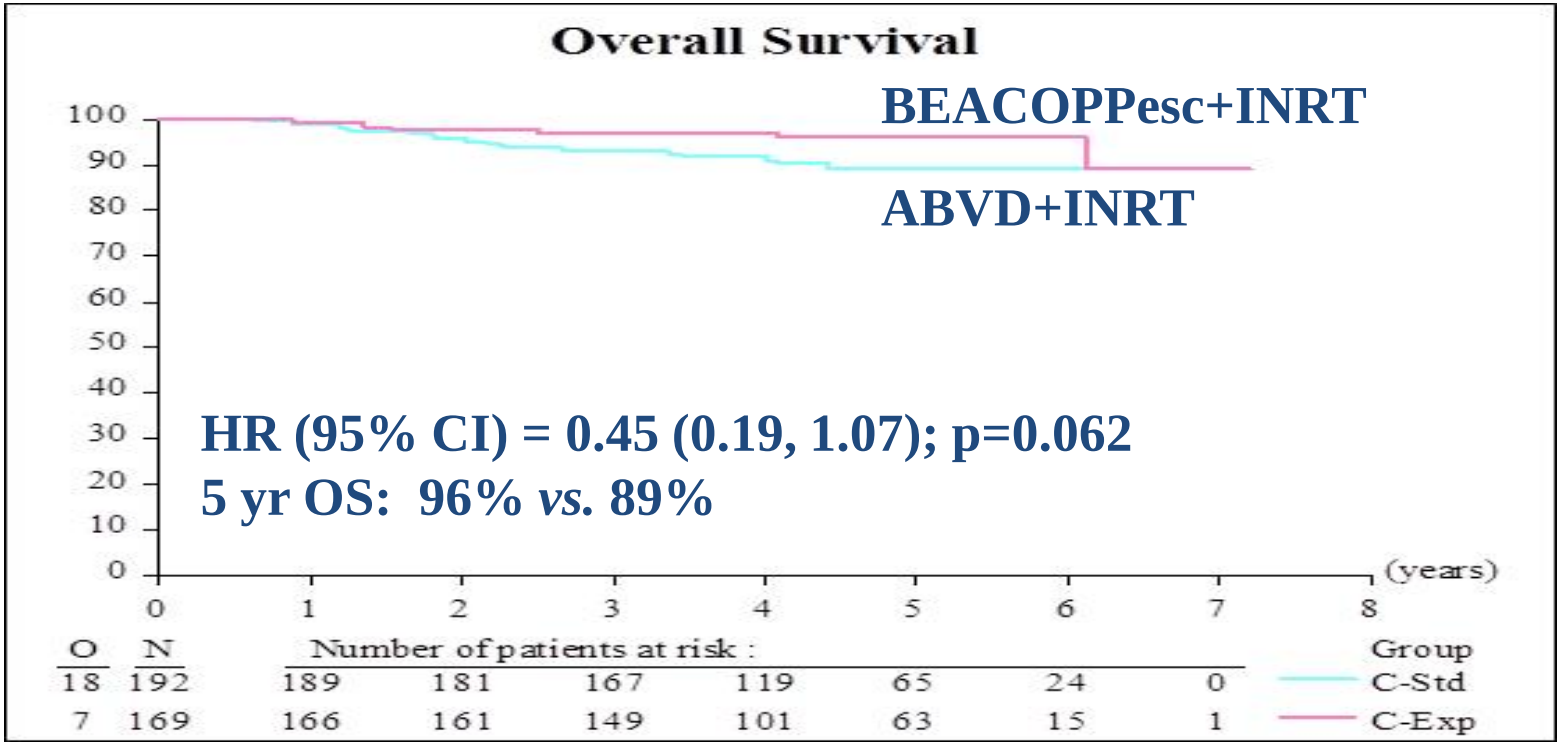
Progression-free survival (PFS)



Raemaekers et at; ICML 2015

PET+ group: BEACOPPesc *vs.* ABVD

Overall Survival (OS)



Raemaekers et at; ICML 2015

Combined Modality Treatment of HL

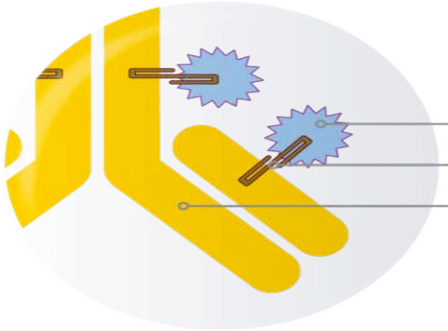
- Background
- Hodgkin lymphoma – early stages
- PET-driven trials
- Chemo-Immunotherapy
- Summary

New Antibodies and Molecules
in Hodgkin Lymphoma

- **Brentuximab Vedotin (anti-CD30 ADC)**
- **AFM13 (CD16/CD30 bispecific)**
- **Lenalidomide (IMID)**
- **Everolimus, (mTor-inhibitor)**
- **Rituximab, Ofatumumab (anti-CD20)**
- **Panobinostat, Mocitinostat (H-DAC inhibitors)**
- **TKI´s, JAK2i, PARPi**
- **PD-1 inhibitors**

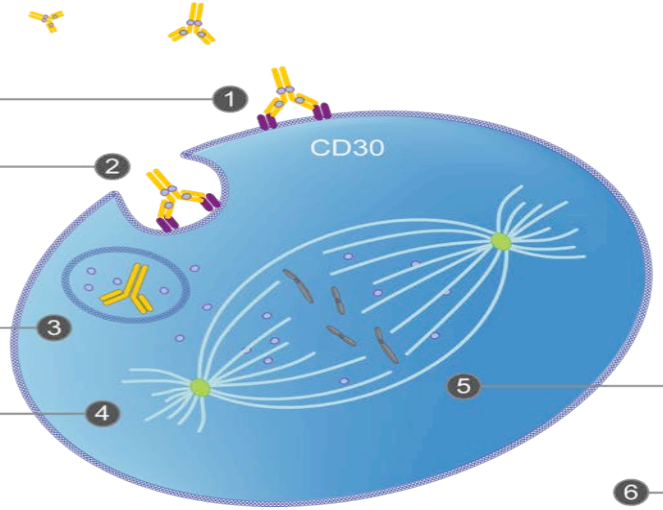
Brentuximab Vedotin (SGN-35)

Mechanism of action



Brentuximab vedotin (SGN-35) ADC

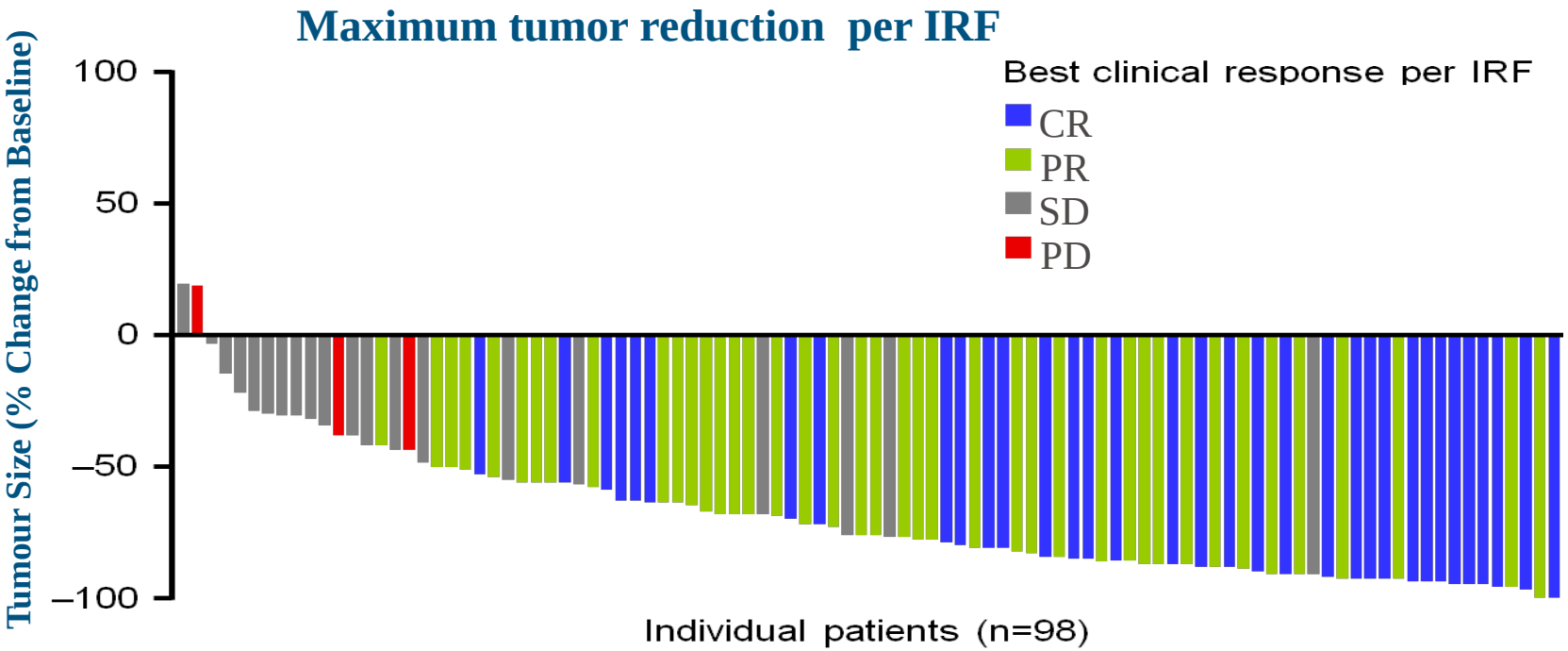
- monomethyl auristatin E (MMAE), potent antitubulin agent
- protease-cleavable linker
- anti-CD30 monoclonal antibody



1. ADC binds to CD30
2. ADC-CD30 complex traffics to lysosome
3. MMAE is released
4. MMAE disrupts Microtubule network
5. G2/M cell cycle arrest
6. Apoptosis

Phase II Pivotal Study of BV

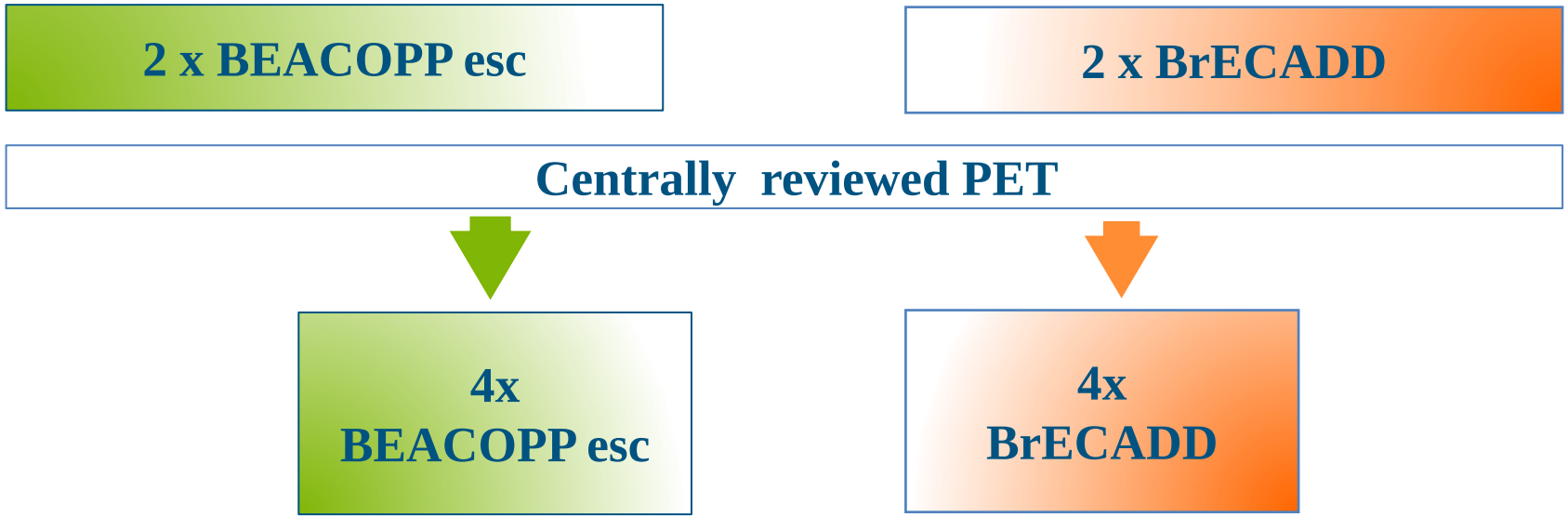
Patients with R/R HL post ASCT



Younes A et al, J Clin Oncol 2012;30: 2183-2189.

HD21: GHSG Perspective

BV in advanced stage HL



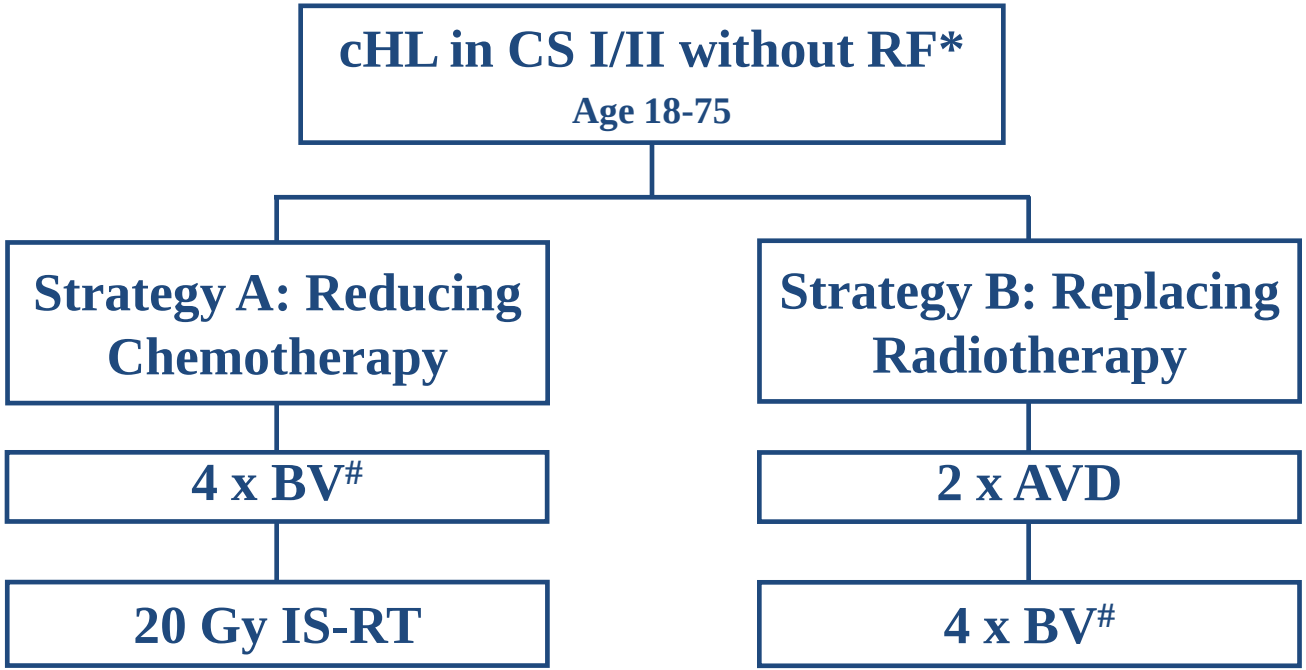
End of therapy and residual nodes > 2.5 cm:

PET positiv: **Rx**

PET negative: **Follow up**

Phase II trial design

BV in early favorable HL

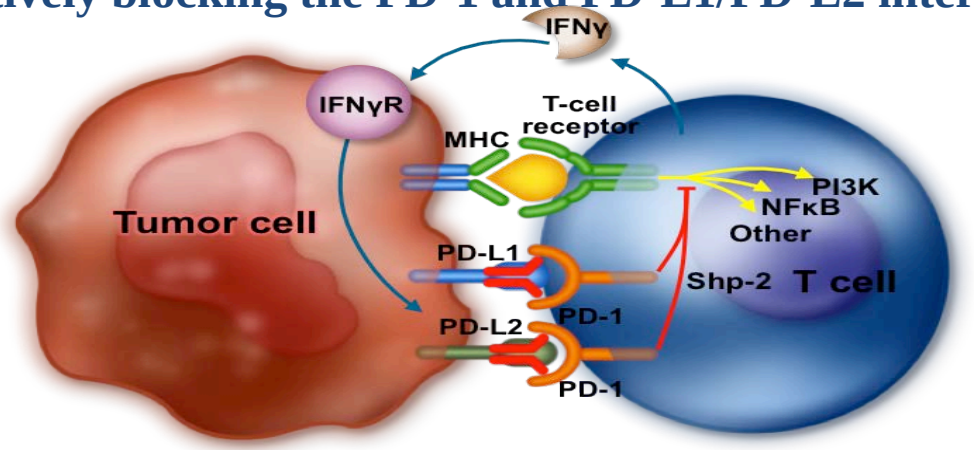


* a) large mediastinal mass b) extranodal disease c) elevated ESR d) ≥3 nodal areas

to be discussed: 1.8 mg/kg every 3 weeks or 1.2 mg/kg every 2 weeks

PD-1 Blockade

- PD-1 engagement by its ligands results in transient down-regulation of T-cell function (T-cell exhaustion).
- Nivolumab (BMS) and Pembrolizumab (MSD) fully human/humanized anti-PD-1 antibody selectively blocking the PD-1 and PD-L1/PD-L2 interaction.



- PD-1 blockade through monoclonal antibody therapy has single-agent activity in a range of solid tumors

Brahmer et al, NEJM 2012;366:2455. Topalian et al, NEJM 2012;366:2443-54

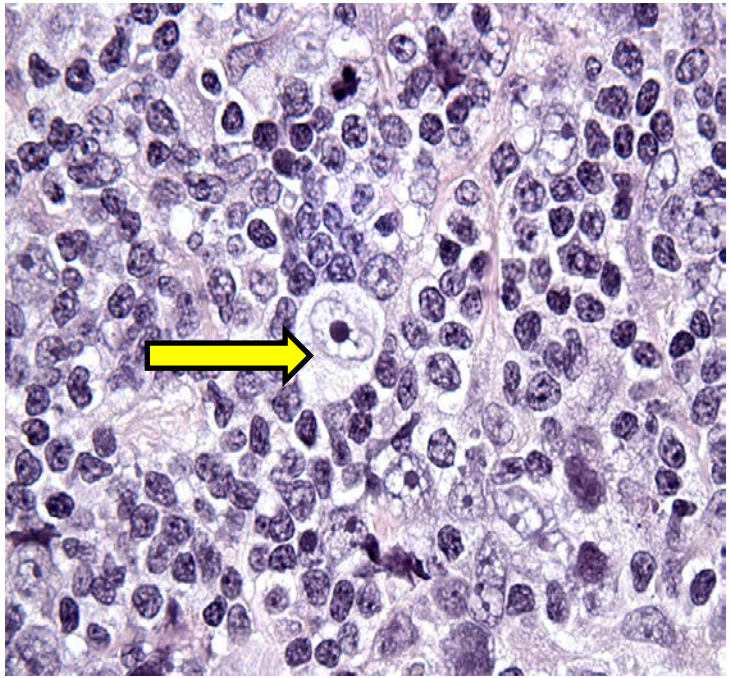
PD-1 Blockade in HL

Background

Pathology of cHL: rare malignant Reed-Sternberg cells within an extensive inflammatory/immune cell infiltrate.

Genetic analyses: frequent 9p24.1 amplification with upregulation of PD-1 ligands and JAK2.

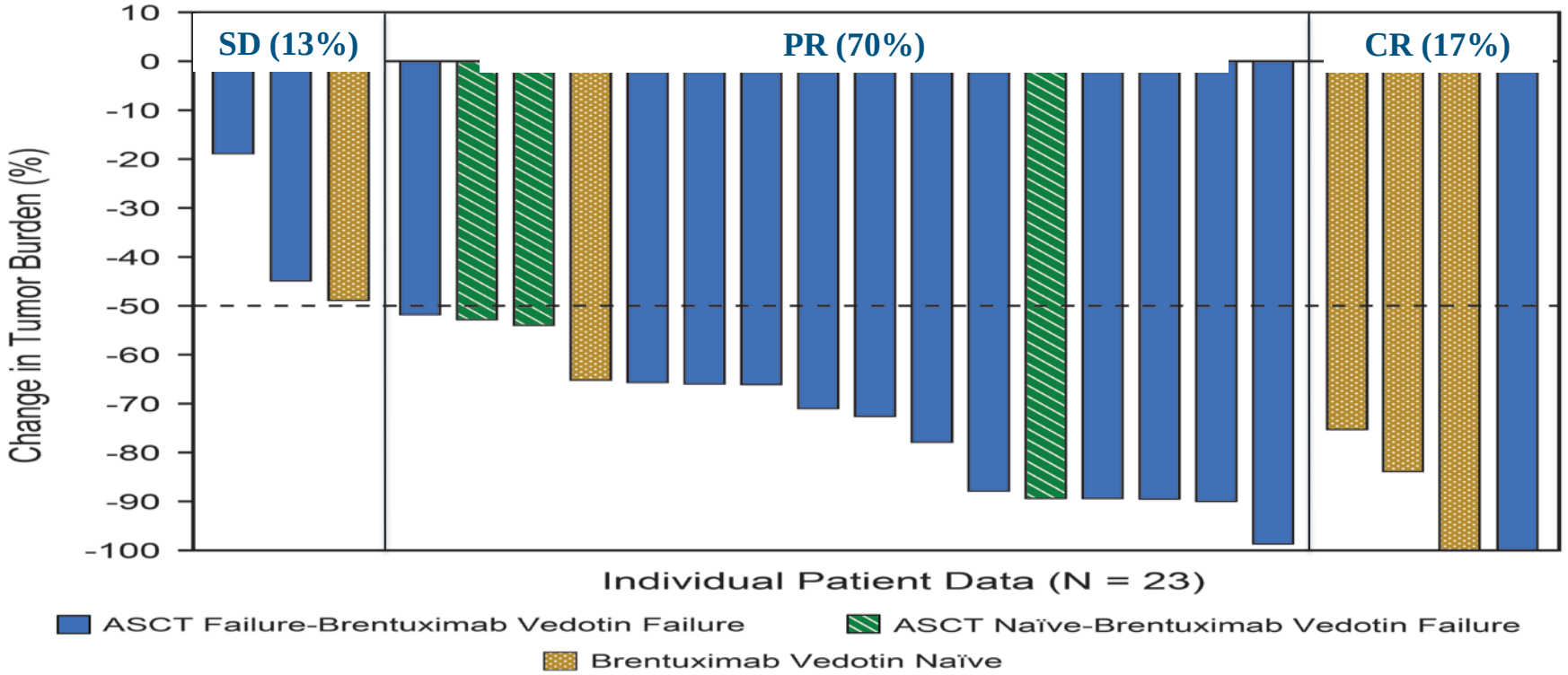
Hypothesis: cHL may have a gene- tically driven dependence on PD-1.



Juszczynski et al, PNAS 2007; 104: 13134
Green et al, Blood 2010; 116: 3268; Chen et al. Clin Cancer Res 2013; 19:3462

Nivolumab in r&r HL

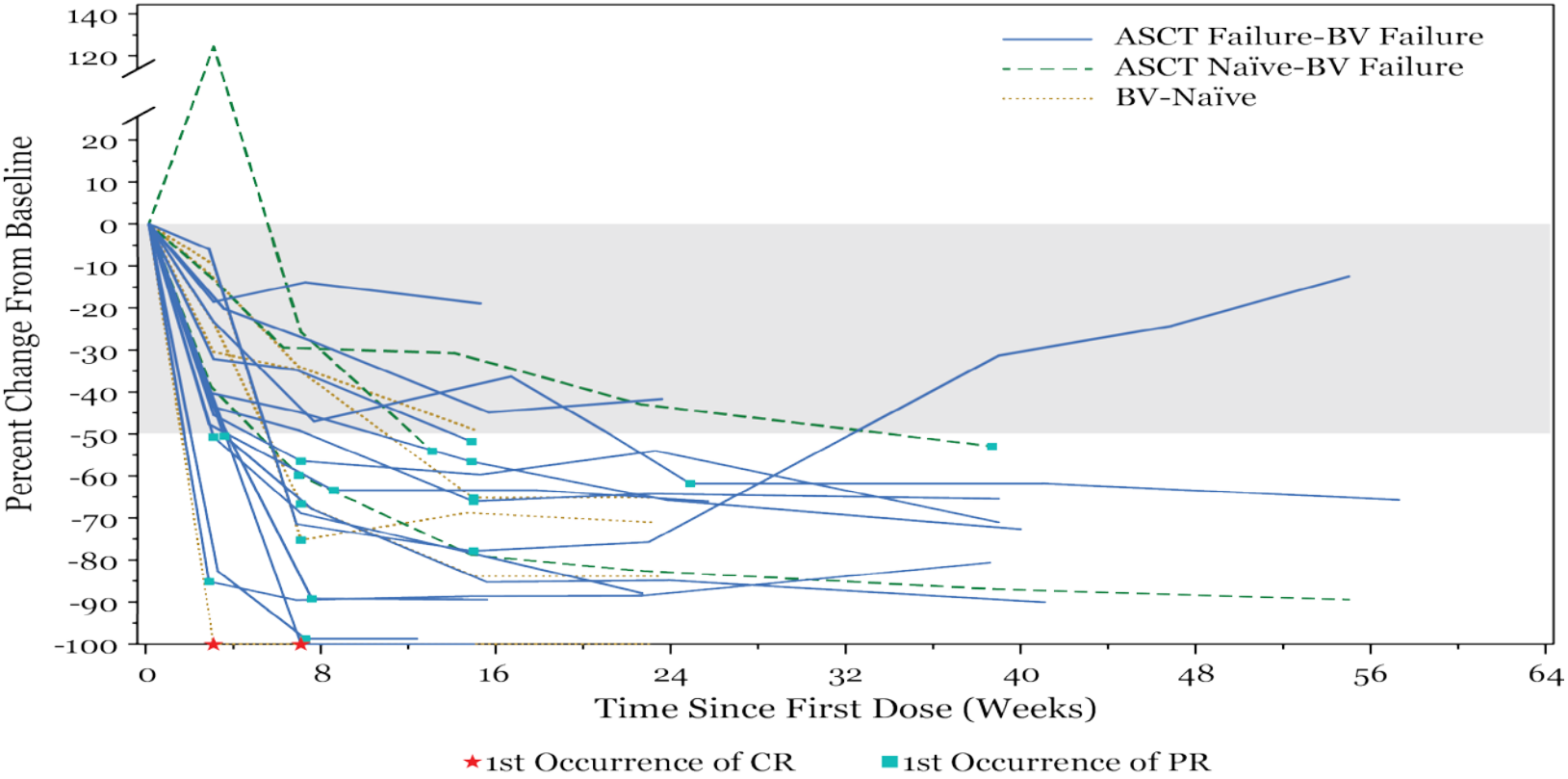
Best Response



Armand P, ASH 2014

Nivolumab Phase I in r&r HL

Response Kinetics



Armand P, ASH 2014

Combined Modality Treatment of HL

- Background
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- Summary

Combined Modality Treatment of Lymphoma

- Despite the impressive cure rate in HL, elderly and r&r pts still constitute an area of unmet medical need
- 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

ESTRO School

WWW.ESTRO.ORG/SCHOOL

Long term toxicity

Late effects after Hodgkin lymphoma: incidence and clinical implications

Berthe Aleman

Radiation oncologist

Content

- Background
- Second malignancies
  - Risks of important SMN (breast, GI and lung cancer)
  - 40 year risk of second malignancies after HL
- Cardiovascular disease
- Clinical implications

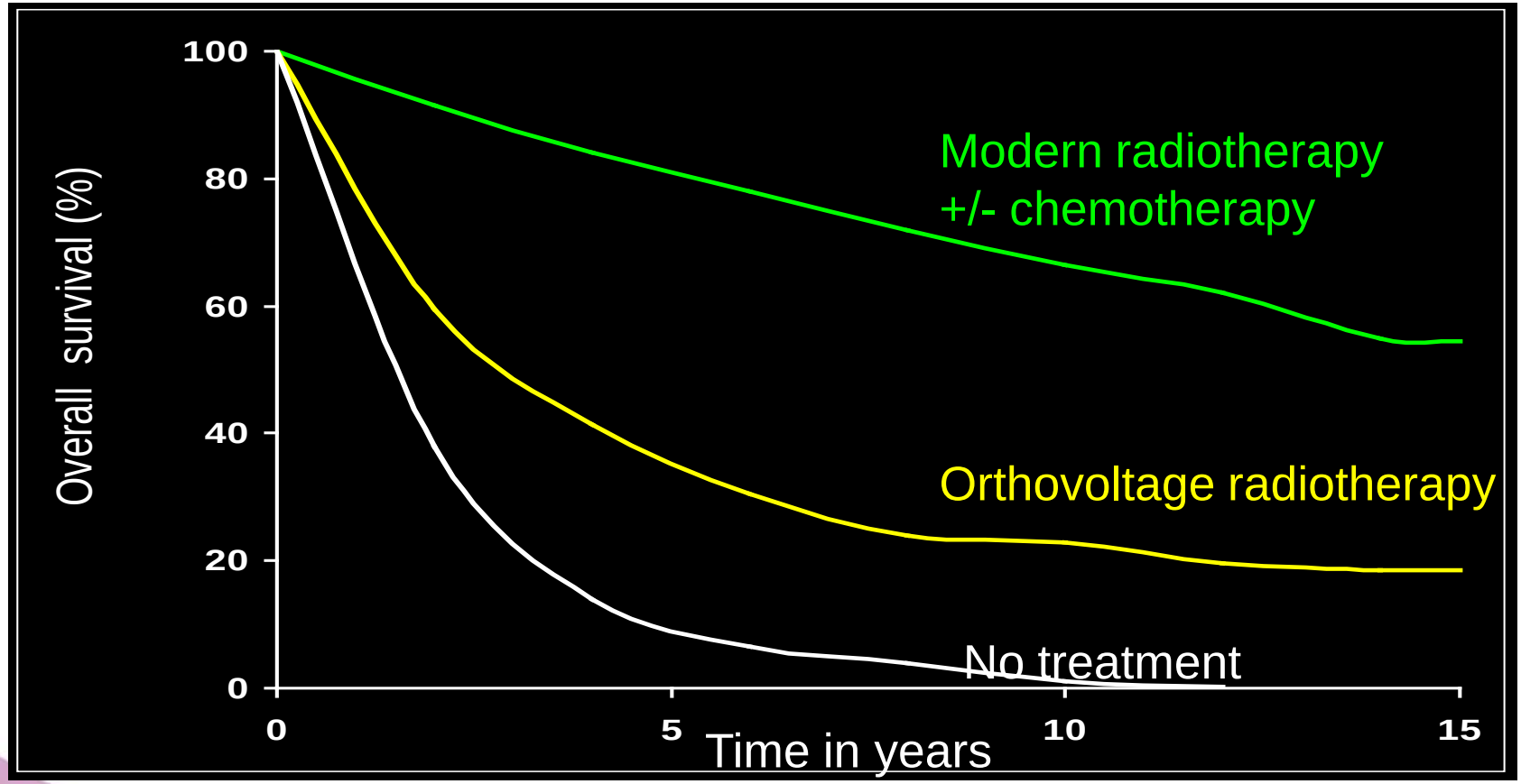
Hodgkin's disease

Nowadays Hodgkin lymphoma

Thomas Hodgkin, 1798-1866

- 0.4% of all new cancers
- 400 new cases per year in NL (16 million inhabitants)
- 67% of all cases below age 45
- Second most common malignancy in young adults
- The prototype of a curable malignancy

Survival after Hodgkin lymphoma

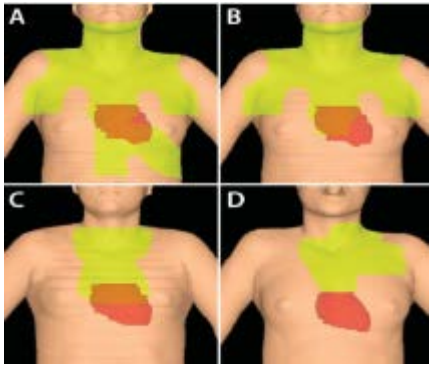


Kaplan 1978

HL treatment changes since 1965

	Chemotherapy Trend: ↓ dose alkylating		**Radiotherapy** Trend: ↓ RT target volumes, ↓ RT dose
<1980	MOPP(like) & single agents	<1980	Classical fields
1980-1995	MOPP/ABVD; MOPP ABV	1980-1995	Classical fields; IFRT
>1995	ABVD; MOPP-ABV; EBVP; BEACOPP	>1995	IFRT
>2012	Brentuximab-vedotin containing regimens	>2006	INRT; ISRT

MOPP: Mechlorethamine, vincristine, procarbazine, prednison
ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine
ABV: Doxorubicin, bleomycin, vinblastine
BEACOPP: Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednison



Hodgson, ASH educational 2011

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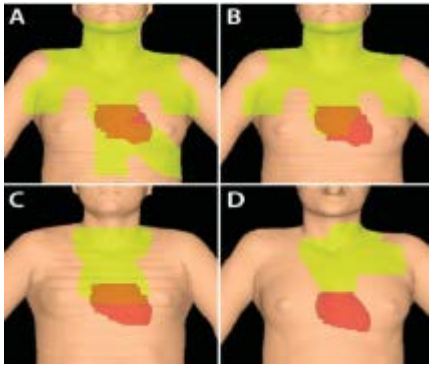


Successes of HL treatment

⬇

Long-term survival

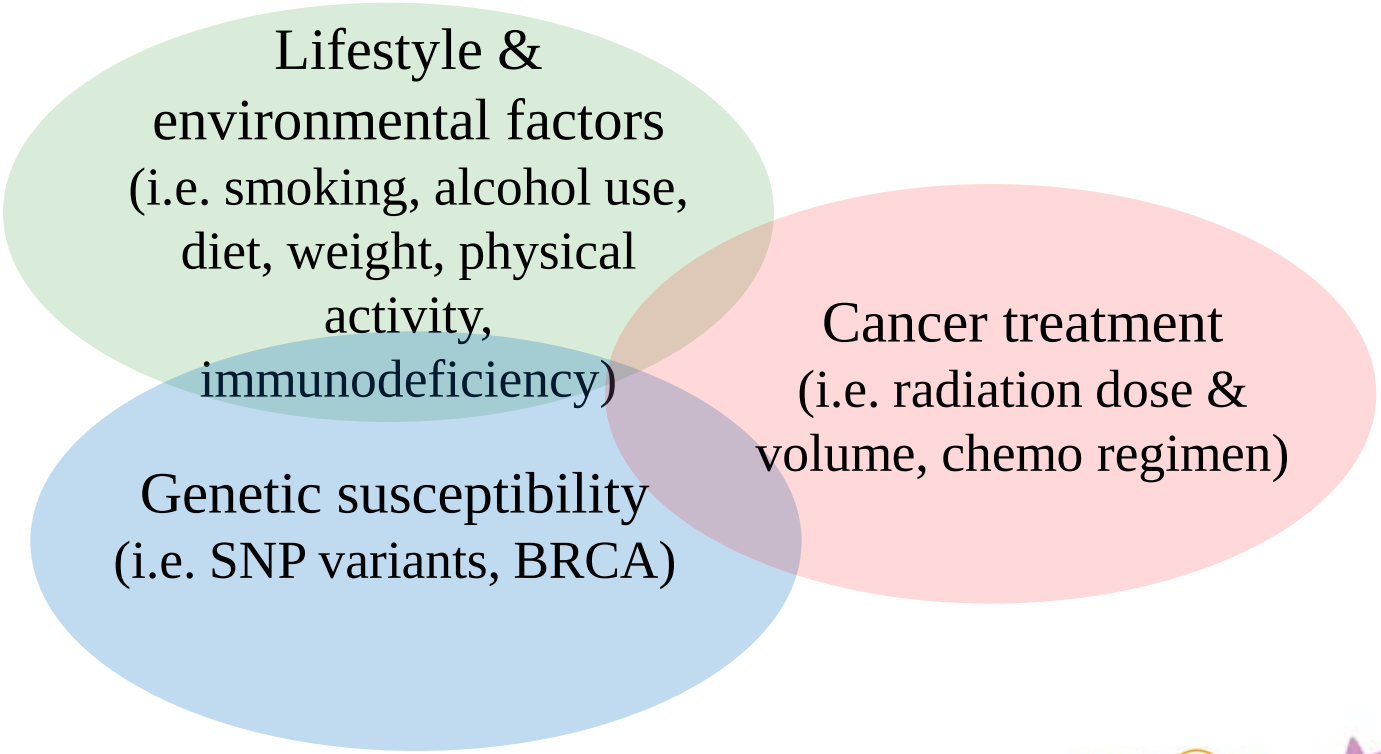
⬇

Possibility to observe late adverse effects of treatment

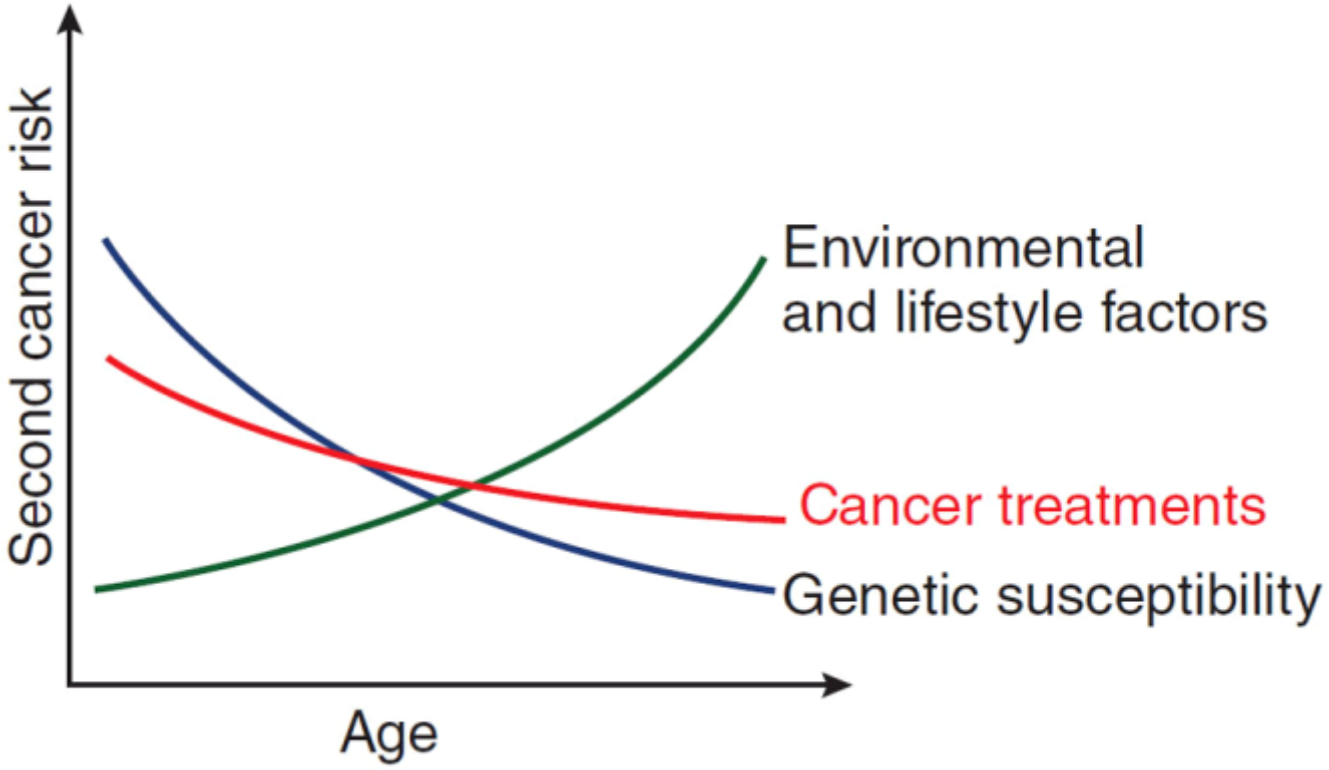
Late effects of treatment for Hodgkin lymphoma

Second malignancies
Cardiovascular disease
Cerebrovascular disease
Diabetes mellitus
Gonadotoxicity
Pulmonary toxicity
Gastrointestinal toxicity
Thyroid dysfunction
Infections
Fatigue

Causes of second cancers



Causes of second cancers in relation to age



Morton & Chanock. Nat Med 2011

Risk measures in late effect research

- Standardized Incidence Ratio (SIR) =

  Observed / Expected numbers of events =

  Relative risk compared to general population

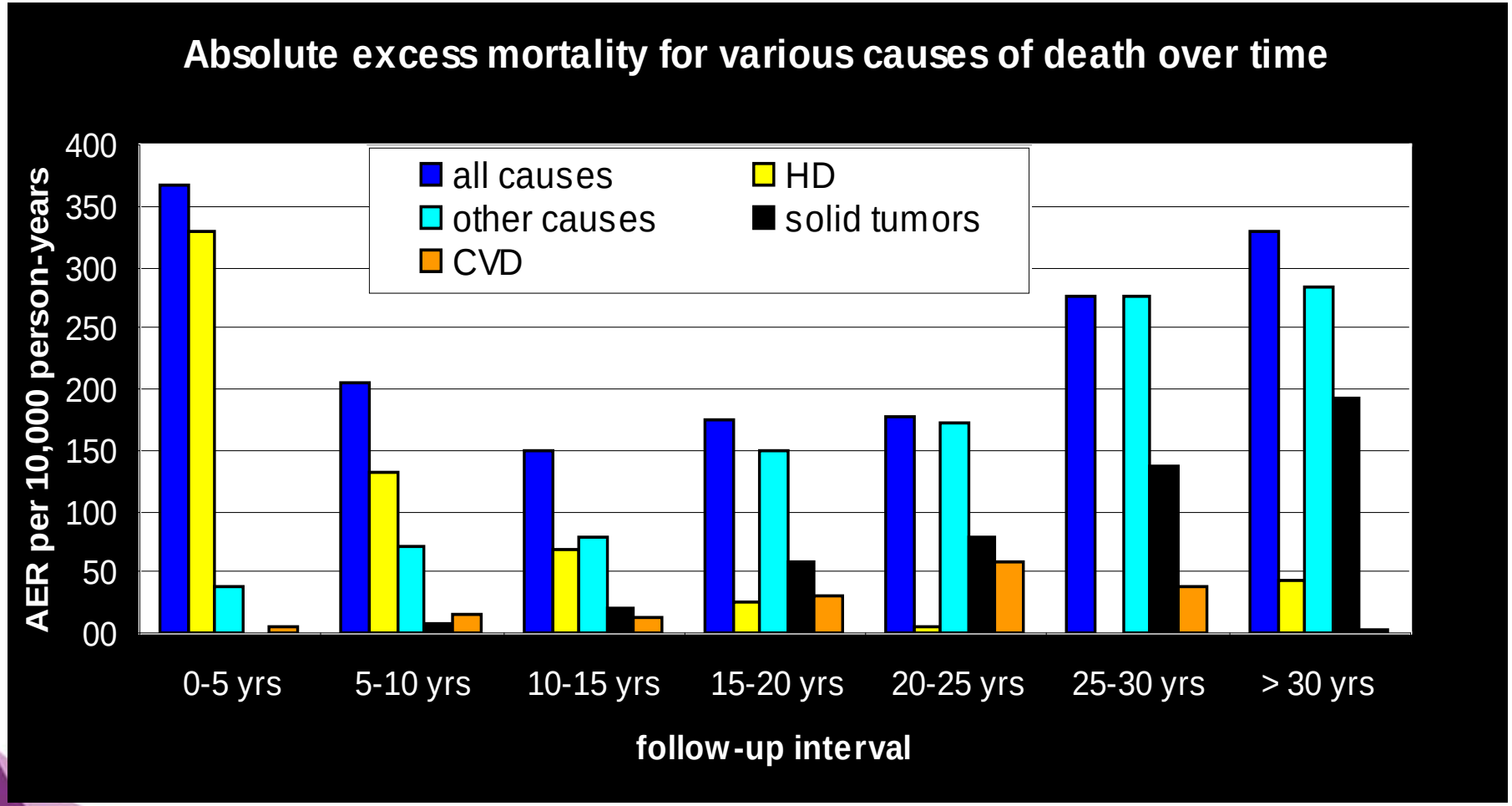
  - High SIR for rare event → low absolute risk

- Absolute excess risk (AER) =

  Excess number of events beyond expected number / 10,000 persons/ year

- Cumulative incidence = % developing event, accounting for death as a competing risk

- Hazard ratio = RR for treatment A vs treatment B



Aleman et al., JCO 2003; 21:3431

Risks of Second Malignancy following HL combined results from 3 large studies* (n=9618)

Site or Type	Obs	SIR	AER
All SMN	747	3.8	62.2
Solid tumors	519	2.8	37.9
Lung	155	4.3	13.4
GI tract	115	2.4	7.0
Stomach	29	2.8	2.1
Female breast	76	2.7	13.2
Thyroid	14	9.2	1.4
Leukemia	116	22.3	12.5
ANLL	63	94.8	14.9

SIR: Standardized Incidence Ratio; AER: Absolute Excess Risk per 10,000 persons/year
*Based on Hancock 1996; Van Leeuwen 2000; Swerdlow 2000

Survival outcome after a second malignancy

n=1319 ; treatment period: 1969 and 1997; median fup 12 years.

Second malignancy	No. of pts	5-yr survival estimate (%)	95% CI	Median survival, yrs
All sites	181	38.1	(29.7-46.5)	3.2
Acute leukemia	23	4.9	(0.0-14.2)	0.4
NHL	24	49.6	(28.0, 71.2)	2.4
All solid tumors	131	42.1	(31.6, 52.5)	4.3
Breast	39	76.1	(57.4-94.8)	Not yet reached
Lung	22	0.0	—	1.0
Gastrointestinal	24	12.4	(0-28.1)	1.9

Ng et al., Blood 2002

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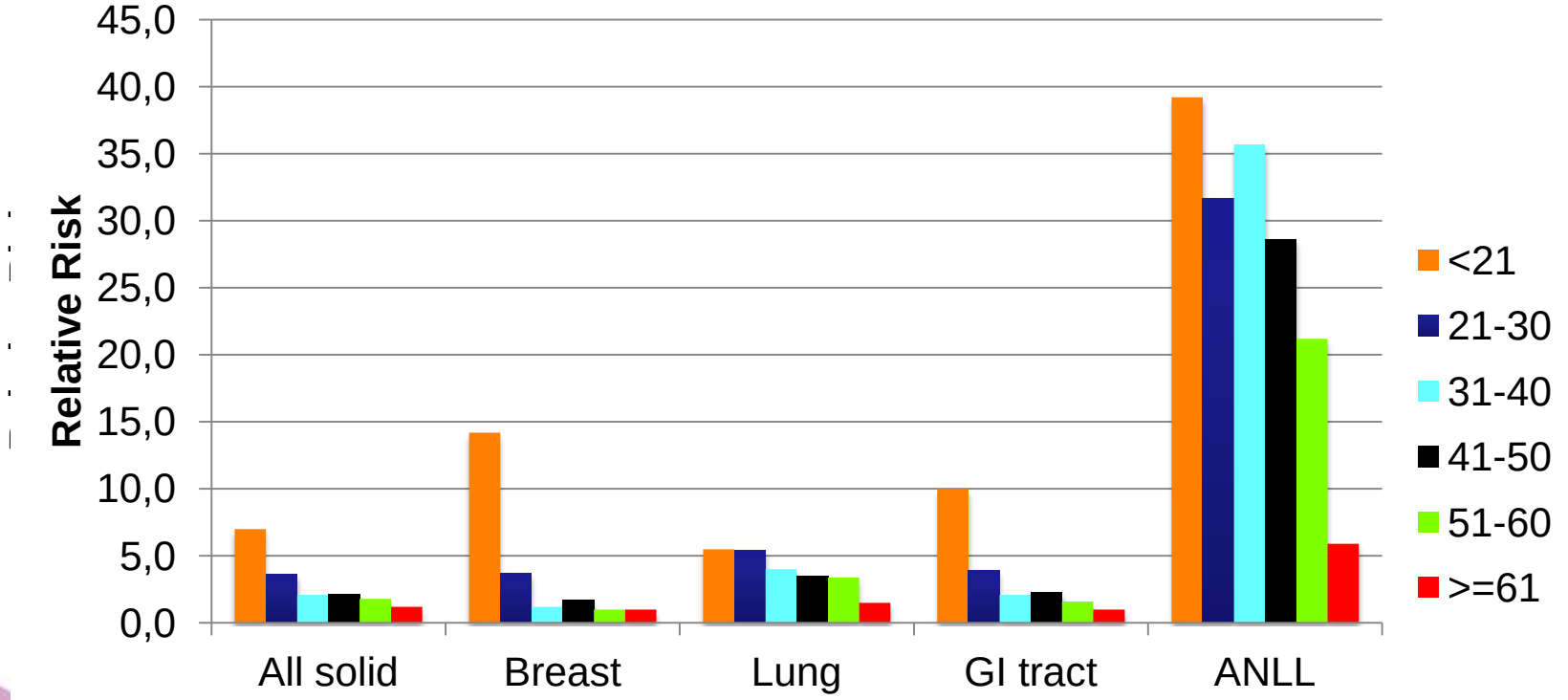
Ng et al., Blood 2002

Relative risks of SMN by age at HL diagnosis

International cohort study: 32,591 HL patients

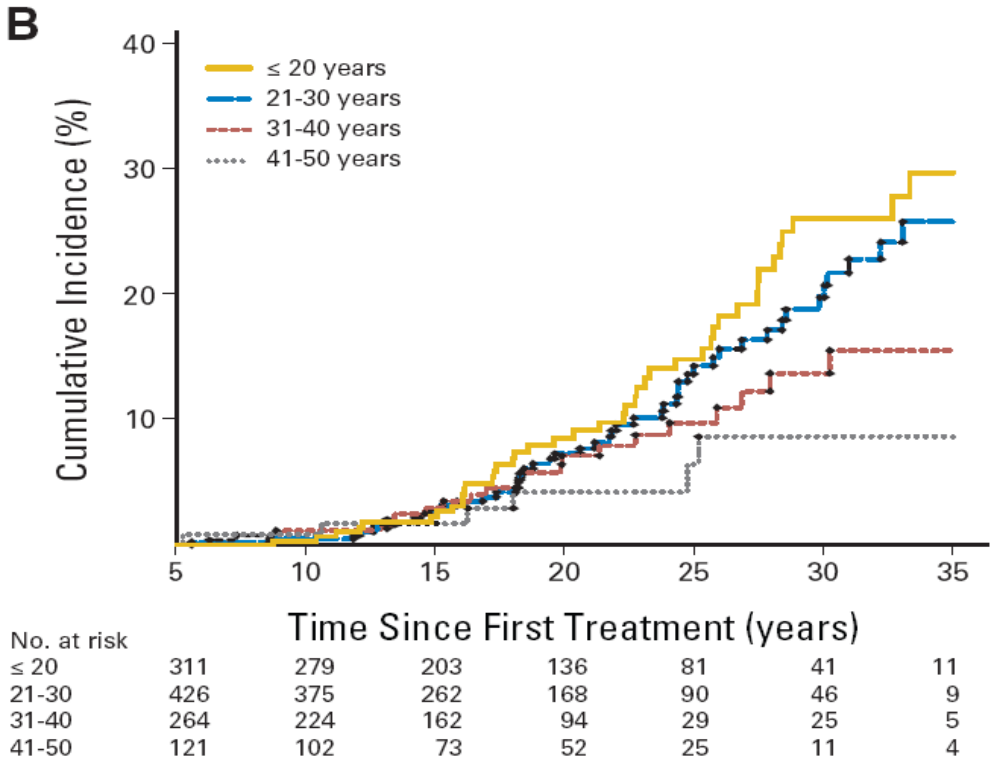
1,111 25-years survivors, population-based



Adapted from Dores JCO 2002; 20:3484

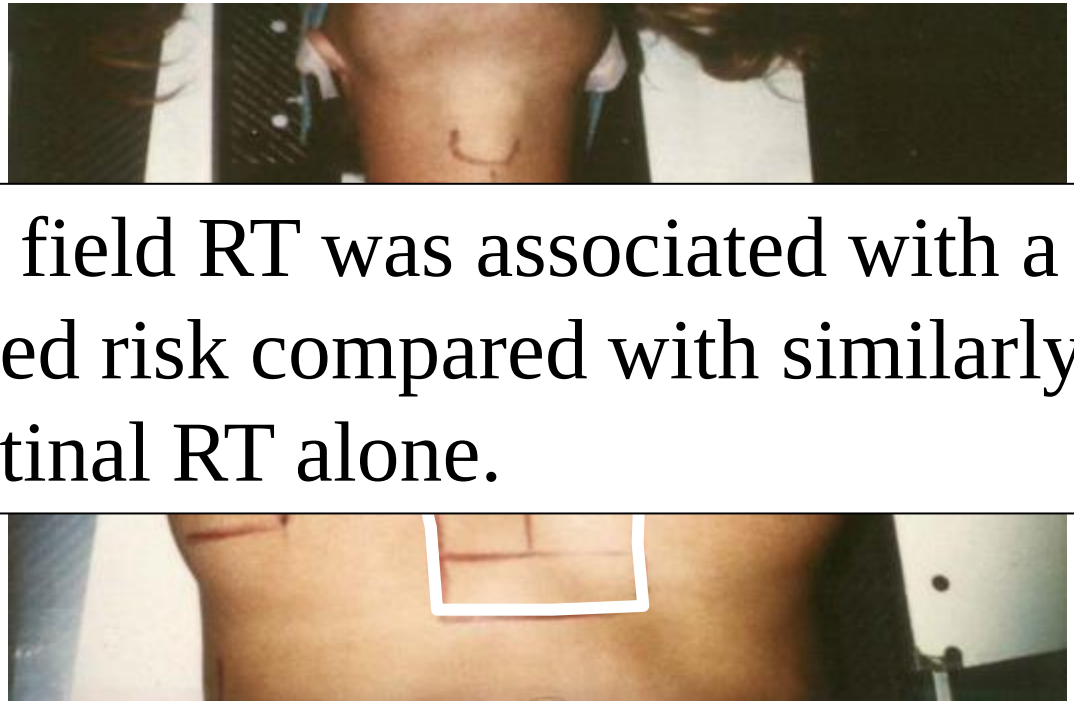
Cumulative incidence of breast cancer by age at HL

(1,122 female 5-year survivors treated for HL <51 years between 1965 and 1995)



De Bruin et al. JCO 2009; 27(26): 4239-4246

From mantle field to IFRT



Mantle field RT was associated with a 2.7-fold increased risk compared with similarly dosed mediastinal RT alone.

De Bruin et al, JCO 2009

Breast cancer following HL

a Dutch case-control study

Radiation dose in Gy (median)	**Cases**	**Controls**	**OR†**	**95%CI**
<4 (3.6)	9	47	1.0*	Ref
4-24 (15.5)	10	39	1.11	0.32-3.85
24-38.5 (30.2)	14	44	4.20	0.99-17.8
≥38.5 (40.7)	15	45	5.16	1.27-21.0

van Leeuwen JNCI 2003: 95;971

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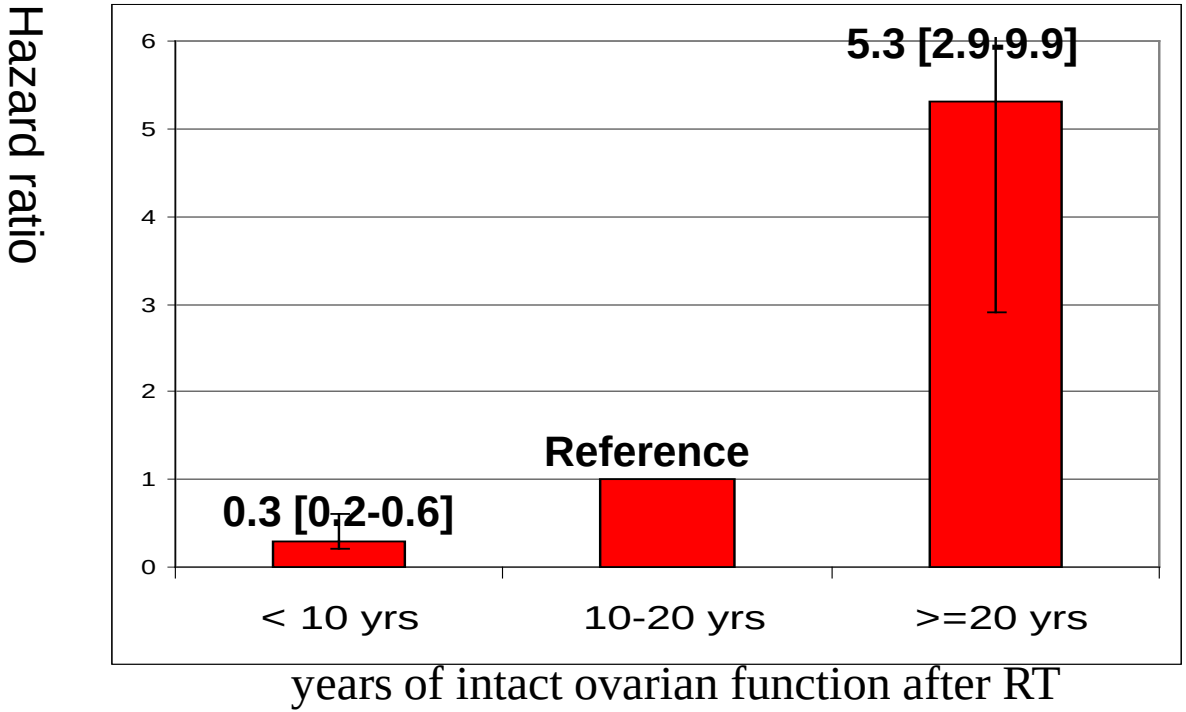
24-38.5 (30.2)	14	44	4.20	0.99-17.8
≥38.5 (40.7)	15	45	5.16	1.27-21.0
Overall treatment	**Cases**	**Controls**	**OR†**	**95%CI**
RT only	30	68	1.0	Ref
RT+CT	18	104	0.45	0.22-0.91

* P trend <0.001; † adjusted for RT dose ovary and CT

- Highest risks in youngest patients
- Induction period: 10-15 years

van Leeuwen JNCI 2003: 95;971

Risk of breast cancer after RT for HL, by duration of ovarian function after RT

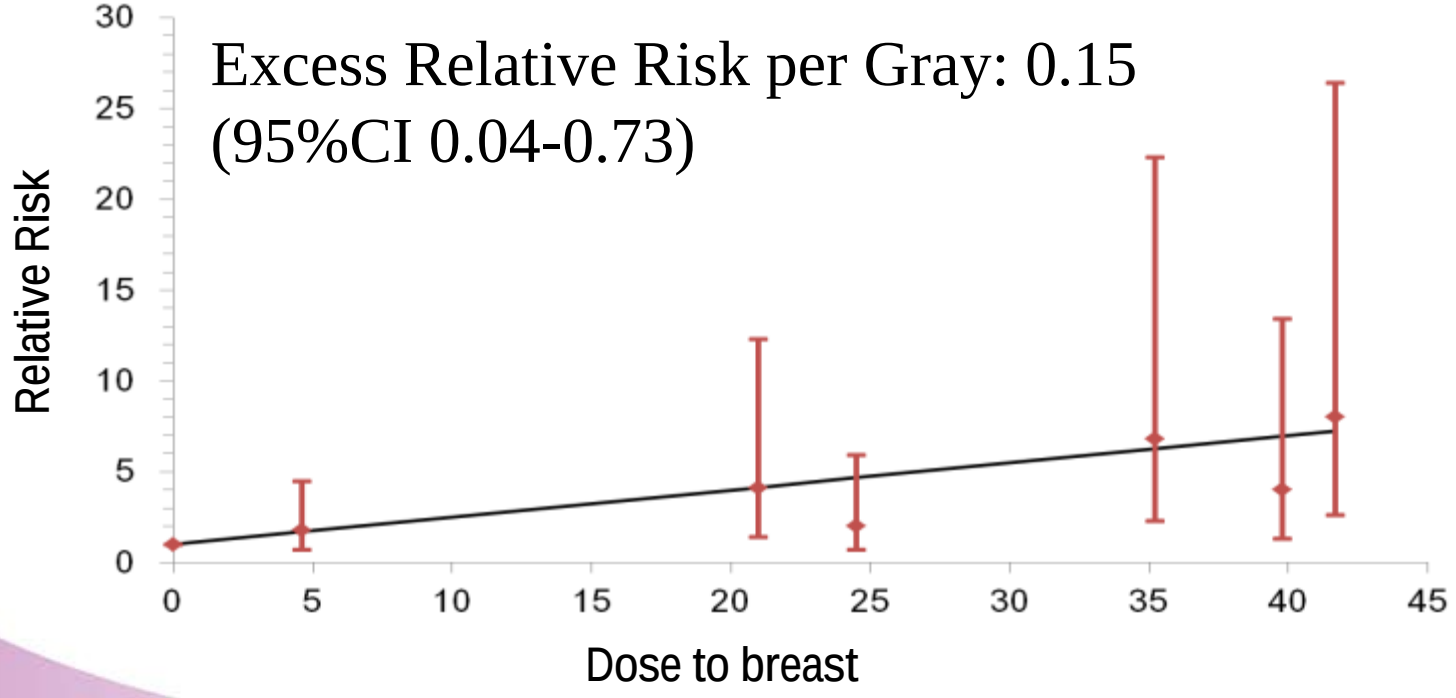


→ Ovarian hormones crucial in radiation-induced breast carcinogenesis

De Bruin et al, JCO 2009

Radiation dose and breast cancer risk in HL survivors (Travis et al. JAMA 2003; 290:465)

International case-control study, 105 breast cancer cases and 266 matched controls; Radiation dose to breast tumor location was estimated.



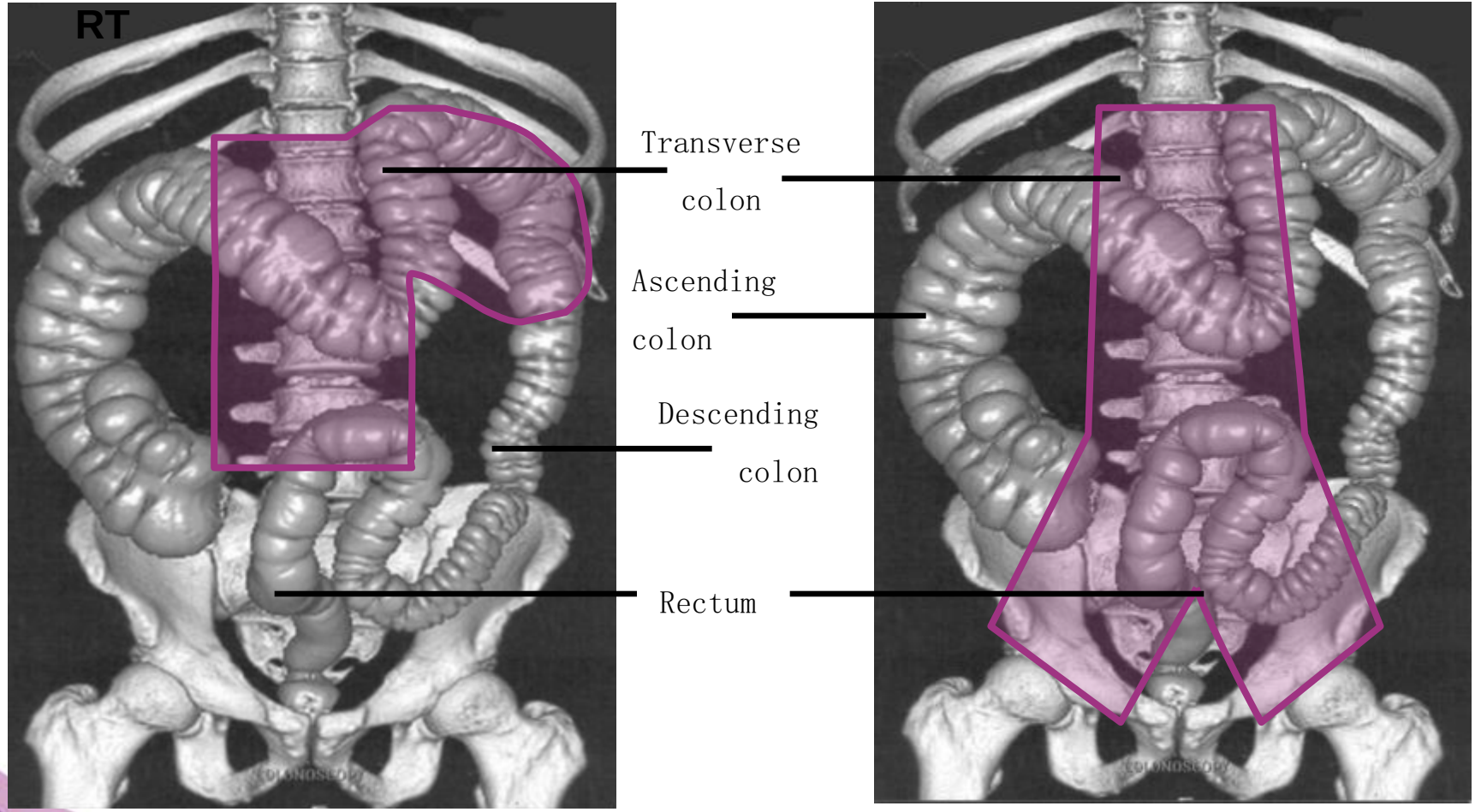
Literature on CRC risk after HL or childhood cancer and in A-bomb survivors

- Colorectum: important site of excess cancer in HL survivors
- ↑ colon cancer risk after exposure to low RT doses, whereas ↑ rectal cancer risk after higher doses
- Excess CRC risk appears 10 years after exposure

Birdwell et al., 1997; Hodgson et al., 2007; Van den Belt-Dusebout et al, 2009; Henderson et al 2012 (CCS); Nottage et al 2012 (CCS);Life Span Studies; Eggermond work in progress

Para-aortic ± spleen RT

Inverted Y RT



Eggermond, work in progress

SIR & AER of CRC

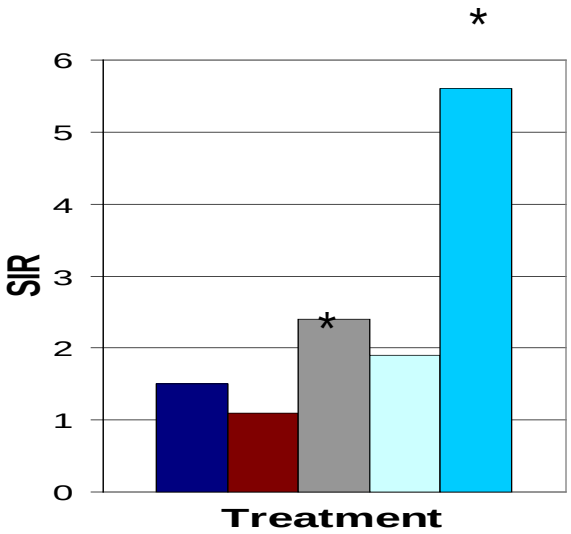
in 2,820 5-year Dutch HL survivors, diagnosed<51 years, treated1965-1995; median fup 21.5 years

Tumor site	O	SIR (95%CI)	AER (95%CI)
Colorectal cancer	49	2.7*	6.3*
Colon	30	2.7*	3.9*
Ascending colon	10	2.3*	1.1
Transverse colon	11	7.5*	2.0
Descending colon	7	1.3	0.4
Colon, NOS	2	5.5	0.3
Rectum	19	2.7*	2.4

SIR = Standardized Incidence Ratio (observed/expected) * p <0.05
AER = Absolute Excess Risk **per 10.000 patients/yr**
NOS = Not otherwise specified

Eggermond, work in progress

Risk of CRC by HL treatment



CT only

Supra RT only

Supra RT + CT

Infra ± supra RT, no CT

Infra ± supra RT + CT

Treatment	Obs	Exp	SIR
CT only	3	2.0	1.5
Supra RT only	3	2.7	1.1
Supra RT + CT	13	5.3	2.4*
Infra ± supra RT, no CT	8	4.2	1.9
Infra ± supra RT + CT	22	4.0	5.6*

* $p < 0.05$

Supra = supradiaphragmatic, infra = infradiaphragmatic

Eggermond, work in progress

Clinical implications

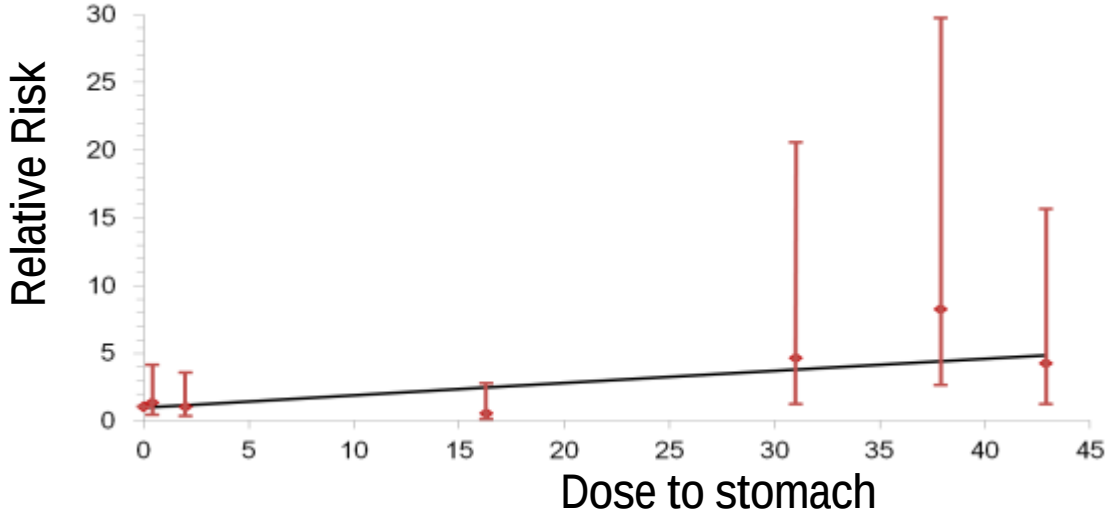
- 47-year old HL survivor (treated < 25 yr) same CRC risk as 55-60 year old person from general population (0.5%)
- Need for screening guidelines for HL survivors
- COG guideline: colonoscopy after ≥ 30 Gy abdominal RT

  10 yrs after RT or at age 35
- Starting age? Also after procarbazine CT?
- Implications for the use of procarbazine in new treatment regimens?

Eggermond, work in progress

Radiation dose and stomach cancer risk in Hodgkin lymphoma survivors

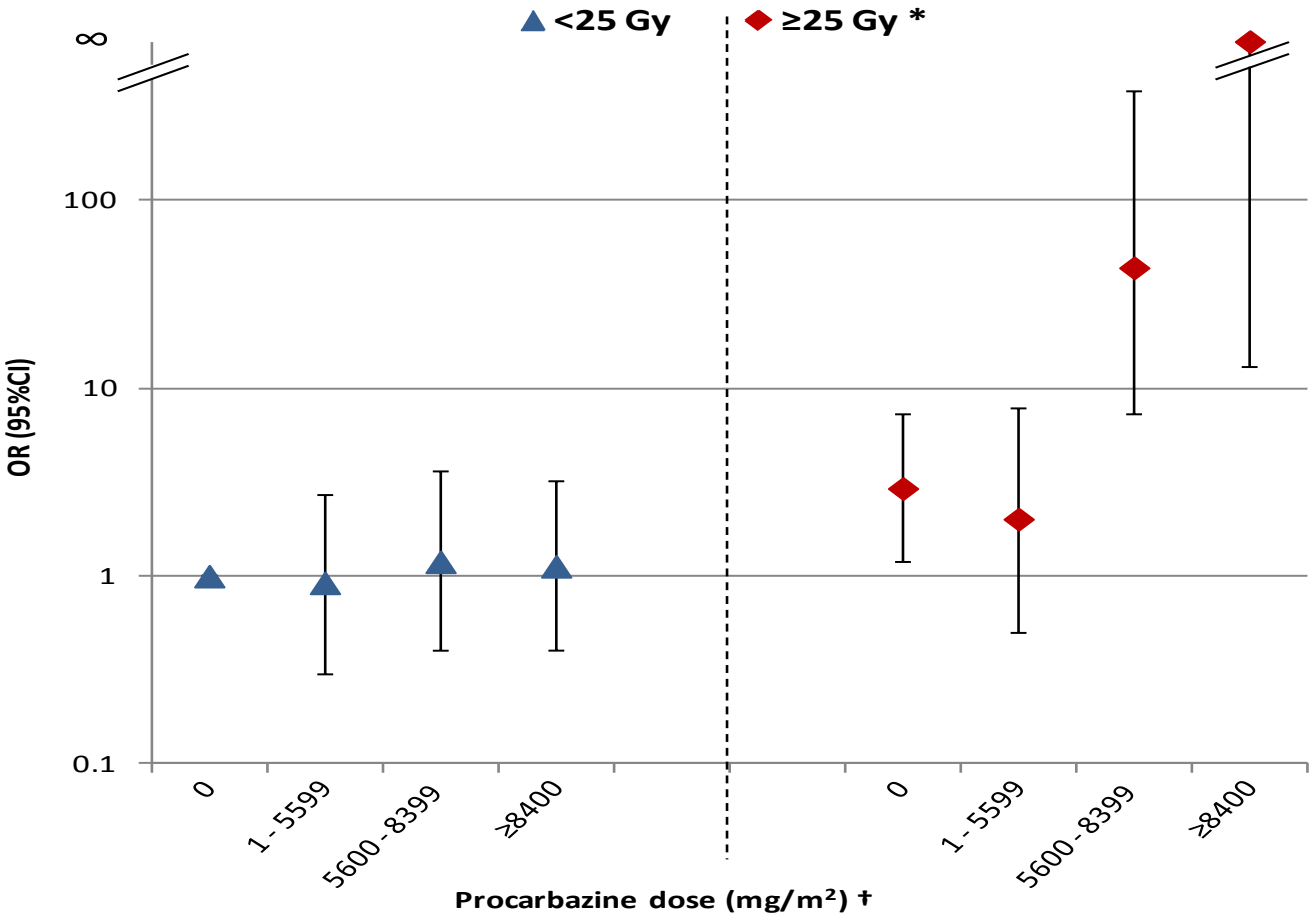
International nested case-control study, 89 stomach cancer cases and 190 matched controls; Radiation dosimetry to estimate dose to area of stomach tumor Morton et al. JCO 2013



RRs adjusted for alkylating agent CT dose

Excess Relative Risk per Gray 0.09 (95%CI 0.04-0.21)

Risk of stomach cancer after HL in relation to radiation dose to the stomach and procarbazine dose.



4.2 g/m^2 procarbazine≈3x MOPP or 6 MOPP-ABV(D)

Morton et al, JCO 2013

Lung cancer after HL
Joint effects of smoking and treatment

- Risks from smoking multiply risks from treatment
- Smoking is the major cause of lung cancer (only 7 out of 222 cases were never smokers)

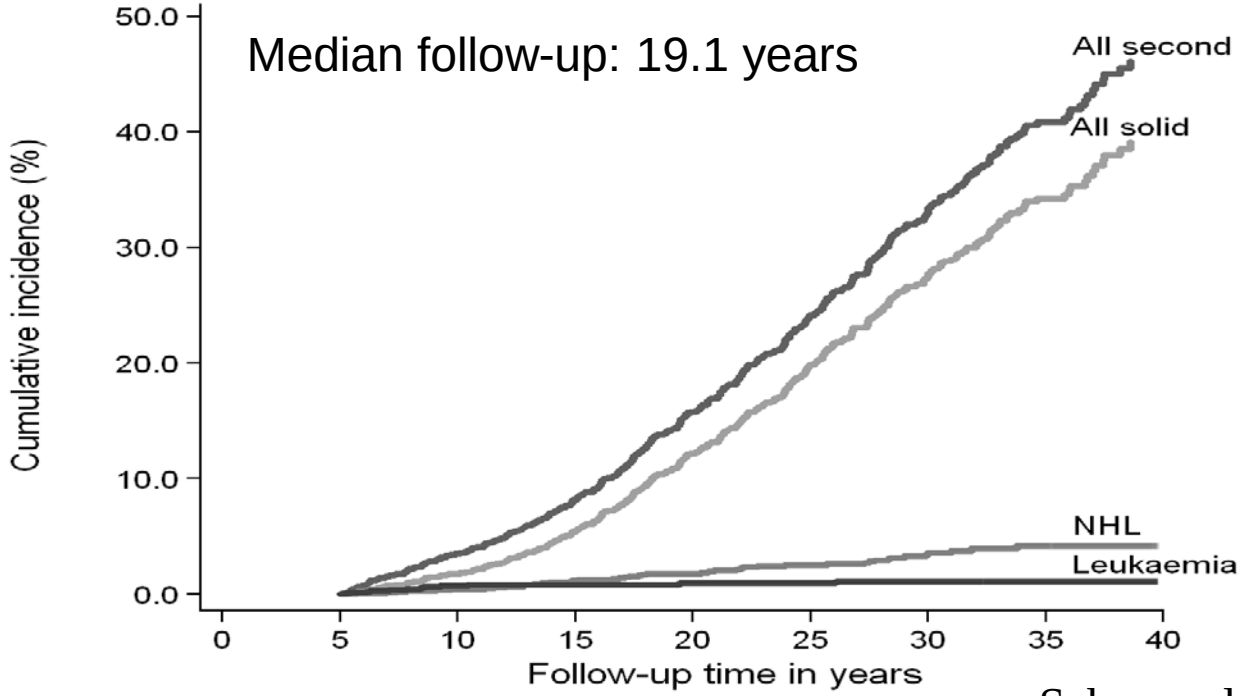
	RR non/light smokers	RR smokers
No RT (< 5 Gy), no CT	1.0 (ref)	6.0 (1.9-20.4)
RT (≥ 5 Gy), no CT	7.2 (2.9-21.2)	20.2 (6.8-68)
No RT (< 5 Gy), CT	4.3 (1.8-11.7)	16.8 (6.2-53)
RT (≥ 5 Gy), CT	7.2 (2.8-21.6)	49.1 (15.1-187)

Travis et al. JNCI 2002; 94:182

Has second malignancy risk changed over time?

Cumulative incidence of second malignancies, in the presence of competing risks

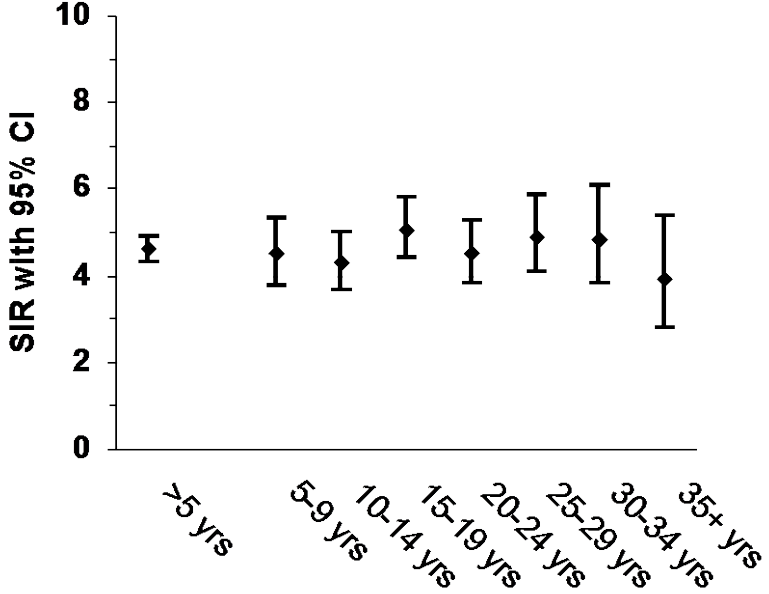
Dutch 5 year HL survivors treated 1965-2000 at age 15-51 years (n=3,905)

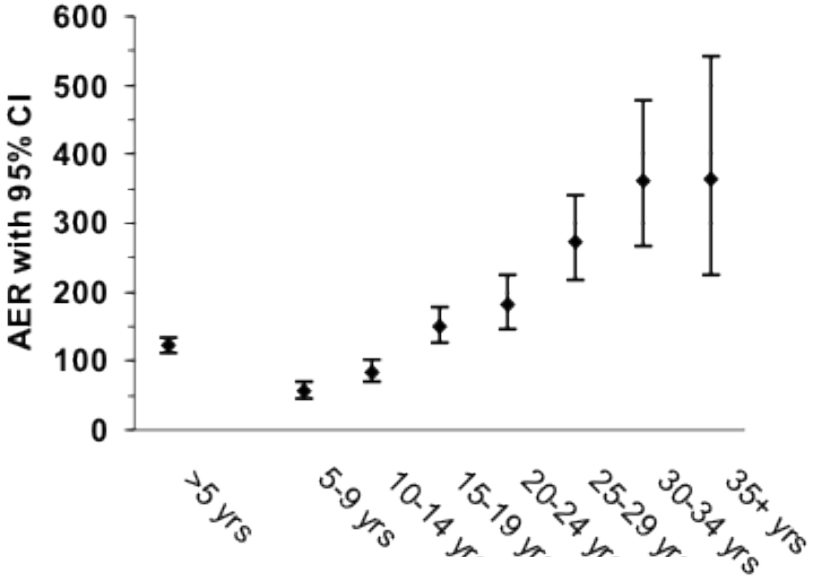


Schaapveld et al , submitted

Solid tumor risk by follow up interval

Dutch 5 year HL survivors treated 1965-2000 at age 15-51 years (n=3,905)

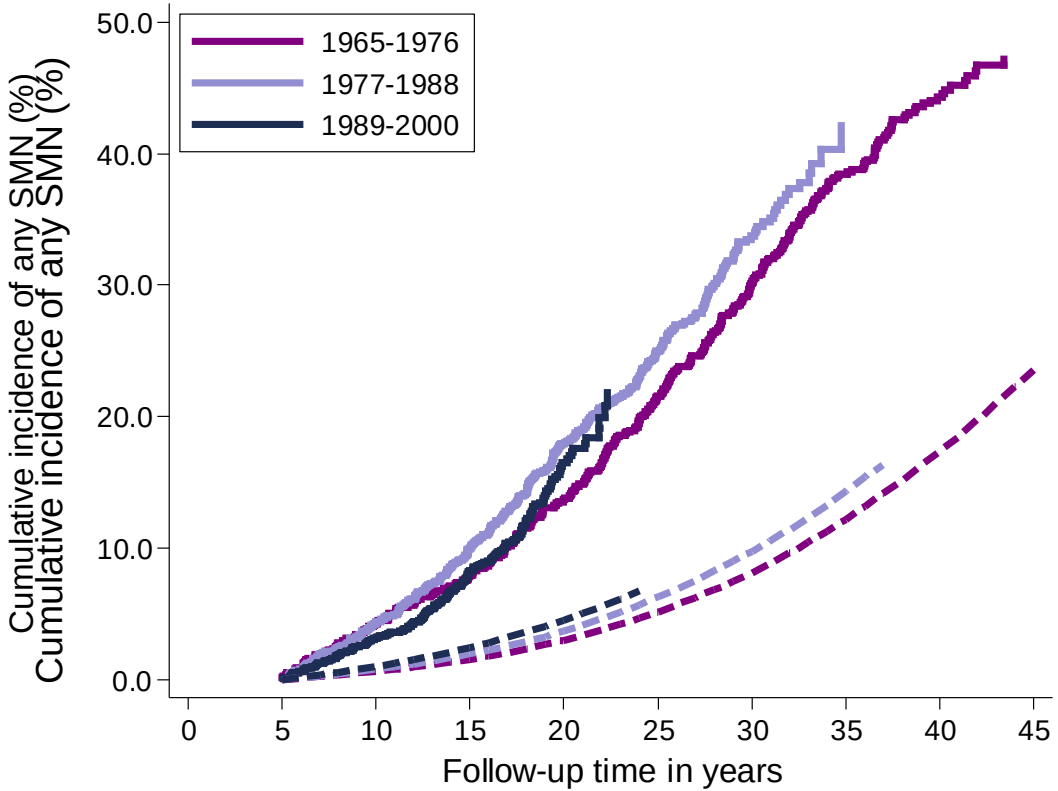




AER per 10,000 patients/yrs

Schaapveld et al , submitted

Cumulative incidence any SMN by period

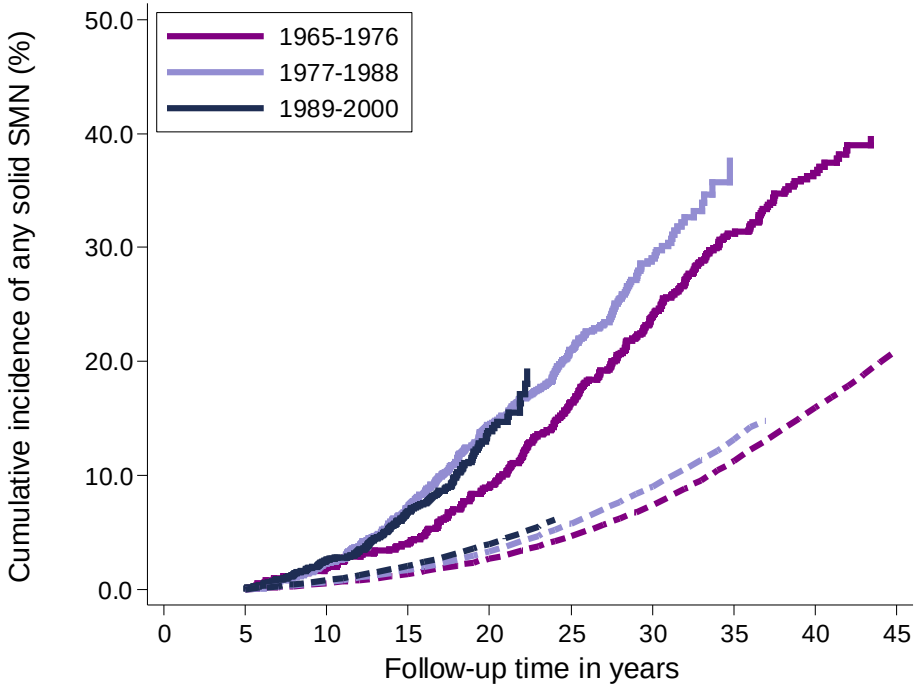


sHR: 0.79 (95%CI 0.65-0.95)
1990-2000 versus 1965-1979
adjusted for age & gender
follow-up<20years
$P_{\text{-trend:}}$0.015

Cumulative incidence
40 yrs after HL: 48.5%

Schaapveld et al , submitted

Cumulative incidence of solid tumors by treatment period

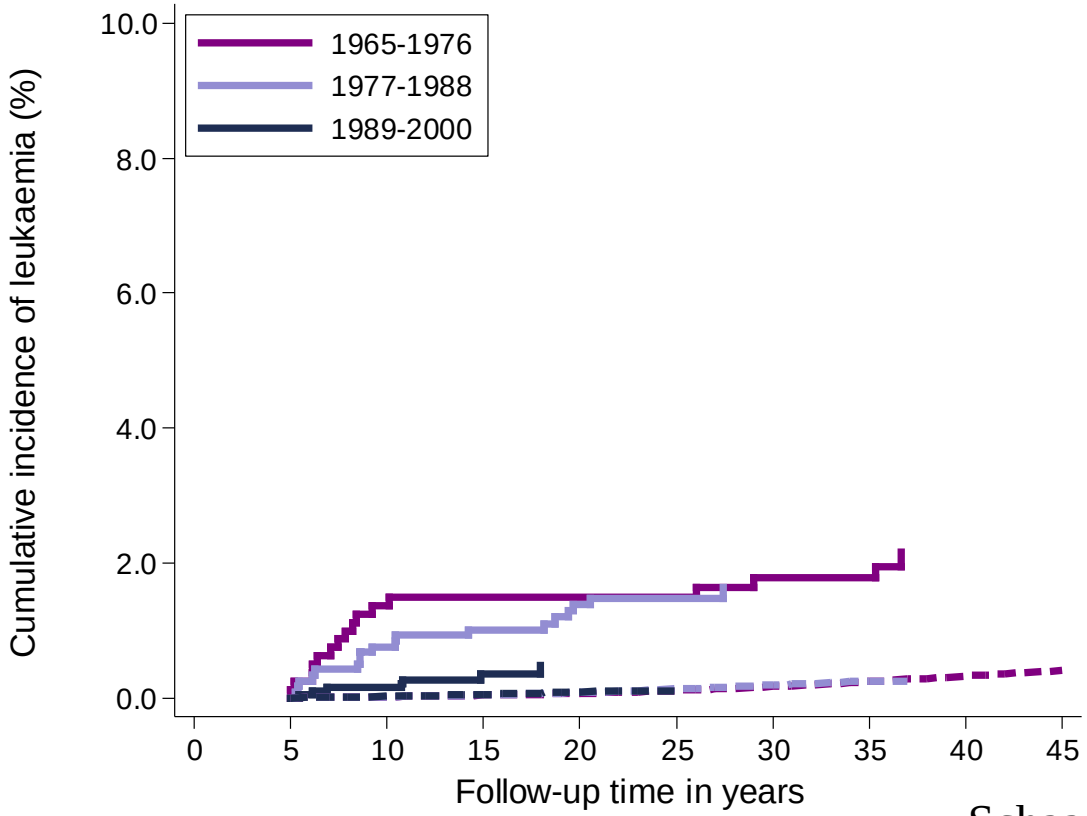


sHR 0.94 (95%CI 0.77-1.15)

1990-2000 versus 1965-1979
adjusted for age & gender
follow-up<20years

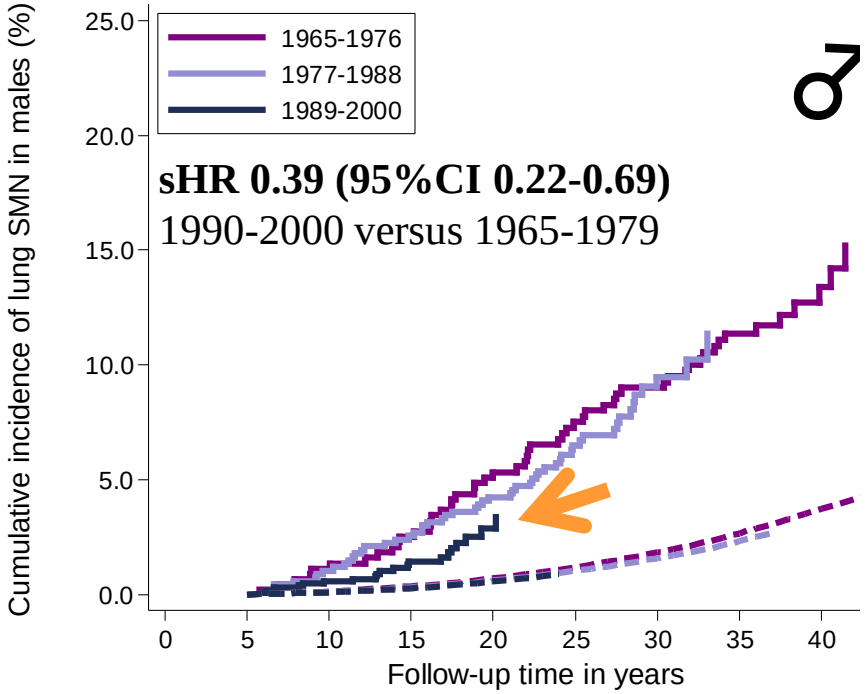
Schaapveld et al , submitted

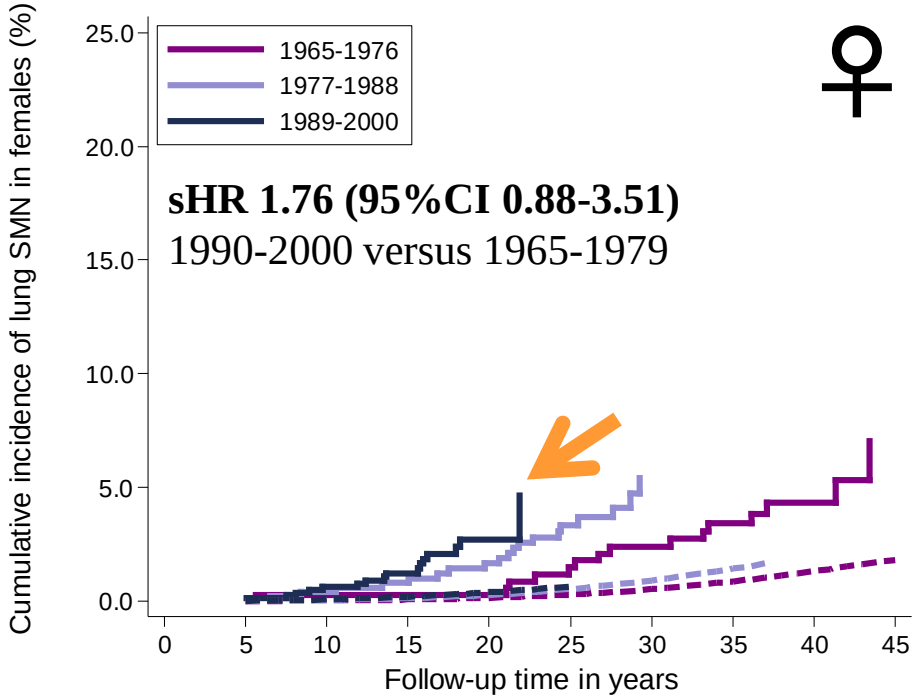
Cumulative incidence of leukemia (excluding MDS)



Schaapveld et al , submitted

Trend in cumulative incidence* of lung cancer by period of treatment and sex in 5 year HL survivors (n=3,905) and the general population





*estimated in the presence of death as a competing risk
Subdistribution HR are adjusted for age and follow-up<20 years

Schaapveld, work in progress

Conclusions

- Risk of hematological SMNs has decreased over time
- Risk solid SMNs does not appear to decrease in patients treated before 2000, potentially due to changes in chemotherapy regimens and more breast cancer screening.
- Awareness of increased SMN risk remains crucial for HL survivors.

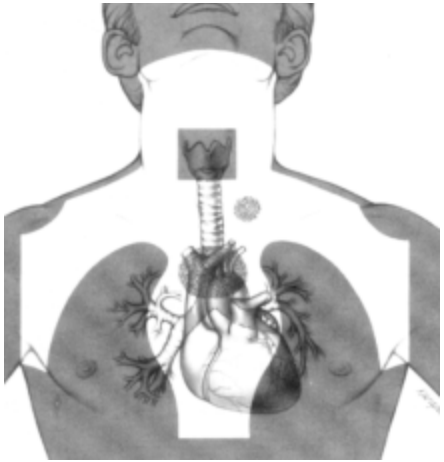
Schaapveld et al , submitted

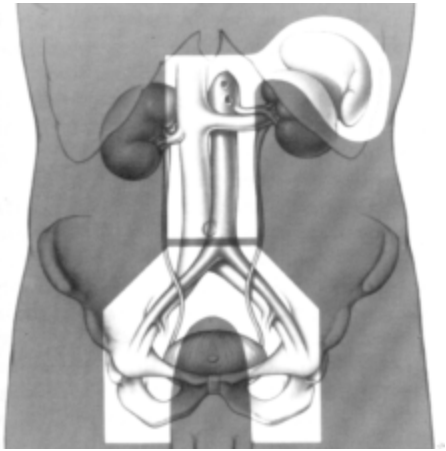
Summary SMN

- Risks of RT associated SMN:
  - Volume related
  - Linear ↑ with dose for most SMN (except thyroid cancer)
- Emerging data on CT related solid ca risks
- Many data on late effects based on outdated treatments
- Imaging and RT techniques have improved → more effective and less toxic treatments

Causes cardiovascular damage

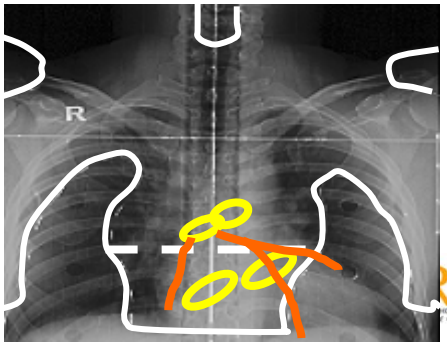
- Chemotherapy (anthracyclines)
- Radiotherapy





RT-associated heart diseases

- Coronary heart disease
- Myocardial dysfunction
- Valvular abnormalities
- Pericardial abnormalities
- Electrical conduction disorders

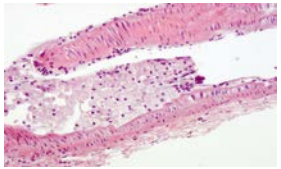


Cardiovascular toxicity

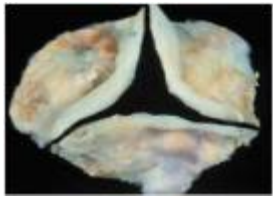
Differences in mechanisms

Radiation

Damage to vasculature (vulnerable plaques*)



Damage to valves



Damage to myocytes

*Russell, Stewart, Hoving
Sawyer et al. Circulation 2002
Lim et al. J Biol Chem. 2004

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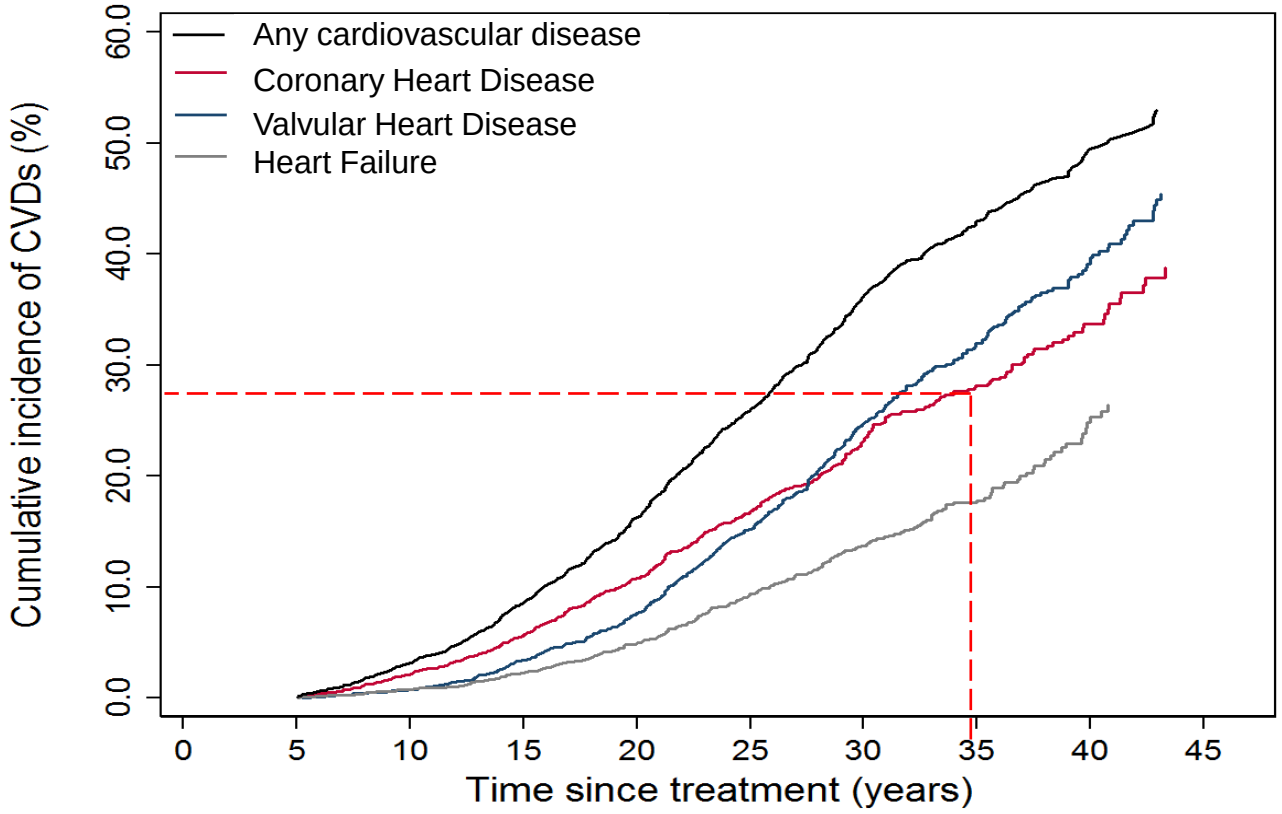
Literature cardiovascular disease after HL

- Mediastinal radiotherapy increases *mortality* of CVD, esp. coronary artery disease
  (Boivin, Cancer 1992; 69:1241; Hancock, JAMA 1993; 270:1949; Swerdlow JNCI 2007; 99:206; Aleman JCO 2003; 21:3431)
- Fewer studies examined CVD *morbidity*
  (Hull JAMA 2003; 290:2831; Aleman, Blood 2007; 109:1878; Glanzmann, Rad Oncol 1998; 46:51)
- Increased mortality for > 25yrs
- Also increased risk for valvular disease *(Aleman, Blood 2007; Hull, JAMA 2003)*

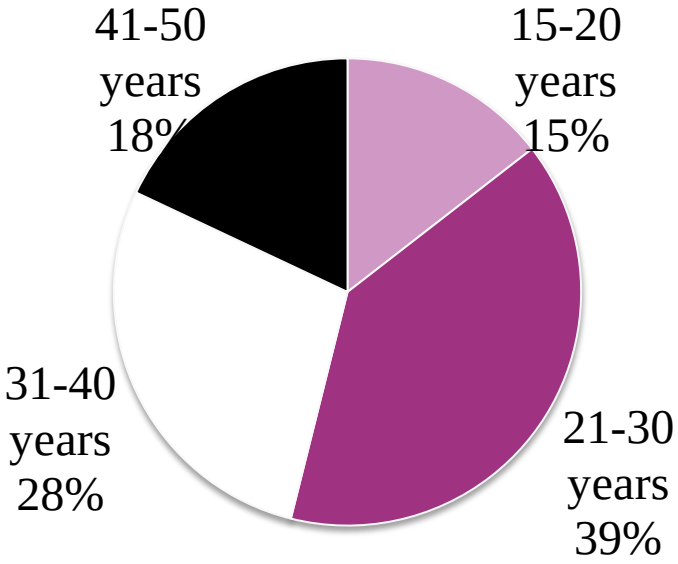
Morbidity of cardiovascular disease

(all events in 2524 5-year survivors of HL treated before age 51 between 1965-1995)

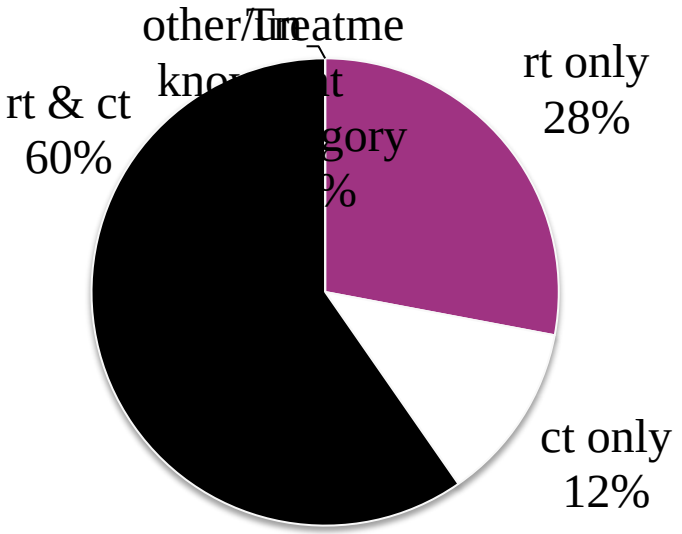


Van Nimwegen et al., JAMA int med 2015

HL age distribution



HL treatment



41% anthracycline-containing chemotherapy

Over time ↓ use mantle field and abdominal RT

Schaapveld, work in progress

Nested case-control studies

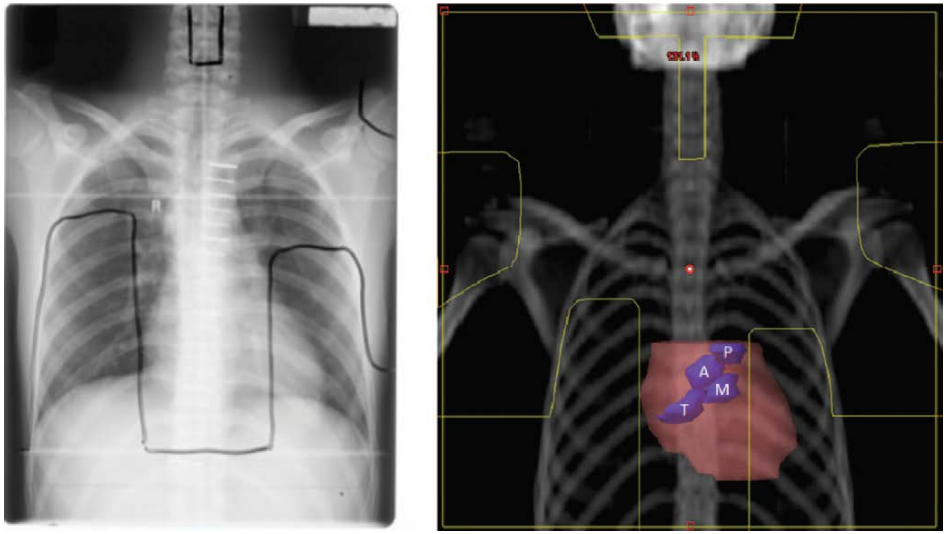
Endpoints:

- Valvular heart disease
- Ischemic heart disease
- Heart failure

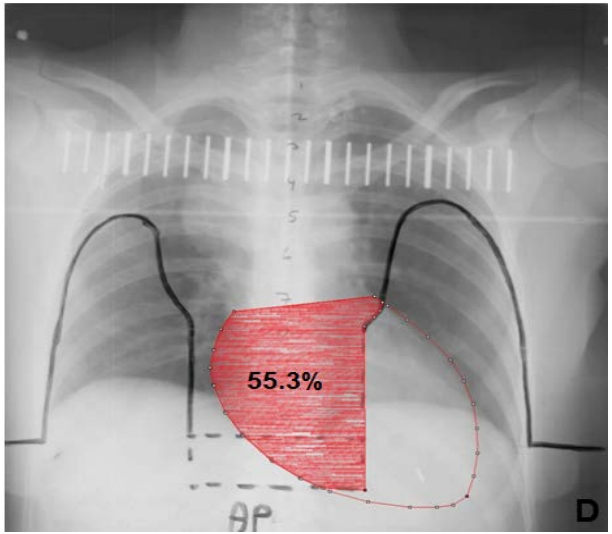
Nested case-control studies

Dosimetry:

CT-based



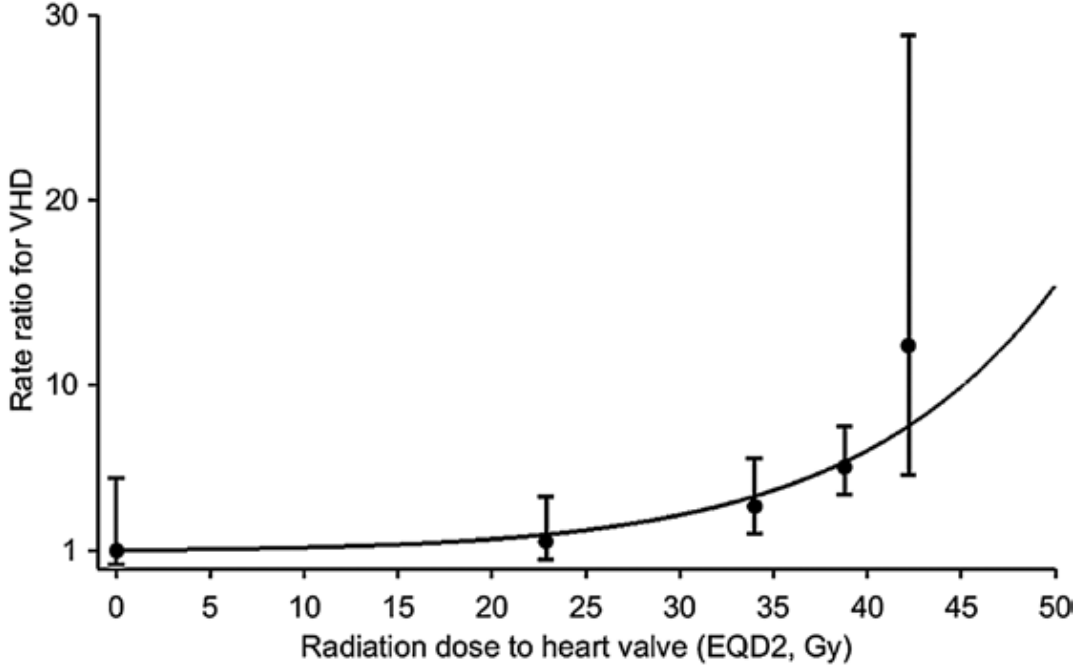
Simplified 2D method



Cutter, Schaapveld et al. JNCI 2015

Valvular heart disease after HL

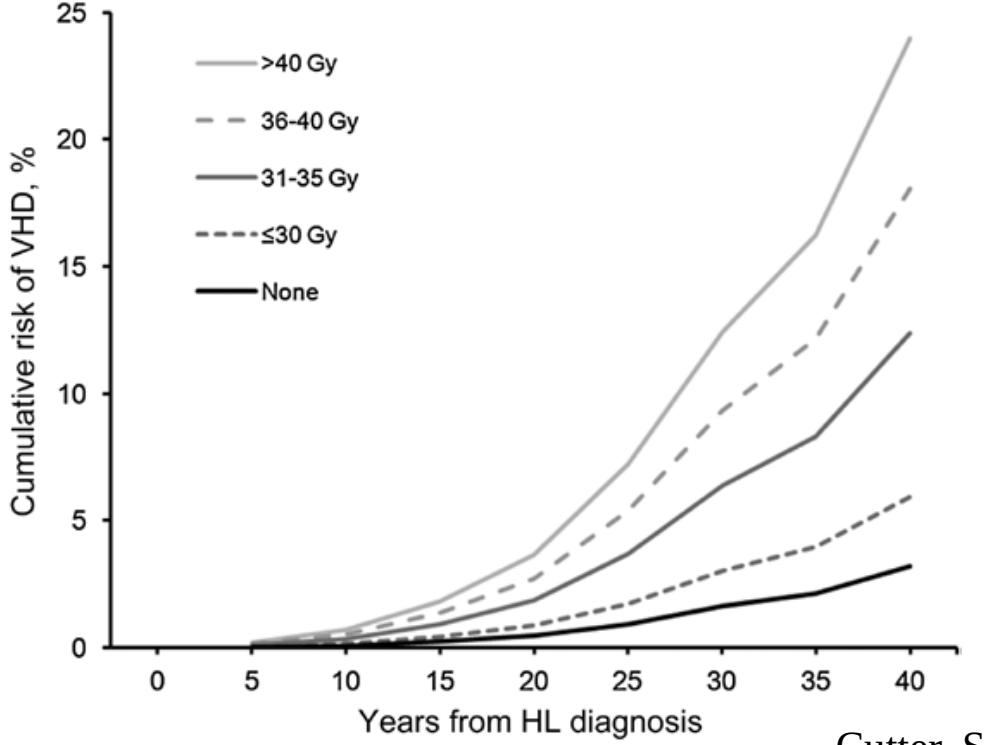
89 cases and 200 controls nested in cohort of 1852 Dutch five-year survivors of HL treated between 1965 and 1995



Cutter, Schaapveld et al. JNCI 2015

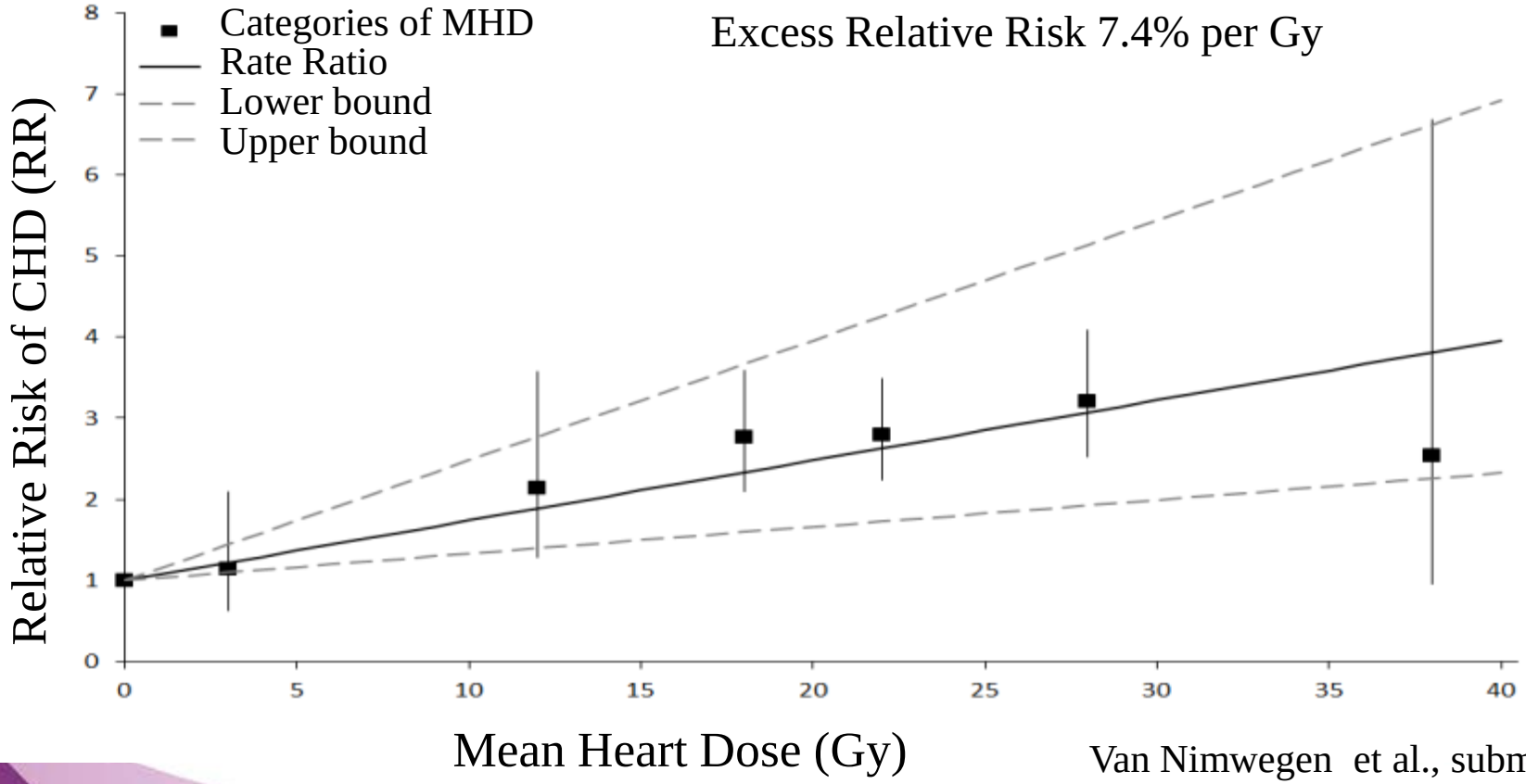
Valvular heart disease after HL

89 cases and 200 controls nested in cohort of 1,852 Dutch five-year survivors of HL treated between 1965 and 1995



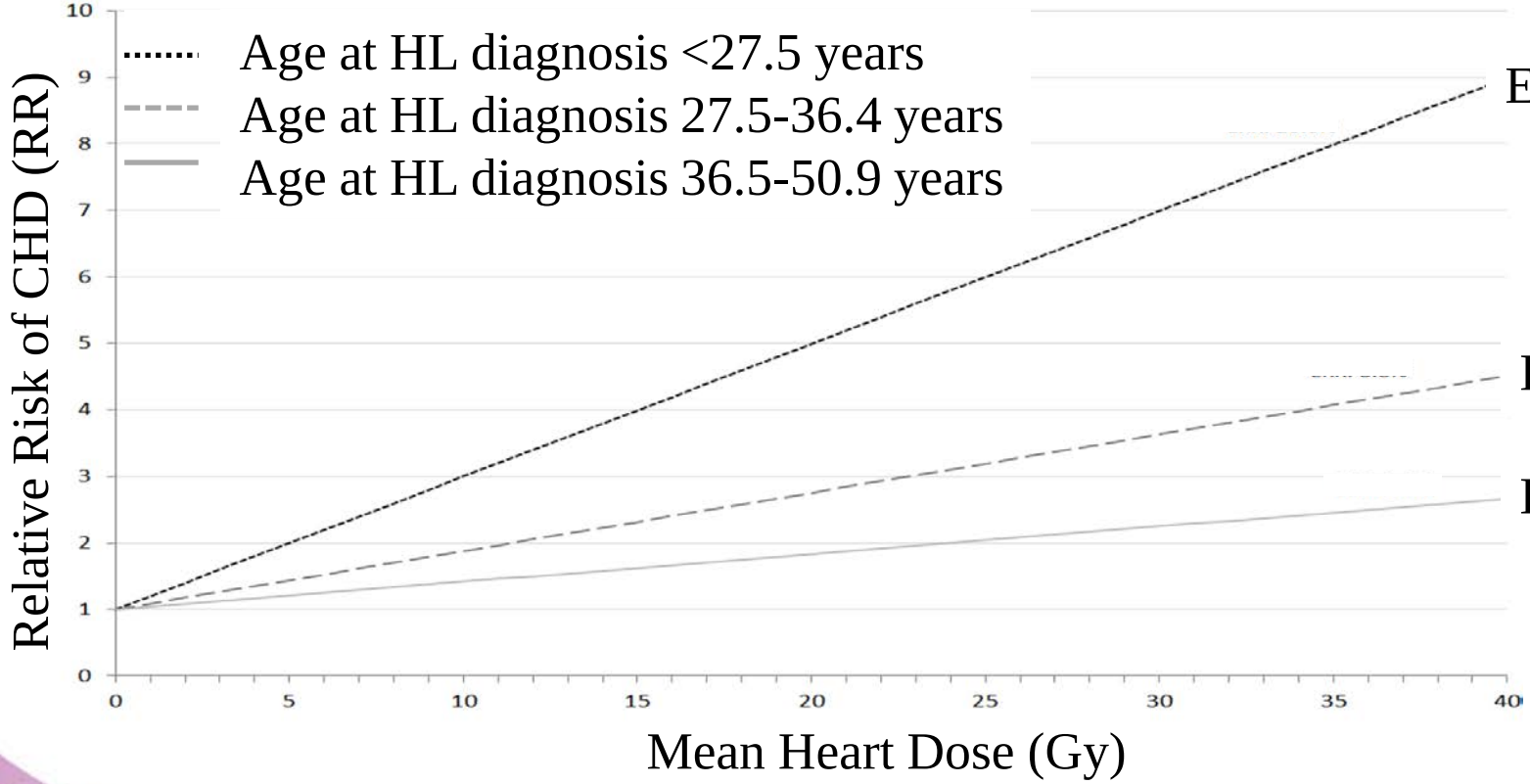
Cutter, Schaapveld et al. JNCI 2015

Coronary heart disease after HL; 325 cases and 1,204 controls nested in a cohort of 2,617 Dutch 5-year HL survivors treated between 1965 and 1995



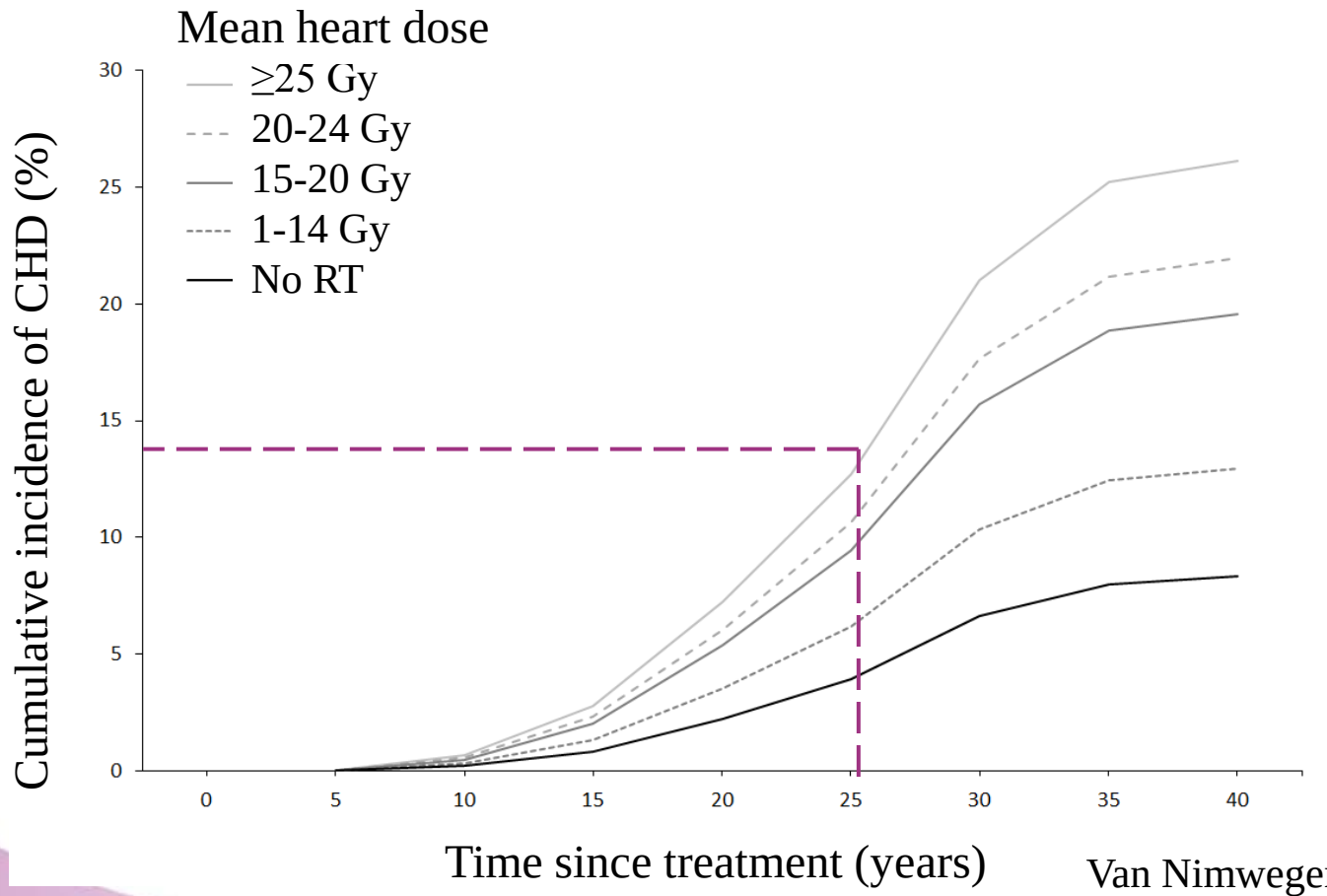
Van Nimwegen et al., submitted

Dose-response by tertiles of age at HL treatment



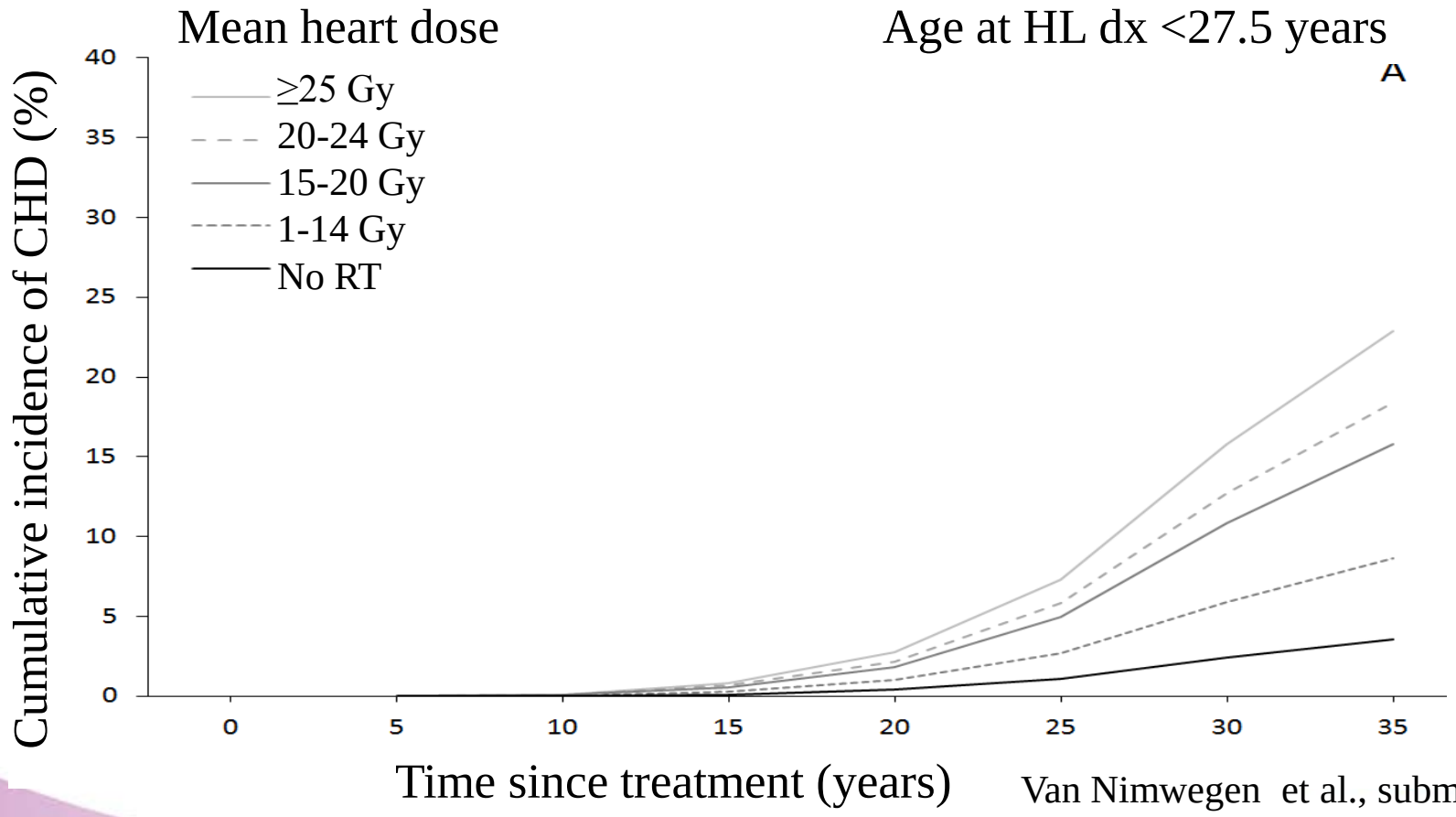
Van Nimwegen et al., submitted

Dose-associated cumulative incidence



Van Nimwegen et al., submitted

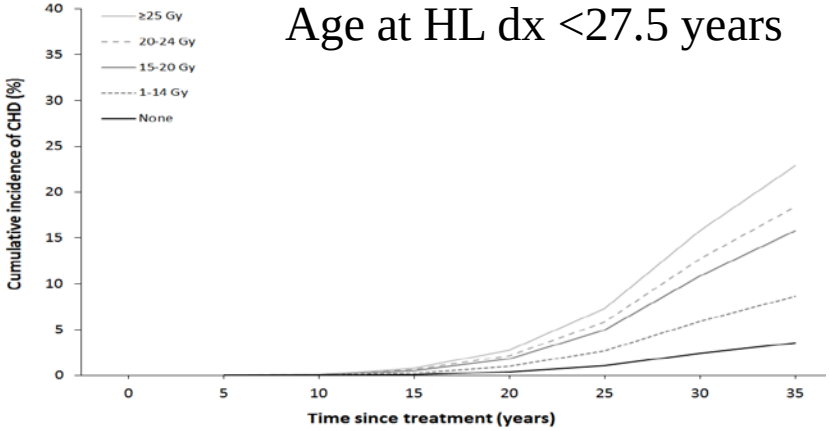
Estimated cumulative incidence by age at treatment



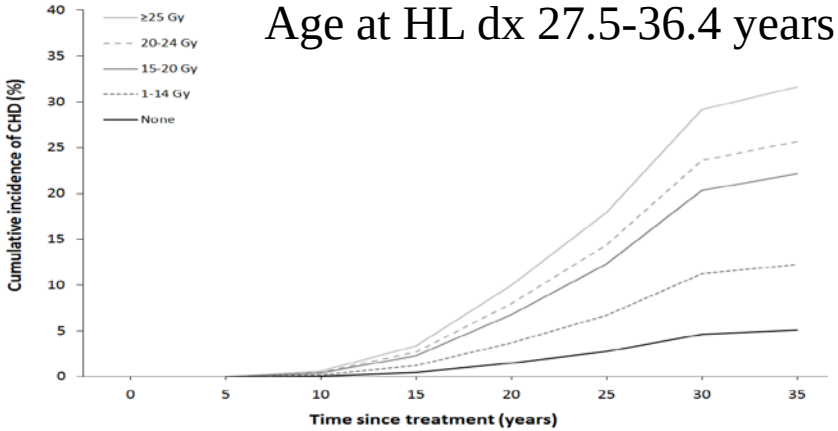
Van Nimwegen et al., submitted

Estimated cumulative incidence by age at treatment

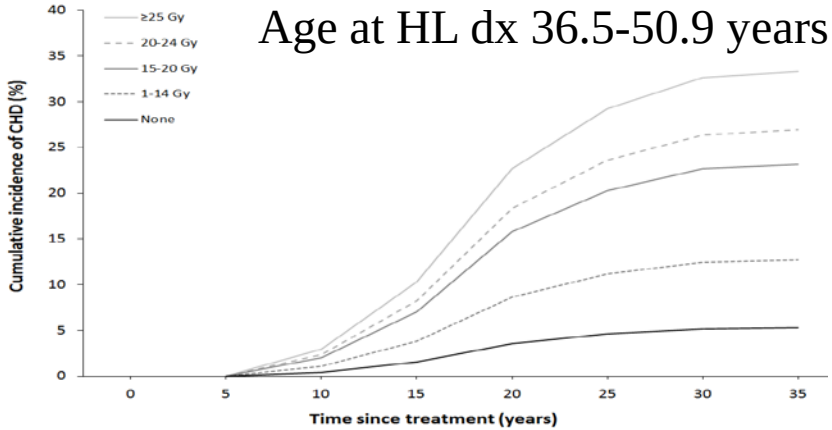
Age at HL dx <27.5 years



Age at HL dx 27.5-36.4 years



Age at HL dx 36.5-50.9 years



Van Nimwegen et al., submitted

Established CVD Risk factors

Risk factor	RR¥	95%CI	p
Diabetes mellitus	2.0	1.4-2.8	<0.001
Hypercholesterolemia	2.1	1.6-2.7	<0.001
Hypertension	1.5	1.2-2.0	0.001
Obesity (BMI≥30) at cut-off	1.6	1.2-2.2	<0.001
≥1 risk factors	2.5	1.8-3.4	<0.001
Recent smoker at cut-off (<5 yrs)	1.6	1.1-2.2	0.007

¥ adjusted for mediastinal radiotherapy

Van Nimwegen et al., submitted

Established CVD Risk factors

Risk factor	RR¥	95%CI	p_{trend}
Physical activity at time of questionnaire¤			
Not active (<1 hour a week)	1.0	0.5-2.2	
Moderately active (1-3 hours a week)	0.7	0.5-1.2	
Very active (≥4 hours a week)	0.5*	0.3-0.8	0.136

*p<0.05

¥ adjusted for mediastinal radiotherapy

¤ analyzed in sub-population of patients who filled in the risk factor questionnaire (84 cases and 158 individual controls), adjusted for the matching factors.

Van Nimwegen et al., submitted

Conclusions ischemic heart disease after HL

- Linear dose response relationship with overall risk increase of 7.4%/Gy
  - 2.5-fold increased risk at MHD of 20 Gy
  - Higher ERR for patients treated <27.5 years
- Established risk factors & recent smoking ↑ CHD risk
- High levels of physicial activity ↓ CHD risk
- Results enable risk prediction

Van Nimwegen et al., submitted

Conclusions CVD after HL (literature and Dutch HL cohort)

- After mediastinal RT increased riks of coronary events, valvular disease, CHF
- After 40 yrs: risk of any CVD after mediastinal RT = 50% vs 26% (no mediastinal RT)
- Risk remains increased ≥ 40 yrs
- Younger age at RT → higher risk
- Additive effects of RT and anthracyclines on CHF risk

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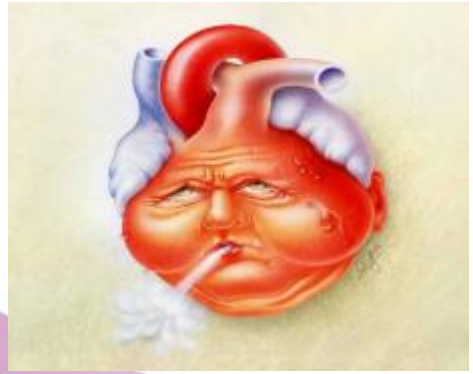
Anthracyclines

- Anthracyclines damage myocytes
- Cardiotoxicity may present as ECG changes and arrhythmias, or as cardiomyopathy possibly leading to heart failure
- Dose-effect relationship

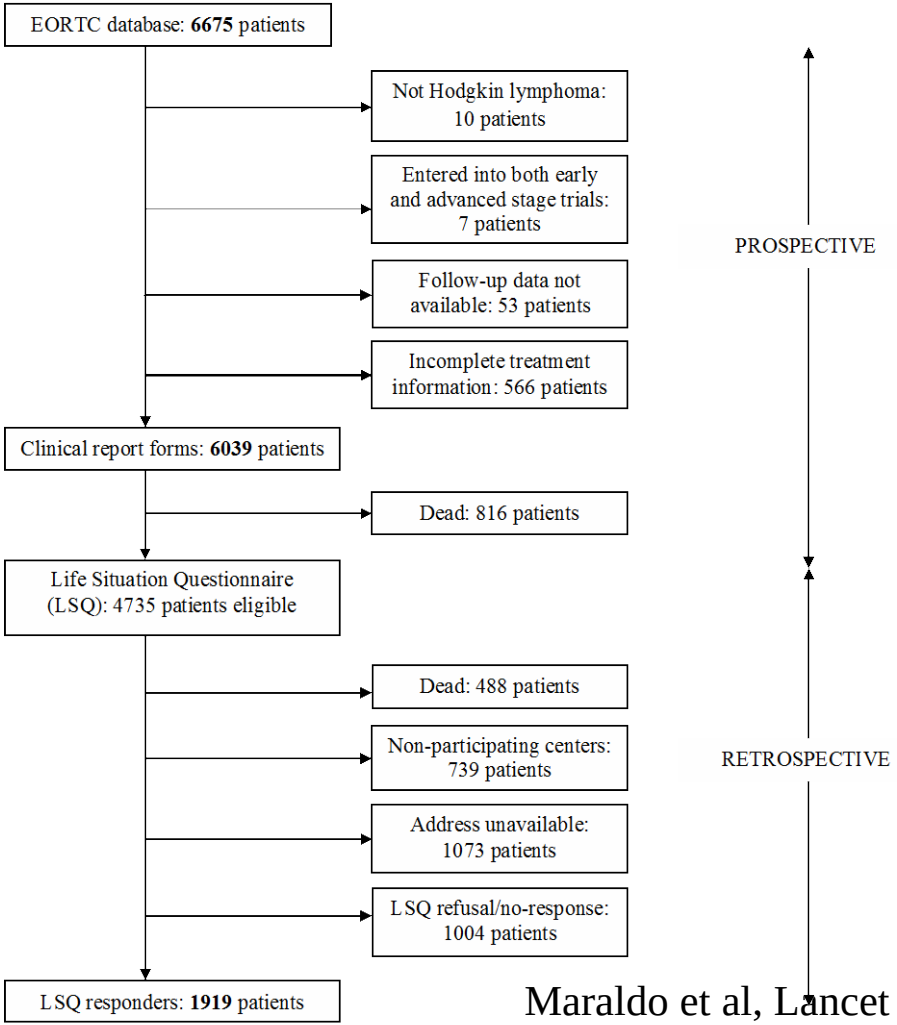


Cardiovascular disease after therapy for HL:
A detailed analysis of 9 collaborative EORTC-LYSA trials

- Incidence of CVD was reported during follow-up and updated through a patient-reported questionnaire, mailed in 2009–2010

Maraldo et al, Lancet Hemat in press

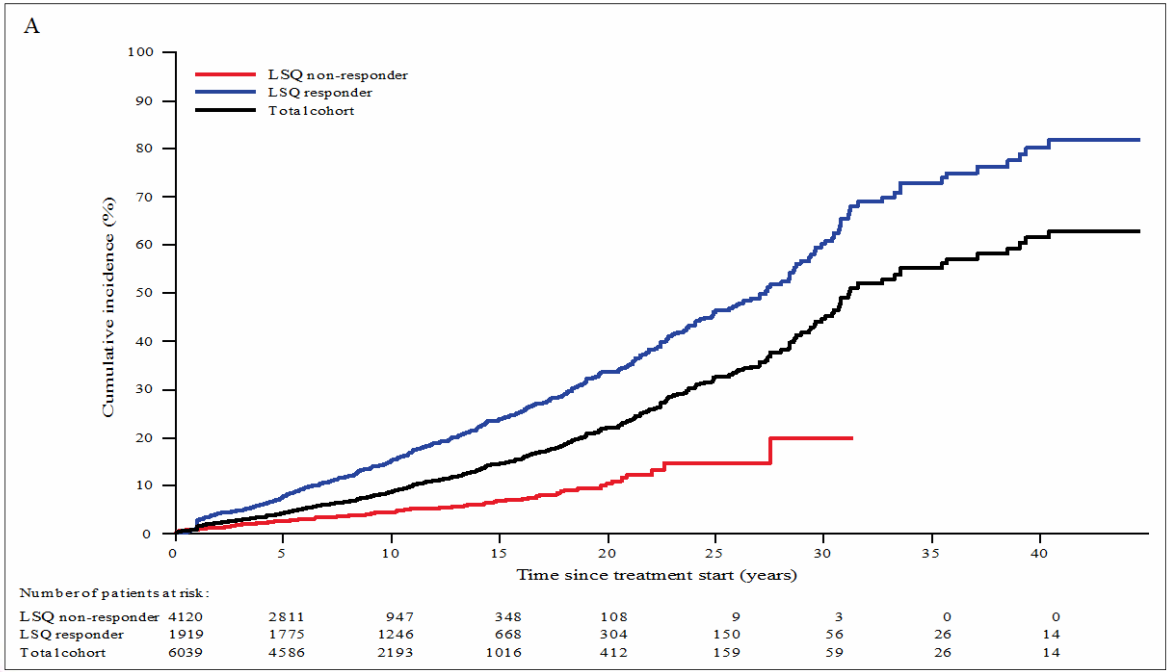
CVD after therapy for HL:
A detailed analysis of 9 collaborative EORTC-LYSA trials



Maraldo et al, Lancet Hemat in press

Cardiovascular disease after therapy for HL:
A detailed analysis of 9 collaborative EORTC-LYSA trials

Cumulative incidence curves of first cardiovascular disease by LSQ-responder status and for the whole cohort (n=6,039)



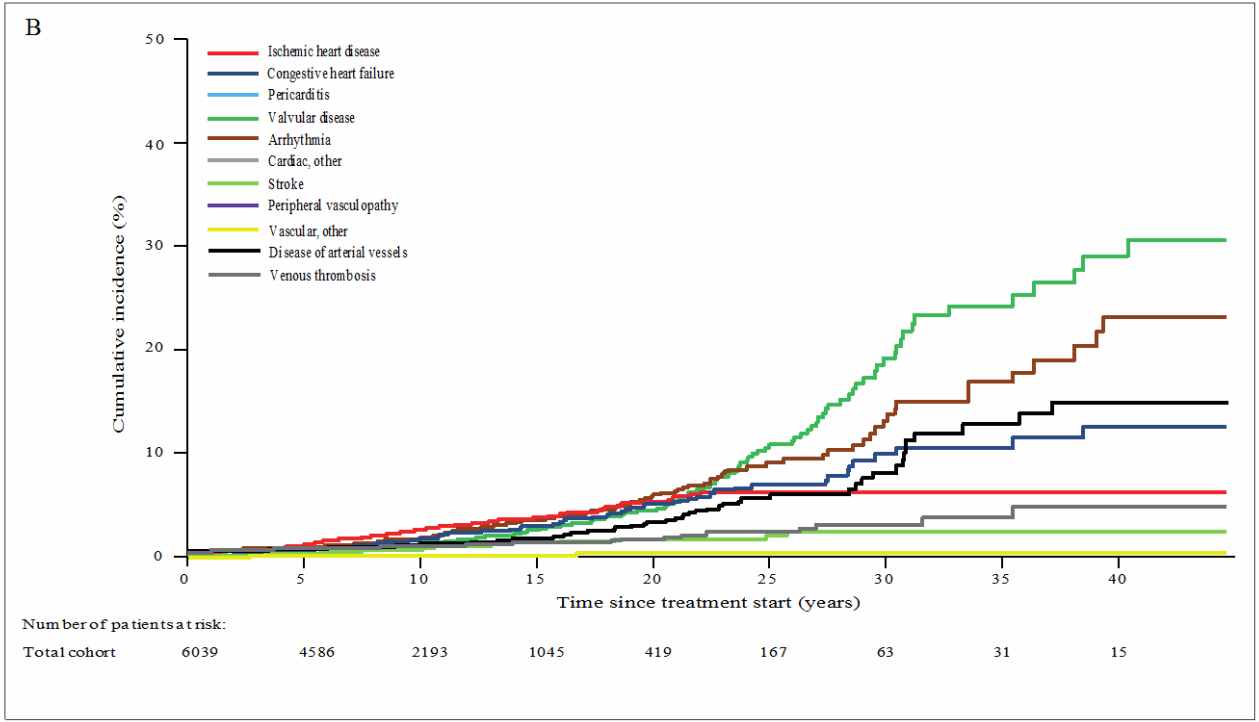
LSQ responder

Total cohort

LSQ non responder

Maraldo et al, Lancet Hemat in press

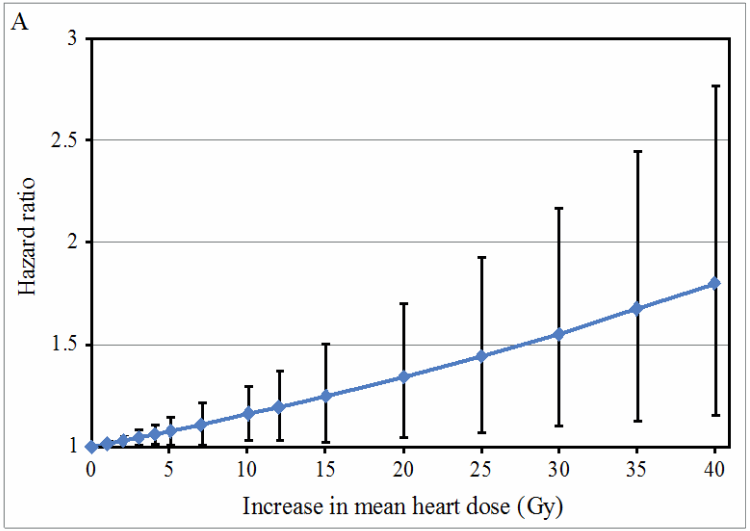
Cardiovascular disease after therapy for HL:
A detailed analysis of 9 collaborative EORTC-LYSA trials

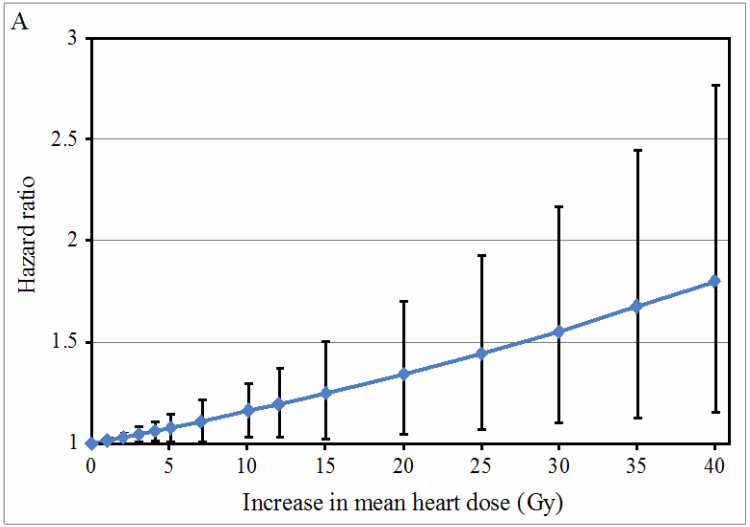


Maraldo et al, Lancet Hemat in press

Cardiovascular disease after therapy for HL:
A detailed analysis of 9 collaborative EORTC-LYSA trials

The mean heart radiation dose and the cumulative dose of anthracyclines were significant predictors of CVD, with an increase in hazard rate of 1·5% (95% CI: 0·6–2·4%) per 1 Gy increase in mean heart dose and 7·7% (95% CI: 2·1–13·7%) per 50 mg/m2 increase in cumulative anthracycline dose.





Maraldo et al, Lancet Hemat in press

Optimize treatment ?

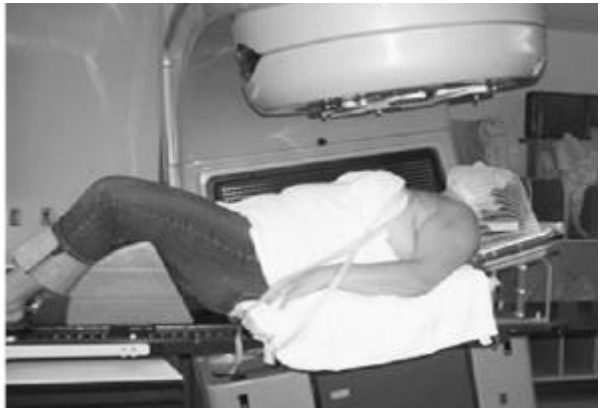
Disease control

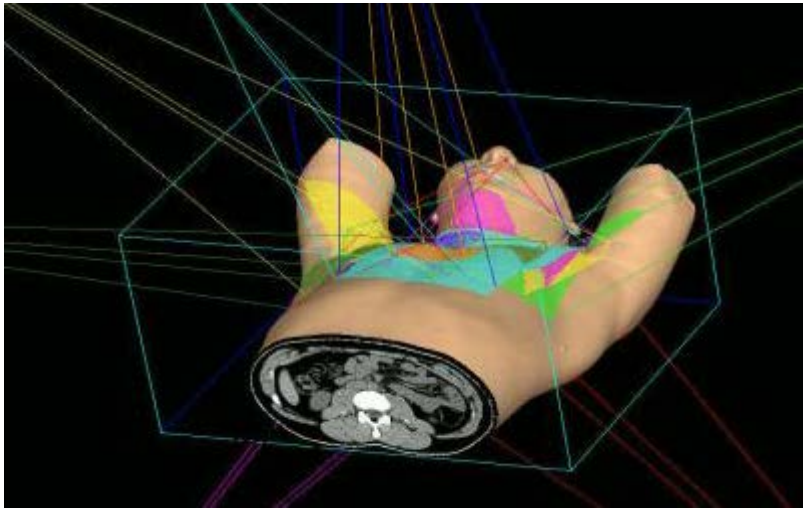
Chance early and late side effects

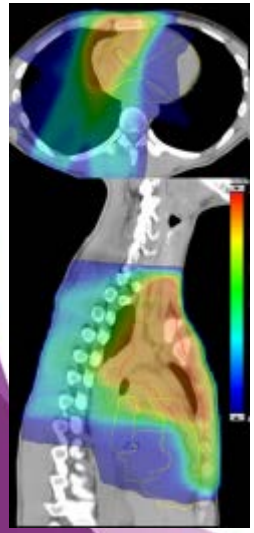
Treatment optimization:

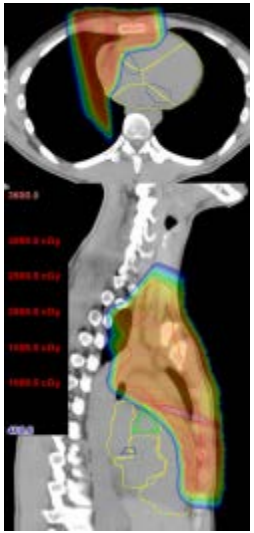
Extensively discussed during course:

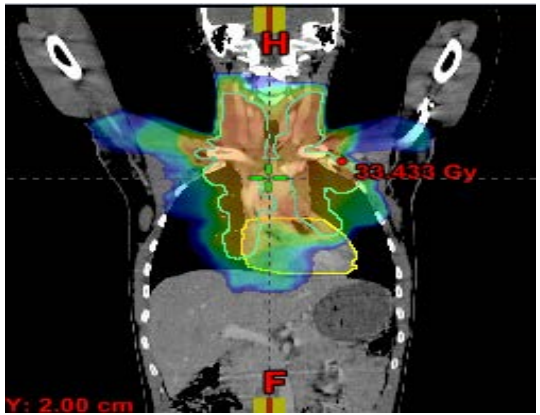
- Balancing systemic and local treatment
- Optimal RT technique (including optimal preparation of RT, careful choice target volume, optimal planning, introduction of DIBH, protons etc)

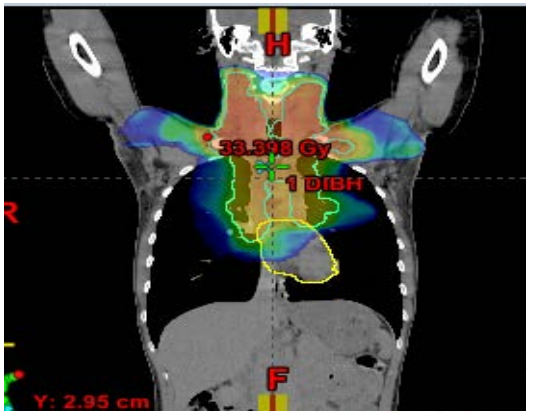






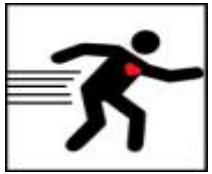



H
33.433 Gy
F
Y: 2.00 cm


H
33.398 Gy
1 DIBH
F
Y: 2.95 cm

Limit risk of (treatment -related) side effects Patient

- Adjust lifestyle - no smoking
- Visit doctor in case of complaints



BETER-project:

A nationwide survivorship care program for adult (non-)Hodgkin lymphoma survivors

Future

- Development of risk prediction models including all available information on late effects
- Improve documentation of applied treatment (including dose to OAR)

Acknowledgements

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Funding by the Dutch Cancer Society
NKI 2004-3068, 2010-4720

Risk of second malignancy, Dutch HL cohort; 3370 5-yr survivors, 15-50 yr at dx, 1965 - 2000

Cancer site	SCs	SIR	(95%CI)
All Malignancies	**709**	**4.5**	**(4.2-4.9)**
Oral cavity/pharynx	15	**3.1**	(1.7-5.1)
Esophagus	23	**7.1**	(4.5-10.7)
Stomach	33	**8.9**	(6.1-12.5)
Colon	25	**2.4**	(1.5-3.5)
Rectum & Rectosigmoid	18	**2.5**	(1.5-4.0)
Lung & Bronchus	129	**6.5**	(5.4-7.7)
Female breast	138	**4.4**	(3.6-5.2)
Leukemia	33	**12.4**	(8.6-17.5)
Non-Hodgkin Lymphoma	78	**11.3**	(9.0-14.2)

Schaapveld, submitted

SIRs and AERs of second malignancy, Dutch HL cohort; 3370 5-yr survivors, 15-50 yr at dx, 1965-2000

Cancer site	SCs	SIR	AER/10,000
All Malignancies	**709**	**4.5**	**114.7**
Oral cavity/pharynx	15	3.1	2.1
Esophagus	23	7.1	3.0
Stomach	33	8.9	6.1
Colon	25	2.4	3.0
Rectum & Rectosigmoid	18	2.5	2.3
Lung & Bronchus	129	**6.5**	**22.6**
Female breast	138	**4.4**	**49.2**
Leukemia	33	**12.4**	**6.3**
Non-Hodgkin Lymphoma	78	11.3	14.8

AER=absolute excess cases per 10,000/yr

Schaapveld, work in progress

SIR of Second Malignancy following HL combined results from 3 large studies* (n=9618)

Site or Type	Obs	SIR	AER
Solid tumors	519	2.8	37.9
Lung	155	4.3	13.4
GI tract	115	2.4	7.0
Stomach	29	2.8	2.1
Female breast	76	2.7	13.2
Bone	7	10.1	0.7
Connective tissue	15	9.8	1.6
Thyroid	14	9.2	1.4

* Based on Hancock 1996; Van Leeuwen 2000; Swerdlow 2000

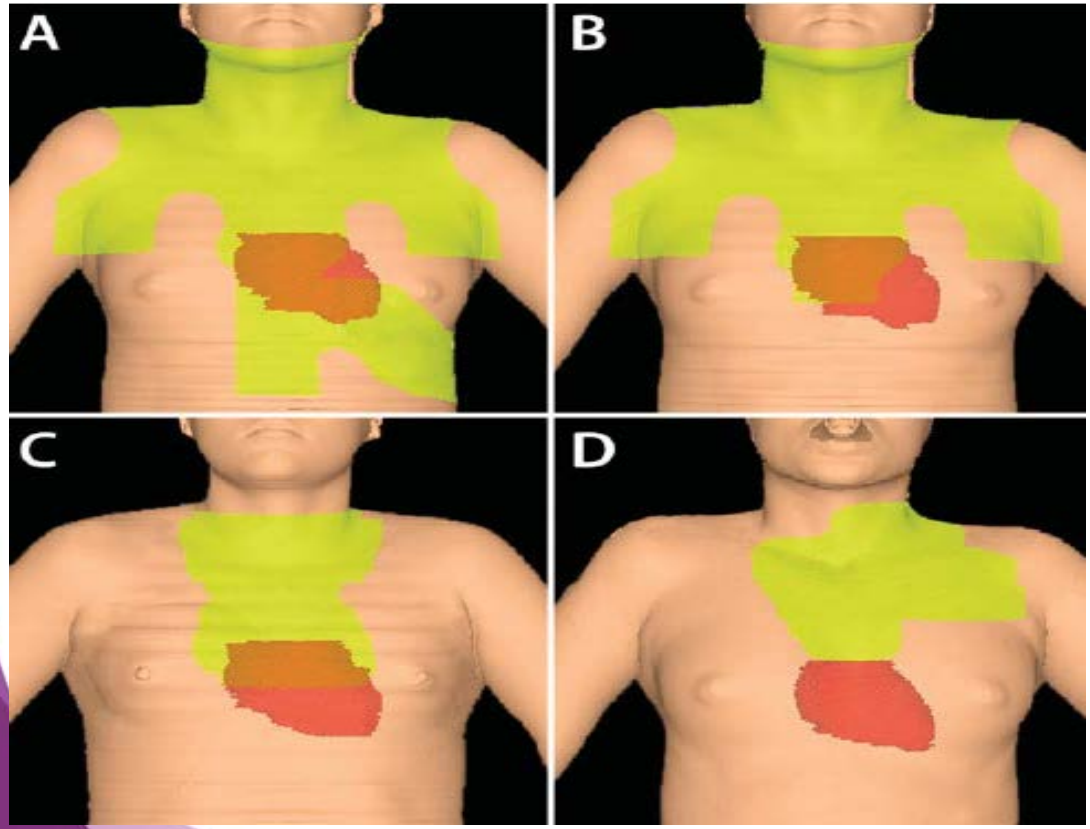
SIR: Standardized Incidence Ratio

AER: Absolute Excess Risk per 10,000 persons/year

Literature cardiovascular disease after HL, II

- Radiation dose-response? Only assessed in childhood cancer, childhood HL and breast cancer
- Schellong PBC 2010 (childhood HL): Effect of prescribed mediastinal RT dose on risk (very small numbers per dose category)
- Mulrooney BMJ 2009 (CCS): increased risk for prescribed doses ≥ 15 Gy
- Dose to heart or cardiac substructures assessed in only two studies *(Darby NEJM 2013; Tukenova JCO 2010)*
- Tukenova JCO 2010 (CCS): for all CVDs combined (n=32) association with average radiation dose to heart

Changes in RT fields over time



Green: Irradiated field
Red: heart

RT fields:
A: Mantle+paraaortic+spleen
B: Mantle field
C: Involved field RT
D: Involved node RT for patient with mediastinal, low neck and high axillary disease

Hodgson, ASH educational 2011

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Survival outcome after a second malignancy

n=1319 ; treatment period: 1969 and 1997; median fup 12 years.

Second malignancy	No. of pts	5-yr survival estimate (%)	95% CI	Median survival, yrs
All sites	181	38.1	(29.7-46.5)	3.2
Acute leukemia	23	4.9	(0.0-14.2)	0.4
NHL	24	49.6	(28.0, 71.2)	2.4
All solid tumors	131	42.1	(31.6, 52.5)	4.3
Breast	39	76.1	(57.4-94.8)	Not yet reached
Lung	22	0.0	—	1.0
Gastrointestinal	24	12.4	(0-28.1)	1.9

Ng et al., Blood 2002

Lung cancer after HL
Joint effects of smoking and treatment

Nested case-control study: 222 cases of lung cancer, 444 matched controls

- Smoking is the major cause of lung cancer (only 7 out of 222 cases were never smokers)

	RR non/light smokers
No RT (< 5 Gy), no CT	1.0 (ref)
RT (≥ 5 Gy), no CT	7.2 (2.9-21.2)
No RT (< 5 Gy), CT	4.3 (1.8-11.7)
RT (≥ 5 Gy), CT	7.2 (2.8-21.6)

Travis et al. JNCI 2002; 94:182

Lung cancer after HL
Joint effects of smoking and treatment

Nested case-control study: 222 cases of lung cancer, 444 matched controls

- Smoking is the major cause of lung cancer
  (only 7 out of 222 cases were never smokers)

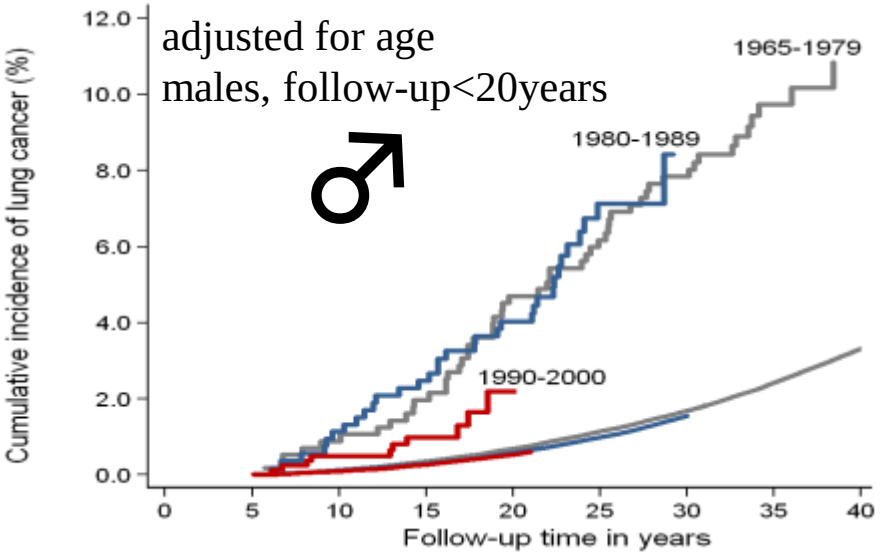
- Risks from smoking multiply risks from treatment

	RR non/light smokers	RR smokers
No RT (< 5 Gy), no CT	1.0 (ref)	6.0 (1.9-20.4)
RT (≥ 5 Gy), no CT	7.2 (2.9-21.2)	20.2 (6.8-68)
No RT (< 5 Gy), CT	4.3 (1.8-11.7)	16.8 (6.2-53)
RT (≥ 5 Gy), CT	7.2 (2.8-21.6)	49.1 (15.1-187)

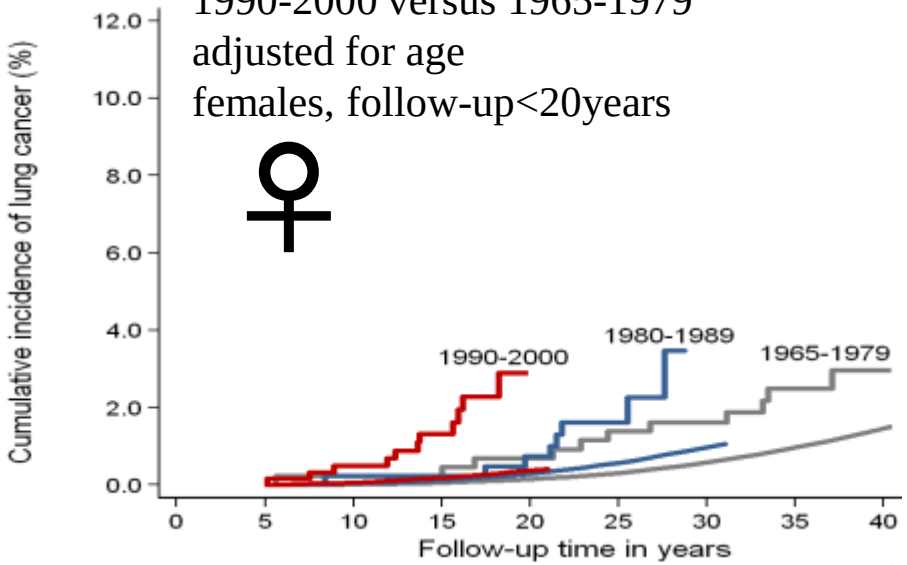
Travis et al. JNCI 2002; 94:182

Trend in cumulative incidence* of lung cancer by period of treatment and sex in 5 year HL survivors (n=3,905) and the general population

pHR 0.35 (95%CI 0.16-0.78)
1990-2000 versus 1965-1979
adjusted for age
males, follow-up<20years



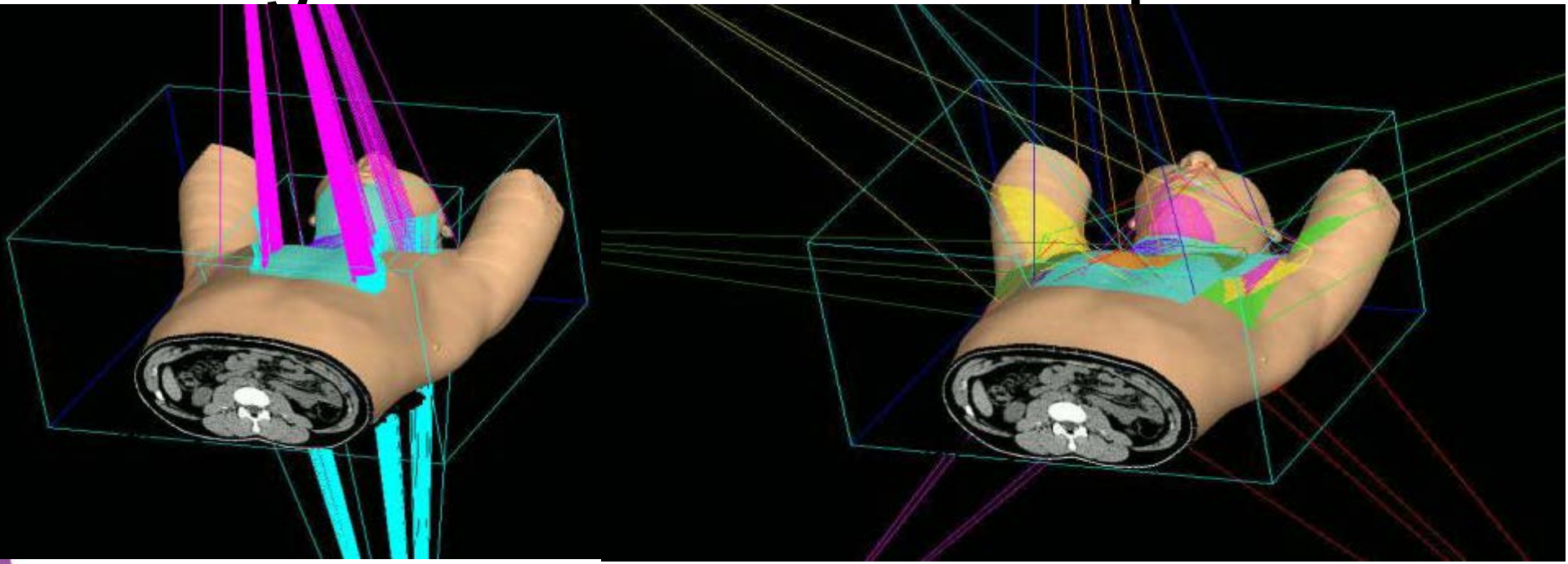
pHR 3.23 (95%CI 0.85-12.29)
1990-2000 versus 1965-1979
adjusted for age
females, follow-up<20years



*estimated in the presence of death as a competing risk

Schaapveld, work in progress

Changes radiation techniques



More (fields) is not always better!

Defining constraints for organs at risk very important

Individualize treatment plan

Screening for second cancers

Breast:

- Women treated with chest RT before age 40
- Start screening 8 years after RT, not before age 25

Colon:

- Screening of colon cancer – under consideration

Lung and stomach:

- No screening for lung cancer or stomach cancer

From current draft Dutch sceening guideline

Future research SMN after HL

- Effects of contemporary RT / systemic therapy
- Interaction between RT and CT (procarbazine)
- Search for susceptibility genes for RT/CT-associated malignancies
- Interaction between treatment and lifestyle
- Risk prediction models
- Efficacy of screening for second malignancies/CVD
- Effect of RT dose/volume on second cancer risk

Acknowledgements

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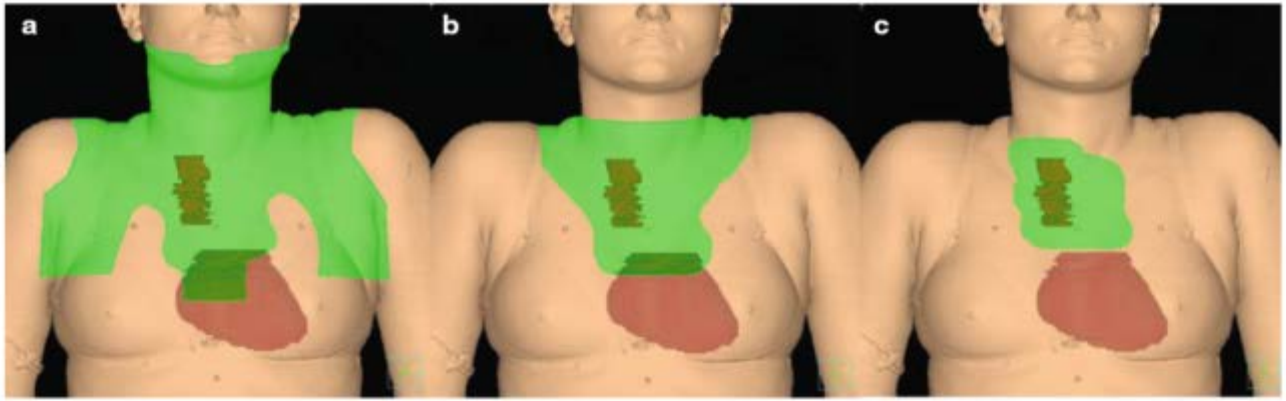
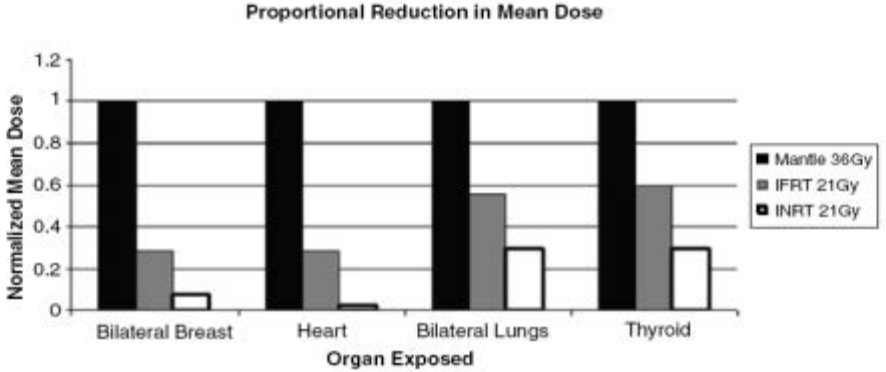
Josée Zijlstra
Netherlands Cancer Registry

Spare slides

Changes in radiation fields





Courtesy: L. Constine

Statistical analyses

- Conditional logistic regression analyses
  - Multivariate
- Modeling dose response
  - CHD rate = $K_m(1+\beta d)$
    - $\mathbf{K_m}$ is constant, specific to each matched set
    - **β** is the proportional increase in CHD rate per unit increase in mean heart dose
    - **d** is the dose

Cardiovascular disease after treatment for HL

- **Patient-related factors**
  - Age at diagnosis/treatment
  - Follow-up time
  - General risk factors cardiovascular disease
  - Genetic factors

- **Treatment-related factors**
  - Chemotherapy agents, doses
  - RT dose and volume
  - Interaction RT and CT

- **Interaction between RT/CT/age/genetic/other risk factors**

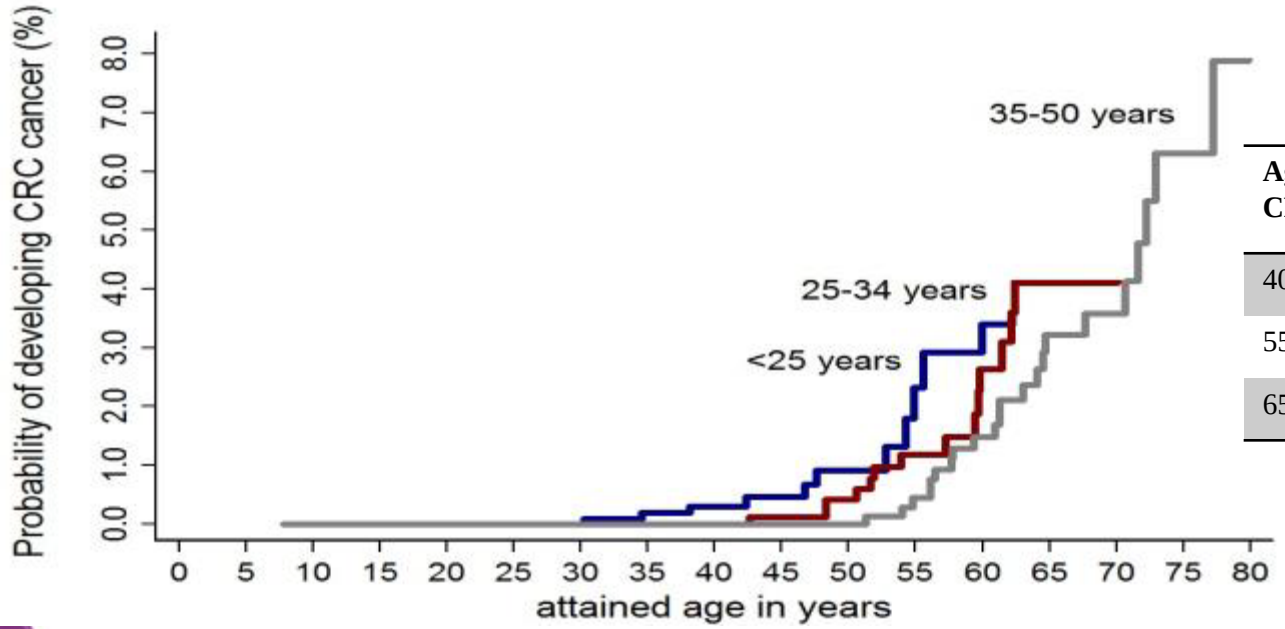
Risk factors for CRC after HL treatment
Multivariable regression analysis

		CRC		*Transverse colon & rectum*
Risk Factor	**HR**	**95% CI**	**HR**	**95% CI**
Treatment				
Procarbazine				
No CT or CT without procarbazine	1.0	Reference	1.0	Reference
CT, ≤ 4.2g/m^2 procarbazine	1.7	0.7-4.4	1.8	0.6-6.0
CT, > 4.2g/m^2 procarbazine	2.7	1.4-5.2	3.6	1.5-8.6
Radiotherapy				
No infradiaphragmatic RT	1.0	Reference	1.0	Reference
Infradiaphragmatic RT	1.8	1.0-3.2	2.2	1.0-4.7

Cox model adjusted for sex and age. HR = Hazard ratio; 95% CI = 95% confidence interval
4.2 g/m^2 procarbazine≈3x MOPP or 6 MOPP-ABV(D)

Eggermond, work in progress

Cumulative incidence of CRC by attained age

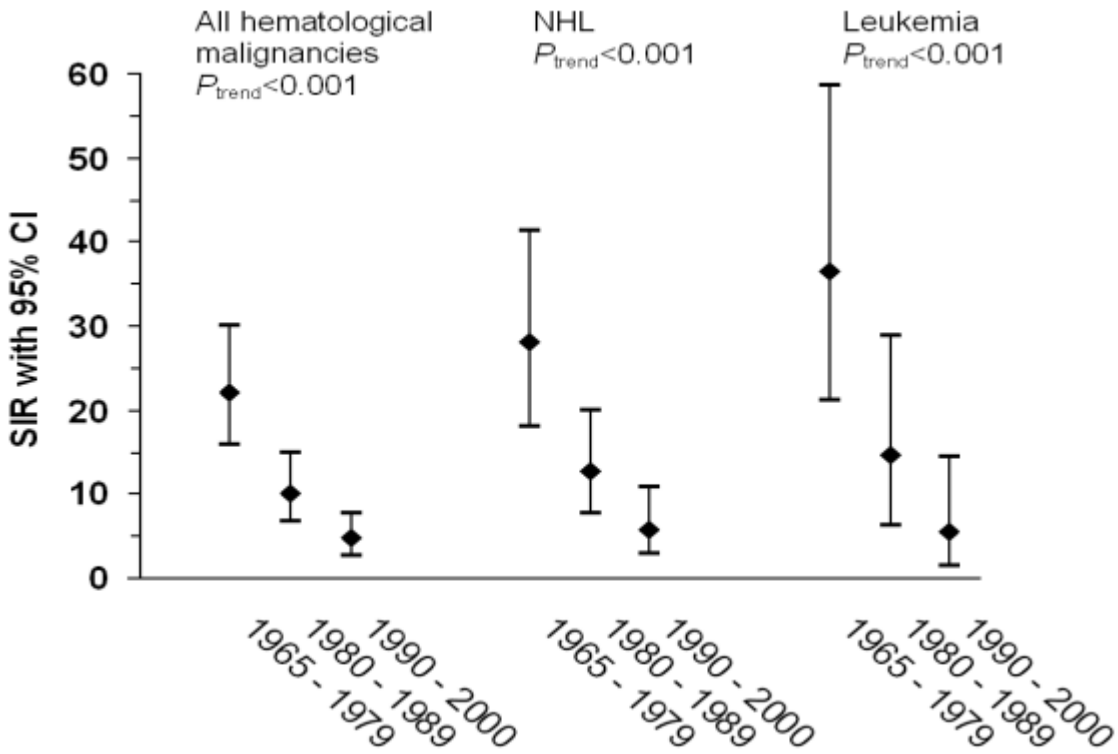


Age at CRC dx	HL survivors	General population
40	0.11%	0.06%
55	1.00%	0.50%
65	2.65%	1.60%

Median age at CRC diagnosis (IQR) = 57.7 years (51.9-62.5)

Eggermond, work in progress

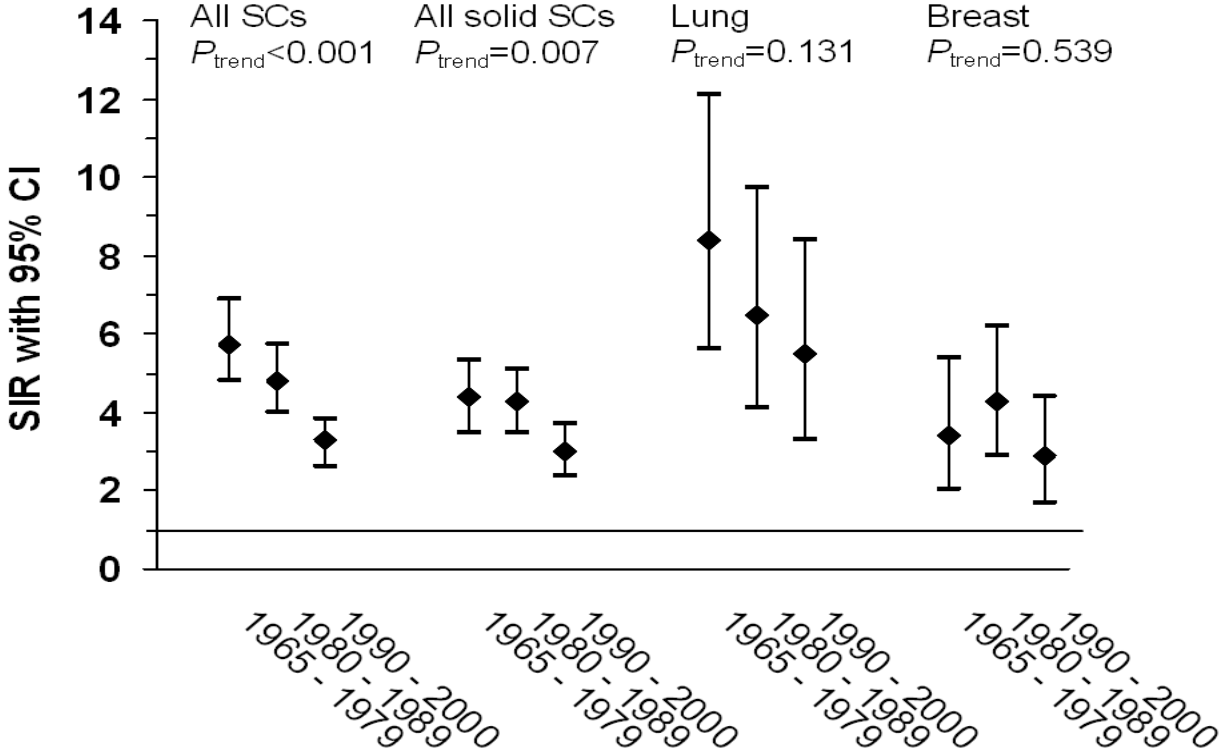
Trends in SIRs of hematological malignancies after HL



SIR = Standardized Incidence Ratio; P*trend* adjusted for gender, age, follow-up (<20yrs)

Schaapveld et al, submitted

Trends in SIRs of solid SCs



SIR = Standardized Incidence Ratio; P*trend* adjusted for gender, age, follow-up (<20yrs)

Schaapveld et al, submitted

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Guy's and St Thomas' NHS
NHS Foundation Trust

Nodular Lymphocyte Predominant HL
Role of Radiotherapy

George Mikhaeel, MD
Department of Clinical Oncology
Guy's & St Thomas' Hospital
KHP Academic Health Sciences Centre
London, UK

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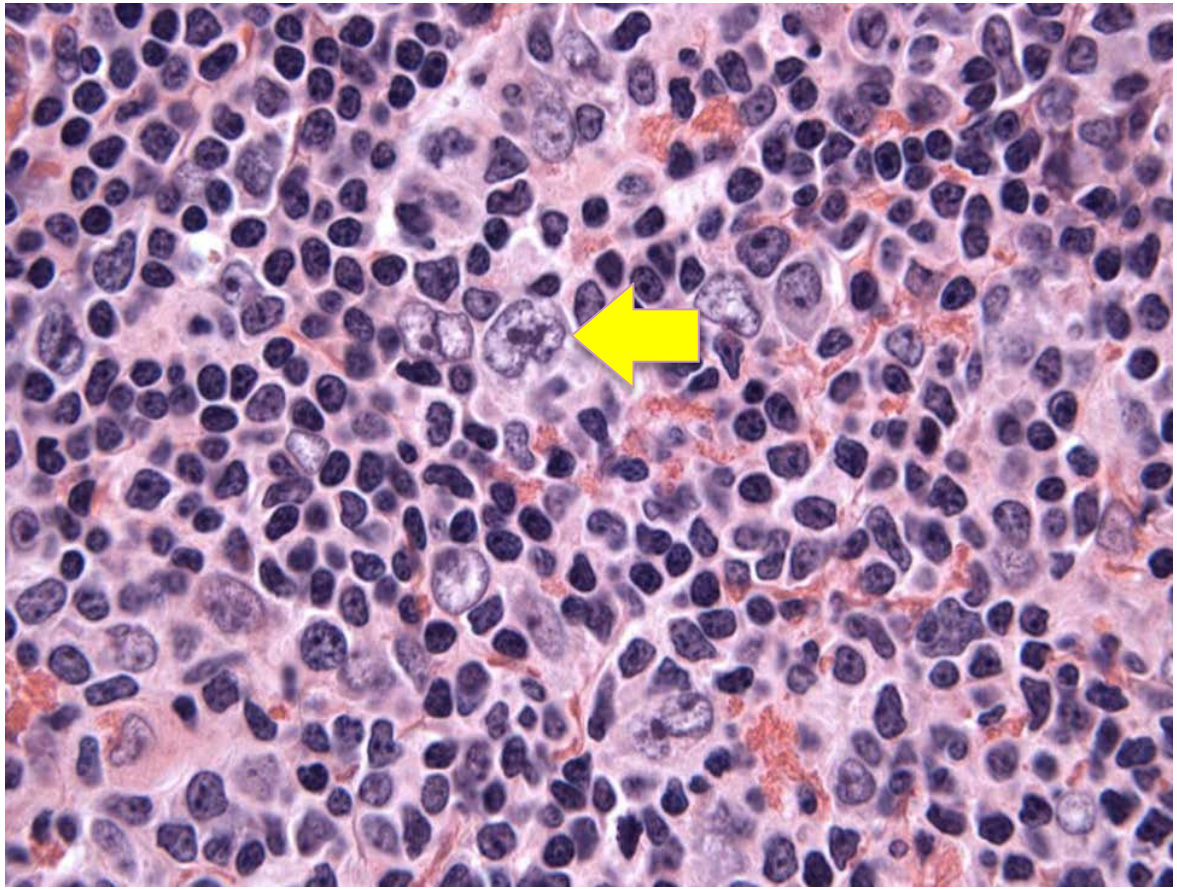
Incidence

- 5% of all HL
- 1.5 / 1m population/ y
- Recently recognized category:
  - 1944: Jackson & Parker: granuloma variant of HL
  - 1994: REAL classification (CD20+ LP, L&H/ popcorn cells)
  - 2001: WHO (separated from cHL as NLP)
- No prospective studies:
  - Re-analysis of previous studies
  - Institutional / registry based retrospective studies

Characteristics

- Histology:
  - LP cells: b-cell markers (CD20, CD79a, CD45) but not CD15, CD30
  - Initially thought: similar to FL, but now thought to be closest to DLBCL (particularly T-cell-rich)
  - NFkB activation
  - DD: progressive transformation of germinal centre.

Popcorn cell



Characteristics (2)

- Clinically:
  - Long history of lymphadenopathy
  - Male predominance (75%)
  - Familial risk described
  - Mediastinal sparing
  - EN sites rare

Characteristics (3)

- Prognosis:
  - Early stage: highly curable
  - Advanced stage: multiply relapsing
  - Transformation to HG-NHL particularly TCR-DLBCL
    - 10 y risk 10-12%
    - 20 y risk up to 30%
    - Risk fs: advanced stage, spleen / abdominal presentation
  - Importance of Bx of every relapse + long FU
  - Death due to NLP is uncommon

VOLUME 28 · NUMBER 5 · FEBRUARY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Transformation to Aggressive Lymphoma in Nodular Lymphocyte-Predominant Hodgkin's Lymphoma

Mubarak Al-Mansour, Joseph M. Connors, Randy D. Gascoyne, Brian Skinnider, and Kerry J. Savage

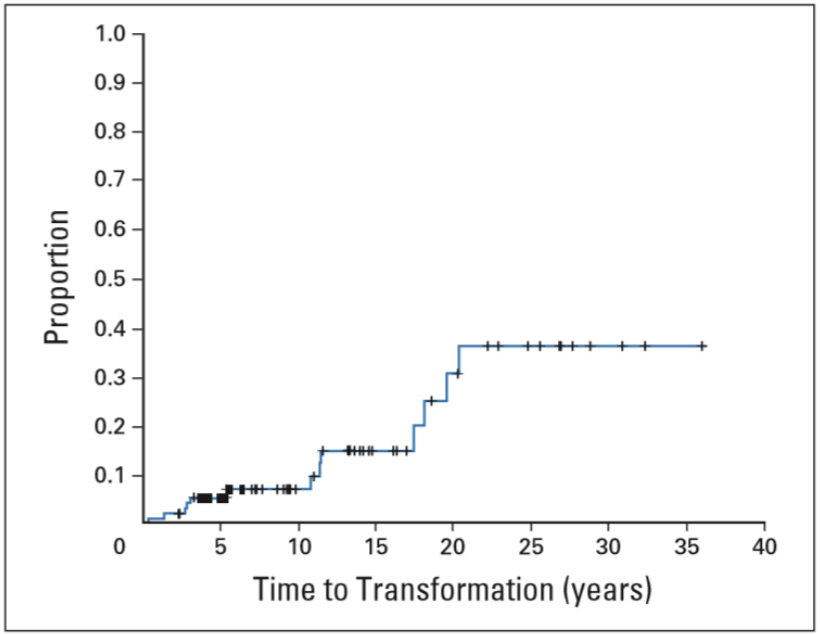


Fig 1. Time to transformation in patients with nodular lymphocyte-predominant Hodgkin's lymphoma.

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International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Characteristics and Outcomes of Patients With Nodular Lymphocyte-Predominant Hodgkin Lymphoma Versus Those With Classical Hodgkin Lymphoma: A Population-Based Analysis

Naamit K. Gerber, MD,* Coral L. Atoria, MPH,† Elena B. Elkin, PhD,† and Joachim Yahalom, MD*

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Received Dec 15, 2014, and in revised form Jan 27, 2015. Accepted for publication Feb 5, 2015.

1,162 NLP 29,000 cHL mFU 7ys

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NLP ——

cHL - - - -

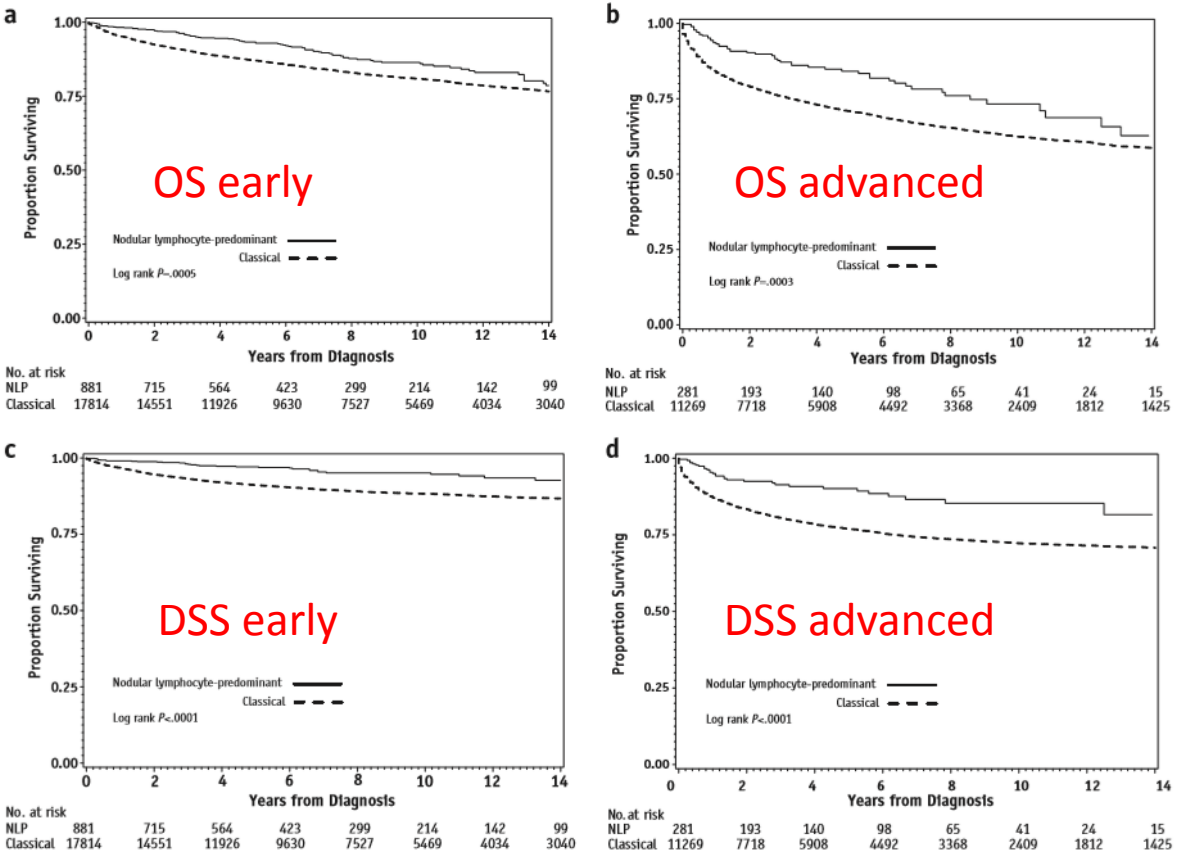

Fig. 1. (a) Overall survival for early stage patients by subtype. (b) Overall survival for advanced stage patients by subtype. (c) Disease-specific survival for early stage patients by subtype. (d) Disease-specific survival for advanced stage patients by subtype. NLP = nodular lymphocyte-predominant Hodgkin lymphoma.

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Diagnostic work up

- As cHL

- NLP is FDG avid:
  - PET is useful for staging and response assessment.
  - Essential for early stage managed by RT alone (more accurate staging)
  - Useful for RT planning

Management

- Generally:
  - Early stage: RT
  - Advanced stage: systemic treatment
- Important considerations in Treatment:
  - Early:
    - Volume & dose of RT
    - Role of CMT
    - Role of excision alone
  - Advanced:
    - Which chemo
    - Role of Rituximab

CMT / Chemo for early stage

- No RCT
- RT outcome is excellent. Difficult to improve on.
- Limited data on role of CMT in early stage dis
  - *Canadian* data on short course ABVD suggests benefit
  - but other studies (*MDACC, GHSG, Harvard*) show no benefit
  - RT alone remains standard
- Chemo alone strategy in children: limited data
- Rituximab alone: limited data (GHSG 28 pts, Stanford 13 pts):
  - 100% response, but 25% relapse. Not recommended.

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Treating limited-stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcome

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The appropriate therapy for limited-stage nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is unclear. In contrast to classical Hodgkin lymphoma (CHL), chemotherapy is often omitted; however, it is unknown whether this impacts the risk of relapse. Herein, we compared the outcome of patients with limited-stage NLPHL treated in an era in which ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy was routinely incorporated into the primary therapy to an earlier era in which radiotherapy (RT) was used as a single modality. Using the British Columbia Cancer Agency Lymphoid Cancer Database, 88 patients with limited-stage NLPHL (stage 1A/1B or 2A, nonbulky disease < 10 cm) were identified. Treatment followed era-specific guidelines: before 1993, (n = 32) RT alone; and 1993 to present (n = 56), ABVD-like chemotherapy for 2 cycles followed by RT with the exception of 14 patients who received ABVD chemotherapy alone. Most patients were male (75%) with stage I disease (61%). In an era-to-era comparison, the 10-year time to progression (98% vs 76% $P = .0074$), progression-free survival (91% vs 65% $P = .0024$), and OS (93% vs 84%, $P = .074$) favored the ABVD treatment era compared with the RT alone era. Treating limited-stage NLPHL similarly to CHL may improve outcome compared with the use of radiation alone. (*Blood*. 2011;118(17): 4585-4590)

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BCCCA study

- Retrospective longitudinal cohort, mFU 6.4y
- 88 pts (1966 – 2009):
  - 121 pts, 33 revised histology = 88
  - 88: 79 confirmed, 10 missing histology
  - <1993: RT alone =32
  - >1993: ABVDx2 +RT =56 (14 ABVD alone)
- Results (CMT v RT):
  - 10y TTP: 91 v 65% (p=0.002)
  - 10y OS: 83 v 84% (0.07)

Surgical resection

- Option for children
- 2 studies:

	EuroNET	COG
No of pts	57	52
	Stage 1A	Stage 1A, no bulk
Complete resection	86%	100%
Median FU	43m	26m
Relapse	27%	17%
Time to relapse	All within 26m	Median 10m
PFS	FFP 67%	2y EFS 80%

Outcome of RT in early stage

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Long-Term Course of Patients With Stage IA Nodular Lymphocyte-Predominant Hodgkin Lymphoma: A Report From the German Hodgkin Study Group

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A B S T R A C T

Purpose
The optimal treatment of stage IA nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is not well defined. Thus, we performed an analysis using the database of the German Hodgkin Study Group.

Patients and Methods
The long-term outcome of 256 patients with stage IA NLPHL was evaluated. Patients had received combined-modality treatment (CMT; n = 72), extended-field radiotherapy (EF-RT; n = 49), involved-field radiotherapy (IF-RT; n = 108), or four weekly standard doses of rituximab (n = 27) within German Hodgkin Study Group clinical trial protocols between 1988 and 2009.

Results
The median age at NLPHL diagnosis was 39 years (range, 16 to 75 years). Most patients were male (76%). The whole patient group had a median follow-up of 91 months (CMT: 95 months; EF-RT: 110 months; IF-RT: 87 months; rituximab: 49 months). At 8 years, progression-free survival and overall survival rates were 88.5% and 98.6% for CMT, 84.3% and 95.7% for EF-RT, and 91.9% and 99.0% for IF-RT, respectively. Patients treated with rituximab had 4-year progression-free and overall survival rates of 81.0% and 100%, respectively. A second malignancy during the course of follow-up was diagnosed in 17 (6.6%) of 256 patients. A total of 12 deaths occurred. However, only one patient died from NLPHL.

Conclusion
Tumor control in this analysis was equivalent with CMT, EF-RT, and IF-RT. Therefore, IF-RT, which is associated with the lowest risk for the development of toxic effects, should be considered as standard of care for patients with stage IA NLPHL. Rituximab alone is associated with an increased risk of relapse in this patient population.

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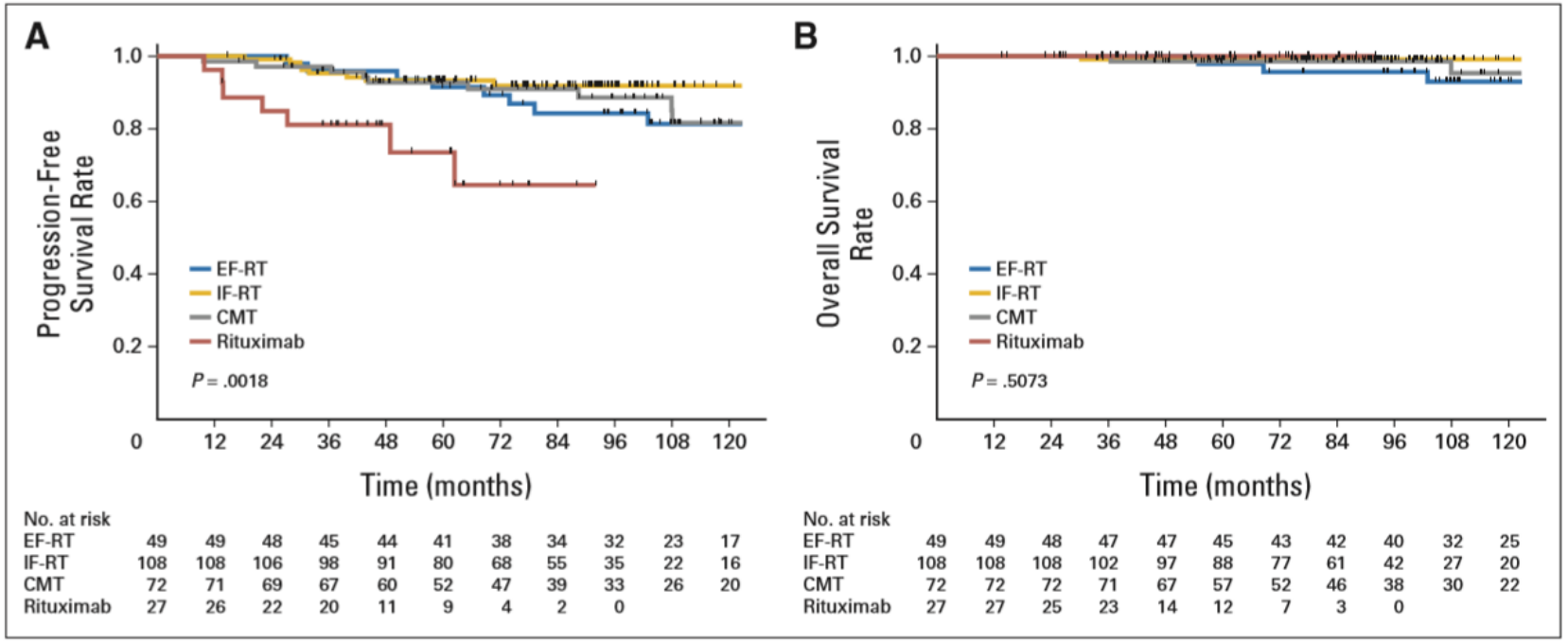

Fig 1. (A) Progression-free survival and (B) overall survival among patients with stage IA nodular lymphocyte-predominant Hodgkin lymphoma treated with combined-modality treatment (CMT), extended-field radiotherapy (EF-RT), involved-field radiotherapy (IF-RT), or rituximab.

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Table 3. Four-Year PFS of Patients Treated for Stage IA NLPHL

Variable	No. of Patients	No. of Events (%)	4-Year PFS Rate (%; 95% CI)	Log-Rank *P*	Cox Univariate Hazard Ratio (95% CI)
Total	256	45 (18)	92.3 (89.0 to 95.6)		—
Treatment modality				.0018	
EF-RT	49	15 (31)	95.8 (90.2 to 100.0)		1.56 (0.68 to 3.58)
IF-RT	108	11 (10)	93.2 (88.4 to 98.1)		—
CMT	72	12 (17)	92.9 (86.8 to 98.9)		1.00 (0.43 to 2.35)
Rituximab	27	7 (26)	81.0 (66.0 to 96.0)		4.99 (1.88 to 13.21)

Abbreviations: CMT, combined-modality treatment; EF-RT, extended-field radiotherapy; IF-RT, involved-field radiotherapy; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; PFS, progression-free survival.

Table 2. Eight-Year PFS of Patients Treated for Stage IA NLPHL

Variable	No. of Patients	No. of Events (%)	8-Year PFS Rate (%; 95% CI)	Log-Rank *P*	Cox Univariate Hazard Ratio (95% CI)
Total	229	38 (17)	88.9 (84.5 to 93.4)		—
Treatment modality				.4305	
EF-RT	49	15 (31)	84.3 (73.6 to 95.0)		—
IF-RT	108	11 (10)	91.9 (86.5 to 97.3)		0.64 (0.28 to 1.47)
CMT	72	12 (17)	88.5 (80.3 to 96.8)		0.64 (0.30 to 1.39)

Abbreviations: CMT, combined-modality treatment; EF-RT, extended-field radiotherapy; IF-RT, involved-field radiotherapy; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; PFS, progression-free survival.

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Table 4. Characteristics of Second Malignancies After Treatment for Stage IA NLPHL

Secondary Malignancy	Chronic Myeloid Leukemia (n = 1)	Non-Hodgkin Lymphoma (N = 7)	Solid Tumor (N = 9)	Total (n = 17)
Time to secondary malignancy, years				
Median	16.6	6.2	5.7	6.2
Range	16.6-16.6	1.0-15.8	2.0-16.4	1.0-16.6
Secondary solid tumors according to localization, No.				
Missing			0	
Colorectal cancer			2	
Lung cancer			2	
Breast cancer			1	
Stomach cancer			1	
Bladder cancer			1	
Salivary gland cancer			1	
Unknown localization			1	
Secondary non-Hodgkin lymphoma according to histology, No.				
Missing		0		
Diffuse large B-cell lymphoma		3		
T-cell–rich B-cell lymphoma		2		
Follicular lymphoma		1		
Marginal zone lymphoma		1		

Abbreviation: NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma.

Only 1 Death from NLP

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Radiotherapy

- ICRU + ILROG guidelines: GTV, CTV, PTV
- PET / planning-CT image registration is ideal to outline GTV (as no prior chemo).
- Volume:
  - No chemo. RT needs to control microscopic disease
  - No benefit to EF over IFRT *(Nogova et al, Ann Oncol 2005)*
  - IFRT / ISRT?

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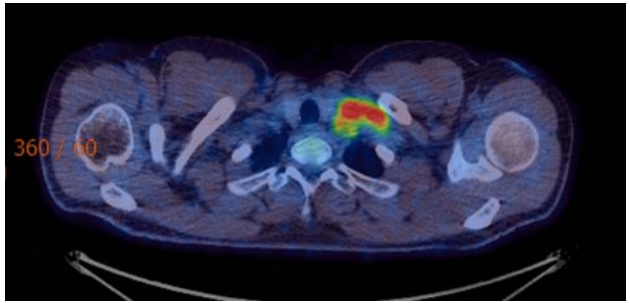
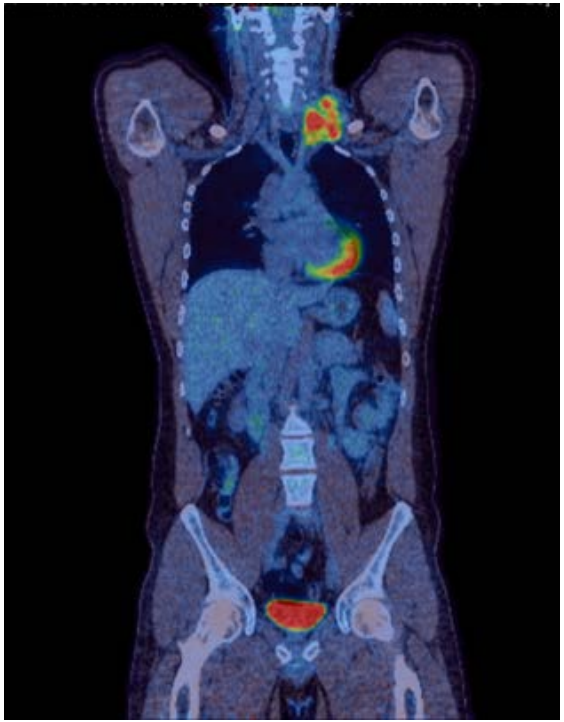
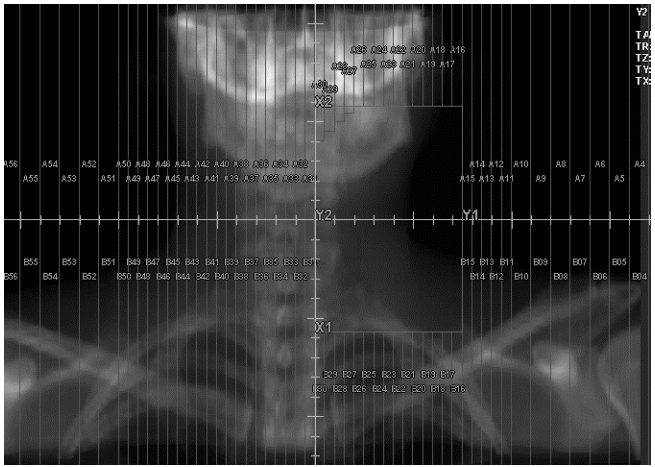
35 yo male
PMH stage 1 NLP
2007 30Gy L Neck

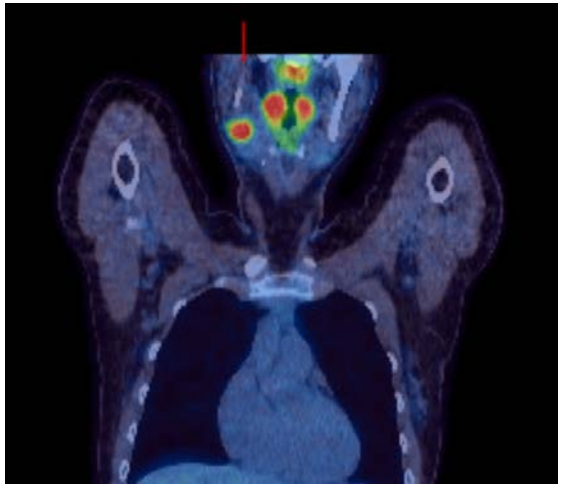
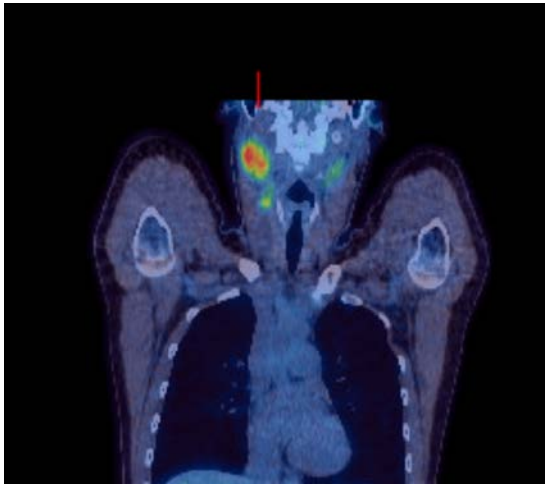
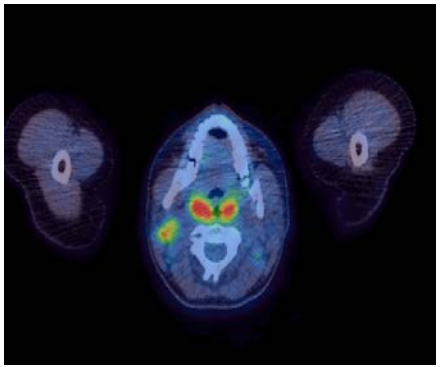
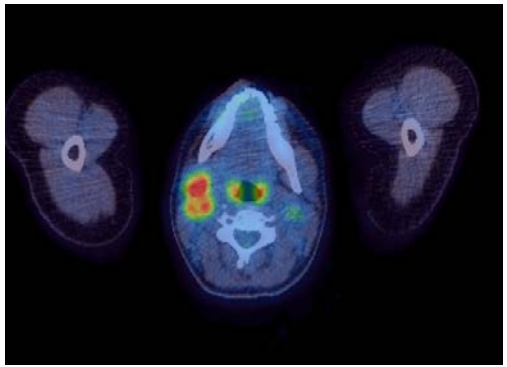
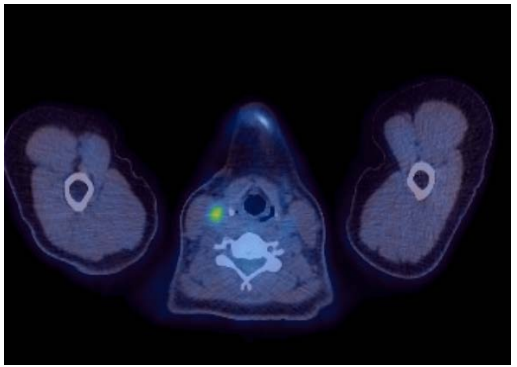


2014





2007

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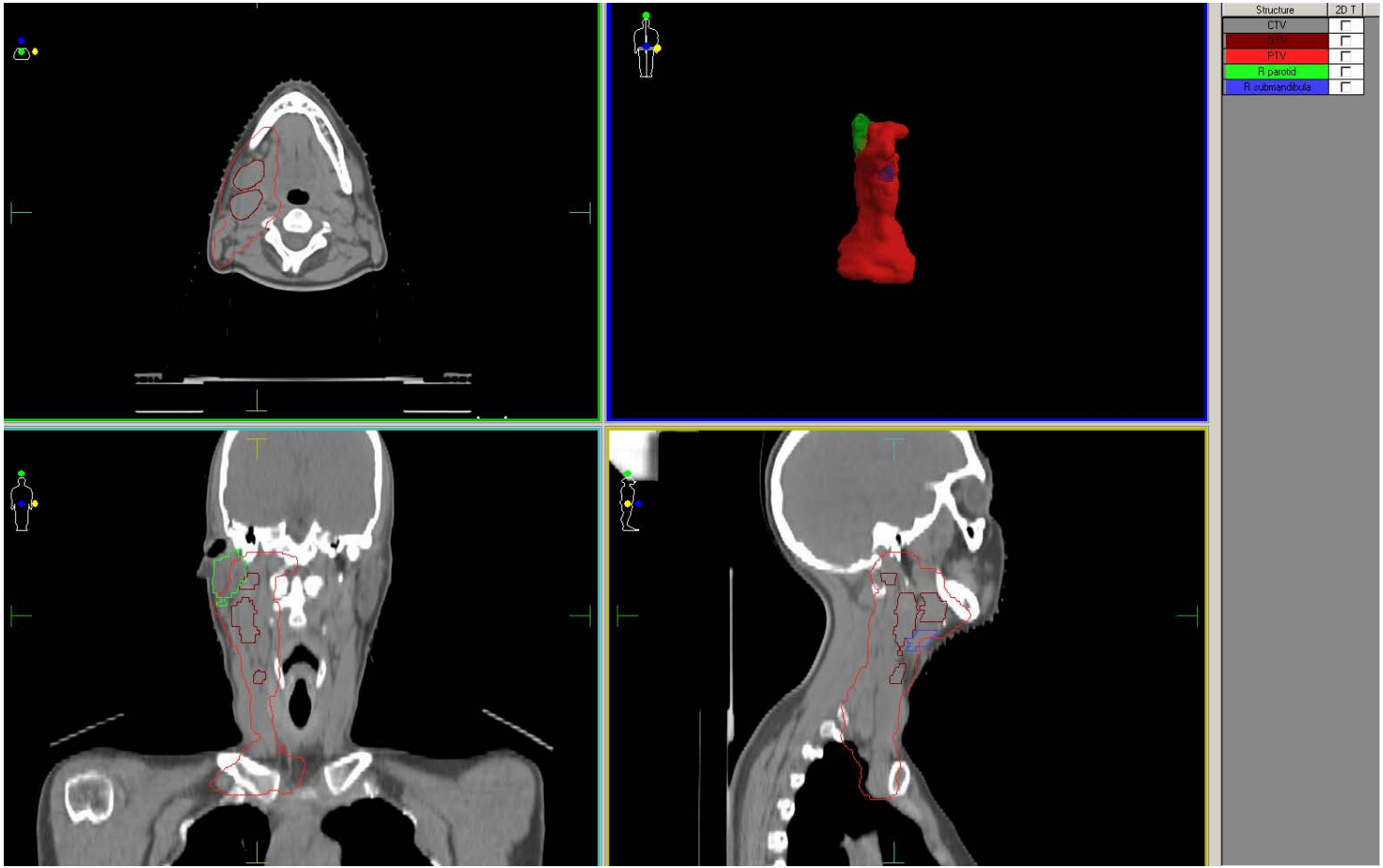

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Radiotherapy (cont.)

- Dose:
  - No conclusive evidence of benefit >30Gy
  - 4Gy: inferior outcome *(local relapse 5/8 pts)*
  - NCCN: 30-36 Gy, ESMO: 30 Gy
  - Standard: 30 Gy……36Gy for bulky disease? (uncommon)

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Key points

- Rare, indolent
- Male predominance, mediastinal sparing
- Better prognosis than cHL, rarely cause of death.
- Tendency to transform
- RT alone for early stage: excellent outcome
- Generous ISRT (no chemo)
- Resection is an option only for children

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Thank you

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The role of radiotherapy in Early stage stage HL

Tim Illidge MD PhD

Professor of Targeted Therapy and Oncology,

Institute of Cancer Sciences

University of Manchester,

Manchester Academic Health Science Centre,

The Christie NHS Foundation Trust, UK

Overview of talk

1. **Review clinical data on management of early stage HL**

– *Should combined modality treatment still be the standard approach ?*

2. **Recent progress in using FDG PET to guide therapy and delivery of RT in HL**

- *Are we ready to make treatments decisions based on FDG-PET to potentially omit RT ?*

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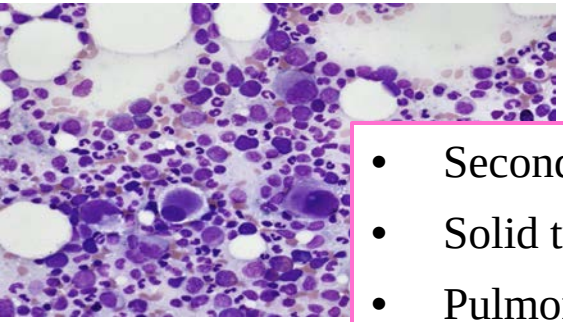
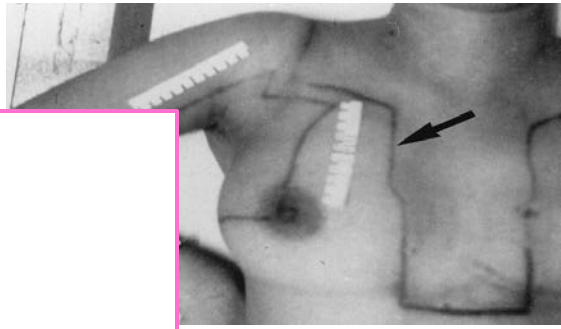
Overall results of therapy for early disease

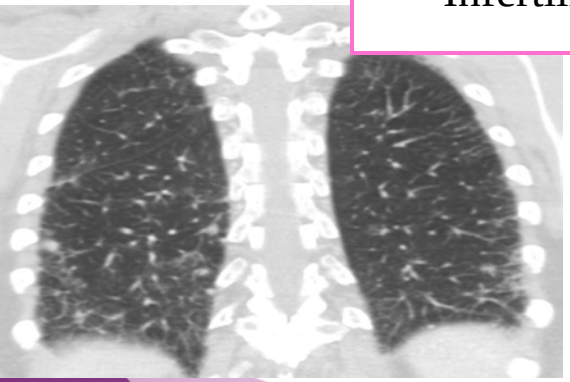
- Up to 90% cures with first line therapy
- About 95% alive at 5 years
- Primary focus of research is to
  - maintain (? improve) this result
  - minimise toxicity

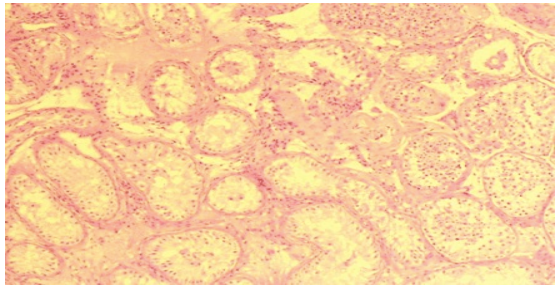
Late effects to avoid as cures increase

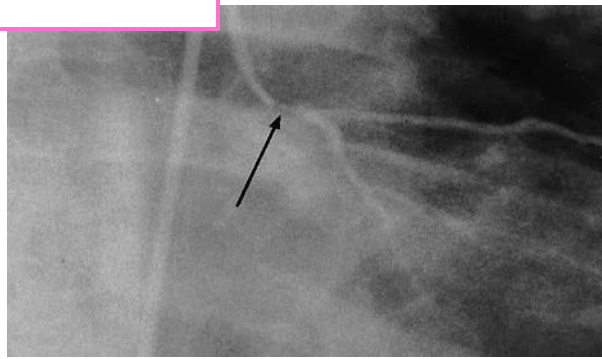




- Secondary MDS/AML from alkylating agents
- Solid tumours from extended field radiation
- Pulmonary fibrosis from bleomycin
- Ischaemic heart disease from mediastinal irradiation and doxorubicin
- Infertility from alkylating agents







Clinical risk-adapted and PET response-adapted approaches

Clinical Risk adapted:

To what degree can we reduce treatment based on clinical prognostic data?

Clinical response adapted:

Is functional imaging response on FDG-PET a better indicator of prognosis?

(and will modifying therapy according to PET CT improve Overall Survival)

Objectives in Early stage Hodgkin Lymphoma

Current standard of care : Baseline risk stratification

	EORTC	GHSG	NCIC/ECOG	NCCN 2010
Risk factors	a) Large mediastinal mass (> 1/3) b) Age ≥50 years c) ESR ≥50 without B-symptoms or ≥30 with B-symptoms d) ≥4 nodal areas	a) Large mediastinal mass b) Extranodal disease c) ESR ≥50 without B-symptoms or ≥30 with B-symptoms d) ≥3 nodal areas	a) Histology other than LP/NS b) Age ≥40 years c) ESR ≥50 d) ≥ 4 nodal areas	a) Large mediastinal mass (> 1/3) or > 10 cm b) ESR ≥50 or any B-ysmptoms c) ≥3 nodal areas d) > 1 extranodal lesion
Favorable	CS I-II (supradiaphragmatic) without risk factors	CS I-II without risk factors	CS I-II without risk factors	CS I-II without risk factors
Unfavorable	CS I-II (supradiaphragmatic) with ≥1 risk factors	CS I or CS IIA with ≥1 risk factors CS IIB with c) or d) but without a) and b)	CS I-II with ≥ 1 risk factors	CS I-II with ≥ 1 risk factors (differentiating between bulky disease and other risk factors for treatment guidelines)

Results from the trials
Early stage disease

- Chemotherapy improves the cure rate over radiation alone (EORTC-H7)
- Sub-optimal chemotherapy (EBVP) needs RT for best results (EORTC-H9)
- 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 may be possible for some patients: can we predict who they are?

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German HD 10 study: reducing therapy in early favourable disease

1370 pts 1998-2003

Early Favourable disease: I_A/II_A

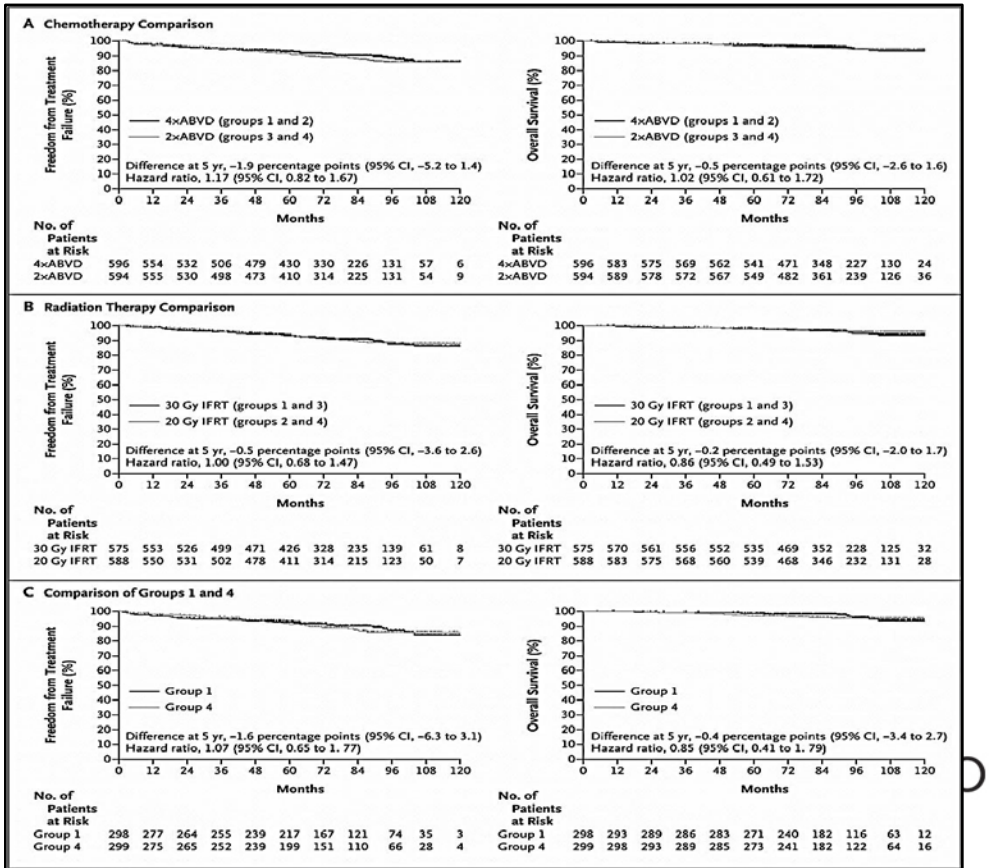
ABVD

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

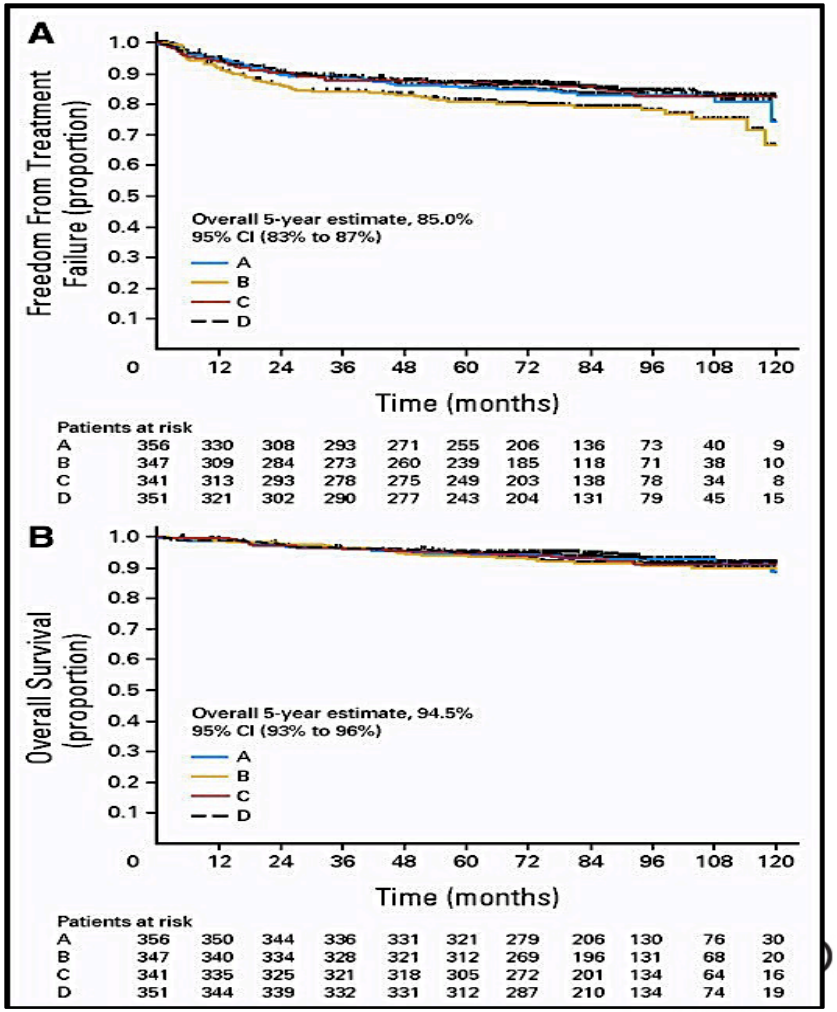
Chemotherapy

4 ABVD 4 BEACOPP

Involved field RT

20 Gy 30 Gy

ABVD + 20Gy inferior on FFTF



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

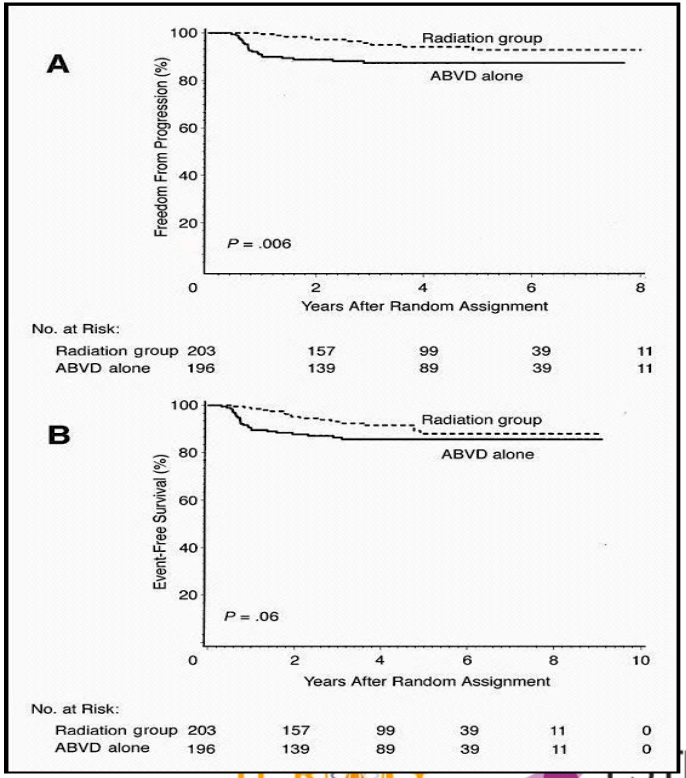
NCIC/ECOG HD6 study: Omitting radiation completely might be detrimental for disease control…

399 patients with early stage disease

Favourable:
STNI vs ABVD 4-6 cycles

Unfavourable:
2 ABVD + STNI vs ABVD 4-6 cycles

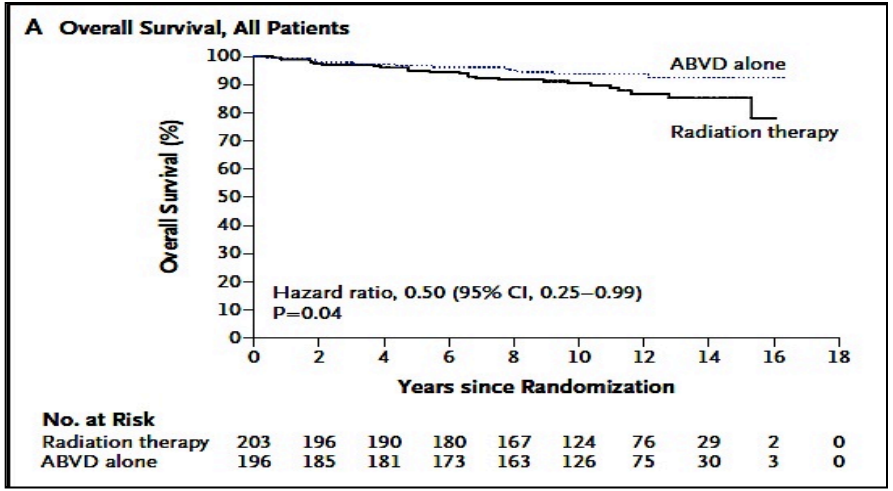
Inferior EFS, FFP with ABVD alone

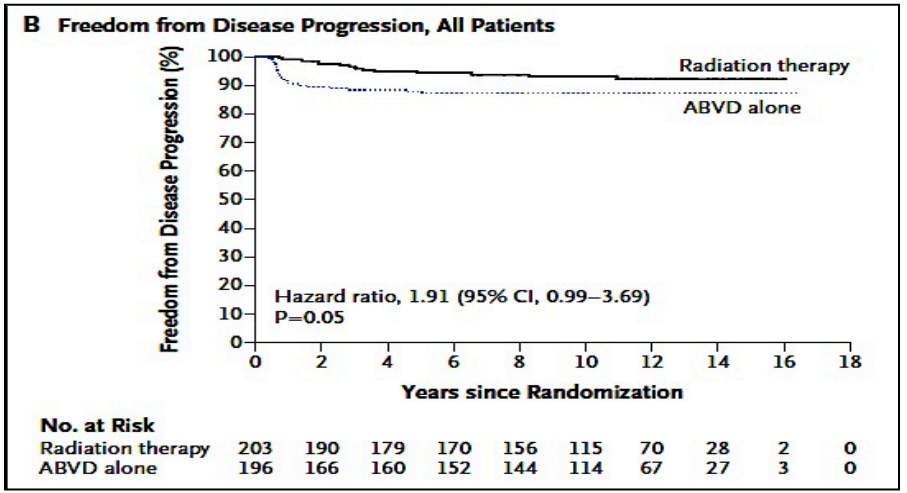


Meyer, R. M. et al. J Clin Oncol; 23:4634-4642 2005

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)

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

NCIC CTG ECOG HD.6 Trial
Small numbers and unusual events

- Unusual deaths correct from statistical point of view - misleading not attributable to radiotherapy.
- No death of "other" causes in chemotherapy alone group or in STNI favourable group. Imbalance misleading in favour of chemotherapy alone group.
- Without these unusual events - negative study without a survival difference but with a significantly better tumor control for the RT group
- Imbalance due to an undersized and incompletely recruited study with a small number of events.

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
- Small studies with just a few unusual events can influence conclusions much less likely to happen in large studies

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

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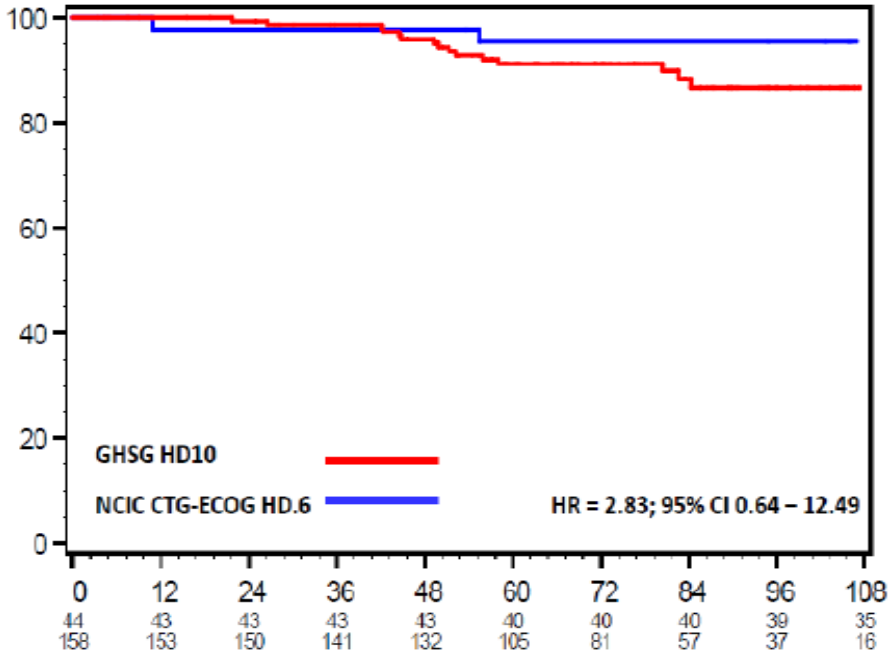
GHSG HD10, HD11 (CMT) Comparison with NCIC CTG HD.6 (ABVD alone)

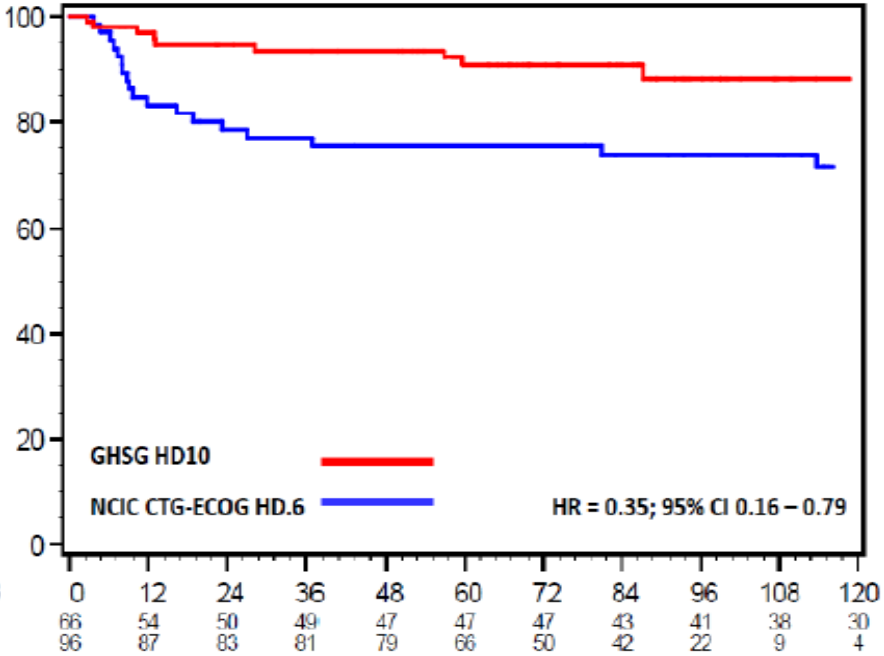
Endpoint	GHSG HD10/11	NCIC CTG HD.6	HR	95% CI
8-yr PFS	89%	86%	0.71	0.42-1.18
8- yr OS	95%	95%	1.09	0.49-2.40
8-yr TTP	93%	87%	0.44	0.24-0.78
# ABVD	2-4 (2.5)	4-6 (~5)		

from Hay AE *et al., ASH Abstract 2012;548*

Combined Modality vs ABVD alone

Status after 2xABVD (HD10 eligible pts; PFS)





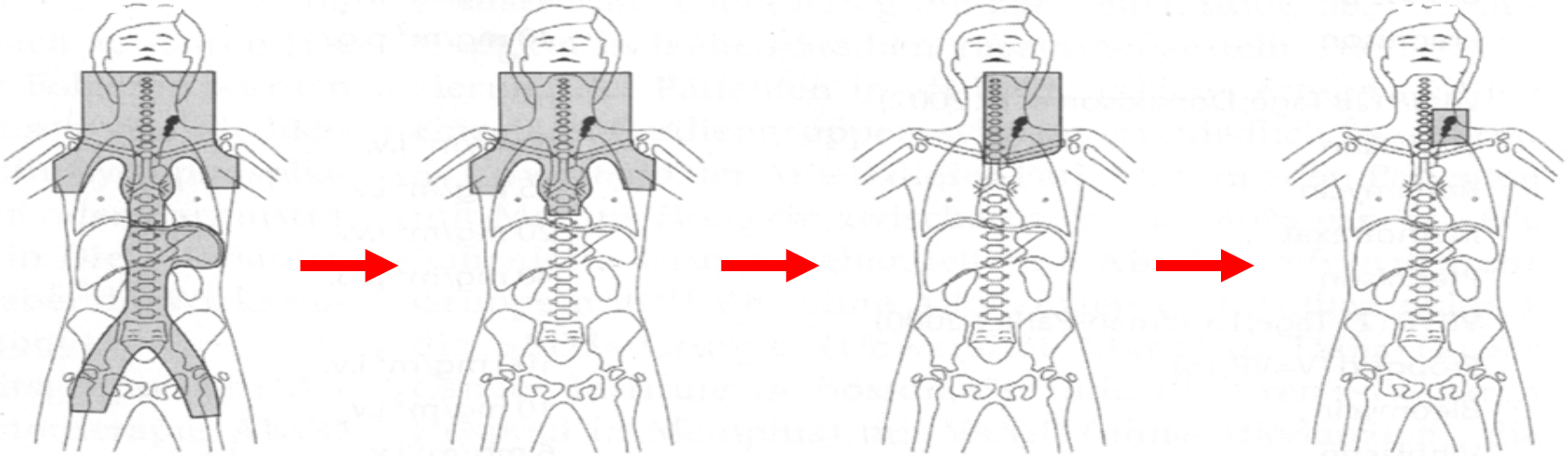
CR/CRu | **No CR/CRu**

Hay A et al, ASH 2012

Key questions in using Combined Modality Treatment in early stage HL

- Is the initial gain in local control with RT offset by the long term risks of RT ?
- Do modern RT approaches with substantial reduction in field size and RT doses maintain excellent initial control and reduce late toxicities leading to improved long term survival over chemotherapy alone ?

Transformation of RT Volumes / Doses in HL
ISRT – Specht L et al IJROBP 2014



Total nodal **Regional nodal** **Involved field** **Involved site**

Dose: 30-44 Gy → **20-30 Gy**

Two thirds of women with early-stage HD do not require radiation of the axillae
Substantial reduction in breast, lung cancer risk, cardiac morbidity

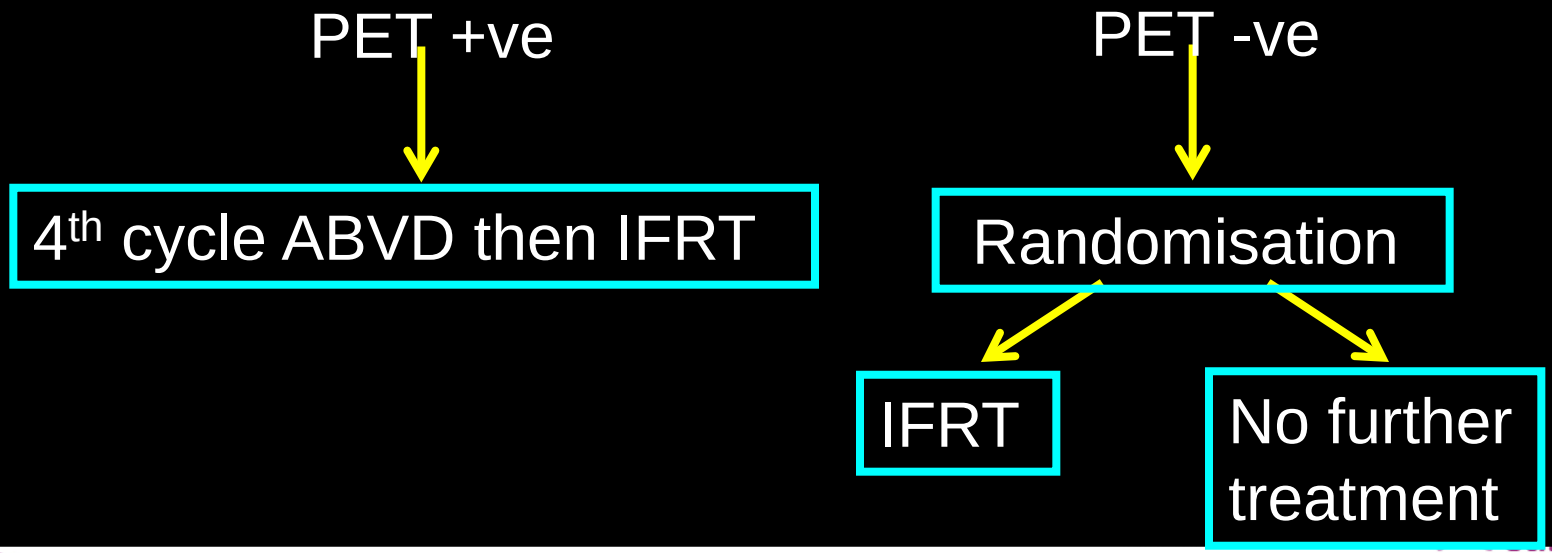
The Challenge of ^{18}FDG PET CT in HL : Converting large SUV numbers into Binary (Positive / Negative) and making sense of it

- 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)*

UK NCRI RAPID - trial design

Initial treatment: **ABVD x 3**

Re-assessment: **if NR/PD, patient goes off study**
FDG-PET scan performed



UK NCRI RAPID in early HL study Demographics

- 602 patients newly diagnosed HL (2003-2010)
- 321 male, 281 female median age - 34 years
- Stage IA, 139 (33%), stage IIA, 281 (67%)
- 67.8% favourable by GHSG criteria

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

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UK NCRI RAPID Trial

	PET3		CT/RT	3-yr PFS (%)	3-yr OS (%)
ABVDx3	**Negative (74.7%)**	→ R →	No Further Rx (N=211)	90.8	99.5
			IFRT (N=209)	94.5	97.0
	Positive (25.3%)		ABVDx1 + IFRT (N=145)	85.9	93.9

3 year PFS 94.5% (91.3%-97.7) versus 90.8% (86.8-94.7%) HR 1.51 in favour of IFRT p=0.23

Radford J *et al., NEJM 2015*

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UK NCRI RAPID Trial

Per protocol analysis of randomised patients

- 28 patients excluded from the 420 randomised

- **26 in the IFRT arm did not receive RT**
  - 19 patient or clinician choice
  - 5 died in IFRT arm (before IFRT)
  - 1 had pneumonia
  - 2 withdrew consent
- 2 in the NFT arm received RT

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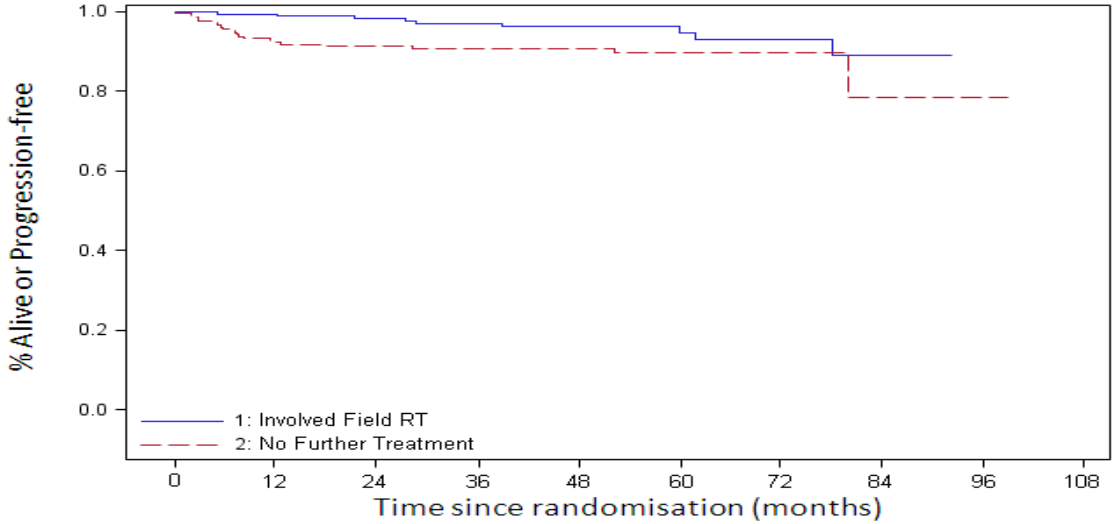
UK RAPID Deaths in IFRT arm that did not receive IFRT : Older patients tolerate ABVD badly

Demographics	Cause of death
Female 73 years, Stage I	died 9 weeks pneumonitis
Male 70 years Stage I	died 4 weeks pneumonitis
Male 62 years stage I	died 7 weeks, intracerebral haemorrhage and respiratory failure
Male 71 years, stage I	died 3 weeks, cause not yet determined
Male 61 years, stage II	died 4 months, AITL

–Böll B, et al ABVD in Older Patients with Early Stage Hodgkin Lymphoma Treated within the German Hodgkin Study Group HD10 and HD11 Trials J Clin Oncol. 2013 Mar 18. [Epub ahead of print]

UK NCRI RAPID Trial

PFS in the randomised PET –ve population (per protocol analysis, n=392)



Number at risk:

IFRT	183	179	162	129	98	65	38	17	0	0
NFT	209	188	163	132	100	60	18	4	2	0

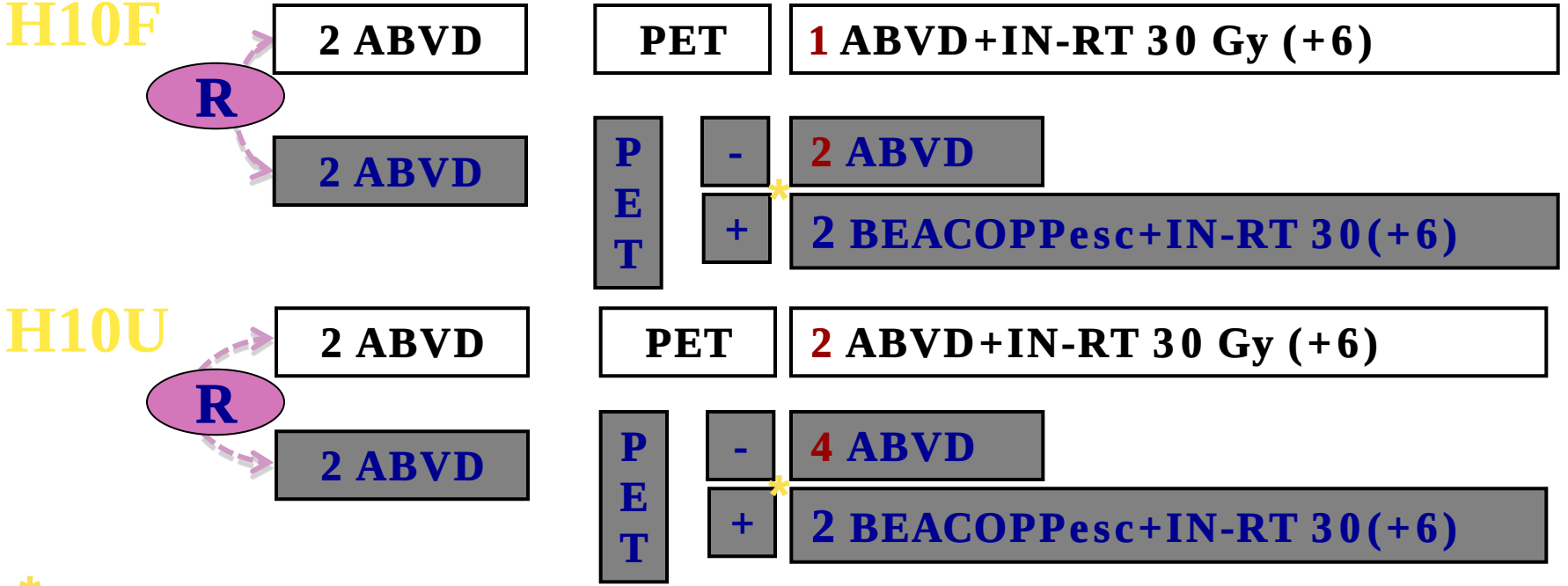
Per protocol analysis in 392 PET – ve patients

3 year PFS 97.0% IFRT vs 90.7% NFT (p=0.03) in favour of RT

Summary of UK NCRI RAPID study

- Analysis presented at 48.6 months and following 36 events
- Conservative definition : 74.7% of patients PET –ve after ABVD x 3
- Per protocol analysis in 392 PET – ve patients 3 year PFS 97.0% IFRT vs 90.7% NFT (p=0.03) in favour of RT

EORTC/ LYSA/ FIL H10 (#20051): study design



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

EORTC/LYSA/FIL H10 Trial

H10F	Chemo	PET2	CT/RT	# Events	1-yr PFS
Standard	ABVDx2 ⟹	+/- ⟹	INRT	1/188	100%
Experimental	ABVDx2 ⟹	negative ⟹	ABVDx2	9/193	94.9%
		positive	BEACOPPesc x2 + INRT		

H10U	Chemo	PET2	CT/RT	# Events	1-yr PFS
Standard	ABVDx2 ⟹	+/- ⟹	ABVDx2 + INRT	7/251	97.3%
Experimental	ABVDx2 ⟹	negative ⟹	ABVDx4	16/268	94.7%
		positive	BEACOPPesc x2 + INRT		

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.

Raemaekers JM, et al; J Clin Oncol. 2014 Apr 20;32(12):1188-94

- Analysis included 1,137 patients.
  - Favorable subgroup - 85.8% negative early PET scan
  - Unfavourable subgroup - 74.8% negative early PET scan

- IDMC concluded unlikely to show non-inferiority in the final results for the experimental arm and advised stopping random assignment for early PET-negative patients.

- CONCLUSION: CMT 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.

Conclusions for FDG PET in Early HL

- Using FDG PET may be possible to identify a group of patients with an excellent “early” outcome from chemotherapy alone
- EORTC H10 trial – failed to achieve this goal
  - Favorable subgroup: 14.2% positive early PET scan
- UK NCRI RAPID results were achieved in the setting of
  - Very conservative definition of PET negative 25.3 % PET positive
  - Quality controlled PET image acquisition / Central review of PET images at the Core Lab
  - What is the QA like in your routine clinical practice ?
- Longer follow-up is required to establish the impact of a PET negative approach on 10 and 20 year survival and cause of death

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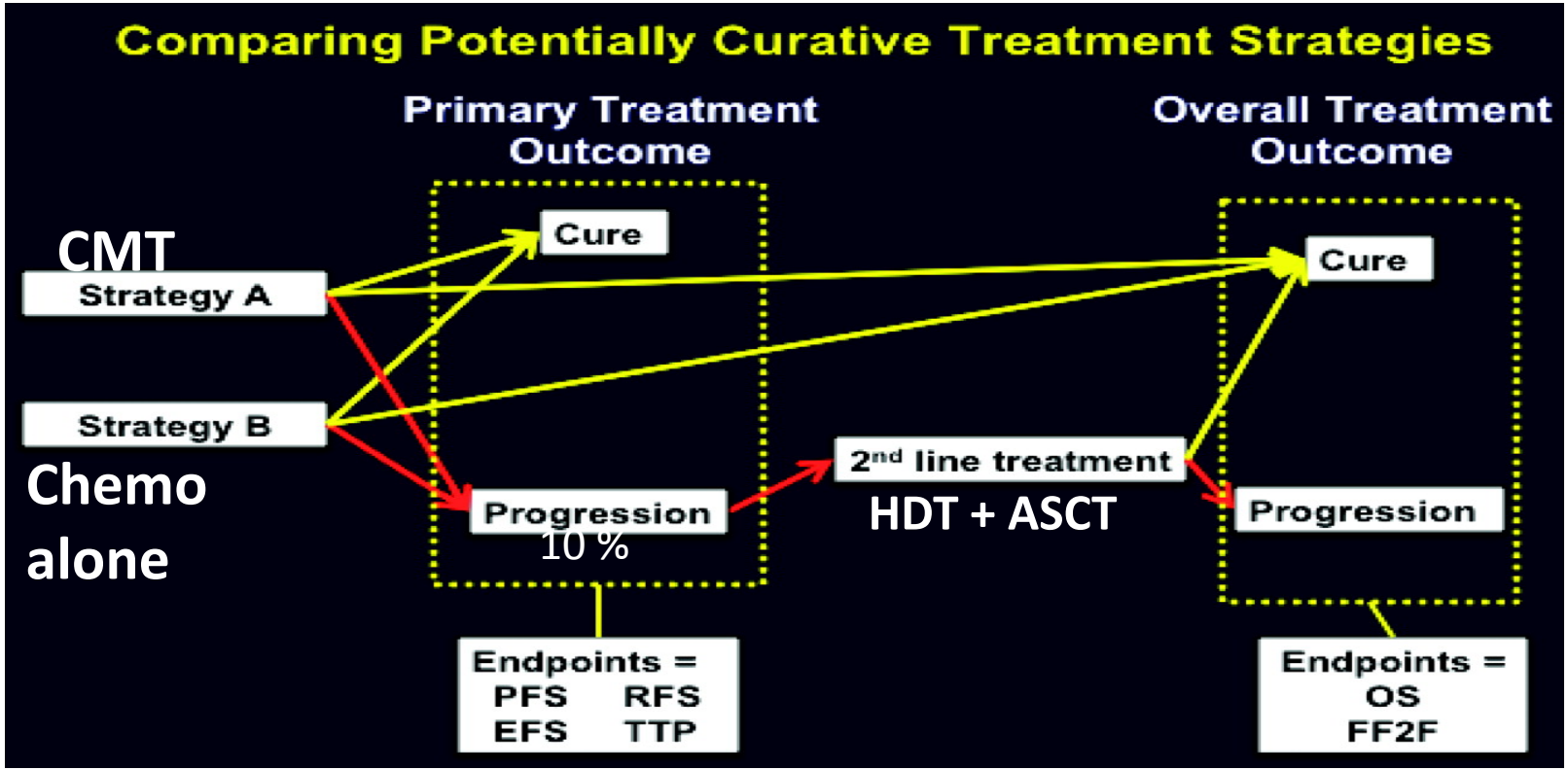
How to compare the effectiveness of two potentially curative treatment strategies.



Connors J M The Oncologist 2012;17:1011-1013

Which Patients with Stage I-II Hodgkin Lymphoma for Contemporary Combined Modality Therapy in PET era ?

- As a treatment option for patients with favorable disease, especially when risk late toxicity of RT considered lower than risk of relapse (Age, site of disease, sex)
- Older patients –risks associated with ABVD
- Definitely for patients with a positive interim PET scan (~25%)
- Definitely for patients with large mediastinal adenopathy - female patients ?

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Conclusions

- Large numbers of well conduction RCT supporting CMT in early stage HL
- Lack of randomised trials comparing chemotherapy alone vs contemporary CMT.
- Recent FDG-PET data inform patient specific discussions about risk of relapse (increased with chemo alone) versus late toxicity (increased with CMT)
- Response adapted treatment using FDG PET - Ongoing challenges to implement in routine clinical practice and QA measures are required to meet Deauville criteria

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Treatment of advanced stage Hodgkin lymphoma

Andreas Engert, MD

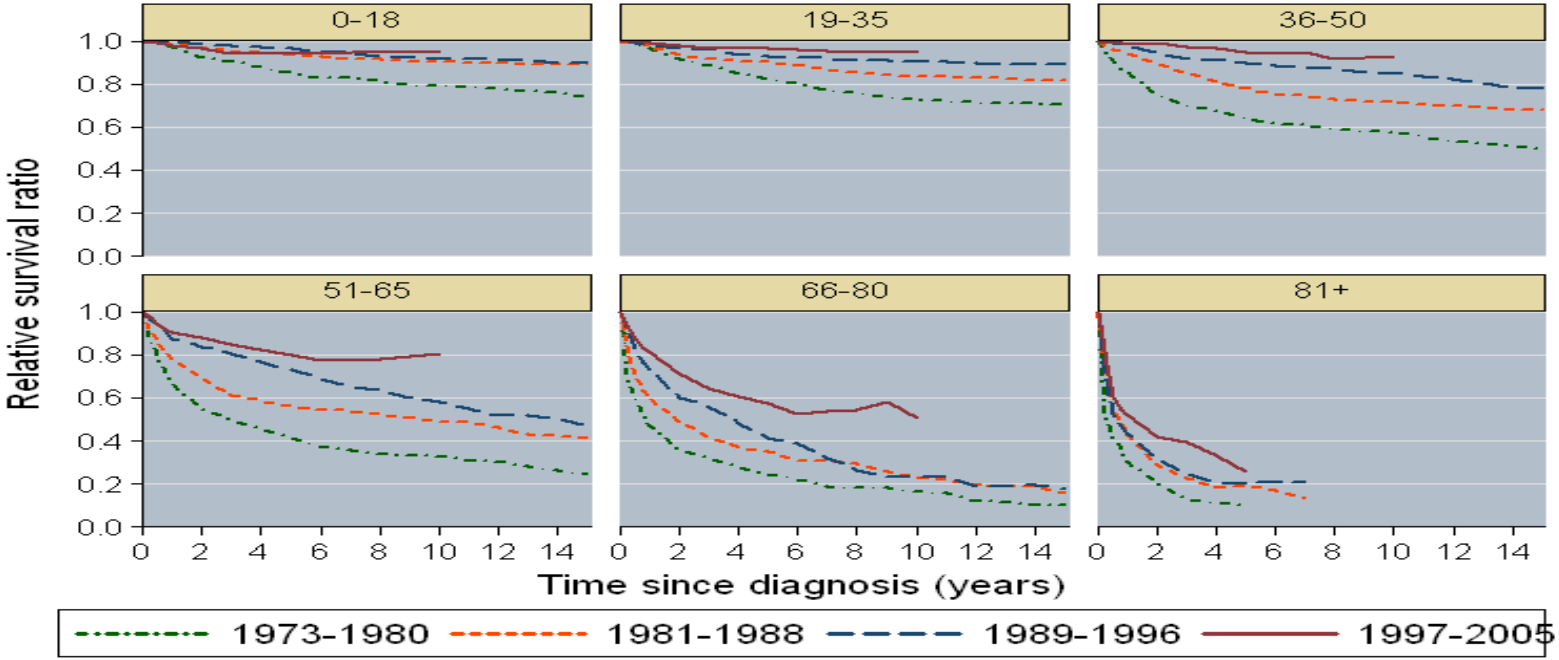
Chairman, German Hodgkin Study Group
University Hospital of Cologne

Treatment of advanced stage HL

- **Background**
- **ABVD, BEACOPP**
- **Radiotherapy in advanced stage HL**
- **Summary**

Hodgkin Lymphoma

Cumulative relative survival of HL pts in Sweden



Courtesy of Magnus Björkholm 2010

GHSG Risk Allocation for HL patients

<table>
<tr><th></th><th colspan="4">Stage (Ann Arbor)</th></tr>
<tr><th>Risk factors</th><th>IA, IB, IIA</th><th>IIB</th><th>IIIA, IIIB</th><th>IVA, IVB</th></tr>
<tr><td>None</td><td colspan="2">Early favorable</td><td colspan="2" rowspan="2">Advanced</td></tr>
<tr><td>≥3 LN areas</td><td colspan="2" rowspan="4">Early unfavorable</td></tr>
<tr><td>Elevated ESR</td><td colspan="3" rowspan="3"></td></tr>
<tr><td>Large med mass</td></tr>
<tr><td>Extranodal disease</td></tr>
</table>

GHSG 2000

Treatment of advanced stage HL

- Background
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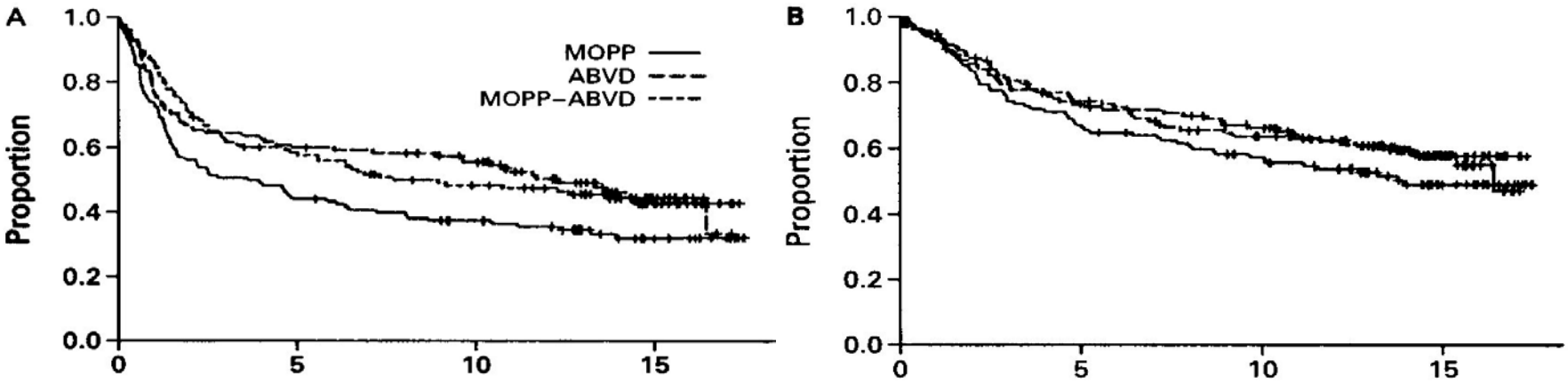
- Summary

Long-term results of HL patients

FFTF **OS**

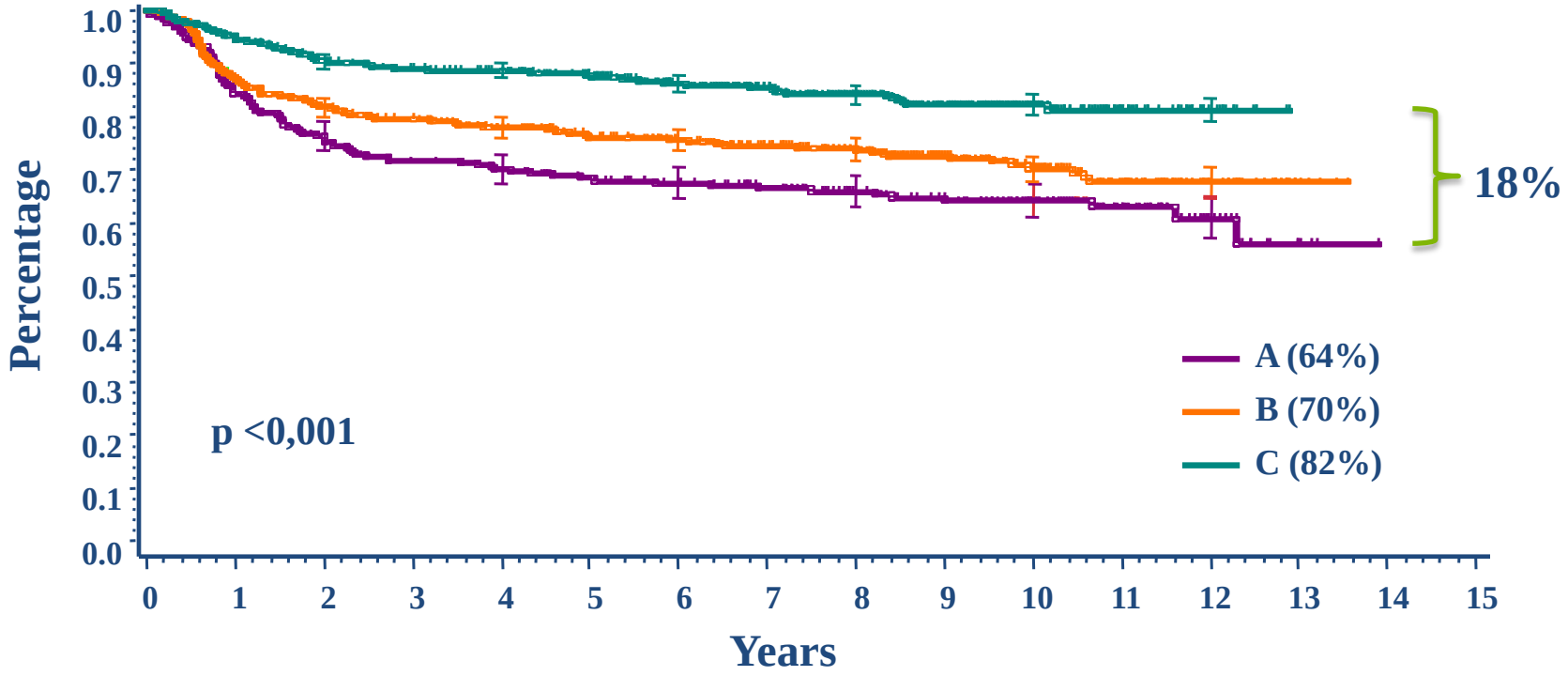


Years after study entry

Canellos G et al NEJM 2002

GHSG HD9 trial

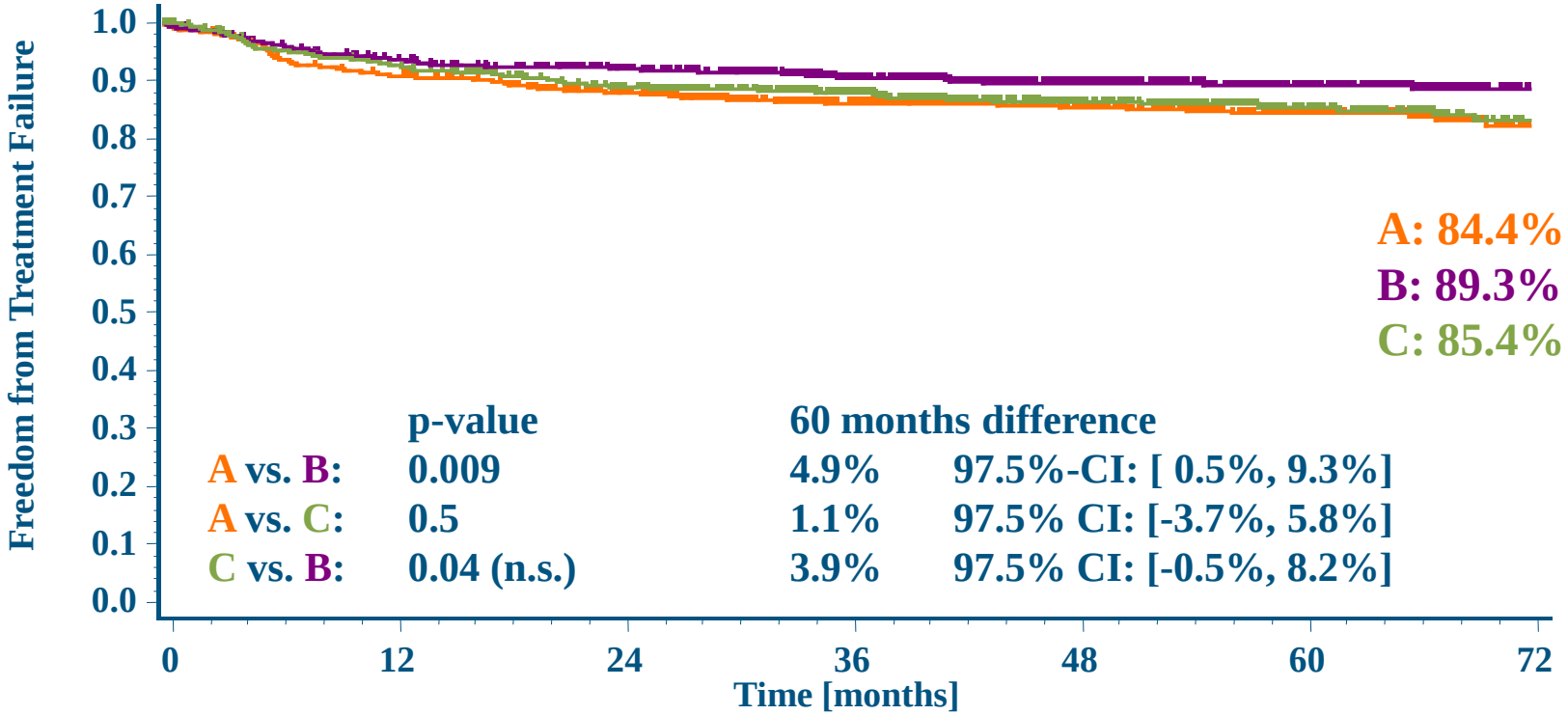
FFTF by treatment arm



Engert A et al, JCO 2009

HD15 in advanced HL

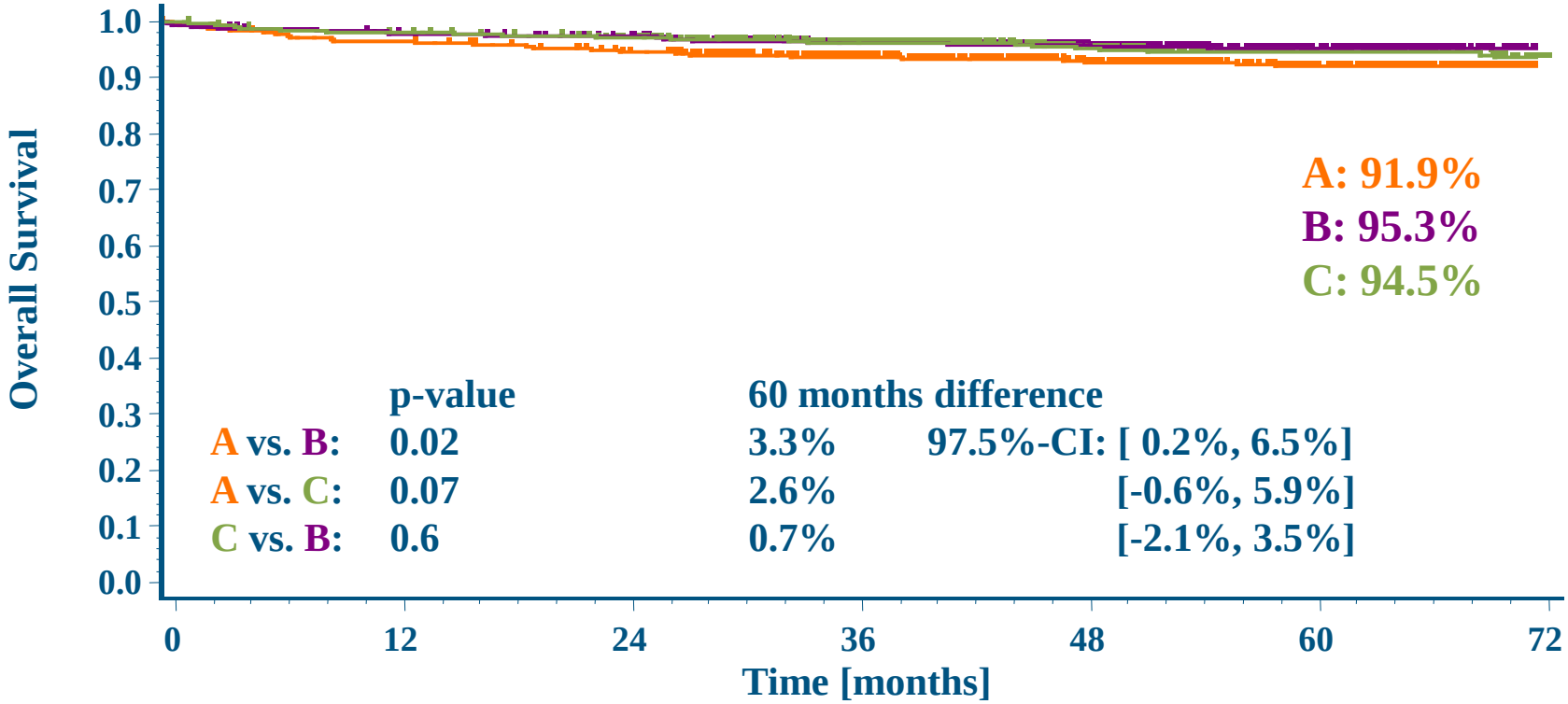
Freedom from Treatment Failure (FFTF)



Engert A et al, Lancet 2012

HD15 in advanced HL

Overall Survival (OS @ 5yrs)



Engert A et al, Lancet 2012

HD15 in advanced HL

Mortality (% of pts)

	8xBesc	6xBesc
HL	1.8	1.5
TRM 1st line	2.1	0.8
2nd NPL	1.8	0.7
Others	1.3	1.2
Overall	7.5	4.6

Direct comparison of
ABVD and BEACOPP variants

Treatment	5-y PFS	Diff. (%)	5-y OS	Diff. (%)	Reference
ABVD	68	13	84	8	Federico JCO 2009
4 + 2	81		92		
ABVD	73	12	84	5	Viviani NEJM 2011
4 + 4	85		89		
ABVD	69	15	87	4	Carde ASCO 2012
4 + 4	84		90		
ABVD	75	18	92	7	Mounier, ISHL9 2013
4 + 4	93		99		

TRM of BEACOPP escalated*

Multivariate model

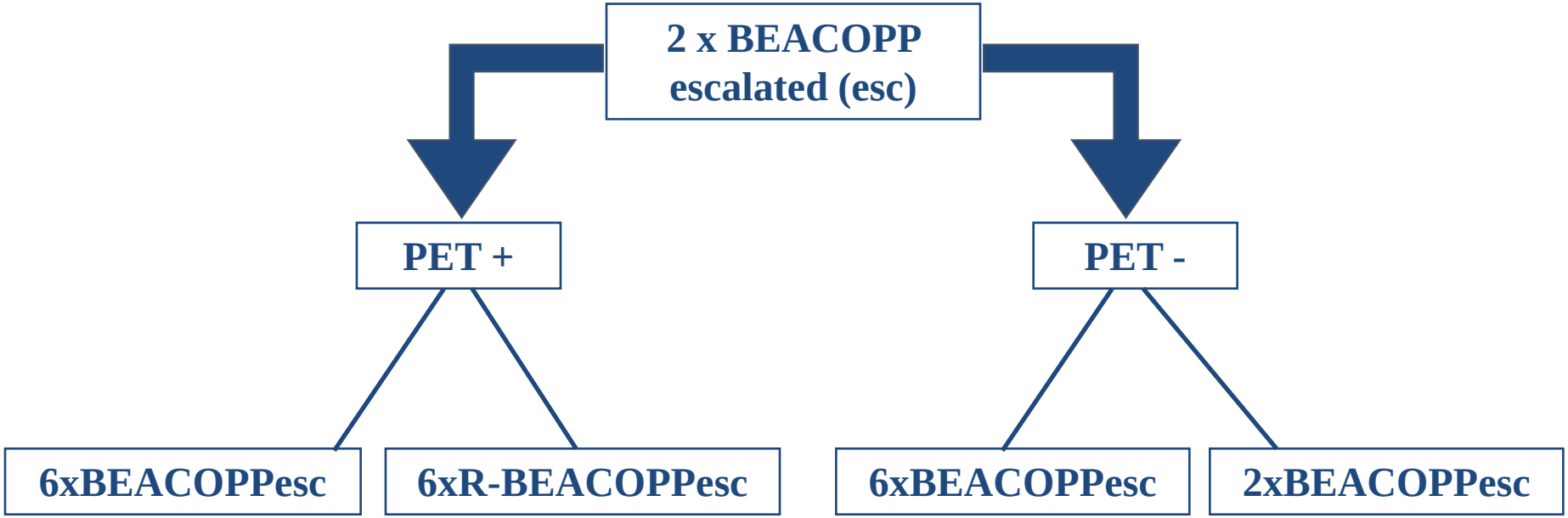
Age≥40	Age≥50	ECOG 2 or Karn.<80	Patients	TRM rate
-	-	-	2156	0.7
+	-	-	590	1.7
-	-	+	108	0.9
+	+	-	445	5.6
+	-	+	40	13.3
+	+	+	45	15.0

*Pts treated in HD9, 12, 15 (64/3565; 1.9%)

Wongso et al, JCO 2013

GHSG HD18 trial

for advanced stages

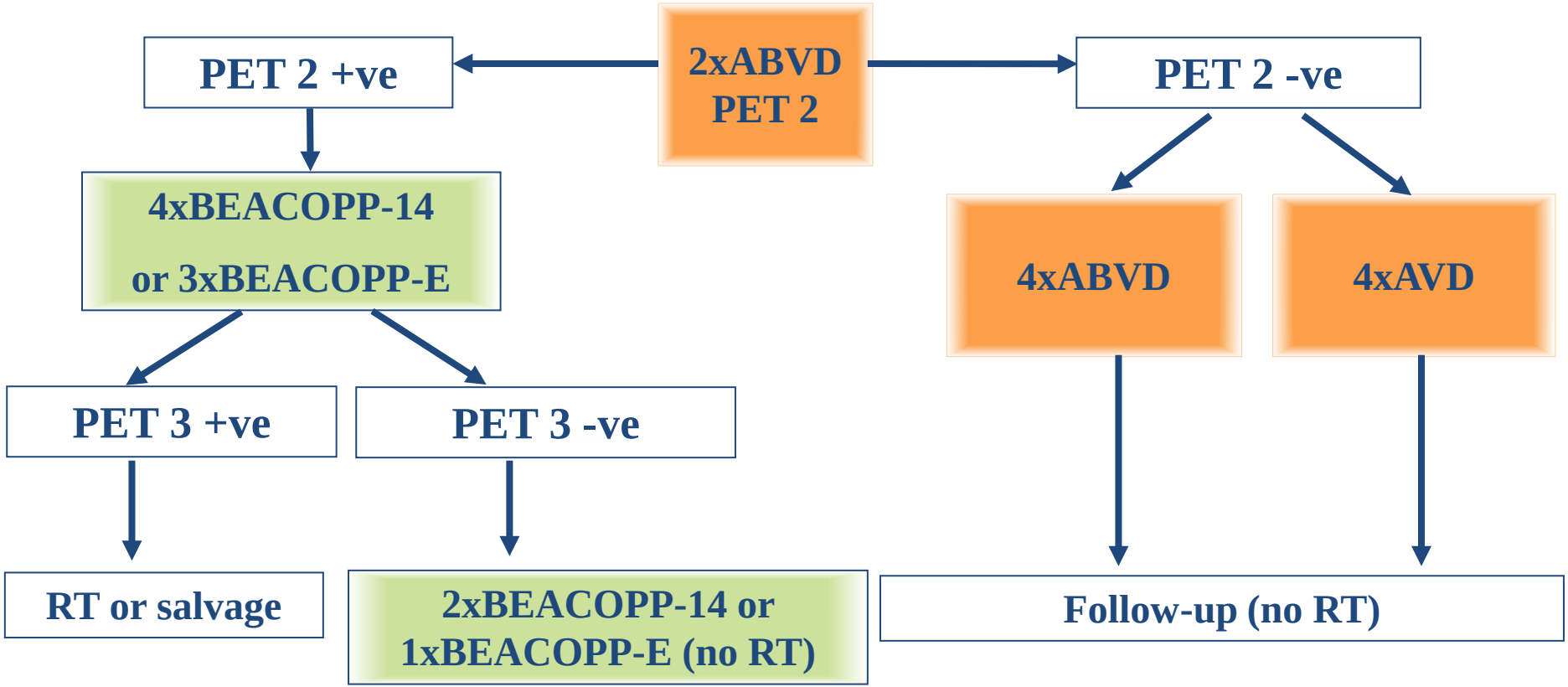


After chemo: PET; RX to PET+ res nodes >2.5 cm

PET-: Follow up

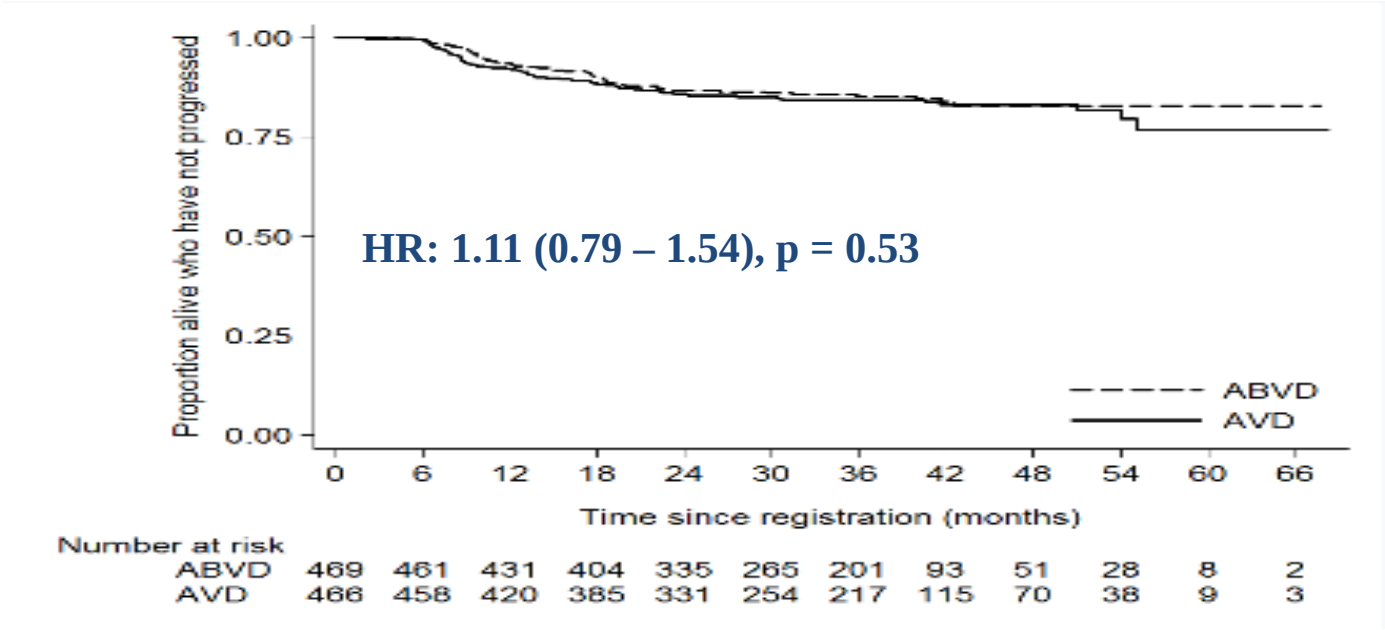
UK RATHL Trial

Advanced stage HL; IPS 0-7



RATHL: Impact of Bleomycin

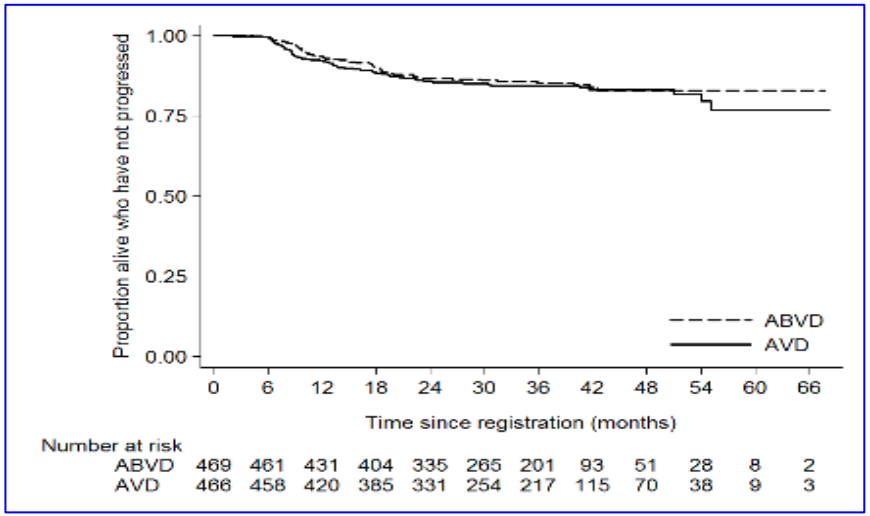
PFS for PET-negative patients (ITT)



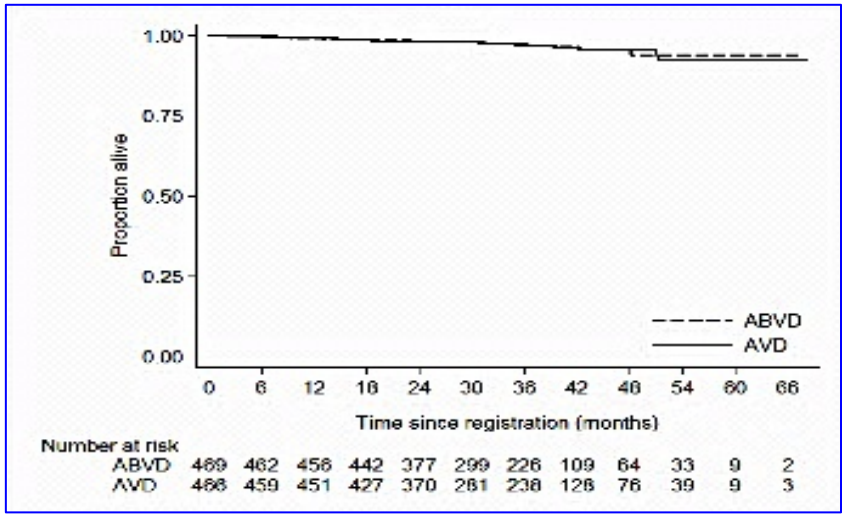
Johnson et al; Lugano 2015

UK RATHL Trial

PFS for PET-negative HL patients (IIT)



3 year PFS (%)
ABVD 85.4 - AVD 84.4



3 year OS (%)
ABVD 97.1 - AVD 97.4

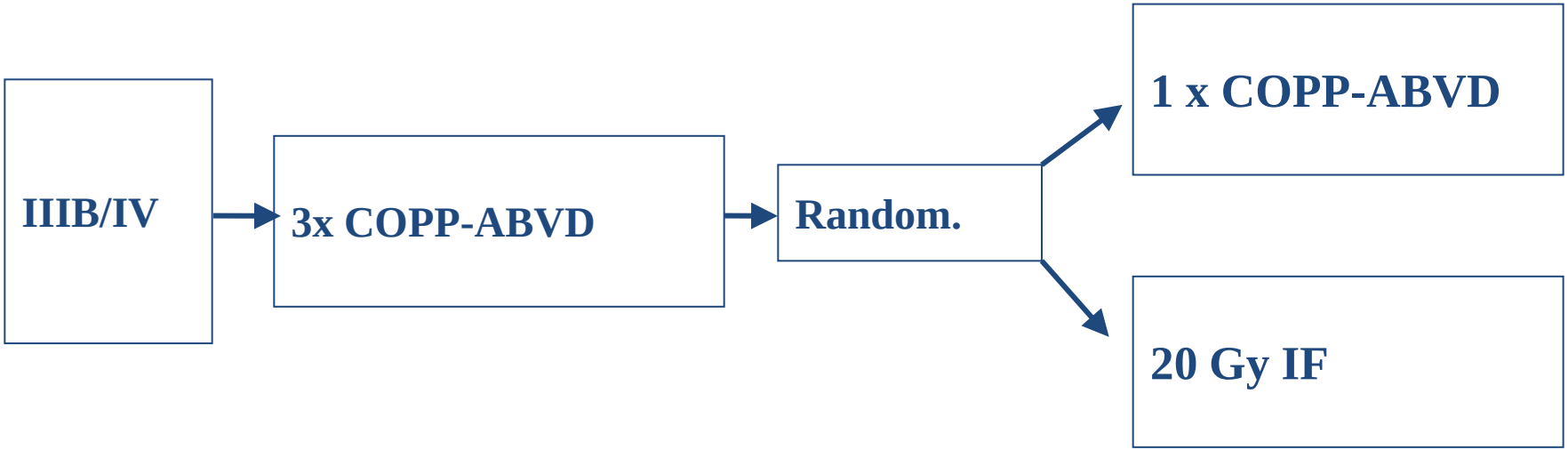
Johnson et al; Lugano 2015

Treatment of advanced stage HL

- **Background**
- **ABVD, BEACOPP**
- **Radiotherapy in advanced stage HL**
- **Summary**

GHSG HD-3 Study

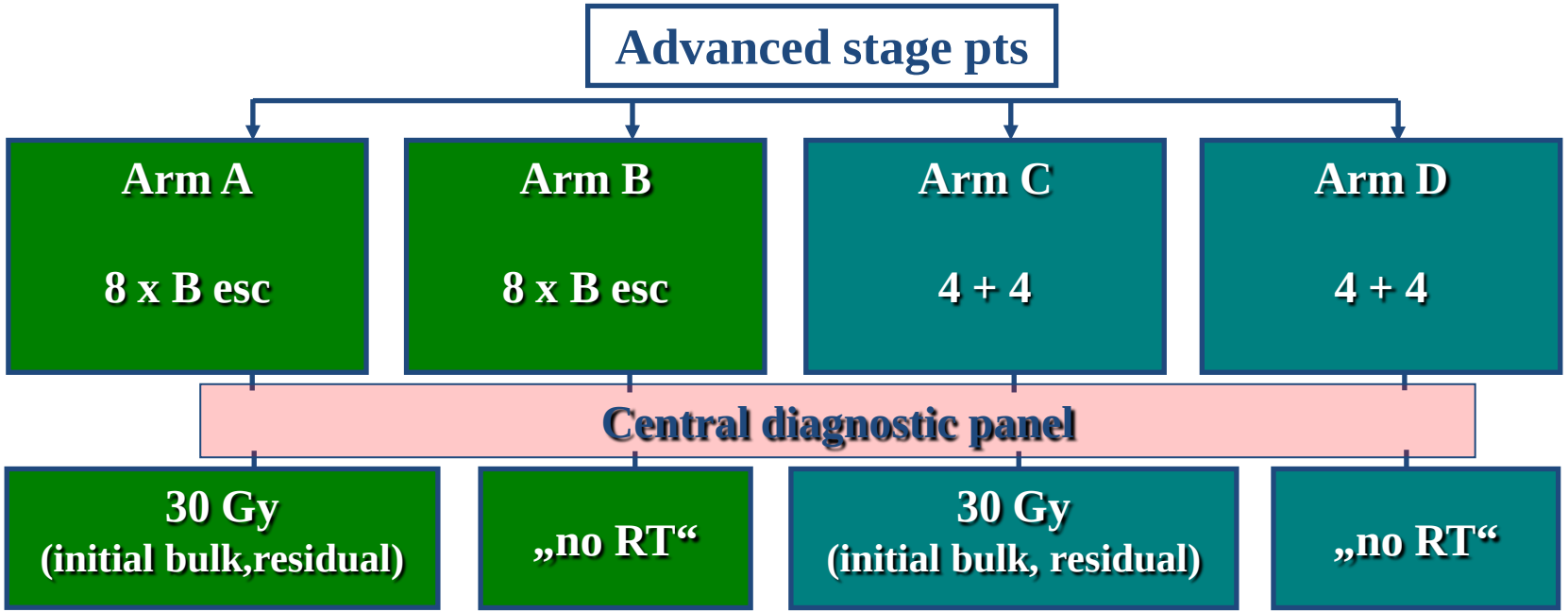
Design



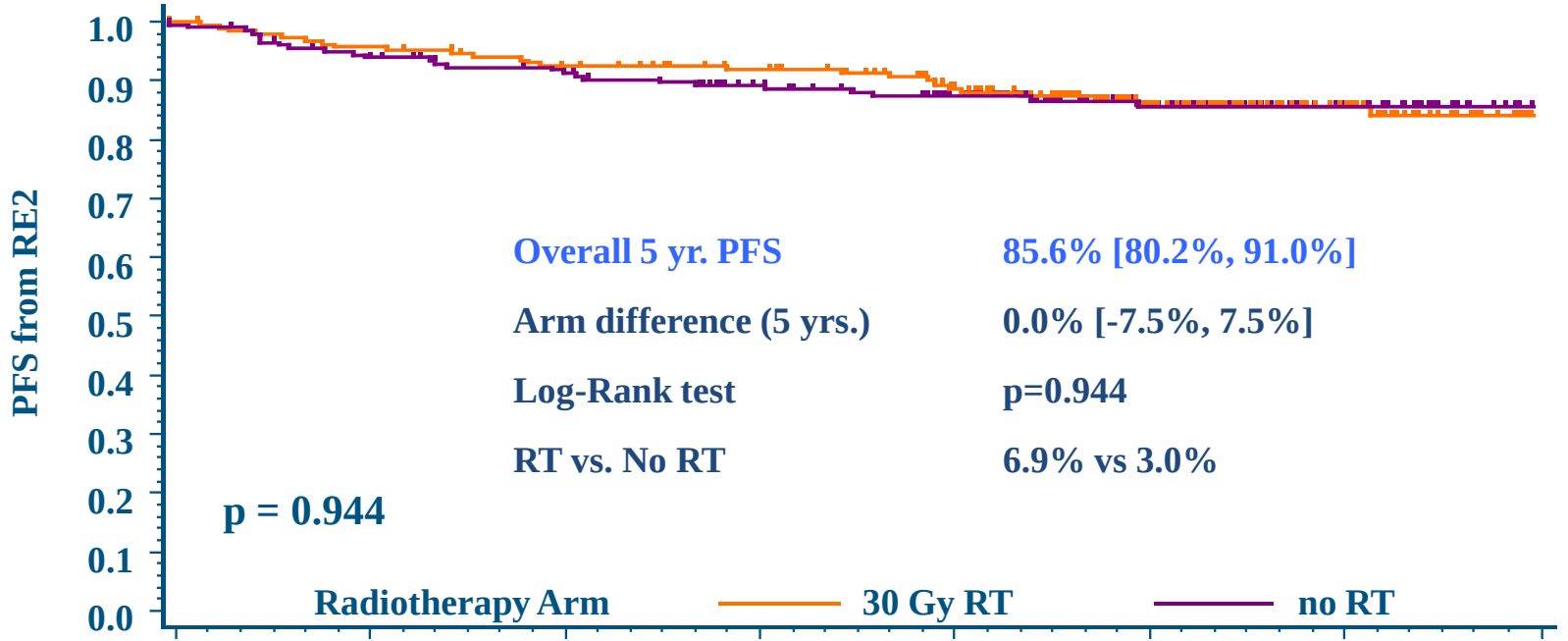
Recruited 199 pts (1982-88)

HD12 trial design for advanced stages

Deescalation possible?

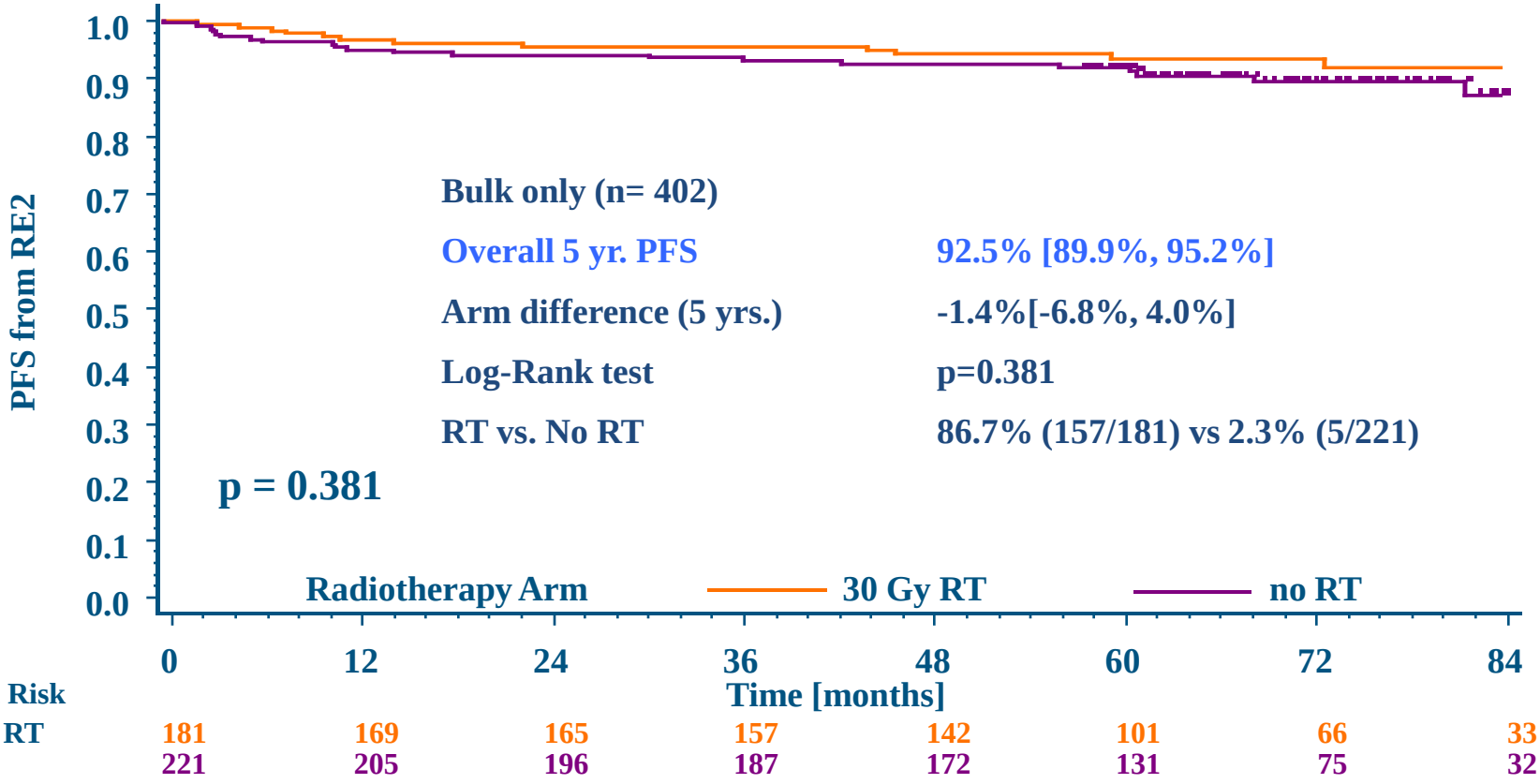


HD12 pts with no bulk and no rest (PFS n=388)



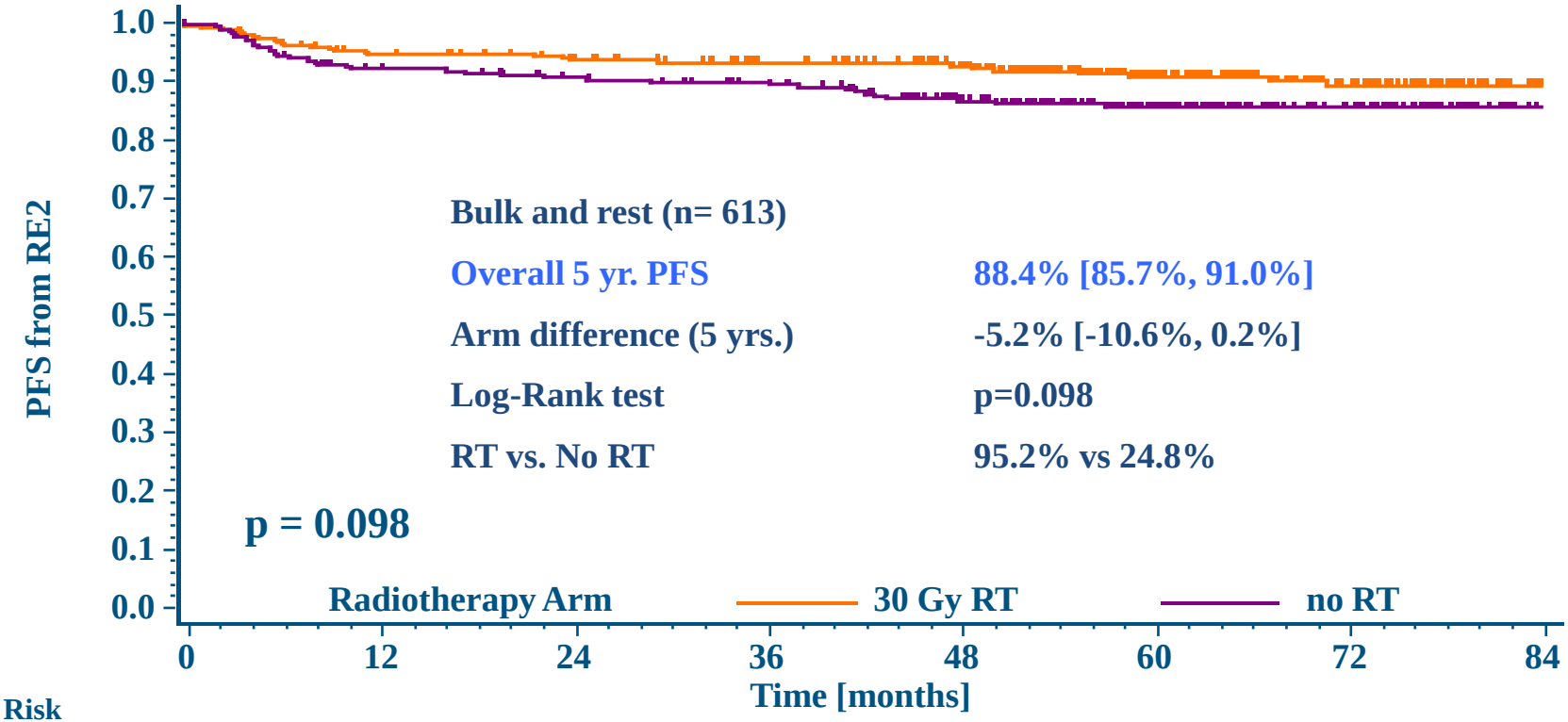
Pts. at Risk								
30 Gy RT	188	177	168	158	139	94	55	20
no RT	200	184	173	155	138	94	53	24

HD12 patients with bulk only (PFS; n=402)



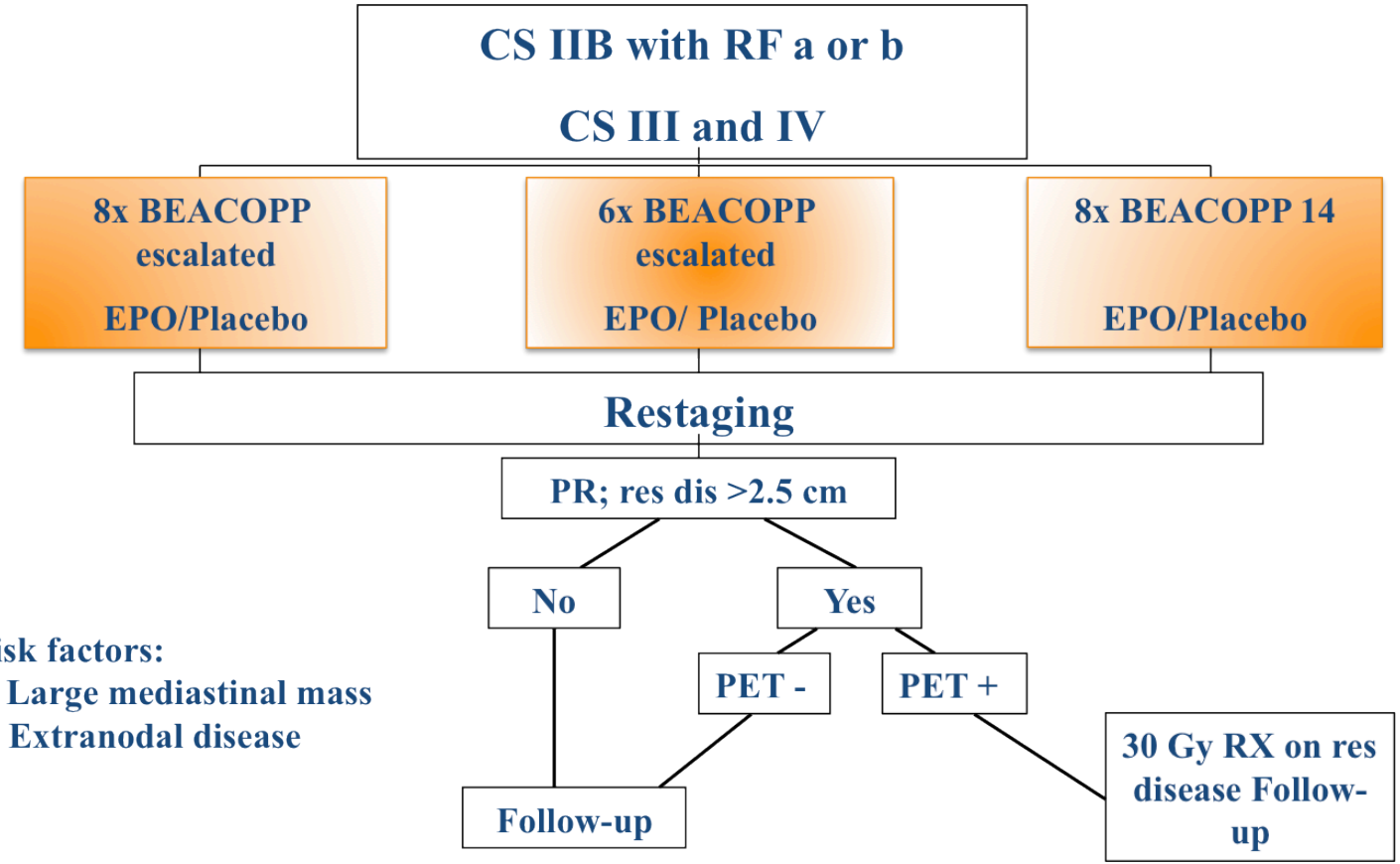
Pts. at Risk								
30 Gy RT	181	169	165	157	142	101	66	33
no RT	221	205	196	187	172	131	75	32

HD12 pts with bulk and rest (PFS n=613)



Pts. at Risk								
30 Gy RT	331	305	294	274	250	175	105	42
no RT	282	250	239	230	198	142	85	38

GHSG HD15 trial
for advanced stages



Risk factors:
a) Large mediastinal mass
b) Extranodal disease

HD15-PET trial

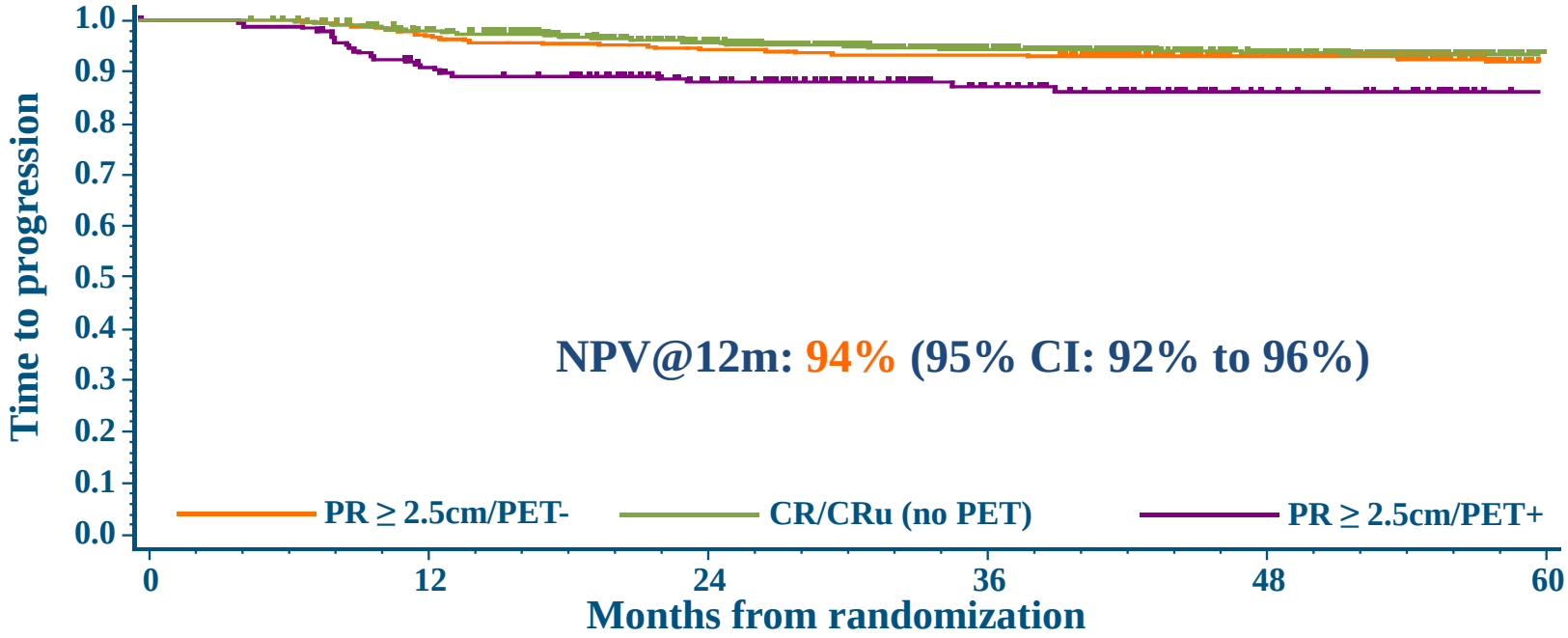
Activity of residual masses ≥ 2.5 cm by PET (n=728)*

PET-negative:	**540 (74%)**
PET-positive:	**188 (26%)**

***Patients qualified for the PET question**
PET evaluated by PET panel

HD15-PET trial

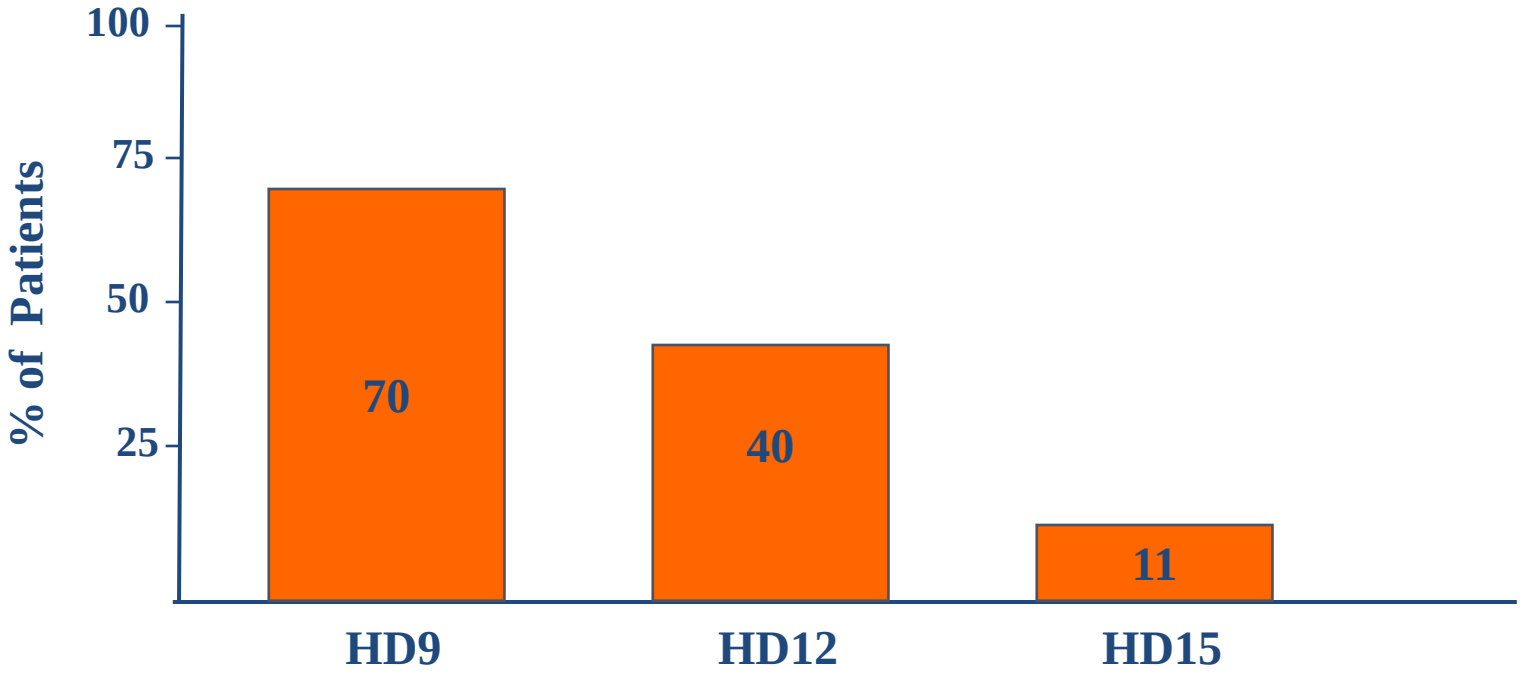
Impact of response and PET status (TTP)



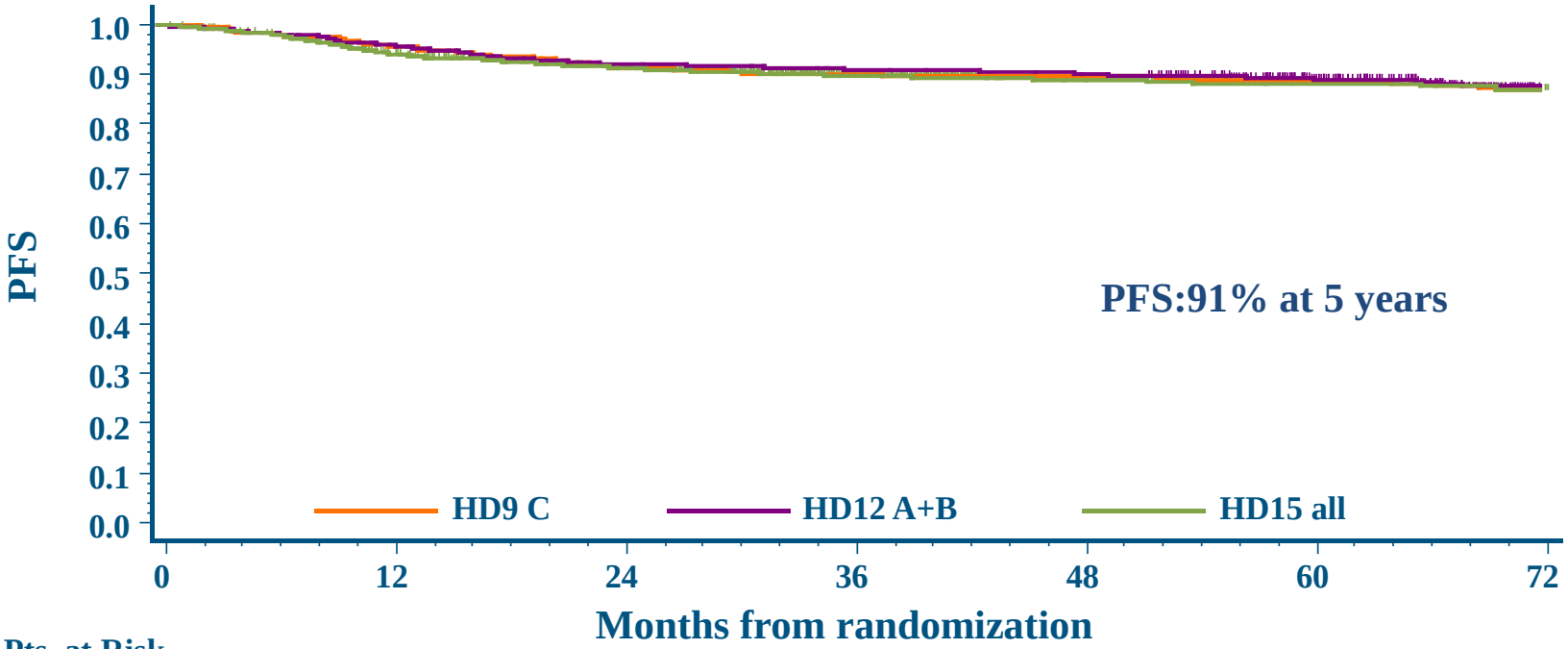
Pts. at Risk						
PET-	540	517	449	338	224	118
PET+	188	166	139	97	58	35
CR/CRu	854	811	690	482	303	155

Additional RT after chemo

GHSG studies HD9, HD12 and HD15 (% of all pts)



Tumour control
in GHSG trials HD9, HD12, HD15



Pts. at Risk							
HD9 C	431	409	385	374	358	334	298
HD12 A+B	715	669	619	592	543	447	282
HD15 all	2012	1848	1560	1122	702	359	122

Treatment of advanced stage HL

- Background
- ABVD, BEACOPP
- Radiotherapy in advanced stage HL
- Summary

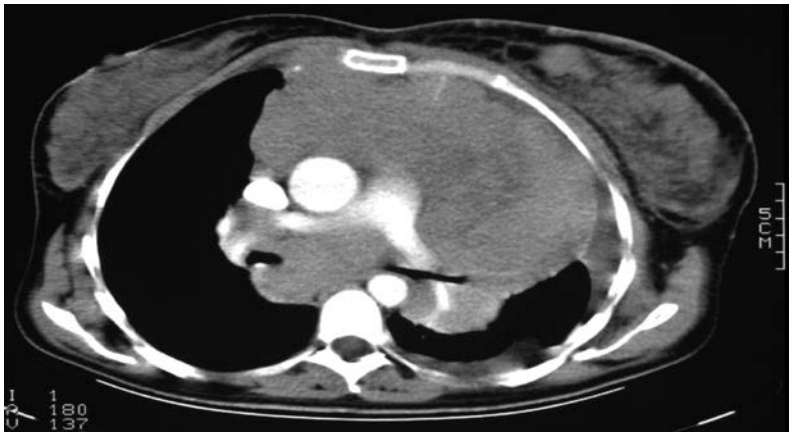
Advanced stage HL

Summary

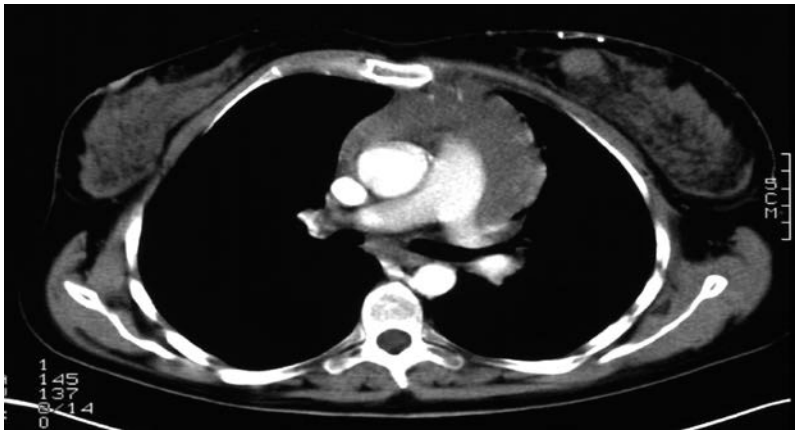
- HL became curable with the introduction of multi-agent chemo
- ABVD associated with 65-70% PFS and 75-80% OS @5yrs
- B.esc gave 15-20% better PFS and 10-15% better OS than ABVD
- Treatment-related mortality and 2nd npl of BEACOPP similar to ABVD; more hematotox and infertility
- 6xB.esc: tumour control 89%, OS 95%; PET-guided RT (HD15)
- B.esc not to be used in pts >40 yrs and poor performance
- Ongoing trials evaluate PET-guided strategies and combining BV with ABVD (enhance efficacy) BEACOPP (reduce toxicity)

HD12: Central multidisciplinary panel

Radiation oncologist, radiologist, medical oncologist



Initial staging



After 8 x BEACOPP

Radiotherapy **independent of randomization** arm

Results - multidisciplinary panel

Analysed RT comparison	**1528**	**pts.**
Panel recommendation	**1093**	**(72%)**
Bulky disease (> 5 cm)	**813**	**(74%)**
Residual tumor (≥1,5 cm)	**607**	**(56%)**
RT according Rando	**939**	**(86%)**
RT independent Rando	**149 ***	**(14%)**
Others	**5**	**(0.5%)**

*** 25 pts. bone involvement with fracture risk**

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WWW.ESTRO.ORG/SCHOOL

Is There Still A Role of RT in Advanced-stage HL?

(…and the background for questioning it…)

Joachim Yahalom, MD
Memorial Sloan-Kettering cancer Center,
New York City, NY, USA

Memorial Sloan Kettering Cancer Center

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Who is an “advanced-stage” patient?

- Stage IV bulky/non-bulky/E site(s)
- Stage III bulky/non-bulky
- Stage II bulky (with/without B symptoms)

FDG-PET assessment

Deauville criteria or 5 point scale

Score	FDG-PET/CT scan result
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately more than liver uptake, at any site
5	Markedly increased uptake at any site or new sites of disease

- Score of 1 or 2 = PET negative

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Type of Chemotherapy

- MOPP/ABV hybrid (obsolete)
- ABVD
  - 4-6 cycles
  - 6-8 cycles
- Stanford V
- Escalated BEACOPP
- BEACOPP/ABVD combinations
- Other

RT in Advanced-Stage HL

- **<u>The prevailing wisdom:</u>** *No role for RT after full dose chemotherapy*
- **<u>The dominant study:</u>** *CALGB/GELA published NEJM 2003*
- **<u>The resulting recommendation</u>:** ABVD X6-8 or escalated BEACOPPX8-6
- **<u>The concern</u>:** 1. Long or intense chemotherapy with higher toxicity

  2. Sub-optimal disease control, higher need for salvage, inferior survival

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“No Role” for Radiotherapy- The Primary Study

EORTC H34 (Aleman et al.) NEJM 248:24, 2003

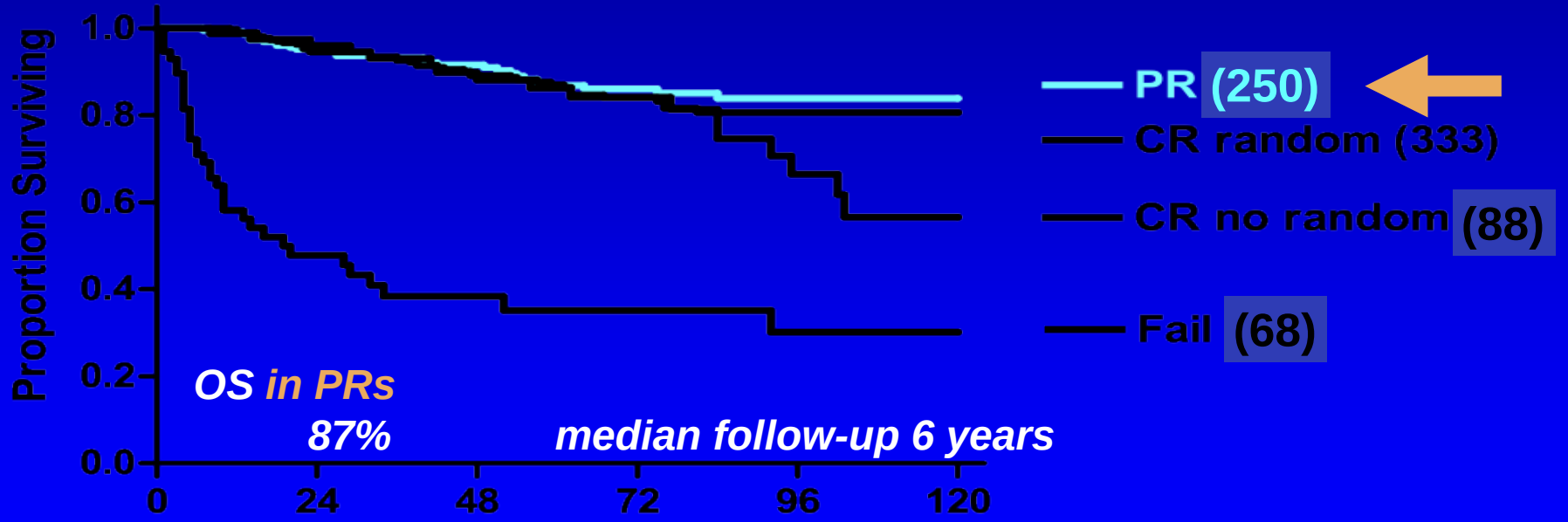
739 Patients III-IV HD

↓

MOPP-ABV x 6-8 (2 cycles after CR)

57% CR	34% PR
333 (45%) CR randomized:	227 (31%) PR
24 Gy IFRT or no RT	30 Gy RT

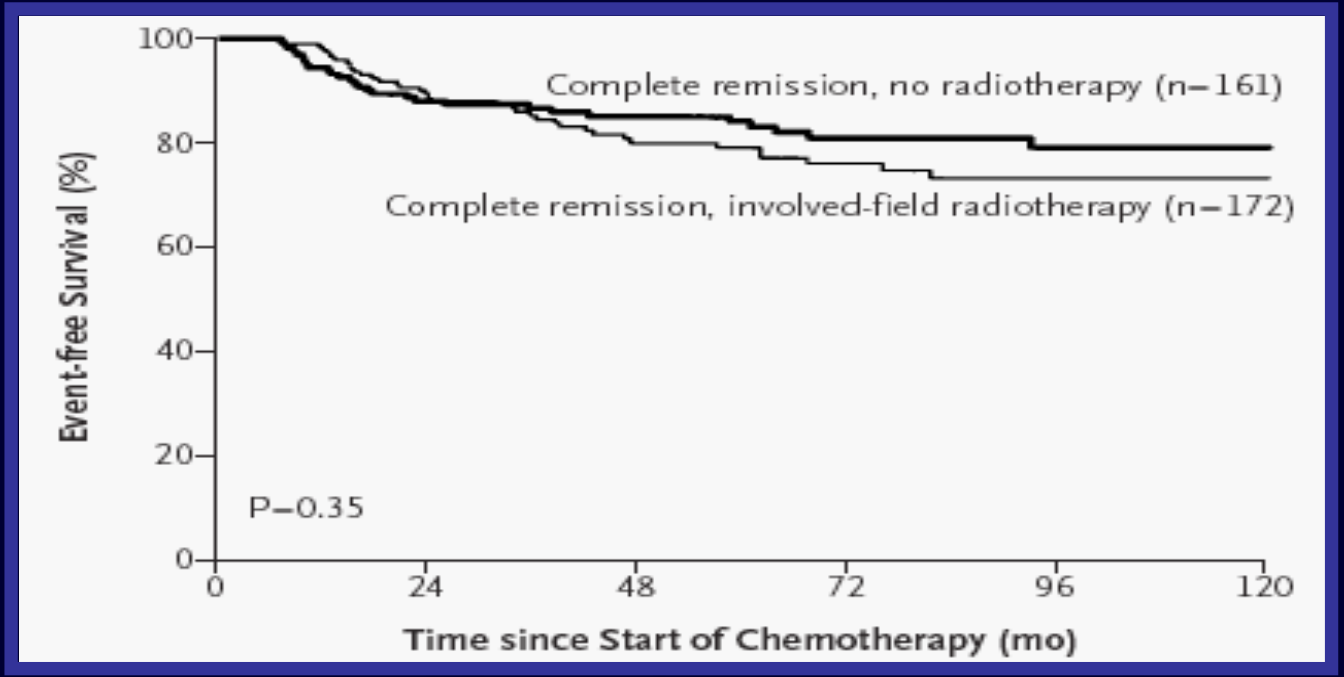
EORTC H34 Trial 1988-2001
PR →IF RT 30Gy Survival (n= 250)



Aleman *et al., NEJM* 2003; 348:2396-406

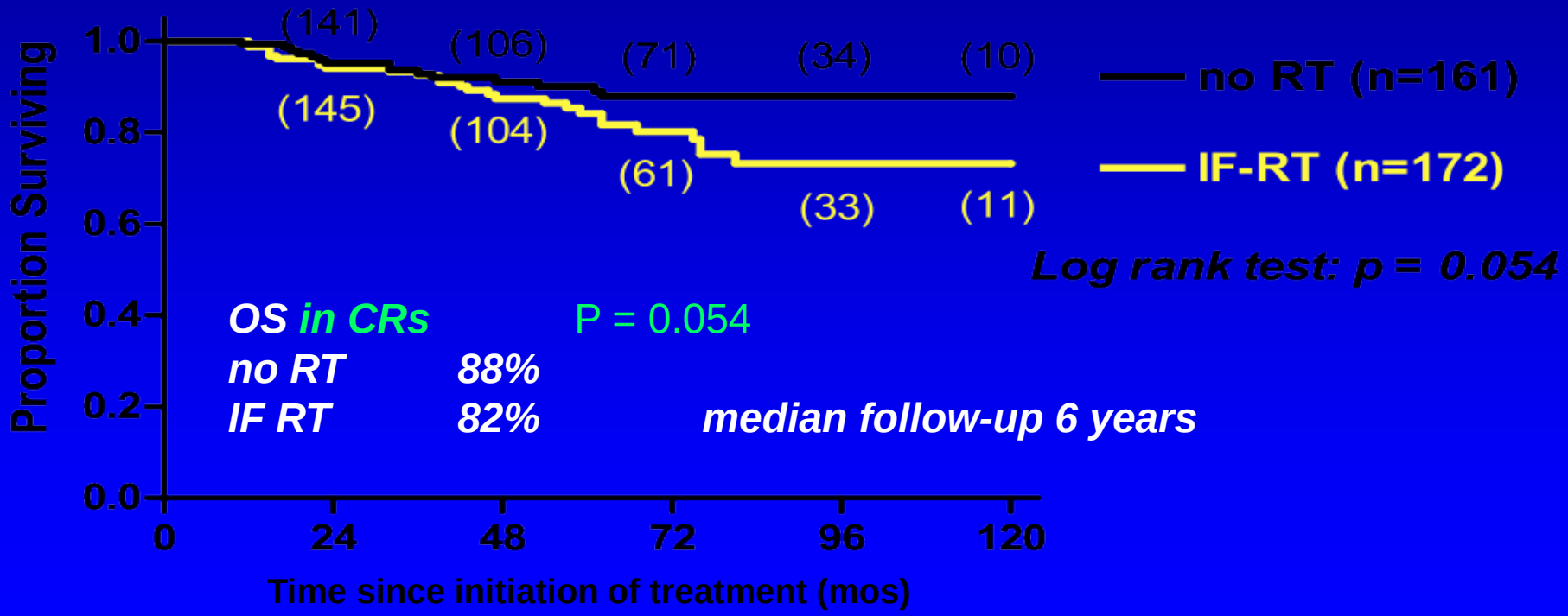
Role of Radiotherapy

EORTC H34



	CR	CR-RT	PR-RT
EFS %	84	79	79

EORTC H34 Trial 1988-2001
Overall Survival n= 736



Aleman *et al., NEJM* 2003; 348:2396-406

Role of Radiotherapy

EORTC H34

Second Cancers and Treatment

		CR		PR
Second cancer * (N pt)	no RT(n=161)	RT(n=172)	NR**	RT (n=227)
Secondary AML (15)	1	8	4	2
NHL (3)	1	2	-	-
Solid tumor (19)	4	5	3	7

* Median FU = 6.5 Y; ** Not randomized

Role of Radiotherapy

EORTC H34

Response and Treatment in Bulky Disease

	CR			PR
Disease (N pt)	no RT	RT	NR*	RT
Bulky mediastinum (208)	29	42	22	96
Bulk ≥10 cm (311)	55	63	33	127

* Not randomized

EORTC Study relevance concerns

- Obsolete Chemotherapy (with often 8 cycles)
- Strict CR definition (only 45%)
- Relatively small numbers for randomization
- Most bulky patients excluded

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Consolidation Radiotherapy in Patients With Advanced Hodgkin's Lymphoma: Survival Data From the UKLG LY09 Randomized Controlled Trial (ISRCTN97144519)

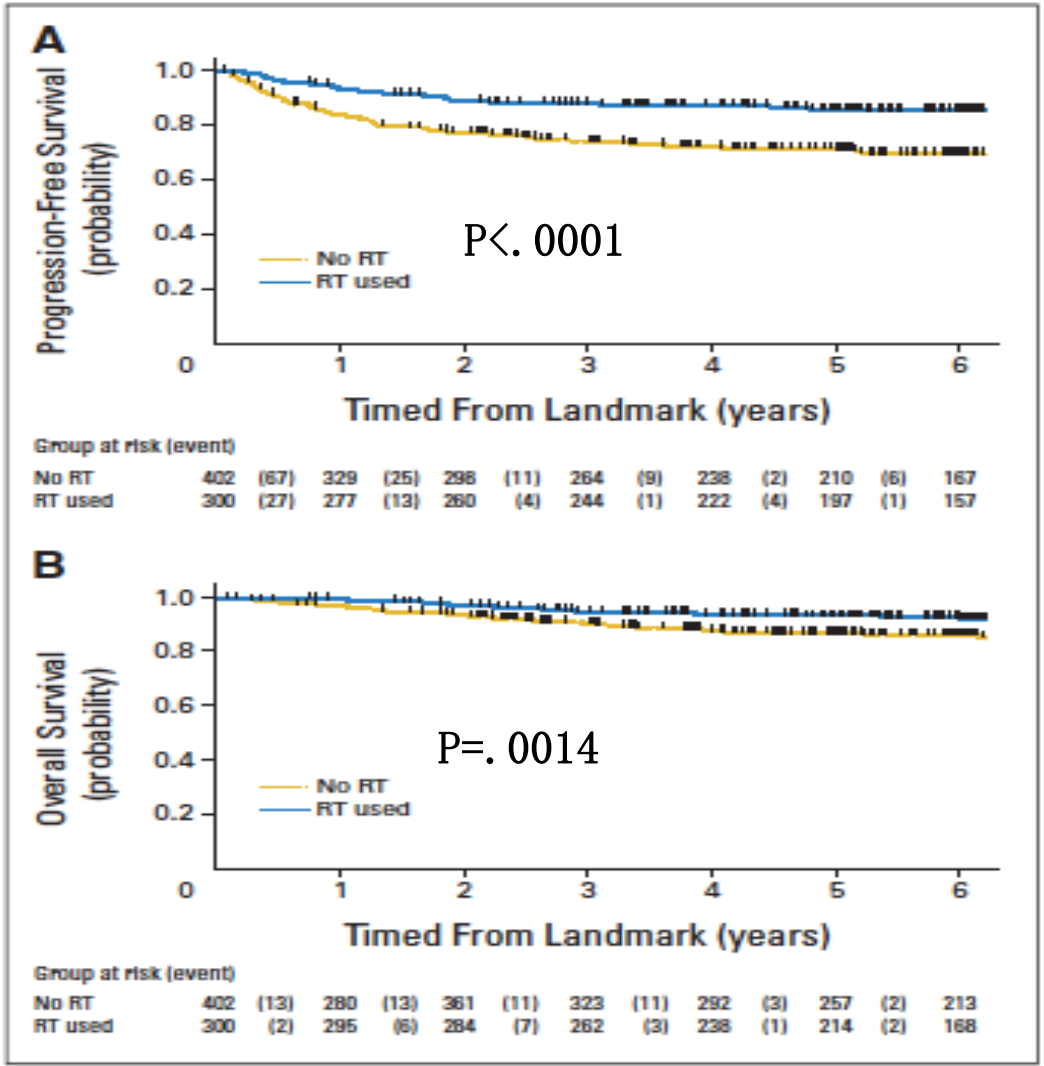
Peter W.M. Johnson, Matthew R. Sydes, Barry W. Hancock, Michael Cullen, John A. Radford, and Sally P. Stenning

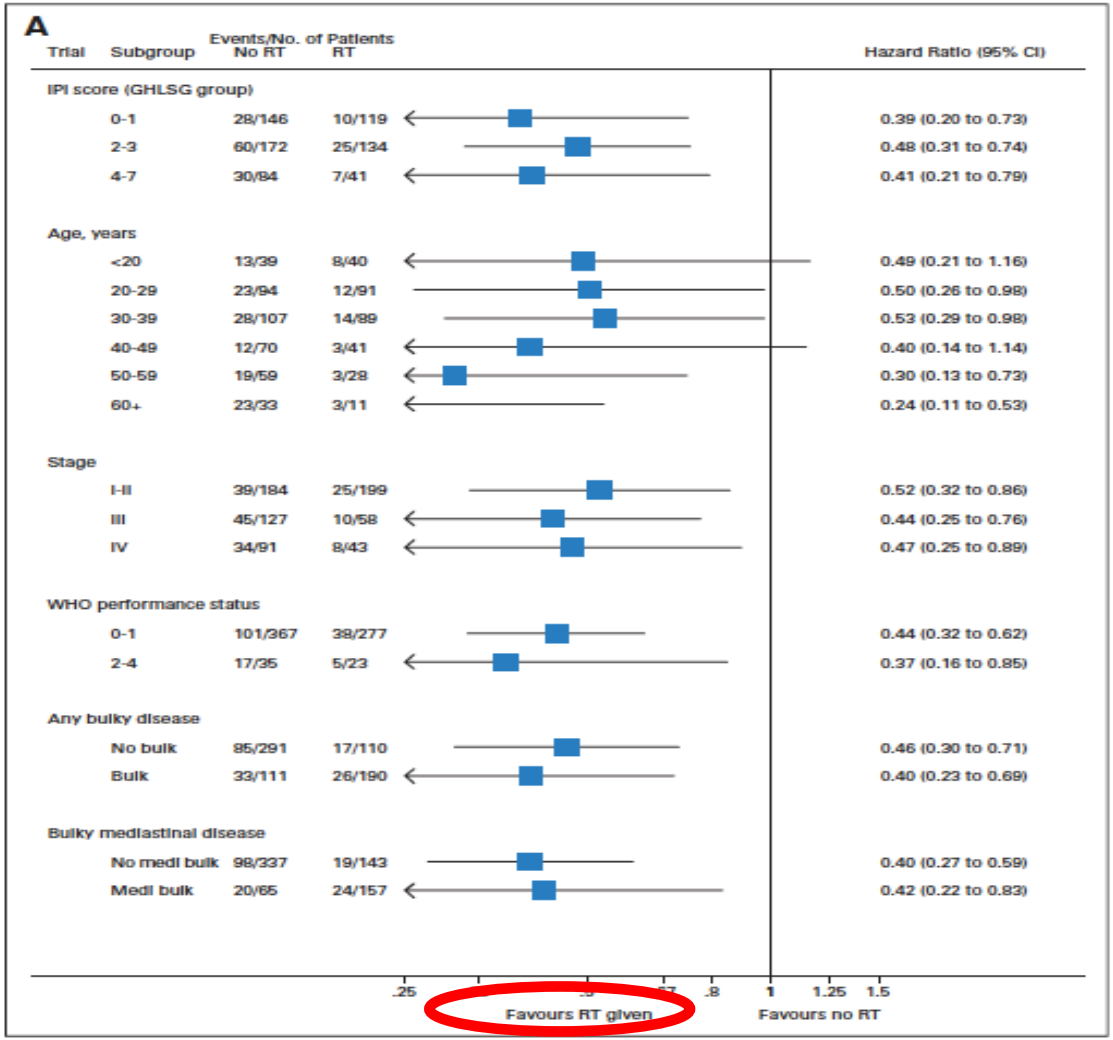
Patients and Methods

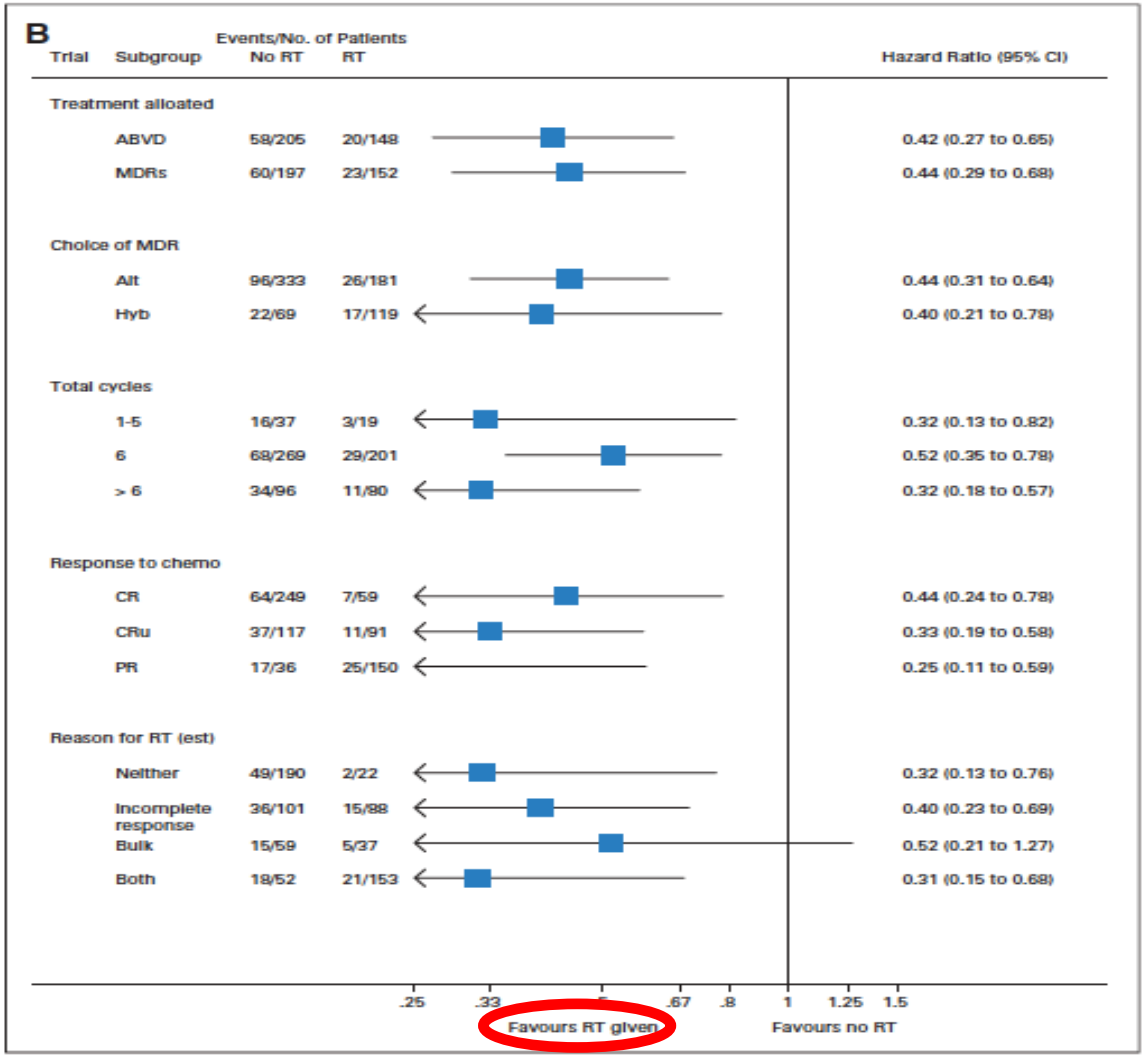
Patients were randomly assigned between doxorubicin, bleomycin, vinblastine, and dacarbazine and one of two prespecified multidrug regimens. At least six cycles of chemotherapy were planned, with up to eight for patients showing slower response. Involved-field RT was recommended for incomplete response to chemotherapy or bulk disease at presentation. The primary outcome measure was progression-free survival (PFS), landmarked from the end of chemotherapy.

Results

Among 807 patients randomly assigned, 702 achieved objective response. Postchemotherapy RT for consolidation was reported in 300 (43%). With median follow-up of 6.9 years, 161 PFS events and 83 deaths were reported. Baseline characteristics showed more patients with bulk disease having RT (190 [63%] *v* 111 [28%]) and only partial response after chemotherapy (150 [50%] *v* 36 [9%]). Other baseline characteristics were similar. PFS was superior for patients having RT (hazard ratio [HR], 0.43; 95% CI, 0.30 to 0.60) with 5-year PFS 71% without RT, 86% with RT. A similar advantage was seen for overall survival (HR, 0.47; 95% CI, 0.29 to 0.77). There was no evidence of heterogeneity of treatment effect across subgroups.


A
Progression-Free Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
No RT
RT used
P<. 0001
0
1
2
3
4
5
6
Timed From Landmark (years)
Group at risk (event)
No RT 402 (67) 329 (25) 298 (11) 264 (9) 238 (2) 210 (6) 167
RT used 300 (27) 277 (13) 260 (4) 244 (1) 222 (4) 197 (1) 157
B
Overall Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
No RT
RT used
P=. 0014
0
1
2
3
4
5
6
Timed From Landmark (years)
Group at risk (event)
No RT 402 (13) 280 (13) 361 (11) 323 (11) 292 (3) 257 (2) 213
RT used 300 (2) 295 (6) 284 (7) 262 (3) 238 (1) 214 (2) 168


A
Trial
Subgroup
Events/No. of Patients
No RT
RT
Hazard Ratio (95% CI)
IPI score (GHLSG group)
0-1 28/146 10/119 0.39 (0.20 to 0.73)
2-3 60/172 25/134 0.48 (0.31 to 0.74)
4-7 30/84 7/41 0.41 (0.21 to 0.79)
Age, years
<20 13/39 8/40 0.49 (0.21 to 1.16)
20-29 23/94 12/91 0.50 (0.26 to 0.98)
30-39 28/107 14/89 0.53 (0.29 to 0.98)
40-49 12/70 3/41 0.40 (0.14 to 1.14)
50-59 19/59 3/28 0.30 (0.13 to 0.73)
60+ 23/33 3/11 0.24 (0.11 to 0.53)
Stage
I-II 39/184 25/199 0.52 (0.32 to 0.86)
III 45/127 10/58 0.44 (0.25 to 0.76)
IV 34/91 8/43 0.47 (0.25 to 0.89)
WHO performance status
0-1 101/367 38/277 0.44 (0.32 to 0.62)
2-4 17/35 5/23 0.37 (0.16 to 0.85)
Any bulky disease
No bulk 85/291 17/110 0.46 (0.30 to 0.71)
Bulk 33/111 26/190 0.40 (0.23 to 0.69)
Bulky mediastinal disease
No medi bulk 98/337 19/143 0.40 (0.27 to 0.59)
Medi bulk 20/65 24/157 0.42 (0.22 to 0.83)
.25
.8
1
1.25
1.5
Favours RT given
Favours no RT


B
Trial
Subgroup
Events/No. of Patients
No RT
RT
Hazard Ratio (95% CI)
Treatment alloated
ABVD 58/205 20/148 0.42 (0.27 to 0.65)
MDRs 60/197 23/152 0.44 (0.29 to 0.68)
Choice of MDR
Alt 96/333 26/181 0.44 (0.31 to 0.64)
Hyb 22/69 17/119 0.40 (0.21 to 0.78)
Total cycles
1-5 16/37 3/19 0.32 (0.13 to 0.82)
6 68/269 29/201 0.52 (0.35 to 0.78)
> 6 34/96 11/80 0.32 (0.18 to 0.57)
Response to chemo
CR 64/249 7/59 0.44 (0.24 to 0.78)
CRu 37/117 11/91 0.33 (0.19 to 0.58)
PR 17/36 25/150 0.25 (0.11 to 0.59)
Reason for RT (est)
Neither 49/190 2/22 0.32 (0.13 to 0.76)
Incomplete response 36/101 15/88 0.40 (0.23 to 0.69)
Bulk 15/59 5/37 0.52 (0.21 to 1.27)
Both 18/52 21/153 0.31 (0.15 to 0.68)
.25
.33
.67
.8
1
1.25
1.5
Favours RT given
Favours no RT

Consolidation Radiotherapy in Patients With Advanced Hodgkin's Lymphoma: Survival Data From the UKLG LY09 Randomized Controlled Trial (ISRCTN97144519)

Peter W.M. Johnson, Matthew R. Sydes, Barry W. Hancock, Michael Cullen, John A. Radford, and Sally P. Stenning

Table 2. Impact of RT on PFS in Unadjusted and Adjusted Cox Models

	Cox Model							
	Unadjusted		Stratification		IPS		Full	
Variable	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
RT given	0.43	0.30 to 0.61	0.50	0.35 to 0.72	0.44	0.31 to 0.63	0.33	0.22 to 0.51
WHO PS	—		1.54	0.97 to 2.46	—		1.54	0.96 to 2.47
Stage	—		1.31	1.08 to 1.59	—		—	
Age	—		1.46	1.05 to 2.04	—		—	
IPS	—		—		1.48	1.20 to 1.82	1.40	1.12 to 1.75
Allocated chemotherapy	—		—		—		1.05	0.77 to 1.44
MDR	—		0.97	0.67 to 1.41	1.09	0.75 to 1.57	1.03	0.71 to 1.51
Bulk disease	—		—		—		0.94	0.67 to 1.33
Response	—		—		—		1.40	1.12 to 1.76
Chemotherapy cycles	—		—		—		0.96	0.72 to 1.27

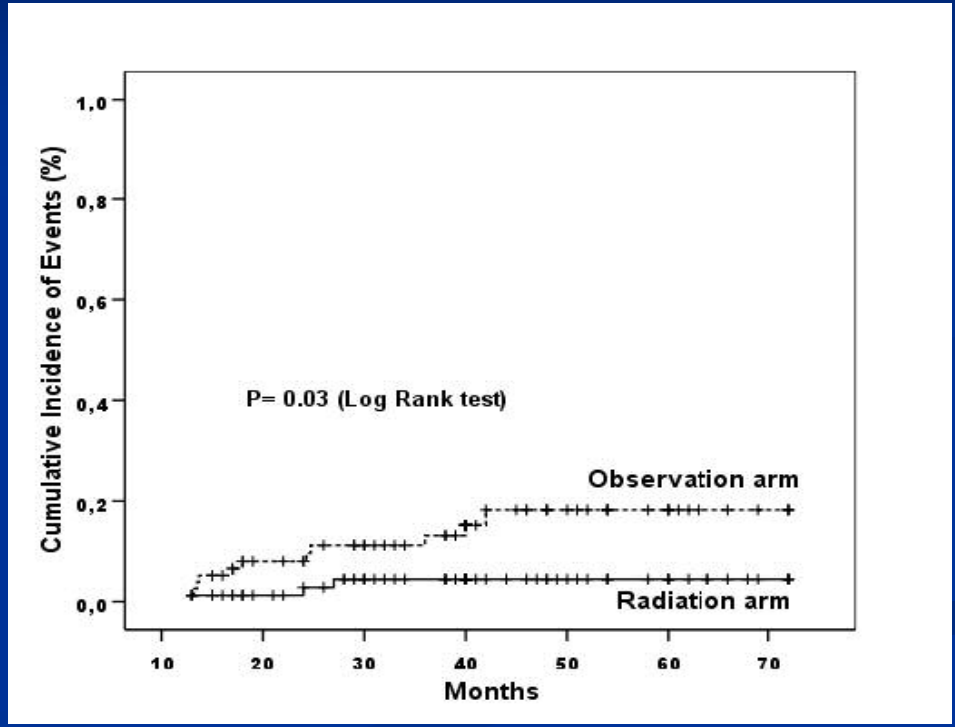
Conclusion

Patients who received consolidation RT apparently had better outcomes, consistently across all prognostic groups which persisted in multivariate analysis. This suggests that RT contributes significantly to the cure rate for advanced HL, although patient selection for combined modality treatment requires better definition in prospective trials.

J Clin Oncol 28:3352-3359.

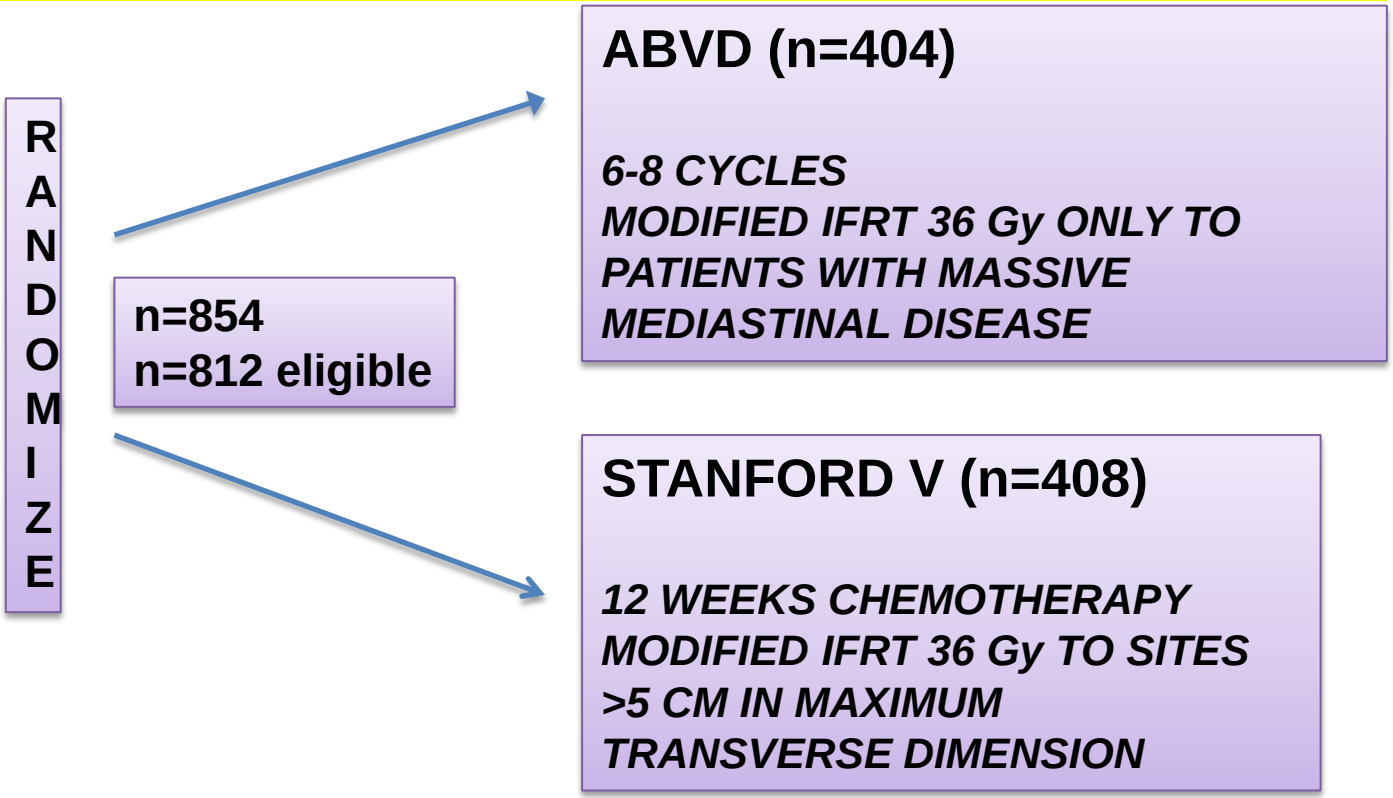
Randomized study of consolidation RT vs. Observation in bulky (>5cm) HL patients who became PET-negative after chemotherapy

- 260 pts. with bulky (>5cm) HL received chemotherapy (VEBEP)
- 30 non-responders. 70 CT-negative and PET-negative
- 160 PET negative with CT≥1.3cm RANDOMIZED
- 80 pts. - Observation
- 80 pts.- IFRT (32 Gy)

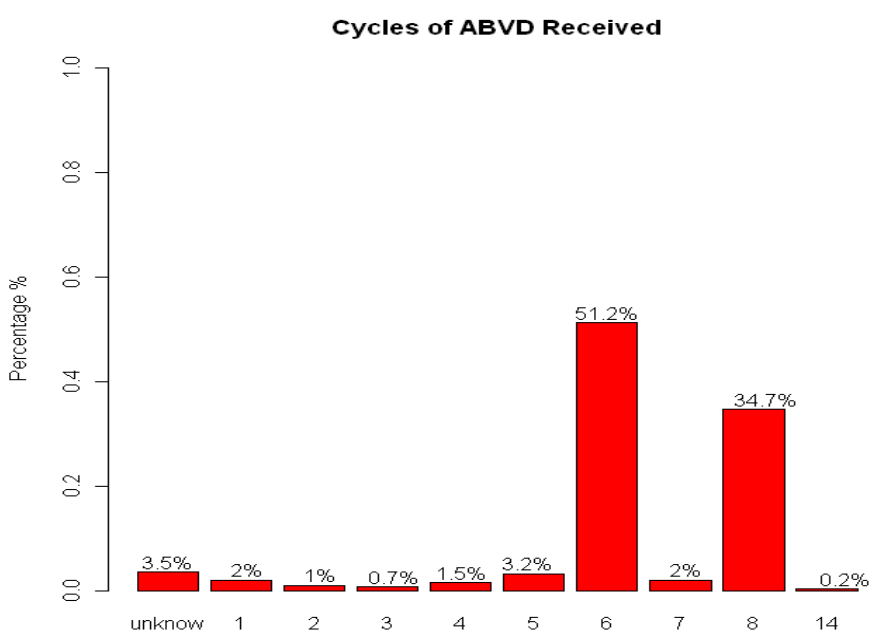


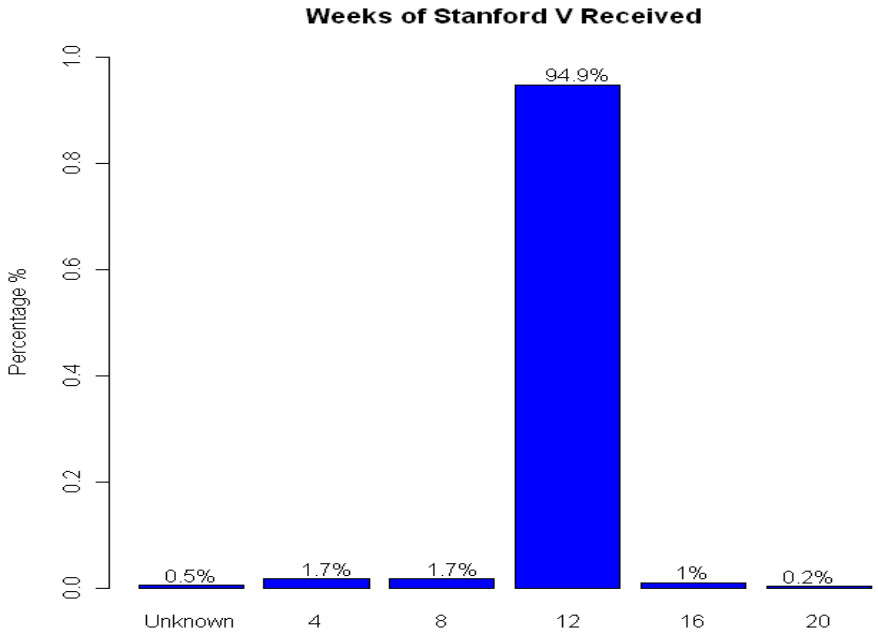
Picardi M. et al. Leukemia & Lymphoma 2007

A Randomized Phase III Trial of ABVD Vs. Stanford V +/- Radiation Therapy In Locally Extensive and Advanced Stage Hodgkin's Lymphoma: An Intergroup Study Coordinated by the Eastern Cooperative Oncology Group (E2496)
Gordon L et al. JCO 2013



Intergroup Trial E2496: # of cycles





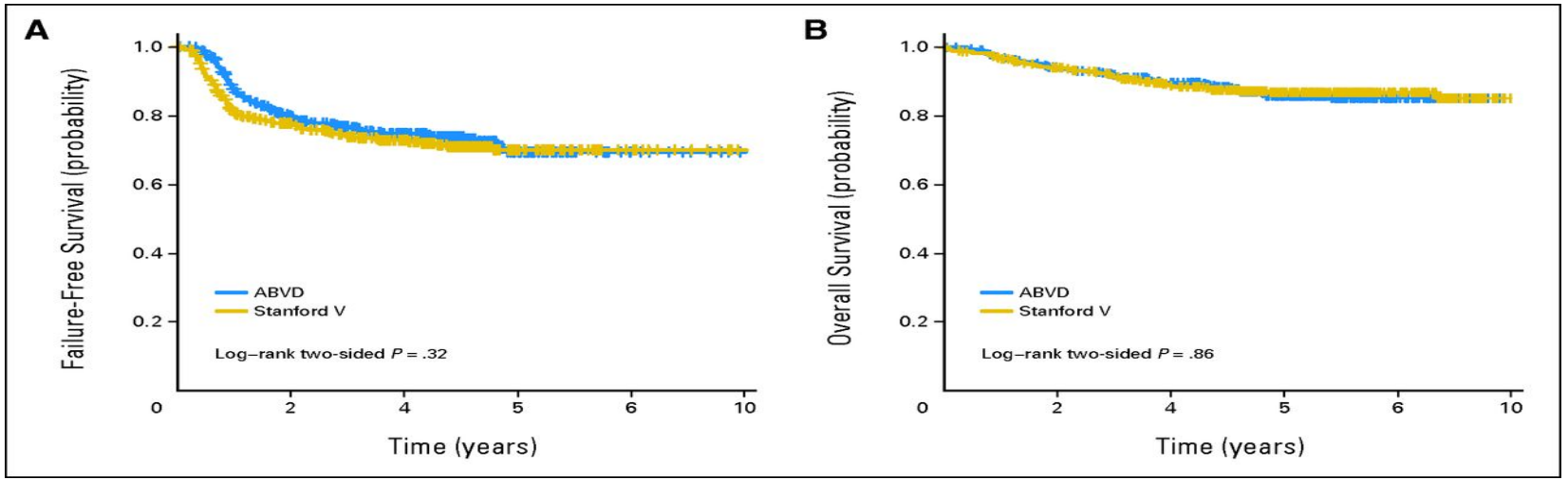
73% of patients had RT on Stanford V
40% of patients had RT on ABVD

Intergroup Trial E2496: Response rates (%)

	CR + CCR	PR	SD	PROG
ABVD	**72**	**7.7**	**7.9**	**<1**
STANFORD V	**69**	**7.4**	**10.3**	**2**

p=ns

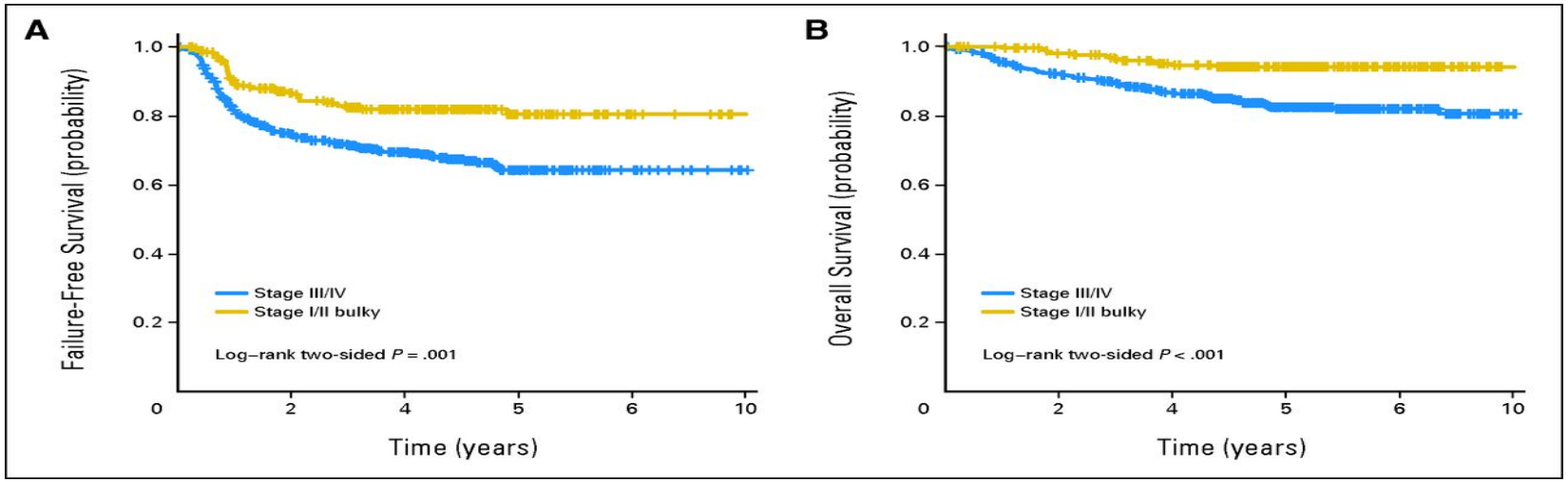
(A) Failure-free (P = .32) and (B) overall survival (P = .86) are shown for all patients, showing no difference between the two arms.



Gordon L I et al. JCO 2013;31:684-691

JOURNAL of CLINICAL ONCOLOGY ASCO

Patients with locally extensive disease (stage I to II bulky) were compared with patients with advanced disease (stage III to IV); patients with locally advanced disease had better (A) failure-free survival (FFS; P = .001) and (B) overall survival (OS; P = ...



Gordon L I et al. JCO 2013;31:684-691

CONCLUSIONS

- There was no significant difference in RR, FFS, OS and 5-year toxicity when ABVD (+RT for BMD) is compared with Stanford V (+ RT for nodal sites >5 cm and macroscopic splenic disease)
- Overall toxicity between the 2 arms was similar, but more lymphopenia and neuropathy was seen in Stanford V
- ***ABVD remains the standard of care***
- Patients with locally extensive disease do better than patients with advanced disease
- For patients with 3-7 IPS risk factors, there is a trend favoring ABVD as measured by FFS

RT in GHSG BEACOPP Studies (1)

- HD 9 established the advantage of escalated BEACOPP. It included 30-40 Gy IFRT to over 2/3 of patients (bulky and/or residual disease).
- In HD 12 esc. BEACOPP cycle reduction and randomization to +/- RT were studied.
- Less esc. BEACOPP was inferior to 8 esc. BEACOPP, but not less toxic.
- FFTP was inferior with no RT particularly if residual CT abnormality. “Our results do not support the omission of consolidation RT for patients with residual disease”.

.

RT in GHSG BEACOPP Studies (2)

- HD15 (Engert et al. Lancet 2012) showed that BEACOPP X6 was as effective and less toxic than BEACOPP X8. OS was better due to less treatment related toxic deaths.
- PET was used for post-chemo evaluation, only if residual CT abnormality (39% of patients).
- There was no randomization to +/- IFRT.
- RT was given only to PET-positive patients (30% of those who had PET). Total receiving RT was 11% compared to 71% in HD9.
- PET- negative patients had outcome similar to CT evaluated CR/Cru and better that those with residual PET.
- The study did not evaluated the contribution to RT to a small remaing number of patents with CT residual mass that remained PET positive, but suggests that with optimal escalated BEACOPP CT-CT patents and PET-CR patients do well with no RT.

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Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial

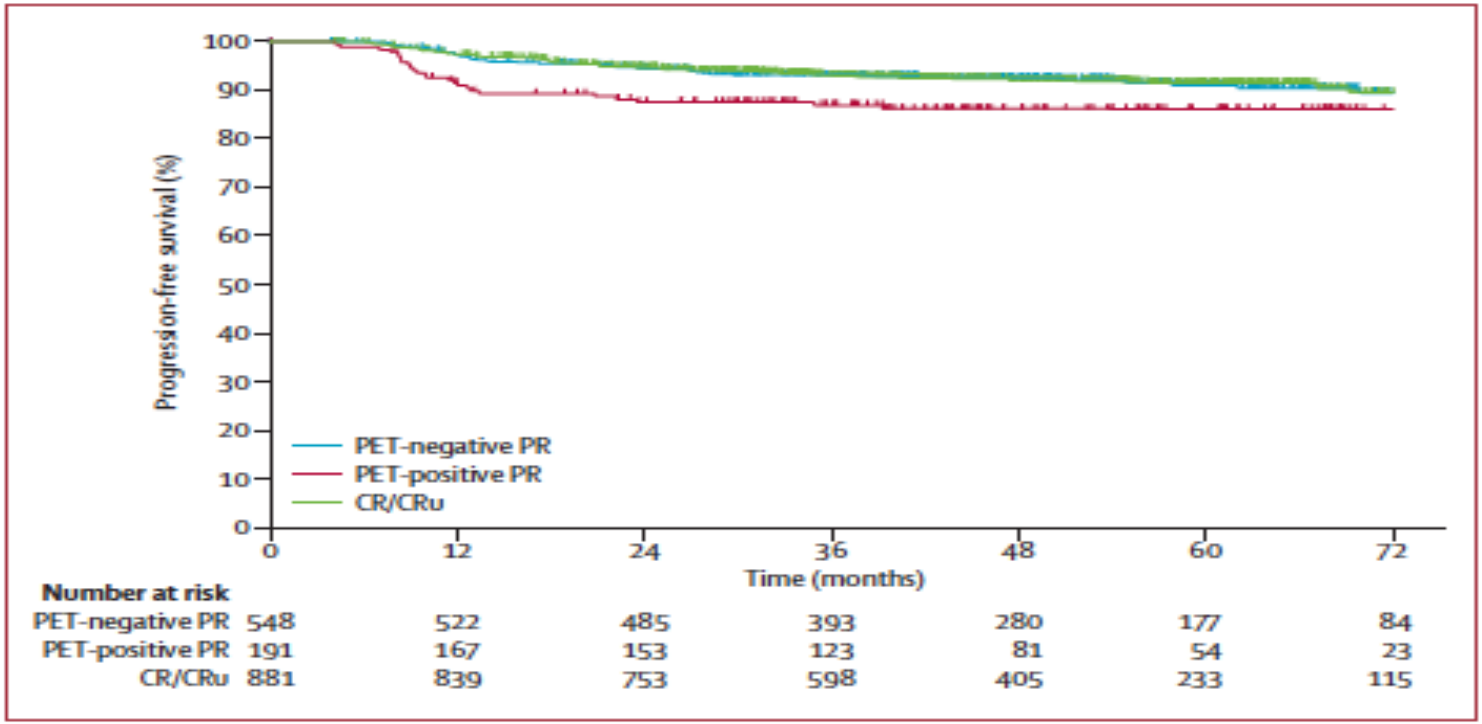


Figure 3: Progression free survival for PET study objective

When RT should be considered in “advanced-stage”?

- With regimens with less excessive chemotherapy (ABVD X6; BEACOPP X6, Stanford V)
- Older patients (>50) tolerate intensive/long chemotherapy poorly.
- Patients with contra-indications for aggressive chemotherapy
- Patients with predominantly bulky site(s)
- Patients with residual disease after chemotherapy
- **Patients with residual disease that remain PET (+)**

RT in Salvage of Refractory or Relapsed patients

- Too many are “salvaged” and re-salvaged without RT and continue to fail in a single site
- NO cross-resistant with chemotherapy (often forgotten)
- RT may (although rarely) be curative as asingle salvage agent
- Best is to design and incorporate RT as part of the salvage protocol
- RT i may be incorporated as:
  - An integral part of the response induction (into PET negative status)
  - As a component of the high-dose transplant regiment (using TLI)
  - As a consolidation post-transplant (to residual or bulky disease)

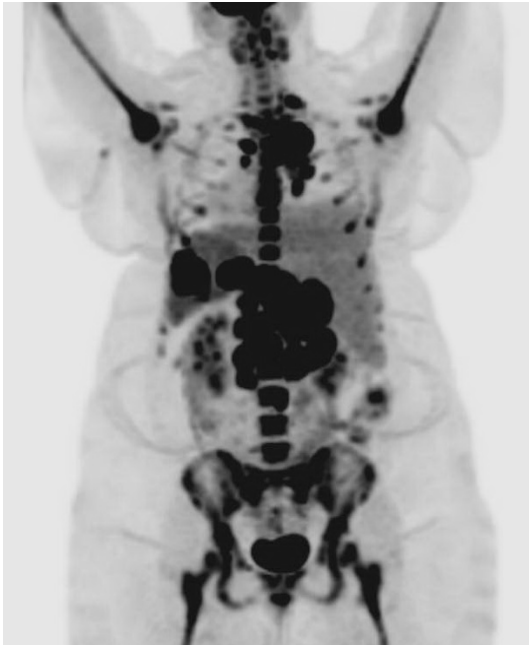
RT for relapsed and refractory lymphoma

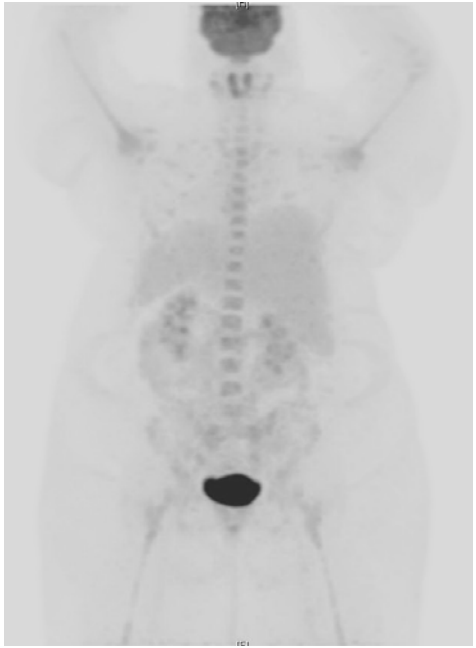
Joachim Yahalom, M.D.
Memorial Sloan-Kettering Cancer Center
New York, NY, U.S.A.

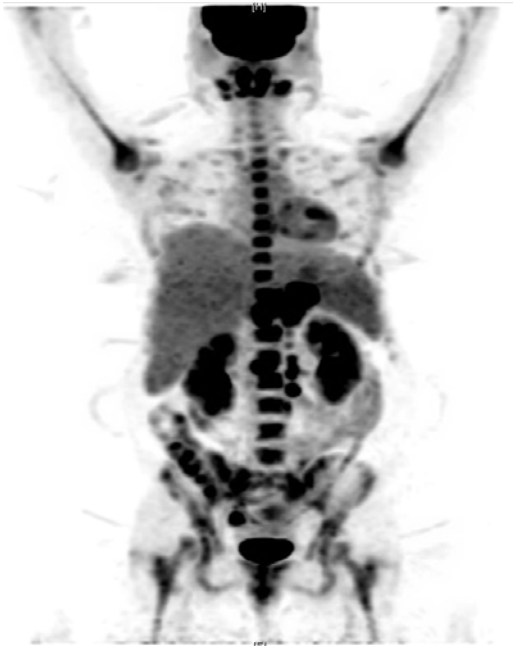
Memorial Sloan Kettering Cancer Center

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School







11/2013: HL-IIIA

6/2014: CR post ABVD

11/2014: retroperitoneal relapse

39 yo woman in CR after ABVD X6 for HL

Radiation Therapy for HD

Recent Trends

- Radiation alone - obsolete
- Combined modality programs
  - Radiation fields – markedly reduced (ISRT by ILROG)
  - Radiation dose – from 40 Gy to 20-30 Gy
- Chemotherapy alone
  - Advanced-stage
  - Early-stage **(>50% of U.S. patients, most women)**

In the United States RT is less commonly used in the management HL
the consequences

- **With the use of PET scans upstaging to stages III/IV is not uncommon; hence less RT is used**
- **How have radiotherapists optimized treatment?**
  - **When administered, Radiation fields are smaller (IF-RT) and doses are lower than in past decades**
  - **More than 2/3 of women do not need axillary irradiation, resulting in minimal (<10%) or no breast exposure**
  - **Bulk decrease by chemotherapy and the benefit of modern imaging allows further radiation field reduction (mediastinum)**
  - **Radiation dose has been cut back from >40 Gy to 30 Gy and more recently to 20 Gy (50% reduction**
- **For unfavorable and bulky stage II HL too many physicians forget that the relapse rate is higher with chemotherapy alone compared to CMT; most failures occur in sites of previous nodal disease!**
- **Most patients who fail chemotherapy alone are still HIGHLY curable but now they need HDT**
  - **Can this paradigm change?**

From medical oncology salvage leader:

- **‘’The fear of RT must stop; it remains the single most effective treatment for HL’’**

HL: the numbers

- 9200 cases estimated in US in 2013-SEER Data

- Approximate numbers based upon MSKCC long term data (GHSG for Early HL, IPI-based for Advanced HL)

  - Favorable Early HL: 15%
  - Unfavorable Early HL: 25%

  - Bulky stage II disease: 20%

  - Favorable Advanced HL (0-3 RF): 30%
  - Unfavorable Advanced HL (4-7 RF): 10%

Memorial Sloan Kettering Cancer Center

High-Dose Therapy Salvage of Hodgkin Lymphoma Enhanced by RT: 30 Years of Experience

MSKCC HL- Salvage with Transplantation Program

- Five consecutive prospective studies (1985, 1994, 1998, 2004, 2011)
- Approx. 500 patients (~18/year)
- Long-term and quality of life study

MSKCC HL- Salvage with Transplantation Program

- All progression/relapses- biopsy proven
- Two-step chemo salvage
  - *Standard dose re-induction*
  - ***High dose***
- Involved-field RT <u>always pre-transplant</u>
- TLI part of the conditioning regimen in previously unirradiated patients

Salvage Therapy of Hodgkin Lymphoma – Why RT?

- Chemotherapy failed in these patients
- Many patients had minimal or no exposure to radiation
- Chemotherapy failures remain responsive to RT
- Previously irradiated sites are amenable to meaningful additional RT by avoiding dose-limiting organs

Integrating Radiotherapy - *Rationale*

- Non-cross-resistant with chemotherapy
- Predictable pattern of relapse
- Unlimited penetration
- Selectivity of dose to site

Integrating Radiotherapy- *Concerns*

- Toxicity
- Treatment delay
- Availability and/or coordination of radiation oncology

Integrating Radiotherapy - *Options*

- ~~Total Body Irradiation~~
- **Post-transplantation RT** to selected sites / patients
  - Delayed or never happens
  - Less effective?
  - Toxic to regenerating marrow (MDS)

Integrating Radiotherapy - *Preferred*

- **Pre-transplantation RT** as part of the response-inducing regimen

✓ Induce maximal tumor reduction when it is most critical

✓ Differential dose to relapse/bulky site vs. all nodal sites (TLI)

✓ Completed within 10 days (36 Gy b.i.d program)

✓ Safe and rarely toxic

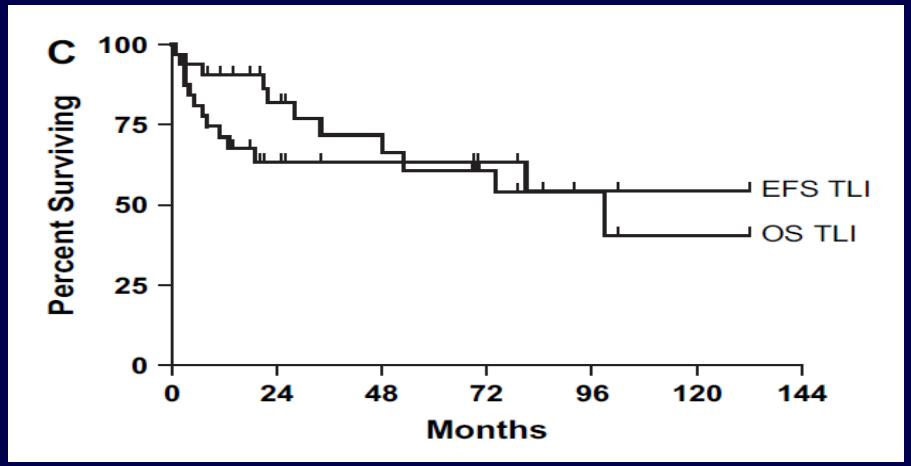
✓ Non-myelosuppressive or leukomogenic

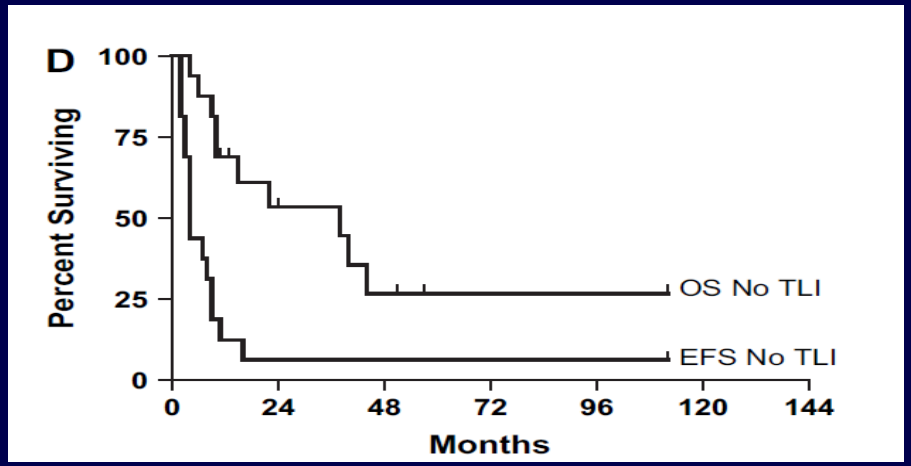
Phase I/II Trial of TLI vs High-Dose Chemotherapy Salvage Regimen

- Patients with primary refractory/relapsed HL (n=48; 1993-2005)
- Conditioning regimen:
  - TLI/chemotherapy
  - Chemotherapy-alone (if prior RT >2000cGy had been given)
- TLI details:
  - Accelerated hyperfractionated TLI 150cGy x10
  - Boost to previous and current disease to 150cGy x10
  - BID regimen
  - Pre-transplant
- Chemotherapy regimen:
  - Carboplatin
  - Cyclohosphamide
  - Etoposide

Evens et al., Ann Oncol 2007

Phase I/II Trial of TLI vs High-Dose Chemotherapy Salvage Regimen





5-year EFS for TLI/chemo vs chemo alone: 63 vs 6% (p<0.0001)

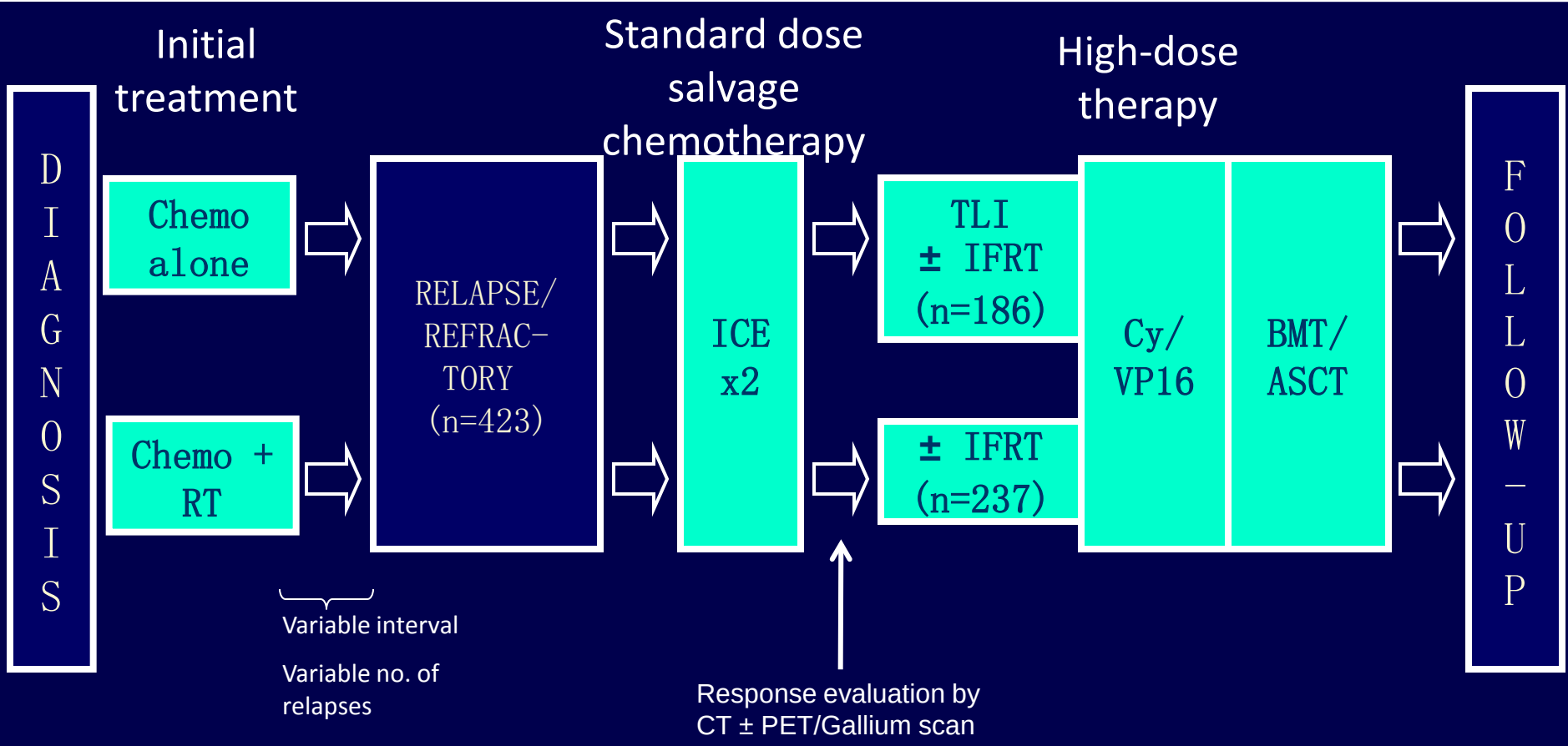
5-year OS for TLI/chemo vs chemo alone: 61 vs 27% (p=0.04)

Predictive factors for EFS: TLI/chemotherapy regimen

Prognostic factors for OS: B-symptoms at relapse

Evens et al., Ann Oncol 2007

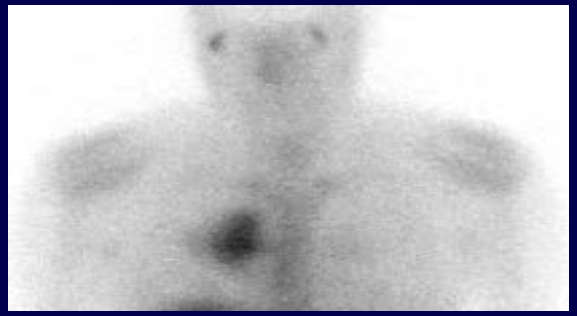
Management of Relapsed HL @MSKCC

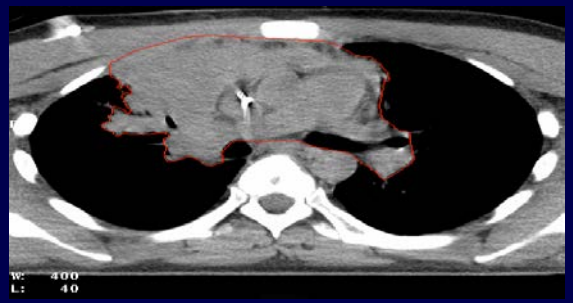


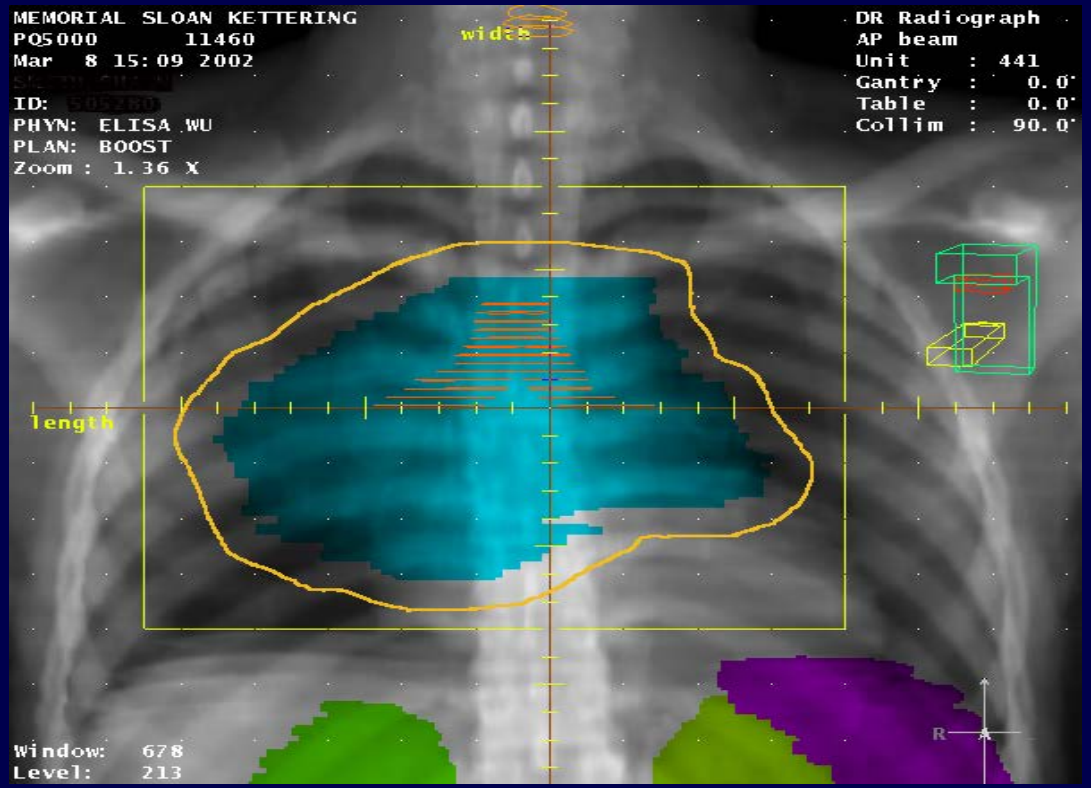
Advantages of Integrated RT in High-Dose Therapy Regimen

- Quick treatment (all treatment delivered over 10 days)
- No interference of RT with salvage chemotherapy and high-dose therapy
- Acute toxicity occurs when patients already admitted for transplantation
- RT pre-ASCT avoids irradiating newly engrafted cells

Boost Field (IFRT)

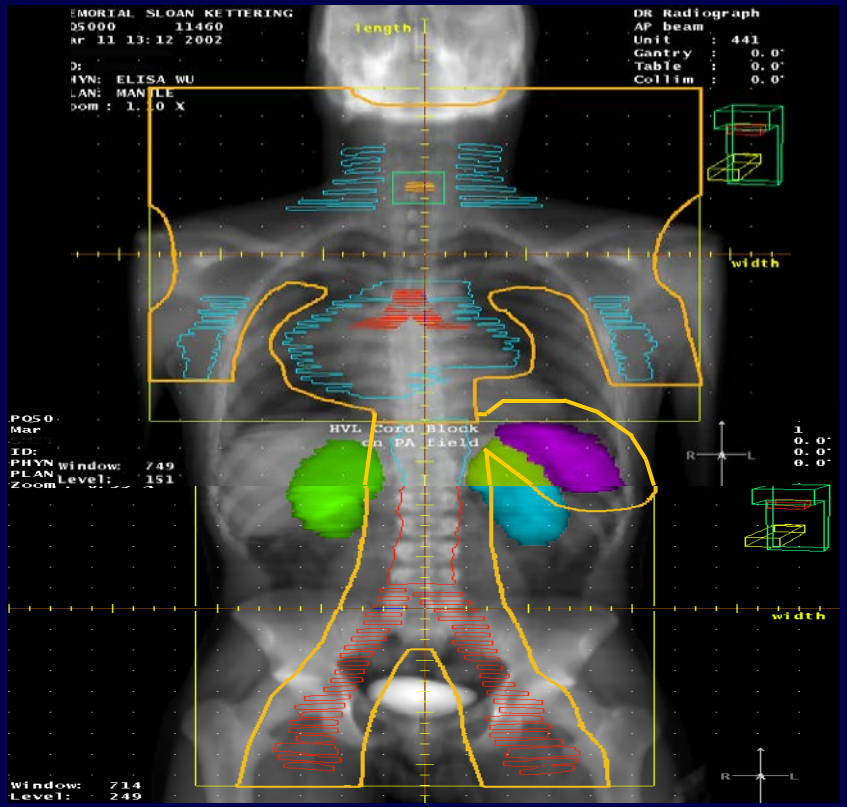






180 cGy x10 fractions
BID

TLI Field



180 cGy x10
fractions BID

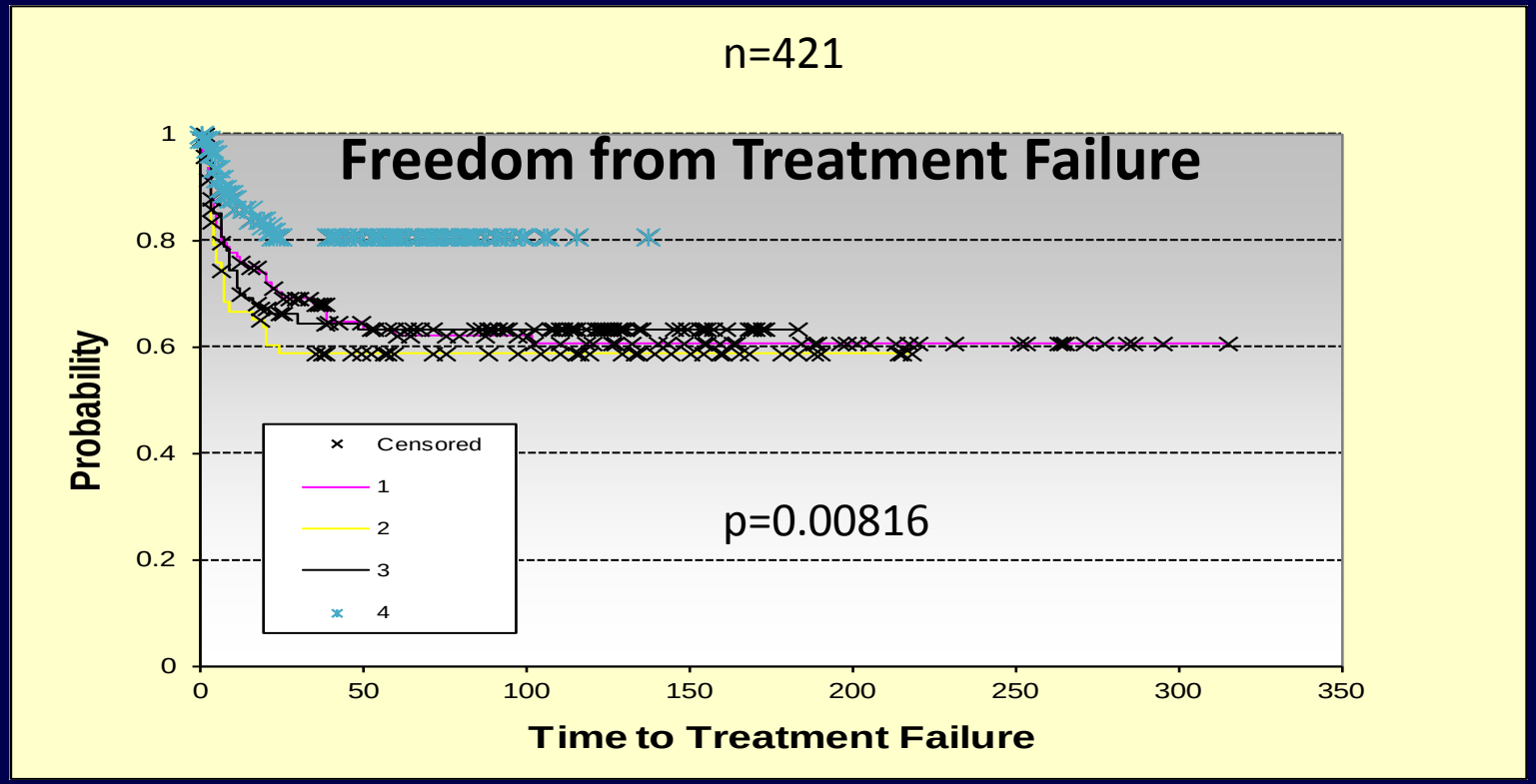
MSKCC Clinical Research Program of Salvage for Hodgkin Lymphoma 1985-2015

- First Generation (1985-1994): 146 pts.
  - Various salvage therapy
  - Pre-transplant IF-RT
  - TLI+CV or CBV/BMT
- Second Generation (1994-1998): 81 pts.
  - Intent to treat analysis
  - ICE salvage therapy
  - IF-RT
  - TLI+CV or CBV/ASCT
- Third Generation (1998- 2004): 105 pts.
  - Risk-adapted program
  - Same principles as 2nd
- Fourth Generation (2004- 2009 98 pts.
  - Achieve minimal disease state pre-ASCT
  - Add GND if PET remains positive
  - Same risk-related concept
- Fifth Generation (2011-2014)
  - Brentuximab followed by ICE—ISRT ± STLI – ASCT 45 pts.

Total = 475 pts.

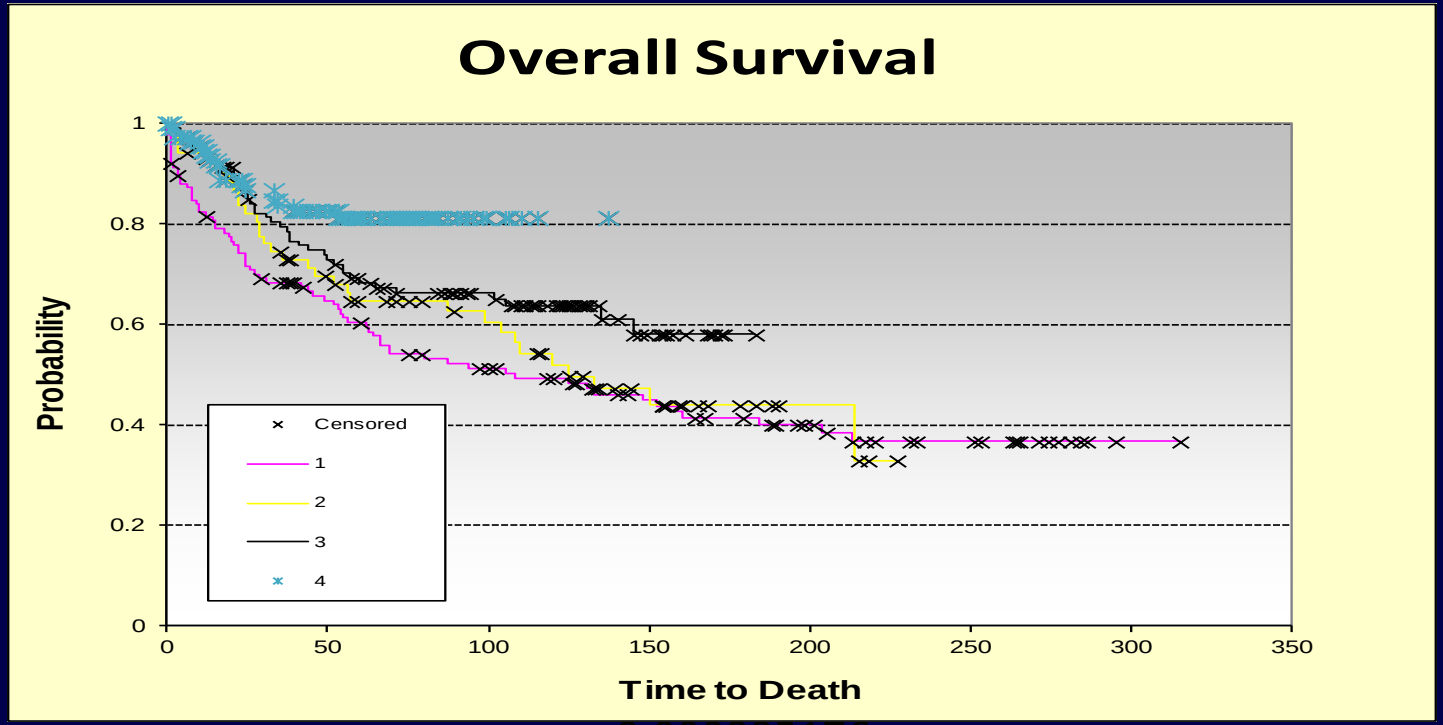
ATHERA trial post-transplant BV maintenance (2010-2014)

Protocol Generation (1-85/86, 2-94, 3-98, 4-04/06)



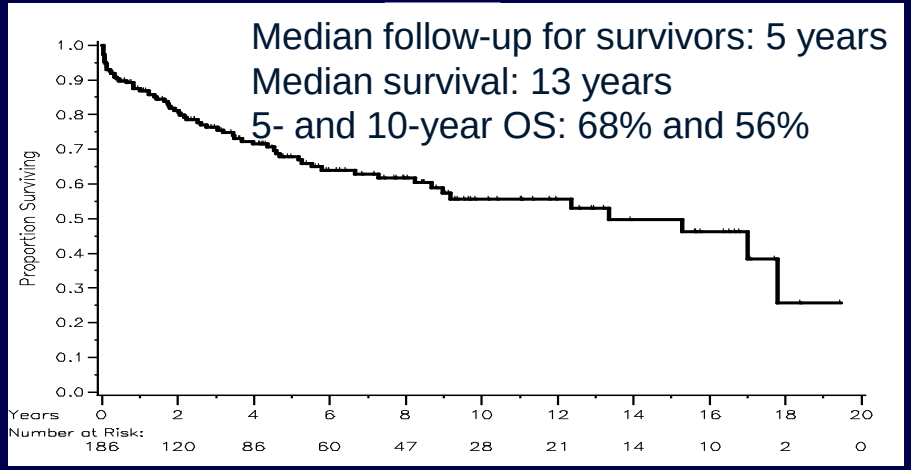
Protocol Generation (1-85/86, 2-94, 3-98, 4-04/06)

n=421



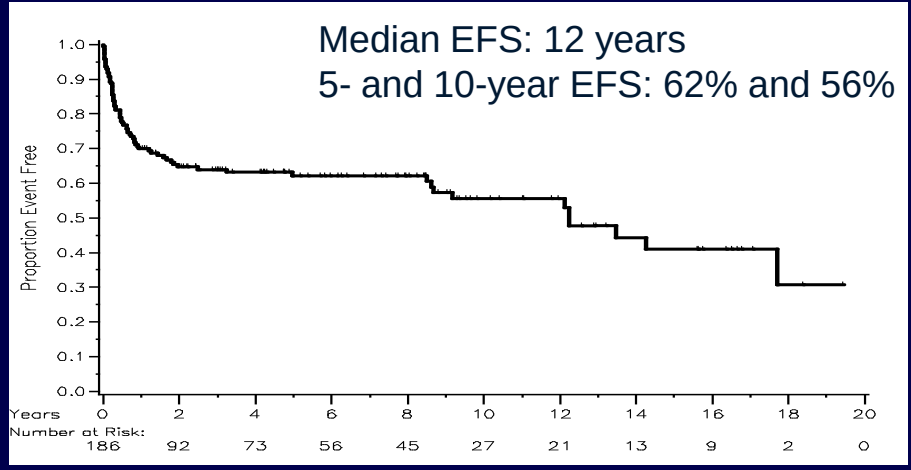
p=0.000885176

Overall Survival



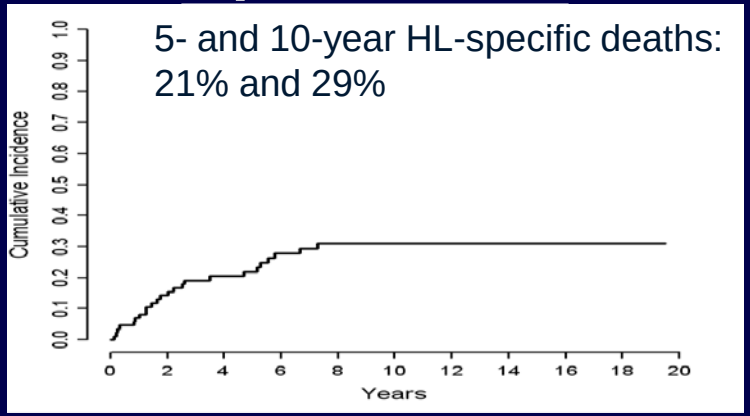
Median follow-up for survivors: 5 years
Median survival: 13 years
5- and 10-year OS: 68% and 56%

Event-Free Survival



Median EFS: 12 years
5- and 10-year EFS: 62% and 56%

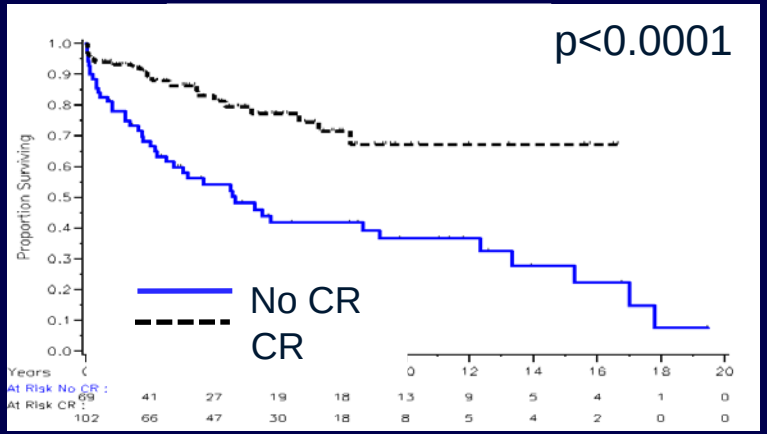
HL-Specific Deaths



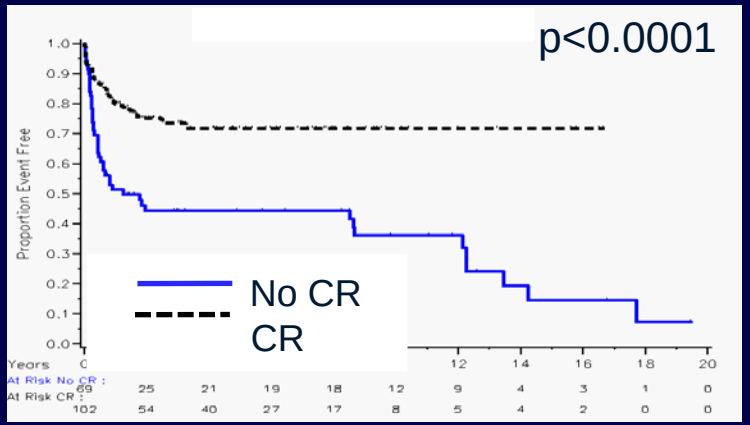
5- and 10-year HL-specific deaths:
21% and 29%

Response to Salvage Therapy

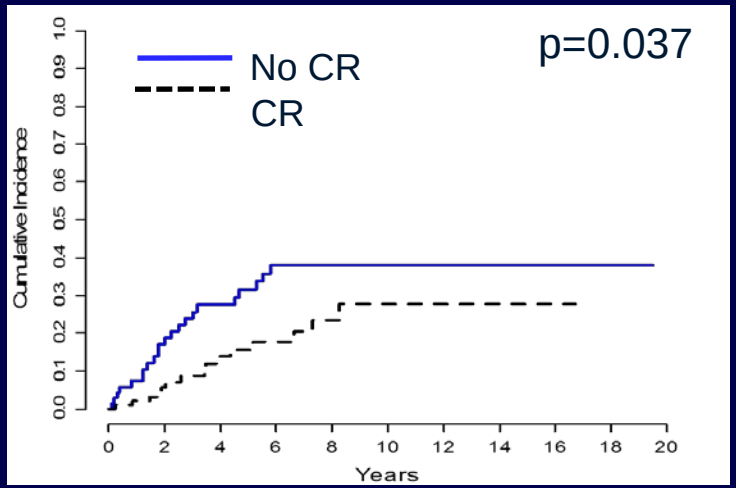
Overall Survival



Event-Free Survival

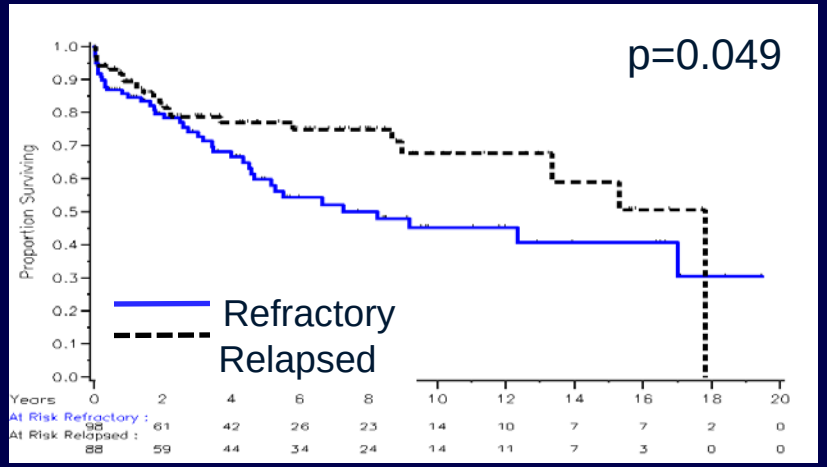


HL-Specific Deaths

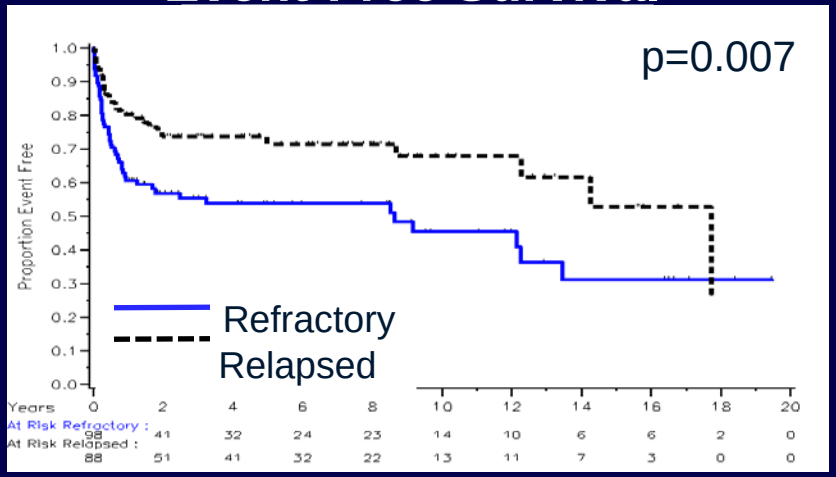


Primary Refractory vs Relapsed HL

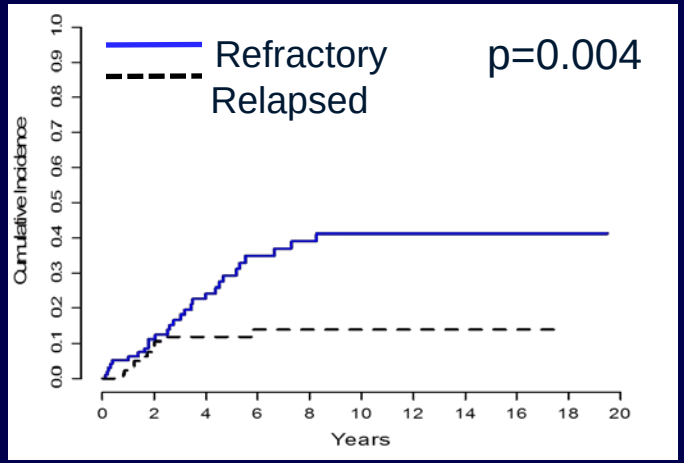
Overall Survival



Event-Free Survival

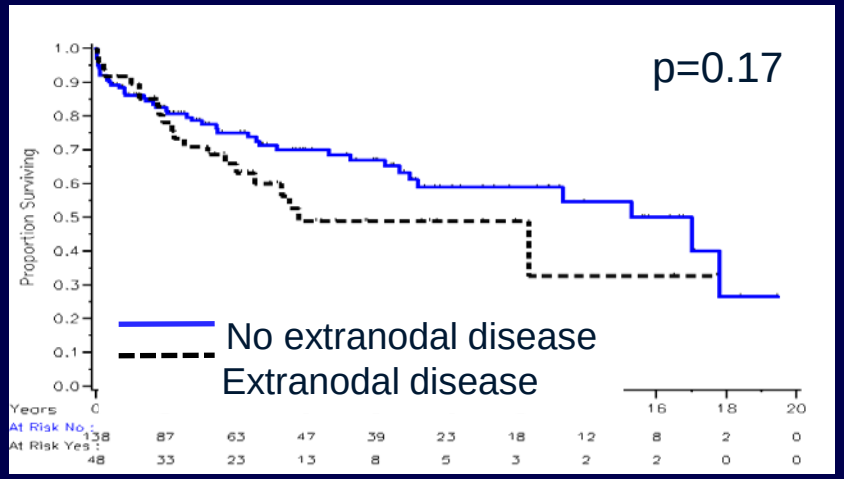


HL-Specific Deaths

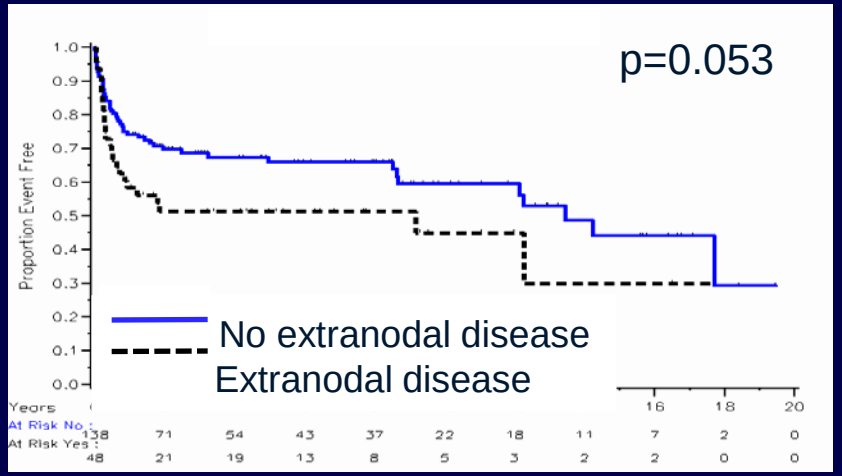


Extranodal Disease at Relapse

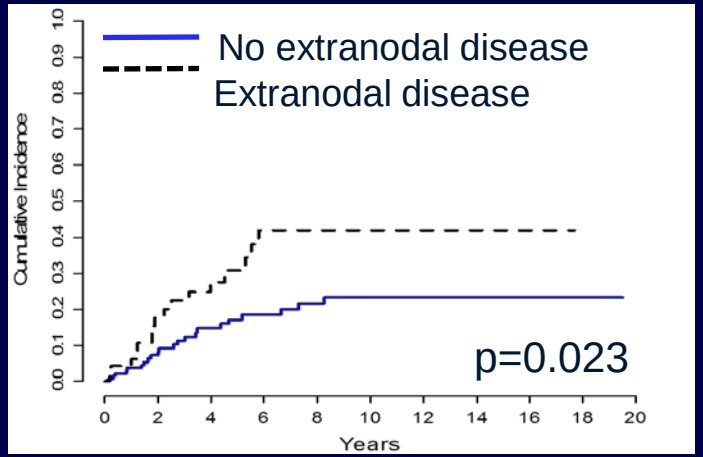
Overall Survival



Event-Free Survival



HL-Specific Deaths



Multivariate Analysis

Variable	OS (HR + 95% CI)	p-value	EFS (HR + 95% CI)	p-value	DSS (HR + 95% CI)	p-value
CR to salvage therapy	0.31 (0.18 to 0.55)	<0.0001	0.34 (0.20 to 0.56)	<0.0001	0.55 (0.29 to 1.06)	0.076
Relapse vs refractory	-	-	0.57 (0.35 to 0.94)	0.029	0.39 (0.19 to 0.83)	0.01
Extranodal disease at relapse	-	-	1.67 (0.99 to 2.80)	0.05	-	-

Toxicity	Early ≥ grade 3 toxicity		Late ≥ grade 3 toxicity	
	n	(%)	n	(%)
Infection	108	(58%)	27	(15%)
Mucositis	41	(22%)	0	(0%)
Pulmonary	33	(18%)	19	(10%)
Other	30	(16%)	20	(11%)
Other GI	24	(13%)	12	(6%)
Esophagus	16	(9%)	6	(3%)
Cardiac	12	(6%)	13	(7%)
Hematologic	11	(6%)	6	(3%)
Renal	11	(6%)	3	(2%)
Skin	6	(3%)	4	(2%)
Thyroid	1	(0.5%)	0	(0%)

Second Malignancies

Number of deaths from second malignancies: 5

Total incidence of second malignancies: 11

- AML (2)
- MDS (1)
- DLBCL (1)
- NHL (1)
- Thyroid (1)
- Lung (1)
- Stomach (1)
- Colon (1)
- Unknown primary (1)

Summary

- Between 10 and 40% of patients with HL fail after initial therapy.
- Patients failing after chemotherapy alone are candidates for salvage RT.
- IFRT/ISRT followed by TLI integrated with high-dose chemotherapy is an effective, feasible and safe salvage therapy for patients with previously unirradiated, relapsed/ refractory HL.
- On multivariate analysis, CR to standard-dose salvage chemotherapy is the most important predictive factor for long-term OS, EFS and DSS after HDT.
- Primary refractory disease and extranodal disease at relapse are associated with worse outcome.
- Long-term morbidity and second malignancy rates are relatively low.

Memorial Sloan Kettering Cancer Center

RECENT MSKCC STUDIES

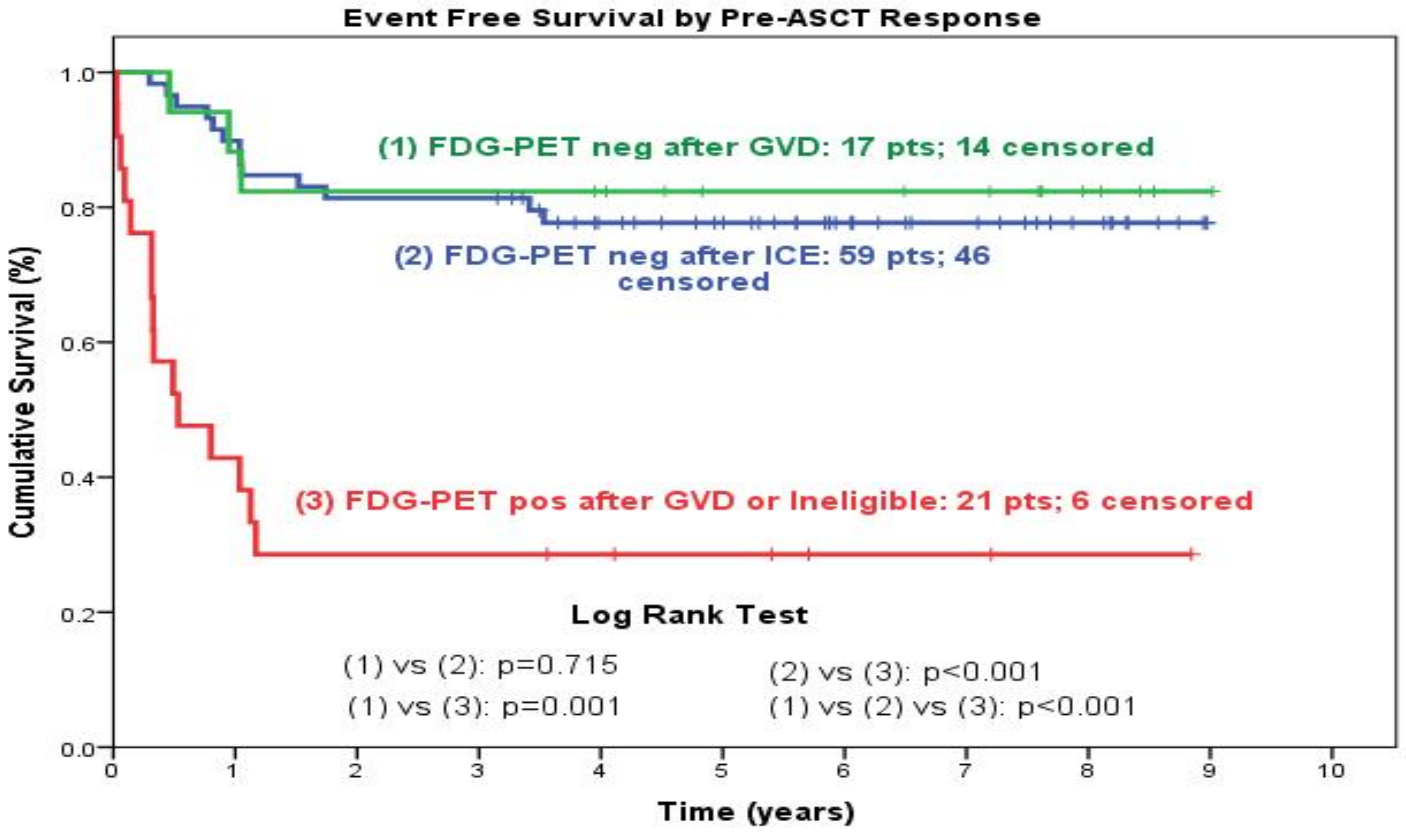
Lesson learned from our first 3 studies ASCT Studies in HL-1985-2004

- **Intensive RT as part of transplant conditioning is safe and effective**
- Goodman K, Moskowitz CH, Riedel E, Serrano V, Gulati S, and Yahalom J. Long-term outcome and quality of life of survivors of ASCT for relapsed and refractory Hodgkin Lymphoma. J Clin Oncol. 2008 Nov 10; 26(32):5240-7.

- **3 pre-salvage therapy risk factors predict outcome** Moskowitz CH, Nimer SD, Portlock CS, Straus DJ, Hedrick EE, Gonzalez M, Walits J, Trippett TM Zelenetz AD, and Yahalom J. A 2-step comprehensive chemoradiotherapy program for relapsed and refractory Hodgkin's disease: intent to treat analysis and development of a prognostic model. Blood 2001, 97:616-623.

- **Normalization of functional imaging pre-ASCT is associated with a survival advantage; however to achieve this, tailored salvage therapy may be required**
- Moskowitz CH, Yahalom J, Zelenetz AD, Zhang Z, Filippa D, Teruya-Feldstein J, Kewalramani T, Moskowitz AJ, Rice RD, Maragulia J, Vanak J, Trippett T, Hamlin P, Horowitz S, Noy A, O'Connor OA, Portlock C, Straus D and Nimer SD. High-dose chemo-radiotherapy for relapsed or refractory Hodgkin lymphoma and the significance of pre-transplant functional imaging. Journal/Br J Haematol 2010; 148 (6): 890-897.

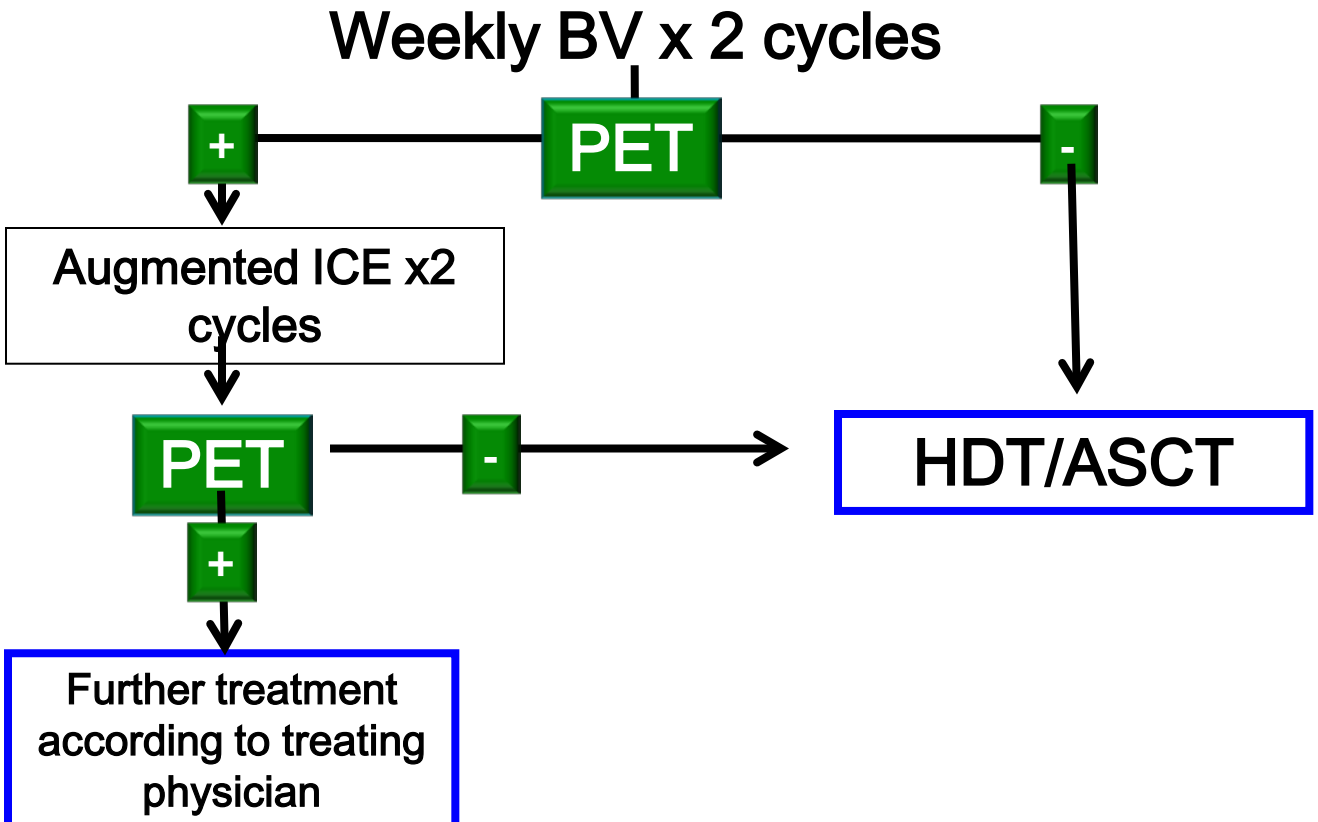
Pre-ASCT Response



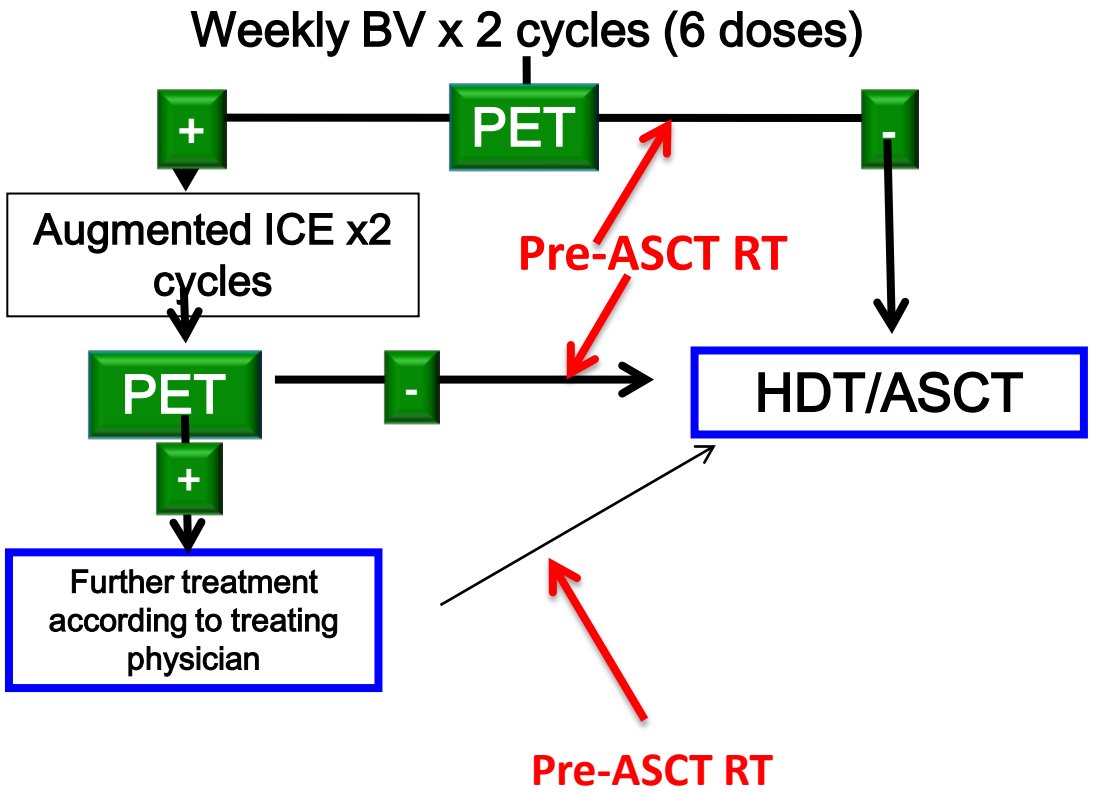
MSKCC 11-142: Relapsed/refractory HL

First TX following upfront therapy

Moskowitz AJ et al Lancet Oncology 16, No 3, 284-292, March 2015



PET-adapted therapy with BV followed by augICE



Summary:

- **45 patients enrolled**
- **27% PET negative after BV alone (avoided ICE)**
- **76% PET negative after whole treatment program**
- **All but 1 patient proceeded to ASCT**

Moskowitz, AJ, et al. Lancet Oncol 2015;16: 284-92

Post-salvage outcome

- 80% CR (Deauville 2) following BV +/- AugICE
- 10 patients did not achieve CR
  - 3 proceeded directly to ASCT (2 deauville 3, 1 deauville 4)
  - 6 received involved field RT followed by ASCT
  - 1 (not eligible for RT) received 3rd AugICE (SD) then ASCT
- Stem cell collection
  - BV alone:
    - Median 6.3 x 10^6/kg (range 2.96-13.29 x10^6/kg)
  - BV-> AugICE
    - Median 9.4 x 10^6/kg (range 5.15-31.43 x10^6/kg)
- Conditioning
  - Chemo (BEAM, CBV): 36
  - TLI/cytoxan/etoposide: 7
  - Pre-transplant IFRT: 17

THE LANCET Oncology

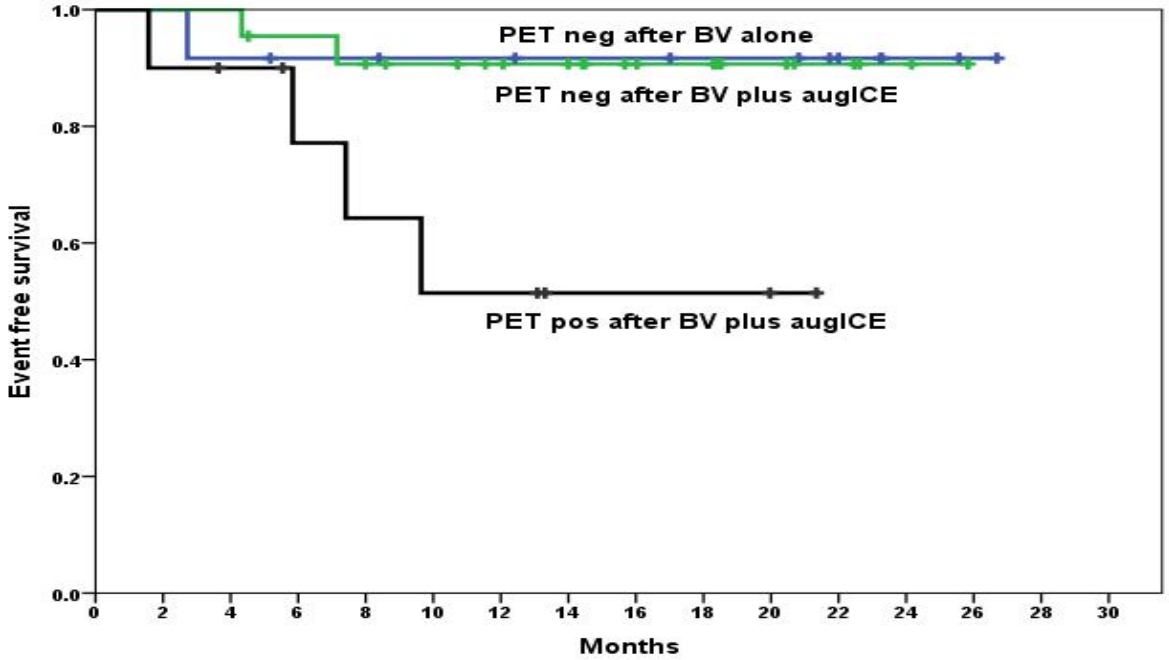
Volume 16, Issue 3, March 2015, Pages 284–292

Articles

PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study

Dr Alison J Moskowitz, MD[a], Prof Heiko Schöder, MD[a], Prof Joachim Yahalom, MD[a], Susan J McCall, NP[a], Stephanie Y Fox, BS[a], John Gerecitano, MD[a], Ravinder Grewal, MD[a], Paul A Hamlin, MD[a], Steven Horwitz, MD[a], Rachel Kobos, MD[a], Anita Kumar, MD[a], Matthew Matasar, MD[a], Ariela Noy, MD[a], M Lia Palomba, MD[a], Miguel-Angel Perales, MD[a], Prof Carol S Portlock, MD[a], Craig Sauter, MD[a], Neerav Shukla, MD[a], Prof Peter Steinherz, MD[a], Prof David Straus, MD[a], Tanya Trippett, MD[a], Prof Anas Younes, MD[a], Prof Andrew Zelenetz, MD[a],

EFS according to treatment and PET status



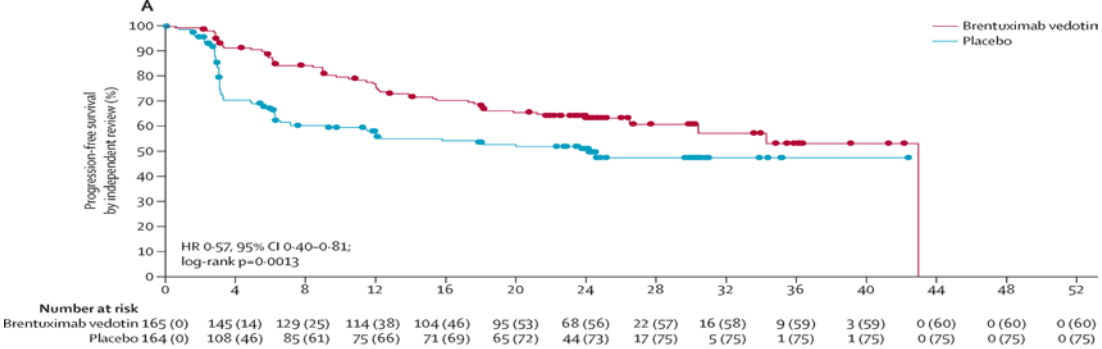
ATHERA Study- Lancet 2015

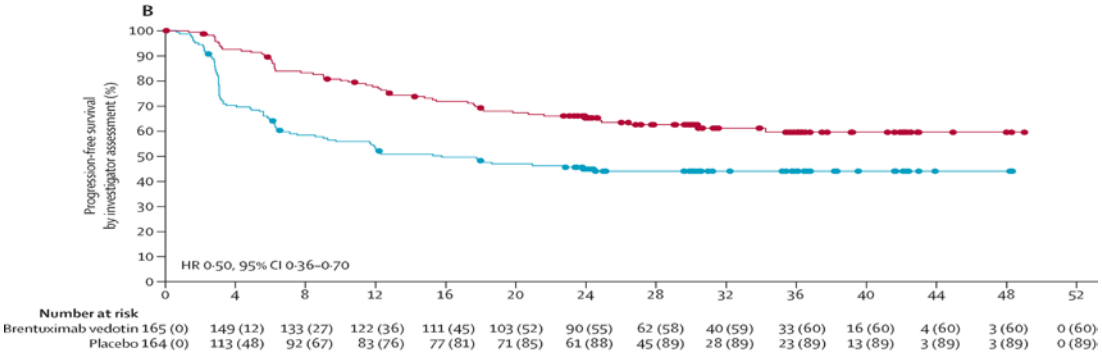
Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial

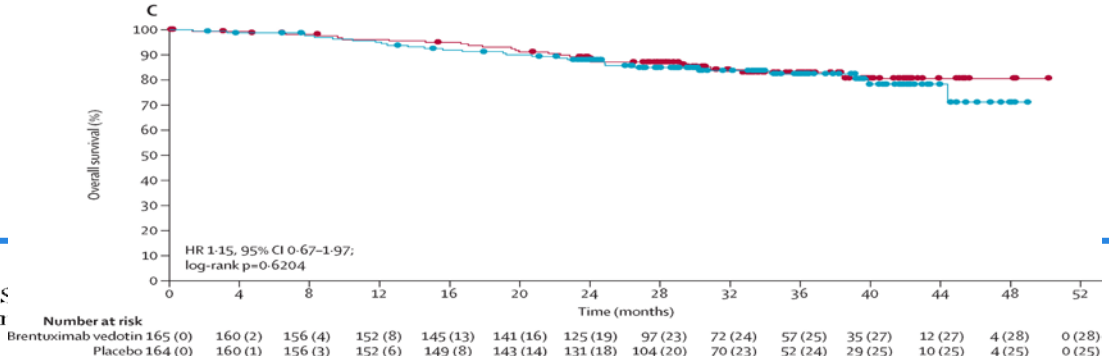
Craig H Moskowitz, Auayporn Nademanee, Tamas Masszi, Edward Agura, Jerzy Holowiecki, Muneer H Abidi, Andy I Chen, Patrick Stiff, Alessandro M Gianni, Angelo Carella, Dzhelil Osmanov, Veronika Bachanova, John Sweetenham, Anna Sureda, Dirk Huebner, Eric L Sievers, Andy Chi, Emily K Larsen, Naomi N Hunder, Jan Walewski, for the AETHERA Study Group

BV post-ASCT

Should this be standard of care?


A
Brentuximab vedotin
Placebo
Progression-free survival by independent review (%)
HR 0·57, 95% CI 0·40–0·81;
log-rank p=0·0013
Number at risk
Brentuximab vedotin 165 (0) 145 (14) 129 (25) 114 (38) 104 (46) 95 (53) 68 (56) 22 (57) 16 (58) 9 (59) 3 (59) 0 (60) 0 (60) 0 (60)
Placebo 164 (0) 108 (46) 85 (61) 75 (66) 71 (69) 65 (72) 44 (73) 17 (75) 5 (75) 1 (75) 1 (75) 0 (75) 0 (75) 0 (75)


B
Progression-free survival by investigator assessment (%)
HR 0·50, 95% CI 0·36–0·70
Number at risk
Brentuximab vedotin 165 (0) 149 (12) 133 (27) 122 (36) 111 (45) 103 (52) 90 (55) 62 (58) 40 (59) 33 (60) 16 (60) 4 (60) 3 (60) 0 (60)
Placebo 164 (0) 113 (48) 92 (67) 83 (76) 77 (81) 71 (85) 61 (88) 45 (89) 28 (89) 23 (89) 13 (89) 3 (89) 3 (89) 0 (89)


C
Overall survival (%)
HR 1·15, 95% CI 0·67–1·97;
log-rank p=0·6204
Time (months)
Number at risk
Brentuximab vedotin 165 (0) 160 (2) 156 (4) 152 (8) 145 (13) 141 (16) 125 (19) 97 (23) 72 (24) 57 (25) 35 (27) 12 (27) 4 (28) 0 (28)
Placebo 164 (0) 160 (1) 156 (3) 152 (6) 149 (8) 143 (14) 131 (18) 104 (20) 70 (23) 52 (24) 29 (25) 10 (25) 4 (25) 0 (25)

Conclusions

- Early consolidation post-ASCT with BV demonstrated improved PFS per IRF in HL patients with risk factors for relapse or progression (HR=0.57, P=0.001)
  - PFS benefit was sustained, with 2-year PFS rates per investigator of 65% and 45% on the BV and placebo arms, respectively
  - Consistent benefit was observed across subgroups
- Interim analysis of overall survival did not show a significant difference between treatment arms (P=0.62)
  - Analysis limited by small number of events and the large number of patients on the placebo arm crossing over to BV after progression
  - More patients on the placebo arm received subsequent anti-tumor therapy and/or allogeneic stem cell transplant
- Consolidation therapy was generally well tolerated
  - Peripheral sensory neuropathy and neutropenia were common, and were manageable with dose reductions or delays
  - Two deaths occurred within 40 days of dosing with BV
- BV consolidation therapy is an important therapeutic option for HL patients undergoing ASCT to reduce the risk of relapse or progression

SUMMARY

- APPROACH TO SALVAGE IS STILL EVOLVING
- RT INCORPORATED IN THE SALVAGE REGIMEN IMPROVES OUTCOME – BUT OFTEN FORGOTTEN
- OUR EXPERIENCE SUGGESTS THAT SANDWICHING RT POST STANDARD SALVAGE AND HIGH-DOSE ASCT IS FEASIBLE EFFECTIVE AND SAFE
- GETTING THE PATIENT INTO A PET-CR IS CRITICALLY IMORTANT- RT CAN HELP
- BEST IS TO AVOID RISK OF RELAPSE BY USING COMBINED MODALITY RATHER THAN CHEMO ALONE.

Thanks

- Dr. Subhash Gulati* - Co-founded the program in 1985
- Dr. Craig Moskowitz- Lymphoma Service
- Dr. Andreas Rimner – Radiation Oncology
- Dr. Alison Moskowitz –Lymphoma Service
- Dr. Craig Sauter – BMT Service
- Dr. Karyn Goodman – Radiation Oncology (long-term analysis)
- Shona Lovie – Research assistant
- Meier Hsu- Statistician
- All members of the Lymphoma and BMT teams at MSKCC
- Hundreds of patients who trusted our team to manage the most difficult life-time event

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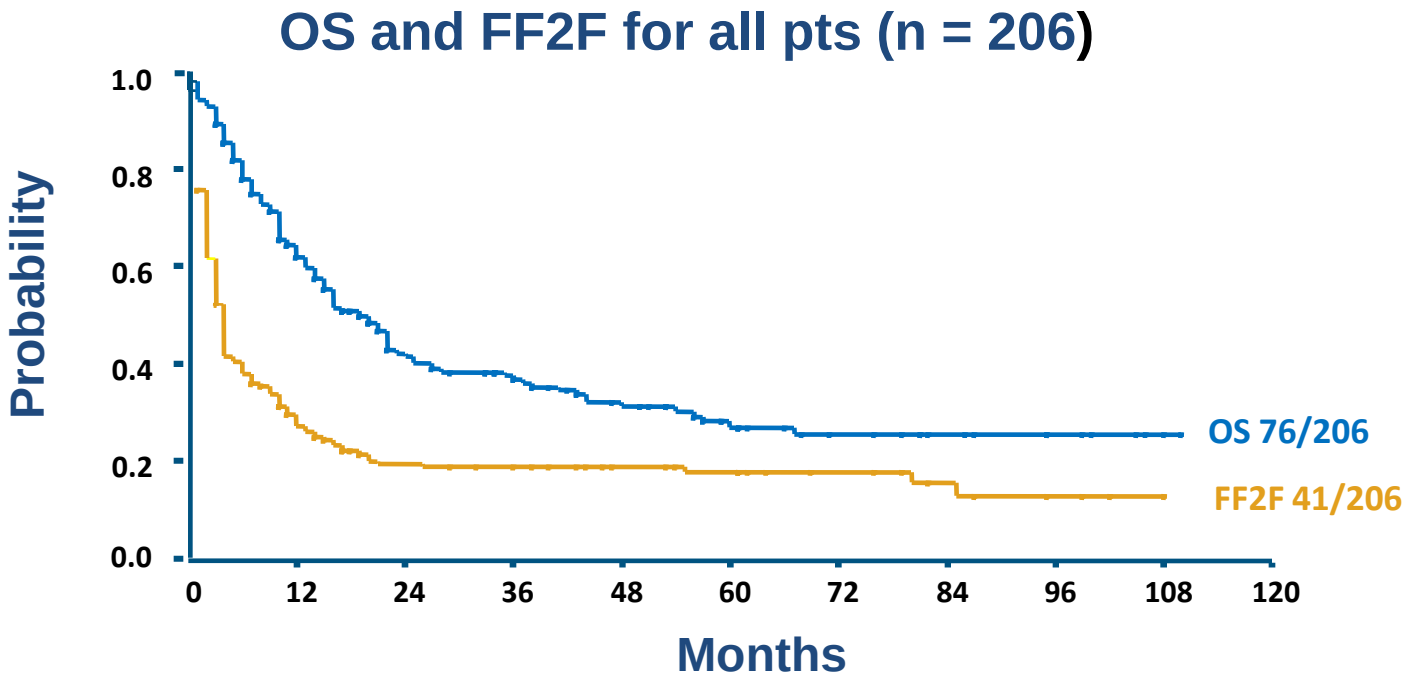
Relapsed and refractory Lymphoma

Andreas Engert, MD

Chairman, German Hodgkin Study Group
University Hospital of Cologne

Primary Progressive HL
1988-1998 (GHSG)



HD – hodgkins disease; OS – overall survival

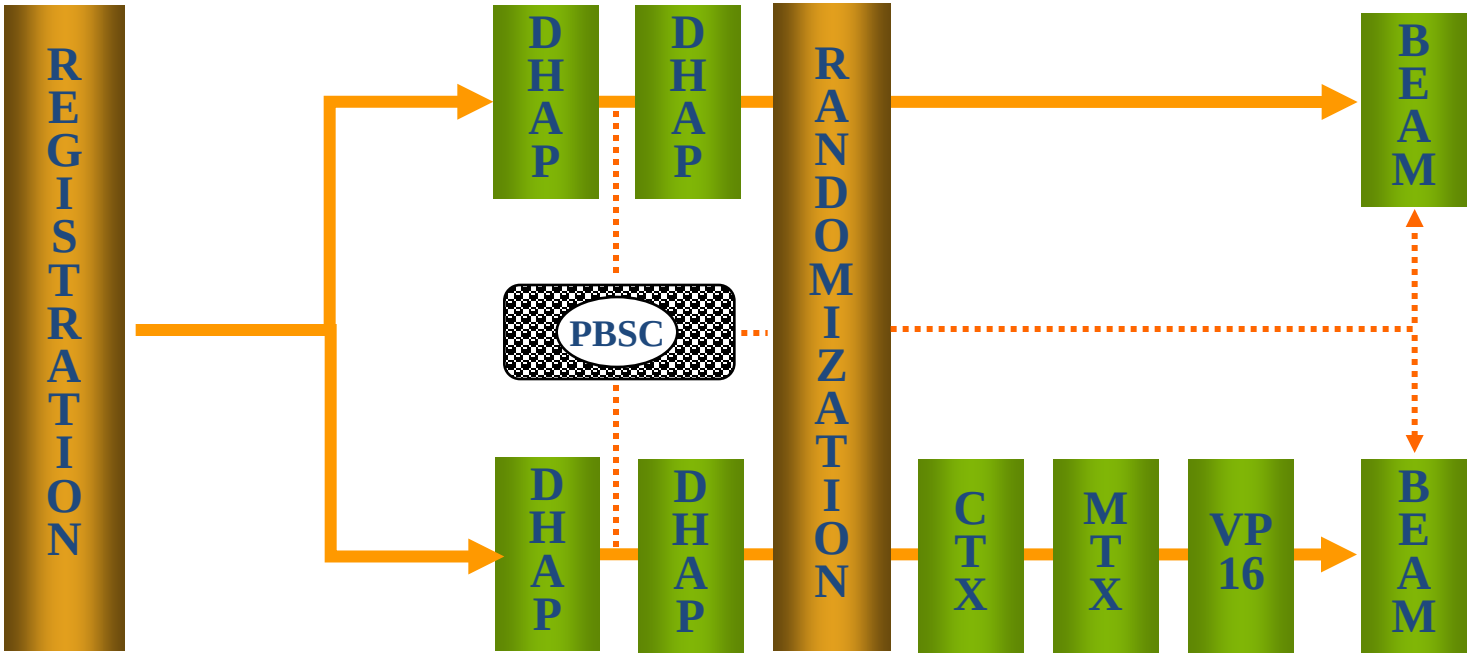
Josting A, et al. Blood. 2000;96(4):1280-1286

Relapsed Hodgkin Lymphoma
Selected conventional salvage regimen

Regimen	n	RR	TRM	Author
DHAP	102	88	0	Josting A Oncol 2002
IGEV	91	81	0	Santoro A Oncol 2007
ICE	65	88	2	Moschkowitz Blood 2001
ASHAP	57	70	0	Rodriguez Blood 1999
GVD	91	70	0	Bartlett A Oncol 2007

HDR2: European Intergroup Trial

Relapsed Hodgkin Lymphoma*

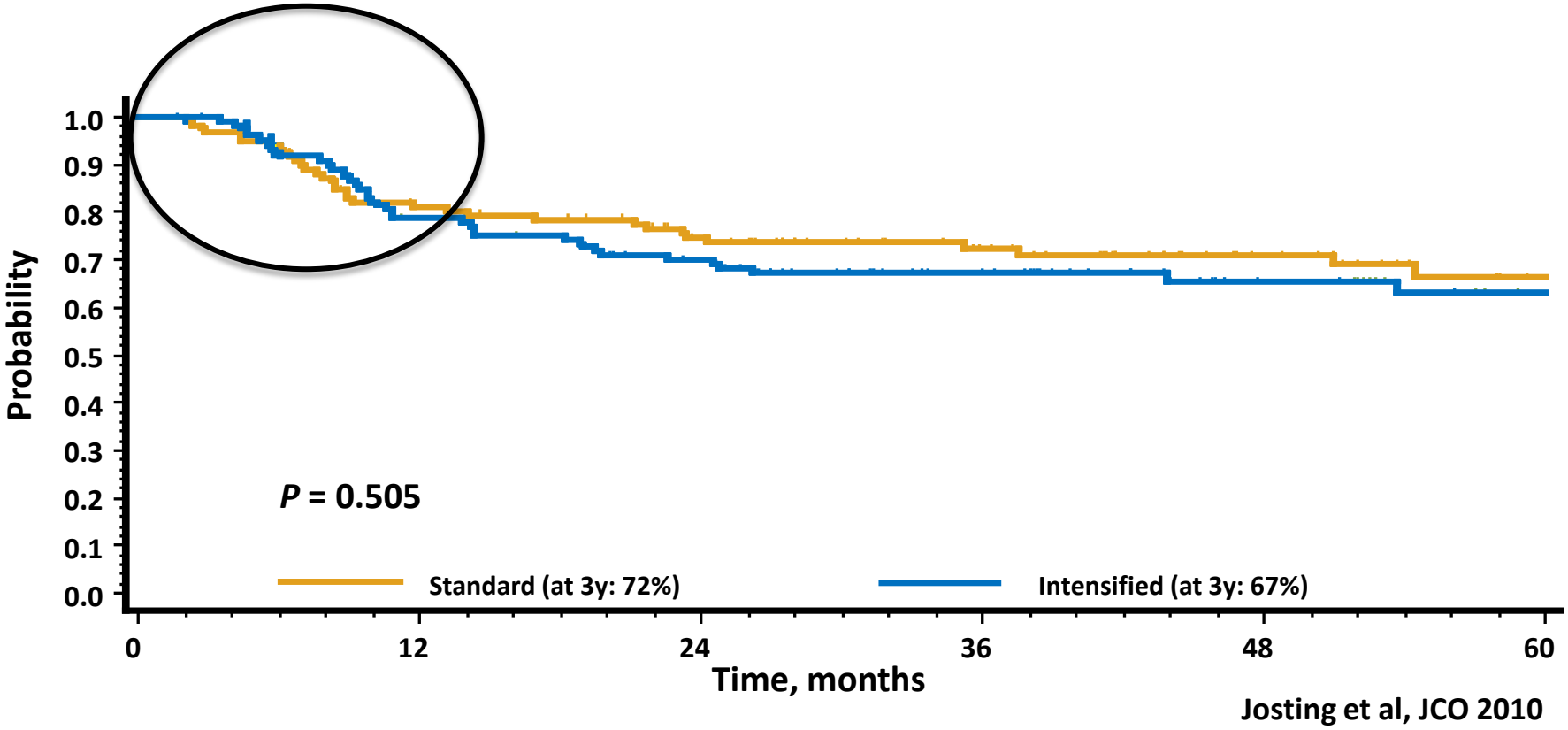


*GHSG, EORTC, EBMT, GELTAMO

Josting A et al, J Clin Oncol. 2010;28(34):5074-5080

HDR2 Study for Relapsed HL

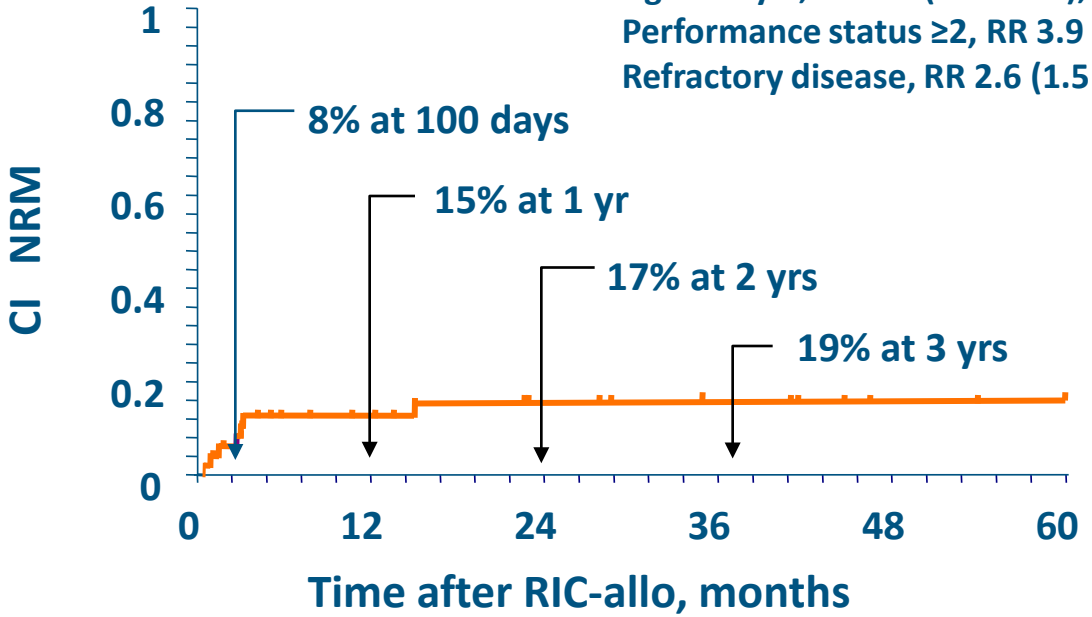
PFS by Treatment Arm (Final Analysis)



Josting et al, JCO 2010

RIC-Allo Trial in Relapsed
or Refractory HL (Non-relapse Mortality)

Age >45 yrs, RR 2.4 (1.1 – 5.0), *P* = .05
Performance status ≥2, RR 3.9 (1.8 – 7.3), *P* = .05
Refractory disease, RR 2.6 (1.5 – 4.5), *P* = .01

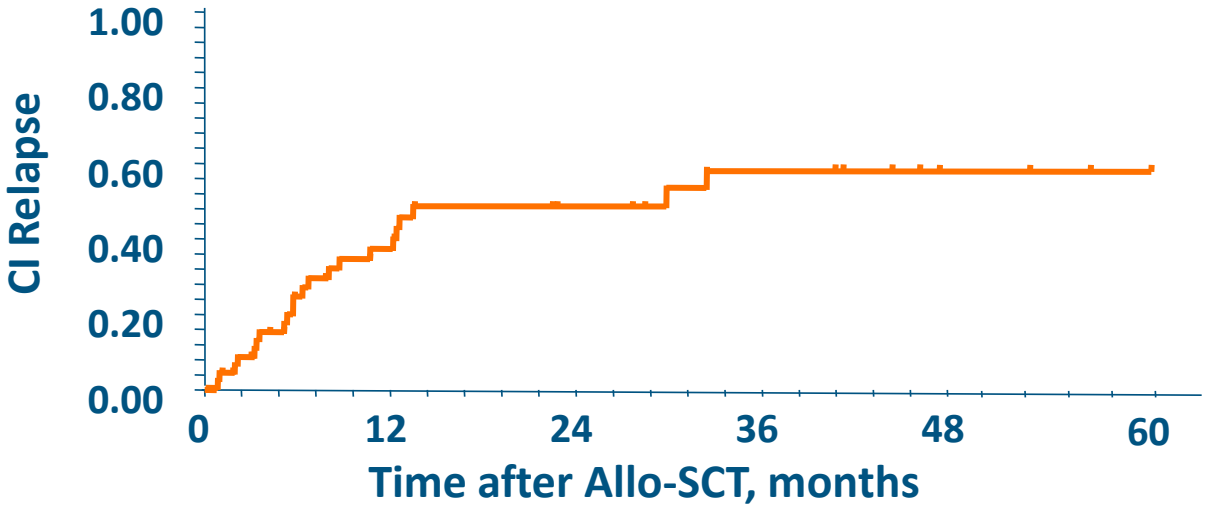


RIC-allo - reduced-intensity conditioning allogenic stem cell transplantation; HL – Hodgkin lymphoma; NRM – non-relapse mortality

Sureda A, et al. Blood. 2009;114: A 658

RIC-Allo Trial in Relapsed
or Refractory HL (Relapse Rate)

≥3 lines of tx, RR 1.7 (1.2 – 2.5), *P* = .03
Refractory disease, RR 2.1 (1.5 – 2.9), *P* = .01



37 % at 1yr
49 % at 2yrs
59 % at 3 yrs

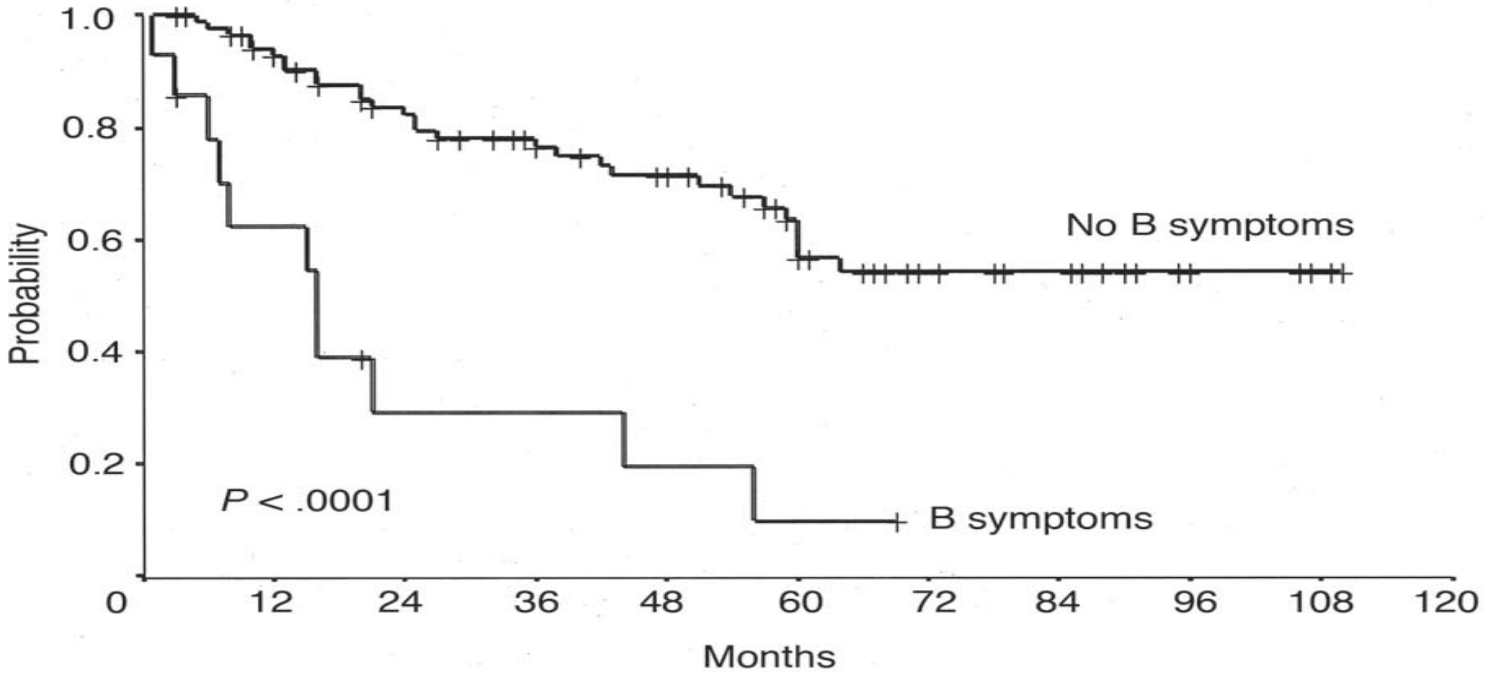
Median time to relapse: 6m (3-35)

RIC-allo - reduced-intensity conditioning allogenic stem cell transplantation; HL – Hodgkin lymphoma; tx – therapy; allo-SCT- allogeneic stem cell transplantation

Sureda A, et al. Blood. 2009;114: A 658

RT in Relapsed/Refractory HL

B-Symptoms at Progression or Relapse



Josting A et al. JCO 2005

RT in Relapsed/Refractory HL

Risk Factors

Factors	OS		FF2F	
	Univariate	Multivariate	Univariate	Multivariate
"B" symptoms	.018	< .001	NS	NS
Stage	.014	.019	NS	NS
Age	NS	NS	NS	NS
Karnofsky performance status	NS	NS	NS	.0001
Duration of first remission	NS	NS	NS	NS

NOTE: All values are *P* values.
Abbreviations: FF2F, freedom from second treatment failure; OS, overall survival; NS, not significant.

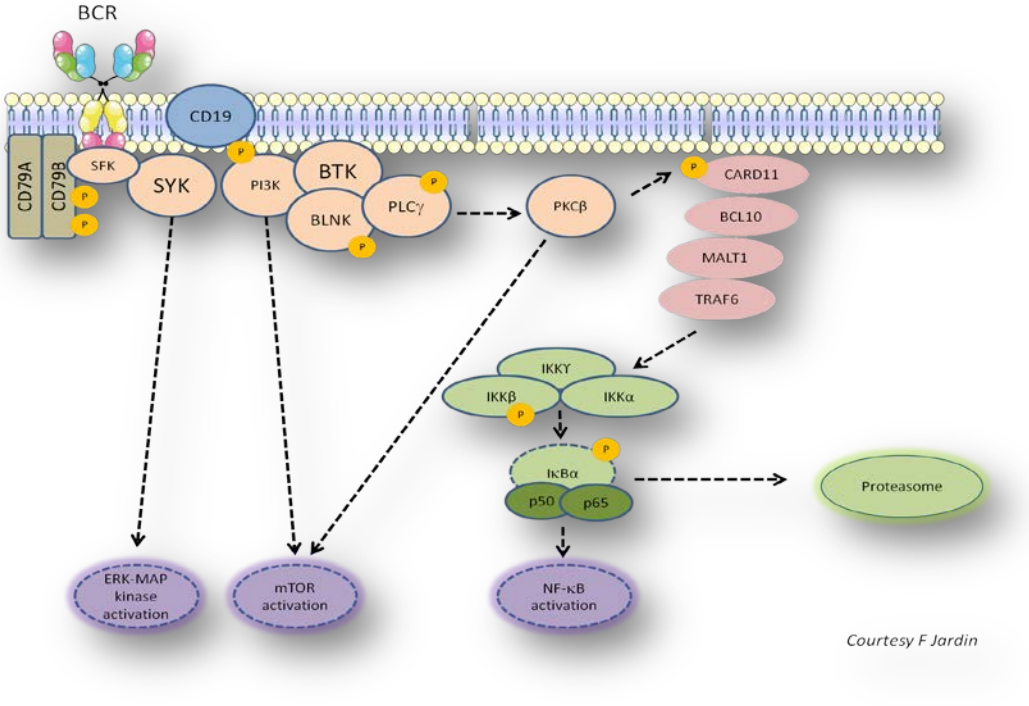
Josting A et al. JCO 2005

New Antibodies and Molecules
in Hodgkin Lymphoma

- **Brentuximab Vedotin (anti-CD30 ADC)**
- **AFM13 (CD16/CD30 bispecific)**
- **Lenalidomide (IMID)**
- **Everolimus, (mTor-inhibitor)**
- **Rituximab, Ofatumumab (anti-CD20)**
- **Panobinostat, Mocitinostat (H-DAC inhibitors)**

- **TKI´s, JAK2i, PARPi**
- **PD-1 inhibitors**

New treatment targeted modalities
Target signaling pathways



BCR signature:

- **SYK**
- **PI3K: idelalisib**
- **PKC-β: enzastaurin**
- **BTK: ibrutinib**
- **PKi: dasatinib**
- **mTOR: everolimus**

BCL6 inhibitors
Proteasome inhibitors
Apoptosis: ABT-199
IMIDS: lenalidomide
Others

Relapsed and refractory lymphoma

- Prognosis of r&r lymphoma still to be improved
- DHAP or other reinduction followed by BEAM and autologous TX standard in relapsed lymphoma
- Intensification of chemotherapy not helpful (HDR2)
- Anti-CD30 ADC BV effective and well tolerated; currently being evaluated in combination with chemo and other drugs
- Anti-PD1´s represent a new class of drugs showing very promising activity in r/r lymphoma
- Can new drugs replace radio- or chemotherapy in lymphoma?


Recruiting Centers (n=320)
+ Radiotherapists (n=80)
+ Follow- Up (n=328)
More Information
www.ghsg.org
Thank you for your attention!
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Image © 2008 GeoContent
© 2008 Europa Technologies
© 2008 Cnes/Spot Image
Google
50°19'23.63" N 10°56'50.73" E
Sichthöhe 1127.37 km


Save The Date * Gürzenich, Cologne
October
22–25
2016
ISHL 10
www.hodgkinsymposium.org
GHSG
www.ghsg.org

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Classical Hodgkin Lymphoma
Radiotherapy volumes, doses and techniques

Umberto Ricardi

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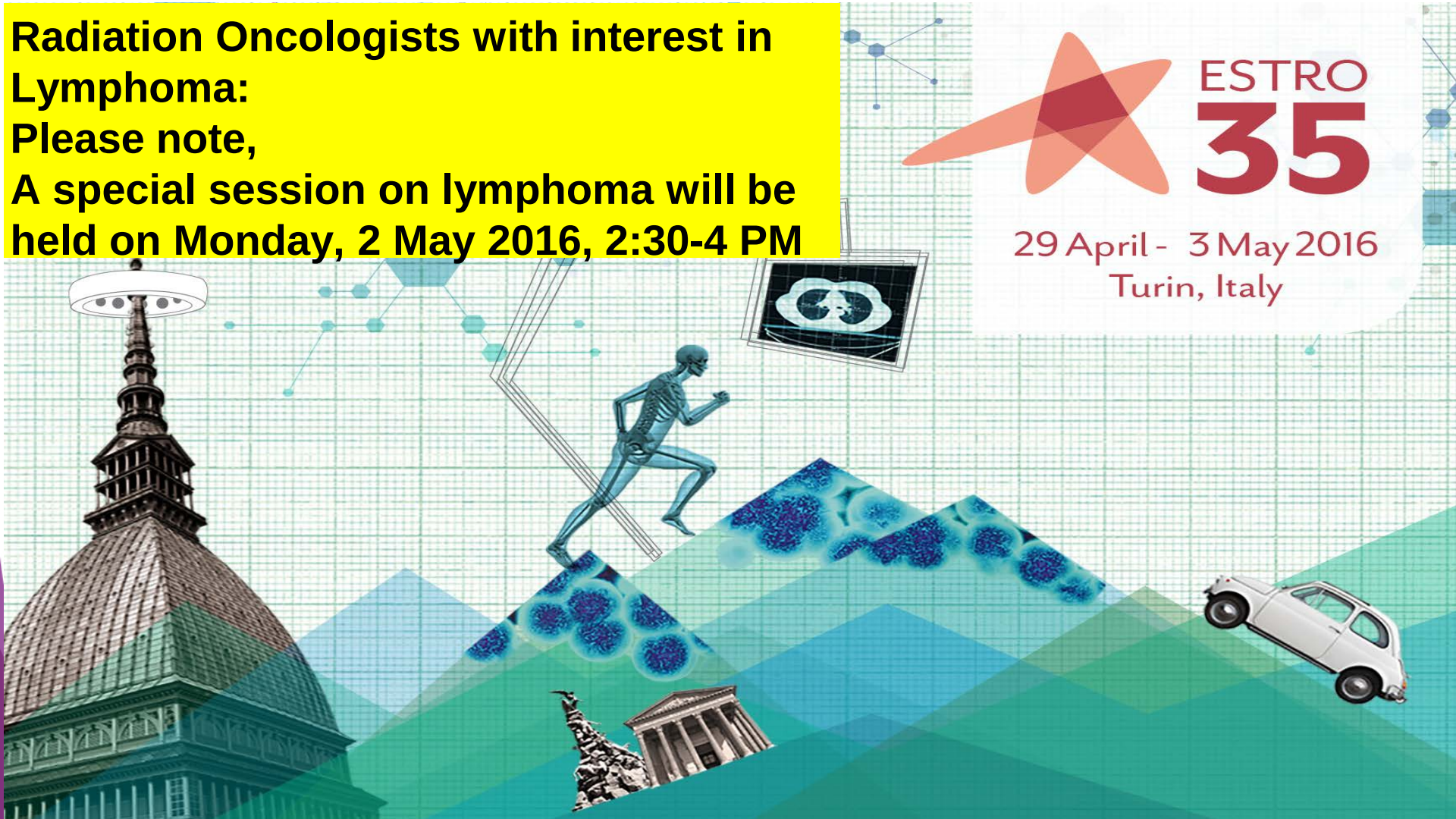
Radiation Oncologists with interest in Lymphoma:
Please note,
A special session on lymphoma will be held on Monday, 2 May 2016, 2:30-4 PM



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

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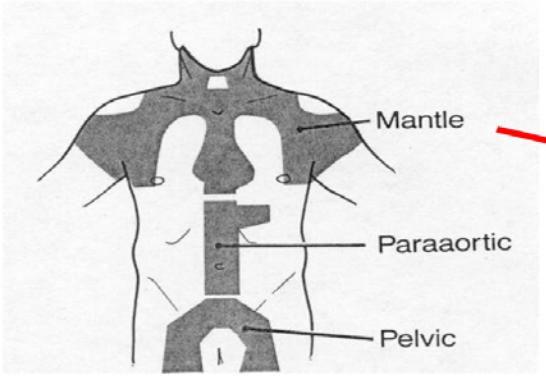
RT in classical Hodgkin Lymphoma

- It is of paramount importance in the delivery of RT to maintain high rates of long-term local control while minimizing radiation exposure to surrounding normal tissues

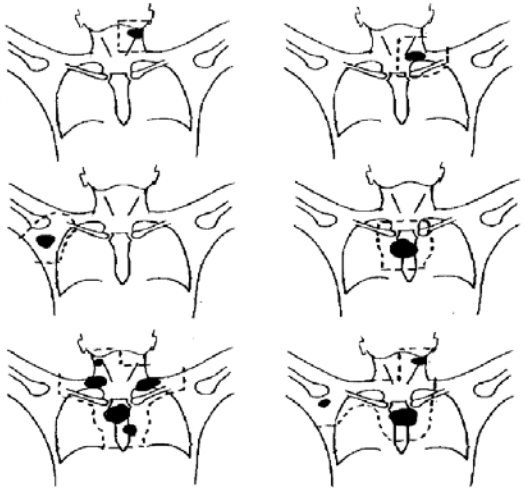
- Furthermore, it is recognized that most recurrences in patients treated for HL occur in sites of previous involvement, and that RT reduces local recurrence

Radiotherapy for Hodgkin lymphoma:
from sole curative treatment to component in combined modality treatment (i.e. no prophylactic radiotherapy for microscopic disease)

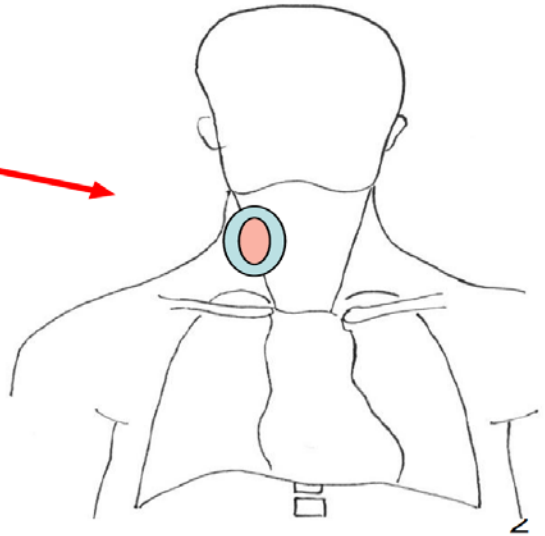
EFRT



IFRT

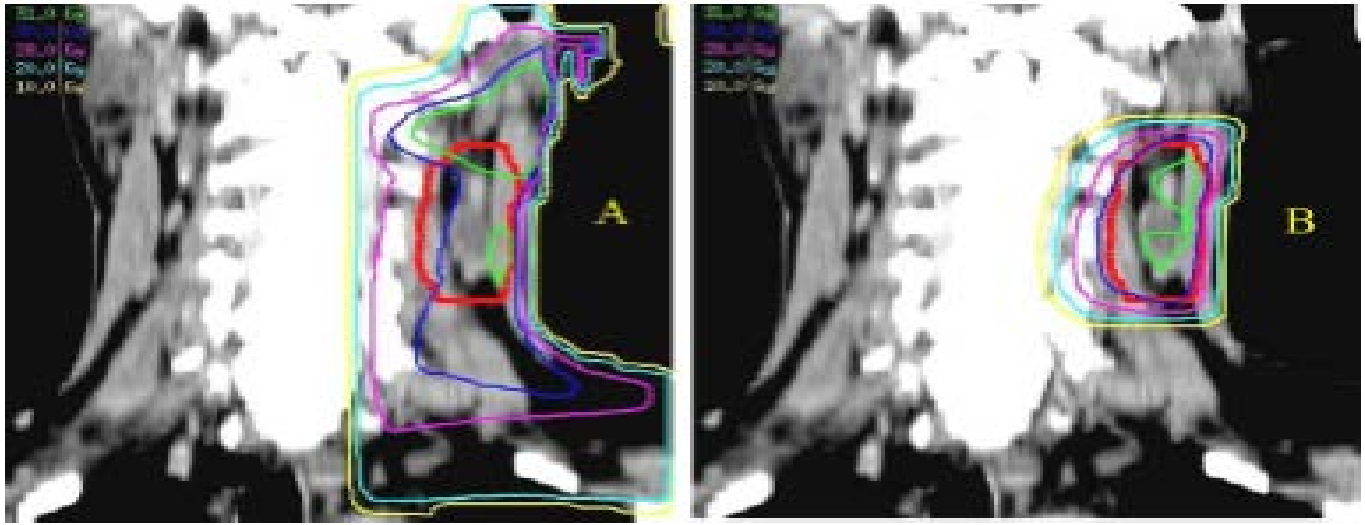


INRT



In the era of combined modality treatment, bigger (radiation fields) is not better !

From IFRT to INRT



•The concept of **IF-RT** which included the whole initially involved lymph node region can now be replaced by the concept of **involved-node RT**, which only includes the initially involved lymph node(s)

RT in classical Hodgkin Lymphoma

- Advances in imaging, treatment planning, treatment delivery, enable irradiation of new volumes with great precision

- The current guidelines for involved field RT based on anatomic landmarks and encompassing adjacent uninvolved lymph nodes are no longer appropriate for modern and more “targeted” RT delivery

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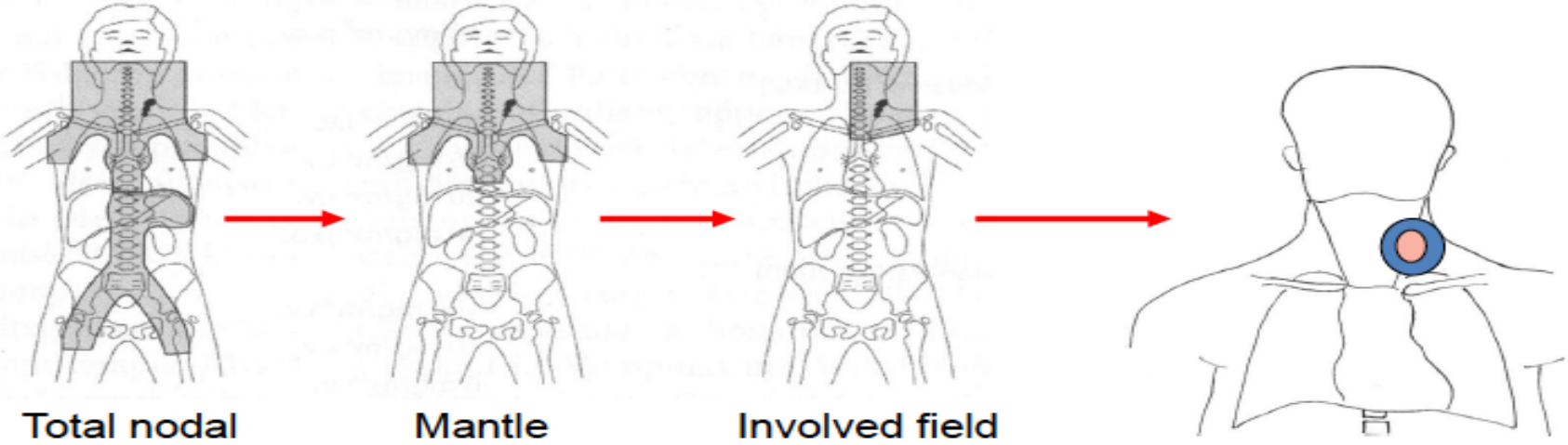
Development of RT volumes



Total nodal Mantle Involved field

2D planning, based on bony landmarks

Involved node

3D planning, based on lymphoma volume

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

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EDITORIAL

The Red Journal's Top Downloads of 2014

Anthony Zietman, MD, FASTRO, *Editor-in-Chief*

Received May 13, 2015. Accepted for publication May 13, 2015.

Table 1 The Red Journal's top downloads of 2014

Rank	Year	Article	Reference
1	2014	Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG)	(15)
2	2014	The Tumor Radiobiology of SRS and SBRT: Are More Than the 5 Rs Involved?	(19)
3	2014	Society of Surgical Oncology-American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer	(17)
4	2014	Modern Radiation Therapy for Nodal Non-Hodgkin Lymphoma-Target Definition and Dose Guidelines From the International Lymphoma Radiation Oncology Group	(16)
5	2014	Final Results of Local-Regional Control and Late Toxicity of RTOG 9003: A Randomized Trial of Altered Fractionation Radiation for Locally Advanced Head and Neck Cancer	(20)
6	2008	Development and Validation of a Standardized Method for Contouring the Brachial Plexus: Preliminary Dosimetric Analysis Among Patients Treated With IMRT for Head-and-Neck Cancer	(10)
7	2011	Consensus Guidelines for Delineation of Clinical Target Volume for Intensity Modulated Pelvic Radiotherapy for the Definitive Treatment of Cervix Cancer	(11)
8	2010	Use of Normal Tissue Complication Probability Models in the Clinic	(9)
9	2004	Review of epidermal growth factor receptor biology	(6)
10	2011	Palliative Radiotherapy for Bone Metastases: An ASTRO Evidence-Based Guideline	(25)

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Treatment Volume Principles

- Modern RT planning in lymphoma incorporates the current concepts of volume determination as outlined by ICRU Report 83
- It is based on defining a gross tumor volume (GTV) and a clinical target volume (CTV), that is expanded to a planning target volume (PTV)
- The PTV is then used to define beam coverage
- This approach allows direct comparison with the diagnostic 3D-imaging, increasing the accuracy with which lymph node volumes are defined

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RT Planning for Lymphomas

- **Role of imaging in radiation planning**
  - 3D imaging (with CT supplemented by functional imaging: PET-CT)
  - The use of diagnostic contrast-enhanced CT is recommended to help to delineate nodal stations and differentiate nodes from vessels
  - Ideally, imaging studies with the patient in the treatment position and using the planned immobilization devices
  - Acquiring high-quality imaging is fundamental to high-quality RT planning

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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)

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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

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Internal target volume (ITV) (ICRU 83)

- Defined in ICRU 62, optional in ICRU 83
- CTV + margin for uncertainties in size, shape, and position of the CTV
- Mostly relevant when the target is moving (chest and upper abdomen)
- Margins may be obtained from 4-D CT, fluoroscopy or from expert clinician
- Margins should be added quadratically: $\sigma' = \sqrt{(\sigma^2_m + \sigma^2_s)}$

Equation for right-angled triangle

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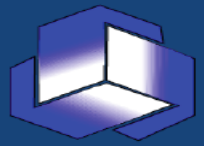
Planning target volume (PTV) (ICRU 83)

- Accounts for set-up uncertainties in patient position and beam alignment during planning and through all treatment sessions
- Function of immobilization device, body site, and patient cooperation
- Geometrical concept introduced to ensure that CTV and/or ITV are properly covered
- Applied by clinician or treatment planner

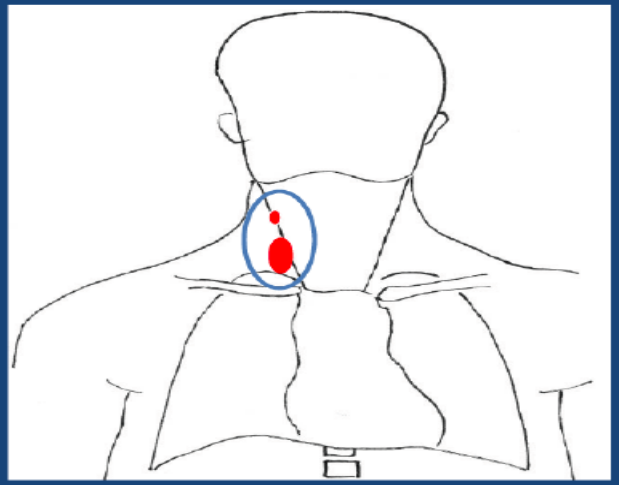
The concepts of INRT and ISRT

EORTC-GELA Lymphoma Group Guidelines



”Involved node radiotherapy”

INRT



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

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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

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INRT: guidelines 2008

- FDG-PET scans have to be meticulously analysed to detect lymph nodes that were overlooked on CT imaging (CT assessment can be extremely difficult)
- Any morphological and/or functional asymmetry has to be taken into account
- A decrease in size or the disappearance of initially visible lymph nodes on the pre-CT scan as compared to the POST-CT scan should be considered as surrogate proof of initial involvement
- All the radiological procedures should be performed on patients in the treatment position for proper coregistration
- It is highly advisable that all CT and/or CT/PET scans should be performed with IV contrast

Girinsky T, R&O 2008

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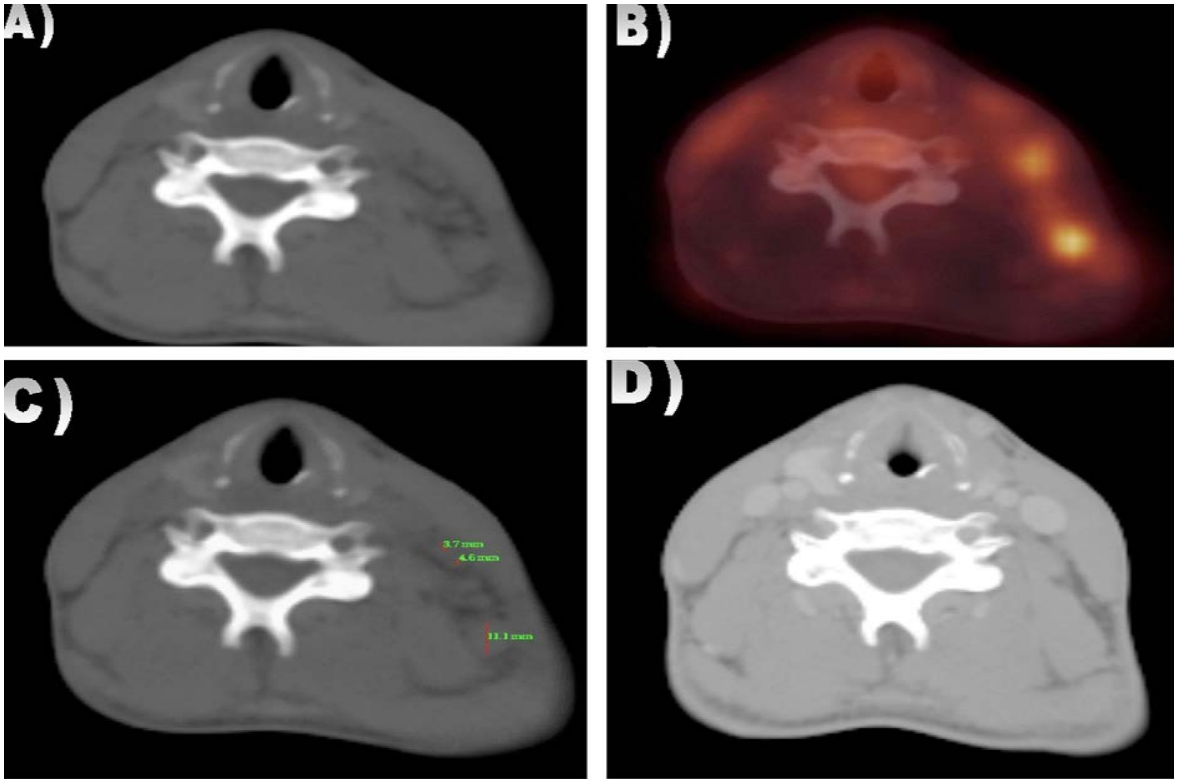
Assessment of initial lymph node involvement



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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

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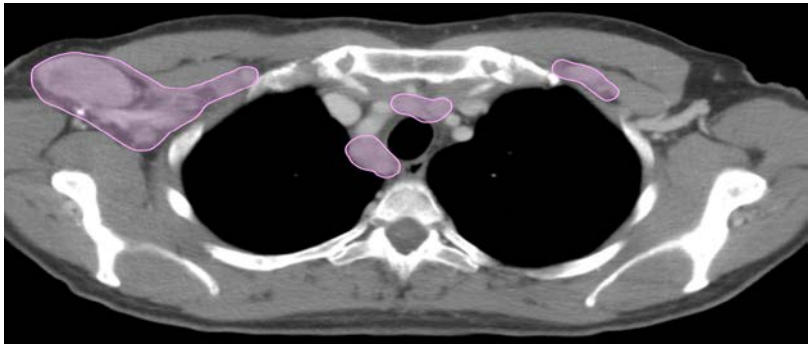
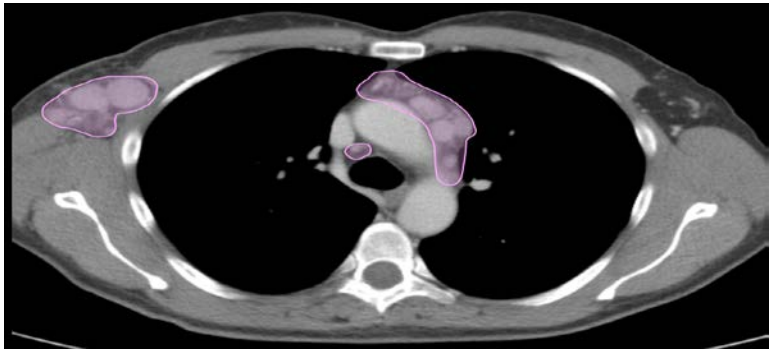
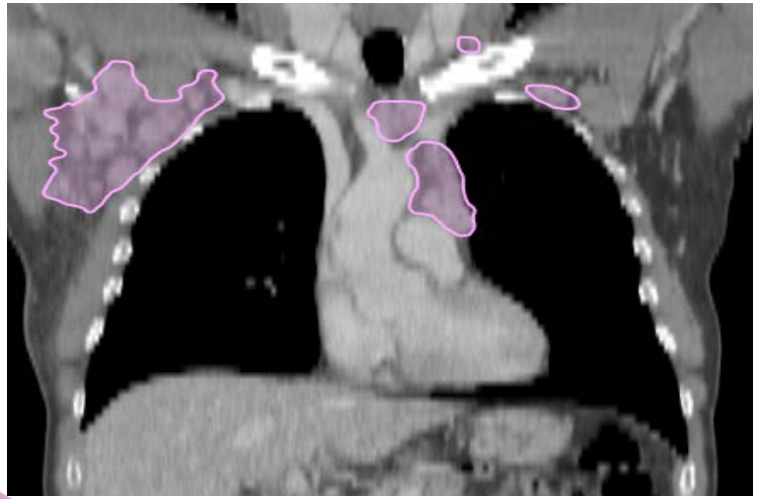
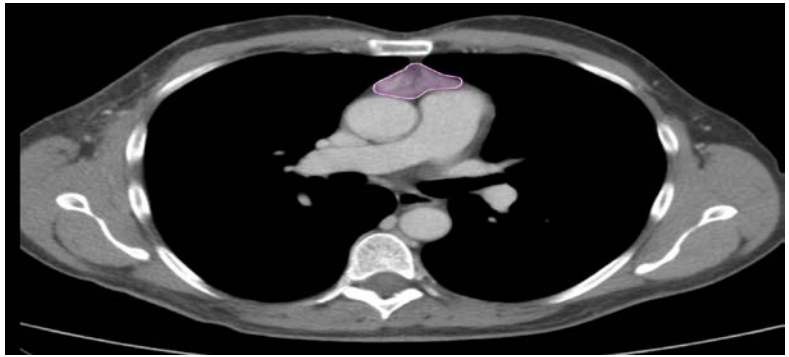
GTV on pre-chemotherapy CT









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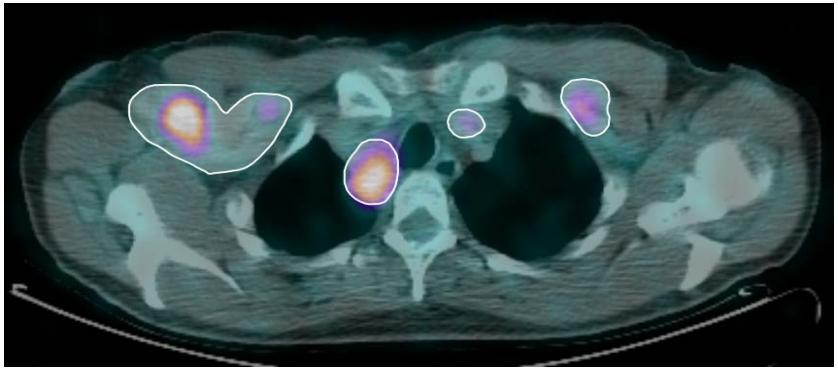
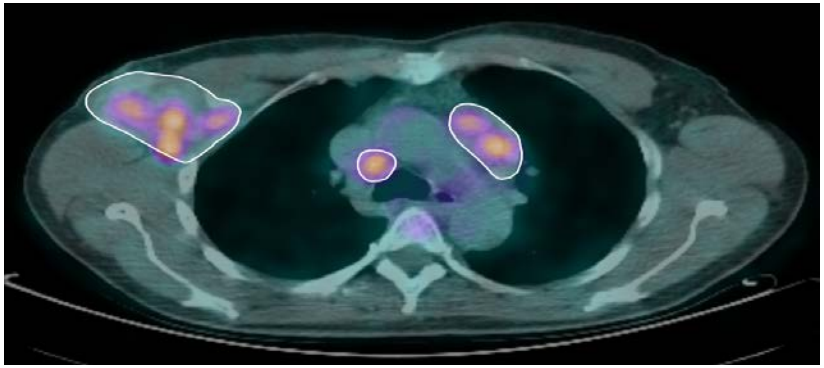
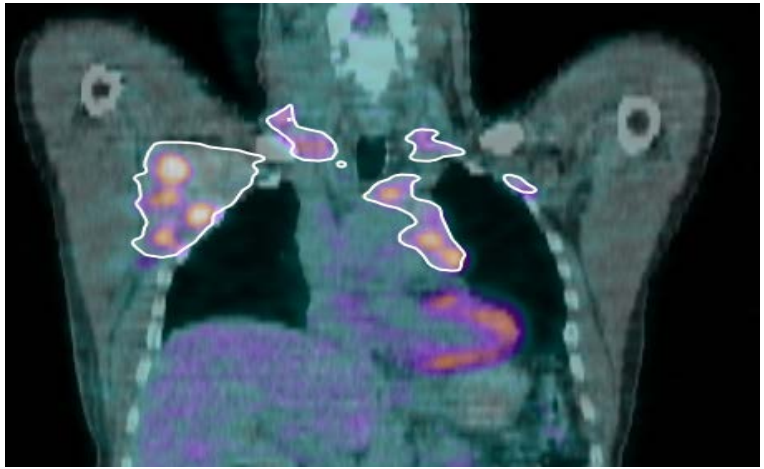
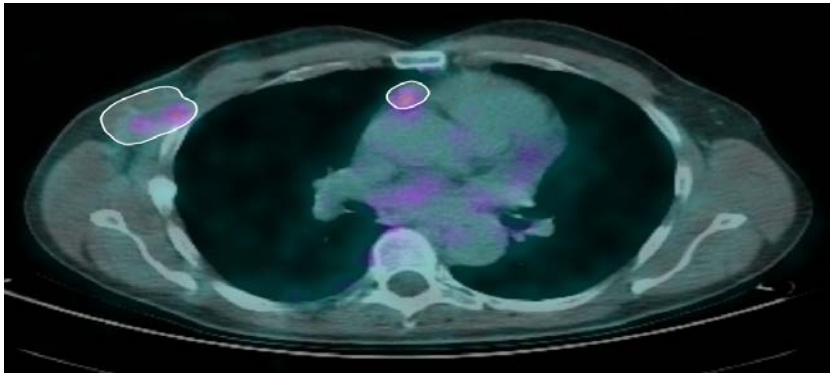
GTV on pre-chemotherapy PET









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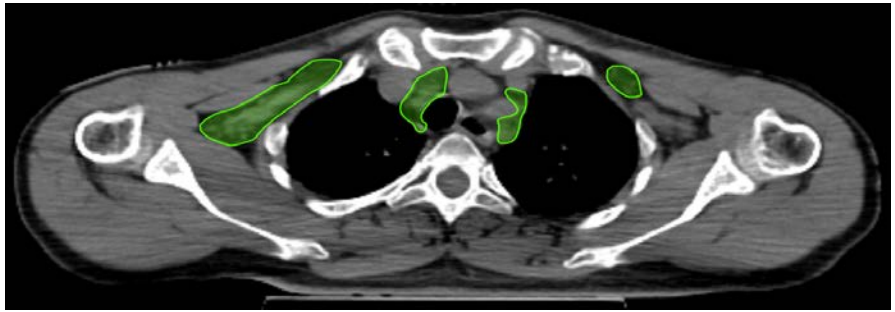
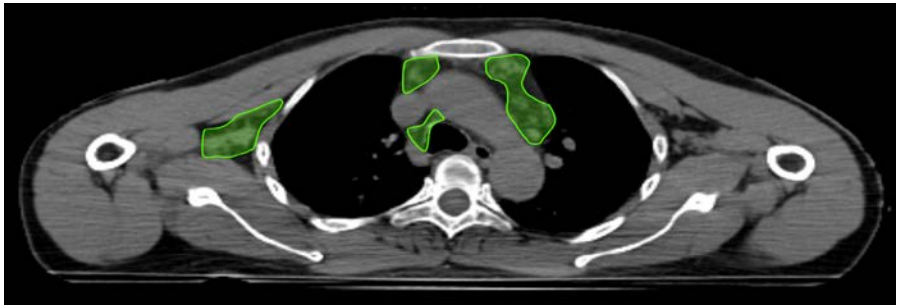
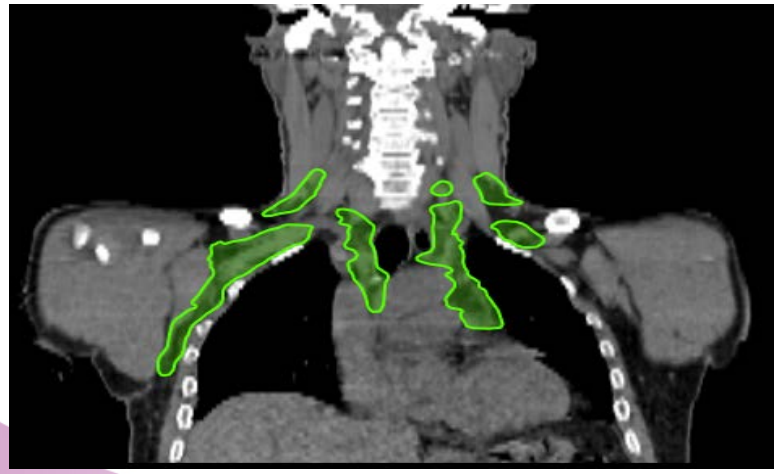
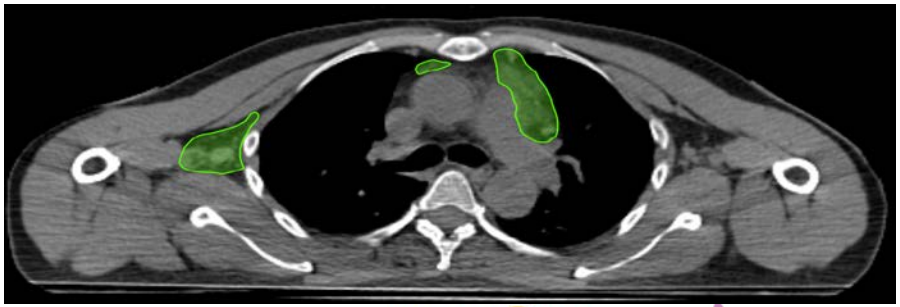
GTV_{CT} and GTV_{PET} import on planning CT→ CTV definition by modifying GTVs according to response and normal tissues displacement → **INRT**









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If prechemotherapy imaging is not optimal…

Involved Site Radiotherapy

ISRT vs INRT

- In both INRT and ISRT, the prechemotherapy GTV determines the CTV, and the irradiated volume is significantly smaller than with IFRT
- However, ISRT accomomodates cases in which optimal prechemotherapy imaging is not available to the radiation oncologist
- In these situations, it is not possible to reduce the CTV to the same extent as with INRT, because the prechemotherapy GTV information may not be optimal
- In ISRT, clinical judgment in conjunction with the best available imaging is used to contour a larger CTV that will be accommodate the uncertainties in defining the prechemotherapy GTV

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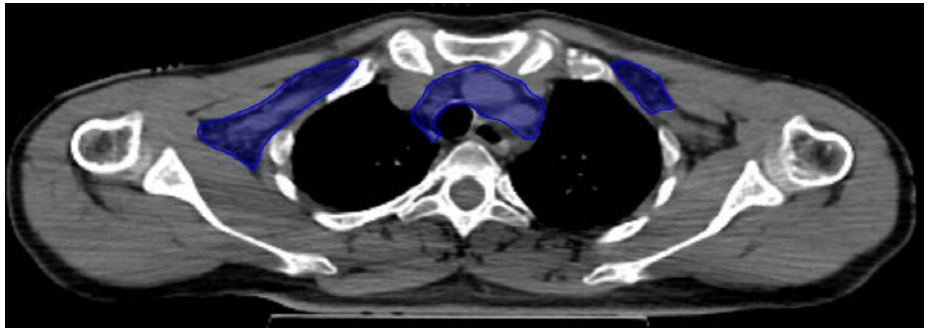
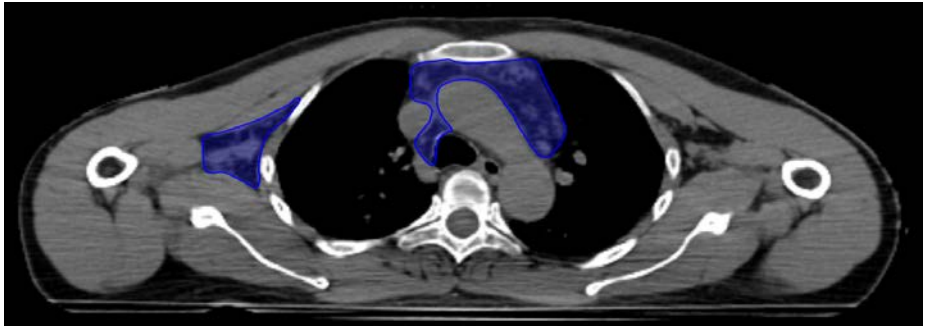
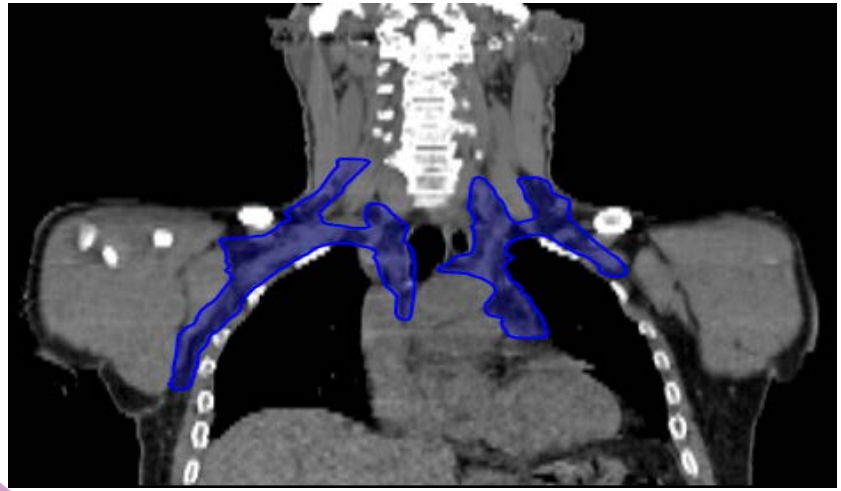
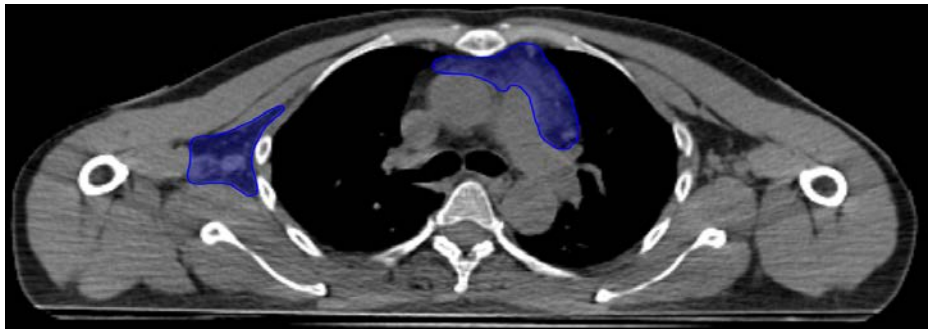
ISRT









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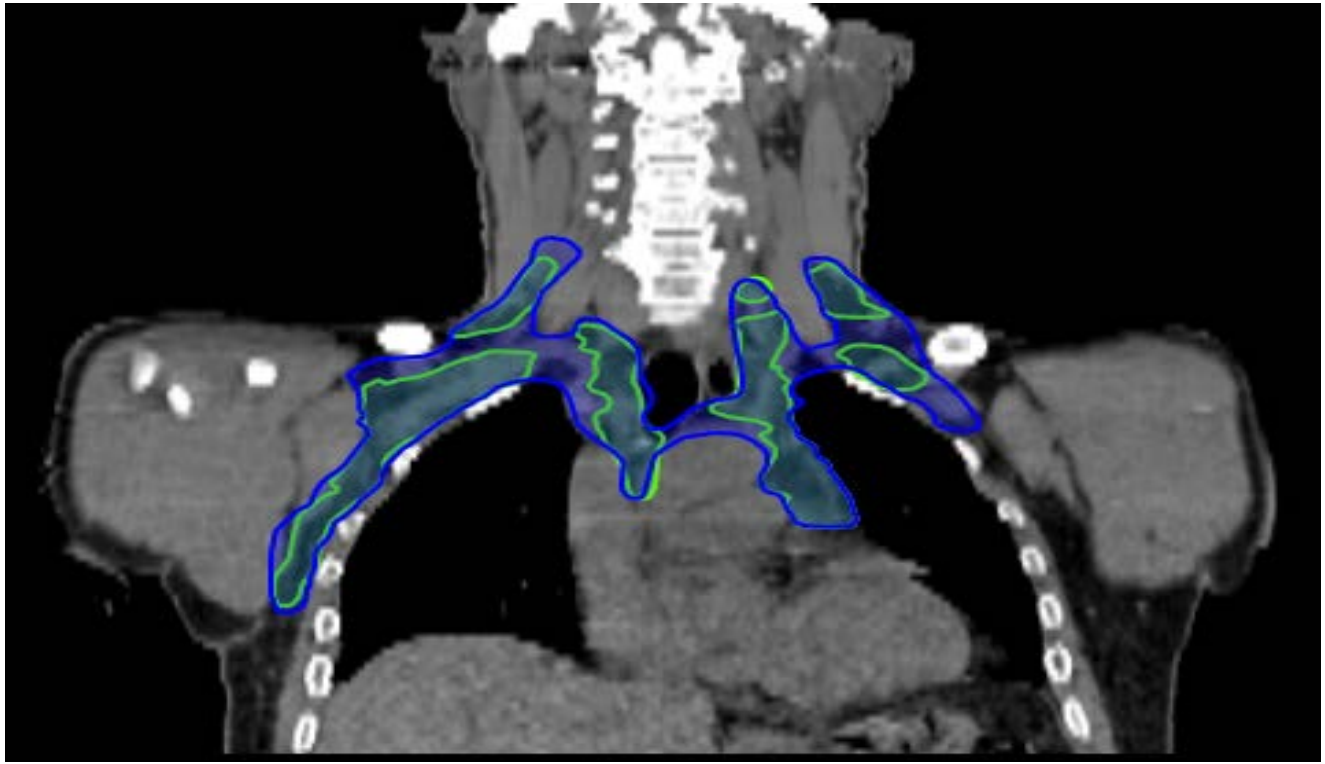
INRT vs ISRT



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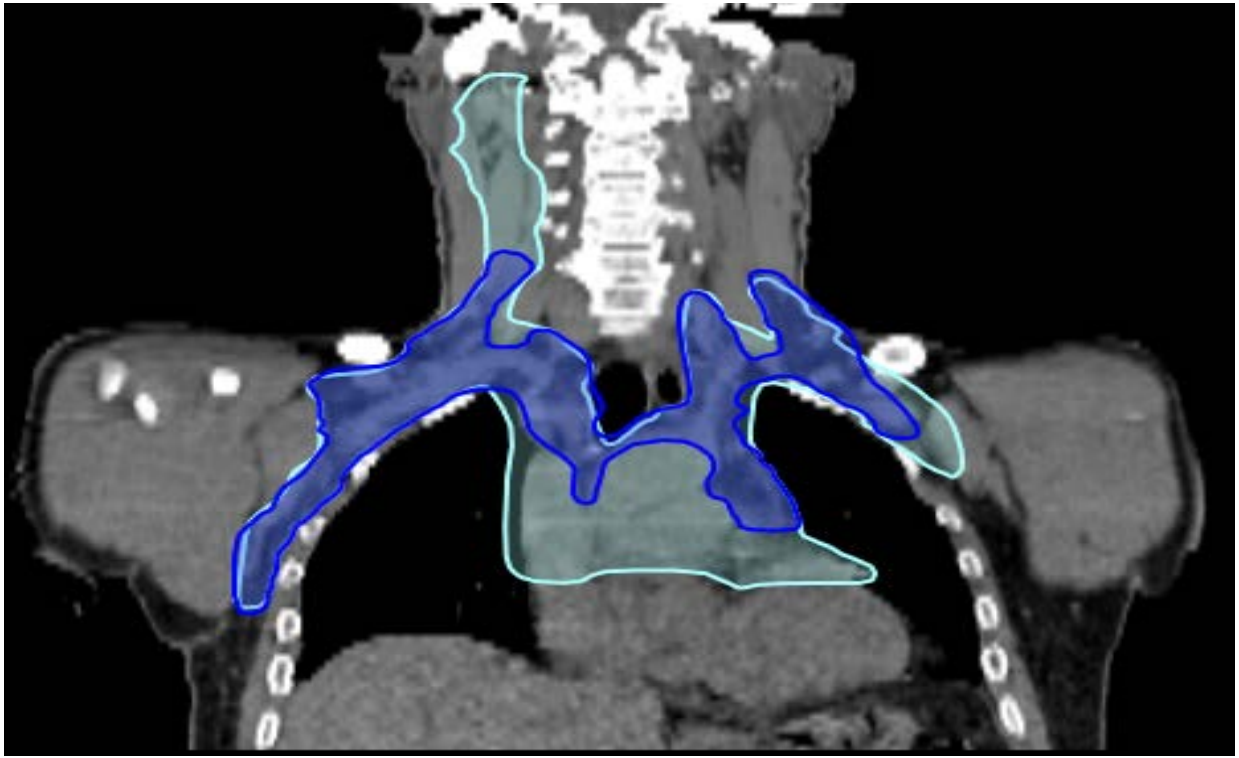
ISRT vs IFRT



In most situations, ISRT will include significantly smaller volumes than IFRT

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Guidelines

Int J Radiation Oncol Biol Phys, Vol. 92, No. 1, pp. 40–45, 2015

Expert Radiation Oncologist Interpretations of Involved-Site Radiation Therapy Guidelines in the Management of Hodgkin Lymphoma

Bradford S. Hoppe, MD, MPH,* and Richard T. Hoppe, MD†

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

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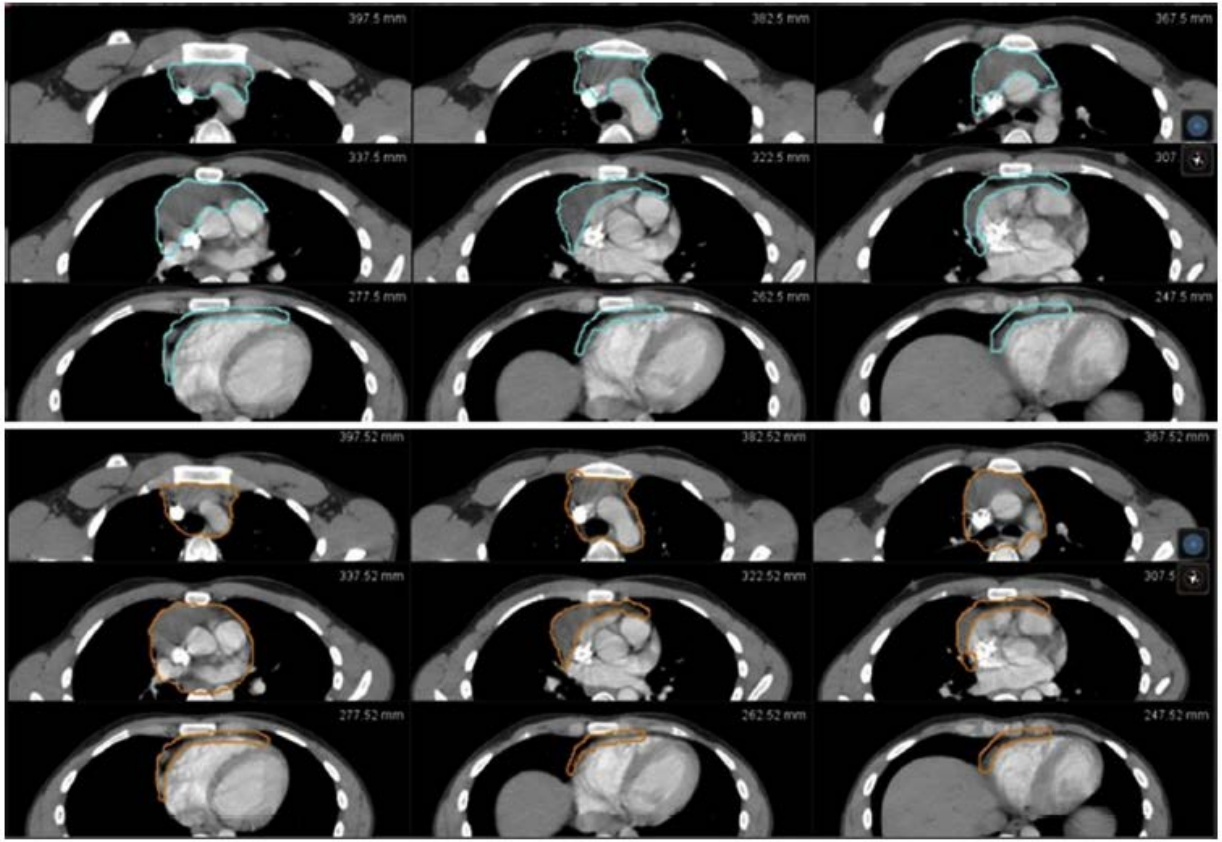


Fig. 2. For this question, respondents were asked to choose the contour in blue, which included only the initially involved nodes, or the contour in orange, which included the uninvolved subcarinal nodes.

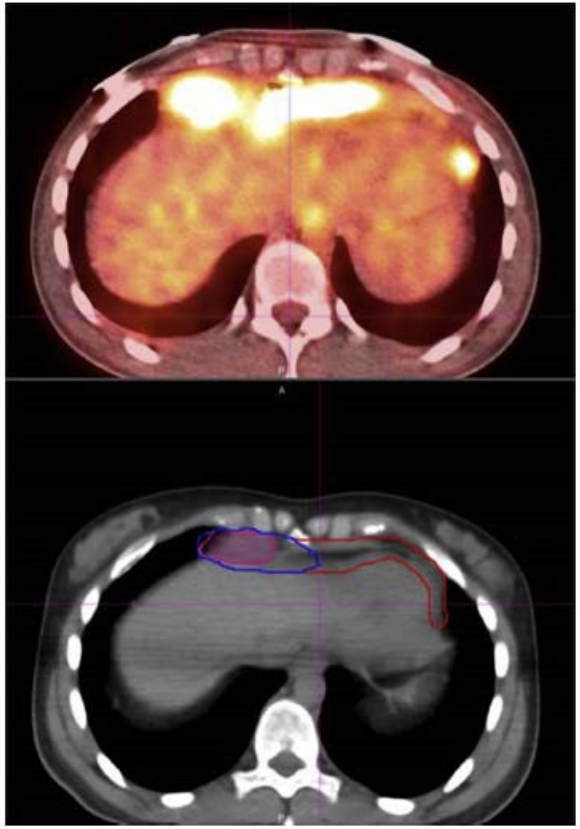


Fig. 3. For this question, respondents were asked to choose the contour in blue, which included the area of postchemotherapy residual disease only (outlined in pink), or the contour in red, which included all of the nodes involved prior to chemotherapy.

Table 1 Survey results

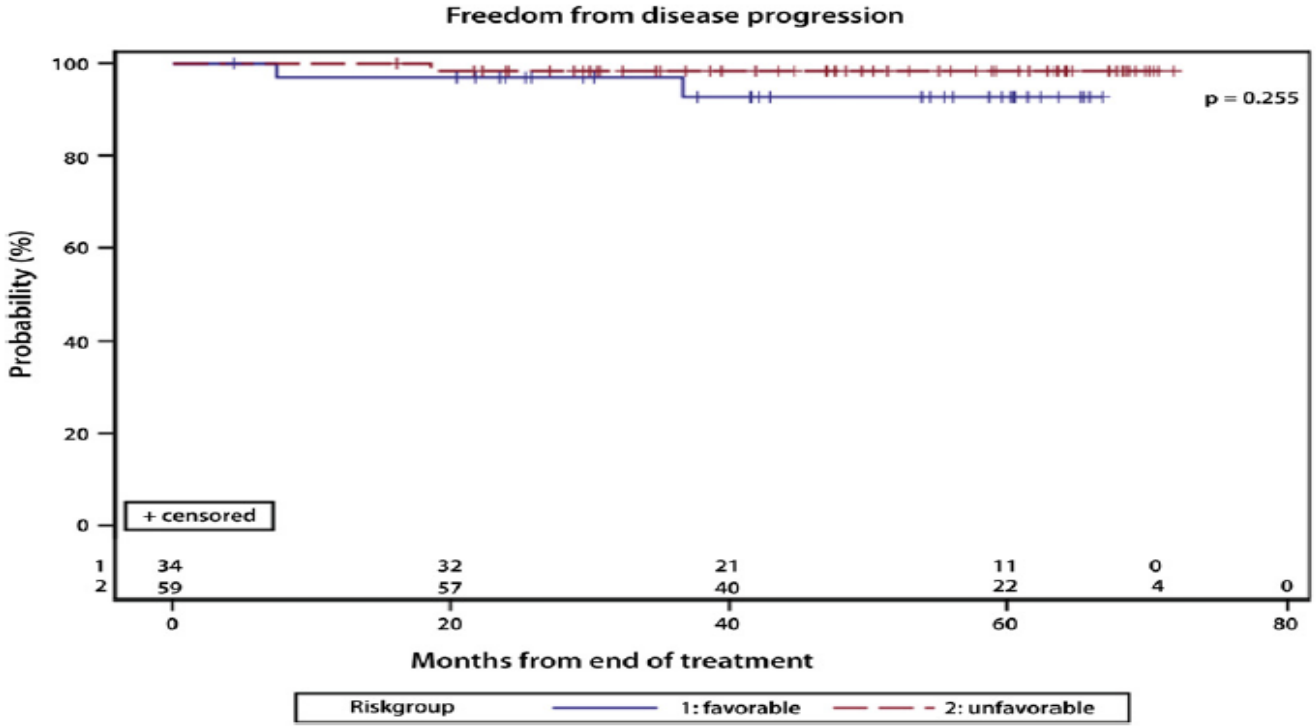
Clinical scenario	Question	% of respondents who chose		
		A	B	Other
1	1	60	35	5
2	2	63	32	5
3	3	28	67	6
	4	67	28	6
4	5	11	89	0
5	6	56	28	17
	7	100	0	0
6	8	72	28	0
7	9	17	67	17

Education and guidelines needed !!!

Conclusions: Even among expert radiation oncologists, interpretation of ISRT guidelines is variable. Further guidance for ISRT field design will be needed to reduce variability among practicing physicians.

Do we have clinical data on safety and efficacy of INRT/ISRT?

Combined Modality Therapy with INRT



Maraldo et al, IJROBP 2012

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

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

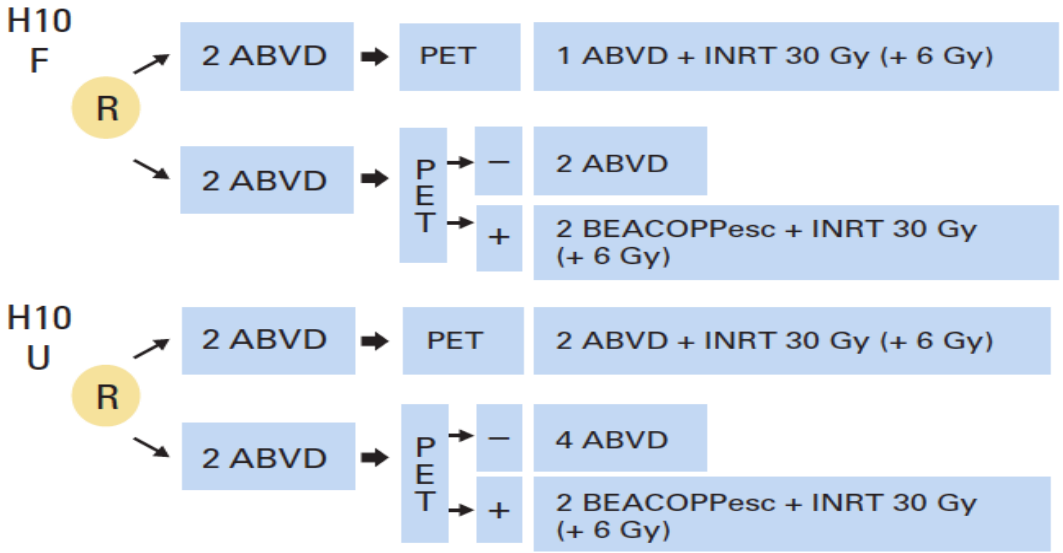


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Table 2. Results of Interim Analysis in Patients With Early PET-Negative Disease

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.

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Optimal radiation doses

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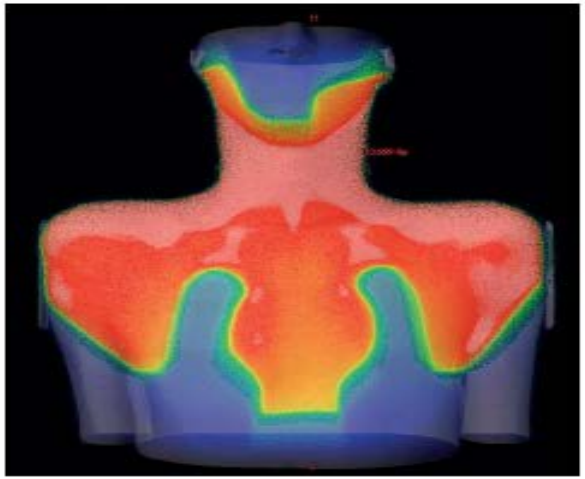
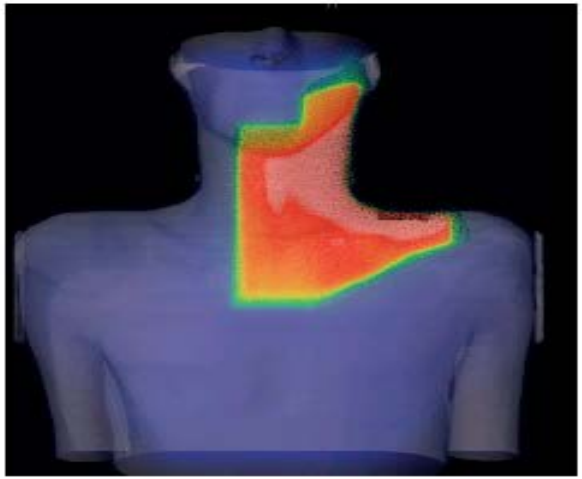
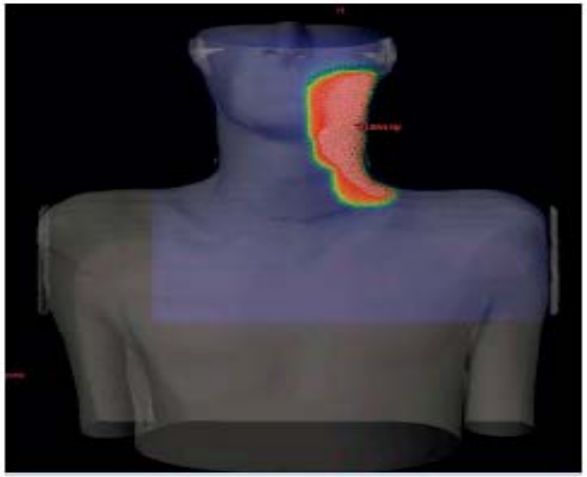
Mantle field, Involved field, Involved Node



40 Gy



30 Gy



20-30 Gy

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Radiation dose

- Early stage favourable: 20 Gy

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

- Early stage unfavourable: 30 Gy

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

	GHSG
Risk factors	a) Large mediastinal mass b) Extranodal disease c) ESR ≥ 50 without B-symptoms or ≥30 with B-symptoms d) ≥ 3 nodal areas
Favourable	CS I-II without risk factors
Unfavourable	CS I or CS IIA with ≥ 1 risk factors CS IIB with c) or d) but without a) and b)

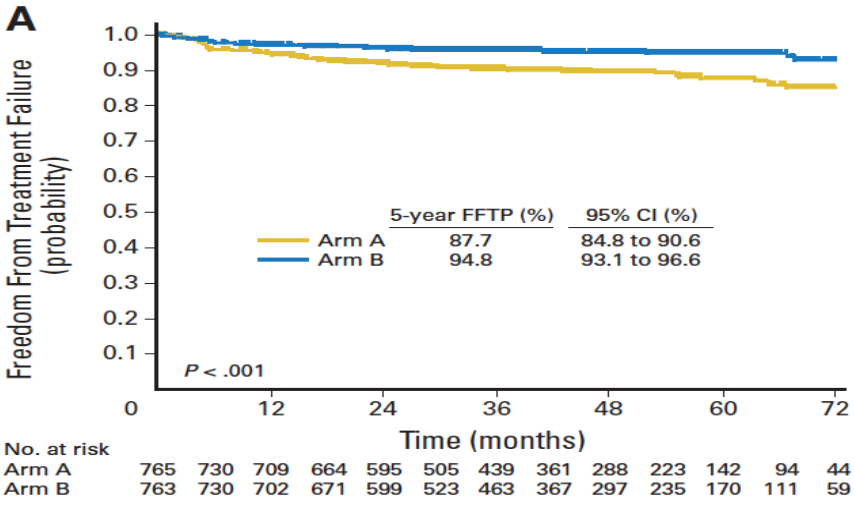
VOLUME 30 · NUMBER 9 · MARCH 20 2012

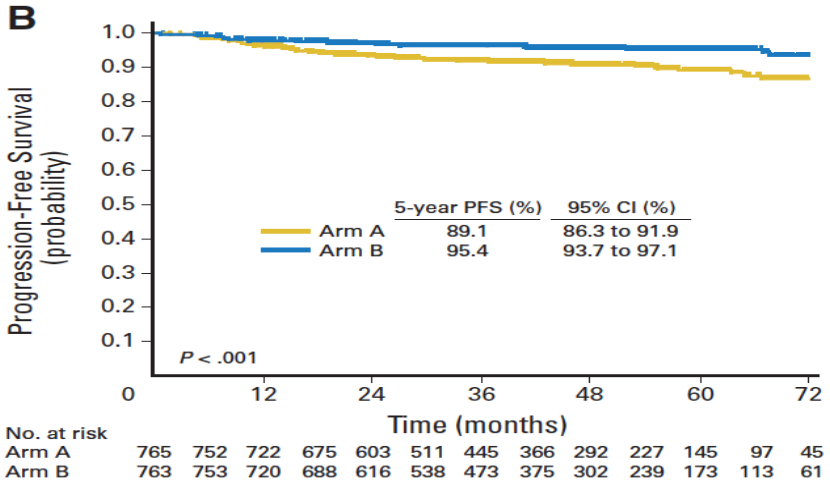
JOURNAL OF CLINICAL ONCOLOGY

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



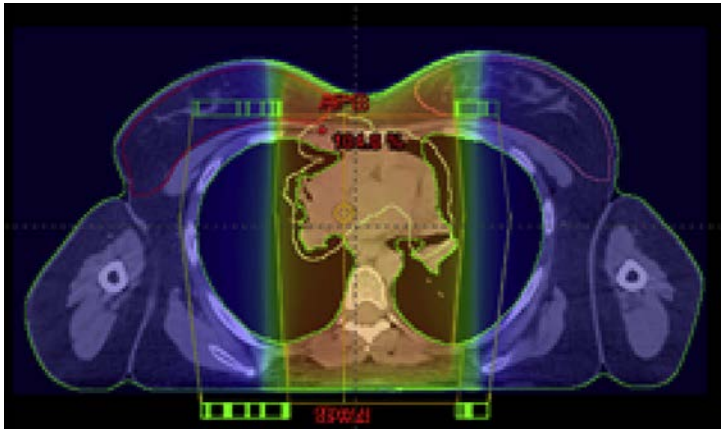


There was more acute toxicity associated with 2+2 than with ABVD, but there were no overall differences in treatment-related mortality or secondary malignancies

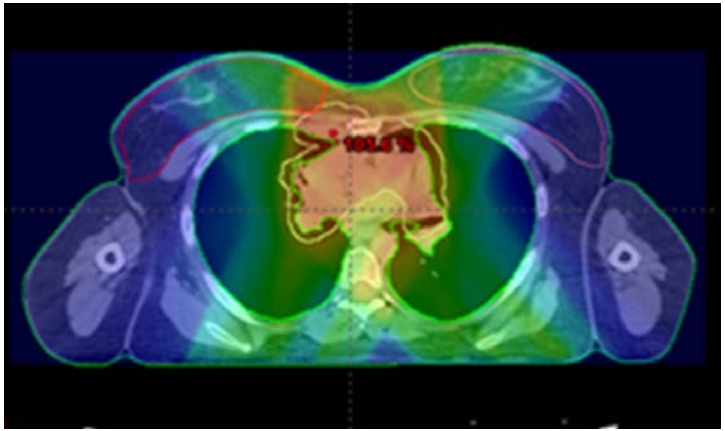
Radiotherapy Techniques

The treating radiation oncologist makes a clinical judgment as to which treatment technique to use, based on comparisons of treatment plans and DVHs with different techniques

3D conformal



IMRT technique



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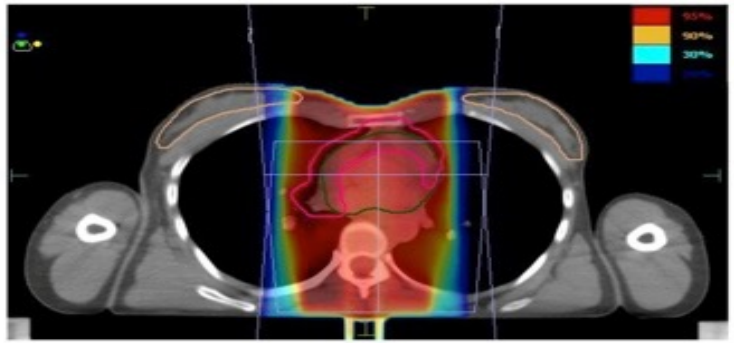
Dose constraints in lymphoma RT

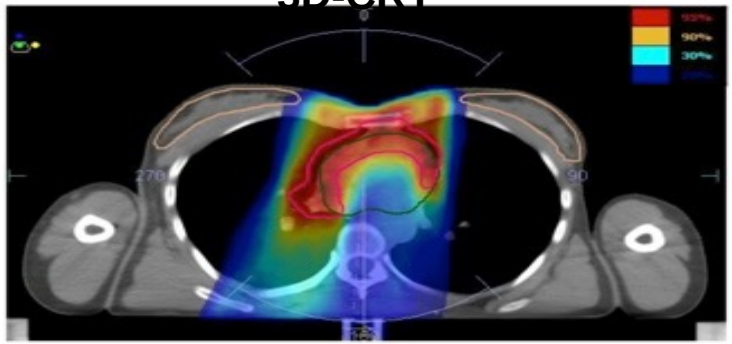
- The relatively low radiation doses needed result in most treatment plans being within the acceptable limits
- Even low doses to normal tissues, previously considered safe, may result in significant risks of morbidity and mortality in long-term survivors
- Doses to all normal structures should be kept as low as possible, but some structures are more critical than others

Highly conformal RT

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



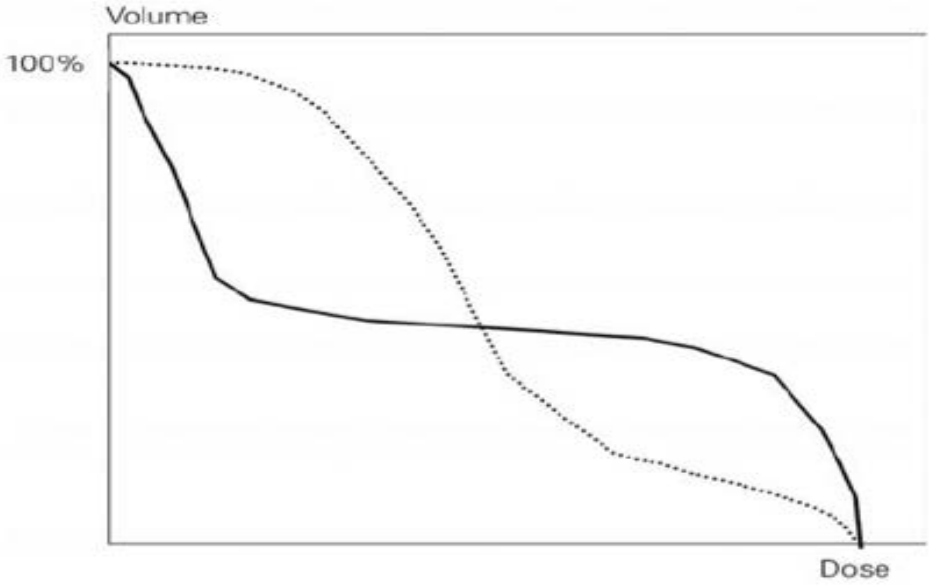
3D-CRT

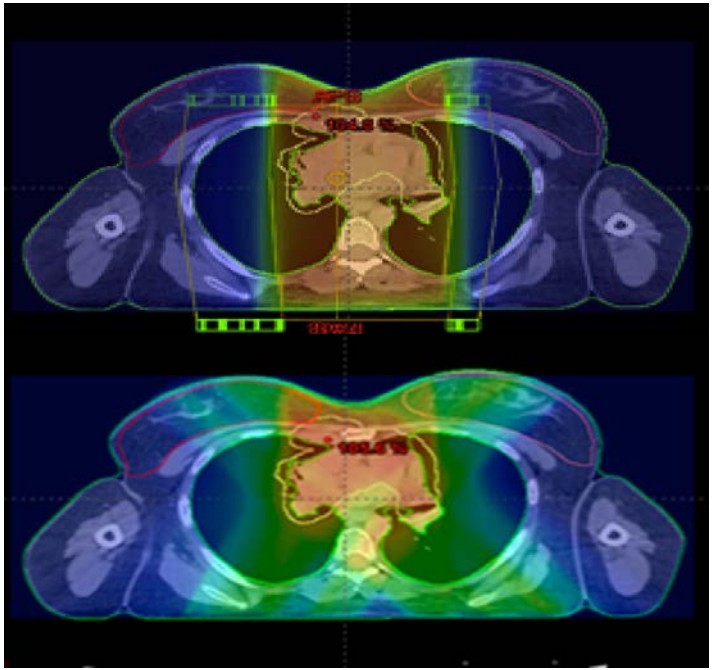


IMRT (VMAT)

A Little to a Lot or a Lot to a Little?

Better sparing of critical normal structures usually at the price of a larger total volume of normal tissue irradiated, albeit to a lower dose





IMRT vs 3D-CRT in lymphoma

- Several published studies investigated the dosimetric profiles of IMRT compared to those of 3D-CRT

- They showed significantly better PTV coverage (V_{90}, V_{95}, conformity index) and/or significantly better sparing effect for different OAR

  - both for the traditional IFRT and for the more recent concept of limited RT (INRT, ISRT)

IMRT in lymphoma RT

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

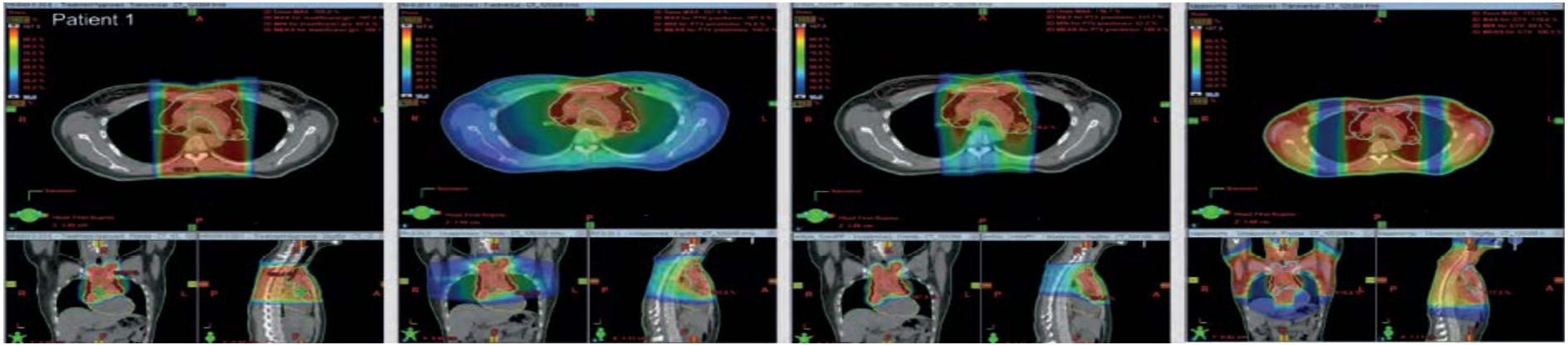
- Lower prescribed doses, generally well below tolerance dose of normal tissues
- Theoretical increased risk of geographic miss, as the dose gradients are steeper around the target volumes
- Fear of late effects secondary to low-dose exposure of larger volumes of healthy tissues

Estimated risk of cardiovascular disease and secondary cancers with modern highly conformal radiotherapy for early-stage mediastinal Hodgkin lymphoma

27 early stage mediastinal HL patients

Treatment: chemotherapy and INRT delivered as 3D CRT (30 Gy)

INRT	INRT	INRT	MF
3D-CRT 30 Gy	VMAT 30 Gy	PT 30 Gy	36 Gy



Maraldo et al., Ann Oncol, 2013

DEPARTMENT OF ONCOLOGY
UNIVERSITY OF TURIN

	3D CRT		VMAT		PT		MF		*P* value[a]			
										Pair-wise comparisons		
	Median	Range	Median	Range	Median	Range	Median	Range	all	3D CRT versus VMAT	3D CRT versus PT	VMAT versus PT
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)	<0.0001	0.528	0.0003	<0.0001
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)	<0.0001	0.854	0.012	0.0002
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)	<0.0001	0.843	0.001	<0.0001
Valvular disease (VD)	0	(0–0.2)	0	(0)	0	(0)	0.4	(0–3.7)	<0.0001	0.338	0.246	0.035
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)	<0.0001	<0.0001	0.0002	<0.0001
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)	<0.0001	0.003	0.002	<0.0001
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)	<0.0001	<0.0001	<0.0001	<0.0001

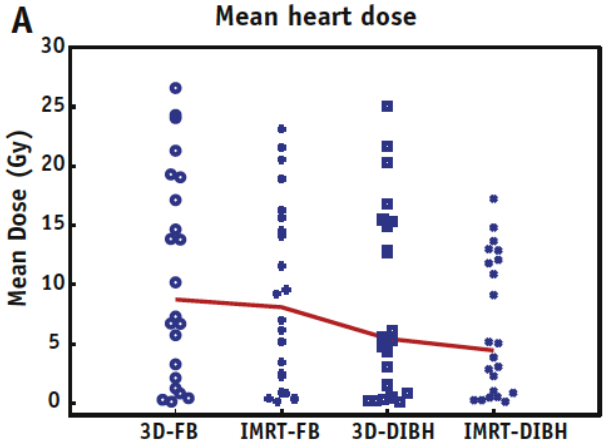
Maraldo et al., Ann Oncol, 2013

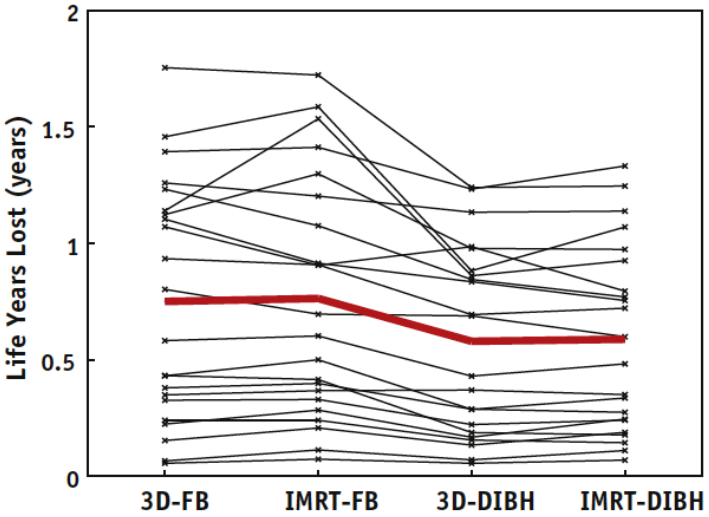
Clinical Investigation

Int J Radiation Oncol Biol Phys, Vol. 92, No. 1, pp. 169–174, 2015

Minimizing Late Effects for Patients With Mediastinal Hodgkin Lymphoma: Deep Inspiration Breath-Hold, IMRT, or Both?

Marianne C. Aznar, PhD,*,† Maja V. Maraldo, MD, PhD,* Deborah A. Schut, BSc,* Michael Lundemann, MSc,*,† N Patrik Brodin, PhD,*,‡ Ivan R. Vogelius, PhD,* Anne K. Berthelsen, MD, PhD,*,§ Lena Specht, MD, DSc,* and Peter M. Petersen, MD, PhD*





Cumulated life years lost including the risks of dying of myocardial infarction, lung cancer, breast cancer and thyroid cancer

Each black line represents 1 patient, and the thick red line represents the median over the whole series

Fiandra *et al. Radiation Oncology* 2012, **7**:186
http://www.ro-journal.com/content/7/1/186

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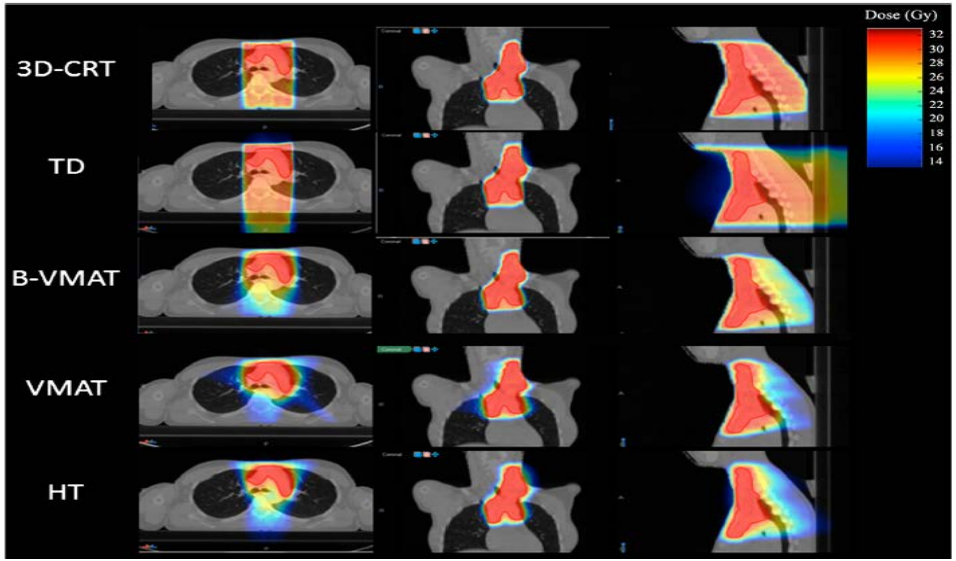
Different IMRT solutions vs. 3D-Conformal Radiotherapy in early stage Hodgkin's lymphoma: dosimetric comparison and clinical considerations

Christian Fiandra[1*], Andrea Riccardo Filippi[1], Paola Catuzzo[3], Angela Botticella[1], Patrizia Ciammella[1], Pierfrancesco Franco[2], Valeria Casanova Borca[3], Riccardo Ragona[1], Santi Tofani[3] and Umberto Ricardi[1]



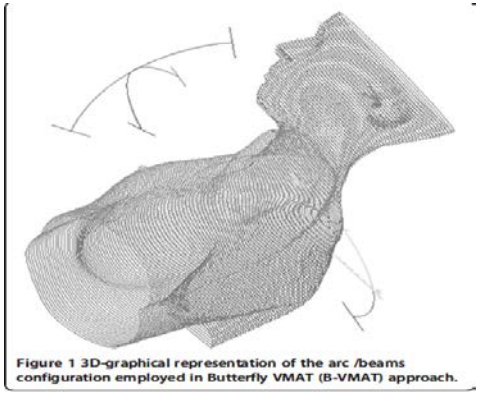
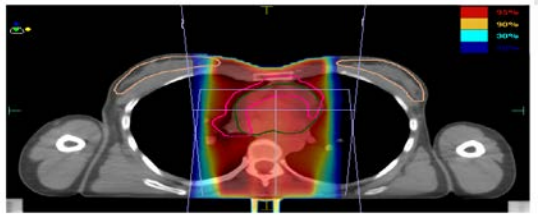
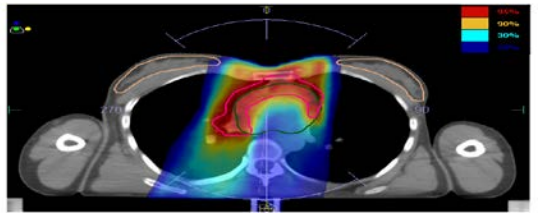


Figure 1 3D-graphical representation of the arc /beams configuration employed in Butterfly VMAT (B-VMAT) approach.





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Optimized Volumetric Modulated Arc Therapy Versus 3D-CRT for Early Stage Mediastinal Hodgkin Lymphoma Without Axillary Involvement: A Comparison of Second Cancers and Heart Disease Risk

Andrea Riccardo Filippi, MD,* Riccardo Ragona, MSc,* Cristina Piva, MD,* Davide Scafa, MD,* Christian Fiandra, MSc,* Marco Fusella, MSc,† Francesca Romana Giglioli, MSc,† Frank Lohr, MD,‡ and Umberto Ricardi, MD*

Int J Radiation Oncol Biol Phys, Vol. 92, No. 1, pp. 161–168, 2015

Table 1 Patient characteristics

Characteristic	n	%
No. of patients	38	
Age (y)		
Range	15-43	
Median	30	
Sex		
Male	13	34.2
Female	25	65.8
Ann Arbor stage		
I	8	21.1
II	30	78.9
Bulky	5	13.1
EORTC prognostic groups		
Favorable	16	42.1
Unfavorable	22	57.9
Involved sites		
Mediastinum alone	8	21.1
Mediastinum and unilateral neck	19	50
Mediastinum and bilateral neck	11	28.9

Abbreviation: EORTC = European Organization for Research and Treatment of Cancer.

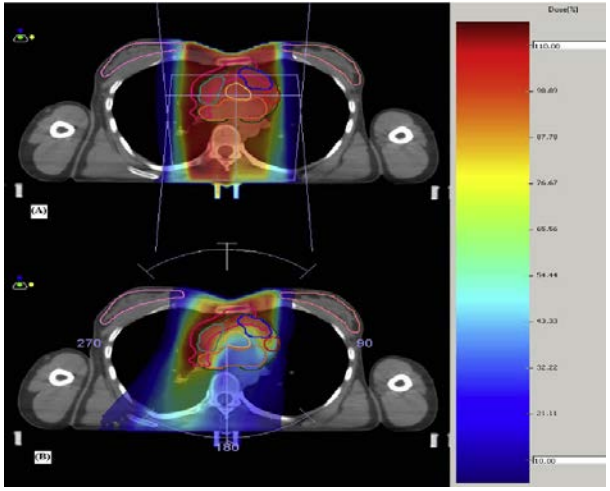

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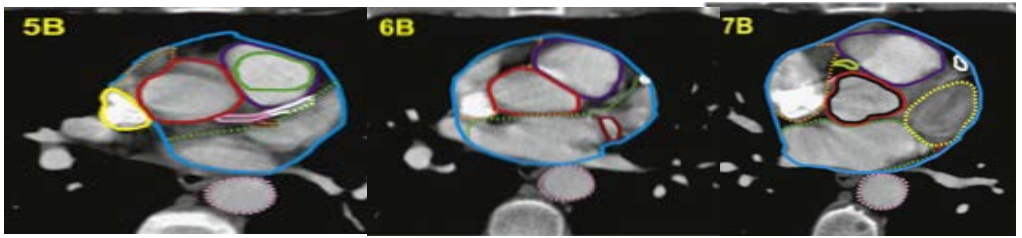
Table 3 Mean OED and SD for lung, breast, and thyroid cancer for all patients and according to HL presentation at diagnosis

Target	Mean OED and SD		*P* value
	3D-CRT	VMAT	
Lung			
All	2.16 ± 0.84	2.28 ± 0.73	.025
No neck	1.59 ± 0.73	1.91 ± 0.62	.001
Unilateral neck	2.31 ± 0.85	2.46 ± 0.81	.03
Bilateral neck	2.33 ± 0.76	2.22 ± 0.57	.23
Breast			
All	0.22 ± 0.15	0.22 ± 0.16	.72
No neck	0.17 ± 0.13	0.20 ± 0.13	.34
Unilateral neck	0.26 ± 0.18	0.25 ± 0.19	.88
Bilateral neck	0.20 ± 0.12	0.16 ± 0.09	.02
Thyroid			
All	3.29 ± 1.77	3.34 ± 1.75	.35
No neck	0.30 ± 0.16	0.41 ± 0.36	.29
Unilateral neck	3.65 ± 0.83	3.73 ± 0.81	.48
Bilateral neck	4.83 ± 0.62	4.83 ± 0.68	.94

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; HL = Hodgkin lymphoma; OED = organ equivalent dose; VMAT = volumetric modulated arc therapy.



Cardiac subunits: heart atlas (Feng, 2011)

Cardiovascular disease – Absolute Excess Risk (AER)

Table 4 AER for heart and valvular diseases for all patients and according to disease presentation

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

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; AER = absolute excess risk; VMAT = volumetric modulated arc therapy.

Data are means ± SD AER.

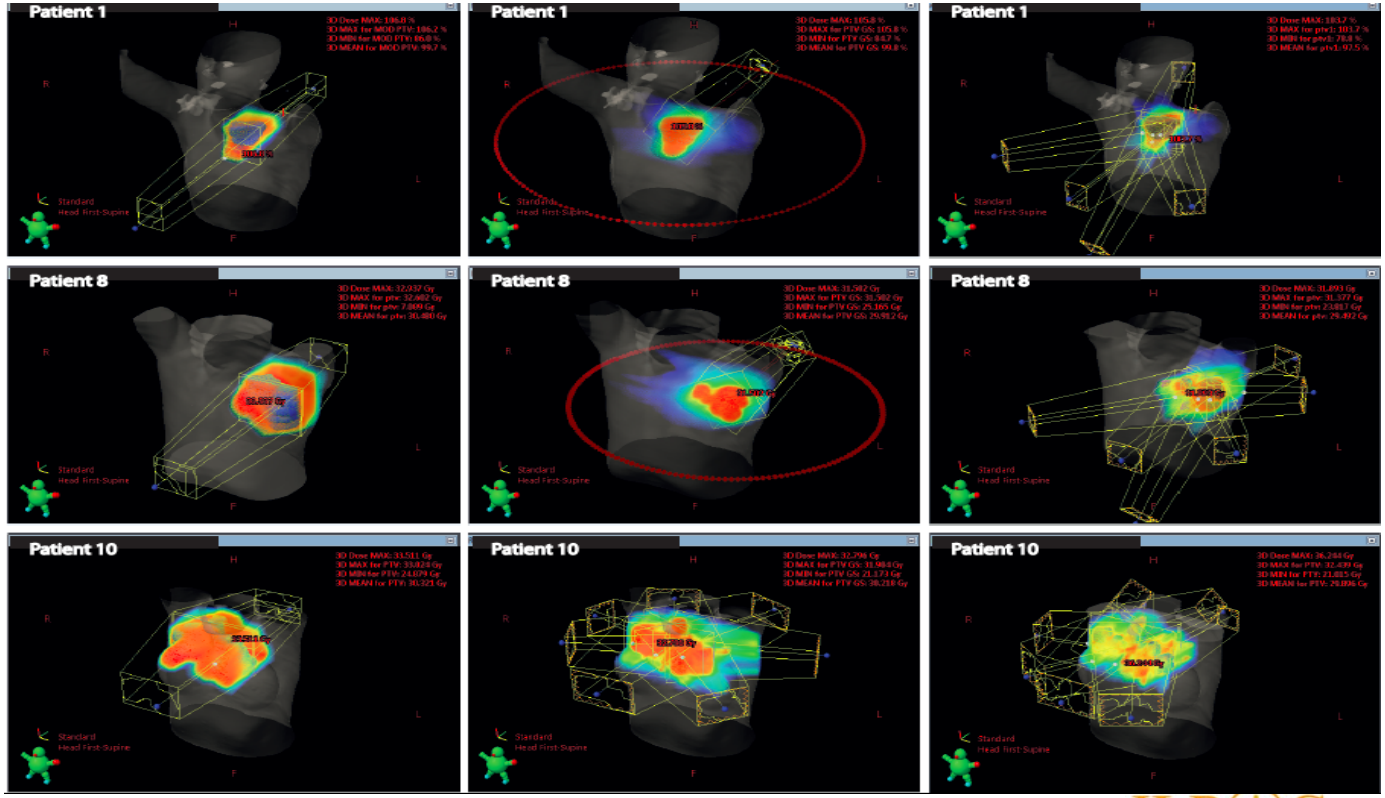
Which technique is preferable?

- There is no single proven best planning and delivery RT technique
- No two lymphomas are the same with regard to localization and extent of disease
- The decision should be made at the individual patient level (i.e., what appears the optimal treatment plan for one patient may not be acceptable for another patient)

Which technique is preferable?

- The degree of modulation should be chosen based on individual treatment goals
- The benefits of advanced conformal radiotherapy techniques depend on the individual patient/target geometry
- Their use should therefore be decided case by case, with comparative treatment planning
  - 3D-CRT vs “optimized” VMAT
  - dose plans and DVHs for different alternatives should be compared

Same patient, different solutions



Maraldo MV et a

Int J Radiation Oncol Biol Phys, Vol. ■, No. ■, pp. 1–9, 2015

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Modern RT in HL

- 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

Modern RT for lymphoma

- Modern RT for HL is a highly individualized treatment restricted to limited treatment volumes

- Radiation oncologists should be involved as part of the multidisciplinary team in the initial management plan and attempt to introduce imaging procedures upfront before the initiation of chemotherapy

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Indolent nodal non Hodgkin Lymphoma
The role of radiotherapy in early stage

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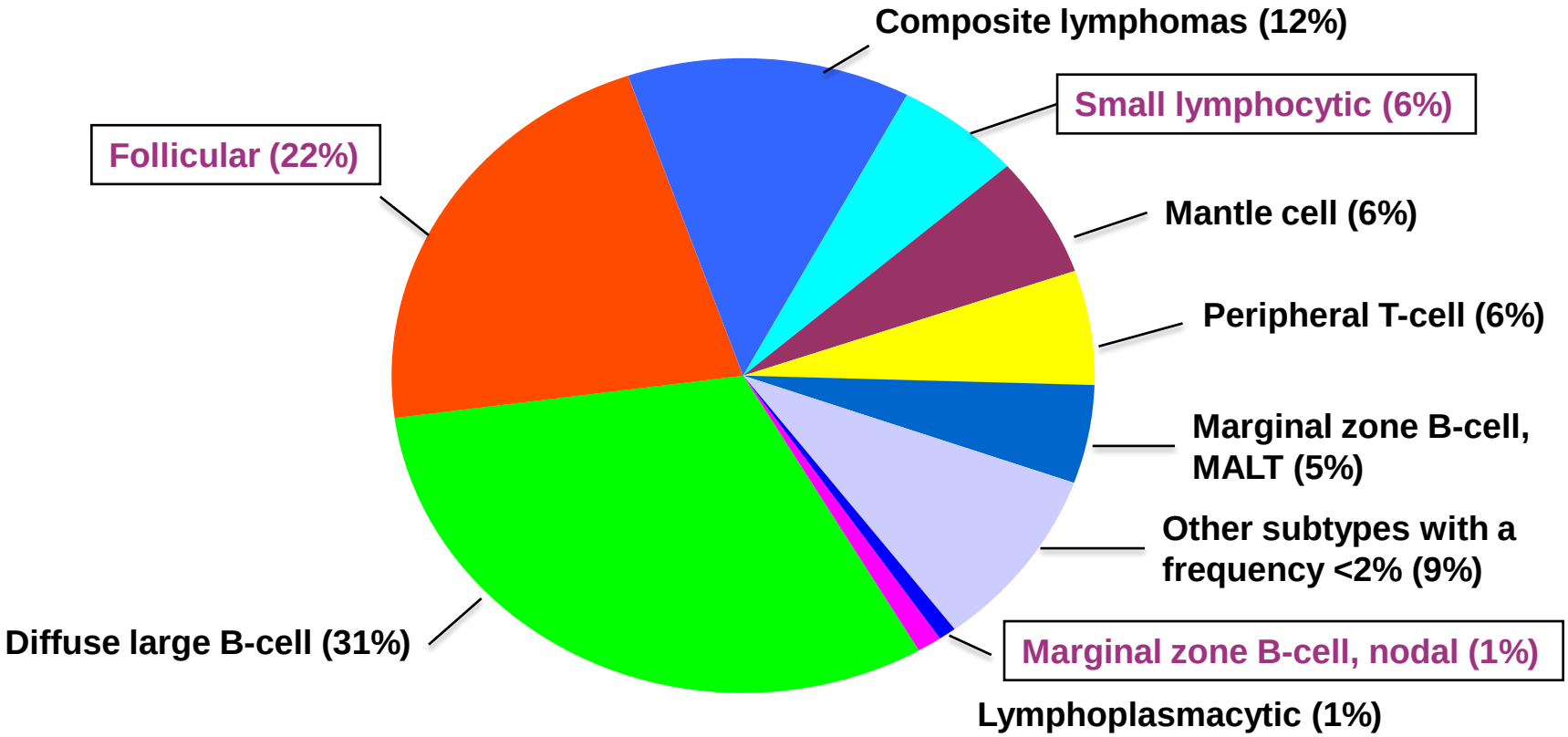
Frequency of NHL Subtypes in Adults



Armitage et al. *J Clin Oncol*. 1998;16:2780–2795.

Indolent lymphomas

- Approximately 40–50 % of all NHL (follicular lymphoma 25%; SLL 6%, Marginal zone 10%)
- Most advanced stage cannot be cured by conventional therapy, minority of patients present with localised disease. Thorough staging with bone marrow biopsy and FDG-PET essential
- Therapy guidelines
  - Stage I/II:radiotherapy
  - Stage III/IV: chemotherapy, when needed

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Indolent Lymphomas
Treatment of stage I and II

- Standard: Involved Field Radiotherapy (IFRT)
- The shape of the survival curve suggests a possible plateau in the potential for a cure
- Most relapses occur outside the radiation field

Results of radiotherapy in stage I/II:

	5 years	10 years	15 years	20 years
Survival	82%	64%	44%	35%
Relapse-free	55%	44%	40%	37%

Ref.: MacManus,MP et al.; JCO 14: 1282-90 (1996)

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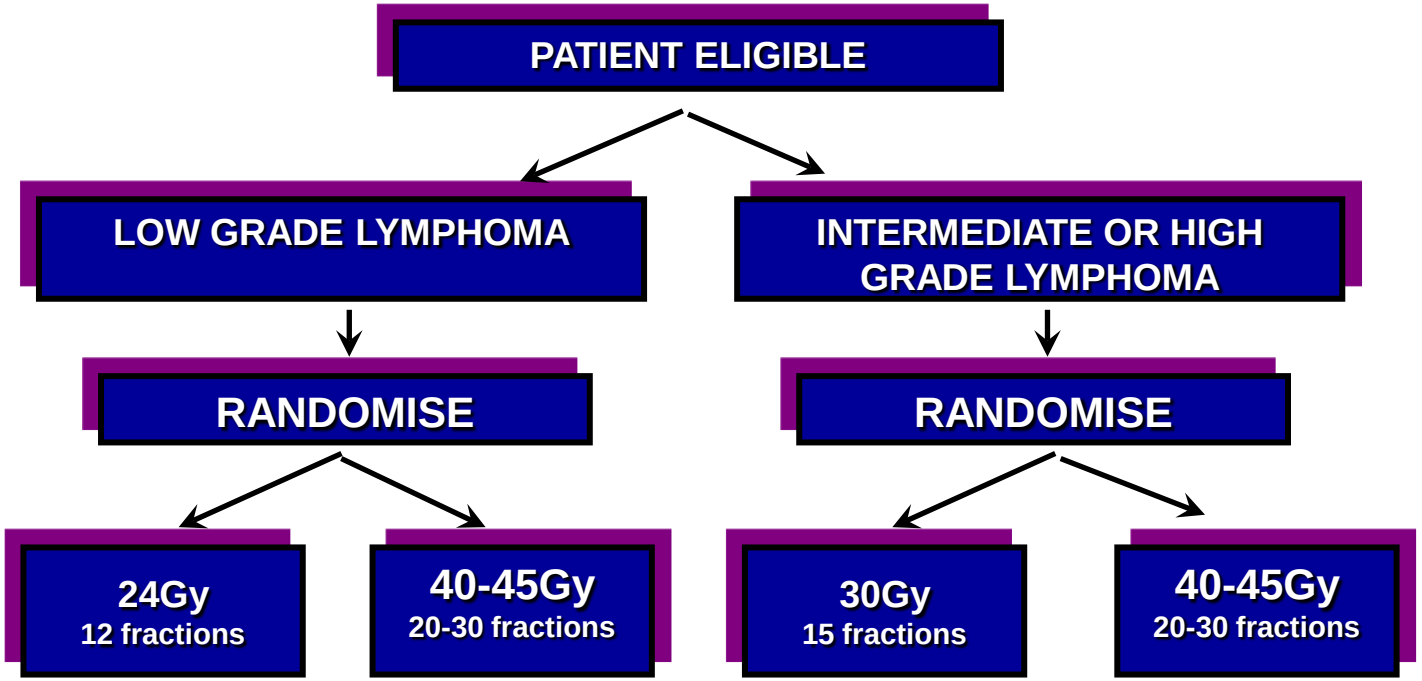
Hypothesis: Is more dose better?

Reduced dose radiotherapy for NHL : A randomised phase III trial

Lowry L, Smith P, Qian W, Falk S, Benstead K, Illidge T, Linch D, Robinson M, Jack A, Hoskin P.

Radiother Oncol. 2011 Jun 9.



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Indications for Radiotherapy

%	LG		IHG	
	24Gy	40-45Gy	30Gy	40-45Gy
Radical	77	79	48	51
Palliative	19	14	7	5
Consolidation	3	7	45	45

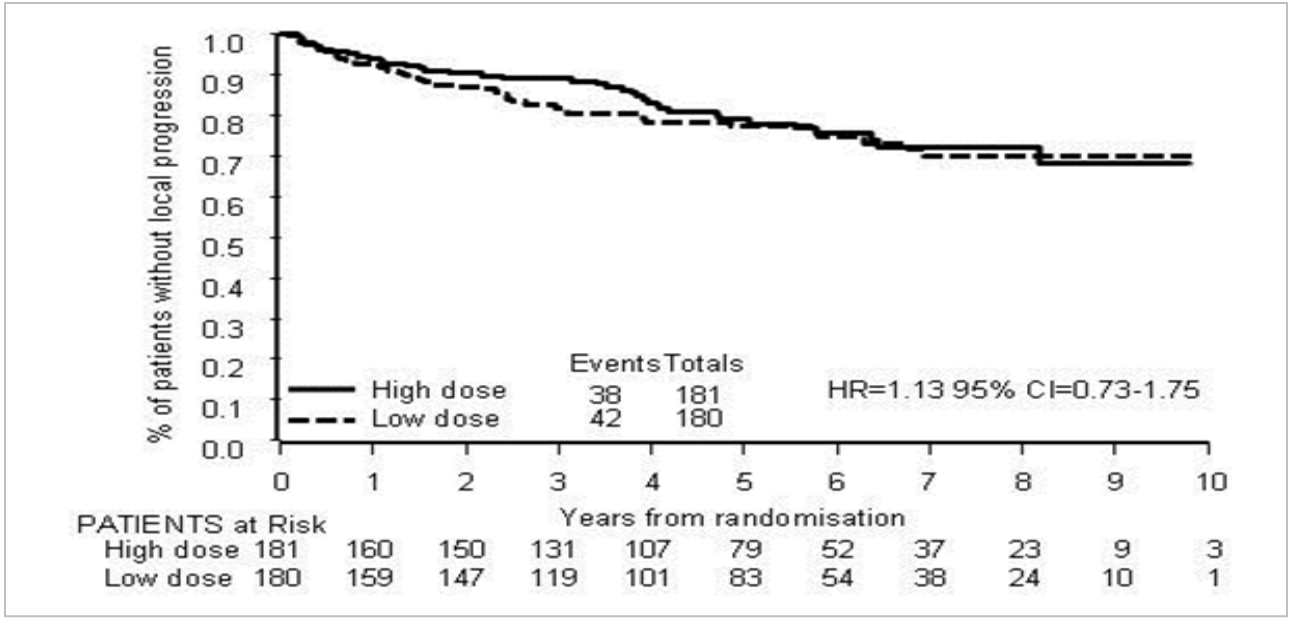
Acute RT Toxicity

%	LG		IHG	
	24Gy	40-45Gy	30Gy	40-45Gy
Erythema	33	49	25	38
Dry desquamation	12	19	12	15
Moist desquamation	1	8	3	5
Mucositis	25	26	17	22
Nausea / Vomiting	10	12	5	6
Diarrhoea	7	12	6	7

Local Control at 1 month

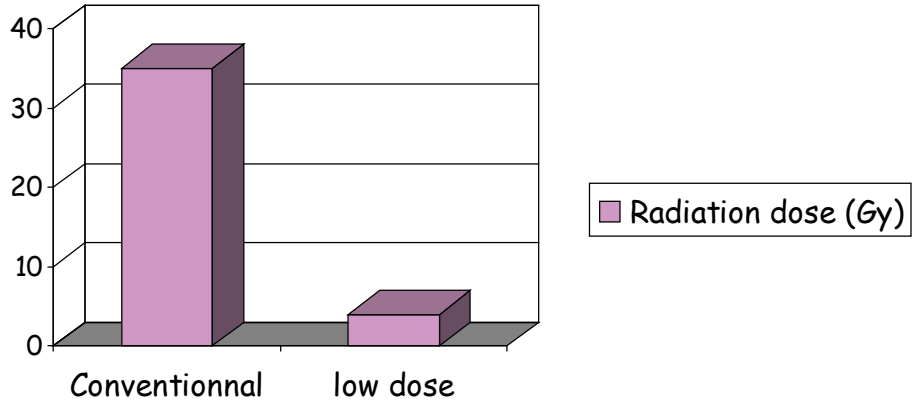
	LG		IHG	
%	24Gy	40-45Gy	30Gy	40-45Gy
Complete Regression	82	80	84	85
Partial Regression (>50%)	11	14	9	8
Stable Disease	6	5	5	5
Progression	2	1	2	3

RT dose 24 Gy vs 40 Gy in indolent NHL



[1] Lisa Lowry, Paul Smith, Wendi Qian, Stephen Falk, Kim Benstead, Tim Illidge, David Linch, Martin Robinson, Andrew Jack, Peter Hoskin *'Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial'* Radiotherapy and Oncology 100 (2011) 86–92

Radiation sensitivity of indolent lymphomas



Clinical study on 109 patients (2003) - (2 X 2 Gy) in indolent Lymphoma
- Local response rate 92 %
- Complete response 61 %
- Very rapid responses, No side effects

(Haas et al. JCO. 2003)

'immune signature' genes, activated by RT including

macrophages (e.g., CD68, TLR4),

TH1 immune response (e.g., IL18, CXCL9, 10, 11),

clearance of apoptotic cells

(Knoops L et al Blood 2007)

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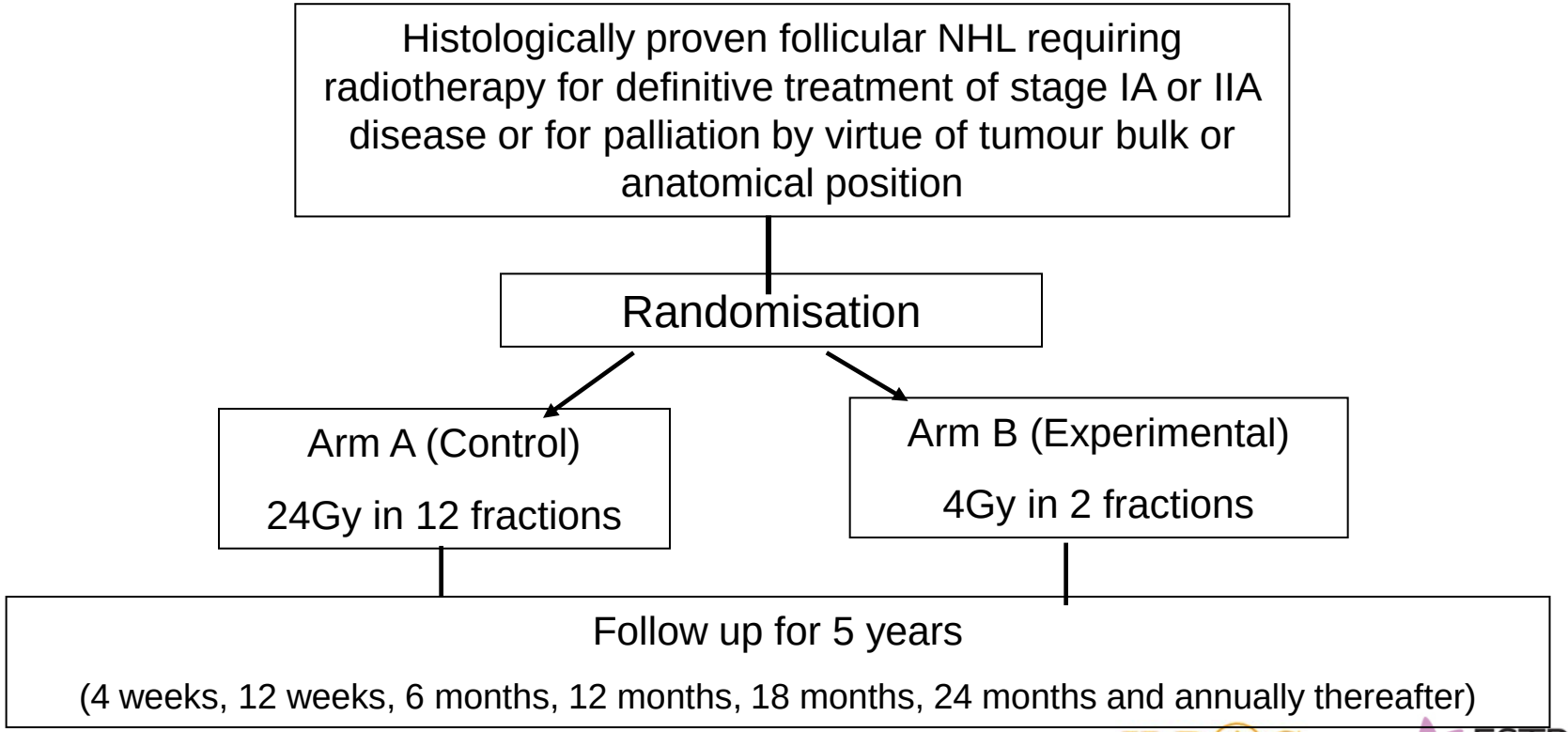
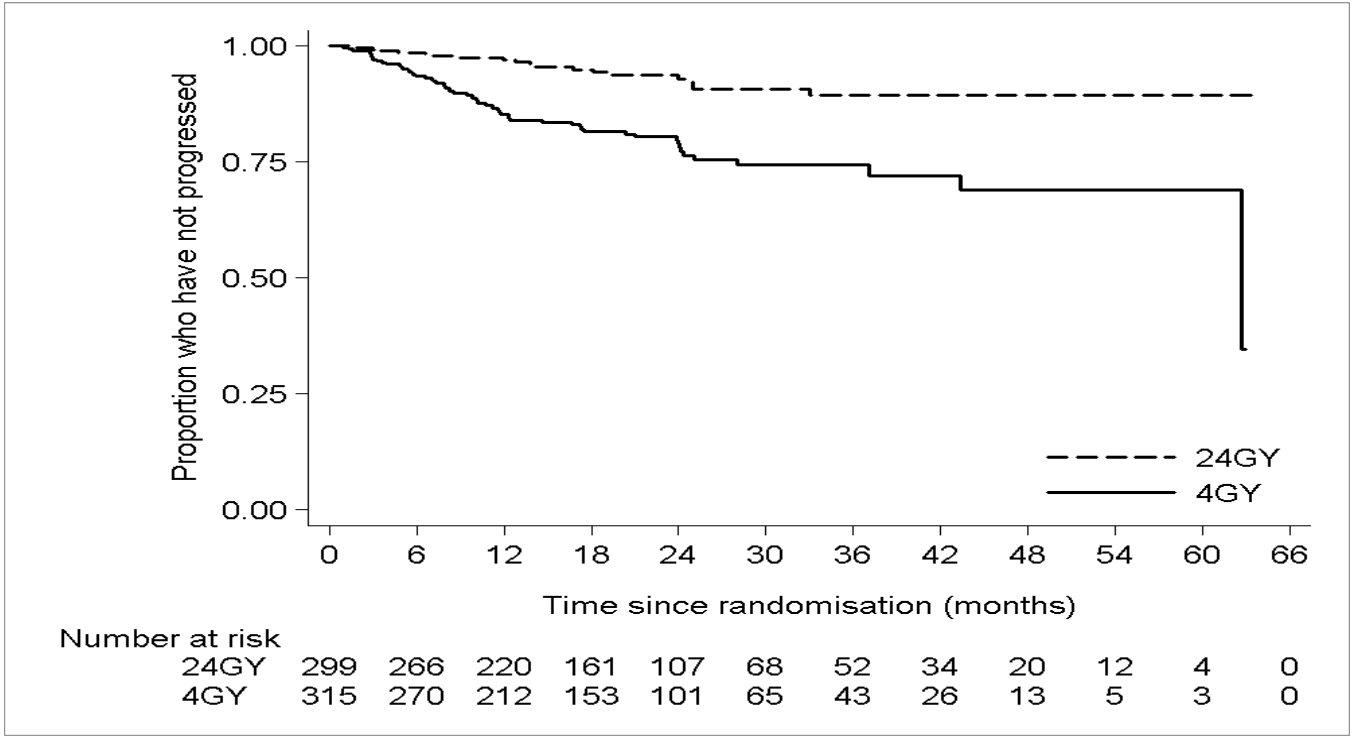
FoRT: Study design : A randomised trial of low dose radiotherapy for follicular lymphoma



NCRI FORT Trial 24 Gy vs 4 Gy : Local PFS



2 Year local progression free rate: 93.7% (24Gy) and 80.4% (4Gy) Hazard Ratio: 3.49 (95% CI: 2.06 - 5.90), p<0.001,

UK NCRI FORT trial Summary and conclusion

- 4Gy in 2 fractions inferior to 24Gy in 12 fractions in achieving a durable local progression free interval in follicular and marginal zone NHL.
- 24Gy in 12 fractions should remain the standard schedule for indolent lymphoma.
- 4Gy in 2 fractions is effective (ORR 74.1%; CR rate: 44.3%, PR rate: 29.8%) and may be considered for palliative treatment or retreatment.

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Is radiotherapy curative for stage I and II low-grade follicular lymphoma?

Results of a long-term follow-up study of patients treated at Stanford University.

Mac Manus MP, Hoppe RT J Clin Oncol 1996 Apr;14(4):1282-90.

- 177 patients with stage I (n = 73 [41%]) and II (n = 104 [59%]) follicular lymphoma Stanford University 1961 and 1994.
- RT either to one side of the diaphragm (IFRT or EFRT or to both sides (total lymphoid irradiation [TLI] or subtotal lymphoid irradiation [STLI]. Doses 35 to 50 Gy.
- Median follow-up 7.7 years, longest 31 years. Median survival time 13.8 years.

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Results of a long-term follow-up study of patients treated at Stanford University.

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- At 5, 10, 15, and 20 years, 55%, 44%, 40%, and 37% of patients, respectively, were relapse-free. Only five of 47 patients who reached 10 years without relapse subsequently developed recurrence.
- Survival and freedom from relapse (FFR) significantly worse for older patients.
- Patients who have remained free of disease for 10 years are unlikely to relapse

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Radiotherapy alone for stage I-III low grade follicular lymphoma: long-term outcome and comparison of extended field and total nodal irradiation.

Guckenberger M Radiat Oncol 2012 Jun 24;7**:103.**

- To analyze long-term results of radiotherapy alone for stage I-III low grade follicular lymphoma and to compare outcome after extended field irradiation (EFI) and total nodal irradiation (TNI).

- Between 1982 and 2007, 107 patients were treated with RT alone for low grade follicular lymphoma at Ann Arbor stage I (n = 50), stage II (n = 36) and stage III (n = 21);

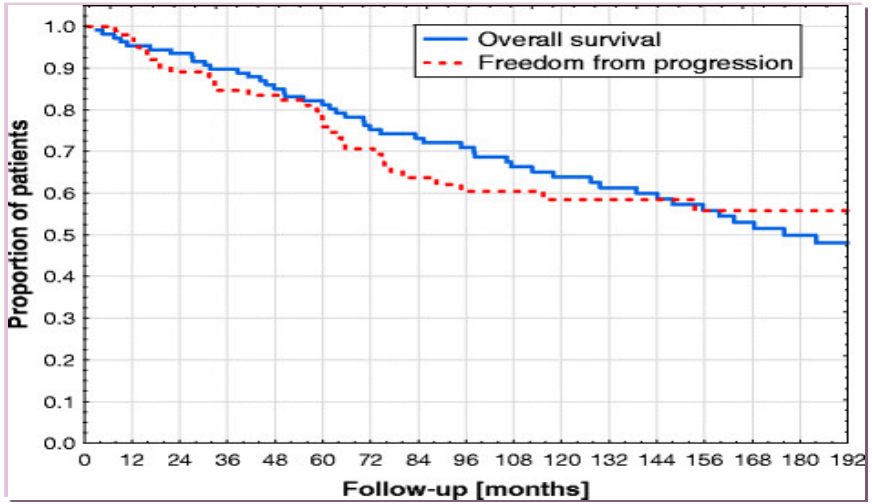
- 48 and 59 patients were treated with EFI and TNI, respectively.

- The median total dose in the first treatment series of the diaphragmatic side with larger lymphoma burden was 38 Gy (25 Gy - 50 Gy) and after an interval of median 30 days, a total dose of 28 Gy (12.6 Gy - 45 Gy) was given in the second treatment series completing TNI.

Radiotherapy alone for stage I-III low grade follicular lymphoma: long-term outcome and comparison of extended field and total nodal irradiation.

Guckenberger M Radiat Oncol 2012 Jun 24;7:103.

- After a median follow-up of 14 years for living patients, 10-years and 15-years overall survival (OS) were 64% and 50%, respectively.
- Survival was not significantly different between stages I, II and III
- Acute toxicity was significantly increased after TNI compared to EFI with a trend to increased late toxicity as well.



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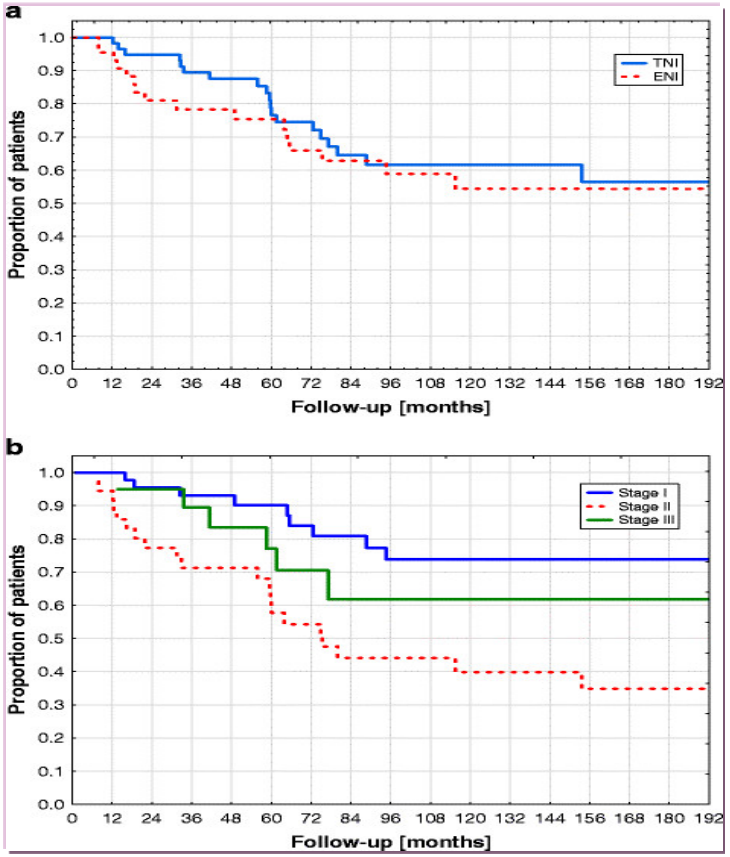

(a) Kaplan Meier Curves showing **freedom from disease progression** in relationship to TNI versus EFI (no significant difference)

(b) Stage of disease (significant difference between stage I and stage II)

Radiotherapy alone for stage I and II follicular lymphoma resulted in long-term OS with high rates of disease control; no benefit of TNI over EFI was observed.

Is radiotherapy curative for stage I and II low-grade follicular lymphoma?
Should RT alone remain standard of care ?

- US lymphocare 206 of 471 patients stage 1 follicular lymphoma “rigorously staged” - Treatments given
  - R-chemo (28%)
  - RT (27%)
  - Observation (17%)
  - Systemic + RT (13%),
  - rituximab monotherapy (12%), and other (3%).
- Median follow-up of 57 months, 44 (21%) progression events. PFS significantly improved with either R-chemo or systemic and RT. No differences in OS. (Friedberg J et al JCO 2012)

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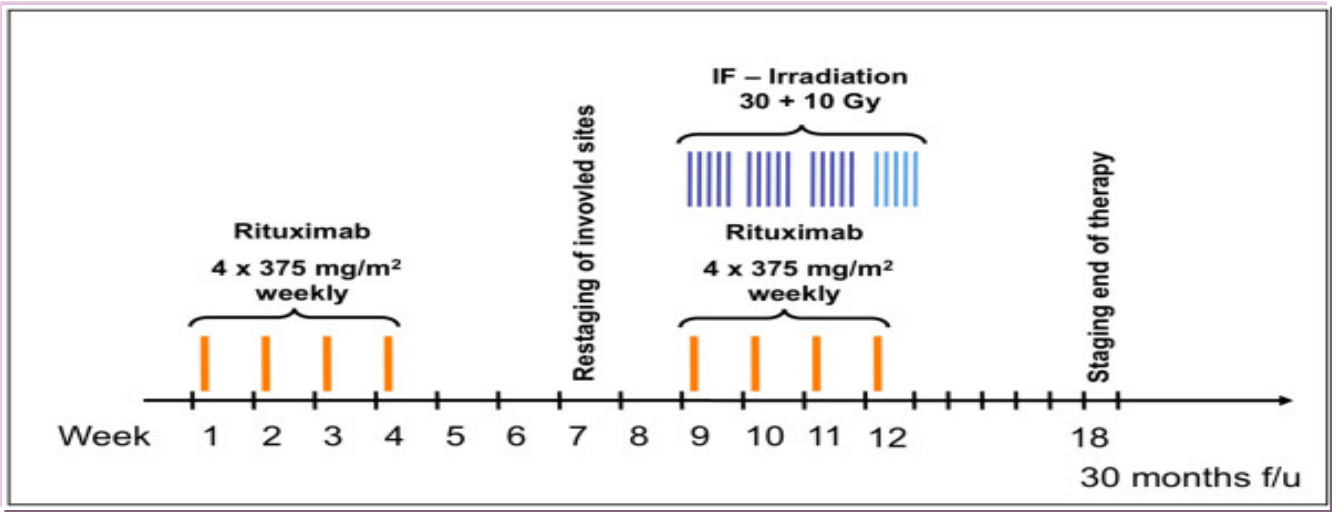
Treatment of limited stage follicular lymphoma with Rituximab immunotherapy and involved field radiotherapy in a prospective multicenter Phase II trial-MIR trial.

Witzens-Harig M, et al BMC cancer. 2011; 11: 87



Treatment of limited stage follicular lymphoma with Rituximab immunotherapy and involved field radiotherapy in a prospective multicenter Phase II trial-MIR trial.

Witzens-Harig M, et al BMC cancer. 2011; 11: 87

- Trial aims at testing the combination's efficacy and safety n= 85 patients.
- Primary endpoint of the study is progression free survival.
- Secondary endpoints are :
    - Response rate to Rituximab,
    - Complete remission rate at week 18,
    - Relapse rate,
    - Relapse pattern,
    - Relapse free survival,
    - Overall survival,
    - Toxicity
    - Quality of life.

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Conclusions

- “Rigorous staging” is required to determine appropriate patients to consider IFRT, including BM biopsy and FDG-PET scan
- RT remains treat of choice of stage I/II indolent lymphomas and results in long term progression free survival and possible “cure” for patients still in remission past 10 years
- For early stage disease 24 Gy in 12 fractions remains the standard of care for most patients and provides better local control and 4 Gy in 2 fractions

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Treatment of Indolent nodal non Hodgkin Lymphoma – including novel agents

Tim Illidge
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Decision making in Follicular Lymphoma

- Follicular lymphoma diverse disease, biologically and clinically.
  - Indolent and asymptomatic disease with low tumor burdens
  - More aggressive and symptomatic disease with high tumor burden.
- Decision-making to treat in the frontline therapy based on
  - Histology
  - Disease burden
  - Patient symptoms
  - Patient characteristics, morbidities and choice

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Goals of therapy versus toxicity / tolerability in Follicular Lymphoma

- FL generally considered incurable - most patients will require additional therapy in their lifetime.
- First line treatment options trade off between remission duration versus toxicity. Eg R-CHOP induces more durable remissions relative to R-CVP but carries more short-term toxicity and more risk for late cardiotoxicity
- In absence of proven OS advantage for one choice versus another, no one ‘‘right’’ approach.
- Treatment decision is patient-specific, incorporating goals of treatment with the patient’s unique situation
  - Age, comorbidities, tumour burden, patient preferences.

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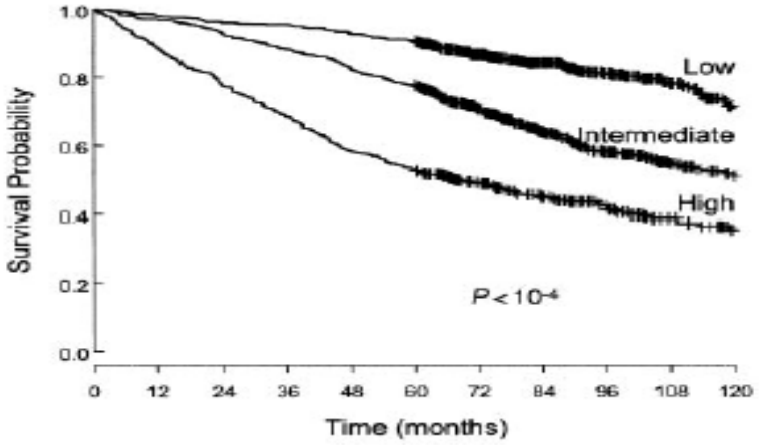
Follicular Lymphoma International Prognostic Index (FLIPI and F2) –

- Nodal regions > 4
- Elevated LDH
- Age > 60
- Stage III/IV
- Haemoglobulin < 12 g/dl
- Serum B2 microglobulin (F2)



Risk Group	# Factors	% Pt	5-yr OS	10-yr OS
Low	0–1	36%	90.6%	70.7%
Intermediate	2	37%	77.8%	50.9%
High	3–5	27%	52.5%	35.5%

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Decision making in Initial treatment of Follicular Lymphoma

Newly diagnosed FL

Symptomatic

High Tumour burden

R-Chemo
(Consider age and comorbidities for chemo backbone)

Low Tumour burden

Rituximab
or
R-Chemo

Asymptomatic

High tumour burden

R-Chemo
Consider GELF or other criteria for Initiation of treatment

Low tumour burden

Watch and wait
vs
Rituximab

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Established definitions of when treatment required

Patients with at least one of the following requiring initiation of treatment:

- Bulky disease (nodal or extranodal mass > 7cm)
- B symptoms
- Elevated serum LDH (> ULN) or β2-microglobulin (> 3mg/L)
- Involvement of ≥ 3 nodal sites (each > 3 cm)
- Symptomatic splenic enlargement, compressive syndrome, pleural/peritoneal effusion

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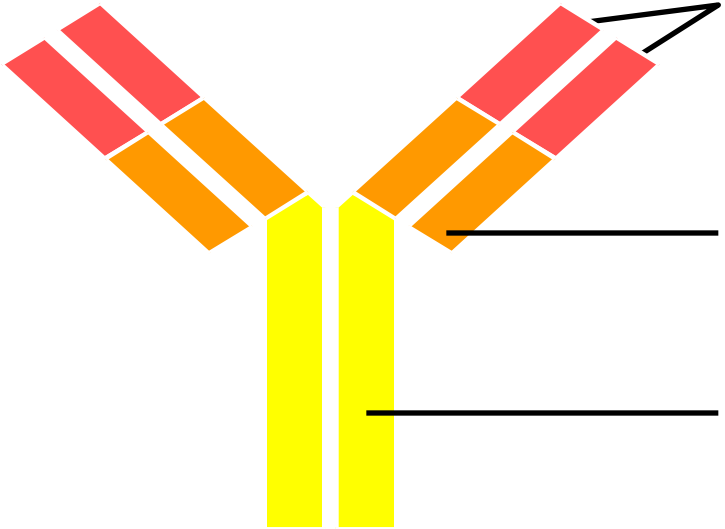
Treatments approaches for those requiring treatment (high tumour burden)

General approach : rituximab and ……

- alkylating agents +/- anthracycline
- Bendamustine / Purine analogues
- alternative non chemotherapy options
- Radioimmunotherapy
- Lenalidomide and rituximab
- New generation anti-CD20 antibodies (Ofatumumab, GA101 [Obinutuzumab]).

Rituximab: An engineered murine/human chimeric monoclonal antibody – granted US FDA approval for treatment of cancer 1997



Murine-variable regions bind specifically to CD20 on B cells

Human κ constant regions

Human IgG_1 Fc domain works in synergy with human effector mechanisms

Rituximab-Chemotherapy in Untreated Advanced Follicular NHL

Study	Treatment, n	Median FU, months	ORR, %	CR, %	Median TTP/ TTF/ EFS, mo	OS, %
Marcus et al. 2008	CVP, 159	53	57	10	15	77
	R-CVP, 162		81	41	34	83
					P<.0001	*P*=.0290
Hiddemann et al. 2005	CHOP-IFN, 205	18	90	17	29	90
	R-CHOP-IFN, 223		96	20	NR	95
					P<.001	*P*=.016
Herold et al. 2007	MCP-IFN, 96	47	75	25	26	74
	R-MCP-IFN, 105		92	50	NR	87
					P<.0001	*P*=.0096
Salles et al. 2008	CHVP-IFN, 183	42	73	63	46	84
	R-CHVP-IFN, 175		84	79	67	91
					P<.0001	*P*=.029

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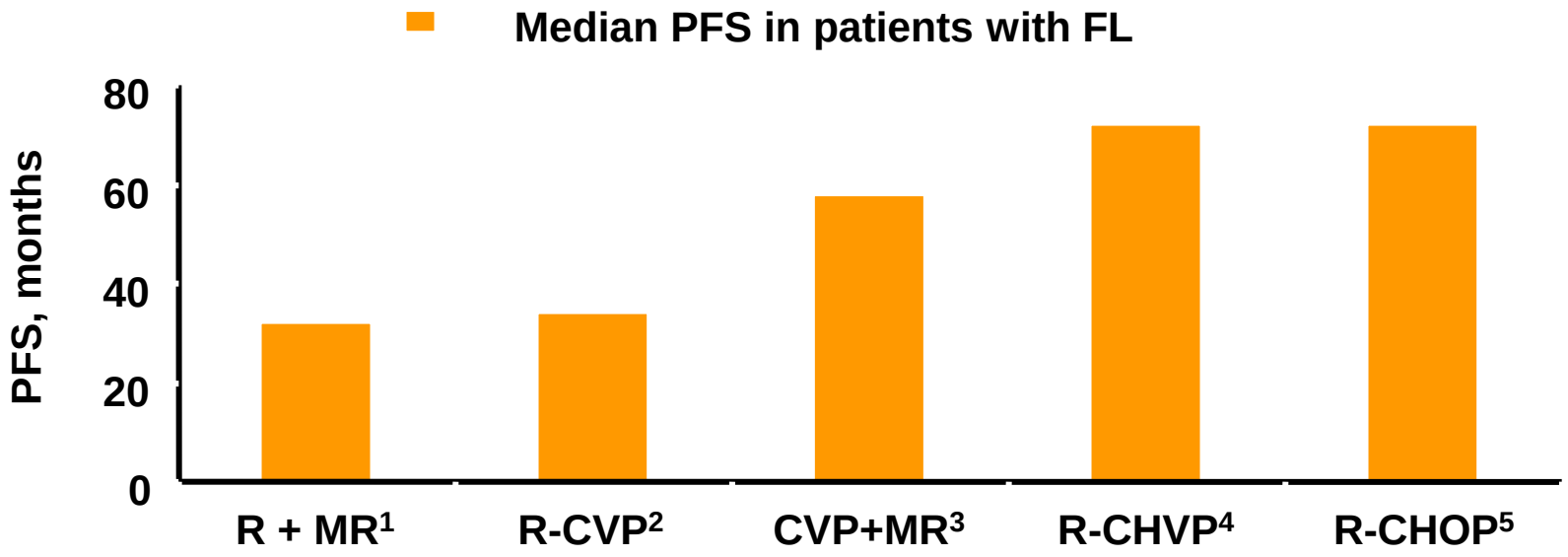
Progression-Free Survival Depends on First-Line Treatment



1. Hainsworth JD, et al. *J Clin Oncol.* 2005;23(6):1088-1095. 2. Marcus R, et al. *J Clin Oncol.* 2008;26(28):4579-4586. 3. Hochster H, et al. *J Clin Oncol.* 2009;27(10):1607-1614. 4. Salles G, et al. *Blood.* 2008;112(13):4824-4831. 5. Buske C, et al. *Blood.* 2008;112: Abstract 2599.

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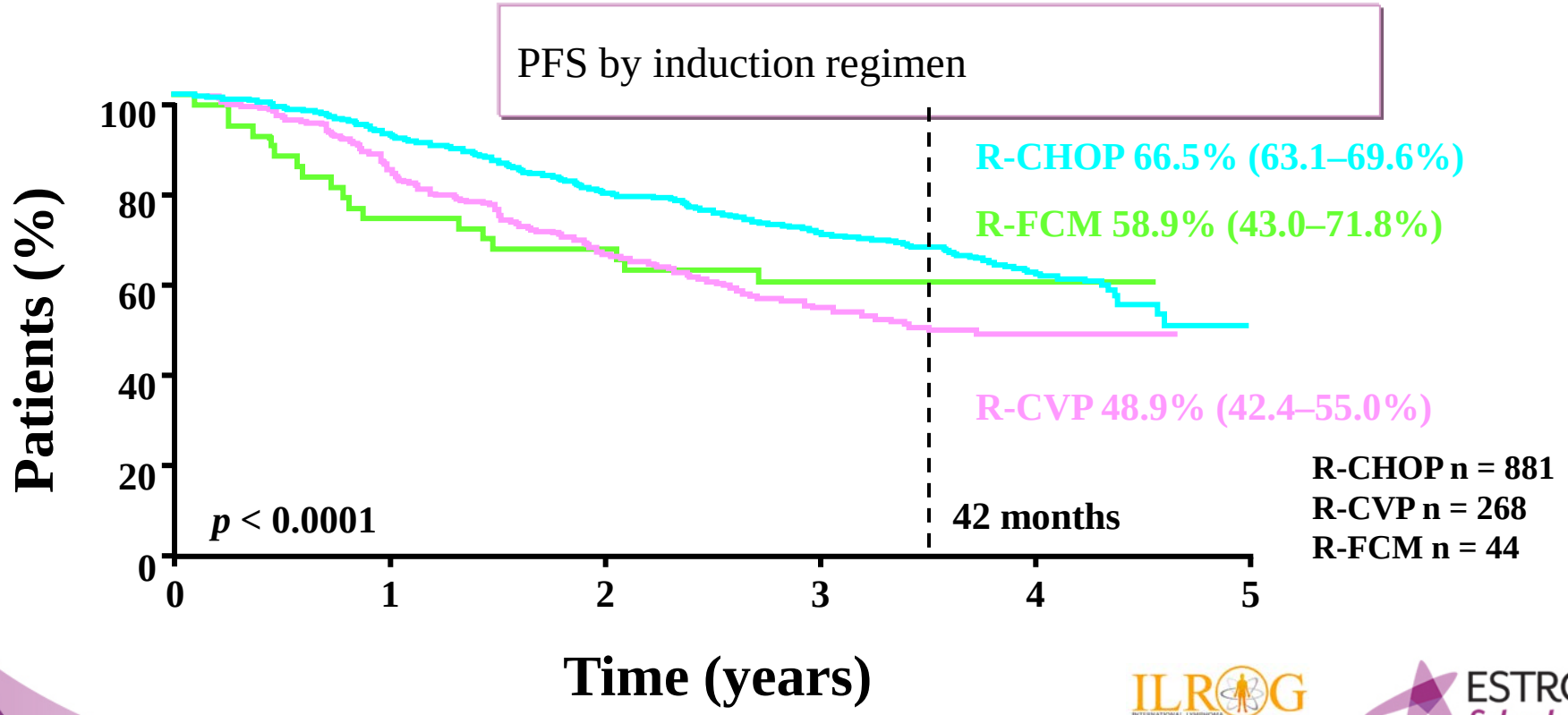
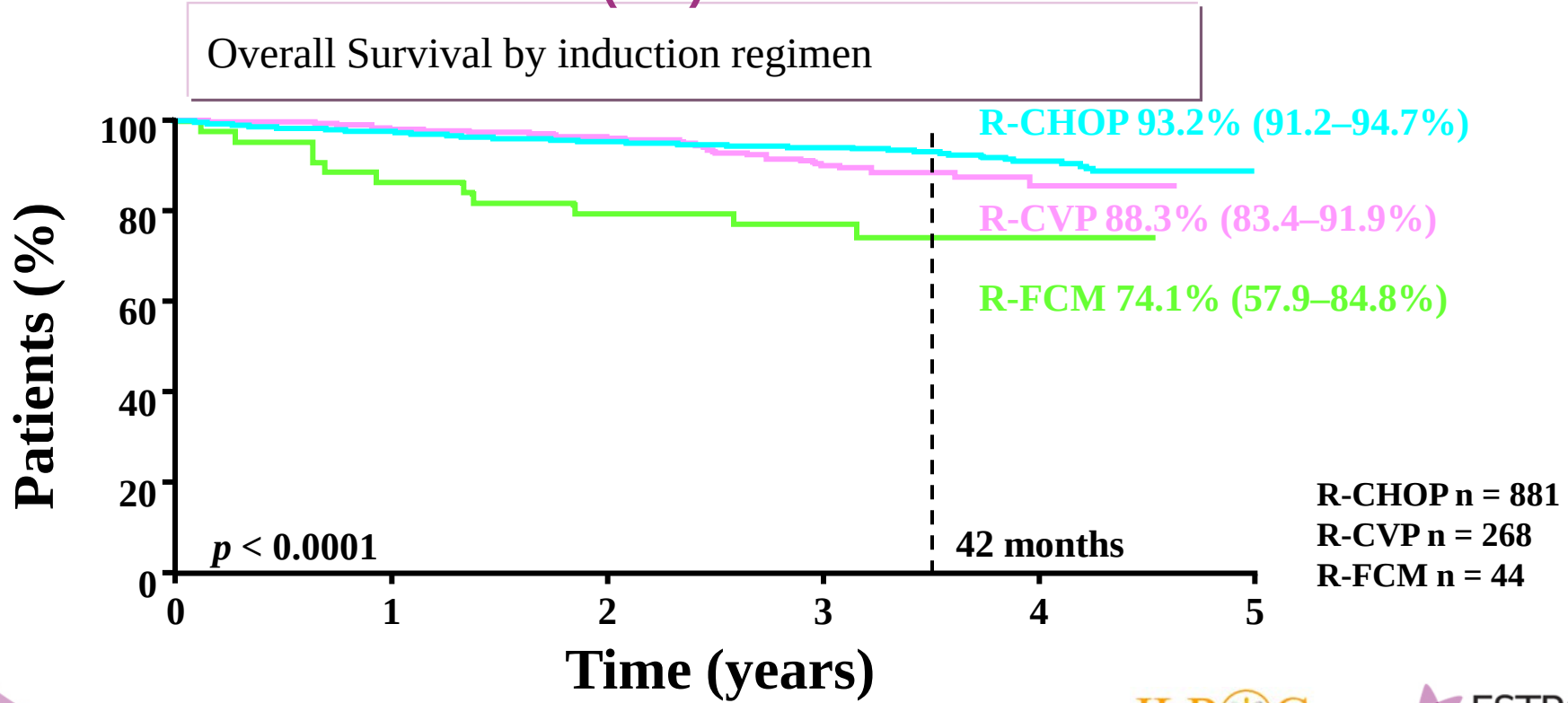
R-CVP versus R-CHOP versus R-FM as first-line therapy for advanced-stage follicular lymphoma: Final results of FOLL05 trial from the Fondazione Italiana Linfomi (FIL). Federico et al J Clin Oncol 2013

- Randomized trial comparing R-CVP with R-CHOP and R-FM.
- 534 patients were enrolled; 30 excluded. Median age 56 years (range 30-75), 63% stage IV disease, 37% had 3-5 FLIPI and 27% 3-5 FLIPI2 scores.
- ORR (CR+ PR) for whole group was 91% (p=0.247). After median follow-up of 34 months, 208 events for TTF were recorded;

R-CVP versus R-CHOP versus R-FM as first-line therapy for advanced-stage follicular lymphoma: Final results of FOLL05 trial from the Fondazione Italiana Linfomi (FIL).Federico et al J Clin Oncol 2013



R-CVP versus R-CHOP versus R-FM as first-line therapy for advanced-stage follicular lymphoma: Final results of FOLL05 trial from the Fondazione Italiana Linfomi (FIL).Federico et al J Clin Oncol 2013



Second malignancies seen in 23 patients (2%, 3% and 8% in R-CVP, R-CHOP and R-FM, respectively).

StiL R-Benda vs R-CHOP

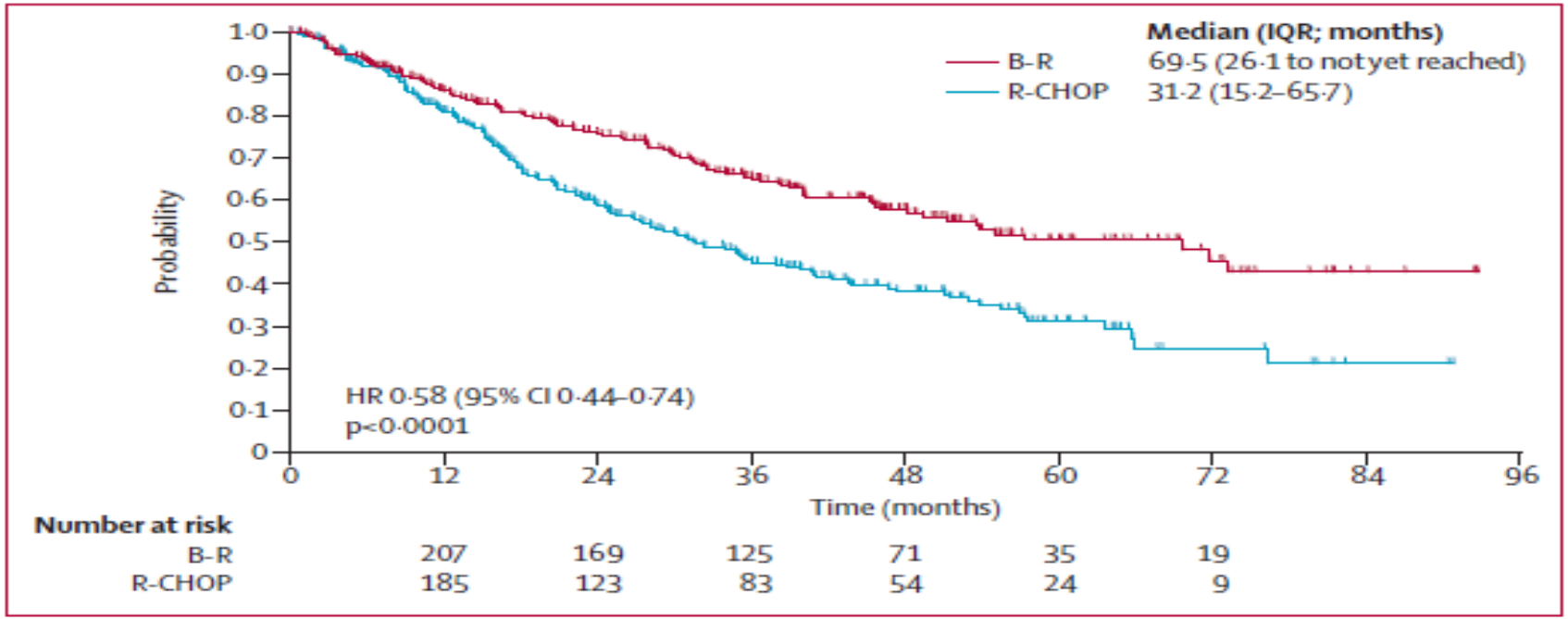
Rummel MJ et al : Lancet Feb 20, 2013

	B-R n = 261	CHOP-R n = 253
Median age, years (range)	64 (34–83)	63 (31–82)
B-symptoms	100 (38)	74 (29)
Ann Arbor stage III/IV, n (%)	252 (96)	244 (97)
Lactate dehydrogenase > ULN, n (%)	100 (38)	84 (33)
Histology n (%)		
Follicular	139 (53)	140 (55)
Mantle cell	46 (18)	48 (19)
Lymphoplasmacytic	22 (8)	19 (8)
SLL	10 (4)	11 (4)
High-risk FLIPI, n (%)	63 (46)	64 (48)

- No observed differences between the two study arms

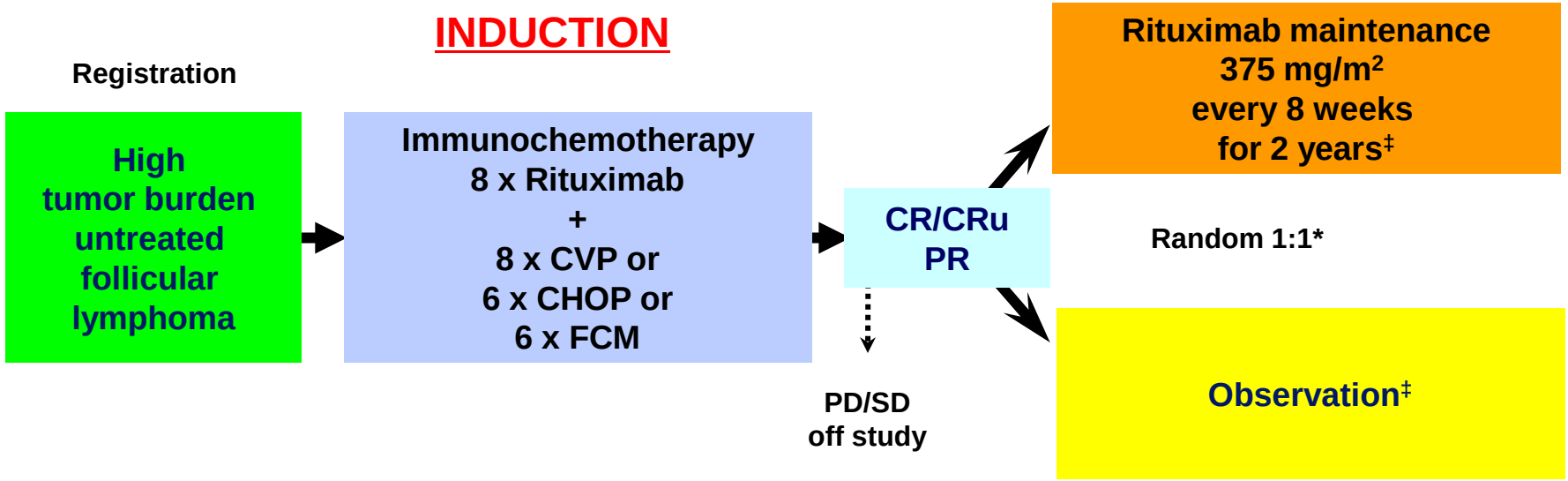
StiL R-Benda vs R-CHOP

Rummel MJ et al : Lancet Feb 20, 2013



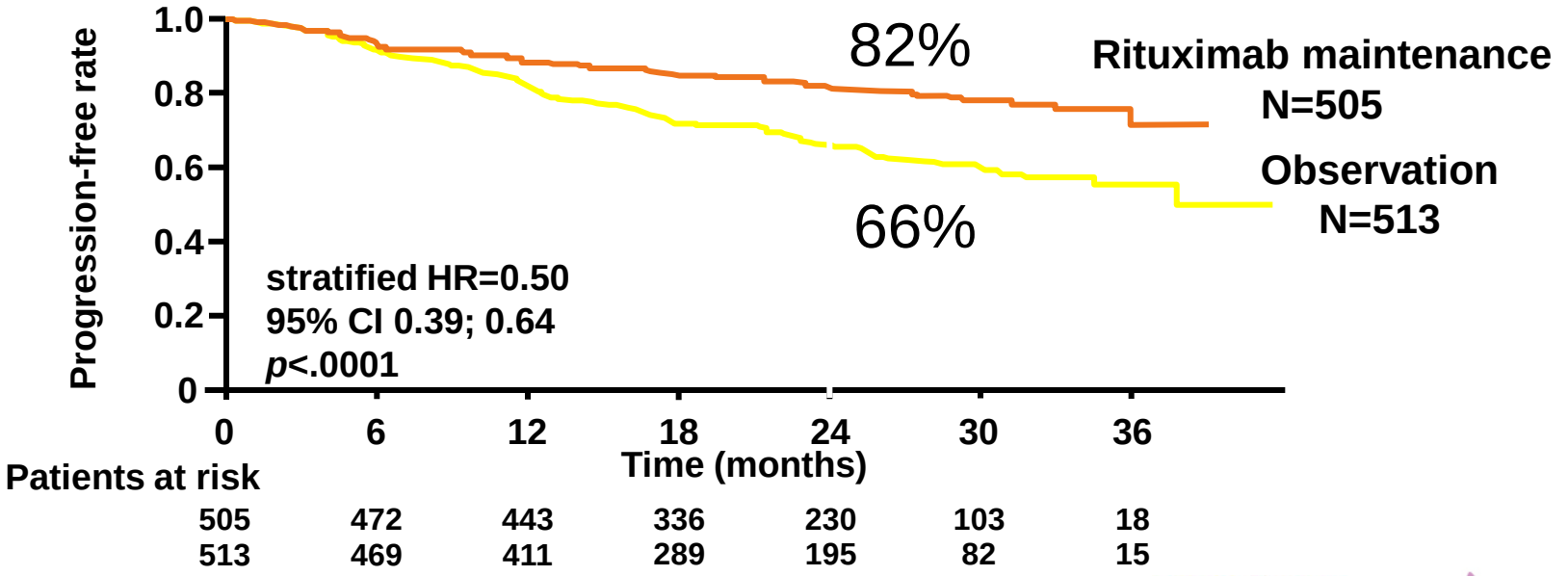
•B-R more favorable acute tolerability profile. Severe neutropenia was markedly decreased with B-R (29% vs. 69% with RCHOP), less parasthesias, stomatitis and infections

Maintenance Rituximab after Induction immunochemotherapy
PRIMA: study design



* Stratified by response after induction, regimen of chemo, and geographic region
‡ Frequency of clinical, biological and CT-scan assessments identical in both arms
Five additional years of follow-up

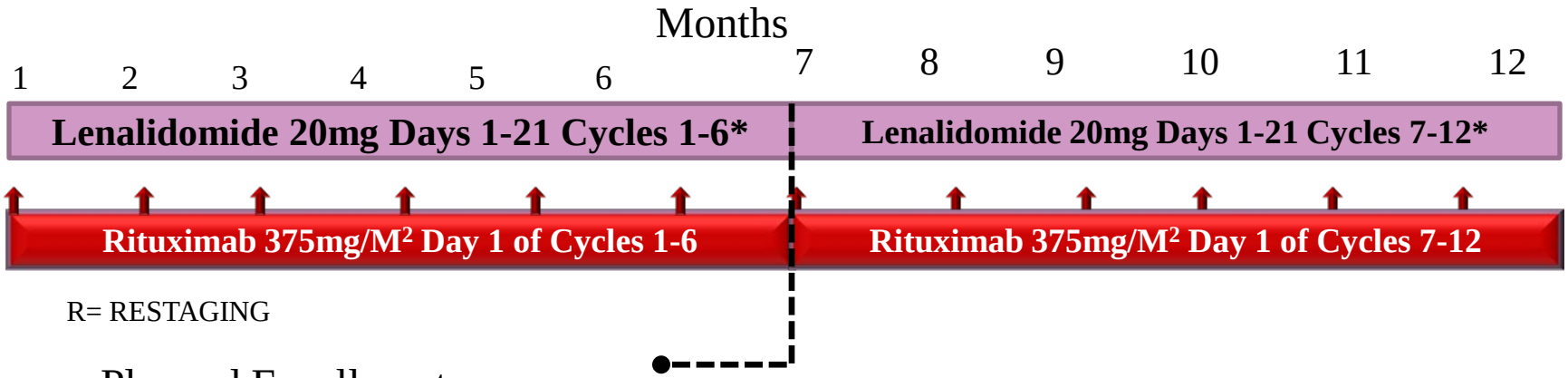
Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to **rituximab** plus chemotherapy (PRIMA): a phase 3, randomised controlled trial.
Salles G et al Lancet. 2011 Jan 1;377(9759):42-51



Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial

Fowler et al Lancet Oncol. 2014 Nov;15(12):15.

Can cytotoxic chemotherapy be avoided ?



- Planned Enrollment
  - N= 50 Follicular lymphoma (grade I/II)
  - N=30 Small lymphocytic lymphoma
  - N=30 Marginal zone lymphoma

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Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial

Fowler et al Lancet Oncol. 2014 Nov;15(12):15.

Response Rates of R^2

				All Patients	
	SLL (N=30)	**Marginal (N=27)***	**Follicular (N=46)***	Eval (N=103)	ITT (N=110)
ORR, n (%)	24 (80)	24(89)	45(98)	93(90)	93(85)
CR/Cru	8(27)	18(67)	40(87)	66(64)	66(60)
PR	16(53)	6(22)	5(11)	27(26)	27(25)
SD, n (%)	4(13)	3(11)	1(2)	8(8)	8(7)
PD, n (%)	2(7)	0	0	2(2)	2(2)

*7 pts not evaluable for response:

- 5 due to adverse event in cycle 1
- 1 due to non-compliance
- 1 due to withdrawal of consent

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Fowler N, et al ASH 2012.

Can cytotoxic chemotherapy be avoided ?

The "RELEVANCE" Trial (Rituximab and Lenalidomide Versus Any Chemotherapy)

- Phase 3 randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Chemotherapy Followed by Rituximab in Untreated Follicular Lymphoma.
- Comparator R-CHOP, R-CVP, R-Bendamustine.
- 7 to 8 weeks later responding patients will continue with 375 mg/m2 rituximab every 8 weeks for 12 cycles.

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Novel agents to target Follicular lymphoma in relapsed and rituximab refractory disease ?

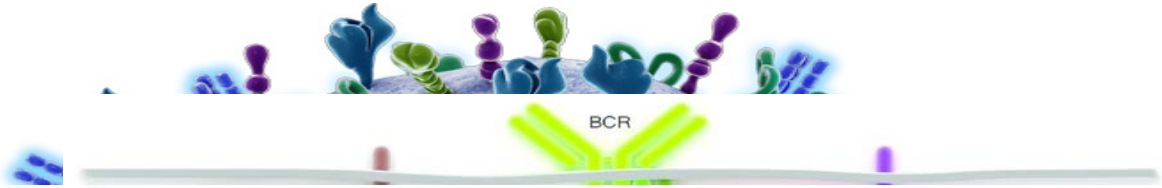
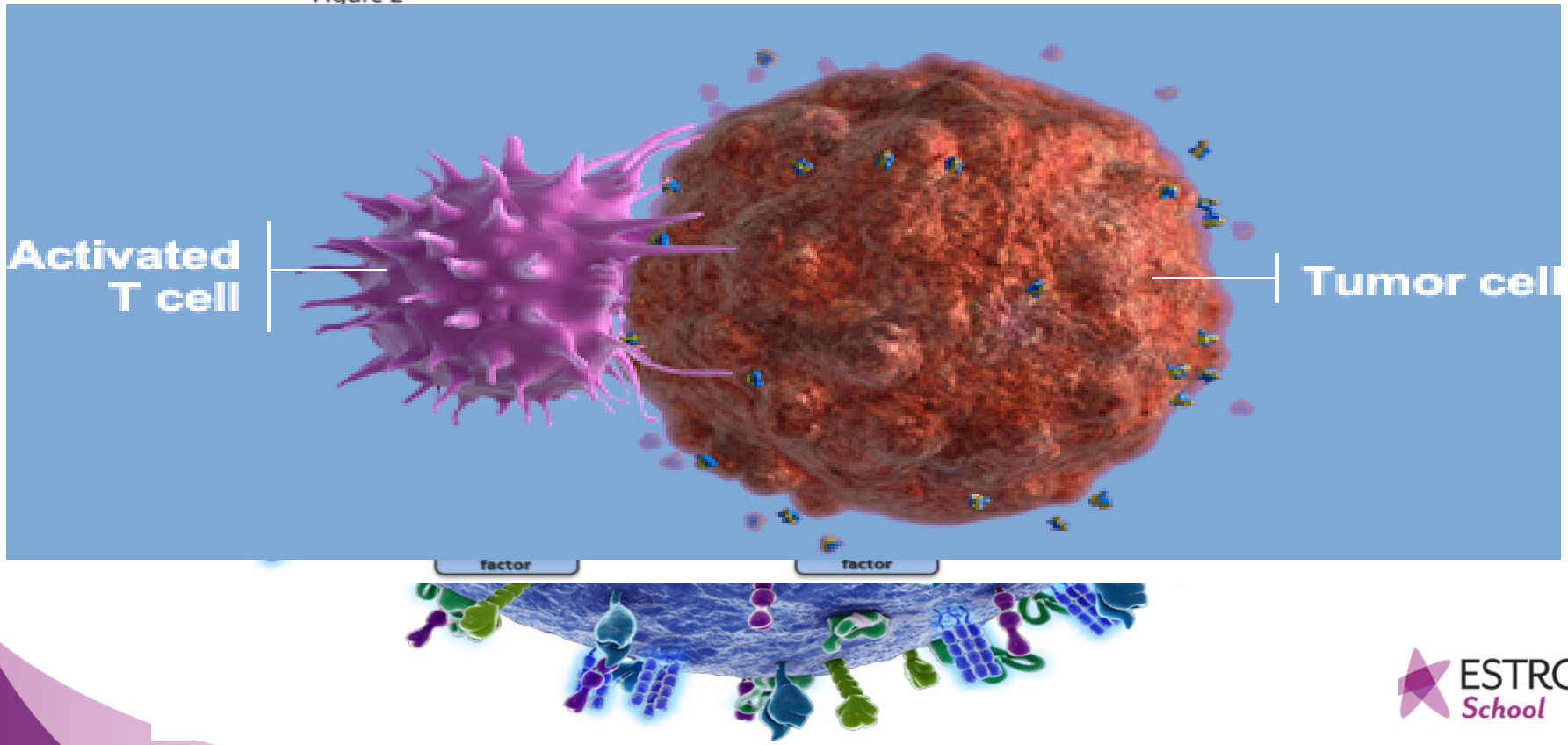


Figure 2



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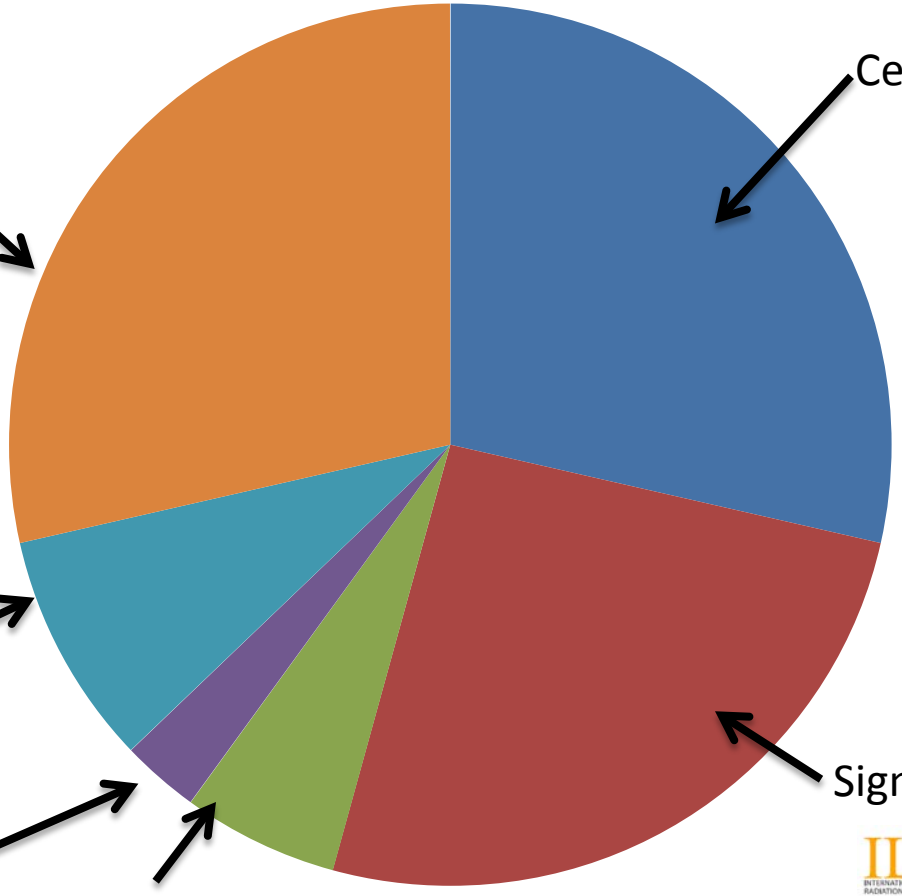
ASCO Lymphoma 2015



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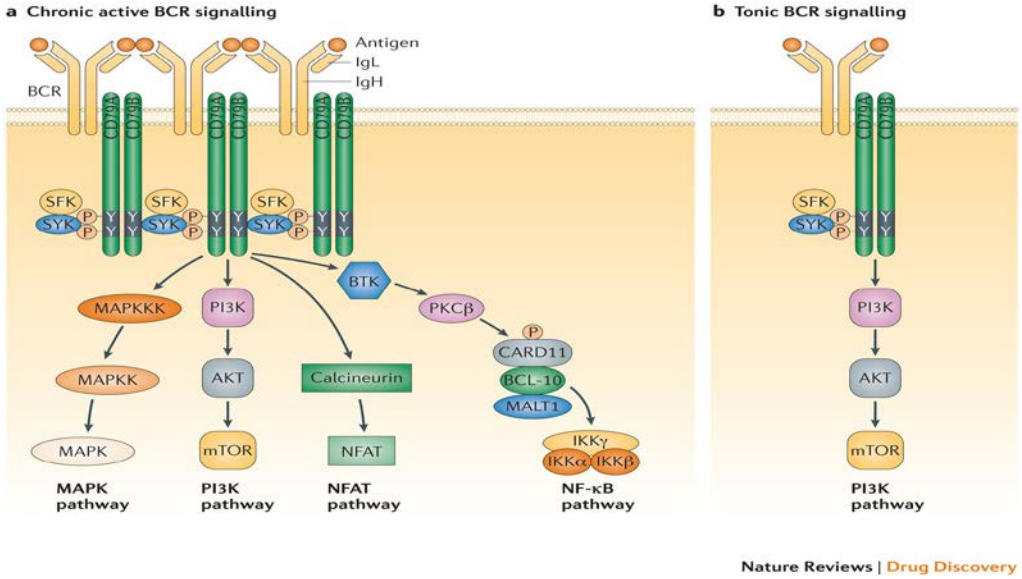
BCR signalling in lymphoid malignancy



- ABC DLBCL
- FL
- CLL
- MCL
- MAL

- Burkitts
- GCB DLBCL

Young & Staudt, Nature Reviews Drug Discovery 12, 229-243 (March 2013)

Presentation by molecule or by disease?

Hairy Cell Leukaemia as example of molecule versus disease

Central role of BRAF pathway

bjh short report

High resolution melting analysis for detection of *BRAF* exon 15 mutations in hairy cell leukaemia and other lymphoid malignancies

Elaine M. Boyd,[1] Anthony J. Bench,[1] Mars B. van 't Veer,[1] Penny Wright,[2] David M. Bloxham,[1] George A. Follows[1] and Mike A. Scott[1]

[1]*Department of Haematology, Haemato-Oncology Diagnostic Service, Addenbrooke's Hospital, and* [2]*Department of Histopathology, Addenbrooke's Hospital, Cambridge, UK*

Summary

The *BRAF* V600E mutation has recently been described in all cases of hairy cell leukaemia (HCL). We have developed and validated a rapid and sensitive high-resolution melting analysis (HRMA) assay that detects *BRAF* exon 15 mutations when hairy cells are as low as 5–10% in a sample. All 48 HCL patients were positive for the *BRAF* V600E mutation, while 114 non-HCL cases were all V600E negative. Interestingly, we detected a novel *BRAF* D594N mutation in one patient with multiple myeloma. The HRMA assay offers a useful tool to aid the laboratory diagnosis of HCL.

Novel agents in Follicular NHL

- PI3Kinase inhibition remains leading pathway target
- Idelalisib most mature data, but
  - Copanlisib
  - Duvelisib
  - TG Therapeutics
  - Curis Incorporated – novel tagged PI3K / HDACi

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma

Ajay K. Gopal, M.D., Brad S. Kahl, M.D., Sven de Vos, M.D., Ph.D., Nina D. Wagner-Johnston, M.D., Stephen J. Schuster, M.D., Wojciech J. Jurczak, M.D., Ph.D., Ian W. Flinn, M.D., Ph.D., Christopher R. Flowers, M.D., Peter Martin, M.D., Andreas Viardot, M.D., Kristie A. Blum, M.D., Andre H. Goy, M.D., Andrew J. Davies, M.R.C.P., Ph.D., Pier Luigi Zinzani, M.D., Ph.D., Martin Dreyling, M.D., Dave Johnson, B.S., Langdon L. Miller, M.D., Leanne Holes, M.B.A., Daniel Li, Ph.D., Roger D. Dansey, M.D., Wayne R. Godfrey, M.D., and Gilles A. Salles, M.D., Ph.D.

- Open-label, phase 2 study
- 125 patients with indolent non-Hodgkin's lymphomas
- No response to rituximab and an alkylating agent or had had a relapse within 6 months after receipt of those therapies

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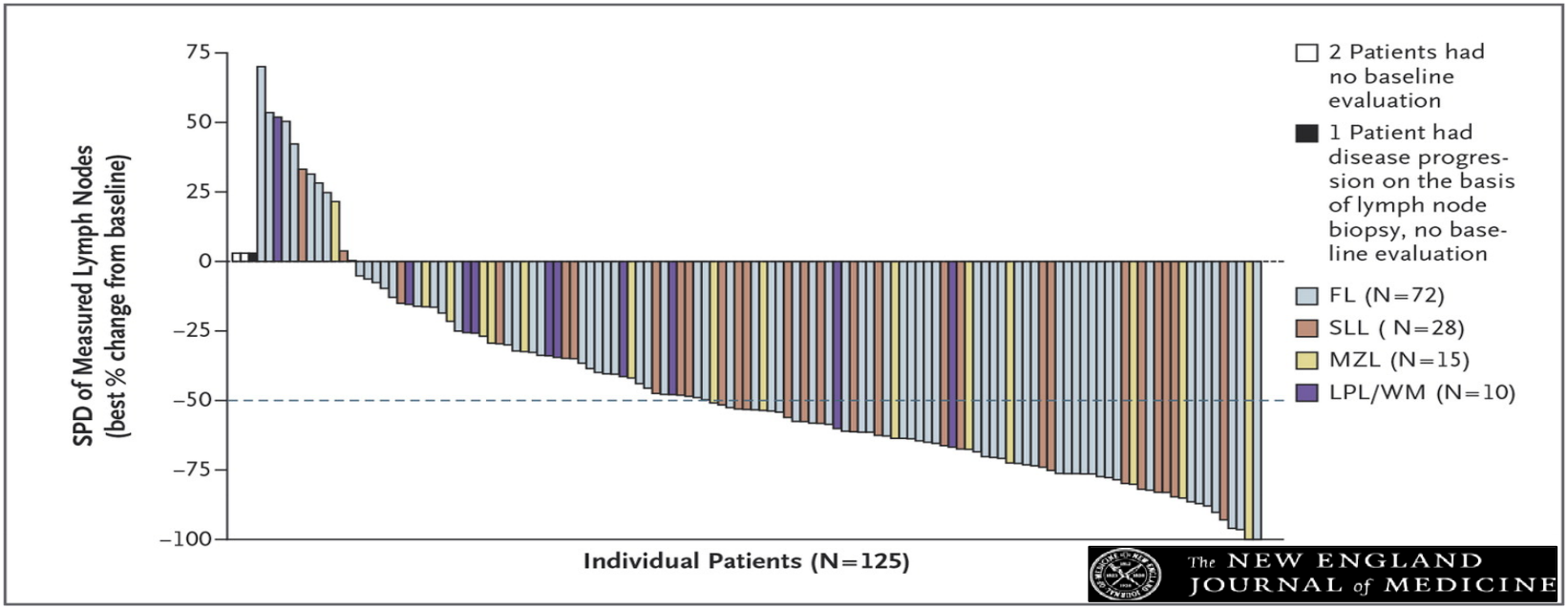
PI3Kδ inhibition by Idelalisib in patients with relapsed indolent lymphoma



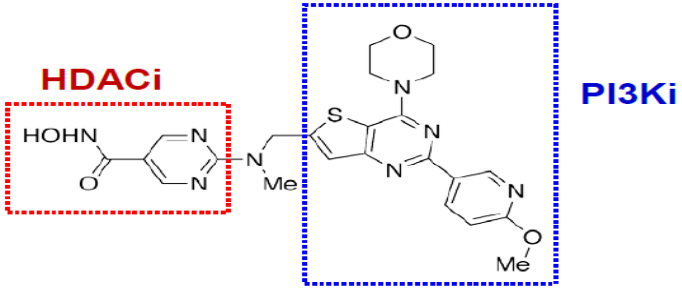
Gopal AK et al. N Engl J Med 2014;370:1008-1018.

Other novel inhibitors in indolent lymphomas

- SYK inhibition
  - GS-9973
- Dual SYK - JAK inhibition
  - PRT062070 – Cerdulatinib
- Combination PI3Ki - HDACi

CUDC-907

- Potent HDAC and PI3K enzyme inhibition in one oral small molecule
- High tissue distribution – significant levels of enzyme inhibition activity
- Active in patients with DLBCL, including transformed follicular DLBCL



IC50 (nM)	HDAC					PI3K			
Enzyme	1	2	3	6	10	Alpha	Delta	Beta	Gamma
IC50 (nM)	1.7	5	1.8	27	2.8	19	39	54	311

Conclusions therapy in advanced stage FL

- Decision-making to treat in the frontline therapy based on; disease burden, patient symptoms, patient characteristics, morbidities and patient choice
- Right choice of initial therapy is the one that gives the best chance of durable remission and lowest toxicity profile for that patient.
- R-Chemo standard of care, randomised studies versus Lenalidomide and Rituximab awaited
- Maintenance Rituximab in responders to induction R-Chemo chemotherapy plus rituximab
- Novel drugs including PI3Kδ inhibition appear effective in relapsed and refractory FL

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NHS Foundation Trust

Indolent NHL-
Comments on RT for advanced stage

George Mikhaeel, MD
Department of Clinical Oncology
Guy's & St Thomas' Hospital
KHP Academic Health Sciences Centre
London, UK

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Outline

- Role and efficacy
- Clinical trials
- Choice of dose

Role of RT in advanced disease

- Indolent NHL is very radio-sensitive (4Gy)
- Indolent lymphoma is systemic disease with many treatment options
- However, RT is useful for:
  - Localised progression / symptomatic areas
  - Consolidation treatment when local control is important e.g. spinal cord compression
  - Certain sites e.g. CNS / meningeal

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Low dose RT in advanced disease

- 4Gy / 2#
- Advantages:
  - Effective
  - Quick, convenient & cheap
  - Min side effects
  - As low dose; can treat large area or multiple areas
  - Can be repeated with equal efficacy
- Probably underutilized;
  - expansion of systemic Rx options (more expensive, lengthy and toxic!)
  - Availability of radiation oncology opinion

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Patient selection

- Which cases benefit from low-dose RT (4Gy):
  - FL, MZL, SLL, MCL
  - Predominant symptomatic area
  - W&W with localized progression
  - Debulking of residual >R-chemo before maint R (?)
  - Re-irradiation
  - Proximity of vital organs
  - Frail patients
- Which cases may need intermediate dose RT (24Gy):
  - When max chance for OR longer duration of control is desirable / advantageous

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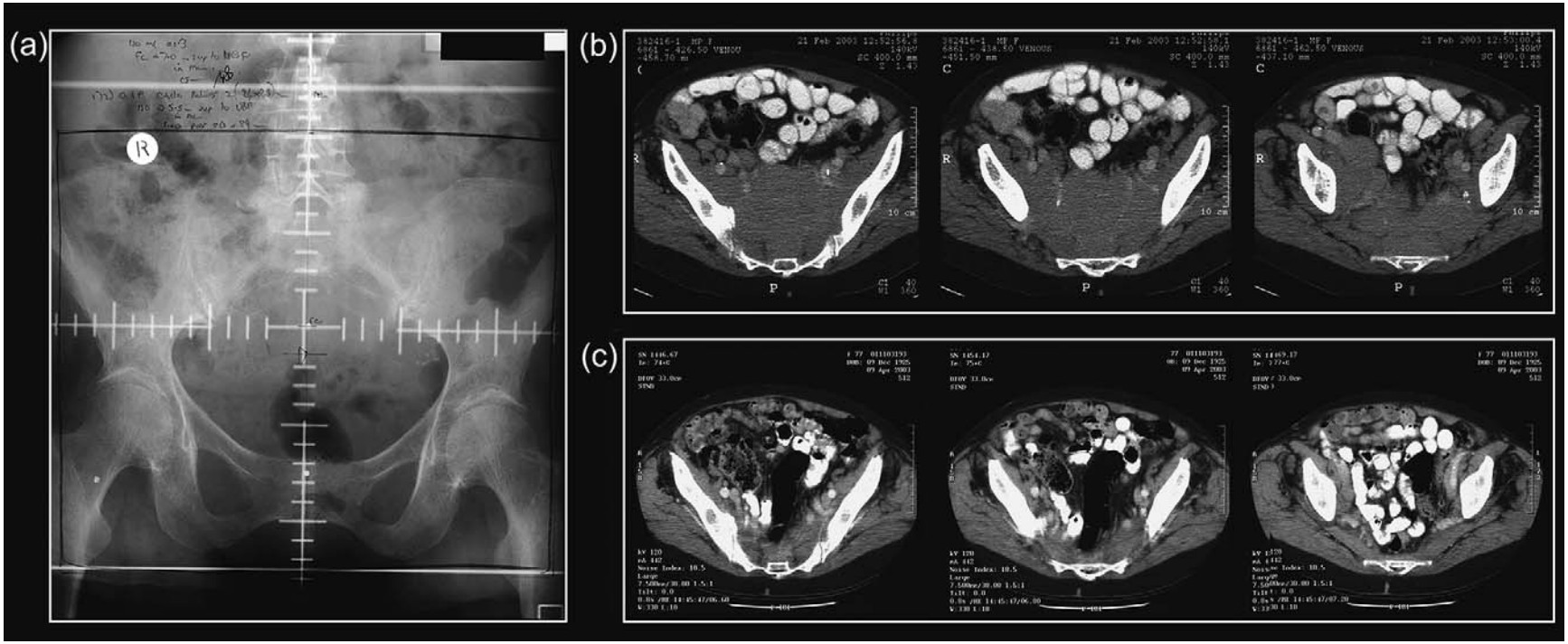
Rapid excellent response with virtually no side effects



Ng M et al. Australas Radiol 2006; 50: 222-7

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4Gy
ORR = 80 - 90%
CR = 50 - 60%

Duration: 2 y (median)
CR = 42 months
PR = 10 months

Table 2. Summary of data on efficacy of low-dose radiotherapy for lymphomas

Series	Patients (*n*)	Follicular lymphoma (%)	CR rate (%)	Median duration of CR (mo)	PR rate (%)
Ganem *et al.* (25), 1994	27	74	37	17	52
Sawyer *et al.* (26), 1997	11	54	36	5–15 (range)	54
Girinsky *et al.* (27), 2001	48	66	57	24	24
Johannsson *et al.* (28), 2002	22	68	55	22	22
Haas *et al.* (29), 2003	109	88	61	42	31
Luthy *et al.* (32), 2008	33	85	84	0–20 (range)	12
Haas *et al.* (30), 2005	71, other than follicular	0	48	23	39
Murthy *et al.* (31), 2008	36, also included aggressive	44	36; 44% for indolent, 23% for aggressive	15 for entire group	39 for those with indolent histologic features
Overall	357	213 (60%)	195 (55%)	5–77	

Ganem IJROBP 2010

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Evidence for choice of dose

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Radiotherapy and Oncology 100 (2011) 86–92

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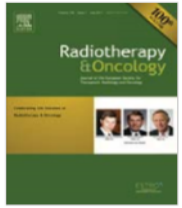
journal homepage: www.thegreenjournal.com



Phase III randomised trial

Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial ☆,☆☆

Lisa Lowry [a], Paul Smith [a], Wendi Qian [b], Stephen Falk [c], Kim Benstead [d], Tim Illidge [e], David Linch [f], Martin Robinson [g], Andrew Jack [h], Peter Hoskin [i,*]

Lancet Oncol 2014

Published Online
February 24, 2014
http://dx.doi.org/10.1016/S1470-2045(14)70036-1

4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial

Peter J Hoskin, Amy A Kirkwood, Bilyana Popova, Paul Smith, Martin Robinson, Eve Gallop-Evans, Stewart Coltart, Timothy Illidge, Krishnaswamy Madhavan, Caroline Brammer, Patricia Diez, Andrew Jack, Isabel Syndikus

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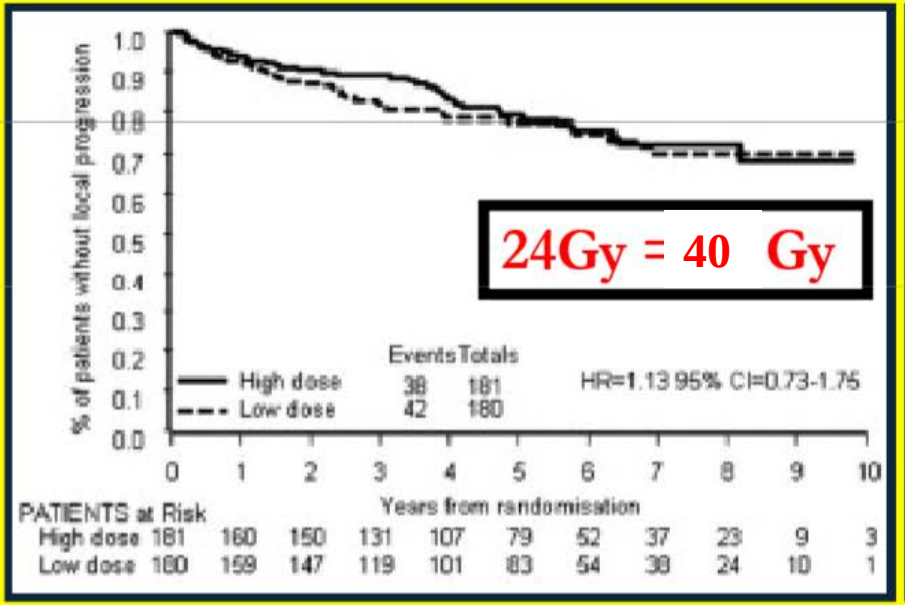

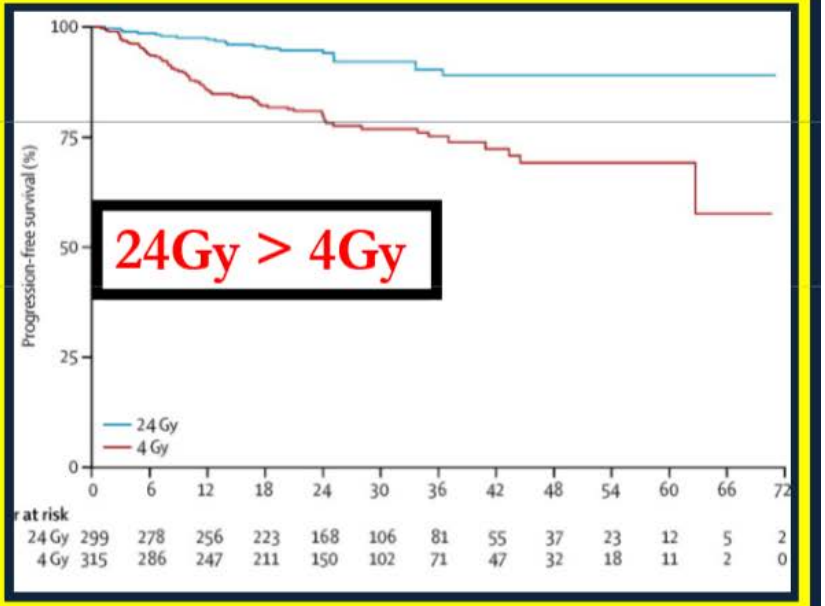

Lowry, Radiotherapy and Oncology, 2011

Hoskin, The Lancet Oncology, 2014

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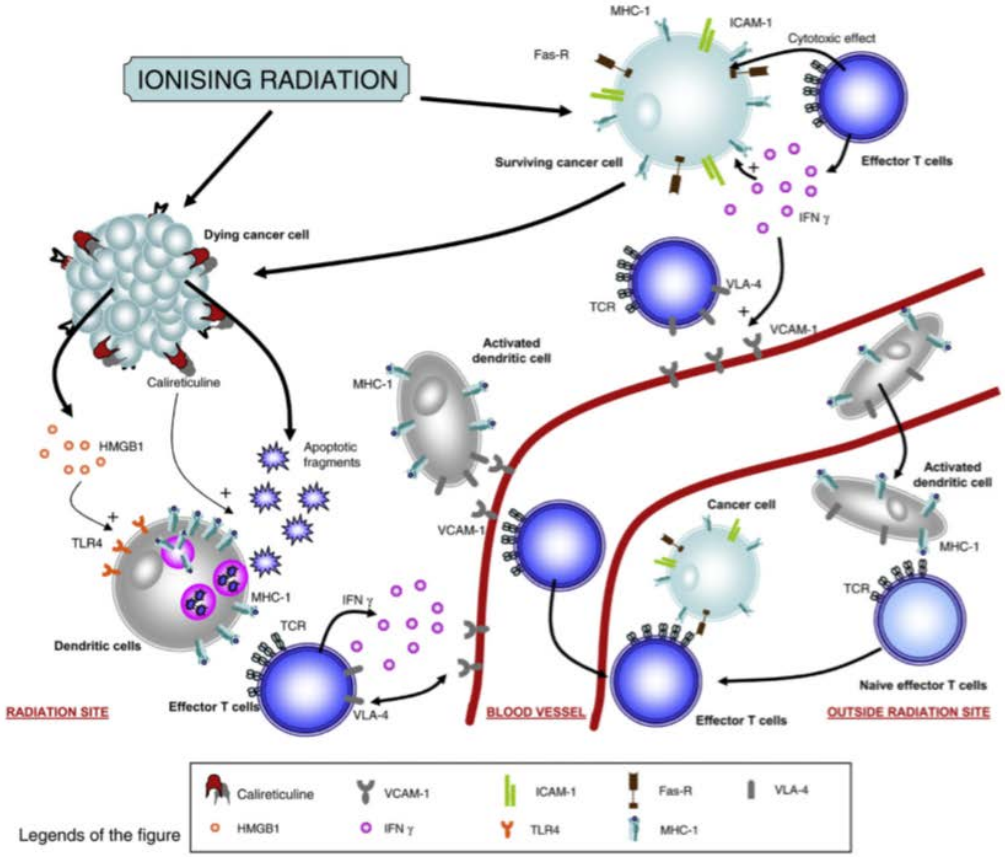

Fig. 1. Mechanisms of action of ionizing radiation.

Ganem IJROBP 2010

Key points

- RT is very effective in palliation of advanced LG-NHL
- 24Gy / 12# is superior to 4Gy / 2#:
  - ORR 91% v 81%
  - CR 68% v 49%
- 4Gy remains a highly effective palliative regime with min toxicity and high patient convenience
- 4Gy is underutilised

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RT for relapsed indolent lymphomas

Joachim Yahalom, M.D.
Memorial Sloan-Kettering Cancer Center
New York, NY, U.S.A.

Memorial Sloan Kettering Cancer Center

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General Treatment Options

- Systemic
  - REPEAT RITUXIMAB
  - ANOTHR CHEMOTHEAPY COMIBNATION
  - EXPERIMENTAL AGENTS
  - HIGH-DOSE WITH AUTOLOGOUS OR ALLOGENEIC TRANSPLANT
- Observation
- Palliation and/or local control with RT

Field Design Concept

- Involved site concept
- Limited to palliation need or local control concerns
- Dose and field considerations
- Toxicity to normal organs (including bone marrow reserve)

RT Dose for Palliation

- These are highly radio-responsive lymphomas
- Lower doses are effective
- Range of 4 Gy to 36 Gy (24 Gy commonly used)

Radiotherapy and Oncology 100 (2011) 86–92

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

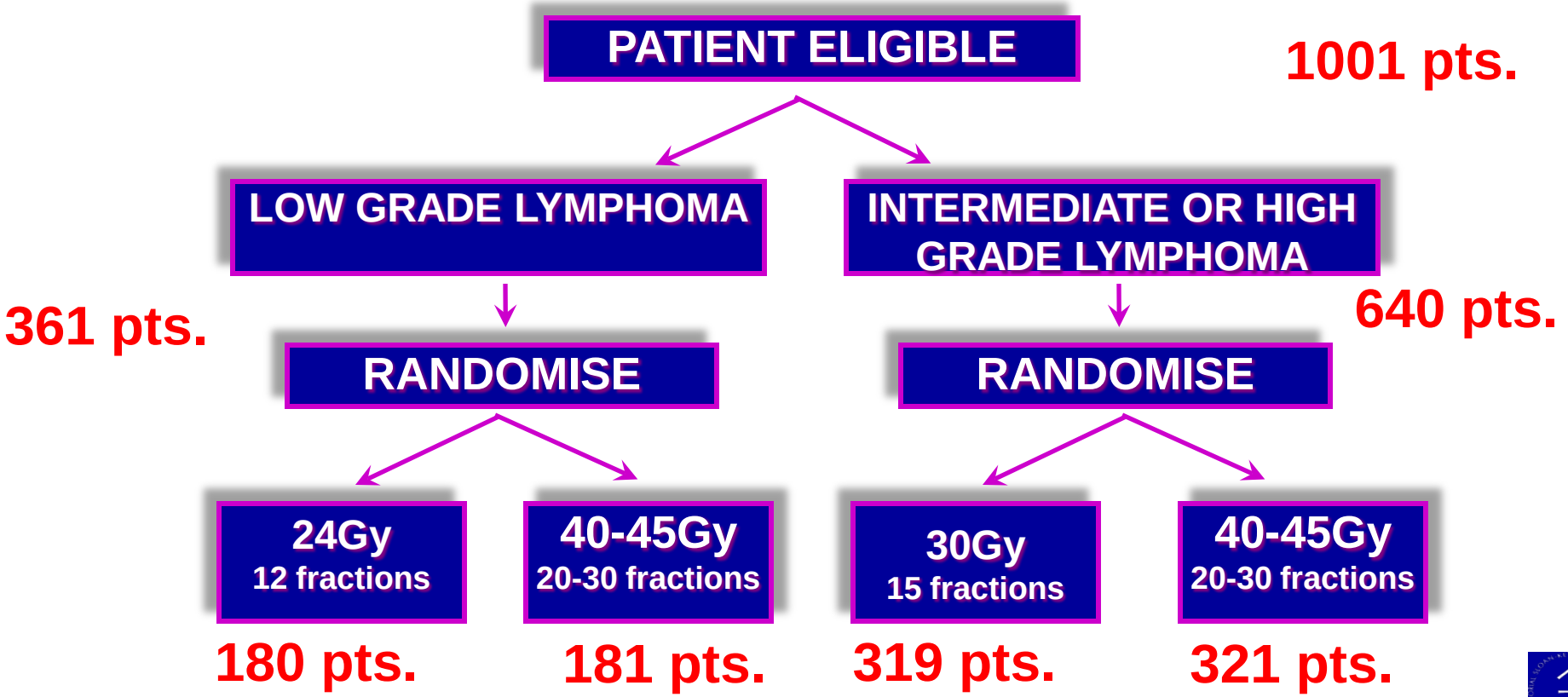
Phase III randomised trial

Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial ☆,☆☆

Lisa Lowry [a], Paul Smith [a], Wendi Qian [b], Stephen Falk [c], Kim Benstead [d], Tim Illidge [e], David Linch [f], Martin Robinson [g], Andrew Jack [h], Peter Hoskin [i,*]

Lowry et al. 2011

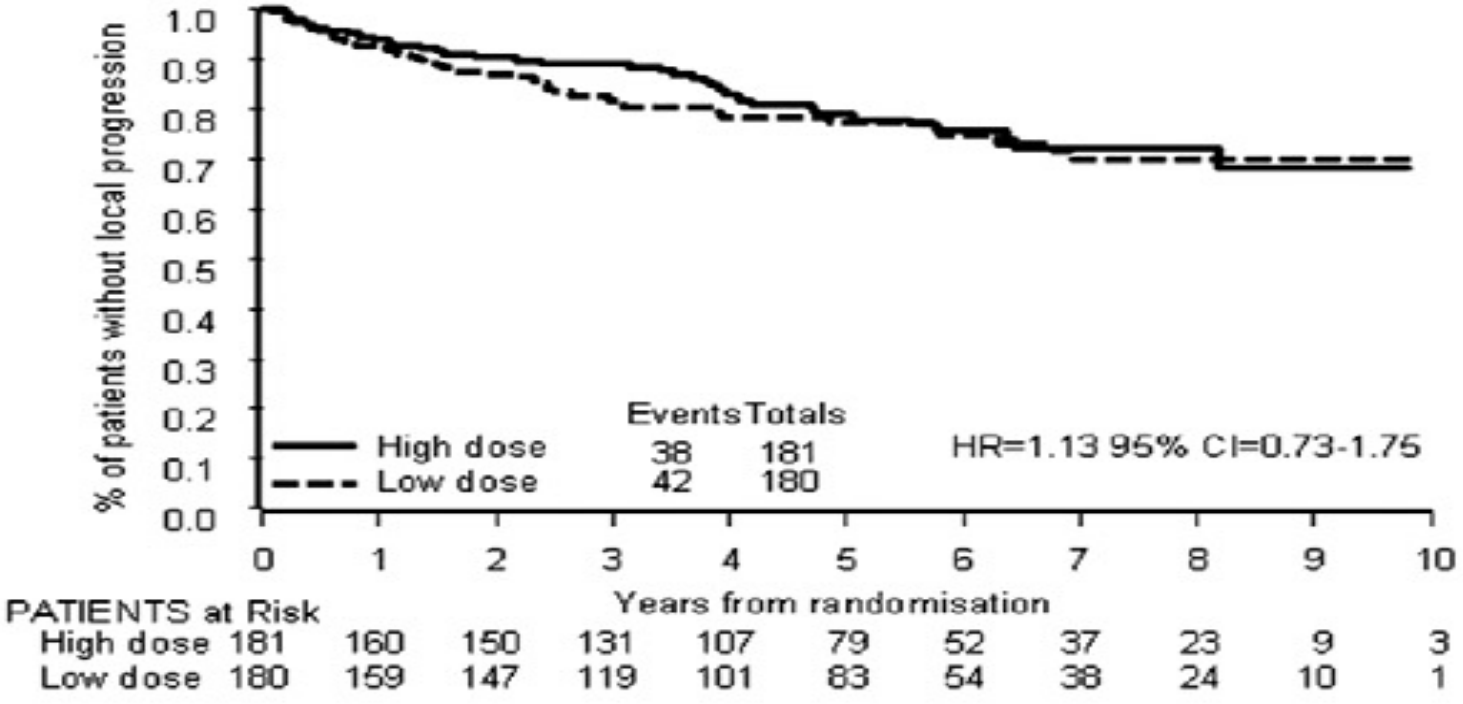
STUDY DESIGN



INDOLENT LYMPHOMAS: Local Control

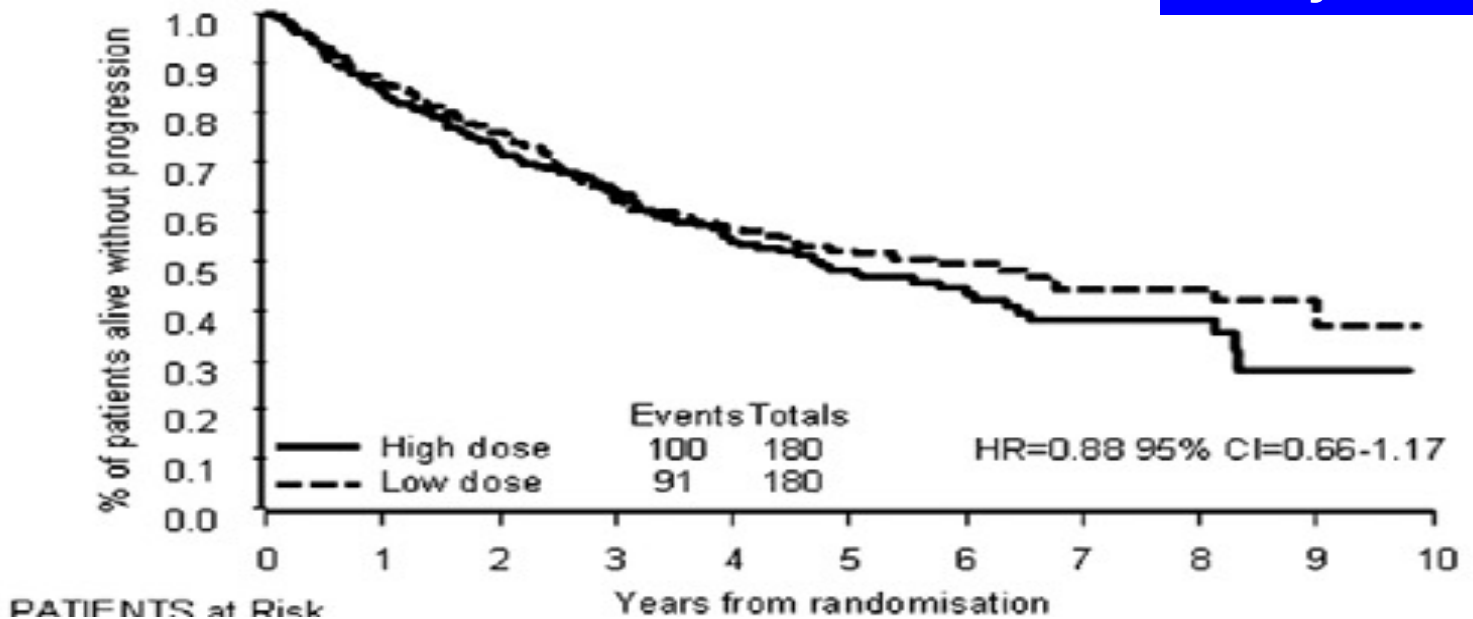
Lowry et al. 2011

(a) Freedom from local progression



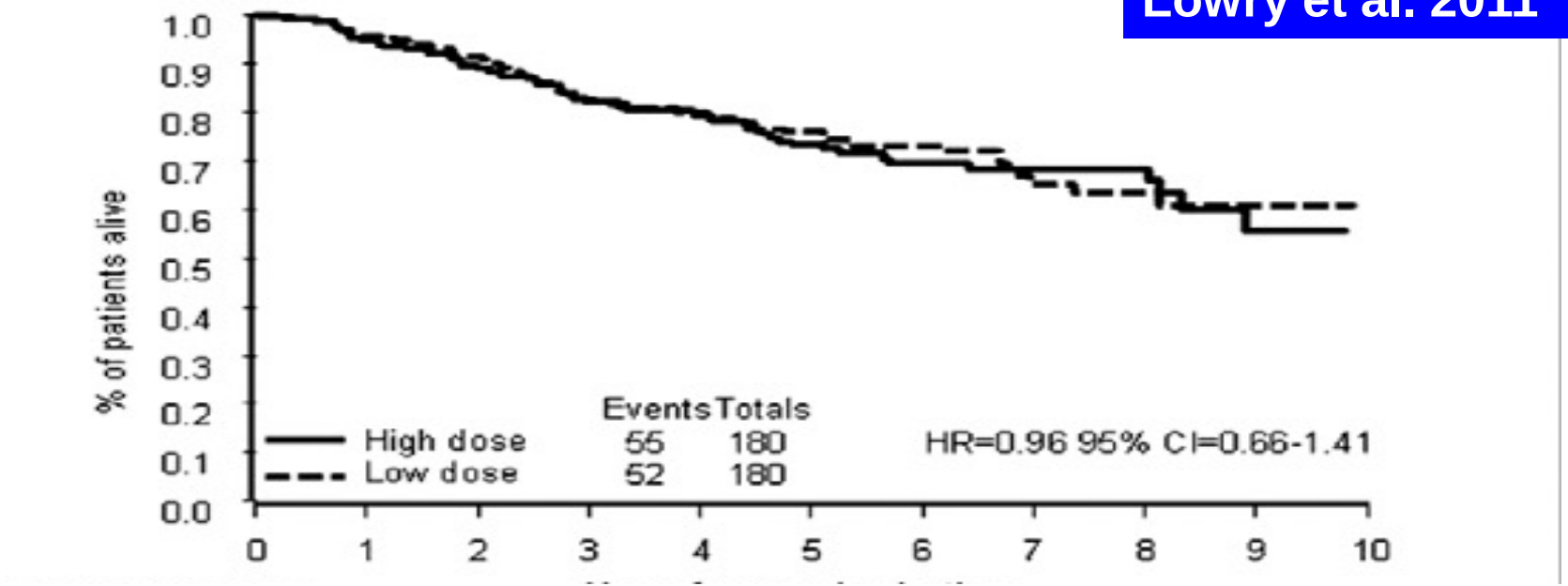
INDOLENT LYMPHOMAS: PFS

Lowry et al. 2011



INDOLENT LYMPHOMAS: Overall Survival

Lowry et al. 2011



BOOM BOOM

Basis for “Boom-Boom” Palliation

- **Institute Gustave Roussy (IGR) patient refused additional palliative WAI after receiving 4 Gy.**

- **At follow-up found to be in CR.**

“Boom-Boom” Palliation of Recurrent/Refractory NHL

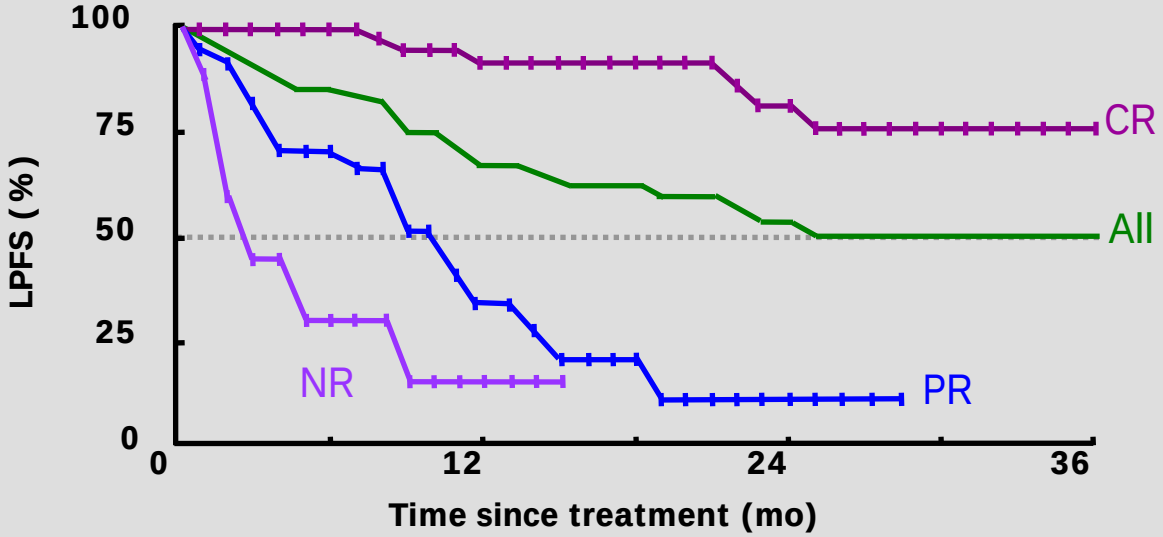
Study	N (pts)	N (sites)	PR	CR	Overall RR	Response duration	Comment
Ganem 1994	27	N/A	52%	37%	89%	Range: 4 – 35 mo	
Sawyer 1997	11	16	38%	56%	94%	Median: 7 mo	
Girinsky 2001	48	135	24%	57%	81%	2 yr actuarial: 56%	
Johannsson 2002	22	31	22%	65%	87%	Median: 22 mo	Prospective Phase II
Haas 2003	109	304	31%	61%	92%	Median: 25 mo	Prospective Phase II
Haas 2005†	71	177	39%	48%	87%	Median: 22 mo	Prospective Phase II
Summary			**34%**	**54%**	**88%**	**Median: 19 mo**	

†Includes 30 patients (42%) with aggressive NHL.

High Response Rates and Lasting Remissions After Low-Dose Involved Field Radiotherapy in Indolent Lymphomas

Journal of Clinical Oncology, Vol 21, No 13 (July 1), 2003: pp 2474-2480

By R.L.M. Haas, Ph. Poortmans, D. de Jong, B.M.P. Aleman, L.G.H. Dewit, M. Verheij, A.A.M. Hart, M.H.J. van Oers, M. van der Hulst, J.W. Baars, and H. Bartelink



Prognostic Factors for Response to “Boom-Boom”

Haas 2003 - RR

Factor	p
CR	Not-tested
Size < 5cm	NS
# prior CTx regimens	NS
Age	NS
Sex	NS
Grade	NS
# positive sites	NS

- **Grinsky 2001 - FFLP**

Factor	p
CR	< 0.001
Size < 5cm	0.041
< 2 prior CTx regimens	< 0.001
Age ≤ 65 yrs	0.07
Histology	NS
Time from diagnosis	NS

Advantages of “Boom-Boom”

- Short treatment duration.
- Minimal morbidity. No myelosuppression.
- High response rate similar to that obtained with primary therapy.
- Effective and simple re-treatment
- Rapid response onset.
- Significant LPFS interval.

FoRT: A phase III multi-centre randomised controlled trial of low dose radiotherapy for follicular and marginal zone lymphoma

Hoskin P, Kirkwood A, Popova B, Brammer C, Diez P, Gallop-Evans E, Jack A, Madhavan K, Robinson M, Syndikus I, Smith P

ELIGIBLE PATIENT

Histologically proven follicular or marginal zone NHL receiving radiotherapy for definitive treatment of stage I/II disease or for palliation by virtue of bulk or anatomical site

RANDOMISATION

Stratified by diagnosis (FL/MZL) and treatment intent (palliative/curative)

ARM A CONTROL
24Gy in 12 fractions

ARM B EXPERIMENTAL
4Gy in 2 fractions

4 weeks:	Local progression and Acute toxicity
12 weeks:	Tumour Response and Late toxicity
Follow up:	Local progression and Late toxicity every 6 months for 2 years, annually thereafter

FoRT: ENTRY CRITERIA

Patient inclusion criteria

- Patients aged over 18 with no upper age limit
- Histologically proven **follicular lymphoma** or **marginal zone lymphoma**
- Biopsy material available for histological review
- Radiation indicated for definitive treatment of stage IA or IIA disease or for palliation by virtue of tumour bulk or anatomical position
- Written informed consent

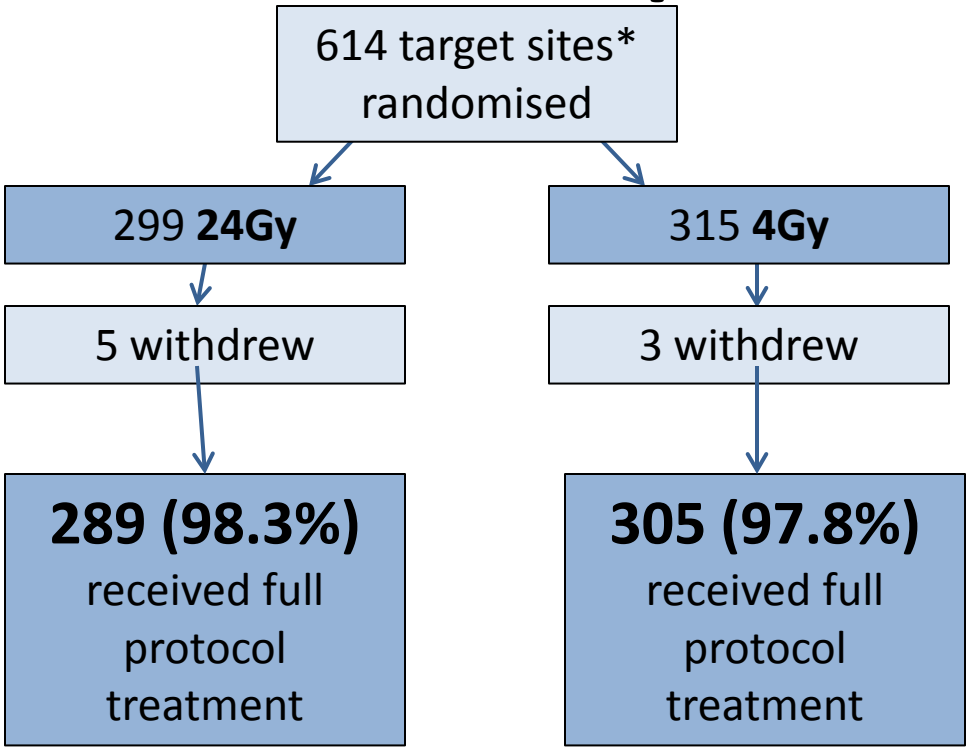
Patient exclusion criteria

- Histological subtypes other than **follicular lymphoma** or **marginal zone lymphoma**
- Predicted prognosis less than 3 months

Statistical considerations

- **Primary Endpoint**
  - Local progression free interval
    (*progression within the radiation field)*
- **Secondary Endpoints**
  - Acute toxicity
  - Late toxicity
  - RECIST response
  - Overall survival
  - Quality of life

Treatment Compliance



* 548 unique patients.

Response to radiotherapy[1]

Response	24Gy N(%)	4Gy N(%)
CR	175 (60.3)	137 (44.3)
PR	60 (20.7)	92 (29.8)
SD	22 (7.6)	44 (14.2)
No progression[2]	20 (6.9)	22 (7.1)
PD	2 (0.7)	9 (2.9)
Missing	11(3.8)	4 (1.3)

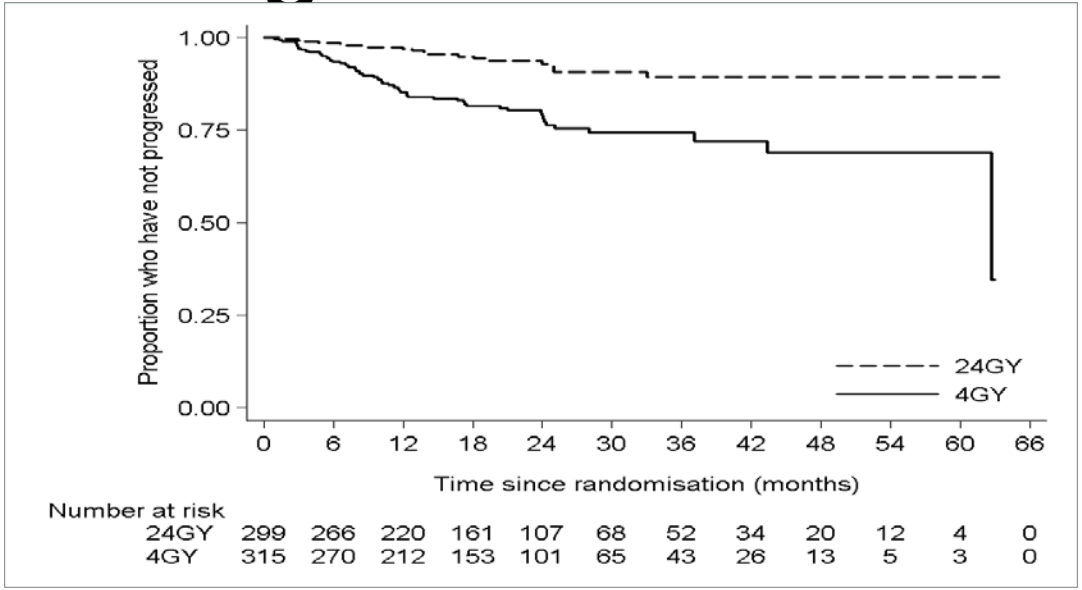
p=0.006

(Chi squared test, response (CR+ PR) vs. No response)

[1] Patients who started treatment only.

[2] No measurable disease at baseline.

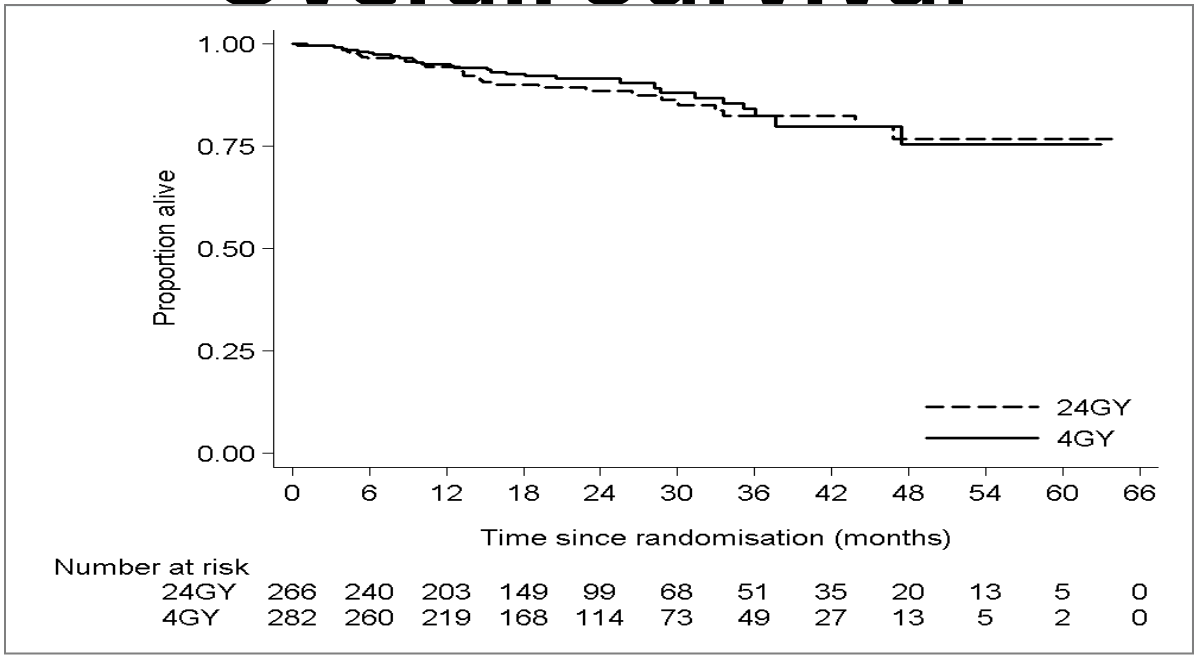
Local Progression Free Interval



Hazard Ratio: 3.49 (95% CI: 2.06 - 5.90), p<0.001

2 Year local progression free rate: 93.7% (24Gy) and 80.4% (4Gy)

Overall Survival



Hazard ratio (each patient counted once): 0.88 (95% CI: 0.53 - 1.46), p=0.61

Median Follow-up time: 22.8 months (0.39 -63.80)

Summary and conclusion

- 4Gy in 2 fractions was inferior to 24Gy in 12 fractions in achieving a durable local progression free interval in follicular and marginal zone NHL.
- 24Gy in 12 fractions should remain the standard schedule for indolent lymphoma.
- 4Gy in 2 fractions is effective (CR rate: 44.3%, PR rate: 29.8%) and may be considered for palliative treatment or retreatment.

Whom to Boom-Boom?

- **Follicular**
- **Mantle-cell**
- **CLL/SLL**
- **Marginal zone**

- **Relapsed, refractory to systemic therapy**
- **Not used as an alternative adequate first-line**

*The wide spectrum of RT responses**

0.1 μSv

Lymphoma	**Medullo**	**Breast Cancer**	**Lung Cancer**	**Prostate Cancer**	**GBM**
4-45 Gy	23.4-36 Gy	50 Gy	60-70 Gy	86.4 Gy	>100 Gy

Outliers… ***Outliers…***

Imagine a 10-fold spread in RT dose for prostate cancer…

Our Central Hypothesis:

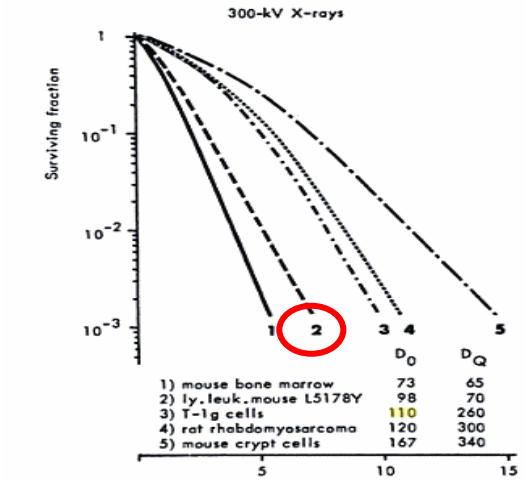
1. Dramatic variations in radiosensitivity can be explained by molecular differences in the tumor
2. Gene expression signatures can be used to predict RT response and to better stratify patients

**Definitive vs. post-op not separated…*
these doses are just for talking points…

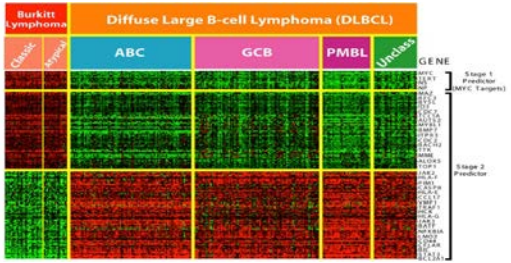
What Drives Radiation Sensitivity in Lymphoma?

The old radiobiology view of RT sensitivity in lymphoma

Lymphoma = Apoptosis = Radiosensitive



RT sensitivity in lymphoma, in the molecular age…



Lymphoma gene expression profiles may predict differences in radiosensitivity

Figure from:
Radiobiology for the Radiologist
By Eric J. Hall, Amato J. Giaccia

It is intrinsic or extrinsic radiosensitivity?

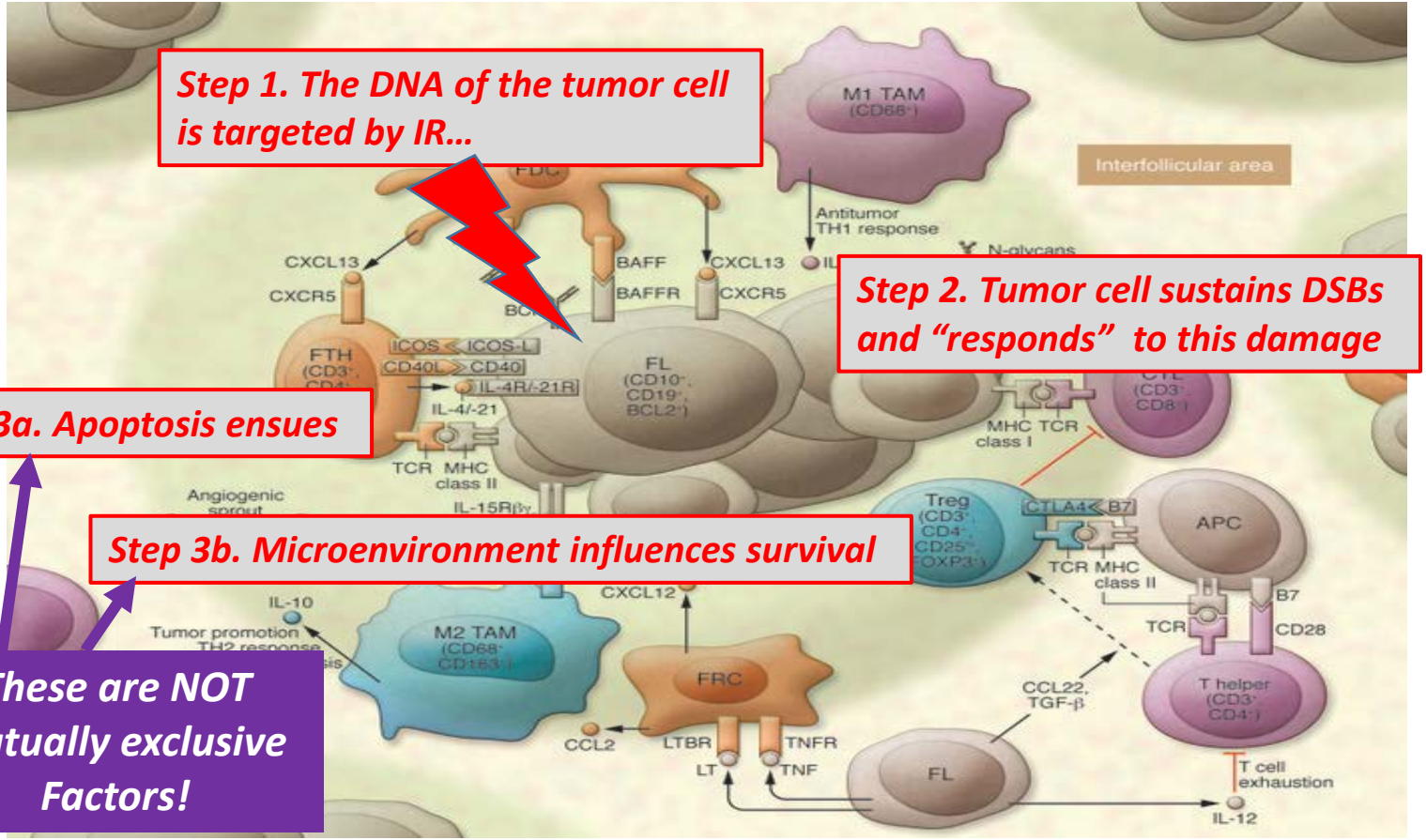
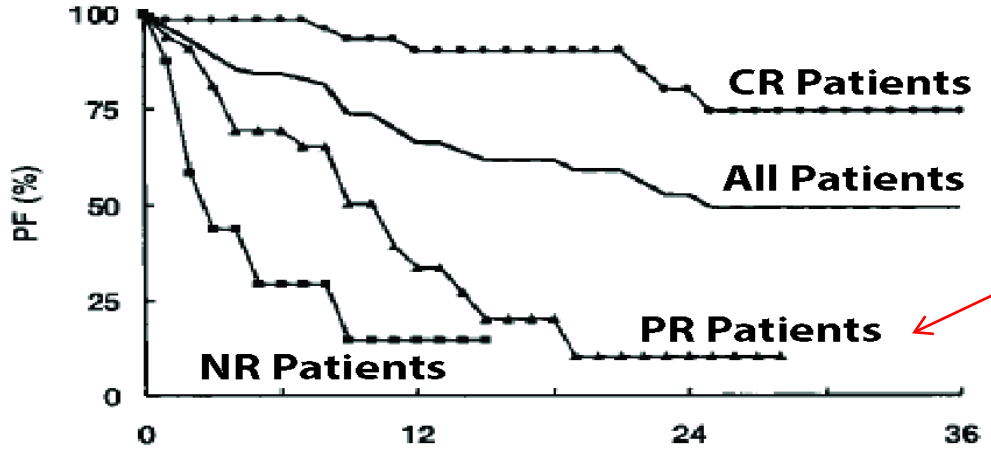


Image from: *J Clin Invest.* 2012;122(10):3424-3431. doi:10.1172/JCI63186.

Response to very low dose RT is variable

Our key questions:

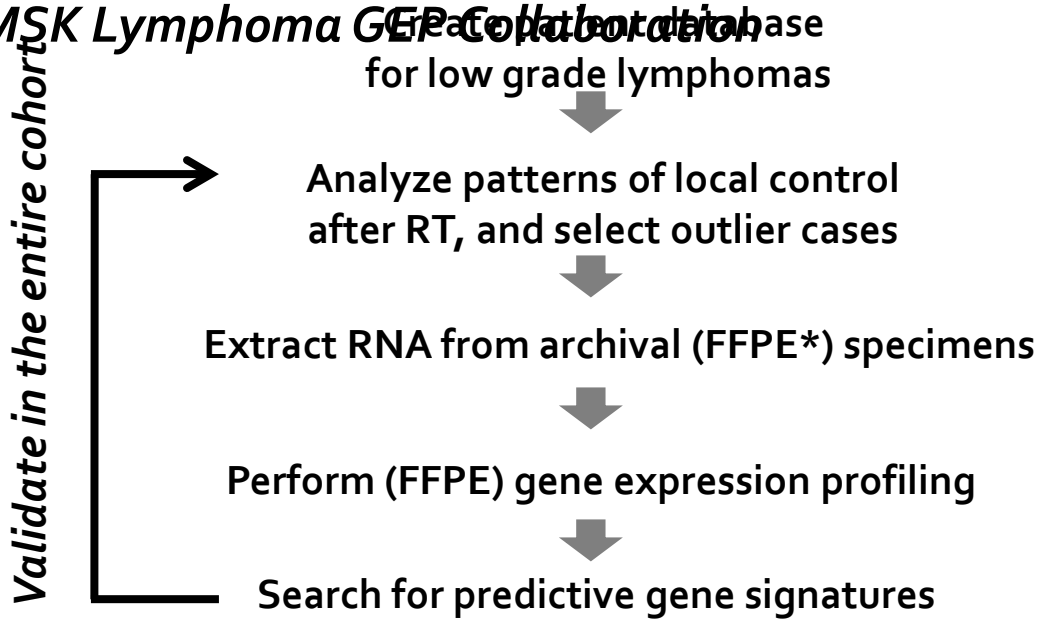
1. **Are there molecular biomarkers that can predict these differences?**
2. **What about gene expression profiles?**



Can we identify these patients up-front?

Materials and Methods: Our Approach

The Yale/MSK Lymphoma GEP Collaboration



*FFPE=Formalin-fixed, paraffin-embedded tissue

Database creation: Low grade lymphomas treated with 2 Gy x 2

- **90 sites in 68 patients**
- **2006-2012**
- **Initial responses assessed by imaging or PE**
  - CR
  - PR
  - NR
- **Local progression free survival**
  - estimated with K-M method
  - compared between response groups via log-rank

Median Age	68
Stage at treatment	
I	11
II	2
III	6
IV	31
Relapsed	40
Histology	
Follicular	62
Marginal Zone	14
Mantle Cell	6
SLL	6
MALT	1
Primary B Cell Cutaneous	1

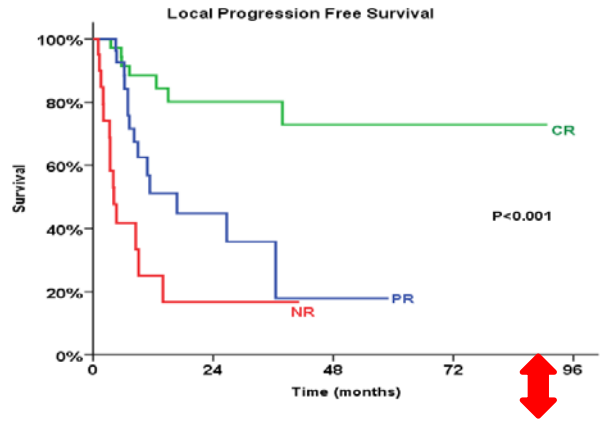
Initial response predicts local progression free survival

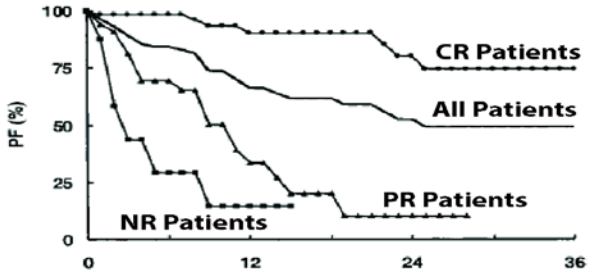
	All	CR	PR	NR
# Patients	67	34	22	21
# Sites	90	37	30	23
Median Follow up (mos)	20.1	30.4	14.6	11.1
Median Time to local progression (mos)	8.6	16.0	8.5	3.4
3 year LPFS	52.0%	80.1%	35.8%	16.7%

High Response Rates and Lasting Remissions After Low-Dose Involved Field Radiotherapy in Indolent Lymphomas

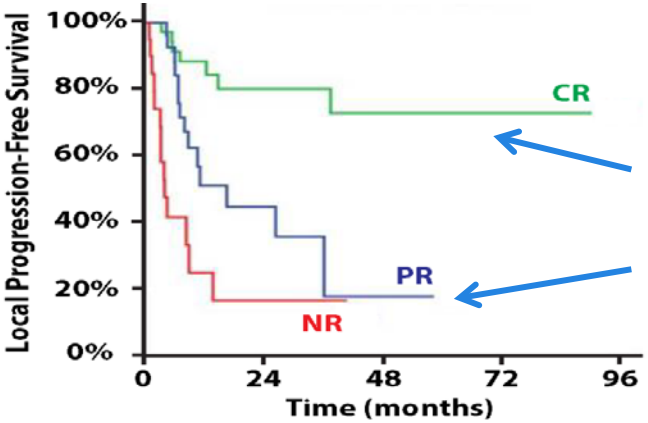
By R.L.M. Haas, Ph. Poortmans, D. de Jong, B.M.P. Aleman, L.G.H. Dewit, M. Verheij, A.A.M. Hart, M.H.J. van Oers, M. van der Hulst, J.W. Baars, and H. Bartelink

Journal of Clinical Oncology, Vol 21, No 13 (July 1), 2003: pp 2474-2480





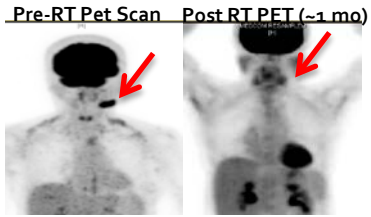
Selection of outlier cases



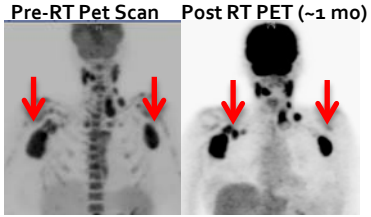
6 CR cases

6 NR/PR cases

Complete Response



Partial/No Response



Patient Sample Summary by Type + Response

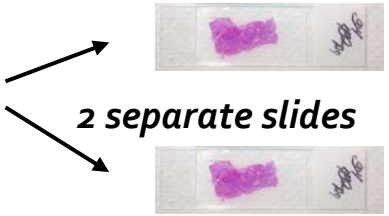
12 FFPE Samples

9 Follicular Lymphoma	
CR	S03 (7/15/13)
	S05 (7/15/13)
	S11-46296 1U1
	S13-62359
PR/NR	S06 (7/15/13)
	S08 (7/15/13)
	S08-1966 1U2
	S14-27031
	S14-62451

1 Low Grade BCL NOS	
CR	S12-16638

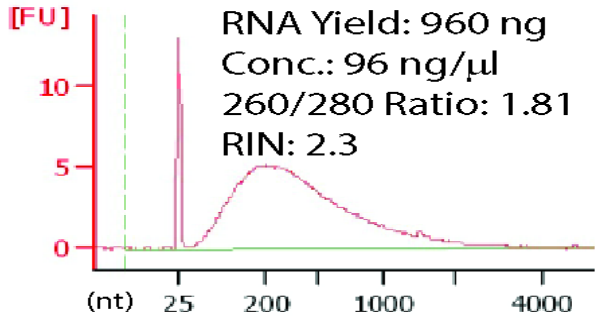
2 Marginal Zone	
CR	S01-41072
PR/NR	S12-52214 1U3

Whole transcriptome profiling with FFPE extracted RNA samples



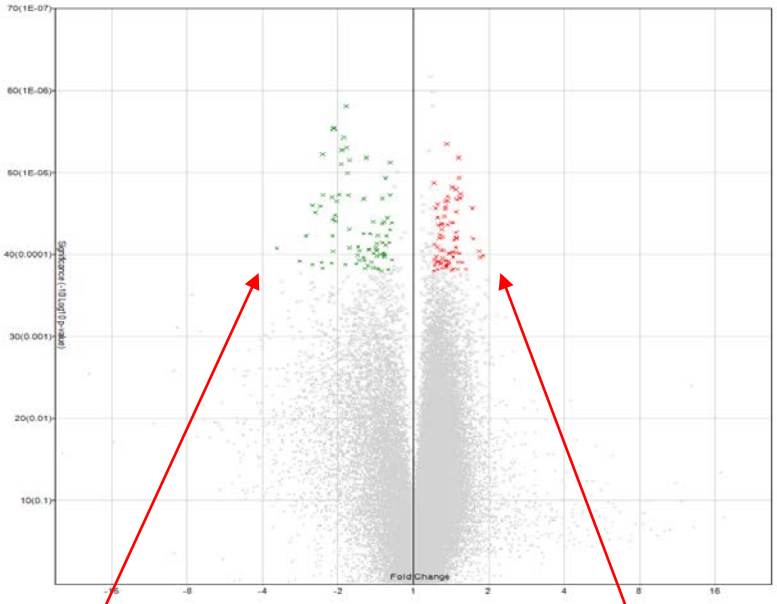
Extract RNA

AFFYMETRIX®



Whole transcriptome profiling with FFPE extracted RNA samples

160 differentially expressed regions with FC > 1.2 and FDR < 0.055



Decreased in CR

Increased in CR

Increased expression in CR vs. PR/NR

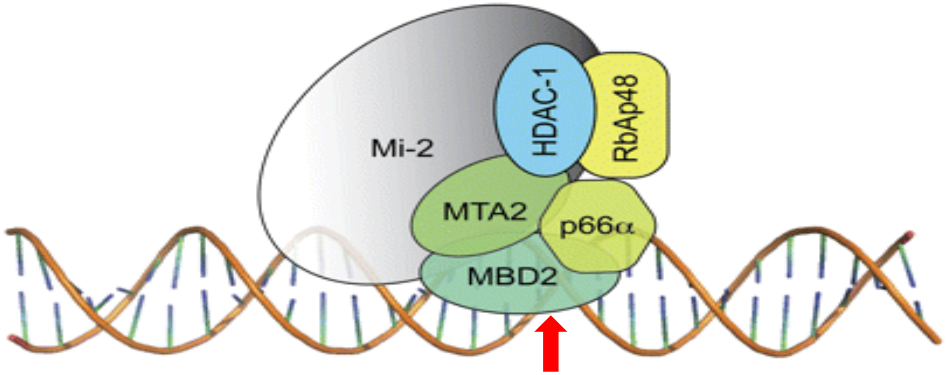
Gene	CR Avg Exp.	NR Avg. Exp	Fold Change	Gene Description
MIR517B	4.94	4.15	1.73	microRNA 517b
MGC13053	5.89	5.19	1.62	uncharacterized MGC13053
OR10J1	4.92	4.32	1.52	olfactory receptor, family 10, subfamily J, member 1
C17orf112	5.06	4.48	1.49	chromosome 17 open reading frame 112
PART1	5.99	5.42	1.48	prostate androgen-regulated transcript 1 (non-protein coding)
SNORD114-20	4.71	4.18	1.44	small nucleolar RNA, C/D box 114-20
TRDV1	6.23	5.71	1.44	T cell receptor delta variable 1
VHLL	5.44	4.96	1.39	von Hippel-Lindau tumor suppressor-like
RERG-AS1	5.46	5	1.37	RERG antisense RNA 1
NRXN1	5.51	5.07	1.36	neurexin 1
ZNF727	6.45	6.01	1.35	zinc finger protein 727
EFCAB1	5.54	5.12	1.34	EF-hand calcium binding domain 1
KLRD1	6	5.63	1.3	killer cell lectin-like receptor subfamily D, member 1
SORBS1	6.05	5.68	1.29	sorbin and SH3 domain containing 1
TRBV6-1	4.83	4.46	1.29	T cell receptor beta variable 6-1
ANGPTL7	6.34	5.99	1.28	angiopoietin-like 7
PCDH20	5.52	5.2	1.25	protocadherin 20
GABRA2	5.52	5.2	1.25	gamma-aminobutyric acid (GABA) A receptor, alpha 2

Decreased expression in CR vs. PR/NR

Gene	CR Avg Exp.	NR Avg. Exp	Fold Change	Gene Description
MBD2	8.95	10.76	-3.51	methyl-CpG binding domain protein 2
RBM6	7.7	9.2	-2.82	RNA binding motif protein 6
SYVN1	9.05	10.47	-2.68	synovial apoptosis inhibitor 1, synoviolin
SRGAP2B	7.87	9.22	-2.54	SLIT-ROBO Rho GTPase activating protein 2B (pseudogene)
EIF3C	8.7	10.03	-2.53	eukaryotic translation initiation factor 3, subunit C
ANKRD36	8.69	9.91	-2.33	ankyrin repeat domain 36; ankyrin repeat domain 36C
DNAJC10	7.48	8.69	-2.31	DnaJ (Hsp40) homolog, subfamily C, member 10
EIF3CL	8.66	9.86	-2.3	eukaryotic translation initiation factor 3, subunit C
ST6GAL1	7.5	8.58	-2.11	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1
LOC100996862	9.23	10.3	-2.1	ankyrin repeat domain-containing protein 36A-like
PSMC4	6.91	7.98	-2.1	proteasome (prosome, macropain) 26S subunit, ATPase, 4
SDHAP1	7.69	8.75	-2.09	succinate dehydrogenase complex, subunit A,
EAF2	6.7	7.73	-2.05	ELL associated factor 2
SEL1L3	8.85	9.88	-2.05	sel-1 suppressor of lin-12-like 3 (C. elegans)
NARS	7.61	8.56	-1.94	asparaginyl-tRNA synthetase
POU2AF1	7.72	8.67	-1.93	POU class 2 associating factor 1
HERC2P9	7.92	8.82	-1.87	hect domain and RLD 2 pseudogene 9
HERC2P2	8.14	9.01	-1.83	hect domain and RLD 2 pseudogene 2

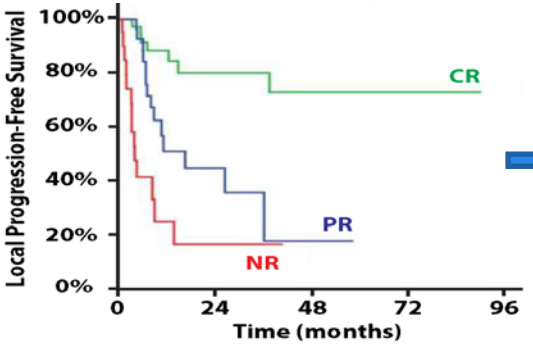
Associated with chromatin modification in cancers

Are the genes relevant to radiosensitivity?



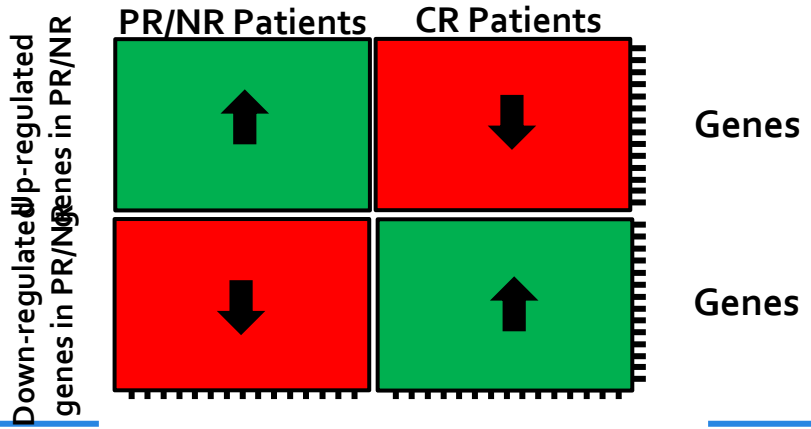
4-fold reduction in MBD2 mRNA in CR patients

What did we do?

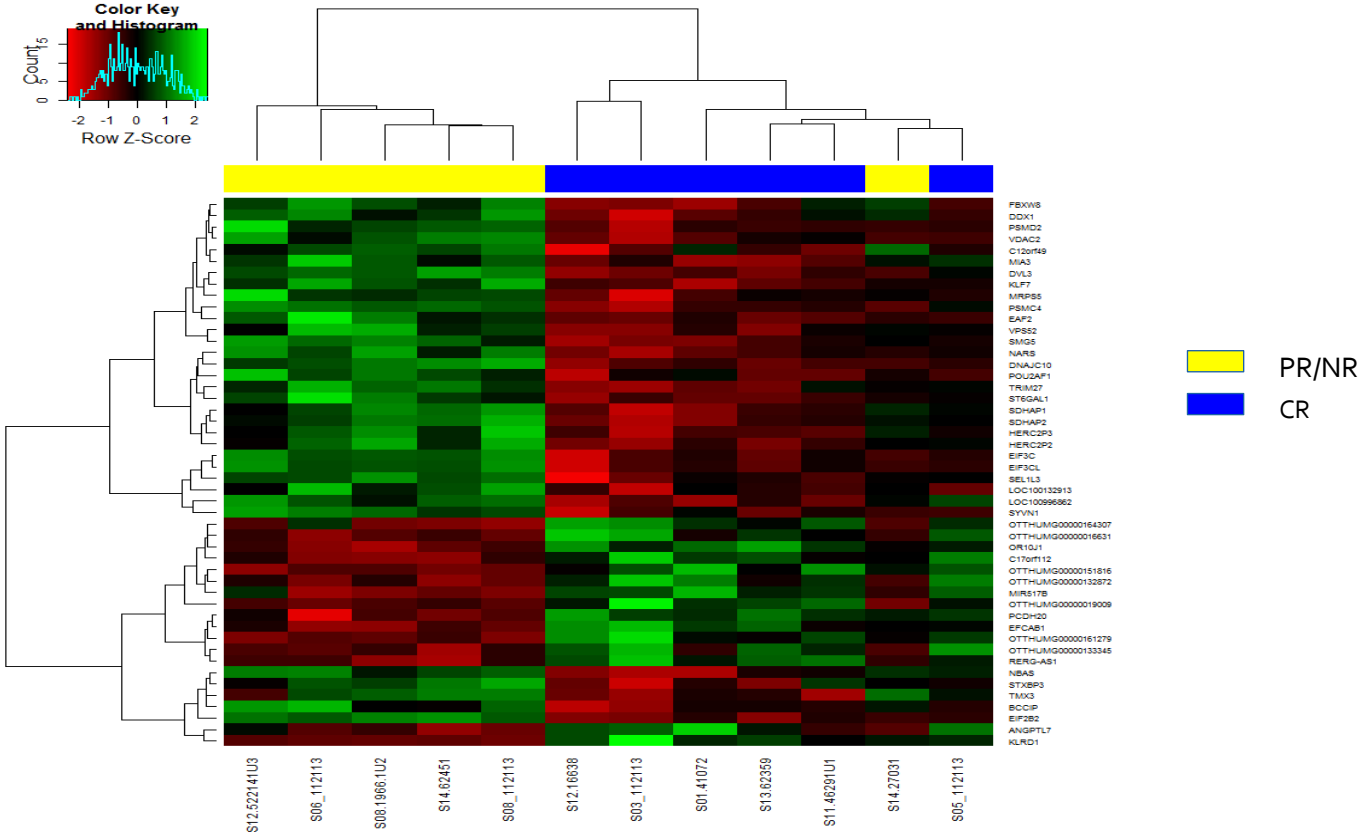


Find FFPE biopsy specimens → Extract RNA → Gene expression profiling → Create an RT response signature

The ideal result



CR vs. PR/NR Gene Pathways



Conclusions

- Intrinsic radiosensitivity exists, but molecular features may trump histology
- "Outlier treatment responders" may provide molecular insights for RT responses
- Archival FFPE tissue now can be used readily for gene expression profiling
- FFPE gene profiling is a viable approach to identify RT response signatures
- RT gene signatures could help better direct treatment choices in lymphoma

Studies are ongoing and we are actively seeking collaborators!

Yale CANCER CENTER
SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

Sloan Kettering Cancer Center

ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

Conclusions

- **Very low dose RT for low grade lymphomas**
  - –Initial response predicts local progression free survival
- **Preliminary microarray profiling studies**
  - –Using FFPE specimens is feasible
  - –Initial studies showed statistically significant changes in relative gene expression between CR and NR groups

Future Directions

1. Expand and validate gene expression signatures in entire low grade lymphoma cohort
2. Translate signatures back to laboratory for functional studies
3. Expand collaboration to other centers/institutes
4. Adapt the proposed workflow to other lymphoma subtypes

Thank you!

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Indolent Nodal non Hodgkin Lymphoma

Volumes, doses and techniques

Umberto Ricardi

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Modern RT in Indolent Lymphoma

- Advances in imaging, treatment planning, treatment delivery, enable irradiation of these volumes with great precision

- The current guidelines for involved field RT based on anatomic landmarks and encompassing adjacent uninvolved lymph nodes are no longer appropriate for modern and more “targeted” RT delivery

Modern radiotherapy guidelines developed by

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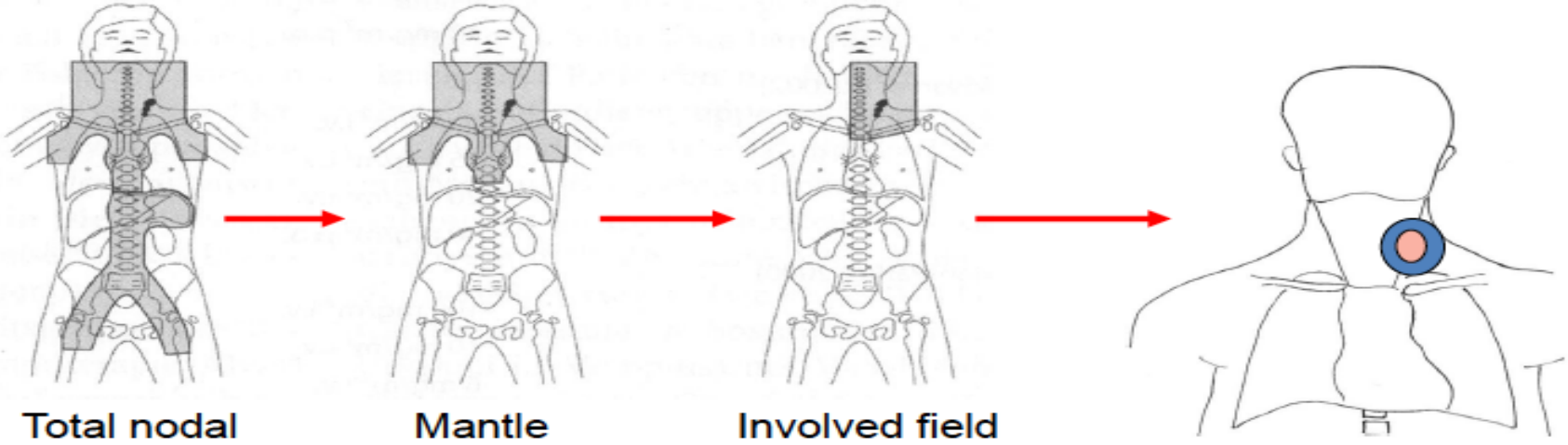
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

- Previous wide field and involved field replaced by limited volumes based solely on detectable involvement at presentation
- ICRU concepts of GTV, CTV, ITV, and PTV are used
- New concept, Involved Site RadioTherapy (ISRT), defines CTV on this basis
- Previous doses were higher that necessary, replaced by lower doses in most lymphoma types

Development of RT volumes



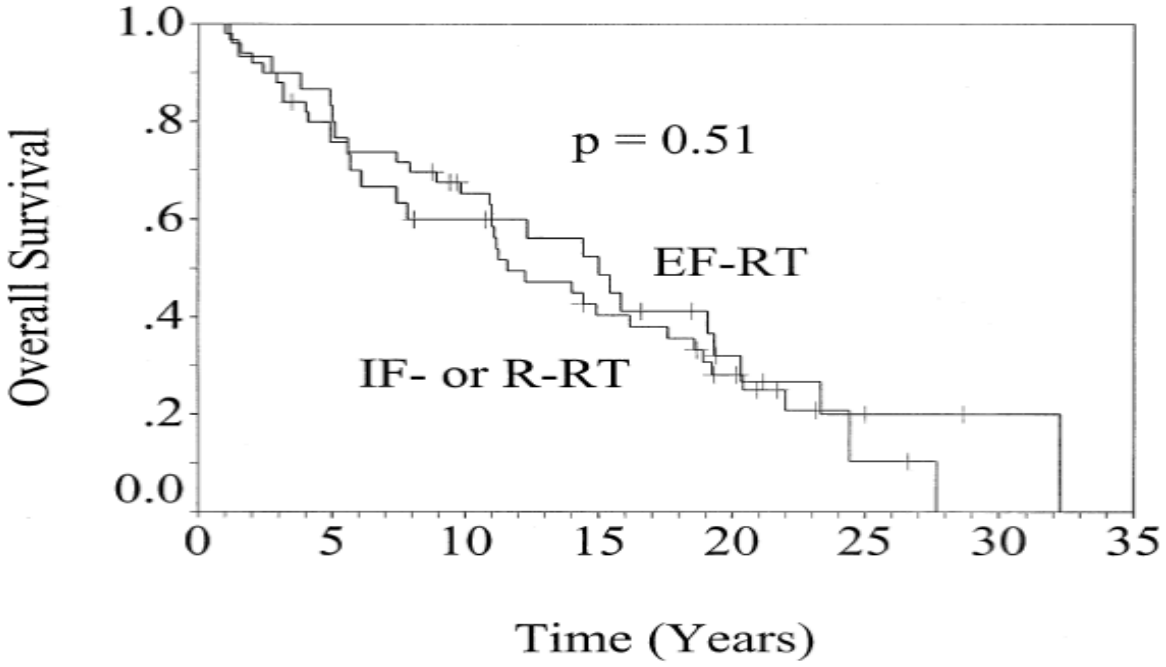
Total nodal Mantle Involved field

2D planning, based on bony landmarks

Involved node

3D planning, based on lymphoma volume

EFRT do not protect from relapses



Wilder et al, IJROBB, 2001

Clinical Investigation: Lymphoma and Leukemia

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

Treatment Volume Principles

- Modern RT planning in lymphoma incorporates the current concepts of volume determination as outlined by ICRU Report 83
- It is based on defining a gross tumor volume (GTV) and a clinical target volume (CTV), that is expanded to a planning target volume (PTV)
- The PTV is then used to define beam coverage
- This approach allows direct comparison with the diagnostic 3D-imaging, increasing the accuracy with which lymph node volumes are defined

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Indolent lymphomas

- In early stage disease, RT is the primary treatment
  - Target is the macroscopic lymphoma AND adjacent nodes in that site with a generous margin
- In advanced disease, RT is palliative
  - Target is localized symptomatic disease

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Role of Radiation Therapy in Indolent Nodal Lymphomas

- **Localized Indolent Lymphoma**

  - For the potentially curative treatment of localized early stage (I and II_1) disease, RT is used as the primary treatment approach

Radiation therapy as primary treatment

In most clinical situations that require RT as primary modality, the GTV should be readily visualized during treatment preparation

The CTV should be more generous in this clinical situation and encompass lymph nodes in the vicinity that, although of normal size, might contain microscopic disease that will not be treated when no chemotherapy is given

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)

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Volume Definitions for Planning RT for Lymphomas

- **Determination of Gross Tumor Volume**

Imaging abnormalities obtained before any intervention should be outlined on the simulation study and included in the CTV

Volume Definitions for Planning RT for Lymphomas

- **Role of imaging in radiation planning**
  - 3D imaging (with CT supplemented by functional imaging: PET-CT)
  - The use of diagnostic contrast-enhanced CT is recommended to help to delineate nodal stations and differentiate nodes from vessels
  - Ideally, imaging studies with the patient in the treatment position and using the planned immobilization devices
  - Four-dimensional CT imaging in determining the ITV for sites that move with respiration
  - Acquiring high-quality imaging is fundamental to high-quality RT planning

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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

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Role of Radiation Therapy in Indolent Nodal Lymphomas

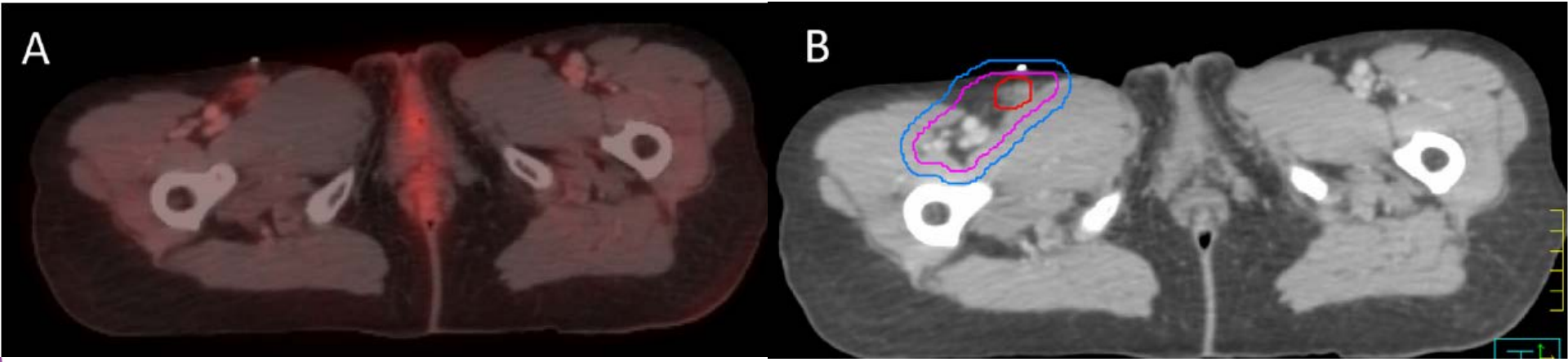
- **Localized Indolent Lymphoma**

  - The CTV must be designed to encompass suspected subclinical disease based on preintervention GTV imaging

  - The CTV should incorporate GTV and include as a minimum adjacent lymph nodes potentially containing microscopic disease in that site, and a generous margin dictated by the clinical situation

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

ISRT: Localized indolent lymphoma



The CTV must be designed to encompass suspected subclinical disease based on the pre interv
The CTV should incorporate GTV and include adjacent lymph nodes in that site and margin di

Illidge et al, IJROBP, 2014

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Defining CTV relies upon

- knowledge of the spread patterns of the disease
- potential subclinical extent of involvement
- adjacent organ(s) at risk constraints

all of which depend on clinical judgment and experience

Considerations on RT dose

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Reduced RT dose in NHL
A randomised phase III trial

361 involved sites of patients with indolent lymphomas

(mostly FL and MZL in early stages)

Baseline characteristics and indications for therapy.

	Indolent	
	24 Gy *N* = 180	40–45 Gy *N* = 181
Age median (range)	62 (29–85)	64 (30–89)
Male gender N (%)	84 (47)	97 (54)
First-line treatment: stage N (%)		
I	69 (40)	72 (41)
IE	38 (22)	47 (27)
II/IIE	11 (6)	13 (7)
III/IV	6 (3)	12 (7)
Relapsed/refractory; any stage N (%)	50 (29)	30 (17)
Not known N	6	7
B symptoms N (%)	13 (8)	4 (2)
Time from diagnosis to randomisation; median months (range)	3.1 (0.2–220)	2.8 (0–179)
Indication for RT radical	119 (66)	130 (72)
Palliation	56 (31	46 (25)
Consolidation	5 (3)	5 (3)
Previous/contemporaneous chemotherapy N (%)	46 (26)	36 (20)
Previous radiotherapy N (%)	15 (8)	24 (13)
Previous rituximab exposure N (%)	2 (1)	2 (1)
Karnofsky scale N (%)		
60–80	16 (12)	16 (11)
90	44 (34)	34 (24)
100	70 (53)	90 (64)
Not known	50	41

Lowry et al, Radiother Oncol, 2011

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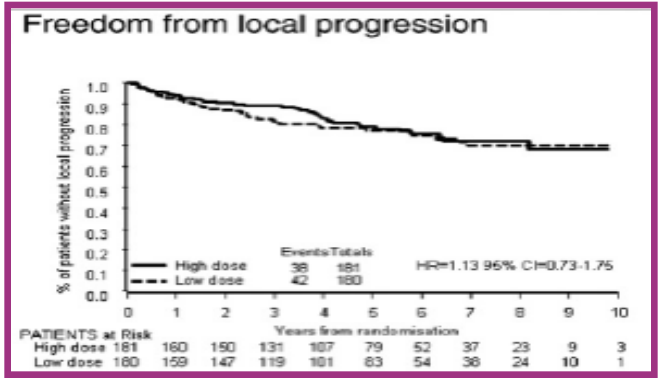
Reduced RT dose in NHL

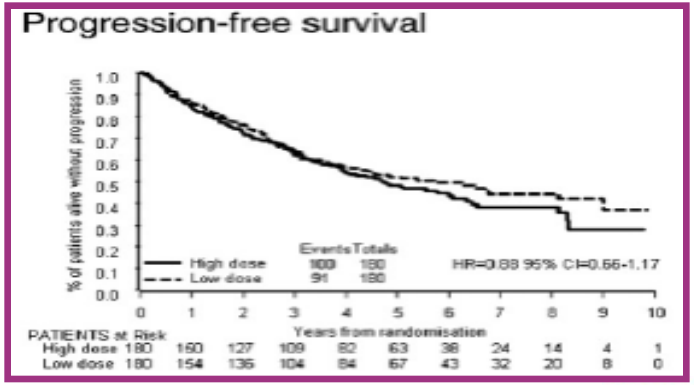
A randomised phase III trial

Median follow-up time: 5.6 years

ORR: 92% in 24 Gy arm *vs* 93% in 40-45 Gy arm

Response	Indolent	
	24 Gy	40–45 Gy
CR	145 (82%)	138 (79%)
PR	18 (10%)	24 (14%)
SD/ progression	14 (8%)	12 (7%)
Death	0 (0%)	0 (0%)
Not assessable	2	2
No RT received	1	1
Missing	0	4
Total	180	181





Lowry et al, Radiother Oncol, 2011

Reduced RT dose in NHL

FORT trial: 4 Gy vs 24 Gy

614 sites in 548 pts with FL and some with MZL

Random to 24 Gy (299 sites) and 4 Gy (315 sites)

Median follow-up time: 26 months

	24 Gy		4 Gy		p value*
	Complete response (%)	Complete response plus partial response (%)	Complete response (%)	Complete response plus partial response (%)	
All patients	176/260 (68%)	236/260 (91%)	137/281 (49%)	227/281 (81%)	0·0095
Follicular lymphoma	152/226 (67%)	205/226 (91%)	116/243 (48%)	194/243 (80%)	0·0096
Marginal zone lymphoma	24/34 (71%)	31/34 (91%)	21/38 (55%)	33/38 (87%)	0·71
Stage I	78/102 (76%)	97/102 (95%)	62/115 (54%)	93/115 (81%)	0·0015
Stage II	21/50 (42%)	39/50 (78%)	22/48 (46%)	37/48 (77%)	0·91
Curative intent	71/95 (75%)	90/95 (95%)	57/105 (54%)	86/105 (82%)	0·0053
Curative intent, confirmed† follicular lymphoma only	38/46 (83%)	44/46 (96%)	35/60 (58%)	47/60 (78%)	0·011

*p value for responders (complete response plus partial response) versus non responders. †Confirmed by central review.

Table 3: **Response by subgroup**

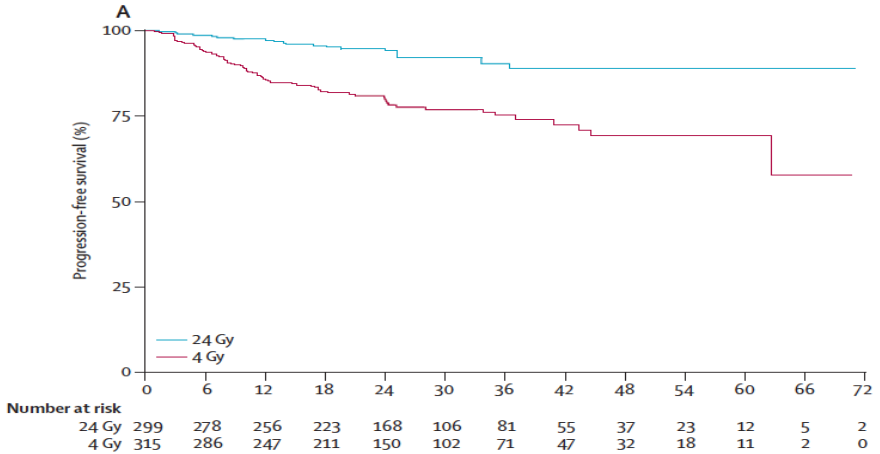
Hoskin et al, Lancet Oncol, 2014

4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial

Peter J Hoskin, Amy A Kirkwood, Bilyana Popova, Paul Smith, Martin Robinson, Eve Gallop-Evans, Stewart Coltart, Timothy Illidge, Krishnaswamy Madhavan, Caroline Brammer, Patricia Diez, Andrew Jack, Isabel Syndikus

Lancet Oncol 2014; 15: 457–63

	24 Gy	4 Gy
All patients*		
Complete regression	176 (68%)	137 (49%)
Partial regression (>30%)	60 (23%)	90 (32%)
Stable disease (including <30% regression)	22 (8%)	44 (16%)
Progression	2 (<1%)	10 (4%)
Total	260	281



Interpretation 24 Gy in 12 fractions is the more effective radiation schedule for indolent lymphoma and should be regarded as the standard of care. However, 4 Gy remains a useful alternative for palliative treatment.

Role of Radiation Therapy in Indolent Nodal Lymphomas

- **Advanced-stage Indolent Lymphoma**
  - Patients with advanced or recurrent indolent disease treated with very low doses of only 4 Gy in 2 fractions achieve high response rates
  - RT provides effective palliation for localized symptomatic disease
  - RT to sites of bulky disease where monitoring clinical progression is challenging and progressive disease may lead to organ failure (such as within the retroperitoneum)

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RT techniques

Dose constraints in lymphoma RT

- The relatively low radiation doses needed result in most treatment plans being within the acceptable limits
- Even low doses to normal tissues, previously considered safe, may 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

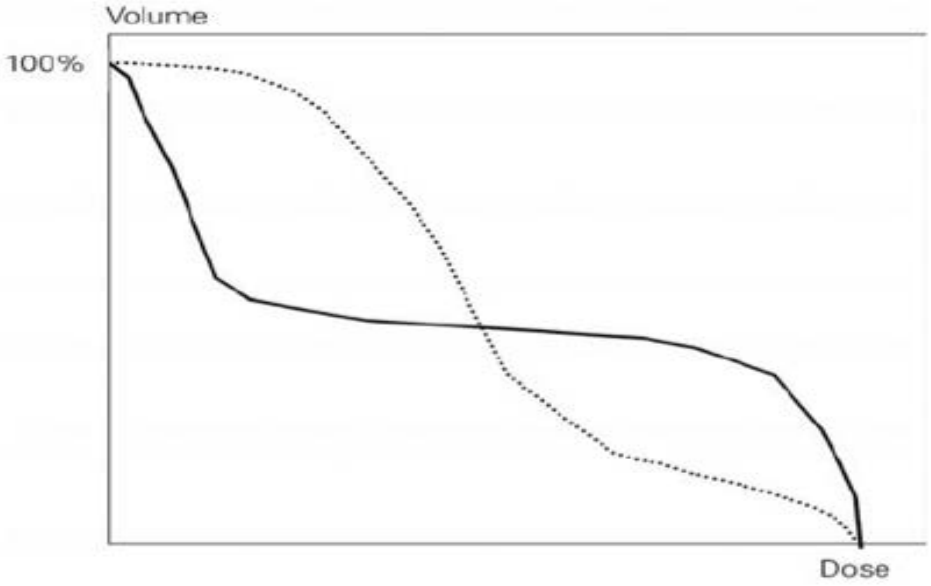
IMRT vs 3D-CRT in lymphoma

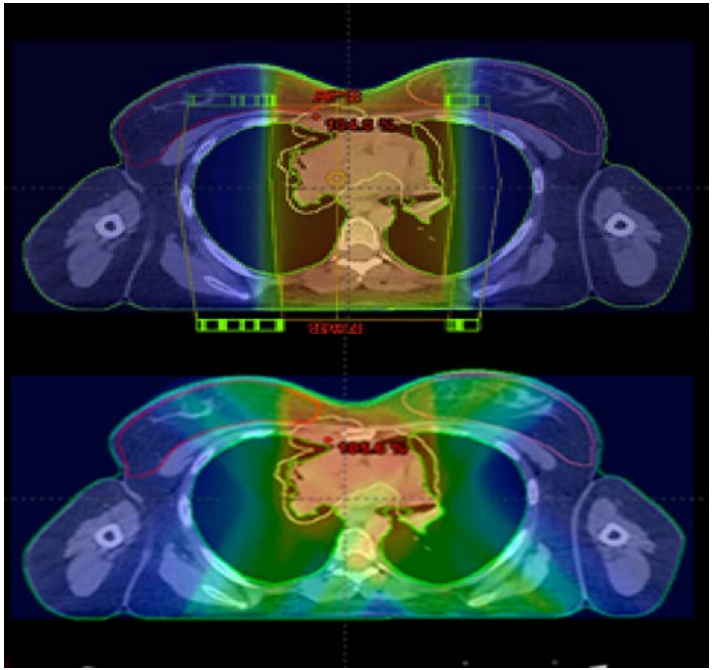
- Several published studies investigated the dosimetric profiles of IMRT compared to those of 3D-CRT

- They showed significantly better PTV coverage (V_{90}, V_{95}, conformity index) and/or significantly better sparing effect for different OAR
  - both for the traditional IFRT and for the more recent concept of limited RT (INRT, ISRT)

A Little to a Lot or a Lot to a Little?

Better sparing of critical normal structures usually at the price of a larger total volume of normal tissue irradiated, albeit to a lower dose

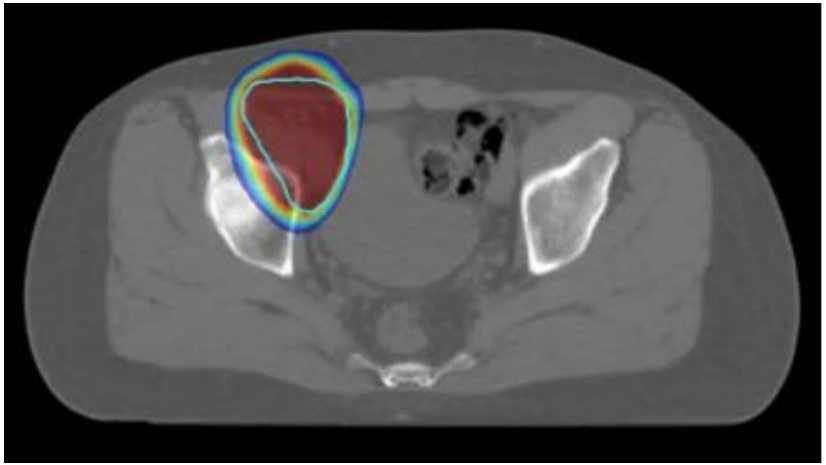


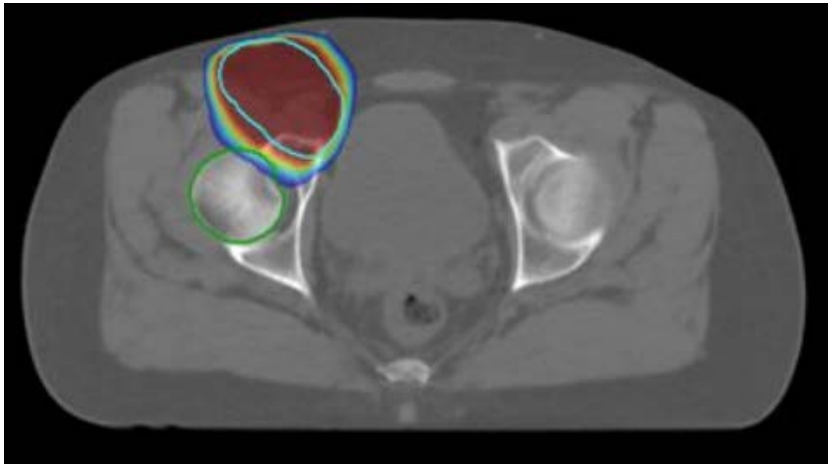


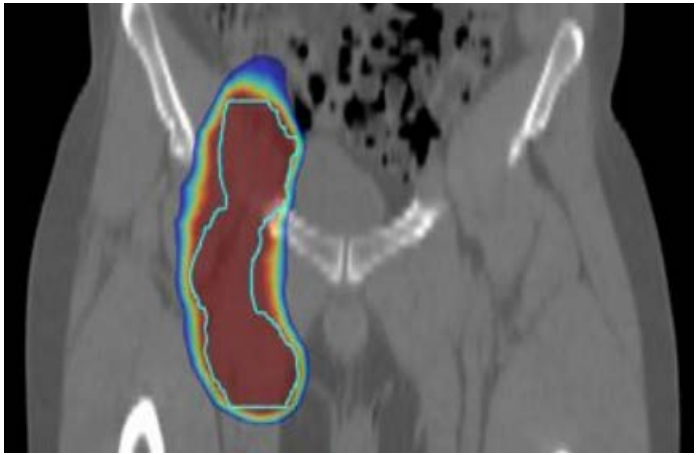
Which technique is preferable?

- There is no single proven best planning and delivery RT technique
- No two lymphomas are the same with regard to localization and extent of disease
- The decision should be made at the individual patient level (i.e., what appears the optimal treatment plan for one patient may not be acceptable for another patient)

M. L., 43 years old, follicular NHL, stage IA







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

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Imaging in Management of Lymphoma

George Mikhaeel, MD
Department of Clinical Oncology
Guy's & St Thomas' Hospital
KHP Academic Health Sciences Centre
London, UK

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Outline

- Staging
- Response assessment
- RT planning

} Lugano Classification 2014

Staging and Response Assessment

Staging:

- Prognosis
- Choice of therapy
- Comparison of treatment outcome
- Clinical trials

Response assessment:

- Cure: maximise cure & minimise toxicity
- Palliation
- Evaluation of new treatments

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The Lugano Classification - 2014

- 2007: IWG-IHP criteria
- 2009: Deauville workshop
- 2011: 11-ICML-Lugano: workshop
- 2012: Imaging workshop, London
- 2013: 12-ICML-Lugano: workshop
  Menton PET meeting
  International consultation
- 2014: 2 JCO consensus publications

(clinical practice & phase III studies)

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The Lugano Classification - 2014

JOURNAL OF CLINICAL ONCOLOGY | SPECIAL ARTICLE

JCO 2014 32:3048-3058

Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group

Sally F. Barrington, N. George Mikhaeel, Lale Kostakoglu, Michel Meignan, Martin Hutchings, Stefan P. Müeller, Lawrence H. Schwartz, Emanuele Zucca, Richard I. Fisher, Judith Trotman, Otto S. Hoekstra, Rodney J. Hicks, Michael J. O'Doherty, Roland Hustinx, Alberto Biggi, and Bruce D. Cheson

JOURNAL OF CLINICAL ONCOLOGY | SPECIAL ARTICLE

JCO 2014 2: 3059-3067

Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister

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What is new?

(compared to 2007)

Staging:

- PET/CT for routine staging of FDG-avid Lymphomas
- BMBx not required for HL and most DLBCL
- Simplification of Ann Arbor

Response assessment:

- PET/CT is standard of care for remission assessment
- Standard tool for reporting response is 5-PS (Deauville criteria)
- Deauville Criteria can be used to assign metabolic response categories (CMR, PMR, NMR, PMD)
- Revised CT size criteria

Surveillance:

- Routine scanning discouraged.

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PET/CT as standard imaging for staging

- PET-CT should be used for routine staging of FDG-avid lymphomas
  - Most lymphomas take up FDG
  - More accurate > CT especially **EN sites**
  - PET results in more **upstaging** > down staging
  - Management change: largest effect in FL (upstaging of early disease)

- PET is important for **RT volumes <IFRT**

- can be used to direct biopsy
  (especially if suspected transformation)

- A baseline PET-CT scan is also desirable for subsequent response assessment

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Histology and numbers of patients included in studies	Percentage FDG-avid
Hodgkin lymphoma (n = 489)	97 - 100
Diffuse Large B cell lymphoma (n = 446)	97 - 100
Follicular lymphoma (n = 622)	91 - 100
Mantle cell lymphoma (n = 83)	100
Burkitt lymphoma (n = 24)	100
Lymphoblastic lymphoma (n = 6)	100
Marginal zone lymphoma, nodal (n = 14)	100
MALT marginal zone lymphoma (n = 227)	54 - 81
Marginal zone lymphoma, splenic (n = 13)	53 - 67
Marginal zone lymphoma, unspecified (n = 12)	67
Small lymphocytic lymphoma (n = 49)	47 - 83
Peripheral T-cell lymphoma (n = 93)	86 - 98
Anaplastic large T-cell lymphoma (n = 37)	94 -100 (but only 27% of cutaneous sites)
Natural killer/T-cell lymphoma (n = 80)	83 - 100
Angioimmunoblastic T-cell lymphoma (n = 31)	78 - 100
Enteropathy type T-cell lymphoma (n = 20)	67 - 100
Mycosis fungoides (n = 24)	83 -100
Sezary Syndrome (n = 8)	100 (but only 62% of cutaneous sites)
Primary cutaneous anaplastic large T-cell lymphoma (n =14)	40-60
Lymphomatoid papulosis (n = 2)	50
Subcutaneous panniculitis-like T-cell lymphoma (n = 7)	71
Cutaneous B-cell lymphoma (n = 2)	0

Modified from Weiler-Sagie et al

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Bone Marrow Assessment

- HL: PET/CT only (BMBx no longer required)

High sensitivity and specificity
Large studies showed: v small % of false -ve but no change in therapy

- DLBCL: PET/CT enough in most cases

High sensitivity and specificity
But: small % of **false –ve** (small volume 10-20%)
possibility of missing **LG** component
Histologically +ve BM may be more **prognostically** important
So BMBx indicated only if result may change management

- FL / LG-NHL: BMBx is mandatory

High false negative rate

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review

Annals of Oncology 00: 1–7, 2013
doi:10.1093/annonc/mdt533

Systematic review and meta-analysis on the diagnostic performance of FDG-PET/CT in detecting bone marrow involvement in newly diagnosed Hodgkin lymphoma: is bone marrow biopsy still necessary?

H. J. A. Adams[1], T. C. Kwee[1*], B. de Keizer[1], R. Fijnheer[2], J. M. H. de Klerk[3], A. S. Littooij[1] & R. A. J. Nievelstein[1]

[1]Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht; [2]Departments of Hematology; [3]Nuclear Medicine, Meander Medical Center, Amersfoort, The Netherlands

Table 5. Results of seven of nine included studies that allowed calculation of sensitivity and specificity

Study (year)	Sensitivity (%)		Specificity (%)	
	Value	95% CI	Value	95% CI
Cortés-Romera et al. (2013) [17]	100	75.3–100	100	92.6–100
Agrawal et al. (2013) [18]	87.5	47.3–99.7	100	85.2–100
Muzahir et al. (2012) [19]	100	90.5–100	100	95.8–100
El-Galaly et al. (2012) [20]	94.9	87.4–98.6	100	99.0–100
Mittal et al. (2011) [22]	100	47.8–100	86.7	59.5–98.3
Cheng et al. (2011) [23]	100	39.8–100	100	87.2–100
Moulin-Romsee et al. (2010) [24]	100	81.5–100	100	94.5–100
Pooled estimate	96.9	93.0–99.0	99.7	98.9–100

N = 955 patients ; weighted summary proportion of patients PET/CT negative and BMB positive 1.1% (95% CI 0.6 – 2.0 %)

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Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-013-2623-4

REVIEW ARTICLE

FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: systematic review and meta-analysis

Hugo J. A. Adams · Thomas C. Kwee · Bart de Keizer · Rob Fijnheer · John M. H. de Klerk · Rutger A. J. Nievelstein

Reference	Sensitivity (%)		Specificity (%)	
	Value	95 % CI	Value	95 % CI
Khan et al. [23]	94.3	80.8 – 99.3	100	96.2 – 100
Cortes-Romera et al. [24]	95.8	78.9 – 99.9	100	93.9 – 100
Berthet et al. [25]	93.9	79.8 – 99.3	99.0	94.6 – 100
Hong et al. [26]	70.8	48.9 – 87.4	100	94.5 – 100
Pelosi et al. [27]	84.0	63.9 – 95.5	100	96.2 – 100
Ribrag et al. [29]	88.9	51.8 – 99.7	100	89.7 – 100
Pooled estimate	88.7	82.5 – 93.3	99.8	98.8 – 100

N = 654 patients ; weighted summary proportion of patients PET/CT negative and BMB positive 3.1% (95% CI 1.8 – 5.0 %)

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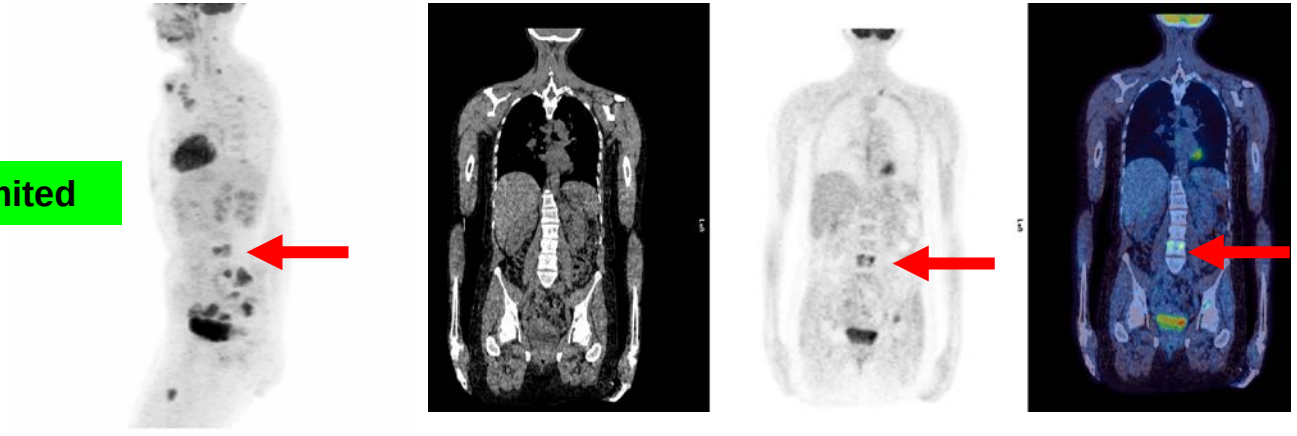
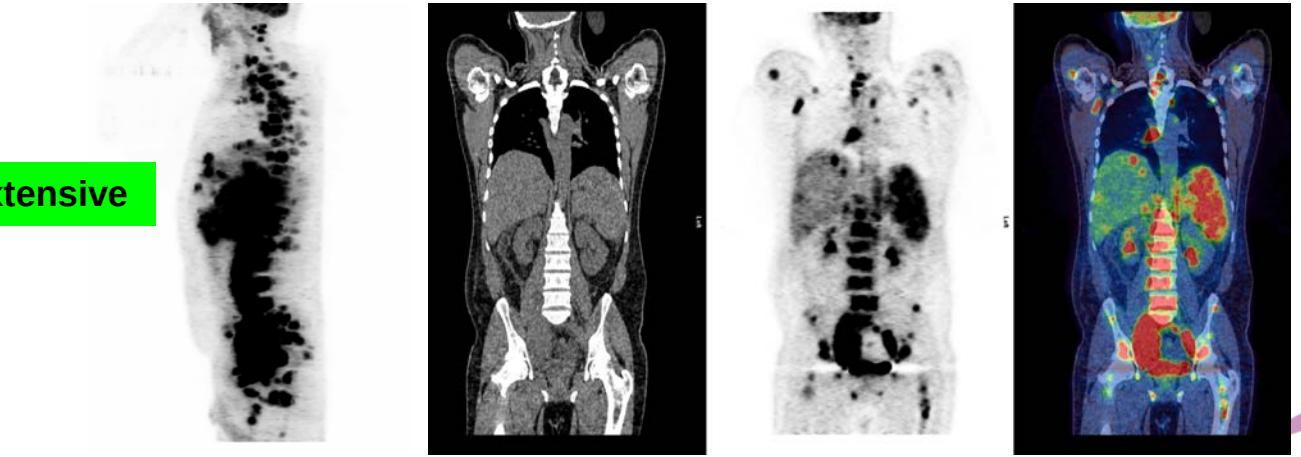
BM Involvement

Limited



Extensive



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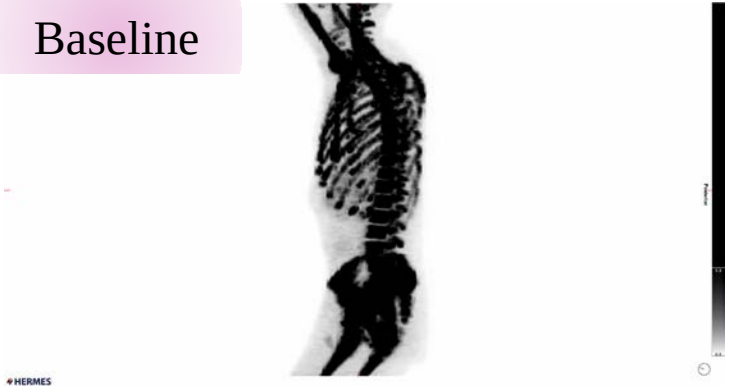
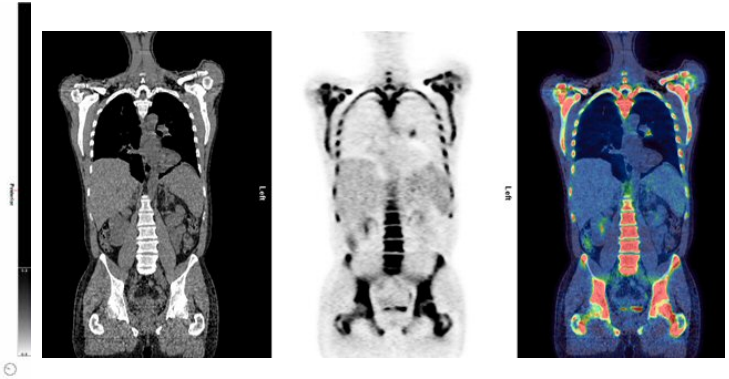
Interpretation of DIFFUSE marrow uptake

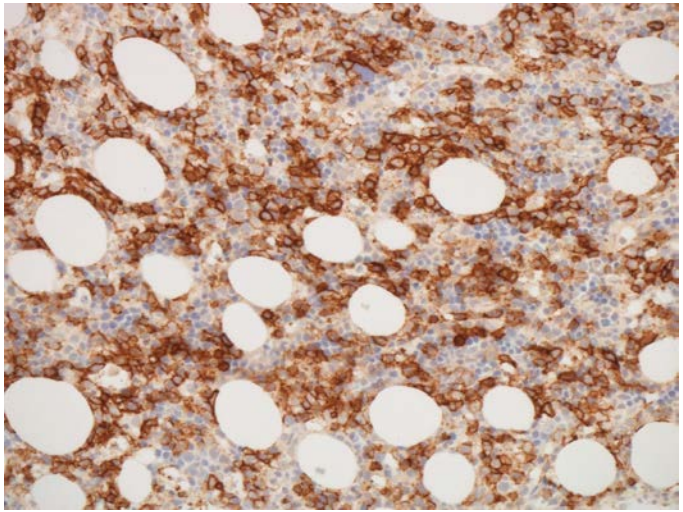
Diffuse uptake may not necessarily indicate BMI

- indicates hyperplasia in HL
- occurs with chemotherapy & GCSF
- can indicate BMI or hyperplasia in DLBCL

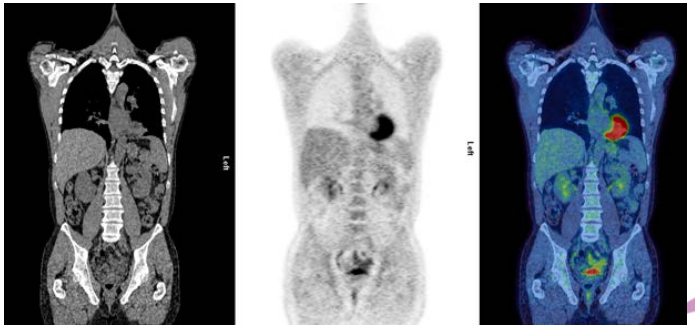
Baseline







Response



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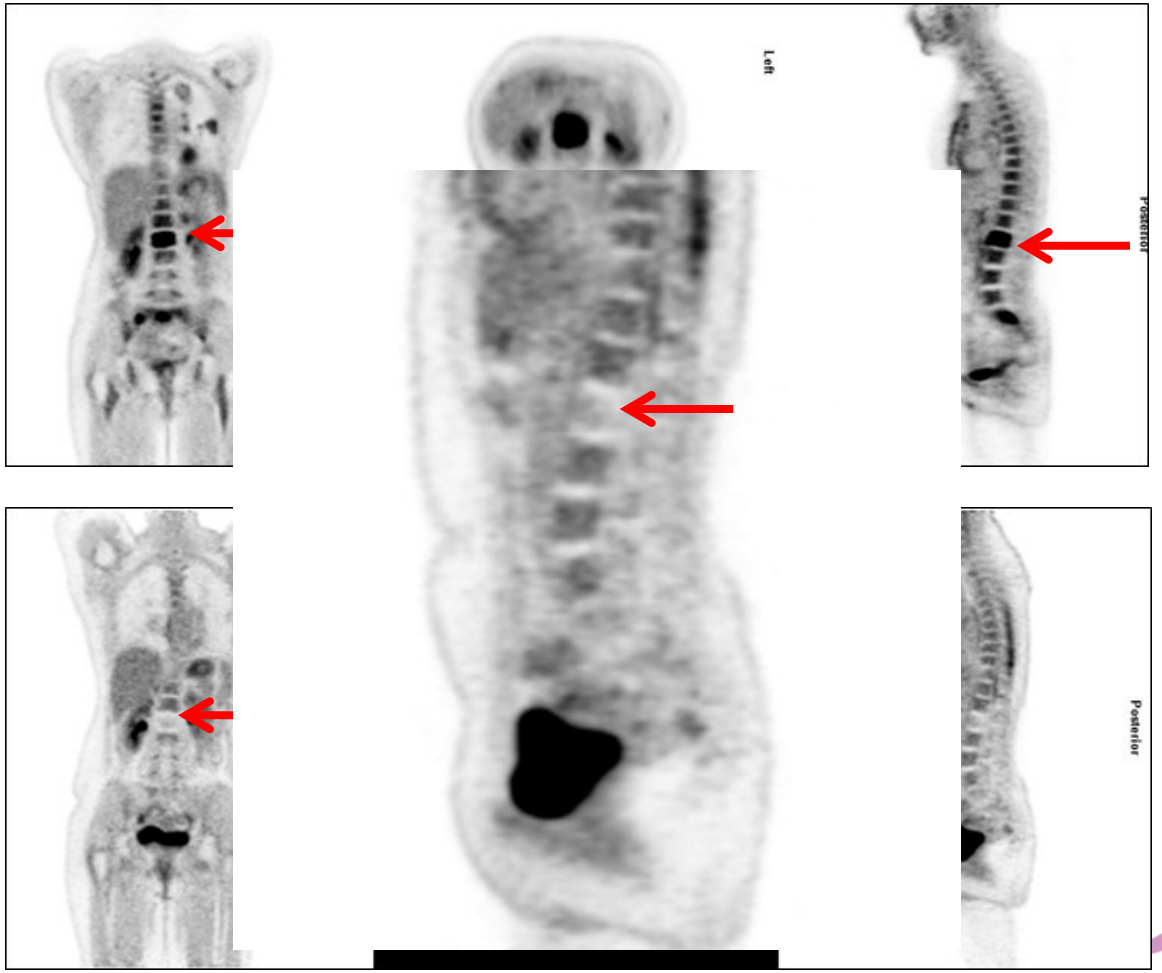
Baseline

Response



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Value of Initial Bulk

- Bulk is –ve prognostic factor
- Bulk in the era of Prognostic scores
  - Prognostic factor (still one of the best ways to reflect disease burden).
  - Choice of Therapy: bulk is part of many treatment algorithms
  - Radiotherapy is frequently based on bulk

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Stage & Bulk in prognostic indices

Disease	Subgroup		Prognostic Index	Includes stage?	Includes bulk?
Hodgkin	Early stage	**GHSG** **EORTC**	Early & Intermediate Favourable &Unfavourable	**Yes** **Yes**	**Yes** **Yes**
	Advanced st	**Hasenclever (IPS)**	Score 0-7	**Yes**	No
DLBCL	All	**IPI**	Score 0-5 (4gps)	**Yes**	No
	<60 ys	**aaIPI**	Score 0-4 (4gps)	**Yes**	No
	Early stage	**Stage adjusted IPI**	Score 0-5		**Yes**
	Rituximab	**R-IPI**	As IPI, but 3 groups	**Yes**	No
	All	**NCCN-IPI**	As IPI but Score 0-8	**Yes**	No
Follicular	all	**FLIPI**	Score 0-5 (3gps)	**Yes**	No
		FLIPI-2	Score 0-5 (3gps)	No	**Yes**
Mantle	all	**MIPI**	Score 0-11	No	No

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Recommendations for Bulk

- No agreed definition:
  - HL: 10 cm or 1/3 thoracic diam at any level?
  - DLBCL: 6 – 10 cm? 7.5cm?
  - FL: 6 cm?

- Maximum tumour dimension (MTD) on CT should be recorded at staging*

  * *Term X need no longer be used*

- Methods of Volumetric Measurement of total tumour volume should be explored

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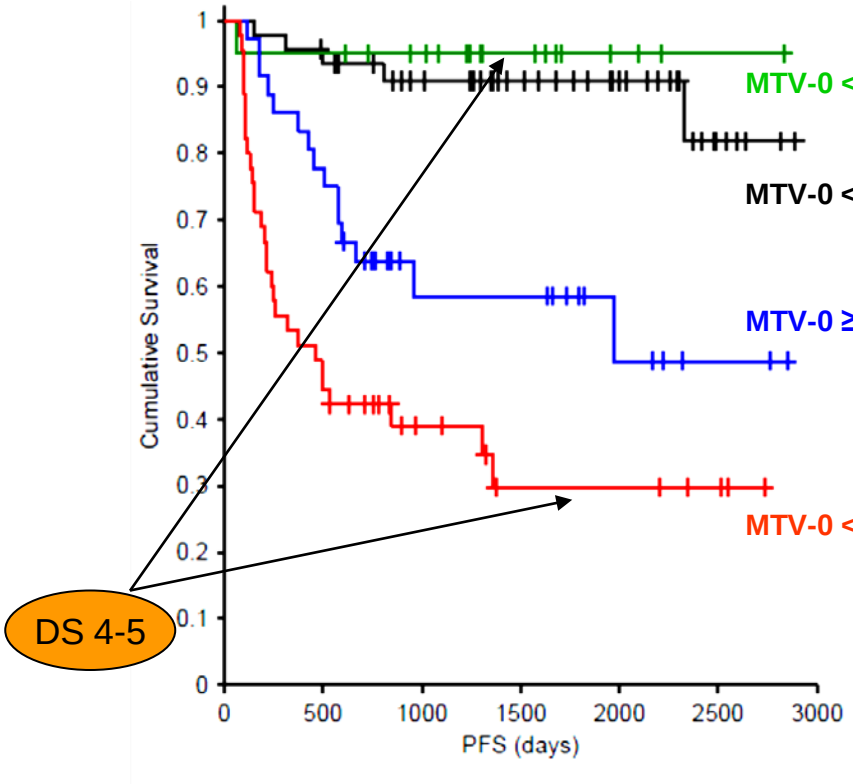
MTV-0 + DS



	At risk	events	5y-PFS
MTV-0 <400 + DS 4-5	20	1	95%
MTV-0 <400 + DS 1-3	46	5	90.9%
MTV-0 ≥400 + DS 1-3	36	15	58.5%
MTV-0 <400 + DS 4-5	45	29	29.7%

Splenic Involvement

SIZE:

- Wide range of size (race, body size and height)

- Normal size spleen may contain lymphoma and enlarged spleen may be due to other causes

- No agreement on:
  - Single, multiple or volumetric measurement
  - Cut-off

Recommendations for splenic evaluation:

- PET/CT: Best method (diffuse, focal)

- CT: cut-off for splenomegaly is 13cm vertical length

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Simplified Ann Arbor

A / B designation only for HL

Table 2. Revised Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

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Response assessment

Change from IHP to Deauville

- IHP (Juweid):
  - Lesions ≥2cm: CMR is <mediastinum (MBP)
  - Lesions <2cm: CMR is <background
- Deauville:
  - 5 degrees of response
  - MBP and liver thresholds
  - No lesion-size dependence
- Main reasons to change:
  - Change in technology
  - Accumulating data on data on 5PS:
    - Several studies reported improved PPV while maintaining NPP
    - High inter-observer agreement
    - At least 8 studies using DS

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Escalation
De-escalation

Negative scan

Score 1 no uptake

Score 2 uptake ≤ mediastinum

Score 3 uptake > mediastinum but ≤ liver

Positive scan

Score 4 uptake > liver at any site

Score 5 uptake > liver and new sites of disease

Score X:

new areas of uptake unlikely to be related to lymphoma

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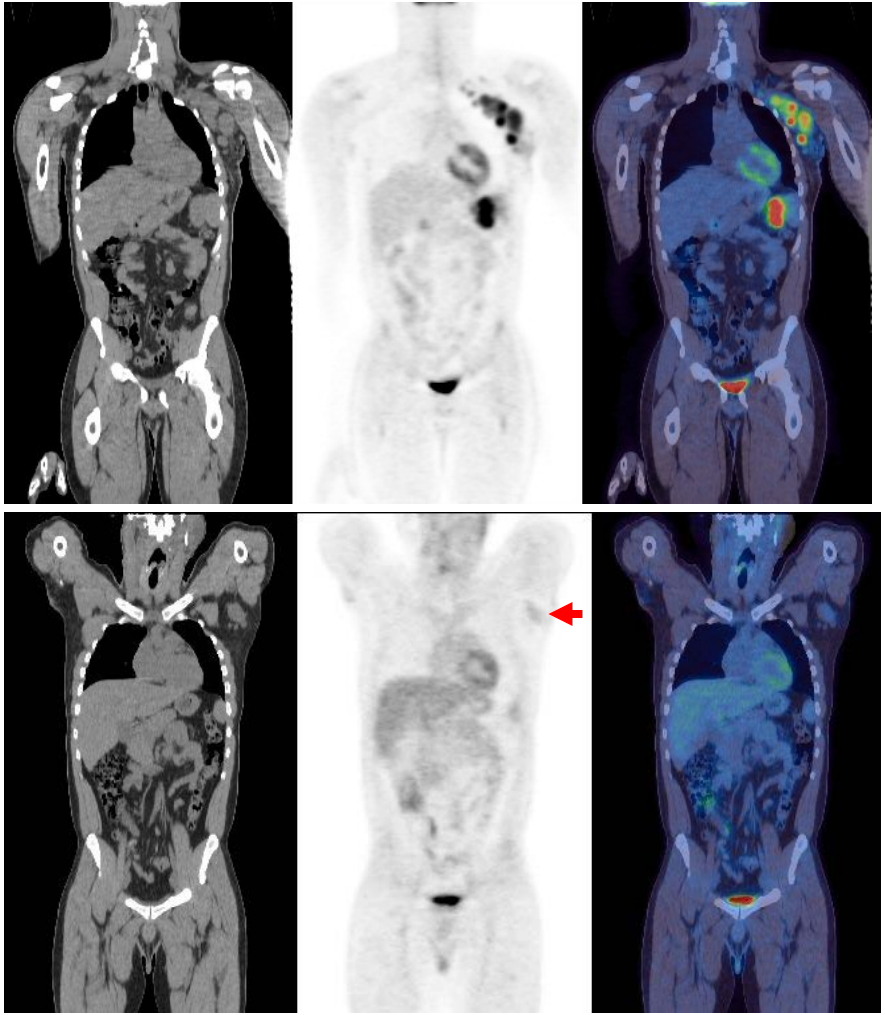
Score 3

Pre

Post



uptake > mediastinum

but < liver

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Score 3

- Main difference with IHP
- Score 3 Definition: uptake > mediast. but ≤ liver
- Is it CMR or PMR? (disease, timing, treatment)

- iPET v ePET:
  - **iPET:** good response (& subsequent Rx planned)
  - **ePET:** CMR?

- Clinical Practice v Trials:
  - Clinical practice: consider prognosis & available options (e.g. RT)
  - Trials: depending on question; escalation v de-escalation

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Score 4 & 5

- Definition:
  - Score 4: **moderately** increased uptake > liver
  - Score 5: **markedly** increased uptake
    OR new lesion(s) likely to be lymphoma

- Difference between “moderate” and “marked”:
  - Moderate: ≥ 130% liver uptake (measured over a large area)
  - Marked: 2 -3 times uptake of liver

- How:
  - Visually
  - SUV aid when close (SUVmax v SUVmean)

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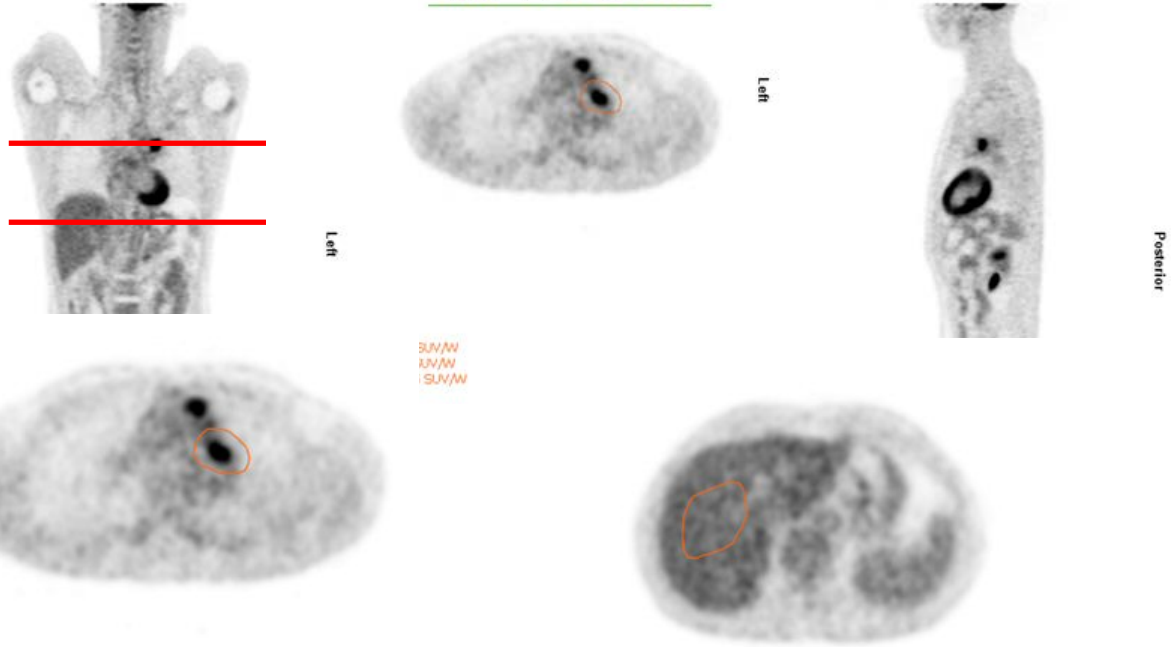

SUVmax lesion 8.51

SUVmax liver 2.44

Score 5

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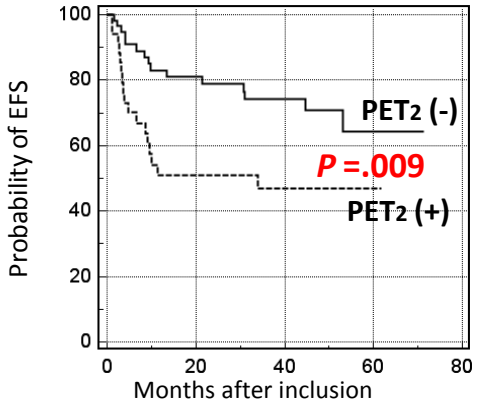
Visual vs. quantitative analysis DLBCL 2 cycles

n = 92 PET 2

Visual analysis

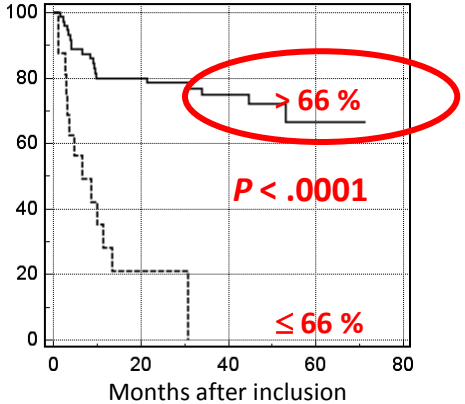


NPV=74%, PPV=50%

n = 80 PET 2

Quantitative analysis

(% reduction SUVmax)



NPV=73.6%, PPV=84.6%

Lin et al al. JNM 2007;48:1626-32

c/o M Meignan, Creteil , France

Challenges with quantitation

Standardised methods :

- PET acquisition
- QC - calibration and monitoring of cameras

Less reliable if low baseline SUV or high residual uptake

Δ SUV cannot always be measured

(17% in Casanovas et al. Blood 2011;118:37-43)

Variation in optimal cut-offs by different groups

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Recommendation:

Quantitation for Response

- Data suggest that Quantitative methods e.g. delta SUV could be used to improve on visual analysis for response assessment in DLBCL but requires further validation in clinical trials [PS: PETAL study ASH 2014]

- Standardisation of PET methods is mandatory for use of quantitative approaches and desirable for routine clinical practice

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Recommendation:

Interim PET-CT

- If mid therapy imaging is performed, PET-CT is superior to CT
- Trials are currently evaluating the role of PET response adapted therapy
- Meantime it is not recommended to change treatment based solely on PET-CT unless there is clear evidence of progression

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Revised criteria for response assessment

	PET-CT BASED RESPONSE	CT-BASED RESPONSE
	Complete Metabolic Response (CMR)	Complete Radiologic Response (CR)
	Partial Metabolic Response (PMR)	Partial Remission (PR)
	No Metabolic Response (NMR)	Stable disease (SD)
	Progressive Metabolic Dis (PMD)	Progressive disease (PD)

	PET-CT BASED RESPONSE	CT-BASED RESPONSE
	Complete Metabolic Response (CMR) ***ALL* of the following**	**Complete Radiologic Response (CR)** ***ALL* of the following**
Lymph nodes and Extranodal sites	**Score 1, 2, or 3* ± a residual mass**	**Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi. No EN sites.**
Non-measured lesion/s	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC -ve
	Partial Metabolic Response (PMR) **ANY of the following**	**Partial Remission (PR)** **ALL of the following**
Lymph nodes and extranodal sites	**Score 4,5** with reduced uptake compared with baseline and residual mass(es) of any size.** *At **interim*** these findings suggest responding disease. *At **end of treatment*** these findings indicate residual disease	**≥ 50% decrease in SPD of up to 6 target measureable nodes and EN sites**
Non-measured lesions	Not applicable	Absent/normal, or regressed but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in spleen length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline	Not applicable

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	No Metabolic Response (NMR)	Stable disease (SD)
Lymph nodes & EN sites	**Score 4 or 5 + no significant change in uptake from baseline**.	**< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes & EN sites;**
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
	Progressive Metabolic Dis (PMD) **ANY of the following**	**Progressive disease (PD)** **ANY of the following**
Lymph nodes & EN sites	**Score 4,5 + an increase in uptake from baseline** **&/or** **New FDG-avid foci consistent with lymphoma**	**PPD Progression:** **An individual node must be abnormal with:** **• LDi > 1.5 cm &** **• Increase by ≥ 50% from PPD nadir AND** **An increase in LDi or SDi from nadir** **0.5 cm for lesions ≤ 2 cm** **1.0 cm for lesions > 2 cm** **Spleen must increase by ≥ 50% of previous increase**
Non-measured lesions	None	**New** or clear **progression** of pre-existing non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another aetiology eg infection/inflammation If uncertain regarding aetiology of new lesions, biopsy or interval scan may be considered	**Regrowth** of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis if less than 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG avid foci.	New or recurrent involvement

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	PET-CT BASED RESPONSE
	Complete Metabolic Response (CMR)
LNs & EN sites	**Score 1, 2, or (3)* ± a residual mass**
	Partial Metabolic Response (PMR)
LNs & EN sites	**Score 4,5** with reduced uptake compared with baseline**
	No Metabolic Response (NMR)
LNs & EN sites	**Score 4,5 + no significant change in uptake from baseline.**
	Progressive Metabolic Dis (PMD)
LNs & EN sites	**Score 4,5 + an increase in uptake from baseline** **&/or** **New FDG-avid foci consistent with lymphoma**

	PET-CT BASED RESPONSE	CT-BASED RESPONSE
	Complete Metabolic Response (CMR)	**Complete Radiologic Response (CR)**
LNs & EN sites	**Score 1, 2, or (3)* ± a residual mass**	**Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi. No EN sites.**
	Partial Metabolic Response (PMR)	**Partial Remission (PR)**
LNs & EN sites	**Score 4,5** with reduced uptake compared with baseline**	**≥ 50% decrease in SPD of up to 6 target measureable nodes and EN sites**
	No Metabolic Response (NMR)	**Stable disease (SD)**
LNs & EN sites	**Score 4,5 + no significant change in uptake from baseline.**	**< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes & EN sites;**
	Progressive Metabolic Dis (PMD)	**Progressive disease (PD)**
LNs & EN sites	**Score 4,5 + an increase in uptake from baseline &/or New FDG-avid foci consistent with lymphoma**	**PPD Progression: An individual node must be abnormal with: • LDi > 1.5 cm & • Increase by ≥ 50% from PPD nadir AND An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm Spleen must increase by ≥ 50% of previous increase**

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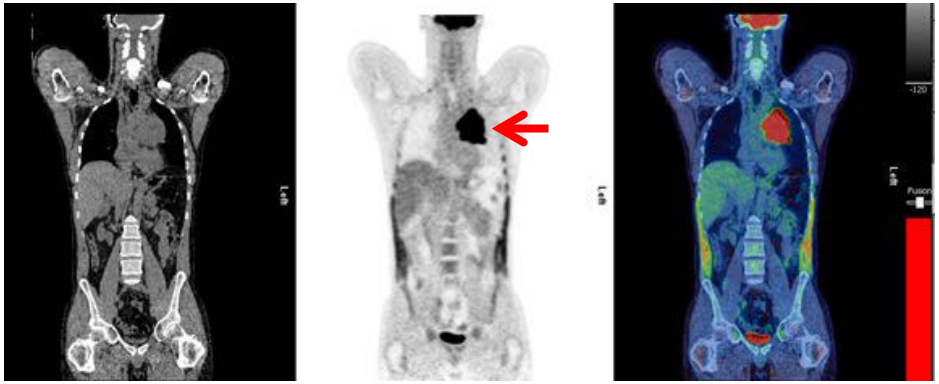
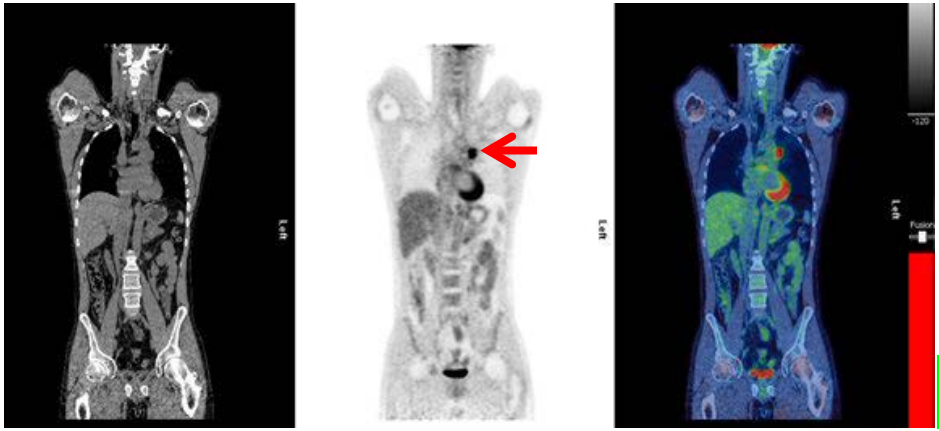
Baseline



Response



Score 5

PMR

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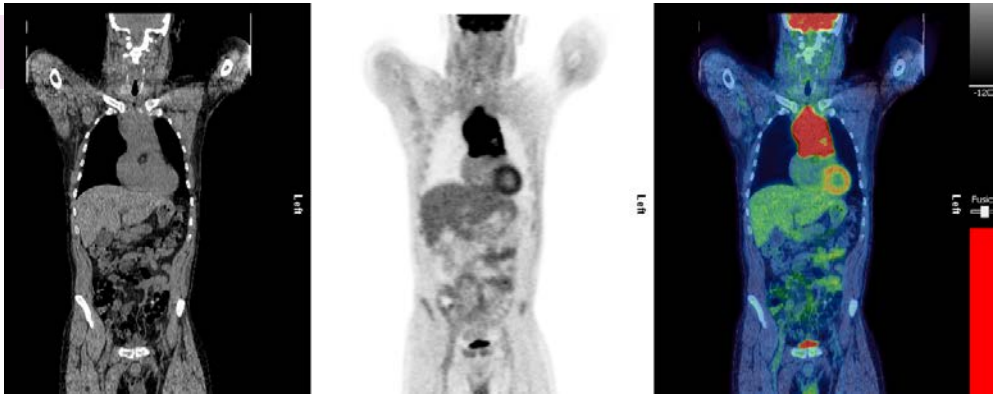
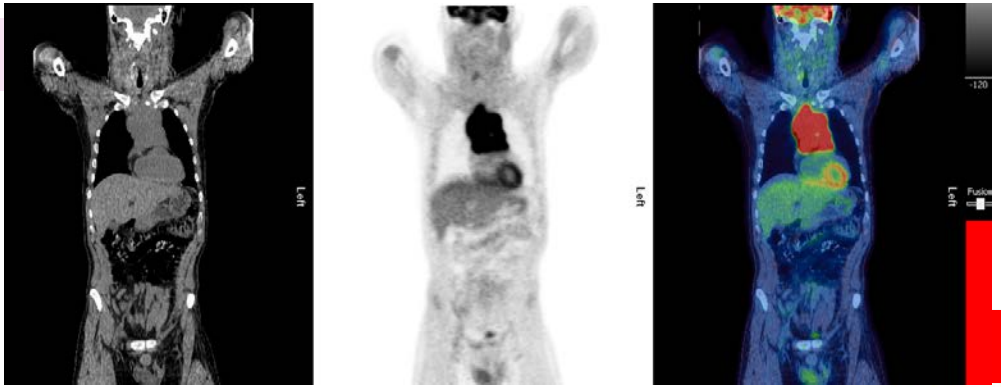
Baseline



Response



Score 5

NMR

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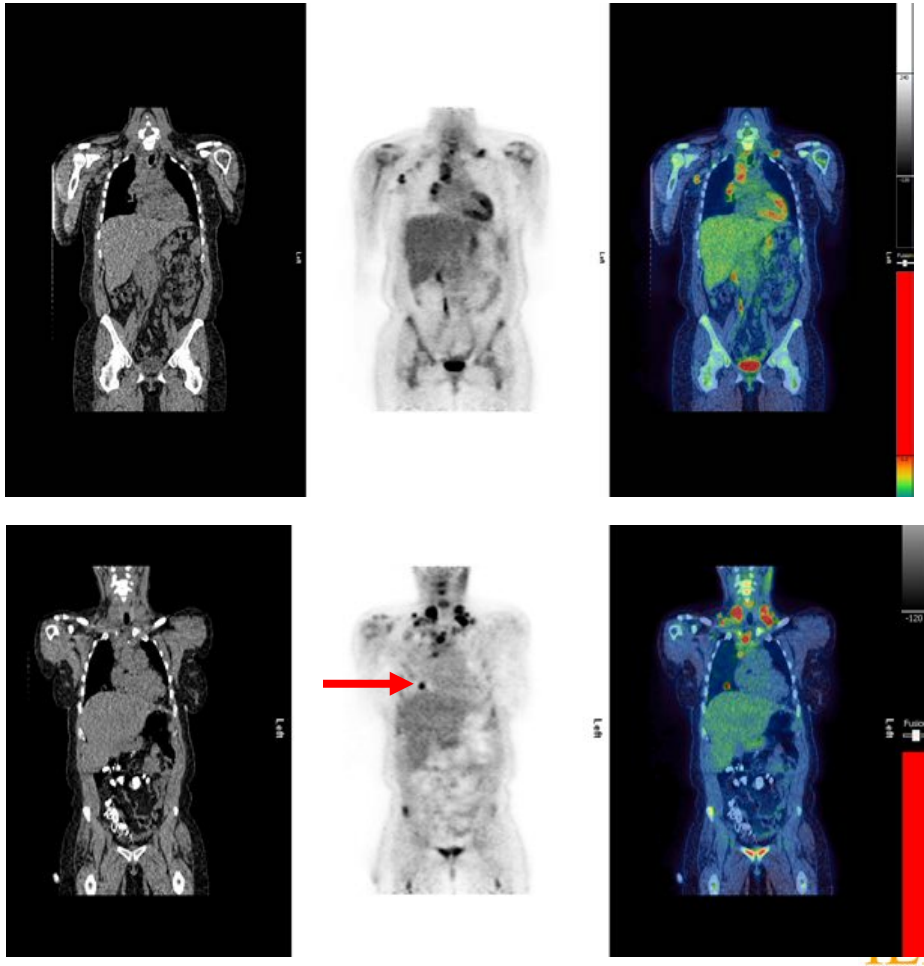

Score 5

PMD

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Recommendation:
Residual metabolic activity

- Biopsy of residual metabolically active tissue is recommended if salvage treatment is considered

Or

- an interval scan where clinical likelihood of disease is low to decide on treatment (or not)

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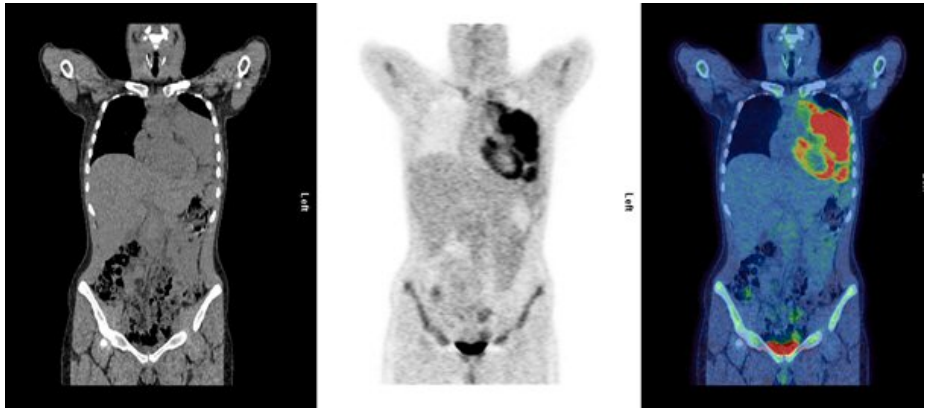
HL

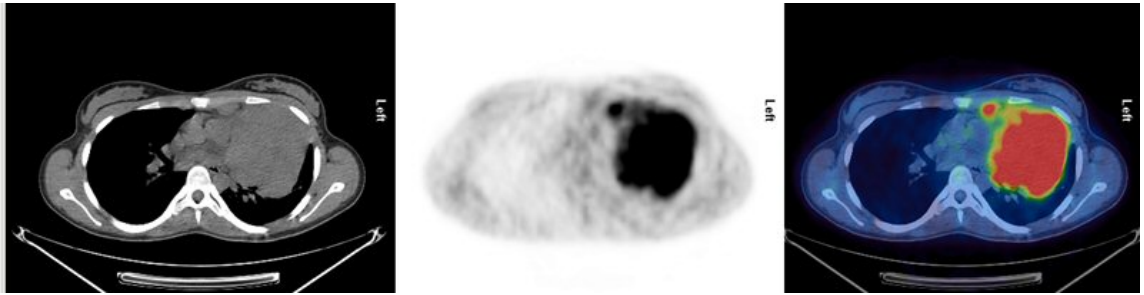
Staging



Mediastinal disease; left internal mammary

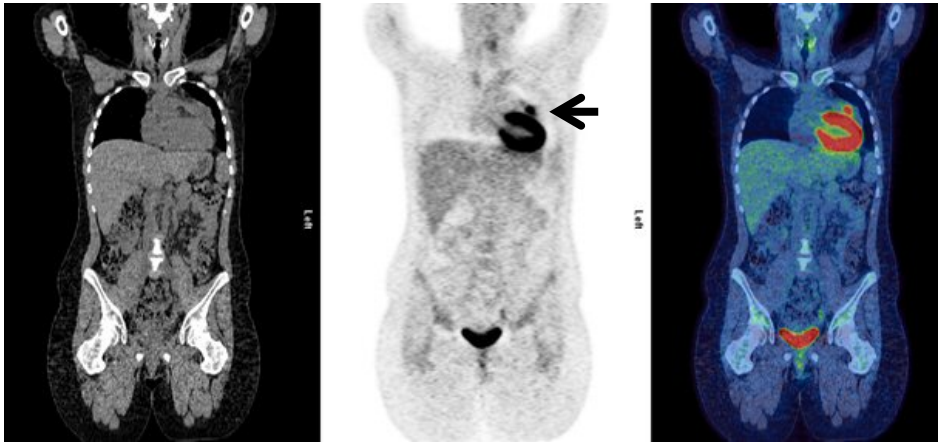
& paracardiac nodes

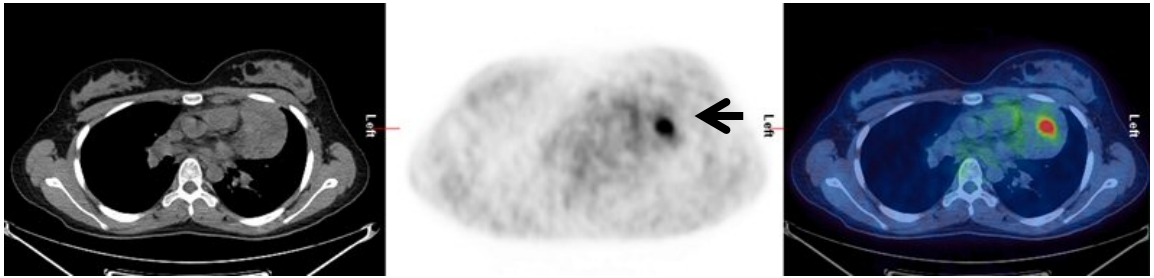
Stage II



6 ABVD

PMR





Residual uptake mediastinum > Liver SUV 7.2 (more than 3 x liver) Score 5

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3 months post chemo + IFRT

PMR

Residual uptake mediastinum > Liver

SUV 4.4 ; Score 4

Interval scan 3 months

Residual uptake mediastinum > Liver

SUV 5.4 ; Score 4

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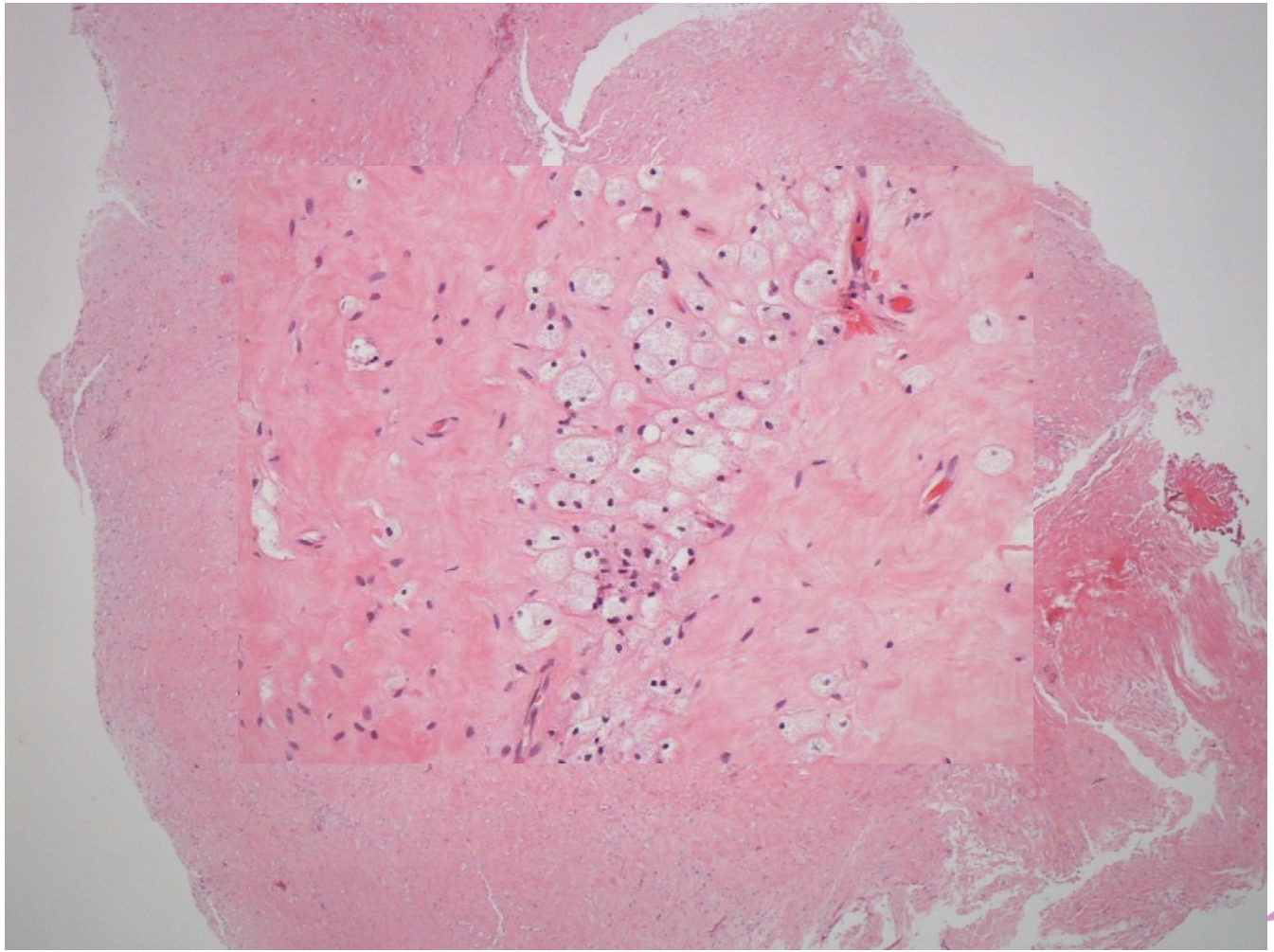

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Other staging & response systems

Primary CNS Lymphoma:
Abrey et al. J Clin Oncol 2005; 23:5034

Gastric MALT: Zucca et al. Ann Oncol 2013; 24:vi144

CTCL: Olsen et al. J Clin Oncol 2011; 29:2598

Abrey LE, Batchelor TT, Ferreri AJ, et al: Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol 23:5034-5043, 2005

Zucca E, Copie-Bergman C, Ricardi U, et al: Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol 24:vi144-vi148, 2013

Olsen EA, Whittaker S, Kim YH, et al: Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: A consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol 29:2598-2607, 2011

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Thanks

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King's College London
& Guy's and St Thomas'
PET Centre

Patients and their families

ILROG Steering Committee Meeting 2012

Guy's Campus

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Supplementary slides

Studies comparing PET or PET-CT with CT for staging

Study	Year	Number	Disease	Upstage %	Downstage %	Management change %
Bangerter [57]	1998	44	**HL**	12	2	14
Partridge [58]	2000	44	**HL**	41	7	25
Jerusalem [59]	2001	33	**HL**	10	10	3
Weihrauch [60]	2002	22	**HL**	18	0	5
Munker [61]	2004	73	**HL**	29	3	NS
Naumann [62]	2004	88	**HL**	13	8	20
Hutchings [9]	2006	99	**HL**	19	5	9
Rigacci [10]	2007	186	**HL**	14	1	6
Buchmann [63]	2001	52	HL (27) NHL (25)	8	0	8
Wirth [64]	2002	50	HL (19) NHL (31)	14	0	18
Raanani [11]	2006	103	HL (32) NHL (68)	31	1	25
Elstrom [12]	2008	61	HL & NHL	18	0	5
Pelosi [13]	2008	65	HL (30) NHL (35)	11	5 (but false -)	8
Karam [14]	2006	17	**FL**	41	0	29
Janikova [15]	2008	82	**FL**	NS	NS	18
Wirth [16]	2008	42	**FL stage I-II on CT**	29	0	45
Le Dortz [17]	2010	45	**FL**	8	0	18
Luminari [18]	2013	142	**FL**	11	1	NS

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Contrast-enhanced CT?

- PET-CT: low-dose non-contrast CT for:
  - Attenuation correction
  - Anatomical localisation

- Pros of Contrast:
  - More **findings** (but rarely change management)
  - Improves **abdo/pelvic** disease detection (bowel physiologic uptake)
  - Shows **vascular** compression/ thrombosis
  - **RT** planning
  - LN **measurement** for clinical trials

- Cons:
  - Additional **radiation**
  - **Resource** implications
  - Small **errors** in FDG measurement in tumours (unlikely to be significant) and 10-15% increase in liver/MBP uptake

Recommendation:

PET –ve Residual masses

- Investigation of significance of PET-negative residual masses should be collected prospectively in clinical trials

- residual mass size and location should be recorded on end-of-

Changes to CT response from 2007

- If a confluent mass splits into discrete nodes when disease is responding, the perpendicular diameters of the nodes should be summed and the combined PPD compared with the PPD of the initial mass
- If nodes later grow the nadir of each node is used to determine progression (or not)
- If target nodes become a confluent mass when disease is progressing, the diameters of those target nodes should be added and the combined PPD compared with the PPD of the subsequent mass
- Splenic enlargement defined as >13cm
- In relapsed disease, CT criteria for PD can be based on increase in a single lesion. SPD eliminated for PD.
- Agents associated with flare reactions may require biopsy or repeat assessment > 2 weeks to determine if there is PD

Follow up

- Clinical judgement, history & examination are cornerstones of FU
- FU freque is determined by histology, if patient is within a trial & clinical setting
- Frequency in curable lymphoma (eg HL, DLBCL) ↓ over time with ↓ likelihood of relapse
- Frequency of FU in other lymphoma (eg FL, MCL) ↑ over time as ↑ likelihood of recurrence
- Surveillance scans should be discouraged
- FP rate > 20% for surveillance PET leads to unnecessary investigations, radiation , biopsies, cost and anxiety

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REGION

Imaging for radiotherapy of lymphomas

Anne Kiil Berthelsen,
Department of Oncology
Section of Radiotherapy
Department of Clinical Physiology, Nuclear Medicin & PET
Rigshospitalet
Denmark

Staging and response criteria

- 1999 National Cancer Institute Working Group
- 2007 International Working Group
- 2211 Lugano imaging

Staging PET/CT

- Flat tabletop
- 2mm slice thickness
- IV-contrast
- Oral contrast
- Arms up if possible
- Both staging and CT for radiation planning

- If suspicion of mediastinal involvment
- Breath hold DIBH

The Copenhagen Model

Staging with CT

- Up to 6 of the largest nodes/nodal masses that are measurable in two diameters, longest and shortest, in different regions, include mediastinal and retroperitoneal disease if involved.
- Node LD longer than 1.5 cm
- Extranodal LD longer than 1.0 cm

PET/CT interpretation

- Indikation :
- Injected dose
- PET interpretation:
- CT interpretation:
- Table of lymphoma measurements:
- Final PET/CT conclusion:

Indikation: Status efter afsluttet kemoterapi for anaplastisk, storcellet ALK negativt lymfom.

18-08-2015 gives i.v. 315 MBq F-18 FDG
mhp. Wb PET/CT FDG. PET 4

Beskrivelse:
PET-scanning:
Sammenholdt med PET/CT-scanning 24.06.15 ses tiltagende metabolisk aktivitet i tidligere beskrevne lymfeknuder periklavikulært og subpektoralt på ve. side samt i ve. aksil. Ligeledes indtryk af tiltagende FDG-optagelse i lymfeknuderne i hø. lyskeregion. Tilkommet moderat øget FDG-optagelse i lymfeknuder langs arcus aortae. Lymfeknuder med den højeste metaboliske aktivitet findes subpektoralt på ve. side og i ve. aksil, hvor aktivitetsniveauet overstiger baggrundsaktiviteten i leverparenkymet. Derudover kan der ikke påvises patologisk øget FDG-optagelse nogetsteds.

CT-scanning af hals, thorax og abdomen efter peroral, men uden i.v. kontrast på baggrund af kendt allergi:
Viser, sammenholdt med CT 24.06.15, tiltagende størrelse af nogle lymfeknuder periklavikulært på ve. side samt i ve. aksil, ligesom der er indtryk af tilkomne, men små, lymfeknuder i mediastinum superius sin. En del af de tidligere sete lymfeknuder i skemaet er dog aftaget i størrelse. Fortsat ikke forandringer i lungeparenkym eller intraabdominale organer. Ossøst uændrede forhold. Tumor 6 målte ved forrige undersøgelse 2,6 x 2,4 cm.

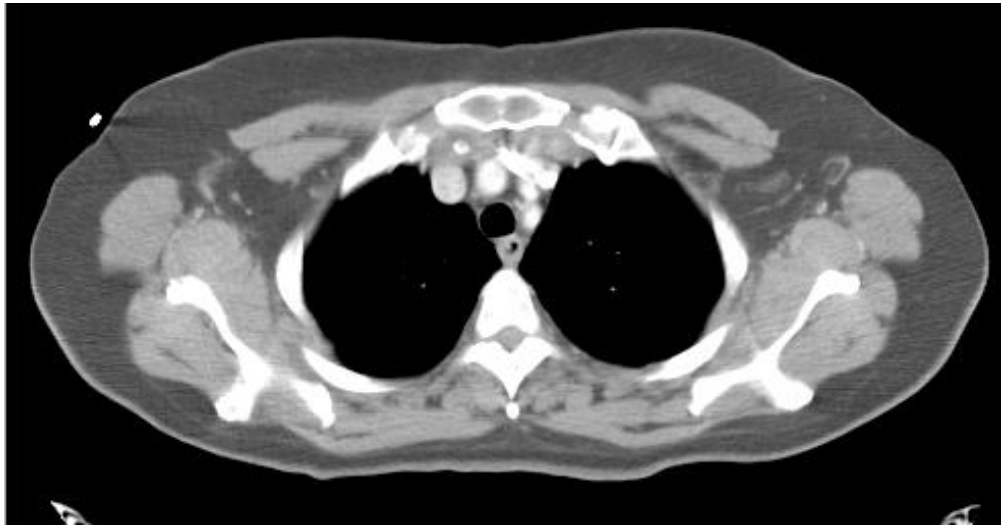
Tumor 1 IMA 102 Ve. halsrod 1,8 x 1,1 cm
Tumor 2 IMA 138 Ve. aksil 3,0 x 1,8 cm
Tumor 3 IMA 155 Distalt i ve. aksil 1,0 x 0,9 cm
Tumor 4 IMA 373 Iliaca externa kar dxt. 1,4 x 0,7 cm
Tumor 5 IMA 390 Hø. ingvinalregion 1,0 x 0,9 cm
Tumor 6 IMA 138 Ve. aksil 3,2, x 3,3 cm.

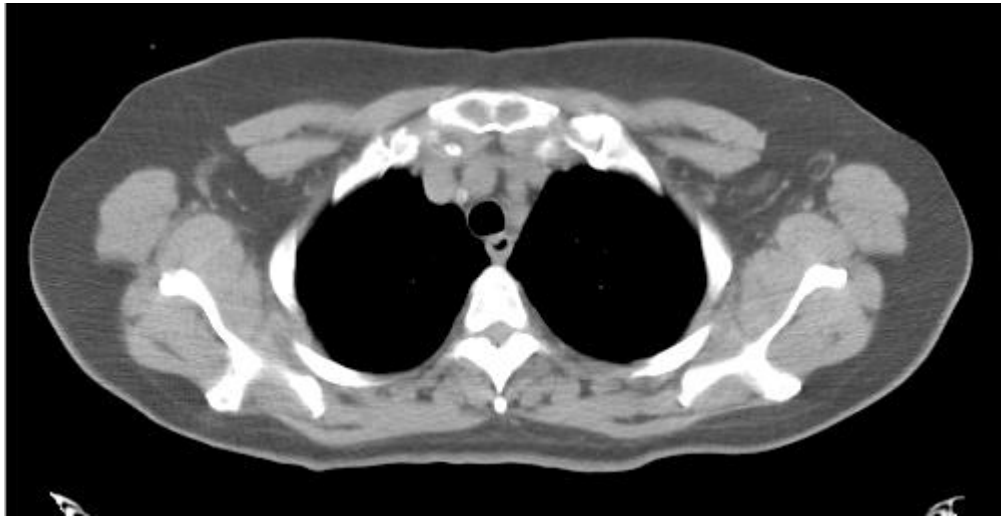
Konklusion:
Sammenholdt med PET/CT-scanning 24.06.15 samlet set indtryk af progression med tiltagende metabolisk aktivitet i lymfeknuder både over og under diaphragma, hvoraf nogle ses med tiltagende størrelse og andre aftagende.

Louise Alslev/Elisabeth Albrecht-Beste/vrø
20-08-2015

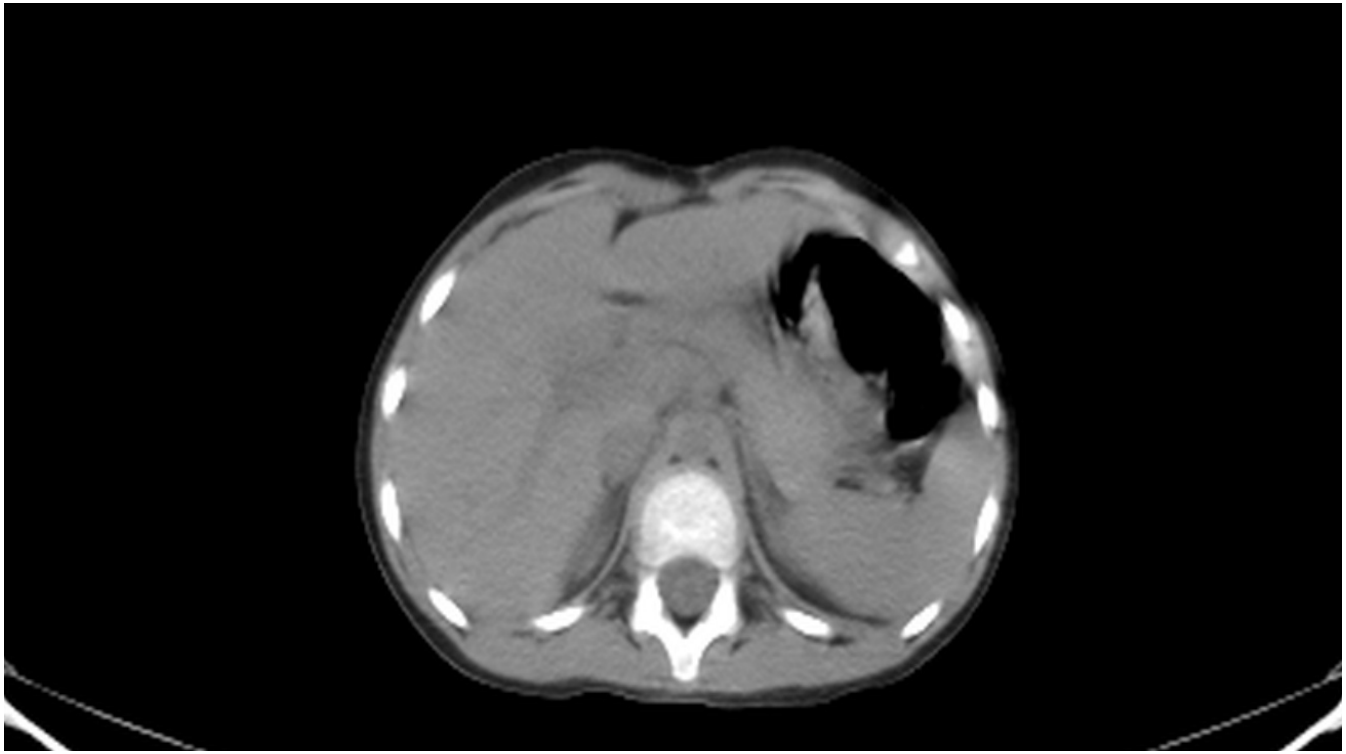
IV-Contrast

with and without IV contrast

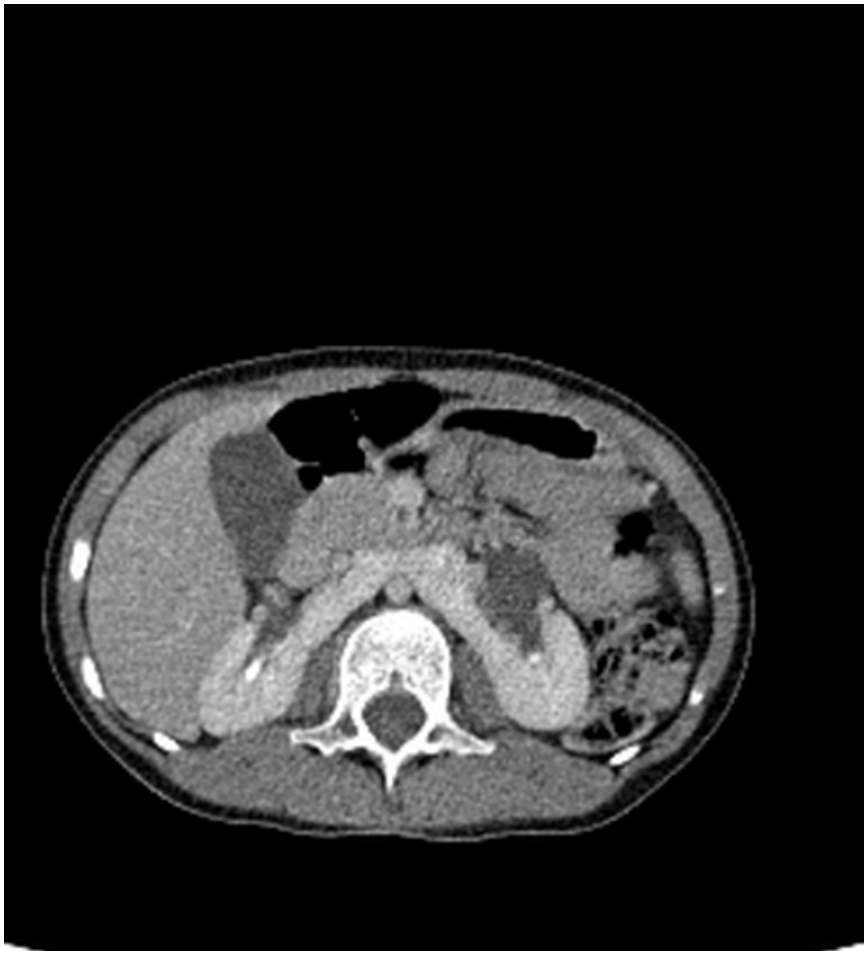




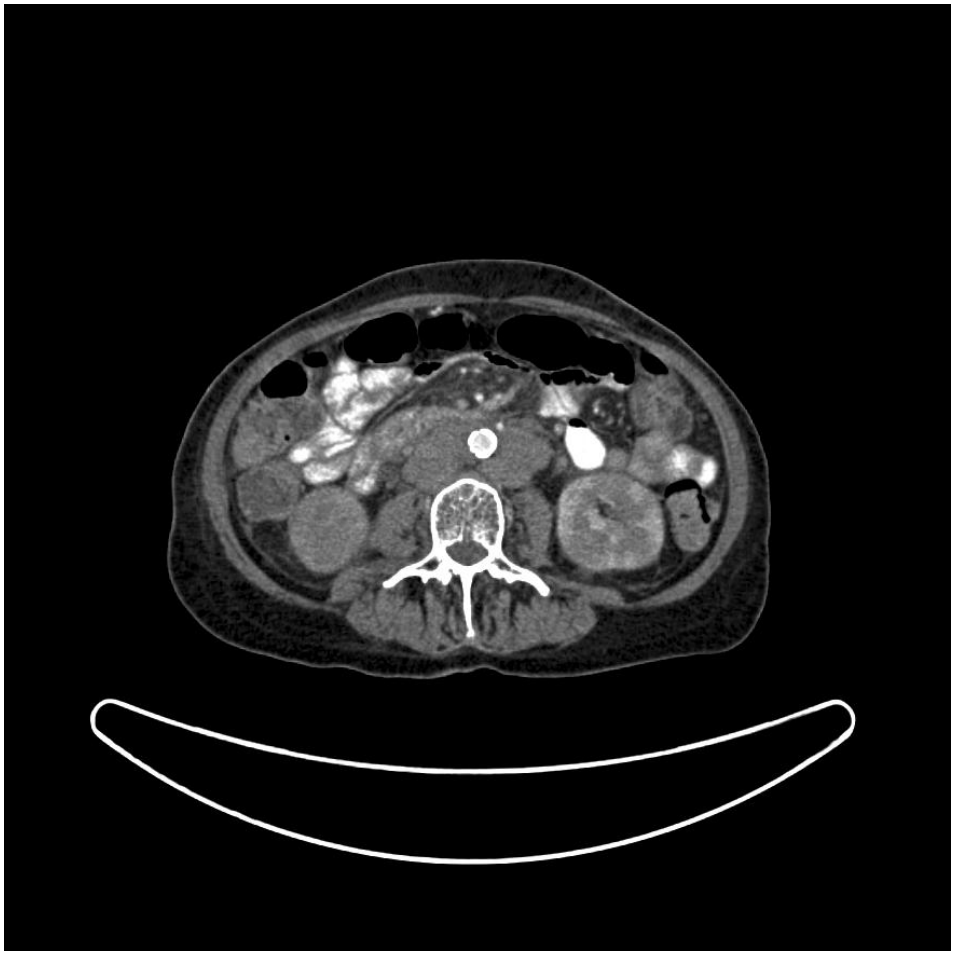
CT scan without IV contrast



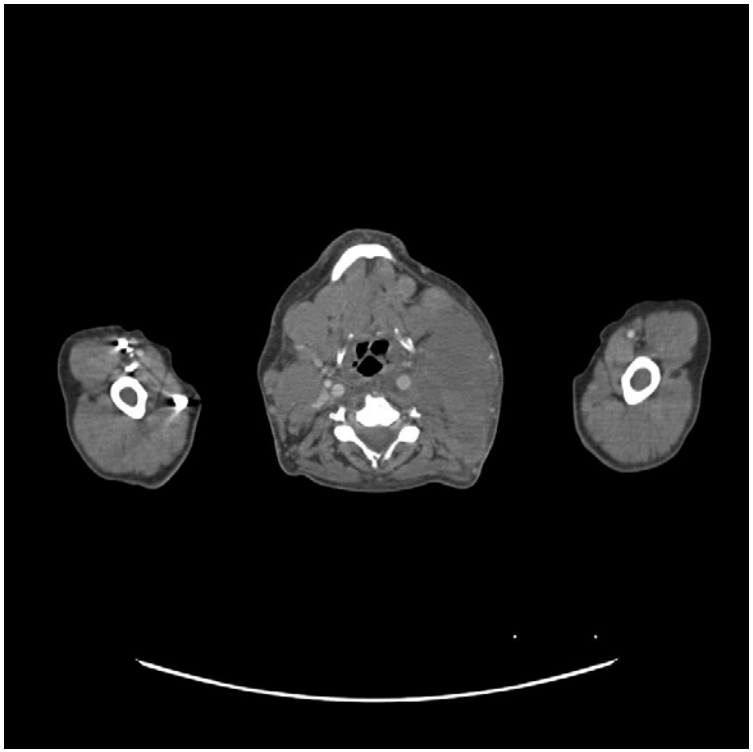
CT scan with IV contrast

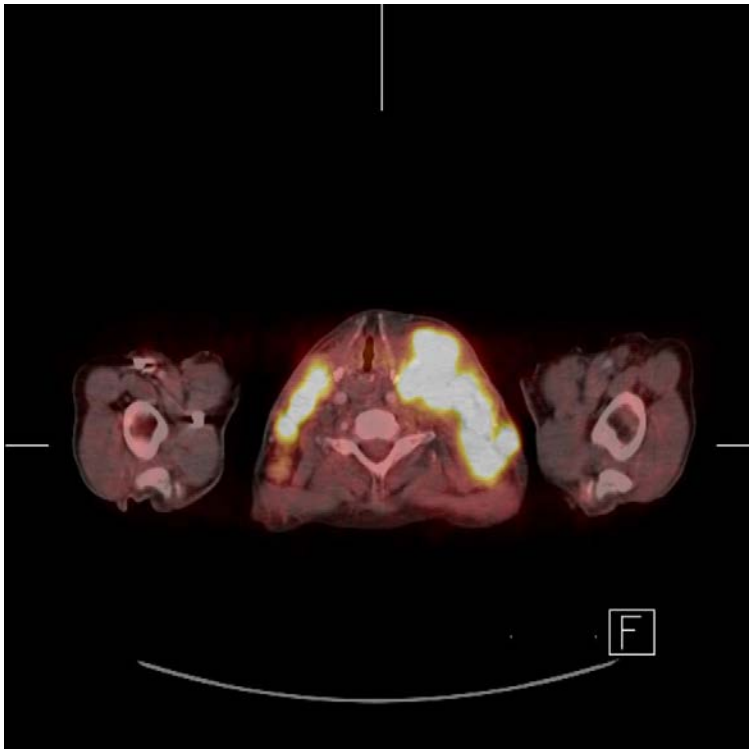


Oral contrast

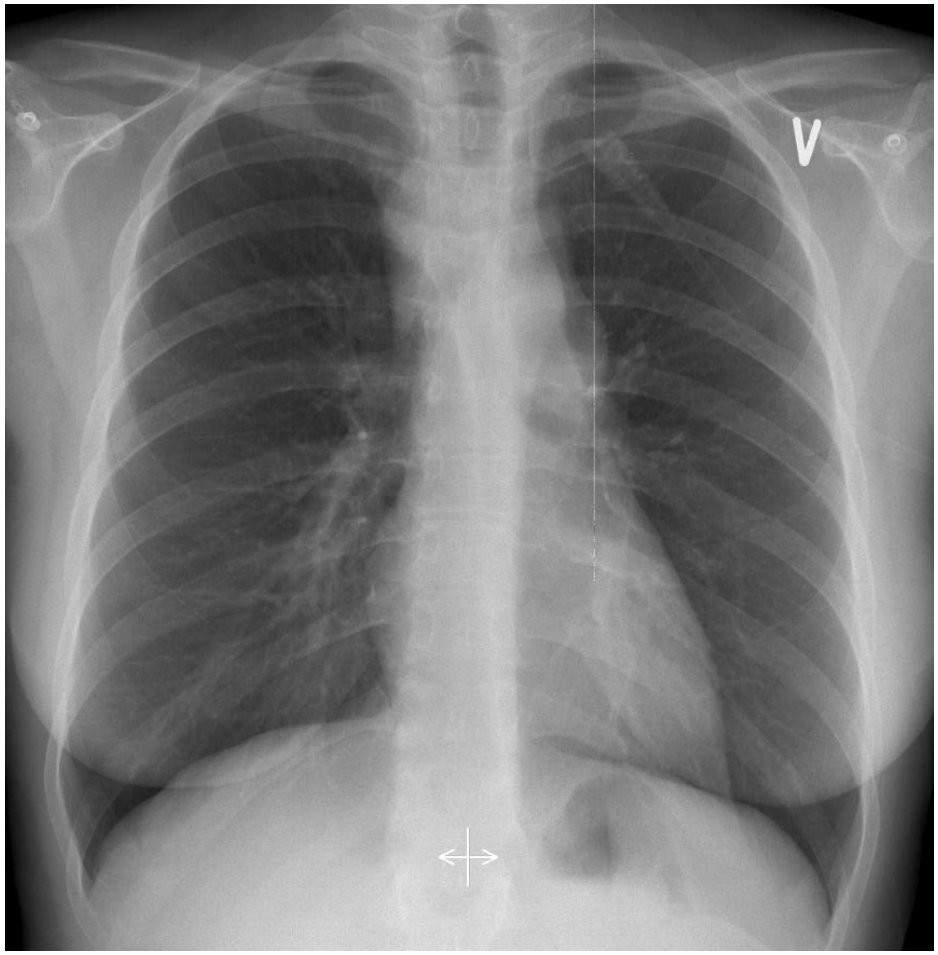


Lymph node > 1.5 cm

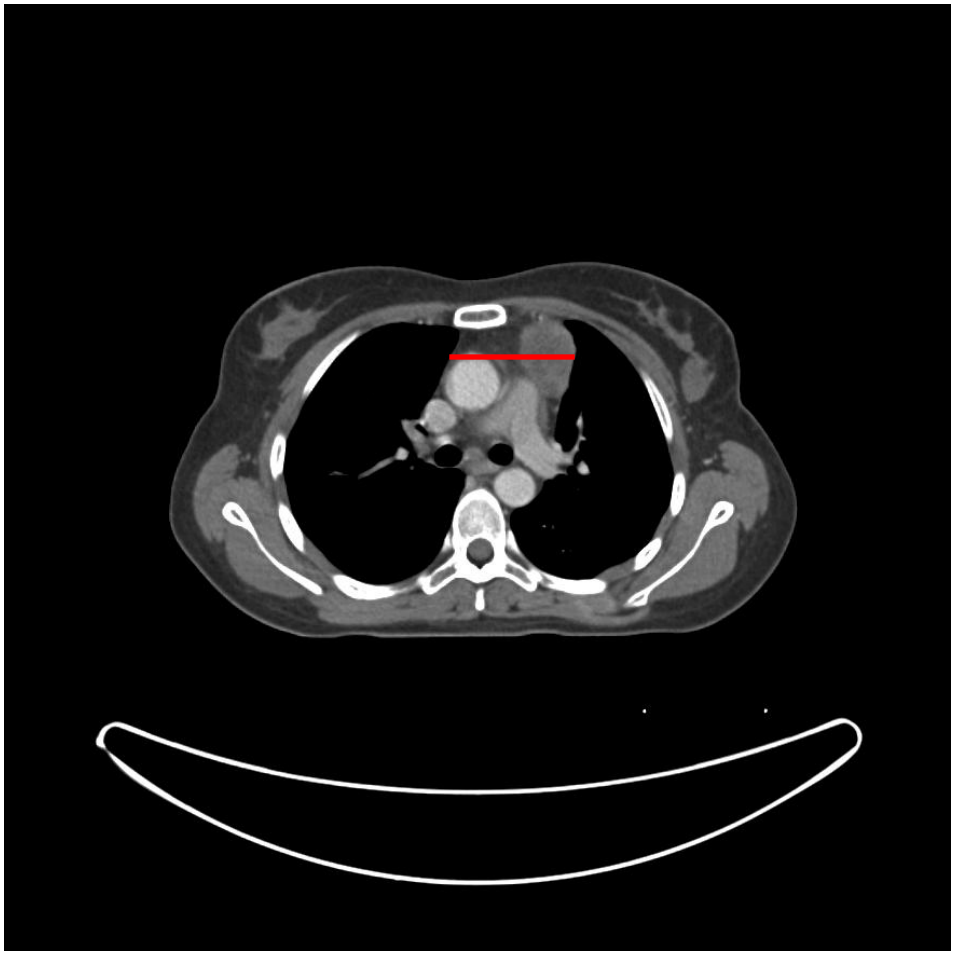


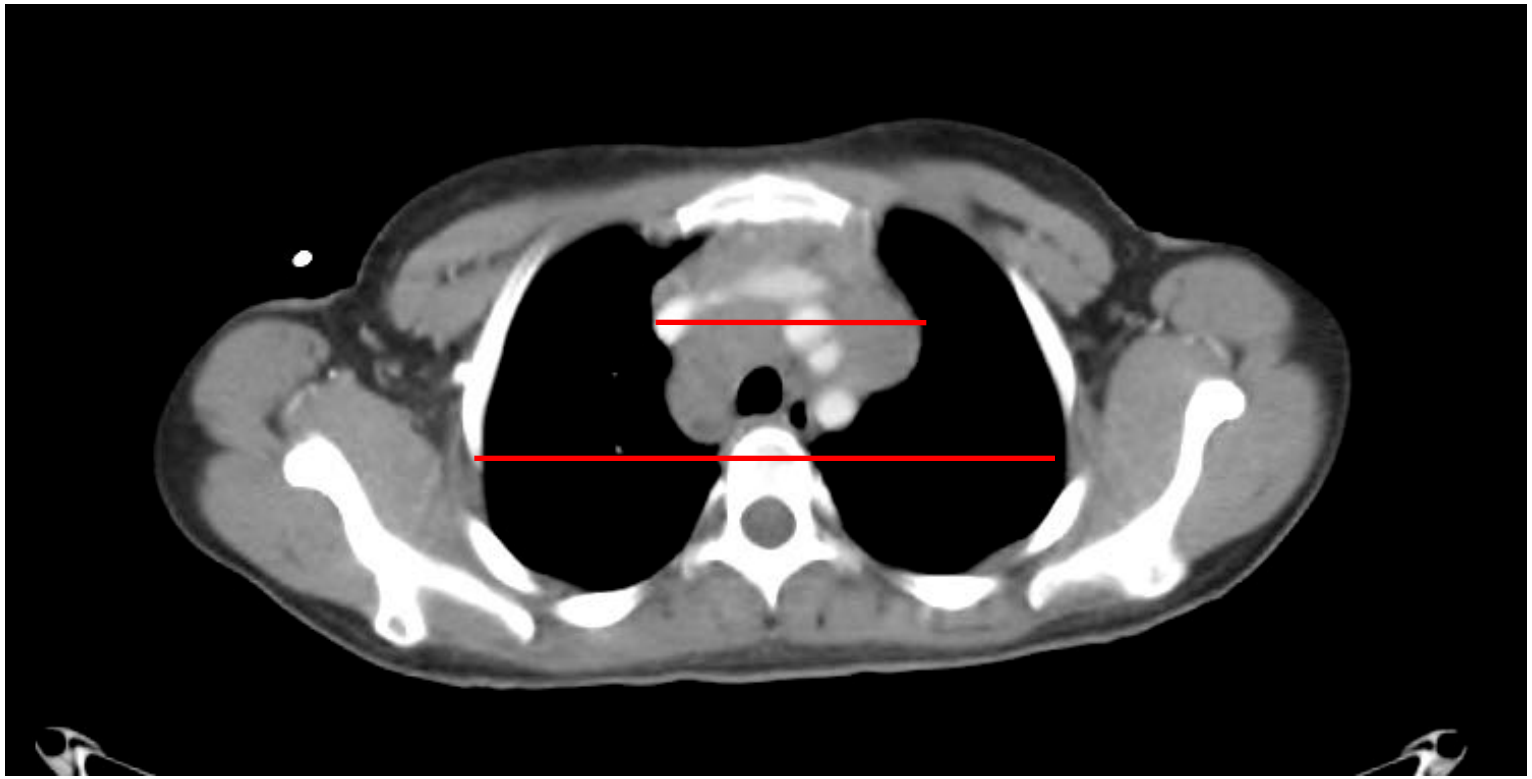


Chest X-ray is not required



10 % have a normal chest x-ray

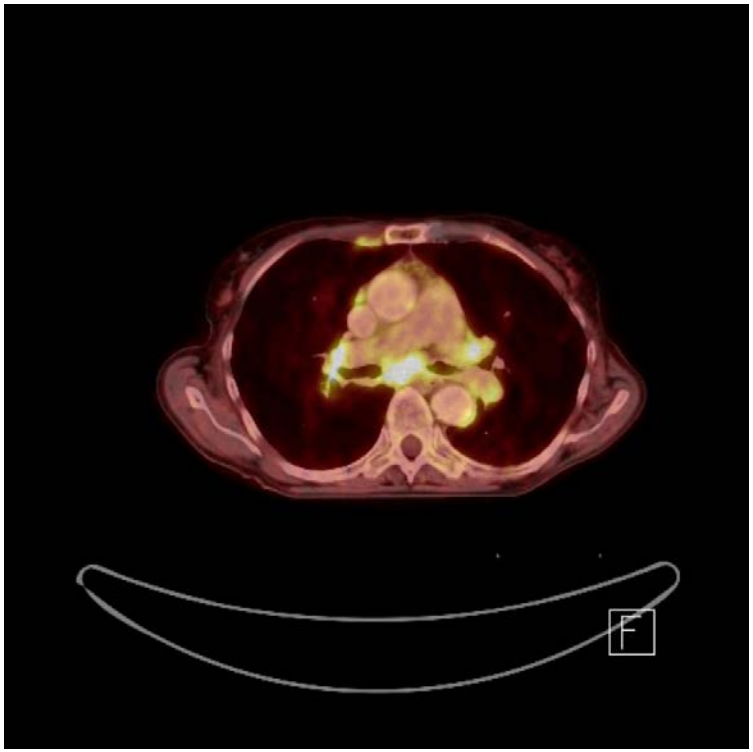


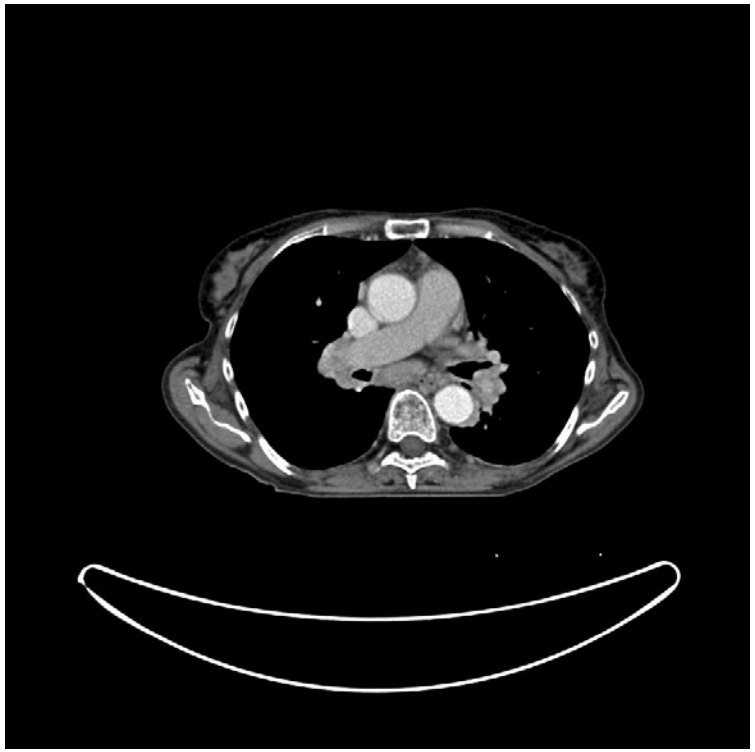


10 cm or greater than 1/3 of the trans-thoracic diameter at any level of thoracic vertebrae

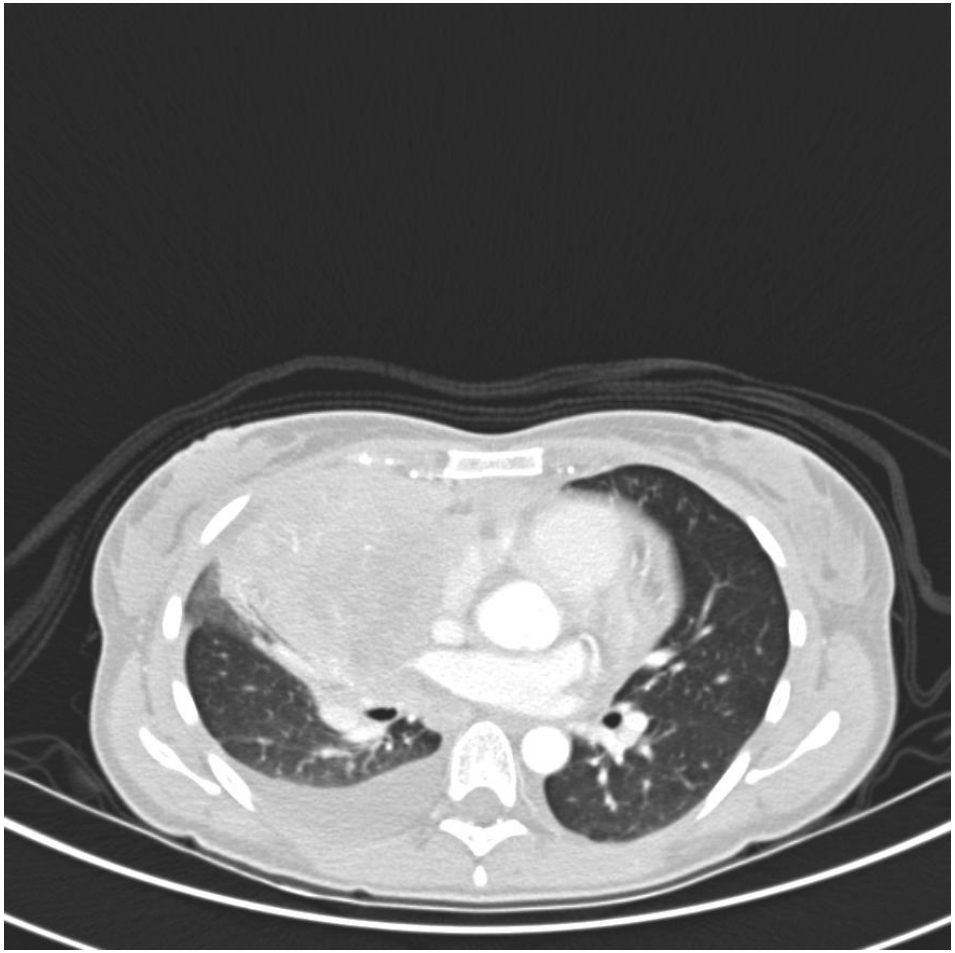
CT identifies more hilar nodes

Lungs, involvement of lymph nodes

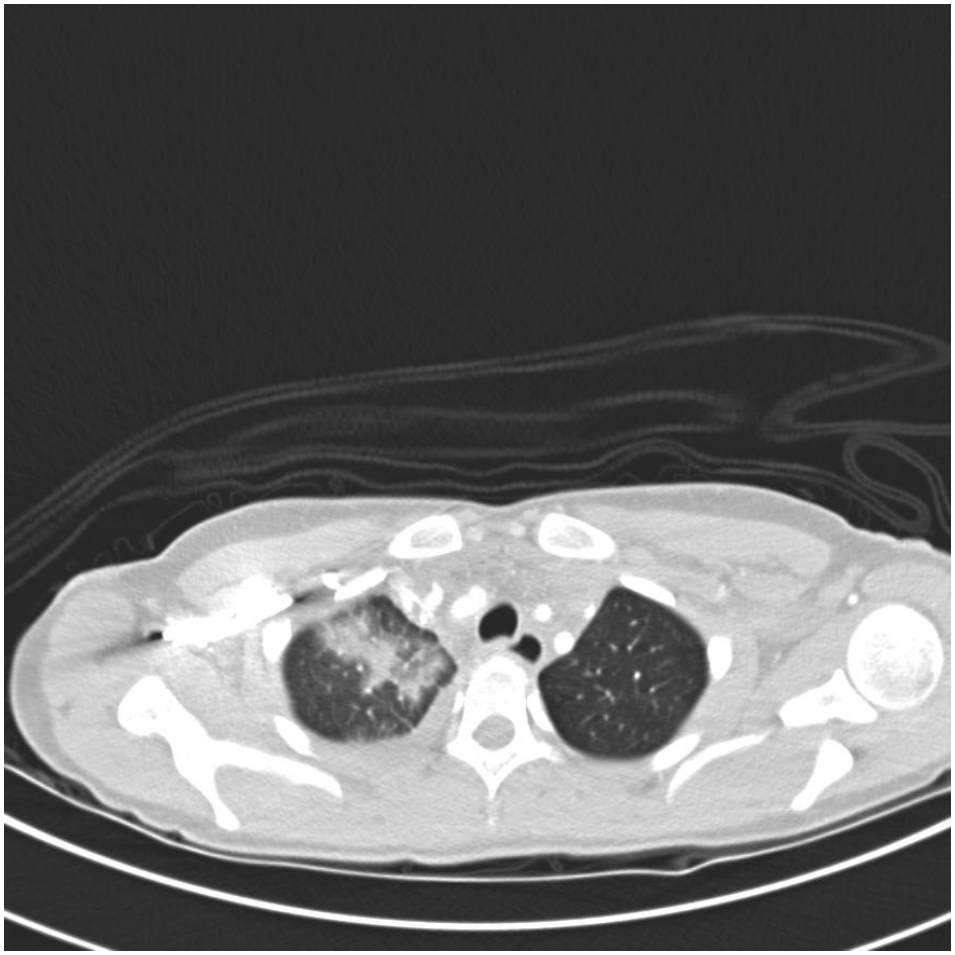




Lungs



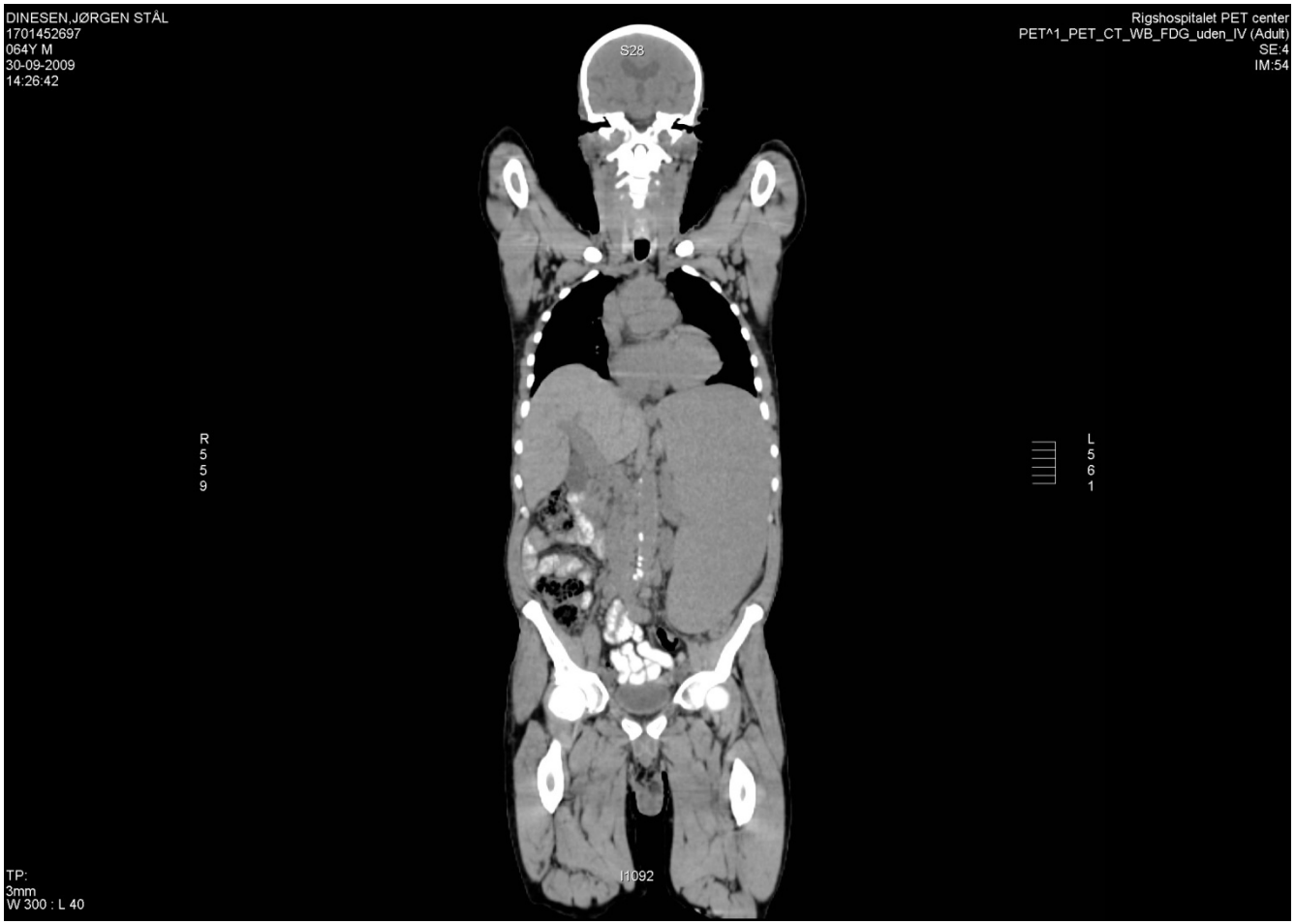
More diffuse infiltration, snow balls



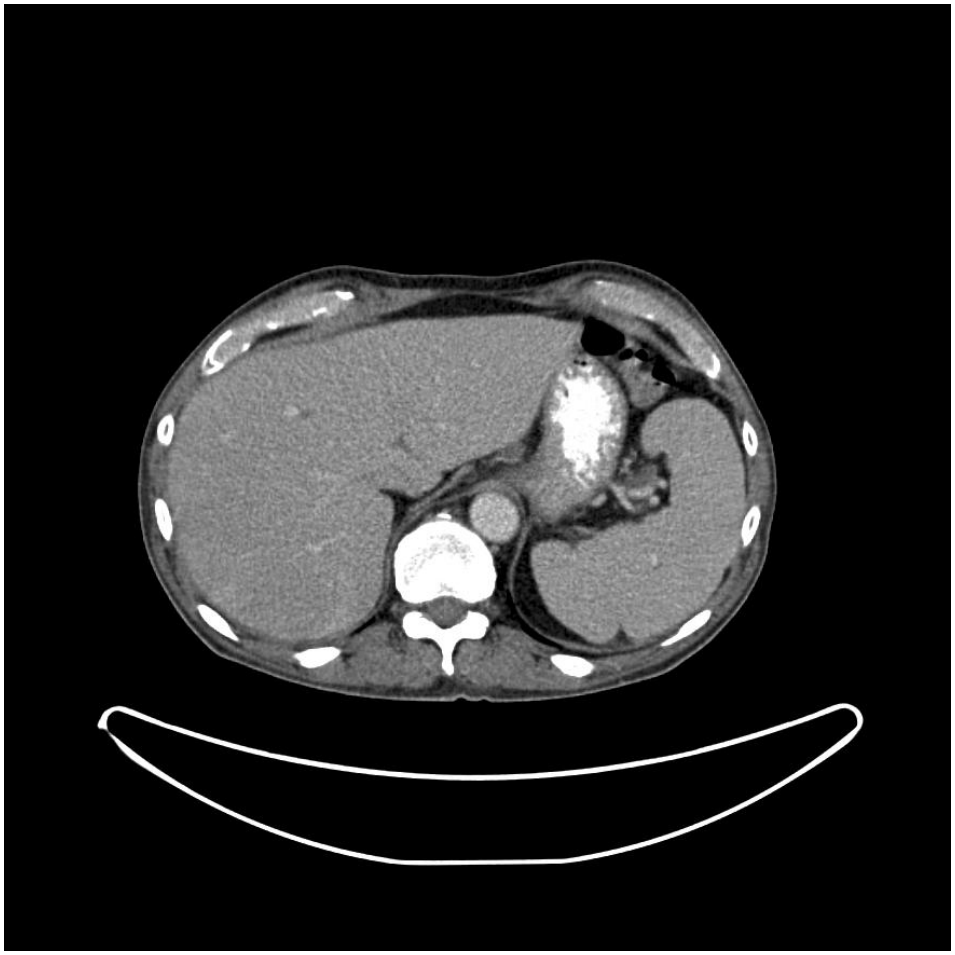
Spleen involvement

- Normal size and still contain lymphoma or enlarged and not involved.
- 10 -12 cm in vertical length. 13 cm.
- Best determined by PET/CT
- Diffuse infiltration
- Focal nodular lesion
- Large solitary mass

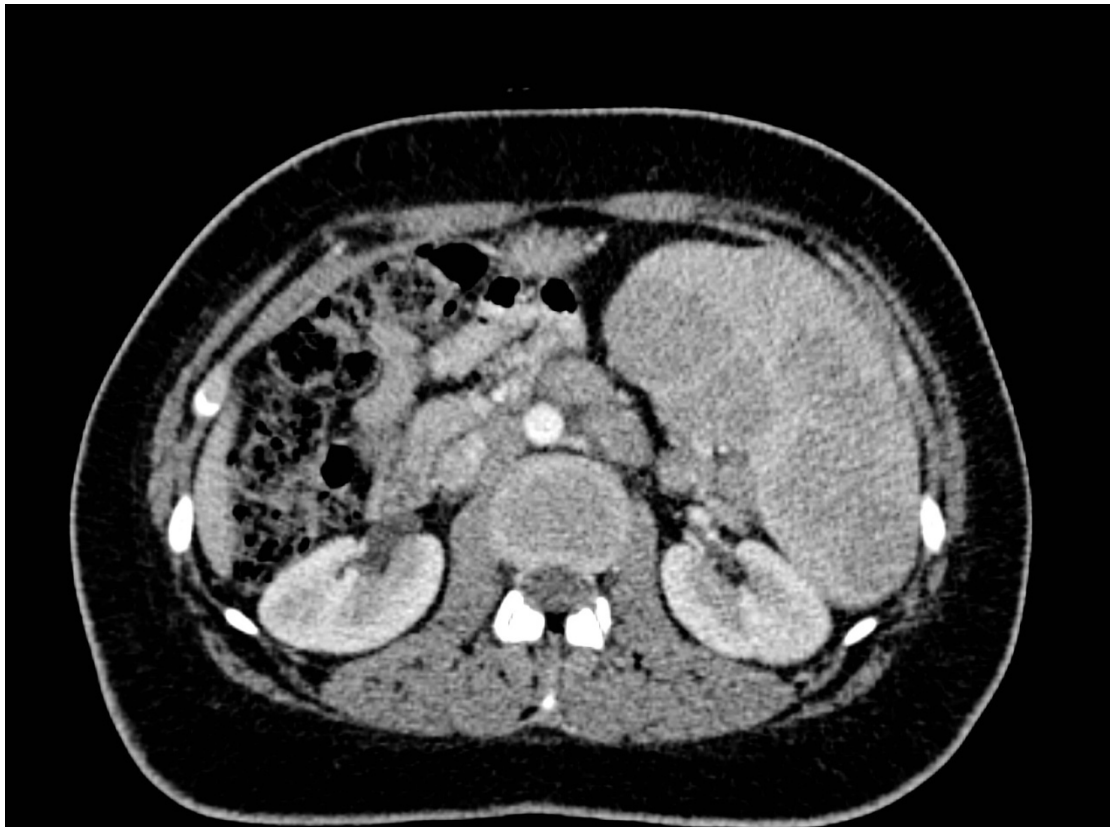
Spleen – large solitary mass



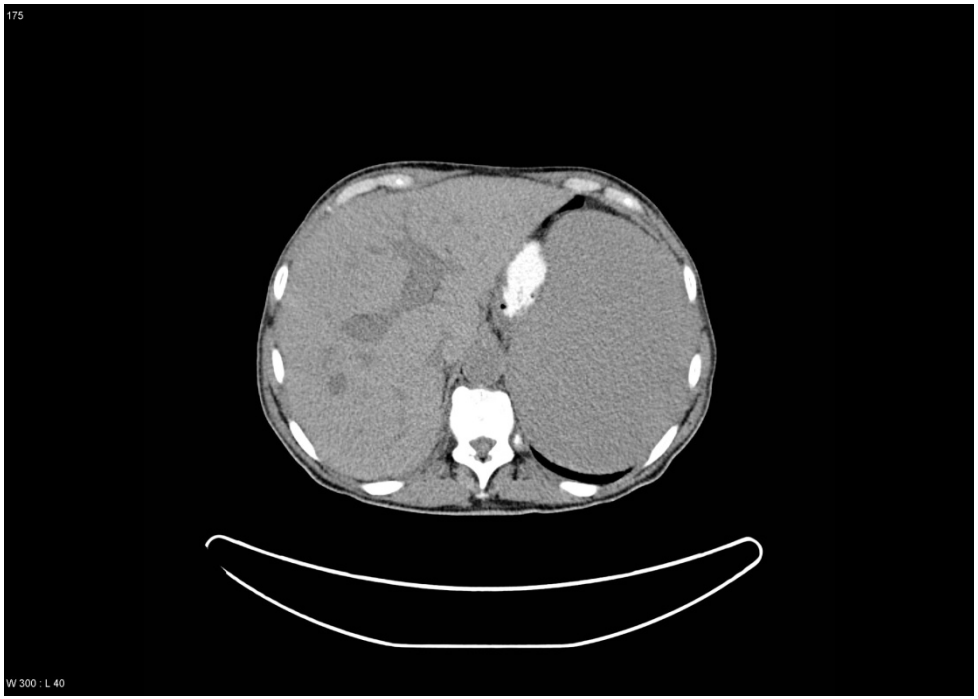
Spleen diffuse infiltration



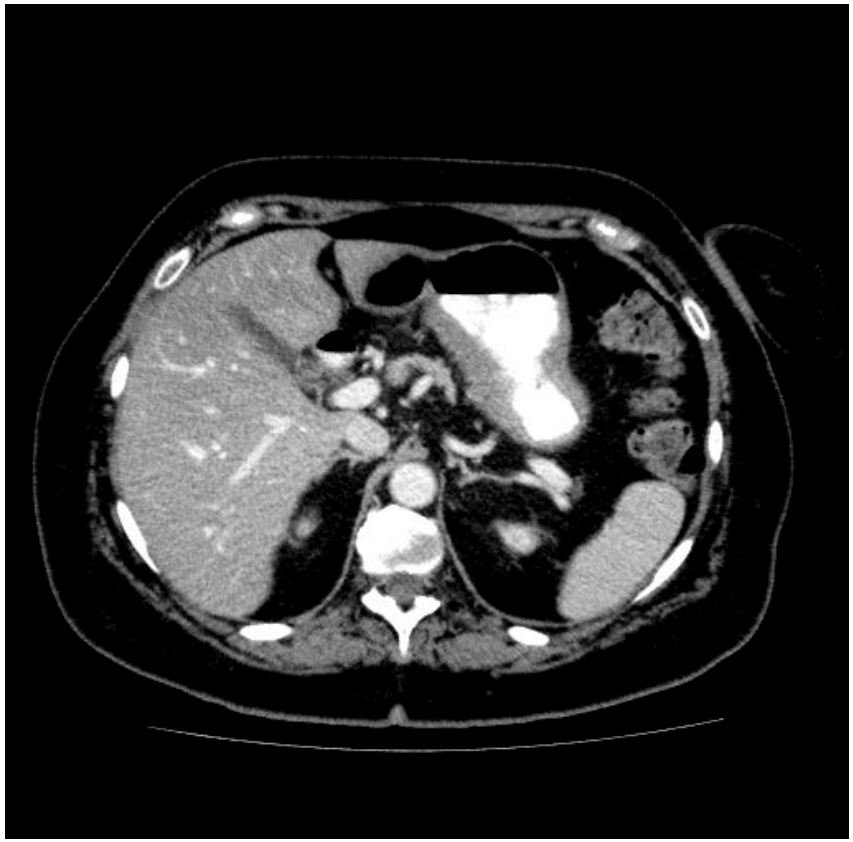
Spleen Focal nodula lesion



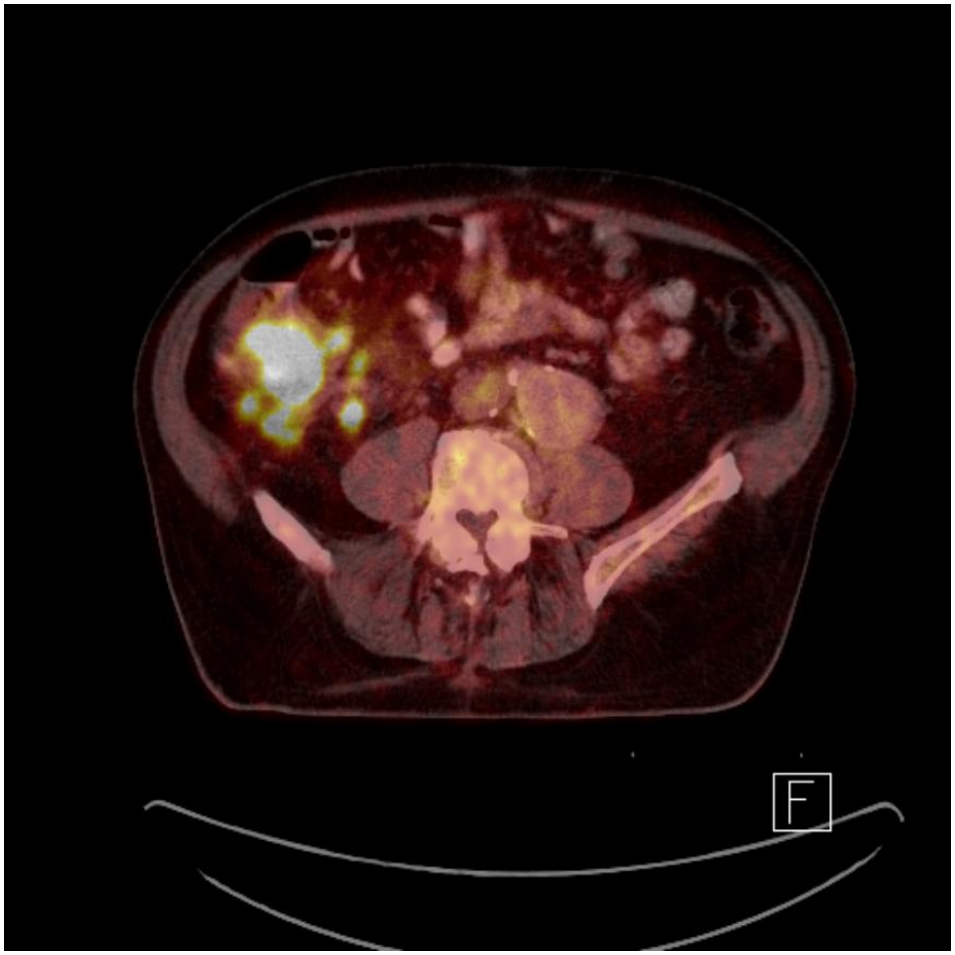
Liver involvement also best detected with PET/CT



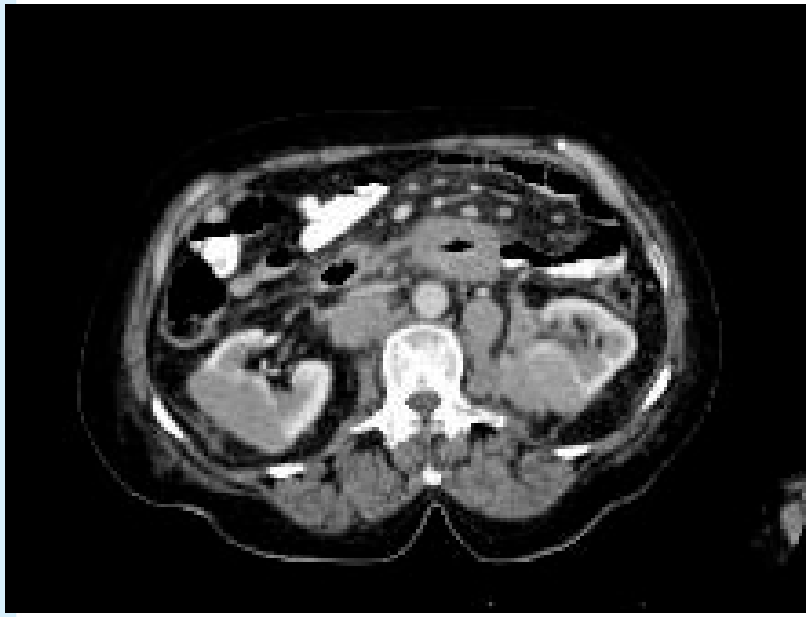
Lymphoma in the stomach

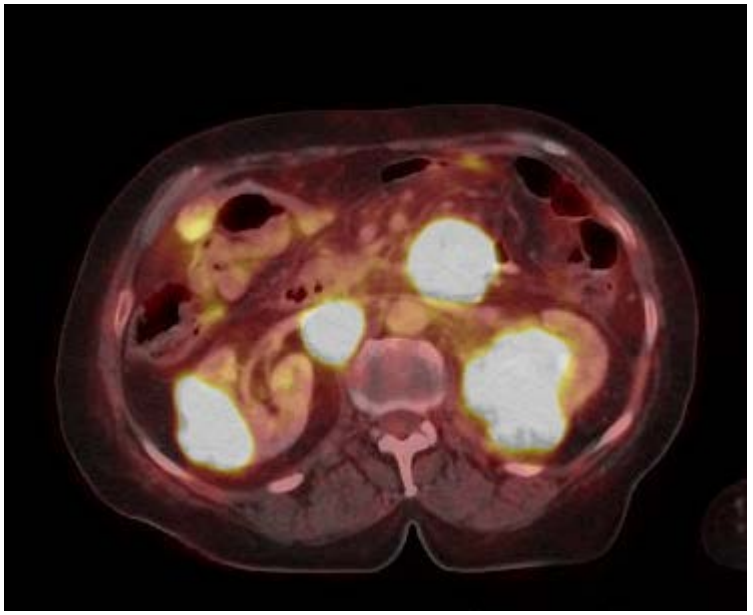


Colon



Lymphoma infiltration of the kidneys





Conclusion

- Good images are nescessary for staging as well as treatment planning
- CT and PET/CT are complementary to the clinical examination for treatment planning
- Lymphoma treatment is difficult and collaboration between experts is mandatory

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Deep inspiration breath hold in thoracic tumours: imaging and treatment

Marianne C Aznar

Dept. Of Oncology, section of radiotherapy

With the help of the Dept. of Clinical Physiology, Nuclear Medicine and PET

Copenhagen University Hospital

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LYMPHOMA: A SPECIAL CASE

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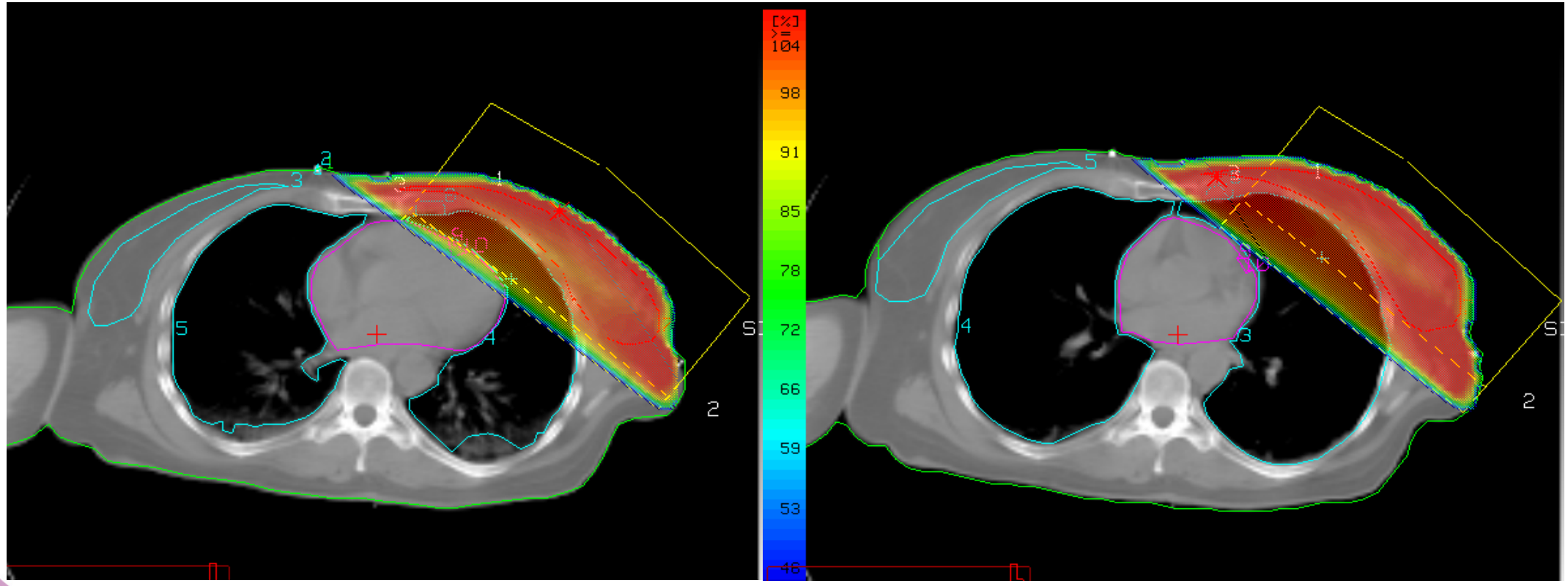
At Rigshospitalet

- Deep inspiration treatment since 2003 in left-sided breast cancer patients
- > 1000 patients



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Methods

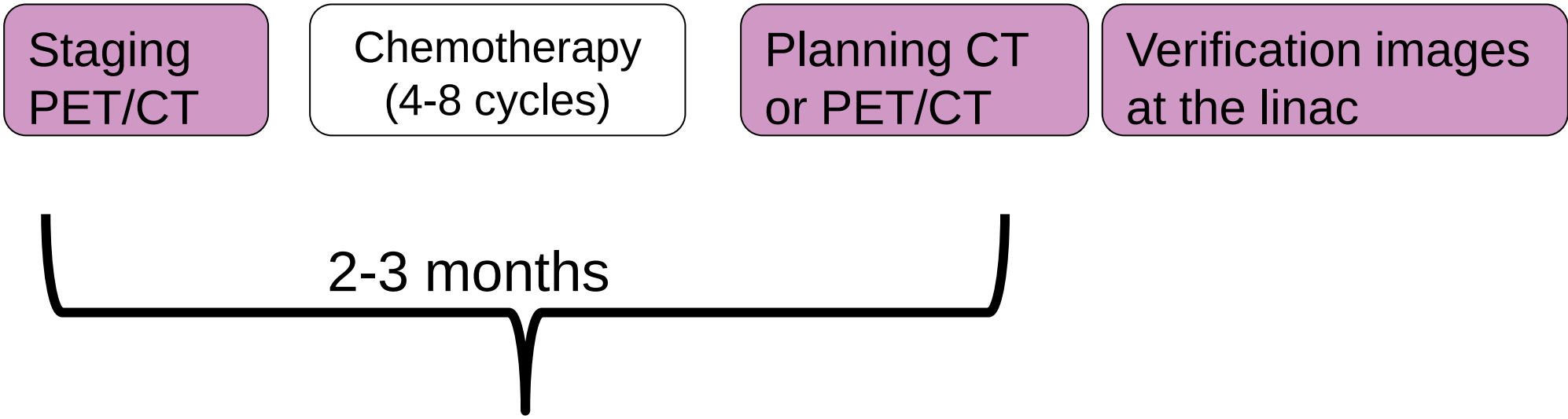
Overall aim:

reduce dose to the heart (heart disease)

And other organs (e.g. Secondary lung cancer)

Prospective phase II trial: 22 patients

All images in DIBH



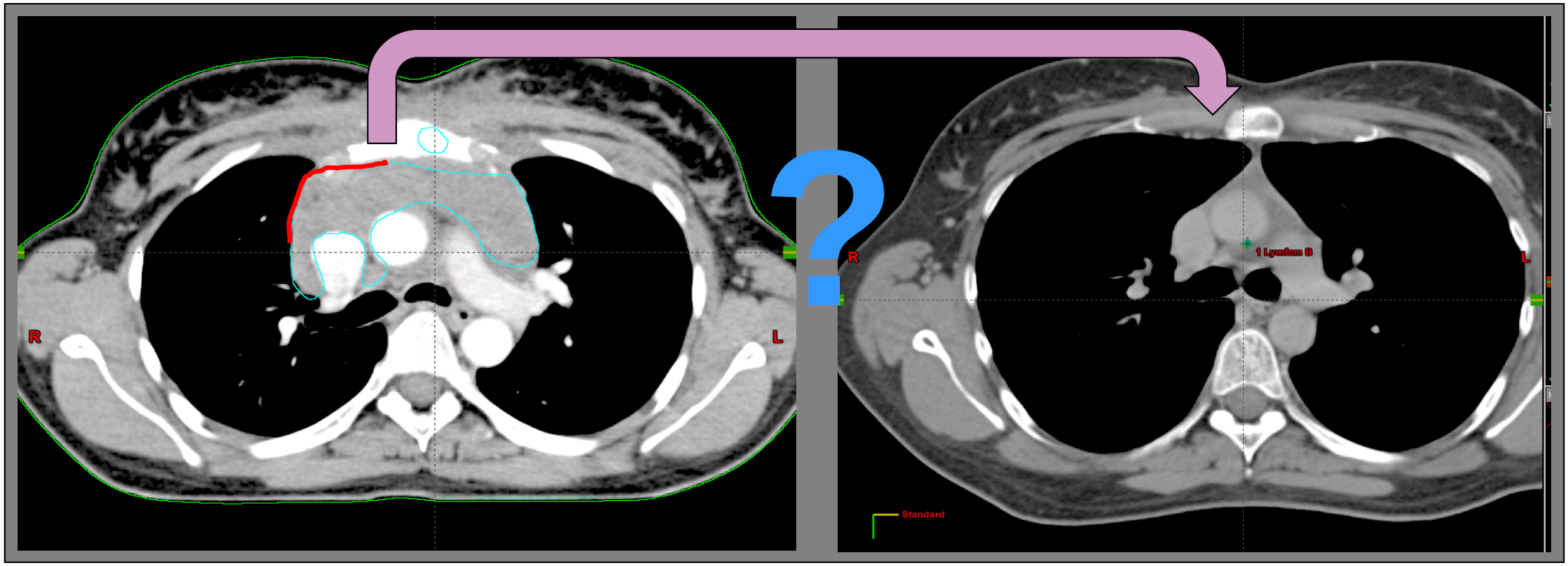
Fusing prechemo and planning images

Pre-chemo PET/CT

free breathing

Planning CT

at deep inspiration



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How to handle registration uncertainties ?

- Ensure a treatment-like position already at staging
  - Flat table top
  - Arms up
  - Chest board

- Provide DIBH PET/CT at staging

- All these take time, logistic effort, and a good collaboration with the PET department!

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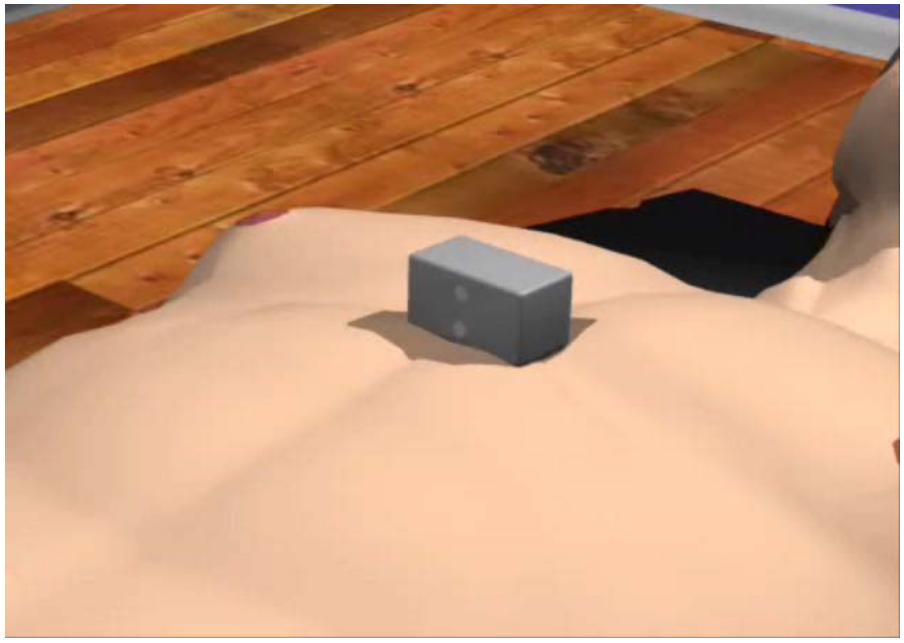
Respiration monitoring



<u>Varian RPM system:</u>
Deep inspiration breath hold
Gating
4D CT

On all linacs and scanners

CT + PET/CT

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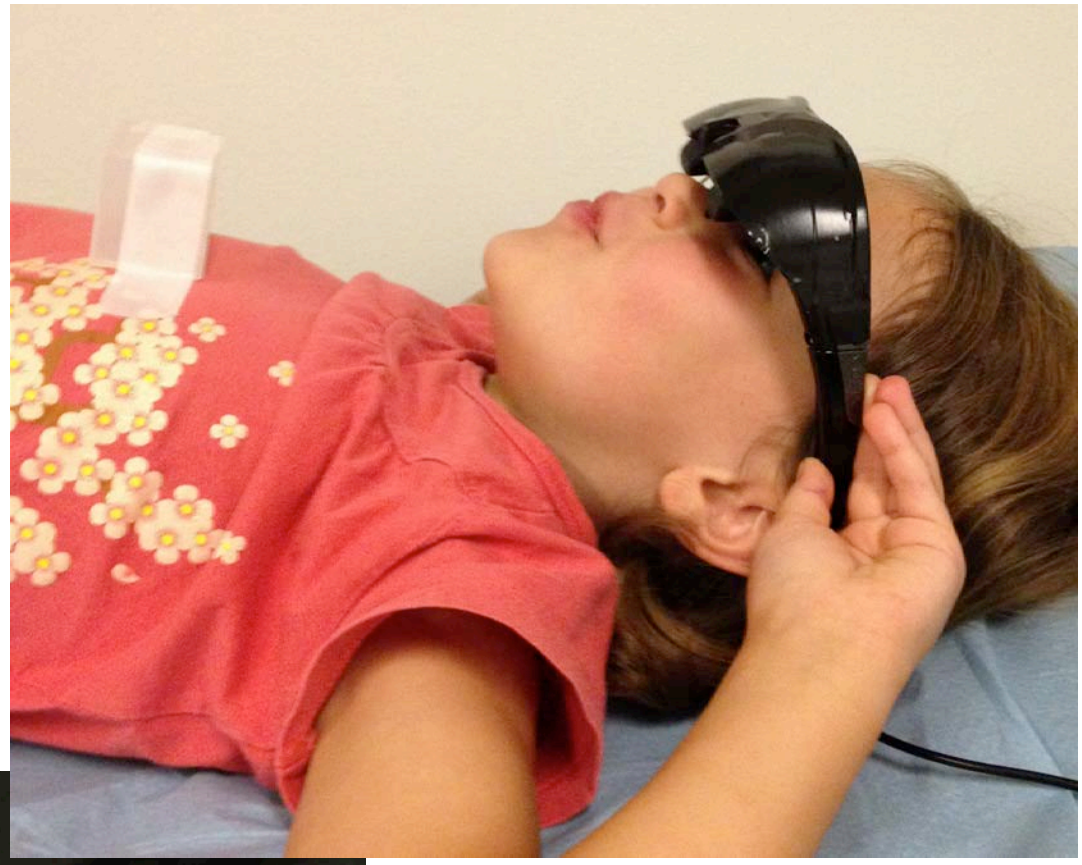
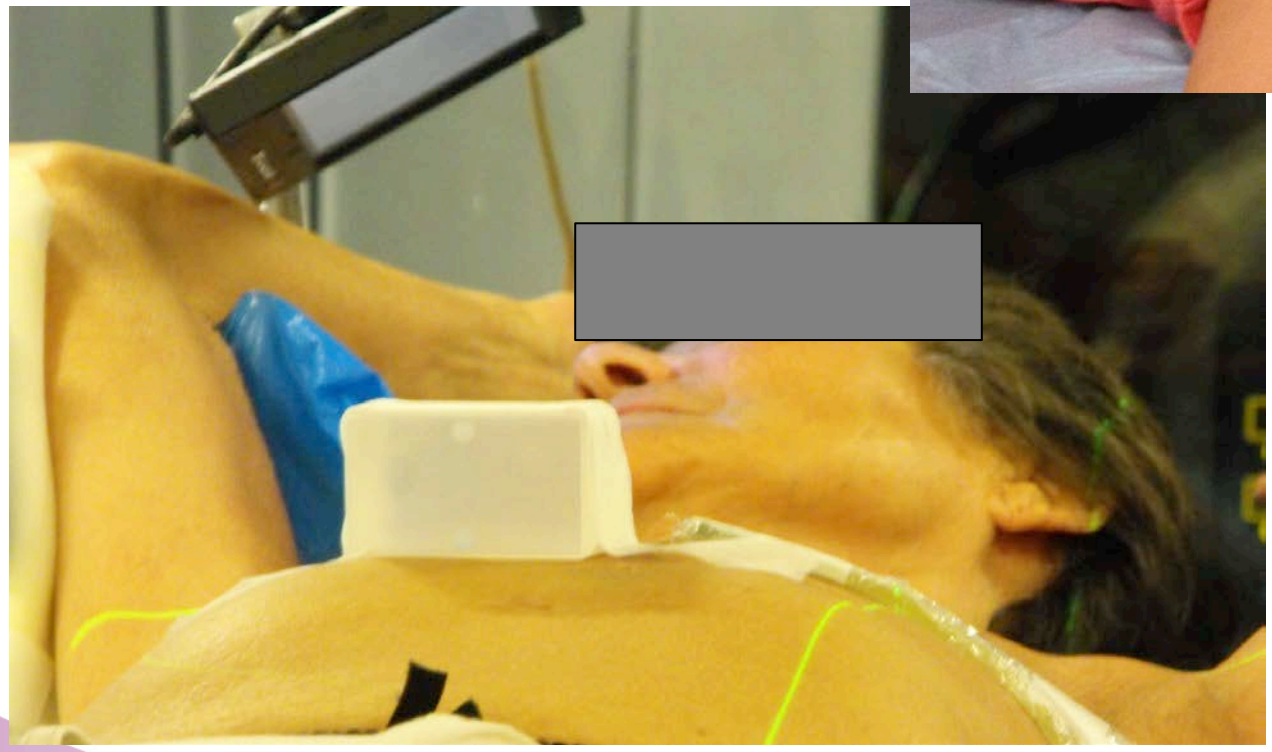
Visual guidance:

- Scanner
- linac





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Free breathing

Deep inspiration
breath hold

Take home message (1)

- Keep patient instruction and information as simple as possible
- Coach before scanning (30 min) or directly at the scanner (5-10 min): equivalent results !!
- Extra time necessary at the scanner (install equipment, etc... plus extra acquisition) : 15-30 min
- Good communication with PET extremely valuable !

PET/CT acquisition in practice

Pre chemo scan: *400 MBq* FDG on Siemens Biograph 40 PET/CT (now depending on bodyweight)

Free breathing scan followed by one FOV scan in breath hold

3 breath holds of 20 seconds each

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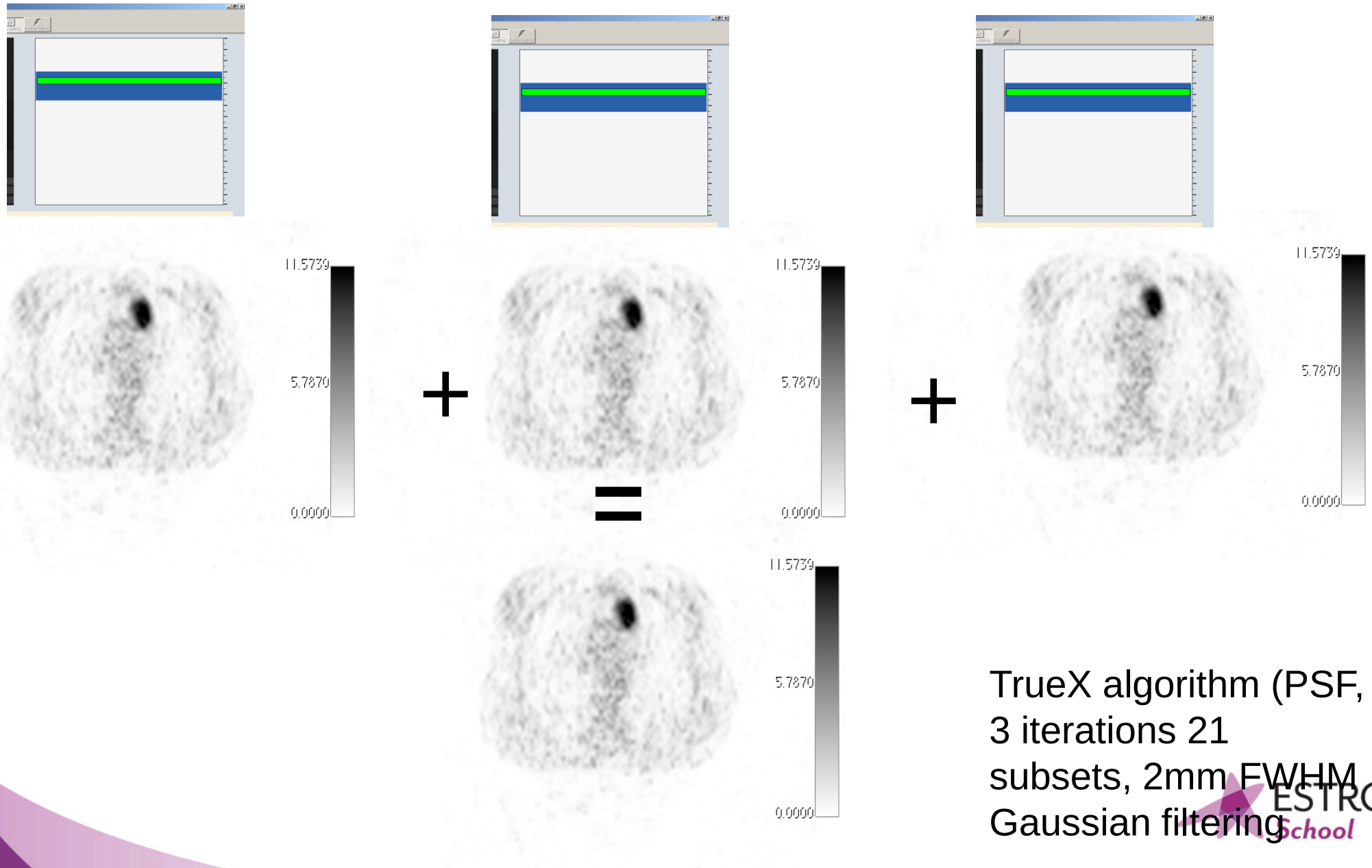
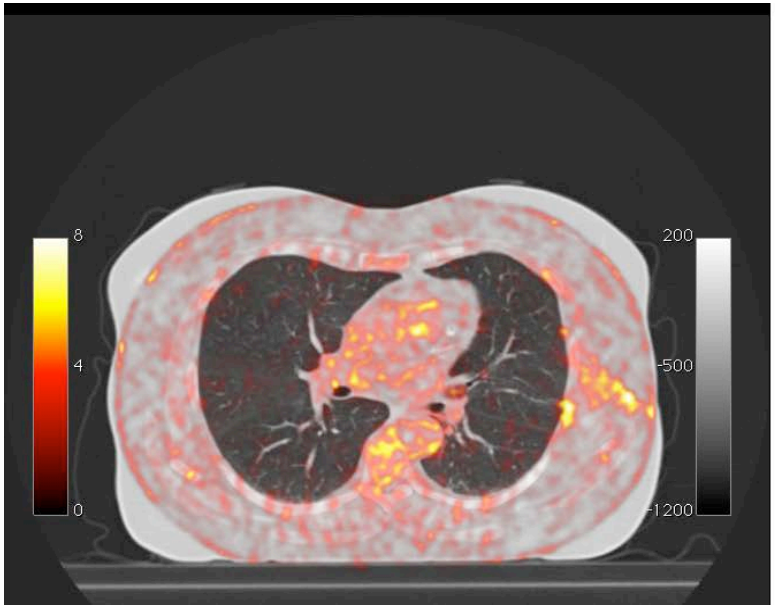
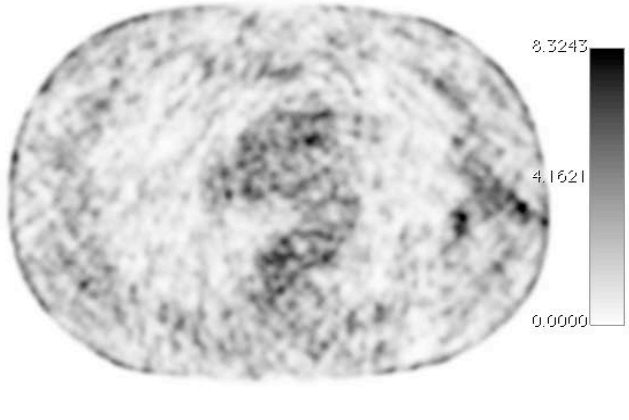
Methods: Image reconstruction

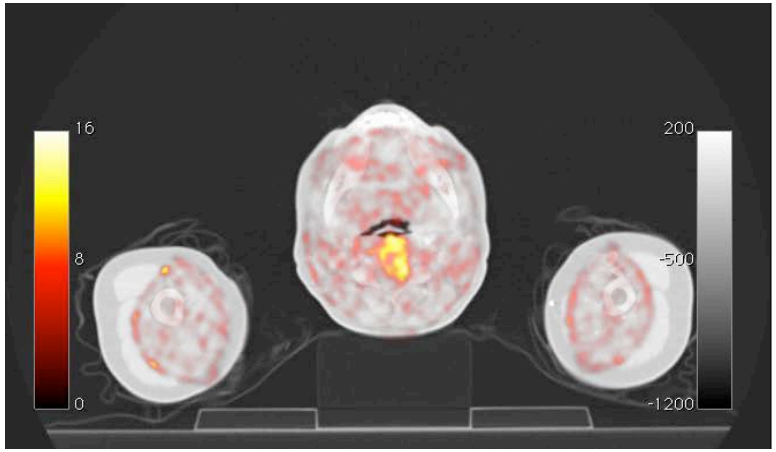


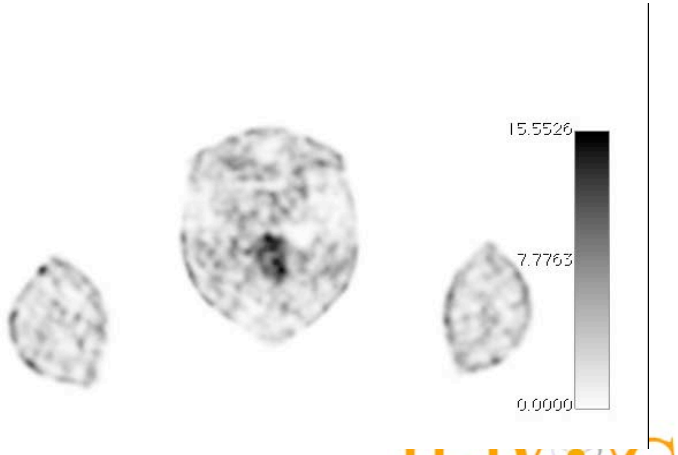
TrueX algorithm (PSF, 3 iterations 21 subsets, 2mm FWHM Gaussian filtering)

Some problems at start-up !!









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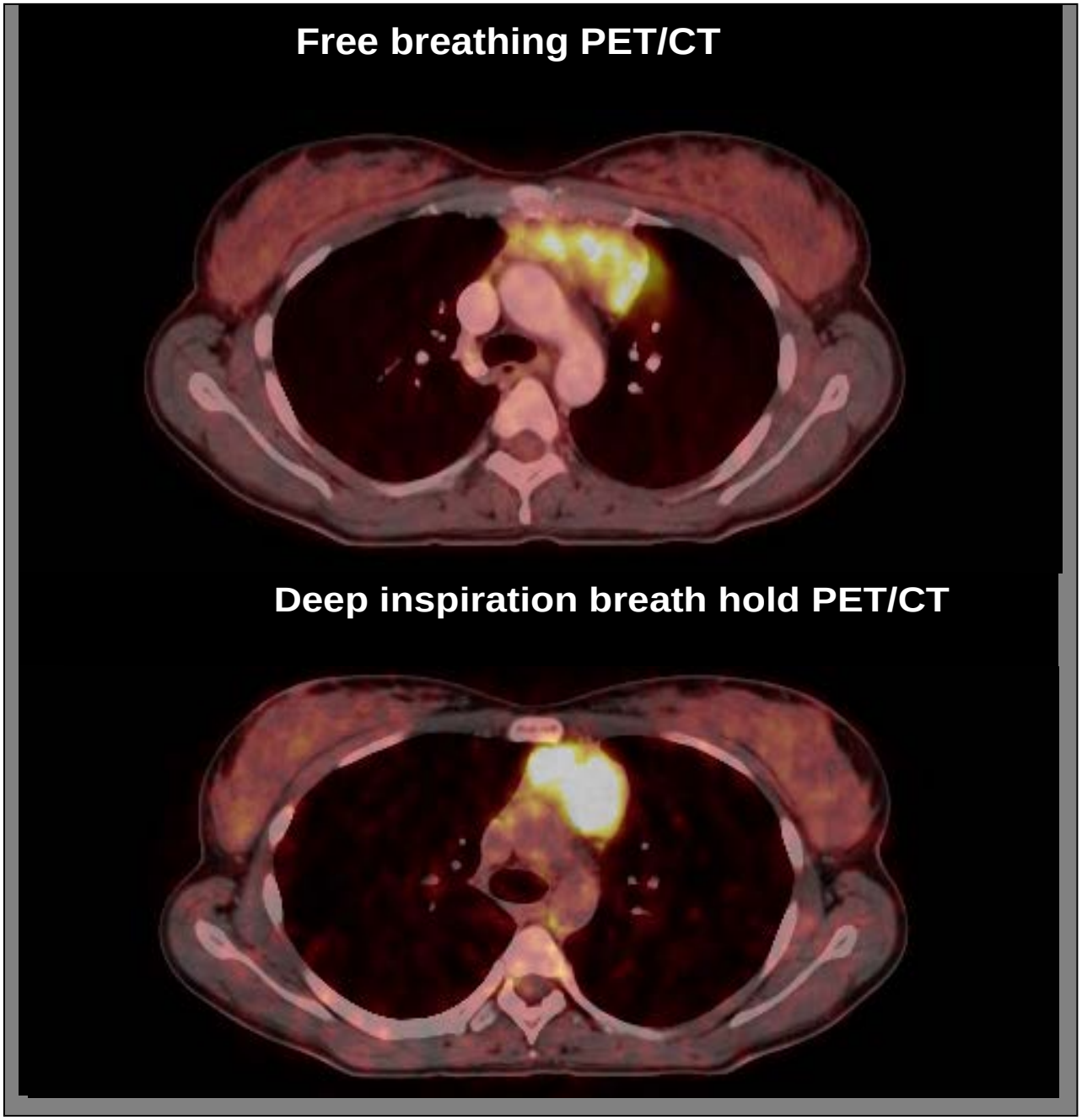
Results: reduced respiration artifacts



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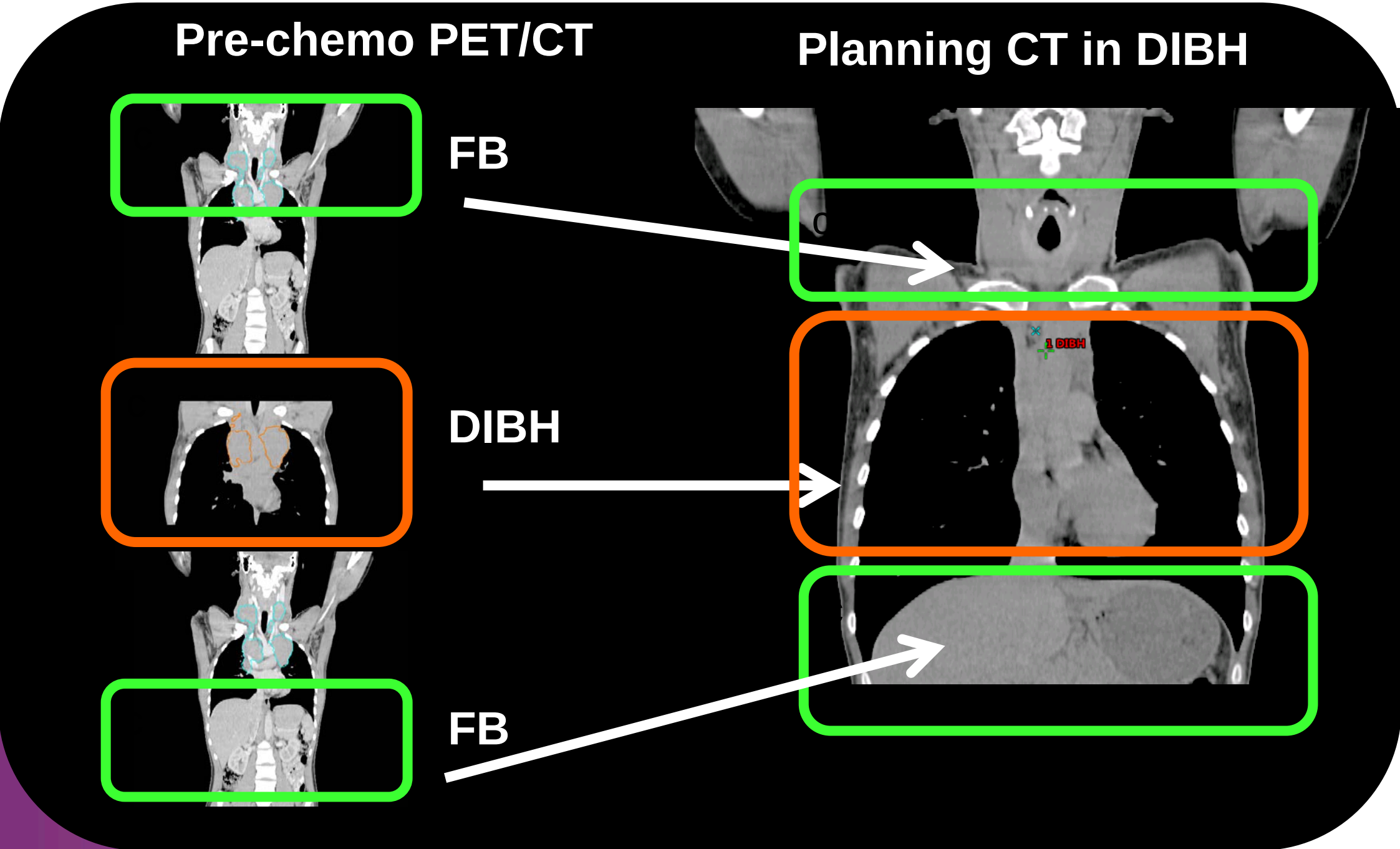
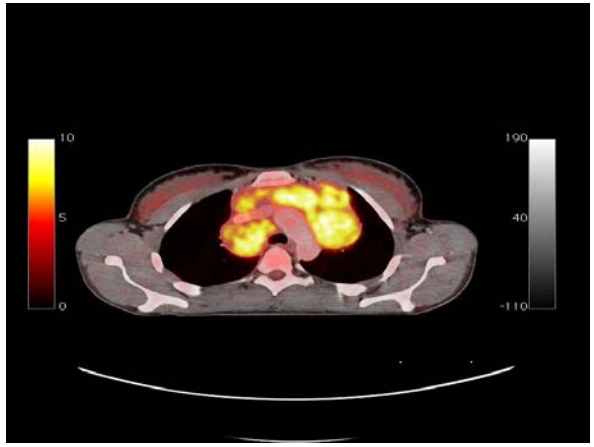
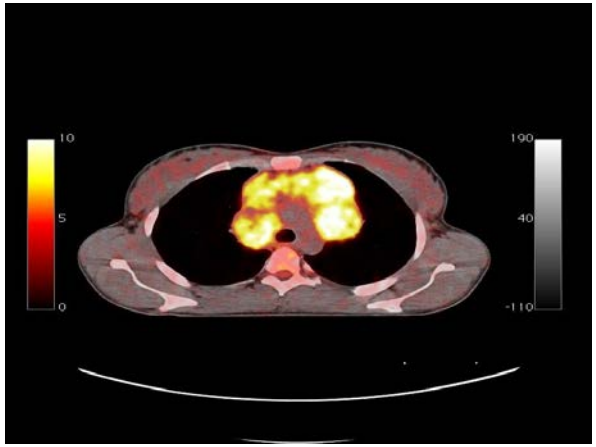
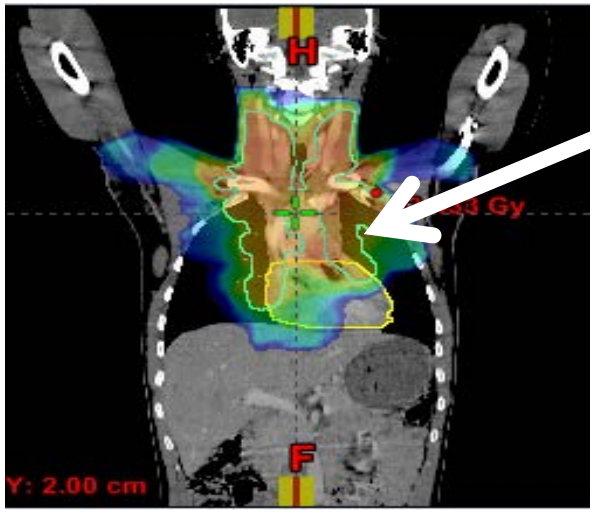
Registration for contouring

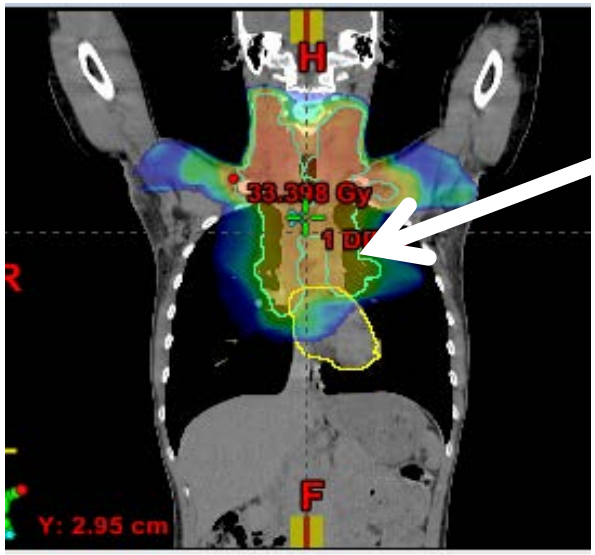


Planning results









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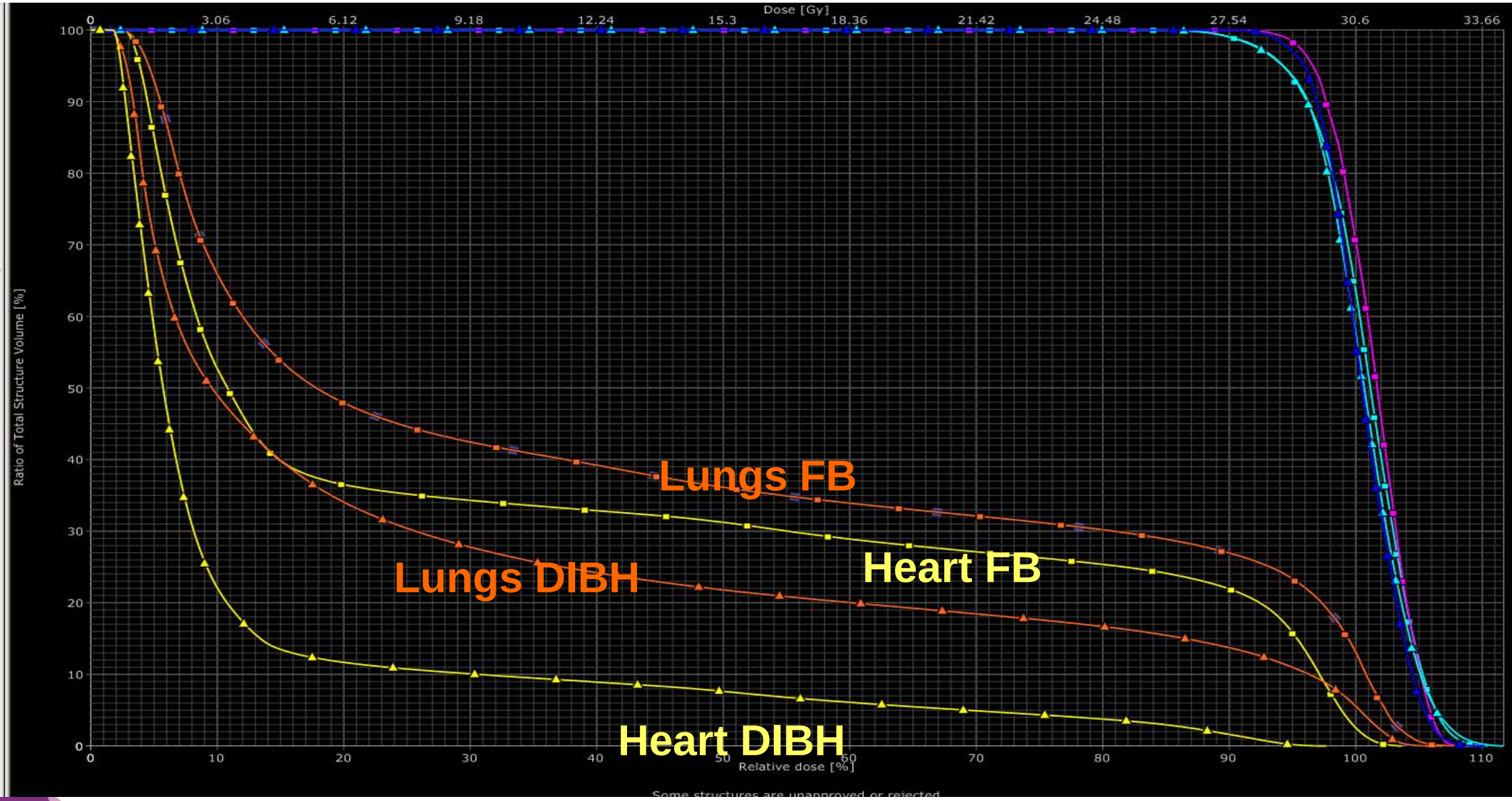
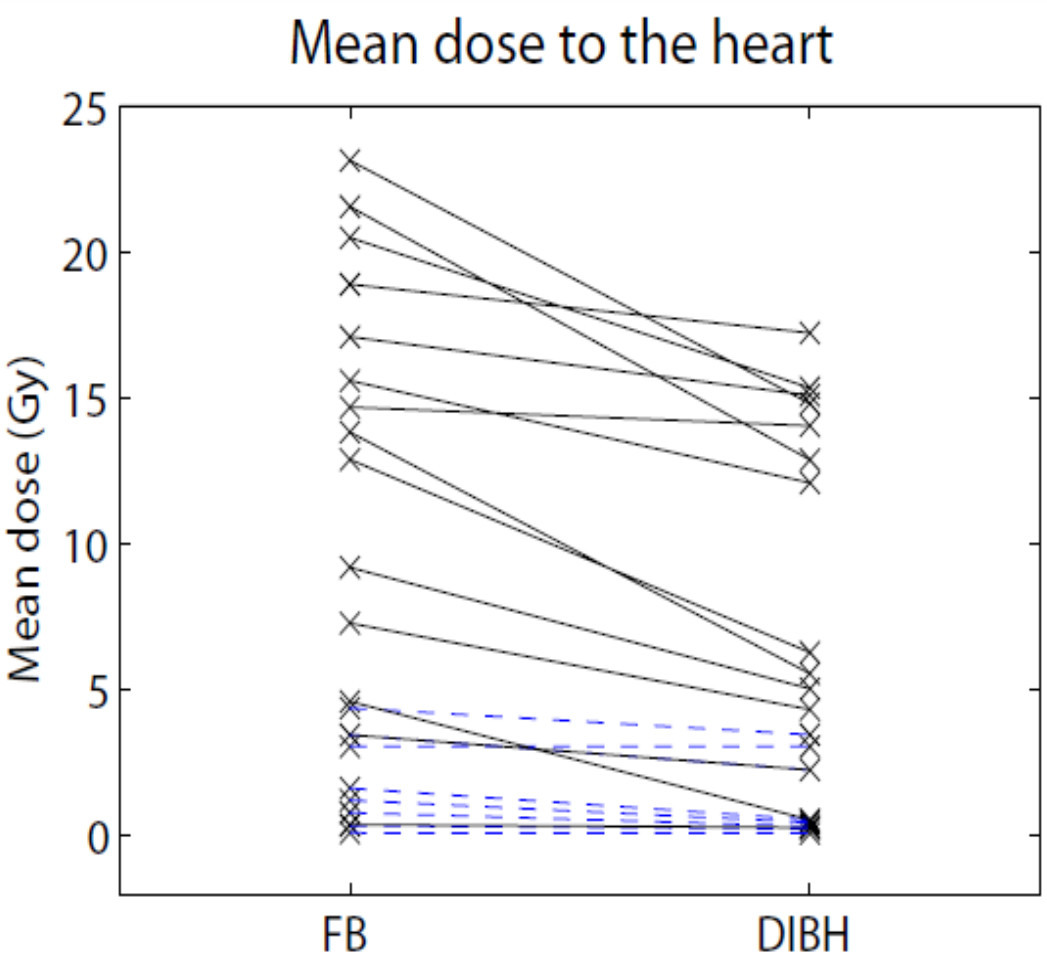
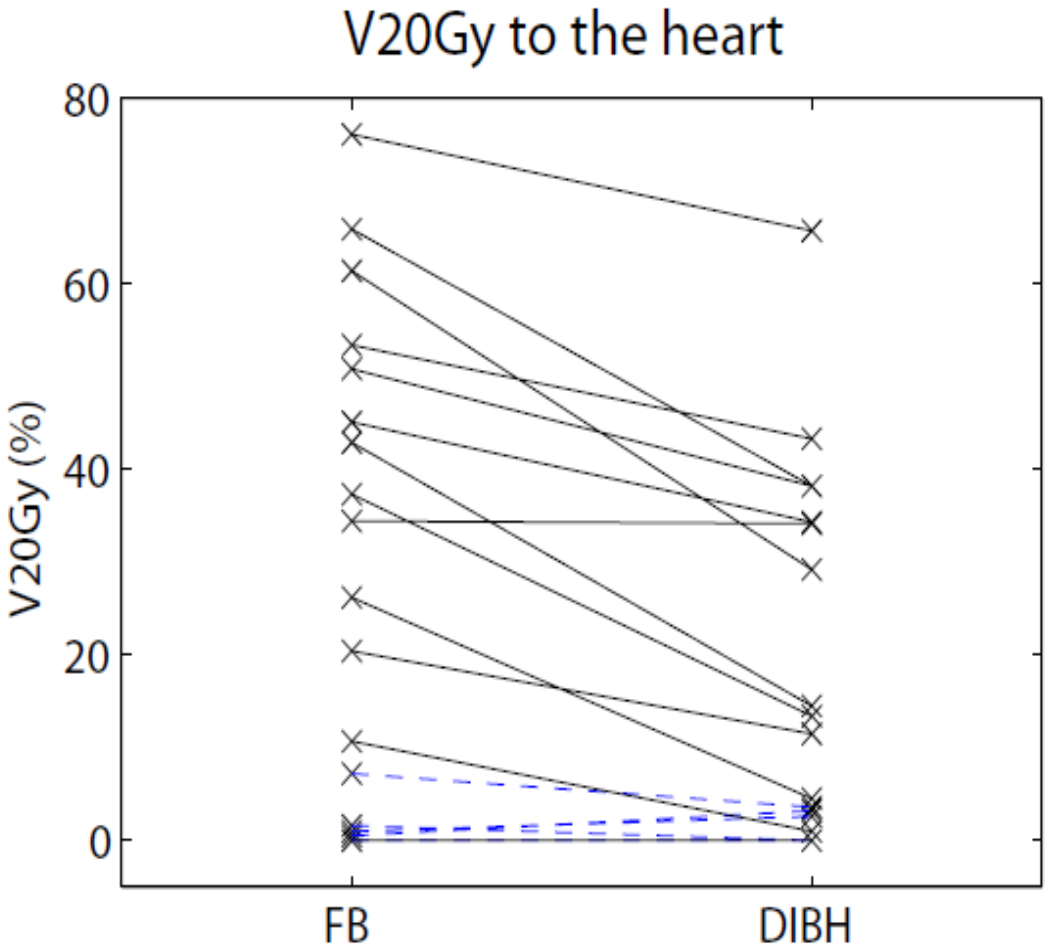
Mean dose to lungs: 8.5Gy vs 12.8 Gy



Benefit: inter-patient variation





Petersen et al. Acta Oncologica 2015

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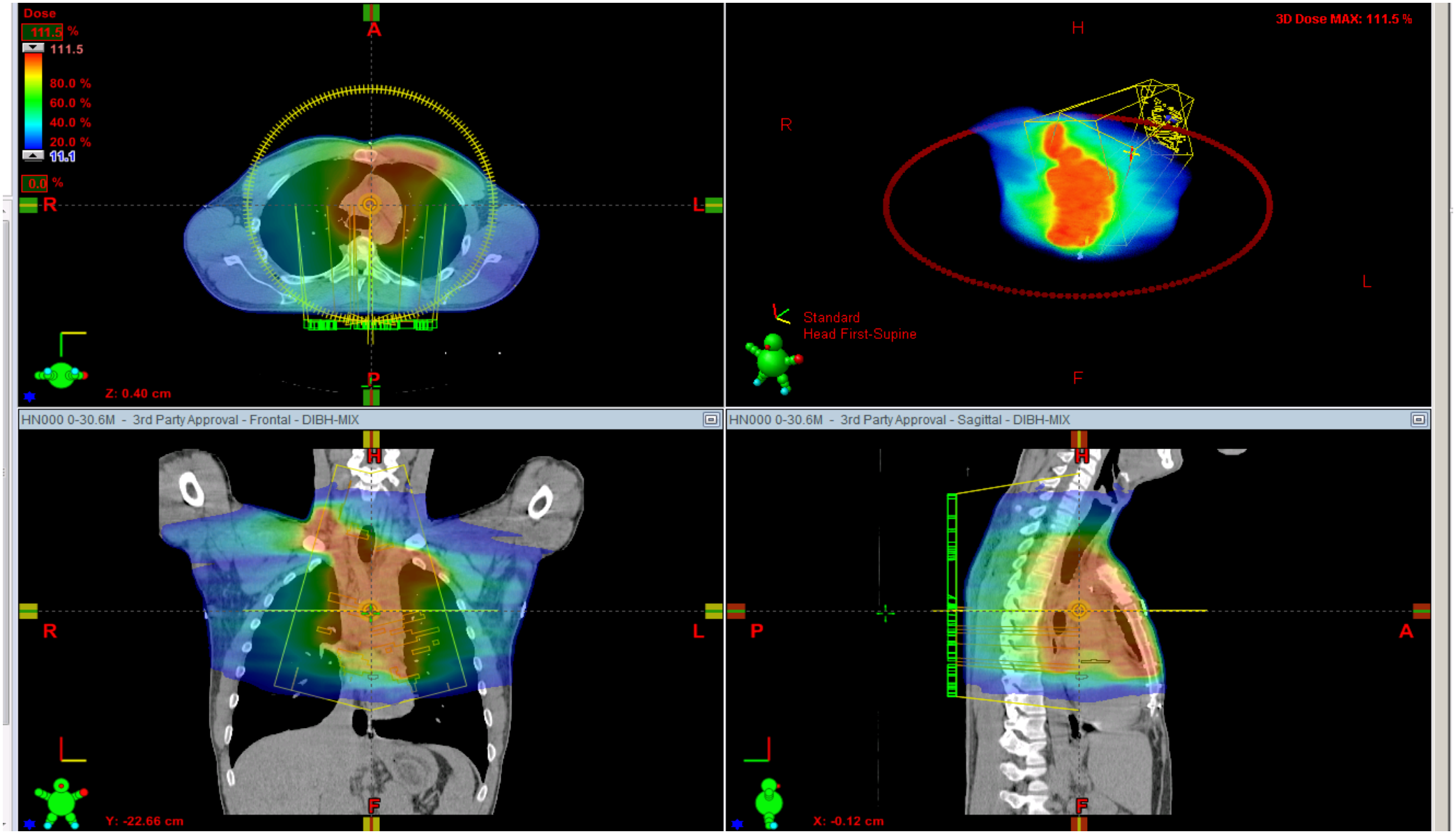
DIBH + VMAT/IMRT



RPM integrated with linac
Beam switches on and off automatically

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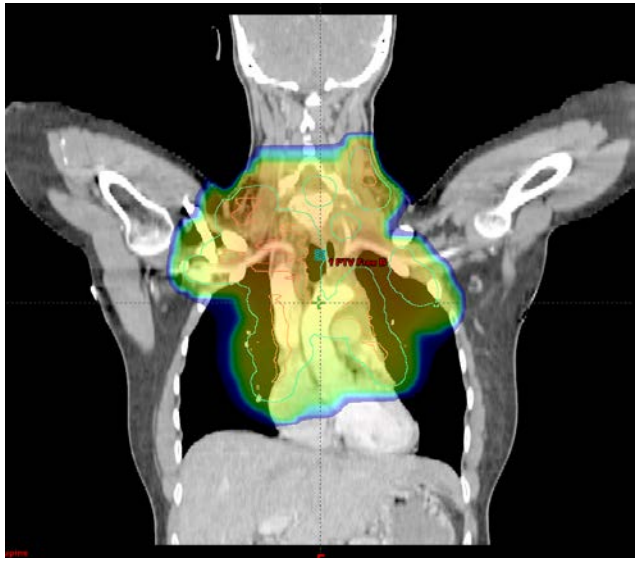
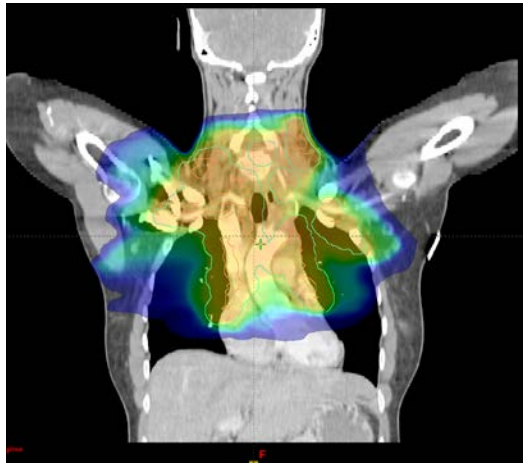
What to choose: IMRT? DIBH or both?

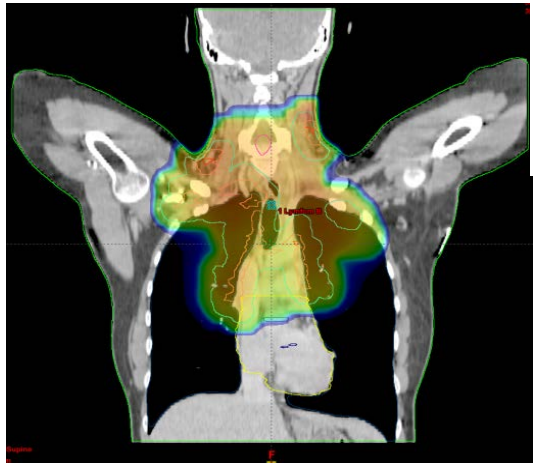
- Free breathing (3DCRT)





•Free breathing (IMRT)

<u>NB: dose bath</u>



- DIBH (3DCRT)

Conclusions DIBH vs IMRT

DIBH-3DCRT was more effective to reduce heart and lung dose
IMRT tended to give a higher mean dose to the breasts

First choice: 3D-DIBH for young women, then IMRT only if the heart dose needs to be further reduced
Men: DIBH+IMRT could be a standard solution

Aznar at al IJROBP 2015

Take home message (2): treatment planning

- Having the staging PET/CT in DIBH increased our physicians' confidence
- The dosimetric benefit was clear enough to make DIBH our standard treatment for HL
- However, we still acquire a free breathing planning CT on top of the DIBH planning CT
- Tendency to combine DIBH with VMAT

IGRT

POSITION VERIFICATION IN DIBH

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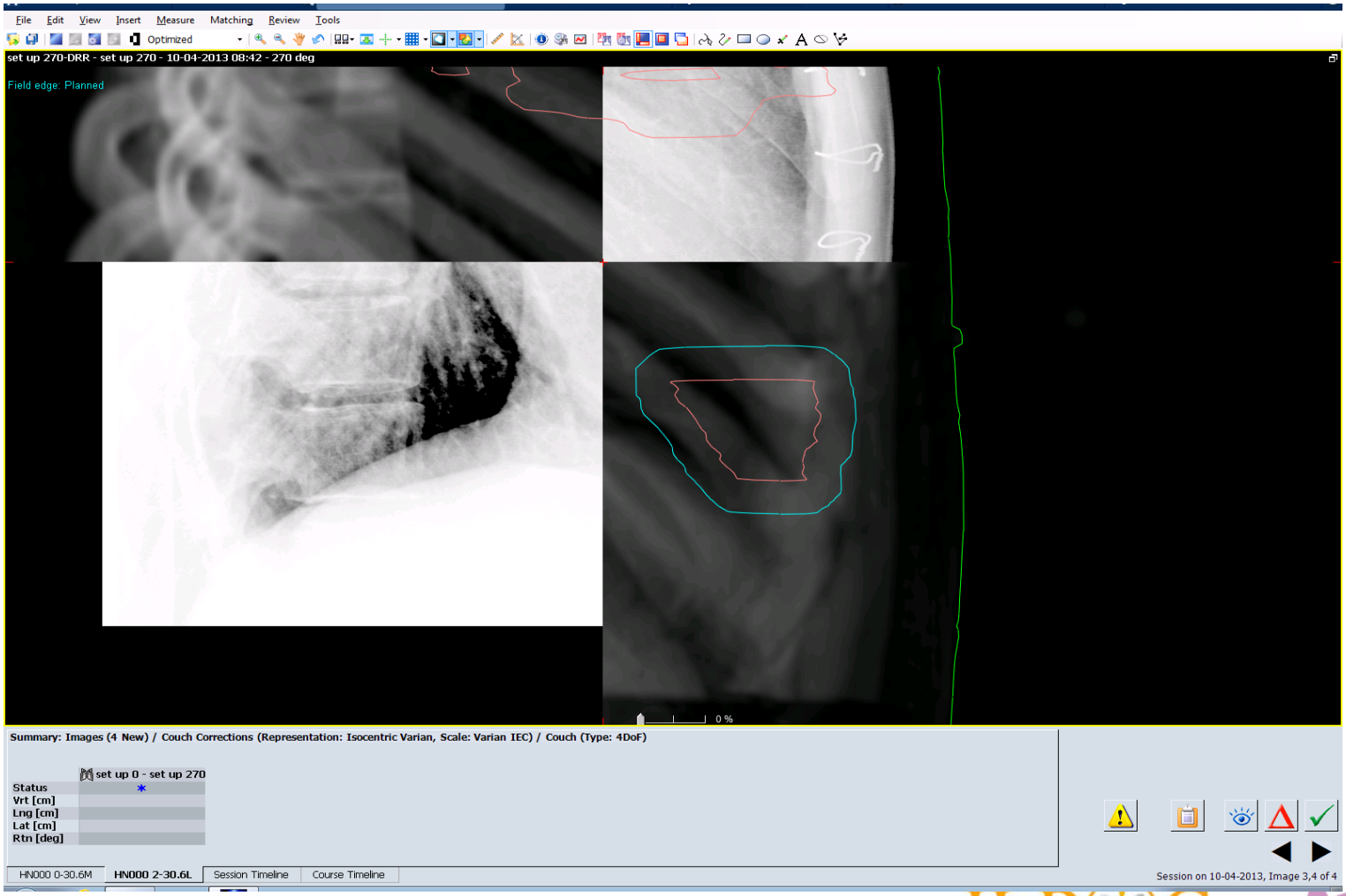
Daily 2D images: fuse on spine, check sternum



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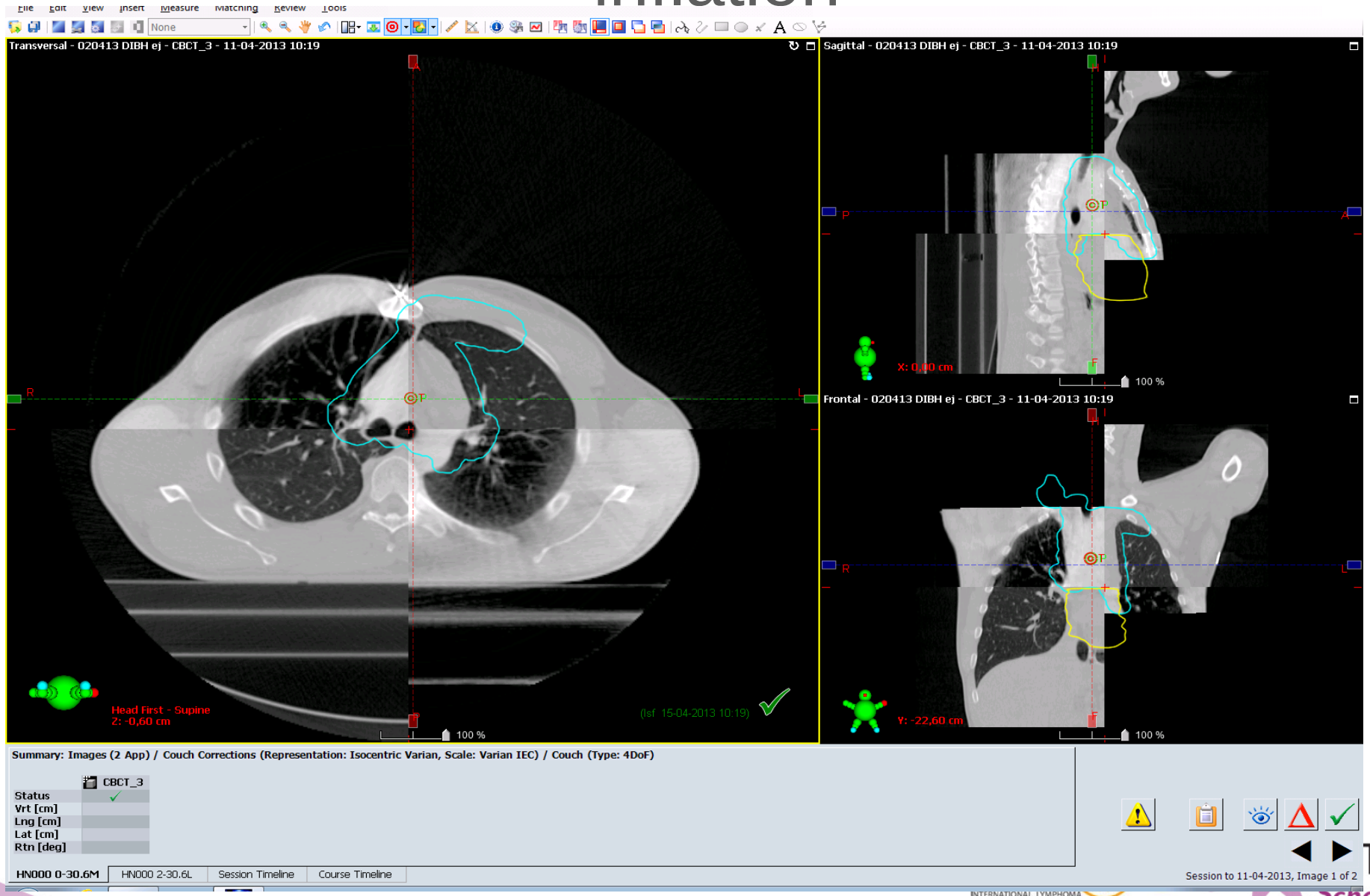
Can check heart position and lung inflation



Some challenges with CBCT in DIBH

- Requires 2-3 additional breath holds
  - But remember: young/fit patients
- Manually operated
- Some resistance to introduce it as a daily modality !

Some possible compromises…

- Daily 2D DIBH images
- Daily 2D DIBH images + weekly DIBH CBCT (with/without a physicist present)
- Daily DIBH CBCT with a longer treatment slot

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A note about margins…

- In free breathing: 1cm, 1.5 cm sup-inf
- In DIBH: 1 cm all around ?
- A study of interfraction variation demonstrated that margins could NOT be reduced with DIBH
  - Back to 1cm, 1.5 cm sup-inf

Take home message (3): treatment delivery

- Patient compliance is excellent
- DIBH CBCT is possible, but there is a learning curve

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Conclusion

- DIBH implementation in lymphoma very succesful
- Protocol in lung cancer patients ongoing

- Clear dosimetric benefit, even when using VMAT/IMRT

- Ressource investment: the ”sore points” are
  - PET scanning time
  - IGRT
  - And even then, they remain very manageable !

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Acknowledgments

Department of radiation therapy, especially:

Peter Meidahl Pedersen

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Lena Specht

Ivan Vogelius

Mirjana Josipovic

Sidsel Damkjær

Deborah Schut

Patrik Brodin

Gitte Persson

Department of Clinical Physiology Nuclear Medicine and PET, especially:

Flemming Andersen

Annika Loft

Anne Kiil Berthelsen

Thomas Levin Klausen

Marianne Federspiel

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Keep breathing ☺

Quiet free breathing

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Contouring Workshop

Anne Kiil Berthelsen
Berthe Aleman
Lena Specht

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

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

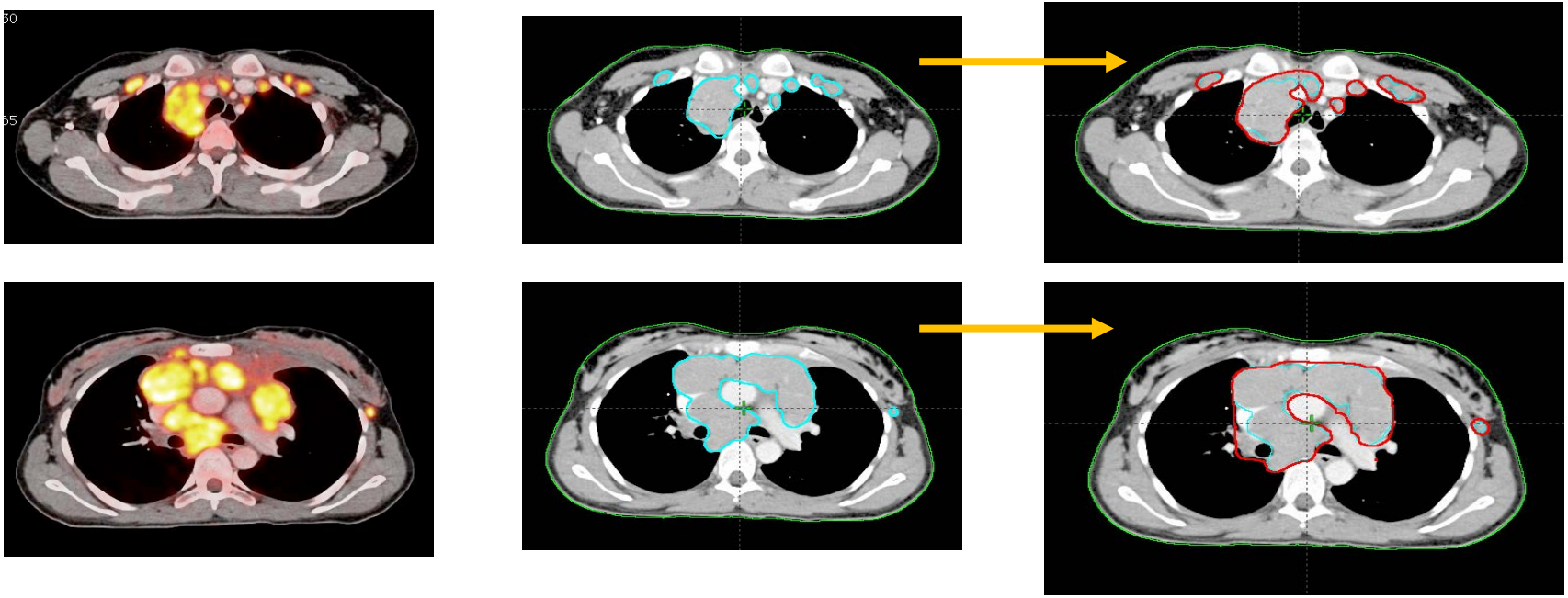
Lena Specht, MD, PhD,* Joachim Yahalom, MD,† Tim Illidge, MD, PhD,‡ Anne Kiil Berthelsen, MD,§ Louis S. Constine, MD,|| Hans Theodor Eich, MD, PhD,¶ Theodore Girinsky, MD,# Richard T. Hoppe, MD,** Peter Mauch, MD,†† N. George Mikhaeel, MD,‡‡ and Andrea Ng, MD, MPH††, on behalf of ILROG

IJROBP 2014; 89: 854-62

Pre-chemo PET/CT scan

PET+ volume

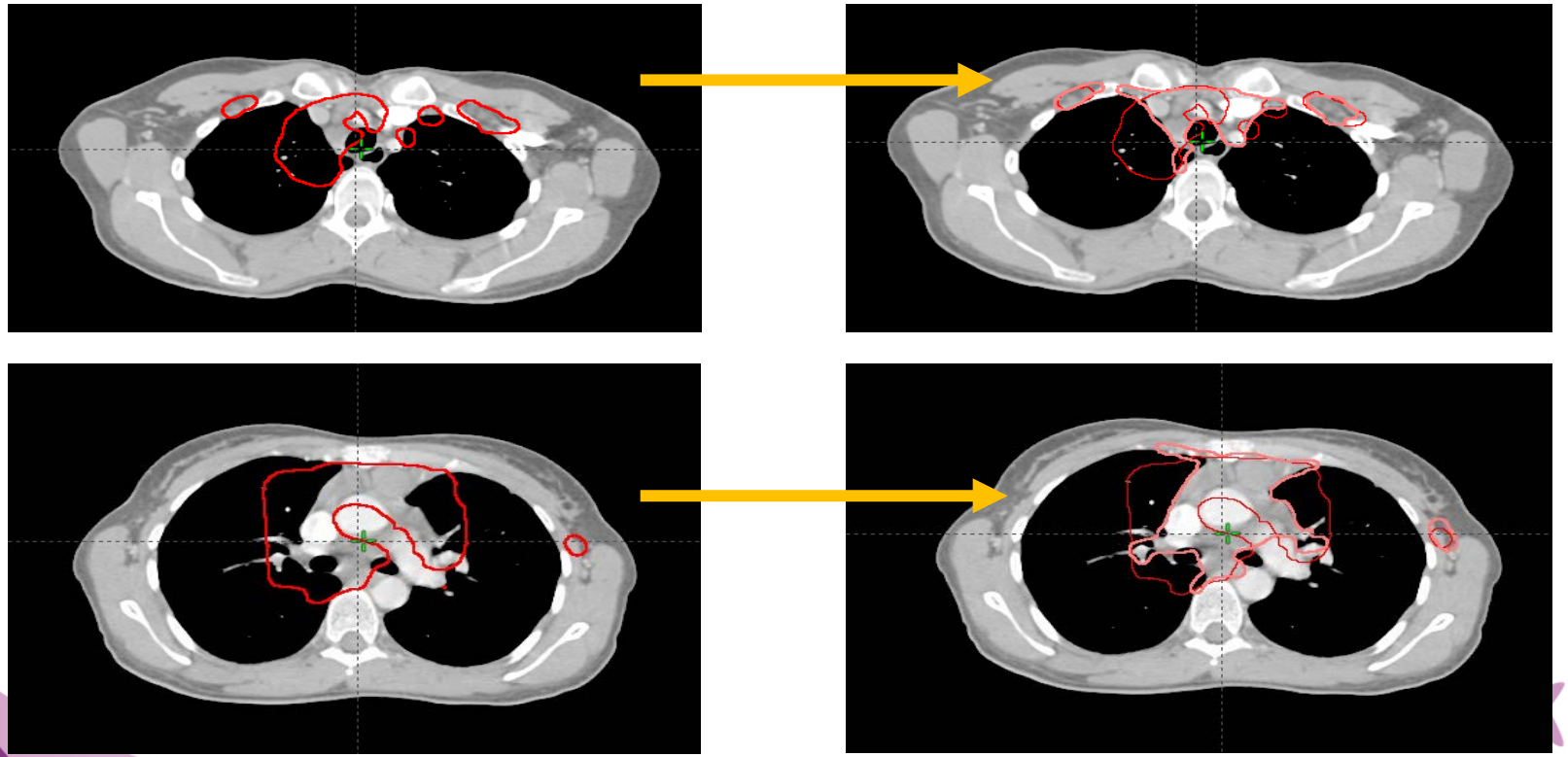
Gross tumour volume GTV



Post-chemo planning CT scan

Pre-chemo gross tumour volume

Post-chemo clinical target volume



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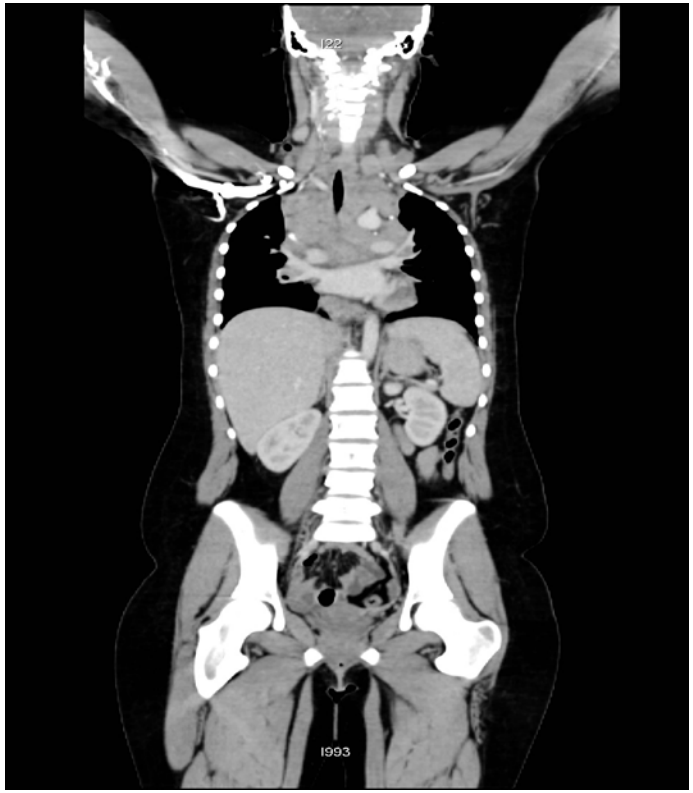
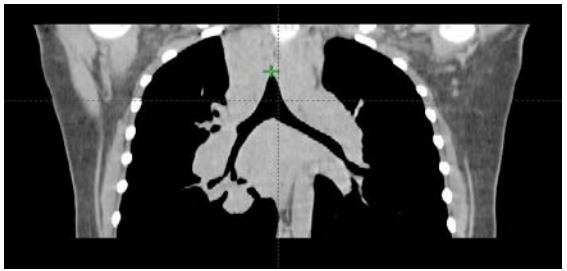
Breathing adaptation, technique





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

+ deep inspiration PET/CT of the chest

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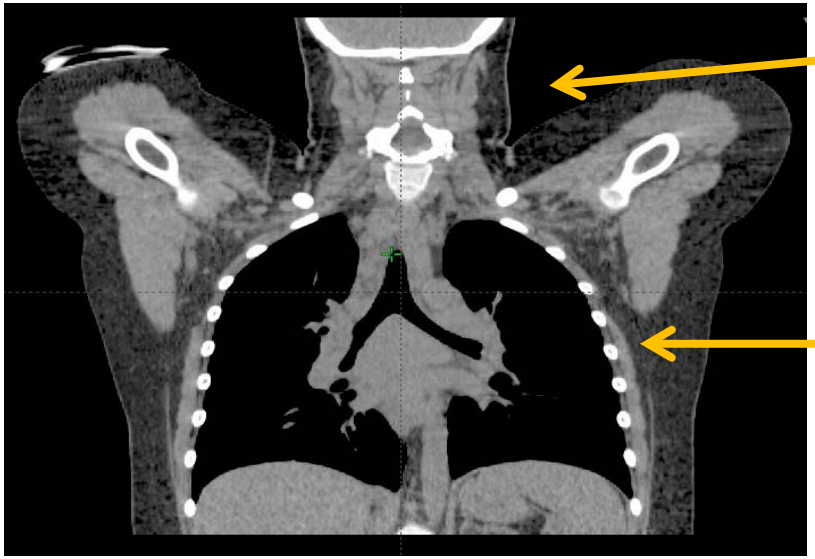
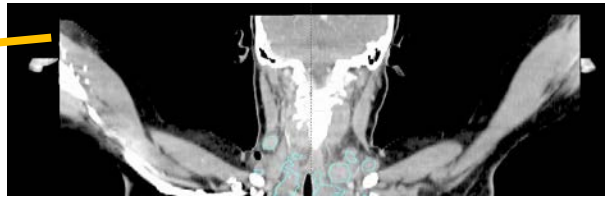
Breathing adaptation, technique

Post-chemo planning CT in DIBH

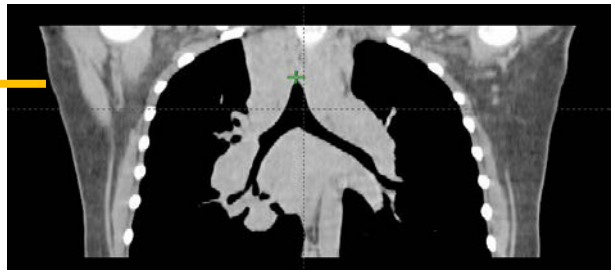


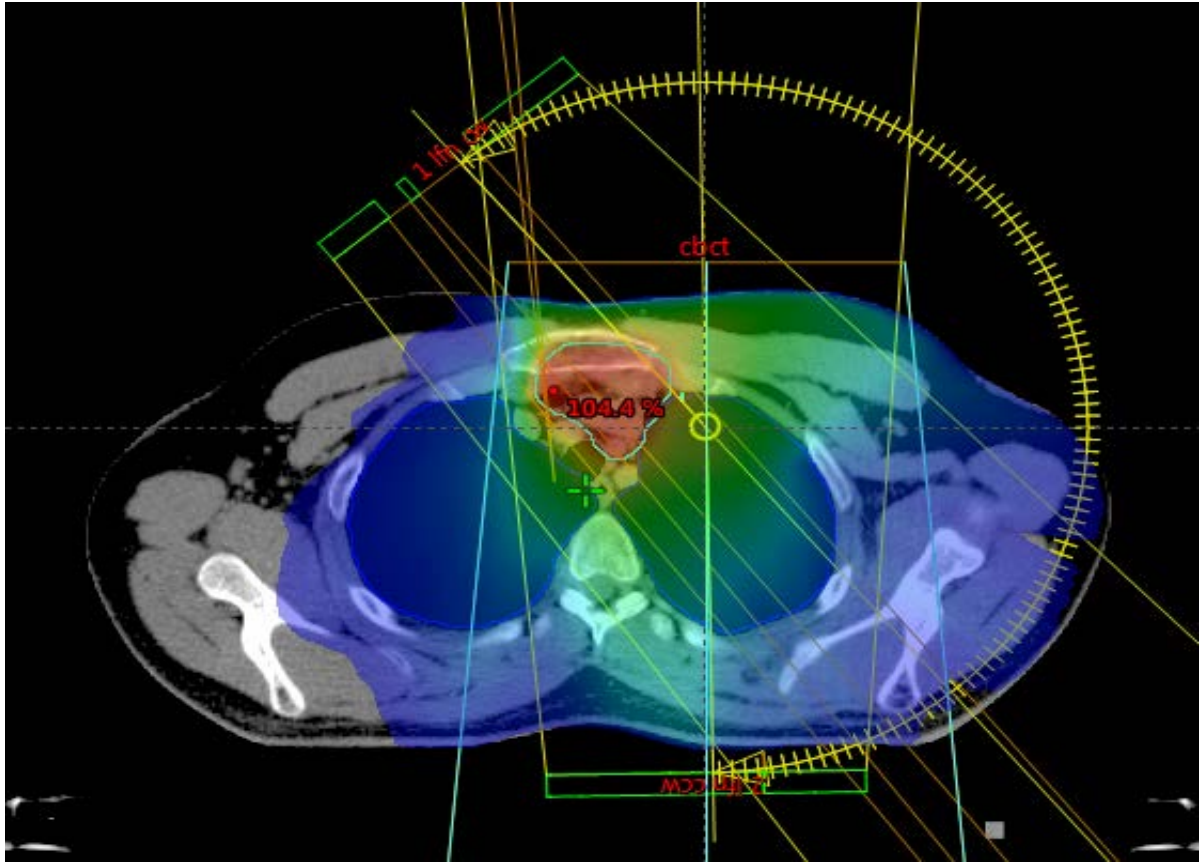
Pre-chemo PET/CT scan



FB

DIBH





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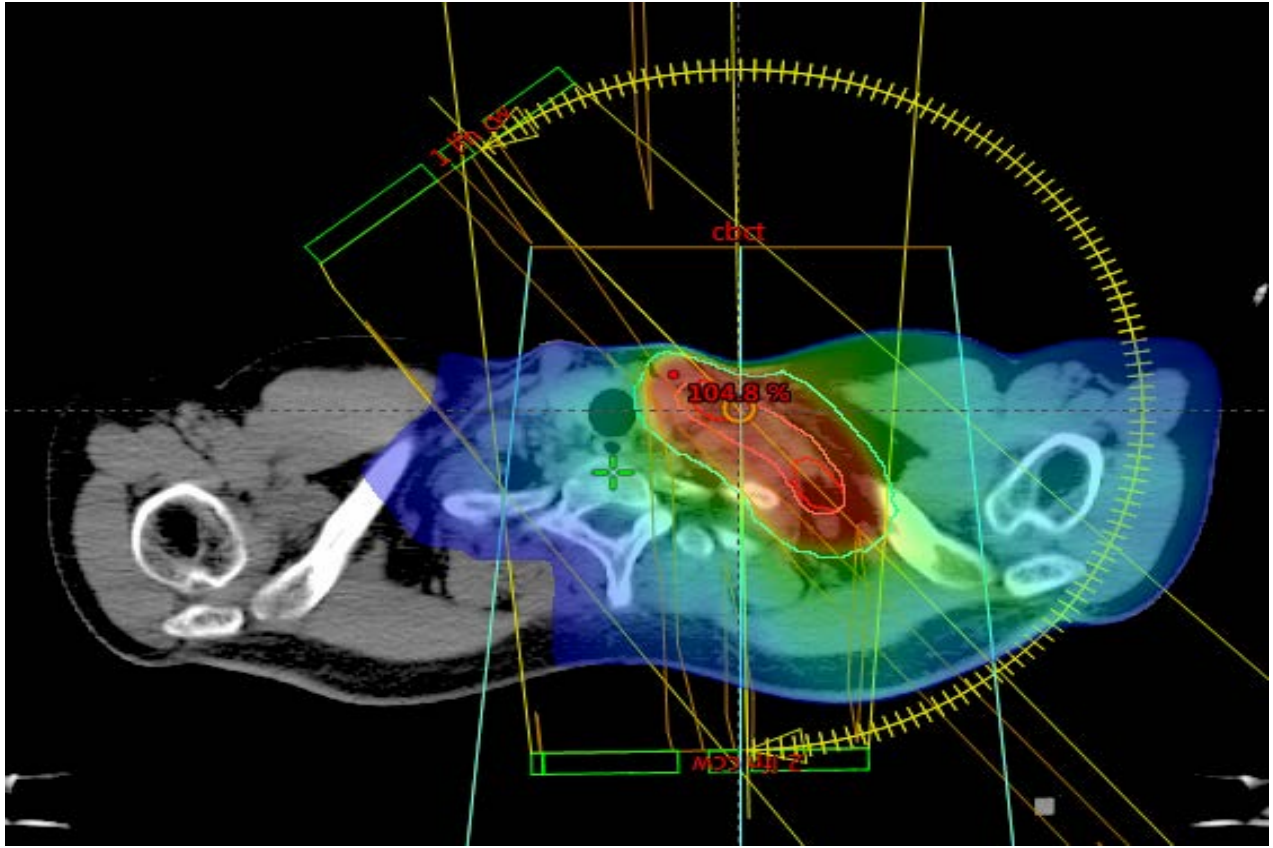

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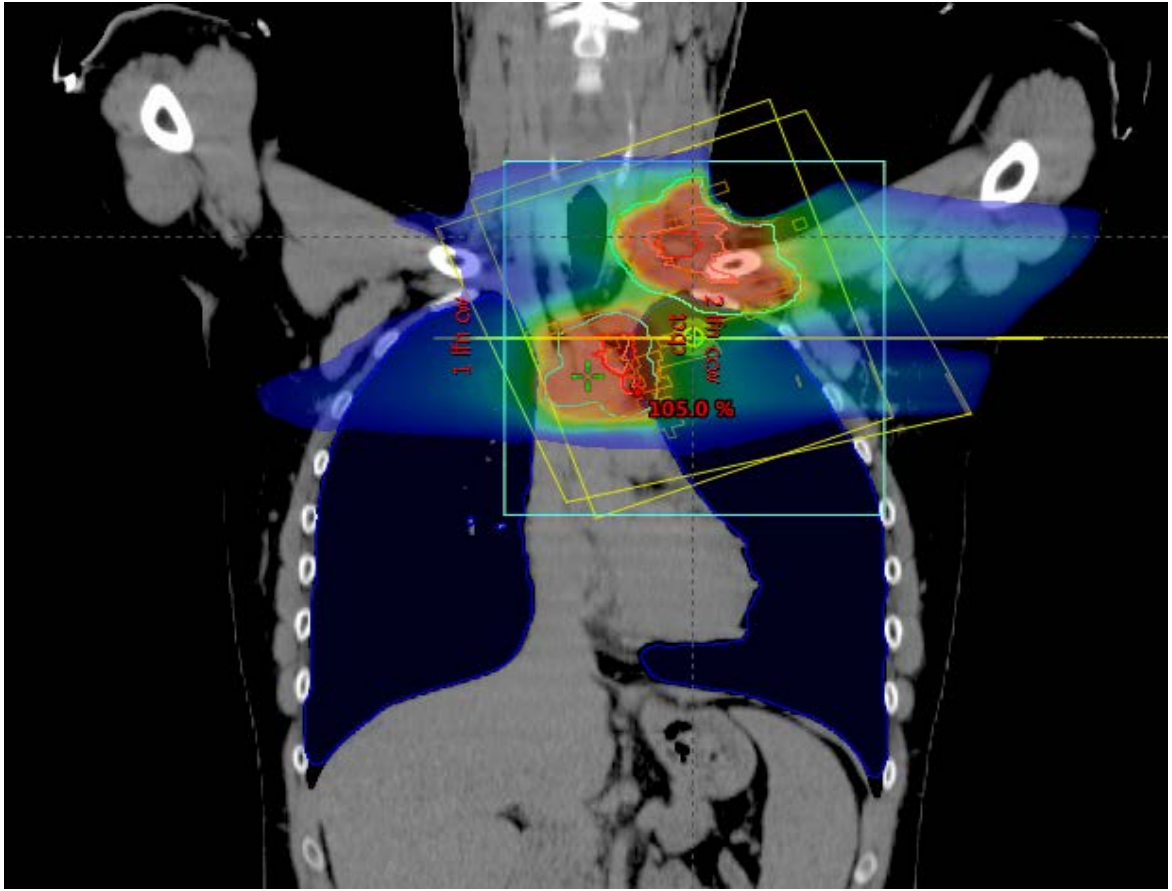
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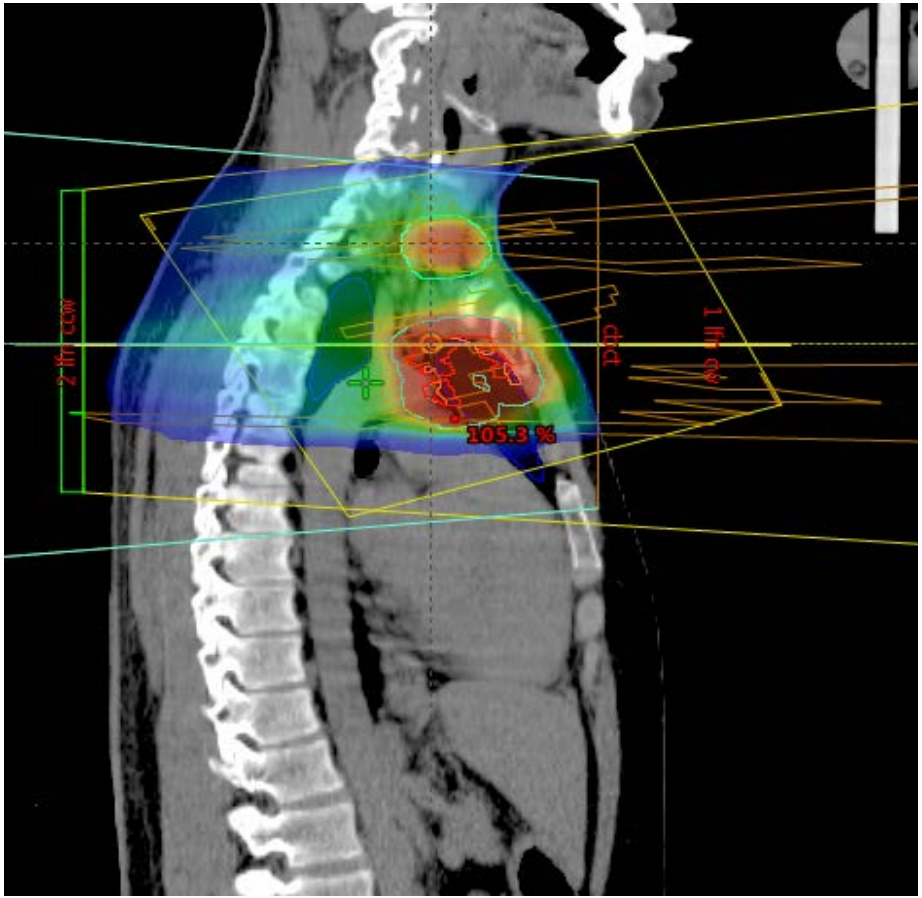
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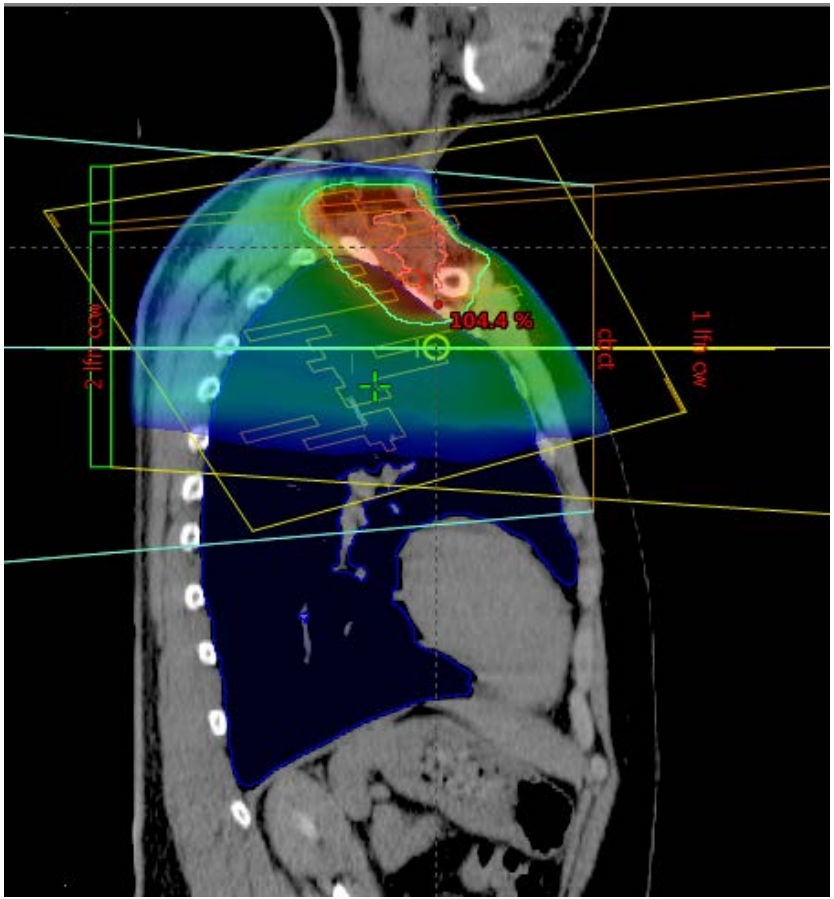
104.4 %
2 lfr ccw
dlcd
1 lfr cw

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AGGRESSIVE NODAL NON-HODGKIN LYMPHOMA, THE ROLE OF RADIOTHERAPY

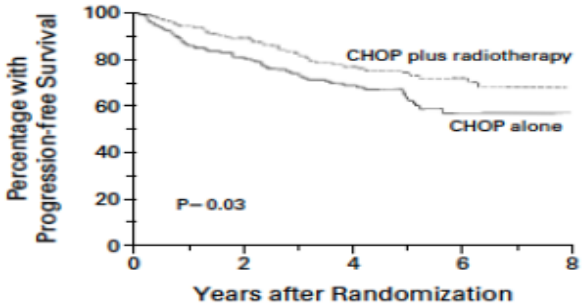
Early Stage

Umberto Ricardi
University of Torino
Department of Oncology

Is there (still) a role for Radiation Therapy in early stage DLCL?

- “Classic” trials investigating the role of CMT in DLBCL (some of them with risk stratification)
- Trials investigating the role of CMT in DLBCL in the Rituximab era
- Data on the role of RT from systematic reviews, retrospective analysis and epidemiologic registry

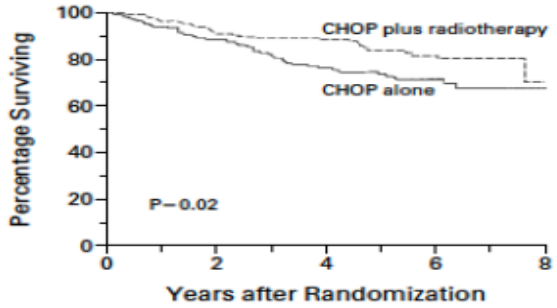
CHOP x 8 vs. CHOP x 3 + IFRT in Stage I/II DLBCL



No. at Risk					
CHOP alone	201	172	111	55	14
CHOP plus radiotherapy	200	178	119	70	17

Figure 1. Progression-free Survival of 201 Patients Receiving Eight Cycles of CHOP Alone and 200 Patients Receiving Three Cycles of CHOP plus Radiotherapy.

Sixty-five patients in the CHOP-alone group died or had progression of their disease, as compared with 45 patients in the CHOP-plus-radiotherapy group. The estimated rates of progression-free survival at five years were 64 percent and 77 percent, respectively.



No. at Risk					
CHOP alone	201	187	120	61	14
CHOP plus radiotherapy	200	185	128	75	17

Figure 2. Overall Survival of 201 Patients Receiving Eight Cycles of CHOP and 200 Patients Receiving Three Cycles of CHOP plus Radiotherapy.

There were 51 deaths in the CHOP-alone group, and 32 in the CHOP-plus-radiotherapy group. The estimated rates of survival at five years were 72 percent and 82 percent, respectively.

Miller et al NEJM 1998; 339:21

ILROG International Lymphoma Radiation Oncology Group

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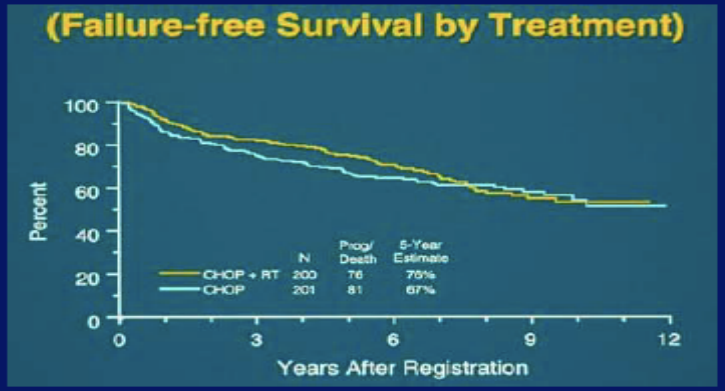
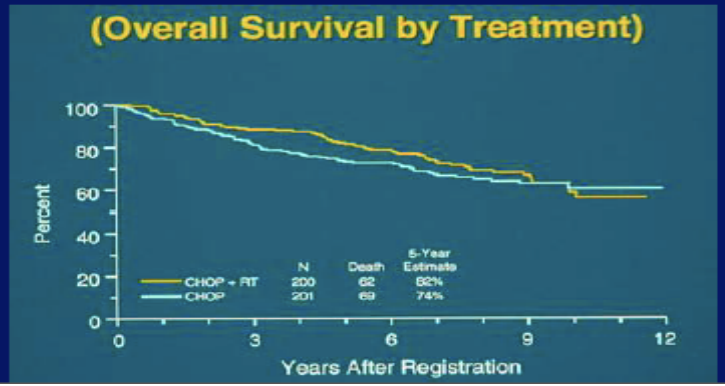
SWOG 8736: Updated Results





- Median f/u= 8.2 yrs
- FFS curves overlap at 7 years
- OS curves overlap at 9 years
- Late relapses and lymphoma deaths in CMT arm

Miller et al. ASH, 2001

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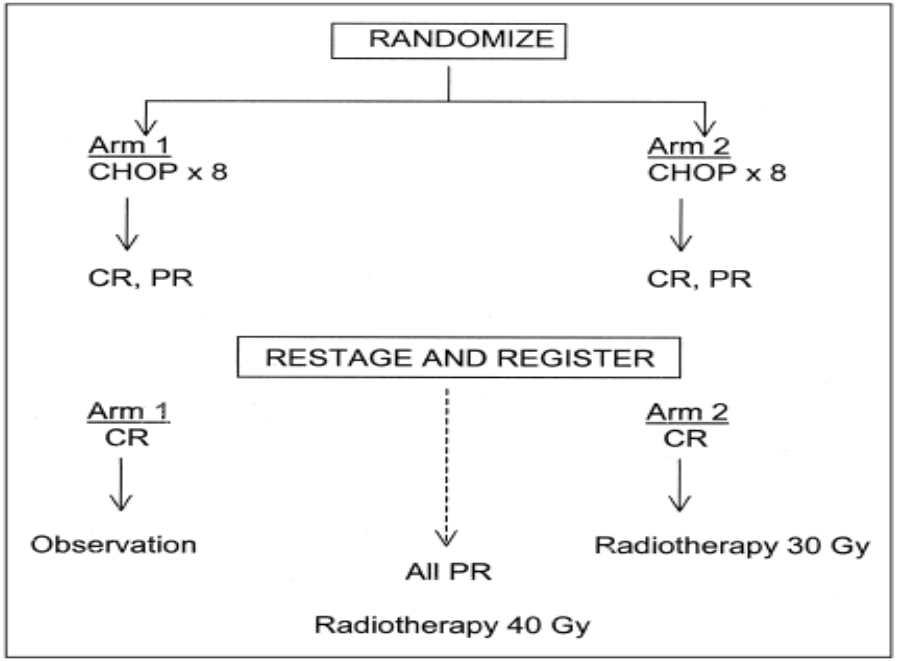
JOURNAL OF CLINICAL ONCOLOGY VOLUME 22 · NUMBER 15 · AUGUST 1 2004

Chemotherapy With or Without Radiotherapy in Limited-Stage Diffuse Aggressive Non-Hodgkin's Lymphoma: Eastern Cooperative Oncology Group Study 1484

Sandra J. Horning, Edie Weller, KyungMann Kim, John D. Earle, Michael J. O'Connell, Thomas M. Habermann, and John H. Glick



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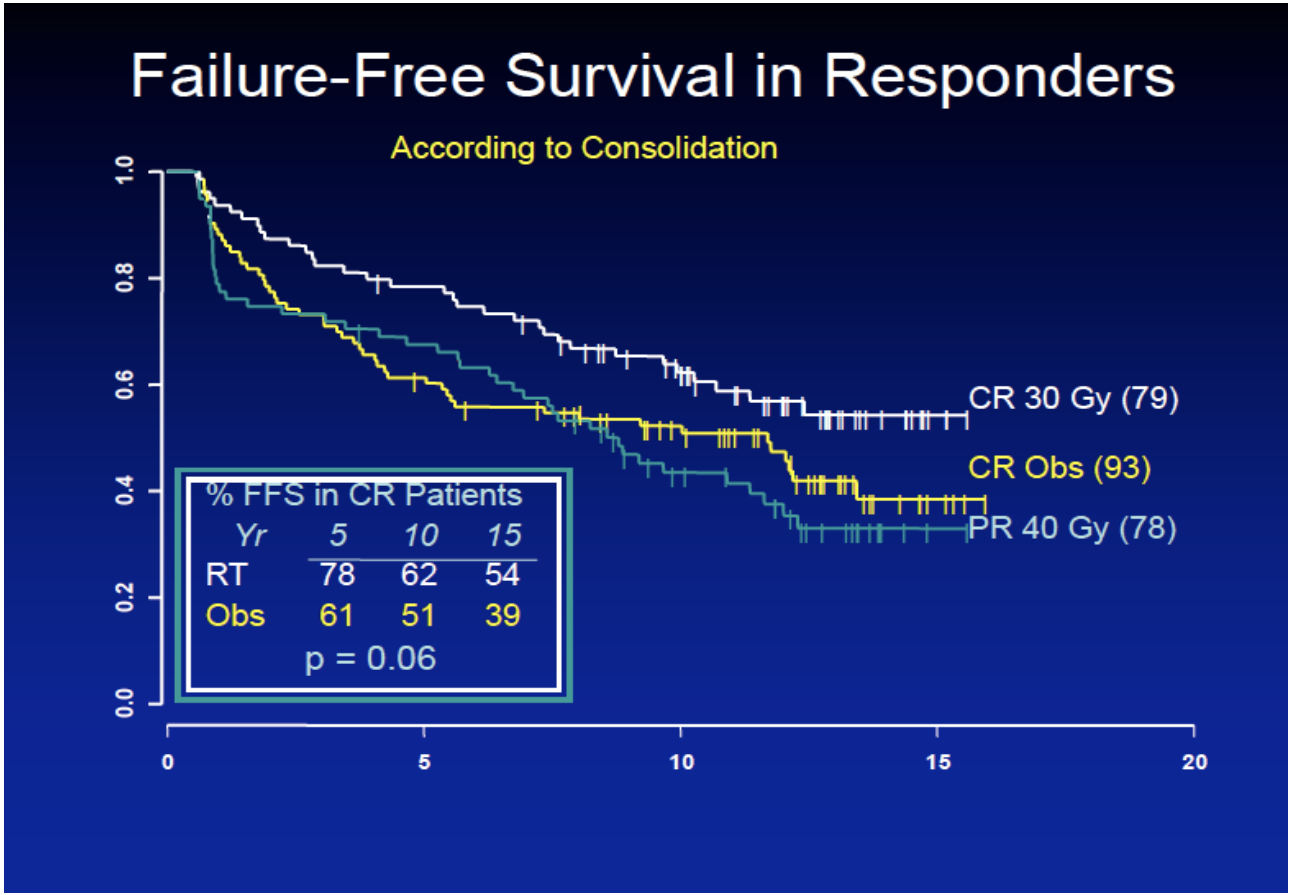
Failure-Free Survival in Responders



The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2005;352:1197-205.

ACVBP versus CHOP plus Radiotherapy for Localized Aggressive Lymphoma

Félix Reyes, M.D., Eric Lepage, M.D., Gérard Ganem, M.D., Thierry J. Molina, M.D., Pauline Brice, M.D., Bertrand Coiffier, M.D., Pierre Morel, M.D., Christophe Ferme, M.D., Andre Bosly, M.D., Pierre Lederlin, M.D., Guy Laurent, M.D., and Hervé Tilly, M.D., for the Groupe d'Etude des Lymphomes de l'Adulte (GELA)*

GELA LNH 93-1

Age < 61, stage I-II, IPI 0

R
647 pts

ACVBP x 3 + intensification CT
318

4 x CHOP 21
+ IFRT (40 Gy)
329

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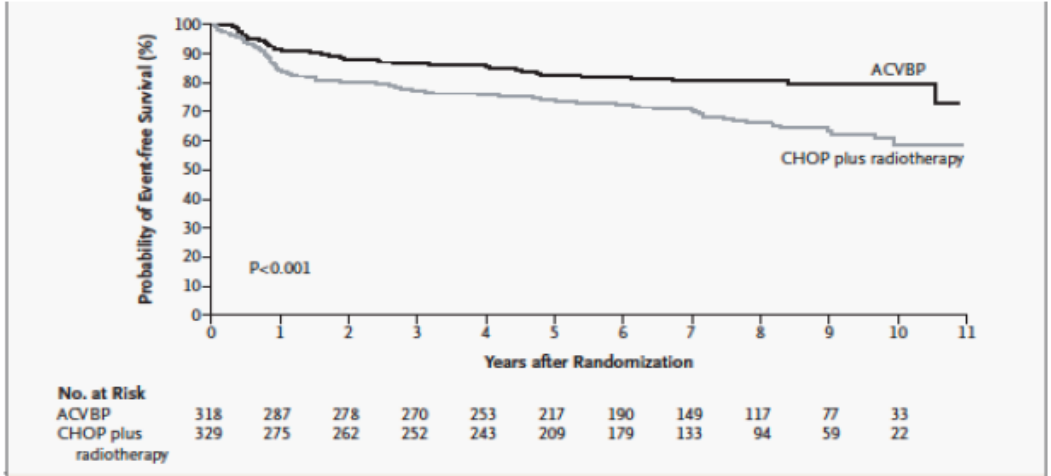
ACVBP vs CHOP + RT in Stage I/II aggressive Lymphoma



No. at Risk

ACVBP	318	287	278	270	253	217	190	149	117	77	33
CHOP plus radiotherapy	329	275	262	252	243	209	179	133	94	59	22

Figure 1. Event-free Survival among 647 Patients Assigned to Chemotherapy Alone with the ACVBP Regimen or to CHOP plus Involved-Field Radiotherapy.

Reyes et al NEJM 2005; 352:1197

Overall Survival

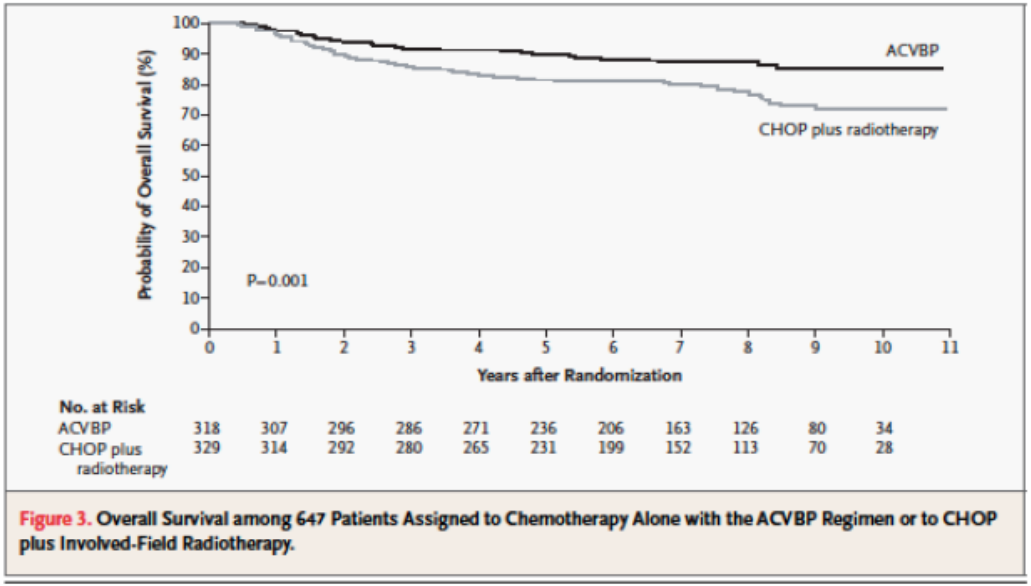


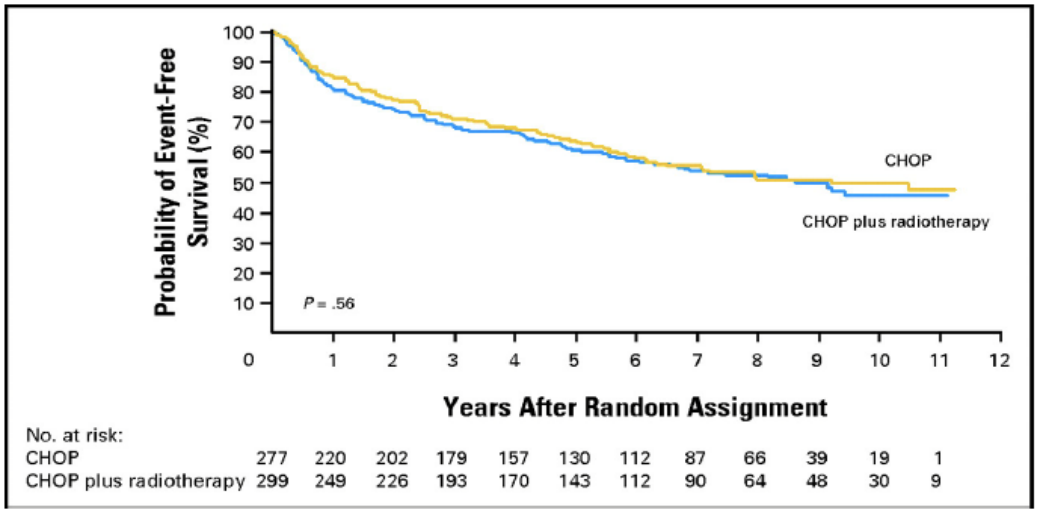
Figure 3. Overall Survival among 647 Patients Assigned to Chemotherapy Alone with the ACVBP Regimen or to CHOP plus Involved-Field Radiotherapy.

Reyes et al NEJM 2005; 352:1197

11% acute severe toxicity

CHOP Alone Compared With CHOP Plus Radiotherapy for Localized Aggressive Lymphoma in Elderly Patients: A Study by the Groupe d'Etude des Lymphomes de l'Adulte

Christophe Bonnet, Georges Fillet, Nicolas Mounier, Gérard Ganem, Thierry Jo Molina, Catherine Thiéblemont, Christophe Fermé, Bruno Quesnel, Claude Martin, Christian Gisselbrecht, Hervé Tilly, and Félix Reyes†



Age > 60 , stage I-II, IPI 0

Bonnet C et al. JCO 2007;25:787-792

GELA LNH 93-4

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CHOP Alone Compared With CHOP Plus Radiotherapy for Localized Aggressive Lymphoma in Elderly Patients: A Study by the Groupe d'Etude des Lymphomes de l'Adulte

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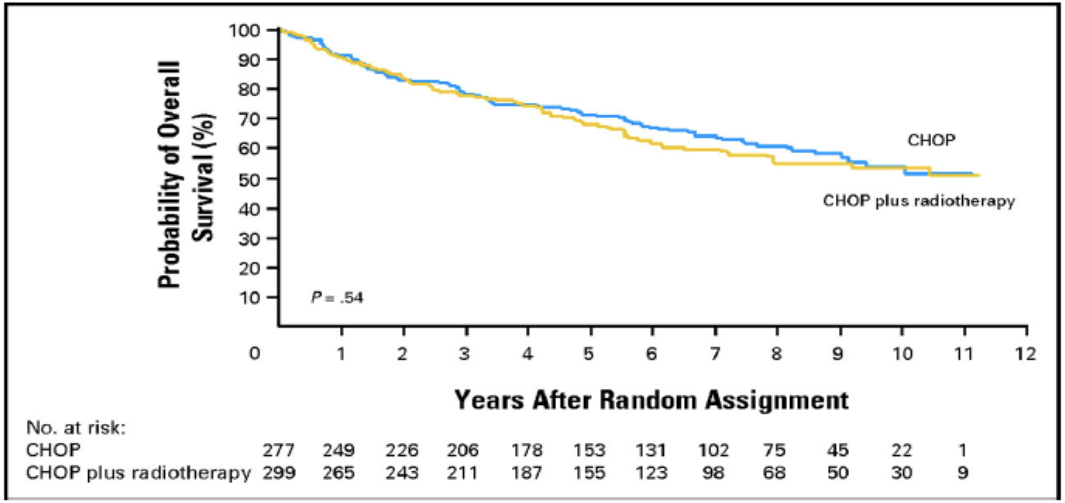

Bonnet C et al. JCO 2007;25:787-792

GELA LNH 93-4

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GELA LNH 93-4: RESULTS

Both arms did significantly worse than CHOP x 3 cycles + IFRT in SWOG 8736 (5-ys OS 82%)

Limited Disease Radiotherapy Details

Treatment Parameter	SWOG 0014 [1]	BCCA	GELA 93-1 [2]	GELA 93-4 [3]
Recv'd RT	95%	90%	92%	88%
RT start < day 35	96%	- - -	- - -	50%
Doses	40-55	30-35	36-40	36-44
Recv'd Planned Doses	95%	96%	93%	
Relapse	0	18%	28%	34%

1. Miller et al, ASH 2003
2. Reyes et al, NEJM 2005
3. Bonnet et al, JCO 2007
4. Shenkier et al, JCO 2002

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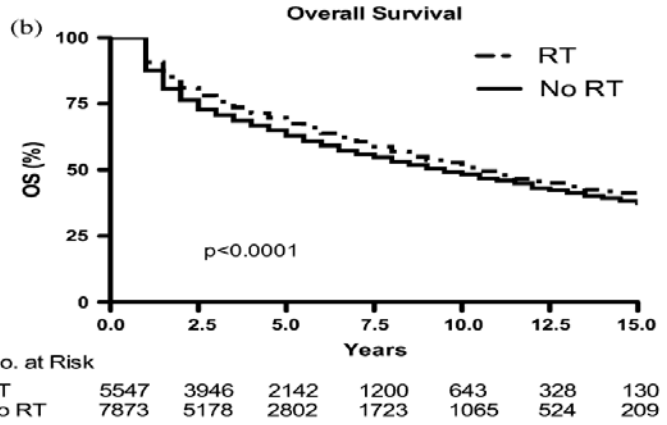
OUTCOMES AND EFFECT OF RADIOTHERAPY IN PATIENTS WITH STAGE I OR II DIFFUSE LARGE B-CELL LYMPHOMA: A SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS ANALYSIS

Characteristic	*n* (%)
Patients	13,420 (100)
RT	
Yes	5,547 (41)
No	7,873 (59)
Age*	
≤60	6,121 (46)
>60	7,299 (54)
Extranodal disease	
No	6,368 (48)
Yes	7,052 (52)
Stage	
I	8,467 (63)
II	4,953 (37)
Gender	
Female	6,323 (47)
Male	7,097 (53)
Race	
White	11,556 (86)
Other	1,864 (14)

Abbreviation: RT = radiotherapy.
* Median, 60 y.



Variable	CHR*	95% CI	*p*†
DSS			
RT (yes vs. no RT)	0.86	0.80–0.93	0.0001
Age (≤60 vs. >60 y)	0.46	0.42–0.50	<0.0001
Extranodal disease (no vs. yes)	1.01	0.94–1.09	0.77
Stage (I vs. II)	0.76	0.70–0.81	<0.0001
Gender (female vs. male)	1.01	0.94–1.08	0.80
Race (white vs. other)	0.94	0.85–1.05	0.31
OS			
RT (yes vs. no)	0.89	0.84–0.94	<0.0001
Age (≤60 vs. >60 y)	0.41	0.38–0.43	<0.0001
Extranodal disease (no vs. yes)	0.92	0.87–0.97	0.0039
Stage (I vs. II)	0.87	0.82–0.92	<0.0001
Gender (female vs. male)	0.91	0.86–0.96	0.0007
Race (white vs. other)	0.99	0.91–1.08	0.81

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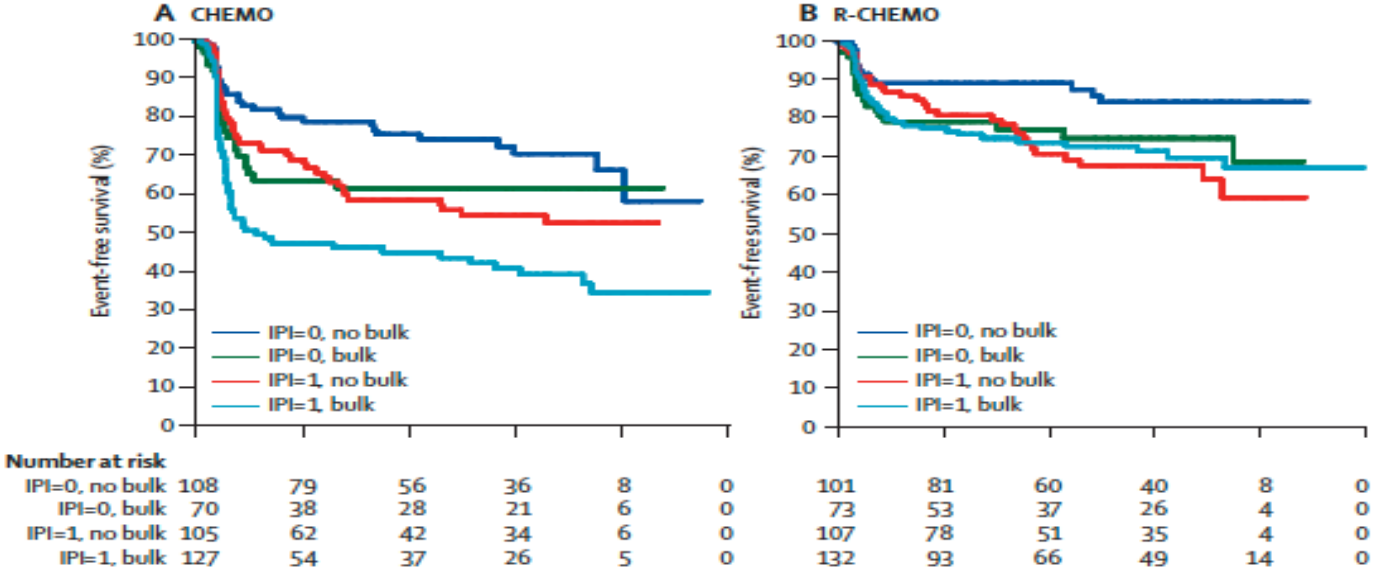
Will Rituximab markedly change the results of CHOP+RT?

CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group

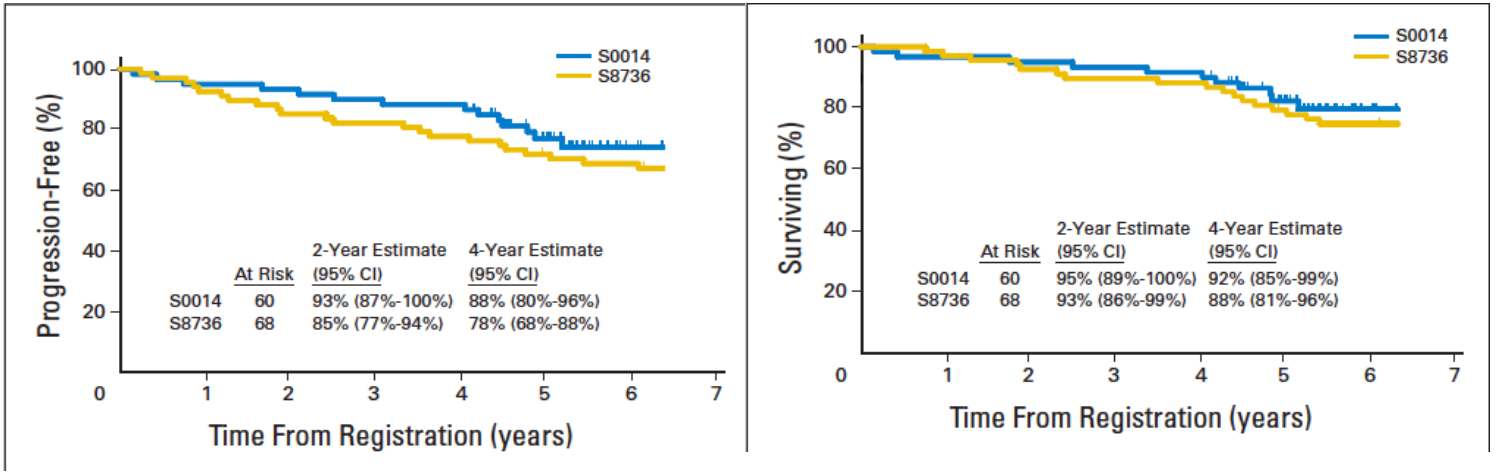
*Michael Pfreundschuh, Evelyn Kuhnt, Lorenz Trümper, Anders Österborg, Marek Trneny, Lois Shepherd, Devinder S Gill, Jan Walewski, Ruth Pettengell, Ulrich Jaeger, Pier-Luigi Zinzani, Ofer Shpilberg, Stein Kvaloy, Peter de Nully Brown, Rolf Stahel, Noel Milpied, Armando López-Guillermo, Viola Poeschel, Sandra Grass, Markus Loeffler, Niels Murawski, for the MabThera International Trial (MInT) Group**



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II Study of Rituximab Plus Three Cycles of CHOP and Involved-Field Radiotherapy for Patients With Limited-Stage Aggressive B-Cell Lymphoma: Southwest Oncology Group Study 0014

Daniel O. Persky, Joseph M. Unger, Catherine M. Spier, Baldassarre Stea, Michael LeBlanc, Matthew J. McCarty, Lisa M. Rimsza, Richard I. Fisher, and Thomas P. Miller



- Lower impact of R in limited stage ?
- Biological explanation : molecular fingerprint GCB in 3/4 of cases (demonstrated lower benefit of R)

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VOLUME 28 · NUMBER 27 · SEPTEMBER 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Benefit of Consolidative Radiation Therapy in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP Chemotherapy

Jack Phan, Ali Mazloom, L. Jeffrey Medeiros, Tony G. Zreik, Christine Wogan, Ferial Shihadeh, Maria Alma Rodriguez, Luis Fayad, Nathan Fowler, Valerie Reed, Patrecia Horace, and Bouthaina Shbib Dabaja

Table 1. Demographic and Clinical Characteristics

Characteristic	No.	%
Sex		
Female	218	46.5
Male	251	53.5
Stage		
I	94	20.0
II	96	20.5
III	77	16.4
IV	202	43.1
Chemotherapy		
6-8 cycles of R-CHOP	327	69.7
Other	142	30.3
Radiotherapy		
Yes	142	30.3
No	327	69.7
Bulky disease status, cm		
≤ 5	260	55.4
> 5	207	44.1
Missing	2	0.4
PET standardized uptake values		
≤ 13	284	60.6
> 13	177	37.5
Missing	8	1.9

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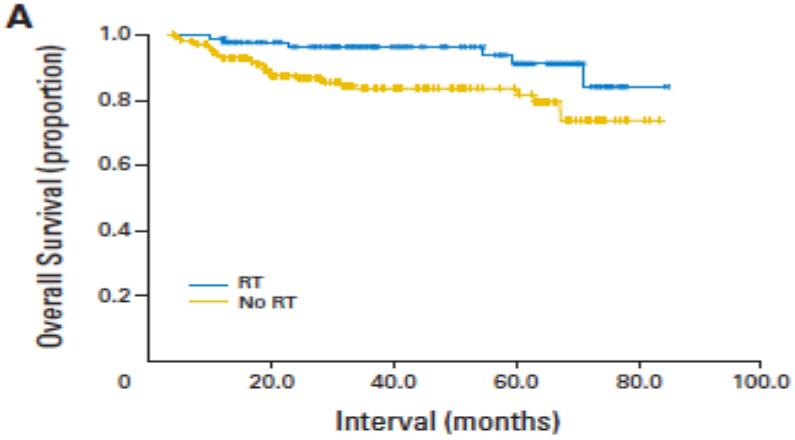

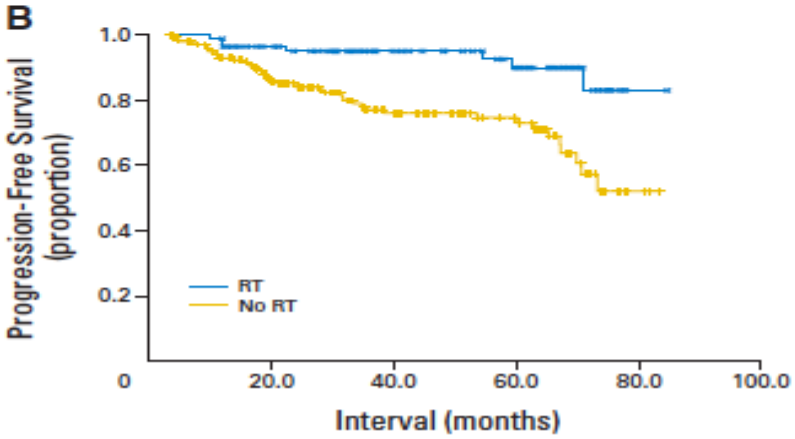

Table 5. Multivariate Analysis of Overall and Progression-Free Survival for All Patients

Variable	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Age, years						
≤ 60	1.00		.051	1.00		.010
> 60	1.34	0.98 to 2.02		1.42	1.00 to 2.15	
Chemotherapy						
6-8 cycles of R-CHOP	0.42	0.27 to 0.65	< .0001	0.57	0.39 to 0.84	.0050
Other	1.00			1.00		
Radiotherapy						
No	1.00		< .0001	1.00		< .0001
Yes	0.19	0.10 to 0.38		0.32	0.17 to 0.51	
Triple negative						
No	1.00		.025	1.00		.038
Yes	0.16	0.03 to 0.79		0.24	0.06 to 0.92	
Triple positive						
No	1.00		.006	1.00		.037
Yes	4.96	1.58 to 15.61		1.39	1.58 to 9.87	
IPI score						
0	1.00			1.00		
1-2	2.53	1.32 to 4.84	.005	2.12	1.34 to 3.69	.001
≥ 3	5.41	2.24 to 8.28	.001	6.03	3.11 to 9.19	.001
Response						
No response	1.00			1.00		
Partial remission	1.96	0.91 to 2.05	< .0001	0.27	0.16 to 0.56	< .0001
Complete remission	3.35	2.33 to 4.59	< .001	0.42	0.33 to 0.72	.0055

Prognostic significance of maximum tumour (bulk) diameter in young patients with good-prognosis diffuse large-B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: an exploratory analysis of the MabThera International Trial Group (MInT) study

Lancet Oncol 2008; 9: 435–44

Michael Pfreundschuh, Anthony D Ho, Eva Cavallin-Stahl, Max Wolf, Ruth Pettengell, Ingrid Vasova, Andrew Belch, Jan Walewski, Pier-Luigi Zinzani, Walter Mingrone, Stein Kvaloy, Ofer Shpilberg, Ulrich Jaeger, Mads Hansen, Claudia Corrado, Adriana Scheliga, Markus Loeffler, Evelyn Kuhnt, for the MabThera International Trial (MInT) Group

- Linear prognostic effect of tumor diameter on OS, which is decreased (but not eliminated) by the addition of rituximab

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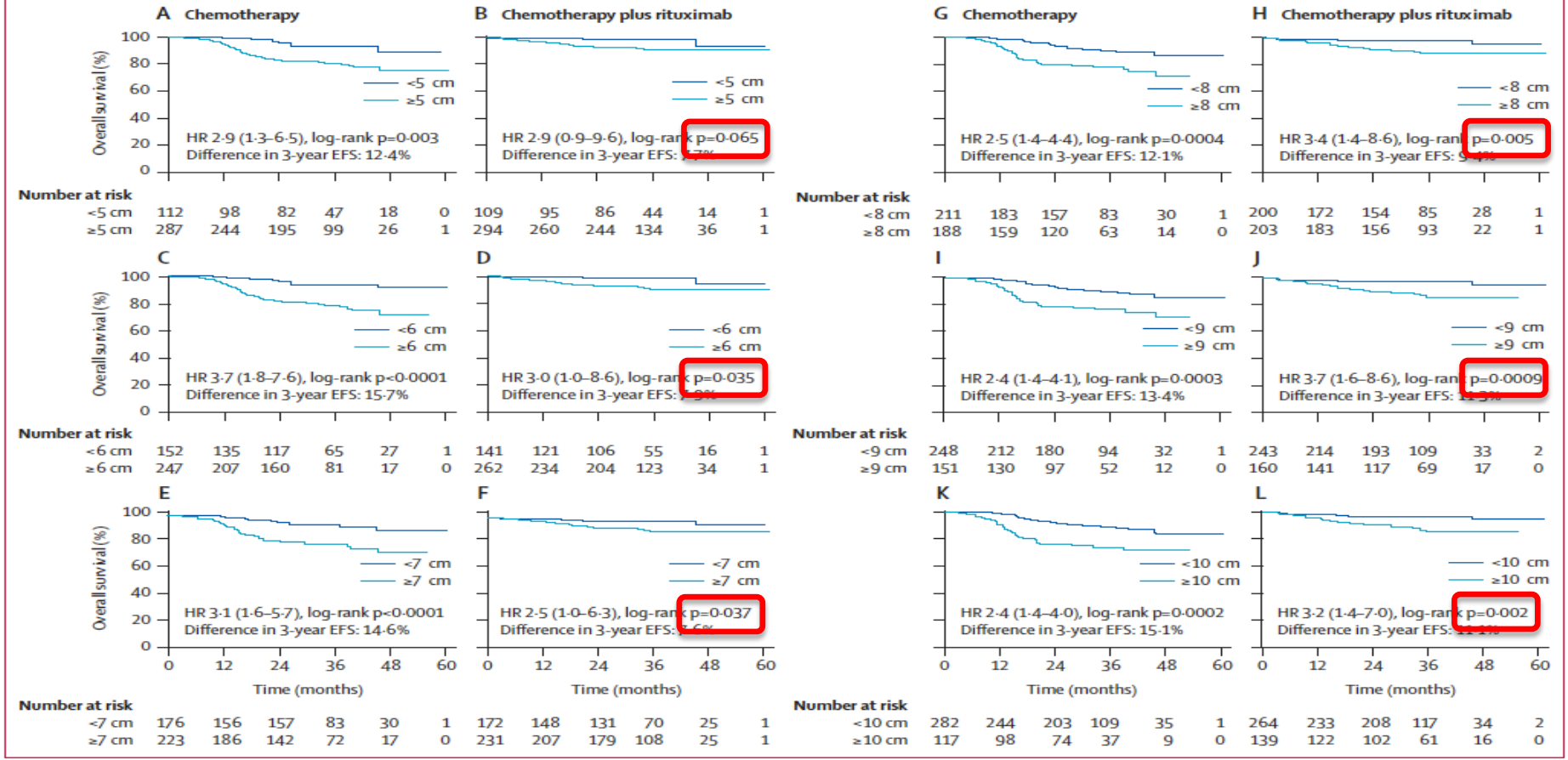
A Chemotherapy
B Chemotherapy plus rituximab
G Chemotherapy
H Chemotherapy plus rituximab
C
D
I
J
E
F
K
L
Overall survival (%)
<5 cm
≥5 cm
HR 2·9 (1·3–6·5), log-rank p=0·003
Difference in 3-year EFS: 12·4%
HR 2·9 (0·9–9·6), log-rank p=0·065
<8 cm
≥8 cm
HR 2·5 (1·4–4·4), log-rank p=0·0004
Difference in 3-year EFS: 12·1%
HR 3·4 (1·4–8·6), log-rank p=0·005
<6 cm
≥6 cm
HR 3·7 (1·8–7·6), log-rank p<0·0001
Difference in 3-year EFS: 15·7%
HR 3·0 (1·0–8·6), log-rank p=0·035
<9 cm
≥9 cm
HR 2·4 (1·4–4·1), log-rank p=0·0003
Difference in 3-year EFS: 13·4%
HR 3·7 (1·6–8·6), log-rank p=0·0009
<7 cm
≥7 cm
HR 3·1 (1·6–5·7), log-rank p<0·0001
Difference in 3-year EFS: 14·6%
HR 2·5 (1·0–6·3), log-rank p=0·037
<10 cm
≥10 cm
HR 2·4 (1·4–4·0), log-rank p=0·0002
Difference in 3-year EFS: 15·1%
HR 3·2 (1·4–7·0), log-rank p=0·002
Time (months)
Number at risk
<5 cm 112 98 82 47 18 0
≥5 cm 287 244 195 99 26 1
109 95 86 44 14 1
294 260 244 134 36 1
<8 cm 211 183 157 83 30 1
≥8 cm 188 159 120 63 14 0
200 172 154 85 28 1
203 183 156 93 22 1
<6 cm 152 135 117 65 27 1
≥6 cm 247 207 160 81 17 0
141 121 106 55 16 1
262 234 204 123 34 1
<9 cm 248 212 180 94 32 1
≥9 cm 151 130 97 52 12 0
243 214 193 109 33 2
160 141 117 69 17 0
<7 cm 176 156 157 83 30 1
≥7 cm 223 186 142 72 17 0
172 148 131 70 25 1
231 207 179 108 25 1
<10 cm 282 244 203 109 35 1
≥10 cm 117 98 74 37 9 0
264 233 208 117 34 2
139 122 102 61 16 0

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma

Multivariable analysis (per protocol)

PROGRESSION-FREE SURVIVAL

Factor	Relative risk	P-value	95% CI
RT vs no RT	*4.4*	*0.001*	*(1.8 – 10.6)*
LDH Elevated	*0.6*	*0.391*	*(0.2 – 1.7)*
ECOG >1	*1.6*	*0.439*	*(0.5 – 4.9)*
Extranodal Involvement	*0.8*	*0.664*	*(0.3 – 2.4)*
Stage III/IV	*1.2*	*0.662*	*(0.5 – 3.4)*
Age > 70 years	*1.6*	*0.271*	*(0.7 – 3.9)*

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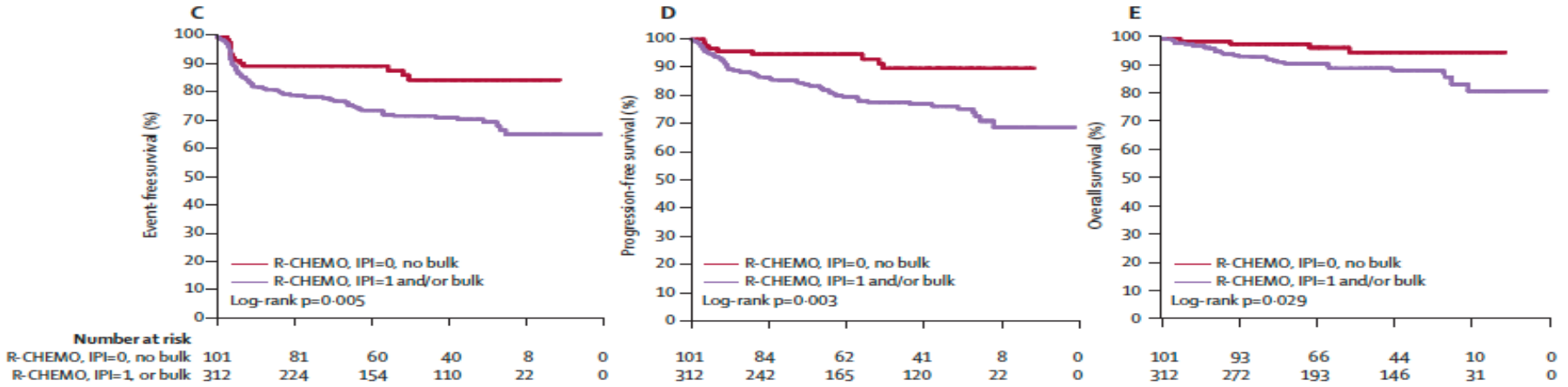
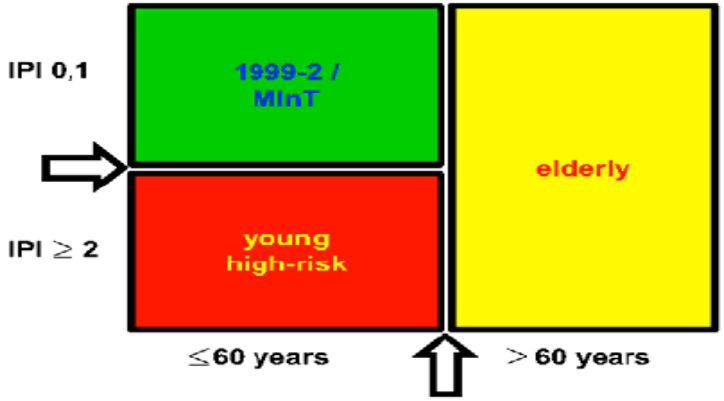


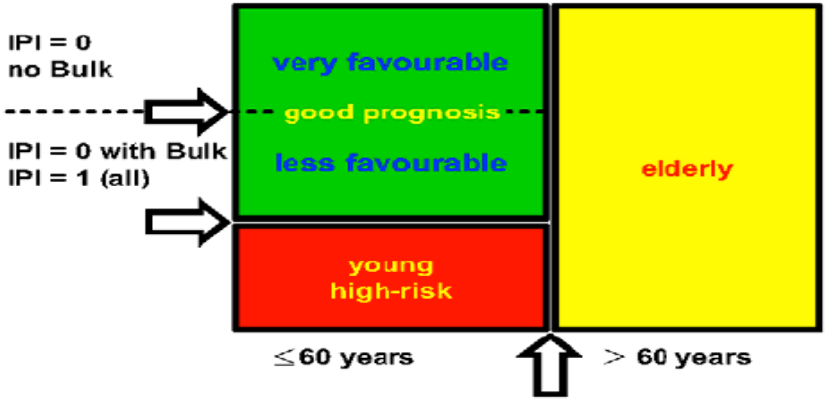
	LNH03-2B		MInT	
	R-ACVBP (n=196)	8×R-CHOP-21 (n=183)	6×R-CHOP-21, IPI 1 (n=118)	6×R-CHEMO, IPI 1 (n=239)
Age (years)	47 (18–59)	48 (19–59)	50 (19–60)	47 (19–60)
Men	116 (59%)	109 (60%)	73 (62%)	137 (57%)
ECOG 0–1	195 (99%)	182 (99%)	116 (98%)	237 (99%)
Stage III and IV	115 (59%)	93 (51%)	58 (49%)	113 (47%)
LDH >ULN	77 (39%)	89 (49%)	58 (49%)	124 (52%)
Bulk ≥10 cm	38 (19%)	45 (25%)	47 (40%)	94 (39%)
3-year EFS (%)	81% (75–86)	67% (59–73)	80% (71–87)	77% (71–82)
3-year PFS (%)	87% (81–91)	73% (66–79)	86% (78–91)	83% (78–88)
3-year overall survival (%)	92% (87–95)	84% (77–89)	92% (85–96)	91% (86–94)
Radiotherapy	0	0	58 (49%)	117 (49%)

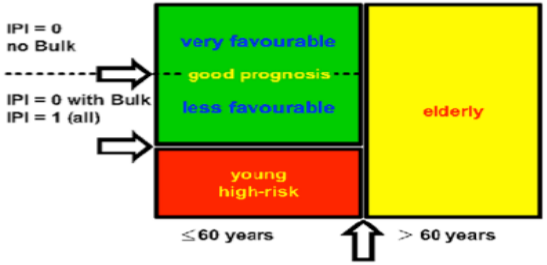
Putative beneficial effect of radiotherapy? (the most obvious difference between MInT and GELA trial is the use of additive radiotherapy, i.e. bulky disease and/or extranodal sites)

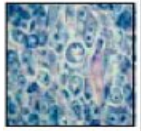
Which is the current Treatment Strategy?

The results of the MInT study demonstrated a difference between two prognostic groups within the population of young good-prognosis (aaIPI=0,1) patients with aggressive lymphoma: young good-prognosis patients with favourable prognosis (young good-prognosis, favourable) and those with less favourable prognosis (young good-prognosis, less favourable). Therefore, these groups should be treated differentially according to new specific treatment strategies (figure 6).









GERMAN HIGH-GRADE NON-HODGKIN'S LYMPHOMA STUDY GROUP*

* (supported by Deutsche Krebshilfe)

Less Favorable
(IPI=1 and/or bulk)

DSHNHL 2004-2

6 R-CHOP 21 x 6
vs
6 R-CHOP 14 x 6

2nd Random

IFRT 30GY

NO IFRT

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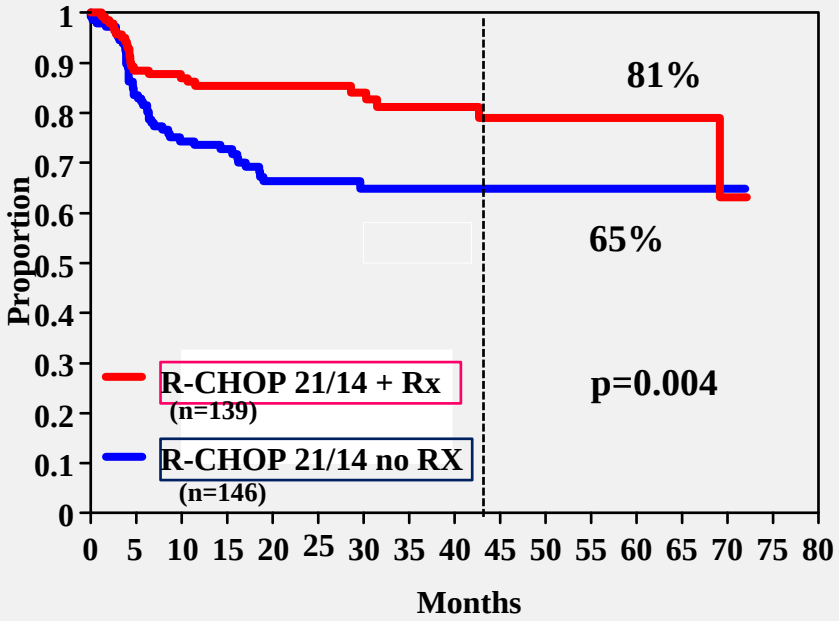
UNFOLDER phase 3 study: preliminary results

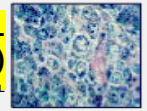
Patients 18- 60 years, aaIPI=0 with bulk or aaIPI=1, ITT (n=443)

Patients randomised to 4 arms (n=285)



GERMAN HIGH-GRADE NHL STUDY GROUP (DSHNHL)

www.lymphome.de/en/Groups/DSHNHL



~20% PMBCL

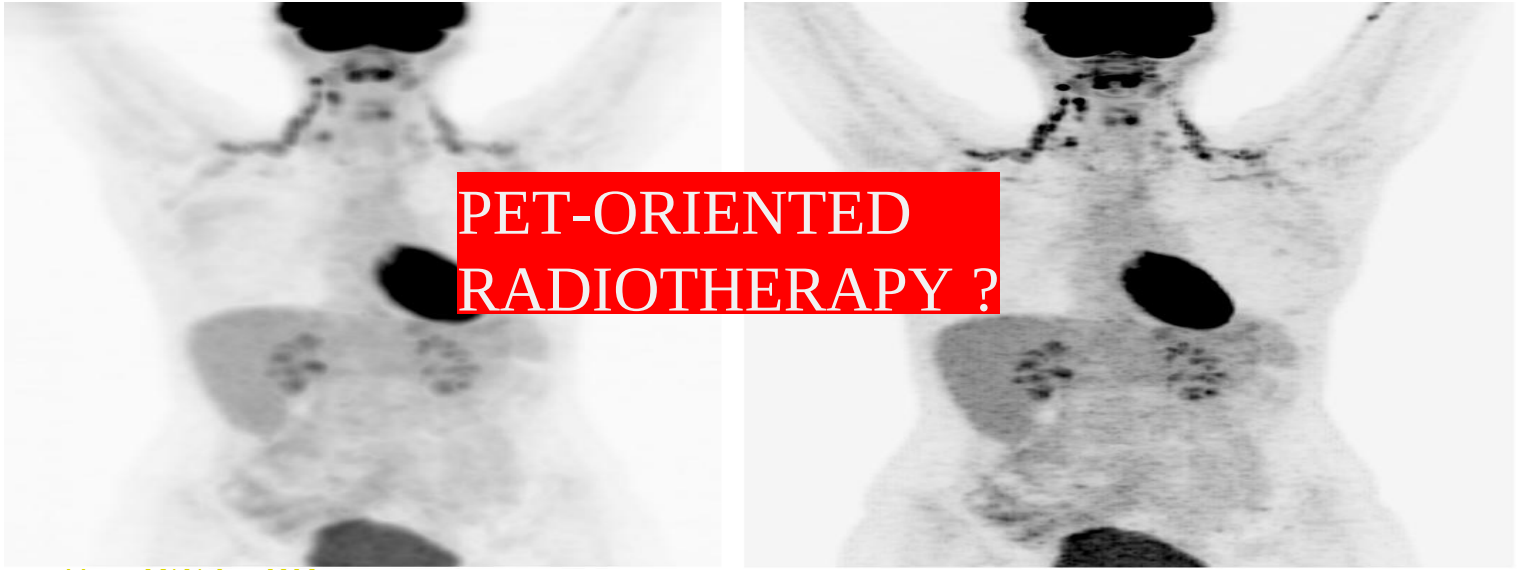
Patients randomized to receive or not IFRT irrespectively of PET response

Discontinuation of the no RT arms due to evident benefit for IFRT in bulky disease

DSHNHL 01.07.12

Courtesy of *M. Pfreundschuh , personal communication*

To irradiate or not to irradiate ?



PET-ORIENTED RADIOTHERAPY ?

- RT in PR cases

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PET-oriented RT: BCCA experience

N=50 ; stage I-II ; no B symptoms; mass < 10 cm

Median FU 17 months

R-CHOP 21 x 3 → PET

	N		Terapia	Recidive	2yFFP	*p*
PET neg →	37	→	CHOP x 1	1	97%	
						.09
PET pos →	13	→	IFRT	3	75%	

Sehn, ASH 2007

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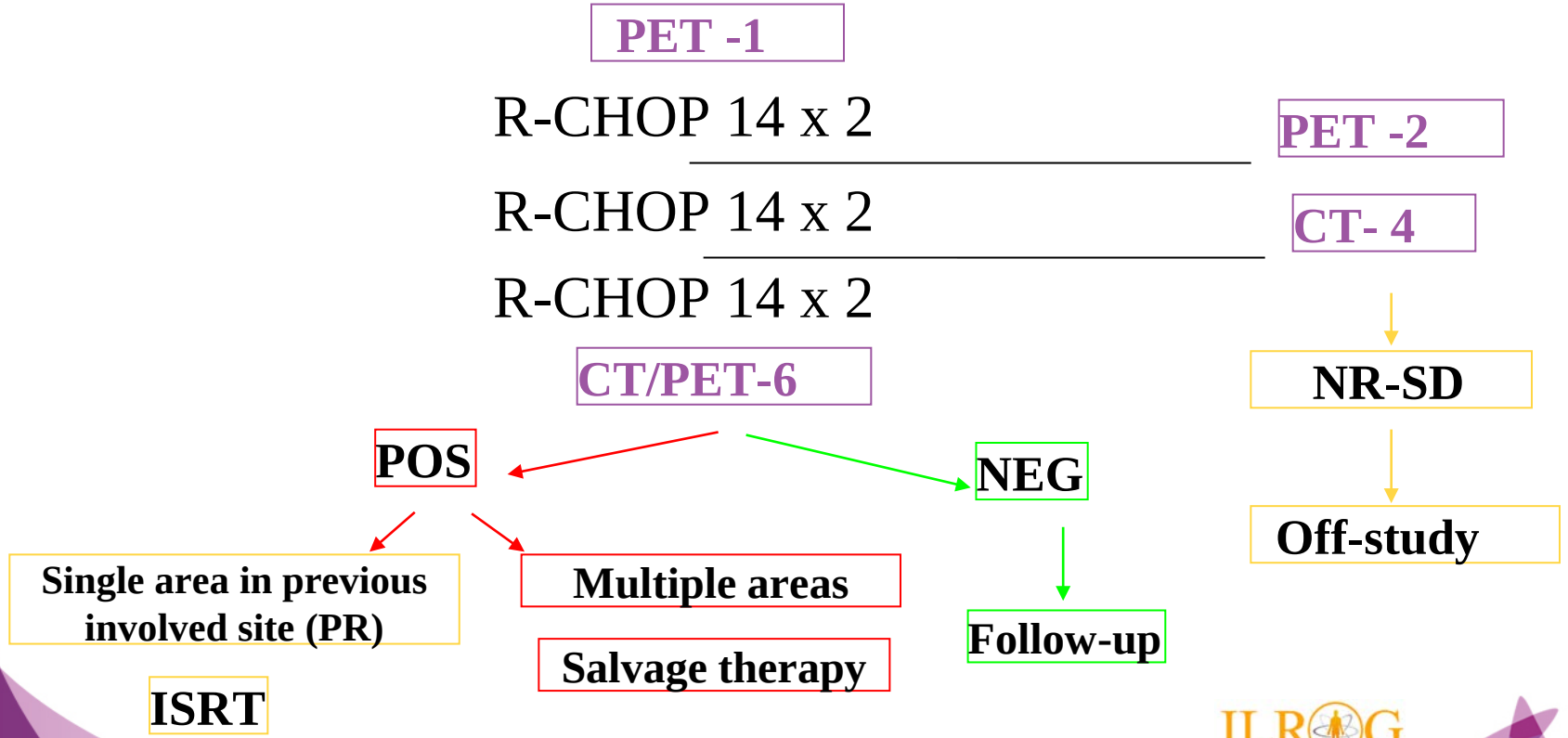
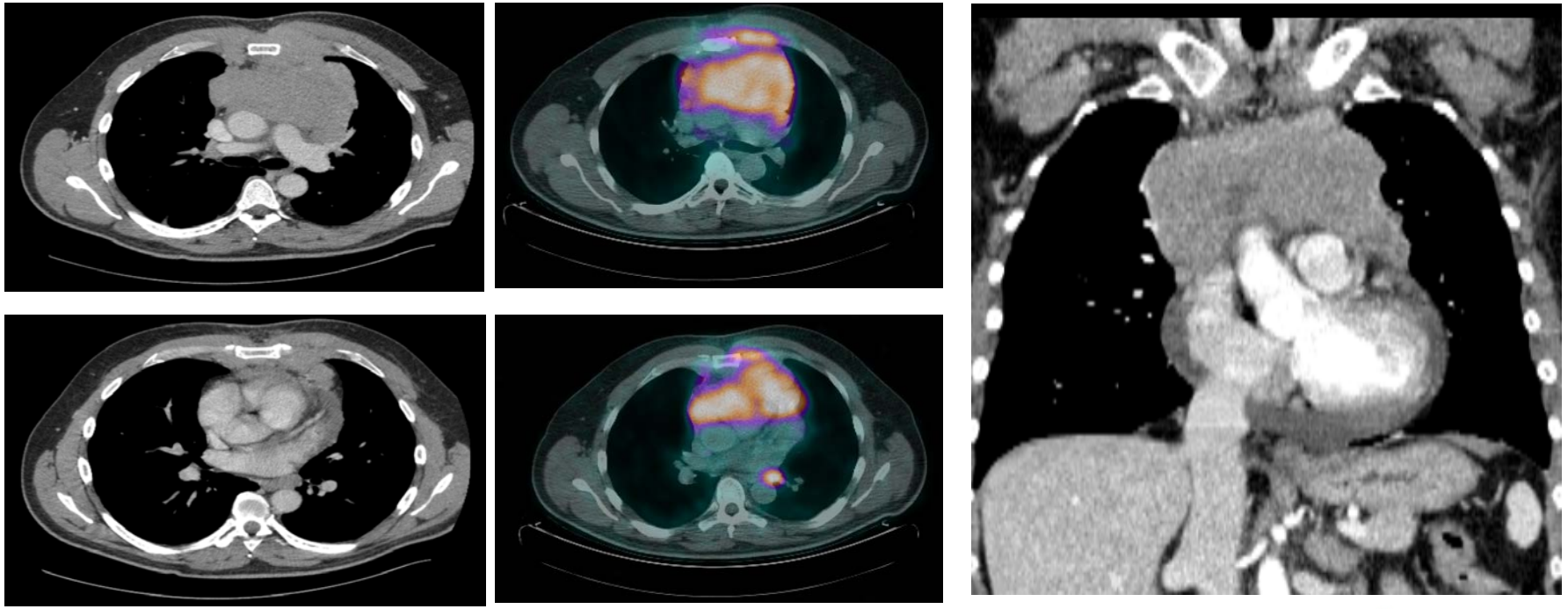
DLCL 10 IPI = 0 bulk, 1 and/or bulk (7.5 cm) (less favourable according MInT)



Primary Mediastinal B Cell Lymphoma



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Background and open questions

- ***R-Chemotherapy plus mediastinal IFRT*** is considered the standard treatment for PMBCL (3-yrs PFS: 80-85%)

- Does mediastinal IFRT still improve the outcome in PMBCL patients treated with R-CHOP/R-CHOP like chemotherapy?

- Is a negative PET-CT scan a reliable indicator of cure following chemotherapy alone, making unnecessary consolidation RT?

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Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma

Kieron Dunleavy, M.D., Stefania Pittaluga, M.D., Ph.D., Lauren S. Maeda, M.D., Ranjana Advani, M.D., Clara C. Chen, M.D., Julie Hessler, R.N., Seth M. Steinberg, Ph.D., Cliona Grant, M.D., George Wright, Ph.D., Gaurav Varma, M.S.P.H., Louis M. Staudt, M.D., Ph.D., Elaine S. Jaffe, M.D., and Wyndham H. Wilson, M.D., Ph.D.

N ENGL J MED 368;15 NEJM.ORG APRIL 11, 2013

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The IELSG-37 study: a randomized trial assessing the role of mediastinal radiotherapy after front-line Rituximab and Anthracycline containing regimens in patients with Primary Mediastinal B Cell Lymphoma (PMBCL)

Clinical Trial Coordinators	
M. Martelli	Roma (Italy)
A.J. Davis	Southampton (UK)
E. Zucca	Bellinzona (Switzerland)

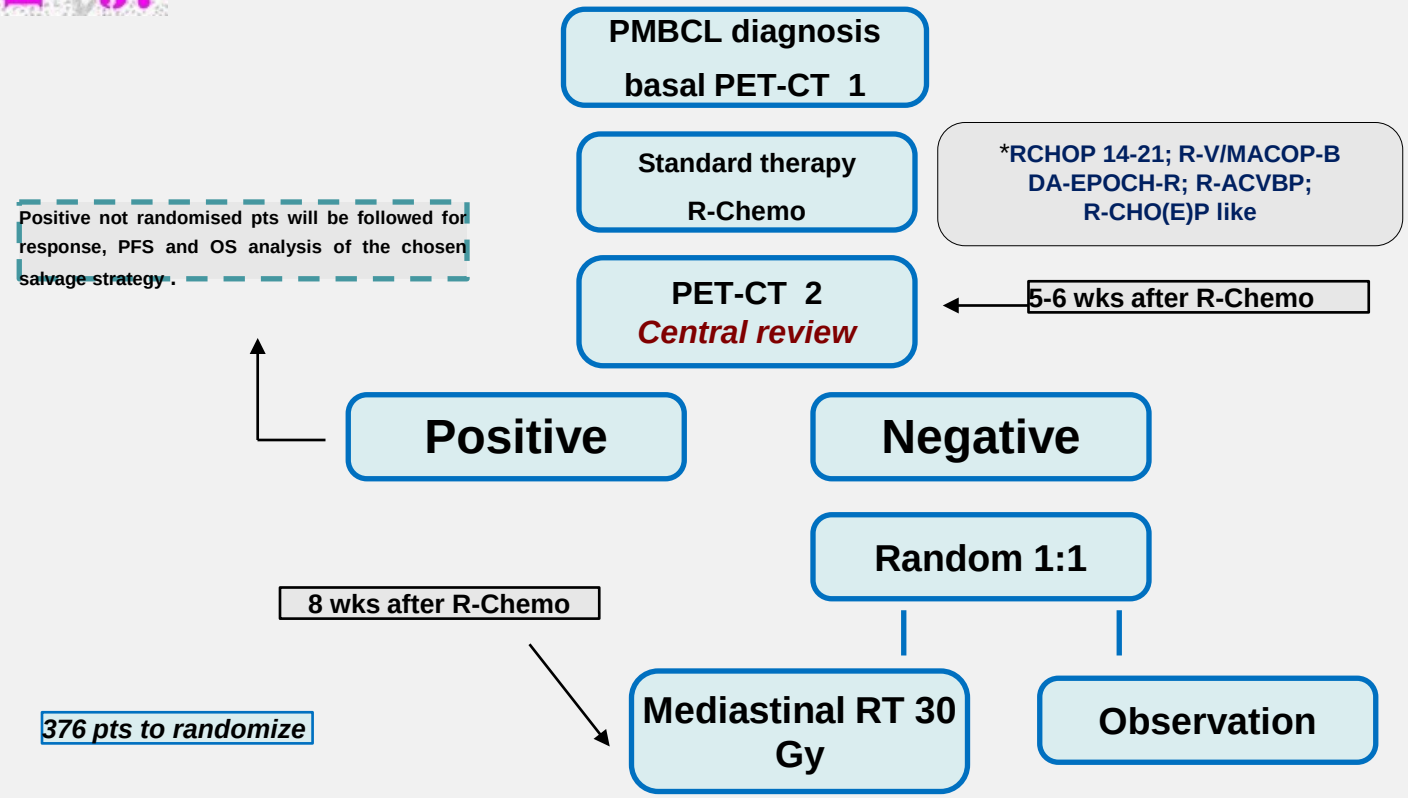
Radiotherapy Coordinators	
M. Gospodarowicz	Toronto (Canada)
U. Ricardi	Torino (Italy)
N.C. Azinwi	Bellinzona (Switzerland)

Statisticians	
G. Ciccone	Torino (Italy)

Medical Physicist	
S. Chauvie	Cuneo (Italy)

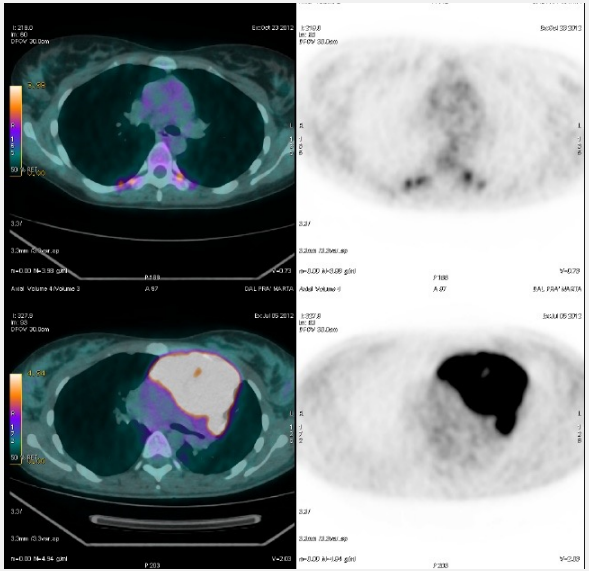
PET Trial Panel	
S. Barrington	London (UK)
A.Biggi	Cuneo (Italy)
L. Ceriani	Bellinzona (Switzerland)
A. Versari	Reggio Emilia (Italy)
B. Malkowski	Bydgoszcz (Poland)
U. Metser	Toronto (Canada)
L. Kostakoglu	New York (USA)

IELSG 37: trial design



IELSG 37: post chemotherapy PET/CT evaluation

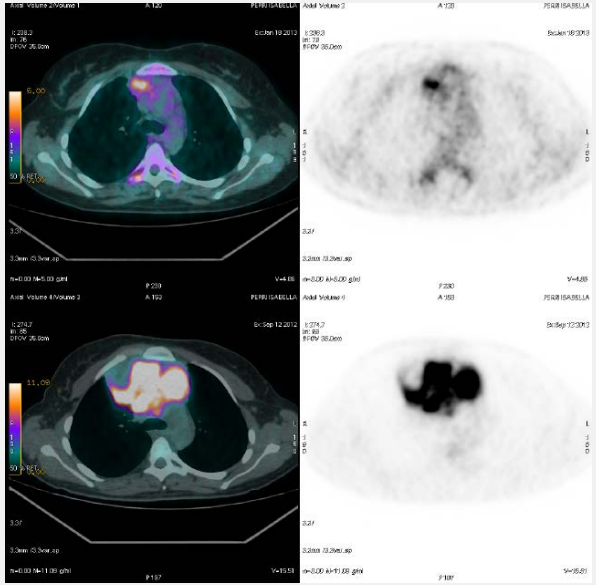
Post-CHT PET



PET-0

Deauville score 2

Post-CHT PET



PET-0

Deauville score 4

Study aim

- *To spare the mediastinal radiotherapy (RT) in patients with "negative PET" after a combined chemo-immunotherapy*

➢ Primary endpoint

- **Progression free survival (PFS) at 2-years from randomization**

➢ Secondary endpoints

- **Overall survival (OS) at 5-years from registration**
- **To define long term toxicities in this patient population**

Cut-off value in the IELSG protocol

- Since the aim of the proposed protocol is **to spare radiotherapy to PET-negative patients**, or, in other words, to de-escalated treatment in favorable-prognosis patients, one should rely on a very sensitive (conservative) threshold to interpret end-therapy scans, in order to avoid false negative results

Score 1: no uptake
Score 2: uptake ≤ mediastinum

→ **NEGATIVE**

Score 3: uptake > mediastinum but ≤ liver
Score 4: moderately uptake > liver
Score 5: markedly uptake > liver AND/or new sites of disease

→ **POSITIVE**

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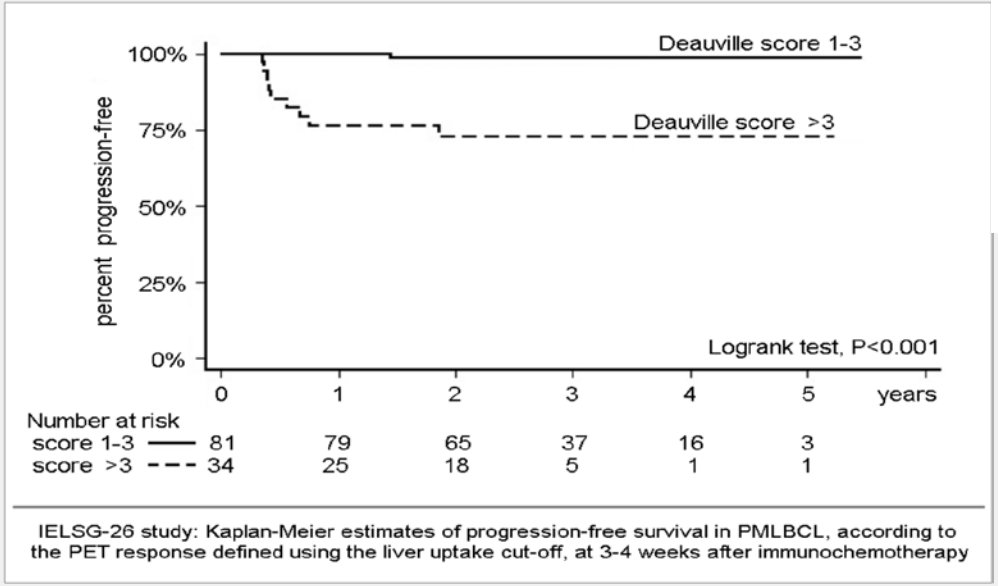
Study background:
PFS better defined by liver cut-point



IELSG-26 study: Kaplan-Meier estimates of progression-free survival in PMLBCL, according to the PET response defined using the liver uptake cut-off, at 3-4 weeks after immunochemotherapy

Consolidation RT given to 102 of 115 pts according to local policy irrespectively of the PET score at the end of R-CHT

- ***The IELSG-26 study did not answer the question on the role of mediastinal RT.***

[^{18}F]Fluorodeoxyglucose Positron Emission Tomography Predicts Survival After Chemoimmunotherapy for Primary Mediastinal Large B-Cell Lymphoma: Results of the International Extranodal Lymphoma Study Group IELSG-26 Study

Maurizio Martelli, Luca Ceriani, Emanuele Zucca, Pier Luigi Zinzani, Andrés J.M. Ferreri, Umberto Vitolo, Caterina Stelitano, Ercole Brusamolino, Maria Giuseppina Cabras, Luigi Rigacci, Monica Balzarotti, Flavia Salvi, Silvia Monioio, Armando Lopez-Guillermo, Erica Finolezzi, Stefano A. Pileri, Andrew Davies, Franco Cavalli, Luca Giovanella, and Peter W.M. Johnson

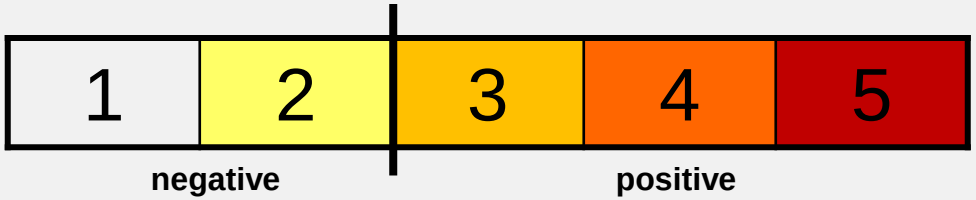
- The incidence of a ***post therapy PET-positive in PMBCL is higher (53%)*** than in others DLBCL using the ***MBP cut-point***
- ***Negative post-therapy PET/CT scan*** after R-CHT is significantly ***associated with a longer PFS.***
- ***Liver uptake*** represents ***a more appropriate cut-point*** **than *MBP*** to identify those patients with *a significant increased risk of relapse or progressive disease.*

Martelli M et al. J.Clin.Oncol. May 5, 2014

PET-CT response evaluation

visual analysis (Deauville score)
at 5-6 weeks after R-CHT

1. **No uptake.**
2. **Uptake ≤ mediastinum.**
3. **Uptake > mediastinum but ≤ liver.**
4. **Uptake moderately more than liver uptake, at any site.**
5. **Markedly increased uptake at any site and new disease sites**



MBP cut-point

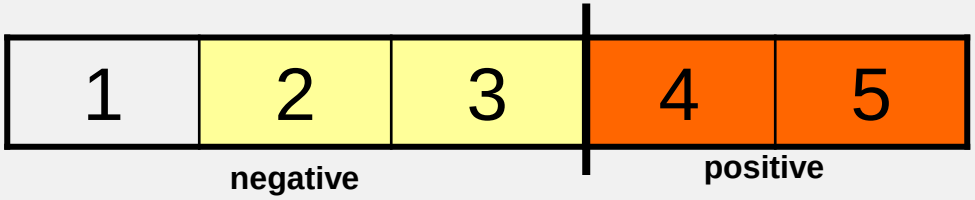
Patients achieving a metabolic CR (mCR) according the IHP criteria are designated by score 1-2 in the Deauville criteria

PET-CT response evaluation

visual analysis (Deauville score)

Amendment April 2014
based on IELSG 26 final results

1. **No uptake.**
2. **Uptake ≤ mediastinum.**
3. **Uptake > mediastinum but ≤ liver.**
4. **Uptake moderately more than liver uptake, at any site.**
5. **Markedly increased uptake at any site and new disease sites**



liver cut-point

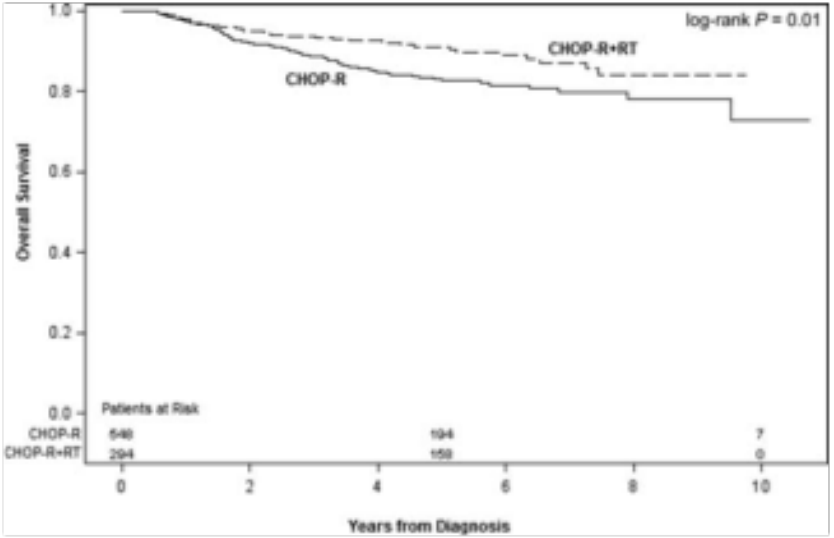
Predicted to improve consensus among PET panel

Enrolled patients by sites (June, 2015)

In Brief	
Total number of patients enrolled	171
Countries enrolling	7
Centres with at least 1 patient	43

Country	Center	Patients
Italy	FIL	130
Ukraine	Kiev	19
Canada	Toronto	1
Norway	Oslo	4
	Trondheim	2
Sweden	Lund	2
Switzerland	Bern	4
	St. Gallen	2
	Bellinzona	1
UK	Southampton	2
	Manchester	1
	London Guy's	1
	Norfolk	1

Radiation for Diffuse Large B-Cell Lymphoma in the Rituximab Era: Analysis of the National Comprehensive Cancer Network Lymphoma Outcomes Project



Dabaja et al Cancer 2014;121:1031-1039

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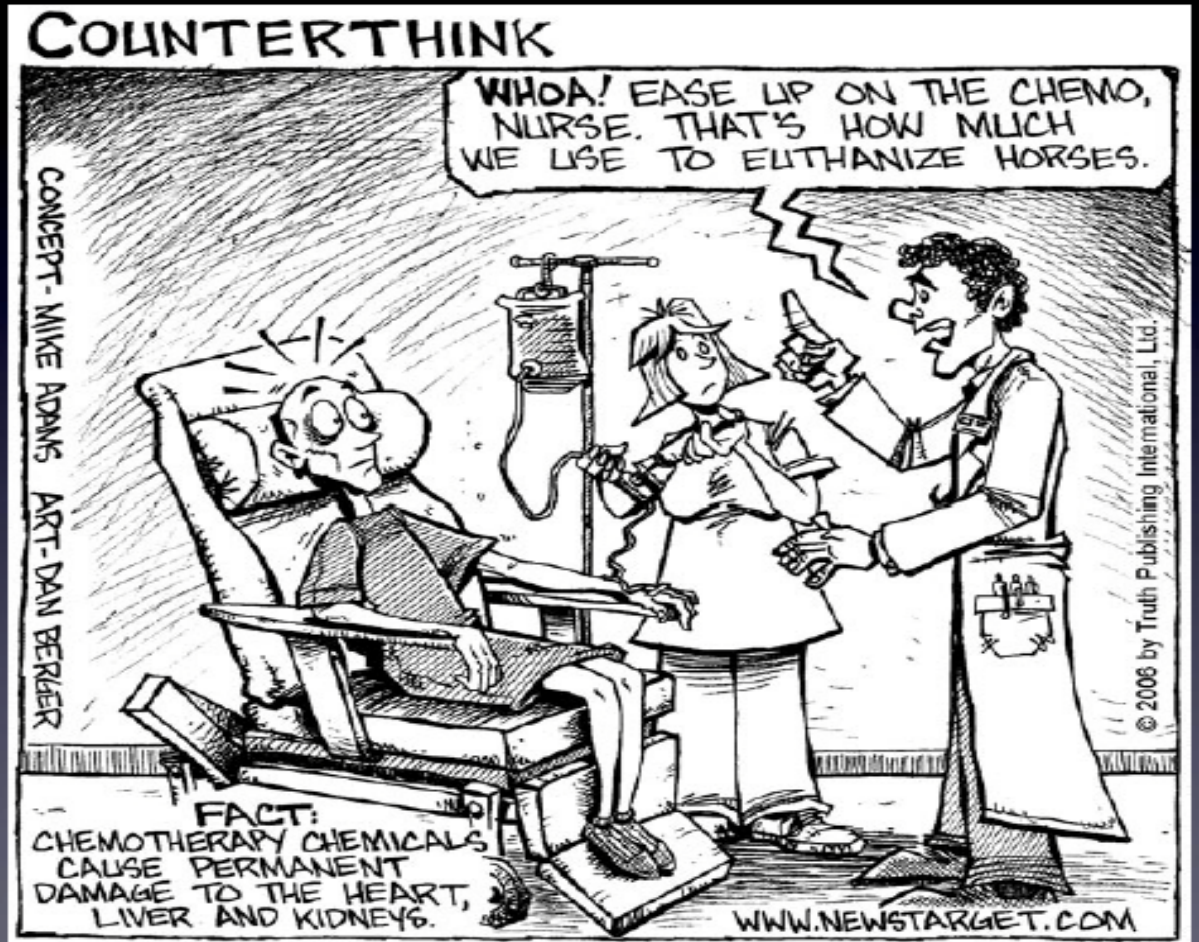
Is more of one modality better (and safer) than less of two?



MODERN, BETTER TARGETED, SAFER, AND LOWER-DOSAGE, CONSOLIDATIVE RT

Therapeutic burden:

R-CHOP x 3 cycles followed by 30 Gy IS-RT probably better than R-CHOP x 6 cycles

CARDIAC MORTALITY IN PATIENTS WITH STAGE I AND II DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH AND WITHOUT RADIATION: A SURVEILLANCE, EPIDEMIOLOGY, AND END-RESULTS ANALYSIS

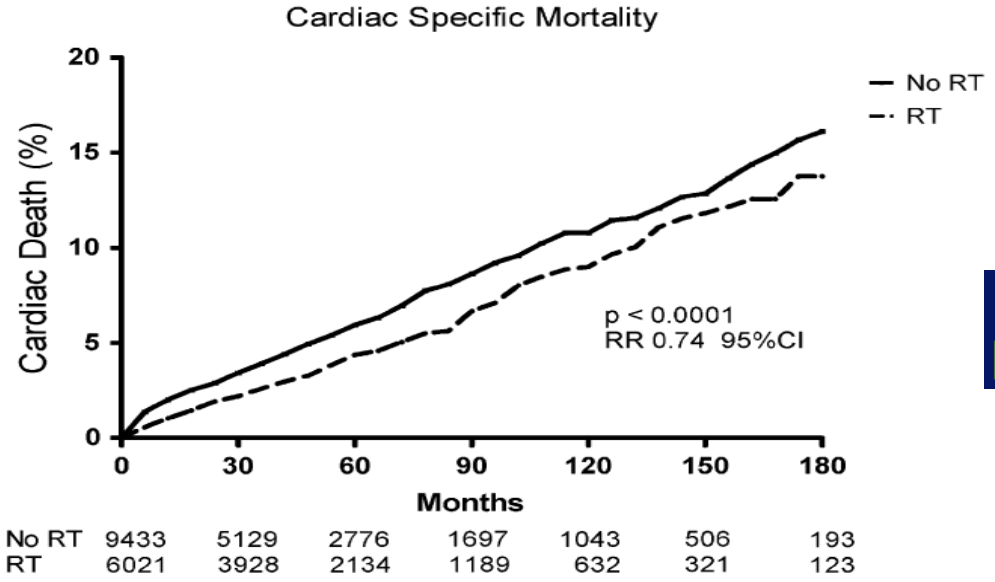


Fig. 1. Cardiac death in patients with stage I–II DLBCL. A comparison between patients treated with and without RT.

Increased Cardiac Death in Patients Treated without RT

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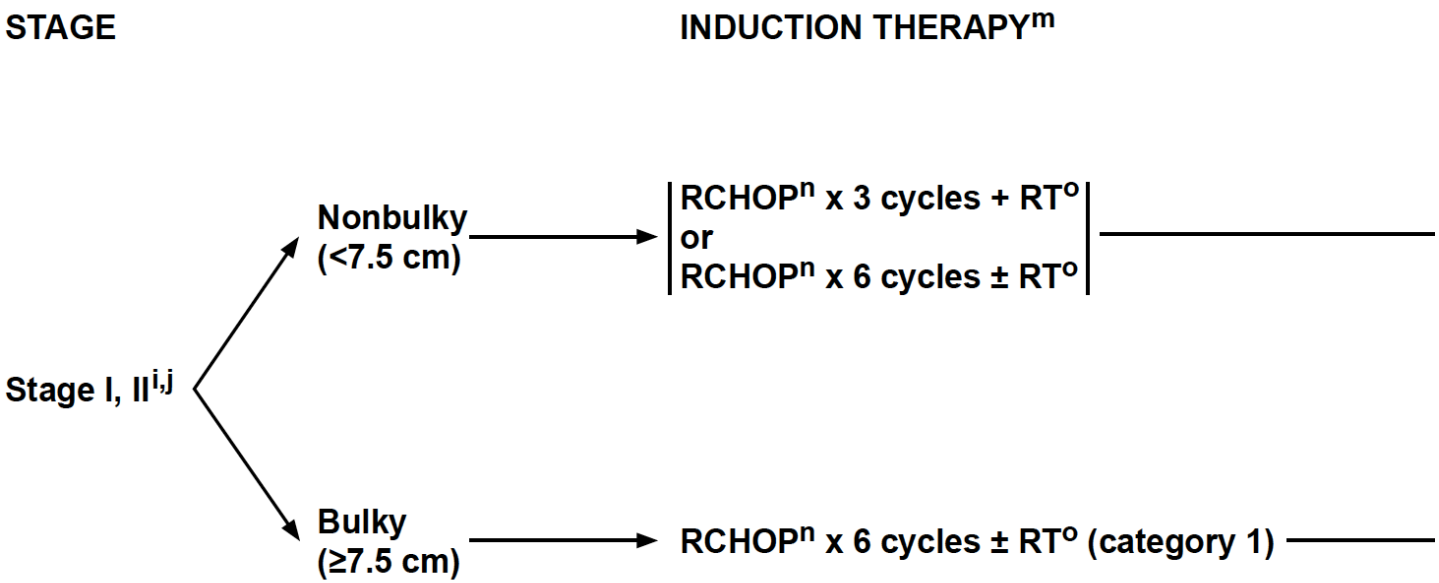
National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Diffuse Large B-Cell Lymphoma



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JOURNAL OF CLINICAL ONCOLOGY

Radiation Therapy After R-CHOP for Diffuse Large B-Cell Lymphoma: The Gain Remains

Joachim Yahalom, *Memorial Sloan-Kettering Cancer Center, New York, NY*

- Clearly, the issue of treatment consolidation after R-CHOP with IFRT, or alternatively with more chemotherapy, has not been resolved
- In an attempt to satisfy all opinions, the National Comprehensive Cancer Network (NCCN) guidelines recommend three cycles of R-CHOP + IFRT for early-stage, non bulky disease, but also allow the administration of six to eight cycles of R-CHOP, with or without IFRT
- The latter is also the NCCN recommendation for bulky disease
- This variety of options in the NCCN guidelines may make everybody happy, but it could be confusing to the nonexpert
- In reality, many hematologists/oncologists simply extend the chemotherapy course and omit radiotherapy (RT)

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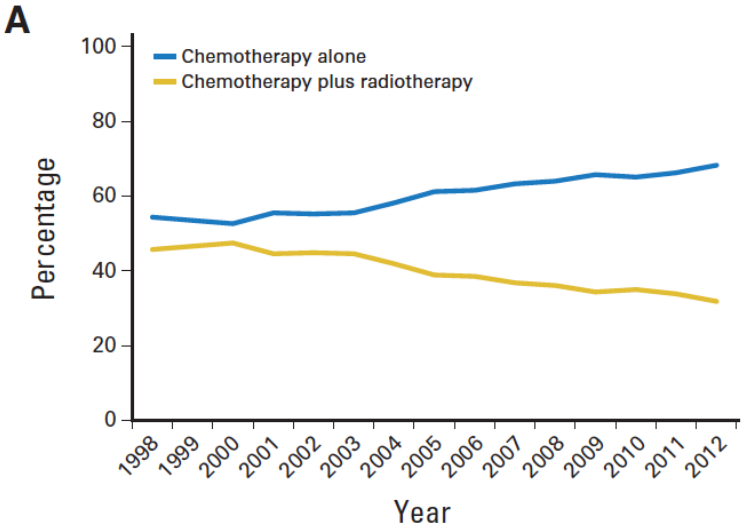
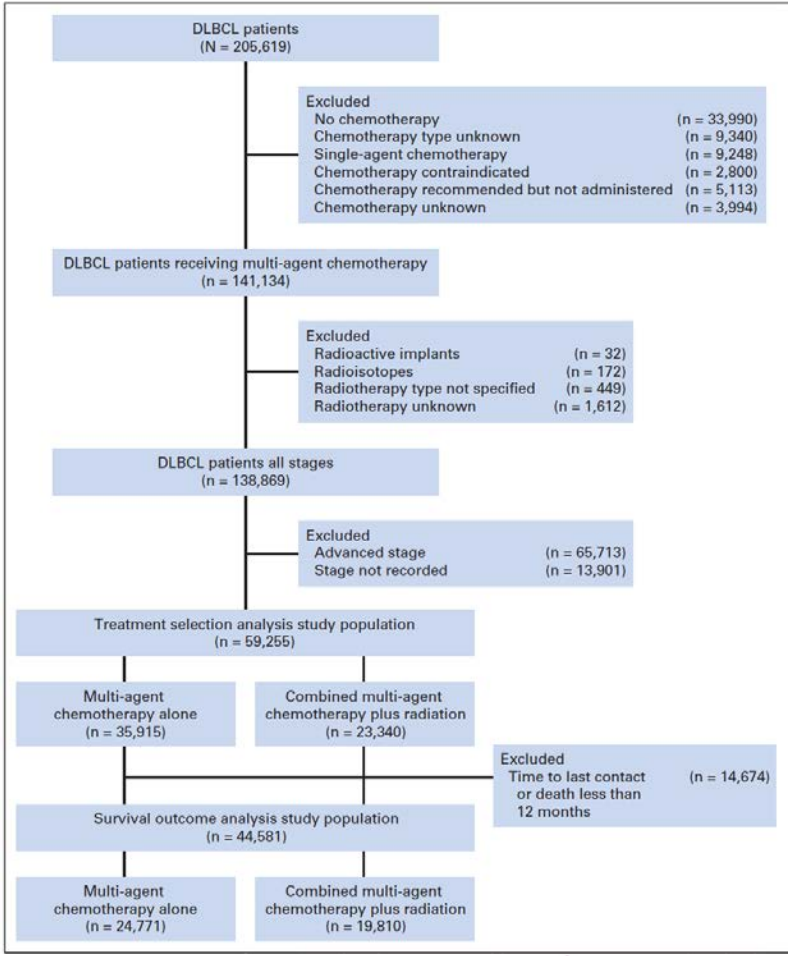
Published Ahead of Print on August 10, 2015 as 10.1200/JCO.2015.61.7654
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.61.7654

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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





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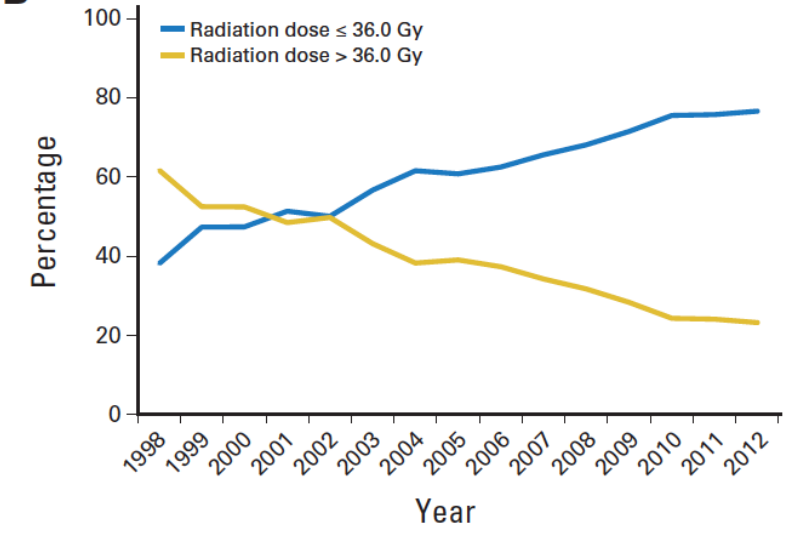
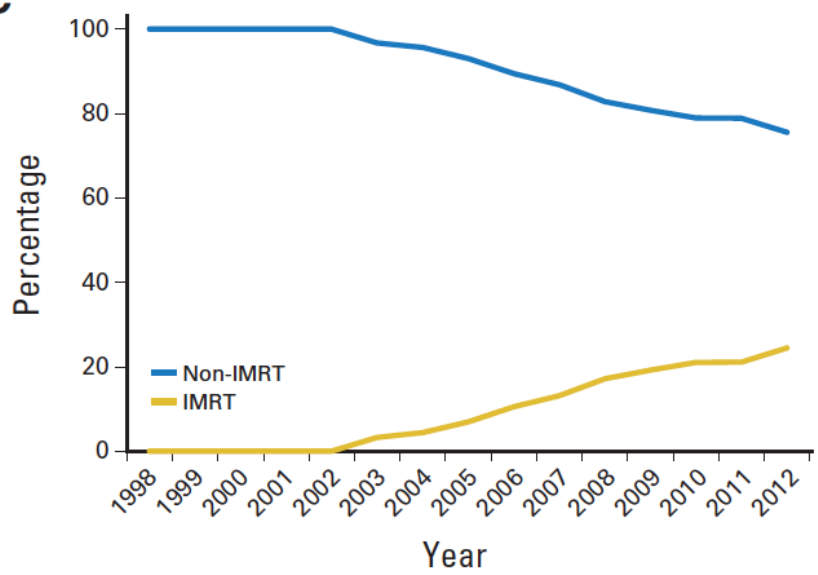
B



C



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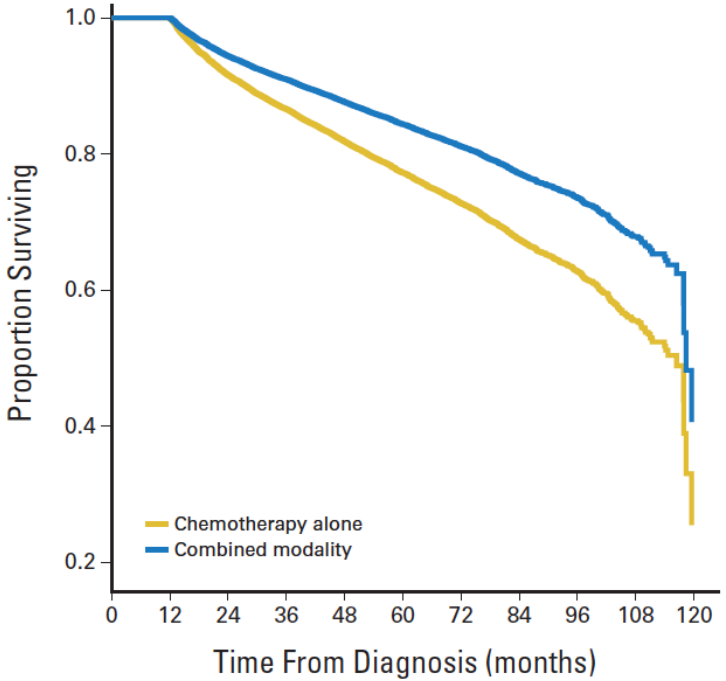
Cox Model With Propensity Score		
Treatment strategy		
Chemotherapy alone	Reference	
Combined modality	0.66 (0.61 to 0.71)	< .001
Sex		
Male	Reference	
Female	0.87 (0.82 to 0.92)	< .001
Income, US dollars		< .001
< 30,000	Reference	
30,000 to 35,000	0.98 (0.88 to 1.10)	.78
35,000 to 45,999	0.94 (0.85 to 1.03)	.19
≥ 46,000	0.81 (0.74 to 0.89)	< .001
Extranodal disease		
Absent	Reference	
Present	1.11 (1.05 to 1.18)	< .001
Propensity score (IPW)*	1.09 (1.02 to 1.15)	.008



Conclusion

Use of consolidative RT after multiagent chemotherapy in DLBCL is decreasing in the modern era. Selection of treatment strategy is affected by both classical prognostic features and socioeconomic factors. Abandonment of combined-modality therapy in favor of chemotherapy alone negatively affects patient survival.

J Clin Oncol 33. © 2015 by American Society of Clinical Oncology

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Combined-Modality Therapy for Early-Stage Diffuse Large B-Cell Lymphoma: Knowing When to Quit

Dan L. Longo, *Harvard Medical School, Brigham and Women's Hospital, Boston, MA*

See accompanying article doi:10.1200/JCO.2015.61.7654

Until we have better evidence for changing our current approach, oncologists should stop using radiation therapy as routine treatment in all patients with stage I and II diffuse large B-cell lymphoma

We should stop arguing and agree that current evidence does not support the use of radiation therapy in all of these patients

Rather, we should focus on conducting prospective clinical trials on selected subsets of patients for whom there may be a reasonable chance of demonstrating improved outcomes with radiation therapy

It is important to know when to quit

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Aggressive nodal non Hodgkin lymphoma, the role of radiotherapy: Advanced stage – indications

Focus on consolidation RT

Berthe Aleman

Radiation oncologist

Courtesy: Andrea Ng

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

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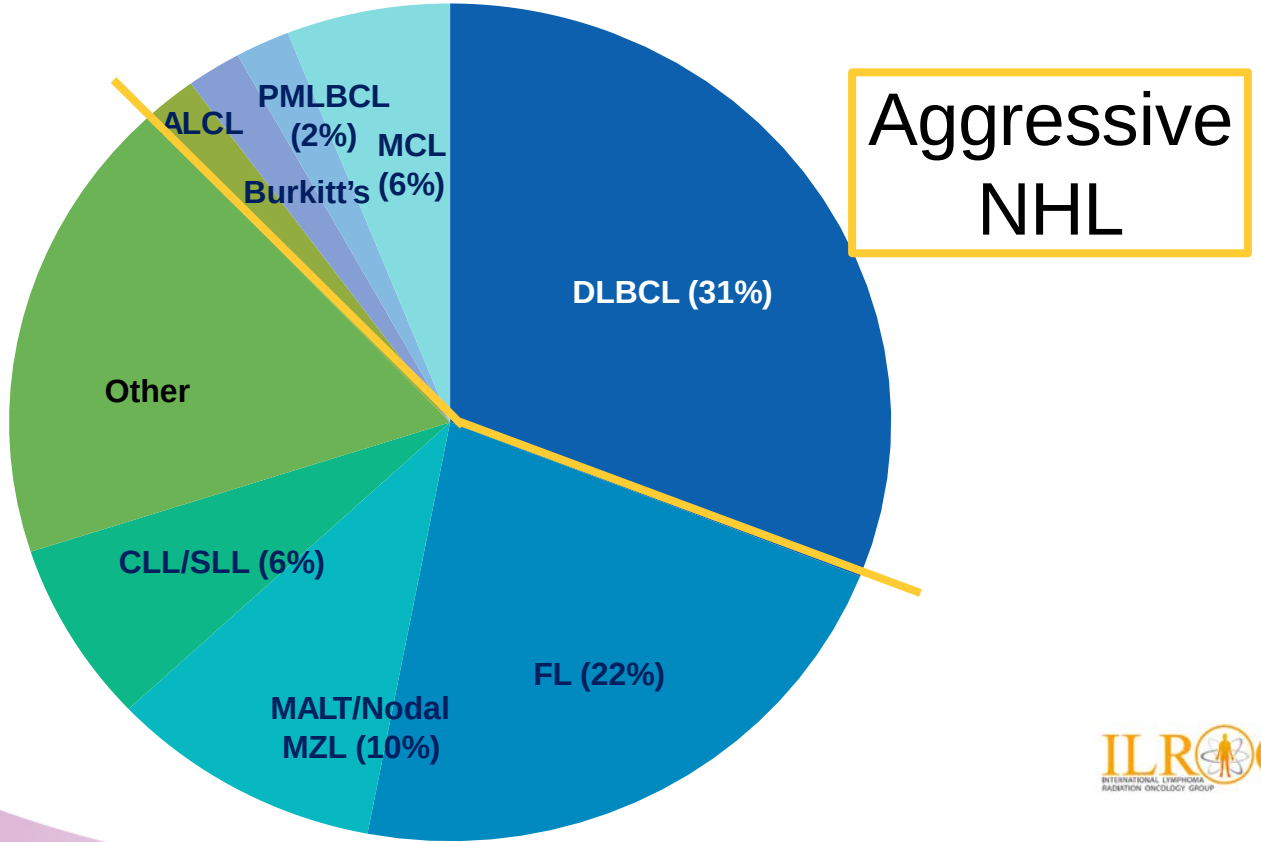
NHL: A Heterogeneous Disease

Frequency of NHL types



Aggressive NHL

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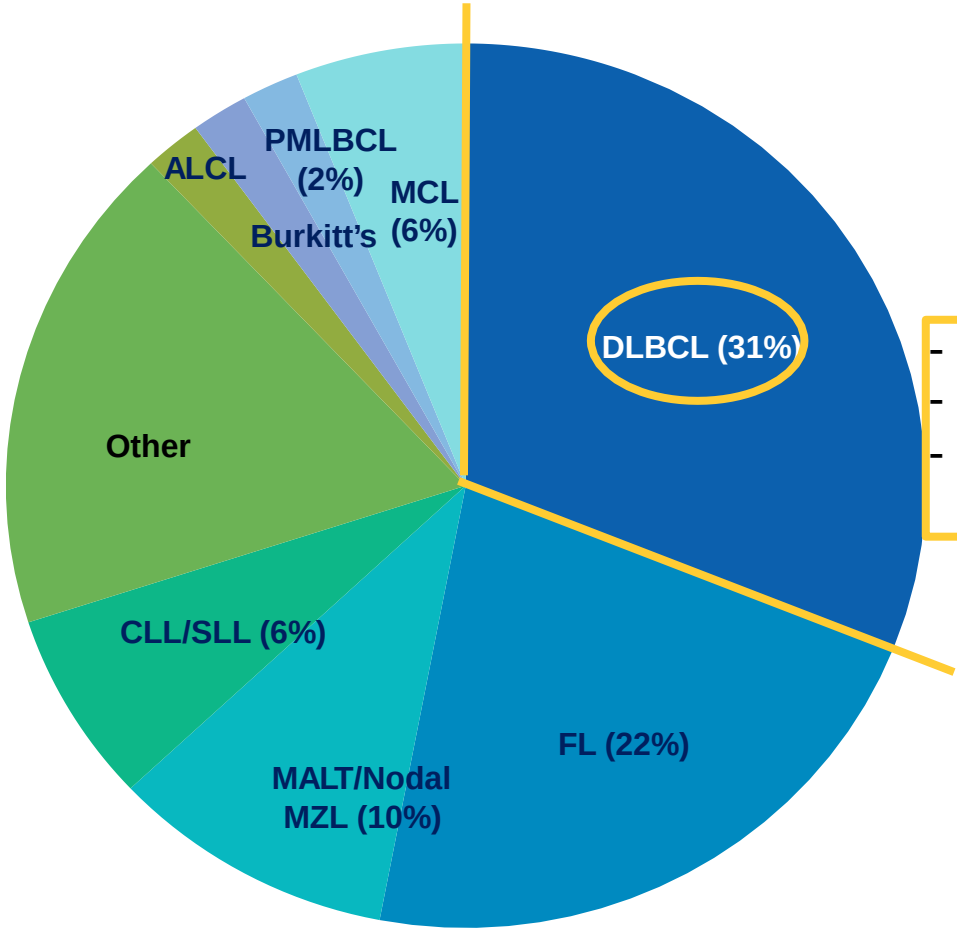
NHL: A Heterogeneous Disease



- 75% of aggressive NHL
- 40%: localized disease
- 40-50%: extranodal disease

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Aggressive nodal non Hodgkin lymphoma, the role of radiotherapy: Advanced stage - general

Literature:

- No randomized trials on role of RT in advanced disease only
- Limited number of retrospective series in stage III-IV or including stage III-IV (limited numbers of patients)

Duke Experience

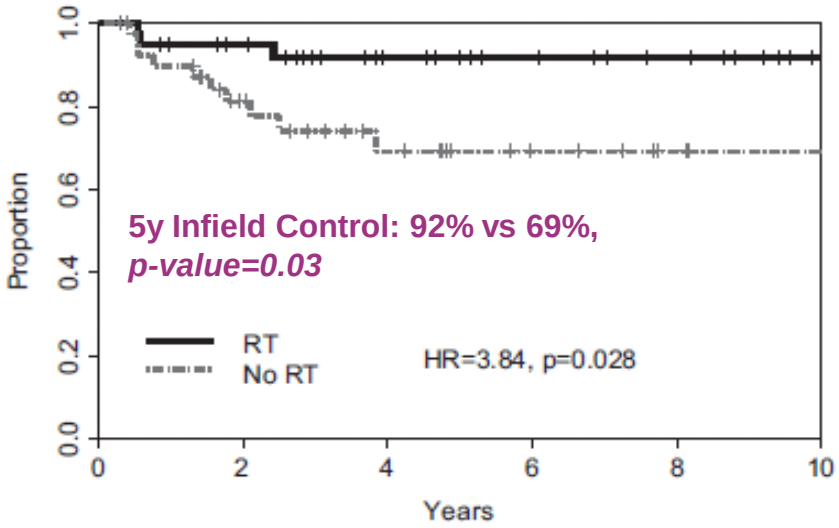
Aim:
Evaluation role of consolidation RT in advanced DLBCL

Patients and methods:

- Retrospective analysis
- 79 stage III-IV DLBCL pts in CR (73% by PET, 14% by gallium) after chemo (65% received R-CHOP) out of a population of 241 patients with DLBCL (any stage) treated between 1991-2009
- 38 (48%) received RT to involved sites (median 25 Gy)

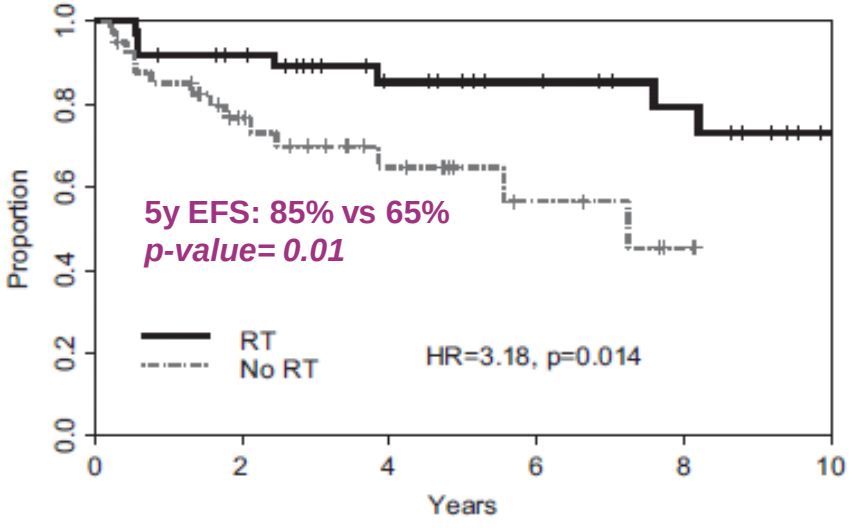
Dorth et al, IJROBP, 2012

Duke Experience
KM curves infield control and EFS



Number of Patients at Risk

RT	38	32	22	17	13	6
No RT	41	24	14	7	3	1



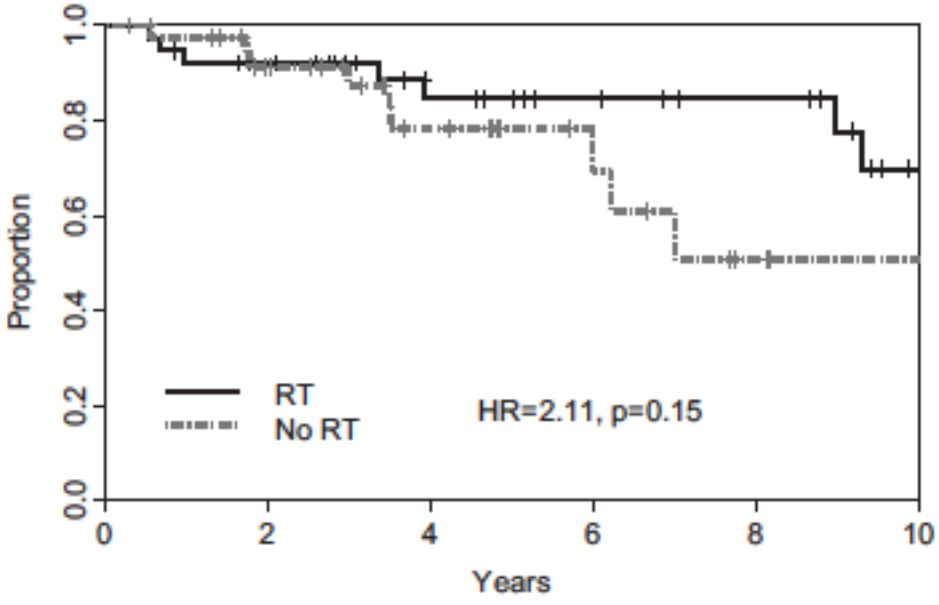
Number of Patients at Risk

RT	38	32	22	17	13	6
No RT	41	23	13	6	2	0

Dorth et al, IJROBP, 2012

Duke Experience

KM curve OS by consolidation RT



Number of Patients at Risk

RT	38	32	22	17	14	6
No RT	41	27	16	8	3	1

Dorth et al, IJROBP, 2012

Duke Experience

Results multivariate analysis:

- No RT associated with significantly higher infield failure *(HR=8, p=0.01)* and event rates *(HR=4.3, p=0.01)*

Conclusion*:*

- Consolidation RT appears to decrease the risk of local disease progression and overall relapse rates in patients with advanced DLBCL having negative functional imaging after chemotherapy.

Dorth et al, IJROBP, 2012

University of Chicago Experience

Patients and methods:

- 211 histologically confirmed stage III-IV DLBCL

patients who received R-CHOP from January 2000 to May 2012 at University of Chicago

- 110 stage III-IV DLBCL pts in CR (86% by PET) after R-CHOP
- 14 (12.7%) received RT

Shi, IJROBP, 2013

University of Chicago Experience

Table 2 Patterns of failure for advanced-stage diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy alone versus R-CHOP chemotherapy plus consolidative RT

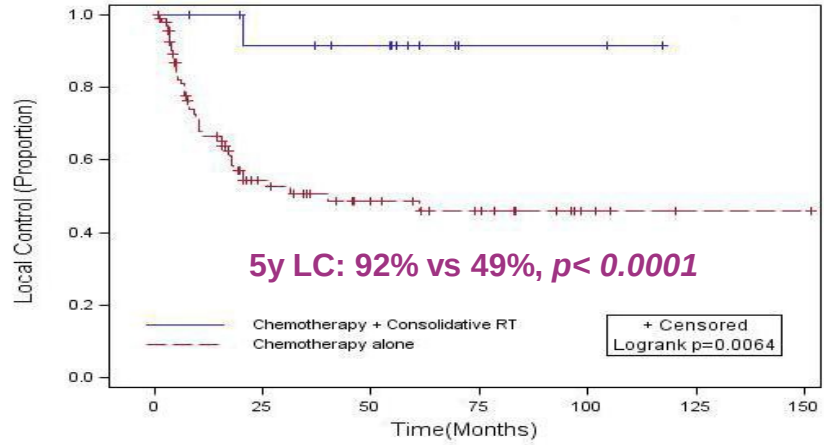
	All N=110		R-CHOP alone n=96		R-CHOP + Consolidative RT n=14		
Location of recurrence	n	%	n	%	n	%	*P* value
LR							
Isolated LR	22	20.0	21	21.9	1	7.1	.2937
Any LR (LR + DR)	43	39.1	42	43.8	1	7.1	.0082
DR							
Isolated DR	4	3.7	3	3.2	1	7.1	.4246
Any DR (DR + LR)	25	22.9	24	25.3	1	7.1	.1835
Concurrent LR and DR	21	19.1	21	21.9	0	0	.0415
Any recurrence	47	42.7	45	46.9	2	14.3	.023

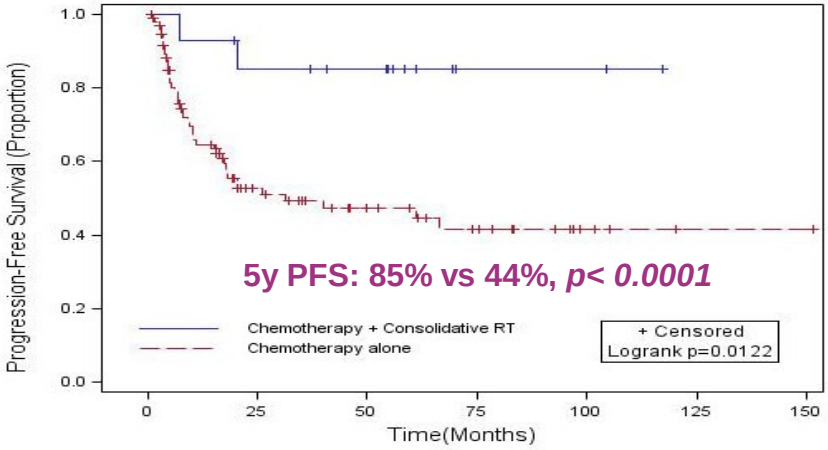
Abbreviations: DR = distant recurrence; LR = local recurrence; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RT = radiation therapy.

Shi, IJROBP, 2013

University of Chicago Experience

- MVA: RT associated with significantly improved LC *(HR= 8.7, p= 0.01)*, PFS *(HR= 9.6, p= 0.03)*, and trend of improved OS *(HR= 5.9, p= 0.08)*





Shi, IJROBP, 2013

University of Chicago Experience

Conclusions:

- 44% of patients with advanced stage DLBCL failed at initial presenting sites after achieving CR to R-CHOP.
- Incorporation of consolidative RT as part of upfront treatment in these patients was associated with improved LC, PFS, and a trend towards improved OS.

Shi, IJROBP, 2013

MD Anderson Experience

Patients and methods:

- Retrospective analysis of 469 pts with DLBCL treated between 2001-2007
- 60% stage III or IV
- Overall 30% received consolidative RT after reaching CR on chemo (dose, 30 to 39.6 Gy); only 39/279 (14%) patients with st III/IV received RT
- Median follow-up was 36 months (range, 8 to 85 months).

Phan et al. JCO, 2010

MD Anderson Experience

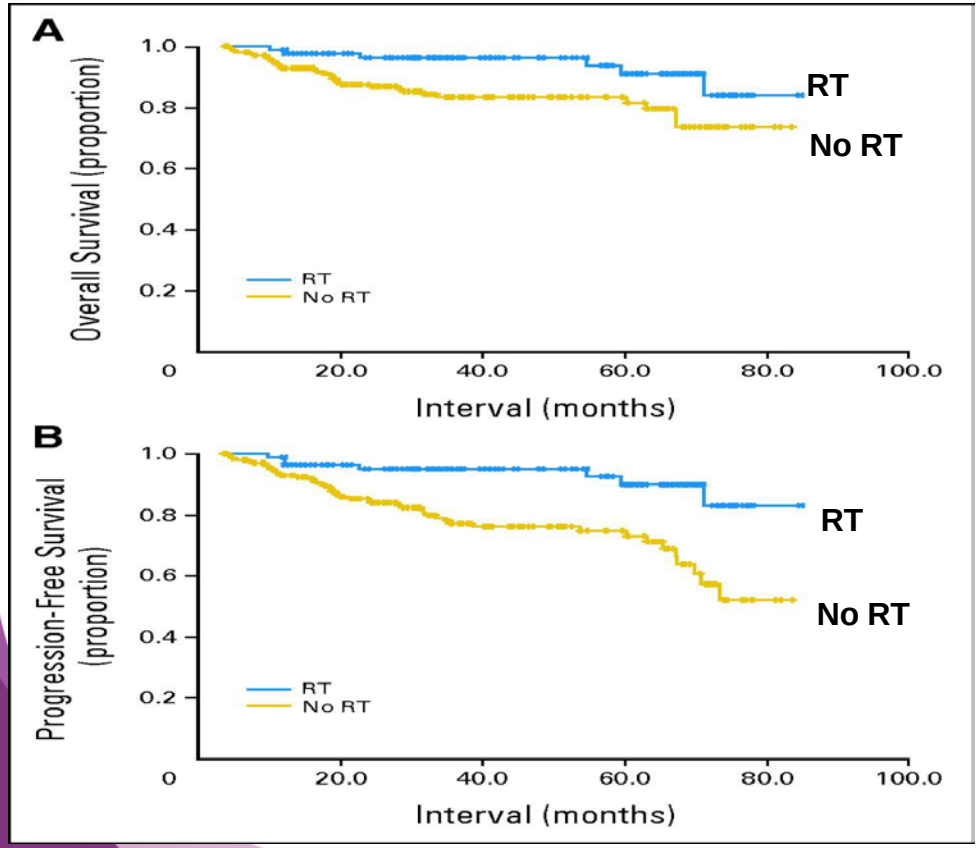
Results:

- Among 291 pts treated with R-CHOP and achieved CR, RT associated with significantly higher 5y OS and PFS (all stages)
- RT associated with significantly improved PFS (HR, 0.19) and OS (HR, 0.32)
- Failure occurred outside of the radiation fields in patients which originally received consolidative RT

Phan et al. JCO, 2010

MD Anderson Experience

OS and PFS for patients in CR after 6-8 R-CHOP



Univariate analysis of OS and PFS for patients in CR after 6-8 R-CHOP

Variable	5-yr OS	95% CI	5-year PFS	95% CI
Stage				
I-II	91	88-94	90	86-94
III-IV	82	78-86	72	67-77

Phan et al. JCO, 2010

MD Anderson Experience

Conclusion:

- This study showed significant improvement in OS and PFS among patients who received consolidation RT after R-CHOP chemotherapy for DLBCL

Phan et al. JCO, 2010

U Modena Experience

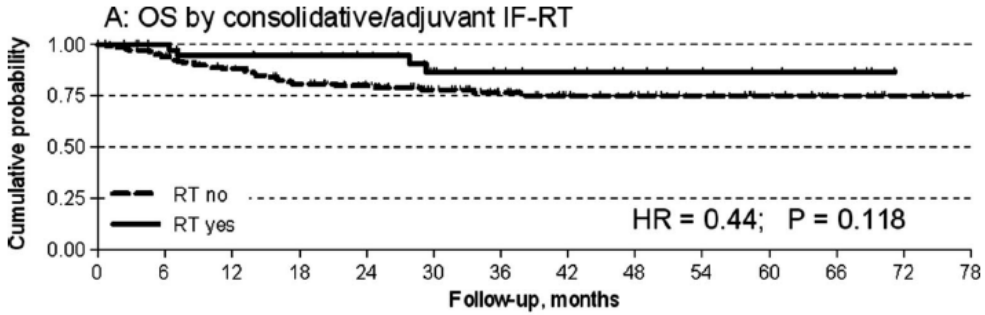
Patients and methods:

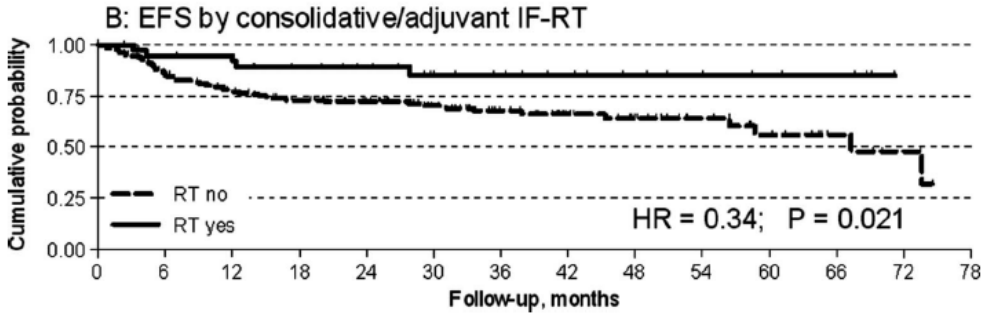
- Retrospective analysis of 216 patients treated in 2 trials from the GISL with 6 x R-CHOP
- Consolidative/adjuvant IFRT was allowed, at the treating physician's discretion, in patients CR/PR on CT
- Treatment period: 2003-2007
- Stage III-IV: 65%
- 182 patients achieved CR/PR on CT
- Stage I-II: 33% received IFRT
- Stage III-IV: 16% received IFRT

Marcheselli et al. Leuk Lymphoma, 2011

U Modena Experience

OS and EFS of patients in CR or PR after CT by consolidative/adjuvant IFRT





Median follow up 30 months

Marcheselli et al. Leuk Lymphoma, 2011

U Modena Experience

Results:

- MVA: in pts in **CR/PR** RT was associated with significantly lower event rates *(HR, 0.33, 95% CI 0.11-0.97)* and in pts with **CR** to R-CHOP *(HR, 0.24, 95% CI 0.06-0.92)*

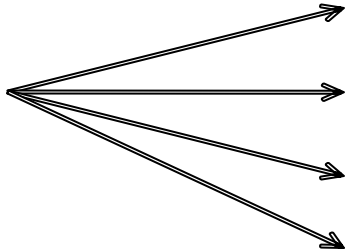
Conclusions:

- The role of RT in the treatment of DLBCL, at either early or advanced stages, is still unclear.
- Prospective studies needed

Marcheselli et al. Leuk Lymphoma, 2011

Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma (n=1,222)

RICOVER-60:



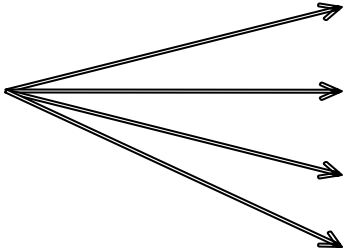
- CHOP- 14 x 8
- CHOP-14 x 6
- R-CHOP-14 x 8
- R-CHOP-14 x 6

RT to pts with bulky disease (≥7.5 cm) or extranodal disease in case of CR(u) or PR after chemotherapy

Held et al, JCO 2014
Pfreundschuh. Lancet Oncol, 2008

Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma (n=1,222)

RICOVER-60:



- CHOP- 14 x 8
- CHOP-14 x 6
- R-CHOP-14 x 8
- **R-CHOP-14 x 6**

Retrospective subgroup analysis of pts with bulky disease (≥7.5 cm) from the R-CHOP14 x 6 arm treated with or without RT

Held et al, JCO 2014
Pfreundschuh. Lancet Oncol, 2008

Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma
Clinical characteristics

	RICOVER-60		**RICOVER-noRT**		**P-value**	
	Total (n=306)	With bulk (n=117)	Total (n=164)	With bulk (n=47)	Total	With bulk
Age (median)	69	68	71	70		
Stage III-IV (%)	152(50)	69(59)	98(60)	36(77)	0.105	0.068

Held et al, JCO 2014

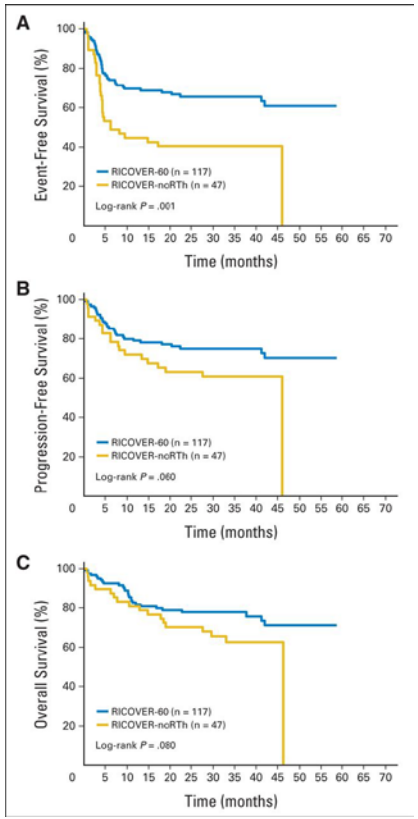
Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma

Intent-To-Treat Analysis:

EFS

PFS

OS

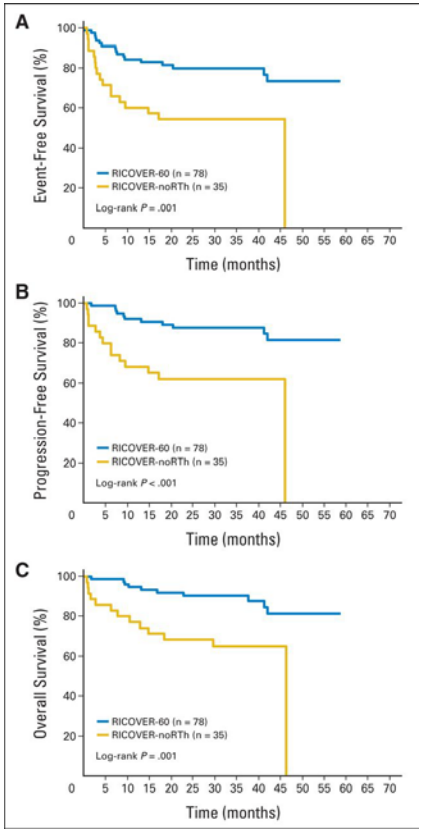


Per-Protocol Analysis:

EFS

PFS

OS



Held et al, JCO 2014

Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma

Conclusions:

- Additive RT to bulky sites abrogates bulky disease as a risk factor and improves outcome of elderly patients with aggressive B-cell lymphoma.
- Whether RT can be spared in patients with (metabolic) CR after immunochemotherapy must be addressed in appropriately designed prospective trials.

Held et al, JCO 2014

Summary role of RT for advanced nodal aggressive NHL

- Multiple retrospective studies showed a significant benefit with addition of RT
- Subgroup analysis of DSHNHL trials showed significant benefit of RT in elderly pts with bulky sites ($\geq$ 7.5 cm)

Spare

UNFOLDER Trial

- Eligibility: DLBCL, aged 18-60, aa-IPI=1 or IPI=0 with bulky disease (≥ 7.5 cm)
- Pts with bulky and/or extranodal disease randomized to 1 of 4 arms:
  - Arm I: R-CHOP 21 x 6 alone
  - Arm II: R-CHOP 21 x 6; if CR - RT
  - Arm III: R-CHOP 14 x 6 alone
  - Arm IV: R-CHOP 14 x 6; if CR - RT

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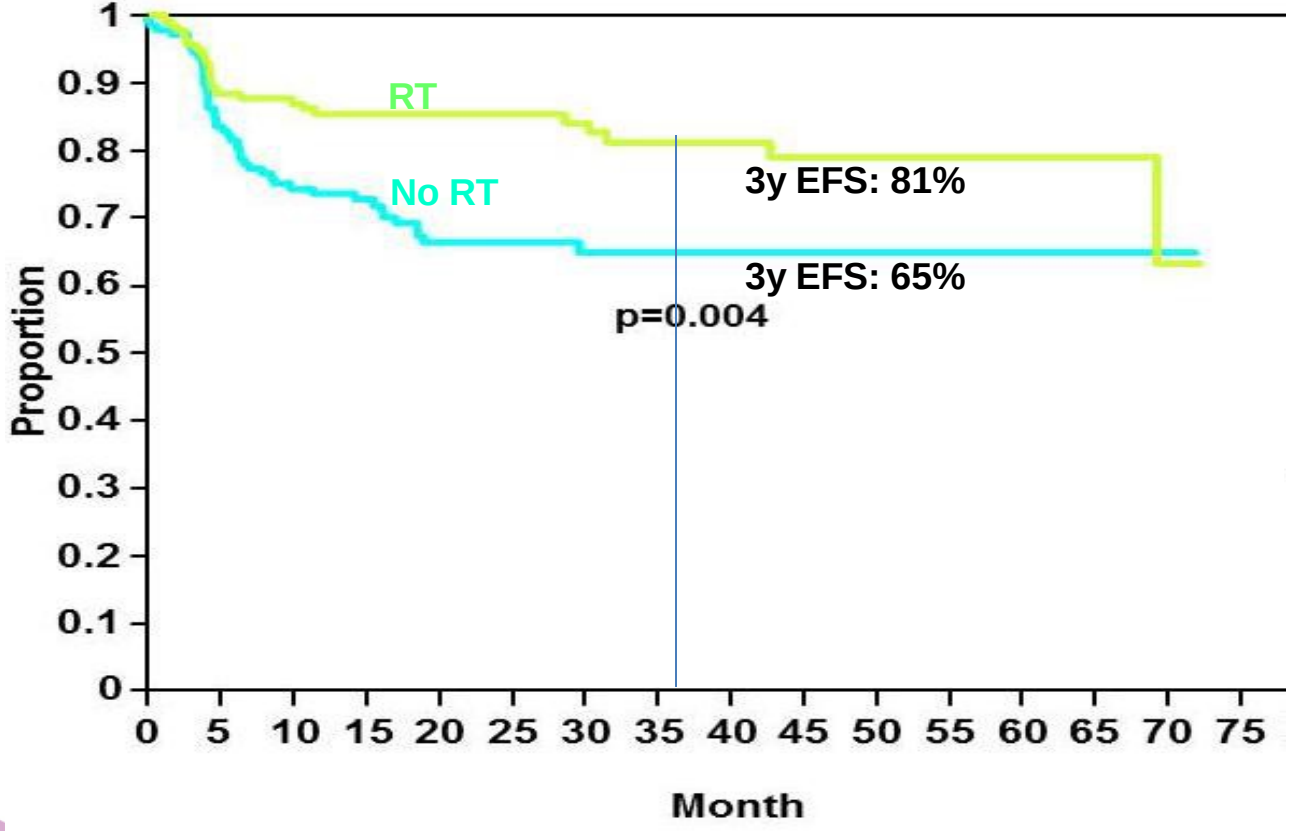
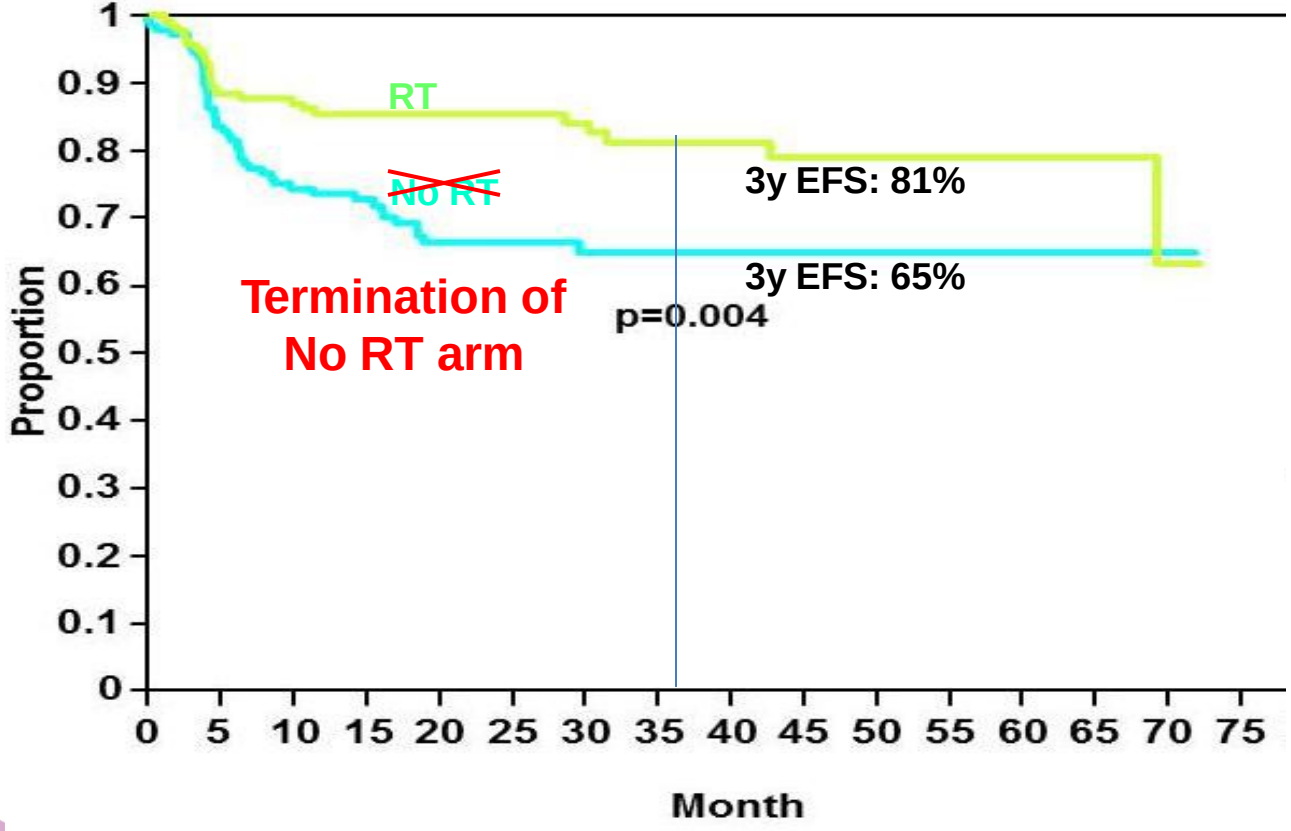
UNFOLDER Trial



Held. ICML RT Workshop, 2013

UNFOLDER Trial



Held. ICML RT Workshop, 2013

Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma
Clinical characteristics

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	RICOVER-60				RICOVER-noRTh				*P*	
	Total (n = 306)		With Bulk (n = 117)		Total (n = 164)		With Bulk (n = 47)			
	No.	%	No.	%	No.	%	No.	%	Total	With Bulk
Sex									.100	.474
Male	168	55	62	53	77	47	22	47		
Female	138	45	55	47	87	53	25	53		
Age, years									.018	.064
Median	69		68		71		70			
Range	61-80		61-80		61-80		61-79			
> 60	306	100	117	100	164	100	47	100		
LDH > normal	152	50	76	65	91	56	37	79	.229	.085
ECOG PS > 1	43	17	27	23	23	14	11	23	.993	.964
Extralymphatic involvement > one	52	14	24	21	38	23	16	34	.105	.068
Stage III to IV disease	152	50	69	59	98	60	36	77	.037	.003

Held et al, JCO 2014

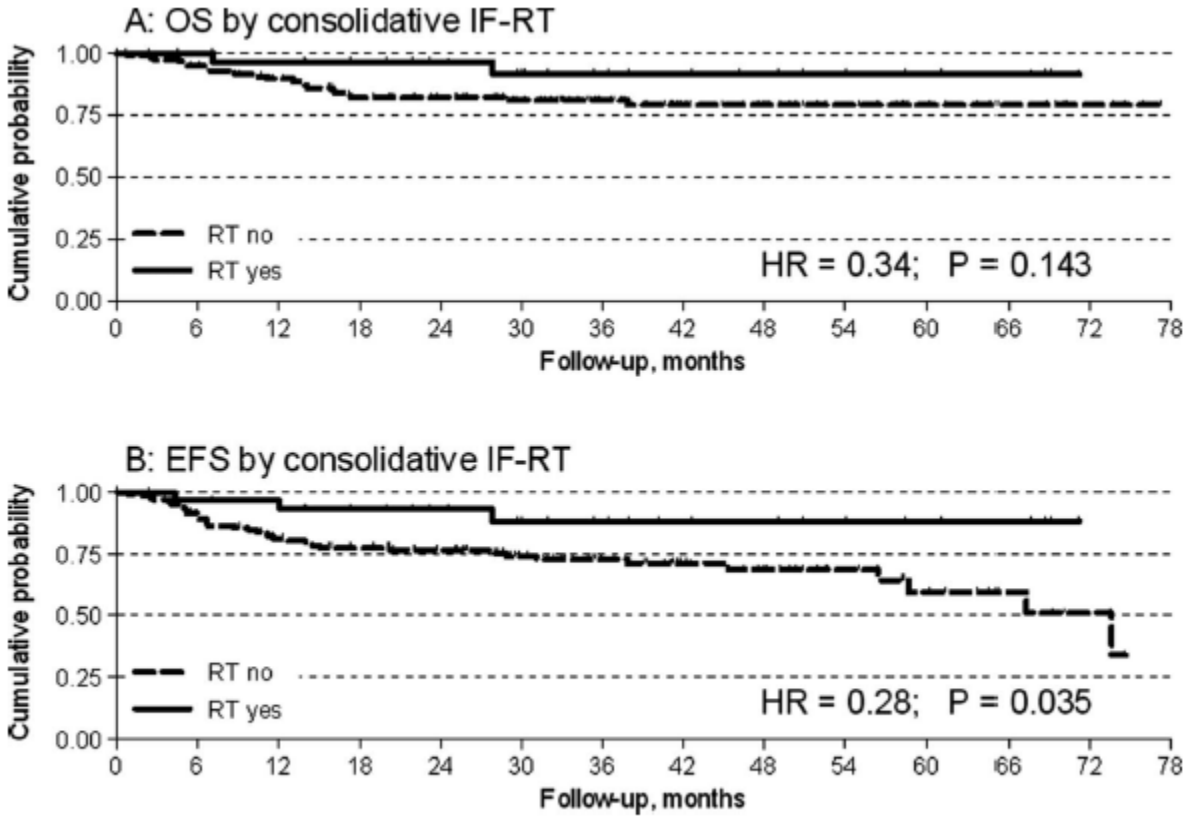


Figure 2. Comparison of (A) overall survival (OS) and (B) event-free survival (EFS) of patients who achieved complete remission after chemotherapy and consolidative IFRT. Solid line: received involved-field radiotherapy (IFRT); dashed line: received no IFRT.

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Aggressive Nodal NHL-
RT for Relapsed / Refractory Disease

George Mikhaeel, MD
Department of Clinical Oncology
Guy's & St Thomas' Hospital
KHP Academic Health Sciences Centre
London, UK

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Outline

- Size of the problem
  - Primary Refractory: failure to achieve remission with 1st line treatment
  - Relapse: recurrence following remission

- Breakdown of clinical scenarios
  1. Persistent PET positivity after chemo
  2. Role in peri-transplant setting
  3. Role in patients who are transplant ineligible or relapsed after Tx

- RT details

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(1) Persistent PET positivity after Primary Chemo

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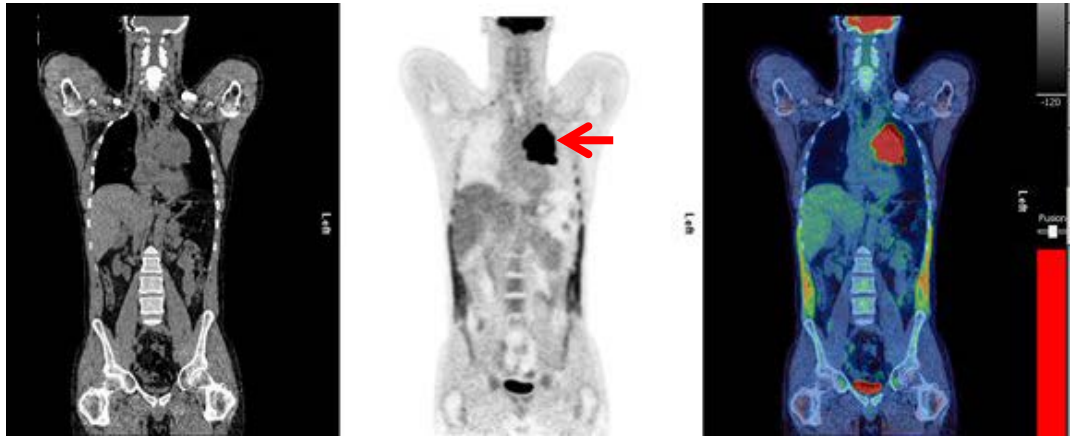
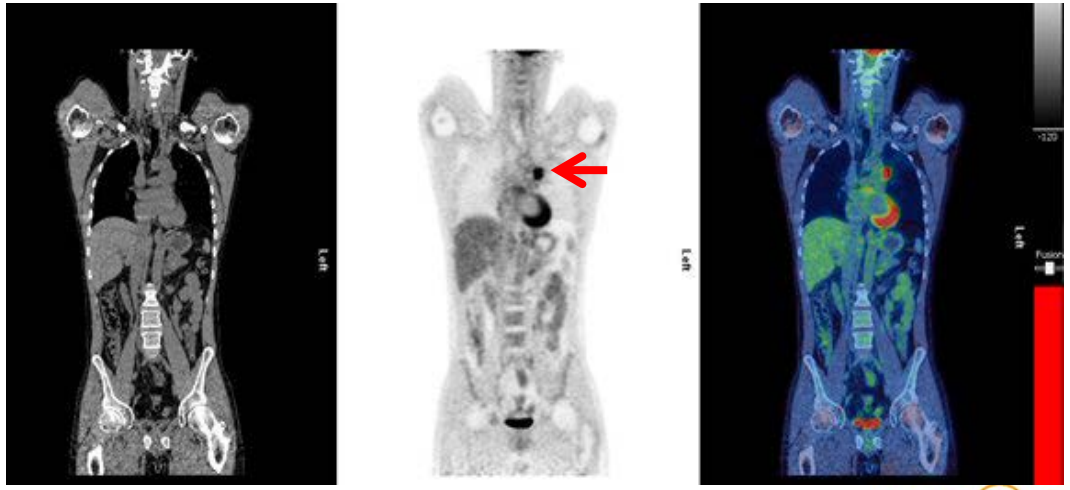
Baseline



Post chemo



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original article

Annals of Oncology 22: 405–410, 2011
doi:10.1093/annonc/mdq389
Published online 30 July 2010

The impact of radiation therapy in patients with diffuse large B-cell lymphoma with positive post-chemotherapy FDG–PET or gallium-67 scans

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Departments of [1]Radiation Oncology; [2]Medicine, Division of Medical Oncology; [3]Radiology, Division of Nuclear Medicine, Duke University Medical Center, Durham, USA

Received 9 December 2009; revised 25 May 2010; accepted 26 May 2010

Background: 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography (PET) and gallium-67 citrate (gallium) response after chemotherapy are powerful prognostic factors in diffuse large B-cell lymphoma (DLBCL). However, clinical outcomes when consolidation radiation therapy (RT) is administered are less defined.

Patients and methods: We reviewed 99 patients diagnosed with DLBCL from 1996 to 2007 at Duke University who had a post-chemotherapy response assessment with either PET or gallium and who subsequently received consolidation RT. Clinical outcomes were estimated using the Kaplan–Meier method and compared using the log-rank test.

Results: Median follow-up was 4.4 years. Stage distribution was I–II in 70% and III–IV in 30%. Chemotherapy was R-CHOP or CHOP in 88%. Median RT dose was 30 Gy. Post-chemotherapy PET ($n = 79$) or gallium ($n = 20$) was positive in 21 of 99 patients and negative in 78 of 99 patients. Five-year in-field control was 95% with a negative PET/gallium scan versus 71% with a positive scan ($P < 0.01$). Five-year event-free survival (EFS; 83% versus 65%, $P = 0.04$) and overall survival (89% versus 73%, $P = 0.04$) were also significantly better when the post-chemotherapy PET/gallium was negative.

Conclusions: A positive PET/gallium scan after chemotherapy is associated with an increased risk of local failure and death. Consolidation RT, however, still results in long-term EFS in 65% of patients.

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Dorth et al

- 99 pts, 1996 – 2007, mFU 4.4y
- All had PET/Ga + RT
- 70% stage 1-2
- 88% CHOP/RCHOP
- 21% PET/Ga +ve

	In-field cont	EFS	OS
PET -ve	95%	83%	89%
PET +ve	71%	65%	73%
	P<0.01	*P=0.04*	*P=0.04*

Factor	Positive (n = 21) PET/gallium (%)	Negative (n = 78) PET/gallium (%)	P value
Median age, years	54	62	0.03
Gender			1
Male	8 (38)	20 (38)	
Female	13 (62)	48 (62)	
Stage			0.76
I–II	16 (76)	62 (79)	
III–IV	5 (24)	16 (21)	
Performance status (ECOG)			0.58
0–1	19 (96)	75 (90)	
2–5	2 (4)	3 (10)	
Elevated LDH	12 (57)	24 (31)	0.03
B symptoms	6 (29)	16 (21)	0.55
IPI score (median)	1	1	0.95
>1 Extranodal sites	3 (14)	9 (12)	0.99
Median tumor diameter, cm	8	4.7	<0.05
Post-chemotherapy scan			1
PET	17 (81)	65 (83)	
Gallium	4 (19)	13 (17)	
Chemotherapy regimen			0.89
R-CHOP	12 (57)	47 (59)	
CHOP	6 (29)	22 (27)	
R-CNOP	1 (5)	2 (3)	
Other	2 (9)	9 (11)	
Chemotherapy cycles (median)	6	6	0.31
Radiation dose (Gy) (median)	36	30	<0.01

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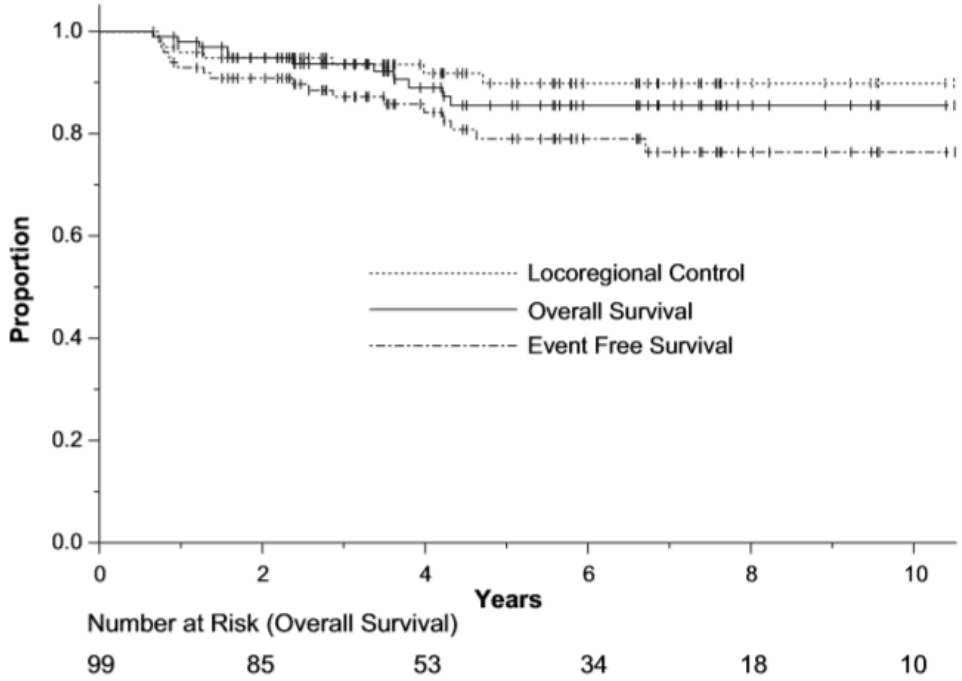

Figure 1. Local control, event-free survival, and overall survival for all patients.

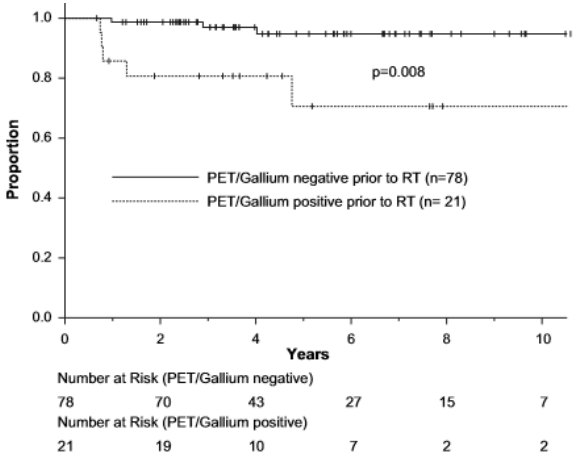

Figure 2. Local control by post-chemotherapy positron emission tomography (PET)/gallium status before radiation therapy (RT).

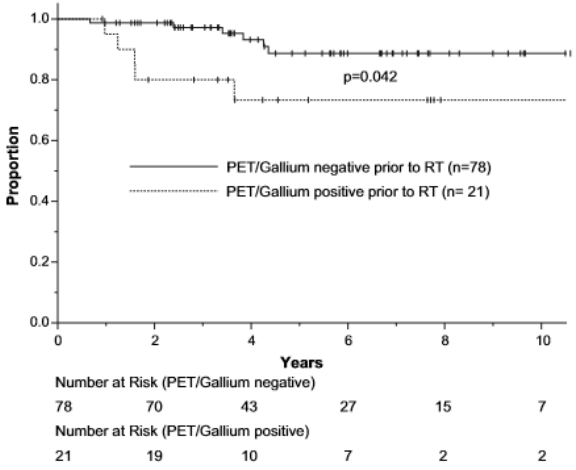

Figure 3. Overall survival by post-chemotherapy positron emission tomography (PET)/gallium status before radiation therapy (RT).

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Table 2. Multivariate analysis of factors associated with local (in-field) failure

Factor	HR	95% CI	*P*
Number of involved regions (per region)	1.14	0.7–1.84	0.6
IPI score (per point)	3.5	1.25–9.86	0.02
B symptoms	1.3	0.152–11.2	0.8
Size (per cm)	1.1	0.87–1.34	0.51
Number chemotherapy cycles (per cycle)	1.33	0.67–2.85	0.47
Use of rituximab	0.23	0.03–1.59	0.14
Radiation dose (per Gy)	1.13	0.99–1.85	0.1
Positive PET/gallium	9.64	1.44–64.5	0.02

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International Journal of Radiation Oncology biology • physics

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Clinical Investigation: Lymphoma

Combined Modality Treatment for PET-Positive Non-Hodgkin Lymphoma: Favorable Outcomes of Combined Modality Treatment for Patients With Non-Hodgkin Lymphoma and Positive Interim or Postchemotherapy FDG-PET

Lia M. Halasz, M.D.,* Heather A. Jacene, M.D.,† Paul J. Catalano, Sc.D.,‡ Annick D. Van den Abbeele, M.D.,† Ann LaCasce, M.D.,§ Peter M. Mauch, M.D.,‖ and Andrea K. Ng, M.D., M.P.H.‖

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Halasz et al

- 59 pts, 2001 – 2008, mFU 3.9y
- All had PET (interim=50 &/or end=28) + RT
- 83% stage 1-2
- 98% RCHOP
- 22 pts had +ve PET
  (7 iPET)

	3y-LC	3y-PFS	Death
PET -ve	100%	97%	1 (2nd lymphoma)
PET +ve	90%	90%	1 (relapse)

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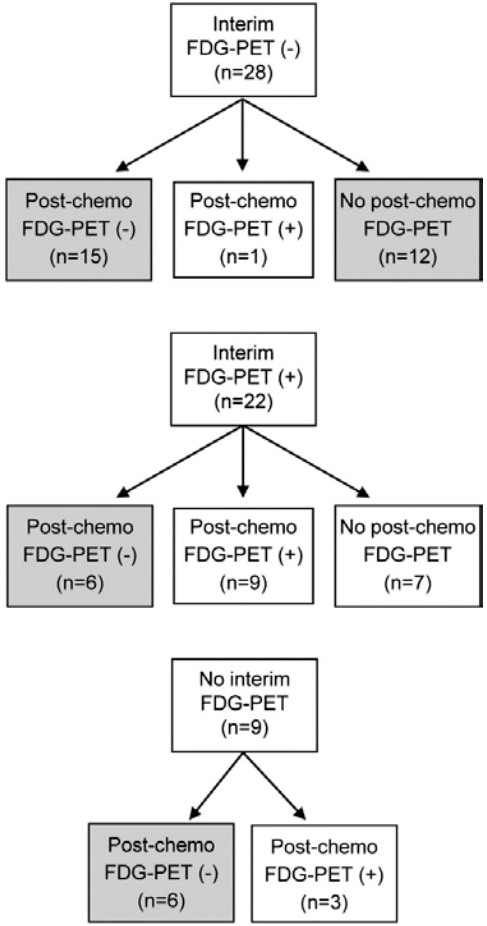
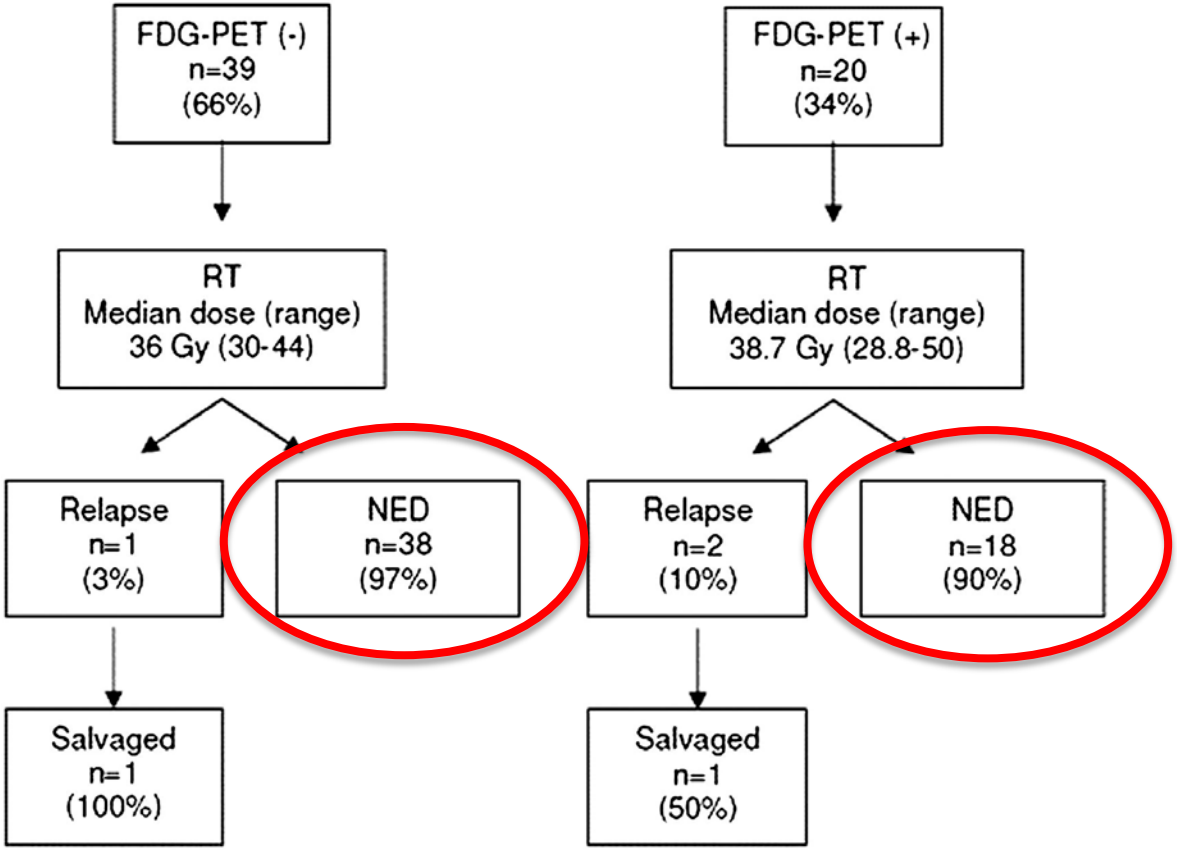
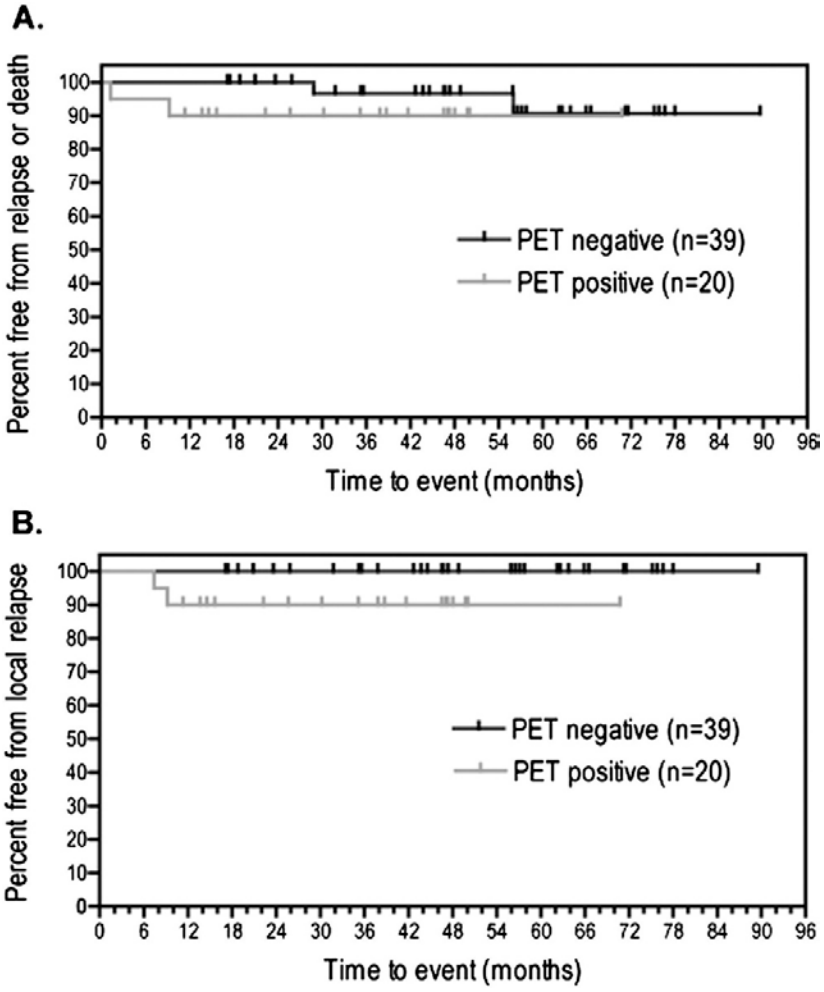



FDG-PET (-)
n=39
(66%)
FDG-PET (+)
n=20
(34%)
RT
Median dose (range)
36 Gy (30-44)
RT
Median dose (range)
38.7 Gy (28.8-50)
Relapse
n=1
(3%)
NED
n=38
(97%)
Relapse
n=2
(10%)
NED
n=18
(90%)
Salvaged
n=1
(100%)
Salvaged
n=1
(50%)

PFS

LC



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COMMENTS

Dorth

	In-field cont	EFS	OS
PET -ve	95%	83%	89%
PET +ve	71%	65%	73%
	P<0.01	*P=0.04*	*P=0.04*

Halasz

	3y-LC	3y-PFS	Death
PET -ve	100%	97%	1 (2nd lymphoma)
PET +ve	90%	90%	1 (relapse)

- Better outcome than would be expected
- Majority early stage
- PET positivity defined by IHP criteria (~ DS 3-5)
- Do these patients need SCT?

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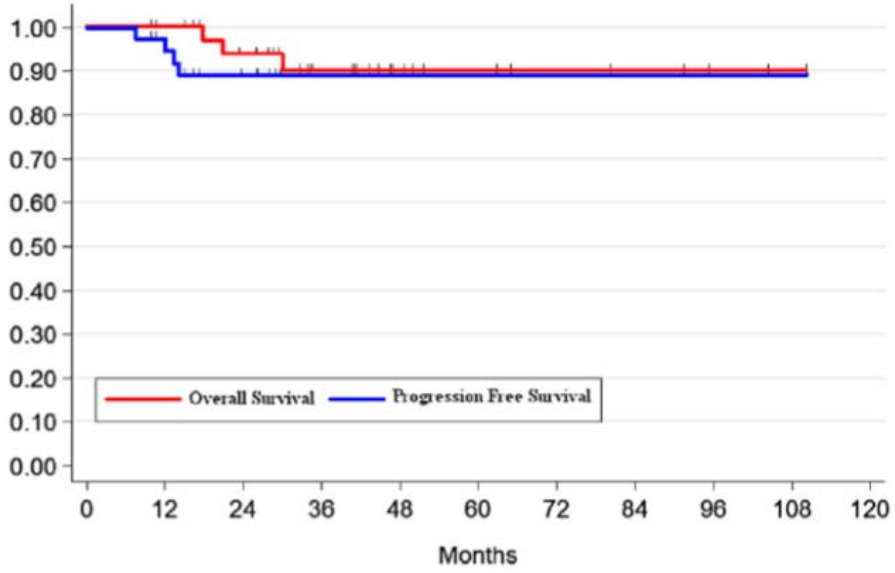
Radiation Therapy in Primary Mediastinal B-Cell Lymphoma With Positron Emission Tomography Positivity After Rituximab Chemotherapy

Andrea Riccardo Filippi, MD,* Cristina Piva, MD,* Francesca Giunta, MD,† Marilena Bellò, MD,† Annalisa Chiappella, MD,§ Daniele Caracciolo, MD,§ Michela Zotta, MD,† Anastasios Douroukas, MD,‖ Riccardo Ragona, PhD,* Umberto Vitolo, MD,§ Gianni Bisi, MD,† and Umberto Ricardi, MD*



Int J Radiation Oncol Biol Phys, Vol. 87, No. 2, pp. 311–316, 2013

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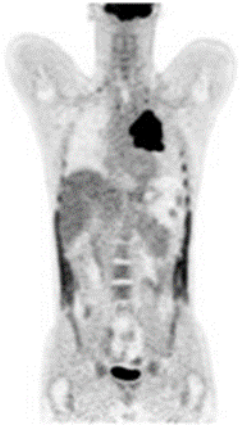
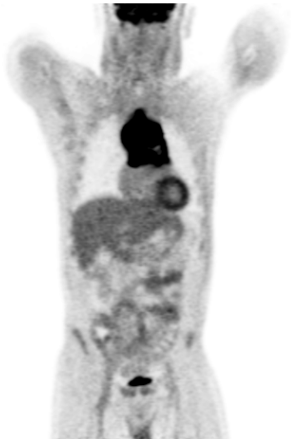
PET +ve Post chemo

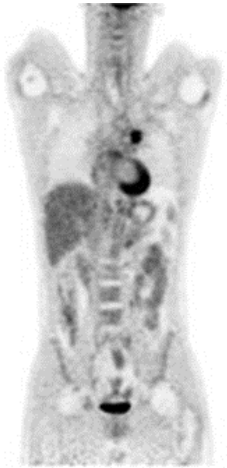
- Selected patients have good prognosis with RT alone (without ASCT):
  - Early stage
  - Advanced stage with a predominant site (+ other sites responded very early)
- PS:
  - PET +vity after chemo is related to bulk
  - PARMA study was relapse from remission

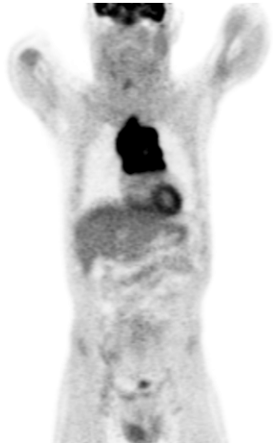
Baseline





Post chemo





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(2) Peri-transplant RT

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2 Facts about ASCT salvage

- Results of salvage ASCT after “R” is worse
  - Relapse after RCHOP defines a worse prognostic group
- CORAL study:
  - RR 51% v 83%
  - 3y EFS of 21 vs. 47%
  - Relapse < 1 year > Rituximab 1st line: particularly poor outcome

- Most recurrences after ASCT are in *previously involved sites*
- PARMA study results were obtained with IFRT

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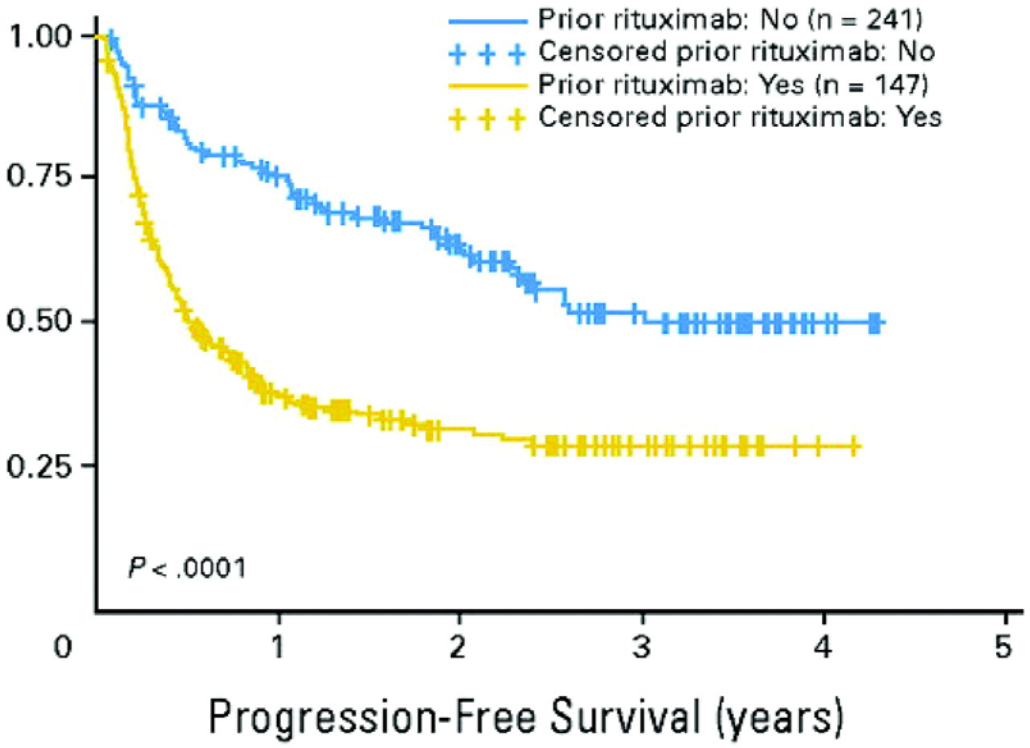
Salvage ASCT in Rituximab Era: CORAL study results.

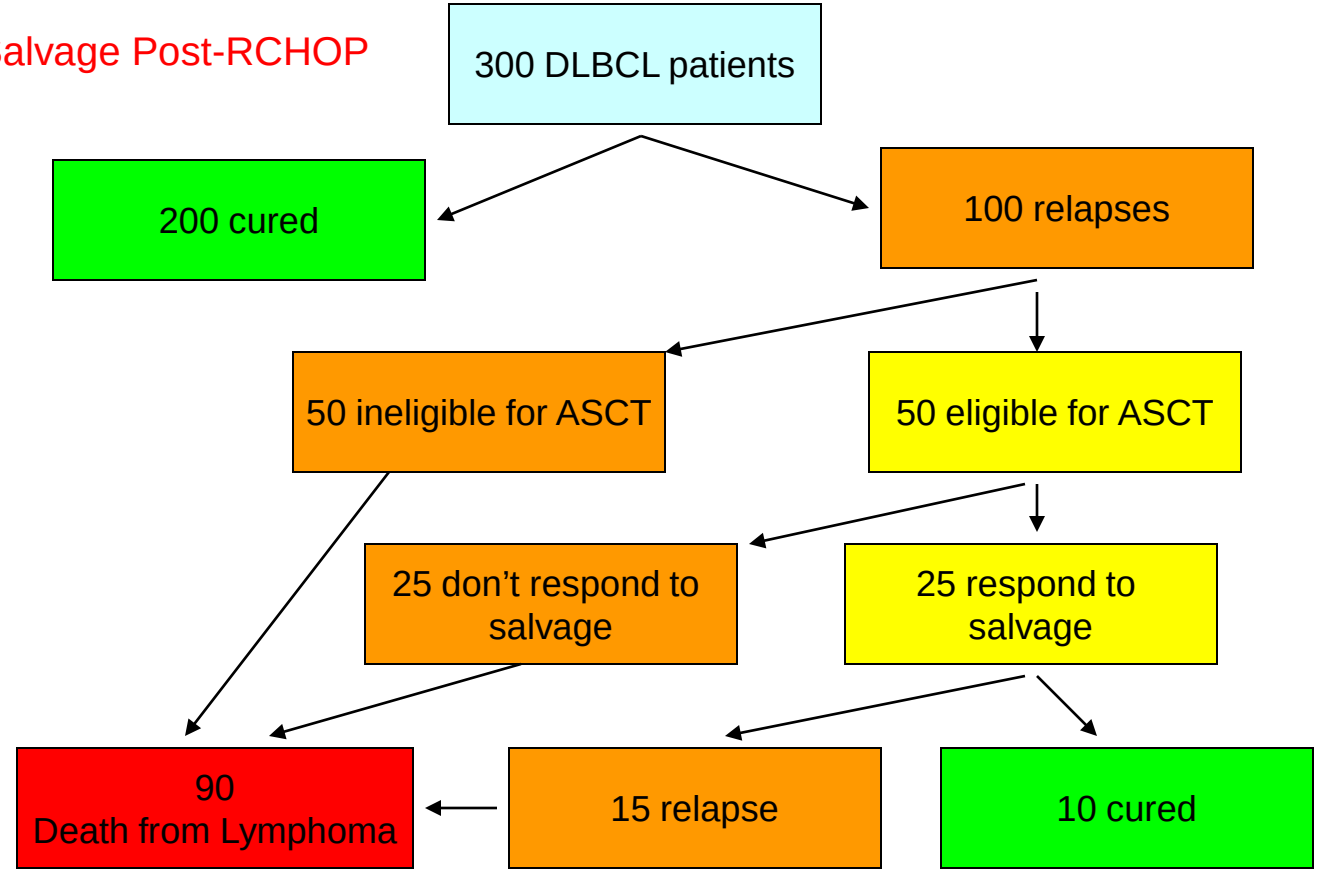


1/3 did not respond to salvage

½ did not get to ASCT

Friedberg J W Hematology 2011;2011:498-505

Salvage Post-RCHOP



Friedberg J W Hematology 2011;2011:498-505

Role of Peri-transplant RT

	Patient No: Total (RT)		Important findings
Poen 1996	100 (24)	92% LC	RFS & OS better (SS) in RT naive
Mundt 1997	53		•2/3 of relapse in old sites •RT improves LC in: all sites, persistent >induction, persistent >ASCT
Rappaport 1997	136 (51)		RT ↑ RFS if >2cm residual at time of transplant
Vose 2001	184 1ry refractory		Registry data No RT was an adverse prognostic factor on MVA
Biswas 2010	164 (79)	10% better LC	•**Survival** benefit for RT •**Benefit in RCHOP > CHOP**

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Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 1, pp. 79–85, 2010

0360-3016/10/$–see front matter

doi:10.1016/j.ijrobp.2009.04.036

CLINICAL INVESTIGATION **Lymphoma**

INVOLVED FIELD RADIATION AFTER AUTOLOGOUS STEM CELL TRANSPLANT FOR DIFFUSE LARGE B-CELL LYMPHOMA IN THE RITUXIMAB ERA

Tithi Biswas, M.D.,* Sughosh Dhakal, M.D.,* Rui Chen, Ph.D.,† Ollivier Hyrien, Ph.D.,† Steven Bernstein, M.D.,‡ Jonathan W. Friedberg, M.D.,‡ Richard I. Fisher, M.D.,‡ Jane Liesveld, M.D.,‡ Gordon Phillips, M.D.,‡ and Louis S. Constine*§

Departments of *Radiation Oncology, †Biostatistics, and ‡Medicine, Division of Medical Oncology, and §Pediatrics, University of Rochester Medical Center, Rochester, New York

Table 2. OS and DSS at 3-year and 5-year stratified by IFRT and rituximab

Period	R+/IFRT+ (n = 13)	R+/IFRT- (n = 20)	R minus/IFRT+ (n = 65)	R minus/no-IFRT (n = 66)
3-year OS	53%	21%	62%	50%
3-year DSS	50%	24%	64%	51%
5-year OS	53%	0%*	58%	41%
5-year DSS	50%	0%*	62%	46%

* 0% = At 5-years, patients were either censored or had died.

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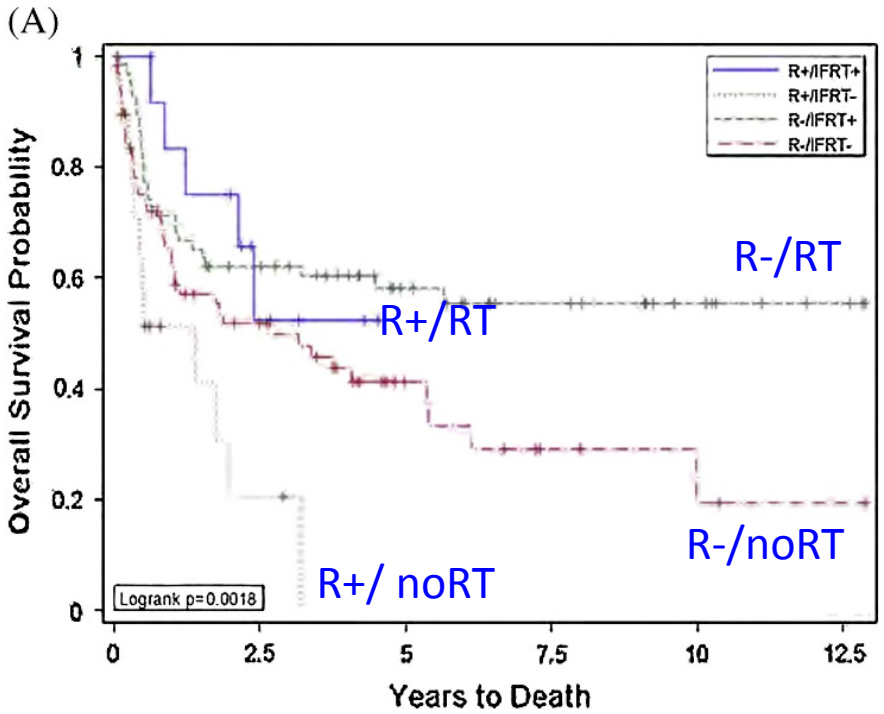
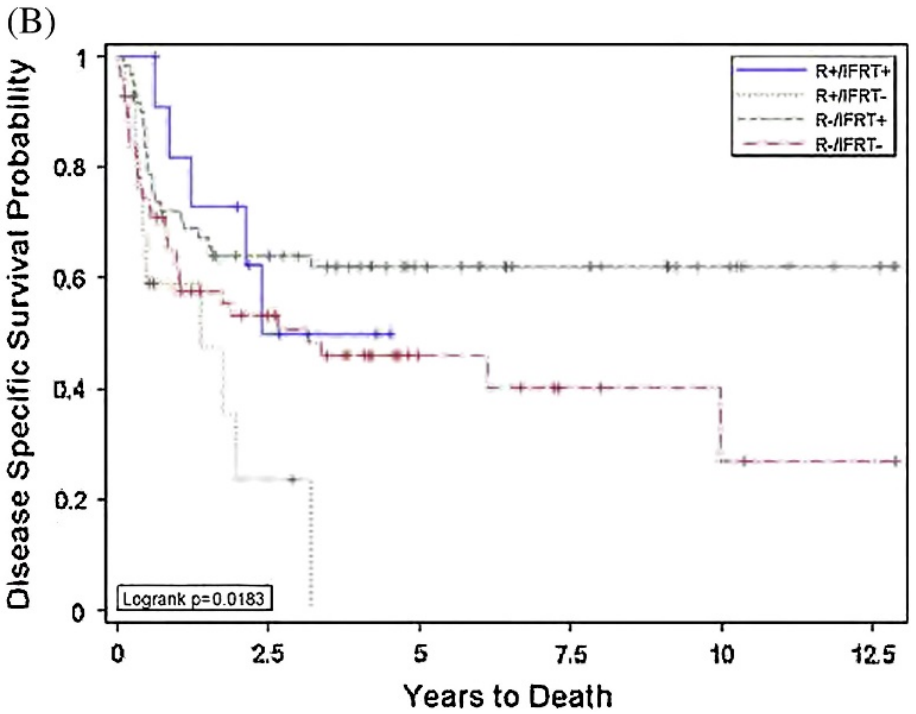
OS

DSS


(A)
Overall Survival Probability
1
0.8
0.6
0.4
0.2
0
R+/IFRT+
R+/IFRT-
R-/IFRT+
R-/IFRT-
R-/RT
R+/RT
R-/noRT
R+/ noRT
Logrank p=0.0018
0
2.5
5
7.5
10
12.5
Years to Death


(B)
Disease Specific Survival Probability
1
0.8
0.6
0.4
0.2
0
R+/IFRT+
R+/IFRT-
R-/IFRT+
R-/IFRT-
Logrank p=0.0183
0
2.5
5
7.5
10
12.5
Years to Death

Timing of peri-transplant RT

PRE- transplant

Pros:

- Cytoreduction if poor salvage chemo response
- Less haematological toxicity
- Ensures administration

Cons:

- Higher risk of pneumonitis
- Delay of HD chemo
- Requires good co-ordination

POST- transplant

Pros:

- Less pneumonitis
- Less GI toxicity / VOD
- No delay in giving HD chemo

Cons:

- More haematological toxicity:
  - Irradiating regenerating marrow
  - MDS / leukemogenic risk
- May be delayed or omitted if recovery is prolonged

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Choice

- Local expertise and practice
- Disease status / response to salvage
- Type & pattern of disease
  - HL v NHL
  - Localised v disseminated
- Site of RT
- Previous chemo, HD chemo

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(3) Relapse after transplant & transplant ineligible patients

Non transplant eligible

3 groups:

- Age / co-morbidities (up to ½ of relapses)

- Transplant eligible but lack of response to salvage (salvage refractory)

- Relapse after transplant (DFI, dis extent, previous RT)

  e.g. late localised relapse, no RT vs early relapse after RT or dissiminated

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What can RT achieve in refractory HG-NHL?

Without transplant:

- High response rate: 75-90%
- Durable LC: 50 – 65%
- Durable PFS in a small group, particularly localised disease and low IPI
- LC / cytoreduction may enable SCT in selected patients
- Excellent palliation with min toxicity

Salvage RT for *relapsed / chemorefractory* disease

Ref	No	patients	Local Control	PFS	Other findings
Aref 1999	35	chemoresitant	LC 47% @2y		Trend to better LC >39.6Gy
Martens 2006	34	Chemo-resistant Twice-daily RT	LC 73% @3y	PFS 15% @3y	ORR 97% (CR 24%, Cru 26%, PR 47%)
Halasz 2012	59	PET+ (interim or post-CT)	3y LC 90% v 100% In PET+ v PET-	3y PFS 90% v 97%	

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International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Rates and Durability of Response to Salvage Radiation Therapy Among Patients With Refractory or Relapsed Aggressive Non-Hodgkin Lymphoma

Yolanda D. Tseng, MD,* Yu-Hui Chen, MS, MPH,† Paul J. Catalano, ScD,†,‡ and Andrea Ng, MD, MPH§

**Department of Radiation Oncology, University of Washington, Seattle, Washington; †Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, Massachusetts; ‡Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts; and §Department of Radiation Oncology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts*

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110 pts, 121 sites. mFU 4.6y

IJROBP, 2015

Table 1 Patient demographic and disease characteristics among patients treated with curative (n=72, 76 sites) and palliative intent (n=38, 45 sites)

Characteristic	Treatment intent: Curative n	Curative %	Palliative n	Palliative %	Total n	Total %
Age at diagnosis (y)* (median and range)	54	19-88	62.5	32-86	55	19-88
Refractory/relapsed						
Refractory	45	63	30	79	75	68
Relapsed	27	38	8	21	35	32
Gender						
Female	28	39	16	42	44	40
Male	44	61	22	58	66	60
Histology						
Diffuse large B-cell lymphoma	56	78	29	76	85	77
Grade 3 follicular lymphoma	5	7	2	5	7	6
T cell lymphoma	3	4	2	6	5	5
Other†	8	11	5	13	13	12

2/3

1/3

2/3

1/3

3/4

Median dose for curative = 40Gy

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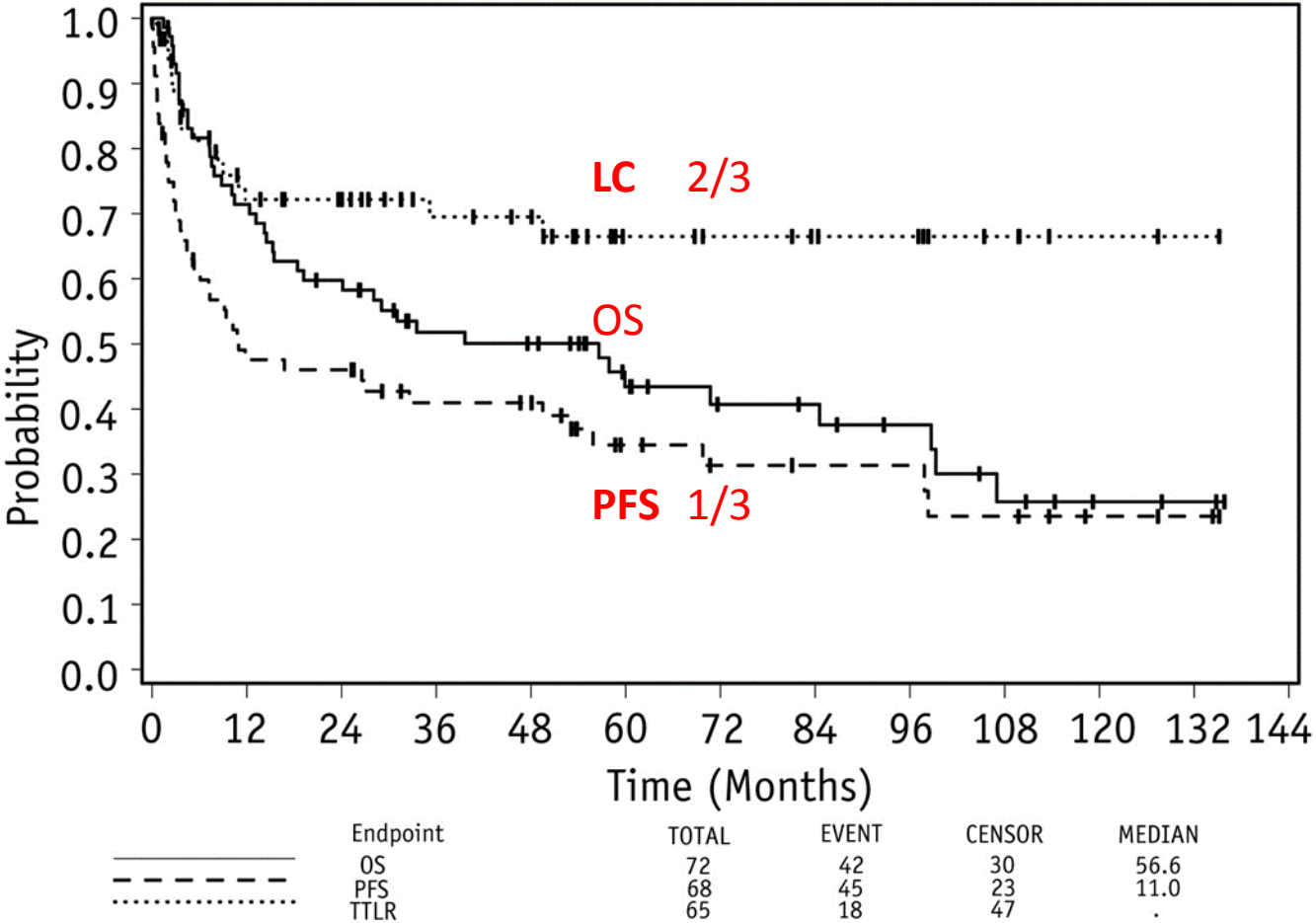

RR 85%

No dose response </> 40Gy

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Implications

- Salvage RT is an option in localized refractory / relapsed DLBCL:
  - Definitive salvage in transplant ineligible pts
  - Additional treatment for transplant eligible pts

- Use of RT in salvage chemotherapy / transplant trials should be controlled for.

- Remaining questions:
  - Can Dose escalation improve outcome of Refractory or Resistant disease?
  - Does higher tumor volume require higher dose?
  - What is the size of ref/rel population that could be salvaged by RT?

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Key points

- Localised PET+ residual disease can be salvaged with RT in selected cases
- Consolidation RT is an option Peri-transplant for selected patients (improves PFS & ?OS)
- Salvage RT is an option for localised chemoresistant disease (durable LC 2/3, PFS 1/3)
- Palliative RT is effective in chemoresistant disease (50 – 80% RR)
- Higher doses are required for resistant disease

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Aggressive nodal NHL, the role of RT: **volume, dose and technique**

Berthe Aleman

Radiation oncologist

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

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Aggressive nodal NHL, the role of radiotherapy: volume, dose and technique

Curative radiotherapy

- Early stage
- Advanced stage
- Relapsed/refractory disease

Palliative radiotherapy

Aggressive nodal NHL – early stage
Target volume

- Past: involved field radiotherapy +/- boost on bulk or residual disease
- Present: involved site radiotherapy +/- boost on bulk or residual disease

Aggressive nodal NHL – early stage
Target volume

CTV:

- Pre-chemotherapy (or pre-surgery) Gross Tumor Volume (GTV)
- Changes in normal anatomy after initial treatment response should be taken into account
- Potential Boost CTV: post-chemotherapy GTV (based op PET-CT-scan)

Illidge et al, IJROBP 2015

Aggressive nodal NHL – advanced stage
Target volume

CTV

- Pre-chemotherapy bulky Gross Tumor Volume (GTV)
- Post-chemotherapy residual mass containing PET positive areas on post-chemotherapy scan
- Potential Boost CTV: post-chemotherapy GTV (on PET-CT-scan)

Illidge et al, IJROBP 2015

Aggressive nodal NHL – refractory disease

Target volume

GTV:

- Site(s) of refractory disease

CTV:

- Usually only site(s) of refractory disease with margin for microscopical disease

Illidge et al, IJROBP 2015

RT Dose

Phase III Trial on RT Dose

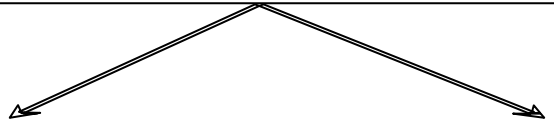
640 Sites of Aggressive NHL

82% DLBCL

86 % stage III-IV

80% as post-chemo consolidative RT

10% received Rituximab



30 Gy in 15 fractions

40-45 Gy in 20-23 fractions

Lowry et al. Rad Onc 2011

30 Gy vs 40-45 Gy

- Median f/u 5.6 years

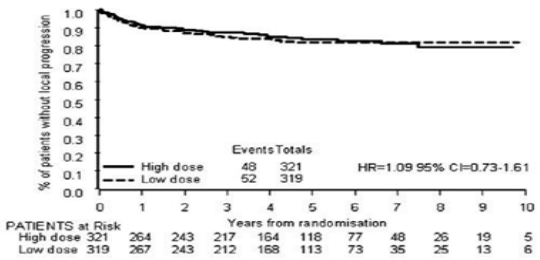
	30 Gy (n=319)	40-45 Gy (n=321)	P-value
5y FFLP	82%	85%	0.66
5y OS	64%	68%	0.29

FFLP: Freedom from local progression; OS: Overall Survival

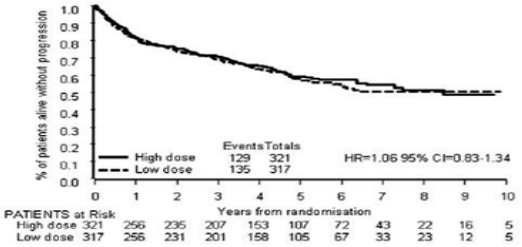
Lowry et al. Rad Onc 2011

Aggressive group

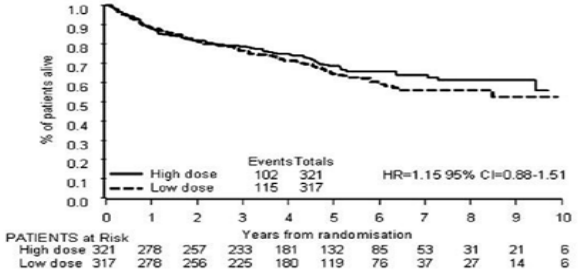
Freedom from local progression



Progression-free survival



Overall survival



Caveats:

- Included pts treated with RT receiving salvage/palliative RT
- No chemo data
- Systemic treatment mostly without rituximab
- Lack of functional imaging of response to chemo

Lowry et al. Rad Onc 2011

CR to Chemo

Study	# Pts in CR	Chemo	Med fu	Response assessment	RT Dose (Gy)	LC
Zinzani, 1999	38	MACOP-B	39 mo	Gallium	30-36	100%
Kahn, 2006	16	CHOP x 4-6	40 mo	PET	Med: 30.6	100%
Halasz, 2010	39	R-CHOP	46.5 mo	PET	Med: 36	100%
Phan, 2010	142	R-CHOP in 70%	36 mo	PET	If no residual CT dz: 30 If > 5 cm or dz: 36-39.6	100%
Dorth, 2012	79	R-CHOP in 65%	56 mo	Gallium (14%) or PET (73%)	Med: 25	92%
Shi, 2013	14	R-CHOP	32.9	PET (85%)	Med: 30.6	92%

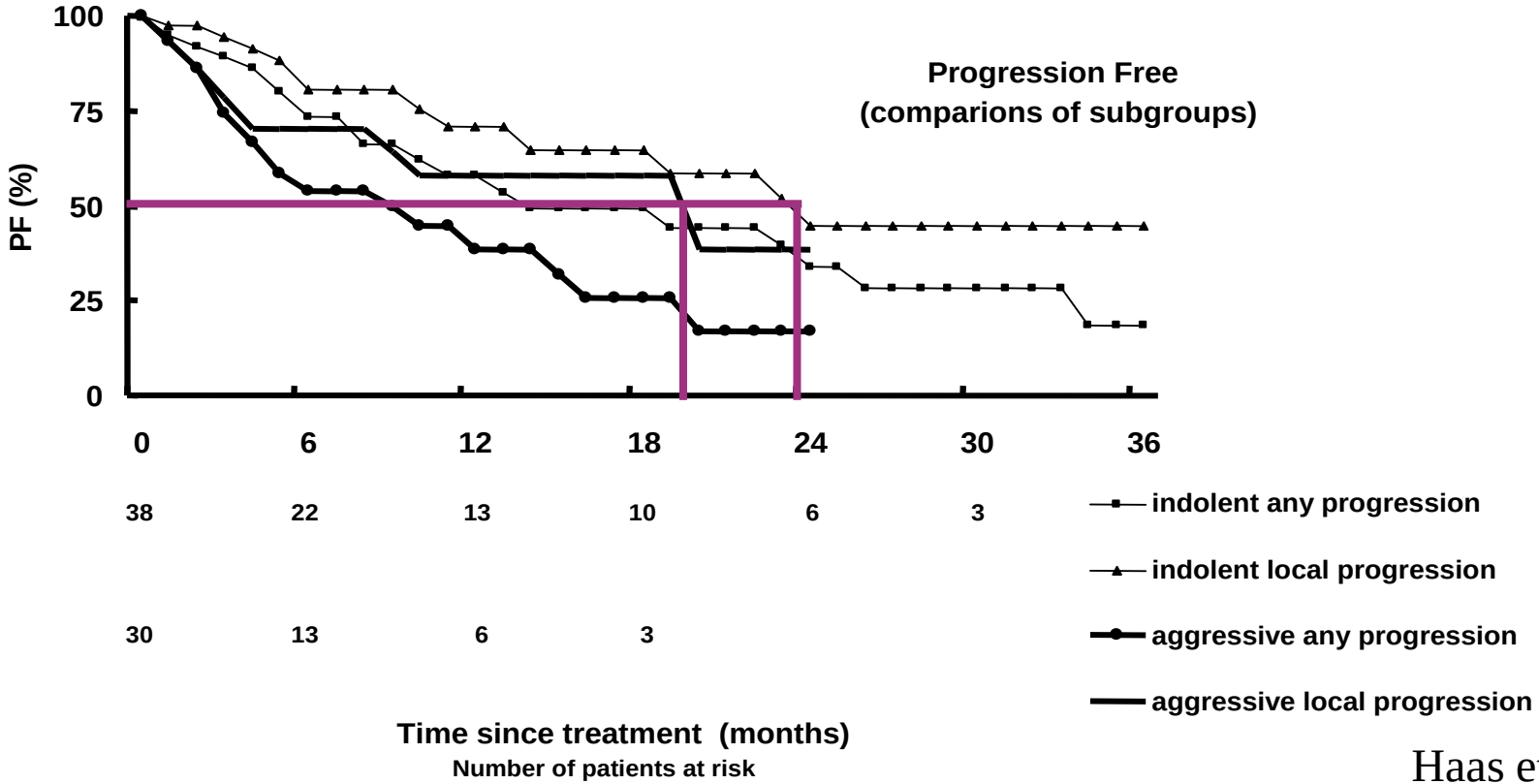
Courtesy: Andrea Ng

Palliative radiotherapy

- RT of nodal areas in case chemotherapy is not feasible/indicated
  - 2x2 Gy – response rate ±80% (CR ±35%)

Haas et al, EJC 2005

LD-IF-RT in other B-cell malignancies; results according to histological subtype



Haas et al, EJC 2005

Palliative radiotherapy

- RT of nodal areas in case chemotherapy is not indicated
  - 2x2 Gy – response rate ±80% (CR ±35%)
  - Schedule equivalent to 10-12x3 Gy

Summary RT Dose to aggressive Nodal NHL

Setting	RT Dose
CR to Chemo	30-36 Gy (1.8- 2 Gy/Fx)
PR to Chemo	40 Gy (1.8-2 Gy/Fx)
Post-ASCT	30-40 Gy (1.8-2 Gy/Fx)
Primary refractory	45-55 Gy (1.8-2 Gy/Fx)
Palliative	4 Gy (2-4 Gy/Fx) 30-36 Gy (3 Gy/Fx)

RT technical isssues

RT technique

- Same as in Hodgkin lymphoma and indolent NHL

Constraints

- Since many patients are > 60 years second malignancy risk is usually not an issue
- OAR usually lungs, heart, kidneys, bowels

Illidge et al, IJROBP 2015

Aggressive nodal NHL- early stage
Principles of ISRT for Nodal Sites

- CT or PET/CT information of pre-chemotherapy disease (ideally in treatment position)
- Planning requirements: CT-based simulation
- Goal to target site of originally involved lymph node(s)
  - Field encompasses the original volume prior to surgery or chemotherapy
  - Spares uninvolved organs once lymph node has regressed
  - Imaging modalities such as PET and MRI can enhance

Courtesy: Terezakis

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Questions?

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Myeloma:
Solitary & Disseminated

Umberto Ricardi
University of Torino
Department of Oncology

Multiple myeloma

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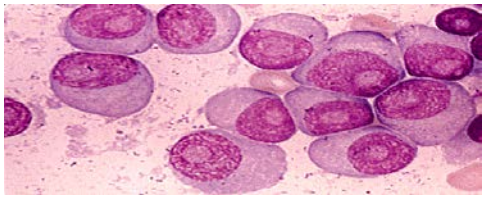
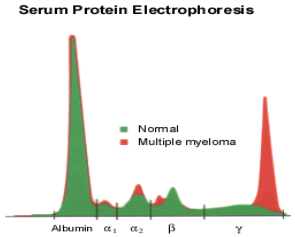


Multiple myeloma



Multiple myeloma is a neoplastic plasma-cell disorder that is characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, and associated organ dysfunction

It accounts for approximately 1% of neoplastic diseases and 13% of hematologic malignancies

In Western countries, the annual age-adjusted incidence is 5.6 cases per 100,000 persons

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The median age at diagnosis is approximately 70 years; 37% of patients are younger than 65 years, and 37% are 75 years of age or older

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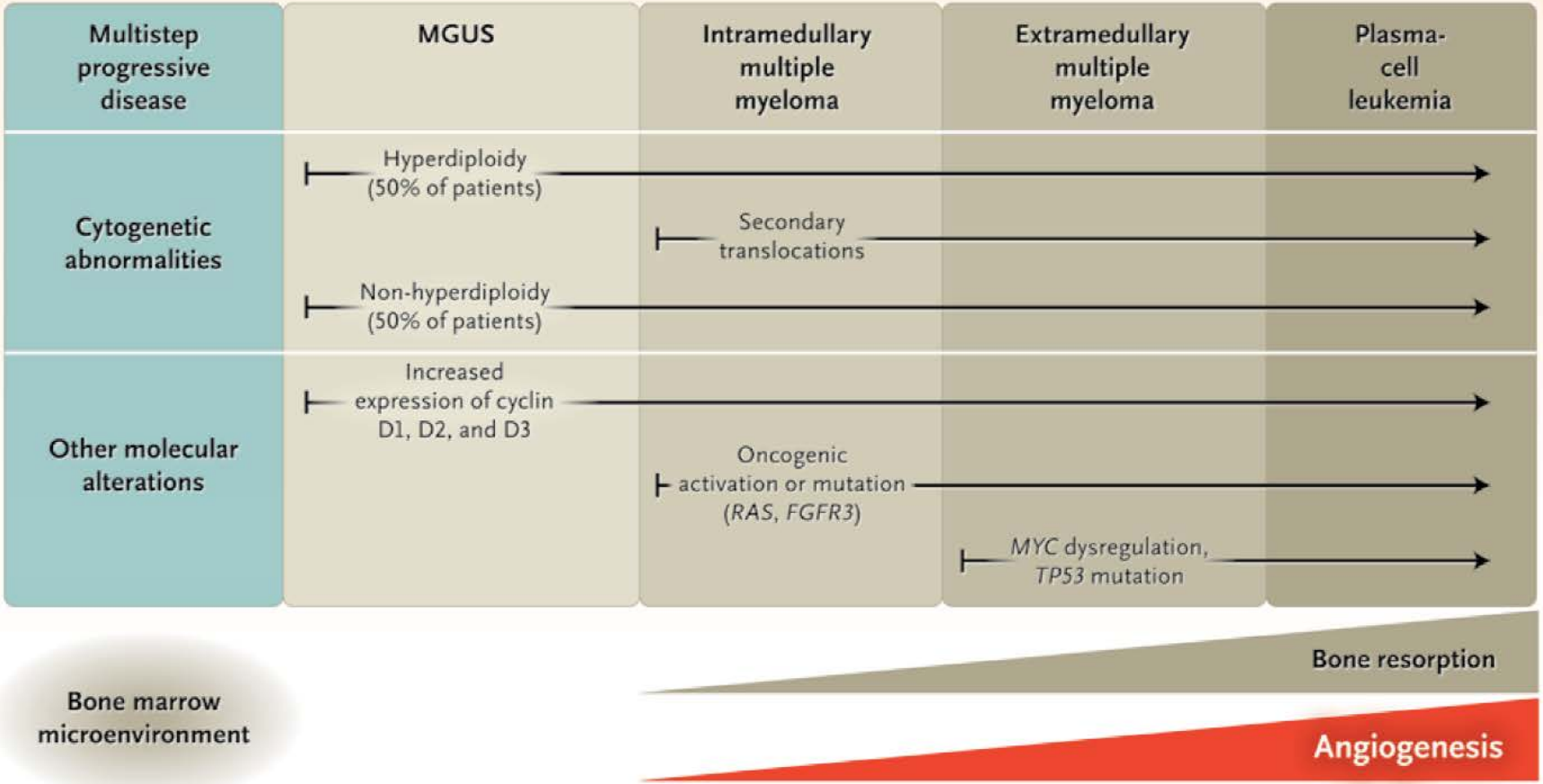
Myeloma arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post-germinal-center B cells

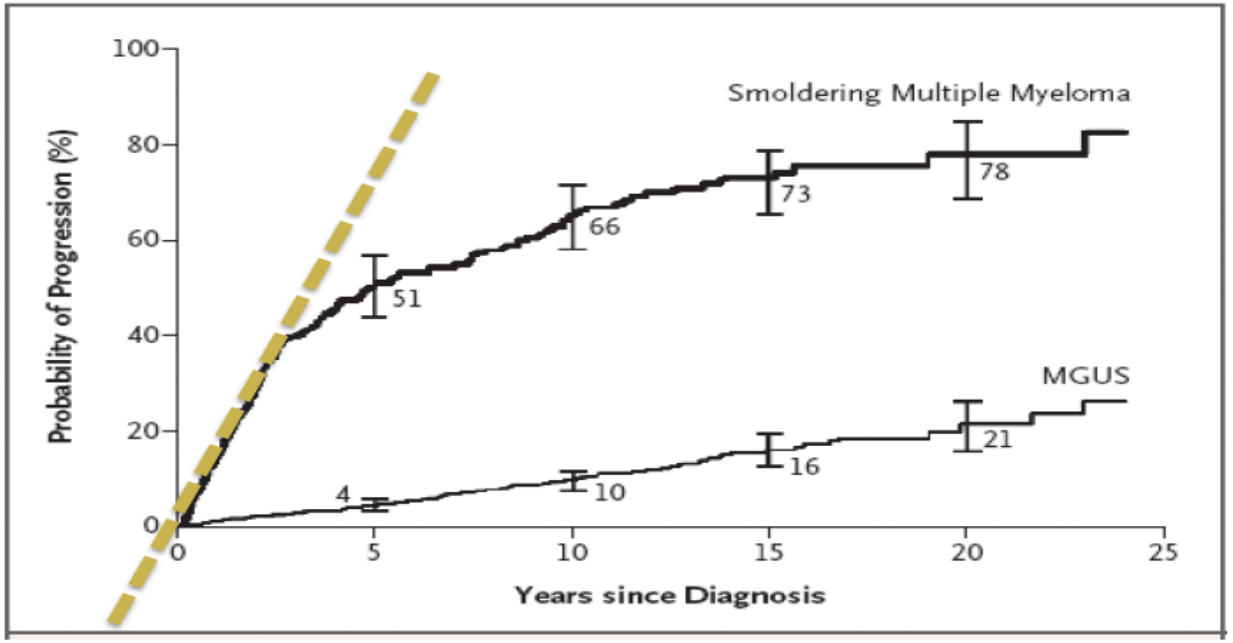
Multistep genetic and microenvironmental changes lead to the transformation of these cells into a malignant neoplasm

Myeloma is thought to evolve most commonly from a monoclonal gammopathy of undetermined clinical significance **(MGUS)** that progresses to **smoldering myeloma** and, finally, to **symptomatic myeloma**



Antonio Palumbo, M.D., and Kenneth Anderson, M.D. **N Engl J Med 2011;364:1046-60.**

High-Risk Smoldering Myeloma Cannot be Ignored*



*Kyle RA, et al. N Engl J Med. 2007;356:2582-2590.

Clinical presentation, diagnosis and staging

The diagnosis of myeloma is based on the presence of at least 10% clonal bone marrow plasma cells and monoclonal protein in serum or urine

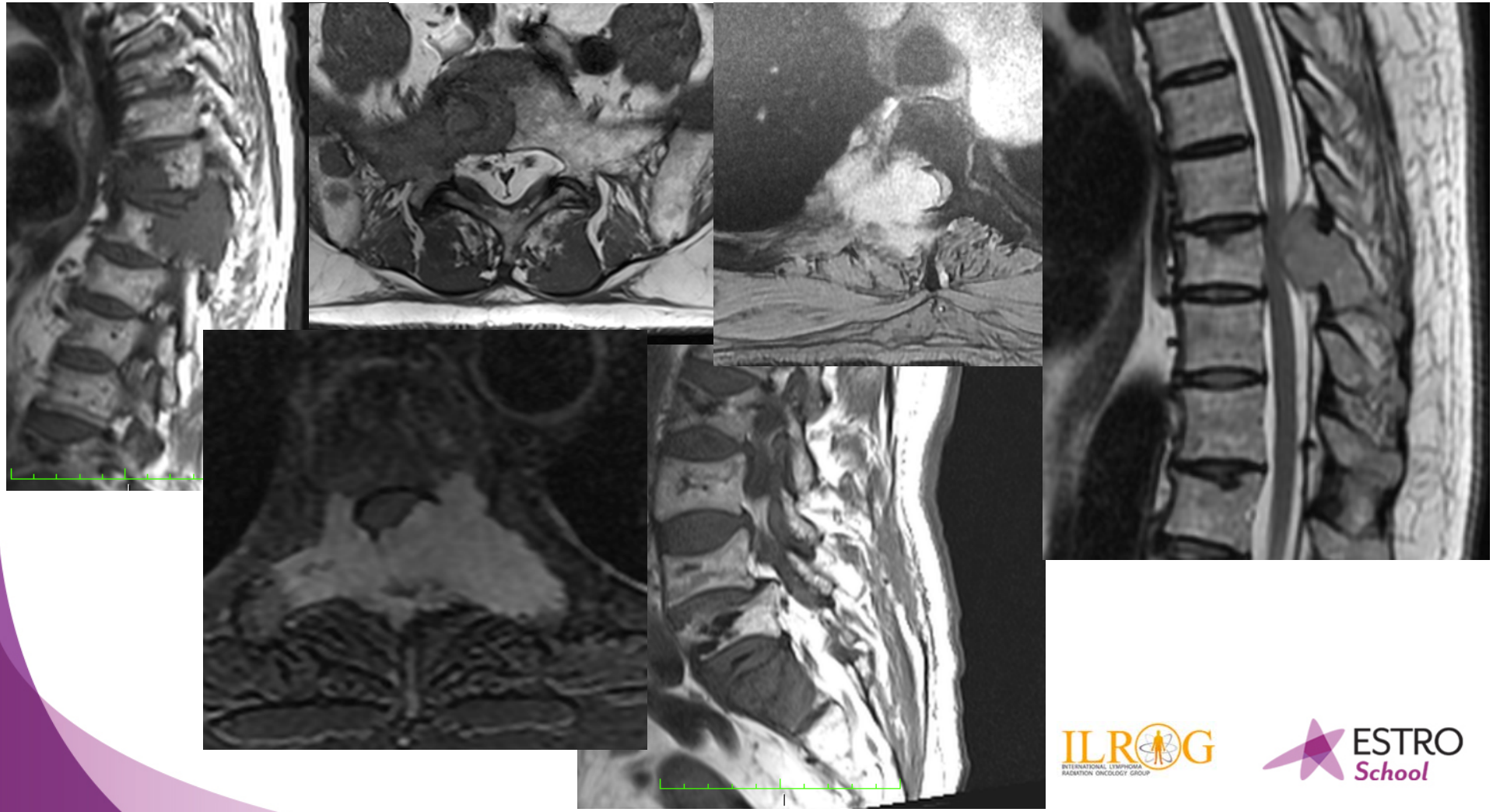
In patients with true nonsecretory myeloma, the diagnosis is based on the presence of 30% monoclonal bone marrow plasma cells or a biopsy-proven plasmacytopma

Clinical presentation, diagnosis and staging

Myeloma is classified as asymptomatic or symptomatic, depending on the absence or presence of myeloma-related organ or tissue dysfunction, including:

- hypercalcemia
- renal insufficiency
- anemia
- bone disease

CRAB criteria



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VOLUME 29 · NUMBER 28 · OCTOBER 1 2011

JOURNAL OF CLINICAL ONCOLOGY

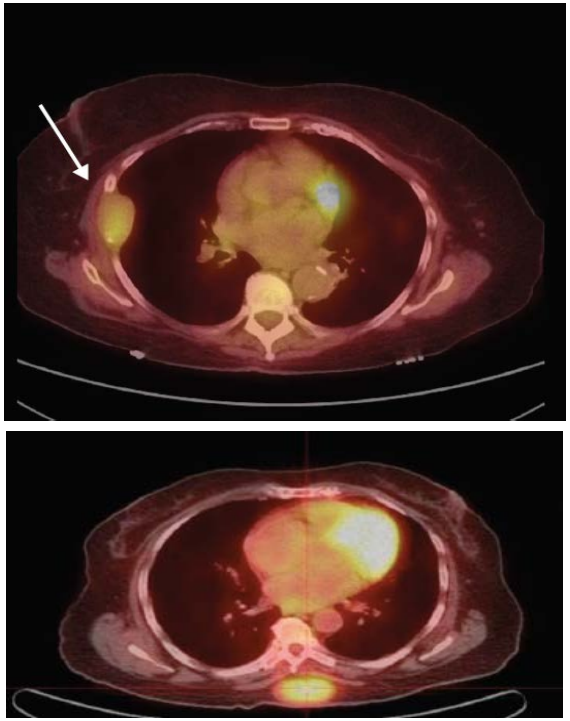
REVIEW ARTICLE

Soft-Tissue Plasmacytomas in Multiple Myeloma: Incidence, Mechanisms of Extramedullary Spread, and Treatment Approach

Joan Bladé, Carlos Fernández de Larrea, Laura Rosiñol, María Teresa Cibeira, Raquel Jiménez, and Ray Powles

Table 1. Extramedullary Myeloma: Growth and Location

Mechanism	Location
Local growth	Soft-tissue masses arising from focal bone involvement (vertebrae, ribs, sternum, skull)
Hematogenous spread	Single or multiple large subcutaneous tumors Multiple nodules (skin, liver, breast, kidney) Lymph nodes CNS
Triggered by invasive surgical procedures	Surgical scars (laparotomy, catheter insertions) Bone surgery and/or fractures (extensive local spread)



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Diagnostic evaluation

Diagnosis

- Medical history and physical examination
- Routine testing: complete blood count, chemical analysis with calcium and creatinine, serum and urine protein electrophoresis with immunofixation, quantification of serum and urine monoclonal protein, measurement of free light chains
- Bone marrow testing: trephine biopsy and aspirate of bone-marrow cells for morphologic features; cytogenetic analysis and fluorescence in situ hybridization for chromosomal abnormalities
- Imaging: skeletal survey, magnetic resonance imaging if skeletal survey is negative

Prognosis

- Routine testing: serum albumin, β_2-microglobulin, lactate dehydrogenase

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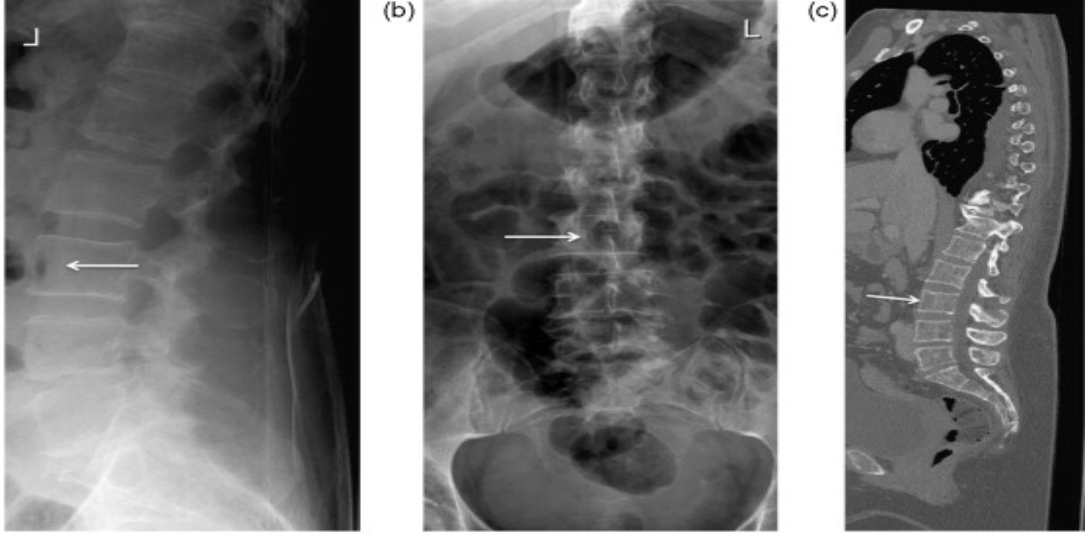
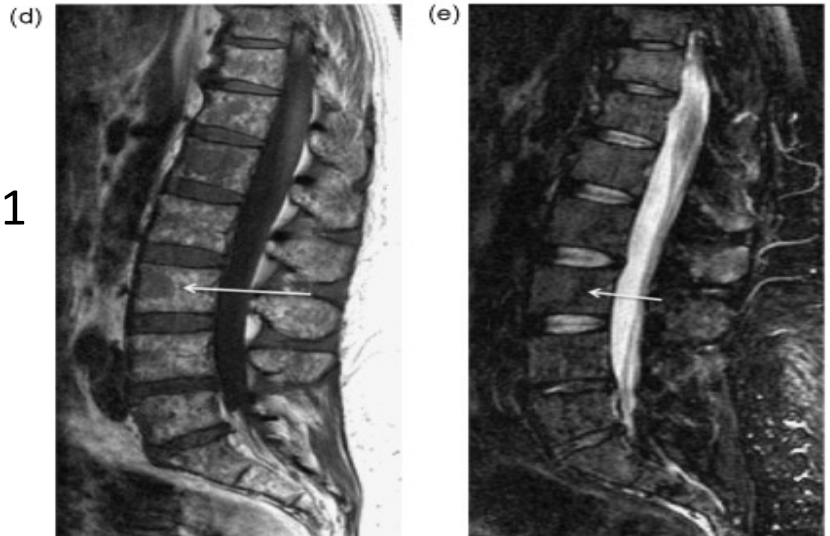
X-Ray plain films:
skeletal survey



whole-body
low-dose CT
(WBCT)

MRI T1



MRI T2

Diagnostic evaluation

Diagnosis

- Medical history and physical examination
- Routine testing: complete blood count, chemical analysis with calcium and creatinine, serum and urine protein electrophoresis with immunofixation, quantification of serum and urine monoclonal protein, measurement of free light chains
- Bone marrow testing: trephine biopsy and aspirate of bone-marrow cells for morphologic features; cytogenetic analysis and fluorescence in situ hybridization for chromosomal abnormalities
- Imaging: skeletal survey, magnetic resonance imaging if skeletal survey is negative

Prognosis

- Routine testing: serum albumin, β_2-microglobulin, lactate dehydrogenase

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Stage	Durie-Salmon staging system (55)	International staging system (56)
I	All of the following: Hemoglobin >10 g/dl Serum calcium ≤12 mg/dl No myeloma-related bone lesions (solitary plasmacytoma excepted) Low M-protein concentration (IgG <5 g/dl, IgA <3 g/dl, and Bence Jones protein <4 g/24 h)	β_2-microglobulin <3.5 mg/L Albumin >3.5 g/dl
II	Neither stage I nor stage III	Neither stage I nor stage III
III	One or more of the following: Hemoglobin <8.5 g/dl Serum calcium >12 mg/dl Extensive lytic bone lesions High M-protein concentration (IgG >7 g/dl, IgA >5 g/dl, or Bence Jones protein >12 g/24 h)	β_2-microglobulin >5.5 mg/L

Subclassification:

Normal renal function (serum creatinine <2.0 mg/dL)

Abnormal renal function (serum creatinine ≥2.0 mg/dL)

MST: **Stage I 62 months**
Stage II 44 months
Stage III 29 months

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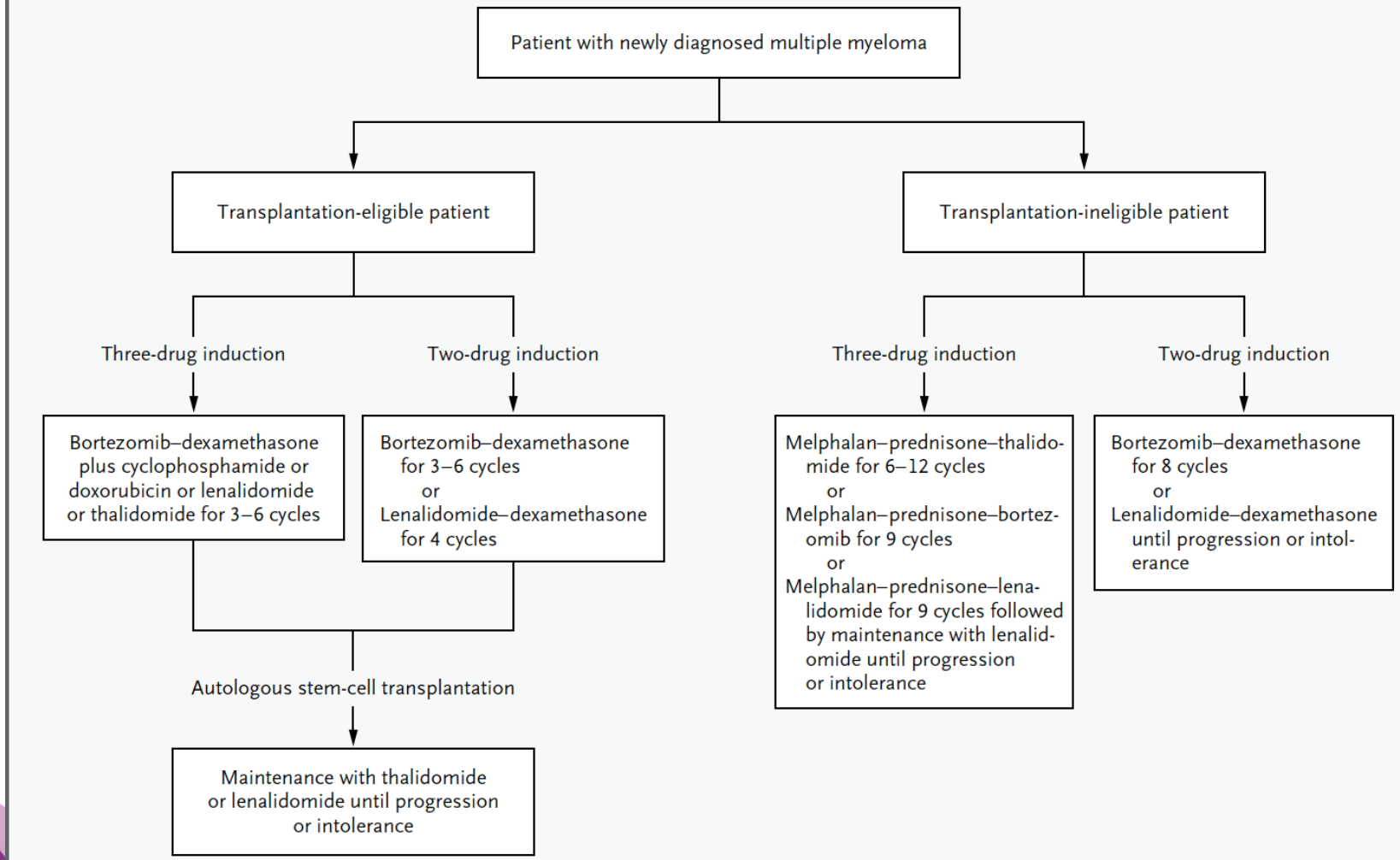
Treatment

Symptomatic (active) disease should be treated immediately, whereas asymptomatic (smoldering) myeloma requires only clinical observation, since early treatment with conventional chemotherapy has shown no benefit

Investigational trials are currently evaluating the ability of immunomodulatory drugs to delay the progression from smoldering myeloma to symptomatic myeloma

The treatment strategy is mainly related to age


Patient with newly diagnosed multiple myeloma
Transplantation-eligible patient
Transplantation-ineligible patient
Three-drug induction
Two-drug induction
Three-drug induction
Two-drug induction
Bortezomib–dexamethasone plus cyclophosphamide or doxorubicin or lenalidomide or thalidomide for 3–6 cycles
Bortezomib–dexamethasone for 3–6 cycles or Lenalidomide–dexamethasone for 4 cycles
Melphalan–prednisone–thalidomide for 6–12 cycles or Melphalan–prednisone–bortezomib for 9 cycles or Melphalan–prednisone–lenalidomide for 9 cycles followed by maintenance with lenalidomide until progression or intolerance
Bortezomib–dexamethasone for 8 cycles or Lenalidomide–dexamethasone until progression or intolerance
Autologous stem-cell transplantation
Maintenance with thalidomide or lenalidomide until progression or intolerance

Treatment

Current data would support the initiation of induction therapy with thalidomide, lenalidomide, or bortezomib, plus hematopoietic stem-cell transplantation for fit patients under the age of 65 years

Autologous stem-cell transplantation with a reduced-intensity conditioning regimen should be considered for older patients or those with coexisting conditions

Conventional therapy combined with thalidomide, lenalidomide or bortezomib should be administered in patients older han 65 years

Less intensive approaches should be considered in patients over 75 years

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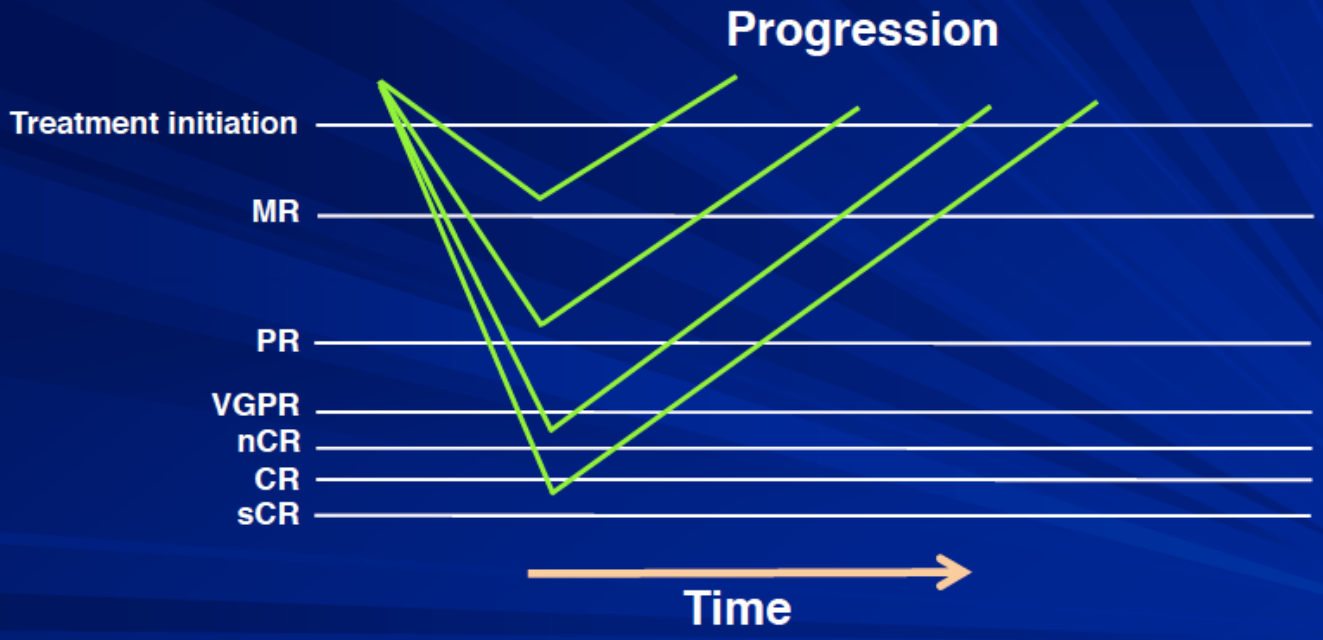
Depth of response



Depth of response is related to TTP

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Radiotherapy in MM

In patients with MM and symptomatic bone disease, significant relief of pain can be achieved with palliative radiotherapy

Radiotherapy can also be used for relief/prevention of neurological symptoms due to spinal cord or nerve root compression

Radiotherapy can be used in MM for prevention - or consolidation after orthopedic stabilization - of a pathologic fracture in the case of severe destruction of the cortical bone (impending fracture)

Radiation doses ranging from 8 Gy in 1 fraction up to 30 Gy in 10 fractions are commonly used

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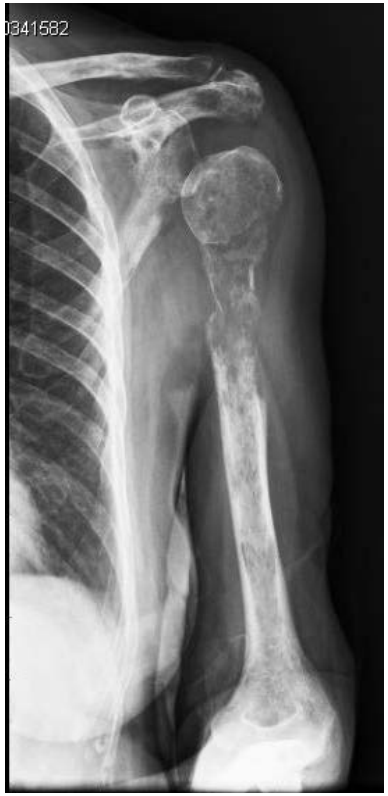
Role of Radiotherapy in MM

- Prompt and highly effective modality in the palliation of of painful bony lesions and mass effects from soft tissue extensions
- Efficacy in the control of lytic bone lesions and in reversing the morbidity of spinal cord and nerve root compression
- 30 Gy in 10 fractions or 40 to 45 Gy in 4 to 4.5 weeks to the lesions with generous margins; 8 Gy/1 fraction may be used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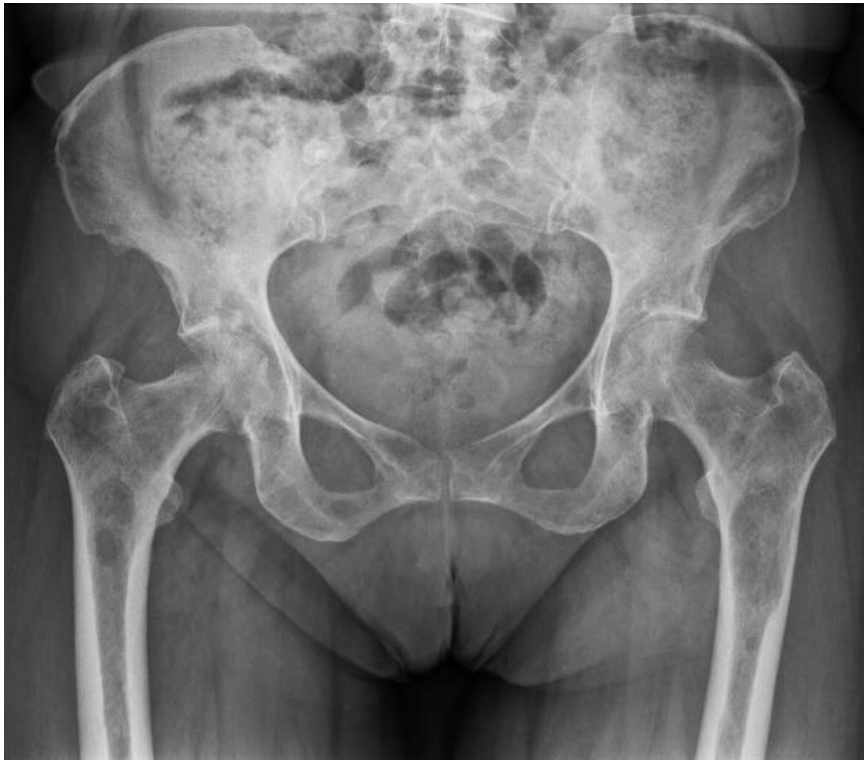
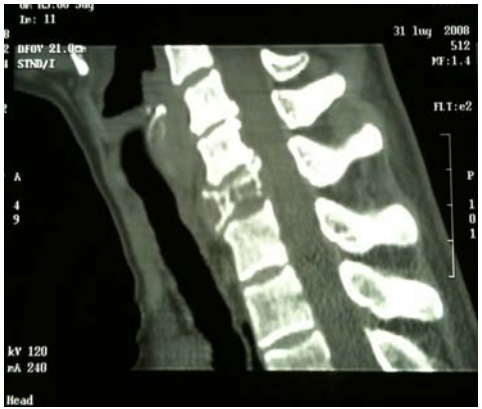
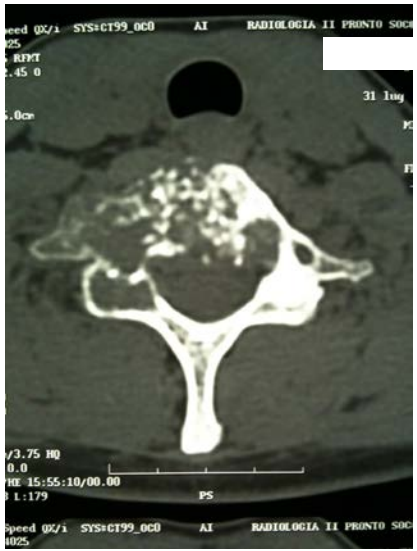
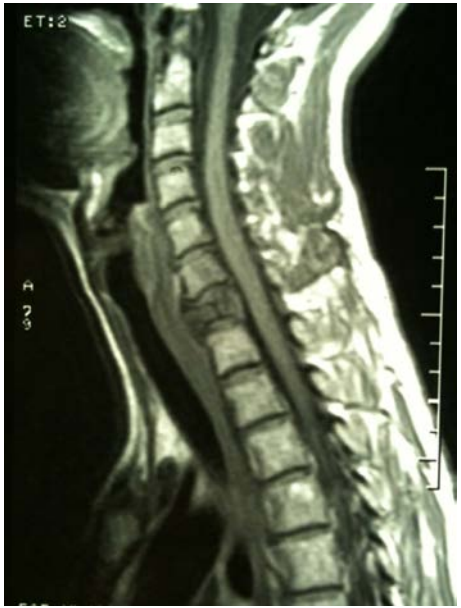


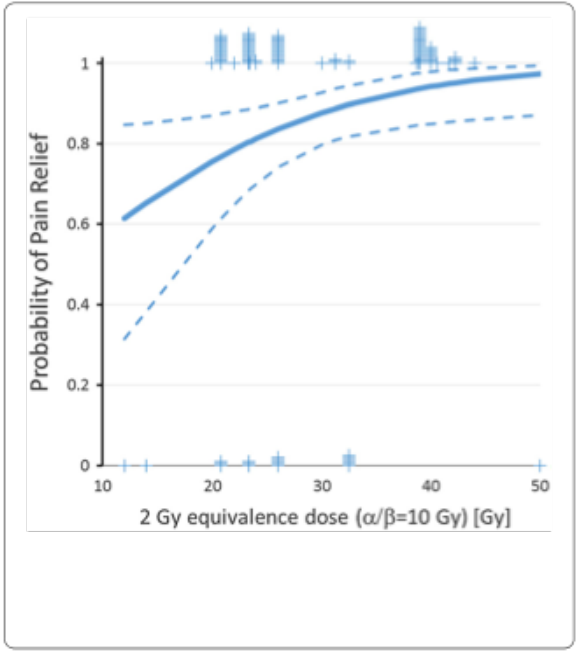
- solitary vertebral body lesion (C7) in MM







Effects of Radiotherapy in the treatment of multiple myeloma: a retrospective analysis of a Single Institution



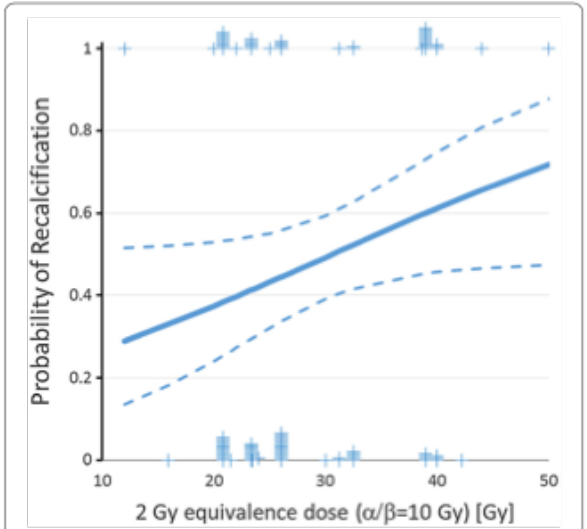


Figure 3 Binary logistic regression analysis of dose effects on recalcification ($\alpha/\beta = 10$ Gy, $p = 0.048$. Dotted lines indicate the 95% confidence limits of the regression line. Tick marks indicate the number of events (0 or 1) at the respective dose.

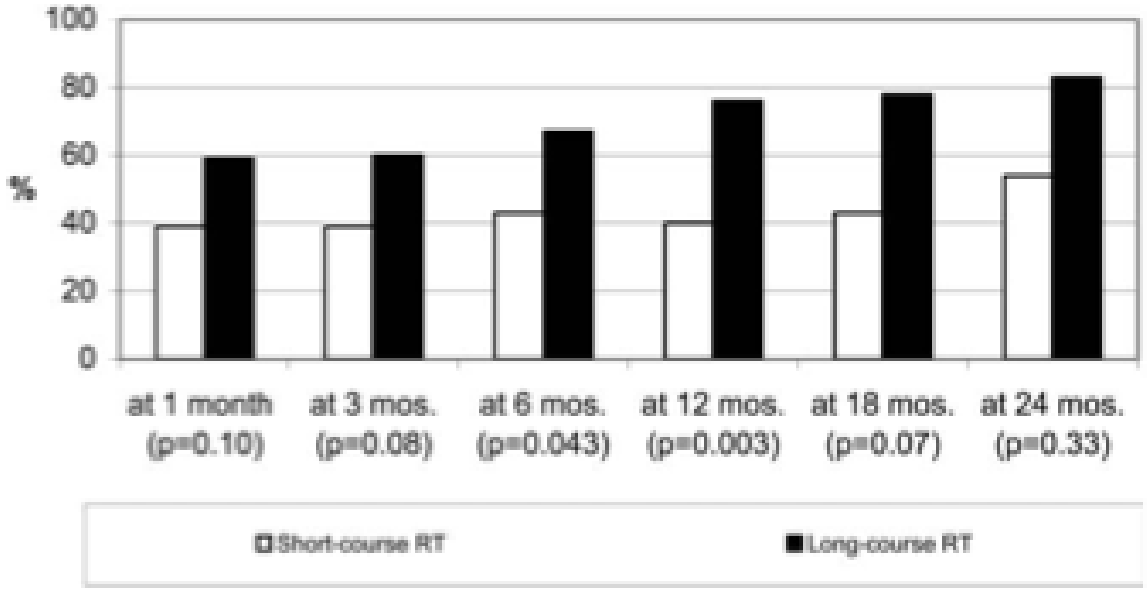
- 153 patients
- 1989-2013

Conclusions:
higher total biological RT dose were associated with better pain relief (**≥30 Gy**) and recalcification (**≥40 Gy**)

Matuschek et al Radiat Oncol 2015;10:71

SHORT-COURSE RADIOTHERAPY IS NOT OPTIMAL FOR SPINAL CORD COMPRESSION DUE TO MYELOMA

IMPROVEMENT OF MOTOR FUNCTION AFTER RADIOTHERAPY



- 172 patients
- 1994-2004

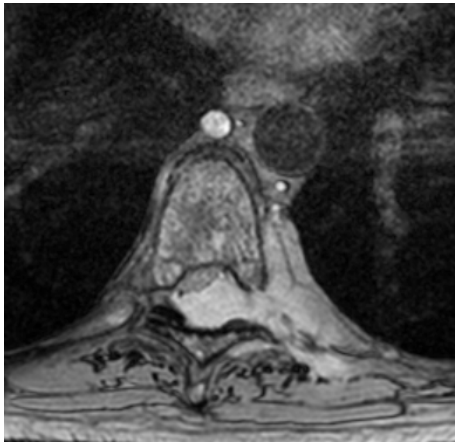
- Short course RT:
  - 8 Gy in single fraction
  - 20 Gy/5 fractions

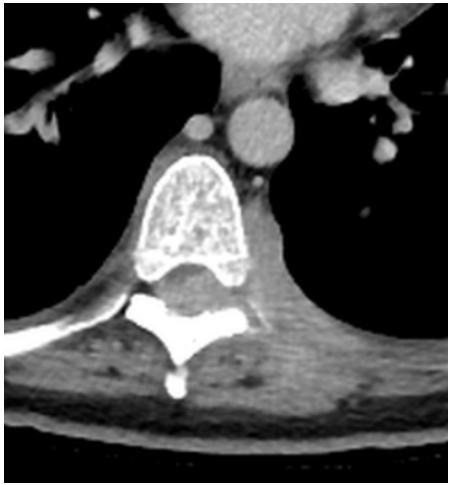
- Long course RT:
  - **30 Gy/10 fractions**
  - **37.5 Gy/15 fractions**
  - **40 Gy/20 fractions**

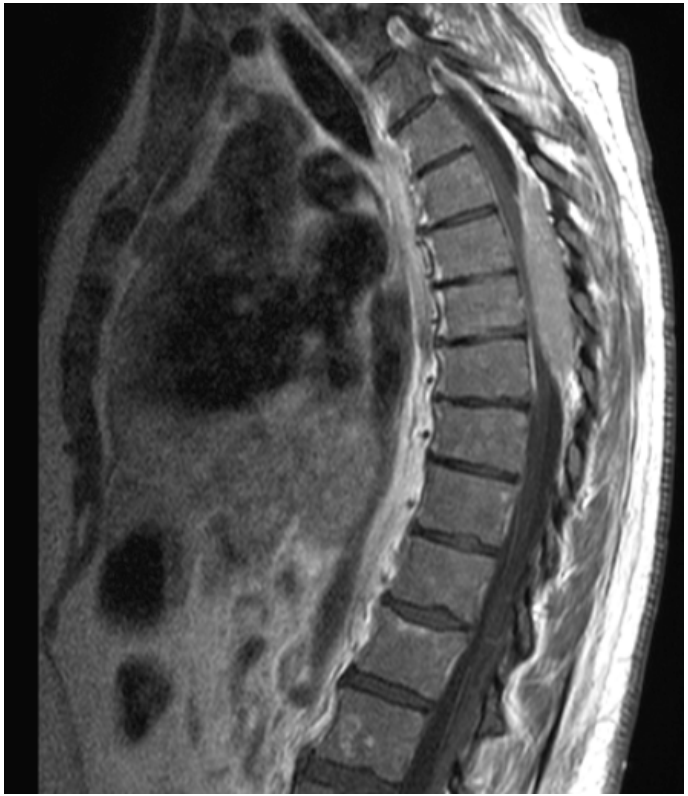
Rades et al IJROBP 2006;64(5):1452-1457

Palliative RT for Multiple Myeloma @ University of Torino

- 40 years old female
- No previous history of cancer.
- Abrupt dorsal pain + left leg weakness and paresthesia that required hospitalization
- Lab: anemia, BJ and M protein elevated
- BM: PC involvement 90%
- **First clinical event of MM**







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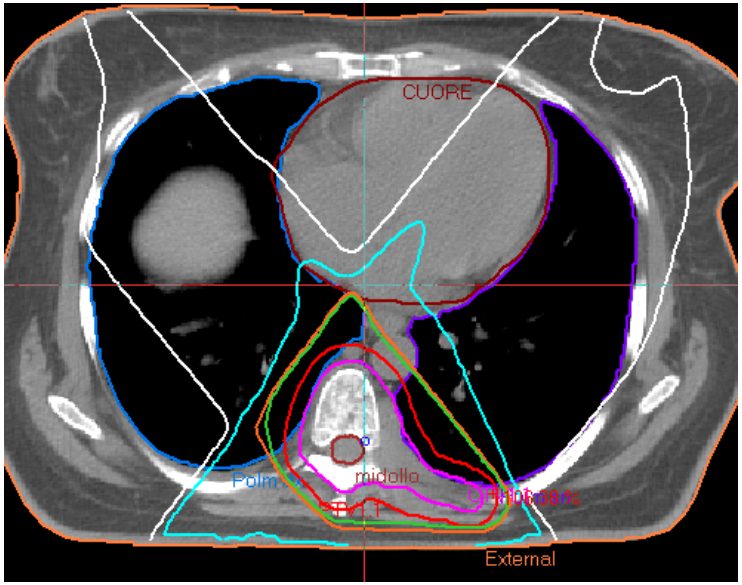
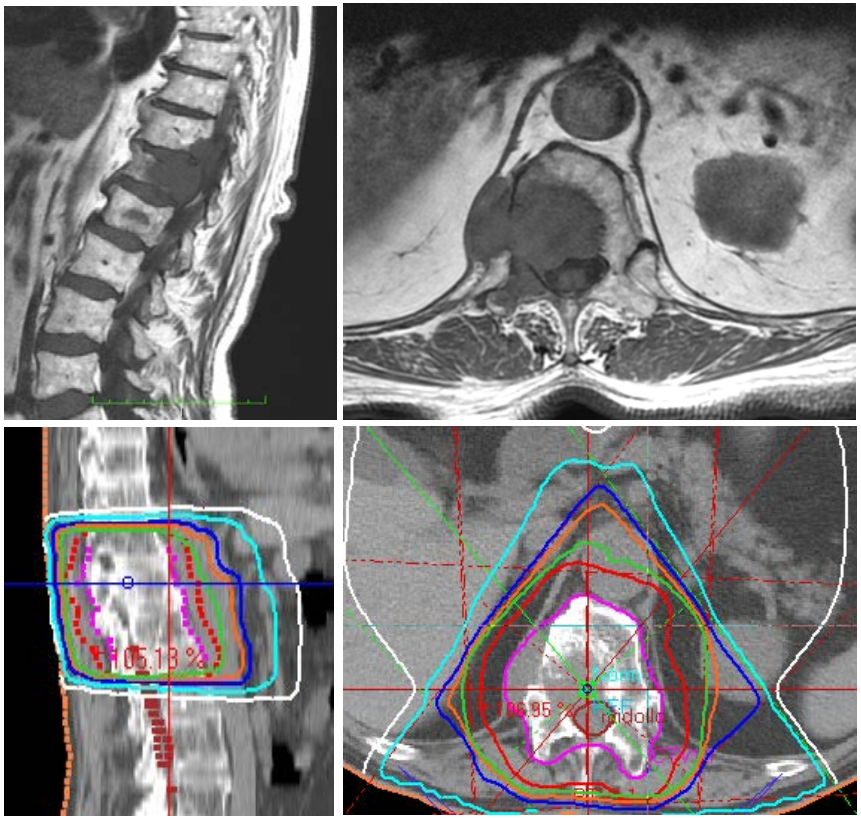


- 30 Gy/10 fractions
- 3DCRT
- Resolution of neurological symptoms after few sessions of RT

Palliative RT for Multiple Myeloma @ University of Torino



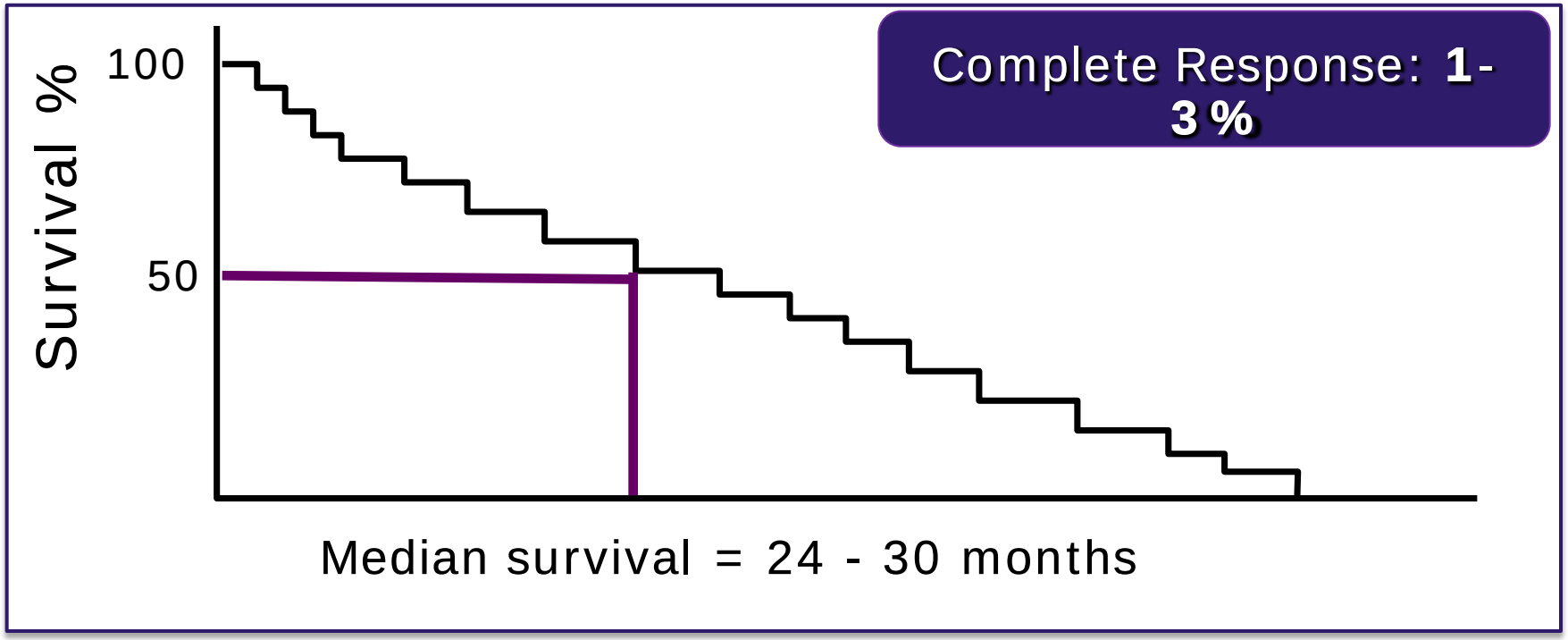
- 72 years old male
- Known history of MM, already treated with multiple lines of chemotherapy
- Osteolytic lesion at D11-D12, determining spinal cord compression, right leg weakness and severe dorsal pain.
- RT dose: 30 Gy/10 fractions
- During treatment neurologic improvement (dorsal pain disappeared and leg weakness significantly reduced)

Systemic radiotherapy in MM:

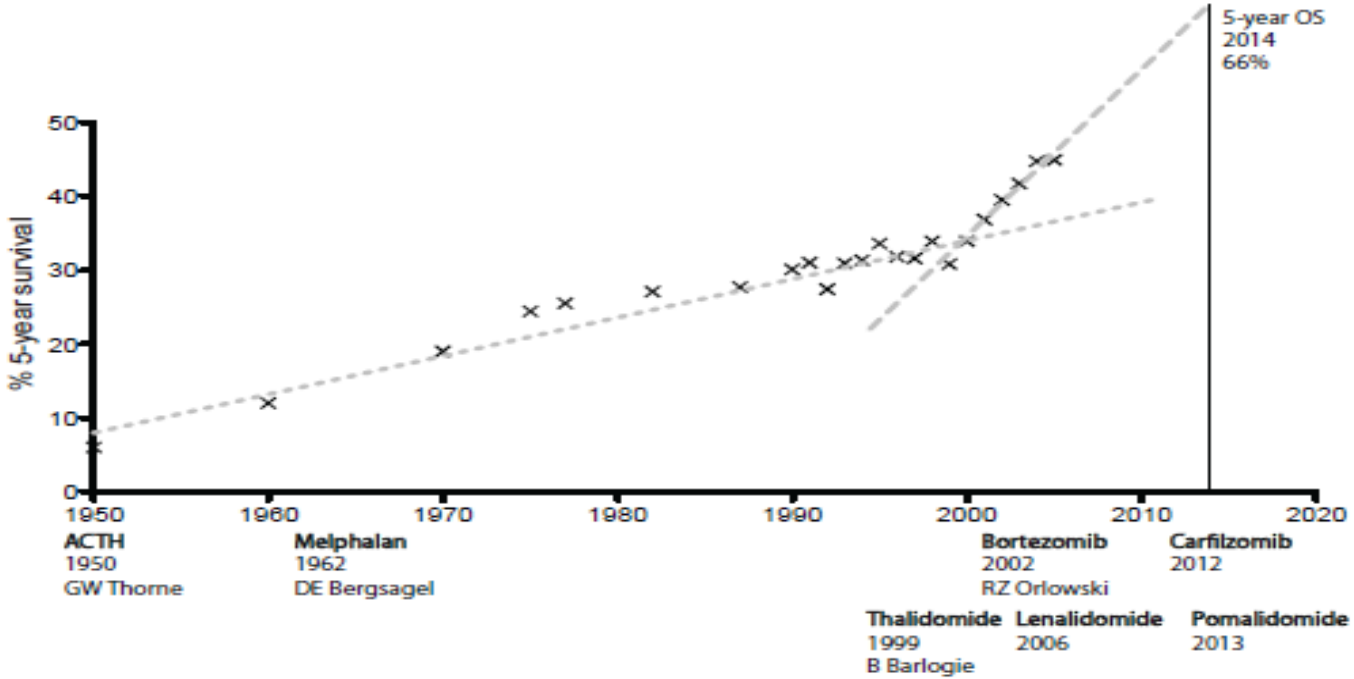
TBI and HBI

- Bone marrow ablative (allo and/or auto) preparative regimens: drugs alone (Melphalan) (more toxicity with TBI)
- Non myeloablative allogeneic transplantations (mini-allo): single dose 2 Gy TBI, combined with various chemotherapy regimens
- HBI (mainly historical)

Multiple Myeloma - incurable disease



Continuous improvement in overall survival



Bergsagel MD 2104 ASCO Educational Book

Solitary plasmacytoma

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- Solitary or localized plasmacytomas are rare diseases that account for less than 10% of all plasma cell neoplasms

- Similar to MM but without infiltration of the bone marrow, these neoplasms are composed of sheets of plama cells involving bone or soft tissue

- When the lesion is isolated in bone, the disorder is called **Solitary Plasmacytoma of Bone (SPB)** [mostly occurs in the bones of the axial skeleton]

- When in soft tissues, the lesion is called **Extramedullary Plasmacytoma (EMP)**, and is found in the head and neck 80% of the time

- SPBs are found predominantly in men (male-to-female ratio of 2:1) and at a median age of 55 years (younger age than MM), and are slightly more common than EMPs

Diagnosis of SPB requires solitary bone lesion confirmed by skeletal survey, plasma cell infiltration proven by biopsy, normal bone marrow biopsy (< 10% plasma cells), and lack of myeloma-related organ dysfunction (CRAB)

- Treatment of SP is largely composed of retrospective studies on small number of patients

- Currently, the standard of care for SBP is definitive RT, being SBP a highly radiosensitive disease, for which excellent local control rates can be achieved with RT alone (lesion size as prognostic factor; cut off 5 cm)

- In some cases (bone instability, rapidly progressive neurological symptoms) surgical intervention may be required

- Even though the optimal dose of RT has not yet established for SBP, it is recommended a radiation dose of at least 40 Gy in 20 fractions

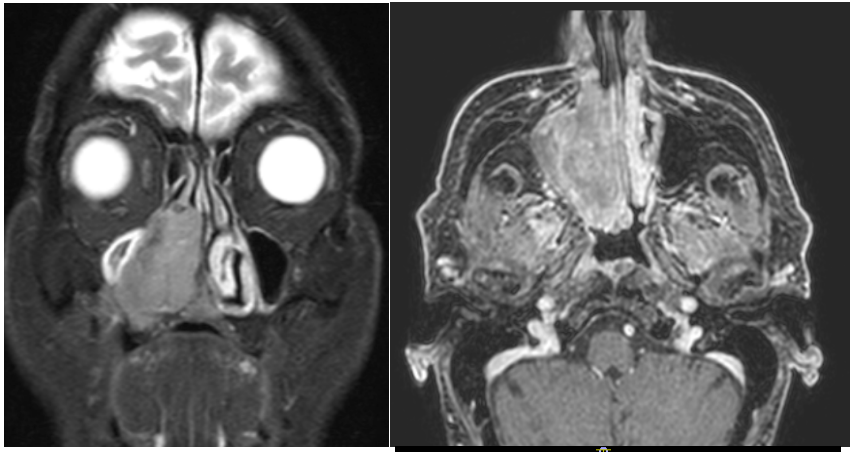
- Local control rates of 94% with doses over 40 Gy, dropped to 64% with doses lower than 40 Gy

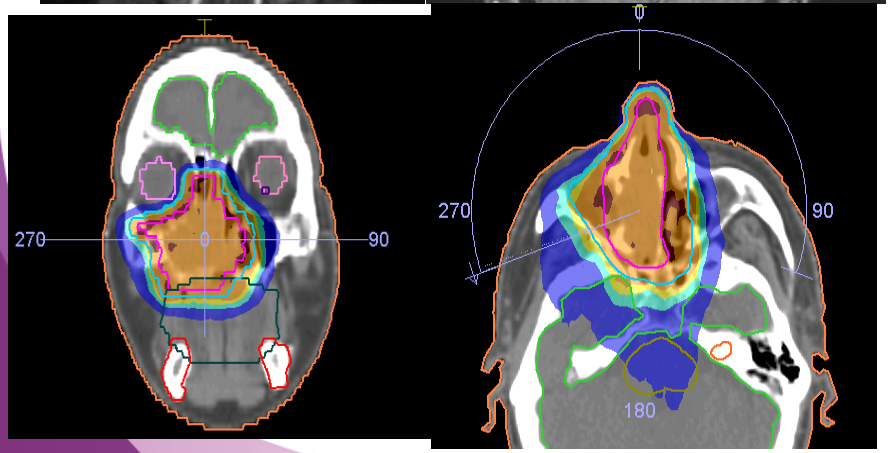
- In clinical practice, a radiation dose of 45-50 Gy with 2 Gy daily fractions is usually recommended

- Since the majority of EMP occurs in head and neck region and radical surgery with curative intent is often a mutilating procedure, radical RT should be preferred

- However, for patients with EMP in other sites, complete surgical removal should be considered, with adjuvant irradiation if appropriate (inadequate surgical margins)

Solitary Plasmacytoma @ University of Torino





- 79 years old patient
- Treatment: Radical RT
- 44 Gy/22 fractions
- IMRT/VMAT

- Although some authors recommend for SPB treatment portals including the entire involved bone (to encompass the entire medullary cavity of the bone), current recommendations favor radiation fields encompassing only the primary lesion, with generous margins (1.5-2 cm) to cover both the osseous and soft tissue extensions of the tumor (shown on CT and/or MRI)

- Prophylactic regional nodes irradiation is not necessary in SPB, as isolated regional node failure is low after local RT without intentional coverage of adjacent nodes

- Elective nodal irradiation is not routinely indicated in EMP patients, unless regional nodes are clinically involved or considered at high risk

Patterns of failure:

- local recurrence
- development of MM
- development of new bone lesions without MM

Table 1: Solitary plasmacytoma of bones: representative treatment results.

Author	*n*	f/u	LC (%)	PMM (%)	OAS (%)
Wilder et al. [35]	60	94 mo	90	62	59
Knobel et al. [25]	206	56 mo	79	51	50
Tsang et al. [32]	32	95 mo	87	64	65
Kilciksız et al. [24]	57	**2.4** y	94	4.1 y	68
Frassica et al. [23]	46	90	89	54	45
Bataille and Sany [33]	114	>10 y	88	58	68
Galieni et al. [40]	32	69 mo	91	68	49

mo: months, y: years f/u: Median followup, LC: Local control (10-year rate), PMM: progression to myeloma (10-year rate), and OAS: over all survival (10- year rate).

Table 2: Solitary Extramedullary Plasmacytoma: Representative Treatment Results.

Author	*n*	f/u	LC (%)	PMM (%)	OAS (%)
Kilciksiz et al. [24]	23	**2.4** y	95	7.4 y	89
Ozsahin et al. [3]	52	56	74	36	72
Galieni et al. [40]	46	118	92	15	78 (15 y)
Tournier-Rangeard [42]	17	80.5	88.2	63.8	63.4
Strojan et al. [43]	26	61	87	8	61
Leibross et al. [44]	22	—	95	32	56
Chao et al. [45]	16	66	100	31	54

- In comparison with EMP, SBP has poor prognosis, with a significantly higher risk for progression to myeloma (65-80% in 10 years), in spite of better local control rates

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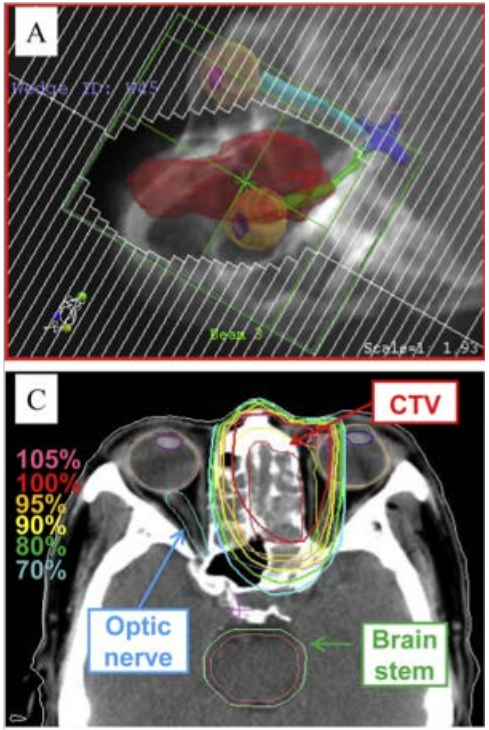
MULTI-INSTITUTIONAL ANALYSIS OF SOLITARY EXTRAMEDULLARY PLASMACYTOMA OF THE HEAD AND NECK TREATED WITH CURATIVE RADIOTHERAPY

- 67 patients
- 1983-2008
- Japanese cohort
- Median RT dose 50 Gy

Table 1. Patients and tumor characteristics

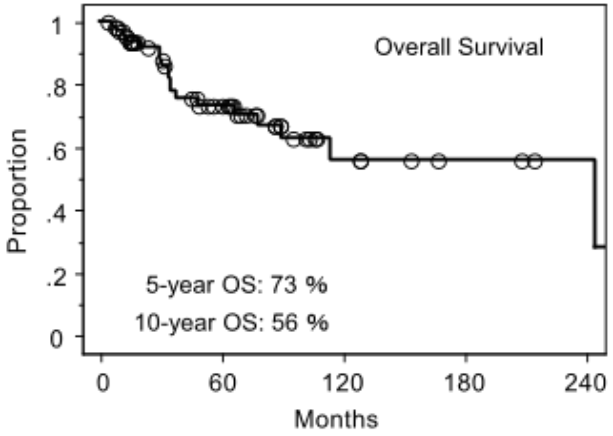
	Number	Percentage (%)
Age	12–83 (64)*	
Gender (M/F)	43/24	
ECOG performance status (0/1/2/unknown)	46/18/1/2	
Tumor size	1–10 cm (3.5)*	
Sites		
Nasal/paranasal	36	54
Oropharynx	9	13
Nasopharynx	7	10
Orbita	6	9
Larynx	3	5
Salivary glands	2	3
Lymph nodes	2	3
Middle ear	1	1.5
Thyroid	1	1.5
Positive for M protein	15/59	22
Positive for Bence-Jones proteins	2/56	4
Concomitant disease		
Amyloidosis	2/67	3

* median age, median tumor size.



Sasaky et al. IJROBP 2012;82(2):626-634

MULTI-INSTITUTIONAL ANALYSIS OF SOLITARY EXTRAMEDULLARY PLASMACYTOMA OF THE HEAD AND NECK TREATED WITH CURATIVE RADIOTHERAPY



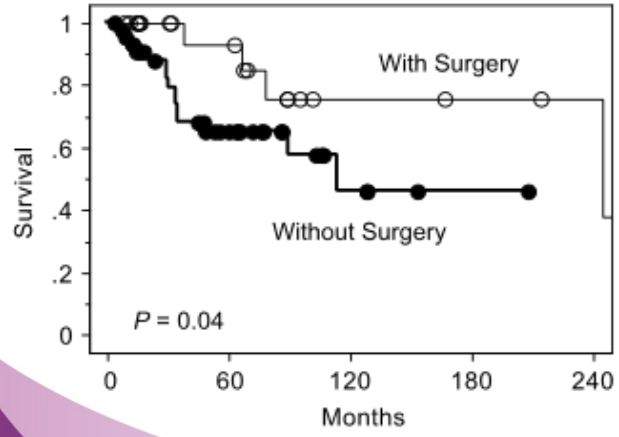


Table 5. Prognostic factors for overall survival

Prognostic factors	*p* value
Tumor size	
≤5 cm (*n* = 45) vs. >5 cm (*n* = 13)	0.59
Age	
≤50 (*n* = 15) vs. >51 (*n* = 52)	0.3
Gender	
Male (*n* = 43) vs. female (*n* = 24)	0.95
Radiation dose	
≤40 Gy (*n* = 13) vs. >40.1 Gy (*n* = 54)	0.82
≤45 Gy (*n* = 17) vs. >45.1 Gy (*n* = 50)	0.73
≤50 Gy (*n* = 56) vs. >50.1 Gy (*n* = 11)	0.72
Surgery	
With surgery (*n* = 23) vs. without surgery (*n* = 44)	0.04
Chemotherapy	
With chemotherapy (*n* = 9) vs. without chemotherapy (*n* = 58)	0.75

Sasaky et al. IJROBP 2012;82(2):626-634

- “Adjuvant” systemic treatments are not of convincing benefit in SBP and EMP

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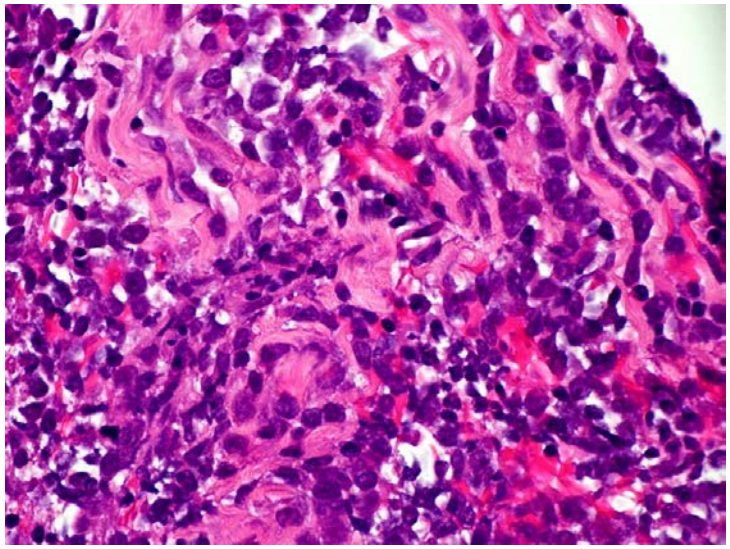
RT for Extramedullary Leukemias

("Granulocytic Sarcomas" –Chloromas) and Leukemia Cutis



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Memorial Sloan Kettering Cancer Center

ILROG International Lymphoma Radiation Oncology Group

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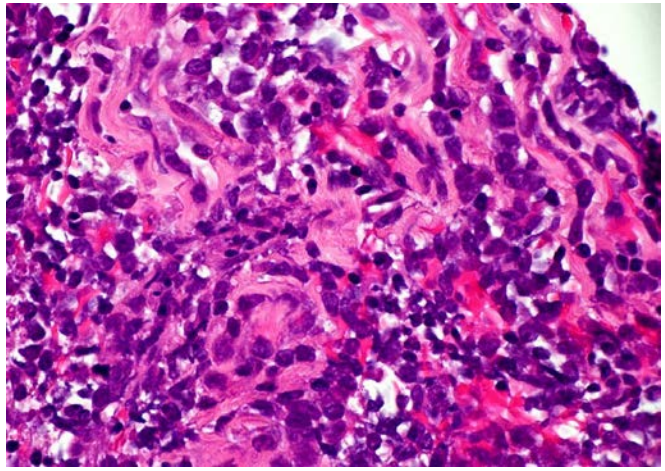
Background

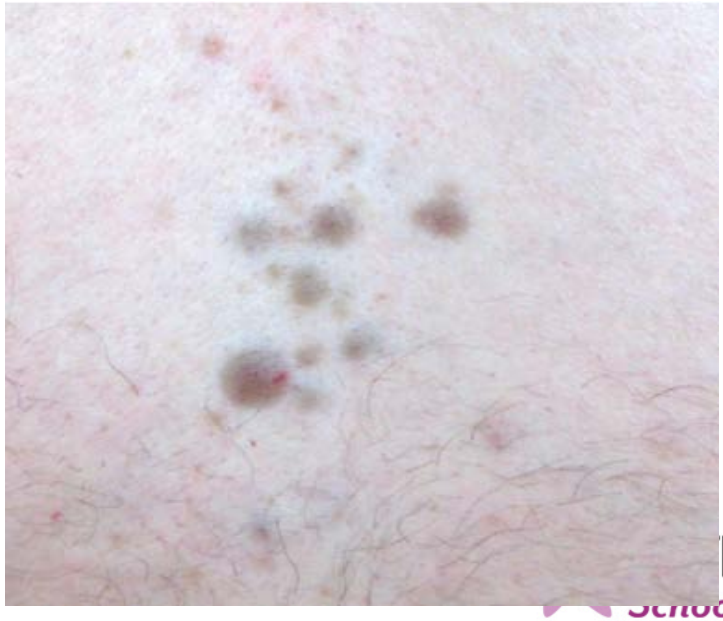
- Myeloid sarcoma (MS) is an extramedullary tumor of immature myeloid cells

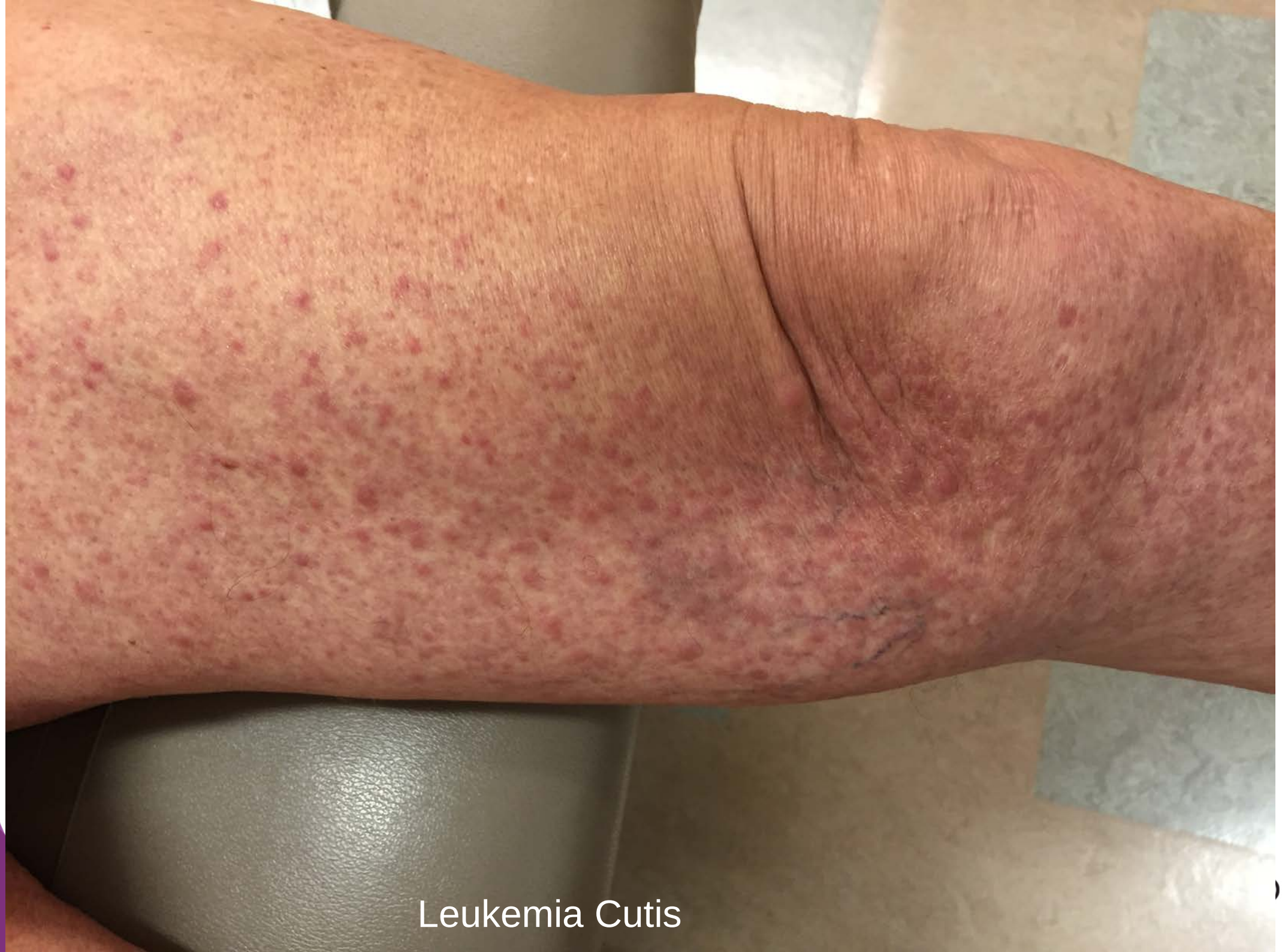
- Leukemia cutis (LC) is the infiltration of the epidermis, dermis or subcutis by neoplastic leukocytes resulting in clinically identifiable cutaneous lesions

Myeloid Sarcoma

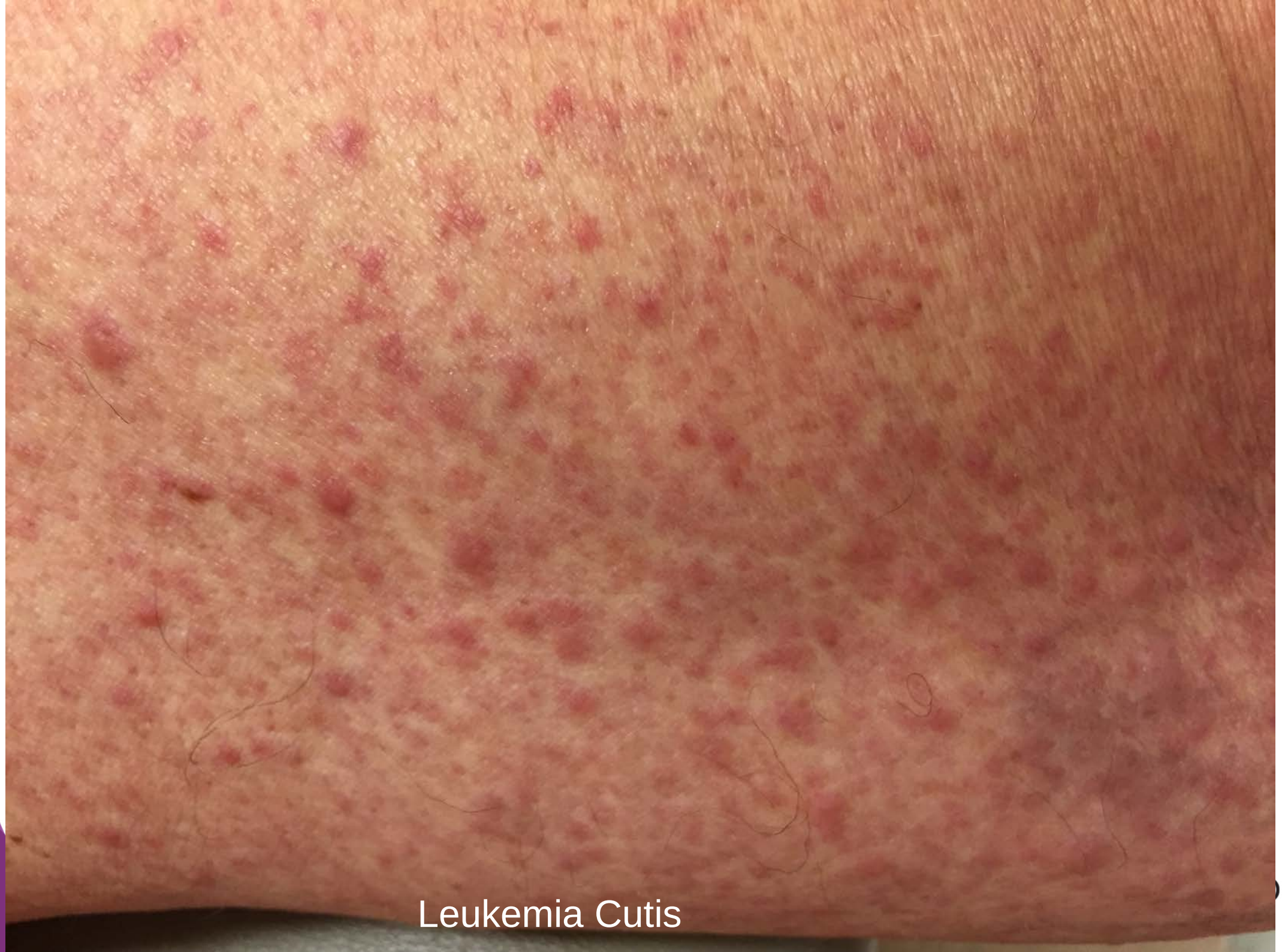


Leukemia Cutis





Leukemia Cutis



Leukemia Cutis

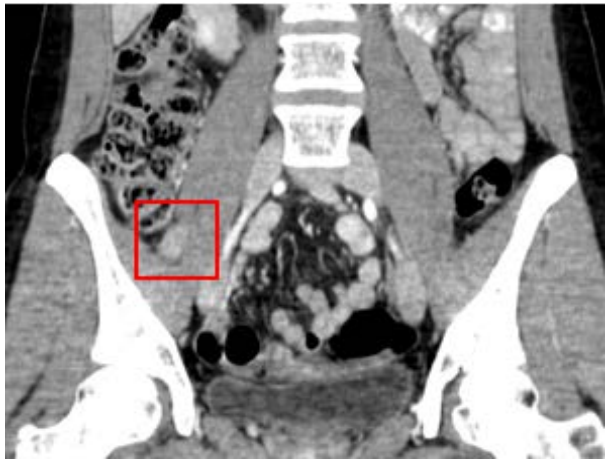
Incidence

- Myeloid Sarcoma is reported in 2.5%-9% of patients with AML

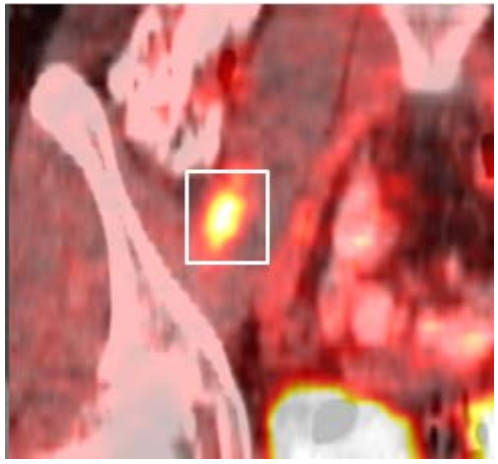
  Occurs concomitantly, following, or, rarely, antedating the onset of leukemia

- LC occurs in approximately 3% of patients with AML, and less frequently in chronic leukemias

CT



PET



Memorial Sloan Kettering Cancer Center

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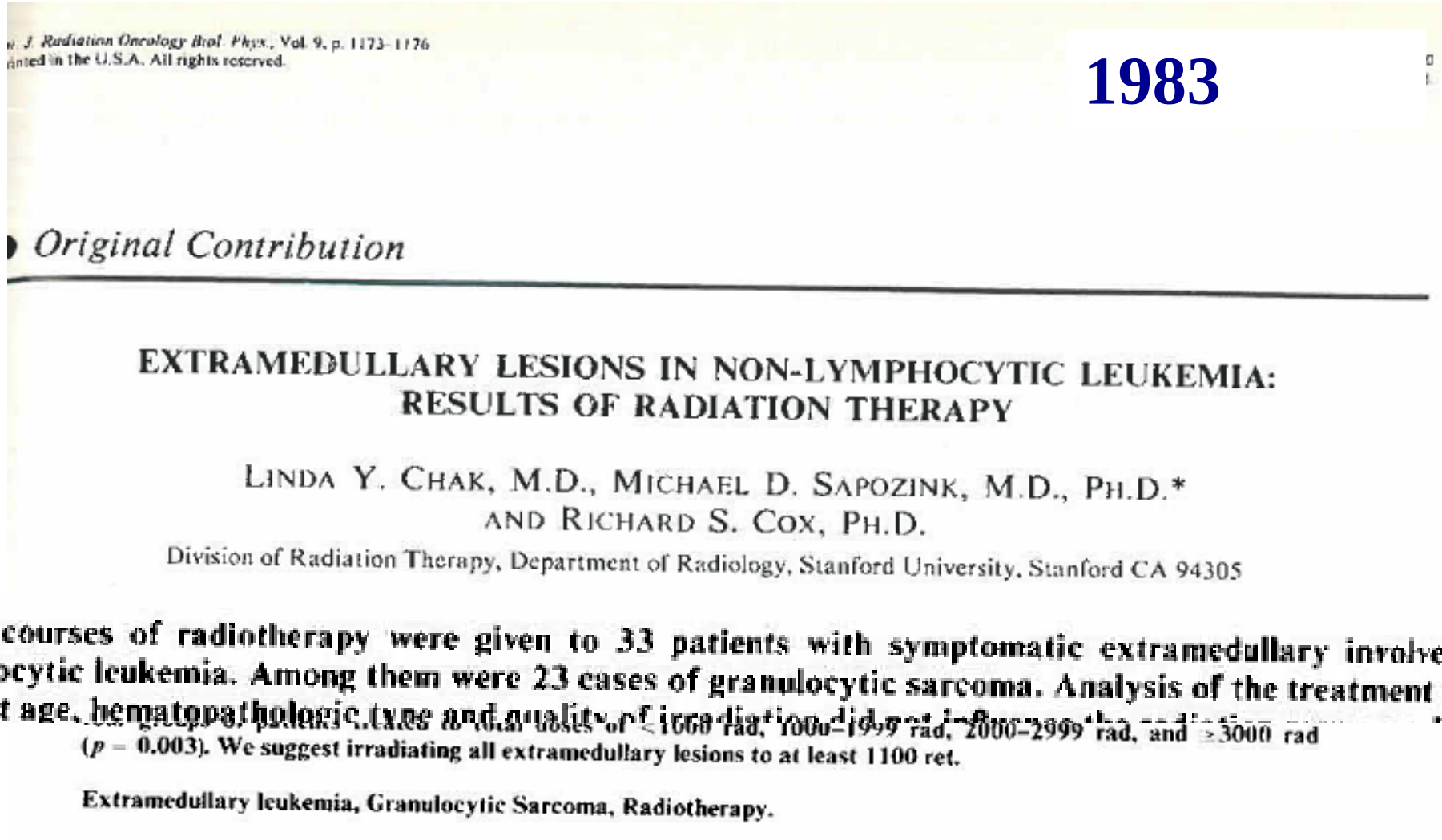
Limited Literature



. J. Radiation Oncology Biol. Phys., Vol. 9, p. 1173–1176

1983

Original Contribution

EXTRAMEDULLARY LESIONS IN NON-LYMPHOCYTIC LEUKEMIA: RESULTS OF RADIATION THERAPY

LINDA Y. CHAK, M.D., MICHAEL D. SAPOZINK, M.D., PH.D.*
AND RICHARD S. COX, PH.D.
Division of Radiation Therapy, Department of Radiology, Stanford University, Stanford CA 94305

Fifty-four courses of radiotherapy were given to 33 patients with symptomatic extramedullary involvement by non-lymphocytic leukemia. Among them were 23 cases of granulocytic sarcoma. Analysis of the treatment response showed that age, hematopathologic type and quality of irradiation did not influence the radiation
($p = 0.003$). We suggest irradiating all extramedullary lesions to at least 1100 ret.

Extramedullary leukemia, Granulocytic Sarcoma, Radiotherapy.

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Limited Literature

Int. J. Radiation Oncology Biol. Phys., Vol. 8, pp. 1587–1592
Printed in the U.S.A.

1982

● *Brief Communication*

TOTAL SKIN ELECTRON BEAM THERAPY FOR CUTANEOUS LYMPHOMAS AND LEUKEMIAS

LOURDES Z. NISCE, M.D.,[1] FLORENCE C. H. CHU, M.D.,[1] HYUN S. LEE, M.D.,[1]
DANIEL FILIPPA, M.D.,[2] SANFORD KEMPIN, M.D.[3]
AND MORTON COLEMAN, M.D.[4]

Departments of Radiation Therapy,[1] Pathology,[2] Hematology/Lymphoma Service,[3] Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021, and Medicine, Division of Hematology/Oncology,[4] New York Hospital Cornell Medical Center, New York, NY 10021

Total skin electron beam therapy (TSEB) was used in the treatment of 33 patients with lymphoma and 13 patients with leukemia involving extensive segments of the skin surface. Twenty-two of 23 had skin lesions as a primary manifestation of lymphoma (primary cutaneous lymphoma—PCL) and 11 developed cutaneous lesions following disseminated nodal lymphoma (secondary cutaneous lymphoma—SCL). A once weekly fractionation scheme was employed to irradiate the entire skin surface with 3.5 to 4 MeV electron beam from a 6 MeV linear accelerator. During each weekly session, 400 rad were delivered to the entire skin and a complete course consisted of 4–6 consecutive weekly sessions. The majority of patients have been previously treated elsewhere for various periods and all patients have been at risk for a median of 12 months, range from 12–117 months following TSEB. Striking predominance of the diffuse pattern (76%) was demonstrated in both the PCL and SCL. There was extracutaneous involvement in 63% (13/22) of the PCL, nodal or visceral at onset of TSEB; median follow-up was 24 months, range 6–117 months; 20/22 (90%) of all patients obtained prompt relief of symptoms and complete regression of cutaneous lesions. Duration of cutaneous remission ranged from 6–96 months, median 18 months; in general, duration was adversely influenced by the presence of visceral involvement at onset of TSEB. Although cutaneous response among the patients with SCL and leukemia was equally good, many of these patients were treated for palliation because of rapid progression of their disease. Once weekly treatments were highly effective, well-tolerated and no untoward immediate or late effects have been noted in the bone marrow or normal skin irradiated.

Cutaneous lymphoma, leukemia, total skin electron beam therapy.

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Acute Myelogenous Leukemia With Leukemia Cutis

Eighteen Cases Seen Between 1969 and 1986

MARIA R. BAER, MD,* MAURICE BARCOS, MD, PHD,† HOWARD FARRELL, BS,*
AZRA RAZA, MD,* AND HARVEY D. PREISLER, MD*

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Leukemia Cutis- MSKCC Experience

15 patients who underwent treatment for LC at our institution from 11/1994-8/2009

LC Cases	15
Gender *Male* *Female*	 9 (60%) 6 (40%)
Cancer Diagnosis *AML*[†] *CML*[††]	 **14 (93%)** 1 (7%)
Median Age at Leukemia Diagnosis (years)	50 (15-81)
Median Interval Between Systemic Leukemia and LC (months)	2 (0-24)
Timing of LC Development: *Prior to Leukemia Diagnosis* *Concurrent with Leukemia Diagnosis* *During Initial Treatment* *Relapse*	 1 (6.5%) 4 (26.5%) 3 (20%) **7 (47%)**
Median Survival Since LC Diagnosis (months)	**23** (0.5-137)

Radiation Technique

Leukemia Cutis: TSEB

Right Anterior Oblique

Anterior

Left Anterior Oblique

Left Posterior Oblique

Posterior

Right Posterior Oblique

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Results: Leukemia Cutis

- 13 courses of RT administered
  - 9 TSEB and 4 focal treatments
- Median survival since completion of RT was 5 months
- 1-year LC was 33%
  - All patients who developed a skin relapse had active marrow disease at time of RT or recurrence shortly after
- No significant acute toxicities
  - one case of radiation recall

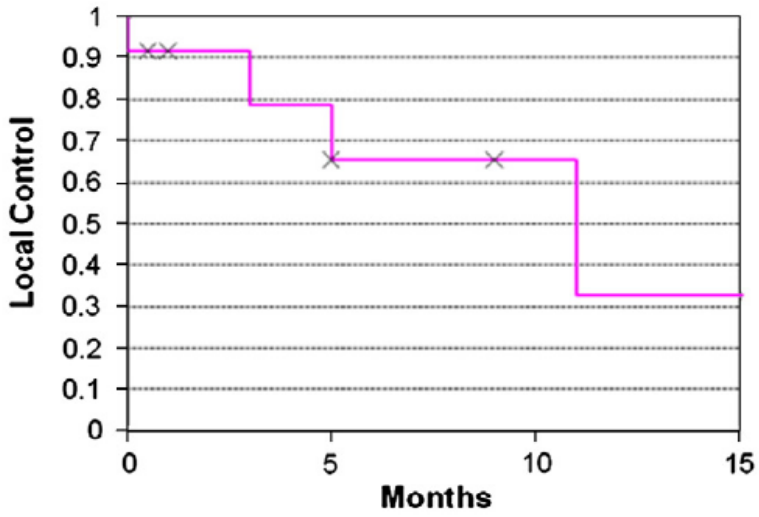


Figure 2 Local control for patients treated with radiation for leukemia cutis.

➢ Bakst R et al Practical Radiation Oncology 2011

Conclusions: Leukemia Cutis

- Patients with LC have aggressive disease with few long-term survivors
- Definitive treatment with TSEB should be utilized only in cases of marrow remission with focal electron therapy reserved for palliation of symptomatic lesions
- Long-term prognosis and durable cutaneous remission is dependent on systemic disease control

Methods: Chloroma

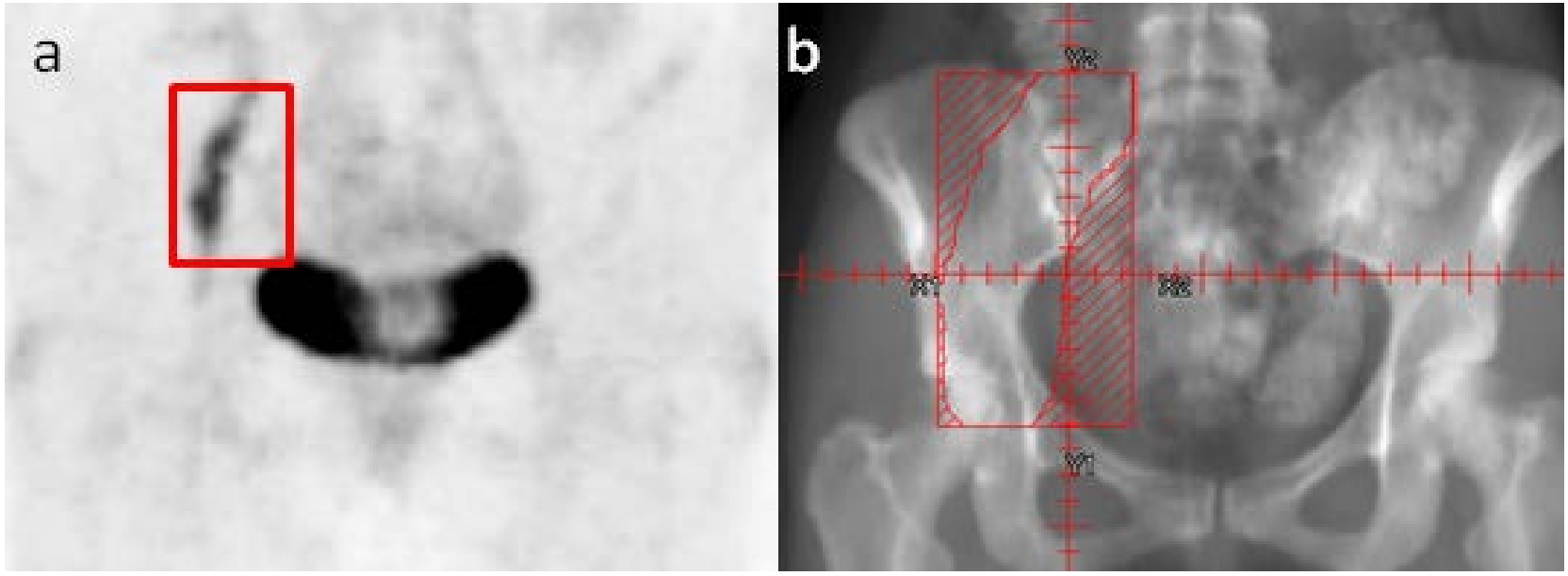
38 patients who underwent treatment for chloromas at MSKCC from 2/1990-6/2010

	Entire Cohort	Radiation	Non-Radiation
Cases	38	**22**	**16**
Gender	M 25 (66%) F 13 (34%)	M 14 (63%) F 8 (36%)	M 11 (69%) F 5 (31%)
Diagnosis	AML 29 (76%) CML 1 (3%) MDS 3 (8%) Isolated 5 (13%)	AML 19 (86%) MDS 2 (9%) Isolated 1 (5%)	AML 10 (63%) CML 1 (6%) MDS 1 (6%) Isolated 4 (25%)
Median Age (yrs)	44 (1-71)	34 (1-71)	49 (10-71)
Chloroma at Presentation	18 (47%)	**4 (18%)**	**14 (89%)**
Median Survival Since Chloroma Diagnosis (months)	23 (1-179)	15 (1-108)	61 (7-179)

- Bakst R et al Int J Radiat Oncol Biol Phys

Radiation Technique

Chloroma: Conventional AP/PA



Results: Chloroma

- At a median follow-up of 11 months since RT, local control was 97%
  - 4 patients developed chloromas at other sites
- Median dose was 20 (6-36) Gy
- RT was well tolerated without significant acute or late effects, and provided symptom relief in 95% of cases

RT Subsites

Site	% of Patients
Head & Neck	39
Extremity	24
Spine	9
Brain	9
GU	6
Breast	6
Pelvis	3
GI	3

➢ *Bakst R et al Int J Radiat Oncol Biol Phys 2012*

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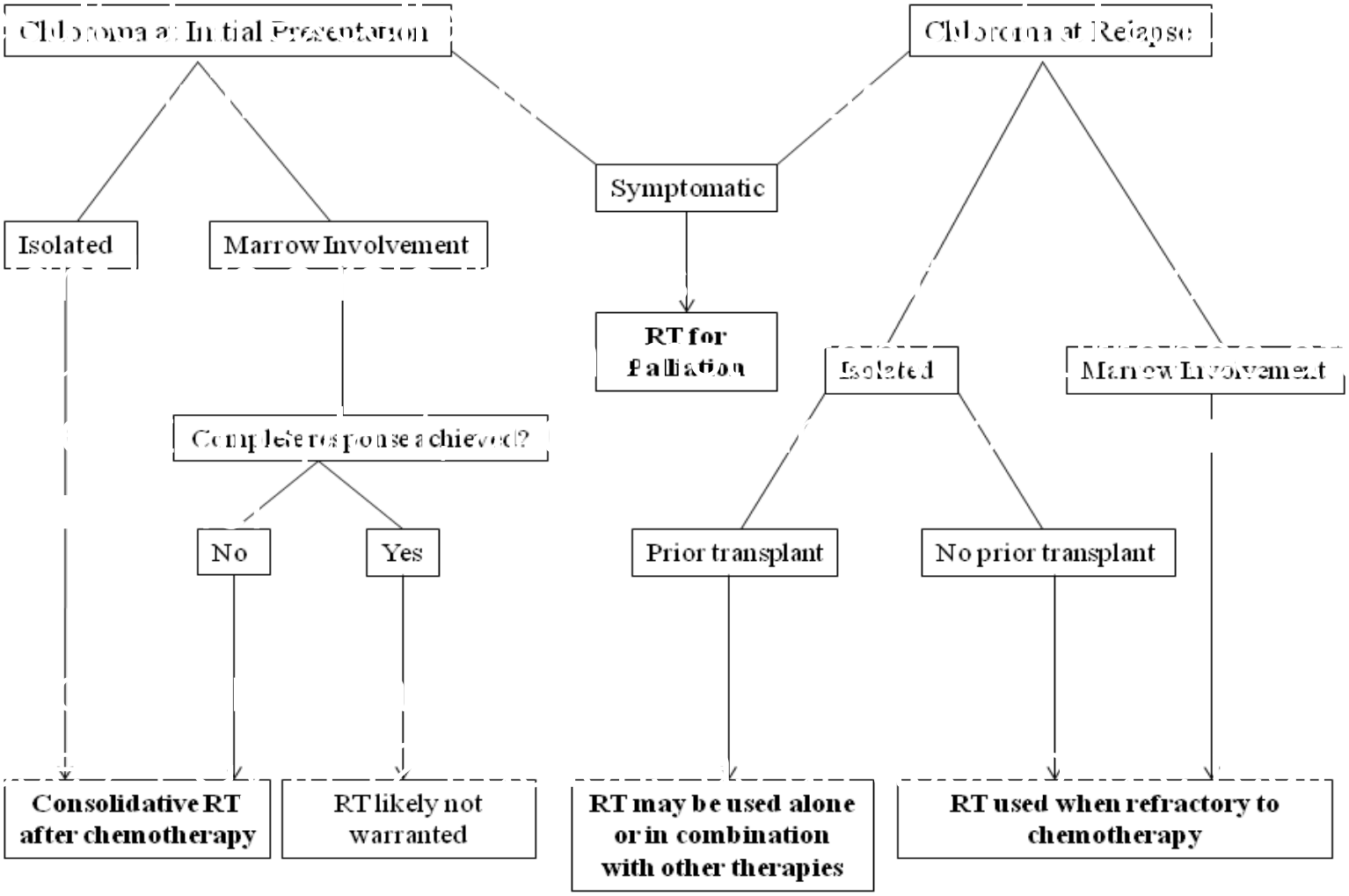
Conclusions: Chloroma



➢ *Bakst R et al Int J Radiat Oncol Biol Phys 2012*

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How I treat extramedullary acute myeloid leukemia

blood

Richard L. Bakst,[1] Martin S. Tallman,[2] Dan Douer,[2] and Joachim Yahalom[1]

[1]Department of Radiation Oncology and [2]Leukemia Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY

MS development	Extent of involvement	Strategies
Initial	Isolated	Intensive AML chemotherapy with consideration of RT as consolidation
	Concurrent MS and marrow	Intensive AML chemotherapy with consideration of HCT; RT if MS persists after induction chemotherapy
Relapse	**Isolated**	
	After chemotherapy	Reinduction AML chemotherapy with consideration of HCT
	After transplant	Donor lymphocyte infusion, tapering of immunosuppression, RT, and/or clinical trial
	MS and marrow	
	After chemotherapy	Reinduction AML chemotherapy with consideration of HCT, RT, and/or clinical trial
LC	**Marrow status**	**Strategies**
	Negative	Intensive AML chemotherapy
	AML	Intensive AML chemotherapy with consideration of HCT; TSEB after chemotherapy for persistent LC if marrow negative

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TBI and local RT in the conditioning regimen of BMT of Leukemia

Joachim Yahalom, M.D.
Memorial Sloan Kettering Cancer Center
New York ,NY, USA

Memorial Sloan Kettering Cancer Center

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Radiation therapy for leukemia

- Cranial irradiation for CNS disease in ALL
  - To prevent relapse in brain (12-18 Gy/6-12 fractions)
  - To treat disease in brain (18-24 Gy/10-16 fractions, with or without 6-12 Gy/3-8 fractions to spine)
- Testicular irradiation for disease in testes in ALL
  - 24-26 Gy/12-18 fractions
- Splenic irradiation in chronic leukemias
  - 1-10 Gy/10-100 fractions
- Total body irradiation as part of hematopoetic stem cell transplant (for any leukemia, and other diseases)
  - With or without any of the above

Total body irradiation as part of conditioning

- Non-myeloablative:
  - Commonly an outpatient procedure
- Myeloablative doses:
  - >5 Gy in a single fraction
  - >8 Gy in multiple fractions
  - Commonly an inpatient procedure (at MSKCC)
  - Can be performed as an outpatient (if patient is reliable)
  - Keep in mind, this is ***lethal*** therapy!

Indications for HSCT

- Center International Bone and Marrow Transplant most common indications for HSCT in 2005 (most to least common)
  - Multiple myeloma (MM)
  - Non-Hodgkin lymphoma (NHL)
  - Acute myelogenous leukemia (AML)
  - Hodgkin disease (HD)
  - Acute lymphoid leukemia (ALL)
  - Myelodysplastic and myeloproliferative disease (MDS)
  - Chronic myelogenous leukemia (CML)
  - Aplastic anemia (AA)
  - Various other leukemias, cancers, and non-malignant diseases

- National Comprehensive Cancer Network guidelines for HSCT (2009)
  - Acute myelogenous leukemia (AML)
  - Multiple myeloma (MM)
  - Myelodysplastic syndrome (MDS)
  - Chronic myelogenous (CML)
  - Hodgkin disease (HD)
  - Non-Hodgkin lymphoma (NHL)
  - Testicular cancer

Biology of TBI

- Normal and malignant blood cells are the major target in TBI
  - Very sensitive to radiation
  - D_0 of 0.5 – 1.5 Gy
  - Very small shoulder on cell survival curve
  - Other radiobiologic phenomena are ill-defined (repair, reoxygenation, repopulation, redistribution)

TBI effects on blood

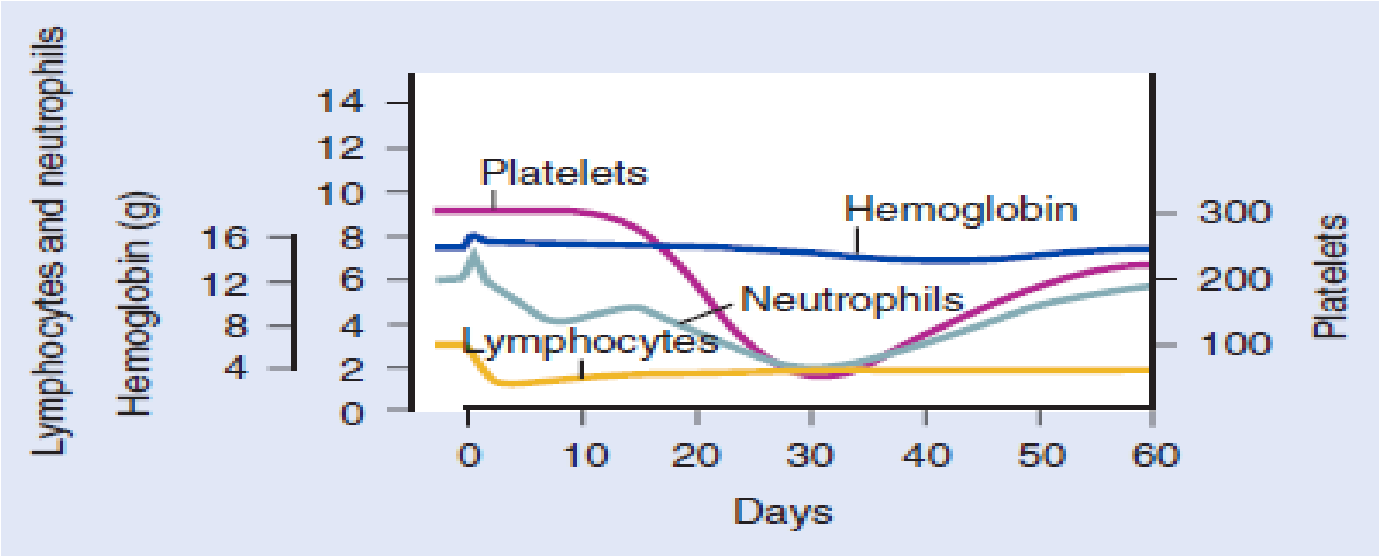

FIGURE 15-3 • Representative hematologic response to total body irradiation, given as a single fraction of 200 cGy on day 0. (From Andrews: Radiation accidents and their management, Radiat Res Suppl 7:390–397, ••••.)

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From *Textbook of Radiation Oncology*, 2010

Acute toxicity of TBI

- Side effects may be due to other components of HSCT

Table 15-1 Signs and Symptoms in Patients After Single-Dose or Fractionated Total Body Irradiation

Symptom/ Sign	Single Fraction TBI		Fractionated TBI
	% of Patients Experiencing **During** TBI	% of Patients Experiencing **After** TBI	% of Patients Experiencing During 3 Days of TBI
Nausea	90%	45%	43%
Vomiting	80%	23%	23%
Parotid gland pain	26%	74%	6%
Xerostomia	61%	58%	30%
Headache	42%	33%	15%
Fatigue	N/R	N/R	36%
Ocular dryness	None	16%	N/R
Esophagitis	N/R	N/R	4%
Loss of appetite	N/R	N/R	16%
Indisposition	N/R	N/R	25%
Erythema	None	None	41%
Pruritis	None	None	4%
Diarrhea	None	None	4%
No symptoms	N/R	N/R	17%
Fever (>38° C)	42%	97%	N/R
Hypertension	42%	None	N/R

Data from Chaillet et al.[86] and Buchali et al.[87]
N/R, Not reported; *TBI*, total body irradiation.

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Late toxicity of TBI and HSCT

- Xerostomia
- Dental caries
- Pneumonopathy, pneumonitis, lung dysfunction – major dose-limiting toxicity
- Cardiovascular disease
- Hepatotoxicity
- Cataracts
- Nephropathy
- Endocrinopathy

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Secondary Malignant Neoplasms after TBI and HSCT

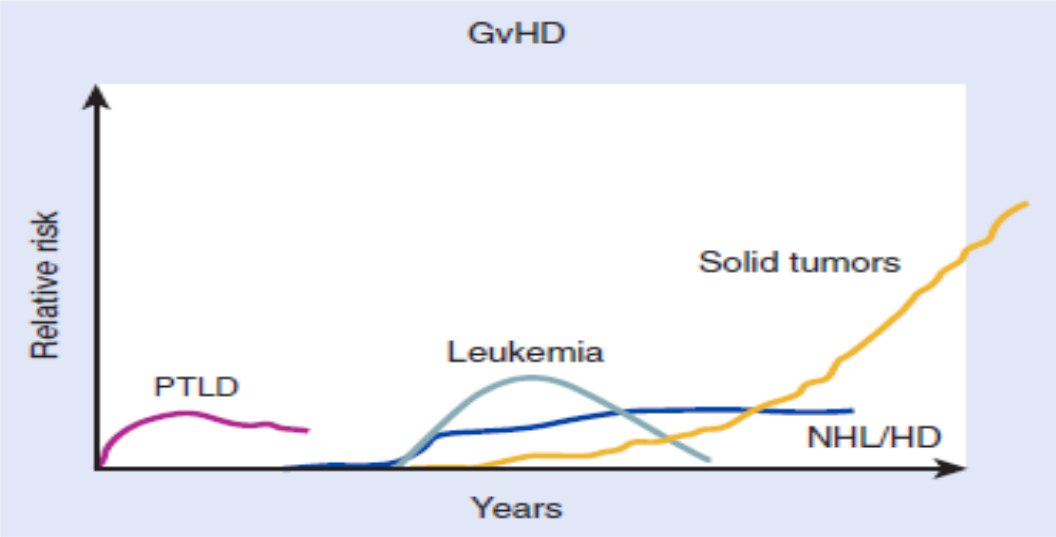

FIGURE 15-5 • Relative risk and chronology of second malignancies after allogeneic hematopoietic stem cell transplant. *GvHD,* Graft-verus-host disease; *HD,* Hodgkin disease; *NHL,* non-Hodgkin lymphoma. (From Adès et al: Second malignancies after allogeneic hematopoietic stem cell transplantation: new insight and current problems, Blood Rev 16:135–146.)

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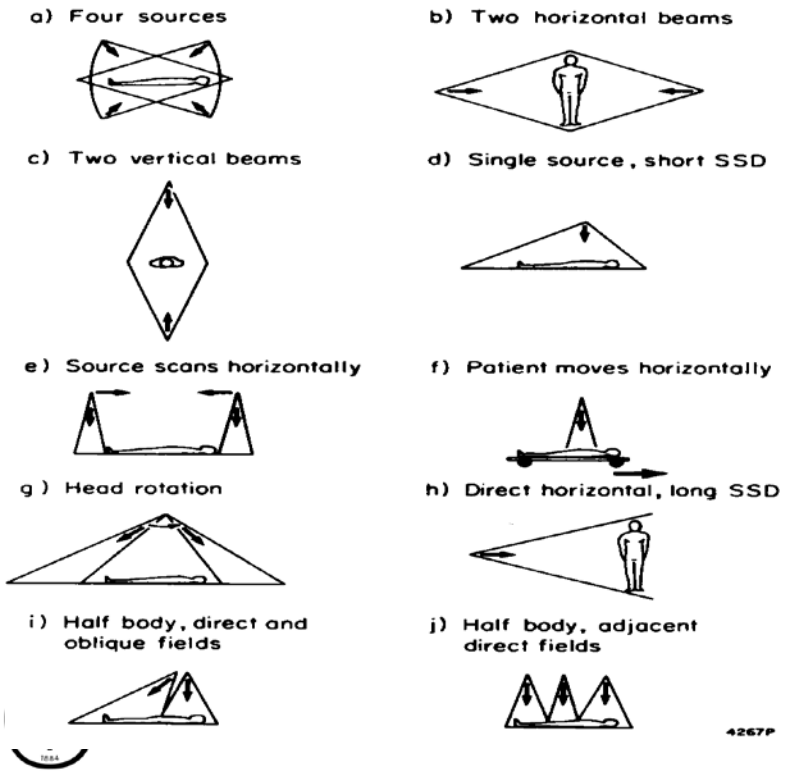
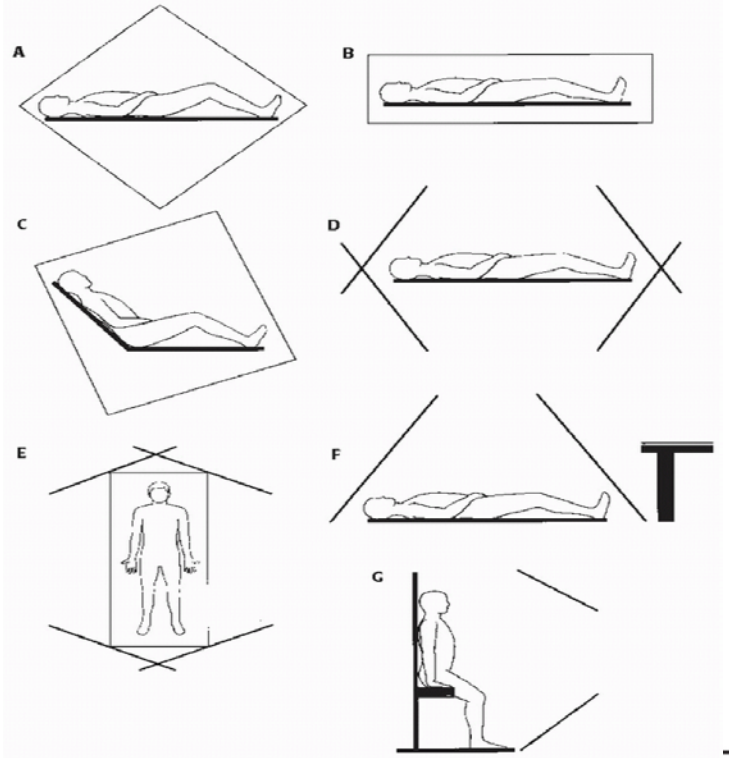
TBI: Techniques





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Courtesy of Tom LoSasso, MSKCC

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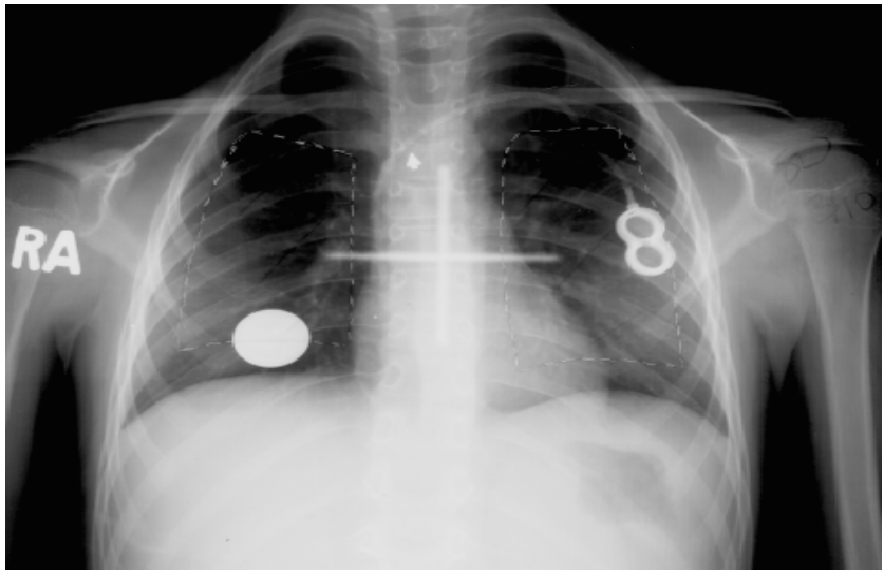
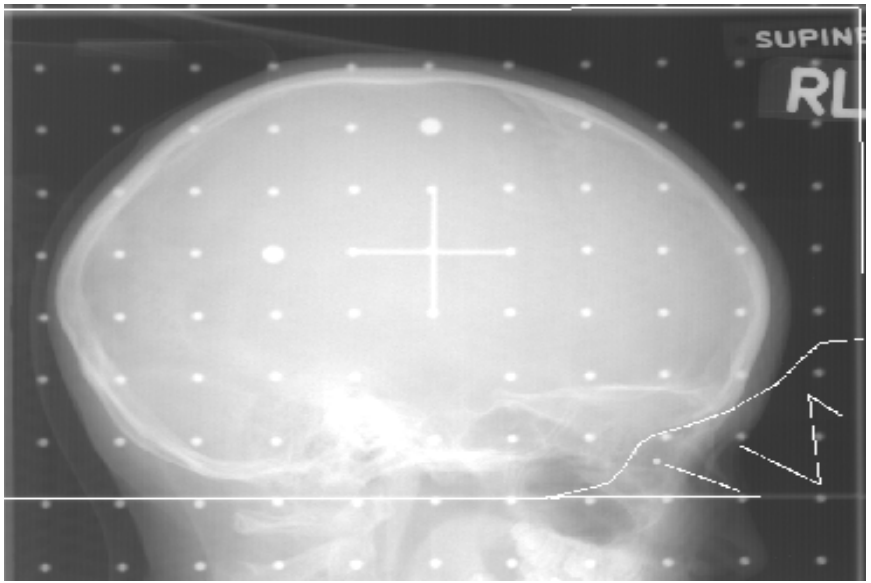
TBI: Simulation Films





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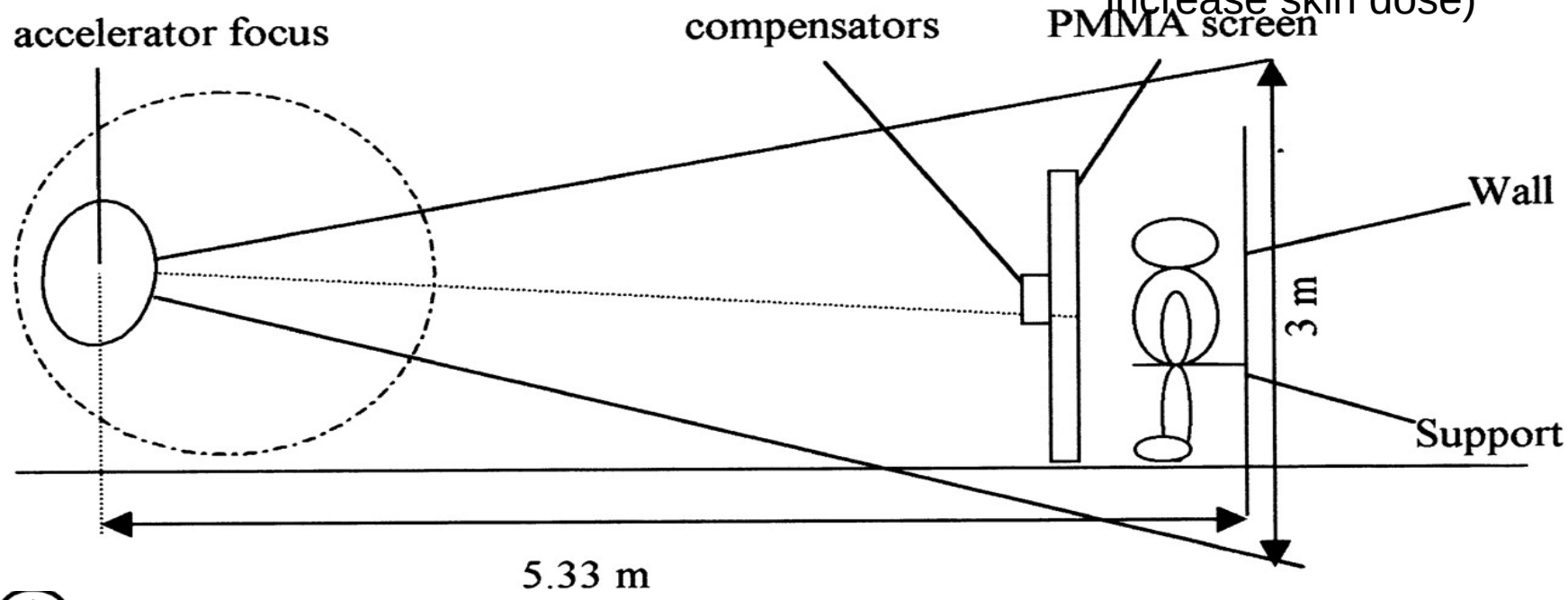
TBI: Technique

(beam spoilers used to increase skin dose)



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From *Br J Radiol*, 2001

TBI: MSKCC Standing AP/PA Technique

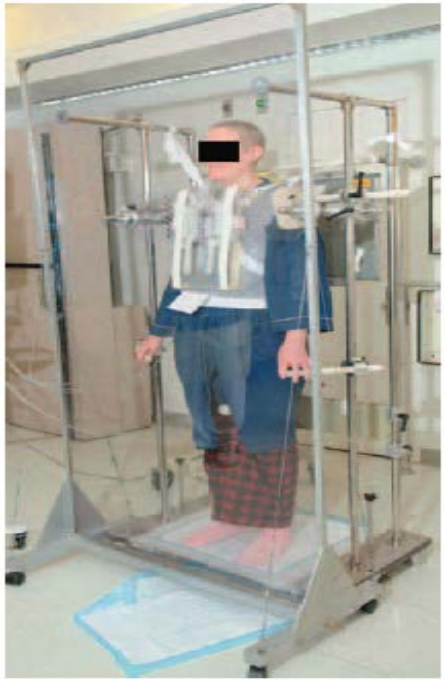

FIGURE 15-6 • Patient in position for total body irradiation using anteroposterior beam arrangement, with lung blocks in place.

Lung shielding used routinely for myeloablative TBI

Beam spoilers used to increase skin dose

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TBI: MSKCC Chest Wall Compensation

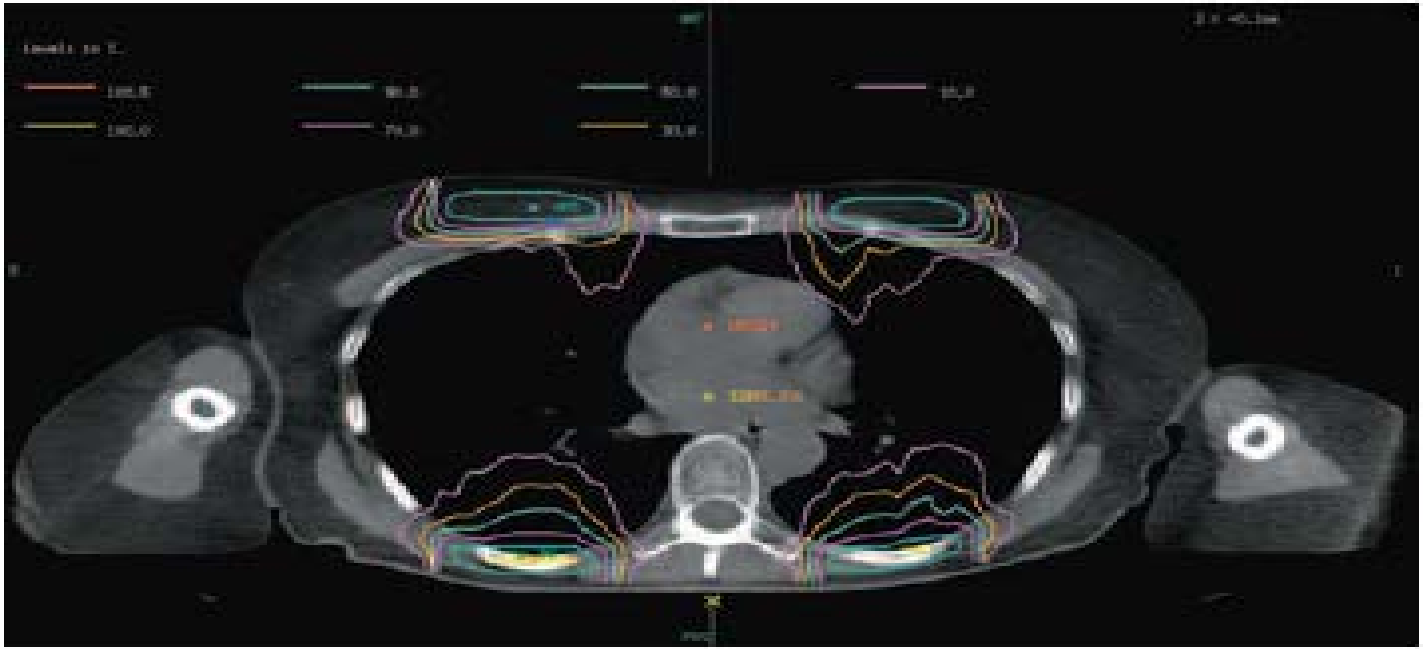

FIGURE E 15-7 • Computed tomography axial section demonstrating electron boost dose distribution.

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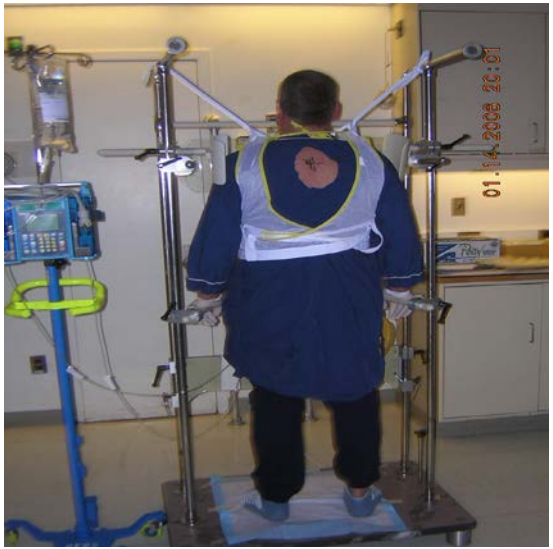
TBI: MSKCC Standing AP/PA Technique



Lung shielding not used for most non-myeloablative TBI regimens

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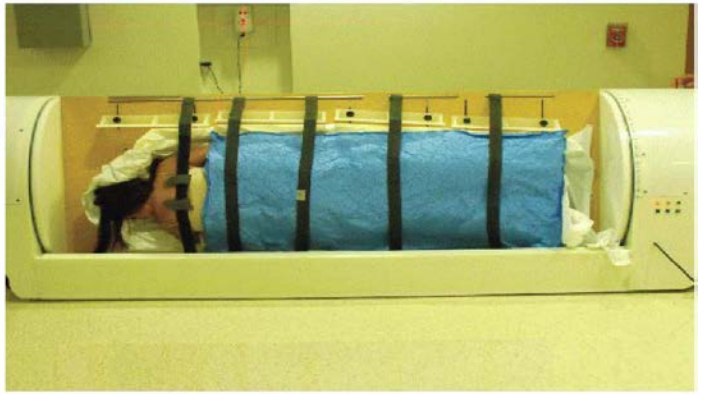
Courtesy of Tom Lo Sasso, MSKCC

TBI: Duke Pediatric Setup



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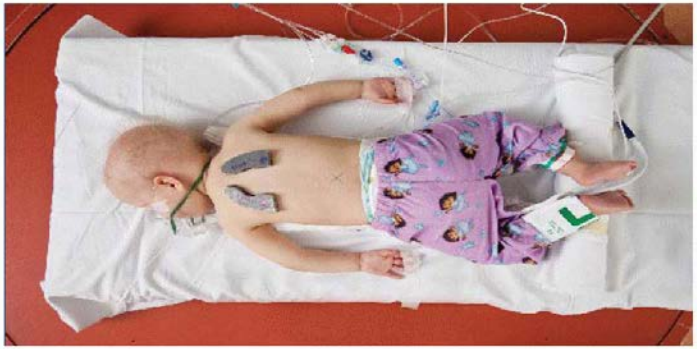

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From *Pediatric Radiation Oncology*, 2011

TBI: MSKCC Techniques

	Standing (adults, children >3 years)	Lying on floor (children <3 years)
energy	15 MV	15/6 MV
SAD (cm)	440	220
CS	40x40	40x40
gantry / collimator	85º / 45º	0º / 45º
dose rate @ midplane (cGy/min)	10-13	13-17
Spoiler (25 cm from pt)	yes	yes
shielding / electrons	yes	yes
max. patient height (ft)	6	3.5

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TBI: Prescription

Fields	01-02	03	04	05-06	07
Energy	15 MV photons	6 MeV electrons	6 MeV electrons	6 MV photons	6 MeV electrons
Site	TBI	Anterior chest wall	Posterior chest wall	Whole brain	Testes
Technique	AP-PA	Anterior	Posterior	Opposed laterals	en face
Rx Point	midplane	90% IDL	90% IDL	midplane	90% IDL
Dose/Fx	125 cGy	300 cGy	300 cGy	180 cGy	400 cGy
Fractions/Day	3	2	2	1	1
Total Dose	1500 cGy	600 cGy	600 cGy	900 cGy	400 cGy

TBI is associated with better survival

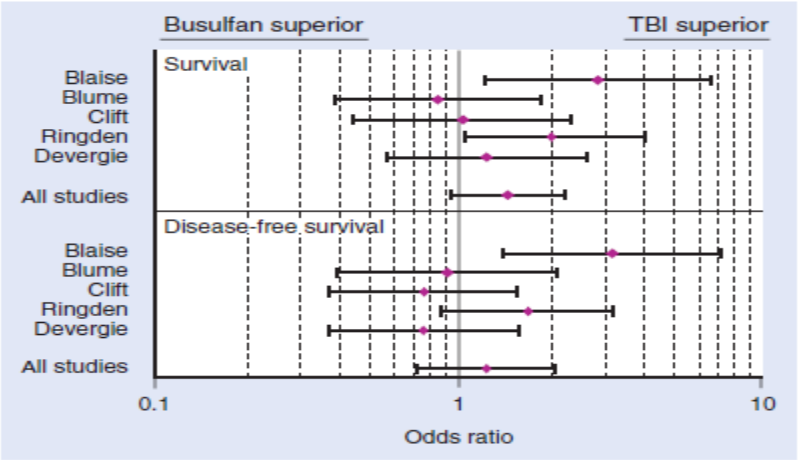

FIGURE 15-8 • Odds ratio and 95% confidence intervals of survival and disease-free survival in a meta-analysis of total body irradiation (TBI)–based conditioning versus non-TBI–based conditioning in five randomized controlled trials. (From Hartman et al: Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs. total body irradiation: a meta-analysis, Bone Marrow Transplant 22:439–443.)

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TBI associated with less veno-occlusive disease (liver complications)

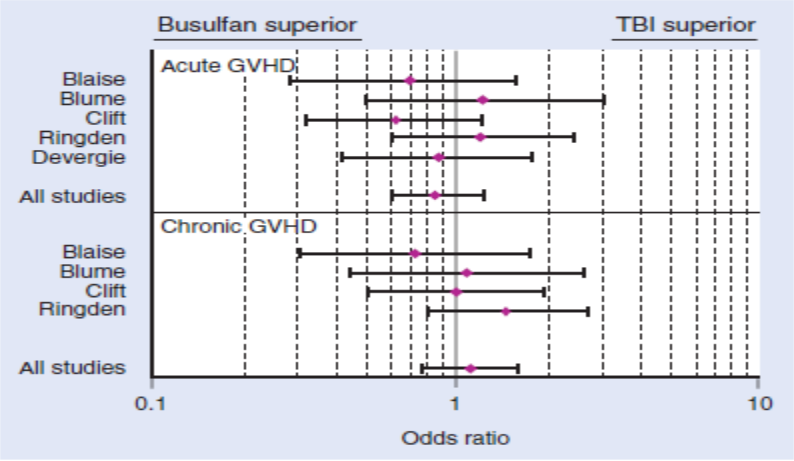

FIGURE 15-9 • Odds ratio and 95% confidence intervals of acute and chronic GVHD in a meta-analysis of total body irradiation (TBI)–based conditioning versus non-TBI–based conditioning in five and four randomized controlled trials, respectively. *GVHD,* Graft-versus-host disease. (From Hartman et al: Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs. total body irradiation: a meta-analysis, Bone Marrow Transplant 22:439–443.)

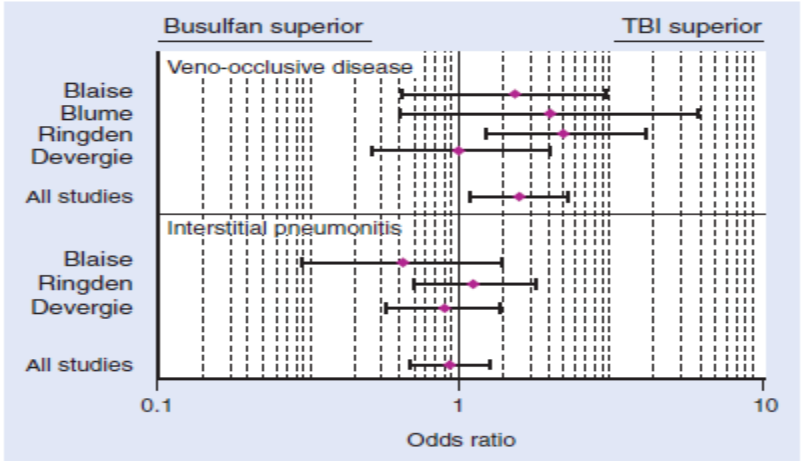

FIGURE 15-10 • Odds ratio and 95% confidence intervals of hepatic veno-occlusive disease and interstitial pneumonitis in a meta-analysis of total body irradiation (TBI)–based conditioning versus non-TBI–based conditioning in four and three randomized controlled trials, respectively. (From Hartman et al: Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs. total body irradiation: a meta-analysis, Bone Marrow Transplant 22:439–443.)

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TBI associated with better outcomes in ALL & AML, but not MM

Table 15-3 Randomized Controlled Trials Comparing Hematopoietic Stem Cell Transplant Conditioning Regimens With and Without Total Body Irradiation

Disease	Author (Group) [Reference]	Number of Patients	Type of Transplant	TBI-Based Conditioning	Non-TBI-Based Conditioning	Total TBI Dose Number & Frequency of Fractions Dose Rate	Technique	Conditioning Regimen	OS	EFS	Relapse	Non-Relapse Mortality	TRM	Other Findings
ALL	Bunin et al. (PBMTC) [270]	43	Allogeneic marrow, cord, or peripheral blood	TBI, etoposide 40 mg/kg in 1 day, then Cy 120 mg/kg in 2 days	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	12 Gy 6 bid Dose rate not described	Not described	TBI Non-TBI	3 yr: 67% 3 yr: 47%	3 yr: 58%* 3 yr: 29%*	43%[1] 32%[1]	24%[1] 9%[1]		No significant difference in GVHD, or pulmonary, cardiac, or neurologic toxicity after HSCT; the TBI group had significantly better EFS among patients who received unrelated donor stem cells, and who were under 6 years
ALL AML CML lymphoma	Ringden et al. (NBMTG) [112, 172]	167	Allogeneic marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	10-12.7 Gy 1-7 given ≥1 times daily 4-12.7 cGy/min	Varied All had lung blocks limiting dose to 9-10 Gy	TBI Non-TBI	7 yr: 63% 7 yr: 54%	7 yr: 62% 7 yr: 51%	7 yr: 29% 7 yr: 29%		7 yr: 14%* 7 yr: 34%*	No significant difference in immunosuppressant use, interstitial pneumonitis, or Karnofsky score, growth, renal, pulmonary, or thyroid function at follow-up; the TBI group had less hepatic VOD, hemorrhagic cystitis, chronic GVHD, death from GVHD, obstructive pronchiolitis, with more cataracts
ALL AML CML	Blume et al. (SWOG) [274]	122	Allogeneic marrow	TBI, then etoposide 60 mg/kg in 1 day	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	13.2 Gy 11 tid Dose rate not described	Not described	TBI Non-TBI	3 yr: ~24% (7 months[2]) 3 yr: ~28% (7 months[2])					No significant difference in GVHD, hemorrhage, sepsis, lung complications, infections, VOD, drug toxicity, relapse, disease free survival
AML	Dusenbery et al. (Minnesota) [261]	35	Autologous marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 200 mg/kg	13.2 Gy 8 bid (4.5 hr apart) 10 cGy/min	6-24 MV photons Bilateral parallel-opposed Head & neck,	TBI Non-TBI	2 yr: 46% 2 yr: 35%	2 yr: 50% 2 yr: 24%	2 yr: 43% 2 yr: 70%	Reported as "not different" Reported as "not different"		No significant difference in time to engraftment, GVHD, time in the hospital, infection, hepative VOD, hemorrhagic cystitis, pneumonitis
AML	Blaise et al. (GEGMO) [260, 262]	101	Allogeneic marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	10-13.5 Gy 1-6 given 1-2 times daily (6 bid[2]) 3-25 cGy/min (5 cGy/min[2])	Varied All had lung blocks (8.8 Gy[2])	TBI Non-TBI	12 yr: 59%* 12 yr: 43%*	12 yr: 55%* 12 yr: 35%*	12 yr: 25% 12 yr: 37%		12 yr: 16% 12 yr: 27%	No significant difference in time to engraftment, GVHD; the TBI group had less chronic GVHD related mortality
CML	Clift et al. (Seattle) [265, 266]	142	Allogeneic marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	12 Gy 6 qd 6-7 cGy/min	Dual opposed 60Co sources Geometry not described Blocks not described	TBI Non-TBI	9 yr: 65% 9 yr: 73%	9 yr: 48% 9 yr: 55%	9 yr: 22% 9 yr: 19%	9 yr: 25% 9 yr: 20%		No significant difference in the rate of engraftment, GVHD, hepatic VOD, number of fevers, deaths from infection, mean duration of first hospitalization; the TBI group did have significantly longer fevers, more blood cultures revealing bacteria or fungi, more than one hospitalization in the 100 days after transplant, and higher incidence of grade 2-4 GVHD
CML	Devergie et al. (SFGM) [267]	120	Allogeneic marrow	TBI, then Cy 120 mg/kg in 2 days	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	10-12 Gy 1-24 given 1-8 times daily (bid[2]) 3-25 cGy/min (8 cGy/min[2])	Varied All had lung blocks (8.8 Gy[2])	TBI Non-TBI	5 yr: 66% 5 yr: 61%	5 yr: 51% 5 yr: 59%	5 yr STBI: 11%* 5 yr FTBI: 31%* 5 yr: 4%*	Not reported Not reported	29%[1] 38%[1]	No significant difference in the rate of engraftment, GVHD, hepatic VOD, interstitial pneumonitis, hemorrhagic cystitis, GVHD
MM	Moreau et al. (IFM) [273]	282	Autologous peripheral blood	TBI, then Mel 140 in 1 day	Mel 200 in 1 day	8 Gy 4 qd Dose rate not described	Not described No lung blocks	TBI Non-TBI	3.75 yr: 45.5% 3.75 yr: 65.8%*	21 months[2] 20.5 months[2]			3.6%[1] 0%[1]	No significant difference in growth factor use, cardiac, pulmonary, renal, liver toxicity, or response rates; the TBI group had significantly higher rates of mucositis and hematologic toxicity, and longer hospitalizations

All drug doses given as mg/m² unless otherwise stated.
bid, Twice daily; *Bu*, busulfan; *Cy*, cyclophosphamide; *EFS*, even-free survival; *Mel*, melphalan; *OS*, overall survival; *tid*, three times daily; *TRM*, transplant related mortality; *qd*, once daily.
*Statistically significant difference; [1]observed incidence; [2]median.

TBI used in non-myeloablative regimens for various diseases

Table 15-4 Representative Total Body Irradiation–Based Reduced Intensity Conditioning Regimens for Allogeneic Hematopoietic Stem Cell Transplant

Disease	Author (Group) [Reference]	Number of Patients	Total TBI Dose Number & Frequency of Fractions Dose Rate	Additional Conditioning Therapy	Technique	Type of Transplant
AML	Hegenbart et al. (multicenter) [282]	122	2 Gy 1 ~~0.07 to~~ ~~0.20 Gy~~/min	84% received Flu 90 in 3 days, then TBI	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic marrow (5%) and peripheral blood (95%)
AML	Stelljes et al. (COSTSG) [283]	71	8 Gy 4 given twice daily 8.9-30 cGy/min	TBI, then Flu 120 in 4 days +/- ATG	Not described	Allogeneic marrow (4%) and peripheral blood (96%)
AML	Hallemeier et al. (Washington U.) [284]	32	5.5 Gy 1 27.6-36.4 cGy/min	Cy 120 in 2 days, then TBI	6 MV photons from linear accelerator Parallel opposed lateral fields Arms at side for lung shielding	Allogeneic peripheral blood
CLL	Sorror et al. (Seattle) [285]	64	2 Gy 1 7 cGy/min	83% received Flu 90 in 3 days, then TBI	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
CML	Kerbauy et al. (Seattle) [286]	24	2 Gy 1 7cGy/min	67% received Flu 90 in 3 days, then TBI	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
CML	Khoury et al. (Washington U.) [287]	30	5.5 Gy 1 26.4-36.0 cGy/min	Cy 120 in 2 days, then TBI	6 MV photons from linear accelerator Parallel opposed lateral fields Arms at side for lung shielding	Allogeneic peripheral blood
Hematologic malignancy	McSweeney et al. (Seattle) [288]	45	2 Gy 1 7 cGy/min	None	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
Hematologic malignancy	Baron et al. (Seattle) [289]	221	2 Gy 1 7 cGy/min	77% received Flu 90 in 3 days, then TBI	Not described	97% allogeneic peripheral blood
Lymphoma	Tomblyn et al. (Minnesota) [290]	76	2 Gy 1 Dose rate not reported	Flu + Cy, then TBI or Flu + Bu, then TBI or Bu + Clad, then TBI	Not described	Allogeneic marrow (10%), peripheral blood (46%), and cord blood (43%)
Mantle cell lymphoma	Maris et al. (Seattle) [291]	33	2 Gy 1 7 cGy/min	Flu 90 in 3 days, then TBI	Linear accelerator Geometry not described Blocks not described	Allogeneic marrow (4%) and peripheral blood (96%)
MDS/AML	Schmid et al. (Wiesbaden) [292]	75	4 Gy 1 Dose rate not reported	TBI, then Cy 80-120 in 2 days, ATG	Not described	Allogeneic marrow (19%) and peripheral blood (81%)
MDS/MPD	Laport et al. (multicenter) [293]	148	2 Gy 1 7 cGy/min	97% received Flu 90 in 3 days, then TBI	Linear accelerator Geometry not described Blocks not described	Allogeneic marrow (2%) and peripheral blood (98%)
MDS/secondary AML	Hallemeier et al. (Washington U.) [294]	51	5.5 Gy 1 25.3-37.2 cGy/min	Cy 120 in 2 days, then TBI	6 MV photons from linear accelerator Parallel opposed lateral fields Arms at side for lung shielding	Allogeneic peripheral blood
MM	Maloney et al. (Seattle) [295]	54	2 Gy 1 7 cGy/min	17% received Flu 90 in 3 days, then TBI	Linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
MM	Badros et al. (Arkansas) [296]	31	2.5 Gy 2 given twice in 1 day Dose rate not reported	TBI and Mel 100, then Flu 60 in 2 days	Not described	Allogeneic peripheral blood

All drug doses given in mg/kg unless otherwise stated.
AML, Acute myelogenous leukemia; *ATG*, antithymocyte globulin; *Bu*, busulfan; *Clad*, cladribine; *CLL*, chronic lymphoid leukemia; *CML*, chronic myelogenous leukemia; *Cy*, cyclophosphamide; *Flu*, fludarabine; *melphalan*; *MDS*, myelodysplastic syndrome; *MM*, multiple myeloma; *MPD*, myeloproliferative disorder.

Memorial Sloan Kettering Cancer Center

From *Textbook of Radiation Oncology*, 2010

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Hypersplenism, splenomegaly

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Vice-chairman, International Lymphoma Radiation Oncology Group

Splenomegaly

- Seen in CML, CLL, myelofibrosis, other myeloproliferative disorders, hairy cell leukemia, splenic marginal lymphoma
- Caused by:
  - Leukemic infiltration
  - Extramedullary hematopoiesis
  - Important (but sometimes difficult) to tell the difference

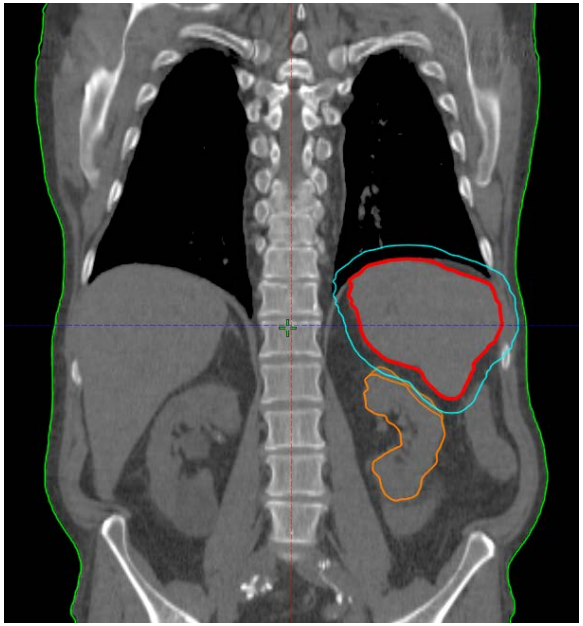
Splenic irradiation

- Used less often than in the past because of more effective systemic treatment
- Indications:
  - Palliative for pain and pressure symptoms
  - Reduction of tumor burden
  - Hypersplenism

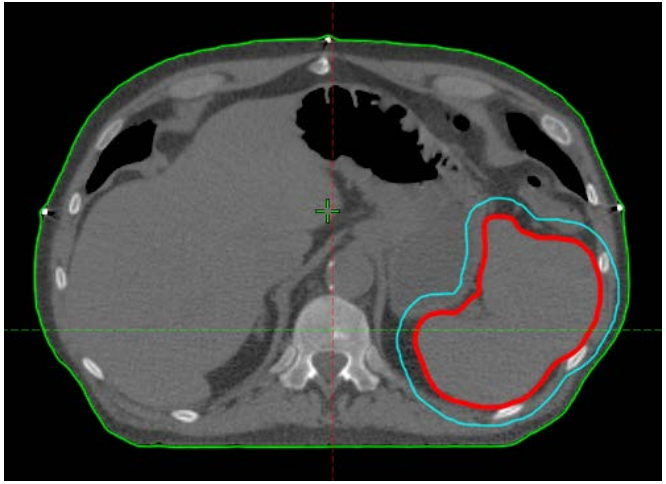
Splenic irradiation

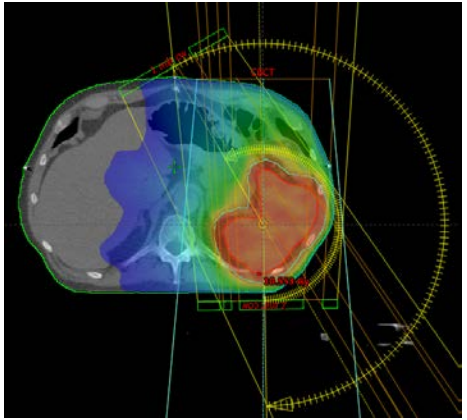
- Often significant extramedullary hematopoiesis in enlarged spleen
- Irradiation must be done with caution, risk of severe long-lasting pancytopenia
- E.g., 0.5 Gy x 20, 5 F/W
- Close monitoring of blood counts

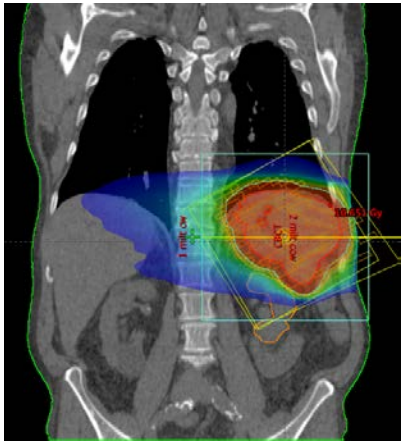
Splenic irradiation



70 year old male,
CMMOL, pain







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WHO Classification of Lymphomas: how pathology reflects biology to inform treatment

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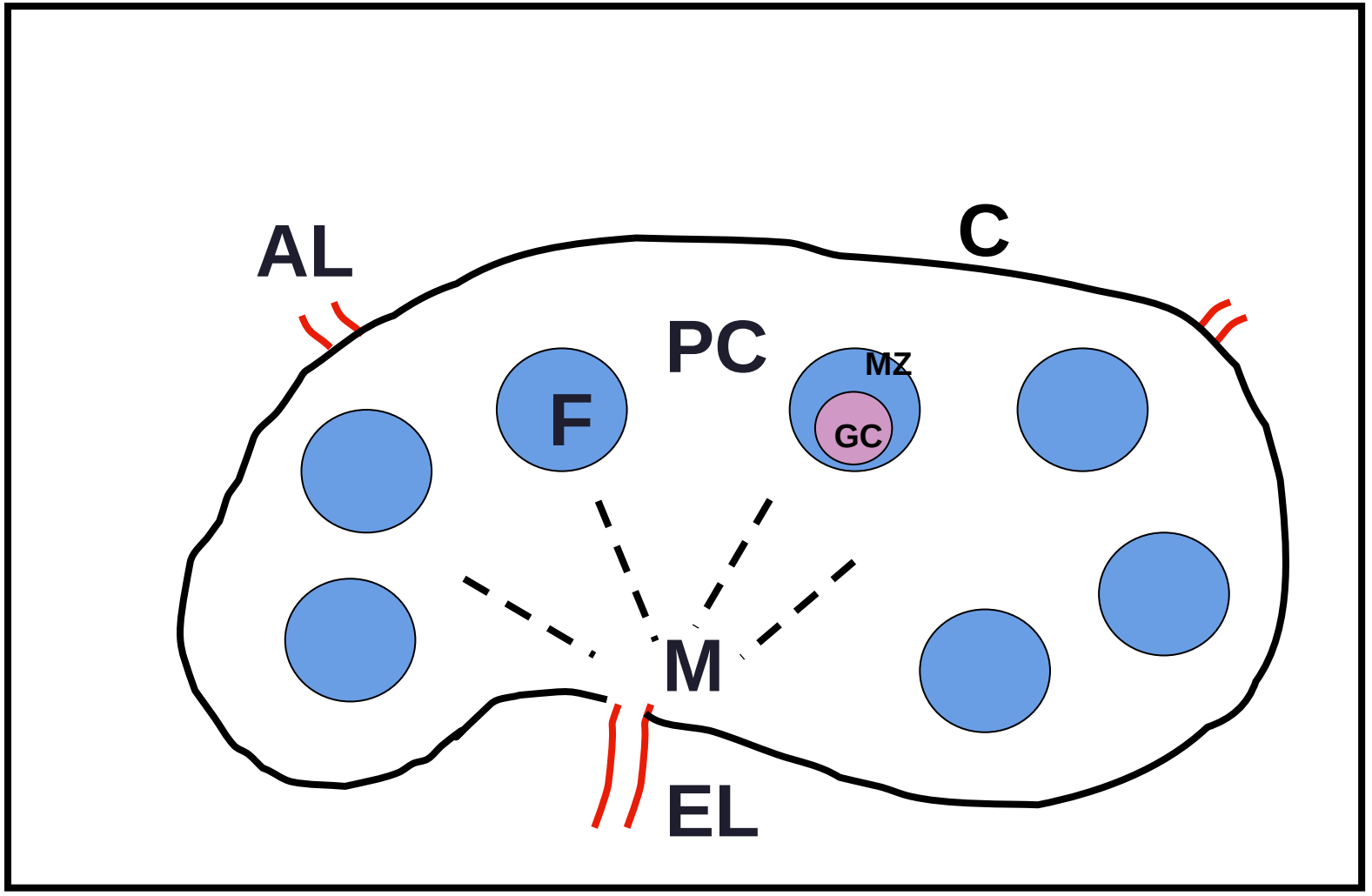
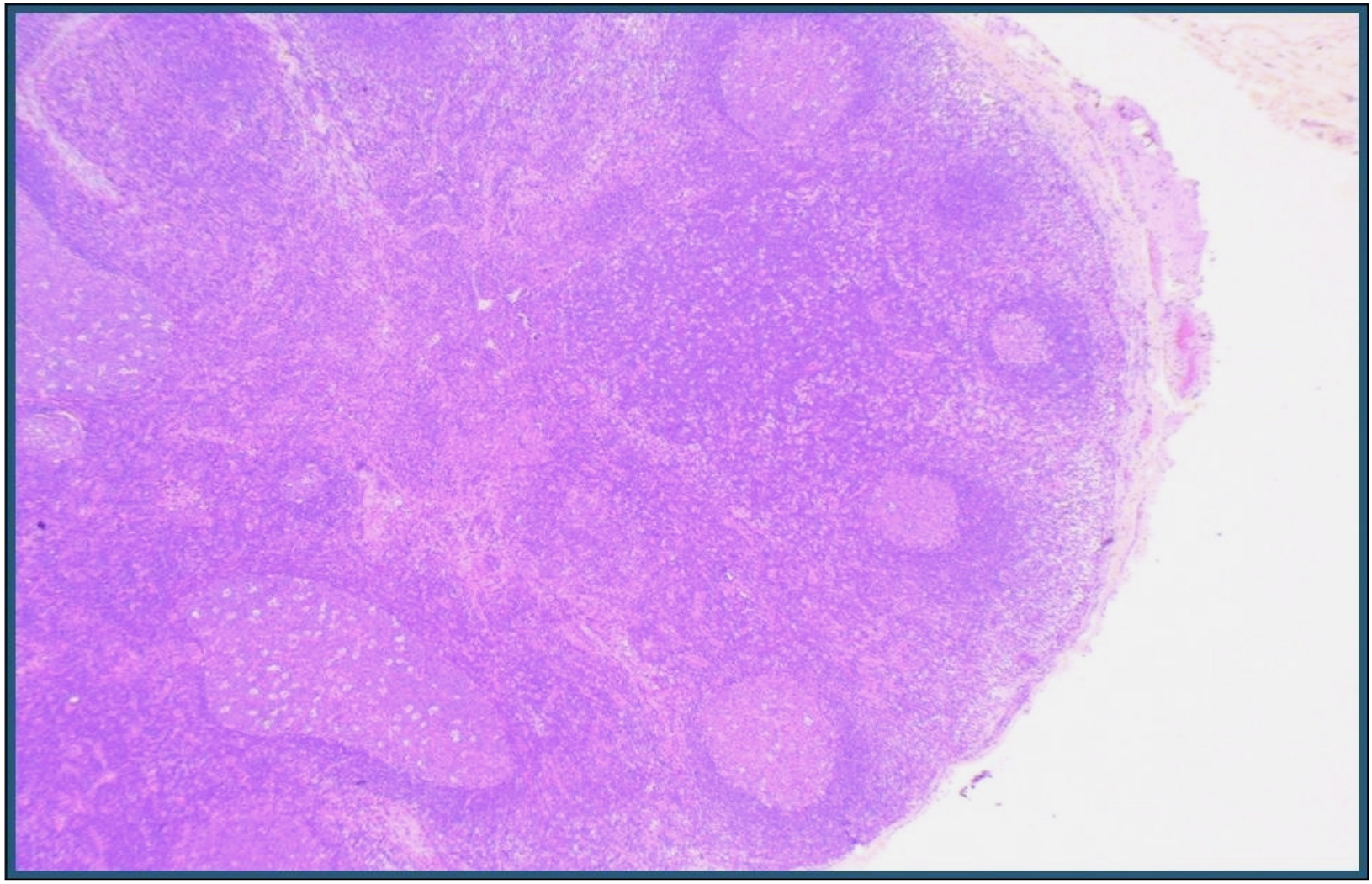
Lymph node structure reflects function



Reactive lymph node



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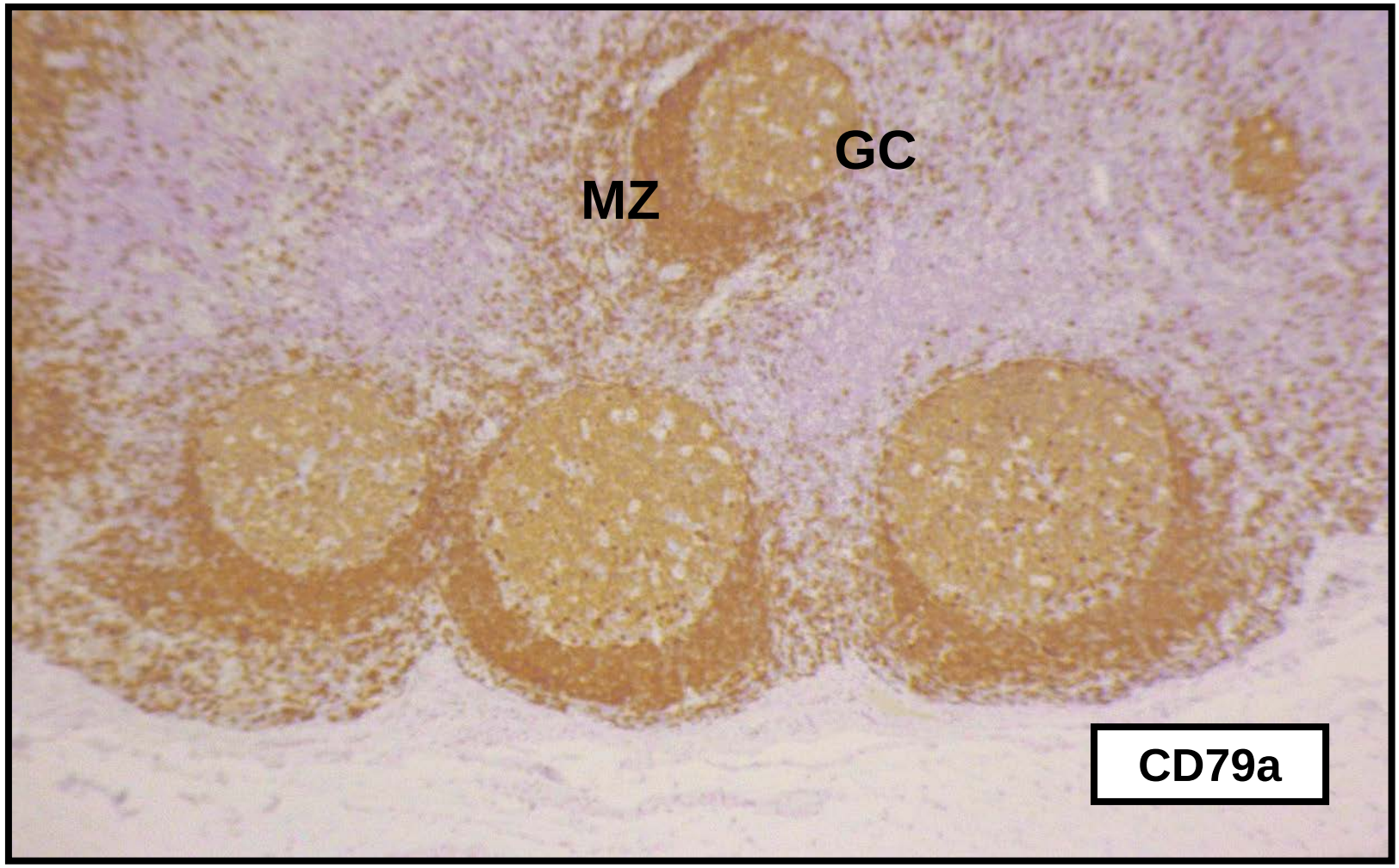
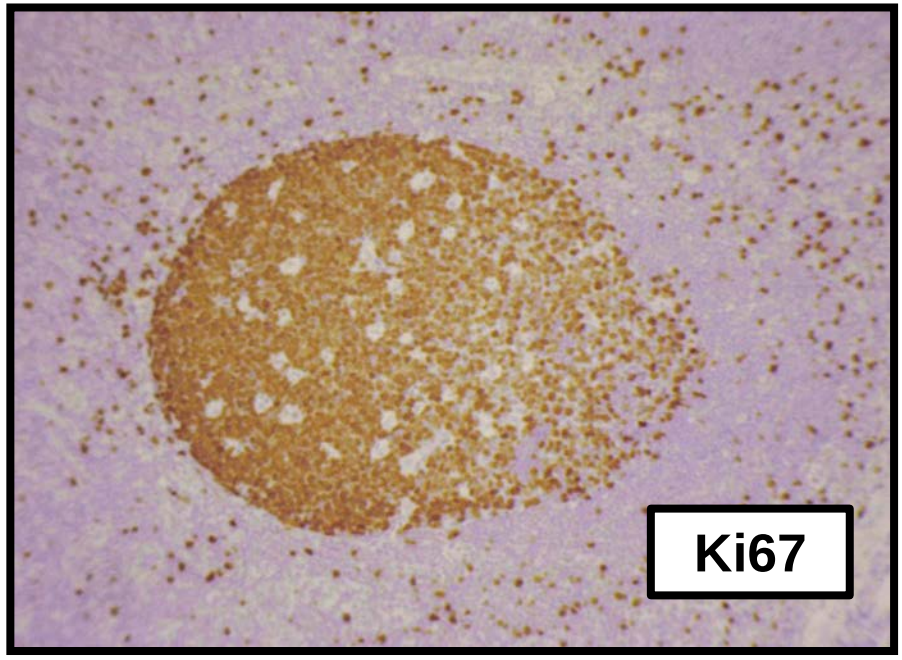
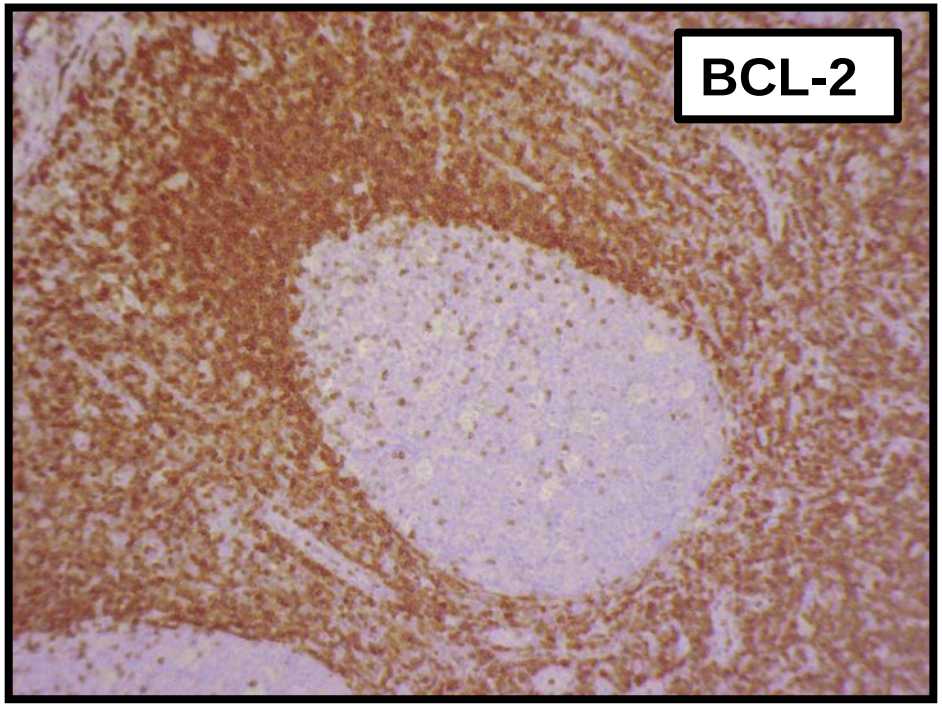
Lymphoid follicles: factories for B-cell production



B-cell proliferation and apoptosis are essential in germinal centres





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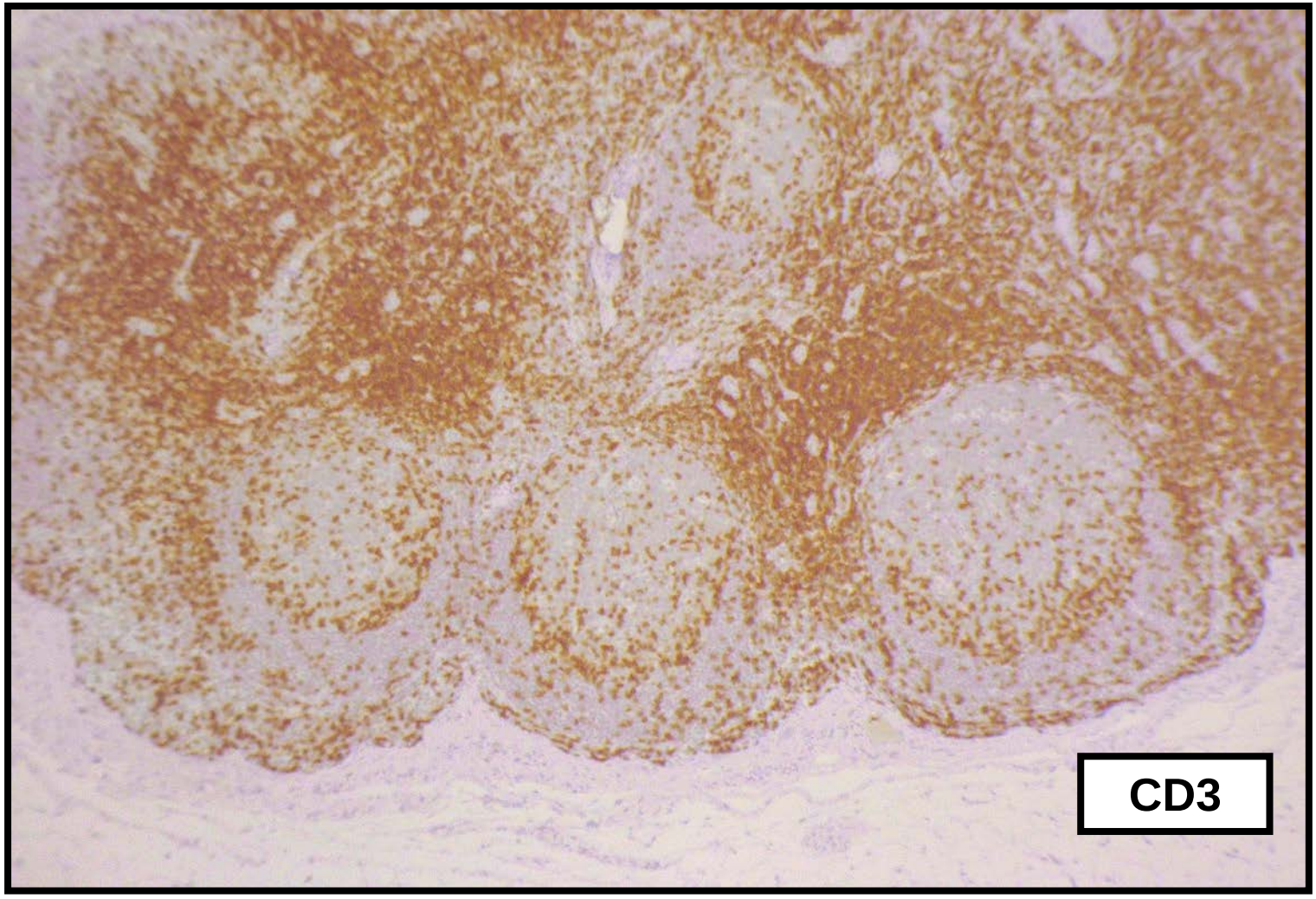
Paracortical T-cell zone and T-cells in follicles



Principles of WHO lymphoma classification

- Aims to define clinically relevant entities
- Diagnosis based on integration of clinical, histological, immunophenotypic and genetic features
- Basic division into ‘precursor’ and ‘mature’ (or ‘peripheral’) lymphomas. Then by lineage (B/T/NK-cell)
- Thymus and bone marrow are primary sites of precursor T- and B-cell development
- ‘Peripheral’ sites are deep and superficial lymph nodes and extranodal (e.g., mucosal) lymphoid tissues

What does histology tell us?

- In the context of clinical information about site(s) of involvement, ‘B’ symptoms etc:
- Small cells (‘-cytes’) vs large cells (-’blasts’) vs mixed small and large
- Presence and extent of accompanying reactions (histiocytes, granulomas, eosinophils, fibrosis, necrosis)
- Architectural features: nodular (potentially follicular) vs diffuse, and mixtures
- Presence of defining cell types; Hodgkin/Reed-Sternberg cells, popcorn cells, hallmark cells...

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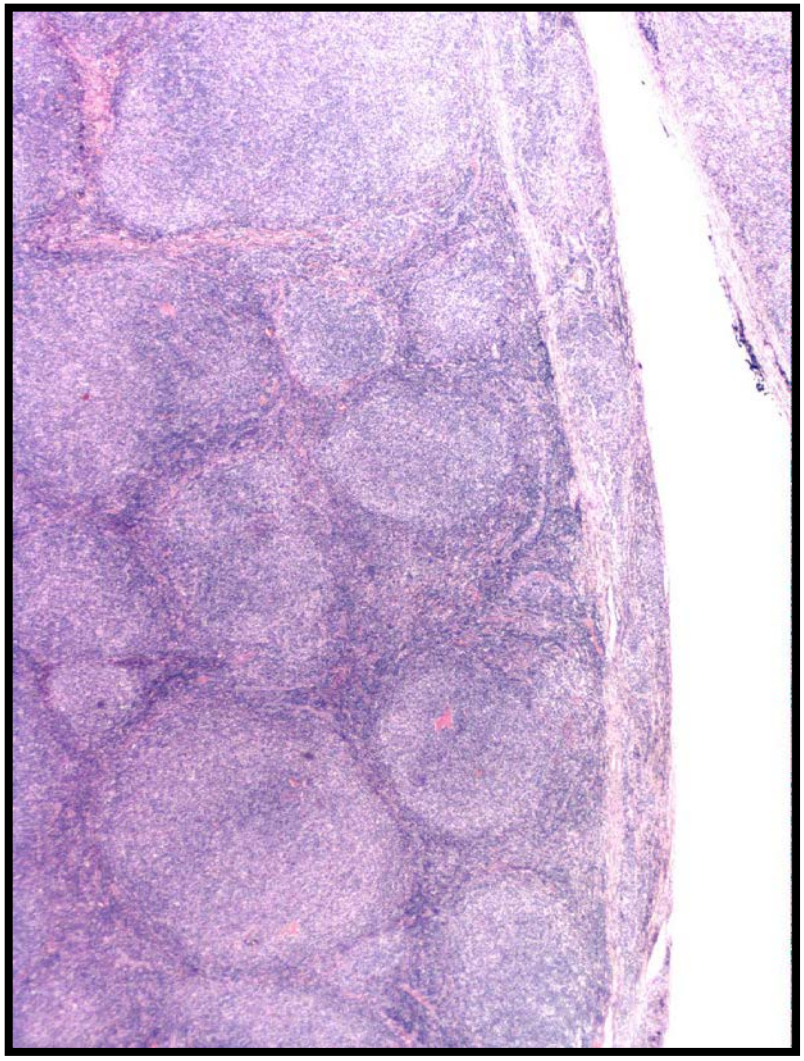
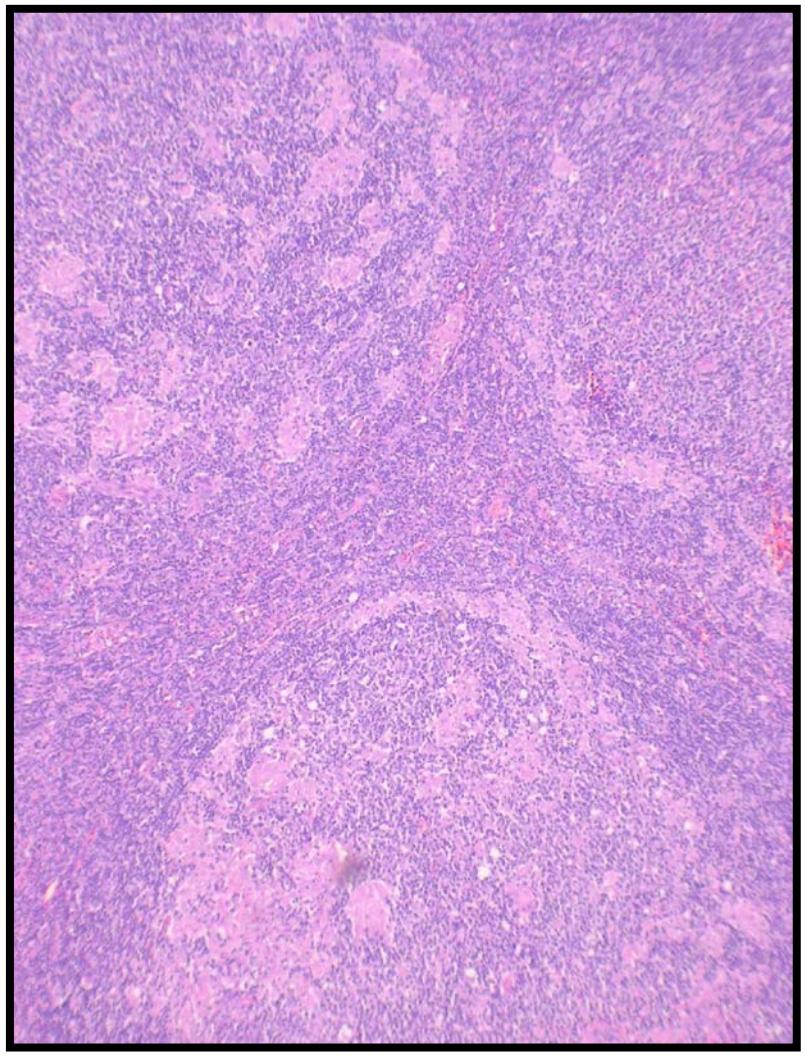
Nodular/Follicular Architecture





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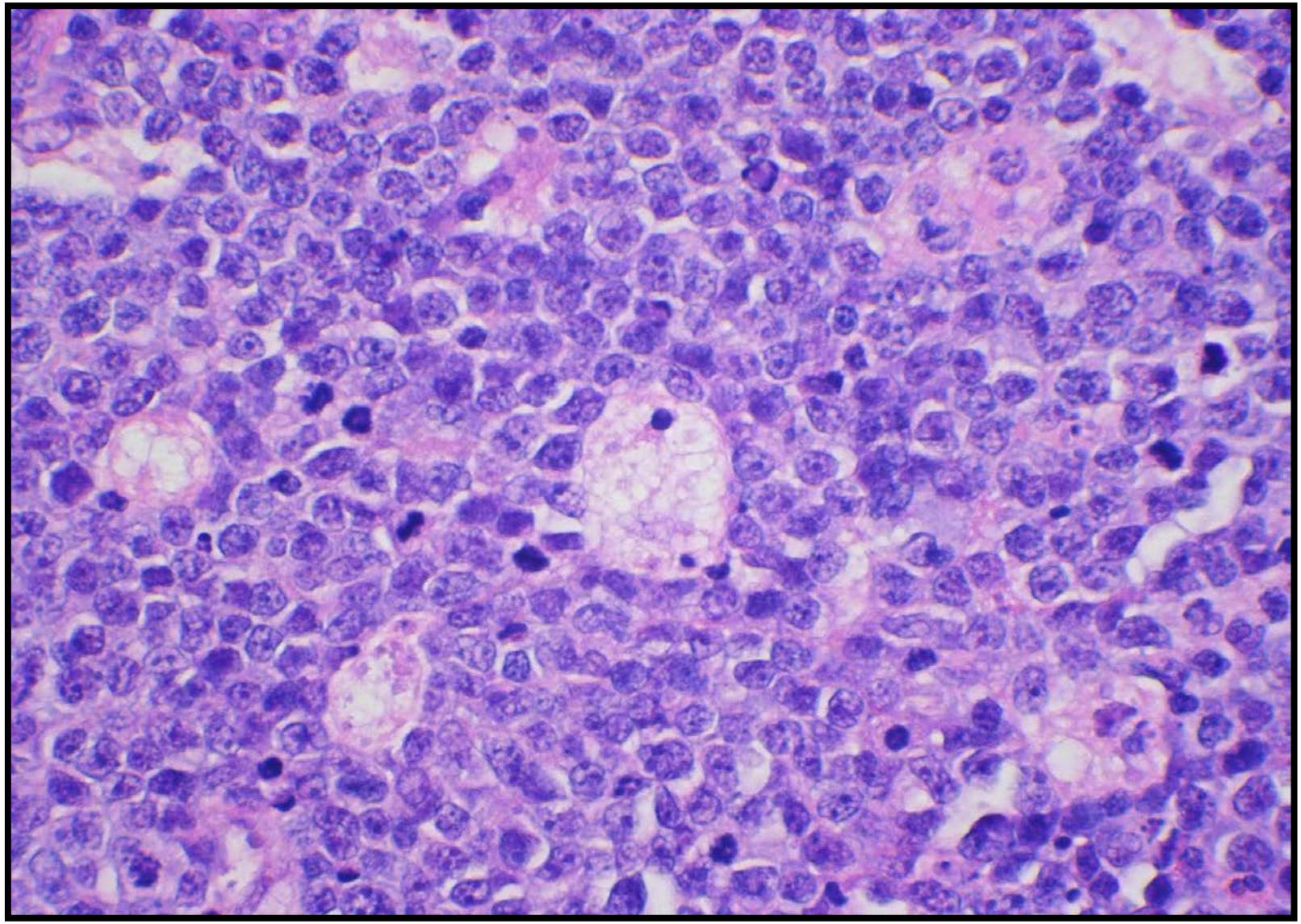
‘Classical’ Morphology in Burkitt Lymphoma



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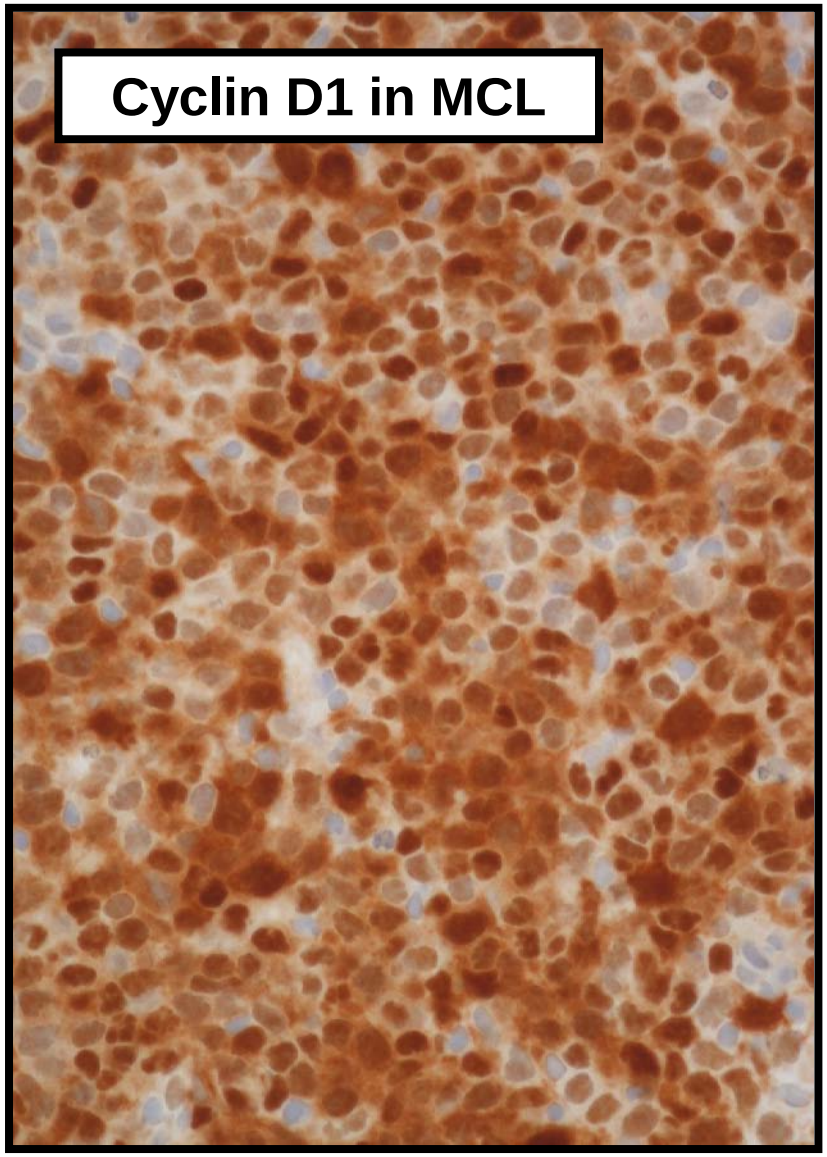
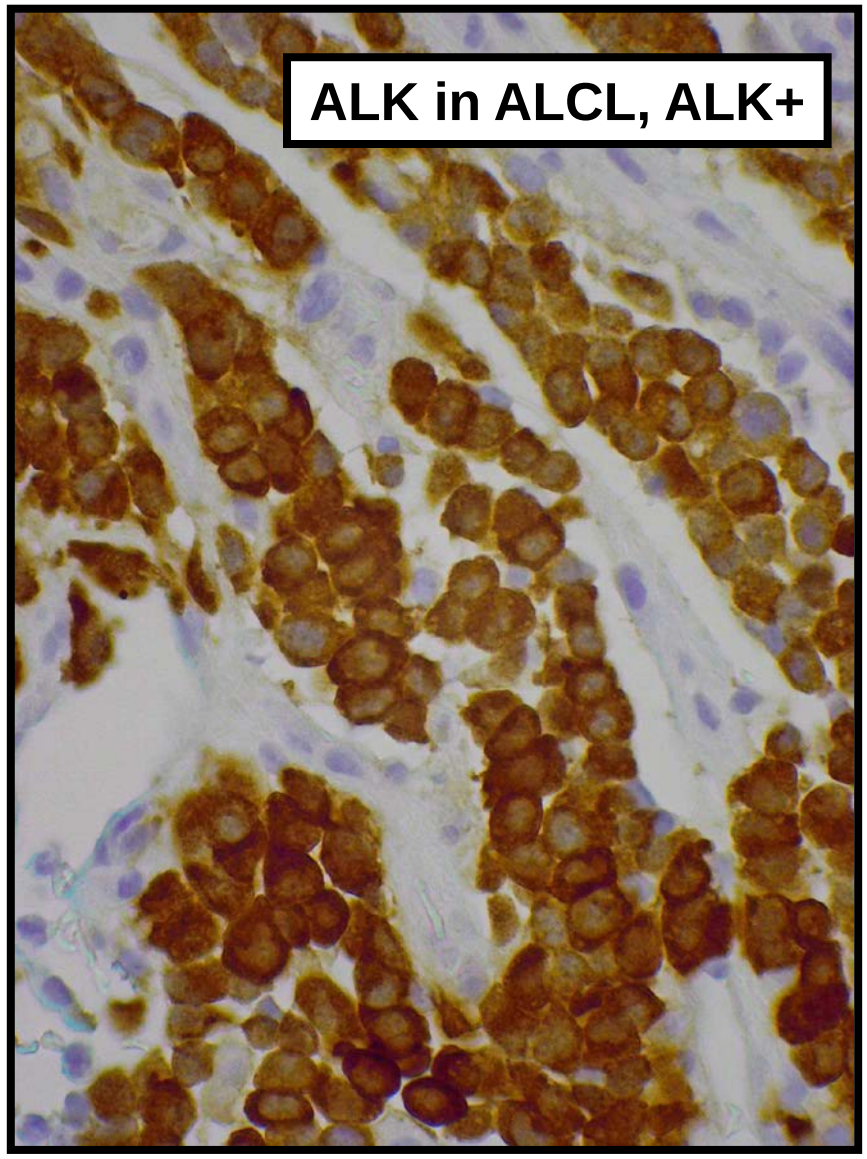
What does immunophenotype tell us?

- In the context of appropriate (consistent) histology:
- Lineage and sub-lineage: B-/ T-/NK-cell, CD4/CD8 T-cells, CD10+/MUM1+ B-cells
- Characterisation of accompanying reactions (histiocytes and histiocyte-derived dendritic cells, mesenchyme-derived dendritic cells, mucosal lympho-epithelial interactions)
- May reinforce architectural features: e.g. revealing subtle nodularity (potential follicularity)
- Some cellular immunophenotypes are defining

Defining Immunophenotypes





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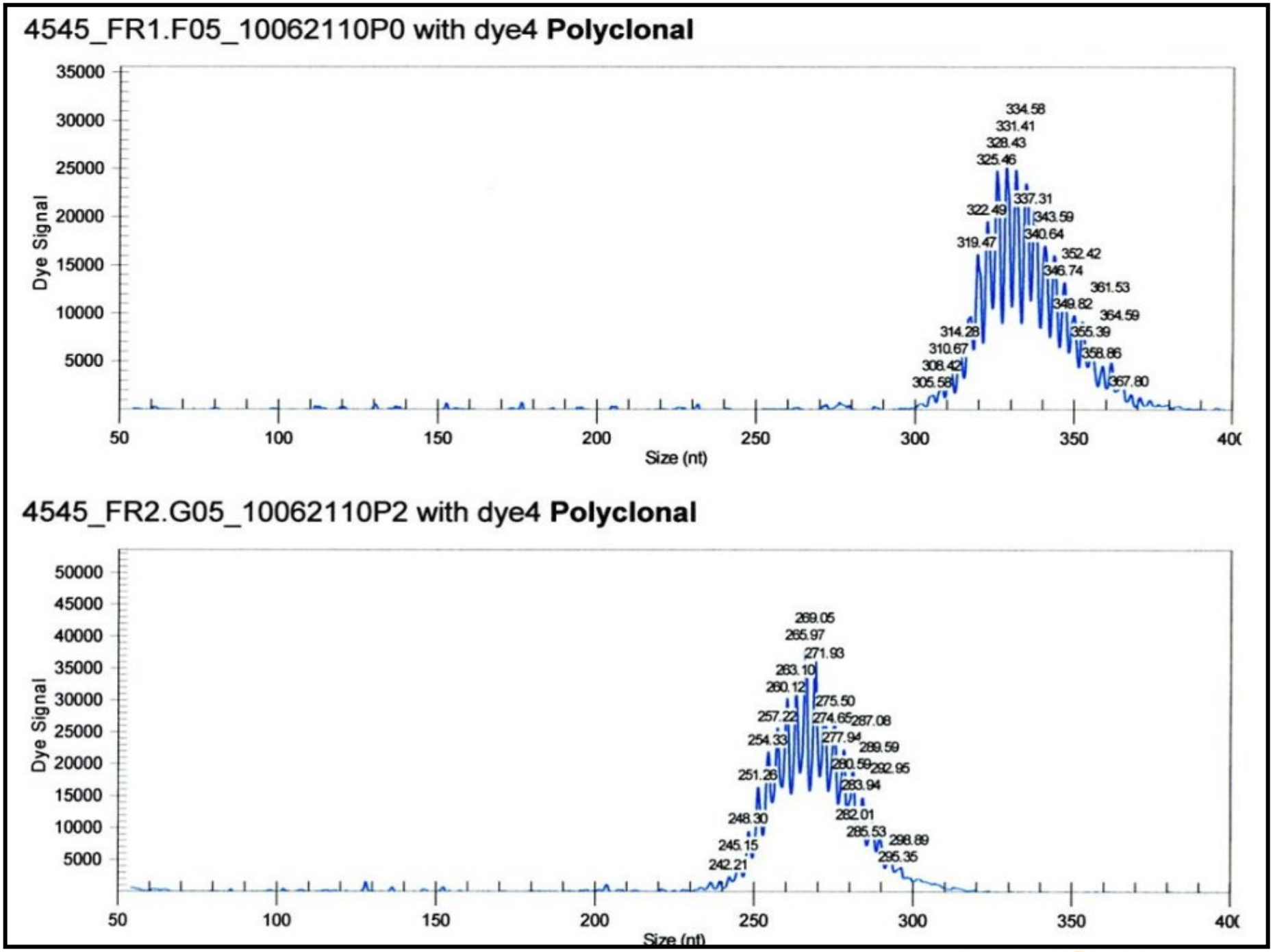
What does genetic information add?

- In the context of appropriate (consistent) histology and immunophenotype:
- Confirmation of monoclonal vs polyclonal lymphoid cell proliferation
- Demonstration of defining rearrangements e.g., *IGH-BCL2, CCND1-IGH, MYC*
- *Rearrangements of prognostic value e.g., MYC, IGH-BCL2 and BCL6, API2-MALT1*

When do we use PCR and when FISH?

- Efficient PCR primer binding requires breakpoints that occur only at restricted, highly consistent areas of the genome.
- Breakpoints in antigen receptor rearrangement (*IGH* and *TCR*) have appropriate properties, favouring PCR.
- IGH-BCL2 breakpoints are variable but partly meet the necessary criteria; CCND1-BCL2 breakpoints are even more variable. MYC rearranges with several partner genes, often unknown.
- FISH probes are much larger and less 'fussy' than PCR primers



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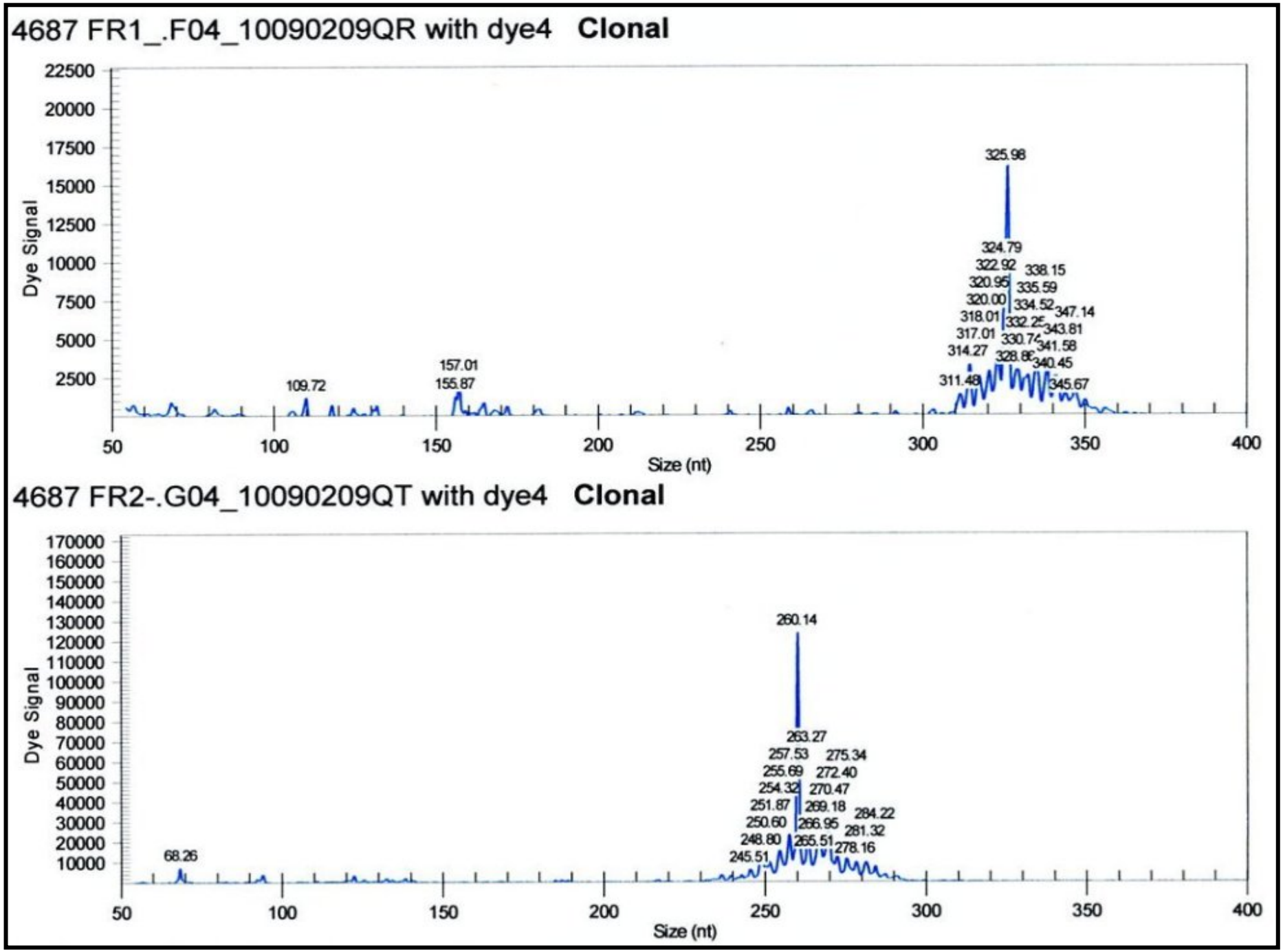
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318.01
332.25
343.81
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341.58
314.27
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340.45
311.48
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157.01
155.87
109.72
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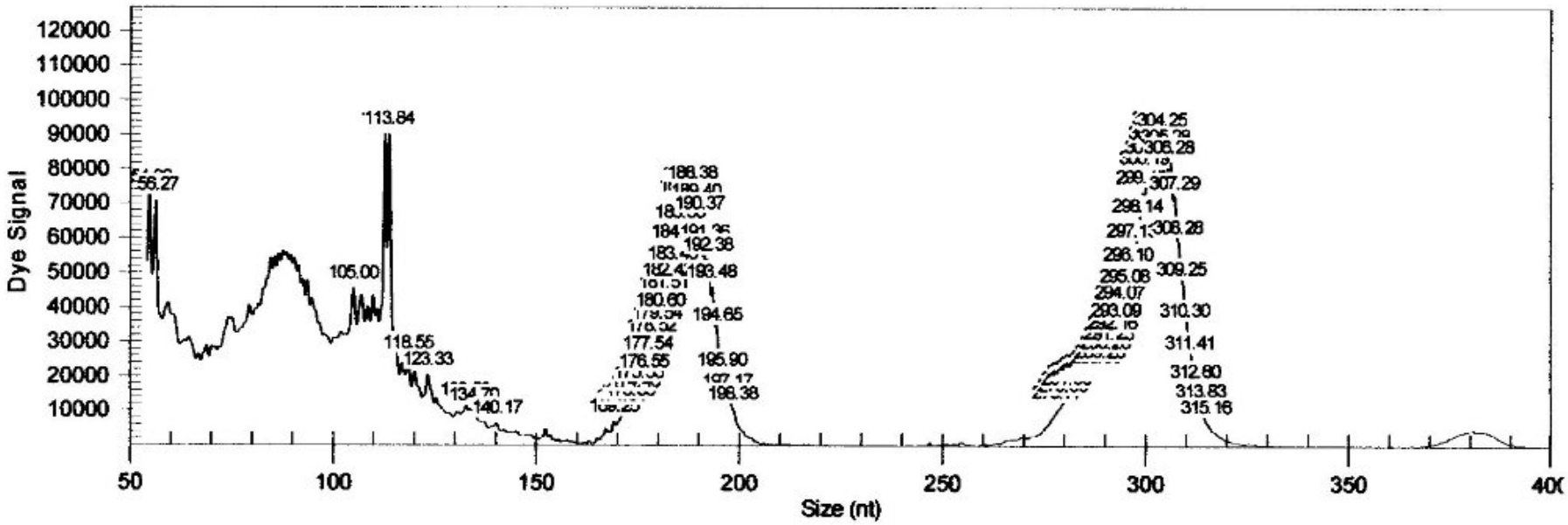
245.51
68.26

ELA322_W7516_BC1.C04_14050808KX with dye4 Polyclonal



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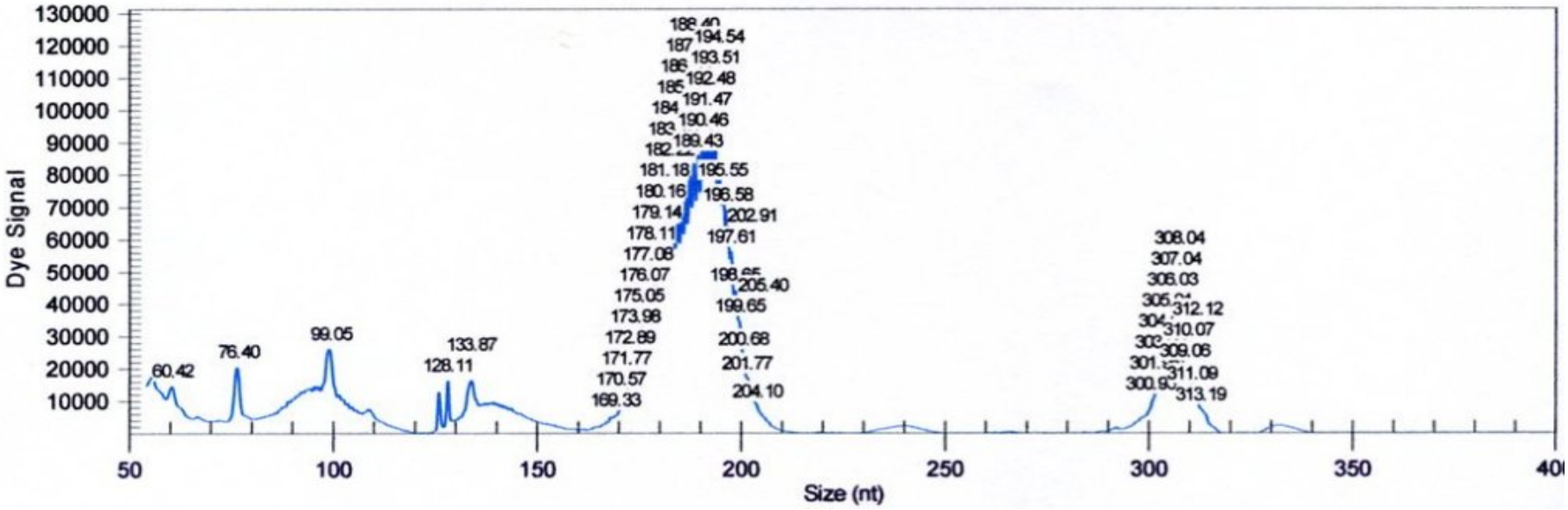

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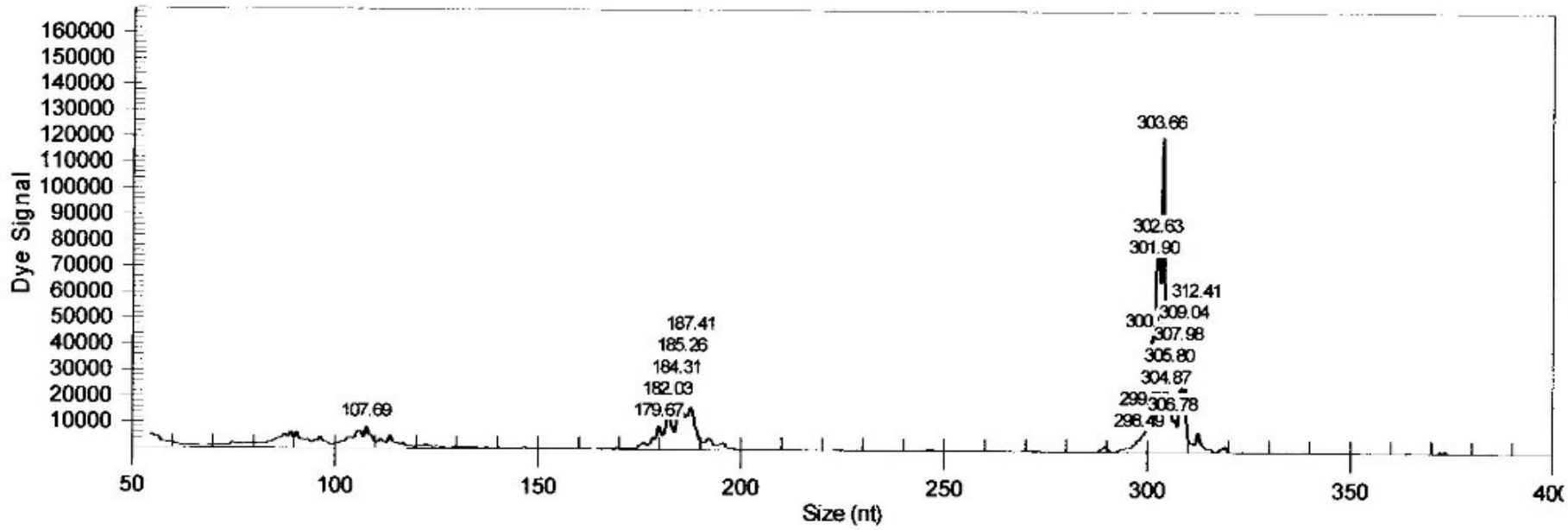
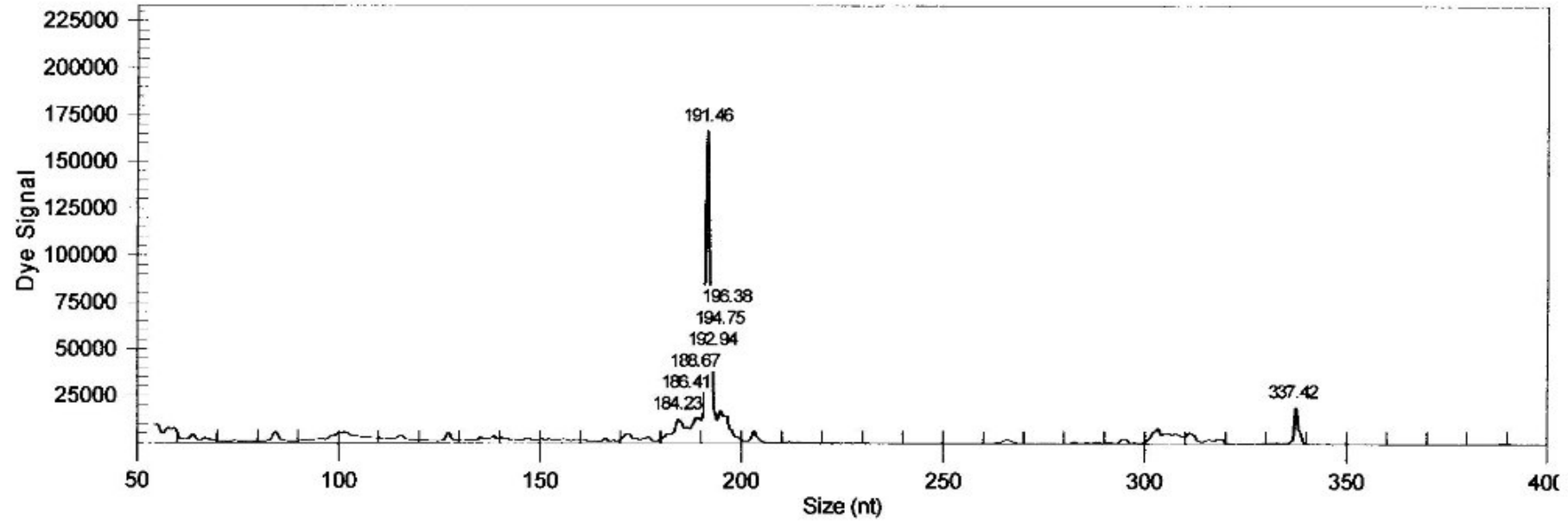


ELA013_W4720_BC2.D09_10092408TU with dye4 **Clonal**



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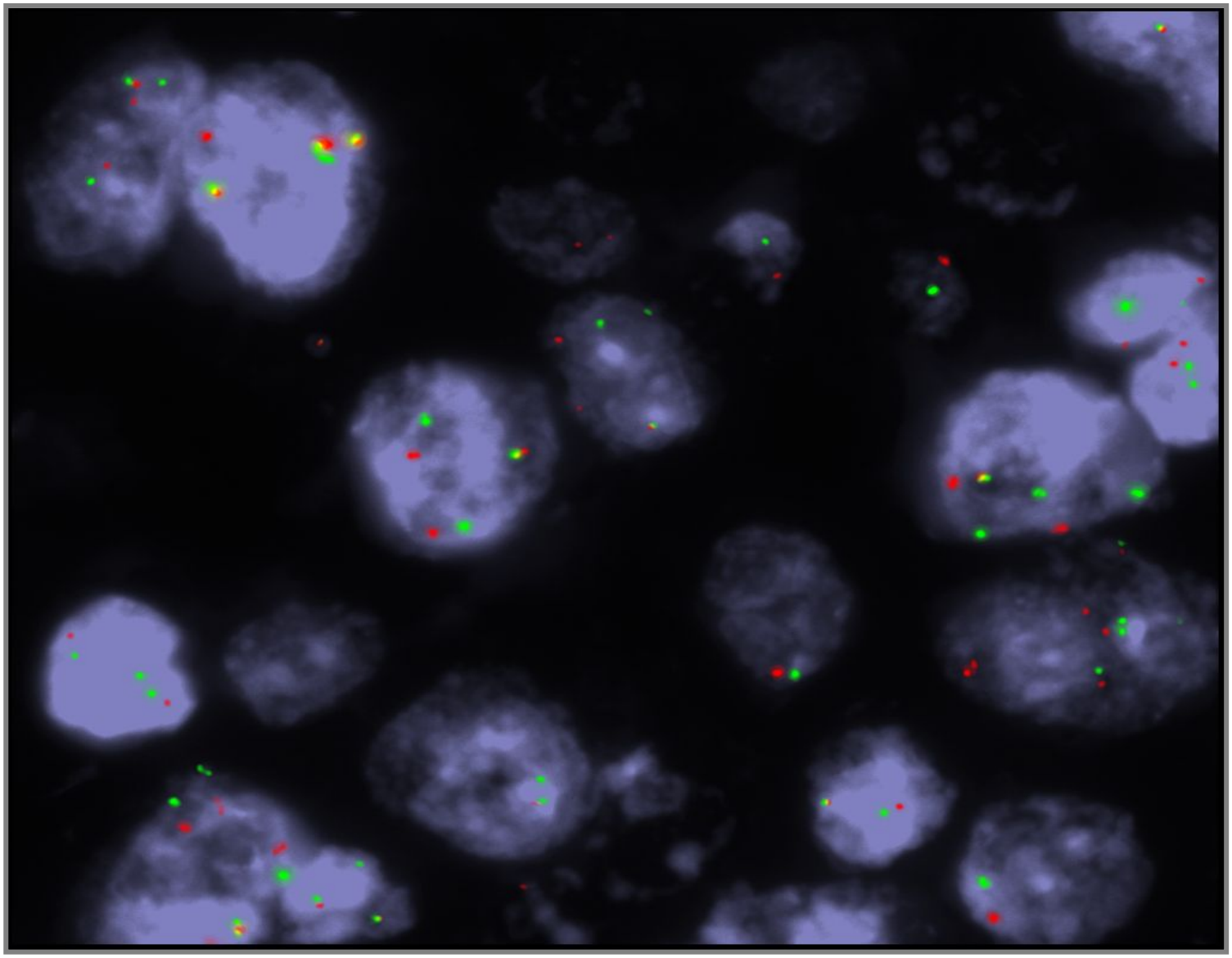
FISH for t(8;14) - *MYC-IGH* Translocation



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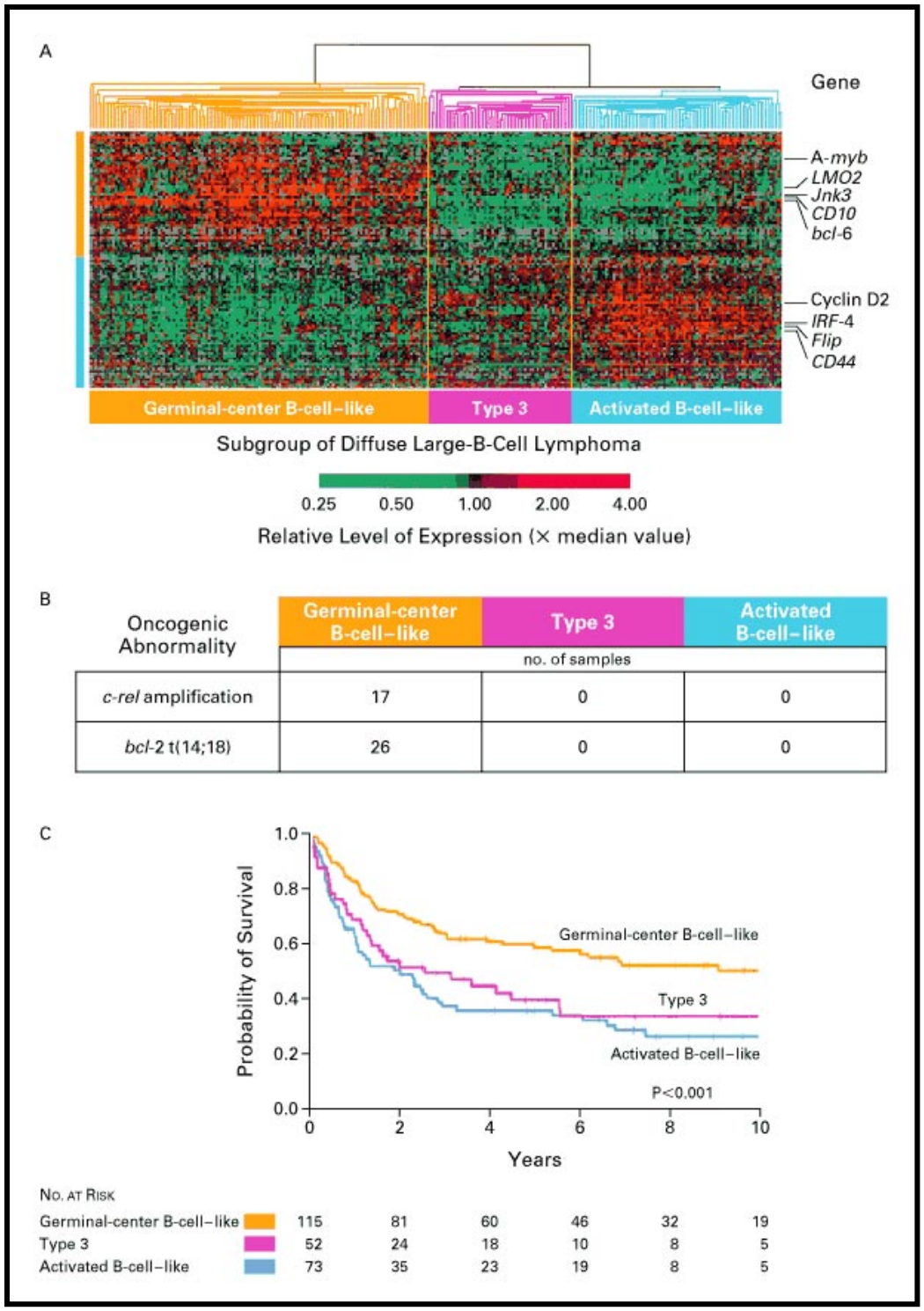

B

Oncogenic Abnormality	Germinal-center B-cell–like	Type 3	Activated B-cell–like
	no. of samples		
c-rel amplification	17	0	0
bcl-2 t(14;18)	26	0	0

Germinal centre (GC) versus Activated B-cell (ABC) subtypes of DLBCL (Dave, 2001)

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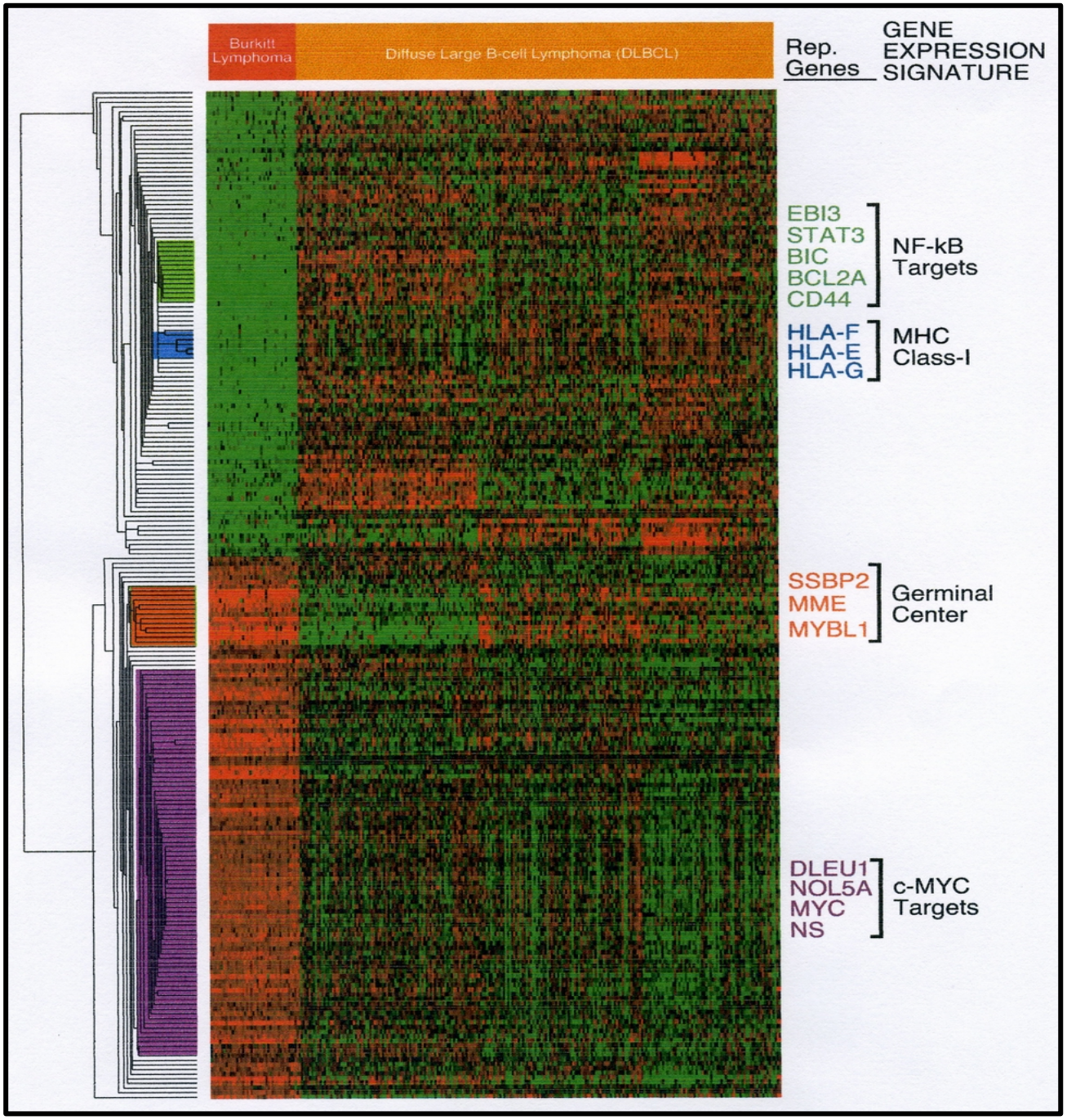

DNA microarray profiling of Burkitt lymphoma vs. DLBCL (Dave, 2006)

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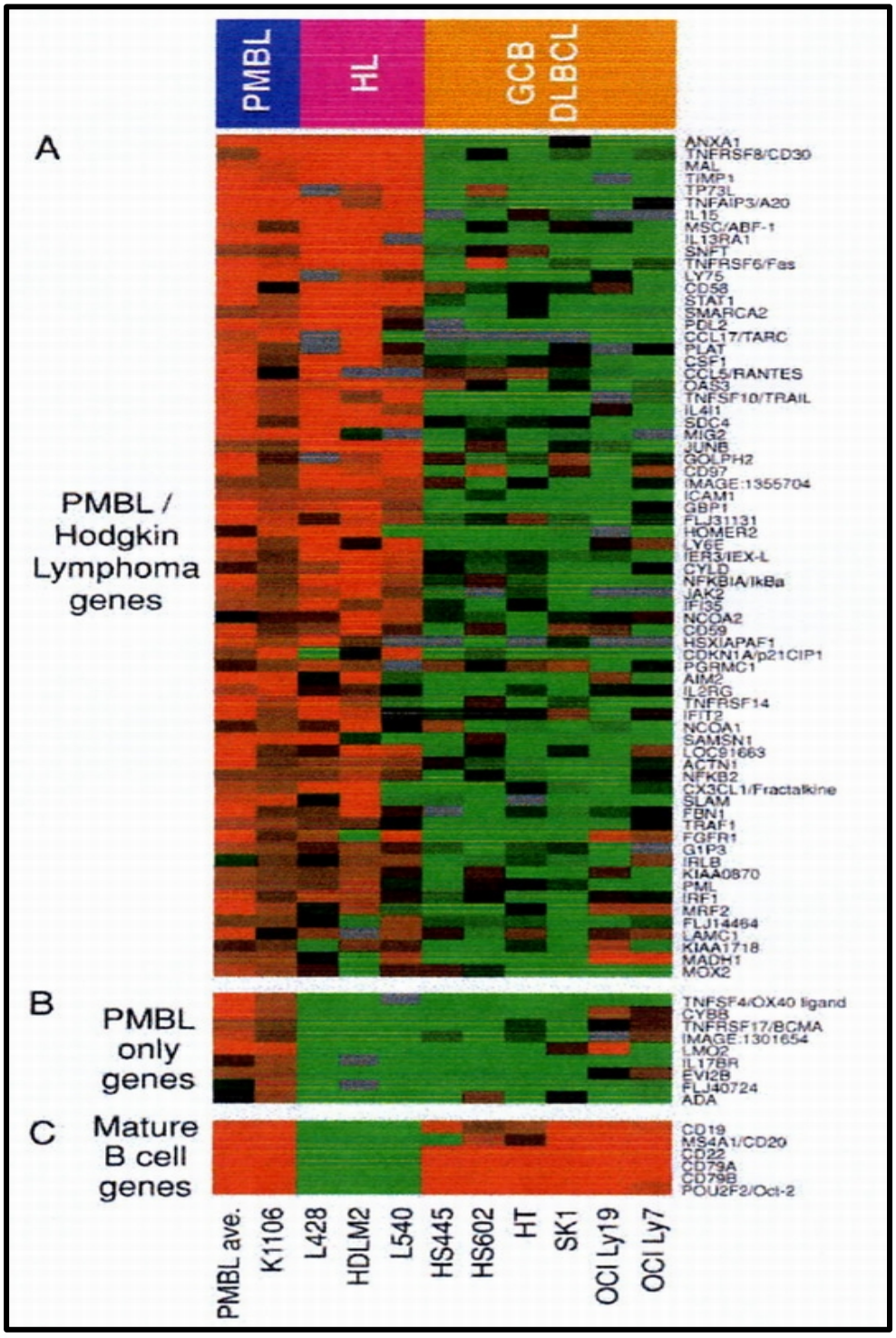

Classical Hodgkin lymphoma DNA microarray vs. nodal GC-DLBCL and mediastinal DLBCL
(Rosenwald, 2003)

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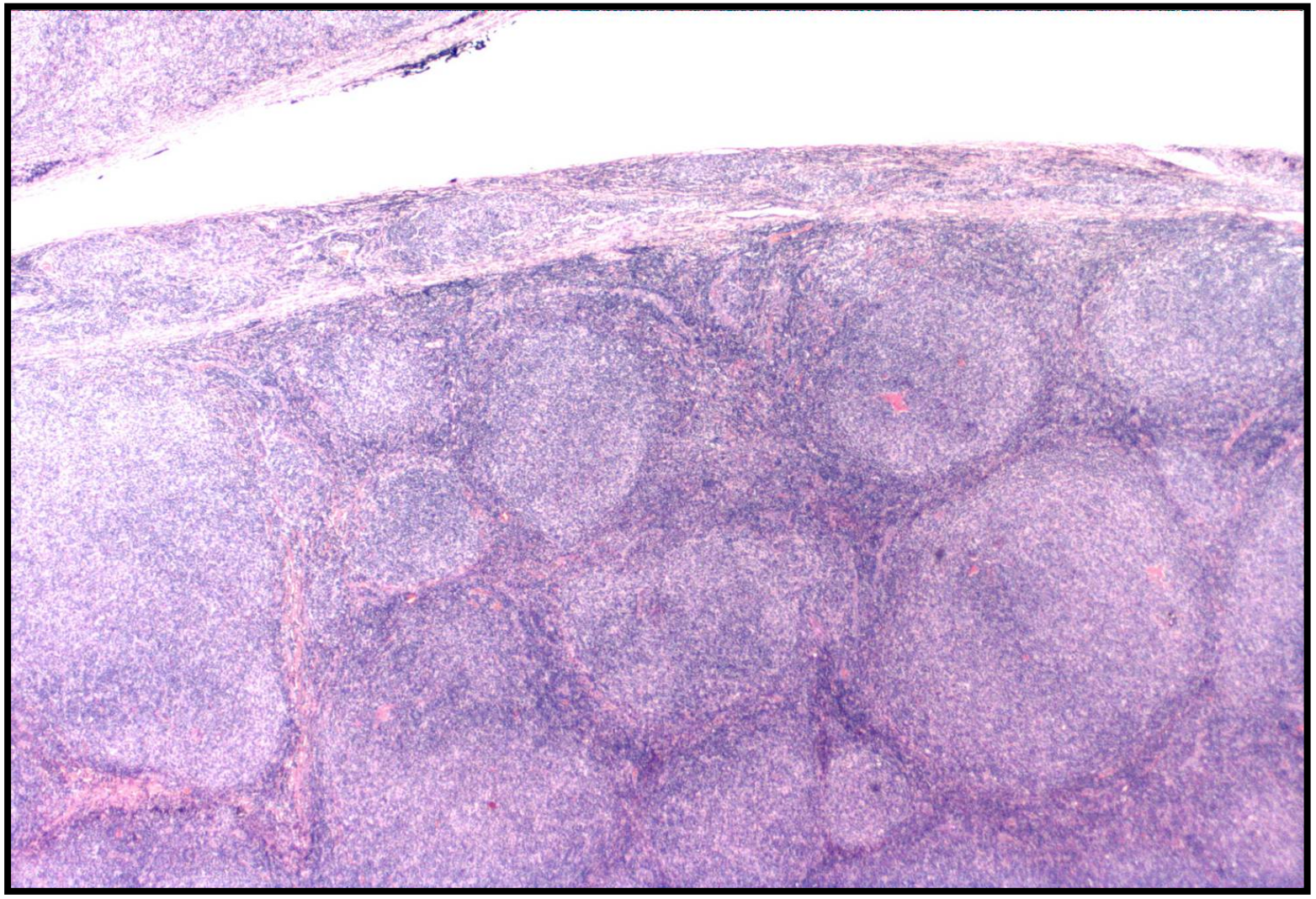
Lymphomas mainly involving lymph nodes

- Follicular lymphoma
  - grades 1-3, with increasing content of centroblasts
  - Grades 1 and 2 - indolent
  - grade 3a (?aggressive) versus grade 3b (aggressive)

- Diffuse large B cell lymphoma (DLBCL)
- Angio-immunoblastic T-cell lymphoma
- Anaplastic large (T-cell) lymphoma

- Classical Hodgkin lymphoma
- Nodular lymphocyte predominant Hodgkin lymphoma

Follicular lymphoma



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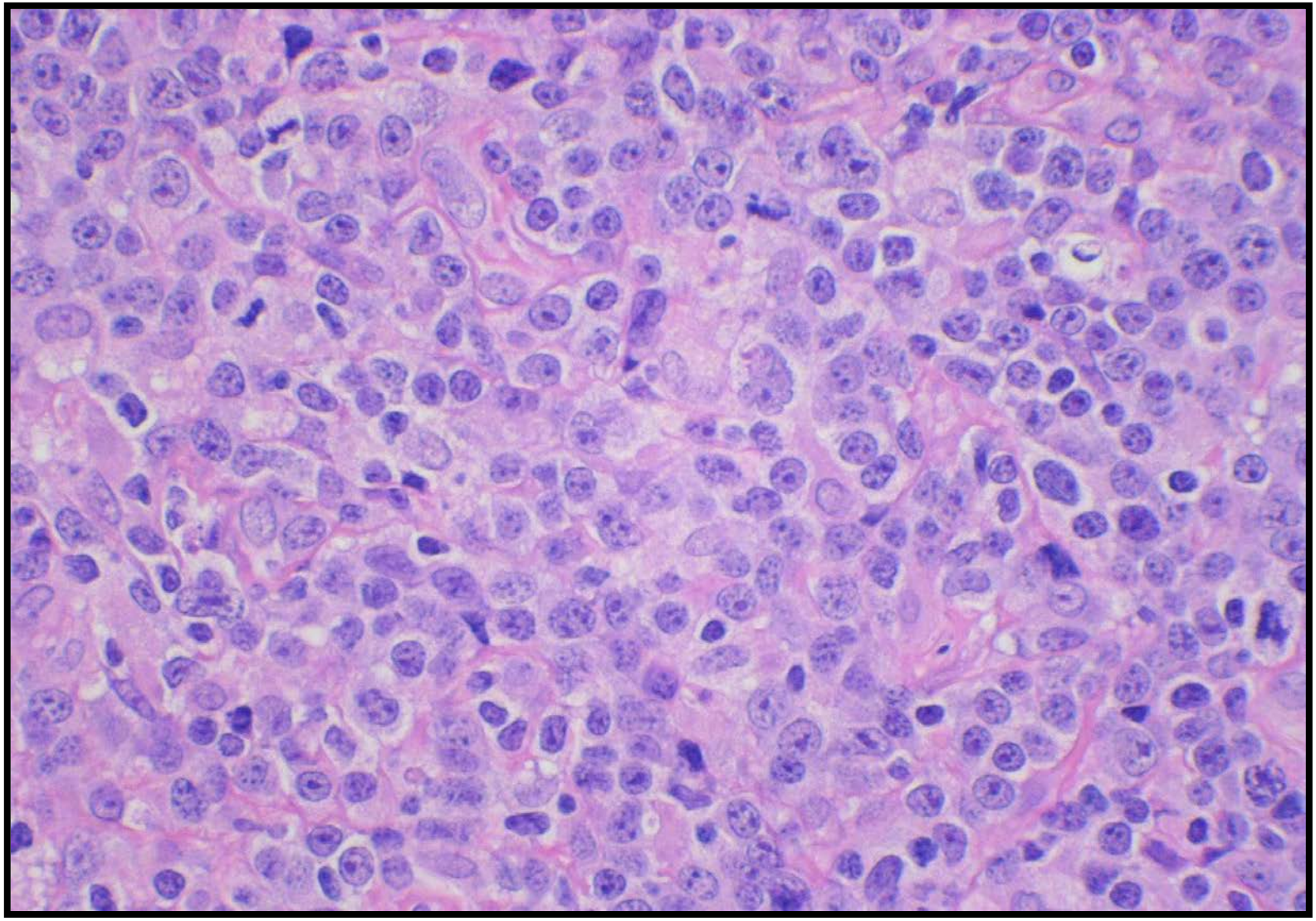
Morphology in DLBCL



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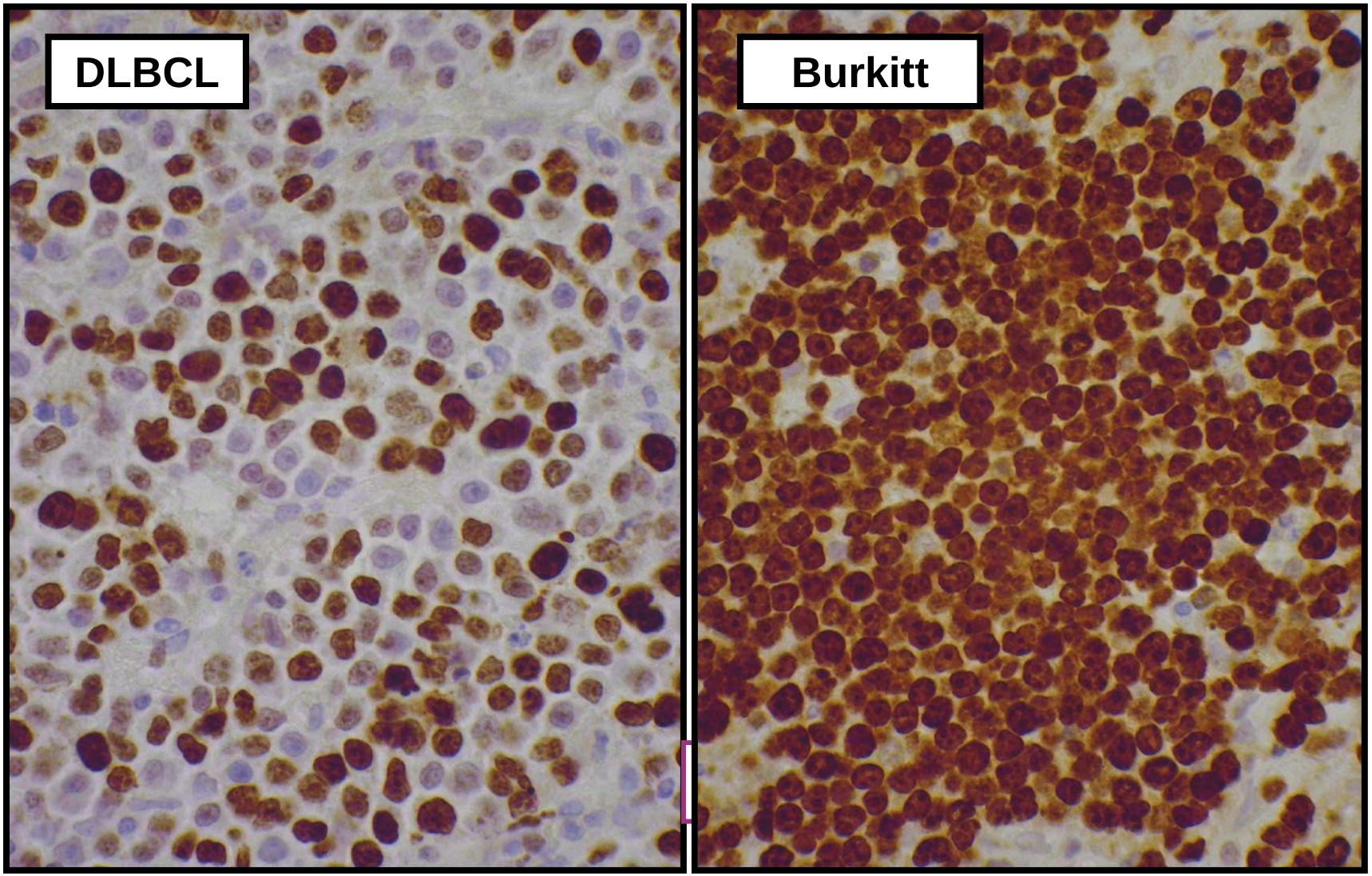
Ki67 Expression in Burkitt and DLBCL



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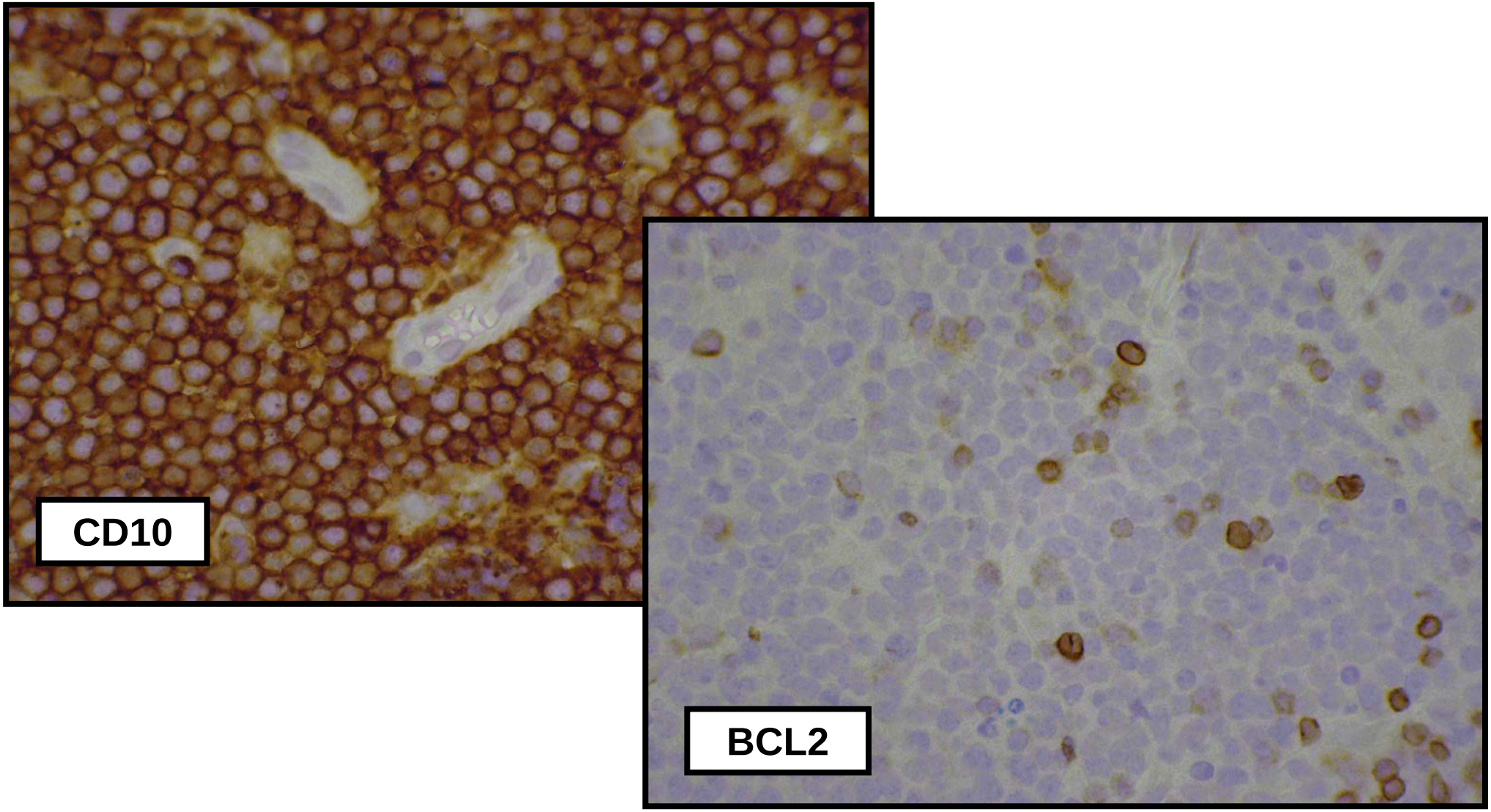
Immunophenotype in Burkitt Lymphoma



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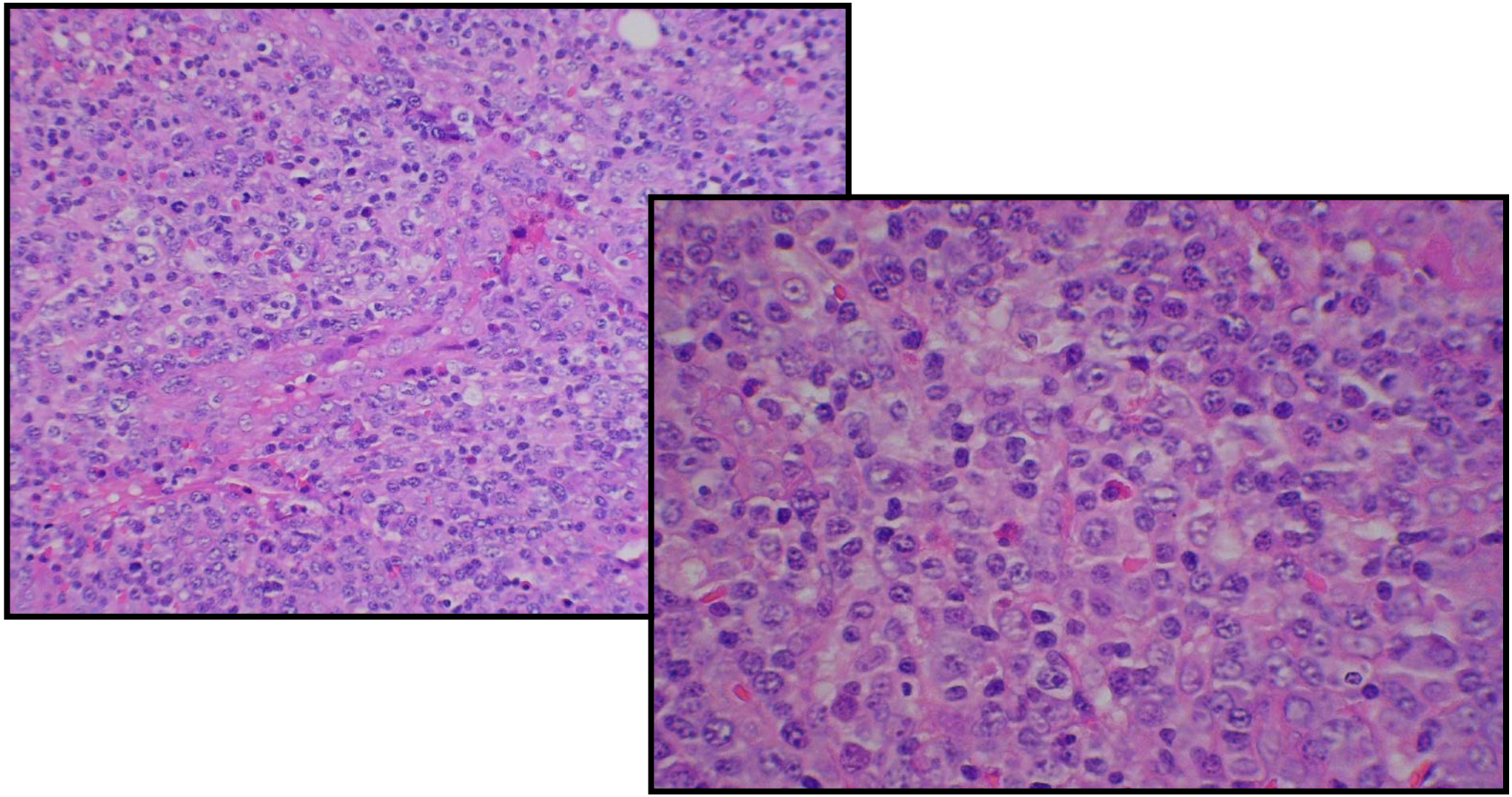
Angio-immunoblastic T-cell Lymphoma



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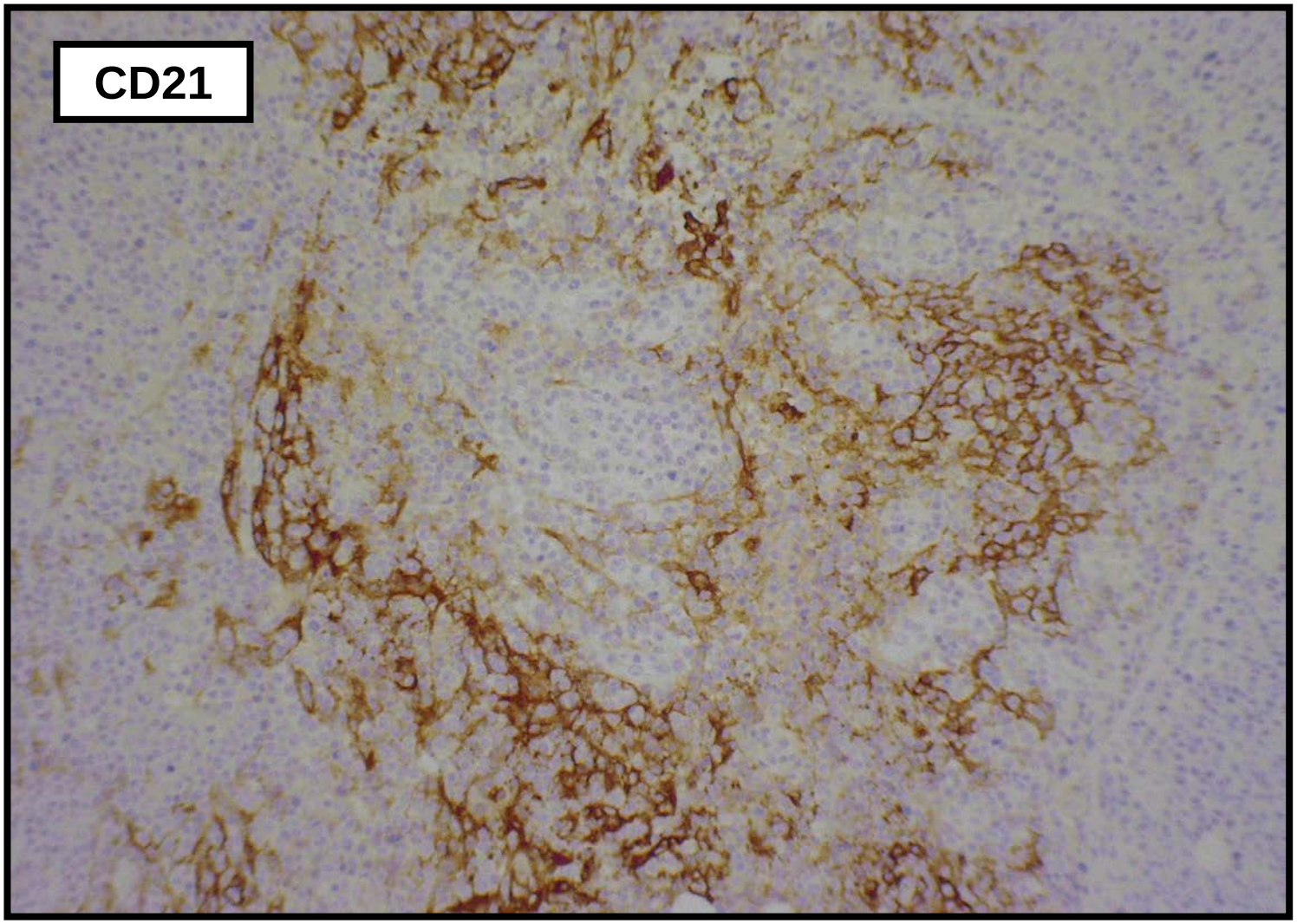
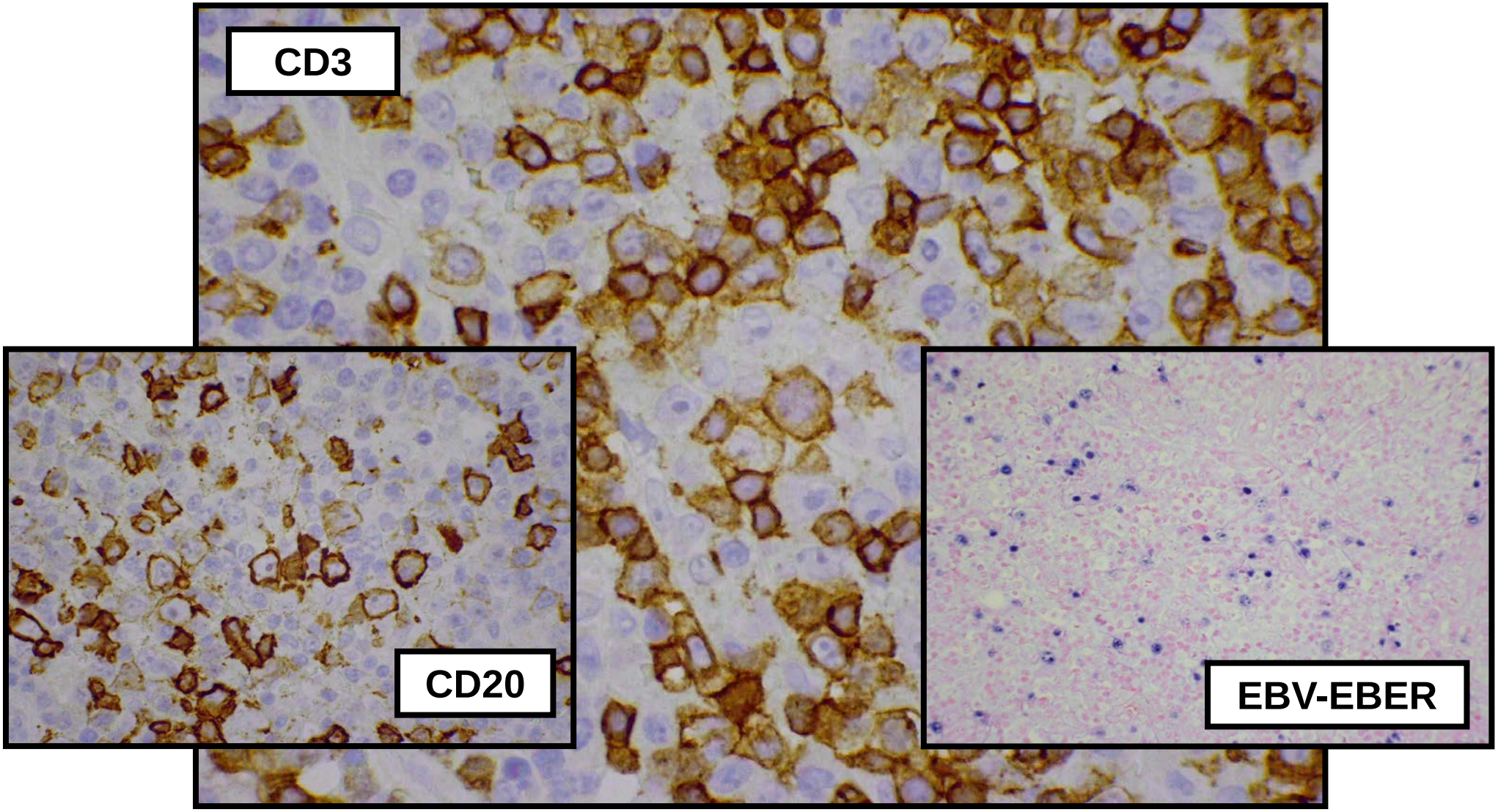
Angio-immunoblastic T-cell Lymphoma



Angio-immunoblastic T-cell Lymphoma



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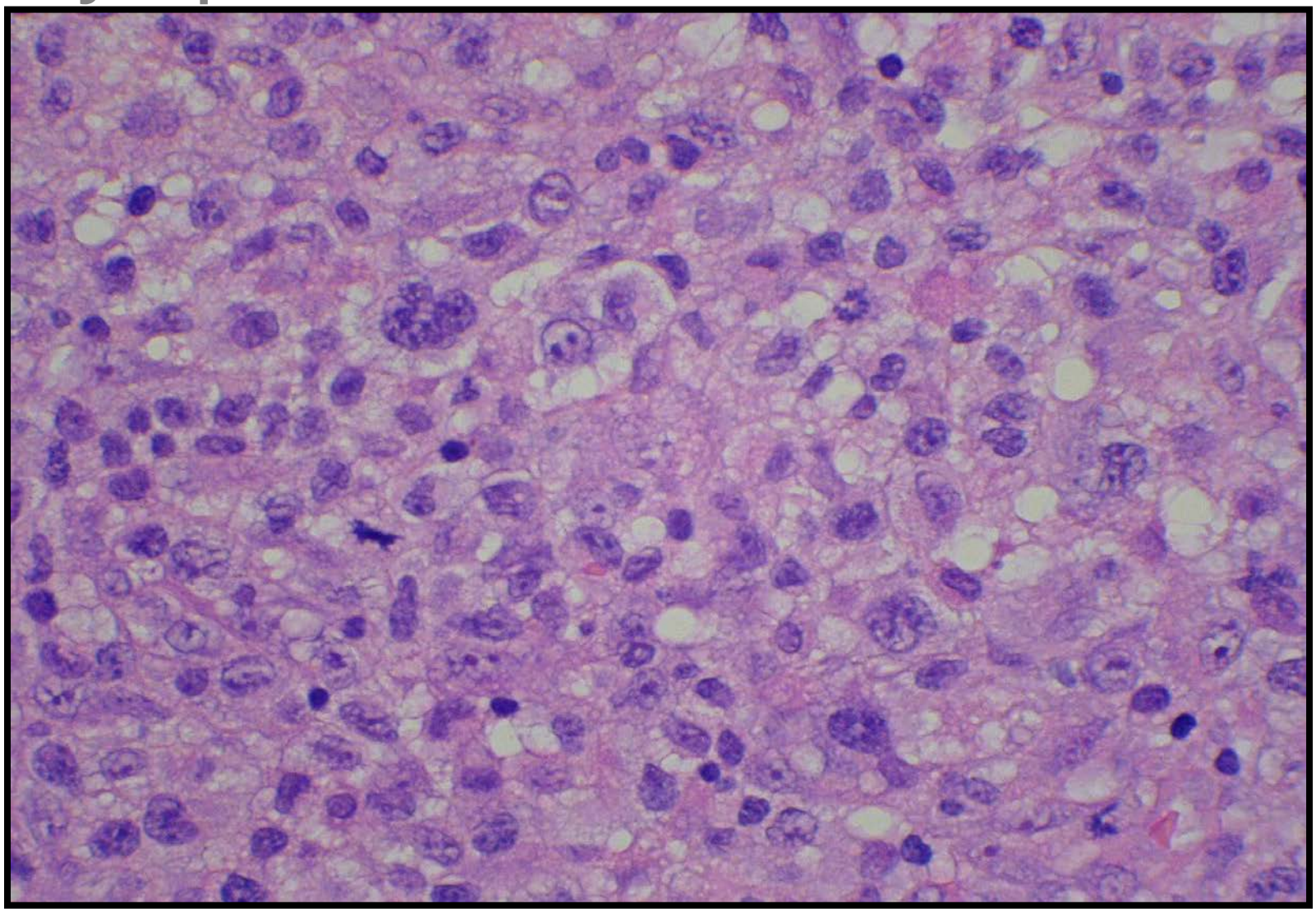
Anaplastic Large Cell Lymphoma



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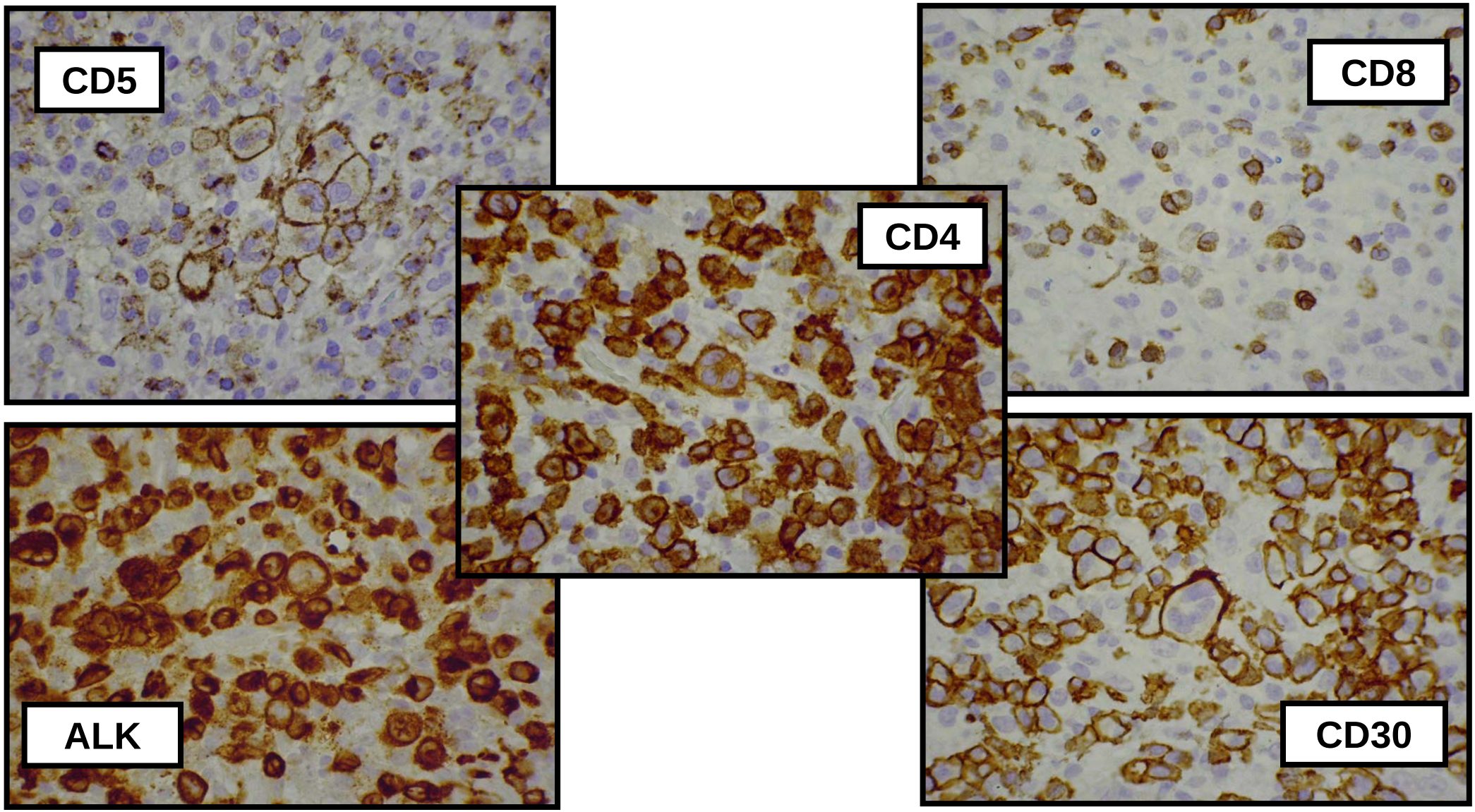
Anaplastic Large Cell Lymphoma, ALK+ve



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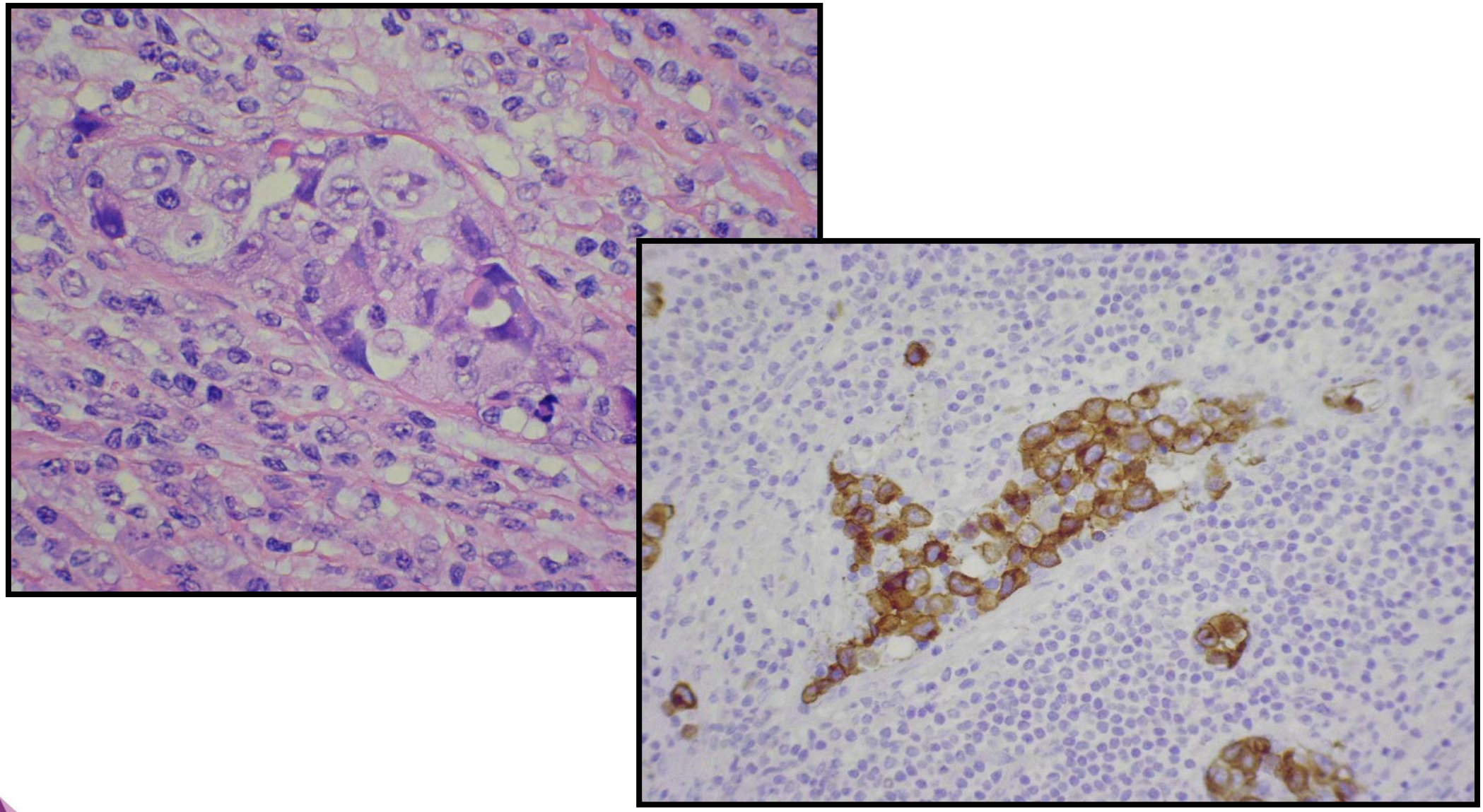
Anaplastic Large Cell Lymphoma, ALK-ve



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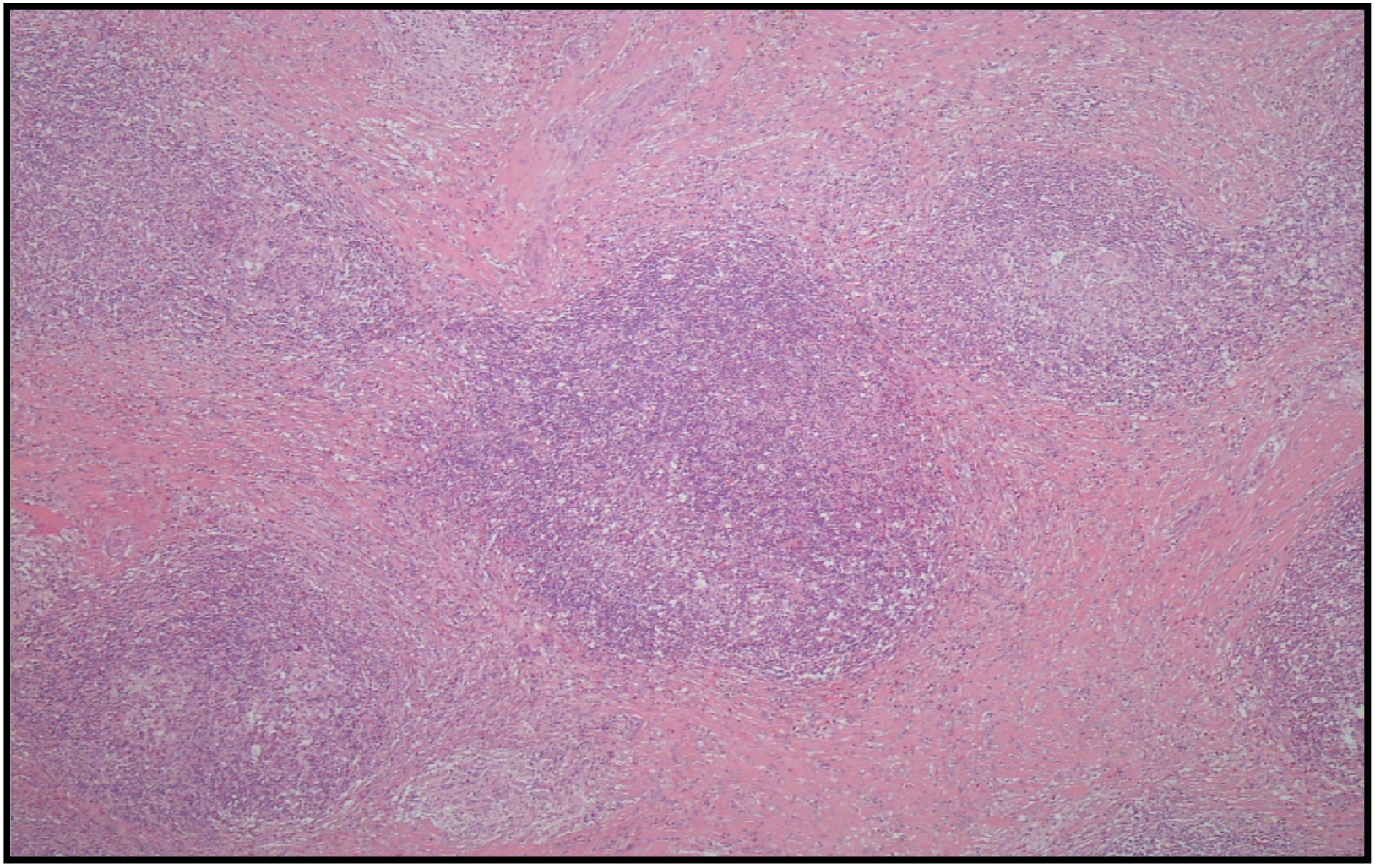
Classical Hodgkin Lymphoma - nodular sclerosis subtype



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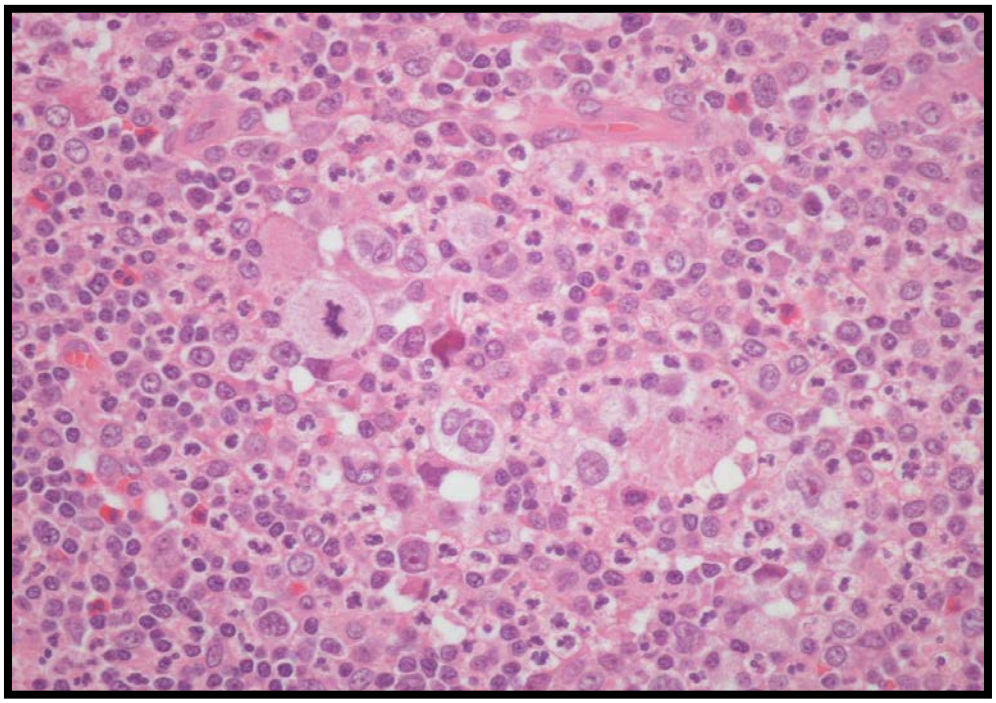
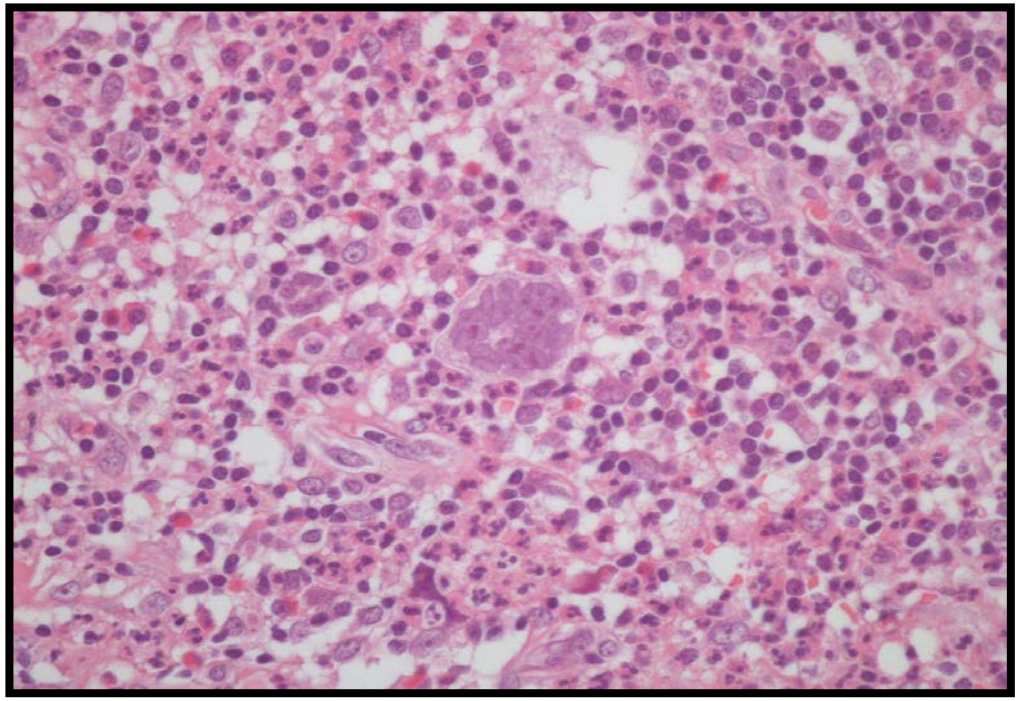
Classical Hodgkin Lymphoma – nodular sclerosis subtype





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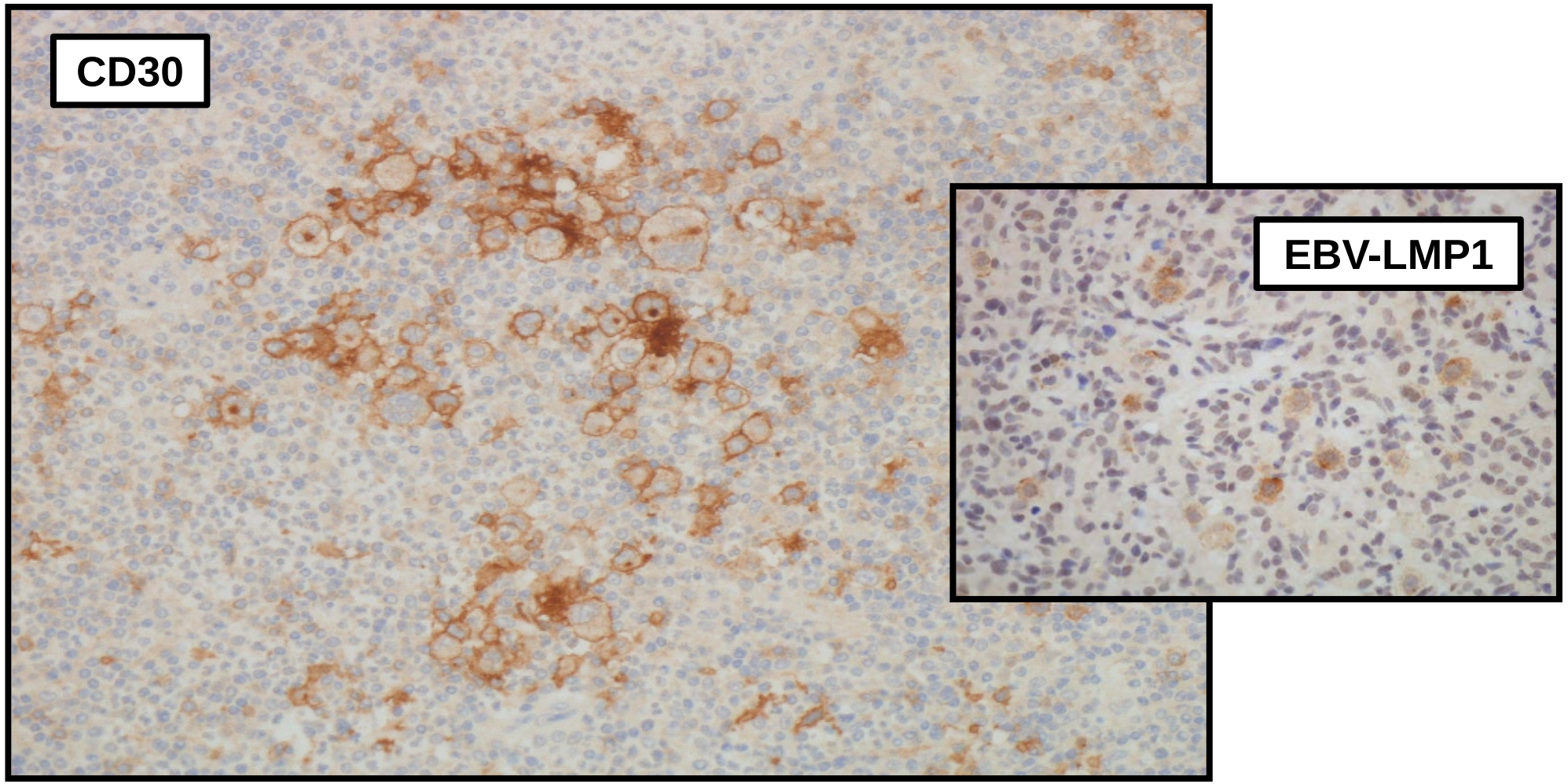

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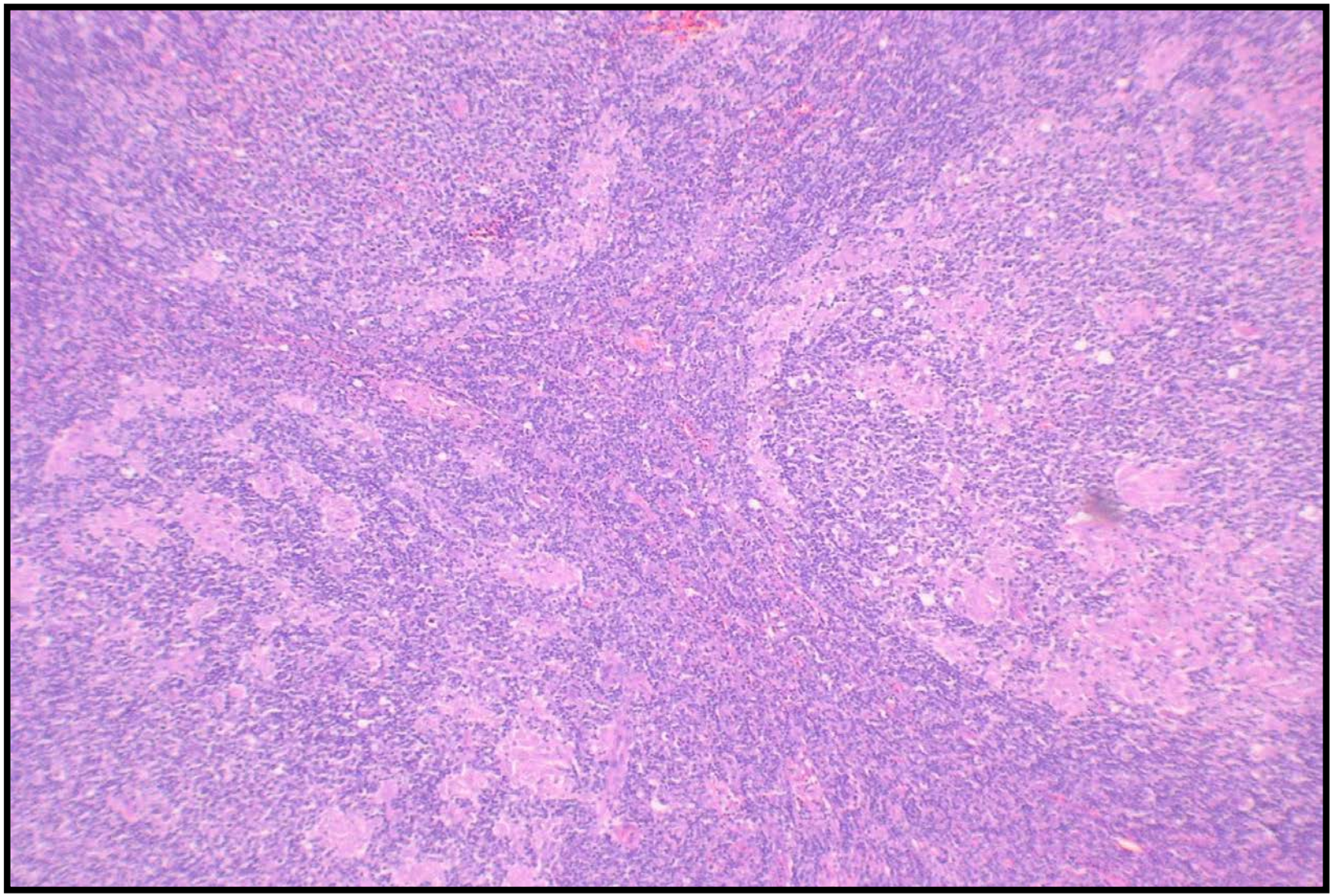
Nodular Lymphocyte Predominant HL



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Lymphomas that like to circulate - ‘leukaemic’ lymphomas

- Small lymphocytic lymphoma/chronic lymphocytic leukaemia
- Mantle cell lymphoma
- Splenic marginal zone lymphoma
- T-prolymphocytic leukaemia
- T- and NK-cell large granular lymphocytic leukaemia

- Aggressive lymphomas much less likely to circulate except ‘precursor’ types (B- and T-cell acute lymphoblastic leukaemias, and rare variants)

- If they are in the circulation, they are in the bone marrow

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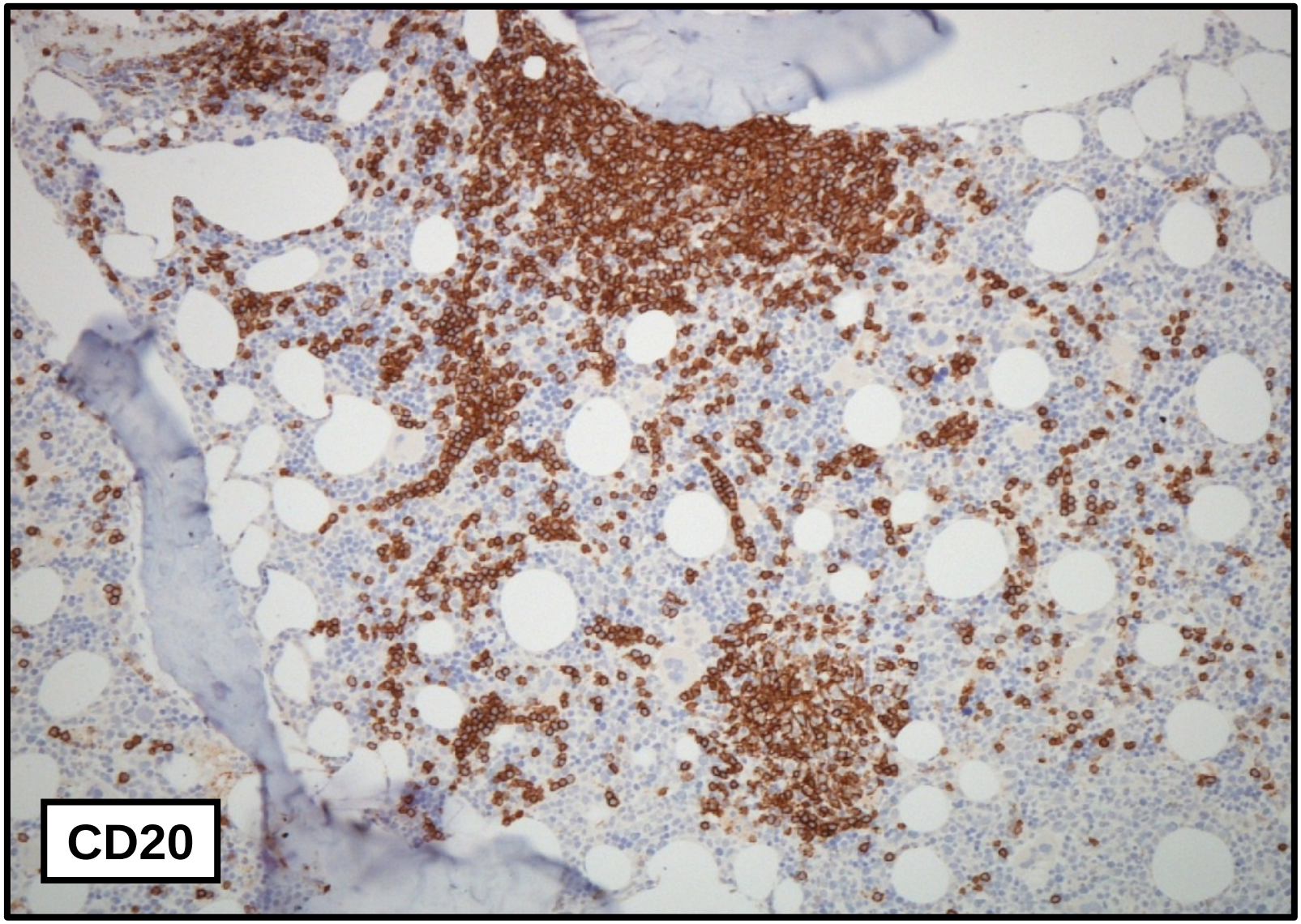
Splenic Marginal Zone Lymphoma



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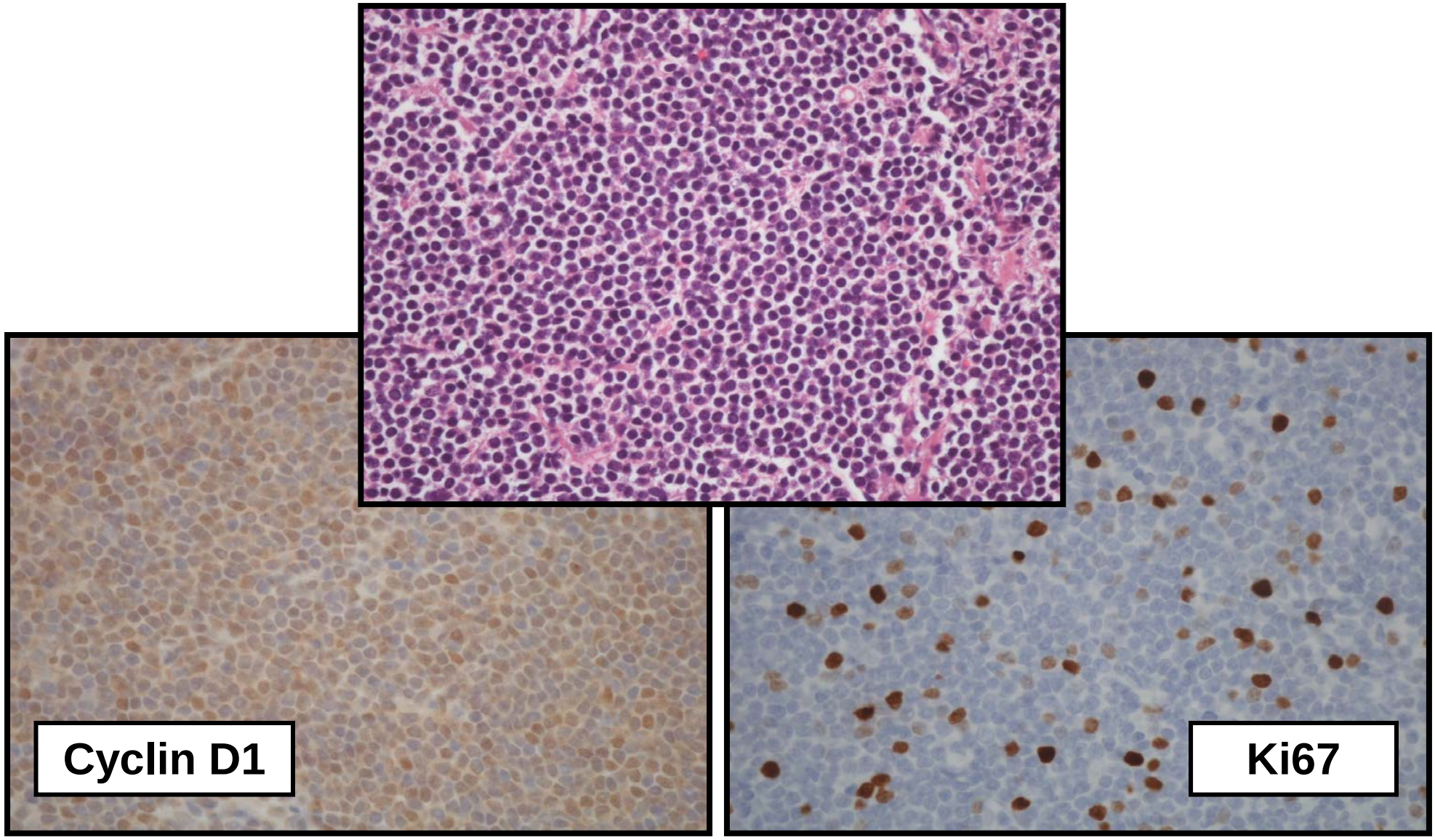
Classical Mantle Cell Lymphoma



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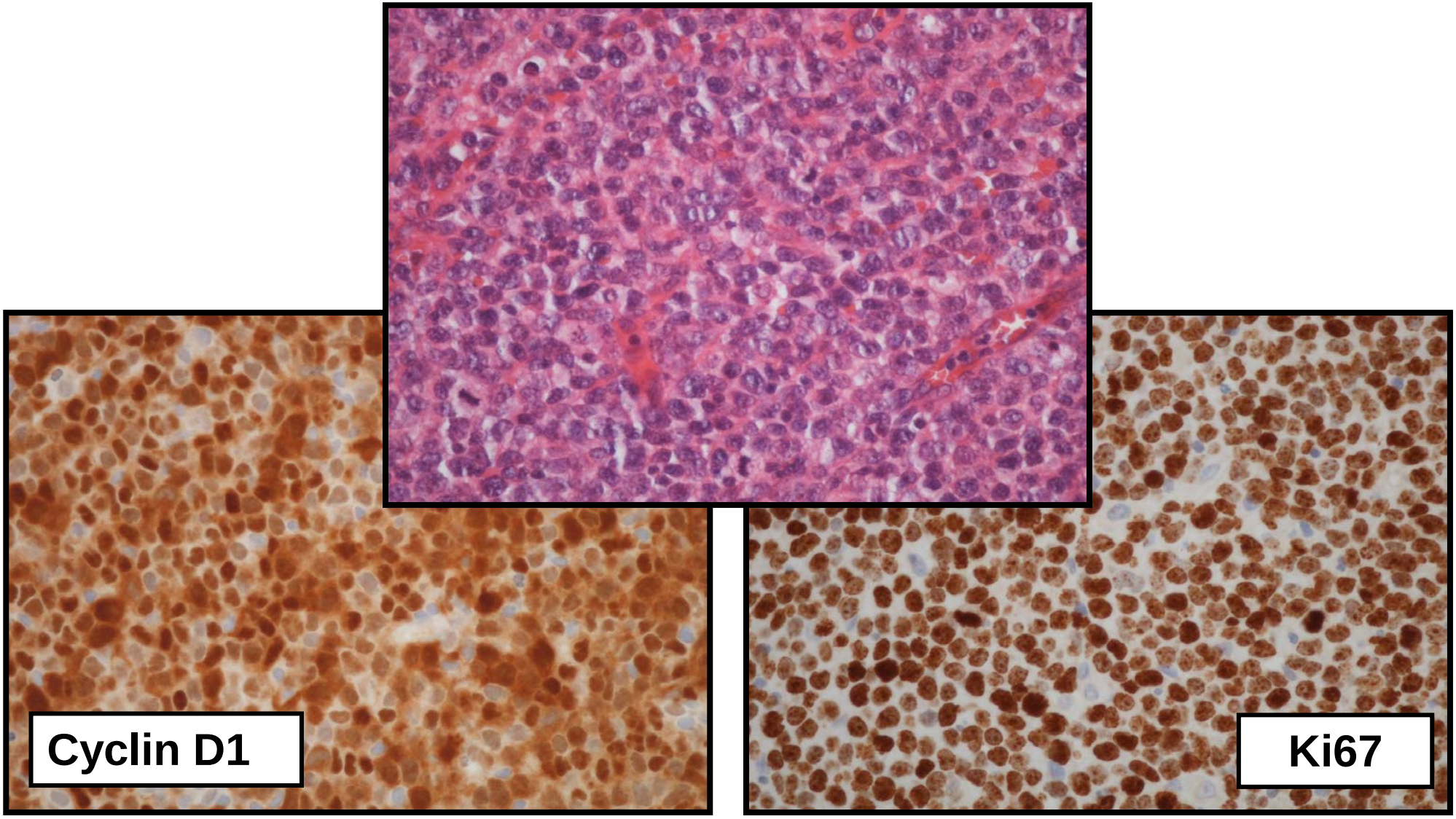
Blastoid Mantle Cell Lymphoma



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Extranodal Lymphomas of Mucosa-associated Lymphoid Tissue

- Mainly indolent, composed of small cells
- Believed to be driven by host immune reactions to chronic infections or auto-immunity
- Form distinctive lympho-epithelial lesions
- Often prominent accompanying reactive lymphoid components

- Enteropathy-associated T-cell lymphoma is classified separately
- Tends to be aggressive, in part due to cytotoxic (perforin etc.) phenotype

Other Extranodal Sites

- Spleen
- Skin
- Testis
- (Ovary)
- Brain
- Bone
- Soft tissue (e.g., extranodal NK/T-cell lymphoma, nasal type)

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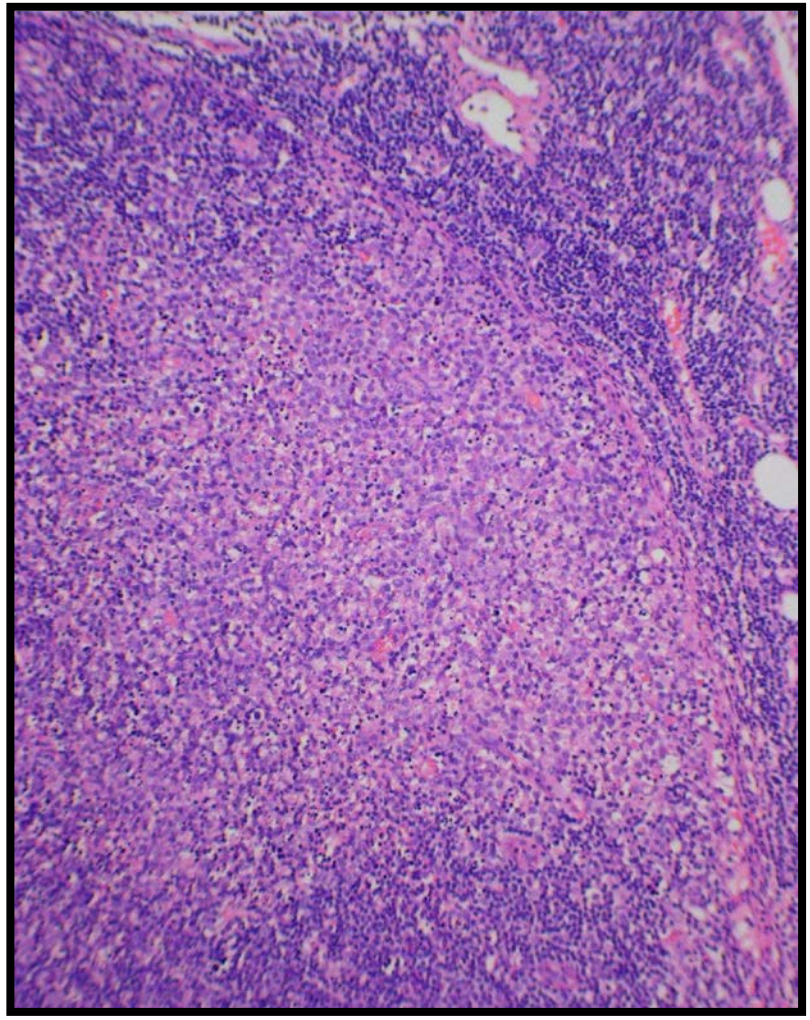
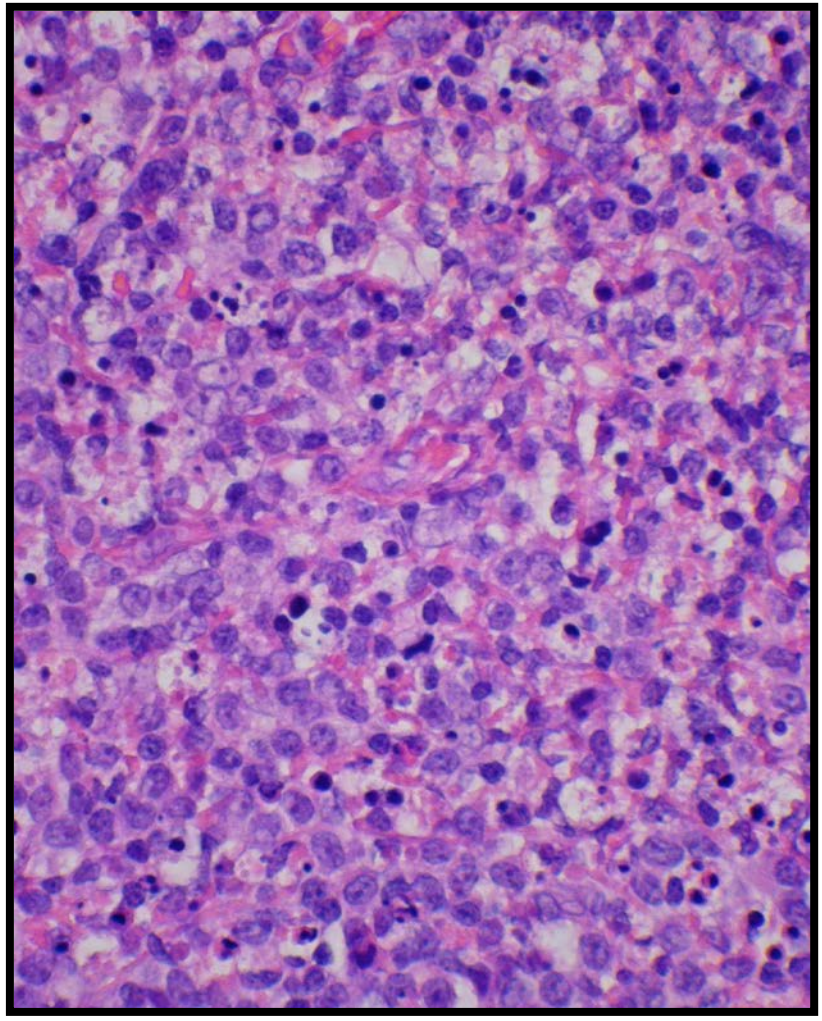
‘Never Events’ in Lymphoma Pathology

- Misinterpreting reactive processes as lymphoma
  - Granulomatous lymph nodes diagnosed as classical Hodgkin lymphoma
  - Histiocytic necrotising lymphadenitis (Kikuchi’s/SLE)

- Misdiagnosing lymphoblastic or Burkitt lymphomas as indolent because the blast cells appear small

Histiocytic Necrotising Lymphadenitis





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What's on the Horizon in WHO 2016?

- Further formal recognition of 'grey zone' lymphomas:
  - Large B-cell lymphomas intermediate between DLBCL and Burkitt
  - Large B-cell lymphomas intermediate between DLBCL and cHL
- Revised classification of some examples of nodal 'peripheral T-cell lymphoma, NOS' in recognition of T-follicular helper cell origin
- Reconsideration of surrogates for molecular genetic signals
  - MYC/BCL2 immunostaining
  - Hans classifier (and others)

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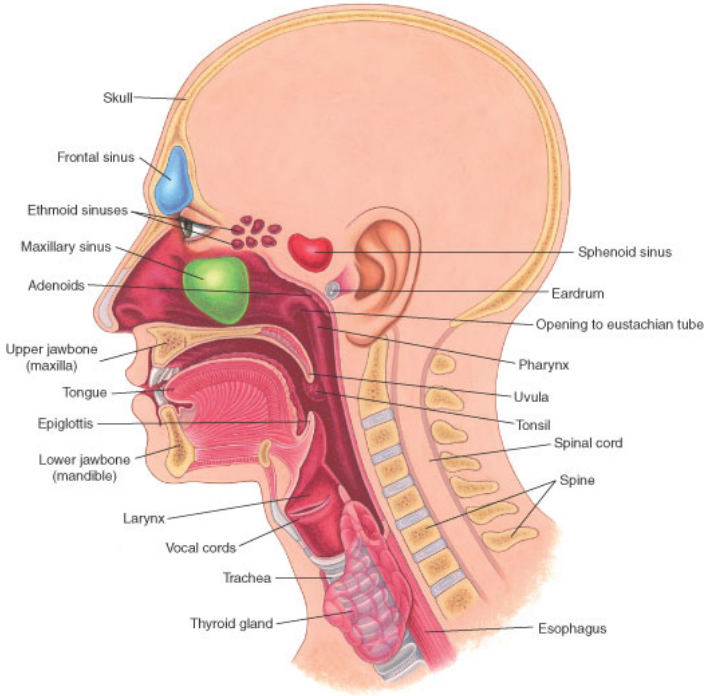
Extranodal lymphomas: Head and neck

Lena Specht MD DMSc
Professor of Oncology, University of Copenhagen, Denmark
Chief Oncologist, Depts. of Oncology and Haematology, Rigshospitalet, Copenhagen
Vice-chairman, International Lymphoma Radiation Oncology Group

Extranodal (not necessarily extralymphatic) sites in the upper aerodigestive tract



- Nasal cavity and paranasal sinuses: NK/T-cell lymphomas (Eastern Asia and South America) and DLBCL (Western countries)

- Pharynx (most often in Waldeyer's ring: lymphatic tissue formed by palatine tonsils, adenoids in posterior nasopharynx, lingual tonsil, and intervening lymphoid tissues): DLBCL

- Oral cavity, larynx and hyphopharynx: rare, include indolent lymphomas, mantle cell lymphomas and DLBCL

- Parotid and other salivary glands: MALT lymphomas

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Head & neck lymphomas, general principles

- Pre-treatment work-up:
  - Detailed ENT examination incl. fiberoptic examination, evt. under general anaesthesia
  - Imaging with PET and CT, MRI for skull base, cranial cavity, cranial nerve, sinuses, and infratemporal fossa

Head & neck lymphomas, general principles

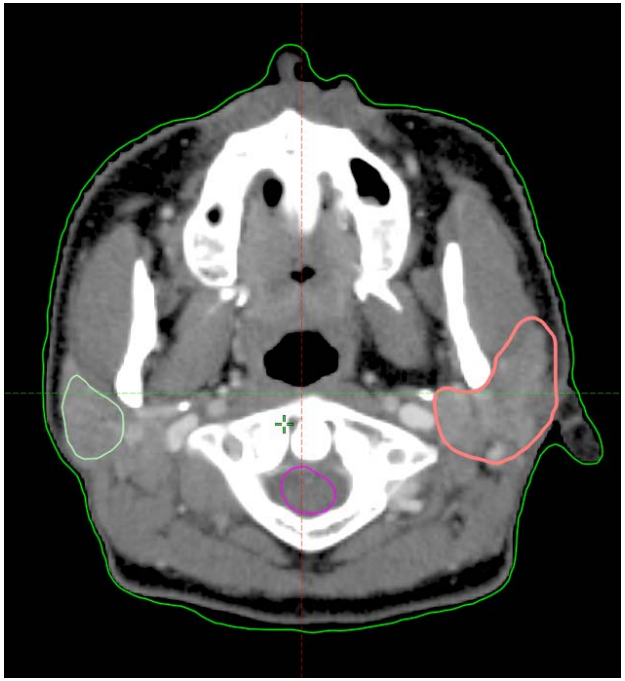
- ISRT to sites of initial definite or suspected involvement
- Prophylactic RT of uninvolved lymph node regions is not routine
- Optimal immobilization, e.g. a 5-point thermoplastic mask
- RT techniques as for solid tumors in the head & neck area often appropriate

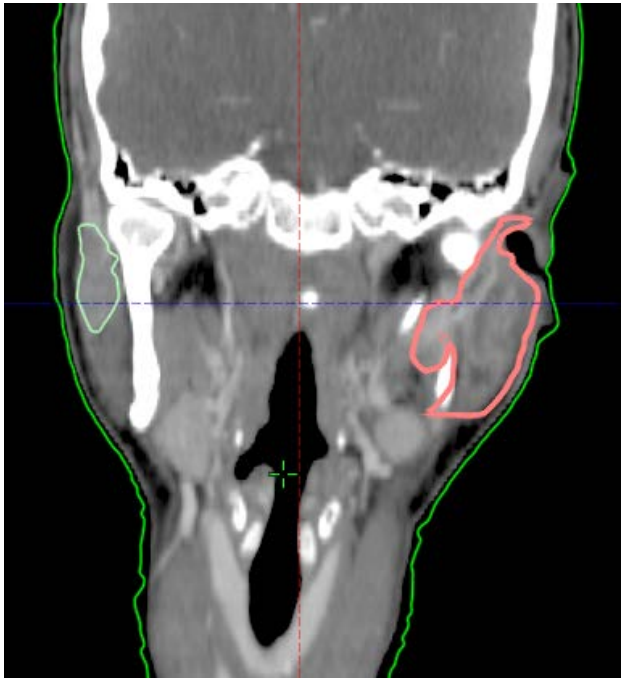
Head & neck lymphomas, indolent

- Localized indolent disease: RT primary curative modality, 24-30 Gy
- Lymphoma is often multifocal, and the involved organ is often treated in its entirety
- First echelon nodes of uncertain status close to the primary organ may be included
- Advanced indolent disease: RT may provide effective palliation, 4 Gy effective in most patients

MALT lymphoma in left parotid gland

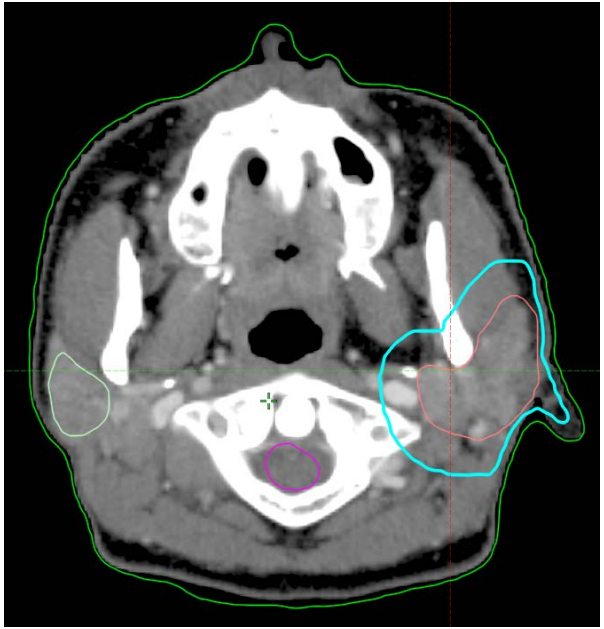
Post-op images

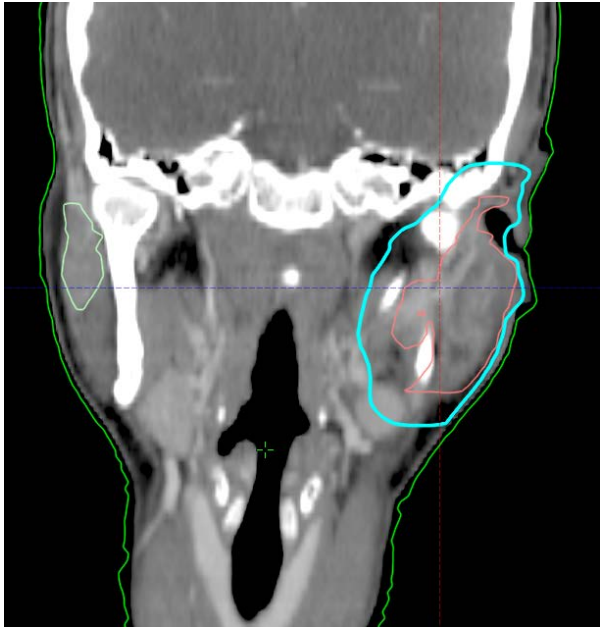




- 40 year female with swelling in left angular and preauricular area, waxing and waning for two years
- Previous FNA inconclusive
- Excisional biopsy: MALT lymphoma
- No post-op abnormality on PET/CT-scan.

PTV





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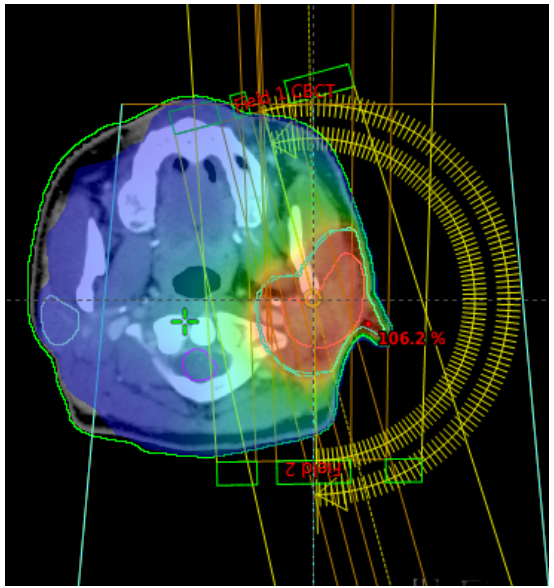
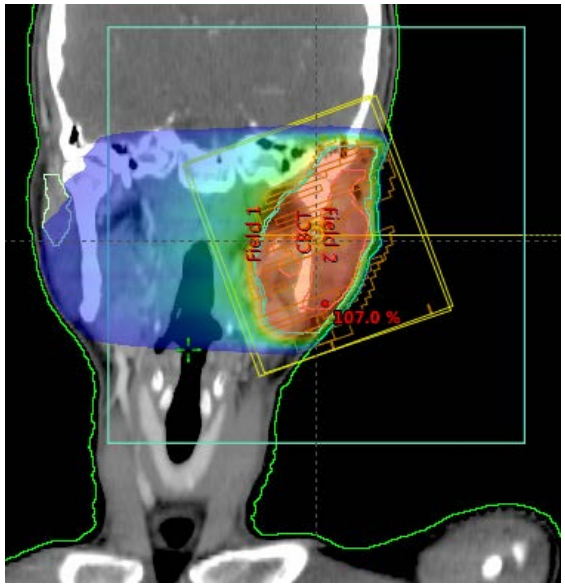
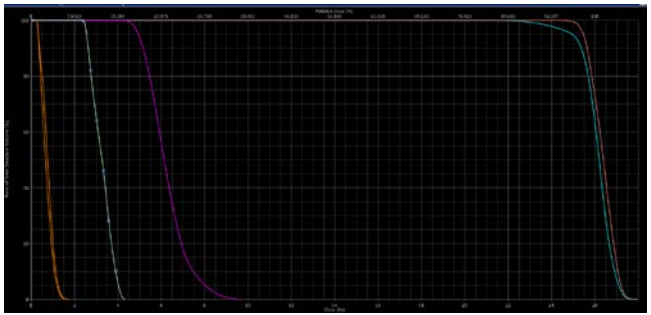
Treatment plan (RapidArc)







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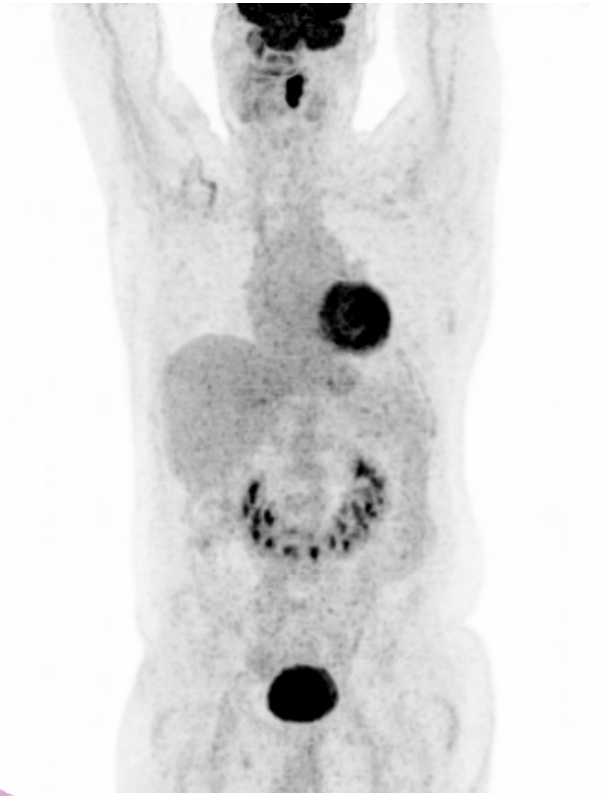
Head & neck lymphomas, aggressive

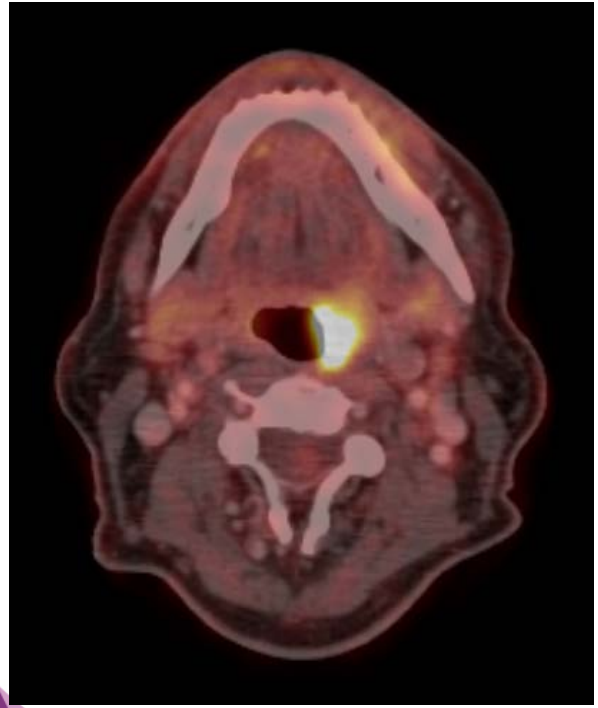
- Localized aggressive disease: Systemic therapy is the primary treatment. RT is used as consolidary treatment, dose 30-36 Gy after CR, 40-45 Gy if gross residual disease
- Radiation volumes may be limited to part of an organ after excellent response to systemic treatment, which controls microscopic disease
- Advanced aggressive disease: RT to initial bulk according to RICOVER and UNFOLDER studies, extranodal disease unclear (Waldeyer's ring was not considered extranodal in RICOVER)

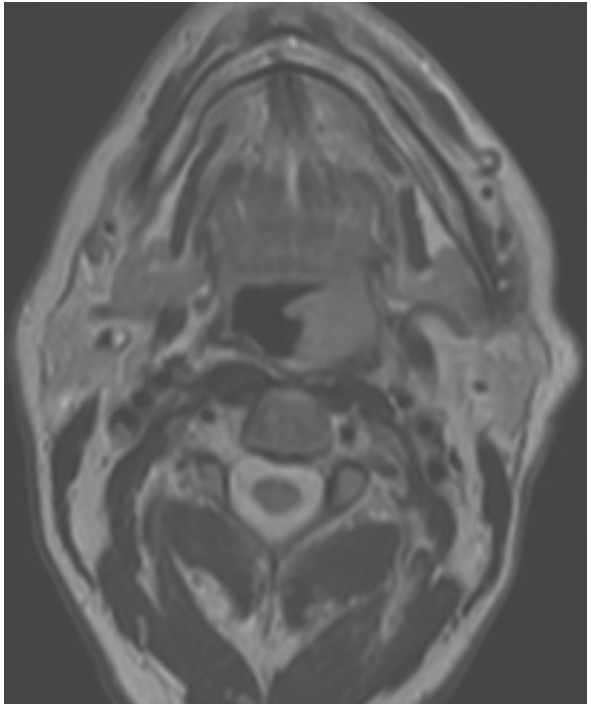
DLBCL in tonsil

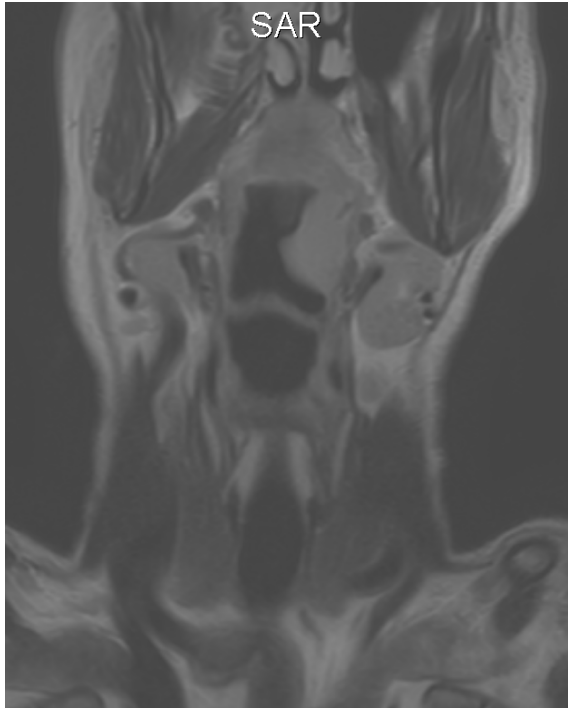


- 74 year old male with DLBCL of the left tonsilla
- Whole body PET/CT (September 4, 2014) showed no signs of lymphoma elsewhere, the patient had no B-symptoms, LDH was normal
- He was in stage IA, and was treated with 3 cycles of R-CHOP followed by ISRT to 30 Gy
- Since then in continuous CR

Pre-chemo images







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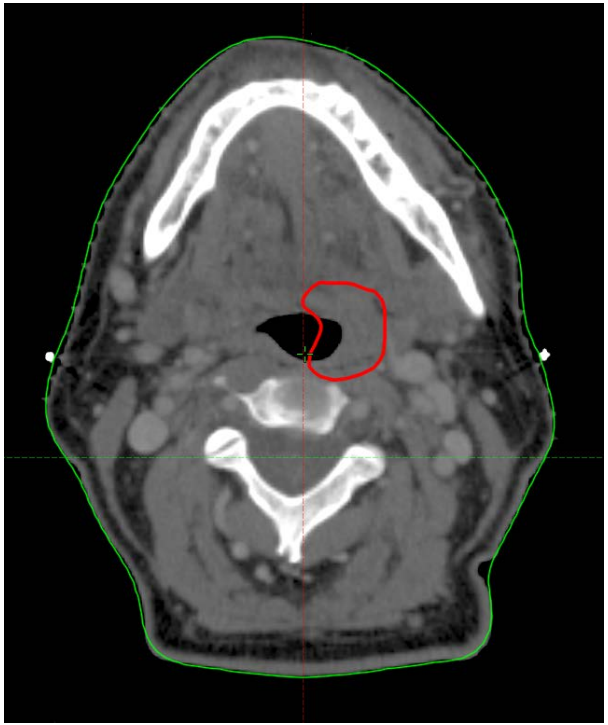
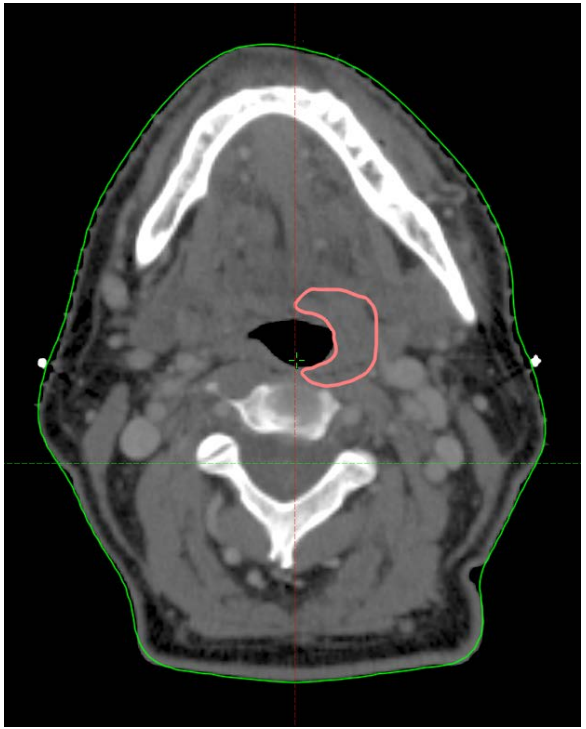
Post-chemo planning CT

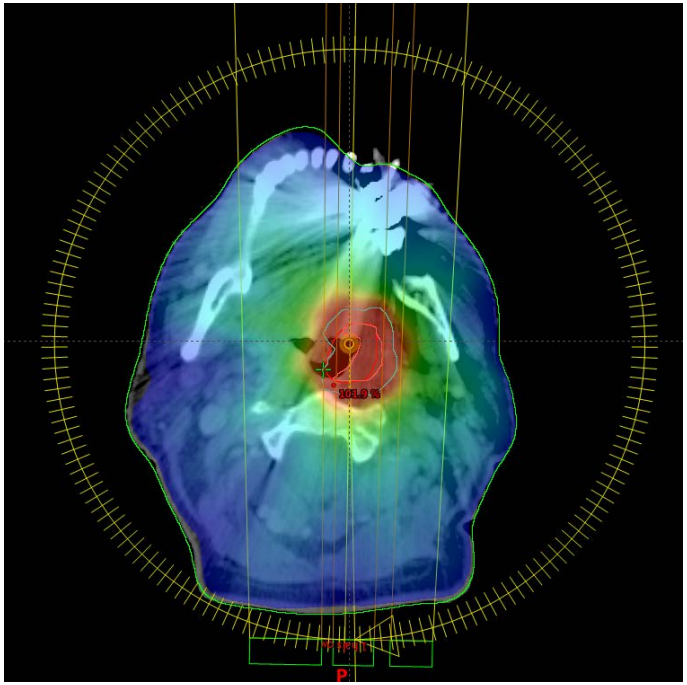
Pre-chemo
GTV

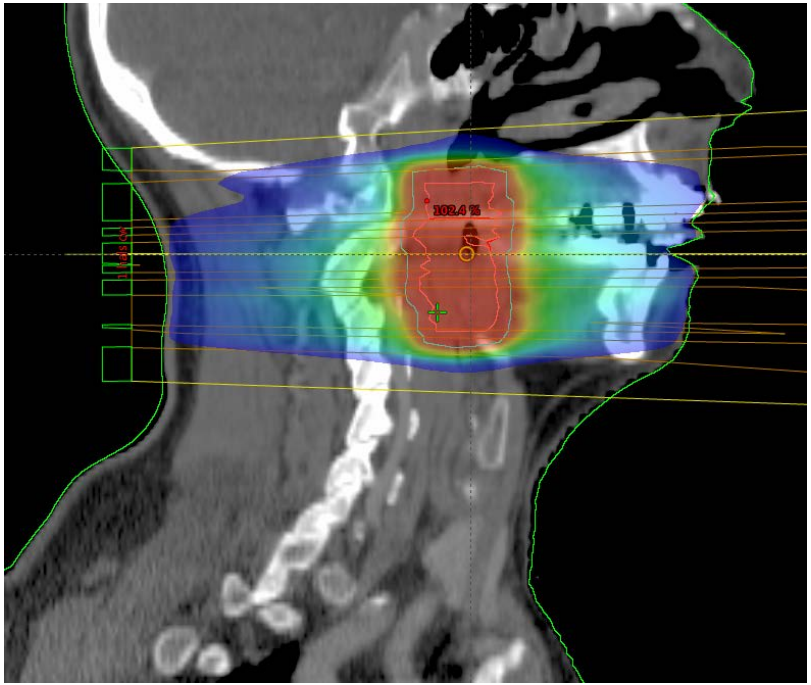




Post-chemo
CTV

Treatment plan (RapidArc)





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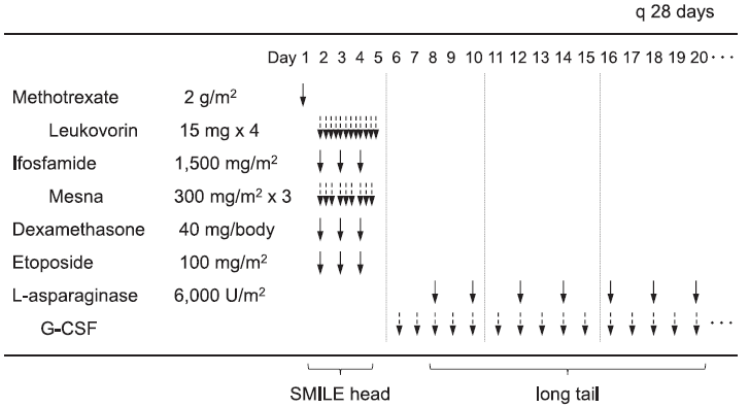
NK/T-cell lymphomas, nasal type

- Associated with Epstein-Barr virus
- More common in Asians and native Americans in Central and South America
- Usually involves nasal cavity and/or paranasal sinuses, Waldeyer's ring may also be involved
- Outside the upper aerodigestive tract it presents in advanced stages and unfavourable prognosis

NK/T-cell lymphomas, nasal type

- Frequently express multidrug resistant P-glycoprotein
- Responds poorly to anthracycline-based chemotherapy (e.g., CHOP-like regimens)
- L-asparaginase is effective: SMILE regimen



NK/T-cell lymphomas, nasal type

- Early stage disease: SMILE (or other effective regimen) x 2
- Radiotherapy is an essential component of treatment and must:
  - Come in early
  - Doses ≥ 50 Gy

NK/T-cell lymphoma, nasal type

Courtesy of Dr. Shunan Qi, Memorial Sloan Kettering Cancer Center, New York, and Chinese Academy of Medical Sciences, Beijing

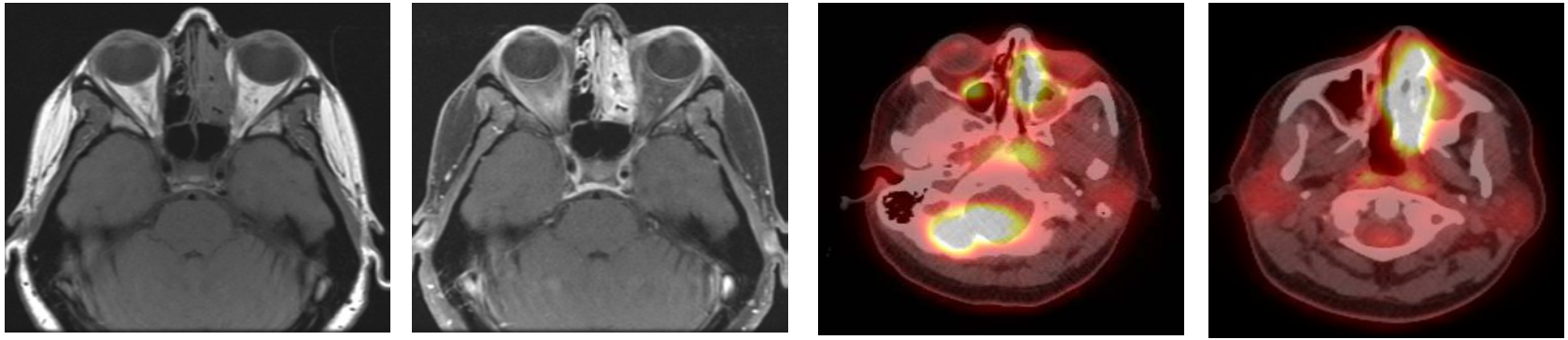
- **Challenges for GTV contouring**
  - Lesions often associated with mucosa surface
  - Lesions are accompanied with inflammation/necrosis
  - Lesions sit in an area with rich lymphoid tissues
- **Rationales guiding CTV contouring**
  - Experience with chemotherapy is limited (SMILE, non-MDR drugs)
  - RT is the most effective treatment
  - Close association between local control and survival
  - Uncertainty of disease boundaries
  - Local invasiveness of the disease nature

Extended ISRT!

- Irradiate the whole involved cavity and adjacent structures!

Extranodal NK/T cell lymphoma, nasal type, CS IEA, involving left nasal cavity, IPI: 0

- The treatment plan was 2 cycles of SMILE followed by extended involved site radiation therapy (extended ISRT) to 45 Gy
- The patient received 2 cycles of SMILE, and responded immediately with CR on the post-chemotherapy planning PET/CT scan



Pre-chemo images

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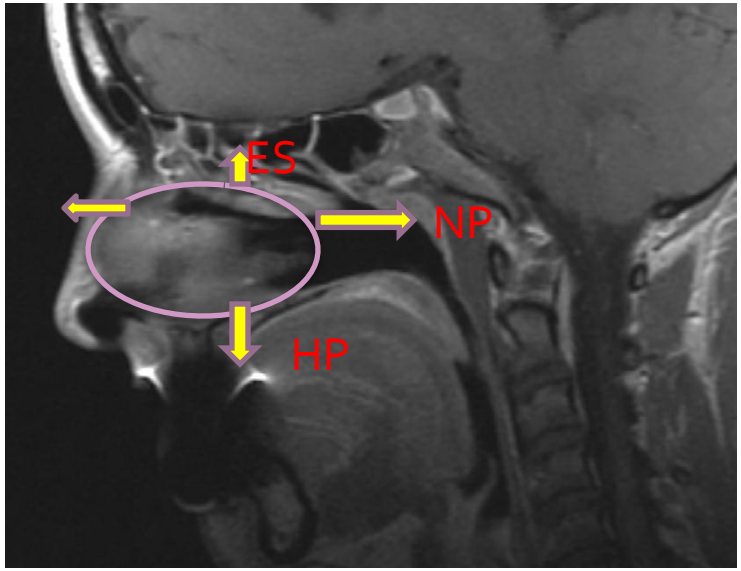
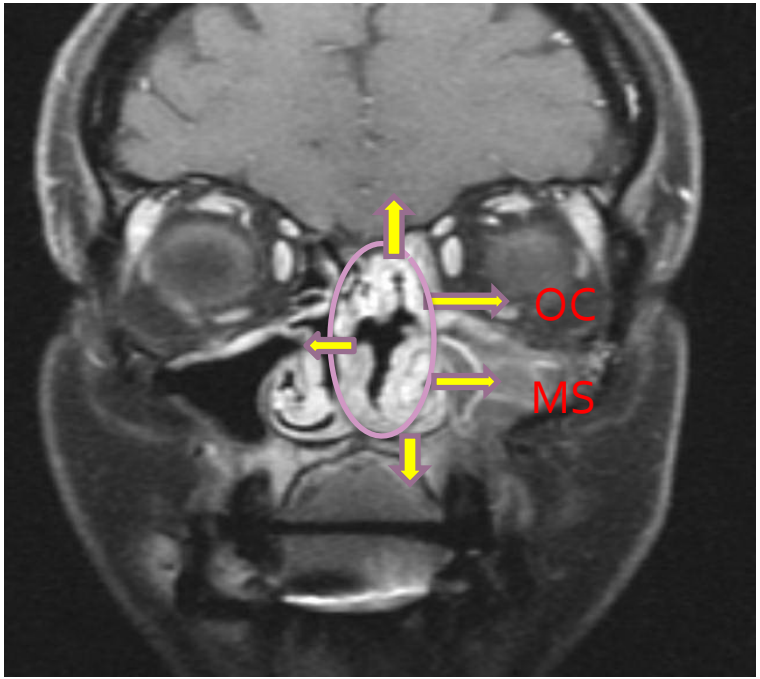
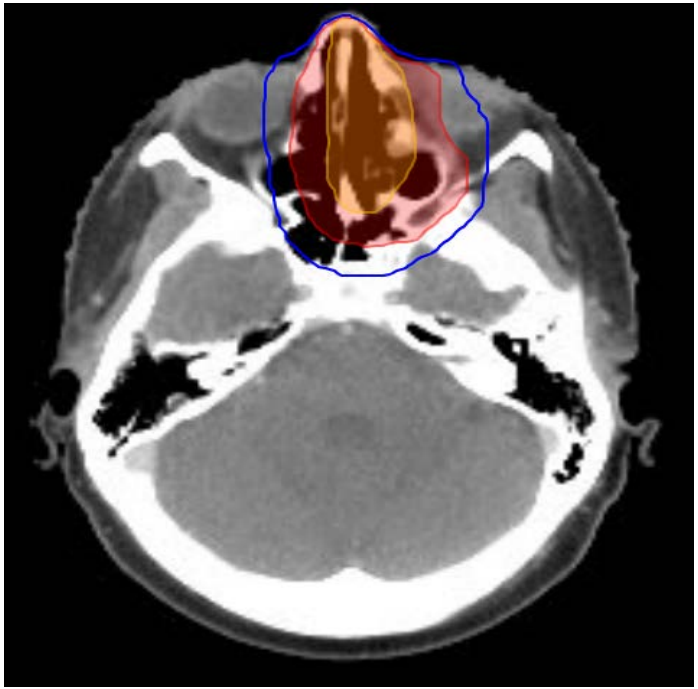
Nasal cavity and adjacent structures



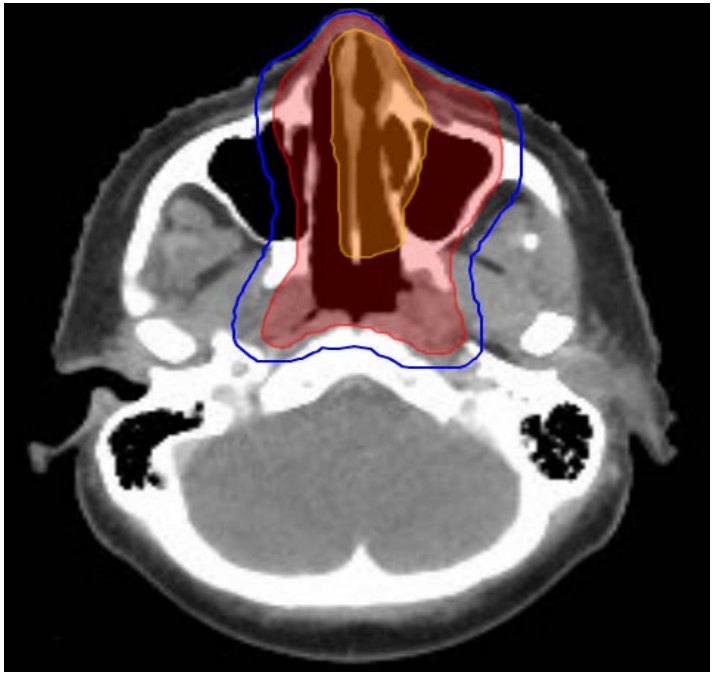


CTV



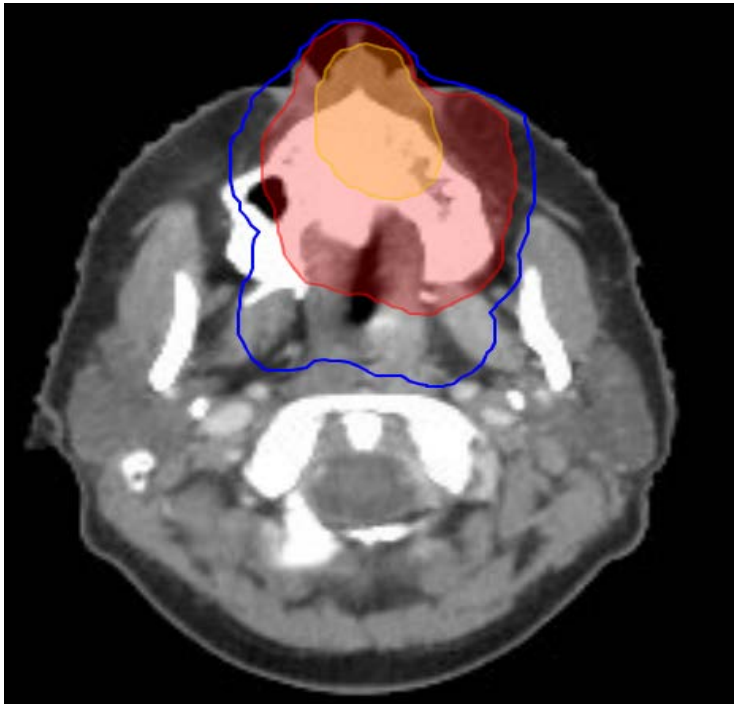
Pre-chemo GTV	CTV	note
left nasal cavity, medial left orbital wall, left ethmoid and medial wall of left maxillary sinuses	bilateral nasal cavity+ left maxillary sinus + bilateral ethmoid sinuses + part of sphenoid sinus	Beginning of maxillary sinus slice to remind the coverage of whole ipsilateral maxillary sinus

CTV



Pre-chemo GTV	CTV	note
Left nasal cavity, medial wall of left maxillary sinuses	bilateral nasal cavity+ left maxillary sinus + nasopharynx	Typical nasal cavity slice with maximum lesion presentation (CTV covering bilateral nasal cavity, nasopharynx, ipsilateral maxillary sinus)

CTV



Pre-chemo GTV	CTV	note
Bottom of left nasal cavity (hard palate)	Bilateral nostril + Left part of hard palate (gum)	Bottom slice of GTV to stress the inclusion of hard palate and gum

Key points

- Multimodality evaluation before treatment
- Non-MDR chemotherapy regimen with L-asparaginase
- Early RT
- Extended ISRT

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KING'S College LONDON
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Thyroid Lymphoma

George Mikhaeel, MD
Department of Clinical Oncology
Guy's & St Thomas' Hospital
KHP Academic Health Sciences Centre
London, UK

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Incidence

- 5% of all thyroid malignancies
- 3% of all extra-nodal NHL
- 1-2 cases / million
- F:M = 3 : 1
- Peak: 7th decade
- 2 main subtypes:
  - DLBCL
  - MALT

Pathogenesis

- Link to autoimmune disease and chronic antigenic stimulation

- *Hashimoto's thyroiditis:*
  - Up to 80% of PTL have HT
  - PTL incidence is 40-80 times higher in HT
  - Typically 20-30 years after diagnosis
  - Only 0.6% of HT pts develop PTL

Histological types

- DLBCL 60-70%
- MALT 20-30%

- FL 3-5%
- cHL 2%
- SLL 2-3%
- T-cell very rare

Clinical Presentation

- Enlarging painless goitre:
  - days – 36 months
  - DLBCL : rapid course
- Compressive symptoms (1/3): dyspnoea, dysphagia and hoarseness. Rarely; stridor, SVCO
- B symptoms: not common (10-20%)
- Cervical LN
- Majority are euthyroid

Staging

- IE: Thyroid only 56%
- IIE: + LNs above diaphragm 32%

88%

- IIIE: + LNs below diaphragm 2%
- IVE: + organ involvement 11%

Based on 1048 cases: Graff-Baker, Surgery 2009

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Imaging

- US:
  - Modality of choice for thyroid assessment
  - Useful for DD of rapidly enlarging goitre:
    - Anaplastic thyroid carcinoma
    - Subacute thyroiditis
    - Haemorrhage into cyst or adenoma
  - 3 patterns: nodular, diffuse & mixed
  - Guides Bx

- Radionuclide scanning: not useful

- Cross-sectional imaging (CT + MRI)
  - Assessment of anatomical extent and airways
  - Staging

- FDG-PET/CT:
  - Standard imaging modality for staging

Biopsy

- FNAC
- Core Bx
- Surgical open biopsy

FNAC

- Initial technique of choice for assessment of thyroid lesions
- simple, usually readily available with US
- Traditionally FNAC alone was considered inadequate
- Increasing accuracy with recent adjuncts: flow cytometry, immunoperoxidase studies & PCR.

Role of Surgery

- Primary role is to establish diagnosis
- Surgical resection is not a treatment option
- Airway compromise:
  - Tracheostomy
  - Steroids (after Bx + PET)

Treatment

- Indolent: Primary RT
- Aggressive: CMT
- CTV: whole thyroid + any involved nodes
- Dose:
  - Indolent 24Gy / 12#
  - Agg: 30 – 36 Gy according to response
- Technique:
  - 3D Conformal
  - IMRT / VMAT

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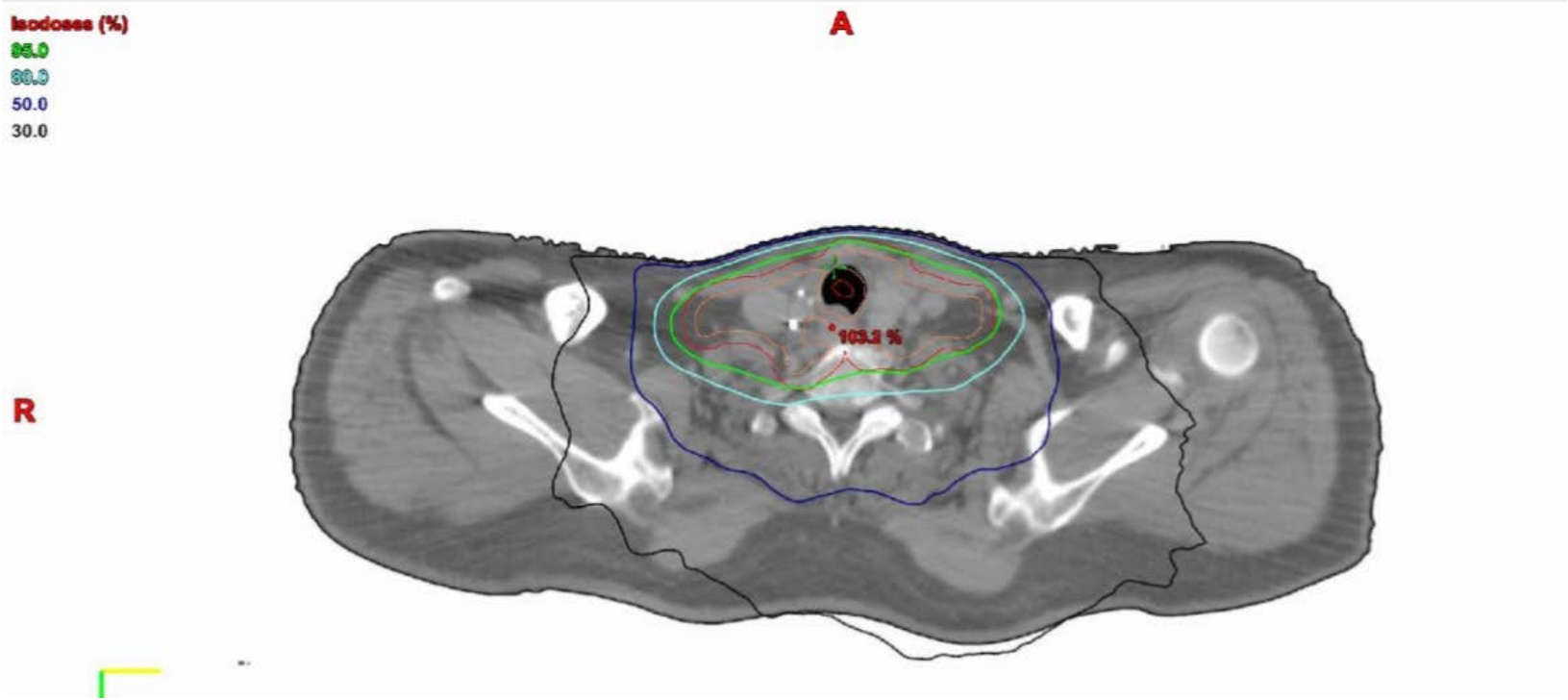
Isodoses (%)
95.0
80.0
50.0
30.0
A
R
103.2 %

QUESTIONS?

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Extranodal lymphomas: characteristics, the role of RT, volumes, doses and techniques

Orbital (ocular adnexal) Lymphoma

Umberto Ricardi

Introduction

- 1-2% of all NHL
- 7-8% of extranodal lymphomas
- Ocular adnexa lymphomas (OAL) include:
  - orbit
  - extra ocular muscles
  - conjunctiva
  - eyelids
  - lacrimal gland
  - apparatus
- Increased incidence by 6.3% annually in the period from 1975 to 2001, more rapidly than other extra nodal sites NHL

Introduction

- Most cases of extraocular orbital lymphoma are MZL and involve the conjunctiva, lacrimal gland, eyelid, or retrobulbar soft tissues
- Approximately 15% of such cases are bilateral (synchronous or metachronous)
- Less common: FL and DLBCL

Introduction

- 95% of OAL are B-cell neoplasms
  - Extranodular marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type = 35-80%
  - Follicular lymphoma = 20%
  - Diffuse large B-cell lymphoma = 8%
  - Mantle cell lymphoma, small lymphocytic lymphoma and lymphoplasmacytic lymphoma = less common

Ocular adnexae marginal lymphoma (OAML)

Clinical presentation

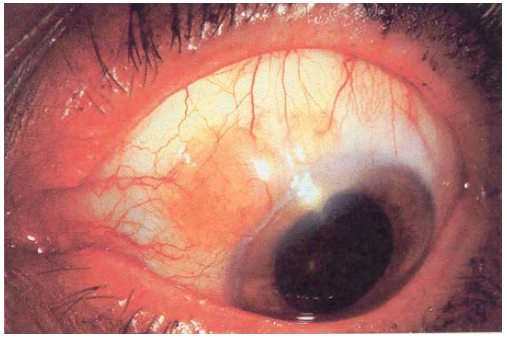
- 5th - 7th decade of life (median age, 65 years)
- female predominance (male:female = 1:1.5/2)
- Korean populations: younger age (median, 46 years) at the time of diagnosis, male rather than female predominance
- Site of origin:
  - orbit = 40%
  - conjunctiva = 35%-40%
  - lacrimal gland = 10%-15%
  - eyelid = 10%
- Bilateral involvement in 10% to 15% of cases (80% simultaneous, 20% sequential events)

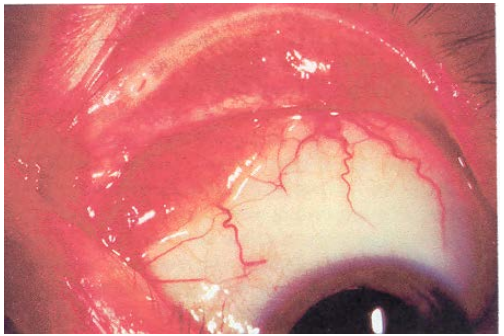
Clinical presentation

- Conjunctival lesions:
  mobile pink infiltrates in the substantia propria (“salmon-pink patch”), causing conjunctival swelling, redness, and irritation

- Orbital lymphoid proliferations:
  palpable, firm or rubbery mass causing progressive proptosis, occasionally associated with periorbital edema, decreased visual acuity, motility disturbances, and diplopia

- Median interval between the onset of symptoms and time of diagnosis:
  7 months





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Pathology

- Expression of IgM (less often IgA or IgG)
- CD21+, CD35+, CD20+, CD79a+
- CD5-, CD10-, CD23-
- CD43+/-, CD11c+/- (weak).
- t(11;18)(q21;q21) in 15-40%
- t(14;18)(q32;q21) in >38%
- t(1;14)(p22;q34) in <5%
- t(3;14)(p14;q32) in 20%

Chlamidophila psittaci (Cp) infection

- **Cp** = etiologic agent of psittacosis, an infection caused by exposure to infected animals
- Cp infection is detected in tumor tissue in 11% of B-cell lymphomas
- In OAML Cp infection between 47% and 80% in countries like Austria, Germany, Italy and Korea

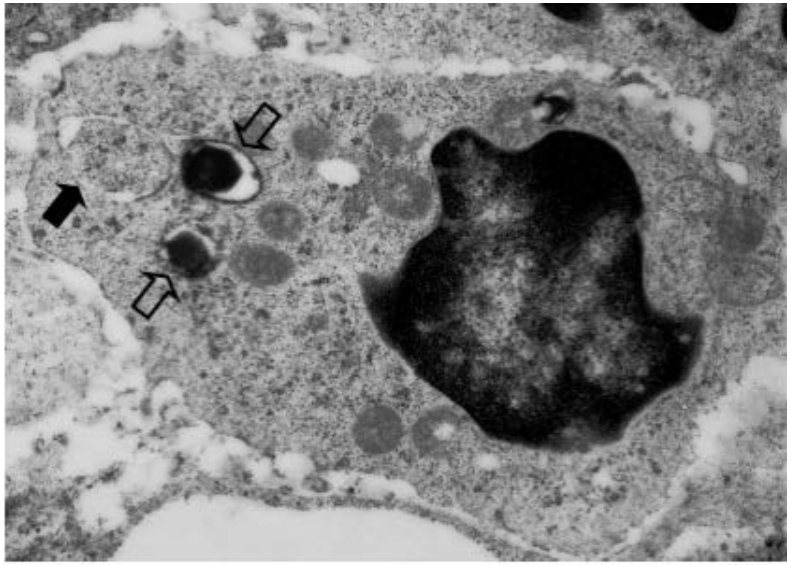

Fig. 2. Elementary bodies (CEB; open arrows) and reticulate body (CRB; full arrow) in an intratumor macrophage of a case of ocular adnexae MALT lymphoma assessed by electron microscopy. Chlamydial infection starts with attachment of a CEB to the host cell, followed by cell invasion. Within eukaryotic cells, chlamydia alternates from a metabolically inactive, highly infective form (*i.e.* the CEB), to a metabolically active, intracellular growing stage form (*i.e.* CRB). Under certain conditions, instead of dividing and differentiating into CEBs, CRBs retain a more stable association within the host cell forming the so-called persistent bodies, an important feature for better understanding the pathogenesis of chronic chlamydial infections.

Ferreri et al, Sem Cancer, 2013

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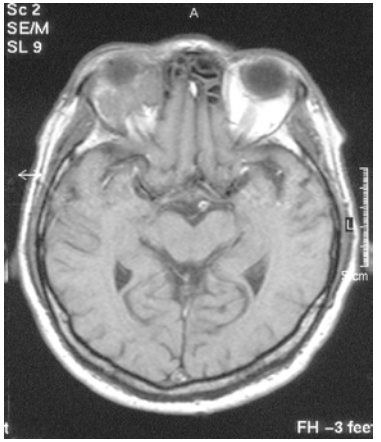
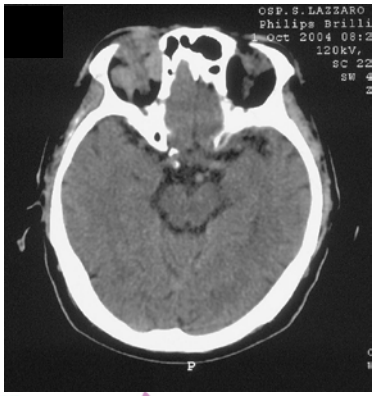
Diagnosis and staging

- Careful ophthalmologic examination
- Adequate tissue sampling
- Complete history and physical examination
- Routine laboratory studies, serum protein electrophoresis, serum LDH, β2-microglobulin
- Chest x-ray
- CT of chest, abdomen, and pelvis
- CT-PET
- Bone marrow biopsy (controversial)
- Orbital CT and MRI with contrast enhancement





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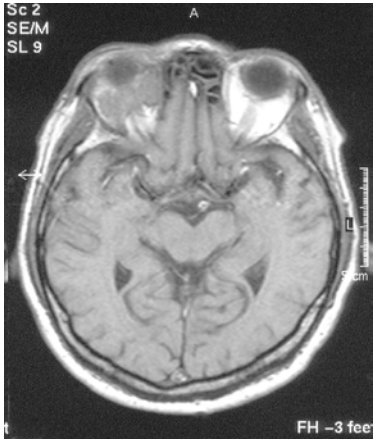
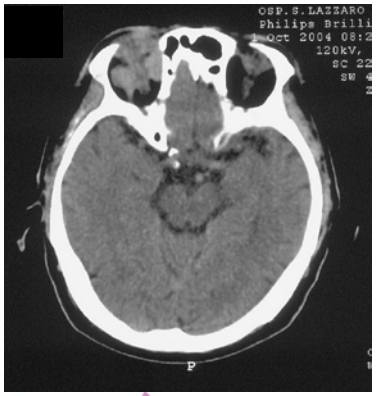
Diagnosis and staging

- Careful ophthalmologic examination:
  - To define the extent of conjunctival disease, which is often not fully appreciated on imaging
  - To assess ocular health before irradiation





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Diagnosis and staging

- Ann Arbor system
- Localized disease (stage I) = 85%-90%
- Nodal involvement = 5%
- Disseminated disease (stage IV) = 10-15%
- Bone marrow involvement in = 5-8%

Treatment
Surgery

- Biopsy: mandatory to determine the histologic subtype of OAL
- Incisional or excisional
- Local relapse has been reported more commonly in patients treated with surgery alone compared with those who also received RT *(Cho et al. 2003; Esik et al. 1996; Lee et al. 2005)*

Treatment

Surgical excision / “Watch and wait”

- 36 patients
- Observation for a median of 7.1 years
- 17 progression (47%)
- 11 required treatment

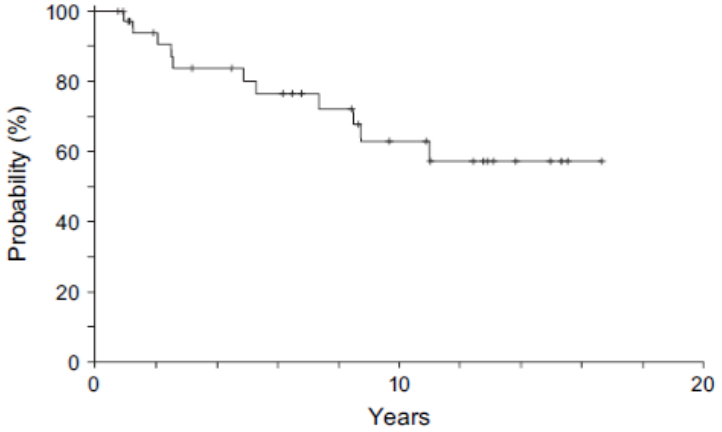

Figure 3. Freedom from requiring treatment. After 5, 10 and 15 years, freedom from requiring treatment was 80%, 63% and 57%, respectively.

This strategy may be appropriate in frail elderly patients with asymptomatic disease or in the setting of severe comorbidities that preclude an aggressive therapeutic approach

Tanimoto et al, Ann Oncol, 2006

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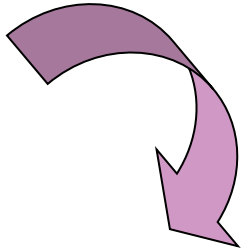
Treatment
Chemotherapy

- Limited data on chemotherapy for patients with OAML
- Different chemotherapy regimens:
  - COP/CVP
  - CHOP
  - C-MOPP
  - Chlorambucil (frail and/or elderly patients)



Complete response: 67-100%
BUT
Local recurrence: >29%

Treatment
Immunotherapy

- Single agent rituximab in previously untreated patients
  - overall response rates: 50-87%
  - median time to disease progression <1 year

Conconi et al. 2003; Ferreri et al. 2005; Benetatos et al. 2006; Heinz et al. 2007

- 90Y ibritumomab tiuxetan for front line treatment of stage IE indolent OAL in 12 patients:
  - complete response in 10 patients
  - partial response in 2 patients

Esmaeili et al. 2009; Shome and Esmaeili 2008

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Treatment
Cp-eradicating antibiotic therapy

- A prospective phase II clinical trial
- **27 patients** (15 newly diagnosed and 12 relapsed)
- Cp infection in 11 pts
- **Treatment:** doxycycline 100 mg orally twice daily for 3 weeks
- CR/PR in 7 of 11 Cp-positive and 6 of 16 Cp-negative patients
- ORR 48%
- 2-year FFS 66%

Ferreri et al, Ann Oncol, 2006

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Treatment

Cp-eradicating antibiotic therapy

- A meta-analysis including 4 studies with a total of 42 pts
- 20 patients achieved some response, 20 patients had stable disease and 2 progressed during antibiotic therapy

Efficacy of Antibiotic Treatment of OAL

Study	Location	No. of patients treated	Median Age, y	Male/Female ratio	*Cps* status	Treatment	Treatment stage (No. of patients)	Objective response, No. of patients	Median follow-up after treatment
Ferreri et al., 2006[19]	Italy	27	56	0.42	11 positive cases per multiplex PCR 16 -	100 mg doxy twice daily × 3 wk	1st line (15) 2nd line (12)	†CR, 6 (22%) PR, 7 (26%) MR, 3 (11%) SD, 9 (33%) PD, 2 (7%)	14 mo
Grunberger et al., 2006[21]	Austria	11	63	0.83	Not performed	200 mg doxy daily × 3 wk	1st line (11)	SD, 11 (100%)	9 mo
Yeung et al., 2004[20]	Taiwan	1	18	Male	Positive serology	100 mg doxy twice daily × 3 wk	2nd line	MR	6 mo
Abramson et al., 2005[17]	U.S.	3	75	2.0	Negative serology in all 3	100 mg doxy daily × 4 wk (1 patient received PrevPak‡ × 14 d)	NA	CR, 2 (66%) PR, 1 (33%)	28 mo

Husain et al, Cancer, 2007

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Role of Radiotherapy

- Primary RT is considered to be the treatment of choice for indolent lymphomas

- Curative RT is appropriate even for bilateral presentations of indolent lymphomas

Reference, year	No. of patients	Stage I, %	Gy	CR, %	LR, %	DR, %	Survival, %	LRM, %
Stafford et al. 2001	40	85	15-54	98	2	25	5-y RFS 88 5-y OS 74 5-y DSS 100	0
Le et al. 2002	31	100	30-40	100	0	16	10-y PFS 71 10-y OS 73	3
Fung et al. 2003	48	81	30.6	100	8	25	10-y OS 81 10-y DSS 100	0
Hasegawa et al. 2003	20	95	30	100	5	20	10-y PFS 70 10-y DSS 100	0
Tsang et al. 2003	30	97	25	97	17	10	5-y DFS 74 5-y OS 97	ND
Uno et al. 2003	50	100	20-46	98	6	6	5-y OS 91	2
Lee et al. 2005	29	100	30-45	100	3	0	3-y EFS 93 3-y OS 100	0
Ejima et al. 2006	42	100	30-36	84	10	10	5-y PFS 77 5-y DSS 100	0
Suh et al. 2006	48	96	30.6	96	6	0	10-y DFS 93 10-y DSS 98	2
Tanimoto et al. 2007	58	94	30-40	83	9	2	10-y PFS 72 10-y OS 92	0
Nam et al. 2009	66	100	20-45	97	3	7.5	5-y RFS 92 5-y OS 96.4	ND
Goda et al. 2011	89	100	25	99	2	22.5	7-y OS 91 7-y DSS 96% 7-y RFS 64%	4
Tran et al. 2013	25	92	24-25	100	4	8	5-y PFS 81 5-y OS 100	0

Role of RT

Local control: 85-100%

Distant recurrence: 10-25%

Long-term RFS or DFS: 70-90%

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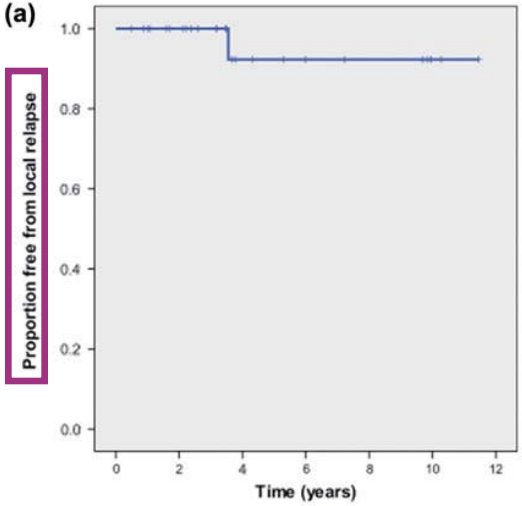
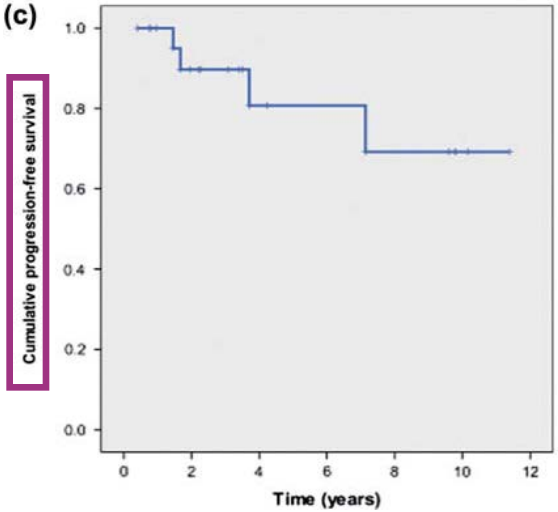
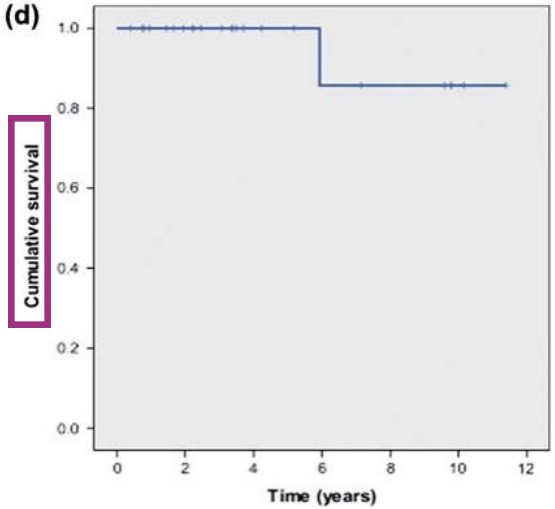
Efficacy of low dose radiotherapy for primary orbital marginal zone lymphoma

- 24 pts (27 orbits)
- median follow-up: 41 months
- CR: 100%
- Relapses: 3 pts (one local, one contralateral and one distant)







Tran et al, Leuk Lymphoma, 2013

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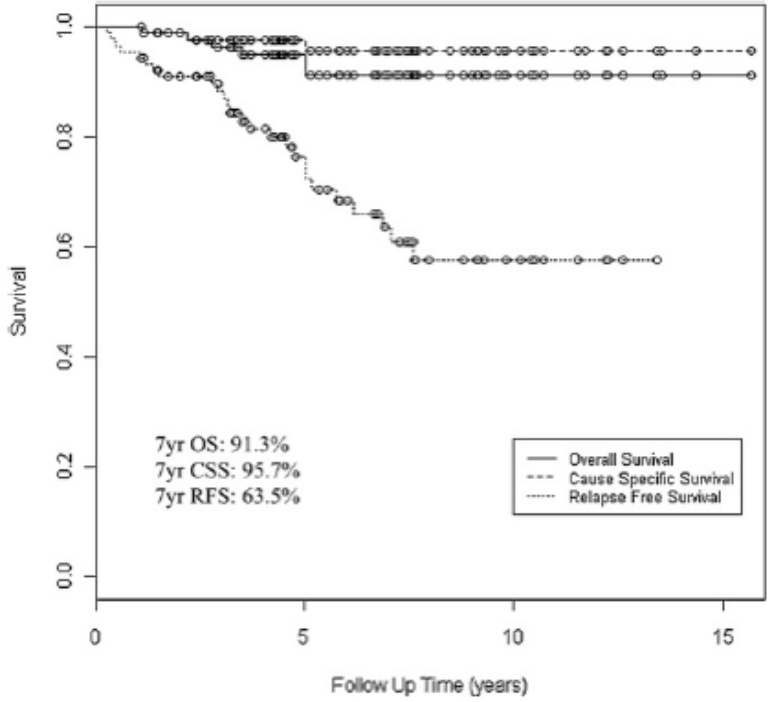
LOCALIZED ORBITAL MUCOSA-ASSOCIATED LYMPHOMA TISSUE LYMPHOMA MANAGED WITH PRIMARY RADIATION THERAPY: EFFICACY AND TOXICITY



89 pts with stage IE OAML treated with RT

Relapse: 22 pts (25%)

- local: 2 pts (9%)
- distant: 15 pts (68%)
- contralateral orbits: 5 pts (23%)

Goda et al, IJROBP, 2011

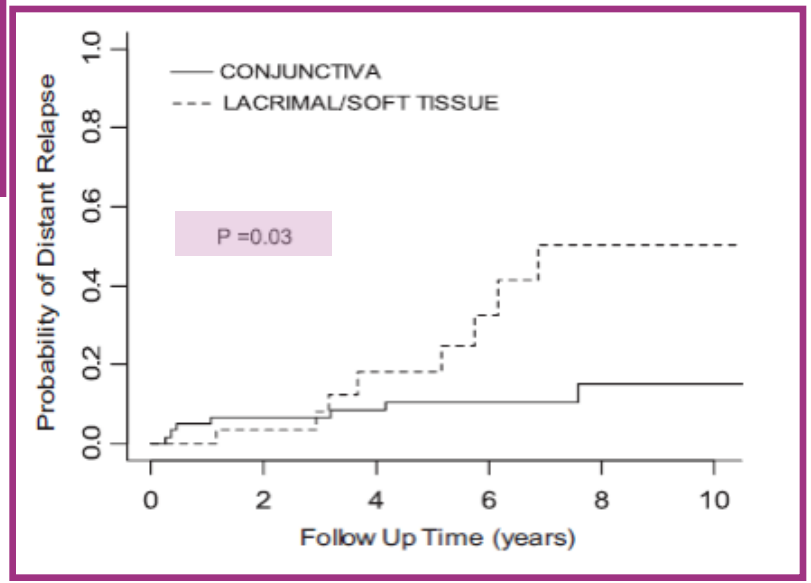
Disease subsite may be a significant prognostic factor

Table 4. Multivariate analysis (Cox model)

Factor	OS	DFS	FFTF
Age (<64 vs. ≥64 y)	<0.0001	0.002	NS
Grade (low vs. high)	0.05	0.02	NS
Response (CR vs. PR)	NS	0.004	0.002
Localization (conjunctiva vs. other)	NS	0.04	0.002
Complete staging (yes vs. no)	NS	0.01	0.03

Abbreviations: OS = overall survival; DFS = disease-free survival; FFTF = freedom from treatment failure; NS = not significant; CR = complete response; PR = partial response.

Martinet et al, IJROBP,2003



Goda et al, IJROBP,2011

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Bilateral orbital lymphoma presentations may be a prognostic factor

Rates of Recurrence According to Patient and Treatment Factors

Characteristic	No. of patients (%)			
	Ocular-adnexal recurrence	*P* value[a]	Recurrence at any site	*P* value[b]
Laterality				
Unilateral	1/43 (2)	0.048	3/43 (7)	0.029
Bilateral	2/7 (29)	—	3/7 (43)	—
Initial response to RT				
CR	0/26 (0)	0.10	1/26 (4)	0.093
Non-CR	3/24 (13)	—	5/24 (21)	—
Age (yrs)				
< 60	2/22 (9)	0.58	2/28 (7)	0.39
≥ 60	1/28 (4)	—	4/22 (18)	—
Gender				
Male	1/33 (3)	0.26	3/33 (9)	0.40
Female	2/17 (12)	—	3/17 (18)	—
Location				
Conjunctiva	3/29 (10)	0.25	4/29 (14)	1.00
Others	0/21 (0)	—	2/21 (10)	—
Dose of RT (Gy)				
≤ 30	2/18 (11)	0.29	3/32 (9)	0.65
> 30	1/32 (3)	—	3/18 (17)	—

Uno et al, Cancer, 2003

Considerations on RT dose

- A dose of at least 25 Gy is required to provide optimal local control and minimize the rate of local failures in OAML
  (Uno et al. 2003; Ejima et al. 2006; Tsang et al. 2003)

- No differences in local or distal recurrence and survival after radiation with less than or equal to 34 Gy compared with higher doses
  (Le et al. 2002)

- Significant ophthalmologic toxicity with vision loss after doses of more than or equal to 34 Gy
  (Le et al. 2002)

Table III. Results of treatment with doses less than 30 Gy for localized orbital MZL lymphoma.

Author	Patients (orbits)	Dose (Gy)	Local failures	Local control	Technical factors for local failure
Stafford, 2001 [16]	29	15–55.8 (median 27)	0	100%	
Fung, 2003 [9]	12 (41)	2–<30	3 (2 con, 1 orbit)	81% 5 years	Suboptimal imaging, not stated if bolus used
		30–45	1 (orbit)	100% 5 years	
Uno, 2003 [8]	18 (32)	20–<30	2	89%	Lens shield, partial orbital RT, not stated if bolus used
		30–46	1	97%	
Zhou, 2005 [7]	11 (19)	18–<30	0	100%	
		30–37.3	0	100%	
Nam, 2009 [4]	66 (80)	20–45 (median 30)	3 (1 con, 2 lac)	95% 5 years	Not stated
Bayraktar, 2010 [10]	18* (52*)	23–<30.6	3	83%	Not stated
		30.6–45	3	94%	
Goda, 2011 [2]	89† (110)	25	2 inferior fornix	97% 7 years	Not stated
Present series	25 (27)	24–25	1 medial canthus	92% 10 years	Likely marginal miss

Tran et al, Leuk Lymphoma, 2013

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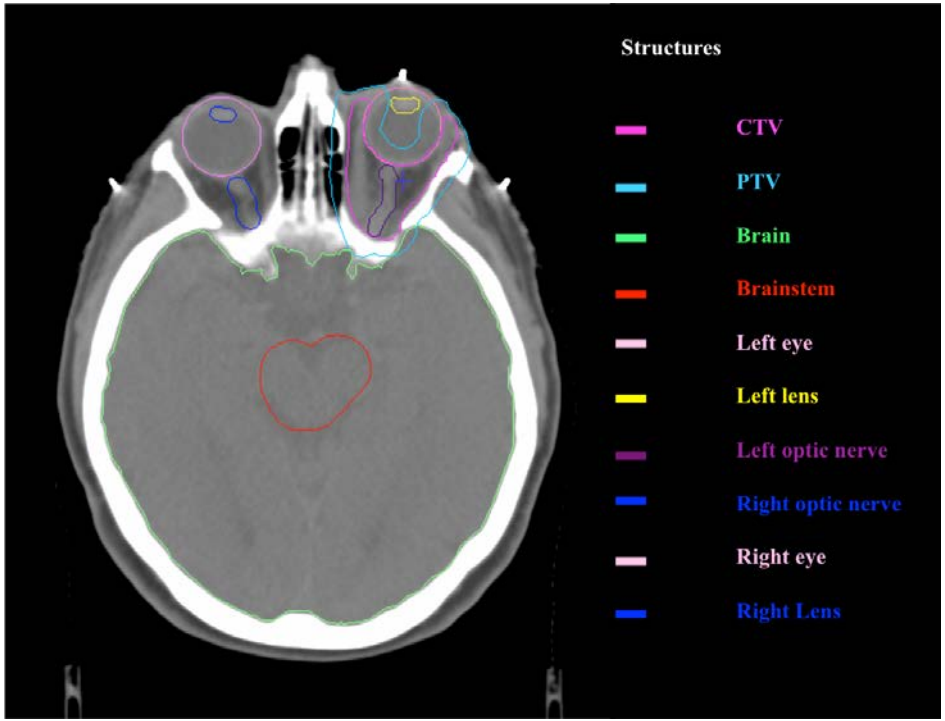
Considerations on RT volume

For retrobulbar, lacrimal gland, and deep conjuctival lymphomas

The intent is to irradiate the whole orbit

CTV = outlined at the orbital bony borders and expanded to include any area of definite or suspected bony or extraorbital extension



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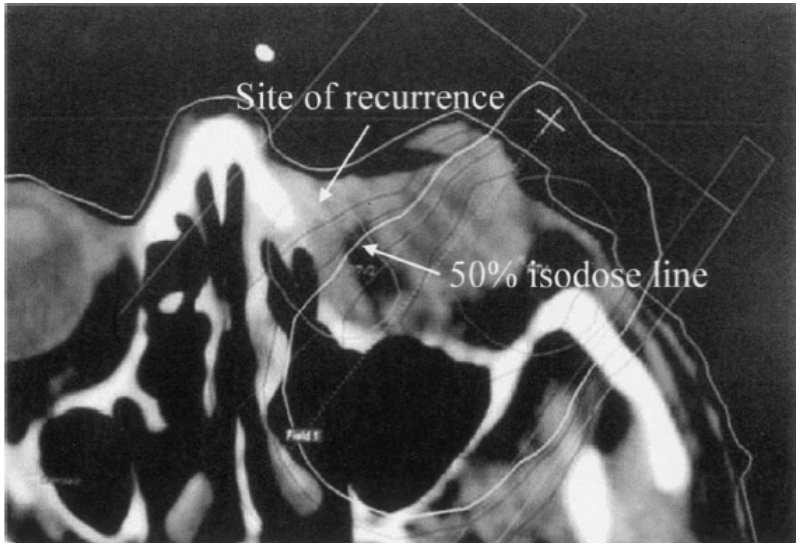
Is it necessary to treat the entire orbit?

Characteristics	Whole orbit	Partial orbit
Patients (*n*)	11 (12 eyes)	12
Age (y)		
Range	40–82	34–81
Median (*n*)	55	70
Gender		
Male	2	8
Female	9	4
Grade (*n*)		
Low	8 (9 eyes)	10
Intermediate/high	3	2
Chemotherapy (n)	2	1
Stage (*n*)		
1E	9 (10 eyes)	11
IV	2	1
Dose (Gy)		
Low grade		
Range	20–30	20–27
Median	25.2	25.2
Intermediate/high grade		
Range	24–39.6	39.6–40
Median	39.6	

Pfeffer et al, IJROBP, 2004

- CR in all pts
- Intraorbital recurrence in previously uninvolved areas not included in the initial target volume: 4 pts (33%) with low-grade lymphoma treated with partial orbit RT



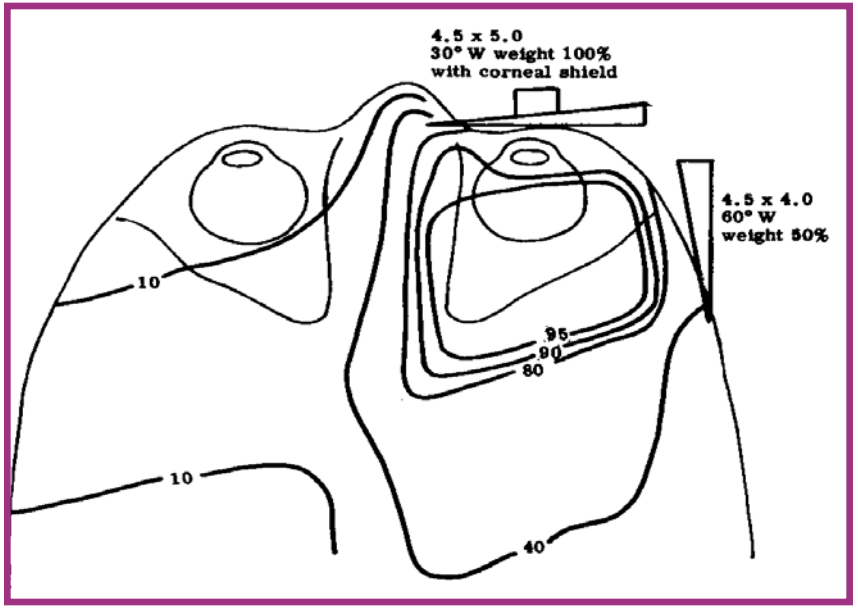
Partial orbital irradiation has been associated with higher risk of local failure

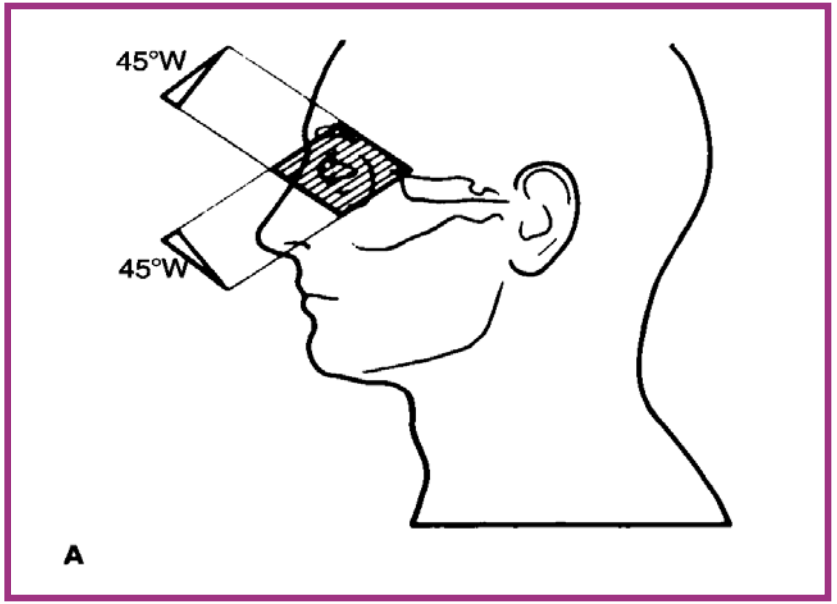
RT technique

- The whole orbit may be treated with 3D conformal or IMRT techniques
- The conjunctival sac and lacrimal gland may be treated with en face electrons
- Bolus should be used in all cases of conjunctival/superficial involvement or definite or suspected extension
- Lens shielding may be used for disease limited to conjunctiva/eyelid, if appropriate and only if there is confidence that disease will not be shielded

RT techniques (3D-CRT)

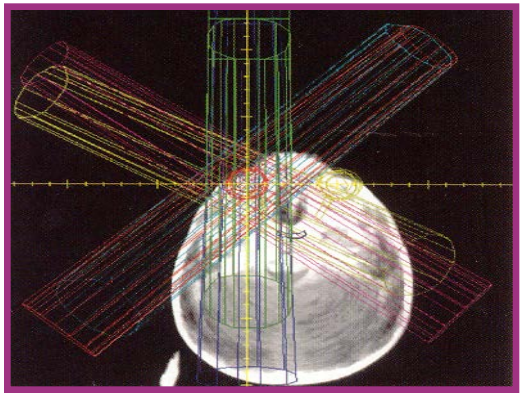
Whole orbit – wedge pair beams

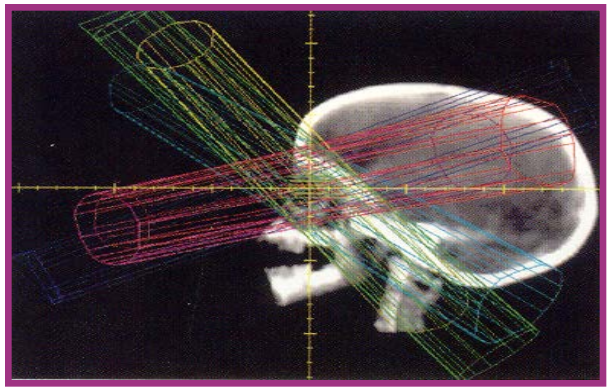


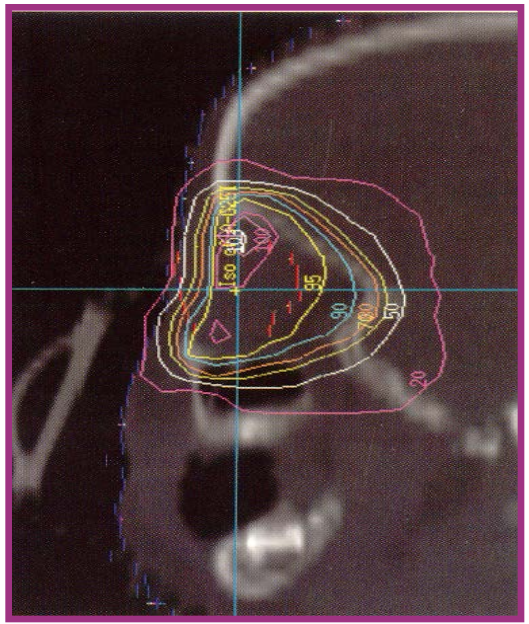


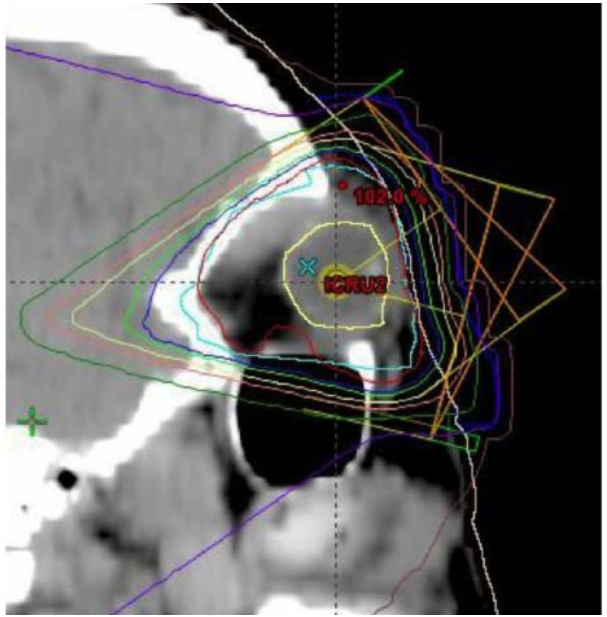
3D CRT

A technique such as a superior-inferior wedge pair has the advantage of sparing the controlateral orbit should metachronous controlateral disease require Rt subsequently









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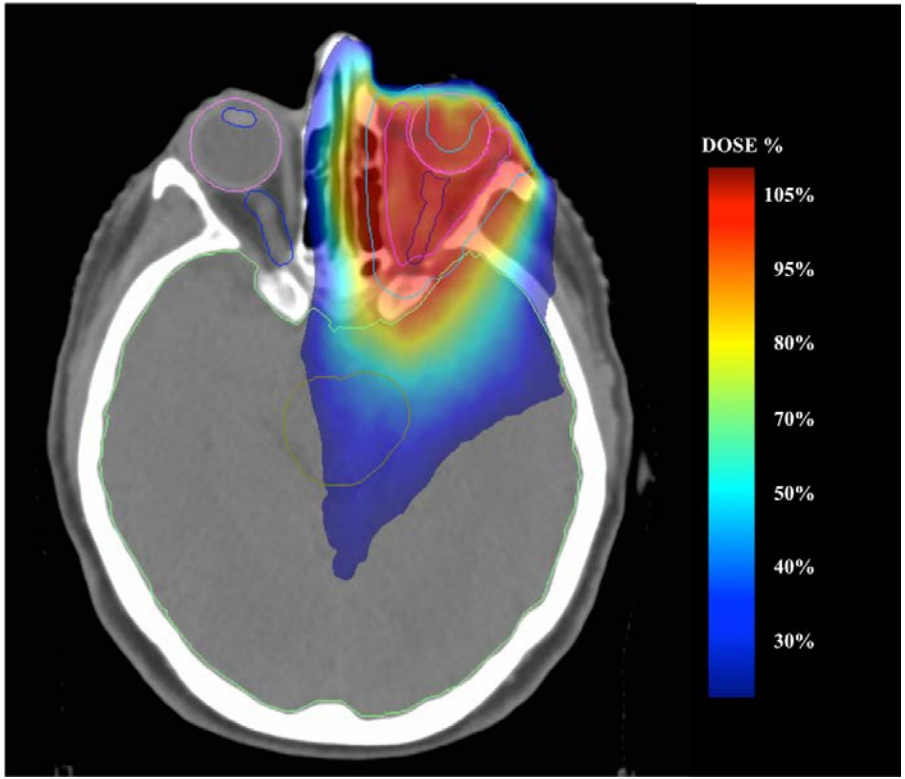
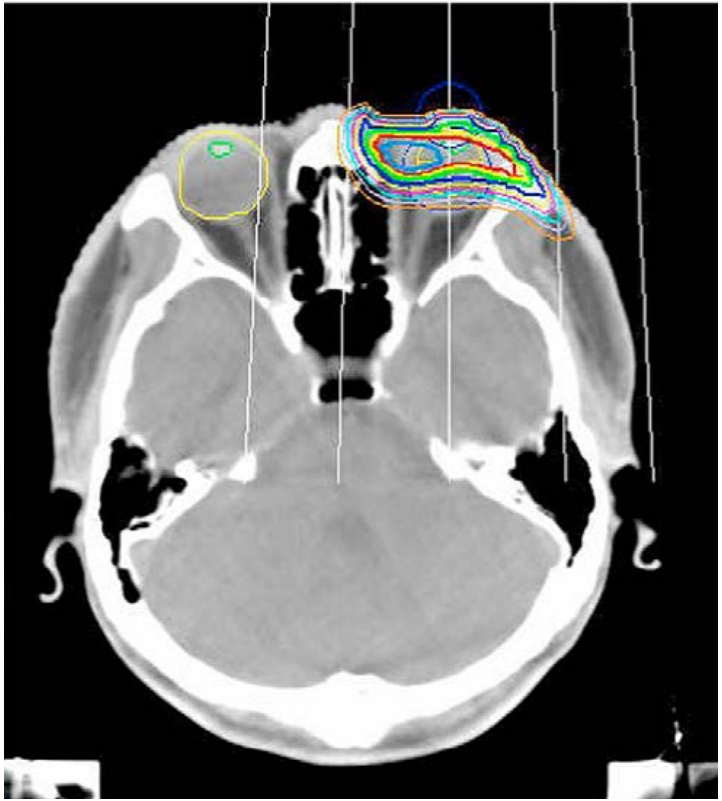
IMRT (VMAT)

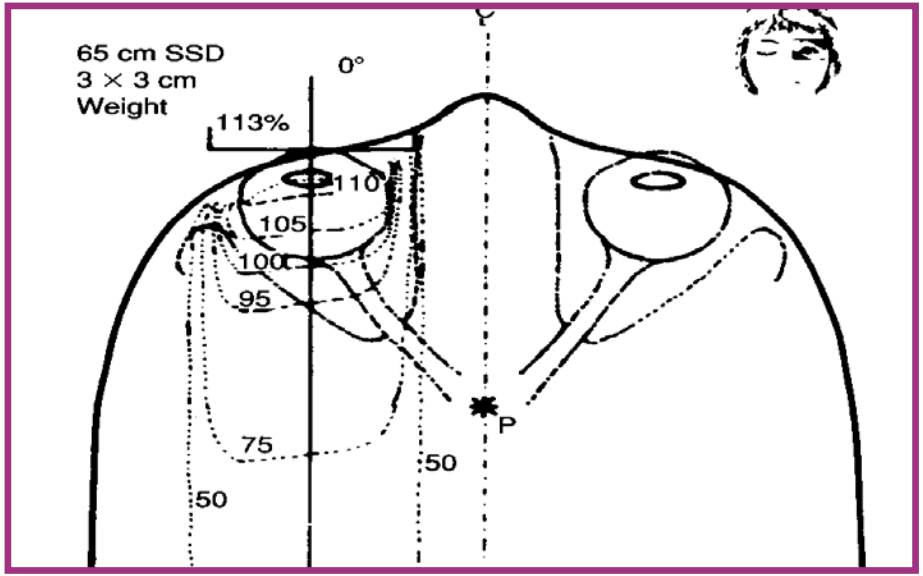


Tumors confined to the conjunctiva or eyelid

CTV = entire conjunctival reflection to the fornices (not to include the entire orbit)



Partial anterior orbit – direct electron beam



- This situation is usually approached with a direct electron beam with bolus
- In selected cases, a lens shield may be used to reduce the risk of cataract formation
- Care must be taken not to shield parts of the conjunctiva because the whole conjunctival sac is the CTV

Lens shielding

- Aim: to reduce the incidence of cataract
- Caution: inadvertent tumor under dosing
- Some reports attributed local relapses to inadvertent partial shielding of tumor *(Uno et al. 2003; Fung et al. 2003)*
- Other reports suggest that the careful use doesn't lead to treatment failure *(Le et al. 2002; Martinet et al. 2003; Son et al. 2010; Tran et al. 2013)*
- ILROG guidelines: lens shielding may be used for disease limited to conjuctiva/eyelid, if appropriate and only if disease will not be shielded

Bolus

- Aim: to ensure that conjunctival tumors or other very superficially located lesions receive the full dose of radiation
- In most reports, local failure in superficial disease sites occurred with no mention of the use of bolus *(Uno et al. 2003; Yamashita et al. 2008; Son et al. 2010)*
- In another report bolus was not used routinely unless there was frank skin involvement, without an apparent increase in relapse rate *(Goda et al. 2011)*
- ILROG guidelines: bolus should be used in all cases of conjunctival/superficial involvement or definite or suspected extension

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

Volumes: indolent disease

- CTV: for most cases of indolent NHL, the entire bony orbit including definite or suspected extraorbital extensions. When disease is limited to the conjunctiva, the CTV includes the entire conjunctival sac and local extensions to eyelid.
- PTV margin is normally 5 mm.

Dose: indolent disease

Dose: 24 to 25 Gy in 1.5- to 2-Gy fractions.

Yahalom et al, IJROBP, 2015

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Ocular adnexae DLBCL

Role of RT

- Consolidation RT after R-chemotherapy

- Radical RT in patients “unfit” for chemotherapy

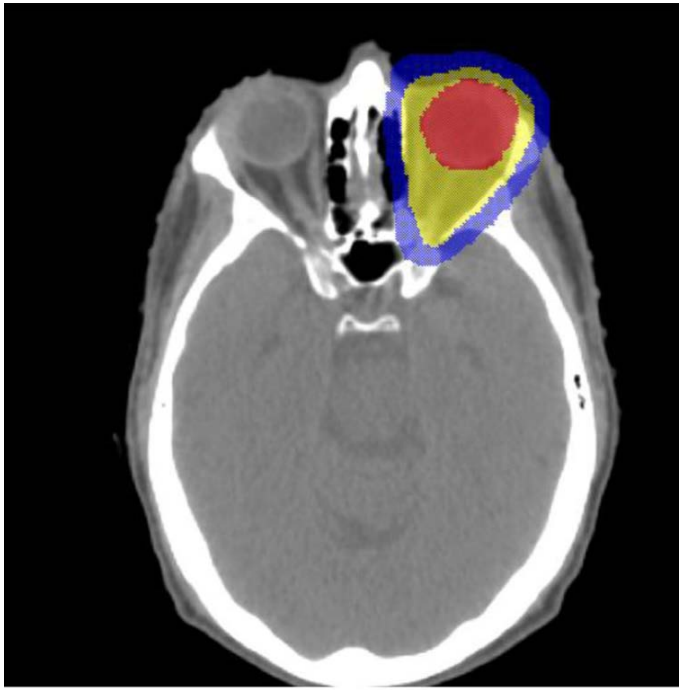
Considerations on RT volume

• **GTV** = residual disease after chemotherapy (if any) for a boost dose

• **CTV** = entire orbit

• **PTV** margin = normally 5 mm

• DLBCL of the lacrimal gland alone
→ CTV for consolidation RT limited to lacrimal gland



Yahalom et al, IJROBP, 2015

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Considerations on RT dose

- CR after chemotherapy → 30 Gy

- PR after chemotherapy
- Relapse
- RT alone (pts “unfit” for chemo)

→ 30 – 36 Gy to whole orbit and extensions

→ 40 – 45 Gy to residual GTV (depending on the volume and proximity to critical structures)

Yahalom et al, IJROBP, 2015

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Toxicity

- Immediate toxicity consists of mild to moderate cutaneous or conjunctival reactions
- Long-term complications are observed in up to 50% of patients
- The complications are relatively minor and include cataract formation (30-50%) and mild xerophthalmia (20-40%)
- RT doses above 36 Gy may result in deleterious ophthalmologic toxicity such as ischemic retinopathy, optic atrophy, corneal ulceration, neovascular glaucoma, associated with significant vision loss

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Gastric Marginal Zone Lymphoma: Role of RT

Joachim Yahalom, M.D.
Memorial Sloan Kettering Cancer Center
New York ,NY, USA

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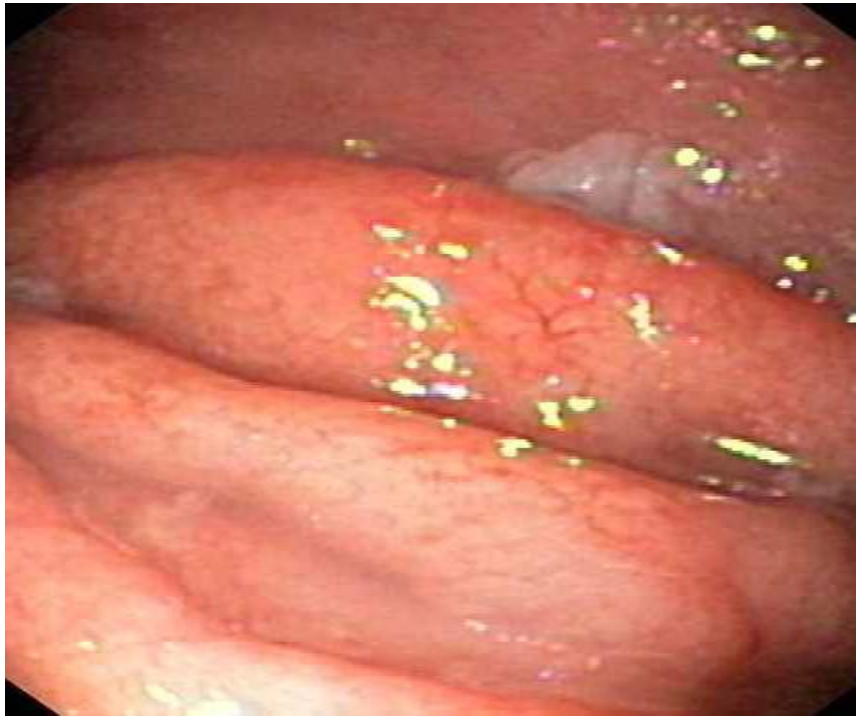

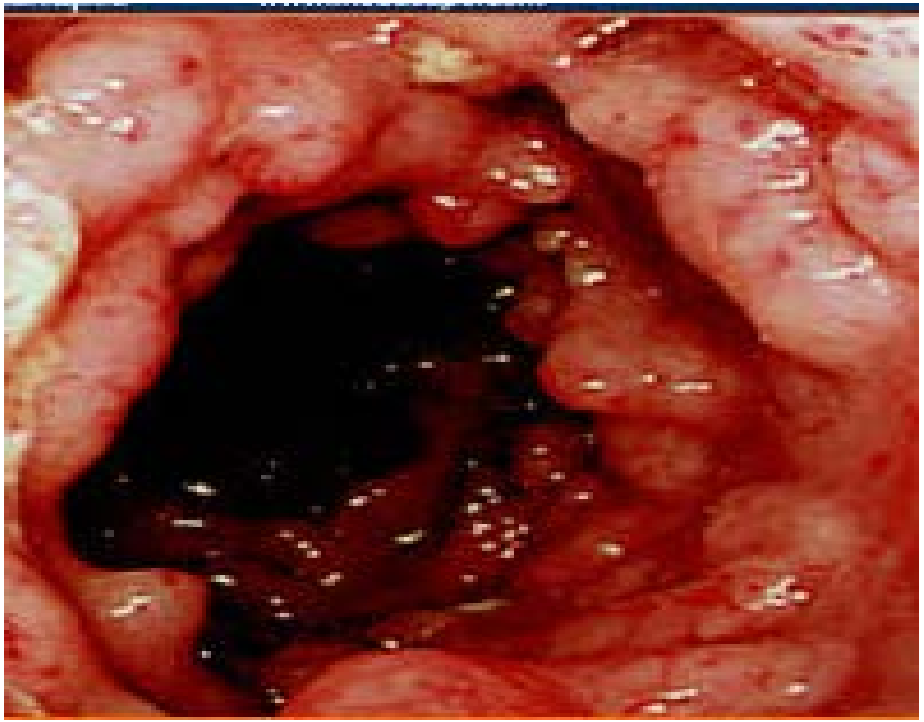

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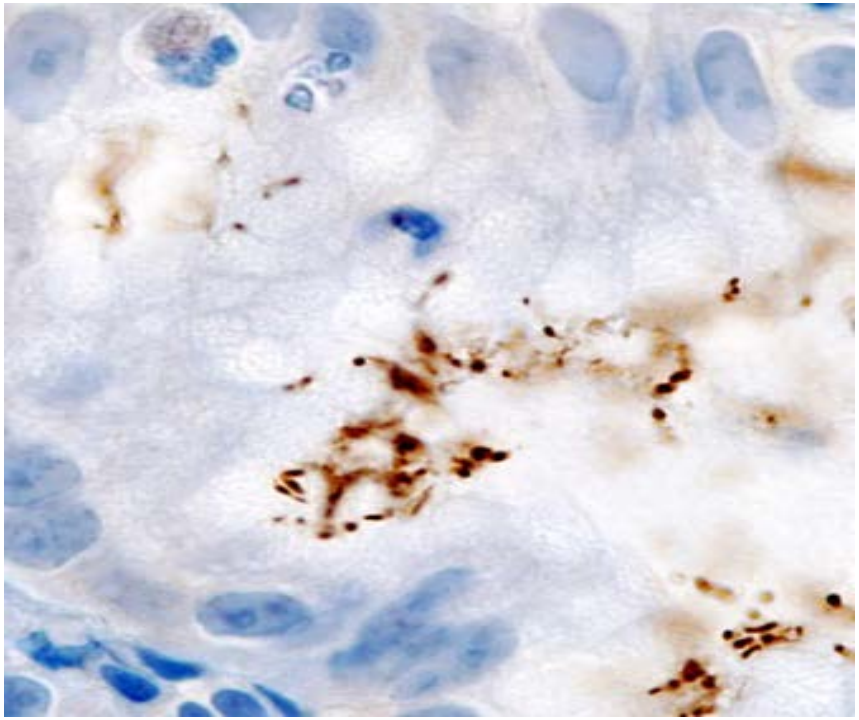
H. Pylori



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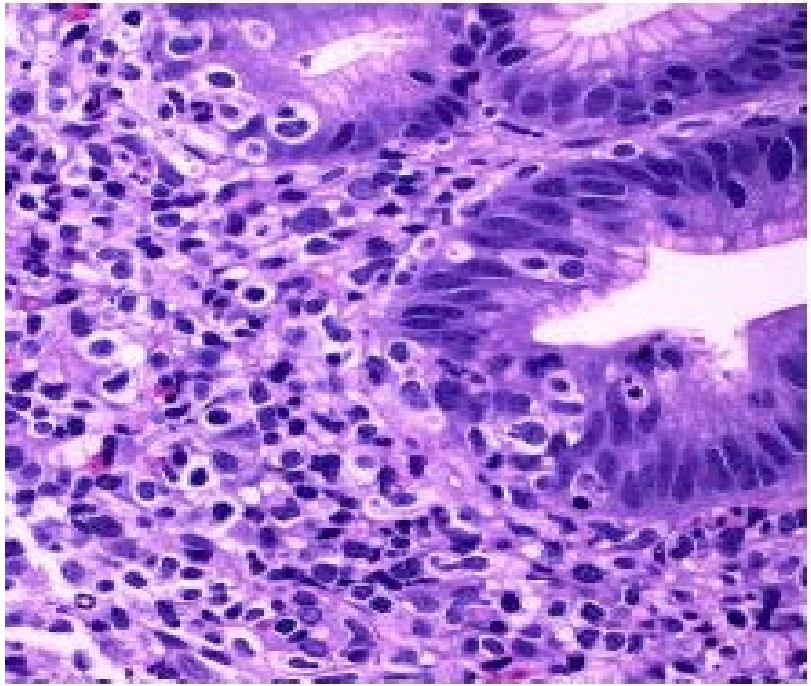

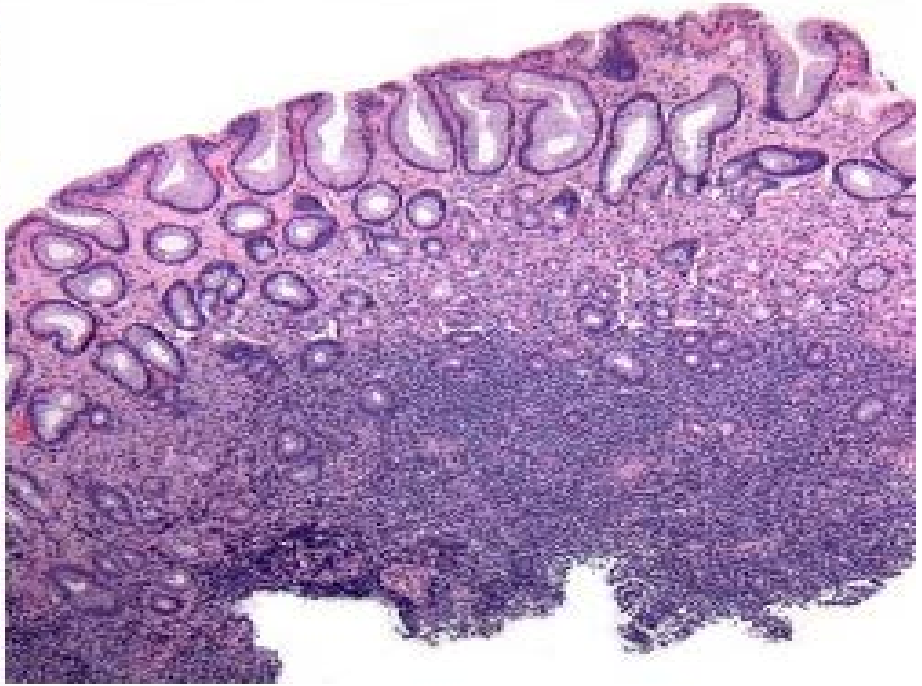

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RT of Gastric Lymphomas

- Marginal Zone Lymphoma (MZL) – Most common
  - RT is the standard treatment in North America for "H. Pylori-independent" Gastric MZL (or "MALT")
  - H. pylori -not present
  - H. pylori responded to antibiotics, but MZL persists for a long time
  - H. pylori resistant to multiple antibiotics, MZL persists
  - Failure of antibiotics - MZL progression
  - Failure of antibiotics - difficult symptoms
- Diffuse Large B-Cell Lymphoma (many are transformed MZL)
  - RT consolidation after R-CHOP induced CR

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Involved-field Radiotherapy for H. pylori-independent Gastric Marginal Zone (MALT) Lymphoma:

23 years of experience with 131 patients

1991-2012 at MSKCC

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Patient Characteristics

Characteristic	# (range)
Median Age at Diagnosis	61 yrs (25-89)
Median Follow-up	4.4 yrs (0-19.9)
Characteristic	**N (%)**
Female	73 (56%)
Male	58 (44%)
Stage at diagnosis	
I	116 (89%)
II	6 (5)
III	0 (0) *
IV	9(5)

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Diagnostic/Staging Workup

Modality	N (%)	% +	% -
EGD	131 (100)	100	0 *
PET Scan	67 (51)	64	36
CT Scan	121 (92)	49	51
Bone Marrow Biopsy	83	99	1

H. Pylori

Characteristic	N (%)
H. Pylori at Diagnosis	
No	107 (82)
Yes	21 (16)
Unknown	3 (2)
Antibiotics given	
No	71 (54)
Yes	60 (46)

Characteristic	N (%)
MALT response to abx	
No response	53 (40)
Relapse	3 (2)
Partial response → POD	1 (1)
Unknown	3 (2)

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Chemotherapy

Characteristic	N (%)
Chemotherapy Treatment	
No	124 (95)
Yes	7 (5)
Chemotherapy Regimens	
CHOP	2 (29)
Rituximab	2 (29)
Fludarabine	1 (14)
Chlorambucil and Prednisone	1 (14)
Multiple Regimens	1 (14)

Radiotherapy

Characteristic	N (%)
RT Dose	
≤3000 cGy	120 (92)
>3000 cGy	11 (8)
Median Dose (cGy)	3000
Treatment Volume	
Stomach	121 (92)
Stomach + Duodenum	1 (1)
Duodenum only	4 (3)
Stomach + lymph nodes	5 (4)

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Response to RT

Response to RT	N (%)
Complete response	127 (97)
Stable disease	3 (2)
POD	0
Other	1 (1)

Stomach relapse after RT

Median time to 1st relapse	13 months (0.0 – 148 months)

Relapses after RT	N (%)
No relapse	124 (95)
Refractory	2 (1.5)
Relapse	5 (4)

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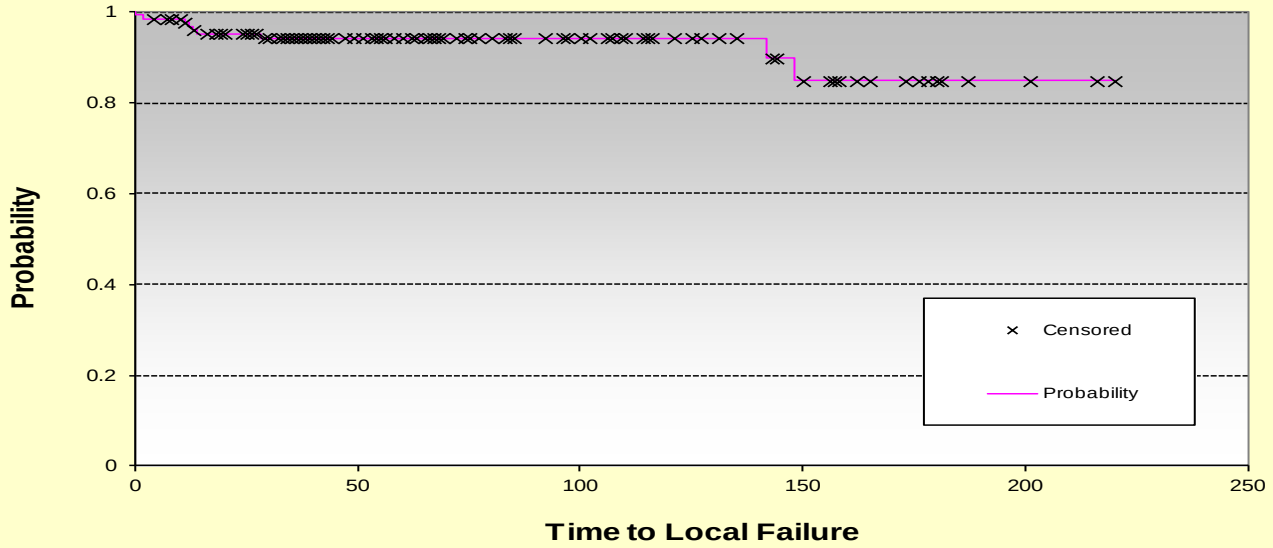
Freedom from Local Failure



5 years	10 years	15 years
94%	94%	85%

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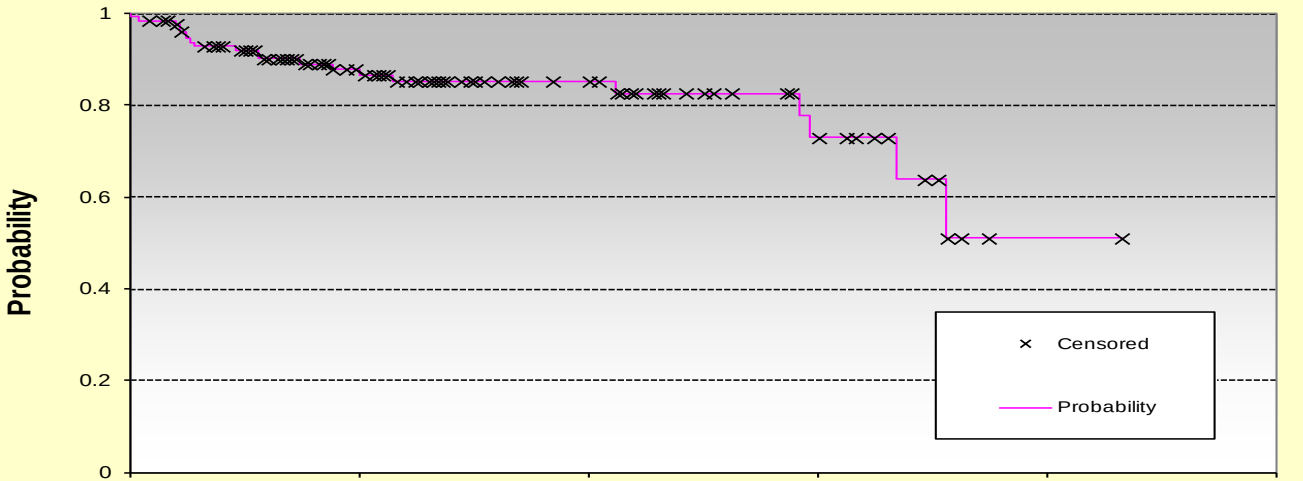
Freedom from Lymphoma Failure



5 years	10 years	15 years
85%	83%	51%

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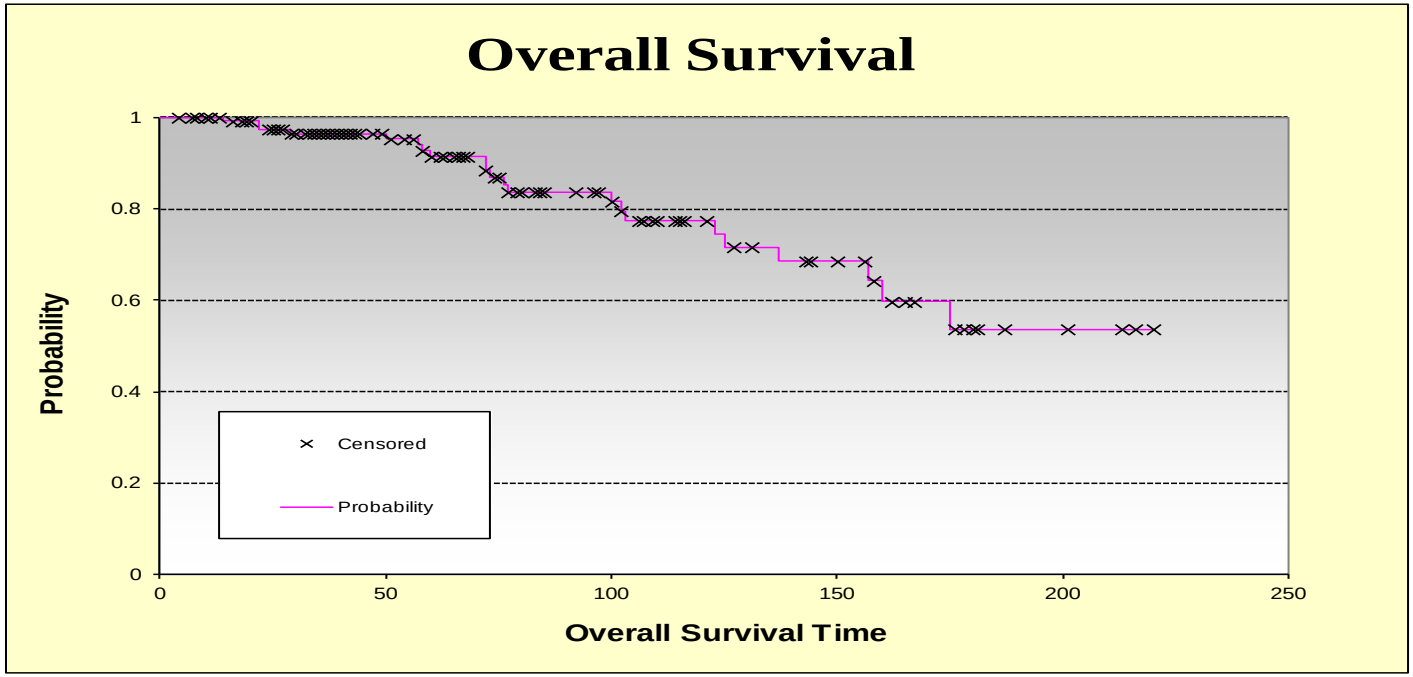

5 years	10 years	15 years
91%	77%	54%

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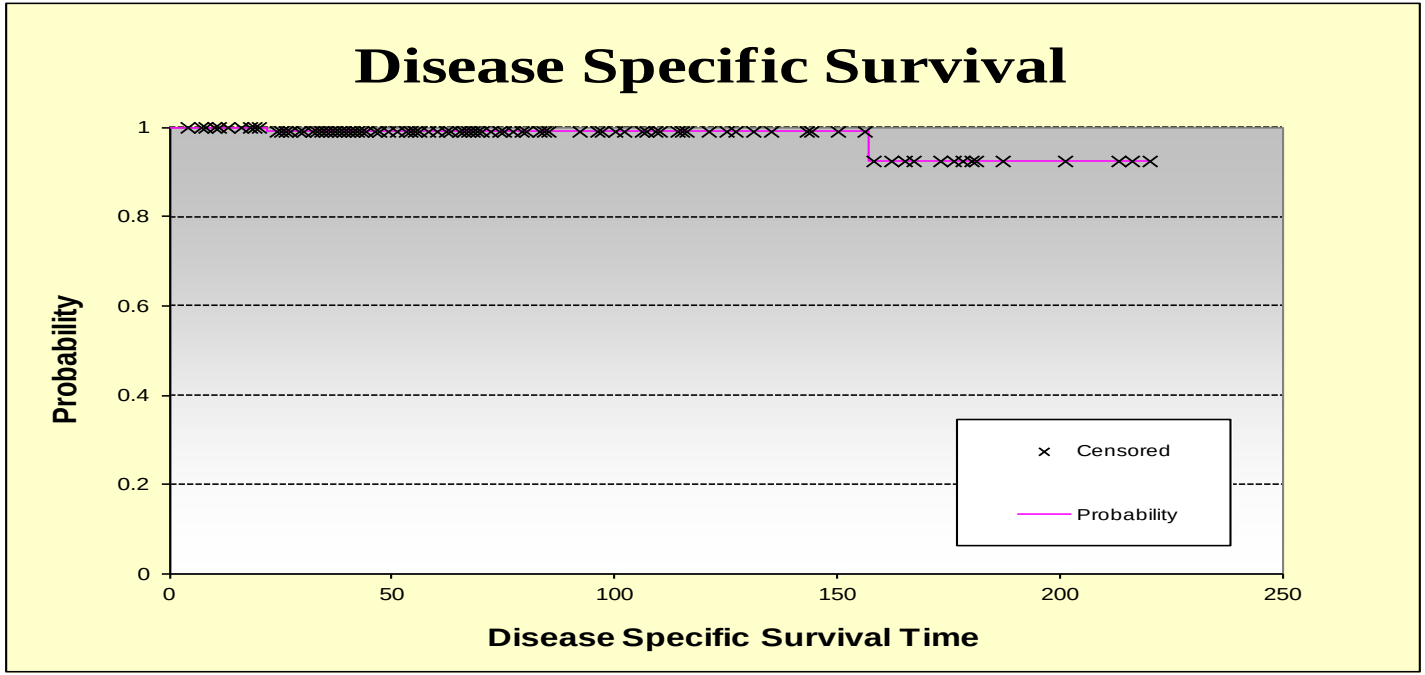
Disease Specific Survival



5 years	10 years	15 years
99%	99%	92%

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Principles of RT of Stomach

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Principles of Gastric Lymphoma RT (1)

- For both MZL and DLBCL – The whole stomach constitutes the Clinical Target Volume (CTV)
- The duodenum is included is it was involved with the stomach
- Peri-gastric and adjacent lymph nodes are included only if suspicious by any imaging including endoscopic ultrasound

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Principles of Gastric Lymphoma RT (2)

- The final volume also accounts for changes in stomach position during respiration
- The stomach is ideally treated while empty; but slight changes in volume should be accounted for
- The dose rarely exceeds 30 Gy; thus, acute or chronic complications are unlikely.
- Yet, RT exposure of kidneys, heart, lung and liver and bowl should be reduced as much as possible

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Gastric Anatomy

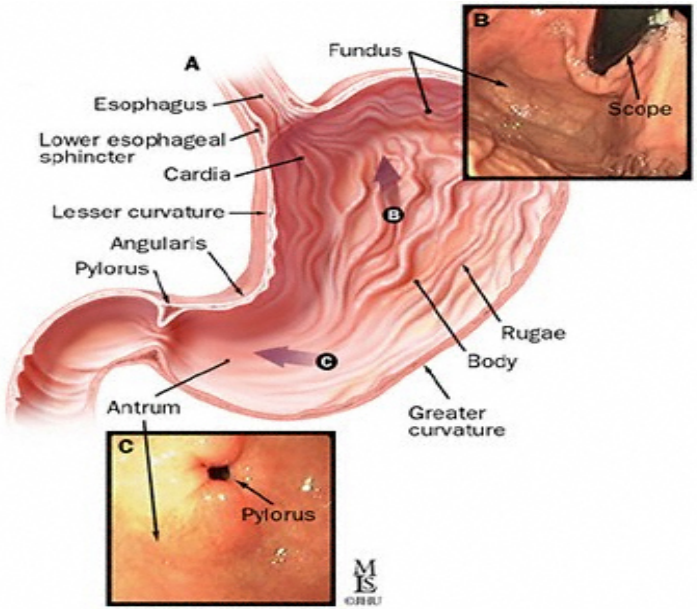

Figure 6. Normal internal anatomy of stomach **(A); B, C,** endoscopic views.

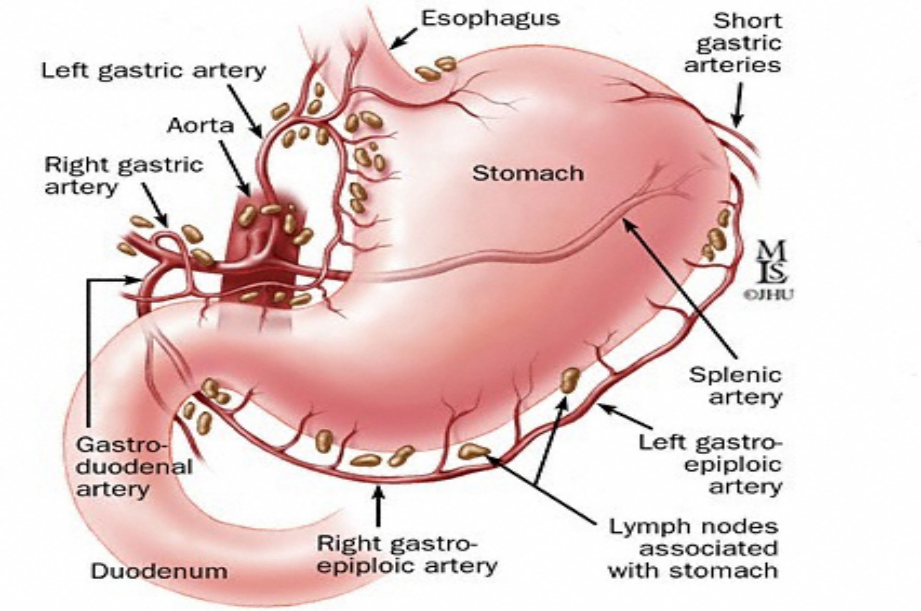

Figure 7. Normal external anatomy of the stomach with arteries and lymph nodes.

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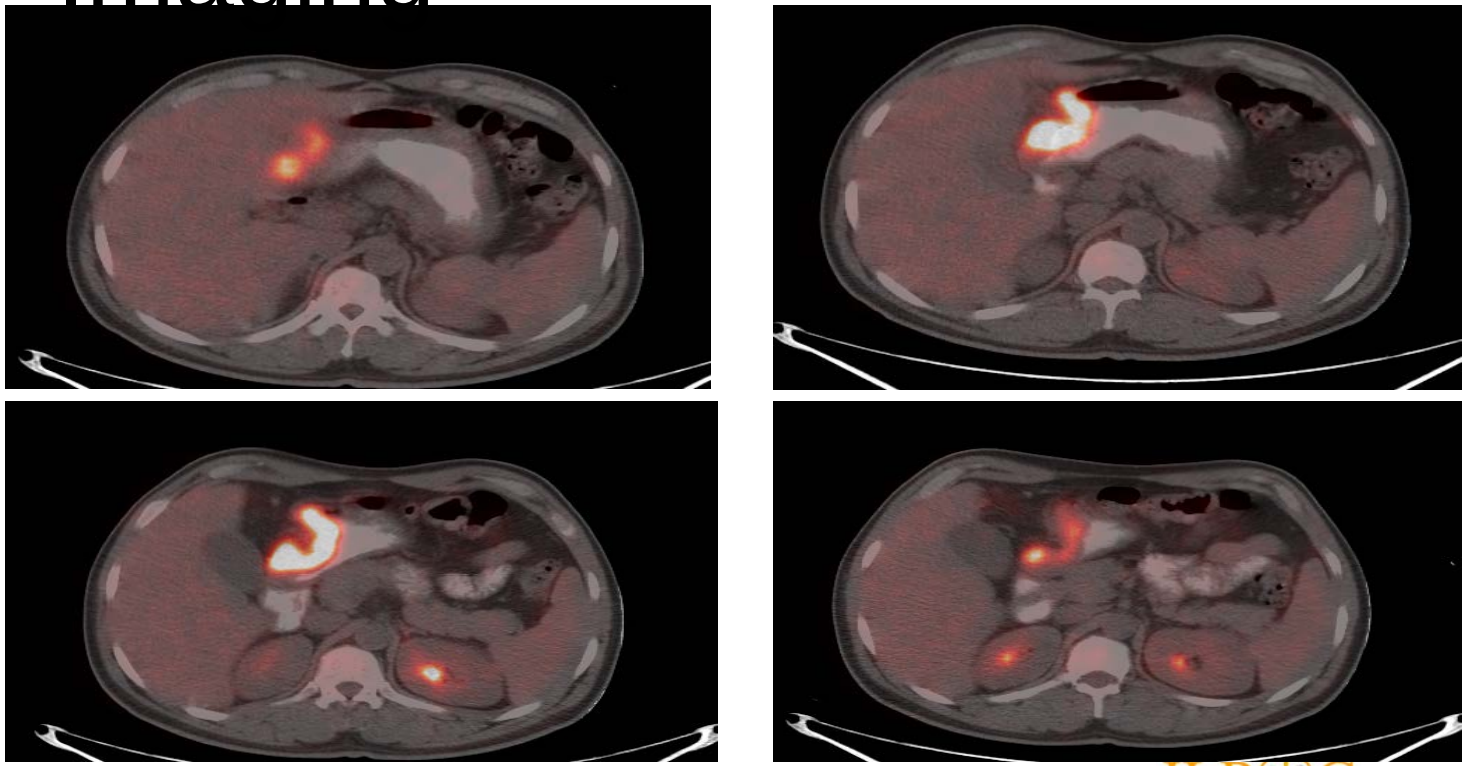
Imaging



*But in MZL often PET and CT may be negative

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RT of Stomach: Pre Planning Studies

- Details of endoscopic studies
- Endoscopic ultrasound and directed biopsy in case of thickened wall/suspected transformation
- In patients that may receive RT to large volume of one kidney, renal scan may provide important information

RT of Stomach: simulation

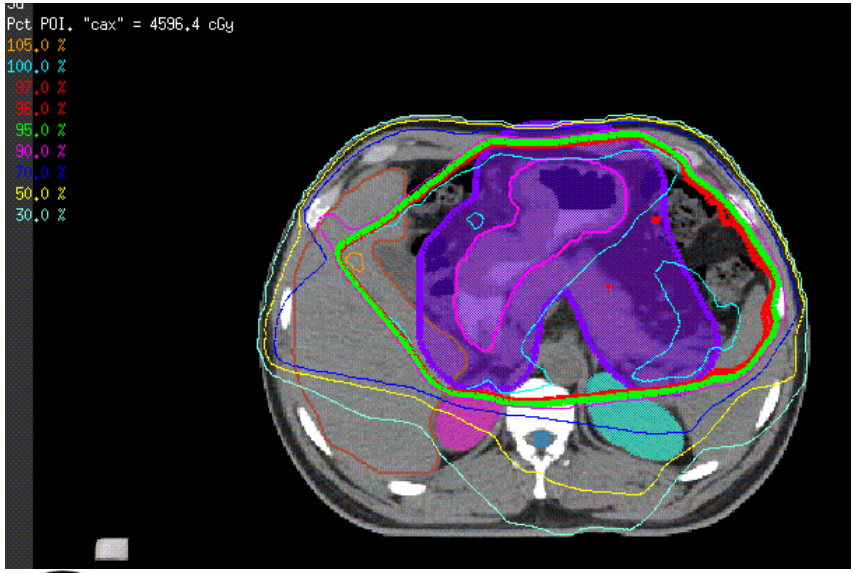
- The stomach volume and position is affected by ingestion of food or liquids. Patients are always simulated and treated with an empty stomach after at least 4 hours/overnight fast.
- Simulate the patient supine with arms up using customized immobilization device.
- A small volume (<50ml) of oral contrast (barium sulfate) should be used in all cases; IV contrast is recommended, if there are suspicious lymph nodes.
- Respiratory motion should be assessed using a 4D-CT scan or fluoroscopy

RT of Stomach: volumes

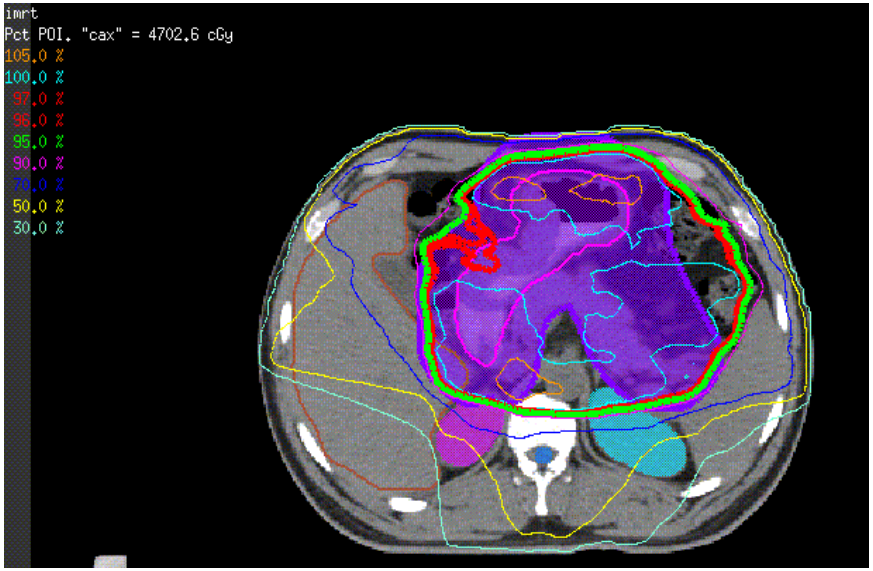
- **GTV:** Gross disease (if visualized on PET and/or CT) and pathologically enlarged lymph nodes
- **CTV**: GTV + stomach volume outlined from gastroesophageal junction to beyond the duodenal bulb; the whole wall is included (perigastric nodes are encompassed, if visible).
- **ITV** is determined by 4-D CT or by fluoroscopy to track variation of stomach position during respiration. An additional margin of at least 1-2 cm may be added to the CTV to accommodate stomach movement or internal volume changes.
- **PTV** is influenced by set-up variation; in the abdomen 1 cm over final ITV is advised.
- **OAR** volumes for consideration in planning include: kidneys, liver, heart. lungs, bowel, cord.

Treatment Planning

3D-CRT



IMRT



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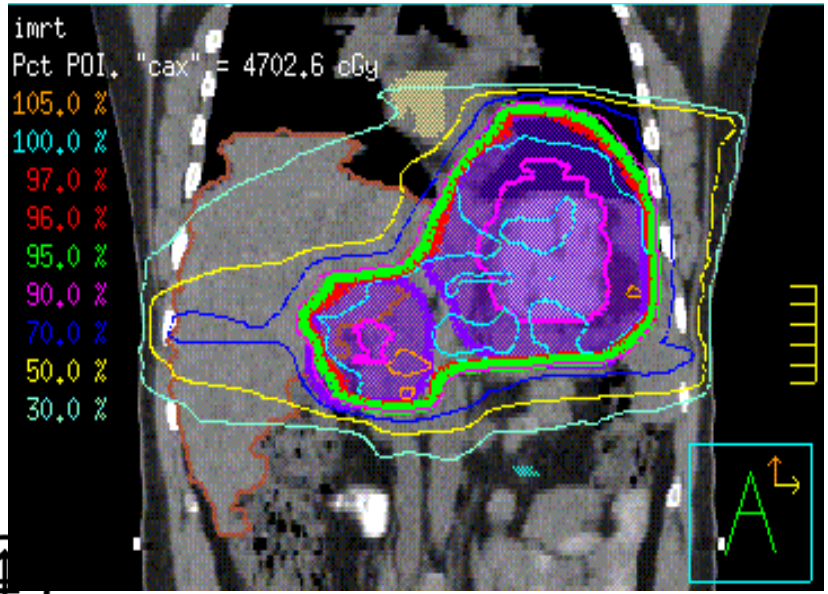
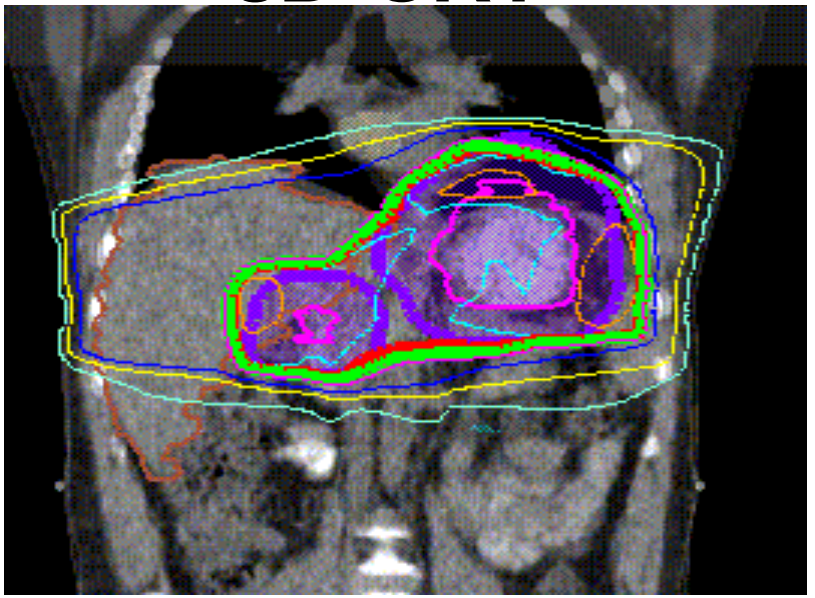
3D-CRT vs. IMRT

IMRT



3D-CRT



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Treatment Planning Goals

Conformal therapy is optimal

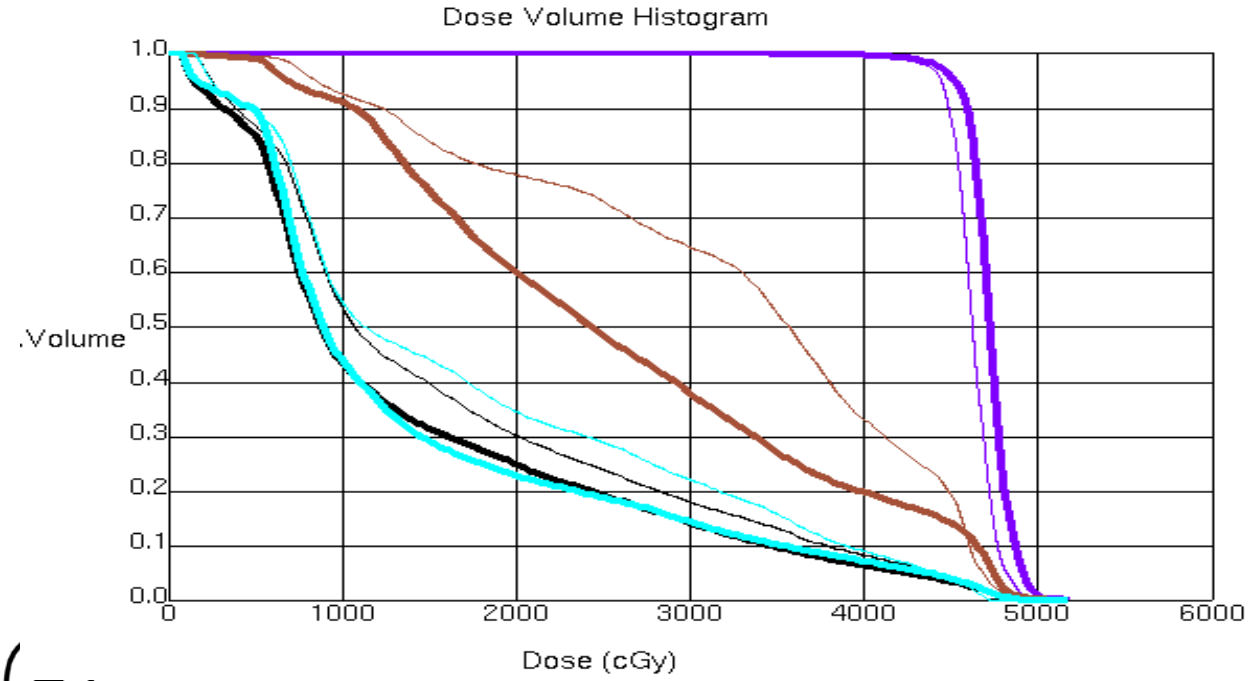
- Della-Bianca et al. compared AP/PA vs. 3D-CRT vs. IMRT
- Advantage to conformal therapy when PTV was in close proximity or overlapped with kidney
- IMRT led to further decrease in left kidney and liver dose

Potential advantages in some cases to IMRT over 3D-CRT
Goal of homogeneous dose delivery (D95 >95%)
Doses to normal structures as low as reasonably achievable (ALARA)

Sparing of kidney and liver

- Kidney dose: limited to <20 Gy to 2/3 of kidney
- Liver dose: Mean dose < 30 Gy

DVH: 3D-CRT vs. IMRT



--- Both Kidneys

--- Left Kidney

--- Liver

--- PTV

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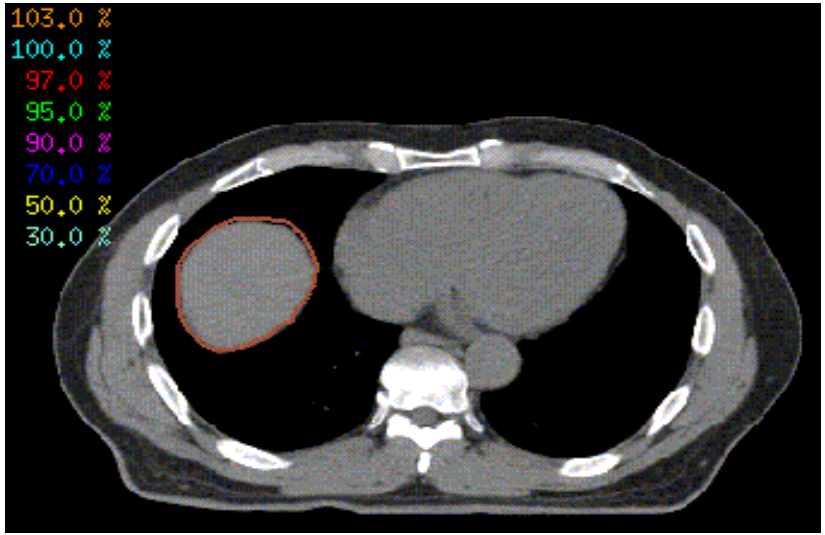
Respiratory Motion

Deep Inspiration



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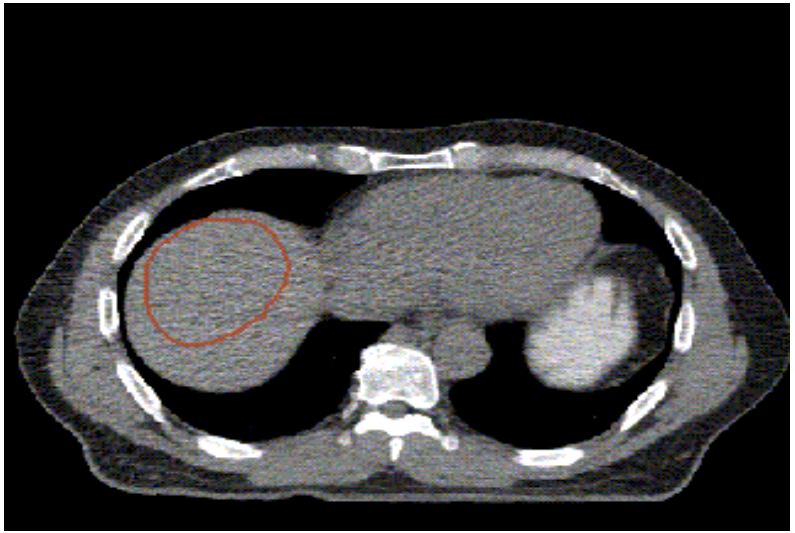

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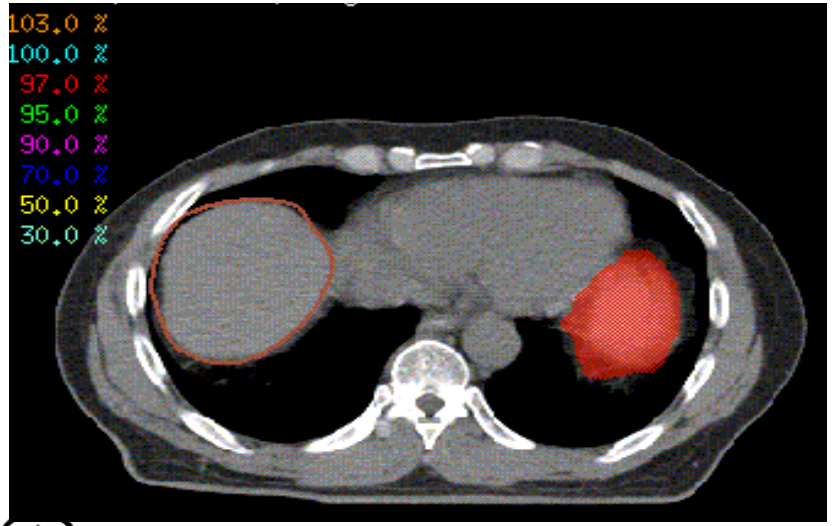
Respiratory Motion

Deep Inspiration



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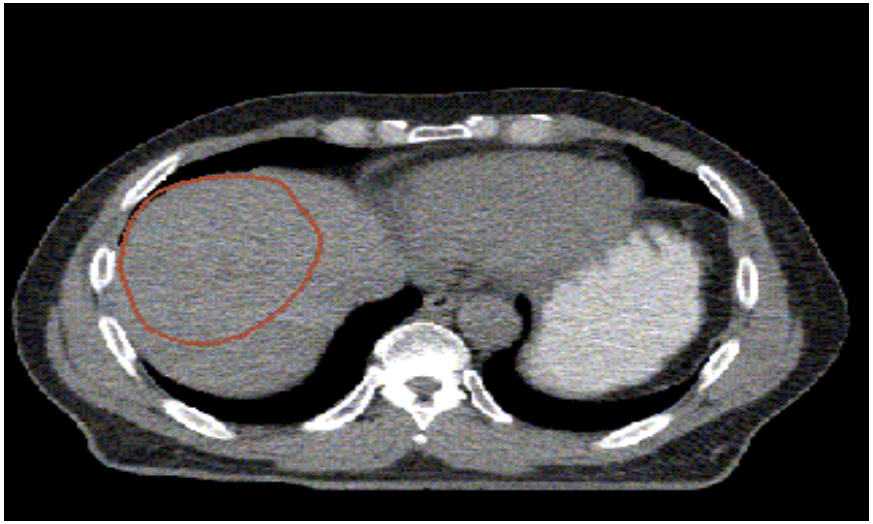

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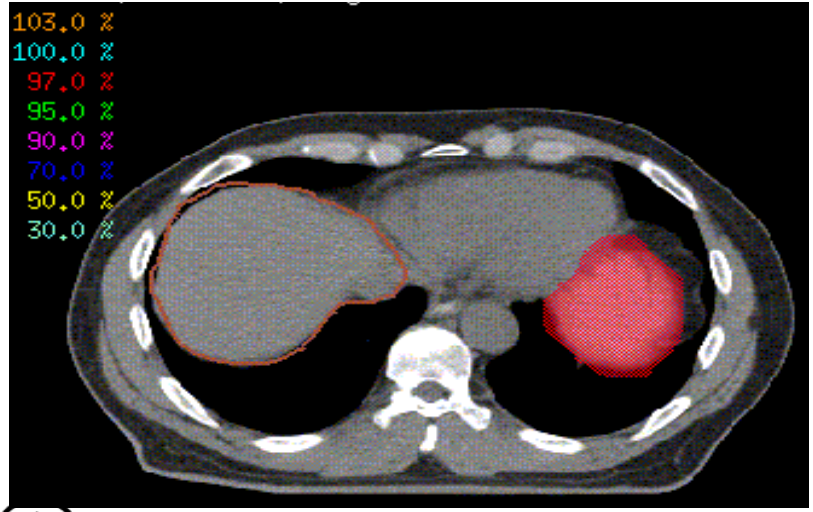
Respiratory Motion

Deep Inspiration



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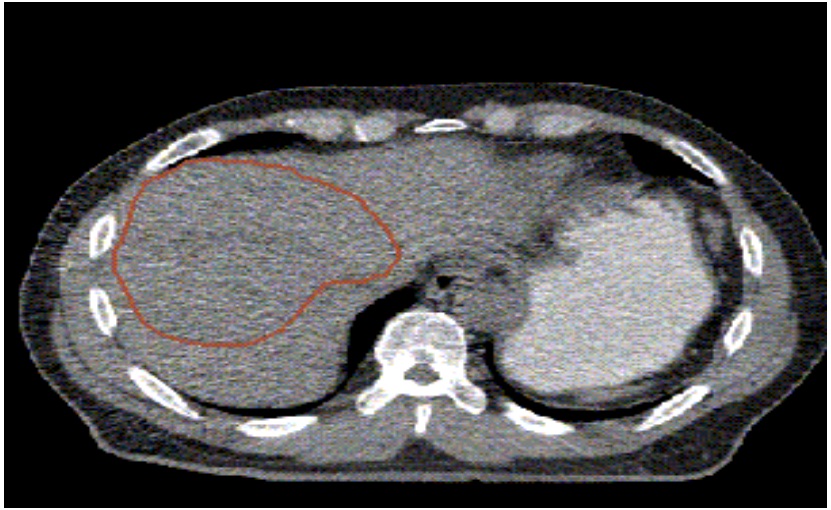

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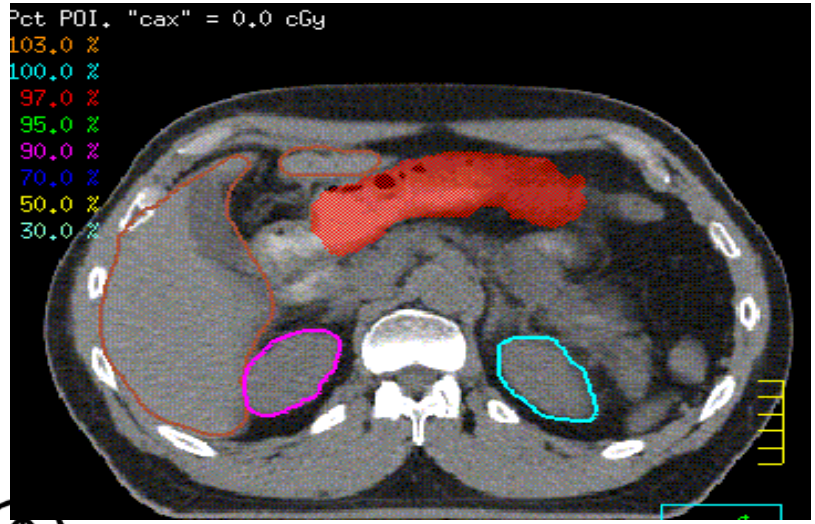
Respiratory Motion

Deep Inspiration



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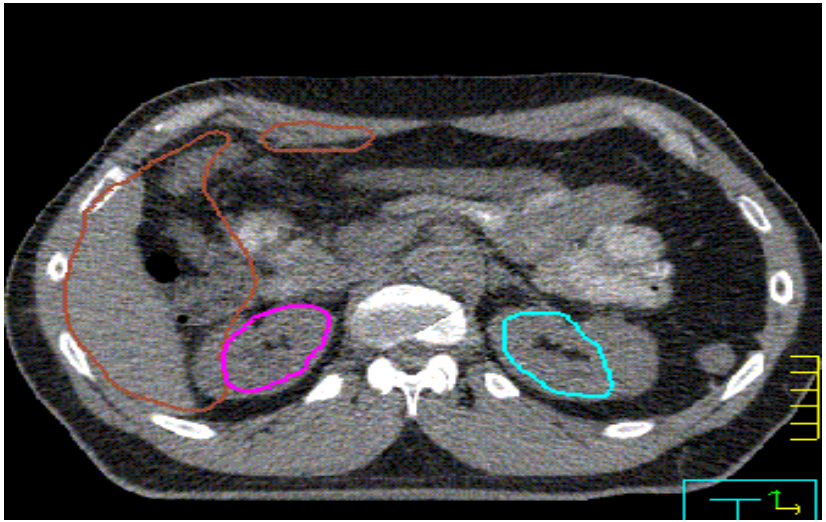

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Conclusions

- Recommend use of modern radiation techniques
- Target volume of stomach and perigastric nodes in gastric lymphoma
- Margin incorporating 4D CT scan for respiration motion assessment
- Radiation dose of : 30 Gy in 15-20 fractions for Gastric MALT and response-based for DLBCL
- Conformal radiation delivery techniques

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Extranodal lymphomas: Skin

Lena Specht MD DMSc
Professor of Oncology, University of Copenhagen, Denmark
Chief Oncologist, Depts. of Oncology and Haematology, Rigshospitalet, Copenhagen
Vice-chairman, International Lymphoma Radiation Oncology Group

Primary cutaneous lymphomas

- Heterogenous group of T- and B-cell lymphomas
- Natural history often more indolent than nodal lymphomas of same histologic subtype
- Solitary or localised skin lesions treated with involved field radiotherapy, long term local control rate generally 80-100 %

(Willemze et al, Blood 1997;90:354-71)

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European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas

Nancy J. Senff,[1] Evert M. Noordijk,[2] Youn H. Kim,[3] Martine Bagot,[4] Emilio Berti,[5] Lorenzo Cerroni,[6] Reinhard Dummer,[7] Madeleine Duvic,[8] Richard T. Hoppe,[9] Nicola Pimpinelli,[10] Steven T. Rosen,[11] Maarten H. Vermeer,[1] Sean Whittaker,[12] and Rein Willemze[1]

(Blood. 2008;112:1600-1609)

Table 1. Overview of previously and currently used classification systems for cutaneous lymphomas and clinicopathologic features of the different CBCL entities

	Previous and current classifications		
EORTC 1997	PCI/ PCMZL	PCFCCL	PCLBCL of the leg
WHO 2001	EMZL	cFCL	DLBCL
		DLBCL	
WHO-EORTC 2005	PCMZL	PCFCL	PCLBCL, LT
WHO 2008	EMZL	PCFCL	PCLBCL, LT
Clinicopathologic features			
Clinical features	Solitary or multiple papules, plaques, or nodules preferentially localized on the extremities	Solitary or grouped tumors presenting on the head or on the trunk	Solitary or multiple tumors presenting mainly on the leg(s) and rarely at other sites
	Sometimes associated with Borrelia burgdorferi infection	Cutaneous relapses in 20%	Frequent relapses and extracutaneous dissemination
	Frequent cutaneous relapses	Extracutaneous dissemination in 5% to 10%	
	Rarely extracutaneous dissemination		
Histopathology	Patchy or diffuse infiltrates composed of small B cells, including marginal zone (centrocyte-like) cells, lymphoplasmacytoid cells, and plasma cells	Follicular, follicular and diffuse, or diffuse infiltrates composed of neoplastic follicle center cells , usually a mixture of centrocytes and variable numbers of centroblasts	Diffuse infiltrates with a predominance or confluent sheets of of centroblasts and immunoblasts
Immunophenotype	Monotypic cIg, CD79a$^+$, Bcl-2$^+$, CD5$^-$, cyclin D1$^-$, Bcl-6$^-$, CD10$^-$, MUM-1$^+$ (on plasma cells)	Monotypic sIg or absence of sIg, CD20$^+$, CD79a$^+$, Bcl-6$^+$, Bcl-2$^-$, MUM-1$^-$, CD10±, FOXP1$^{-(\pm)}$	Monotypic sIg and/or cIg, CD20$^+$, CD79a$^+$, Bcl-6$^{+(-)}$, CD10$^-$, Bcl-2$^+$, MUM-1$^+$, FOXP1$^+$
Prognosis	5-year survival: > 95%	5-year survival: 95%	5-year survival: 50%

PCI indicates primary cutaneous immunocytoma; PCMZL, primary cutaneous marginal zone lymphoma; PCFCCL, primary cutaneous follicle center cell lymphoma; PCLBCL of the leg, primary cutaneous large B-cell lymphoma of the leg; EMZL, extranodal marginal zone lymphoma; cFCL, cutaneous follicle center lymphoma (for cases with a follicular or follicular-diffuse growth pattern); DLBCL, diffuse large B-cell lymphoma (for cases with a diffuse growth pattern); PCFCL, primary cutaneous follicle center lymphoma; and PCLBCL, LT, primary cutaneous diffuse large B-cell lymphoma, leg type.

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Table 4. Recommendations for initial management of the 3 main types of CBCL

Disease type and extent	First-line therapy	Alternative therapies
PCMZL		
Solitary/localized	Local radiotherapy Excision Antibiotics*	IFN-α i.l. Rituximab i.l. i.l. steroids
Multifocal	Wait-and-see Local radiotherapy Chlorambucil† Rituximab i.v. Antibiotics*	IFN-α i.l. Rituximab i.l. Topical or i.l. steroids
PCFCL		
Solitary/localized	Local radiotherapy Excision	IFN-α i.l. Rituximab i.l.
Multifocal	Wait-and-see Local radiotherapy Rituximab i.v.	R-CVP/CHOP‡
PCLBCL, LT		
Solitary/localized	R-CHOP ± IFRT	Local radiotherapy Rituximab i.v.
Multifocal	R-CHOP	Rituximab i.v.

IFRT indicates involved field radiotherapy; i.l., intralesional; and i.v., intravenous.
*In case of evidence for *B burgdorferi* infection.
†Or other single or combination regimens appropriate for low-grade B-cell lymphomas.
‡In exceptional cases or for patients developing extracutaneous disease.

ESMO guidelines, Ann Oncol 2013; 24 (Suppl 6): 149-54

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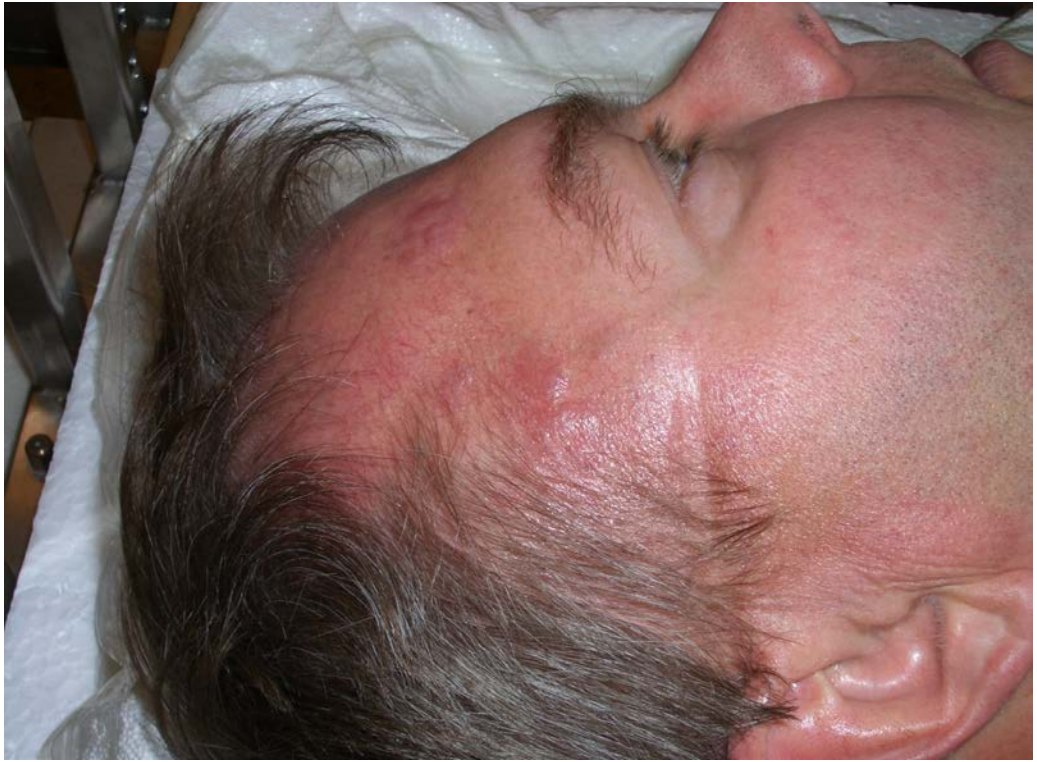
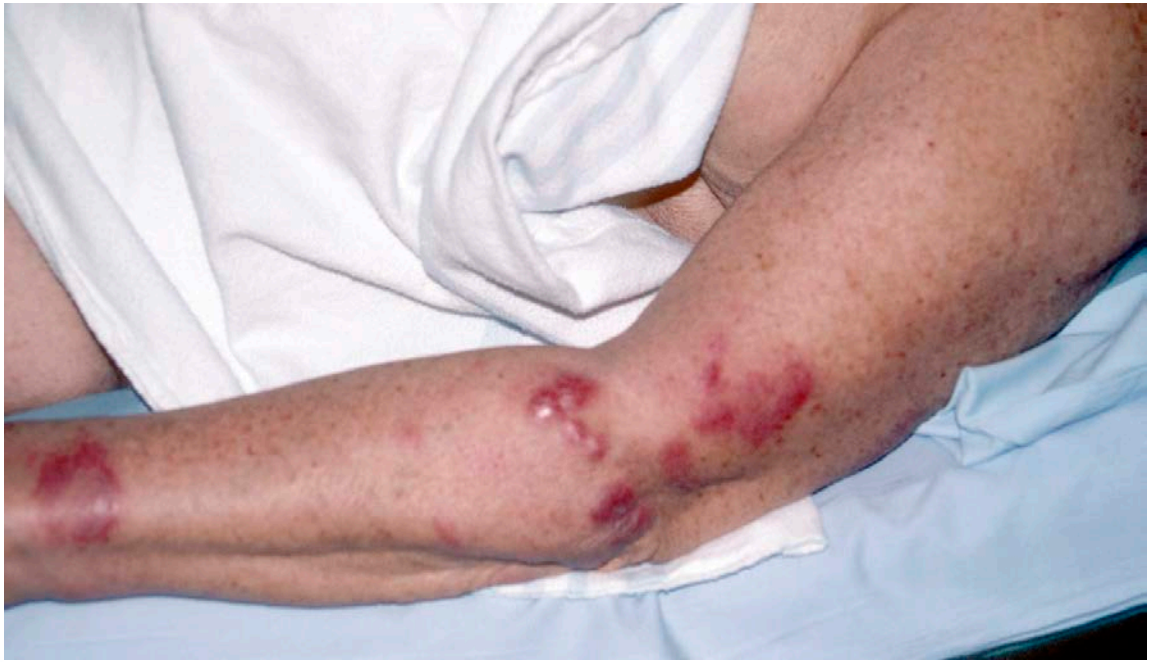
Marginal zone lymfom



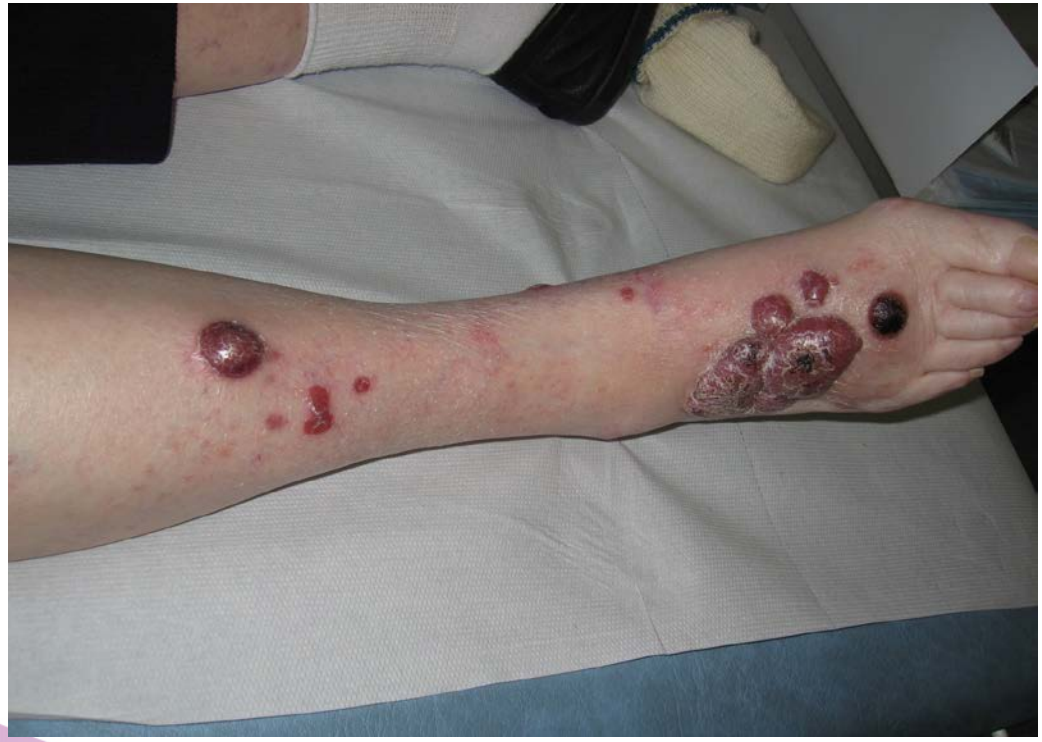
Dose for localized disease:
24-30 Gy

Primary cutaneous follicle center lymphoma PCFCL



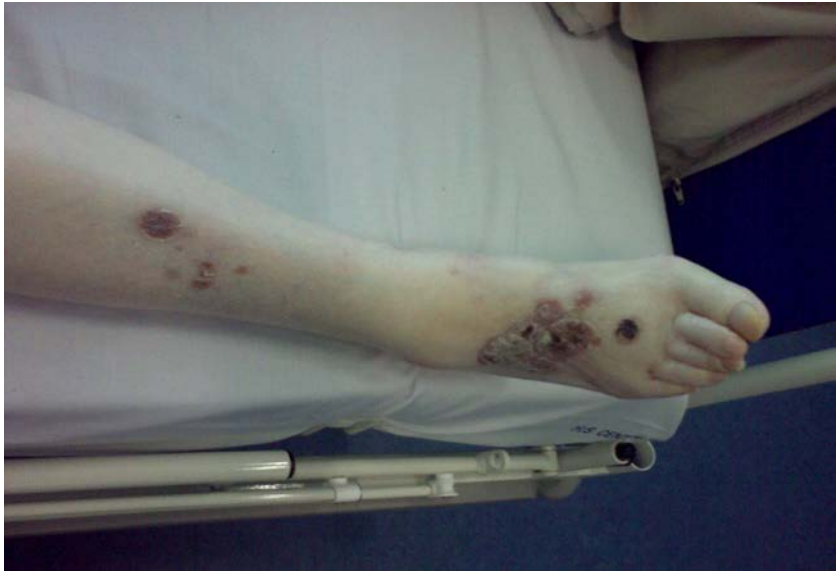
Dose for localized disease:
24-30 Gy

Primary cutaneous diffuse large B-cell lymphoma, leg type

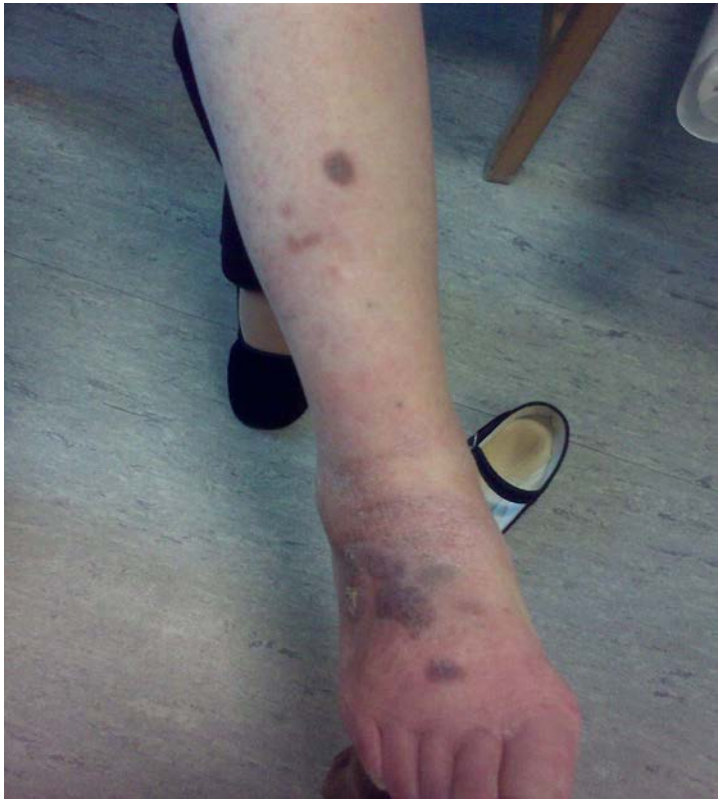


Dose for localized disease: 36-40 Gy

If no systemic treatment is given, 40 Gy is recommended

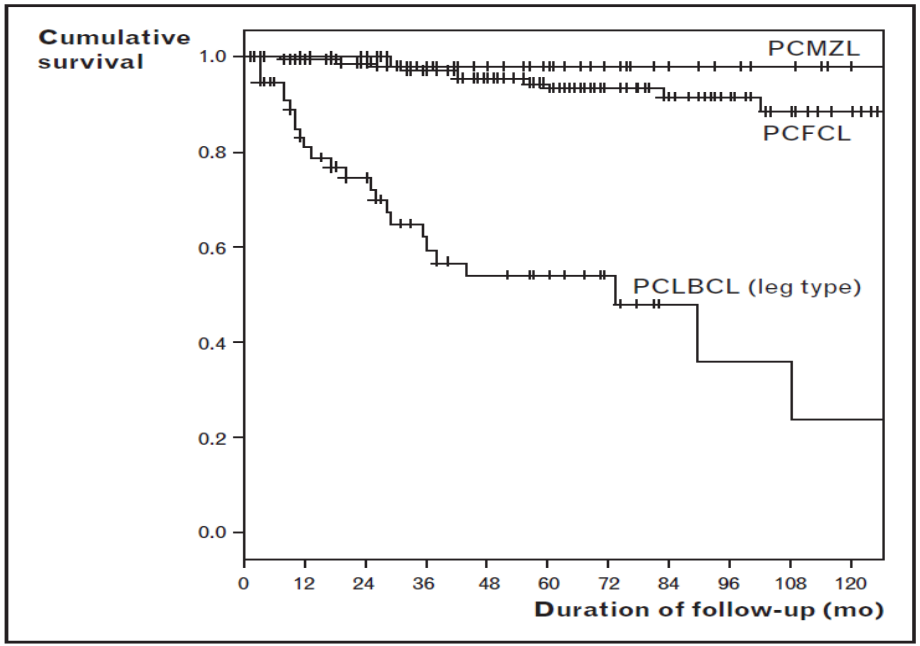


After 2 cycles R-CHOP21



After radiotherapy

Figure 1 Disease-related 5-year-survivals of 280 Dutch patients with cutaneous B-cell lymphoma reclassified according to the World Health Organization–European Organization for the Research and Treatment of Cancer classification (N.J. Senff, unpublished data)



This group includes 64 primary cutaneous marginal zone B-cell lymphomas (PCMZL), 156 primary cutaneous follicle center lymphomas (PCFCL), and 60 primary cutaneous large B-cell lymphomas (PCLBCL) (leg type).

WHO-EORTC classification for cutaneous lymphomas

Rein Willemze, Elaine S. Jaffe, Günter Burg, Lorenzo Cerroni, Emilio Berti, Steven H. Swerdlow, Elisabeth Ralfkiaer, Sergio Chimenti, José L. Diaz-Perez, Lyn M. Duncan, Florent Grange, Nancy Lee Harris, Werner Kempf, Helmut Kerl, Michael Kurrer, Robert Knobler, Nicola Pimpinelli, Christian Sander, Marco Santucci, Wolfram Sterry, Maarten H. Vermeer, Janine Wechsler, Sean Whittaker, and Chris J. L. M. Meijer

(Blood. 2005;105:3768-3785)

WHO-EORTC classification	No.	Frequency, %*	Disease-specific 5-year survival, %
Cutaneous T-cell lymphoma			
Indolent clinical behavior			
Mycosis fungoides	800	44	88
Folliculotropic MF	86	4	80
Pagetoid reticulosis	14	< 1	100
Granulomatous slack skin	4	< 1	100
Primary cutaneous anaplastic large cell lymphoma	146	8	95
Lymphomatoid papulosis	236	12	100
Subcutaneous panniculitis-like T-cell lymphoma	18	1	82
Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma†	39	2	75
Aggressive clinical behavior			
Sézary syndrome	52	3	24
Primary cutaneous NK/T-cell lymphoma, nasal-type	7	< 1	NR
Primary cutaneous aggressive CD8+ T-cell lymphoma†	14	< 1	18
Primary cutaneous γ/δ T-cell lymphoma†	13	< 1	NR
Primary cutaneous peripheral T-cell lymphoma, unspecified‡	47	2	16

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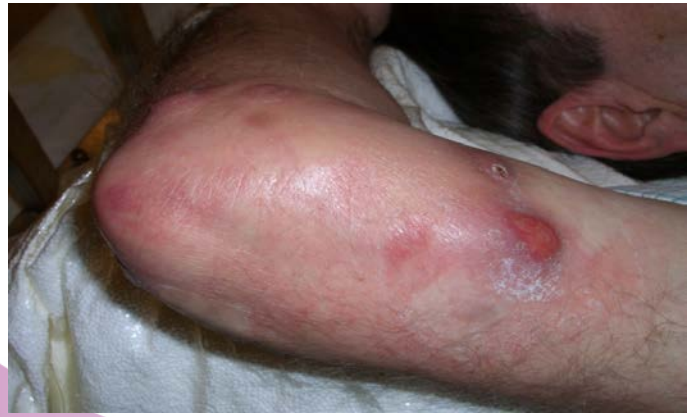
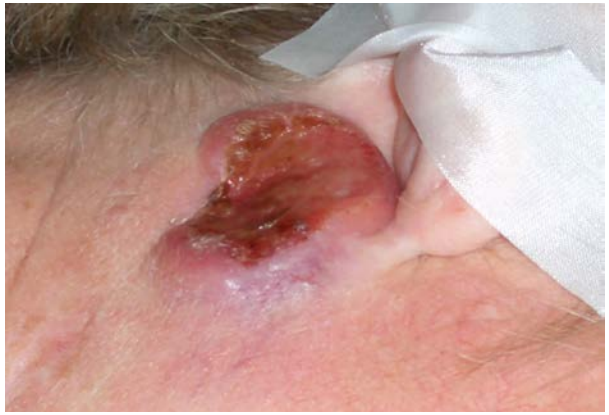
Primary Cutaneous CD30+ neoplasms (lymphomatoid papulosis, ALCL)

- LyP: Chronic, recurrent, self-healing
- In up to 20 % associated with other types of lymphoma



- C-ALCL: 80 % present with solitary or localized nodules
- Local radiotherapy, dose 24-30 Gy



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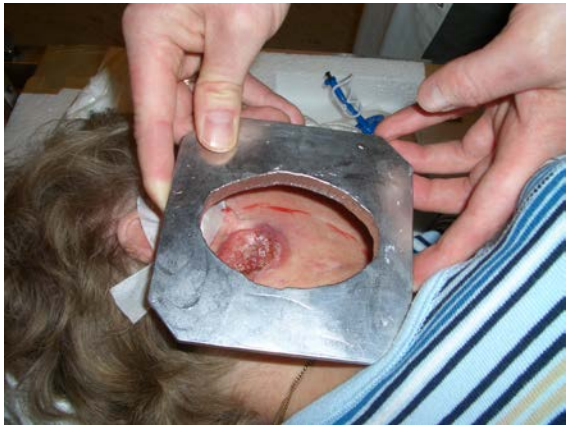
Localized skin lymphomas: ISRT



- Margin beyond clinically evident erythema/ induration 1-2 cm
- Thickness of lesion must be determined to ensure adequate coverage in depth
- Most lesions can be treated with electrons
- Bolus is required to avoid skin sparing
- Low energy X-rays (100 kV) may sometimes be used
- For deep, bulky or circumferential lesions photons may be needed

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Mycosis fungoides

- Most common cutaneous T-cell lymphoma
- 4 % of all lymphomas, 50 % of all cutaneous lymphomas
- Indolent clinical course
- Limited to the skin for many years
- Patches → Plaques → Tumors
- Skin directed therapies unless extracutaneous

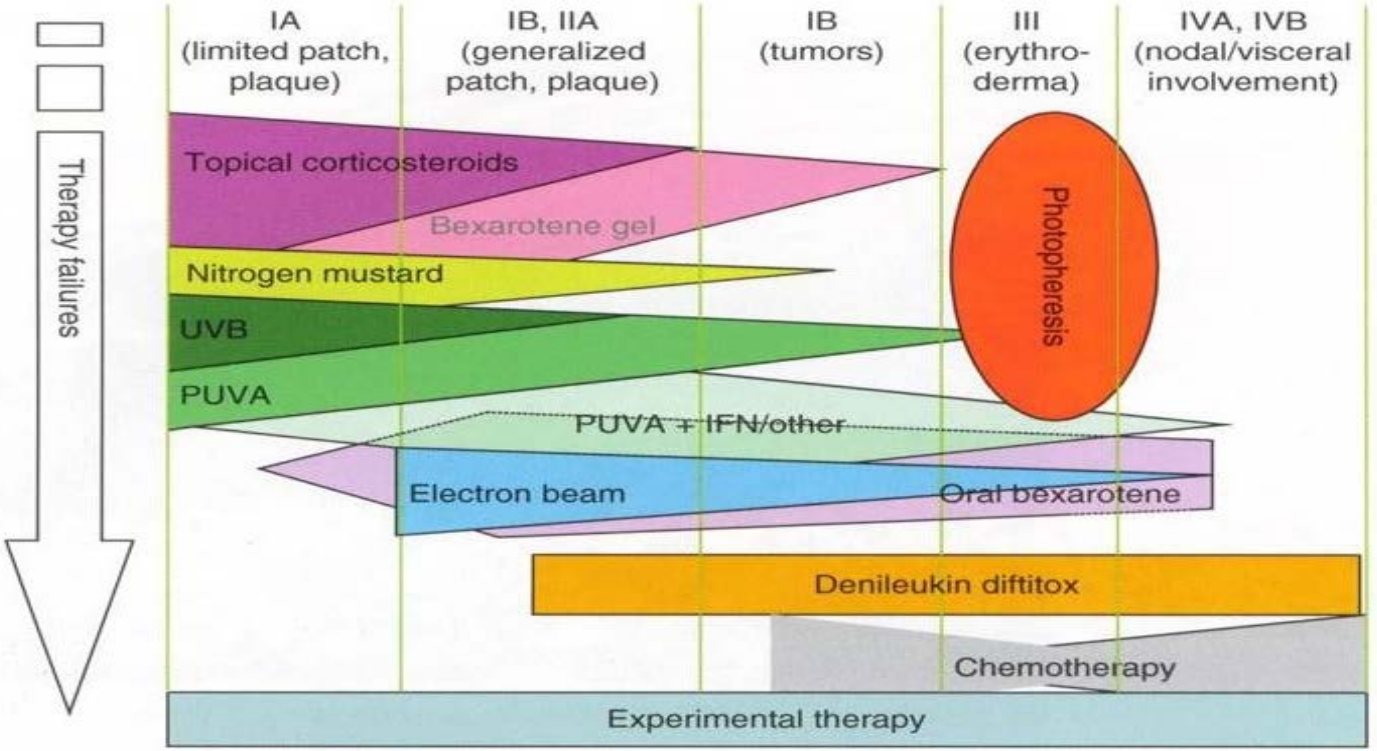
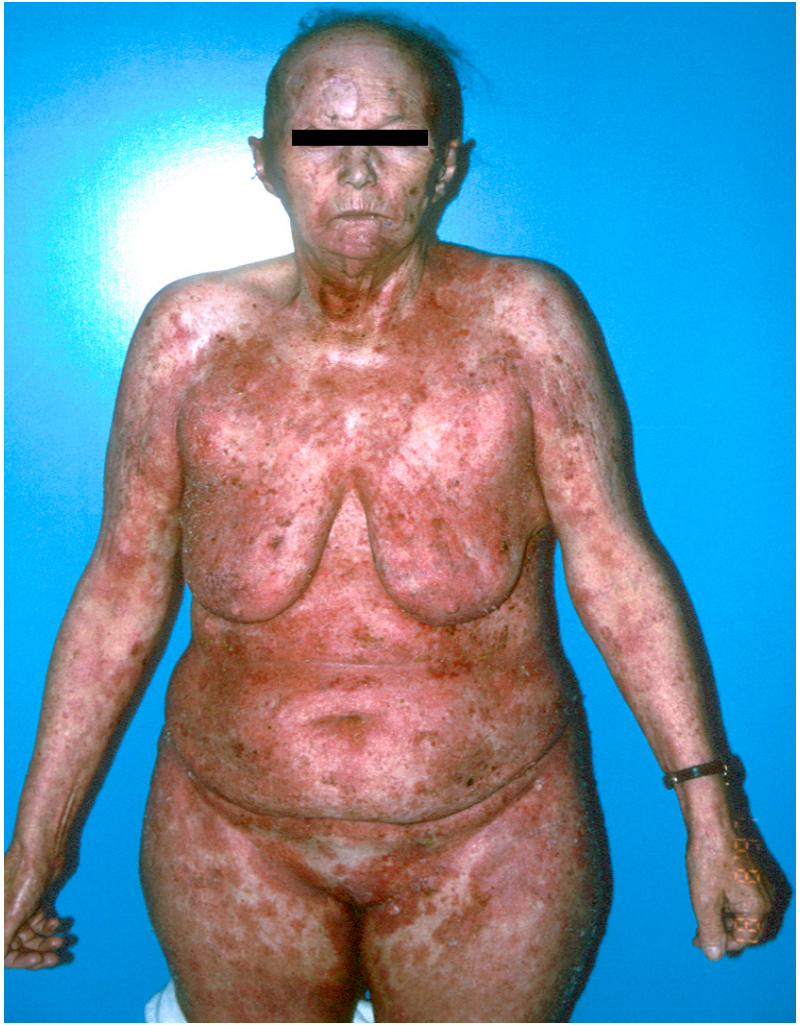


Fig. 19.3 Treatment of MF by stage. Stage is across the *top* of the diagram from T1 (*left*) to T4 (*right*)

+ HDAC inhibitors, low-dose Alemtuzumab, Adcetris,



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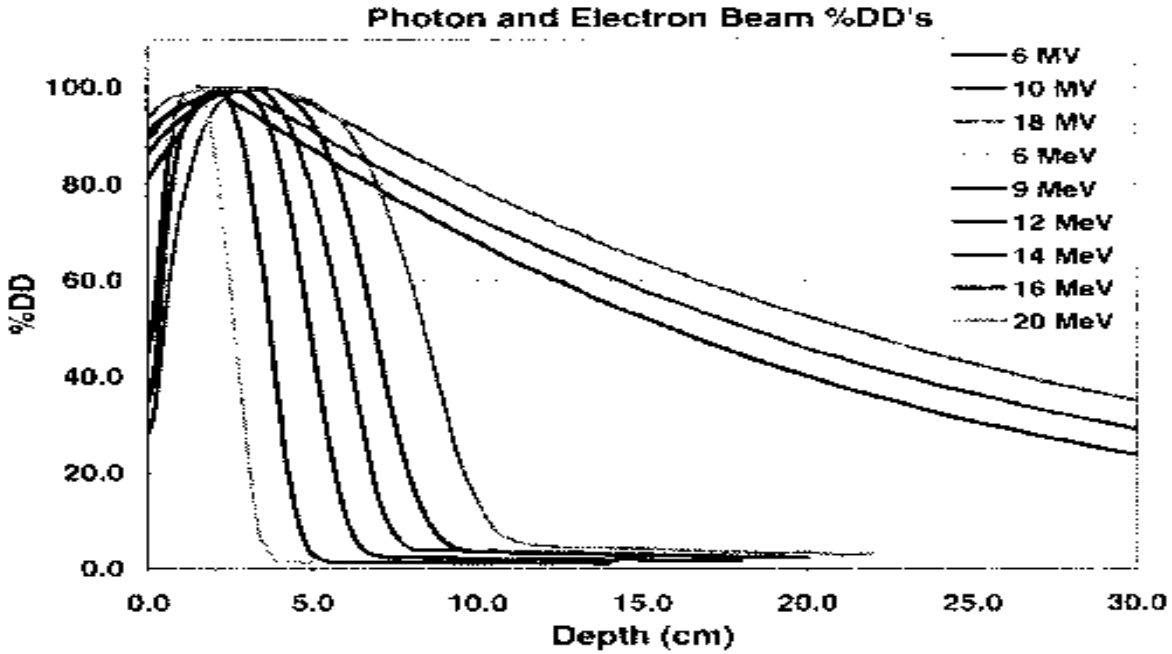
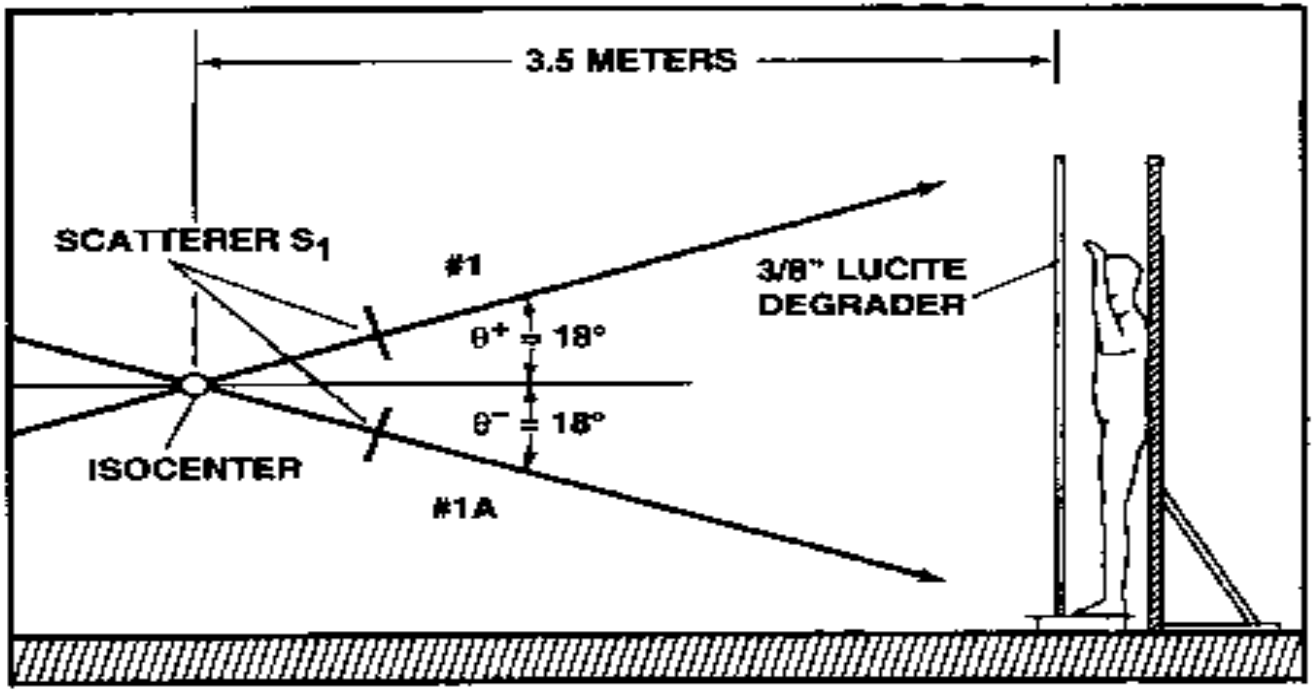
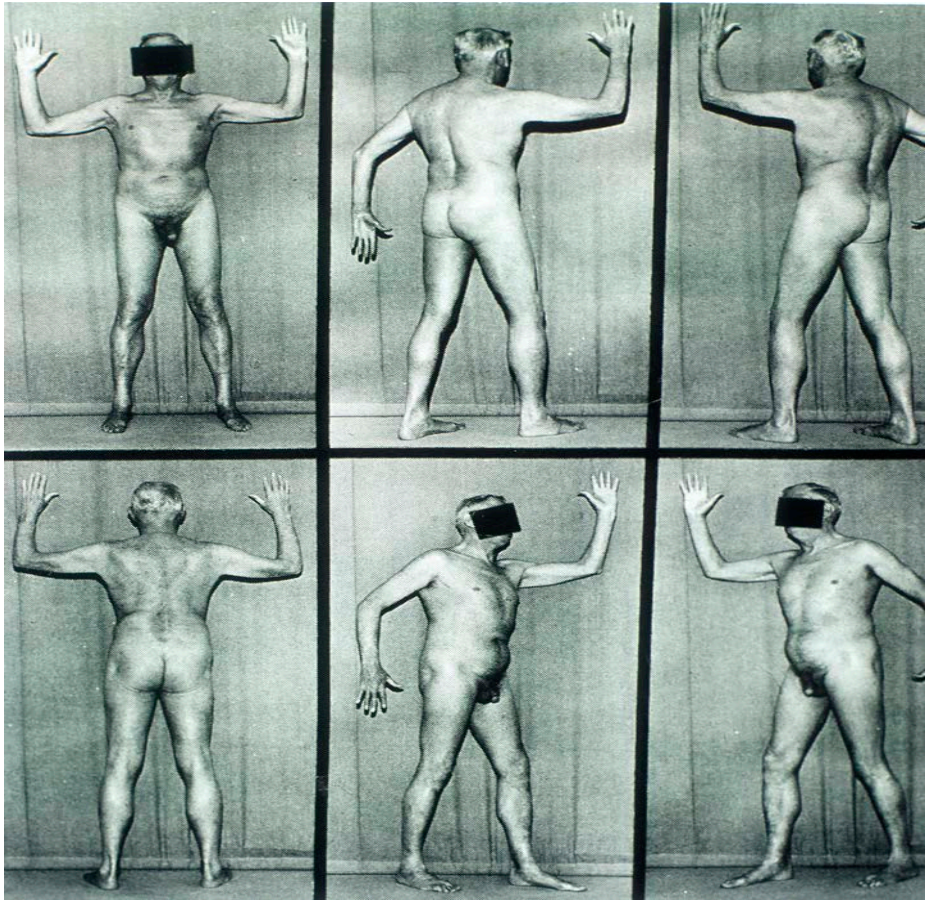
X-ray vs. electron depth-dose-curves



Total skin electron beam therapy (TSEBT)





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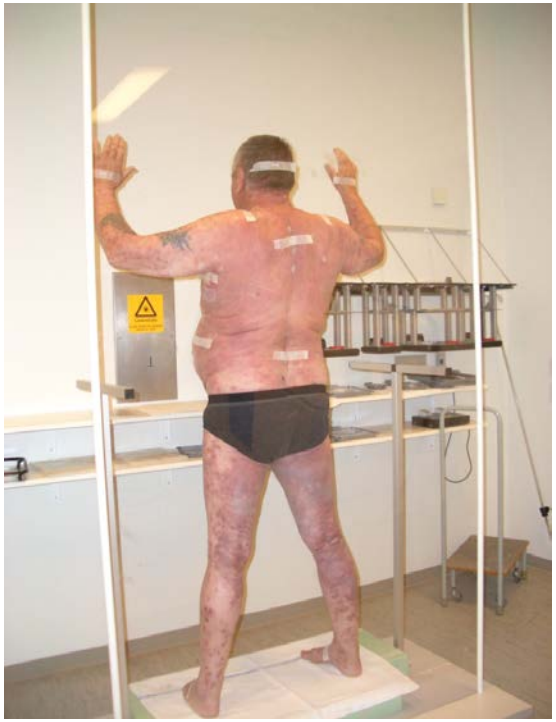
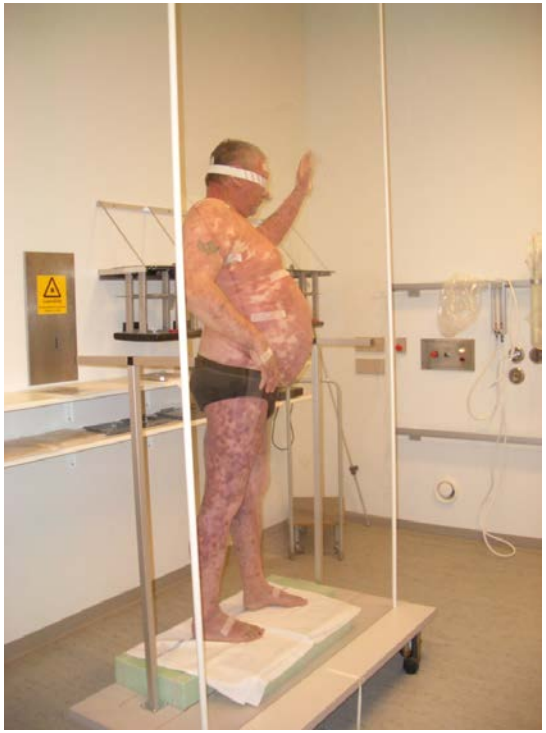
TSEBT





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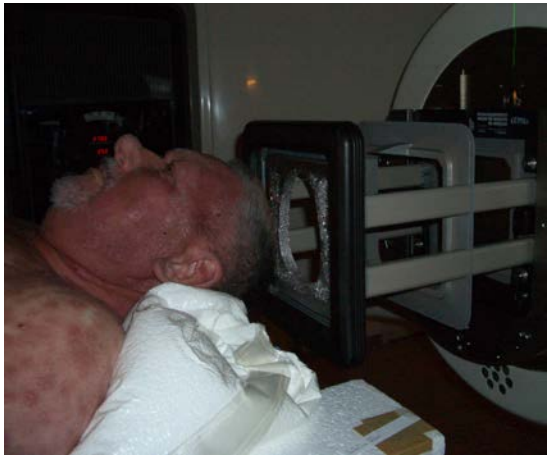
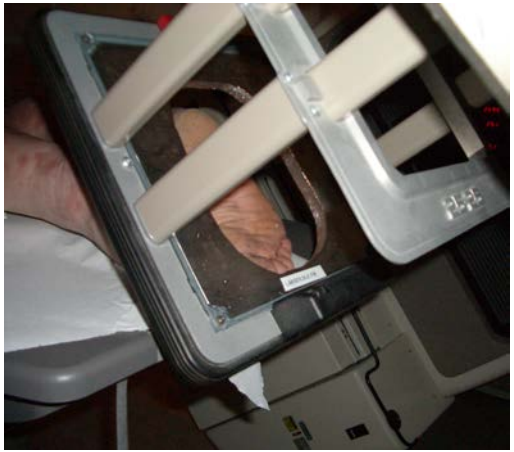
Additional treatment of ”shadowed areas”



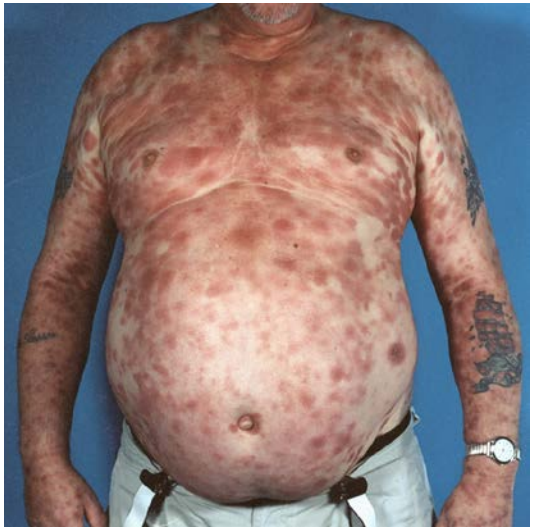
Scalp

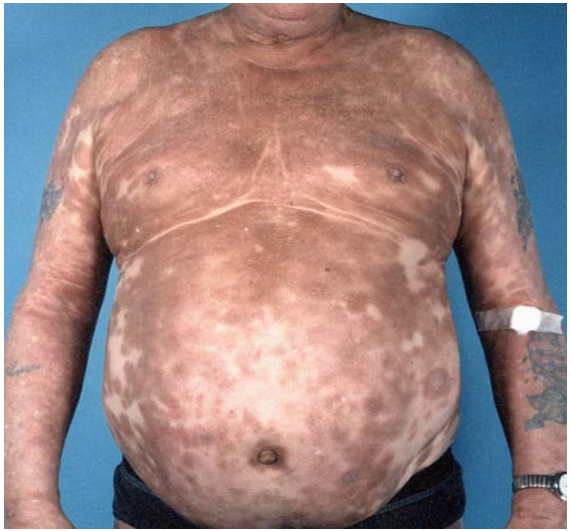
Perineum

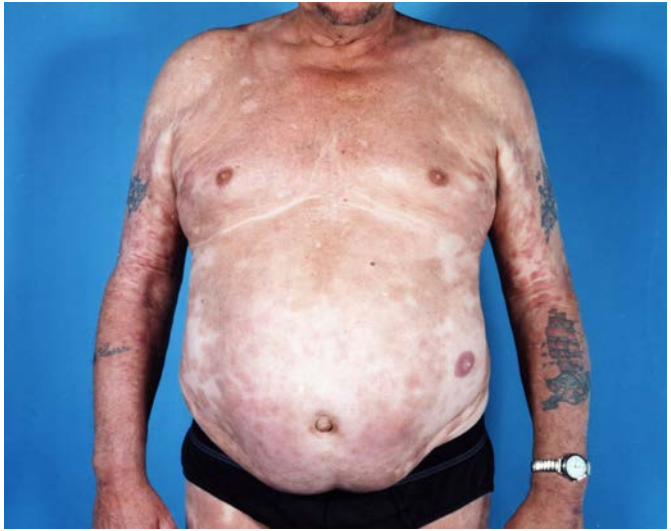


Soles

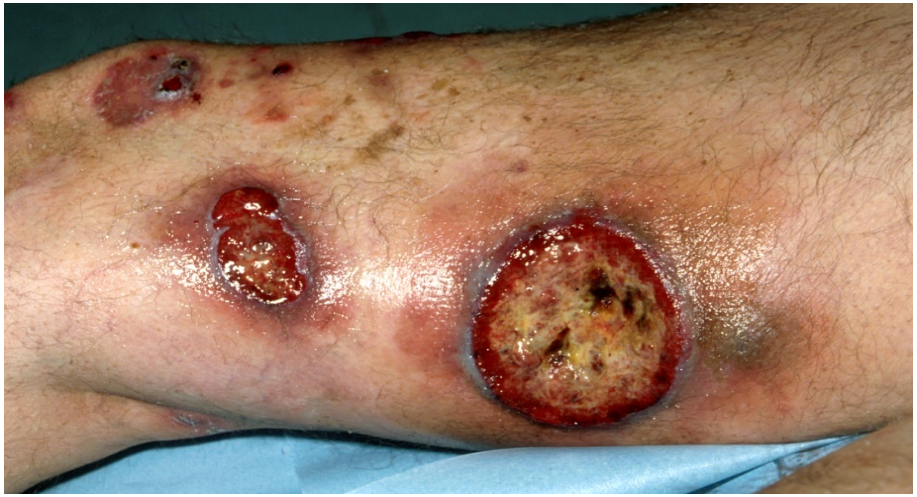
TSEBT, pt. with generalized plaques, before and 1 month after and 1 year after

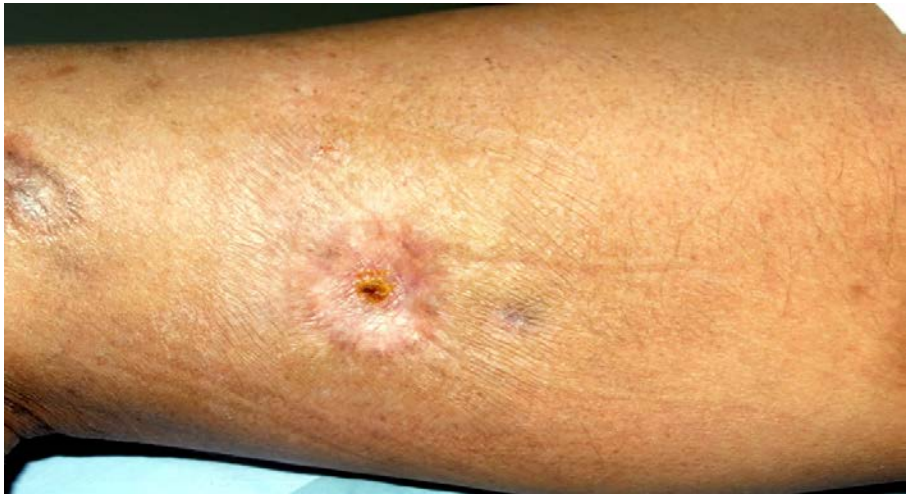






TSEBT, pt. with tumors, before and 6 months after





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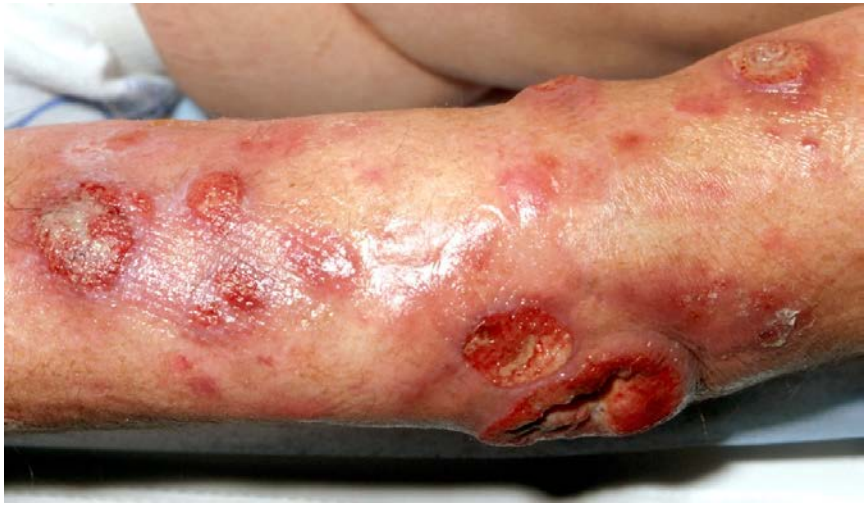
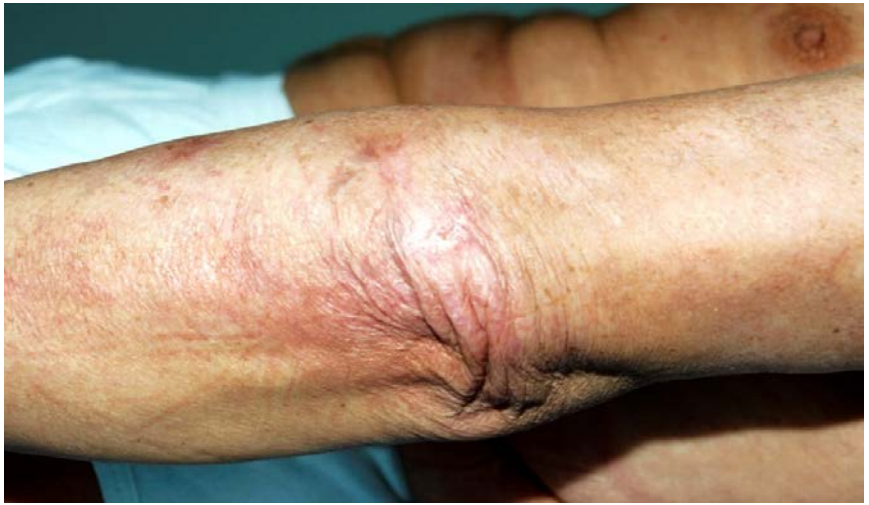
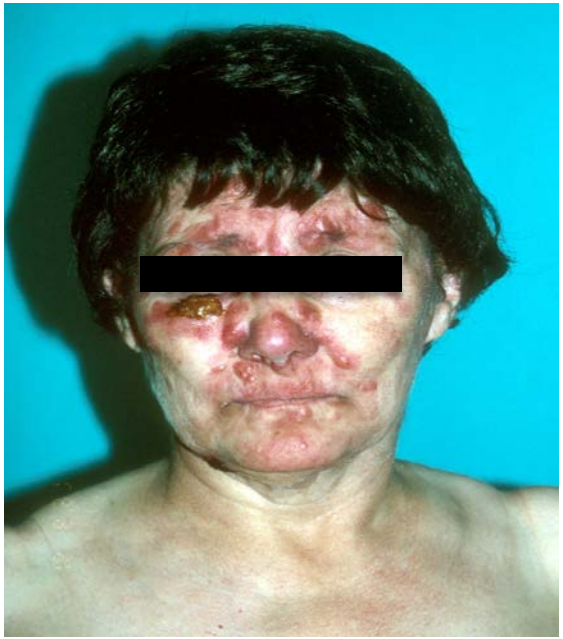
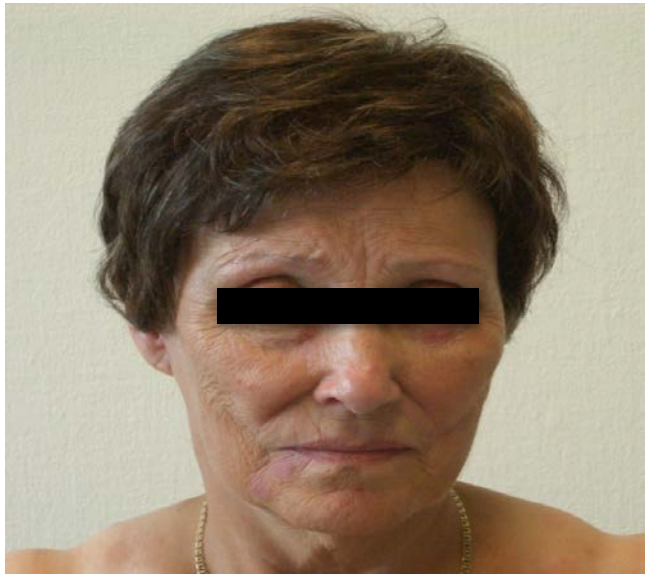
TSEBT, pt. with tumors, before and 6 months after





TSEBT, pt. with plaques and small tumors, before and 7 years after





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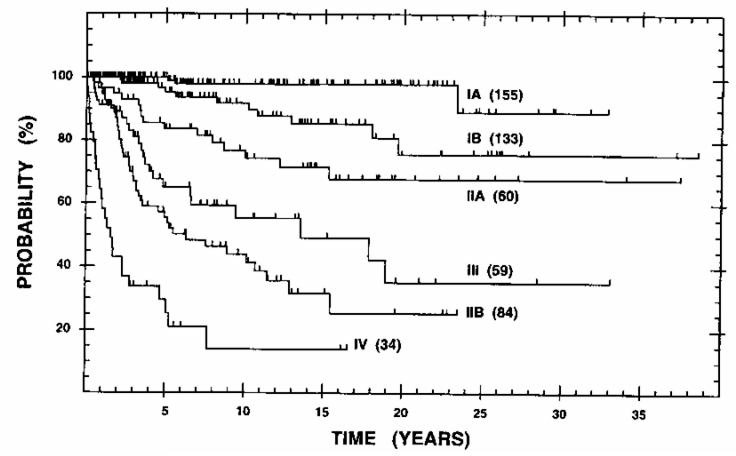
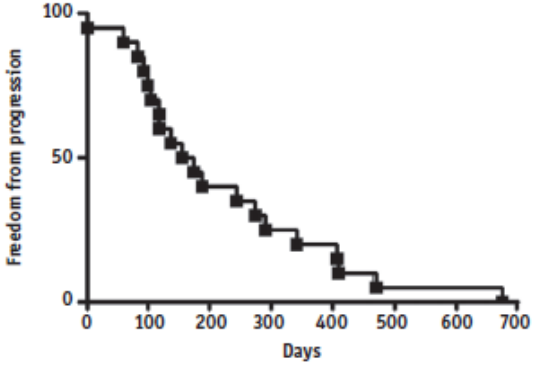
TSEBT outcome



Cause-specific survival after 30 Gy
(Stanford data)



PFS with low dose 10-12 Gy
(Kampstrup, IJROBP 2015; 92: 138-43

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Extranodal lymphomas: Characteristics, the role of radiotherapy, volumes doses and techniques:

Testicular lymphoma

Berthe Aleman

Radiation oncologist

NETHERLANDS CANCER INSTITUTE
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Testicular lymphoma

General

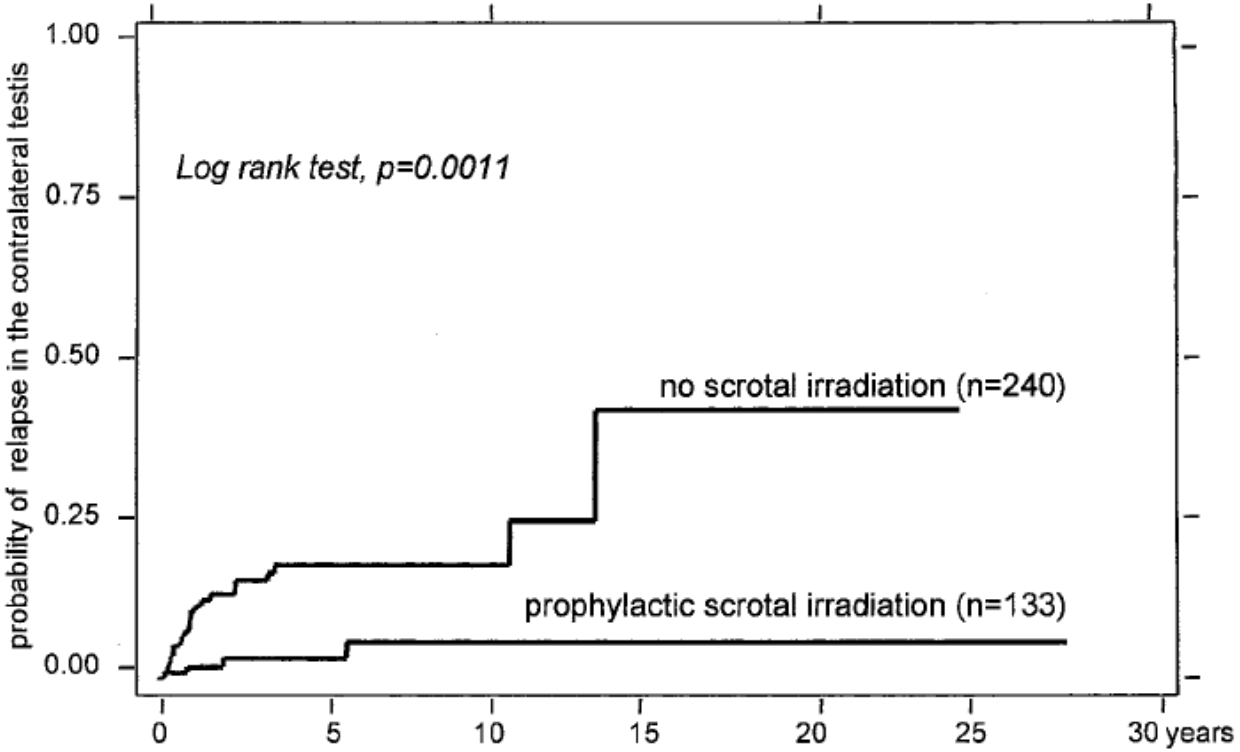
- Primary testicular lymphoma (PTL) is an uncommon and aggressive form of extranodal non-Hodgkin lymphoma (NHL)
- Annual incidence at 0.09 to 0.26 per 100 000 population
- 0,5% of testicular malignancies and 1-2% of all NHL cases
- Median age at diagnosis: 66 - 68 years

Testicular lymphoma

General (continued)

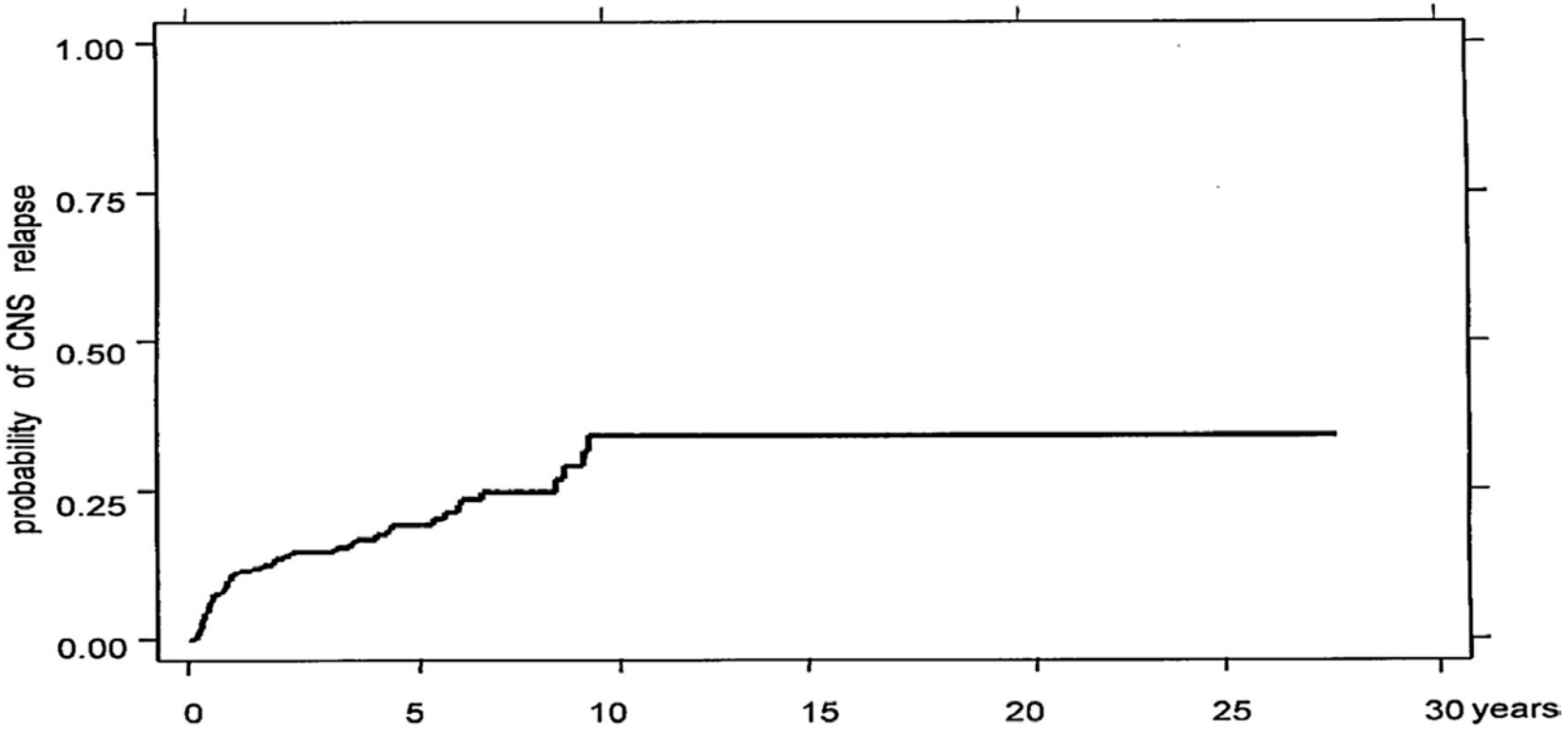
- PTL is both the most common testicular malignancy in men age >60 years and the most common bilateral testicular neoplasm.
- 20-30% present with systemic disease
- Common histology: DLBCL
- Sanctuary sites:
  - Contralateral testicle
  - Central nervous system

Risk of recurrence in contralateral testis



Zucca et al, JCO 2003

Time to CNS recurrence in the IELSG retrospective study, demonstrating ongoing risk of late CNS relapses.



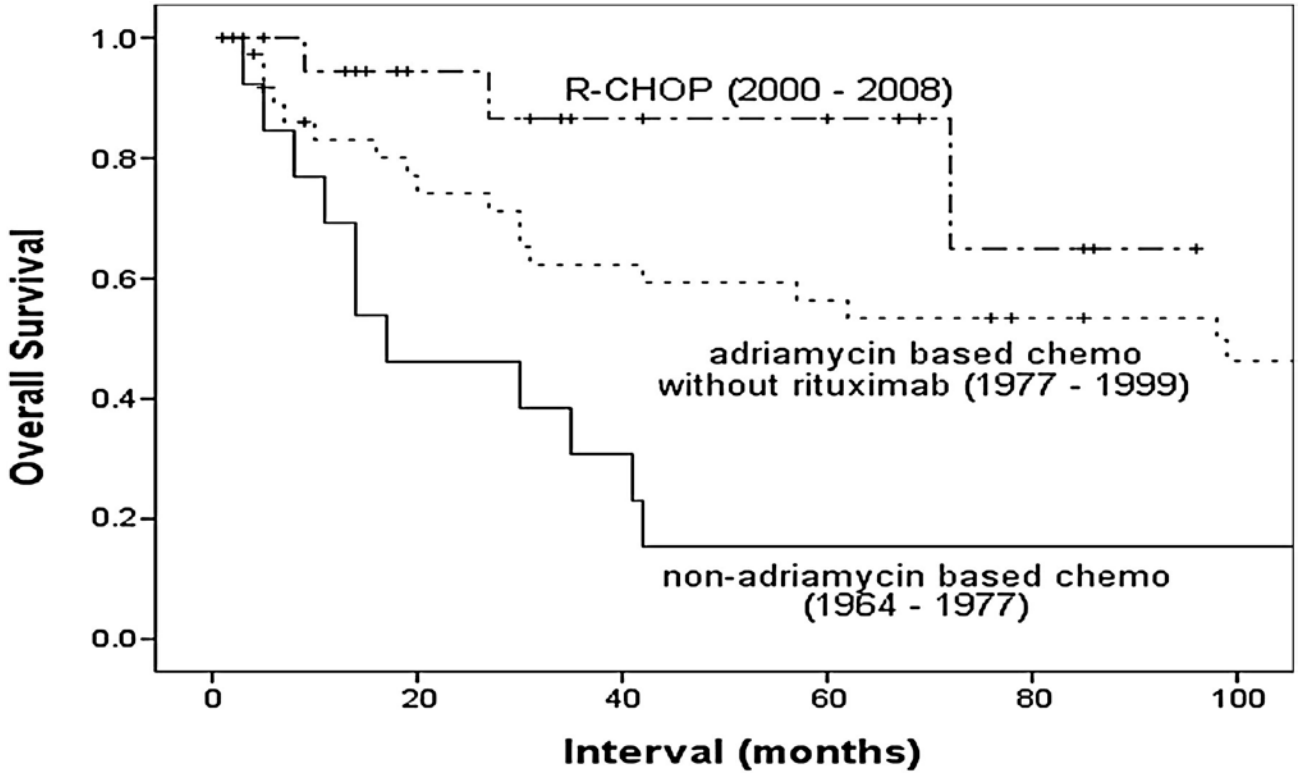
Chan Y. Cheah et al. Blood 2014;123:486-493

Prognostic factors for PFS in PTL

Adverse prognostic factors for PFS in studies of PTL
Age >70 y
Advanced stage
B symptoms
ECOG performance status >1
>1 extranodal site
Involvement of extranodal sites other than testis
Tumor diameter >10 cm
Raised serum LDH
Raised serum β_2-microglobulin
Hypoalbuminemia
Involvement of the left testis

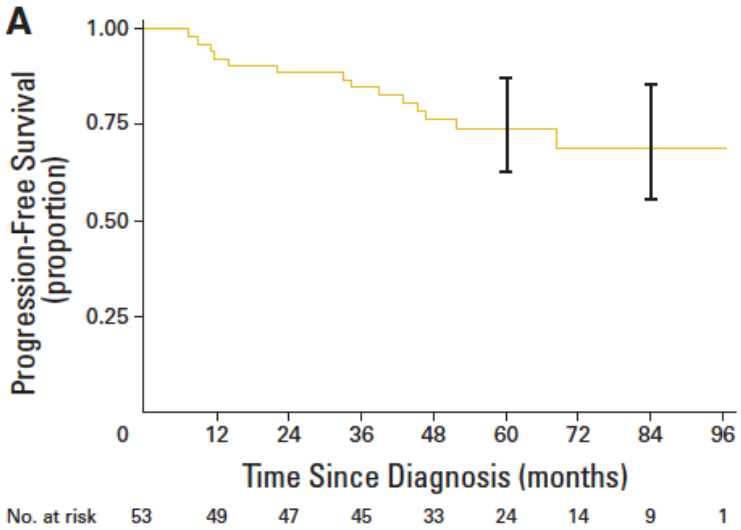
Chan Y. Cheah et al. Blood 2014;123:486-493

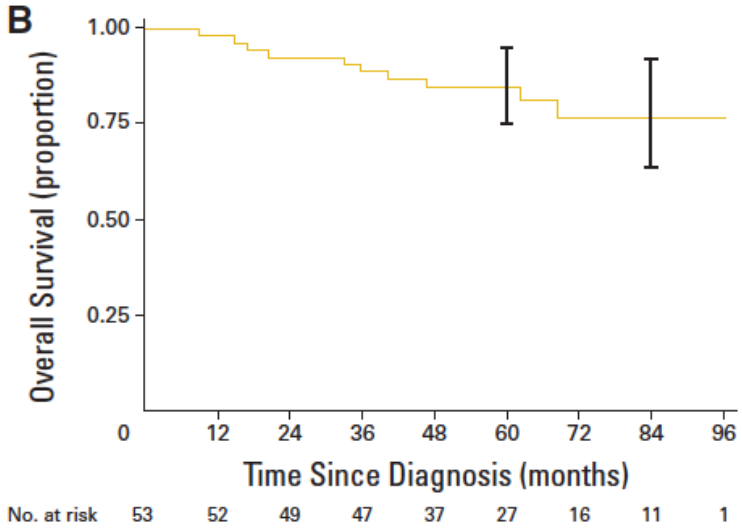
OS of patients with PTL treated at MDACC, by chemotherapy strategy



Chan Y. Cheah et al. Blood 2014;123:486-493

First-Line Treatment for Primary Testicular DLBCL With R-CHOP, CNS Prophylaxis, and Contralateral Testis RT: an International Phase II Trial (n=53, stage I-II)





No testicular relapses following 30 Gy

Vitolo et al, JCO 2011

Testicular lymphoma

Treatment

- R-CHOP (or more aggressive regimens)
- Intrathecal or intravenous methotrexate
- RT is given to the involved testis (if not resected) and to the remaining testis and scrotum
- RT may be given to involved abdominopelvic nodes in stage IIE disease.

Yahalom et al. ILROG guideline, IJROBP 2015

Testicular lymphoma
Prophylactic RT contralateral testicle

Volume

- An anterior electron field with energy calculated according the thickness of the scrotum/testis is set; bolus may be required.

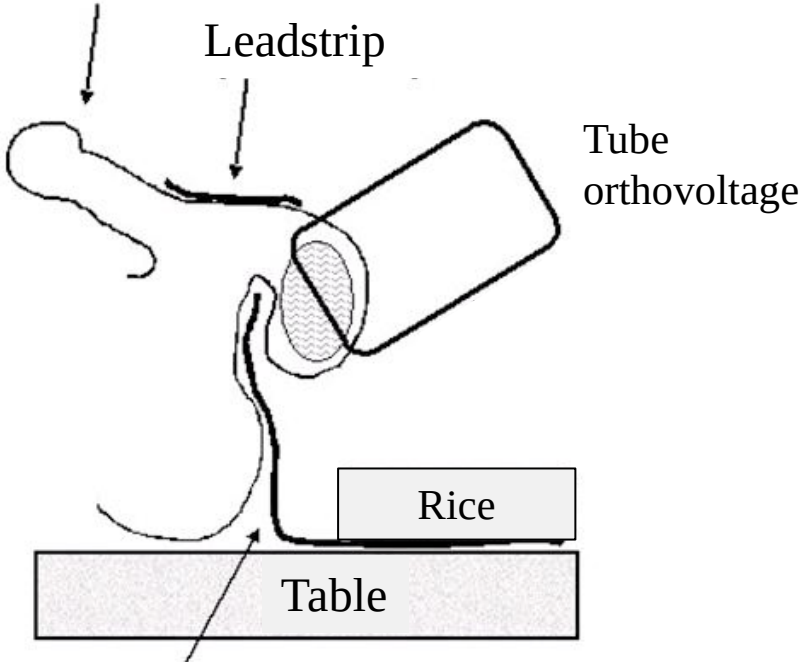
Yahalom et al. ILROG guideline, IJROBP 2015

Setup radiotherapy testicle

With the patient supine in a frog-leg position, the penis is lifted and taped to the abdominal wall, and the scrotum is supported and immobilized with bolus under and around the scrotum.

Yahalom et al. ILROG guideline, IJROBP 2015

Penis taped to the abdominal wall



Leadstrip on perineum and anus

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Testicular lymphoma

Dose

- Dose to testis: 25 to 30 Gy in 1.5 to 2 Gy per fraction

Yahalom et al. ILROG guideline, IJROBP 2015

Testicular lymphoma

Questions:

- Is 25-30 Gy safe?
- Could we use a lower dose ? 18 Gy? 20 Gy?
- Could surgery be an alternative?

- What to do during follow up?
  - Lab? Testosterone?

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Extranodal lymphomas: Characteristics, the role of radiotherapy, volumes doses and techniques:

Primary breast lymphoma

Berthe Aleman

Radiation oncologist

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Breast lymphoma

General

- Clinical presentation: usually unilateral painless breast mass
- Average age at diagnosis: 55 to 60 years

Pathology:

- Mostly DLBCL
- Also: indolent lymphomas such as marginal zone lymphoma and follicular lymphoma

Primary diffuse large B-cell lymphoma of the breast: a study by the International Extranodal Lymphoma Study Group

Patients and methods:

- A retrospective international study in 204 patients
- Treatment period: 1980 to 2003
- Median age: 64 years
- Unilateral disease (stage IE or IIE): 95% of patients

Ryan et al, Ann Oncol 2008

Primary diffuse large B-cell lymphoma of the breast: a study by the International Extranodal Lymphoma Study Group

Treatment	No of pts	%
Surgery only	11	5
RT only	14	7
CT only	31	15
S + RT	15	7
S + CT	32	16
RT + CT	59	29
S + RT + CT	42	21
Any surgery	100	49
Any RT	130	64
Any CT	164	80

- 87% of CT- regimens contained anthracycline
- Intrathecal CT as CNS prophylaxis: 8 patients

Ryan et al, Ann Oncol 2008

Primary diffuse large B-cell lymphoma of the breast: a study by the International Extranodal Lymphoma Study Group

Treatment	No of pts	%
Surgery only	11	5
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S + RT	15	7
S + CT	32	16
RT + CT	59	29
S + RT + CT	42	21
Any surgery	100	49
Any RT	130	64
Any CT	164	80

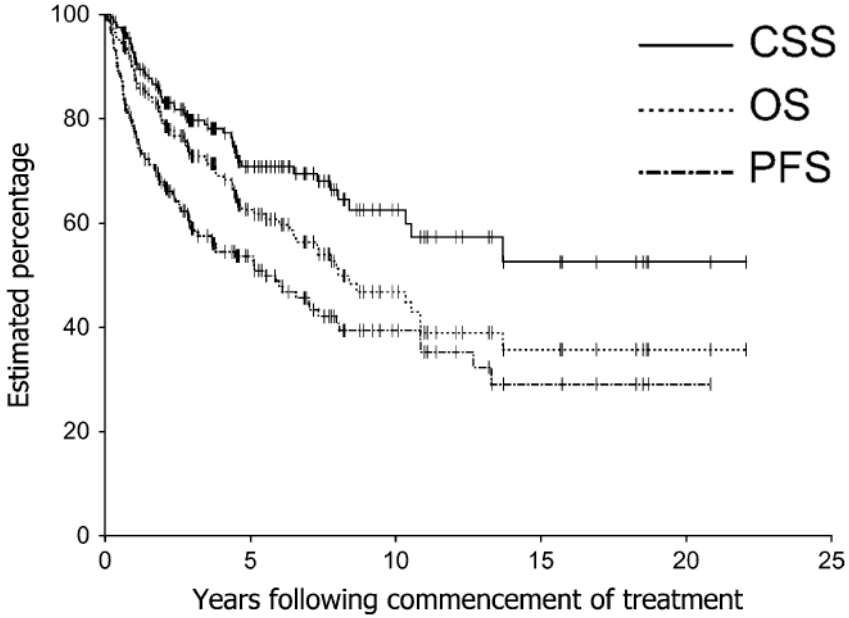
Initially involved breast only: 50%
Initially involved breast + regional lymph nodes: 35%

Median RT dose: 40 Gy
Range RT dose: 4-60 Gy

Ryan et al, Ann Oncol 2008

Primary diffuse large B-cell lymphoma of the breast: a study by the International Extranodal Lymphoma Study Group;

cause specific survival, overall survival and progression free survival



Number at risk

CSS	204	68	25	9	2	0
OS	204	68	25	9	2	0
PFS	204	58	20	6	1	0

Median CSS: not reached

Median OS: 8.0 years

Median PFS: 5.5 years

Ryan et al, Ann Oncol 2008

Primary diffuse large B-cell lymphoma of the breast: a study by the International Extranodal Lymphoma Study Group

Results:

- MFA: favourable International Prognostic Index score, anthracycline-containing chemotherapy, and radiotherapy (RT) were significantly associated with longer OS (each $P \leq 0.03$).
- There was no benefit from mastectomy, as opposed to biopsy or lumpectomy only.
- At a median follow-up time of 5.5 years, 37% of patients had progressed—16% in the same or contralateral breast, 5% in the central nervous system, and 14% in other extranodal sites.

Ryan et al, Ann Oncol 2008

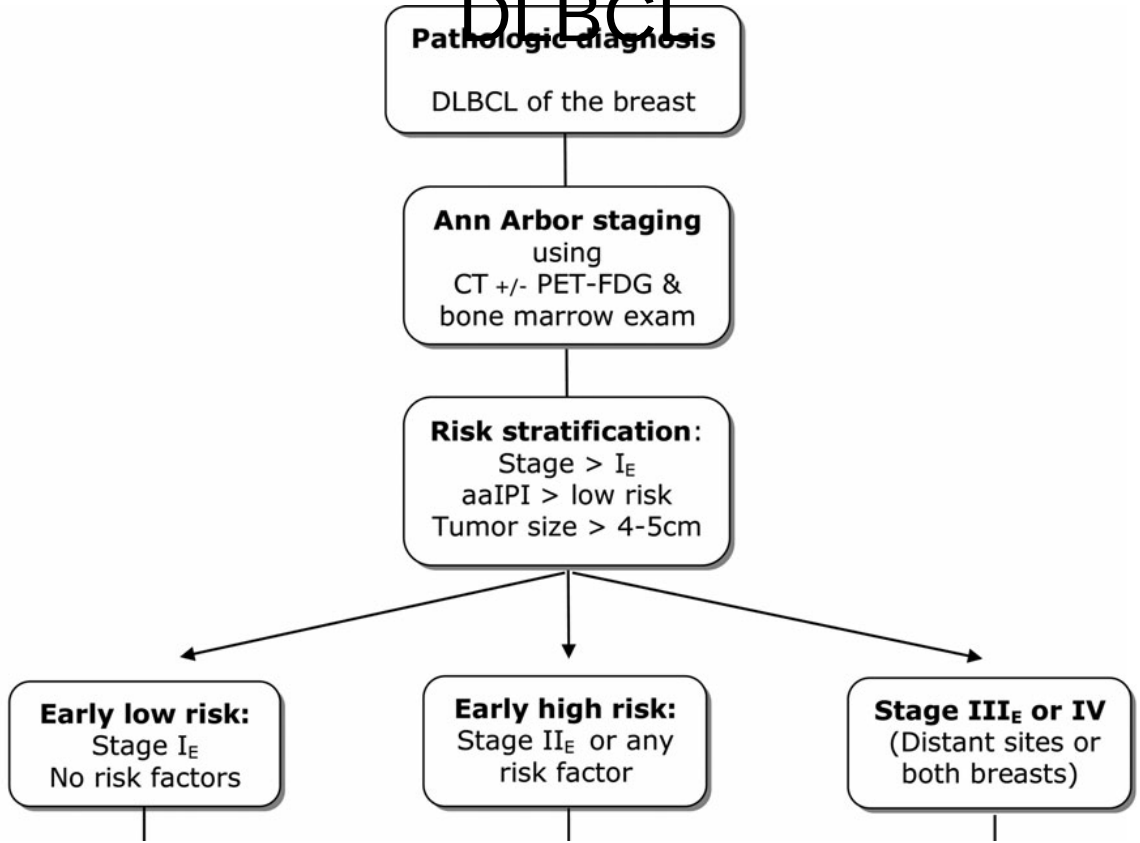
Primary diffuse large B-cell lymphoma of the breast: a study by the International Extranodal Lymphoma Study Group

Conclusions:

- Limited surgery+anthracycline-containing CT +IFRT: best outcome in the pre-rituximab era
- Prospective study needed

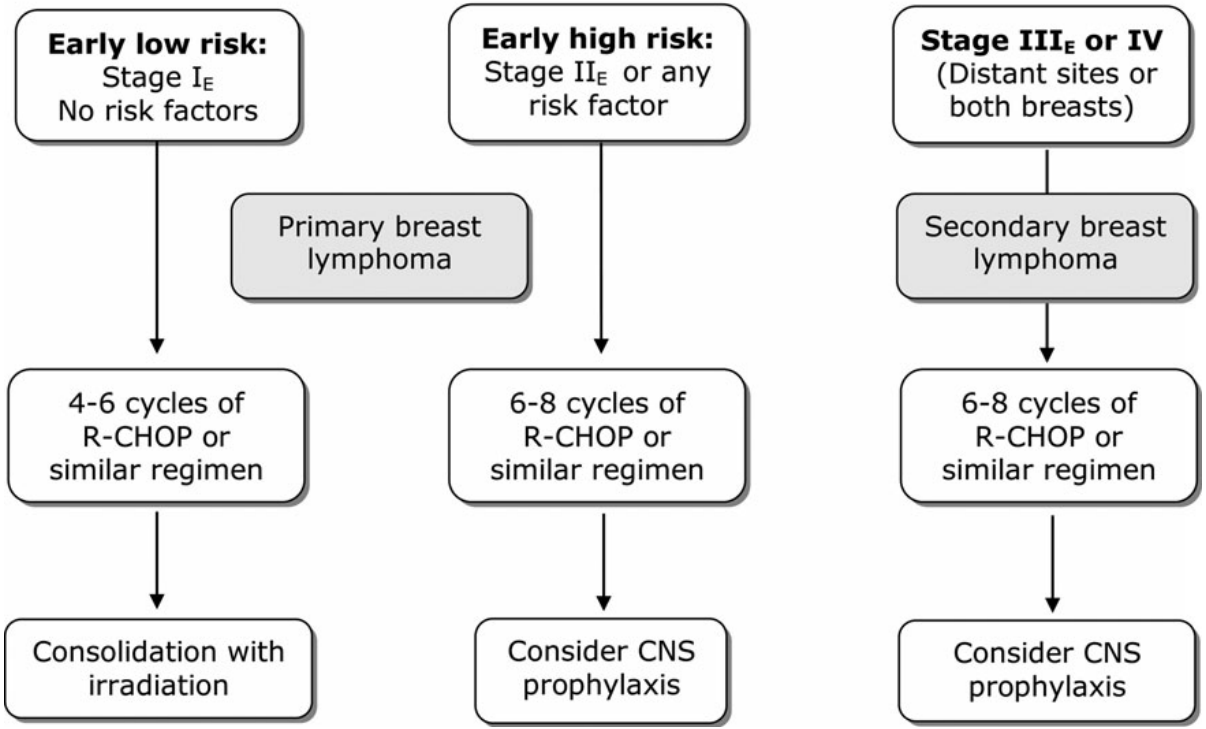
Ryan et al, Ann Oncol 2008

Suggested algorithm for newly diagnosed PB-DLBCL



Aviv et al, Ann Oncol 2013

Suggested algorithm for newly diagnosed PB-DLBCL



No recommendation on RT dose/fields

Aviv et al, Ann Oncol 2013

Follicular and marginal zone primary breast lymphoma (PBL): results from International Extranodal Lymphoma Study Group

Patients and methods:

- International retrospective study
- 60 cases of PBL (36 follicular and 24 marginal-zone lymphoma)
- Stage IE or IIE: 57 patients and IVE: 3 patients (bilateral breast)
- Treatment period: 1980 to 2003

Martinelli et al, Ann Oncol 2009

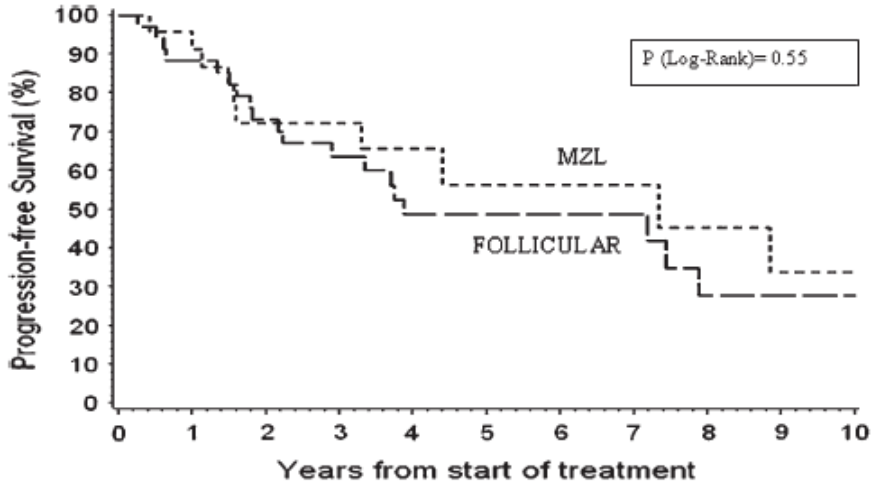
Follicular and marginal zone primary breast lymphoma (PBL): results from International Extranodal Lymphoma Study Group

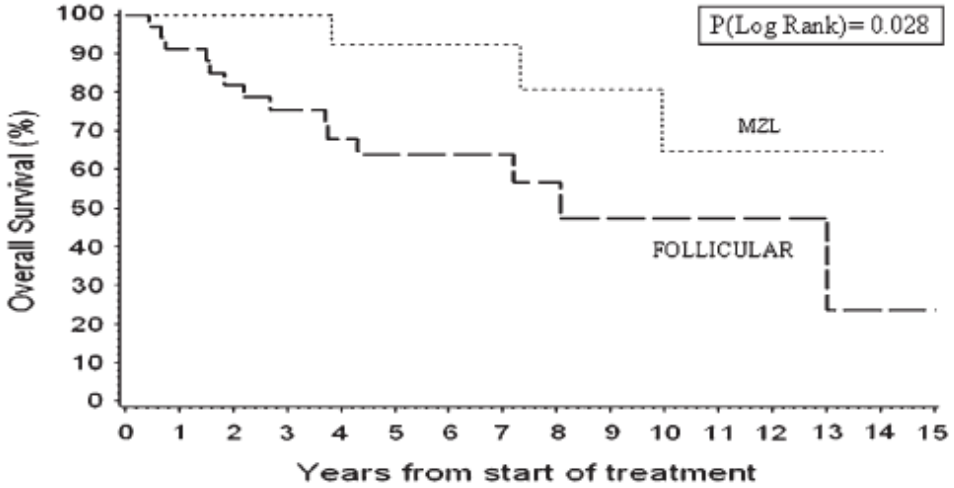
Results:

- First-line treatment:
  - Surgery +/- other: 67%
  - CT +/- other: 42%
  - RT +/- other: 52%
- RT to breast fields in 36 patients (dose range 25–50 Gy, median 38 Gy) and nodal fields (axilla and supraclavicular) in 18 patients (dose range 30–46 Gy, median 36 Gy).

Martinelli et al, Ann Oncol 2009

15-year PFS and OS in follicular and marginal zone primary breast lymphoma

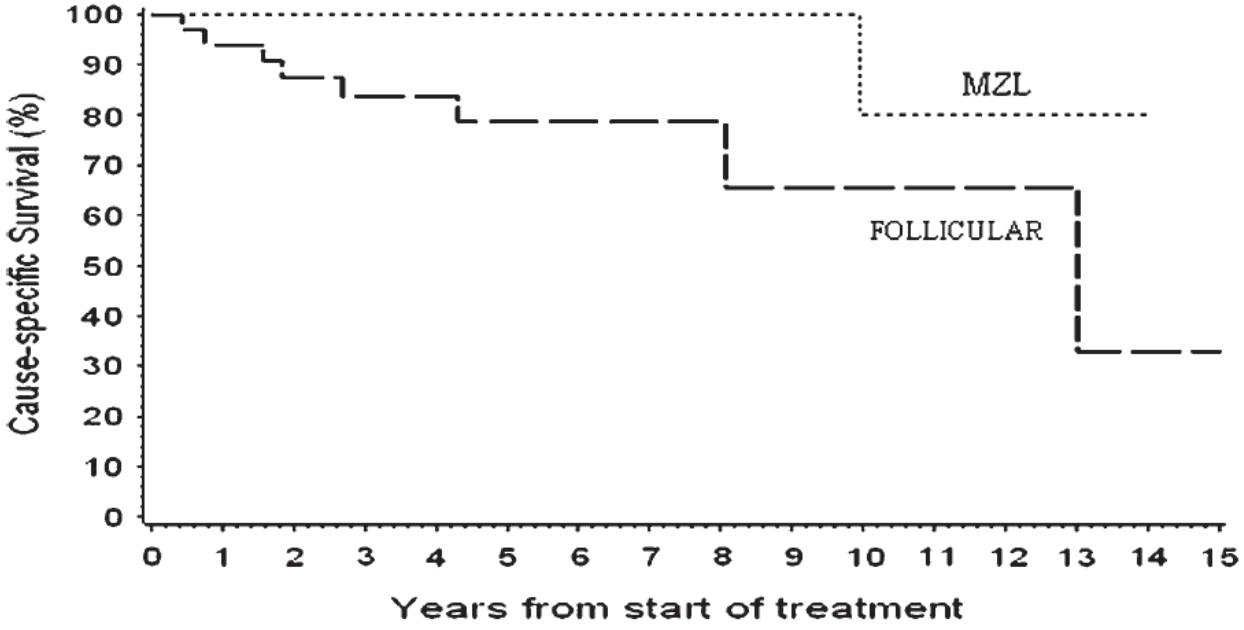




Overall response rate: 98% (93% complete response)
Relapses were mostly in distant sites (18 of 23 cases)
No patients relapsed within RT fields.

Martinelli et al, Ann Oncol 2009

15-year cause specific survival in follicular and marginal zone primary breast lymphoma



Martinelli et al, Ann Oncol 2009

Follicular and marginal zone primary breast lymphoma (PBL): results from International Extranodal Lymphoma Study Group

Conclusions:

- Outcome MZL PBL comparable to other primary extranodal MZL (=indolent)
- Patients with follicular PBL had inferior PFS and OS when compared with limited-stage nodal follicular non-Hodgkin’s lymphomas.

Martinelli et al, Ann Oncol 2009

Radiotherapy

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Breast lymphoma

Volume

- CTV for primary or consolidation RT: whole breast
- Uninvolved lymph nodes need not be included in CTV
- Partial breast irradiation is considered by some experts under special circumstances

Yahalom et al. ILROG guideline, IJROBP 2015

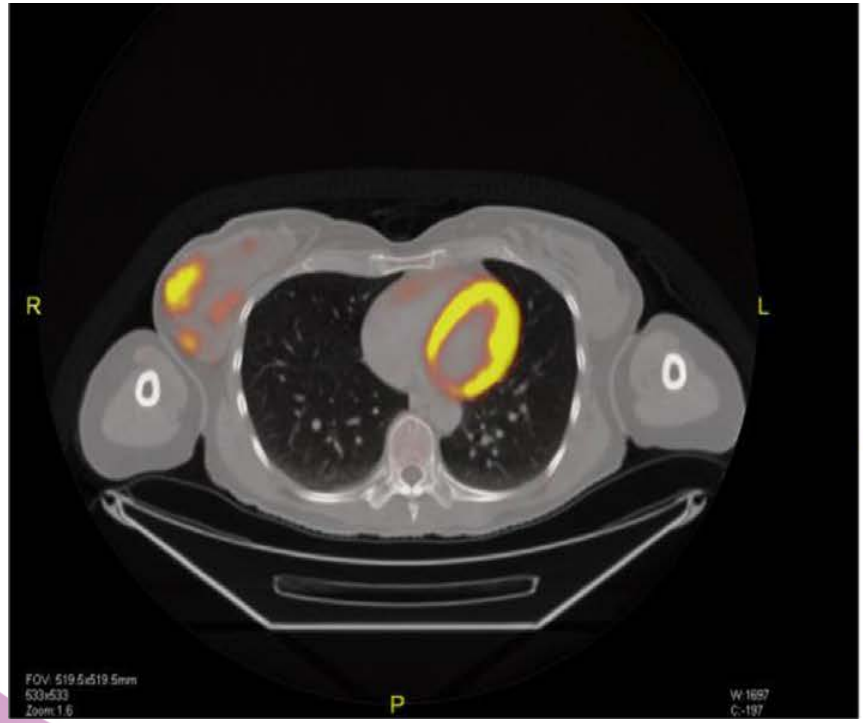
Breast lymphoma

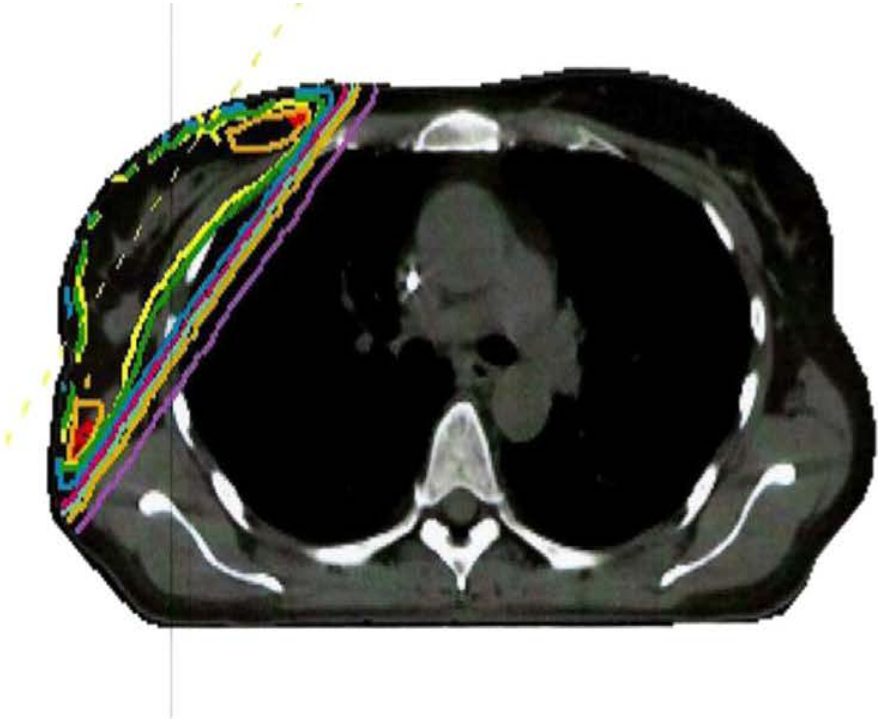
Technique

- Breast immobilization with the arm up, or prone technique for large pendulous breast.
- 3D conformal or IMRT depending on local preference

Yahalom et al. ILROG guideline, IJROBP 2015

49-year old woman with DLBCL right breast in CR after chemo





Yahalom et al. ILROG guideline, IJROBP 2015

Breast lymphoma

Radiation dose (curative setting):

- Indolent lymphoma: 30 Gy/15 fx
- DLBCL:
  - CR after chemo: 30 Gy/15 fx
  - PR after chemo: 40 Gy/20 fx

Questions?

Treatment specification IELSG series.

	MZL PBL ($N = 24$), n (%)	Follicular PBL ($N = 36$), n (%)	Total, n (%)
Surgery alone	5 (21)	6 (17)	11 (18)
CT alone	1 (4)	6 (17)	7 (12)
RT alone	5 (21)	4 (11)	9 (15)
Surgery and CT	2 (8)	4 (11)	6 (10)
Surgery and RT	8 (34)	7 (19)	15 (25)
Surgery + CT + RT	2 (8)	6 (17)	8 (13)
CT + RT	1 (4)	3 (8)	4 (7)
Surgery (alone or not)	17 (71)	23 (64)	40 (67)
CT (alone or not)[a]	6 (25)	19 (53)	25 (42)
RT (alone or not)	16 (67)	20 (56)	36 (52)

[a]$P = 0.03$, Pearson's chi-square test.

MZL, marginal-zone lymphoma; PBL, primary breast lymphoma; CT, chemotherapy; RT, radiotherapy.

Martinelli et al, Ann Oncol 2009

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Lung Lymphoma

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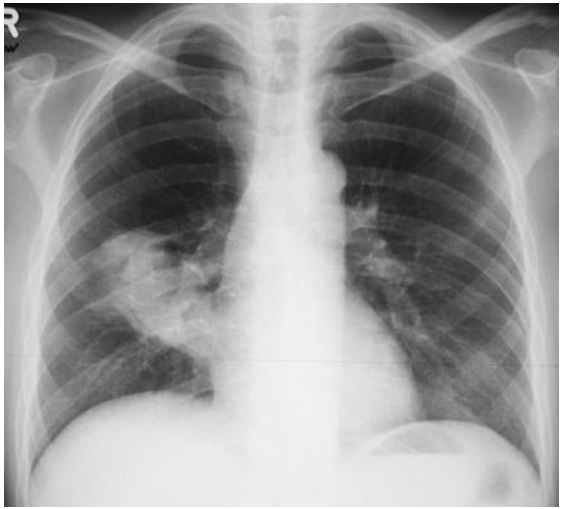
Background

- Primary pulmonary lymphoma is a very rare neoplasm, representing only 2-4% of extranodal non-Hodgkin lymphoma and only 0.4% of all malignant lymphomas

- Most cases are represented by MZL

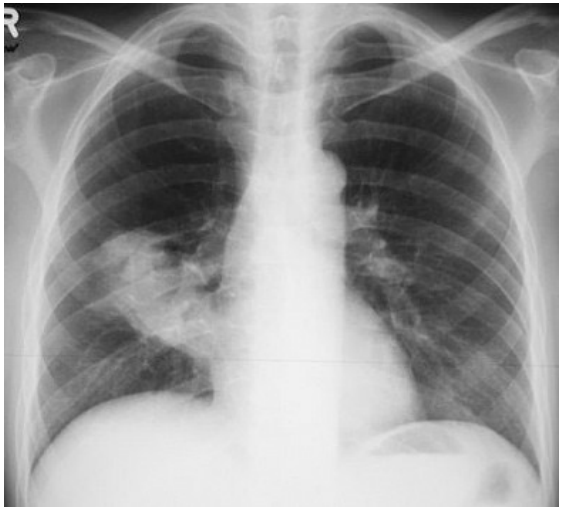
- Primary pulmonary lymphoma is defined as a clonal lymphoma proliferation affecting one or both lungs in a patient with no detectable extrapulmonary involvement at diagnosis or during the subsequent 3 months



Background

- MZL (bronchial associated lymphoid tissue lymphoma [BALT lymphoma]) may involve any element of the bronchial tree, often as an isolated lesion

- Surgery as first treatment: pulmonary lesion as a potential lung cancer

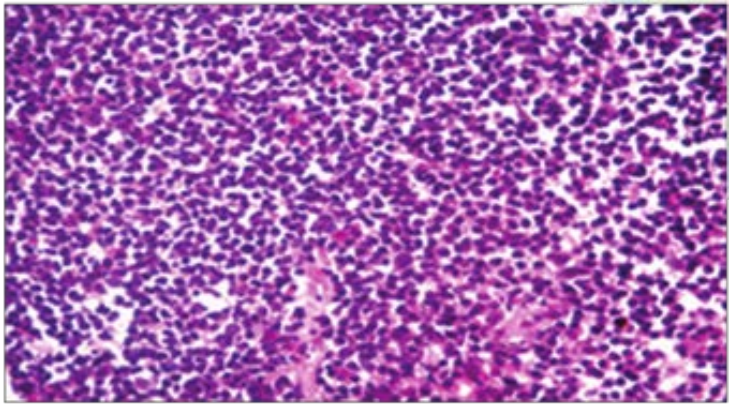


Histology

- BALT lymphoma 80-90%
- DLBCL 10%

- Most common immunohistochemical features:

  - CD 20+
  - CD19+
  - CD22+
  - CD10-
  - CD5-
  - Bcl2+



Cytogenetics

- t(11;18)(q21;q21) is documented in 30-40% of BALT lymphoma
- The fusion product , cIAP2-MALT1, may concomitantly contribute to lymphomagenesis both as a tumor suppressor gene and as an oncogene

Bertoni et al. J Clin Invest 2006;116(1): 22-26

- The role of chronic infections, toxic exposure, or underlying autoimmune diseases in BALT lymphoma is unknown

- Achromobacter (Alcaligenes) xylosoxidans, a Gram negative bacterium with low virulence but with high resistance treatment, has been recently detected

- Whether this finding indicates a potential etiopathogenetic role of this bacterium in BALT lymphoma will however require further studies

Clinical presentation

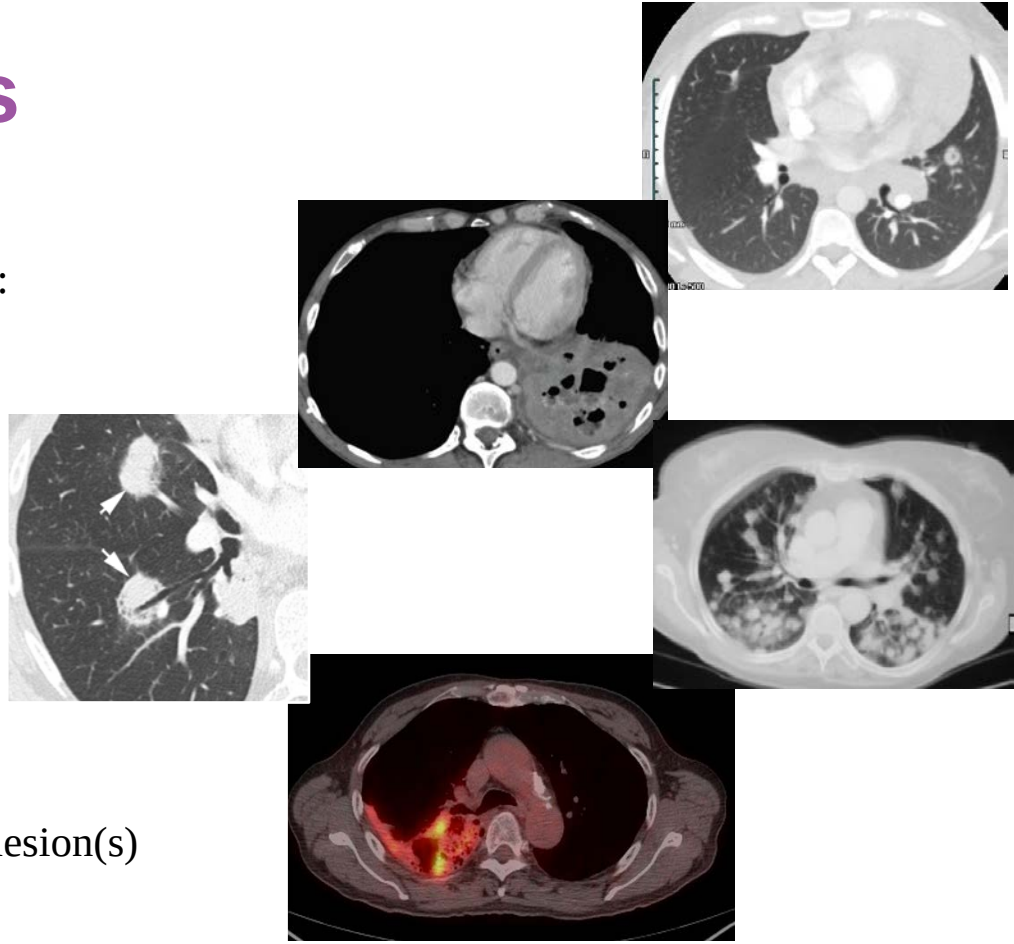
- Most patients (90%) are asymptomatic at diagnosis and disease is incidentally discovered

- When present, symptoms are unspecific, such as:
  - Cough
  - Mild dyspnea
  - Chest pain
  - Hemoptysis

- B symptoms are uncommon

Diagnosis

- Radiologic findings are nonspecific and include:
  - Solitary nodule
  - Multiple ill-defined nodules
  - Mass with air bronchograms
  - Pleural effusion
  - Atelectasis
  - Cavities



- FDG-PET usually reports a mild uptake of the lesion(s)

Staging

Ann Arbor system modified by Ferraro

Stage	Description
I E	Unilateral or bilateral presentation of the lung
II 1E	Lung presentation with hilar lymph node involvement
II 2E	Lung presentation with mediastinal lymph node involvement
II 2EW	Lung presentation with chest wall or diaphragm involvement
III E	Lung presentation with abdominal lymph node involvement
IV E	Lung presentation with extra-lymphatic organs or tissue involvement

Ferraro et al. Ann Thorac Surg 2000;69:993-997

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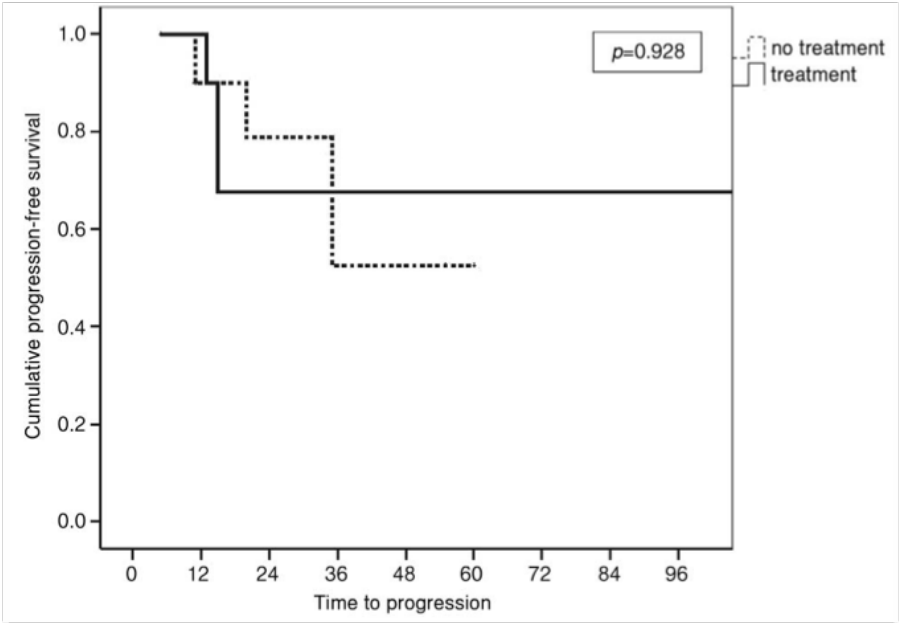
Treatment

Clinical features, clinical course, optimal treatment, role of surgery and prognostic factors are not well defined

- Surgery
- Watch and wait
- Chemotherapy
- Radiotherapy

Does MALT Lymphoma of the Lung Require Immediate Treatment? An Analysis of 11 Untreated Cases with Long-term Follow-up



"MALT lymphoma of the lung is a very indolent disease with the potential for spontaneous regression. For this reason, patients diagnosed with pulmonary MALT lymphoma might not require immediate treatment in the absence of symptoms and a watch-and-wait policy could be adopted."

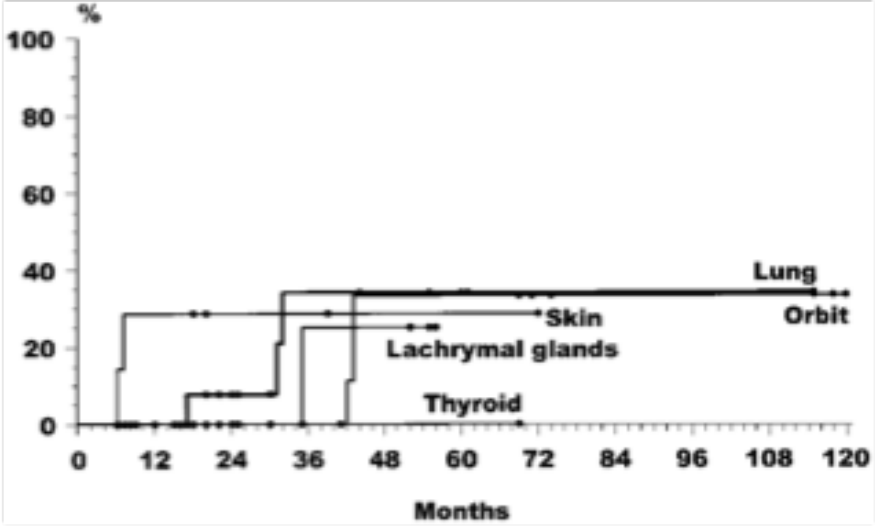
Troch et al. Anticancer Research 2007;27:3633-3638

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Nongastrointestinal Low-Grade Mucosa-Associated Lymphoid Tissue Lymphoma: Analysis of 75 Patients

LUNG lymphoma

- 19 patients
- 17/19 treated with CT (as single agent or in combined modality schedules)
- 2/19 received surgery alone



- 100% ORR (79% CR and 21% PR)
- 3 relapses (15.7%)
- 100% OS at 5 years

Zinzani et al. JCO 1999;17:1254-1258

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Clinical characteristics and prognostic factors of pulmonary MALT lymphoma

Borie et al. Eur Respir J 2009;34:1408-1416

TABLE 1 Main clinical and biological characteristics of the 63 patients

Characteristics	Value
Age yrs	60 (24–83)
Females	29 (47)
Active or former tobacco use	24 (37)
Respiratory tract infection	6 (9)
Including tuberculosis	4 (6)
Autoimmune background	10 (16)
Respiratory symptoms	37 (58)
B symptoms	14 (22)
Cytopenia	12 (19)
LDH level more than twice the upper limit	2 (3)

TABLE 3 Remission and outcome according to type of therapy

Treatment group	Subjects	DCR	Death	Relapse or progression	Median PFS yrs	3-yr PFS %
Abstention	6 (9)	0 (0)	1 (16)	0 (0)	NA	66 (0–94)
Local therapy	20 (32)[#,¶]	20 (100)	1 (5)	7 (35)	NA	83 (55–94)
Chlorambucil	19 (30)	17 (87)	2 (10)	3 (15)	8.2	75 (41–91)
Cyclophosphamide	10 (16)	7 (70)	2 (20)	8 (80)	0.7	40 (12–67)
Anthracyclin/fludarabine	8 (13)[+]	8 (100)	3 (37)	6 (75)	0.7	25 (0–63)

Data are presented as n (%) or with 95% confidence intervals, unless otherwise stated. All treatment groups were compared with chlorambucil. Treatment groups are defined in the Methods section. DCR: disease control rate; PFS: progression-free survival; NA: not achieved. [#]: only one patient was treated by radiotherapy without relapse; [¶]: one patient received chlorambucil adjuvant therapy after surgery; [+]: one patient received fludarabine in combination with rituximab.

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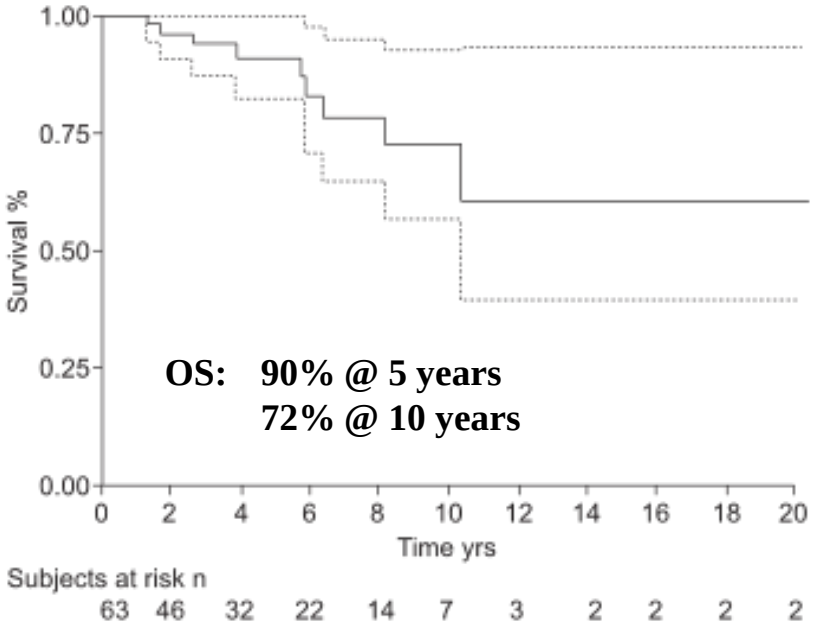
Clinical characteristics and prognostic factors of pulmonary MALT lymphoma



OS: 90% @ 5 years
72% @ 10 years

TABLE 5 Hazard ratios for overall survival

	Univariate analysis	
	Hazard ratio (95% CI)	p-value
Age >60 yrs	12.5 (1.5–104.0)	0.02
Male sex	0.7 (0.2–2.5)	0.5
ECOG		
0	1	
1	20.3 (2.1–190.4)	0.008
2–3	38.6 (4–374)	0.002
Diagnosis delay (per 1 month increase)	1.0 (0.99–1.02)	0.8
Extrapulmonary location	2.2 (0.6–8.4)	0.2
Gastric	1.8 (0.4–7.8)	0.4
Nodal	6.0 (0.6–58.8)	0.1
Medullar		0.52[#]
Pulmonary extension		
Mediastinal adenopathy	2 (0.2–17.7)	0.5
Bilateral involvement	1.7 (0.4–6.4)	0.4
Pleural effusion	5.4 (0.9–30.6)	0.1
Treatment		
Chlorambucil	1	
Cyclophosphamide based chemotherapy	0.9 (0.1–6.6)	0.9
Anthracyclin- or fludarabine-based chemotherapy	2.6 (0.4–6)	0.3
Local therapy	0.2 (0.02–2.7)	0.2
Abstention	4.6 (0.4–54)	0.2

Borie et al. Eur Respir J 2009;34:1408-1416

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Clinical characteristics and prognostic factors of pulmonary MALT lymphoma

TABLE 4 Hazard ratios for progression-free survival

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age >60 yrs	1.0 (0.5–2.2)	0.9	0.8 (0.3–1.7)	0.52
Male sex	0.7 (0.3–1.5)	0.3		
ECOG				
0	1		1	
1	2.0 (0.8–5.0)	0.1	1.9 (0.7–5.1)	0.22
2–3	1.99 (0.8–5)	0.1	3.0 (1.0–9.5)	0.05
Diagnosis delay (per 1-month increase)	1.0 (0.99–1.01)	0.8		
Extrapulmonary location	1.4 (0.7–3.0)	0.4	0.9 (0.4–2.2)	0.86
Gastric	1.3 (0.6–3.0)	0.6		
Nodal	0.7 (0.1–5.1)	0.7		
Medullar	1.1 (0.3–3.7)	0.9		
Pulmonary extension				
Mediastinal adenopathy	3.5 (1.3–9.0)	0.01	1.0 (0.3–3.3)	0.99
Bilateral involvement	1.8 (0.9–3.9)	0.6		
Pleural effusion	1.7 (0.6–4.9)	0.7		
Treatment				
Chlorambucil	1		1	
Cyclophosphamide-based chemotherapy	6.1 (2–18.6)	0.001	6.1 (1.6–23.7)	0.01
Anthracyclin or fludarabine-based chemotherapy	4.4 (1.3–15.0)	0.02	4.9 (1.3–17.6)	0.02
Local therapy	1.0 (0.3–3.2)	0.9	1.1 (0.3–3.8)	0.96
Abstention	1.2 (0.1–10.1)	0.8	1.2 (0.1–11)	0.84

Borie et al. Eur Respir J 2009;34:1408-1416

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A retrospective international study on primary extranodal marginal zone lymphoma of the lung (BALT lymphoma) on behalf of International Extranodal Lymphoma Study Group (IELSG)

Abstract

Primary lymphoma of the lung is a rare entity. Clinical features, optimal treatment, role of surgery and outcomes are not well defined, and the follow-up is variable in published data. Clinical data of 205 patients who were confirmed to have bronchus mucosa-associated lymphoid tissue lymphoma from December 1986 to December 2011 in 17 different centres worldwide were evaluated. Fifty-five per cent of the patients were female. The median age at diagnosis was 62 (range 28–88) years. Only 9% had a history of exposure to toxic substances, while about 45% of the patients had a history of smoking. Ten per cent of the patients had autoimmune disease at presentation, and 19% patients had a reported preexisting lung disease. Treatment modalities included surgery alone in 63 patients (30%), radiotherapy in 3 (2%), antibiotics in 1 (1%) and systemic treatment in 128 (62%). Patients receiving a local approach, mainly surgical resection, experienced significantly improved progression-free survival ($p = 0.003$) versus those receiving a systemic treatment. There were no other significant differences among treatment modalities. The survival data confirm the indolent nature of the disease. Local therapy (surgery or radiotherapy) results in long-term disease-free survival for patients with localized disease. Systemic treatment, including alkylating-containing regimens, can be reserved to patients in relapse after incomplete surgical excision or for patients with advanced disease. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: BALT lymphoma; marginal zone lymphoma; *Achromobacter* (*Alcaligenes*) *xylosoxidans*

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Sammassimo et al. Hematol Oncol 2015;DOI:10.1002/hon.2243

A retrospective international study on primary extranodal marginal zone lymphoma of the lung (BALT lymphoma) on behalf of International Extranodal Lymphoma Study Group (IELSG)

Table 2. Main clinical patients' characteristics

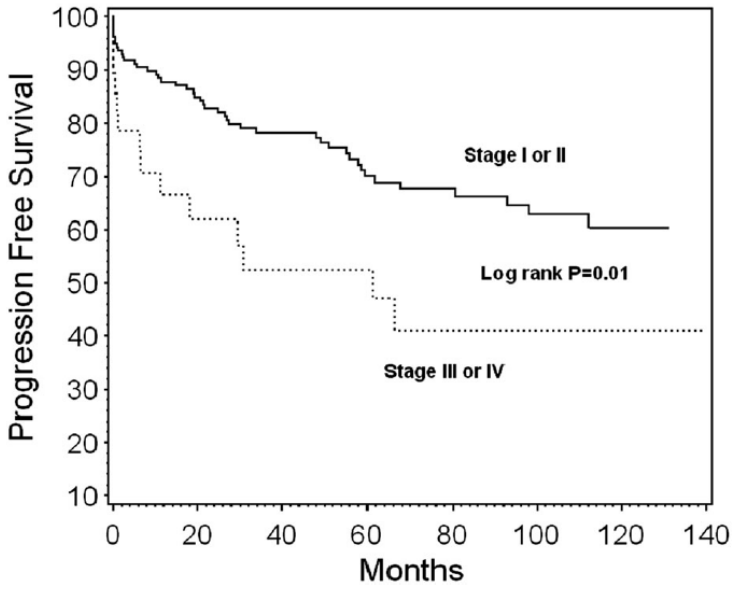
Characteristic	
All	205
Median age at diagnosis (range)	62 years (28–88)
	n (%)
Sex	
Male/female	91 (45)/114 (55)
Pre-existing risk factors	
Exposure to toxic substances	17/185 (9)
Smoking	88/197 (45)
Autoimmune disorders	19/184 (10)
Pre-existing lung disease	38/202 (19)
Stage	
I–II	169/197 (86)
III–IV	28/197 (14)
PS	
0–1	192/198 (97)
2–3	6/198 (3)
IPI score	
0–2	187/196 (95)
3–4	9/196 (5)
Constitutional symptoms	29/199 (15)
Respiratory symptoms	100/183 (55)

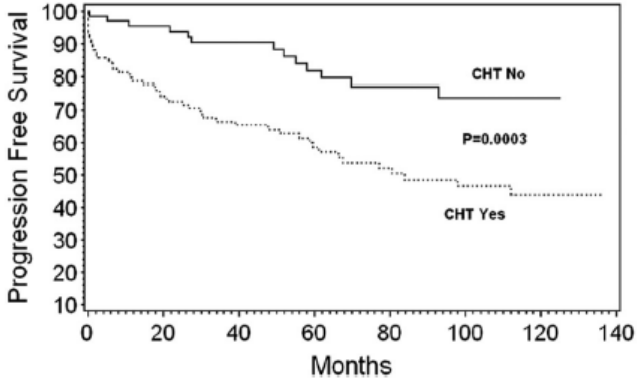
Table 3. Treatments, response and disease progression after first line treatment

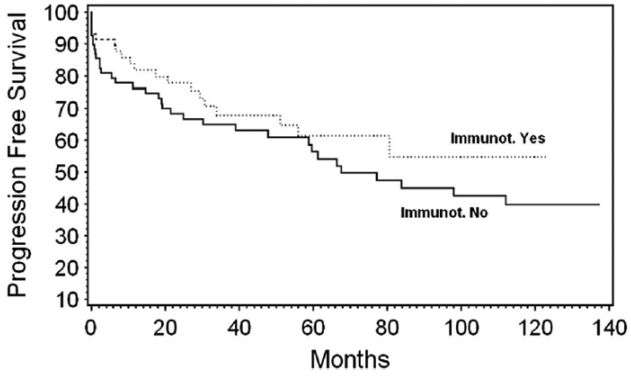
Treatment (*n*)	Response	*n* (%)	PFS (months)
Local treatment (67)			66
Surgery (63)	CR	58 (92)	
	PR	4 (6)	68
	UN	1 (2)	
Antibiotics (1)	SD	1 (100)	5
Radiotherapy (3)	CR	2 (67)	62
	PR	1 (33)	
Systemic treatment (128)			33
Immunochemotherapy (38)	CR	20 (53)	
	PR	13 (34)	
	SD	1 (3)	33
	PD	2 (5)	
	UN	2 (5)	
Immunotherapy — rituximab (20)	CR	4 (20)	
	PR	4 (20)	
	SD	10 (50)	24
	UN	2 (10)	
Chemotherapy (70)	CR	31 (44)	
	PR	25 (36)	
	SD	8 (11)	37
	PD	3 (4)	
	UN	1 (1)	
	NE	2 (3)	
Watch and wait (10)[a]	SD	8 (80)	26
	UN	2 (20)	

Sammassimo et al. Hematol Oncol 2015;DOI:10.1002/hon.2243

A retrospective international study on primary extranodal marginal zone lymphoma of the lung (BALT lymphoma) on behalf of International Extranodal Lymphoma Study Group (IELSG)







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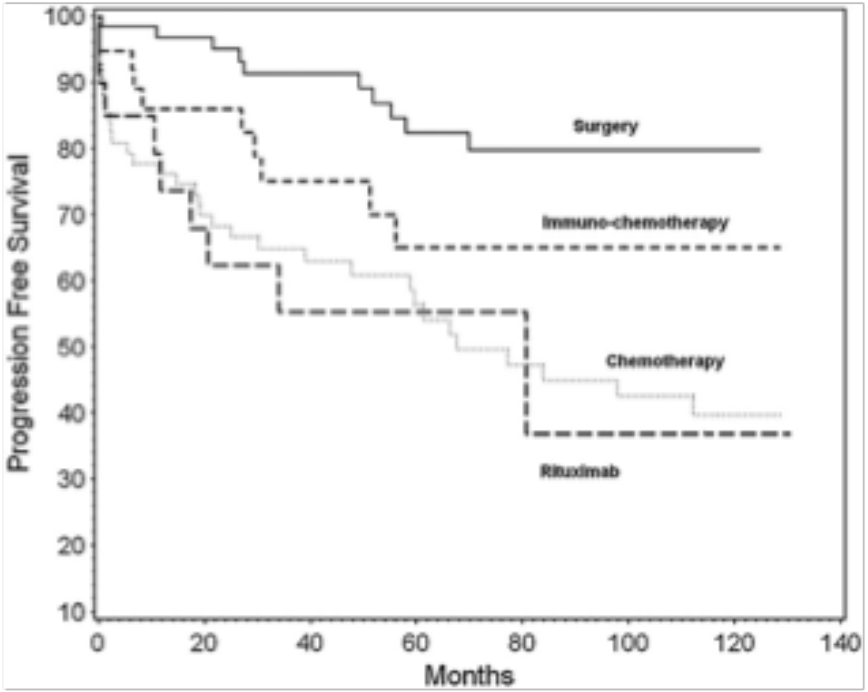


Conclusion:

Local therapy (surgery or radiotherapy) results in long-term disease-free survival for patients with localized disease.

Systemic treatment can be reserved for patients in relapse after incomplete surgical excision or for patients with advanced disease.

Sammassimo et al. Hematol Oncol 2015;DOI:10.1002/hon.2243

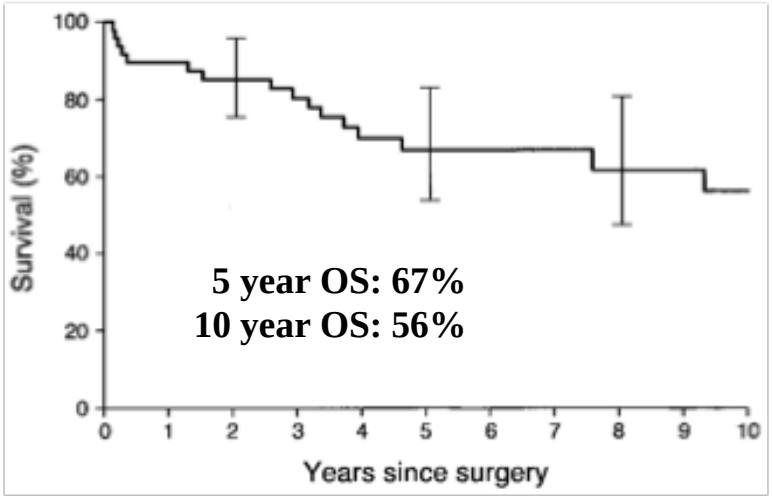
Surgical approach

Table 2. Diagnostic Procedures and Surgical Interventions[a]

Variable	No. of Patients
Bronchoscopy (n = 39)	
Biopsy positive for lymphoma	5 (10)
Washings positive for lymphoma	2 (4)
Normal or nonspecific findings	32 (67)
Not done	9 (19)
Open thoracotomy (n = 43)	
Biopsy	7 (16)
Wedge resection	21 (49)
Segmentectomy	2 (5)
Lobectomy	11 (26)
Pneumonectomy	2 (5)
VATS (n = 5)	
Diagnostic lymphoma	4 (80)
Converted to open procedure	1 (20)
Additional procedure	
Chest wall resection	1 (2)
Lymphadenectomy	27 (56)
Pleurodesis	8 (17)

[a] Numbers in parentheses are percentages.

- 48 patients
- 35 MALT lymphomas
- 13 Aggressive B cell lymphomas
- 1975-1995
- **All patients underwent surgical resection**



Ferraro et al. Ann Thorac Surg 2000;69:993-997

Surgical approach

Table 5. Influence of Prognostic Factors on Survival in Different Patient Groups

Prognostic Factor	All Patients (n = 48) 5-Year Survival (%)	All Patients (n = 48) *p* Value	Malt Lymphoma Only (n = 35) 5-Year Survival (%)	Malt Lymphoma Only (n = 35) *p* Value	Stage I Tumors Only (n = 37) 5-Year Survival (%)	Stage I Tumors Only (n = 37) *p* Value
Complete resection						
Chemotherapy postoperatively	75.0	0.35	66.7	0.56	66.7	0.55
No chemotherapy	57.5		62.9		53.5	
Incomplete resection						
Chemotherapy postoperatively	66.7	0.94	68.2	0.96	62.5	0.66
No chemotherapy	77.8		75.0		75.0	

MALT = mucosa-assisted lymphoid tissue.

Ferraro et al. Ann Thorac Surg 2000;69:993-997

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Radiotherapy

- Few retrospective studies with a limited number of patients

- Radiotherapy may play a role in the treatment of BALT lymphoma

Practice guidelines for the management of extranodal non-Hodgkin's lymphomas of adult non-immunodeficient patients. Part I: primary lung and mediastinal lymphomas. A project of the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation

Zinzani et al. Haematologica 2008;93(9):1364-1371

Table 1. Case series including cases of primary pulmonary MALT lymphomas.

	Number of patients	*Lung surgical resection*	*Chemotherapy*	*Rituximab*	*Radiotherapy*	*CR/PR*	*5 yr OS % (10 yr OS)*	*5 yr RFS %*
Koss *et al.*, 1983[14]	44	NR	NR	NR	NR	NR	95 (85)	NR
Kennedy *et al.*, 1985[15]	32	10	18	NR	NR	NR	90 (78)	NR
Li *et al.*, 1990[16]	33	14	14	NR	5	NR	85 (75)	<54
Cordier *et al.*, 1995[17]	64	42	18	NR	5	NR	94 (50)	NR
Fiche *et al.*, 1995[18]	69	46	20	NR	6	NR	93.6% in low grades	NR
Wislez *et al.*, 1999[19]	13	3	10	NR	NR	7/5	100	NR
Ferraro *et al.*, 2000[20]	35	19	26	NR	2	NR	68 (53)	NR
Kurtin *et al.*, 2001[21]	50	NR	NR	NR	NR	NR	85 (72)	NR
Zinzani *et al.*, 2003[22]	12	4	10	NR	NR	12/0	100	>50
Zucca *et al.*, 2003[23]	15	NR	NR	NR	NR	NR	100	75
Ahmed *et al.*, 2004[24]	22	6	10	10	2	9/10	<100	<60
Graham *et al.*, 2005[25]	17	6	8	1	NR	NR	82%	NR

NR: not reported.

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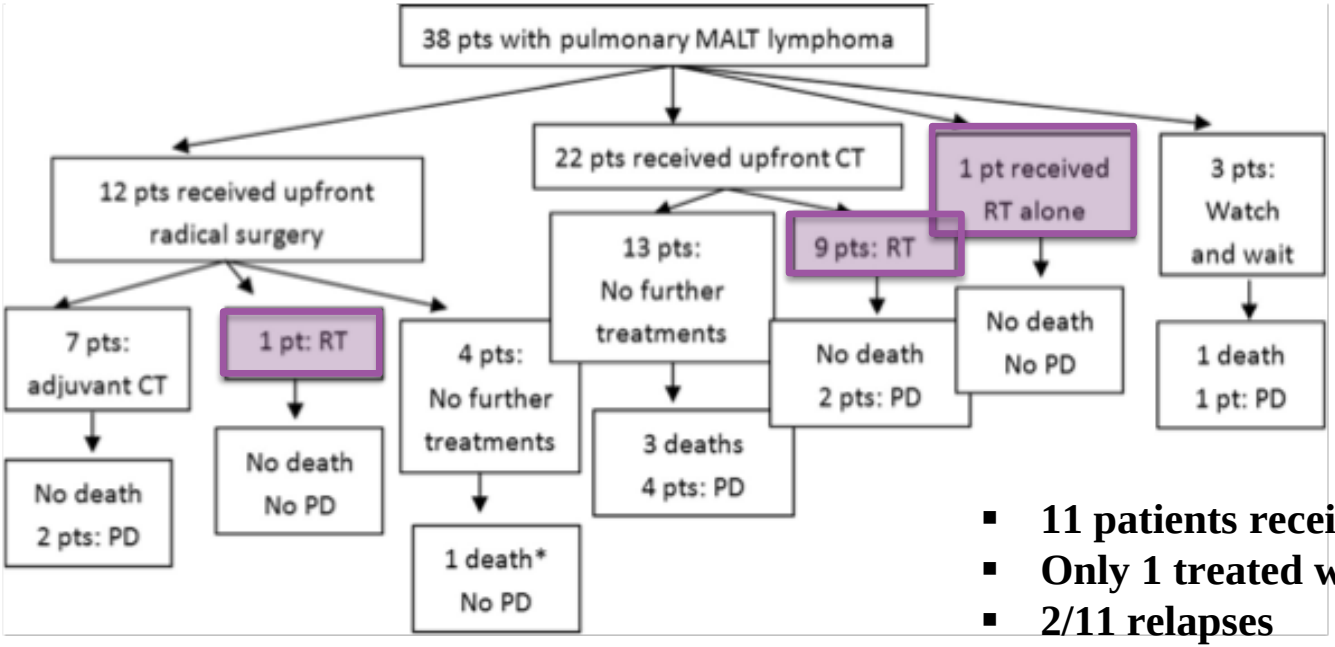
Radical surgery may be not an optimal treatment approach for pulmonary MALT lymphoma

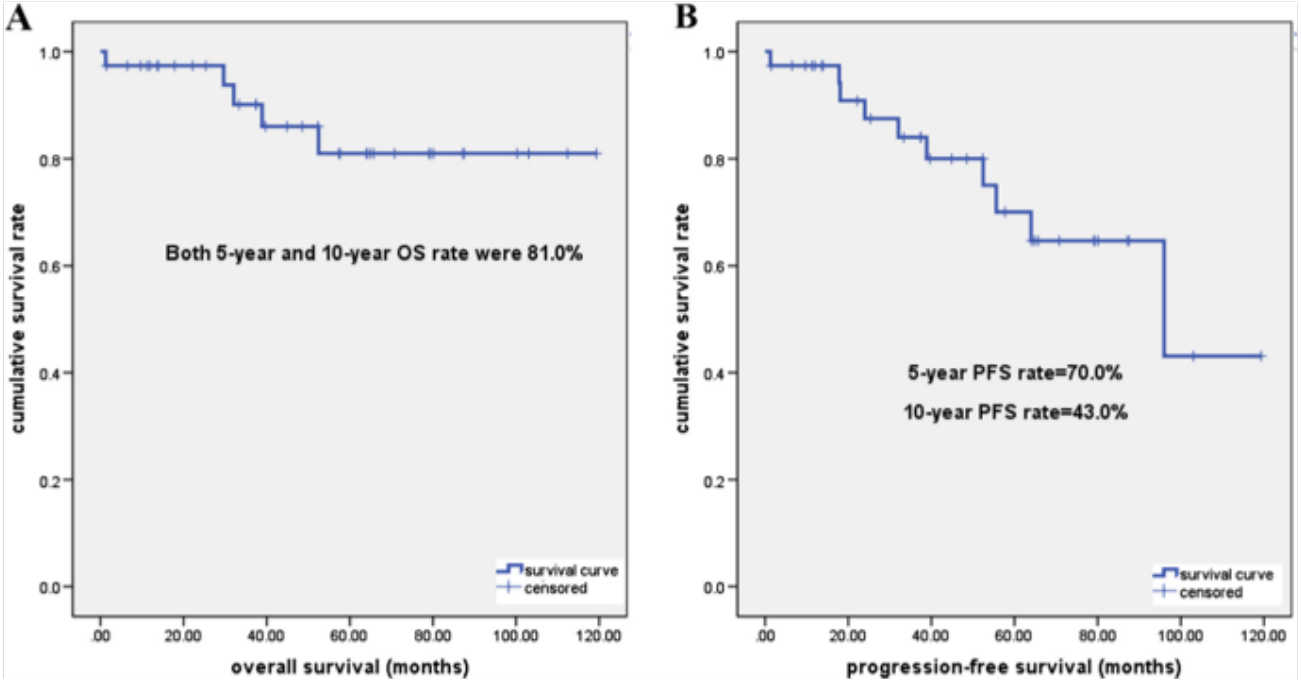


- **11 patients received RT**
- **Only 1 treated with RT alone**
- **2/11 relapses**
- **Median RT dose 30.6 (range 30-40 Gy)**

Wang et al. Tumor Biol. 2015;DOI10.1007/s13277-015-3329-y

Radical surgery may be not an optimal treatment approach for pulmonary MALT lymphoma

Overall Population



Wang et al. Tumor Biol. 2015;DOI10.1007/s13277-015-3329-y

Long-Term Outcome in Localized Extranodal Mucosa-Associated Lymphoid Tissue Lymphomas Treated With Radiotherapy

Table 2. Radiation Doses with Respect to Anatomical Locations for MALT Lymphomas

Anatomic Site	No. of Patients	25 Gy	>25-30 Gy	35 Gy	Other[a]
Orbital adnexa	71	65	5	1	
Stomach	25	8	10	5	2
Salivary glands	28	2	24	1	1
Thyroid	21	1	12	8	
Other H & N sites	6	1	5		
Lung	3		2		1
Urinary bladder	4			2	2
Skin and soft tissue	3		3		
Breast	4		1	3	
Other GI sites (rectum)	1			1	
Meninges	1		1		

31 Gy

NO RELAPSES

Goda et al. Cancer 2010;116:3815-3824

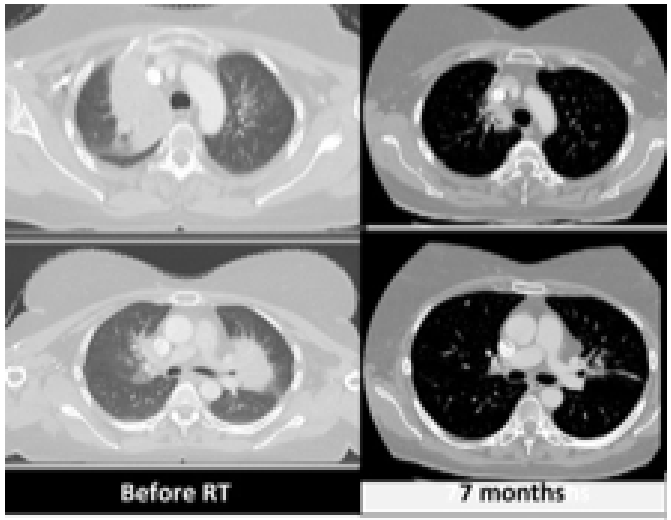
Low-Dose Radiation Treatment in Pulmonary Mucosa-Associated Lymphoid Tissue Lymphoma: A Plausible Approach? A Single-Institution Experience in 10 Patients

International Journal of Radiation Oncology biology • physics

BOOM-BOOM RADIOTHERAPY

- 4 Gy/2 fractions

Median follow up 56 months



Girinsky et al. IJROBP 2012;83(3): 385-389

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Table 2 Treatment outcome

Patient number, gender, and age (y)	Previous treatment	CT findings	Treatment response (2 mo)	Outcome	Follow-up (mo)
1. F, 45	6 mo of chlorambucil for a solitary pulmonary mass	Lobar consolidation	PR	Alive (CRu)	103
2. F, 51	CHOP therapy for Stage III disease (lung recurrence 5 y later)	Consolidation in each lung	PR	Alive (PR)	103
3. M, 46	None	Consolidations in the right lung	CR	Alive (CR)	84
4. M, 59	None	Consolidation	CRu	Alive (CRu)	75
5. F, 34	Initial wedge resection for a solitary mass in the upper left lobe (local relapse 6 mo later)	Nodule	PR	Alive (CRu)	56
6. F, 31	Rituximab (4 cycles) (PR) for tracheal infiltration	Infiltration of upper trachea	CR	Alive (CR)	56
7. M, 74	Pneumonectomy for a single pulmonary lesion (bronchial recurrence 3 mo later)	No visible lesion on CT	CR on fibroscopy	Alive (CR)*	28
8. M, 54	None	Bilateral diffuse involvement	CRu	Alive (CRu)	14–10†
9. F, 68	None	Single consolidation in each lung	CRu	Alive (CRu)	7
10. F, 45	R-CHOP chemotherapy for Stage IV disease (in CR except in the upper right lobe)	Consolidation in the upper right lobe	PR	Alive (PR)	6

Abbreviations: CR = complete response; CRu = unconfirmed CR; PR = partial response.

* Massive bilateral orbital relapses (possibly endangering patient's vision) were successfully treated with radiotherapy (30 Gy), and the patient is presently in CR.

† Different follow-ups because the left and right lung were treated separately. The left lung was treated first.

Girinsky et al. IJROBP 2012;83(3): 385-389

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Conclusions

- Most cases of primary lung lymphomas (80-90%) are MALT lymphoma

- BALT lymphoma tends to be an indolent disease with prolonged survival (70-80% @ 10 years), although with frequent relapses (30-40% @ 5 years)

- The optimal management of BALT lymphoma has yet to be clearly determined:

  - **Surgery** is preferable for localized disease
  - **Chemotherapy** is the treatment of choice for extensive disease
  - **Observation** is a good alternative for asymptomatic patients with localized disease

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Conclusions

- Data regarding a precise role for radiotherapy are lacking
- RT can be reserved for patients with a unique small lesion
- Planning procedures with 4D-CT is highly recommended to account for organ motion during the respiratory phases
- Modern radiation techniques (IMRT/IGRT) are recommended to reduce radiation exposure to ipsilateral and controlateral lung
- RT dose should be in the range of 24-30 Gy
- Low dose schedule (2 Gy x 2) has obtained promising results and could be argument of research in future trials

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

RECOMMENDATIONS FOR PLANNING AND TREATMENT

VOLUMES:

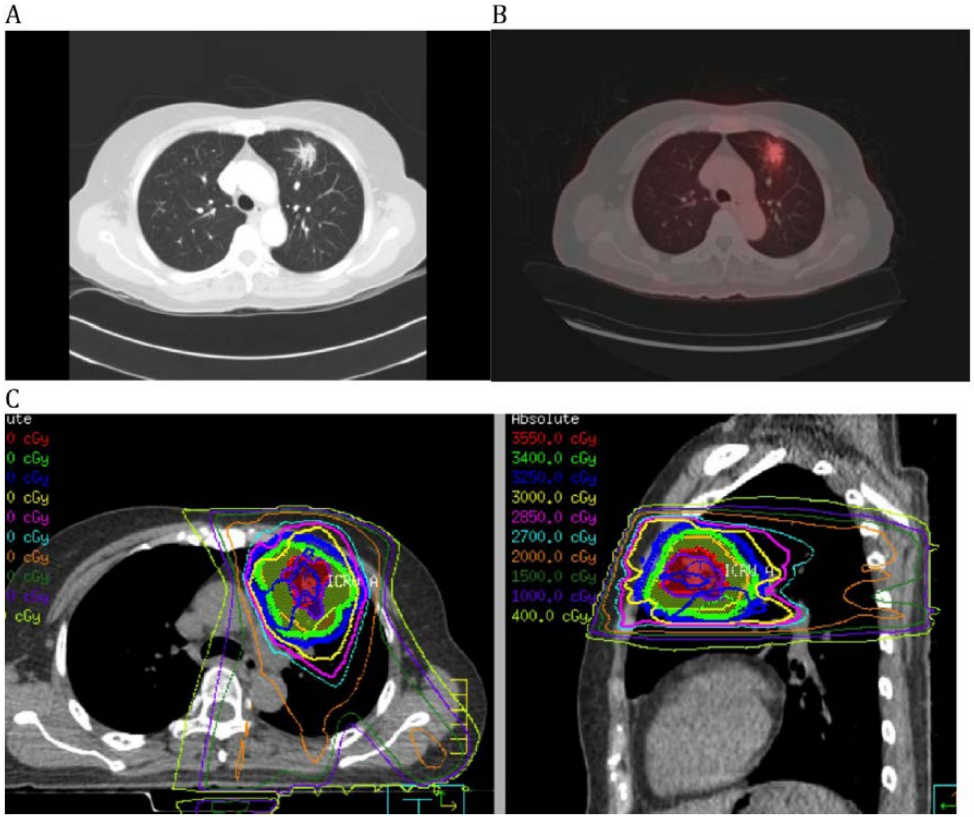
- CTV: preintervention (biopsy, surgery or systemic therapy) GTV, expanded by clinical judgment to accommodate imaging uncertainties and suspected adjacent microscopic infiltration
- ITV: expansion for respiratory motion (use 4DCT if available)

TECHNIQUE:

- 3D conformal or IMRT
- V20 and pulmonary function status should be taken into account

Yahalom et al. IJROBP 2015;92(1):11-31

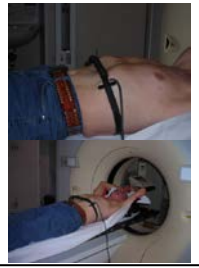
Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

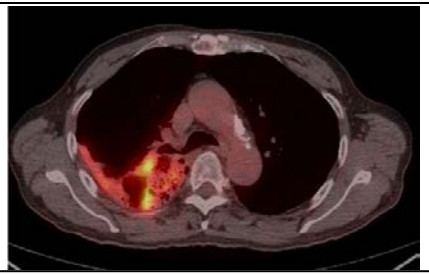


Yahalom et al. IJROBP 2015;92(1):11-31

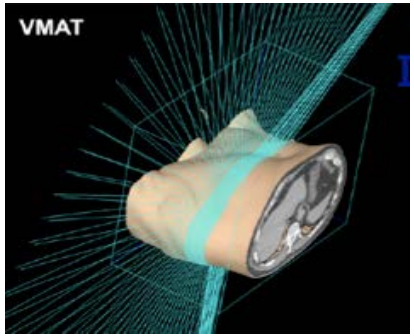
Modern RT for lung lymphoma

1. **Use of 4D-CT**: accounting for tumor motion during breathing
2. **GTV-Definition**: minimization based on functional Imaging (PET-CT) and shift to smaller CTV volumes

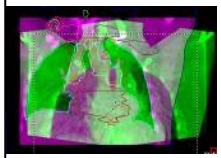


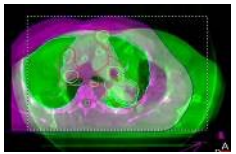


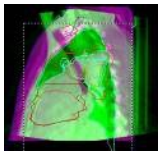
3. Treatment Planning as IMRT based on Monte-Carlo Dose calculation (dose-painting)



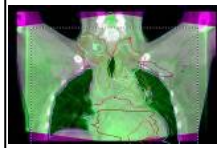
4. Image Guided Radiotherapy Treatment with Cone-Beam-CT at Linac for margins reduction

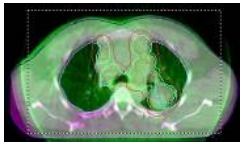


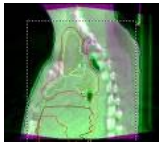




Suboptimal Positioning







Optimal Positioning

Practice guidelines for the management of extranodal non-Hodgkin's lymphomas of adult non-immunodeficient patients. Part I: primary lung and mediastinal lymphomas. A project of the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation

Zinzani et al. Haematologica 2008;93(9):1364-1371

RECOMMENDATIONS

MALT lymphomas

- **Surgery** is the treatment of choice for localized presentations
- **Chemotherapy** (anthracycline or fludarabine based regimens) is the treatment of choice for extensive disease
- **Observation** is a good alternative for asymptomatic patients with localized disease
- **Radiotherapy** may be an option (small lesion, histology available)

DLBCL

- **Recommended first line therapy** includes anthracycline based CT (CHOP or MACOP-B like regimens)
- **Surgical resection** requested in some cases
- Rituximab association with CT needs to be evaluated within approved clinical trials
- As for nodal DLBCL, second-line therapy with CT + ASCT is recommended

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Systemic approaches to early and advanced marginal zone lymphoma

Andy Davies
University of Southampton
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September 2015

The faces of MZL

Third most common NHL (5-17% of total)

	Extra nodal MZL	Splenic MZL	Nodal MZL
% on MZL	70%	20%	10%
Median age	60	65	50-60
Pathogenesis	Hp, C.jejuni, C. psittaci, B burgdoferi	Unknown, HCV	Unknown, HCV
	t(11;18)	3q and gain 12q	Nil typical
Typical clinical presentation	I_E disease	Abnormal blood count, splenomegaly	Adenopathy

Splenic Marginal Zone Lymphoma

- Prominent splenomegaly: variable involvement of lymph nodes, bone marrow, peripheral blood, Splenic hilar lymph nodes and bone marrow are often involved
- lymphoma cells may be found in the peripheral blood as villous lymphocytes <1%
- Association with hepatitis C infection has been reported, although the prevalence ranges from 36% to less than 10%
- Abdominal discomfort due to splenomegaly
- Modest cytopenias that are primarily due to splenic sequestration (less marrow infiltration).
- Typically diagnose on BM, may need splenectomy
- Intergruppo Italian Linformi 309 patients, 5-year cause-specific survival 76%.

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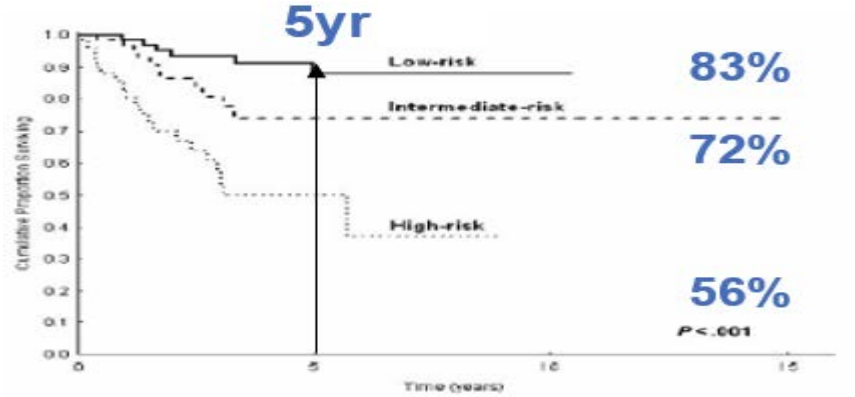
SMZL : LDH Hb=12 Albumin

SMZL score : 0 factor / 1 F / ≥ 2 F = IIL score

	OS p
Hemoglobin 12g/dl	0.05
LDH	0.008
Albumin	<0.001

Arcaini L. et al. 2006



CSS of 233 patients with splenic MZL

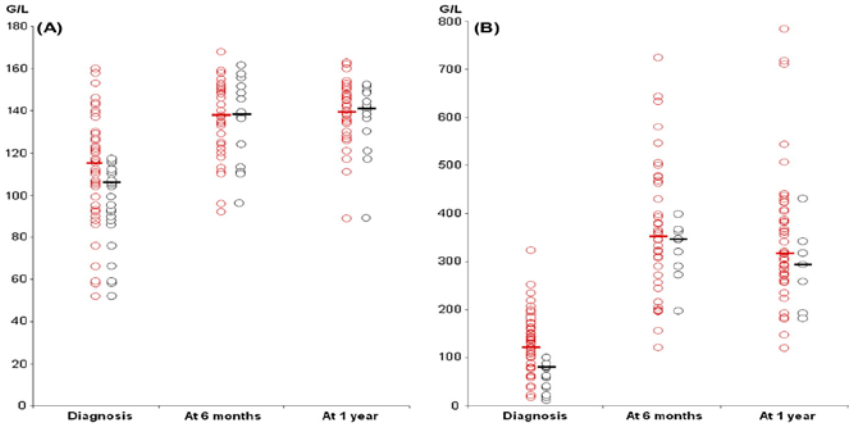
Many asymptomatic at diagnosis…watch and wait

If associated with HCV, then treat. May induce remission

More common HCV neg. Initiate therapy when nodal disease bulky, patient symptomatic or cytopenias

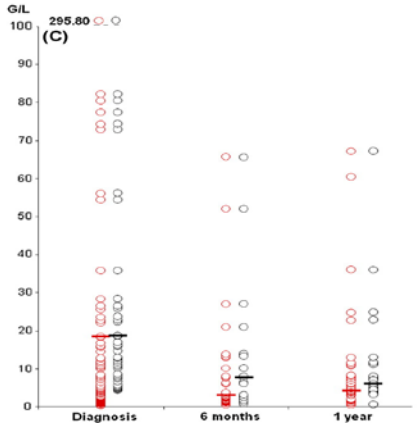
…..Splenectomy

Haemoglobin



Platelets

Lymphocytes



- Clearly improves haematological parameters
- Symptomatic improvement
- Associated morbidity

Lenglet et al 2014

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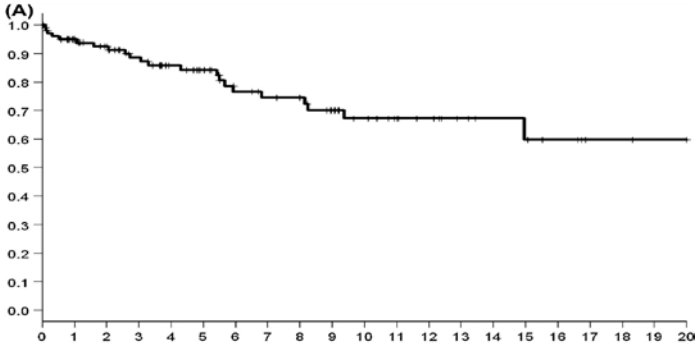
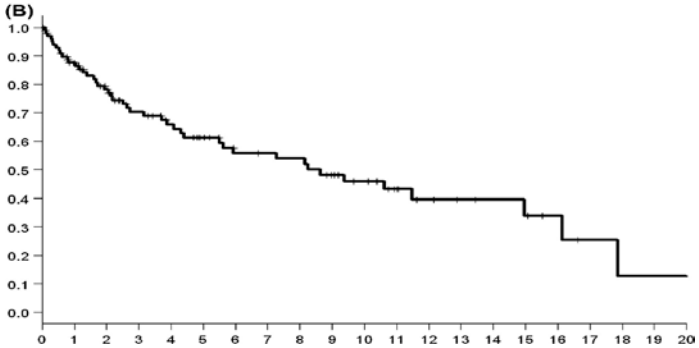
OS



PFS



	PFS	OS
5 year	61%	84%
10 year	46%	67%

Lenglet et al 2014

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Rituximab

Response	No. of Patients (%)			Total (n = 43)
	Rituximab (n = 26)†	Chemoimmunotherapy (n = 6)‡	Chemotherapy (n = 11)	
CR	8 (31)	1 (17)	2 (18)	11 (26)
Cru	3 (12)	1 (17)	0	4 (9)
PR	12 (46)	3 (50)	4 (36)	19 (44)
CR, CRu, and PR	23 (88)	5 (83)	6 (55)	34 (79)

Tsimberidou et al. 2006

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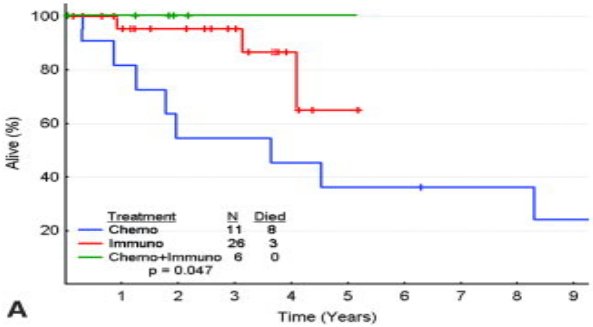
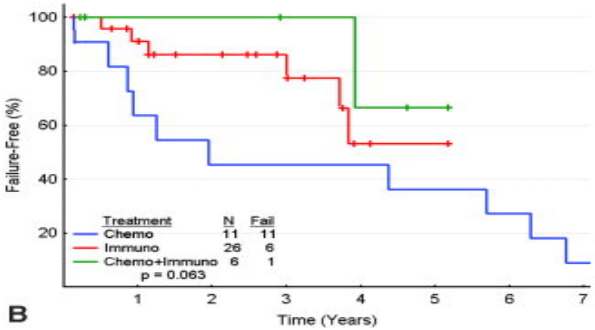
Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone

OS



FFS



Cancer
Volume 107, Issue 1, pages 125-135, 12 MAY 2006 DOI: 10.1002/cncr.21931
http://onlinelibrary.wiley.com/doi/10.1002/cncr.21931/full#fig3

Authors	Schedule	n	Status of disease	Response Rate	CR /CRu	PR	PFS (At n years)	OS (At n years)
Rituximab alone								
Tsimberidou et al. 2004	R once/W x 4 or 8	26	1rst line	88%	43%	46%	86% (3y)	95% (3y)
Kalpadakis et al. 2007	R once/W x 6	16	1rst line	100%	79%	11%	92% (2.1y)	100% (3y)
Bennett et al. 2005	R once/W x 4	14	1rst line	78%	57%	21%	60% (6y)	80% (6y)
Kalpadakis et al. 2013	R once/W x 6	85	1rst line	95%	71%	24%	92% (5y)	73% (5y)
Rituximab and Chemotherapy								
Tsimberidou et al. 2004	R-FMD or RFC	6	1rst line	83%	34%	50%	100% (3)	100% (3)
Arcaini et al. 2004	R-CVP	3	1rst line	100%	-	-	100% (1.3)	100% (1.3)
Cervetti et al. 2004	2-Cda	50	1rst line or relapsed	63%	62%	-	83% (2)	NA

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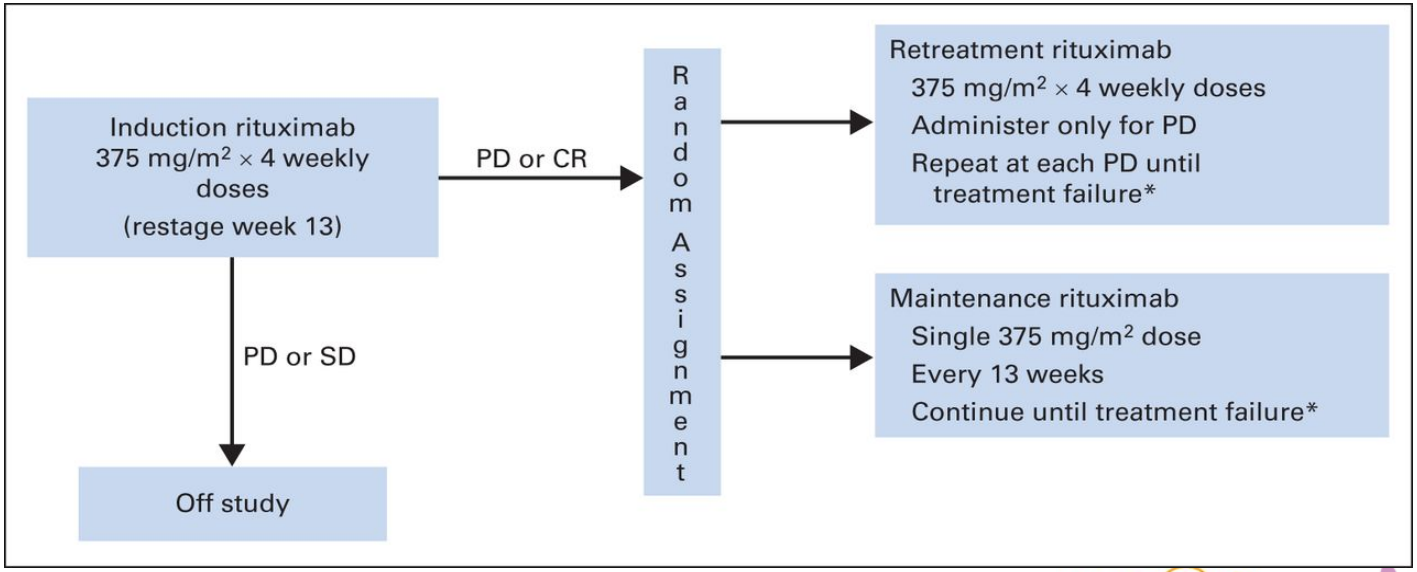
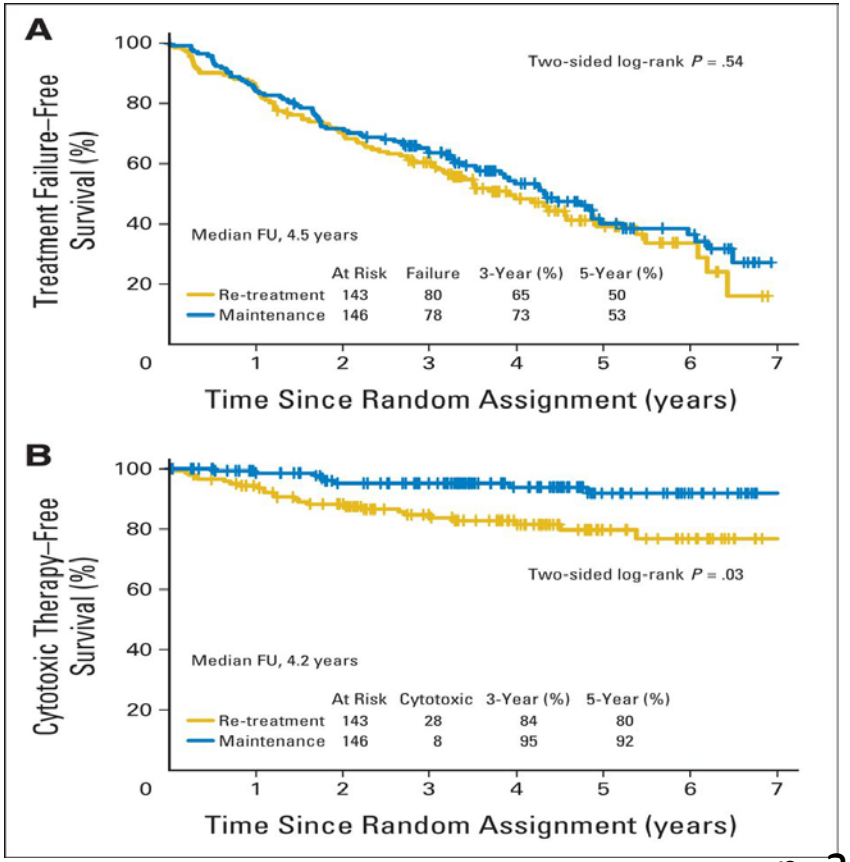
RESORT trial

Rituximab Extended Schedule or Re-Treatment Trial

N=289. Previously untreated low burden



Brad S. Kahl et al. JCO **2014;32:3096-3102**



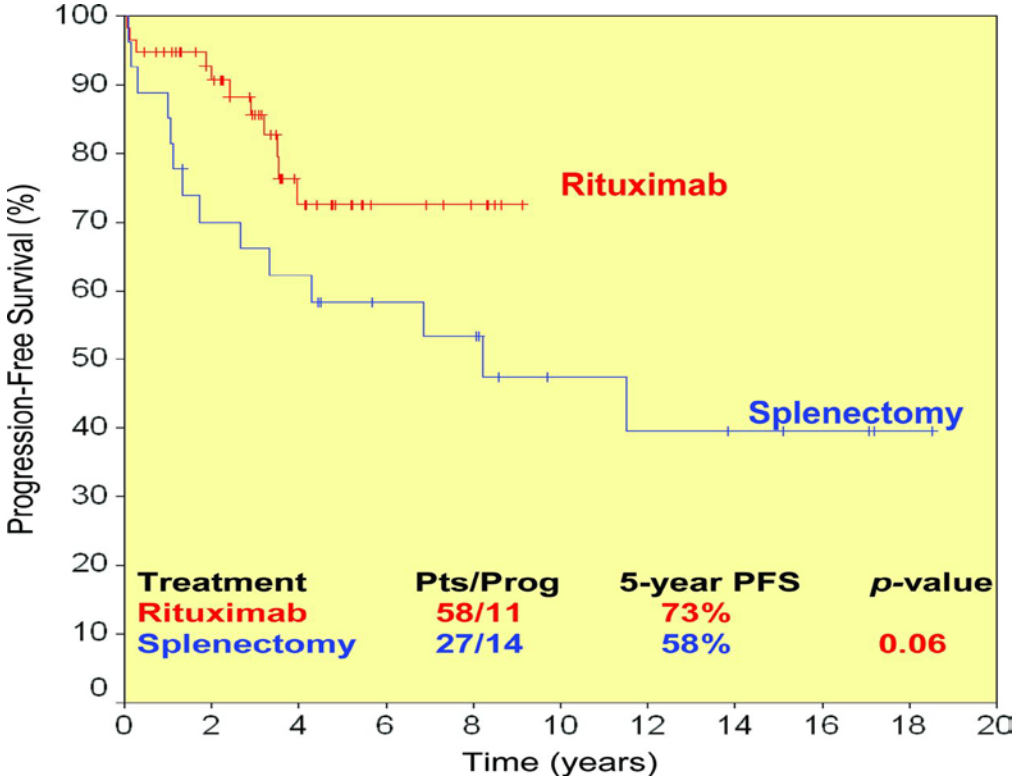
Time to treatment failure

Time to first cytotoxic therapy

n=298

Brad S. Kahl et al. JCO 2014;32:3096-3102

Progression-free survival (PFS) probability in rituximab-treated (red line) and splenectomized patients (blue line) after 5 years.



Christina Kalpadakis et al. The Oncologist 2013;18:190-197

So…first line rituximab…

Maintenance rituximab can be considered, but not standard of care

Splenectomy for poor responders and relapse

Patient specific discussion

Nodal MZL

- <2% NHL median age 60
- Upto 30% have Hep C + serology (variable)
- Generalised asymptomatic LN;
- BM in 30-60%..exclude dissemination of ENMZL
- Few therapeutic trials – same principles as other ‘indolent’ lymphomas..watch and wait
- 60-80% alive at 5 years

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BR vs. R-CHOP as First Line Treatment in Patients with Indolent and Mantle Cell Lymphomas (MCL): Updated Results from the StiL NHL1 Study

Eligible patients:

- CD20-postiive FL, WM, MZL, SLL, MCL (elderly)
- No previous treatment
- Stage III or IV

(n = 549)

RANDOMISE

Bendamustine-Rituximab (BR)

Bendamustine 90 mg/m² days 1-2
Rituximab 375 mg/m² day 1

CHOP-Rituximab (R-CHOP)

Cyclophosphamide 750 mg/m² day 1
Doxorubicin 50 mg/m² day 1
Vincristine 1.4 mg/m² day 1
Prednisone 100 mg/days days 1-5
Rituximab 375 mg/m² day 1

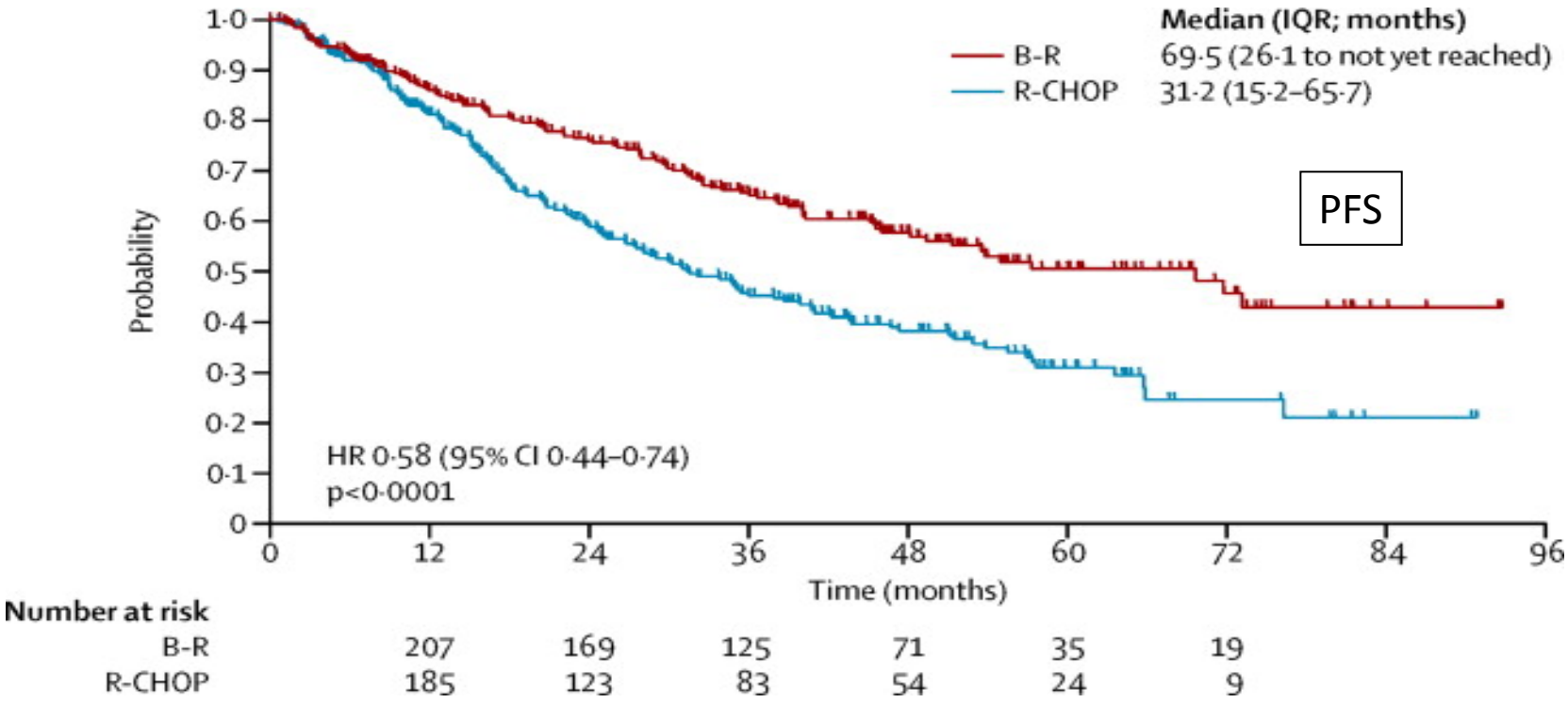
Primary objective

- **To prove the non-inferiority of BR vs. R-CHOP defined as a decrease of < 10% in progression-free survival (PFS) after 3 years**

Secondary objectives

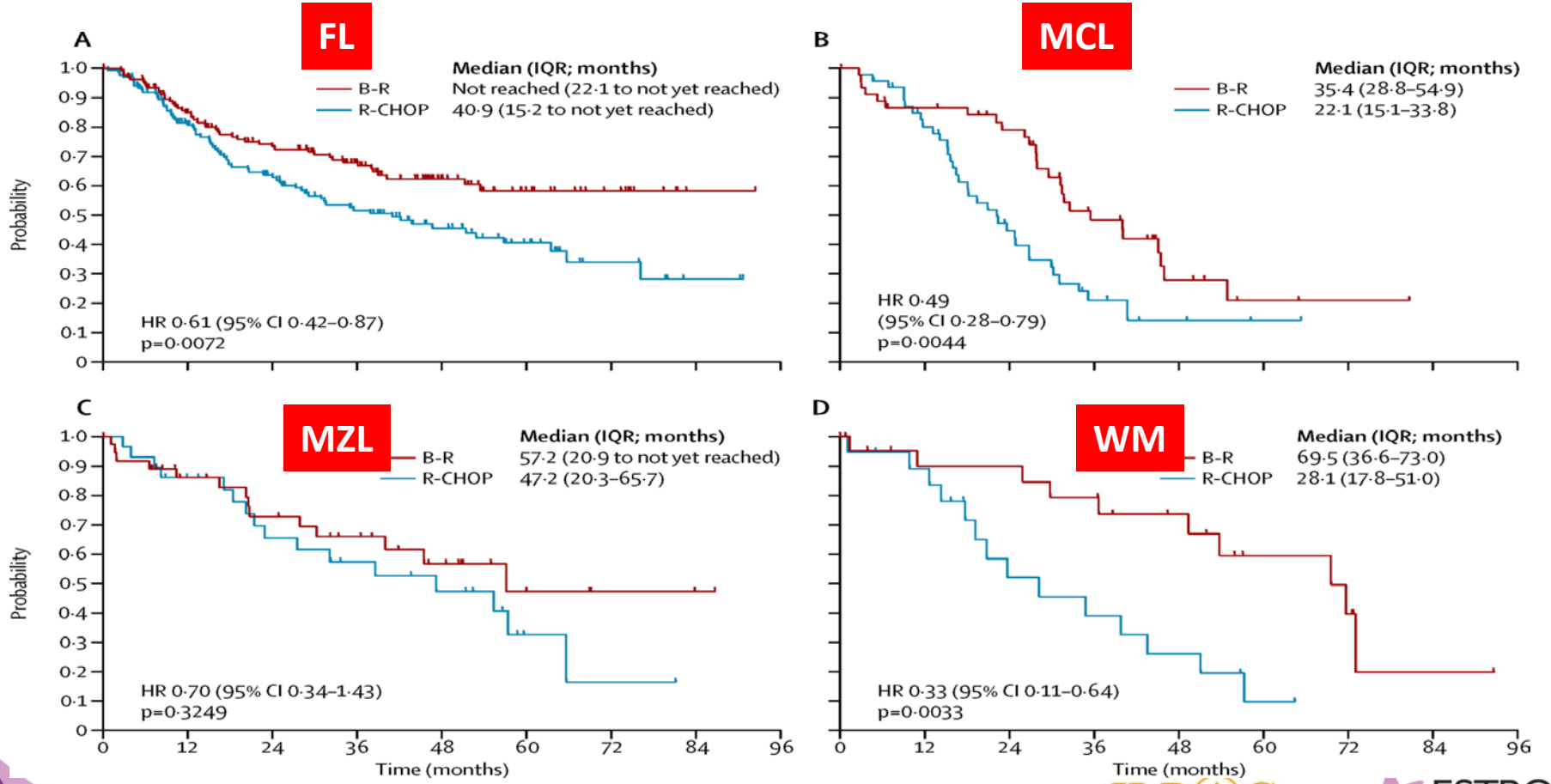
- **Time to next treatment (TTNT), event-free survival (EFS), overall survival (OS)**
- **Acute and late toxicities, infectious complications**
- **Stem cell mobilization capacity in younger patients**

StiL Study



No difference in OS

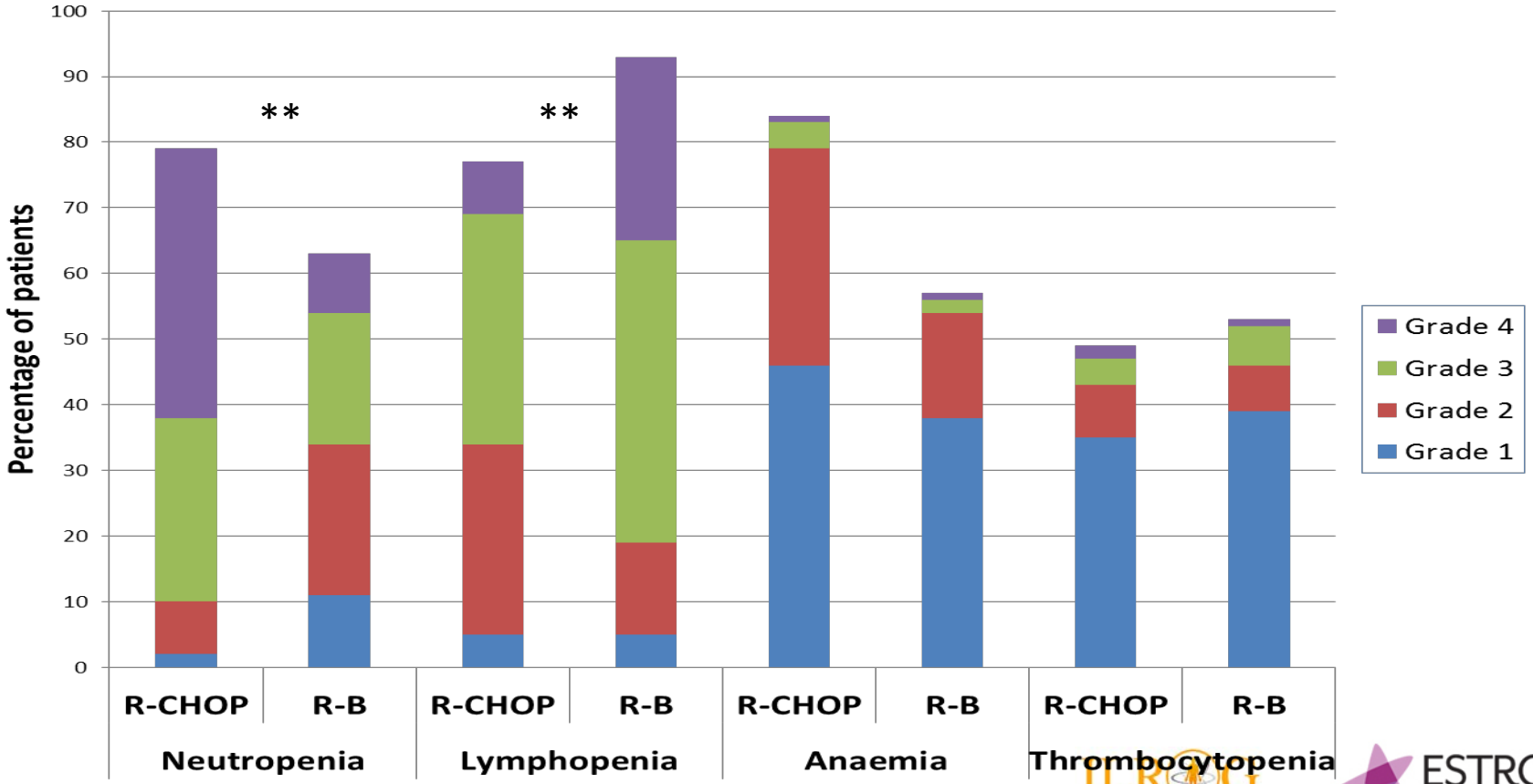
Rummel et al Lancet April 2013



Progression Free Survival

Rummel et al. Lancet 2013

Haemtological toxicity



** P<0.0001 for grade 3/4

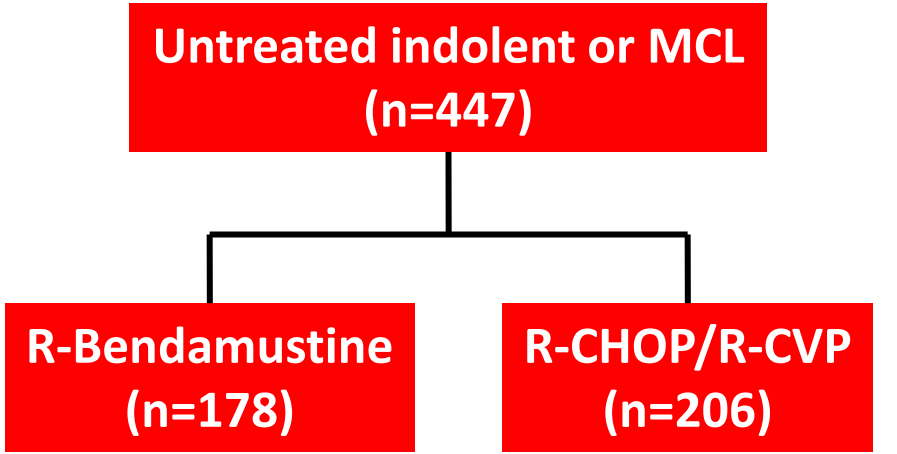
Rummel et al Lancet April 2013

Non-haematological toxicity

	B-R (n=261)	R-CHOP (n=253)	p value
Alopecia	0	245 (100%)*	<0·0001
Paresthesia	18 (7%)	73 (29%)	<0·0001
Stomatitis	16 (6%)	47 (19%)	<0·0001
Skin (erythema)	42 (16%)	23 (9%)	0·024
Skin (allergic reaction)	40 (15%)	15 (6%)	0·0006
Infectious episodes	96 (37%)	127 (50%)	0·0025
Sepsis	1 (<1%)	8 (3%)	0·019

Rummel et al Lancet April 2013

The BRIGHT STUDY

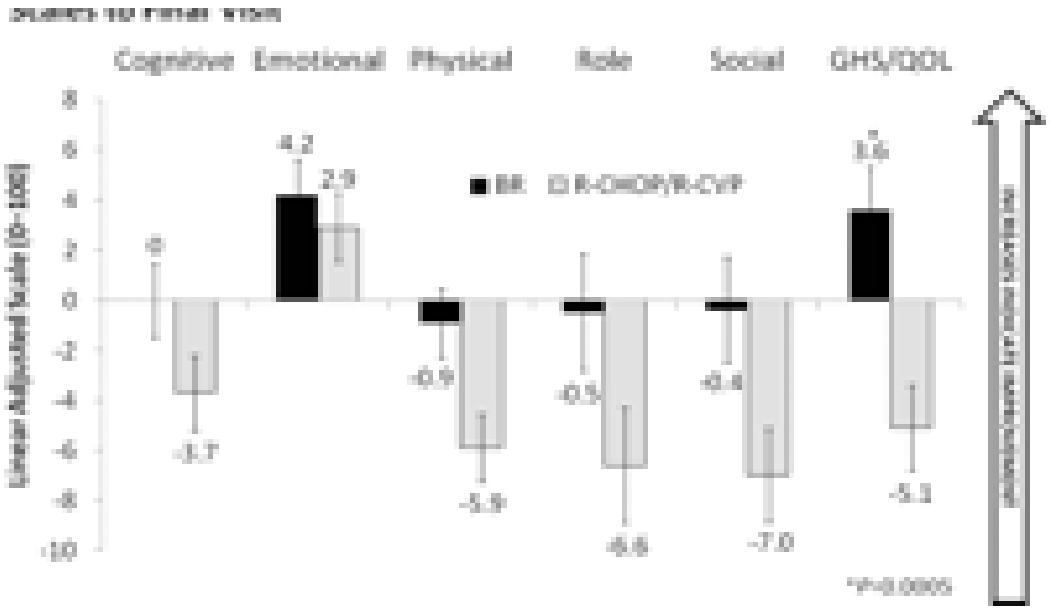


Powered for non-inferiority in CR rate

CR rate	R-B	R-CHOP/ R-CVP	Ratio	*P* (s
Evaluable, IRC	31%	25%	1.25 (0.93–1.73)	0.0225
Randomized, IRC NHL	27%	23%	1.16 (0.81–1.65)	0.1289
Randomized IRC MCL	51%	24%	1.95 (1.01–3.77)	0.0180

Flinn et al ASH 2012

Quality of life….



Burke et al ASH 2012

BR significantly improved GHS/QOL, compared with R-CHOP/R-CVP

BR provided improved patient QOL scores for most aspects of functioning and symptoms, as measured by the QLQ-C30

Extranodal MZL

- Can arise in virtually every tissue
- Chronic antigen stimulation
- Impressive results with H. pylori eradication in gastric…reasonable impressive outcomes in occular adnexal and HCV management
- Systemic therapies traditionally reserved for local treatment failure or advanced stage

Involved organ	Targeted pathogen	Antibiotic regimen	Type of study	Patients (n)	Overall lymphoma remission rate
Stomach	H. pylori	Mostly proton pump inhibitor plus clarithromycin-based triple therapy with either amoxicillin or metronidazole for 10–14 days	>30 studies either retrospective or prospective	>1,400	~75%
Ocular adnexa	C. psittaci	Doxycycline, 100 mg twice a day × 21 days	2 prospective, 4 retrospective, 1 case report	120	48%
Skin	B. burgdorferi	Ceftriaxone, 2 g/day ×14 days (in most cases)	Case reports	5	40%
Various (also including nodal and splenic MZL)	HCV	IFN plus ribavirin	7 retrospective series and several case reports	>110	~75%

Zucca et al Clin Cancer Res 2014

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

Chemotherapy: IELSG 19

Response	Chl	R-Chl	R
ORR	110 (85%)	124 (95%)	104 (79%)
CR*	**80 (62%)**	**104 (80%)**	**73 (55%)**
PR	30 (23%)	20 (15%)	31 (23%)
SD	11 (8%)	1 (<1%)	15 (11%)
PD	7 (5%)	4 (3%)	9 (7%)
NA	2 (1.5%)	2 (1.5%)	4 (3%)

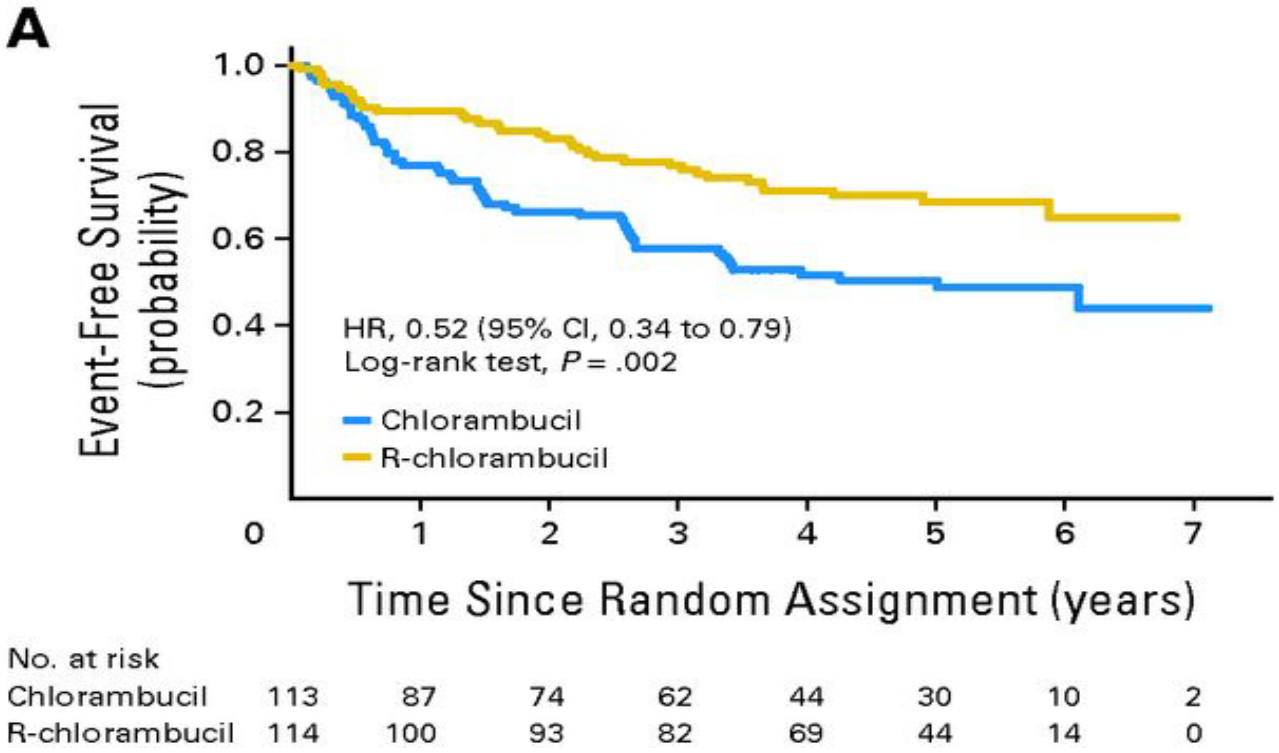
* R-Chl *vs.* Chl, P=0.001 R-Chl *vs.* R, P<0.001; Chl *vs.* R, P= 0.372

Emanuele Zucca et al. JCO 2013;31:565-572

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

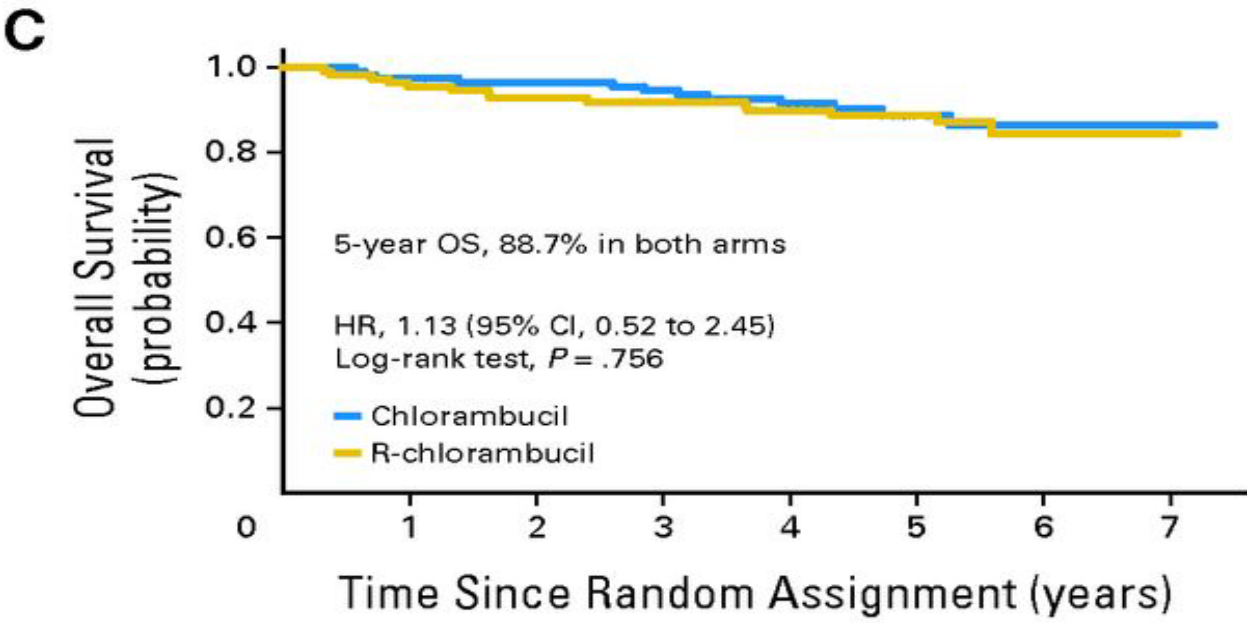
ESTRO School

Event-free survival



Emanuele Zucca et al. JCO 2013;31:565-572

Overall survival.



No. at risk								
Chlorambucil	113	110	107	100	79	49	18	3
R-chlorambucil	114	106	103	97	85	56	19	2

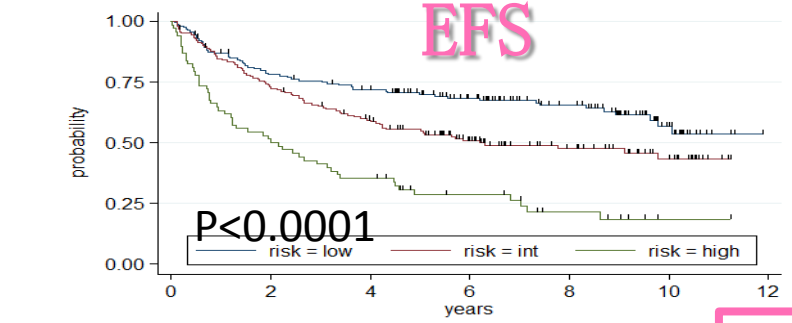
Emanuele Zucca et al. JCO 2013;31:565-572

MALT lymphoma : LDH, Age, Stage

MALT score : 0 factor / 1 F / ≥ 2

0 factor, n=167
1 factor, n= 164
2-3 factors n=68

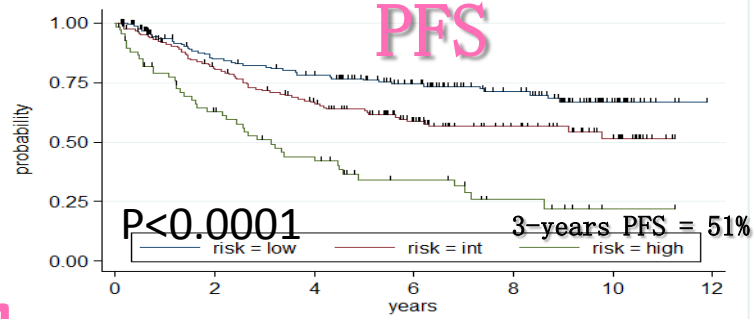
EFS



Number at risk

risk = low	167	126	112	84	57	20	
risk = int	164	119	92	59	34	16	
risk = high	68	35	24	14	7	1	

PFS

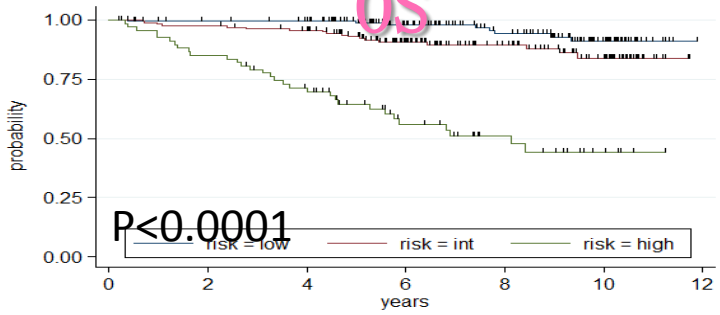


er at risk

isk = low	167	126	112	84	57	20	0
risk = int	164	120	93	60	35	17	0
sk = high	68	38	25	14	7	1	0

LDH >N
AGE >70
STAGE>2

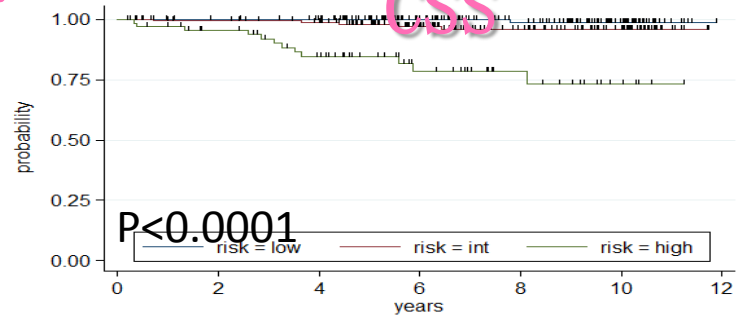
OS



Number at risk

risk = low	167	159	154	113	78	31	0
risk = int	164	159	150	96	61	31	0
risk = high	68	57	45	25	15	6	0

CSS

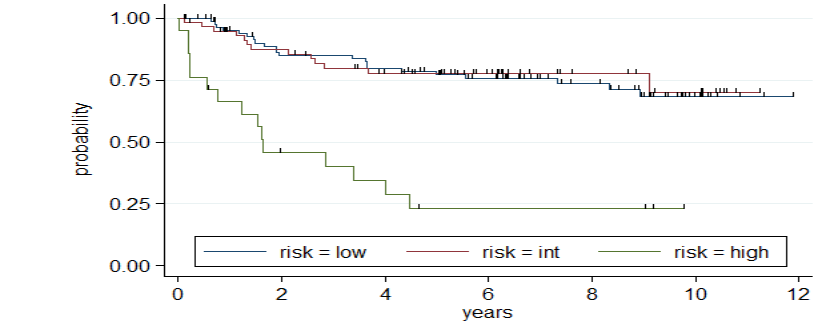


Number at risk

risk = low	167	159	154	113	78	31	0
risk = int	164	159	150	96	61	31	0
risk = high	68	57	45	25	15	6	0

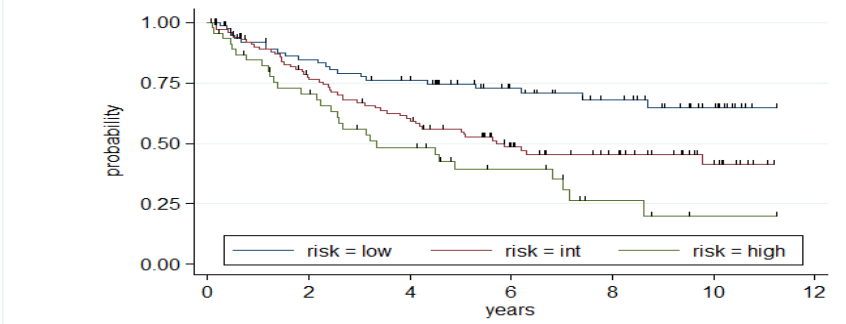
PFS by MALT prognostic score

gastric MALT



Number at risk							
risk = low	89	67	62	50	33	9	0
risk = int	60	47	37	26	12	8	0
risk = high	21	8	6	3	3	0	0

Non-gastric MALT



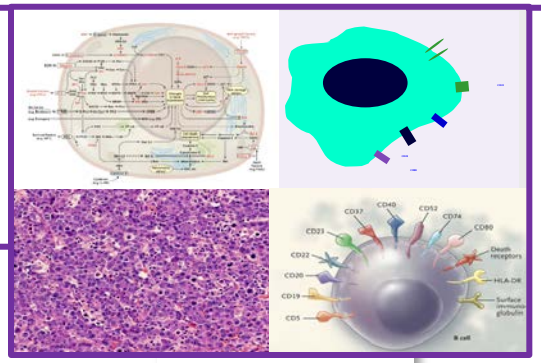
Number at risk							
risk = low	78	59	50	34	24	11	0
risk = int	104	73	56	34	23	9	0
risk = high	47	30	19	11	4	1	0

Microenvironment

- Lenalidomide
- T-cell exhaustion

Actionable mutations

- **EZH2** E7438
- **CD79a/b** AEB071



Pathways

- **Proteosome inhibitors** Bortezomib
- **PI3k inhibitor** idelalisib, copanlisib, duvelisib
- **Survivin inhibitors** YM155
- **Syk inhibitor** Fostamatinib
- **mTOR inhibitors** Everolimus, Temsirolimus
- **Bcl-2 family inhibitors** ABT-199
- **Btk inhibitor** Ibrutinib + others
- **Hsp 90 inhibitors** KW 2478

Surface markers

- **Anti CD20 moAb** Ofatumumab, GA-101
- **Anti CD40 moAb** Dacetuzumab
- **Anti CD22** Epratuzumab, Inotuzumab Ozogamicin, polatuzumab
- **HDAC inhibitors** Vorinostat, Panobinostat
- **PKC inhibitors** Enzastaurin
- **Aurora kinase inhibitors**
- **Nedd8-activating enzyme inhibitor** MLN4924

Microenvironment

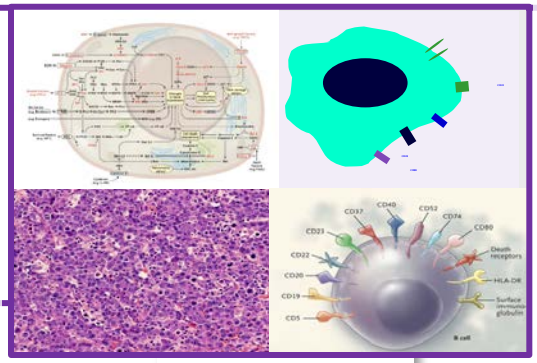
Lenalidomide

T-cell exhaustion

Actionable mutations

EZH2
E7438

CD79a/b
AEB071



Surface markers

Anti CD20 moAb
Ofatumumab
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Anti CD40 moAb
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Anti CD22
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Inotuzumab Ozogamicin
polatuzumab

Pathways

Proteosome inhibitors
Bortezomib

Bcl-2 family inhibitors
ABT-263

Survivin inhibitors
YM155

Syk inhibitor
Fostamatinib

mTOR inhibitors
Everolimus
Temsirolimus

PI3k inhibitor
GS1101
BAY80

Btk inhibitor
Ibrutinib + others

Hsp 90 inhibitors
KW 2478

HDAC inhibitors
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Panobinostat

PKC inhibitors
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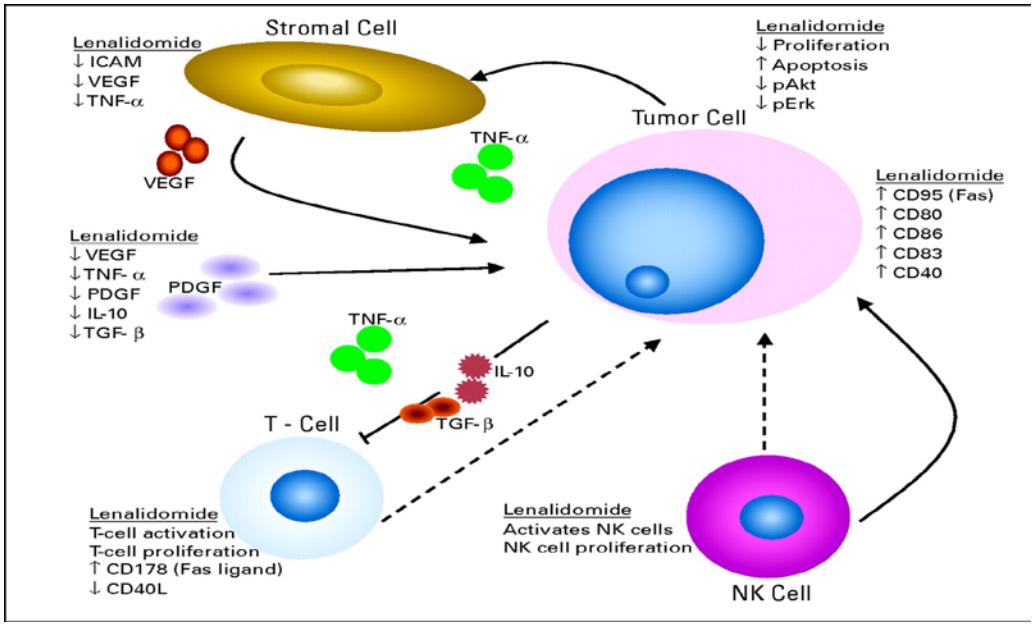
MLN4924

Lenalidomide

- Immunomodulatory properties
- Modulation of both cellular and cytokine tumour cell microenvironment
- Activates T cell and NK response to tumour cell
- Down regulates pro-survival cytokines
- Approval in myeloma



Chanan-Khan, A. A. et al. J Clin Oncol; 26:1544-1552 2008

The R^2 regimen (Fowler at al. Lancet Oncol 2014)

- Preclinical data suggests that lenalidomide may augment immune effector function and enhance rituximab mediated ADCC
- Previously untreated advanced stage ‘indolent lymphoma’

Lenalidomide	20mg po	Day 1-21 q28
Rituximab	375mg iv	Day 1
6 cycles. Responders continued to 12 cycles		

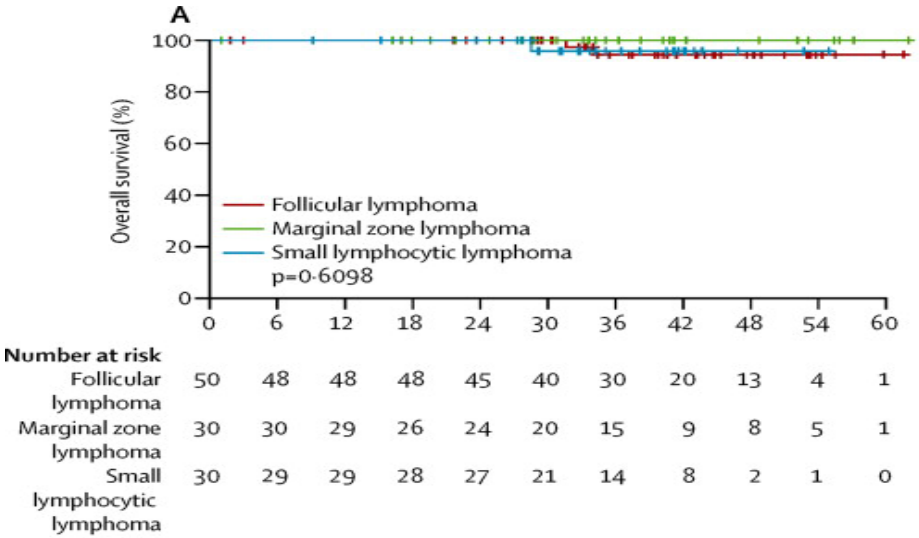
- n=110 (103 pts. evaluable) 57% GELF criteria for high tumour burden

Chanan-Khan, A. A. et al. J Clin Oncol; 26:1544-1552 2008

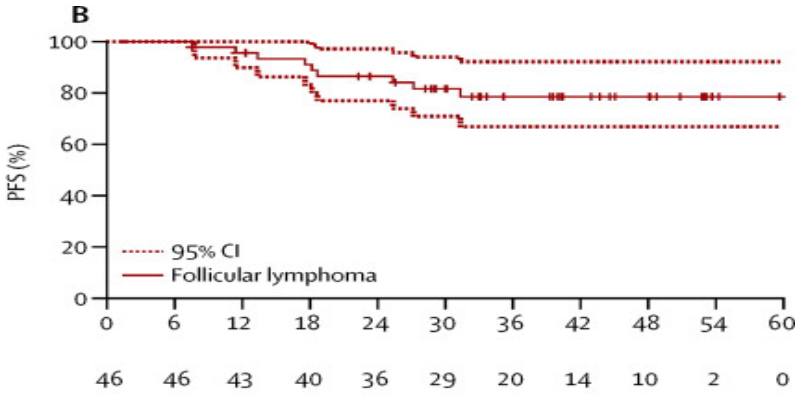
%	ORR	CR/CR(u)	PR	SD	PD
Follicular (n=46)	98	87	11	2	0
Small lymphocytic (n=30)	80	27	53	13	7
Marginal zone (n=27)	89	67	22	11	0
All (n=103)	**90**	**64**	**26**	**8**	**2**

Fowler et al Lancet Oncol 15 (12), 2014, 1311-1318

Overall survival



Progression-free survival: Follicular lymphoma



Fowler et al Lancet Oncol 15 (12), 2014, 1311-1318

Toxicity of R^2

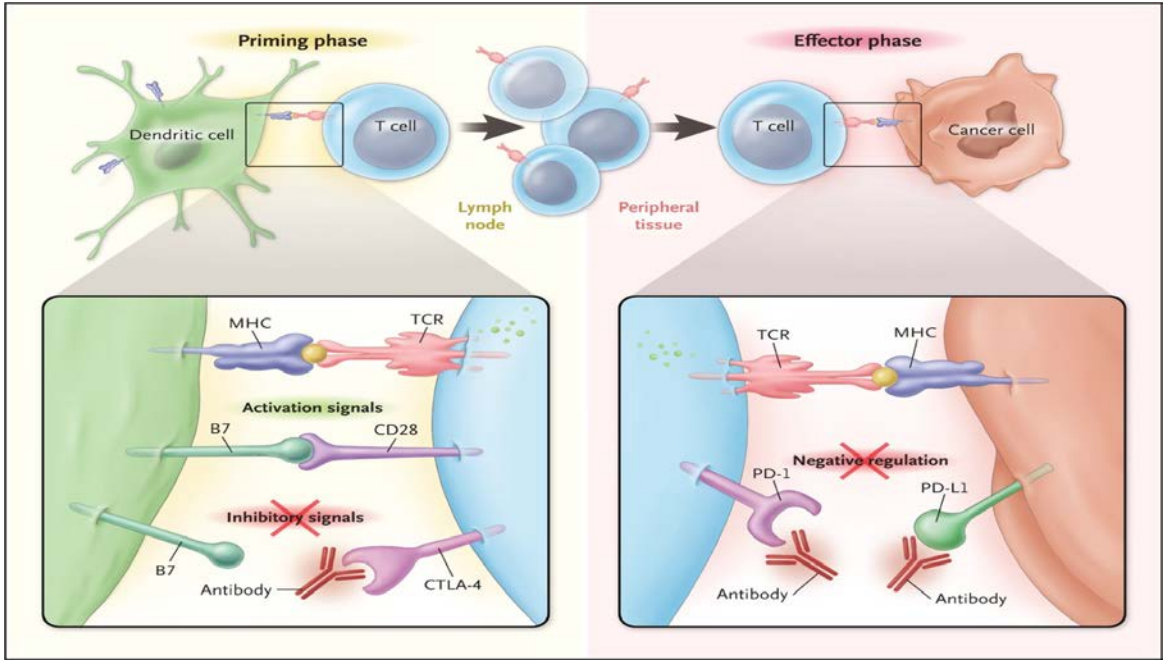
	Grade >3
Neutropenia	40%
Thrombocytopenia	4%
Rash	7%
Muscle pain	6%
fatigue	3%
VTE	3%

Fowler et al Lancet Oncol 15 (12), 2014, 1311-1318

Long term???

Exhausted T-cells

- Blocking immune checkpoints may promote endogenous antitumour activity
- PD1: Inhibitory receptor on activated T-cells, B-cells, NK and myeloid cells. Inhibition of T-cell activation when engaged by ligands (PDL1/2)
- PD1 expressed on T-cells when exposed to tumour, and associated with exhaustion. Blocking can restore function



Ribas A. N Engl J Med 2012;366:2517-2519.

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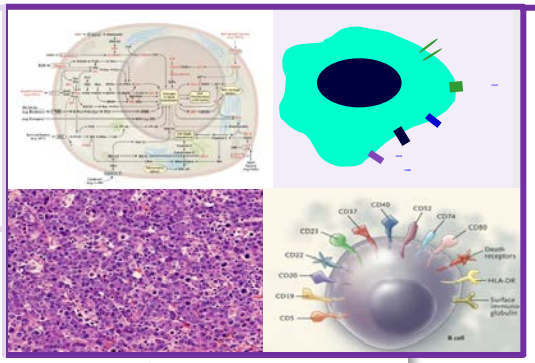

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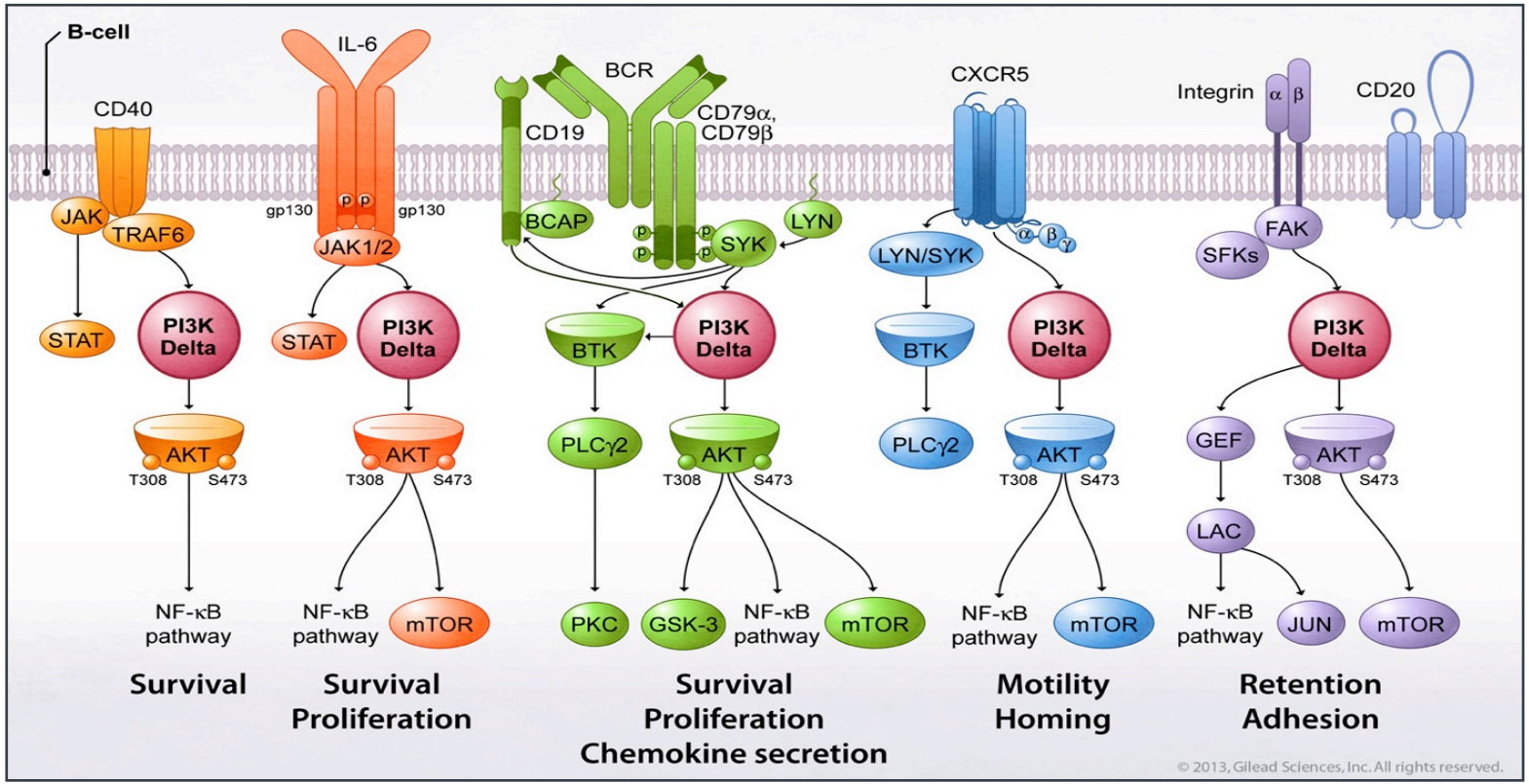
- **Nedd8-activating enzyme inhibitor**: MLN4924

PI3Kδ Inhibition Impacts Multiple Critical Pathways in iNHL



Idelalisib is highly selective for PI3Kδ isoform

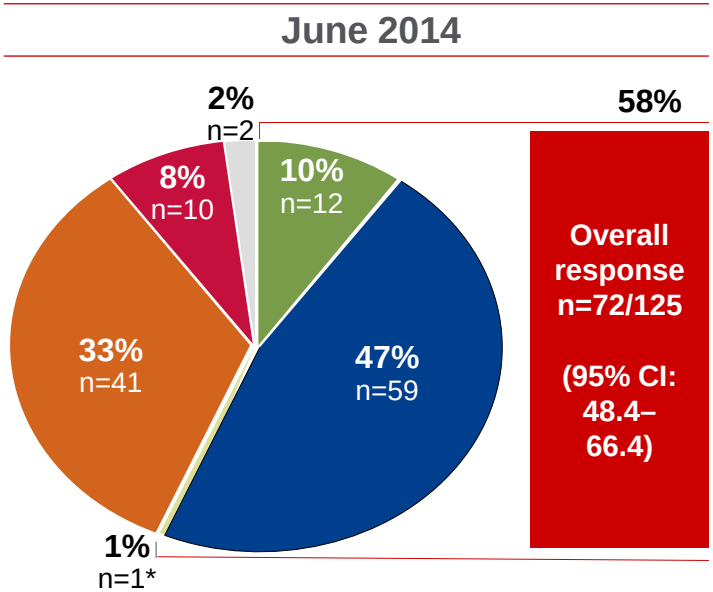
Class I PI3K isoform[1]

Expression	Ubiquitous	Ubiquitous	Leukocytes	Leukocytes
EC_{50} nM	>20,000	1900	3000	8

- Promising activity in relapsed / refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) in a Phase I study[2]

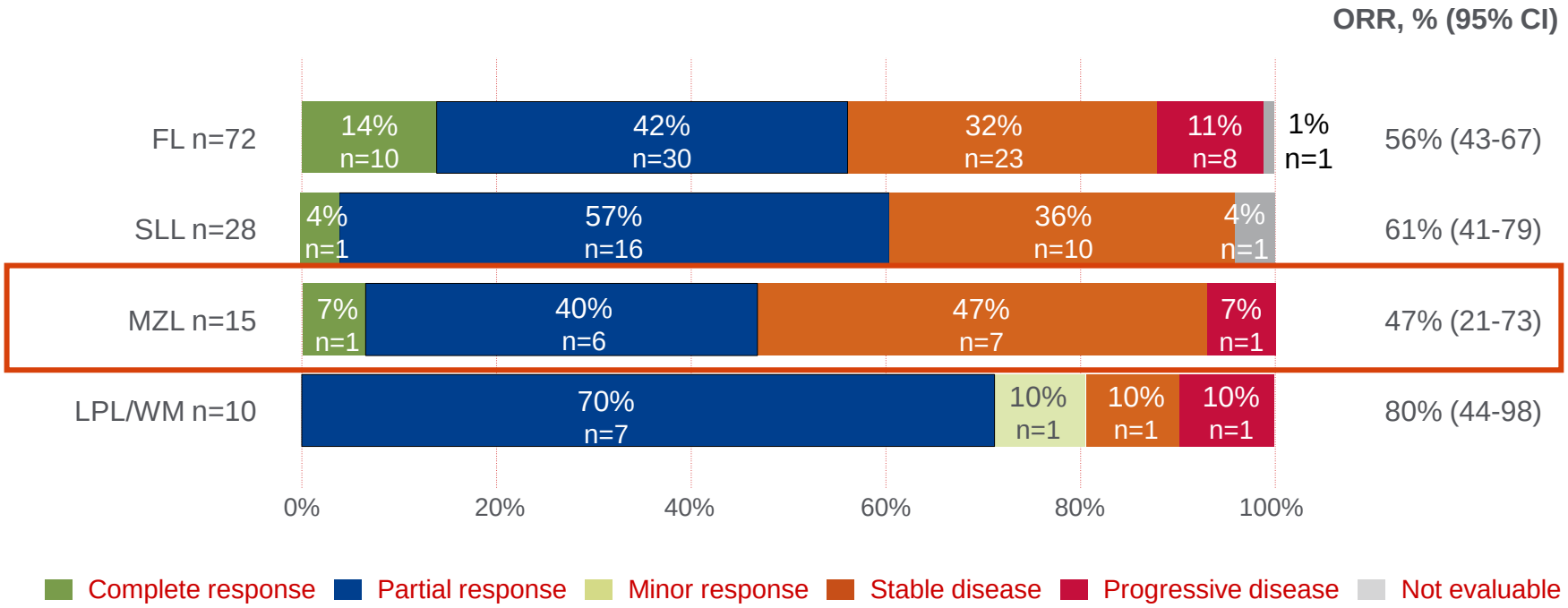
1. *Lannutti BJ, et al. Blood 2011;117:591-4;*
2. *Flinn IW, et al. Blood 2014;123:3406-13*;

Overall response rate: 09 study



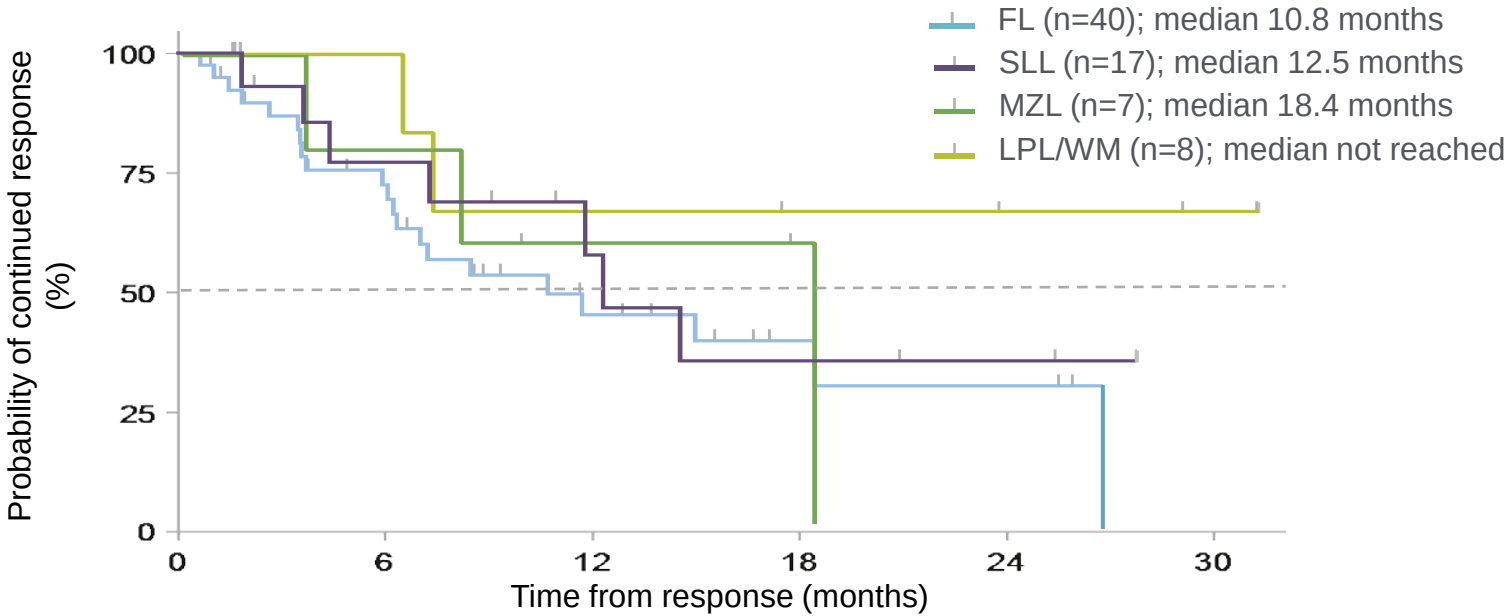
*LPL/WM patient

Overall response rate by disease subgroups*



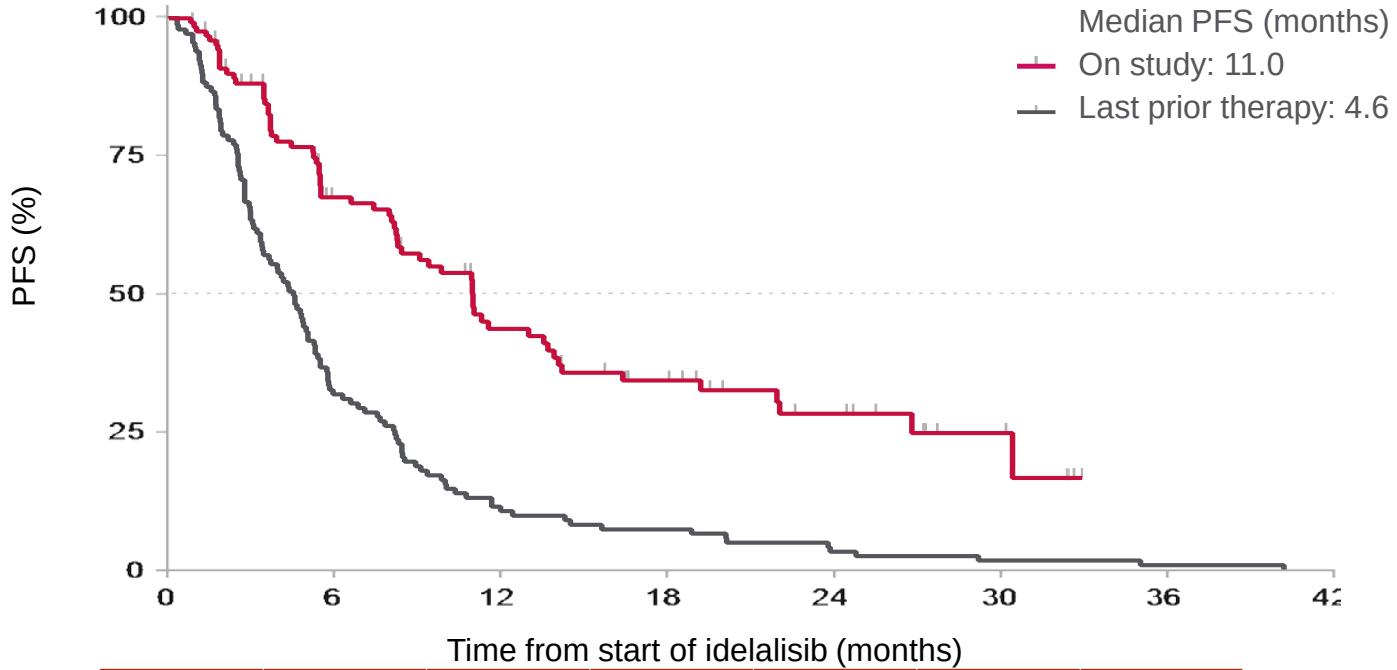
*2014 data

Duration of response by disease group



Patients at risk, n						
40	24	10	4	3		
17	9	5	3	2		
7	4	2	1			
8	6	4	3	2	1	

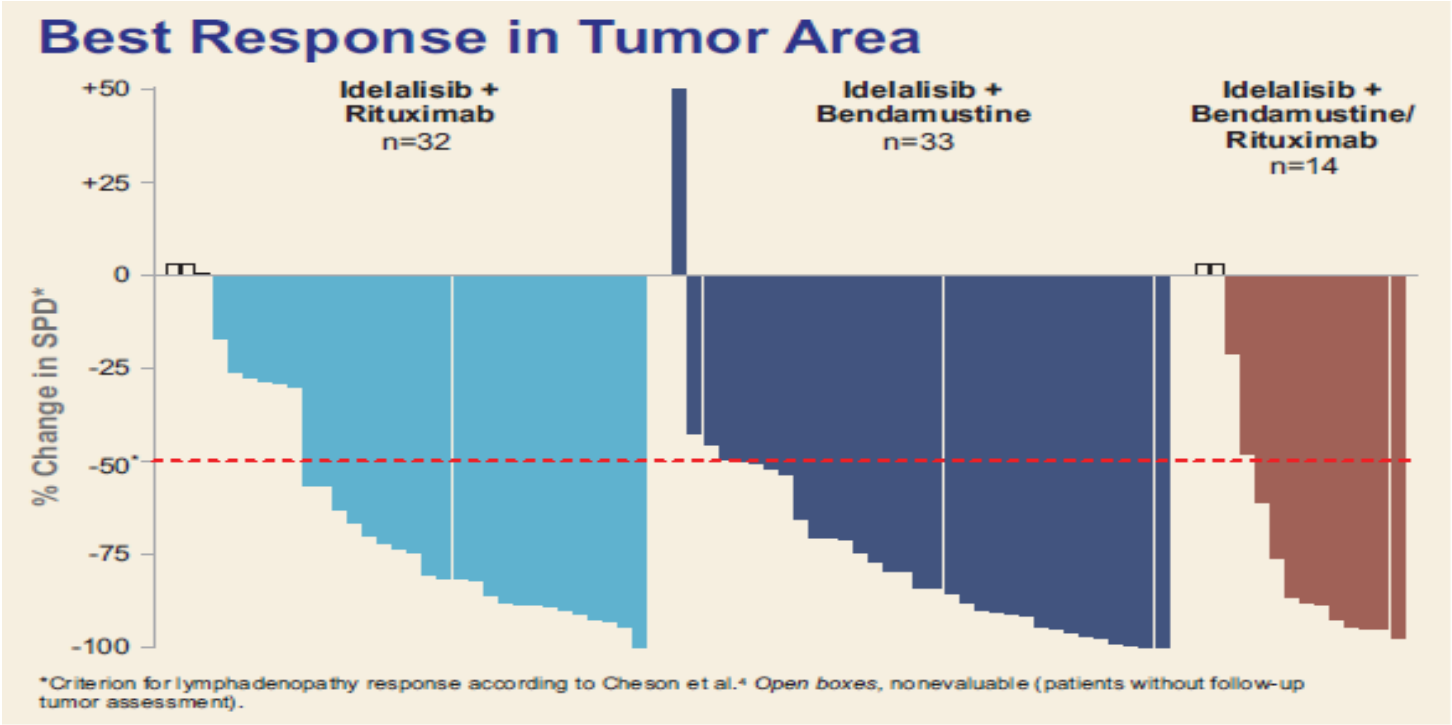
PFS: On study vs. last prior therapy



Patients at risk, n							
	125	60	33	22	12	4	
	125	40	14	9	5	2	1

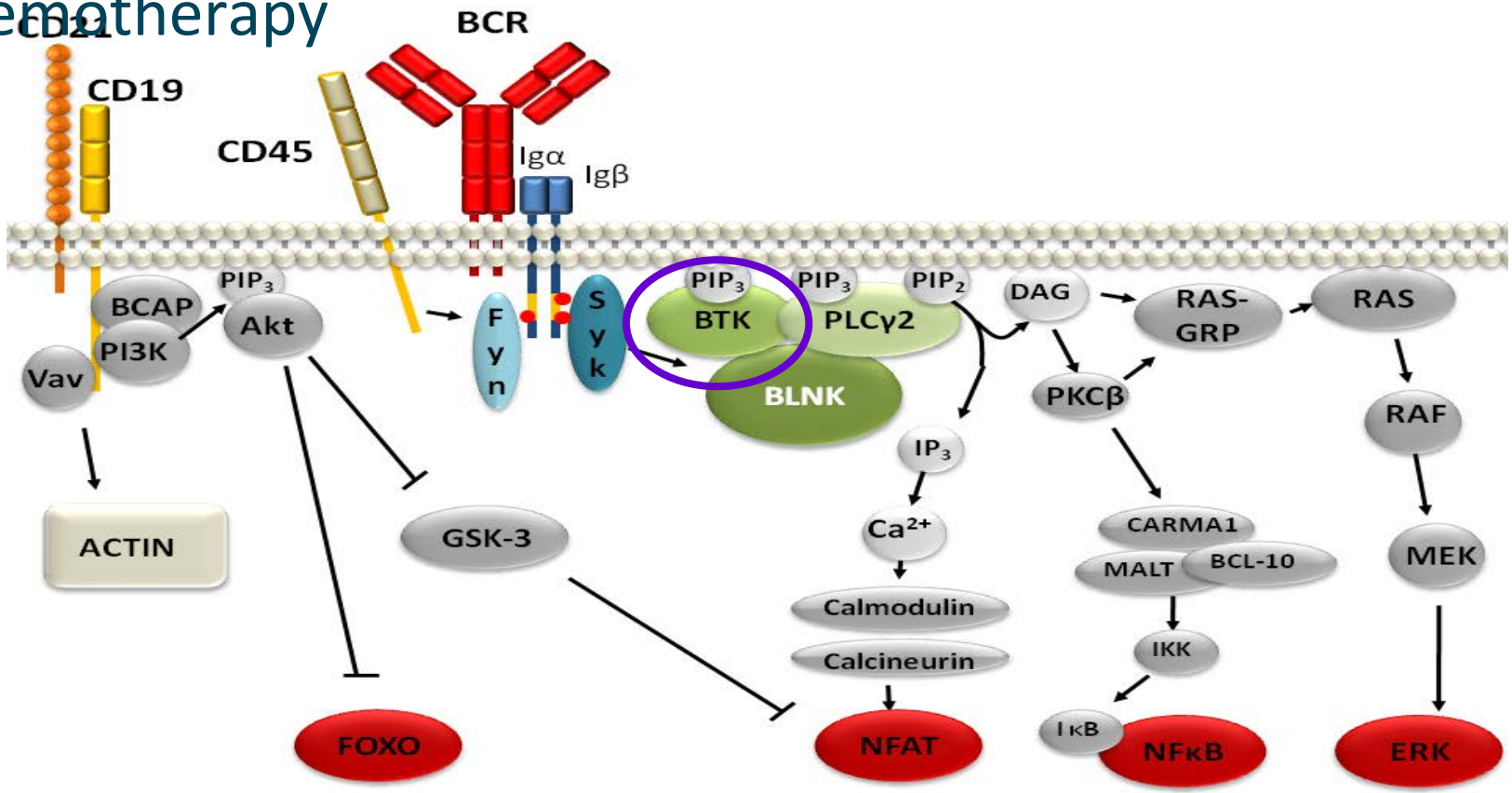
Adverse events occurring in >12% of patients

AE, n (%)	Any grade	Grade ≥3
Diarrhoea/colitis	63 (50)	24 (19)
Cough	40 (32)	0
Nausea	39 (31)	2 (2)
Fatigue	38 (30)	2 (2)
Pyrexia	38 (30)	4 (3)
Dyspnoea	23 (18)	6 (5)
Decreased appetite	23 (18)	1 (1)
Abdominal pain	21 (17)	3 (2)
Upper respiratory infection	21 (17)	0
Vomiting	20 (16)	3 (2)
Decreased weight	19 (15)	0
Night sweats	18 (14)	0
Pneumonia	18 (14)	15 (12)
Rash	17 (14)	2 (2)
Asthenia	16 (13)	4 (3)
Headache	16 (13)	1 (1)

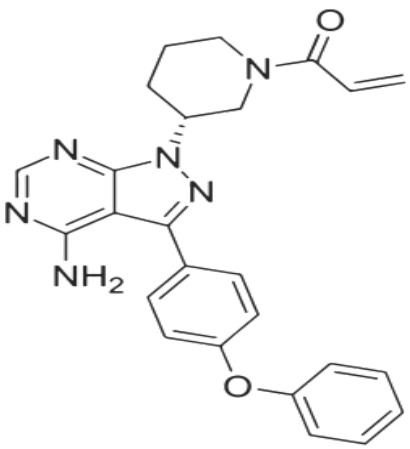


de Vos et al ASH 2014

B-cell receptor signalling. ..Inhibit and spare the chemotherapy



Ibrutinib: Mechanism of action



Chemical structure of ibrutinib [4]

Interactions between the tumour microenvironment and malignant B cells play an important role in B-cell homing, adhesion and migration through activation of intracellular pathways in the B cells.[1,2]

BTK's pivotal role in signalling through B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis and adhesion.[3]

Covalent binding in ATP pocket of BTKL….believed to disrupt key malignant processes and:[3,4]

- Induce apoptosis; Inhibit adhesion (may lead to lymphocytosis)

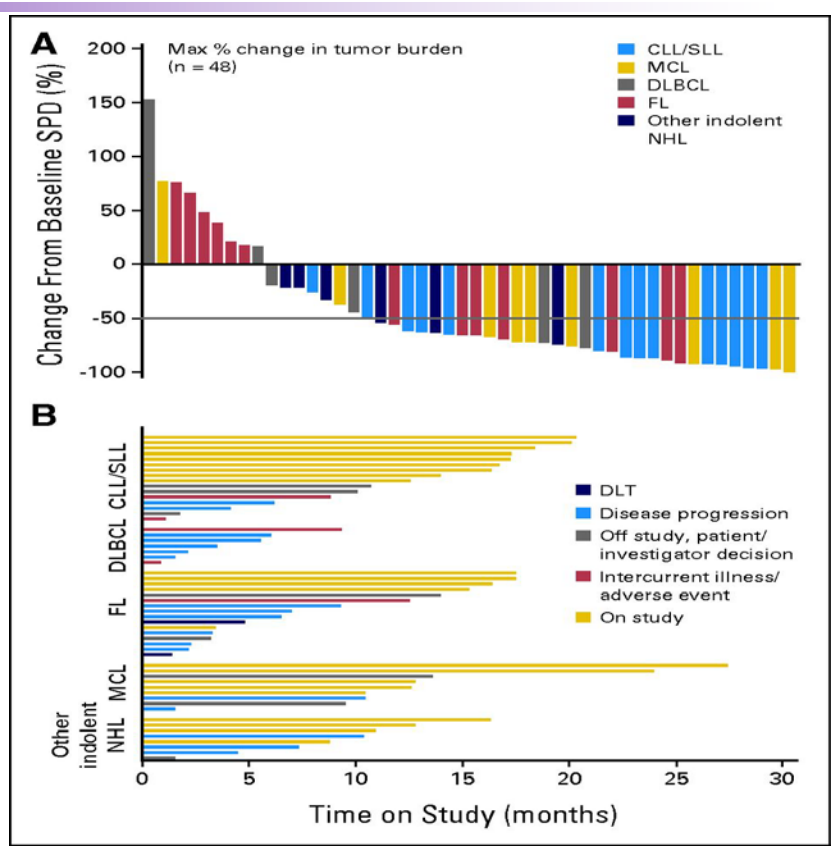
1. de Gorter DJJ, et al. Immunity 2007;26:93-104. **2.** Burger JA, et al. Bloo
2. d 2009;114:3367-3375. **3.** Buggy J et al. Int Rev Immunol 2012; 31:119-132. **4.** Chavez J, et al. Core Evid 2013; 8:37-45.

Ibrutinib in B-cell lymphoma

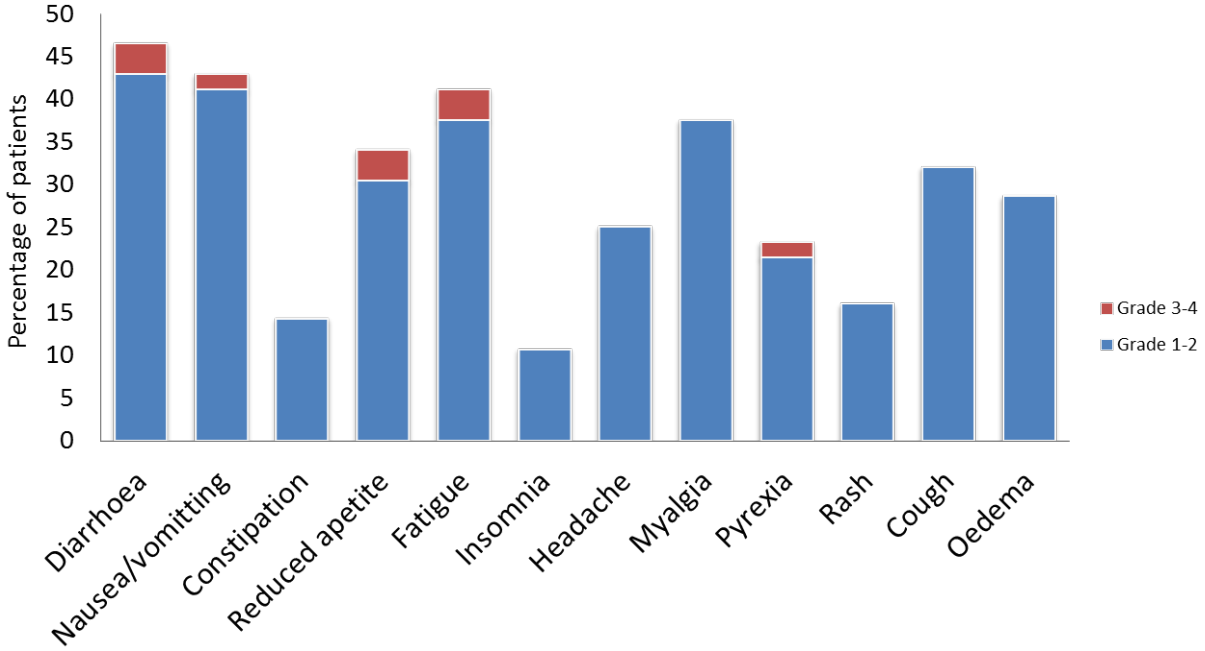
	Responders (n/N)
Mantle cell	7/9
CLL/SLL	11/16
FL	6/16
DLBCL	2/7
WM	3/4
ORR	**60%**

N=56. Median 3 (1-10) prior therapies

Advani R H et al. JCO 2013;31:88-94



Toxicity



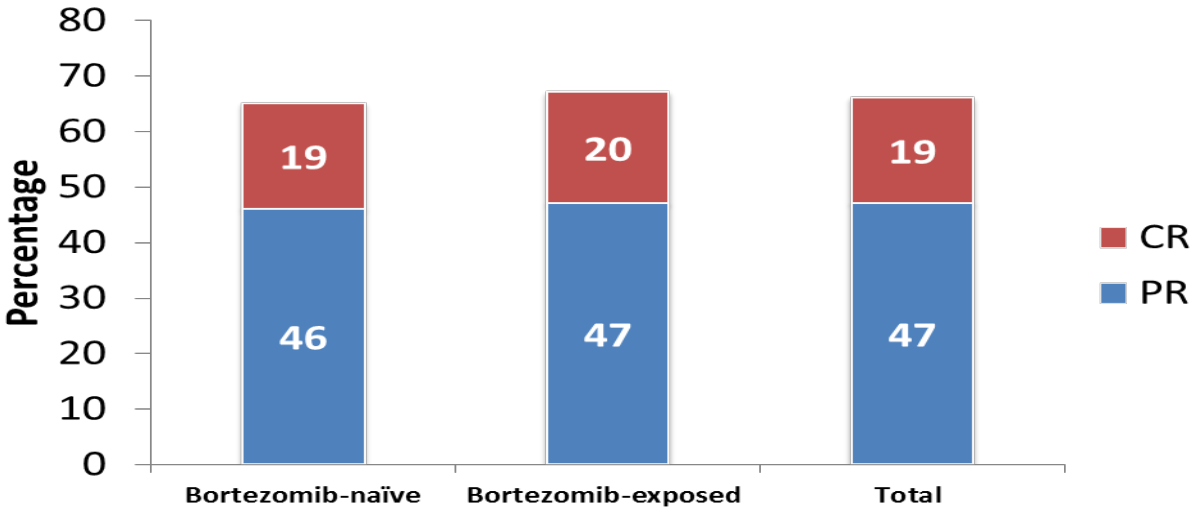
Grade ≥3 haematological toxicity:
Neutropenia 13%, thrombocytopenia 7%;
anaemia 7%
No decrease in Igs

Advani R H et al. JCO 2013;31:88-94

Ibrutininb in Mantle cell

115 pts with MCL (bortezomib-naïve n=65; bortezomib-exposed n=50); median age 68; median 3 (1-6) prior therapies;
44% refractory

17.5 months estimated median response duration
13.9 months estimated median progression-free survival

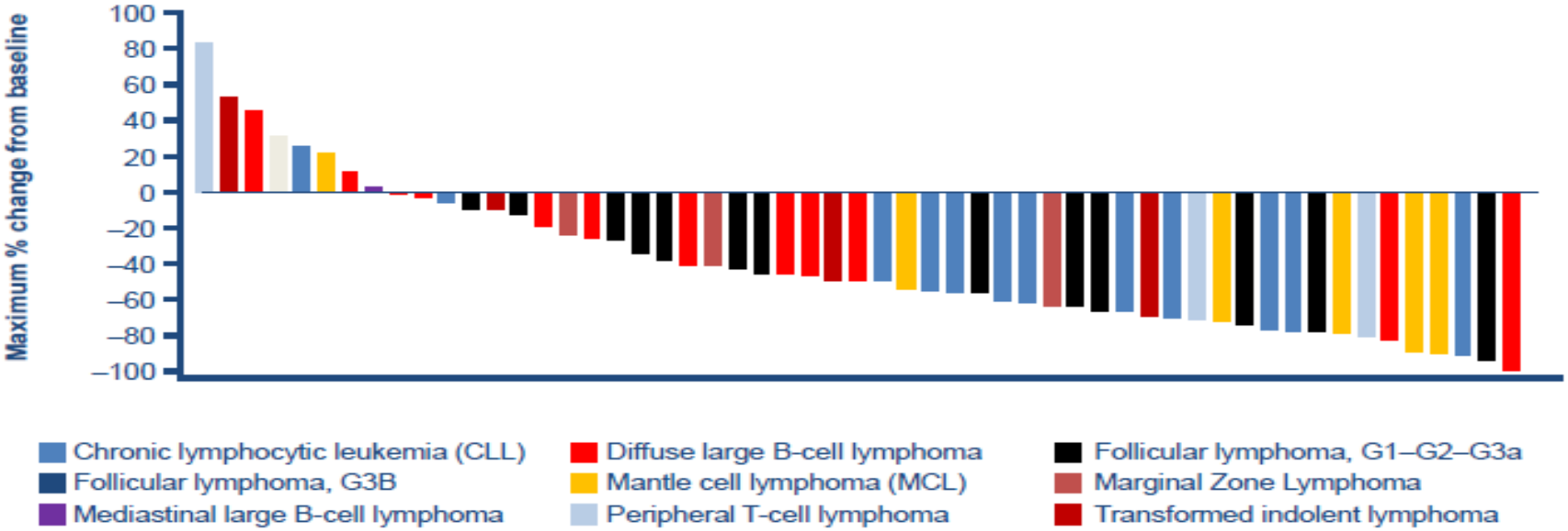


Wang M et al. N Engl J Med 2013; 369: 507-516.

Other inhibitors of PI3K

Class I PI3K Isoform	α	β	γ	δ
Expression	**Ubiquitous**	**Ubiquitous**	**Leukocytes**	**Leukocytes**
	Insulin signaling Mutated in solid tumours	Platelet activation Neutrophil function Insulin signaling	Mast cell activation Innate immunity Immune tracking	B and T cell activation Fc receptor signaling

Copanlisib



AEs ≥3. Neutropenia 24% ; hypertension 37%; hyperglycaemia 22%

Dreyling et al ASH 2014

BCL-2 Inhibition

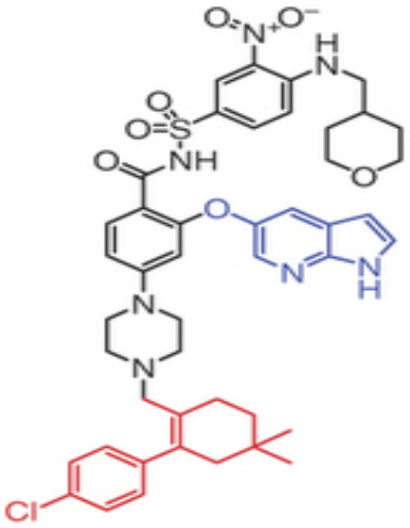
Bcl-2 highly expressed in FL

GDC-0199 oral active Bcl-2 inhibitor
Phase I dose escalation
200-900 mg cohorts
N=44 with NHL
FL =11 (26%)

Nausea (34%), diarrhoea (25%), fatigue (21%)

Tumour lysis in 1 patient each with DLBCL and MCL

3/11 responses in FL



GDC-0199

Obinutuzumab: Putative mechanism(s) of action

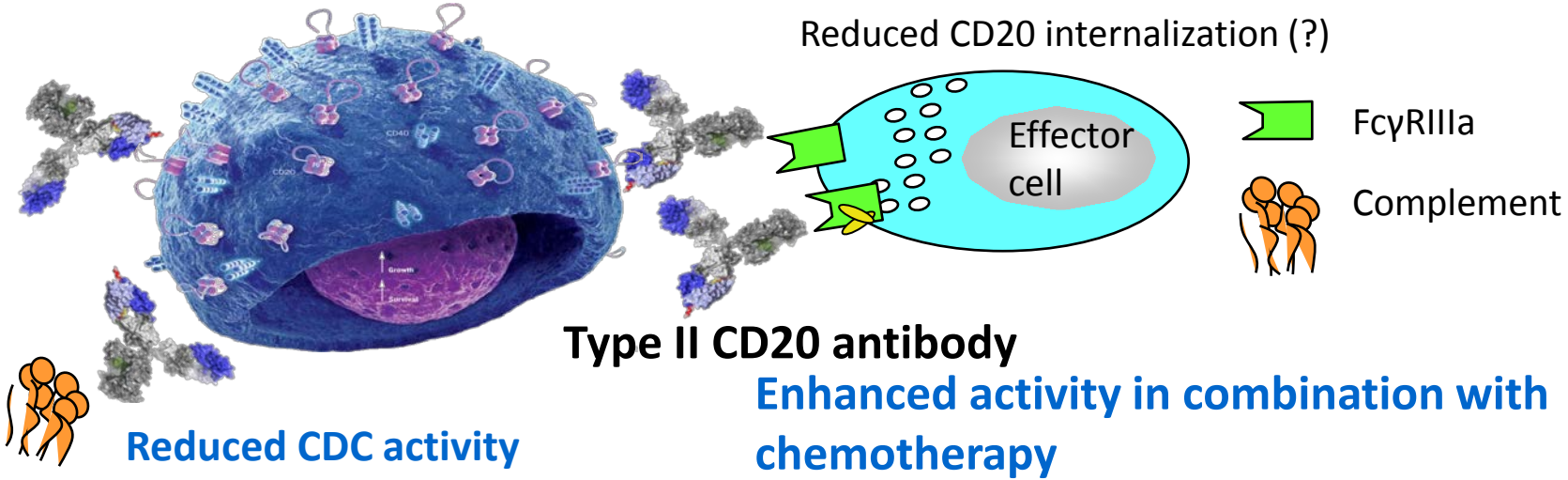
Increased direct cell death

Type II antibody & elbow-hinge modification

Increased ADCC

Higher affinity to the 'ADCC receptor' FcγRIIIa (GlycoMab TM technology) &

Reduced CD20 internalization (?)

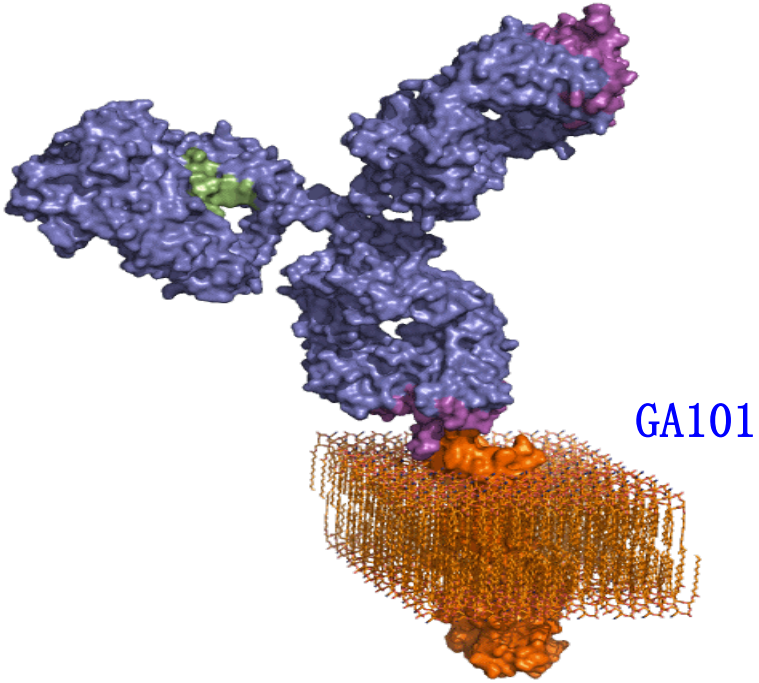


Reduced CDC activity

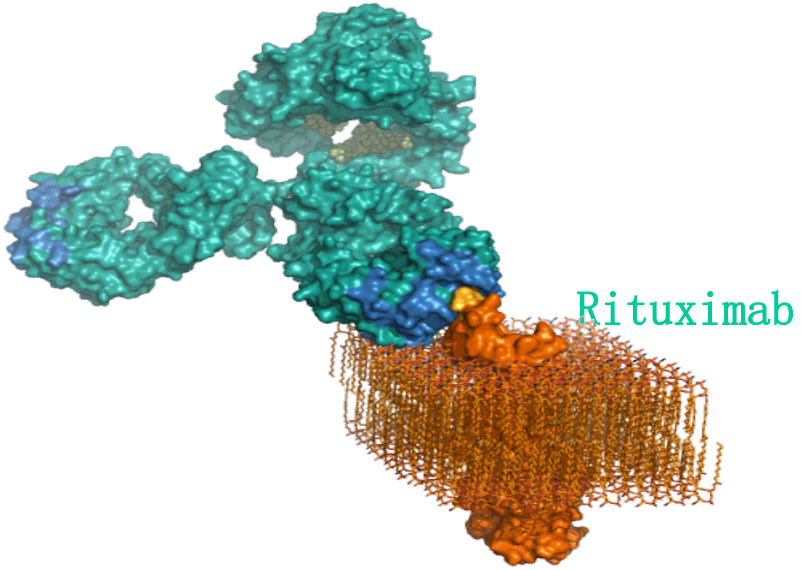
Type II antibody

Enhanced activity in combination with chemotherapy

ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity



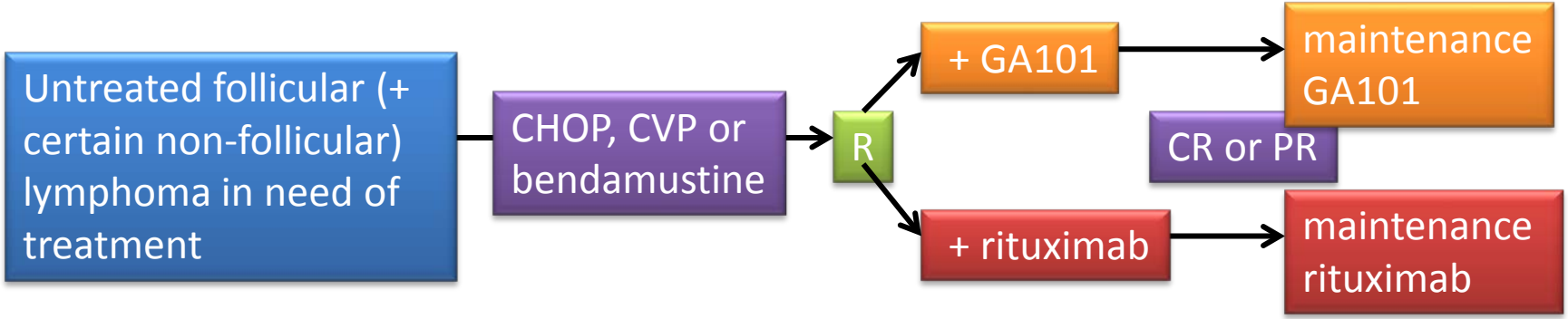
GA101



Rituximab

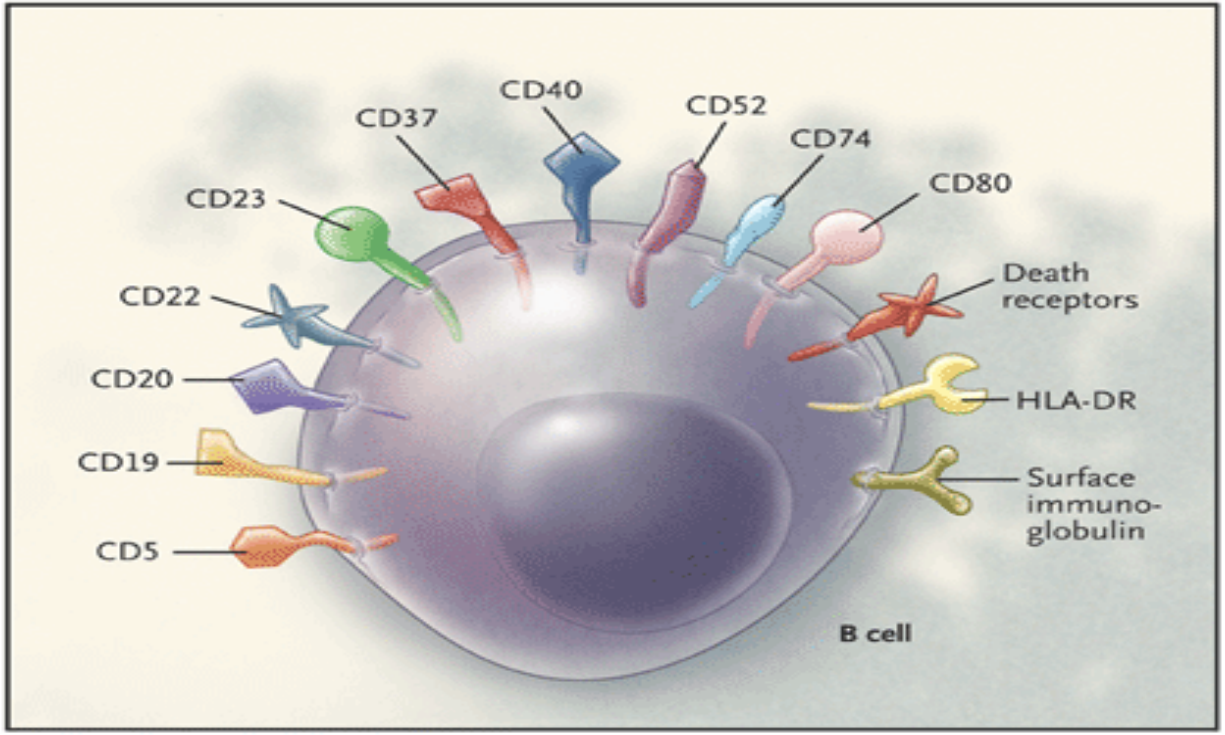
M. Schwaiger, W. Schäfer

GALLIUM



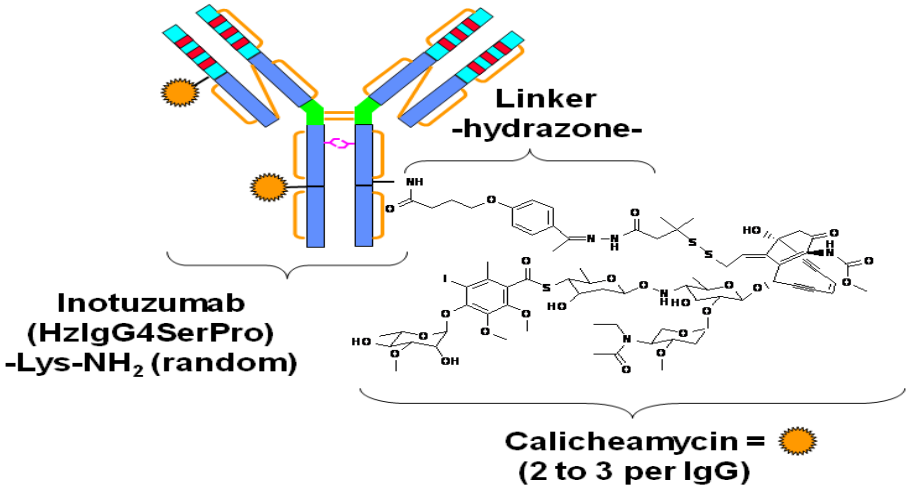
Target 1200 FL, 200 non-follicular

What about the other targets?

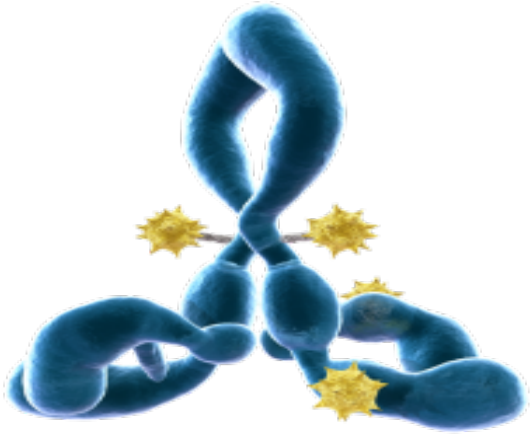


Targeted chemotherapy in clinical development

Antibody-drug conjugates



Target CD22



Polatuzumab
Vedotin

Target CD79b

In summary…

- Huge progress in our understanding of MZL
- Lack of good data
- A wealth of new therapies
- International collaboration to test and define treatment strategies

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Extranodal lymphomas: characteristics, the role of RT, volumes, doses and techniques

Bone

Umberto Ricardi

Introduction

- Primary bone lymphoma (PBL) constitutes approximately 5% of all extranodal NHLs, <1% of all NHLs, and 3-7% of all malignant primary bone tumours
- Median age at diagnosis: 45 – 60 years old
- A slight preponderance of males over females (male/female ratio 1.5)

Introduction

- Most patients with bone lymphoma have DLBCL (80% of cases)
- Approximately 80% of patients present in stage IE (about 10% of patients have a polyostotic presentation)
- The most common involved bones are femur (most often diaphyseal involvement) and pelvis

Table 1
Patient's characteristics at presentation in the IELSG-14 series.

	Limited stage DLBCL ($n = 161$)	MB-DLBCL ($n = 37$)	Stage IV DLBCL ($n = 63$)
Males	51%	59%	40%
Median age; years (range)	55 (18–99)	53 (17–75)	62 (28–83)
Clinical presentation (%)			
ECOG-PS > 1	15%	38%	62%
High LDH serum level	34%	30%	65%
B symptoms	9%	24%	30%
Pain	82%	92%	90%
Swelling	40%	45%	34%
Bulky disease	23%	15%	32%
Fracture	15%	25%	29%
Sites of involvement (%)			
Skull	15%	32%	19%
Spinal cord	17%	65%	51%
Pelvis	17%	32%	33%
Humerus	7%	13%	17%
Forearm	7%	16%	8%
Femur	20%	38%	24%
Forefoot	13%	19%	14%
Lymph nodes	–	–	28%
Cerebrospinal fluid	–	3%	1%
Bone marrow	–	–	35%
Other	4%	–	–

DLBCL = diffuse large B-cell lymphoma; MB-DLBCL = multifocal bone diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; LDH lactate dehydrogenase.

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Clinical presentation

- Symptoms:
  - pain 80–95%
  - tumour mass 30–40%
  - pathological fracture 15–20%
- Mean time between symptoms and diagnosis: 8 months
- Spinal cord compression: 16%

Radiographic findings

- **Rx:**
  - mostly lytic lesions
  - a mixture of permeative, moth-eaten or destructive patterns of the bone cortex
  - often reactive changes of the periosteum
- **contrast-enhanced CT scan:**
  - demonstrates the boundaries of any extraosseous extension
  - indicates cortical breakthrough by the tumour
  - detects osteolysis, osteosclerosis and fragments of bone sequestra
- **MRI:**
  - more detailed extension of disease
  - evidence of cortical changes, intratumoural fibrosis, replacement of trabecular bone and bone marrow by tumour
- **PET-CT:**
  - recommended for initial evaluation, staging and response assessment

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Cancer Treatment Reviews 41 (2015) 235–246

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Tumour Review

Primary and secondary bone lymphomas

Carlo Messina [a,1], David Christie [b,1], Emanuele Zucca [c,1], Mary Gospodarowicz [d,1], Andrés J.M. Ferreri [a,1,*]

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Staging

Staging procedures in patients with bone lymphoma.

Test/procedure
Demographics and medical history*
Physical examination
Blood tests#
Chest X-ray
Contrasted CT scan of the neck, chest, abdomen, and pelvis
MRI of bony lesions
^{18}FDG-PET
Bone marrow biopsy
In case of suspicion of involvement of particular organs
Cerebrospinal fluid (CSF) examination§
Gadolinium-enhanced brain MRI§
Gastrointestinal tract endoscopy
Blood smears

IELSG staging system for DLBCL of the bone.

IELSG stage	Lymphoma extension	Ann Arbor stage
IE	Single bony lesion	IE
IIE	Single bony lesion with involvement of regional lymph nodes	IIE
IVE	Multifocal disease in a single bone or lesions in multiple bones in a disease exclusively limited to the skeleton (without lymph nodal or visceral disease) – called also "multifocal osteolymphoma" or "polyostotic lymphoma"	IV
IV	Disseminated lymphoma with at least one bony lesion	IV

Messina et al, Cancer Treat Rev, 2015

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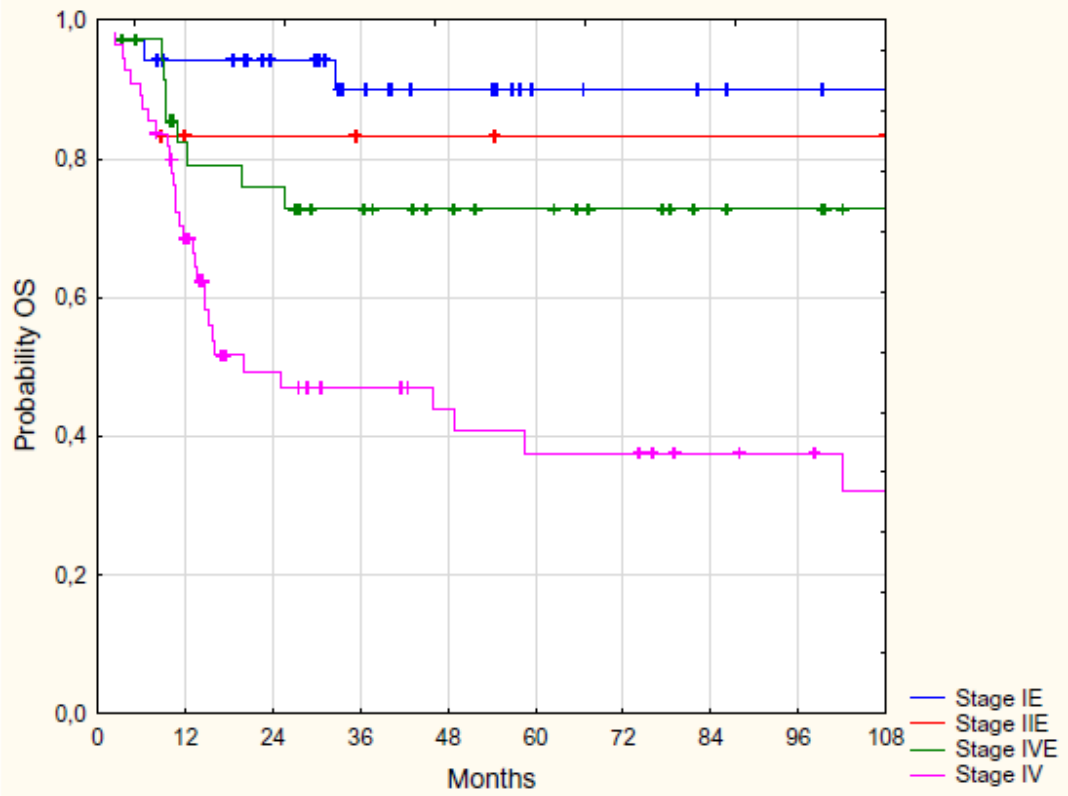
Prognosis according to stage

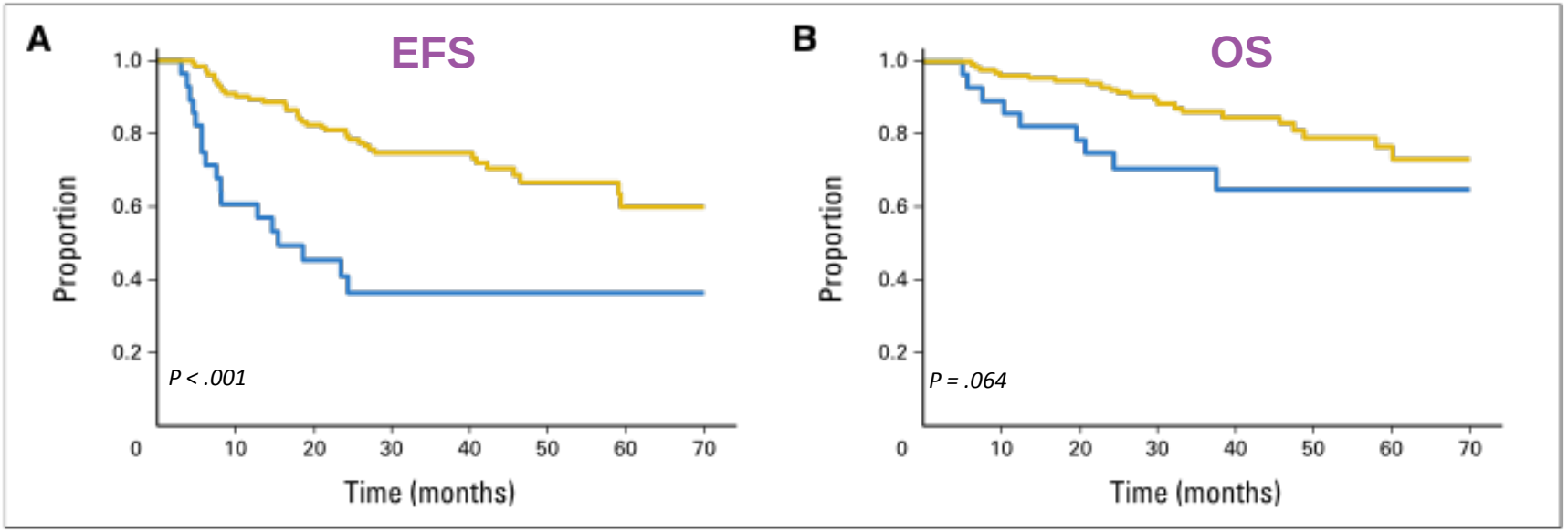


Messina et al, Cancer Treat Rev, 2015

Impact of Rituximab and Radiotherapy on Outcome of Patients With Aggressive B-Cell Lymphoma and Skeletal Involvement

Radiotherapy

NO Radiotherapy



3-year EFS:

75% RT; 36% NO RT

3-year OS:

86% RT; 71% NO RT

Held et al. JCO 2013;31(32):4115-4122

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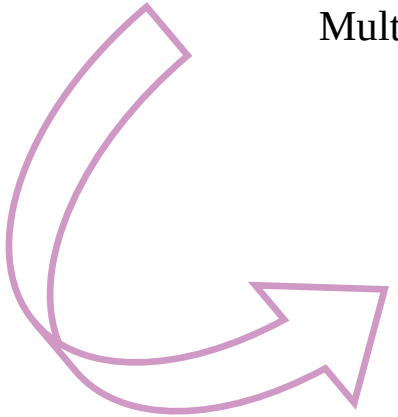
Characteristics of Patients With Skeletal Involvement Treated With and Without Radiotherapy to Sites of Skeletal Involvement and Achieving a CR, CRu, or PR (n = 161)

Characteristic	With Radiotherapy (n = 133)		Without Radiotherapy (n = 28)		P
	No.	%	No.	%	
Sex					
Male	82	61.7	10	35.7	.012
Female	51	38.3	18	64.3	
Age > 60 years	58	43.6	22	78.6	.001
ECOG PS > 1	21	15.8	6	21.4	.577
Stage III/IV	63	47.4	20	71.4	.021
LDH > N	41	30.8	12	42.9	.218
Extralymphatic involvement > 1	67	50.4	18	64.3	.180
Bulk	45	33.8	5	17.9	.097
IPI					
0, 1	61	45.9	8	28.6	
2	33	24.8	3	10.7	.017
3	18	13.5	7	25.0	
4, 5	21	15.8	10	35.7	



Multivariate Analysis of Additive Radiotherapy in Patients With Skeletal Involvement (adjusting for IPI score and bulky)

Variable	EFS (n = 161)			OS (n = 161)		
	HR	P	95% CI	HR	P	95% CI
LDH > N	1.9	.032	1.1 to 3.5	1.4	.413	0.6 to 3.1
Stage III/IV	2.4	.015	1.2 to 5.0	2.2	.110	0.8 to 6.0
ECOG PS > 1	0.6	.211	0.3 to 1.3	0.8	.680	0.3 to 2.0
Extralymphatic involvement > 1	0.8	.609	0.4 to 1.7	0.8	.683	0.3 to 2.2
Age > 60 years	1.0	.987	0.5 to 1.9	1.9	.147	0.8 to 4.5
Bulk	1.6	.133	0.9 to 2.9	2.8	.010	1.3 to 6.3
Additive radiotherapy	0.3	.001	0.2 to 0.6	0.5	.111	0.2 to 1.2

Held et al, JCO, 2013

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Treatment

- *Combined modality therapy:*

R-CHOP followed by RT

Largest available series of bone lymphomas.

Reference	No. of patients	Median age	Years of enrollment	Most common primary site	Aggressive type (%)	Stage I–II (%)	CT (%)	RT (%)	CT + RT (%)	Rituximab (%)	ORR (%)	DFS	OS (years)
Ostrowski [6]	261	45	1907–1982	Femur (21%)	77	68	6	63	22	0	NA	NR	53% (10 – uni) 35% (10 – mul)
Heyning [81]	60	48	1943–1996	Femur (24%)	92	62	NR	8	58	0	56	46% (5)	61% (5)
Dosoretz [57]	30	58	1950–1978	Femur (30%)	93	100	0	76	12	0	NR	40% (5)	63% (5)
De Camargo [125]	24	38	1955–1999	Spine (25%)	83	NA	37	8	43	0	NR	NR	70% (5)
Ueda [126]	34	56	1961–1988	Pelvis (29%)	53	44	26	10	41	0	NR	NR	75% (5 – st I) 50% (5 – st II)
Beal [1]	82	48	1963–2003	Femur (27%)	80	81	30	14	56	6	NR	81% (5)	88% (5)
Marshall [127]	28	52	1962–1997	Femur (18%)	100	100	0	32	68	0	100	48% (10)	53% (10)
Rathmell [5]	27	53	1967–1988	NR	85	100	0	56	33	0	NR	39% (10)	40% (10)
Dubey [128]	45	52	1967–1992	Femur (20%)	98	100	9	11	80	0	NR	63% (10)	60% (10)
Fidias [129]	37	41	1970–1995	Appendix (75%)	100	100	0	0	100	0	100	73% (10)	87% (10)
Fairbanks [3]	63	63	1970–1989	Long bone (57%)	93	100	3	79	16	0	NR	90% (5 – CT + RT) 57% (5 – RT)	NR
Horsman [27]	37	55	1970–2003	Pelvis (24%)	73	100	16	41	38	0	57	NR	50% (10)
Bacci [82]	26	NR	1972–1982	Fenur (23%)	80	100	0	0	100	0	100	88% (13)	88% (13)
Baar [116]	17	36	1975–1992	Femur (29%)	100	88	30	6	64	0	94	77% (3)	77% (3)
Christie [124]	70	60	1973–1999	Spine (29%)	65	80	0	44	56	0	83	NR	59% (5)
Stein [130]	19	54	1979–2000	NR	95	58	42	0	58	0	95	90% (6 – st I–II) 87% (6 – st IV)	NR
Messina [9]	37	53	1980–2005	Spine (65%)	100	0	35	0	65	0	92	56% (5)	74% (5)
Govi [55]	26	60	1980–2005	Pelvis (47%)	0	42	30	15	55	0	73	25% (10)	29% (10)
Bruno Ventre [26]	161	55	1980–2005	Femur (20%)	100	100	8	14	78	0	91	68% (5)	75% (5)
Zinzani [59]	52	58	1982–1998	Femur (27%)	85	79	16	21	63	0	90	84% (8 – CR pts)	68% (9)
Gianelli [62]	28	51	1982–1999	Femur (24%)	93	100	20	3	74	0	NA	75% (4)	78% (4)
Barbieri [76]	77	42	1983–2001	Extremities (51%)	97	100	0	13	87	0	95	76% (15)	88% (15)
Ramadan [29]	131	63	1983–2005	Spine (29%)	79	46	44	8	48	21	NR	40% (10)	41% (10)
Lewis [131]	28	45	1984–1994	Femur (39%)	89	71	36	14	50	0	NA	46% (6)	60% (6)
Ford [86]	22	50	1985–2003	Long bone (50%)	91	77	18	0	82	0	NR	85% (10)	74% (10)
Bayrakci [87]	20	48	1986–1997	Femur (24%)	NR	70	35	0	65	0	65	NR	78% (st I) 16% (st IV)
Cai [72]	116	51	1987–2008	Spine (28%)	86	100	13	12	75	3	91	62% (4)	72% (10)
Catlett [90]	30	49	1989–2005	Long bone (57%)	90	70	16	10	71	40	NR	NR	73% (5)
de Leval[65]	20	44	1990–2000	Femur (35%)	100	90	15	15	65	0	NA	NR	74% (5)
Kim [132]	33	40	1992–2010	Pelvis (39%)	100	39	48	0	52	39	88	NR	75% (4)
Maruyama [30]	28	47	1995–2004	Pelvis (41%)	68	32	50	0	50	0	89	77% (3)	84% (3)
Pellegrini [89]	21	34	1999–2009	Long bone (38%)	100	10	48	0	52	100	95	100% (8 – CR pts)	95% (8)
Alencar[91]	53	52	2000–2007	Femur (24%)	90	77	12	21	62	37	92	83% (4)	100% (4)
Christie [133]	31	55	2000–2007	Femur (26%)	97	68	0	0	100	19	96	64% (5)	90% (5)
Nasiri [134]	28	41	2001–2009	Femur (25%)	100	78	30	3	66	0	NR	62% (2)	NR

Treatment: CMT as standard approach

• *Dosoretz et al.* treated 30 PBLs with RT alone

5 year-DFS: 53%; OS:63% Cumulative incidence of local recurrence: 14%

No local failures if dose up to 50 Gy

• *Fairbanks et al.* reported on 63 Stage IE PBLs

50 pts received RT alone, 10 CMT, 2 CT alone, 1 surgery alone

Univariate analysis: improved 5-year DFS with CMT vs RT alone (90% vs 57%) Doses over 40 Gy improved OS

• *Bacci et al.* 30 pts with localized PBL with 10 yrs follow-up

26 pts CT with anthracycline-chemo: 3 systemic relapses

4 RT only (30-45 Gy whole bone; 10-15 Gy boost): 1 local relapse

DFS 88 % at 87 months mean follow-up

Excellent cure rates with the addition of CT to RT

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

Int. J. Radiation Oncology Biol. Phys., Vol. 59, No. 3, pp. 760–764, 2004

0360-3016/04/$–see front matter

doi:10.1016/j.ijrobp.2003.11.020

CLINICAL INVESTIGATION **Bowel**

PRIMARY NON-HODGKIN'S LYMPHOMA OF THE BONE: TREATMENT AND ANALYSIS OF PROGNOSTIC FACTORS FOR STAGE I AND STAGE II

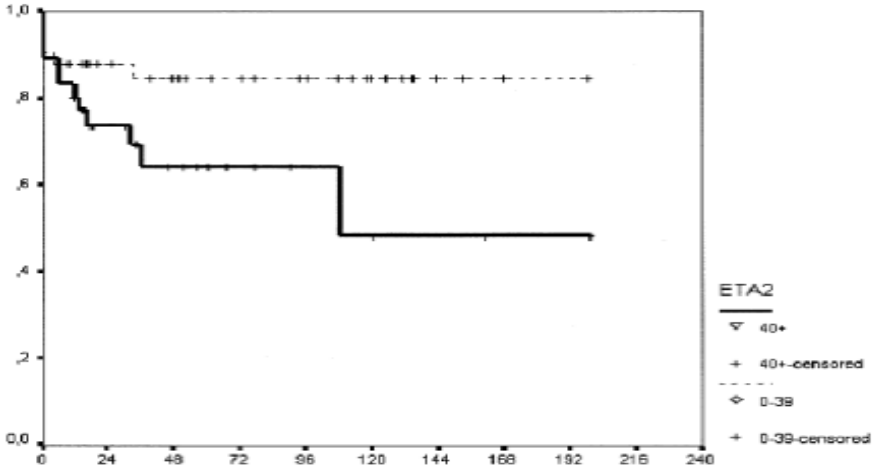
Enza Barbieri, M.D.,* Silvia Cammelli, M.D.,* Floranna Mauro, M.D.,†
Francesco Perini, M.D.,* Alberto Cazzola, Ph.D.,‡ Stefano Neri, M.D.,*
Feisal Bunkheila, M.D.,* Stefano Ferrari, M.D.,§ Vladimiro Brandoli, M.D.,*
Pierluigi Zinzani, M.D.,‖ Mario Mercuri, M.D.,§ and Gaetano Bacci, M.D.§

Male	56/77 (72.7%)
Female	21/77 (27.3%)
Median age	41.8 years (range, 16–84)
Median follow-up	149 months (range, 12–199)
Histology	
NHL B-cell high grade	75/77 (96.9%)
NHL B-cell low grade	1/77 (1.5%)
NHL T-cell intermediate grade	1/77 (1.5%)
Stage	
IE	44/77 (55.7%)
IIE	33/77 (44.3%)
Bulky (>6 cm)	
Yes	11/77 (14.4%)
No	66/77 (86.6%)

- 77 PBL treated with RT from 1983 to 2001
- 67/77: combined modality
- 14/77 relapsed:
  - 4/14 RT alone (lesion < 3 cm)
  - 10/14 CMT (CHOP regimen)

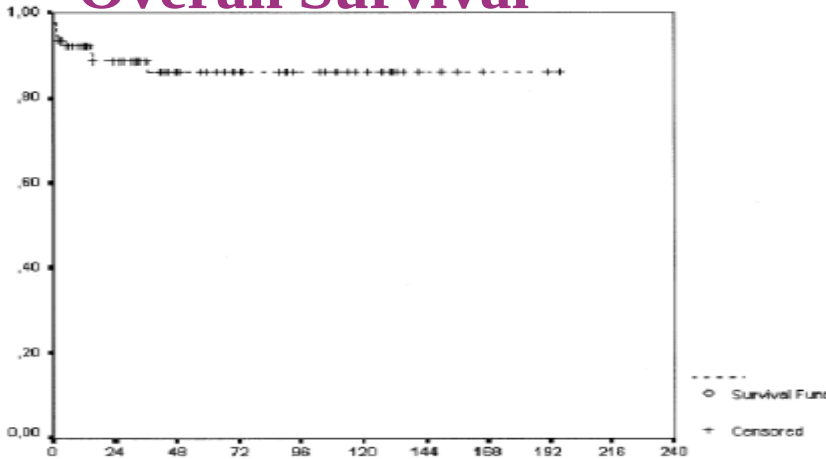
Prognostic factors

Failure-Free Survival by Age

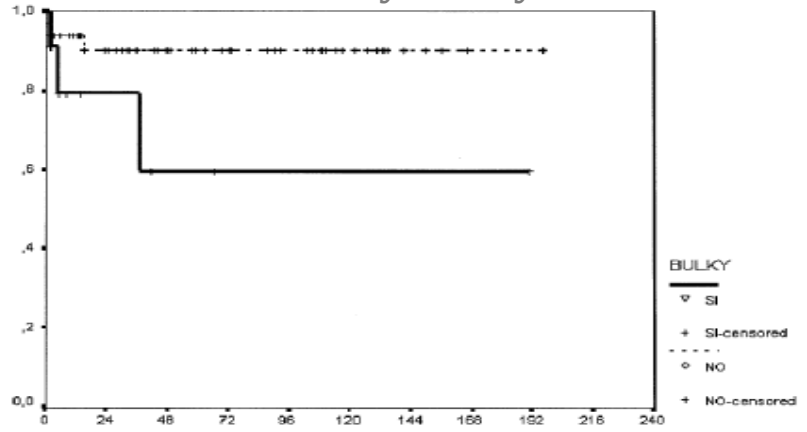


Barbieri et al, IJROBP, 2004

Overall Survival



Overall Survival by Bulky Lesion



The Oncologist®

Lymphoma

Clinical Features, Management, and Prognosis of an International Series of 161 Patients With Limited-Stage Diffuse Large B-Cell Lymphoma of the Bone (the IELSG-14 Study)

Marta Bruno Ventre,[a] Andrés J.M. Ferreri,[a] Mary Gospodarowicz,[b] Silvia Govi,[a] Carlo Messina,[a] David Porter,[c] John Radford,[d] Dae Seog Heo,[e] Yeon Park,[f] Giovanni Martinelli,[g] Emma Taylor,[h] Helen Lucraft,[i] Angela Hong,[j] Lydia Scarfò,[a] Emanuele Zucca,[k] David Christie,[l] on behalf of the International Extranodal Lymphoma Study Group (IELSG)

The Oncologist 2014;19:291–298

Implications for Practice: Patients with limited-stage diffuse large B-cell lymphoma of the bone exhibit a favorable prognosis when treated with primary anthracycline-based chemotherapy whether followed by radiotherapy or not. In patients treated with chemoradiotherapy, the use of larger radiation fields and doses are not associated with better outcome. Central nervous system dissemination is a rare event in these patients, suggesting that specific prophylaxis is superfluous.

ILROG International Lymphoma Radiation Oncology Group

ESTRO School

Parameter	Value
Patients, *n* (%)	161 (100)
Median age (yr) (range)	55 (18–99)
Age >60 years old, *n* (%)	62 (39)
Male gender, *n* (%)	90 (51)
Male/female ratio	1:2
Stage IIE, *n* (%)	20 (13)
B symptoms, *n* (%)	14 (9)
High LDH serum level, *n* (%)[a]	54/158 (34)
IPI risk group (score), *n* (%)	
Low (0–1)	113 (70)
Low intermediate (2)	36 (22)
High intermediate (3)	7 (4)
Unknown	5 (3)
Site, *n* (%)	
Femur	33 (20)
Spine	27 (17)
Pelvis	27 (17)
Skull	25 (15)
Lower limb, excluding femur	21 (13)
Upper limb, excluding humerus	11 (7)
Humerus	11 (7)
Others	6 (4)

Parameter	Combined treatment	Chemotherapy alone	Radiotherapy alone
Patients, *n*	125	13	23
Median age (yr) (range)	54 (18–99)	52 (27–68)	64 (27–85)
Age >60 years old, *n* (%)	43 (34)	2 (15)	14 (61)
Male gender, *n* (%)	66 (53)	9 (69)	14 (61)
Stage IIE, *n* (%)	15 (12)	2 (15)	3 (13)
B symptoms, *n* (%)	12 (10)	2 (15)	0 (0)
High LDH serum level[a]	46/123 (37)	6/12 (50)	2/23 (9)
IPI risk group (score), *n* (%)			
Low (0–1)	86 (69)	10 (77)	17 (74)
Low intermediate (2)	31 (25)	1 (8)	4 (17)
High intermediate (3)	4 (3)	1 (8)	2 (9)
Unknown	4 (3)	1 (8)	0 (0)

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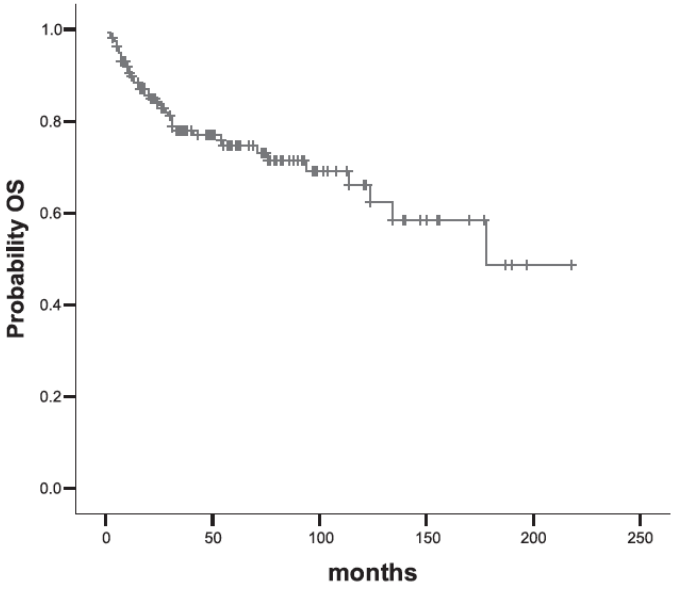

Table 4. Multivariate analysis

Variable	Subgroup	Odds ratio	95% CI	*p*
Age	Continuous	1.04	1.02–1.07	.0001
ECOG-PS	0–1	1.88	0.98–3.61	.057
	2–4			
Stage	I	1.27	0.44–3.67	.65
	II			
LDH	Normal	0.92	0.44–1.93	.83
	High			
B symptoms	No	1.25	0.37–4.27	.71
	Yes			
Fracture	No	0.87	0.41–1.85	.71
	Yes			
Primary chemotherapy	No	0.42	0.22–0.81	.009
	Yes			

Treatment	Stage IE disease (*n* = 141)	Stage IIE disease (*n* = 20)	Whole series (*n* = 161)
Chemotherapy alone, *n* (%)	11 (8)	2 (10)	13 (8)
Anthracycline-based regimen, *n* (%)	11 (100)	2 (100)	13 (100)
CHOP regimen, *n* (%)	5 (45)	0 (0)	5 (38)
Median number of courses (range)	4 (1–8)	3; 4[a]	4 (1–8)
Radiotherapy alone, *n* (%)	20 (14)	3 (15)	23 (14)
Median dose (Gy) (range)	40 (30–55)	50 (40–56)	40 (30–56)
Whole affected bone, *n* (%)	14 (70)	1 (33)	15 (65)
Partial affected bone, *n* (%)	6 (30)	2 (66)	8 (35)
Chemoradiotherapy, *n* (%)	110 (78)	15 (75)	125 (78)
Chemotherapy → radiotherapy, *n* (%)	94 (85)	15 (100)	109 (87)
Radiotherapy → chemotherapy, *n* (%)	16 (15)	0 (0)	16 (13)
Anthracycline-based regimen, *n* (%)	95 (86)	11 (73)	106 (85)
CHOP regimen, *n* (%)	74 (67)	9 (60)	83 (66)
Median number of courses (range)	6 (1–8)	6 (3–8)	6 (1–8)
Median radiation dose (Gy) (range)	40 (30–56)	40 (35–50)	40 (30–56)
Whole affected bone, *n* (%)	78 (71)	9 (60)	87 (70)
Partial affected bone, *n* (%)	32 (29)	6 (40)	38 (30)

Conclusion. Patients with PB-DLBCL exhibit a favorable prognosis when treated with primary anthracycline-based chemotherapy whether followed by radiotherapy or not. In patients treated with chemoradiotherapy, the use of larger radiation fields and doses is not associated with better outcome. Central nervous system dissemination is a rare event in PB-DLBCL patients. ***The Oncologist*** 2014;19:291–298

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Therapeutic issues

- Anthracycline-based chemotherapy as first line treatment for patients affected with primary bone DLBCL
- A survival benefit of the addition of the anti-CD20 monoclonal antibody rituximab to CHOP in primary bone DLBCL has not been demonstrated

- **The survival benefit of adjuvant irradiation after primary R-chemotherapy is a matter of debate**
- **Optimal radiation volumes and doses**

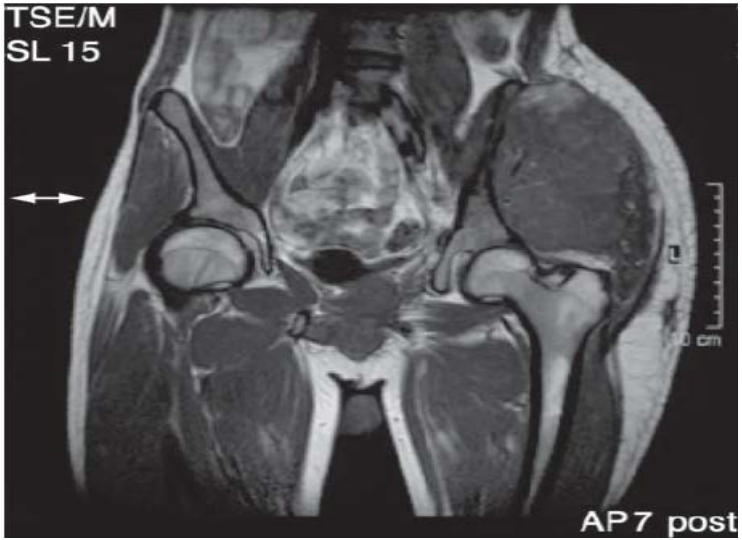
Considerations on RT volumes

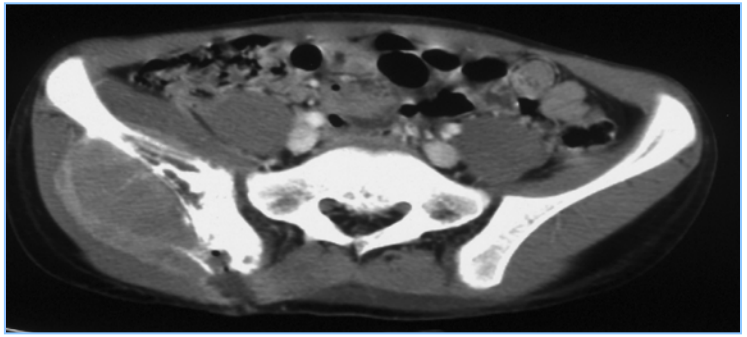
- IELSG-14 study:
  - primary bone DLBCL treated with CHOP followed by RT of the whole bone: 5-year PFS 76%
  - primary bone DLBCL treated with CHOP followed by RT of a part of the affected bone (IF-RT): 5-year PFS of 64%

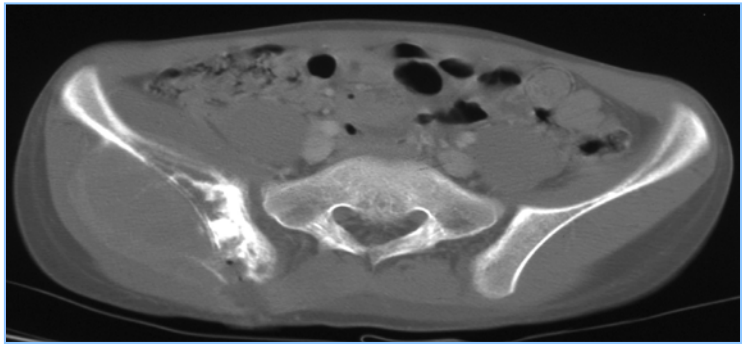
Radiation volumes

- CTV: Prechemotherapy GTV (preferably on MRI) with margins added to accommodate uncertainties in subclinical tumor extension and quality of imaging, and fusion into simulation CT

- PTV is between 0.5-1 cm, depending on site and immobilization







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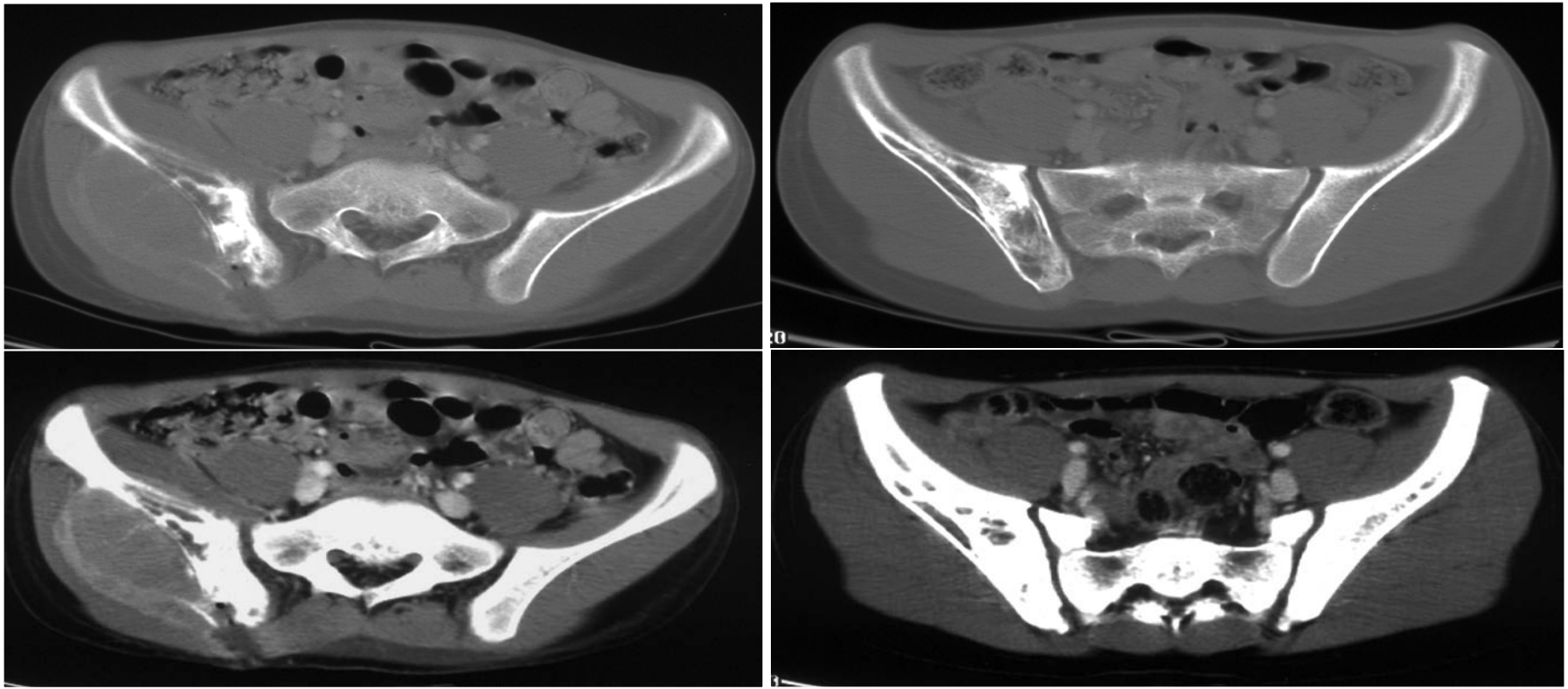

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Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

Yahalom et al, IJROBP, 2015

Considerations on RT dose

- Radiation dose depends on:
  - the size of the irradiated volume
  - the anatomical area
  - the response to primary chemotherapy

- IELSG-14 study:
  - 47 pts irradiated with a dose ≤ 36 Gy: 5-year PFS 72%
  - 58 pts irradiated with a dose > 36 Gy: 5-year PFS 75%

Early-Stage Primary Bone Lymphoma: A Retrospective, Multicenter Rare Cancer Network (RCN) Study

Ling Cai, M.D.,*,‡ Michael C. Stauder, M.D.,† Yu-Jing Zhang, M.D.,‡ Philip Poortmans, M.D.,§ Ye-Xiong Li, M.D.,¶ Nicolaos Constantinou, M.D.,‖ Juliette Thariat, M.D.,** Sidney P. Kadish, M.D.,†† Tan Dat Nguyen, M.D.,‡‡ Youlia M. Kirova, M.D.,§§ Pirus Ghadjar, M.D.,¶¶ Damien C. Weber, M.D.,‖‖ Victoria Tuset Bertran, M.D.,*** Mahmut Ozsahin, M.D., Ph.D.,* and René-Olivier Mirimanoff, M.D.*

Int J Radiation Oncol Biol Phys, Vol. 83, No. 1, pp. 284–291, 2012

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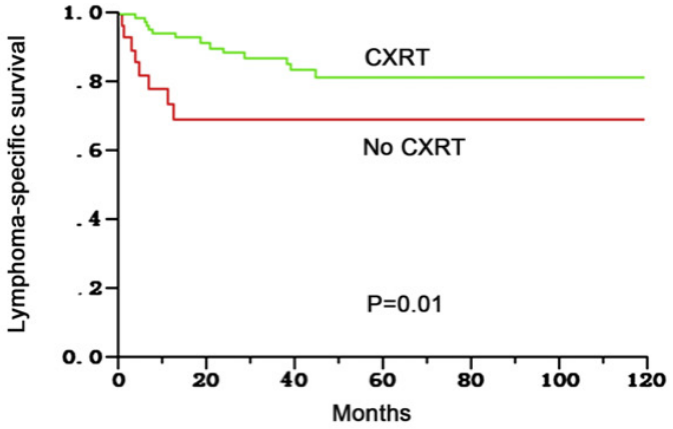
Rare Cancer Network study

116 PBL pts



CXRT = chemoradiotherapy

CXT = chemotherapy

RT = radiotherapy

Table 2 Univariate analyses (log–rank test)

Variable	*n*	5-y OS (%)	95% CI	*p*	5-y LSS (%)	95% CI	*p*	5-y LC (%)	95% CI	*p*
Treatment modality										
CXRT	87	79	69–89	0.001	81	72–90	<0.001	93	87–99	0.13
CXT	14	92	78–106		92	78–106		77	54–100	
RT	15	49	22–76		49	22–76		100	100	
CXRT vs. RT and CXT										
CXRT	87	79	69–89	0.05	81	72–90	0.01	93	87–99	0.66
RT and CXT	29	69	51–87		69	51–87		87	73–101	
Treatment modality of CXRT and RT vs. CXT										
CXRT and RT	102	75	66–84	0.27	94	89–99	0.08	94	89–99	0.08
CXT	14	92	78–106		77	54–100		77	4–100	
Treatment modality of CXRT and CXT vs. RT										
CXRT and CXT	101	80	71–89	0.004	82	73–91	<0.0001	91	85–97	0.24
RT	15	49	22–76		49	22–76		100	100	

Cai et al, IJROBP, 2011

Early-Stage Primary Bone Lymphoma: A Retrospective, Multicenter Rare Cancer Network (RCN) Study

Ling Cai, M.D.,*,‡ Michael C. Stauder, M.D.,† Yu-Jing Zhang, M.D.,‡ Philip Poortmans, M.D.,§ Ye-Xiong Li, M.D.,¶ Nicolaos Constantinou, M.D.,‖ Juliette Thariat, M.D.,** Sidney P. Kadish, M.D.,†† Tan Dat Nguyen, M.D.,‡‡ Youlia M. Kirova, M.D.,§§ Pirus Ghadjar, M.D.,¶¶ Damien C. Weber, M.D.,‖‖ Victoria Tuset Bertran, M.D.,*** Mahmut Ozsahin, M.D., Ph.D.,* and René-Olivier Mirimanoff, M.D.*

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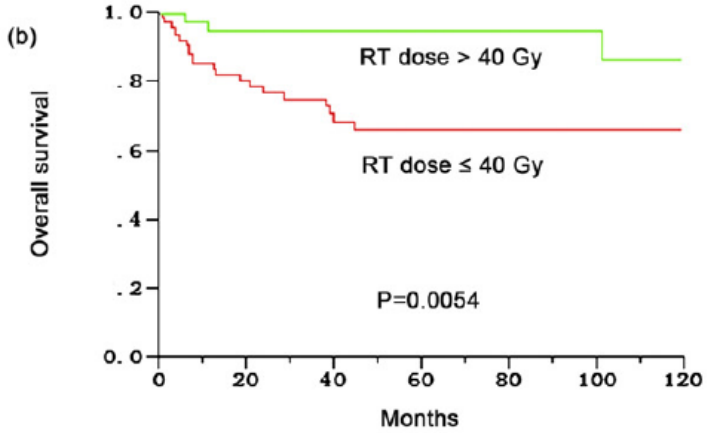

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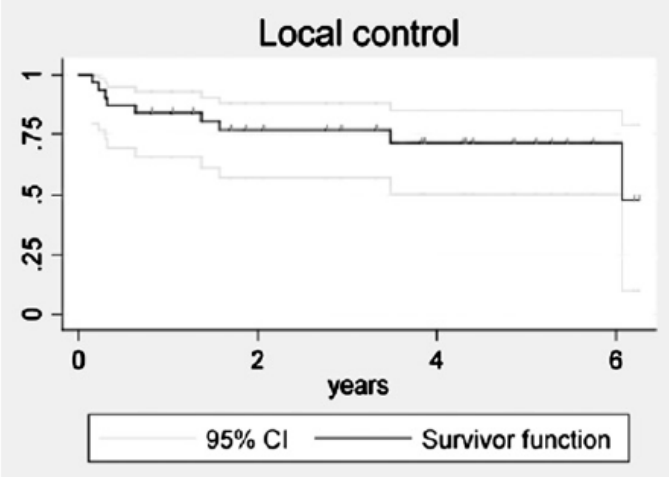
LIMITED CHEMOTHERAPY AND SHRINKING FIELD RADIOTHERAPY FOR OSTEOLYMPHOMA (PRIMARY BONE LYMPHOMA): RESULTS FROM THE TRANS-TASMAN RADIATION ONCOLOGY GROUP 99.04 AND AUSTRALASIAN LEUKAEMIA AND LYMPHOMA GROUP LY02 PROSPECTIVE TRIAL

DAVID CHRISTIE, F.R.A.N.Z.C.R.,* KEITH DEAR, M.STAT.,† THAI LE, B.H.B.,‡
MICHAEL BARTON, F.R.A.N.Z.C.R.,§ ANDREW WIRTH, F.R.A.N.Z.C.R.,‖ DAVID PORTER, F.R.A.C.P.,¶
DANIEL ROOS, F.R.A.N.Z.C.R.,# AND GARY PRATT, F.R.A.N.Z.C.R.**



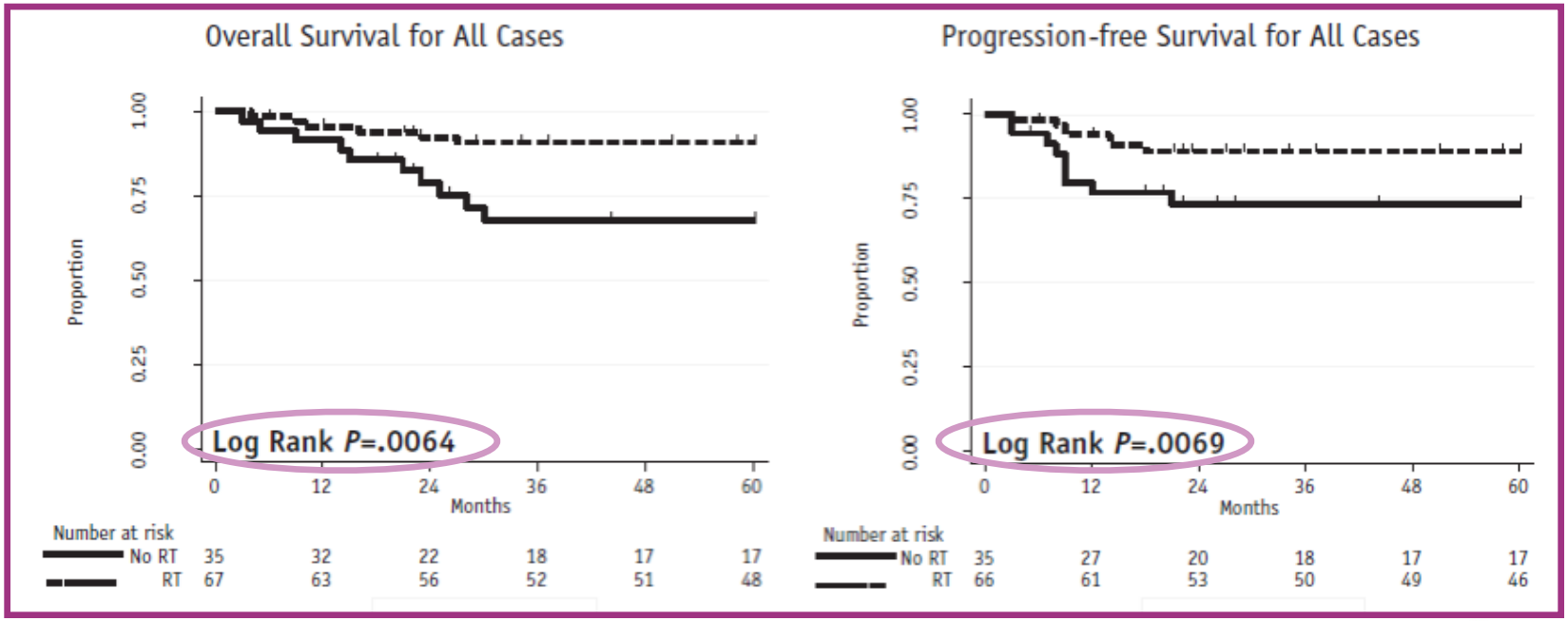
Int. J. Radiation Oncology Biol. Phys., Vol. 80, No. 4, pp. 1164–1170, 2011

radiation to a dose of 45 Gy in 25 fractions

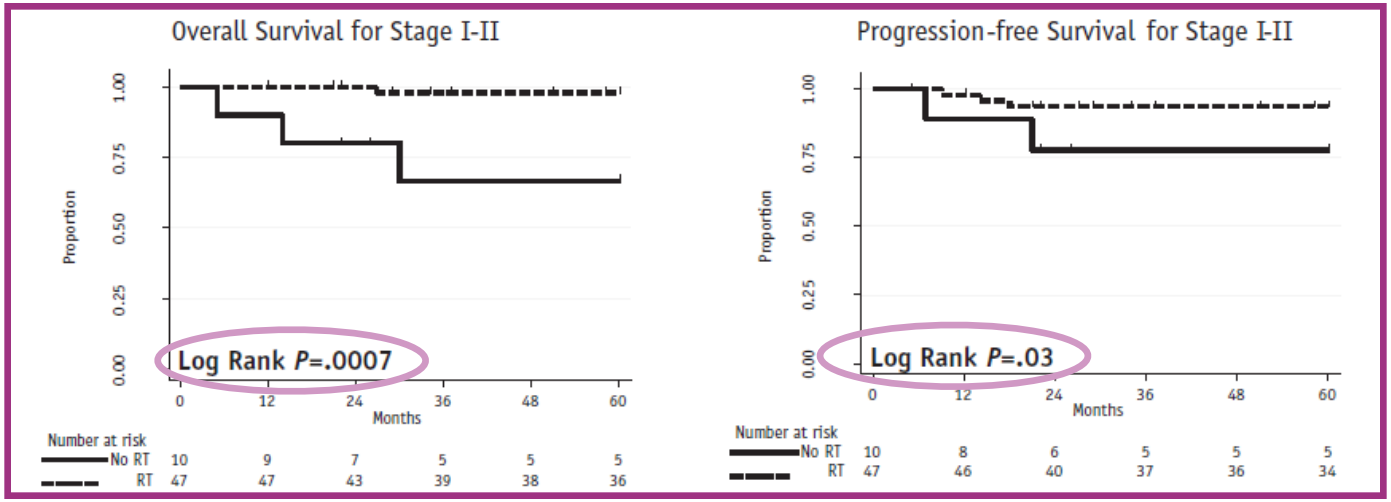
Conclusions: Relatively high rates of survival were achieved but the number of local failures suggests that the dose of radiotherapy should remain higher than it is for other types of lymphoma. Disability after treatment due to pathological fracture was not seen.

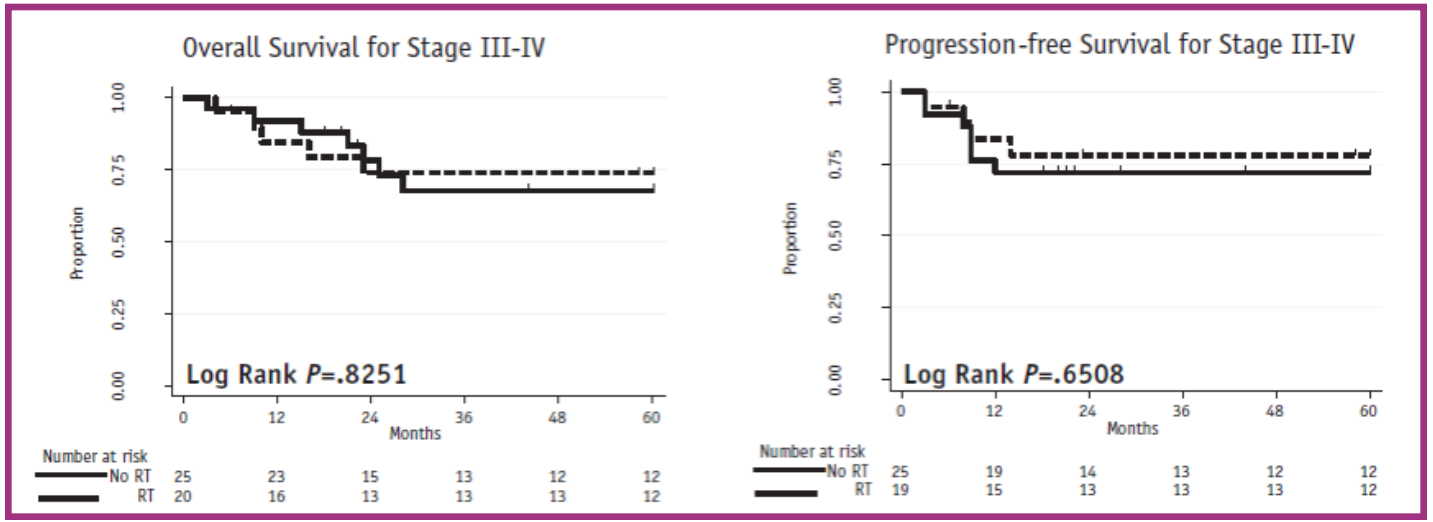
- 102 patients with primary bone DLBCL
- median age: 55 years (range, 16-87 years)
- most common site of presentation: long bones

- RT: 67 pts (66%)
  - 47 pts stage I – II
  - 20 pts stage III – IV
- median RT dose: 44 Gy



Tao et al, IJROBP, 2015





Tao et al, IJROBP, 2015

Table 3 Patient characteristics with overall and progression-free survival in multivariate Cox regression model

Characteristic	Overall survival		Progression-free survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
IPI score				
0-1	Ref		Ref	
2-3	2.1 (0.3-16.8)	.481	0.4 (0.06-2.4)	.303
4-5	13.5 (6.9-114.7)	.037	24.3 (3.3-178.2)	.002
Single or multiple bony sites				
Single	Ref		Ref	
Multiple	18.0 (2.1-157.4)	.035	11.7 (1.7-79.4)	.012
Response to chemotherapy				
Complete	Ref		Ref	
Partial	1.7 (0.4-7.2)	.075	4.5 (0.7-29.6)	.118
No response/progression	5.2 (1.3-19.8)	.003	30.8 (4.1-233.7)	.001
Radiation therapy				
No	Ref		Ref	
Yes	0.3 (0.09-1.01)	.053	0.14 (0.03-0.72)	.014

Abbreviations: CI = confidence interval; HR = hazard ratio; IPI = International Prognostic Index.

No significant difference in PFS or OS was found between patients treated with 30 to 35 Gy versus ≥ 36 Gy

Tao et al, IJROBP, 2015

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

After chemotherapy, complete regression of PET uptake may not be clear at the time of RT

Dose range is 30 to 40 Gy, depending on the certainty that a CR has been obtained with systemic treatment

Yahalom et al, IJROBP, 2015

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Treatment

- *Combined modality therapy:*

R-CHOP x 6 cycles followed by 30-40 Gy ISRT

Therapeutic issues

- Risk of CNS recurrence associated with skeletal involvement is a matter of debate, with rates of 4% and 0.6% respectively for DLCL patients with and without skeletal involvement

- In the IELSG-14 study, CNS involvement occurred in 2.5% of patients with primary bone DLCL

- Available evidence suggests that CNS prophylaxis is superfluous in primary bone DLCL

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Primary CNS Lymphoma (PCNSL)

Joachim Yahalom, M.D.
Memorial Sloan Kettering Cancer Center
New York ,NY, USA

Memorial Sloan Kettering Cancer Center

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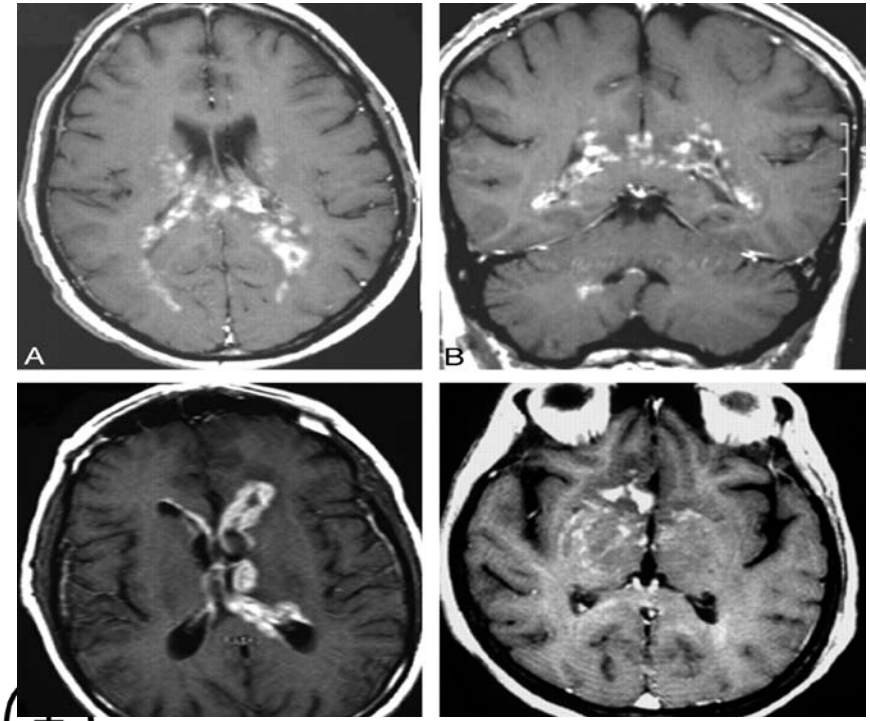
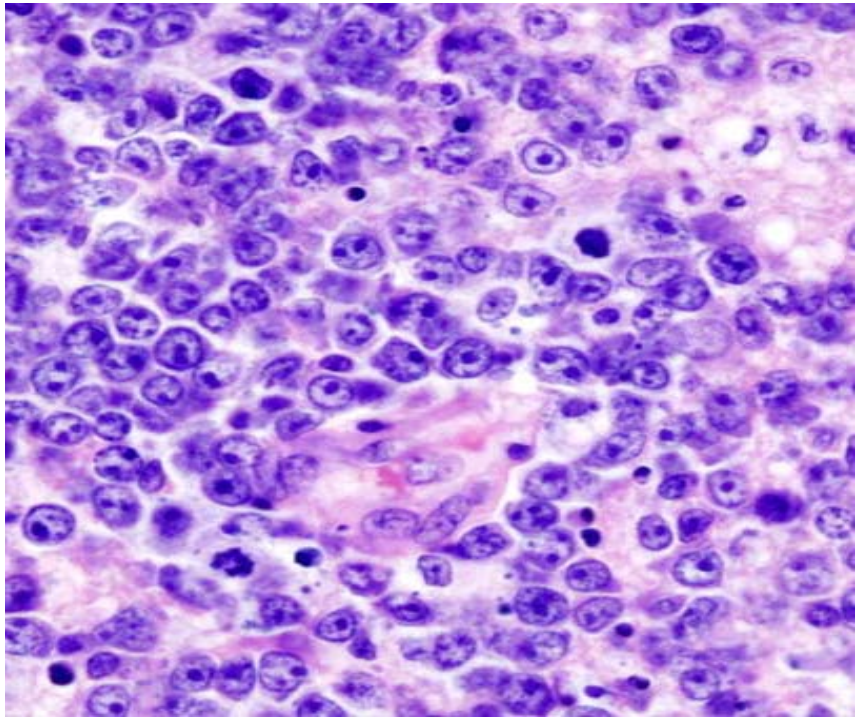
Definitions

- **PCNSL -** Extranodal non-Hodgkin's lymphoma confined to the cranio-spinal axis without evidence of systemic involvement
- **Secondary Nervous System Lymphoma (SNSL)-** Systemic lymphoma with involvement of the nervous system

Primary CNS Lymphoma (PCNSL)





Memorial Sloan Kettering Cancer Center

ILROG International Lymphoma Radiation Oncology Group

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Primary CNS Lymphoma: A unique lymphoma entity

- Increasing incidence (immunocompetent, older)
- PCNSL- Confined to brain (occasionally to eyes and CSF)
- Systemic spread is very rare
- Multi-centric in the brain in presentation and in relapse (unlike gliomas)
- Resection is not associated with better outcome
- May initially improve and even temporarily disappear with steroids (may mask a diagnosis)

PCNSL

Epidemiology

- ***Central Brain Tumor Registry of the United States (CBTRUS), 1998-2002***
  - Brain Lymphoma
    - 3.1% of all primary CNS tumors
    - 0.46/100,000 person years
    - ~1000-1500 cases per year in the United States
    - Median age at diagnosis = 60
    - Incidence increased ~3-fold from 1973-1984 but recent SEER data suggests plateau of incidence

PCNSL

Epidemiology

- ***Risk Factors***
  - Immunosuppression
    - Congenital (SCID, Wiskott-Aldrich Syndrome)
    - Acquired (HIV)
      - The risk of PCNSL in HIV patients is 3600-fold higher than general population
      - Up to 2/100 HIV infected persons develop PCNSL
    - Iatrogenic (Organ allograft recipients)

PCNSL in “immunocompetent” hosts

(non-HIV)

Primary CNS Lymphoma

- Type

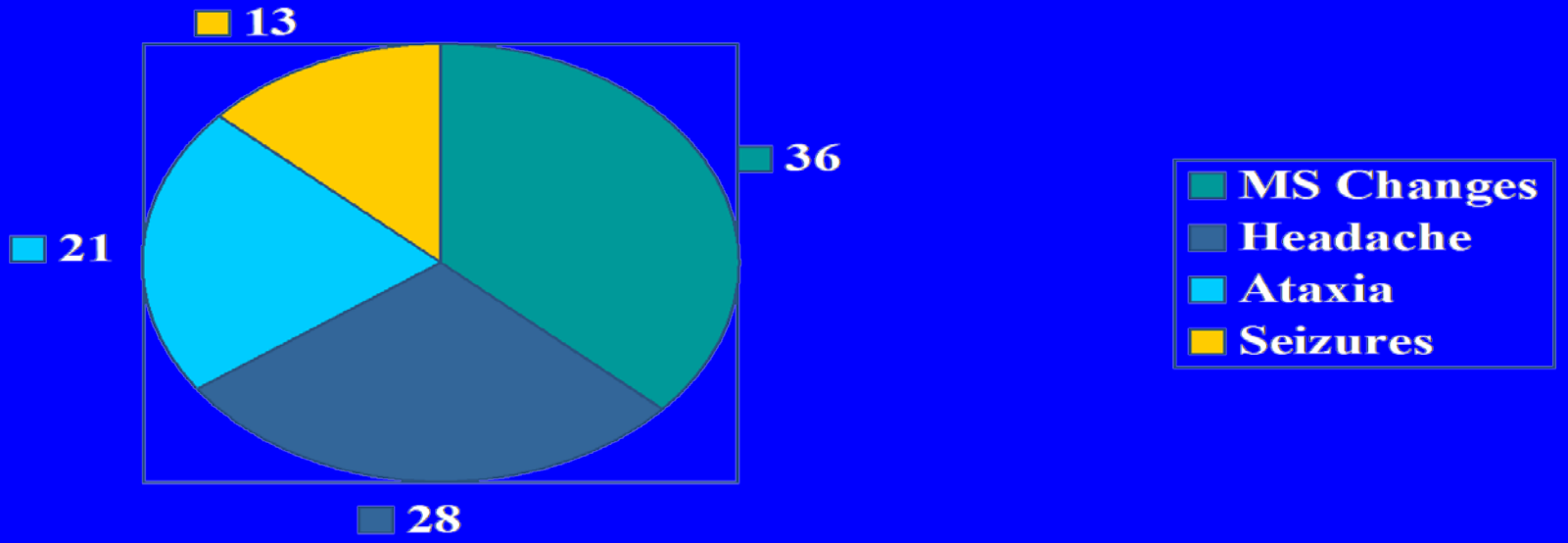
- Primary
  - Brain
  - Leptomeninges
  - Eye
  - Spinal cord
- Metastatic
  - Leptomeninges 4-11%
  - Epidural 3-5%
  - Brain 1%

- Clinical Features

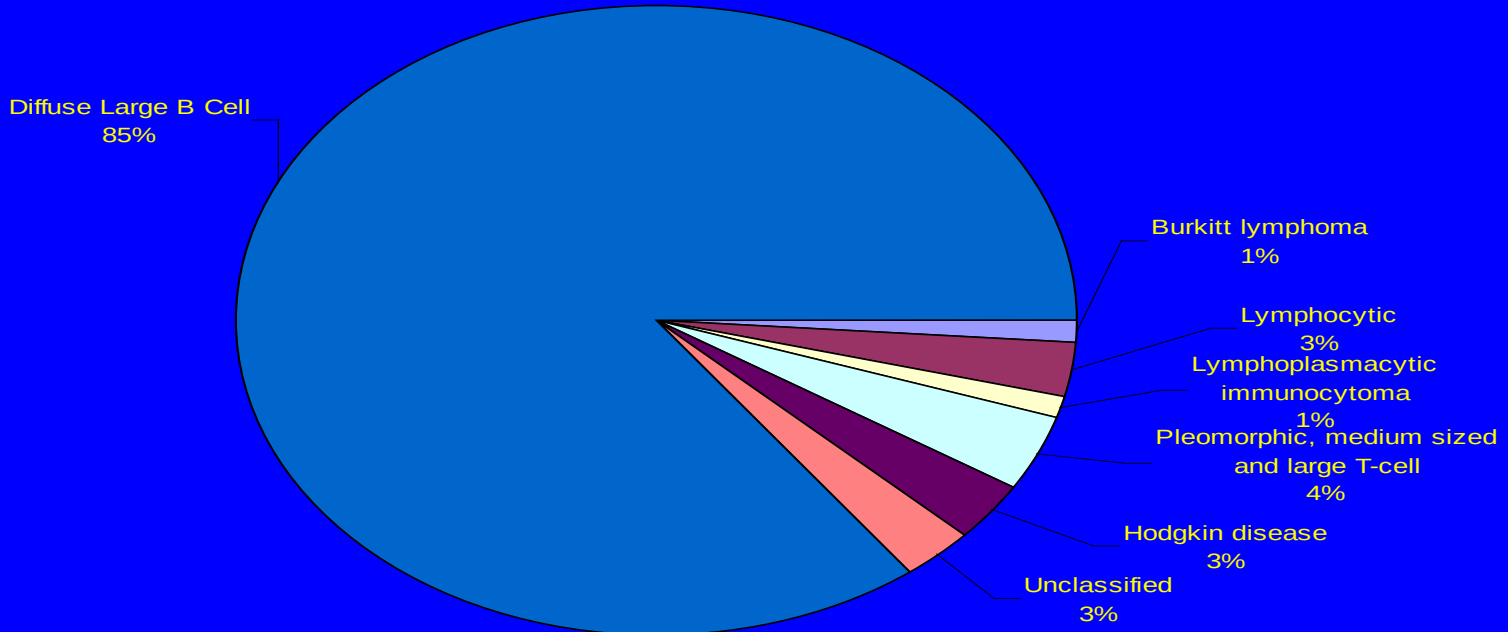
- Mean age = 60
- Gender: men: women - 1:1
- 23% ocular involvement
- 17% positive CSF cytology
- Clinical features
  - 51% behavioral/personality
  - 28% hemiparesis
  - 13% seizure
- DLBCL histology
  - ~85% Non-GC

PCNSL

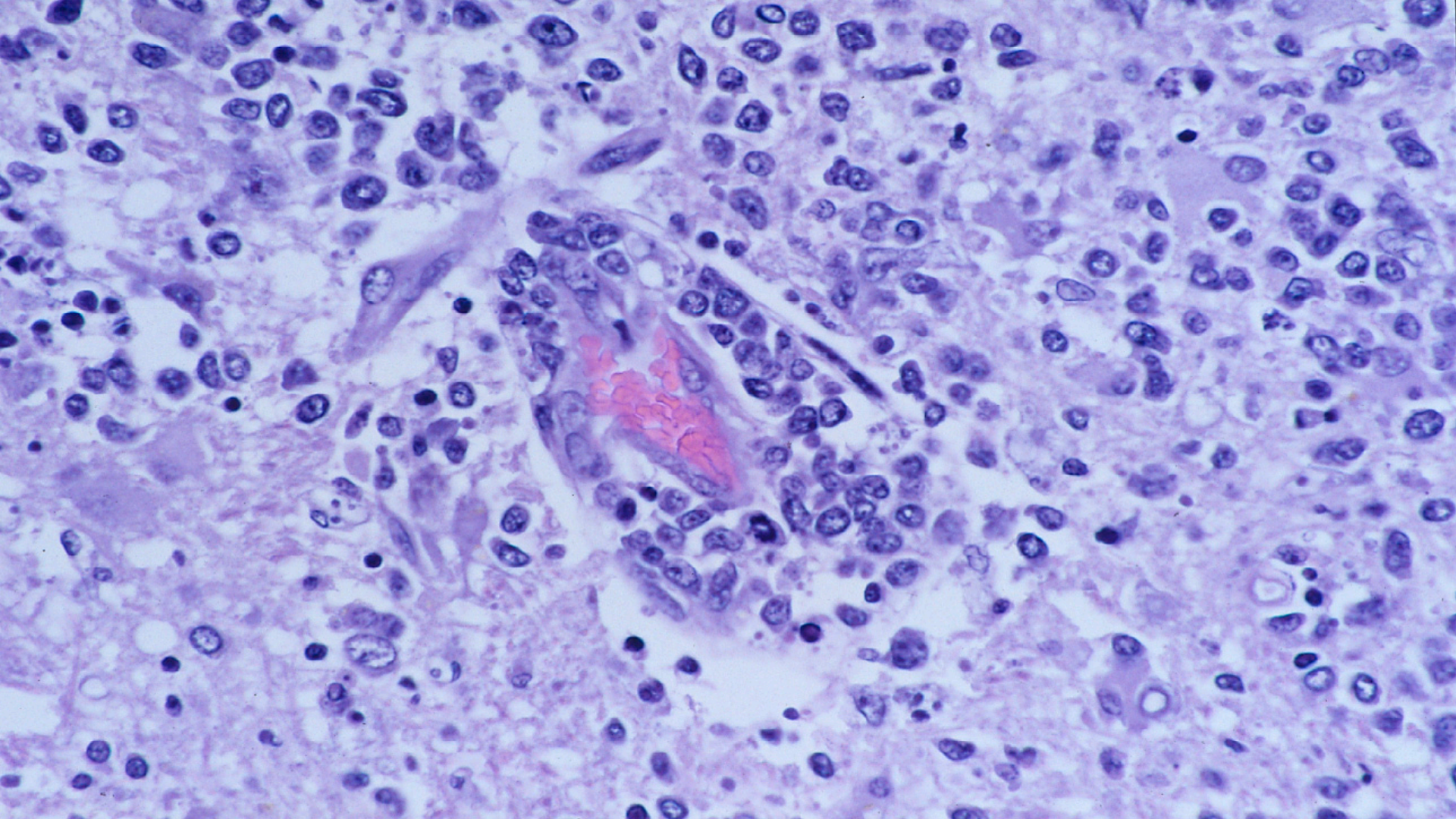
Symptoms

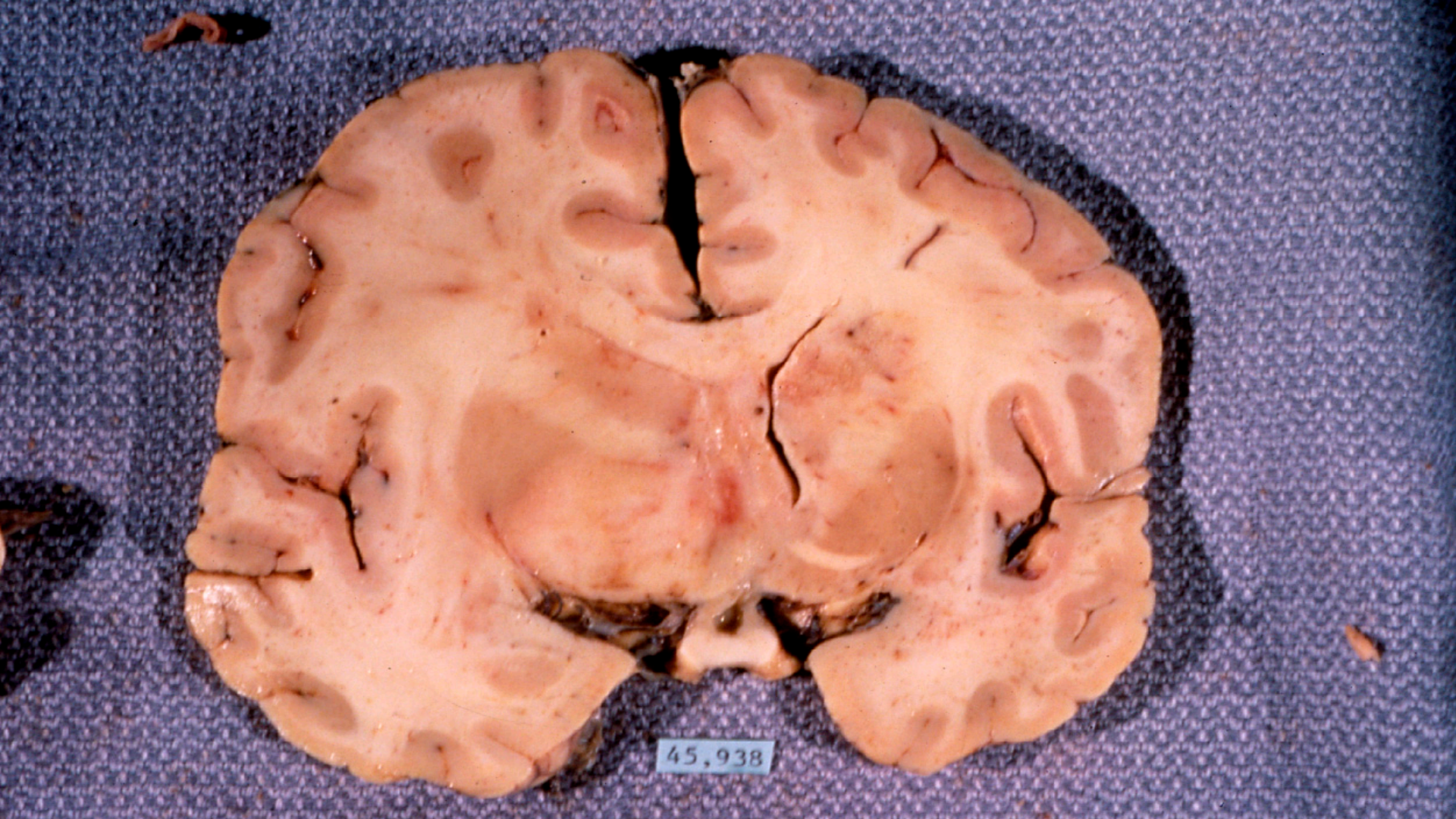


REAL classification of 72 Immunocompetent PCNSL Patients1



[1]*Am J Clin Pathol 1998;110:607-612.*

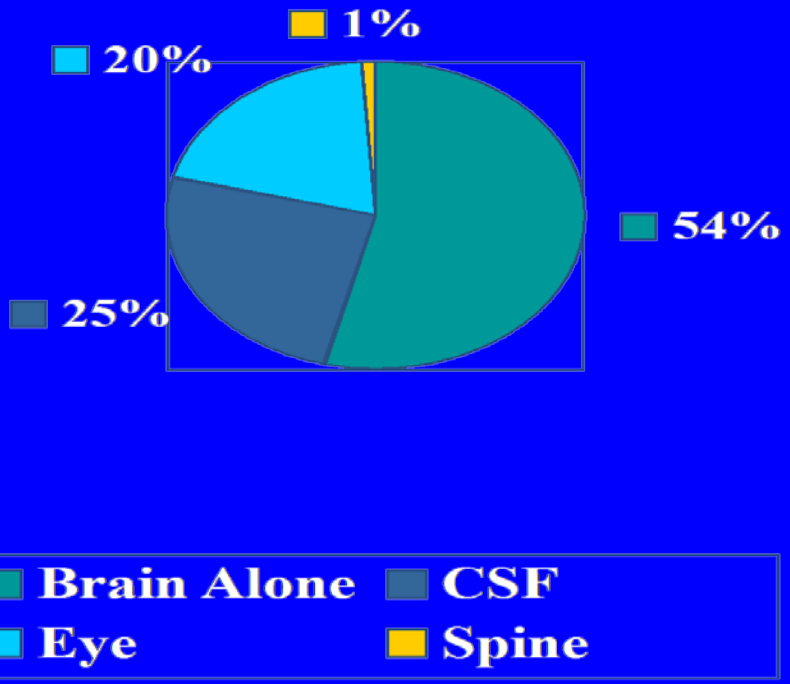



45.938

PCNSL

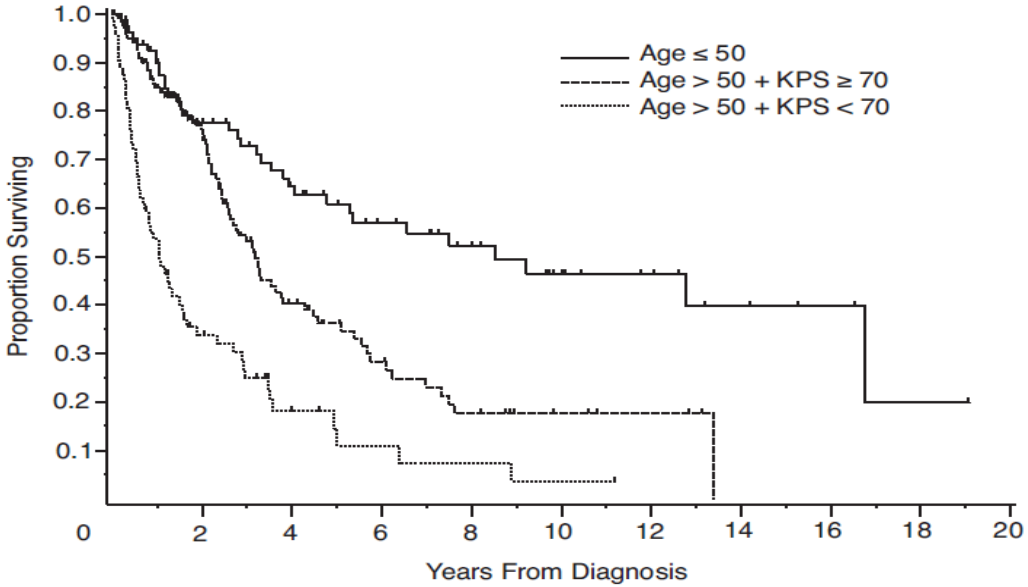
Extent of Disease

- Brain
  - 2/3 supratentorial, 1/3 infratentorial
  - 3/4 solitary, 1/4 multiple
- CSF (13-41%)
- Eye (5-20%)
- Spine (<1%)



Primary CNS Lymphoma

- Prognostic factors critical: age and KPS
- Prognostic model in pts treated with HD MTX-based Rx
- Pathologic subtype important?



(Abrey et al., JCO 2002)

Memorial Sloan Kettering Cancer Center

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PCNSL: A unique treatment challenge

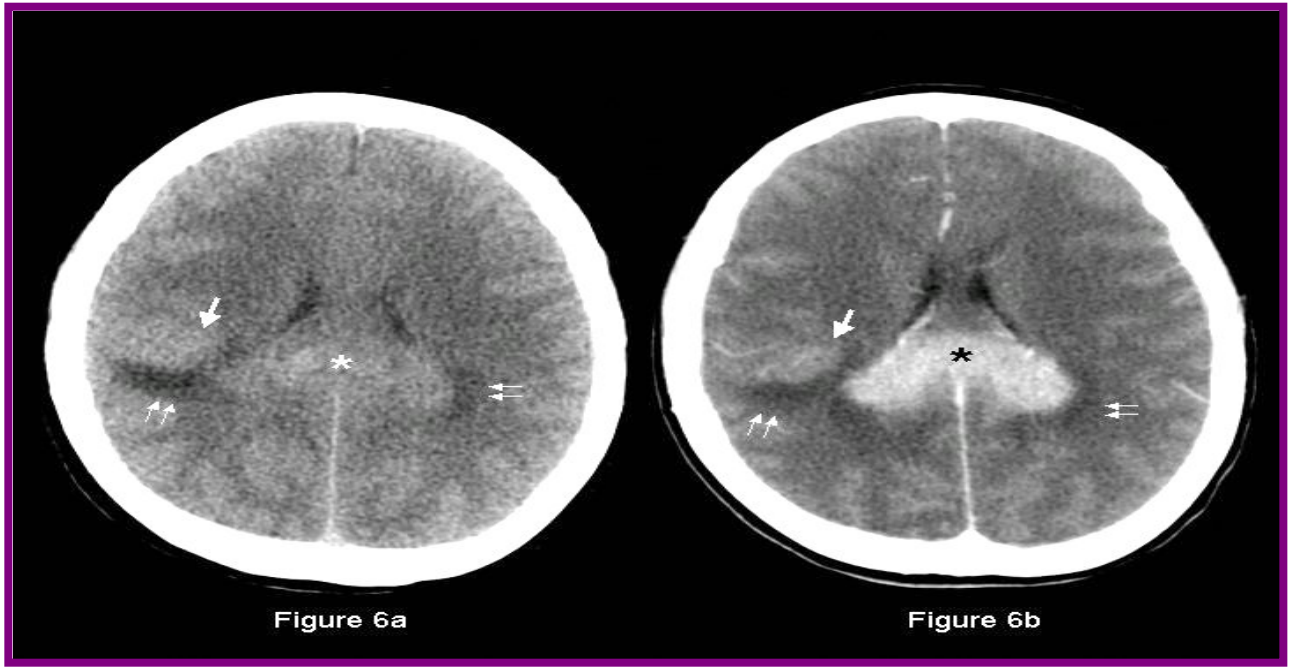
- Rapidly lethal if not treated or responsive
- **RT alone is effective**, but CRs are brief (median survival– 1 yr)
- Adding CHOP or CHOD does not improve RT alone results
- **High-Dose Methotrexate** is the mainstay of effective treatment best for inducing a complete response
- There may be a small benefit from adding rituximab
- High-dose ARA-C has also been used for consolidation and salvage
- High-dose chemotherapy with autologous stem cell rescue has been suggested as an alternative to RT consolidation for fit patients

PCNSL Baseline Evaluation

- **Pathologic Evaluation**
  - Centralized confirmation of pathology with immunopathology when possible
- **Clinical Evaluation**
  - Complete medical, neurological, cognitive examination
  - Determination of prognostic factors (age, PS)
- **Laboratory Evaluation**
  - HIV, lactate dehyrogenase, creatinine clearance
- **Extent of Disease Evaluation**
  - Brain- Contrast-enhanced cranial MRI
  - CSF- Cytology, flow cytometry, IgH PCR
  - Eye- Slit lamp evaluation
  - Body- CT of chest/abdomen/pelvis; BM biopsy + aspirate. Consider testicular US in older men

PCNSL

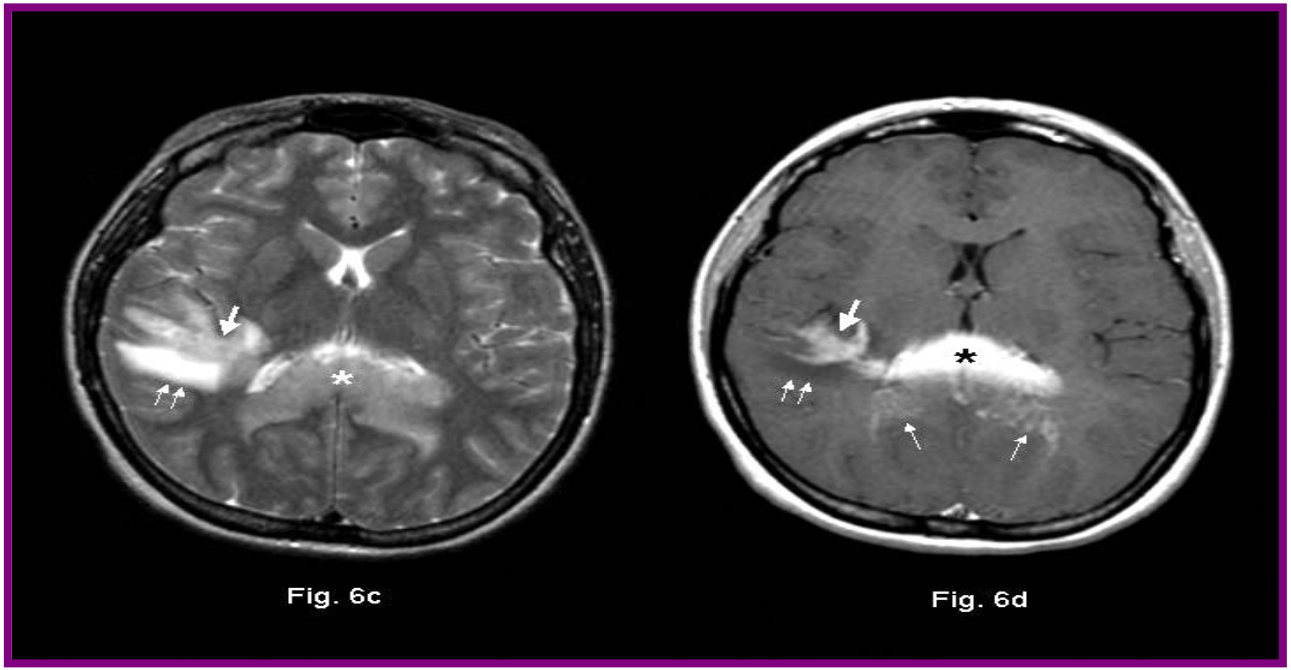
CT Appearance



From: Batchelor TT, Buchbinder BD, Harris NL. Case records of the Massachusetts General Hospital, A 32 year old woman with difficulty walking, headache and nausea. *N Engl J Med* 2005; 352: 185-194

PCNSL

MRI Appearance



From: Batchelor TT, Buchbinder BD, Harris NL. Case records of the Massachusetts General Hospital, A 32 year old woman with difficulty walking, headache and nausea. *N Engl J Med* 2005; 352: 185-194

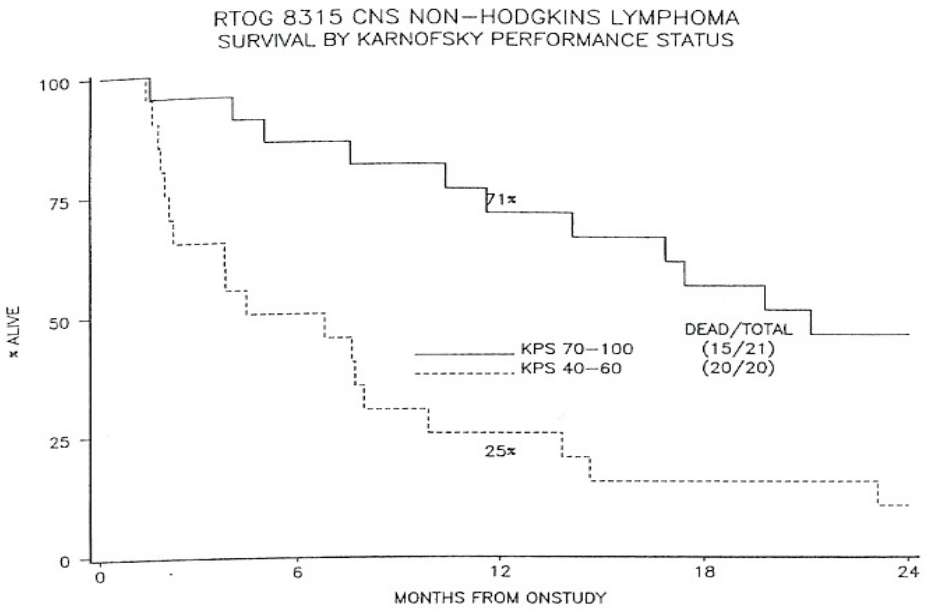
The debated role of RT consolidation

- A brief (forgotten) history of WBRT alone
- The breakthrough for cure with MTX followed by WBRT
- The great concern of post-MTX radiation-related neurotoxicity
- Efforts to match the results of combined modality with higher dose chemotherapy alone and effective salvage
- The controversial phase III study
- High-dose chemotherapy with autologous stem cell transplantation
- An alternative combined modality with low-dose RT and rare toxicity

RTOG 83-15 WBRT alone

- 41 patients
- WBRT of 20 RT of 40 Gy + boos
  Gy to lesion (+ 2 cm margin)

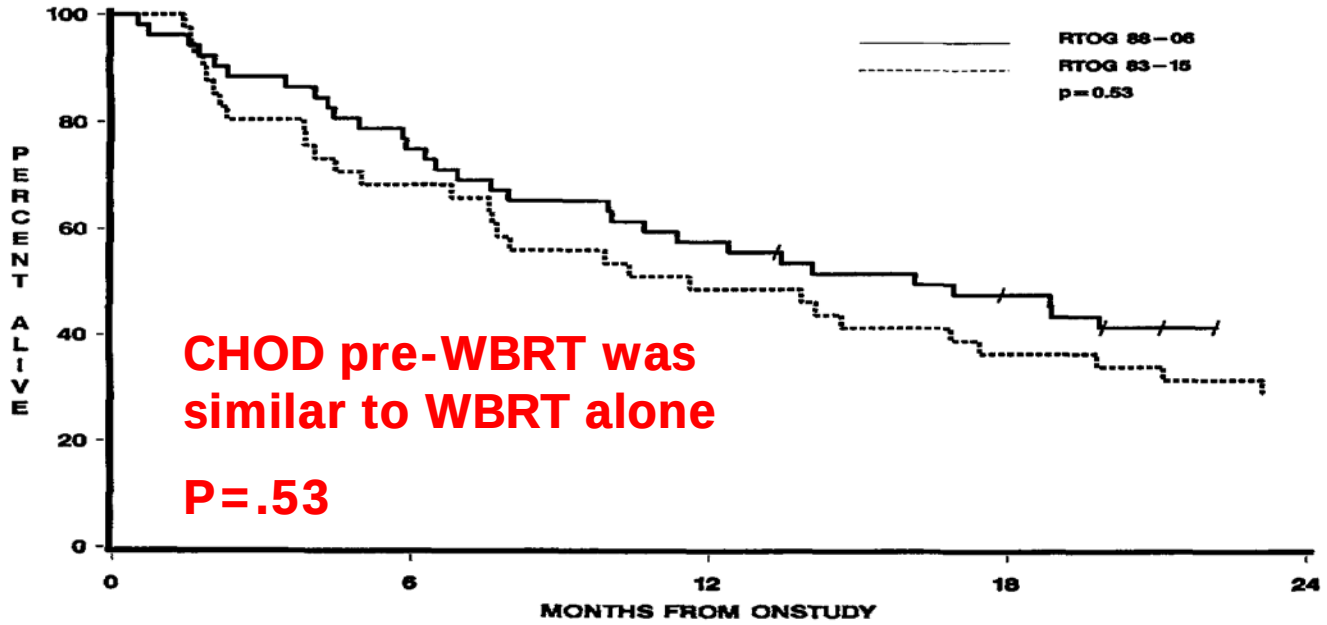
- **Overall median survival: 12 months**
  - <60 years: 23 months
  - ≥60 years: 8 months
  - KPS≥70: 21 month
  - KPS<70: 6 months
  - Relapses inside and outside the “boost” area



Nelson DF et al: IJROBP 1992; 23:9-17

Preirradiation Chemotherapy With Cyclophosphamide, Doxorubicin, Vincristine, and Dexamethasone for Primary CNS Lymphomas: Initial Report of Radiation Therapy Oncology Group Protocol 88-06

By Christopher Schultz, Charles Scott, William Sherman, Bernadine Donahue, Joseph Fields, Kevin Murray, Barbara Fisher, Ross Abrams, and Jeanne Meis-Kindblom



CHOD pre-WBRT was similar to WBRT alone

P=.53

JCO 1996;14:556-564

Diagnosis

↓

Dexamethasone 16mg/day

↓

Ommaya placement

↓

IV MTX (1 gm/M^2) Day 1,8

Intra-Ommaya MTX (12 mg/dose) Day 1,4,8,11,15,18

Taper dexamethasone (off by completion of RT)

↓

WBRT 200 cGyx20 (total 4000 cGy)

Coned-down 180 cGyx8 (total 1440 cGy)

↓

3 week rest

↓

IV cytosine arabinoside (3 gm/M^2/dose)

1 dose/day for 2 consecutive days

↓

3 week rest

↓

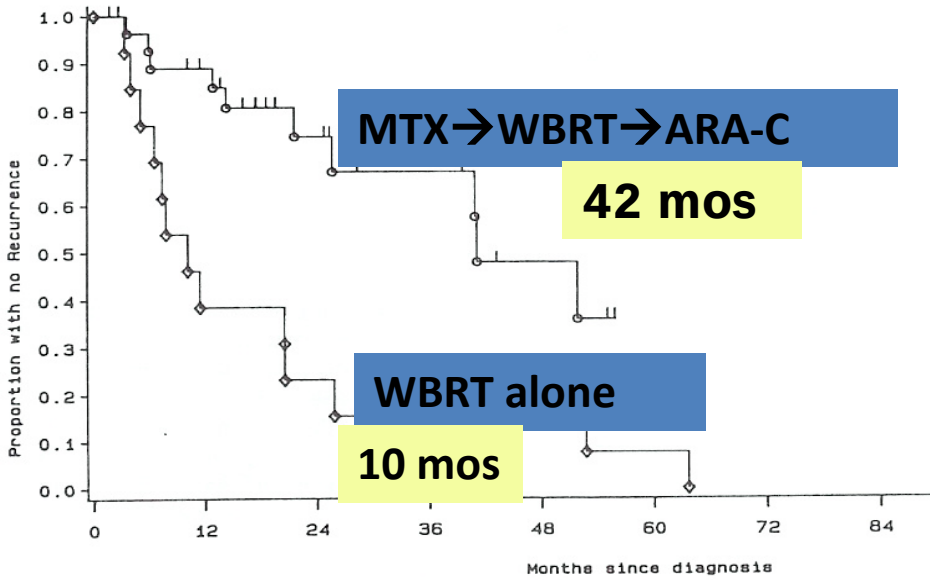
IV cytosine arabinoside (3 mg/M^2/dose)

Combined Modality Therapy for Primary CNS Lymphoma

By Lisa M. DeAngelis, Joachim Yahalom, Howard T. Thaler, and Uma Kher

Diagnosis
↓
Dexamethasone 16mg/day
↓
Ommaya placement
↓
IV MTX (1 gm/M^2) Day 1,8
Intra-Ommaya MTX (12 mg/dose) Day 1,4,8,11,15,18
Taper dexamethasone (off by completion of RT)
↓
WBRT 200 cGyx20 (total 4000 cGy)
Coned-down 180 cGyx8 (total 1440 cGy)
↓
3 week rest
↓
IV cytosine arabinoside (3 gm/M^2/dose)
1 dose/day for 2 consecutive days
↓
3 week rest
↓
IV cytosine arabinoside (3 mg/M^2/dose)
1 dose/day for 2 consecutive days

Fig 1. Outline of treatment protocol for PCNSL at MSKCC.



JCO 1992; 10:635-643

Long-Term Survival in Primary CNS Lymphoma

By Lauren E. Abrey, Lisa M. DeAngelis, and Joachim Yahalom

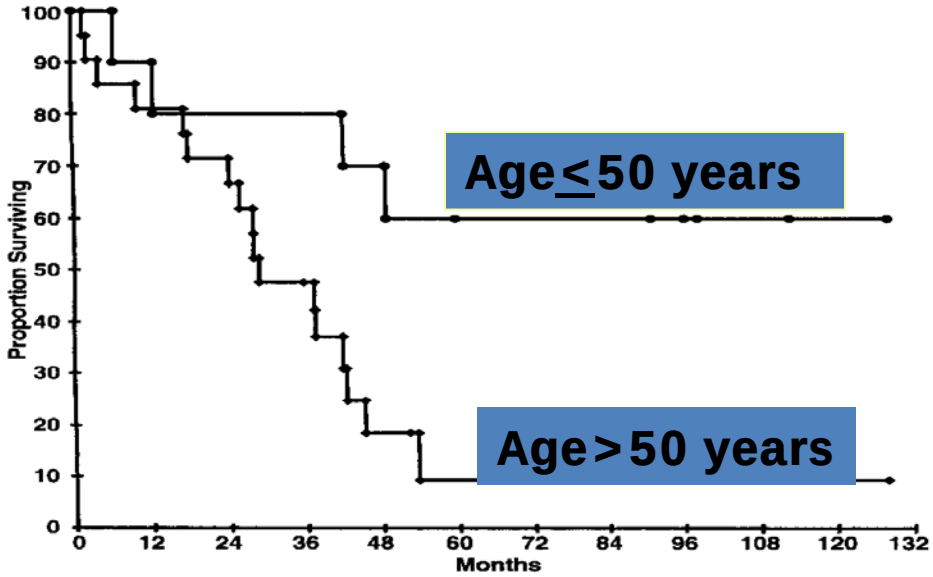
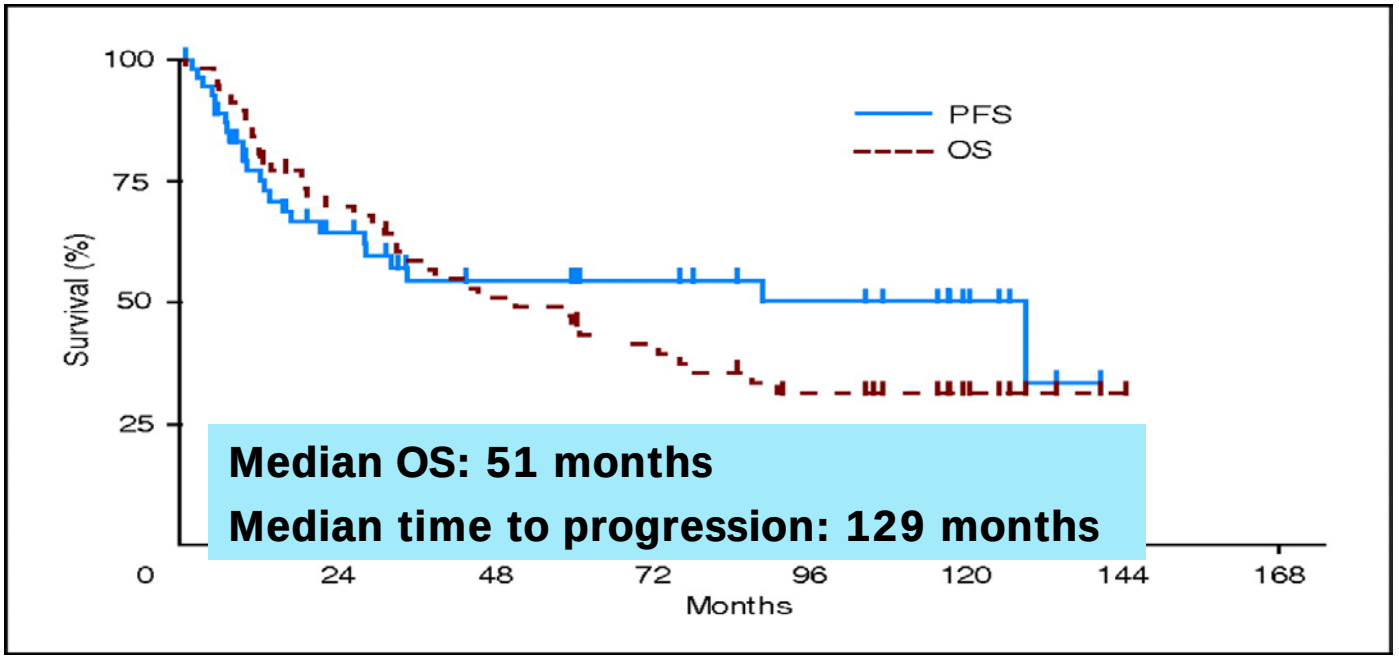


Fig 3. Kaplan-Meier plot: cause-specific survival comparing patients less than 50 years of age at diagnosis (circles) with patients aged more than 50 years (diamonds); $P = .01$ (Mantel-Cox method).

JCO 1992; 10:635-643

Overall survival (OS) and progression-free survival (PFS) for the entire cohort
Median follow-up of 115 months



Gavrilovic, I. T. et al. J Clin Oncol; 24:4570-4574 2006

JOURNAL OF CLINICAL ONCOLOGY

Neurotoxicity by Age

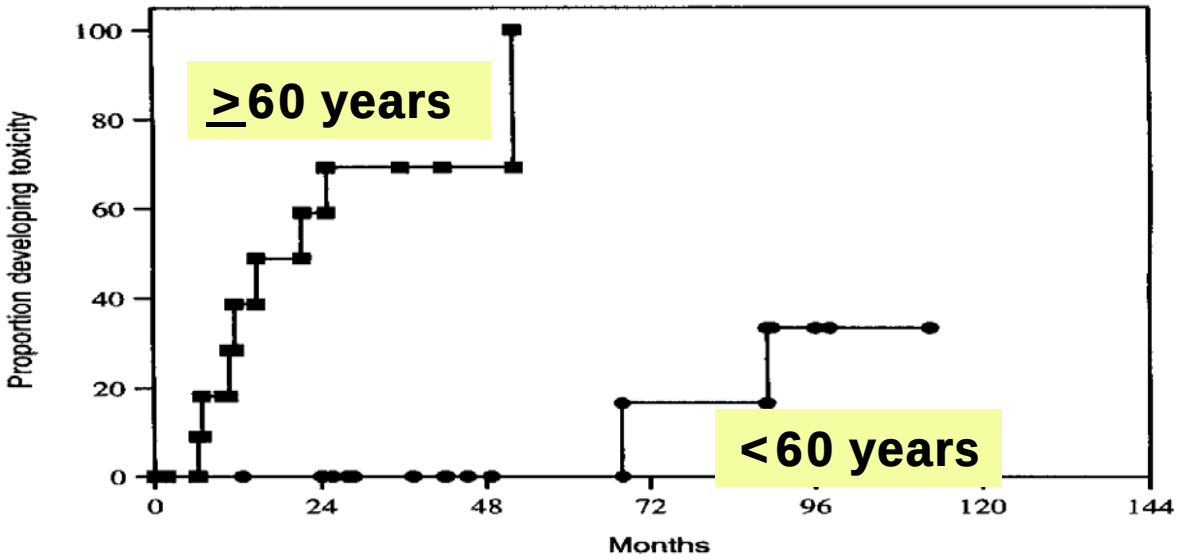
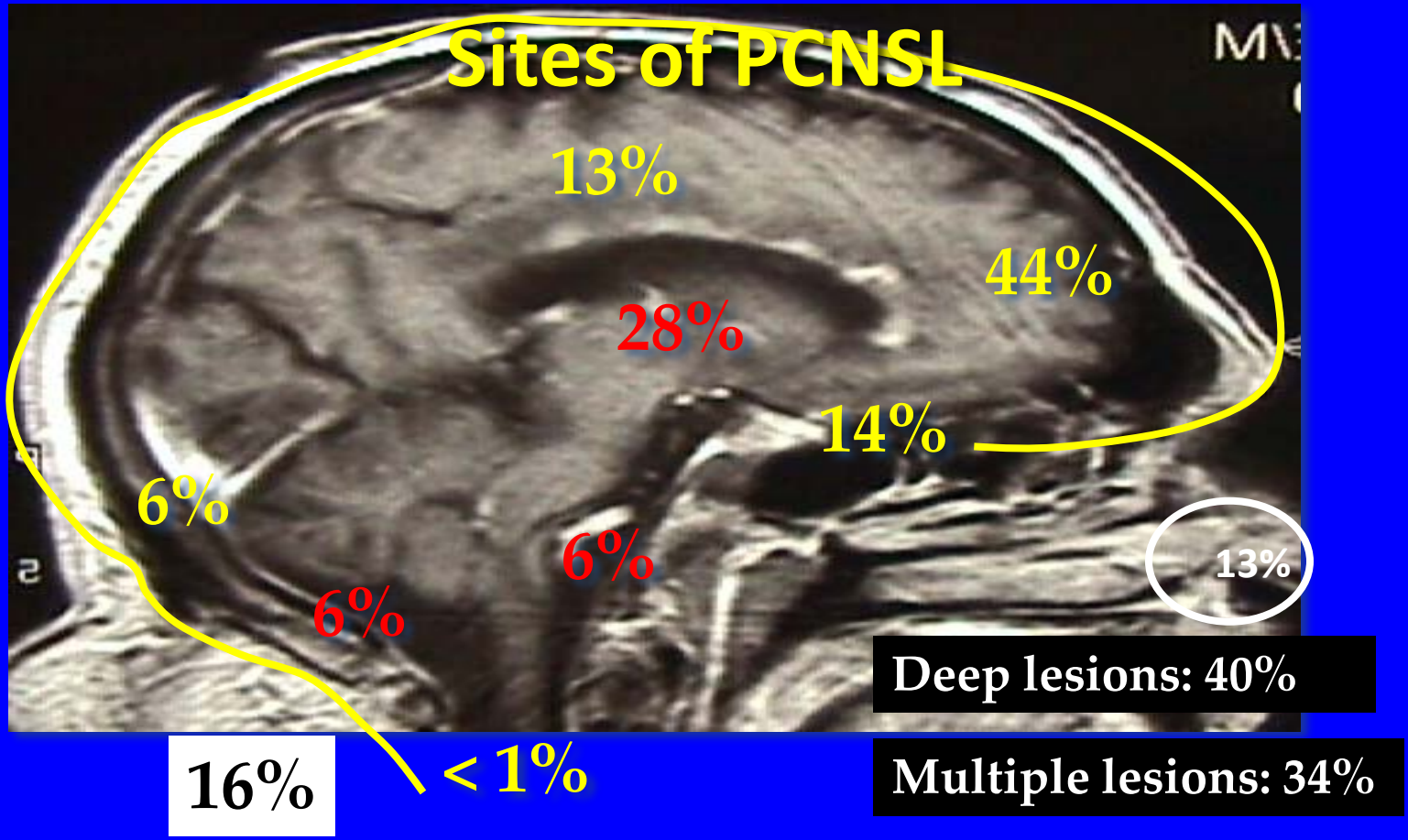
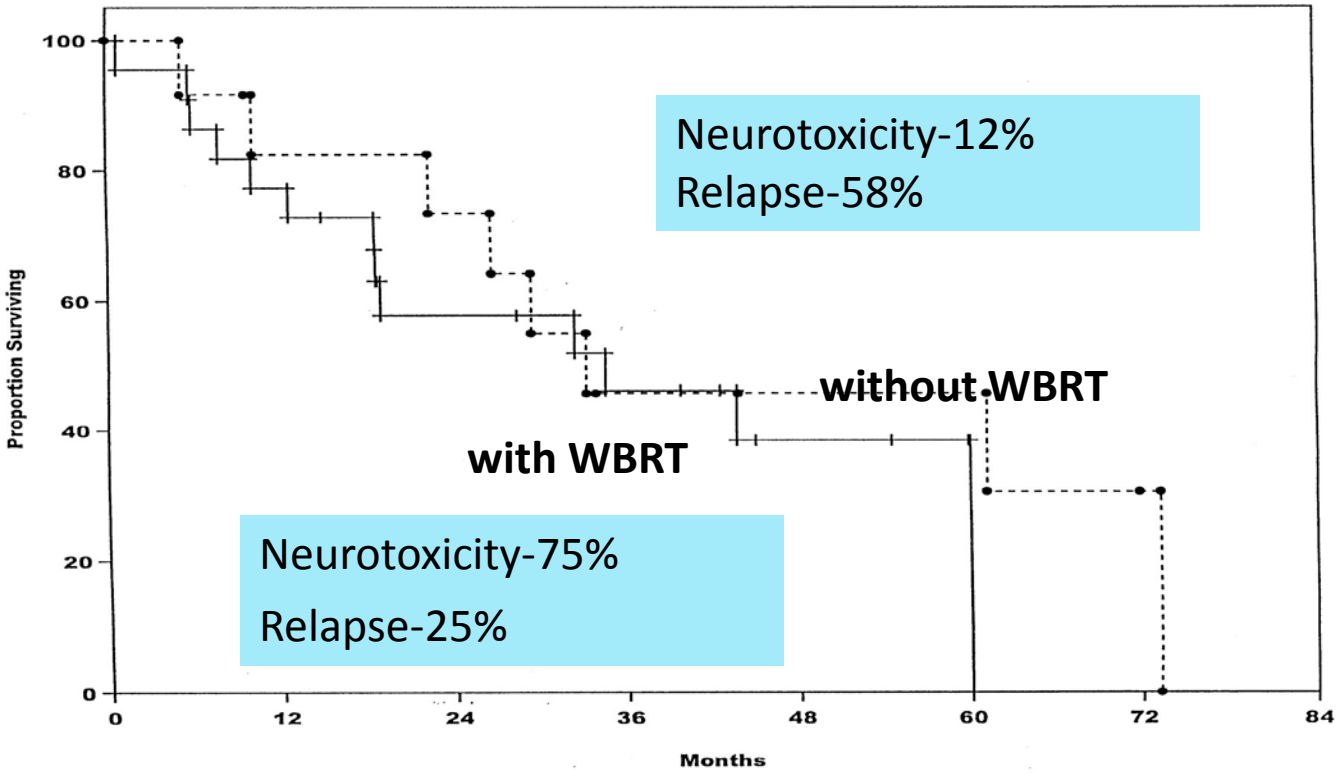


Fig 1. Proportion of patients who developed neurotoxicity with increasing duration of follow-up. Patients less than 60 years of age (circles) are compared with patients aged more than 60 years (squares); $P < .0001$ (Mantel-Cox method).


Sites of PCNSL
13%
44%
28%
14%
6%
6%
6%
13%
16%
< 1%
Deep lesions: 40%
Multiple lesions: 34%

Overall survival of patients ≥ 60 years who did (n = 12) or did not (n = 22) receive whole-brain RT



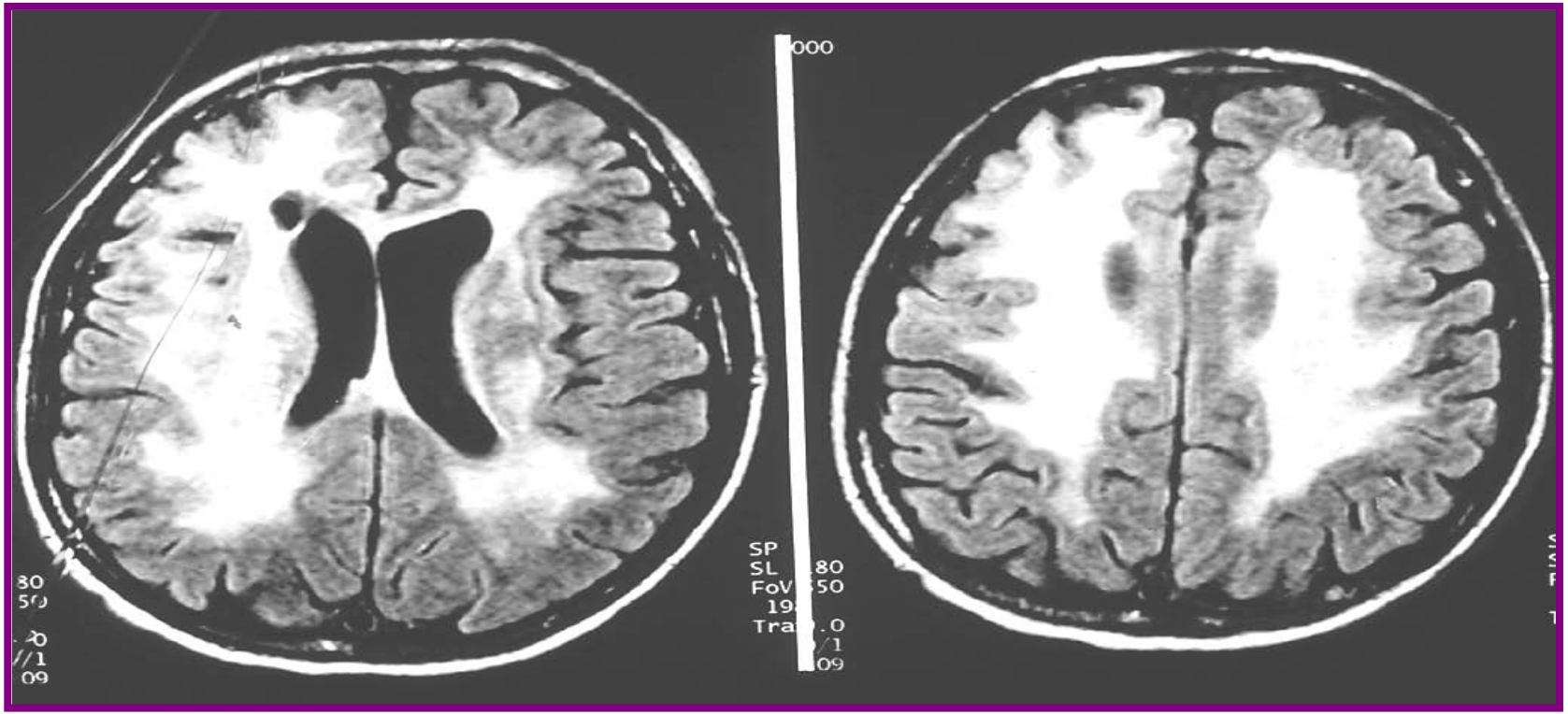
Abrey, L. E. et al. J Clin Oncol; 18:3144-3150 2000

JOURNAL OF CLINICAL ONCOLOGY

PCNSL - Neurotoxicity

- **Risk Factors**
  - Age > 60, MTX followed by full-dose whole brain RT
- **Clinical Features**
  - Imaging changes evident in most patients by 6 months after radiation
  - Clinical changes began at a median of 1 month in one study
  - Four domains most sensitive to disease and treatment
    - **Attention**
    - **Executive Functions**
    - **Memory**
    - **Psychomotor Speed**
  - **Occurs in many patients > 60 treated with MTX-WBRT (full dose)**

PCNSL- Neurotoxicity



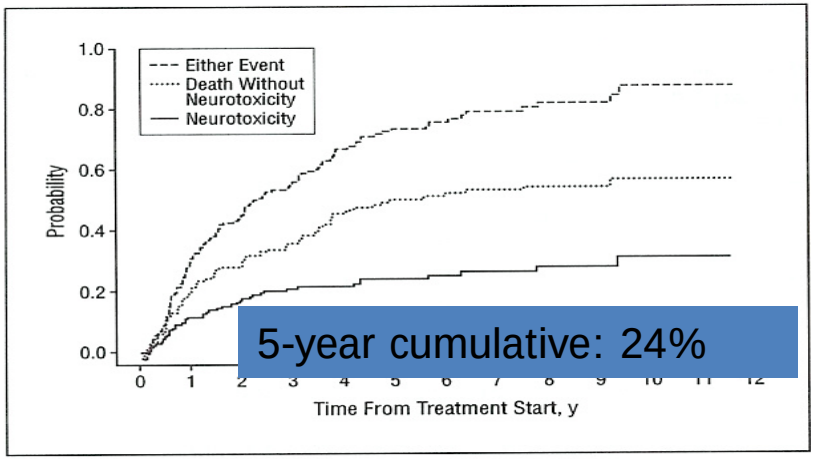
Increased T2 and FLAIR subcortical white matter signal abnormality associated with diffuse cerebral atrophy and ventricular enlargement

ORIGINAL CONTRIBUTION

Delayed Neurotoxicity in Primary Central Nervous System Lymphoma

Antonio M. P. Omuro, MD; Leah S. Ben-Porat, MS; Katherine S. Panageas, DrPH; Amy K. Kim, BA; Denise D. Correa, PhD; Joachim Yahalom, MD; Lisa M. DeAngelis, MD; Lauren E. Abrey, MD

MSKCC Experience: 185 pts (1985-2000)



5-year cumulative: 24%

Figure 1. Incidence of neurotoxicity, death, and either neurotoxicity or death (either event).

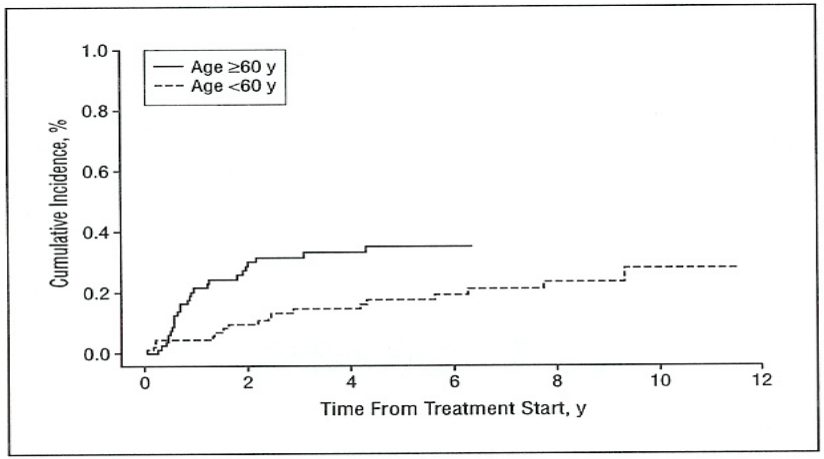


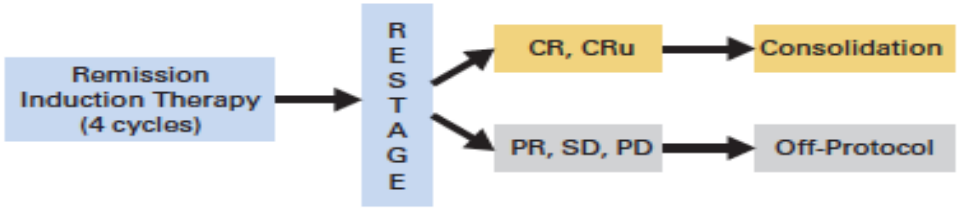
Figure 2. The incidence of neurotoxicity stratified by age, showing that although older patients are at a significantly higher risk, the development of neurotoxicity is also a concern in long-term survivors younger than 60 years.

***Arch Neurol.* 2005; 62:1-6**

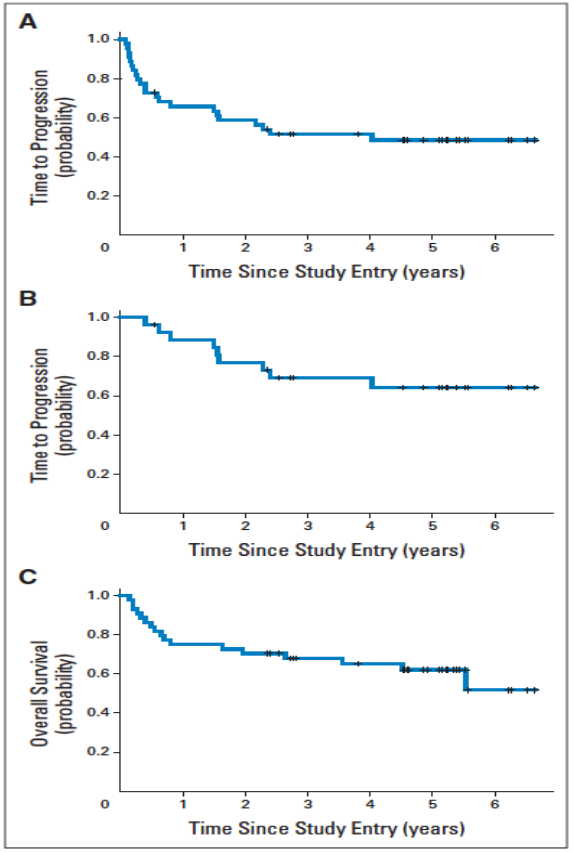
Intensive Chemotherapy and Immunotherapy in Patients With Newly Diagnosed Primary CNS Lymphoma: CALGB 50202 (Alliance 50202)

James L. Rubenstein, Eric D. Hsi, Jeffrey L. Johnson, Sin-Ho Jung, Megan O. Nakashima, Barbara Grant, Bruce D. Cheson, and Lawrence D. Kaplan

41 Patients- 26 completed treatment



Remission Induction Therapy: MT-R (14-day cycle)	
Day 1	Methotrexate 8 grams/m² IV over 4 hrs
Day 2	Leucovorin 100 mg/m² every 6 hrs, until methotrexate < 0.05 mM
Day 3	Rituximab 375 mg/m² IV cycles 1 through 6
Day 7-11	Temozolomide 150 mg/m² PO (odd cycles only)
Consolidation Therapy: EA	
Day 1-4	Etoposide 40 mg/kg continuous IV over 96 hrs
Day 1-4	Cytarabine 2 gm/m² IV over 2 hrs every 12 hrs × 8 doses



VOLUME 31 · NUMBER 25 · SEPTEMBER 1 2013
JOURNAL OF CLINICAL ONCOLOGY

High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial

Eckhard Thiel, Agnieszka Korfel*, Peter Martus, Lothar Kanz, Frank Griesinger, Michael Rauch, Alexander Röth, Bernd Hertenstein, Theda von Toll, Thomas Hundsberger, Hans-Günther Mergenthaler, Malte Leithäuser, Tobias Birnbaum, Lars Fischer, Kristoph Jahnke, Ulrich Herrlinger, Ludwig Plasswilm, Thomas Nägele, Torsten Pietsch, Michael Bamberg, Michael Weller*

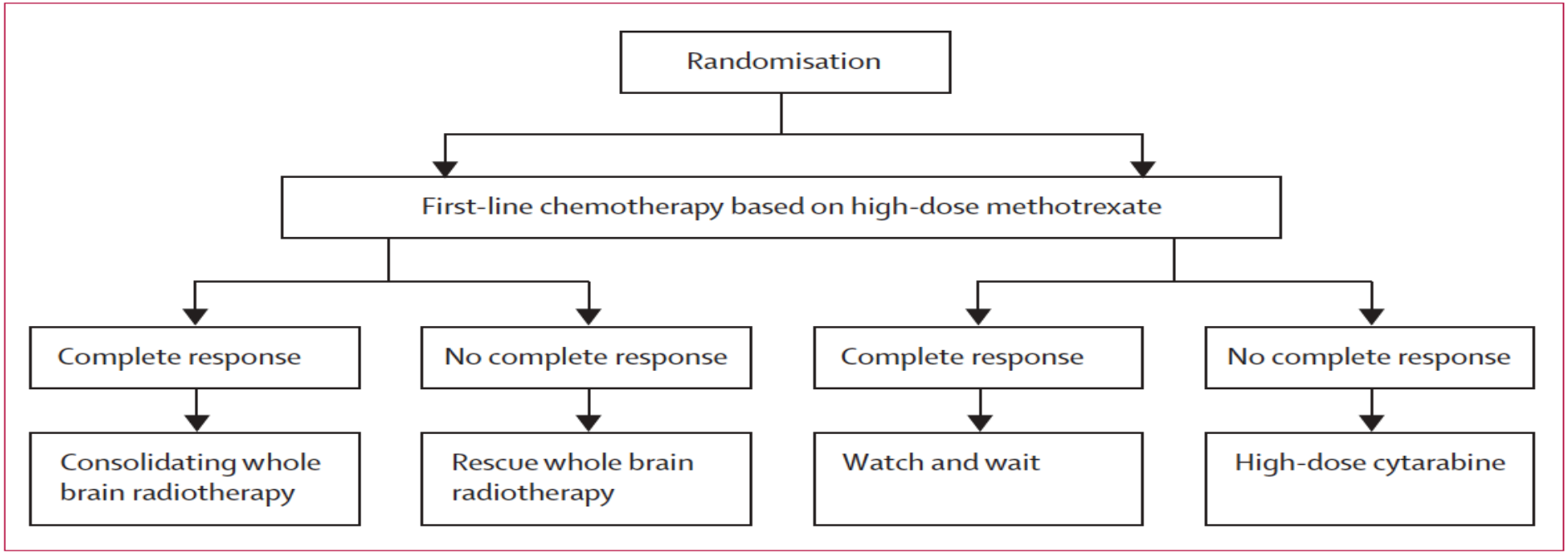
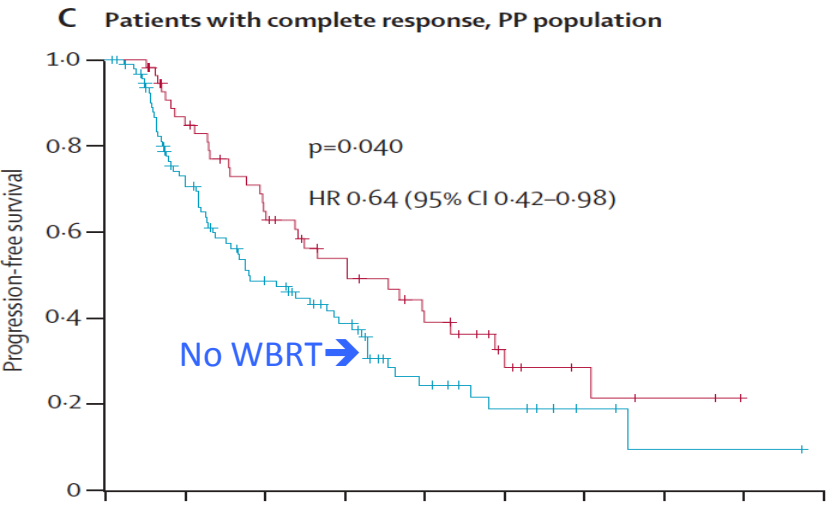
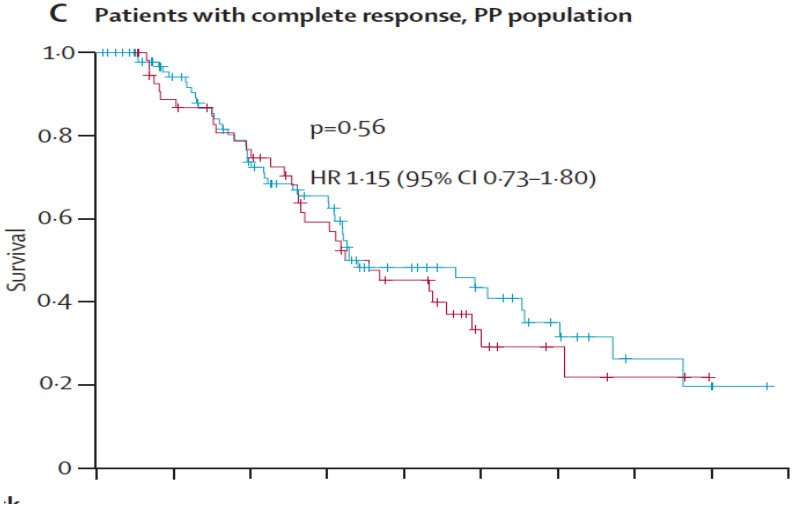


Figure 1: **Trial design**





Highly criticized:

- Poor protocol adherence
- Non-inferiority goal in OS not met
- Insufficient toxicity evaluation
- Overall poor results, sub-optimal chemo
- Neurotoxicity even with chemo alone (26%), with RT (49%)
- Salvage improved survival, but carries high QOL/toxicity cost

Hypothesis

Reduced-dose WBRT following effective immuno-chemotherapy will result in lower neurological toxicity while providing adequate disease control in all age groups

Chemotherapy Schedule

- **Day 1**
  - Rituximab 500 mg/m2
- **Day 2**
  - MTX 3.5 gm/m2
  - VCR 1.4 mg/m2
  - Procarbazine 100 mg/m2/d x 7 d. (cycles 1, 3, 5, 7)

X5 cycles (or X7, if PR)

- **Following WBRT**
  - ARA-C 3 gm/m2 (2 cycles)

RT Schedule

- **IF CR** after R-MVP X5 or X7 →**WBRT of 2340 cGy**

- **IF PR** after R-MVP X7 →**WBRT of 4500 cGy**

VOLUME 25 · NUMBER 30 · OCTOBER 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Combined Immunochemotherapy With Reduced Whole-Brain Radiotherapy for Newly Diagnosed Primary CNS Lymphoma

Gaurav D. Shah, Joachim Yahalom, Denise D. Correa, Rose K. Lai, Jeffrey J. Raizer, David Schiff, Renato LaRocca, Barbara Grant, Lisa M. DeAngelis, and Lauren E. Abrey

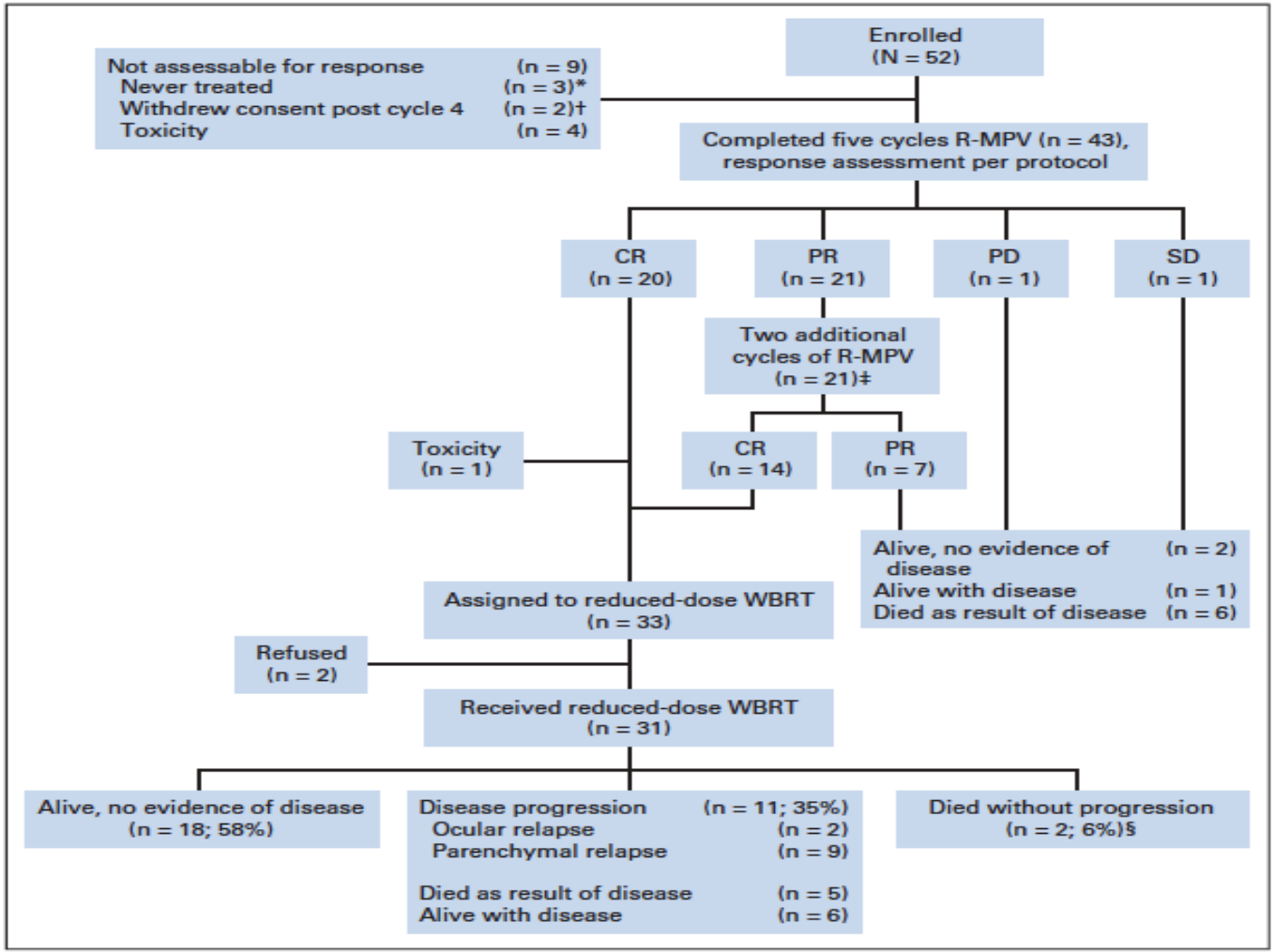
VOLUME 31 · NUMBER 31 · NOVEMBER 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Rituximab, Methotrexate, Procarbazine, and Vincristine Followed by Consolidation Reduced-Dose Whole-Brain Radiotherapy and Cytarabine in Newly Diagnosed Primary CNS Lymphoma: Final Results and Long-Term Outcome

Patrick G. Morris, Denise D. Correa, Joachim Yahalom, Jeffrey J. Raizer, David Schiff, Barbara Grant, Sean Grimm, Rose K. Lai, Anne S. Reiner, Kathy Panageas, Sasan Karimi, Richard Curry, Gaurav Shah, Lauren E. Abrey, Lisa M. DeAngelis, and Antonio Omuro


Enrolled
(N = 52)
Not assessable for response (n = 9)
Never treated (n = 3)*
Withdrew consent post cycle 4 (n = 2)†
Toxicity (n = 4)
Completed five cycles R-MPV (n = 43), response assessment per protocol
CR (n = 20)
PR (n = 21)
PD (n = 1)
SD (n = 1)
Two additional cycles of R-MPV (n = 21)‡
Toxicity (n = 1)
CR (n = 14)
PR (n = 7)
Alive, no evidence of disease (n = 2)
Alive with disease (n = 1)
Died as result of disease (n = 6)
Assigned to reduced-dose WBRT (n = 33)
Refused (n = 2)
Received reduced-dose WBRT (n = 31)
Alive, no evidence of disease (n = 18; 58%)
Disease progression (n = 11; 35%)
Ocular relapse (n = 2)
Parenchymal relapse (n = 9)
Died as result of disease (n = 5)
Alive with disease (n = 6)
Died without progression (n = 2; 6%)§

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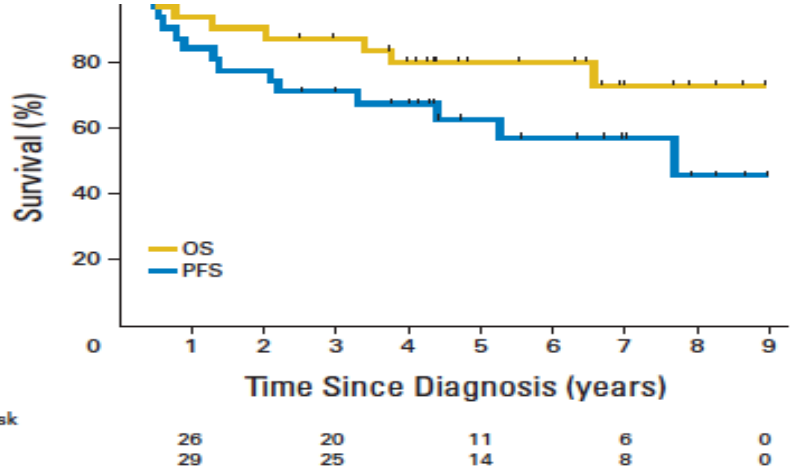

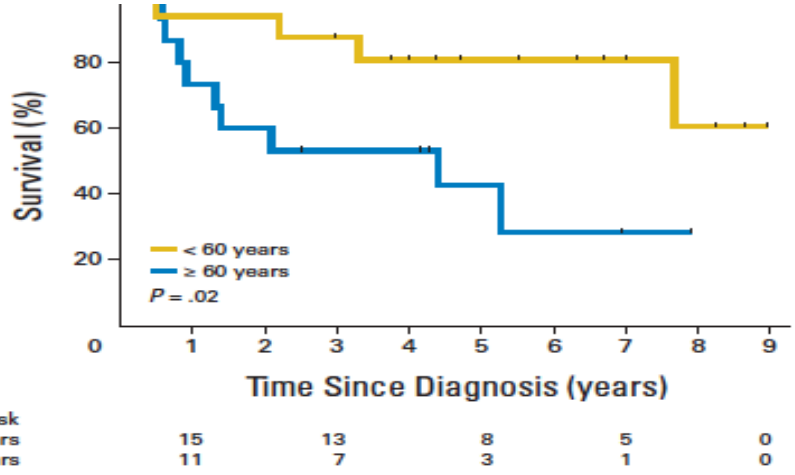

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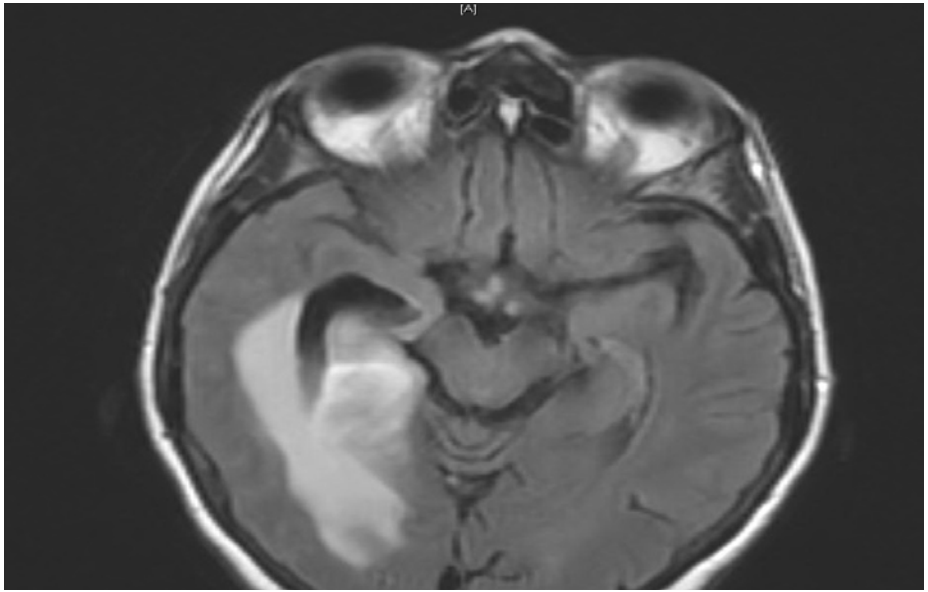
Rituximab, Methotrexate, Procarbazine, and Vincristine Followed by Consolidation Reduced-Dose Whole-Brain Radiotherapy and Cytarabine in Newly Diagnosed Primary CNS Lymphoma: Final Results and Long-Term Outcome

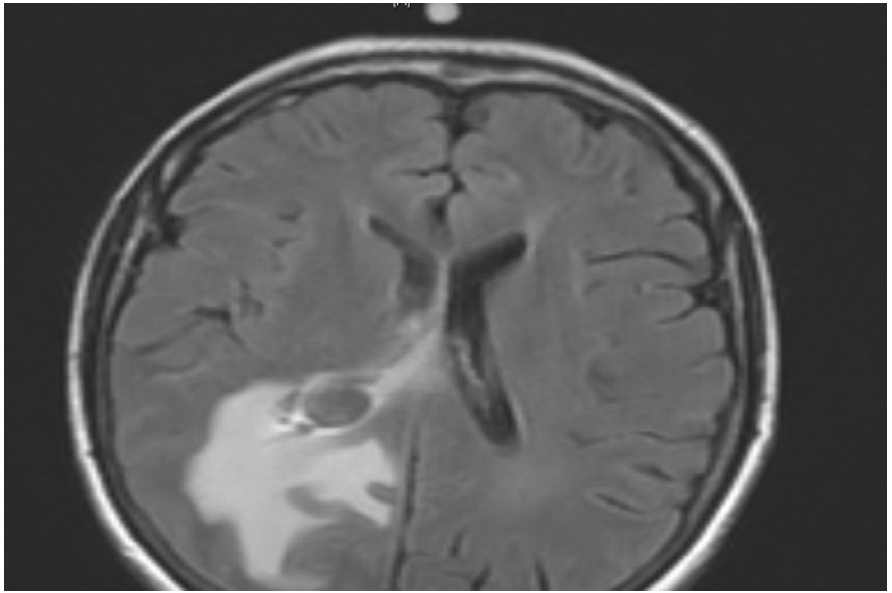
Patrick G. Morris, Denise D. Correa, Joachim Yahalom, Jeffrey J. Raizer, David Schiff, Barbara Grant, [illegible]geas, Sasan Karimi, Richard Curry, Gaurav Shah, [illegible]uro

Exploratory Neuropsychological and Imaging Correlates

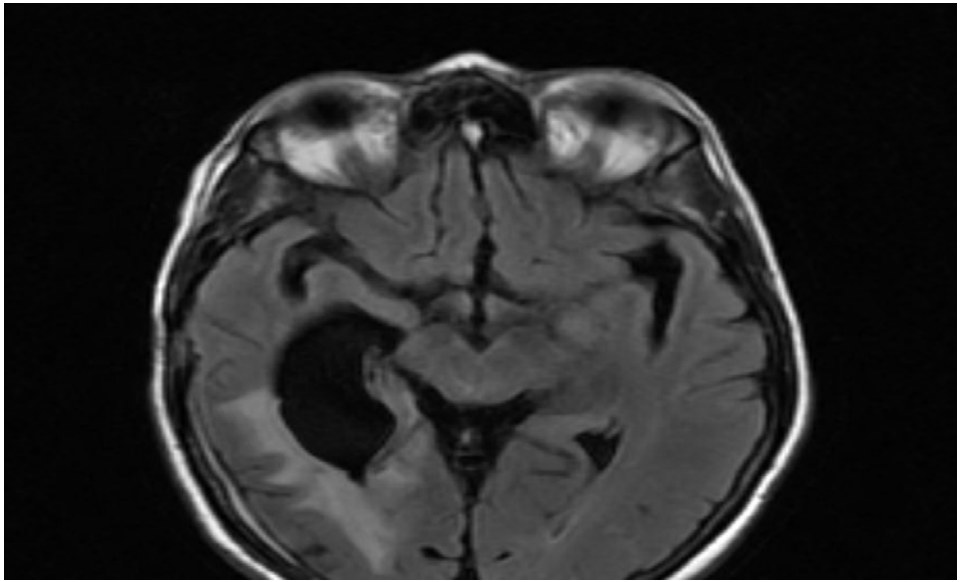
Among 31 patients who received rdWBRT, 12 patients (median age, 58 years, including three patients age ≥ 60 years) were progression-free and completed neuropsychological evaluations up to 48 months. At baseline, cognitive impairment was present in several domains. After induction chemotherapy, there was a significant improvement in executive ($P < .01$) and verbal memory ($P < .05$). There was no evidence of significant cognitive decline during the follow-up period, except for motor speed ($P < .05$). Minor fluctuations were observed on memory performance over time. There was no evidence of depressed mood, and self-reported quality of life remained stable during the follow-up period (Table 1).

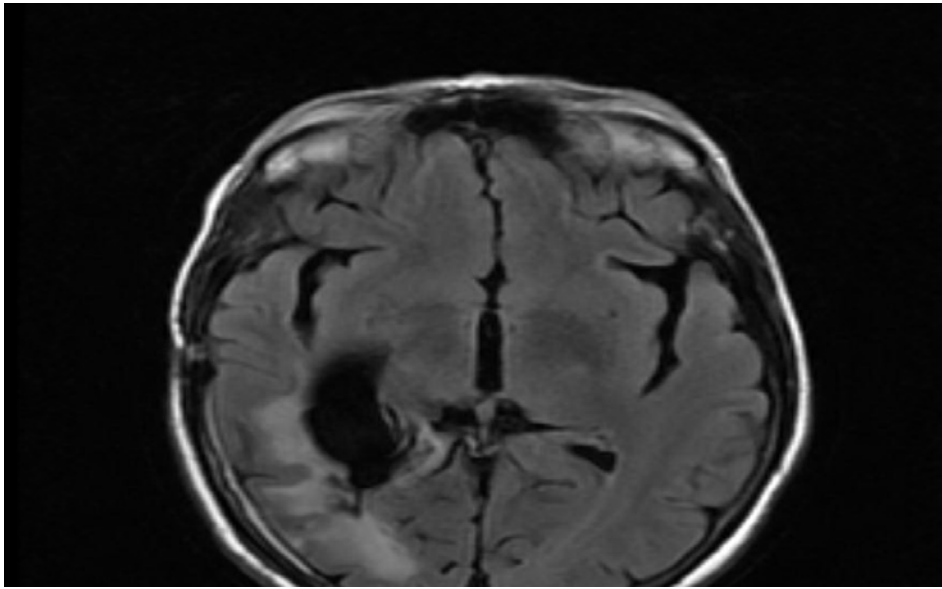
70 year old lady with severe headaches
Stereotactic biopsy- Diffuse large B-Cell Lymphoma



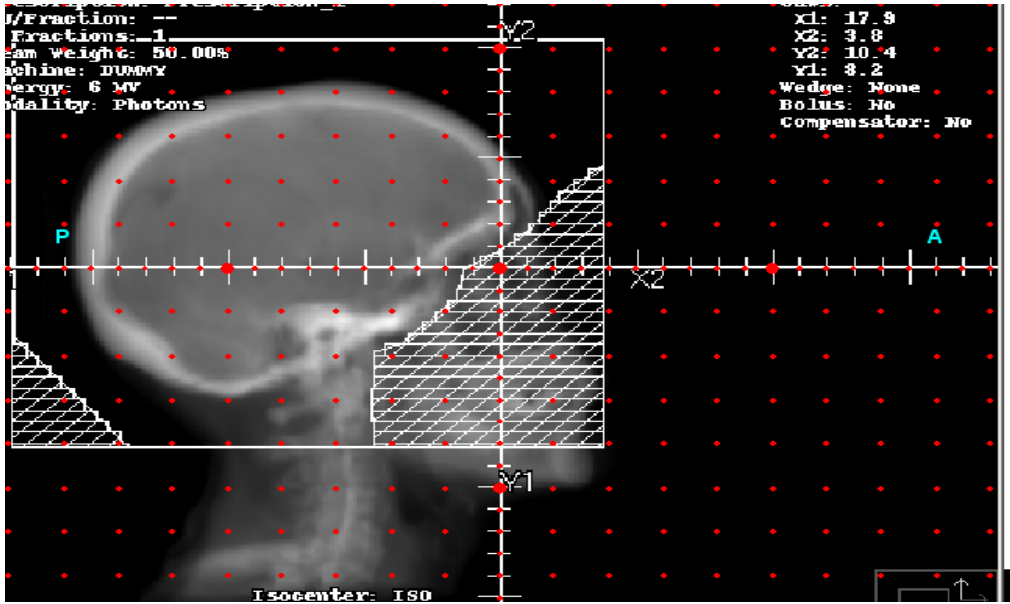


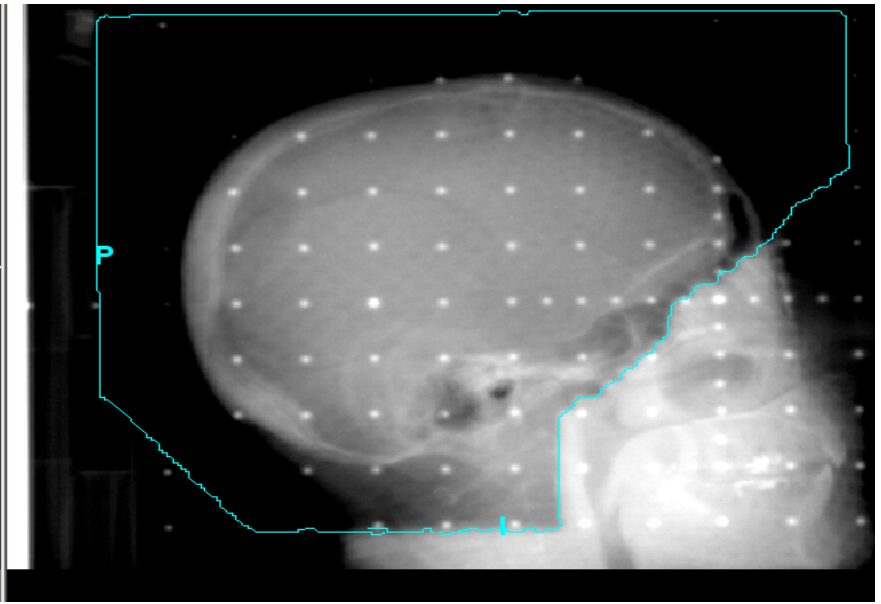
Randomized on RTOG-MSKCC protocol to receive low-dose RT after CR to R-MPV





RT Dose- 23.4 Gy (1.8 Gy X13)





Role of RT in PCNSL

- **Consolidation** after MTX-based chemo
  - Low dose after CR
  - Full dose after PR
- **Salvage** of chemotherapy alone failures (progression or relapse)
- **Palliation** of poor chemotherapy candidates

Salvage of chemotherapy alone failures **(MSKCC)**

- Progression- 24; relapse- 24 pts.
- WBRT- Median- 40 Gy (21-50 Gy)
- CR-58%; PR- 21%
- 15 pts (31%) remained in remission
- Median survival-16 months
- 54% survived >1 year
- Relapses 33 pts:
  - Brain- 22
  - Spine/lepto-8
  - Eyes- 3

Salvage whole brain radiotherapy for recurrent or refractory primary CNS lymphoma

Neurology® 2007;69:1178-1182

Andreas F. Hottinger, MD, PhD
Lisa M. DeAngelis, MD
Joachim Yahalom, MD
Lauren E. Abrey, MD

ABSTRACT

Background: High-dose methotrexate (MTX) and whole brain radiation therapy (WBRT) prolong survival in primary CNS lymphoma (PCNSL) patients but have been associated with delayed neurotoxicity. Consequently, patients are often treated with chemotherapy alone, and WBRT is deferred until relapse.

Methods: We performed a retrospective study to evaluate the safety and efficacy of salvage WBRT. Radiographic response, survival, and late neurotoxicity were assessed as the main endpoints.

Figure 1 Overall and progression-free survival (PFS) from start of whole brain radiation therapy

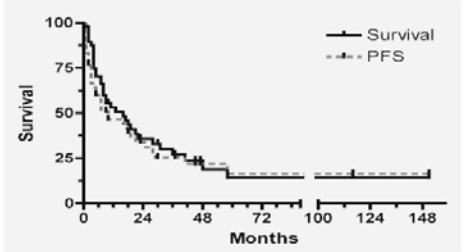
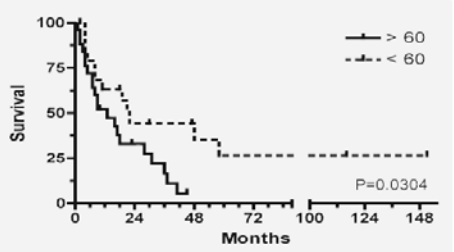


Figure 2 Survival from start of whole brain radiation therapy, separated by age group



Salvage of chemotherapy alone failures **(MGH)**

- Progression- 17; relapse- 10 pts.
- WBRT- Median- 36 Gy (28-45 Gy)
- CR-37%; PR- 37%
- Median survival- 9.7 from relapse
    - 29 mos from diagnosis
- 33% survived >1 year
- Relapses from CR- 8 pts:
    - Brain- 4
    - Systemic- 4

Results of Whole-Brain Radiation As Salvage of Methotrexate Failure for Immunocompetent Patients With Primary CNS Lymphoma

Paul L. Nguyen, Arnab Chakravarti, Dianne M. Finkelstein, Fred H. Hochberg, Tracy T. Batchelor, and Jay S. Loeffler

J Clin Oncol 23:1507-1513. © 2005

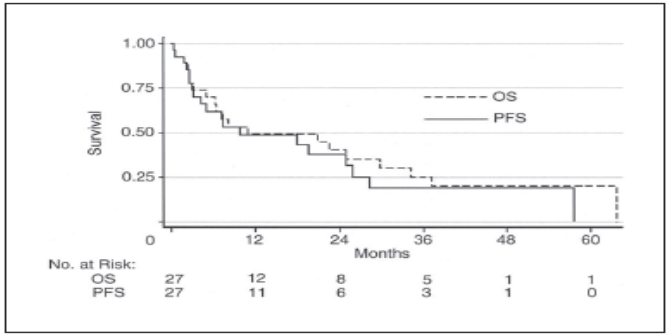


Fig 1. Overall survival (OS) and progression-free survival (PFS) from start of whole-brain radiotherapy.

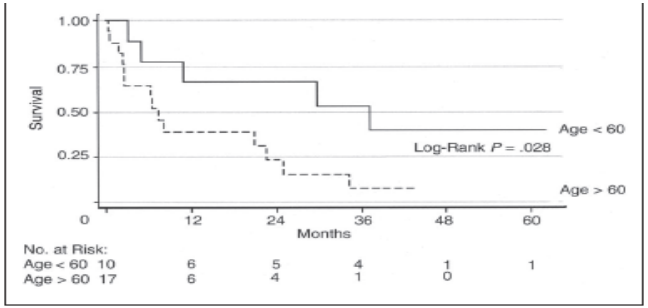


Fig 2. Survival from start of whole-brain radiotherapy, separated by age group.

RT in PCNSL: Field design

- **CTV**: Whole brain including C1 and C2 and the posterior aspect of the eyes.
- The iso-center is set anteriorly and bisects the bony canthi (to reduce divergence in possible future match to ocular field).
  - Alternatively, anterior border of PTV is set with the isocenter 5 mm behind the lens.
- If the eyes were originally involved, both eyes should be included in their entirety in WBRT field.
- The role of tumour site boost is uncertain and is not recommended by most experts
- It is not standard to irradiate the whole cranio-spinal axis

Is Whole-Brain Irradiation Necessary for Primary Central Nervous System Lymphoma?

Patterns of Recurrence after Partial-Brain Irradiation

Yuta Shibamoto, M.D.[1]
Naofumi Hayabuchi, M.D.[2]
Jun-ichi Hiratsuka, M.D.[3]
Sunao Tokumaru, M.D.[4]
Hiroki Shirato, M.D.[5]
Mitsuharu Sougawa, M.D.[6]
Natsuo Oya, M.D.[7]
Yuji Uematsu, M.D.[8]
Masahiro Hiraoka, M.D.[7]

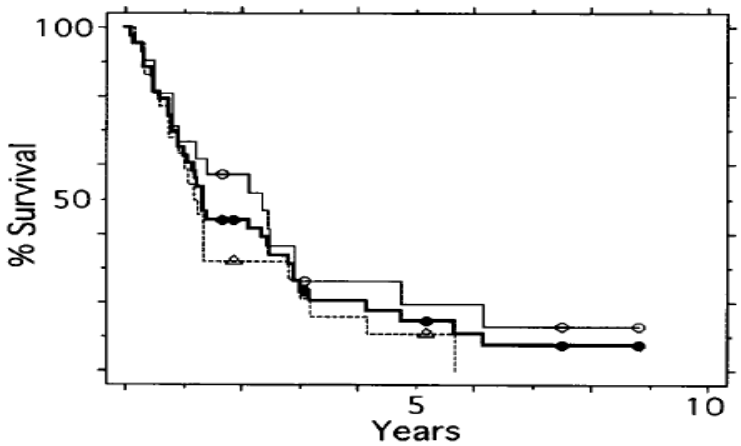


FIGURE 4. Overall survival curves for all 43 patients (—●—), for 21 patients treated with safety margins of ≥ 4 cm (—○—), and for 22 patients treated with safety margins of < 4 cm margins (--△--).

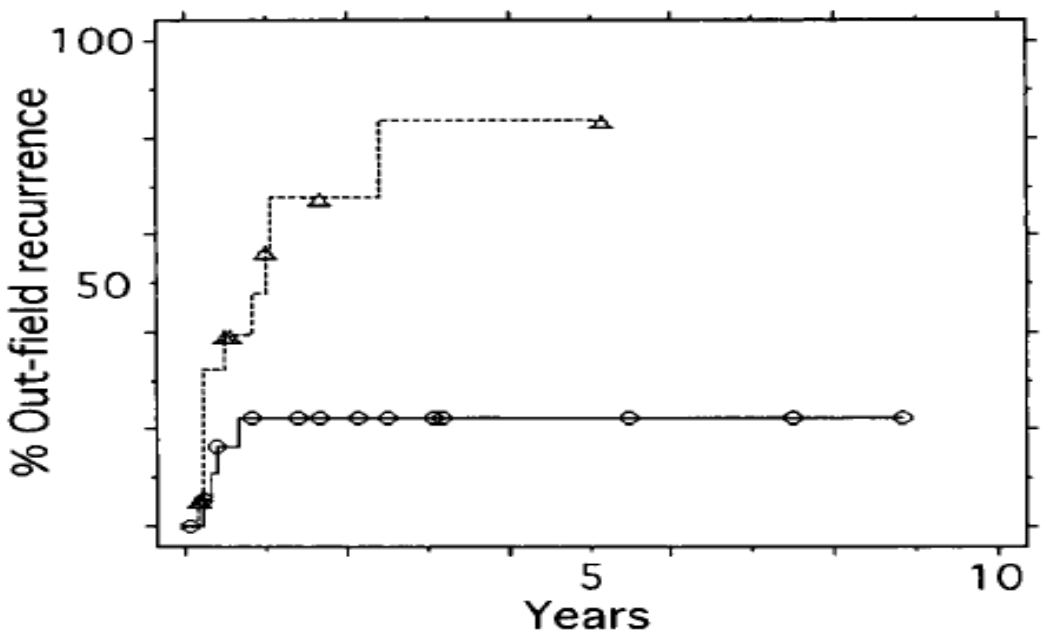
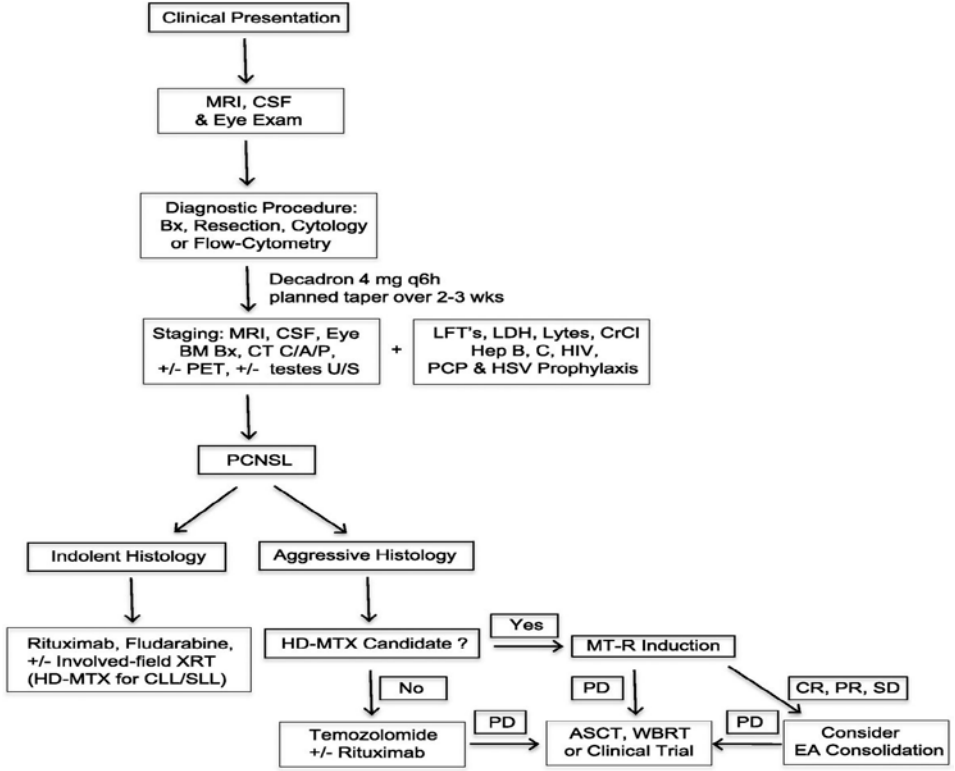


FIGURE 3. Cumulative incidence of out-field recurrences according to the safety margins of the radiation field. —○—: margins ≥ 4-cm; --△--: margins of < 4-cm.

RT in PCNSL: Dose

- Consolidation dose after MRI-CR to chemotherapy: 23.4 Gy in 1.8 Dose per fraction. (13 treatments)
- WBRT after incomplete response to chemotherapy: 36 Gy to 45 Gy (1.5 to 1.8 Gy/fraction)
- WBRT for salvage of chemotherapy failure (progression or relapse) 36 – 40 Gy (1.5 Gy-1.8 Gy/fraction)
- WBRT as primary treatment for non-candidates for chemotherapy: 40-50 Gy
- Whole orbit (if included)- only up to 36 Gy
- For palliation: WBRT dose is 30-36 Gy in 10 or 15 fractions.

How I treat PCNSL. In the diagnostic work-up, an MRI of the spine (± gadolinium) may be useful if warranted by neurologic symptoms or if CSF analysis is contraindicated.



James L. Rubenstein et al. Blood 2013;122:2318-2330

RT in PCNSL – Take home

- WBRT an effective tool in many stages of treatment
- Best use of RET is as low dose (24 Gy) after CR to MTX
- Full dose RT after MTX is toxic in age >60 years
- Chemotherapy alone in “full” MTX doses or with ASCT transplant is also toxic, but is often considered
- Patients respond (yet, temporarily) to salvage with RT alone or with chemotherapy

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Guy's and St Thomas' NHS
NHS Foundation Trust

Extra-nodal Lymphoma
Rare sites

George Mikhaeel, MD
Department of Clinical Oncology
Guy's & St Thomas' Hospital
KHP Academic Health Sciences Centre
London, UK

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INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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Rare sites

- Kidneys
- Bladder
- Prostate
- Small intestine / Duodenum
- Large intestine
- Liver
- Uterus
- Ovaries
- Endocrine organs
- Heart

Histologies

- Most common:
  - DLBCL: virtually any organ
  - Marginal Zone Lymphoma

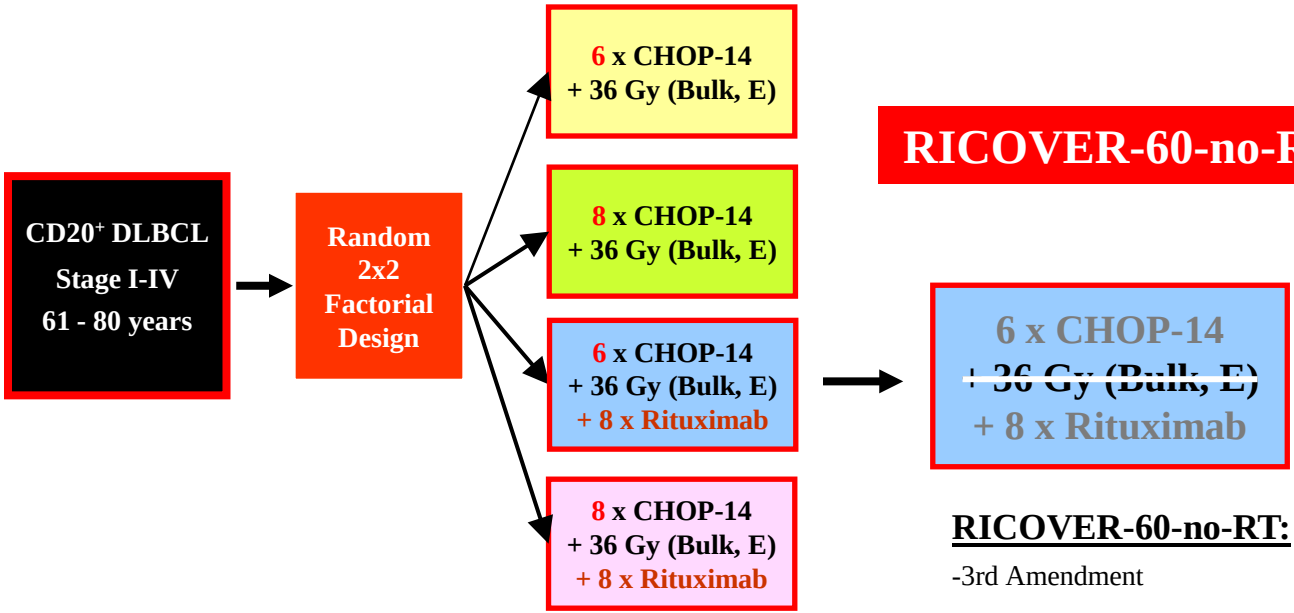
- Presentation:
  - Main presentation
  - Extra-nodal involvement in context of stage IV disease (not strictly EN lymphoma)

General principles of management

- Early stage:
  - Low-grade: curative RT
  - High-grade: CMT if RT feasible. Full course chemo alone if not.
    - Tolerability of chemo
    - Response to chemo
    - Morbidity of RT
    - Suitability for future salvage

- Advanced stage:
  - Low-grade: systemic Rx ± RT for local control
  - High-grade: systemic Rx ± consolidation RT to sites of EN disease

RICOVER-60



RICOVER-60-no-RT Held, JCO 2014l

6 x CHOP-14
~~+ 36 Gy (Bulk, E)~~
+ 8 x Rituximab

RICOVER-60-no-RT:

-3rd Amendment

-Recruitment 08/2005 – 10/2007

-Number of Patients 166

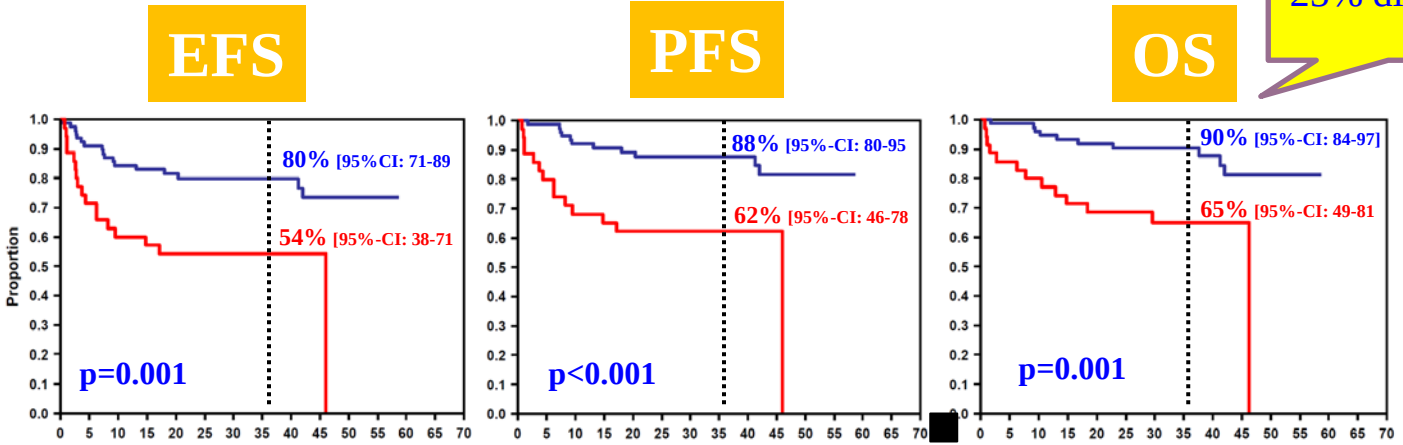
-Median Observation 39 Months

Pfreundschuh, Lancet Oncol, 2008

RICOVER-60-no-RT

per protocol Analysis

25% difference



RICOVER-60 (n=78)

RICOVER-60-no-RX (n=35)

Held, JCO 2014

DSHNHL

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Characteristic	RICOVER-60				RICOVER-noRTh				*P*	
	Total (n = 306)		With Bulk (n = 117)		Total (n = 164)		With Bulk (n = 47)			
	No.	%	No.	%	No.	%	No.	%	Total	With Bulk
Sex									.100	.474
Male	168	55	62	53	77	47	22	47		
Female	138	45	55	47	87	53	25	53		
Age, years									.018	.064
Median	69		68		71		70			
Range	61-80		61-80		61-80		61-79			
> 60	306	100	117	100	164	100	47	100		
LDH > normal	152	50	76	65	91	56	37	79	.229	.085
ECOG PS > 1	43	17	27	23	23	14	11	23	.993	.964
Extralymphatic involvement > one	52	14	24	21	38	23	16	34	.105	.068
Stage III to IV disease	152	50	69	59	98	60	36	77	.037	.003
IPI score									.202	.074
1	94	31	20	17	39	24	4	9		
2	89	29	36	31	43	26	8	17		
3	78	26	34	29	50	31	19	40		
4	45	15	27	23	32	20	16	34		
Extralymphatic involvement	161	53	66	56	104	63	34	72	.024	.059
Extralymphatic involvement surgically removed	35*	12	7†	6	31‡	20	7§	15	.020	.118
Liver‖	15	5	11	9	10	6	5	11	.582	.778
Lung‖	16	5	5	4	11	7	4	9	.511	.279
Bulky disease	117	38	117	100	47	29	47	100	.038	—
Bulky sites surgically removed	—		11¶	10	—		6#	13	—	.572
B symptoms	98	32	54	46	62	38	29	62	.208	.072
BM involvement	14	5	5	4	15	9	5	11	.050	.152
Reference histology available	297	97	113	97	159	97	45	96	.817	.488
DLBCL	237	80	84	74	130	82	39	87		
B cell, other subtypes	37	13	14	12	17	11	3	7		
B cell, unspecified	14	5	8	7	9	6	2	4		
Other	9	3	7	6	3	2	1	2		

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RICOVER-60: RT to extra-lymphatic tissue

Patients with initial bulky disease (defined as lymphoma masses or conglomerates with diameter ≥ 7.5 cm) or extralymphatic involvement were to receive RT to these areas if complete remission (CR), unconfirmed CR (CRu), or partial remission (PR) was achieved after chemotherapy except when these lymphoma manifestations were completely removed by surgery. Start of RT was planned to be 3 to 6 weeks after the last chemotherapy cycle. A central RT reference panel developed an individual RT plan for each patient. RT to bulky disease was applied as involved-field RT. If a residual tumor remained after chemotherapy, target volume was adapted. If CR was achieved after chemotherapy, the target volume included the lymph node region of the initial bulk. Lymph node regions were defined according Ann Arbor. Target volume of extralymphatic disease included the complete initially involved extralymphatic area. Patients received RT 36 Gy, at 1.8 to 2 Gy per fraction, administered 5× per week. No RT was to be administered in the RICOVER-noRTh cohort.

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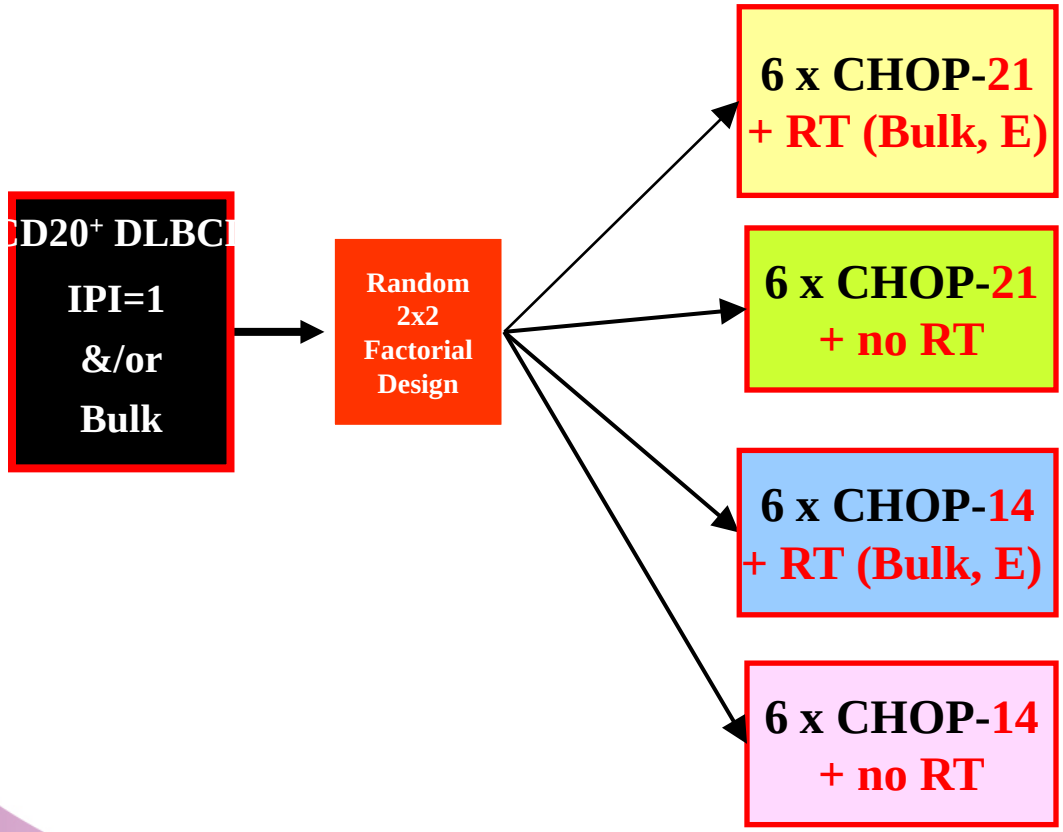
UNFOLDER



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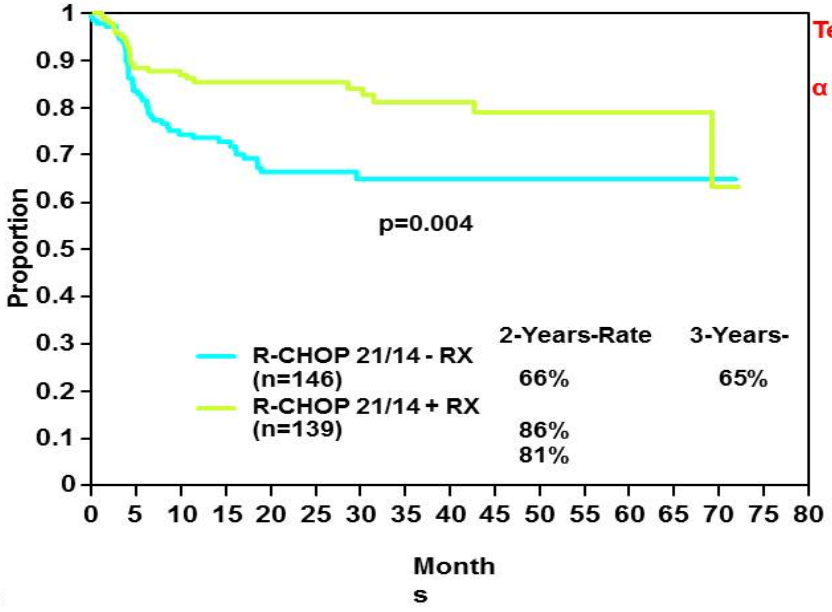
UNFOLDER – Trial initial results- RT v no RT

UNFOLDER study

Patients 18- 60 years, B-cell (CD20+), aaIPI=0 with bulk or aaIPI=1, ITT (n=443)

EFS – Patients randomised to 4 arms with RX, according to RX (n=285)



Termination!!!

α Spending 0.008

DSHNHL 01.07.12

Abdominal lymphoma

- Duodenum:
  - FL increasingly recognised
  - Obstructive symptoms / pain
  - May be part of multifocal small bowel lymphoma. Small foci in bowel not appear on PET due to physiological FDG in bowel
  - Small bowel capsule endoscopy
  - Local RT is an option for localised indolent disease.

- Small bowel:
  - Indolent (FL, MZL), T-cell, DLBCL
  - Treatment according to histology
  - Sometimes diagnosed after resection
  - Whole abdominal RT has been reported

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Abdominal lymphoma

- Kidneys:
  - Rare as primary presentation
  - High risk of CNS disease
  - Primary treatment: chemo
- Adrenals:
  - High risk of CNS disease

Pelvic Lymphoma

- Bladder: DLBCL or MZL. FL reported
- Prostate: MZL, FL
- Uterus / ovaries: DLBCL. High risk of CNS disease

Considerations:

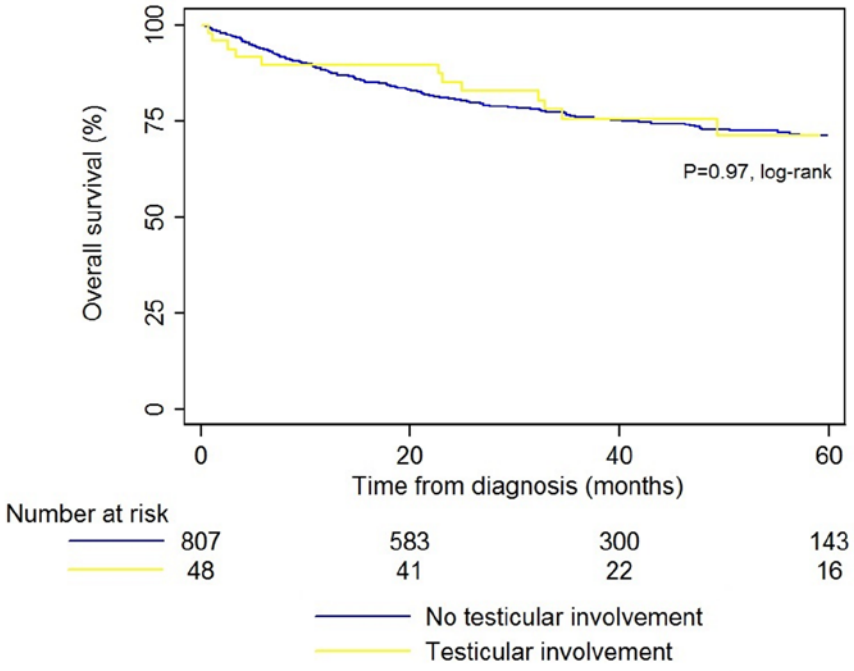
- Bladder: FDG excretion is urine (PET for staging nodes / others sites)
- Planning: bladder full v empty. Rectal volume. IV contrast
- CTV: whole organ
- Fertility issues

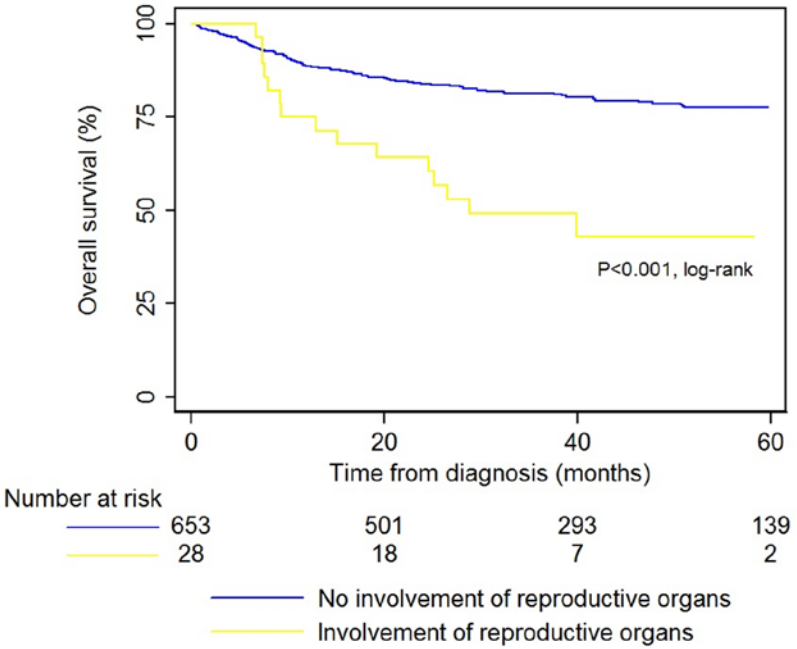
Female patients with DLBCL and involvement of the reproductive organs have poor outcomes and markedly increased risk of CNS relapse with R-CHOP(-like) therapy

Tarec C. El-Galaly,[1] Chan Y. Cheah,[2] Martin Hutchings,[3] George Mikhaeel,[4] Laurie H. Sehn,[5] Kerry J. Savage,[5] Sally Barrington,[6] Jakob W. Hansen,[3] Mette Ø. Poulsen,[1] Daniel Smith,[4] Kirsty Rady,[2] Karen J. Mylam,[7] Thomas S. Larsen,[7] Staffan Holmberg,[8] Maja B. Juul,[9] Sabrina Cordua,[10] Michael R. Clausen,[11] Kristina B. Jensen,[12] Martin Bøgsted,[1] Hans E. Johnsen,[1] John Seymour,[2] Joseph M. Connors,[5] Peter d.N. Brown,[3] and Diego Villa[5]

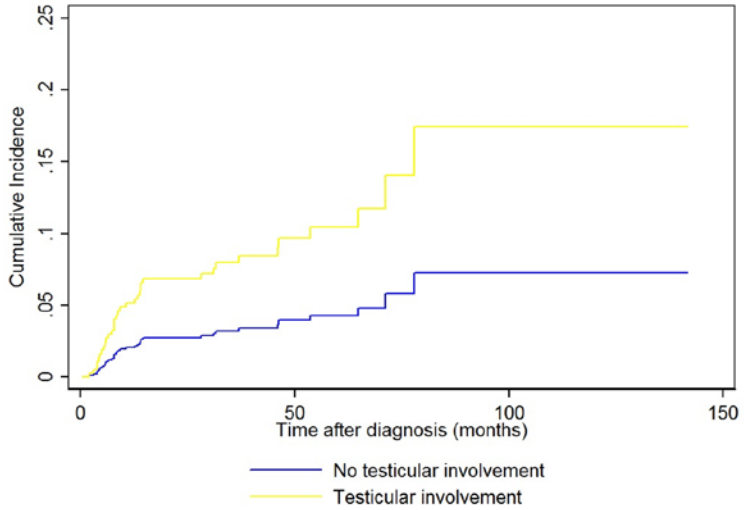
- 1,536 patients, 76 (5%): reproductive organ involvement.
- Testicular involvement = 48 (6%) of men
- Female reproductive organ involvement = 28 (4%) of women
  (uterus n=15, ovaries n=11, both n=2).

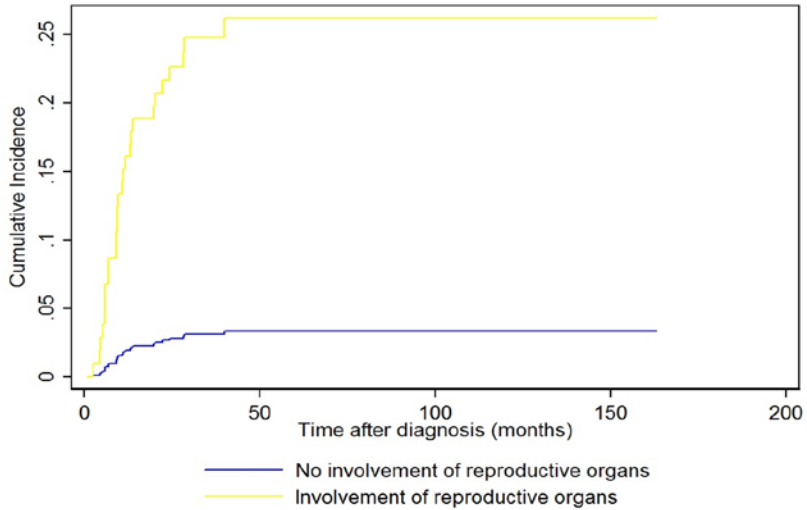
OS


Overall survival (%)
0
25
50
75
100
P=0.97, log-rank
0
20
40
60
Time from diagnosis (months)
Number at risk
807 583 300 143
48 41 22 16
No testicular involvement
Testicular involvement


Overall survival (%)
0
25
50
75
100
P<0.001, log-rank
0
20
40
60
Time from diagnosis (months)
Number at risk
653 501 293 139
28 18 7 2
No involvement of reproductive organs
Involvement of reproductive organs

CNS relapse


Cumulative Incidence
0
.05
.1
.15
.2
.25
0
50
100
150
Time after diagnosis (months)
No testicular involvement
Testicular involvement


Cumulative Incidence
0
.05
.1
.15
.2
.25
0
50
100
150
200
Time after diagnosis (months)
No involvement of reproductive organs
Involvement of reproductive organs